REVIEW

Mechanisms of β-cell dedifferentiation in diabetes: recent findings and future research directions

Mohammed Bensellam[1,2], Jean-Christophe Jonas[2] and D Ross Laybutt[1,3]

[1]Garvan Institute of Medical Research, Sydney, New South Wales, Australia
[2]Université Catholique de Louvain, Institut de Recherche Expérimentale et Clinique, Pôle d'Endocrinologie, Diabète et Nutrition, Brussels, Belgium
[3]St Vincent's Clinical School, UNSW Sydney, Sydney, New South Wales, Australia

Correspondence should be addressed to M Bensellam or D R Laybutt: **mohammed.bensellam@uclouvain.be** or **r.laybutt@garvan.org.au**

Abstract

Like all the cells of an organism, pancreatic β-cells originate from embryonic stem cells through a complex cellular process termed differentiation. Differentiation involves the coordinated and tightly controlled activation/repression of specific effectors and gene clusters in a time-dependent fashion thereby giving rise to particular morphological and functional cellular features. Interestingly, cellular differentiation is not a unidirectional process. Indeed, growing evidence suggests that under certain conditions, mature β-cells can lose, to various degrees, their differentiated phenotype and cellular identity and regress to a less differentiated or a precursor-like state. This concept is termed dedifferentiation and has been proposed, besides cell death, as a contributing factor to the loss of functional β-cell mass in diabetes. β-cell dedifferentiation involves: (1) the downregulation of β-cell-enriched genes, including key transcription factors, insulin, glucose metabolism genes, protein processing and secretory pathway genes; (2) the concomitant upregulation of genes suppressed or expressed at very low levels in normal β-cells, the β-cell forbidden genes; and (3) the likely upregulation of progenitor cell genes. These alterations lead to phenotypic reconfiguration of β-cells and ultimately defective insulin secretion. While the major role of glucotoxicity in β-cell dedifferentiation is well established, the precise mechanisms involved are still under investigation. This review highlights the identified molecular mechanisms implicated in β-cell dedifferentiation including oxidative stress, endoplasmic reticulum (ER) stress, inflammation and hypoxia. It discusses the role of *Foxo1, Myc* and inhibitor of differentiation proteins and underscores the emerging role of non-coding RNAs. Finally, it proposes a novel hypothesis of β-cell dedifferentiation as a potential adaptive mechanism to escape cell death under stress conditions.

Introduction

All the cells of an organism, including pancreatic β-cells, originate from embryonic stem cells through a complex cellular process termed differentiation (Keller 2005). β-cell differentiation involves the coordinated and tightly controlled activation/repression of specific transcription factors and downstream gene clusters in a time-dependent manner. These complex signalling events drive the transition from definitive endoderm cells to mature
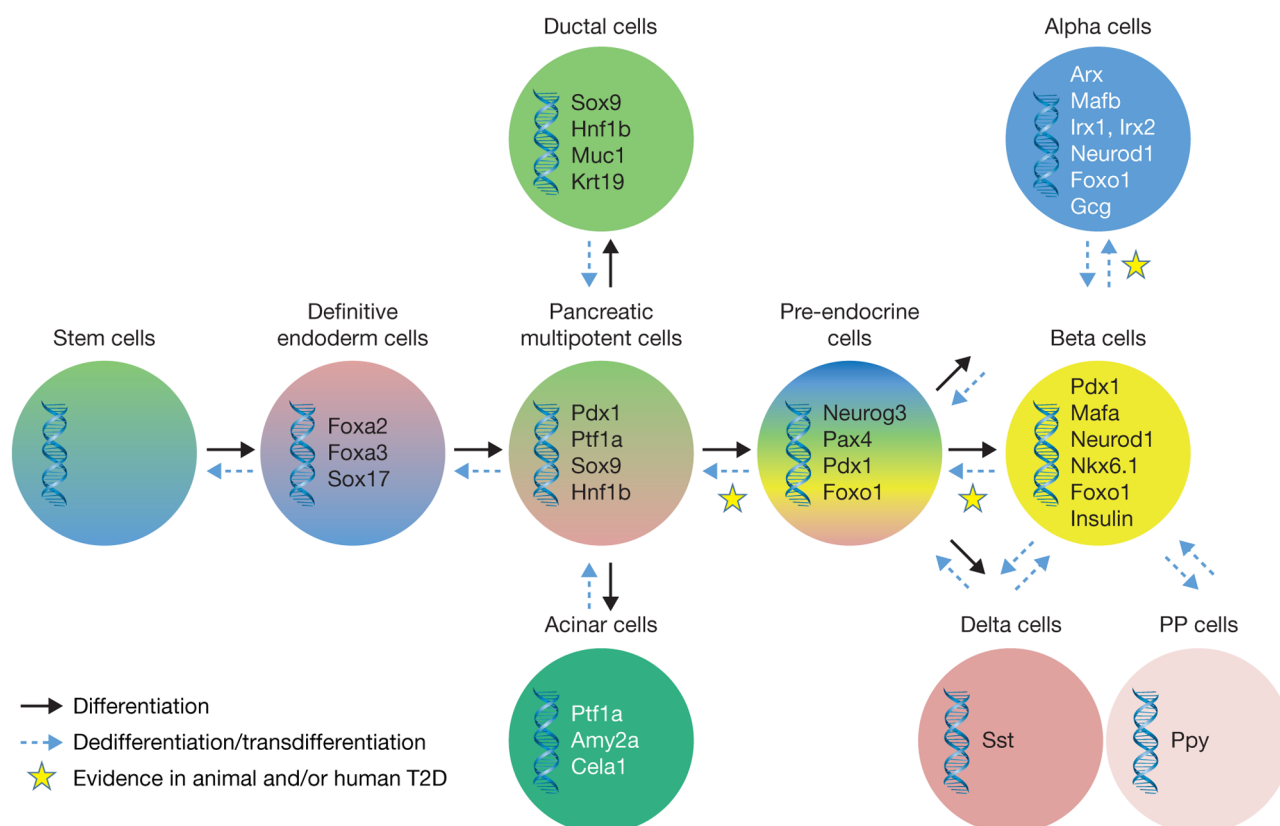
Figure 1

Schematic representation of the process of β-cell differentiation. This process involves coordinated and tightly controlled activation/repression of specific transcription factors that drive the transition from a stem cell to a mature β-cell during embryonic development and the postnatal period until weaning. Evidence from animal and human studies suggest that mature β-cells could regress backwards to a precursor-like stage and/or transdifferentiate into other islet cells in type 2 diabetes.

insulin-secreting β-cells with the progressive acquisition of specific morphological and functional cellular features (Puri & Hebrok 2010, Seymour & Sander 2011, Stanger & Hebrok 2013) (Fig. 1).

Interestingly, cellular differentiation is not unidirectional. Indeed, growing evidence suggests that under specific conditions, mature β-cells can lose, to various degrees, their differentiated phenotype and cellular identity and regress to a less differentiated or even a precursor-like state (Fig. 1). This concept, termed dedifferentiation, has been implicated in the pathogenesis of diabetes (Weir *et al.* 2013). Several *in vivo* studies in animal models and in humans over the last two decades suggest that, in addition to cell death (Butler *et al.* 2003, Jurgens *et al.* 2011), dedifferentiation (Jonas *et al.* 1999, Kjorholt *et al.* 2005, Talchai *et al.* 2012, Marselli *et al.* 2014, Cinti *et al.* 2016) may be an important contributing factor to the loss of functional β-cell mass in type 2 diabetes (Sakuraba *et al.* 2002, Yoon *et al.* 2003, Deng *et al.* 2004, Rahier *et al.* 2008).

β-cell dedifferentiation is manifested by reduced expression of β-cell-enriched genes, including key transcription factors, insulin, glucose metabolism genes, protein processing and secretory pathway genes and the concomitant upregulation of genes suppressed or expressed at very low levels in normal β-cells; the so-called β-cell disallowed or forbidden genes (Bensellam *et al.* 2012*b*, Schuit *et al.* 2012, Rutter *et al.* 2015, Lemaire *et al.* 2016, 2017). Moreover, the presence of progenitor cell markers has been observed in the dedifferentiated islets of diabetic animals (Talchai *et al.* 2012, Wang *et al.* 2014, Kim-Muller *et al.* 2016) and even markers of α-cells have been detected suggesting the transdifferentiation of β-cells to α-cells in diabetic animals and humans (Spijker *et al.* 2013, 2015, Brereton *et al.* 2014, Cinti *et al.* 2016). These alterations lead to metabolic and structural reconfiguration of β-cells and ultimately defective insulin secretion. While earlier and recent reports have well established the major role of hyperglycemia and the ensuing glucotoxicity in β-cell dedifferentiation (Bensellam *et al.* 2012*b*), the

precise molecular mechanisms involved are still under investigation. Understanding these mechanisms opens novel therapeutic horizons to preserve/restore the functional β-cell mass in diabetes.

In this extensive review, we first highlight the close relationship between the degree of β-cell differentiation and insulin secretory function. We then describe the known molecular mechanisms involved in β-cell dedifferentiation in diabetes with a focus on the role of glucotoxicity and its downstream pathways including oxidative stress, endoplasmic reticulum (ER) stress, inflammation and hypoxia. We depict the roles of the transcriptional regulators such as *Foxo1, Myc* and the inhibitors of differentiation and discuss the role of the failure of adaptive unfolded protein response (UPR). We also discuss the mounting role of non-coding RNAs in β-cell dedifferentiation. Finally, based on our and others emerging evidence, we propose a novel view of dedifferentiation as a potential adaptive mechanism to escape cell death under stress conditions.

Relationship of β-cell differentiation to insulin secretory function

Pancreatic β-cells play a fundamental role in the maintenance of glucose homeostasis in mammalians. They synthesize and secrete insulin after meals to keep blood glucose levels within a tight range (between 4 and 6 mM in fasting adult humans). Glucose is the major physiological modulator of β-cell function and undeniable evidence indicates that glucose must be metabolized by β-cells in order to stimulate insulin secretion (Malaisse *et al.* 1979, Newgard & McGarry 1995, Jitrapakdee *et al.* 2010). Thus, upon a rise in its plasma concentration, glucose rapidly equilibrates across the β-cell plasma membrane via the high-capacity, low-affinity glucose transporter GLUT2 (also known as SLC2A2) (Thorens 2015). In humans, the high-affinity glucose transporter GLUT1 prevails instead of GLUT2 (De Vos *et al.* 1995, Ferrer *et al.* 1995). Nevertheless, in both human and rodent β-cells, glucose transport exceeds glucose utilization and is therefore not limiting (Newgard 1996). In the cytosol, glucose is then phosphorylated by glucokinase (GCK); a low-affinity type IV hexokinase. GCK regulates the rate of glucose utilization and is therefore considered as the glucose sensor of β-cells (Matschinsky 2009). Interestingly, β-cells present the remarkable feature of an almost complete repression of high-affinity type I–III hexokinases to avoid insulin release at low plasma glucose concentrations in the

fasted state (Sekine *et al.* 1994, Schuit *et al.* 1999). Glucose-6-phosphate is then oxidized by glycolysis to generate ATP, NADH and pyruvate. Because β-cells present another remarkable feature of expressing very low levels of lactate dehydrogenase (LDH) and monocarboxylate transporter (MCT) (Sekine *et al.* 1994, Ishihara *et al.* 1999, Zhao *et al.* 2001, Thorrez *et al.* 2011), almost all the pyruvate enters mitochondria to provide a substrate for the Krebs cycle (Fig. 2). This particular design also avoids exercise-induced insulin release (Otonkoski *et al.* 2007). To compensate for the low LDH activity and maintain the glycolytic flux, β-cells present a third notable characteristic of two highly active mitochondrial membrane electron shuttles: the glycerol-3-phosphate and the malate-aspartate shuttles that couple the regeneration of cytosolic NAD^+ with the production of NADH or $FADH_2$ in the mitochondria (MacDonald 1981, 1982, Sekine *et al.* 1994, Eto *et al.* 1999). This NADH shuttle system allows tight coupling of glycolysis to mitochondrial metabolism (Fig. 2). In the mitochondria, pyruvate is either oxidized to acetyl-CoA (~50%) by pyruvate dehydrogenase (PDH) or carboxylated to oxaloacetate (~50%) by pyruvate carboxylase (PC) (MacDonald 1993, Khan *et al.* 1996). The latter enzyme replenishes Krebs cycle intermediates (anaplerosis) to compensate for their removal for biosynthetic purposes (cataplerosis) (Brun *et al.* 1996, Schuit *et al.* 1997, Farfari *et al.* 2000). Pyruvate metabolism in the Krebs cycle generates reducing equivalent NADH and $FADH_2$ which together with those generated by the mitochondrial shuttles transfer electrons to the respiratory chain to generate ATP (Duchen *et al.* 1993, Eto *et al.* 1999) (Fig. 2). The resulting atypical rise in ATP/ADP ratio (Detimary *et al.* 1996, 1998) leads to the closure of ATP-gated K^+ (K_{ATP}) channels, plasma membrane depolarization, opening of voltage-gated Ca^{2+} channels (VDCC), Ca^{2+} influx and the elevation of cytosolic free Ca^{2+} concentration ($[Ca^{2+}]_i$), which is the triggering signal for insulin secretion (Fig. 2). This sequence of events is referred to as the triggering pathway of glucose-stimulated insulin secretion (GSIS) (Henquin 2011). Besides, glucose can modulate insulin secretion independently from its action on K_{ATP} channels by generating signals that amplify the action of Ca^{2+} on insulin granule exocytosis, provided that Ca^{2+} influx is already stimulated and $[Ca^{2+}]_i$ is high. It is called the metabolic amplifying pathway of GSIS (Henquin 2011). This pathway requires glucose metabolism but the coupling factors have not been identified with certainty with a probable implication of NADPH (Ivarsson *et al.* 2005, Ferdaoussi *et al.* 2015) and other effectors (Fig. 2). Moreover, other nutrients (such as free fatty acids
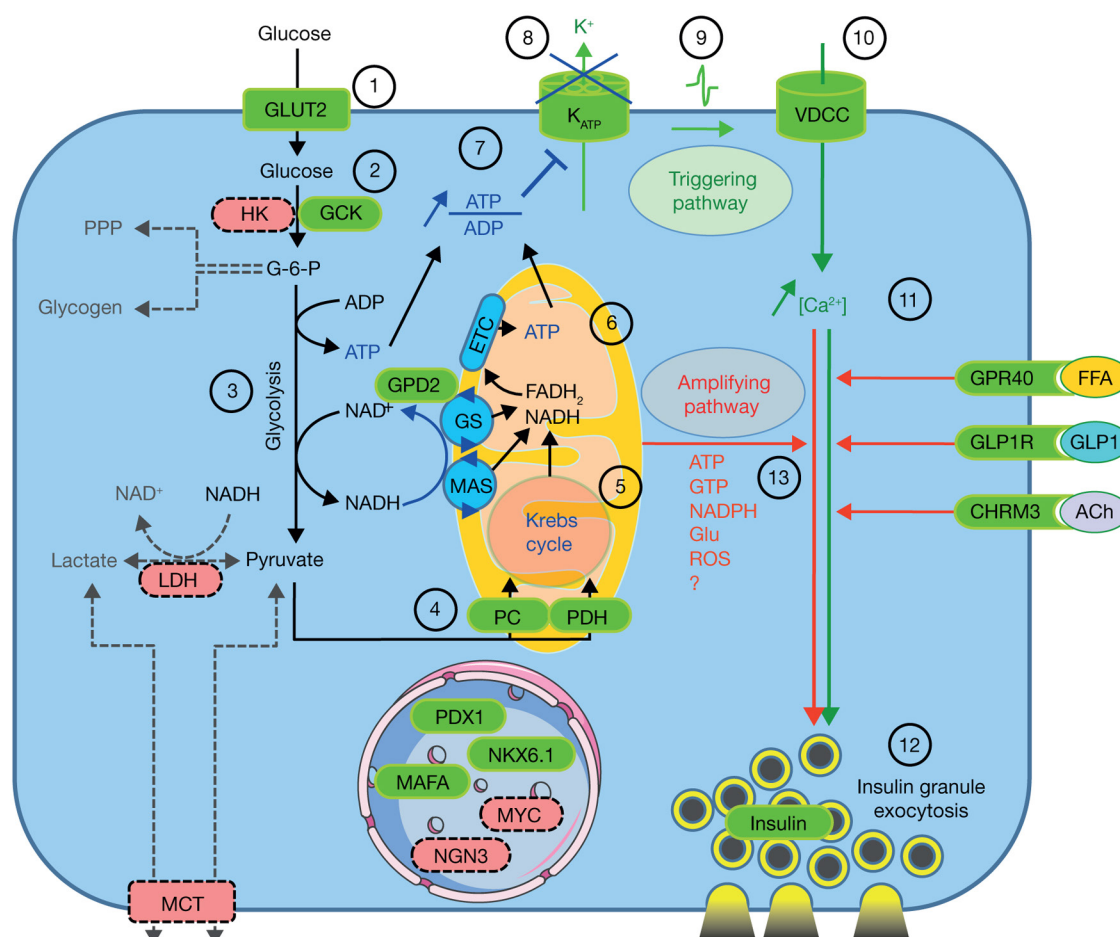
Figure 2

Schematic summary of the stimulus-secretion coupling mechanism in mature differentiated β-cells with emphasis on key steps and principal components. Upon a rise in its extracellular concentration, glucose rapidly equilibrates across the plasma membrane via the glucose transporter GLUT2 (1) and is phosphorylated by glucokinase (GCK) (2). Glucose-6-phosphate (G-6-P) is further metabolized by glycolysis to generate pyruvate, ATP and NADH (3). The latter requires the mitochondrial shuttles glycerol-3-phosphate (GS) and malate-aspartate (MAS) to regenerate NAD^+ to compensate for low lactate dehydrogenase (LDH) activity. Because β-cells express low levels of monocarboxylate transporter (MCT), pyruvate is channelled to mitochondria where it is transformed into acetyl coenzyme A and oxaloacetate by pyruvate dehydrogenase (PDH) and pyruvate carboxylase (PC) respectively (4). Acetyl coenzyme A and oxaloacetate are used by the Krebs cycle (5) to generate NADH and $FADH_2$ that, together with those produced by the shuttles, transfer electrons to the electron transport chain (ETC) to generate ATP (6). The latter, together with ATP generated from glycolysis, increases the ATP/ADP ratio (7). This leads to the closure of ATP-dependent K^+ (K_{ATP}) channels (8), plasma membrane depolarization (9) and opening of voltage-dependent Ca^{2+} channels (VDCCs) (10). The ensuing Ca^{2+} influx and rise in cytosolic free Ca^{2+} concentration ($[Ca^{2+}]$) (11) is the triggering signal for insulin secretion (12) and this sequence of events is referred to as the triggering pathway. On the other hand, other metabolic coupling factors generated by glucose metabolism or other nutrient such as free fatty acids in addition to intracellular messengers affected by hormones such as glucagon-like peptide 1 (GLP1) and neurotransmitters such as acetylcholine (Ach) can amplify the effect of Ca^{2+} on insulin granule exocytosis (13). This is known as the amplifying pathway of insulin secretion. Green arrows: triggering pathway; red arrows: amplifying pathway. Effectors in green: β-cell-enriched genes; effectors in red: β-cell forbidden genes.

(Gravena *et al*. 2002, Itoh *et al*. 2003)), hormones (such as GLP1 (Campbell & Drucker 2013)) and neurotransmitters (such as acetylcholine (Gautam *et al*. 2007, Molina *et al*. 2014)) can also augment the action of Ca^{2+} on exocytosis (Fig. 2). The effect of hormones and neurotransmitters is known as the neurohormonal amplification of insulin secretion (Henquin 2011) (Fig. 2).

Adequate β-cell function relies on a specialized pattern of gene expression. Interestingly, the mature metabolic phenotype of pancreatic β-cells is acquired only several weeks after birth (Asplund *et al*. 1969, Pildes *et al*. 1969, Lavine *et al*. 1971, Grill *et al*. 1981). The immaturity of neonatal β-cells and their poor GSIS have been correlated with low expression of key metabolic genes, high expression of the β-cell forbidden genes *Hk2*, *Ldha* and *Mct1* and changes in the expression of specific microRNAs (miRNAs) (Rorsman *et al*. 1989, Tan *et al*. 2002, Jermendy *et al*. 2011, Martens *et al*. 2014, Jacovetti *et al*. 2015).

Dietary differences between neonates and adults, in particular glucose, may drive the maturation of the β-cell phenotype. Indeed, strong evidence indicates that physiological glucose stimulation is a major regulator of the β-cell differentiated phenotype (Table 1). We and others have shown that the function and survival of rat islets and purified β-cells are optimally preserved by culture in the presence of 10 mM glucose (G10), whereas marked alteration accompanies culture at lower (G2–5) or higher glucose concentrations (G30; glucotoxicity will be discussed in 'The loss of functional β-cell differentiation in diabetes: causes and mechanisms' section) (Efanova *et al.* 1998, Flamez *et al.* 2002, Khaldi *et al.* 2004, Bensellam *et al.* 2009). The beneficial physiological glucose stimulation (G10 vs G2–5) is associated with increased mRNA levels of several critical genes including insulin, components of the triggering pathway of insulin secretion, such as *Glut2*, subunits of the K_{ATP} channel *Kir6.2* (also known as *Kcnj11*) and *Sur1* (also known as *Abcc8*) and metabolic genes including glycolysis and Krebs cycle genes, subunits of the mitochondrial electron transport chain, genes implicated in cataplerosis, fatty acid biosynthesis and cholesterol biosynthesis, in parallel with the upregulation of the mRNA levels of the transcription factors *Srebp1*, *Srebp2* and *Chrebp* (Flamez *et al.* 2002, Van Lommel *et al.* 2006, Bensellam *et al.* 2009) (Table 1). These findings are corroborated by the observation that prolonged fasting (72 h) markedly decreases insulin, *Glut2*, *Gck* and voltage-dependent L-type Ca^{2+} channel α1 subunit mRNA levels. Interestingly, these alterations were rapidly reversed after refeeding in association with the normalization of β-cell function (Iwashima *et al.* 1994).

In addition to metabolic genes, physiological glucose stimulation improves and maintains the β-cell differentiated phenotype by modulating several stress responses and prosurvival/proapototic effectors and pathways (Van de Casteele *et al.* 2003, Martens *et al.* 2005, Hou *et al.* 2008*a*, Bensellam *et al.* 2009, Roma *et al.* 2012, Sarre *et al.* 2012). Among them, the UPR occupies a central place (Elouil *et al.* 2007, Bensellam *et al.* 2009). β-cells are highly specialized secretory cells that synthesize large amounts of proinsulin in response to glucose stimulation (Schuit *et al.* 1988, Ling & Pipeleers 1996). To cope with this heavy ER load, β-cells are endowed with a fundamental adaptive response to prevent accumulation of misfolded or unfolded proteins in the ER when client protein load overwhelms the ER folding capacity. UPR activity is orchestrated by three sensors located in the membrane of the ER, namely the pancreatic ER kinase (PERK also known as EIF2AK3), the endoribonuclease/

kinase inositol requiring 1 (IRE1 also known as ERN1) and the activating transcription factor 6 (ATF6). Active PERK phosphorylates the α-subunit of the translation initiation factor 2 (eIF2α) thereby leading to a transient and global attenuation of protein translation to decrease ER load in parallel with a paradoxical increase in the translation of special transcripts such as ATF4. This transcription factor upregulates the expression of chaperones and antioxidant genes as well as proapoptotic genes like *Ddit3* (also known as *Chop/Gadd153*), *Atf3* and *Trb3* (also known as *Trib3*) that contribute to β-cell death under prolonged or unresolved ER stress. Because eIF2α can be phosphorylated by kinases other than PERK in response to other types of stress, we will refer to the eIF2α-ATF4 arm of the UPR by Integrated Stress Response (ISR) if PERK activation has not been demonstrated. Activation of IRE1 leads to the unconventional splicing of *Xbp1* pre-mRNA and the ensuing upregulation of active X-Box-binding protein 1 (XBP1s). This key transcription factor, together with active ATF6, stimulates the expression of *Xbp1*, chaperones, foldases and genes of the ER-associated degradation (ERAD) pathway thereby leading to improved ER folding capacity and enhanced clearance of unfolded proteins from the ER (Schroder & Kaufman 2005). Interestingly, glucose stimulation exerts opposite effects on the PERK-eIF2α-ATF4 and IRE1-XBP1s/ATF6 arms of the UPR. Thus, the PERK-eIF2α-ATF4 arm is maximally activated at low glucose concentrations (PERK and eIF2α phosphorylation, upregulation of ATF4 and downstream target genes such as *Ddit3*), where protein synthesis, ATP levels and $[Ca^{2+}]_{ER}$ are low, while the IRE1-XBP1 arm is maintained at basal level. Glucose stimulation rapidly repressed the ISR and triggered *Xbp1* pre-mRNA splicing leading subsequently to the upregulation of XBP1s and a wide array of downstream target genes to face the ER synthetic load (Elouil *et al.* 2007, Vander Mierde *et al.* 2007, Gomez *et al.* 2008, Bensellam *et al.* 2009, Jonas *et al.* 2009, Moore *et al.* 2011). Of note, an inverse relationship between blood glucose levels and eIF2α phosphorylation in whole pancreatic extracts has been reported in the models of fasting mice and mice receiving an intraperitoneal glucose load (Zhang *et al.* 2002*a*). The fine-tuning of this adaptive response is vital for the preservation of the β-cell differentiated phenotype. Indeed, our and others recent evidence indicated that the failure of adaptive UPR is associated with the progression to diabetes and altered β-cell differentiation (Herbert & Laybutt 2016) (see 'The loss of β-cell differentiation in diabetes: causes and mechanisms' section).

Besides the role of nutrient-induced stimulation of gene expression, the acquisition and maintenance of

Table 1 Physiological glucose stimulation plays a key role in the maintenance of the differentiated β-cell phenotype.

Genes	Physiological glucose stimulation	Effect	Models	References
Islet hormones				
Preproinsulin	G10 vs G2–5	Up (also protein)	Cultured male Wistar rat islets (18h) and purified β cells (3–10 days)	Schuit *et al.* (2002), Van Lommel *et al.* (2006), Bensellam *et al.* (2009)
	Fed vs fasted	Up	Fasted male C57BL6 mice (overnight) and male Sprague–Dawley rats (72h)	Iwashima *et al.* (1994), Van Lommel *et al.* (2006)
Iapp	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Transcription factors				
Pdx1	G10 vs G5	Up	Cultured C57BL6J mouse islets (24h)	(Supplementary Fig. 1)
Chrebp	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Srebp1 (Srebf1)	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h) and purified β cells (24h)	Bensellam *et al.* (2009), Flamez *et al.* (2002)
Srebp2 (Srebf2)	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Glucose transport and metabolism				
Glut2 (Slc2a2)	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h) and purified β cells (24–72h) and cultured C57BL6J mouse islets (24h)	Bensellam *et al.* (2009), Flamez *et al.* (2002), Martens & Pipeleers (2009), (Supplementary Fig. 1)
	Fed vs fasted	Up	Fasted male Sprague–Dawley rats (72h)	Iwashima *et al.* (1994)
Gck (Hk4)	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h) and purified β cells (72h)	Bensellam *et al.* (2009), Martens & Pipeleers (2009)
	Fed vs fasted	Up	Fasted male Sprague–Dawley rats (72h)	Iwashima *et al.* (1994)
Gapdh	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
G6pd	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h) and purified β cells (24h)	Bensellam *et al.* (2009), Flamez *et al.* (2002)
NADH:ubiquinone oxidoreductase subunits Ndufa1, Ndufa4, Ndufa11, Ndufb4, Ndufs5, Nd3	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Cycs	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Cytochrome c oxidase subunits Cox2, Cox3 (Cytb), Cox5b, Cox6b1, Cox7b, Cox17	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h) and purified β cells (24h)	Bensellam *et al.* (2009), Flamez *et al.* (2002)
ATP synthase subunits Atp5a1, Atp5e, Atp5g1, Atp5i, Atp5j, Atp5o	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Ant2 (Slc25a5)	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Gpd2	G10 vs G5	Up	Cultured C57BL6J mouse islets (24h)	(Supplementary Fig. 1)
Anaplerosis/cataplerosis				
Acly	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h) and purified β cells (24h)	Bensellam *et al.* (2009), Flamez *et al.* (2002)
Mdh1	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)
Me1	G10 vs G2–5	Up	Cultured male Wistar rat islets (18h)	Bensellam *et al.* (2009)

(Continued)

Table 1 Continued.

Genes	Physiological glucose stimulation	Effect	Models	References
Fatty acid metabolism				
Fasn	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h) and purified β cells (24 h)	Bensellam et al. (2009), Flamez et al. (2002)
Hadh	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h) and purified β cells (72 h)	Bensellam et al. (2009), Martens & Pipeleers (2009)
Scd1	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h)	Bensellam et al. (2009)
Scd2	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h) and purified β cells (24 h)	Bensellam et al. (2009), Flamez et al. (2002)
Cholesterol metabolism				
Hmgcs1, Hmgcr, Mvd, Idi1, Fdps, Fdft1, Sqle, Lss, Sc4mol, Nsdhl, Sc5dl, Dhcr7, Soat1, Scp2, Ldlr	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h) and purified β cells (24 h)	Bensellam et al. (2009), Flamez et al. (2002)
Vldlr	G10 vs G2–5	Down	Cultured male Wistar rat islets (18 h) and purified β cells (24 h)	Bensellam et al. (2009), Flamez et al. (2002)
Ion channels, pumps and receptors				
Kcnj11 (Kir6.2)	G10 vs G3	Up	Cultured purified male Wistar rat β cells (24 h)	Flamez et al. (2002)
Abcc8 (Sur1)	G10 vs G3	Up	Cultured purified male Wistar rat β cells (24 h)	Flamez et al. (2002)
Vdccα1D	Fed vs fasted	Up	Fasted male Sprague–Dawley rats (72 h)	Iwashima et al. (1994)
Serca2b (Atp2a2)	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h)	Bensellam et al. (2009)
Serca3 (Atp2a3)	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h)	Bensellam et al. (2009)
Gipr	G10 vs G5	Up	Cultured purified male Wistar rat β cells (72 h)	Martens & Pipeleers (2009)
Gpr40 (Ffar1)	G10 vs G5	Up	Cultured C57BL6J mouse islets (24 h)	(Supplementary Fig. 1)
Slc30a1 (ZnT-1)	G10 vs G2–5	Down	Cultured male Wistar rat islets (18 h)	Bensellam et al. (2009)
Proinsulin processing and insulin granule exocytosis				
Pcsk1, Pcsk2, Cpe, Scg3, Syt13, Sytl4, Snap25, Syp, Scfd1, Ykt6	G10 vs G2–5	Up	Cultured male Wistar rat islets (18 h) and purified β cells (72 h)	Bensellam et al. (2009), Martens & Pipeleers (2009)

the differentiated β-cell phenotype also relies on gene repression. The latter involves particular mechanisms including epigenetic and miRNA regulation. Thus, histone and DNA methylation are implicated in the metabolic maturation of β-cells in the postnatal period by repressing the expression of Hk1, Mct1 and Ldha (Thorrez et al. 2011, Dhawan et al. 2015). Moreover, a growing body of data suggests that miRNAs are implicated not only in the repression of β-cell forbidden genes (Pullen et al. 2011, Martinez-Sanchez et al. 2015), but also in the modulation of insulin gene expression (El Ouaamari et al. 2008, Tang et al. 2009, Melkman-Zehavi et al. 2011, Zhao et al. 2012), the metabolic reconfiguration of neonatal β-cells (Jacovetti et al. 2015) and insulin granule exocytosis (Poy et al. 2004, Lovis et al. 2008, Latreille et al. 2014). The switch from high-fat milk in newborns to carbohydrate-rich diet post-weaning has been suggested as an important driver of changes in miRNA expression that paralleled the maturation of the β-cell phenotype (Jacovetti et al. 2015). In agreement, glucose stimulation has been shown to regulate the expression of several miRNAs in β-cell lines and isolated islets (El Ouaamari et al. 2008, Esguerra et al. 2011). Recent reports have revealed another mechanism of gene repression whereby the transcription factors NK2 homeobox 2 (NKX2.2), paired box 6 (PAX6) and Regulatory Factor X, 6 (RFX6) play a dual role by activating the expression of various β-cell-enriched genes and also by directly binding to and repressing the expression of

non-β-cell endocrine genes and other islet forbidden genes such as *Ldha* (Piccand *et al.* 2014, Gutierrez *et al.* 2017, Swisa *et al.* 2017). Of note, *Nkx2.2* mRNA levels were upregulated in rat islets cultured in the presence of G10 instead of G2–5 (Bensellam *et al.* 2009).

However, while physiological glucose stimulation plays a key role in the maintenance of the β-cell differentiated phenotype, exposure to supraphysiological glucose levels, such as in the context of diabetes, leads to β-cell dedifferentiation. This may contribute to the progressive loss of functional β-cell mass and the aggravation of the disease over time. Our understanding of this phenomenon has markedly expanded in the last two decades with the identification of various mechanisms and effectors.

The loss of β-cell differentiation in diabetes: causes and mechanisms

The loss of functional β-cell mass does not only result from apoptosis but also result from a loss of differentiation

It is now well recognized that the β-cell mass is reduced by 25–60% in T2D patients in comparison to weight-matched normal subjects (Sakuraba *et al.* 2002, Butler *et al.* 2003, Yoon *et al.* 2003, Deng *et al.* 2004, Rahier *et al.* 2008). The observation that β-cell mass decline correlated with the duration of T2D (Rahier *et al.* 2008) supports a role of chronic hyperglycemia and glucotoxicity. Indeed, prolonged or intermittent exposure of rodent and human islets to elevated glucose concentrations *in vitro* has been shown to increase β-cell apoptosis (Ling *et al.* 1994, Efanova *et al.* 1998, Piro *et al.* 2002, Khaldi *et al.* 2004, DelGuerra *et al.* 2007, Hou *et al.* 2008*b*, Bensellam *et al.* 2009, Jonas *et al.* 2009). These results are strongly supported by the observation of increased β-cell apoptosis in different animal models of T2D (Koyama *et al.* 1998, Pick *et al.* 1998, Donath *et al.* 1999, Finegood *et al.* 2001, Huang *et al.* 2007, Song *et al.* 2008) and in human patients (Butler *et al.* 2003, Jurgens *et al.* 2011). However, the rate of β-cell apoptosis is relatively low and may not fully explain the loss of β-cell mass in T2D. Thus, alternative mechanisms are possible. The concept of the loss of differentiation, introduced in the late nineties (Jonas *et al.* 1999), has been recently proposed as an important contributor to the reduced β-cell mass in T2D (Talchai *et al.* 2012, Marselli *et al.* 2014, Spijker *et al.* 2015, Cinti *et al.* 2016). Similar to apoptosis, chronic hyperglycemia has been shown to be a major inducer of β-cell dedifferentiation.

Role of hyperglycemia and glucotoxicity

In T2D, the complex interaction of genetic and environmental factors leads ultimately to defective insulin secretion. The latter is a consequence of the failure of β-cells to cope with the important metabolic demand imposed on them by insulin resistance. The ensuing chronic hyperglycemia exerts further damage on the β-cell phenotype thereby leading to the progressive decline of functional β-cell mass and deterioration of the disease over time. This is the concept of glucotoxicity (Bensellam *et al.* 2012*b*). Glucotoxicity-related loss of β-cell identity is characterised by alterations in the expression of many genes, with much initial and recent attention focused on the reduced expression of β-cell-enriched genes, in particular insulin.

Downregulation of insulin gene expression

Earlier studies in β-cell lines and isolated rodent and human islets have shown that prolonged exposure to elevated glucose concentrations markedly reduced the mRNA levels of insulin (Robertson *et al.* 1992, Olson *et al.* 1995, 1998, Briaud *et al.* 1999, Marshak *et al.* 1999). In agreement, a similar reduction was observed in the islets of Zucker diabetic fatty (ZDF) rats (Harmon *et al.* 2001) and 90% pancreatectomized (Px) rats (Jonas *et al.* 1999). Interestingly, in these animal models, insulin mRNA levels were restored by phlorizin treatment (an inhibitor of renal glucose reabsorption) and normalization of glycaemia (Jonas *et al.* 1999, Harmon *et al.* 2001). Reduced insulin mRNA levels have also been confirmed in β-cells of human T2D subjects (Marchetti *et al.* 2004, DelGuerra *et al.* 2005, Marselli *et al.* 2010, Guo *et al.* 2013). This reduction has been attributed to reduced expression and binding of the key transcription factors, pancreatic and duodenal homeobox 1 (PDX-1 also called IPF-1, STF-1, IUF-1, IDX-1 or GSF) and V-maf musculoaponeurotic fibrosarcoma oncogene homolog A (MAFA also known as RIPE3b1), to the insulin gene promoter (Olson *et al.* 1995, Sharma *et al.* 1995, Poitout *et al.* 1996, Moran *et al.* 1997, Harmon *et al.* 1998, Marshak *et al.* 1999, Gleason *et al.* 2000, Pino *et al.* 2005, Matsuoka *et al.* 2010) (Fig. 3 and Supplementary Fig. 1, see section on supplementary data given at the end of this article). Reduced mRNA levels of *Pdx1* and *Mafa* and nuclear expression of their proteins has also been reported in the islets of T2D patients (Guo *et al.* 2013). The reduction of the mRNA levels of *Pdx1* in the islets of Px rats and *Neurod1* in the islets of *db/db* mice was prevented by phlorizin treatment, thereby demonstrating the role of glucotoxicity (Jonas *et al.* 1999,
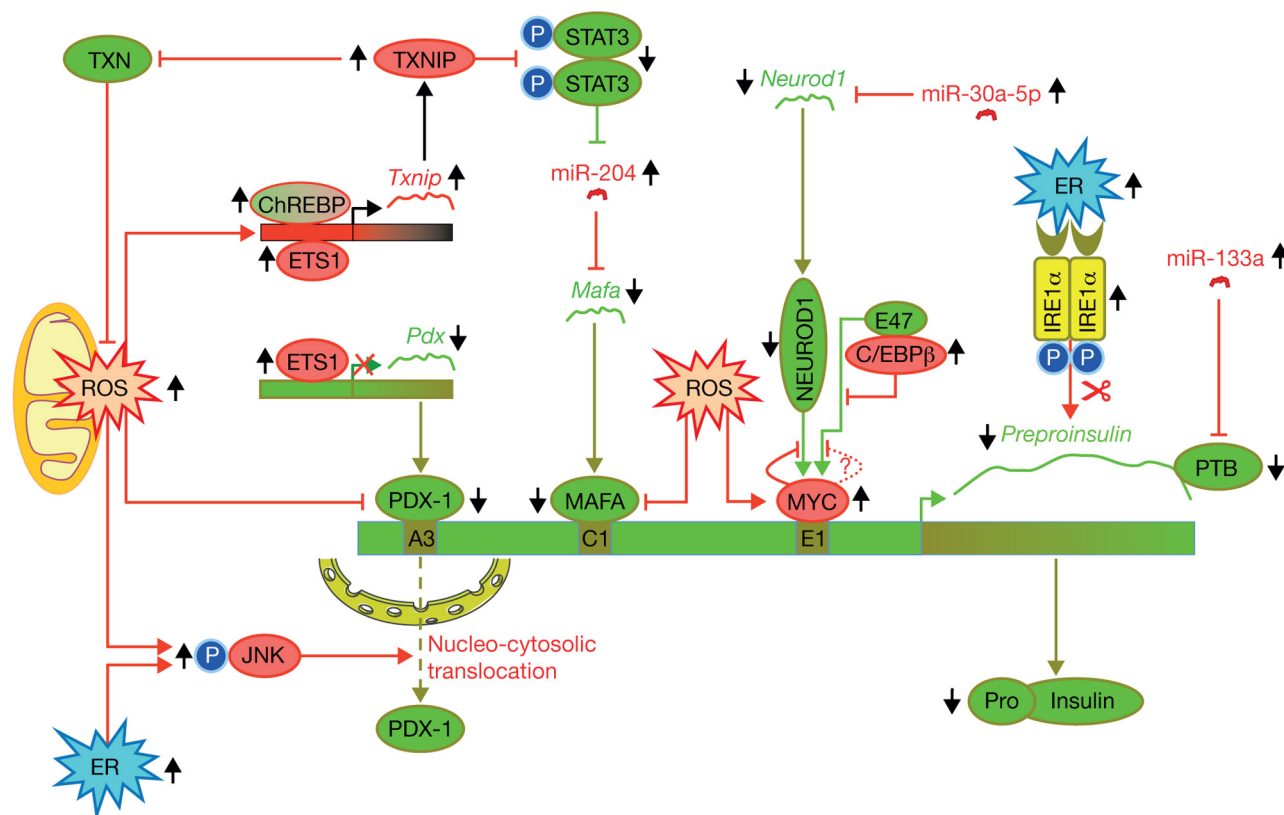
Figure 3

Schematic representation of the key effectors and mechanisms implicated in the loss of insulin gene expression in type 2 diabetes. Please see the text for details. Direction of the vertical black arrows close to proteins, mRNAs, miRNAs or stresses indicate the effect of glucotoxicity. C/EBPβ, CCAAT/enhancer-binding protein β; ChREBP, carbohydrate response element binding protein; ER, endoplasmic reticulum; JNK, c-Jun N-terminal kinase; ROS, reactive oxygen species; ETS1, V-ets avian erythroblastosis virus E26 oncogene homolog 1; IRE1α, inositol requiring 1α; MAFA, V-maf musculoaponeurotic fibrosarcoma oncogene homolog A; MYC, myelocytomatosis viral oncogene homolog (avian); NEUROD1, neurogenic differentiation 1; PDX-1, pancreatic and duodenal homeobox 1; PTB, polypyrimidine tract binding protein; STAT3, signal transducer and activator of transcription 3; TXN, thioredoxin; TXNIP, thioredoxin-interacting protein.

Kjorholt *et al.* 2005). These results are further corroborated by a study showing that treatment of *db/db* mice with the sodium glucose cotransporter 2 (SGLT2) inhibitor luseogliflozin upregulated islet mRNA levels of insulin, *Pdx1* and *Mafa* (Okauchi *et al.* 2016).

The observation that the alteration of insulin gene expression was prevented by antioxidant treatment suggested an implication of oxidative stress (Tanaka *et al.* 1999, Robertson & Harmon 2006). In support of this idea, hydrogen peroxide treatment of β-cell lines and isolated islets has been shown to alter the nuclear expression and DNA-binding activity of MAFA and PDX1 (Kaneto *et al.* 2002b, Harmon *et al.* 2005, Guo *et al.* 2013). Moreover, reduced nuclear expression of MAFA in the islets of diabetic *db/db* mice was restored by transgenic expression of the antioxidant gene *Gpx1* (Harmon *et al.* 2009, Guo *et al.* 2013). Similarly, altered nuclear expression of PDX1

and MAFA in the islets of diabetic ZDF rats was markedly prevented by treatment with the glutathione peroxidase (GPX) mimetic ebselen (Mahadevan *et al.* 2013). Oxidative stress-mediated alteration of PDX1 nuclear localization and DNA-binding activity has been proposed to involve the activation of c-Jun N-terminal kinase (JNK) (Kaneto *et al.* 2002b, Kawamori *et al.* 2003) (Fig. 3). Besides oxidative stress, it has been proposed that chronic ER stress could affect the specificity of the endoribonuclease activity of IRE1, thus leading to the cleavage of ER-associated RNAs including that of insulin (Hollien & Weissman 2006, Pirot *et al.* 2007, Lipson *et al.* 2008, Han *et al.* 2009, Hollien *et al.* 2009) (Fig. 3). Moreover, other mechanisms have been identified implicating novel effectors, in particular miRNAs. Thus, it has been demonstrated that the high glucose-induced redox protein thioredoxin-interacting protein (TXNIP) (Shalev *et al.* 2002, Saxena *et al.* 2010),

via a STAT3-dependent pathway, upregulated miR-204 thereby leading to reduced *Mafa* mRNA levels (Xu *et al.* 2013) (Fig. 3). In addition, upregulation of miR-30a-5p by high glucose levels in INS1 cells and rat islets has been shown to inhibit *Neurod1* expression (Kim *et al.* 2013) (Fig. 3). Furthermore, in human islets exposed to high glucose, the induction of miR-133a targeted the polypyrimidine tract-binding protein and led to reduced insulin biosynthesis, although insulin mRNA levels were not significantly affected in this study (Fred *et al.* 2010) (Fig. 3). Another report has also shown that miR-124a is markedly upregulated in the islets of human T2D subjects and targeted *Foxa2* and *Neurod1* in MIN6 cells. Interestingly, overexpression of miR-124a blunted GSIS in MIN6 cells (Sebastiani *et al.* 2015). However, it is unclear whether miR-124a is regulated by glucotoxicity or another mechanism in T2D. On the other hand, the alteration of insulin gene expression under glucotoxic conditions also involves transcriptional repression by transcriptional repressor proteins. Thus, upregulation of CCAAT/enhancer-binding protein β (C/EBPβ) in β-cell lines and islets of ZDF and Px rats has been implicated in the downregulation of insulin gene expression (Lu *et al.* 1997, Seufert *et al.* 1998). C/EBPβ interacted with the basic helix-loop-helix transcription factor E47 thereby inhibiting its DNA binding to the insulin gene promoter and its transactivation ability (Fig. 3). High glucose also affected insulin gene transcription by upregulating the expression of myelocytomatosis viral oncogene homolog (avian) (MYC). MYC has been shown to inhibit neurogenic differentiation 1 (NEUROD1, also known as BETA2)-mediated transcriptional activation of the insulin gene promoter in β-cell lines and isolated rat islets (Kaneto *et al.* 2002*a*) (Fig. 3). Of note, *Myc* is also an oxidative stress-responsive gene (Elouil *et al.* 2005, Jonas *et al.* 2009) that has been implicated in β-cell dedifferentiation (Jonas *et al.* 2001, Laybutt *et al.* 2002*c*, Pascal *et al.* 2008, Robson *et al.* 2011). On the other hand, it has been proposed that *Myc* expression is negatively regulated by PDX1 (Chen *et al.* 2007). More recently, V-ets avian erythroblastosis virus E26 oncogene homolog 1 (ETS1) has been shown to repress the expression of *Pdx1* under glucotoxicity by directly binding to its promoter and inhibiting its transcription in rodent β-cells (Chen *et al.* 2016) (Fig. 3). This study also suggested that ETS1 could interact with the transcription factor forkhead box O1 (FOXO1) and increase its binding to the *Pdx1* promoter (Chen *et al.* 2016). FOXO1 has previously been proposed to repress FOXA2-dependent *Pdx1* transcription and to be involved in the nucleocytoplasmic translocation of PDX1 under

oxidative stress (Kitamura *et al.* 2002, Kawamori *et al.* 2006). However, findings in the last decade revealed that the loss of FOXO1 under severe hyperglycemia is implicated in β-cell dedifferentiation thereby indicating a complex role of this transcription factor in β-cell pathophysiology (discussed in the next section).

Downregulation of β-cell-enriched genes

Besides the insulin gene and key upstream transcription factors, glucotoxicity alters the expression of additional genes that maintain the differentiated β-cell phenotype including other transcription factors such as *Nkx6.1*, *Hnf1α* (also known as *Tcf1*) and *Hnf4α*, glucose sensing and metabolism genes such as *Glut2*, *Gck* and *Gpd2* (Supplementary Fig. 1), stimulus-secretion coupling genes such as *Kcnj11* and *Abcc8*, amplification of insulin secretion genes such as *Glp1r*, *Chrm3* and *Gpr40* (Supplementary Fig. 1) and insulin granule exocytosis genes such as N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) complex proteins. A comprehensive and up to date list of the most important genes and the models in which they are affected are presented in Table 2. Many of these alterations, but not all, have also been confirmed in islets of human T2D subjects (Table 2). The normalization of these alterations in diabetic animals using phlorizin treatment, sulfonylureas or insulin therapy, but not bezafibrate treatment, strongly supports the implication of glucotoxicity rather than lipotoxicity (Jonas *et al.* 1999, Harmon *et al.* 2001, Gaisano *et al.* 2002, Kjorholt *et al.* 2005, Xu *et al.* 2007, Brereton *et al.* 2014, Wang *et al.* 2014). Several pathways downstream of glucotoxicity (Bensellam *et al.* 2012*b*) have been implicated in the loss of β-cell-enriched genes including oxidative stress (Tanaka *et al.* 1999, Kaneto *et al.* 2002*b*, Harmon *et al.* 2005, Robertson & Harmon 2006, Guo *et al.* 2013), ER stress (Hollien & Weissman 2006, Pirot *et al.* 2007, Lipson *et al.* 2008, Han *et al.* 2009, Szabat *et al.* 2011, Lombardi *et al.* 2012), the hexosamine pathway (Kaneto *et al.* 2001, Yoshikawa *et al.* 2002), inflammation (Nordmann *et al.* 2017) and hypoxia (Puri *et al.* 2013, Sato *et al.* 2014, 2017).

Downregulation of the β-cell-enriched genes is linked with altered expression of key transcription factors. Indeed, above and beyond the regulation of insulin gene expression, the β-cell key transcription factors PDX1, MAFA and NEUROD1, in addition to hepatocyte nuclear factors (HNF1α, HNF4α and HNF3β/FOXA2) and PAX6, are implicated in a complex network of inter-regulation (Ben-Shushan *et al.* 2001, Samaras *et al.* 2002, 2003, Shih *et al.* 2002, Pedersen *et al.* 2005) and regulation of other β-cell-enriched genes including key metabolic genes such

Table 2 Downregulation of β-cell-enriched genes under glucotoxicity.

Genes	Glucotoxicity model		Confirmation in human T2D	Glucotoxic effect
	In vitro/ex vivo	*In vivo*		
Islet hormones				
Preproinsulin	HIT-T15 cells (Robertson *et al.* 1992, Sharma *et al.* 1995) β-TC6 cells (Poitout *et al.* 1996) INS1 cells (Olson *et al.* 1998) Wistar rat islets (Briaud *et al.* 1999) Human islets (Marshak *et al.* 1999)	Px rat islets (Zangen *et al.* 1997) ZDF rat islets (Tokuyama *et al.* 1995) Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007) *Psammomys obesus* islets (Leibowitz *et al.* 2001) MKR mouse islets (Lu *et al.* 2008)	Yes: (Marchetti *et al.* 2004, DelGuerra *et al.* 2005, Masini *et al.* 2012, Guo *et al.* 2013)	mRNA, protein and volume density of insulin granules
Iapp		Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003) Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007)	Yes: (Marselli *et al.* 2010, Bugliani *et al.* 2013)	mRNA
Transcription factors				
Pdx1	INS1 cells (Wang *et al.* 2005) INS 832/13 (Yang *et al.* 2012) Sprague–Dawley rat islets (Hou *et al.* 2008*b*) C57BL6J mouse islets (Supplementary Fig. 1)	Px rat islets (Zangen *et al.* 1997, Jonas *et al.* 1999) Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007) *db/db* mouse islets (Kjorholt *et al.* 2005, Chan *et al.* 2013) NZO mouse islets (Kluth *et al.* 2011)	Controversial Yes: (Ostenson *et al.* 2006, Yang *et al.* 2012, Guo *et al.* 2013) Upregulated: (DelGuerra *et al.* 2005)	DNA methylation, mRNA, protein, and subcellular localization
Mafa	HIT-T15 cells (Sharma *et al.* 1995)	*db/db* mouse islets (Harmon *et al.* 2009, Chan *et al.* 2013, Guo *et al.* 2013) NZO mouse islets (Kluth *et al.* 2011) βV59M mouse islets (Brereton *et al.* 2014)	Yes: (Guo *et al.* 2013, Cinti *et al.* 2016)	mRNA, protein and subcellular localization
Mafb			Yes: (Bugliani *et al.* 2013, Guo *et al.* 2013)	mRNA, protein and subcellular localization
Neurod1 (Beta2)		Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003) Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007) *db/db* mouse islets (Kjorholt *et al.* 2005, Chan *et al.* 2013)		mRNA
Nkx6.1		Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003) Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007) *db/db* mouse islets (Kjorholt *et al.* 2005, Chan *et al.* 2013, Guo *et al.* 2013) NZO mouse islets (Kluth *et al.* 2011) βV59M mouse islets (Brereton *et al.* 2014)	Yes: (Guo *et al.* 2013, Cinti *et al.* 2016)	mRNA, protein and subcellular localization
Hnf1α (Tcf1)		Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003)	Yes: (Marselli *et al.* 2010)	mRNA
Hnf4α		Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003)	Yes: (Gunton *et al.* 2005)	mRNA

(Continued)

Table 2 Continued.

Genes	Glucotoxicity model		Confirmation in human T2D	Glucotoxic effect
	In vitro/ex vivo	*In vivo*		
Hnf3β (Foxa2)		Px rat islets (Jonas *et al.* 1999)		mRNA
Pax6		Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007)		mRNA
		db/db mouse islets (Kjorholt *et al.* 2005, Swisa *et al.* 2017)		
Foxo1		GIRKO mouse islets (Talchai *et al.* 2012)	Controversial Yes: (Marselli *et al.* 2010, Cinti *et al.* 2016)	mRNA and protein
		db/db mouse islets (Kim-Muller *et al.* 2014)	Upregulated: (DelGuerra *et al.* 2005)	
Tcf7l2 (Tcf4)		Vancouver Diabetic Fatty (VDF) Zucker rat islets (Shu *et al.* 2009)	Yes: (Shu *et al.* 2009)	Protein
		db/db mouse islets (Shu *et al.* 2009)		
Pparα	INS 832/13 (Roduit *et al.* 2000)	Px rat islets (Laybutt *et al.* 2002*b*)		mRNA and protein
	Wistar rat islets (Roduit *et al.* 2000)	ZDF rat islets (Wang *et al.* 1998)		
Glucose transport and metabolism				
Glut1			Yes: (DelGuerra *et al.* 2005, Guo *et al.* 2013)	mRNA
Glut2	INS1 cells (Wang *et al.* 2005) C57BL6J mouse islets (Supplementary Fig. 1)	Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003)	Yes: (DelGuerra *et al.* 2005, Ostenson *et al.* 2006, Marselli *et al.* 2010, Taneera *et al.* 2012, Guo *et al.* 2013)	mRNA and protein
		Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007)		
		db/db mouse islets (Thorens *et al.* 1992, Kjorholt *et al.* 2005, Chan *et al.* 2013, Guo *et al.* 2013)		
		βV59M mouse islets (Brereton *et al.* 2014)		
Gck	INS1 cells (Wang *et al.* 2005)	Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003)	Yes: (DelGuerra *et al.* 2005)	mRNA
		ZDF rat islets (Tokuyama *et al.* 1995)		
		Rat islets transplanted into diabetic rats (Laybutt *et al.* 2007)		
		db/db mouse islets (Kjorholt *et al.* 2005, Chan *et al.* 2013)		
Pc		Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003)	Yes: (MacDonald *et al.* 2009)	mRNA, protein and enzyme activity
		ZDF rat islets (MacDonald *et al.* 1996)		
		db/db mouse islets (Kjorholt *et al.* 2005, Chan *et al.* 2013)		
		MKR mouse islets (Lu *et al.* 2008)		
Gpd2 (mGpdh)	C57BL6J mouse islets (Supplementary Fig. 1)	Px rat islets (Jonas *et al.* 1999, Laybutt *et al.* 2003)	Yes: (MacDonald *et al.* 2009, Marselli *et al.* 2010)	mRNA and enzyme activity
		ZDF rat islets (Tokuyama *et al.* 1995, MacDonald *et al.* 1996)		
		db/db mouse islets (Kjorholt *et al.* 2005, Chan *et al.* 2013)		
		MKR mouse islets (Lu *et al.* 2008)		

(Continued)

Table 2 Continued.

Genes	Glucotoxicity model		Confirmation in human T2D	Glucotoxic effect
	In vitro/ex vivo	*In vivo*		
Acly		GK rat islets (Homo-Delarche et al. 2006, Hasan et al. 2010)	Yes: (MacDonald et al. 2009, Marselli et al. 2010, Bugliani et al. 2013)	mRNA and enzyme activity
Receptors, ion channels and pumps				
Glp1r	Sprague–Dawley rat islets (Xu et al. 2007)	Px rat islets (Xu et al. 2007) GK rat islets (Homo-Delarche et al. 2006) Glucose-infused rat islets (Xu et al. 2007) db/db mouse islets (Chan et al. 2013)	Yes: (Shu et al. 2009, Taneera et al. 2012, Guo et al. 2013)	mRNA and protein
Gipr		Px rat islets (Xu et al. 2007) db/db mouse islets (Chan et al. 2013)	Yes: (Shu et al. 2009)	mRNA and protein
Gpr40	C57BL6J mouse islets (Supplementary Fig. 1)	db/db mouse islets (Chan et al. 2013)		mRNA
Chrm3	ICR mouse islets (Hauge-Evans et al. 2014)	ob/ob mouse islets (Hauge-Evans et al. 2014)		mRNA and protein
Kcnj11 (Kir6.2)		Px rat islets (Jonas et al. 1999, Laybutt et al. 2003) ZDF rat islets (Tokuyama et al. 1995) db/db mouse islets (Kjorholt et al. 2005, Chan et al. 2013)	Yes: (Ostenson et al. 2006, Taneera et al. 2012)	mRNA
Abcc8 (Sur1)			Yes: (Ostenson et al. 2006, Marselli et al. 2010)	mRNA
Vdccα1D		Px rat islets (Jonas et al. 1999) ZDF rat islets (Tokuyama et al. 1995)	Yes: (Marselli et al. 2010)	mRNA
Vdccβ		Px rat islets (Laybutt et al. 2003)		mRNA
Serca2b (Atp2a2b)		Px rat islets (Jonas et al. 1999) db/db mouse islets (Kjorholt et al. 2005)	Yes: (Bugliani et al. 2013)	mRNA
Serca3 (Atp2a3)		Px rat islets (Jonas et al. 1999) db/db mouse islets (Kjorholt et al. 2005)		mRNA
Hormone processing and insulin granule exocytosis				
Pcsk1 (Pc1)		MKR mouse islets (Lu et al. 2008)	Yes: (Masini et al. 2012)	mRNA and protein
Pcsk2 (Pc2)		MKR mouse islets (Lu et al. 2008)		Protein
Cpe		MKR mouse islets (Lu et al. 2008)	Yes: (Masini et al. 2012)	mRNA and protein
Stx1a	INS1E cells (Dubois et al. 2007) Sprague–Dawley rat islets (Torrejon-Escribano et al. 2011)	GK rat islets (Nagamatsu et al. 1999, Gaisano et al. 2002, Zhang et al. 2002b) db/db mouse islets (Do et al. 2014)	Yes: (Ostenson et al. 2006)	mRNA and protein
Stxbp1 (Munc18-1)		GK rat islets (Zhang et al. 2002b)	Yes: (Ostenson et al. 2006)	mRNA and protein
SNAP-25		GK rat islets (Nagamatsu et al. 1999, Gaisano et al. 2002, Zhang et al. 2002b)	Yes: (Ostenson et al. 2006)	mRNA and protein

(Continued)

Table 2 Continued.

| | Glucotoxicity model | | | |
Genes	In vitro/ex vivo	In vivo	Confirmation in human T2D	Glucotoxic effect
Vamp2	INS1E cells (Dubois *et al.* 2007) Wistar (Gaisano *et al.* 2002) and Sprague–Dawley rat islets (Torrejon-Escribano *et al.* 2011) Human islets (Dubois *et al.* 2007)	Px rat islets (Torrejon-Escribano *et al.* 2011) GK rat islets (Gaisano *et al.* 2002, Zhang *et al.* 2002*b*) Rat islets transplanted into diabetic rats (Torrejon-Escribano *et al.* 2011) MKR mouse islets (Lu *et al.* 2008)	Yes: (Ostenson *et al.* 2006)	mRNA and protein
Vamp3	Sprague–Dawley rat islets (Torrejon-Escribano *et al.* 2011)	Px rat islets (Torrejon-Escribano *et al.* 2011) Rat islets transplanted into diabetic rats (Torrejon-Escribano *et al.* 2011)		Protein
Syp			Yes: (Ostenson *et al.* 2006)	mRNA and protein
Sytl4		MKR mouse islets (Lu *et al.* 2008)		mRNA and protein

as *Glut2*, *Gck* and *Pc*, ion channel genes such as *Abcc8* and receptor genes such as *Glp1r* (Waeber *et al.* 1996, Cha *et al.* 2000, Shih *et al.* 2001, Sund *et al.* 2001, Kim *et al.* 2002, Moates *et al.* 2003, Zhang *et al.* 2005, Wang *et al.* 2007). Interestingly, PDX1, NKX6.1 and PAX6 have also been shown to play a key role in preserving β-cell identity by repressing the expression of other islet cell type genes (Schaffer *et al.* 2013, Taylor *et al.* 2013, Gao *et al.* 2014, Mitchell *et al.* 2017, Swisa *et al.* 2017). Besides these canonical transcription factors, recent evidence has suggested that reduced expression of sex-determining region Y-box 5 (SOX5) may also contribute to the downregulation of β-cell-enriched genes in T2D (Axelsson *et al.* 2017). Adequate regulation of β-cell-enriched gene expression by these transcription factors depends on correct binding to specific promoters, but also on promoter-enhancer looping of chromatin and formation of multimeric transcriptional complexes. This has been shown to involve LIM domain-binding protein 1 (LDB1). LDB1, together with its binding partner islet 1 (ISL1), was enriched at DNA regions occupied by PDX1, NKX2.2, NKX6.1 and FOXA2 and LDB deletion in adult murine β-cells markedly affected the expression of β-cell-enriched genes including *Mafa*, *Pdx1*, *Nkx6.1*, *Glut2*, *Kcnj11*, *Abcc8* and *Glp1r*. Interestingly, reduced LDB1 enrichment in a putative active enhancer nearby *GLUT2* gene has been observed in islets from T2D donors (Ediger *et al.* 2017). But whether dysregulation of LDB1 is involved in downregulation of other β-cell-enriched genes in human T2D requires further exploration.

Gene inhibition/overexpression strategies *in vitro* and *in vivo* have allowed a better understanding of the implication of these genes in the alteration of β-cell identity and function. The numerous forms of the maturity-onset diabetes of the young (MODY) best illustrate this in humans. These monogenic disorders result from mutations in transcription factor genes such as *Hnf4α* (MODY1), *Hnf1α* (MODY3), *Pdx1* (MODY4), *Hnf1β* (MODY5) and *Neurod1* (MODY6), and mutations in ion channel and metabolic genes such as *Gck* (MODY2), *Abcc8* (MODY12) and *Kcnj11* (MODY13) (Hattersley & Patel 2017). However, despite important advances in this field, there are still significant gaps of knowledge with regards to the precise targets of these transcription factors, their complex interaction network and the identification of novel transcription factors implicated in the loss of β-cell identity.

In recent years, FOXO1 has received much attention as a potential transcription factor linking metabolic stress with β-cell dedifferentiation in T2D. FOXO1 is a multifunctional transcription factor that has been shown to play complex adaptive/deleterious roles in β-cells under stress depending on the context. Thus, evidence showed that FOXO1 translocates to the nucleus under oxidative stress and promotes the expression of *Neurod1* and *Mafa* (Kitamura *et al.* 2005). In transgenic mouse models, FOXO1 has been shown to play a role in β-cell compensation during insulin resistance via increasing β-cell proliferation, mass, function and antioxidant gene expression (Okamoto *et al.* 2006, Zhang *et al.* 2016). Interestingly, *Foxo1* somatic deletion in β-cells resulted in β-cell dedifferentiation in ageing male mice and multiparous female mice in parallel with the upregulation of progenitor and pluripotency markers (Talchai *et al.* 2012). Furthermore, loss of FOXO1

has been observed in the islets of severely hyperglycemic *db/db* mice and insulin-resistant GIRKO mice (Talchai *et al.* 2012, Kim-Muller *et al.* 2014). This observation was confirmed by the same group in human T2D islets and was associated with altered expression and nuclear localization of MAFA and NKX6.1 (Cinti *et al.* 2016). In contrast, FOXO1 nuclear translocation in response to glucose starvation or palmitate treatment has been implicated in β-cell apoptosis, at least in part, via the stimulation of *Ddit3* gene expression (Martinez *et al.* 2006, 2008). FOXO1 subcellular localization and activity are modulated by posttranslational modifications including phosphorylation, ubiquitination, *O*GlcNacylation and acetylation (Kitamura 2013). In the NZO mouse model, a dietary carbohydrate challenge and the ensuing hyperglycemia were associated with rapid and marked dephosphorylation of FOXO1 (activation) followed by reduced GLUT2, PDX1, MAFA and NKX6.1 protein levels and increased apoptosis (Kluth *et al.* 2011), in agreement with the previously reported role of FOXO1 in the inhibition of *Pdx1* transcription (Kitamura *et al.* 2002). However, in this model, it is unclear whether nuclear expression of active FOXO1 is upregulated and whether it declines thereafter or not (Kluth *et al.* 2011). Another study has shown increased nuclear expression of FOXO1 in β-cells of diabetic *db/db* mice in association with downregulation of PDX1, MAFA and NKX6.1. Interestingly, caloric restriction for three months markedly reversed these alterations and normalized glycaemia and β-cell function (Sheng *et al.* 2016). Furthermore, increased mRNA levels of *Foxo1* have been reported in the islets of T2D subjects (DelGuerra *et al.* 2005). All in all, although undeniable evidence supports an important adaptive role of FOXO1 in the preservation of β-cell identity, especially under hyperglycemia and subsequent oxidative stress, additional work is required to further elucidate the mechanisms and timing of activation/inhibition of FOXO1 in diabetes and identify its precise targets and interacting network. The use of models of inducible expression/deletion in adult animals could be useful.

Besides altered expression and subcellular localization of transcription factors, downregulation of β-cell-enriched genes also involves gene repression by epigenetic mechanisms and miRNAs. Thus, in the islets of human T2D patients, increased DNA methylation in the promoter and enhancer regions of *Pdx1* has been proposed to be involved in its downregulation under hyperglycemia (Yang *et al.* 2012). Similarly, increased DNA methylation in the *Glp1r* promoter has been observed in

the islets of human T2D subjects (Hall *et al.* 2013). We have highlighted in the previous section the implication of several miRNAs in the inhibition of insulin gene expression and upstream transcription factors (Fred *et al.* 2010, Kim *et al.* 2013, Xu *et al.* 2013, Sebastiani *et al.* 2015). In addition, various miRNAs upregulated in the islets of GK rats have been shown to target transport and secretory pathway genes (Esguerra *et al.* 2011). Moreover, it has recently been shown that upregulation of miR-130a-3p, miR-130b-3p and miR-152-3p in the islets of GK rats was associated with reduced protein expression of GCK and pyruvate dehydrogenase E1-α and reduced intracellular ATP levels. Upregulation of these miRNAs has also been confirmed in the islets of hyperglycemic human donors (Ofori *et al.* 2017). Furthermore, upregulation of miR-187 in the islets of human T2D subjects was associated with altered GSIS and has been proposed to target *Hipk3* (Locke *et al.* 2014), a gene encoding for a serine-threonine kinase implicated in the regulation of β-cell function and survival (Shojima *et al.* 2012). However, transfection of INS1 cells with miR187 mimetic had only a minor effect on *Hipk3* mRNA levels and promoter activity, thereby suggesting the implication of other effectors (Locke *et al.* 2014). Thus, growing evidence supports an important role of miRNAs in the alteration of β-cell identity. Future studies are needed in this emerging field of research to identify which miRNAs are directly implicated in the loss of β-cell identity in T2D, map their precise targets and determine the upstream mechanisms of induction. A special attention in the *in vitro* studies must be paid to the duration of exposure to elevated glucose levels when evaluating the effects of glucotoxicity. Indeed, acute and sub-acute/chronic exposure may have different/opposite effects on the expression of some miRNAs (El Ouaamari *et al.* 2008, Esguerra *et al.* 2011, Sun *et al.* 2011). Altogether, these findings show the multiple levels at which glucotoxicity affects the β-cell phenotype as well as the various potential mechanisms of β-cell dedifferentiation in T2D. More large-scale studies, especially using human islets, human cell lines and/or human β-cells derived from induced pluripotent stem cells, are needed to validate and extend the findings in rodents and to understand the pathophysiological role of β-cell dedifferentiation in T2D.

In addition to the loss of insulin, transcription factor, metabolism and secretory pathway genes, a growing body of data indicates that the loss of the adaptive UPR is a key event that accompanies β-cell decompensation and progression towards diabetes.

Failure of the adaptive UPR and progression towards diabetes

β-cells are vulnerable to ER stress due to their elevated rate of insulin biosynthesis in response to glucose stimulation. Therefore, an operational and fine-tuned UPR is fundamental for the preservation of β-cell function and survival under physiological conditions, and even more under conditions of high insulin demand, such as obesity and pregnancy. Indeed, genetic disruption of several UPR components, including *Perk*, *eIF2α*, *Ire1*, *Xbp1* and *Dnajc3* leads to β-cell demise and the development of insulin-dependent diabetes in man and rodents (Delepine *et al.* 2000, Harding *et al.* 2001, Zhang *et al.* 2002a, Ladiges *et al.* 2005, Back *et al.* 2009, Iwawaki *et al.* 2010, Julier & Nicolino 2010, Lee *et al.* 2011, Synofzik *et al.* 2014, Xu *et al.* 2014, Han *et al.* 2015, Hassler *et al.* 2015). The UPR is thus an important trait of differentiated β-cells. Until recently, the accepted concept was that excessive stimulation of the UPR under chronic/unresolved ER stress plays an important role in β-cell decompensation and failure. This view was supported by several studies showing increased activation of ER stress sensors and downstream effectors and target genes in different *in vitro* and *in vivo* models in addition to human T2D (reviewed in Bensellam *et al.* 2012b). Furthermore, ablation of the ISR gene *Ddit3* in different animal models of diabetes has been shown to be protective (Oyadomari *et al.* 2002, Song *et al.* 2008), while overexpression of *Trib3* altered glucose tolerance and GSIS and increased β-cell apoptosis (Qian *et al.* 2008, Liew *et al.* 2010, Fang *et al.* 2014). Moreover, adenovirus-mediated overexpression of *Atf6* in INS1 cells was associated with altered GSIS and reduced expression of insulin, *Pdx1* and *Mafa* (Seo *et al.* 2008). Likewise, overexpression of *Xbp1* in primary rat β-cells was correlated with impaired function, increased apoptosis and reduced expression of insulin, *Pdx1*, *Mafa* and *Glut2* (Allagnat *et al.* 2010). As described earlier, chronic IRE1 activation has also been shown to alter β-cell differentiation via the degradation of ER-localized insulin mRNA (Pirot *et al.* 2007, Lipson *et al.* 2008, Han *et al.* 2009).

However, emerging evidence has challenged this concept by showing in different models of obesity and insulin resistance that the loss of β-cell differentiation and progression towards diabetes is accompanied by failure of the adaptive UPR. This led to the hypothesis that β-cell dysfunction in T2D may result from a failure of the UPR to adequately adapt rather than from a maladaptive UPR (Herbert & Laybutt 2016). By comparing time-dependent gene expression changes in islets of diabetes-prone (*db/db* mice on C57BL/KsJ genetic background)

and diabetes-resistant (*ob/ob* mice on C57BL/6J genetic background) mouse models of obesity, we observed in *ob/ob* mice a progressive upregulation of adaptive UPR genes, including *Hspa5*, *Fkbp11* and *Dnajc3*, in parallel with the maintenance of increased spliced/total *Xbp1* (*Xbp1s/t*) mRNA ratio. In contrast, adaptive UPR genes were upregulated in prediabetic *db/db* mouse islets (6 weeks of age) but declined in diabetic mice (16 weeks of age) in parallel with a similar decline in *Xbp1s/t* mRNA ratio. Moreover, despite partial downregulation of some β-cell key transcription factor genes and other β-cell-enriched genes in prediabetic *db/db* mice and age-matched *ob/ob* mice, the β-cell phenotype recovered in 16-week-old *ob/ob* mice. On the contrary, there was a further loss of these genes in 16-week-old diabetic *db/db* mice. Interestingly, downregulation of β-cell-enriched genes in *db/db* mouse islets was partially restored with the chemical chaperone 4-phenylbutyrate suggesting that the inactivation of the adaptive UPR plays a role in β-cell dedifferentiation (Chan *et al.* 2013). Downregulation of adaptive UPR gene expression is unlikely to result from reduced proinsulin biosynthesis since the latter has been shown to be increased in diabetic *db/db* mice (Alarcon *et al.* 2016). These results were corroborated by similar observations in the islets of female ZDF (fZDF) rats. Thus, adaptive UPR genes were upregulated in the islets of obese, prediabetic fZDF rats fed a chow diet (model of β-cell compensation) in comparison to age-matched lean controls. However, UPR gene expression was downregulated in diabetic fZDF rats fed a high-fat diet (model of β-cell decompensation) in comparison to age-matched obese, prediabetic fZDF rats fed a chow diet, in parallel with altered β-cell differentiation (Omikorede *et al.* 2013). Noteworthy, *in vitro*, proteomic analysis of glucose-responsive (low passage; more differentiated) vs glucose non-responsive (high passage; less differentiated) MIN6 cells also revealed downregulation of HSPA5, HSP90B1, PDI and ERP29 (Dowling *et al.* 2006). In humans, a previous microarray study has revealed a significant downregulation of *Hsp90b1* in the islet of T2D donors (Gunton *et al.* 2005). A more recent study has confirmed and extended this finding by showing that numerous UPR, ER-Golgi (retrograde)transport, ER quality control, ERAD and (retro)translocon-related genes were significantly downregulated in islets of T2D donors vs BMI-matched non-diabetic subjects, including *Perk*, *Hsp90b1*, *Hspa8*, *Hspa13*, *Ero1β*, *Pdia6*, *Ppib*, *Erp44*, *Dnaja2*, *Dnajb9*, *Dnajc6*, *Dnajc9*, *Dnajc10*, *Dnajc12*, *Serp1*, *Man1a1*, *Cnx*, *Herpud1*, *Ssr1*, *Ssr3*, *Sec11a*, *Sec13*, *Sec23a*, *Sec23b*, *Sec23ip*, *Sec24a*, *Sec24b*, *Sec24d*, *Sec62*, *Sec63*,

Copb1, *Copb2* and *Copz1*, in addition to downregulation of the ubiquitin-proteasome system genes and reduced proteasome activity (Bugliani *et al.* 2013). A following report examining protein expression of XBP1s, ATF6 and phosphorylated-eIF2α in pancreatic sections from non-BMI-matched normal, prediabetic and diabetic women with different durations of diabetes has shown an overall decreased staining in the islets of diabetic vs control and prediabetic women for the three markers (Engin *et al.* 2014). Collectively, these observations support the notion that adaptive UPR inactivation occurs during the progression towards diabetes in rodents and humans and may play an important role in β-cell dedifferentiation. But what could be the mechanism(s) behind this inactivation?

Hyperglycemia and the ensuing glucotoxicity are primary candidates. Indeed, downregulation of adaptive UPR and ISR gene expression has been observed in mouse islets transplanted into diabetic mice with a non-sufficient islet number, in comparison to those transplanted into non-diabetic control mice. These alterations were paralleled by similar changes in the expression of β-cell key transcription factors and other β-cell-enriched genes, thereby further supporting a link between β-cell dedifferentiation and failure of the UPR. Interestingly, these alterations were prevented in mouse islets transplanted into diabetic mice with a sufficient number to restore normoglycaemia, thereby suggesting that hyperglycaemia contributes to the downregulation of the UPR (Walters *et al.* 2013). Glucotoxicity exerts its deleterious effects via myriad mechanisms, including hypoxia (Sato *et al.* 2011, 2014, Bensellam *et al.* 2012*a*,*b*). We have recently provided evidence that hypoxia could be an important cellular mechanism for the inactivation of the adaptive UPR in T2D. Thus, we have shown that
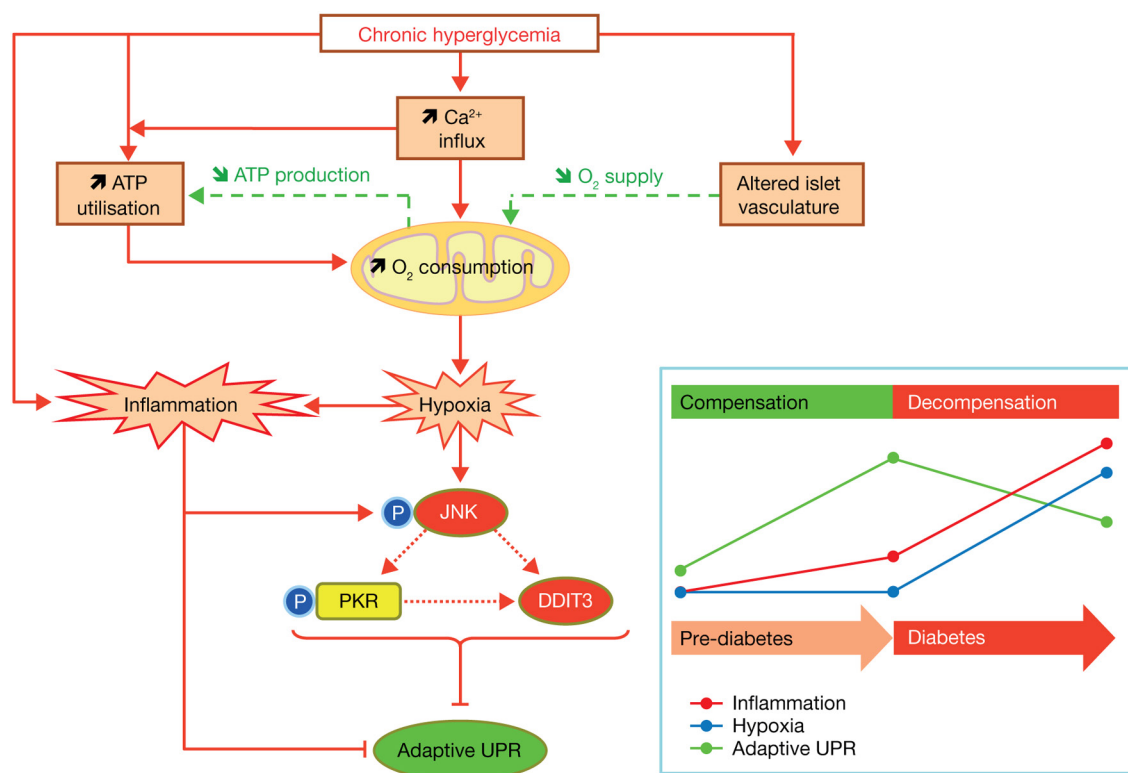

Figure 4

Schematic representation of the role of hypoxia and inflammation in the loss of adaptive UPR under chronic hyperglycemia. Under chronic hyperglycemia, the acceleration of mitochondrial metabolism and the stimulation of ATP consuming cellular processes, increases β-cell O_2 consumption. On the other hand, chronic hyperglycemia negatively affects islet vasculature thereby resulting in reduced O_2 supply. These events lead to β-cell hypoxia and activation of downstream pathways including c-Jun N-terminal kinase (JNK), double-stranded RNA-dependent protein kinase (PKR) and downstream DNA damage inducible transcript 3 (DDIT3). Activation of these effectors plays an important role in the inhibition of the adaptive unfolded protein response (UPR) under hypoxia. Inflammation induced by chronic hyperglycemia, but also by hypoxia, can also increase JNK phosphorylation and has been proposed to play a role in the failure of adaptive UPR. The timing of these complex events is represented in the insert. In the prediabetic phase (β-cell compensation), the UPR is markedly upregulated in parallel with a moderate activation of inflammatory signaling in the absence of signs of islet hypoxia. However, in the diabetic phase (β-cell decompensation), the adaptive UPR declines concomitantly with strong upregulation of inflammatory and hypoxia-response genes.

hypoxia-response genes were upregulated in the islets of diabetic, but not prediabetic, *db/db* mice in an inverse relationship with UPR gene expression (Fig. 4). We have demonstrated that hypoxia inhibits the adaptive UPR specifically in β-cells and that this inhibition was associated with impaired ER-to-Golgi protein trafficking and was implicated in increased apoptosis under hypoxic stress. These effects were mediated by the activation of JNK and *Ddit3*, but were independent of hypoxia-inducible factor 1 α (HIF1α) (Bensellam *et al.* 2016) (Fig. 4). Interestingly, JNK activation has also been observed in the islets of diabetic *db/db* mice and its inhibition increased adaptive UPR gene expression and reduced apoptosis (Chan *et al.* 2015).

In addition to hypoxia, inflammation is another potential mechanism that may be involved in UPR inactivation (Fig. 4). T2D is characterized by a low-grade inflammation and proinflammatory cytokines released by immune cells, endothelial cells and adipose tissue under chronic hyperglycemia have been proposed to contribute to islet inflammation and β-cell dedifferentiation (Donath & Shoelson 2011, Nordmann *et al.* 2017). Interestingly, cytokine treatment of mouse islets downregulated the mRNA levels of several adaptive UPR genes including *Hspa5*, *Hsp90b1*, *Fkbp11* and *Dnajc3* (Chan *et al.* 2011). Importantly, the progression towards diabetes in *db/db* mice was accompanied by a progressive upregulation of inflammatory genes including *Il6*, *Il1β*, *Cxcl1*, *Tnfα*, *Ccl2* and the macrophages marker gene *Cd68* (Fig. 4). This inflammatory signature was however absent in the islets of *ob/ob* mice (Chan *et al.* 2013). Moreover, assessment of time-dependent changes in XBP1s and ATF6 protein expression in the islets of mouse models of type 1 diabetes (T1D), which is an immune-mediated disease, revealed a progressive downregulation. These alterations were also observed on pancreatic section of humans T1D donors (Engin *et al.* 2013). Of note, hypoxia also upregulated inflammatory genes in mouse islets (Bensellam *et al.* 2016) (Fig. 4). Altogether, these observations suggest a role for inflammatory signalling in the downregulation of the adaptive UPR in T2D.

Very interestingly, in rat models of hypertrophic and failing heart, myocardial XBP1s and HSPA5 protein levels were upregulated in the early phase of the disease (adaptive phase) but declined in the late phase (maladaptive phase), very similarly to what has been observed in *db/db* mouse islets. In the cardiac context, it has been shown that miR-30-p3 family and miR-214 were implicated in XBP1s downregulation (Duan *et al.* 2015). Likewise, miRNAs may also be involved in UPR inactivation in β-cells. The expression of various miRNAs is affected in prediabetic and diabetic *db/db* mouse islets in comparison to their age-matched lean controls (Nesca *et al.* 2013), and miR-200 has been shown to negatively regulate *Dnajc3* expression (Belgardt *et al.* 2015). Studies comparing the time-dependent changes in miRNA expression in obese models of β-cell compensation and decompensation are needed to shed more light on this possibility.

In sum, there is growing evidence that failure of the adaptive UPR in T2D is linked with β-cell dedifferentiation and dysfunction. Our evidence strongly supports the implication of hypoxia and very likely inflammatory signalling in UPR inactivation. But how the inactivation of the UPR could affect the differentiated β-cell phenotype is unclear at this stage. One possibility is that failure of the adaptive UPR exacerbates hyperglycemia-induced oxidative stress. Not only is the role of the latter in β-cell dedifferentiation well established, but oxidative stress is also linked with ER stress. Indeed, defective ER protein folding machinery and subsequent accumulation of unfolded proteins in the ER has been shown to trigger oxidative stress and damage in association with altered β-cell differentiation (Back *et al.* 2009, Han *et al.* 2015). Moreover, expression of a mutant form of proinsulin that is prone to misfolding in Akita mouse islets has also been associated with increased oxidative stress and damage (Yuan *et al.* 2012). Furthermore, treatment of glucose-infused rats with chemical chaperones reduced islet superoxide anion generation and preserved β-cell function (Tang *et al.* 2012). Thus, it is postulated that the inactivation of the UPR in T2D leads to progressive accumulation of unfolded proteins in the ER; this potentiates hyperglycemia-induced reactive oxygen species (ROS) production and oxidative stress, which leads to a gradual loss of β-cell identity. Future work in this field is needed to verify this hypothesis and explore the mechanism(s) by which protein misfolding in the ER induces/aggravates oxidative stress and whether a crosstalk between the ER and mitochondria may be involved.

Upregulation of β-cell forbidden genes

As well as the downregulation of β-cell-enriched genes (addressed above), β-cell dedifferentiation in T2D features upregulation of genes that are either suppressed or expressed at very low levels in mature β-cells under physiological conditions. These genes that we term as β-cell forbidden genes enclose various types including metabolic genes, transcriptional regulators, signalling effectors and stress response genes (Table 3 and Bensellam *et al.* 2012b). Upregulation of these genes under hyperglycemia has important consequences on β-cell identity and function.

Table 3 Upregulation of β-cell forbidden genes under glucotoxicity.

Genes	Glucotoxicity model		Confirmation in human T2D	Glucotoxic effect
	In vitro/ex vivo	*In vivo*		
Transcriptional regulators				
C/EBPβ	HIT-T15 cells (Lu et al. 1997) INS1 cells (Lu et al. 1997)	Px rat islets (Seufert et al. 1998) ZDF rat islets (Seufert et al. 1998)		mRNA and protein
Crem	Wistar and Sprague–Dawley rat islets (Bensellam et al. 2009, Zhou et al. 2003)			mRNA
Myc	Wistar rat islets (Bensellam et al. 2009, Elouil et al. 2005, Kaneto et al. 2002a)	Px rat islets (Jonas et al. 2001, Jonas et al. 1999) Gk rat islets (Lacraz et al. 2010)		mRNA
Id1	Human islets (Wice et al. 2001)	db/db mouse islets (Kjorholt et al. 2005, Chan et al. 2013, Bensellam et al. 2015)		mRNA and protein
Id2		GK rat islets (Homo-Delarche et al. 2006) db/db mouse islets (Bensellam et al. 2015)		mRNA
Id3		db/db mouse islets (Bensellam et al. 2015)		mRNA and protein
Id4		db/db mouse islets (Bensellam et al. 2015)		mRNA
Ngn3		db/db mouse islets (Talchai et al. 2012) K$_{ATP}$-GOF mice (Wang et al. 2014) GIRKO mouse islets (Talchai et al. 2012) Multiparous and ageing FoxO1-KO mice (Talchai et al. 2012)		Protein
Nanog		Multiparous FoxO1-KO mice (Talchai et al. 2012)		Protein
Oct4		db/db mouse islets (Talchai et al. 2012) GIRKO mouse islets (Talchai et al. 2012) Multiparous FoxO1-KO mice (Talchai et al. 2012)		Protein
L-Myc		db/db mouse islets (Talchai et al. 2012) GIRKO mouse islets (Talchai et al. 2012) Multiparous FoxO1-KO mice (Talchai et al. 2012)		Protein
Sox9			Yes: (Marselli et al. 2010, Bugliani et al. 2013)	mRNA
Metabolic genes				
Hk1		Px rat islets (Jonas et al. 1999) ZDF rat islets (Cockburn et al. 1997) db/db mouse islets (Kjorholt et al. 2005) Psammomys obesus (Nesher et al. 1999)		mRNA and enzymatic activity
Hk2	Rat islets (Ghanaat-Pour et al. 2007)			mRNA
G6pase		Px rat islets (Laybutt et al. 2002b) GK rat islets (Ling et al. 2001)		mRNA and enzymatic activity
Fbp1		Px rat islets (Laybutt et al. 2002b)		mRNA
Pck1	Human islets (Shalev et al. 2002)		Yes: (Marselli et al. 2010)	mRNA
Ldha	Wistar rat islets (Bensellam et al. 2009, Bensellam et al. 2012a)	Px rat islets (Jonas et al. 1999, Laybutt et al. 2003) GK rat islets (Homo-Delarche et al. 2006, Sasaki et al. 2013) ZDF rat islets (Li et al. 2006b) Rat islets transplanted into diabetic rats (Laybutt et al. 2007)	Yes: (Marselli et al. 2010)	mRNA, protein and lactate production
Mct1		Px rat islets (Laybutt et al. 2002b)		mRNA
Mct2		Px rat islets (Laybutt et al. 2002b)		mRNA

(Continued)

Table 3 Continued.

Genes	Glucotoxicity model		Confirmation in human T2D	Glucotoxic effect
	In vitro/ex vivo	*In vivo*		
Mct4	Wistar rat islets (Bensellam *et al.* 2012*a*)	Px rat islets (Laybutt *et al.* 2002*b*)		mRNA
Ucp2	Wistar rat islets (Khaldi *et al.* 2004)	Glucose-infused rats (Kassis *et al.* 2000) Px rat islets (Laybutt *et al.* 2002*b*) ZDF rat islets (Oberkofler *et al.* 2009) *db/db* mouse islets (Kjorholt *et al.* 2005) *ob/ob* mouse islets (Zhang *et al.* 2001)		mRNA and protein
Acot7		ZDF rat islets (Parton *et al.* 2006)	Yes: (Marselli *et al.* 2010)	mRNA
Aldh1a3		*db/db* mouse islets (Ishida *et al.* 2017, Kim-Muller *et al.* 2016) *Abcc8*-KO mice (Stancill *et al.* 2017)	Yes: (Cinti *et al.* 2016)	mRNA, protein and enzymatic activity

Metabolic genes A major earlier and recent focus in this field has been on metabolic genes, in particular *Ldha* and *Mct1*. Pioneering studies have shown that LDHA activity is markedly lower in β-cells in comparison to other islet cells, exocrine cells and hepatocytes (Hellman & Taljedal 1967, Sekine *et al.* 1994). Ensuing large-scale studies comparing gene expression patterns of different mouse tissues with pancreatic islets confirmed low expression of *Ldha* and *Mct1* and identified other β-cell forbidden genes (Pullen *et al.* 2010, Thorrez *et al.* 2011). Interestingly, *Ldha* and various *Mct* isoform genes were upregulated in the islets of rodent models of hyperglycemia and diabetes (Jonas *et al.* 1999, Laybutt *et al.* 2002*b*, 2007, Homo-Delarche *et al.* 2006, Li *et al.* 2006*b*). Upregulation of *Ldha* has also been reported in β-cells of human T2D subjects (Marselli *et al.* 2010) (Table 3). The role of hyperglycemia in this induction has been demonstrated by phlorizin treatment experiments in Px rats (Jonas *et al.* 1999, Laybutt *et al.* 2002*b*). In addition, we have previously reported upregulation of *Ldha* mRNA levels, along with other glycolytic and hypoxia-response genes, in cultured rat islets exposed to elevated glucose levels (Bensellam *et al.* 2009). The prevention of this induction by hyperoxia suggested an implication of high glucose-induced β-cell hypoxia and activation of HIF1/2α (Bensellam *et al.* 2012*a*). Another pathway implicating oxidative stress may be involved in LDHA induction in the islets of GK rats (Sasaki *et al.* 2013). Evidence has also shown a role of miRNAs in the regulation of *Mct1* expression (Pullen *et al.* 2011, Martinez-Sanchez *et al.* 2015). But whether altered expression of specific miRNAs in T2D is involved in the upregulation of *Mct1* requires further proof. Upregulation of *Ldha* and *Mct* genes may alter β-cell function by diverting the glycolytic flux from mitochondrial pyruvate oxidation to lactate production and transport. This could

alter glucose homeostasis by sensitising β-cells to secrete insulin in response to non-physiological stimuli (Ishihara *et al.* 1999, Ainscow *et al.* 2000, Otonkoski *et al.* 2007, Pullen *et al.* 2012).

As explained in 'Relationship of β-cell differentiation to insulin secretory function' section, the repression of high-affinity type I–III hexokinases in β-cells prevents insulin release in response to low non-stimulatory glucose levels such as in the fasted state (Sekine *et al.* 1994, Schuit *et al.* 1999). In the context of diabetes, increased mRNA levels of *Hk1* have been reported in Px rats and *db/db* mouse islets (Jonas *et al.* 1999, Kjorholt *et al.* 2005). In agreement, HK enzymatic activity was upregulated in the islets of ZDF rats (Cockburn *et al.* 1997), DBA/2 mice (Kooptiwut *et al.* 2002) and *Psammomys obesus* on high energy diet (Nesher *et al.* 1999). Moreover, exposure of rat islets to elevated glucose levels *in vitro* upregulated the mRNA levels of *Hk2* (Ghanaat-Pour *et al.* 2007) (Table 3). Upregulation of *Hks*, and likely other glycolytic genes, may explain the reduced threshold glucose concentration for the stimulation of insulin secretion (glucose hypersensitivity) observed in INS1 cells (Roche *et al.* 1997), rat and mouse islets (Khaldi *et al.* 2004, Bensellam *et al.* 2009, Pascal *et al.* 2010) and purified rat and human β-cells (Ling & Pipeleers 1996, Ling *et al.* 1996) cultured in the presence of supraphysiological glucose levels, as well as in the islets of animal models of diabetes, including glucose-infused rats (Ammon *et al.* 1998), Px rats (Leahy *et al.* 1993, Hosokawa *et al.* 1995), ZDF rats (Tokuyama *et al.* 1995), *ob/ob* mice (Chen *et al.* 1993) and *Psammomys obesus* (Pertusa *et al.* 2002). In support of this hypothesis, overexpression of *Hk1* in MIN6 cells and primary rat islets has been shown to increase the basal glycolytic flux and insulin release along with altered GSIS (Becker *et al.* 1994, Ishihara *et al.* 1994).

Other metabolic genes presenting low expression under physiological conditions and upregulated in diabetes include the gluconeogenic genes *G6pase* (Ling *et al.* 2001, Laybutt *et al.* 2002b), *Fbp1* (Laybutt *et al.* 2002b) and *Pck1* (Marselli *et al.* 2010). The latter gene was also upregulated in isolated human islets cultured in the presence of high glucose levels (Shalev *et al.* 2002) (Table 3). Upregulation of *G6pase* may divert glucose from its classical metabolic route by inducing glucose cycling (GC). GC is a futile cycle where glucose is phosphorylated to glucose-6-phosphate by GCK and then dephosphorylated to glucose by glucose-6-phosphatase (G6Pase) with consumption of an ATP molecule. Indeed, *G6pase* overexpression in INS1 cells has been shown to increase GC and reduce GSIS (Trinh *et al.* 1997). Upregulation of *G6pase* mRNA and enzymatic activity in the islets of Px and GK rats was reversed by phlorizin treatment thereby underscoring the role of hyperglycemia (Ling *et al.* 2001, Laybutt *et al.* 2002b).

Another β-cell forbidden gene, *Acot7* (Pullen *et al.* 2010), which encodes for mitochondrial and cytosolic isoforms of acyl-CoA thioesterase 7 (ACOT7), hydrolyses long-chain acyl-CoA esters. Its expression was upregulated in the islets of ZDF rats and β-cells of human T2D patients (Parton *et al.* 2006, Marselli *et al.* 2010) (Table 3). Interestingly, repression of *Acot7* in mouse has been proposed in a recent study to be necessary for adequate insulin secretion. Indeed, *s*elective overexpression of the mitochondrial *Acot7* in β-cells of adult mice impaired glucose tolerance as a consequence of altered insulin secretion (Martinez-Sanchez *et al.* 2016). However, further work is needed to determine the precise mechanism(s) involved.

Recently, *Aldh1a3* has been proposed as a novel β-cell forbidden gene and putative marker of dedifferentiated β-cells (Kim-Muller *et al.* 2016). Aldehyde dehydrogenase family 1 member A3 (ALDH1A3) expression and activity were upregulated in the islets of various animal models including *db/db* mice (Kim-Muller *et al.* 2016, Ishida *et al.* 2017, Stancill *et al.* 2017). Increased ALDH1A3 immunostaining has also been confirmed in the islets of diabetic human subjects and was associated in some β-cells with cytoplasmic expression of NKX6.1 (Cinti *et al.* 2016) (Table 3). However, overexpression of *Aldh1a3* in MIN6 cells did not alter the expression of β-cell-enriched genes and was even associated in mouse islets with a slight potentiation of GSIS thereby ruling out a causative role of ALDH1A3 in β-cell dedifferentiation (Kim-Muller *et al.* 2016). Aldh1a3 is a detoxifying enzyme that catalyses the oxidation of retinal to retinol using NAD+. It is also involved in other metabolic processes including amino acid metabolism and the metabolism of lipid peroxidation products (Duan *et al.* 2016). Therefore, its upregulation in the islets of diabetic animals and T2D subjects could be a response to oxidative stress and the ensuing damage.

Transcriptional regulators Besides metabolic genes, β-cell forbidden genes also enclose transcriptional regulators. We have described in 'Down regulation of insulin gene expression' section the role of C/EBPβ, MYC and ETS1 in the alteration of insulin gene expression. In addition, several transcription factors typically expressed in progenitor cells at the embryonic stage and repressed in adult β-cells were upregulated in β-cells of various diabetic animal models, including neurogenin 3 (NGN3), nanog homeobox (NANOG), octamer-binding transcription factor 4 (OCT4 also known as POU5F1) and v-myc avian myelocytomatosis viral oncogene homolog 1, lung carcinoma derived (L-Myc) (Talchai *et al.* 2012, Brereton *et al.* 2014, Wang *et al.* 2014) (Table 3). Lineage trancing studies confirmed that these dedifferentiated cells originate from cells that expressed insulin and also suggested their transdifferentiation in other islet non-β-cells, including α-cells (Talchai *et al.* 2012, Wang *et al.* 2014) (Fig. 2). Interestingly, NGN3 reexpression in the islets of a diabetic mouse model with K_{ATP} channel mutation was reversed by insulin therapy (Wang *et al.* 2014). This observation is of importance. Together with the phlorizin and caloric restriction studies mentioned in previous sections, these reports highlight the astonishing plasticity of the β-cell phenotype and indicate the possibility to reverse β-cell dedifferentiation, at least in rodents. Furthermore, a recent study has also shown the possibility to prevent downregulation of some β-cell key transcription factor genes *in vitro* under cytokine treatment and *in vivo* in *db/db*, *ob/ob* and Akita mice using small-molecule inhibitors of the tumour growth factor β (TGFβ) pathway that target the TGFβ receptor I (also known as ALK5) (Blum *et al.* 2014). In humans, to date and to our knowledge, there is no confirmation of such expression of endocrine progenitor transcription factors in β-cells of T2D patients, except for upregulation of *POU5F1* mRNA levels (Guo *et al.* 2013). However, two studies have reported increased mRNA levels of the pre-endocrine gene *SOX9* (Marselli *et al.* 2010, Bugliani *et al.* 2013). Evidence suggests that *SOX9* upregulation in T2D may result from hypoxia and activation of HIF1 and could play a role in the downregulation of β-cell-enriched genes (Puri *et al.* 2013).

Inhibitor of differentiation (ID) proteins are another class of transcriptional regulators induced in response to glucose stimulation in β-cell lines and human islets (Wice *et al.* 2001) and upregulated in the islets of diabetic *db/db* mice and GK rats (Kjorholt *et al.* 2005, Homo-Delarche *et al.* 2006, Bensellam *et al.* 2015) (Table 3). They have been proposed to act as repressors of basic helix-loop-helix (bHLH) transcription factors thereby modulating cell differentiation and proliferation (Lasorella *et al.* 2014, Nair *et al.* 2014). Upregulation of *Id1* under high-fat diet has been implicated in the inhibition of insulin secretion and alteration of glucose homeostasis (Akerfeldt & Laybutt 2011). We have subsequently demonstrated that IDs are a novel class of oxidative stress-responsive genes in β-cells. Surprisingly, under oxidative stress conditions, deletion of *Id1* and/or *Id3* resulted in mitochondrial impairment and induced a global attenuation of antioxidant gene expression in association with a further increase in intracellular ROS levels and apoptosis. These effects involved a novel interaction of IDs with the NFE2L2-small Mafs antioxidant pathway (Bensellam *et al.* 2015). These findings suggest that IDs are key components of the antioxidant response and play an important role in the promotion of β-cell survival under oxidative stress. However, these observations also raise the question of whether dedifferentiation could be an adaptive mechanism to escape cell death under stress conditions (discussed in the next section).

Stress response genes Chronic hyperglycemia exposes β-cells to higher levels of stress than under physiological conditions. To face such threat, β-cells upregulate endogenous stress responses to uphold homeostasis. Thus, the induction and the regulatory mechanisms of the antioxidant and the ER stress responses have received much attention given the important role of these pathways in β-cell pathophysiology (reviewed in Bensellam *et al.* 2012b). We have described in 'Failure of the adaptive UPR and progression towards diabetes' section the regulation of the UPR in diabetes and the emerging evidence linking the failure of this response with the progression towards diabetes and β-cell dedifferentiation. In the following paragraphs, we will focus on the antioxidant response and its potential implication in β-cell dedifferentiation.

Upregulation of antioxidant gene expression in response to elevated glucose levels has been well documented *in vitro* and in diabetic animals, and has also been confirmed in human T2D for some antioxidant genes (reviewed in Bensellam *et al.* 2012b). The primary role of the antioxidant response is to relieve hyperglycemia-induced oxidative stress and promote cell survival. Nevertheless, β-cell mass is reduced by about 60% in GK rats although the mRNA and protein levels of *Nfe2l2* and several other antioxidant genes were markedly upregulated (Movassat *et al.* 1997, Lacraz *et al.* 2009). Moreover, the β-cell differentiated phenotype is noticeably altered in Px rats despite strong upregulation of the mRNA levels of *Hmox1* and *Gpx1* (Jonas *et al.* 1999, Laybutt *et al.* 2002a). Similarly, β-cell mass is reduced in human T2D patients even with upregulated mRNA levels of several antioxidant genes including various isoforms of metallothioneins (Marchetti *et al.* 2004, Marselli *et al.* 2010). These observations suggest that either the endogenous antioxidant response triggered by hyperglycemia is not robust enough to efficiently protect the β-cell differentiated phenotype or its strong and sustained activation under chronic hyperglycemia is deleterious and may play a role in β-cell dedifferentiation.

In support of the first possibility, previous evidence has shown that rat islets express low levels of several antioxidant genes in comparison to other tissues (Lenzen *et al.* 1996, Tiedge *et al.* 1997). The H_2O_2 detoxifying enzyme catalase is specifically repressed in adult mouse β-cells in comparison to other tissues (Thorrez *et al.* 2011, Pullen *et al.* 2017). Lower GPX1 expression and activity has also been confirmed in isolated human islets (Tonooka *et al.* 2007). In highly metabolically active β-cells, such low antioxidant gene expression signature is undoubtedly an Achilles' heel, especially under prolonged hyperglycemia. Interestingly, β-cell-specific overexpression of *Gpx1* in *db/db* mice prevented the loss of the β-cell-enriched genes MAFA, NKX6.1 and GLUT2 (Harmon *et al.* 2009, Guo *et al.* 2013). Similarly, antioxidant supplementation has been proven beneficial, at least *in vitro* and in rodent models (reviewed in Bensellam *et al.* 2012b). Why β-cells exhibit lower antioxidant gene expression in comparison to other tissues is unclear. However, some studies have proposed that physiological levels of H_2O_2 may play the role of a coupling factor for GSIS (Pi *et al.* 2007, Leloup *et al.* 2009). In addition, it has been shown that catalase or metallothionein overexpression in β-cells, while reducing cytokine-induced ROS generation, accelerated diabetes onset in male NOD mice in association with increased β-cell death and reduced PDX1 protein levels (Li *et al.* 2006a). It should be emphasized here that the antioxidant arsenal of β-cells is not limited to the classically studied genes such as *Gpx1* and catalase but encloses many other players including those of the glutathione system, the peroxiredoxin system, the thioredoxin system, haem oxygenases and metallothioneins and many of these genes are either expressed at high levels under

basal conditions or markedly upregulated under stress (Bensellam *et al.* 2009). The scenery is even more complex as some antioxidant genes can play other roles and be involved in different cellular processes such as the zinc buffering properties of metallothioneins (Chabosseau & Rutter 2016) or the involvement in iron metabolism for *Hmox1* (Gozzelino & Soares 2014). Therefore, one may propose that sustained upregulation of this wide battery of antioxidant genes under chronic hyperglycemia may exert a negative impact on the β-cell differentiated phenotype by yet to be defined mechanisms.

Dedifferentiation as a potential adaptive mechanism

Despite marked alteration of the β-cell differentiated phenotype and reduction of β-cell mass in human T2D, the β-cell apoptosis rate remains relatively low. This phenomenon is also observed in experimental models such as Px rats, *db/db* mice, *Foxo1*-KO mice and K_{ATP}-GOF mice. An emerging body of data suggests that β-cell dedifferentiation could be an adaptive mechanism to escape cell death under chronic hyperglycemia at the price of altered identity and function.

As mentioned in the previous section, we found that upregulation of IDs (inhibitors of bHLH transcription factors) during oxidative stress played a key role in maintaining the antioxidant response and mitochondrial integrity and thereby promoting β-cell survival (Bensellam *et al.* 2015). In addition, previous reports have shown that β-cell line maturation from a glucagon-producing phenotype to an insulin-producing phenotype was associated with increased sensitivity to several toxic agents such as cytokines, streptozotocin and alloxan (Nielsen *et al.* 1999). Further studies revealed an important role of increased expression of *Pdx1* and *Nkx6.1* in this acquired sensitivity (Nielsen *et al.* 2004). The potential link between dedifferentiation and adaptation/resistance to stress seems to be a conserved biological mechanism that has also been described in other cell types and models including cancer cells (Del Vecchio *et al.* 2014, Li *et al.* 2016, Roesch *et al.* 2016) and even plant cells (Grafi & Barak 2015). Future work is needed to validate this hypothesis in β-cells and to fully characterize the response of dedifferentiated β-cells to different types of stress.

From a therapeutic perspective, alleviating β-cell stress may provide a novel strategy to reverse the process of dedifferentiation and restore functional β-cell mass. Previous β-cell rest approaches have shown promising results *in vitro* and in animal models (Grill *et al.* 2009). Noteworthy, in isolated rat islets, high glucose-induced upregulation of several β-cell forbidden genes and other stress response genes such as *Ldha*, *Crem*, *Myc*, *Adm* and *Hmox1* was markedly prevented by diazoxide treatment (Jonas *et al.* 2001, 2003, Ma *et al.* 2007). However, until now, these methods failed to improve glycemic control in T2D patients (reviewed in Bensellam *et al.* 2012*b*). Given the key role of hyperglycemia in β-cell dedifferentiation and the demonstrated beneficial effects of the glucose lowering strategies in rodents, SGLT2 inhibition by gliflozins merits further attention in humans (Abdul-Ghani *et al.* 2017). The use of these drugs in combination with other therapies such as incretins may exert beneficial effects on the β-cell phenotype (Busch & Kane 2017, Kaneto *et al.* 2017). The potential combination with antioxidants such as GPX mimetics and/or chemical chaperones such as the recently identified small-molecule azoramide (Fu *et al.* 2015) merits further experimental and clinical testing.

Conclusion

Growing evidence indicates that β-cell dedifferentiation plays a key role in the loss of functional β-cell mass in T2D. Over the last decades, *in vitro* and animal studies implicated glucotoxicity and downstream pathways in this process. Dysregulation of numerous – and not fully identified – transcriptional regulators, genes, miRNAs, stress responses, metabolic processes and epigenetic mechanisms converge to compromise β-cell identity in T2D. Based on emerging data and observations in other cell types and models, we proposed that β-cell dedifferentiation could be an adaptive mechanism to escape cell death under stress conditions. Interestingly, animal studies suggest the possibility to reverse β-cell dedifferentiation by reducing β-cell stress strategies. More large-scale studies using human β-cells are needed to validate the findings in rodents and shed more light on the different signalling effectors and pathways involved in the alteration of the β-cell differentiated phenotype. A better understanding of the physiological and pathological regulation of these pathways may pave the way to reverse β-cell dedifferentiation and restore the functional β-cell mass in human T2D.

References

Abdul-Ghani M, Al Jobori H, Daniele G, Adams J, Cersosimo E, Triplitt C & DeFronzo RA 2017 Inhibition of renal sodium-glucose cotransport with empagliflozin lowers fasting plasma glucose and improves beta-cell function in subjects with impaired fasting glucose. *Diabetes* **66** 2495–2502. (https://doi.org/10.2337/db17-0055)

Ainscow EK, Zhao C & Rutter GA 2000 Acute overexpression of lactate dehydrogenase-A perturbs β-cell mitochondrial metabolism and insulin secretion. *Diabetes* **49** 1149–1155. (https://doi.org/10.2337/diabetes.49.7.1149)

Akerfeldt MC & Laybutt DR 2011 Inhibition of Id1 augments insulin secretion and protects against high-fat diet-induced glucose intolerance. *Diabetes* **60** 2506–2514. (https://doi.org/10.2337/db11-0083)

Alarcon C, Boland BB, Uchizono Y, Moore PC, Peterson B, Rajan S, Rhodes OS, Noske AB, Haataja L, Arvan P, *et al.* 2016 Pancreatic beta-Cell adaptive plasticity in obesity increases insulin production but adversely affects secretory function. *Diabetes* **65** 438–450. (https://doi.org/10.2337/db15-0792)

Allagnat F, Christulia F, Ortis F, Pirot P, Lortz S, Lenzen S, Eizirik DL & Cardozo AK 2010 Sustained production of spliced X-box binding protein 1 (XBP1) induces pancreatic beta cell dysfunction and apoptosis. *Diabetologia* **53** 1120–1130. (https://doi.org/10.1007/s00125-010-1699-7)

Ammon HP, Bacher M, Brandle WF, Waheed A, Roenfeldt M, el-Sayed ME, Ahmed AA & Wahl MA 1998 Effect of forty-eight-hour glucose infusion into rats on islet ion fluxes, ATP/ADP ratio and redox ratios of pyridine nucleotides. *Journal of Endocrinology* **156** 583–590. (https://doi.org/10.1677/joe.0.1560583)

Asplund K, Westman S & Hellerstrom C 1969 Glucose stimulation of insulin secretion from the isolated pancreas of foetal and newborn rats. *Diabetologia* **5** 260–262. (https://doi.org/10.1007/BF01212095)

Axelsson AS, Mahdi T, Nenonen HA, Singh T, Hanzelmann S, Wendt A, Bagge A, Reinbothe TM, Millstein J, Yang X, *et al.* 2017 Sox5 regulates beta-cell phenotype and is reduced in type 2 diabetes. *Nature Communications* **8** 15652. (https://doi.org/10.1038/ncomms15652)

Back SH, Scheuner D, Han J, Song B, Ribick M, Wang J, Gildersleeve RD, Pennathur S & Kaufman RJ 2009 Translation attenuation through eIF2alpha phosphorylation prevents oxidative stress and maintains the differentiated state in beta cells. *Cell Metabolism* **10** 13–26. (https://doi.org/10.1016/j.cmet.2009.06.002)

Becker TC, BeltrandelRio H, Noel RJ, Johnson JH & Newgard CB 1994 Overexpression of hexokinase I in isolated islets of Langerhans via recombinant adenovirus. Enhancement of glucose metabolism and insulin secretion at basal but not stimulatory glucose levels. *Journal of Biological Chemistry* **269** 21234–21238.

Belgardt BF, Ahmed K, Spranger M, Latreille M, Denzler R, Kondratiuk N, von Meyenn F, Villena FN, Herrmanns K, Bosco D, *et al.* 2015 The microRNA-200 family regulates pancreatic beta cell survival in type 2 diabetes. *Nature Medicine* **21** 619–627. (https://doi.org/10.1038/nm.3862)

Ben-Shushan E, Marshak S, Shoshkes M, Cerasi E & Melloul D 2001 A pancreatic beta -cell-specific enhancer in the human PDX-1 gene is regulated by hepatocyte nuclear factor 3beta (HNF-3beta), HNF-1alpha, and SPs transcription factors. *Journal of Biological Chemistry* **276** 17533–17540. (https://doi.org/10.1074/jbc.M009088200)

Bensellam M, Van Lommel L, Overbergh L, Schuit FC & Jonas JC 2009 Cluster analysis of rat pancreatic islet gene mRNA levels after culture in low-, intermediate- and high-glucose concentrations. *Diabetologia* **52** 463–476. (https://doi.org/10.1007/s00125-008-1245-z)

Bensellam M, Duvillie B, Rybachuk G, Laybutt DR, Magnan C, Guiot Y, Pouyssegur J & Jonas JC 2012a Glucose-induced O(2) consumption activates hypoxia inducible factors 1 and 2 in rat insulin-secreting pancreatic beta-cells. *PLoS ONE* **7** e29807. (https://doi.org/10.1371/journal.pone.0029807)

Bensellam M, Laybutt DR & Jonas JC 2012b The molecular mechanisms of pancreatic beta-cell glucotoxicity: recent findings and future research directions. *Molecular and Cellular Endocrinology* **364** 1–27. (https://doi.org/10.1016/j.mce.2012.08.003)

Bensellam M, Montgomery MK, Luzuriaga J, Chan JY & Laybutt DR 2015 Inhibitor of differentiation proteins protect against oxidative stress by regulating the antioxidant-mitochondrial response in mouse beta cells. *Diabetologia* **58** 758–770. (https://doi.org/10.1007/s00125-015-3503-1)

Bensellam M, Maxwell EL, Chan JY, Luzuriaga J, West PK, Jonas JC, Gunton JE & Laybutt DR 2016 Hypoxia reduces ER-to-Golgi protein trafficking and increases cell death by inhibiting the adaptive unfolded protein response in mouse beta cells. *Diabetologia* **59** 1492–1502. (https://doi.org/10.1007/s00125-016-3947-y)

Blum B, Roose AN, Barrandon O, Maehr R, Arvanites AC, Davidow LS, Davis JC, Peterson QP, Rubin LL & Melton DA 2014 Reversal of beta cell de-differentiation by a small molecule inhibitor of the TGFbeta pathway. *eLife* **3** e02809. (https://doi.org/10.7554/eLife.05105)

Brereton MF, Iberl M, Shimomura K, Zhang Q, Adriaenssens AE, Proks P, Spiliotis, II, Dace W, Mattis KK, Ramracheya R, *et al.* 2014 Reversible changes in pancreatic islet structure and function produced by elevated blood glucose. *Nature Communications* **5** 4639. (https://doi.org/10.1038/ncomms5639)

Briaud I, Rouault C, Reach G & Poitout V 1999 Long-term exposure of isolated rat islets of Langerhans to supraphysiologic glucose concentrations decreases insulin mRNA levels. *Metabolism* **48** 319–323. (https://doi.org/10.1016/S0026-0495(99)90079-3)

Brun T, Roche E, Assimacopoulos-Jeannet F, Corkey BE, Kim KH & Prentki M 1996 Evidence for an anaplerotic/malonyl-CoA pathway in pancreatic beta-cell nutrient signaling. *Diabetes* **45** 190–198. (https://doi.org/10.2337/diab.45.2.190)

Bugliani M, Liechti R, Cheon H, Suleiman M, Marselli L, Kirkpatrick C, Filipponi F, Boggi U, Xenarios I, Syed F, *et al.* 2013 Microarray analysis of isolated human islet transcriptome in type 2 diabetes and the role of the ubiquitin-proteasome system in pancreatic beta cell dysfunction. *Molecular and Cellular Endocrinology* **367** 1–10. (https://doi.org/10.1016/j.mce.2012.12.001)

Busch RS & Kane MP 2017 Combination SGLT2 inhibitor and GLP-1 receptor agonist therapy: a complementary approach to the treatment of type 2 diabetes. *Postgraduate Medical* **129** 686–697. (https://doi.org/10.1080/00325481.2017.1342509)

Butler AE, Janson J, Bonner-Weir S, Ritzel R, Rizza RA & Butler PC 2003 β-cell deficit and increased β-cell apoptosis in humans with type 2 diabetes. *Diabetes* **52** 102–110. (https://doi.org/10.2337/diabetes.52.1.102)

Campbell JE & Drucker DJ 2013 Pharmacology, physiology, and mechanisms of incretin hormone action. *Cell Metabolism* **17** 819–837. (https://doi.org/10.1016/j.cmet.2013.04.008)

Cha JY, Kim H, Kim KS, Hur MW & Ahn Y 2000 Identification of transacting factors responsible for the tissue-specific expression

of human glucose transporter type 2 isoform gene. Cooperative role of hepatocyte nuclear factors 1alpha and 3beta. *Journal of Biological Chemistry* **275** 18358–18365. (https://doi.org/10.1074/jbc.M909536199)

Chabosseau P & Rutter GA 2016 Zinc and diabetes. *Archives of Biochemistry and Biophysics* **611** 79–85. (https://doi.org/10.1016/j.abb.2016.05.022)

Chan JY, Cooney GJ, Biden TJ & Laybutt DR 2011 Differential regulation of adaptive and apoptotic unfolded protein response signalling by cytokine-induced nitric oxide production in mouse pancreatic beta cells. *Diabetologia* **54** 1766–1776. (https://doi.org/10.1007/s00125-011-2139-z)

Chan JY, Luzuriaga J, Bensellam M, Biden TJ & Laybutt DR 2013 Failure of the adaptive unfolded protein response in islets of obese mice is linked with abnormalities in beta-cell gene expression and progression to diabetes. *Diabetes* **62** 1557–1568. (https://doi.org/10.2337/db12-0701)

Chan JY, Luzuriaga J, Maxwell EL, West PK, Bensellam M & Laybutt DR 2015 The balance between adaptive and apoptotic unfolded protein responses regulates beta-cell death under ER stress conditions through XBP1, CHOP and JNK. *Molecular and Cellular Endocrinology* **413** 189–201. (https://doi.org/10.1016/j.mce.2015.06.025)

Chen NG, Tassava TM & Romsos DR 1993 Threshold for glucose-stimulated insulin secretion in pancreatic islets of genetically obese (ob/ob) mice is abnormally low. *Journal of Nutrition* **123** 1567–1574.

Chen L, Yan HX, Chen J, Yang W, Liu Q, Zhai B, Cao HF, Liu SQ, Wu MC & Wang HY 2007 Negative regulation of c-Myc transcription by pancreas duodenum homeobox-1. *Endocrinology* **148** 2168–2180. (https://doi.org/10.1210/en.2006-1221)

Chen F, Sha M, Wang Y, Wu T, Shan W, Liu J, Zhou W, Zhu Y, Sun Y, Shi Y, *et al*. 2016 Transcription factor Ets-1 links glucotoxicity to pancreatic beta cell dysfunction through inhibiting PDX-1 expression in rodent models. *Diabetologia* **59** 316–324. (https://doi.org/10.1007/s00125-015-3805-3)

Cinti F, Bouchi R, Kim-Muller JY, Ohmura Y, Sandoval PR, Masini M, Marselli L, Suleiman M, Ratner LE, Marchetti P, *et al*. 2016 Evidence of beta-cell dedifferentiation in human type 2 diabetes. *Journal of Clinical Endocrinology and Metabolism* **101** 1044–1054. (https://doi.org/10.1210/jc.2015-2860)

Cockburn BN, Ostrega DM, Sturis J, Kubstrup C, Polonsky KS & Bell GI 1997 Changes in pancreatic islet glucokinase and hexokinase activities with increasing age, obesity, and the onset of diabetes. *Diabetes* **46** 1434–1439. (https://doi.org/10.2337/diab.46.9.1434)

De Vos A, Heimberg H, Quartier E, Huypens P, Bouwens L, Pipeleers D & Schuit F 1995 Human and rat beta cells differ in glucose transporter but not in glucokinase gene expression. *Journal of Clinical Investigation* **96** 2489–2495.

Del Vecchio CA, Feng Y, Sokol ES, Tillman EJ, Sanduja S, Reinhardt F & Gupta PB 2014 De-differentiation confers multidrug resistance via noncanonical PERK-Nrf2 signaling. *PLoS Biology* **12** e1001945. (https://doi.org/10.1371/journal.pbio.1001945)

Delepine M, Nicolino M, Barrett T, Golamaully M, Lathrop GM & Julier C 2000 EIF2AK3, encoding translation initiation factor 2-alpha kinase 3, is mutated in patients with Wolcott-Rallison syndrome. *Nature Genetics* **25** 406–409. (https://doi.org/10.1038/78085)

DelGuerra S, Lupi R, Marselli L, Masini M, Bugliani M, Sbrana S, Torri S, Pollera M, Boggi U, Mosca F, *et al*. 2005 Functional and molecular defects of pancreatic islets in human type 2 diabetes. *Diabetes* **54** 727–735. (https://doi.org/10.2337/diabetes.54.3.727)

DelGuerra S, Grupillo M, Masini M, Lupi R, Bugliani M, Torri S, Boggi U, Del CM, Vistoli F, Mosca F, *et al*. 2007 Gliclazide protects human islet beta-cells from apoptosis induced by intermittent high glucose. *Diabetes/Metabolism Research and Reviews* **23** 234–238. (https://doi.org/10.1002/dmrr.680)

Deng S, Vatamaniuk M, Huang X, Doliba N, Lian MM, Frank A, Velidedeoglu E, Desai NM, Koeberlein B, Wolf B, *et al*. 2004 Structural and functional abnormalities in the islets isolated from type 2 diabetic subjects. *Diabetes* **53** 624–632. (https://doi.org/10.2337/diabetes.53.3.624)

Detimary P, Jonas JC & Henquin JC 1996 Stable and diffusible pools of nucleotides in pancreatic islet cells. *Endocrinology* **137** 4671–4676. (https://doi.org/10.1210/endo.137.11.8895332)

Detimary P, Gilon P & Henquin JC 1998 Interplay between cytoplasmic Ca^{2+} and the ATP/ADP ratio: a feedback control mechanism in mouse pancreatic islets. *Biochemical Journal* **333** 269–274. (https://doi.org/10.1042/bj3330269)

Dhawan S, Tschen SI, Zeng C, Guo T, Hebrok M, Matveyenko A & Bhushan A 2015 DNA methylation directs functional maturation of pancreatic beta cells. *Journal of Clinical Investigation* **125** 2851–2860. (https://doi.org/10.1172/JCI79956)

Do OH, Low JT, Gaisano HY & Thorn P 2014 The secretory deficit in islets from db/db mice is mainly due to a loss of responding beta cells. *Diabetologia* **57** 1400–1409. (https://doi.org/10.1007/s00125-014-3226-8)

Donath MY & Shoelson SE 2011 Type 2 diabetes as an inflammatory disease. *Nature Reviews Immunology* **11** 98–107. (https://doi.org/10.1038/nri2925)

Donath MY, Gross DJ, Cerasi E & Kaiser N 1999 Hyperglycemia-induced β-cell apoptosis in pancreatic islets of *Psammomys obesus* during development of diabetes. *Diabetes* **48** 738–744. (https://doi.org/10.2337/diabetes.48.4.738)

Dowling P, O'Driscoll L, O'Sullivan F, Dowd A, Henry M, Jeppesen PB, Meleady P & Clynes M 2006 Proteomic screening of glucose-responsive and glucose non-responsive MIN-6 beta cells reveals differential expression of proteins involved in protein folding, secretion and oxidative stress. *Proteomics* **6** 6578–6587. (https://doi.org/10.1002/pmic.200600298)

Duan Q, Chen C, Yang L, Li N, Gong W, Li S & Wang DW 2015 MicroRNA regulation of unfolded protein response transcription factor XBP1 in the progression of cardiac hypertrophy and heart failure in vivo. *Journal of Translational Medicine* **13** 363. (https://doi.org/10.1186/s12967-015-0725-4)

Duan JJ, Cai J, Guo YF, Bian XW & Yu SC 2016 ALDH1A3, a metabolic target for cancer diagnosis and therapy. *International Journal of Cancer* **139** 965–975. (https://doi.org/10.1002/ijc.30091)

Dubois M, Vacher P, Roger B, Huyghe D, Vandewalle B, Kerr-Conte J, Pattou F, Moustaid-Moussa N & Lang J 2007 Glucotoxicity inhibits late steps of insulin exocytosis. *Endocrinology* **148** 1605–1614. (https://doi.org/10.1210/en.2006-1022)

Duchen MR, Smith PA & Ashcroft FM 1993 Substrate-dependent changes in mitochondrial function, intracellular free calcium concentration and membrane channels in pancreatic beta-cells. *Biochemical Journal* **294** 35–42. (https://doi.org/10.1042/bj2940035)

Ediger BN, Lim HW, Juliana C, Groff DN, Williams LT, Dominguez G, Liu JH, Taylor BL, Walp ER, Kameswaran V, *et al*. 2017 LIM domain-binding 1 maintains the terminally differentiated state of pancreatic beta cells. *Journal of Clinical Investigation* **127** 215–229. (https://doi.org/10.1172/JCI88016)

Efanova IB, Zaitsev SV, Zhivotovsky B, Kohler M, Efendic S, Orrenius S & Berggren PO 1998 Glucose and tolbutamide induce apoptosis in pancreatic beta-cells. A process dependent on intracellular Ca2+ concentration. *Journal of Biological Chemistry* **273** 33501–33507. (https://doi.org/10.1074/jbc.273.50.33501)

El Ouaamari A, Baroukh N, Martens GA, Lebrun P, Pipeleers D & van Obberghen E 2008 miR-375 targets 3′-phosphoinositide-dependent protein kinase-1 and regulates glucose-induced biological responses in pancreatic beta-cells. *Diabetes* **57** 2708–2717. (https://doi.org/10.2337/db07-1614)

Elouil H, Cardozo AK, Eizirik DL, Henquin JC & Jonas JC 2005 High glucose and hydrogen peroxide increase c-Myc and haeme-oxygenase 1 mRNA levels in rat pancreatic islets without activating NFkappaB. *Diabetologia* **48** 496–505. (https://doi.org/10.1007/s00125-004-1664-4)

Elouil H, Bensellam M, Guiot Y, Vander Mierde D, Pascal SM, Schuit FC & Jonas JC 2007 Acute nutrient regulation of the unfolded protein response and integrated stress response in cultured rat pancreatic islets. *Diabetologia* **50** 1442–1452. (https://doi.org/10.1007/s00125-007-0674-4)

Engin F, Yermalovich A, Nguyen T, Hummasti S, Fu W, Eizirik DL, Mathis D & Hotamisligil GS 2013 Restoration of the unfolded protein response in pancreatic beta cells protects mice against type 1 diabetes. *Science Translational Medicine* **5** 211ra156. (https://doi.org/10.1126/scitranslmed.3006534)

Engin F, Nguyen T, Yermalovich A & Hotamisligil GS 2014 Aberrant islet unfolded protein response in type 2 diabetes. *Scientific Reports* **4** 4054. (https://doi.org/10.1038/srep04054)

Esguerra JL, Bolmeson C, Cilio CM & Eliasson L 2011 Differential glucose-regulation of microRNAs in pancreatic islets of non-obese type 2 diabetes model Goto-Kakizaki rat. *PLoS ONE* **6** e18613. (https://doi.org/10.1371/journal.pone.0018613)

Eto K, Tsubamoto Y, Terauchi Y, Sugiyama T, Kishimoto T, Takahashi N, Yamauchi N, Kubota N, Murayama S, Aizawa T, *et al*. 1999 Role of NADH shuttle system in glucose-induced activation of mitochondrial metabolism and insulin secretion. *Science* **283** 981–985. (https://doi.org/10.1126/science.283.5404.981)

Fang N, Zhang W, Xu S, Lin H, Wang Z, Liu H, Fang Q, Li C, Peng L & Lou J 2014 TRIB3 alters endoplasmic reticulum stress-induced beta-cell apoptosis via the NF-kappaB pathway. *Metabolism* **63** 822–830. (https://doi.org/10.1016/j.metabol.2014.03.003)

Farfari S, Schulz V, Corkey B & Prentki M 2000 Glucose-regulated anaplerosis and cataplerosis in pancreatic beta-cells: possible implication of a pyruvate/citrate shuttle in insulin secretion. *Diabetes* **49** 718–726. (https://doi.org/10.2337/diabetes.49.5.718)

Ferdaoussi M, Dai X, Jensen MV, Wang R, Peterson BS, Huang C, Ilkayeva O, Smith N, Miller N, Hajmrle C, *et al*. 2015 Isocitrate-to-SENP1 signaling amplifies insulin secretion and rescues dysfunctional beta cells. *Journal of Clinical Investigation* **125** 3847–3860. (https://doi.org/10.1172/JCI82498)

Ferrer J, Benito C & Gomis R 1995 Pancreatic islet GLUT2 glucose transporter mRNA and protein expression in humans with and without NIDDM. *Diabetes* **44** 1369–1374. (https://doi.org/10.2337/diab.44.12.1369)

Finegood DT, McArthur MD, Kojwang D, Thomas MJ, Topp BG, Leonard T & Buckingham RE 2001 Beta-cell mass dynamics in Zucker diabetic fatty rats. Rosiglitazone prevents the rise in net cell death. *Diabetes* **50** 1021–1029. (https://doi.org/10.2337/diabetes.50.5.1021)

Flamez D, Berger V, Kruhoffer M, Orntoft T, Pipeleers D & Schuit FC 2002 Critical role for cataplerosis via citrate in glucose-regulated insulin release. *Diabetes* **51** 2018–2024. (https://doi.org/10.2337/diabetes.51.7.2018)

Fred RG, Bang-Berthelsen CH, Mandrup-Poulsen T, Grunnet LG & Welsh N 2010 High glucose suppresses human islet insulin biosynthesis by inducing miR-133a leading to decreased polypyrimidine tract binding protein-expression. *PLoS ONE* **5** e10843. (https://doi.org/10.1371/journal.pone.0010843)

Fu S, Yalcin A, Lee GY, Li P, Fan J, Arruda AP, Pers BM, Yilmaz M, Eguchi K & Hotamisligil GS 2015 Phenotypic assays identify azoramide as a small-molecule modulator of the unfolded protein response with antidiabetic activity. *Science Translational Medicine* **7** 292ra298.

Gaisano HY, Ostenson CG, Sheu L, Wheeler MB & Efendic S 2002 Abnormal expression of pancreatic islet exocytotic soluble N-ethylmaleimide-sensitive factor attachment protein receptors in Goto-Kakizaki rats is partially restored by phlorizin treatment and accentuated by high glucose treatment. *Endocrinology* **143** 4218–4226. (https://doi.org/10.1210/en.2002-220237)

Gao T, McKenna B, Li C, Reichert M, Nguyen J, Singh T, Yang C, Pannikar A, Doliba N, Zhang T, *et al*. 2014 Pdx1 maintains beta cell identity and function by repressing an alpha cell program. *Cell Metabolism* **19** 259–271. (https://doi.org/10.1016/j.cmet.2013.12.002)

Gautam D, Han SJ, Duttaroy A, Mears D, Hamdan FF, Li JH, Cui Y, Jeon J & Wess J 2007 Role of the M3 muscarinic acetylcholine receptor in beta-cell function and glucose homeostasis. *Diabetes, Obesity and Metabolism* **9** (Supplement 2) 158–169. (https://doi.org/10.1111/j.1463-1326.2007.00781.x)

Ghanaat-Pour H, Huang Z, Lehtihet M & Sjoholm A 2007 Global expression profiling of glucose-regulated genes in pancreatic islets of spontaneously diabetic Goto-Kakizaki rats. *Journal of Molecular Endocrinology* **39** 135–150. (https://doi.org/10.1677/JME-07-0002)

Gleason CE, Gonzalez M, Harmon JS & Robertson RP 2000 Determinants of glucose toxicity and its reversibility in the pancreatic islet β-cell line, HIT-T15. *American Journal of Physiology: Endocrinology and Metabolism* **279** E997–E1002.

Gomez E, Powell ML, Bevington A & Herbert TP 2008 A decrease in cellular energy status stimulates PERK-dependent eIF2alpha phosphorylation and regulates protein synthesis in pancreatic beta-cells. *Biochemical Journal* **410** 485–493. (https://doi.org/10.1042/BJ20071367)

Gozzelino R & Soares MP 2014 Coupling heme and iron metabolism via ferritin H chain. *Antioxidants and Redox Signaling* **20** 1754–1769. (https://doi.org/10.1089/ars.2013.5666)

Grafi G & Barak S 2015 Stress induces cell dedifferentiation in plants. *Biochimica et Biophysica Acta* **1849** 378–384. (https://doi.org/10.1016/j.bbagrm.2014.07.015)

Gravena C, Mathias PC & Ashcroft SJ 2002 Acute effects of fatty acids on insulin secretion from rat and human islets of Langerhans. *Journal of Endocrinology* **173** 73–80. (https://doi.org/10.1677/joe.0.1730073)

Grill V, Lake W & Freinkel N 1981 Generalized diminution in the response to nutrients as insulin-releasing agents during the early neonatal period in the rat. *Diabetes* **30** 56–63. (https://doi.org/10.2337/diab.30.1.56)

Grill V, Radtke M, Qvigstad E, Kollind M & Bjorklund A 2009 Beneficial effects of K-ATP channel openers in diabetes: an update on mechanisms and clinical experiences. *Diabetes, Obesity and Metabolism* **11** (Supplement 4) 143–148. (https://doi.org/10.1111/j.1463-1326.2009.01119.x)

Gunton JE, Kulkarni RN, Yim S, Okada T, Hawthorne WJ, Tseng YH, Roberson RS, Ricordi C, O'Connell PJ, Gonzalez FJ, *et al*. 2005 Loss of ARNT/HIF1beta mediates altered gene expression and pancreatic-islet dysfunction in human type 2 diabetes. *Cell* **122** 337–349. (https://doi.org/10.1016/j.cell.2005.05.027)

Guo S, Dai C, Guo M, Taylor B, Harmon JS, Sander M, Robertson RP, Powers AC & Stein R 2013 Inactivation of specific beta cell transcription factors in type 2 diabetes. *Journal of Clinical Investigation* **123** 3305–3316. (https://doi.org/10.1172/JCI65390)

Gutierrez GD, Bender AS, Cirulli V, Mastracci TL, Kelly SM, Tsirigos A, Kaestner KH & Sussel L 2017 Pancreatic beta cell identity requires continual repression of non-beta cell programs. *Journal of Clinical Investigation* **127** 244–259. (https://doi.org/10.1172/JCI88017)

Hall E, Dayeh T, Kirkpatrick CL, Wollheim CB, Dekker Nitert M & Ling C 2013 DNA methylation of the glucagon-like peptide 1 receptor (GLP1R) in human pancreatic islets. *BMC Medical Genetics* **14** 76. (https://doi.org/10.1186/1471-2350-14-76)

Han D, Lerner AG, Vande Walle L, Upton JP, Xu W, Hagen A, Backes BJ, Oakes SA & Papa FR 2009 IRE1alpha kinase activation modes control alternate endoribonuclease outputs to determine divergent cell fates. *Cell* **138** 562–575. (https://doi.org/10.1016/j.cell.2009.07.017)

Han J, Song B, Kim J, Kodali VK, Pottekat A, Wang M, Hassler J, Wang S, Pennathur S, Back SH, *et al*. 2015 Antioxidants complement the requirement for protein chaperone function to maintain beta-cell function and glucose homeostasis. *Diabetes* **64** 2892–2904. (https://doi.org/10.2337/db14-1357)

Harding HP, Zeng H, Zhang Y, Jungries R, Chung P, Plesken H, Sabatini DD & Ron D 2001 Diabetes mellitus and exocrine pancreatic dysfunction in perk-/- mice reveals a role for translational control

in secretory cell survival. *Molecular Cell* **7** 1153–1163. (https://doi.org/10.1016/S1097-2765(01)00264-7)

Harmon JS, Tanaka Y, Olson LK & Robertson RP 1998 Reconstitution of glucotoxic HIT-T15 cells with somatostatin transcription factor-1 partially restores insulin promoter activity. *Diabetes* **47** 900–904. (https://doi.org/10.2337/diabetes.47.6.900)

Harmon JS, Gleason CE, Tanaka Y, Poitout V & Robertson RP 2001 Antecedent hyperglycemia, not hyperlipidemia, is associated with increased islet triacylglycerol content and decreased insulin gene mRNA level in Zucker diabetic fatty rats. *Diabetes* **50** 2481–2486. (https://doi.org/10.2337/diabetes.50.11.2481)

Harmon JS, Stein R & Robertson RP 2005 Oxidative stress-mediated, post-translational loss of MafA protein as a contributing mechanism to loss of insulin gene expression in glucotoxic beta cells. *Journal of Biological Chemistry* **280** 11107–11113. (https://doi.org/10.1074/jbc.M410345200)

Harmon JS, Bogdani M, Parazzoli SD, Mak SS, Oseid EA, Berghmans M, Leboeuf RC & Robertson RP 2009 beta-Cell-specific overexpression of glutathione peroxidase preserves intranuclear MafA and reverses diabetes in db/db mice. *Endocrinology* **150** 4855–4862. (https://doi.org/10.1210/en.2009-0708)

Hasan NM, Longacre MJ, Seed Ahmed M, Kendrick MA, Gu H, Ostenson CG, Fukao T & MacDonald MJ 2010 Lower succinyl-CoA:3-ketoacid-CoA transferase (SCOT) and ATP citrate lyase in pancreatic islets of a rat model of type 2 diabetes: knockdown of SCOT inhibits insulin release in rat insulinoma cells. *Archives of Biochemistry and Biophysics* **499** 62–68. (https://doi.org/10.1016/j.abb.2010.05.007)

Hassler JR, Scheuner DL, Wang S, Han J, Kodali VK, Li P, Nguyen J, George JS, Davis C, Wu SP, *et al.* 2015 The IRE1alpha/XBP1s pathway is essential for the glucose response and protection of beta cells. *PLoS Biology* **13** e1002277. (https://doi.org/10.1371/journal.pbio.1002277)

Hattersley AT & Patel KA 2017 Precision diabetes: learning from monogenic diabetes. *Diabetologia* **60** 769–777. (https://doi.org/10.1007/s00125-017-4226-2)

Hauge-Evans AC, Reers C, Kerby A, Franklin Z, Amisten S, King AJ, Hassan Z, Vilches-Flores A, Tippu Z, Persaud SJ, *et al.* 2014 Effect of hyperglycaemia on muscarinic M3 receptor expression and secretory sensitivity to cholinergic receptor activation in islets. *Diabetes, Obesity and Metabolism* **16** 947–956. (https://doi.org/10.1111/dom.12301)

Hellman B & Taljedal IB 1967 Quantitative studies on isolated pancreatic islets of mammals. Activity and heterogeneity of lactate dehydrogenase in obese-hyperglycemic mice. *Endocrinology* **81** 125–131. (https://doi.org/10.1210/endo-81-1-125)

Henquin JC 2011 The dual control of insulin secretion by glucose involves triggering and amplifying pathways in beta-cells. *Diabetes Research and Clinical Practice* **93** (Supplement 1) S27–S31. (https://doi.org/10.1016/S0168-8227(11)70010-9)

Herbert TP & Laybutt DR 2016 A reevaluation of the role of the unfolded protein response in islet dysfunction: maladaptation or a failure to adapt? *Diabetes* **65** 1472–1480. (https://doi.org/10.2337/db15-1633)

Hollien J & Weissman JS 2006 Decay of endoplasmic reticulum-localized mRNAs during the unfolded protein response. *Science* **313** 104–107. (https://doi.org/10.1126/science.1129631)

Hollien J, Lin JH, Li H, Stevens N, Walter P & Weissman JS 2009 Regulated Ire1-dependent decay of messenger RNAs in mammalian cells. *Journal of Cell Biology* **186** 323–331. (https://doi.org/10.1083/jcb.200903014)

Homo-Delarche F, Calderari S, Irminger JC, Gangnerau MN, Coulaud J, Rickenbach K, Dolz M, Halban P, Portha B & Serradas P 2006 Islet inflammation and fibrosis in a spontaneous model of type 2 diabetes, the GK rat. *Diabetes* **55** 1625–1633. (https://doi.org/10.2337/db05-1526)

Hosokawa H, Hosokawa YA & Leahy JL 1995 Upregulated hexokinase activity in isolated islets from diabetic 90% pancreatectomized rats. *Diabetes* **44** 1328–1333. (https://doi.org/10.2337/diab.44.11.1328)

Hou N, Torii S, Saito N, Hosaka M & Takeuchi T 2008*a* Reactive oxygen species-mediated pancreatic beta-cell death is regulated by interactions between stress-activated protein kinases, p38 and c-Jun N-terminal kinase, and mitogen-activated protein kinase phosphatases. *Endocrinology* **149** 1654–1665. (https://doi.org/10.1210/en.2007-0988)

Hou ZQ, Li HL, Gao L, Pan L, Zhao JJ & Li GW 2008*b* Involvement of chronic stresses in rat islet and INS-1 cell glucotoxicity induced by intermittent high glucose. *Molecular and Cellular Endocrinology* **291** 71–78. (https://doi.org/10.1016/j.mce.2008.03.004)

Huang Q, Bu S, Yu Y, Guo Z, Ghatnekar G, Bu M, Yang L, Lu B, Feng Z, Liu S, *et al.* 2007 Diazoxide prevents diabetes through inhibiting pancreatic beta-cells from apoptosis via Bcl-2/Bax rate and p38-beta mitogen-activated protein kinase. *Endocrinology* **148** 81–91. (https://doi.org/10.1210/en.2006-0738)

Ishida E, Kim-Muller JY & Accili D 2017 Pair feeding, but not insulin, phloridzin, or rosiglitazone treatment, curtails markers of beta-cell dedifferentiation in db/db mice. *Diabetes* **66** 2092–2101. (https://doi.org/10.2337/db16-1213)

Ishihara H, Asano T, Tsukuda K, Katagiri H, Inukai K, Anai M, Kikuchi M, Yazaki Y, Miyazaki J & Oka Y 1994 Overexpression of hexokinase I but not GLUT1 glucose transporter alters concentration dependence of glucose-stimulated insulin secretion in pancreatic beta-cell line MIN6. *Journal of Biological Chemistry* **269** 3081–3087.

Ishihara H, Wang H, Drewes LR & Wollheim CB 1999 Overexpression of monocarboxylate transporter and lactate dehydrogenase alters insulin secretory responses to pyruvate and lactate in beta cells. *Journal of Clinical Investigation* **104** 1621–1629. (https://doi.org/10.1172/JCI7515)

Itoh Y, Kawamata Y, Harada M, Kobayashi M, Fujii R, Fukusumi S, Ogi K, Hosoya M, Tanaka Y, Uejima H, *et al.* 2003 Free fatty acids regulate insulin secretion from pancreatic beta cells through GPR40. *Nature* **422** 173–176. (https://doi.org/10.1038/nature01478)

Ivarsson R, Quintens R, Dejonghe S, Tsukamoto K, in 't Veld P, Renstrom E & Schuit FC 2005 Redox control of exocytosis: regulatory role of NADPH, thioredoxin, and glutaredoxin. *Diabetes* **54** 2132–2142. (https://doi.org/10.2337/diabetes.54.7.2132)

Iwashima Y, Kondoh-Abiko A, Seino S, Takeda J, Eto M, Polonsky KS & Makino I 1994 Reduced levels of messenger ribonucleic acid for calcium channel, glucose transporter-2, and glucokinase are associated with alterations in insulin secretion in fasted rats. *Endocrinology* **135** 1010–1017. (https://doi.org/10.1210/endo.135.3.8070343)

Iwawaki T, Akai R & Kohno K 2010 IRE1alpha disruption causes histological abnormality of exocrine tissues, increase of blood glucose level, and decrease of serum immunoglobulin level. *PLoS ONE* **5** e13052. (https://doi.org/10.1371/journal.pone.0013052)

Jacovetti C, Matkovich SJ, Rodriguez-Trejo A, Guay C & Regazzi R 2015 Postnatal beta-cell maturation is associated with islet-specific microRNA changes induced by nutrient shifts at weaning. *Nature Communications* **6** 8084. (https://doi.org/10.1038/ncomms9084)

Jermendy A, Toschi E, Aye T, Koh A, Aguayo-Mazzucato C, Sharma A, Weir GC, Sgroi D & Bonner-Weir S 2011 Rat neonatal beta cells lack the specialised metabolic phenotype of mature beta cells. *Diabetologia* **54** 594–604. (https://doi.org/10.1007/s00125-010-2036-x)

Jitrapakdee S, Wutthisathapornchai A, Wallace JC & MacDonald MJ 2010 Regulation of insulin secretion: role of mitochondrial signalling. *Diabetologia* **53** 1019–1032. (https://doi.org/10.1007/s00125-010-1685-0)

Jonas JC, Sharma A, Hasenkamp W, Ilkova H, Patane G, Laybutt R, Bonner-Weir S & Weir GC 1999 Chronic hyperglycemia triggers loss of pancreatic beta cell differentiation in an animal model of diabetes. *Journal of Biological Chemistry* **274** 14112–14121. (https://doi.org/10.1074/jbc.274.20.14112)

Jonas JC, Laybutt DR, Steil GM, Trivedi N, Pertusa JG, Van de Casteele M, Weir GC & Henquin JC 2001 High glucose stimulates early response

gene c-Myc expression in rat pancreatic beta cells. *Journal of Biological Chemistry* **276** 35375–35381. (https://doi.org/10.1074/jbc.M105020200)

Jonas JC, Guiot Y, Rahier J & Henquin JC 2003 Haeme-oxygenase 1 expression in rat pancreatic β-cells is stimulated by supraphysiological glucose concentrations and by cyclic AMP. *Diabetologia* **46** 1234–1244. (https://doi.org/10.1007/s00125-003-1174-9)

Jonas JC, Bensellam M, Duprez J, Elouil H, Guiot Y & Pascal SM 2009 Glucose regulation of islet stress responses and beta-cell failure in type 2 diabetes. *Diabetes, Obesity and Metabolism* **11** (Supplement 4) 65–81. (https://doi.org/10.1111/j.1463-1326.2009.01112.x)

Julier C & Nicolino M 2010 Wolcott-Rallison syndrome. *Orphanet Journal of Rare Diseases* **5** 29. (https://doi.org/10.1186/1750-1172-5-29)

Jurgens CA, Toukatly MN, Fligner CL, Udayasankar J, Subramanian SL, Zraika S, Aston-Mourney K, Carr DB, Westermark P, Westermark GT, *et al.* 2011 beta-cell loss and beta-cell apoptosis in human type 2 diabetes are related to islet amyloid deposition. *American Journal of Pathology* **178** 2632–2640. (https://doi.org/10.1016/j.ajpath.2011.02.036)

Kaneto H, Xu G, Song KH, Suzuma K, Bonner-Weir S, Sharma A & Weir GC 2001 Activation of the hexosamine pathway leads to deterioration of pancreatic beta-cell function through the induction of oxidative stress. *Journal of Biological Chemistry* **276** 31099–31104. (https://doi.org/10.1074/jbc.M104115200)

Kaneto H, Sharma A, Suzuma K, Laybutt DR, Xu G, Bonner-Weir S & Weir GC 2002*a* Induction of c-Myc expression suppresses insulin gene transcription by inhibiting NeuroD/BETA2-mediated transcriptional activation. *Journal of Biological Chemistry* **277** 12998–13006. (https://doi.org/10.1074/jbc.M111148200)

Kaneto H, Xu G, Fujii N, Kim S, Bonner-Weir S & Weir GC 2002*b* Involvement of c-Jun N-terminal kinase in oxidative stress-mediated suppression of insulin gene expression. *Journal of Biological Chemistry* **277** 30010–30018. (https://doi.org/10.1074/jbc.M202066200)

Kaneto H, Obata A, Kimura T, Shimoda M, Okauchi S, Shimo N, Matsuoka TA & Kaku K 2017 Beneficial effects of sodium-glucose cotransporter 2 inhibitors for preservation of pancreatic beta-cell function and reduction of insulin resistance. *Journal of Diabetes* **9** 219–225. (https://doi.org/10.1111/1753-0407.12494)

Kassis N, Bernard C, Pusterla A, Casteilla L, Penicaud L, Richard D, Ricquier D & Ktorza A 2000 Correlation between pancreatic islet uncoupling protein-2 (UCP2) mRNA concentration and insulin status in rats. *International Journal of Experimental Diabetes Research* **1** 185–193. (https://doi.org/10.1155/EDR.2000.185)

Kawamori D, Kajimoto Y, Kaneto H, Umayahara Y, Fujitani Y, Miyatsuka T, Watada H, Leibiger IB, Yamasaki Y & Hori M 2003 Oxidative stress induces nucleo-cytoplasmic translocation of pancreatic transcription factor PDX-1 through activation of c-Jun NH(2)-terminal kinase. *Diabetes* **52** 2896–2904. (https://doi.org/10.2337/diabetes.52.12.2896)

Kawamori D, Kaneto H, Nakatani Y, Matsuoka TA, Matsuhisa M, Hori M & Yamasaki Y 2006 The forkhead transcription factor Foxo1 bridges the JNK pathway and the transcription factor PDX-1 through its intracellular translocation. *Journal of Biological Chemistry* **281** 1091–1098. (https://doi.org/10.1074/jbc.M508510200)

Keller G 2005 Embryonic stem cell differentiation: emergence of a new era in biology and medicine. *Genes and Development* **19** 1129–1155. (https://doi.org/10.1101/gad.1303605)

Khaldi MZ, Guiot Y, Gilon P, Henquin JC & Jonas JC 2004 Increased glucose sensitivity of both triggering and amplifying pathways of insulin secretion in rat islets cultured for one week in high glucose. *American Journal of Physiology: Endocrinology and Metabolism* **287** E207–E217. (https://doi.org/10.1152/ajpendo.00426.2003)

Khan A, Ling ZC & Landau BR 1996 Quantifying the carboxylation of pyruvate in pancreatic islets. *Journal of Biological Chemistry* **271** 2539–2542. (https://doi.org/10.1074/jbc.271.5.2539)

Kim-Muller JY, Zhao S, Srivastava S, Mugabo Y, Noh HL, Kim YR, Madiraju SR, Ferrante AW, Skolnik EY, Prentki M, *et al.* 2014 Metabolic inflexibility impairs insulin secretion and results in MODY-like diabetes in triple FoxO-deficient mice. *Cell Metabolism* **20** 593–602. (https://doi.org/10.1016/j.cmet.2014.08.012)

Kim-Muller JY, Fan J, Kim YJ, Lee SA, Ishida E, Blaner WS & Accili D 2016 Aldehyde dehydrogenase 1a3 defines a subset of failing pancreatic beta cells in diabetic mice. *Nature Communications* **7** 12631. (https://doi.org/10.1038/ncomms12631)

Kim JW, Seghers V, Cho JH, Kang Y, Kim S, Ryu Y, Baek K, Aguilar-Bryan L, Lee YD, Bryan J, *et al.* 2002 Transactivation of the mouse sulfonylurea receptor I gene by BETA2/NeuroD. *Molecular Endocrinology* **16** 1097–1107. (https://doi.org/10.1210/mend.16.5.0934)

Kim JW, You YH, Jung S, Suh-Kim H, Lee IK, Cho JH & Yoon KH 2013 miRNA-30a-5p-mediated silencing of Beta2/NeuroD expression is an important initial event of glucotoxicity-induced beta cell dysfunction in rodent models. *Diabetologia* **56** 847–855. (https://doi.org/10.1007/s00125-012-2812-x)

Kitamura T 2013 The role of FOXO1 in beta-cell failure and type 2 diabetes mellitus. *Nature Reviews Endocrinology* **9** 615–623. (https://doi.org/10.1038/nrendo.2013.157)

Kitamura T, Nakae J, Kitamura Y, Kido Y, Biggs WH 3rd, Wright CV, White MF, Arden KC & Accili D 2002 The forkhead transcription factor Foxo1 links insulin signaling to Pdx1 regulation of pancreatic beta cell growth. *Journal of Clinical Investigation* **110** 1839–1847. (https://doi.org/10.1172/JCI200216857)

Kitamura YI, Kitamura T, Kruse JP, Raum JC, Stein R, Gu W & Accili D 2005 FoxO1 protects against pancreatic beta cell failure through NeuroD and MafA induction. *Cell Metabolism* **2** 153–163. (https://doi.org/10.1016/j.cmet.2005.08.004)

Kjorholt C, Akerfeldt MC, Biden TJ & Laybutt DR 2005 Chronic hyperglycemia, independent of plasma lipid levels, is sufficient for the loss of β-cell differentiation and secretory function in the db/db mouse model of diabetes. *Diabetes* **54** 2755–2763. (https://doi.org/10.2337/diabetes.54.9.2755)

Kluth O, Mirhashemi F, Scherneck S, Kaiser D, Kluge R, Neschen S, Joost HG & Schurmann A 2011 Dissociation of lipotoxicity and glucotoxicity in a mouse model of obesity associated diabetes: role of forkhead box O1 (FOXO1) in glucose-induced beta cell failure. *Diabetologia* **54** 605–616. (https://doi.org/10.1007/s00125-010-1973-8)

Kooptiwut S, Zraika S, Thorburn AW, Dunlop ME, Darwiche R, Kay TW, Proietto J & Andrikopoulos S 2002 Comparison of insulin secretory function in two mouse models with different susceptibility to beta-cell failure. *Endocrinology* **143** 2085–2092. (https://doi.org/10.1210/endo.143.6.8859)

Koyama M, Wada R, Sakuraba H, Mizukami H & Yagihashi S 1998 Accelerated loss of islet beta cells in sucrose-fed Goto-Kakizaki rats, a genetic model of non-insulin-dependent diabetes mellitus. *American Journal of Pathology* **153** 537–545. (https://doi.org/10.1016/S0002-9440(10)65596-4)

Lacraz G, Figeac F, Movassat J, Kassis N, Coulaud J, Galinier A, Leloup C, Bailbe D, Homo-Delarche F & Portha B 2009 Diabetic beta-cells can achieve self-protection against oxidative stress through an adaptive up-regulation of their antioxidant defenses. *PLoS ONE* **4** e6500. (https://doi.org/10.1371/journal.pone.0006500)

Lacraz G, Figeac F, Movassat J, Kassis N & Portha B 2010 Diabetic GK/Par rat beta-cells are spontaneously protected against H2O2-triggered apoptosis. A cAMP-dependent adaptive response. *American Journal of Physiology: Endocrinology and Metabolism* **298** E17–E27. (https://doi.org/10.1152/ajpendo.90871.2008)

Ladiges WC, Knoblaugh SE, Morton JF, Korth MJ, Sopher BL, Baskin CR, MacAuley A, Goodman AG, LeBoeuf RC & Katze MG 2005 Pancreatic beta-cell failure and diabetes in mice with a deletion mutation of the endoplasmic reticulum molecular chaperone gene P58IPK. *Diabetes* **54** 1074–1081. (https://doi.org/10.2337/diabetes.54.4.1074)

Lasorella A, Benezra R & Iavarone A 2014 The ID proteins: master regulators of cancer stem cells and tumour aggressiveness. *Nature Reviews Cancer* **14** 77–91. (https://doi.org/10.1038/nrc3638)

Latreille M, Hausser J, Stutzer I, Zhang Q, Hastoy B, Gargani S, Kerr-Conte J, Pattou F, Zavolan M, Esguerra JL, *et al.* 2014 MicroRNA-7a regulates pancreatic beta cell function. *Journal of Clinical Investigation* **124** 2722–2735. (https://doi.org/10.1172/JCI73066)

Lavine RL, Chick WL, Like AA & Makdisi TW 1971 Glucose tolerance and insulin secretion in neonatal and adult mice. *Diabetes* **20** 134–139. (https://doi.org/10.2337/diab.20.3.134)

Laybutt DR, Kaneto H, Hasenkamp W, Grey S, Jonas JC, Sgroi DC, Groff A, Ferran C, Bonner-Weir S, Sharma A, *et al.* 2002*a* Increased expression of antioxidant and antiapoptotic genes in islets that may contribute to beta-cell survival during chronic hyperglycemia. *Diabetes* **51** 413–423. (https://doi.org/10.2337/diabetes.51.2.413)

Laybutt DR, Sharma A, Sgroi DC, Gaudet J, Bonner-Weir S & Weir GC 2002*b* Genetic regulation of metabolic pathways in beta-cells disrupted by hyperglycemia. *Journal of Biological Chemistry* **277** 10912–10921. (https://doi.org/10.1074/jbc.M111751200)

Laybutt DR, Weir GC, Kaneto H, Lebet J, Palmiter RD, Sharma A & Bonner-Weir S 2002*c* Overexpression of c-Myc in beta-cells of transgenic mice causes proliferation and apoptosis, downregulation of insulin gene expression, and diabetes. *Diabetes* **51** 1793–1804. (https://doi.org/10.2337/diabetes.51.6.1793)

Laybutt DR, Glandt M, Xu G, Ahn YB, Trivedi N, Bonner-Weir S & Weir GC 2003 Critical reduction in β-cell mass results in two distinct outcomes over time. Adaptation with impaired glucose tolerance or decompensated diabetes. *Journal of Biological Chemistry* **278** 2997–3005. (https://doi.org/10.1074/jbc.M210581200)

Laybutt DR, Hawkins YC, Lock J, Lebet J, Sharma A, Bonner-Weir S & Weir GC 2007 Influence of diabetes on the loss of beta cell differentiation after islet transplantation in rats. *Diabetologia* **50** 2117–2125. (https://doi.org/10.1007/s00125-007-0749-2)

Leahy JL, Bumbalo LM & Chen C 1993 Beta-cell hypersensitivity for glucose precedes loss of glucose-induced insulin secretion in 90% pancreatectomized rats. *Diabetologia* **36** 1238–1244. (https://doi.org/10.1007/BF00400800)

Lee AH, Heidtman K, Hotamisligil GS & Glimcher LH 2011 Dual and opposing roles of the unfolded protein response regulated by IRE1alpha and XBP1 in proinsulin processing and insulin secretion. *PNAS* **108** 8885–8890. (https://doi.org/10.1073/pnas.1105564108)

Leibowitz G, Ferber S, Apelqvist A, Edlund H, Gross DJ, Cerasi E, Melloul D & Kaiser N 2001 IPF1/PDX1 deficiency and β-cell dysfunction in *Psammomys obesus*, an animal with type 2 diabetes. *Diabetes* **50** 1799–1806. (https://doi.org/10.2337/diabetes.50.8.1799)

Leloup C, Tourrel-Cuzin C, Magnan C, Karaca M, Castel J, Carneiro L, Colombani AL, Ktorza A, Casteilla L & Penicaud L 2009 Mitochondrial reactive oxygen species are obligatory signals for glucose-induced insulin secretion. *Diabetes* **58** 673–681. (https://doi.org/10.2337/db07-1056)

Lemaire K, Thorrez L & Schuit F 2016 Disallowed and allowed gene expression: two faces of mature islet beta cells. *Annual Review of Nutrition* **36** 45–71. (https://doi.org/10.1146/annurev-nutr-071715-050808)

Lemaire K, Granvik M, Schraenen A, Goyvaerts L, Van Lommel L, Gomez-Ruiz A, in 't Veld P, Gilon P & Schuit F 2017 How stable is repression of disallowed genes in pancreatic islets in response to metabolic stress? *PLoS ONE* **12** e0181651. (https://doi.org/10.1371/journal.pone.0181651)

Lenzen S, Drinkgern J & Tiedge M 1996 Low antioxidant enzyme gene expression in pancreatic islets compared with various other mouse tissues. *Free Radical Biology and Medicine* **20** 463–466. (https://doi.org/10.1016/0891-5849(96)02051-5)

Li X, Chen H & Epstein PN 2006*a* Metallothionein and catalase sensitize to diabetes in nonobese diabetic mice: reactive oxygen species may have a protective role in pancreatic beta-cells. *Diabetes* **55** 1592–1604. (https://doi.org/10.2337/db05-1357)

Li X, Zhang L, Meshinchi S, Dias-Leme C, Raffin D, Johnson JD, Treutelaar MK & Burant CF 2006*b* Islet microvasculature in islet hyperplasia and failure in a model of type 2 diabetes. *Diabetes* **55** 2965–2973. (https://doi.org/10.2337/db06-0733)

Li F, Zhou K, Gao L, Zhang B, Li W, Yan W, Song X, Yu H, Wang S, Yu N, *et al.* 2016 Radiation induces the generation of cancer stem cells: a novel mechanism for cancer radioresistance. *Oncology Letters* **12** 3059–3065.

Liew CW, Bochenski J, Kawamori D, Hu J, Leech CA, Wanic K, Malecki M, Warram JH, Qi L, Krolewski AS, *et al.* 2010 The pseudokinase tribbles homolog 3 interacts with ATF4 to negatively regulate insulin exocytosis in human and mouse beta cells. *Journal of Clinical Investigation* **120** 2876–2888. (https://doi.org/10.1172/JCI36849)

Ling Z & Pipeleers DG 1996 Prolonged exposure of human beta cells to elevated glucose levels results in sustained cellular activation leading to a loss of glucose regulation. *Journal of Clinical Investigation* **98** 2805–2812. (https://doi.org/10.1172/JCI119108)

Ling Z, Hannaert JC & Pipeleers D 1994 Effect of nutrients, hormones and serum on survival of rat islet beta cells in culture. *Diabetologia* **37** 15–21. (https://doi.org/10.1007/BF00428772)

Ling Z, Kiekens R, Mahler T, Schuit FC, Pipeleers-Marichal M, Sener A, Kloppel G, Malaisse WJ & Pipeleers DG 1996 Effects of chronically elevated glucose levels on the functional properties of rat pancreatic beta-cells. *Diabetes* **45** 1774–1782. (https://doi.org/10.2337/diab.45.12.1774)

Ling ZC, Hong-Lie C, Ostenson CG, Efendic S & Khan A 2001 Hyperglycemia contributes to impaired insulin response in GK rat islets. *Diabetes* **50** (Supplement 1) S108–S112. (https://doi.org/10.2337/diabetes.50.2007.S108)

Lipson KL, Ghosh R & Urano F 2008 The role of IRE1alpha in the degradation of insulin mRNA in pancreatic beta-cells. *PLoS ONE* **3** e1648. (https://doi.org/10.1371/journal.pone.0001648)

Locke JM, da Silva X, Dawe HR, Rutter GA & Harries LW 2014 Increased expression of miR-187 in human islets from individuals with type 2 diabetes is associated with reduced glucose-stimulated insulin secretion. *Diabetologia* **57** 122–128. (https://doi.org/10.1007/s00125-013-3089-4)

Lombardi A, Ulianich L, Treglia AS, Nigro C, Parrillo L, Lofrumento DD, Nicolardi G, Garbi C, Beguinot F, Miele C, *et al.* 2012 Increased hexosamine biosynthetic pathway flux dedifferentiates INS-1E cells and murine islets by an extracellular signal-regulated kinase (ERK)1/2-mediated signal transmission pathway. *Diabetologia* **55** 141–153. (https://doi.org/10.1007/s00125-011-2315-1)

Lovis P, Gattesco S & Regazzi R 2008 Regulation of the expression of components of the exocytotic machinery of insulin-secreting cells by microRNAs. *Biological Chemistry* **389** 305–312.

Lu M, Seufert J & Habener JF 1997 Pancreatic beta-cell-specific repression of insulin gene transcription by CCAAT/enhancer-binding protein beta. Inhibitory interactions with basic helix-loop-helix transcription factor E47. *Journal of Biological Chemistry* **272** 28349–28359. (https://doi.org/10.1074/jbc.272.45.28349)

Lu H, Yang Y, Allister EM, Wijesekara N & Wheeler MB 2008 The identification of potential factors associated with the development of type 2 diabetes: a quantitative proteomics approach. *Molecular and Cellular Proteomics* **7** 1434–1451. (https://doi.org/10.1074/mcp.M700478-MCP200)

Ma Z, Portwood N, Brodin D, Grill V & Bjorklund A 2007 Effects of diazoxide on gene expression in rat pancreatic islets are largely linked to elevated glucose and potentially serve to enhance β-cell sensitivity. *Diabetes* **56** 1095–1106. (https://doi.org/10.2337/db06-0322)

MacDonald MJ 1981 High content of mitochondrial glycerol-3-phosphate dehydrogenase in pancreatic islets and its inhibition by diazoxide. *Journal of Biological Chemistry* **256** 8287–8290.

MacDonald MJ 1982 Evidence for the malate aspartate shuttle in pancreatic islets. *Archives of Biochemistry and Biophysics* **213** 643–649. (https://doi.org/10.1016/0003-9861(82)90594-X)

MacDonald MJ 1993 Glucose enters mitochondrial metabolism via both carboxylation and decarboxylation of pyruvate in pancreatic islets. *Metabolism* **42** 1229–1231. (https://doi.org/10.1016/0026-0495(93)90118-8)

MacDonald MJ, Tang J & Polonsky KS 1996 Low mitochondrial glycerol phosphate dehydrogenase and pyruvate carboxylase in pancreatic islets of Zucker diabetic fatty rats. *Diabetes* **45** 1626–1630. (https://doi.org/10.2337/diab.45.11.1626)

MacDonald MJ, Longacre MJ, Langberg EC, Tibell A, Kendrick MA, Fukao T & Ostenson CG 2009 Decreased levels of metabolic enzymes in pancreatic islets of patients with type 2 diabetes. *Diabetologia* **52** 1087–1091. (https://doi.org/10.1007/s00125-009-1319-6)

Mahadevan J, Parazzoli S, Oseid E, Hertzel AV, Bernlohr DA, Vallerie SN, Liu CQ, Lopez M, Harmon JS & Robertson RP 2013 Ebselen treatment prevents islet apoptosis, maintains intranuclear Pdx-1 and MafA levels, and preserves beta-cell mass and function in ZDF rats. *Diabetes* **62** 3582–3588. (https://doi.org/10.2337/db13-0357)

Malaisse WJ, Sener A, Herchuelz A & Hutton JC 1979 Insulin release: the fuel hypothesis. *Metabolism* **28** 373–386. (https://doi.org/10.1016/0026-0495(79)90111-2)

Marchetti P, Del GS, Marselli L, Lupi R, Masini M, Pollera M, Bugliani M, Boggi U, Vistoli F, Mosca F, *et al*. 2004 Pancreatic islets from type 2 diabetic patients have functional defects and increased apoptosis that are ameliorated by metformin. *Journal of Clinical Endocrinology and Metabolism* **89** 5535–5541. (https://doi.org/10.1210/jc.2004-0150)

Marselli L, Thorne J, Dahiya S, Sgroi DC, Sharma A, Bonner-Weir S, Marchetti P & Weir GC 2010 Gene expression profiles of beta-cell enriched tissue obtained by laser capture microdissection from subjects with type 2 diabetes. *PLoS ONE* **5** e11499. (https://doi.org/10.1371/journal.pone.0011499)

Marselli L, Suleiman M, Masini M, Campani D, Bugliani M, Syed F, Martino L, Focosi D, Scatena F, Olimpico F, *et al*. 2014 Are we overestimating the loss of beta cells in type 2 diabetes? *Diabetologia* **57** 362–365. (https://doi.org/10.1007/s00125-013-3098-3)

Marshak S, Leibowitz G, Bertuzzi F, Socci C, Kaiser N, Gross DJ, Cerasi E & Melloul D 1999 Impaired beta-cell functions induced by chronic exposure of cultured human pancreatic islets to high glucose. *Diabetes* **48** 1230–1236. (https://doi.org/10.2337/diabetes.48.6.1230)

Martens GA & Pipeleers D 2009 Glucose, regulator of survival and phenotype of pancreatic beta cells. *Vitamins and Hormones* **80** 507–539.

Martens GA, Cai Y, Hinke S, Stange G, Van de Casteele M & Pipeleers D 2005 Glucose suppresses superoxide generation in metabolically responsive pancreatic beta cells. *Journal of Biological Chemistry* **280** 20389–20396. (https://doi.org/10.1074/jbc.M411869200)

Martens GA, Motte E, Kramer G, Stange G, Gaarn LW, Hellemans K, Nielsen JH, Aerts JM, Ling Z & Pipeleers D 2014 Functional characteristics of neonatal rat beta cells with distinct markers. *Journal of Molecular Endocrinology* **52** 11–28. (https://doi.org/10.1530/JME-13-0106)

Martinez-Sanchez A, Nguyen-Tu MS & Rutter GA 2015 DICER inactivation identifies pancreatic beta-cell "disallowed" genes targeted by microRNAs. *Molecular Endocrinology* **29** 1067–1079. (https://doi.org/10.1210/me.2015-1059)

Martinez-Sanchez A, Pullen TJ, Chabosseau P, Zhang Q, Haythorne E, Cane MC, Nguyen-Tu MS, Sayers SR & Rutter GA 2016 Disallowance of Acot7 in beta-cells is required for normal glucose tolerance and insulin secretion. *Diabetes* **65** 1268–1282. (https://doi.org/10.2337/db15-1240)

Martinez SC, Cras-Meneur C, Bernal-Mizrachi E & Permutt MA 2006 Glucose regulates Foxo1 through insulin receptor signaling in the pancreatic islet beta-cell. *Diabetes* **55** 1581–1591. (https://doi.org/10.2337/db05-0678)

Martinez SC, Tanabe K, Cras-Meneur C, Abumrad NA, Bernal-Mizrachi E & Permutt MA 2008 Inhibition of Foxo1 protects pancreatic islet beta-cells against fatty acid and endoplasmic reticulum stress-induced apoptosis. *Diabetes* **57** 846–859. (https://doi.org/10.2337/db07-0595)

Masini M, Marselli L, Bugliani M, Martino L, Masiello P, Marchetti P & De Tata V 2012 Ultrastructural morphometric analysis of insulin secretory granules in human type 2 diabetes. *Acta Diabetologica* **49** (Supplement 1) S247–S252. (https://doi.org/10.1007/s00592-012-0446-6)

Matschinsky FM 2009 Assessing the potential of glucokinase activators in diabetes therapy. *Nature Reviews Drug Discovery* **8** 399–416. (https://doi.org/10.1038/nrd2850)

Matsuoka TA, Kaneto H, Miyatsuka T, Yamamoto T, Yamamoto K, Kato K, Shimomura I, Stein R & Matsuhisa M 2010 Regulation of MafA expression in pancreatic beta-cells in db/db mice with diabetes. *Diabetes* **59** 1709–1720. (https://doi.org/10.2337/db08-0693)

Melkman-Zehavi T, Oren R, Kredo-Russo S, Shapira T, Mandelbaum AD, Rivkin N, Nir T, Lennox KA, Behlke MA, Dor Y, *et al*. 2011 miRNAs control insulin content in pancreatic beta-cells via downregulation of transcriptional repressors. *EMBO Journal* **30** 835–845. (https://doi.org/10.1038/emboj.2010.361)

Mitchell RK, Nguyen-Tu MS, Chabosseau P, Callingham RM, Pullen TJ, Cheung R, Leclerc I, Hodson DJ & Rutter GA 2017 The transcription factor Pax6 is required for pancreatic beta cell identity, glucose-regulated ATP synthesis, and Ca2+ dynamics in adult mice. *Journal of Biological Chemistry* **292** 8892–8906. (https://doi.org/10.1074/jbc.M117.784629)

Moates JM, Nanda S, Cissell MA, Tsai MJ & Stein R 2003 BETA2 activates transcription from the upstream glucokinase gene promoter in islet beta-cells and gut endocrine cells. *Diabetes* **52** 403–408. (https://doi.org/10.2337/diabetes.52.2.403)

Molina J, Rodriguez-Diaz R, Fachado A, Jacques-Silva MC, Berggren PO & Caicedo A 2014 Control of insulin secretion by cholinergic signaling in the human pancreatic islet. *Diabetes* **63** 2714–2726. (https://doi.org/10.2337/db13-1371)

Moore CE, Omikorede O, Gomez E, Willars GB & Herbert TP 2011 PERK activation at low glucose concentration is mediated by SERCA pump inhibition and confers preemptive cytoprotection to pancreatic beta-cells. *Molecular Endocrinology* **25** 315–326. (https://doi.org/10.1210/me.2010-0309)

Moran A, Zhang HJ, Olson LK, Harmon JS, Poitout V & Robertson RP 1997 Differentiation of glucose toxicity from beta cell exhaustion during the evolution of defective insulin gene expression in the pancreatic islet cell line, HIT-T15. *Journal of Clinical Investigation* **99** 534–539. (https://doi.org/10.1172/JCI119190)

Movassat J, Saulnier C, Serradas P & Portha B 1997 Impaired development of pancreatic beta-cell mass is a primary event during the progression to diabetes in the GK rat. *Diabetologia* **40** 916–925. (https://doi.org/10.1007/s001250050768)

Nagamatsu S, Nakamichi Y, Yamamura C, Matsushima S, Watanabe T, Ozawa S, Furukawa H & Ishida H 1999 Decreased expression of t-SNARE, syntaxin 1, and SNAP-25 in pancreatic beta-cells is involved in impaired insulin secretion from diabetic GK rat islets: restoration of decreased t-SNARE proteins improves impaired insulin secretion. *Diabetes* **48** 2367–2373. (https://doi.org/10.2337/diabetes.48.12.2367)

Nair R, Teo WS, Mittal V & Swarbrick A 2014 ID proteins regulate diverse aspects of cancer progression and provide novel therapeutic opportunities. *Molecular Therapy* **22** 1407–1415. (https://doi.org/10.1038/mt.2014.83)

Nesca V, Guay C, Jacovetti C, Menoud V, Peyot ML, Laybutt DR, Prentki M & Regazzi R 2013 Identification of particular groups of microRNAs that positively or negatively impact on beta cell function in obese models of type 2 diabetes. *Diabetologia* **56** 2203–2212. (https://doi.org/10.1007/s00125-013-2993-y)

Nesher R, Gross DJ, Donath MY, Cerasi E & Kaiser N 1999 Interaction between genetic and dietary factors determines β-cell function in

Psammomys obesus, an animal model of type 2 diabetes. *Diabetes* **48** 731–737. (https://doi.org/10.2337/diabetes.48.4.731)

Newgard CB 1996 Regulatory role of glucose transport and phosphorylation in pancreatic islet β-cells. *Diabetes Reviews* **4** 191–206.

Newgard CB & McGarry JD 1995 Metabolic coupling factors in pancreatic β-cell signal transduction. *Annual Review of Biochemistry* **64** 689–719. (https://doi.org/10.1146/annurev.bi.64.070195.003353)

Nielsen K, Karlsen AE, Deckert M, Madsen OD, Serup P, Mandrup-Poulsen T & Nerup J 1999 Beta-cell maturation leads to in vitro sensitivity to cytotoxins. *Diabetes* **48** 2324–2332. (https://doi.org/10.2337/diabetes.48.12.2324)

Nielsen K, Kruhoffer M, Orntoft T, Sparre T, Wang H, Wollheim C, Jorgensen MC, Nerup J & Karlsen AE 2004 Gene expression profiles during beta cell maturation and after IL-1beta exposure reveal important roles of Pdx-1 and Nkx6.1 for IL-1beta sensitivity. *Diabetologia* **47** 2185–2199. (https://doi.org/10.1007/s00125-004-1578-1)

Nordmann TM, Dror E, Schulze F, Traub S, Berishvili E, Barbieux C, Boni-Schnetzler M & Donath MY 2017 The role of inflammation in beta-cell dedifferentiation. *Scientific Reports* **7** 6285. (https://doi.org/10.1038/s41598-017-06731-w)

Oberkofler H, Hafner M, Felder T, Krempler F & Patsch W 2009 Transcriptional co-activator peroxisome proliferator-activated receptor (PPAR)gamma co-activator-1beta is involved in the regulation of glucose-stimulated insulin secretion in INS-1E cells. *Journal of Molecular Medicine* **87** 299–306. (https://doi.org/10.1007/s00109-008-0425-0)

Ofori JK, Salunkhe VA, Bagge A, Vishnu N, Nagao M, Mulder H, Wollheim CB, Eliasson L & Esguerra JL 2017 Elevated miR-130a/miR130b/miR-152 expression reduces intracellular ATP levels in the pancreatic beta cell. *Scientific Reports* **7** 44986. (https://doi.org/10.1038/srep44986)

Okamoto H, Hribal ML, Lin HV, Bennett WR, Ward A & Accili D 2006 Role of the forkhead protein FoxO1 in beta cell compensation to insulin resistance. *Journal of Clinical Investigation* **116** 775–782. (https://doi.org/10.1172/JCI24967)

Okauchi S, Shimoda M, Obata A, Kimura T, Hirukawa H, Kohara K, Mune T, Kaku K & Kaneto H 2016 Protective effects of SGLT2 inhibitor luseogliflozin on pancreatic beta-cells in obese type 2 diabetic db/db mice. *Biochemical and Biophysical Research Communications* **470** 772–782. (https://doi.org/10.1016/j.bbrc.2015.10.109)

Olson LK, Sharma A, Peshavaria M, Wright CV, Towle HC, Rodertson RP & Stein R 1995 Reduction of insulin gene transcription in HIT-T15 beta cells chronically exposed to a supraphysiologic glucose concentration is associated with loss of STF-1 transcription factor expression. *PNAS* **92** 9127–9131. (https://doi.org/10.1073/pnas.92.20.9127)

Olson LK, Qian J & Poitout V 1998 Glucose rapidly and reversibly decreases INS-1 cell insulin gene transcription via decrements in STF-1 and C1 activator transcription factor activity. *Molecular Endocrinology* **12** 207–219. (https://doi.org/10.1210/mend.12.2.0066)

Omikorede O, Qi C, Gorman T, Chapman P, Yu A, Smith DM & Herbert TP 2013 ER stress in rodent islets of Langerhans is concomitant with obesity and beta-cell compensation but not with beta-cell dysfunction and diabetes. *Nutrition and Diabetes* **3** e93. (https://doi.org/10.1038/nutd.2013.35)

Ostenson CG, Gaisano H, Sheu L, Tibell A & Bartfai T 2006 Impaired gene and protein expression of exocytotic soluble N-ethylmaleimide attachment protein receptor complex proteins in pancreatic islets of type 2 diabetic patients. *Diabetes* **55** 435–440. (https://doi.org/10.2337/diabetes.55.02.06.db04-1575)

Otonkoski T, Jiao H, Kaminen-Ahola N, Tapia-Paez I, Ullah MS, Parton LE, Schuit F, Quintens R, Sipila I, Mayatepek E, *et al.* 2007 Physical exercise-induced hypoglycemia caused by failed silencing of monocarboxylate transporter 1 in pancreatic beta cells. *American Journal of Human Genetics* **81** 467–474. (https://doi.org/10.1086/520960)

Oyadomari S, Koizumi A, Takeda K, Gotoh T, Akira S, Araki E & Mori M 2002 Targeted disruption of the Chop gene delays endoplasmic reticulum stress-mediated diabetes. *Journal of Clinical Investigation* **109** 525–532. (https://doi.org/10.1172/JCI0214550)

Parton LE, McMillen PJ, Shen Y, Docherty E, Sharpe E, Diraison F, Briscoe CP & Rutter GA 2006 Limited role for SREBP-1c in defective glucose-induced insulin secretion from Zucker diabetic fatty rat islets: a functional and gene profiling analysis. *American Journal of Physiology: Endocrinology and Metabolism* **291** E982–E994. (https://doi.org/10.1152/ajpendo.00067.2006)

Pascal SM, Guiot Y, Pelengaris S, Khan M & Jonas JC 2008 Effects of c-MYC activation on glucose stimulus-secretion coupling events in mouse pancreatic islets. *American Journal of Physiology: Endocrinology and Metabolism* **295** E92–E102. (https://doi.org/10.1152/ajpendo.90235.2008)

Pascal SM, Veiga-da-Cunha M, Gilon P, Van Schaftingen E & Jonas JC 2010 Effects of fructosamine-3-kinase deficiency on function and survival of mouse pancreatic islets after prolonged culture in high glucose or ribose concentrations. *American Journal of Physiology: Endocrinology and Metabolism* **298** E586–E596. (https://doi.org/10.1152/ajpendo.00503.2009)

Pedersen JK, Nelson SB, Jorgensen MC, Henseleit KD, Fujitani Y, Wright CV, Sander M, Serup P & Beta Cell Biology Consortium 2005 Endodermal expression of Nkx6 genes depends differentially on Pdx1. *Developmental Biology* **288** 487–501. (https://doi.org/10.1016/j.ydbio.2005.10.001)

Pertusa JA, Nesher R, Kaiser N, Cerasi E, Henquin JC & Jonas JC 2002 Increased glucose sensitivity of stimulus-secretion coupling in islets from Psammomys obesus after diet induction of diabetes. *Diabetes* **51** 2552–2560. (https://doi.org/10.2337/diabetes.51.8.2552)

Pi J, Bai Y, Zhang Q, Wong V, Floering LM, Daniel K, Reece JM, Deeney JT, Andersen ME, Corkey BE, *et al.* 2007 Reactive oxygen species as a signal in glucose-stimulated insulin secretion. *Diabetes* **56** 1783–1791. (https://doi.org/10.2337/db06-1601)

Piccand J, Strasser P, Hodson DJ, Meunier A, Ye T, Keime C, Birling MC, Rutter GA & Gradwohl G 2014 Rfx6 maintains the functional identity of adult pancreatic beta cells. *Cell Reports* **9** 2219–2232. (https://doi.org/10.1016/j.celrep.2014.11.033)

Pick A, Clark J, Kubstrup C, Levisetti M, Pugh W, Bonner-Weir S & Polonsky KS 1998 Role of apoptosis in failure of beta-cell mass compensation for insulin resistance and beta-cell defects in the male Zucker diabetic fatty rat. *Diabetes* **47** 358–364. (https://doi.org/10.2337/diabetes.47.3.358)

Pildes RS, Hart RJ, Warrner R & Cornblath M 1969 Plasma insulin response during oral glucose tolerance tests in newborns of normal and gestational diabetic mothers. *Pediatrics* **44** 76–83.

Pino MF, Ye DZ, Linning KD, Green CD, Wicksteed B, Poitout V & Olson LK 2005 Elevated glucose attenuates human insulin gene promoter activity in INS-1 pancreatic beta-cells via reduced nuclear factor binding to the A5/core and Z element. *Molecular Endocrinology* **19** 1343–1360. (https://doi.org/10.1210/me.2003-0493)

Piro S, Anello M, Di Pietro C, Lizzio MN, Patane G, Rabuazzo AM, Vigneri R, Purrello M & Purrello F 2002 Chronic exposure to free fatty acids or high glucose induces apoptosis in rat pancreatic islets: possible role of oxidative stress. *Metabolism* **51** 1340–1347. (https://doi.org/10.1053/meta.2002.35200)

Pirot P, Naamane N, Libert F, Magnusson NE, Orntoft TF, Cardozo AK & Eizirik DL 2007 Global profiling of genes modified by endoplasmic reticulum stress in pancreatic beta cells reveals the early degradation of insulin mRNAs. *Diabetologia* **50** 1006–1014. (https://doi.org/10.1007/s00125-007-0609-0)

Poitout V, Olson LK & Robertson RP 1996 Chronic exposure of betaTC-6 cells to supraphysiologic concentrations of glucose decreases binding

of the RIPE3b1 insulin gene transcription activator. *Journal of Clinical Investigation* **97** 1041–1046. (https://doi.org/10.1172/JCI118496)

Poy MN, Eliasson L, Krutzfeldt J, Kuwajima S, Ma X, Macdonald PE, Pfeffer S, Tuschl T, Rajewsky N, Rorsman P, *et al*. 2004 A pancreatic islet-specific microRNA regulates insulin secretion. *Nature* **432** 226–230. (https://doi.org/10.1038/nature03076)

Pullen TJ, Khan AM, Barton G, Butcher SA, Sun G & Rutter GA 2010 Identification of genes selectively disallowed in the pancreatic islet. *Islets* **2** 89–95. (https://doi.org/10.4161/isl.2.2.11025)

Pullen TJ, da Silva Xavier G, Kelsey G & Rutter GA 2011 miR-29a and miR-29b contribute to pancreatic beta-cell-specific silencing of monocarboxylate transporter 1 (Mct1). *Molecular and Cellular Biology* **31** 3182–3194. (https://doi.org/10.1128/MCB.01433-10)

Pullen TJ, Sylow L, Sun G, Halestrap AP, Richter EA & Rutter GA 2012 Overexpression of monocarboxylate transporter-1 (SLC16A1) in mouse pancreatic beta-cells leads to relative hyperinsulinism during exercise. *Diabetes* **61** 1719–1725. (https://doi.org/10.2337/db11-1531)

Pullen TJ, Huising MO & Rutter GA 2017 Analysis of purified pancreatic islet beta and alpha cell transcriptomes reveals 11beta-hydroxysteroid dehydrogenase (Hsd11b1) as a novel disallowed gene. *Frontiers in Genetics* **8** 41.

Puri S & Hebrok M 2010 Cellular plasticity within the pancreas – lessons learned from development. *Developmental Cell* **18** 342–356. (https://doi.org/10.1016/j.devcel.2010.02.005)

Puri S, Akiyama H & Hebrok M 2013 VHL-mediated disruption of Sox9 activity compromises beta-cell identity and results in diabetes mellitus. *Genes and Development* **27** 2563–2575. (https://doi.org/10.1101/gad.227785.113)

Qian B, Wang H, Men X, Zhang W, Cai H, Xu S, Xu Y, Ye L, Wollheim CB & Lou J 2008 TRIB3 is implicated in glucotoxicity- and ER-stress-induced beta-cell apoptosis. *Journal of Endocrinology* **199** 407–416. (https://doi.org/10.1677/JOE-08-0331)

Rahier J, Guiot Y, Goebbels RM, Sempoux C & Henquin JC 2008 Pancreatic β-cell mass in European subjects with type 2 diabetes. *Diabetes, Obesity and Metabolism* **10** (Supplement 4) 32–42. (https://doi.org/10.1111/j.1463-1326.2008.00969.x)

Robertson RP & Harmon JS 2006 Diabetes, glucose toxicity, and oxidative stress: a case of double jeopardy for the pancreatic islet beta cell. *Free Radical Biology and Medicine* **41** 177–184. (https://doi.org/10.1016/j.freeradbiomed.2005.04.030)

Robertson RP, Zhang HJ, Pyzdrowski KL & Walseth TF 1992 Preservation of insulin mRNA levels and insulin secretion in HIT cells by avoidance of chronic exposure to high glucose concentrations. *Journal of Clinical Investigation* **90** 320–325. (https://doi.org/10.1172/JCI115865)

Robson SC, Ward L, Brown H, Turner H, Hunter E, Pelengaris S & Khan M 2011 Deciphering c-MYC-regulated genes in two distinct tissues. *BMC Genomics* **12** 476. (https://doi.org/10.1186/1471-2164-12-476)

Roche E, Assimacopoulos-Jeannet F, Witters LA, Perruchoud B, Yaney G, Corkey B, Asfari M & Prentki M 1997 Induction by glucose of genes coding for glycolytic enzymes in a pancreatic beta-cell line (INS-1). *Journal of Biological Chemistry* **272** 3091–3098. (https://doi.org/10.1074/jbc.272.5.3091)

Roduit R, Morin J, Masse F, Segall L, Roche E, Newgard CB, Assimacopoulos-Jeannet F & Prentki M 2000 Glucose down-regulates the expression of the peroxisome proliferator-activated receptor-alpha gene in the pancreatic beta -cell. *Journal of Biological Chemistry* **275** 35799–35806. (https://doi.org/10.1074/jbc.M006001200)

Roesch A, Paschen A, Landsberg J, Helfrich I, Becker JC & Schadendorf D 2016 Phenotypic tumour cell plasticity as a resistance mechanism and therapeutic target in melanoma. *European Journal of Cancer* **59** 109–112. (https://doi.org/10.1016/j.ejca.2016.02.023)

Roma LP, Duprez J, Takahashi HK, Gilon P, Wiederkehr A & Jonas JC 2012 Dynamic measurements of mitochondrial hydrogen peroxide concentration and glutathione redox state in rat pancreatic beta-cells using ratiometric fluorescent proteins: confounding effects of pH with HyPer but not roGFP1. *Biochemical Journal* **441** 971–978. (https://doi.org/10.1042/BJ20111770)

Rorsman P, Arkhammar P, Bokvist K, Hellerstrom C, Nilsson T, Welsh M, Welsh N & Berggren PO 1989 Failure of glucose to elicit a normal secretory response in fetal pancreatic beta cells results from glucose insensitivity of the ATP-regulated K+ channels. *PNAS* **86** 4505–4509. (https://doi.org/10.1073/pnas.86.12.4505)

Rutter GA, Pullen TJ, Hodson DJ & Martinez-Sanchez A 2015 Pancreatic beta-cell identity, glucose sensing and the control of insulin secretion. *Biochemical Journal* **466** 203–218. (https://doi.org/10.1042/BJ20141384)

Sakuraba H, Mizukami H, Yagihashi N, Wada R, Hanyu C & Yagihashi S 2002 Reduced beta-cell mass and expression of oxidative stress-related DNA damage in the islet of Japanese Type II diabetic patients. *Diabetologia* **45** 85–96. (https://doi.org/10.1007/s125-002-8248-z)

Samaras SE, Cissell MA, Gerrish K, Wright CV, Gannon M & Stein R 2002 Conserved sequences in a tissue-specific regulatory region of the pdx-1 gene mediate transcription in Pancreatic beta cells: role for hepatocyte nuclear factor 3 beta and Pax6. *Molecular and Cellular Biology* **22** 4702–4713. (https://doi.org/10.1128/MCB.22.13.4702-4713.2002)

Samaras SE, Zhao L, Means A, Henderson E, Matsuoka TA & Stein R 2003 The islet beta cell-enriched RIPE3b1/Maf transcription factor regulates pdx-1 expression. *Journal of Biological Chemistry* **278** 12263–12270. (https://doi.org/10.1074/jbc.M210801200)

Sarre A, Gabrielli J, Vial G, Leverve XM & Assimacopoulos-Jeannet F 2012 Reactive oxygen species are produced at low glucose and contribute to the activation of AMPK in insulin-secreting cells. *Free Radical Biology and Medicine* **52** 142–150. (https://doi.org/10.1016/j.freeradbiomed.2011.10.437)

Sasaki M, Fujimoto S, Sato Y, Nishi Y, Mukai E, Yamano G, Sato H, Tahara Y, Ogura K, Nagashima K, *et al*. 2013 Reduction of reactive oxygen species ameliorates metabolism-secretion coupling in islets of diabetic GK rats by suppressing lactate overproduction. *Diabetes* **62** 1996–2003. (https://doi.org/10.2337/db12-0903)

Sato Y, Endo H, Okuyama H, Takeda T, Iwahashi H, Imagawa A, Yamagata K, Shimomura I & Inoue M 2011 Cellular hypoxia of pancreatic β-cells due to high levels of oxygen consumption for insulin secretion in vitro. *Journal of Biological Chemistry* **286** 12524–12532. (https://doi.org/10.1074/jbc.M110.194738)

Sato Y, Inoue M, Yoshizawa T & Yamagata K 2014 Moderate hypoxia induces beta-cell dysfunction with HIF-1-independent gene expression changes. *PLoS ONE* **9** e114868. (https://doi.org/10.1371/journal.pone.0114868)

Sato Y, Tsuyama T, Sato C, Karim MF, Yoshizawa T, Inoue M & Yamagata K 2017 Hypoxia reduces HNF4alpha/MODY1 protein expression in pancreatic beta-cells by activating AMP-activated protein kinase. *Journal of Biological Chemistry* **292** 8716–8728. (https://doi.org/10.1074/jbc.M116.767574)

Saxena G, Chen J & Shalev A 2010 Intracellular shuttling and mitochondrial function of thioredoxin-interacting protein. *Journal of Biological Chemistry* **285** 3997–4005. (https://doi.org/10.1074/jbc.M109.034421)

Schaffer AE, Taylor BL, Benthuysen JR, Liu J, Thorel F, Yuan W, Jiao Y, Kaestner KH, Herrera PL, Magnuson MA, *et al*. 2013 Nkx6.1 controls a gene regulatory network required for establishing and maintaining pancreatic Beta cell identity. *PLoS Genetics* **9** e1003274. (https://doi.org/10.1371/journal.pgen.1003274)

Schroder M & Kaufman RJ 2005 ER stress and the unfolded protein response. *Mutation Research* **569** 29–63. (https://doi.org/10.1016/j.mrfmmm.2004.06.056)

Schuit FC, In't Veld PA & Pipeleers DG 1988 Glucose stimulates proinsulin biosynthesis by a dose-dependent recruitment of pancreatic beta cells. *PNAS* **85** 3865–3869. (https://doi.org/10.1073/pnas.85.11.3865)

Schuit F, De Vos A, Farfari S, Moens K, Pipeleers D, Brun T & Prentki M 1997 Metabolic fate of glucose in purified islet cells. Glucose-regulated anaplerosis in beta cells. *Journal of Biological Chemistry* **272** 18572–18579. (https://doi.org/10.1074/jbc.272.30.18572)

Schuit F, Moens K, Heimberg H & Pipeleers D 1999 Cellular origin of hexokinase in pancreatic islets. *Journal of Biological Chemistry* **274** 32803–32809. (https://doi.org/10.1074/jbc.274.46.32803)

Schuit F, Flamez D, De Vos A & Pipeleers D 2002 Glucose-regulated gene expression maintaining the glucose-responsive state of beta-cells. *Diabetes* **51** (Supplement 3) S326–S332. (https://doi.org/10.2337/diabetes.51.2007.S326)

Schuit F, Van Lommel L, Granvik M, Goyvaerts L, de Faudeur G, Schraenen A & Lemaire K 2012 beta-cell-specific gene repression: a mechanism to protect against inappropriate or maladjusted insulin secretion? *Diabetes* **61** 969–975. (https://doi.org/10.2337/db11-1564)

Sebastiani G, Po A, Miele E, Ventriglia G, Ceccarelli E, Bugliani M, Marselli L, Marchetti P, Gulino A, Ferretti E, *et al*. 2015 MicroRNA-124a is hyperexpressed in type 2 diabetic human pancreatic islets and negatively regulates insulin secretion. *Acta Diabetologica* **52** 523–530. (https://doi.org/10.1007/s00592-014-0675-y)

Sekine N, Cirulli V, Regazzi R, Brown LJ, Gine E, Tamarit-Rodriguez J, Girotti M, Marie S, MacDonald MJ & Wollheim CB 1994 Low lactate dehydrogenase and high mitochondrial glycerol phosphate dehydrogenase in pancreatic β-cells. Potential role in nutrient sensing. *Journal of Biological Chemistry* **269** 4895–4902.

Seo HY, Kim YD, Lee KM, Min AK, Kim MK, Kim HS, Won KC, Park JY, Lee KU, Choi HS, *et al*. 2008 Endoplasmic reticulum stress-induced activation of activating transcription factor 6 decreases insulin gene expression via up-regulation of orphan nuclear receptor small heterodimer partner. *Endocrinology* **149** 3832–3841. (https://doi.org/10.1210/en.2008-0015)

Seufert J, Weir GC & Habener JF 1998 Differential expression of the insulin gene transcriptional repressor CCAAT/enhancer-binding protein beta and transactivator islet duodenum homeobox-1 in rat pancreatic beta cells during the development of diabetes mellitus. *Journal of Clinical Investigation* **101** 2528–2539. (https://doi.org/10.1172/JCI2401)

Seymour PA & Sander M 2011 Historical perspective: beginnings of the beta-cell: current perspectives in beta-cell development. *Diabetes* **60** 364–376. (https://doi.org/10.2337/db10-1068)

Shalev A, Pise-Masison CA, Radonovich M, Hoffmann SC, Hirshberg B, Brady JN & Harlan DM 2002 Oligonucleotide microarray analysis of intact human pancreatic islets: identification of glucose-responsive genes and a highly regulated TGFbeta signaling pathway. *Endocrinology* **143** 3695–3698. (https://doi.org/10.1210/en.2002-220564)

Sharma A, Olson LK, Robertson RP & Stein R 1995 The reduction of insulin gene transcription in HIT-T15 beta cells chronically exposed to high glucose concentration is associated with the loss of RIPE3b1 and STF-1 transcription factor expression. *Molecular Endocrinology* **9** 1127–1134.

Sheng C, Li F, Lin Z, Zhang M, Yang P, Bu L, Sheng H, Li H & Qu S 2016 Reversibility of beta-cell-specific transcript factors expression by long-term caloric restriction in db/db mouse. *Journal of Diabetes Research* **2016** 6035046.

Shih DQ, Screenan S, Munoz KN, Philipson L, Pontoglio M, Yaniv M, Polonsky KS & Stoffel M 2001 Loss of HNF-1alpha function in mice leads to abnormal expression of genes involved in pancreatic islet development and metabolism. *Diabetes* **50** 2472–2480. (https://doi.org/10.2337/diabetes.50.11.2472)

Shih DQ, Heimesaat M, Kuwajima S, Stein R, Wright CV & Stoffel M 2002 Profound defects in pancreatic beta-cell function in mice with combined heterozygous mutations in Pdx-1, Hnf-1alpha, and Hnf-3beta. *PNAS* **99** 3818–3823. (https://doi.org/10.1073/pnas.062605899)

Shojima N, Hara K, Fujita H, Horikoshi M, Takahashi N, Takamoto I, Ohsugi M, Aburatani H, Noda M, Kubota N, *et al*. 2012 Depletion of

homeodomain-interacting protein kinase 3 impairs insulin secretion and glucose tolerance in mice. *Diabetologia* **55** 3318–3330. (https://doi.org/10.1007/s00125-012-2711-1)

Shu L, Matveyenko AV, Kerr-Conte J, Cho JH, McIntosh CH & Maedler K 2009 Decreased TCF7L2 protein levels in type 2 diabetes mellitus correlate with downregulation of GIP- and GLP-1 receptors and impaired beta-cell function. *Human Molecular Genetics* **18** 2388–2399. (https://doi.org/10.1093/hmg/ddp178)

Song B, Scheuner D, Ron D, Pennathur S & Kaufman RJ 2008 Chop deletion reduces oxidative stress, improves beta cell function, and promotes cell survival in multiple mouse models of diabetes. *Journal of Clinical Investigation* **118** 3378–3389. (https://doi.org/10.1172/JCI34587)

Spijker HS, Ravelli RB, Mommaas-Kienhuis AM, van Apeldoorn AA, Engelse MA, Zaldumbide A, Bonner-Weir S, Rabelink TJ, Hoeben RC, Clevers H, *et al*. 2013 Conversion of mature human beta-cells into glucagon-producing alpha-cells. *Diabetes* **62** 2471–2480. (https://doi.org/10.2337/db12-1001)

Spijker HS, Song H, Ellenbroek JH, Roefs MM, Engelse MA, Bos E, Koster AJ, Rabelink TJ, Hansen BC, Clark A, *et al*. 2015 Loss of beta-cell identity occurs in type 2 diabetes and is associated with islet amyloid deposits. *Diabetes* **64** 2928–2938. (https://doi.org/10.2337/db14-1752)

Stancill JS, Cartailler JP, Clayton HW, O'Connor JT, Dickerson MT, Dadi PK, Osipovich AB, Jacobson DA & Magnuson MA 2017 Chronic beta-cell depolarization impairs beta-cell identity by disrupting a network of Ca2+-regulated genes. *Diabetes* **66** 2175–2187. (https://doi.org/10.2337/db16-1355)

Stanger BZ & Hebrok M 2013 Control of cell identity in pancreas development and regeneration. *Gastroenterology* **144** 1170–1179. (https://doi.org/10.1053/j.gastro.2013.01.074)

Sun LL, Jiang BG, Li WT, Zou JJ, Shi YQ & Liu ZM 2011 MicroRNA-15a positively regulates insulin synthesis by inhibiting uncoupling protein-2 expression. *Diabetes Research and Clinical Practice* **91** 94–100. (https://doi.org/10.1016/j.diabres.2010.11.006)

Sund NJ, Vatamaniuk MZ, Casey M, Ang SL, Magnuson MA, Stoffers DA, Matschinsky FM & Kaestner KH 2001 Tissue-specific deletion of Foxa2 in pancreatic beta cells results in hyperinsulinemic hypoglycemia. *Genes and Development* **15** 1706–1715. (https://doi.org/10.1101/gad.901601)

Swisa A, Avrahami D, Eden N, Zhang J, Feleke E, Dahan T, Cohen-Tayar Y, Stolovich-Rain M, Kaestner KH, Glaser B, *et al*. 2017 PAX6 maintains beta cell identity by repressing genes of alternative islet cell types. *Journal of Clinical Investigation* **127** 230–243. (https://doi.org/10.1172/JCI88015)

Synofzik M, Haack TB, Kopajtich R, Gorza M, Rapaport D, Greiner M, Schonfeld C, Freiberg C, Schorr S, Holl RW, *et al*. 2014 Absence of BiP co-chaperone DNAJC3 causes diabetes mellitus and multisystemic neurodegeneration. *American Journal of Human Genetics* **95** 689–697. (https://doi.org/10.1016/j.ajhg.2014.10.013)

Szabat M, Kalynyak TB, Lim GE, Chu KY, Yang YH, Asadi A, Gage BK, Ao Z, Warnock GL, Piret JM, *et al*. 2011 Musashi expression in beta-cells coordinates insulin expression, apoptosis and proliferation in response to endoplasmic reticulum stress in diabetes. *Cell Death and Disease* **2** e232. (https://doi.org/10.1038/cddis.2011.119)

Talchai C, Xuan S, Lin HV, Sussel L & Accili D 2012 Pancreatic beta cell dedifferentiation as a mechanism of diabetic beta cell failure. *Cell* **150** 1223–1234. (https://doi.org/10.1016/j.cell.2012.07.029)

Tan C, Tuch BE, Tu J & Brown SA 2002 Role of NADH shuttles in glucose-induced insulin secretion from fetal beta-cells. *Diabetes* **51** 2989–2996. (https://doi.org/10.2337/diabetes.51.10.2989)

Tanaka Y, Gleason CE, Tran PO, Harmon JS & Robertson RP 1999 Prevention of glucose toxicity in HIT-T15 cells and Zucker diabetic fatty rats by antioxidants. *PNAS* **96** 10857–10862. (https://doi.org/10.1073/pnas.96.19.10857)

Taneera J, Lang S, Sharma A, Fadista J, Zhou Y, Ahlqvist E, Jonsson A, Lyssenko V, Vikman P, Hansson O, *et al.* 2012 A systems genetics approach identifies genes and pathways for type 2 diabetes in human islets. *Cell Metabolism* **16** 122–134. (https://doi.org/10.1016/j.cmet.2012.06.006)

Tang X, Muniappan L, Tang G & Ozcan S 2009 Identification of glucose-regulated miRNAs from pancreatic {beta} cells reveals a role for miR-30d in insulin transcription. *RNA* **15** 287–293. (https://doi.org/10.1261/rna.1211209)

Tang C, Koulajian K, Schuiki I, Zhang L, Desai T, Ivovic A, Wang P, Robson-Doucette C, Wheeler MB, Minassian B, *et al.* 2012 Glucose-induced beta cell dysfunction in vivo in rats: link between oxidative stress and endoplasmic reticulum stress. *Diabetologia*.

Taylor BL, Liu FF & Sander M 2013 Nkx6.1 is essential for maintaining the functional state of pancreatic beta cells. *Cell Reports* **4** 1262–1275. (https://doi.org/10.1016/j.celrep.2013.08.010)

Thorens B 2015 GLUT2, glucose sensing and glucose homeostasis. *Diabetologia* **58** 221–232. (https://doi.org/10.1007/s00125-014-3451-1)

Thorens B, Wu YJ, Leahy JL & Weir GC 1992 The loss of GLUT2 expression by glucose-unresponsive beta cells of db/db mice is reversible and is induced by the diabetic environment. *Journal of Clinical Investigation* **90** 77–85. (https://doi.org/10.1172/JCI115858)

Thorrez L, Laudadio I, Van Deun K, Quintens R, Hendrickx N, Granvik M, Lemaire K, Schraenen A, Van Lommel L, Lehnert S, *et al.* 2011 Tissue-specific disallowance of housekeeping genes: the other face of cell differentiation. *Genome Research* **21** 95–105. (https://doi.org/10.1101/gr.109173.110)

Tiedge M, Lortz S, Drinkgern J & Lenzen S 1997 Relation between antioxidant enzyme gene expression and antioxidative defense status of insulin-producing cells. *Diabetes* **46** 1733–1742. (https://doi.org/10.2337/diab.46.11.1733)

Tokuyama Y, Sturis J, DePaoli AM, Takeda J, Stoffel M, Tang J, Sun X, Polonsky KS & Bell GI 1995 Evolution of β-cell dysfunction in the male Zucker diabetic fatty rat. *Diabetes* **44** 1447–1457. (https://doi.org/10.2337/diab.44.12.1447)

Tonooka N, Oseid E, Zhou H, Harmon JS & Robertson RP 2007 Glutathione peroxidase protein expression and activity in human islets isolated for transplantation. *Clinical Transplantation* **21** 767–772.

Torrejon-Escribano B, Escoriza J, Montanya E & Blasi J 2011 Glucose-dependent changes in SNARE protein levels in pancreatic beta-cells. *Endocrinology* **152** 1290–1299. (https://doi.org/10.1210/en.2010-0898)

Trinh K, Minassian C, Lange AJ, O'Doherty RM & Newgard CB 1997 Adenovirus-mediated expression of the catalytic subunit of glucose-6-phosphatase in INS-1 cells. Effects on glucose cycling, glucose usage, and insulin secretion. *Journal of Biological Chemistry* **272** 24837–24842. (https://doi.org/10.1074/jbc.272.40.24837)

Van de Casteele M, Kefas BA, Cai Y, Heimberg H, Scott DK, Henquin JC, Pipeleers D & Jonas JC 2003 Prolonged culture in low glucose induces apoptosis of rat pancreatic β-cells through induction of c-myc. *Biochemical and Biophysical Research Communications* **312** 937–944. (https://doi.org/10.1016/j.bbrc.2003.11.013)

Van Lommel L, Janssens K, Quintens R, Tsukamoto K, Vander Mierde D, Lemaire K, Denef C, Jonas JC, Martens G, Pipeleers D, *et al.* 2006 Probe-independent and direct quantification of insulin mRNA and growth hormone mRNA in enriched cell preparations. *Diabetes* **55** 3214–3220. (https://doi.org/10.2337/db06-0774)

Vander Mierde D, Scheuner D, Quintens R, Patel R, Song B, Tsukamoto K, Beullens M, Kaufman RJ, Bollen M & Schuit FC 2007 Glucose activates a protein phosphatase-1-mediated signaling pathway to enhance overall translation in pancreatic β-cells. *Endocrinology* **148** 609–617. (https://doi.org/10.1210/en.2006-1012)

Waeber G, Thompson N, Nicod P & Bonny C 1996 Transcriptional activation of the GLUT2 gene by the IPF-1/STF-1/IDX-1 homeobox factor. *Molecular Endocrinology* **10** 1327–1334.

Walters SN, Luzuriaga J, Chan JY, Grey ST & Laybutt DR 2013 Influence of chronic hyperglycemia on the loss of the unfolded protein response

in transplanted islets. *Journal of Molecular Endocrinology* **51** 225–232. (https://doi.org/10.1530/JME-13-0016)

Wang MY, Koyama K, Shimabukuro M, Mangelsdorf D, Newgard CB & Unger RH 1998 Overexpression of leptin receptors in pancreatic islets of Zucker diabetic fatty rats restores GLUT-2, glucokinase, and glucose-stimulated insulin secretion. *PNAS* **95** 11921–11926. (https://doi.org/10.1073/pnas.95.20.11921)

Wang H, Kouri G & Wollheim CB 2005 ER stress and SREBP-1 activation are implicated in beta-cell glucolipotoxicity. *Journal of Cell Science* **118** 3905–3915. (https://doi.org/10.1242/jcs.02513)

Wang H, Brun T, Kataoka K, Sharma AJ & Wollheim CB 2007 MAFA controls genes implicated in insulin biosynthesis and secretion. *Diabetologia* **50** 348–358. (https://doi.org/10.1007/s00125-006-0490-2)

Wang Z, York NW, Nichols CG & Remedi MS 2014 Pancreatic beta cell dedifferentiation in diabetes and redifferentiation following insulin therapy. *Cell Metabolism* **19** 872–882. (https://doi.org/10.1016/j.cmet.2014.03.010)

Weir GC, Aguayo-Mazzucato C & Bonner-Weir S 2013 beta-cell dedifferentiation in diabetes is important, but what is it? *Islets* **5** 233–237. (https://doi.org/10.4161/isl.27494)

Wice BM, Bernal-Mizrachi E & Permutt MA 2001 Glucose and other insulin secretagogues induce, rather than inhibit, expression of Id-1 and Id-3 in pancreatic islet beta cells. *Diabetologia* **44** 453–463. (https://doi.org/10.1007/s001250051643)

Xu G, Kaneto H, Laybutt DR, Duvivier-Kali VF, Trivedi N, Suzuma K, King GL, Weir GC & Bonner-Weir S 2007 Downregulation of GLP-1 and GIP receptor expression by hyperglycemia: possible contribution to impaired incretin effects in diabetes. *Diabetes* **56** 1551–1558. (https://doi.org/10.2337/db06-1033)

Xu G, Chen J, Jing G & Shalev A 2013 Thioredoxin-interacting protein regulates insulin transcription through microRNA-204. *Nature Medicine* **19** 1141–1146. (https://doi.org/10.1038/nm.3287)

Xu T, Yang L, Yan C, Wang X, Huang P, Zhao F, Zhao L, Zhang M, Jia W, Wang X, *et al.* 2014 The IRE1alpha-XBP1 pathway regulates metabolic stress-induced compensatory proliferation of pancreatic beta-cells. *Cell Research* **24** 1137–1140. (https://doi.org/10.1038/cr.2014.55)

Yang BT, Dayeh TA, Volkov PA, Kirkpatrick CL, Malmgren S, Jing X, Renstrom E, Wollheim CB, Nitert MD & Ling C 2012 Increased DNA methylation and decreased expression of PDX-1 in pancreatic islets from patients with type 2 diabetes. *Molecular Endocrinology* **26** 1203–1212. (https://doi.org/10.1210/me.2012-1004)

Yoon KH, Ko SH, Cho JH, Lee JM, Ahn YB, Song KH, Yoo SJ, Kang MI, Cha BY, Lee KW, *et al.* 2003 Selective β-cell loss and α-cell expansion in patients with type 2 diabetes mellitus in Korea. *Journal of Clinical Endocrinology and Metabolism* **88** 2300–2308. (https://doi.org/10.1210/jc.2002-020735)

Yoshikawa H, Tajiri Y, Sako Y, Hashimato T, Umeda F & Nawata H 2002 Glucosamine-induced beta-cell dysfunction: a possible involvement of glucokinase or glucose-transporter type 2. *Pancreas* **24** 228–234. (https://doi.org/10.1097/00006676-200204000-00004)

Yuan Q, Tang W, Zhang X, Hinson JA, Liu C, Osei K & Wang J 2012 Proinsulin atypical maturation and disposal induces extensive defects in mouse Ins2+/Akita beta-cells. *PLoS ONE* **7** e35098. (https://doi.org/10.1371/journal.pone.0035098)

Zangen DH, Bonner-Weir S, Lee CH, Latimer JB, Miller CP, Habener JF & Weir GC 1997 Reduced insulin, GLUT2, and IDX-1 in beta-cells after partial pancreatectomy. *Diabetes* **46** 258–264. (https://doi.org/10.2337/diab.46.2.258)

Zhang CY, Baffy G, Perret P, Krauss S, Peroni O, Grujic D, Hagen T, Vidal-Puig AJ, Boss O, Kim YB, *et al.* 2001 Uncoupling protein-2 negatively regulates insulin secretion and is a major link between obesity, beta cell dysfunction, and type 2 diabetes. *Cell* **105** 745–755. (https://doi.org/10.1016/S0092-8674(01)00378-6)

Zhang P, McGrath B, Li S, Frank A, Zambito F, Reinert J, Gannon M, Ma K, McNaughton K & Cavener DR 2002*a* The PERK eukaryotic initiation factor 2 alpha kinase is required for the development of the

skeletal system, postnatal growth, and the function and viability of the pancreas. *Molecular and Cellular Biology* **22** 3864–3874. (https://doi.org/10.1128/MCB.22.11.3864-3874.2002)

Zhang W, Khan A, Ostenson CG, Berggren PO, Efendic S & Meister B 2002*b* Down-regulated expression of exocytotic proteins in pancreatic islets of diabetic GK rats. *Biochemical and Biophysical Research Communications* **291** 1038–1044. (https://doi.org/10.1006/bbrc.2002.6555)

Zhang C, Moriguchi T, Kajihara M, Esaki R, Harada A, Shimohata H, Oishi H, Hamada M, Morito N, Hasegawa K, *et al.* 2005 MafA is a key regulator of glucose-stimulated insulin secretion. *Molecular and Cellular Biology* **25** 4969–4976. (https://doi.org/10.1128/MCB.25.12.4969-4976.2005)

Zhang T, Kim DH, Xiao X, Lee S, Gong Z, Muzumdar R, Calabuig-Navarro V, Yamauchi J, Harashima H, Wang R, *et al.* 2016 FoxO1 plays an important role in regulating beta-cell compensation for insulin resistance in male mice. *Endocrinology* **157** 1055–1070. (https://doi.org/10.1210/en.2015-1852)

Zhao C, Wilson MC, Schuit F, Halestrap AP & Rutter GA 2001 Expression and distribution of lactate/monocarboxylate transporter isoforms in pancreatic islets and the exocrine pancreas. *Diabetes* **50** 361–366. (https://doi.org/10.2337/diabetes.50.2.361)

Zhao X, Mohan R, Ozcan S & Tang X 2012 MicroRNA-30d induces insulin transcription factor MafA and insulin production by targeting mitogen-activated protein 4 kinase 4 (MAP4K4) in pancreatic beta-cells. *Journal of Biological Chemistry* **287** 31155–31164. (https://doi.org/10.1074/jbc.M112.362632)

Zhou YP, Marlen K, Palma JF, Schweitzer A, Reilly L, Gregoire FM, Xu GG, Blume JE & Johnson JD 2003 Overexpression of repressive cAMP response element modulators in high glucose and fatty acid-treated rat islets A common mechanism for glucose toxicity and lipotoxicity? *Journal of Biological Chemistry* **278** 51316–51323. (https://doi.org/10.1074/jbc.M307972200)