Sweet and Sour β-Cells: ROS and Hif1α Induce Warburg-Like Lactate Production During Type 2 Diabetes

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β-Cell dysfunction is a hallmark of type 2 diabetes (T2DM) and comprises insulin secretory dysfunction and/or reduced β-cell mass (1). Normal β-cell function requires tight coupling of glucose metabolism with insulin secretion via a well-defined pathway utilizing oxidative metabolism and ATP production (2). Moreover, β-cell gene expression and metabolism are tuned to suppress pathways that would otherwise disrupt glucose-stimulated insulin secretion (GSIS), such as lactate production (3,4). Oversupply of glucose during T2DM can disrupt GSIS (glucotoxicity) via excessive generation of reactive oxygen species (ROS) causing oxidative stress: β-cells are particularly susceptible due to relatively low expression of antioxidant enzymes (5). Therefore, understanding the mechanisms by which ROS contribute to β-cell dysfunction during T2DM is an important research goal.

The new study by Sasaki et al. (6) identifies a novel mechanism by which ROS impair β-cell function during T2DM: by activating hypoxia-inducible factor 1α (Hif1α), switching on lactate production and impairing glucose oxidation and insulin secretion (Fig. 1). The authors studied Goto-Kakizaki (GK) rats, an inbred, polygenic model of nonobese T2DM with β-cell dysfunction, originally derived from Wistar rats, and found that dual antioxidant treatment significantly improved GSIS in vivo and in vitro, consistent with previous studies using the GK rat and other diabetic models such as Zucker diabetic fatty rats and *db/db* mice (5). Taken together, these findings reinforce the role of glucotoxicity and oxidative stress in β-cell dysfunction during T2DM. Furthermore, Sasaki et al. found that antioxidant treatment enhanced glucose-stimulated ATP production in GK islets, as well as restoring glucose oxidation and GSIS to levels comparable with Wistar (nondiabetic) rat islets, indicating that GSIS coupling efficiency is improved by antioxidant treatment. The authors measured a concomitant elevation of lactate production in untreated GK islets, revealing that glucose-derived pyruvate drives lactate production, rather than mitochondrial ATP generation, thereby short-circuiting GSIS. This increase in lactate production despite adequate oxygen availability is akin to the Warburg effect reported in many cancers.

Overexpression of lactate dehydrogenase isoform A (*Ldha*) is sufficient to disturb GSIS (7), and increased expression of *Ldha* in diabetic islets, indicative of a lactate shunt, has been reported in several diabetic models including GK (8), Zucker diabetic fatty (9), and *db/db* (10) islets, suggesting that this defect is a common feature of diabetic β-cells in both obese and lean models. What is most striking about the observations by Sasaki et al. is the rapid suppression of lactate production and restoration of GSIS by antioxidant treatment.

So what is the ROS-dependent mechanism driving the lactate shunt and β-cell dysfunction? Activation of Hif1α is known to increase the expression of *Ldha* and other genes involved in glycolytic lactate production (11) and, moreover, has been shown to disrupt glucose sensing and GSIS in β-cells (12–15), as reviewed previously (16). Hif1α activity is upregulated by ROS in other cell types (17), making this a strong candidate for inducing a lactate shunt in diabetic β-cells. As such, the authors found that the Hif1α protein, along with *Ldha*, were suppressed by antioxidant treatment demonstrating that ROS are necessary to sustain Hif1α activation and secretory dysfunction in diabetic GK islets. Finally, the authors treated GK islets with a Hif1α inhibitor, which suppressed lactate production and enhanced GSIS, demonstrating that Hif1α activation underpins lactate shunt–mediated β-cell dysfunction.

The study by Sasaki et al. is well conducted and uses a robust rodent model of β-cell dysfunction: a logical extension of this study will be to investigate if a ROS-induced, Hif1α-mediated, lactate shunt contributes to β-cell dysfunction in human T2DM. The authors' focus on *Ldha* is understandable given the observation of increased lactate production in GK islets; however, because Hif1α exerts pleiotropic effects it would have been prudent to measure other Hif1α-regulated β-cell genes and assess their dependence on ROS. For example, β-cell glucose uptake is disrupted by Hif1α activation (12,14), suggesting that there may be additional Hif1α-induced defects in GK islets besides the lactate shunt. Likewise, Hif1α is probably not the sole means by which ROS enhances *Ldha*, as this was only partially blocked by the Hif1α inhibitor used in GK islets. Moreover, ROS-independent mechanisms might also apply in the GK model, as the Inagaki laboratory had previously demonstrated a role for Src activation in secretory dysfunction (18). In the current study, Src inhibitors further enhanced GSIS even in antioxidant-treated islets, suggesting additional ROS-independent mechanisms of β-cell dysfunction.

A key goal for future research will be to establish if Hif1α activation causes β-cell dysfunction leading to

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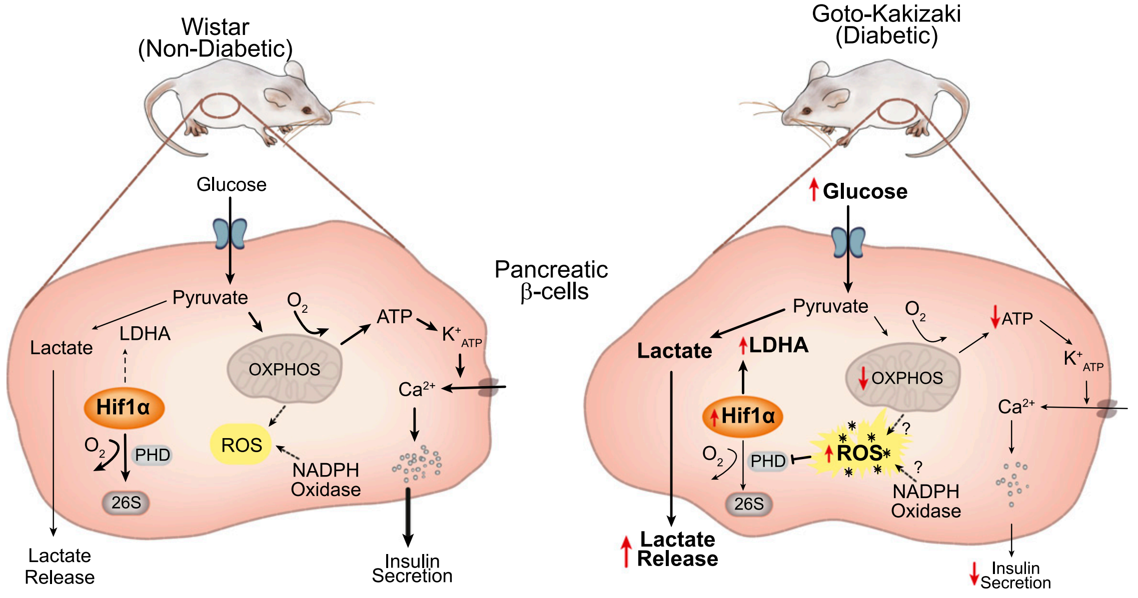

FIG. 1. Summary of findings by Sasaki et al. In nondiabetic Wistar rat β-cells, efficient coupling of glucose-stimulation with oxidative metabolism and ATP production facilitates appropriate insulin secretion, while Hif1α is targeted for proteasomal degradation by the oxygen-dependent prolylhydroxlase (PHD) enzymes. In diabetic GK rat β-cells, glucose drives excessive lactate production, while glucose oxidation, ATP production, and insulin secretion are impaired. This lactate shunt was found to be dependent both on elevated ROS and activation of Hif1α, a transcription factor targeting lactate dehydrogenase A (LDHA). The precise source and species of ROS, along with the mechanism for Hif1α activation in β-cells, has yet to be established; however, studies in other cell types suggest that a likely mechanism involves antagonism of prolylhydroxlase activity. Red arrows indicate changes identified in GK β-cells by Sasaki et al. Illustration by Kate Patterson.

hyperglycemia, or if Hif1α activation is a reaction to hyperglycemia and oxidative stress that exacerbates β-cell dysfunction during diabetes. One clue is offered by a previous pancreatectomy study: onset of hyperglycemia was associated with increased *Ldha* expression, which was reversed upon pharmacological correction of blood glucose levels (19), therefore arguing for lactate production as a secondary glucotoxic mechanism. Although several laboratories have reported that β-cell Hif1α activation impairs GSIS and glucose tolerance (12–15), there are reports that Hif1α is required for normal β-cell function (20), suggesting that Hif1α activation may not always be deleterious. We speculate that a potential role for β-cell Hif1α activation in response to elevated ROS levels could be to limit further generation of mitochondrial ROS, thereby protecting the β-cell from severe long-term oxidative stress at the immediate expense of GSIS and glucose homeostasis.

Another future research goal will be to determine how ROS activates Hif1α, whether via inhibition of prolylhydroxylases as suggested for other cell types (17) or by other means. It also remains to be established what source of ROS activates Hif1α in β-cells (mitochondrial, NADPH oxidase, or other), and if this ROS source colocalizes with prolyl-hydroxylases or other components of these oxygen-sensing pathways.

In summary, the study by Sasaki et al. has revealed a key role for ROS in stabilizing Hif1α, driving lactate production and disrupting glucose sensing and insulin secretion in T2DM islets.

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