IL-1β delivers a sweet deal

Marit Hjorth & Mark A Febbraio

Interleukin 1β (IL-1β) is a cytokine associated with inflammation, obesity and metabolic dysregulation. Surprisingly, IL-1β is also required for maintaining steady-state glucose homeostasis by potentiating postprandial insulin secretion.

The cytokine IL-1β is a central mediator of inflammation and is crucial for defense against infections and injuries. Increased circulating IL-1β is, however, also a hallmark of the chronic, low-grade inflammation associated with obesity and related diseases such as cardiovascular disease and type 2 diabetes[1]. IL-1-blocking therapies, therefore, might be useful for the treatment of cardiometabolic conditions, and this is currently being tested in clinical studies. One example is the CANTOS study, which is a large randomized trial on more than 10,000 survivors of myocardial infarction[2]. In this issue of *Nature Immunology*, Dror *et al.* identify a role IL-1β serves in maintaining postprandial glucose homeostasis by potentiating insulin secretion from the pancreas[3].

IL-1β is known to influence glucose metabolism in very different ways depending on the circumstances. For example, mice given injection of recombinant IL-1β become hypoglycemic[4] but, in contrast, chronic elevation of IL-1β signaling is linked to type 2 diabetes[1]. In an inflammatory setting, IL-1β is thought to cause β-cell dysfunction and death, an effect that is linked to the activation of macrophages in the pancreas[5]. Indeed, treatment of patients with type 2 diabetes with an IL-1 receptor (IL-1R) antagonist diminishes plasma glucose and markers of systemic inflammation[6]. Most studies have focused on the metabolic consequences of IL-1β in states of disease and inflammation. Less is known about the physiological effect of IL-1β on glucose homeostasis. In the study by Dror *et al.*, IL-1β is reported to increase the postprandial secretion of insulin and clearance of glucose from plasma[3] (**Fig. 1**). Furthermore, after mice are fed, IL-1β promotes the uptake of glucose selectively into immune cells, possibly to supply the immune system with energy to fight off pathogens in food. This interaction between insulin and IL-1β is a good example of the close association between the immune system and metabolic pathways, a concept often called 'immunometabolism'[7].

To investigate the postprandial regulation of IL-1β and metabolic effects, Dror *et al.* perform comprehensive analyses of various mouse models and of cells *in vitro*[3]. Fasting and refeeding leads to a rise in circulating IL-1β in mice. The source of this is, at least to a large extent, intraperitoneal macrophages. To determine this, the authors measure the expression of mRNA encoding IL-1β in several tissues and detect higher expression in cells isolated from the peritoneal cavity. Dror *et al.* also find more peritoneal macrophages in mice after feeding[3]. Indeed, these macrophages secrete IL-1β *ex vivo*, and although macrophages from mice that underwent fasting followed by refeeding release as much IL-1β as do those from mice that underwent fasting alone, they display greater ATP-stimulated release of IL-1β. Finally, postprandial IL-1β does not increase in a genetic mouse model that lacks IL-1β in the myeloid lineage.

In general, macrophages produce IL-1β in a two-step fashion[5]. First, they are primed to produce pro-IL-1β. Priming is induced by activation of the transcription factor NF-kB downstream of pattern-recognition receptors, often as a response to microbial products. Pro-IL-1β is then cleaved by caspase-1 to form active IL-1β; this process is initiated by activation of inflammasomes.

Dror *et al.* demonstrate that in a postprandial setting, IL-1β is produced by macrophages in response to a higher concentration of glucose and insulin, which involves increased glucose metabolism, production of reactive oxygen species and activation of the NLRP3 inflammasome[3]. The postprandial release of IL-1β is glucose dependent. When mice are treated with canagliflozin to inhibit renal glucose reabsorption, both hyperglycemia and the rise in circulating IL-1β are prevented. Insulin induces signaling via the kinases PI(3)K-AKT, glucose metabolism and the production of reactive oxygen species in macrophages *in vitro*. All these factors are necessary for insulin-stimulated production of IL-1β. It is also dependent on the NLRP3 inflammasome, because insulin lacks an effect on macrophages from NLRP3-deficient mice. This makes sense. The NLRP3 inflammasome is a sensor of nutrient overload and can assemble in response to the formation of reactive oxygen species and hyperglycemia[5]. The NLRP3 inflammasome is also activated to produce IL-1β in response to saturated fatty acids[8]; therefore, it would be of interest to investigate IL-1β secretion after mice are fed a high-fat meal.

Macrophages are primed by bacterial products to produce IL-1β, but whether this is necessary for the postprandial release of IL-1β is not clear. Dror *et al.* treat mice with antibiotics to diminish the intestinal microbiota and demonstrate less release of IL-1β[3], indicative of a potential link between the microbiota and the postprandial IL-1β and insulin response. For a clearer indication of this, it would be of interest to study the release of IL-1β in germ-free mice. It is also possible that macrophages are activated after feeding to fight potential microbes in food, a proposal supported by the finding of an increased number of peritoneal macrophages after feeding, reported by Dror *et al.*[3]. These findings indicate that both bacterial products and increased glucose metabolism are involved in inducing IL-1β production after feeding.

Interestingly, the authors are able to show that macrophage-derived IL-1β contributes to the postprandial increase in insulin secretion, which also leads to significantly increased glucose clearance. *In vivo*, this is demonstrated by injection of mice with a single dose of IL-1β,

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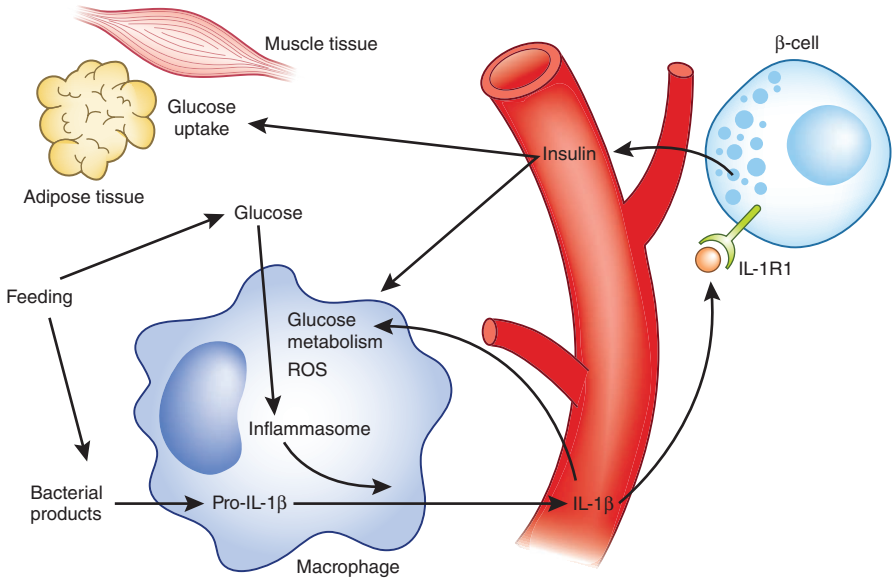

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Figure 1 IL-1β potentiates postprandial secretion of insulin. Feeding leads to a rise in circulating IL-1β, which potentiates postprandial insulin secretion and glucose clearance. Glycemia after feeding leads to activation of the NLRP3 inflammasome and the release of IL-1β from intraperitoneal macrophages. Bacterial products in food or microbiota might also stimulate the release of IL-1β. Macrophage-derived IL-1β increases the secretion of insulin from β-cells via IL-1R signaling, which leads to the uptake of glucose into muscle and adipose tissue, as well as increased uptake and metabolism of glucose in immune cells. This again leads to the release of IL-1β from macrophages and selective distribution of glucose to immune cells. Ultimately, insulin and IL-1β promote each other after feeding, which consequently decreases glycemia.

which increases insulin concentrations and glucose clearance during an intraperitoneal glucose-tolerance test. Furthermore, mice lacking IL-1β in the monocyte-macrophage lineage do not show a postprandial increase in IL-1β, and these mice have a significantly diminished insulin response. The effect of IL-1β on insulin secretion is direct, through the activation of signaling via IL-1R in β-cells. Dror *et al.* demonstrate this in both cultured cells and *in vivo*; diabetic mice given transplantation of IL-1R1-deficient islets have a blunted insulin response to IL-1β during glucose-tolerance testing[3].

In the study by Dror *et al.*, injection of IL-1β into mice leads to an increased uptake of glucose into immune cells and, to a lesser degree, muscle and adipose tissue[3]. In mice lacking macrophages, T cells and B cells, the effect of IL-1β on postprandial disposal of glucose is diminished. This indicates that postprandial IL-1β functions by distributing glucose to the immune system, both via increased insulin secretion and via a direct effect of IL-1β on macrophages.

Glucose is the main fuel for immune cells, and activation of the immune system leads to markedly increased glucose consumption. There is evidence that IL-1β can increase the uptake of glucose into immune cells, a finding also reported by Dror *et al.*[3]. However, given the findings of Dror *et al.*[3], it is now evident that IL-1β also potentiates postprandial insulin secretion; this leads to increased glucose consumption in macrophages, which again leads to IL-1β production.

The findings reported above emphasize the pleiotropic roles of IL-1β. It is well documented that IL-1β is involved in chronic inflammation and metabolic disease. However, the findings reported by Dror *et al.*[3] demonstrate that IL-1β also contributes to steady-state metabolic homeostasis. This gives further support to the concept that inflammatory mediators not only mediate metabolic disease but also take part in physiological metabolic regulation. Another example of the pleiotropic nature of cytokines is IL-6. IL-6 is associated with obesity and insulin resistance. However, IL-6 is secreted from muscles during exercise, and it has been shown that exercise-induced IL-6 has beneficial effects on metabolism by increasing insulin sensitivity in several organs[9].

In conclusion, insulin and IL-1β promote each other after feeding, which leads to increased glucose clearance and selective distribution of glucose to immune cells. The interaction between IL-1β and insulin might represent a mechanism for providing the immune system with enough energy to respond to pathogens in food and represents a link between metabolic homeostasis and immunity.

COMPETING FINANCIAL INTERESTS
The authors declare no competing financial interests.

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Innate B cells cleave to the marginal zone

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The kinase Taok3 and protease ADAM10 mediate determination of the fate of marginal zone B cells.

In this issue of *Nature Immunology*, Hammad *et al.* identify the molecular pathway that leads immature B cells to 'choose' the marginal-zone B cell (MZB cell) fate[1]. It is already known that to adopt this fate, immature B cells must receive signals via the receptor Notch2 from one of its ligands, Delta-like 1 (Dll1), expressed by fibroblastic reticular stromal cells in the spleen[2,3]. In addition, it is known that signals from the B cell antigen receptor (BCR) are important for accessing this fate[4], but how they participate has been unknown until now. This new study shows that BCR signaling via the serine-threonine kinase Taok3 causes rapid translocation of the transmembrane metalloprotease ADAM10 from intracellular vesicles to the cell surface, where it enables Notch2 signaling by performing

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