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IMMUNOMETABOLISM

Physiologic role of IL-1β in glucose homeostasis

New research published in *Nature Immunology* shows that elevated glucose levels after feeding induce macrophages to secrete IL-1β, which in turn promotes postprandial insulin secretion. As insulin enhances macrophage production of IL-1β, the findings might explain why insulin treatment can result in insulin resistance. The findings also support the use of therapeutic strategies in type 2 diabetes mellitus (T2DM) that avoid high levels of insulin.

"The deleterious role of chronic activation of the IL-1β system in T2DM is well documented; however, little attention has been paid to a possible physiologic role of IL-1β in glucose metabolism," explains lead investigator Marc Donath. "We hypothesized that IL-1β might contribute to postprandial inflammation, regulating whole-body glucose homeostasis along with an innate immune response."

Overnight fasting followed by refeeding increased circulating levels of IL-1β in wild-type mice but not in mice deficient in IL-1β (*Il1b*$^{-/-}$ mice). In wild-type mice, the expression of *Il1b* mRNA and IL-1β-dependent gene expression in macrophage-laden omental fat were increased, as was trafficking of macrophages from omental fat to the peritoneum. Macrophages were confirmed as the source of IL-1β, as circulating levels of the cytokine were not increased during refeeding in mice with myeloid-compartment-specific deletion of *Il1b*. Increased secretion of IL-1β by macrophages was mediated by elevated postprandial glucose levels (evidenced by abrogation of the effect with a sodium/glucose cotransporter 2 inhibitor) and by bacterial products (demonstrated by reduction of the effect with a broad-spectrum antibiotic).

Next, the team investigated the effect of elevated IL-1β levels on insulin secretion. Circulating levels of insulin were lower after refeeding in *Il1b*$^{-/-}$ mice than in wild-type littermates. Insulin levels were also reduced in wild-type mice depleted of macrophages (by treatment with clodronate liposomes) and in mice with myeloid-compartment-specific deletion of *Il1b*. Furthermore, acute injection of wild-type mice with IL-1β increased insulin secretion and improved glucose tolerance, confirming that postprandial macrophage-derived IL-1β promotes insulin secretion.

Finally, the team investigated the effect of insulin on the immune system. Insulin enhanced M1 (pro-inflammatory) macrophage production of IL-1β, and both insulin and IL-1β regulated glucose disposal, with IL-1β preferentially stimulating glucose uptake into the immune cell compartment. "IL-1β thereby alerts and fuels the immune system, possibly to prevent dissemination of microorganisms contained in food," explains Donath.

Overall, the findings reveal an unexpected role of IL-1β in glucose disposal and of insulin in macrophage activity. The identification of a physiologic role for IL-1β in glucose homeostasis lends support to the emerging concept that inflammatory mediators have integral roles in physiology and pathophysiology. "As the physiologic role of the immune system in regulating metabolism is certainly not limited to IL-1β, we are currently looking into other components of the immune system that might be involved in this process," adds Donath.

David Holmes

> "…postprandial macrophage-derived IL-1β promotes insulin secretion"

ORIGINAL ARTICLE Dror, E. *et al.* Postprandial macrophage-derived IL-1β stimulates insulin, and both synergistically promote glucose disposal and inflammation. *Nat. Immunol.* http://dx.doi.org/10.1038/ni.3659 (2017)

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