Milestone 19

Islet inflammation in T2D

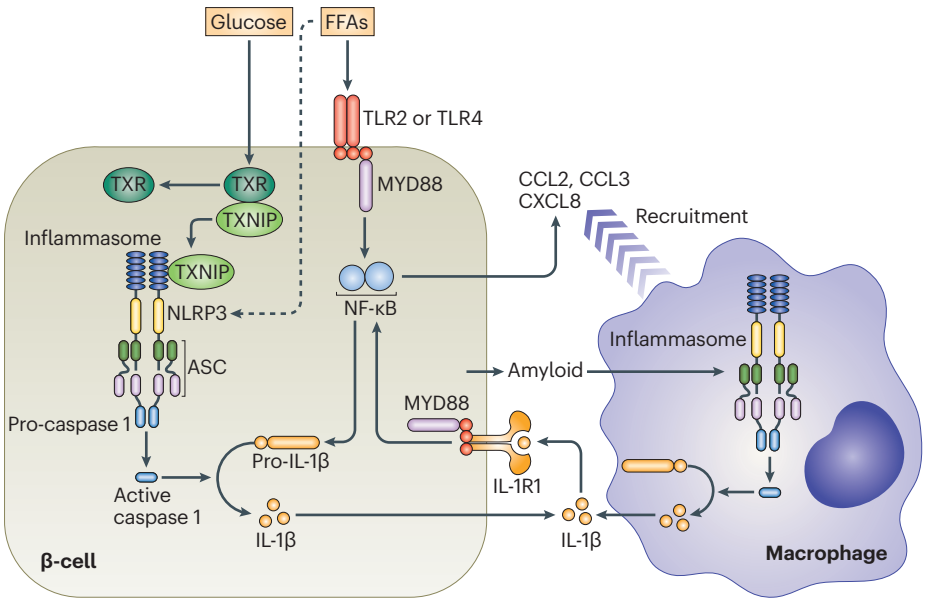
Type 1 and type 2 diabetes (T1D and T2D) converge in the later stages of disease on dysfunction of pancreatic islet β-cells and a progressive loss of insulin production. Seminal studies in the 1980s had shown the involvement of autoantibodies (Milestone 7) and islet inflammation (Milestone 8) in β-cell death in T1D. Furthermore, obesity-induced chronic inflammation was known to be a risk factor for T2D (Milestone 12). However, the general assumption was that overnutrition induces β-cell apoptosis directly and there was not thought to be a unifying mechanism of cell death in T1D and T2D.

Observations of islet macrophages in T2D were considered to be a consequence rather than a cause of β-cell death, and studies suggesting that glucose-induced IL-1β production in islets leads to β-cell apoptosis in T2D (Maedler et al., 2002) had not been replicated by others in vivo. In 2007, however, a study by Marc Donath and colleagues reported that islet-derived inflammatory factors induced by a T2D milieu of excess circulating nutrients led to macrophage infiltration of islets, thus showing that insulitis has a role in T2D as well as T1D.

Ehses et al. observed increased numbers of islet-associated $CD68^+$ macrophages in autopsy and resection samples from patients with T2D compared with nondiabetic controls. In C57BL/6J mice fed a high-fat diet, the number of $CD11b^+$ myeloid cells in islets was doubled after 8 weeks compared with standard diet controls. No apoptotic cells were detected in islets at 8 weeks, suggesting that islet inflammation precedes β-cell apoptosis. Macrophage infiltration of islets was also reported for the GK rat and *db*/*db* mouse models of T2D.

"islet-derived inflammatory factors induced by a T2D milieu of excess circulating nutrients led to macrophage infiltration of islets"

After treatment with glucose and palmitate in vitro, mouse and human islets and islet cell lines secreted increased levels of the inflammatory factors IL-6, CXCL8, G-CSF, KC (mice; the orthologue of human CXCL1) and CCL3 (human). Chemically induced apoptosis was used to rule out an indirect effect of nutrient-induced β-cell death on cytokine release. Furthermore, KC and G-CSF themselves were shown to have minimal effects on β-cell apoptosis and glucose-stimulated insulin secretion. Thus, excess nutrients were shown to directly induce the release of inflammatory factors by islet cells, which in turn had indirect effects on islet function rather than directly mediating β-cell death.



Given that CXCL8 was known to be a chemotactic factor for myeloid cells, the authors hypothesized that the factors released by pancreatic islets exposed to a T2D milieu are responsible for the macrophage infiltration of islets. Indeed, conditioned medium from human islets exposed to glucose and palmitate increased the migration of neutrophils and monocytes in vitro, which could be abrogated by neutralization of CXCL8.

The study concluded that nutrient-induced T2D involves an immune-mediated islet inflammatory process. Intriguingly, the discussion section of the paper mentioned the unpublished observation that the release of KC and G-CSF by islets could be blunted by treatment with IL-1Ra, the endogenous receptor antagonist of IL-1β. This involvement of IL-1β in type 2 insulitis was in line with the earlier results of Maedler et al. and was clarified by later studies showing that T2D is associated with inflammasome activation by thioredoxin-interacting protein (TXNIP) (Zhou et al., 2010) or by islet amyloid polypeptide (Masters et al., 2010). The findings of Ehses et al. also suggested that inflammatory mediators such as IL-1β could be a potential therapeutic target in T2D. A proof-of-concept trial by Larsen et al. (2007) in 70 patients with T2D, 34 of whom received subcutaneous IL-1Ra for 13 weeks, showed improved glycaemic control correlating with increased β-cell secretory function. The recent Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) confirmed the ability of targeting IL-1β to improve T2D in the short term, although it did not reduce the incidence of new-onset T2D in trial participants with pre-diabetes. A recent meta-analysis of 2,921 patients with T2D (Kataria et al., 2019) concluded that IL-1 blockade can significantly improve glycaemic control. Thus, although it is now well accepted that T2D is an inflammatory disease, the jury is still out on to what extent and at what stage of disease anti-inflammatory therapies might be beneficial.

Kirsty Minton Senior Editor,
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Milestone study

Ehses, J. A. et al. Increased number of islet-associated macrophages in type 2 diabetes. *Diabetes* **56**, 2356–2370 (2007)

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