

Milestone 8

Cytokines directly implicated in T1D

The discovery of islet cell-specific antibodies in patients with type 1 diabetes (T1D) (Milestone 7) and the subsequent revelation that these antibodies could be present years before disease onset turned the prevalent theory that an initial viral insult precipitated T1D on its head. Histological analysis of pancreatic tissue from patients with acute T1D in the 1960s (Milestone 2) had revealed immune cell infiltrates in affected pancreatic islets, but whether the immune cells represented a primary immune response to an infection or a response secondary to islet cell damage or death was unknown. A more detailed immunohistochemical analysis of islets published in 1985 (Bottazzo et al.) pinpointed T cells as the most abundant infiltrating cell type, as well as showing the deposition of islet cell-specific antibodies and high levels of expression of MHC class I and class II molecules on surviving β -cells. When coupled with results from transplantation studies in identical twins, in which insulinitis and β -cell death occurred in the affected twin within weeks of partial pancreatic transplantation from an unaffected twin, these findings were strongly suggestive of an autoimmune pathology for T1D.

Several theories abounded as to how the immune system had turned on itself to destroy β -cells. One idea was that an environmental insult of some sort (possibly a virus) damaged β -cells, causing them to release proteins that could be picked up by antigen-presenting cells such as macrophages and used to stimulate self-reactive T helper cells that, in turn, stimulated B cells to produce antibodies and activate cytotoxic T cells. An alternative theory was that an environmental factor (possibly a cytokine such as IFN γ) caused β -cells to overexpress MHC class II molecules on their cell surface and act as antigen-presenting cells themselves. Both of these theories centred on MHC class II molecule expression and antigen presentation, firmly implicating the adaptive immune system in T1D but relegating innate immunity to the side lines.

The idea that innate immunity had, at best, a supporting role in the pathogenesis of T1D came to an abrupt end in 1986 with the publication of a study in *Science* that showed a direct role for the cytokine IL-1 in mediating β -cell death. IL-1 is predominantly produced by innate immune cells such as macrophages and monocytes and can activate a whole range of

cells, including T cells and B cells. The study by Bendtzen et al. showed that supernatant from polyclonally activated blood mononuclear cells could inhibit the production of insulin by isolated pancreatic islets in vitro, and that this effect could be reversed by the addition of IL-1-specific antibodies and restored again by removal of the antibodies using an acid wash. These findings suggested that, in the absence of self-antigen recognition, a cytokine was able to produce a cytotoxic effect on a non-immune cell – something that had been only rarely reported at the time.

Bendtzen et al. went on to evaluate the effects of other cytokines on insulin production by islet cells, concluding that IFN γ was unlikely to be toxic and that, although tumour necrosis factor (TNF) reduced insulin release, it did not alter the amount of insulin within the β -cells and therefore had limited effects. By contrast, both naturally occurring and laboratory-produced IL-1 (specifically the p17 type of IL-1 that is now known as IL-1 β) were able to reduce both released and intracellular insulin, indicating that this cytokine was toxic to β -cells. These results suggested a new theory in which circulating IL-1 (and potentially other cytokines) causes damage to β -cells, thereby triggering an autoimmune response that perpetuates damage.

Initial attempts to stop the autoimmune response using the immunosuppressant cyclosporine (Feutren et al., 1986) showed some promise, but any beneficial effects soon wore off when treatment was stopped, and cyclosporine could not prevent insulinitis from developing in patients with T1D following pancreas transplantation. Targeting individual cytokines offered a more selective approach but would take several decades to develop and test. Unfortunately, IL-1 inhibition has not shown efficacy in clinical trials for T1D, but targeting TNF has proved more successful and is still being explored as a potential therapy, alongside other immunotherapies (Milestones 17 and 20).

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Milestone study

Bendtzen, K. et al. Cytotoxicity of human p17 interleukin-1 for pancreatic islets of Langerhans. *Science* **232**, 1545–1547 (1986)

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