

## **ISLET AMYLOID POLYPEPTIDE AGGREGATION IS A LOCAL TRIGGER FOR PANCREATIC ISLET INFLAMMATION**

Patients with type 2 diabetes experience an inevitable deterioration of glycemic control leading to long-term complications and dependence on exogenous insulin. Amyloid deposition, macrophage infiltration, and upregulation of pro-inflammatory cytokines are common pathological features of both type 2 diabetic and transplanted islets. Islet amyloid is comprised primarily of aggregates of islet amyloid polypeptide (IAPP), a peptide that is co-secreted with insulin by beta cells. IAPP fibrils share a common cross- $\beta$ -sheet structure with other amyloids of eukaryotic and microbial origin that activate innate immune cells via interaction with pattern recognition receptors. We therefore hypothesized that IAPP aggregation acts as a local trigger for islet inflammation.

We found that human IAPP, but not non-amyloidogenic rodent IAPP, induced a potent pro-inflammatory response in islets and macrophages that was amplified by autocrine/paracrine induction of interleukin-1 (IL-1). Pre-fibrillar IAPP activated the membrane-associated pattern recognition receptor Toll-like receptor 2 (TLR2) to induce expression of proIL-1 $\beta$ . Secretion of mature IL-1 $\beta$  required fibrillar IAPP and was attenuated by inhibitors of caspase-1 and the cytosolic NLRP3 inflammasome. Pancreatic islets from transgenic mice with beta cell expression of human IAPP expressed higher levels of pro-inflammatory cytokines than islets from wild-type littermates. Transgenic expression of human IAPP also altered the activation state of resident islet macrophages, the primary cell type responsible for IAPP-induced upregulation of IL-1 $\beta$ . Clodronate liposome-mediated macrophage depletion improved islet function in human IAPP transgenic mice. Moreover, administration of IL-1 receptor antagonist improved human IAPP-induced glucose intolerance in mouse models of islet transplantation and type 2 diabetes. Inhibition of a local IAPP-induced pro-inflammatory response mediated by islet macrophages may therefore help to explain the islet-specific effects of anti-IL-1 therapies in patients with type 2 diabetes.

Collectively, these data suggest a novel – and potentially reversible – mechanism by which IAPP aggregation contributes to beta cell dysfunction and implicate the resident islet macrophage as a critical mediator of chronic islet inflammation in the setting of amyloid formation. Strategies to block TLR2 or NLRP3 activation, inhibit IL-1 signalling, or alter macrophage polarization may improve IAPP-induced islet dysfunction in type 2 diabetes and islet transplantation.