INDUCTION OF TNF-α BY HUMAN ISLET AMYLOID POLYPEPTIDE IS DEPENDENT ON IL-1 BUT NOT TLR2 OR TLR4 SIGNALLING

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Introduction: Human islet amyloid polypeptide (hIAPP) is a 37-amino acid peptide co-secreted with insulin by pancreatic β-cells. Pathological IAPP aggregation occurs in type 2 diabetic islets in association with macrophage infiltration. hIAPP fibrils share a common cross beta-sheet structure with amyloid-β aggregates, which induce a potent pro-inflammatory response by activation of both Toll-like receptors (TLRs) and the NLRP3 inflammasome.

Aims: To evaluate the role of TLR2, TLR4, and the downstream adaptor protein MyD88 in hIAPP-induced cytokine release by macrophages.

Methods: Bone marrow-derived macrophages (BMDMs) from C57BL/6 mice were treated with varying concentrations of synthetic hIAPP. Supernatants were analyzed for pro-inflammatory cytokines and changes in global gene expression were evaluated by microarray and quantitative real-time PCR. hIAPP-induced TNF-α release was assessed in macrophages from mice deficient in TLR2, TLR4, or the TLR adaptor protein MyD88.

Results: hIAPP but not non-amyloidogenic rat IAPP caused release of TNF-α, IL-1α, IL-1β, CCL3, CCL4, CCL5, CXCL1, and CXCL2 by BMDMs. Maximal cytokine release occurred in response to pre-fibrillar aggregates. hIAPP-induced TNF-α secretion was markedly diminished in MyD88-deficient macrophages, and in cells treated with an IL-1 receptor antagonist or inhibitors of NLRP3.

Conclusions: Signalling via IL-1R/MyD88 but not TLR2 or TLR4 signalling is required for maximal macrophage responsiveness to pre-fibrillar hIAPP aggregates. These data suggest that islet amyloid-induced inflammation may contribute to beta cell dysfunction in type 2 diabetes. Furthermore, NLRP3 activation but not TLR signalling may represent a common pathway of immune cell activation shared by distinct amyloidogenic peptides.