Dangerous Liaisons – candidate genes, pancreatic beta cells and the innate immune system in T1D

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Genome wide association studies (GWAS) have identified more than 50 loci associated with genetic risk of type 1 diabetes (T1D). Several T1D candidate genes have been suggested or identified within these regions, but the molecular mechanisms by which they contribute to insulitis and beta-cell destruction remain to be clarified. More than 60% of the T1D candidate genes are expressed in human pancreatic islets, suggesting that they contribute to T1D by regulating at least in part pathogenic mechanisms at the beta-cell level. Recent studies by our group indicate that important genetically regulated pathways in beta-cells include innate immunity and antiviral activity, involving RIG-like receptors (particularly MDA5) and regulators of type I IFNs (i.e. PTPN2 and USP18), and genes related to beta-cell phenotype and susceptibility to pro-apoptotic stimuli (i.e. GLIS3). These observations reinforce the concept that the early pathogenesis of T1D is characterized by a dialog between the immune system and pancreatic beta-cells. This dialog is probably influenced by polymorphisms in genes expressed at the beta-cell and/or immune system level, leading to inadequate responses to environmental cues such as viral infections. Our ongoing work aims to clarify how these disease-associated variants affect pancreatic beta-cell responses to inflammation and the subsequent triggering of autoimmune responses and the specific and progressive beta-cell loss.