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AUTOIMMUNITY

INNATE CELL CROSSTALK IN T1DM

Crosstalk between innate immune cells initiates autoimmune diabetes in young nonobese diabetic (NOD) mice, report researchers in *Nature Medicine*.

The early stages of the pathogenesis of type 1 diabetes mellitus (T1DM), before the destruction of insulin-producing pancreatic β cells by autoreactive T cells, remains poorly understood. Diana *et al.* shed light on the immune events that take place in the pancreas of female NOD mice starting at 2 weeks of age, the age at which early immune cell infiltration occurs.

"IFNα was already proposed to play a deleterious role in T1DM," explains senior author Agnès Lehuen. "As plasmacytoid dendritic cells are the main cell type to produce IFNα we sought to investigate the role of these cells in T1DM in the early phase of T1DM development."

The researchers detected and visualized plasmacytoid dendritic cells, neutrophils and B1-a cells inside the pancreas of these young NOD mice by flow cytometry and confocal microscopy. The investigators also show that a cascade of innate cell activation is triggered by β-cell debris present after β-cell death that occurs spontaneously in young NOD mice during organogenesis and after weaning. In this cascade, activated B1-a cells secrete IgGs specific for the double-stranded DNA (dsDNA) in the β-cell debris. Neutrophils are then activated by the dsDNA-specific IgGs, which activate plasmacytoid dendritic cells. The activation of plasmacytoid dendritic cells leads to local secretion of IFNα in the pancreatic islets.

In NOD mice of 6 weeks of age, the researchers demonstrate that streptozotocin-induced β-cell death leads to production of IgGs specific to the dsDNA and set up the same innate immune cell cascade.

"The most significant finding is to observe neutrophils so early in the pancreas," comments Lehuen. "Neutrophils are usually associated with infection but evidence is mounting that they play a major role in autoimmune diseases such as lupus and psoriasis. In both pathologies, a similar mechanism occurs that involves neutrophils and plasmacytoid dendritic cells for the production of IFNα." The findings could help identify new targets for immune therapy for T1DM.

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Original article Diana, J. *et al.* Crosstalk between neutrophils, B-1a cells and plasmacytoid dendritic cells initiates autoimmune diabetes. *Nat. Med.* doi:10.1038/nm.3042