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Yin and Yang of the Fas pathway in regulating self-tolerance

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Type1 diabetes (T1D) results from autoimmune destruction of pancreatic insulin-producing ß-cells. Autoreactive T cells are activated by islet autoantigens in pancreatic lymph nodes (PLN) from where they infiltrate pancreatic islets of Langerhans to cause insulitis and ß-cell destruction. Although present within the normal repertoire of healthy individuals, autoreactive T cells are held in check by suppressive cytokines and specialized subsets of regulatory cells. In disease-susceptible individuals and the widely used "non-obese diabetic (NOD) mouse model," these immunoregulatory mechanisms fail, thereby permitting diabetogenic T cells to infiltrate islets, cause insulitis, and destroy ß-cells. What causes these mechanisms to fail and how the failures can be avoided/rectified are current questions of paramount scientific and clinical significance. Our group is interested in understanding mechanisms that potently control ß-cell-specific autoreactive T-cells when Fas ligand (FasL), an apoptosis-inducing member of the tumor necrosis factor (TNF) family, is genetically or pharmacologically inactivated. Disruption of the Fas pathway causes massive T cell lymphoproliferation but instead of causing or aggravating organ specific autoimmunity, as is the case with CTLA-4 or Foxp3 deficiency, it restores organ-specific T cell tolerance in several autoimmune models. This paradox is best illustrated in NOD mice carrying homozygous gld or lpr mutations.

Our mouse data support the hypothesis that defects in IL-10 utilization underlie autoimmune diabetes and that IL-10-producing B cells induced in pancreata by inactivating FasL are capable of controlling diabetogenic T cells. We will discuss the role of FasL in compromising and negating the role of IL-10 in antagonizing the diabetogenic process especially at the effector site, the pancreas.

Biography

Abdel Rahim A. Hamad has received his Ph.D. from University of Colorado Health Sciences in Denver and postdoctoral training at the Johns University School of Medicine where he is now an Assistant Professor of Pathology and of Medicine. He has published more than 27 papers in reputed journals, has written reviews and a book chapter.

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