A-06

Heparanase is Indispensable for Autoreactive T cell's Infiltration into Islets in Type 1 Diabetes

Zuopeng Wu, Andrew F. Ziolkowski, Craig Freeman, Gerard F. Hoyne, Charmaine J. Simeonovic & Christopher R. Parish

Dept. of Immunology, JCSMR, The Australian National University, Acton, Canberra, ACT, Australia

Abstract

T cell-mediated autoimmune responses are the driving force in the pathogenesis of type 1 diabetes (T1D) but the processes involved in the infiltration of autoreactive T cells into islets is less clearly understood. Recent studies by our laboratory have led to a new understanding of how the glycosaminoglycan, heparan sulfate (HS), a linear polysaccharide chain attached to cell surface and extracellular matrix (ECM) proteoglycans (HSPG), can protect pancreatic islet beta cells from metabolic stress and autoimmune attack. Heparanase (Hpse), the only known mammalian endoglycosidase that can degrade HS, is identified here as a key factor in controlling the entry of autoreactive T cells into islets by specifically degrading HS in the islet basement membrane and by inducing beta cell destruction via degrading HS within the islet beta cells. Using a modified transgenic system involving co-transferring naive ovalbumin (OVA)-specific $CD8^+$ OT-I T cells with activated OVA-specific $CD4^+$ OT-II T cells into RIP-OVA^{hi} recipients, we observed rapid induction of T1D. Subsequent studies with this model, using $Hpse^{-/-}$ mice, demonstrated that Hpse deficiency in both OT-I and OT-II T cells and the host mice preserved HS within islets, inhibited lymphocyte accumulation in islets, reduced the severity of beta cell damage, and dramatically diminished the incidence of diabetes. In contrast, Hpse deficiency in either donor T cells or host mice only partially reducing T1D incidence. While adoptive transfer of both transgenic T cell populations was required for T1D induction, the presence of OT-II T cells had little effect on OT-I T cell activation and proliferation but aided the entry of effector T cells into the islets. Interestingly, activated $CD4^+$ OT-II T cells alone were capable of degrading intra-islet HS and initiating islet inflammation, whereas $Hpse^{-/-}$ OT-II T cells failed to do so. These studies indicate that heparanase derived from autoreactive T cells and unidentified bystander cells is essential for T1D development. It not only sheds light on our understanding of T1D pathogenesis but also on T cell-mediated inflammatory responses in general.