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Early immunoproteasome activation in mouse pancreatic beta-cells - new insights into auto-antigen generation in type I Diabetes

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Autoimmune destruction of insulin producing pancreatic β-cells is the hallmark of type 1 diabetes. One of the key molecules implicated in the disease onset is immunoproteasome, a protease with multiple proteolytic sites that collaborates with the 19S and 11S activators to produce immunogenic peptides for MHC class I molecules. Despite its importance, little is known about the function and regulation of immunoproteasome in pancreatic β-cells, especially during early antiviral responses mediated by type I interferons (IFNs). Of special interest are effects of IFNβ that is secreted directly by infected cells and typically not associated with the immune response, compared to IFNγ, a classic immuno-stimulator. qPCR analysis of total mRNA isolated from the mouse insulinoma cell line MIN6 and islets shows that they express similar levels of immune proteolytic subunits and the 11S activator in a manner dependent on the IRF1 transcription factor when exposed to IFNβ or IFNγ. IFNs do not change expression of regular proteolytic subunits, and immuno-precipitation and quantitative Western blot analyses of cell extracts fractionated by size exclusion suggest that immune and regular proteolytic subunits co-exist in the same complexes. These complexes have normal activities in extracts with high ATP concentrations, implicating normal regulation by the 19S activator, but ATP depletion is required to stimulate their regulation by the 11S activator. These findings suggest that stochastic combinations of regular and immune proteolytic sites increase the probability with which unique immunogenic peptides are produced in pancreatic β-cells exposed to IFNβ, but primarily in cells with reduced ATP levels

Biography

Skowyra is an established, independent investigator with a long-term interest in ubiquitin-mediated proteolysis, a process that regulates many aspects of cell function and generates immunogenic peptides for presentation by MHC class I molecules. The focus on immunoproteasome function and regulation during early antiviral defenses of pancreatic beta-cells represents a new research direction in the Skowyra lab that is currently sponsored by a research grant from the American Diabetes Association, and that, via a multidisciplinary, highly collaborative effort, aims at explaining the mechanism by which immunoproteasome activation by type I IFNs contributes to onset of type 1 diabetes.

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