Denver

CHEMISTRY

Spring 2023
Seminar Series

11 am - 12 pm
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NC 1130

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"The roles of disulfide specific T cells in type 1 diabetes"

Evidence has accumulated supporting the important role played by post-translationally modified new antigens (neoantigens) in the pathogenesis of autoimmune diseases, like type 1 diabetes. Autoimmune T cell responses that are specific to neoantigens formed in peripheral tissues may explain how and why T cell responses are not subject to the usual tolerance mechanisms. Recent data showed that posttranslational modifications (PTMs) at the peptides from some self-proteins create the pathogenic neoantigens and may drive type 1 diabetes. Disulfide bond formation is an important PTM, with implications for structure, function, and stability of numerous proteins. However, disulfides can be detrimental for other proteins. Reactive oxygen species (ROS) induces post-translational modifications. Importantly, ROS can also readily oxidize the free thiol group. This free thiol can form either an inter- or intra-molecular disulfide bond with another neighboring free thiol. Islet amyloid polypeptide (IAPP) is a peptide co-secreted with insulin by the beta cells of the pancreas. We showed that IAPP forms a disulfide bond that is critical to activate pathogenic CD4 T cells. We then generated an anti-disulfide monoclonal antibody. The evaluation of its ability to inhibit development of diabetes in a mouse model showed this antibody effectively delayed diabetes onset and blocked the disease progression. We further characterized the disparate T cell recognition of the disulfide modified peptides and understand the novel antigen processing and presentation mechanisms. The study could provide novel therapeutic strategies to prevent or treat type 1 diabetes.

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