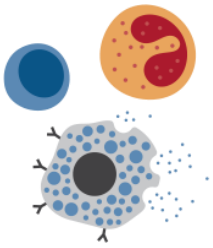

DISCOVERY 2025

Mechanisms of Type 2 Inflammation in Disease and Beyond

2025 Abstract Book

Flcn regulates Plasma cells, IgE and anaphylaxis
Keyword: Immunoglobulin E

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Plasma cells are terminally differentiated antibody producing cells responsible for proper immune defense but also autoimmunity and allergic reactions. We have found a hypomorphic missense mutation in Flcn named pansy, which was linked to mild (30%) decreased T-dependent and T-independent IgG responses, but a 90% decrease in total IgE response to Ova/Alum. These findings were validated by CRISPR/Cas9 induced knock-in of the Flcn-pansy allele. Biochemically, RNA and protein levels were not affected, which suggests structure is intact, but function is impaired.Folliculin (FLCN) is mutated in Birt-Hogg-Dube' syndrome and regulates mTOR through folliculin-interacting proteins (FNIP)1 and FNIP2. They create a unique activation of mTOR such that the TFE3/TFB transcription factors are activated to regulate metabolism or lysosomes for phagocyte specific deletions, but our hypomorphic mutation has no change in phagocyte numbers and is phenotypically healthy, fertile, and viable. Instead, we found novel changes in plasma cell numbers and function. Study of in vitro plasma cell differentiation showed a developmental block at the plasmablast stage with 50% decreased plasma cells. However, the effects in vivo were more profound with >90% decrease in IgG1 and IgE plasma cell and germinal center cells when immunized with the model allergen, papain. Finally, Flcn deficient mice were re-challenged with papain they were immune to anaphylaxis while age and sex matched wild type controls (n=10) experienced profound hypothermia, shock or death ($p<0.0001$).This study identifies Flcn as a potential target to block plasma cell development to prevent the pathogenic effects of IgE.