Novel Insights on Mast Cell and Basophil Signaling and Function

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Mast cells and basophils are key in innate immunity and function to amplify adaptive immunity. However, mast cells and basophils are well known for mediating allergic responses via the high affinity IgE receptor (FcεRI); thus understanding the function of these cells and of the FcεRI holds therapeutic promise in disease. In this talk I will discuss new insights on the role of FcεRI and Lyn kinase (a key enzyme that phosphorylates FcεRI) in basophil-mediated amplification of autoantibody production in systemic lupus erythematosus (SLE). Our findings show that a deficiency of Lyn kinase (a gene shown to be associated with SLE) in a mouse predisposes to allergic hypersensitivity. This depends on an enhanced basophil-induction of T_H2 cell differentiation through increased production of IL-4 in the absence of Lyn kinase. Unexpectedly, this T_H2-skewed environment was linked to the development of an SLE-like disease in the late life of Lyn-deficient mice. Our findings showed that the presence of autoreactive IgE's in these mice induced FcεRI activation of basophils, which promoted the overproduction of autoantibodies seen in lupus. The presence of autoreactive IgE, activated basophils and their association with SLE in humans was also confirmed and will be discussed.

In addition, this talk will cover new findings on the role of mast cells in promoting regulatory T cell function (Treg) during chronic allergic dermatitis (AD). Using a mouse model of oxazolone-induced chronic AD, we uncovered a role for mast cells in suppression of this disease during its chronic phase. Mast cells were found to produce IL-2 and this was required to maintain the normal ratio of Treg:Teffector at the site of inflammation (skin). Intriguingly, the findings showed that mast cells were not required to populate the site of inflammation, and IL-2 production and its suppression of AD was associated with increased expansion of mast cells in the spleen in an IgE-dependent manner. Additionally, we have used this model to investigate potential factors that may link dermatitis to an enhanced asthma susceptibility or severity (atopic march). The findings of this unpublished work will also be discussed. Collectively, the covered studies provide a new paradigm for the role of mast cells and basophils in allergy and beyond opening new areas of investigation with therapeutic potential.