The impact of obesity on immunometabolic dysregulation in asthma

Sarah Henrickson, MD, PhD

Abstract

Asthma and obesity are two of the most common chronic inflammatory diseases and each has been shown to cause immune dysregulation. As body mass increases, the risk of developing asthma increases, suggesting a mechanistic link between asthma and obesity. Obese asthmatics (OA) have a challenging to manage disease; prevention with inhaled corticosteroids is less effective than in normal weight asthmatics and patients with OA have severe, virally induced, asthma exacerbations. However, the impact of obesity on immune function in asthma remains unclear. In our work, $CD8^+$ T cells (CD8T) in OA show evidence of T cell exhaustion (Tex) in mice and humans, which is characterized by increased expression of inhibitory receptors, altered transcriptional and epigenetic state, mitochondrial dysfunction and impaired effector function. We hypothesize that mitochondrial dysfunction causes Tex in OA. We will use a transcriptional lens to evaluate the mechanisms of Tex in OA, including examining the role of mitochondrial dysfunction in our mouse model of OA. In Aim 1, we will test the hypothesis that Tex is found in mouse OA by comparing normal weight asthma, obese non-asthmatic, obese asthmatic, and control mice at baseline using bulk RNA sequencing to evaluate Tex using a T cell exhaustion transcriptional signature as well as performing transcriptional evaluation of T cell effector function. In Aim 2, we will evaluate the role of mitochondrial dysfunction in lung Tex in all four groups using a flow cytometric strategy and lung CD8 T cell cellular metabolomics and BAL metabolomics. Together, these aims will utilize cutting edge techniques to test mechanisms of Tex in OA, fostering the potential development of novel therapies in the future.