OR01-1: Leveraging Immunometabolic Control to Prevent and Treat Obesity Related Asthma

M. Furkan Burak. *Brigham and Women's Hospital, Harvard T.H. Chan School of Public Health*

M. Furkan Burak, MD[1,2], Nurdan Dagtekin, BSc[2], Presila Bejo, BSc[2], Eric Vaillancourt, BSc[2], Lydia Liu, MSc[3], Cem Z. Gorgun, MD, PhD[2], Eric Rimm, ScD3, Gurol Tuncman, MD, PhD[2], Gokhan S. Hotamisligil, MD, PhD[2]. [1]Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, [2]Department of Genetics and Complex Diseases, Sabri Ulker Center, Harvard T.H. Chan School of Public Health, Boston, MA, [3]Department of Nutrition, Harvard T.H. Chan School of Public Health, Boston, MA.

Asthma is a chronic inflammatory disease of the airways with an increasing prevalence but limited treatment options. Although the pathogenesis is not fully understood, it has a major immunometabolic component including contribution of lipid mediators to airway inflammation. Interestingly, accumulating evidence implicates obesity as a critical risk factor for asthma where these lipid mediators are upregulated. However, how obesity leads to asthma remains a critical but poorly understood area. There is a great need for novel treatments for obesity-related asthma as this group of patients are less-responsive to conventional therapies.

The fatty acid binding protein aP2 is a fundamental immunometabolic regulator, which is increased in obese mice and humans. aP2 deficiency in mice improves the dysregulated metabolic outcomes of obesity and related diseases such as diabetes and atherosclerosis, which share similar lipid derangements and immunometabolic underpinnings. Moreover, we reported that aP2 secreted from adipose tissue acts as a hormone, supporting inter-organ communication. We and others have shown that increased serum aP2 levels strongly correlate with poor metabolic, inflammatory and cardiovascular outcomes in multiple independent human studies. Lastly, humans who carry a haploinsufficiency allele of aP2 have reduced risk for developing dyslipidemia, diabetes, and cardiovascular disease. Together, these findings indicate that the biological functions of aP2 are conserved and highly relevant to human pathophysiology.

Interestingly, in recent studies we detected increased expression of aP2 in lung and bronchoalveolar lavage fluid (BALF) in obese mice. Strikingly, severely obese (ob/ob) aP2 deficient mice were markedly protected against obesity-related airway hyperresponsiveness. These data strongly support that aP2 is a mediator of this unique form of airway disease associated with obesity in experimental models. To evaluate the translational implications of these observations, we measured serum aP2 in humans and found 25.4% higher aP2 concentrations (54.5 ± 19.2 vs 43.4 ± 20.1 ng/ml *$p<0.05$) in overweight and obese asthmatics compared to obese non-asthmatics. Importantly, higher levels of serum aP2 was positively correlated with asthma status only in overweight and obese individuals, whereas there was no significant difference between lean asthmatics vs non-asthmatics. (Groups; non-asthmatics and asthmatics BMI<25 vs BMI>25, n= 510, 15, 370, 15, respectively, analyzed by two-way ANOVA *$p<0.05$). The frequency of asthma was also 8% higher (50% vs 42%) in overweight and obese group as compared to lean subjects. With this line of investigation, we generated critical insights into obesity related asthma pathogenesis and showing that secreted aP2 might represent a well-validated and promising target for the development of a novel therapeutic strategy in humans.

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