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Interplay between Immune and Airway Smooth Muscle Cells in Obese Asthma

Increasing rates of obesity in children and adults have been associated with the development of severe, difficult-to-control asthma (1). Although some people with asthma and comorbid obesity have type 2–high disease, others experience airway disease associated with insulin resistance and metabolic dysfunction, with little in the way of type 2 inflammation. Asthma in obese people likely consists of many different endotypes of disease, and earlier work by Rastogi and colleagues identified a type of asthma in children with obesity characterized by insulin resistance, augmented T-helper cell type 1 (Th1) function, and upregulation of a pathway related to the Rho-family GTPase cell division cycle 42 (CDC42) in Th1 cells (2). CDC42 is critical in actin cytoskeleton assembly and mediates functions such as vesicle trafficking, orientation of receptors on the cell surface, chemotaxis, and cell adhesion (3). Although the observation of induction in this CDC42 pathway is fascinating, it provides limited insights into how changes in Th1 cell function might be linked to airway disease.

Clearly, airway reactivity is not simply mediated by T cells in isolation; many other cell types are involved. In this context, earlier work by Hakonarson and colleagues is relevant: Cooperative signaling between human airway smooth muscle (ASM) cells and T lymphocytes mediated induction of proasthmatic changes in ASM (4). Furthermore, Orfanos and colleagues identified hypercontractility of ASM cells isolated from individuals with obesity (5), suggesting that ASM changes could be involved in the asthma of obesity. However, the reasons for ASM dysfunction in obesity are not known. In this issue of the *Journal*, Yon and colleagues (pp. 461–474) set out to determine if perhaps there could be a link between Th1 cell dysfunction and ASM dysfunction that might provide insights into the pathogenesis of asthma in children with obesity (6).

Yon and colleagues first studied Th1 cells, then the ASM cells, and finally the interaction between these two cell types. The team used Th1 cells from obese children with asthma that expressed high levels of CDC42 and those from lean children that expressed very low levels of CDC42. The Th1 cells were first stimulated *in vitro* with CD3-CD28. The Th1 cells from obese children tended to have higher levels of the integrin LFA-1 (lymphocyte function–associated antigen 1), and migration in response to the ligand SDF-1 (stromal differentiation factor 1) was independent of CDC42. Although CDC42 is a biomarker identifying these cells, inhibition of this pathway did not affect migration. The investigators also included Th1 cells from three obese and three healthy-weight children without asthma as a control. A higher proportion of T-helper cells from obese children with asthma than from obese children without asthma migrated in response to SDF-1. These data suggest there may be altered expression of cell surface integrins and differences in chemotaxis responses between Th1 cells isolated from lean and obese children that are specific to obese asthma rather than just obesity.

The investigators then studied ASM from obese individuals and lean individuals without asthma obtained from lungs not suitable for transplant. The investigators found that cells from obese individuals expressed higher levels of ICAM-1 (intercellular adhesion molecule 1), the ligand for LFA-1 that mediates adherence of immune cells to smooth muscle. This suggests that ASM from obese individuals is more primed for adherence of immune cells than ASM from lean individuals. Indeed, in coculture experiments, Th1 cells from obese individuals with asthma adhered in greater number to ASM isolated from obese individuals than Th1 cells from

Supported by National Institutes of Health (R01 HL133920).

Originally Published in Press as DOI: 10.1164/rccm.202210-1870ED on October 11, 2022

lean individuals with asthma adhered to ASM from lean individuals. In addition, more Th1 cells from obese children with asthma (than obese children without asthma) adhered to ASM isolated from nonobese individuals. These data suggest enhanced interactions between T cells and ASM in the setting of obese asthma.

The team then investigated the molecular consequences of these enhanced interactions using total RNA sequencing and phosphoproteomics to understand changes in gene expression and protein modifications that might be involved in this phenotype of obese asthma. The combination of obese Th1 cells from individuals with asthma with obese ASM was associated with increased expression of genes and proteins involved in actin polymerization, endocytosis, cytokine signaling, chromatin remodeling, protein polymerization, and protein folding and decreased expression of genes and proteins involved in extracellular matrix function, muscle development, and carbohydrate metabolism. Effects on protein modifications and extracellular matrix are particularly relevant because obesity has been associated with changes in markers of extracellular remodeling (7, 8), and obesity (not just obese asthma) is associated with excessive dynamic airway collapse (9). These results illustrate that it is not just changes in the Th1 cells and the ASM cells individually but also likely the interaction between immune and structural cells that changes key pathways to induce airway disease related to obesity in children.

Although this was a small study, only 10 obese and 10 lean children with asthma (from a cohort of Hispanic and African American children aged 7–11 years with asthma), and focused only on Th1 cells and ASM cells, it illustrates that to understand how obesity affects the lung, we need to consider not just changes in the individual cell types but also how these come together to produce changes in system function. Obesity is not simply a physical impediment to lung expansion. Obesity fundamentally alters homeostasis of every cell, every cellular interaction, and every organ system. The paper by Yon and colleagues is a critical step forward in elucidating how changes in immune cell function and ASM exist in obesity and that the sum of the individual cellular changes can interact to produce major changes of relevance to the pathogenesis of airway disease in obesity. Future studies need to investigate how these interactions change over time and to unravel effects of obesity on other immune cells and structural cells in the lung to piece together the complex symphony of changes that contribute to altered airway function in obesity. Such studies are likely to reveal fundamental biological insights into how changes in subcellular metabolic function contribute to disease in the lung. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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