Scavenger Hunt: SR-B1, Adrenal Insufficiency, IL-17A, and Neutrophilic Airway Inflammation in Asthma

High-density lipoproteins (HDLs) are beneficial for both cardiovascular risk reduction and asthma (1, 2). APOA1 (apolipoprotein A1), which is the main structural protein of HDLs, is primarily synthesized in the liver and small intestine. APOA1 is then secreted into the blood where it interacts with ABCA1 (ATP-binding cassette subfamily A member 1) to efflux cholesterol from cells, which generates nascent HDL particles (3). HDL particles further interact with ABCG1 (ATP-binding cassette subfamily G member 1) on cells to efflux additional cholesterol and are ultimately taken up by hepatocytes via an interaction with SR-B1 (scavenger receptor, class B type 1), which functions as the physiologically relevant HDL receptor (3–5). Cholesterol is then metabolized into bile acids in the liver and excreted from the body. This process of HDL-mediated reverse cholesterol transport, in addition to maintaining normal cellular cholesterol homeostasis, also has antiinflammatory, antioxidative, antifibrotic, antithrombotic, and vasoprotective properties (4).

Pathways involving APOA1 and ABC transporters also modulate disease severity in asthma. APOA1 is expressed by alveolar epithelial cells and macrophages in the lung, whereas ABCA1 is expressed by pulmonary vascular endothelial cells and macrophages and ABCG1 is expressed by multiple cell types, including T cells, dendritic cells, macrophages, epithelial cells, and smooth muscle cells (6–8). For example, in an OVA (ovalbumin) model of allergic airways disease, *Apoa1*$^{-/-}$ mice have increased neutrophilic airway inflammation that was primarily mediated by G-CSF (granulocyte colony–stimulating factor) but was also associated with increased levels of IL-17A (6). Reciprocally, mice overexpressing the ABCA1 transporter under the control of the Tie2 promoter on vascular endothelial cells and macrophages have attenuated OVA-induced neutrophilic airway inflammation as well as G-CSF expression, whereas IL-17A was not modified (7). Following sensitization and challenge with OVA, *Abcg1*$^{-/-}$ mice display a phenotype of increased IL-17–mediated neutrophilic airway inflammation (8). Furthermore, T-helper 17 cells, γδ T cells, and neutrophils were identified as cellular sources of IL-17 in this model. Collectively, these studies support a link between cholesterol transport pathways and neutrophilic airway inflammation in the asthmatic lung (9).

The role of SR-B1 in modulating the pathogenesis of asthma, however, has not yet been established. In addition to serving as an HDL receptor, SR-B1 can bind a variety of other ligands including native and oxidized lipoproteins, advanced glycosylation end-product proteins, serum amyloid A, LPS, and apoptotic cells (5). In the lung, SR-B1 is expressed by alveolar macrophages, neutrophils, and alveolar epithelial cells and has been shown to play an important role in integrating innate immune responses during bacterial pneumonia (10). *Scarb1*$^{-/-}$ mice have a phenotype of increased mortality during pneumonia caused by *Klebsiella pneumoniae* due to impaired phagocytic killing by neutrophils that was associated with an increased bacterial burden, as well as defective LPS clearance. Furthermore, *Scarb1*$^{-/-}$ mice are adrenally insufficient, and corticosterone supplementation attenuated increases in neutrophilic inflammation but not mortality. Interestingly, SR-B1 also functions as a receptor on macrophages for silica that mediates canonical inflammasome activation, as well as lung inflammation and fibrosis (11).

In this issue of the *Journal*, Reece and colleagues (pp. 698–708) extend this line of investigation by assessing the role of SR-B1 in mediating IL-17A–dependent neutrophilic airway inflammation in asthma (12). Using house dust mite (HDM) and OVA as models of allergic airway inflammation, they show that *Scarb1*$^{-/-}$ mice have increased pulmonary neutrophilic airway inflammation and IL-17 production, thereby demonstrating generalizability of this finding across different antigens. Furthermore, HDM-challenged mice have increased SR-B1 expression in the lung. The authors next sought to characterize the cellular sources of IL-17 in the lungs of HDM-challenged *Scarb1*$^{-/-}$ mice. Flow cytometry experiments showed that there was no difference in the number of CD4^{+} T-helper 17 cells in the lungs of HDM-challenged wild-type and *Scarb1*$^{-/-}$ mice. In contrast, HDM-challenged *Scarb1*$^{-/-}$ mice had increased numbers of CD4^{-}/IL-17A^{+} cells, including CD45^{+}/Ly-6G^{+}/IL-17A^{+} neutrophils. This shows that the HDM-induced increases in IL-17A primarily emanated from non–T-cell sources. The causal role of IL-17 in mediating HDM-induced increases in neutrophilic lung inflammation was confirmed by experiments showing a reduction in lung neutrophils when a neutralizing anti–IL-17 antibody was administered. Taken collectively, these results are significant as they for the first time establish a function for SR-B1 in the pathogenesis of allergen-induced airways disease. Thus, all the cellular receptors (ABCA1, ABCG1, and SR-B1) that interact with HDL and/or APOA1 have now been shown to modulate neutrophilic airway inflammation in asthma. This provides strong support for the authors' conclusion that cholesterol receptors and/or cholesterol trafficking play a mechanistic role in IL-17–dependent neutrophilic inflammation in the lung.

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The authors also identify adrenal insufficiency as the mechanism underlying the increased neutrophilic inflammation and IL-17A production in HDM-challenged *Scarb1*$^{-/-}$ mice. This conclusion is based upon data showing that serum corticosterone levels were decreased 4 hours after the last HDM challenge and that corticosterone replacement reduced both neutrophils and IL-17A in the lungs of *Scarb1*$^{-/-}$ mice. SR-B1 is highly expressed in the adrenal gland, and multiple studies have shown that the HDL/SR-B1 pathway is necessary for the generation of stress-induced glucocorticoids (13). Consistent with this finding, adrenal insufficiency increases L-selectin expression on neutrophil cellular membranes, which promotes neutrophil influx into sites of inflammation (14). Thus, this study identifies a SR-B1/adrenal/IL-17A/neutrophil axis that regulates neutrophilic airway inflammation in asthma.

As with all interesting studies, this report also raises several questions for future investigations. Intriguingly, when neutrophils were depleted by anti-Gr1 antibodies, excess IL-17A production was not reduced in the lungs of HDM-challenged *Scarb1*$^{-/-}$ mice. This suggests that neutrophils were not the cellular source of IL-17A in this model. One limitation of this study, as pointed out by the authors, is that the relevant cellular source of IL-17A was not identified. Macrophages or γδ T cells were considered as possible sources, but these were not assessed experimentally. Other non-CD4^{+} T cells that express IL-17A include CD8^{+} (Tc17) cells, group 3 innate lymphoid cells, and natural killer T cells (15). Therefore, additional studies will be needed to identify the cellular source of IL-17A in the lungs of HDM-challenged *Scarb1*$^{-/-}$ mice. Future studies may also assess whether SR-B1 expression in the lung is necessary to modulate neutrophilic airway inflammation or whether SR-B1 expression in the adrenal gland is sufficient. If SR-B1 expression in the lung regulates neutrophilic airway inflammation in the setting of allergic airways disease, it would be interesting to identify the relevant SR-B1–expressing cell types and whether these lung cells coexpress IL-17A. The clinical relevance of SR-B1 in individuals with asthma and a neutrophilic inflammatory phenotype will also need to be ascertained. Thus, the report by Reece and colleagues in this issue of the *Journal* can serve as the foundation for future studies that continue the hunt for mechanisms by which the scavenger receptor, SR-B1, regulates IL-17–mediated neutrophilic airway inflammation in asthma (12). ■

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