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An innate link between obesity and asthma

Juan C Celedón & Jay K Kolls

The concordant epidemics of asthma and obesity are both associated with inflammation, and obesity has been shown to be an independent risk factor for asthma. A new study in mice indicates that part of the immunological connection between obesity and asthma involves inflammasome activation and production of the cytokine interleukin-17 by innate lymphoid cells in the lung (pages 54–61).

The last few decades have witnessed parallel epidemics of obesity and asthma among children and adults living in developed countries. In the United States, there were over 90 million obese people (~17% of children and ~36% of adults) in 2009–2010 (ref. 1). In this country, 26 million people (9.3% of children and 8.2% of adults) were affected with asthma in 2010 (ref. 2). Both obesity and asthma disproportionately affect certain minority groups (for example, African Americans and Puerto Ricans) and inner-city residents. Although multiple studies have supported an association between obesity and asthma, the underlying mechanisms for this link are largely unknown³. Most, but not all, population-based studies suggest that ‘obese asthma’ is mediated by nonatopic (meaning nonallergic) mechanisms. Of therapeutic relevance, being overweight or obese may lead to a decreased response to inhaled corticosteroids, which are the most commonly used type of medication for controlling asthma⁴. This effect may be mediated through nonatopic mechanisms, for example, those involving T helper type 17 (T_H17) cells⁵.

In this issue of *Nature Medicine*, Kim *et al.*⁶ provide new insights into the immunological basis of the link between obesity and asthma. In two different mouse models of obesity (wild-type mice fed a high-fat diet and mice fed a regular diet that are obese due to a mutation

in the gene encoding leptin (*ob/ob* mice)) they show that obesity leads to a profound increase in airway hyperresponsiveness (AHR), a key feature of asthma.

It was previously shown in mice that the adoptive transfer of T_H17 cells, which express interleukin-17 (IL-17), but not T_H2 cells, which express IL-4, IL-5 and IL-13 (and are more closely associated with atopic asthma), results in many features of nonatopic asthma, including neutrophilic airway inflammation and AHR that is refractory to steroid treatment⁵. As IL-17 has been reported to be a potential mediator of steroid-refractory asthma and nonatopic asthma⁵, the authors examined the role of IL-17 in obesity-associated asthma⁶. They found that mice deficient in IL-17A fed a high-fat diet became obese but lacked an increase in AHR, suggesting that IL-17A is required for this effect. These data are also consistent with recent

findings that, in addition to causing neutrophilic airway inflammation, IL-17A can also act directly on airway smooth muscle cells to increase their contractile response to cholinergic stimuli, which is a cardinal feature of AHR⁷ (Fig. 1).

Kim *et al.*⁶ then investigated which cells produce IL-17 in their diet-induced model of obesity, homing in on a subgroup of innate lymphoid cells (ILCs) that are lineage marker negative and positive for the markers Thy1.2, Sca-1, Ror γ t and IL-7 receptor (IL-7R). These ILCs did not express c-Kit or produce IL-5 or IL-13, similar to ILC2 cells⁸. Like T_H17 cells, the ILCs also expressed CCR6 but had low levels of T-bet and IL-22 and did not express interferon- γ (IFN- γ). Many IL-17-producing cells express the cytokine receptors IL-23R and IL-1R1, and the authors found that the IL-17-producing ILCs they identified (dubbed ILC3 cells) could be activated by the intrapulmonary

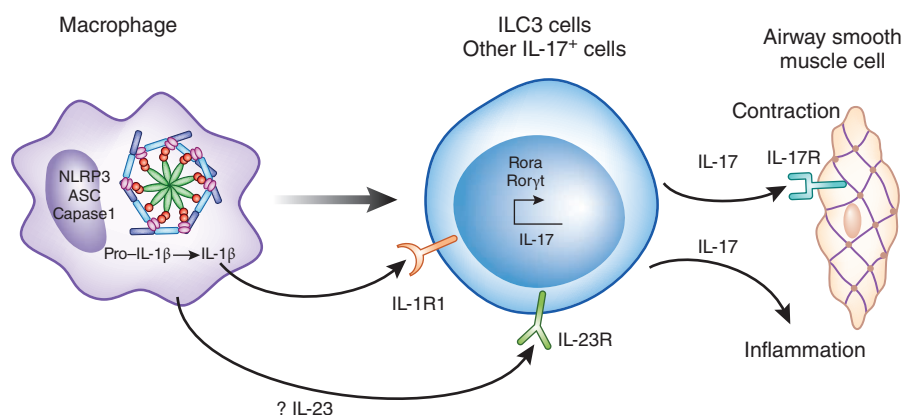


Figure 1 A model for the immunological mechanisms involved in obesity-induced AHR. The work of Kim *et al.*⁶ suggests that in the obese state, macrophages, the numbers of which increase in fat tissue in obesity, have an increase in NLRP3-mediated processing of IL-1 β . IL-1 β can induce the proliferation and activation of a group of ILCs (ILC3 cells) that produce IL-17, leading to increased AHR. The increase in AHR was reduced when IL-1R1 signaling was blocked or when IL-17 secretion was abrogated. It is possible that IL-23 may also have a role in this mechanism. It remains to be determined whether the IL-17-mediated increase in AHR requires IL-17-dependent inflammation, a direct effect of IL-17 on airway smooth muscle or both. ASC, apoptosis-associated speck-like protein containing a CARD; Rora, retinoid-related orphan receptor α ; Ror γ t, retinoid-related orphan receptor γ t.

Juan C. Celedón is in the Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Pediatric Environmental Medicine Center, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, USA. Jay K. Kolls is in the Division of Pediatric Pulmonary Medicine, Allergy and Immunology, Richard King Mellon Foundation Institute for Pediatric Research, Children's Hospital of Pittsburgh of UPMC, Pittsburgh, Pennsylvania, USA.
e-mail: juan.celedon@chp.edu or jay.kolls@chp.edu

administration of IL-1 β (which acts through IL-1R1) and activated to a lesser extent with IL-23 (ref. 6).

IL-1 β is expressed as a precursor that needs to be cleaved, which leads to its activation. This process involves the formation of a protein complex called the inflammasome, which, once assembled, leads to the caspase-1-mediated processing of IL-1 β . Kim *et al.*⁶ showed that obese mice have increased expression of IL-1 β and the inflammasome component NLRP3 in their lung tissue. *Nlrp3*^{-/-} mice fed a high-fat diet did not show an increase in lung IL-1 β production or develop AHR, indicating that NLRP3 is crucial for IL-1 β activation and subsequent AHR (Fig. 1). The authors then showed that this pathway could be successfully targeted using a recombinant protein, anakinra, which antagonizes IL-1R1 signaling.

Kim *et al.*⁶ then found that ILC3 cells responded to IL-1 β in obese *Rag2*^{-/-} mice, which lack T_H17 cells, suggesting that production of IL-17 by ILC3 cells, but not T_H17 cells, is crucial for obesity-associated AHR. Consistent with this finding, the authors showed that anti-Thy1.2 antibodies, which deplete ILC3 cells, could abolish IL-1 β -induced AHR. Administration of IL-1 α increased AHR in obese *Rag2*^{-/-} mice, presumably by also acting on IL-1R1. When the authors adoptively transferred ILC3 cells into *Rag2*^{-/-}; *Il2rg*^{-/-} mice, lacking mature T and B cells and ILCs, they were able to induce IL-1 β -mediated AHR in these mice.

Finally, Kim *et al.*⁶ detected ILC3-like cells analogous to those they found in mice in the bronchoalveolar lavage fluid in a small cohort of patients with asthma, representing the first time to our knowledge that such cells have been identified in human lungs. However, these cells were also present in two control individuals after nonantigenic phorbol myristate acetate and ionomycin stimulation, suggesting that there may be a stable subset of ILC3 cells in healthy human lungs.

Moving forward, it is currently unclear whether the NLRP3–IL-1–IL-17 pathway identified in this study (Fig. 1) only plays a part in regulating the basal tone of bronchial hyper-sensitivity or whether this pathway may also be potentially important in exacerbating asthma. In addition, it is unclear how IL-17 modulates AHR. Given the recent data that IL-17 itself can shift the cholinergic dose response in airway smooth muscle *ex vivo*⁷, IL-17 may be able to act directly on airway smooth muscle *in vivo* to mediate AHR (Fig. 1).

It will also be important to assess the immunological pathway identified by Kim *et al.*⁶ in stable subjects who have both obesity and asthma, as well as at the time of disease exacerbation. The authors' current preclinical study was limited to obese, non-allergen-sensitized mice, but given that some obese people have prior allergen sensitization, the cellular environment in the lung and the source of IL-17 may be different in this clinical setting from the mouse model described in this study. Although the experimental findings in mice may be not directly applicable

to all human subjects with asthma, the work of Kim *et al.*⁶ emphasizes the need to characterize subphenotypes of what is now broadly encompassed as 'obese asthma', which consists of both atopic and nonatopic versions of the disease. Given the existing challenges to clinical care such as achieving weight loss and controlling asthma in obese subjects, such phenotypic characterization could have profound implications in the diagnosis and treatment of this increasingly common condition.

Importantly, the pathway identified by the authors may be manipulated by the US Food and Drug Administration–approved IL-1R1 antagonist anakinra, as well as by drugs that target IL-1, IL-17A and IL-17RA currently in clinical trials. However, careful phenotyping of patients at the cellular level will be necessary to define the optimal subgroups for clinical trials to evaluate the therapeutic potential of these candidate drugs in obese asthma.

COMPETING FINANCIAL INTERESTS

The authors declare no competing financial interests.

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