



Guest Editorial

Revisiting fatal asthma

Severe asthma affects up to 10% of the asthma population and remains poorly understood with few therapeutic options. Unfortunately, asthma deaths still occur, yet the reasons why some patients succumb to asthma compared with others is unknown. Given that many phenotypes of asthma have now been described, it is likely that different mechanisms may lead to death in select subgroups of asthmatics. Those with virally-induced exacerbations may have more prominent mediators of innate inflammation, including neutrophils, while those with other triggers, including allergens, with or without infections, demonstrate more prominent eosinophilia.¹ In this issue of the *Annals of Allergy Asthma and Immunology*, Oda et al. describe a novel association of increased interleukin (IL)-18 and IL-18 receptor expression in inflammatory cells, epithelial cells, and smooth muscle in non-smoking subjects with fatal asthma, as compared with those with mild asthma and controls.² Consistent with prior studies of fatal asthma, they also observed evidence of severe airway remodeling, including mucus plugging, goblet cell hyperplasia, smooth muscle hypertrophy, submucosal gland hyperplasia, basement membrane thickening, and eosinophilic inflammation. The authors note that similar to a few earlier reports, they found a marked increase in CD8+ T cells in fatal asthma, ultimately theorizing that IL-18 may activate CD8+ T cells in subjects with severe asthma, potentially leading to a fatal outcome. Neutrophilic inflammation was notably similar between those with fatal asthma and mild asthma.

Perhaps the most novel aspect to their study was an increase in IL-18 positive cells. IL-18 was initially described as an IFN γ -inducing cytokine, though it has also been demonstrated to affect Type-2 cytokine expression (by T cells, natural killer cells, mast cells, and basophils) and immunoglobulin E production. It is primarily produced by macrophages, but T cells, B cells and epithelial cells, among others, have also been demonstrated to produce IL-18.³ Models of asthma in IL-18 deficient mice have less airway remodeling and inflammation, while increased IL-18 expression is associated with increased airway inflammation and hyper responsiveness.⁴ In humans, serum IL-18 levels were shown to be significantly higher in association with an acute exacerbation in mild-moderate asthmatic patients.⁵ Further, polymorphisms in the IL-18 receptor have been consistently associated with asthma in multiple genome wide association studies.⁶ Yet the mechanisms by which IL-18 worsens asthma remains poorly understood.

While the link between IL-18 and asthma risk and severity, although small, has been quite consistent, the role of CD8+ T cells in asthma is still not entirely clear. CD8+ memory T cells inhibited allergic sensitivity in mice in one study, yet in another mouse study

inhibition of CD8+ T cells attenuated respiratory syncytial virus-enhanced allergic inflammation.^{7,8} It appears that a subset of CD8+ T cells that produce type 2 cytokines might be important in airway hyper-responsiveness and inflammation.⁹ Interestingly, the percentage of CD8+ T cells producing IFN γ from the blood of asthmatics was correlated with asthma severity, eosinophil counts, and bronchial hyperresponsiveness.¹⁰ Whether these cells represent different subsets of CD8+ T cells or a single population that can produce both IFN γ and type 2 cytokines remains to be determined.

Oda et al.'s results suggest there may be a role for an action of IL-18 on CD8+ T cells that may contribute to fatal asthma. Perhaps in the presence of virus and/or allergen, IL-18 overproduction in genetically susceptible individuals induces CD8+ T cell subpopulations to produce both Th1 and Th2 cytokines. This paradoxical combination of cytokines could increase the complexity of the inflammatory process and contribute to the bronchoconstriction and mucus plugging that causes asthma deaths. Whether these results can be generalized to a more genetically diverse population remains to be seen. Mechanistic studies are now required using both animal models and human in vitro systems to determine the activation pathways which contribute to the inflammatory process. Depending on these results, targeting the IL-18 pathway for novel asthma treatments should be considered.

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