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Shedding LIGHT on severe asthma

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Abstract

Moderate to severe asthma is difficult to treat because recurring bouts of inflammation in the lungs induce fibrosis, which reduces lung elasticity, gas exchange and responses to conventional therapy. A recent study identifies the tumor necrosis factor family member LIGHT as an essential mediator of airway fibrosis in a mouse model of chronic asthma (pages 596–603).

The majority of asthma cases can be effectively managed with a combination of inhaled medications. Corticosteroids, which are slow-acting anti-inflammatory drugs, reduce the frequency and severity of asthma attacks, and faster-acting bronchodilators relax airway smooth muscles. However, these treatments are much less effective in the 5–10% of people who suffer from severe asthma¹. These individuals typically have more frequent attacks and are at an increased risk of dying during an attack, because their airways have permanently narrowed as a result of chronic inflammation and its associated scarring (lung remodeling). Although asthma mortality rates are typically low, severe asthma attacks can result in death by suffocation. Indeed, there are approximately 4,200 asthma-related deaths each year in the US alone², thus emphasizing the need for more aggressive treatment strategies that can decrease the progression of lung remodeling in asthma.

Asthma is associated with a T cell-mediated immune response and is typically regarded as a T helper 2 type 2 (T_H2) disorder. CD4⁺ T_H2 cells produce the cytokines interleukin-4 (IL-4), IL-5 and IL-13, which participate in the recruitment of eosinophils, one of the dominant inflammatory cell types in the airways of people with asthma. However, as the disease advances and becomes chronic, it can adopt additional characteristics that include corticosteroid refractoriness and neutrophilic inflammation. When this happens, T_H1 and T_H17 responses emerge, which are defined by the production of interferon- γ and IL-17, respectively. These cytokines show strong proinflammatory activity and participate in neutrophil recruitment. Thus, it has been hypothesized that when asthma progresses from a mild to a severe form of the disease, the immune response switches to a mixed cytokine response involving T_H2, T_H1 and T_H17 cells. At this stage, increases in the production of tumor necrosis factor- α (TNF- α), lymphotoxin and other TNF family members are also commonly seen³.

In this issue of *Nature Medicine*, Doherty *et al.*⁴ identify the TNF family member LIGHT (lymphotoxin-related inducible ligand that competes for glycoprotein D binding to herpesvirus entry mediator on T cells; also known as TNFSF14) as a crucial regulator of airway remodeling in mouse models of chronic asthma. They show that blockade or absence

of LIGHT reduced subepithelial fibrosis, smooth muscle hypertrophy and hyperplasia, and airway hyper-responsiveness after allergen challenge but did not affect airway eosinophilia⁴. The authors also show that the production of the profibrotic cytokines transforming growth factor- β (TGF- β) and IL-13 by macrophages and eosinophils, respectively, is important in LIGHT-induced remodeling⁴. These results suggest that LIGHT could be targeted to treat airway remodeling in asthma. This is noteworthy because there are currently no drugs available that specifically target the mechanisms of asthmatic lung remodeling.

LIGHT is a membrane-expressed protein related to the membrane form of lymphotoxin (LT $\alpha\beta$)⁵. Both proteins are expressed in various tissues, with the greatest expression found in the lung, spleen and thymus. LIGHT binds the herpesvirus entry mediator (HVEM) and competes with LT $\alpha\beta$ for binding to the lymphotoxin β receptor (LT β R)^{5,6}. LIGHT was originally characterized as a co-stimulatory factor on lymphoid cells and as an inhibitor of herpesvirus infection⁶⁻⁸; however, it has also been shown to increase the severity of various T cell-mediated diseases^{8,9}.

Because other TNF family members have been shown to be involved in the pathogenesis of asthmatic inflammation³, Doherty *et al.*⁴ examined whether the development of allergen-induced asthma is regulated by LIGHT. Using a soluble inhibitor of LIGHT (a fusion protein of LT β R) or LIGHT-deficient mice, they showed that development of peribronchial fibrosis and smooth muscle hypertrophy was markedly reduced in the absence of LIGHT after chronic exposure to house dust mite allergen or to ovalbumin, a model allergen. The decrease in lung remodeling was also associated with a marked reduction in airway hyperresponsiveness, suggesting an overall improvement in airway physiology in the absence of LIGHT.

Notably, production of the profibrotic cytokine TGF- β , which is known to stimulate extracellular matrix production by fibroblasts¹⁰, was significantly reduced in allergen-challenged LIGHT-deficient mice. Agonists of LT β R signaling were also shown to induce TGF- β -dependent peribronchial fibrosis. The authors identified LT β R-expressing macrophages located in the subepithelial region of the lung as the primary producers of TGF- β in their model system. Because TGF- β -producing macrophages have been implicated in the pathogenesis of a number of lung remodeling diseases, including chronic obstructive pulmonary disease, asthma and hypersensitivity pneumonitis¹¹, they concluded that controlling the number of TGF- β -producing lung macrophages might be, at least in part, how LIGHT stimulates subepithelial fibrosis in asthma.

Eosinophils have also been implicated in the development of subepithelial fibrosis in asthma, largely because they are important producers of the profibrotic cytokine IL-13 (ref. 12). Like TGF- β , IL-13 is an important mediator of lung remodeling, and expression of IL-13 is elevated in the lungs of people with evidence of asthmatic remodeling¹³. TGF- β and IL-13 have also been shown to synergistically increase the development of pulmonary fibrosis¹¹. Doherty *et al.*⁴ observed a marked reduction in IL-13 expression in the lungs of allergen-challenged LIGHT-deficient mice. Notably, they observed no reduction in T_H2 cell differentiation or recruitment, thereby suggesting that the impaired IL-13 response in *Tnfrsf14*^{-/-} mice might be attributed to another cell type.

The authors then identified eosinophils as the likely culprit, as these cells had high intracellular expression of IL-13 in mice that had been subjected to the chronic asthma protocol⁴. They found that eosinophils expressed HVEM, and recombinant LIGHT treatment of cultured eosinophils from antigen-sensitized mice triggered IL-13 production, presumably by LIGHT binding to HVEM. Thus, the studies of Doherty *et al.*⁴ show that LIGHT-LT β R or LIGHT-HVEM interactions promote lung remodeling in asthma by simultaneously

increasing TGF- β production by macrophages and IL-13 expression in eosinophils. Moreover, both of these mechanisms have been implicated in asthmatic airway remodeling in humans¹².

TNF family members have been identified as therapeutic targets in a variety of chronic inflammatory diseases, including rheumatoid arthritis and Crohn's disease¹⁴. Similarly to LIGHT, TNF- α has been implicated in asthma pathogenesis. This factor upregulates adhesion molecules, facilitates the migration of inflammatory neutrophils and eosinophils (Fig. 1), and activates profibrotic mechanisms in the airway. Recombinant TNF- α has also been shown to directly increase airway hyper-reactivity³. Production of TNF- α and LIGHT in the lung also correlates with decreased lung function in people with asthma, suggesting a possible role for both TNF- α and LIGHT in the pathogenesis of severe asthma¹⁴. Thus, LIGHT could represent a new target for therapy of asthma-related airway remodeling.

Given that TNF- α , LIGHT and LT $\alpha\beta$ have all been linked to airway remodeling in asthma, it is necessary to better understand how these proteins are regulated at various stages of the disease. The major cell types that produce TNF- α , LT $\alpha\beta$ and LIGHT also remain unclear. Because LIGHT and LT $\alpha\beta$ are expressed on the cell surface, it will be crucial to understand whether they require direct cell-to-cell contact or whether they must be shed or cleaved before engaging their receptors. Also, because herpes simplex virus establishes infection by binding to HVEM, it will be interesting to determine whether recurrent HSV infection and HVEM engagement predisposes individuals to pulmonary fibrosis.

Although Doherty *et al.*⁴ showed that LIGHT directly upregulated the production of TGF- β 1 in macrophages and IL-13 production in eosinophils, IL-13 blocking and cell depletion studies were not done to definitively prove that LIGHT-induced remodeling is dependent on IL-13, macrophages and eosinophils. Finally, if LIGHT is to be developed as a treatment for asthma-related remodeling, future research should focus on determining whether anti-LIGHT therapeutics can slow or reverse the progression of established airway disease.

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Figure 1.

Direct and indirect effects of LIGHT signaling in chronic asthma. Doherty *et al.*⁴ show that the TNF family member LIGHT, which is expressed by activated B and T lymphocytes, can bind and signal through HVEM or LTβR, which is expressed on many cell types. Effects of LIGHT during chronic asthma may result from its direct interactions with fibroblasts, smooth muscle cells (SMCs) and epithelial cells. The effects of LIGHT on these cells may also be amplified indirectly via TGF-β and IL-13, which are induced in macrophages and eosinophils, respectively, thereby facilitating subepithelial fibrosis, smooth muscle hypertrophy and hyperplasia, epithelial-mesenchymal transition (EMT) and airway hyper-reactivity.