

Inhibiting or blocking LIGHT, a TNF superfamily member, for treating airway remodeling

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Evaluation of: Doherty TA, Soroosh P, Khorram N *et al.* The tumor necrosis factor family member LIGHT is a target for asthmatic airway remodeling. *Nat. Med.* 17, 596–603 (2011).

Individuals with chronic asthma demonstrate a progressive decline in lung function that is thought to be due to structural remodeling of the airways, characterized by subepithelial fibrosis and smooth muscle hyperplasia. Here we report on a recent publication showing that the tumor necrosis factor family member LIGHT is expressed on lung inflammatory cells after allergen exposure. Pharmacological inhibition of LIGHT using a fusion protein between the IgG Fc domain and lymphotoxin- β -receptor reduces lung fibrosis, smooth muscle hyperplasia and airway hyperresponsiveness in mouse models of chronic asthma, despite having little effect on airway eosinophilia. LIGHT-deficient mice also show a similar impairment in fibrosis and smooth muscle accumulation. Blockade of LIGHT suppresses expression of lung TGF- β and IL-13, cytokines implicated in remodeling in humans, whereas exogenous administration of LIGHT to the airways induces fibrosis and smooth muscle hyperplasia; thus, LIGHT may be targeted to prevent asthma-related airway remodeling.

KEYWORDS: airway remodeling • asthma • LIGHT • TNF superfamily members • TNF- α

Asthmatic airway remodeling is the pathophysiological modification of the normal airway wall structure, which includes changes in the composition and organization of its cellular and molecular constituents. These modifications are the major cause of the symptoms associated with decreased pulmonary function. TNF- α might play a central role in airway remodeling [1]. However, in the absence of human studies specifically examining airway tissue, there is little evidence that anti-tumor necrosis factor (TNF) agents affect remodeling in asthmatic subjects.

TNF- α is just the prototype of several members of the TNF superfamily (TNFSF). TNFSF members, including TNF itself, are being recognized as key mediators in asthmatic inflammation and might play a central role in airway remodeling. In addition, the TNFSF ligand LIGHT (TNFSF14) might be involved in driving aspects of lung inflammation or have a role in airway remodeling. Using two mouse models of chronic asthma and a therapeutic blocking strategy, Doherty and colleagues [2] have explored the role of LIGHT in controlling the extent of airway remodeling.

Summary of methods & results

Doherty and colleagues [2] have hypothesized that LIGHT might be involved in driving aspects of lung inflammation or have a role in airway remodeling. Using two mouse models of chronic asthma and a therapeutic blocking strategy, they have shown that LIGHT is crucial for airway remodeling and airway hyperresponsiveness. In particular, the authors have documented that LIGHT is expressed on lung inflammatory cells after allergen exposure. Pharmacological inhibition of LIGHT using a fusion protein between the IgG Fc domain and lymphotoxin- β -receptor (LT β R) reduces lung fibrosis, smooth muscle hyperplasia and airway hyperresponsiveness in mouse models of chronic asthma, despite having little effect on airway eosinophilia. LIGHT-deficient mice also show a similar impairment in fibrosis and smooth muscle accumulation. Interestingly, blockade of LIGHT suppresses expression of lung TGF- β and IL-13. Collectively, the data of this study indicate that LIGHT is required in models of chronic asthma for maximal expression of two of the primary cytokines thought to promote

airway remodeling, and that LIGHT–LT β R or LIGHT–herpesvirus entry mediator (HVEM) interactions promote proremodeling activities of lung macrophages and lung eosinophils, two of the cell types associated with chronic asthma and remodeling in humans.

Discussion

A body of evidence suggests that TNF- α plays a significant role in many inflammatory diseases of the lung [1]. TNF- α is expressed in asthmatic airways and may play a key role in amplifying asthmatic inflammation through the activation of nuclear factor κ -B, AP-1 and other transcription factors [3]. Elevated levels of TNF- α have been observed in induced sputum and in bronchoalveolar lavage fluid (BALF) from asthmatic patients, and upregulated TNF expression has been detected in alveolar macrophages, mast cells and bronchial epithelial cells [1].

Considering the critical role of TNF- α in the pathogenesis of asthma and the need for alternative treatments for those asthmatic patients with severe disease who are particularly resistant to conventional therapy, molecules targeted at blocking the effects of TNF- α are likely to constitute a considerable advance in the management of these difficult patients [1,4]. Indeed, some trials have explored the possibility of using TNF- α inhibitors, such as infliximab, golimumab and etanercept in asthmatic patients. However, some uncontrolled or small studies reported in the literature indicate that TNF- α inhibitors are only effective in a relatively small subgroup of patients with severe asthma, possibly defined by an increased TNF axis [1,4]. Moreover, a large multicenter trial with golimumab showed no beneficial effect on lung function, symptoms or exacerbations, and there were increased reports of pneumonia and cancer [5].

We could postulate that heterogeneity in response to TNF- α antagonism could lie in the genetics of TNF- α , as polymorphisms in the gene encoding TNF- α , particularly in the guanine to adenine transition at position 308, have been associated with an increased risk of asthma in some studies [6]. This aspect needs to be addressed in future studies of anti-TNF- α .

On the other hand, we cannot exclude that the true problem is that patients enrolled in the different trials have been considered as subjects of a general population with the same characteristics, since we consider severe asthma as a homogeneous disease, and recruited using arbitrary clinical and physiological criteria [1]. On the contrary, severe asthma is a heterogeneous disease that has features that occur with different phenotypes that remained poorly characterized and with little known about the underlying pathobiology contributing to them [7]. It is likely that the definition of these phenotypes will allow us to study the correct patient population and it is likely that, if we choose the right outcome measure, we will understand which kind of patients can benefit from TNF- α inhibitors.

TNF- α might play a central role in airway remodeling and induce glucocorticoid resistance, myocyte proliferation, vascular remodeling, and stimulation of fibroblast growth and maturation into myofibroblasts by promoting TGF- β expression [4]. However, Wenzel and colleagues [5] found patients with reversible airflow

obstruction at enrollment had a significantly improved response to golimumab therapy, as reflected by a decrease in exacerbations, thus suggesting that patients with fixed airway disease represent a phenotype that is less responsive to anti-TNF agents. In the absence of human studies specifically examining airway tissue, there is little evidence that anti-TNF agents affect remodeling in asthmatic subjects.

There is another possibility that must be considered: TNF- α is the most widely studied cytokine member of TNFSF but it is just the prototype of several members of this family of related proteins that share common features [8]. Building on TNF as a prototype, the past 27 years have seen the identification and exploration of an entire TNFSF and TNF receptor-like molecules. The TNFSF includes receptors for the TNFSF ligands (TNFRSF) and there are at least 19 ligands and 30 receptors [9]. Ligand activation of TNFRSF members modulates cell proliferation, survival, differentiation and apoptosis. Such cellular events participate in a broad array of biological processes such as inflammation, fibrosis, the immune response and tissue repair [8].

LIGHT is a TNFSF member that is naturally expressed on activated CD4⁺/CD8⁺ T cells, dendritic cells (DCs), monocytes and natural killer cells, is a key component of the communication system that controls the responses of T cells [10] and is implicated as a mediator of inflammatory, metabolic and malignant diseases. It is an acronym for homologous to lymphotoxins that shows inducible expression and competes with herpes simplex virus glycoprotein D for HVEM, a receptor expressed by T lymphocytes [11] and the LT β R [12], and is inhibited by soluble decoy receptor-3 [13]. The LIGHT–HVEM pathway is an important cosignaling pathway for T cells, whereas LIGHT–LT β R modifies the functions of DCs and stromal cells by creating tissue microenvironments, that promote immune responses. HVEM also binds an immunoglobulin superfamily member and B and T lymphocyte attenuator, which inhibits T-cell activation [10].

Tumor necrosis factor-related cytokines function as key communication systems between cells of the immune system and mediate inflammation and tissue destruction [1,4]. Multiple lines of evidence indicate the involvement of different TNFSF cytokines in the pathogenesis of asthma [14]. Consequently, it is likely that there is no effect or only a moderate clinical benefit when a single TNFSF molecule–TNFRSF interaction is manipulated.

The study by Doherty and colleagues [2] is extremely important for two main reasons. First of all, the documentation that by neutralizing LIGHT we can reduce airway hyperresponsiveness, despite no robust effects on the peribronchial immune infiltrates, supports the opinion that airway hyperresponsiveness correlates more with remodeling changes than the degree of cellular infiltrates in the lung. This finding questions the importance of anti-inflammatory therapy with corticosteroids in influencing the natural history of asthma and is the likely explanation of the fact that there are patients suffering from severe asthma that is not controlled even by high doses of systemic corticosteroids [15]. In effect, the severity of asthma and level of lung function impairment are also associated with increased mass of peribronchial smooth muscle [16]. Second, but no less important, the role for

LIGHT in airway remodeling may lead to strategies targeting this molecule in asthmatic airway remodeling, or other diseases involving fibrosis and remodeling.

Expert commentary & five-year view

TNFSF/TNFRSF members mediate different functions that depend on the surrounding milieu [8]. Unraveling their complex and pleiotropic actions will be essential for their use as therapeutic targets. The lymphotoxin signaling axis, consisting of LIGHT and LT α 1 β 2 ligands interacting with HVEM and LT β R receptors, has strong support as an inflammatory pathway in animal models [17]. Inhibiting or blocking LIGHT from interacting with its receptors, HVEM or LT β R, can be used as an anti-inflammatory, for example, to inhibit or suppress asthmatic inflammation, as well as treat airway remodeling, among other inflammatory conditions, diseases and disorders. However, efforts to interfere with this pathway in human disease have been disappointing, at least in rheumatoid arthritis [8]. As we have stressed previously, it is likely that there is no effect or only a moderate clinical benefit when a single TNFSF molecule–TNFRSF interaction is manipulated.

This is especially true for airway remodeling in asthma, in which several mediators of remodeling have been identified including TGF- β , IL-4, IL-9, IL-11, IL-13, IL-17 and VEGF [18], but the relationship between inflammation and remodeling is still highly debatable and incompletely understood. In any case, we must still establish individual components of airway remodeling that contribute to the clinical manifestations of asthma, ascertain whether all remodeling is detrimental to asthma, and identify the components of remodeling that should be targeted and at what point in the natural history of treatment they should be initiated to achieve the best results [19]. It is unlikely that in the next 5 years we will achieve all of this.

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Key issues

- Tumor necrosis factor family member LIGHT is essential for airway remodeling in several mouse models of chronic asthma.
- Blockade of LIGHT, after acute inflammation is established in the lung, substantially reduces airway fibrosis and smooth muscle hyperplasia, two factors associated with a decline in lung function in human asthmatics.
- The role for LIGHT in airway remodeling may lead to strategies targeting this molecule in asthmatic airway remodeling or other diseases involving fibrosis and remodeling.

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