

INSIGHTS

Sounding the alarm in the lung with TL1A

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Environmental airborne antigens are central to the development of allergic asthma, but the cellular processes that trigger disease remain incompletely understood. In this report, Schmitt et al. (<https://doi.org/10.1084/jem.20231236>) identify TNF-like protein 1A (TL1A) as an epithelial alarmin constitutively expressed by a subset of lung epithelial cells, which is released in response to airborne microbial challenge and synergizes with IL-33 to drive allergic disease.

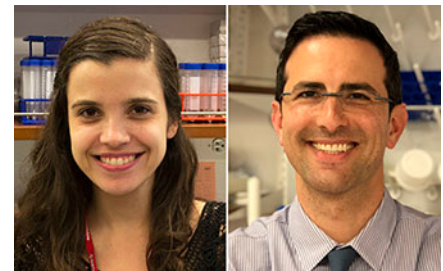
TL1A is a TNF superfamily member that signals through its monomeric receptor, called death receptor 3 (DR3) (Bamias et al., 2013). Genetic variants in *TNFSF15* (which encodes TL1A) have been linked to the pathogenesis of several autoimmune diseases and confer higher risk for more aggressive inflammatory bowel disease. TL1A is highly expressed in human colonic tissue during active colitis, and emerging data from clinical trials suggest that its blockade reduces inflammation in ulcerative colitis (Danese et al., 2021). Schmitt et al. (2024) now demonstrate a new role for TL1A as an alarmin in the lung that coordinates rapid and transient responses to allergic challenges.

Immune complexes as well as bacterial products are known inducers of TL1A in immune cells (Shih et al., 2009). In the intestine, inflammation induces TL1A production primarily by mononuclear phagocytes (MNP) in the lamina propria (Longman et al., 2014). Microbiota and MyD88 are required for induction of *TNFSF15* transcription in intestinal MNP, and gut epithelial cell-adherent bacteria are sufficient to promote this in vivo (Castellanos et al., 2018). Here, Schmitt et al. (2024) reveal a new mechanism by which lung epithelial cell damage induced by the fungal aeroallergen *Alternaria alternata* triggers rapid and transient release of TL1A.

Surprisingly, the authors find that alveolar epithelial cells profiled in human lung

single cell datasets constitutively express *TNFSF15*. This finding contrasts with the intestinal model in which *TNFSF15* is: (i) produced by immune cells or endothelial cells and (ii) regulated by transcription. The human datasets map *TNFSF15* expression to basal cells in both the upper and lower airways, which are spatially positioned to respond to external signals and cooperate with other alarmins including IL-33. Mouse single cell data revealed that TL1A is preferentially expressed by alveolar type 1 (AT1) cells, while IL-33 is primarily expressed by AT2 cells. This cell type specificity may reflect distinct basal transcription machinery in contrast to the inducible transcription in immune cells. In addition, the impact of *TNFSF15* variants on TL1A expression in immune cells may depend on cell type specificity (Richard et al., 2018). A recent study also linked *TNFSF15* variants associated with childhood asthma (Kim et al., 2022) and it will be of interest to know how risk variants may impact TL1A levels in the bronchoalveolar lavage (BAL).

Constitutive expression of TL1A highlights the need for a new mechanism by which TL1A regulates the immune response. Here, the authors propose that membrane damage and cell death (as measured by lactate dehydrogenase increase) enable rapid (and transient) release of TL1A as an alarmin into the BAL fluid. In vitro experiments showing TL1A release following exposure to



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other inducers of cell damage suggest that this mechanism could be shared by multiple allergens that induce cell damage. TL1A is a type II membrane protein which exists as a stable membrane-bound trimer and can be cleaved by matrix metalloproteinases to release a soluble functional TL1A, but the mechanism of TL1A release into the BAL fluid remains to be elucidated. Repeated allergen exposure induced similar immune responses supporting the potential role for this process in both acute as well as chronic exposure. These kinetics parallel observations of TL1A in BAL from humans with both mild asthma and severe eosinophilic asthma following allergen challenge and may help to explain the broader impact of TL1A in human asthma (Machida et al., 2020).

Another exciting aspect of this work is the identification of the role for TL1A in promoting IL-9-producing ILC2s. Early

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studies revealed a role for TL1A in enhancing effector T cell responses including pathogenic Th1 and Th17 cells (Valatas et al., 2019). TL1A was found to be a key regulator in the differentiation of IL-9-producing T cells (Th9) which promoted immunopathology in allergic lung models (Richard et al., 2015). In addition to T cells, TL1A also activates a broad range of innate lymphoid cells (ILCs) including ILC2 expansion and pathogenicity in innate models of allergic lung inflammation (Meylan et al., 2014). By blocking TL1A, this work highlights the role for TL1A in driving rapid production of IL-9 (within 6 h of exposure) and, in contrast to IL-33, independent of IRF4 expression. Adoptive transfer experiments performed in this work revealed that TL1A combined with IL-33 (compared to IL-33 alone) activated ILC2s to induce more IL-5-dependent disease-associated eosinophilia in the BAL fluid and lungs. Although human data are limited, analysis of serum cytokines from a Phase 2 study evaluating anti-TL1A therapy for the treatment of ulcerative colitis identified a reduction in IL-5 following therapy, which was more significant in clinical responders (Hassan-Zahraee et al., 2022). Further work is needed to determine if this lung-associated TL1A-ILC2 pathway is driving allergic lung disease in humans.

TL1A is well known as a “amplifier” of cytokine signaling in T cells, macrophages, and ILCs (Valatas et al., 2019). TL1A “co-stimulation” of CD4⁺ lymphocytes enhances production of IL-2 and promotes activation even in suboptimal conditions. In macrophages, TL1A induces autocrine signaling that synergizes with bacterial-derived triggers of NOD2 to enhance cytokine production (Hedl and Abraham, 2014).

Similarly, in ILCs, TL1A synergizes with macrophage-derived IL-23 to promote IL-22 production and mucosal healing (Castellanos et al., 2018). These findings highlight not only TL1A’s ability to amplify cytokines signals, but also a unique ability to confer context-dependence of tissue-specific responses. The synergy identified in this work between lung epithelium-derived IL-33 and TL1A confers a mechanism for both tissue-specific amplification as well as rapid and transient regulation of the ILC9 response during allergic immunopathology. Thus, key features of the rapid and potent regulation are coordinated by lung tissue cell residents which afford a tight regulation of this immune response. IRF4, JunB, and BATF are all highly expressed in ILC9 cells, but the authors identify the specific upregulation and phosphorylation of STAT5 which was mechanistically required for IL-9 expression. Molecular specificity of the cell type and tissue-specific responses may provide key insights into managing TL1A-related therapeutic strategies in a variety of disease areas.

The molecular factors regulating tissue fibrosis downstream of chronic inflammation also remain a major challenge in the study of lung and intestinal diseases. While TL1A amplification of cytokine signaling during chronic inflammation may contribute to fibrosis and tissue remodeling, the identification here of TL1A as an epithelial alarmin helps to reinforce the possibility of a direct epithelial-stromal cell communication (Valatas et al., 2019). Recent studies revealing TL1A receptor expression on human lung fibroblasts as well as the ability of TL1A to promote fibroblast proliferation and

collagen deposition highlight the therapeutic potential for targeting this pathway in chronic disease (Herro et al., 2020).

Overall, this work highlights a new role for TL1A as an epithelial cell alarmin in the lung and introduces a new mechanism by which TL1A regulates the immune response. The cell and tissue specificity as well as the molecular mechanisms enable a rapid, transient, and repeatable process of immune activation. These findings will help guide the potential use of emerging anti-TL1A therapies in human disease.

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