



Recent advances in epithelium-derived cytokines (IL-33, IL-25, and thymic stromal lymphopoietin) and allergic inflammation

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Purpose of review

Allergic diseases are thought to be driven by aberrant immune responses. Epithelium responds to various environmental factors by releasing key cytokines, such as thymic stromal lymphopoietin (TSLP), IL-33, and IL-25. Although there are important differences among these cytokines, there are also similarities which confound a clear understanding of the exact roles of these cytokines. The purpose of this review is to analyze the advances in biology and functions of these cytokines over recent years, elucidate their differences and similarities, and provide new conceptual understanding as to their roles in allergic diseases.

Recent findings

There are distinct differences in the timing, onset, and kinetics of the responses and perhaps in the potency of action of TSLP, IL-33, and IL-25. Newer roles of these cytokines have been described, including airway remodeling and fibrosis-related functions (TSLP, IL-33, and IL-25), fetal–maternal interface (IL-33 and TSLP), T-cell biology (TSLP), group 2 innate lymphoid cell biology (TSLP, IL-33, and IL-25), and mast cell–neutrophil axis (IL-33). Novel roles of these cytokines in the pathogenesis of atopic dermatitis and asthma have also been described.

Summary

TSLP, IL-25, and IL-33 are increasingly recognized to play important roles in the pathophysiology of allergic diseases. More clear recognition of the differences and similarities of the immunological pathways mediated by these cytokines would help optimize the treatment for allergic diseases.

Keywords

airway remodeling, allergic inflammation, asthma, atopic dermatitis, IL-25, IL-33, thymic stromal lymphopoietin

INTRODUCTION

Thymic stromal lymphopoietin (TSLP), IL-25, and IL-33 are produced by the epithelial cells as well as other cell types, and they show profound downstream effects on various immune cells. There have been important advances in recent years regarding the function of these cytokines, including induction of Th2-type adaptive responses and discovery of the group 2 innate lymphoid cells (ILC2s) [1]. Genome-wide association studies (GWAS) have shown the association of asthma and polymorphisms of several genetic loci, including *IL1RL1*, *TSLP*, and *IL-33* [2]; *IL1RL1* encodes ST2, the receptor for IL-33. Increasing evidence suggests the associations between these cytokines and allergic diseases, but the immunologic mechanisms, by which these cytokines influence the allergic immune responses, have only

recently begun to be revealed. Although there are some similarities in the biology and function of these cytokines, better understanding of the differences is also likely to be critical of the elucidation of roles of these cytokines in human disease. This review will focus on the important recent advances in the fields of TSLP, IL-33 and IL-25 biology, and provide a high-level view with a specific focus on overlapping and distinct features.

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KEY POINTS

- TSLP, IL-33, and IL-25 may play important roles in tissue remodeling, regulation of innate and adaptive type 2 immune responses, and maintenance of tissue homeostasis.
- There are both similarities and distinct differences in the biological functions and potency of these cytokines.
- These cytokines likely play important roles in the initiation, regulation, and persistence of allergic diseases.

RECENT ADVANCES IN THYMIC STROMAL LYMPHOPOIETIN BIOLOGY

Regulation of TSLP function, newly described roles of TSLP in disease and clinical associations are described below.

Regulation of thymic stromal lymphopoietin function

Several biological processes and molecules have been shown to induce or repress TSLP expression by tissue cells. Mechanical injury, proinflammatory milieu, and proteases, such as trypsin and papain, cause TSLP production and release from the epithelial compartments [3–5]. Newer factors modulating TSLP production have been described and include regulation of TSLP by microRNA and suppression of TSLP by inflammasome in keratinocytes [6,7]. Furthermore, TSLP expression was reduced in the cells overexpressing caveolin-1, indicating a functional cross-talk between epithelial cell–cell adhesion and induction of airway inflammation [8]. In addition to the triggers mentioned above, TSLP stimulation via peptidoglycan matrix of bacterial *Lactococcus* bacteria-like particles (BLPs) has also been reported [9]. These findings suggest that regulators for TSLP release are more diverse than previously anticipated and that multiple pathways may be involved in the pathogenesis of allergic diseases.

Role of thymic stromal lymphopoietin in disease

Effect of TSLP on induction of Th2-type immune responses and generation of allergic inflammation has been known. A novel mechanism for the induction of Th2 response by TSLP was reported by Siracusa *et al.* [10[¶]], who reported that TSLP-mediated extra-medullary hematopoiesis leads to expansion and differentiation of antigen-presenting

cells (APCs – dendritic cells, macrophages, and granulocytic cells). These APCs then likely promote Th2-type immune responses in lymphocytes. Another new mechanism by which TSLP may regulate allergic inflammation is by promoting Th9-type lymphocyte differentiation. Th9 cells in conjunction with Th2 cells were shown to be important in allergen-induced airway inflammation [11[¶]]. The clinical importance for the role of TSLP in allergic airway inflammation has also been demonstrated in a therapeutic context in primates and humans. Blocking of the TSLP pathway with anti-TSLP receptor antibody or anti-TSLP antibody (AMG157) showed promising efficacy in reducing allergen-induced airway inflammation in cynomolgus monkeys and patients with asthma [12,13]. Interestingly, TSLP was also reported to have an additional role in lymphocyte differentiation in nonmucosal compartments. For example, TSLP derived from the trophoblasts induced regulatory T cells by activating decidual dendritic cells, and TSLP produced from hepatitis-C-virus-infected hepatocytes promoted a Th17-type response [14,15]. In addition, TSLP by acting directly on neurons promote itch sensation, suggesting a pruritogenic role along with an inflammatory role in atopic skin disease [16]. Indeed, abrogation of atopic dermatitis-like responses were seen in TSLPR-deficient (TSLP-receptor) mice, whereas mice deficient in IL-33 or IL-25 receptor (IL17RB) demonstrated inflammatory changes, supporting the role of TSLP in evolution of atopic skin diseases [17].

Clinical associations of thymic stromal lymphopoietin

In addition to atopic dermatitis and allergic asthma, TSLP is thought to be associated with other diseases as well. In patients with chronic rhinosinusitis with nasal polyps (CRSwNP), increased activity of TSLP was reported in nasal polyp tissue, whereas degradation of TSLP by tissue proteases led to reduced protein amount but augmented cytokine activity [18]. TSLP was also reported to be upregulated in the lung fibroblasts in idiopathic pulmonary fibrosis (IPF) and in the pleural fluid of patients with eosinophilic effusion in primary spontaneous pneumothorax [19,20]. Thus, a new role of TSLP in several human diseases has emerged.

RECENT ADVANCES IN IL-25 BIOLOGY

Regulation of IL-25 function, newly described roles of IL-25 in disease and clinical associations are described below.

Regulation of IL-25 function

IL-25 and IL-33 appear functionally similar, but they have important differences. Unlike IL-33, which is stored in the nucleus, IL-25 is stored in and released from the extranuclear cellular compartments. Kouzaki *et al.* [21] have reported that IL-25 is constitutively expressed in the epithelial cells and is released upon exposure to proteases, such as trypsin, papain or in a more clinically relevant context, allergen proteases present in the house dust mite (HDM) extract. Given the immunological effects of IL-25, release of this cytokine by environmental proteases could have important implications in allergic disease. Although the cellular mechanisms of IL-25 release and regulation of IL-25 activity are not totally understood, tissue microenvironment likely plays a role. For example, ILC2s activated by IL-25 (and IL-33) showed reduced Th2 cytokine secretion in the presence of plate-bound E-cadherin [22²³], suggesting that cell–cell adhesion may play a regulatory role in the biological effects of IL-25. Furthermore, IL-25 inhibited filaggrin gene expression as well as protein level in normal human keratinocytes [23]. As filaggrin is important in skin barrier function, a defective barrier may promote IL-25 release, which in turn affects *FLG* expression and thus may initiate a ‘feed-forward’ loop sustaining the responses in atopic skin.

Role of IL-25 in disease

Aside from its role in atopic inflammation, IL-25 has been shown to be involved in fibrotic lung disease. IL-25 expression was increased in the lungs of IPF patients and correlated with periostin [24]. The authors speculate that IL-25 drives IL-13 production by ILC2s, leading to fibrosis independently of T cells. Additionally, IL-25 may directly induce collagen production in human fibroblasts [24]. The profibrotic role for IL-25 was further supported in the HDM-induced airway response model, in which blockade of IL-25 abolished airway remodeling in mice exposed to HDM [25]. Although results suggest that fibrosis mediated by IL-25 may be a result of direct and indirect mechanisms, there may be a dichotomy in the role of IL-25 in relation to airway remodeling versus hyperresponsiveness. IL-25 was shown to be less critical than IL-33 in airway hyperactivity in mouse airway inflammation model using ovalbumin antigen and ragweed allergens [26].

Clinical associations of IL-25

IL-25 has been known to play a robust role in immunity against helminths in the gastrointestinal

tract [27], but its role in airway is still being characterized. Serum levels of IL-25 were higher in allergic and nonallergic patients with asthma compared with control individuals [28]. Similarly, increased expression of IL-25 in nasal polyp tissues in patients with CRSwNP correlated with worse computerized tomography scores and blood eosinophilia [29]. On the other hand, decreased levels of IL-25 in serum and mucosal tissues were reported in patients with active inflammatory bowel diseases compared with controls [30]. Thus, IL-25 function may depend on the anatomic location and tissue microenvironment.

RECENT ADVANCES IN IL-33 BIOLOGY

Regulation of IL-33 function, newly described roles of IL-33 in disease and clinical associations are described below.

Regulation of IL-33 function

IL-33 is produced and stored in the nucleus of tissue cells, such as epithelial cells and fibroblasts. The exact pathway for IL-33 production, transport within the cells, and extracellular release is still not well understood. IL-33 activity is likely regulated at several levels, including genetic encoding [single-nucleotide polymorphisms (SNPs)], factors affecting its biological activity and degradation. Biological activity of IL-33 may be regulated by the presence its decoy receptor, soluble ST2 (sST2). Ho *et al.* [31] described the results from a GWAS, in which SNPs in *IL1RL1* locus correlate with sST2 concentrations in the sera. ST2 molecules may influence the activity of IL-33 by functioning as a receptor when membrane bound or as a decoy if free in the sera. Indeed, overproduction of sST2 was shown to prevent airway disease in a lung injury model by reducing in part the IL-33 levels [32]. Other factors in addition to ST2 may also affect IL-33 activity. In a HDM model of airway inflammation, IL-33 secretion was dependent on IL-25, suggesting synergistic interaction between these epithelium-derived cytokines [25]. In addition, Roy *et al.* [33] reported the ability of mast cell chymase to degrade IL-33, suggesting a complex balance of production and degradation of IL-33 in the tissues that affects its biological function.

Role of IL-33 in disease

Several recent reports add to our knowledge regarding the role of IL-33 in pathophysiology of diseases. The roles for IL-33 and IL-25 may vary depending on the disease studied and the organ affected. In atopic

dermatitis, skin ILC2s express ST2, respond to IL-33 and home to skin, leading to the production of type 2 cytokines in the tissues [22²²]. Using mice deficient in ST2 (i.e. IL-33 receptor) or IL17RB (i.e. IL-25 receptor), IL-33 played a more important role than IL-25 in the induction of IL-13 and airway hyper-reactivity [26]. Also, IL-33 has been reported to be crucial for the development of HDM-induced allergic airway inflammation and peanut anaphylaxis. IL-33 derived by exposure to peanut and HDM induced OX40L expression by dendritic cells, leading to the development of Th2-type CD4⁺ T cells; TSLP or IL-25 did not show similar roles to IL-33 in this model [34]. A profibrotic role for full-length IL-33 independently of Th2-type cytokines was also reported, suggesting that IL-33 may directly act on the tissue cells similarly to IL-25. For example, increased levels of IL-33 were seen in the lung sections of patients with IPF and those with scleroderma as well as in a bleomycin-induced lung injury model in mice [35]. Interestingly, IL-33 showed its inhibitory effect on mast cells. Prolonged exposure of mast cells to IL-33 inhibited mast cell functions, including degranulation [36]. In addition, IL-33 induced neutrophil chemotaxis in cystic fibrosis patients and in mouse peritoneum [37,38]; this IL-33-mediated neutrophil influx was dependent on the mast cells. Thus, considering the effect of mast cell chymase on IL-33 proteins and the effect of IL-33 on mast cell function, a complex interplay may exist among IL-33, neutrophils, mast cells, and epithelial cells. Finally, IL-33 derived from the human placental and decidual macrophages induced proliferation of placental trophoblasts, suggesting a potential but intriguing role for IL-33 in gestation [39].

Clinical associations of IL-33

Several clinical studies suggest associations of IL-33 with allergic diseases and airway inflammation, including increased levels of IL-33 in patients with asthma, chronic obstructive pulmonary disease (COPD), primary pneumothorax, and CRSwNP. For example, not only were sST2 and IL-33 levels reportedly higher in induced sputum and serum from asthmatic children compared with controls, but also IL-33 correlated with the severity of asthma [40]. In addition to asthma, increased levels of IL-33 were observed in whole-lung explants of patients with severe COPD [41]. The mechanistic role for IL-33 in COPD was further supported in a mouse model of COPD, in which IL-33 appears to be the primary factor driving IL-13-dependent lung disease, such as prolonged lung inflammation and mucin production [41]. In patients with CRSwNP, IL-33 was

reported to drive ILC2-dependent IL-13 production [42]. Finally, higher amounts of IL-33 along with TSLP were reported in the pleural fluids of patients with eosinophilic primary spontaneous pneumothorax [18].

NETWORK STUDY OF RECENT CONCEPTS IN IL-25, IL-33, AND THYMIC STROMAL LYMPHOPOIETIN BIOLOGY

In order to illuminate emerging themes in the recently described functions and roles of IL-25, IL-33, and TSLP, we constructed a 'concept association network'. Each concept (biological process, cell type, mediator, etc.) was assigned as a node with a line (edge) connecting the nodes depicting the relationship. Diseases, pathological processes, cells/tissues, and biological factors (cytokines, etc.) were assigned distinct shapes (see legend), and networks for each cytokine were generated (see Supplemental Figures 1–3, <http://links.lww.com/COAI/A9>). To understand the commonalities and differences, we then merged the individual networks on common nodes into a single network (Fig. 1). After application of a force-directed layout (which pulls connected nodes together and pushes disconnected nodes apart) to the combined network, emergent themes from the recent literature related to the biology of these cytokines were explored. Some evolving and recognizable subgroups were identified using domain knowledge as are discussed below:

- (1) Airway tissue remodeling: Many of the recent advances in the biology of all these cytokines suggest their roles in tissue remodeling. The role of IL-33, IL-25, and TSLP in tissue repair and possible secretion of these cytokines mediated by tissue proteases points to a reparative role in health with association with fibrotic disease, polyposis, and airway remodeling in asthma and pulmonary fibrosis in disease.
- (2) Feto-maternal interface biology (IL-33 and TSLP): Placental macrophage-derived IL-33 induced trophoblast proliferation, whereas TSLP from trophoblast induced Tregs. Both TSLP and IL-33 seem to have implications in the biology of pregnancy.
- (3) T helper biology (TSLP): Influence of TSLP in Th9-type and Th2-type adaptive immune responses was noted. Also was seen the influence of TSLP on Treg and Th17 pathways. These observations suggest that epithelium-derived cytokines, such as TSLP, have the ability to influence downstream adaptive immune responses.

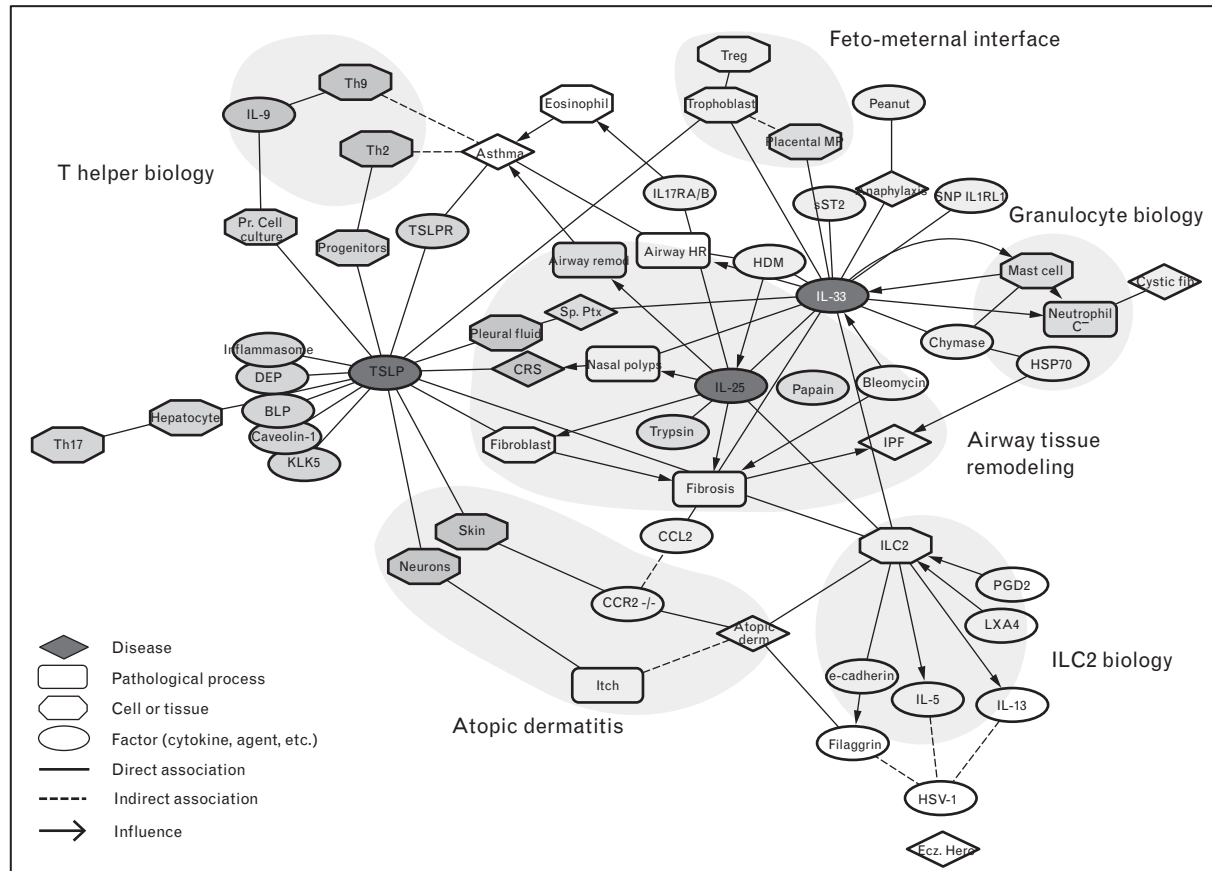


FIGURE 1. Concepts influencing IL-33, TSLP, and IL-25 biology are depicted as nodes. Distinct shapes are assigned to a unique biological concept with rhomboid (disease state), rounded squares (biological process), octagon (cell or tissue), and ellipse (factor such as cytokine or allergen). Network was generated using Cytoscape (<http://www.cytoscape.org/v3.1.1>). Force-directed algorithm was applied, which pulls connected nodes together and pushes the disconnected nodes apart. Modules are identified based on the emergent patterns and domain knowledge. TSLP, thymic stromal lymphopoietin.

- (4) Atopic dermatitis related (TSLP, IL-25, and IL-33). All three cytokines were shown to be involved in atopic dermatitis either working directly on tissues cells (TSLP) or indirectly via regulating functions of intermediaries, such as ILC2s.
- (5) ILC2 biology related: Many of the recent reports pertain to ILC2 biology. TSLP, IL-25, and IL-33 may be involved in the regulation of ILC2s directly or indirectly. Effects of these cytokines in ILC2 cytokine production suggest their potential roles in the amplification of immune response and inflammation.
- (6) Mast cell–neutrophil (granulocyte) biology related: The relationship between mast cells, IL-33, and neutrophils is likely complex but noteworthy. IL-33 induced mast cell refractoriness and mast-cell-dependent neutrophil chemotaxis, whereas mast cell chymase degrades IL-33.

IL-33, in the regulation of Th2-type immunity and allergic responses. Several recent advances in the biology of these cytokines also point to shared functions as well as distinct characteristics. Discovery of additional information will only add to the growing body of literature that defines the exact role of these important cytokines in allergic diseases. Such knowledge will expedite the clinical application of the modulators of these cytokines to treat allergic diseases and help us to predict potential side-effects if these strategies are implemented.

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CONCLUSION

A growing body of literature suggests critical roles for epithelium-derived cytokines, TSLP, IL-25, and

Conflicts of interest

There are no conflicts of interest.

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