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Protease/antiprotease network in allergy: The role of *Staphylococcus aureus* protease-like proteins

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Abstract

Staphylococcus aureus is being recognized as a major cofactor in atopic diseases such as atopic dermatitis, chronic rhinosinusitis with nasal polyps, and asthma. The understanding of the relationship between *S aureus* virulence factors and the immune system is continuously improving. Although the precise mechanism of the host's immune response adaptation to the variable secretion profile of *S aureus* strains continues to be a matter of debate, an increasing number of studies have reported on central effects of *S aureus* secretome in allergy. In this review, we discuss how colonization of *S aureus* modulates the innate and adaptive immune response, thereby predisposing the organism to allergic sensitization and disrupting immune tolerance in the airways of patients with asthma and chronic rhinosinusitis with nasal polyps. Next, we provide a critical overview of novel concepts dealing with *S aureus* in the initiation and persistence of chronic rhinosinusitis with nasal polyps and asthma. The role of the *S aureus* serine protease-like proteins in the initiation of a type 2 response and the contribution of the IL-33/ST2 signaling axis in allergic responses induced by bacterial allergens are discussed.

KEYWORDS

allergy, inflammation, interleukin-33, protease, SpID, *Staphylococcus aureus*

1 | INTRODUCTION

Exogenous proteases derived from a variety of different species such as mites, fungi, and bacteria are constantly challenging the body-own homeostasis and increasing the complexity of the protease network. Allergens with protease activity can be a seasonal trigger for atopic diseases like allergic rhinitis or allergic asthma, and the constant exposure of perennial allergens can persistently aggravate

Abbreviations: A1AT, α1-antitrypsin; AR, allergic rhinitis; CMA1, mast cell chymase; CRSwNP, chronic rhinosinusitis with nasal polyps; HDM, house dust mite; IgE, immunoglobulin E; IL, interleukin; ILCs, innate lymphoid cells; MMP, matrix metalloproteinase; NF-Kb, nuclear factor kappa-light-chain enhancer of activated B cells; OVA, ovalbumin; PARs, proteinase-activated receptors; *S. aureus*, *Staphylococcus aureus*; SERPIN, serine protease inhibitor; SPINK5, Serine peptidase inhibitor, Kazal-type 5; SpI, *Staphylococcus aureus* protease-like protein; sST2, soluble ST2 receptor; Th2, T helper 2; TLR, Toll-like receptor; TNF, tumor necrosis factor; TSLP, thymic stromal lymphopoietin.

Krysko and Teufelberger have equal contribution.

the chronic inflammation.[1] Recent studies have demonstrated that microbiota plays an essential role in fine-tuning the immune response.[2,3] *S aureus* became an important player in the type 2 biased immune responses in the airways.[4,5] *S aureus* is a Gram-positive, commensal organism with pathogenic properties. Over 30 percent of the human population are carriers of *S aureus*, harboring the bacteria either transiently or persistently in their nasal cavities.[6] In the majority of human carriers, *S aureus* causes no detectable adverse effects. However, in patients with chronic rhinosinusitis with nasal polyps (CRSwNP), nasal colonization with *S aureus* and sensitization to *S aureus* enterotoxins are linked to a type 2 inflammatory response and asthma comorbidity.[7] *S aureus* enterotoxin-specific immunoglobulin E was shown to be functional independent of the atopic status of patients.[8,9] Importantly, *S aureus* enterotoxin sensitization is associated with allergic polysensitization in adolescents.[10] Immunoproteomic analyses of the nasal polyps have identified detectable amounts of more than 600 *S aureus* proteins including α-hemolysin, γ-hemolysin, panton-valentine leukocidin, *S aureus* toxins, and *S aureus* protease-like proteins (Spls).[4,11] Furthermore, *Spls* were shown to induce a specific immunoglobulin E (IgE) response in asthmatic patients.[4]

Moreover, *S aureus* contributes to the initiation of a type 2 immune response by fast induction of innate cytokines and chemokines from airway epithelial cells. In murine models of co-exposure to *Spls* and ovalbumin (OVA), SplD breaks immune tolerance to the inert OVA, inducing the production of OVA-specific IgE and strong airway inflammatory responses.[5] Recently, it has been stressed that IL-33 is a critical cytokine in allergic polysensitization and plays an essential role in an altered immune tolerance[12] via activation of dendritic cells[13] and the induction of a type 2 immune response.[14] *S aureus* induces an increase in IL-33 protein levels in *S aureus*-infected nasal polyp tissue.[15] It has been shown that mice treated with SplD could initiate an IL-33 mediated airway inflammation,[5] supporting the role of *S aureus*-secreted factors. This mechanism could substantially contribute to the development of a severe and difficult to control airway disease (Figure 1).

In the current review, we position Spls among other allergens with protease activity and provide a critical overview of emerging roles of Spls in a type 2-biased immune response. Finally, we delineate the role of proteases in the activation of the IL-33 signaling pathway, which is upstream of a type 2 inflammatory response. We

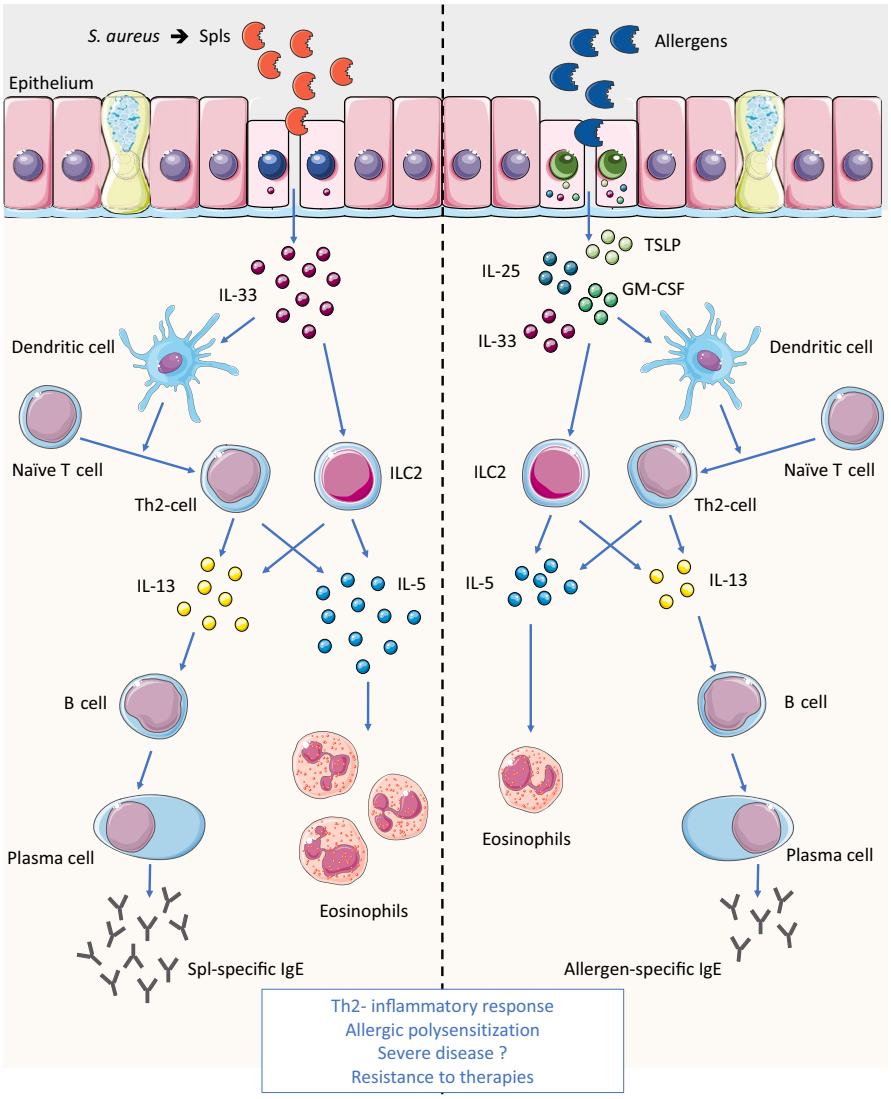

FIGURE 1 Induction of an allergic immune response by *Staphylococcus aureus* serine protease-like protein D (SplD) in the airways. Airborne exposure to SplD causes a synergistic effect in allergic sensitization. SplD activates airway epithelial cells to release IL-33, which acts via ST2 receptors on innate lymphoid cells type 2 (ILC2), T helper cells type 2 (Th2), dendritic cells. These events cause an amplification of adaptive immunity and production of type 2 cytokines and result in reduced tolerance to allergens and aggravation of airway inflammation. Repeated exposures to SplD are associated with increased production of SplD-specific and allergen-specific immunoglobulin E (IgE). SplD facilitates the production of mucus due to proliferation of goblet cells. Airway hyperreactivity is also increased after SplD exposure

discuss how interventions with the IL-33/ST2 signaling axis could modify allergic responses induced by bacterial allergens.

2 | EXOGENOUS PROTEASES—SEASONAL AND PERENNIAL ALLERGENS

2.1 | Airborne house dust mite allergens activate the airway epithelium

There are 24 groups of house dust mite (HDM) allergens out of which one comprises cysteine proteases and three groups are serine proteases. These proteases present a high IgE binding frequency, up to 100% in HDM allergic patients, and are thus major allergens.[16] Der p 1 alone can decrease the epithelial barrier by disrupting tight junctions and increase specific IgE production due to its proteolytic activity, cleaving the low-affinity IgE receptor CD23, which leads to IgE upregulation, and the IL-2 receptor CD25 on T cells resulting in a shift toward Th2 cell activation.[17]

Allergens with protease activity mediate their action through cleavage of a family of G protein–coupled receptors called protease-activated receptors (PARs). PAR2 is activated by cleavage of Der p 1.[18] Toll-like receptor 4 (TLR4), expressed on structural lung cells, was shown to interact with PAR2, strongly supporting the inflammatory response toward HDM.[19] PAR2 activation by HDM is important for IgE formation; however, airway inflammation occurs independently of PAR2.[20] Furthermore, most allergens with protease activity (HDM, *A alternata*, cockroach) induce release of damage-associated molecular patterns, such as IL-33, thymic stromal lymphopoietin (TSLP), adenosine triphosphate, and IL-1α, from epithelial cells in mice in vivo and airway epithelial damage.[21-23] Furthermore, HDM as well as the cysteine proteases bromelain and papain induce uric acid release while *A alternata*, *Artemisia vulgaris*, and *Betula pendula* extracts do not.[24,25] This release of uric acid can further skew the T cell response toward a Th2 bias.[23] The diminished response against heat-inactivated or protease inhibitor–treated HDM allergens suggests that the proteolytic function is necessary for their allergenicity.[24] The cysteine proteases of HDM seem to be more important for allergic sensitization than the serine proteases because the allergic response toward HDM extract with lower serine protease activity was more pronounced than in extracts with higher activity.[26]

House dust mite induces an upregulation of IL-33, triggering innate lymphoid cells type 2 (ILC2) and eosinophil recruitment to the lungs through RAGE-dependent VCAM expression.[24]

Der p 1 can cleave IL-33 and thereby increase its cytokine activity.[27] In addition to their own allergens, HDM extracts can also contain IgE reactive bacterial products of *S aureus* or *E coli* derived from their natural microbiome.[28] Whether these products are proteases still needs to be elicited and it can only be speculated that they could have an adjuvant effect for HDM allergens. It was, however, shown that Der p 1 and Der f 1 degrade lung surfactant proteins A and D and thereby decrease the host's antimicrobial actions.[29]

2.2 | Fungal allergens as triggers for IL-33 production

Several fungal serine proteases from *Aspergillus* spp, *Penicillium* spp, *Curvularia lunata*, *A alternata*, and others have been described as allergens[30,31] (summarized in Table 1). *Alternaria* spp is a common outdoor mold but can also occur indoors in moldy dwellings.[31] *A alternata* exposure in children is associated with elevated IgE levels and higher airway IL-33 levels. In mice, *A alternata* inhalation caused steroid-resistant airway hyperreactivity, dependent on IL-33.[32] In humans, exposure to these fungal spores can lead to airway diseases such as allergic asthma, allergic rhinitis and sinusitis, allergic alveolitis, allergic pulmonary aspergillosis, or rhinosinusitis.[31]

Alternaria alternata extract induces allergic asthma via IL-33 activation, dependent on the serine proteases in the extract.[22,33] This further leads to activation of ILC2s and IL-5 production which causes the maturation of eosinophils in the bone marrow in response to *A alternata*.[34] Next to the serine protease activity in the *A alternata* extract, an aspartic protease of *A alternata* activates PAR2 and triggers degranulation of eosinophils.[35] Contradicting data can be found concerning the importance of protease activity in asthma induction. While heat-inactivated or protease inhibitor–treated *A alternata* extracts induce allergic asthma to the same extent as nondenatured extract in one study,[36] another study shows that the protease activity is necessary for the development of lung inflammation and PAR2 activation.[37]

Aspergillus fumigatus has four different proteases, the metalloprotease Asp f 5, an aspartic protease Asp f 10, and two serine proteases Asp f 13 and Asp f 18.[31] Asp f 5 and Asp f 13 deletion mutants showed reduced inflammatory cell recruitment and IL-13 production compared to the wild type in a murine inhalation model; however, IgE levels and Th2 cytokine levels were comparable to the wild-type treated mice.[38] Asp f 13 disrupts the epithelial barrier and the extracellular matrix of airway smooth muscle cells, leading to airway hyperreactivity in mice.[39] Pen c 13, a serine protease from *Penicillium citrinum*, also increased epithelial permeability and allergic airway inflammation in mice.[40,41]

2.3 | Bacteria as a source of allergens with protease activity

The fungal allergens Cur l 1 from *Curvularia lunata* and Cla h 9 from *Cladosporium herbarum* are subtilisin-like serine proteases.[42,43] Subtilisin (also called Alcalase) is a serine protease from *Bacillus spp* acting as a bacterial allergen, as it can induce specific IgE and IgG4 formation, accumulation of eosinophils in the airway lumen and goblet cell hyperplasia in mice. The active subtilisin triggers an early release of amphiregulin, TSLP, IL-1α, and IL-33, while proteolytically inactive subtilisin cannot induce this response.[44] IL-33 is processed to a more bioactive cytokine by subtilisin.[27] In humans, subtilisin and savinase, another *Bacillus* spp protease, cause specific IgE formation.[45] These findings are of special interest, because detergents contain protein engineered mutants of subtilisin and other bacterial

proteases that have an increased stability. Some of these bacterial proteases are also used by the food industry.[46]

2.4 | Staphylococcus aureus proteases in type 2 immune responses

Staphylococcus aureus possesses ten major secreted proteases including a serine protease (V8 protease), a metalloprotease (aureolysin), two cysteine proteases (staphopain A and staphopain B), and six serine protease-like proteins (SplA, SplB, SplC, SplD, SplE, and SplF). Spls are proteases encoded by the *spl* operon, located on the pathogenicity island vSab.[47] The *S aureus* V8 protease and staphopains were shown to alter airway epithelial barrier integrity, modulate cytokine synthesis, and activate nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB) in the airway epithelial cells, therefore predisposing to allergic sensitization.[48] Recently, it has been shown that the majority of nasal polyp tissue colonized with *S aureus* contained IgG binding to SplA, SplB, and SplD/F.[4] Importantly, serum of asthmatic patients contained higher titers of SplA, SplB, SplD, and SplE-specific IgE compared to controls suggesting their role in the pathogenesis of asthma.[4] Moreover, SplD is produced by *S aureus* in measurable amounts in the airways of patients with CRSwNP.[11] Ex vivo nasal tissue explants produce IL-5 in response to SplD and intratracheal applications of SplD in mice result in induction of SplD-specific IgE.[4] All these data demonstrate that, next to their detrimental role in the airway epithelial barrier integrity, *S aureus* proteases act as allergens by inducing specific IgE response in humans and in mice.

SplD-induced inflammation in mouse lungs is not accompanied by the release of TSLP, IL-25, or GM-CSF,[5] which is in contrast to experimental models using other allergens with protease activity such as HDM and *A alternata* extracts.[49,50] However, repeated intratracheal exposure of mice to SplD leads to a sustained production of IL-33 in the lungs and the development of key features of

TABLE 1 Overview of allergens with proteolytic functions from different taxonomic kingdoms

Protease type	Allergen name	Origin species	Class (kingdom)	Reference
Cysteine	Blo t 1	*Blomia tropicalis*	Arachnida (animalia)	16
Serine	Blo t 3, 6, 9	*Blomia tropicalis*	Arachnida (animalia)	16
Cysteine	Der f 1	*Dermatophagoides farinae*	Arachnida (animalia)	16
Serine	Der f 3, 6, 9	*Dermatophagoides farinae*	Arachnida (animalia)	16
Cysteine	Der p 1	*Dermatophagoides pteronyssinus*	Arachnida (animalia)	16
Serine	Der p 3, 6, 9	*Dermatophagoides pteronyssinus*	Arachnida (animalia)	16
Serine	nd	*Alternaria alternata*	Dothideomycetes (fungi)	22
Aspartic	nd	*Alternaria alternata*	Dothideomycetes (fungi)	35
Serine	Cla c 9	*Cladosporium cladosporioides*	Dothideomycetes (fungi)	97
Serine	Cla h 9	*Claudosporium herbarum*	Dothideomycetes (fungi)	43
Serine	Cur l 1	*Curvularia lunata*	Dothideomycetes (fungi)	98
Serine	Epi p 1	*Epicoccum purpurascens*	Dothideomycetes (fungi)	99
Metallo-	Asp f 5	*Aspergillus fumigatus*	Eurotiomycetes (fungi)	38
Aspartic	Asp f 10	*Aspergillus fumigatus*	Eurotiomycetes (fungi)	31
Serine	Asp f 13	*Aspergillus fumigatus*	Eurotiomycetes (fungi)	38,39
Serine	Asp f 18	*Aspergillus fumigatus*	Eurotiomycetes (fungi)	31
Serine	Asp fl 13	*Aspergillus flavus*	Eurotiomycetes (fungi)	100
Serine	Asp n 18	*Aspergillus niger*	Eurotiomycetes (fungi)	100
Serine	Asp o 13	*Aspergillus oryzae*	Eurotiomycetes (fungi)	100
Serine	Pen c 2	*Penicillium citrinum*	Eurotiomycetes (fungi)	101
Serine	Pen c 13	*Penicillium citrinum*	Eurotiomycetes (fungi)	40
Serine	Pen ch 13	*Penicillium chrysogenum*	Eurotiomycetes (fungi)	41
Serine	Pen ch 18	*Penicillium chrysogenum*	Eurotiomycetes (fungi)	97
Serine	Pen o 18	*Penicillium oxalicum*	Eurotiomycetes (fungi)	43
Serine	alcalase/subtilisin	*Bacillus subtilis*	Bacilli (bacteria)	44,45
Serine	Esperase	*Bacillus licheniformis*	Bacilli (bacteria)	102
Serine	Savinase	*Bacillus licheniformis*	Bacilli (bacteria)	45
Serine	Spls (A,B,D,E,F)	*Staphylococcus aureus*	Bacilli (bacteria)	5,103

nd, not determined.

allergic asthma including eotaxin production, eosinophilia, bronchial hyperreactivity, goblet cell hyperplasia, and ILC2s infiltration of the airways.[5]

It has been shown that the release of IL-33 upon exposure to SpID could exacerbate features of allergic asthma and contribute to an altered immune tolerance to other allergens. IL-33 is sufficient to aggravate airway hyperresponsiveness and type 2 airway inflammation in mice exposed to OVA[12] or house dust mite.[51] SpID mediates an IL-33-dependent sensitization to OVA.[5] Likewise, increased levels of IL-33 positively correlate with specific IgE to inhalant allergens and polyclonal sensitization in allergic children with severe refractory asthma.[52]

Initially, the mechanism of action of SpID in airway inflammation in mice was mainly attributed to the increased expression of IL-33 in airway epithelial cells type II and the activation of ILC2s, Th2 cells, and eosinophils.[5] It was shown in the murine model of SpID-triggered allergic asthma that neutralizing IL-33 by sST2 efficiently blocks SpID-induced airway inflammation in mice as it significantly reduces the numbers of eosinophils, IL-13$^+$ ILC2s as well as IL-13$^+$ CD4$^+$ T cells, and IL-5 and IL-13 production in the lung draining lymph nodes.[5] However, sST2 treatment does not significantly reduce the SpID-induced airway hyperreactivity and airway remodeling. Moreover, the adaptive immune response is crucial for the SpID-induced airway inflammation because inflammatory changes are fully abrogated in the SpID treated Rag2$^{-/-}$ mice.[5] Since ILC2 population is preserved in Rag2$^{-/-}$ mice,[53] it is conclusive that ILC2s are necessary but not sufficient for the induction of SpID-induced inflammation. In the model of SpID-induced airway inflammation, ILC2s have a rather supportive role via production of Th2 cytokines. It is important to mention that SpIF shows 94.6% sequence homology with SpID.[54] In mice, SpIF induces airway inflammation comparable to SpID.[5] These data suggest a novel potent group of bacterial allergens present in *S aureus*.

However, we have shown that SpID does not directly activate PAR2 and its downstream signaling in vitro, while in vivo PAR2 is increased in the SpID-exposed lungs. This indicates an indirect activation of PAR2.[5] Moreover, IL-33 is an important regulator in the SpID-induced PAR2 activation, since in mice treated with SpID and sST2, the levels of PAR2 in the lungs were significantly decreased.[5] These data support the notion that endogenous proteases facilitate innate immune response induced by allergens.

2.5 | The role of proteases in the activation of IL-33

Interleukin-33 is one of the major cytokines in the regulation of the innate and adaptive immunity in the allergic airways.[22,55,56] Repeated exposure to environmental factors and allergens with protease activity triggers the activation of the airway epithelium and the release of TSLP, IL-25 and IL-33, which in turn triggers a sustained immune response in dendritic cells and ILC2s and activation of type 2 immune response.[27,57,58] Once released, IL-33 mediates its function upon binding to the ST2 receptor, a member of the Toll-like/IL-1 superfamily of receptors,[59] widely expressed on ILC2s, Th2 cells, eosinophils, invariant natural killer T cells, natural killer cells, basophils, and mast cells.[59-63] IL-33 binding to ST2 leads to the formation of a complex with the interleukin-1 receptor, and a receptor accessory protein,[64] resulting in the recruitment of the adaptor protein MyD88.[65] This recruitment activates the interleukin-1 receptor-associated kinase-1,-4, mitogen-activated protein kinase, and TNF receptor-associated factor-6, which results in the activation of NF-κB, p36, and the protein kinase c-Jun N-terminal kinases.[59]

Unlike other members of the IL-1 family, such as IL-1β and IL-18, IL-33 does not require caspase-1 cleavage for its activation.[66] IL-33 is inactivated by caspase-3- and caspase-7-mediated cleavage of its cytokine domain during apoptosis.[67] It is known that the activity of IL-33 is regulated by endogenous proteases released during inflammation from epithelial cells, neutrophils, and mast cells. Endogenous proteases such as neutrophil elastase or cathepsin G were shown to activate IL-33 during bacterial, fungal, or viral infections.[68] Cleavage of IL-33 by mast cell tryptase results in the generation of shorter mature forms of IL-33. Mature IL-33 is up to 30-fold more potent than the full-length IL-33 in its capacity to induce an expansion of ILC2s and Th2 cells, next to their IL-5 and IL-13 production.[62] There are inconsistent data concerning the activation or degradation of IL-33 by human mast cell chymase.[62,69] The murine mast cell chymase mMCP-4 has been shown to degrade IL-33.[69,70] When IL-33 is incubated with allergens that have protease activity, it gets cleaved in its central cytokine domain, generating a shorter and more active form of IL-33, which efficiently activates ILC2s, basophils, mast cells, and eosinophils.[27] Therefore, IL-33 acts as a sensor for aeroallergens with proteases activity to trigger the downstream inflammatory cascade.[27]

It has been shown that the oxidation state of IL-33 affects the binding capacity of IL-33 to ST2.[71] Oxidized IL-33 is most commonly found in the sputum from exacerbating asthmatics, which could be an intrinsic mechanism to limit an extensive inflammation. Both forms of IL-33, oxidized and reduced, are found during disease exacerbations in sputum of patients with moderate and severe asthma.[71] Endogenous calpains, from damaged airway epithelial cells, can process full-length IL-33 and increase its alarmin activity up to ~60-fold.[72]

It is important to point out that several alternatively spliced variants of IL-33 were detected in asthmatic patients.[73] Among them, an IL-33 isoform lacking exons 3 and 4, that was shown to have a cytoplasmic localization in airway epithelial cells, could be actively secreted and activate mast cells and basophils.[73] In asthmatic patients, this isoform is strongly associated with type 2 biased airway inflammation.[73]

In CRSwNP mucosa, *S aureus* induces epithelial cell-derived release of IL-33 and TSLP via cell wall compartment-induced TLR2 activation.[15] However, it has been shown that SpID does not activate TLR2 directly[5] suggesting that other recognition mechanisms are in place.

2.6 | Endogenous protease inhibitors in the airways

Natural protease inhibitors exist for serine, cysteine, metallo-, and aspartic proteases.[74] Cystatin A is a cysteine protease inhibitor, and in combination with the serine protease inhibitor Kazal-type 5 (SPINK5), it is involved in the regulation of the innate cytokine (IL-25, IL-33, and TSLP) response of *A alternata* extract or *S aureus* V8 protease, when exposed to human bronchial epithelial cells. In eosinophilic CRSwNP, the expression of cystatin A and SPINK5 is decreased compared to nasal tissue of noneosinophilic CRS.[75]

These findings underline the importance of antiprotease activity in the nasal mucosa for the prevention of detrimental effects of exposure to environmental allergens with protease activity and provide a possible explanation for the reduced capacity of epithelium to counteract the protease activity in CRSwNP, resulting in a sustained chronic type 2 inflammation. The role of this antiprotease network still needs to be discovered in the regulation of SpIs' activity in chronic airway inflammation.

α1-Antitrypsin (A1AT) inhibits trypsin, KLK7, KLK14, neutrophil elastase, proteinase 3, and matriptase. It is an acute-phase protein with a high abundance in serum. Apart from inhibiting neutrophil proteases, A1AT also inhibits the migration and activation of neutrophils,[76] next to preventing the proteolytic maturation of matrix metalloproteinase-9 (MMP-9) by serine proteases from German cockroach extract.[77] IL-6 and to a lesser extent LPS, tumor necrosis factor-α (TNF-α), and IL-1β stimulate A1AT secretion from monocytes.[78] Proteome analysis of nasal secretion from allergic rhinitis (AR) patients and healthy controls revealed 2.5-fold higher levels of A1AT in AR patients.[79] The mast cell chymase mMCP-1 can be inhibited by A1AT1, A1AT2, and A1AT4 in the serum.[80]

Serine protease inhibitor B1 is produced by neutrophils and inhibits the neutrophil proteases elastase, cathepsin G, and proteinase-3. In a lung-infection model of *Pseudomonas aeruginosa* with SERPINB1-deficient mice, SERPINB1 proved to be an important factor for the survival, bacterial clearance, and SP-D degradation.[81]

Furthermore, serum levels of SERPINB3 and SERPINB4 are increased in asthma, chronic obstructive pulmonary disease, and atopic dermatitis patients. SERPINB3 inhibits cathepsins S, K, L, and papain, while SERPINB4 inhibits mast cell chymase, cathepsin G, granzyme M, and Der p 1. IL-4 and IL-13-stimulated bronchial epithelial cells upregulate these two serpins. In mice, serpinb3a also inhibits papain, Der p 1 and the cathepsins S, K, L, and G, as well as V. The activation of serpinb3a is dependent on IL-13 as IL-13-treated serpinb3a-deficient mice have a significantly diminished inflammatory response. In an allergic asthma model, HDM-treated serpinb3a-deficient BALB/c mice developed a similar eosinophilic response as the wild-type mice, but have a decreased mucus production.[82]

Genetic variations within proteases and their inhibitors have also been associated with asthma, atopy, or chronic inflammatory lung diseases. For example, two polymorphisms of the MMP9 gene are associated with childhood atopic asthma risk, one of which upregulates the expression levels of MMP9.[83] A polymorphism downstream of mast cell chymase gene (CMA1) is associated with bronchial asthma, atopic asthma, and IgE levels.[84,85] Furthermore, one polymorphism in the promoter region of CMA1 is associated with atopic eczema.[86] The variability in copy number of human α-tryptase can also have an impact on total and HDM-specific IgE levels in asthmatic patients. Patients carrying one copy of α-tryptase had lower IgE levels and worse lung function, but two copies correlated with higher total and HDM-specific IgE levels.[87] Interestingly, α-tryptase is suggested to be enzymatically inactive.[88] Hereditary loss of α1-antitrypsin/SERPINA1 results in early-onset chronic obstructive pulmonary disease and emphysema.[89] A downstream mutation in serine protease inhibitor A3 (SERPINA3) has been identified as a possible susceptibility locus for childhood asthma.[90] Interestingly, cystic fibrosis patients deficient of α1-antichymotrypsin/SERPINA3 have significantly milder symptoms of lung inflammation than non-α1-antichymotrypsin deficient patients.[91]

Whether there is a possible link of serine protease inhibitor production with the susceptibility of chronic inflammatory airway disease development upon *S aureus* colonization still needs to be investigated.

2.7 | Interference with the ST2/IL-33 signaling axis for therapeutic purposes

Blocking of the IL-33 pathway by different pharmacological and genetic tools can be a promising and an efficient strategy to inhibit inflammatory changes induced by different groups of allergens. Indeed, the critical role of IL-33 in the initiation and modulation of allergic airway disease has been already proven (Table 2). Next to IL-33 blocking or IL-33 neutralizing antibodies, sST2 is an elegant way to inhibit the IL-33 signaling pathway. sST2 functions antagonistically to IL-33, acting as a decoy receptor and preventing IL-33 from binding to the membrane bound isoform ST2, thereby inhibiting its effector function.[92,93] Anti-IL-33 antibodies as well as sST2 were shown to be efficient in reduction of the most prominent features of murine OVA-induced allergic asthma models such as eosinophil counts and IL-4, IL-5, and IL-13 in bronchoalveolar lavage fluid.[94,95] Airway hyperreactivity to methacholine was also efficiently downregulated by this treatment in mice. However, the relatively short half-life of existing pharmacological compounds for binding active IL-33 does not allow the full prevention of airway remodeling and specific IgE production when using these compounds in the therapeutic regimens in a murine model of asthma, for example, induced by SpID[5] or combination of HDM and diesel exhaust particles.[96] A phase 1 clinical study to evaluate the safety and tolerability of a single dose of anti-IL-33R antibody (CNTO 7160) in healthy participants and multiple doses in participants with asthma and atopic dermatitis has been completed; however, no results have been reported yet. All these studies indicate that interference with the IL-33/ST2 signaling axis is a very promising strategy in preventing type 2 inflammation in diseases like CRSwNP and asthma induced by bacterial allergens.

TABLE 2 The role of different IL-33 targeting strategies on inflammatory changes in mouse models of allergic asthma

	Allergen	AHR	Inflammatory infiltration of lungs	Th2 cytokines/chemokines	IgE response	References
IL-33 knockout	OVA	ns	↓ Eosinophils	↓ IL-4, IL-5, IL-13, CCL-11, CCL-5, CCL22, CXCL2	ns	104
	OVA/ aluminum hydroxide	↓ AHR	↓ Eosinophils	ns	ns	105
	HDM	na	↓ Eosinophils	na	na	105
	Papain	na	↓ Eosinophils	na	na	105
ST2 knockout	HDM	↓ AHR	↓ Eosinophils	↓ IL-4, IL-5, IL-13, IL-33, GM-CSF, IL-1b, TSLP, MCP-1	↓	106
	OVA	na	↓ Eosinophils	↓ IL-4, IL-5, IL-13, CCL-11, CCL-5, CCL22, CXCL1, CXCL2	↓	107
	Alternaria alternata	na	↓ Eosinophils	↓ IL-5 ns IL-13	na	33
IL-33 neutralizing antibodies	OVA	na	↓ Eosinophils	↓ IL-4, IL-5, IL-13	↓	108
ST2 blocking monoclonal antibodies	OVA	↓AHR	na	↓ IL-4 ns IL-13	na	109
sST2 soluble receptor	OVA	na	na	↓IL-4, IL-5, IL-13	na	95
	OVA	na	↓ Eosinophils	↓ IL-4, IL-5,	na	110
	OVA-DCs	na	↓ Eosinophils	na	na	111
	HDM	na	↓ Eosinophils	ns	↓ Total IgE	49
	S aureus SplD	↓ AHR	↓ Eosinophils	↓ IL-4, IL-5, IL-13	↓ Total IgE ns specific IgE	4,5

DCs, dendritic cells; HDM, house dust mite; IgE, immunoglobulin E; na, not analyzed; ns, not significant; OVA, ovalbumin.

3 | CONCLUDING REMARKS AND FUTURE PERSPECTIVES

In this review article, we underlined that the IL-33/ST2 signaling axis is activated in response to the major inhaled allergens from fungi, mites, and bacteria and highlighted the role of protease/anti-protease network in balancing the activity of exogenous proteolytic enzymes. Therefore, both signaling pathways represent potential targets for the future therapeutic interventions to prevent severe chronic type 2 biased airway inflammation. Deeper understanding of the interaction of *S aureus*-secreted compounds and subsequent immune responses in the host might help to understand how colonization of *S aureus* or exposure due to inhaled *S aureus* compounds can bias toward type 2 immune response in asthma and CRSwNP. Identification of these complex interactions between *S aureus* and the immune system may lead to the development of novel efficient therapeutics to prevent an exuberant activation of the immune system induced by pathogenic germs colonizing mucosal surfaces. It is important to state that many questions remain regarding the predisposition to a conversion of commensal *S aureus* lifestyle into pathologic colonization. It remains to be analyzed whether *S aureus* proteins contribute to initiation and acute exacerbations of human asthma and CRSwNP in the same way as shown in mice. Answers to these remaining questions will eventually provide us with the necessary insights on how to modulate either *S aureus* and its proteases or the host response in order to treat chronic type 2 diseases when other treatment strategies fail.

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CONFLICTS OF INTEREST

The authors declare that there is no conflict of interest.

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REFERENCES

1. Tung H-Y, Li E, Landers C, et al. Advances and evolving concepts in allergic asthma. *Semin Respir Crit Care Med*. 2018;39:64-81.
2. Belkaid Y, Hand TW. Role of the microbiota in immunity and inflammation. *Cell*. 2014;157:121-141.
3. Kim B-s, Lee E, Lee M-j, et al. Different functional genes of upper airway microbiome associated with natural course of childhood asthma. *Allergy*. 2018;73:644-652.
4. Stentzel S, Teufelberger A, Nordengrün M, et al. Staphylococcal serine protease–like proteins are pacemakers of allergic airway reactions to Staphylococcus aureus. *J Allergy Clin Immunol*. 2017;139:492-500.
5. Teufelberger AR, Nordengrün M, Braun H, et al. The IL-33/ST2 axis is crucial in type 2 airway responses induced by the *Staphylococcus aureus* protease SplD. *J Allergy Clin Immunol*. 2018;141:549–559.
6. Mehraj J, Witte W, Akmatov MK, Layer F, Werner G, Krause G. Epidemiology of *Staphylococcus aureus* nasal carriage patterns in the community. In: Stadler M, Dersch P, eds. *How to Overcome the Antibiotic Crisis*. Current Topics in Microbiology and Immunology. 2016:55–87.
7. Tomassen P, Vandeplas G, Van Zele T, et al. Inflammatory endotypes of chronic rhinosinusitis based on cluster analysis of biomarkers. *J Allergy Clin Immunol*. 2016;137:1449–1456.
8. Altrichter S, Hawro T, Liedtke M, et al. In chronic spontaneous urticaria, IgE against staphylococcal enterotoxins is common and functional. *Allergy*. 2018;73:1497–1504.
9. Zhang N, Holtappels G, Gevaert P, et al. Mucosal tissue polyclonal IgE is functional in response to allergen and SEB. *Allergy*. 2011;66:141–148.
10. Sørensen M, Klingenberg C, Wickman M, et al. *Staphylococcus aureus* enterotoxin sensitization is associated with allergic polysensitization and allergic multimorbidity in adolescents. *Allergy*. 2017;72:1548–1555.
11. Schmidt F, Meyer T, Sundaramoorthy N, et al. Characterization of human and *Staphylococcus aureus* proteins in respiratory mucosa by in vivo- and immunoproteomics. *J Proteomics*. 2017;155:31–39.
12. Sjöberg LC, Nilsson AZ, Lei Y, Gregory JA, Adner M, Nilsson GP. Interleukin 33 exacerbates antigen driven airway hyperresponsiveness, inflammation and remodeling in a mouse model of asthma. *Sci Rep*. 2017;7:1–10.
13. Besnard A-G, Togbe D, Guillou N, Erard F, Quesniaux V, Ryffel B. IL-33-activated dendritic cells are critical for allergic airway inflammation. *Eur J Immunol*. 2011;41:1675–1686.
14. Rank MA, Kobayashi T, Kozaki H, Bartemes KR, Squillace DL, Kita H. IL-33-activated dendritic cells induce an atypical TH2-type response. *J Allergy Clin Immunol*. 2009;123:1047–1054.
15. Lan F, Zhang N, Holtappels G, et al. *Staphylococcus aureus* induces mucosal type 2 immune response via epithelial cell derived cytokines. *Am J Respir Crit Care Med*. 2018;198(4):452-463.
16. Calderón MA, Linneberg A, Kleine-Tebbe J, et al. Respiratory allergy caused by house dust mites: what do we really know? *J Allergy Clin Immunol*. 2015;136:38–48.
17. Hammad H, Lambrecht BN. Barrier epithelial cells and the control of type 2 immunity. *Immunity*. 2015;43:29–40.
18. Asokananthan N, Graham Pt, Stewart Dj, et al. House dust mite allergens induce proinflammatory cytokines from respiratory epithelial cells: the cysteine protease allergen, der p 1, activates protease-activated receptor (par)-2 and inactivates PAR-1. *J Immunol*. 2002;169:4572–4578.
19. Hammad H, Chieppa M, Perros F, Willart MA, Germain RN, Lambrecht BN. House dust mite allergen induces asthma via Toll-like receptor 4 triggering of airway structural cells. *Nat Med*. 2009;15:410–416.
20. Post S, Heijink IH, Petersen AH, De Bruin HG, Van Oosterhout A, Nawijn MC. Protease-activated receptor-2 activation contributes to house dust mite-induced IgE responses in mice. *PLoS One*. 2014;9:e91206.
21. Kale SL, Agrawal K, Gaur SN, Arora N. Cockroach protease allergen induces allergic airway inflammation via epithelial cell activation. *Sci Rep*. 2017;7:1–12.
22. Kouzaki H, Iijima K, Kobayashi T, O'Grady SM, Kita H. The danger signal, extracellular ATP, is a sensor for an airborne allergen and triggers IL-33 release and innate Th2-type responses. *J Immunol*. 2011;186:4375–4387.
23. Kool M, Willart M, van Nimwegen M, et al. An unexpected role for uric acid as an inducer of T helper 2 cell immunity to inhaled antigens and inflammatory mediator of allergic asthma. *Immunity*. 2011;34:527–540.
24. Ramu S, Menzel M, Bjermer L, Andersson C, Akbarshahi H, Uller L. Allergens produce serine proteases-dependent distinct release of metabolite DAMPs in human bronchial epithelial cells. *Clin Exp Allergy*. 2018;48:156–166.
25. Hara K, Iijima K, Elias Mk, et al. Airway uric acid is a sensor of inhaled protease allergens and initiates type 2 immune responses in respiratory mucosa. *J Immunol*. 2014;192:4032–4042.
26. Post S, Nawijn Mc, Hackett Tl, et al. The composition of house dust mite is critical for mucosal barrier dysfunction and allergic sensitisation. *Thorax*. 2012;67:488–495.
27. Cayrol C, Duval A, Schmitt P, et al. Environmental allergens induce allergic inflammation through proteolytic maturation of IL-33. *Nat Immunol*. 2018;19:375–385.
28. Dzoro S, Mittermann I, Resch-Marat Y, et al. House dust mites as potential carriers for IgE sensitization to bacterial antigens. *Allergy*. 2018;73:115–124.
29. Deb R, Shakib F, Reid K, Clark H. Major house dust mite allergens Dermatophagoides pteronyssinus 1 and Dermatophagoides farinae 1 degrade and inactivate lung surfactant proteins A and D. *J Biol Chem*. 2007;282:36808–36819.
30. Tripathi P, Kukreja N, Singh BP, Arora N. Serine protease activity of Cur l 1 from Curvularia lunata augments Th2 response in mice. *J Clin Immunol*. 2009;29:292–302.
31. Prester L. Indoor exposure to mould allergens. *Arh Hig Rada Toksikol*. 2011;62:371–380.
32. Castanhinha S, Sherburn R, Walker S, et al. Pediatric severe asthma with fungal sensitization is mediated by steroid-resistant IL-33. *J Allergy Clin Immunol*. 2015;136:312–322.
33. Snelgrove RJ, Gregory LG, Peiró T, et al. Alternaria-derived serine protease activity drives IL-33-mediated asthma exacerbations. *J Allergy Clin Immunol*. 2014;134:24–26.
34. Anderson EL, Kobayashi T, Iijima K, Bartemes KR, Chen CC, Kita H. IL-33 mediates reactive eosinophilopoiesis in response to airborne allergen exposure. *Allergy*. 2016;71:977–988.
35. Matsuwaki Y, Wada K, White Ta, et al. Recognition of fungal protease activities induces cellular activation and eosinophil-derived neurotoxin release in human eosinophils. *J Immunol*. 2009;183:6708–6716.
36. Denis O, Vincent M, Havaux X, De Prins S, Treutens G, Huygen K. Induction of the specific allergic immune response is independent of proteases from the fungus Alternaria alternata. *Eur J Immunol*. 2013;43:907–917.
37. Boitano S, Flynn AN, Sherwood CL, et al. Alternaria alternata serine proteases induce lung inflammation and airway epithelial cell activation via PAR2. *Am J Physiol Lung Cell Mol Physiol*. 2011;300:L605–L614.
38. Namvar S, Warn P, Farnell E, et al. Aspergillus fumigatus proteases, Asp f 5 and Asp f 13, are essential for airway inflammation and remodelling in a murine inhalation model. *Clin Exp Allergy*. 2015;45:982–993.

39. Balenga NA, Klichinsky M, Xie Z, et al. A fungal protease allergen provokes airway hyper-responsiveness in asthma. *Nat Commun*. 2015;6:1–13.
40. Chen JC, Chuang JG, Su YY, Chiang BL, Lin YS, Chow LP. The protease allergen Pen c 13 induces allergic airway inflammation and changes in epithelial barrier integrity and function in a murine model. *J Biol Chem*. 2011;286:26667–26679.
41. Tai H-y, Tam Mf, Chou H, et al. Pen ch 13 allergen induces secretion of mediators and degradation of occludin protein of human lung epithelial cells. *Allergy*. 2006;61:382–388.
42. Tripathi P, Nair S, Singh BP, Arora N. Molecular and immunological characterization of subtilisin like serine protease, a major allergen of Curvularia lunata. *Immunobiology*. 2011;216:402–408.
43. Pöll V, Denk U, Shen H-D, et al. The vacuolar serine protease, a cross-reactive allergen from Cladosporium herbarum. *Mol Immunol*. 2009;46:1360–1373.
44. Florsheim E, Yu S, Bragatto I, et al. Integrated innate mechanisms involved in airway allergic inflammation to the serine protease subtilisin. *J Immunol*. 2015;194:4621–4630.
45. Arlian LG, Vyszenski-Moher DL, Merski JA, Ritz HL, Nusair TL, Wilson ER. Antigenic and allergenic characterization of the enzymes alcalase and savinase by crossed immunoelectrophoresis and crossed radioimmunoelectrophoresis. *Int Arch Allergy Immunol*. 1990;91:278–284.
46. Gupta R, Beg Q, Lorenz P. Bacterial alkaline proteases: molecular approaches and industrial applications. *Appl Microbiol Biotechnol*. 2002;59:15–32.
47. Zdzalik M, Kalinska M, Wysocka M, et al. Biochemical and structural characterization of SplD protease from Staphylococcus aureus. *PLoS One*. 2013;8:e76812.
48. Rudack C, Sachse F, Albert N, Becker K, von Eiff C. Immunomodulation of nasal epithelial cells by Staphylococcus aureus-derived serine proteases. *J Immunol*. 2009;183:7592–7601.
49. Willart MAM, Deswarte K, Pouliot P, et al. Interleukin-1α controls allergic sensitization to inhaled house dust mite via the epithelial release of GM-CSF and IL-33. *J Exp Med*. 2012;209:1505–1517.
50. Iijima K, Kobayashi T, Hara K, et al. IL-33 and thymic stromal lymphopoietin mediate immune pathology in response to chronic airborne allergen exposure. *J Immunol*. 2014;193:1549–1559.
51. Canbaz D, Utsch L, Logiantara A, Van Ree R, Van Rijt LS. IL-33 promotes the induction of immunoglobulin production after inhalation of house dust mite extract in mice. *Allergy*. 2015;70:522–532.
52. Wisniewski JA, Muehling LM, Eccles JD, et al. TH1 signatures are present in the lower airways of children with severe asthma, regardless of allergic status. *J Allergy Clin Immunol*. 2017;141:2048–2060.
53. Walker JA, McKenzie A. Development and function of group 2 innate lymphoid cells. *Curr Opin Immunol*. 2013;25:148–155.
54. Reed Sb, Wesson Ca, Liou Le, et al. Molecular characterization of a novel *Staphylococcus aureus* serine protease operon. *Infect Immun*. 2001;69:1521–1527.
55. Liew FY, Girard J-P, Turnquist HR. Interleukin-33 in health and disease. *Nat Rev Immunol*. 2016;16:676–689.
56. Oboki K, Nakae S, Matsumoto K, Saito H. IL-33 and airway inflammation. *Allergy Asthma Immunol Res*. 2011;3:81–88.
57. Cianferoni A, Spergel J. The importance of TSLP in allergic disease and its role as a potential therapeutic target. *Expert Rev Clin Immunol*. 2014;10:1463–1474.
58. Aron JL, Akbari O. Regulatory T cells and type 2 innate lymphoid cell-dependent asthma. *Allergy*. 2017;72:1148–1155.
59. Schmitz J, Owyang A, Oldham E, et al. IL-33, an interleukin-1-like cytokine that signals via the IL-1 receptor-related protein ST2 and induces T helper type 2-associated cytokines. *Immunity*. 2005;23:479–490.
60. Cherry WB, Yoon J, Bartemes KR, Iijima K, Kita H. A novel IL-1 family cytokine, IL-33, potently activates human eosinophils. *J Allergy Clin Immunol*. 2008;121:1484–1490.
61. Allakhverdi Z, Smith DE, Comeau MR, Delespesse G. Cutting edge: the ST2 ligand IL-33 potently activates and drives maturation of human mast cells. *J Immunol*. 2007;179:2051–2054.
62. Lefrancais E, Duval A, Mirey E, et al. Central domain of IL-33 is cleaved by mast cell proteases for potent activation of group-2 innate lymphoid cells. *Proc Natl Acad Sci U S A*. 2014;111:15502–15507.
63. Pecaric-petkovic T, Didichenko SA, Kaempfer S, Spiegl N, Clemens A, Dahinden CA. Human basophils and eosinophils are the direct target leukocytes of the novel IL-1 family member IL-33 Human basophils and eosinophils are the direct target leukocytes of the novel IL-1 family member IL-33. *Blood*. 2009;113:1526–1534.
64. Chackerian AA, Oldham ER, Murphy EE, Schmitz J, Pflanz S, Kastelein RA. IL-1 receptor accessory protein and ST2 comprise the IL-33 receptor complex. *J Immunol*. 2007;179:2551–2555.
65. Kakkar R, Lee RT. The IL-33/ST2 pathway: therapeutic target and novel biomarker. *Nat Rev Drug Discov*. 2008;7:827–840.
66. Afonina IS, Müller C, Martin SJ, Beyaert R. Proteolytic processing of interleukin-1 family cytokines: variations on a common theme. *Immunity*. 2015;42:991–1004.
67. Lüthi AU, Cullen SP, McNeela EA, et al. Suppression of interleukin-33 bioactivity through proteolysis by apoptotic caspases. *Immunity*. 2009;31:84–98.
68. Lefrancais E, Roga S, Gautier V, et al. IL-33 is processed into mature bioactive forms by neutrophil elastase and cathepsin G. *Proc Natl Acad Sci U S A*. 2012;109:1673–1678.
69. Waern I, Lundequist A, Pejler G, Wernersson S. Mast cell chymase modulates IL-33 levels and controls allergic sensitization in dust-mite induced airway inflammation. *Mucosal Immunol*. 2013;6:911–920.
70. Roy A, Ganesh G, Sippola H, et al. Mast cell chymase degrades the alarmins heat shock protein 70, biglycan, HMGB1, and interleukin-33 (IL-33) and limits danger-induced inflammation. *J Biol Chem*. 2014;289:237–250.
71. Cohen ES, Scott IC, Majithiya JB, et al. Oxidation of the alarmin IL-33 regulates ST2-dependent inflammation. *Nat Commun*. 2015;6:8327.
72. Scott IC, Majithiya JB, Sanden C, et al. Interleukin-33 is activated by allergen- and necrosis-associated proteolytic activities to regulate its alarmin activity during epithelial damage. *Sci Rep*. 2018;8:3363.
73. Gordon ED, Simpson LJ, Rios CL, et al. Alternative splicing of interleukin-33 and type 2 inflammation in asthma. *Proc Natl Acad Sci U S A*. 2016;113:8765–8770.
74. Krowarsch D, Cierpicki T, Jelen F, Otlewski J. Canonical protein inhibitors of serine proteases. *Cell Mol Life Sci*. 2003;60:2427–2444.
75. Kouzaki H, Matsumoto K, Kikuoka H, et al. Endogenous protease inhibitors in airway epithelial cells contribute to eosinophilic chronic rhinosinusitis. *Am J Respir Crit Care Med*. 2017;195:737–747.
76. Ehlers MR. Immune-modulating effects of alpha-1 antitrypsin. *Biol Chem*. 2014;395:1187–1193.
77. Hughes VS, Page K. German cockroach frass proteases cleave pro-matrix metalloproteinase-9. *Exp Lung Res*. 2007;33:135–150.
78. Kalsheker N, Morley S, Morgan K. Gene regulation of the serine proteinase inhibitors alpha1-antitrypsin and alpha1-antichymotrypsin. *Biochem Soc Trans*. 2002;30:93–98.
79. Tomazic PV, Birner-Gruenberger R, Leitner A, Obrist B, Spoerk S, Lang-Loidolt D. Nasal mucus proteomic changes reflect altered immune responses and epithelial permeability in patients with allergic rhinitis. *J Allergy Clin Immunol*. 2014;133:741–750.
80. Pemberton AD, Wright SH, Knight PA, Miller H. Anaphylactic release of mucosal mast cell granule proteases: role of serpins in the differential clearance of mouse mast cell proteases-1 and -2. *J Immunol*. 2006;176:899–904.
81. Benarafa C, Priebe GP, Remold-O'Donnell E. The neutrophil serine protease inhibitor *serpinb1* preserves lung defense functions in *Pseudomonas aeruginosa* infection. *J Exp Med*. 2007;204:1901–1909.

82. Sun Y, Sheshadri N, Zong WX. SERPINB3 and B4: from biochemistry to biology. *Semin Cell Dev Biol*. 2017;62:170–177.
83. Nakashima K, Hirota T, Obara K, et al. A functional polymorphism in MMP-9 is associated with childhood atopic asthma. *Biochem Biophys Res Commun*. 2006;344:300–307.
84. Sharma S, Rajan UM, Kumar A, Soni A, Ghosh B. A novel (TG) n(GA)mrepeat polymorphism 254 bp downstream of the mast cell chymase (CMA1) gene is associated with atopic asthma and total serum IgE levels. *J Hum Genet*. 2005;50:276–282.
85. Hossny EM, Amr NH, Elsayed SB, Nasr RA, Hossny EM. Association of polymorphisms in the mast cell chymase gene promoter region (-1903 G/A) and (TG)n(GA)m repeat downstream of the gene with bronchial asthma in children. *J Investig Allergol Clin Immunol*. 2008;18:376–381.
86. Weidinger S, Rummler L, Klopp N, et al. Association study of mast cell chymase polymorphisms with atopy. *Allergy Eur J Allergy Clin Immunol*. 2005;60:1256–1261.
87. Abdelmotelb Am, Rose-Zerilli Mj, Barton Sj, Holgate St, Walls Af, Holloway Jw. Alpha-tryptase gene variation is associated with levels of circulating IgE and lung function in asthma. *Clin Exp Allergy*. 2014;44:822–830.
88. Marquardt U, Zettl F, Huber R, Bode W, Sommerhoff CP. The crystal structure of human α1-tryptase reveals a blocked substrate-binding region. *J Mol Biol*. 2002;321:491–502.
89. Ishii T, Matsuse T, Teramoto S, et al. Association between alpha-1-antichymotrypsin polymorphism and susceptibility to chronic obstructive pulmonary disease. *Eur J Clin Invest*. 2000;30:543–548.
90. Rogers Aj, Chu J-h, Darvishi K, et al. Copy number variation prevalence in known asthma genes and their impact on asthma susceptibility. *Clin Exp Allergy*. 2013;43:455–462.
91. Mahadeva R, Sharples L, Ross-Russell RI, Webb AK, Bilton D, Lomas DA. Association of alpha(1)-antichymotrypsin deficiency with milder lung disease in patients with cystic fibrosis. *Thorax*. 2001;56:53–58.
92. Braun H, Afonina IS, Mueller C, Beyaert R. Dichotomous function of IL-33 in health and disease: From biology to clinical implications. *Biochem Pharmacol*. 2018;148:238–252.
93. Trajkovic V, Sweet MJ, Xu D. T1/ST2 - An IL-1 receptor-like modulator of immune responses. *Cytokine Growth Factor Rev*. 2004;15:87–95.
94. Lee HY, Rhee CK, Kang JY, et al. Blockade of IL-33/ST2 ameliorates airway inflammation in a murine model of allergic asthma. *Exp Lung Res*. 2014;40:66–76.
95. Hayakawa H, Hayakawa M, Kume A, Tominaga SI. Soluble ST2 blocks interleukin-33 signaling in allergic airway inflammation. *J Biol Chem*. 2007;282:26369–26380.
96. De Grove KC, Provoost S, Braun H, et al. <scp>IL</scp> -33 signalling contributes to pollutant-induced allergic airway inflammation. *Clin Exp Allergy*. 2018;48:1665–1675.
97. Chou H, Tam MF, Lee LH, et al. Vacuolar serine protease is a major allergen of Cladosporium cladosporioides. *Int Arch Allergy Immunol*. 2008;146:277–286.
98. Gupta R, Sharma V, Sridhara S, Singh BP, Arora N. Identification of serine protease as a major allergen of Curvularia lunata. *Allergy*. 2004;59:421–427.
99. Bisht V, Arora N, Singh BP, Pasha S, Gaur SN, Sridhara S. Epi p 1, an allergenic glycoprotein of Epicoccum purpurascens is a serine protease. *FEMS Immunol Med Microbiol*. 2004;42:205–211.
100. Shen HD, Tam MF, Chou H, Han SH. The importance of serine proteinases as aeroallergens associated with asthma. *Int Arch Allergy Immunol*. 1999;119:259–264.
101. Chow LP, Su NY, Yu CJ, Chiang BL, Shen HD. Identification and expression of Pen c 2, a novel allergen from Penicillium citrinum. *Biochem J*. 1999;341:51–59.
102. Bernstein DI, Bernstein IL, Gaines WG, Stauder T, Wilson ER. Characterization of skin prick testing responses for detecting sensitization to detergent enzymes at extreme dilutions: inability of the RAST to detect lightly sensitized individuals. *J Allergy Clin Immunol*. 1994;94:498–507.
103. Stentzel S, Teufelberger A, Nordengrün M, et al. Staphylococcal serine protease-like proteins are pacemakers of allergic airway reactions to Staphylococcus aureus. *J Allergy Clin Immunol*. 2017;139:492–500.
104. Morita H, Arae K, Unno H, et al. IL-25 and IL-33 contribute to development of eosinophilic airway inflammation in epicutaneously antigen-sensitized mice. *PLoS One*. 2015;10:e0134226.
105. Oboki K, Ohno T, Kajiwara N, et al. IL-33 is a crucial amplifier of innate rather than acquired immunity. *Proc Natl Acad Sci U S A*. 2010;107(43):18581–18586.
106. Zoltowska AM, Lei Y, Fuchs B, Rask C, Adner M, Nilsson GP. The interleukin-33 receptor ST2 is important for the development of peripheral airway hyperresponsiveness and inflammation in a house dust mite mouse model of asthma. *Clin Exp Allergy*. 2016;46:479–490.
107. Morita H, Arae K, Ohno T, et al. ST2 requires Th2-, but not Th17-, type airway inflammation in epicutaneously antigen- sensitized mice. *Allergol Int*. 2012;61:265–273.
108. Liu X, Li M, Wu Y, Zhou Y, Zeng L, Huang T. Anti-IL-33 antibody treatment inhibits airway inflammation in a murine model of allergic asthma. *Biochem Biophys Res Commun*. 2009;386:181–185.
109. Kearley J, Buckland KF, Mathie SA, Lloyd CM. Resolution of allergic inflammation and airway hyperreactivity is dependent upon disruption of the T1/ST2-IL-33 pathway. *Am J Respir Crit Care Med*. 2009;179:772–781.
110. Oshikawa K, Yanagisawa K, Tominaga S, Sugiyama Y. Expression and function of the ST2 gene in a murine model of allergic airway inflammation. *Clin Exp Allergy*. 2002;32:1520–1526.
111. Lambrecht BN, De Veerman M, Coyle AJ, Gutierrez-Ramos J-C, Thielemans K, Pauwels RA. Gutierrez-Ramos JC, Thielemans K, Pauwels R a. Myeloid dendritic cells induce Th2 responses to inhaled antigen, leading to eosinophilic airway inflammation. *J Clin Invest*. 2000;106:551–559.

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