The central role of IL-33/IL-1RL1 pathway in asthma

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The central role of IL-33/IL-1RL1 pathway in asthma: From pathogenesis to intervention

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ABSTRACT

Interleukin-33 (*IL-33*), a member of the IL-1 family, and its cognate receptor, Interleukin-1 receptor like-1 (*IL-1RL1 or ST2*), are susceptibility genes for childhood asthma. In response to cellular damage, IL-33 is released from barrier tissues as an 'alarmin' to activate the innate immune response. IL-33 drives type 2 responses by inducing signalling through its receptor IL-1RL1 in several immune and structural cells, thereby leading to type 2 cytokine and chemokine production. *IL-1RL1* gene transcript encodes different isoforms generated through alternative splicing. Its soluble isoform, IL-1RL1-a or sST2, acts as a decoy receptor by sequestering IL-33, thereby inhibiting IL1RL1-b/IL-33 signalling. IL-33 and its receptor IL-1RL1 are therefore considered as putative biomarkers or targets for pharmacological intervention in asthma. This review will provide an overview of the genetics and biology of the IL-33/IL-1RL1 pathway in the context of asthma pathogenesis. It will discuss the potential and complexities of targeting the cytokine or its receptor, how genetics or biomarkers may inform precision medicine for asthma targeting this pathway, and the possible positioning of therapeutics targeting IL-33 or its receptor in the expanding landscape of novel biologicals applied in asthma management.

Contents

1. Introduction: The IL-33/IL-1RL1 pathway as a central nexus in asthma . . . 2
2. The IL-33/IL-1RL1 pathway in asthma . . . 3
3. Genetics of the IL-33/IL-1RL1 pathway . . . 9
4. Towards precision medicine . . . 10
5. Conclusion . . . 13

Abbreviations: A disintegrin and metalloproteinase domain-containing protein 33, ADAM33; Activator protein-1, AP-1; Airway Hyperresponsiveness, AHR; Airway Smooth Muscle Cells, ASMCs; Alternaria alternata, ALT; Amphiregulin, AREG; Atopic dermatitis, AD; Bronchoalveolar lavage fluid, BALF; c-Jun N-terminal kinase, JNK; Carcinoma Cell Line, CCL; Damage Associated Molecular Pattern, DAMP; Dendritic cells, DCs; Early-Associated-Response, EAR; Expression quantitative trait loci, eQTL; Extracellular Receptor Kinase, ERK; Forced Expiratory Volume in one second, FEV1; GATA Binding Protein 1, GATA 1; Genome-Wide Association Study, GWAS; Granulocyte-macrophage colony-stimulating factor, GM-CSF; Histone 2A - Histone 2B, H2A-H2B; Histone-lysine N-methyltransferase, SUV39H1; IKappaB Kinase, IκB; Immunoglobulin E, IgE; Inhaled Corticosteroids, ICS; Interferon gamma, INFγ; Interleukin 1 receptor accessory protein, IL-1RAcP; Interleukin 1 Receptor Like 1, IL-1RL1; Interleukin - 33, IL-33; Interleukin -, IL-; Interleukin receptor associated kinases, IRAK1/4; Invariant natural killer T, iNKT; Janus Kinase pathway, JAK; Late-Associated-Response, LAR; Linkage Disequilibrium, LD; Long-acting beta-adrenoceptor agonist, LABA; Major histocompatibility complex, MHC; mammalian target of rapamycin, mTOR; Mast cells, MCs; MyD88-adapter-like, MAL1; Myeloid differentiation primary response 88, MyD88; N-acetylglucosamine, NAG; Natural Killer cells, NKs; NLR family pyrin domain containing 3 - nucleotide-binding oligomerization domain, NLRP3-NOD; Nuclear Factor Kappa-light-chain-enhancer of activated B cells, NF-κB; Nuclear Factor-High Endothelial Venules, NF-HEV; phosphoinositide 3-kinase, PI3k; Protein quantitative trait loci, pQTL; Regulatory T cells, Treg; Reticular Basement Membrane, RBM; Short-acting beta-adrenoceptor agonist, SABA; Signal Transducer And Activator Of Transcription 5A, STAT5A; Single Ig IL-1-related receptor, SIGIRR; Single nucleotide polymorphisms, SNP; Stem cells antigen-1, Sca-1; T helper 2 lymphocyte, Th2; T helper 17 cells, Th17; T-cell receptor, TCR; The Toll/interleukin-1 receptor, TIR; Thymic stromal lymphopoietin, TSLP; Toll/Interleukin-1 receptor 8, TIR8; TRAF6, Tumor necrosis factor receptor (TNFR)-associated factor 6, TRAF6; Tumour Necrosis Factor alpha, TNF-α; Type 2 innate lymphoid cells, ILC2; Type 2, T2.

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Declaration of Competing Interest . . . 13
Acknowledgements . . . 13
Declaration of Competing Interest . . . 13
References. . . . 13

1. Introduction: The IL-33/IL-1RL1 pathway as a central nexus in asthma

1.1. Asthma

Asthma is a heterogeneous disease, characterized by airway inflammation and airway hyperresponsiveness (AHR). It is a chronic respiratory disease affecting 1-18% of the population across the world. Asthma patients report respiratory symptoms such as dyspnoea, wheeze, cough and/or chest tightness. These symptoms increase in frequency and intensity in more severe disease, accompanied by expiratory airflow limitation and an overall decline in lung function (Global Initiative for Asthma, 2019, 2020). Asthma symptoms often start early in life, but are at that time not specific since approximately 40 % of all preschool children have wheeze and shortness of breath during the course of a viral respiratory tract infection (Savenije, Kerkhof, Koppelman, & Postma, 2012). Only approximately a third of these children will eventually be diagnosed with asthma (Martinez et al., 1995; Mommers, Gielkens-Sijstermans, Swaen, & Van Schayck, 2005). Severity of symptoms for many children with asthma diminishes in early puberty, while these symptoms remain in children with severe asthma or may return in adulthood (van Aalderen, 2012). Incidence of asthma in childhood shows a sex-specific pattern: incidence rates were found to be higher in males than in females from infancy through young adolescence. This pattern changed after the age of 15, with higher incidence rates in females than in males (Butland & Strachan, 2007; Szefler, 2015; Yunginger et al., 1992). In a 15-year follow-up study, it was reported that asthma patients can experience alternating periods of remission and relapse of the disease, indicating that asthma is a disease with variable expression through the lifespan of the patient (Lange, Parner, Vestbo, Schnohr, & Jensen, 1998). Moreover, onset and exacerbations of the disease are often triggered by a range of environmental stimuli, such as exposure to allergen, air pollutants and respiratory viral infections (von Mutius & Smits, 2020). The underlying cause for the variability in asthma is not yet fully understood. In addition to variability in symptoms, asthma is a heterogeneous disease with multiple phenotypes, thereby posing a challenge for epidemiological and pathophysiological research.

Based on pathophysiology, clinical, and demographical data, asthma has been proposed to fall into several main 'phenotypes' (Bel, 2004; Moore et al., 2010; Wenzel, 2012), including allergic asthma, non-allergic asthma, adult or late-onset asthma, asthma with persistent airflow limitation and asthma with obesity. Although these categories describe phenotypes that are clinically relevant, these do not easily provide insight into the underlying mechanisms of disease since several discrete biological pathways can produce similar clinical symptoms. This means that, using traditional clinical and physiological parameters, it is very hard to define distinct subgroups of asthma patients that can be treated by addressing one common pathogenic mechanism. To account for this, asthma phenotypes were recently categorized into so-called 'endotypes' with the aim to identify groups of patients that each share a unique cellular and molecular pathogenic mechanism as the cause of their disease (Lötvall et al., 2011). These 'endotypes' are thought to reflect subtypes of the disease, defined on the basis of a shared functional and pathophysiological mechanism, and as a consequence, a shared treatment response. Large, multicentre studies that subclassify the disease, have consistently identified phenotypes that support the presence of endotypes (Anderson, 2008; Kaur & Chupp, 2019). Currently, there is one recognized endotype, which is the Type 2 (T2)- high endotype. Other endotypes, such as T helper 17 cell (Th-17) or Interleukin - 6 (IL-6) trans-signalling endotypes, are putative endotypes that need further validation. A detailed description of the endotypes of asthma based on clinical and genetic information may help to define novel biomarkers and therapeutic targets specific for each endotype (Anderson, 2008; Kaur & Chupp, 2019; Moore et al., 2010). Here, we propose the IL-33/Interleukin 1 Receptor Like 1 (IL-33/IL-1RL1) pathway may contribute to specific endotypes in asthma and may therefore help predict treatment response to currently available or novel treatment options.

The most common form of asthma is childhood-onset allergic asthma, primarily characterized by the presence of eosinophilic airway inflammation, driven by a T2-dominated immune response, which at least in part is directed to environmental allergens (Busse & Lemanske, 2001). Childhood onset asthma is associated with chronic T helper 2 cell (Th2)-driven allergic inflammatory process (Holgate, 2012). Allergic sensitization is induced by dendritic cells (DCs) presenting allergen-derived peptides in the context of major histocompatibility complex (MHC) class II to naïve T cells in the lymph nodes. In atopic individuals, this process induces Th cell differentiation into Th2 cells that secrete the pro-inflammatory cytokines such as IL-4, IL-5, IL-9, and IL-13 (Doucet et al., 1998; Kay, 2006). Allergen-specific Th2 cells can then activate allergen-specific B cells to induce IgE class switching and production of allergen-specific IgE. The presence of allergen-specific Immunoglobulin E (IgE) will result in binding of the IgE molecules to the high-affinity Fcε-receptors present on the cell-surface of mast cells (MCs), basophilic and eosinophilic granulocytes allowing these effector cells to respond to the allergen upon a subsequent exposure (Jain, Perkins, & Finn, 2008; Kay, 2006; Lambrecht & Hammad, 2015). In a sensitized individual, exposure to allergen then leads to early (EAR) and late phase allergic responses (LAR). The EAR is IgE-dependent, and is the result of degranulation of MCs, basophils and eosinophils. MC degranulation results in release of mediators from the granules such as histamine and leukotrienes that induces bronchoconstriction, mucus hypersecretion, vasodilation, and influx of inflammatory cells into the tissue. The EAR is induced within seconds after allergen exposure and lasts up to 90 minutes (Bousquet, Jeffery, Busse, Johnson, & Vignola, 2000; Rothenberg, 1998). As a consequence of the release of vasodilating and pro-inflammatory mediators during the EAR, inflammatory cells will enter the inflamed tissue, and allergen-specific Th2 cells will be activated by tissue-resident antigen-presenting cells such as macrophages or DCs. In turn, the Th2 effector cells activate the tissue resident or recruited innate immune cells including MCs, eosinophils and basophils, leading to the LAR. The LAR starts 3-4 hours after allergen exposure, and is characterized by bronchoconstriction, as well as an inflammation (Boulet et al., 1997; Kirby, Robertson, Hargreave, & Dolovich, 1986; Pepys, Hargreave, Chan, & McCarthy, 1968). Ongoing inflammation of the airway wall is related to permanent changes of the airways, collectively called airway remodelling (Al-Muhsen, Johnson, & Hamid, 2011).

The structural changes include epithelial changes such as goblet cell hyperplasia, subepithelial reticular lamina fibrosis, angiogenesis and activation of fibroblasts and myofibroblasts, an increase in smooth muscle mass and excessive deposition of extracellular matrix, including basement membrane thickening (Halwani, Al-Muhsen, & Hamid, 2010; Homer & Elias, 2005). The airway epithelium is vulnerable in patients with asthma and shows an exaggerated response to environmental

challenges. Epithelial injury in asthmatic airways can lead to detachment of basal and columnar cells due to epithelial frailty, detected as Creola bodies in the sputum of asthmatic patients (Liesker et al., 2009; Roche, Williams, Beasley, & Holgate, 1989). Moreover, a developmental cell-cell interaction between epithelial and mesenchymal cells called the epithelial-mesenchymal trophic unit, has been proposed to be reactivated in chronic asthma and to contribute to remodelling of the airway wall (Holgate et al., 2004). Airway wall thickening, and smooth muscle proliferation is also induced by the secretion of interstitial collagen and proteoglycans (Chetta et al., 1997; Postma & Timens, 2006). Together with migrating microvascular pericytes and differentiation of myofibroblasts that enhance fibrosis and muscle hyperplasia, these are some of the contributing factors of airway remodelling (Desideria et al., 2008; Johnson et al., 2015; Pepe et al., 2005).

In summary, asthma is a syndrome that encompasses many different clinical, environmental, genetic, and pathophysiological factors. It has been difficult to dissect asthma based on these factors. However, genetics may provide an unbiased method to identify causes and pinpointing pathways, that may be related to certain asthma endotypes and be amendable for targeted intervention. One such pathway is the IL-33/IL-1RL1 receptor pathway, which will be the focus of this review.

1.2. IL-33 and IL-1RL1 are important asthma genes

Genome-wide and candidate gene-based association studies have identified common single nucleotide polymorphisms (SNPs) in the *IL-33* and IL-1 receptor-like 1 (*IL-1RL1*) loci to be associated with asthma, in particular childhood onset asthma (El-Husseini, Gosens, Dekker, & Koppelman, 2020). Proteins encoded by these loci act in the IL-33/IL-1RL1 pathway. IL-33 is a cytokine predominantly secreted by structural cells at barrier tissues, such as epithelial cells, endothelial cells, and fibroblasts. IL-33 is thought to act as an alarmin in response to tissue injury, necrosis and infectious agents (Kakkar & Lee, 2008). Upon release, IL-33 binds to a heterodimeric receptor complex consisting of IL-1RL1-b (or ST2L) and Interleukin-1 receptor accessory protein (IL-1RAcP), inducing downstream signalling events leading to the activation of immune cells and of structural cells such as bronchial epithelial cells, fibroblasts and airway smooth muscle cells (ASMCs) (Funakoshi-Tago et al., 2008; Kakkar & Lee, 2008). Through the years, the molecular mechanisms of this pathway, and the genetic regulation of *IL-1RL1* and *IL-33* in asthma development have been studied in great detail. However, it is vital to understand the regulation of gene expression of *IL-1RL1* and *IL-33*, its protein localization and posttranslational regulation in immune and structural cells, to help chart specific endotypes of asthma that involve dysregulation of this signalling pathway.

2. The IL-33/IL-1RL1 pathway in asthma

2.1. IL-33

Interleukin-33 (IL-33) is a member of the IL-1 family of cytokines and plays a vital role in a number of inflammatory processes and disorders, such type 2 immune responses and allergic airway disease. IL-33 was originally identified as a protein (DVS27) present in canine endothelial cells and as a nuclear factor in human endothelial cells located in high endothelial venules (NF-HEV) (Baekkevold et al., 2003; Onda et al., 1999). Later, it was recognized as a member of the IL-1 family and as an extracellular ligand for the orphan IL-1 receptor IL-1RL1b (ST2) through computational approaches (Schmitz et al., 2005). Located on chromosome 9p24.1, the *IL-33* gene contains one non-coding (exon 1) and seven coding exons (exons 2-8). A number of IL-33 splice variants have been described that display different use of the coding regions located at exons 3, 4 and 5, and which were found to amplify type-2 responses in asthmatic patients when exposed to viral infection (Ferreira et al., 2017; Jurak et al., 2018; Smith et al., 2017). One rare genetic variant in the *IL-33* gene has been described to disrupt a canonical splice acceptor site before the last coding exon. Subjects who carry a copy of this rare allele were shown to have 40% lower total IL-33 mRNA expression than non-carriers. This mutation causes retention of the last intron, predicted to result in a premature stop codon and reduces asthma risk by half (Smith et al., 2017).

IL-33 mRNA and protein are constitutively and abundantly expressed in many human tissues (Moussion, Ortega, & Girard, 2008). IL-33 expression in human lung is observed in basal cells of the airway epithelium, endothelial cells, and fibroblasts. Under steady-state conditions, IL-33 is stored as a full-length protein (~31kDa) in the cell nucleus and serves as a transcription factor (Gordon et al., 2016; Polumuri et al., 2012; Schmitz et al., 2005; Tsuda et al., 2012). Upon cellular damage induced by physical insults, pathogen or allergen exposure, IL-33 is released into the extracellular environment and functions as an endogenous danger signal or alarmin (Cayrol & Girard, 2014; Moussion et al., 2008). Bioactive IL-33 is released directly from necroptosis, but not apoptotic cells, implying that IL-33 is a necroptotic damage-associated molecular pattern (DAMP) (Shlomovitz et al., 2019). Upon release, IL-33 signals tissue damage to the innate and adaptive immune system (Küchler et al., 2008). IL-33 can activate a large number of immune cells such as MCs, basophils, DCs, innate lymphoid cells (ILCs) and Th2 cells as well as structural cells such as epithelial and mesenchymal cells, by binding to the IL-33 receptor complex (Barlow et al., 2013; Hardman, Panova, & Mckenzie, 2013; Hsu & Bryce, 2012; Pecaric-Petkovic, Didichenko, Kaempfer, Spiegl, & Dahinden, 2009; Rank et al., 2009).

Besides its role as an alarmin, IL-33 expression was first observed in nuclei of endothelial cells (Carriere et al., 2007a). Due to the presence of a helix-turn-helix domain in the N-terminal part of the protein, IL-33 has the potential to directly bind to histone proteins. Amino acids 40 to 53 of the IL-33 protein were found to bind to the H2A-H2B acidic pocket (Roussel, Erard, Cayrol, & Girard, 2008). Direct binding of IL-33 to DNA was reported in chromatin immunoprecipitation experiments, showing that IL-33 can bind multiple putative homeodomain protein binding motifs in the promoter of the *IL-1RL1* gene, in addition to creating a complex with the histone methyltransferase SUV39H1 (suppressor variegation 3-9 homolog 1), a transcriptional repressor (Carriere et al., 2007b). These data suggest that IL-33 can bind DNA at specific loci as well as histone proteins and transcriptional co-regulators, resulting in transcriptional repression. Despite this highly relevant function for IL-33, no data is available on the specific role of the transcription factor activity of IL-33 in biological processes relevant to the pathogenesis of asthma, or even in the specific cell types relevant to asthma inception or exacerbation.

Hence, due to its dual role as both a transcription factor and a cytokine, in humans, IL-33 has an unconventional secretory mechanism compared to other IL-1 family members. Most IL-1 family members (such as IL-1β, IL-18) require posttranslational processing of the protein to allow secretion of the active cytokine, which is dependent on activation of the inflammasome (Dinarello, 2009; Ghayur et al., 1997; Thornberry et al., 1992). In contrast, IL-33 is active in its full-length form, and is passively released upon cellular damage (Cayrol & Girard, 2009; Lefrançais et al., 2012). Moreover, cleavage of the N-terminal portion of IL-33 by the inflammasome complex and caspases-1, -3 and -7, which is the activating event for IL1β and IL-18, in fact inactivates IL-33, as has also been reported for IL-1α (Lüthi et al., 2009; Talabot-Ayer, Lamacchia, Gabay, & Palmer, 2009). Furthermore, these executor caspases cleave the IL-33 protein after aspartic acid residue D178 inside the IL-1 domain, rendering the cytokine inactive during apoptosis (Ali, Nguyen, Falk, & Martin, 2010) (Fig. 1). Additionally, caspases cleave the C-terminal domain, specifically between the β4 and β5 region of IL-33, which is absent from other IL-1 cytokine members (Lingel et al., 2009). Inactivation of IL-33 is also observed through oxidation of critical cysteine residues of IL-33 a few hours after its extracellular release (Cohen et al., 2015). Hence, while full-length IL-33 released from the cell during necrosis acts as an alarmin, IL-33 is inactivated during

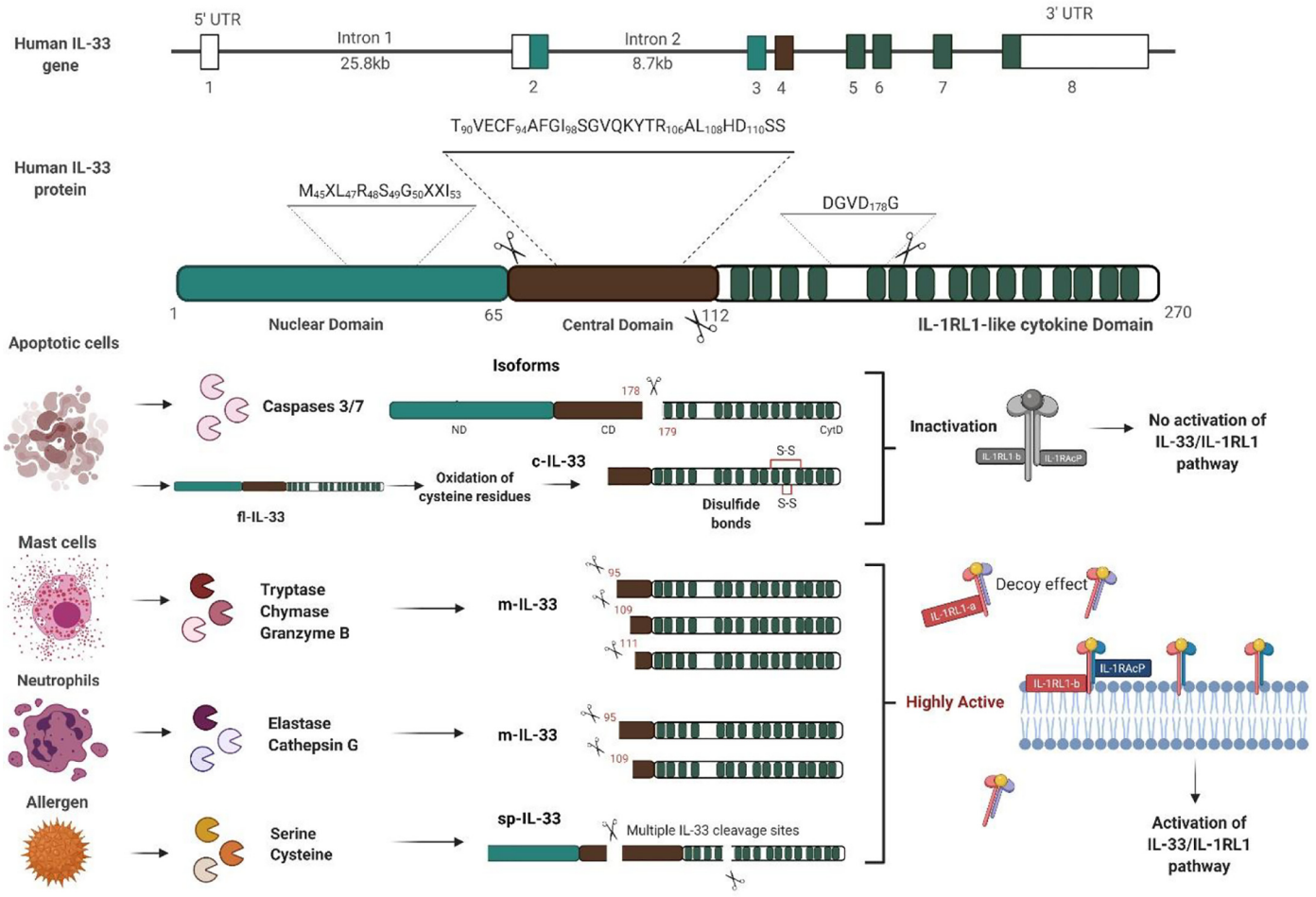

Fig. 1. Mechanism of proteolytic cleavage of IL-33. Different biological processes (such as apoptotic stress, inflammation, and necrosis) lead to various IL-33 protein variants with high or no biological activity. Apoptotic cells cleave IL-33 in the caspase site with the help of caspase-3/-7 generating inactive fragments of IL-33 (cleaved IL33, c-IL-33). Alternatively, oxidation of cysteine residues in full-length IL-33 (fl-IL-33), undergoes a conformational change of the protein by formation of disulphide bridges. This in-turn leads to inactivation of the signalling pathway. In the case of inflammation or necrosis; mast cells, neutrophils and other inflammatory cells release enzymes that cleave the IL-33 protein at the Inflammatory site inside the central region. This in-turn, releases highly active forms of mature IL-33 (m-IL-33), that stably bind to a plethora of IL-1RL1 expressing cells . In other cases; active IL-33 also binds to the soluble form of its receptor (IL-1RL1a), which acts as a decoy receptor. When IL-33 is cleaved by environmental allergens, their enzymatic activity at the inflammatory site gives rise to multiple peptide products and splice variants (sc-IL-33) sharing the whole IL-1 like region of IL-33. Created with BioRender.com

apoptotic cell death by the executor caspases. Interestingly, elevated expression levels of nucleotide-binding oligomerization domain-like receptors (NOD-like receptor) (NLR) family pyrin domain containing 3 (NLRP3), caspase-1 and IL-1β were associated with neutrophilic asthma (Baines, Simpson, Wood, Scott, & Gibson, 2011; Kim et al., 2015; Simpson et al., 2014). In mouse models, targeted therapy towards NLRP3 and caspase-1 reduced IL-1β production and was able to suppress steroid-resistant neutrophilic inflammation and airway hyperresponsiveness (Kim et al., 2017; Simpson et al., 2014), indicating that IL-1 family members IL-33 and IL1β might have contrasting regulation by the inflammasome and apoptosis-associated executioner caspases, and contribute to steroid sensitive versus resistant asthma phenotypes, respectively.

In marked contrast to its inactivation by executor caspases in the cytoplasm, the IL-33 protein in IL-33 deficient mice, has been proposed to act as an extracellular sensor for proteolytic activity (Cayrol & Girard, 2014). The IL-33 protein was found to contain a so-called 'sensor' domain, that is sensitive to the proteolytic activity of a range of extracellular proteases. Cleavage of the IL-33 protein at this sensor domain will also result in removal of an N-terminal domain, but the fragment cleaved off is much smaller compared to that released by the apoptotic caspases. The removal of the N terminus after proteolytic cleavage in the sensor domain does not inactivate the protein, but instead results in strongly increased affinity of the short isoform of IL-33 for the receptor (Lefrançais et al., 2014; Liu et al., 2013). In addition, IL-33 acts as a substrate for serine proteases released by other inflammatory cells such as MCs, eosinophils, and Th2 cells, which also results in IL-33 isoforms with increased biological activity in both murine and human models (Lefrançais et al., 2014). Consequently, neutrophil proteases that increase the activity of extracellular IL-33 can contribute to virus-induced exacerbations of asthma and other inflammatory or infectious conditions (Chang et al., 2011; Monticelli et al., 2011). For instance, elastase, cathepsin G and proteinase 3 released from neutrophils were reported to cleave full-length human IL-$33_{1–270}$ into the protein isoforms IL-$33_{95–270}$, IL-$33_{99–270}$, and IL-$33_{109–270}$. These isoforms have a nearly 10-fold increase in activity compared to full-length IL-33 in cellular assays (Lefrançais et al., 2012; Lefrançais & Cayrol, 2012) (Fig. 1). Finally, specific allergens that have serine protease activity such as those from fungi (*Alternaria alternate* (ALT) or *Aspergillus fumigatus*), house dust mite (*Dermatophagoides pteronyssinus*), cockroaches and allergens can cleave IL-33 in the sensor domain, thereby strongly enhancing the activity of the protein (Cayrol et al., 2018; Scott et al., 2018). Similarly, protease activity from allergens or innate effector cells activated during allergic inflammation in murine models increase IL-33, further increasing the numbers of infiltrating macrophages and type 2 innate lymphoid cells (ILC2), thereby enhancing eosinophilia, bronchial

hyperreactivity, and goblet cell hyperplasia (Lefrançais et al., 2014; Snelgrove et al., 2014; Teufelberger et al., 2018).

In addition to posttranslational modifications, IL-33 also has been shown to be quickly oxidized, following by formation of a disulphide bridges that impairs receptor binding and renders the cytokine biologically inactive (Fig. 1). Transgenic mice carrying the human *IL-33* gene challenged with ALT extract release IL-33 in its reduced form in lung tissue. This human IL-33 then rapidly undergoes a conformational switch to a biologically inactive, oxidized form through formation of a disulphide bridge (Cohen et al., 2015). While this form of IL-33 was also detected in sputum of exacerbating asthmatics, it is likely that at the time of the exacerbation, the reduced, biologically active form of IL-33 is released, which is then rapidly oxidized (Cohen et al., 2015).

Quantification of IL-33 in human serum or tissue samples is severely limited by the low levels of IL-33 and the aforementioned posttranslational modifications such as cleavage or oxidation. Most commercial ELISA kits lack sensitivity and specificity for detection of IL-33 in serum (Asaka et al., 2012; Ketelaar, Nawijn, Shaw, Koppelman, & Sayers, 2016; Rivière et al., 2016). Improved highly sensitive methods for detection of IL-33 in both its reduced and its oxidized form are therefore urgently needed.

2.2. IL-1RL1

The *IL-1RL1* gene is located on human chromosome 2q12.1 and spans approximately 40 kb. The locus encodes 4 different *IL-1RL1* transcript isoforms generated through alternative splicing. The two main isoforms are the transmembrane receptor (IL-1RL1-b, also known as ST2L), consisting of extracellular, transmembrane and cytoplasmic toll-like receptor (TIR) domains capable of inducing signal transduction, and the secreted isoform (IL-1RL1-a, also known as sST2), which carries the extracellular domains of IL-1RL1-a, with an additional 9 amino acids C-terminal sequence. The two other mRNA isoforms encode IL-1RL1-c (also known as ST2V), which is similar to sST2 but lacks the third extracellular immunoglobulin domain, along with alternative splicing at the C-terminal portion of ST2, leading to a hydrophobic tail, and lastly IL-1RL1-d (also known as ST2VL, isoform 4), with alternative splicing leading to deletion of IL-1RL1-b transmembrane domain (Bergers, Reikerstorfer, Braselmann, Graninger, & Busslinger, 1994; Iwahana et al., 1999; Iwahana et al., 2004; Tago et al., 2001; Thomassen et al., 1995). By cloning the cDNAs of *IL-1RL1* gene, it was found that the transmembrane and secreted isoforms have different exon 1 sequences, reflecting differences in promoter usage (Bergers et al., 1994). The usage of these two alternative promoters leads to differential 3' processing of the mRNA isoforms (Bergers et al., 1994; Iwahana et al., 1999). Mapping the promoter regions confirmed that the transcription start site for *IL-1RL1-b* is in the distal promoter region while the transcription start site for *IL-1RL1-a* is in the proximal promoter region. Additionally, GATA1 and GATA2 transcription factors were identified to bind to the distal promoter region within 1,001 bp in the human *IL-1RL1* gene, resulting in expression of *IL-1RL1-b* (Gächter, Werenskiold, & Klemenz, 1996; Griesenauer & Paczesny, 2017; Iwahana et al., 1999). PU.1, another transcription factor acting synergistically with GATA1/2, can also bind to the *IL-1RL1* distal promoter near the GATA elements and cooperatively transactivates the promoter inducing expression of *IL-1RL1* (Baba et al., 2012b). Post-translational modifications of IL-1RL1 involves glycosylation at Asn232 to Gly271, and Gly279 to Arg317 in addition to three N-acetyl-D-glucosamine (NAG) glycans linked to Asn95, Asn140, and Asn191, respectively (Liu et al., 2013). Interestingly, polymorphisms affecting the Toll/IL-1 receptor(TIR) signalling domain of the IL-1RL1 receptor affected the strength of IL-33 induced NF-κB signalling in primary bronchial epithelial cells, underscoring the relevance of genetic variation for the activity of this pathway (Portelli et al., 2020).

2.3. IL-33 induced signalling through IL-1RL1

The alarmin IL-33 exerts its cytokine activity primarily through the IL-1RL1 receptor that upon binding of IL-33, heterodimerizes with its accessory receptor IL-1RAcP to form the functional IL-33 receptor complex (Schmitz et al., 2005). Signalling by the receptor complex is then initiated by exposure of the TIR domains of IL-1RL1 and IL-1RAcP and the recruitment of a TIR-domain containing signalling adaptor such as myeloid differentiation primary response gene 88 (MyD88) or MyD88 adapter-like 1 (MAL1) into the heterodimeric IL-1RL1/IL-1RAcP complex. Recruitment of MyD88 or MAL1 in turn leads to recruitment of IL-1 receptor–associated kinase 1 (IRAK1) and IRAK4, through their death domains (Andrade et al., 2011; Barlow et al., 2013). IRAK4 activates IRAK1, allowing IRAK1 to auto-phosphorylate. This complex then activates downstream signalling, including TRAF6, p38-, c-Jun N-terminal kinases (JNK) and NF-κB, extracellular receptor kinase (ERK) and Janus kinase pathway 2(JAK2) (Funakoshi-Tago et al., 2008; Funakoshi-Tago, Tago, Sato, Tominaga, & Kasahara, 2011; Lott, Sumpter, & Turnquist, 2015) (Fig. 2). Lastly, the phosphoinositide-3 kinase(PI3K) and the mTOR pathway are also activated by human IL-33 in immune cells such as Th2, eosinophils and macrophages (Salmond et al., 2012). These downstream signalling events will induce the expression of several pro-inflammatory cytokines depending on the target cell (Funakoshi-Tago et al., 2008; Kakkar & Lee, 2008).

Two key mechanisms regulate IL-33-induced IL1RL1 receptor activity *in vivo*. The first mechanism is IL-1RL1-a (soluble ST2), which acts as a decoy receptor for IL-33, increasing the threshold for activation of the transmembrane IL-1RL1 receptor (Griesenauer & Paczesny, 2017; Molofsky, Savage, & Locksley, 2015). This soluble IL-1RL1 protein was initially thought to be generated by proteolytic cleavage of the extracellular portion of IL-1RL1 transmembrane receptor (Robb & Kutny, 1987; Symons, Eastgate, & Duff, 1991). This is further supported by the mRNA transcripts of *IL-1RL1-a* and *IL-1RL1-b* which are also expressed by different promoter regions, and produced by alternative 3′ splicing of the primary transcript of the *IL-1RL1* gene (Bergers et al., 1994). The soluble isoform of IL-1RL1 is constitutively expressed by a range of cells including bronchial epithelial cells and fibroblasts (Gordon et al., 2016). In addition, expression can be induced by IL-33 in MCs and activated $CD4^+$ and $CD8^+$ T cells (Bandara, Beaven, Olivera, Gilfillan, & Metcalfe, 2015; Mildner et al., 2010; Zhang et al., 2015).

In addition to IL1RL1a-dependent regulation of IL-33 levels available for inducing signal transduction through the IL1RL1/IL1RacP receptor complex, single immunoglobulin IL-1R-related receptor (SIGIRR)/ Toll IL-1R8 (TIR8) was found to negatively regulate activity of the receptor complex. SIGIRR was found to form a complex with IL-1RL1 upon IL-33 stimulation, resulting in decreased levels of ERK, JNK and IκB phosphorylation (Bulek et al., 2009).

Upon IL-1RL1 receptor binding and signal transduction through the IL-33 receptor complex, IL-33 can induce different inflammatory responses depending on the cell type. IL-33 stimulation supports both myeloid and lymphoid cell growth, proliferation, and survival as well as type-2 immune responses by inducing release of IL-4, IL-5 and IL-13 in specific immune cell subsets expressing the IL-1RL1 receptor (Lott et al., 2015; Molofsky et al., 2015). Here, we will discuss the effects of IL-33 induced signalling on the major cell types involved in allergic inflammation and asthma (Fig. 3).

2.4. IL-33 effects on cells of the immune system

2.4.1. Treg cells and innate lymphoid cells type 2

In regulatory T cells (Treg), IL-33 induces proliferation and expression of the epidermal growth factor-like molecule amphiregulin (AREG), thereby enhancing immune regulatory functions and tissue repair (Arpaia et al., 2015; Burzyn et al., 2013; Zaiss, Gause, Osborne, & Artis, 2015). ILC2 were first discovered as lineage marker negative, c-Kit positive, Sca-1 positive, and IL-1RL1 positive cells in the mouse and

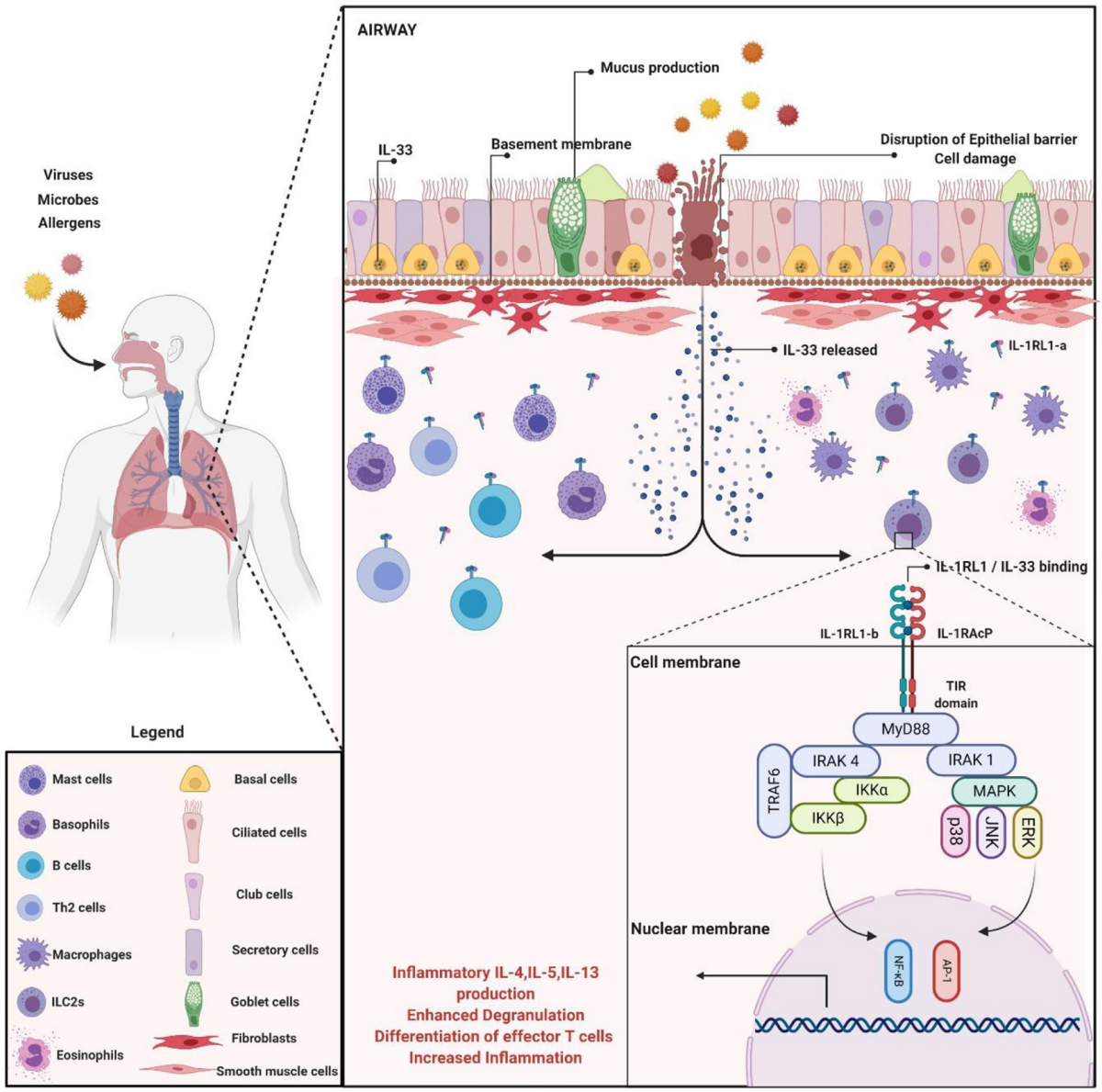

Fig. 2. Signalling pathway of IL-33/IL-1RL1 in allergic inflammation. In response to allergens, microbes and viruses, IL-33 is released as an alarmin from epithelial cells as a result of disruption in the epithelial barrier and cell damage. This in turn leads to binding of IL-33 to IL-1RL-b/ST2L heterodimerization with IL-1RAcP at the TIR domain and recruiting MyD88 to its intracellular domain, or the sST2 decoy receptor, which does not signal. MyD88 recruits either IRAK1 leading to activation of MAPK and AP-1 pathway or IRAK4 through TRAF6, leading to NF-κB pathway activation. Activation of NF-κB and AP-1 in the nuclear membrane further promotes inflammatory cytokine production such as IL-4, IL-5, IL-13, enhanced degranulation and inflammation. On the other hand, IL-33 also binds to IL-1RL1-a (soluble sST2), acting as a negative regulator of the pathway Created with BioRender.com

human mesenteries (Moro et al., 2010; Neill et al., 2010). These cells express GATA-3 and produce the type 2 cytokines IL-5 and IL-13, and have a protective role against helminth infection (Neill et al., 2010), while contributing to AHR after allergen or viral exposure in the respiratory system (Salimi et al., 2013; Wilhelm et al., 2011). IL-33/IL-1RL1 signalling in murine lung-resident ILC2s is also important during influenza infection. Blocking IL-1RL1 signalling in mice resulted in lower ILC2 numbers in the lung, which was associated with decreased lung function and loss of airway epithelial integrity, thereby indicating the importance of IL-33 activation of ILC2s in antiviral responses and airway epithelial repair (Monticelli et al., 2011). IL-1RL1 expression level in murine bone marrow ILC2s was significantly increased by IL-33 treatment (Brickshawana, Shapiro, Kita, & Pease, 2011), suggesting a positive feedback loop capable of amplifying ILC2 activation by IL-33 (Spooner et al., 2013) in mice. Likewise, another study indicated that thymic stromal lymphopoietin (TSLP) treatment of murine lung-derived ILC2s enhanced the expression of the IL-1RL1 receptor and enhanced phosphorylation of STAT5 upon IL-33 stimulation (Toki et al., 2020), indicating crosstalk between these epithelial alarmins.

Like Treg cells, activation of ILC2 by IL-33 also induce AREG release, contributing to epithelial repair (Liew, Girard, & Turnquist, 2016). Several studies have shown that IL-33 potently activates the expression of cell surface molecules and IL-6 production on DCs (Matta et al., 2014; Rank et al., 2009; Heth R. Turnquist et al., 2010). IL-33 has also been observed to enhance type 1 responses that are controlled by Tumour Necrosis Factor alpha (TNF-α) and interferon-γ (IFN-γ). After IL-33 exposure to IL-1RL1-expressing cells, production of IFN-γ is enhanced. Activation of Th1, Natural killer cells (NK) and $CD8^+$ T cells by IL-33 can thereby contribute to elimination of intracellular pathogens (Baumann et al., 2015; Bonilla et al., 2012; Komai-Koma et al., 2016; Smithgall et al., 2008). While activation of Th2 cells contributes to clearance of large extracellular parasites, IL-33 induced ILC2s and Treg cells

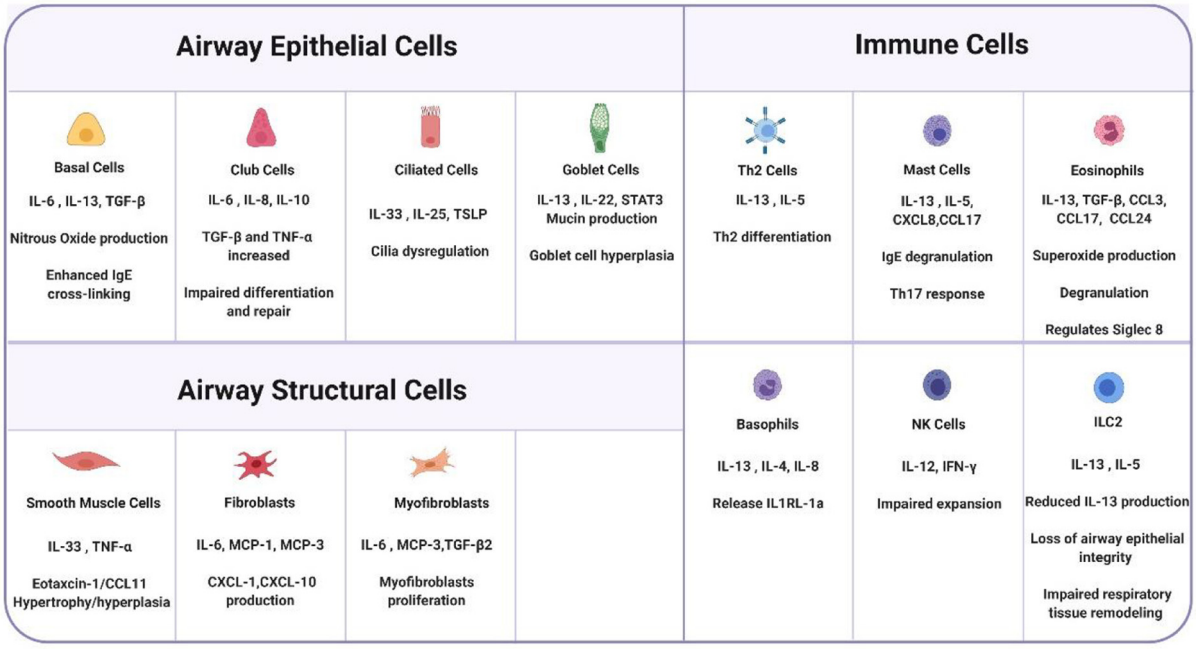

Fig. 3. Effects of IL-33/IL-1RL1 pathway in immune cells and structural cells. As a result of mechanical and environmental stress, IL-33 signals through different epithelial cells, structural cells and immune cells, enhancing their function during inflammation. The tabular figure summarizes the cytokine release and other changes that contribute to inflammation and airway remodelling by immune and structural cells. Created with BioRender.com

in mouse models are subsequently involved in tissue regeneration and wound healing at the site of pathogen infiltration (Arpaia et al., 2015). In this way, IL-33 might regulate different stages of the immune response to a range of pathogens.

2.4.2. Th2 cells

The expression of IL-1RL1, then known as ST2 was initially described *in vitro* and *ex vivo* on murine Th2 cells (Löhning et al., 1998; Xu et al., 1998). The basal expression of IL-1RL1 is independent of IL-4, IL-5, and IL-10, hence, loss of any of these cytokines does not affect IL-1RL1 expression on Th2 cells (Löhning et al., 1998). However, IL-1RL1 expression is GATA3 dependent in human Th2 cells (Guo et al., 2009; Nawijn et al., 2001) and can further enhanced by IL-6, IL-1 and IL-5 (Meisel et al., 2001; Molofsky et al., 2015; Hēth R. Turnquist et al., 2011) (Fig. 2). In activated specific Th2 cells, IL-33 exposure induces IL-5 and IL-13 secretion leading to mucosal inflammation (Komai-Koma et al., 2007; Löhning et al., 1998).

2.4.3. $CD8^+$ T cells

Loss of IL-33 or IL-1RL1 causes impaired $CD8^+$ T cell response against viral infections (Baumann et al., 2019). In this study, IL-33 was found to synergize with IL-12 and T cell receptor (TCR) to enhance IFN-γ production by $CD8^+$ T cells (Yang et al., 2011). Moreover, eradication of viral infection caused by lymphocytic choriomeningitis and other viruses by memory $CD8^+$ T cells is mediated through IL-33 signalling in murine models. IL-33 was found to play a critical role in expansion of murine memory $CD8^+$ T cells in addition to memory recall during secondary infection and effector cell differentiation (Baumann et al., 2019; Bonilla et al., 2012).

2.4.4. B cells

Little data are available regarding a role for IL-33 signalling in the regulation of B cell function. Murine B-1 B cells express the IL-1RL1 receptor unlike B-2 B cells, and IL-33 stimulation of B-1 B cells induces enhanced production of IgM in the presence of bacteria and viruses (Komai-Koma et al., 2011). In addition, it has been shown that IL-10 deficient and wild-type IL-33 treated mice have increased numbers of circulating IL-10-producing B cells regulatory B cells (Bregs), which exhibit a protective role against inflammation through suppressing the expansion of inflammatory innate immune cells, such as neutrophils and reduction of serum IFN-γ levels (Sattler et al., 2014).

2.4.5. Basophils

Basophils are recruited from the blood to peripheral organs, play a pivotal role in protection against helminths, toxic venoms and contribute to allergic inflammation. Recent *in-vitro* studies revealed that basophils express relatively low levels of *IL-1RL1* mRNA due to their high expression levels of GATA1, which serves as a negative regulator of IL-1RL1 (Baba et al., 2012a). However, when stimulated with IL-33, human-derived basophils strongly induce expression of both IL-1RL1-a and IL-1RL1-b at the mRNA and protein levels along with expression of Th2-type cytokines (Smithgall et al., 2008; Suzukawa et al., 2008). IL-33 has been shown to increase integrin glycoprotein (β1 and β2) expression and basophil adhesion. Basophils express both β1 and β2 integrins on their surface (Bochner et al., 1990), where β2 serves as an adhesion molecule for basophil trans-endothelial migration (Iikura et al., 2004) and trans-basement membrane migration (Suzukawa et al., 2006). Basophil adhesion enhancement by IL-33 may be due to augmented expression of β2 integrin, which in-turn leads to increased accumulation of basophils at inflammatory sites. In addition, IL-33 enhances IgE-dependent degranulation, cytokine synthesis and basophil migration towards eotaxin (Suzukawa, Iikura, et al., 2008). Thus, IL-33 acts as a vital regulator of effector functions of human basophils in the pathogenesis of Th2-driven inflammation (Suzukawa et al., 2006; Suzukawa, Iikura, et al., 2008).

2.4.6. Eosinophils

Eosinophilic asthma is one of the dominant phenotype of asthma, characterised by chronic eosinophilic inflammation of the airways (Jacobsen et al., 2008). In severe asthma, high numbers of eosinophils can still be observed despite treatment with corticosteroids, this is further classified as severe refractory eosinophilic asthma (Giuseppe &

Andrea, 2020). There are several lines of evidence indicating a role for IL-1RL1/IL-33 signalling in eosinophil biology. For instance, IL-1RL1-deficient mice infected with parasites have a 10-fold reduction in eosinophil numbers in blood compared to control and lack tissue eosinophils, causing a severe impairment in their ability to generate Th2 inflammatory response and clear the parasitic infection (Fulkerson et al., 2006). Alternatively, large numbers of eosinophils infiltrating the airways were observed in naïve healthy mice challenged with intra-nasal delivery of exogenous IL-33 (Kondo et al., 2008; Sjöberg et al., 2017). In humans, IL-33 has also been shown to enhance a variety of eosinophil functions, such as eosinophil survival (Cherry, Yoon, Bartemes, Iijima, & Kita, 2008; Suzukawa et al., 2008), CD11b expression and eosinophil adhesion to extracellular matrix proteins (Suzukawa, Koketsu, et al., 2008). In addition, IL-33 induces the degranulation of eosinophils and activation of superoxide production more rapidly and potently than IL-5 (Cherry et al., 2008), controls Siglec 8 responsiveness (Na, Hudson, & Bochner, 2012) and increases cytokine and chemokine expression (IL-13, TGF-β, CC- chemokine Ligands (CCL3) and CCL24) in the human and murine lungs during airway inflammation (Stolarski, Kurowska-Stolarska, Kewin, Xu, & Liew, 2010) (Fig. 2). Most of these results presented above in experimental models were validated in primary human cells and patient studies as well. IL-33 was found to promote eosinophil production of the neutrophil chemokine CXCL8(IL-8), in the presence of IL-3, IL-5 or granulocyte-macrophage colony-stimulating factor (GM-CSF) (Cherry et al., 2008; Pecaric-Petkovic et al., 2009). One observational study reported a rare sequence variant (rs146597587-C) in the *IL-33* gene, which resulted in a strongly reduced production of IL-33 protein and reduced capacity to bind its receptor (Smith et al., 2017). This rare variant was associated with a reduced number of eosinophils in blood and thereby associated with reduced risk of asthma. The role for IL-1RL1 signalling on IL-33 mediated eosinophil activation was further supported by a significantly reduced eosinophil CD11b expression induced by IL-33 upon anti-IL-1RL1 antibody stimulation addition (Suzukawa, Koketsu, et al., 2008). Locally derived IL-33 could thus provide a potent signal to help mobilize, maintain and enhance the function of eosinophils within inflamed mucosal tissue.

2.4.7. Mast cells

Mast cells (MC) are tissue-resident effector cells that contribute both to innate and adaptive immunity. In asthma, allergic and non-allergic inflammatory diseases, the affected tissues can show a strong increase in MC numbers, thereby amplifying the chronic inflammation (Nigrovic et al., 2007; Theoharides et al., 2012). The IL-33/IL-1RL1 pathway has been shown to induce maturation of MCs in tissue (Wang et al., 2014). MCs express the GATA2 transcription factor which is a positive regulator of *IL-1RL1* expression (Baba et al., 2012a; Inage et al., 2014). MCs have high levels of IL-1RL1 protein expression on their cell surface. When stimulated directly with IL-33, MCs produce several pro-inflammatory cytokines and chemokines such as IL-6, IL-8, IL-13, TNF-α, CCL1 and CXCL8 through the exocytotic pathway (Allakhverdi, Smith, Comeau, & Delespesse, 2007; Ho et al., 2007; Makrinioti, Toussaint, Jackson, Walton, & Johnston, 2014; Schnyder et al., 2005). In addition, IL-33 markedly reduces the threshold for MCs for degranulation induced by IgE crosslinking (Taracanova et al., 2018). In asthma, MCs have also shown to contribute to the development of airway pathophysiology through MC-airway smooth muscle (ASM) interactions (Brightling et al., 2002). MC location in ASM is a notable feature of asthma wherein ASM-derived IL-33 may play an important role on MC activation which is independent of FCεR1 cross-linking (Kaur et al., 2015). Also, IL-33 promoted ASM mediated wound repair and indirectly contributed to ASM contraction and AHR via upregulation of MC-derived IL-13 *in vivo*.

2.4.8. NK and iNKT cells

IL-1RL1 is constitutively present on Natural Killer (NK) cells and IL-33/IL-1RL1 signalling enhances IL-12 induced IFN-γ production by murine NK cells (Bourgeois et al., 2009; Smithgall et al., 2008). In addition, IL-33 was found to increase rhinovirus-induced IFN-γ production by NK cells which was shown to suppress ILC2 proliferation in wild-type mice (Bi et al., 2017). IL-33/IL-1RL1 signalling in iNKT cells causes their expansion and activation in murine models, where IL-33 administration through intraperitoneal injections doubled the number of iNKT cells present in liver and spleen compared to control, thereby leading to increased Th2 cytokine production involved in pulmonary and mucosal inflammation (Bourgeois et al., 2009).

2.5. IL-33 effects on structural cells

2.5.1. Epithelial and endothelial cells

The basal cells in the bronchial epithelium and arterial endothelial cells have been shown to be the main cells expressing IL-33 (Préfontaine et al., 2010). Both epithelial and endothelial cells can respond to IL-33 as well, although IL-1RL1 receptor expression is relatively low and does not overlap with IL-33 expression (Fujita et al., 2012; Yagami et al., 2010). In experimental studies conducted *in-vitro*, IL-33 was shown to act on pulmonary microvascular endothelial cells and airway epithelial cells by inducing CXCL8 expression in an IL-1RL1-dependent fashion (Yagami et al., 2010). In other studies, enhanced IL-1RL1 expression and function were observed in both endothelial and epithelial cells primarily contributed by Th2 cytokines IL-4 and IL-5 (Fahy & Locksley, 2011; Yagami et al., 2010). Overexpression of IL-33 in human bronchial epithelial cells lead to a paracrine effect of cell homeostasis, including reduced cell viability and reactive oxygen species scavenging activity of bronchial cells (Ketelaar et al., 2020). These studies therefore suggest the critical balance of IL-RL1 and IL-33 expression in epithelial and endothelial cells during homeostasis and disease state.

2.5.2. Smooth muscle cells

Airway smooth muscle cells (ASMCs) in lung tissue of asthma patients express increased IL-33 expression compared to healthy subjects (Préfontaine et al., 2009). Multiple studies have shown that pro-inflammatory cytokines TNF-α and IFN-γ increase IL-33 expression in cultured ASMC (Saunders et al., 1997) along with various chemokines such as CCL5, CCL11/eotaxin, CXCL8 and chemotactic proteins involved in leukocyte recruitment (Ghaffar et al., 1999; John et al., 1998) (Fig. 2). However, release of IL-33 from the ASMC was not observed, implying that IL-33 in ASMC has a cell-autonomous role as a nuclear factor present at the heterochromatin (Carriere et al., 2007a; Gadina & Jefferies, 2007; Roussel et al., 2008). In contrast to the cell-autonomous effects proposed previously, another study observed exogenous, ASM-derived IL-33 in wound repair, along with augmented MC mediator release and increased ASM contraction via upregulation of MC-derived IL-13 in murine and *in vitro* cell culture models (Kaur et al., 2015). In human studies, the number of MCs were found to be higher in the smooth muscle bundles of allergic asthmatics compared to non-allergic asthmatics (Amin, Janson, Boman, & Venge, 2005; Brightling et al., 2002). IL-33 gene and protein expression levels were further shown to be increased in ASMC bundles of endobronchial tissue sections from asthmatic patients when compared to healthy controls, suggesting their pivotal role as airway structural cells in lung inflammatory responses and asthma pathogenesis (Préfontaine et al., 2009).

2.5.3. Fibroblasts and myofibroblasts

Human lung fibroblasts contribute to increased reticular basement membrane (RBM) thickening by altering and adopting a myofibroblast phenotype in asthma (Saglani et al., 2013). These myofibroblasts were shown to have increased type III and type IV collagen deposition that contributed to RBM thickening in bronchial airway wall in asthma. Interestingly, it was reported that IL-33 induces increased collagen release from airway fibroblasts cultured from asthmatic patients, which can be associated with increased IL-33 expression in submucosal cells and

corresponding increase in RBM thickening of the biopsy specimens observed from asthmatic patients (Saglani et al., 2013). Moreover, IL-33 induced the production of fibronectin 1 and type I collagen in asthma-derived human lung fibroblasts *in vitro*, further contributing to RBM thickening and airway remodelling compared to healthy controls (Guo et al., 2014).

Taken together, IL-33 and the IL-33/IL-1RL1 signalling pathway may play an active role in airway inflammation and remodelling in asthma by acting on several immune and structural cells as presented above (Fig. 2).

3. Genetics of the IL-33/IL-1RL1 pathway

Recent advances in genetic studies such as genome-wide association studies (GWAS) and whole genome sequencing (WGS) have identified a large number of genes associated with asthma and its phenotypes, including *IL-1RL1* and *IL-33* (Akhabir & Sandford, 2011; Moffatt et al., 2010). Currently, 128 asthma SNPs have been identified. SNPs in *IL-33* and *IL-1RL1* are amongst the most strongly associated genetic variants for asthma (El-Husseini et al., 2020). Here, we will review the genetic association of these two genes with asthma and its phenotypes in detail.

3.1. Genetics of IL-33

Polymorphisms in the *IL-33* gene have also been associated with asthma. Several GWA studies have identified multiple SNPs in *IL-33* to be associated with asthma (Demenais et al., 2018; El-Husseini et al., 2020; Grotenboer, Ketelaar, Koppelman, & Nawijn, 2013; Shrine et al., 2019). The discovery of a rare IL-33 loss-of-function variant (s146597587-C) showed that IL-33 haplo-insufficiency led to a 40% reduction of *IL-33* mRNA expression and a reduction in eosinophil counts and to protect from asthma (Smith et al., 2017), further supporting the role for IL-33 in the disease. Some studies have also indicated a role of *IL-33* in the 'atopic march'. The atopic march is a concept which describes the temporal relationship between atopic diseases (Han, Roan, & Ziegler, 2017). It is characterized by the progression of atopic dermatitis (AD) to asthma and allergic rhinitis during the first years of life (Spergel, 2010). Studies have shown positive correlations between AD severity and the risk of asthma (Dhar & Srinivas, 2016; Zheng, Yu, Oh, & Zhu, 2011). The pathologic concept is that epicutaneous allergen sensitization through an impaired skin barrier stimulates antigen presenting cells and induces Th2 responses, thereby leading to subsequent atopic manifestations such as asthma or allergic rhinitis (Czarnowicki, Krueger, & Guttman-Yassky, 2017). The compromised epithelial barrier leads to antigen penetration and activation of Toll-like receptors, thereby leading to the release of the epithelium-derived alarmins IL-33, TSLP, and IL-25 to promote Th2 skewing (Egawa & Kabashima, 2016; Salimi et al., 2013). Genetic studies have provided evidence of the importance of epithelial barrier defects in the pathophysiology of atopic dermatitis and other atopic diseases. SNPs in the distal promoter of the IL-1RL1 gene locus (*IL-1RL1*) are significantly linked to AD prevalence, suggesting the IL-33-IL-1RL1 pathway might be a risk factor for AD, in addition to asthma (Ferreira et al., 2017; Marenholz et al., 2015). Recent evidence from longitudinal cohort studies, however, suggests that the atopic march merely reflects one of many possible patterns of allergic comorbidity that can occur in the first years of life (Belgrave et al., 2014). Given the association with multiple atopic disorders, the IL-33/IL1RL1 pathway likely plays a central role in susceptibility for this allergic comorbidity.

While an analysis of the genetic signals present in the *IL-33* locus based on the LD structure identified five LD blocks ($R2>0.8$) associated with asthma phenotypes (Grotenboer et al., 2013; Ketelaar et al., 2020), conditional analysis of these genetic signals showed that the gene has two main independent genetic signals ($R2<0.3$), one tagged by SNP rs992969, which is associated with asthma, as well as blood eosinophils both in asthma and in the general population, independent of the presence of asthma/ allergy phenotypes. Furthermore, a second independent signal, tagged by SNP rs4008366, was identified that was associated with eosinophilic asthma (Ketelaar et al., 2020). These two independent genetic signals in the *IL-33* locus were both found to be eQTLs in bronchial epithelial cells. In addition to the association with eosinophils and asthma, SNPs in *IL-33* are also associated with intermediate-onset wheezing phenotypes in early childhood (Savenije et al., 2014a), which is strongly associated with atopy. The Southampton Women's study cohort also confirmed the strong correlation of intermediate-onset wheeze with atopy in 926 children post sensitization, thereby suggesting that polymorphisms in *IL-33* or *IL-1RL1* could influence the development of wheeze, leading to intermediate- or late-onset wheeze and subsequent asthma after sensitization in early childhood (Granell, Henderson, Timpson, & Sterne, 2012; Spycher et al., 2012). Interestingly, children carrying risk alleles in both *IL-1RL1* and *IL-33* showed an increased risk for asthma compared to children carrying the risk allele in only one of the two genes (O. E. Savenije et al., 2014a). These results strongly indicate that genetic variation in the IL-33/IL-1RL1 pathway is a critical determinant of childhood asthma susceptibility.

3.2. Genetics of IL-1RL1

In 2008, Reijmerink *et al.* were the first to identify *IL-1RL1* as a susceptibility gene for asthma and atopy (Reijmerink et al., 2008). This study reported association of SNPs in the *IL-1RL1* gene and the juxtaposed *IL18R1* and *IL18RAP* genes with asthma. This observation was replicated in several other candidate-gene and GWAS studies recently summarized by El-Husseini *et al.* (El-Husseini et al., 2020). Interestingly, the *IL-1RL1* locus has been found to harbour multiple genetic signals, that independently contribute to asthma and allergy susceptibility (Ferreira, Vonk, et al., 2017; Grotenboer et al., 2013). Thus far, at least 130 different *IL-1RL1* SNPs have been identified to be associated with asthma (M. A. Portelli et al., 2020). An initial analysis of the LD structure of the *IL-1RL1* locus and its surrounding genomic region revealed at least 5 discrete LD blocks and 1 independent SNP that were associated with asthma (Grotenboer et al., 2013). Interestingly, some of these *IL-1RL1* SNPs are in LD with SNPs in the two other genes juxtaposed with *IL-1RL1* on chromosome 2q, encoding IL-18 receptor 1 (*IL18R1*) and IL-18 receptor accessory protein (*IL18RaP*) (Reijmerink et al., 2008; Reijmerink, Postma, & Koppelman, 2010), making it difficult to pinpoint the causal gene or genes in this chromosomal region.

Asthma-associated SNPs in the *IL-1RL1* gene may cause functional alterations through two different mechanisms. First non-synonymous, coding SNPs causing amino acid substitutions will lead to altered protein function, whereas SNPs located in- or outside of the gene body can act as expression or protein quantitative trait loci (eQTL or pQTL) resulting in changes in the level of IL-1RL1 mRNA and/or protein expression (Akhabir et al., 2014; Dijk et al., 2018; Ho et al., 2013; Li et al., 2016; Ramirez-Carrozzi, Dressen, Lupardus, Yaspan, & Pappu, 2015; Traister et al., 2015). Four out of the six non-synonymous coding SNPs at exon 11 in *IL-1RL1* have been found to be associated with asthma. Remarkably, these 5 non-synonymous coding SNPs are in full LD with each other (rs6749114, rs4988956, rs10204137, rs10192157, rs10206753). These SNPs encode 3 amino-acid substitutions near the TIR domain of IL-1RL1-b, which has been predicted to influence protein-protein interaction with IL1RAcP and the adaptor proteins (MyD88, Mal). Careful analysis of IL-33-induced signalling has shown that the two protein isoforms have a strikingly different sensitivity for IL-33-induced activation, leading to an increased IL-33 sensitivity in the IL-1RL1 isoform encoded by the asthma-associated haplotype (J. E. Ho et al., 2013; M. A. Portelli et al., 2020). Another study suggested SNPs rs1420101 and rs11685480 are eQTLs in airway epithelial cells and distal lung parenchyma, respectively (Gordon et al., 2016; M. A. Portelli et al., 2020). Moreover, these SNPs were found to act as pQTLs in a Dutch birth cohort and a cohort of asthma patients, in which the

asthma risk alleles were associated with lower soluble IL-1RL1-a levels in serum (Dijk et al., 2018; Savenije et al., 2011).

In a recent study, the association of the different independent signals in the *IL-1RL1* locus with sub-phenotypes of asthma was studied in detail (M. A. Portelli et al., 2020). This study identified 4 genetic signals in the IL-1RL1 locus that were considered to be independent from each other based on an LD<0.1 in the 1000 Genomes dataset. Three of these LD blocks, tagged by the SNPs rs4142132, rs72825929, and rs10192157, were shown to be IL-1RL1 specific eQTLs and pQTLs in lung tissue (Grotenboer et al., 2013; Portelli et al., 2020). In addition, the LD block encoding the 4 amino acid changes in the IL-1RL1 TIR domains was confirmed to affect NF-κB activation in response to IL-33 (M. A. Portelli et al., 2020). This study also found that these independent genetic signals in IL-1RL1 may be associated with divergent asthma phenotypes. For instance, rs12474258-A allele is mainly associated with eosinophilic asthma, whereas rs72825929 is associated with severe asthma (Portelli et al., 2020). Some asthma risk alleles have opposing increasing and decreasing effects on IL-1RL1 expression, which highlights the complexity of this locus. Together, the asthma-associated genetic signals in the IL-1RL1 locus, significantly affect IL-1RL1 mRNA and protein levels and increase affecting NF-κB activation, in an isoform-specific way, thereby complicating the study of its contribution to the mechanism of disease. In addition, SNPs in the *IL-1RL1*, *IL18R1*, *IL18RAP* locus have also been associated with other inflammatory diseases, such as Crohn's disease (rs917997) (Zhernakova et al., 2008), celiac disease (rs917997 and rs13015714) (Hunt et al., 2008) and atopic dermatitis (rs6543116) (Shimizu et al., 2005), further supporting the need for a careful dissection of the functional genetics of this pathway in order to develop relevant biomarkers and guide rational interventions.

3.3. Epigenetic signals regulating the IL-33/IL-1RL1 pathway

Epigenetic changes are stable, heritable modifications of the DNA that regulate gene transcription without altering the primary DNA sequence. The three main mechanisms through which epigenetics affect gene expression are DNA modifications, histone modifications, and non-coding RNA (Knight & Hirota, 2014; Moheimani et al., 2016). Several DNA methylation signatures have been reported to be present in asthma airway epithelium, leading to hyper-or-hypo-methylated genes such as *STAT5A* and *ADAM33* (Baccarelli et al., 2012; Breton et al., 2011; Stefanowicz et al., 2012; Yang et al., 2008). Similarly, adult airway epithelium of asthmatic patients has been shown to have elevated histone H3 lysine 18 (H3K18) acetylation and trimethylation near STAT6-I and STAT6-II loci which leads to increased protein expression of STAT6 (Stefanowicz et al., 2012). The contribution of epigenetic regulation of IL-33 and IL-1RL1 to asthma has not been studied in great detail. One study showed that methylation levels at four *IL-1RL1* CpG sites in whole blood were associated with *IL-1RL1* SNPs in five different LD blocks, which indirectly also correlates with peripheral blood eosinophil counts in asthma or serum IL-1RL1-a levels (Gudbjartsson et al., 2009). Moreover, methylation levels of two CpG sites, cg26748568 and cg08889789, were found to be associated with IL-1RL1-a serum levels (Dijk et al., 2018). In another study, DNA-methylation levels at the *IL-33* locus in bronchial epithelial cells was reported to be reduced in asthmatic compared to healthy controls, although no effect on gene expression levels was observed (Larouche et al., 2018).Thus, more work needs to be done to fully understand the interaction of genetic and epigenetic markers in asthma development.

4. Towards precision medicine

Asthma is a complex, heterogeneous disease characterised by airflow obstruction, chronic inflammation and increased bronchial hyper-responsiveness. There is marked heterogeneity in age of onset and symptoms such as coughing or wheezing, dyspnoea and tightening of the chest; impairment in lung function and presence of exacerbations (Hansbro, Kaiko, & Foster, 2011; Hansbro et al., 2013; Kim et al., 2016). Scientists have attempted to relate the phenotypic heterogeneity of asthma to differences in causative mechanisms, proposing that asthma is a syndrome composed of multiple diseases with shared symptoms, rather than one disease with one shared pathogenic mechanism. The aforementioned endotypes of asthma can be used to summarize the heterogeneity of the disease into discrete entities that share a pathogenic mechanism and consequently should respond to the same intervention strategy. The main endotypes that have been proposed include four groups (1) early-onset allergic asthma, (2) early-onset allergic moderate-to-severe asthma, (3) late-onset nonallergic eosinophilic asthma, and (4) late-onset nonallergic non-eosinophilic asthma (R. Kaur & Chupp, 2019) (Fig. 3). So far, current evidence on the phenotypic associations of the *IL-33/IL-1RL1-33* loci with asthma subphenotypes strongly suggest that this pathway is involved in childhood onset asthma, associated with early life symptoms and onset of sensitization, atopic comorbidity and blood eosinophilia, which may relate to group 1 and potentially group 2 of the asthma endotypes (Grotenboer et al., 2013; Ketelaar et al., 2020; Portelli et al., 2020; Smith et al., 2017) (Fig. 4).

This section of the review presents an overview on the existing therapies for asthma along with their limitations, and will discuss strategies to enhance targeted therapy for the disease (Barnes, 2013). This targeted therapy has been termed personalized medicine or precision medicine, which can be defined as a form of medicine, where one utilizes the information of a person's genetic, biomarker, environment and lifestyle factors to select the most appropriate disease treatment and prevention (Kaur & Chupp, 2019). Our main question is how information on genetics or function of the IL-33/IL-1RL1 pathway can be used to help precision medicine address this pathway.

Current asthma therapies primarily focus on reducing symptoms in order to prevent exacerbations and necessitating emergency visits to the hospitals by bronchodilation and non-specifically suppressing airway inflammation, rather than targeting the pathogenesis of the disease. In most patients, combined therapy with inhaled corticosteroids and SABAs as needed are given, where symptomatic relief is provided through administration of SABAs. Moreover, corticosteroids help in reducing inflammation through the suppression of pro-inflammatory gene transcription (Wang, Jing Li, Foster, Hansbro, & Yang, 2010). Some patients are also prescribed with long-acting β-agonists (LABAs) along with corticosteroids to control asthma and prevent exacerbations (Barnes & Adcock, 2003; Hirst, Calingaert, Stanford, & Castellsague, 2010). Since steroid therapy merely alleviates the symptoms of disease but fails to offer a cure, a plethora of novel therapies have been tested for allergic asthma with the aim to provide targeted therapy as well as long term benefits (Kim et al., 2016). However, no curative treatment has been developed to date. Therefore, novel strategies need to be considered, that include (1) identification of biomarkers for asthma endotypes; (2) selection of patients for targeted therapy, and (3) the potential use of pharmacogenetics for stratification of patient selection (Hansbro et al., 2011, 2013) (Fig. 5). Pharmacogenetic GWAS have not identified the *IL-33* or *IL1LR1* loci as important modifiers of steroid response or beta-agonists response (Kersten & Koppelman, 2017). However, a recent candidate-gene study showed that *IL-1RL1*- gene variations were associated with increased asthma exacerbations in children using ICS in the worldwide pharmacogenetic PICA consortium (Dijk et al., 2020). This may suggest that that *IL-1RL1* SNPs may modify the asthma phenotype into a more severe phenotype, with more severe exacerbations, which are insufficiently treated with the ICS dosages prescribed to the children in this study. Alternatively, SNPs in *IL-1RL1* may have a direct pharmacogenetic interaction with steroids resulting in reduced efficacy of the steroids, as suggested previously in patients with ulcerative colitis (Díaz-Jiménez et al., 2017). As mentioned before, there are limitations in detecting human IL-33 in serum samples of patients. Post-translational modifications through cathepsins or elastase could interfere with detection of IL-33 in antibody kits. Alternatively,

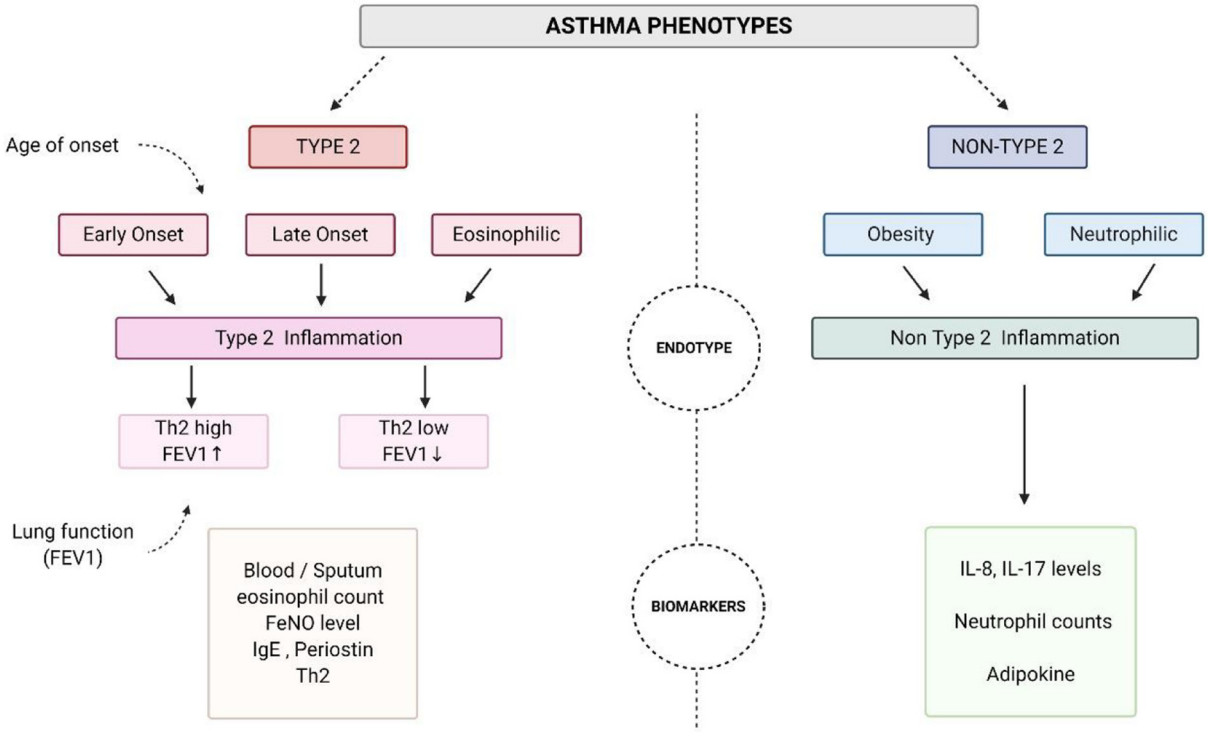

Fig. 4. Asthma phenotypes, endotypes and biomarkers. Asthma phenotypes can be predominantly categorized into Type-2 and Non-Type2 phenotypes. Based on the age of onset, they are further classified as early onset (EOA) and late onset (LOA), eosinophilic under Type-2 leading to Type 2 inflammation. Based on physiological conditions, Non-Type-2 comprises of obesity-related and neutrophilic asthma which leads to Non-Type 2 inflammation. Based on lung function (FEV1) and allergic tests, several biomarkers are used to further categorize asthma phenotypes. Created with BioRender.com

interfering factors such as levels of IL-1RL1-a that binds IL-33 or rapid oxidation of cell-free IL-33 could interfere with antibody detection. Several studies in allergic and non-allergic disorders have reported difficulties in detecting IL-33 in serum using ELISA and immunoassays (Asaka et al., 2012; Ketelaar et al., 2016; Rivière et al., 2016). Alternatively, some possible novel methods for measuring human IL-33 could be digital or multiplex immunoassays (Voloshyna et al., 2015).

4.1. Role of biomarkers in asthma management

An ideal biomarker for asthma should possess the sensitivity and specificity to accurately identify subtypes of the disease in addition to predicting the response to therapy and other prognostic information of the disease. Biomarkers that accurately identify the different phenotypes and predict the therapeutic responses to inhaled corticosteroids or alternative therapies are urgently needed. Moreover, such biomarkers can offer prognostic information such as expected of lung function decline or time to the next exacerbation (Mohan, Grace, Mainardi, Chupp, & Lugogo, 2020). Currently available biomarkers such as blood and sputum eosinophil counts or lung function parameters offer limited help in phenotyping and identifying patients that may respond to specific therapies (Fricker, Heaney, & Upham, 2017).

Sputum eosinophil counts are considered as a non-invasive gold standard method for assessing airway inflammation in asthma. In bronchoalveolar (BAL) fluid or induced sputum, a relative proportion of eosinophils in BAL or sputum above >3% is often used as threshold for the presence of airway eosinophilia. Multiple studies have shown increased sputum eosinophil counts to be associated with exacerbation in asthma, thereby indicating sputum eosinophils as a reliable biomarker for eosinophilic inflammation and severe asthma (Berry & Busse, 2016; Kim et al., 2017; Schleich, Demarche, & Louis, 2016; Tiotiu, 2018). Treatments that target mechanisms of eosinophilic inflammation (such as anti-IL5) have benefited from selecting subgroups of asthma patients with eosinophilic disease for treatment. Intravenous treatment with mepolizumab (anti-IL-5 monoclonal antibody therapy) significantly reduced blood and sputum eosinophil counts in patients having more than 3% sputum eosinophil counts and resulted in a decreased frequency of exacerbations, thereby improving their overall quality of life (Haldar et al., 2009). Likewise, dupilumab, a monoclonal antibody targeting IL-4R, improved overall lung function in asthmatic patients with sputum eosinophilia (≥3%) or increased blood eosinophil count (≥300 cells/μL) (Sally Wenzel et al., 2013). Similarly, any biological designed to interfere in the IL-33/IL-1RL1 pathway will need to be targeted to the patient group most likely to show an optimal clinical response to this novel intervention.

Another biomarker that has been studied is Exhaled Nitric Oxide (FeNO) that serves both as a diagnostic and predictive marker for atopic and eosinophilic airway inflammation with type-2 phenotype (Ricciardolo, Sorbello, & Ciprandi, 2015; Wagener et al., 2015; Westerhof et al., 2015). In contrast, non-type2 type asthma, which is more challenging to diagnose, has few potential biomarkers that can aid in diagnosis and prediction of treatment response (Robinson et al., 2017). IL-17, a cytokine associated with the neutrophilic inflammation characteristic on non-T2 asthma, has been associated with severe asthma in a variety of studies (Grayson et al., 2018; Silverpil & Lindén, 2012). However, the phase II trial of the IL-17 inhibitor, secukinumab was terminated early due to insignificant difference in the sputum neutrophil levels from baseline healthy volunteers and lack of a response in the Asthma Control Questionnaire scores (Kirsten et al., 2013; Novartis, 2015).

Which biomarker or biomarkers may be beneficial if interventions targeted at the IL-33-IL-1RL1 pathway will become available? First, given the consistent association of this pathway with eosinophilia and childhood onset asthma, it may be expected that blood or sputum eosinophils and asthma onset may predict potential treatment response and periostin due its role in the Th2 inflammatory response. A second possible biomarker may be the IL-1RL1-a or sST2 protein. Since many asthma risk variants relate to lower IL-1RL1-a levels, these lower levels may be hypothesized to predict treatment response (El-Husseini et al., 2020).

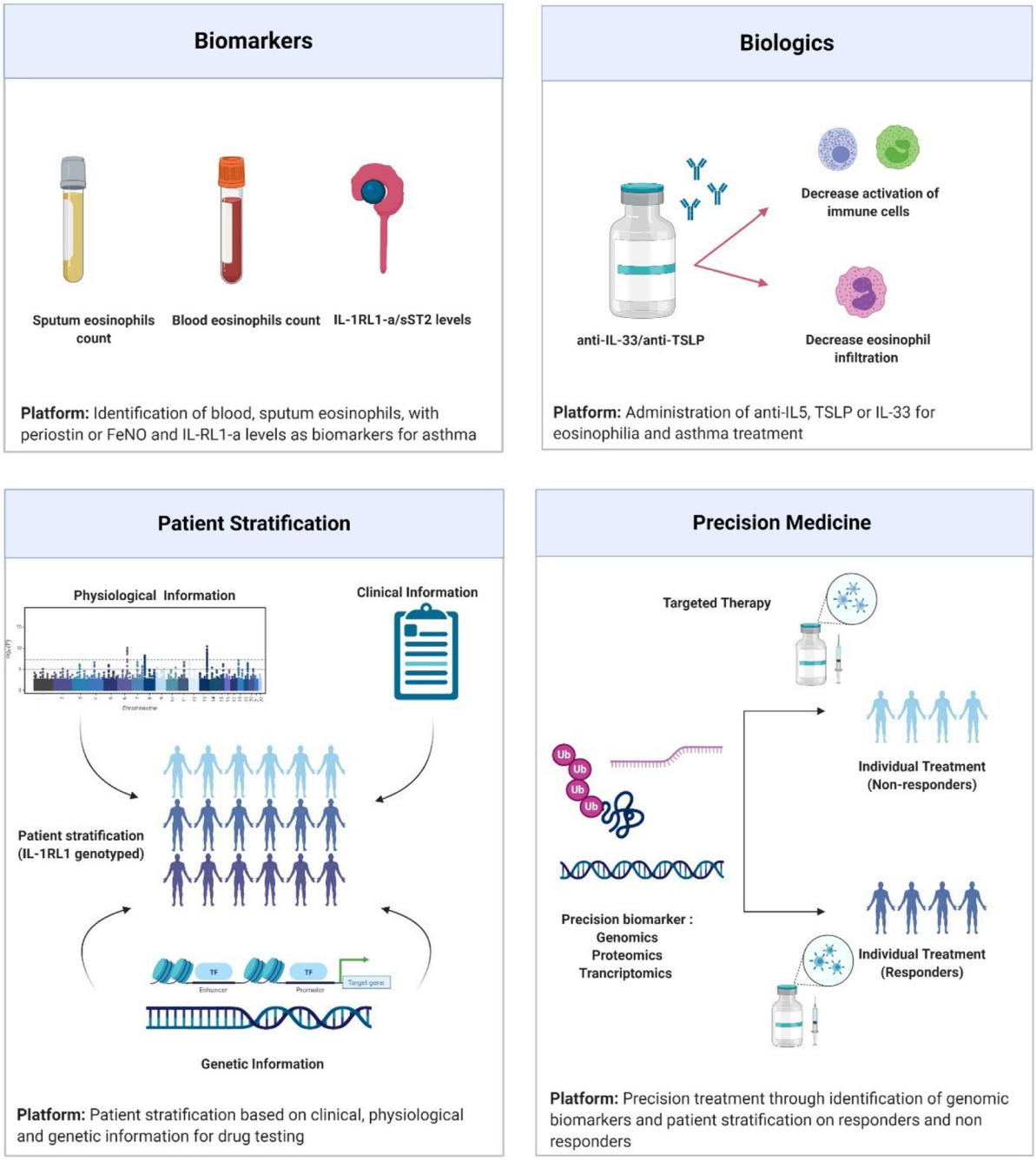

Fig. 5. Different diagnostic and therapeutic strategies for asthma using IL-1RL/IL-33 pathway. Sputum eosinophil and blood eosinophil counts were gold-standard non-invasive measurement used for assessing airway inflammation. However, periostin and FeNO served both as a diagnostic and predictive marker for atopic and eosinophilic airway inflammation. Recently, IL-1RL1-a has been predicated as a possible biomarker for treatment response. In biologics, anti-IL-5 therapy was used to alleviate eosinophilia, however anti-IL33 and anti-TSLP has proven to reduce eosinophil infiltration and currently in phase IIa study. Patient stratification and precision medication is currently used to segregate responders and non-responders in novel drug therapies. Created with BioRender.com

Finally, the risk SNPs themselves may be used to select subjects at risk, as previous research has indicated that subjects carrying risk variants in both the *IL-33* and the *IL-1RL1* gene are at increased asthma risk (Savenije et al., 2014a). These hypotheses clearly need verification by large, stratified clinical trials.

4.2. IL-1RL1 and IL-33 as therapeutic targets in asthma treatment

Antibody-based drugs are also being developed for other alarmins such as TSLP. Such drugs could also be relevant competitors for anti-IL-33 treatment as IL-33 and TSLP have a synergistic effect on type 2 cytokine production, eosinophil levels and proliferation of human ILC2s (Liu et al., 2018; Nakajima, Kabata, Kabashima, & Asano, 2020; Roan, Obata-Ninomiya, & Ziegler, 2019). Tezepelumab (AMG 157/MEDI9929) is an investigational monoclonal antibody that binds to TSLP, thereby preventing its interaction with its receptor. A proof-of-concept study showed that tezepelumab inhibited both early and late asthmatic responses in addition to suppressing type 2 inflammation (IL-4,IL-5 and IL-13) in mild, atopic asthmatic patients (Corren et al., 2017; Gauvreau et al., 2014). In addition, tezepelumab also reduced

blood eosinophil counts, FeNO levels, and total serum IgE levels just over 4 weeks of treatment. These studies have also highlighted the potential importance of targeting an upstream cytokine such as TSLP, that may affect disease activity more broadly than inhibition of a single downstream pathway. Whereas these strong effects need replication in a Phase III study, it suggests that targeting an epithelial cytokine and alarmin may be very beneficial in asthma. Moreover, there is still an unmet need for treating neutrophilic and non-type 2 asthma phenotypes (Corren et al., 2017; Simpson et al., 2019).

In asthma, the use of biologics marked a next step on the way to precision medicine. Several drugs for the IL-33 pathway are in clinical development. GSK3772847 is an IL1RL1 antibody that is in phase II studies (NCT03207243) along with two other anti-IL-33 antibodies REGN3500 (SAR440340) (NCT03387852) and Etokimab (ANB020) (AnaptysBio, 2019; GlaxoSmithKline, 2017). In an unpublished, not peer-reviewed study, REGN3500 met not only its primary endpoint of improvement in loss of asthma control when comparing REGN3500 monotherapy to placebo as well as its secondary endpoint by significantly improving patient's blood eosinophil levels ≥300 cells/microliter in a randomized double-blind trial in 296 moderate-to-severe asthma patients (Sanofi, 2019). However, combination with Dupilumab (another anti-IL-4 Receptor monoclonal antibody), REGN3500 did not demonstrate increased benefit compared to Dupilumab monotherapy in this trial. Hence, REGN3500, could be an alternative for Dupilumab monotherapy for moderate-to-severe asthma (Sanofi, 2019). As note of caution, these results were shared in a press release and have not been published to date.

In a proof of concept phase IIa study of etokimab, severe eosinophilic asthma patients showed a significant improvement of lung function (FEV1) after etokimab-treatment compared to placebo-treated patients at day 2 till day 64 (AnaptysBio, 2019). Improvements in lung function also correlated with reductions in blood eosinophil numbers. In light of the proposed mechanisms of this pathway in asthma, main questions are if treatment targeted at the IL-33-IL-1RL1 pathway in childhood asthma, could it potentially stop the disease from developing in wheezing preschool children; and secondly, if this treatment has any additional benefit above the current type-2 monoclonal antibodies that are available. Again, publication of these insights in peer-reviewed journals is eagerly awaited.

5. Conclusion

Our understanding of the IL-33-IL-1RL1 pathway has extended well beyond its original identification as an inducer of type 2 immune responses. There has been rapid progress in the last decade, with large prospective studies that have elucidated the genetic and functional role of IL1RL1 and IL-33 in health and disease. IL-33 was shown to act as an epithelial and endothelial alarmin in allergic and inflammatory diseases. In addition, extracellular IL-33 acts as a sensor for proteolytic activity from external factors or from local innate immune effector cells, thereby harbouring the capacity to dramatically amplify an ongoing immune response. The genetic association studies have shown the presence of multiple discrete genetic signals in both the *IL33* and *IL1RL1* loci, that all independently contribute to asthma susceptibility. Identification of causal gene variants and unravelling functional relevance of these genetic signals in individual cell types and tissues relevant to asthma is needed to understand the heterogeneity of the disease. Such insights are essential to allow stratification of patients on the basis of the pathobiological process underlying their disease, and therefor for the design of precision therapeutic intervention based on individual genetic risk factors. Given the central role in susceptibility for the disease and the unique biological activities of this pathway, we envisage a clear niche for IL-33/IL1RL1 targeted therapies in the future portfolio of precision medicine for asthma.

Declaration of Competing Interest

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