

Mini review

Pathophysiology of IL-33 and IL-17 in allergic disorders

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ABSTRACT

Allergic diseases are among common clinical conditions, affecting millions of children and adults throughout the world. Food allergies, skin allergies (atopic dermatitis), and respiratory allergies (allergic rhinitis and asthma) are the common types of allergies. Recently discovered cytokines IL-17 and IL-33 have been found to play an important role in the pathogenicity of various hypersensitive disorders. After exposure to allergens or infection with parasites or viruses, IL-17 and IL-33 producing cells, such as Th17 and specialized epithelial cells respectively, become activated and trigger the pathogenic immune responses in different susceptible conditions. Potent inhibitors of these cytokines have been identified recently that may represent potential therapeutic agents to overcome the clinical complications of allergies. In the present review, we have discussed the cellular sources, modes of action and regulation of IL-17 and IL-33 in the context of hypersensitive diseases. We have also assessed the therapeutic potential of inhibitory molecules that may alter production of both these cytokines, and thus modulate susceptible conditions.

1. Introduction

Prevalence of hypersensitive diseases that include Allergic Rhinitis (AR), Allergic Asthma (AA), Atopic Dermatitis (AD) and Food Allergy (FA) have increased drastically throughout the world [1–3]. Hypersensitive diseases are more common in westernised or urbanized societies due to modern lifestyle as compared to the rural population or people of developing countries [4–6]. Typically, allergic diseases are the result of pathogenic allergic immune responses with dominant Th2 mediated immune response. The exposure of allergens/antigens may lead to hyper-reactivity of different resistant cells. Hyper activity includes recruitment of eosinophil, activation of mast cells, dendritic cells (DCs), epidermal keratinocytes, lymphocytes and goblet cells in varied targeted organs. These activated immune cells trigger the provocative cascade generating the local as well as systemic inflammatory protected responses involving multiple organs. Cytokines produced by above said immune cells are involved in the onset of susceptible diseases. Both types of T helper (Th) cells known as Th1 and Th2, play an important role in the onset as well as progression of hypersensitive diseases. These immune cells produce a variety of Th1 and Th2 cytokines that are well known to cause pro-inflammatory as well as inflammatory responses. These cytokines activate the various other immune cells as well as to self-producing cells. Recent focus has been on the identification of newly discovered cytokines that are responsible for modulating the healthy immune system, hence leading to the development of allergic

diseases.

Apart from Th2/Th1 concept, recently two more cytokines namely interleukin -17 (IL-17) and interleukin -33 (IL-33) are emerging key players in mounting as well as progression of various susceptible diseases. A Th-cell lineage entirely distinct from Th1/Th2 called Th17 (IL-17 producing cells) is a key player in inflammation during sensitive conditions. In addition, IL-33 is another newly discovered cytokine that is produced by epithelial cells as well as other cell types. IL-33 has been found to play a critical role in mediating the inflammatory responses. It regulates the immune response by activating various resistant cells like Th2 cells and lately identified group 2 innate lymphoid cells (ILC2s) [7]. Number of studies focused on the investigation of the pathogenic role of both cytokines (IL-17 and IL-33), suggest that these two intracellular molecules significantly contribute to the pathogenicity of classically recognized Th2 mediated allergic diseases by modulating the functionality of other immune cells. Studies on these cytokines provided new insights into the molecular mechanisms involved in immune responses and/or disease development. Many current studies on IL-17 and IL-33 have prompted the authors to discuss the existing knowledge regarding the pathogenic role of these cytokines and mitigation of sensitive manifestation by inhibition of the same. A systematic discussion on their contribution in susceptible diseases is required for better understanding of disease and also related future therapeutic option. In this review, we have summarized the available findings related to IL-17 and IL-33 cytokines and discussed their pathogenic roles in the allergic

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Table 1

IL-33 secreting cells in mice as well as in human.

Cellular Source	Site of cellular source	Reference	Organism
Cytotoxic CD8 + memory T cells	Hepatocellular carcinoma	[149]	Liver (human)
Monocyte	PBMCs as well as Human monocytic leukemia cell line THP-PBMCs and human monocyte carcinoma cell line THP-1	[150]	Human
Macrophages	Peritoneal	[150]	Mouse
Epithelial cells	Airway	[151]	Human
Fibroblasts	Airway	[151]	Human
Smooth muscle cells	Airway	[151]	Human
Endothelial cells	Digestive tract	[14]	Human
Intestinal epithelial cells	Digestive tract	[152]	Human
Colonic sub-epithelial myofibroblasts	Digestive tract	[153]	Human
Alveolar M2 macrophages	Lung	[154,155]	Mice
Dendritic cell	Lung	[154,155]	Mice
Epithelial cells	Lung	[154,156]	Mice
Bone marrow derived mast cells	Bone	[157]	Mice
Stratified squamous epithelia	Vagina and skin	[9]	Mice
Cuboidal epithelium	Lung, salivary gland, stomach	[9]	Mice
Endothelial cells	Blood vessels	[9]	Human
Glial cells	Brain	[158]	Mice
Colonic epithelial cells	Intestine	[159]	Human
Vessels	Skin	[160]	Pig, Mice
Dermal macrophages	Skin	[161]	Mice
Epidermal keratinocytes	Skin	[162,163]	Human, Mice

disorders. This review will also highlight the cellular sources as well as receptors/target cells of both cytokines.

2. Interleukin-33

Interleukin-33 (IL-33) has been considered an alarming molecule as it is secreted from damaged and/or stressed cells to alert the immune system. This cytokine has been suggested to be a critical component of immune system involved in pathophysiology of allergic diseases. The IL-33 belongs to IL-1 superfamily is mainly secreted by numerous structural cells, including macrophages, dendritic cells, fibroblasts, adipocytes, smooth muscle cells, endothelial cells, bronchial, osteoblast and intestinal epithelial cells (Table 1) [7–11]. The IL-33 binds to a specific receptor of toll like receptor (TLR)/IL1R super family i. e. ST2 receptor that forms a heterodimer with the IL-1 receptor accessory protein (IL-1RAcP) to trigger the immune cascade [12]. Heterodimerization of this receptor is an essential step in the ligand binding and action of IL-33 cytokine. The ST2 receptor is found in two forms within a cell, as a membrane bound or trans membrane form (ST2 or ST2L) and a secreted or soluble form (sST2) also termed as the endogenous form [10]. The trans membrane isoform of ST2 is mainly expressed on variety of immune cells that include innate lymphoid group 2 cells (ILC2s), mast cells, basophils, dendritic cells, NK cells and Th2 lymphocytes [10–12].

The IL-33 mediated downstream signalling cascade commences through its binding to ST2 or IL-1RAcP receptors (Fig. 1). The binding of IL-33 with ST2 receptor acts as docking site for the MyD88 adapter protein that may additionally recruit the IL-1R-associated kinase 1 (IRAK1), IRAK4 and TNFR-associated factor 6 (TRAF6) [13,14]. These signalling molecules may in addition lead to the activation of different types of the transcription factors (TFs) such as NF- κ B, various kinases including ERK1/2, p38MAPK and JNK, thereby triggering the production of inflammatory cytokines [8,12]. MyD88 is considered a central molecule for IL-33 induced functional immune responses like maintenance of Th2 cytokine production and MCs (mast cells) proliferation as well as degranulation [15,16]. IL-33 is linked with the development of several allergic diseases such as asthma and atopic dermatitis. IL-33 can also exacerbate Th17 cell-mediated airway inflammation [17]. Therefore, IL-33 acts not only as Th2-inducing cytokine, but may work as the pro-inflammatory cytokine in various immune responses.

2.1. Role of IL-33 in food allergy

Food allergy (FA) is an imbalanced immune response with increased number/activity of allergen specific T helper (Th) 2 immune cells that may lead to allergic manifestations involving different organs of the body such as skin, intestine and lungs. The production of allergen specific IgE is characteristics of FA. Some individuals having a high titer of food allergen specific IgE has no clinical sign and symptoms of FA, suggesting that IgE production alone cannot be the sole cause of provoking food induced anaphylaxis (FIA) [18].

The Th2 cytokines such as IL-4, IL-5 and IL-13 produced by allergen specific Th2 cells are the hallmark in FA. Recent studies carried out in IL-33 deficient mice have shown that IL-33 also has a key role in the activation as well as persistence of Th2 type immune response [19]. Interleukin-33 is a unique cytokine that has an essential role in causing immune response triggered by mast cells (MCs). The IL-33 may contribute in allergic sensitization and anaphylaxis via various routes of exposure as it is expressed on specific cells located on gastrointestinal tract, lung as well as skin. In order to confirm the same, intra gastric peanut allergen exposure could evoke the production of IL-33 cytokine, suggesting that IL-33 signalling may have a significant role in the gut mediated allergen sensitization [20]. Furthermore, it intensifies the IgE cross linking and augments the onset of anaphylaxis via MCs degranulation as well as enhanced production of IL-6 and IL-13 by MCs and eosinophils [21–24]. In addition to gastric route, IL-33 also mediates the allergic sensitization by exposure through the skin. Recently, Muto et al. (2014) reported that IL-33 could promote the cutaneous sensitization of food allergen as well, suggesting that IL-33-ST2 pathway might be a risk factor for the development of food allergy via epicutaneous route. Thus, IL-33 pathway could be a major target for post-sensitized individuals to prevent anaphylaxis. Before discussing association between IL-33 and MCs stimulation, it is worth mentioning that mast cells are the main effector cells and act as a bridge in the inter-conversion of allergic diseases such as FA, AA, AR and AD. Several studies carried out by our group have also demonstrated the central role of MCs between food allergy and allergic asthma. In many studies, patients with asthma, rhinitis as well as dermatitis were found sensitive to food allergens, indicating a positive correlation among these organ specific allergic manifestations [25–27].

Several studies have indicated that MCs derived from human, and mice are a chief source of a soluble receptor isoform (sST2) for IL-33 cytokine (Fig. 2). In a study, MCs stimulated with antigen and/or IL-33

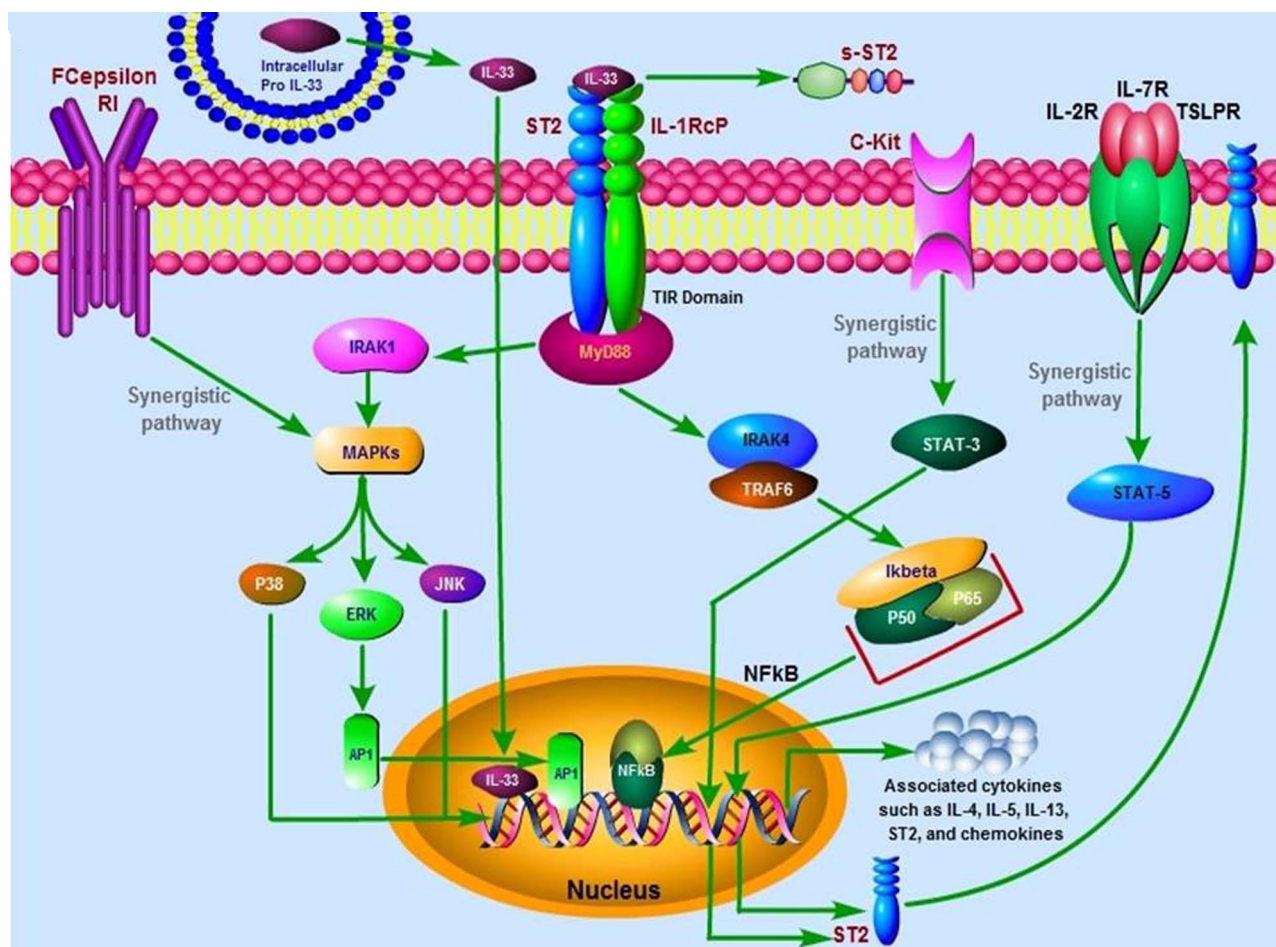


Fig. 1. IL-33 binds to its receptor complex composed of ST2L (the transmembrane isoform of ST2) and the IL-1 receptor accessory protein (IL-1RAcP). After IL-33 stimulation, recruitment of MyD88 at Toll/Interleukin-1 receptor (TIR) domain and downstream activation of TNF receptor-associated factor 6 (TRAF6) via Interleukin-1 receptor-associated kinase (IRAK) proteins. Thereafter TRAF6 activates the inhibitor of nuclear factor- κ B kinase (IKK) complex leading to liberation of NF- κ B from the complex. NF- κ B is then able to bind DNA and can induce the transcription of various genes associated with Th2 cytokines. On the other hand, MyD88 mediated IL-33 signaling may also include MAPKs activation leading to activation of another transcription factor AP-1, but it does not require TRAF6. IL-33 receptor complex can also act in synergistic manner with other receptors that include Fc ϵ RI, C-Kit and IL-2, IL-7 as well as TSLP receptor complex. IL-33 can also directly binds to DNA and regulate the transcription of various genes.

were found synthesizing as well as releasing sST2 receptor. Moreover, an elevated level of circulating sST2 receptor has been found associated with the presence of MCs during anaphylaxis in mice, suggesting that Fc ϵ RI and sST2 receptor may act synergistically when added together or in combination with antigen and IL-33 cytokine [28]. Therefore, MCs have the ability to modulate the biological impact of IL-33 produced by surrounding cell types during sensitizing condition by allergens. Later studies have revealed that IL-33 can also activate many other immune cells, such as granulocytes, macrophages, NK and Th2 cells that can actively participate in the pathophysiology of FA [29]. From these studies, it can be concluded that IL-33 may have a significant role via MCs in crosstalk between the various allergic diseases such as food allergy, allergic rhinitis, asthma and atopic dermatitis. Accordingly, the IL-33/ST2 pathway is being used as a novel therapeutic target to combat the MCs associated pathogenesis in allergic diseases. Hence, attention is warranted towards the investigating role of IL-33/ST2 pathway in the food allergy development and progression.

2.2. Role of IL-33 in allergic asthma

Asthma is characterized by chronic inflammation of the airways involving the activation of MCs, Th2 cells, IgE producing B cells, basophils, eosinophils, macrophages, lung epithelial and smooth muscle cells. In addition to MCs, T cells are also considered as main linker cells for Th2 type immune response to an allergen. However, Oboki et al.

(2010) [29] reported that inhalation of protease allergen or IL-33 protein in T/B cell deficient mice were able to induce Th2 mediated unsusceptible responses suggesting that resistant cell other than T and B cell is required to initiate the lung inflammation. Few studies based upon IL-33 have demonstrated its increased expression during pathological conditions in airway smooth muscle cell and lung epithelial cells of asthmatic patients. Enhanced expressions of IL-33 have also been noted in airway epithelial cells of COPD patients. However, its mechanism of action is yet to be explored [30,31]. An elevated level of soluble ST2 and IL-33 mRNA expression were observed in the both serum as well as lung tissues in ovalbumin (OVA) induced murine asthma model [32,33]. This indicates the involvement of IL-33/ST2 pathway in AA. Specific antibodies against the ST2, IL-33 and soluble ST2-Fc fusion protein have recently been used to explore the underlying mechanism of the ST2/IL-33 pathway in the asthma model [34–36]. Antibody pretreated mice failed to develop airway inflammation and the Th2-mediated immune responses, confirming their pivotal role in the setting of AA. Apart from this, these antibodies significantly reduced the IgE production as well as the eosinophil number in bronchoalveolar lavage in the murine model of allergic asthma. In a study, higher protein expression of IL-33 has also been detected in lung tissue of mice suffering from OVA induced airway inflammation [37]. IL-33 has also been reported to cause allergic bronchoconstriction through mast cell activation in expression of tryptophan hydroxylase 1, synthesis and storage of serotonin. This protein, consequently, causes airway

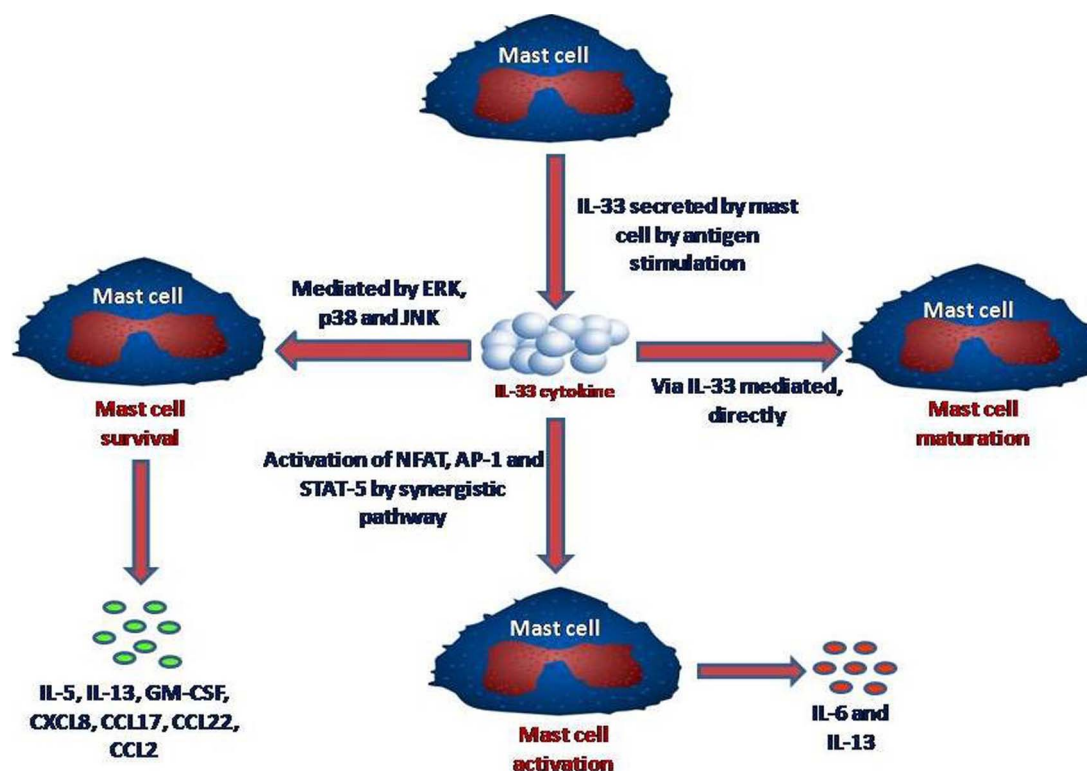


Fig. 2. Mast cells (MCs) induce IL-33 production in response to antigen that in turn can also promote MCs maturation, activation and survival by activation of various kinds of signaling pathway.

obstruction in asthma [37]. Therefore, inactivation of IL-33 as well as its receptor may be used as a therapeutic target in asthma resolution. Besides the pathogenic role of mast cells, eosinophilic infiltration has also been suggested as a phenotypic characteristic in allergic asthma. In this context, Th2 cell differentiation and eosinophilic lung inflammation were impaired in intranasally challenged IL-33-deficient mice suggesting that IL-33 acts as a causal factor for severe hypersensitive lung inflammation [38–40]. Recently, innate lymphoid group 2 cells (ILC2s) derived from lungs have been found to be involved in the eosinophilic accumulation at inflamed site of airways (Fig. 3). The ILC2s are members of the ILC family and possess CD127 (IL-7 receptor α) as a cell-surface marker. This distinct group of cell is activated by the epithelium derived IL-33 cytokine after the allergen encounter. ILC2s cells have been found in the lungs, skin and gut suggesting that these cells may have a significant contribution in allergic sensitization during allergic conditions. However, surface phenotypes of ILC2s have been found to vary; for instance, intestinal ILC2s possess lower expression of ST2 as compared to ILC2s derived from lungs, therefore, more studies focusing on IL-33/ST2 pathway associated with ILC2s in airway hypersensitivity have been carried out [41,42]. The ILC2s activated by IL-33 produce type 2 cytokines namely IL-5 and IL-13 that exhibit a pathogenic role in asthma by causing the eosinophil infiltration (Fig. 3), mucus hyper production and airway hyper-reactivity [43]. IL-33 is being considered a more potent stimulator of ILC2s than other cytokines like IL-25 [44]. Although, ILC2s secrete little IL-4 but the mechanism of action in the production of IL-5 and IL-13 is still unclear [41].

2.3. Role of IL-33 in allergic rhinitis (AR)

Since the decisive role of IL-33 in the setting of other allergic diseases is proven, it has been suggested a pathogenic factor for the development of early and late-phase immune responses in patients with AR. Nasal responses in AR can be differentiated in terms of early and late phase responses. Early phase responses such as sneezing and

rhinorrhoea are governed by more IgE synthesis, whereas Th2 cytokines play a critical role in the induction of late phase responses that include congestion, fatigue, malaise, and irritability [45]. Apart from Th2 cytokine production, the influx of mast cells, basophils as well as eosinophils into the nasal mucosa are considered a pathologic change in late-phase responses of AR [46]. The IL-33 is capable of inducing Th2 cytokine production by several resistant cells that include Th2 cells, B cells, mast cells, macrophages, dendritic cells, basophils, eosinophils and newly identified innate protected cells (ILC2, natural helper cells and nuocytes). This suggests that IL-33 has the potential to induce Th2 cytokine-mediated allergic inflammation (Fig. 3) [23]. Therefore, it can be concluded that IL-33 might be crucial in the induction and augmentation of Th2 mediated immune response in AR. In past, serum level of IL-33 was found to be significantly increased in the patients with seasonal AR that shows a significant association between susceptibility to AR and IL-33 polymorphism. The elevated serum level of IL-33 not only induces the inflammatory response, but also its concentration is positively correlated with AR severity [47,48]. Further, researchers have shown their keen interest towards the establishment of a pathologic role of endogenous IL-33 in the setting of early and late phase AR manifestation. Given the difficulty in examining the mechanisms in human subjects, a murine model of AR has been extensively used to study the pathophysiology of AR. Lately, a pivotal role of IL-33 in the AR development has been investigated using the anti-IL-33 antibody and IL-33 deficient mice. In an earlier study, it was found that IL-33 deficient mice immunized with pollen allergen showed a significant reduction in the frequency of sneezing, reduced total/ specific IgE responses and accumulation of eosinophils in the nasal mucosa and cervical lymph nodes after nasal challenge of pollen allergen. In addition, histologic analysis revealed that same mice showed a reduced degree of multilayer formation in the epithelium and goblet cell hyperplasia in the nasal mucosa. Moreover, cervical lymph node cells from challenged mice showed a markedly lower IL-4, IL-5 and IL-13 production upon stimulation with ragweed extract protein *in vitro* [23], demonstrating that IL-33 triggers the setting of both early as well as late

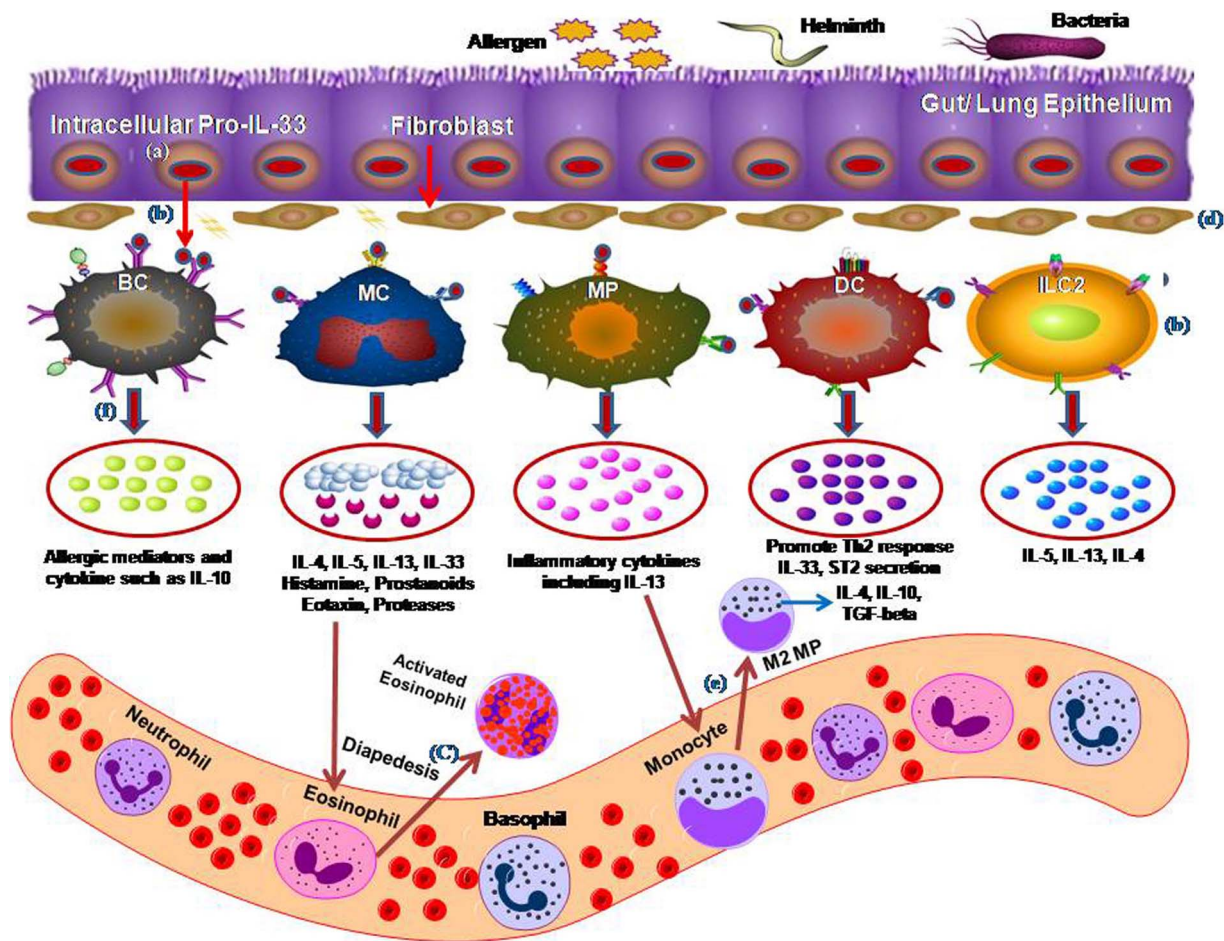


Fig. 3. IL-33 act as an alarmin and conductor of local inflammation. (a) In the healthy state, IL-33 resides in the nuclei of the resting epithelial cells. (b) Upon barrier damage by any stimulus, epithelial cells release a few molecules of the stored IL-33 cytokine. This cytokine activates various immune cells including resident mast cells, B-cells, macrophages, dendritic cells and innate lymphoid cells group 2 (ILC2s). These cellular targets secrete cytokines and chemoattractants to local recruitment of innate immune cells circulating in the blood stream. In addition, activated mast cells and DCs continue to produce cytokine IL-33 to maintain the homeostatic condition (c) An acute inflammation commences to recruitment of leukocyte such as eosinophil from the blood stream by diapedesis process. (d) Fibroblasts are stimulated and initiate a wound-healing process to repair the barrier damage. (e) In the late phase of local inflammatory process, incoming monocytes are skewed to an M2 phenotype (MP) synthesizing anti-inflammatory cytokines. (f) Further, IL-33 triggers B1 lymphocytes to produce IL-10 responsible for dampening of the inflammation.

phase AR manifestations. Allergen exposure through the rhinal route promptly stimulates the endogenous IL-33 production from rhinal epithelial cells that suggests the IL-33 release could act as an ‘alarmin’ and initiate the allergic reaction cascade in collaboration with other cytokines. Elevated expression of IL-33 and ST2 found in human nasal epithelium cells (HNECs) from patients with AR supports this finding [49]. In the AR patients, histamine released from activated mast cells and basophils have a key role in the induction of sneezing [50]. Ragweed pollen-induced endogenous IL-33 stimulates the connective tissue mast cells as well as mucosal mast cells to increase histamine secretion under the condition of cross-linkage of FcεRI with IgE-ragweed pollen [23]. Additionally, ragweed pollen-driven endogenous IL-33 also plays an essential role in the recruitment of eosinophils and basophils by inducing the production of various chemo-attractant, including eotaxin, MIP-1α, RANTES, and MCP-1 for both the eosinophils as well as basophils [23]. Considering these facts, activated mast cells as well as basophils might contribute to both early-phase (sneezing) and late-phase (eosinophilic accumulation) manifestations in AR. Furthermore, IL-33 mediated downstream signalling in the HNECs has been also investigated. IL-33 promotes the direct inflammatory responses in the HNECs via ST2 receptor that causes higher IL-8 and GM-CSF production. Recently, it was reported that IL-33 could enhance MAP kinases (ERK and p38 MAPK) phosphorylation in human airway epithelial cells [51]. In an earlier study, IL-33-mediated production of IL-8 from HNECs

was significantly inhibited by treatment with the ERK and the NF-κβ inhibitors, whereas reduction in production of GM-CSF was achieved by treatment with not only ERK and NF-κβ inhibitor but also by the p38 MAPK and the JNK inhibitor [49]. Therefore, it may be concluded that IL-33-mediated production of IL-8 and GM-CSF from HNECs is regulated by multiple distinct signalling pathways.

Indeed, IL-33 regulates the AR pathology by many distinct pathways. Since, the production of Th2 cytokines are stimulated by IL-33, it affects the AR by modulating Th17 mediated immune response, also. Additionally, IL-33 targeting ST2 receptor is found to be associated with the IL-17 as well as IL-31 production in allergy driven pathologies of AR. In a recent study, increased plasma levels of IL-33, sST2, IL-31 and IL-17 in the AR patients were found [52]. Thus, IL-33/ST2 axis is involved in Th2/IL-31 and Th17 immune response during the AR progression. IL-31, a novel cytokine produced particularly by Th2 cells has been implicated in the pathophysiology of allergic diseases, but its mode of action is different from typical Th2 cytokines such as IL-4, IL-5 and IL-13 in terms of its independent role in the AR [53]. Stimulation of cultured PBMCs with rhIL-33 could produce higher levels of CD3+ T-cells expressing intracellular IL-31 and IL-17A cytokines, indicating that IL-33 is able to provoke both the Th2/IL-31 and Th17 mediated immune responses [52]. Therefore, activation of the IL-33/ST2 axis, as a biomarker of both Th2/IL-31 and Th17 immune response, might represent a critical cross-talk between the immune system and resident

airways, and may be relevant for the diagnosis, staging and monitoring of the AR severity/progression. The pharmacological depletion of IL-33/ST2 biology may be a potential target in the development of original therapeutic approaches for the resolution of AR. After the multi-dimensional studies that focused on the association between IL-33 and AR progression, researchers got interested in the resolution of AR pathophysiology by targeting such unusual and potent factors. In order to do this, remedial potential of Anti-IL-33 antibody in the murine model of AR had been well studied. Anti-IL-33 treatment significantly attenuated early (nose-scratching events and specific IgE production) and late phase responses (ameliorated skin denudation, diminished eosinophilic infiltration in the nasal cavity and depleted IL-4, IL-5, and IL-13 cytokine's production in BAL fluid) [54]. Further, more attention is needed to identify newer IL-33 inhibiting agents that may reduce the clinical complications associated with AR.

2.4. Role of IL-33 in atopic dermatitis

The interleukin-33 is also considered a danger alarm in allergic condition in the skin such as atopic dermatitis (AD). Classical Th2 cytokines such as IL-4, IL-5 and IL-13 are hallmarks of acute AD, whereas IFN γ producing Th1 cells dominate in chronic stage of AD [55]. Apart from Th2 cytokines, tissue-derived IL-33 has also been suggested to have a crucial role in the maintenance of AD [56]. In addition to its role in airway inflammation, IL-33 has been shown to be a potent stimulator for ILC2s originated from skin that had links to skin inflammation in the mouse model of atopic dermatitis [57]. Typically, Th2 cells are the main producers of IL-5 and IL-13 cytokines during the episode of AD [58]. However, recently identified innate lymphoid cells (ILCs) may have potential involvement in AD as they can also produce Th2 cytokines in allergic conditions. The ILC2 cells express the various cytokine receptors that include ST2 (for IL-33 also called IL-33R), TSLPR as well as IL-17BR (for IL-25 also called IL-25R). Type 2 ILCs (ILC2s) derived from skin of human and mice are a resident population of ILCs expressing the cell-surface markers, including IL-7R α , CRTH2 and CD45 and transcription factor ROR α and GATA3. The frequencies of ILC2s have been found to be elevated during the onset of AD and got expanded after allergen exposure [57]. Recently, AD patients have been reported to over-express IL-33 in the epidermis and infiltration of ST2-positive cells in the dermis of the skin lesion, concluding that IL-33/ST2 pathway has a pivotal role in the pathogenesis of AD [59]. IL-33 triggers the skin homing ILC2s to produce Th2 cytokines such as IL-5 as well as IL-13. This also regulates its migration in the different tissues. Although, TSLP and IL-25 can also induce cytokine production and ILC2s migration, but their induction and regulation potential is lower than that of IL-33 [57,59]. IL-33 can also enhance the amphiregulin production by stimulating the ILC2s that has been implicated in barrier mend mechanisms in dermatitis [60]. In addition, amphiregulin can contribute to the innate immune responses and subsequently exacerbate the pathogenicity in AD as well [61]. Increased numbers of mast cells, basophils and eosinophils have been reported as phenotypic characteristics in the lesional skins of AD patients and mouse model of AD [62]. These immune cells exacerbate the AD pathogenicity by producing a number of inflammatory cytokines as well as allergic mediators. Mast cells produce both IL-33 and ST2 receptor in response to IgE/allergen cross linking [59]. However, their secretory mechanism is yet to be explored. IL-33 also triggers the MC and basophil activation and reportedly provokes the overproduction of pro-inflammatory cytokines by these cells. It also induces the migration, maturation, adhesion and survival of these immune cells [63–65]. Further, IL-33 derived from epidermal keratinocytes triggers the ILC2s in the skin as well as lymph nodes to produce IL-5 from these cells, resulting in appearance of dermatitis along with eosinophilia [62]. The IL-5 cytokine causes eosinophilic infiltration at the inflamed site. Filaggrin is a structural component of the skin and is essential for skin barrier function therefore; defect in filaggrin gene can lead to increased risk of developing

AD. There may be connection between filaggrin deficiency and IL-33 mediated immune response as it is a cytokine derived from barrier tissue. In this context, up regulated expressions of both IL-33 and ST2 have been found in the skin of filaggrin deficient mice [59], confirming the correlation between IL-33 production and filaggrin impairment. In future, mechanistic aspects of this phenomenon should be investigated to identify the new therapeutic targets.

Recombinant IL-33 injection in mice intradermally elicits a scleroderma-like reaction with an increase in dermal collagen fibers or a psoriasis-like dermatitis with a thickened epidermis [66,67]. However, the exact phenotypic hallmark more compatible with AD is now well studied in the various transgenic murine models. For instance, a transgenic mouse namely hK14mIL-33tg strain specific for higher epidermal IL-33 production has been implicated as a murine model of AD to establish the pathogenic role of IL-33 in AD. This murine model demonstrated that the over-expression of skin-specific IL-33 is responsible for AD-like cutaneous manifestations with eosinophil as well as mast cell accumulation [62]. Unlike the classical Th2 cells, ILC2s hardly produce IL-4; however, IL-33 could induce the elevated levels of IL-4. It may be speculated that eosinophils in the skin might produce IL-4 in response to IL-33 as it stimulates the production of IL-4 by eosinophils [68]. Considering the above-mentioned phenotypes of hK14mIL-33tg mice strongly suggests that IL-33 potentially takes part in the development of AD. This strain may be useful for studying the mechanisms of release, activation and regulation of IL-33 *in vivo* that might open the way to find novel therapeutic drugs targeting ILC2s mediated immune responses.

3. Interleukin IL-17

Recently, the identification of novel helper T (Th) cell subsets, i.e., IL-17-producing Th cells (Th17 cells) provided new insights to our understanding of the molecular mechanisms involved in the development of allergic diseases. Much evidence from gene-deficient mice indicated that Th17 cells may also contribute to the pathogenesis of classically recognized Th2-mediated disorders that include FA, AR, AA and AD. The IL-17 producing T cells were recognized in the year 2000 for the first time as a distinct Th subset from Th1 and Th2 cells in both mice as well as in humans, expanding Th1/Th2 dichotomy in allergy to another T cell effector subsets called Th17 cells (Fig. 4) [69]. The Th17 cells are distinguished by production of IL-17 and are negatively regulated by IFN- γ as well as IL-4 [70,71]. The differentiation of Th17 cells from Th cell lineage is triggered by TGF- β associated with T reg cells that also regulates the Th2 mediated immune response [72,73]. Understanding how these cytokines regulate the generation of Th17 cells is still unrevealed. In addition to this, recently discovered ILC cells also secrete IL-17 cytokine. The differentiation and development of these ILCs are summarized in Fig. 5. Commensal bacteria in human gut have been reported as potent inducers of Th17 cells in the lamina propria of the small intestine [74,75].

The IL-17 is a group of many homologous proteins produced by the memory T cells termed as Th17 cells [76]. The first member of this cytokine family has been identified as IL-17A. This was originally cloned as cytotoxic T-lymphocyte antigen-8, as a close homologue of a protein of the T cell tropic Herpes virus Saimiri [77]. Thereafter, other members, IL-17B to IL-17F were found and nominated based upon their homology to IL-17A [78]. The production of these cytokines is regulated at the transcription levels by various transcription factors [79]. Similarly, members of the IL-17 receptor family were also identified i.e. IL-17RA to IL-17RE. When these receptors interact with their corresponding cytokines, pro-inflammatory programs are induced [78]. Recently, IL-17 has been extensively studied for its pathogenic role in allergic conditions.

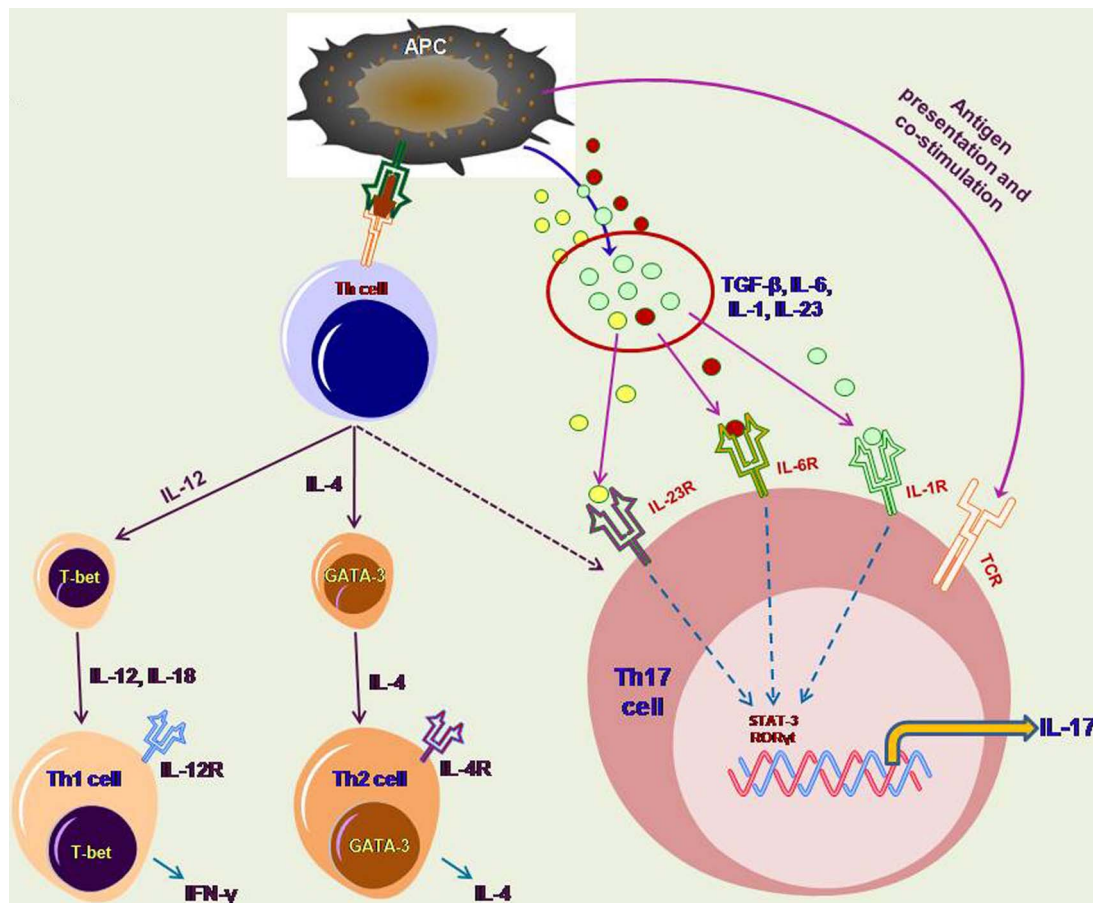


Fig. 4. Differentiation and proliferation of IL-17 producing Th17 cells: Left-hand panel, naive mouse T-cells can be differentiated by antigen presenting cell into three subsets of effector Th cells under the control of a distinct set of cytokines. IL-12 and IL-4 promote Th1 and Th2 differentiation respectively, whereas the Th17 differentiation is under the control of TGF β , IL-6, IL-1, IL-23. T-bet, GATA3 or ROR γ t is the lineage-specific transcription factors of Th1, Th2 and Th17 respectively. Right-hand panel, regulation of Th17 cell differentiation and IL-17 production that requires antigen presentation and co-stimulation and activation of APCs to produce TGF β , IL-6, IL-1 and IL-23. These molecules trigger the activation and up-regulation of STAT3 and ROR γ t transcriptional factors into the Th cells (represented by dash arrow) leading to differentiate into IL-17 producing Th17 cells. After many rounds of proliferation and differentiation in the lymph node, polarized Th17 cells having stable expression of ROR γ t, becomes ready to migrate into target tissues.

3.1. Role of IL-17 in food allergy

Food allergy is regarded as Th2 mediated immunity, as food allergen specific Th2 cells have been reported in patients with food allergies [80,81]. Numerous clinical and experimental studies have clearly defined the role of Th1/Th2 axis in food allergy. Recently, this Th1/Th2 dichotomy in allergy has been expanded to Th17 cells. In the past few years, IL-17 has been implicated in various allergic as well as autoimmune diseases, although its role in food allergy is not well defined. Recently, IL-17A has been found to be negatively correlated with allergic sensitization to certain food allergens [82]. In order to confirm this, Dhuban et al. reported that Th17 responses to antigen stimulation are found to be impaired in food-allergic children [83]. Furthermore, IL-17 could suppress Th2 cytokines and also Th2-recruiting chemokine production, suggesting that it is likely to play a suppressive role of either Th1 or T-reg cells, especially in case of food allergy [84]. However, unlike allergen specific T-cells, Th17 cells do not exhibit specificity against food allergens. Therefore, Th-17 subset of T-cells plays a possible role in the management of food allergy. Thus, this subset may be considered a likely biomarker for prevention and management of food allergy.

3.2. Role of IL-17 in allergic asthma

Allergic asthma is a complex and heterogeneous disease that may appear as bronchial hypersensitivity and airways with the intermittent

reversible obstruction, chronic inflammation, eosinophilia as well as leukocyte infiltration. In the pathophysiology of AA, CD4 $^{+}$ subset of T lymphocyte plays a fundamental role in the features of allergic asthma, i.e., allergen-specific IgE production, bronchial hyper responsiveness (BHR). Allergic asthma is also accompanied with accumulation of eosinophil, neutrophils and mast cells [85,86]. The role of allergen specific Th2 cell producing IL-4, IL-5 and IL-13 in sensitive asthma (AA) is well defined. These interleukins have been shown to play a fundamental role in the stimulation and maintenance of the invulnerable cascade in AA. In addition, integration of various immune cells, including mast cells, basophils, eosinophils as well as neutrophils act as effector cells in allergic inflammation through the production of pro-inflammatory, vasoactive and fibrogenic factors (histamine, peptide leukotrienes, platelet activating factor, tryptase and chymase, etc.) resulting in the severity of AA [87]. Another distinct T-cell lineage to Th1 and Th2 cells, known as Th17 producing a family of IL-17 cytokines has been identified with the pathogenic potential in allergic asthma [70,71]. The elevated levels of IL-17 mRNA as well as protein has been found in the lungs, sputum, tracheal aspirate, bronchoalveolar lavage (BAL) and sera from asthmatic patients, indicating the contribution of IL-17 to the pathogenesis of asthma [88,89]. Numerous evidences suggests that Th17 cells produce IL-17 (also known as the prototype IL-17A) and IL-17F that plays an important role in the pathophysiology of asthma. Both the cytokine members share strongest homology to each other and act as pro-inflammatory cytokines, thus have overlying role in the development of various allergic conditions such as autoimmune

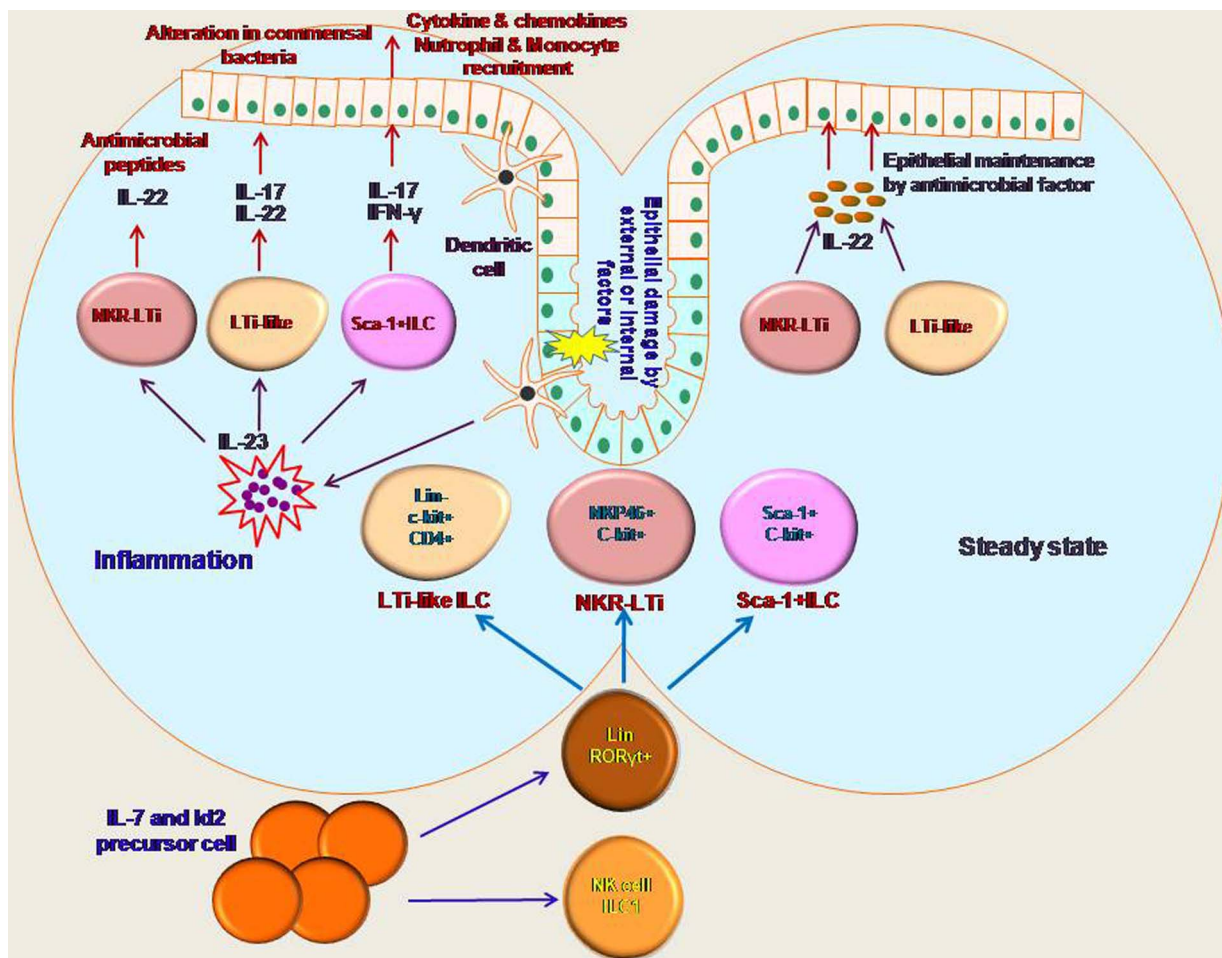


Fig. 5. Origin and function of IL-17 producing innate lymphoid cells (ILCs). From below: Lineage relationship and phenotype of IL-17-producing ILCs. All ILC subsets originated from IL-7 as well as transcriptional repressor Id2 dependent precursors. The ROR γ t-expressing ILC subsets are the chief source of IL-17 and depend on ROR γ t for their development. LTi-like cells with CD4 expression have been shown to secrete IL-17, IL-22 or both, whereas NKR-LTi cells predominantly produce IL-22 cytokine. Sca-1-expressing ILCs produce both the IL-17 as well as IFN- γ and play a pivotal role in driving inflammation in the intestine. In the steady state conditions LTi-like and NKR-LTi cells spontaneously secrete IL-22 to enhance secretion of antimicrobial factors and maintain epithelial barrier function. In response to inflammatory stimuli or epithelial cell damage activate TLRs expressed by DCs, inducing IL-23 production. Cytokine IL-23 induces to all subset of ILCs including Sca-1+ ILCs to produce IL-17, leading to the recruitment of myeloid cells and the development of colitis.

disorders, asthma and airway inflammation [90,91]. Both cytokines are secreted as either homo or heterodimer linked with disulphide linkage [92,93]. A heterodimeric receptor consisting of IL-17RA and IL-17RC chains has been recognized for IL-17 cytokine family. This receptor complex is expressed on the various tissue-specific cells. Although, expression of IL-17RC is limited to non hematopoietic cells, IL-17A is detected ubiquitously, suggesting that IL-17 may promote inflammatory responses in the lung through IL-17RA rather than IL-17F receptor (Fig. 6). However, IL-17A homo dimer up-regulates the pro inflammatory molecules with more potency as compared to IL-17F homo dimer or heterodimer [94–96].

Interleukin-17A and IL-17F promote lung tissue-mediated innate immunity caused by pro-inflammatory molecules. Collectively, both the cytokines enhance IL-6, IL-8, IL-11 and CXCL1/Gro α production by compassionate bronchial fibroblasts and production of β -defensin-2, ICAM-1, IL-8, CXCL1, CCL20, G-CSF, MUC5B and MUC5AC by human bronchial epithelial cells. These cytokines also promote IL-6 and IL-8 production by human airway smooth muscle cells, production of different cytokines [TNF- α , IL-1, IL-6, and granulocyte-macrophage and granulocyte colony-stimulating factors (GM-CSF and G-CSF)] as well as anti-microbial peptides (mucins, β -defensins, S100A7-9) from differing tissue and tissue remodeling and acute phase responses (SAA, MMP1, RANKL; Fig. 6) [97–108].

The development of allergic asthma occurs via two different

mechanism i. e. “Th2 type” and “non Th2 type.” The ‘Non Th2 type’ asthma found in several asthmatic patients had neutrophil rather than eosinophil infiltration in pulmonary inflammation [85]. Moreover, infiltration of neutrophil is found to be correlated with severity of allergic asthma. The IL-17 induces the production of CXCL8 (IL-8), CXCL1 and Gro α cytokines that are potent chemo-attractant factors for neutrophil’s accumulation. In addition, IL-6 and G-CSF are important factors for granulopoiesis, especially neutrophil development. This observation gets substantiated by study of IL-17 inhalation that leads to accumulation of neutrophil rather than eosinophil in the airways and also promotes neutrophil mobilization caused by granulopoiesis in the murine model [70,95,109–112]. Thus, IL-17 induced neutrophil infiltration in the airways of asthmatic patients exacerbates the severity and may contribute in mucus hyper secretion in airway, bronchial hyper-reactivity and remodeling of the airway wall in asthma. Clinically, asthma progression is differentiated into two stages i. e. atopic and non atopic. Atopic asthma is characterized by increased serum IgE levels and Th2-type airway inflammation with the elevated IL-4+ as well as IL-5+ cells and eosinophils in bronchial tissues, whereas a non-Th2 type airway inflammation is associated with enhanced IL-8+ cells and neutrophils in bronchial tissues [113]. Therefore, it may be concluded that IL-17 may act as a trigger for the onset of non atopic stage by neutrophil infiltration [113]. In addition, non-atopic asthma can also be characterized by the presence of IL-17 cytokine.

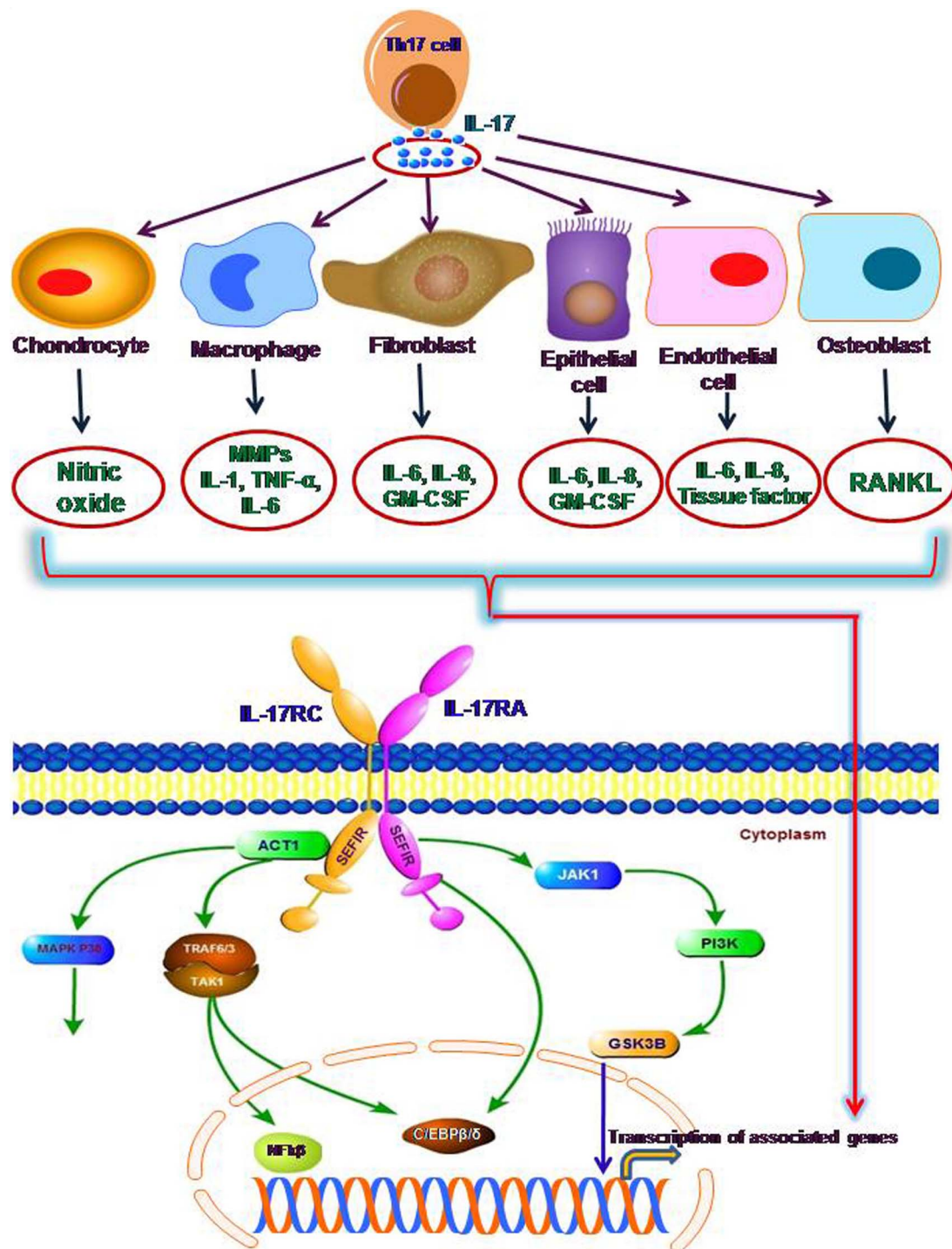


Fig. 6. Cellular targets of Th17 cells and its cellular mechanism. Interleukin-17 (IL-17) acts on various cellular targets, including chondrocyte, macrophage, fibroblast, epithelial cell, endothelial cell and osteoblast leading to their activation. From lower panel, IL-17 receptor (IL-17R) complex found in above mentioned cells, is made up of IL-17RA and IL-17RC and both possess an SEFIR domain. IL-17RA has two extra domains called the TILL domain and distal domain. Left-hand side, after binding with IL-17 both IL-17RA and IL-17RC form a heterodimeric complex to recruit Act1 through the SEFIR domain interaction. Act1 then recruits TRAF6 and the TAK1 complex, leading to IKK and NF- κ B activation. On the other hand, IL-17-induced Act1 signaling also activates MAPKs as well as JAK/PI3K pathway. The entire IL-17-stimulated signaling cascade leads to the activation of various transcription factors such as C/EBPs and NF- κ B to induce gene transcription. From upper panel, each cellular target stimulated by IL-17 participate differently in the onset of pathogenic response. For instance, endothelial cells lead to inflammation and procoagulant activity in response to IL-17, whereas epithelial cells and fibroblasts lead to cytokine and enzyme production. When IL-17 acts on monocytes and dendritic cells they contribute to inflammation by increasing the production of pro-inflammatory cytokines. In the osteoblasts and chondrocytes, IL-17 activates matrix destruction in cartilage and bone leading to joint inflammation.

3.3. Role of IL-17 in allergic rhinitis

Allergic rhinitis (AR) is characterized by a nasal sensitive inflammation, because of Th2 mediated immune responses. Peripheral-blood mononuclear cells (PBMC) of many AR patients have been found

to have predominant IL-4 production by Th2 cells. Another T lymphocyte subset known as Th17 cells have been involved in the development and progression of AR. In the beginning, patients with viral rhinitis had reported to have elevated concentration of IL-17 in nasal secretion [114]. Further, a detectable serum IL-17 level was found in patients

suffering from allergic rhinitis caused by birch allergen [115]. Several earlier reports have indicated that elevated serum levels of IL-17 represent the hypersensitive severity in AR [115,116]. Furthermore, *ex-vivo* analysis of PBMCs from AR patients displayed two subsets of T effector cells belonging to the Th17 family, i.e. CD8+IL-17+ and CD8+IFN γ +IL-17+ cells. In addition, significantly higher percentages of both CD4+IL-17+ and CD4+IFN γ +IL-17+ cells have been found in the above said AR patients [117]. These findings clearly indicate the potential role of Th17 cells in the AR pathogenesis. However, further studies are required to clarify the issues regarding the importance of two subsets of T effector cells in the same AR patients.

Recent studies based on IL-17 deficient mice have clearly shown that IL-17A secreted by Th17 cells plays a crucial role in the setting of AR. An earlier study on AR murine model, investigated the role of IL-17A on the onset of allergic mucosal inflammation. In this study, allergic mice challenged with OVA via intranasal route had elevated serum IL-17A levels. Further, frequency of nose rubbing and sneezing was decreased in OVA allergic IL-17A-deficient mice as compared with wild type OVA sensitized mice. Decreased eosinophil, neutrophil and mast cell recruitment were also observed after ova-albumin challenge in IL-17A impaired mice, demonstrating that IL-17A recruits the above said immune cells at the site of the nasal mucosa [118]. In addition to supporting role of IL-17A in AR, it can as well regulate the AR pathogenesis through the inhibition of mast cell degranulation and the modulation of Th2 cytokines (IL-4, IL-5 and IL-13) along with pro-inflammatory cytokines including TNF- α and IL-1 β expressions [119]. Therefore, IL-17A can act as both the positive and negative regulator in allergic rhinitis.

Besides, IL-17A producing Th17 cells, another distinct lineage of IL-17 producing CD4+ T cells, have been recognized with the characteristics of pro-inflammatory helper T cell in an asthmatic mouse model [71]. A newly discovered IL-17 producing FOXP3+ regulatory T (T-reg) cell was recently identified that exists only in the peripheral blood of humans. This special type of T-regs possesses phenotypic characteristics of the both Th17 as well as T-reg cells [120]. The discovery of unusual sub-population of T-reg cells has suggested that IL-17A-producing T-reg cells may have critical roles in IL-17 mediated allergic diseases. In this regard, elevated levels of IL-17A secreted by special type of regulatory T cells have been reported in AR patients. Similarly, in other studies, IL-17A producing T-reg population was found to be higher in AR patients [121,122].

In the context of regulation of Th17 responses, several molecules, including platelet-activating factor, retinoic acid, osteopontin, thymic stromal lymphopoietin and prostaglandin E2 have been notified to modulate the differentiation, function or chemotaxis of Th17 cells in patients with sensitive diseases. Thus, distinct mechanism of Th17 response regulation by these molecules must be addressed, especially in the context of AR. In a recent study, Clara cell 10-kDa protein (CC10) has been proven as an excellent candidate for drug development to treat allergic airway's diseases, including AR [123]. CC10 is an anti-inflammatory and immunomodulatory protein secreted by the epithelial lining of the lung and nose. The results from both *in vivo* and *in vitro* experiments revealed an inhibitory role of CC10 in Th17 responses in the setting of AR. It regulated the Th17 cell chemotaxis and local expansion by inhibition of IL-23 and CCL20 expressions in airway epithelial mucosal cells as both the molecules are involved in proliferation and migration of Th17 cells, respectively. Regulatory roles of this protein in allergic diseases, including AR had been implicated via inhibition of Th2 response as well [124,125]. Assuming above facts, IL-17A may be considered as a new biomarker of disease progression as well as disease severity in AR and it can also offer a therapeutic target to overcome the clinical complications associated with AR.

3.4. Role of interleukin-17 (IL-17) in atopic dermatitis

The role of IL-17 in provocative skin disorders has been suggested as

IL-17 plays an important role in the pathology of a variety of skin diseases, including psoriasis, contact hypersensitivity as well as in AD [126]. AD is a common, lasting, relapsing, provocative skin disease often linked with other atopic disorders such as asthma, food allergy and allergic rhinitis. The course of AD is biphasic inflammation, with predominant Th2 response in acute stage that switch towards the Th1 like profile in lingering stage [127,128]. Both the phases of AD exhibit a significant amount of Th2 cytokines compared to normal skin, although chronic stages are characterized by reduced IL-4 and IL-13 production and enhanced secretion of IL-5 and IL-12 [129]. Apart from the crucial role of Th2 cells in AD, Th17 cells as well as other IL-17-producing cells are also suggested to take part in AD [130]. Several findings indicated the association between IL-17 and the cutaneous milieu. Various immune cells have been suggested as a potential source of IL-17 secretion during the AD progression. Not only CD4+ Th17 cells, but also subsets of CD8+ T cells, $\gamma\delta$ T cells, NKT cells, monocytes, natural killer cells and lymphoid tissue inducer-like cells have been found to produce IL-17A (also regarded as IL-17) [131]. Amongst the sources, $\gamma\delta$ T cells have been identified as IL-17 producer in the psoriasis skin lesions of murine models as well as in humans skin [132,133]. Thereafter, this cell has also been reported as a chief source of IL-17 in the skin of mice with AD [134]. The memory features of skin exposed to IL-17 might play a key role to provide the protection against repeated exposure of bacteria or fungal pathogens. The immunological memory of $\gamma\delta$ -T cells in the lesional as well as non lesional skin has been explored, recently. The V γ 4+ subset of $\gamma\delta$ T cells have to be responsible for memory phenotype. In the lesional skin V γ 4+ $\gamma\delta$ T17 cells accumulate in numbers and augment inflammation by neutrophilic recruitment. Neutrophil on the other hand also sensitizes distant sites to inflammation by further migrating of V γ 4+ $\gamma\delta$ T cells, and subsequently persisting in healthy skin to support rapid secondary responses. It has been demonstrated that V γ 4+ $\gamma\delta$ T17 cells having memory like characteristics respond rapidly to their inducer like IL1 β [135]. Therefore, particular V γ 4+ $\gamma\delta$ T17 population may be targeted to prevent the fast and strong secondary responses to the same stimulus.

The IL-17 may affect the pathology of AD by distinct mechanism. For instance, Th2 mediated immune response in AD may be regulated by the IL-17 cytokines as seen in the murine model of AD. Lack of IL-17A attenuated skin inflammation, production of IL-4, specific IgG1 as well as IgE production, corroborating the above-said statement. Further, IL-17A triggered the differentiation of IL-4 producing Th2 cell, confirming that IL-17 regulates the pathophysiology of AD by modulating the Th2 mediated immune response [134]. IL-17 can also regulate the Th2 mediated immune response in AD by modulating the production of other Th2 chemokines such as TSLP and CCL17/thymus- and activation-regulated chemokine. The IL-17 induces production of certain cytokines, chemokines, and antimicrobial peptides by keratinocytes that include GM-CSF, TNF- α , IL-8, CXCL10, and VEGF having the crucial role in the pathophysiology of AD [136–138]. In a recent study, it has been found that IL-17A exacerbates both the phases of AD by producing the downstream chemokines like CXCL1, CXCL2, CXCL10, and CCL2 through the inhibition of EGFR (epidermal growth factor receptor) signalling pathway [130]. In this study, EGFR signalling was recognized as a therapeutic target to attenuate the IL-17A mediated immune responses in AD. This pathway may help in the developing preventive strategies that particularly target the immune-suppressing pathway without affecting cellular proliferation. IL-17 has been found to induce the expression of cell cycle-related genes in keratinocytes that include cyclin E1 (CCNE1), cell division cycle associated 5 (CDCA5), and cell division cycle 25 homologue A (CDC25A), suggesting that it has a positive role in keratinocyte proliferation. Over-expression of C/CAAT enhancer-binding proteins (C/EBP)- β that is known as a transcription factor to regulate the IL-17 responsive genes as found in differentiated keratinocyte corroborated that IL-17 has a central role in the pathogenesis of various skin diseases by modulating the keratinocyte division and differentiation directly [139].

Elevated serum level of IgE is the characteristics of acute phase in AD. Initially, B cells displayed increased survival, proliferation, and differentiation into plasma cells when cells were stimulated by IL-17A, indicating that B cells might be a substantial target for IL-17A [140]. In a recent study, IL-17A has been found to provoke the IgE production by B cells in human [141]. In another study, the IgE production by B cell stimulation with IL-17 was found to be higher than un-stimulated cells. Therefore, it may be concluded that IL-17A has the direct positive impact on the number of IgE producing B cells. Furthermore, no significant change in other isotypes such as IgM, IgA, and IgG production was observed, suggesting that the IgE promoting effect of IL-17A was not isotype specific. It has also been proved that IL-17A causes differentiation of B cells into IgE producing plasma cells. Stimulation of IL-17 enhances the gene expressions of activation-induced deaminase (AID), epsilon germ-line transcript (eGLT) and IFN regulatory factor 4 that is involved in the IgE class switching recombination (CSR). Further, it was demonstrated that the most important downstream target of IL-17A is NF- κ B that is crucial in CSR IgE. It triggers rapid degradation of I κ B α and subsequent translocation of NF- κ B into the B-cell nucleus causing them to differentiate into IgE producing plasma cells [141]. This study suggests that IL-17A might be a target for the treatment of not only AD but also for other IgE-dependent diseases. Further, IL-17 mRNA expression has been found in the skin with allergic contact dermatitis as well as psoriasis [142,143]. Initially, enhanced Th17 population was considered to be indicative of AD severity in human patients, however, based upon recent studies it may be suggested to be a key element actively involved in the immune pathway leading to AD [137]. The IL-17 deficient murine model of AD demonstrated decreased AD like symptoms as well as IgE production [134]. The infiltration of IL-17 cells has been reported in cutaneous lesions of AD patients. The distribution of IL-17 secreting cells was found greater in the region of upper papillary dermis and also noticed in the epidermis region. Interestingly, enhanced IL-17 expression is much more evident in acute as compared to chronic phases of AD [137,144]. The IL-1 β and IL-6, combined with TGF- β has been found elevated in skin lesion of AD [144] and could impose Th17 polarization. On the other hand, IL-17A and IL-17F also promote the production of IL-1 β and IL-6, suggesting that polarization of Th17 cells also contributes to their own secreted cytokines. Eosinophil and neutrophil infiltration has been observed in acute as well as chronic stages of AD. The IL-17A and IL-17F can promote the production of CXCL1, IL-8 and CCL4 by eosinophils, indicating cross-talk between Th17 cells and eosinophils in AD. The IL-17 has been reported a key stimulator of neutrophil chemo-attractants and anti-microbial peptide that might be involved in the chronic stage of AD [145].

In addition to immune disturbance, skin barrier dysfunction is also considered to be the key element in the development and progression of AD. An altered skin barrier has been suggested as a causative factor in the pathogenesis of AD. Impairment in filaggrin due to gene defect resulting into the defective epidermal barrier may lead to an increased risk in the development of AD. However, recent data indicate the existence of non-genetic factors that can affect barrier function by decreasing filaggrin content in the skin independently of the genetic background. Some Th2 cytokines such as IL-4, IL-13 and TNF- α were reported to modulate the filaggrin levels in the skin [27,146]. In addition to these cytokines, IL-17 may alter the filaggrin expression as indicated by constitutive expression of IL-17 receptor in keratinocytes of skin with AD [138]. Therefore, researchers have recently emphasized investigation on the effect of IL-17 on the filaggrin protein function and pro-filaggrin processing enzymes. In an earlier study, impact of IL-17 on the filaggrin level and epidermal barrier constituents has been explored. A number of genes encoding proteins are thought to be important in profilactin and filaggrin-processing pathways. All the genes described by Gutowska-Owsiak et al. [147] were affected by elevated IL-17 levels. However, cathepsin D and kallikrein-related peptidase 5, as well as two transcripts of calpain small subunit 1 (essential for the formation of calpain I), were specifically found to be down regulated.

Cuticular keratinocytes play an important role in the formation and maintenance of an operational mechanical barrier. IL-17 has been found to down regulate the genes encoding various cellular (keratinocytes) adhesion molecules, including integrins, plakoglobins, plakophilins, cadherins (including E-cadherin), claudin 7 and ZO-2 proteins that are involved in the formation of working epidermic barrier. In the same study, IL-17 could reduce the expression of filaggrin monomer as this protein is made up of two monomeric subunits [147]. In addition to filaggrin, claudin 1 and claudin 4 have also been suggested as major constituents of epidermal skin barrier. In an earlier study, reduced expression of filaggrin and claudin 1 has been found in lesional skin of AD patients. Filaggrin expression not only got reduced but also its expression was inversely correlated with the clinical severity of AD as well as the phenotype [148]. On the basis of these results, it may be concluded that exposure of epidermis to IL-17 alters many cellular processes and could result in decreased barrier dysfunction that has the critical role in the setting of AD.

4. Conclusion and future perspective

The data available through several studies on the role of Th17 as well as IL-33 in hypersensitive diseases suggests that both the cytokines have the pivotal role in the setting of allergic diseases. In this review, we have tried to summarize the existing knowledge of IL-17 as well as IL-33 cytokines and discuss the possible pathogenic role in the immune diseases like AA, AR, AD and FA. Targeting of both the cytokines to overcome the pathogenicity of hypersensitive diseases can be an inference. ILC2s cells have emerged as an important effector's cells in the pathophysiology of hypersensitive diseases. Association between the IL-33/ST2 pathway, IL-17 and ILC2 cells has been investigated recently but mechanism involved in this connection is still awaited. Elevated levels of IL-33 and ST2 have been found to be associated with the decreased levels of filaggrin protein, but underlying mechanism behind the IL-33/ST2 pathway that caused reduced level of filaggrin is yet to be investigated. Till date, role of IL-17 in FA has not been investigated in a systematic manner; however, existing data demonstrates that this cytokine has some biological role similar to T-regs. Therefore, study of mechanistic aspects regarding the suppressive role of IL-17 in food allergy should be carried out in the future. Research is also needed towards the novel class of molecules with IL-17 and IL-33 inhibiting potential so that risk factors could be minimized in the development and severity of allergic diseases. Intestine resident bacteria or their products have been found associated with activation of Th17 cells but how these bacteria or their products trigger the Th17 cells is not very well defined. Is there any specific mechanism involved behind this immune activation? These are some important questions that need an answer. The basic knowledge regarding memory features of IL-17 has been studied but a systematic study focusing on the behavior of particular V γ 4 + γ T17 memory cell is still awaited. Furthermore, some compounds or molecules with inhibiting potential for IL-33 and IL-17 have been identified at the screening levels, but their inhibiting potential in an *in vivo* system should be validated. In addition, identification of some novel compounds with inhibiting properties, especially derived from natural source, may be a promising approach to manage the hyperactivity of memory cells activated by previously exposed stimulus. As discussed that IL-17 can act either as a positive or negative regulator, therefore, our efforts should focus on biological or cellular conditions that can guide to the Th17 cell to behave in whatever way we want. Then only we could find treatments for the diseases like AR, FA, AD and other such disorders.

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Conflict of interest

The authors declare no competing financial interest.

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