Review Article

Cytokines (interleukin-9, IL-17, IL-22, IL-25 and IL-33) and asthma

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Abstract

Asthma is a reversible airway obstruction that is characterized by constriction of airway smooth muscle, hyper secretion of mucus, edema and airway hyper responsiveness (AHR), mucus secretion and thickening of the basement membrane underlying the airway epithelium. During the process of airway inflammation, complex interactions of innate and adaptive immune cells as well as structural cells and their cytokines have many important roles. It was believed that airway inflammation is orchestrated by allergen specific T helper (Th) 2 cells, which recruit and accumulate in the lungs and produce a range of different effector cytokines. However, more recent studies have revealed the potential collaboration of other helper T cells and their cytokines in this process. Th17 cell may have a role in severe asthma and chronic obstructive pulmonary disease (COPD). Interleukin (IL)-9-producing subset called Th9 cell, Th22 cells which primarily secrete IL-22, IL-13 and tumor necrosis factor-α and Th25 cells via producing IL-25 are believed to be important for initiating allergic reactions and developing airway inflammation. Cytokines are important in asthma and play a critical role in orchestrating the allergic inflammatory response, although the precise role of each cytokine remains to be determined. The aim of this review is to summarize the current knowledge about the possible roles of newly identified helper T cells derived cytokines (IL-9, 17, 22, 25 and IL-33) in asthma. The potential therapeutic applications emerging from the roles of these cytokines will be discussed as well.

Key Words: Asthma, interleukin-17, interleukin-22, interleukin-25, interleukin-33, interleukin-9

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Received: 15.09.2013, Accepted: 27.10.2013

INTRODUCTION

Asthma is one of the most common lifelong chronic diseases. It affects approximately 24 million persons in the United States. It is the most common chronic disease in childhood, affecting an estimated 7 million children.[1] The prevalence of asthma in developed countries is approximately 10% in adults and even higher in children, whereas in developing countries, the prevalence is lower but increasing rapidly.[2] The strongest risk factors for developing asthma are a combination of genetic predisposition with environmental exposure to inhaled substances and particles that may provoke allergic reactions or irritate the airways. Asthma is a reversible airway obstruction that is characterized by hyperirritability of the

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.133249

How to cite this article: Farahani R, Sherkat R, Hakemi MG, Eskandari N, Yazdani R. Cytokines (interleukin-9, IL-17, IL-22, IL-25 and IL-33) and asthma. Adv Biomed Res 2014;3:127.

airways. Substances that have no effect when inhaled by normal individuals cause broncho-constriction in patients with asthma. Pathophysiologically, asthma is characterized by constriction of airway smooth muscle, hyper secretion of mucus, edema and airway hyper responsiveness (AHR),[3] mucus secretion and thickening of the basement membrane underlying the airway epithelium.

During the process of development of airway inflammation, complex interactions of innate and adaptive immune cells as well as structural cells have many important roles.[4] After allergen exposure, airway inflammation is orchestrated mainly by allergen specific T helper (Th) 2 and other T cells, which recruit and accumulate in the lungs and produce a range of different effector cytokines.[5] Th2 cells play this central role by producing a number of key cytokines interleukin (IL-4, IL-5 and IL-13), which have been shown to contribute many of the pathophysiological features of asthma.[6] However, discovering more subtypes of helper T cells and their cytokines led to re-considering the immunopathology of asthma.

It is shown that, Th17 cells may have a role in severe asthma and chronic obstructive pulmonary disease (COPD). In the late 2008, two groups have shown that a combination of transforming growth factor β (TGFβ) and IL-4 is capable of differentiating naive murine CD4+ T cells into a unique IL-9-producing subset called Th9 cells.[4] Th22 cell, another subtype of human CD4 + T cells, primarily secretes IL-22, IL-13 and tumor necrosis factor-α (TNFα).[7] The latest subset which is termed Th25 via producing IL-25 initiates allergic reactions by bridging the innate and adaptive immune responses of asthma. IL-25 is also able to amplify allergic type inflammatory responses through its actions on other cell types.[7] However, here we have tried to review the recent articles on the relationship of cytokines to allergy and asthma.

CYTOKINES

All cells within airways such as fibroblasts, smooth muscle cells and epithelial cells play key roles in orchestrating the chronic inflammation of asthma and COPD by recruiting, activating and promoting the survival of multiple inflammatory cells in the respiratory tract.[2,8] These inflammatory processes are connected by a complex molecule as cytokine network. Asthma pathology is associated with different release of pro-inflammatory substances (lipid mediators, chemokines, cytokines…). Cytokines are important in asthma and play a critical role in orchestrating the allergic inflammatory response, although the precise role of each cytokine remains to be determined. Cytokines often have overlapping biological activities, exert different effects at different concentrations, can synergize or antagonize the effects of other cytokines and regulated in a complex manner and function via cytokine cascade. Modulating the cytokine network in respiratory diseases such as asthma, with expected therapy presents a new but confronting standard for treatment of asthma.

IL-9

Th9 cells were first identified as a Th2 subpopulation that produced exceptionally large quantities of cytokine IL-9. However, experimental analyses revealed that Th9 cells have divergent regulatory capabilities and are critically involved in different immune processes.[9] As the main product of Th9 cells, IL-9 is a pleiotropic cytokine that has several effects on numerous hematopoietic cells, which are central to the pathogenesis of asthma. IL-9 stimulates the proliferation of activated T cells, promotes the proliferation and differentiation of mast cells (MCs) and increases production of immunoglobulin (IgE) by B cells.[10,11] It also promotes expression of MC proteases, up-regulates the high-affinity IgE receptor and induces IL-6 production.[12] Evidence from both human/murine studies suggested that IL-9 is associated with susceptibility to develop AHR.[10,11]

IL-9 in mice elicits a prominent phenotype in the lung (eosinophilic and lymphocyte inflammation, increased mucus production, AHR and sub-epithelial collagen deposition), suggesting that IL-9 may play a role in chronic allergic inflammation. Studies using neutralizing IL-9 antibodies have shown some reduction in inflammation and AHR, whereas a study using IL-9-deficient mice described a redundant role for this cytokine in a similar model of asthma.[12]

IL-9 is also expressed by human eosinophils and MCs and there is compelling evidence that MCs contribute to the acute symptoms of asthma, including bronchoconstriction, mucus secretion and mucosal edema. More recently, MCs are shown to be implicated in chronic inflammation and shown to promote angiogenesis and tissue remodeling in a mouse model of asthma. Other studies have demonstrated a critical role for IL-9 in regulating MCs numbers in the airways after allergen challenge.[9-11] Applying anti-IL-9 antibody was associated with a decrease in lung expression of the growth factors TGFβ, VEGF and FGF-2. TGFβ has a critical role in airway remodeling and is a key player in the tissue repair response.[9] This could be as a novel IL-9-TGFβ axis that regulates airway fibrosis.

Newly defined Innate lymphoid cells (ILCs)-2 are also able to produce IL-9 as well as IL-5 and IL-13 and hence, are the other contributors in the immunopathogenesis of asthma.[13,14] Recently, RORα is identified as a key transcription factor involved in ILC2 development and this raises the possibility of producing therapeutic RORα inhibitors that would specifically block the development of ILC2 in lung type 2 inflammatory disease.[13]

IL-17

About 1 decade ago, Infante-Duarte *et al*. demonstrated that IL-17-producing T cells are a distinct Th population from Th1 and Th2 cells in both mice and humans. Then, the significance of Th17 cells rather than Th1 cells for the development of certain diseases such as contact hypersensitivity and arthritis was demonstrated in IL-17-deficient mice. IL-17A is a pro-inflammatory cytokine and is the main member of a family with five more additional members including IL-17B, IL-17C, IL-17D, IL-17E and IL-17F.[15,16] Both IL-17A and F could make airway epithelial cells to produce pro-inflammatory mediators such as chemokines (CXCL1 and CXCL8), which may possibly attract inflammatory cells (neutrophils) and cytokines (IL-6) which promotes the activation of Th17 cells. Moreover, Th17 cells stimulate other cells to release cytokines IL-21 and IL-23 that in turn, can induce differentiation or development of Th17 cells.[17-19] It is also reported that MCs release mediators which are able to up-regulate the expression of IL-17 by macrophages.[20]

Beyond its roles in host defense, IL-17A is known to be associated with several inflammatory and autoimmune diseases, such as rheumatoid arthritis, psoriasis, multiple sclerosis, inflammatory bowel disease and periodontitis.[17,21,22] For the first time, Bullens *et al*. demonstrated that the level of IL-17A messenger ribonucleic acid (mRNA) is elevated in the sputum sample of asthmatic patients.[23] Other studies have reported that the level of IL-17 in asthma is increased and this may be one of the risk factors for severe asthma.[17,22,24] More recently, Lu *et al*. have reported that high levels of IL-17A and IgE could play an important role in the development of bronchial asthma.[25] It's now revealed that moderate and severe asthma are associated with increased neutrophils and increased Th17 cytokines such as IL-17A, IL-17F and IL-22, in the bronchoalveolar lavage fluid of patients.[19] Despite of the past extensive studies, the exact role for Th2 and Th17 cytokines in allergic airway inflammation is still unclear.[26] However, it seems that IL-4 and IL-17A provide a chronic inflammatory milieu that favors TGF-β1 to induce epithelial cells re-entering cell cycle and to promote epithelial to mesenchymal morphological transition.[26] Therapeutics targeting of IL-17A and IL-17 receptor signaling in current clinical trials may clarify the role of Th17 cells in asthma.[19]

As we mentioned earlier, allergic asthma is an inflammatory process driven by allergen-specific Th2 lymphocytes, whereas Th17 cells seems to be involved in those forms of asthma in which, neutrophils more than eosinophils, supply to the inflammation.[27] However, a numbers of studies have shown that Th2 cells have the potential to produce IL-17 after stimulation with pro-inflammatory cytokines IL-1 β, IL-6 and IL-21, suggesting that plasticity between the development of Th2 and Th17 cells may exist.[28,29] Moreover, Wang *et al*. have reported that Th2 polarizing condition (thymic stroma lymphopoietin (TSLP) activated Dendritic cells (DCs) or IL-4) could induce the freshly isolated human CCR6 + Th17 cells to produce IL-4 with dual expression of the Th17-transcription factor retinoic acid-related orphan receptor γt (RORγt) and the Th2-transcription factor GATA3.[29] However, the exact mechanisms involved in the differentiation of such helper T cells remain unclear.[28] These Th2/Th17 cells are shown to be increased in the blood of patients with atopic asthma as well as in the inflamed lung of a mouse model of allergic asthma and persisted as the dominant IL-17-producing T cell population during the chronic stage of asthma.[29] Recognition of Th17/Th2 cells which are capable to produce both IL-4 and IL-17 in patients with allergic asthma is consistent with the observation that different clinical phenotypes can coexist in the same patient. Different T-cell subpopulations are active in a different phase of bronchial asthma and the wide spectrum of clinical phenotypes is probably the expression of different cellular characters playing a role in respiratory inflammation.[30]

IL-22

IL-22 is a member of a group of cytokines called the IL-10 family or IL-10 superfamily. Firstly, it was recognized as a gene induced by IL-9 in T cells and MCs.[31,32] IL-22 can produce by activated DC, Th1, Th17 and especially Th22 cells. Other cells, such as cytotoxic T cells, γδT cells, natural killer (NK), natural killer T (NKT) cells and RORγt + ILCs, which include lymphoid tissue inducer (LTi) cells and ILCs producing IL-17 and IL-22, are reported to be able to secrete this cytokine as well.[14,33] Newly identified transcription factor Aryl hydrocarbon receptor is responsible for producing IL-22.[18] IL-22 initiates innate immune responses against bacterial pathogens especially in epithelial cells such as respiratory and gut epithelial cells. It has been reported that neither resting nor

activated immune cells express IL-22 receptor, thus, IL-22 do not have any effects on these cells.[31-34]

At the site of allergic airway inflammation, IL-22 is produced by Th17, Th22 and LTi-like cells and attenuates antigen-induced eosinophilic inflammation in airways, probably by altering the function of DCs and inhibiting IL-25 production from lung epithelial cells.[34-36] Another possibility is that other subsets of ILCs, including IL-22-producing RORγt-dependent ILCs, may be able to regulate ILC2 behavior and function.[13] Administration of anti-IL-22 antibody to different murine models of asthma, significantly enhances the secretion of IL-25 and IL-33 which are epithelial cell derived cytokines that stimulate Th2 responses, cellular infiltration and IL-13-responsive chemokine production.[13,34] Similarly, knocking out of IL-22 gene in a murine model of asthma was correlated with an increase in lung IL-33 and a more severe form of allergic inflammation and AHR.[13] When recombinant IL-22 administered intranasally, IL-25 expression decreased and eosinophil recruitment and AHR ameliorated.[13] These findings indicate that IL-22 may restrain antigen induced airway inflammation by suppressing cytokine and chemokine production from lung epithelial cells.[5,34] However, IL-22 was mostly described as a pro-inflammatory cytokine, as it elevates in autoimmune diseases, such as psoriasis, rheumatoid arthritis and inflammatory bowel disease.[7,31,37] Accordingly, the effect of IL-22 on airway inflammation in mice, have shown significantly higher airway hyper reactivity upon challenge with allergen.[5] Farfariello *et al*. reported that IL-22 mRNA is elevated in chronic severe asthma, allergic asthma and rhinitis.[38]

This paradox is mainly due to the fact that, IL-22 could also induce mucous cell metaplasia and has stimulatory effects on airway smooth muscle cells (ASMCs) in humans, resulting in airway narrowing.[19] It is shown that IL-22 receptor is expressed on both lung epithelial cells and ASMCs in humans. Therefore, IL-22 enhances the proliferation and migration of human ASMCs and smooth muscle cell hyperplasia while, reduces the apoptotic rate of ASMCs, raising the possibility that this cytokine may contribute to increasing airway smooth muscle mass and airway remodeling in asthma.[34,39] All together, these studies suggest that IL-22 plays inhibitory roles in the development of allergic airway inflammation in asthma patients, but it could stimulate airway remodeling if its secretion during the remission phase of allergic inflammation is uncontrolled.[34] More detailed studies are required to explain the precise function of IL-22 at different stages of asthma immunopathogenesis in order to provide an advantage for the development of a novel therapeutic approach against asthma.

IL-25

IL-25 (IL-17E), a newly identified cytokine, is produced mainly by Th2 cells, MCs and epithelial cells. IL-25 induces the expression of IL-4, IL-5, IL-9 and IL-13, resulting in inflammation mediated by eosinophils, increased IgE production and AHR in mice.[7,40,41] The enhanced Th2 differentiation mediated by IL-25 require signals induced by a heterodimeric receptor complex composed of both IL-17RB and IL-17RA.[42] During early T cell activation, IL-25 promotes expression of the NFATc1 and JunB transcription factors, which apparently increases the levels of initial IL-4 production, up-regulation of GATA-3 expression and enhanced differentiation towards Th2 cells. Therefore, IL-25 is an important factor regulating the initiation of innate and adaptive pro-allergic responses.[43] More recent studies has also shown that IL-25 is able to promote the differentiation and effector functions of Th2 cells through induction of IL-4 and has a significant role in the pathogenesis of asthma.[42,44] IL-25 mRNA level is increase in lung epithelial cells after exposure to common allergens and mice with force expression of IL-25 in lung epithelium displayed features of allergic asthma (eosinophilia, epithelial and goblet cells hyperplasia).[45] Injection of IL-25 to mice has been shown to be inductive for IL-4, IL-5 and IL-13 gene expression. The up-regulation of these cytokines could increase levels of IgE in blood, eosinophilia and also possibly will change pathological features in the respiratory tract such as eosinophilic infiltrations, increased mucus secretion and epithelial cell hyperplasia/hypertrophy.[45] Conversely, blockade of IL-25 decreases the airway inflammation and production of Th2 type cytokines in allergen-induced asthma models.[40,43,46] Xi Bao *et al*. have reported that IL-25 produced by epithelial cells has the potential to promote airway remodeling in asthma. It has been shown that elevated sputum IL-5, IL-17A and IL-25 level is associated with uncontrolled asthma and worse lung function.[40,47] On activation, eosinophils and basophils secrete bioactive IL-25 protein, which may enhance the allergic inflammation.[48] Hence, further researches may provide novel therapeutic approaches to target IL-25 and/or IL-17RB + for the treatment of allergic asthma.[44]

IL-33

Members of the IL-1 family play a critical role in the inflammatory responses. The best characterized members of this family include IL-1 α, IL-1 β, IL-1Ra, IL-18 and IL-33.[49,50] IL-33 is expressed by many cells and tissues, including the stomach, brain, spleen, heart, bronchial epithelial cells, fibroblasts,

smooth muscle cells, keratinocytes, macrophages and DCs.[51] The first component of the IL-33 receptor was originally identified in 1989 as a serum-inducible secreted protein from murine fibroblasts.[52,53] The receptor was termed ST2 (also called DRE4, Fit-1, or T1 in the older literature). ST2 was subsequently found to be preferentially expressed in Th2 cells and started to attract many researchers involved in allergy.[54] This receptor is highly expressed on MCs and is a highly selective marker of Th2 cells. Additional cells include macrophages, hematopoietic stem cells, NK cells, NKT cells, eosinophils, basophils, nuocytes and fibroblasts.[53,55,56]

ST2 receptor has been described as a negative regulator of Toll-like receptor (TLR)/IL-1 receptor signaling, but it also functions as an important effector molecule of Th type 2 responses. The binding of IL-33 to IL-33 receptor results in the recruitment of MyD88 to the Toll-interleukin-1 receptor (TIR) domain in cytoplasmic region of ST2, leading to the induction of inflammatory mediators by activating transcription factors such as nuclear factor kappa B (NF-κB) and activator protein-1 through interleukin-1 receptor-associated kinase, TNF receptor associated factor-6 and/or mitogen-activated protein (MAP) kinases, like other IL-1 family receptor or TLR activation.[51]

IL-33 in asthma

One of the most important cytokines responsible for Th2 immune deviation are IL-33.[57] Kurowska-Stolarska *et al*. reported that IL-33 induces the differentiation of IL-5$^+$ IL-4$^-$ CD4$^+$ Th cells from naïve CD4$^+$ T cells independently of IL-4, STAT-6 and GATA-3, which are important factors for the typical Th2 cell differentiation.[58] As we mentioned earlier, polarization toward Th2 cells by IL-33 involved activation of the NF-κB and MAP kinase pathways.[58] Similarly, differentiation of human CD4 + cells *in vitro* in the presence of IL-33 enhanced antigen-dependent IL-5 and IL-13 production.[56] In addition to influencing CD4 cellular differentiation, IL-33 is a chemoattractant for Th2 cells, recruiting Th2 cells to lymph nodes and tissue.[59] IL-33 can influence DC maturation and activity, leading to their enhanced expression of major histocompatibility complex-II, CD86 and IL-6. These activated DCs, when cultured with naïve CD4 + T cells, lead to their differentiation in a fashion characterized by production of IL-5 and IL-13.[60]

MCs and basophils play a central role in allergic inflammation and asthma through their release of a variety of mediators. Several studies have demonstrated that binding of IL-33 and subsequent signaling leads to expression of many pro-inflammatory cytokines, chemokines and lipid mediators, including CXCL8 (IL-8), IL-5, IL-13, IL-6, IL-1 β, TNF-α, GM-CSF, CCL2 (monocyte chemoattractant protein-1) and prostaglandin D_2.[61-64] The ability of IL-33 to stimulate MCs cytokine production depends in part on its ability to form a receptor complex composed of a combination of the ST2/IL-1RAcP heterodimer with c-Kit; the combination of signaling from the two receptors results in activation of multiple pathways leading to increased cytokine expression.[65] A similar synergy is observed with IL-33 and TSLP. Basophils are potential primary sources of IL-4, are also considered as the major target of IL-33. In comparison with Th2 cells and MCs, human and mouse basophils constitutively express ST2 at the relatively low level on their cell surface.[55,66,67]

IL-33 promotes maturation of CD34 + MCs precursors, which was accelerated with the addition of TSLP as measured by the acquisition of tryptase.[62] Using a murine model of cutaneous and systemic anaphylaxis, IL-33 was critical for the induction of anaphylaxis that occurred in a T-cell-independent and MCs-dependent manner in IgE-sensitized animals.[68] Thus, MCs sensitized with IgE expressed higher levels of ST2 than non-sensitized MCs, a step critical for the anaphylactic response.[68] Overall, IL-33 could influence MCs to influence allergic reactions and it is central to mite and peanut allergic sensitization.[69]

In presence of IL-33, eosinophils respond by increasing superoxide, eosinophil-derived neurotoxin, CXCL8, CCL2 and IL-6 production.[55,70,71] In addition, IL-33 promotes eosinophil survival, although not as effective as IL-5 and increases the cell surface expression of intercellular adhesion molecule-1.[70,71] In lung tissue, higher expression of IL-33 is detected from asthmatics, its expression does not respond to classic anti-inflammatory drug, thus reinforcing its relevance as a potential therapeutic target to treat asthma.[72,73] A recent study indicates that IL-33 is a relatively steroid-resistant mediator that promotes airway remodeling in patients with severe therapy-resistant asthma and is an important therapeutic target.[74]

CONCLUSION

Based on the above study it can be concluded that allergic asthma is a chronic inflammatory disease of the airways caused by dysregulated immune responses to allergens. Despite compelling evidence that Th2-mediated immune responses orchestrate the pathogenesis of asthma diseases, the mechanisms underlying their initiation remain elusive.[44] New advances regarding to the interaction among immune and inflammatory cells through cytokines, particularly the expansion of the knowledge about reciprocal regulation and counterbalance among subsets of Th1,

Th2, Th9, Th17, Th22, T follicular helper cells and regulatory T cells, as well as B-cells, NK cells, DCs and ILC subsets, offers new possibilities for advanced immune interventions.[36] However, the discovery of these cell subtypes and the roles of their cytokines in inflammatory diseases may add an additional layer of complexity to the understanding of the pathogenesis of allergic diseases. Finally, better understanding of the immunopathology of allergic inflammation in recent years has offered novel targets for immunotherapy of asthma, particularly in its severe form.

ACKNOWLEDGMENT

The research was funded by a grant (#188084) from the Isfahan University of Medical Sciences, Isfahan, Iran.

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Source of Support: The research was funded by a grant (#188084) from the Isfahan University of Medical Sciences, Isfahan, Iran, **Conflict of Interest:** None declared.