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Relationship between various cytokines implicated in asthma

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ABSTRACT

Asthma is a complex disorder involving immunologic, environmental, genetic and other factors. Today, asthma is the most common disease encountered in clinical medicine in both children and adults worldwide. Asthma is characterized by increased responsiveness of the tracheobronchial tree resulting in chronic swelling and inflammation of the airways recognized to be controlled by the T-helper 2 (Th2) lymphocytes, which secrete cytokines to increase the production of IgE by B cells. There are many cytokines implicated in the development of the chronic inflammatory processes that are often observed in asthma. Ultimately, these cytokines cause the release of mediators such as histamine and leukotrienes (LT), which in turn promote airway remodeling, bronchial hyperresponsiveness and bronchoconstriction. The $CD4^+$ T-lymphocytes from the airways of asthmatics express a panel of cytokines that represent the Th2 cells. The knowledge derived from numerous experimental and clinical studies have allowed physicians and scientists to understand the normal functions of these cytokines and their roles in the pathogenesis of asthma. The main focus of this review is to accentuate the relationship between various cytokines implicated in human asthma. However, some key findings from animal models will be highlighted to support the discoveries from clinical studies.

1. Introduction

The number of T-cell subsets has expanded over the years. Initially, there were two main subsets of T-helper (Th) cells i.e. Th1 and Th2; based on the cytokines produced by these cells [1]. The undifferentiated Th cells (Th0) cells secrete both Th1 and Th2 cytokines whilst Th1 cells secrete IL-2, Interferon-gamma (IFN-γ), Tumor Necrosis Factor-alfa (TNF-α), IL-12 [1]. The Th2 cells secrete cytokines such as Interleukin IL-4, IL-5, IL-9 and IL-10 and IL-13 [1,2]. The Th1 cells are reported to play a key role in the pathogenesis of autoimmune diseases such as insulin-dependent diabetes mellitus (IDDM) [51], experimental allergic encephalomyelitis (EAE) [51], rheumatoid arthritis(RA) [119], whilst the Th2 cells are implicated in the pathogenesis of atopic and allergic diseases [1,3].

Several new Th subsets have been discovered in the last two decades; such as Th3 [148], Th9 [144], Th17 [163], Th22 [145,149] and Th25 [150]. The major cytokines produced by Th3 cells include transforming growth factor-beta (TGF-β) [38], IL-4 [76], IFN-γ [94] and IL-10 [148] whilst Th9 secrete only IL-9 [144]. Th17 cells produce IL-17A [156], IL-17F [159], IL-21 [145], IL-22 [164], TNF-α [125] and IL-6 [146,147] whilst Th22 cells secrete IL-13 [142], IL-22 [164] and TNF-a [145,149]. Recently, another Th subset, Th25 was discovered [150]. The Th25 cells produce mainly IL-25, also known as IL-17E [150]. The possible roles of the Th subsets and their cytokines in the pathogenesis of asthma is illustrated in Fig. 1.

When a Th cell is activated, it will respond to the stimuli and

Abbreviations: Th, T helper; IgE, Immunoglobulin; LT, leukotrienes; IL, Interleukin; IFN-γ, Interferon-gamma; TNF-α, Tumour Necrosis Factor-alfa; IDDM, Insulin-dependent diabetes mellitus; EAE, Experimental allergic encephalomyelitis; RA, Rheumatoid arthritis; mRNA, messenger RNA; BAL, Bronchoalveolar lavage; EGF, epidermal growth factor; FGF, Fibroblast growth factors; GM-CSF, granulocyte-monocyte colony stimulating factor; IGF, Insulin-like growth factor; MCP, macrophage chemotactic protein; MIP, macrophage inflammatory protein; RANTES, regulated on activation, normal T-cell expressed and secreted; PDGF, platelet-derived growth factor; SCF, stem cell factor; TGF, transforming growth factor; AHR, Airway hyper-responsiveness; TCR, T-cell receptor (TCR); LAK, lymphokine-activated killer; ICOS, Inducible T-cell COStimulator; Af, *Aspergillus fumigates*; SNP, Single Nucleotide Polymorphism; APC, Antigen-presenting cells; COPD, chronic obstructive pulmonary disease; TARC, Thymus and activation-regulated chemokine

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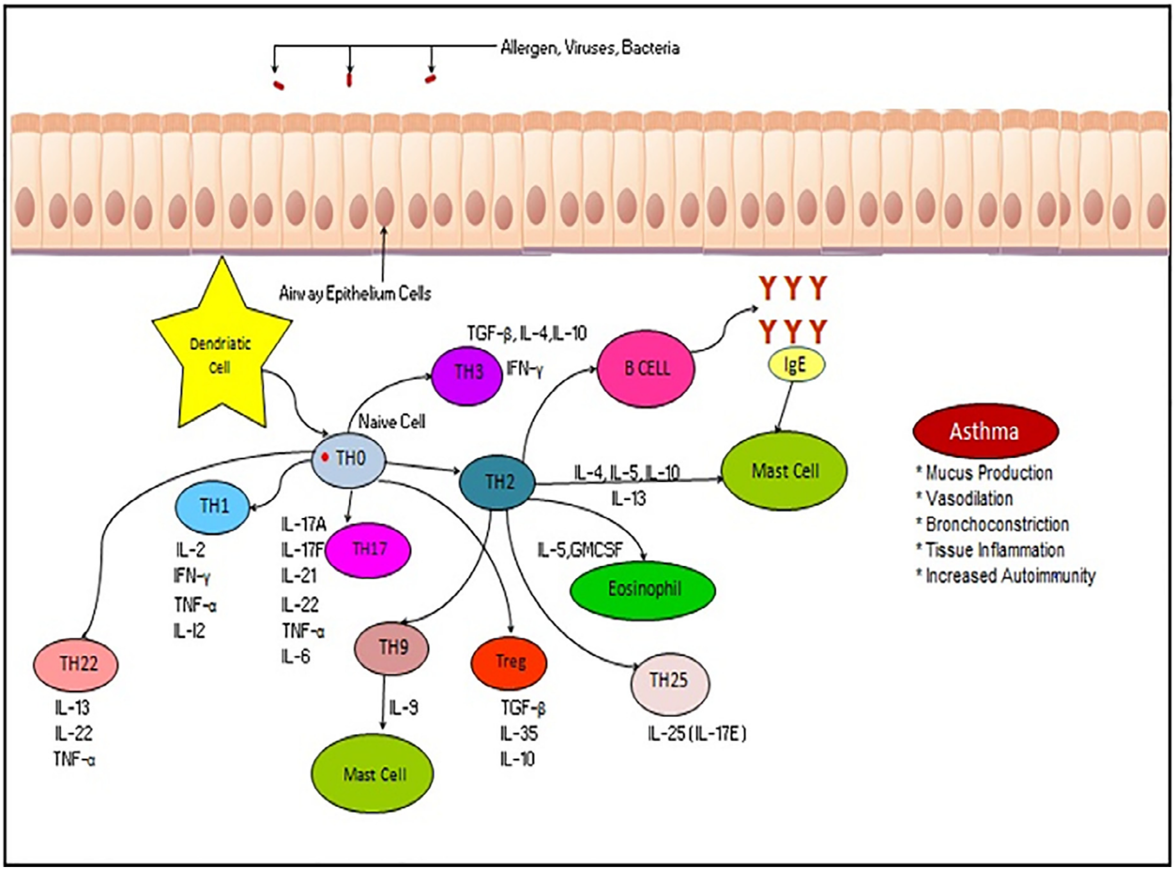

Fig. 1. Role of CD4 + T helper subsets in asthma pathogenesis. [IL: Interleukin; IFN: Interferon; TGF: Transforming Growth Factor; TNF: Tumor Necrosis Factor; GMCSF: Granulocyte-Monocyte Colony Stimulating Factor; TH: T helper].

Table 1
Cytokine Groups.

Groups	Cytokines	References
Lymphokines	• IL-2, IL-3, IL-4, IL-5, IL-13, IL-15, IL-16, IL-17	[1,13,68,75]
Pro-inflammatory cytokines	• IL-1,TNF, IL-6, IL-11, GM-CSF, SCF	[96,99,101]
Anti-inflammatory cytokines	• IL-10, IL1rα, IFN-γ, IL-12, IL-18	[31,36,94]
Chemotactic cytokines (chemokines)	• RANTES, MCP-1, MCP-2, MCP-3, MCP-4, MCP-5, MIP-1α, eotaxin, IL-8	[97,116,118]
Growth factors	• PDGF, TGF-β, FGF, EGF, IGF	[38,41,42]

[EGF: epidermal growth factor; FGF: Fibroblast growth factors; GM-CSF: granulocyte-monocyte colony stimulating factor; IGF: Insulin-like growth factor; IFN: interferon; IL: interleukin; MCP: macrophage chemotactic protein; MIP: macrophage inflammatory protein; RANTES: regulated on activation, normal T-cell expressed and secreted; PDGF: platelet-derived growth factor; SCF: stem cell factor; TGF: transforming growth factor; TNF: tumour necrosis factor].

undergo clonal expansion i.e., proliferate or "expand." The clonally expanded cells produce appropriate cytokines that are used to communicate with other cells and to initiate an appropriate immune response [151]. There is growing evidence to support a role for Th2 cells and cytokines in the pathogenesis of asthma [4,16,113]. Several studies have found elevated mRNA expression of Th2 cytokine genes as well as increased levels of Th2 cytokines in bronchoalveolar lavage (BAL) cells [4,5,112], bronchial biopsies [16,44,80] and blood samples [5,52,68] from asthmatic patients. In addition, some cytokines identified in asthmatic subjects have been shown to be associated to the severity of inflammation in these patients [21]. Interleukin-4 and IL-13 are two Th2 cytokines reported to be strongly associated with the pathogenesis of asthma [10,14]. For instance, airway inflammation was reported to be a common feature in transgenic mice which over-express Th2 cytokines [31]. However, there are also studies, which have found that IL-4 is not essential for the development of asthma in humans [13,15].

The prevalence, morbidity and mortality rates of asthma appear to be increasing, especially in industrialized countries [9,22]. It has been proposed that asthma might be preventable if the patients at risk are identified early, so that they could take the correct precautions before the onset of this disease [9]. Most studies have focused on the roles of cytokines, Th2 cells as well as IgE on the pathogenesis of asthma. However, much remains to be discovered in order to understand the exact mechanisms that can explain the pathogenesis of asthma. Polymorphisms in cytokine genes have been reported to have a profound effect on cytokine production and plasma levels of cytokines by regulating transcriptional elements [67].

1.1. Cytokines

Cytokines are a vast group of proteins, peptides or glycoproteins secreted by specific cells of the immune system [4]. These are extracellular signaling molecules that have the ability to mediate and regulate immune response, inflammation and haematopoiesis [4]. Cytokines can be categorized into five functional groups (Table 1). In addition, cytokines can have autocrine or paracrine effects [17].

Cytokines with autocrine effects bind to cytokine receptors on the cell that produces the cytokine [17]. In contrast, cytokines with paracrine effects are produced by one cell-type, but it binds to cytokine receptors of other cells [17]. The paracrine cytokines can stimulate synthesis of other cytokines that supports the stimulatory effects of the first cytokine; thereby initiating an increase in the effects [67].

1.2. Cytokines and asthma

Numerous biopsy studies in asthma research have reported increased expression of many cytokines associated with asthma. Currently, data on the relationship between cytokines and asthma relies on both human studies and interventional studies using animal models [66].

Airway hyperresponsiveness (AHR) is one of the hallmark features of asthma [59,120]. Other features of asthma include eosinophilic inflammation, mucus hypersecretion, reversible airway obstruction and subepithelial fibrosis [6,10]. Leukocytes such as basophils, eosinophils, mast cells and Th2 cells contribute to the development of inflammatory responses in asthma [8,20,22]. Asthma patients can develop airway obstruction. The main factors that can cause airway obstruction are AHR and mucus hyper secretion [7].

Genomic research studies have shown that occurrence of asthma can be linked to various genes located on human chromosome 5q31-33 [54,55]. Coincidently, it was found that the genes that code for many of the Th2 cytokines are located as a cluster on the same chromosome i.e., chromosome 5q [62]. This cluster contains genes that encode for (IL-3 [143], IL-4 [61], IL-5 [143], IL-9 [61], IL-13 [142], β-chain of IL-12 [57] and granulocyte-macrophage colony stimulating factor (GM-CSF) [142,143]. Some of the genes located on human chromosome 5q31-33 are also linked with increased levels of serum IgE and bronchial hyperreactivity (BHR) [56,60]. It should be emphasized here that asthma often presents with elevated levels of circulating IgE in the blood [180]. Several studies have reported a link between total serum IgE levels and markers at chromosome 5q31-33; for instance, in Amish [58], Dutch [62] and UK [63] populations.

A link between BHR and various genes located on chromosome 5q31-q33 was also subsequently established [49]. There were also studies reporting lack of evidence to support a genetic linkage between clinical asthma and atopy with genes on chromosome 5q31-q33 [64]; for instance, in an Australian [56] and Finnish [65] populations. However, in 1997, Noguchi et al. [61] provided statistical evidence to demonstrate a link between asthma, IL-4 and IL-9 levels in a Japanese population [61]; suggesting that there might be a link between clinical asthma or atopy with genes on chromosome 5q31-q33.

Allergic asthma is characterized by airway inflammation and hyper reactivity [6]. These clinical features are induced by cytokines produced by $CD4^{+}$Th2 cells such as IL-4, IL-5, IL-9, IL-13, which are collectively known as Th2-cytokines [31].

1.2.1. Interleukin 2

Interleukin-2 plays a crucial role in T-cell activation [68]. This cytokine is generally produced by T-cells that are activated by specific antigen [71]. It can also be produced by eosinophils and airway epithelial cells [68,69]. This cytokine is also involved in other biological processes such as T-cell receptor (TCR)-induced apoptosis in T-cells [137], development of lymphokine-activated killer (LAK) cells [138] and activation of macrophages [139]. It is also implicated in promoting the proliferation and differentiation of T-cells [71], B-cells [70,141] and natural killer (NK) cells [140].

Increased IL-2 levels were reported in the BAL from asthma patients [72,109,110]. In addition, there was also higher expression of *IL-2* mRNA in lymphocytes isolated from BAL obtained from atopic patients with bronchial asthma [111]. A clinical study involving steroid-resistant and steroid-sensitive asthmatics found that BAL cells from steroid-resistant asthmatics expressed higher levels of *IL-4* mRNA compared with steroid-sensitive asthmatics [73].

1.2.2. Interleukin 3

Interleukin 3 is a pluripotential haematopoietic growth factor that acts together with other cytokines such as GM-CSF to promote the development of erythroid progenitors [75], megakaryocytes [75], neutrophils [74], eosinophils [20], basophils [20], mast cells [20] and monocytes [75]. It is generally produced by activated Th cells [136] and mast cells [75]. IL-3 also reported to enhance survival of eosinophils in BAL fluids of mild allergic asthmatics [135]. In addition, IL-3 was reported to cause an increase in the number of mast cells and eosinophils around the airway in rats following an antigenic challenge [171].

There are some single nucleotide polymorphism (SNP) reported in the human *IL-3* gene [172]. A genetic association study reported decreased risk of asthma and atopy with SNP at IL3 + 79 T > C (Ser27Pro) locus [172]. This study found a dominant and protective genetic effect on the risk of asthma development in non-atopic subjects compared to atopic subjects by this gene [172].

1.2.3. Interleukin 4

Interleukin 4 is a multi-functional Th2 cytokine that plays a key role in the development of Th2 cells and other biological activities such as promote isotype switching from IgM or IgG to IgE [79] and induce production of IgE by B-cells [92]. This cytokine has been described to be the main cytokine responsible for pathogenesis of allergic responses [134] as it has been shown that IL-4 can induce production of mucus and hyperplasia of goblet cells [76]. Nevertheless, IL-4 plays a key role in stimulating airway changes [27,66,105] and is widely accepted as a vital cytokine involved in the development of allergic inflammation by stimulating lg-E dependent mast cell activation [77,78,92]. Binding of IL-4 to the IL-4 receptor (IL-4R) will initiate a signaling pathway through the JAK 1 and JAK 3 tyrosine kinase pathways [11], consequently induce phosphorylation of tyrosine residues and activate the signal transducer and activator of transcription factor-6 (STAT 6) [10,11]. Once STAT 6 is activated, it forms a homodimer and translocate to nucleus and bind to specific sequences in the promoters of a number of genes including genes that promote isotype switching to IgE [10,12].

Interleukin-4 also plays a role in inducing germline transcription in B-cells to synthesize IgE [12]. Although IgE can contribute to some aspects of asthmatic pathophysiology [12], some studies have found that AHR and inflammation can fully manifest without IgE i.e., these are IgE-independent responses [23,24]. For instance, AHR and inflammation have been reported in IgE-deficient mice, which strongly support this proposal [23]. The IgE-deficient mice can be sensitized intra-nasally with extracts from *Aspergillus fumigatus* similar to what was observed in wild-type mice; where both mice developed eosinophilia in the BAL and lung parenchyma [23]. Furthermore, active anaphylaxis was also observed in IgE-deficient mice [26]. Another evidence of this proposal is that mice that lack B-cells (i.e., unable to produce antibodies) are still able to develop allergic eosinophil-rich inflammation in the lungs and airway [25]. These findings suggest that B-cells may not be important for antigen presentation in asthma and that clinical features of asthma can develop in the absence of immunoglobulins.

It was demonstrated that Th2 responses could still be observed in IL-4 knockout (IL-4 −/−) mice [6]. This could be because the function(s) of IL-4 is reported to overlap with IL-13 [6], another Th2 cytokine. Hence, IL-13 may be able to compensate the loss of action of IL-4 in the IL-4 knockout mice. It is reported that IL-4 and IL-13 work through the STAT 6 pathway [11]. So, in STAT 6 knockout (STAT 6 −/−) mice, there was a complete obliteration of Th2 responses [6,10]. Few researchers have proposed that IL-13 plays a more important role compared to IL-4, in the pathogenesis of asthma [34]. This is mainly due to the observations that eosinophilia, mucus production and AHR can still be induced without IL-4 [13,18]. In IL-4 deficient mice, eosinophil recruitment was impaired but response to allergen was not abolished [13]. In addition, blocking the action of IL-4 during allergen sensitization was shown to prevent development of asthma [15]. However, blockade of IL-4 before or during antigen challenge failed to inhibit AHR [15]. These observations strongly suggest that IL-4 is important for initial T-cell differentiation but is redundant for the development of asthma.

In terms of gene polymorphisms, it was reported that there was an association between SNP in the human *IL-4* gene (G/C 3′-UTR) and bronchial asthma severity in a Russian population [173]. Interestingly, SNP at allele R576 of the human *IL-4 receptor-alpha* (*IL-4Rα*) gene is reported to be associated with atopy [50]. Furthermore, mutations in the *IL-4Rα* gene were found to predispose an individual to atopy due to alterations in the signaling functions of this receptor [50].

1.2.4. Interleukin 5

Interleukin-5 produced by T-lymphocytes [1] is a major cytokine involved in the development of eosinophilia *in vivo* [106,107,132]. Increased expression of *IL-5* mRNA was demonstrated in $CD4^+$ T cells isolated from airways of asthmatics [133]. There are two main signaling pathways of IL-5 in eosinophils namely, the tyrosine kinases Lyn, Syk and JAK2 and the Ras-MAPK and JAK-STAT pathways [81]. Transgenic mice overexpressing IL-5 in lung epithelial cells showed raised levels of IL-5 in BAL fluid and serum, which displayed baseline AHR [84]. Administration of exogenous IL-5 was shown to affect eosinophilia in guinea pig airways [28,114].

A notable association of allele C-703T IL5 with bronchial asthma was reported in Russians families [173]. In addition, the IL-5 levels were selectively raised in BAL from symptomatic asthmatics [82,108]. Furthermore, an increase in IL-5 levels was observed in induced sputum following allergen challenge of asthmatic patients [83].

1.2.5. Interleukin 9

Interleukin 9 is reported to be a cytokine with pleiotropic actions on allergic mediators such as mast cells [86], eosinophils [130], B-cells and epithelial cells [131] as well as stimulate mucus production in asthma [85]. The lungs from IL-9 transgenic mice showed selective expression of IL-9 and a large infiltration by eosinophils and lymphocytes [86] with increased numbers of mast cells within the airway epithelium [86]. It has been proposed that IL-9 might be a good target for therapeutic interventions in asthma [57] as it has been reported to regulate BHR in mice [87]. Some researchers have also proposed that the IL-9 receptor (IL-9R) to be a potential therapeutic target for asthma [88].

1.2.6. Interleukin 13

Interleukin 13 is Th2 cytokine, a critical mediator of allergic asthma [19]. This is because IL-13 can induce expression of CD23 on purified human B cells [91], which acts as a switch factor that directs synthesis of IgE [92], similar to the actions of IL-4 [92]. Elevated levels of *IL-13* mRNA were also reported in the bronchial mucosa of asthmatic subjects [30]. Other researchers have reported increased expression of *IL-13* mRNA in airway mucosa of patients with atopic and non-atopic asthma [90]. It has been shown that allergy asthma is related with down regulation of *IL-12* mRNA expression, and an up regulation of *IL-13* mRNA expression due to steroid therapy [89]. Other studies have shown that pulmonary expression of *IL-13* gene can cause eosinophilic inflammation, deposition of Charcot-Leyden like crystals [6], mucus hypersecretion, sub-epithelial airway fibrosis, airway obstruction, AHR and production of eotaxin [6].

The major role played by IL-13 in mediating the effector phase of was demonstrated using a mouse model of asthma [7]. In this study, the authors administered a recombinant fusion protein consisting of soluble human IL-13 receptor-alpha 2 (IL-13Rα2) Fc region of antibody to mice sensitized to ovalbumin (OVA) and compared their response with mice that received the control protein [7]. Administration of the IL-13Rα2-Fc recombinant protein reversed the allergen-induced AHR as the soluble receptor was able to bind to the murine IL-13 [7]. The authors also carried out similar studies using mice that were deficient of the *recombinase activating gene* (*RAG*) i.e. *RAG−/−* mice. Administration of IL-13 to non-immunized *RAG−/−* mice also resulted in asthma [7]. It should be noted that *RAG−/−* mice lack B and T cells. These findings strongly suggest that IL-13 can induce asthma independent of T-cells [7]. Interleukin-13 can induce production of 15-lipoxygenase (15-LOX) an enzyme which catalyses' production of 15-hydroxy eicosatrienoic acid [52]. The 15-hydroxy eicosatrienoic acid involved in mucus production [52] and bronchoconstriction [52]. Hence, the present literature appears to support the idea that IL-13 can indirectly result in AHR.

Interestingly, polymorphism in the promoter of the human *IL-13* gene at position −1055 (C to T exchange) reported to increase binding of nuclear proteins to this region, was observed in allergic asthma patients [174].

1.2.7. Interleukin 12

Interleukin-12 is a cytokine that plays a key role in Th1/Th2 differentiation during primary antigen presentation [93]. This cytokine promotes differentiation of $CD4^+$Th0 cells to $CD4^+$Th1 cells, which produce cytokines like IL-2, TNF-α and interferon-gamma (IFN-γ) [19]. The Th1 and Th2 cells balance the responses mediated by each other by reciprocal regulation of each other's functions [51]. Antigen-presenting cells (APC) such as dendritic cells and macrophages are the main producers of IL-12 [94]. The combined action of IL-12 and IL-18 is reported to induce production of IFN-γ [94] and inhibit IL-4 dependent IgE synthesis [94]. Nevertheless, IL-12 is reported to have direct and indirect inhibitory effects on Th2-mediated allergic airway inflammation [31]. After a single antigenic challenge, it was shown that IL-12 can inhibit AHR and pulmonary inflammation [32]. Consequently, administration of IL-12 inhibited expression of Th2 cytokine genes in mice [32].

Studies have also shown that IL-12 can induce production of IL-10 from $CD4^+$ and $CD8^+$ T-cells [36]. However, the ability of IL-12 to counterbalance Th2-mediated allergic airway inflammation does not require IL-10 [31]. In atopic and asthmatic individuals, there is overproduction of IL-13 and impaired production of IL-12 [34]. These findings suggest that IL-12 could have beneficial effects on asthmatic patients. However, IL-12 cannot be used to treat asthma as there is concern that it may trigger Th1-mediated inflammatory disorders as IL-12 can induce Th1- immune responses, as well inhibiting development of Th2 cells [35]. Furthermore, Th1 cells can cause airway inflammation but not airway hyperreactivity [33]. Thus, reversal of TH2 responses alone will not benefit asthmatic patients. Clinical studies using recombinant IL-12 have shown some effects but these are not promising enough to support the use of recombinant IL-12 as a treatment approach for asthma [176].

In terms of SNP in the IL-12 and IL-12 receptor genes, it was reported that there was an association with SNP in the promoter of *IL-12 receptor beta 1* (*IL12RB1*) gene and increased risk of atopic dermatitis and other allergic phenotypes in a Japanese population [175].

1.2.8. Interleukin 10

Interleukin 10 is a cytokine with anti-inflammatory properties; as such it offers therapeutic assurance for the management of asthma and allergy [128]. The main sources of IL-10 are T-cells, which promote distribution of this cytokine at the sites of inflammation to produce immune responses [129]. Interleukin-10 can inhibit antigen-induced cellular recruitment into the airway of sensitized mice [37]. Administration of recombinant murine IL-10 (rm IL-10) with ovalbumin (OVA), inhibited eosinophilia and neutrophilia airway of sensitized mice [37]. In contrast, *in vivo* neutralization of IL-10 enhanced cellular recruitment in the BAL fluid [37]. However, these effects are not observed if IL-10 is administered one hour after antigen challenge [37]. Whereas, administration of IL-12 to allergen-challenged IL-10 knockout mice (IL-10−/−) resulted in a complete inhibition of the airways due to influx of eosinophils [31]. In addition, there was a change in cytokine profile from Th2 to Th1 in these animals. However, inflammation was observed despite down regulation of Th2 responses; indicating that in the absence of IL-10, administration of IL-12 can also cause unwanted inflammation.

1.2.9. Interleukin 17

The Th17 cells produce the IL-17 family of cytokines, which include IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (IL-25) and IL-17F [156]. When production of IL-17 compared between atopic and non-atopic asthmatics together with control subjects, it was shown that IL-17 production in response to exposure to extract from *Dermatophagoides farinae* was significantly induced only in atopic asthmatics [157]. In addition, asthmatics with elevated sputum IgE are reported to have higher IL-17 levels compared to asthmatics with low sputum IgE levels [158].

IL17-A has been shown to have direct influence on contractile responses of airway smooth muscle cells [162]. Most recently, it was reported that IL-17A plays an important role in asthmatic exacerbation with up regulation of Th2 and other cytokines [179]. Other studies have shown that IL-17F plays an imperative role in the asthma pathogenesis [160,161,178] as it can induce significant pulmonary neutrophilia in mice [161]. Interestingly, a variant of IL-17F (His161Arg) is reported to control the risk of asthma [159].

1.2.10. Interleukin 22

Human Th1, Th17 and Th22 cells can produce IL-22 [164]. It is possible to use plasma levels of IL-22 as a sign of asthma severity [163]. There is evidence to suggest that IL-22 could regulate the expression of the pro-inflammatory cytokine, IL-17A in allergic mice [165]. Increased numbers of immunoreactive cells that produce IL-22 are also reported in the bronchial mucosa of patients with chronic obstructive pulmonary disease (COPD) [166].

1.2.11. Interleukin 23

Interleukin-23 is a novel member of the IL-12 cytokine family with two subunits p40 and p19 [167]. Production of IL-23 increased in OVA-induced murine asthma models through IL-17 secretion and Th2 polarization [168]. The importance of IL-23R in allergic asthma was demonstrated using a mice model [169]. In a study carried out in Iran, there was a significant rise in IL-23 serum levels in children with persistent asthma compared to healthy children in Iran [170].

1.2.12. TGF-beta

The TGF-β belongs to a large family of cytokines that consist of TGF-β1, activins, inhibins, bone morphogenetic proteins and mullerian-inhibiting substance [38]. These growth factors are produced in large quantities by eosinophils, fibroblasts, and epithelial cells [57]. Most of the cytokines in the TGF-β family are reported to be involved in the pathogenesis of asthma [38]. Apart from asthma, TGF-β is also implicated on other biological processes such as cell proliferation and differentiation [43], wound healing [126], eosinophil development [45] and matrix production [127]. Large quantities of TGF-β found in BAL fluid of asthma patients produced by eosinophils [44,45]. In addition, a higher number of airway mucosal eosinophils expressing TGF β1 mRNA and protein were found to correlate with the severity of asthma [95]. These findings suggest that TGF- β1 may plays a role to regulating the proliferation of immune cells and their recruitment into tissues.

Signaling of TGF-β from cell membrane to nucleus is reported to take place through SMAD proteins [41]. Binding of TGF-β to its receptor (TGF-β R) activates the phosphorylation of SMAD 2 and SMAD 3 [41]. Phosphorylated SMAD 2 and 3 will form complexes with SMAD 4 and translocate to nucleus, this initiates transcription of target genes [41]. The TGF-β/SMAD signaling pathway is reported to be important in the regulation of inflammatory responses in asthma [39,42]. Genes like SMAD and SMAD 7 can inhibit transcription of TGF-β [39]. Mice that lacked expression of TGF-β1 died early and pathological examination indicated that the lungs and other organs from these animals were infiltrated by lymphocytes and macrophages [40]. However, antigen-induced inflammation was enhanced in transgenic mice that express SMAD 7 [39]. Consequently, there was high production of Th1 and Th2 cytokines in these mice [39]. These findings suggest that SMAD 7 blockade of TGF-β may facilitate differentiation of Th0 cells into Th1 and Th2 cells.

1.2.13. Tumor necrosis factor-alpha

Tumor necrosis factor-alpha (TNF-α) is a member of the TNF family [125]. There are two forms of TNF i.e. TNF-α and TNF-β [125]. Cells that produce TNF-α include T-lymphocytes, macrophages, epithelial cells and mast cells [96]. Production of TNF-α by macrophages can be strongly enhanced by cytokines such as IL-1, GM-CSF and IFN-γ [96]. It has been reported that TNF-α stimulates airway epithelial cells to produce cytokines such as IL-8, GM-CSF and RANTES [96,97]. In addition, TNF-α was reported to increase airway responsiveness in rats [100]. Increased expression of TNF-α was observed in blood monocytes and alveolar macrophages following IgE-mediated triggering enhanced by IFN-γ [99]. Other researchers have shown that alveolar macrophages of asthmatics produce TNF-α upon exposure to allergens [98]. These findings reveal the potential importance of TNF-α in the pathogenesis and control of asthma.

1.2.14. Granulocyte-macrophage colony stimulating factor

The granulocyte-macrophage colony stimulating factor, a cytokine that is also known as colony stimulating factor 2 (CSF2) produced by many cells in the airway such as macrophages, T Lymphocytes, mast cells, eosinophils, fibroblasts, endothelial cells and epithelial cells [124]. Studies using cultured bronchial epithelial cells from asthmatics showed that GM-CSF could be involved in chronic eosinophilia and airway remodelling [102]. The culture media harvested from bronchial epithelial cell culture could increase viability, superoxide ability and leukotriene C4 production by cultured eosinophils [102]. These effects are abolished when a neutralizing antibody to GM-CSF was used [102]. Increased expression of GM-CSF was also observed in the epithelium of bronchial biopsy specimens from asthmatics [103], T-lymphocytes and eosinophils after endo-bronchial challenge with allergen [104]. However, phase II clinical trials involving severe asthma patients using human anti-GM-CSF antibody (KB003) showed little success [177]. More work needs to be carried out using this approach to identify the best time that this therapeutic agent should be administered to benefit the asthma patients.

1.3. Other genes associates with asthma

A growth factor termed "regulated on activation, normal T-cell expressed and secreted" (RANTES) is a chemokine, which is reported to play an important role in asthma [123]. RANTES is 8–10 kDa protein [122] with conserved N-terminal cysteines. There are four subclasses of RANTES, namely C, CC, CXC, and CX_3C [117]. The gene encoding RANTES is usually expressed in IL-2 dependent T-cell lines [115]. Generally, RANTES is an effective eosinophil chemoattractant that is 2 to 3 times more potent than macrophage inflammatory protein-1α (MIP-1α) [29,116]. Increased expression of *membrane cofactor protein* (MCP-3) mRNA and RANTES have been reported in the airway submucosa of patients with allergic and non-allergic asthma [118].

Other associated member of the Immunoglobulin (Ig) superfamily such as the Inducible T-cell COStimulator (ICOS) is also reported to play a significant role in allergy and asthma [121]. ICOS is an inducible costimulatory protein expressed on activated T-cells [46]. This protein is a member of CD28 and cytotoxic T-lymphocyte associated protein 4

(CTLA 4) family [47], implying that it is essential for activation and function of T-cells. It is also reported to play an important role in generating IL-4 producing cells [46,47]. Mice that were deficient in ICOS i.e., ICOS knockout (ICOS-/-), were more susceptible to experimental autoimmune encephalomyelitis (EAE) [47] and were unable to produce ovalbumin-specific IgG1 and IgE antibodies [46–48]. Inhibition of ICOS pathway might be a potential therapeutic target which should be considered for treatment of asthma [121].

Several researchers have suggested that thymus and activation-regulated chemokine (TARC) could be a useful inflammatory marker for chronic asthma [152,153] as it was found that plasma TARC levels were significantly higher in asthmatic children compared to healthy controls [154]. Another study also confirmed these findings as they showed that sputum and serum samples of asthmatic patients had increased TARC levels compared to healthy subjects [155]. Hence, current data appear to support a critical role for TARC in promoting Th2 immune responses as it is able to recruit more Th2 cells into inflammatory sites.

1.4. Conclusion

Undoubtedly, there is a huge amount of information gathered over the past years on the importance of cytokine networks in the pathogenesis of asthma. The current literature supports a clear role for IL-4 in initiating immune responses that are involved in pathogenesis of allergic asthma. However, IL-4 is not the sole cytokine that plays this role as evidence is also showing that IL-13 can function similarly, as both IL-4 and IL-13 can play a role in development of AHR [53]. However, it should be noted that the initial T-cell activation and differentiation may not take place in the absence of IL-4 whilst IL-13 appears to be an essential mediator for the effectors phase of asthma. The importance of other cytokines such as IL-5, TGF-β1, IL-12, TNF-α, RANTES, TARC and ICOS in the pathogenesis of asthma are becoming more apparent. Some of these cytokines have the potential to be developed as a novel therapeutic target. However, more fundamental and experimental studies have to be carried out before we can embark on a clinical study. Further studies on asthma will help to manage the pathways involved in asthma aetiology. Thus, with a combined teamwork among researchers in pathophysiology, epidemiology and pharmacogenomics, this century holds potential for a better understanding and management of asthma.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.humimm.2019.04.018.

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