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The role of IL-13 gene polymorphism in the exacerbation of Asthma severityKabir, I.M.¹, Ibrahim, S.², Badamasi, I. M.³, Ibrahim H.S.⁴, Bala J.A.¹, Aliyu I.A.^{1*}.

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Summary

Asthma is a chronic airway inflammatory disorder characterized by persistent airway inflammation, obstruction, and hyper-responsiveness. The role of cytokines, particularly Interleukin-13 (IL-13), in the pathogenesis of asthma has been extensively studied. IL-13 is involved in Th2 inflammation and has been identified as a possible therapeutic target in asthma treatment. This review focuses on the role of IL-13 gene polymorphism in exacerbating asthma severity. IL-13 is responsible for various key pathological features of asthma, including airway hyper-responsiveness, mucus production, and induction of allergic responses. The release of IL-13 is triggered by exposure to allergens, which activate dendritic cells and promote the differentiation of Th2 cells. IL-13 interacts with its receptors, IL-13R α 1 and IL-13R α 2, and initiates signaling pathways involving JAK1, JAK3, and STAT6. Biomarkers such as total serum IgE, exhaled nitric oxide (FeNO), airway epithelial proteins, blood eosinophil counts, and sputum eosinophil counts have been used to assess IL-13 activity and predict treatment response. Polymorphisms in the IL-13 gene and its receptors have been associated with asthma susceptibility, severity, and response to therapy. Understanding the role of IL-13 gene polymorphism in asthma can provide insights into disease mechanisms and contribute to personalized treatment approaches. Further studies are needed to elucidate the association between IL-13 polymorphisms, asthma severity, and response to inhaled corticosteroids (ICS).

Keywords: Asthma, IL-13, gene polymorphism, airway inflammation, biomarkers, IL-13 receptors, signaling pathways.

Introduction

Asthma is a chronic airway inflammatory disorder characterized by persistent airway inflammation, airway obstruction, hyper responsiveness and remodeling (Hill & Wood, 2009). It affects over 300 million people globally (Global Initiative for Asthma (GINA), 2017). Exposure to destructive stimuli such as irritants, microbial pathogens or toxic cellular elements triggers inflammatory responses (Brennan & Bowie, 2010). This entails a cascade of activities involving various inflammatory cells such as basophils, neutrophils, eosinophils, macrophages, mast cells, dendritic cells, monocytes, B-cells as well as T-cells. Inflammatory processes are regulated in such a way that appropriate leukocytes are recruited to the site of inflammation (Turner *et al.*, 2014). Chronic airway inflammation in asthma leads to recurrent airway obstruction resulting in wheezing, coughing, shortness of breath and chest tightness. Uncontrollable and life-threatening episodic asthma exacerbations or “flare-ups” could occur as a result of severe expiratory airway flow limitations (Keglowich and Borger, 2015; GINA, 2017). Management of mild intermittent asthma requires an initial administration of short-acting beta-2 agonists (SABA). Depending on the severity, treatment can be stepped-up by co-administration of graded (low to middle to high) doses of inhaled corticosteroids (ICS) with SABA or long-acting beta-2 agonists (LABA) (Reddel *et al.*, 2015).

Furthermore, the pathogenesis of asthma depends on the interaction between several cellular elements and mediators (such as cytokines) in response to trigger, sensitizer, and irritants. Airway inflammatory reactions are brought about by activated stationary and recruited inflammatory cells through inflammatory mediators (Holgate, 2008). These mediators include cytokines which exert paracrine, autocrine or endocrine functions and the chemokines which perform the function of attracting cells to the site of action via chemotaxis (Turner *et al.*, 2014). Cytokines such as IL-4, IL-5, IL-9, IL-13, IL-17, stem cell factor (SCF) and thymic stromal lymphopoietin (TSLP) have been implicated in the pathophysiology of asthma (Turner *et al.*, 2014).

Exposure of the airway to aeroallergens such as house dust mites, pollens and animal dander elicit a series of biological events leading to airway inflammation. This involves the interaction of the allergens with receptors such as the toll-like receptors (TLR), which stimulate the release of epithelial mediators such as IL-25, IL-33 and TSLP aimed at enhancing the development and activation of dendritic and Th2 cells (Wilson *et al.*, 2012). The TSLP activates myeloid dendritic cells (mDCs) to induce the proliferation of naïve T-helper cells (Th0) and memory CD4⁺ T cells. The activated dendritic cells serve as antigen presenting cells that recognizes, fragments and presents allergenic peptides to lymph nodal Th0 via its major histocompatibility complex (MHC) class II (Kallinich *et al.*, 2007). Depending on the cytokine milieu, the Th0 cells may differentiate into Th1 or Th2. High concentration of IL-4 and low IL-2 favours Th2 cells, while higher IFN- γ and low IL-4 favours Th1. Matured Th2 cells produces IL-4, IL-5, IL-9 and IL-13 which further improve Th0 differentiation to Th2 in a positive feedback loop (Kaiko *et al.*, 2008). Interleukin-13 is implicated in the recruitment of inflammatory cells from the blood to the lung, regulation of matrix metalloproteinases induction of airway hyper-reactivity and stimulation of mucin production and secretion. Furthermore, Interleukin-13 alongside IL-4, enhances the production of Immunoglobulin E (IgE) from B lymphocytes which act on mast

cells to induce degranulation and consequently leads to atopy, an important risk factor of asthma (Wenzel, 2013).

About 5–10% of asthmatic patients suffer from severe asthma worldwide. Experimental and clinical studies have demonstrated that IL-13 is an important cytokine in chronic airways inflammation. IL-13 is involved in Th2 inflammation and has been identified as a possible therapeutic target in the treatment of asthma (Marone *et al.*, 2019). It has a single open reading frame with 132 amino acids, and also contains 20 amino acid signal sequence and secreted as a 10kda unglycosylated specie (Seyfizadeh *et al.*, 2015).

Single-nucleotide polymorphisms (SNPs) are increasingly studied as possible markers for predicting response to treatment (Wadsworth and Sandford, 2013). Many genes have been associated with variation in therapeutic response among asthmatics, whereby presence of multiple polymorphisms could affect severity of asthma and response to treatment. Although some studies have associated IL-13 SNPs with asthma risk and severity, the critical pro-inflammatory role of IL-13 in pathogenesis of asthma mandates the need for further study.

Role of IL-13 in Airway inflammation

The key to unraveling the importance of IL-13 Does not depend on comparing its importance to IL-4 in terms of lymphocyte function, where it is clearly of secondary relevance, but in translational studies of cytokine function using more complex in vivo disease models. Several years after the discovery of IL-13, independent research groups tilted towards the immunological basis of allergic disease, focusing on two disease models, parasitic infestation of the gut and allergic airway disease (asthma). Despite involving two entirely different organs (gut and lung, respectively), these models are otherwise seemingly similar, involving at a purely immune level substantially similar patterns of inflammation involving Th2 cells, eosinophils and IgE-secreting B cells, and at a physiological level, significantly similar outcomes of this inflammation that include enhanced luminal smooth muscle-based

contractility and excess mucus secretion that cause temporary obstruction. For the parasitized gut however, these changes are directly mediated by Th2 cells, and were shown to be adaptive as they resulted in the expulsion of the causative organism. In asthma models, these changes lead to airway obstruction and were therefore believed to be maladaptive- precisely mirroring the clinical impression that asthma is a harmful response to otherwise innocuous inhaled substances masquerading as parasites. The question for both models became, what are the essential molecule(s) that mediate the all-important physiological changes. Given that they had previously been linked to allergic disease for many decades, IgE and eosinophils seemed to be obvious targets, and IL-13 and IL-5 were eventually shown to be the principal cytokines driving these markers of allergic disease, respectively (Grünig *et al.*, 2012).

The release of TSLP, epithelial cytokines and the CC family chemokines are among the first events involved in the initiation of allergic inflammation. These cytokines further induce the influx of circulating inflammatory cells to the airway, thereby leading to the activation and mobilization of dendritic cells. T cells in lymph node emigrate either to B cell zones and differentiate into T follicular helper cells or to the lungs to mature as Th2 cells. These Th2 cells secrete IL-4, IL-5, and IL-13 to augment chemotaxis and survival of eosinophil and basophils. Despite all the aforementioned cytokines play important roles in the initiation of airway inflammation, IL-13 has been found to be the central mediator of asthma by eliciting most of the key pathologic and physiologic feature of asthma. IL-13 is responsible for switching plasma cell antibody synthesis from IgM to IgE production, increased permeability and shedding of airway epithelial cells, proliferation of airway smooth muscle, transformation of airway fibroblast to myoblast, leading to collagen deposition, goblet cell hyperplasia and increased mucus production, production of inducible nitric oxide synthase and stimulation of airways hyper-responsiveness (Corren, 2013).

IL-13 in Asthma

Asthma is a chronic inflammatory disease that is

yet to be fully understood. Even though it was identified centuries ago in ancient Egypt, its incidence has been increasing even in developed countries. The most frequent symptoms of asthma including breathlessness, wheezing, coughing, and chest tightness have been found to be triggered by allergens, irritants, infectious stimuli, air pollutants and pharmacological agents. The presence of immune cells along with goblet cell hyperplasia, epithelial desquamation and thickening of the submucosa results in airway obstruction (Seyfizadeh *et al.*, 2015).

Asthma is thought to be caused by T-lymphocyte response to non-infectious environmental antigens along the respiratory tract. The respiratory tract of Asthmatics is characterized by the presence of activated Th2 cytokine producing cells. The role of IL-13 in the regulation of allergic predisposition has been well established in animal models, with strong evidences indicating its sole role in eliciting all known features of allergic asthma, without the influence of other Th2 cytokines (Seyfizadeh *et al.*, 2015).

Some studies demonstrated that specific blockade of IL-13 using sIL-13Ra2 chain in allergen-challenged mice in a way that the sIL-13Ra2 binds only IL-13 (and not IL-4) reversed mucus production and Airway Hyper-Responsiveness (AHR). At the same time, acute administration of IL-13 in non-immunized mice was found to recapitulate almost all the features of allergic asthma (Grünig *et al.*, 1998; Wills-Karp *et al.*, 1998). A study conducted on a IL-13 knock-out mice provided a conclusive evidence of the crucial role of IL-13 in mediating allergen-driven AHR and mucus hypersecretion, hence confirming the fact that IL-13 alone may mediate the physiologic consequences of Asthma (Walter *et al.*, 2001).

Studies performed on asthma in allergic mouse models have demonstrated that IL-13 alone is sufficient to cause many of the pathophysiologic characteristics of asthma. Studies of asthmatics support the hypothesis that IL-13 is also a critical mediator of human asthma. Segmental allergen challenge studies in mild allergic asthmatics showed an increase in IL-13 protein and mRNA in bronchoalveolar lavage fluid, thus suggesting that IL-13 may contribute to asthma

pathophysiology. Genetic research also indicates the potential role of IL-13 asthma, as genome-wide association studies in large populations have linked IL-13 polymorphisms and its receptors with asthma prevalence and bronchial hyper-responsiveness (Grunig *et al.*, 1998).

Great progress had been made in understanding how influential Th2 cytokine directs airway remodeling, airway inflammation, and asthma pathogenesis and IL-13 is recognized as a central mediator of human asthma. This role has been supported by showing that IL-13 polymorphisms, such as G+2044A, C-1112T, and A1512C, are strongly associated with asthma susceptibility and by finding that many IL-13-induced pathways are associated with asthmatic airway responses. IL-13 and IL-4 activate STAT6 since they both share the IL-4R α subunit in their receptors. In addition, STAT activation is crucial for the differentiation of T-cells into Th2 effector cells. It regulates IL-13- and IL-4-induced production of Th2 cytokines such as eotaxin, smooth muscle cells and fibroblasts (Seyfzadeh *et al.*, 2015). Therefore, the IL-13/IL-4/STAT-6 pathway has been proved to be a prominent player in asthma pathogenesis.

Biomarkers for IL-13

Th2 phenotype is characterized by inflammation and cytokine expression in approximately 50% of Asthmatics. This phenotype have been found to show better response to treatment with inhaled corticosteroids (ICS) compared to other non-Th2 phenotypes (Berry *et al.*, 2007; Woodruff *et al.*, 2009). The following approaches have been used to differentiate the subgroups of asthmatics:

Total Serum IgE

The total serum IgE represents a biomarker for assessing asthma phenotype as well as its exacerbation because its synthesis is regulated by both IL-4 and IL-13. However, a poor correlation between IgE and eosinophilic inflammation and presents the lowest sensitivity among other biomarkers (Corren, 2013).

Exhaled Nitric oxide

Forced exhaled nitric oxide (FeNo) is produced by most tissues of the body, especially the lung. It is produced by the enzyme nitric oxide synthase

under the control of IL-13 and has been found to correlate moderately with eosinophils in body fluids. An elevated level of FeNo indicates an increased Th2 inflammation and IL-13 activity, thus predicting a better response to ICS than inhaled methacholine (Smith *et al.*, 2005). A study correlated FeNO values with FEV1 improvement following ICS treatment and found an optimum discriminating nitric oxide level of 47ppb, while other studies found ICS responsiveness at 33ppb, thus predicting the likelihood of successful discontinuation of ICS at level lower than 22ppb (Corren, 2013).

Airway Epithelial Proteins

Different studies have tried to identify bronchial-derived proteins associated with Th2 airway inflammation to be used as proxy markers for Th2 cytokines. Expression of three genes that encode serpin peptidase inhibitor clade B member 2 (SERPINB2), calcium-activated chloride channel regulator 1 (CLCA1) and periostin (POSTN) were analyzed, all of which are regulated by IL-13 (Woodruff *et al.*, 2009). Periostin exerts an autocrine and paracrine effect on epithelial cell function and fibroblast respectively, leading to airway remodeling. It was observed that subjects with elevated levels of the aforementioned Th2-proteins showed better response to ICS therapy compared to non-Th2 subjects (Corren, 2013).

Blood Eosinophil Counts

Blood eosinophilia is a common finding in patients with asthma, especially in asthmatics with elevated bronchial expression of IL-5 and IL-13. It was also observed that blood eosinophil values were not significantly correlated with airway eosinophil numbers. Therefore, while an elevated blood eosinophil count may provide some information regarding TH2 status, this measure appears to be insensitive and poorly reproducible, limiting its value as a biomarker (Woodruff *et al.*, 2009; Corren, 2013). Molecular phenotyping of asthma patients has been most valuable in developing novel targeted therapies, particularly in understanding the biology of type 2/eosinophilic asthma. Eosinophils have been found in increased numbers in peripheral blood of asthma patients. It has also been reported that elevated eosinophil counts are significantly

correlated with disease severity, indicating that these cells may play an important role in asthma pathogenesis.

Sputum Eosinophil Counts

A substantial number of studies have demonstrated that sputum eosinophil numbers in patients with asthma are distributed along a continuum, and a high proportion of asthmatics consistently show low numbers of eosinophils that are similar to the values found in people who do not have such condition. These findings are consistent with data from bronchoscopy studies, which have classified patients as having eosinophilic or non-eosinophilic types of asthma (Woodruff *et al.*, 2009). The presence or absence of sputum eosinophilia may be determined using a 2 % cutoff inferred from published reference values for eosinophils in induced sputum from healthy subjects; in essence, subjects with 2 % or greater sputum eosinophils have sputum eosinophilia, and subjects with less than 2 % sputum eosinophils do not (Wenzel, 2013). In a group of 995 adult asthmatics, sputum eosinophilia (defined as ≥ 2 % eosinophils) was found in 36 % of inhaled corticosteroid (ICS)-naive subjects and 17 % of ICS-treated subjects (McGrath *et al.*, 2012). A longitudinal subset analysis of ICS-naive patients in a study, 22% had persistent sputum eosinophilia, 31 % had intermittent eosinophilia, and 47 % had no eosinophilia (Corren, 2013). Sputum eosinophilia was correlated positively with IL-13 expression in the bronchial submucosa, indicating that sputum eosinophil counts may serve as a marker of TH2 inflammation.

IL-13 receptors

IL-13 is a type I cytokine that signals through the type I cytokine receptors. Some of the known features of type I receptors are proline-rich box region in the intracellular domain, fibronectin type II module in the extracellular domain, a W-S-X-W-S motif, four conserved cysteine residues and most importantly binding of Janus tyrosine kinases (JAK) which eventually results in the recruitment of downstream signalling molecules (Leonard & Lin, 2000). Two receptors (Type II IL-13R, and IL-13R α 2) of IL-13 have been found so far, and are briefly discussed as follows:

Type II IL-13R

IL-13 response has been found to remain intact in immunodeficiency patients even in the absence of γ c (responsible for several types of immunodeficiency in humans). This suggests that an alternate receptor for IL-13 exist, which was found to be IL-13R α , a heterodimer. Even though the γ c is not a component of the type II IL-13 receptor, it is evident that overexpression of the γ c might affect the function of IL-13 (Seyfizadeh *et al.*, 2015). It should be noted that IL-13 has two related receptors, IL-13R α 1 and IL-13R α 2 that share a 37% homology at the amino acid level, and specifically bind IL-13. However, IL-13R α 1 serves as an alternative receptor for IL-4. Therefore an imbalance may occur between IL-13R α 1 and the γ c for IL-4R α with overexpression of the γ c by means of transfection, resulting in an increase of IL-4R α / γ c heterodimers and subsequently reducing the IL-13 signalling (Andrews *et al.*, 2001; Gemou-Engesaeth, 2014; Reddel *et al.*, 2015).

IL-13R α 2

This receptor is not required for IL-13 functioning despite the presence of its transcripts in the brain spleen, lung, liver and thymus. This is because the expression of IL-13R α 1 and IL-4R α is adequate for administering cells to respond to IL-13. However, the expression of IL-13R α 2 in vitro yielded a high-affinity binding of IL-13, it was insufficient in to render cells responsive cells to IL-13, even in the presence of IL-4R α . IL-13R α 2 exist as an intracellular molecule in large colonies in primary respiratory epithelium, primary human monocytes and cultured monocytes, indicating that the binding ability of this receptor is not specific to a given cell type.

Despite many similarities between IL-13R α 1 and IL-13R α 2, there exist different expression patterns on different cell type, with IL-13R α 1 being expressed on human skin fibroblasts, non-haematopoietic cells, monocytes, human Th17 and M2 subset of macrophages, while IL-13R α 2 expressed as an intracellular molecule in airway fibroblast, monocytes and bronchial epithelial cells (Seyfizadeh *et al.*, 2015).

IL-13 signalling Pathways

IL-13 and IL-4 share familiar signalling

pathways because they contain common subunits. IL-13 signalling uses the JAK1 and JAK3 as signal transducer and STAT6 as transcription activator. Stimulation of complex by IL-4 and IL-13 result in activation of signalling intermediates of IL-4 responses, including phosphorylation of IL-4R α , insulin receptor substrate 2 (IRS-2), tyrosine kinase 2 and JAK1, and consequently resulting in signalling of the IL-4R α /IL-13R α 1 receptors via the IL-4R α .

The IL-4R α have been found to contain five conserved tyrosine residues (Y497, Y575, Y603, Y631, and Y713) that are essential in signalling. Y713 is part of an immunotyrosine-based inhibitory motif (ITIM) that is crucial in negative regulation of IL-13 and IL-4 responses, Y497 is part of IL-4R motif that is responsible for IL-4-dependent cell proliferation and recruitment of insulin receptor substrate-1 (IRS-1) and IRS-2 to IL-4R α , while Y575, Y603, and Y631 acts as STAT6 docking sites (Kashiwada et al., 2001; Seyfizadeh, Narges *et al.*, 2015).

Polymorphisms in IL-13/IL-4 Receptor Complex Associated with Asthma

Polymorphisms have been identified both in the IL-13 promoter (IL-13-1112 T) and coding region (IL-13+Arg 130Gen, IL-13+2044G > A) in asthmatic patients (Cameron et al., 2006). One of the polymorphisms (Arg 130 Gln) (A/G) identified occurs in the region essential for receptor-ligand interactions. Multiple polymorphisms in IL-4R gene have also been identified and associated with asthma. Other meta-analyses of IL-13 polymorphisms in adults and children suggested that the IL-13+1923 C/T polymorphism is associated with increased risk of asthma (Xu *et al.*, 2017).

Conclusion

Inhaled corticosteroids inhibit many inflammatory cell functions in asthma, including the production of IL-13. Despite this, a significant proportion of patients with uncontrolled asthma have been found to have increased concentrations of IL-13 despite the use of corticosteroids. This might be attributed to certain polymorphisms and/or serum IgE level. Therefore, there is need for further studies to

determine the association between IL-13 polymorphism with risk of asthma severity and response to ICS.

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