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Allergenicity Evaluation of Cytokines in Asthma Endotypes

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Abstract

Chronic inflammation of the lungs and airway hyper reactivity are among the key features of asthma. Asthma is a major public health problem; no active treatments are presently available which are capable of rectifying the related airway hypertrophy. Many researchers focus on the component of an acuteanaphylaxis. Concisely, different allergens "cross-links IgE molecules attached to high-affinity Fc epsilon receptors on the surface of mast cells", which produces chemical mediators that contract the bronchi, cause edema, increase blood vessels, and novice eosino-phils. Chronic eosino-philic airway inflammation describes the mechanisms of a complex multicellular chain of reactions that not only involve basophils and mast cells.Nonethelessendothelial cells, lymphocytes and epithelial cells may also involve macrophages, neutrophilsand platelets. Moreover, Th2-like lymphocytes in airway release cytokines that in turn recruit and activate eosino-phils. Furthermore, on the endothelial cell surface these cytokines activate the adhesion molecules that indorse diapedesis of the eosin-ophils out of the circulation into the submucosa, mucosa, and lumen of the airway. In addition, inside the tissue eosino-phils degranulation, as result toxin proteins are released those damages the respiratory epithelium and account for numerous histopathologic abnormalities of asthma. Herein, we will discuss different roles of cytokines expression.

Keywords: Inflammation, Cytokines, Eosino-phils, Asthma,

1. Introduction

Asthma is a heterogeneous medical condition categorized via alteration in airway milieu and chronic inflammation(Reddel et al., 2015; Vuolo et al., 2019). An inflammatory state of asthma of the respiratory tract, leading to airway hyper responsiveness, wall thickening, smooth muscle cell hyperplasia and hypertrophy, mucous metaplasia, myofibroblast hyperplasia, modifications in extracellular matrix, vascular proliferation, such as fiber collagen deposition and elastic fiber fragmentation(Holgate et al., 2004; Xisto et al., 2005).Furthermore, eosino-philic inflammation is also associated with allergic asthma. Airway lumen has an increased number of eosino-philsin asthmatic conditions and reducing eosinophil infiltration decreases the exacerbation rates of asthma. Eosino-phils have a vital function in the development of novel targets to decrease mucosal inflammation in patients with asthma (Cherry et al., 2008; Green et al., 2002). The worldwide prevalence of allergic asthma Allergic asthma prevalence worldwide has intensively grown in the previous 25 years, impacting almost 330 million individuals. In allergic asthma the inflammatory response is marked via marked by prominent cytokines for instance IL-4, 1L-5, IL-13, formed via both 'innate lymphoid cells (ILCs)" and "T helper (Th2) cells".(Lambrecht & Hammad, 2015). These cytokines contribute to the pathological changes of the respiratory tract as described earlier. Conventionally, two different types of asthma have been defined; allergic asthma and non-allergic. The former is present mostly in child and nearly about 50% of adults, and is distinguished via the occurrence of "serum immunoglobulin E (IgE)" antibodies or by positive skin-prick examination to the (lipo) proteins of ingested or common allergen to be inhaled for instance fungal spores, tree or plant, house dust mite (HDM), fungal spores, animal dander, or peanuts. The condition starts with allergic sensitivity in beginning stage of the

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child's life, frequently related with eczema.

Later these children progress allergic rhinitis that gradually developed to asthma(Spergel & Paller, 2003).

The asthma with non-allergic symptoms has no IgE reactivity to the allergens in the serum and neither has any evident adaptive immune system participation such Th2 cells. Furthermore, this condition develops later in life and is more frequent in woman, associated with nasal polyps, chronic rhinosinusitis and obesity, with the help of systemic steroids frequently needed a long-term treatment. The area of clinical asthma identification and therapy has endured tremendous intangible shift, with the introduction of genome-wide expression lessons, and the chief clinical trials with selective therapy via bio mediators. Clinicians now recognize, various chronic inflammatory disorders, and the classification of asthma into two clinical types has been considered a generalization. Multiple asthma pheno-types are now being characterized as asthma endo-types, each with its own distinct pathophysiology. The endo-types vary in reference of genetic vulnerability, risk factors, clinical appearance, age of inception, projection and reaction to normal and novel therapies (Anderson, 2008; Wu et al., 2014).Moderately, than a particular disease asthma is hence, held to be a syndrome having numerous endo-types described by various overlying phenotypes(S. E. Wenzel, 2012; Wu et al., 2014).The process of sensitization involves the simultaneous exposure to allergen probably via disrupting epithelial tight junctions, allowing accessibility of allergen to DC cells , activating the crucial molecules which are tangled in the regulation of IgE.

For example the IgE low-affinity receptor CD23 and IL-2 receptor CD25 (C. Robinson et al., 1997; Schulz et al., 1999). Herein, we will concentrate on the primary immunological base of certain asthma endo-types focusing mainly on eosino-philic asthma, combining results from human as well as animal studies targeting particular pathways with substantial molecular detail.

2. Eosinophilic airway inflammation in allergic and non-allergic asthma

In allergic eosino-philic asthma, the lymphocytes Th2 are thought to direct asthma pathobiology (**Fig. 1**) exhibited in non-allergic and allergic asthma patients(Nelson et al., 2020) (Akdis et al., 2011). For specific asthma phenotype, eosinophil is the major type of granulocyte instigating chronic respiratory inflammation. In allergic asthma, the origin of eosinophilia is largely understood, while in non-allergic eosino-philic asthma the triggers for eosinophilia remains to be elucidated. The "Th2 lymphocytes" seem to govern the pathobiology of asthma. Furthermore, in genetically susceptible individuals the aeroallergens during inhalation activate specific APC (antigen-presenting cells) that in turn differentiate "naive T lymphocytes" toward "Th2 cells" and as result they formed a cytokine for instance interleukin-4 (IL-4), (IL-5), (IL-9), and interleukin -13 (IL-13). In the maturation, survival and activation of eosinophil the Interleukin- 5 a plays a vital role, making it an fascinating drug target for activation and high level of eosinophil number related through severe asthma exacerbation (Lambrecht & Hammad, 2010). Anti-IL-5 therapies including monoclonal antibody drugs are used to combat eosino-philic asthma(Menzella et al., 2020) mepolizumab being among the prominent candidates(Hart et al., 2001). Pavord et al. indicated that treatment through mepolizumab, monoclonal humanized antibody against IL-5 reduced eosinophil number, down-scaling the risk of asthma exacerbations. These consequences propose that eosino-phils have a critical role in the asthma exacerbations pathogenesis. Furthermore, mepolizumab are considered to be safe and effective therapeutic alternative, allowing individuals with severe asthma to safely discontinue oral corticosteroids(Pavord et al., 2012).

Interestingly, in this study half of the severe eosino-philic asthmatics were not allergic. Hence it gives us an idea that in allergy, the pathogenesis of severe asthma is important wherein, the questions arises that which molecular and cellular mecha-nisms initiate airway eosinophilia in non-allergic asthma. Additionally, eosino-philic asthma in childhood is related with nasal polyps and chronic rhinosinusitis, often nonallergic and severe. Moreover, by the characterization of eosino-phils increased numbers of type2 innate lymphoid cells (ILC2s) are identified in nasal polyps of chronic rhi-nosinusitis. ILC2s plus epithelial cytokines "thymic stromal lymphopoietin" (TSLP) forms Th2-associated cytokines for instance IL-13 and IL-5 and, to some extent, IL-4 consequently of stimulation via IL-33.

This showed that IL-5 production may possibly clarify the occurrence of severe eosino-philic inflammation in late-onset eosino-philic asthma despite the lack of traditional "Th2-mediated allergy (allergen-specific IgE)"(Mjösberg et al., 2011; Spits et al., 2013; Walker et al., 2013). As shown in Fig: 1. various evidences suggest a

function for ILC2s in airway eosino-philia in non-allergic eosino-philic asthma. A significant amount of ILC2s is being identified

peripheral blood and in lung of asthmatic patients with chronic sinusitis and eosino-philic nasal polyps. While ROR-a encoding gene

fundamentally contributes to "ILC2 differantiation, the genes encoding IL-1 receptor like 1 and IL-33, having the part the receptor complex of IL-33 likewise, called as ST2 are also significant as they mediate IL-33" signaling and activate ILC2s(Barnig et al., 2013; Mjösberg et al., 2011; Moffatt et al., 2010).

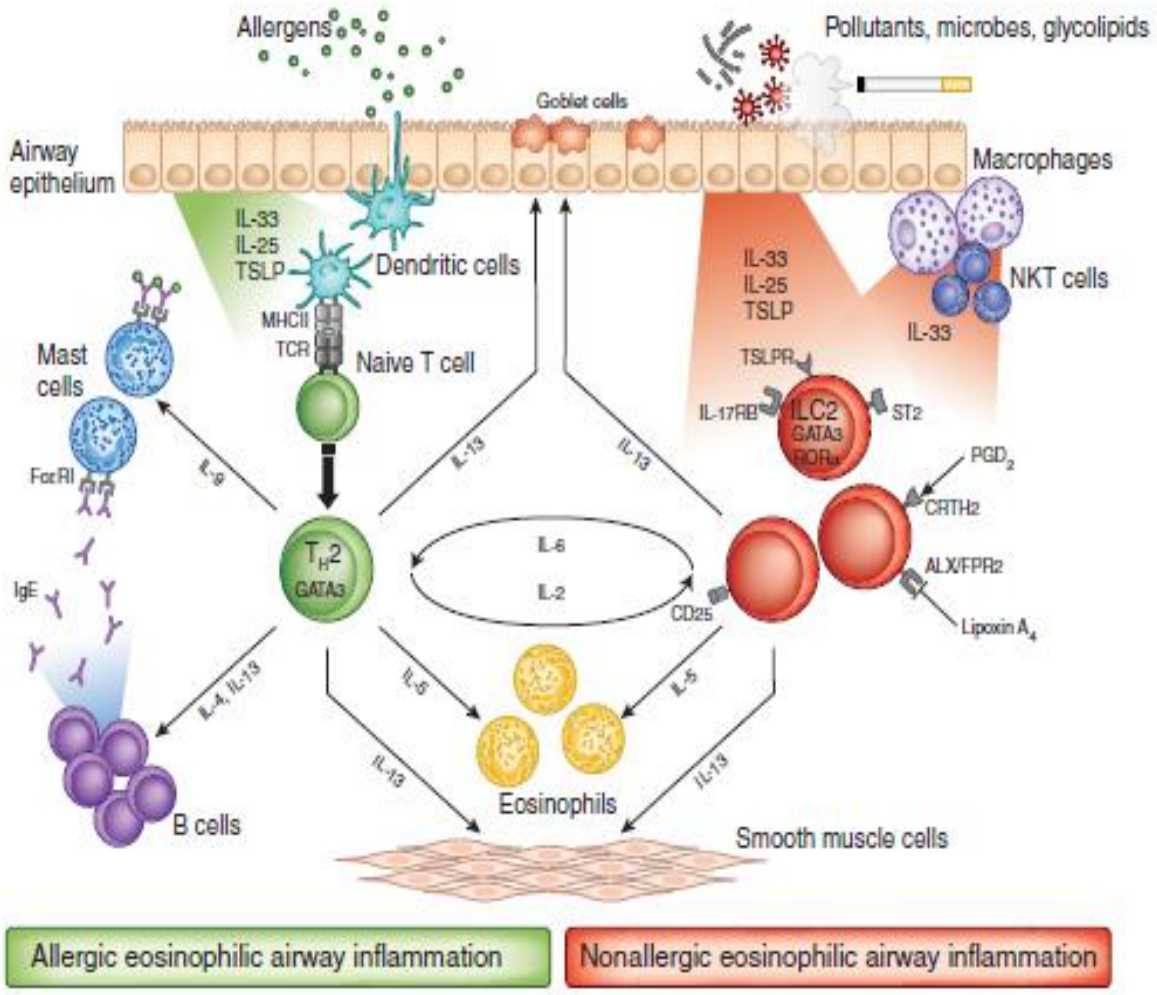

Figure 1. **In asthma, eosinophilic airway inflammation is caused by two distinct routes.**

DC cells deliver allergens to CD4+ T cells in allergic asthma, triggering TH2 cells to release (IL-13, 5, 4) as well as IgE substituting in B cells, airway eosino-philia, and mucus hyper-secretion. Conversely, polluted air, microorganisms and glycol-lipids in nonallergic eosinophilic asthma causes the release of cytokines IL-25, 33, TSLP. It activates ILC2s in an antigen-independent method through a particular receptor "TSLPR, ST2, IL-17RB"

airway hyperreactivity, Eosino-philia, mucous hypersecretion entirely produced by activated ILC2s producing large levels of (IL-5, 13). CRTH2, "chemoattractant receptor-homologous molecule are expressed on TH2 cells. receptor for lipoxin A4 (ALX/FPR2), high-affinity receptor for IgE (FcεRI), GATA-binding protein 3 (GATA3), (D2) prostaglandin,

retinoic acid receptor–related orphan receptor α (RORα) molecule which are being expressed on TH2 cells. receptor for lipoxin A4 (ALX/FPR2), high-affinity receptor for IgE (FcεRI), GATA-binding protein 3 (GATA3), prostaglandin D2 (PGD2), retinoic acid receptor–related orphan receptor α (RORα). This figure has been taken from Guy G

Brusselle et all (Brusselle et al., 2013).

3. The contribution of hematopoietic processes in eosinophilic asthma:

In allergic disease tissue eosino-philia may occur in the occurrence of nearby cytokines, especially IL-5, due to localised maturation of eosinophil lineage-controlled progenitors(EoPs), called 'in situ hematopoyesis', and/or the recruitment of mature eosinophils from the periphery stimulated by local production of chemo-attractants(Cameron et al., 2000; Dorman et al., 2004; Punia et al., 2012; D. S. Robinson et al., 1999; R. Sehmi et al., 2016; Roma Sehmi et al., 1997).

Furthermore, (IL-4,13) contribute to EoPs migration to nearby expanded chemokines such as SDF-1a (Punia et al., 2012), where they contribute to the inflated eosinophilopoietic environment found in severe asthmatics through continual airway eosinophilia. In addition, eosinophilic asthmatics associated to mild asthmatics showed a higher IL-5 response. Mepolizumab treatment of severe asthmatics reduced blood eosinophils and raised EoP levels, indicating that systemic eosinophilopoiesis was blocked. However, there was no substantial therapeutic impact on developed eosinophils, "sputum EoP" counts, or the prednisone conservation dosage indicating that local eosinophilopoesis is amplified in a patients airway via severe asthma(R. Sehmi et al., 2016).This shows native eosinophilopoeitic processes and the potential of eosinophils and associated cytokines as therapeutic targets for eosinophilic asthma.

4. The role of ILC cytokines in eosinophilic asthma:

"Moro et al. (2010)" first designated ILCs as natural helper cells that have the function to express the receptor of c-kit, Sca-l, IL-33, the IL-7 and CD25 receptor which upon the stimulation of (IL,25 -33) produced increased amounts of (IL,5 -13) (Neill et al., 2010). Later on, (IL,4-13) were used in reported mice to recognize innate (Th2 in mesenteric lymphoid nodes), liver as well as in spleen to show their reaction to (IL,25-33) (Price et al., 2010).

In joint nomenclature these cells were termed as ILSc which was proposed in 2013. Depending on the TF (transcription factors) which are imperative for the evolvement of asthma ILCs are classified in three subgroups (ILC1,ILC2,ILC3) (Spits et al., 2013). Moreover, ILCs do not have the ability to express the "antigen-specific receptors" and lack of granulocyte, lymphocyte, monocyte lineage markers. Common lymphoid progenitors (CLPs)differentiate ILCs known as CD34+RORγt+ cells in humans that also activate T and B cells lymphoid progenitors (LPs).The downstream signaling is dependent upon the TF and regulators including , NF IL-3, T cell factor 1, thymocyte selection associated HMBboxprotein, Id2, GATA-3 and Notch signaling(Aliahmad et al., 2010; Klose et al., 2014; Seillet et al., 2014; Serafini et al., 2014; Spits et al., 2013; Wong et al., 2012; Yang et al., 2013).

5. The T_H2-High Phenotype in eosinphillic asthma:

The diversity in asthmatic patients with respect to disease severity, allergic sensitization, age of onset, response to treatments enables the researchers to comprehend the basic mechanisms of asthma via dividing patients in different phenotypes(De Ferrari et al., 2016; S. Wenzel, 2012).Several approaches have been planned for the group's dividing based on the airflow limitation, comorbidities, lung function,use of corticosteroids, atopyand age at onset etc.The "Severe Asthma Research Program (SARP)" recognized 4 clusters(Fitzpatrick et al., 2011) and categorized five groups of asthmatic patients(Moore et al., 2010). Furthermore, based on the molecular technique, IL-13 activates the chloride channel expression, (CLCA1) calcium-activated family member 1, serpin family B member 2 (serpinB2), and (ovalbumin) periostin, serine peptidase inhibitor clade B, all of them are over-expressed in patients with asthema (Woodruff et al., 2007). The patients with TH2-high are being categorized via the (IL,5-13)

expression, responsiveness to gulped corticosteroids (ICS), airway hyper responsiveness, high serum IgE levels and blood and airway eosinophilia. However, the group of "T_H2-low (healthy) group, does not extant these features. Eosino-philic inflammation classify as the T_H2-high phenotype. IL-5 cytokines play a vital role in activation, persistence and differentiation of eosino-phils where upon they migrate in to the lungs where they perform their own function(Broughton et al., 2015; De Ferrari et al., 2016; Lloyd & Hessel, 2010; Varricchi et al., 2016; Woodruff et al., 2009).As shown in figure 2. By contrast, in TH2-low, the relationship among inflammation and the activity of the aforesaid cytokines is misunderstood, and the mechanisms behind the disease suffer limited identification in these individuals(Busse et al., 2015; Thomson, 2016).

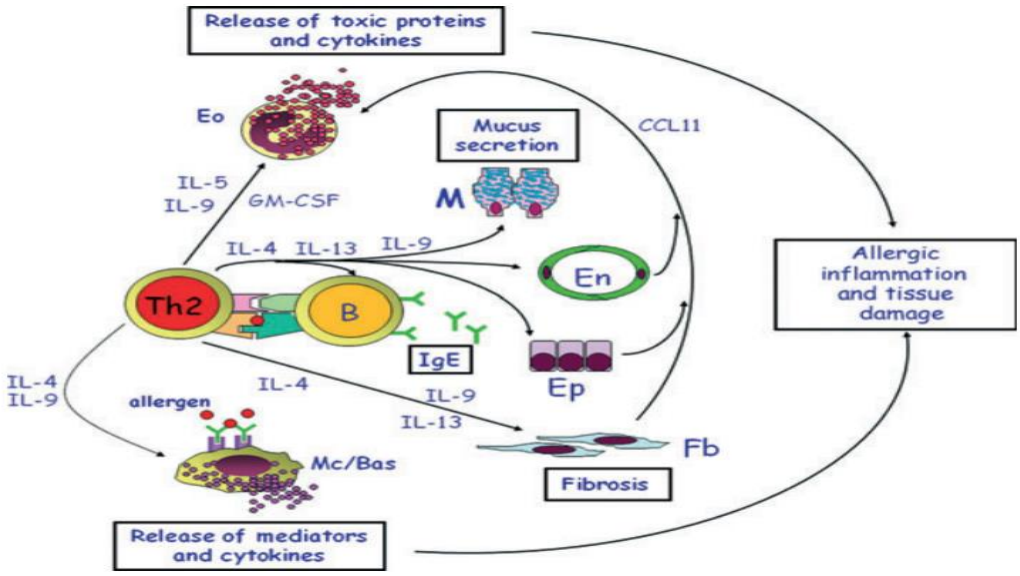

Figure 2. **Asthma pathogenesis and the role of Th2 Lymphocytes.**

Chemokines and cytokines are generated via Th2 cells, comprising , colony stimulatory factors GM (IL-4,5, 9,13) and those generated via other cell varieties in reaction to cytokines Th2 or in response to Th2-associated (CCL11) tissue damage are responsible for most pathophysiologic elements of allergic disorders, for example the assembly IgE antibodies, activation and recruitment basophils, eosinophils granulocytes, mast cells, subepithelial fibrosis, mucus hyper secretion and tissue remodeling.. This figure has been taken from Romagnani(Romagnani, 2000).

6. Asthma and Th17 lymphocytes

In allergy asthma, the function of "IL-17" is an area of intense recent research. Asthma patients in which inflammation is non-eosinophilic, non-IgEdependent, and nonatopic, the asthma severity is correlated with airway neutrophilia, signifying a vital role for neutrophils (Louis et al., 2000; Woodruff et al., 2001). The neutron-philic inflammation has shown sudden-onset fatal asthma and status asthmaticus, where the number of neutrophils are incredibly high(Lamblin et al., 1998) elucidating a potential contribution of these cells in fatal and severe asthma. Different researchers aim to unearth the association between asthma and Th17 lymphocytes. However, the function of IL-17F in neutrophil recruitment to the respiratory tract is well pronounced(Choi et al., 2010; Laan et al., 1999). In addition, Th17 cells promote neutrophilic inflammation in asthma animal models.And is significant in the development of airway hyperresponsiveness(Wilson et al., 2009). Increased expression of IL-17 cytokines is demonstrated in bronchial submucosa of moderate to severe asthma patients, indicating that neutrophilic inflammation was commonly existent, especially in severe cases of the condition(Al-Ramli et al., 2009; Doe et al., 2010; Molet et al., 2001). Additionally, it is documented that elevated airway hyperresponsiveness in reaction to methacholine in asthma patients absolutely associates through IL-17A levels in the mucus. Lastly, IL-17F polymorphism causes a loss of purpose alteration is contrariwise associated to the peril of asthma disease (Barczyk et al., 2003; Kawaguchi et al., 2006).

7. Th9 cells development and their role in asthma:

Several cytokines promoted the development of IL-9 production. IL-4 is the most important cytokines amongst them. However, different TFs downstream of IL- 4 such as GATA3, IRF4 and STAT6 are essential for the Th9 cells differentiation (Awasthi et al., 2009; Goswami et al., 2012; Veldhoen et al., 2008). However, Th2 differentiation only requiresIL-4 signaling. TGFb receptor superfamily signals are required for the switching of Th2-inducing signals into Th9-inducing signals. With no IL-4, the TGFb signal leads to the improvement of inducible Treg (Tregulatory) cells(Josefowicz et al., 2012; Josefowicz & Rudensky, 2009; Wan & Flavell, 2007). In Th9 cells the TGFb signaling stimulates the activation of Smad protein and expression of PU.1(Chang et al.,

2010; Elyaman et al., 2012; Goswami et al., 2012). Moreover, the TGFb signaling condition may not be absolute. The IL-9 production during the infection caused by parasite is unchanged via the expression of a TGFb dominant negative receptor (Reynolds & Maizels, 2012).Furthermore, Jones and his colleague demonstrated that Activin (A) can substituteTGFb, as a (Th9- inducing factor). In vivo both models Activin and TGFb in allergic inflammation are necessary to be neutralized to check the reduces in IL- 9 cytokine (Jones et al., 2012).Significantly, the Th9 cells development involves an equilibrium of signals from cytokines that produce different T-helper subsets. Numerous other cytokines play a vital part in IL-9 and T-cell productions and probably factor STAT5 downstream endorses IL- 9 and T- cell productions. However, both in vivo and in-vitro has not point out that how this pathway

Is important for the Th9 cells development. In addition, the IFNc (interferon-c) inhibits the production of IL-9 from T cells (Fung et al., 2005; Schmitt et al., 1994).

Review of literature shows that "CD4+ T cells" cultured with "IL- 4, IFNc and TGFb "developed in different cell types and are related to the Th1 phenotype rather than Th9 cells(Tofukuji et al., 2012). In intraepithelial lymphocytes the IFNc + T+ CD103 cells population is observed. That whether this population has a useful function in-vivo is quite not clear. IL-9 production is suppressed by the IL-23 cytokines, however, a conclusion sustained together via in vitro culture effects and as well elevated the formation of IL- 9 from Il23r $^{-/-}$ T cells" (Jäger et al., 2009; Purwar et al., 2012). "Th17 cells can generate IL-9", but not at the concentrations found with polarised Th9 cell cultures, may be IL-23 can improve the production of cytokines, leading the Th17 cells to perform the specific functions. The family of IL-1 members might be contribute in the production of IL-9(Beriou et al., 2010; Blom et al., 2011; Ramming et al., 2012). Members of the IL-1 family work along with other cytokines to induce cytokine production for example IL-1 combines with IL- 23 in the initiation of IL- 17, as well IL- 18 combines IL- 12 in the initiation of IFNc (Guo et al., 2009). Emerging evidence showed the role of IL- 25 in IL- 9 formation via T cells. Th-9 cells have a higher level of receptor chain (IL- 25) and IL-17RB than other Th cell subsets, indicating that they are only responsive to this cytokine (Angkasekwinai et al., 2010). Transgenic mice tests show that IL- 25 leads to IL- 9 production, and onset of inflammation in those animals is reliant on IL- 9. Furthermore, blocking IL- 25 reduces production of IL-9 in vivo. Thus, it shows that IL-25 shows a vital contribution in endorsing IL-9-dependent immune responses(Angkasekwinai et al., 2010).

8. (ACOS) Asthma-COPD overlap syndrome

The overlap of chronic obstructive pulmonary disease (COPD) through asthma is categorized as (ACOS) Asthma-COPD overlap syndrome (Willsie, 2016). ACOS constitute a discrete clinical phenotype with more common aggravations, hospitalization, unhealthy quality of life, and ACOS patients' outcomes may be worse than COPD asthma patients' alone(Alshabanat et al., 2015). To distinguish these clinical diseases, the eosinophilia may signify the appropriate criteria. A subset COPD patients show eosino-philic, instead of neutron-philic inflammation(Saha & Brightling, 2006).The Assessment of COPD classify Prognostic Substitute (ECLIPSE) End-points regiment detected 37% of participants insistently prominent blood (eosinophil counts ≥ 2%) above 3 years and stated patients have different features, such as male gender, seniority, the indications of fever as well as airflow obstruction(Singh et al., 2014).This study revealed that sputum eosinophilia and blood were correlated. The eosinophilia from sputum was observed to be associated with reactivity to both inhaled and systemic corticosteroid individuals with COPD(C. E. Brightling et al., 2005; Christopher E. Brightling et al., 2000; Leigh et al., 2006; Siva et al., 2007). Furthermore, benralizumab, a monoclonal antibody, inhibits the activity of interleukin-5 and is recommended for eosinophilic COPD patients as an alternative to corticosteroids.(Christopher E. Brightling et al., 2014). Briefly, ACOS describes a distinct disease process with its own pathophysiology and therapeutic response.

9. Viral infections and innate immune sensing

For viral infection and replication, the airway epithelium is the main site. Viruses penetrate via mucus layer first, which provides a defense against assaulting pathogens. However, if the first line of defense fails, then innate immune system is set in motion. Innate immunity depends upon on the encoded receptors of germ-line which are uttered on innate immune and epithelial cells. These types of proteins are called as "pattern recognition receptor (PRR)" which are sensors for pathogens, termed as (PAMP/MAMP) pathogen or microbe related molecular patterns. Or endogenous molecules referred as (DAMP) damage- related molecular patterns are usually reprocessed and emitted from infected, fading or damaged cells to

caution the immune cells of the existence of danger. PRR have four main categories, (CLR) C-type lectin receptors

(RLR) retinoic acid-inducible gene-I RIG-1- like receptors, (NLRs) nucleotide- binding oligomerization domain NOD-like receptors and Toll-like receptors (TLR). Most TLRs

(TLR 1, −2, −4, −5, −6, 10) are expressed at the surface of cells , where they can interact with viral proteins and bacterial componentssuch asbacterial lipoproteins, peptidoglycans, RV(Rhinovirus) capsid and RSV(Murawski et al., 2009; Triantafilou et al., 2011). TLR-4 is a sensor for Respiratory syncytial virus (RSV) F protein and bacterial lipopolysaccharide. Furthermore, it responds to DAMPs e.g. (S100A9, HMBG1, oxidized phospholipids) during theinfection of IAV. Futhermore, these reactions are supposed to be harmful to the host as provoking TLR4 signaling throughout infection of IAV and can defend the mice from fatal disease(K. A. Shirey et al., 2016; Kari Ann Shirey et al., 2013; Tsai et al., 2014).In endosomes the residual TLRs (TLR3, −7, −8, −9) are being expressed, while in the cytoplasm RLRs (e.g. MDA5, RIG-I) and expressed the NLRs.

RNA receptors that provoke reactions to “RSV contain Nod2 (NLRC2), TLR7, TLR3, MDA5, RIG-I, NLRX-1, and PKR shows a responses to RV RNA (Edwards et al., 2007; Hatchwell et al., 2015; Kim & Lee, 2014; Wang et al., 2009, 2011). IAV is detected via TLR3, TLR7 and RIG-I(Iwasaki & Pillai, 2014). Infection induced by host response can be activated via fusion of viral envelope with the endoplasmic reticulum and cell membrane anxiety caused by viruses(Holm et al., 2012, 2016; Hrincius et al., 2015).

10. Conclusions

The importance of immune system in triggering asthma is extensively acknowledged. Emerging evidence shows that eosinophilia inflammation is being considered as a major mechanism in the asthma development. Allergen sensitization includes several characteristics of inborn or adaptive immunity to allergens, pathogens or environmental stimuli. Furthermore, for the initiation and continuation of this disease, there is signaling communication between the immune cells and the airway epithelium. In addition, COPD is a predominant and serious illness that is exacerbated by concomitant disorders and overlying pulmonary syndromes. Improved diagnostic approaches, as well as treatment strategies and better prognosis results, might result from a better understanding of these overlapping disorders.

Conflict of interest

The authors declare that they have no conflicts of interest or competing interests

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