

Asthma and innate immunity; current perspective

Waqas Afzal

The lung functions as a gas exchange organ and therefore invariably encounters a wide range of environmental factors including particulate matter, toxins, allergens and microbes. Various innate mechanisms are set in motion as a response and to counteract these factors. These include a role of two types of cells invariant natural killer T (iNKT) cells and innate lymphoid cells (ILCs) which produce a range of cytokines like interleukin-4 (IL-4), IL-5, IL-13, interferon gamma (IFN γ), IL-17, and IL-22.¹ Both these cell types are presumed to be important as this innate mechanism leads to lung inflammation and Asthma.

The resolution of inflammation is a key part of the body's response to tissue injury. Recent discoveries have shed light on the innate mechanisms responsible for this inflammation resolution. Several mediators play integral roles in this process. These include Lipoxin A4, eosinophils and protectin D1. Lipoxin A4 has dual anti-inflammatory action on lymphoid cells and natural killer cells. Uncontrolled asthma has been associated with defect in generation of these pro-resolving mediators.²

Recent evidence indicates that the lower respiratory microbiotas are changed in asthmatic individuals. Attributes of these microbiomes are linked to inflammatory and clinical features of asthma. The importance of innate immunity and mucosal defence system is increasingly appreciated and may be dysregulated in asthmatic individuals.³

Asthma is considered a Th2 cell mediated disease which is instigating many current therapeutic strategies. However, researchers have discovered that in mice damaged epithelium of mucosa containing innate immune cells secrete Th2 cytokines IL13 and IL5 in response to IL33 and IL25. These cells named innate lymphoid cells group 2 (ILC2s) cells are rare, systematically dispersed and exist in humans. Recent work has shown that these cells are critical for development of asthma in mice. Their role in humans has not been adequately studied because they are difficult to access in peripheral tissue. Vercelli et al and

other authors have proposed in their reviews that they may turn out to be critical in the pathogenesis of human asthma.⁴

In 2010 three ground-breaking research studies were conducted by Moro et al, Neil et al and Price et al. The first reported the identification of fat associated lymphoid clusters (FALC). The novel cell population in FALC was named natural helper (NH) cells. NH cells produce large amount of IL5 and IL13 in response to IL33 or a combination IL2 and IL25. The second study reported that IL33 and IL25 administered to IL13 reporter mice led to accumulation of lineage negative IL13 positive population named nuocytes. The third study identified lineage negative IL13 positive cells which were named innate helper type 2 cells (Ih2) using IL4 and IL13 reporter mice. All of these lymphoid cells have no antigen specific receptors and cause non-specific immune responses. Hence, these cells were named innate lymphoid cells.

In 2013 the classification of innate lymphoid cells was proposed on the basis of their phenotypical and functional characteristics into three groups. Group 1 producing IFN gamma, Group 2 producing IL5 and IL13, Group 3 producing IL17 and/or IL22. NH cells, nuocytes and Ih2 cells are able to produce IL5 and IL13 in response to IL25 OR IL33. These cells depend on transcription factors GATA3 RORalpha for their function and development. They are therefore classified as ILC2's because of their common features.

Human studies have shown that there is a difference in ILC2's of mice and humans in responsiveness and production of cytokines. It has been proposed that ILC2's are involved in allergic type of asthma and exacerbations.⁵

A recent US study comparing the Amish and Hutterites population prevalence of asthma by Stein et al showed that Amish population who adhere to traditional farming practices had lower prevalence of asthma relative to Hutterite population who use industrialised farming. The researchers measured whole blood levels of IgE, cytokine level, gene expression and peripheral blood leucocytes phenotyped by flow cytometry in 60 Amish and Hutterite children. The effect of dust extracts

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Department of Medicine, City Hospital, Mirpur, Azad Kashmir, Pakistan.

Correspondence: Email: mrwaqasafzal@hotmail.com

from both population homes were also measured on immune and airway responses in a murine model of experimental allergic asthma. Differences in microbial composition were also observed in dust from Amish and Hutterite homes.

The prevalence of asthma was 4-6 times less in Amish population compared to Hutterite even though they share common ancestry and lifestyle practices. Significant differences between phenotype, proportions and functions of innate immune cells were also found in the two groups. In the mouse model of experimental allergic asthma, intranasal instillation of dust extracts from Amish homes lead to significantly inhibited airway hyper reactivity and eosinophilia. These protective effects were abolished in mouse deficient in MyD88 and Trif molecules which are critical in innate immune signalling. These results show that Amish environment provides protection against Asthma by engaging and shaping the immune response.⁶

In Puerto Rico African dust storms (ADE) have been widely thought to be associated with high prevalence of asthma. Endotoxins have been associated with ADE particulate matter and are known to promote proinflammatory responses in lung cells of susceptible individuals through Toll-like receptor signalling pathways (TLR2/4). The researchers evaluated a series of nine single nucleotide polymorphisms (SNP's) in TLR genes which have been positively or negatively associated with asthma prevalence or risk in the asthmatic population.

The SNP's were evaluated through PCR assay in 62 asthmatics and 61 controls. Genotypes were assessed for asthma association. Two TLR SNP's showed to more represented in the asthma population namely 596C/T and 399A/G. Only TLR2 596 SNP was found to be significantly associated with asthma and particularly to females. This identification of TLR SNP's will bear clues to potential candidates for gene environment interactions.⁷

Stimulation by allergens of toll like receptors TLR's of innate cells leads to accelerated and regulated allergic airway inflammation. The interaction between TLR's and environmental allergens lead to release of pro inflammatory cytokines which support the hypothesis that they play pivotal role in asthma development.⁸

Childhood asthma is a multifactorial disease involving mast cell and eosinophil infiltration which in turn causes airway hyper responsiveness, inflammation and

airway obstruction. A combination of genetic predisposition, environmental insults and epigenetic changes account for proinflammatory cytokines, IgE and eosinophil infiltrates which are produced in response to immune system polarisation towards T helper type 2 cells (Th2). Aside from Th cell responses the role of surfactant protein A (SP-A) and surfactant protein D (SP-D) are important as SP-A and SP-D enhance pathogen phagocytosis and cytokine production by alveolar macrophages, bind and clear pathogens and interact with dendritic cells to mediate immune response.⁹

Smith et al performed a cross sectional study involving severe asthmatics, steroid naïve atopic asthmatics and control non atopic subjects. Greater number of type 2 cytokine producing ILC2's were detected in sputum and blood of patients with severe asthma compared to mild asthmatics. Intracellular cytokine expression by CD4 cells and eosinophiliopoietic progenitor cells (EoPs) within the airways did not differ between the asthmatic groups. In patients with severe asthma sputum CD4 cells were more abundant than ILC2s and EoPs. ILC2s were the major progenitors of type 2 cytokines. There were also greater number of IL5 and IL13 ILC2s in patients with severe asthma whose airway eosinophilia was greater than 3% even though they had normal blood eosinophil levels. These findings by Smith et al suggest that ILC2s can promote the persistence of airway eosinophilia in patients with severe asthma through uncontrolled production of type 2 cytokines IL5 and IL13 despite high dose oral corticosteroid therapy.¹⁰

These studies indicate that the ultimate quest for finding more effective treatments for asthma depend on further analysis and high quality studies using the information base provided by the studies discussed. Further investigation of TLRs and ILC2s can yield fruitful information which may pave the way for next generation of drugs for treatment of asthma.

Disclaimer: None to declare.

Conflict of Interest: None to declare.

Funding Disclosure: None to declare.

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