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The Immunology of Asthma

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Abstract

The immune system is a complex collection of cells, tissues, and soluble mediators positioned throughout the body, whose primary purpose is to protect us against infection however its function is fundamental not only in protection from infectious disease but also as a consequence of an aberrant response in allergy.

Asthma is much more than a T cell-mediated disease, and innate epithelial and immune cell functions are critical in its pathogenesis. A hyperactive type 2 immune response contributes to the pathogenesis of asthma in a subgroup of patients however not in all patients with asthma. Blood, and airway biomarkers of increased, IL4, IL5, IL-13 activity(eosinophilia) can identify those with a so-called "Th2-high" type of disease. The pathophysiology of T2 low asthma is not well under-stood, but is characterized by the absence of T2 markers of activation and downstream signatures, such as eosinophilia. The interaction between the airway epithelium and the inhaled environment is crucial to understanding the immunology of asthma. Both the innate and adaptive immune system contribute to the immune pathogenesis of asthma in children and Adults. Lung tissue, the cells of the immune system and numerous inflammatory mediators interact in a specific fashion to cause asthma.

Keywords: *Immunology; asthma; Alarmins; TH2 High; TH2 Low; IL2 Cells; Clara Cells (CC16); Thymic Stromal Lympho-Poietin (TLSP), Interleukin (IL)-33; Phenotypes; Endo-types; GAT3 in Asthma; Air Way Epithelial Cells; Biological Agents*

Introduction

Asthma is a complex heterogeneous syndrome characterized by increased inflammatory cells, airway hyper-reactivity (AHR), and structural changes in the lung [1]. The histological features include oedema, cellular infiltration (typically with a prominent T lymphocyte and eosinophil component), and sub-basement membrane collagen deposition. Asthma is driven by an inflammatory response against normally harmless environmental inorganic and organic compounds in the respiratory tract. Immune responses to airborne pathogens such as viruses and bacteria may reduce the allergic responses but are also known to trigger asthma attacks and eventually lead to severe disease condition.

Definition of asthma: (International guidelines)

Asthma is a chronic lung disease that inflames and narrows the airways. Asthma causes recurring periods of wheezing (a whistling sound when you breathe), chest tightness, shortness of breath, and coughing. The coughing often occurs at night or early in the morning. Asthma affects people of all ages, but it most often starts during childhood [2]. The Global Initiative for Asthma (GINA) defines asthma

as "a chronic inflammatory disorder of the airways in which many cells and cellular elements play a role [3]. It has variations in severity, natural history, and response to therapy.

Asthma affects an estimated 300 million individuals worldwide. It is a serious global health problem affecting all age groups, with increasing prevalence in many developing countries, rising treatment costs, and a rising burden for patients and the community. Asthma still imposes an unacceptable burden on health care systems, and on society through loss of productivity in the workplace and, especially for pediatric asthma, disruption to the family [3,4]. The nature and development airway inflammation may be driven by numerous factors, including pathogenic infections, pollution, or even relatively innocuous inhaled particles, such as allergens. Guidelines are available for the management of severe asthma in Children by the European Respiratory Society and the American Thoracic Society.

Methodology

A comprehensive review of all aspects of Immunology, components of the immune system, immune responses to asthma in Children and Adults and airway epithelial cell mucosal immunology of was done in a systematic and explicit search of Pub MED, and HINARI identifying, selecting, and critically appraising relevant research and textbooks of Immunology from Europe and the United States of America used in undergraduate and postgraduate Medical Education [5-8].

Results and Discussion

Critical analysis of scientific concepts in pulmonary immune-inflammation of asthma

Knowledge of our immune system functions is critical for understanding allergic airway disease development as well as for selection of appropriate diagnostic and therapeutic options for patients with asthma. The immune system can be divided to 2 main defense systems that function differently-innate immunity and adaptive immunity. Innate immunity includes several defensive mechanisms such as anatomic or physical barriers, physiological barriers, phagocytosis, and inflammation. The adaptive immune response is activated in an antigen-specific way to provide for the elimination of antigen and induce lasting protection. Hypersensitivity reactions including asthma occur when an exaggerated adaptive immune response is activated.

A robust inflammatory response is essential to control asthma and both active and innate mechanisms of immunity are important in this regard. The failure of resolution or persistent pro-inflammatory immune responses results in chronic inflammatory airway diseases like asthma. It is also becoming increasingly important to phenotype airway inflammation in individual patients to allow targeted treatment as we move towards personalized therapies for asthma.

The majority of patients of asthma suffer from an allergic variant of the disease that is triggered by an IgE-driven immune response directed against inhaled antigens and leads to various symptoms, such as wheezing, coughing, and breathing difficulties. The immuno-pathogenesis of allergic asthma involves a complex interplay between the immune system and parenchymal cells of the lung, including the airway epithelium [9,10].

Innate immune cells such as neutrophils and macrophages function both to cause direct killing of the invading pathogen, largely through phagocytosis, and to activate other immune cells to amplify the defense response. Both neutrophils and macrophages, when activated through PRRs, synthesize and secrete a wide variety of different soluble chemical substances termed inflammatory mediators. Some are directly toxic to the pathogen, whereas others (cytokines) function to recruit and activate other immune cells.

Inhaled allergens are phagocytosed by macrophages and dendritic cells (DCs) presented on Major Histocompatibility Complex (MHC) class II molecules and initiate the differentiation of Th2 cells and a humoral immune response. Following class switching, Ag-specific B cells secrete Immunoglobulin E (IgE) which causes degranulation of mast cells.

Cytokines, such as IL-4, IL-5, and IL-13, are produced by Th2 cells, type 2 innate lymphoid cells (ILC2s), and airway epithelial cells, and they trigger pathological events, including airway wall remodeling, bronchial hyper responsiveness, and goblet cell metaplasia. The generation of eosinophils and mast cells are regulated by various cytokines - IL-5 has a particularly important role in eosinophil biology and IL-3/IL-9 is implicated in mast cell development and growth. IL-5 is critical in the release of bone marrow eosinophils into the circulation and in the survival and priming of eosinophils.

Once the immune response has been initiated, eosinophils become the major effector cells that are responsible for airway dysfunction. In addition to the importance of immune cells in allergic asthma, there is evidence for a prominent role for airway epithelial cells in this disease.

	Pulmonary Immune Cell Types/Receptors	Summary of Function(s)
A. Innate immune system	Dendritic Cells Mast Cells Eosinophils Basophils Pattern Recognition Receptors TREG cell Natural Killer Cells NKT cells IL2 cells	-Airway dendritic cells (DC) are critical mediators of immune responses in the lung by virtue of their ability to sample, process and present inhaled antigens to T cells.
B. Adaptive immune response	T and B cells	
C. Epithelial cells and cell-cell adhesion molecules	Clara cells Ciliated cells Goblet cells Intercellular adhesion molecule-1 (ICAM-1)	The interleukins IL-25 and IL-33 and thymic stromal lymphopoietin (TSLP) are produced by injured epithelium and play critical roles in driving expression of Th2 cytokines

Table 1: *Classification of the immune cells and the inflammatory response in asthma.*

The innate inflammatory immune response and asthma

Innate immunity is the body's immediate response to an infection. It is a nonspecific response, meaning that the same response is mounted to a large number of different pathogens. When activated, the innate response is often seen as an inflammatory response. Inflammation is the body's response to injury or tissue damage.

Neutrophils and monocytes, precursors of macrophages, are normally found circulating in the bloodstream and are recruited to sites of infection by the process of extravasation. Receptors on the phagocyte interact with ligands on vascular endothelium, and the cells attach, arrest, and move from the circulation to the diseased tissue/lungs.

Monocytes, similar to neutrophils, can also migrate into tissue, and on doing so differentiate into macrophages. Macrophages have a number of key functions, including phagocytosis of infecting microbes, antigen presentation, and general removal of dying or damaged host cells.

Dendritic cells, mast cells, eosinophils, basophils, NK cells, NKT cells, TLSP, IL 25, IL33, IL2 cells, CC16 (Club/Clara cells).

Dendritic cells

These are bone marrow derived cells, found in most tissues, including lymphoid tissues. Discovered by Ralph Steinman in the mid-1970s, dendritic cells are critical for the initiation of the immune response. They are so named, because of being covered with long membranous extensions that resemble the dendrites (extensions) of nerve cells.

Dendritic cells capture antigens e.g. pollen/animal dander and process these antigens' and then present them to naïve T cells, initiating the adaptive immune response.

Dendritic cells (DC) are the major Antigen presenting Cells (APC) and are found in tissues throughout the body. The skin and different organs each have resident populations of such cells. Like macrophages, DCs have cell-surface and internal receptors, including TLRs, that allow them to interact with pathogens in the infected tissue; however, whereas macrophages respond to pathogens locally by increasing phagocytosis and producing cytokines, DCs engulf the pathogen and migrate out of the tissue and into the lymphatic circulation, then enter specialized secondary lymphoid organs such as lymph nodes. On uptake of antigen, APCs can process and reexpress it, in the context of specialized structures on the cell surface, to allow presentation to the T cell. Dendritic cells are termed "professional APCs" because, in addition to being able to present the antigen, they also possess a number of other cell-surface molecules (e.g. CD80, CD86, and CD40), which provide additional signals to the T cell. These additional signals are called "co-stimulation" and are required by a naïve T cell for complete activation.

Pattern recognition receptors

These are receptors of the innate immune system that recognize common molecular patterns on pathogen surfaces called pathogen-associated molecular patterns (PAMPS), structures that are conserved in broad classes of pathogens for their functional importance. Many of these receptors reside at the plasma membrane.

They are proteins expressed, mainly, by cells of the innate immune system, such as dendritic cells, macrophages, monocytes, neutrophils and epithelial cells. Although the identification of allergen-specific pattern recognition receptors is in its infancy, studies to date have shown that allergens drive Th2-biased immune responses via directly engaging C-type lectin receptors (dectin-2, DC-SIGN, mannose receptor) on dendritic cells and/or mimicking toll-like receptor 4 signaling complex molecules expressed on airway structural cells. Also note that not all allergens that are implicated in causing asthma are infectious in etiology and include diverse substances as animal dander and pollens.

i) One group of receptors, C-type lectins, recognize certain sugar units that are typically located at the terminal position of carbohydrate chains on pathogen surfaces.

ii) One of the best-characterized signaling PRR families is the evolutionary conserved toll-like receptor (TLR) system in mammals, named after a homologous receptor system used by the Drosophila fruit fly for protection from infection. In humans, there are 10 expressed TLR genes (13 in mice), their products forming homo- or heterodimers with other family members, thus increasing the repertoire for recognition. TLR4, for example, has been shown to be the receptor recognizing lipopolysaccharide (LPS) found on the surface of Gram-negative bacteria such as Escherichia coli but not present on mammalian cells. The effect of pathogen components binding to TLRs on innate immune cells is TLR activation, which

initiates signaling into the immune cell and the increased expression of a large number of target genes. The genes involved depend on the pattern of TLRs engaged, but common outcomes include increased production of inflammatory mediators such as cytokines and chemokines, enhanced phagocytosis (internalization and killing of the pathogen), upregulation of costimulatory molecules on the cell surface, cell migration, and in the case of macrophages, increased processing and presentation of pathogen antigens to activate an adaptive immune response.

There are also three other families of receptors sense PAMPS when pathogens arrive in the cytoplasm:

i) **NOD-like receptors (NLRs):** e.g. NOD1 and NOD2.

ii) **RIG-like helicases (RLHs):** The cytoplasmic RNA-helicase RIG-I and related proteins act as virus receptors.

iii) **Cyclic GMP-AMP synthase (cGAS):** Double-stranded DNA "belongs" to the nucleus and to mitochondria. As soon as DNA appears in the cytosol, something has gone wrong. Either a virus has entered the cell, or cell organization itself is falling apart. In response, interferon genes and other emergency programs are activated via the cGAS-STING (stimulator of interferon genes) pathway. This system, too, is used by many cell types, not only by cells of the immune system.

TREG cells

Treg cells were initially described as a population of CD4+T cells expressing the IL-2 receptor α chain (CD25) and CD45RB, able to protect mice from developing autoimmune diseases. Further studies revealed that Treg cells also play an important role in other diseases, such as asthma.

There are two major categories of T reg cells described.

The first is the naturally occurring, thymically derived CD4+veCD25*ve T reg cells that express high levels of the transcription factor Foxp3, which is essential for their development and function.

The other category is the antigen-specific T reg cells, which can be induced *in vitro* and *in vivo* under particular conditions of antigenic stimulation.

That regulatory T cells (Tregs) have a crucial role in controlling allergic diseases such as asthma is undisputed. The cytokines most commonly implicated in Treg-mediated suppression of allergic asthma are transforming growth factor-β (TGF-β) and interleukin (IL) [10].

Mast cells

A large granule-rich cell found in connective tissue the body, most abundantly in the submucosal tissues and the dermis. The granules store bioactive molecules including the vasoactive amine, which are released on mast cell-activated and are involved in the pathogenesis of bronchoconstriction in asthmatics airways [11,12].

Eosinophils

A type of white blood cell containing granules that stain with eosin and is an effector cell in asthma as well as produces cytokines e.g. IL-5 [13,14].

Basophils

A type of white blood cell containing granules that stain with basic dyes. Basophils are non-phagocytic granulocytes. In response to binding of circulating antibodies, basophils release their contents including histamine which cause smooth muscle contraction in asthmatic airways as well as increasing blood permeability which may account for edema of the airways in asthma and inflammation [15,16].

Cytokines

Proteins made by a cell that affect the behavior of other cells, particularly immune cells.

Cytokines are produced by a variety of cell types, including those of the innate and adaptive immune responses. Covering a large number and different families, cytokines are small peptides or glycoproteins. In general, macrophages are often their main producers during innate responses, and T cells are the main producers during adaptive responses. Many cell types other than those of the immune system, including fibroblasts, epithelial cells, and adipocytes, can also secrete cytokines.

Natural killer cells

A type of innate lymphoid cell (ILC) that is important in innate immunity to viruses and other intracellular pathogens, and in antibody-dependent cell mediated cytotoxicity (ADCC).

They do not express antigen receptors and are considered part of the innate immune system, despite being lymphoid cells.

NKT cells

Is another type of cell in the lymphoid lineage that shares features with both conventional T lymphocytes and NK cells like a T cells, NKT cells have T-cell receptors (TCRs) and some express CD4. Unlike most T cells, however the TCRs of NKT cells are not very diverse and recognize specific lipids and glycolipids presented by a molecule related to the Major Histocompatibility Complex (MHC) proteins called CD1.

Like their innate immune counterparts, NK cells, NKT cells have antibody receptors.

NKT cells are considered as a cell subset belonging to the innate immune system with the capacity to amplify adaptive immune responses in asthma.

ICAM-1

Adhesion molecules mediate adhesion between cells. Cellular interactions during an immune response are dependent on the expression of the molecules and ligands that mediate adhesion between cells or between cells and the extracellular matrix. These are termed “adhesion molecules”. They are found on a wide variety of cell types, not only cells of the immune system but also, for instance, on vascular endothelium. A major determinant of their expression is the prevailing cytokine environment and the surrounding connective tissue matrix. Typically, they are transmembrane glycoproteins. They deliver intracellular signals, and during immune responses, they are primarily involved in promoting cell-cell interactions and cell migration.

Cytokines, such as TNF, IL-1 and γ-interferon (γ-IFN) appear to contribute to epithelial cell and inflammatory cell interactions by enhancing ICAM-1 expression on epithelial cells. The potential therapeutic implications of the central role of ICAM-1 in airways inflammation have been documented in a primate model of asthma [24].

Defining the roles of thymic stromal lymphopoietin, IL-25 and IL-3 in human asthma

TLSP

Several studies have identified an important role of airway epithelial-derived cytokines, IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) in asthma pathogenesis. These cytokines have been described as epithelial-derived alarmins that activate and potentiate the innate

and humoral arms of the immune system in the presence of actual or perceived damage. Each of the three epithelial-derived alarmins has been implicated in the immunology of inhaled allergen-induced airway response.

TSLP is a key initiator of allergic inflammation and considered to be one of the two major cytokines involved in mucosal TH2 immune deviation along with IL-33. The cytokine is increased in asthmatic airways and mast cells, and in the lungs is produced mainly by airway epithelial cells.

IL25

The interleukins IL-25 and IL-33 and thymic stromal lymphopoietin (TSLP) are produced by injured epithelium and play critical roles in driving expression of Th2 cytokines. TSLP acts on dendritic cells to direct them to promote the differentiation of naive T cells into Th2 cells. By contrast, IL-25 and IL-33 act directly on the naive T cells to promote Th2 immune deviation.

In addition, these three cytokines can generate a Th2 cytokine milieu independent of the adaptive immune system. TSLP and IL-33 directly induce the full repertoire of Th2 cytokine secretion from mast cells. Similarly, IL-25, TSLP and IL-33 act on type 2 innate lymphoid cells (ILC2) to drive their more restricted secretion of IL-5 and IL-13.

IL33

Interleukin-33 (IL-33), which belongs to the larger family of damage-associated molecular pattern molecules, has been considered as an 'alarmin'. It is released to alert the immune system by first-line cells, such as tissue epithelial cells, following exposure to exogenous stimuli, including allergens. This cytokine is also expressed in endothelial cells, fibroblasts, smooth muscle cells, osteoblast, adipocytes and several immune cells including macrophages and dendritic cells (DCs). IL-33 level is increased in bronchial mucosa of asthmatics and is related to disease severity [22,23].

ILC2

Innate lymphoid cells (ILCs) are a group of lymphoid cells with a recently recognized role as regulators of innate immunity, inflammation, and tissue repair at the barrier surfaces [17]. They are a lymphoid subclass characterized by the lack of either B- or T-cell receptors but retain cytotoxic and immunomodulatory capacity. [18].

The Innate defense system contains cells that look just like B or T lymphocytes under the microscope, yet express neither B nor T cells receptors. These cells are known as innate lymphoid cells.

Innate lymphoid cells (ILCs) are classified into three groups based on their transcription factors and cytokine production patterns, which mirror helper T-cell subsets. Unlike T cells and B cells, ILCs do not have antigen receptors. They respond to innate factors released by the bronchial epithelium, such as cytokines and alarmins, including IL-33, IL-25 and thymic stromal lymphopoietin (TSLP) [18,19]. LCs produce multiple pro-inflammatory and immune-regulatory cytokines for the induction and regulation of inflammation.

CC16 (Club Cells/Clara Cells)

Clara cells are non-ciliated, non-mucous, secretory cells in respiratory epithelium. These epithelial cells secrete several distinctive proteins, including Clara cell 10-kDa secretory protein (CCSP). Clara cells are most predominant in the terminal and respiratory bronchioles of humans.

Club cells, also known as bronchiolar exocrine cells and originally known as Clara cells, are dome-shaped cells with short microvilli, found in the small airways (bronchioles) of the lungs.

Club cells are found in the ciliated simple epithelium. Bronchiolar cells gradually increase in number as the number of goblet cells decrease. One of the main functions of club cells is to protect the bronchiolar epithelium. Clara cell secretory protein (also known as CCSP, CC10, CC16, Clara cell antigen, secretoglobin, and uteroglobin) is the most abundant secretory protein found in airway surface fluid.

Of recent Clara cells (CC16) have re-emerged in the immune-pathogenesis of Asthma. In mice, Clara epithelial cell depletion in the lung strongly reduced eosinophil influx, which correlated with decreased eotaxin levels and, moreover, diminished the T-helper cell type 2 inflammatory response, including interleukin (IL)-4, IL-5 and IL-13. In contrast, airway hyper responsiveness was increased. Further investigation revealed Clara cells as the principal source of eotaxin in the lung. These findings showed that Clara airway epithelial cells substantially contribute to the infiltration of eotaxin-responsive CCR3+ immune cells and augment the allergic immune response in the lung and identify Clara cells as a potential therapeutic target in inflammatory lung diseases such as allergic asthma [5,20].

The adaptive inflammatory cells

T cell responses to antigens consist of a combination of pro-inflammatory (effector) and anti-inflammatory (regulatory) cells. The effector cells primarily involved in the adaptive immune response are the T and B Lymphocytes. Adaptive immune responses are essential when our innate defenses are unsuccessful. The adaptive response is slower than the innate, but it is highly specific and very effective.

Distinct populations of T cells exist. All T cells, once they have left the thymus, express either CD4 or CD8 on their surface. This phenotypic distinction also has major consequences for effector function: CD4+ T cells are often called T helper cells (TH), whereas CD8+ cells are cytotoxic T lymphocytes (CTL). TH cells can be further subdivided. They were originally divided into TH1 and TH2 cells, but there are now recognized to be many such functional subsets.

T-helper lymphocytes conventionally are TH1 and TH2 cells.TH1 cells produce cytokines that down regulate the atopic response. In those who are genetically susceptible to developing asthma, antigen presentation to T-helper cells leads to a TH2 response.pro-inflammatory cytokines and up-regulation of airway inflammation of asthma by enhancing Immunoglobulin E (IgE) synthesis, eosinophils and mast cell activation/function.

There is much current interest in TH17 cells and T follicular helper cells (TFH), for example. TH17 cells are so named due to their release of the cytokine IL-17.

B lymphocytes and plasma cells secrete antibodies in response to antigen challenge.

Antigen presentation describes a vital immune process which is essential for T cell immune response triggering immunity. B and T lymphocytes produce and express specific receptors for antigens.

The respiratory airway cells/mucosal immunology

The epithelium of the human lower airways/bronchial tree is composed of several different cell types. In the proximal parts of the lower airways, the basal cell, the goblet cell, and the ciliated cell are the principal cell types. In the distal airways, the Clara cell and the ciliated cell are present. Serous and mucous cells are the secretory cell types of the glands which are found in the wall of the large airways.

The epithelium contains ciliated columnar cells, basal cells, goblet cells and neuroendocrine cells amongst others. Some of these cells but not all are involved in the immune-pathogenesis of asthma e.g. Goblet cells produce mucous. Increased number of goblet cells (Goblet cell hyperplasia) is part of airway remodeling in Asthma. Mucus is a complex solution of lipids and proteins that lines the airway lumen. In respiratory conditions like asthma that are associated with mucus hypersecretion, mucus ceases to be protective and instead contributes to the immunopathology of asthma. The function of mucous is to trap inhaled particles/allergen and the interaction with the tips of beating cilia, remove particles/allergen from the airways, a process termed muco-ciliary clearance.

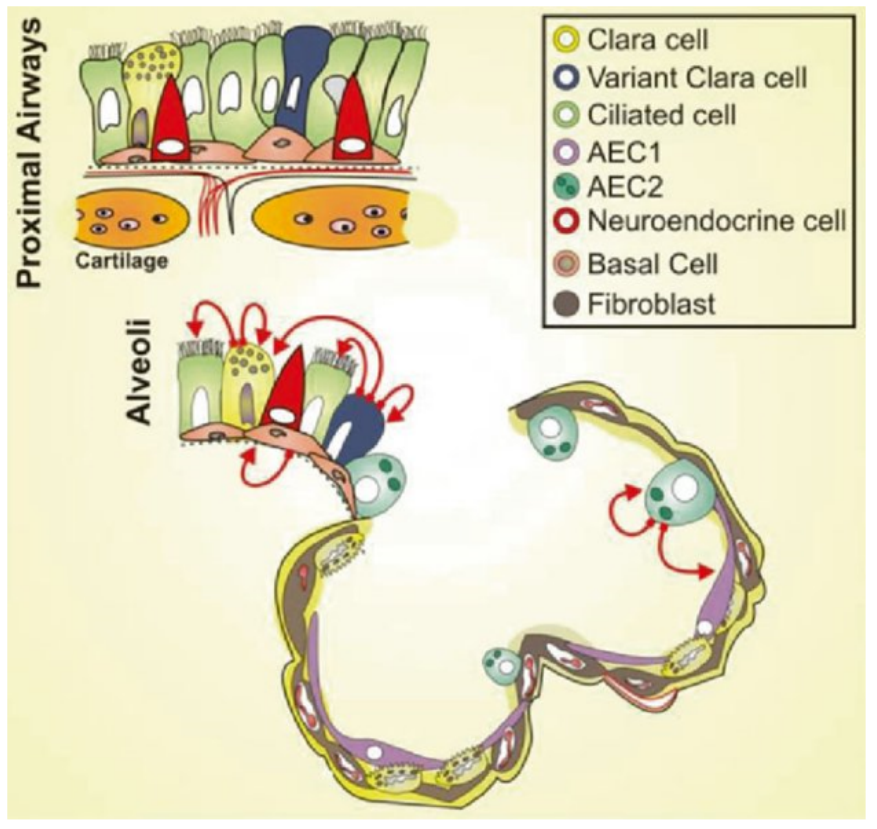

Figure 1: *The respiratory tract and airway cells.*

Other cells of the epithelium e.g. Neuroendocrine cells are not directly involved in the immune-pathogenesis of Asthma. Neuroendocrine cells are small round cells with dark staining nucleus and clear cytoplasm. These cells contain characteristic neuroendocrine granules and secrete hormones and active peptides including serotonin.

Smooth muscle, lymphoid tissue and sero-mucous glands are present in the wall of the bronchi. In the last few years, several cell- and molecular-biological characteristics of these cell types have been investigated and their importance to physiological and pathological processes has been clarified. The products of secretory cell types are essential for the muco-ciliary clearance and thus play an important part in host- defense. In many diseases, such as asthma the structure and function of these cells are altered in a characteristic way.

As a consequence of the events described above. the wall of the airway in asthma becomes thickened by edema, cellular infiltration, increased smooth muscle mass and glands. i.e. Remodeling of the airways occurs. (Bronchial thermoplasty targets this phenomenon).

Structural changes in the epithelium of the airway, termed "airway remodeling," consists of airway wall thickening, epithelial hypertrophy and mucous metaplasia, sub-epithelial fibrosis, myo-fibroblast hyperplasia, and smooth muscle cell hyperplasia and hypertrophy. Airway remodeling is thought to represent a response to ongoing tissue injury caused by infectious agents, allergens, or inhaled particulates and by the host responses to these stimuli.

Two airway cell types are critical for asthma pathogenesis: epithelial cells as previously described above and smooth muscle cells. Airway epithelial cells, which are the first line of defense against inhaled pathogens and particles, initiate airway inflammation and produce mucus, an important contributor to airway obstruction. The other main cause of airway obstruction is contraction of airway smooth muscle.

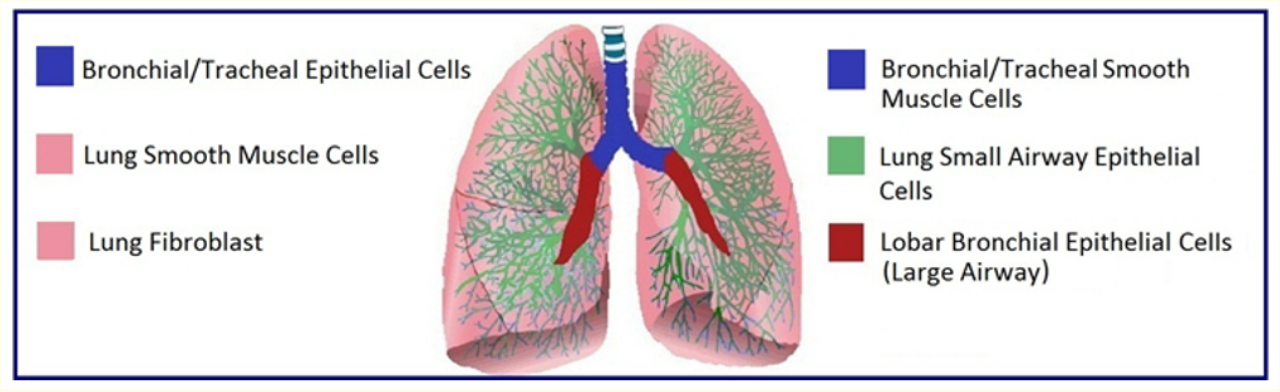

Figure 2

A layer of epithelial cells lines the respiratory tract. This epithelium provides a barrier against the external environment and protects against infection from airborne pathogens. Defective barrier function or viral infection can lead to respiratory tract disease like asthma.

The analysis of molecular markers of airways inflammation has provided promising and non-invasive techniques that facilitate the detection of disease phenotypes as well as measurement of therapeutic efficacy for asthma.

Treatment options for severe or uncontrolled asthma are increasing, especially pertaining to novel biologic therapies. The 2 primary asthma endotypes, T2 high and T2 low, are defined by the level of type 2 T helper and innate lymphoid cell activity and mediators. Most therapies for severe asthma target T2 high asthma, including the five biologic agents approved for use in the United States i.e. Omalizumab, Mepolizumab, Reslizumab, Benrazilumab and Dupilumab.

T2 high asthma is characterized by eosinophilic inflammation and elevated type 2 cytokines, such as IL-4, IL-13, and IL-5. Both TH2 cells and ILC2s produce these cytokines and are regulated by the transcription factor GATA-3.

IL-25, IL-33, and thymic stromal lymphopoietin (TSLP) are epithelial-derived mediators that regulate the expression of type 2 cytokines [9,10]. These mediators are upstream innate factors that drive IL-13 and IL-5 production.

The pathophysiology of T2 low asthma is not well under-stood, but is characterized by the absence of T2 markers of activation and downstream signatures, such as eosinophilia.

Instead, T2 low asthma is marked by neutrophilic or paui-granulocytic inflammation as a result of the activation of TH1 and/or TH17 cells and the release of their specific cytokines, such as IFN- and IL-17. These cells are specifically produced at mucosal surfaces and thus are important in airway inflammation. The role of ILCs, and more specifically type 2 ILCs, in the pathogenesis of allergic airways diseases has been extensively investigated over the last decade.

Conclusion

Asthma is a complex heterogeneous syndrome that affects both children and adults worldwide. Through the use of molecular and cellular immunology conceptual shifts have been made in the understanding of this disease involving both innate and adaptive immunity as well examination of airway epithelial changes that occur with asthma, evolving into personalized targeted therapy for asthma in view of these mechanisms.

Recommendation

Biomarkers and Biological agents should be made more accessible to resource limited countries including those in Sub-Saharan Africa.

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