ASTHMA: AN IMMUNOLOGICAL PERSPECTIVE

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Abstract: *Asthma continues to be an extremely actual issue and constantly redefining. Inflammation is the main feature of asthma with all the structures, cells and mechanisms involved. An essential part of the asthmatic inflammation is based on immune processes involving both local and general immune structures and the cooperation of the innate and acquired immunity, the cellular with the humoral immunity. Within this large framework, we can speak about the lung as a genuine immune organ, and about the asthma as an alteration of homeostasis. Intimate knowledge of the mechanisms involved can generate solutions in terms of diagnosis, long-term monitoring, targeted therapy for the asthmatic patient and can improve its prognosis.*

Considering its growing prevalence, the fact that 235 million people suffer from asthma worldwide and it is the most common chronic disease of children, being at the same time a public burden, asthma continues to be a very actual concern.

The definition is permanently updated, asthma's defining feature being the inflammation with all its aspects, which stands as baseline for all the other features: bronchial hyperreactivity, bronchospasm, bronchial remodelling. A complete and accurate definition is most important considering that each feature may be a therapeutic target and may influence the natural history of the disease with prognostic, social and economic implications.

In a time when the most accurate and rigours description of the mechanisms involved is a mandatory requirement, the idea of an exhaustive description of the most intimate phenomena of asthmatic inflammation appears, however, pretentious. Thus, it seems likely that new issues should be discovered, understood and then integrated into the large and promising picture of asthma.

Lung as an immune organ

The immune system includes all the structures responsible for the defence of the body against foreign substances, called "non-self". Immunity may be innate (native, non-specific) or acquired (adaptive), strong cooperation between them increasing the efficiency of the immune system.(3,4,5,6,7,8)

The innate immunity includes the epithelial barriers, cells, the complement system, and the acquired immunity has two components: cellular immunity centred on T lymphocyte and humoral immunity with B-lymphocyte as central part.(3,5,6,7,8,9)

Respiratory system in general, and lung, in particular, are among the most exposed structures of the body, to infectious agents, as well as the pollution, allergens and foreign molecules. So, it is imperative to exist an optimal defence system using of all its components: inborn or acquired, local or general, specific or nonspecific, acellular, cellular or molecular.

Innate immunity is achieved through the lung epithelium, imonocompetente cells, muco-ciliary clearance, bronchial secretions and surfactant.

Respiratory epithelium exerts its function as a mechanical barrier, whose integrity depends on the integrity of cells and intercellular junctions, but also the epithelial cells produce mucin as a facilitator of muco-ciliary clearance, beta-defensins, various proteic molecules such as lysozyme and lactoferrin, as well as surfactant.(3,10)

Surfactant produced by alveolar type II cells, is a secretion with high content of phospholipids, its essential role being to reduce surface tension, with remarkable immunologic role through surfactant proteins SP-A and SP-D.

Surfactant proteins are involved in the regulation of immune processes by:

- high affinity for binding multiple species of bacteria, viruses, fungi, and allergens, aggregating these pathogens, microorganisms, facilitating the phagocytosis, opsonization, amplificating oxidative destruction mechanisms, bacteriostatic, fungostatic and virus neutralization effects, modulating the cytokines and chemokines secretion at the site of infection;(11,12,13,14,15,16,17)
- modulation of the inflammatory responses by direct interaction with cellular receptors responsible for recognition;(18)
- SP-A has an inhibitory effect on of dendritic cells maturation and their ability to respond to chemotactic stimuli; (19)
- SP-A and SP-D mediate anti-allergic effects: inhibition of allergen- IgE binding, suppress histamine release by basophils, inhibitory effects on lymphocyte proliferation;(12,20)

The immune cells involved in innate immunity in the lung are:

- alveolar macrophages as an important part of the inflammatory response by producing tumour necrosis factor (TNF), Interleukin (IL1), interleukin (IL6), cleavage of the antigen, presentation and activation of lymphocytes,

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phagocytosis of apoptotic cells with crucial role in the resolution of inflammation;(3,21)

- dendritic cells, the second line of immune defence, those from the epithelium serve as sentinel cells, with complex role by their co-stimulating molecules- IL 1β, IL6, IL12, Interferon gamma (IFNγ), expressing various receptors as response to infection: Toll-like receptor (TLR2), TLR4 being the liaison between the innate and acquired immunity;(3)
- mast cells from the surface of the epithelium are involved in phagocytosis, recruitment of inflammatory cells, the recognition of pathogens, their role being linked to preformed or newly formed inflammatory mediators, responsible for the characteristic inflammatory changes;(21)
- Natural killer constitute a class of lymphocytes (10%) that do not require prior sensitization to express their function, respond to intracellular microorganisms, destroying infected cells by producing IFNγ, are able to recognize and destroy antibody molecules tied to foreign cells. They are abundant in the lungs of asthmatic patients, playing an important role in pathogenesis of asthma;(6,10,18,22)
- Neutrophils are involved in phagocytosis and have chemotactic function.(3)

Acquired immunity has the two components: cellular immunity achieved through T lymphocytes and the humoral immunity cantered on B lymphocytes.(23)

Lymphocyte population is organized in BALT (Bronchus Associated Lymphoid Tissue), part of MALT (Mucosal Associated Lymphoid Tissue) along with NALT (Nasal Associated Lymphoid Tissue) and GALT (Gut Associated Lymphoid Tissue).(24) Based on Cluster of differentiation, T lymphocytes are T helper, and T cytotoxic. T helper is CD4 positive (cluster of differentiation) and has two subtypes T helper1 and T helper 2, which recognize the antigen attached to Major histocompatibility complex (MHC) type II. T cytotoxic / suppressor is CD8 positive and that recognizes antigen molecules attached to MHC type I.(10,24,25)

The cytokinic environment is responsible of the polarization of T lymphocytes to CD4 positive or CD8 positive, as well as the polarization of Th into Th1 or Th2. Therefore, the presence of IFNγ, TGF-β, IL-12 causes polarization to LyTh1 while the presence of increased amounts of IL-4 causes the polarization to Th2.(10,24,26,27) The most common receptors of lung T lymphocytes are called TCR with two subtypes: αβ TCR, identified at the 90-95% of lung T lymphocytes and γδ TCR.(24)

B cells formed from lymphoid progenitors in the bone marrow become antibody-producing cells and represent the canter of humoral immunity. A special category is represented by memory B cells with a long life (years) and remember the first contact with a specific antigen.(5,8) All types of Ig were identified in the bronchial secretions, reflecting the local secretion and plasma transudation.(21) They are small proteic molecules produced by plasma cells, have different structure and are classified based on this structure in:

- IgA- mucosal Ig with two subtypes IgA1- serum component and IgA2 , the mucosal component;(8,21,28,29)
- IgD are involved in the activation of B cells by antigen;
- IgE involved in allergic reactions, mostly bound to mast cells and basophils, only a small fraction circulating free in the plasma;(28,29)
- IgG are the smallest molecules, penetrating both tissues and placenta, and thus offering protection to the newborn;
- IgM – is a pentameric molecule with a higher molecular weight, does not have ability to penetrate tissues and has a reduced affinity to antigen, being mainly responsible for the neutralization of viruses.(8,28,29)

Asthma inflammation from the immunological perspective

Asthma is a distress of all pulmonary structures, involved in different degrees to create its essential physiological traits. In the current perspective this chronic distress is correlated with a deviation from respiratory immuno-tolerance.(30)

Innate immunity is impaired in all its levels, epithelial cells release cytokines responsible for the inflammatory response and chemokine with recruitory effects on inflammatory cells in the airway, these structural changes being characteristic.(26,31) Late phenomena as airway remodelling as result of chronic evolution may precede the onset of symptoms up to 4 years, apoptosis being also elevated.(32,33,34) There are notable changes in ***surfactant*** proteins, registering the increased levels of Sp-D during asthma attacks.(3,35)

Macrophages are abundantly present in the asthmatic lung, actively participating to inflammation by producing proinflammatory IL, degradation and antigen presentation to Ly T CD4 +, release of metalloenzymes implicated in the digestion of elastic fibers, respectively proteolytic enzymes responsible for tissue destructions.(30,36)

Mast cells have well numerical representation being found different stages of degranulation. They control, along with *eosinophils* the IgE mediated reactions, also produce IL as a inflammation promoter, having also chemotactic functions inducing bronchial hyperreactivity.(10,24,37,38,39)

Eosinophils release eosinophilic cationic protein and major basic protein, two major proteins playing a major role in the evolution of structural and functional changes, responsible for both ciliary dysfunction, bronchial epithelium damage and cell denudation and nonspecific bronchial hyperreactivity, having late bronchial remodelling as consequence.(36,39)

Neutrophils recruited to site of inflammation are source of lipid mediators, oxygen free radicals, enzymes with cytotoxic and ciliostatic effects.(24,36) Acquired immunity through its two components suffers alterations responsible for implementing asthmatic inflammation. Lymphocytes accumulate in the respiratory tissue within hours of exposure to the allergen, the changes of cellular immunity involve the imbalance between Th1 / Th2, the high level of Th2 leads to release of cytokines realizing favourable environment for stimulating the synthesis of IgE, eosinophil stimulation and pro-inflammatory status. The cellular immunity is implicated by differentiation of B lymphocytes with consequent production of IgE involved in allergy.(36,40) Immunoglobulins E have primary low affinity for allergen and aquire, after repeated exposure, high affinity for allergen. This explains why subsequent exposure to a particular allergen results in faster reactions.(10) At a further contact with an allergen, IgE detach from mast cells and basophils leading to their degranulation and consecutive release of preformed or de novo synthesized mediators responsible for phenotypic changes of asthma.(1,41,42) Th2 lymphocyte together with IL 4 represent the centre of the asthma pathogenesis, acting directly on target tissues through the IL4 receptor, therefore expressing asthmatic phenotype, consistent with type IV hypersensitivity, and IL 4 stimulates Ly B effector differentiation and synthesis of IgE consistent with type I hypersensitivity.(9)

Conclusions:

- The perspective of asthma in terms of inflammation as a result of interconnections between cells, mediators, cytokines is plausible not only by explaining the many issues involved, but by giving the asthma the truthfulness

as a complex and incomplete deciphered nosological entity;
- The inflammatory process is designed to maintain homeostasis, its failure generating disease;
- The asthmatic inflammation gathers mechanisms belonging to both innate and acquired immunity, humoral and cellular immunity;
- Th2 lymphocyte is one of the central elements of inflammation, along with cellular components and IgE being involved in both type I and type IV hypersensitivity.
- Asthmatic inflammation, as a result of the immunological involvement can be the keystone of the pathogenesis of asthma.

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