

Nasal sensitization

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Because humans breathe through the nose, the nasal mucosa becomes sensitized to inhaled allergens. Allergic rhinitis is, together with allergic conjunctivitis, the best example of a type I hypersensitivity reaction. It is an inflammation of the nasal mucosa induced by specific immune recognition of exogenous allergens. The production of IgE plays a major role in the pathophysiology. During the sensitization phase, an antigen is presented to an antigen-presenting cell at the epithelial level. Cells that express class II major histocompatibility complex Ia on their surface can act as an antigen-presenting cell for immunocompetent cells (dendritic cells, monocytes, macrophages, B lymphocytes and epithelial cells). Macrophages and Langerhans cells are increased in number in the nasal mucosa of patients with seasonal allergic rhinitis during the season and also after allergen challenge. Topical corticosteroid treatment reduces the number of Langerhans cells in the epithelium. The epithelium also participates in antigen presentation through its possession of antigen-binding surface proteins. The antigen is finally presented to CD4 T-helper cells and B cells; this is monitored by cytokines and leads to the development of memory cells and IgE-producing plasmacytes. In humans, IL-4 has been shown to be capable of differentiating B cells into IgE-producing plasma cells. The IL-4 production is inhibited by interferon γ and by prostaglandin E2. The CD4+ cells also produce IL-2, which causes differentiation and proliferation of T lymphocytes, and IL-3, IL-5, IL-6 and IL-7, which stimulate the B lymphocytes. Topical administration of anti-allergic drugs or immunotherapy seems to be a logical approach in the treatment of patients with allergic rhinitis, because it has very direct activity on the main components of nasal sensitization.

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Nasal allergy is the most common allergic disease in humans. This is certainly due to the localization, anatomy and ultrastructure of the nasal mucosa. Indeed, because humans breathe through the nose in normal circumstances, the inhaled air first contacts the nasal mucosa. Every 24 hours about 10 000 liters of air pass through the nose.

The nasal mucous membranes are very well equipped to handle all the noxious elements present in the ambient air: microorganisms, allergens, other organic and inorganic particles, etc. There is first of all a mechanical barrier constituted by the mucus layer covering the epithelium, the epithelial lining with the ciliated cells and the goblet cells, the basement membrane and finally the lamina propria.

Inhaled particles larger than 10 μm are trapped by the mucus layer and transported by the mucociliary transport system towards the rhinopharynx and oropharynx from which they can be swallowed.

The mucus has, in addition, a variety of antibodies, proteolytic enzymes and other substances with activity against microorganisms. The specific immunity is formed by the antibodies, mainly secretory IgA and to a lesser extent, IgG and by the immunocompetent cells situated in the lamina propria.

Because the nasal mucosa is the first tissue of our body that comes into contact with the noxious agents from the ambient air, it also suffers more frequently than other tissues from these agents, when the quantity of these agents surpasses the defense capacity of the nasal mucosa or when the defense systems are insufficient or dysfunctional. A good example of this phenomenon is the much higher frequency of allergic rhinitis than allergic asthma among patients with grass pollen allergy. Grass pollen indeed has a diameter greater than 10 μm and are trapped in the mucus blanket of the nasal mucosa, where they can initiate an allergic process. They do not penetrate easily into the lower

airways except in cases of mouth breathing. Also in viral and bacterial respiratory tract infections, involvement of the nasal mucosa is much more frequent than that of the lower airways.

Allergic rhinitis is, together with allergic conjunctivitis, the best example of a type I hypersensitivity reaction, especially the cases of seasonal rhinitis and recent cases of non-seasonal rhinitis. In long-lasting cases of nasal allergy, chronic tissue lesions may be present and modify – worsen – the typical symptoms of an IgE-mediated allergic reaction. Other types of immune-mediated allergic reactions, e.g. type 3 or 4, are very rarely involved in the pathogenesis of nasal allergy. It is not the allergen itself that causes the symptoms but the inflammatory reactions resulting from a network of cellular, antibody, cytokine and mediator activities. There may be some overlap and interaction with other types of allergy, as the immediate reaction can participate in the IgG complement mediator hypersensitivity because also C3A, C5A and anaphylatoxins can stimulate the degranulation of mast cells. In addition, many other chemical and physical stimuli, neurotransmitters, drugs, hormones, etc. can degranulate the mast cell (1).

Most cases of allergic rhinitis are atopic cases, in which a hereditary condition of spontaneously increased production of specific IgE results in a higher amount of total IgE.

Immunoglobulin E

IgE is a classic immunoglobulin with 2 heavy chains and two light chains. The Fc fragment binds with the cell membrane receptor and the Fab fragment with the specific antigen. In normal circumstances the human body responds to the presentation of an antigen with minimal specific IgE production. IgE constitutes only 0.004% of the total immunoglobulin content, and the total basic IgE production is very low (<300 IU/ml). The total concentration always remains under 300 ng/ml. IgE can only perform its action by transferring a message to the mast cell or basophil to which it is attached. Most of the IgE is cell bound; the free fraction is minute (2).

Sensitization phase

Allergic rhinitis is inflammation of the nasal mucosa induced by specific immune recognition of exogenous allergens.

It is not yet known why innocuous substances are recognized as strange and noxious and what the system is that determines the production of specific IgE instead of IgA, IgG or IgM. During the sensitization phase, an antigen is presented to an

antigen-presenting cell (APC) at the epithelial level. When the responsible allergen comes into contact with the nasal mucosa of a patient with allergic rhinitis, the proteins of the allergen come into contact with cells capable of presenting these proteins to immunocompetent cells.

Cells that express class II major histocompatibility complex (MHC) Ia on their surface can act as an APC for immunocompetent cells. These cells include the dendritic cells, monocytes, macrophages, B lymphocytes and even epithelial cells. It was shown that both macrophages and Langerhans cells are increased in number in the nasal mucosa of patients with seasonal allergic rhinitis during the season and also after allergen challenge (3, 4). Topical corticosteroid treatment reduced the number of Langerhans cells in the epithelium (5). It has also been suggested that the epithelium not only functions as a mechanical barrier and transport system but may also participate in antigen presentation through its possession of antigen-binding surface proteins. The epithelium is also capable of generating mediators and cytokines, which suggests its active involvement in inflammatory processes (6).

The antigen is ingested and the APC migrates to the lamina propria, while the antigen is further processed by the APC and will be finally presented to CD4 T-helper cells and the B cells in a recognizable manner. Interaction within the new complex is monitored by cytokines – especially interleukin-1 (IL-1) and IL-6 – and leads to the development of memory cells and IgE-producing plasmocytes. Further and new contact will lead to the production of IgE that will bind to the high-affinity IgE receptors of the mast cells and the basophils and the low-affinity IgE receptors of the B cells, macrophages, monocytes, platelets and eosinophils (7).

Whether the APCs play an important role in regulating allergy is not yet clear. At this moment it is known that different APCs exist for antigen presentation to T-helper cells, cytotoxic T cells or B cells. One can imagine that the mode of response is determined at this level: complement-fixing antibodies for acute bacterial infections or cytotoxic cells for many viral infections. It is well known that different adjuvants injected in conjunction with the same antigen tend to favor different modalities of response (8).

Regulation of IgE synthesis

Human antibody production is up- or downregulated by respectively T-helper and T-suppressor cells. In cases of hyper-IgE syndrome, suppressor cells have decreased in number. In addition, B cells

of normal individuals cultured *in vitro* in the presence of T cells of patients with hyper-IgE syndrome start to produce IgE. The same effect is found when B cells are cultured in a medium that contained T cells before. Soluble factors from T cells are responsible for this effect (9).

At first sight it seems that the regulatory dysfunction resulting in production of specific IgE is located at the T-cell level rather than at the B-cell level. Several recent studies with animal and/or human cells show that the situation is more complex (10, 11). In the hypothesis of Coffman et al. (12), IL-4 produced by T cells plays an important role. CD4⁺ cells, activated in the production of IgE, release enormous amounts of IL-4. In humans IL-4 has been shown to be capable of differentiating B cells into IgE-producing plasma cells, although other lines of antibodies are stimulated as well. IL-4 also causes an increase of the expression of the low-affinity Fc receptors on the B cells. The IL-4 production is inhibited by interferon γ and by PGE₂. The CD4⁺ cells also produce IL-2, which causes differentiation and proliferation of T lymphocytes and IL-3, IL-5, IL-6 and IL-7, which stimulates the B lymphocytes (13). At this moment it is not known whether allergy is due to a deficiency of interferon γ and/or whether it is the result of immune dysregulation with increased production of IL-4 or another interleukin. The differentiation of the B cell into an IgE plasmacyte will still remain an enigma for a while.

Conclusion

Probably the most important step in the pathophysiology of allergic rhinitis is the sensitization phase. At this first step it is determined whether the individual becomes allergic or not and to what allergen. Antigen-presenting cells and the interac-

tion with CD4⁺ cells seem to play the key roles in this process.

Topical administration of anti-allergic drugs or immunotherapy seem to be logical approaches in the treatment of patients with allergic rhinitis, because they have very direct activity on the main components of nasal sensitization.

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