

LITERATURE REVIEW

Mediators involved in the pathophysiology of allergic rhinitis

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ABSTRACT

Many cytokines and chemokines, lipid mediators, histamine and neurogenic mediators are involved in the IgE-mediated inflammation of the nasal mucosa in allergic rhinitis. Understanding of their complex actions is important to elucidate the pathogenic mechanisms of allergic rhinitis, and to discover new pharmacotherapeutic and immunotherapeutic targets and strategies in this global health problem.

KEYWORDS: mediators, cytokines, allergic rhinitis

INTRODUCTION

The interest in novel cytokines and other mediator studies in allergy was recently revealed at the latest Congress of the European Academy and Clinical Immunology (Istanbul, Turkey, 2011).

Allergic rhinitis is defined as an immune-mediated inflammatory disease of the nasal mucosa, induced after allergen exposure by an IgE-mediated hypersensitivity reaction in the nose, clinically characterized by suggestive symptoms of sneezing, nasal pruritus, rhinorrhea and nasal obstruction. Allergic rhinitis is a risk factor for asthma, commonly associated with allergic conjunctivitis (Johansson et al, 2004; Bousquet et al, 2008; Scadding et al, 2011)^{1,2,3}. Furthermore, allergic rhinitis has many other inflammatory comorbidities such as allergic asthma, rhinosinusitis, otitis media and nasal polyposis (Andiappan et al., 2011)⁴.

ALLERGIC RHINITIS PATHOPHYSIOLOGY

The **pathophysiologic mechanism** of allergic rhinitis is very complex and it is a result of complex interactions between genetic and environmental factors. Atopy is vital in the physiopathology of allergic diseases through IgE-mediated mechanism, such as allergic rhinitis.

Inflammation is a key pathogenic mechanism in allergic rhinitis and it is responsible for symptom development. In patients with this respiratory allergic disease,

allergen challenge increases inflammatory markers and inflammatory mediator application elicits symptoms (Bousquet et al., 2008)². The symptoms of allergic rhinitis result from a complex allergen-driven mucosal inflammation, caused by interplay between many resident and infiltrating inflammatory cells and various **proinflammatory and vasoactive mediators**, including cytokines, histamine and cysteinyl leukotrienes. Sensory nerve activation, plasma leakage and congestion of venous sinusoids also have a pathogenic role. Specific IgE-mediated rhinitis may be characterized by early-phase and late-phase allergic responses (Wallace et al., 2008)⁵. This early phase of allergic response in allergic reaction is characterized by sneezing, nasal itching and rhinorrhea, while the late phase reaction is manifested by nasal congestion and nasobronchial hyperreactivity (Mandhane et al., 2011)⁶.

Many inflammatory and immune cells are involved in the IgE-mediated inflammation of the nasal mucosa in allergic rhinitis. Dendritic cells (DC), some of the most organized of antigen presenting cells (APC), are key players in allergic inflammation. Th2 cells are critically important in IgE synthesis and they produce a set of proinflammatory cytokines that include IL-4, IL-5, IL-9, IL-13, IL-25, and IL-31. Allergen-specific CD4+Th2 cells produce IL-4 and IL-13, which induce B cell class-switch into the antibody isotypes of ϵ immunoglobulin heavy chain and the production of allergen-specific IgE antibody. These specific IgE molecules bind to high affinity receptor for IgE (Fc ϵ RI receptors) on the surface membrane of mast cells and basophils. Moreover, there is an

essential role of the regulatory T cells in immune tolerance to allergens. In addition, Th17 cells, a subset of T helper lymphocytes with pro-inflammatory activities, may also be involved in allergic rhinitis. Eosinophils play a key role in allergic inflammation. Last mentioned, but not least, mast cells have long been recognized to have a critical role in allergic rhinitis.

A plethora of **inflammatory mediators and cytokines** is involved in the allergic inflammatory process of allergic rhinitis.

Histamine, an important organic nitrogen compound, is generated by activated mast cells and basophils. Histamine induces, mainly via H1 receptors, vasodilatation and increased capillary permeability, sensory neural stimulation and hypersecretion from glandular cells (Popescu, 2003)⁷. The local release of histamine is largely responsible for the early response to inhaled allergen, although its contribution to the late response is less well understood. Histamine has been reported to increase eosinophil chemotaxis, and in lymphocytes, augments the generation of IL-4 and IL-5. Moreover, histamine activates the inflammatory regulatory protein nuclear factor NF- κ B (which orchestrates the upregulation of cytokine gene expression) and increases the TNF alpha-induced IL-6 and IL-8 production by endothelial cells and the expression of adhesion molecules, such as ICAM-1 and E-selectin (Bachert, 1998; Nathan, 2008)^{8,9}.

Histamine concentrations in nasal secretion are elevated in patients with allergic rhinitis (Wang et al., 1995)¹⁰. Allergen challenge increases histamine and elicits symptoms in these patients. Furthermore, histamine challenge increases nasal airway resistance and elicits symptoms in allergic rhinitis (Wagenmann et al., 1997)¹¹.

Although histamine is considered one of the major mediators in allergic rhinitis, many others are additionally involved, such as lipid mediators, proinflammatory cytokines, chemokines, neuropeptides and adhesion molecules, all cooperating in a complex network involved in provoking specific symptoms and nonspecific hyperreactivity (Bousquet et al., 2008)².

Cysteinyl leukotrienes, LTC₄, LTD₄, LTE₄, are inflammatory lipid mediators synthesized from arachidonic acid by many cells, including mast cells, eosinophils, basophils and macrophages, which play multifunctional roles in allergic rhinitis. Acting on the cysLT 1 receptor, these leukotrienes induce nasal vasodilatation and increase blood-vessel permeability, mucus secretion and the recruitment of additional cellular inflammatory mediators (Nathan, 2008)⁹. Cysteinyl leukotrienes may facilitate the maturation of eosinophil precursors and act as eosinophil chemoattractants, promoters of eosinophil adhesion and inhibitors of eosinophil apoptosis (Naclerio et al., 2010)¹². Therefore, these leukotrienes are involved in both early and late phase responses in allergic rhinitis.

LTC₄/D₄ and PGD₂ in nasal secretion are increased in symptomatic allergic rhinitis (Knani et al., 1992)¹³. In

subjects with allergic rhinitis, allergen challenge increases cysteinyl leukotriene concentrations in nasal secretions in a dose-response manner, and their production is correlated with sneezing as a clinical response (Creticos et al., 1984)¹⁴. LTD₄ plays also a role in nasal secretion (rhinorrhea) and increases nasal airway resistance longer than histamine. LTD₄ is a mediator of nasal response stronger than histamine, having a threshold concentration approximately 5000-fold lower (Okuda et al., 1988)¹⁵. LTC₄ is released in upper respiratory mucosa during natural exposure to allergen in children with allergic rhinitis, and increased LTC₄ concentrations are correlated with symptom severity (Volovitz et al., 1988)¹⁶.

Type 2 **cytokines**, small cell-signaling molecules secreted by Th2 cells, and other interleukins or cytokines with other cellular origin, are of great importance for intercellular communication in allergic rhinitis inflammation.

IL-5 is a main regulator of eosinopoiesis, eosinophil maturation, activation and survival. Its receptor is a heterodimer, whose beta subunit is shared with the receptors for interleukin 3 (IL3) and colony stimulating factor 2 (CSF2/GM-CSF). It was supposed for more than a decade that IL-5 was involved in the pathogenesis of allergic rhinitis (Garrelds et al., 1995)¹⁷. More recent data in animal models of rhinitis do not support a significant involvement of this cytokine in experimental allergic rhinitis (Yamasaki et al., 2002)¹⁸.

IL-4 is a key Th2 cytokine critical for Th2 cell differentiation, B-cell class switching to IgE, and eosinophil recruitment. This cytokine is a ligand for interleukin 4 receptor. The interleukin 4 receptor also binds IL-13, which may contribute to many overlapping functions of this cytokine and IL-13. STAT6, a signal transducer and activator of transcription, has been shown to play a central role in mediating the immune regulatory signal of this cytokine.

IL-9 stimulates mucus production (upregulating the mucin synthesis), predominantly via calcium-activated chloride channels (CLCAs), and the development of airway inflammation, largely by increasing mast cell numbers and activity in the airways; this cytokine is known to stimulate cell proliferation and to prevent apoptosis. IL-9 enhances the growth of CD34⁺CD38⁺c-kit⁺ human mast cell progenitors (which express IL-9R mRNA) under stimulation with SCF (Stem Cell Factor, also known as kit-ligand), which binds to its c-Kit receptor (CD117). The Th9 cells were initially identified as a Th2 subpopulation that produced exceptionally large quantities of the Th2-specific cytokine IL-9 (Matsuzawa et al., 2003; Lai and Rogers, 2010; Oh et al., 2011)^{19,20,21}. High serum IL-9 levels are related to symptom severity in patients with allergic rhinitis (Ciprandi et al., 2011)²².

IL-13 is involved in several stages of B-cell maturation and differentiation and promotes IgE isotype switching of B cells. IL-13 induces its effects through a

multi-subunit receptor that includes the alpha chain of the IL-4 (IL-4R α) and at least one of two known IL-13-specific binding chains. Most of the biological effects of IL-13, like those of IL-4, are linked to the transcription factor STAT6 (signal transducer and activator of transcription⁶). The effects of an anti-IL-13 monoclonal antibodies on cytokine levels and nasal symptoms following nasal allergen challenge were recently evaluated (Nicholson et al., 2011)²³.

Some authors found an up-regulation of IL-18 in nasal secretions in allergic rhinitis. The persistence of high IL-18 concentrations until after the season and the high concentrations in persistent allergic rhinitis compared to seasonal forms suggest its role in persistent allergic inflammation (Verhaeghe et al., 2002)²⁴.

IL-25 is also a proinflammatory cytokine favoring Th2-type immune responses. Despite of the opposing effects of IL-17A and IL-25 on TSLP regulation in human nasal epithelial cells, IL-25 seems to be dominant (Xu et al., 2010)²⁵. More recently, it was characterized the allergen-induced IL-31 production in patients with allergic rhinitis (Okano et al., 2011)²⁶.

IL-32 presents a significant increase as protein and mRNA in the nasal mucosa of allergic rhinitis, and the level of IL-32 production is correlated with inflammation, IL-1 β , IL-18, and granulocyte-macrophage colony-stimulating factor (GM-CSF).

IL-33, a novel member of the IL-1 cytokine family and a ligand for the orphan IL-1 family receptor ST2, plays also important roles in allergic rhinitis (Kamekura et al., 2011)²⁷. Recently, anti-IL-33 antibody revealed its therapeutic effect in a murine model of allergic rhinitis (Kim et al., 2012)²⁸.

Other proinflammatory interleukins (IL-1 β , IL-6 and IL-8) are elevated in patients with allergic rhinitis and have been shown to promote the activation of immune cells as well as to enhance expression of receptors for cell adhesion molecules.

TNF- α is a well known key inflammatory mediator of the late-phase response. It activates T cells, endothelial cells, fibroblasts and macrophages to express cell surface receptors and to release additional inflammatory cytokines, and increases the expression of ICAM-1 and VCAM-1 (Naclerio et al., 2010)¹². The TNF- α inhibitor infliximab is able to induce anti-allergic effects by decreasing local and systemic Th2 cytokine (IL-4) production, total and specific IgE levels, adhesion molecule (E-selectin) expression and eosinophil infiltration into the nasal mucosa in an allergic rhinitis model (Mo et al., 2011)²⁹.

Moreover, the thymic stromal lymphopoietin (TSLP), a new key mediator of allergic inflammation, is associated with allergic rhinitis in children with asthma (Bunyavanich et al., 2011)³⁰.

The roles of **chemokines** and their receptors in the pathogenesis of allergic rhinitis were analysed evaluating their complementary DNA (cDNA) expression in the

nasal mucosa of patients with allergic rhinitis, using gene chips. The cDNAs of the following chemokines were up-regulated: CCL1, CCL2, CCL5, CCL7, CCL8, CCL11, CCL13, CCL14, CCL17, CCL18, CCL19, CCL24 and CX3CL1 in most of the allergic rhinitis sample chips, while CCR2, CCR3, CCR4, CCR5, CCR8 and CX3CR1 were the highly expressed receptor genes. Low expression of CXCL4 was found (Zhang et al., 2007)³¹. RANTES (regulated on activation of normal T cells expressed and secreted), among other chemokines, plays a crucial role in chemotaxis of eosinophils into airway mucosa. Nasal allergen challenge induces the enhanced secretion of RANTES in the lower airways of nonasthmatic patients with allergic rhinitis (Semik-Orzech et al., 2009)³². Allergen-induced secretion of eotaxin, but not IL-8, in the nasal mucosa of allergic rhinitis is involved in determining the cellular character of both upper and lower airway inflammation (Semik-Orzech et al., 2011)³³. Moreover, inflammatory crosstalk via IL-15/IL-8 axis can be modulated by vitamin D3 (El-Shazly et al., 2011)³⁴.

Between **adhesion molecules**, E-selectin (also known as CD62 antigen-like family member E, CD62E, or endothelial-leukocyte adhesion molecule-1, ELAM-1) is expressed only on endothelial cells activated by cytokines, such as TNF- α . It binds to sialylated carbohydrates present on the surface proteins of certain leukocytes and plays an important part in recruiting them to the site of inflammation. Vascular cell adhesion molecule-1 (VCAM-1, also known as CD106), an endothelial ligand for VLA-4 (Very Late Antigen-4 or α 4 β 1) of the β 1 subfamily of integrins, mediates the adhesion of leukocytes to vascular endothelium. There is a synergistic effect of TNF- α and IL-4 on VCAM-1 expression. Intercellular adhesion molecule-1 (ICAM-1, also known as CD54), a member of the immunoglobulin superfamily which binds to integrins of type CD11a/CD18 or CD11b/CD18, is an important endothelial transmembrane protein, known for its importance in stabilizing cell-cell interactions and facilitating leukocyte endothelial transmigration. ICAM-1 mediates local infiltration at the site of allergen challenge, increased expression following allergen challenge being important in allergic rhinitis. ICAM-1 is enhanced by cytokines such as TNF- α . In addition, ICAM-1 is the receptor for 90% of human rhinoviruses. Attachment, adhesion and transendothelial migration of eosinophils to the site of nasal allergic inflammation is associated with the expression induction of these three adhesion molecules on the vascular endothelium (Canonica and Compalati, 2009; Naclerio, 2010; Mandhane et al., 2011)^{6,12,35}.

Other mediators were also investigated for their role in the pathogenesis of allergic rhinitis.

Prostaglandin D2 (PGD2), a major prostanoid produced in the acute phase of allergic reactions, seems to be associated with hypertrophic nasal inflammation and

recruitment of eosinophils (Naclerio et al, 2010)¹². Allergen challenge increases PGD2 in nasal secretion of patients with allergic rhinitis (Wagenmann et al, 1996), while PGD2 and bradykinin challenge increase congestion in this condition (Doyle et al., 1990)^{36,37}.

Kinins are vasoactive peptides that are directly or indirectly associated with inflammation. Allergen challenge increases also bradykinin levels in the nasal lavage of patients with allergic rhinitis (Wihl et al., 1995)³⁸. Bradykinin in nasal lavage is elevated during natural allergen exposure in such patients (Svensson et al., 1990)³⁹.

Platelet-activating factor, also known as a PAF, PAF-acether or acetyl-glycerol-ether-phosphorylcholine, induces chemotaxis/activation of leukocytes and increases vascular permeability (Nathan, 2008; Bousquet et al., 2008)^{2,9}.

Tryptase, a neutral protease, is a dominant protein component of the secretory granules of human mast cells, being a marker for mast cell activation. Allergen challenge increases tryptase concentrations in nasal secretions of patients with allergic rhinitis (Wang et al., 1995)¹⁰. Nasal lavage tryptase is elevated during natural allergen exposure in patients with allergic rhinitis and correlates with symptoms (Di Lorenzo et al., 1997)⁴⁰.

Eosinophil cationic protein (ECP), a cytotoxic ribonuclease located in the granule matrix of eosinophils, has increased serum concentrations among patients with allergic rhinitis, in correlation with the allergic symptoms (Cheng et al., 2009)⁴¹. Signalling through PI3K is involved in ECP and EPO release in allergic rhinitis; in allergic asthma it is demonstrated less inhibition of ECP release via phosphatidylinositol 3-kinase (PI3K) during natural allergen exposure (Kämpe, Lampinen et al., 2011)⁴². Systemically activated eosinophils and neutrophils have similar patterns of degranulation after allergen exposure in allergic rhinitis and allergic asthma, the released amount of ECP and EPO being similar in allergen challenge models in both groups (Kämpe, Stolt et al., 2011)⁴³. Evidence for a local allergic rhinitis is supported by a positive response to nasal allergen provocation with local nasal production tryptase and ECP (Rondón et al., 2010)⁴⁴.

Neurogenic mediators could have a role in the non-specific hyperreactivity, frequently seen in allergic rhinitis and defined as an increased nasal response to a stimulus such as nasal mucosa heating, cold air, strong odors, distilled water, body temperature changes, hot drinks, capsaicin, histamine or methacholine (Bousquet et al., 2008)². Neurotrophins, such as the nerve growth factor (NGF) and brain-derived neurotrophic factor (BDNF), are expressed in nasal mucosa and exert immunomodulatory functions on eosinophils. In patients with allergic rhinitis, exposure to nasal allergen induces upregulation of BDNF and NGF expression (Greiner et al., 2011)⁴⁵.

CONCLUSIONS

In conclusion, many mediators are involved in the IgE-mediated inflammation of the nasal mucosa in allergic rhinitis. There is a need of understanding of their actions in order to elucidate the complex pathogenic mechanisms of allergic rhinitis and to discover new pharmacotherapeutic and immunotherapeutic targets and strategies.

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