Allergic rhinitis and CXCR3 chemokines

V. Mazzi¹, P. Fallahi²

¹ Azienda USL Toscana Nord-Ovest, Ospedale di Livorno, Livorno, Italy; ² Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Abstract

The underlying mechanism of allergic rhinitis involves IgE antibodies attaching to the allergen and causing the release of inflammatory chemicals such as histamine from mast cells. Cytokines are very important in this process. Many data suggest a systemic shift to more intensely type 1-dominated immune responses in non-allergic individuals and, conversely, to more type 2-dominated responses in allergic individuals upon natural re-exposure to grass pollen. However other studies have found that chemokine (C-X-C motif) ligand (CXCL)10/interferon (IFN)-γ-induced protein 10 (IP-10) and CXCL9/monokine induced by IFN-γ (MIG) concentrations are elevated in nasal lavages from allergic patients suggesting that these chemokines may play a role in chronic allergic inflammation. Several studies have also evaluated the effect of different immune-modulating drugs in allergic rhinitis showing local and peripheral increase of IFN-γ and IP-10, associated with a reduction of symptoms. Further studies are needed to clarify the role of T helper (Th)1 chemokines in the pathogenesis of allergic rhinitis, and to evaluate their role as biomarkers of disease and of response to treatments. Clin Ter 2017; 168(1):e54-58. doi: 10.7417/CT.2017.1983

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State of the Art

Allergic rhinitis is a type of inflammation in the nose which occurs when the immune system overreacts to allergens in the air (1). Signs and symptoms include a runny or stuffy nose, sneezing, red, itchy, and watery eyes, and swelling around the eyes (2). Symptom onset is often within minutes following exposure (3). Many people with allergic rhinitis also have asthma, allergic conjunctivitis, or atopic dermatitis (3). Allergic rhinitis is typically triggered by environmental allergens such as pollen, pet hair, dust, or mold. Inherited genetics and environmental exposures contribute to the development of allergies (4). Occupational rhinitis is also characterized by nasal congestion, rhinorrhea, nasal itching, and/or sneezing that occur secondary to exposures in the workplace. There are certain professions and occupational exposures that place workers at a higher risk for developing the disease. Additionally, occupational rhinitis can be associated with occupational asthma and upper airway symptoms may precede those of the lower respiratory tract. Taken together, occupational rhinitis is an important disease for study given its medical as well as socioeconomic implications (5-7). Diagnosis is usually based on a medical history in combination with a skin prick test or blood tests for allergen-specific IgE antibodies. In Western countries, about 20% of people are affected in a given year (8, 9). It is most common between the ages of twenty and forty (8). Allergic rhinitis triggered by the pollens of specific seasonal plants is commonly known as “hay fever”, because it is most prevalent during haying season. However, it is possible to have allergic rhinitis throughout the year. The pollen that causes hay fever varies between individuals and from region to region; in general, the tiny, hardly visible pollens of wind-pollinated plants are the predominant cause (10). Allergic rhinitis may be seasonal or perennial (11). One way to prevent allergic rhinitis is to wear a respirator or mask when near potential allergens.

Intranasal corticosteroids are the preferred treatment if medications are required, with other options used only if these are not effective (12). Antihistamine drugs can be taken orally and nasally to control symptoms such as sneezing, rhinorrhea, itching, and conjunctivitis.

Ophthalmic antihistamines are used for conjunctivitis (13). The underlying mechanism of allergic rhinitis involves IgE antibodies attaching to the allergen and causing the release of inflammatory chemicals such as histamine from mast cells (8). Cytokines are very important in this process. The objective of this narrative review is to evaluate chemokine (C-X-C motif) receptor (CXC3) chemokines in allergic rhinitis. The presentation of data has been reported according to the International Narrative Systematic Assessment (INSA) tool (14).
**IP-10 in inflammation**

Interferon (IFN-γ)-induced protein 10 (IP-10) is a chemokine that induces integrin activation and generates directional migration of multiple cell types [including activated T cells, monocytes, and natural killer (NK) cells], for these reasons it can potentially regulate inflammation at several levels (15).

Furthermore IP-10 induces apoptosis of pancreatic beta cells and inhibits the proliferation of both epithelial and endothelial cells (16, 17).

Other IP-10 proinflammatory functions are: induction of molecules [as interleukin (IL)-8 and chemokine (C-X-C motif) ligand (CXCL)-5]; up-regulation of costimulatory cell surface molecules (as CD54, CD80, and CD86), on monocytes.

IP-10 secretion is dependent on IFN-γ, which is itself mediated by the IL-12 cytokine family. Under the influence of cytokines, IP-10 is secreted by several cell types, including T lymphocytes, monocytes, splenocytes, fibroblasts, keratinocytes, thyrocytes, preadipocytes, etc. Determination of high level of IP-10 in peripheral liquids could be used as a marker of host immune response, especially T helper (Th1) orientated T-cells. Recruited Th1 lymphocytes may be responsible for enhanced IFN-γ and tumour necrosis factor (TNF)-α production, which in turn stimulates IP-10 secretion from the above mentioned cells, therefore creating an amplification feedback loop (18).

Circulating levels of IP-10 are increasing with age. Furthermore, recent reports have shown that as the serum levels (IFN-γ) and tumour necrosis factor (TNF)-α production, in which turn stimulates IP-10 secretion from the above mentioned cells, therefore creating an amplification feedback loop (18).

Circulating levels of IP-10 are increasing with age. Furthermore, recent reports have shown that serum levels of IP-10 are increased in organ specific autoimmune diseases (19), such as type 1 diabetes (T1D) (20), Graves’ disease (GD), or Graves’ ophthalmopathy (GO) (21-23), autoimmune thyroiditis (24-29), or systemic rheumatological disorders like rheumatoid arthritis (RA) (30), systemic sclerosis (SSc) (31-33), psoriasis or psoriatic arthritis (34-38), sarcoidosis (39, 40), HCV-related cryoglobulinemia (41-45), other HCV immune mediated disorders (46, 47), lupus (48, 49), and also in cancers (50-58).

**Allergic rhinitis and IP-10**

In a first study it was hypothesized that natural exposure to environmental grass pollen would induce differential systemic chemokine and chemokine receptor expression patterns in individuals with allergic rhinitis compared to healthy controls with type 2- and type 1-dominated responses to allergen respectively. CXCR3 expression increased over the grass pollen season solely in non-allergic subjects. In contrast, for both allergic and non-allergic subjects, CC chemokine receptor (CCR)5 (Th1-associated) and CCR3 (Th2-associated) were weakly expressed during the grass pollen season. Systemic CXCL9/monokine induced by IFN-γ (MIG) levels decreased from pre- to grass pollen season in alligics. Taken together, these longitudinal data suggest a systemic shift to more intensely type 1-dominated responses in non-allergic individuals and, conversely, to more type 2-dominated responses in allergic individuals upon natural re-exposure to grass pollen (59).
Th2-associated chemokines CCL17 and CCL22 were assessed in cord blood of asymptomatic at-risk newborn children from the Copenhagen Prospective Study on Asthma in Childhood (COPSAC (2000)) birth cohort and associated with the longitudinal development of biomarkers and clinical end-points of asthma, eczema, and allergic rhinitis during the first 6 years of life (64). Cord blood CCL22 levels were significantly associated to total-IgE levels measured at four time-points during the first 6 years of life; IP-10 and I-TAC were not associated with the development of any atopic disorders or biomarkers. High cord blood levels of the Th2 related chemokine CCL22 were significantly associated with high total-IgE levels during the first 6 years of life, but not with specific sensitization, asthma, eczema or allergic rhinitis (64).

The aim of another study (65) was to examine the changes in concentrations of MIG, IP-10 and I-TAC in nasal lavages collected from healthy and allergic patients during nasal allergen challenge. Subjects allergic to grass pollen and healthy controls were included. Nasal lavages were collected before and 30 min after application of the placebo and 30 min after allergen administration. Significantly higher concentrations of IP-10 in allergic patients compared to the healthy subjects before, and 30 min after allergen administration, were observed. A significant rise in MIG concentration was noted in allergic patients 30 min after the allergen. I-TAC concentrations increased after placebo as well as the allergen in both groups. The Authors concluded that IP-10 and MIG concentrations are elevated in nasal lavages from allergic patients and this chemokine may play a role in chronic allergic inflammation (65).

Modulation of the airways’ immune milieu is a key therapeutic goal for remission from respiratory allergies. To explore this hypothesis, GSK2245035, a selective Toll-like receptor 7 (TLR7) agonist with preferential Type-1 IFN-stimulating properties, was developed for intranasal application (66). Randomized, double-blind, placebo-controlled trials in healthy volunteers and patients with allergic rhinitis demonstrated that intranasal GSK2245035 doses <100 ng were tolerated and did not cause nasal inflammation. Clear target engagement, reflected by local and peripheral increase of IP-10, was observed indicating IFN-stimulated effects. This was associated with a sustained reduction in allergen responsiveness (67).

**Discussion**

The underlying mechanism of allergic rhinitis involves IgE antibodies attaching to the allergen and causing the release of inflammatory chemicals such as histamine from mast cells. Cytokines are very important in this process. Many data suggest a systemic shift to more intensely type 1-dominated immune responses in non-allergic individuals and, conversely, to more type 2-dominated responses in allergic individuals upon natural re-exposure to grass pollen. However other studies have found that IP-10 and MIG concentrations are elevated in nasal lavages from allergic patients suggesting that these chemokines may play a role in chronic allergic inflammation. Several studies have also evaluated the effect of different immune-modulating drugs in allergic rhinitis showing local and peripheral increase of IFN-γ and IP-10, associated with a reduction of symptoms. In conclusion, further studies are needed to clarify the role of Th1 chemokines in the pathogenesis of allergic rhinitis, and to evaluate their role as biomarkers of disease and of response to treatments.

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