Hypersensitivity pneumonitis and alpha-chemokines

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Abstract

Hypersensitivity pneumonitis (HP) is categorized as a Th1 helper (Th1) disease. The resulting granuloma formation is dependent on T cells and the Th1 cytokine interferon (IFN)-γ. In experimental setting, the production of IFN-γ-induced protein 10 (IP-10), monokine induced by IFN-γ (MIG), IFN-inducible T-cell-alpha chemotactic (I-TAC), has been shown (in mice exposed to the particulate antigens that cause HP) during the development of HP. The production of these chemokines was associated with an influx of chemokine (C-X-C motif) receptor (CXCR)3 CXCR3(+)CD4(+) T cells into lungs. This suggests that IFN-γ mediates the recruitment of CXCR3(+)CD4(+) T cells into the lung via the production of IP-10, MIG, and I-TAC, resulting in granuloma formation. In humans it has been shown that lymphocytes infiltrating lung biopsies are CD8 T cells for CXCR3. Furthermore, the T cells accumulating in the bronchoalveolar lavage (BAL) of HP were CXCR3(+)IFN-γ(+) type 1 CD8(+) T cells (Tc1) exhibiting a strong in vitro migratory capability in response to IP-10. Alveolar macrophages express and secrete, in response to IFN-γ, high levels of IP-10, capable of inducing chemotaxis of the CXCR3(+) T-cell line. High levels of CXCR3 ligands were shown in the fluid of the BAL in HP patients. These data confirm that IFN-γ mediates the recruitment of lymphocytes into the lung via production of IP-10, resulting in Tc1-like alveolitis and granuloma formation. It has been suggested that differences in the expression of CXC chemokines and Th1 cytokines may contribute to different immunopathogenesis, clinical course and responsiveness to treatment of HP. Clin Ter 2017; 168(2):e140-145.

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State of the Art

Hypersensitivity pneumonitis (HP; or allergic alveolitis or extrinsic allergic alveolitis, EAA) is an inflammation of the lung alveoli caused by hypersensitivity to inhaled organic dusts. Sufferers are commonly exposed to the dust by their occupation or hobbies. HP may also be called many different names, based on the provoking antigen. These include: pigeon breeder’s lung, and poultry worker’s lung (avian proteins), Bagassosis (thermophilic actinomycetes), Chemical worker’s lung - Isocyanate HP toluene diisocyanate (TDI), Hexamethylene diisocyanate (HDI), or Methylene bisphenyl isocyanate (MDI); and others (1-11). Of these types Farmer’s Lung and Bird-Breeder’s Lung are the most common, with 10-500 cases per 100,000 persons per year for farmers and 5,000-20,000 cases per 100,000 persons per year for pigeon breeders. Prevalence varies by region, climate, and farming practices. HP affects 0.5-5% of the farming population (12). HP is categorized as acute, subacute, and chronic (13). In the acute form of HP, symptoms (chills, malaise, cough, fever, rash, chest tightness, dyspnea) may develop 4-6 hours following exposure to the provoking antigen. Usually symptoms resolve within 12 hours to several days upon cessation of exposure (12). Histologically acute HP is characterized by poorly formed noncaseating interstitial granulomas, with giant cells and mononuclear cell infiltration in a peribronchial areas (12). On chest radiographs, a diffuse micronodular interstitial pattern (at times with ground-glass density in the lower and middle lung zones) may be observed. In high-resolution Computed tomography (CT) scans, ground-glass opacities or diffusely increased radiodensities are present. Pulmonary function tests show reduced diffusion capacity of lungs for carbon monoxide (DLCO). Many patients have hypoxemia at rest, and all patients desaturate with exercise (12). Patients with subacute HP gradually develop symptoms that are similar to the acute form of the disease, but are less severe and last longer. The subacute, or intermittent, form produces well-formed noncaseating granulomas, bronchiolitis with or without organizing pneumonia, and interstitial fibrosis (12). In chronic HP, patients often lack a history of acute episodes. They have an insidious onset of cough, progressive dyspnea, fatigue, and weight loss. This is associated with partial to complete but gradual reversibility. Avoiding any further exposure is recommended. On chest radiographs, progressive fibrotic changes with loss of lung volume par-
particularly affect the upper lobes. Nodular or ground-glass opacities are not present. Features of emphysema are found on significant chest films and CT scans (12). Chronic forms reveal additional findings of chronic interstitial inflammation and alveolar destruction (honeycombing) associated with dense fibrosis. Many patients have hypoxemia at rest. The pathophysiology of hypersensitivity pneumonitis involves inhalation of an antigen, that leads to an exaggerated immune response (hypersensitivity). Type III hypersensitivity and type IV hypersensitivity can both occur depending on the cause (14). The diagnosis is based upon a history of symptoms after exposure to the allergen and clinical tests. The ImmunoCAP technology with automated CAP assays and FEIA (Fluorescence enzyme immunoassay) can detect IgG antibodies against Aspergillus fumigatus (Farmer’s lung or for ABPA) or avian antigens (Bird Fancier’s Lung) (15). Lung biopsies can be diagnostic in cases of chronic HP (16).

When fibrosis develops in chronic HP, the differential diagnosis in lung biopsies includes the idiopathic interstitial pneumonias (17). Corticosteroids such as prednisolone may help to control symptoms but may produce side-effects (13).

The prognosis is generally fairly good if the allergen is identified and exposures to it significantly reduced or eliminated. Cytokines, interferon-gamma (IFN-γ), and interferon-gamma dependent alpha-chemokines are very important in the pathogenesis of HP. The objective of this narrative review is to evaluate the role of alpha-chemokines [monokine induced by IFN-γ (MIG), IFN-γ-induced protein 10 (IP-10), IFN-inducible T-cell-alpha chemoattractant (I-TAC)] in HP. The presentation of data has been reported according to the International Narrative Systematic Assessment (INSA) tool (18).

IP-10 in inflammatory disorders

The chemokine IP-10 regulates inflammation at different levels. It generates directional migration of multiple cell types, including activated T cells, monocytes, and natural killer (NK) cells, inducing integrin activation, too (19). Furthermore, IP-10 stimulates apoptosis of pancreatic beta cells and inhibits the proliferation of both epithelial and endothelial cells (20, 21). In addition, the chemokine IP-10 shows proinflammatory function by induction of molecules, as interleukin (IL)-8 and chemokine (C-X-C motif) ligand (CXCL) 5, and by 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. Several cell types, as T lymphocytes, monocytes, splenocytes, fibroblasts, keratinocytes, thyrocytes, precapacites, etc., stimulated by cytokines, release IP-10. The detection of high levels of IP-10 in peripheral liquids is therefore a marker of host immune response, especially Th1 orientated T-cells.

Recruited Th1 lymphocytes may be responsible for enhanced IFN-γ and tumor necrosis factor (TNF)-α production, that in turn stimulates IP-10 secretion from a variety of the above mentioned cells, creating an amplification feedback loop (22).

Circulating levels of IP-10 are increasing with age. Moreover, it has been recently evidenced that serum and/or tissue expressions of IP-10 are increased in organ specific autoimmune diseases (23), such as type 1 diabetes (TID) (24), Graves’ disease (GD), or Graves’ ophthalmopathy (GO) (25-27), autoimmune thyroiditis (28-33), or systemic rheumatological disorders like rheumatoid arthritis (RA) (34), systemic sclerosis (SSc) (35-37), psoriasis or psoriatic arthritis (38-42), sarcoidosis (43, 44), HCV-related cryoglobulinemia (45-49), other HCV immune mediated disorders (50, 51), lupus (52, 53), and also in cancers (54-62).

Alpha chemokines in HP

Since HP is categorized as a Th1 disease, and granuloma formation is dependent on T cells and the Th1 cytokine IFN-γ, a first study (63) analyzed the expression of multiple chemokines in the lungs of wild-type (WT) and IFN-γ-knockout (GKO) mice exposed to the particulate antigen Saccharopolyspora reactivirula (SR). The results demonstrated the production of IP-10, MIG, and I-TAC in WT mice during the development of HP, whereas GKO mice had reduced IP-10 levels and no MIG or I-TAC mRNA in the lungs in response to SR exposure. The production of these chemokines was associated with an influx of CXCR3(+) CD4(+) T cells into lungs of WT mice. These results suggested that IFN-γ mediates the recruitment of CXCR3(+) CD4(+) T cells into the lung through the production of the chemokines IP-10, MIG, and I-TAC, resulting in granuloma formation (63).

In a second study (64) using flow cytometry, immunohistochemistry, confocal microscopy analysis and chemotaxis assays, it was evaluated whether CXCL10 and its receptor CXCR3 regulate the trafficking of CD8(+) T cells in HP lung. It was shown that lymphocytes infiltrating lung biopsies are CD8(+) T cells overexpressing for CXCR3. Furthermore, T cells accumulating in the bronchoalveolar lavage (BAL) of HP were CXCR3(+)/CD8(+) T cells (Tc1) exhibiting a strong in vitro migratory capability in response to CXCL10. Alveolar macrophages expressed and secreted, in response to IFN-γ, high levels of CXCL10 capable of inducing chemotaxis of the CXCR3(+) T-cell line. High levels of CXCR3 ligands were shown in the fluid of the BAL in individuals with HP. These data confirm that IFN-γ mediates the recruitment of lymphocytes into the lung via production of the chemokine CXCL10, resulting in Tc1-cell alveolitis and granuloma formation (64).

Chronic bird fancier’s lung (cBFL) can present with a histological pattern of usual interstitial pneumonia (UIP)-like lesions. To evaluate the relevance of Th1-type chemokines (interferon-inducible protein, IP-10) and Th2-type chemokines (thymus- and activation-regulated chemokine, TARC) and their receptors (CXCR3 and CCR4) to the histological patterns of cBFL, 40 patients with cBFL who underwent surgical lung biopsies, 12 with acute BFL (aBFL) and 10 healthy volunteers were analysed (65). The ratio of TARC to IP-10 in the serum of patients with UIP-like lesions was significantly higher than in patients with cNSIP/OP-like lesions, aBFL and healthy volunteers. The ratio of CCR4 to CXCR3 in patients with UIP-like lesions was significan-
tly higher than in those with cNSIP/OP-like lesions and fNSIP-like lesions. The ratio of CCR4(+) to CXCR3(+) cells correlated with the ratio of TARC to IP-10 in serum. These results suggest a Th1 predominance may play a role in the development of cNSIP/OP-like lesions in cBFL (65).

However another study did not find any relationship between the severity of HP and circulating chemokines (66).

EAA and idiopathic pulmonary fibrosis (IPF) share the presence of varying degree interstitial involvement and fibrosis. Vascular changes were often reported to accompany the development of fibrosis. The aim of a subsequent study (67) was to examine the differences in angiogetic and angiogenic chemokine milieu in both diseases. Correlations between chemokine levels in bronchoalveolar lavage fluid (BALF), expression of chemokine receptors on CD4+ T cells (CXCR2, CXCR3) in BALF and high-resolution computed tomography (HRCT) pattern of the diseases were investigated. There was no significant difference in the BALF chemokine levels between the EAA and IPF group. IL-8 BALF concentrations correlate with the extent of fibrosis in both EAA and IPF (p<0.01). The IP-10 BALF concentrations do not correlate either with the HRCT alveolar or interstitial score (67).

To investigate the relative contribution of angiogenic and angiogetic CXC chemokines to the pathogenesis of IPF and granulomatous lung diseases, it was examined the in vitro production of an angiogenic chemokine (IL-8), and 2 angiogetic chemokines (IP-10 and MIG) by alveolar macrophages (68). In IPF patients, IL-8 was increased and correlated with BAL neutrophils, whereas the levels of IP-10 and MIG were normal. In EAA patients, IL-8, IP-10, and MIG were all increased and IP-10 and MIG correlated with the percentage and number of BAL lymphocytes. The Authors suggested that difference in the expression of CXC chemokines and Th1 cytokines may contribute to the different immunopathogenesis, clinical course and responsiveness to treatment of these diseases (68).

Osteopontin is a key cytokine involved in pro-inflammatory Th1-associated immune responses, which has recently been implicated in allergic diseases. It was investigated the pathogenic role of osteopontin in eosinophilic pneumonia. Osteopontin circulating concentrations were elevated at the time of exacerbation, decreased during clinical improvement, either spontaneously or as a result of corticosteroid therapy. Elevated concentrations of IP-10, CCL17 and IL-10 were also detected in BALF from patients with eosinophilic pneumonia (69).

The last study (70) was to investigate changes in levels of the cathelicidin related antimicrobial peptide (CRAMP), laminin (LAM-A1), selected Toll-like receptors (TLR) and chemokines in experimental HP in mice. C57BL/6J mice underwent inhalations of the saline extract of Pantoea agglomerans cells, Gram-negative bacterium common in organic dust and known for its pathogenic impact. Levels of TLR2, TLR4 and MIG were significantly higher in both young and old mice lungs already after 7 days of inhalations, while significant increase of LAM-A1 and CXCL10 was noted after 28 days, compared to untreated samples (70).

**Discussion**

HP is categorized as a Th1 disease, and granuloma formation is dependent on T cells and the Th1 cytokine IFN-γ. In experimental setting it has been shown (in mice exposed to the particulate antigens that cause HP) the production of IP-10, MIG, and I-TAC during the development of HP. The production of these chemokines was associated with an influx of CXCR3+/CD4+ T cells into lungs, suggesting that IFN-γ mediates the recruitment of CXCR3+/CD4+ T cells into the lung via production of the chemokines IP-10, MIG, and I-TAC, resulting in granuloma formation. In humans it has been shown that lymphocytes infiltrating lung biopsies are CD8 T cells overexpressing for CXCR3. Furthermore, T cells accumulating in the BAL of HP were CXCR3(+) and IFN-γ (+) Tc1 cells exhibiting a strong in vitro migratory capability in response to CXCL10. Alveolar macrophages express and secrete, in response to IFN-γ, high levels of CXCL10 capable of inducing chemotaxis of the CXCR3(+) T-cell line. High levels of CXCR3 ligands were shown in the fluid of the BAL in individuals with HP. These data confirm that IFN-γ mediates the recruitment of lymphocytes into the lung via production of the chemokine CXCL10, resulting in Tc1-cell alveolitis and granuloma formation.

**Conclusion**

It has been suggested that difference in the expression of CXC chemokines and Th1 cytokines may contribute to the different immunopathogenesis, clinical course and responsiveness to treatment of HP.

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