Sarcoidosis and the Th1 chemokine MIG

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Abstract

Sarcoidosis is a systemic inflammatory disease, affecting any organ, and that can be discovered by accident in approximately 5% of cases.

High levels of the type-1 helper (Th1)-dependent chemokine, monokine induced by interferon (IFN-)γ (MIG)/chemokine (C-X-C motif) ligand (CXCL)9, and its receptor CXCR3 have been reported in bronchoalveolar lavage and biopsy samples of patients with sarcoidosis. These elevated levels are related with the amount of CD4+ lymphocytes and total lymphocytes. Alveolar macrophages resulted stained positive for all CXCR3 ligands and produced elevated levels of these chemokines.

It has been shown that the epithelioid and giant cells of the sarcoid lungs were stained positive for MIG, IFN-inducible T-cell α chemotactractant (I-TAC) and IFN-γ-inducible protein 10 (IP-10), suggesting that MIG plays an important role in the accumulation of Th1 lymphocytes in sarcoid lungs. In addition, serum levels of MIG were related with the severity of the disease, and a correlation between the serial measurements of MIG and the clinical course of the disease was shown, indicating MIG as a potentially useful biomarker of sarcoidosis and its severity. Clin Ter 2018; 169(6):e308-313. doi: 10.7417/CT.2018.2099

Key words: CXCR3, IP-10, I-TAC, MIG, sarcoidosis

Introduction

Sarcoidosis is a systemic inflammatory disease, affecting any organ, and that can be discovered by accident in approximately 5% of cases. The most common symptoms are fatigue, weight loss, lack of energy, arthritis (14–38% of subjects), joint aches, swelling of the knees, dry eyes, blurry vision, shortness of breath, skin lesions, or a dry cough: any organ system can be involved. The cutaneous symptoms include rashes and noduli, erythema nodosum, lupus pernio, or granuloma annulare (1-4).

Granulomatous inflammation is characterized by a Type-1 helper (Th1)-mediated immune response with accumulation of macrophages, monocytes, and activated T-lymphocytes, and an elevated production of key inflammatory mediators (as tumor necrosis factor (TNF)-α, interleukin (IL)-12, interferon (IFN)-γ, IL-2, Tumor growth factor (TGF)-β, IL-18, and IL-8) (5, 6).

Sarcoidosis is associated with autoimmune disorders, as thyroid autoimmune diseases (7, 8). The treatment of sarcoidosis depends on patients (9). Usually, half of patients require no systemic therapy (10). More than 75% of patients require symptomatic treatment with non-steroidal anti-inflammatory drugs (NSAIDs), like ibuprofen or aspirin.

Drugs include glucocorticoids, antimitabolites, biologic agents (like monoclonal anti-TNF antibodies), while investigational treatments include specific antibiotic combinations and mesenchymal stem cells (10). The standard drugs used until now are corticosteroids, especially prednisone or prednisolone (11). Some people respond to this treatment with a slowdown or an inversion of the disease course, while others do not respond to steroid therapy. In case of mild disease, the use of corticosteroids is controversial because sometimes the disease remits spontaneously (12, 13).

MIG and CXCR3

Th1-dependent chemokines, monokine induced by IFN-γ (MIG)/chemokine (C-X-C motif) ligand (CXCL)9, IFN-γ-inducible protein 10 (IP-10)/CXCL10 and IFN-inducible T-cell α chemotactractant (I-TAC)/CXCL11 bind the receptor CXCR3. These chemokines bind CXCR3-A and CXCR3-B, two isoforms of the CXCR3 that is a Gαi protein-coupled receptor; CXCR3-B shows high affinity binding to chemokine CXCL4 (14).

Natural Killer (NK) cells, activated T lymphocytes, some endothelial and epithelial cells express CXCR3, and it is extremely expressed by Th1 cells, as the chemokine (C-C motif) receptor (CCR)5.

Local cells produce the chemokines IP-10, I-TAC and MIG, that recruit Th1 cells in inflamed site. In the recruitment of inflammatory cells CXCR3 and its ligands are determinant (15).
The gene for MIG is located on human chromosome 4, near to the genes for the chemokines IP-10 and I-TAC, that are closely related to MIG. MIG is a small chemokine induced by IFN-γ, that attracts T-cell (16, 17). In the Th1 response, elevated serum MIG levels are considered a marker of host immune response (18, 19). In the inflamed site IFN-γ and TNF-α, produced by Th1 lymphocytes, stimulate MIG secretion from several cells, amplifying a feedback disorders, and also in cancers (61-82).

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Several studies indicate high serum MIG levels (and of other Th1 chemokines) and/or an elevated tissue expression in different organ of specific autoimmune diseases, as autoimmune thyroiditis (20-25), Graves’ disease (26, 27), Graves’ ophthalmopathy (28-31), type 1 diabetes (32-36), or systemic lupus erythematosus (38, 39), systemic sclerosis (40-43), psoriasis or psoriatic arthritis (44-46), rheumatoid arthritis (RA) (37), systemic lupus erythematosus (38, 39), systemic sclerosis (40-43), psoriasis or psoriatic arthritis (44-46), and healthy subjects, had elevated serum levels of both CXCL9 and CXCL10, that are closely related to MIG. MIG is a small chemokine (4, near to the genes for the chemokines IP-10 and I-TAC), that is induced by IFN-γ, that attracts T-cell (16, 17). In the Th1 response, elevated serum MIG levels are considered a marker of host immune response (18, 19).

Here we review the role of the Th1-dependent chemokine MIG in sarcoidosis.

The presentation of data has been reported in line with the International Narrative Systematic Assessment (INSA) tool (83).

MIG in sarcoidosis

In a first paper circulating CXCL8, CXCL9, CXCL10, CCL2, and CCL5 levels were evaluated in 17 patients with active ocular sarcoidosis, with respect to 18 healthy subjects (84). The patients with diagnosed or suspected ocular sarcoidosis, compared with patients with other types of uveitis and healthy subjects, had elevated serum levels of both CXCL9 and CXCL10, that correlated with ocular disease activity and angiotensin converting enzyme (ACE) level (84).

Another study evaluated 20 patients with sarcoidosis, 20 patients with idiopathic pulmonary fibrosis (IPF), and 10 control subjects (85). In IPF patients, circulating MIG levels were significantly upregulated than in sarcoidosis patients and healthy controls. In sarcoidosis patients, MIG and IP-10 bronchoalveolar lavage fluid (BALF) levels (1,136 pg/mL vs 66 pg/mL (p < 0.001) and 112 pg/mL vs 56 pg/mL (p = 0.037), respectively) were significantly higher in comparison to IPF patients. IFP and sarcoidosis could have distinct angiogenic profiles, that suggest a potential different role of the CXC chemokines in the local immunologic response in IPF and pulmonary sarcoidosis (85).

A paper evaluated MIG, IP-10 and I-TAC in BALF and serum in patients with pulmonary sarcoidosis (86). In BALF MIG and IP-10 levels were significantly higher in stage II sarcoidosis than in healthy volunteers. In stage II of the disease MIG and I-TAC were elevated. In BALF it was observed a correlation between the levels of all CXCR3 ligands and the numbers of both total and CD4+ lymphocytes. All CXCR3 ligands were expressed by alveolar macrophages that produced increased amounts of these chemokines. In the sarcoid lungs, the epithelioid and giant cells were stained positive for MIG, I-TAC and IP-10, suggesting that these chemokines could have a determinant role in the accumulation of Th1 lymphocytes (86).

Another study evaluated the chemokines in BALF of 10 patients with polycystic sarcoidosis, i.e. Löfgren’s syndrome (LS) and more advanced chest X-ray (CXR) stage III disease (87). In CXR stage III patients elevated levels of CXCL8, CXCL9, CXCL10, CCL15, CCL16, CCL24, IL-16, macrophage migration inhibitory factor, macrophage stimulatory protein (MSP) and matrix metalloproteinase 1 were present in comparison to patients with LS (87). In this study it was demonstrated that CCL15 and MSP were associated with the disease course. Increased level of CCL15 was related with the progression of the disease at 2 years from the beginning of the disease. MSP was associated with the treatment; in particular its levels resulted increased in those patients who needed treatment with corticosteroids.

In BALF of sarcoid patients (n = 72) and healthy controls (n = 8) chemokine levels were measured. CXCL9 levels were higher in BALF of sarcoid patients with respect to control subjects (88). The epithelioid histiocytes, multinucleated giant cells and other inflammatory cells forming sarcoid lung granulomas expressed CXCL9, CXCR3 and CXCL11. It was observed that CXCL9 and CXCL11 could be important mediators in recruiting CXCR3-expressing cells (88).

In order to estimate the relative contribution of angiogenic and angiostatic CXC chemokines to the pathogenesis of IPF and granulomatous lung diseases, the in vitro production of 2 angiostatic chemokines (IP-10 and MIG), and an angiogenic chemokine (IL-8) by alveolar macrophages was evaluated (89). In IPF, IL-8 was elevated and correlated with bronchoalveolar lavage (BAL) neutrophils while IP-10 and MIG were normal. In sarcoidosis and extrinsic allergic alveolitis (EAA) patients, IL-8, IP-10, and MIG were raised, and IP-10 and MIG correlated with IL-18, and the number and percentage of BAL lymphocytes (89). A murine model generated with Propionibacterium acnes was used to identify immunological targets for the treatment of pulmonary granulomatosis (90). To produce pulmonary granulomatosis in C57BL/6 mice were used heat-killed P. acnes and dendritic cells (DCs). The cytokines or chemokines, associated with the formation of granulomas in the lungs, have been searched by ELISA and cDNA microarray analysis. During granulomatosis the gene expression of CXCL9 and CXCL10 (ligands for CXCR3), and of CCL4 (a ligand for CCR5) was highly upregulated, as shown by cDNA microarray assay. CXCL9 and CXCL10 levels, and those of Th1 cytokines and chemokines as TNF-α and IFN-γ were elevated in BALF, as confirmed by ELISA. In BALF a reduced numbers of CXCR3+CD4+ and CCR5+CD4+ T-cells was observed with the use of TAK-779, a dual blocker for CXCR3 and CCR5 that blocks Th1 chemokine receptors. The Authors concluded that the targeted inhibition of Th1 chemokines might be useful for inhibiting Th1-biased granulomatous diseases, as sarcoidosis (90).

Another study evaluated if chemokines levels were high in sera and identified patients with remitting vs chronic progressive sarcoidosis longitudinally (91). CXCL9, CXCL10, and soluble IL-2 receptor serum levels in 36 non-immunosuppressed sarcoidosis patients were significantly more...
elevated with respect to 46 controls (p<0.0001), as shown by a cross-sectional analysis. There was a strong correlation between CXCL9 and CXCL10 (p=0.0009). CXCL10 and CXCL9 were inversely correlated with forced vital capacity (FVC)% predicted and diffusing capacity (DLCO)% predicted, respectively, and significantly correlated with sarcoidosis severity score. In the longitudinal analysis of 26 subjects, changes were observed gradually in serum CXCL10 levels, that corresponded with progression versus remission of disease (91).

A further study estimated the role of CXCR3 ligands in the pathogenesis of sarcoidosis and the predictive value of their concentrations in BAL fluid in 59 patients with sarcoidosis and 34 control subjects (92). It has been hypothesized that cytokines CXCL9, CXCL10, and CXCL11 could play a role in the pathogenesis of chronic sarcoidosis, but they should not be considered as potential prognostic markers, because there were not considerable differences between the sarcoidosis and control groups and there was no association with the chronic course of the disease (92).

Another paper hypothesised that expression levels of candidate genes in sarcoidosis blood could predict and track with disease outcomes longitudinally (93). Upregulation of genes related to IFN signaling and the role of pattern recognition receptors, and downregulation of T-cell receptor (TCR) signaling pathways in sarcoidosis were shown by pathway analysis in the cross-sectional derivation study. In the longitudinal cohort, coregulation of genes marking these pathways was confirmed by factor analysis that identified CXCL9 as a further candidate pathway. CXCL9 and TCR factors differentiated between chronic vs non progressive disease, and CXCL9 predicted disease outcomes longitudinally, demonstrating blood transcriptomic signatures reflecting TCR signaling and that longitudinally CXCL9 predict sarcoidosis chronicity and correlate with disease severity (93).

Effective biomarkers for the diagnosis and therapy of pulmonary sarcoidosis were identified by another study (94), conducted in pulmonary sarcoidosis samples, that identified a total of 208 differentially expressed genes (DEGs), including 179 up-regulated genes and 29 down-regulated genes. DEGs could distinguish the pulmonary sarcoidosis samples from the normal lung samples, as shown by hierarchical clustering. In the protein-protein interaction network generated by STRING database, signal transducer and activator of transcription 1 (STAT1), CCL5, CXCL11, guanylate binding protein 1 (GBP1), and CXCL9 had higher functional importance and produced elevated levels of these chemokines.

It has been shown that the epithelioid and giant cells of the sarcoid lungen were stained positive for MIG, I-TAC and IP-10, suggesting that MIG plays an important role in the accumulation of Th1 lymphocytes in sarcoid lungs. In addition, serum levels of MIG were related with the severity of the disease, and a correlation between the serial measurements of MIG and the clinical course of the disease was shown. This could indicate MIG as a potentially useful biomarker of sarcoidosis and its severity.

### Conclusion

High levels of MIG and its receptor CXCR3 in BAL and biopsy samples of patients with sarcoidosis have been reported. These elevated levels are related with the amount of CD4+ lymphocytes and total lymphocytes, too. Alveolar macrophages resulted stained positive for all CXCR3 ligands and produced elevated levels of these chemokines.

References

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