Review

Dermatomyositis and MIG

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Abstract

Several studies demonstrated the presence of an elevated expression of chemokine (C-X-C motif) ligand (CXCL)9/monokine induced by interferon (IFN)-γ (MIG) on macrophages and in T cells in perimysial infiltrates of patients with dermatomyositis (DM), and of chemokine (C-X-C motif) receptor (CXCR)3 expression on the majority of T cells in the same patients. This underlines the importance of T helper 1-mediated immunity, and in particular the MIG/CXCR3 interaction, in the immunopathogenesis of DM.

The importance of MIG has been confirmed by a study on patients with DM about the presence of chemokines and their receptors in infiltrating cells at the level of lesional skin. This study showed that type 1 IFN chemokines, in particular MIG, are firmly related with the active disease and its clinical score in juvenile DM, suggesting the importance of chemokines trend in monitoring disease activity and in the treatment indication.

Key words: CXCR3, Dermatomyositis, MIG

Introduction

Dermatomyositis

Dermatomyositis (DM) is a systemic autoimmune disease characterized by muscles and skin inflammation, that affects more frequently females. Inflammation can also involve joints, esophagus, lungs and, less commonly, heart (1-4).

Skin rash and symmetric proximal muscle weakness, accompanied by pain, ranging from light to severe, are the main symptoms of DM. Sometimes patients can be temporarily unable to walk due to muscle problems.

Some examples of skin findings that occur in DM are: Gottron’s sign (an erythematous, symmetric, scaly eruption which manifests at the metacarpophalangeal joints), “lilac” rash (a violaceous eruption at the level of upper eyelids). Calcinosis cutis, that is a deposition of calcium in the skin, is present frequently in the juvenile form of DM, while dysphagia occurs in about 33% of cases (5, 6).

The cause of DM is not yet known. It has been hypothesized that it could depend on an initial viral or bacterial infection; indeed, different patients with DM have been previously affected by infectious mononucleosis, Epstein-Barr virus, Chlamydia pneumoniae, psittacosis, and other types of infections. Since several cases of DM are paraneoplastic, the presence of cancer has been suggested.

DM is characterized by a complement-mediated damage of microscopic vessels with tissue ischemia, accompanied by muscle atrophy and lymphocytic inflammation. B-lymphocytes and T-lymphocytes aggregate surrounding vessels (7, 8).

The presence of myositis-specific autoantibodies (MSAs), especially anti-Mi-2 antibodies, but also anti-Jo-1 antibodies in a minor percentage, is associated with DM (9, 10). Sometimes, antinuclear antibody may be positive, too. It was demonstrated an increased expression of Jo-1 and Mi-2 in regenerating fibers in muscle biopsies obtained from DM patients with respect to normal samples; autoantigen expression is restricted to regenerating muscle cells rather than mature myotubes, both in inflamed muscle tissue and in non-inflamed regenerative myofibers. MSAs and target autoantigens are both involved in the induction of muscle damage and disease perpetuation. The detection of MSAs in the early phase of the disease could help to predict the clinical course and prognosis of the patients (10).

In some patients DM co-exists with other autoimmune diseases such as Sjögren’s syndrome, lupus, scleroderma, or vasculitis.

Many studies have evaluated the importance of cytokines and chemokines in DM (7, 11).

Here, we explore in particular the role of chemokines in DM.

MIG, and CXCR3

Chemokine (C-X-C motif) receptor (CXCR)3, a Gαi protein-coupled receptor which is part of CXC chemokine receptor family, exists as two different isoforms: CXCR3-A and CXCR3-B. CXC chemokines, like (C-X-C motif) ligand (CXCL)9/monokine induced by interferon (IFN)-γ (MIG), CXCL10/IFN-γ-inducible protein 10 (IP-10) and CXCL11/
IFN-inducible T-cell chemoattractant (I-TAC), are binded by the two isoforms of CXCR3, while chemokine CXCL4 binds only CXCR3-B (12).

It has been shown an expression of CXCR3 by different cells, like activated T lymphocytes and Natural Killer cells, and some epithelial and endothelial cells. Type-1 helper (Th1) cells express CXCR3 and the chemokine (C-C motif) receptor (CCR)5 at high level. In inflammatory lesions, the local cells usually produce MIG, IP-10 and I-TAC, which in turn attract Th1 cells; this support the idea that CXCR3 and its ligands have a central role in the recruitment of inflammatory cells (13).

MIG is induced by IFN-γ and acts as T-cell chemoattractant. There is a strong correlation between the three chemokines, MIG, IP-10 and I-TAC, whose genes are all located on human chromosome 4 (14, 15). In peripheral liquids, high circulating levels of MIG could be considered as marker of host immune response involving especially Th1 cells (16, 17).

Th1 lymphocytes release IFN-γ and tumor necrosis factor (TNF)-α, which in turn stimulate several cells in the inflamed site to produce MIG; all this results in an amplification feedback loop (16, 17), that cause the recruitment of Th1 lymphocytes in the inflammatory site.

In several organ specific autoimmune diseases, such as autoimmune thyroiditis (18-23), Graves’ disease (24-27), Graves’ ophthalmopathy (28-31), type 1 diabetes (32-36), or systemic rheumatological disorders, such as rheumatoid arthritis (37), systemic lupus erythematosus (SLE) (38, 39), systemic sclerosis (SSc) (40-45), psoriasis or psoriatic arthritis (37), systemic lupus erythematosus (SLE) (38, 39), or systemic rheumatological disorders, such as rheumatoid arthritis (37), systemic lupus erythematosus (SLE) (38, 39), or systemic rheumatological disorders, such as rheumatoid arthritis (37), systemic lupus erythematosus (SLE) (38, 39), systemic sclerosis (SSc) (40-45), psoriasis or psoriatic arthritis (46-49), sarcoidosis (50-52), HCV-related cryoglobulinemia (53-56), different HCV immune mediated disorders (21, 57-64), other disorders, and also in cancers (65-80), it has been shown an increased tissutal expression, and high circulating levels, of MIG, and other Th1 chemokines.

Here we study the role of MIG in DM. The presentation of data has been reported according to the International Narrative Systematic Assessment (INSA) tool (81).

**MIG chemokine and DM**

In order to understand if in patients with (SSc) serum levels of chemokines preferentially chemoatctic for Th1 cells (IP-10 and MIG) and predominantly chemoatctic for Th2 cells [thymus and activation regulated chemokine (TARC) and macrophage-derived chemokine (MDC)] are elevated and in relationship with clinical disorders, such as rheumatoid arthritis (37), systemic lupus erythematosus (SLE) (38, 39), systemic sclerosis (SSc) (40-45), psoriasis or psoriatic arthritis (46-49), sarcoidosis (50-52), HCV-related cryoglobulinemia (53-56), different HCV immune mediated disorders (21, 57-64), other disorders, and also in cancers (65-80), it has been shown an increased tissutal expression, and high circulating levels, of MIG, and other Th1 chemokines.

The gene expression has an important biological signifiance in the pathogenesis of inflammatory myopathies. For this reason, experiments of microarray followed by real-time PCR and immunohistochemistry have been conducted on muscle biopsies obtained before and after therapy from patients with DM who improved and from patients with sporadic inclusion body myositis (sIBM) who did not improve after controlled trials consisting of intravenous immunoglobulin infusions every three months. In pretreatment biopsies, the results showed a high expression of immunoglobulin, adhesion molecules, chemokines and cytokine genes in both sIBM and DM, although more in sIBM than in DM. In repeated biopsies of DM patients who clinically improved, 2206 genes resulted downregulated more than 1.5-fold; 1700 of the these same genes maintained their expression unchanged in sIBM patients who did not improve. In addition, in improved muscles of DM it has been shown an upregulation of MIG and I-TAC, and several immunoglobulin-related genes, supporting the idea of their effect on muscle remodelling and regeneration (83). The idiopathic inflammatory myopathies (IIM) represent an heterogeneous family of neuromuscular disorders, which include polymyositis (PM), sIBM and DM. Through immunohistochemistry, immunofluorescence and Western blotting it has been investigated the distribution of the alpha-chemokine receptors CXCR1, 2, 3 and their ligands I-TAC, IP-10, MIG and growth-related oncogene (GRO) in IIM. IP-10 was present at high concentrations on macrophages and T cells which surrounded and invaded non-necrotic muscle fibers in PM and sIBM, but also in T cells in perimsial infiltrates of DM patients. In addition, IP-10 has been detected on endothelial cells of blood vessels in all inflammatory and normal muscle tissues. On the contrary, MIG and I-TAC have been detected at low levels. GRO expression has been revealed at level of endomysial infiltrates of some PM and sIBM samples, but not in DM. Finally, it has been shown a strong expression of CXCR3 on the majority of T cells in each IIM (84).

A further study investigated the relationship between the vasculopathy of juvenile DM and the balance between the angiostatic ELR- and angiogenic ELR+ CXC chemokines in the muscle of patients with this disease. In most juvenile DM samples, the angiostatic ELR- chemokines resulted expressed at high levels, while the angiogenic ELR+ chemokines were poorly detectable. All this is in contrast with the results obtained in both normal muscle biopsy specimens and juvenile rheumatoid arthritis synovial tissue specimens. Fall et al. showed a relationship between the expression of the ELR- chemokines in juvenile DM samples and the intensity of mononuclear cell infiltration. Immunohistochemistry analysis confirmed the presence of IP-10 and MIG in juvenile DM muscle specimens. Furthermore, immunohistochemical staining of muscle tissue highlighted the expression of CXCR3, a receptor utilized by ELR- CXC chemokines, in vascular endothelial cells. These findings supported the idea that increased expression of the IFN-induced angiostatic ELR-CXC chemokines can be a caracteristic of juvenile DM that related to the degree of vasculopathy in patients with this disease (85).

A review about cytokine-chemokine patterns in some
recent studies in IIMs provided further evidence of three concepts: 1) the importance of Th1-mediated reactions in the different IIMs; 2) the inflammation-induced degenerative phenomena in IBM; 3) the possible important role of lymphoneogenesis in the sustained inflammatory response in DM (86).

Another review showed that MIG and IP-10 are expressed in IIMs muscle, and that drugs which block the IP-10/CXCR3 axis could suppress inflammation in muscle (87). In particular it was observed an abundant expression of IP-10 on macrophages and T cells which surround and invade non-necrotic muscle fibers in PM and sIBM, but also in T cells at the level of perimysial infiltrates of DM. IP-10 was also localized to blood vessel endothelial cells in all inflammatory and normal muscle tissues. In patients with inflammatory myopathies it was also observed a high expression of serum IP-10 (87).

Another study described the extensive cytokine network involved in IIM muscle, characterized by an elevated expression of TNFs (TNFα, LTα, BAFF), Interferons (IFNα/β/γ), Interleukins (IL-1/6/12/15/18/23) and Chemokines (CXCL9/10/11/13, (C-C motif) ligand (CCL)2/3/4/8/19/21). In this paper the authors suggested new therapeutic strategies, and explored the potential disease modifying agents which are based on manipulation of the cytokine axis. Discordant results have been reported about the responses to anti-TNFα treatment in IIM; furthermore it has been described a new onset DM/PM after administration of anti-TNFα agents used to treat other diseases, highlighting the complex effects of TNFα neutralization. In DM/PM patients, treatment with anti-IFNα seems to suppress the IFN type 1 gene signature and to improve muscle strength. In addition, the authors described the beneficial effects of anti-IL-1 and anti-IL-6 therapy (88).

Chemokines play an important role in the pathophysiology of DM with interstitial pneumonia (IP), Oda et al. evaluated the serum chemokine profiles of CCL2, Th1 chemokines (MIG, IP-10, I-TAC), and Th2 chemokine (CCL17) in 30 patients, in order to examine the relationship between these chemokines and the disease activity or prognosis of DM-IP. They found that initial serum CCL2 level are higher in the death group (P=0.007); the serum CCL2, MIG, IP-10 and I-TAC levels are lower 2 weeks after the start of treatment with prednisolone and other drugs (alone or in combination) compared to chemokines values observed before treatment. These results suggested that the serum levels of Th1 chemokines could be biomarkers of activity and prognosis disease in DM-IP (89).

Conclusion

In DM, MIG is expressed at elevated levels on macrophages and in T cells in perimysial infiltrates, while CXCR3 has been observed on the majority of T cells. This could suggest the idea that the Th1-mediated immunity in general, and the interaction between CXCR3 and MIG in particular, play an important role in the immunopathogenesis of DM. The studies on infiltrating cells, related cytokines and chemokine receptors in lesional skin in DM patients underline the importance of Th1 chemokines. In juvenile DM, type I IFN chemokines, particularly MIG, are closely linked to active disease and are correlated with the clinical scores; this could help to monitor the activity of the disease and to guide the treatment.

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