The MIG Chemokine in Inflammatory Myopathies

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Abstract

The chemokine monokine induced by interferon (IFN)-γ (MIG) is expressed in idiopathic inflammatory myopathies muscle. Abundant expression of MIG was observed on macrophages and T cells surrounding and invading non-necrotic muscle fibers in polymyositis and in inclusion-body myositis and in T cells in perimysial infiltrates of dermatomyositis. MIG is also localized to blood vessel endothelial cells in all inflammatory and normal muscle tissues and it exerts its biological effects mainly via binding to the chemokine (C-X-C motif) receptor (CXCR)3. Serum MIG is high in patients with inflammatory myopathies. Human skeletal muscle cells might actively self-promote muscular inflammation by eliciting MIG secretion, under the influence of cytokines (IFN-γ, tumor necrosis factor-α), which can amplify Th1 cell tissue infiltration in vivo. It has been shown that drugs able to block the MIG/CXCR3 axis can suppress inflammation in muscle.

Key words: CXCR3, Dermatomyositis, Inflammatory Myopathies, MIG

Introduction

CXCR3 and MIG

The chemokines monokine induced by interferon (IFN)-γ (MIG), IFN-γ-inducible protein 10 (IP-10) and IFN-inducible T-cell α chemoattractant (I-TAC) are CXC chemokines than bind the chemokine (C-X-C motif) receptor (CXCR)3. CXCR3 is a Gα protein-coupled receptor belonging to CXC chemokine receptor family, with two isoforms: CXCR3-A and CXCR3-B. Both isoforms bind MIG, IP-10 and I-TAC; CXCR3-B also binds chemokine CXC ligand (CXCL)4 (1).

Activated T lymphocytes, Natural Killer (NK) cells and some epithelial and endothelial cells express CXCR3 such as other various cells. Type-1 helper (Th1) cells highly express CXCR3 as well as chemokine (C-C motif) receptor (CCR)5.

In the inflammatory lesions local cells produce commonly chemokines MIG, IP-10 and I-TAC that are able to attract Th1 cells; then both CXCR3 and its ligands have a central role in the recruitment of inflammatory cells (2).

MIG is a small cytokine known as CXCL9, a T-cell chemoattractant, induced by IFN-γ and is strictly associated to two other CXC chemokines called IP-10 and I-TAC, whose genes are located near the gene for MIG on human chromosome 4 (3, 4).

Therefore high level of MIG, revealed in peripheral liquids, can be considered as a marker of host immune response, especially of that involving Th1 cells (5, 6).

Indeed in the inflamed site several cells secrete MIG that is stimulated by increasing production of IFN-γ and tumor necrosis factor (TNF)-α from recruited Th1 lymphocytes, leading to an amplification feedback loop (5, 6).

Different studies report high level of serum MIG (and of other Th1 chemokines) and/or of the tissue expressions in different organ specific of autoimmune diseases.

Actually this has been found in several specific autoimmune diseases such as: autoimmune thyroiditis (7-12), Graves’ disease (13, 14) Graves’ ophthalmopathy (15-18), type 1 diabetes (19-23), or systemic rheumatological disorders, like rheumatoid arthritis (24), systemic lupus erythematosus (25, 26), systemic sclerosis (27-31), psoriasis or psoriatic arthritis (32-35), sarcoidosis (36-38), HCV-related cryoglobulinemia (39-44), other HCV immune mediated disorders (11, 45-50), other disorders, and also in cancers (51-66).

Inflammatory myopathies

Inflammatory myopathy (also known as inflammatory muscle disease or myositis) is characterized by weakness and inflammation of muscles and sometimes muscle pain.

This disease is an immune-mediated inflammation direct against skeletal muscles not recognized as “self” and the specific cause of inflammatory myopathies is unknown (idiopathic). Similar cases are classified on the basis of their signs, symptoms, laboratory findings, electromyography and Magnetic Resonance Imaging. Idiopathic inflammatory
myopathies are divided in these major group according to
different clinical, histological and pathogenic characteristics:
polymyositis (PM), dermatomyositis (DM), and inclusion-
body myositis (IBM).

These rare disorders may affect both adults and chil-
dren, although DM is the most common chronic form in
children. PM and DM are more common in women than in
men. A rare childhood onset form of PM and DM can occur
in children between the ages of 2 and 15 years. IBM usually
affects individuals over age 50.

In inflammatory myopathies the body’s white blood cells
attack normal muscle fibers, blood vessels and connective
tissue in organs, bones and joints (67-73) since they are
autoimmune diseases.

The aim of this narrative review is to investigate the role
of MIG in inflammatory myopathies. The presentation of
data has been reported according to the International Nar-
rative Systematic Assessment (INSA) tool (74).

MIG in inflammatory myopathies

In the muscle biopsies of patients with sporadic inclusion
body myositis (s-IBM) and controls, Raju R et al. evaluated
MIG, IP-10, I-TAC and their receptor CXCR3 (75). They
observed a high level of MIG and IP-10 mRNA expression
in s-IBM muscles in comparison to controls. Moreover
human myotubes produced IFN-γ upregulating MIG and
IP-10 mRNA expression in a dose-dependent manner. By
double-label immunohistochemistry, MIG was expressed
more on CD8(+) cells in the areas of the muscle fiber near
to the T cells; CXCR3 was expressed only in autoinvasive
CD8(+)/T cells and not the myofibers. IP-10 and I-TAC were
not detected by immuno-cytochemistry. These findings lead
to hypothesize that IFN-γ is involved in the upregulation
and in situ production of chemokines that take part in the
recruitment of activated T cells (75).

A study performed microarray experiments followed
by real-time PCR and immunohistochemistry on muscle
biopsies obtained before and after therapy from patients
with DM who improved and patients with s-IBM who did
not improve after controlled trials with three monthly intra-
venous immunoglobulin (IVIg) infusions (76). This study
evaluated the biological significance of gene expression in
the pathogenesis of inflammatory myopathies. In both s-IBM
and DM (s-IBM > DM) the pretreatment biopsies showed
high expression of chemokines and cytokine genes. In the
repeated biopsies of DM patients who clinically improved,
2206 genes were downregulated more than 1.5-fold while
1700 of the same genes remained unchanged in s-IBM
patients who did not improve. In DM but not in s-IBM,
interleukin (IL)-22 and Kallmann syndrome 1 (KAL-1;
an adhesion molecule shown for the first time in muscle)
endothelial cells in all inflammatory and normal muscle
tissues. GRO was localized to the endomysial infiltrates of
muscle fibers in PM and s-IBM and in T cells in perimysial
infiltrates of DM. IP-10 was also localized to blood vessel
endothelial cells in all inflammatory and normal muscle
tissues. GRO was localized to the endomysial infiltrates of
some PM and s-IBM samples, but not in DM, while only
low levels of chemokines MIG and I-TAC were measured.
All IIM presented a strong expression of CXCR3 on most
of T cells. This study demonstrates the predominance of
Th1-driven reactions in the immunopathogenesis of all three
diagnostic subgroups (77).

Another paper evaluated the relationship between the
vasculopathy of juvenile dermatomyositis (juvenile DM) and
the balance between the angiostatic ELR- and angiogenic
ELR+ CXC chemokines in the muscle of patients with the
disease (78). The authors quantified the expression of 3
ELR- CXC chemokines (IP-10, MIG and I-TAC) and the
expression of 2 ELR+ CXC chemokines in muscle biopsy
samples from 7 patients with juvenile DM and 7 healthy
children. The angiogenic ELR+ chemokines were scarcely
measurable in various juvenile DM samples while the an-
giostatic ELR- chemokines were highly expressed in the
sample. This contrasted sharply with the findings in both
normal muscle biopsy specimens. The expression of the
ELR- chemokines in juvenile DM samples correlated with
the intensity of mononuclear cell infiltration. Moreover, the
highest levels of ELR- CXC chemokines were present in the
juvenile DM samples with the highest degree of capillary
loss. Furthermore, CXCR3, a receptor utilized by ELR- CXC
chemokines, was expressed in vascular endothelial cells,
as shown by analyzing immunohistochemical staining of
muscle tissue. This paper demonstrated that the elevated
expression of the IFN-induced angiostatic ELR- CXC che-
mosines is a feature of juvenile DM that parallels the degree
of vasculopathy in patients with the disease (78).

A large cohort study of patients with anti-Jo-1 antibodies
evaluated the relation between chemokines and interstitial
lung disease (ILD) (79). Among the 77 anti-Jo-1 antibody-
positive individuals, computed tomography scans showed a
variety of patterns suggestive of underlying usual interstitial
pneumonia (UIP) or nonspecific IP, and a review of the hi-
stopathologic abnormalities demonstrated a preponderance
of UIP and diffuse alveolar damage. By multiplex ELISA it
was shown a statistically significant associations between
anti-Jo-1 antibody-positive ILD and elevated circulating
levels of C-reactive protein (CRP), MIG and IP-10. This
association distinguished this disease entity from idiopa-
thic pulmonary fibrosis and anti-signal recognition particle
antibody-positive myositis. Disease-specific associations
between anti-Jo-1 antibody-positive ILD and serum levels
of CRP and IP-10 and MIG highlighted the potential of this
approach to define biologically active molecules contributing
to the pathogenesis of myositis-associated ILD (79).
Additioanal evidence for predominance of Th1-mediated reactions (IP-10, MIG) in the different IIMs, inflammation-induced degenerative phenomena in inclusion body myositis was given by a review and a possible role for lymphopenogenesis in the sustained inflammatory response in DM (80).

IVIg and prednisone are used in the therapy of inflammatory myopathies but are not effective in s-IBM. Relevant inflammatory and degeneration-associated markers were evaluated by quantitative PCR and immunohistochemistry in repeated muscle biopsy specimens from patients with s-IBM treated in a controlled study with IVIg and prednisone (n = 5) or with prednisone alone (n = 5).

After treatment, mRNA expression of the proinflammatory chemokines MIG, macrophage inflammatory protein 1-α (MIP-1-α), macrophage inflammatory protein-1β (MIP-1β) and of the cytokines IFN-γ and IL-1β was significantly decreased in muscle biopsy samples of both groups (81). After treatment with IVIg considerable staining of IgG was observed indicating penetration of infused IgG into the muscle and a possible local effect. The mRNA expression of IL-1β was down-regulated 2.5-fold in muscle cells exposed to IFN-γ with IL-1β. IgG and/or prednisone showing that IVIg and prednisone reduce some inflammatory and degenerative molecules in muscle of patients with s-IBM and in vitro (81).

Under the influence of IFN-γ and TNF-α, which can amplify Th1 cell tissue infiltration in vivo, skeletal muscle cells can actively self-promote muscular inflammation by stimulating MIG and IP-10 secretion as reported by a further review (82). Drugs able to block the IP-10/CXCR3 axis can suppress inflammation in muscle (82).

Another study analysed the extensive cytokine network within IIM muscle, characterized by strong expression of TNFs (TNF-α, LTβ), BAFF, IFNs (IFN-αβ/γ), ILs (IL-1β/6/12/15/18/23) and chemokines (MIG/IP-10/I-TAC/BCA-1, MCP1/ MIP-1-α/MIP-1β/MCP2/MIP-3β/6Ckine) (83). This manuscript reviewed the current therapeutic strategies and potential disease modifying agents based on modification of the cytokine network. The reported obtained data of the reaction to anti-TNF-α treatment in IIM are conflicting and new onset DM/PM has been described after administration of anti-TNF-α agents to treat other diseases, revealing the complex effects of TNF-α neutralization. It has been shown that treatment with anti-IFN-α improves muscle strength and reduces the IFN type 1 gene signature in DM/PM patients. Advantageous effects of anti-IL-1 and anti-IL-6 therapy have also been reported (83).

**Conclusion**

The chemokine MIG is expressed by IMM muscles. In macrophages and T cells surrounding and invading nonnecrotic muscle fibers in PM and s-IBM and in T cells in perimysial infiltrates of DM an elevated expression of MIG was found. The MIG chemokine exerts its biological roles binding CXCR3 and was also localized in blood vessel endothelial cells of all inflammatory and normal muscle tissues. Patients with inflammatory myopathy present high levels of serum MIG chemokine. Under the influence of cytokines (IFN-γ, TNF-α), which can amplify Th1 cell tissue infiltration in vivo, human skeletal muscle cells might actively self-promote muscular inflammation by eliciting MIG secretion. It has been reported that inflammation in muscle can be reduced by drugs that are able to block the bond of MIG with CXCR3 receptor.

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