The Th1 chemokine MIG in Graves’ ophthalmopathy
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Abstract

Chemokine (C-X-C motif) ligand (CXCL)9/monokine induced by interferon (IFN)-γ (MIG) and its receptor, chemokine (C-X-C motif) receptor (CXCR)3, are involved in the pathogenesis of Graves’ ophthalmopathy (GO). In tissues, recruited Type 1 helper (Th1) lymphocytes could cause an increased production of IFN-γ and tumor necrosis factor (TNF)-α, which in turn stimulate MIG secretion from these cells; all this creates an amplification feedback loop, and perpetuates the autoimmune process. In particular, MIG is secreted by fibroblasts and preadipocytes under the influence of IFN-γ. The IFN-γ induced MIG secretion in vitro, in GO fibroblasts and preadipocytes can be modulated by peroxisome proliferator-activated receptors (PPAR)-γ and PPAR-α activators.

High levels of MIG in peripheral liquids could be considered as a marker of an especially Th1 orientated immune response. The presence of circulating MIG is associated with the active phase of GO. An increased concentrations of MIG in patients with GO reflect, at least in part, the orbital inflammation activity.

Since MIG concentrations are significantly reduced during corticosteroids and/or radiotherapy treatments, with respect to control group and basal values of patients with GO, MIG has been proposed as a marker in the therapy choice for patients with GO.

More studies are needed to investigate interactions between chemokines and cytokines in the GO pathogenesis and to evaluate whether MIG is a novel therapeutic target in these autoimmune disorders. Clin Ter 2019; 170(5):e368-372. doi: 10.7417/CT.2019.212

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Introduction

Graves’ ophthalmopathy

Graves’ ophthalmopathy (GO) is clinically relevant in about 50% of patients with Graves’ disease (GD), severe forms affecting 3%-5% of patients. Two age peaks of incidence occur usually in the fifth and seventh decades of life, with an higher frequency in women than in men. Until now, the natural history of GO is not yet clear; in many cases the disease may remit or improve spontaneously, especially in mild forms. In most cases, the onset of the ophthalmopathy occurs in concomitance with the onset of hyperthyroidism, even if sometimes eye disease could precede or follow hyperthyroidism. It has been shown an important role of cigarette smoking in the occurrence of GO.

Actually GO primary prevention, is not feasible. Stop smoking, an early and accurate control of thyroid function, early diagnosis, treatment of mild eye disease are helpful for a secondary prevention (for example to avoid progression of subclinical eye disease into overt and severe ophthalmopathy) (1).

About the role of the management of hyperthyroidism in the course of GO, antithyroid drugs and thyroidectomy are not considered disease-modifying treatments, while radioiodine therapy is able to cause a progression of the ophthalmopathy in about 15% of patients. The risk of progression is higher especially in patients who smoke, patients with a severe hyperthyroidism or uncontrolled hypothyroidism, patients with high levels of thyroid-stimulating hormone (TSH)-receptor antibody, or patients with preexisting eye disease. Nevertheless, the risk of the progression of the ophthalmopathy associated to radioiodine can be eliminated by concomitant treatment with middle-dose of glucocorticoids.

An early immunosuppressive treatment (corticosteroids, rituximab, others) or orbital decompression, according to the cases, represents the tertiary prevention, to avoid the deterioration and complications of overt disease (2-6).

MIG, and CXCR3

The chemokine (C-X-C motif) receptor (CXCR3), a receptor belonging to the family of CXC chemokine receptors, exists in two different isoforms: 1) CXCR3-A, which binds chemokine (C-X-C motif) ligand (CXCL)10/interferon (IFN)-γ-inducible protein 10 (IP-10), CXCL9/monokine induced by IFN-γ (MIG), and CXCL11/IFN-inducible T-cell α chemoattractant (I-TAC); 2) CXCR3-B, which binds CXCL4 in addition to the three previous chemokines (7).
CXCR3 is expressed on different cells (activated T lymphocytes, Natural Killer, epithelial and endothelial cells). Type 1 helper cells (Th1) exhibit CXCR3 at elevated levels, but also the chemokine (C-C motif) receptor (CCR). It has been shown that cells of the inflammatory lesions secrete chemokines MIG, IP-10 and I-TAC, which in turn attract Th1 cells; then suggesting the central role performed by both CXCR3 and its ligands in the recruitment of the inflammatory cells (8). MIG, a T-cell chemoattractant induced by IFN-γ, is closely linked to IP-10 and I-TAC chemokines. All their genes are located on human chromosome 4 (9, 10). For this reason, high levels of MIG in peripheral fluids could represent a marker for the host immune response, in particular that involving Th1 cells (11, 12). The presence of high MIG levels reflects an amplification feedback loop in the inflamed site, in which recruited Th1 lymphocytes cause elevated levels of IFN-γ and tumor necrosis factor (TNF-α), that in turn induce several cells to produce MIG (11, 12). Different studies have reported high MIG tissue expression and high MIG serum levels in various organs specific for autoimmune diseases.

Indeed, high levels of MIG, but also that of the other Th1 chemokines, have been found in different specific autoimmune diseases, such as autoimmune thyroiditis (13-19), GD (20, 21) GO (22-24), type 1 diabetes (25-29), or systemic rheumatological disorders, like systemic lupus erythematosus (30, 31), rheumatoid arthritis (32), systemic sclerosis (33-37), sarcoidosis (38-40), vitiligo (41,42), psoriasis or psoriatic arthritis (43-45), HCV-related cryoglobulinemia (46-52), other HCV immune mediated disorders (17, 53-60), other disorders, and also in cancers (61-78).

This narrative review aims to study the importance of MIG in GO. The presentation of data has been reported in accordance to the International Narrative Systematic Assessment tool (79).

**MIG in GO**

A study assessed the serum IP-10 levels (sIP-10) in patients with active or inactive GO, investigating also the effect of IFN-γ and TNF-α on the IP-10 secretion in primary cultures of thyrocytes, orbital fibroblasts, and preadipocytes. GO patients with active disease had higher values of sIP-10 than subjects with inactive disease. IP-10 was not secreted in primary cultures of retrobulbar fibroblasts and retrobulbar preadipocytes obtained from GO patients under basal conditions; it was not released under the only effect of TNF-α, while IFN-γ alone or combined with TNF-α, was able to stimulate its release. These data showed that the release of chemokines from GO thyrocytes and retrobulbar cell types, under the influence of cytokines, causes a self-perpetuation of the inflammation (80); this has been supported by another study showing higher sIP-10 in GD patients with ophthalmopathy in comparison to GD patients without ophthalmopathy (81).

The effect of IFN-γ and TNF-α stimulation and PPAR-γ activation on MIG and I-TAC secretion in primary cultures of orbital fibroblasts, and preadipocytes from patients with GO has been investigated by another study. Under basal conditions the production of MIG and I-TAC was absent; their secretion was dose dependently stimulated by treating cells with IFN-γ, while TNF-α alone had no effect. MIG and I-TAC release was induced by a synergistic effect of the treatment with TNF-α plus IFN-γ. The IFN-γ plus TNF-α-induced MIG and I-TAC release was dose dependently suppressed by the treatment of these cells with the PPAR-γ agonists, rosiglitazone, or pioglitazone.

This study suggested that thyrocytes and retrobulbar cell types obtained from GD and GO patients are involved in the self-perpetuation of inflammation, by releasing MIG and I-TAC chemokines under the stimulation with cytokines. In this process PPAR-γ have an inhibitory role. IFN-γ and TNF-α stimulate a huge response of MIG, underlining its leading role among CXC chemokines (82).

The presence of PPAR-α, -δ and -γ in GO fibroblasts and preadipocytes was shown by another study. In fibroblasts and preadipocytes the secretion of MIG and I-TAC chemokines, induced by IFN-γ and TNF-α, was inhibited by PPAR-α activators. The potency of the different compounds in GO fibroblasts was different for each chemokine. PPAR-γ activators were weaker inhibitors of MIG and I-TAC (in GO fibroblasts and preadipocytes) than PPAR-α agonists. This study first suggested that MIG and I-TAC chemokines are inhibited by PPAR-α activators in normal and GO fibroblasts and preadipocytes, underlining that PPAR-α may take part in the modulation of the immune response in GO (83).

Mysliwiec et al. aimed to evaluate the utility of circulating chemokines MIG and I-TAC levels as markers of GO activity and as a guideline for therapeutic decision-making in 42 GD patients: 1) 10 GD patients in euthyreosis (Gtu); 2) 15 euthyroid patients with clinical symptoms of orbitopathy treated with corticosteroid therapy [intravenous infusions of methylprednisolone (MP) and teleradiotherapy (TR)]; 3) 10 patients with hyperthyroid GD (Gtx). Dose-dependent changes in the bioactivity levels of MIG and I-TAC and the activity of orbital inflammation; at least in part, between the increased concentrations of MIG and I-TAC during corticosteroid and TR treatments has been shown in comparison to control group and to basal values in GO patients. In the group of GO patients corticosteroid-responders, MIG values notably reduced 24h after the first dose of MP, in comparison with the group of non-responders. These findings suggested a relationship, at least in part, between the increased concentrations of MIG and I-TAC and the activity of orbital inflammation; therefore, these chemokines could be useful as a guideline in therapeutic decision-making in GO patients (84).

The utilization of new molecules that operate as antagonists of CXCR3, or by blocking IP-10, in GO, and autoimmune thyroid disorders, has been explored by two recent papers, and many interesting patents have been lately applied. Some randomized studies evaluated the efficacy of two monoclonal antibodies, teprotumumab (monoclonal anti-IGF-1R antibody) and tocilizumab (monoclonal antibody anti-soluble-IL-6 receptor), in GO patients. Also rituximab has been suggested as an alternative to corticosteroids for the treatment of GO (85,86).
Conclusion

MIG and its receptor, CXCR3, seem to contribute to the pathogenesis of GO. Under the influence of IFN-γ, fibroblasts and preadipocytes secrete MIG. In tissues, increased IFN-γ and TNF-α production, under the stimulation of recruited Th1 lymphocytes, stimulate MIG secretion from these cells, therefore perpetuating the autoimmune process and creating an amplification feedback loop. In GO fibroblasts and preadipocytes, the IFN-γ-induced MIG secretion in vitro is modulated by PPAR-γ and PPAR-α activators. High levels of MIG in peripheral liquids could be considered as a marker of an especially Th1 orientated immune response. The active phase of GO is associated with the presence of circulating MIG. In GO patients the activity of orbital inflammation, at least in part, is reflected by the increased concentrations of MIG. During corticosteroids and/or radiotherapy treatments a significant reduction in MIG concentrations has been shown, as compared both to control group and to basal values in GO patients; these data suggest that MIG could be useful as a guideline in therapeutic decision-making in patients with GO. More studies are needed to investigate interactions between chemokines and cytokines in the GO pathogenesis and to evaluate whether MIG is a novel therapeutic target in these autoimmune disorders.

References


