The Th1 chemokine MIG in Graves’ Disease: a narrative review of the literature

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Abstract

Type-1 helper (Th1) dependent chemokines, such as monokine induced by interferon (IFN)-γ (MIG) seem to contribute to the Graves’ disease (GD) pathogenesis. The thyrocytes secrete the chemokine (C-X-C motif) ligand (CXCL)10 under the IFN-γ influence. Therefore, high levels of MIG in peripheral liquids indicate a Th1 orientated immune response and are associated with the active phase of GD in hyperthyroid patients (newly diagnosed and relapsing).

Methimazole (MMI), used for the hyperthyroidism treatment, causes a reduction of the MIG secretion by isolated thyrocytes, a decrease of serum MIG levels and leads to a shift from a Th1 to Th2 response in patients with GD in the active phase. The Th1 lymphocytes recruited in the tissues enhance the IFN-γ and tumor necrosis factor (TNF)-α production, that in turn stimulate MIG secretion from these cells; this mechanism originates an amplification feedback loop, causing a perpetuation of the autoimmune process. It has been seen that peroxisome proliferator-activated receptors (PPAR)-γ and PPAR-α activators can modulate the IFN-γ induced MIG secretion in vitro, in GD thyrocytes. More studies are needed to examine the interactions between cytokines and chemokines in the GD pathogenesis and to evaluate the role of MIG as a new therapeutic target.

Key words: Graves’ disease, MIG

Introduction

Graves’ disease

Graves’ disease (GD) is a systemic autoimmune disorder caused by a complex interplay of genetic, environmental and endogenous factors. GD complications affect thyroid and orbital connective tissues.

The most common symptoms affecting about fifty% of patients are fatigue, weight loss, palpitations, tremor and heat intolerance. Among extrathyroidal physical signs, in addition to ophthalmopathy, between 1 to 4% of patients can manifest thyroid dermatopathy too (1).

It has been shown the dominant role played by the autoimmune response in the development of GD, as well as the pathogenetic role covered by thyroid stimulating autoantibodies in the pathogenesis of this disorder (2).

T-helper cell 17 (Th17)/Treg cell infiltration, Th1/Th2 cytokine and chemokine production, and the presence of subtypes of immunoglobulins are some of the inflammatory events occurring during the development of GD.

MIG, and CXCR3

The Th1 dependent chemokines interferon (IFN)-γ-inducible protein 10 (IP-10)/chemokine (C-X-C motif) ligand (CXCL)10, monokine induced by IFN-γ (MIG)/CXCL9 and IFN-inducible T-cell α chemoattractant (I-TAC)/CXCL11 act by binding the chemokine (C-X-C motif) receptor (CXCR)3. CXCR3 is a receptor belonging to the family of CXC chemokine receptors, having two isoforms CXCR3-A and CXCR3-B (3).

Several cells such as activated T lymphocytes, Natural Killer, some epithelial and endothelial cells express CXCR3. CXCR3 is highly expressed on Th1 cells, as well as the chemokine (C-C motif) receptor (CCR)5.

Th1 cells are attracted in the tissue by MIG, IP-10 and I-TAC chemokines that are released by the cells of the inflamed tissue. Therefore, this mechanism underlines the central role played by both CXCR3 and its ligands in the recruitment of inflammatory cells (4).

The IFN-γ induced chemokine MIG, is a T-cell chemoattractant, closely linked to IP-10 and I-TAC chemokines; their genes are all located on human chromosome 4 (5, 6).

Therefore, the high level of MIG present in peripheral fluids can be considered as a marker for the host immune response involving the Th1 cells (7, 8).

The Th1 lymphocytes recruited in the inflamed tissue increase the IFN-γ and tumor necrosis factor (TNF)-α production, that lead to a MIG secretion by several cells, creating an amplification feedback loop (7, 8).

In different studies have been shown high MIG tissue expression in various organs specific of autoimmune diseases.

Moreover, high circulating levels of MIG and of other Th1 chemokines have both been found in many specific autoimmune diseases, such as: autoimmune thyroiditis (AT) (9-15), GD (16, 17) Graves’ ophthalmopathy (18-23), type 1 diabetes (24-28), or systemic rheumatological disorders,
like systemic lupus erythematosus (29, 30), rheumatoid arthritis (31), systemic sclerosis (32-37), sarcoidosis (38-40), psoriasis or psoriatic arthritis (41-44), HCV-related cryoglobulinemia (45-54), other HCV immune mediated disorders (13, 55-57), other disorders, and also in cancers (58-76). The aim of this review is to assess the importance of MIG in GD in line with the International Narrative Systematic Assessment tool (77).

**MIG in GD (Tab. 1)**

The characteristic markers of GD are the thyroid stimulating hormone receptor (TSHR) autoantibodies (2). GD is recognized as an autoantibody-mediated Th2-dominant disease, even though a Th1 immune response predominates at the beginning of the disease (78).

Unlike IP-10 which was observed either in infiltrating inflammatory and endothelial cells and thyrocytes, CXCR3 receptor turned out to be more expressed only in the first two types of cells in GD (79). A further study showed that in GD, the recruitment of cells and the following amplification of inflammation are dependent by CXCR3-binding chemokine IP-10 which plays an important part; moreover this work suggested that at the beginning of GD the recruitment of CXCR3-expressing Th1 cells can be caused by the production of these chemokines by resident follicular epithelial cells (80). Th1 chemokines serum levels have been observed in patients with GD respect to the controls (matched by age and sex) (81).

Differently from GD patients with untreated hyperthyroidism, subjects with euthyroid or hyperthyroid GD under Methimazole (MMI) treatment had lower serum IP-10 levels; meanwhile these levels were higher in hyperthyroid GD patients compared to hypothyroid or euthyroid GD ones (145 ± 92, 105 ± 46 and 107 ± 56 pg/mL, respectively; p=0.01).

Serum IP-10 levels turned out to be similar both in untreated patients with relapse of hyperthyroidism who previously took MMI and in recently diagnosed untreated hyperthyroid GD subjects. The Authors concluded that either in relapsing hyperthyroid patients and in the newly diagnosed ones, the active phase of GD is associated with elevated serum IP-10 levels (82).

Circulating concentration of CCL2, CCL5, MIG and IP-10 in patients with GD, Hashimoto thyroiditis (HT) and nontoxic nodular thyroid disease (NNT) have been assessed in a study.

Despite CCL2 and MIG, whose concentrations were similar in patients with autoimmune thyroid disease (AITD) and NNT, CCL5 was substantially higher in GD patients than in HT or NNT ones. Conversely, IP-10 levels were lower in patients with GD, with a difference that reached the significativity only when compared with subjects with HT. Noteworthy, different statistically significant levels of MIG (p=0.0252) were observed in GD patients who relapsed or went into remission. These findings showed that the distinct immune responses in GD and HT could be related to the different expression patterns of chemokines in the various thyroid diseases (83).

### Table 1. Summary of data about chemokines in Graves’ Disease (GD).

<table>
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<tr>
<th>In vivo studies</th>
<th>In vitro studies</th>
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<td>IP-10 expression observed in infiltrating inflammatory, endothelial cells and thyrocytes in GD (79).</td>
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<td>Different expression patterns of chemokines in the various thyroid diseases (GD, HT, NNT) (83).</td>
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<td>TNF-α plus IFN-γ have a synergistic effect on MIG and I-TAC secretion; this effect was dose dependently suppressed after the addition of the PPAR-γ agonists. Thyrocytes from patients with GD under the cytokines stimulation participate to the self-protraction of inflammation by releasing MIG and I-TAC (84).</td>
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<td>A strong dose-dependent inhibition on the cytokines-stimulated secretion of I-TAC and MIG by PPAR-α-agonists has been observed in both primary culture thyroid cells (from GD subjects and controls) (85).</td>
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<td>MIG and I-TAC serum levels were higher in GD patients respect to that measured in subjects with AT, MNGs, TNGs and healthy controls (age- and sex-matched) (86).</td>
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<td>Association between the intractability of GD and the MIG rs2276886 AG genotype (87).</td>
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AT: autoimmune thyroiditis; GD: Graves’ disease; HT: Hashimoto thyroiditis; MNGs: nontoxic multinodular goiters; NNT: nontoxic nodular thyroid disease; TNGs: toxic nodular goiters
Another study assessed the effect of peroxisome proliferator-activated receptor (PPAR)-γ activation and of the IFN-γ and TNF-α stimulation on the secretion of MIG and I-TAC, in primary cultures of GD thyrocytes. The production of these chemokines was absent under basal condition; they were dose dependently released after the treatment of the cells with IFN-γ, while TNF-α alone had no effect. TNF-α plus IFN-γ had a synergistic effect on MIG and I-TAC secretion; this effect was dose dependently suppressed after the addition of the PPAR-γ agonist, rosiglitazone, or pioglitazone. Finally they observed that thyrocytes from patients with GD under the cytokines stimulation participate to the self-protraction of inflammation by releasing MIG and I-TAC. This process is inhibited by PPAR-γ activation. The MIG leading role among the CXC chemokines is suggested by its high response to the IFN-γ plus TNF-α stimulation (84).

The effect of PPAR-α activation on MIG and I-TAC chemokines in general or on secretion of these chemokines in thyroid cells has been assessed by another study (85). The Real-time-PCR was used in order to evaluate the presence of PPAR-α and PPAR-γ in GD and control cells in primary culture. The role of PPAR-α and PPAR-γ activation on chemokines secretion has been also evaluated after the treatment of GD and control cells with IFN-γ and TNF-α. The Authors showed the presence of PPAR-α and PPAR-γ in GD and control cells. A strong dose-dependent inhibition on the cytokines-stimulated secretion of I-TAC and MIG by PPAR-α-agonists has been observed in both primary culture cells. The power of this drugs was highest on the secretion of MIG reaching the inhibition, that was 85% with ciprolibrate and 90% with fenofibrate. The potency exerted by the compounds was different for each chemokine; for instance the inhibition exerted by gemfibrozil on I-TAC was of 55%, while it exerted a lower inhibition on MIG secretion that was of 40%. In thyrocytes, the inhibition of MIG and I-TAC secretion was greater with PPAR-α agonists (ANOVA, p<0.001) than with PPAR-γ agonists. To sum up this study demonstrated: 1) the presence of PPAR-α in GD and control thyrocytes; 2) the strong inhibition exerted by PPAR-γ on MIG and I-TAC secretion, suggesting that the immune response in thyroid may be modulated by PPAR-α (85).

In another study, MIG and I-TAC serum levels were measured in ninety-one GD patients, ninety-one AT, thirty-four nontoxic multinodular goiters (MNGs), thirty-one toxic nodular goiters (TNGs), and ninety-one healthy controls (age- and sex-matched). The mean chemokines levels were that were measured in GD, controls, euthyroid AT, MNG, or TNG were the following: p < 0.05, ANOVA; MIG: 274 ± 265, 76 ± 33, 132 ± 78, 87 ± 48, and 112 ± 56 pg/mL; I-TAC: 140 ± 92, 64 ± 20, 108 ± 48, 76 ± 33, 91 ± 41 pg/mL, respectively. These levels were higher in GD patients respect to that measured in others subjects. Chemokines levels were also significantly higher in hyperthyroid GD patients than hypothyroid or euthyroid ones. Furthermore, these levels were higher in GD patients with untreated hyperthyroidism than euthyroid or hyperthyroid GD subjects treated with MMI. Similar chemokines levels were measured in newly diagnosed hyperthyroid GD (not in treatment) versus untreated patients with relapse of hyperthyroidism (previously in treatment with MMI). In conclusion the serum chemokines levels were associated with the active phase of GD (newly diagnosed and relapsing) and their reduction in treated patients with GD may be related to the immunomodulatory effects of MMI (86).

A further study investigated about the relationship between the pathogenesis of AITD and functional polymorphisms in genes encoding some chemokines. This study genotyped the following polymorphisms: interleukin (IL)8 -251TT/A, Monocyte Chemotactic Protein 1 (MCP1)-2518/G/A, Regulated upon Activation, Normal T cell Expressed and presumably Secreted (RANTES)-403GA, -28CG/G, MIG rs2276886G/A, IP-10 -1596C/T and IL16 -295T/C. In the study were enrolled 149 GD patients of whom 53 patients having GD in remission, 59 with intractable GD and also 131 Hashimoto’s disease (HD) patients of whom 54 patients with severe HD and 46 with mild HD and 99 healthy controls. In AITD patients MIG rs2276886 A allele and IL8 -251TT genotype were more frequent unlike the RANTES -403AA and -28GG genotypes which were less recurrent. MIG rs2276886 AG genotype was less common in patients with intractable GD and the MCP1 -2518GG genotype was more frequent in HD patients. It’s interesting that in GD patients with -28CG and GG genotypes the age of onset was higher compared with GD patients having RANTES -28CC genotype. This study firstly reported the association between the intractability of GD and the MIG rs2276886 AG genotype (87).

Conclusion

The pathogenesis of GD can be related to MIG and its receptor CXCR3. The thyrocytes (in GD) secrete MIG when stimulated with IFN-γ. Furthermore, high levels of MIG in peripheral liquids indicate a Th1 orientated immune response and are associated with the active phase of GD in hyperthyroid patients (newly diagnosed and relapsing). The Th1 lymphocytes recruited in the tissues enhance the IFN-γ and TNF-α production, that in turn stimulate MIG secretion from these cells, this mechanism originates an amplification feedback loop, causing a perpetuation of the autoimmune process. The MIG secretion in vitro induced by IFN-γ can be modulated by PPAR-γ and PPAR-α activators in GD thyrocytes. In patients with GD active phase, MIG secretion from isolated thyrocytes is reduced by MMI which also promotes a transition from Th1 to Th2 dominance and decreases the serum MIG levels.

More studies are needed to examine the interactions between cytokines and chemokines in the GD pathogenesis and to investigate the role of MIG as a new therapeutic target.

References


