MIG in autoimmune thyroiditis: review of the literature

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Abstract

The monokine induced by interferon (IFN)-γ (MIG) and its receptor, the chemokine (C-X-C motif) receptor (CXCR)3, appear to contribute to the pathogenesis of autoimmune thyroiditis (AT). MIG is secreted by thyrocytes under the influence of IFN-γ. In tissue, recruited Th1 lymphocytes may be responsible for enhanced IFN-γ, which in turn stimulates MIG secretion from thyrocytes creating an amplification feedback loop, and perpetuating the autoimmune process. Circulating MIG and IFN-inducible T-cell α chemoattractant (I-TAC) levels are increased in patients with thyroiditis and hypothyroidism and are related to each other. The importance of a Th1 immune attack in the initiation of AT has been demonstrated. MIG levels were significantly higher in elder patients, or in those with a hypoechoic ultrasonographic pattern, or with hypothyroidism. In peripheral fluids, high MIG levels are considered a marker of host immune response, in particular Th1 orientated T-cells. Other studies are needed to continue to investigate the role of MIG as a novel therapeutic target in AT.

Key words: autoimmune thyroiditis, CXCR3, MIG

Introduction

Autoimmune thyroiditis (AT), also known as chronic lymphocytic or Hashimoto’s thyroiditis (HT), is a disease in whose main features are: the production of autoantibodies to thyroid-specific antigens thyroglobulin and thyroperoxidase and the infiltration of the thyroid gland by the inflammatory cells (1). It is characterized by hypothyroidism that is caused by destruction and eventual fibrous replacement of the follicle cells. Genetic and environmental factors contribute to AT that has a multifactorial etiology (2).

MIG and CXCR3

The CXC chemokine receptor-3 (CXCR3) is a receptor that links to the protein that belong to the family of CXC chemokine receptors. We know two isoforms of CXCR3: CXCR3-A and CXCR3-B. These two isoforms bind CXC chemokines: interferon (IFN)-γ-inducible protein 10 (IP-10)/chemokine (C-X-C motif) ligand 10 (CXCL10), monokine induced by IFN-γ (MIG)/CXCL9 and IFN-inducible T-cell α chemoattractant (I-TAC)/CXCL11. CXCR3-B binds the three mentioned chemokines and CXCL4 (3). Different cells, such as activated T lymphocytes and Natural Killer (NK) cells, some epithelial and endothelial cells exhibit CXCR3, that is strongly expressed by Type 1 helper (Th1) cells. Furthermore, these cells show an high expression of the chemokine (C-C motif) receptor (CCR)5.

The chemokines MIG, IP-10 and I-TAC, released by cells in the inflammatory lesions, attract Th1 cells; suggesting that CXCR3 and its ligands have a central role in the recruitment of inflammatory cells (4).

MIG, IP-10 and I-TAC genes are located on human chromosome 4. MIG, also known as CXCL9, is a T-cell chemoattractant that is induced by IFN-γ (5,6); and the high level of MIG in peripheral fluids is considered a marker of host immune response, in particular Th1 orientated T-cells (7,8). Th1 lymphocytes recruitment cause an increased production of IFN-γ and tumor necrosis factor (TNF)-α, which stimulate the MIG secretion by several cells creating an amplification feedback loop in the inflamed site and therefore an increase of MIG levels (7,8).

High serum MIG levels and high MIG tissue expression in various organs specific for autoimmune diseases are reported in some studies. In fact, increased levels of MIG and other Th1 chemokines have been detected in many specific autoimmune diseases, such as: autoimmune thyroiditis (AT) (9-13), Graves’ disease (GD) (14-16) Graves’ ophthalmopathy (17-20), type 1 diabetes (21-25), or systemic rheumatological disorders, like systemic lupus erythematosus (SLE) (26,27), rheumatoid arthritis (28), systemic sclerosis (29-33), sarcoidosis (34-36), psoriasis or psoriatic arthritis (37-40), HCV-related cryoglobulinemia (41-46), other HCV immune mediated disorders (13, 47-52), other disorders, and also in cancers (53-75).

This narrative review has the objective to evaluate the importance of MIG in AT. The presentation of data has been reported according to the International Narrative Systematic Assessment tool (76).
The selective migration of lymphocytes in autoimmune thyroid disorders (AITDs) was investigated by García-López MA et al. This group, analyzing thyroid samples obtained from AITD patients, observed an enhanced expression of the IP-10 and that Regulated upon Activation, Normal T cell Expressed and Presumably Secreted (RANTES) is expressed and secreted by T lymphocytes. In vivo, thyroid follicular cells (TFCs) from AITD thyroids express IP-10 and MIG, which are induced in these cells by the same stimuli. The supernatants obtained from stimulated TFCs induced an increased migration of T lymphoblasts that express CXCR3; these chemotactic responses were abolished when specific antibodies were added that block the chemokines IP-10 and MIG, or their receptor CXCR3. The authors suggested that TFCs have a central role in the production of the chemokines IP-10, MIG and RANTES and in regulating the recruitment of specific subsets of activated lymphocytes in AITDs (77).

C57BL6 transgenic mice were used in a further study to define the chemokines profile expressed in the thyroid gland upon chronic exposure to IFN-γ. These mice have an aberrant expression of IFN-γ under control of the thyroglobulin promoter. The thyroidal expression of 10 chemokines (CCL1 through 5 and CXCL9 through 13) was compared in thyrin-IFN-γ transgenics and wild-type littermates by reverse transcriptase PCR. CCL4, MIG, and I-TAC were exclusively expressed in transgenics, that have an increased expression of CCL5 and IP-10. There was an association between this chemokine profile and a moderate mononuclear cell infiltration of the thyroid stroma. In addition, it was observed that this infiltration decreased significantly after 2 months of age and did not organize into lymphoid structures. These data suggested that the isolated expression of IFN-γ induces the recruitment of the mononuclear cells, which don’t evolve to full lymphoid transformation of the thyroid (78).

Other authors measured the circulating levels of CCL2, CCL5, MIG, and IP-10 in patients with GD, HT, and non-toxic nodular thyroid disease (NNT). In patients with AITD or NNT, CCL2 and CXCL9 levels were similar, while CCL5 concentrations was significantly increased in GD patients compared with HT or NNT subjects. They observed lower concentrations was significantly increased in GD patients or NNT, CCL2 and CXCL9 levels were similar, while CCL5, MIG, and IP-10. There was an association between this infiltration decreased significantly after 2 months of age and did not organize into lymphoid structures. These data suggested that the isolated expression of IFN-γ induces the recruitment of the mononuclear cells, which don’t evolve to full lymphoid transformation of the thyroid (78).

Another study evaluated the circulating levels of MIG and I-TAC in AT. In this study serum levels of MIG and I-TAC were evaluated in 141 consecutive patients with newly diagnosed AT (AT-p), 70 euthyroid controls, and 35 patients with nontoxic multinodular thyroid. Gender distribution and age were similar in the three groups; among the AT-p, 26% had subclinical hypothyroidism. Serum CXCL9 and I-TAC levels were significantly higher in AT-p than in controls, or patients with multinodular thyroid. Among AT-p, patients older than 50 years or those with a hypoechoic ultrasonographic pattern or with hypothyroidism had levels significantly higher of MIG and I-TAC. In a multiple linear regression model including age, thyroid volume, echochogenicity, hypervascularity, TSH, anti-thyroglobulin, and anti-thyroid peroxidase, it was observed that only age and TSH were related to serum MIG or I-TAC levels. Moreover, TSH and I-TAC (P = 0.001) were significantly and independently correlated to CXCL9 in a multiple linear regression model of MIG vs. age, TSH, and I-TAC. The authors showed that circulating MIG and I-TAC are increased in patients with thyroiditis and hypothyroidism and are related to each other. The importance of a Th1 immune attack in the initiation of AT have been demonstrated by these data (11).

Other authors evaluated MIG in HCV infection-related mixed cryoglobulinemia (MC) patients in presence/absence of AT. Serum MIG and IP-10 were measured in 60 patients with MC (MCo), in 35 patients with MC and AT (MC-AT), in 60 sex and age-matched healthy controls (Control 1); 35 patients with AT without cryoglobulinemia (Control 2). It has been observed that MIG and IP-10 levels were higher in MC-AT patients than Control 2 and MCo, in MCo than Control 1, and in Control 2 than Control 1. Moreover, it was defined a high MIG level as a value>2 SD above the mean value of the Control 1 (x212 pg/mL): 5% of Control 1, 34% of Control 2, 91% of MCo, and 97% of MC+AT had high CXCL9 (P<0.0001, chi-square). MIG and IP-10 were related to each other in MCo, and in MC-AT by a simple regression analysis. This study showed that high serum levels of MIG were present in cryoglobulinemic patients, especially with AT. Also, in patients with MC in presence/absence of AT there is a strong association between serum MIG and IP-10 (80).

Another study observed serum MIG and I-TAC levels in patients with AT and recurrent spontaneous abortions (RSA). In this study were enrolled forty-one euthyroid, non-pregnant women with AT and a history of unexplained first trimester RSA, 35 euthyroid women with AT, and 29 healthy controls matched for age and body mass index. Serum MIG and I-TAC levels resulted significantly higher than in both control groups. Moreover, patients with AT without RSA had higher MIG levels than healthy controls. The subjects with a history of RSA did not show differences in MIG and I-TAC levels in relation to the number of previous abortions. Abortions were significantly related to MIG, I-TAC, by a multiple linear regression analyses. Non-pregnant AT patients with a history of RSA showed higher circulating levels of MIG and I-TAC if compared to both control groups: these results suggested that a more dominant Th-1 cytokine profile was produced by this subgroup (81).

Some authors to define the association between functional polymorphisms in genes encoding some chemokines and the pathogenesis of AITD genotyped IL8 -251T/A, RANTES -403G/A, -28C/G, MIG rs2276886G/A, IL-10 -1596C/T, Monocyte Chemoattractant Protein1 (MCP1) -2518G/A and IL16 -295T/C polymorphisms in: 149 GD patients, including 59 patients with intractable GD and 53 patients with GD in remission, as well as 131 Hashimoto’s disease (HD) patients, including 54 patients with severe HD, 46 patients with mild HD and 99 healthy controls. In patients with
AITD were more frequent the IL8-251TT genotype and MIG rs2276886 A allele (p = 0.0139 and p = 0.0005, respectively) and the RANTES -403AA and -28GG genotypes were less frequent (p = 0.0164 and p = 0.0221, respectively). In HD patients, it was observed a higher frequency of the MCP1 -2518GG genotype (p = 0.0323), while the MIG rs2276886 AG genotype resulted less frequent in patients with intractable GD (p = 0.0051) (82).

Another study aimed to evaluate if the blood mononuclear cells (PBMC) from both control women and women with HT were protected from in vitro H2O2-induced oxidative stress after addition of antioxidants. In this study, PBMC obtained from 8 HT women and 3 healthy women (controls), were cultured in the presence of 200 µM H2O2 alone, with subsequent addition of myo-inositol (Myo) (0.25, 0.5, 1.0 µM), selenomethionine (SelMet) (0.25, 0.5, 1.0 µM), or their combination (0.25+0.25, 0.5+0.5, 1.0+1.0 µM). PBMC proliferation, vitality, genotoxicity (Comet score) and secretion in the medium of the chemokines IP-10, CCL2 e MIG were evaluated. The results showed a decrease of PBMC proliferation caused by H2O2 alone, which was reduced further and dose-dependently in both groups (greatest decrease with Myo+SelMet in HT). Vitality was reduced by 5% in controls and 10% in the HT group by H2O2 alone, but it was rescued by the three additions. In controls and in HT women the Comet score was increased by +505% above baseline and +707%, respectively, for the addition of H2O2 alone. In both groups each addition dose-dependently contrasted genotoxicity. H2O2 also raised the concentrations of chemokines in the medium, in HT women more than in controls. In either groups the concentrations of chemokines were decreased by each addition dose-dependently; besides the concentrations often decreased below baseline levels: with Myo+SelMet decreased up to approximately -80% of baseline being this the most potent addition.

The conclusion of this study was that the tested antioxidants had beneficial effects on PBMC exposed in vitro to H2O2-induced oxidative stress in both control and HT women and that the association Myo+SelMet was the most effective (83).

Myeloid-related protein 14 (MRP14) has an important role in inflammatory reactions. However, there is still no clear association between this protein and HT. The status of MRP14 in thyroid tissues and sera of HT patients and the mechanism of IL-1β -mediated regulation of MRP14 expression, including the effects of MRP14 on pro-inflammatory chemokine secretion in TFCs, were evaluated. The group found that in thyroid tissues and sera from HT patients there was an elevated MRP14 expression. Besides, IL-1β remarkably increased the expression of MRP14 in TFCs, which was mediated by activation of the MAPK/NF-kB signalling pathway. Finally, they showed how IL-1β induced the secretion of the chemokines GRO-2, CXCL9 and CCL22 and how this process was dependent on the regulation of MRP14 in TFCs. These data showed that under pro-inflammatory conditions, TFCs secreted chemokines with the help of MRP14 regulation, which might indicate a potential pathological mechanism of lymphocyte infiltration into the thyroid gland in HT (84).

Conclusion

MIG, and its receptor, CXCR3 are important in the development of AT. In tissue, recruited Th1 lymphocytes may be responsible for enhanced IFN-γ that induce MIG secretion by thyrocytes creating an amplification feedback loop, and perpetuating the autoimmune process. Elder patients or those with a hypoechoic ultrasonographic pattern or with hypothyroidism, showed MIG levels significantly higher. Thus, high level of MIG in peripheral liquids is a marker of Th1 orientated immune response. We need to continue to study the role of MIG as a novel therapeutic target in AT.

References


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