Rheumatoid arthritis and the Th1 chemokine MIG

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Abstract

Monokine induced by interferon (IFN)-γ (MIG) and its receptor chemokine (C-X-C motif) receptor 3 (CXCR3) seem to play an important role in the pathogenesis of rheumatoid arthritis (RA). MIG expression has been observed in sera, synovial fluid (SF) and synovial tissue of RA patients; it is highly expressed in RA synovium by infiltrating macrophage-like cells and fibroblast-like synoviocytes. A Type-1 helper-response orientated disease was suggested because of the high expression of CXCR3 in SF T cells and the presence of elevated IFN-γ levels. It has been observed a decrease of the inflammation by anti-CXCR3, and anti-MIG molecules, in fact they inhibit CXCR3-enhanced cell migration and pro-inflammatory cytokine expression, leading to an amelioration of the arthritis progression. These findings suggest a possible therapeutic role of these molecules in humans.

Key words: MIG, rheumatoid arthritis

Introduction

MIG, and CXCR3

In the inflamed site local cells release Type-1 helper (Th1) dependent chemokines, monokine induced by interferon (IFN)-γ (MIG)/chemokine (C-X-C motif) ligand 9 (CXCL9), (IFN)-γ-inducible protein 10 (IP-10)/CXCL10 and IFN-inducible T-cell α chemoattractant (ITAC)/CXCL11, which play an important role in the recruitment of activated Th1 cells. Indeed, these chemokines bind a Gαq protein-coupled CXC receptor 3 (CXCR3) that is expressed by several cells including activated T lymphocytes and natural killer cells, some epithelial and endothelial cells, and it is highly expressed on Th1 cells (1, 2).

The Th1 dependent chemokines are closely related, their genes are all located on human chromosome 4. MIG is a small cytokine induced by IFN-γ, attracting T-cell (3, 4); therefore high MIG serum levels, can be considered especially as a marker of a Th1 driven host immune response (5, 6). Th1 lymphocytes recruited in the inflamed site increase IFN-γ and tumor necrosis factor (TNF)-α production, which stimulate MIG secretion from several cells, causing an amplification feedback loop (5, 6).

The increase of serum MIG levels (and of other Th1 chemokines) and/or an increase of the tissue expressions in different organ has been observed in several autoimmune diseases, such as: autoimmune thyroiditis (7-13), Graves’ disease (14, 15) Graves’ ophthalmopathy (16-20), type 1 diabetes (21-26), or systemic rheumatological disorders, like rheumatoid arthritis (RA) (27), systemic lupus erythematosus (28, 29), systemic sclerosis (30-34), psoriasis or psoriatic arthritis (PA) (35-37), sarcoidosis (38, 39), HCV-related cryoglobulinemia (40-45), other HCV immune mediated disorders (11, 46-53), other diseases, and also in cancers (54-81).

RA is an autoimmune disease leading to a systemic and chronic inflammatory disorder. Many tissues and organs can be involved, but principally it attacks flexible (synovial) joints. If not properly treated can be followed by a substantial loss of function and mobility causing a disabling condition (82).

The correlation between pathogenesis of RA and autoimmunity is sustained by several points, such as the presence of a genetic link with HLA-DR4 and related haplotypes of major histocompatibility complex class II and the T cell-associated protein PTPN22 (83); a link to the pathogenesis of vascular disease (rheumatoid vasculitis); a significant deceleration of disease progression often obtained by blockade of TNF-α (84); the presence of antibodies to citrullinated peptides (ACPA) and rheumatoid factors (RF) (85); and also it affects most female gender. Therefore, an abnormal B cell - T cell interaction seems to be involved in the pathogenesis of RA; B cells present antigens to T cells via HLA-DR stimulating T cells help and production of RF and ACPA. Either B or T cell products can lead to inflammation by stimulating release of TNF and other cytokines and chemokines (86-89).

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MIG and arthritis

MIG in RA

In a first study synovial membranes and cytocentrifuge preparations of seven RA, eight PA and ten osteoarthritides (OA) patients were examined in order to evaluate lymphocyte and monocyte, recruited by specific chemokine expression, in the synovial tissues of these subjects. In the synovial lining layer and in cellular infiltrates were detected MIG and Regulated on Activation Normal T Cell Expressed and Secreted, while Growth-regulated Oncogene (GRO)-α expression was localized exclusively in the lining layer of the synovial lining layer and in cellular infiltrates were detected expression, in the synovial tissues of these subjects. In the study, IFN-γ, TNF-α, GM-CSF, IL-1β, IL-6, IL-8, IL-12, IL-17, and IFN-α were found in tissues of RA patients (respectively 100, and 50-fold more) compared to the controls. Higher levels of IP-10, and MIG were found in tissues of RA than in OA (92).

A further paper investigated the expression and regulation of different chemokines: IP-10; MIG, and the chemokine (C-C motif) receptor (CCR)5 ligands [macrophage inflammatory protein (MIP)-1α/CC ligand 3 (CCL)3; and MIP-1β/CCL4] in synovial fluids (SF) and tissues (ST), and also in blood of RA patients. The protein levels of IP-10 and MIG were higher in SF of RA patients (respectively 100-, and 50-fold more) than in OA (92).

Another study analyzed gene expression patterns in ST from RA and OA patients. Among a set of 7131 genes displayed on the microarray chip, were found 300 genes downregulated and 101 genes upregulated in RA respect to OA subjects. Also they noticed an upregulation of CXCR1, -2 and -3 mRNAs, and of MIG and IP-10 mRNAs in RA patients in comparison to the ones affected by OA. Furthermore, they revealed an important expression of CXCR3 protein on mast cells within ST from RA patients; thus suggesting its significant role in the pathophysiology of RA, that is followed by elevated levels MIG and IP-10 chemokines (93).

An additional study investigated about MIG, IP-10, and ITAC production by ST cells and synovial fibroblast-cell lines obtained from RA and OA patients. The levels of Th1 dependent chemokines were higher in the SF of RA patients than OA patients; also the mRNA expression of these chemokines in ST cells was higher in the group of RA patients. They showed a significant secretion of MIG and IP-10 proteins, but not of ITAC by synovial fibroblast, after IFN-γ stimulation (94).

The accumulation of plasma cells expressing CXCR3 in the synovial sublining regions of early RA in association with production of MIG by synovial fibroblasts were demonstrated in a subsequent paper (95).

Toll-like receptors (TLR) identify microbial components and are also activated by endogenous molecules that could be involved in autoimmune arthritis. Peptidoglycan (PGN), lipopolysaccharide or double-stranded RNA (TLR ligands) synergized with IFN-γ leading to MIG and IP-10 induction. Similarly TNF-α or interleukin (IL)1β, combined with IFN-γ, induced MIG and ITAC in a synergistic manner in two important cell types that characterize the joint cavity, HMVEC and human fibroblasts. MIG production induced by TNF-α plus IFN-γ was neutralized by Etanercept (a humanized soluble recombinant p75 TNF-receptor/IgG1Fc fusionprotein), while it didn’t exert this effect on the MIG production induced from IFN-γ and the TLR ligands PGN or lipopolysaccharide association (96).

A study aimed to investigate a possible correlation between serum levels of CC and CXC chemokines and disease activity in RA patients. Subjects with active RA reported significantly elevated serum basal levels of CC and CXC chemokines respect to healthy controls (p < 0.05), not the same for CCL2. Clinicians followed the European League Against Rheumatism (EULAR) response criteria in order to evaluate the response to the treatment, reporting a significant improvement in all disease activity after a treatment of 12 weeks. According to EULAR response criteria, a good to moderate response was reached by 17 patients and the remission was observed in 5 patients. A significant reduction of MIG and IP-10 serum concentrations was observed in patients that reached an improvement of the clinical activity, therefore Authors concluded that serum concentrations of these chemokines may be useful as sensitive biomarkers for disease activity in patients affected by RA (97).

An additional study evaluated gene expression in the micro-dissected synovial lining cells of RA patients, considering OA patients as the control. They observed a statistically significantly higher expression of signal transducer and activator of transcription 1, interferon regulatory factor 1 (IRF1), and of the MIG, IP-10, and CCL5 chemokines in the synovium of RA respect to the controls. These results were also confirmed by immunochemistry (98).

A subsequent study was conducted in order to assess whether histone deacetylase (HDAC) expression and function in fibroblast-like synoviocytes (FLS) could be regulated by pro-inflammatory factors of the inflamed joint of RA patients. They showed an association between TNF and matrix metalloproteinase-1 and synovial class I HDAC expression, whereas an inverse association arose between class IIa HDAC5 and the parameters of disease activity. In FLS of RA patients, TNF or IL-1β downregulate HDAC5 expression; this induced an IP-10, IFN-β, CXCL11 and MIG production and it was associated with a nuclear accumulation of IRF1 (99).

To investigate the association between RA and polymorphisms in the IP-10 gene (rs8878 A>G) and MIG (rs3733236 G>A) genes, was the goal of another study. In neither of the two groups (RA patients and controls) substantial differences in alleles and MIG genotypes distribution were found (100).

The inhibition of inflammatory mediators synthesis is associated with the Methotrexate (MTX) treatment in RA. The correlation between the response to therapy with MTX and MIG/IP-10 gene polymorphisms in RA patients was evaluated in a study but no statistically significant outcomes were obtained (101).

Anti-inflammatory features appear either in vivo and in vitro models of RA after a non-selective HDAC inhibitors (HDACi) treatment. A feasible contribution given by specific class I and class IIb HDACs to inflammatory gene expression in RA FLS has been examined by a paper. The Authors ob-
served that the majority of IL-1β-inducible genes targeted by pan-HDACi in RA FLS were suppressed by HDAC3/6i, but not by HDAC1/2i and HDAC8i. HDAC3/6i suppressed type I IFN release, followed by a reduced expression of a subset of IFN-dependent genes, such as MIG and ITAC (102).

IL-17 and TNF take part, in an independent way, to the pathophysiology of RA. These two cytokines (TNF and IL-17A) are targeted at the same time and also selectively by a new dual variable domain immunoglobulin: ABT-122. This characteristic of ABT-122 hopefully would give a major clinical response. A study was carried out to show the pooled tolerability, safety, and pharmacodynamics of ABT-122 on the base of two phase I (placebo-controlled, multiple ascending-dose) studies in subjects affected by primarily inactive RA; not any clinically significant results about the safety were reported. Reduced levels of CCL23, MIG, soluble E-selectin and IP-10 were reported in patients treated with ABT-122 respect to placebo-treated ones. This therapy could have anti-inflammatory effects according to the clinical results, even if patients in the study had inactive RA (103).

According to a study the antibody JN-2, a new discovered CXCR3 antagonist, can inhibit in vitro the pro-inflammatory cytokine production either by bone marrow-derived macrophages and CD4+ T cells (assessed by RT-PCR and ELISA) and the cell migration induced by CXCR3 (evaluated by a migration assay), then diminishing the inflammation. Moreover JN-2 improved the progression of the arthritis in an animal model induced by collagen. A histological evaluation was performed to assess the cartilage damage (104).

**Conclusion**

The pathogenesis of RA seems to be related to MIG and CXCR3, which is its receptor. In fact, in RA patients, MIG can be found in ST, SF and sera. The synoviocytes, similar to fibroblasts, and the infiltrating cells, similar to macrophages, are present in the synovium of RA, and express mainly MIG. A disease Th1-response orientated was suggested because are present in the synovium of RA, and express mainly MIG. A disease Th1-response orientated was suggested because of the high expression of CXCR3 in ST T cells associated with elevated IFN-γ levels.

The inflammation, as it was proven by other outcomes, was reduced by anti-MIG and anti-CXCR3 molecules that inhibit the pro-inflammatory cytokines expression and the CXCR3-enhanced cell migration, then giving an improvement in the arthritis progression. These findings could suggest a useful therapeutic employment of these molecules in humans affected by RA.

**References**

16. Antonelli A, Ferrari SM, Frascerra S, et al. CXCL9 and CXCL11 chemokines modulation by peroxisome proliferator-
activated receptor-α agonists secretion in Graves’ and normal thyroids. J Clin Endocrinol Metab. 2010;95:E413–20 https://doi.org/10.1210/jc.2010-0923


