MIG in psoriatic arthritis

G. Elia

1Department of Clinical and Experimental Medicine, University of Pisa, Pisa, Italy

Abstract

Monokine induced by interferon (IFN)-γ (MIG) / chemokine (C-X-C motif) ligand 9 (CXCL9) is involved in the pathogenesis of psoriatic arthritis (PsA). It was demonstrated that both blood plasma-derived dendritic cells (pDCs) and pDCs isolated from rheumatoid arthritis (RA) and PsA synovial fluid (SF), expressed CXCR3 receptor (R) 3 and CXCR4, and that the chemotaxis of blood-derived pDCs is stimulated by MIG, (IFN)-γ-inducible protein 10 (IP-10)/CXCL10, IFN-inducible T-cell α chemoattractant (I-TAC) /CXCL11 and stromal cell-derived factor 1 (SDF-1)/ CXCL12, present in RA and PsA SF. In PsA patients have been found a Th1 immune predominance at early stage of disease, while a reduction of these chemokines has been observed in long lasting PsA, with a significant increase of monocyte chemoattractant protein-1/IP-10 ratio. This suggest a shift from Th1 to the Th2 immune response in long lasting PsA. High levels of MIG has been found in patients with PsA and autoimmune thyroiditis too. This chemokine has been proposed as a useful marker to monitor the activity as well the progression of PsA. Efforts have been made to modulate or prevent the production of MIG in PsA aiming to alter the course of the disease. Clin Ter 2018; 169(6):e297-302. doi: 10.7417/CT.2018.2097

Key words: psoriatic arthritis, MCP-1, MIG, CXCR3, IP-10

Introduction

MIG, and CXCR3

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 (I-TAC) /CXCL11 bind CXC receptor(R) 3. CXCR3 is a Gq protein-coupled receptor having two isoforms CXCR3-A and CXCR3-B, both binding the above-mentioned chemokines; CXCR3-B also binds chemokine (C-X-C motif) ligand 4 (CXCL4) (1).

CXCR3 is expressed by several cells including activated T lymphocytes and Natural Killer (NK) cells, some epithelial and endothelial cells, and it is highly expressed on Th1 cells, as well as the chemokine (C-C motif) receptor (CCR)5.

Th1 cells are recruited in inflamed site thanks to the chemokines MIG, IP-10 and I-TAC produced by local cells. Both CXCR3 and its ligands are important in the recruitment of inflammatory cells (2).

MIG, also known as CXCL9, is a small cytokine, closely related to two other chemokines IP-10 and I-TAC, whose genes are located near the gene for MIG on human chromosome 4. MIG is a T-cell chemoattractant, and it is induced by IFN-γ (3, 4). High CXCL9 serum levels, can be then considered as a marker of host immune response, especially of a Th1 driven response (5, 6). Actually recruited Th1 lymphocytes increase IFN-γ and tumor necrosis factor (TNF)-α production stimulating CXCL9 secretion from several cells of the inflamed site, this lead to an amplification feedback loop (5, 6).

High serum MIG levels (as well as that of other Th1 chemokines) and/or an increase of the tissue expressions in different organ specific of autoimmune diseases have been reported by various studies. This has been observed in different specific autoimmune diseases including: autoimmune thyroiditis (7-12), Graves’ disease (13, 14) Graves’ ophthalmopathy (15-18), type 1 diabetes (19-23), or systemic rheumatological disorders, like rheumatoid arthritis (RA) (24), systemic lupus erythematosus (25, 26), systemic sclerosis (27-30), psoriasis (Ps) or psoriatic arthritis (PsA) (31-33), other HCV immune mediated disorders (11, 42-47), other disorders, and also in cancers (48-70).

Psoriatic arthritis

Psoriasis, also called psoriasis vulgaris, is a chronic relapsing / remitting, autoimmune disease involving the skin. Its features are red, and usually itchy, scaly patches,
plaques and papules (71). Skin lesions found in Ps patients may vary from localized patches to complete body coverage (71). From two to four percent of the general population is affected by Ps (72, 73).

Psoriatic arthritis is a type of chronic inflammatory arthritides with a highly varied clinical presentation and is often associated with skin and nails Ps (74, 75). It involves painful inflammation of the joints and surrounding connective tissue, usually affecting fingers and toes, leading them to a swelling sausage-shaped, known as dactylitis (74). Other joints can be affected such as that of the knees, hips, sacroiliac joint (sacroilitis) and spine (spondylitis) (76). About thirty percent of people having Ps will develop PsA (77).

Seventy-five percent of Ps showed dermatologic manifestations before arthritic manifestations (75). The etiology of Ps and PsA is not completely understood. Ps and PsA have been associated with an augmented risk of other immune-mediated disorders such as ulcerative colitis, Crohn’s disease, and autoimmune thyroid disorders (AITD) (71, 31). These diseases are immune-mediated disorders involving dendritic cells (DCs), macrophages, and T cells (77, 78). These immune cells secrete cytokines such as TNF-α, interleukin (IL)-1β, IL-6, and IL-22 (78) that induce inflammatory signals and chemokines secretion (78).

An important challenge is to discover new biomarkers in order to improve the early PsA diagnosis as well as the response to the treatment (79).

Here we review the role of the Th1 dependent chemokines MIG in PsA. The presentation of data has been reported in line with the International Narrative Systematic Assessment (INSA) tool (80).

**MIG in psoriatic arthritis**

In a first study synovial membranes and cytocentrifuge preparations of 7 RA, 8 PsA and 10 osteoarthritis (OA) patients were examined by in situ hybridisation with antisense probes of Mig, growth-regulated oncogene (GRO) α and Regulated upon Activation Normal T cell Expressed and Secreted (RANTES) and by immunohistochemistry in order to investigate the specific chemokine expression in synovial tissues from these patients involved in lymphocyte and monocyte recruitment (81). In the synovial lining layer and in cellular infiltrates too were detected Mig and RANTES hybridisation signals, while GRO α expression was localised only in the lining layer of RA and RA. Monocytic cells expressing KIM6 showed mainly Mig and GRO α mRNA, while lymphocytic cells expressing CD3 showed RANTES mRNA, as revealed by the cytological analysis. Few hybridisation signals were present in OA synovial membranes respect to that of RA and PA patients. PA and RA patients reported mild to severe local disease activity, only mild disease activity has been showed by OA patients. On the basis of these findings authors conclude that a different Mig, GRO α and RANTES expression, in resident and in inflammatory cells play an important role in directing leucocyte traffic in inflammatory arthropathies. The recruitment of various leucocyte populations should then be guided by the different leucocyte specificity to Mig, GRO α and RANTES, as detected in PA and RA (81).

In a second study was investigated the role of toll-like receptors (TLR), that recognize microbial components and are also activated by endogenous molecules, in autoimmune arthritis. MIG, IP-10 and I-TAC chemokines, were not induced by bacterial TLR ligands in human microvascular endothelial cells (HMVEC), in contrast to CXC full-length (82). Despite this, MIG and IP-10 production was induced by a synergistic action of peptidoglycan (PGN), double-stranded (ds) RNA or lipopolysaccharide (LPS) TLR2, TLR3 or TLR4 ligands, respectively) with IFN-γ. An enhanced I-TAC secretion was only obtained by IFN-γ and TLR ligand combination. Similarly with TLR ligands, TNF-α or IL-1β, combined with IFN-γ, synergistically induced Mig and I-TAC human fibroblasts and in HMVEC, two crucial cell types delineating the joint cavity. MIG production induced by TNF-α plus IFN-γ is neutralized by Etanercept, a humanized soluble recombinant p75 TNF-receptor-IgG1Fc fusion protein, that is not able to neutralize synergistic MIG production induced by IFN-γ and the TLR ligands PGN or LPS. Significantly high levels of MIG were detected in synovial fluids of patients affected by spondylarthropathies, (such as ankylosing spondylitis or PsA) or RA, respect to that of patients with metabolic crystal-induced arthritis, while no high I-TAC levels were shown. Thus it was shown the important role covered by MIG in autoimmune arthritis (82).

A further study evaluated serum levels of IP-10, MIG (α) and monocyte chemotactic protein-1 (MCP-1/CCL2) (β) chemokines in a large series of patients with PsA, with or without autoimmune thyroid (AT) disorders (33). Thirty seven patients with PsA without AT (PsA) and 28 with AT (PsA+AT) were enrolled in the study; as well as, two control groups, gender- and age-matched (1:1), the first one without AT (control 1), and the other with AT (control 2). In all subjects IP-10 and MCP-1 levels were measured. They found higher serum IP-10 levels in control 2 respect to control 1 (p < 0.001) and in PsA than control 1 or 2 (p < 0.0001). Higher IP-10 levels have been found in patients with PsA+AT, respect to both controls 1 and 2 (p < 0.0001, for both), and also respect to the PsA group without AT (p < 0.001). IP-10 levels were defined high when at least 2 Standard Deviation (SD) above the mean value of the control group (>192 pg/ml). On this basis they have found high IP-10 levels in: 5% of control 1; 19% of control 2; 42% of PsA and 63% of PsA+AT (p < 0.0001; χ2). MCP-1 levels were: similar in both controls; significantly higher in PsA or PsA+AT patients respect to both the controls (p < 0.01, for both). As regard MIG serum levels they were not significantly different in the study groups. Therefore authors have demonstrated higher serum levels of IP-10 and MCP-1 chemokines in patients having PsA respect to the controls. In addition serum IP-10 (α chemokine) levels were significantly higher in PsA patients with AT (33).

Phosphodiesterase 4 (PDE4) is a central enzyme in the degradation of cyclic adenosine monophosphate and plays a key role in cytokine production of inflammatory cells, angiogenesis, and in the functional properties of other cell types, like keratinocytes (83). Apremilast is a drug that acts by blocking pro-inflammatory chemokines and cytokines synthesis, such as MIG, IP-10, IL-23 and TNF-α, in several cell types. It is also able to reduce complex inflammatory processes (dendritic cell infiltration, epithelial skin thicke-
MIG in PsA

small molecule inhibitor of PDE4.

such as Ps and PsA, has been shown by Apremilast, a new disease, and in human chronic inflammatory diseases too, inflammatory properties in animal models of inflammatory disease, and in human chronic inflammatory diseases too, such as Ps and PsA, has been shown by Apremilast, a new small molecule inhibitor of PDE4.

Another study aimed to investigate Th1-related chemokines levels in Ps and to evaluate any association with disease severity, or the presence of PsA. Thirty-eight patients with Ps, and thirty-three controls were enrolled in the study (84). In PsA patients, median concentration of IP-10 was lower compared to controls (p = 0.03). There have been no significant correlations between the analyzed serum chemokines and the disease severity. MIG, IP-10 and CXCL16 serum concentrations did not increase in the Ps group and did not correlate with the severity of the disease (84).

The role of IFN-γ-inducible protein chemokines has recently been examined in different types of arthritis (85). It was demonstrated that both blood plasma-derived dendritic cells (pDCs) and pDCs isolated from RA and PsA synovial fluid (SF) expressed CXCR3 and CXCR4; and that the chemotaxis of blood-derived pDCs is stimulated by MIG, IP-10, I-TAC and stromal cell-derived factor 1 (SDF-1)/CXCL12 present in RA and PsA SF. In PsA patients it has been found a Th1 immune predominance at early stage of disease, while a reduction of these chemokines has been observed in long lasting PsA, with a significant increase of MCP-1/IP-10 ratio. This suggest a shift from a Th1, to a Th2 immune response in long lasting PsA (85).

Osteoclast progenitors (OCPs), of the monocyte pool in the peripheral blood (PB), contribute to the osteoresorption in inflammatory arthritis that is also influenced by the cytokine and chemokine milieu (86). A study was conducted in order to define the importance of chemokine signals for migration and activation of OCPs, enrolling 129 patients affected by RA, 53 patients affected by PsA, and 110 control patients. A cytometric bead array or enzyme-linked immunosorbent assay has been used to measure the MCP-1, CCL3, CCL4, CCL5, MIG, IP-10, and SDF-1 levels. They found that in RA there was a moderately enlarged OCP population among PB cells correlating with levels of TNF-α, rheumatoid factor, MCP-1, and CCL5. The receptor activator of NF-κB (RANK)+ subpopulation was augmented in SF, compared with PB, and correlated with the number of tender joints. The increased RANK expression rather than total OCP population could be used to distinguish PsA patients. An high expression of CCR1, CCR2, CCR4, CXCR3, and CXCR4 has been found in OCPs obtained from patients affected by arthritis. In parallel, patients with RA had augmented MCP-1, CCL3, CCL4, CCL5, MIG, and IP-10 levels, with significant elevation in SF vs PB for IP-10. MCP-1, CCL5, and IP-10 had similar osteoclastogenic effects, with CCL5 showing the greatest chemoattractant action on OCPs (86).

The dysregulation of IL-22 has been associated with autoimmune diseases, but efforts to determine its effect on pathogenesis have been hampered because of their divergent effects upon inflammation (87). One study investigated the role of IL-22 in patients with PsA. In PB of PsA patients, the number of IL-22+ CD4+ T cells decreased respect to healthy controls, leading to an increased CD4+ IFN-γ+ / IL-22+ ratio associated with decreased CCR6 expression. Furthermore, in PsA patients IL-22 expressing cells were depleted primarily from the central memory CD4 T-cell subset. The IL-22 and particularly the IFN-γ production were paradoxically augmented within a CD4+ T-cell subset having phenotypic markers characteristic of naïve T cells (CD3+CD4+CD27+CD45RA+CCR7+CD95−IL-2Rβ−), obtained from PsA patients with the highest IFN-γ+/IL-22+ ratio of all the CD4 subsets. Some of the phenotypic and functional properties showed by these unconventional “naïve” CD4+ T cells, from PsA patients, are characteristics of memory cells, including an important proliferative response. These unusual “naïve” T-cells, from PsA patients, increased the IFN-γ production thus promoting an higher MIG expression by HaCaT keratinocytes respect to their healthy counterparts. These abnormalities in this T-cell subset were reversed by an anti-TNF therapy, although it did not influence the frequency of IL-22+ T cells overall. In addition, the block of IL-22 increased IFN-γ mediated release of MIG (87).

Conclusion

MIG chemokine is involved in the pathogenesis of PsA. It was demonstrated that both blood-derived pDCs and pDCs isolated from RA and PsA SF, expressed CXCR3 and CXCR4, and that the chemotaxis of blood-derived pDCs is stimulated by MIG of RA and PsA SF. In PsA patients it has been found a Th1 immune predominance at an early stage of disease, while a reduction of Th1 chemokines has been observed in long lasting PsA, with a significant increase of Th2/Th1 ratio. This suggest a shift from Th1 to the Th2 immune response in long lasting PsA. MIG has been proposed as a useful marker to monitor the activity as well the progression of PsA. Efforts have been made to modulate or prevent the production of MIG in PsA aiming to alter the course of the disease.

References


MIG in PsA

https://doi.org/10.1186/1465-9921-14-121


82. Loos T, Dekeyzer L, Struyf S, et al. TLR ligands and cytokines induce CXCR3 ligands in endothelial cells: enhanced CXCL9 in autoimmune arthritis. Lab Invest. 2006;86:902-16