MIG in Cutaneous Systemic Lupus Erythematosus

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Abstract

Many studies reported that monokine induced by interferon (IFN)-γ (MIG), and its receptor chemokine (C-X-C motif) receptor (CXCR)3, are expressed by T cells in different types of cutaneous damages associated with lupus, and that the CXCR3-activating chemokines are produced locally, suggesting that they play a significant role in the recruitment of T cells in these inflammatory lesions. Circulating MIG levels are increased in cutaneous Systemic Lupus Erythematosus (SLE) patients and strongly correlated with the disease activity. The data discussed in this review show that there is an increasing evidence that MIG may participate in the pathogenesis of a variety of the manifestations of cutaneous SLE, even if the exact role of MIG in the pathogenesis of this disease remains to be clarified.

Key words: Cutaneous Systemic Lupus Erythematosus, MIG

Introduction

MIG, and CXCR3

Chemokine (C-X-C motif) receptor (CXCR)3 is a Gα protein-coupled receptor belonging to CXC chemokine receptor family, that has two isoforms: CXCR3-A and CXCR3-B. These receptors bind CXC chemokines, monokine induced by interferon (IFN)-γ (MIG), IFN-γ-inducible protein 10 (IP-10) and IFN-inducible T-cell α chemoattractant (I-TAC). Chemokine (C-X-C motif) ligand (CXCL)4 is only binded by CXCR3-B (1).

CXCR3 is expressed by different cells, as activated T lymphocytes and Natural Killer (NK) cells, some epithelial and endothelial cells. CXCR3 and the chemokine (C-C motif) receptor (CCR)5 are highly expressed on Type-1 helper (Th1) cells.

In inflammatory lesions, the local cells usually produce the chemokines MIG, IP-10 and I-TAC that attract Th1 cells; this suggest the central role of CXCR3 and its ligands in the recruitment of inflammatory cells (2).

MIG is a T-cell chemoattractant induced by IFN-γ. There is a strong correlation between MIG, IP-10 and I-TAC. The genes of these three chemokines are all located on human chromosome 4 (3, 4).

High circulating levels of MIG detected in peripheral liquids can be considered as a marker of an host immune response that involve especially Th1 cells (5, 6).

Th1 lymphocytes release IFN-γ, and tumor necrosis factor (TNF)-α, which stimulate the production of MIG from several cells in the inflamed site, causing an amplification feedback loop (5, 6), by recruiting new recruitment of Th1 lymphocytes in the inflammatory site. Several studies reported an increased tissutal expression, and high circulating levels, of MIG, and other Th1 chemokines, in different organ specific autoimmune diseases [like autoimmune thyroiditis (7-12), Graves’ disease (13, 14) Graves’ ophthalmopathy (15-18), type 1 diabetes (19-23)], or systemic rheumatological disorders [like rheumatoid arthritis (24), systemic lupus erythematosus (SLE) (25, 26), systemic sclerosis (27-31), psoriasis or psoriatic arthritis (32-35), sarcoidosis (36-38), HCV-related cryoglobulinemia (39-42), other HCV immune mediated disorders (11, 43-48)], other disorders, and also in cancers (49-64).

Systemic Lupus Erythematosus (SLE)

SLE is a systemic autoimmune disease which affects heart, joints, skin, lungs, blood vessels, liver, kidneys, and nervous system. Like other autoimmune diseases, the immune system attacks cells and tissues causing inflammation and tissue damage (65, 66). The disease course oscillates from periods of illness, called flares, to period of remissions. SLE happens more frequently in women than in men (9:1), and it is also more common in non-European descent (65).

The disease is characterized by the presence of several autoantibodies (67). The complexity of genetic, hormonal, and environmental factors, involved in the disease, and the wide array of circulating autoantibodies, give reason of the diversity of the clinical features (67, 68).

SLE is associated with other autoimmune diseases, such as autoimmune thyroid disorders, but also other disease (26, 69). Because of SLE is characterized by the production of a
wide array of autoantibodies, it can be considered a “B-cell disease”. Mak A et al. have shown that “helpless” B cells have difficulty in triggering SLE-related inflammation without the assistance of the T helper (Th) lymphocytes (70). Peripheral blood lymphocytes in SLE patients show Th2-like profiles (71), even if Th1 cells and IFN-γ have been shown to be important for SLE development (72).

The production of autoantibodies and the deposition of immune complex are typical of SLE. However, there is growing evidence of the role of different cytokines in SLE pathogenesis. Cytokines like B lymphocyte stimulator, interleukin (IL)-6, IL-17, IL-18, type I IFNs, and tumour necrosis factor TNF-α are able to orchestrate differentiation, maturation and activation of various inflammatory cell types, thus mediating local inflammatory process and tissue injury. The knowledge on the importance of cytokines in this process could represent the starting point for the definition of biomarkers and targeted therapies (73-76).

The ratio of Th1 and Th2 cytokines has been investigated to study the cytokine homeostasis in SLE. Because of the production of autoantibodies specific for self-antigens, at the beginning SLE was thought to be a Th2-polarized disease (77). More recently in SLE patients it was found a significantly elevated circulating Th1 cytokines, such as IFN-γ (78-80), suggesting the importance of the Th1 immune response in the initial, or active phase, of the disease. The prototype of the Th1 chemokine (C-X-C motif) family, IP-10, plays a chemotactic role mainly for activated Th1 cells and is involved in the pathogenesis of various Th1-dominant autoimmune diseases (81), and in SLE too.

In this narrative review we would study the role of MIG in cutaneous SLE. The presentation of data has been reported according to the International Narrative Systematic Assessment (INSA) tool (82).

MIG in cutaneous SLE

Meller et al. studied the pathways of activation and recruitment of leukocyte during the phases of initiation and amplification of cutaneous SLE. In this study they showed that the CXCR3 ligands MIG, IP-10 and I-TAC are the most abundantly expressed chemokine family members in cutaneous SLE. The expression of these ligands related to the presence of a marked inflammatory infiltrate consisting of a lot of different cells, like skin-homing lymphocytes and blood dendritic cell antigen 2-positive plasmacytoid dendritic cells (PDCs), which represent CXCR3 expressing cells. In particular, within cutaneous SLE, PDCs accumulated at the level of dermis and, when activated, they produced type I IFN, as demonstrated by the expression of Interferon regulatory factor 7 (IRF7) and myxovirus protein A (MxA), that are IFN-α-inducible genes. IFN-α, in turn, induced CXCR3 ligands in cellular constituents of the dermis in a potent and rapid manner. In this study, it was also demonstrated that, under UVB irradiation, epidermal compartments released the chemokine (C-C motif) ligand (CCL)27 (cutaneous T cell-attracting chemokine) into dermal compartment and up-regulated the expression of other chemokines in keratinocytes. That all indicate the presence of an amplification cycle in which apoptosis, necrosis, and chemokine production are stimulated by ultraviolet (UV) light-induced injury. This is the basis for the recruitment and activation of autoimmune T cells and IFN-α-producing PDCs, which in turn release more effector cytokines. This mechanism amplifies the production of chemokines and the recruitment of leukocytes, leading to the development of a cutaneous SLE phenotype (83).

Another study evaluated the role of inflammation in the pathogenesis of SLE and in the activity of disease. Plasma levels of IP-10, regulated on activation normal T cell expressed and secreted (RANTES), MIG, Monocyte chemoattractant protein 1 (MCP-1), growth-regulated protein alpha (GRO-alpha), and IL-18 concentrations were evaluated in SLE patients and controls, resulting higher in SLE patients and significantly related with Systemic Lupus Erythematosus Disease Activity Index (SLEDAI) scores (all p<0.05). This results suggested the presence of a relationship between increased plasma concentration and ex vivo production of inflammatory chemokines with the disease activity, supporting the thesis that Th1/Th2 lymphocytes and neutrophils chemotaxis have an important role in pathogenesis of SLE (84).

PDCs and type I IFNs should have central proinflammatory role in the pathogenesis of cutaneous SLE. The recruitment of CXCR3+ effector lymphocytes from the peripheral blood into cutaneous lesions of SLE is under the effect of MIG and IP-10. The distribution of the inflammatory infiltrate in different types of cutaneous SLE depends on the expression pattern of IFN-inducible proteins. Wenzel et al. investigated lesional skin biopsies obtained from patients with different types of SLE [chronic discoid SLE (CDLE), n = 12; subacute cutaneous SLE (SCLE), n = 5; SLE tumidus (LET), n = 4; SLE profundus (LEP), n = 6] by immunohistochemistry. A directly proportional correlation between the type I IFN-inducible protein MxA expression pattern and the distribution of the inflammatory infiltrate was observed, as usually observed in the investigated cutaneous SLE subsets. In particular, in CDLE and SCLE MxA expression was mainly found in epidermis and upper dermis, in LET at perivascular level and in LEP at subcutaneous level. Similar results were observed for MIG and IP-10. These findings show the presence of a correlation between the distribution of CXCR3+CD3+ lymphocytes and the expression pattern of IFN-inducible proteins in all investigated subsets of cutaneous SLE, supporting the importance of an IFN-driven inflammation in a pathology like cutaneous SLE (85).

In another study, type III IFNs were investigated because of their possible involvement in the pathogenesis of cutaneous SLE. A strong expression of IFN-λ and IFN-λ receptor was found in the epidermis of cutaneous SLE skin lesions and also in related autoimmune diseases, such as lichen planus and dermatomyositis.

In this study the level of serum IFN-λ1 was measured in cutaneous SLE patients with active skin lesions, and it resulted significantly increased. As revealed by functional analyses, human keratinocytes produce high levels of IFN-λ1, but only low amounts of IFNα/β/γ in response to immunostimulatory nuclear acids; this suggests that IFN-λ is the principal IFN produced by these cells. As consequence to the exposition to IFN-λ1, human keratinocytes produce several proinflammatory cytokines, like MIG, which in turn induced the recruitment of immune cells and the formation
of skin lesions in cutaneous SLE (86).

By comparing cytokine and chemokine profiles in patients with different types of cutaneous SLE (CDLE, n=15; SCLE, n=11; LET, n=21), the TNF-α, INF-γ, TGF-β, IL-6, IL-10, IL-12p40, MIG, and IP-10 mRNA expression results were significantly increased in SCLE patients compared to those with CDLE. In addition, the mRNA expression of TNF-α, TGF-β, IL-10, IL-12p40 and MIG results significantly increased in LET patients, with respect to CDLE patients. In all SLE subtypes, there is a strong correlation between MIG and IP-10 mRNA expression and INF-γ mRNA expression. All these results suggest that Th1 and Th2 cytokines are expressed in CDLE, SCLE, and LET in a differentially manner. Anyway, the highest cytokine and chemokine ligand expression are found in SCLE followed by CDLE and then by LET (87).

The angiostatic effects of inflammation are mediated by GTPase human guanylate binding protein-1 (GBP-1), which in endothelial cells (ECs) is induced by IFN-α and IFN-γ.

GBP-1 belongs to the large GTPase family, that includes seven homologous members. GBP-1 has been shown to be a marker of the proinflammatory microenvironment dominated by these by IFN-α and IFN-γ during inflammation-associated skin diseases.

Naschberger E. et al. investigated the role of GBP-1 as a marker of skin lesions in cutaneous SLE. In vitro studies demonstrated that IFN-α and IFN-γ induced GBP-1 in primary keratinocytes obtained from healthy controls. In addition, the authors shown that GBP-1 was expressed by keratinocytes and ECs in primary and UV-induced skin lesions in patients with different subtypes of cutaneous SLE, with respect to non-lesional skin. In skin diseases of different inflammatory etiology (for example atopic dermatitis) GBP-1 resulted not expressed. This suggests that the expression of GBP-1 is closely associated with skin lesions in cutaneous SLE patients, thus contributing in the disease (88).

A study was stimulated by the clinical observation of a rapid response of a chilblain lupus patient to treatment with JAK1/2-kinase inhibitor ruxolitinib. It was investigated the in vivo expression of phospho-JAK2 in cutaneous SLE skin samples as well as the immunomodulatory in vitro effect of ruxolitinib in cultured immortalized keratinocytes and in a 3D human epidermis model (epiCS). The results demonstrate that ruxolitinib significantly decreases the production of cutaneous SLE-typical cytokines (IP-10, MIG, MxA) and might be a promising drug for future clinical studies in patients with cutaneous SLE and related autoimmune skin diseases (89).

PDCs are dendritic cells specialized in the production of type I interferon (IFN-α/β); these cells are involved in different skin inflammatory and autoimmune disorders, like cutaneous SLE and vitiligo. Heat shock proteins (HSPs) are essential in maintenance of cellular functions; therefore these molecular chaperones could act as a danger signal during inflammation. The role of HSP70 in the production of IFN-α by PDCs in cutaneous SLE has been explored by Jacquemin C. et al (90). They analysed the expression of HSP70 and CD123+ PDCs in cutaneous SLE (90). In these patients at the beginning PDCs infiltrated in the epidermis, in particular into keratinocytes which express HSP70. Through in vitro experiments it has been shown that the PDCs, that express HSP70 the receptor lectin-like oxidized low-density lipoprotein-receptor-1 (Lox-1), were able to aggregate HSP70. Exogenous HSP70 induced the activation of PDCs and increased the uptake of exogenous DNA. In addition, in PDCs HSP70 reinforced the production of DNA-induced IFN-α, which in turn stimulated the expression of MIG and IP-10 by keratinocytes. All this showed as the interaction between HSP70 and PDCs is important in cutaneous SLE for the enhancement of IFN-α production (90).

The relationships among IFN-γ, type I IFNs and clinical features have been studied in peripheral blood samples obtained from 44 SLE patients and 36 healthy donors (HDs). In SLE patients the levels of mRNA of type II IFN-inducible genes [IFN-γ, T-box transcription factor 21 (TBX21), and Eomesodermin (EOMES)] were significantly higher than those in HDs. Also the percentages of IFN-γ-producing cells in lymphocytes and their subsets were significantly increased in patients with SLE compared to HDs. Linear regression indicated that IFN-γ expression levels and type II IFN scores were positively related with anti-double-stranded DNA autoantibody levels and SLEDAI scores (91).

Conclusion

In several types of cutaneous damages associated with lupus it was demonstrated that T cells express MIG and its receptor CXCR3, and that the CXCR3-activating chemokines are produced locally. This suggests a significant role of MIG and CXCR3 in the recruitment of T cells in these inflammatory lesions. Moreover, in cutaneous SLE patients there are increased circulating levels of MIG. Some results suggested the presence of a relationship between increased plasma MIG concentration and ex vivo production of inflammatory chemokines with the disease activity. On the whole, these data suggest that MIG could be involved in the pathogenesis of a variety of cutaneous SLE manifestations, although the exact role of MIG is not yet clear; further studies will be needed.

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