MIG chemokine in systemic sclerosis. MIG in Systemic sclerosis

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Abstract

Several studies have proposed in Systemic sclerosis (SSc) patients that the monokine induced by interferon (IFN)-γ (MIG)/chemokine receptor (CXCR)3 axis has a determinant role in the autoimmune process and in fibrosis. Elevated MIG levels were linked to a more severe clinical phenotype, with kidney, lung and thyroid involvement. Then MIG could be considered a marker of a more aggressive autoimmune process. In vitro, SSc fibroblasts have different kinds of dysregulation in the secretion of MIG, once treated with cytokines (as interferons). Moreover, MIG has been suggested as a serologic marker of a more severe SSc form, so it could be useful for the risk stratification of SSc patients. Clin Ter 2018; 169(4):e178-183. doi: 10.7417/CT.2018.2075

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Introduction

Systemic sclerosis

Systemic sclerosis (SSc), known also as scleroderma, is an autoimmune disease whose features are thickening of the skin, accumulation of collagen, and lesions to the smallest arteries.

There are two forms of overlap: 1) limited cutaneous scleroderma involving the skin of the face, hands and feet; 2) diffuse cutaneous scleroderma covers other areas of the skin, involving also the visceral organs (kidneys, lungs, heart, or gastrointestinal tract).

Patients with limited scleroderma have a good prognosis, with a 10-year survival rate of 75%, but approximately 10% develop pulmonary arterial hypertension after 15 years. Patients affected of diffuse scleroderma have a 10-year survival rate of 55%; death is mostly linked to heart, kidney and pulmonary involvement.

Immunosuppressive drugs are indicated for the treatment, albeit glucocorticoids have limited application (1, 2).

Tools for a good diagnosis, in addition to a clinical suspicion, are the search of autoantibodies (specifically anti-centromere and anti-scl70/anti-topoisomerase antibodies) and only occasionally biopsy.

Ninety% of SSc patients have a detectable anti-nuclear antibody, anti-centromere antibody is more frequent in the limited form (80-90%) with respect to the diffuse form (10%), and anti-scl70 is more prevalent in the diffuse form (30-40%) (3). Diagnostic criteria for scleroderma were defined in 1980 by the American College of Rheumatology (4).

SSc etiology is not clear. Despite a familial predisposition for autoimmune disease is frequent, the genetic concordance is small and then genetic predisposition is limited. Severity and development of the disease could be influenced by the polymorphisms in COL1A2 and transforming growth factor (TGF)-β1.

There is limited evidence implicating Cytomegalovirus (CMV) as the original epitope of the immune reaction, as well as parvovirus B19 (5, 6). Other causes of SSc can be find in the occupational exposure to solvents (7) as well as could be linked to chemotherapeutic agents such as Bleomycin (8) and probably to taxane chemotherapy too (9). Among the suspected mechanisms behind the autoimmune phenomenon, it has been hypothesized that microchimerism (i.e. fetal cells circulating in maternal blood), could lead to an immune reaction against what is recognized as “foreign” material (10).

The cause of the overproduction of collagen is thought to be the attack by immune system of the kinetochore of the chromosomes that should lead to genetic malfunction of nearby genes.

T cells accumulate in the skin; these are thought to secrete cytokines and other proteins able to stimulate collagen deposition. Stimulation of fibroblasts seems particularly important for the disease process, and studies gather about the potential factors that give this effect (3).

TGF-β plays a significant role in the process, indeed it appears to be overproduced, and also the fibroblasts (possibly in response to other stimuli) overexpresses the receptor for this protein. The collagen deposition is the result of proteins and enzymes whose transcription is induced by the activation of an intracellular pathway (including SMAD2/SMAD3, SMAD4 and the inhibitor SMAD7). Sp1 is a transcription factor most closely studied in this context.

A possible role in the disease is played, in addition to the TGF-β, by the connective tissue growth factor (CTGF)
too (3). It is indeed present, at an increased rate in SSc, a common CTGF gene polymorphism (11).

Endothelial hyper-reactivity is an early anomaly in the pathogenesis of scleroderma and it’s associated to excessive collagen production by fibroblasts; however in this process cytokine change, type II hypersensitivity and platelet adhesion reactions are importantly involved such as decreased vasodilation and endothelial hyperactivity (3, 6).

**MIG, and CXCR3**

The chemokine receptor (CXCR)3 is a receptor linked to the protein belonging to the family of CXC chemokine receptors. There are two CXCR3 isoforms: 1) CXCR3-A; 2) CXCR3-B. CXCR3-A binds CXC chemokines, interferon (IFN)-γ-inducible protein 10 (IP-10)/chemokine ligand 10 (C-X-C motif) (CXCL10), monokine induced by IFN-γ (MIG)/CXCL9 and IFN-inducible T-cell α chemoattractant (I-TAC)/CXCL11. Instead CXCR3-B binds the three above-mentioned chemokines plus CXCL4 (12).

CXCR3 is expressed by different cells, such as activated T lymphocytes and Natural Killer (NK) cells, some epithelial and endothelial cells. Type 1 helper cells (Th1) exhibits a strongly expression of CXCR3 and some epithelial and endothelial cells. Type 1 helper T lymphocytes and Natural Killer (NK) cells, involving Th1 cells (16, 17).

High MIG levels are the results of an amplification feedback loop in the inflamed site, indeed MIG is secreted by several cells under the IFN-γ and tumor necrosis factor (TNF)-α stimuli, whose increased levels are the results of the Th1 lymphocytes recruitment (16, 17).

In several studies high MIG tissue expression was reported in various organs specific for autoimmune diseases and high serum MIG levels too.

In fact, high MIG levels, as well as that of other Th1 chemokines, has been found in many specific autoimmune diseases, such as: autoimmune thyroiditis (18-23), Graves’ disease (24, 25) Graves’ ophthalmopathy (26-29), type 1 diabetes (30-34), or systemic rheumatological disorders, like systemic lupus erythematosus (SLE) (35, 36), rheumatoid arthritis (37), systemic sclerosis (38-41), sarcoidosis (42, 43), psoriasis or psoriatic arthritis (44-46), HCV-related cryoglobulinemia (47-52), other HCV immune mediated disorders (22, 53-58), other disorders, and also in cancers (59-72).

The objective of this narrative review is to evaluate the importance of MIG in SSc. The presentation of data has been reported according to the International Narrative Systematic Assessment (INSA) tool (73).
ce. Human fibroblasts and peripheral blood mononuclear cells (PBMCs) were treated with IL-13, TGF-β, TSLP, or poly(I-C), and gene expression, and protein levels of phospho-Smad2 and macrophage marker CD163 were evaluated by microarray analysis and quantitative polymerase chain reaction. The expression of TSLP was elevated in the skin of patients, particularly in immune cells and in perivascular areas. Almost the same up-regulated clusters of gene expression (as interferon-dependent genes, MIG, and protesome) were present in mice treated with IL-13, TSLP, and TGF-β. TNF-α, MIG, MS-1, and IFN-γ were up-regulated by TSLP in PBMCs. These data demonstrated that TSLP is strongly expressed in the skin of dSSc patients, interacting with other profibrotic cytokines, and in this way inducing profibrotic genes (78).

Another paper investigated the effects of glucocorticoids (GC) on serum chemokines and cytokines in 15 SSc patients (in therapy or not with systemic GC), in comparison to 8 controls. In PBMC supernatants, and serum, chemokines [as IL-8, IP-10, MIG, MCP-1, and RANTES] or cytokines (as IL-8, IP-10, MIG, MCP-1, and RANTES) were tested. In patients using corticosteroids serum levels of chemokines and cytokines were similar in patients in therapy or not with corticosteroids. After treatment with anti-CD3/CD28, a significant reduction of MCP-1, IL-8, and RANTES was shown in SSc PBMC treated with methylprednisolone, but not of the other cytokines/chemokines. These data proposed a possible effect of GCs on SSc treatment (79).

Conclusion

Chemokines and/or cytokines importance in the immunopathogenesis of different autoimmune disorders has been demonstrated by many studies (31, 50, 57, 80-89).

The above reported papers have proposed in SSc patients that the MIG/CXCR3 axis has a determinant role in the autoimmune process and in fibrosis. Elevated MIG levels were linked to a more severe clinical phenotype (with kidney, lung and thyroid involvement). Then MIG could be considered a marker of a more aggressive autoimmune process. In vitro, SSc fibroblasts have different kinds of dysregulation in the secretion of MIG, once treated with cytokines (as interferons). Moreover, MIG has been suggested as a serologic marker of a more severe SSc form and could be useful for risk stratification of SSc patients.

References


52. Antonelli A, Ferri C, Fallahi P, et al. Thyroid cancer in...


89. Ragusa F. Th1 chemokines in ulcerative colitis. Clin Ter. 2015;166:e126-31