Sjögren syndrome and MIG
I. Ruffilli

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

Abstract

In the ductal epithelium adjacent to lymphoid infiltrates and in lymphocytes of salivary glands in patients with Sjögren syndrome (SS), there is an increased expression of monokine induced by interferon (IFN-γ)(MIG) and chemokine (C-X-C motif) receptor 3 (CXCR)3, which therefore seems to participate in the SS pathogenesis. Cultured SS salivary epithelial cells treated with IFN-γ release high levels of IFN-γ-inducible protein 10 (IP-10) and MIG. MIG secreted by salivary epithelial cells (under IFN-γ influence), recruits Type-1 helper (Th1) lymphocytes that create an amplification feedback loop, and perpetuates the autoimmune process, through an enhanced IFN-γ induction, that in turn stimulates an MIG secretion from epithelial cells. The high levels of MIG in saliva and tears indicate an immune Th1 dependent response. An amelioration of autoimmune sialadenitis with MIG antagonists has been observed in experimental settings, suggesting a possible therapeutic approach to SS. More investigations are needed to assess whether MIG is a novel therapeutic target for SS in humans. Clin Ter 2019; 170(6):e478-482. doi:10.7417/CT.2019.2179

Key words: MIG, Sjögren syndrome

Introduction

Sjögren syndrome (SS), is a chronic autoimmune disease in which the exocrine glands (in particular salivary and lacrimal) are destroyed by an autoimmune process (1).

In SS patients, xerostomia (dry mouth) and keratoconjunctivitis sicca (dry eyes) are the results of an immune-mediated attack plus lymphocytic infiltration of the salivary and lacrimal glands (2). Clinician classified SS in: primary, that occurs by itself, and secondary that arises in association with another rheumatological disease.

The SS pathogenesis is not widely clarified; genetic, as well as environmental and hormonal factors are thought to contribute to lymphocytes infiltration (specifically CD4+ T cells, B cells and plasma cells), that cause glandular dysfunction (3). An important role in the SS immunopathogenesis is conducted by cytokines and chemokines (4).

Several studies reported high serum levels of monokine induced by interferon (IFN-γ)(MIG) / chemokine (C-X-C motif) ligand 9 (CXCL)9, and also of other Type-1 helper (Th1) chemokines [IFN-γ-inducible protein 10 (IP-10)/CXCL10 and IFN-inducible T-cell α chemoattractant (I-TAC) / CXCL11 bind CXCR3 receptor] and/or an augment of their tissue expression in different organ specific of autoimmune diseases. This has been revealed in different specific autoimmune diseases such as: autoimmune thyroiditis (5-11), Graves’ disease (12, 13) Graves’ ophthalmopathy (14-18), type 1 diabetes (19-23), or systemic rheumatological disorders, like rheumatoid arthritis (24), systemic lupus erythematosus (25, 26), systemic sclerosis (27-31), psoriasis or psoriatic arthritis (32-34), sarcoidosis (35, 36), HCV-related cryoglobulinemia (37-43), other HCV immune mediated disorders (5, 44-51), other disorders, and also in cancers (52-79).

Th1 dependent chemokines bind CXCR3, that is a Gα protein-coupled receptor having two isoforms CXCR3-A and -B (80). Several cells such as activated T lymphocytes, Natural Killer (NK), and some epithelial and endothelial cells express CXCR3. This receptor is highly expressed on Th1 cells, as well as the chemokine (C-C motif) receptor (CCR)5.

Chemokines MIG, IP-10 and I-TAC released by local cells of the inflamed site, recruit Th1 cells. Either CXCR3 and its ligands are crucial in the recruitment of inflammatory cells (81).

MIG is a small cytokine induced by IFN-γ, its gene is located near that of IP-10 and I-TAC on human chromosome 4. It is a T-cell chemoattractant (82, 83), whose high serum levels can be considered as a marker of Th1 driven host immune response (84, 85). Indeed, in the inflamed site occurs an amplification feedback loop because of an increased IFN-γ and tumor necrosis factor (TNF)-α production (by recruited Th1 lymphocytes), that stimulates the MIG secretion from different cells of the site (84, 85). This review is focused on the role of MIG in SS; the reported data are in line with the International Narrative Systematic Assessment tool (86).
**MIG in Sjögren syndrome**

A paper investigated chemokines and their receptors, in order to understand the development of T cell infiltrates in the salivary glands of patients affected by SS. Authors showed a significantly mRNA up-regulation of IP-10 and MIG in these patients with respect to normal salivary glands (P < 0.01 for both); while no significant difference arose for stromal cell-derived factor 1 (SDF-1) mRNA expression. In particular IP-10 and MIG proteins expression has been observed in the ductal epithelium near the lymphoid infiltrates. In dense periductal foci most of the infiltrate CD3+ expressed CXCR3. Cultured SS salivary epithelial cells under IFN-γ stimulation released high levels of IP-10 and MIG proteins. This research suggested that in the SS ducal epithelium the production of the above mentioned chemokines was stimulated by IFN-γ, and that they are implicated in the accumulation of T cell infiltrates in the SS salivary gland (87).

The aim of another paper was to analyze the Th1 dependent chemokines and their receptor expression in the ocular surface and in the tear film of patients with dry eye syndrome. Thirty-three subjects having dry eyes, of whom 16 with SS, and 15 controls, were enrolled. The chemokines concentrations observed for the subjects with dry eyes were: 1,148 +/- 1,088 pg/ml for MIG; 24,338 +/- 8,706 pg/ml for IP-10 and 853 +/- 334 pg/ml for I-TAC; while for controls were: 272 +/- 269 (P = 0.01) pg/ml for MIG; 18,149 +/- 5,266 (P = 0.02) pg/ml for IP-10; and 486 +/- 175 (P < 0.01) pg/ml for I-TAC. Increased concentrations of these chemokines have been detected in the SS patients with respect to those with non-SS dry eye syndrome (P < 0.05); as well as it was increased the staining for them, and for CXCR3. These data clearly showed that the expression of the Th1 dependent chemokines and of their receptor raised in the tear film and ocular surface of patients with dry eye syndrome, in particular in those affected by SS (88).

Increased levels of interleukin (IL)-7 were associated with multiple autoimmune disorders, such as SS. Lately, the important role played by this cytokine in the development and onset of primary SS in a mouse model, C57BL/6. NOD-Aec1Aec2 mice was shown. The effects of the administration of poly I:C (a double-stranded RNA analog and toll-like receptor 3 agonist) to this mouse model, showed that it induce the IL-7 expression in the salivary glands in a type 1 IFN- and IFN-γ-dependent manner; this contributes to a MIG upregulation that may furtherly promote the recruitment of more IFN-γ-producing T cells. A neutralization by anti-IL-7 antibody was able to abolish the development of SS-like exocrinopathy due to poly I:C administration. The Authors also observed that IL-7 gene expression and proteins production in a human salivary gland epithelial cell line is induced by poly I:C or a combination of IFN-α and IFN-γ (89).

A further study was undertaken in a non-obese diabetic (NOD) mouse model to determine the role covered by endogenously produced TNF-α in the pathogenesis of SS. Female NOD mice treated, prior of the disease onset, with neutralizing anti-TNF-α antibody, showed an improvement of the salivary secretion suggesting a remission of the clinical symptoms of SS. The block of TNF-α also led to a reduction of T, and B cells, and of the leukocyte foci or the T-bet protein levels in the submandibular glands (SMG), thus indicating a decrease in Th1 and T cytotoxic 1 cells. A reduction of MIG and CXCL13 was associated with these cellular changes induced by TNF-α neutralization (90).

Another study investigated the pathological and immunological features of ocular lesions in a mouse model of SS. Corneal epithelial injury and hyperplasia were confirmed pathologically. SS mouse models with respect to control mice, showed: a significantly lower number of conjunctival mucin-producing goblet cells; a significantly higher expression levels of transforming growth factor (TGF)-β, IL-6, TNF-α, and SDF-1 in the corneal epithelium; higher TNF-α, TGF-β, MIG, and lysozyme mRNA expression in the extraocular lacrimal glands. The presence of an autoimmune response in the ocular glands was sustained by the inflammatory lesions observed in the Harderian, intraorbital, and extraorbital lacrimal glands in the SS mouse model. An infiltration by CD4+ T cells occurred in the lacrimal glands of the SS model mice (91).

Elevated levels of IL-7 and its receptor were detected in the salivary glands of SS patients. This last study aimed to determine whether IL-7 sustains SS pathologies after the disease onset, using a NOD mice model. An amelioration of SS in female NOD mice aged 10 weeks, exhibiting newly onset clinical SS, was obtained after a treatment with antibody against the IL-7 receptor α chain (IL-7Rα). In the SMGs a decrease in IFN-γ-producing CD4 and CD8 T cells, B cells, MIG, IP-10, I-TAC, B lymphocyte chemoattractant (BLC), and TNF-α occurred; while there was an increase of claudin-1 and aquaporin 5 levels, important for normal salivary secretion. Also the block of IFN-γ and TNF-α in combination, or not, led to: an improvement of salivary secretion, a reduced leukocyte infiltration and a down-regulation of MIG and BLC expression in the SMGs. Therefore, IL-7 and Th1 cytokines appeared to be hopeful therapeutic targets (92).

**Conclusion**

MIG and its receptor showed a higher expression in the ductal epithelium adjacent to lymphoid infiltrates as well as in lymphocytes of salivary glands of patients with SS; this suggests their feasible involvement in the SS pathogenesis. Cultured SS salivary epithelial cells treated with IFN-γ release high levels of MIG and IP-10. MIG, secreted by salivary cells (under IFN-γ influence), recruits Th1 lymphocytes that create an amplification feedback loop, and perpetuate the autoimmune process, through an enhanced IFN-γ induction, that in turn stimulates an additional MIG secretion from epithelial cells. The high levels of MIG in saliva and tears indicate an immune Th1 dependent response. An amelioration of autoimmune sialadenitis with MIG antagonists has been observed in experimental settings, suggesting a possible therapeutic approach to SS. More investigations are needed to assess whether MIG is a novel therapeutic target for SS in humans.
References


