Application of Agents Against Interferon-Gamma-Dependent Chemokines in Immunotherapy.

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Abstract

The C-X-C chemokine receptor (CXCR)3 and its chemokines (CXCL9, CXCL10, CXCL11) are involved in the pathogenesis of autoimmune disesases. Under the influence of interferon(IFN)γ, the IFNγ-inducible chemokines are secreted by lymphocytes, and by target cells (fibroblasts, epithelial cells, etc). In target tissues, Th1 lymphocytes are recruited; hence IFNγ is enhanced, which stimulates IFNγ-inducible chemokines (CXCL9, CXCL10, CXCL11) secretion reiterating the autoimmune process.

Many studies have evaluated if blockade of CXCR3 or its chemokines have therapeutic significance in autoimmune diseases (for example in thyroid autoimmune disorders, etc).

Peroxisome proliferator-activated receptor (PPAR)γ or -α agonists show a strong inhibitory effect on the expression and production of CXCR3 chemokines *in vitro*, in various kinds of cells, such as denditric cells, monocytes, macrophages, endothelial and vascular smooth muscle cells, intestinal cells, thyrocytes, fibroblasts, preadypocytes and mesangial cells, and *in vivo* in animal models.

Further studies are ongoing to explore the use of new molecules that act as antagonists of CXCR3, or block CXCL10, in autoimmune disorders, and many interesting patents have been recently applied. Phase II studies have assessed the efficacy and safety of fully human, monoclonal antibodies to CXCL10, for the treatment of autoimmune disorders (for example rheumatoid arthritis, or ulcerative colitis).

Keywords: CXCR3 chemokines, autoimmune thyroiditis, Graves' disease and ophthalmopathy, inflammatory myopathies, rheumatoid arthritis, type 1 diabetes.

1. INTRODUCTION

Chemokines are a family of small cytokines that are able to induce chemotaxis in responsive cells. They are small proteins (about 8-10 KDa in size), with four cysteine residues in conserved locations important for their three-dimensional shape [1, 2]. The classification of chemokines is based on the position of the first two cysteine residues within the N-terminal; there are four chemokines subfamilies: C, CC, CXC, and CX3C chemokines [3, 4].

Interferon (IFN)γ-inducible chemokines [IFNγ-induced protein 10 (IP-10/CXCL10), monokine induced by IFNγ (Mig/CXCL9), and IFN-inducible T-cell chemoattractant (I-TAC/CXCL11)] were initially identified as chemokines that were induced by IFNγ and in various cell types, such as neutrophils, endothelial cells, keratinocyte, fibroblasts, hepatocytes and thyrocytes (and others); however, these chemokines are preferentially expressed on T helper (Th)1 lymphocytes [5, 6].

The IFNγ-inducible chemokines belong to the C-X-C subfamily, and bind specifically to the C-X-C chemokine receptors 3 (CXCR3), that is a seven trans-membrane-spanning G protein receptor expressed in activated Th1 lymphocytes [7], natural killer (NK) cells, macrophages, and other immune competent cells [7, 8].

IFNγ-inducible chemokines are involved in the pathogenesis of human diseases, such as infectious, inflammatory [9], autoimmune [10], and neoplastic disorders [11]. IFNγ-inducible chemokines are important in leukocyte homing in inflamed tissues, and exacerbate inflammation, causing tissue damage.

IFNγ-inducible chemokines attract activated Th1 lymphocytes to the sites of inflammation and their expression is associated with a Th1 immune response [12, 13].

For this reason the determination of circulating levels of IFNγ-inducible chemokines could be a marker of a Th1 orientated immune response. Serum and/or tissue levels of IFNγ-inducible chemokines are raised in organ specific autoimmune diseases [14], as autoimmune thyroiditis (AT) [15], Graves' disease (GD) and ophthalmopathy (GO) [16], type 1 diabetes (T1D) [17], or systemic rheumatological disorders, as rheumatoid arthritis (RA) [18], psoriatic arthritis, systemic lupus erythematosus [19], systemic sclerosis [20, 21], sarcoidosis [22], psoriatic arthtritis [23], hepatitis C associated autoimmunity [24, 25] and cryoglobulinemia [25, 26].

Recently several studies have focused on the possibility to modulate CXCR3 and its chemokines, utilizing modified chemokines, small antagonist molecules, neutralizing monoclonal antibodies,

binding proteins or other drugs [27]. The possibility of modulating the cytokine-induced CXCR3 chemokine secretion, *in vitro*, through primary human cell cultures, has been evaluated [28]. However, efforts aimed at the pharmacological use of the above mentioned agents in human diseases have been made.

2. TYPE 1 DIABETES

Many studies have suggested that the CXCL10/CXCR3 axis is critical in the autoimmune process and in β-cell destruction in T1D.

Lymphocytes infiltrating the human islet secrete CXCL10, and β-cells [upon stimulation by cytokines, as IFNγ and tumor necrosis factor (TNF)α] modulate the autoimmune response secreting CXCL9, CXCL10 and CXCL11. These chemokines induce the migration of Th1 lymphocytes into the islets, that secrete more IFNγ and TNFα, inducing a further stimulation of the chemokine production by the β-cells, thus reiterating the autoimmune process. Moreover, CXCL10 was identified as the more important chemokine expressed *in vivo* in the islet of prediabetic animals and patients with T1D [17, 28, 29].

CXCL10 serum levels (sCXCL10) ("Th1 chemokine") is high in T1D patients, and this suggests that CXCL10 may be a candidate for a predictive marker of T1D. Furthermore, sCXCL10 measurement may be useful to assess the pathophysiology of the disease course in T1D [17, 28, 29].

Blockade of CXCL10 or the presence of genetic deletion of CXCR3 lead to a reduction of T1D in animal models.

A study evaluated neutralizing monoclonal antibody to CXCL10 in a T1D mouse model. It was found that blockade of CXCL10 with this neutralizing antibody abrogated the appearance of T1D in 60% of all lymphocytic choriomeningitis virus (LCMV)-infected mice [30] interfering with the migration of LCMV-auto-aggressive CD8 T-cells into the pancreatic islets [30].

Recently the administration of a DNA plasmid encoding CXCL10 in young NOD mice has been conducted to neutralize CXCL10 [31]. This DNA vaccination led to the generation of neutralizing anti-CXCL10 antibodies and reduced the development of diabetes [31].

A small molecule CXCR3 antagonist (NIBR2130) has been recently studied in a virus-induced mouse model for T1D [32]. The frequency of T1D did not decrease in mice treated with NIBR2130, and no significant differences were found in the islet infiltration rate by islet antigen-specific T cells. These

data suggest that unlike the direct inhibition of CXCL10, blocking CXCR3 with NIBR2130 is not sufficient to prevent T1D [32].

Peroxisome proliferator-activated receptor (PPAR)-γ activators are used as antidiabetic agents [33] and are involved in the modulation of inflammatory responses.

PPAR-γ activity may be involved in the regulation of IFN-γ-induced chemokine expression in human autoimmunity, and its ligands might attenuate the recruitment of activated T cells at sites of Th1-mediated inflammation [12].

3. TARGETING CXCR3 AND ITS CHEMOKINES IN THYROID AUTOIMMUNITY

Infiltration of the thyroid by lymphocytes and other inflammatory cells and production of thyroglobulin and thyroperoxidase autoantibodies are typical of AT. The destruction of thyrocytes by the autoimmune process is frequently associated with the appearance of hypothyroidism.

Genetic and environmental factors contribute to the pathogenesis of AT [34], such as CXCR3 and its chemokines. A significant increase of CXCL10 in thyroid tissue specimens obtained from AT was found in lymphocytes, but also in epithelial cells, by immunohystochemistry [35].

It has been shown that thyroid follicular cells, upon stimulation by cytokines (IFNγ and TNFα), partecipate in the autoimmune response producing CXCR3 chemokines. These chemokines induce the migration of Th1 lymphocytes into the thyroid, that in turn, secrete more IFNγ and TNFα, stimulating the chemokine production by the target cells, in this way initiating and perpetuating the autoimmune process [34].

High levels of circulating IFNγ-inducible chemokines have been shown in patients with AT, overall with hypothyroidism [36].

A modulatory role of PPAR-γ or -α agonists on CXCR3 chemokines in AT has been shown. Further studies are ongoing to explore the use of new molecules that act as antagonists of CXCR3, or block the IFNγ-inducible chemokines, in AT [37].

The hallmark of GD is the presence of thyrotropin receptor autoantibodies of the stimulating variety, and a Th1-dominance prevails in its initial phase [38, 39]. CXCR3 chemokines are highly expressed in infiltrating inflammatory cells, and in thyrocytes [35], and the secretion of these chemokines by follicular cells is linked to the recruitment of Th1 cells in the active phases of GD [40].

sCXCL10 are elevated in GD patients, and decline after methimazole treatment. High sCXCL10 are associated with the active phase of the disease in both newly diagnosed and relapsing hyperthyroid patients [36, 41].

The reduction of circulating IFNγ chemokine levels in patients with GD after near-total thyroidectomy, or radioiodine ablation, suggests that these chemokines are produced into the thyroid of GD patients [42-44].

A CXCL10 polymorphism is a marker to predict severity of GD [45], and sCXCL10 remain elevated during the remission of this disease [46].

GO is present in approximately 50% of GD patients. Among GO patients, sCXCL10 are significantly higher in those with active disease. The secretion of CXCR3 chemokines was absent in basal conditions in retrobulbar fibroblasts and preadipocytes from GO patients in primary cultures; the stimulation with IFNγ alone and/or TNFα induced the release of these chemokines, suggesting that these cells participate in the self-perpetuation of inflammation through the release of chemokines [47].

In GO, a significant reduction in CXCL9 and CXCL10 serum concentrations during intravenous infusions of methylprednisolone and teleradiotherapy treatment was evidenced, suggesting these chemokines could help as a guideline in therapeutic decision-making in these patients [48]. These findings were more recently confirmed in another study that showed a reduction of CXCL10 in patients treated with intravenous corticosteroids [49].

The involvement of PPAR-γ in the regulation of IFNγ-induced chemokine expression in human autoimmunity has been shown recently, and PPAR-γ ligands attenuate the recruitment of activated T cells to areas of Th1-mediated inflammation [50-52]. The treatment of thyrocytes, orbital fibroblasts, and preadipocytes with the PPAR-γ agonists inhibit IFNγ plus TNFα-induced CXCR3 chemokines production, suggesting an inhibitory role of PPAR-γ agonists in the modulation of these chemokines [47, 53]. Additional studies are necessary to verify if new targeted PPAR-γ agonists could exert anti-inflammatory effects without the risk of expanding retrobulbar fat mass in GO [54].

Ligands for PPAR-α have immune-modulating activity in several rodent models of autoimmune diseases [55, 56]. PPAR-α activators inhibit the IFNγ-induced secretion of CXCR3 chemokines in primary cells (thyrocytes, fibroblasts and preadipocytes) suggesting that PPAR-α may be involved in the modulation of the immune response in AT, GD, and GO [16, 57].

PPAR ligands inhibit transcriptional activation by nuclear factor-kB *via* ligand-dependent transrepression [58, 59].

4. RHEUMATOID ARTHRITIS

CXCL10 and its receptor, CXCR3, appear to contribute to the pathogenesis of rheumatoid arthritis (RA). CXCL10 has been evidenced in sera, synovial fluid (SF), and synovial tissue in RA patients. CXCL10 is expressed in particular by infiltrating macrophage-like cells and fibroblast-like synoviocytes in RA synovium. The increased expression of CXCR3 on T cells from SF has been associated with high levels of IFNγ, which suggest a preferential Th1 phenotype [18, 60-68]. **Anti-inflammatory agents [69] are used in the therapy of RA.**

A phase II study in RA patients [70] evaluated the efficacy of MDX-1100, a fully human, anti-CXCL10 (anti-IP-10) monoclonal antibody, who did not respond adequately to methotrexate. The response rate was significantly higher in patients treated with MDX-1100 (54%) than among placebo-control patients (17%), suggesting that MDX-1100 is well tolerated and can be considered an effective treatment in RA patients not responders to traditional therapies.

5. ULCERATIVE COLITIS

Many studies have shown that CXCR3 and its ligand chemokines (CXCL9, CXCL10, CXCL11) are strongly overexpressed in the intestinal mucosa of mice with experimental colitis, and in patients with ulcerative colitis (UC) both in lymphocytes, in macrophages and in epithelial cells. IFNγ induces CXCR3 and its chemokines expression in epithelial colonic cells; CXCL9, CXCL10, CXCL11 are important for the recruitment of granulocytes and mononuclear cells and thus for the maintenance of inflammation in UC. sCXCL10 reflected UC disease activity, and it may be a marker for the responsiveness of patients to treatments [71-80].

Many studies have evaluated the therapeutic effect of blockade of CXCR3 or its chemokines in UC.

Anti-IP-10 monoclonal antibodies were investigated in colitis induced in B6 IL-10 mice [81], showing a decreased clinical and histological disease severity and a reduction of chemokine expression in colon, and the recruitment of Th1 lymphocytes [81].

An anti-IP-10 antibody was evaluated into mice with newly established acquired immunodeficiency syndrome (MAIDS) colitis [82]. Blockade of CXCL10 attenuated MAIDS colitis reducing the number of colon infiltrating cells through blocking cellular trafficking [82].

Another study evaluated the effect of fenofibrate on the progression of colitis in C3H.IL-10 (-/-) mice, showing a delayed onset of colitis, a reduction of the colonic histopathology score, and of expression of genes encoding the inflammatory cytokines IFN-γ, and of CXCL10 [83].

A phase II, double-blind, multicentre, randomised study, studied a fully human, monoclonal antibody to CXCL10 (BMS-936557), in the treatment of patients with moderately-to-severely active UC [84]. One hundred and nine patients were included (BMS-936557: n=55; placebo: n=54). Higher BMS-936557 steady-state trough concentration (Cminss) was associated with increased clinical response and histological improvements, suggesting that BMS-936557 is a potentially effective therapy for moderately-to-severely active UC [84].

6. IDIOPATHIC INFLAMMATORY MYOPATHIES

The α-chemokines CXCL9 and CXCL10 are expressed in idiopathic inflammatory myopathies (IM) muscle. An elevated CXCL10 expression was evidenced on macrophages and T cells surrounding and invading non-necrotic muscle fibers in polymyositis and sporadic inclusion body myositis and in T cells in perimysial infiltrates of dermatomyositis. Moreover, it was also present in blood vessel endothelial cells in all inflammatory and normal muscle tissues. sCXCL10 are high in patients with IM. Eliciting the CXCL10 secretion, human skeletal muscle cells might actively self-promote muscular inflammation, under the influence of cytokines (IFNγ, TNFα), which can amplify Th1 cell tissue infiltration *in vivo* [85-92].

Attempts have been made to modulate CXCR3 chemokines in IM.

In a study the effect of the Vitamin D receptor (VDR) agonist BXL-01-0029 on IFNγ/TNFα-induced CXCL10 secretion by human skeletal muscle cells was evaluated in comparison with elocalcitol (VDR agonist). BXL-01-0029 decreased IFNγ/TNFα induced CXCL10 protein secretion in human skeletal muscle cells, suggesting BXL-01-0029 as a novel pharmacological tool for IM treatment [93].

Another study evaluated the effects of IFNγ and TNFα stimulation, and of increasing concentrations of the PPAR-γ agonists (pioglitazone or rosiglitazone; 0.1μM-20μM), on Th1-chemokine CXCL10 in primary extraocular muscle (EOM) cultures from patients with thyroid-associated ophthalmopathy

(TAO-p). In primary EOM cultures from TAO-p: a) CXCL10 was undetectable in the supernatant, IFNγ dose-dependently induced it, whereas TNFα did not; b) EOM produced basally low amounts of CCL2, TNFα dose-dependently induced it, whereas IFNγ did not; c) the cotreatment with TNFα and IFNγ had a significant synergistic effect on CXCL10 and CCL2 secretion; and d) PPAR-γ agonists have an inhibitory role on the modulation of CXCL10, while they stimulate CCL2 secretion. These results suggest that EOM participates in the self-perpetuation of inflammation releasing both Th1 (CXCL10) and Th2 (CCL2) chemokines upon stimulation by cytokines, in TAO. PPAR-γ agonist activation inhibits CXCL10, but stimulates the release of CCL2 [94].

The effect of anti-IP-10 antibody treatment was studied in an animal model of C protein-induced myositis (CIM). C57BL/6 mice with CIM were treated with anti-IP-10 antibody or control antibody (anti-RVG1) and the inflammation in muscle tissue was assessed by immunohistochemistry that showed increased expression of CXCL10 and CXCR3 in the inflammatory lesions of muscle in CIM, especially, in CD8+ T cells invading myofiber. CIM mice treated with anti-IP-10 antibody showed a lower inflammation score in muscles than those with anti-RVG1, showing that IP-10/CXCR3 blockade suppresses inflammation in muscle [95].

7. MULTIPLE SCLEROSIS

CXCR3 and its ligands (CXCL9, CXCL10) have a key role in multiple sclerosis (MS). The CXCR3 receptor is expressed on the majority of T cells in the cerebrospinal fluid (CSF) of patients with MS, suggesting that the CXCR3 receptor may mediate the trafficking of T cells into the central nervous system. CXCL10, and CXCL9 are elevated in the CSF of patients with MS during relapse. These chemokines were also detected in actively demyelinating lesions, and upregulation of CXCR3 expression on peripheral blood $CD4^+$ lymphocytes was associated with MS relapses [96-108].

The impact of the immunomodulatory drugs used in the MS therapy on blood and CSF levels of chemokines in MS was investigated.

IFNβ is widely used in relapsing-remitting multiple sclerosis (RRMS); the mechanisms of action is still not fully understood, but it is known that IFNβ suppresses the proliferation of autoreactive T cells and the production of proinflammatory cytokines, as IL-8, CXCL9, CXCL10, etc. [109, 110].

More recently, it has been shown that better treatment responses were associated with decreased CXCL10, IL-18, IFNγ, and TNFα transcript levels [111].

Another study showed sCXCL10 were higher in MS patients, were positively correlated with T2 lesions (on magnetic resonance) and increased during relapses. Treatment with IFNβ-1a or IFNβ-1b was associated with elevated levels of CXCL10 [107].

Natalizumab reduces the transmigration of leukocytes into the central nervous system, exerting therapeutic effects in patients with MS. The effects of natalizumab on cytokine and chemokine profiles in blood and CSF in patients with relapsing MS before and after one year of natalizumab treatment were evaluated [108]. A strong decrease of pro-inflammatory cytokines (IL-1β, IL-6 and IL-8) and of chemokines associated with Th1 (CXCL9, CXCL10, CXCL11) immune response [108] was observed in CSF.

CONCLUSION

CXCR3, and its chemokines (CXCL9, CXCL10, CXCL11), contribute to the pathogenesis of many autoimmune disorders, as T1D, AT, GD and GO, RA, MS, IM, or UC. Under the influence of IFNγ, CXCL10 is secreted by epithelial cells, or fibroblasts or synovial cells, or other cell types; in tissue, recruited Th1 lymphocytes may be responsible for enhanced IFNγ, that stimulates CXCL10 secretion from these cells creating an amplification feedback loop, reiterating the autoimmune process.

Recently several studies have focused on the possibility to modulate CXCR3 and its chemokines, using modified chemokines, small antagonist molecules, neutralizing monoclonal antibodies, binding proteins or other drugs. The possibility of modulating the cytokine-induced CXCR3 chemokine secretion, *in vitro,* using mainly primary human cell cultures has been evaluated. Furthermore, phase II trials have studied monoclonal antibody to CXCL10 in the treatment of patients with UC or RA, with promising results. However, further studies are ongoing to explore the use of new molecules that act as antagonists of CXCR3, or block CXCL10, in autoimmune disorders.

LIST OF ABBREVIATIONS

Interferon (IFN)

IFNγ-induced protein 10 (IP-10)

Monokine induced by IFNγ (Mig)

IFN-inducible T-cell chemoattractant (I-TAC)

Chemokine Receptors (CXCR)

Natural killer (NK)

Autoimmune thyroiditis (AT)

Graves' disease (GD)

Graves' ophthalmopathy (GO)

Type 1 diabetes (T1D)

Rheumatoid Arthritis (RA)

Tumor necrosis factor (TNF)

CXCL10 serum levels (sCXCL10)

Lymphocytic choriomeningitis virus (LCMV)

Peroxisome proliferator-activated receptor (PPAR)

Synovial fluid (SF)

Ulcerative colitis (UC)

Murine acquired immunodeficiency syndrome (MAIDS)

Inflammatory myopathies (IM)

Vitamin D receptor (VDR)

Extraocular muscle (EOM)

Patients with thyroid-associated ophthalmopathy (TAO-p)

Model of C protein-induced myositis (CIM)

Multiple sclerosis (MS)

Cerebrospinal fluid (CSF)

Relapsing-remitting multiple sclerosis (RRMS)

CONFLICT OF INTEREST

The authors have no conflict of interest to declare.

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