Mig chemokine in primary biliary cirrhosis

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Abstract

Different studies investigated about the role of T-helper 1 cytokines and chemokines in primary biliary cirrhosis (PBC). Animal models with autoimmune cholangitis have been used to investigate the involvement of (C-X-C motif) receptor (CXCR)3 and its ligand (C-X-C motif) ligand (CXCL)9/monokine induced by interferon (IFN)-γ (MIG) in the pathogenesis of PBC, suggesting a contribution of MIG in the development of PBC. In patients with PBC, in particular at the level of the portal areas of diseased livers, MIG expression and CXCR3+ cells have been found. MIG is positively associated with the severity of liver fibrosis. In PBC, circulating MIG levels and CXCR3+ cells are related with the progression of the disease; in fact, their expression increases significantly in PBC patients with respect to controls. Furthermore, it has been shown a significant reduction of these chemokines in the serum of PBC patients after treatment with ursodeoxycholic acid.

Ursodeoxycholic acid (UDCA) is the most commonly helpful treatment used for the cholestasis reduction, albeit its ability in improving PBC prognosis is controversial.

It has been shown a significant association between PBC and human leukocyte antigen (HLA) class II, IL12A, and IL12RB2 loci, and other genes involved in cytokine regulation such as TYK2, SH2B3 and TNFSF11 (1-3).

Since chemokines play a crucial role in PBC, we review the role of Type helper 1 (Th1) cytokines and chemokines focusing more specifically on monokine induced by interferon (IFN)-γ (MIG).

MIG and CXCR3

CXC chemokines, MIG, IFN-γ-inducible protein 10 (IP-10) and IFN-inducible T-cell α chemoattractant (I-TAC) bind chemokine (C-X-C motif) receptor (CXCR)3, that is a Gα protein-coupled receptor belonging to CXC chemokine receptor family (4).

Activated T lymphocytes, Natural Killer cells, some epithelial and endothelial cells express CXCR3. High expressions of CXCR3 and of the chemokine (C-C motif) receptor (CCR)5 are found on Th1 cells.

Th1 cells were attracted in the inflammatory lesions through the chemokines MIG, IP-10 and I-TAC produced by the local cells. Thereby CXCR3 and its ligands play a pivotal role in the recruitment of inflammatory cells (5). MIG is induced by IFN-γ and it is a T-cell chemoattractant, strongly correlated with IP-10 and I-TAC; their genes are located on human chromosome 4 (6, 7).

High levels of MIG in peripheral fluids may be considered as markers of a host Th1-immune response (8, 9).

IFN-γ, and tumor necrosis factor (TNF)-α released by Th1 lymphocytes, stimulate the production of MIG from several cells in the inflamed site. This process leads to an amplification feedback loop (8, 9), through the recruitment of other Th1 lymphocytes in the inflammatory site.

High tissutal expression, and high circulating levels of MIG, as well as that of other chemokines, were found...
in several organ specific autoimmune disorders, such as autoimmune thyroiditis (10-16), Graves’ disease (17, 18), Graves’ ophthalmopathy (19-23), type 1 diabetes (24-28), or systemic rheumatological disorders, such as rheumatoid arthritis (29), systemic lupus erythematosus (30, 32), systemic sclerosis (33-38), psoriasis or psoriatic arthritis (39-42), sarcoidosis (43-45), HCV-related cryoglobulinemia (46-49), different HCV immune mediated disorders (14, 50-57), other diseases, and also in cancers (58-74).

In this review the role of MIG in PBC has been investigated, reporting all the presentation of data in line with the International Narrative Systematic Assessment tool (75).

MIG in PBC

Infiltrating memory T cells are important in the destruction of the biliary tract in PBC, and inflammatory chemokines, interacting with T cell chemokine receptors, guide the lymphocytes traffic. Plasma levels of IP-10, MIG, and the expression of CXCR3, have been studied in 53 patients with PBC, 26 first degree relatives, and 26 healthy controls. The results showed that plasma IP-10 and MIG levels were significantly increased in PBC with respect to controls, and an increasing trend was shown with the progression of the disease. Immunohistochemistry revealed the expression of IP-10 and MIG in the portal areas in PBC patients. These data suggested the involvement of specific chemokine-chemokine receptor interactions in the pathogenesis of PBC (76).

A literature review studied PBC, progressive sclerosing cholangitis (PSC), and homoing mechanisms. In addition to a specific role for CCL25 in PSC, the chemokines CCL21, CCL28, MIG and IP-10 were shown to have an important role in the recruitment of T lymphocytes into the portal tract in both disorders. It was demonstrated that as soon as lymphocytes enter in the liver, they localize in the bile ducts maintaining the combined or sequential action of CXCL12, CXCL16, CX3CL1, CCL28, MIG and IP-10. These data underlined how recruitment and homing are important in PBC (77).

Another study evaluated the serum concentrations of MIG, IP-10 and I-TAC, in 53 healthy controls, 109 subjects with histologically determined liver fibrosis and 153 patients with different stages of cirrhosis of various disease aetiologies. The results showed that serum concentrations of all three chemokines were significantly increased in patients with chronic liver diseases compared with healthy controls (P<0.001). In the biopsied fibrosis group, MIG and IP-10 were positively associated with the severity of liver fibrosis, according to histology and serum markers, this was not observed for I-TAC. As regard the group of cirrhotic patients it has been observed an increase of MIG in early Child-Pugh stages, whereas I-TAC was elevated only in Child B and C patients, and IP-10 in all stages. CXCR3 chemokines were associated with clinical complications of cirrhosis, particularly with the portal hypertension. These findings suggested a different expression of the chemokines in chronic liver diseases, across different stages and aetiologies (78).

The mRNAs expression of MIG, IP-10 and I-TAC has been investigated and compared through semi-quantitative multiplex reverse transcription-polymerase chain reaction (RT-PCR) in biopsies obtained from the liver of twenty patients with a first diagnosis of PBC, respect to twenty patients with normal liver biopsy [normal controls (NCs)]. PBC patients showed a high mRNA expression of MIG and IP-10, as well as an increment of the serum levels of these chemokines respect to NCs. After UDCA treatment it has been observed a significant reduction of these chemokines in the serum of the patients. It was also observed a mRNA expression of CXCR3B in the peripheral blood lymphocytes in 4 out of 20 NCs, and in 20 out of 20 PBC patients. A significantly lower CXCR3 expression in NCs respect to PBC has been shown by flow cytometry; after the treatment with UDCA the CXCR3 expression in PBC decreased (P<0.01). These findings highlight a possible role for these chemokines and their receptor in the recruitment of lymphocytes in PBC as well as a new mechanism of action for UDCA (79).

A cholecystojejunostomy procedure to reconstruct biliary flow after bile duct iligation in C57BL/6 mice to generate a model of fibrosis resolution was developed in another study. Injections of vascular endothelial growth factor (VEGF)-neutralizing (mcr84) or control antibodies were performed to these mice, while other received an adenosine expressing mouse VEGF or a control vector. The procedure was made also in mice in which macrophages were selectively depleted through a macrophage fas-induced apoptosis. The development of fibrosis but the repair of the disrupted hepatic tissue and the resolution of the fibrosis too, were prevented by VEGF-neutralizing antibodies. In the process of fibrosis resolution, the liver sinusoidal permeability was impaired by VEGF inhibition, and is associated with a reduction of the monocyte migration, and of infiltration of fibrotic liver.

A contribution to this process was made by the scar-associated macrophages through the production of the chemokine MIG and matrix metalloproteinase-13. In macrophage FAS-induced apoptosis mice the fibrosis resolution was impaired, while it increased after overexpression of MIG (80).

A recent paper reviewed the involvement of CXCR3 and its ligands in the PBC pathogenesis, suggesting that IP-10 and MIG expressions, and CXCR3-positive cells were present in the portal areas of livers of patients with PBC, and that these chemokines were associated in a positive manner with the severity of liver fibrosis (81). In particular, it was investigated the role of these chemokines in the recruitment of autoreactive memory T cells, showing that more than half of CD4+ lymphocytes were CXCR3+ in PBC (76, 81).

Despite several biologic agents have been studied in murine models as well as in human patients with PBC, the results have been relatively disappointing. A study evaluated an interleukin (IL)-22 expressing adeno-associated virus (AAV-IL-22) to investigate the potential role of IL-22 in protecting mice from autoimmune cholangitis, and in treating animals with confirmed portal inflammation. In the study we used mouse model of 2-OA-OVA immunization, that include α-galactosylceramide (α-GalCer) stimulation. The mice were treated with AAV-IL-22 before and after the onset of clinical disease. The AAV-IL-22 treatment given to 2-OA-OVA and α-GalCer exposure, before the onset of disease, reduces in a significant manner the portal inflammatory response, the Th1 cytokines production and the appearance of liver fibrosis. The liver lymphotrophic chemokines CCL5, CCL19, CXCL9, and CXCL10 were reduced too (82).
Conclusion

The contribution of MIG and CXCR3 in the pathogenesis of PBC cirrhosis was suggested by studies conducted on autoimmune cholangitis animal models.

Other studies showed that MIG expression, and CXCR3-positive cells were present in the portal areas of diseased livers of humans affected by PBC. A positive association between MIG and the severity of liver fibrosis has also been observed. Furthermore, both circulating MIG levels, and CXCR3-expressing cells, increased in a significant manner in PBC respect to controls and appeared to increase along the disease progression. Lastly, it has been shown a significant reduction of these chemokines in the serum of PBC patients after treatment with UDCA.

References


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