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CXC-Chemokines and Thyroid Associated Autoimmunity

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Chemokines

Chemokines are a group of peptides of low molecular weight that induce the chemotaxis of different leukocyte subtypes [1]. The major function of chemokines is the induction of leukocyte migration to inflammation sites, but they also play a role in tumoral growth, in angiogenesis and in organ sclerosis [2]. At the present more than 50 chemokines have been described, which can be classified in 4 major families on the basis of the position of the cysteine residues in their NH_2 terminal portion [1]. So far, only two of these families have been extensively studied and characterized. They are CC and CXC (target of our interest), chemokines which are defined on the fact that between two cysteine residues another aminoacid is inserted.

Chemokine effects are mediated by specific membrane receptors coupled with G proteins [3]. In general, one receptor binds to more than one chemokine and one chemokine binds to more than one receptor. This property reduces the specificity of pharmacological intervention [4]. Exception is provided by a small group of chemokines inducible by interferon (IFN)- (CXCL9, CXCL10, CXCL11), which are associated with Th1-mediated immune responses. They interact indeed with a unique receptor, named CXCR3. Every compound able to interact with CXCR3 receptor can therefore modulate (positively or negatively) the effects of these chemokines.

Role of CXCL9, CXCL10 and CXCL11 in Thyroid Associated Autoimmunity (AITD)

The interest on IFN-γ inducible chemokines started from previous studies on the anti-angiogenetic effects of these compounds. In Graves' disease, CXCR3 receptor was found to be highly expressed in endothelial cells as well as in infiltrating inflammatory cells, while CXCL10/IP-10 was observed not only on these cells, but also on thyrocytes. In fact, it was shown that human thyrocytes in primary cultures, stimulated by IFN-, produce large amounts of CXCL10/IP-10, CXCL9, and CXCL11 [5-8].

In addition, by using immunohystochemistry, a statistically significant increase of CXCL10/IP-10 and CXCL9/MIG in thyroid tissue specimens obtained from subjects affected by Hashimoto's thyroiditis was found [5]. By using combined *in situ* hybridization and immunohistochemistry, it has been shown the expression of CXCL10/IP-10 in thyrocytes of patients affected by Graves'disease, while CXCR3 receptor was found only in inflammatory and endothelial cells.

Also orbital fibroblasts and preadipocytes from patients with Graves' ophthalmopathy are able to secrete CXCL10, CXCL9, and CXCL11 chemokines, under the influence of IFN-γ, and the combination of IFN-γ and tumor necrosis factor (TNF)-α [7-9].

These findings strongly suggest that CXCL9, CXCL10 and CXCL11 chemokines are secreted by thyrocytes, and orbital cells, under the influence of IFN- and TNF-α produced by T lymphocytes, in the initial phases of thyroid autoimmune disorders. CXCL9, CXCL10 and CXCL11 chemokines secreted by thyrocytes recruit and activate other Th1 lymphocytes in the sites of inflammation, reinforcing and perpetuating the autoimmune process.

This hypothesis is also confirmed by the dosage of CXCL9, CXCL10 and CXCL11 chemokines in the circulation of patients with thyroid autoimmune disorders.

In fact serum CXCL9, CXCL10, and CXCL11 are increased in patients with autoimmune thyroiditis (AIT), at the initial diagnosis, with respect to controls, in particular in the presence of hypothyroidism [10-12].

The association between AIT and increased circulating levels of CXCL10 was also oberved in patients with other immune-mediated disorders such as chronic hepatitis C, mixed cryoglobulinemia, and sclerodermia. These results suggest a common immunological pattern of AIT when associated with immunomediated disorders [13-15].

In Graves' disease, circulating CXCL10 is high in the active phase of the disease, is not related to the hyperthyroidism per se (in fact CXCL10 is not increased in patients with toxic nodular goiter), and it has been recently shown that a CXCL10 polymorphism is a marker to predict severity of Graves' disease [16].

Antithyroid drugs reduced CXCL10 serum levels, and ablation of thyroid tissue by radioiodine or thyroidectomy reduced CXCL10 levels in the normal range. These last results suggest that the source of CXCL10 increase in Graves' disease is thyroid tissue itself [17-20].

However circulating levels of CXCL10 might remain elevated also during the remission of Graves' disease [21].

Conclusion

In conclusion, on the basis of the above mentioned data, it is evident that thyroid follicular cells, and orbital cells, under the influence of cytokines (such as IFN-γ and TNF-α), can modulate the autoimmune response through the production of CXCL9, CXCL10 and CXCL11 chemokines. These chemokines can induce the migration of Th1 lymphocytes into the thyroid or the orbit, which in turn, secrete more IFN-γ and TNF-α, stimulating the chemokine production by the target cells, thus initiating and perpetuating the autoimmune cascade. The importance of IFN-γ inducible CXC chemokines in the pathogenesis of glandular autoimmunity represents an expanding field of interest, and trials that evaluate the immunomodulatory effect on these chemokines of various drugs (such as Peroxisome proliferator-activated receptor-γ, and -α, vitamin D analogs, and others) in AITD have been planned [6,7,22].

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