MIG Th1 chemokine in Vitiligo

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Abstract

The importance of the Type-1 helper immune response in the development of Vitiligo (Vit), and of chemokine receptor (CXCR)3 receptor and its chemokine monokine induced by interferon (IFN)-γ(MIG) has been shown by several studies.

MIG/ interferon (IFN)-γ-inducible protein 10 (IP10) CXCR3 axis mediated T-cell recruitment into the skin in Vit is an early event in the progression of the disease. MIG and IP10 circulating levels are increased in progressive Vit. It has been suggested that MIG and CXCR3 could be novel targets of future therapeutic approaches. Other studies have suggested that measuring MIG directly in the skin might be effective in clinical trials as an early marker of treatment response.

Further studies are needed to explore the use of new molecules that act as antagonists of CXCR3, or block MIG, in Vit in a clinical setting.


Key words: CXCR3, MIG, Vitiligo

Introduction

Vitiligo

Vitiligo (Vit) is a disease characterized by the presence of bleach patches in depigmented skin of the hands, face, and wrists, that are initially small, but often can grow and changing shape (1). There are two forms: 1- non-segmental vitiligo (NSV) in which the location of depigmentation is usually symmetrical; 2- and segmental vitiligo (SV) in which the appearance is different, and this form it is not associated with autoimmunity (2).

The most common treatments for Vit are local steroids and ultraviolet light. Vitiligo is an autoimmune skin disease caused by an abnormal immune response to melanocytes. The presence of various relationships between Vit and other autoimmune diseases has been demonstrated. Indeed generalized Vit is a component of autoimmune disease, such as autoimmune polyendocrinopathy syndrome type 1 (APS1) and APS2, as well as it has been linked with pernicious anemia and Addison’s disease (3). Patients with Vit are also affected by thyroid disease with a mean prevalence of 15%; by autoimmune thyroid disease in a 14% of cases and 21% of them showed thyroid-specific autoantibodies (4, 5).

An important role in the pathogenesis of Vit is played by genetic and environmental factors. Genetic studies mainly concern patients affected by NSV. The “gold standard” to detect sensitivity genes are the Genomewide linkage studies and genome-wide association studies (6). Until now, it has been identified approximately thirty-six NSV sensitivity loci of which 90% encode for immunoregulatory proteins, while 10% encode for melanocyte proteins. Major associations were identified in the major histocompatibility complex (MHC), in the class I gene region (between HLA-A and HLA-HGC9) and in the class II gene region (between HLA-DRB1 and HLA-DQA1). Also PTPN22, LPP, IL2-RA, GZMB, UBASH3A and C1QTNF6 genes, implicated in autoimmune diseases, were identified as associated with Vit (6). Among melanocyte proteins, TYR encodes the enzyme tyrosinase, that is a major autoantigen implicated in generalized Vit that catalyzes melanin biosynthesis (7).

Also NALP1 gene, regulating inflammation and cell death of myeloid and lymphoid cells, is associated with Vit. Caspase 1 and caspase 7 are the inflammatory products of NALP1 gene, which activate the cytokine interleukin(IL)-1β that is highly expressed in patients with Vit (8). Naive CD4+ T cells are induced to produce cytokines (thanks to thymic stromal lymphopoietin that is encoded by TSLP gene) that cause a Type-2 helper (Th2) response [IL-4, IL-5, IL-13, tumor necrosis factor (TNF)-α] while inhibit a Th1 cytokines [IL-10, interferon (IFN)-γ] production, (9). Indeed TSLP gene expression deficiency produce the dominance of the Th1 immune response, that is implicated in Vit development.

The MIG IFN-γ dependent chemokine

Activated T lymphocytes, Natural Killer (NK) cells, as well as some epithelial and endothelial cells express Chemokine (C-X-C motif) receptor (CXCR)3. CXCR3 is a Gq protein-coupled receptor that belongs to CXC chemokine receptor family. CXCR3 has two isoforms: CXCR3-A and CXCR3-B; both binding CXC chemokines, monokine induced by IFN-γ (MIG)/chemokine (C-X-C motif) ligand
9 (CXCL9), IFN-γ-inducible protein 10 (IP10) /CXCL10 and IFN-inducible T-cell α chemokactant (I-TAC)/CXCL11. CXCR3-B also binds CXCL4 (10). CXCR3 is highly expressed on Th1 cells, as well as chemokine (C-C motif) receptor (CCR)5.

Th1 cells are attracted by MIG, IP10 and I-TAC chemokines that are commonly produced by local cells in inflammatory lesions; so in the recruitment of inflammatory cells both CXCR3 and its ligands play an important role (11). Chemokine CXCL9 also known as MIG, is closely related to CXCL10 and CXCL11, whose genes are located near the gene for CXCL9 on human chromosome 4. MIG is a T-cell chemokactant, that is induced by IFN-γ (12, 13). For this reason, the high level of MIG revealed in peripheral liquid can be considered as a marker of host immune response, particularly that including Th1 cells (14, 15). In fact, Th1 lymphocytes recruited in the inflamed site increase the IFN-γ and TNF-α production, which stimulate MIG secretion from several cells of the site, so leading to an amplification feedback loop (14, 15).

Different studies reported a serum increase of MIG, and of other Th1 chemokines, as well as their increased tissue expressions in different organ specifically involved in many diseases including cancers (16-29), and several autoimmune diseases, such as: autoimmune thyroiditis (30-35), Graves’ disease (36, 37) Graves’ ophthalmopathy (38-41), HCV-related cryoglobulinemia (42-47), other HCV immune mediated disorders (34, 48-53), type 1 diabetes (54-58), or systemic rheumatological disorders, like rheumatoid arthritis (59), systemic lupus erythematosus (60, 61), systemic sclerosis (4, 62-64), psoriasis or psoriatic arthritis (65-67), and in sarcoidosis (68, 69).

The aim of this narrative review is to investigate the role of MIG in Vit. The presentation of data has been reported in line with the International Narrative Systematic Assessment (INSA) tool (70).

**MIG in Vitiligo**

A first study reported that plasmacytoid dendritic cells (pDC), are part of the infiltrate of progressive Vit. pDC are the major IFN-α-producing cells, they secrete MxA (a IFN-α induced protein) that was associated with the MIG expression and correlated with the recruitment of CXCR3(+) immune cells. It is interesting that a strong MxA expression was revealed in perilesional skin tightly near to remaining melanocytes, surrounded by a prominent T-cell infiltrate. Conversely, since MxA was not detectable in lesional skin, it has been suggested that the production of IFN-α is an early event in the progression of the disease (71).

In another study has been showed that gene expression in lesional skin from Vit patients revealed an IFN-γ-specific signature that include IP10 chemokine. IP10 was elevated in both skin and serum of patients affected by Vit, and CXCR3 was expressed on pathogenic T cells.

To investigate the role of IP10 in Vit, it has been used a mouse model of disease exhibiting an IFN-γ-specific gene signature, IP10 expression in the skin, and up-regulation of CXCR3 on antigen-specific T cells. A minimal depigmentation has been observed in mice receiving CXCR3(-/-) T cells, as well in mice lacking IP10 or treated with IP10-neutrallizing antibody. MIG was able to recruit autoreactive T cells to the skin, without promoting effector function, while IP10 was required for effector function and localization within the skin. It is remarkable that IP10 neutralization in mice having established, widespread depigmentation induces reversal of disease, shown by repigmentation (72).

A third study showed that serum MIG and IP10 were significantly higher in patients with Vit and were higher also in patients in progressive stages than in stable stages. Also CXCR3 mRNA expression in peripheral blood mononuclear cells was higher in Vit patients; as well as high percentages of both circulating CXCR3(+) CD4(+) and CXCR3(+) CD8(+) T cells were revealed in patients with progressive Vit respect to controls, while only the expression of CXCR3(+) CD8(+) T cells was increased in patients with stable Vit. An abundance of CXCR3(+) cells has been revealed by histological findings in Vit lesions. The authors concluded that the MIG/IP10/CXCR3 axis mediates T-cell recruitment into the skin in progressive Vit (73).

A strongly correlation between MIG and IP10 expression and disease activity has been also shown in mouse skin with Vit, whereas IP10 alone correlates with severity; therefore these chemokines can be used as biomarkers for following disease progression. Additional studies conducted on mouse model and human patients revealed that the major chemokines producers throughout the course of disease are the keratinocytes. Through functional studies carried out using a conditional signal transducer and activator of transcription (STAT)-1 knockout mouse, it has been demonstrated that IFN-γ signaling in keratinocytes was critical for proper autoreactive T-cells homing to the epidermis and for disease progression. In contrast, epidermal immune cell populations such as endogenous T cells, Langerhans cells, and γδ T cells were not required. Therefore, topical therapies targeting IFN-γ signaling in keratinocytes could be safe and effective new treatments, and skin expression of the above mentioned chemokines may be used to monitor disease activity and treatment responses (74).

These results were partially confirmed in another study (75). CD8+ T-cell and MIG protein concentrations were significantly high in the skin biopsy of active lesions compared to nonlesional skin. MIG protein concentration achieved greater sensitivity and specificity by receiver operating characteristic analysis. Suction blistering also allowed for phenotyping of the T-cell infiltrate, which overwhelmingly expresses CXCR3. The Authors suggested that measuring CXCL9 directly in the skin might be effective in clinical trials as an early marker of treatment response (76).

Immunohistochemistry or immunofluorescence have been used to analyze HSP70 and CD123+ expression in Vit skin samples. Infiltration of pDCs in progressive Vit was primarily located in the epidermis, near to keratinocytes expressing HSP70. It has been revealed by in vitro experiments, that pDCs were able to aggregate HSP70 thanks to their HSP70 receptor Lox-1 (lectin-like oxidized low-density lipoprotein-receptor-1). Exogenous HSP70 induced activation of pDCs and increased the uptake of exogenous DNA. Moreover, HSP70 potentiad DNA-induced IFN-α production by pDCs, that in turn induced MIG and IP10 expression by keratinocytes (77). A systematic review eva-
luated biomarkers of disease activity in Vit showing that in skin, MIG and NLRP1 demonstrated a good association with progressive disease.

As regard circulating biomarkers autoantibodies, oxidative stress markers, soluble CDs (sCD25, sCD27), immune cells (Tregs), cytokines [IL-1β, IL-17, IFN-γ, Transforming growth factor (TGF)-β], and chemokines (MIG, IP10) are increased in Vit (78).

These observations were also confirmed in another review (79).

**Conclusion**

The importance of cytokines and chemokines in the pathogenesis of different and/or associated autoimmune diseases has been shown by many studies (29, 47, 54, 80-89). The aforementioned studies, show the importance of the Th1 immune response in the development of Vit, and of CXCR3 receptor and its chemokine MIG. MIG/IP10/CXCR3 axis mediated T-cell recruitment into the skin in Vit is an early event in the progression of the disease. High MIG and IP10 circulating levels have been observed in progressive Vit. It has been proposed that MIG and CXCR3 could be novel targets of future therapeutic approaches.

Other studies have suggested that measuring CXCL9 directly in the skin might be effective in clinical trials as an early marker of treatment response. Further studies are needed to explore the use of new molecules that act as antagonists of CXCR3, or block MIG, in Vit in a clinical setting.

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