Developing targeted immunotherapies for vitiligo: focusing on the IFN-g/CXCL10 axis

M. Rashighi, J.E. Harris

Division of Dermatology, Department of Medicine, University of Massachusetts Medical School, Worcester, Massachusetts, USA

Correspondence to:
John E. Harris, MD, PhD
University of Massachusetts Medical School
Division of Dermatology, Department of Medicine
364 Plantation Street
Worcester, MA 01605, USA
Tel: 508-856-1982
Email: john.harris@umassmed.edu

Vitiligo is a common autoimmune disease resulting from the destruction of epidermal melanocytes by cytotoxic T cells. It presents with disfiguring macules and patches of depigmentation that significantly affect patients' self-esteem and quality of life. The mainstay of treatment for vitiligo is phototherapy and topical immunosuppressants, including steroids and calcineurin inhibitors. These treatments are non-targeted, time-consuming and only offer modest efficacy.[1] Recent advances in understanding vitiligo pathogenesis have enabled us to identify the key signaling pathways that drive the disease. This provides us the opportunity to develop more effective targeted treatments, which could potentially have more favorable safety profiles.

We recently identified that IFN-g is a key pathogenic cytokine in vitiligo pathogenesis. Gene expression profiling in lesional skin of patients and a mouse model of vitiligo indicated an increase in expression of IFN-g and IFN-g-induced genes. We found that CXCL10, an IFN-g-induced chemokine, was elevated in serum of patients with vitiligo, and that CXCR3, its cognate receptor, was upregulated on autoreactive T cells in the blood and skin of patients with vitiligo. Mechanistic experiments in our mouse model demonstrated that the IFN-g/CXCL10 axis is functionally required for both progression and maintenance of the disease, and therefore may be therapeutically targeted to reverse depigmentation.[2,3]

The initial events that lead to activation of IFN-g signaling in vitiligo, and the primary cellular source of the cytokine, are not fully understood. However, at least two distinct pathways have been generally described to induce production of this cytokine from T helper (Th1) cells. First, activated Th1 cells can produce IFN-g upon recognition of their T cell receptor (TCR) cognate antigen. Second, differentiated Th1 cells have been also shown to secrete IFN-g in response to IL-12 and IL-18 in an antigen-nonspecific manner.[4] If the second, IL-12/IL-18-induced pathway is critical for IFN-g production in vitiligo, it may be possible to block either cytokine as a therapeutic strategy for vitiligo. Ustekinumab is a human monoclonal antibody against the p40 subunit of both IL-12 and IL-23. It is approved for the treatment of moderate to severe plaque psoriasis, primarily through targeting IL-23[5], however it may be effective in vitiligo through targeting of IL-12. Currently, there are no approved treatments to block IL-18 in humans. But a first-in-man study of a humanized monoclonal IL-18 antibody is completed[6], and recently a phase 2 trial is recruiting patients with adult-onset Still's disease to test the safety and efficacy of a recombinant human IL-18 binding protein to block its activity.[7]

The IFN-g/CXCL10 signaling pathway begins with binding of IFN-g to its heterodimeric receptor on target cells. This induces the activation of the intracellular tyrosine kinase proteins Janus kinases (JAK), which promotes dimerization of Signal Transducers and Activators of Transcription1 (STAT1) monomers in the cytoplasm. The STAT1 dimer is then actively transported in the nucleus, where it binds to the promoter region of immediate-early IFN-g-inducible genes and induces gene transcription, including the IFN-g induced chemokine CXCL10.[8] Several small molecule inhibitors and antibodies have been developed to target distinct key components of this pathway. Two different human monoclonal antibodies against IFN-g have been tested but failed in clinical trials in patients with psoriasis, Crohn's, and systemic lupus erythematosus.[9-11] This is because other cytokines appear to

be the main contributors of pathogenesis in those diseases while vitiligo, in contrast, is primarily IFN-g driven.

Members of JAK family include JAK1, JAK2, JAK3, and TYK2. IFN-g specifically relies on JAK1 and JAK2 for signal transduction.[12] Recently, two JAK inhibitors, tofacitinib (pan-JAK inhibitor, approved for rheumatoid arthritis) and ruxolitinib (JAK1/2 inhibitor, approved for myelofibrosis and polycythemia vera), were each reported to induce substantial repigmentation in two separate vitiligo patients.[13,14] The observation that serum CXCL10 declined shortly after initiating ruxolitinib supports the hypothesis that JAK inhibition targets IFN-g signaling in vitiligo.[14]

Using a similar rationale, we also hypothesized that STAT1 inhibitors could potentially treat vitiligo by blocking IFN-g signaling. A previous study demonstrated that statins, or HMG-CoA reductase inhibitors, could block STAT1 function in vitro[15], and a patient with vitiligo reportedly improved significantly after taking high-dose simvastatin.[16] Using our mouse model, we found that simvastatin was effective at both preventing and reversing vitiligo, however its exact mechanism of its action was not clear, as it also appeared to have pleiotropic effects, affecting melanocyte-specific T cell activation and proliferation in vitro.[17] Studies are ongoing to test the efficacy of simvastatin in vitiligo patients, and a phase 2 controlled trial is currently recruiting patients to test the efficacy of adding atorvastatin to UVB in treatment of active vitiligo.[18,19]

Further downstream of IFN-g signaling, it is possible to directly target CXCL10 or its receptor CXCR3. This could potentially be a safer approach, as it does not interfere with other functions of IFN-g, and we found that this was highly effective in both preventing and reversing vitiligo in our mouse model.[3] Two separate human anti-CXCL10 monoclonal antibodies have been tested in phase 2 clinical trials in patients with rheumatoid arthritis and ulcerative colitis, with only modest clinical efficacy.[20,21] Several classes of CXCR3 small molecule inhibitors have been developed and tested in experimental animal models, but only one has been progressed to a phase 2 clinical trial. This was to test the safety and efficacy of AMG-487 for the treatment of psoriasis, and it was terminated early due to lack of efficacy.[22] However unlike those diseases, CXCL10 and CXCR3-expressing T cells appear to be the key pathogenic contributor in vitiligo, and thus trials to test the efficacy of these drugs in vitiligo patients may be more successful.

Taken together, developing a better understanding of the immune mechanisms involved in vitiligo pathogenesis by using both a mouse model and human tissues has enabled us to identify potential targets to develop new treatments. Recent discoveries indicate IFN-g-CXCL10 is a key signaling pathway in vitiligo, and strongly support testing new treatments that target the pathway in clinical trials.

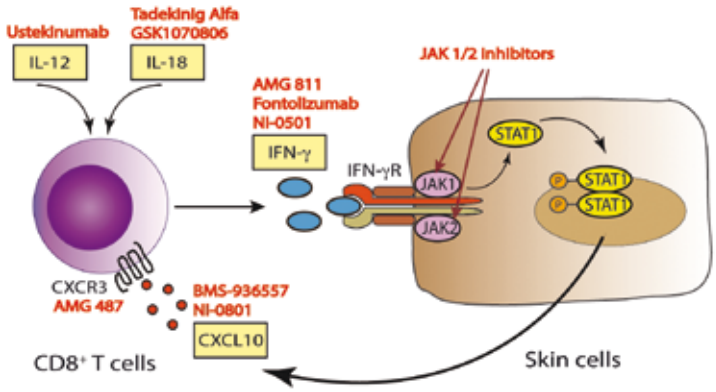

Figure 1. IFN-g/CXCL10 signaling pathway in vitiligo. Activated CD8+ T cells produce IFN-g either upon recognition of their cognate antigen or in response to IL-12 and IL-18. Binding of IFN-g to its membrane-bound heterodimeric receptor (IFN-gR) activates intracellular JAK1 and JAK2, leading to phosphorylation and translocation of STAT1 to the nucleus, and subsequently transcription of CXCL10. This creates a positive feedback loop to recruit more CD8+ T cells through CXCL10-CXCR3 interaction. Compounds that have been developed to target each step are indicated in red.

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SUMMARY

Vitiligo is a disfiguring autoimmune skin disease that significantly affects patients' quality of life. Despite its high prevalence, there are currently no FDA approved treatments, and existing treatments are non-targeted and limited in efficacy. Recently, we identified the IFN-g/CXCL10 axis as a critical signaling pathway for vitiligo pathogenesis. Multiple antibodies and small molecule inhibitors have been developed to target this axis, but they have been ineffective in early-phase clinical trials for other autoimmune diseases, likely because cytokines other than IFN-g are responsible for driving their pathogenesis. However, our basic and translational research findings indicate that vitiligo may be the optimal disease to test these agents.

KEYWORDS

vitiligo – IFN-g – CXCR3 – CXCL10 – JAK inhibitor – targeted treatments

DISCLOSURE

The authors have no conflict of interest to declare