

Review

IFN- γ Signaling in Lichen Planus

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ABSTRACT

Lichen planus (LP) is a chronic inflammatory disease that affects the skin, nails, urogenital tract, and oral mucosa. It ranges from mild inflammation to the destruction of the epithelial surface with painful wounds and squamous cell carcinoma development. The LP lesion differences in location and morphology determine the clinical disease subtypes which all share a histological feature of dense band-like sub-epithelial infiltration of lymphocytes and keratinocyte apoptosis. Despite the well-characterized clinical manifestations of LP, its pathogenesis remains mostly unknown. Recent studies revealed a role of IFN- γ signaling that renders keratinocytes more susceptible to T-cell-mediated cytotoxicity via upregulation of MHC class I molecules. Targeting IFN- γ signaling in LP has been proposed as a treatment option. These latest developments in research on the etiology of LP will be discussed herein.

KEYWORDSIFN-Gamma; Lichen planus

Introduction

Lichen planus (LP) is a chronic mucocutaneous inflammatory disease with an estimated prevalence ranging from 0.22% to 5% of populations worldwide (1). LP lesions most commonly present as purplish pruritic papules or plaques of flat polygonal shape that range from mild inflammation to painful wounds and typically affect middle-aged adults of both sexes and all races (2). In addition to the classical presentation, variations in the site of involvement and morphology of LP lesions give rise to various clinical variants, including oral, nail, vulvovaginal, hypertrophic, linear, annular, atrophic, inverse, and ulcerative, among others (3). Histologically, LP variants share a distinctive feature: degeneration of basal layer and dense band-like subepithelial lymphocytes infiltrate (1, 4) (**Figure 1**). The damage to basal keratinocytes is thought to be caused by autoreactive T cells targeting basal layer antigens. However, specific antigens and other characteristics of the microenvironment that promote this autoimmune response remain mostly unidentified. There is a lack of a clear understanding of molecular disease mechanisms, and no FDA-approved treatments are currently available for LP. Treatment options are limited to

off-label medications, most often topical steroids (5). Recent studies have shed light on the role of IFN- γ in the etiology of LP that includes priming keratinocytes for T cell-mediated cytotoxicity through the induction of MHC I on keratinocytes (6), and targeting IFN- γ signaling is being considered for novel therapeutics of LP.

Mechanism of IFN- γ -driven pathogenesis in LP keratinocytes

IFN- γ , the only member of the Type II interferons, initiates a cellular response to microbial infections and plays a central role in inflammation and autoimmunity (7, 8). IFN- γ can be produced by leukocytes including T (9) and B (10) lymphocytes, natural killer (NK) cell (11), natural killer T (NKT) cell (12), dendritic cell (DC) and macrophage (M ϕ) (13), and it even has been suggested to be expressed in keratinocytes (14). As such, IFN- γ acts in both autocrine (15) and paracrine (16) manner to exert a wide range of pro-inflammatory and immunomodulatory effects in innate and adaptive immunity. The binding of an active IFN- γ homodimer to its receptor, an IFNGR1/ IFNGR2 heterodimer, activates the JAK-STAT pathway, resulting in transcription of numerous genes involved in immune

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response, inflammation, proliferation, and apoptosis. For example, priming with IFN- γ results in “super-activation” of macrophages that develop resistance to anti-inflammatory stimuli and become more responsive to pro-inflammatory stimuli (17). IFN- γ enhances motility and cytotoxicity of CD8 $^{+}$ T cells (18) and regulates the

expansion, contraction, and memory phases of CD8 $^{+}$ T cell response (19). Unsurprisingly, dysregulated IFN- γ signaling has been implicated in auto-inflammatory and autoimmune diseases (20, 21). Overexpressing IFN- γ in the epidermis causes an inflammatory skin disease resembling cutaneous lupus erythematosus in mice (22).



Figure 1. Common histological features in various clinical manifestations of LP.

A broad range of clinical manifestations of LP is demonstrated in the clinical photographs of hypertrophic LP (top left), nail LP (top right), and oral erosive LP (bottom left). The histology of a typical lymphoid infiltrate in the upper dermis is demonstrated in a case of cutaneous LP (bottom right), where the presence of dyskeratosis (apoptosis of the epidermis), saw toothing (the sharp pointy rete ridges), hypergranulosis (increased number of cells in the granular layer), and scaling (flakiness and peeling in the outermost epidermis caused by excessive cell death) are also evident.

In keratinocytes, IFN- γ induces expressions of T cell-recruiting chemokines CXCL9, CXCL10, and CXCL11 that are elevated in oral LP (23). Culturing keratinocytes with IFN- γ induces synthesis of selected MHC class I (24, 25) and MHC class II molecules (26, 27), including HLA-DR antigen, which is not expressed in keratinocytes under normal conditions but is present in LP (26). IFN- γ also upregulates Keratin 6, inflammatory and hyperproliferative keratin, in keratinocytes (28), primes keratinocytes for inflammasome activation (29), suppresses keratinocyte proliferation (28, 30), and can induce keratinocyte necroptosis (31) and apoptosis under pro-inflammatory conditions (32). The multi-faceted action of IFN- γ on the activation of keratinocytes in LP (**Figure 2**) is supported by the genetic associations of *IFNG* polymorphisms with oral LP (33, 34). Indeed, recent global transcriptomic profiling of LP lesions identified an IFN- γ inflammation response as the major pathway of pathogenesis in LP (6).

LP is associated with a chronic hepatitis C virus (HCV) infection, with an average of 22.3% of oral LP patients having anti-HCV antibodies (35). The link between the two diseases suggests that the IFN-mediated host immune

response to the viral infection evokes cutaneous inflammation. However, more research is needed to dissect the contribution of type I interferons versus IFN- γ in HCV-associated LP, as IFN- α and IFN- β are also increased in LP skin lesions compared to normal skin (6, 36). The *in vitro* priming of keratinocytes with Type I IFNs promotes keratinocyte susceptibility to T cell-mediated cytotoxicity to a lesser extent than priming with IFN- γ (6).

In addition to HCV, other viral (37) and bacterial (38) infections have been implicated in the etiology of LP. Furthermore, immunization against a range of infections has been shown to trigger LP, with hepatitis B, influenza, and herpes zoster vaccines found to be among the most commonly associated types (39). All of these seemingly unrelated causes may converge on the IFN- γ signaling. However, it is worth noting that the exposure to certain metals, pigments, chemicals, or drugs has also been linked to LP (1). More research is needed to discern the mechanism of the disease in these various conditions.

MHC molecules in T cell toxicity of LP

The main histological feature of LP is the increased accumulation of CD4+ and CD8+ T cells (40) and antigen-presenting Langerhans cells (41) in the epidermis and dermis of LP lesions compared to non-lesional skin. Chemokines, secreted by IFN- γ -stimulated keratinocytes, including CXCL9 and CXCL10, can attract CXCR3+ CD8+ T effector cells in the dermal-epidermal junctional zone of LP (42) where they recognize antigens presented by MHC class I positive cells and trigger cell death (43). CD4+T cells are also recruited to the site where, upon activation by MHC class II, they further activate cytotoxic CD8+ T cells (44). Immunofluorescence studies show that MHC class I molecules are abundant in the epidermis of LP lesions. In contrast, MHC class II molecules are absent in the epidermis and instead localized to the upper dermis along the epidermal-dermal junction in LP (6).

Although all primary MHC class I and II molecules are expressed higher in LP than normal controls (6) and thus

may contribute to the LP pathogenesis, only blocking MHC class I molecules to limit antigen presentation was shown to decrease these cytotoxic responses against lesional keratinocytes (40). *In vitro* co-culture of IFN- γ -primed keratinocytes and activated peripheral blood mononuclear cell (PBMCs) was shown to upregulate HLA-A, HLA-C, and HLA-DR, but not HLA-B, HLA-DP, or HLA-DQ, in keratinocytes (6). When this IFN- γ priming was combined with a pan anti-MHC class I blocking antibody, cytotoxic activity towards keratinocytes was entirely abolished *in vitro*. In contrast, anti-HLA-DR antibodies only partially inhibited the cytotoxicity and anti-HLA-DP or anti-DQ antibodies did not have an effect. Interestingly, a variant of HLA-DR, HLA-DRB1*0101, is associated with predisposition to LP (45).

In addition to the upregulation of MHC class I molecules, IFN- γ also enhances cytotoxicity by inducing the expression of IRF1-dependent antigen-processing machinery in keratinocytes (46).

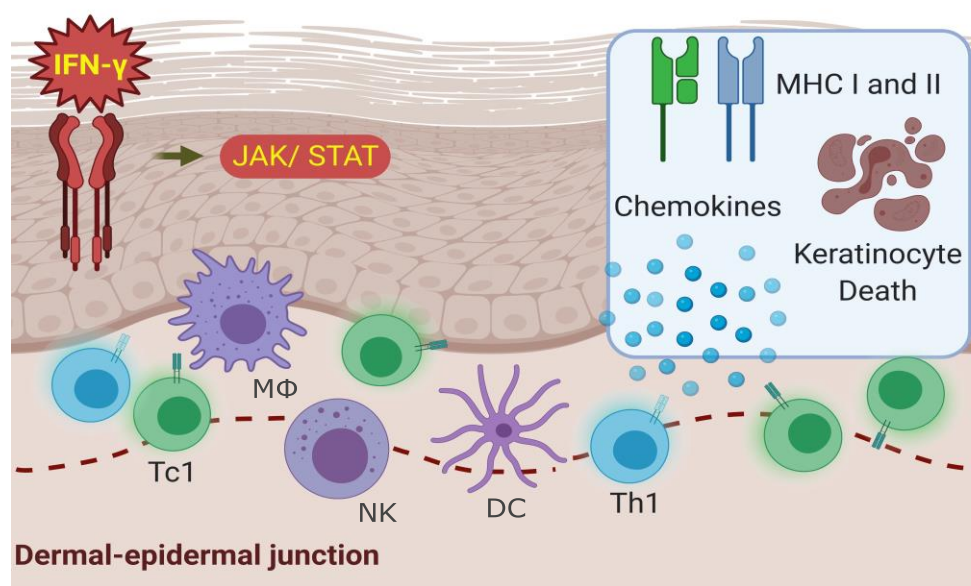


Figure 2. IFN- γ signaling renders keratinocytes more susceptible to T-cell-mediated cytotoxicity in LP.

Macrophages (MΦ), natural killer (NK), and dendritic cells (DC) are some of the cells that produce IFN- γ , which binds to its receptor on keratinocytes and initiates JAK/STAT-dependent signaling that causes the upregulation of primarily MHC class I and possibly some induction of MHC class II molecules, and in turn, promotes keratinocyte apoptosis/ necroptosis and the release of chemokines. These chemokines, including CXCL9, CXCL10, and CXCL11, promote additional Th1/Tc1 cells migrating to the dermal-epidermal junction. Cytotoxic CD8+Tc1 cells, the major effector cells in LP, recognize putative self-antigens presented by MHC class I positive keratinocytes and are responsible for triggering keratinocyte cell death.

Targeting JAK/ STAT signaling for treatment

Identifying novel treatment targets for LP is of utmost importance. So far, there are no FDA-approved treatments specifically for this condition. The off-label use of systemic immuno-suppressants, including glucocorticoids and immunomodulators, such as acitretin, have considerable side effects. Previously investigated treatments include a) mycophenolic acid that preferentially depletes guanosine in T and B lymphocytes to inhibit their proliferation and

suppress cell-mediated cytotoxicity that was shown to reduce pain severity and ulcer size of ulcerative oral LP (47); b) secukinumab, a monoclonal antibody that blocks IL-17A, to target Th17/Tc17 cells, that showed clinical amelioration of mucosal and cutaneous LP (48); c) etanercept, a TNF blocker, that was used to treat nail LP (49); and others (50, 51). However, inadequate sample size, insufficient efficacy, such as clinical case reports of secukinumab (52) or etanercept (53) inducing LP, might be the cause of inconsistent results.

Targeting IFN- γ has recently been proposed as a promising treatment option for LP (54) among other inflammatory skin diseases (55-57). Because IFN- γ activates JAK/STAT intracellular signaling to induce MHCs expression in keratinocytes, blocking this signaling cascade may protect keratinocytes from cytotoxicity. A comprehensive literature-based network analysis of most highly connected nodes in IFN signaling confirmed the involvement of JAK2 and STAT1, with the latter being the most highly expressed gene among all STAT genes in LP (6). The active, phosphorylated form of STAT1 is localized to the epidermis of LP lesions, while phosphorylated STAT2 is predominantly expressed in the inflammatory infiltrates at the dermal-epidermal junction (6). When the genes differentially expressed in LP were subjected to drug target analysis using a word-embedding-based machine learning approach (58), top predicted drugs were JAK inhibitors. Either knocking-out *JAK2* or *STAT1* or chemically inhibiting JAK with baricitinib was shown to indeed significantly protect IFN- γ -primed keratinocytes from the cell-mediated cytotoxic responses by reducing expression of HLA-A/B/C (6).

Following these promising findings, several studies reported successful outcomes after treatment with JAK inhibitors: a) three patients with recalcitrant erosive LP, who previously failed to respond to treatment with other medications, showed dramatic improvement after treatment with tofacitinib, a JAK1/3 inhibitor (59); b) a patient with a 30-year history of hypertrophic LP showed a notable improvement in all observed parameters after treatment with tofacitinib; c) Nine lichen planopilaris patients, who had failed other forms of therapy, responded positively to tofacitinib, with better clinical outcomes in those on systemic rather than topical therapy (60); d) Treatment with tofacitinib in a case of typically irreversible lichen planopilaris reduced scalp visibility, led to hair regrowth, and eliminated itch (61). It is worth noting that tofacitinib is a JAK1/3 inhibitor that also targets JAK2 to a lesser extent. More research and clinical data are needed to evaluate the relative effectiveness of targeting different JAK isoforms as well as other downstream components of the IFN- γ signaling for the treatment of LP.

Thus, the mechanistic research findings narrowing down on IFN- γ signaling in the pathophysiology of LP lead to the identification of JAK/STAT pathway as a potential treatment target that is now showing promising initial clinical results. Several other JAK inhibitors are available and have been FDA approved. Some are currently being tested for the treatment of numerous autoimmune/autoinflammatory conditions, including rheumatoid arthritis (62), systemic lupus erythematosus (63), psoriasis (64), and others.

In conclusion, recent research findings identify IFN- γ as a master regulator of cytotoxic responses in LP. Initial clinical studies support IFN- γ signaling as a novel promising therapeutic target for LP.

Conflicts of Interest

Olesya Plazyo and Shuai Shao report no conflict of interest. Johann E. Gudjonsson serves on the advisory boards for Eli Lilly, Almirall, BMS, Novartis, Sanofi, and AnaptysBio.

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