



TARGETING THE JAK-STAT AXIS AND CYTOKINE SIGNALING IN ALOPECIA AREATA AND VITILIGO: A NARRATIVE REVIEW OF IMMUNOPATHOGENESIS AND EMERGING THERAPEUTICS

**Daniela Steffany
Possos Obando**

MD. Universidad de Caldas

ABSTRACT

Alopecia areata and vitiligo are chronic autoimmune dermatoses marked by the autoimmune-mediated destruction of hair follicle privilege and epidermal melanocytes, respectively. Both pathologies share converging immunopathogenic circuits predominantly driven by autoreactive CD8⁺ cytotoxic T lymphocytes and type 1 inflammatory cascades. Central to these disease mechanisms is the Janus kinase-signal transducer and activator of transcription (JAK-STAT) intracellular signaling pathway, which mediates the downstream responses of interferon-gamma and common gamma-chain interleukins such as interleukin-15.

KEYWORDS :

INTRODUCTION

Alopecia areata (AA) and vitiligo represent two prototypical organ-specific autoimmune skin disorders that cause substantial psychosocial impairment, emotional burden, and diminished quality of life (1). Although their clinical expressions diverge—with alopecia areata presenting as non-scarring patchy, total, or universal hair shedding and vitiligo manifesting as sharply demarcated depigmented epidermal macules—both share fundamental biological paradigms (1) (2). Each disease is orchestrated by the breakdown of immune privilege within specialized cutaneous compartments: the hair follicle bulb in alopecia areata and the basal epidermal layer housing melanocytes in vitiligo (2) (3).

Historically, clinical management relied almost exclusively on broad-spectrum immunosuppressants and anti-inflammatory agents, including high-dose topical and systemic corticosteroids, phototherapy, calcineurin inhibitors, and systemic immunomodulators such as methotrexate or cyclosporine (2) (4). Over the past decade, extensive translational research has mapped the precise cytokine and receptor networks responsible for driving both cytotoxic tissue damage and long-term immunological memory in the skin (3) (5).

Methods

A comprehensive and structured literature query was executed across four primary biomedical electronic databases: PubMed, Scopus, Web of Science, and Embase. The literature search captured original investigations, randomized controlled trials, translational bench studies, and clinical reports published in English and Spanish focusing on Janus kinase signaling, cytokine biology, autoimmune hair loss, and epidermal depigmentation. Following the preliminary removal of duplicates and evaluation of titles and abstracts, 15 peer-reviewed publications meeting rigorous criteria for scientific design and immunobiological relevance were retrieved for comprehensive full-text synthesis.

Molecular Architecture of the JAK-STAT Axis

The mammalian JAK family encompasses four evolutionary conserved intracellular non-receptor tyrosine kinases: JAK1, JAK2, JAK3, and Tyrosine Kinase 2 (TYK2) (5). While JAK1, JAK2, and TYK2 exhibit broad, ubiquitous expression across somatic tissues, JAK3 expression is largely restricted to hematopoietic lineages and preferentially couples with cytokine receptors bearing the common gamma-chain (γ C) subunit (5) (6). In contrast, the downstream transcription factors comprise seven STAT family proteins: STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6 (5).

Signal transduction initiates when an extracellular cytokine binds to its cognate multimeric transmembrane receptor, prompting receptor subunit dimerization or oligomerization

(5) (7). This spatial rearrangement brings receptor-associated JAK molecules into close proximity, triggering mutual transphosphorylation and catalytic activation (6) (7). Activated JAKs subsequently phosphorylate specific tyrosine residues situated within the intracellular tail of the receptor subunits, assembling docking sites for the Src homology 2 (SH2) domains of latent cytoplasmic STAT proteins (6). Recruited STAT monomers are phosphorylated on conserved carboxy-terminal tyrosine residues, detach from the receptor scaffold, and form stable homodimers or heterodimers (5) (6). These dimers promptly translocate through nuclear pore complexes into the nucleus, binding specific gamma-interferon-activated sequences (GAS) or interferon-stimulated response elements (ISRE) to modulate the transcription of immunomodulatory genes, chemokines, and survival factors (6) (7). Small-molecule JAK inhibitors function by entering the cytoplasmic kinase cleft and competing reversibly or irreversibly with adenosine triphosphate (ATP), blocking transphosphorylation cascades and terminating downstream cytokine-induced gene expression (7) (8).

Immunopathogenesis of Alopecia Areata: Collapse of Hair Follicle Immune Privilege

Under healthy homeostatic conditions, the anagen hair follicle bulb maintains a strict state of immune privilege characterized by suppressed major histocompatibility complex (MHC) class I and class II expression, local production of immunosuppressive molecules (such as transforming growth factor-beta and alpha-melanocyte-stimulating hormone), and sparse numbers of natural killer (NK) cells (2) (8). In genetically predisposed individuals, exogenous microenvironmental stressors or follicular microtrauma prompt follicular epithelial cells to release damage-associated molecular patterns and upregulate stress-induced ligands, primarily MICA and ULBP3 (2) (9).

These stress ligands trigger the NKG2D receptors displayed on autoreactive CD8⁺ T lymphocytes and natural killer cells, prompting an initial influx of immune effectors around the follicular bulb (2) (8). The infiltrating cytotoxic lymphocytes produce massive amounts of IFN- γ , which binds to follicular epithelial IFN- γ receptor complexes (8) (9). This ligation engages intracellular JAK1 and JAK2 heterodimers, driving the downstream phosphorylation and dimerization of STAT1 (8). Nuclear translocation of STAT1 upregulates classical MHC class Ia/b molecules, completely dismantling hair follicle immune privilege and exposing anagen-specific trichohyalin and melanogenic autoantigens to cytotoxic scrutiny (8) (9).

Simultaneously, STAT1 activation drives follicular epithelial cells to produce interleukin-15 (IL-15) and downstream chemokines such as CXCL9 and CXCL10 (8) (9). Interleukin-15 signals back to the infiltrating CD8⁺NKG2D⁺ T cells through a multimeric receptor complex composed of IL-15R α , IL-2/15R β

(CD122), and the common gamma-chain (CD132) (8). Intracellularly, this receptor couples to JAK1 and JAK3, eliciting robust phosphorylation of STAT3 and STAT5 (8) (9). Phosphorylated STAT5 promotes cytotoxic granule release (perforin and granzyme B), prevents activation-induced cell death, and amplifies further IFN- γ production (8) (9). This vicious, self-amplifying feed-forward loop between follicular epithelium and cytotoxic lymphocytes induces premature catagen transition, follicular dystrophy, and catastrophic hair shaft extrusion without permanent follicular stem cell destruction (2) (9).

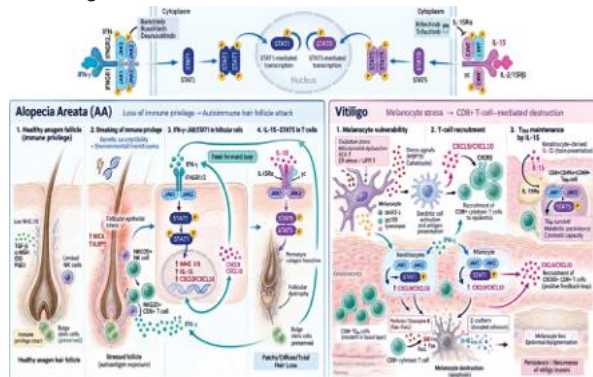
Immunopathogenesis of Vitiligo: Melanocyte Destruction and Autoimmune Memory

Vitiligo presents an analogous mechanistic architecture situated in the epidermal melanin unit (3) (10). Melanocytes residing in vulnerable individuals exhibit intrinsic metabolic defects, including mitochondrial respiratory chain instability, elevated baseline reactive oxygen species (ROS), and heightened sensitivity to external stressors like ultraviolet radiation and phenolic chemicals (3) (10). Accumulation of intracellular oxidative stress leads to protein misfolding within the endoplasmic reticulum, initiating an unfolded protein response and the extracellular discharge of heat shock protein 70 (HSP70i) and calreticulin (3).

Plasmacytoid and conventional dendritic cells recognize these stress signals, migrate to regional skin-draining lymph nodes, and prime naive T cells against melanocytic antigens, including MART-1, gp100, and tyrosinase (3) (10). Effector CD8+ cytotoxic T cells subsequently home to the epidermis, guided by the chemokine gradient formed by CXCL9 and CXCL10 interacting with chemokine receptor CXCR3 (10) (11). Upon recognizing melanocyte antigens, these CD8+ T cells produce high levels of IFN- γ (10) (11).

In keratinocytes and melanocytes, IFN- γ engagement of its receptor triggers JAK1 and JAK2 activation with consequent STAT1 homodimerization (10) (11). Phosphorylated STAT1 orchestrates transcriptional programs that synthesize massive amounts of CXCL9 and CXCL10, recruiting additional CXCR3+ cytotoxic T lymphocytes into the epidermal perimeter (10) (11). Concurrently, IFN- γ signaling impairs melanocyte adhesion by disrupting E-cadherin junctions and directly induces apoptotic pathways via granzyme, perforin, and Fas-FasL interactions (3) (11).

Critically, active vitiligo lesions harbor a persistent population of non-circulating CD8+CD49a+CD69+ tissue-resident memory T (T_{RM}) cells embedded within the basal epidermal layer (10) (12). These T_{RM} cells remain poised for rapid reactivation and depend on keratinocyte-derived IL-15 presented in trans via IL-15R α (10) (12). Interleukin-15 signaling through JAK1/JAK3 and STAT5 maintains the survival, metabolic longevity, and cytotoxic capacity of these T_{RM} cells (10) (12). This explains why classic depigmented vitiligo patches often recur at identical anatomical sites following the cessation of conventional treatments (3) (12).



Immunopathogenesis of Alopecia Areata and Vitiligo Through JAK-STAT Signaling.

Schematic representation of the distinct but interconnected mechanisms underlying both autoimmune diseases. In alopecia areata, follicular stress and loss of immune privilege promote IFN- γ /JAK1-JAK2/STAT1 and IL-15/JAK1-JAK3/STAT5 signaling, driving cytotoxic CD8+ T-cell activation, follicular dystrophy, premature catagen transition, and hair shaft loss. In vitiligo, oxidative stress and melanocyte injury induce CXCL9/CXCL10-mediated recruitment of cytotoxic CD8+ T cells, while IFN- γ /JAK1-JAK2/STAT1 signaling promotes melanocyte destruction and IL-15/JAK1-JAK3/STAT5 signaling sustains tissue-resident memory T cells, contributing to persistent and recurrent depigmentation.

Emerging Therapeutics and Clinical Milestones

The dissection of cytokine transduction through the JAK-STAT axis directly propelled Janus kinase inhibitors to the forefront of clinical therapeutics for both disorders (7) (13). In alopecia areata, the landmark phase 3 BRAVE-AA1 and BRAVE-AA2 trials demonstrated the superior efficacy of baricitinib, an oral selective JAK1/JAK2 inhibitor, over placebo (13). Patients receiving 4 mg daily achieved a Severity of Alopecia Tool (SALT) score of 20 or less (denoting 80% or greater scalp hair coverage) at week 36 in roughly 35% to 40% of cases (13). This success established baricitinib as the first systemically approved targeted molecule for severe alopecia areata (7) (13). Soon after, ritlecitinib, an irreversible oral inhibitor with dual selectivity for JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases, showed substantial therapeutic efficacy in the phase 3 ALLEGRO trial (14). Because ritlecitinib spares JAK1 and JAK2, it selectively dampens γ C-cytokine and cytolytic lymphocyte function, earning regulatory approval for adults and adolescents aged 12 years and older (7) (14). Furthermore, deuruxolitinib (CTP-543), an oral deuterated JAK1/JAK2 inhibitor, proved highly effective in the THRIVE-AA trials, offering robust hair regrowth through improved metabolic stability (7).

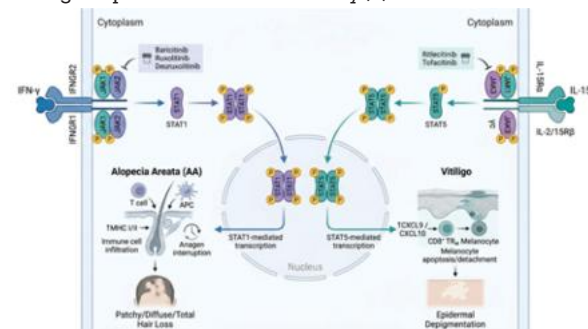


Figure 1. Cytokine-receptor Signal Transduction and Therapeutic Targeting in Alopecia Areata and Vitiligo.

Schematic representation of the IFN- γ /JAK1-JAK2/STAT1 and IL-15/JAK1-JAK3/STAT5 signaling pathways. Cytokine receptor activation induces JAK phosphorylation, STAT activation and nuclear translocation, promoting inflammatory and immune-survival programs implicated in alopecia areata and vitiligo. Selected JAK inhibitors are shown according to their principal signaling targets.

In vitiligo, topical ruxolitinib, a selective JAK1/JAK2 inhibitor cream formulated at 1.5%, achieved landmark success in the pivotal phase 3 TRuE-V1 and TRuE-V2 clinical trials (15). Application of 1.5% ruxolitinib cream twice daily produced notable facial and total-body repigmentation, with approximately 30% of patients reaching a 75% or greater improvement in the facial Vitiligo Area Scoring Index (F-VASI75) at week 24, climbing to over 50% at week 52 (15).

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