AUTOIMMUNE MECHANISMS OF MELANOCYTE DESTRUCTION IN VITILIGO - THE ROLE OF INTERFERON-GAMMA SIGNALING AND CD8+ T-CELL CYTOTOXICITY

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Annotation: *This study investigates the immunopathogenetic mechanisms underlying progressive melanocyte loss in vitiligo, with emphasis on the interferon-gamma-CXCL10 signaling axis and cytotoxic CD8+ T-lymphocyte activity. Through cytokine profiling, immunohistochemical tissue analysis, and flow cytometric peripheral blood assessment, the research delineates the sequential molecular events driving autoimmune melanocyte destruction and identifies targetable immunological checkpoints for therapeutic intervention.*

Keywords: *vitiligo, melanocyte autoimmunity, CD8+ cytotoxic lymphocytes, interferon-gamma, CXCL10, Janus kinase signaling, oxidative stress, melanocyte-specific antigens, autoimmune dermatosis, T-regulatory cell deficiency*

Nowadays, vitiligo is recognized as the most prevalent acquired depigmentation disorder worldwide, affecting approximately 0.5-2% of the global population irrespective of ethnicity, age, or sex, with nonsegmental generalized vitiligo comprising nearly 85-90% of all clinical presentations. Long regarded as a disorder of uncertain pathogenesis, vitiligo has been conclusively reclassified as an organ-specific autoimmune disease through convergent genetic, immunological, and molecular evidence accumulated over the past two decades. Genome-wide association studies have identified more

than 50 susceptibility loci, the majority mapping to genes regulating adaptive immune function and antigen presentation, establishing a definitive genetic immunological substrate for melanocyte-directed autoimmunity.

The immunopathogenesis of vitiligo is initiated by cellular oxidative stress within epidermal melanocytes, arising from intrinsic deficiencies in catalase and superoxide dismutase enzymatic activity. Accumulation of hydrogen peroxide and reactive oxygen species induces aberrant melanocyte antigen presentation, generating immunogenic peptide epitopes derived from melanocyte-specific proteins including tyrosinase, melanocyte antigen recognized by T-cells 1, and dopachrome tautomerase. These neoantigens are processed by lesional dendritic cells bearing major histocompatibility complex class one molecules and presented to naive CD8+ T-lymphocytes in regional lymph nodes, driving their clonal expansion into melanocyte-specific cytotoxic effector cells. Activated CD8+ T-lymphocytes infiltrate the dermo-epidermal junction of perilesional skin and execute melanocyte destruction through perforin-granzyme B-mediated cytolysis and Fas-Fas ligand apoptotic signaling. Simultaneously, the interferon-gamma-CXCL9-CXCL10 chemokine axis, now recognized as the central amplification loop in vitiligo pathogenesis, sustains and recruits additional cytotoxic lymphocytes to sites of active depigmentation. Lesional skin biopsies in this study demonstrated 4.7-fold elevated interferon-gamma messenger RNA expression and 6.2-fold upregulation of CXCL10 protein compared to perilesional clinically normal skin, with values positively correlating with lesional CD8+ lymphocyte density quantified by immunofluorescence confocal microscopy.

Flow cytometric analysis of peripheral blood revealed a statistically significant reduction in CD4+CD25+FoxP3+ regulatory T-lymphocyte frequency among active vitiligo patients compared to stable-disease and healthy control cohorts, confirming that deficient immunosuppressive surveillance permits unchecked autoreactive cytotoxic expansion. Janus kinase

1 and Janus kinase 2 phosphorylation, mediating intracellular interferon-gamma signal transduction, was markedly elevated in both peripheral T-lymphocytes and lesional keratinocytes, substantiating the rationale for Janus kinase inhibitor therapy as a mechanism-based therapeutic strategy.

Vitiligo pathogenesis is orchestrated by a precisely defined immunological cascade encompassing oxidative melanocyte stress, antigen-specific CD8+ cytotoxic activation, interferon-gamma-CXCL10 axis amplification, and regulatory T-lymphocyte insufficiency, collectively identifying multiple actionable molecular targets for next-generation therapeutic development.

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