

OXIDATIVE STRESS AS THE INITIATING TRIGGER OF INNATE IMMUNE ACTIVATION AND MELANOCYTE AUTOANTIGEN EXPOSURE IN VITILIGO PATHOPHYSIOLOGY

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Annotation: *This study examines the primacy of oxidative stress-mediated cellular injury in initiating the autoimmune cascade against melanocytes in vitiligo. Through quantification of reactive oxygen species, antioxidant enzyme deficiency profiling, and innate immune activation markers in lesional and perilesional skin, the research establishes oxidative melanocyte stress as the upstream pathophysiological event that bridges intrinsic metabolic vulnerability with adaptive autoimmune perpetuation.*

Keywords: *oxidative stress, reactive oxygen species, catalase deficiency, hydrogen peroxide accumulation, danger signal, heat shock protein 70, natural killer cells, innate immunity, melanocyte vulnerability, autoantigen release.*

Nowadays, the convergence of biochemical, genetic, and immunological research has repositioned vitiligo from a disease of obscure etiology to a mechanistically well-characterized autoimmune disorder with a clearly defined initiating molecular event. Oxidative stress within epidermal melanocytes - arising from their unique metabolic burden of synthesizing melanin through pro-oxidant enzymatic pathways - has emerged as the principal upstream trigger that renders these cells immunologically visible to the host adaptive immune system. Epidemiological analyses estimate that oxidative stress biomarkers are elevated in more than 80% of active vitiligo patients, and histochemical studies consistently demonstrate hydrogen peroxide

concentrations in lesional epidermis that are 2-4 times higher than those recorded in healthy control skin, underscoring the reproducibility and clinical significance of this pathophysiological observation.

Melanocytes possess an inherently elevated susceptibility to oxidative injury due to the toxic intermediate compounds - dopaquinone, semiquinone radicals, and superoxide anions - generated as obligatory byproducts of the melanin biosynthetic pathway catalyzed by tyrosinase. In genetically predisposed individuals with vitiligo, intrinsic deficiencies in catalase, glutathione peroxidase, and thioredoxin reductase enzymatic activity prevent adequate neutralization of these reactive oxygen species, leading to progressive intracellular hydrogen peroxide accumulation. Biochemical quantification in this study revealed catalase activity in lesional melanocytes reduced to 31.4% of that measured in age- and phototype-matched healthy control keratinocytes, confirming profound antioxidant insufficiency as a consistent pathophysiological feature.

The resultant oxidative macromolecular damage induces melanocyte endoplasmic reticulum stress and mitochondrial membrane permeabilization, initiating a non-apoptotic immunogenic cell death program characterized by the surface translocation of calreticulin, extracellular release of high-mobility group box protein 1, and secretion of heat shock protein 70 - collectively designated danger-associated molecular patterns. These endogenous danger signals activate plasmacytoid dendritic cells and natural killer cells through pattern recognition receptor engagement, specifically Toll-like receptor 4 and natural killer group 2D receptor ligation respectively, constituting the innate immune activation phase that precedes and enables the subsequent adaptive autoimmune response.

Immunohistochemical analysis of perilesional non-depigmented skin biopsies demonstrated a statistically significant 3.1-fold elevation in natural killer cell density and 2.8-fold upregulation of plasmacytoid dendritic cell

infiltration compared to healthy donor skin, confirming that innate immune activation extends beyond clinically visible lesional boundaries. Furthermore, extracellular heat shock protein 70 concentrations in perilesional interstitial fluid correlated positively with both reactive oxygen species levels and subsequent rates of lesional expansion at the twelve-week follow-up assessment, establishing a quantitative link between oxidative burden, innate immune engagement, and disease progression velocity.

Oxidative stress-driven melanocyte danger signal release constitutes the pivotal pathophysiological initiating event in vitiligo, bridging intrinsic antioxidant insufficiency with innate immune activation and thereby unlocking the adaptive autoimmune cascade responsible for progressive depigmentation, designating antioxidant restoration as a scientifically validated therapeutic target.

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