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METABOLIC DYSREGULATION AND IMMUNE ACTIVATION IN VITILIGO: UNVEILING THE MITOCHONDRIAL AND INFLAMMATORY IMPRINT OF DISEASE PATHOGENESIS

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Vitiligo pathogenesis involves a complex interplay of genetic susceptibility, oxidative stress, and autoimmune-mediated melanocyte destruction. While impaired adhesion and defective regeneration contribute to the disease, recent evidence highlights the role of early metabolic alterations in triggering pathogenesis. Clinically, patients frequently present systemic metabolic comorbidities, including dyslipidemia, altered glucose homeostasis, and compromised antioxidant capacity. This study evaluated the in vitro metabolic profiles of dermal and epidermal cells isolated from the non-lesional skin of vitiligo patients compared to matched healthy controls. Our findings reveal that vitiligo-derived melanocytes, keratinocytes, and fibroblasts exhibit severe mitochondrial dysfunction, resulting in depleted ATP levels and elevated reactive oxygen species (ROS). To compensate for this energetic deficit, cells implement a metabolic adaptation mimicking hypoglycemia, characterized by upregulated Glut-4 expression, increased glucose uptake, and activation of autophagic pathways. This excessive glucose influx leads to the intracellular accumulation and microenvironmental release of advanced glycation end-products (AGEs), which may act as tissue messengers. However, the resulting cytoplasmic hyperglycemia over activates the mTOR/S6 pathway, inducing a negative feedback loop in IGFR/InsR signaling via chronic hyperphosphorylation of IRS1 at Ser612. This modification blunts the insulin response, establishing a state of cellular insulin resistance. Notably, chronic stimulation with insulin and IGF-1 worsens the ATP deficit, further elevating ROS and AGEs. Among the analyzed cell types, keratinocytes demonstrated high sensitivity to glucotoxicity. Their metabolic impairment triggers a robust inflammatory response, marked by the secretion of innate immunity mediators, including CXCL10, IL-6, IL-8, IL-1α, IL-1β, and TNFα, which promote THP-1 monocyte differentiation. In turn, THP-1 cells exposed to vitiligo keratinocyte-conditioned medium release high levels of immunostimulatory molecules (IL-1α, IL-1β, IL-6, IL-8, CXCL10, CXCL12, CXCL16, PD-L1), amplifying the inflammatory network. This mechanism is critical, as the transition from a diffuse chronic inflammation to a localized form of autoimmunity represents the key turning point of vitiligo onset, likely driven by the loss of an precarious homeostatic equilibrium. Ultimately, the engagement of innate immune cells facilitates adaptative immune response. These data substantiate the link between metabolic dysfunction and vitiligo onset, offering new translational perspectives for early therapeutic intervention.