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EXPLORING THE ROLE OF IMMUNOMETABOLISM AND MICROBIOME IN VITILIGO: OPPORTUNITIES FOR NEW THERAPEUTICS

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ABSTRACT

Vitiligo, a chronic autoimmune depigmentation disorder affecting 0.5-2% globally, manifests through melanocyte destruction driven by immunometabolic dysregulation, oxidative stress, and gut microbiota dysbiosis. This review elucidates metabolic reprogramming in immune cells—monocytes shifting to glycolysis, M1 macrophages favoring PPP, and CD8+ T cells/TRMs relying on FAO—alongside gut-skin axis disruptions marked by reduced SCFAs, altered bile acids, and tryptophan metabolites that exacerbate IFN-γ/CXCL10-mediated inflammation. Emerging therapies targeting JAK-STAT, Nrf2-ARE, IL-15/CD122, and microbiome modulation offer promising avenues for restoring immune-metabolic homeostasis and achieving durable repigmentatio. Vitiligo emerges as a systemic immunometabolic disorder in which oxidative stress, immune dysregulation, and gut microbiota–derived metabolites

converge to drive melanocyte destruction and defective repigmentation.

KEYWORDS: Vitiligo, Immunometabolism, Gut-skin axis, SCFAs, Oxidative stress, Microbiome dysbiosis.

1. INTRODUCTION

Vitiligo is a skin condition characterised by the loss of melanocytes and a decrease in pigmentation, impacting 0.5-2% of people worldwide. It is linked to metabolic problems such as insulin resistance and lipid imbalances, as well as comorbidities like type 1 diabetes and metabolic syndrome, especially in non-segmental vitiligo (NSV), which is the most prevalent systemic subtype. Divided into NSV, segmental vitiligo (SV), and forms that are unclassified, vitiligo is characterized by mechanisms involving genetics, autoimmunity, oxidative stress, and inflammation, which lead to the destruction of melanocytes. NSV exhibits increased innate immune activity, B-cell stimulation, and broader metabolic associations when compared to SV. Immunometabolism—referring to the metabolic alteration of immune cells through glucose and lipid pathways—fuels immune dysfunction in vitiligo, leading to disrupted homeostasis. These findings provide promising opportunities for innovative therapies aimed at targeting the intersection of metabolic and immune processes[1] Oxidative stress plays a crucial role in the initiation and progression of vitiligo, leading to the death of melanocytes and loss of skin color. Despite progress in understanding the condition, the underlying internal triggers are still unclear, and localized treatments often do not succeed, indicating a potential systemic cause beyond just the skin. The gut-skin connection offers an important perspective, with imbalances in gut microbiota—observed in vitiligo patients compared to healthy individuals—associated with skin conditions such as atopic dermatitis, psoriasis, and urticaria. Research has demonstrated changes in the composition of microbiota in those with vitiligo, and the use of antibiotics has been shown to reduce pigmentation loss in experimental models, implying that microbial metabolites may increase serum levels and disturb skin immunity.[2] Vitiligo lesions are described with the following characteristics: Light or depigmented spots and areas Typically have clear edges Can be round, oval, or elongated Borders may appear convex Vary in size from a few millimeters to several centimeters Gradually expand outward over time at an irregular pace.[3]

2. Immunometabolism in Vitiligo

Vitiligo is an autoimmune skin condition characterised by the loss of melanocytes and resulting depigmentation. It affects about 0.5-2% of people worldwide and is associated with

conditions like insulin resistance, lipid abnormalities, and metabolic disorders. Its mechanisms involve genetics, immune responses, oxidative stress, and inflammation, although the exact immunometabolic causes are still unclear. Vitiligo is classified into non-segmental (NSV, most common and systemic), segmental (SV), and unclassified types. NSV is marked by a strong innate immune response, B-cell activation, and associations with type 1 diabetes, cardiovascular diseases, and metabolic syndrome, unlike SV.[1] Emerging evidence links metabolic syndrome and dyslipidemia to various skin conditions, including psoriasis, lichen planus, and vitiligo.Leptin, a polypeptide hormone secreted by adipocytes and enterocytes, modulates energy homeostasis and body weight, with prior studies associating its levels to insulin resistance, obesity, hypertension, and dyslipidemia. To date, no data exist on lipid profiles, leptin, and C-reactive protein (CRP) levels in Iranian vitiligo patients. This study therefore evaluates these metabolic markers in this population.[4]

2.1 Metabolic Reprogramming of Immune Cells

Cell type	Subset	Stimuli / Status	Metabolic change	Functional change	Signal molecules	PMID
Monocyte	CD14+	LPS	↑ Glycolysis, ↓ OXPHOS	↑ Inflammatory cytokines (TNF-α, IL-6, IL-1β, IL-10), ↑ Phagocytosis	TLR4	27991883
	CD14+	P3C	↑ Glycolysis, ↑ OXPHOS	–	TLR2	27991883
	–	Fungi *Candida*	↑ Glycolysis, ↑ OXPHOS, ↑ Glutaminolysis	↑ Inflammatory cytokines (TNF-α, IL-6, IL-1β), ↑ ROS	C-type lectin	28922415
	CD14++CD16−	NA	↑ Glycolysis, ↑ PPP	Defense response	NA	24671955
	CD14+CD16++	NA	↑ OXPHOS	Anti-inflammatory	NA	24671955
	CD14+CD40+	Hcy (CKD)	↑ Hcy, ↑ SAH, ↑ SAM/SAH	↓ DNA methylation, ↑ inflammatory cytokines and chemokines	↓ DNMT1 – ↑ CD40	27992360
Macrophage	M1	LPS / IFN-γ	↑ Glycolysis, ↑ PPP	Pro-inflammatory	AKT / mTOR / HIF1α	29777212

	M2	IL-4	↑ FAO, ↑ OXPHOS, ↓ PPP	Anti-inflammatory	STAT6 – AMPK	29777212
	Mox	OxPL	↓ Glycolysis, ↑ Glutaminolysis	Anti-oxidant activity, anti-inflammatory	TLR2 – Syk	29891687
Dendritic cell	BM-derived DC	No stimuli	↑ Lipid β-oxidation / OXPHOS	Antagonize DC activation	AMPK	20351312
	BM-derived DC	LPS / Zymosan / Curdlan	↑ Glycolysis, ↓ OXPHOS	↑ Maturation, motility, migration	PI3K / AKT	20351312
	BM-derived DC	CCL21 / CCL19	↑ Glycolysis	↑ Migration, trafficking to draining lymph node	CCR7 – HIF1α	30824325
	CD1c+ mDC	TLR agonists	↑ Glycolysis, ↑ Mitophagy, ↓ OXPHOS	Activation	TLR7/8 – BNIP3	30455688
Dendritic cell	pDC	TLR agonists	↑ OXPHOS, ↑ Glutaminolysis	Activation	TLR7/8 – BNIP3	30455688
	Tolerogenic DC	Dexamethasone & vitamin D3	↑ OXPHOS, ↑ FAO	Tolerogenic, ↑ ROS	NA	25917094
T cell	Naïve	NA	OXPHOS, FAO	Homeostasis	TSC1 – mTORC1	29677474
	Th1	NA	↑ Glycolysis	↑ Inflammatory cytokine (IFN-γ)	LDHA, histone acetylation of *Ifng*	27708054
	Th17	NA	↑ Glycolysis	Pro-inflammatory	HIF1	21871655
	Treg	NA	↑ OXPHOS	Anti-inflammatory	Myc	28416194
	Memory CD8+ T cell	NA	↑ OXPHOS, FAO	Longevity, quick response	NA	22889213
B cell	Mouse splenic B	BCR engagement	↑ Glycolysis	↑ Proliferation / growth	PI3K / AKT / mTOR	16449529
	Mouse splenic B	IL-4	↑ Glycolysis	↑ Survival	STAT6	17911579
	Peripheral blood B	anti-IgM / LPS	↑ Glycolysis, ↑ OXPHOS	↑ Proliferation and antibody production	HIF1α, c-Myc	24616478

	Memory B cell	NA	↑ OXPHOS	Durable antibody production	Mpc2	27396958

Table 1: Metabolic reprogramming in immune cells.[5]

Monocytes serve as innate immune sentinels that detect environmental alterations and maintain pools of tissue macrophages and dendritic cells[6] Upon LPS stimulation, human CD14+ monocytes preferentially shift to glycolysis rather than OXPHOS, rapidly mounting host defense through inflammatory cytokine production (TNF-α, IL-6, IL-1β) and enhanced phagocytosis.[7] This mirrors the Warburg effect characteristic of cancer cells.[8][9] Under glucose deprivation, monocytes sustain pro-inflammatory functions by enhancing fatty acid oxidation (FAO) to power OXPHOS, compensating for impaired Warburg metabolism and meeting elevated energy demands during LPS activation.[10] Unlike LPS stimulation, synthetic bacterial lipopeptide P3C or *Candida albicans* simultaneously boost both glycolysis and OXPHOS, driving pro-inflammatory cytokine release and reactive oxygen species (ROS) production via Toll-like receptor 2 or C-type lectin signaling pathways[11]

2.2 Oxidative Stress and Melanocyte Dysfunction

Lipids, as primary constituents of cellular membranes, play a critical role in oxidative stress processes. Additionally, dyslipidemia and conventional atherosclerosis risk factors—such as diabetes, hypertension, and smoking—activate the NADPH oxidase system, resulting in excessive superoxide anion generation that exacerbates oxidative stress.[12] Pietrzak et al. were the first to propose that lipid peroxidation contributes to vitiligo pathogenesis.[13] Karadağ et al. demonstrated that hyperhomocysteinemia—not only a recognized cardiovascular risk factor—may also promote vitiligo development by inhibiting tyrosinase activity.[14] Studies report significantly elevated homocysteine levels in patients with active vitiligo compared to those with stable disease, potentially triggering oxidative stress, endoplasmic reticulum stress, and proinflammatory cytokine expression.[15] N-homocysteinylated proteins—formed via N-linkage of homocysteine's carboxyl group to lysine residues' ε-amino groups—act as neoantigens, triggering CD8+ T cell-mediated autoimmune destruction of melanocytes[16]

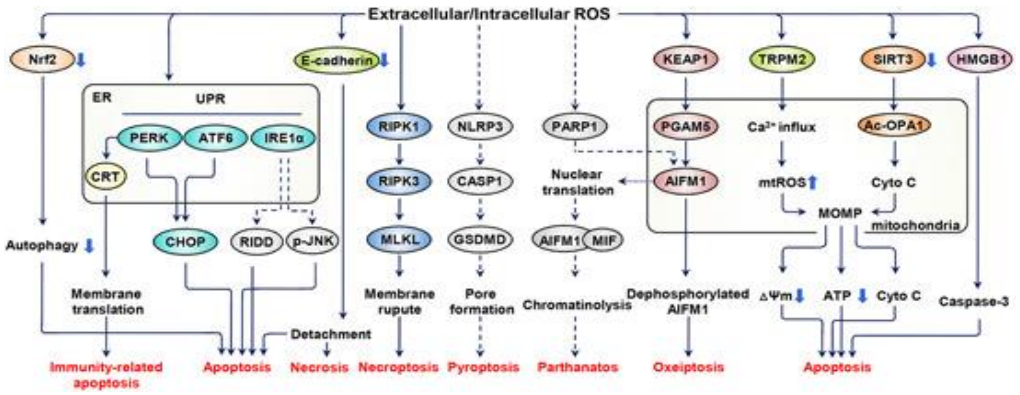

Figure: Interconnected Regulated Cell Death Pathways in Vitiligo Melanocytes.[17]

Melanocytes produce melanin, the pigment imparting color to skin, hair, and eyes, while shielding skin from damaging UV radiation, modulating pigmentation, and contributing to sensory/neurological functions. Their dysfunction underlies hypopigmentation/hyperpigmentation disorders, skin cancers, and neurological conditions. Compared to humans, animals exhibit greater pigment diversity—including melanin, carotenoids, oxyhemoglobin, and reduced hemoglobin—alongside more complex vertebrate skin architecture, yielding richer cutaneous coloration.[18] Melanocytes, specialized dendritic cells, uniquely synthesize melanin via complex chemical and enzymatic pathways. Animal melanin primarily comprises **eumelanin** (dark, black/brown, insoluble pigment in dark skin/hair) and **pheomelanin** (light red/yellow, sulfur-containing, alkali-soluble pigment)[18][19] Melanoblasts (melanocyte precursors) serve as key models in developmental and structural biology research. These cells draw global interest from scientists and clinicians developing novel therapeutic approaches for biological, pathophysiological, and technological challenges in pigmentation disorders. Extensive animal melanocyte model studies reveal critical genes, proteins, and signaling pathways underlying dermatological conditions.[18][20] Melanocyte stem cells (McSCs), skin stem cells originating from the neural crest in vertebrates [21] During embryogenesis, neural crest cells migrate dorsolaterally—connecting somites to non-neural ectoderm—to form melanoblasts, which then disperse to colonize developing hair follicles (HFs) and epidermis. In the epidermal basal layer, these melanoblasts progress to precursor cells, an intermediate stage before differentiating into mature, functional melanocytes (MCs).[18]

2.3 Adaptive immunity in vitiligo

Numerous studies confirm that antigen-specific CD8+ T cells drive melanocyte destruction in human vitiligo, with early observations documenting T-cell infiltration in lesional skin of

affected patients.[22] CD8+ T cells were observed in close proximity to degenerating melanocytes within the epidermis.[23] Furthermore, the frequency of melanocyte antigen tetramer-positive CD8+ T cells in vitiligo patients' blood correlates with disease severity, and these cells demonstrate melanocyte-killing capacity in vitro.[24][25] Finally, purified CD8+ T cells from vitiligo lesional skin—but not CD8-depleted T cells—infiltrate patients' healthy skin ex vivo and trigger melanocyte apoptosis in situ, confirming CD8+ T cells as both necessary and sufficient for melanocyte destruction in human vitiligo.[26] Key antigenic proteins identified in vitiligo include gp100, MART1, tyrosinase, and tyrosinase-related proteins 1 and 2 (TYRP1/2).[24][27][28][29] Certain mouse models of vitiligo similarly identify CD8+ T cells as primary disease effectors, with IFN-γ emerging as a pivotal pathogenic cytokine.[30][31] CD4+ T cells are also present within vitiligo lesions.[23] CD4+ T cells are present in vitiligo lesions, yet their direct role in pathogenesis remains unconvincing. They prove dispensable in mouse vitiligo models, where their absence actually exacerbates disease—suggesting potential Treg suppressive functions.[30] Other mouse models of vitiligo have been established that depend on CD4+ T cells.[32][33] Regulatory T cells (Tregs) exhibit dysregulation in vitiligo patients, though the precise nature of these defects remains controversial and lacks consensus across studies. Reported abnormalities include reduced circulating Treg numbers, impaired skin-homing capacity due to defective CXCR3/CCR4 expression, and compromised suppressive function characterized by FoxP3 instability, diminished IL-10 secretion, and metabolic exhaustion from impaired FAO/OXPHOS switching. These heterogeneous Treg deficiencies fail to counterbalance effector CD8+ T-cell expansion, allowing unchecked IFN-γ/CXCL10-driven melanocyte destruction. Therapeutic strategies enhancing Treg stability (e.g., low-dose IL-2) or function (e.g., PI3Kδ inhibitors) show promise in restoring immune tolerance.[34][35][36][37]

2.4 Therapeutic Targets in Immunometabolism (e.g., IFN-γ axis, JAK-STAT, Nrf2-ARE)

Uncovering the biological mediators and the molecular mechanisms of metabolic defects in melanocyte degeneration and autoimmunity is essential for novel therapeutic targets and drugs intercepting the process of vitiligo. The experience with systemic biological therapies for psoriasis suggests that a similar approach might be successfully used in vitiligo. Promising treatments targeting the IFN-γ chemokine axis, JAK-STAT pathway, and Nrf2-ARE pathway, have recently emerged.[1]

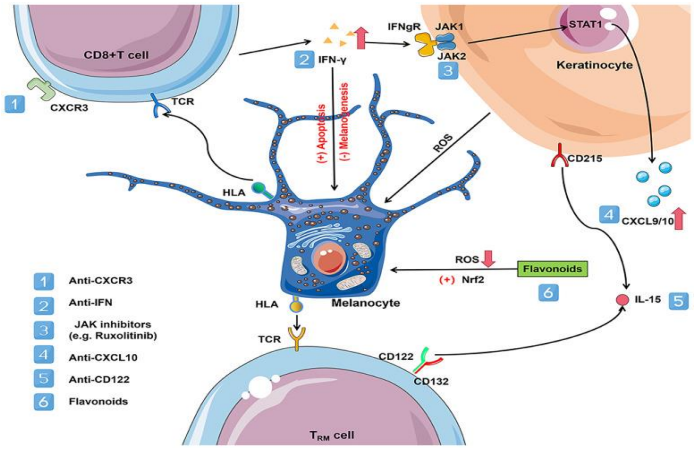

Figure: Therapeutic Pathways in Melanocyte Protection.[1]

I. The IFN-γ chemokine axis

The reduction in the level of IFN-γ, a key cytokine of the immune system in glucose metabolism, can improve glucose metabolism, as demonstrated in a mouse model with low IFN-γ levels[38] Furthermore, functional studies in mouse models confirm that IFN-γ, its receptor (IFNγR), STAT1, CXCL10, and CXCR3 play critical roles in inducing hypopigmentation characteristic of vitiligo.[39][31][40] In a mouse model, CXCR3-targeting depleting antibodies reduced self-reactive T cell numbers and reversed vitiligo manifestations [41] In conditional STAT1 knockout mice, functional studies demonstrate that keratinocyte-derived chemokines and IFN-γ signaling drive vitiligo development and homing of autoreactive T cells to the epidermis. Conversely, epidermal immune cells—including endogenous T cells, Langerhans cells, and γδ T cells—are dispensable for this process [42] IFN-γ directly suppresses melanogenesis and triggers melanocyte apoptosis.[43] A recent single-cell sequencing study in vitiligo revealed that fibroblasts from different sites exhibit varying IFN-γ responsiveness, which governs their capacity to recruit CD8+ T cells. The study further showed greater upregulation of CXCL9 and CXCL10 in high-incidence areas. Using the Cre-loxP system, researchers generated IFN-γ receptor knockout mice that were protected from vitiligo development.[44] Thus, the IFN-γ axis offers promising therapeutic targets for vitiligo treatment.[45]

II. JAK-STAT pathway

Recent evidence links JAK-STAT pathway dysregulation to metabolic disorders. Janus kinase 2 (JAK2) specifically associates with central obesity and elevated waist circumference.[45] JAK3-deficient mice display metabolic disturbances, including insulin resistance, weight gain, elevated fasting insulin and glucose levels, impaired glucose tolerance, and hepatic

steatosis.[46] Recent reports highlight JAK inhibitors' therapeutic potential in vitiligo. A case report also documented a JAK inhibitor improving glucose levels in a 19-year-old with type 1 diabetes.[47] Topical JAK inhibitor ruxolitinib cream achieved its primary endpoint in two pivotal phase 3 trials, along with key secondary endpoints. A significantly higher proportion of patients reached ≥75% improvement in F-VASI score (quantifying vitiligo skin symptoms) at week 24 compared to placebo[1] Ruxolitinib cream is the first FDA-approved topical therapy for nonsegmental vitiligo in adults and children aged 12 years and older.[48] Shiu et al. suggest that combining JAK inhibitors with therapies addressing keratinocyte metabolic defects could offer a novel vitiligo treatment strategy.

3. gut skin axis

The gut-skin axis forms part of the larger gut-organ axis framework, highlighting bidirectional gut-organ communication through neural, endocrine, and immune pathways.[50] This framework integrates the gut microbiota with multiple organs, the immune system, and the gut itself.[51] The gut-skin axis forms part of the larger gut-organ axis framework, highlighting bidirectional gut-organ communication through neural, endocrine, and immune pathways.[52] The gut and skin exhibit structural and functional parallels, including shared embryonic origins, symbiotic microbiomes, innervation patterns, and immune capabilities[53] The gut microbiota plays a central role in sustaining gut-skin homeostasis and forms the foundation of the gut-skin axis theory[54] The gut microbiota comprises bacteria, fungi, parasites, protozoa, and viruses, with bacteria being predominant.[55] Over 90% of gut bacteria belong to the phyla Bacteroidetes and Firmicutes.[56] The Bacteroidota:Firmicutes ratio serves as a standard metric for evaluating gut microbiota composition and diversity.[57] Gut bacteria are classified as beneficial (e.g., Bifidobacteria, Lactobacillus) or opportunistic pathogens (e.g., Staphylococci, Clostridia) that can cause infections under dysbiotic conditions.[58]

3.1 Immune Modulation\

Vitiligo, a chronic condition, demands lifelong management through immunomodulators, phototherapy, or surgical grafting. Yet, approximately 40% of patients experience relapse within one year of discontinuing therapy.[59] Technological advances have spurred alternative targeted therapies for vitiligo. Recent immunomodulation targeting JAK signaling, TRM cells, and Tregs shows strong therapeutic promise.

The IFN-γ–CXCL9/10–CXCR3 axis critically drives CD8+ T cell-mediated melanocyte destruction. Keratinocytes detect IFN-γ, triggering JAK-STAT-mediated production of CXCL9/10. The JAK family—JAK1, JAK2, JAK3, TYK2—forms cytokine-induced heterodimers that activate distinct STAT proteins[60]. JAK inhibitors represent a novel class of small molecule-targeted therapies for rheumatoid arthritis, a chronic inflammatory joint disease. In dermatology, topical and systemic JAK inhibitors have shown substantial progress.[61] A case report documented hair regrowth and skin repigmentation in a patient with comorbid alopecia areata and vitiligo following ruxolitinib treatment, a JAK1/2 inhibitor.[62] This offers potential vitiligo therapy, as both conditions share IFN-γ-driven pathogenesis reliant on CD8+ T cells.[63] Recent phase 2 trials demonstrated ruxolitinib's efficacy in treating vitiligo, exhibiting strong clinical relevance and therapeutic impact[64] Tofacitinib, another pan-JAK inhibitor, demonstrates repigmentation potential, particularly when combined with phototherapy to stimulate melanocytes, yielding superior treatment outcomes.[65] Literature indicates maximal repigmentation occurs on facial lesions, while trunk and lower extremity patches respond less robustly. This highlights regional specificity in vitiligo, with some lesions exhibiting bilateral symmetric distribution.[66] Notably, much of the regained pigmentation faded after discontinuing ruxolitinib, whereas hair regrowth proved more durable[62] Although these autoimmune diseases share similar pathogenesis, JAK inhibitors produce divergent clinical outcomes. Given JAK signaling complexity, potential toxicities from broad inhibition warrant consideration.

The rapid yet transient repigmentation by JAK inhibitors underscores vitiligo's persistent recurrence. These agents block cytotoxic cell chemotaxis without eliminating long-lived skin-resident TRM cells sustained by IL-15 signaling. Subsequent research has targeted IL-15 pathways; anti-CD122 antibody (targeting the IL-15 receptor β subunit shared by human/mouse TRM cells) reduces IFN-γ production and depletes autoreactive CD8+ TRM cells in established murine vitiligo.[67] Treg cells possess immunosuppressive properties, making their expansion a promising strategy. This can be accomplished through ectopic expression of key regulators: IL-2, TNF receptor 2, and Notch-1.[68] IL-2 drives Treg differentiation, while Tregs express high-affinity IL-2 receptors to preferentially capture it. TNF receptor 2, highly expressed on Tregs, efficiently expands natural Tregs when stimulated, as seen in graft-versus-host disease models. Notch-1 inhibition boosts Treg numbers and suppressive function in transplantation settings.

Treg cell therapy offers another avenue: harvesting patient-derived Tregs, expanding them ex vivo, and reinfusing them. Challenges include their low blood abundance and slow in vitro expansion for clinical-scale application.[69] Gene gun-mediated CCL22 overexpression enhances Treg recruitment to the epidermis, representing the preferred current approach to boost Treg numbers and slow vitiligo progression.[70] CAR-Treg therapy enhances Treg quality by engineering antigen-specific Tregs ex vivo. These modified cells recognize targeted antigens upon reinfusion, triggering intracellular signaling for superior suppression compared to nonspecific bystander Tregs.[68] CAR technology enables efficient in vitro expansion of abundant, antigen-specific Treg cells. By conferring specificity, conventional antigen-specific T cells can be reprogrammed into functional Tregs.[71]

3.2 Microbial Metabolites

Research observed a decline in bacterial taxa usually linked to a healthy gut microbiome and a reduction in SCFA-producing taxa in people with vitiligo.[72] Butyrate is essential for maintaining gut barrier integrity and has anti-inflammatory and immune-regulatory effects in autoimmune conditions. Nonetheless, its effectiveness depends on factors like concentration, site of action, and the host's physiological state.[72][73] Studies on neonatal melanocytes indicate that butyrate is cytotoxic at concentrations over 1 mM.[74] Conversely, at lower, non-toxic levels (0.5 and 1 mM), butyrate greatly promotes melanocyte differentiation, leading to melanosome formation and increased pigmentation.[75] Topical use of butyrate, alone or combined with S. epidermidis and glycerol, notably decreased UVB-induced IL-6 levels.[76] Propionate lowers melanin synthesis in melanocytes, and at 4 mM, it significantly inhibits tyrosinase activity without harming cell growth, suggesting that propionate reduces melanogenesis by downregulating tyrosinase gene expression.[77] While prior studies seem to challenge SCFAs' anti-inflammatory effects, note that vitiligo patients often exhibit reduced SCFA levels, potentially limiting their anti-inflammatory and high-dose cytotoxic benefits. Tissue-specific GPCR expression and SCFA affinity variations must also be factored in. Collectively, SCFAs likely mediate diverse physiological effects via multiple pathways, with outcomes shaped by concentration gradients, tissue distribution, and host metabolism.

Studies show gut microbiota-derived ursodeoxycholic acid (UDCA, a secondary bile acid formed by hydroxylating primary bile acids) counters UV-induced skin damage by curbing intracellular oxidative stress and inflammation. In experiments, UDCA reduced melanin content in normal human melanocytes.[78] However, this study utilized an aging skin model

inconsistent with vitiligo pathogenesis. Moreover, UDCA exhibits anti-inflammatory and antioxidant properties, warranting further investigation of its role in vitiligo.At 5 mM concentration, kynurenine (KYN) significantly suppressed melanocyte DNA synthesis.[79] Further studies confirm that kynurenine (KYN), derived from microbial metabolism and fibroblast activity, suppresses DNA synthesis and markedly reduces metabolic function in primary human melanocytes. Kynurenine accumulation also disrupts tyrosinase activity in vitiligo lesions, downregulates tyrosinase expression in melanocyte-keratinocyte co-cultures, and diminishes melanosome formation in 3D human skin equivalents.As noted earlier, vitiligo patients show elevated serum kynurenine aminotransferase levels, causing kynurenine pathway shunting and systemic KYNA buildup.[82] Thus, excessive kynurenine (KYN) buildup in vitiligo patients likely harms melanocytes and drives disease pathogenesis. Oxidative stress depletes epidermal tryptophan, reducing serotonin and melatonin levels.[83] In vitro studies demonstrate that melanophores in lower vertebrates show dose-dependent pigmentation responses to 5-HT1 and 5-HT2 receptor agonists, whereas 5-HT3 and 5-HT4 receptor agonists trigger dose-dependent pigment aggregation.[84][85][86] The serotonin/5-HT7 receptor triggers an adaptive response that boosts pigmentation during environmental stress via multiple signaling pathways, such as cAMP-PKA-MAPK, Rab27a/RhoA, and PI3K/AKT.[87] Emotional stress lowers skin serotonin levels, thereby impairing melanin production.[88] Consequently, fluoxetine, a selective serotonin reuptake inhibitor, effectively treats pigment loss disorders.[89] Indole derivatives, acting as endogenous AHR ligands, activate AHR signaling and alleviate psoriasis and certain dermatitis conditions.[90][91]

3.3 Immune Dysregulation

Abnormal activation and dysregulated antigen-presenting functions of dendritic cells (DCs) arise from multiple interconnected factors. DAMPs trigger PRR activation, promoting DC maturation and migration, which subsequently activates T cells in lymph nodes. Inflammatory cytokines like TNF-α, IL-6, and IL-1β further amplify DC activation and antigen presentation.[92] Additionally, innate immune mediators like IFN-γ, produced by natural killer (NK) cells and innate lymphoid cells, upregulate HLA class I expression on melanocytes, thereby enhancing CD8+ T cell recognition.[93] TLR signaling in dendritic cells (DCs) concurrently upregulates HLA molecules and promotes their maturation, reinforcing the innate-adaptive immunity interface. However, the exact mechanisms by which these cytokines regulate DC function in vitiligo remain poorly understood.

DC dysfunction in antigen presentation is closely linked to melanocyte damage and apoptosis[94] Studies demonstrate that dendritic cells (DCs) activate specific T cells through melanocyte antigen presentation, resulting in melanocyte damage and apoptosis.[95] DCs also secrete cytokines such as TNF-α and IFN-γ, further damaging melanocytes and causing their apoptosis and functional impairment.[96] Thus, dysregulated DC activation and defective antigen presentation, combined with innate immune-driven HLA expression changes, critically contribute to vitiligo pathogenesis and offer novel therapeutic targets. Inhibiting DC antigen presentation or their CD8+ T-cell interactions could effectively interrupt a pivotal step in the autoimmune cascade.[97]

4. Impact of Microbiome on Immune Cell Metabolic Pathways

Short-chain fatty acids (SCFAs) modulate innate immune cells including macrophages, neutrophils, and dendritic cells (DCs). Additionally, SCFAs exert bidirectional regulation on antigen-specific adaptive immunity mediated by T cells and B cells.[101] Regulating metabolic processes in immune cells is essential for maintaining homeostasis and driving immunopathogenesis. Recent evidence shows that the gut microbiota influences immunometabolism, particularly via metabolites like short-chain fatty acids, bile acids, and tryptophan derivatives.[102]

5. Therapeutics: Current and Emerging Therapeutic Opportunities

Vitiligo is a skin disorder marked by the progressive loss of melanocytes, resulting in depigmented white patches on the skin[98] Vitiligo's pathogenesis is currently linked to immune dysregulation, particularly the hyperactivation of CXCR3+ CD8+ cytotoxic T cells[99] Current vitiligo treatments like tofacitinib (JAK-STAT inhibitor) and tacrolimus (calcineurin inhibitor) face challenges: poor delivery to CXCR3+CD8+ T cells at the dermal-epidermal junction, systemic side effects, and limited topical penetration. Microneedles (MNs), especially solid MNs, offer a promising alternative by creating skin micropores for targeted drug delivery to this site, with studies showing significant lesion improvement without notable side effects in treatment-resistant cases.[100]

5.1 Targeting Immunometabolic Pathways

Recent therapeutic advances have introduced promising treatments that target the IFN-γ chemokine axis, JAK-STAT signaling pathway, and Nrf2-ARE pathway[1]. In vitiligo mouse models, an anti-CD122 antibody targeting IL-15 signaling effectively reversed depigmentation. Systemic or local anti-CD122 treatment reduced IFN-γ production by tissue-

resident memory T cells (TRMs) and achieved sustained repigmentation.[103] Antioxidant pathways are under active investigation for their clinical potential in vitiligo treatment. The Nrf2/ARE pathway can enhance antioxidant gene expression, while the PI3K/AKT pathway regulates melanocyte proliferation and maturation.[104]

CONCLUSION

Vitiligo emerges as a systemic immunometabolic disorder in which oxidative stress, immune dysregulation, and gut microbiota–derived metabolites converge to drive melanocyte destruction and defective repigmentation. Metabolic reprogramming of innate and adaptive immune cells, coupled with dysbiosis and altered SCFAs, bile acids, and tryptophan pathways, sustains chronic inflammation and tissue-specific autoimmunity. Integrating gut–skin axis modulation with therapies targeting IFN-γ, JAK–STAT, Nrf2/ARE, and Treg/TRM biology offers a rational framework for next-generation, mechanism-based interventions in vitiligo.

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