Clinical, Cosmetic and Investigational Dermatology

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REVIEW

Updates on the Role of Innate Immunity's Pattern Recognition Receptors in Vitiligo Pathogenesis and Therapeutic Potential

Jindi Feng, Lu Lu, Huimin He, Yubin Peng, Shiyu Zhang, Lu Yang, Yuehua Liu, Tao Wang

Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, State Key Laboratory of Complex Severe and Rare Diseases, National Clinical Research Center for Dermatologic and Immunologic Diseases, Beijing, People's Republic of China

Correspondence: Yuehua Liu; Tao Wang, Department of Dermatology, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, 100730, People's Republic of China, Tel +86-10-69151543, Fax +86-10-69151502, Email yuehualiu63@163.com; wangtaopumch@126.com

Abstract: Vitiligo is a complex, multifactorial disorder characterized by acquired skin pigment loss that strongly influences the physical and mental well-being of patients with vitiligo. The precise pathogenesis remains incompletely elucidated, but recent studies emphasize the significant roles of both innate and adaptive immunity. Pattern recognition receptors (PRRs), essential for innate immune sensing, significantly contribute to melanocyte destruction in vitiligo. In vitiligo patients, melanocytes and keratinocytes secrete substances like heat shock protein 70 (HSP70), high-mobility group box 1 protein (HMGB1), calreticulin (CRT), and S100 calcium-binding protein B (S100B) due to various internal and external influences. PRRs are capable of recognizing these "danger signals". This recognition activates the immune response by stimulating innate immune cells, like plasmacytoid dendritic cells (pDCs) and natural killer cells (NK cells). The activation of innate immune cells leads to the release of cytokines and the presentation of melanocyte antigens to T cells, triggering the adaptive immune response. Activated $CD8^+$ T cells release cytotoxic substances such as perforin and granzyme, which directly target and kill melanocytes. Cytokines like IFN-γ can concurrently stimulate keratinocytes to produce chemokines such as CXCL9 and CXCL10, which further recruit additional T cells, establishing an inflammatory amplification loop. This loop leads to continuous damage of melanocytes and ultimately results in the development of vitiligo. PRR inhibitors target the initial phase of the immune response cascade in vitiligo, offering a more fundamental and precise therapeutic approach with potential advantages in controlling disease activity and preventing recurrence. This review provides an overview of current research regarding PRRs and their ligands in vitiligo pathogenesis, with a focus on potential therapeutic strategies.

Keywords: vitiligo, pattern recognition receptors, innate immunity, pathogenesis, damage-associated molecular patterns, pathogen-associated molecular patterns

Introduction

Vitiligo, an autoimmune disorder marked by the loss of melanocytes in specific regions, affects about 1% of the population and significantly influences psychological health and daily activities.[1,2] The pathogenesis is not fully understood, but oxidative stress, along with innate and adaptive immunity, is believed to be crucial, with innate immune activation possibly acting as an initiating factor.[3] Genetic and transcriptional studies of vitiligo lesions underscore the significant contribution of the innate immune response in the disease's pathogenesis.[4,5] PRRs play an essential role in the innate immunity and are involved in the pathogenesis of vitiligo. PRRs are crucial elements of innate immunity, acting as vital mediators. They detect pathogen-associated molecular patterns (PAMPs) to fight infections and identify damage-associated molecular patterns (DAMPs) from damaged or dying cells, aiding in host defense and tissue remodeling.[6] Both PAMPs and DAMPs can bind to PRRs of innate immune cells, inducing conformational changes that promote downstream signaling cascades, transcriptional regulation, and post-transcriptional modifications.[7] PRRs are categorized

Received: 16 October 2025
Accepted: 14 December 2025
Published: 20 December 2025

into five primary types based on protein domain homology: membrane-bound Toll-like receptors (TLRs) and C-type lectin receptors; cytoplasmic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) and retinoic acid-inducible gene I-like receptors; and intracellular DNA sensors. Beyond traditional PRRs, several non-PRR transmembrane proteins have been discovered, including the receptor for advanced glycation end products (RAGE), triggering receptors on myeloid cells, G protein-coupled receptors, and ion channels.[8] The innate immune system contains various PRRs capable of recognizing both intracellular and extracellular PAMPs and DAMPs. While PRRs play a crucial role in detecting and eliminating pathogens, their improper activation is linked to the development of vitiligo.[9]

In vitiligo patients, melanocytes and keratinocytes emit danger signals like HSP 70, HMGB1, calreticulin (CRT), and S100 calcium-binding protein B (S100B) due to internal and external factors, including oxidative stress, ultraviolet radiation, and chemical exposure.[10–13] Pattern recognition receptors (PRRs) detect "danger signals", triggering the initiation of an immune response. This activation recruits and stimulates innate immune cells, including pDCs, NK cells, and innate lymphoid cells (ILCs),[14,15] which then release type I and II interferons along with other immunologically active molecules. These events play a direct role in triggering long-term adaptive immunity against melanocytes.[14–16] From the perspective of the mechanism of melanocyte destruction, after PRRs activate the immune response, immune cells will attack melanocytes. For instance, activated T cells can directly kill melanocytes or indirectly destroy them through the release of perforin/granzymes.[17] The activation of PRRs in immune responses can create an inflammatory environment that may harm melanocyte survival and function, disrupting normal processes like melanin synthesis and transport.[18] This ultimately results in decreased melanocyte count, impaired function, and the characteristic white patches on the skin associated with vitiligo. From the perspective of disease progression, if the immune response mediated by PRRs persists and is overly active, cytokines such as IFN-γ will be continuously produced, inducing keratinocytes to generate chemokines like CXCL9 and CXCL10,[3] which further recruit more T cells, forming an inflammatory amplification loop. This leads to continuous damage to melanocytes and the continuous progression and deterioration of vitiligo. Exploring the contribution of PRRs in vitiligo may facilitate the progression of treatments that target this immune pathway. By modulating PRR activity, it is possible to precisely control immune response intensity, offering novel targets and strategies for vitiligo therapy.

Studies of vitiligo pathogenesis have emphasized that PRR-detected danger signals are associated with melanocyte stress and inflammation.[19,20] Previous reviews on the pathogenesis of vitiligo have predominantly centered on the adaptive immune system, particularly the role of $CD8^+$ T cells and related components in mediating targeted destruction of melanocytes. While innate immunity is occasionally mentioned, it is typically presented as a secondary or supportive element, with limited attention to its core molecular networks. The comprehensive regulatory axis of "danger signals (DAMPs/PAMPs) – PRRs – inflammation amplification loop" remains underexplored and insufficiently elucidated. Although accumulating evidence indicates that PRRs contribute to the pathogenesis of vitiligo, current reviews frequently fail to provide a systematic synthesis of the roles of major PRR families, including TLRs, NLRs, intracellular DNA sensors, and RAGE, in initiating and amplifying autoimmune responses against melanocytes. Furthermore, the therapeutic potential of targeting these receptors and their ligands remains underexplored. This review integrates recent findings on multiple PRR signaling pathways and their associated danger signals, highlighting the central role of innate immune activation in bridging oxidative stress and adaptive autoimmunity.

Methods

This review focuses on the PRRs and their relationship with the pathogenesis and therapeutic potential of vitiligo. A comprehensive literature search was conducted in databases including PubMed and Web of Science, restricted to English-language studies published between 2000 and 2025. Key search terms included "vitiligo," "pattern recognition receptors", "DAMPs", "PAMPs", and "innate immunity". Original research articles and high-quality reviews investigating the involvement of PRRs in mediating immune dysregulation, melanocyte injury, and targeted interventions were selectively included. Duplicate and marginally relevant publications were excluded through rigorous screening. Ultimately, over 80 articles were synthesized to analyze PRR-driven immune activation mechanisms, key signaling pathways, and their emerging implications for clinical translation.

Membrane-Bound Toll-Like Receptors

TLRs constitute a class of PRRs located on the cell membrane or within endosomal and lysosomal membranes. These receptors activate inflammatory responses by binding both intracellular and extracellular DAMPs and PAMPs.[21,22] *TLR2* Arg753Gln and *TLR4* Asp299Gly polymorphisms, as well as the SNP rs179020 in *TLR7* were confirmed involved in vitiligo pathogenesis through genome wide association studies.[23–25] In vitiligo, TLRs can be activated by HMGB1, HSP70, S100B, and lipopolysaccharide (LPS) (Figure 1). TLR signaling involves at least two distinct pathways: a MyD88-dependent pathway that drives the production of inflammatory cytokines, and a MyD88-independent pathway that drives the production of interferon (IFN)-β and promotes dendritic cell maturation. The activation of transcription factors such as nuclear factor-κB (NF-κB), activator protein 1, and interferon regulatory factor induces proinflammatory cytokine secretion.[26] TLR4 activation can inhibit melanin production in melanocytes.[18] TLR3 detects viral infections and the production of double-stranded RNA, triggering melanocyte apoptosis and a localized cellular immune response that promotes vitiligo progression.[27]

DAMPs

HMGB1

HMGB1, a non-histone chromatin-binding protein in eukaryotic cell nuclei, is involved in DNA repair and maintaining genomic stability. HMGB1, part of the HMG protein family, is characterized by its rapid migration and non-aggregation in polyacrylamide gel electrophoresis.[28] Intracellular HMGB1 regulates transcriptional repair and recombination by modifying chromosomal structure.[29] HMGB1 is typically found in the cell nucleus in normal physiological states, where it is crucial for chromatin structure maintenance.HMGB1 is released into the extracellular space during cell necrosis, the late stages of apoptosis, or cellular stress, functioning as a "danger signal" and proinflammatory mediator by interacting with cell surface receptors like RAGE, TLR2, and TLR4 on target cells.[30,31] Recent researches indicate that HMGB1 is upregulated in the peripheral blood and lesional specimens of vitiligo patients.[10,32–34] External stressors, such as oxidative stress and ultraviolet B radiation, prompt keratinocytes to release HMGB1,[10,35,36] thereby influencing the survival of melanocytes and the expression of molecules related to melanin biosynthesis.[33] In addition, HMGB1 activates the nuclear factor-kappa B (NF-κB) signaling pathway, which in turn promotes the production of chemokines, enhancing chemokine production such as CXCL16 and IL-8, which subsequently induce the migration of $CD8^+$ T cells.[10] There is also evidence indicating that oxidative stress can trigger the autocrine translocation and release of HMGB1 in melanocytes, which suppresses the expression of nuclear factor erythroid 2-related factor 2 (Nrf2) and its downstream antioxidant genes, ultimately resulting in melanocyte apoptosis.[37] HMGB1-induced melanocyte autophagy could be significant in the pathogenesis.[38] It is worth noting that some drugs used in the treatment of vitiligo, such as folic acid, pioglitazone and compound glycyrrhizin, have been confirmed to downregulate the expression of HMGB1.[39–41]

To summarize, HMGB1 is released by melanocytes and keratinocytes under oxidative stress and UV exposure in vitiligo. It binds RAGE and TLR2/4, activating NF-κB to promote CXCL16 and IL-8 production, recruiting $CD8^+$ T cells that damage melanocytes. HMGB1 also suppresses Nrf2 and downstream antioxidant genes, inducing melanocyte apoptosis, and may contribute to disease progression through autophagy.

HSP70

Heat shock proteins (HSPs) function as protein-folding chaperones that are induced by cellular stress and activation of the unfolded protein response. These proteins prevent misfolding and aggregation under stress conditions, thereby exerting cytoprotective effects. However, during inflammation, injured or necrotic cells release HSPs, which serve as intermediaries between stressors and autoimmune responses.[42] Research on HSP70 gene variations in non-segmental vitiligo patients indicates that the C allele of HSPA1L rs2227956 and the GAC haplotype, which includes this allele, are linked to a decreased risk of developing vitiligo.[43] Previous Research has also demonstrated that HSP70 is upregulated in vitiligo patients,[44] with its expression linked to disease activity.[45] Melanocyte-derived inducible HSP70 (iHSP70) enhances dendritic cell activation and accelerates depigmentation in a vitiligo mouse model.[12,46] In patients with advanced vitiligo, mechanical friction or high-intensity light stimulation induces keratinocytes to release HSP70, whereas

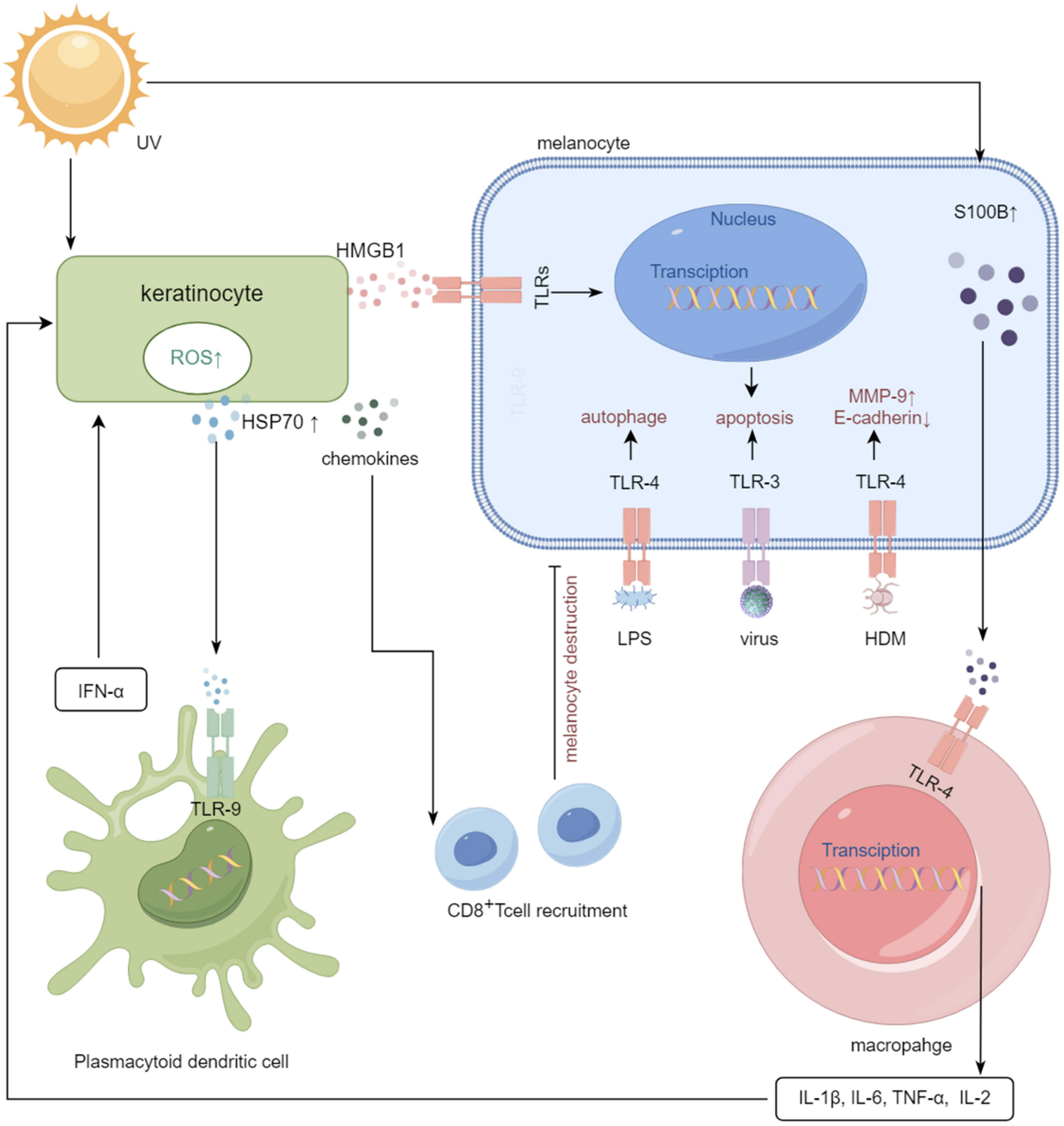

Figure 1 The roles of TLRs and their ligands in vitiligo pathogenesis. UV radiation stimulates keratinocytes to secrete HMGB1 and HSP70. HMGB1 binds to TLR2 and TLR4, inducing melanocyte apoptosis. HSP70 enhances TLR9 activation in pDCs, leading to IFN-α production, which subsequently acts on keratinocytes to promote the secretion of chemokines such as CXCL9 and CXCL10. This cascade facilitates $CD8^+$ T cell migration and mediates melanocyte destruction. Melanocytes produce and release high levels of S100B under UV stress, which stimulates macrophages via TLR4 and ROS to secrete IL-1β, IL-6, TNF-α, and IL-2. ROS further induce chemokine production in keratinocytes. Exogenous LPS binds to TLR4 and upregulates its expression on melanocytes. This interaction increases IL-6 and IL-8 secretion and activates autophagy. HDMs upregulate TLR4, activate MMP-9, downregulate E-cadherin, and induce melanocyte detachment in previously healthy skin. TLR3 detects viral infections and the production of double-stranded RNA, triggering melanocyte apoptosis. This figure illustrates how diverse environmental triggers converge on TLR pathways to initiate autoimmunity and melanocyte death, highlighting potential therapeutic targets to intercept disease initiation.
Abbreviations: UV, ultraviolet radiation; ROS, reactive oxygen species; pDCs, plasmacytoid dendritic cells; HDMs, house dust mites; MMP-9, metalloproteinase-9.

TLR9-activated plasmacytoid dendritic cells produce IFN-α to promote $CD8^+$ T cell migration.[16] Interestingly, bilobalide has been shown to protect melanocytes from oxidative damage by inhibiting H_2O_2-induced apoptosis and reducing autoimmune responses, achieved through decreased HSP 70 release.[47]

In conclusion, extracellular HSP70, released by melanocytes and keratinocytes, activates dendritic cells and $CD8^+$ T cells, thereby promoting autoimmune responses and accelerating depigmentation in vitiligo.

S100B

The S100 protein is a dimeric protein composed of S100β and S100α subunits. When passively released into the extracellular space, it initiates downstream inflammatory responses by interacting with the receptors RAGE and TLR4. Because of its detectability in bodily fluids, S100 protein serves as a biomarker for specific diseases.[48] S100B, a member of the S100 protein family, is found in several cell types, including melanocytes, and serves as an indicator of melanocyte cytotoxicity. Serum S100B levels were significantly higher in patients with non-segmental vitiligo and correlated with the extent of body surface area affected.[49] There is increasing recognition of an association between S100B level and vitiligo disease activity.[50,51] S100B at low concentrations safeguards melanocytes by inhibiting p53 and averting apoptosis through activation of the phosphoinositide-3 kinase (PI3K)/protein kinase B (AKT) pathway.[11] Conversely, Niven et al demonstrated that melanocytes produce large quantities of extracellular S100B, which in turn prompts macrophages to release proinflammatory cytokines, including IL-1β, IL-6, tumor necrosis factor (TNF)-α, and IL-2.[52] These cytokines induce reactive oxygen species, prompting keratinocytes to generate chemokines that attract cytotoxic $CD8^+$ T cells to the skin, resulting in melanocyte destruction.[53] However, the relationship between its concentration and the severity of vitiligo has yet to be fully elucidated,[54] although the latest research shows that the S100B level in vitiligo patients has a weak correlation with the Vitiligo European Task Force (VETF) scoring.[55]

To conclude, low concentrations of S100B protect melanocytes through activation of the PI3K/AKT pathway; however, under pathological conditions, excessive extracellular S100B acts as a DAMP signal. By engaging its receptors, including TLR4, it triggers innate immune activation, stimulates macrophages to release pro-inflammatory cytokines, and ultimately promotes $CD8^+$ T cell–mediated autoimmune responses, resulting in melanocyte destruction.

PAMPs

Lipopolysaccharide (LPS)

LPS, an integral component of the outer membrane of gram-negative bacteria, is firmly embedded in the bacterial cell wall. Its most well-characterized biological activity involves macrophage activation, which facilitates infection prevention, wound healing, and metabolic regulation.[56] LPS interacts with melanocytes by binding to and upregulating TLR4. Subsequently, melanocytes enhance the secretion of IL-6 and IL-8, trigger autophagy, and downregulate melanogenesis-related proteins such as microphthalmia-associated transcription factor, premelanosome protein, and tyrosinase, thereby inhibiting melanogenesis.[57]

House Dust Mites (HDMs)

HDMs (*Demodex*) are the largest and most complex organisms in the human skin microbiota; they ubiquitously reside in hair follicles and sebaceous glands of normal adult skin. HDMs have been implicated in atopic dermatitis, acne, and rosacea.[58,59] They comprise potent allergens, proteases, along with bacterial cell wall components (such as LPS) and fungal cell wall components (such as β-D-glucan). Although these components can penetrate the skin, their capacities to stimulate inflammatory factor production or alter melanocyte function and adhesion remain unclear. HDMs induce the production of chemokines (C-X-C motif chemokine ligand [CXCL]1, CXCL5, CXCL9, CXCL10, and CXCL12), chemokine receptors (C-C motif chemokine ligand [CCL]3, CCL7, CCL17, and CCL20), and cytokines (IL-1α, IL-8, IFN-γ, migratory inhibition factor, granulocyte-macrophage colony-stimulating factor, IL-5, IL-10, IL-24, and IL-17A). Moreover, TLR4 expression is upregulated, matrix metalloproteinase-9 (MMP-9) is activated, E-cadherin is downregulated, and melanocyte detachment is induced in healthy skin upon exposure to house dust mites (HDMs).[60] MMP-9 inhibitors could serve as an effective therapeutic strategy.

Cytoplasmic NLRs

NLRs are highly conserved cytoplasmic PRRs that play crucial roles in innate immune responses. In humans, 22 NLRs have been identified; mutations or SNPs in their genes have been associated with various diseases, highlighting their

importance in host defense.[61] In the NLR family, pyrin domain-containing proteins (including NLRP1, NLRP3, NLRP6, NLRP7, NLRP12), caspase recruitment domain-containing protein 4 (NLRC4), and neuronal apoptosis inhibitory protein all exert their functions via inflammasomes. By contrast, other NLR members—such as NOD1, NOD2, NLRP10, domain-like receptor X1 (NLRX1), NLRC5, and class II transactivator—fail to directly activate inflammatory caspases. Instead, they trigger the activation of NF-κB, MAPK, as well as interferon regulatory factor, which in turn modulates innate immunity.[62] Patients with vitiligo exhibit intestinal microbiota dysbiosis, and the NOD-like receptor signaling pathway may contribute to the pathogenesis of the disease. However, direct supporting evidence remains limited. Previous metagenomic sequencing of the gut microbiota in patients with vitiligo, followed by KEGG functional analysis, revealed enrichment of the NOD-like receptor signaling pathway in these individuals.[63] We propose that, under the pathological conditions of vitiligo, hydrolytic fragments and metabolites derived from intestinal microbiota may aberrantly activate the NOD signaling pathway, thereby disrupting immune homeostasis. These dysregulated immune signals could be propagated via the gut-skin axis to the skin, triggering localized immune attack and ultimately resulting in melanocyte damage.[63–65]

For patients with non-segmental vitiligo, their skin lesions exhibit a notable association between NLRP1, IL-1β, and the advancement of the disease.[66] The results of a genetic association analysis further suggested that the SNP rs2670660 in *NLRP1* is linked to an increased risk of non-segmental vitiligo.[67] In another study, it was observed that the NLRP1 inflammasome was activated in Langerhans cells within vitiligo lesions.[68] Under stress conditions, the NLRP1 inflammasome may undergo assembly via the PYD-ASC-CARD signaling axis; this assembly then induces keratinocytes to secrete inflammatory factors like IL-1β, which in turn enhances local inflammatory responses and worsens melanocyte damage.[61,69] Notably, NLRP3 has been confirmed to play a distinct role in vitiligo pathogenesis. Research has confirmed that NLRP3 and IL-1β are substantially upregulated in perifocal keratinocytes of vitiligo patients—a finding that points to the activation of the NLRP3 inflammasome as a critical driver of disease progression. Additionally, it is proposed that oxidative stress triggers TRPM2 (transient receptor potential cation channel subfamily M member 2)-mediated calcium influx into the cytoplasm and mitochondria of keratinocytes; this influx then activates NLRP3 inflammasomes and enhances cutaneous T-cell responses.[70] Additionally, NLRP3 inflammasome activation can be triggered by elevated extracellular adenosine triphosphate (ATP) levels[71,72] (Figure 2).

Extracellular Adenosine Triphosphate (ATP)

During inflammatory responses, extracellular ATP is released by damaged parenchymal cells, dying leukocytes, and activated platelets. This extracellular ATP directly triggers the activation of the plasma membrane channel P2X7 receptor (P2X7R), which in turn induces intracellular K^+ influx and the subsequent the activation process of the NLRP3 inflammasome.[71] In vitro experiments have shown that oxidative damage induced by H_2O_2 promotes the release of ATP from keratinocytes and skin tissue. When ATP binds to the P2X7R, it facilitates the activation of caspase-1 as well as the secretion of IL-1β and IL-18—findings that imply this process may contribute to inflammasome activation in patients with vitiligo. Additionally, an increase in CXCL9 secretion by keratinocytes was detected, and this elevated CXCL9 further promotes the migration of $CD8^+$ T cells into the epidermis.[72]

Intracellular DNA Sensors

Intracellular DNA sensors, a type of pattern recognition receptors (PRRs), are found within the cytoplasm or other cellular compartments like endosomes. Their main role is to identify abnormal or misplaced DNA in cells as a "danger signal", including the generation of type I interferons and inflammatory cytokines, to combat infection, cellular stress, or tissue damage. A variety of key intracellular DNA sensors have been identified, each acting through distinct signaling pathways. Among these pathways, the cGAS-STING pathway stands out as the antiviral DNA-sensing mechanism with the most well-defined characteristics and the broadest research coverage; it is also widely recognized as a central element of the innate immune response.[73] The cGAS-STING axis represents a central pathway in innate immunity. Upon detection of abnormal double-stranded DNA—whether of viral origin or derived from cellular damage—in the cytoplasm, the cGAS protein recognizes this threat and synthesizes the second messenger cGAMP. This molecule activates the STING protein, initiating a signaling cascade that results in the production of type I interferons and inflammatory

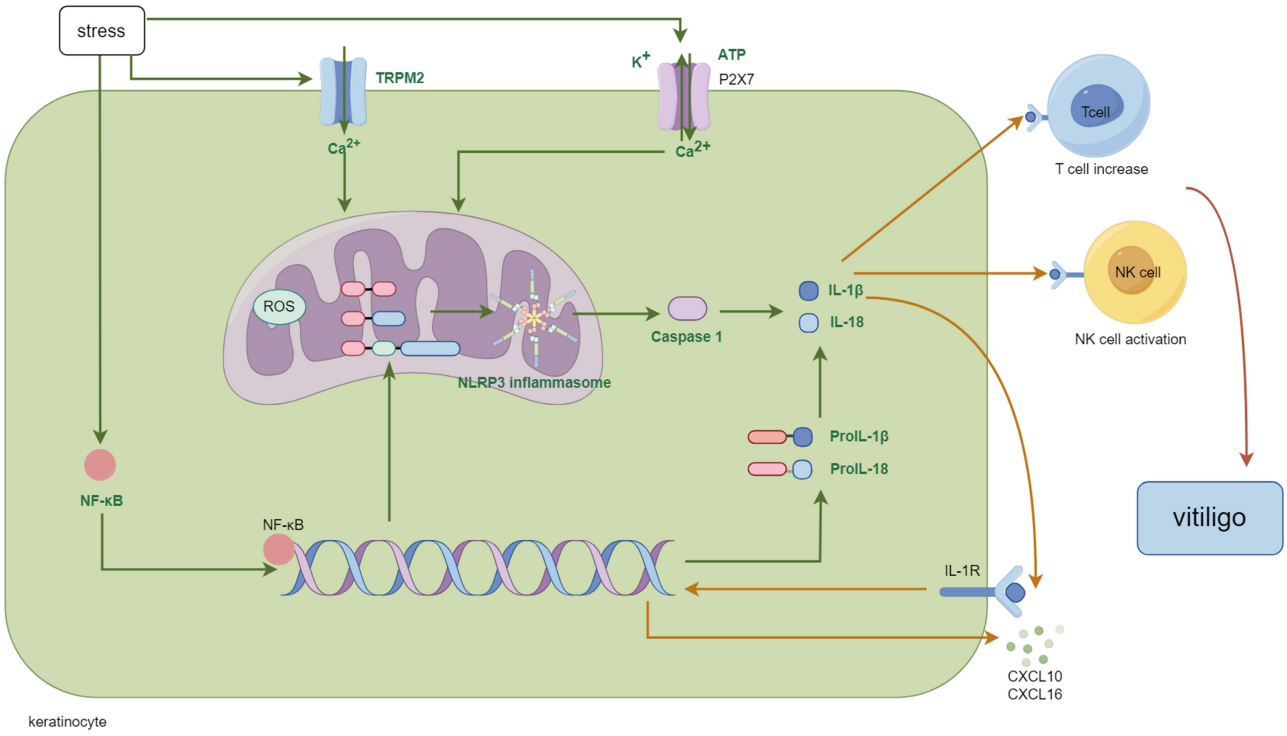

Figure 2 The role of NLRP3 in vitiligo pathogenesis. Under stress conditions, NF-κB signaling is activated, leading to upregulation of NLRP3 expression in keratinocytes. NLRP3 inflammasome activation depends on TRPM2-mediated intracellular and mitochondrial calcium influx, as well as mtROS production. Extracellular ATP, released under stress conditions, binds to P2X7R on keratinocyte surfaces to facilitate potassium efflux and calcium influx. This process induces NLRP3 oligomerization, resulting in inflammasome formation, caspase-1 activation, and enhanced IL-1β and IL-18 secretion. IL-1β enhances CXCL10 and CXCL16 release from keratinocytes; it also acts directly on downstream T cells and natural killer cells. This cascade ultimately initiates an autoimmune attack by $CD8^+$ T cells against melanocytes. This figure delineates the NLRP3 inflammasome as a central driver of autoimmune priming in vitiligo, identifying actionable targets for mitigating inflammatory and cytotoxic responses in patient care.
Abbreviations: NF-κB, nuclear factor-κB; NLRP3, NOD-like receptor family pyrin domain-containing 3; TRPM2, transient receptor potential cation channel subfamily M member 2; ATP, adenosine 5′-triphosphate; mtROS, mitochondria reactive oxygen species; P2X7R, P2X7 receptor; IL-1β, interleukin-1β; IL-18, interleukin-18; CXCL10, C-X-C motif chemokine ligand 10; CXCL16, C-X-C motif chemokine ligand16.

cytokines. These responses are critical for combating infections and activating immune surveillance. Nonetheless, overactivation of this pathway could lead to autoimmune disease development.[74] Mitochondrial DNA (mtDNA), released from damaged mitochondria, is extensively studied due to its distinct localization and bacterial-like CpG islands that promote its release and recognition. In vitiligo, a proportion of patients' melanocytes harbor numerous somatic mtDNA mutations. Elevated reactive oxygen species (ROS) lead to the release of mtDNAs into the cytoplasm, which activates the cGAS-STING pathway and triggers the production of type I interferons and inflammatory cytokines like CXCL9 and CXCL10. These signaling molecules attract $CD8^+$ T cells, triggering autoimmune responses.[75] Additionally, the pathway reduces the quantity and functionality of regulatory T cells (Tregs), facilitating autoimmune attacks on melanocytes and hastening disease progression.[76] In addition, studies have demonstrated that cytosolic mtDNA triggers the activation of the cGAS-STING axis; this axis then initiates pyroptosis in a manner dependent on the NLRP3/Caspase-1/GSDMD signaling pathway. This process leads to the secretion of IL-1β and IL-18 from melanocytes, which in turn enhances both the activation and cytotoxic activity of $CD8^+$ T cells in affected individuals.[77] These results establish a direct connection between oxidative stress and autoimmune responses, emphasizing the pivotal role of the mtDNA-cGAS-STING pathway in triggering vitiligo.

In summary, Oxidative stress induces mitochondrial damage in melanocytes, leading to the release of mtDNA into the cytosol. This aberrant mtDNA is sensed by intracellular DNA sensors, activating the cGAS-STING pathway, which drives the production of type I interferons and chemokines such as CXCL9 and CXCL10. These factors promote $CD8^+$ T cell recruitment while impairing the number and function of regulatory T cells. Concurrently, mtDNA triggers melanocyte pyroptosis via the NLRP3/Caspase-1/GSDMD pathway, thereby initiating and amplifying the autoimmune response against melanocytes.

RAGE

RAGE was first recognized for binding advanced glycation end products, playing a role in inflammation and vascular complications associated with diabetes. RAGE is a 35-kDa transmembrane protein with multiple ligands; it consists of 404 amino acids and is made up of three key domains: the cytoplasmic domain, the extracellular domain, and the transmembrane domain. Through binding to downstream signaling effectors (eg, Toll-interleukin 1 receptor domain adaptor protein, hyaluronan-associated formamin-1, extracellular signal-regulated kinases), the cytoplasmic domain of RAGE triggers the activation of the MAPK pathway. Because RAGE plays a role in oxidative stress and inflammation—two processes that lead to impaired cellular function—its signaling pathway is connected to conditions including cancer, diabetes, cardiovascular disease, and neurodegenerative disorders.[78,79] Research indicates that HMGB1 translocates to the cytoplasm in melanocytes near vitiligo-affected skin. Subsequently, the serum HMGB1 (high mobility group box 1 protein) levels of patients with vitiligo were quantified using enzyme-linked immunosorbent assays. The study found significantly elevated HMGB1 levels in patients with active progressive disease compared to those with slow disease progression or healthy controls. Melanocyte-secreted HMGB1, in response to oxidative stress, enhances CXCL16 and IL-8 secretion from keratinocytes through RAGE, leading to $CD8^+$ T cell infiltration and dendritic cell maturation in the skin. The study also demonstrated that RAGE expression was specifically increased in vitiligo lesions and in keratinocytes exposed to recombinant human HMGB1 (rhHMGB1). Additionally, RAGE knockdown significantly reduced CXCL16 and IL-8 production in rhHMGB1-treated keratinocytes. These findings indicate that in the keratinocytes of vitiligo patients, RAGE acts as PRR that mediates the pro-inflammatory effects of HMGB1.[10]

In short, HMGB1 released by melanocytes activates RAGE on keratinocytes, inducing the secretion of CXCL16 and IL-8. These chemokines recruit $CD8^+$ T cells and promote dendritic cell maturation, thereby facilitating the initiation and progression of an autoimmune attack against melanocytes.

PRR Inhibitors

Considering that PRRs play a central role in driving the pathogenesis of vitiligo, PRR inhibitors have the potential to inhibit both the onset and progression of the disease by disrupting the DAMPs/PAMPs-PRRs-inflammation/immune cascade. The primary mechanism of action of PRR inhibitors involves modulating receptor activity and specifically disrupting the interaction between PRRs and their cognate ligands, thereby attenuating downstream inflammatory and immune signaling pathways.[80,81]

Several PRR inhibitors are currently in clinical development, with therapeutic applications being evaluated across a spectrum of immune-mediated and inflammatory conditions. Notably, the TLR4 antagonist ApTOLL has progressed to clinical trials for COVID-19 and acute ischemic stroke, where it aims to mitigate disease severity by suppressing TLR4 mediated hyperinflammatory responses. Meanwhile, the multi-target TLR7/8/9 antagonist IMO-8400 is under investigation for autoimmune skin disorders such as psoriasis and dermatomyositis, offering a novel targeted approach for the management of these refractory conditions.[82,83] Numerous studies have been conducted on inhibitory strategies targeting the NLRP3 inflammasome, revealing a multi-faceted landscape of intervention targets and technical approaches. These include suppression of upstream transcriptional activation, modulation of post-translational modifications, inhibition of downstream effector molecules such as IL-1β and caspase-1, and direct targeting of NLRP3 by small-molecule inhibitors.[84] Among representative compounds, MCC950 has demonstrated robust therapeutic efficacy in mouse models of multiple NLRP3-driven diseases, including cryopyrin-associated periodic syndrome (CAPS), Alzheimer's disease, and myocardial infarction. However, its development was discontinued after Phase II clinical trials due to safety concerns associated with elevated liver enzymes.[84] Another inhibitor, OLT1177, has advanced into clinical evaluation and is currently undergoing validation for the treatment of acute gout flares and heart failure.[85]

PPR inhibitors offer a novel targeted therapeutic option for vitiligo patients who exhibit inadequate response to JAK inhibitors. By acting on an upstream node in the inflammatory cascade, these inhibitors may be particularly effective in patients experiencing rapid disease progression, a phase characterized by substantial release of DAMPs and robust activation of the innate immune system. Although the safety profile of PRR inhibitors currently lags behind that of conventional phototherapy, the risk of systemic adverse effects, such as hepatotoxicity and increased susceptibility to

infections, can be mitigated through the development and application of targeted drug delivery systems[82] or topical formulations. Notably, research on PPR inhibitors for vitiligo treatment remains in its early stages. To date, no mature clinical trial data are available to confirm the efficacy of PRR pathway inhibition in promoting repigmentation of vitiligo lesions. Therefore, the clinical translatability and therapeutic potential of PPR inhibitors require further validation in well-designed preclinical and clinical studies.

Conclusion

Vitiligo is a prevalent autoimmune disease that substantially impacts the mental health of affected individuals. Although the part of adaptive immunity in disease progression is well-recognized, the initial triggers remain largely unknown. In recent years, increasing attention has been directed toward the roles of PRRs and their ligands in vitiligo pathogenesis and progression. There is evidence that exogenous PAMPs and endogenous DAMPs, produced and released by stressed melanocytes and keratinocytes, activate the innate immune system via PRRs. This activation initiates danger signals, triggers downstream inflammatory pathways, and activates the adaptive immune system, ultimately leading to vitiligo onset and progression. However, the mechanisms underlying PRR activation remain incompletely understood and highly complex. Further research is required to elucidate vitiligo pathogenesis and provide prevention and treatment insights that would facilitate the development of safer and more effective therapeutic strategies. Future investigations should focus on clarifying the interplay of melanocyte stress responses with innate and adaptive immune mechanisms.

Ethical Approval

This article does not contain any studies with human participants or animals.

Acknowledgments

We thank Ryan Chastain-Gross, Ph.D., from Liwen Bianji (Edanz) (https://www.liwenbianji.cn/) for polishing the English version of this article draft. All the figures in the manuscript were drawn in Figdraw.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This work was supported by National High Level Hospital Clinical Research Funding (2022-PUMCH-B-092, to Tao Wang), Beijing Municipal Natural Science Foundation (Z210017, to Tao Wang), Beijing Key Clinical Specialty Construction Project and National Key Clinical Specialty Project of China.

Disclosure

The authors, Jin-di Feng, Lu Lu, Hui-min He, Yu-bin Peng, Shi-yu Zhang, Lu Yang, Yue-hua Liu, and Tao Wang, declare no conflicts of interest related to this article.

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