See related commentary on pg 1547

Focusing on the Dark Side of the Moon: Involvement of the Nonlesional Skin in Vitiligo

JID Open

Meri K. Tulic[1], Daniela Kovacs[2], Emanuela Bastonini[2], Stefania Briganti[2], Thierry Passeron[1,3] and Mauro Picardo[4]

Research over the last decade has revealed that the normally pigmented skin of patients with vitiligo is not normal at all, as evidenced by alterations in cutaneous morphology and modifications in cellular and metabolic functions that ultimately drive immune activation against melanocytes. Furthermore, nonlesional skin is in a state of subclinical inflammation until triggered by internal and/or external exposomal events. Therefore, targeting early processes that drive immune dysregulation in normally pigmented skin may avoid or reduce melanocyte loss. Thus, shifting the focus to nonlesional skin may prevent the appearance of clinical manifestations of the disease rather than treating the lesions.

Keywords: Cell metabolism, Innate immunity, Nonlesional skin, Vitiligo, Vitiligo treatment

Journal of Investigative Dermatology (2025) **145,** 1612–1621; doi:10.1016/j.jid.2024.10.598

Vitiligo is a complex autoimmune skin disease characterized by the loss of melanin-producing melanocytes, resulting in appearance of white patches. It is the most common depigmenting disorder, affecting ~1% of world population. Its incidence is not restricted by ethnicity or geographical region. Although the disease is not fatal, patients have reduced QOL and struggle with mental well-being owing to their enduring stigmatization and social isolation. Research over the last 20 years has significantly improved our understanding concerning vitiligo pathophysiology. To date, we know that vitiligo is a chronic, multifactorial skin disease whose pathogenesis involves a convergence of genetic, autoimmune, environmental (exposomal), and metabolic factors. Owing to this complexity, the disease and its treatment represent a challenge for the dermatologists; however, there may exist a potential solution if we shift our focus to 'the dark side of the moon,' that is, the normal-appearing, nonlesional (NL) skin of subjects with vitiligo.

THE ABNORMALITY OF NL, 'NORMAL-APPEARING' SKIN IN PATIENTS WITH VITILIGO

Accumulating evidence suggests that the NL, normal-appearing pigmented skin is not normal at all (Figure 1). We know that compared with healthy skin, NL skin has increased epidermal thickness and altered expression of E-cadherin (adhesion protein critical in anchoring melanocytes to the basement membrane), and it displays evidence of inflammation and cellular alterations similar to what is reported in lesional, depigmented areas. In addition, there are intrinsic defects in NL melanocytes, keratinocytes, and fibroblasts that include not only changes in their morphology and physiology but also dysregulation in their differentiation and immune and metabolic function (Bastonini et al, 2019; Bellei et al, 2013; Kovacs et al, 2022, 2018; Wu et al, 2024). NL skin is the site of dysregulated cutaneous immunity with increased presence of not only innate immune cells such as NK and type 1 innate lymphoid cells but also long-term effectors, that is, activated cytotoxic $CD8^+$ T cells and resident memory T cells (TRMs); the latter of which have been shown to have a similar transcriptional profile as those found in the perilesional (PL) (normal-appearing skin just outside of the lesional site) and lesional sites (Migayron et al, 2024). Furthermore, T-cell clones in NL and PL skin have been shown to have similar antigen specificity, and after in situ activation, resident T cells in NL areas seem to have comparable function. This evidence suggests that NL site is in a state of subclinical inflammation until triggered by internal and/or external events. It has been proposed that the dormant state of TRMs in NL skin may be controlled by their expression of immune checkpoint receptors such as PD-1, CTLA-4, LAG-3, and/or TIM-3 (Migayron et al, 2024). For all these reasons, the attention should be turned toward the dark side of the skin of patiens with vitiligo as a target for future interventions. To achieve this goal, we should identify the initial events driving immune dysregulation to be able to halt or even better, to prevent subsequent antimelanocytic immunity at NL sites. Targeting these early steps is critical to avoid melanocyte loss and/or reduce vitiligo flares leading to skin depigmentation.

[1]*Team 12, University of Cote d'Azur, INSERM U1065, Mediterranean Centre for Molecular Medicine, Nice, France;* [2]*Laboratory of Cutaneous Physiopathology and Integrated Center of Metabolomics Research, San Gallicano Dermatological Institute, IRCCS, Rome, Italy;* [3]*Dermatology Department, University Hospital (CHU), University of Cote d'Azur, Nice, France; and* [4]*Immaculate Institute of Dermatopathology and Scientific Institute of Recovery, Hospitalisation and Cure (IDI-IRCCS), Rome, Italy*

Correspondence: Meri K. Tulic, Team 12, INSERM U1065, Centre Méditerranéen de Médecine Moléculaire (C3M), Université Nice Côte d'Azur, 151 route Saint-Antoine de Ginestière, Nice 06200, France. E-mail: meri.tulic@unice.fr

Abbreviations: ALA, alpha-linolenic acid; CER, ceramide; CHS, cholesterol sulphate; FA, fatty acid; HDM, house dust mite; MMP-9, matrix metalloproteinase-9; NL, nonlesional; PL, perilesional; SC, stratum corneum; SOD, superoxide dismutase; STAT, signal transducer and activator of transcription; Th, T helper; TRM, resident memory T cell

Received 2 July 2024; revised 14 October 2024; accepted 17 October 2024; corrected proof published online 20 December 2024

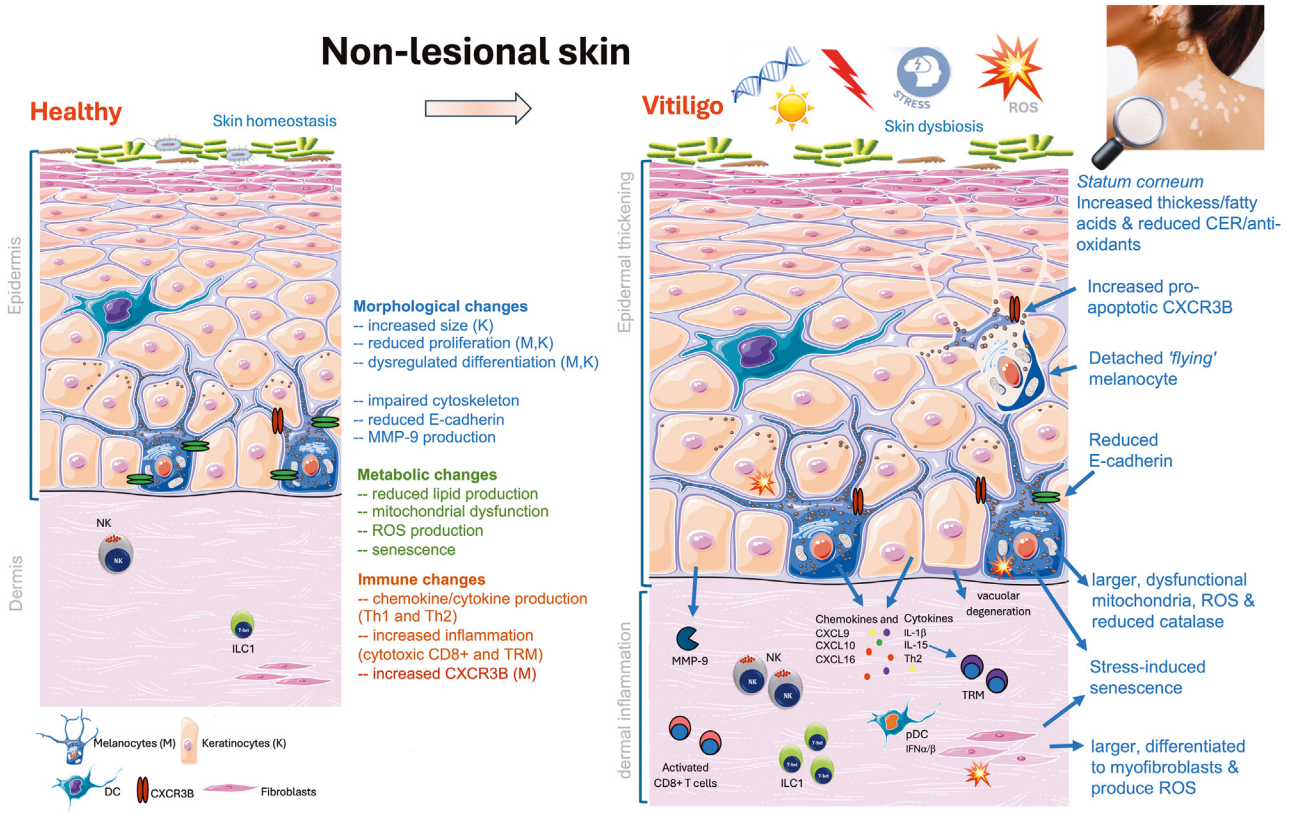

Figure 1. Changes in nonlesional skin of patients with vitiligo. Shown are healthy skin (left) and normal-appearing, nonlesional skin (right) of patients with vitiligo depicting morphologic, immune, and metabolic changes. DC, dendritic cell; ILC1, innate lymphoid cell 1; MMP-9, matrix metalloproteinase 9; pDC, plasmacytoid dendritic cell; Th1, T helper 1; Th2, T helper 2.

MELANOCYTES ARE NOT THE VICTIMS BUT ACTIVE PARTICIPANTS

Traditional way of looking at vitiligo is to understand the pathophysiology and mechanisms driving the loss of melanocytes, focusing on the lesional and PL sites where there is presence of $CD8^+$ cytotoxic T cells directed against melanocytes and accumulation of TRMs, which maintain local cutaneous memory response. As a result, growing knowledge was obtained over the years on the functional characterization of melanocytes, which have been traditionally considered the leading players of the disease. At NL sites, we already know that melanocytes are more fragile than melanocytes in normal skin, detach easier from the basal layer of epidermis, and are more prone to apoptosis. This is the reason why there is an increased number of suprabasal melanocytes found in NL vitiligo skin compared with that in healthy skin, which is supported by the melanocytorrhagy theory (Gauthier et al, 2003). Moreover, we now know that melanocytes are not simply bystanders or the victims of inflammation, but they directly and actively contribute and participate in the cutaneous inflammatory process. Latest data demonstrate that melanocytes from patients with vitiligo produce not only T helper (Th)1 but also Th2 cytokines and chemokines, which again increases their complexities (Martins et al, 2022). Furthermore, Le Poole et al (1993) have shown more than 30 years ago that melanocytes have antigen-processing and -presenting function, capable of being direct target cells for T-cell–mediated cytotoxicity. More recently, interest has been turned towards other local skin populations such as keratinocytes and fibroblasts, to examine their own intrinsic abnormalities compared with their healthy counterparts and, importantly, to study how these impairments impact cutaneous microenvironment and ultimately the fate of melanocytes.

CONTRIBUTION OF KERATINOCYTES TO MELANOCYTE DESTRUCTION

Keratinocytes outnumber melanocytes by 40:1, and they play a decisive pathogenetic role for melanocytes. This is because in the presence of stress-related stimuli or inflammatory messengers, including ROS and/or IFN-γ, keratinocytes are major producers of chemokines CXCL-9, CXCL-10, and CXCL-16, which promote the local recruitment of autoreactive cytotoxic T cells that directly attack melanocytes (Li et al, 2017; Richmond et al, 2017). We demonstrated that keratinocytes extracted from the NL skin of patients with vitiligo produce high constitutive levels of inflammatory mediators, particularly IL-1β and CXCL10, compared with keratinocytes from normal skin, and this production is further increased after moderate mechanical stress (Kovacs et al, 2022). Consequently, keratinocyte dysfunctions may render vitiligo skin more vulnerable against environmental injuries and promote the onset of a persistent local inflammatory milieu, which in turn may favor the activation of the autoimmune reactions that ultimately destroy melanocytes (Kovacs et al, 2022). In line with these data, increased expression of

CXCL10 and presence of activated $CD8^+$ T cells have been reported at NL sites (Gellatly et al, 2021; Wagner et al, 2015), indicating low-level immune activation even in unaffected skin. Defective keratinocytes can constitute the causative factors for the onset of new lesions in uninvolved skin after different types of nonspecific mild injuries, for example, mechanical, physical, chemical trauma defined as Koebner phenomenon (van Geel et al, 2011). Proof that vitiligo keratinocytes from NL skin show alterations at multiple levels, including morphologic, metabolic, and functional abnormalities, is constantly increasing. NL keratinocytes revealed early onset of p16 expression in comparison with the involved ones (Bondanza et al, 2007). We highlighted that cultured NL keratinocytes display enlarged morphology, reduced growth, and deregulated expression of proteins and enzymes associated with their differentiation process and their metabolism of epidermal lipids. Moreover, keratinocytes present an impaired cytoskeleton arrangement in association with low expression and a modified distribution of the cell—cell adhesion protein E-cadherin (Kovacs et al, 2022). Alterations in E-cadherin expression has been directly involved in melanocyte loss (Gauthier et al, 2003). Employing in vitro and in vivo models, Boukhedouni et al (2020) demonstrated that the disruption of E-cadherin expression with its cleavage into a soluble form appears to be mediated by the matrix metalloproteinase-9 (MMP-9).

DYSBIOSIS IN NORMAL-APPEARING VITILIGO SKIN

Along with inflammation and structural changes, we have previously reported skin dysbiosis in NL skin of patients with vitiligo (Bzioueche et al, 2021). In that study, we have shown dysregulation in the amount and diversity of bacterial species at NL sites compared with that in the healthy skin, with loss of protective commensals and enrichment of pathogenic bacteria. Dysbiosis of microbiota and alteration of the epidermal homeostasis can compromise the gut epithelial barrier and can negatively impact the host immune system and metabolism. These modifications can be driven by vitiligo keratinocytes at NL sites who are now known to have abnormal lipid production (Kovacs et al, 2022), which are critical for the growth of a number of different bacterial species. It can also be due to the direct impact in changes in microbial flora. One of the prominent components of the cutaneous microflora (particularly the hair follicles) are the skin mites. When in excess, they have been shown to exacerbate atopic dermatitis (Maeda et al, 1992) and *rosacea*, dermatitis-like lesions due to *Demodex folliculorum* (Aktaş Karabay and Aksu Çerman, 2020). We have recently demonstrated that the ubiquitous environmental house dust mites (HDMs) can be an initial trigger driving vitiligo-like pathology because it can induce melanocyte detachment in healthy human skin through its potent *Der p1* protease activity, which drives E-cadherin degradation by activation of MMP-9 (Bzioueche et al, 2023a). Keratinocytes extracted from NL skin of subjects with vitiligo were 10—100-fold more sensitive to HDM than keratinocytes from healthy individuals, and keratinocyte conditioned media had a direct effect on melanocyte immunity, detachment, and viability. Our clinical study has demonstrated that these HDM-induced detrimental changes in the skin can be repaired and skin function restored using ceramides (CERs)-containing creams (Bzioueche et al, 2023b). Together, these data suggest that cutaneous mites can trigger and/or exacerbate flares in susceptible patients. It remains to be tested whether individuals who display skin sensitization to HDM are also more likely to respond to HDM and therefore may contribute to explaining the link between vitiligo and allergic skin diseases such as atopic dermatitis and eczema (Eleftheriadou et al, 2024).

OXIDATIVE STRESS IN NL SKIN

In vitro and in vivo studies have widely demonstrated that the oxidative stress is a pivotal player in the onset and spread of vitiligo (Białczyk et al, 2023; Chang and Ko, 2023; Schallreuter et al, 1991; Speeckaert et al, 2018; Xuan et al, 2022). Specifically, high ROS levels contribute to trigger and perpetuate melanocyte damage by inducing structural and functional impairment of DNA, lipids, proteins, and metabolites (Sastry et al, 2019). Furthermore, alterations of the antioxidant system have also been highlighted in NL skin as well as in the blood of patients with vitiligo (Abdel-Malek et al, 2020; Agarwal et al, 2015; Kostyuk et al, 2010; Maresca et al, 1997; Sravani et al, 2009). Over the last 5 years, this concept was not only strengthened but also refined, showing how oxidative stress and defects in metabolic pathways can trigger cellular senescence and immune responses in vitiligo. Very recently, we have demonstrated a direct link between mitochondrial oxidative stress in patients' melanocytes to their accumulation of mtDNA variants, its sensing by the cGAS—STING pathway, and subsequent activation of autoimmune antimelanocytic responses (Sant'Anna-Silva et al, 2024). Together, this latest evidence led to a proposal for reclassification of the disease as a systemic rather than a depigmentation skin disorder (Bergqvist and Ezzedine, 2020; Xuan et al, 2022). Consequently, beneficial results of a variety of antioxidants have been reported, and most studies have investigated (*pseudo*)catalase or superoxide dismutase (SOD) in clinical trials using concomitant UV exposure (Speeckaert et al, 2023). Our latest study has demonstrated that using therapeutic strategies that directly target stressed mitochondria such as recombinant SOD2 or NRF2 activators (including dimethyl fumerate and NK-252) abolishes oxidative stress—induced melanocyte destruction (Sant'Anna-Silva et al, 2024). Moreover, the use of a wheat gliadin biopolymer combined with SOD and narrow-band UVB in our clinical study demonstrated significant superiority to narrow-band UVB and placebo in a double-blind prospective study performed in patients with severe vitiligo (Fontas et al, 2021). The persistent, deregulated intracellular reduction—oxidation status that promotes the acquisition of a stress—induced senescent phenotype has been described in melanocytes and fibroblasts of normally pigmented skin (Bastonini et al, 2019; Bellei et al, 2013; Kovacs et al, 2018). Intrinsic defects in melanocytes can be responsible for the high expression of CXCR3B-induced melanocyte death (Tulic et al, 2019). Recently, oxeiptosis, a caspase-independent, apoptosis-like, ROS-induced cell death, has been proposed as a novel molecular mechanism involved in oxidative stress—induced melanocyte degeneration in vitiligo (Kang et al, 2022a).

CONTRIBUTION OF FIBROBLASTS TO THE COMPLEX CELL ENVIRONMENT

Fibroblast-to-myofibroblast transition, resulting in enlarged cell shape associated with increased generation of extracellular matrix proteins, such as collagen IV, fibronectin, and vimentin, is an intrinsic transdifferentiated process that participates in the occurrence of a senescent phenotype in NL vitiligo skin. Dermal fibroblast senescence may concur at the onset and/or spread of the disease through the release of GFs and cytokines such as DKK1, hepatocyte GF, endothelin-1, and IL-6 that downregulate the expression of E-cadherin on melanocytes (Kovacs et al, 2018). DKK1 is known to inhibit the Wnt pathway and thus can potentially decrease differentiation and proliferation of melanocyte stem cells, thereby preventing repigmentation (Yamaguchi et al, 2008). Furthermore, it has been recently demonstrated that fibroblasts play a central role in the recruitment of reactive $CD8^+$ T cells in vitiligo skin. Employing single-cell analysis, cell-type–specific genetic knockouts, and engraftment experiments, Xu et al (2022) identified subsets of IFN-γ–responsive dermal fibroblasts that are capable of recruiting T cells in a paracrine manner through the production of the CXCL9 and CXCL10 chemokines. To add complexity to this pathophysiology, there are many studies now focusing on investigating the reciprocal regulation of stress responses and metabolism.

THE ROLE OF METABOLISM IN VITILIGO PATHOGENESIS

Metabolism has generally been seen as a downstream effector in the regulatory architecture of the skin. Instead, cellular metabolism is at the foundation of all biological activities, and emphasis is increasingly placed on understanding how metabolism directs cellular physiology and how cell changes are linked to metabolic adaptation. Modifications of metabolic pathways, including those linked to glucose and lipids, are involved in the activation, differentiation, and functionality of the immune cells (Buck et al, 2017). Accordingly, translational implications of defective cellular metabolic processes are being identified in vitiligo, most notably the complex interplay between metabolic pathways and immune cells activation (Kovacs et al, 2022; Lyu and Sun, 2022). Melanocytes and fibroblasts isolated from the NL skin display induction of autophagy process that is beneficial to vitiligo cells, which are characterized by an intrinsic metabolic impairment (Bastonini et al, 2021; Kovacs et al, 2022). Hence, inhibition of autophagy exacerbates the features of cellular degeneration and senescence in vitiligo. A similar scenario emerges from stable and active lesions, where increased autophagy makes cells able to counteract the pro-oxidant insults, thus revealing that the activation of the catabolic process might be a protective or restorative response hindering disease progression (Yu et al, 2021). A number of reports have demonstrated an association of vitiligo and type 1 diabetes and obesity (Chang et al, 2019; D'Arino et al, 2021; Tanacan and Atakan, 2020) (Figure 2), and its association with atherosclerotic cardiovascular disease is starting to emerge. However, the reports have been conflicting, even showing a beneficial effect (Rodríguez-Martín et al, 2013). For this reason, more extensive studies are needed to help us better understand the contribution of intrinsic metabolic abnormalities in skin cells of patients with vitiligo.

Evidence of the relationship between vitiligo and abnormal lipid metabolism is also rapidly growing in the literature (Kang et al, 2022b). Nontargeted metabolomic analyses have denoted that dysregulated fatty acids (FAs) metabolic pathways are involved in the pathogenesis of the disease (Liang et al, 2019) as well as a recent targeted metabolomics study providing evidence that metabolic abnormality of FAs, especially alpha-linolenic acid (ALA) and arachidonic acid, was tightly associated with vitiligo (Ye et al, 2022). The demonstration that ALA was positively correlated with the disease severity (Vitiligo Area Scoring Index scores) suggests the potential of serum ALA as a new biomarker to assess vitiligo severity. A general increase of free FAs has been demonstrated in the stratum corneum (SC) from NL skin of patients with vitiligo (Kovacs et al, 2022), associated with a marked decrease in CER levels, highlighting an alteration of the integrity of the skin barrier. The formation of a functional SC and a fully competent skin barrier is highly linked to a correct balance between synthesis, release, localization, and binding of epidermal lipids (Haftek et al, 2021). Impairment of the permeability barrier is known to be associated with alterations in the amount and subclass ratios of CERs (Yokose et al, 2020). Furthermore, keratinocyte differentiation is increased by glycosylated short-chain and long-chain CERs (Vietri Rudan et al, 2020). The reduced amount of CERs detected in vitiligo may be the index of an altered balance between proliferation and differentiation within the epidermal layers. The evidence that keratinocytes from NL skin showed impaired expression of CERS3 and ELOVL4, which are enzymes related to skin-barrier lipids, as well as reduced levels of CERs linked to very long chain and ultra-long chain FAs (Kovacs et al, 2022) support this hypothesis. NL SC displays also a markedly increased cholesterol and cholesterol sulphate (CHS). Because high amounts of cholesterol and CHS are associated with the inhibition of epidermal desquamation and SC thickness (Sato et al, 1998), these data may also explain the thickening of the epidermis (Figure 1). Increased levels of cholesterol and its oxidative products oxysterols were also found in NL vitiligo fibroblasts as key aspects for the induction of myofibroblast phenotype and imbalance of reduction–oxidation status in the dermis, leading to premature senescence (Kovacs et al, 2018). Agarwal et al (2015) found that simvastatin both prevented vitiligo and reversed depigmentation in mice with established, widespread disease by activating multiple pleiotropic effects on melanocyte-specific T cells, such as reduction of their numbers in the skin as well as their proliferation and production of IFN-γ. Unfortunately, these results were not reproduced in man; however, the doses used were at least 3 times lower than in mice, and although higher statin doses may be required, their use is limited owing to their potential adverse effects (Nguyen et al, 2018; Vanderweil et al, 2017).

MITOCHONDRIA AS A DRIVER OF METABOLIC DYSFUNCTION

Mitochondria play a key role in continuous ROS production and metabolism/energy balance in vitiligo (Dell'Anna et al, 2017; Lin et al, 2024). Their complex nature results in the

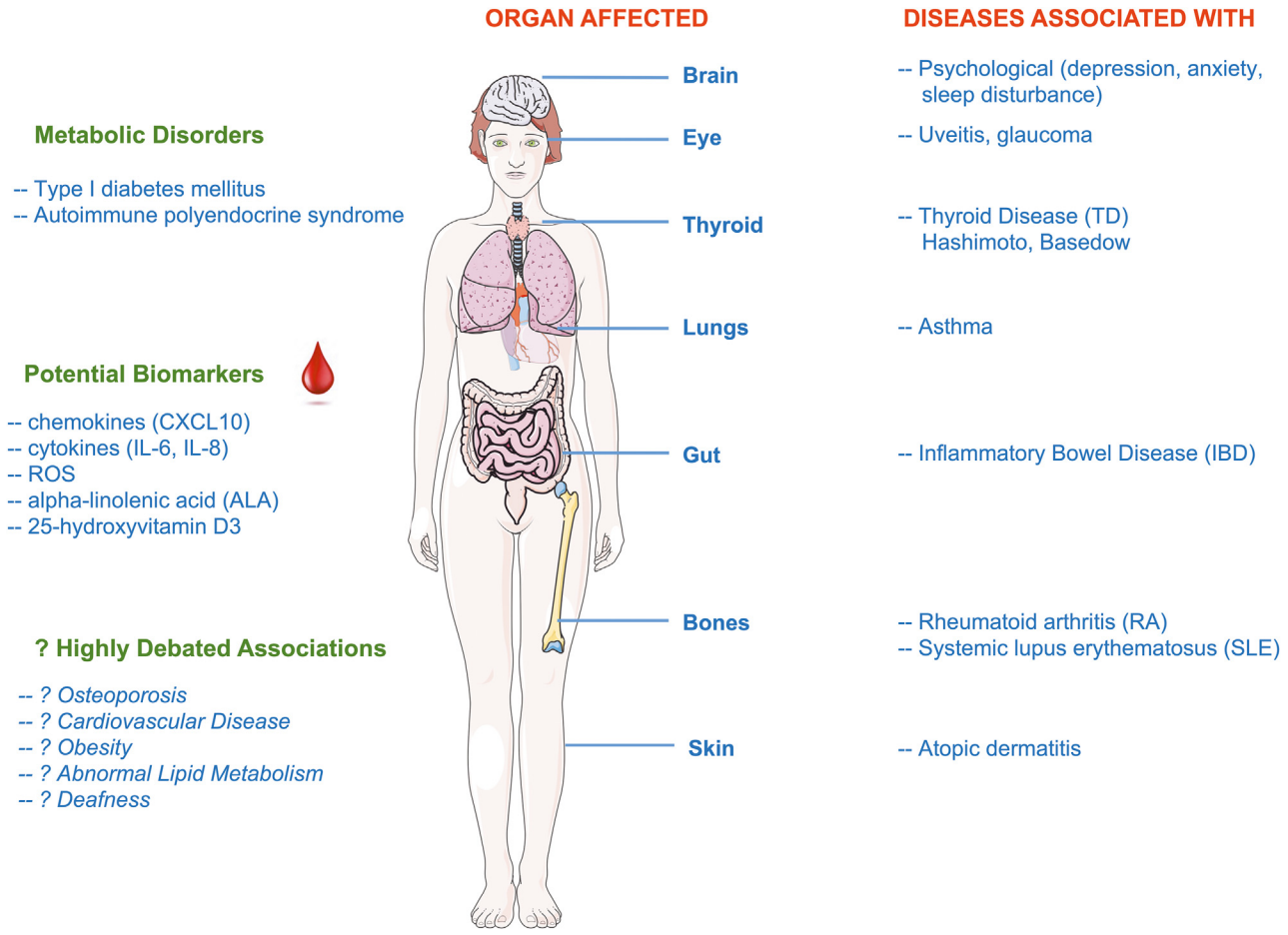

Figure 2. Comorbidities associated with vitiligo. Multiple organs are affected in patients with vitiligo, and the diseases associated with those changes are shown on the right. Highly debated associations are shown in italic. ALA, alpha-linolenic acid.

appearance of individual units or of a network that allows them to stay in tune with cellular needs, thus creating a mitocellular communication (Mottis et al, 2019). Melanocytes from NL skin are found to possess mitochondria with higher mass as a compensatory mechanism to maintain sufficient energy supply for the cells (Dell'Anna et al, 2017). More specifically, we have demonstrated a direct link between the number of mtDNA variants in patients' melanocytes and their hypomorphic mutations in catalase, mtDNA release, initiation of innate immunity, and subsequent recruitment of cytotoxic $CD8^+$ T cells (Sant'Anna-Silva et al, 2024). Altered mitochondrial functionality has been also marked in PBMCs of patients with vitiligo (Dell'Anna et al, 2003, 2001), the release of circulating mtDNA has been detected in peripheral blood of patients (Vaseghi et al, 2017), and we have demonstrated deposit of mtDNA in the skin of some patients with vitiligo (Tulic et al, 2019). Moreover, recent data suggest that perturbation of mitochondrial function, resulting in reduced intracellular adenosine triphosphate synthesis, can be accountable for the impaired ability of vitiligo keratinocytes from NL skin to undergo proper differentiation and stratification, thus leading to an intimate relationship between mitochondria and cellular behavior (Kovacs et al, 2022). Moreover, the concomitant reduced expression of TFAM, which is essential for the maintenance and expression of mtDNA as well as the generation of the mitochondrial-encoded respiratory chain subunits involved in energy production, further emphasizes the role of mitochondrial metabolism impairment in vitiligo pathogenesis. In this scenario, impairment of mitophagy, which is a protective biochemical mechanism that removes damaged mitochondria produced in response to external stimuli such as ROS or as a result of cellular aging (Choubey et al, 2021), may also contribute to vitiligo (Ding et al, 2015). By crossing vitiligo differentially expressed genes with mitophagy-related genes, a recent bioinformatics analysis identified 5 mitophagy-related hub genes (*GABARAPL2*, *SP1*, *USP8*, *RELA*, and *TBC1D17*) with high diagnostic specificity for vitiligo (Luo et al, 2023). These 5 hub genes are correlated with immune infiltration in vitiligo, hence suggesting a link between mitophagy and vitiligo development.

Collectively, this evidence reveals that normal-appearing, NL vitiligo skin shows abnormal alterations at multiple levels and modifications in cutaneous morphology and cellular and metabolic functions and immunity, together driving changes in immune activation and function. Furthermore, these complexes and interconnected abnormalities appear to extend to blood cells, suggesting that, perhaps, we can start to hypothesize vitiligo to be a systemic disorder (Figure 2). However, this needs to be formally

investigated in future, well-controlled epidemiologic studies before any firm conclusions can be made.

CLINICAL IMPLICATIONS

The notion that NL skin is not normal at all and is the potential site of disease trigger has important implications in the clinic. These findings may suggest targeting NL skin as future preventative treatment. However, this idea has potentially many practical problems such as which part of NL skin to treat,for how long and when? There is now abundant evidence to suggest that vitiligo is not just a local depigmentation skin disorder but affects multiple organs. There are clear findings of vitiligo's association with thyroid disease and increased incidence of other autoimmune diseases such as type 1 diabetes, systemic lupus erythematosus, rheumatoid arthritis, and *alopecia areata* compared with general population (Figure 2). Nevertheless, other proposed comorbidities remain to be directly proven. We have previously documented dysbiosis in NL skin microbiota of subjects with vitiligo, which was also associated with gut dysbiosis of the same individuals; giving support for the gut–skin axis in vitiligo and clearly suggesting that vitiligo extends beyond the white patches on the skin (Bzioueche et al, 2021). This was further supported by Dellacecca et al (2020) whereby antibiotics given to mice to deplete their gut flora resulted in modification of their cutaneous flora. Furthermore, evidence of the involvement of extralesional sites is the increase in CXCL9 (Lin et al, 2021), CXCL10 (Maouia et al, 2017), IFN-γ signature, and granzyme B (Ng et al, 2022) as well as a number of alarmins (He et al, 2022) in the peripheral blood of patients with vitiligo compared with those in the blood of healthy subjects, and these have been proposed as potential vitiligo biomarkers. Together, these associations highlight the importance of a multidisciplinary approach in managing patients with vitiligo.

The first (and only) approved treatment for repigmentation of vitiligo lesions has become recently available in the United States and Europe. Ruxolitinib (Opzelura) is a topical treatment for patients with nonsegmental (generalized) vitiligo and is a specific Jak1 and Jak2 inhibitor (Table 1). It works by blocking Jak/signal transducer and activator of transcription (STAT) signaling pathway in keratinocytes to inhibit overall inflammation in both lesional and NL sites and does not target specific cytokine(s) and/or chemokine(s). The most recent clinical trials with Jak1 oral inhibitors povorcitinib (Pandya et al, 2023) and upadacitinib (Passeron et al, 2023) have shown promising phase 2 results for severe and active forms of vitiligo. The other promising candidate, ritlecitinib, an oral irreversible Jak3/TEC family kinase inhibitor, currently in phase 3 trials for patients with active disease, works by downregulating general proinflammatory biomarkers in the blood and increasing melanogenesis in the skin (Ezzedine et al, 2023). In addition, baracitinib (Jak1/2 inhibitor) when combined with phototherapy has shown good efficacy and tolerance (Seneschal et al, 2023a,b). Unfortunately, these treatments often take several months (if not years), and most patients do not achieve complete repigmentation. The effectiveness of all these agents is also not specific for vitiligo because beneficial effects have been demonstrated in other skin pathologies where similar Jak/STAT-driven mechanisms are activated with induction of IFN-γ production such as in *alopecia aerata*. Further supporting evidence of systemic involvement in vitiligo are data using antioxidant SOD as an add-on to phototherapy (Fontas et al, 2021), suggesting the possibility that stabilizing the disease and reducing the overall systemic oxidative stress can promote skin repigmentation. Finally, we should not forget that immune checkpoints, which suppress T-cell function (such as PD-1 and CTLA-4), are present in NL skin. Interestingly, melanocytes at nonaffected sites have been shown to express checkpoint inhibitor PD-L1 and therefore may ensure tolerance and could explain why primed NL sites are not depigmented (Awad et al, 2020). With excessive production of IFN-γ when PD-L1 expression on melanocytes is impaired (Willemsen et al, 2022), it is possible that this tolerance is no longer effective, and antimelanocytic immunity is initiated. However, this remains to be formally tested.

MESSAGE TO PATIENTS

Vitiligo is a true autoimmune disorder with chronic evolution and is associated with increased risk of development of some other autoimmune diseases, particularly thyroid diseases; hence, patients should be checked for dysthyroiditis. Extensive research over the last decade has demonstrated that the normal-appearing, pigmented skin in patients with vitiligo is not the same as the skin of healthy subjects without vitiligo and that the disease may be triggered in the normal-appearing skin. Once the NL vitiligo skin becomes overwhelmed (hyperactivated), it may induce the subsequent cascade of events leading to melanocyte destruction, which may or may not be permanent. It is important to make known to patients with vitiligo that contrary to the advice given 20 years ago to protect their white patches from direct sunlight, today, we know that these patients have a reduced risk of developing skin cancer compared with the general population (Ferguson et al, 2023; Rooker et al, 2024) and that moderate sun exposure is required to achieve optimal repigmentation. Finally, given the evidence we presented in this review, it is important that patients themselves learn how to distinguish their lesional from their NL skin. This is not always easy, especially in fair skin types. Interestingly, the blue light of a smartphone can be easily used by patients to mimic Wood's lamp examination and help in assessing their lesions if they have a fair skin (Agrawal et al, 2023). Patients should also be educated to recognize signs of activity with active Koebner phenomenon, hypochromic borders (assessed again using blue light from their smartphone), and confetti-like depigmentation (van Geel et al, 2020). Oral mini pulse of steroids combined with narrow-band UVB, if possible, can thus be prescribed as a matter of urgency to halt disease progression (Seneschal et al, 2023). In the near future, other systemic treatment, such as Jak inhibitors, could be also prescribed for such active forms if their efficacy is confirmed in the current phase 3 trial (Passeron et al, 2024).

FUTURE RESEARCH DIRECTION

Knowing that environment and lifestyle factors contribute to melanocyte stress, we must revisit more closely exposomal factors such as air pollution, UVR, phenolic compounds and trauma (Koebner), poor diet, smoking, and psychological

Table 1. Current and Future Nonsurgical Medical Therapy for Treatment of Vitiligo

Group	Targets	Compound	Clinical Indications	Local and/or Systemic
Immunity	CD4/CD8 T cells	Topical Jaki (Jak1/2)	Localized forms of vitiligo	Lesional skin
	CD4/CD8 T cells + NK	Oral Jaki (Jak1/2; Jak3/TEC)	Widespread vitiligo +/− active forms	Lesional + NL skin, systemic
	CD8 T cells + NK	Anti-NKG2D antibodies	Repigmenting widespread +/− active forms	Lesional + NL skin, systemic
	CD8 T cells/IFN-γ	Topical IFN-γ siRNA delivery	Selective silencing Jak1/preventing extension	Lesional + NL skin
		Skin-tethered anti−IFN-γ antibody	Localized skin treatment	
	Dendritic cells	Oral Jaki (TYK2i)	Early stage/preventing extension/widespread	Lesional + NL skin, systemic
	Plasmacytoid dendritic cells	Anti-aBCDA2 antibodies	Early stage/preventing extension	Lesional + NL skin, systemic
	DAMPs	Topical mutant *HSP70* gene-gun	Early stage/preventing extension	Lesional skin
	PAMPs/microbiome	Oral/topical pro/postbiotics	Early stage/preventing extension	Lesional + NL skin, systemic
	Tregs	Low-dose new-generation IL-2	Repigmenting widespread +/− active forms, preventing relapse	Lesional + NL skin, systemic
	Tregs	Anti−CD86/IL-10 antibodies	Repigmenting widespread +/− active forms	Lesional + NL skin, systemic
			preventing relapse	
	Tregs	Topical *CCL22* gene-gun delivery	Repigmenting localized forms	Lesional skin
			preventing relapse	
	CD8 T cells + TRM	Anti−IL-15 and IL-15R	Promoting repigmentation/preventing relapse	Lesional + NL skin, systemic
	Melanocytes	Anti−CXCR3B-blocking antibodies	Early stages and widespread vitiligo + preventing relapses	NL skin
	Transcription factors	Topical BETis	Repigmenting localized forms	Lesional + NL skin
Antioxidants	DAMPs	New-generation antioxidants	Early stage/preventing oxidative stress/extension	Lesional + NL skin, systemic
Melanocyte	Melanocyte detachment	MMP-9 inhibitors	Early stages/preventing extension	Lesional + NL skin
	Melanocyte stem cells	Topical Wnt agonists and GSK3b antagonists	Stimulate differentiation/proliferation of stem cells to enhance repigmentation	Lesional + NL skin
	Skin	Afamelanotide (αMSH analog) + UVB	Stimulate melanin production/proliferation of mature melanocytes	Lesional + NL skin, systemic
Metabolism	mTOR	pioglitazone	Active vitiligo	Systemic

Abbreviations: αMSH, alpha melanocyte stimulating hormone; BETi, bromodomain and extra-terminal motif inhibitor; DAMP, damage-associated molecular pattern; Jaki, Jak inhibitors; MMP-9, matrix metalloproteinase 9; NL, nonlesional; PAMP, pathogen-associated molecular pattern; siRNA, small interfering RNA; Treg, regulatory T cell; TRM, resident memory T cells.

stress, which may be the initial triggers that would then drive long-term autoimmunity against melanocytes. There are very few data on the potential deleterious role of UV in vitiligo. However, severe sunburns, acting as an aggressor by provoking strong DNA damages, oxidative stress, and inflammation, can activate the disease in genetically susceptible individuals and has been shown to be a potential trigger of vitiligo flares (Dunlap et al, 2017; Vrijman et al, 2013). An alternative approach for vitiligo may focus on compounds that act to improve and/or restore the proper composition and assembly of the skin barrier to render patients' epidermis less susceptible against external injuries. In this regard, we have recently demonstrated that the peroxisome proliferator–activated receptor-γ agonist pioglitazone is able to promote the differentiation process and decrease the synthesis and release of the CXCL10 chemokine in NL vitiligo keratinocytes (Bastonini et al, 2024). After all, melanocytes are located in the organ with the greatest exposure to external environment, the skin, and are therefore particularly vulnerable to excessive production of ROS. There has been a longstanding interest in the use of systemic antioxidants; however, these results are quite conflicting. To date, no single study has demonstrated decreased evolution of vitiligo when antioxidants are used as monotherapy, and there is ongoing effort to examine their role in combination with other proposed treatments to help reduce general oxidative stress and inflammation. In light of our most recent results, using antioxidants that specifically target stressed mitochondria in melanocytes (such as recombinant SOD2 and NRF2 activators) as an add-on therapy could prove beneficial for the patients (Sant'Anna-Silva et al, 2024).

So far, we have focused on cutaneous treatment to initiate melanogenesis and hence repigmentation of lesional skin with significant advances as evidenced by the effectiveness of Jak/STAT inhibitors. However, the question remains about whether we could prevent the appearance of clinical manifestations of the disease by changing our focus toward normal-appearing skin to reduce initial cutaneous trauma in subjects who may be genetically or environmentally prone to vitiligo rather than only treating existing lesions. Although tempting, first, we must continue to characterize the extend of NL skin abnormalities and to understand their implications for effective treatment. Moreover, we must emphasize that evolution of vitiligo is unpredictable, and usefulness of systemic treatment for all patients is currently unknown. It would be interesting to assess in future well-controlled clinical trials whether systemic treatment (especially if introduced during early stages of the disease) could help to prevent flares and/or evolution of the more severe forms of the disease.

The good news is that there are a number of new developments currently on the horizon that focus not only on the topical and systemic immune–mediated therapeutic solutions but also on wide range of mechanisms that can directly target innate immunity microbiota, regulatory pathways, oxidative stress (with new-generation antioxidants), metabolism, melanocyte stem cells, as well as mature melanocyte differentiation and proliferation (Table 1). Many of those developments have a potential to affect both lesional and NL skin. Given the evidence presented in this review, there is an urgent need for more clinical trials targeting specifically the NL skin to determine whether we can prevent new lesions and/or promote more effective and sustainable treatment of patients with vitiligo.

OPEN QUESTIONS TO READER

Question 1

Are the inherited metabolic alterations the initial events leading to the release of damage-associated-molecular patterns and pathogen-associated-molecular patterns, that trigger the activation of the innate immunity in vitiligo?

Question 2

Is it possible that a subclinical inflammatory status is present on the entire body surface of susceptible individuals, producing low but constant amounts of IFN-γ leading to metabolic alteration, which amplifies the inflammatory process and ultimately leads to vitiligo?

What is your opinion? What is your experience? Could this new point of view change our therapeutic approach? Topical or systemic treatments? Do we treat the lesional white spots or the normal-appearing pigmented skin? In light of recent research, would a combination of treatment strategies (ie, inducers of repigmentation at lesional sites and anti-inflammatory/antioxidant treatments at pigmented sites) be more feasible? We look forward to your comments, opinions, and feedback on this topic.

ORCIDs

Meri K. Tulic: http://orcid.org/0000-0002-2661-2369
Daniela Kovacs: http://orcid.org/0000-0003-1873-0549
Emanuela Bastonini: http://orcid.org/0000-0003-3110-354X
Stefania Briganti: http://orcid.org/0000-0003-2000-006X
Thierry Passeron: http://orcid.org/0000-0002-0797-6570
Mauro Picardo: http://orcid.org/0000-0003-4899-6639

CONFLICT OF INTEREST

The authors state no conflict of interest.

ACKNOWLEDGMENTS

There are no funders to be acknowledged for writing of this review.

AUTHOR CONTRIBUTIONS

Conceptualization: MKT, MP; Data curation: MKT, DK, EB, SB, TP, MP; Writing - Original Draft Presentation: MKT, DK, MP; Visualization: MKT; Writing - Review and Editing: MKT, DK, EB, SB, TP, MP

REFERENCES

Abdel-Malek ZA, Jordan C, Ho T, Upadhyay PR, Fleischer A, Hamzavi I. The enigma and challenges of vitiligo pathophysiology and treatment. Pigment Cell Melanoma Res 2020;33:778–87.

Agarwal P, Rashighi M, Essien KI, Richmond JM, Randall L, Pazoki-Toroudi H, et al. Simvastatin prevents and reverses depigmentation in a mouse model of vitiligo. J Invest Dermatol 2015;135:1080–8.

Agrawal S, Sharma A, Dhurat R, Chahal K. Using the blue screen of a smartphone as an alternative to Wood's lamp for examination of vitiligo. J Am Acad Dermatol 2023;88:e5–6.

Aktaş Karabay E, Aksu Çerman A. Demodex folliculorum infestations in common facial dermatoses: acne vulgaris, rosacea, seborrheic dermatitis. An Bras Dermatol 2020;95:187–93.

Awad SS, Touni AA, Gabril MY. Expression of immune checkpoints in active nonsegmental vitiligo: a pilot study. Int J Dermatol 2020;59:982–8.

Bastonini E, Bellei B, Filoni A, Kovacs D, Iacovelli P, Picardo M. Involvement of non-melanocytic skin cells in vitiligo. Exp Dermatol 2019;28:667–73.

Bastonini E, Kovacs D, Briganti S, Ottaviani M, D'Arino A, Migliano E, et al. Effects of pioglitazone on the differentiation and inflammation in vitiligo keratinocytes. J Eur Acad Dermatol Venereol 2024;38:e573–5.

Bastonini E, Kovacs D, Raffa S, Delle Macchie M, Pacifico A, Iacovelli P, et al. A protective role for autophagy in vitiligo. Cell Death Dis 2021;12:318.

Bellei B, Pitisci A, Ottaviani M, Ludovici M, Cota C, Luzi F, et al. Vitiligo: a possible model of degenerative diseases. PLoS One 2013;8:e59782.

Bergqvist C, Ezzedine K. Vitiligo: a review. Dermatology 2020;236:571–92.

Białczyk A, Wełniak A, Kamińska B, Czajkowski R. Oxidative stress and potential antioxidant therapies in vitiligo: a narrative review. Mol Diagn Ther 2023;27:723–39.

Bondanza S, Maurelli R, Paterna P, Migliore E, Giacomo FD, Primavera G, et al. Keratinocyte cultures from involved skin in vitiligo patients show an impaired in vitro behaviour. Pigment Cell Res 2007;20:288–300.

Boukhedouni N, Martins C, Darrigade AS, Drullion C, Rambert J, Barrault C, et al. Type-1 cytokines regulate MMP-9 production and E-cadherin disruption to promote melanocyte loss in vitiligo. JCI Insight 2020;5:e133772.

Buck MD, Sowell RT, Kaech SM, Pearce EL. Metabolic instruction of immunity. Cell 2017;169:570–86.

Bzioueche H, Boniface K, Drullion C, Marchetti S, Chignon-Sicard B, Sormani L, et al. Impact of house dust mite in vitiligo skin: environmental contribution to increased cutaneous immunity and melanocyte detachment. Br J Dermatol 2023;189:312–27.

Bzioueche H, Simonyté Sjödin K, West CE, Khemis A, Rocchi S, Passeron T, et al. Analysis of matched skin and gut microbiome of patients with vitiligo reveals deep skin dysbiosis: link with mitochondrial and immune changes. J Invest Dermatol 2021;141:2280–90.

Bzioueche H, Tamelghaghet M, Chignon-Sicard B, Bazile N, Hauchecorne P, Barbero Calderón M, et al. Ceramide AD™ Restores Skin Integrity and Function following Exposure to house dust mite. Int J Mol Sci 2023;24:9234.

Chang HC, Lin MH, Huang YC, Hou TY. The association between vitiligo and diabetes mellitus: a systematic review and meta-analysis. J Am Acad Dermatol 2019;81:1442–5.

Chang WL, Ko CH. The role of oxidative stress in vitiligo: an update on its pathogenesis and therapeutic implications. Cells 2023;12:936.

Choubey V, Zeb A, Kaasik A. Molecular mechanisms and regulation of mammalian mitophagy. Cells 2021;11:38.

D'Arino A, Picardo M, Truglio M, Pacifico A, Iacovelli P. Metabolic comorbidities in vitiligo: a brief review and report of new data from a single-center experience. Int J Mol Sci 2021;22:8820.

Dellacecca ER, Cosgrove C, Mukhatayev Z, Akhtar S, Engelhard VH, Rademaker AW, et al. Antibiotics drive microbial imbalance and vitiligo development in mice. J Invest Dermatol 2020;140:676–87.e6.

Dell'Anna ML, Maresca V, Briganti S, Camera E, Falchi M, Picardo M. Mitochondrial impairment in peripheral blood mononuclear cells during the active phase of vitiligo. J Invest Dermatol 2001;117:908–13.

Dell'Anna ML, Ottaviani M, Kovacs D, Mirabilii S, Brown DA, Cota C, et al. Energetic mitochondrial failing in vitiligo and possible rescue by cardiolipin. Sci Rep 2017;7:13663.

Dell'Anna ML, Urbanelli S, Mastrofrancesco A, Camera E, Iacovelli P, Leone G, et al. Alterations of mitochondria in peripheral blood mononuclear cells of vitiligo patients. Pigment Cell Res 2003;16:553–9.

Ding GZ, Zhao WE, Li X, Gong QL, Lu Y. A comparative study of mitochondrial ultrastructure in melanocytes from perilesional vitiligo skin and perilesional halo nevi skin. Arch Dermatol Res 2015;307:281–9.

Dunlap R, Wu S, Wilmer E, Cho E, Li WQ, Lajevardi N, et al. Pigmentation traits, sun exposure, and risk of incident vitiligo in women. J Invest Dermatol 2017;137:1234–9.

Eleftheriadou V, Delattre C, Chetty-Mhlanga S, Lee C, Girardat-Rotar L, Khan I, et al. Burden of disease and treatment patterns in patients with vitiligo: findings from a national longitudinal retrospective study in the UK. Br J Dermatol 2024;191:216–24.

Ezzedine K, Peeva E, Yamaguchi Y, Cox LA, Banerjee A, Han G, et al. Efficacy and safety of oral ritlecitinib for the treatment of active nonsegmental vitiligo: a randomized phase 2b clinical trial. J Am Acad Dermatol 2023;88:395–403.

Ferguson J, Eleftheriadou V, Nesnas J. Risk of melanoma and nonmelanoma skin cancer in people with vitiligo: United Kingdom population-based cohort study. J Invest Dermatol 2023;143:2204–10.

Fontas E, Montaudié H, Passeron T. Oral gliadin-protected superoxide dismutase in addition to phototherapy for treating non-segmental vitiligo: a 24-week prospective randomized placebo-controlled study. J Eur Acad Dermatol Venereol 2021;35:1725–9.

Gauthier Y, Cario Andre M, Taïeb A. A critical appraisal of vitiligo etiologic theories. Is melanocyte loss a melanocytorrhagy? Pigment Cell Res 2003;16:322–32.

Gellatly KJ, Strassner JP, Essien K, Refat MA, Murphy RL, Coffin-Schmitt A, et al. scRNA-seq of human vitiligo reveals complex networks of subclinical immune activation and a role for CCR5 in Treg function. Sci Transl Med 2021;13:eabd8995.

Haftek M, Roy DC, Liao IC. ARTICLE: Evolution of skin barrier science for healthy and compromised skin. J Drugs Dermatol 2021;20:s3–9.

He K, Wu W, Wang X, Dai W, Wang S, Li C, et al. Circulatory levels of alarmins in patients with non-segmental vitiligo: potential biomarkers for disease diagnosis and activity/severity assessment. Front Immunol 2022;13:1069196.

Kang P, Chen J, Zhang W, Guo N, Yi X, Cui T, et al. Oxeiptosis: a novel pathway of melanocytes death in response to oxidative stress in vitiligo. Cell Death Discov 2022a;8:70.

Kang P, Zhang WG, Ji ZH, Shao ZJ, Li CY. Association between vitiligo and relevant components of metabolic syndrome: a systematic review and meta-analysis. J Dtsch Dermatol Ges 2022b;20:629–41.

Kostyuk VA, Potapovich AI, Cesareo E, Brescia S, Guerra L, Valacchi G, et al. Dysfunction of glutathione S-transferase leads to excess 4-hydroxy-2-nonenal and H(2)O(2) and impaired cytokine pattern in cultured keratinocytes and blood of vitiligo patients. Antioxid Redox Signal 2010;13:607–20.

Kovacs D, Bastonini E, Briganti S, Ottaviani M, D'Arino A, Truglio M, et al. Altered epidermal proliferation, differentiation, and lipid composition: novel key elements in the vitiligo puzzle. Sci Adv 2022;8:eabn9299.

Kovacs D, Bastonini E, Ottaviani M, Cota C, Migliano E, Dell'Anna ML, et al. Vitiligo skin: exploring the dermal compartment. J Invest Dermatol 2018;138:394–404.

Le Poole IC, Mutis T, van den Wijngaard RM, Westerhof W, Ottenhoff T, de Vries RR, et al. A novel, antigen-presenting function of melanocytes and its possible relationship to hypopigmentary disorders. J Immunol 1993;151:7284–92.

Li S, Zhu G, Yang Y, Jian Z, Guo S, Dai W, et al. Oxidative stress drives $CD8^+$ T-cell skin trafficking in patients with vitiligo through CXCL16 upregulation by activating the unfolded protein response in keratinocytes. J Allergy Clin Immunol 2017;140:177–89.e9.

Liang L, Li Y, Tian X, Zhou J, Zhong L. Comprehensive lipidomic, metabolomic and proteomic profiling reveals the role of immune system in vitiligo. Clin Exp Dermatol 2019;44:e216–23.

Lin F, Hu W, Xu W, Zhou M, Xu AE. CXCL9 as a key biomarker of vitiligo activity and prediction of the success of cultured melanocyte transplantation. Sci Rep 2021;11:18298.

Lin Y, Ding Y, Wu Y, Yang Y, Liu Z, Xiang L, et al. The underestimated role of mitochondria in vitiligo: from oxidative stress to inflammation and cell death. Exp Dermatol 2024;33:e14856.

Luo L, Zhu J, Guo Y, Li C. Mitophagy and immune infiltration in vitiligo: evidence from bioinformatics analysis. Front Immunol 2023;14:1164124.

Lyu C, Sun Y. Immunometabolism in the pathogenesis of vitiligo. Front Immunol 2022;13:1055958.

Maeda K, Yamamoto K, Tanaka Y, Anan S, Yoshida H. The relationship between eosinophils, OKT6-positive cells and house dust mite (HDM) antigens in naturally occurring lesions of atopic dermatitis. J Dermatol Sci 1992;3:151–6.

Maouia A, Sormani L, Youssef M, Helal AN, Kassab A, Passeron T. Differential expression of CXCL9, CXCL10, and IFN-γ in vitiligo and alopecia areata patients. Pigment Cell Melanoma Res 2017;30:259–61.

Maresca V, Roccella M, Roccella F, Camera E, Del Porto G, Passi S, et al. Increased sensitivity to peroxidative agents as a possible pathogenic factor of melanocyte damage in vitiligo. J Invest Dermatol 1997;109:310–3.

Martins C, Migayron L, Drullion C, Jacquemin C, Lucchese F, Rambert J, et al. Vitiligo skin T cells are prone to produce Type 1 and Type 2 cytokines to induce melanocyte dysfunction and epidermal inflammatory response through jak signaling. J Invest Dermatol 2022;142:1194–205.e7.

Migayron L, Merhi R, Seneschal J, Boniface K. Resident memory T cells in nonlesional skin and healed lesions of patients with chronic inflammatory diseases: appearances can be deceptive. J Allergy Clin Immunol 2024;153:606–14.

Mottis A, Herzig S, Auwerx J. Mitocellular communication: shaping health and disease. Science 2019;366:827–32.

Ng CY, Chiu YC, Chan YP, Lin YJ, Chung PH, Chung WH, et al. Skin interstitial fluid and plasma multiplex cytokine analysis reveals IFN-γ signatures and granzyme B as useful biomarker for activity, severity and prognosis assessment in vitiligo. Front Immunol 2022;13:872458.

Nguyen S, Chuah SY, Fontas E, Khemis A, Jhingan A, Thng STG, et al. Atorvastatin in combination with narrowband UV-B in adult patients with active vitiligo: a randomized clinical trial. JAMA Dermatol 2018;154:725–6.

Pandya AG, Ezzedine K, Rosmarin D, Passeron T, Desai TS, Lebwohl M, et al. Treatment-emergent adverse events of interest for Janus kinase inhibitors: pooled analysis of the 52-week TRuE-V Phase 3 studies of Ruxolitinib cream treatment for vitiligo. Presented at the American Academy of Dermatology (AAD) Annual Meeting, 17–21 March, 2023, New Orleans, LA.

Passeron T, Ezzedine K, Hamzavi I, van Geel N, Schlosser BJ, Wu X, et al. Once-daily Upadacitinib versus placebo in adults with extensive non-segmental vitiligo: a phase 2, multicentre, randomised, double-blind, placebo-controlled, dose-ranging study. EClinicalmedicine 2024;73:102655.

Richmond JM, Bangari DS, Essien KI, Currimbhoy SD, Groom JR, Pandya AG, et al. Keratinocyte-derived chemokines orchestrate T-cell positioning in the epidermis during vitiligo and may serve as biomarkers of disease. J Invest Dermatol 2017;137:350–8.

Rodríguez-Martín M, de Paz NM, Mehtani P, Ferrer PC, Eliche MP, Martín BR, et al. Patients with vitiligo present fewer cardiovascular risk factors: results from a case-control study. J Eur Acad Dermatol Venereol 2013;27:124–5.

Rooker A, Ouwerkerk W, Bekkenk MW, Luiten RM, Bakker WJ. The risk of keratinocyte cancer in vitiligo and the potential mechanisms involved. J Invest Dermatol 2024;144:234–42.

Sant'Anna-Silva ACB, Botton T, Rossi A, Dobner J, Bzioueche H, Thach N, et al. Vitiligo auto-immune response upon oxidative stress-related mitochondrial DNA release opens up new therapeutic strategies. Clin Transl Med 2024;14:e1810.

Sastry KS, Naeem H, Mokrab Y, Chouchane AI. RNA-seq reveals dysregulation of novel melanocyte genes upon oxidative stress: implications in vitiligo pathogenesis. Oxid Med Cell Longev 2019;2019:2841814.

Sato J, Denda M, Nakanishi J, Nomura J, Koyama J. Cholesterol sulfate inhibits proteases that are involved in desquamation of stratum corneum. J Invest Dermatol 1998;111:189–93.

Schallreuter KU, Wood JM, Berger J. Low catalase levels in the epidermis of patients with vitiligo. J Invest Dermatol 1991;97:1081–5.

Seneschal J, Speeckaert R, Taïeb A, Wolkerstorfer A, Passeron T, Pandya AG, et al. Worldwide expert recommendations for the diagnosis and management of vitiligo: position statement from the International Vitiligo Task Force-Part 2: Specific treatment recommendations. J Eur Acad Dermatol Venereol 2023a;37:2185–95.

Seneschal J, Wolkerstorfer A, Ezzedine K, Pandya AG, Lynde C, Nuara A, et al. Efficacy and safety of Ruxolitinib cream through Week 104. In: Patients with vitiligo: subgroup analysis of the TRuE-V long-term extension Phase 3 study. Presented at the European Academy of Dermatology and Venereology (EADV) Congress, 11–14 October 2023b; Berlin, Germany.

Speeckaert R, Bulat V, Speeckaert MM, van Geel N. The impact of antioxidants on vitiligo and melasma: A scoping review and meta-analysis. Antioxidants (Basel) 2023;12:2082.

Speeckaert R, Dugardin J, Lambert J, Lapeere H, Verhaeghe E, Speeckaert MM, et al. Critical appraisal of the oxidative stress pathway in vitiligo: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2018;32:1089–98.

Sravani PV, Babu NK, Gopal KV, Rao GR, Rao AR, Moorthy B, et al. Determination of oxidative stress in vitiligo by measuring superoxide dismutase and catalase levels in vitiliginous and non-vitiliginous skin. Indian J Dermatol Venereol Leprol 2009;75:268–71.

Tanacan E, Atakan N. Higher incidence of metabolic syndrome components in vitiligo patients: A prospective cross-sectional study. An Bras Dermatol 2020;95:165–72.

Tulic MK, Cavazza E, Cheli Y, Jacquel A, Luci C, Cardot-Leccia N, et al. Innate lymphocyte-induced CXCR3B-mediated melanocyte apoptosis is a potential initiator of T-cell autoreactivity in vitiligo. Nat Commun 2019;10:2178.

Van Geel N, Passeron T, Wolkerstorfer A, Speeckaert R, Ezzedine K. Reliability and validity of the Vitiligo Signs of Activity Score (VSAS). Br J Dermatol 2020;183:883–90.

van Geel N, Speeckaert R, Taieb A, Picardo M, Böhm M, Gawkrodger DJ, et al. Koebner's phenomenon in vitiligo: European position paper. Pigment Cell Melanoma Res 2011;24:564–73.

Vanderweil SG, Amano S, Ko WC, Richmond JM, Kelley M, Senna MM, et al. A double-blind, placebo-controlled, phase-II clinical trial to evaluate oral simvastatin as a treatment for vitiligo. J Am Acad Dermatol 2017;76:150–1.e3.

Vaseghi H, Houshmand M, Jadali Z. Increased levels of mitochondrial DNA copy number in patients with vitiligo. Clin Exp Dermatol 2017;42:749–54.

Vietri Rudan M, Mishra A, Klose C, Eggert US, Watt FM. Human epidermal stem cell differentiation is modulated by specific lipid subspecies. Proc Natl Acad Sci USA 2020;117:22173–82.

Vrijman C, Hosseinpour D, Bakker JG, Wolkerstorfer A, Bos JD, van der Veen JP, et al. Provoking factors, including chemicals, in Dutch patients with vitiligo. Br J Dermatol 2013;168:1003–11.

Wagner RY, Luciani F, Cario-André M, Rubod A, Petit V, Benzekri L, et al. Altered E-cadherin levels and distribution in melanocytes precede clinical manifestations of vitiligo. J Invest Dermatol 2015;135:1810–9.

Willemsen M, Krebbers G, Tjin EPM, Willemsen KJ, Louis A, Konijn VAL, et al. IFN-γ-induced PD-L1 expression on human melanocytes is impaired in vitiligo. Exp Dermatol 2022;31:556–66.

Wu Y, Yang Y, Lin Y, Ding Y, Liu Z, Xiang L, et al. Emerging role of fibroblasts in vitiligo: a formerly underestimated rising star. J Invest Dermatol 2024;144:1696–706.

Xu Z, Chen D, Hu Y, Jiang K, Huang H, Du Y, et al. Anatomically distinct fibroblast subsets determine skin autoimmune patterns. Nature 2022;601:118–24.

Xuan Y, Yang Y, Xiang L, Zhang C. The role of oxidative stress in the pathogenesis of vitiligo: A culprit for melanocyte death. Oxid Med Cell Longev 2022;2022:8498472.

Yamaguchi Y, Passeron T, Hoashi T, Watabe H, Rouzaud F, Yasumoto K, et al. Dickkopf 1 (DKK1) regulates skin pigmentation and thickness by affecting Wnt/beta-catenin signaling in keratinocytes. FASEB J 2008;22:1009–20.

Ye Z, Chen J, Du P, Ni Q, Li B, Zhang Z, et al. Metabolomics signature and potential application of serum polyunsaturated fatty acids metabolism in patients with vitiligo. Front Immunol 2022;13:839167.

Yokose U, Ishikawa J, Morokuma Y, Naoe A, Inoue Y, Yasuda Y, et al. The ceramide [NP]/[NS] ratio in the stratum corneum is a potential marker for skin properties and epidermal differentiation. BMC Dermatol 2020;20:6.

Yu H, Lin X, Huang Y, Cheng H, Seifert O. The difference in expression of autophagy-related proteins in lesional and perilesional skin in adult patients with active and stable generalized vitiligo-a cross-sectional pilot study. Indian J Dermatol 2021;66:331–6.