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REVIEW ARTICLE

Melanogenesis and Hypopigmentation: The Case of Vitiligo

M. Pilar Vinardell, Adriana Solange Maddaleno, Montserrat Mitjans

From the Department Biochemistry and Physiology of the Universitat de Barcelona, Spain

Address for correspondence:
Prof. M. Pilar Vinardell, Department Biochemistry and Physyology, Faculty of Pharmacy and Food Sciences, Av. Joan XXIII 27-31, Barcelona, Spain.
E-mail: mpvinardellmh@ub.edu

Abstract

Melanocytes are highly specialized dendritic cells that synthesize and store melanin in subcellular organelles called melanosomes, before transfer to keratinocytes. Melanin is a complex pigment that provides colour and photoprotection to the skin, hair and eyes. The process of synthesis of melanin is called melanogenesis and is regulated by various mechanisms and factors such as genetic, environmental and endocrine factors. The knowledge of the pigmentation process is important to understand hypopigmentation disorders such as vitiligo and also to design adequate treatments. In the present work, we review the signalling pathways involved in vitiligo. Finally, current therapies and treatments including topical, oral and phototherapies are discussed and described, emphasizing future therapies based on different pigmentation mechanisms.

Key Words: *Hypopigmentation, melanin synthesis, melanocyte, treatment, vitiligo*

Introduction

Melanin is a complex pigment that provides colour and photoprotection to the skin, hair and eyes of mammals. Melanogenesis is the process through which melanocytes synthesise melanin and can be altered by decreasing the production of the pigment such as in the case of vitiligo.

Melanogenesis can be regulated by genetic, environmental (ultraviolet [UV] radiation) and endocrine factors. Knowledge of the pigmentation process is important for designing tanning products to treat hypopigmentation disorders such as vitiligo.[1]

Vitiligo is an autoimmune acquired chronic skin disorder that is characterised by white macules resulting from the damage and loss of melanocytes. Although many disorders induce hypopigmentation, vitiligo is the most frequent cause of depigmentation worldwide affecting about 1% in the population.[1,2] Vitiligo can be segmental, non-segmental or mixed. Segmental vitiligo presents one or more areas of depigmented skin usually only on one side of the body such as on the face, neck, trunks, arms or legs during childhood and usually stabilises in a few years. Non-segmental vitiligo is a chronic and progressive loss of melanin with well-defined white patches in the middle of normally pigmented skin, increasing in size over time and located on the hands, underarms, eyelids, ears, knees and ankles and whose progression is unpredictable. Vitiligo is usually associated with different autoimmune disorders such as thyroid diseases, diabetes mellitus, lupus, inflammatory bowel disease, psoriasis and atopic dermatitis among others.[3] Other authors have observed also metabolic comorbidities[4] and psychological and psychiatric disorders.[5]

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Signalling Pathways in Vitiligo

Vitiligo is a complex disease and different hypotheses have been proposed for the multifactorial feature of vitiligo pathogenesis involving immunological, genetic, biochemical and environmental factors [Figure 1].[6]

Oxidative stress

Oxidative stress has been suggested to be the first step in the loss of melanocytes in vitiligo, but it is not the unique initiating mechanism involved in the disease.[1,7]

High levels of reactive oxygen species (ROS) are found in lesioned and non-lesioned skin, damaging melanocytes by generating autoantigens whose presentation by Langerhans cells and dendritic cells initiate an autoimmune response, bridging the gap between oxidative stress and adaptive immunity.[8,9] Disruptions in metabolic processes such as melanogenesis and immune reactions can lead to the accumulation of ROS, although several studies suggest that mitochondrial damage altering the mitochondria structure of melanocytes is

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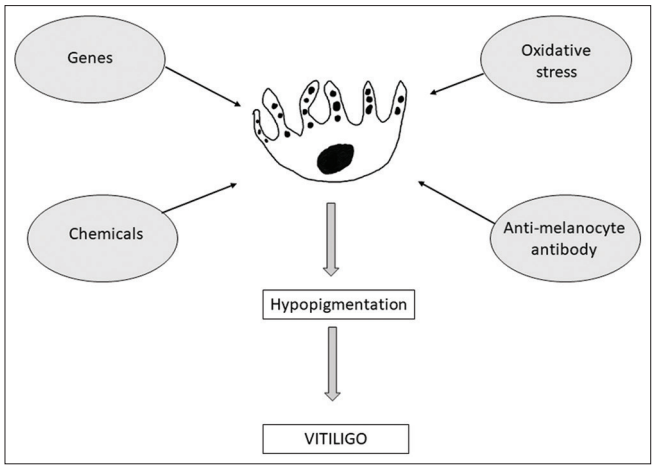

Figure 1: Multifactorial feature of vitiligo pathogenesis

the main cause of ROS accumulation.[10,11] A recent study has observed that molecular hydrogen revers hydrogen peroxide-induced apoptosis in melanocytes, protecting mitochondrial morphology and function in melanocytes under stress and promoting the activation of Nrf2 signalling.[12]

ROS generation can also be induced by exogenous factors such as the environment, medical applications and other diseases.[13,14] Studies have reported that melanocytes from vitiligo patients die upon exposure to exogenous stress *in vitro*, such as peroxide exposure, whereas melanocytes from healthy controls do not.[15] Intracellular ROS include hydrogen peroxide (H_2O_2), superoxide anions and hydroxyl radicals. H_2O_2 can disrupt melanin synthesis and can deactivate and deregulate acetylcholinesterase in the epidermis, providing more evidence of the role of oxidative stress in vitiligo.[16] Zhang *et al.*[17] showed that H_2O_2-induced apoptosis increases the level of calreticulin, which induces the expression of pro-inflammatory cytokines such as interleukin-6 (IL-6) and tumour necrosis factor-α (TNF-α).

The activity of superoxide dismutase (SOD), a metalloprotein that scavenges O_2^- and converts it into H_2O_2, is increased in the erythrocytes of vitiligo patients. H_2O_2 is converted into O_2 by catalase, whose expression is down regulated in vitiligo. The imbalance in the oxidative/antioxidative equilibrium is another cause of ROS accumulation. Several studies have reported an increase in malondialdehyde (MDA) levels in vitiligo patients, which is a product of lipid peroxidation reactions induced by oxidative stress.[7]

Immunity

The immune-mediated destruction of melanocytes is the main factor causing vitiligo. Stressed melanocytes activate the innate immune system through cytokines secreted within the skin, that is, induced by the generation and release of damage-associated molecular patterns (DAMPs).[13] This has been demonstrated through the recruitment of innate immune cells, such as natural killer cells, as well as the production and release of highly pro-inflammatory proteins and cytokines including heat shock proteins, IL-1β, IL-6 and IL-8. Moreover, it has been reported that $CD8^+$ T cells induce the destruction of melanocytes.[18,19]

Autoreactive T cells locate stressed melanocytes using the cytokines secreted within the skin. Studies have shown that IFN-γ and the IFN-γ-induced chemokines CXCL9 and CXCL10, which act as chemoattractants to guide T cell migration, are highly expressed in the skin and blood of vitiligo patients. The CXCL10/CXCR3 axis mediates T cell recruitment in progressive vitiligo, suggesting that the blocking of this mechanism could be a new form of therapy.[20]

El-Gayyar *et al.*[21] suggested that anti-melanocyte antibodies have an important role in the pathogenesis of non-segmental vitiligo, correlating with the severity of the disease. Furthermore, a higher prevalence of anti-thyroperoxidase, anti-thyroglobulin, antinuclear, anti-gastric parietal cell and anti-adrenal antibodies has been reported in vitiligo patients compared to healthy controls.[22] Indeed, autoantibodies have an important role in disease pathology, confirming the important role of humoral immunity in vitiligo. Major melanocytic antigens include the proteins tyrosinase, TRP-1, TRP-2, Pmel17, SOX9, SOX10 and the type 1 membrane receptor for melanin-concentrating hormone (MCH-R1).[23] SOX9 and SOX10, key transcription factors for melanocyte differentiation, have been reported many years ago to be autoantigens in vitiligo.[24]

One of the proposed mechanisms for melanocyte destruction in vitiligo is the autoimmune intolerance via CD8+ and T helper 17 (Th17), which have an important role in exosomes in melanogenesis serving as mediators in the communication between keratinocytes and melanocytes.[25]

Pro-inflammatory cytokines, such as IL-6, TNF-α, IL-1β, IFN-γ and IL-8 and some anti-inflammatory/immunoregulatory cytokines such as IL-5 and IL-10 are increased in vitiligo patients. Mitra *et al.*[26] suggested that the high level of IL-10 is due to the attempt to avoid the loss of melanocytes by the organism. However, other studies have shown a low level of IL-10.[27] Zhou *et al.*[28] indicated that IL-17 induces a stressful microenvironment for melanocytes, promoting autophagic cell apoptosis in vitiligo.

Microbiome

Different studies have demonstrated the relationship between alterations in the skin microbiome and some skin diseases such as psoriasis and atopic dermatitis.[29,30] The first study correlating microbiota

and vitiligo demonstrated a dysbiosis in the diversity of the bacterial community of the areas with vitiligo hypopigmentation compared to normal skin. The authors observed distinctive distribution of bacterial populations with more *Actinobacterial* species, such as Actinomycetes, in areas of the skin without lesions and Firmicutes in areas with lesions.[31]

More recent studies observed similar alterations in microbiota and associated the dysbiosis with mitochondrial damage. Moreover, the loss of protective bacteria in patients can be associated with an increase in immune responses.[32]

Moreover, the role of the gut microbiome is known in the development of other skin diseases such as psoriasis autoimmune diseases. In the case of vitiligo, authors have found alterations in the gut microbiome composition and serum metabolites usually used as biomarkers of vitiligo. These findings can implicate the gut–skin axis in vitiligo pathogenesis.[33]

Genetics

Among vitiligo patients, 15–20% have at least one first-degree relative with this disease. Furthermore, the risk of a patient's sibling developing vitiligo is 6%, whereas that of a monozygotic twin is 23%, illustrating the genetic basis of vitiligo.[34]

At least 50 susceptibility loci for vitiligo have been identified by genome-wide association studies (GWAS), with 90% of these loci associated with innate and adaptive immunity and 10% associated with melanocytic antigens and stress response pathways, further demonstrating that immune mechanisms are the key in vitiligo.[35]

The most significant genetic risk for vitiligo involves HLA-A polymorphisms, followed by HLA-DRB1/DQA1 and CPVL, which are related to antigen presentation. Moreover, genes associated with immune target cell lysis (*GZMB* and *FASLG*), adaptive immunity (*FOXP3*, *CTLA4*, *IL2RA*, *BACH2*, *CD80*, *CCR6*, *PTPN22* and *α-GZMB*), innate immunity (*TICAMI*, *IFIH1*, *CD80*, *NLRP1*, *CASP7*, *C1QTNF6* and *TRIF*), and melanocytes (*TYR*, *PMEL*, *MC1R*, *OCA2-HERC2* and *IRF4*) have been identified as risk factors for vitiligo.[36]

Previous studies have demonstrated that the polymorphisms of superoxide dismutase (SOD), a crucial mitochondrial reactive oxygen species (ROS) scavenger, are genetic risk factors for the susceptibility and progression of vitiligo.[37]

Chemical inducers

Different chemicals have been observed to induce skin depigmentation, that is, indistinguishable from idiopathic vitiligo. The mechanism of chemical-induced vitiligo is complex and still not clear.[38,39] It has been observed that some chemicals such as monobenzyl ether of hydroquinone (MBEH) and 4-tertiary butyl phenol can downregulate microphthalmia-associated transcription factor (MITF) leading to decreased melanin synthesis and thereby initiation of vitiligo.[40] MBEH was the first chemical known as causing depigmentation and nowadays, MBEH is approved by the US Food and Drug Administration (FDA) and is used therapeutically to complete and accelerate depigmentation to make the skin tone of patients with severe vitiligo uniform.[41]

Several studies have confirmed that exposure to chemical agents, specifically phenolic and catechol derivatives found in dyes (including hair dyes), resins/adhesives and leather is associated with vitiligo. Phenols can act as tyrosinase analogues, affecting melanin synthesis and causing high levels of stress in melanocytes. Cell stress leads to ROS accumulation and the unfolded protein response, triggering immune reactions that destroy melanocytes and result in skin depigmentation.[42]

Treatments and Future Perspectives

Finding the best treatment for vitiligo has become a challenge due to the complexity of the pathology of the condition. Therefore, vitiligo therapy must be personalised depending on each case and the degree of depigmentation. Safer and more effective treatments with long-lasting benefits are being studied because current treatments do not provide a long-lasting effect [Table 1].

Phototherapy

Phototherapy is the first-line treatment of choice for vitiligo. Narrowband UVB (NB-UVB) phototherapy induces re-pigmentation and is an effective treatment of vitiligo. This therapy provides good results on the face, trunk and limbs but topical treatment must be applied after phototherapy to prevent skin depigmentation. NB-UVB phototherapy can decrease the rate of new vitiligo lesions in non-segmental vitiligo patients, with earlier re-pigmentation in non-progressive vitiligo. Progressive patients required more doses of NB-UVB than non-progressive patients.[43] The action of NB-UVB in the re-pigmentation of the skin can be attributed to an increase in the expression of the genes involved in pigmentation such as the TYR gene family constituted by tyrosinase (TYR), tyrosinase-related protein 1 (TYRP1) and tyrosinase-related protein 2 (TYRP2).[44]

However, there are patients who do not respond to conventional phototherapies and in these cases, some studies have demonstrated that UVA1 laser can be an applicable therapeutic option.[45,46]

Topical therapies

Topical corticosteroids are the most commonly used drug to treat vitiligo but there are concerns over side effects. Topical corticosteroids have been observed as effective

Table 1: Current therapies for vitiligo

Current therapies	References
Vitiligo	
Phototherapy	Frisoli[36] *et al.* (2020), Bhatia[43] *et al.* (2021), Awad[44] *et al.* (2021)
Topical therapies	Dellatorre[48] *et al.* (2020), Rokni[52] *et al.* (2017)
Surgery	Nahhas[53] *et al* (2017), Thakur[55] *et al.* (2019)
Chemical depigmentation	Rahman and Hasija[35] (2018),
Laser therapy	Rahman and Hasija[35] (2018),
Skin camouflaging	Derbyshire[56] (2019) Levy[57] *et al.* (2012)
Immunotherapy	Rashighi[60] *et al.* (2015), Speeckaert[61] *et al.* (2017)

in recent and facial lesions; however, to reduce the risk of side effects the administration should be limited to small areas, avoiding prolonged use and introducing another topical therapy after some weeks of continuous administration.[47,48]

Topical corticosteroids exert anti-inflammatory responses, but re-pigmentation is more likely to occur on the face and neck than in the other areas. Moreover, topical corticosteroids can increase the efficacy of UVB and are indicated for small-localised patches. A combination of NB-UVB and topical corticosteroids has been demonstrated to be more effective than topical corticosteroids alone, presenting good tolerability both in adults and children.[49,50]

Topical immunomodulators such as corticosteroids reduce the production of proinflammatory cytokines by inhibiting T-cell activity, thereby increasing pigmentation. Other immunomodulators can be used such as the macrolide antibiotic tacrolimus, which inhibits calcineurin action, thus preventing T-cell activation and the production of various inflammatory cytokines. Tacrolimus has been demonstrated to increase the proliferation of melanocytes.[51] The topical application of tacrolimus is effective in the treatment of vitiligo and does not present the adverse effects observed with corticosteroids.[52]

Other therapies

Surgery is used when medical therapies are not effective and consists of pigment cell transplantation. The melanocyte–keratinocyte transplantation procedure (MKTP) is the most popular option for the management of select patients with vitiligo. MKTP consists of cellular grafting in which cells from a donor are grafted to a treated area as a cellular suspension covering a larger area. The combination of surgery and other therapies as topical administration of immunomodulators is used to reduce immune response.[53] Other adjuvant therapies include narrowband UVB phototherapy with a proliferative and stimulatory effect on transplanted melanocytes.[54] The use of epidermal cell suspension is usually performed in patients with clinical stability of a minimum of 12 months. The combination of epidermal suspension and dermal cell suspension gives a better response in patients with vitiligo and can be used early in the course of stable vitiligo without waiting for 12 months or more.[55]

The best option to treat extensive vitiligo is the depigmentation of the pigmented areas by chemical or laser therapy. However, the efficacy of this treatment and the duration of its benefits are not enough.[41]

Skin camouflage is the traditional application of pigmented creams that are designed to mask skin discolouration and can be useful where dermatological or surgical treatments may be considered invasive.[56] Camouflaging the depigmented areas with cosmetic products can improve the social life of patients with vitiligo despite potential risks.[57] Cosmetics can have a transient, semi-permanent or permanent (tattoos) effect. The most commonly used self-tanning product is dihydroxyacetone, whose effects increase with concentration.[58] It is noticeable that 10% is the highest concentration allowed in the European Union for the purpose of tanning, and from 2022, all cosmetics containing more than 10% of dihydroxyacetone will be banned in Europe.[59]

Future Perspectives

Emerging treatments will focus on the re-pigmentation of the skin through regulating autoimmunity, controlling melanocyte stress, and regenerating or depigmenting the remaining small-pigmented areas of the skin.

Targeted immunotherapy is one of the most important ways of treating vitiligo. Examples of this type of emerging therapy include the interference of IFN-γ-CXCL10 signalling,[60] and the use of JAK inhibitors, STAT inhibitors and immune checkpoint inhibitors.[61]

The regeneration of melanocytes can be stimulated with α-MSH analogues such as afamelanotide, which can improve the efficacy of phototherapy,[62] and with Wnt activators.[63]

ROS generation in patients with vitiligo can be resolved by reducing melanocyte stress through the use of antioxidants such as oral or topical natural health products.[64]

As mentioned above, in vitiligo patients with small areas of pigmentation, depigmenting products can be used to achieve a uniform skin tone. For this reason, compounds with low toxicity and no side effects are currently being investigated for depigmenting skin.

As reviewed, several factors account for the pathophysiology of vitiligo but still open questions

remain. However, a better knowledge of the pathogenesis of hypopigmentation epigenetic regulation by genomic imprinting can reveal the specific functional genes and their regulatory elements and pathways. In this sense, omics analysis, by Cai *et al*.[65] performed for vitiligo, can open a new perspective to understanding the causes, mechanisms and specific treatments for different skin pigmentation disorders.

Conclusions

In vitiligo, the destruction of melanocytes by the immune system is the major cause of this disease. Although the main signalling pathways are known, new therapies should be developed to treat vitiligo due to the low efficacy or side effects of current treatments. Therapies that can modulate the immune system, which is the main driver of hypopigmentation, are the best option to repigment the skin. Other agents that stimulate melanocytes can also be useful in inducing pigmentation.

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Conflicts of interest

There are no conflicts of interest.

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