REVIEW

Vitiligo as a potential degenerative disease: from oxidative stress to cellular senescence

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Abstract

Vitiligo is a depigmentation disorder characterized by the loss of melanocytes in the skin, which is aggravated by oxidative stress. The relationship between oxidative stress and cellular senescence is still unclear despite considerable research on melanocyte senescence in vitiligo in recent years. Many chronic diseases associated with oxidative stress, that is, degenerative diseases, have been shown to ultimately result in cellular senescence due to sustained activation of reactive oxygen species. This study advances research on the pathophysiology of vitiligo and its treatment options by summarizing the role of oxidative stress and melanocyte senescence in vitiligo and investigating the mechanisms behind the interaction of melanocyte senescence with oxidative stress.

Keywords: Vitiligo, melanocytes, oxidative stress, cellular senescence, age

Introduction

Vitiligo is characterized by the death or loss of melanocytes. Its etiology is complex and unclear [1]. In several investigations, oxidative stress has been implicated in the etiology of vitiligo and melanocyte destruction [2]. Oxidative stress causes a redox homeostasis imbalance in melanocytes, characterized by excessive synthesis and poor clearance of reactive oxygen species (ROS). Due to the oxidation-promoting state produced by epidermal melanocytes and the disruption of internal antioxidant defenses during melanin synthesis, the melanocytes produce too much ROS to form hydrogen peroxide (H_2O_2) during melanogenesis, leaving the melanocytes vulnerable to oxidative stress attack [3, 4]. Previous research has shown that melanocytes in nonlesional skin of vitiligo patients have abnormal characteristics compared to normal melanocytes [5-7], including increased susceptibility to oxidative stress, easy shedding of skin after friction, and

increased production of bioactive proteins (e.g., IL-6 and matrix metalloproteinase-3) of the senescence-associated secretory phenotype (SASP) [5-7].

Hayflick and Moorhead (1961) were the first to characterize cellular senescence. Cellular senescence is defined as the cessation of normal cell division due to cellular stressors such as DNA damage, pro-inflammatory responses, mitochondrial malfunction, or telomere shortening [8, 9]. Tissue regeneration, wound healing, and embryonic development have all been demonstrated to benefit from senescent cells *in vivo* [10, 11]. SASP, which comprises several pro-inflammatory cytokines, chemokines, and growth factors, is primarily responsible for the negative impacts of senescent cells [12, 13]. Senescent cells can also communicate with neighboring cells by transferring proteins to them. For example, senescent cells can secrete SASP factors, which can cause paracrine senescence in normal neighboring cells [13, 14], and long-term exposure to SASP impairs the regenerative capacity of mouse keratin-forming cells (KCs) [13]. Senescent cells can also modulate the immune response and thereby facilitate their own clearance [15]. Numerous studies have demonstrated that oxidative stress has an important role in the process of melanocyte senescence. In this review, we discuss how ROS are generated, how vitiligo melanocytes respond to oxidative stress, and the molecular and signaling pathways by which oxidative stress induces vitiligo melanocyte senescence.

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Oxidative and antioxidant systems of cells

Although there is no consensus yet on the exact cause of vitiligo, oxidative stress is considered one of the most critical triggers of the disease [2]. Oxidative stress is a disturbance in redox homeostasis characterized by an imbalance of pro-oxidants and antioxidants. Oxidative stress in tissues and cells is always caused by an excess of ROS, which contain H_2O_2, hydroxyl radicals, hypochlorous acid, and H_2O_2 radicals [16]. Previous studies have focused on endogenous ROS production due to metabolic activity, but many environmental stimuli, including cytokines, ultraviolet (UV) radiation, chemotherapeutic drugs, high temperatures, and even growth factors, can produce high levels of ROS that disrupt normal redox homeostasis and convert cells to a state of oxidative stress [17-19]. On the other hand, ROS can be attributed to a range of internal stimuli: (a) cellular metabolic processes, which are inherited, such as melanogenesis, which requires more energy; and (b) abnormal mitochondrial energy metabolism, which ultimately leads to cell proliferation, differentiation, and apoptosis [20, 21]. During melanogenesis, the production of ROS generates dopaquinone from dopa and then dopachrome, making melanocytes more susceptible to oxidative damage [22]. In addition, melanogenesis is an energy-consuming process that requires large amounts of adenosine triphosphate (ATP). The biogenesis of ATP itself is accompanied by the production of ROS in the mitochondria and the formation of H_2O_2 in the epidermis [23]. Overall, these changes place the melanocyte at the center of ROS accumulation.

In addition, a complex system of enzymatic and non-enzymatic antioxidant defenses, including catalase (CAT), superoxide dismutase, and glutathione peroxidase, can counteract and regulate overall ROS levels to maintain physiological homeostasis [24]. Several studies have also found that oxidative stress is an important factor of the activation of DNA damage repair (DDR) and that telomeres are particularly sensitive to a homeostatic imbalance of ROS [25, 26]. Mitochondria are a major source of ROS production and are considered a key component of the generation and replenishment of DNA damage foci, which are important effectors of cellular senescence [27, 28]. Thus, under the influence of external and internal factors, melanocytes can produce more ROS that cause an imbalance in the intracellular antioxidant system and induce apoptosis and loss of melanocytes.

Overview of cellular senescence

Cellular senescence occurs in damaged cells and prevents their proliferation in organisms. Cell damage itself does not directly lead to obvious signs of aging; but when the damage accumulates and reaches a certain limit, the cells stop proliferating, resulting in macroscopic tissue weakness and a physiologically senescent phenotype [29]. Cellular senescence is a tumor-suppressive program initiated by many stress signals, including telomere wear, DDR, oxidative damage, subculture conditions, and abnormal oncogene activation [30]. The hallmark of cellular senescence is the permanent inhibition of proliferation, which cannot be overcome by physiological mitogenic stimuli. Depending on the method of induction and the mechanisms involved, cellular senescence can be classified into three types. The earliest and most intensively studied type of cellular senescence is replicative senescence (RS), which is characterized early on by telomere wear and activation of the p53/p21 pathway [31, 32]. The second type of cellular senescence is stress-induced premature senescence (SIPS), which is induced by various stresses, such as oxidative stress and UV light [33-35]. The third type is oncogene-induced senescence (OIS), which is overactivated by several oncogenes, particularly, the RAS gene [36-38]. SIPS and OIS have no apparent telomere wear, but they play an important role in the activation of the p16/p38 pathway [39, 40].

Skin cellular senescence is also accompanied by some phenotypic changes, such as SASP [41]. Coppe *et al.* (2008) first proposed the concept of SASP [42]. They found that senescent cells can promote carcinogenesis of adjacent precancerous cells by secreting inflammatory and oncogene-related factors that they called the SASP. Senescent cells accumulate in various organs accompanied by a series of complex SASPs, in which the expression and secretion of different types of cytokines are significantly increased. SASPs are the most important environmental effect of senescent cells. The deleterious effects of senescent cells are mainly attributed to SASPs, which include proinflammatory cytokines (e.g., IL-1α, IL-1β, IL-6, and IL-8), growth factors (e.g., HGF, TGF-β, and GM-CSF), chemokines (e.g., CXCL-1/3 and CXCL-10), and matrix remodeling enzymes (e.g., metalloproteinases) [41, 43]. The SASP of senescent human hepatocytes expresses other unique secretory phenotypes and promotes macrophage migration in addition to the characteristic factors IL-8 and IL-6 [44].

Senescent cells can induce paracrine senescence in normal neighboring cells by secreting the SASP factor [14]. Chronic exposure to SASPs can impair the regenerative capacity of mouse KCs [13]. Several essential phenotypes have been used to identify senescent cells. They include (1) cell cycle arrest in the G1 phase, which is often detected as a lack of DNA replication; (2) a flattened and enlarged cell morphology; (3) abnormal activation of lysosomes, as evidenced by positive staining for senescence-associated β-galactosidase activity (SA-β-gal) [45-48]; (4) significant chromatin heterogeneity (senescence-associated heterochromatin foci, SAHF) [49, 50]; (5) telomere shortening, but as mentioned above, is not a reliable signal for SIPS and OIS [34, 51]; and (6) high expression of several cell cycle repressor genes, such as p16, p53, and p21 [31, 52-54].

Melanocyte senescence

Melanocytes: the main senescent population in the human epidermis

Melanocytes are the main senescent cells in the skin senescence process. As we age, senescent cells accumulate in human skin [46, 55]. Most studies on skin cell senescence have focused on skin fibroblasts, and little is known about the effect of melanocytes on skin senescence. Recent reports have shown that melanocytes can express the senescence marker p16ink4a and accumulate in human skin [56]. Senescent melanocytes also exhibit other senescence markers, such as reduced HMGB1 and telomere dysfunction, but not telomere shortening. Waaijer et al. found that p16ink4a markers are localized almost exclusively in melanocytes in the epidermis [56, 57]. Therefore, melanocytes are the major senescent cell population in the human epidermis.

RS is not a major factor in melanocyte senescence. Victorelli *et al* [58]. found that telomeres in skin senescent melanocytes were not significantly shortened and that telomeres were unlikely to occur due to extensive loss of telomeric repeat sequences. Therefore, the telomere length was not a limiting factor in melanocyte senescence. Furthermore, fully differentiated melanocytes in the skin have an extremely low proliferative capacity *in vivo* and are thus unlikely to experience sufficient telomere wear to induce RS [59]. Oxidative stress disrupts the binding of certain telomeric protein complexes to telomeres, thereby providing a novel mechanism for telomere shortening [60]. However, the mechanisms of melanocyte senescence and whether melanocytes have a causal effect on the phenotype of skin aging remain unclear.

Senescent melanocytes: inducing senescence in neighboring cells

In the vitiligo skin microenvironment, senescent melanocytes can induce senescence in neighboring keratinocytes. Nelson *et al*. demonstrated that senescent cells can induce DNA damage and senescence in neighboring healthy cells through the mechanism of SASP secretion and increased ROS [61, 62]. Victorelli *et al*. showed that senescent melanocytes surrounding KCs exhibited significant telomere damage, providing evidence of the bystander effect of senescent melanocytes in human skin [58]. They also found that the conditioned medium from senescent melanocytes induced the tumor angiogenesis factor(TAF) in dermal fibroblasts *in vitro*, suggesting that the induction of paracrine TAF is mediated by soluble factors released from senescent melanocytes. Senescent melanocytes have also been shown to induce telomere dysfunction in periepidermal KCs. Dysfunctional telomeres provide a source of persistent DDR for the keratinocyte population, further limiting the replicative capacity of the cells [63-65]. However, the molecular mechanisms and signaling pathways of senescence inducement by senescent melanocytes in neighboring healthy cells are not yet fully understood. Victorelli *et al*. also showed that the release of IP-10 from senescent melanocytes activated the CXCR3 signaling pathway in peripheral cells, which would increase mitochondrial ROS production and lead to telomere dys-

function [58]. Previous studies have also demonstrated increased ROS production from stimulation of CXCR3 receptors [66] and that these components of SASP, particularly TGF-β1, induce paracrine telomere dysfunction in a ROS-dependent manner [62]. Although the mechanisms that lead to enhanced mitochondrial ROS production downstream of the CXCR3 signaling pathway have not yet been fully elucidated, several studies have demonstrated that Akt is phosphorylated as a consequence of CXCR3 activation [67, 68]. Indeed, Akt is involved in the signaling cascade that enhances mitochondrial ROS production during aging [28].

Interference between senescent skin cells and immune cells

The skin contains many types of immune cells, including mononuclear phagocytes (MNPs) such as Langerhans cells (LCs), dendritic cells, macrophages, monocytes, and T cells [69] .The exact relationship between skin immune cells and skin stromal cells is not yet correctly understood, but more evidence suggests that the cellular crosstalk between aging skin stromal cells and immune cells leads to the aging phenotype of the skin [70].

Among MNPs, LCs are epidermal dendritic cells with self-renewal properties. Due to the low expression level of IL-1 in aged skin, the number of LCs is reduced and shows reduced cell migration to regional lymph nodes [71]. Reduced migration of LCs may lead to the activation of antigen-specific T cells and regulatory T cells and maintain the skin's immune homeostasis [72]. Macrophages and monocytes are two other major classes of MNPs in the skin. Senescent fibroblasts produce several SASPs, including the C-C-triggered chemokine ligand 2, which then recruit prostaglandin E2 to produce monocytes and inhibit T cell immune responses [70]. Under inflammatory conditions, skin-infiltrating monocytes are guided to differentiate into macrophages by a cytokine environment containing monocyte colony-stimulating factor. These macrophages release high levels of MMPs and ROS to reduce the skin's ECM and contribute to chronic inflammation [70]. These results strongly suggest that the MNP of the skin actively promotes inflammation and promotes the skin aging phenotype. In addition, T cells resident in the skin express a memory phenotype, called skin-resident memory T cells [73]. It has been demonstrated that aged skin cells can increase the ratio of CD4+ to CD8+ T cells [74]. Further studies are needed to understand the role of these in inflammation.

Relationship between oxidative stress and melanocyte senescence in vitiligo

Oxidative stress: inducing premature senescence of vitiligo melanocytes

Vitiligo melanocyte senescence is closely related to the inducement of oxidative stress. Harman *et al*. (1998) proposed the senescence radical theory, which suggests that

senescence is caused by harmful tissue damage from oxidative stress-induced ROS, a key factor of the inducement of melanocyte senescence in vitiligo. There is evidence of elevated levels of H_2O_2 in the epidermal environment of melanocytes and KCs of damaged and undamaged skin in vitiligo patients [75], which suggests the importance of oxidative stress in the pathogenesis of vitiligo. High levels of ROS have been associated with various aspects of melanocyte damage, including the destruction of their DNA, lipids, proteins, and structural and functional metabolites [76]. In addition, ROS-induced oxidative stress causes widespread abnormal organelle function, disrupts metabolic pathways, and impairs antioxidant defense mechanisms.

Previous studies have shown that melanocytes may not be completely absent in damaged skin and that they can proliferate and be passed on to vitiligo patients in both lesions and nonlesions. However, disrupted growth of these melanocytes was observed in an *in vitro* setting, and the addition of CAT to the culture medium significantly improved this situation. Therefore, some researchers have suggested that increasing H_2O_2 in lesions may not be sufficient to kill melanocytes in the early stages of vitiligo but that H_2O_2 may eventually destroy these melanocytes in the late stages of vitiligo [77]. In addition, many chronic diseases associated with oxidative stress are known as degenerative diseases, and vitiligo may have similar features. High doses of H_2O_2 affect the cellular mitochondrial function and trigger apoptosis. Low doses of H_2O_2 induce cellular senescence and expression of cell cycle proteins [78, 79]. Thus, in the early stages of vitiligo, impaired melanocyte growth induced by oxidative stress may be due to premature cellular senescence [33], Furthermore, several molecular and cellular signaling pathways are involved in oxidative SIPS-like phenotypes of melanocytes, and skin biopsies from vitiligo patients have shown a senescent phenotype, which supports the concept that early vitiligo may be a degenerative disease [5, 33]. However, the signaling cascade associated with H_2O_2-induced premature senescence of melanocytes is not yet fully understood.

Signaling mechanisms involved in vitiligo melanocyte senescence due to oxidative stress

There is evidence that oxidative stress causes genomic DNA damage and ROS leads to cellular senescence. Many signaling proteins are involved in cellular senescence, such as p53, the mitogen of the p38 protein kinase (MAPK), the nuclear factor kappa-B, the mammalian target of rapamycin (mTOR), the transforming growth factor (TGF) beta (-β), and other signaling channels [80].

(1) p38 signaling pathway

The p38 signaling pathway consists of MAPK and the TGF-activated protein kinase (AKT)-binding protein 1, which inhibits telomerase activity and induces human T cell senescence, proliferation, and expression of T cell receptor (TCR) signaling molecules [81]. p38 MAPK signaling activation induces mTOR-mediated autophagy in senescent CD8+ T cells and enhances telomerase activity

[82]. p38 MAPK activation would also trigger a DDR-independent SASP senescence phenotype [83]. Cell proliferation can be enhanced by blocking the p38 and PD1 signaling pathways [82]. Similarly, P38 MAPK inhibitors inhibit the aging of corneal endothelial cells, providing evidence for the treatment of corneal endothelial dysfunction [84]. Hou et al. showed that oxidative stress increases ROS in melanocytes, which activates the ERK1/2 and p38MAPK pathways, and increases the p53-independent cell cycle protein-dependent kinase (CDK) inhibitor p21 (CDKN1A), prompting the blocking of the cell cycle in the M phase and preventing its entry in the G1 phase, which makes the cells incapable of replicating properly and thus, inducing premature melanocyte failure (Figure 1) [85].

(2) p53/p21 and p16

p53/p21 and p16(CDKN2A) signaling are the main pathways that induce melanocyte senescence [33, 81, 86-89]. In response to oxidative stress, p53 may be activated, which in turn activates p21 for senescence induction. However, p21 can also be induced in a non-p53-dependent manner [90, 91]. Previous studies have shown that p16 plays a major role in vitiligo melanocyte senescence [5] or in normal melanocyte senescence [92]. p53 signaling in cellular senescence has been studied for many years, and some proteins promote p53-mediated cellular senescence, such as Aurora B kinase [93], secretory phospholipase A(2) [94], and IFN-γ [95], while other proteins inhibit p53-mediated cellular senescence, such as Sirt2 [96], Hsp27 [97], and MAD2 [98]. p53 is a molecular switch that regulates IGF1-induced premature aging [99]. Short-term exposure to IGF1 promotes cell proliferation, and long-term exposure induces cellular senescence [100]. In addition, Akt and p21 are required to induce cellular senescence downstream of p53 [100]. The p21 gene is a member of the CLP family of cell cycle-dependent kinase inhibitors located downstream of the p53 gene. Together with p53, p21 can constitute a cell cycle G1 checkpoint that cannot be passed on without repair due to DNA damage, thereby reducing the replication and accumulation of damaged DNA and producing an oncogenic effect [53].

Antioxidant and antiaging treatment for vitiligo

Vitiligo therapy has always been challenging for dermatologists. The current vitiligo therapy does not appear to be curative. Phototherapy (psoralen mixed with UVA and narrowband UVB [NBUVB]), topical therapies (corticosteroids and calcineurin inhibitors), and systemic treatments (corticosteroids) remain in use, with high side effects to patients and financial burden heavy. Therefore, it is very important to use some anti-oxidant and anti-aging related treatments [4, 101].

Exercise

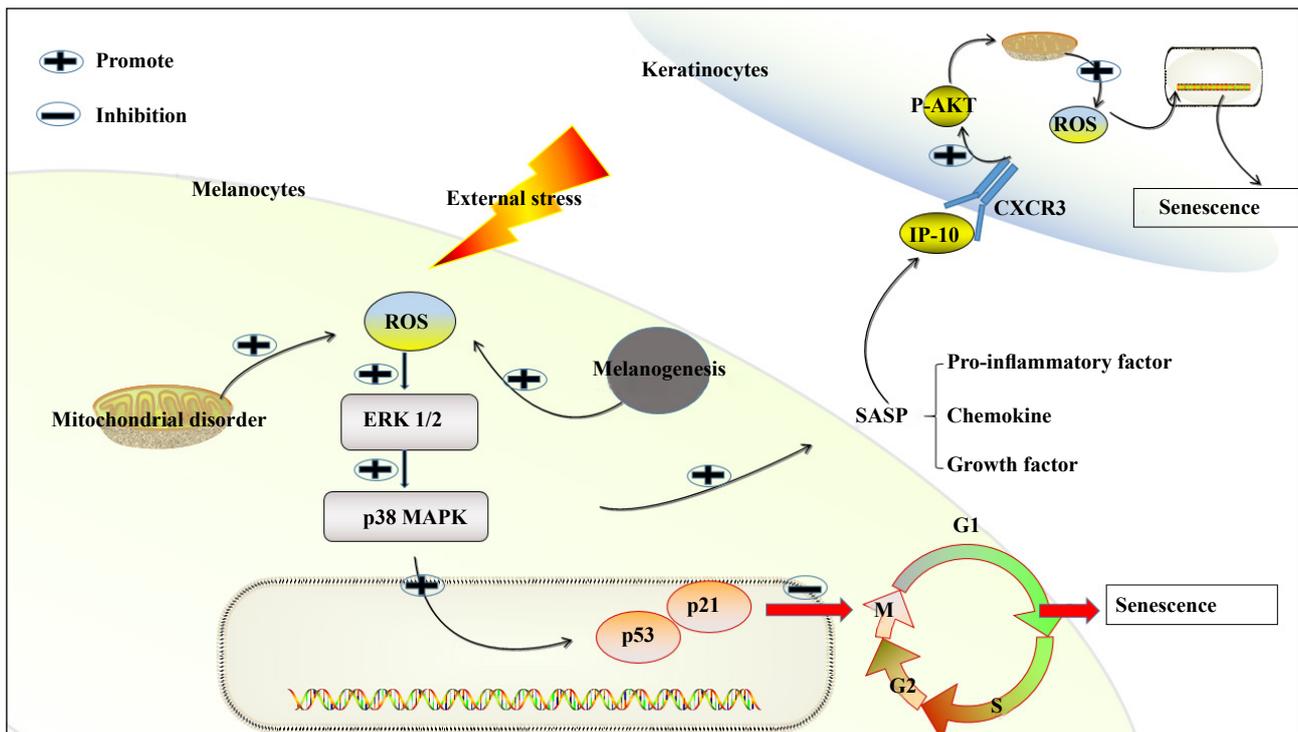Several studies have shown that overnutrition significantly increases the expression of senescence-associated

Figure 1. **Schematic illustration of oxidative stress-induced skin cell senescence.** (1) Oxidative stress increases ROS in melanocytes, which activates the ERK1/2 and p38MAPK pathways and causes the p53-independent cell cycle protein-dependent kinase (CDK) inhibitor p21 (CDKN1A) to increase. This prompts the blocking of the cell cycle in the M phase and prevents its entry in the G1 phase, which makes the cells unable to replicate properly and thus, inducing premature melanocyte failure. (2) The IP-10 released from senescent melanocytes activates the CXCR3 signaling pathway in peripheral keratinocytes, which phosphorylates it by activating Akt and increasing the mitochondrial ROS. This would increase mitochondrial ROS production and lead to telomere dysfunction as well as peripheral keratinocyte senescence.

proteins, including the activity of p16, p53, p21, and SA-β-gal [102]. Exercise can inhibit the expression of SASP-related genes and prevent the accumulation of senescent cells caused by overeating [103]. Mechanistically, exercise may reduce the metabolic and replicative stress of adipose tissue and limit the transition to senescence. In addition, exercise may promote the elimination of senescent cells by the immune system [102, 103].

Inhibition of melanocyte senescence by inhibiting oxidative stress

To understand the mechanisms of oxidative stress and cellular senescence in healthy and vitiligo melanocytes and to use these pathways for effective and targeted therapeutic and preventive measures. Natural chemicals with antioxidant potential can inhibit oxidative stress-induced aging. For example, baicalein is a flavonoid derived from the root of Scutellaria baicalensis with anti-cytotoxic, anti-inflammatory, and antitumor effects [104, 105]. In an H_2O_2-induced oxidative stress model of PIG1 in vitro, baicalein protected PIG1 cells from H_2O_2-induced oxidative stress and senescence through a mechanism that involved activation of mitochondria-dependent caspases and regulation of the p38MAPK pathway [106]. In H_2O_2-induced human vitiligo melanocytes (PIG3V), baicalein increased the expression of Nrf2 and its downstream gene HO-1 in the PIG3V cells and promoted the translocation of Nrf2 from the cytoplasm to the nucleus, indicating that the protective effect of baicalein on melanocytes depends on the

Nrf2 signaling pathway [107]. Baicalein also has an antioxidant effect on keratinocytes [108]. Therefore, the development of topical formulations of baicalein for vitiligo may be a feasible approach. In addition, some molecules can slow down aging by directly inhibiting ROS production. For example, nicotinamide, an amide derivative of vitamin B3, can slow down aging by reducing the ROS levels [109].

Inhibition of cellular senescence-related pathways

Given that many signaling pathways play an important role in the process of senescence, senescence may be inhibited by inhibiting these pathways. In one study, treatment induced tumor cell senescence, during which Bcl2-associated athanogene 3 (Bag3) increased [110]. Importantly, the knockdown of Bag3 or vault protein (MVP) impairs ERK1/2 activation and promotes treatment-induced apoptosis in senescent cells [110]. A similar study found that inhibition of the MEK/ERK pathway promotes the clearance of RAS-transformed senescent cells, which prevents these cells from forming the necessary autophagosomes to clear damaged mitochondria and cause apoptosis [111].

Outlook

In summary, we discussed the following aspects. First, oxidative stress is a key initiating factor of vitiligo. Sec-

ond, ROS-induced melanocyte senescence in vitiligo is the major senescent group of skin cells. Third, the IP-10 released from the senescent melanocytes *in vivo* activates the CXCR3 signaling pathway in peripheral keratinocytes, which phosphorylates them by activating Akt, which increases mitochondrial ROS production, leading to telomere dysfunction and causing senescence in peripheral keratinocytes. Fourth, oxidative stress drives increased ROS in melanocytes, activating the ERK1/2 and p38MAPK pathways and increasing CDKN1A, which induce premature melanocyte senescence. Finally, we explored the role and mechanisms of some antioxidant and antiaging drugs in vitiligo treatment.

In the context of genetic susceptibility, ROS plays a key role in the development of vitiligo. ROS contributes to the destruction of melanocytes in many ways in the early stages, such as in melanocyte senescence. Furthermore, cellular senescence plays an important role in both normal states and physiological conditions. Since its discovery, many important studies on the role and molecular mechanisms of cellular senescence have been completed. However, the role of melanocyte aging in the development of vitiligo has not been fully elucidated yet. More challenging questions have been raised. First, the relationship between cellular senescence and the immune response remains elusive. For example, it is unclear whether senescent cells activate adaptive immunity and defend the body. It is also possible that other novel signaling pathways are involved in the aging of vitiligo melanocytes. Overall, the study of cellular senescence is only the beginning, and there are more interesting questions to be addressed in the future.

Declarations

Authors' contributions: Qiang Li is responsible for the direction and overall revision of the article. Yaojun Wang wrote the main content of the manuscript.Jiaoni Chi, Tao Wang, Yue Zhang, Zhimin Li, Jie Chen and Haixia Liu, revised the manuscript.

Availability of data and materials: Not applicable.

Financial support and sponsorship: None.

Conflicts of interest: The authors declare no conflict of interest.

Ethical approval and consent to participate: Not applicable.

Consent for publication: Not applicable.

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