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International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

The Role of Melanogenesis in Sking Aging

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A B S T R A C T

Skin frequently exhibits degenerative indications that support many disease processes as well as the ageing phenotype. Interactions among several skin cell types, including fibroblasts, endothelial cells, keratinocytes, and melanocytes, during the ageing process may be crucial for melanogenesis and the consequent pigmentation associated with ageing. Melanocytes and fibroblasts are the most often observed senescent skin cells in the skin, and their populations grow with age. It has been noted that melanocytes and surrounding cells, such as keratinocytes and fibroblasts, undergo senescence. Considering changes in ageing skin phenotypes, interaction between senescent skin cells may be crucial. Reduced melanogenesis, which gives ageing skin its pale appearance, is a known factor in skin ageing and may be partly explained by decreasing vascularity. Independent of skin phototype, a number of investigations have shown that there is an inverse association between age and melanocyte proliferative activity. One potential therapy approach to prevent and restore skin-aging characteristics is to target senescent cells and associated components.

Keywords: melanogenesis, melanocyte, melanin, skin aging

1. Introduction

The skin serves as the first line defence of internal organs against a wide range of environmental contaminants. Skin serves as an essential barrier between the internal milieu and the outside world, making it a vital tool for maintaining bodily homeostasis. Nonetheless, skin frequently exhibits degenerative indications that support many disease processes as well as the ageing phenotype (Rusanova *et al.*, 2019).

Ageing is a diverse and time-dependent process that progressively advances in accordance with human chronological age and is impacted by a number of factors, including genetic and environmental elements (Blokzijl *et al.*, 2016). Senescent cells accumulate in ageing organs as a result of the ageing process, which affects different organs to varying degrees. Pigmentation, atrophy, elasticity loss, and a compromised defence mechanism against harm are clinical signs of ageing skin that lead to future pathologic dermatological issues (Wong and Chew, 2021).

The topic of skin pigmentation during ageing has received a lot of attention lately, with cellular senescence being considered a major contributor to skin-aging pigmentation. Interactions among several skin cell types, including fibroblasts, endothelial cells, keratinocytes, and melanocytes, during the ageing process may be crucial for melanogenesis and the consequent pigmentation associated with ageing (Okazaki, 2016). Strong anti-aging properties have been found in melatonin, a potent free radical scavenger with antioxidant, anti-inflammatory, and the capacity to preserve mitochondrial homeostasis in various experimental settings (Sayed *et al.*, 2019)

2. Literature Review

2.1 Changes in Aging Skin Cells

Melanocytes and fibroblasts are the most often observed senescent skin cells in the skin, and their populations grow with age (Kim *et al.*, 2022). A study of morphological alterations in cells can be useful in identifying senescent cells, which are primarily distinguished by an irregular, swollen, and flattened appearance. Other senescent cell indicators confirm that senescent keratinocytes and UVB-induced senescent melanocytes in skin cells exhibit an increase in cell size (Martic *et al.*, 2020). Furthermore, the intracellular deposition of lipofuscin in lysosomes and glycogen particles has been linked to an increase in the granular content in senescent fibroblasts and melanocytes (Choi *et al.*, 2018). All senescent skin cells exhibit an age-related sequential increase in the exposed skin, even if fibroblast senescence occurs before melanocyte senescence. Additionally, it has been noted that melanocytes and the cells that surround them, such as keratinocytes and fibroblasts, undergo simultaneous senescence. When considering changes in age-associated phenotypes in ageing skin, the interaction between senescent skin cells may be crucial (Kim, Park and Kang, 2022).

2.2 Factors Triggering Cellular Aging

Similar to ageing other organs, ageing skin is a result of numerous intricate variables and processes. It is commonly acknowledged that there are two basic categories of causative causes for skin ageing: extrinsic and intrinsic. The term "intrinsic skin ageing" describes the physiological alterations in the skin that take place throughout time; this condition is clinically defined as dry, pale skin with fine wrinkles and decreased flexibility. Since the oestrogen underpinning UVB exposure can sustain pigmentation by increasing the number of blood vessels, an acquired chronic relapsing hyperpigmented condition like melasma can improve in terms of skin pigmentation when the oestrogen level declines (Cario, 2019).

Extrinsic skin ageing can be brought on by a variety of external environmental variables, which are commonly referred to as the "exposome." These factors include UVB and UVA radiation, infrared and visible light, air pollution, cigarette smoking, chemical exposure, nutrition, stress, sleep deprivation, and trauma (Passeron *et al.*, 2020). Because UV radiation is the primary cause of extrinsic skin ageing, it can result in reactive oxygen species (ROS) and DNA damage in cells. As a result, clinically, extrinsic skin ageing is linked to uneven pigmentation, coarse wrinkles, and lentigines (Krutmann *et al.*, 2021).

In particular, telomere shortening—which is regarded as replicative senescence—as well as reactions to a variety of stressors, including oxidative stress, paracrine factors, DNA damage, oncogenes, mitochondrial malfunction, and epigenetic modifications, can cause ageing at the cellular level. Replicative cellular senescence is the outcome of sustained DDR pathway activation brought on by significantly shortened telomeres (Kim, Park and Kang, 2022).

Ageing is also influenced by oxidative damage-induced cellular senescence. Increased levels of oxidative stress can cause the upregulation of stress-induced factors and, in turn, different cytokines, such as VEGF, TNF-α, interleukin (IL)-1, IL-6, nuclear factor κB (NF-κB), and hypoxia-inducible factors (HIFs). These elements cause senescent cells to become inflamed. Furthermore, disruption of the 3′ overhang at the end of the telomeres caused by oxidative damage to DNA might alter the normal structure of telomeres and cause apoptosis or proliferative senescence mediated by p53 to occur prematurely (Kim, Park and Kang, 2022).

2.3 Melanogenesis

Melanin determines the colour of the skin, eyes, and hair. The final products of a few-stage transformation of L-tyrosine, such as eumelanin, pheomelanin, neuromelanin, and mixed melanin pigments, are polymorphous and multifunctional biopolymers that make up melanin. The activity of pigment cells, such as melanocytes and retinal pigment epithelial cells (RPE), between melanosomes produces melanin. Lysosomal membrane-protecting membrane proteins, or LAMPs, are found in membrane-associated proteins with lysosomes. Because they convert anaerobic glycolysis from oxidative catabolism, change the ratios of NAD/NADH and NADP/NADPH, and activate the pentose phosphate pathway, melanosomes change how cells metabolise their energy (Videira, Moura and Magina, 2013).

In a physiological environment, melanocytes synthesise melanin. Its structural and enzymatic components are arranged independently in a manner similar to the creation of lysosomes. The presence of tyrosinase initiates melanogenesis by oxidising tyrosine or L-DOPA to dopaquinone. The oxidation of L-DOPA to melanins is also triggered by a high concentration of metal ions (Mn^{2+} or Cu^{2+}). Proopiomelanocortin peptides (POMC), cytokines, nitric oxide (NO), prostaglandins, and leukotrienes are produced by melanocytes and have either an autocrine or paracrine effect on keratinocytes. They also have a role in the immunological response. Melanin granules are seen in humans between days 27 and 30 of foetal development, although melanosomes at all phases of maturation are seen prior to week 14. Within a few weeks, the melanogenesis process ends before cells fully pigment (Skoczyńska *et al.*, 2017).

A broad schematic of melanin biosynthesis is presented in Figure 1. When L-phenylalanine is hydroxylated to L-tyrosine or straight from L-tyrosine, which is then converted to L-DOPA, the biosynthesis of melanin begins. L-DOPA is oxidised to dopaquinone in the following step. A fibrillar matrix forms during the second step of the eumelanogenic pathway. Dopaquinone is converted to leukodopachrome via the eumelanogenic pathway, which is preceded by oxidation and reduction processes. As a result, intermediates such dihydroxyindole (DHI) and dihydroxyindole carboxylic acid (DHICA) are created, which then polymerise to form eumelanin. Eumelanosomes can mature in two different ways. Melanosomes that arise from the Golgi apparatus and the endoplasmic reticulum are supplied with enzymes via vesicles. Tyrosinase and other melanogenesis-related proteins are deposited in late-developed endosomes after initially being deposited in early-developed endosomes with the help of adaptor protein 3. They later establish a connection with melanosomes at the initial stage. Dopaquinone is the precursor of phenomelanogenesis and is coupled to either glutathione or cysteine. Glutathionyldopa and cysteinyldopa are the products of this. Pheomelanin is then produced by converting these components. Because vitamin E suppresses tyrosinase activity during post-translational processing, it is a powerful inhibitor of melanogenesis. Melanocyte maturation is stimulated by retinoic acid. Only white-skinned individuals can have tyrosinase induced in the basal layer of the epidermis (Skoczyńska *et al.*, 2017), (Hughes and Bishop, 2022)

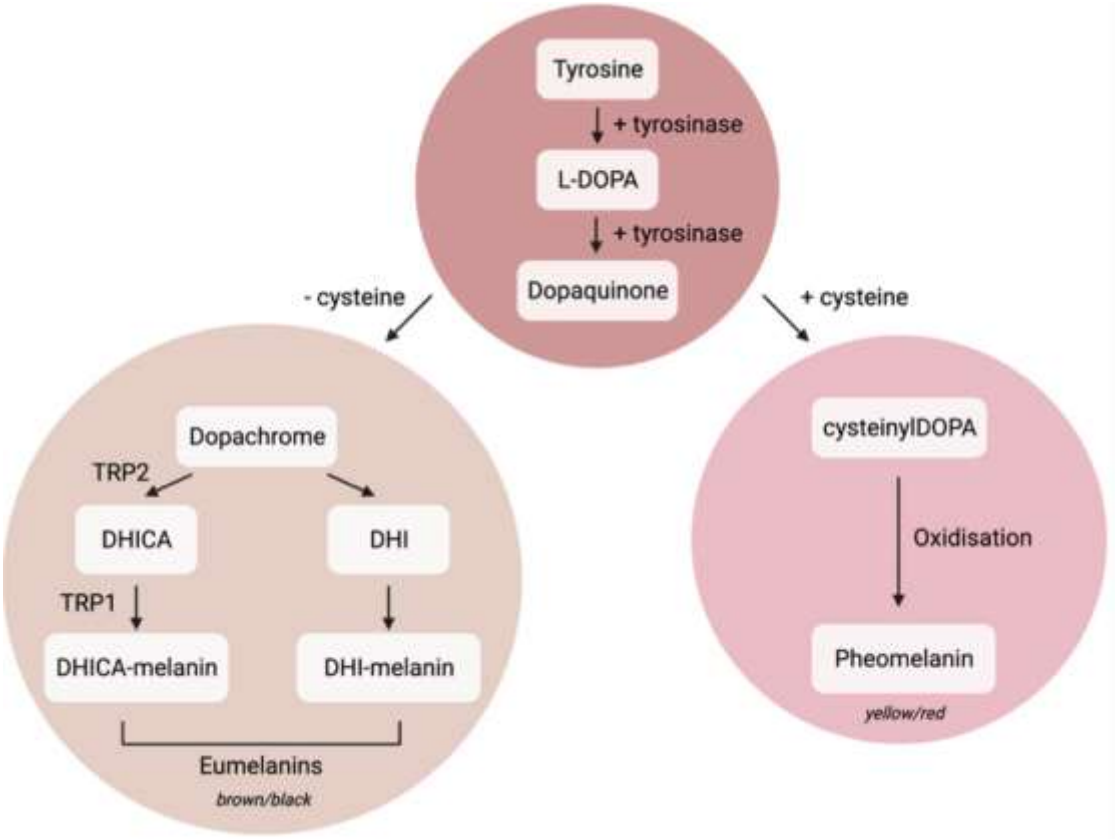

Fig. 1 - General scheme of melanin biosynthesis (Hughes and Bishop, 2022).

2.4 Cellular Senescence in Skin-Aging Pigmentation

The number of functioning melanocytes gradually decreases with chronological ageing, and melanogenic activity, particularly tyrosinase activity, is decreased. These factors combine to give elderly people's skin a pale appearance. Nonetheless, compared to unexposed ageing skin, photoexposed skin's melanocytes are comparatively well-maintained, most likely as a result of melanocytes' sensitivity to ongoing UV stimulation (Kang *et al.*, 2021). While it might be viewed as a defence mechanism to shield the skin from photodamage, melanocytes undergo morphological and functional phenotypic alterations as a result, which leads to the development of pigmentary conditions. Age-related pigmentary alterations that are typical of ageing include melasma and senile lentigo. Senile lentigo most frequently affects exposed skin areas, like the face and the dorsum of the forearm or hand, and is frequently seen in the elderly. It is distinguished by light- to dark-brownish macules and patches of varying sizes. Another typical pigmentary problem that appears on sun-exposed skin areas is melasma, which is not age-related. Melasma is a chronic, recurring illness characterised by clinically diffuse light- to dark-brown pigmentation over the centrofacial and malar regions (Passeron and Picardo, 2018).

Melasma and senile lentigo both have hyperpigmented skin, with active melanocytes being the main cause of the elevated pigmentation. The decreased quantity of melanocytes and melanin content is the cause of the hypopigmentation of IGH. However, melanocytes alone are not the main source of pigmentation associated with ageing skin. When the homeostasis of the pigmentation system is disrupted, pigmentary cells interact with typical neighbouring skin cells such as keratinocytes, fibroblasts, and endothelial cells. Therefore, in order to explore the function of cellular senescence in a variety of pigmentary illnesses, it is imperative to comprehend the cellular interaction between melanocytes and the surrounding cells in skin-aging pigmentation (Rani *et al.*, 2018).

When keratinocytes are exposed to UV radiation, particularly UVB, they break their DNA, which activates p53 and causes an increase in POMC. This causes keratinocytes to produce more α-melanocyte-stimulating hormone (α-MSH), which is a post-translational cleavage product of POMC. α-MSH then stimulates neighbouring melanocytes' MC1Rs, activating melanogenesis and microphthalmia-associated transcription factor (MITF) (Swope and Abdel-Malek, 2018). Furthermore, through the TGF-β–PAX3 and ATP–P2X7 signalling pathways, respectively, the downregulation of transforming growth factor (TGF)-β1 and the upregulation of adenosine 5′-triphosphate (ATP) production in keratinocytes caused by UV radiation also lead to enhanced MITF and melanogenesis (Lee *et al.*, 2019).

Senescent melanocytes have a very small regulatory role in the pigmentation associated with ageing skin. On the contrary, it seems that the senescent melanocytes are a consequence of the elevated melanogenesis brought on by prolonged sun exposure. UV radiation causes nearby cells, including fibroblasts and keratinocytes, to release a variety of melanogenic substances, which increases the formation of melanin. It is a little effect, but UV irradiation directly stimulates melanocytes, which prolongs p53 expression and increases melanin pigment. Senescent alterations in melanocytes can arise from repeated stimulation of melanocytes in skin exposed to light. Melanocyte senescence is repeatedly accelerated by melanin buildup. Senescent

melanocytes do, in fact, appear on human skin, usually in the forties. Melanin accumulates in the cytoplasm of IGH patients' melanocytes due to retracted or underdeveloped dendrites and decreased melanin transport to neighbouring keratinocytes. This illustrates how melanocyte senescence contributes to hypopigmented, ageing skin (Choi *et al.*, 2018),(Rani *et al.*, 2018).

In a recent investigation, senescent melanocytes were proposed to play a propagator role in skin ageing through paracrine telomere dysfunctions of keratinocytes and fibroblasts, in addition to their role in the formation of ageing pigmentation. Telomere dysfunctions can be brought on by the expression of SASPs and other inflammatory indicators by senescent melanocytes alone. Through CXCL3-dependent mitochondrial ROS, this process subsequently causes the growth arrest of nearby cells, such as keratinocytes, and accelerates the ageing of the skin. More research is required to determine the functions of senescent melanocytes in the pigmentation associated with ageing skin. However, senescent melanocytes may also be involved in the senescence of nearby skin cells and hypopigmentation associated with ageing of the skin (Victorelli *et al.*, 2019).

2.5 Age-Related Changes in Pigmentation

Reduced melanogenesis, which gives ageing skin its pale appearance, is a known factor in skin ageing and may be partly explained by decreasing vascularity. Independent of skin phototype, a number of investigations have shown that there is an inverse association between age and melanocyte proliferative activity. According to Bennett and Medrano, there is a substantial correlation between senescence and the loss of functioning pigment cells. Adult melanocytes demonstrated a lower proliferative potential when compared with foetal and neonatal melanocytes. Adult melanocytes were shown to be bigger, more dendritic, and to have lower Tyrosinase (TYR) activity in addition to having a lower number. On the other hand, melanocyte counts in sun-exposed areas show a comparatively slower drop, indicating that prolonged sun exposure, which increases their functional activity, may be able to stop them from disappearing. Ageing was associated with an increase in POMC expression, the precursor of alpha-melanocyte-stimulating hormone (α-MSH), and a decrease in the expression of the corresponding melanocortin receptors1, 2 (MC1R and MC2R). Nevertheless, there is insufficient data to determine if decreased levels of the peptide's receptor serve as a negative feedback loop for changes in POMC mRNA levels, or if elevated α-MSH functions as a compensatory mechanism for pigmentary equilibrium. It's interesting to note that genome-wide association studies showed that skin ageing was caused by polymorphic loss-of-function mutations of the MC1R gene, independent of the melanogenic biosynthesis pathway (Kang *et al.*, 2021).

It has been demonstrated that senescent melanocytes can aggregate in human skin, leading to an increase in face wrinkles and age-dependent irregular elastin deposition in the papillary dermis (Waaijer *et al.*, 2016). Melanocytes are put into a senescent-like state when exposed to UVR repeatedly (Martic *et al.*, 2020). Elevated melanogenesis and cell differentiation may be linked to melanocyte senescence. The main indicator of cell senescence, p16INK4A, is involved in the process by which the buildup of cytoplasmic melanosomes under UVB irradiation speeds up melanocyte senescence. According to Zhang et al., melanocytes that were cultivated with autophagy inhibited experienced early senescence and a dysregulated antioxidant response (Zhang *et al.*, 2015).

More data highlights the critical part melanocytes play in the ageing of the skin. It has been noted that p16INK4A is nearly exclusively expressed by melanocytes in the epidermis. Interestingly, high levels of paracrine activity linked with senescent melanocytes may act as triggers for skin ageing. Skin is most likely caused by melanocytes, which have a low rate of replication and typically divide when necessary, such as after being injured or exposed to UV light. As a result of their transition to a senescent phenotype and related paracrine telomere failure, melancholy develops. The senescent-prone characteristic of melanocytes is likely due to their restricted programmed stem cell turnover during their lifetime, in contrast to robustly proliferating and constantly replenishing cells, like keratinocytes (Victorelli *et al.*, 2019).

Kim et al. proposed a link between nearly nonexistent melanin pigmentation and hypopigmentation, as well as a decreased melanocyte count. The IGH skin shows signs of photodamage, including p16INK4A-positive fibroblasts, an altered basement membrane, and elevated matrix metalloproteinase-1 (MMP1) expression (Kim *et al.*, 2020). Patients with IGH were found to have larger, cultured melanocytes with smaller, retracted dendrites. This suggests a decreased ability to transmit melanin to nearby cells, suggesting the advent of senescence (Rani *et al.*, 2018).

2.6 Mechanisms Implicated in Skin Aging with Skin Pigmentation

Considered to be one of the key factors contributing to skin ageing is oxidative stress. Oxidative stress arises if the cellular production of reactive oxygen species (ROS), a class of free radicals based on oxygen that includes hydrogen peroxide (H_2O_2), surpasses the antioxidant capacity of the cell. Exogenous stimuli like UV light and endogenous stimuli like cellular metabolism both produce ROS. On the other hand, ROS may result in mutations in the mitochondrial DNA, which could compromise the mitochondria. Because of this connection, it makes sense to take oxidative stress and mutations in the mitochondrial DNA into account. Lipids, proteins, and DNA are only a few of the many possible biological targets for oxidative damage that are found in the skin. Because oxidative damage causes cellular senescence, which in turn causes skin ageing, using antioxidants can have anti-aging benefits (Gu *et al.*, 2020).

Whenever DNA damage occurs, homeostasis should be preserved by activating DNA repair processes such double-strand breaks and nucleotide excision repair. Ageing is caused by the buildup of DNA damage and the downregulation of DNA repair. There is compelling evidence linking DNA damage to ageing, including the progeroid syndromes, which are a set of premature ageing disorders characterised by impaired DNA replication and repair due to mutations. Although UV radiation has an inverse connection with constitutive skin pigmentation, it is a well-known inducer of DNA damage in all skin types (Lee, 2021).

At the end of chromosomes, telomeres are dynamic nucleoprotein-DNA complexes that cap and shield the linear chromosomal ends. They are made up of long tandem TTAGGG repeats, which are rich in guanine. While telomere length varies throughout chromosome arms, telomeres decrease during cell division, and their initial length is correlated with the potential of the cell to replicate. Telomere shortening may be one of the main indicators of ageing, as seen by the accelerated ageing in short telomere syndromes brought on by inheritable gene abnormalities that result in reduced telomere lengths (Wang and Dreesen, 2018).

Skin function can be regulated by cutaneous neuroendocrine systems in response to environmental stressors including pollution and UV radiation. Melatonin is a member of the neurohormone family. The primary organ involved in melatonin synthesis and secretion is the pineal gland. To preserve homeostasis in the face of environmental stressors, human skin may, nevertheless, synthesise and metabolise melatonin quickly (Bocheva, Slominski and Slominski, 2019). Numerous physiological processes, such as immunological responses, oxidative processes, apoptosis, circadian rhythm, and mitochondrial homeostasis, are regulated by melatonin. Melatonin's antioxidant properties shield skin from UVB ray damage, highlighting the essential function melatonin plays in photoaging (Bocheva, Slominski and Slominski, 2019).

2.7 Senescent Melanocytes Impact Human Skin Ageing

In 2019, Victorelli et al., explored the impact of senescent melanocytes within human skin further. The scientists observed a substantial drop in HMGB1 expression with age, but no change in p21 expression. They also found an increased number of p16-positive melanocytes in older skin biopsies. In their investigation of DNA damage, the team observed that melanocytes with ageing had more γH2AX foci, and more significantly, TAFs, which indicated damage specific to telomeres. Moreover, there was no correlation observed between the number of γH2AX foci and somewhat shorter telomeres. This implies that telomere shortening might not be the primary cause of melanocyte senescence in living things (Victorelli *et al.*, 2019).

They also found that in human skin samples, the keratinocytes that surrounded the TAF-positive melanocytes had more TAFs themselves, indicating that the senescent melanocytes had the ability to cause adjacent cells to undergo secondary DNA damage. This was also replicated in melanoderms and in vitro models with stratified keratinocytes and senescent melanocytes produced by UVA and UVB. Senescent melanocyte-containing melanoderms also exhibited fewer keratinocytes and keratinocytes that expressed less of the proliferation marker Ki-67. A crucial sign of skin ageing was a thinner epidermis in melanoderms with senescent melanocytes. This implies that the primary cause of skin ageing may be senescent melanocytes (Victorelli *et al.*, 2019).

One potential therapy approach to prevent and restore skin-aging characteristics is to target senescent cells and associated components (Fig 2). There are two types of strategies for blocking senescent-cell-mediated responses: senomorphic and senolytic. Senolytics are medications that selectively induce cell death to eliminate senescent cells, while senomorphics control the microenvironment or extrinsic factors without removing senescent cells (Kim, Park and Kang, 2022).

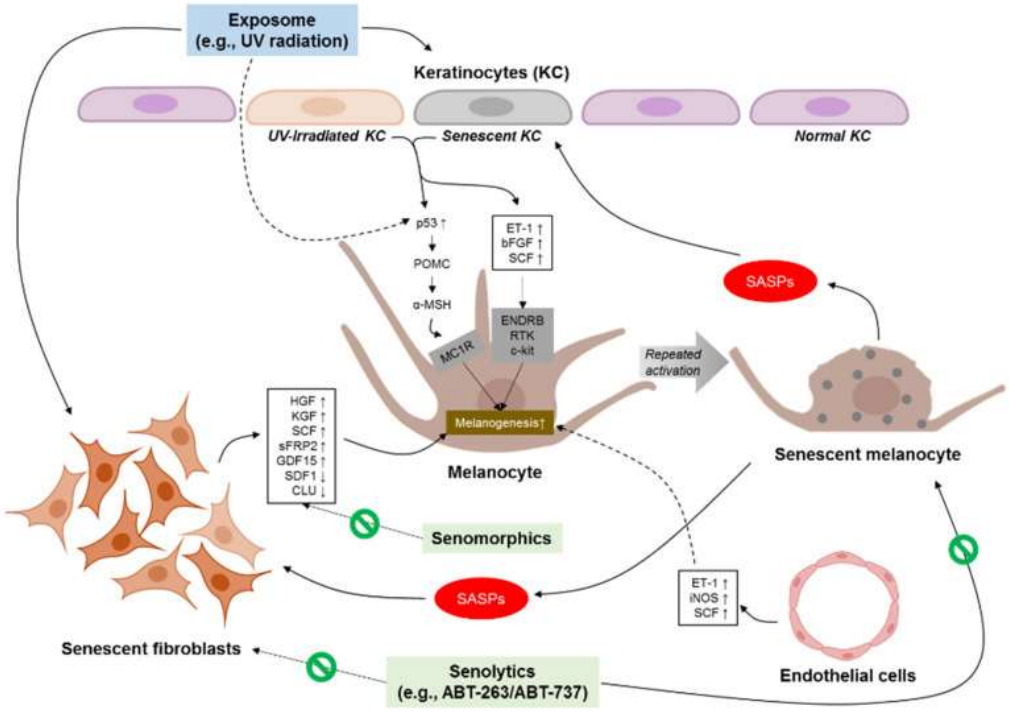

Fig. 2 - Cellular crosstalk between melanocytes and neighboring cells in skin-aging pigmentation (Kim, Park and Kang, 2022).

Previous research have revealed a number of potential senotherapeutics in senescent cells, including senescent fibroblasts, as well as a number of potential candidate variables, including target-regulating SASPs, to prevent skin-aging pigmentation. In normal human melanocytes, melanogenic activation can

be suppressed through β-catenin signalling when SFRP2 and GDF15 are inhibited. Through the downregulation of cAMP/phosphor-CREB/MITF/tyrosinase signalling in melanocytes, SDF1 can function as an anti-melanogenic agent (Yoon *et al.*, 2018).

Furthermore, senolytics and the well-known B-cell lymphoma 2 (BCL-2) inhibitors ABT-263 and ABT-737 caused the selective removal of senescent dermal fibroblasts. Additionally, Park et al. recently demonstrated that ABT-263's specific senolytic activity on senescent fibroblasts confers anti-melanogenic effects and skin-lightening properties (Park *et al.*, 2022). In vivo 3D human epidermal, ABT-737 also caused the removal of senescent melanocytes, which in turn prevented the nearby cells from turning senescent (Georgakopoulou *et al.*, 2021)

3. Conclusion

Melanocytes and surrounding cells are known to undergo senescence. Considering changes in ageing skin phenotypes, interaction between senescent skin cells may be crucial. Reduced melanogenesis is a known factor in skin ageing and may be partly explained by decreasing vascularity. Independent of skin phototype, a number of investigations have shown that there is an inverse association between age and melanocyte proliferative activity.

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