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Cellular Senescence and the Senescence-Associated Secretory Phenotype as Drivers of Skin Photoaging

Eleni Fitsiou^{1,4}, Tanya Pulido^{2,4}, Judith Campisi^{2,3}, Fatouma Alimirah² and Marco Demaria¹

Chronic exposure to UVR is known to disrupt tissue homeostasis, accelerate the onset of age-related phenotypes, and increase the risk for skin cancer—a phenomenon defined as photoaging. In this paper, we review the current knowledge on how UV exposure causes cells to prematurely enter cellular senescence. We describe the mechanisms contributing to the accumulation of senescent cells in the skin and how the persistence of cellular senescence can promote impaired regenerative capacity, chronic inflammation, and tumorigenesis associated with photoaging. We conclude by highlighting the potential of senolytic drugs in delaying the onset and progression of age-associated phenotypes in the skin.

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Introduction

In response to DNA damage and to prevent cancer development, cells can enter a state of permanent growth arrest known as cellular senescence. The senescence response depends on the activation of the p16^{INK4a}/pRB and p53/p21^{WAF1} tumor suppressor pathways (Rodier and Campisi, 2011). Many stress-inducing stimuli such as telomere dysfunction, oncogenic mutations, strong mitogenic signals, mitochondrial dysfunction, and many forms of genotoxic stress can lead to senescence induction (Campisi, 2013; Coppé et al., 2010; Rodier and Campisi, 2011; Wiley et al., 2016). In addition to acquiring a stable growth arrest, senescent cells secrete a collection of cytokines, chemokines,

GFs, proteases, and extracellular vesicles (EVs) known as the senescence-associated secretory phenotype (SASP) (Coppé et al., 2008; Takasugi, 2018).

The transient presence of senescent cells and the SASP can be beneficial during embryogenesis (Muñoz-Espín et al., 2013; Storer et al., 2013), parturition (Menon et al., 2016), and tissue remodeling and repair, especially during wound healing (Demaria et al., 2014). However, senescent cells gradually increase during aging, where they can persist in tissues and contribute to various age-related disorders (Baker et al., 2016; Campisi, 2013; Demaria et al., 2017; Kirkland and Tchikona, 2017; Pereira et al., 2019). Interestingly, the stress induced by certain environmental factors can lead to the premature accumulation of senescent cells and, consequently, accelerate aging phenotypes (Chinta et al., 2018; Ryu et al., 2019; Sorrentino et al., 2014).

UVR is a potent inducer of tissue dysfunction in the skin, which is thought to derive in part from UV-induced senescent cells (Debacq-Chainiaux et al., 2012; Demaria et al., 2015; Sorrentino et al., 2014; Yoshimoto et al., 2018).

Characteristics of photoaging

Skin aging can be divided into two types: chronological or intrinsic aging, presented mainly in photoprotected areas of the body, and extrinsic aging, also known as photoaging. Photoaged skin is characterized by epidermal thickening (Figure 1), dryness, deep wrinkles, loss of elasticity, delayed wound healing, and susceptibility to cancer (Gosain and DiPietro, 2004; Kammeyer and Luiten, 2015; Rittié and Fisher, 2015).

Photoaging is mainly caused by exposure to UVR from the sun. There are three types of UVR: UVA (320–400 nm), UVB (280–320 nm), and UVC (100–280 nm). UVC is absorbed in the stratosphere, and therefore, only UVA and UVB reach the surface of the earth (~95% UVA, ~5% UVB). Although UVA is more abundant in sunlight, UVB has higher energy and is responsible for sunburns. Owing to its shorter wavelength, most UVB is absorbed by the epidermis, whereas a small percentage reaches the papillary dermis (Battie et al., 2014).

In contrast, UVA can penetrate deep into the epidermis and is now considered a major factor in skin photoaging, including the development of melanomas (Noonan et al., 2012). Both UVA and UVB can damage DNA indirectly through the generation of damaging ROS. Furthermore, UVB can damage DNA directly through the formation of cyclobutane pyrimidine dimers (CPDs) and 6–4 photoproducts (PPs), a feature that is also observed in case of UVA but to a much lower extent (Besaratina et al., 2008; Schuch et al., 2017). For these reasons, both UVA and UVB represent

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Abbreviations: AP-1, activator protein-1; bp, base pair; CM, conditioned medium; CPD, cyclobutane pyrimidine dimer; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; ET, endothelin; EV, extracellular vesicle; KC, keratinocyte; LC, Langerhans cell; miRNA, microRNA; MMP, matrix metalloproteinase; NER, nucleotide excision repair; PP, photoproduct; SA- β gal, senescence-associated β -galactosidase; SASP, senescence-associated secretory phenotype; SCF, stem cell factor

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Figure 1. UVA and UVB radiation induces senescence in various skin cell types. The resulting altered senescence-associated gene expression profile affects cell communication and function and leads to the disruption of tissue homeostasis. MMP, matrix metalloproteinase.

major drivers of photoaging and of melanomas and non-melanoma skin cancers.

Senescence in photoaged skin

Epidermis. Keratinocytes (KCs) form the epidermis, the outermost layer of the skin, and are thus in direct contact with the external environment. Proliferating KCs reside in the basal layer, and these cells terminally differentiate as they move toward the skin surface in the stratum corneum (Figure 1) (Bikle et al., 2012). Several studies report the expression of senescence markers in human KCs after UVB exposure in culture; these markers include p16INK4a and p21 and p53 induction, increased senescence-associated β -galactosidase (SA- β gal) activity, and loss of LMNB1 expression (Chazal et al., 2002; Lewis et al., 2008; Wang et al., 2017). Interestingly, skin samples from photoprotected areas from young and aged donors showed that p16INK4a-positive cells were generally melanocytes and not KCs in the epidermis, highlighting that differences in senescent phenotypes can occur depending on the cell type and stimulus (Vitorelli et al., 2019; Waaijer et al., 2016). Other studies reported the detection of p16INK4a-positive cells in human skin biopsies from sun-exposed areas (Chung et al., 2019; Yoon et al., 2018). However, it is difficult to determine whether these cells are the result of intrinsic or extrinsic aging processes or a combination of these factors.

The generation of ROS by UV irradiation can lead to the phosphorylation and subsequent activation of MAPKs/extracellular signal-regulated kinase (ERK), p38, and c-Jun N-terminal kinase. These activated kinases in turn can activate the c-Jun and c-Fos components of the transcription factor activator protein-1 (AP-1). AP-1 can increase the expression of matrix metalloproteinases (MMPs), which are known SASP factors. Notably, MMPs are highly expressed in UV-induced senescent KCs in culture (e.g., MMP-1) (Quan et al., 2009) and in the epidermis of irradiated human skin samples (e.g., MMP-1, MMP-3, and MMP-9) (Dong et al., 2008). Other

SASP factors elevated in UV-induced senescent KCs in culture include proinflammatory cytokines such as TNF- α , IL-1 α , IL-1 β , and IL-6 (Bashir et al., 2009; Chung et al., 1996; Kondo et al., 1994; Petit-Frère et al., 1998).

Melanocytes, which reside primarily in the basal layer of the epidermis (Figure 1), produce the pigment melanin and rarely proliferate (Shain and Bastian, 2016). Melanin production increases after UV irradiation, and the pigment is then transferred to KCs where it absorbs UV irradiation and protects the cells, and ultimately the skin, from DNA damage. Melanogenesis is a tightly regulated process involving many intracellular molecules (Serre et al., 2018). Among these regulators is p53, which modulates the expression of melanogenesis-related genes (Lim et al., 2016; Murase et al., 2009). Furthermore, p53 inhibition reduces the levels of tyrosinase, an important enzyme in melanogenesis (Choi et al., 2018).

UVB irradiation of melanocytes elevates the levels of p53, p21, and c-Fos and inhibits RB phosphorylation (Medrano et al., 1995). Repeated exposure of human melanocytes to UVB also causes hyperpigmentation through prolonged p53 expression (Choi et al., 2018). Similar to KCs, melanocytes secrete cytokines, specifically IL-6 and IL-8, after UV exposure in culture (Vitorelli et al., 2019). The secretion of inflammatory factors is mediated by HMGB1, which is released to the extracellular milieu shortly after irradiation (≤ 24 hours), also leading to increased expression of ISGs and resistance to apoptosis (Zhang et al., 2019). These phenotypes are characteristic of senescent cells, including the secretion of IL-6 and IL-8 (Coppé et al., 2008) and the release of HMGB1 (Davalos et al., 2013).

Dermis. Fibroblasts are the most common cell type used in cellular senescence studies. In the skin, fibroblasts are the major cell type of the dermis, producing components of the extracellular matrix (ECM), including collagen (Debaq-Chainiaux et al., 2012). Human dermal fibroblasts acquire a senescent-like phenotype after UVB and UVA exposure in

culture, as indicated by elevated p16INK4a, p21, and p53 levels and the expression of SA- β gal. In addition, a 4,977–base pair (bp) deletion in mtDNA was reported in photoaged skin compared with that in chronologically aged skin (Berneburg et al., 1997; Chainiaux et al., 2002; Chung et al., 2015; Debacq-Chainiaux et al., 2005; Wiley et al., 2016). The deleted region contains transfer RNA genes but also genes involved in oxidative phosphorylation (Yusoff et al., 2019) and has been detected in the dermis of UVA-irradiated skin, caused by the production of singlet oxygen related to UVA (Berneburg et al., 1999). Because the 4,977-bp deletion can impair the function of mitochondria and mitochondrial damage can induce senescence (Velarde et al., 2012; Wiley et al., 2016), it is possible that this UV-induced deletion plays a role in the development and progression of skin photoaging and senescence. Despite its wide use as a senescence biomarker, reduced LMNB1 was not detected in UVB-irradiated murine dermis (Wang et al., 2017). UV-irradiated cultured fibroblasts show a significant increase in the expression and secretion of MMPs through MAPK and AP-1 activation (Fagot et al., 2004, 2002). Significant levels of MMPs were also observed in the dermis of sun-exposed areas compared with the levels observed in the dermis of sun-protected areas of the body (Quan et al., 2013). Furthermore, AP-1 downregulated TGF β /SMAD signaling, which is linked to collagen synthesis, through reduced expression of the TGF β type II receptor (Pittayapruek et al., 2016; Quan et al., 2004). The activation of these pathways after UV and leading to photoaging coincides with the hallmarks of senescent cells (Hernandez-Segura et al., 2018).

MicroRNAs (miRNAs) are emerging regulators of senescent phenotypes (Suh, 2018). Repeated exposure of dermal fibroblasts to UVB induced senescence in culture, particularly 7 days after irradiation, with an upregulation of senescence markers, including p21 mRNA. UVB also downregulated miRNAs such as miR-20a/b and miR-93, which suppress the expression of p21 (Greussing et al., 2013). It is possible that UVB irradiation induced senescence by downregulating miRNAs and leading to the upregulation of cell-cycle inhibitors such as p21.

Autophagy plays a role in the senescence response, but the exact mechanisms are still unclear. Autophagy can act through both anti and prosenescence mechanisms, depending on the type of autophagy that is activated and the subcellular compartment where it acts as well as the cell type (Kwon et al., 2017). Conflicting roles of autophagy were observed in the skin. On the one hand, autophagy protects skin cells and delays photoaging by removing macromolecules oxidized by ROS (Wang et al., 2019). On the other hand, it is required for UVB-induced senescence in human foreskin fibroblasts (Cavinato and Jansen-Dür, 2017).

Finally, the dermis contains blood vessels that are composed primarily of microvascular endothelial cells responsible for regulating blood pressure, temperature, and nutrient supply as well as inflammatory responses through the secretion of cytokines (Gutterman et al., 2016). On prolonged exposure to TNF- α , endothelial cells undergo senescence and increase the secretion of IL-6 and IL-8 (Khan et al., 2017). TNF- α is produced by UV-irradiated KCs and fibroblasts (Bashir et al., 2009; Lee et al., 2019), suggesting a

mechanism by which UV could lead to the senescence of endothelial cells in the skin.

Detrimental functions of senescent cells in photoaged skin

The presence of senescent cells in the skin can have deleterious effects through different mechanisms. UV-induced senescent cells can alter the ECM as well as the function of the neighboring cells, causing photodamage and increasing the risk of carcinogenesis. For example, the cytokines IL-1 α , IL-1 β , IL-6, and TNF- α are highly secreted by senescent cells and were reported to drive skin carcinogenesis by inducing the expression of angiogenic and invasion factors such as VEGF and MMP-1 through NF- κ B signaling (Bou-Dargham et al., 2017; Campisi, 2013; Coppé et al., 2008; Lederle et al., 2011; Rodier and Campisi, 2011). Upregulation and secretion of MMPs lead to collagen degradation, epithelial–mesenchymal transitions, angiogenesis, and inflammation (Nagase et al., 2006; Pittayapruek et al., 2016). UVA or a mixture of UVA and UVB upregulated MMP-1 levels in cultured fibroblasts but not cultured KCs; however, conditioned medium (CM) from irradiated KCs increased MMP-1 levels in the fibroblasts (Fagot et al., 2004, 2002). Another report suggested that the secretion of MMP-1 is mediated by IL-1 α and IL-1 β signaling (Wang et al., 2005).

VEGF secretion is a hallmark of senescent fibroblasts (Coppé et al., 2006). VEGF expression is also linked to increased vascular permeability, cancer, and erythema (Brown et al., 1995; Claffey et al., 1996). UVB irradiation increased VEGF expression in cultured KCs and mouse skin (Brauchle et al., 1996; Hirakawa et al., 2005), whereas the use of an angiogenesis inhibitor led to decreased wrinkle formation and photodamage (Yano et al., 2002).

mTOR signaling has been implicated in senescence through the regulation of the SASP. Rapamycin, an mTOR inhibitor, suppressed IL-1 α upregulation in human fibroblasts during senescence, which in turn suppressed IL-1 α -induced secretion of other proinflammatory SASP factors (Laberge et al., 2015; Qin et al., 2018; Tomimatsu and Narita, 2015). Consistent with this observation, rapamycin reduced senescence markers in UVB-exposed mouse dermal fibroblasts in culture (Qin et al., 2018). Similarly, in sun-exposed human skin, senescence markers were reduced, and skin aging was improved with rapamycin (Chung et al., 2019). Together, these observations suggest that senescent cells may, in part, contribute to skin damage and photoaging through mTOR signaling.

Crosstalk between fibroblasts and KCs is also achieved through the IGF pathway. Although KCs do not normally secrete IGF, they express a functional receptor, IGF-1R. UVB causes the secretion of IGF from fibroblasts, which binds to and activates IGF-1R and protects KCs from UVB-induced cell death, whereas the surviving cells enter senescence with p21 upregulation and p53 phosphorylation (Lewis and Spandau, 2008). Senescent fibroblasts, whether from aged skin or hydrogen peroxide-induced skin, failed to express IGF (Lewis et al., 2010), and reduced IGF secretion was observed in sun-protected aged skin (Lewis et al., 2011). In these systems, the reduced expression and secretion of IGF resulted in a deficit in activated IGF-1R. This deficit caused UVB-irradiated KCs to die through apoptosis, whereas cells

that survived continued to proliferate with unrepaired DNA, increasing the risk of nonmelanoma skin cancer (Loesch et al., 2016). Exogenous supplementation of IGF restored the response of UVB-treated basal KCs, suggesting a new strategy for nonmelanoma skin cancer prevention (Lewis et al., 2011).

The transcription factor NRF2 is essential for mounting antioxidant defenses, which can have either beneficial or detrimental effects on the skin. Thus, constitutively activated NRF2 induced senescence in human and mouse skin fibroblasts, which accelerated KC proliferation and wound healing. However, active NRF2 also caused cells to behave as cancer-associated fibroblasts by directly downregulating ECM components and inducing paracrine fibroblast senescence through the secretion of PAI-1 (Hiebert et al., 2018). UVA, but not UVB, was shown to increase nuclear *Nrf2* levels in murine fibroblasts, protecting them from UV-induced apoptosis (Hirota et al., 2005). Although senescence was not determined in this study, it is possible that cells underwent senescence to mitigate oxidative damage but were potentially exposed to a higher risk of skin carcinogenesis if the *Nrf2* signal persisted.

An increase in melanin can induce melanocyte senescence through the p16/CDK4/pRB pathway (Bandyopadhyay and Medrano, 2000), suggesting that cells involved in melanogenesis may also be implicated in melanocyte senescence. The main cell type that signals the need for melanogenesis is KCs. On UV irradiation, KCs secrete factors such as α -melanocyte-stimulating hormone, endothelin (ET)-1, and stem cell factor (SCF) (in a p53-dependent manner), which bind MC1R, ETB receptors, and c-Kit receptors, respectively (Hachiyu et al., 2004; Murase et al., 2009; Niwano et al., 2015). ET-1 and SCF binding activates ERK1/2/MAPK (Hyter et al., 2013; Murase et al., 2009). ERK/MAPK signaling can stimulate melanogenesis as well as melanoma formation (D'Mello et al., 2016; Flaherty et al., 2012; Samatar and Poulidakos, 2014). Apart from KCs, CM from cultured irradiated human endothelial cells promoted melanogenesis through the secretion of SCF (Kim et al., 2018). A recent study showed that GDF15 increased in UVA-induced senescent skin fibroblasts and that GDF15 increased melanocyte pigmentation through β -catenin in cell cultures, melasmas, and aged skin (Kim et al., 2020b). Fibroblasts from old photoaged skin compared with those from young tissue also induced hyperpigmentation (Duval et al., 2014). Furthermore, repeated exposure to UVA or UVB resulted in SCF secretion and senescence in skin fibroblasts. The culture of fibroblasts with CM from irradiated KCs also increased SCF secretion at higher levels than that from direct UV exposure, although senescence was not determined after incubation with the CM (Shin et al., 2012).

The accumulation of CPDs and 6–4 PPs as well as any deficiencies in their repair can lead to skin cancer (Liu-Smith et al., 2017). These DNA alterations are repaired primarily by the nucleotide excision repair (NER) pathway (Liu-Smith et al., 2017). NER repair efficiency has been suggested to be impaired with sustained UVR-induced oxidative stress (McAdam et al., 2016). Interestingly, deficiency in ERCC1, a protein required for incision of the damaged DNA strand during NER, in fibroblasts induced cellular senescence,

followed by apoptosis in the neighboring cells as well as in senescent cells themselves. Moreover, apoptosis was accompanied by a decrease in the expression of stem cell markers, indicating that in addition to altering the tissue microenvironment, senescent cells may also affect the stem cell pool, which provides a possible explanation for other age-related phenotypes observed in the skin (Kim et al., 2020a).

In addition, UV-irradiated quiescent melanocytes entered senescence with a downregulation of genes in the NER pathway, especially genes involved in the recognition of DNA damage (*RAD23B*, *XPC*, *ERCC3*, *ERCC8*, and *RPAT*). These irradiated melanocytes produced and secreted exosomes, which contained miRNAs whose targets modulate the SASP, cell cycle, and DNA repair pathways (Sha et al., 2020). EVs were also secreted by melanocytes shortly after UVA but not UVB irradiation. These vesicles are of lysosomal origin and are released before melanin secretion. EVs are taken up by KCs, which increase proliferation in response, possibly explaining the sun-induced thickening of the epidermis. These EVs were microvesicles, not exosomes, although, at later times, a mixture of different vesicles was present in CM. The EVs altered gene expression patterns (including SASPs) and contained miR-21, TGF- β , and IL-6, which activate MAPK, decrease PTEN levels, and increase BCL-2 and BCL-XL, rendering KCs resistant to apoptosis even after lethal doses of UVA or UVB. Similarly, UVA-irradiated melanoma cells secreted EVs with increased miR-21 levels that induced proliferation in both KCs and melanocytes (Wäster et al., 2020, 2016). These different types of vesicles may be of the same origin. In any case, they can stimulate cell hyperproliferation at early stages after irradiation but, at later stages, can cause senescence.

Senescent melanocytes can also affect neighboring KCs by different mechanisms. Melanocytes irradiated with a mixture of UVA and UVB caused paracrine senescence and telomere dysfunction in neighboring KCs in a 3-dimensional cell culture model (Vicarelli et al., 2019). Moreover, the clearance of senescent melanocytes with ABT-737, a BCL-2 inhibitor, or MitoQ, a mitochondria-targeted antioxidant, reversed the telomere dysfunction, suggesting that ROS are involved in this paracrine effect, contributing to photoaging (Vicarelli et al., 2019).

Immune clearance of senescent cells and photoaging

Despite the beneficial role of senescent cells in certain biological processes, their persistence in tissues can have deleterious effects. Furthermore, in a context-dependent fashion, senescent cells can either activate the immune system, leading to tumor suppression, or lead to immunosuppression and tumor promotion (Burton and Stolz, 2018; Eckhart et al., 2019). In the skin, the chronic presence of senescent stromal cells led to inflammation and an immunosuppressive microenvironment associated with increased tumor growth through an IL-6-dependent network (Ruhland et al., 2016). Thus, effective clearance of these cells is important for tissue homeostasis. For example, immune clearance of senescent cells limited liver fibrosis and resulted in tumor inhibition (Krizhanovsky et al., 2008; Xue et al., 2007).

It has been suggested that UVR has immunomodulatory roles. Some studies showed that the adaptive immune response was suppressed after UV exposure. This suppression is likely due to the activation of the innate immune response, leading to increased T regulatory cells, which regulate immune tolerance (Bernard et al., 2019). UVR can also affect Langerhans cells (LCs), the dendritic cells of the skin, as their number and migration to the lymph nodes decline on both intrinsic and extrinsic aging (Chambers and Vukmanovic-Stejić, 2020; Grewe, 2001). However, little is known about the effects of chronically present UV-induced senescent cells in the skin on LC activity. It is also not known whether these immune cells are involved in the persistence of senescent cells.

A mutation in *p53* causing partial cell-cycle arrest led to decreased apoptosis and increased senescence, followed by increased UVB-induced immunosuppression in mice, suggesting a link between the presence of senescent cells and immune modulation (Tavana et al., 2010). When senescence was induced in dermal fibroblasts (using ionizing radiation, replicative exhaustion, or oncogene expression), the expression of the atypical major histocompatibility complex molecule HLA-E, which binds to the inhibitory CD94/NKG2A receptor on NK and CD8⁺ T cells, increased, thereby reducing immune cell surveillance; this receptor was also found to be more highly expressed in the skin from old people compared with those from young individuals (Pereira et al., 2019). HLA-E expression and secretion also increased in skin endothelial cells after stimulation with TNF- α or IFN- γ , and its knockdown increased cytotoxicity by NK cells (Coupel et al., 2007). This scenario could also be the case for UV-induced senescent skin cells and awaits further investigation into their role in the immune response in the skin.

The persistence of senescent cells has, in part, been attributed to their resistance to apoptosis. This feature of senescent cells has led to the development of senolytics, drugs that can selectively target and eliminate senescent cells through the activation of pro-apoptotic signaling pathways (van Deursen, 2019). It has been shown that senescent cells upregulate anti-apoptotic BCL-2 family proteins BCL-W and BCL-XL, and the combined inhibition of these proteins by small-molecule inhibitor ABT-737 resulted in senescent cell death (Yosef et al., 2016). Similar senolytic agents have been developed, including ABT-236, A1331852, and A1155463 (Wang et al., 2016; Zhu et al., 2017). In addition, some naturally occurring compounds such as piperlongumine and fisetin have been identified as senolytic agents (Wang et al., 2016; Zhu et al., 2017). Senescent cell elimination using a transgenic mouse model delayed aging and improved healthspan, which demonstrates the potential benefits of developing senolytics (Baker et al., 2016, 2011).

Conclusions

Photodamage is a major health concern associated with visible and undesirable effects on the skin, such as wrinkles and hypo or hyperpigmentation, loss of insulation and protection from external pathogens, and increased risk for skin cancer. Key hallmarks for the detrimental effects of photoaging are enhanced ROS and DNA damage levels, which can lead to the premature induction of senescence in most skin cell types. Senescent cells in turn can contribute to skin aging

through cell-autonomous, by reducing regenerative potential, and noncell-autonomous, by promoting aberrant remodeling and chronic inflammation, mechanisms. Because the senescent phenotype is variable and depends on the cell type and the inducing stimulus, research should be focused on determining which cells senesce after UV and the cell-specific mechanisms they use to maintain the senescent phenotype, persist and escape cell death, and contribute to skin carcinogenesis. The role of the immune system and how UV-induced senescent cells manage to bypass immune clearance are also of interest but poorly studied until now. This will allow for better and more targeted drugs for the prevention and treatment of photoaging. The most common way to protect the skin from UV is by using sunscreens. Although, to date, no direct relationship has been shown between UV-induced senescence and sunscreens, their use has been shown to improve skin appearance, protect against DNA damage, and reduce the levels of MMP-1 and MMP-9. On the basis of these findings, it is possible that topical sunscreen application prevents or delays the accumulation of senescent cells in the skin, but further studies are required to validate this hypothesis. Current treatment options mainly include naturally derived antioxidants. However, these treatments fail to address the nuclear damage that could lead to cellular senescence and cancer and are only applicable for prevention. Thus, other options need to be explored, and therefore, further investigation into the pathways that regulate photo-damage and senescence may have great therapeutic potential. The use of senolytics is a promising strategy for the treatment of many age-related pathologies, although this approach is still in its infancy. Developing senolytics that can be applied topically may serve as a promising treatment strategy to reduce the undesirable and potentially toxic effects of sun exposure on the skin and thus improve overall health and QoL. However, senolytic interventions need to be carefully characterized and optimized, in particular, to avoid interference with the tissue repair properties of certain senescent cells.

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CONFLICT OF INTEREST

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AUTHOR CONTRIBUTIONS

Conceptualization: EF, MD; Investigation: EF, TP, FA; Supervision: MD, FA, JC; Visualization: EF, TP; Writing - Original Draft Preparation: EF, TP; Writing - Review and Editing: EF, TP, FA, MD, JC

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