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Review

Biomarkers, oxidative stress and autophagy in skin aging

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ABSTRACT

Aging is a major cause of many degenerative diseases. The most intuitive consequence of aging is mainly manifested on the skin, resulting in cumulative changes in skin structure, function and appearance, such as increased wrinkles, laxity, elastosis, telangiectasia, and aberrant pigmentation of the skin. Unlike other organs of the human body, skin is not only inevitably affected by the intrinsic aging process, but also affected by various extrinsic environmental factors to accelerate aging, especially ultraviolet (UV) radiation. Skin aging is a highly complex and not fully understood process, and the lack of universal biomarkers for the definitive detection and evaluation of aging is also a major research challenge. Oxidative stress induced by the accumulation of reactive oxygen species (ROS) can lead to lipid, protein, nucleic acid and organelle damage, thus leading to the occurrence of cellular senescence, which is one of the core mechanisms mediating skin aging. Autophagy can maintain cellular homeostasis when faced with different stress conditions and is one of the survival mechanisms of cell resistance to intrinsic and extrinsic stress. Autophagy and aging have many features in common and may be associated with skin aging mediated by different factors. Here, we summarize the changes and biomarkers of skin aging, and discuss the effects of oxidative stress and autophagy on skin aging.

1. Introduction

Everyone experiences aging from birth, and skin aging has both intrinsic and extrinsic factors (Tobin, 2017). Intrinsic aging occurs not only on the skin, but also on all tissues (Makrantonaki et al., 2013). At the same time, as the outermost organ of the human body, the skin suffers from environmental damage to agents such as air pollution and cigarette smoking, the resulting skin aging is called extrinsic aging, which is also known as photoaging or the exposure to sunlight via UV radiation. (Koohgoli et al., 2017; Rittié and Fisher, 2015). Skin that only undergoes intrinsic aging is usually present in unexposed areas to sunlight, and photoaging can be thought of as a superposition of chronological skin aging by UV radiation. Both intrinsic and extrinsic aging can lead to a decrease in the structural integrity of the skin and loss of physiological function (Durai et al., 2012). Aging skin becomes dry, dysfunctional and increases the risk of skin diseases. Another health deficiency is the increased risk of skin malignancy (Kammeyer and Luiten, 2015). Skin can be used as a model organ to study endogenous and exogenous aging.

Reactive oxygen species (ROS) induce and accelerate the aging process including skin aging, although the presence of small amounts of ROS has been proved to play a beneficial role in maintaining the health of the body or cells, such as activating cyclooxygenase and lipoxygenase, regulating inflammatory process and so on (Birch-Machin and Bowman, 2016; Lephart, 2016). ROS is continuously produced as a by-product of the mitochondrial aerobic metabolism electron transport chain and considered to be the main cause of intrinsic aging in addition to genetic factors. In the skin, approximately 1.5 ~ 5% of oxygen consumption is converted to ROS by the intrinsic process (Poljšak et al., 2012). Similarly, the occurrence of photoaging is also associated with the production of ROS. As the most dangerous component of the sun, UV can cause an increase in ROS, damage the structure and function of cells, and mediate inflammatory responses (Petruk et al., 2018; Sajo et al., 2017). ROS activate a myriad of signaling pathways that result in reduced collagen production, synthesis and activation of matrix metalloproteinases (MMPs) responsible for degrading connective tissue, secretion of senescence-associated secretory phenotype (SASP) which ultimately promote aging of skin (Kammeyer and Luiten, 2015).

Autophagy can remove damaged proteins, lipids and other cytoplasmic substances, and act as a protective response in conditions of starvation or nutritional deficiency, and autophagy-lysosome pathway is the only way to clear entire organelles such as mitochondria (Mizushima, 2007). Autophagy is closely related to aging and has many common characteristics, indicating that both may play similar functions

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and roles in cells (Leidal et al., 2018). Activation of autophagy can delay aging, but many studies hold the opposite view at the same time. Therefore, more and further studies are needed on the relationship between autophagy and aging.

In recent years, with the continuous improvement of material life, and the amount of UV radiation has been increasing along with the deterioration of the ecological environment, how to prevent or delay skin aging, especially photoaging, has attracted great attention. Understanding the process and mechanism of skin aging is necessary for developing skin care products and reducing the risk of skin aging. Here, we describe the changes, mechanisms and biomarkers of skin aging. Oxidative stress, aging and autophagy are inextricably linked, and this review discusses the interrelationships between each other.

2. Skin aging

2.1. Skin structure and function

The skin is the largest organ in the human body, accounting for about 10～15 % of the body weight (Jabłońska-Trypuć et al., 2018). It is the first barrier between human body and extrinsic environment, and plays a role in protection, regulation of body temperature, sensation, secretion, excretion and immunity (Blume-Peytavi et al., 2016). The skin is also the most complex organ, mainly divided into three areas: epidermis layer, dermis layer and subcutaneous tissue, as well as skin appendages such as hairs, sebaceous glands, sweat glands and nails (Campbell and Lichtensteiger, 2004). The outermost epidermis includes cornified, granular, spinous and basal layer, and keratinocyte is the most common cell type (approximately 95 % of all epidermal cells) (Eckhart and Zeeuwen, 2018). The pigment-producing melanocytes are scattered in the basal layer, which determine the color of the skin and have a photoprotective function. Langerhans cells as the farthest antigen presenting cells are also scattered in the epidermis (Arda et al., 2014).

The epidermis and dermis are connected by dermal-epidermal junction (Briggaman and Wheeler, 1975). The dermis is mainly composed of extracellular matrix (ECM) secreted by fibroblasts, including connective tissue composed of glycosaminoglycans, proteoglycans, structural proteins such as collagen and elastin and some special macromolecules such as fibrin and hyaluronic acid provide strong mechanical resistance and elasticity to the skin (Campbell and Lichtensteiger, 2004). Blood vessels and lymphatics are embedded in the dermis, providing oxygen and nutrition, regulating temperature, and acting as highways to transport immune cells. A huge network of dermal nerve endings extends down to the epidermis and transmits sensory sensations such as temperature, touch, and pain (McGlone and Reilly, 2010). Subcutaneous tissue is composed of adipocytes that reinforce the connective tissue framework, which can resist temperature fluctuation and also be used as energy storage (Shimizu, 2016). Excretion through sweat and sebum is another important skin function.

2.2. Intrinsic aging

Intrinsic aging regulated by genetic factors affects all areas of the skin. As shown in Table 1, intrinsic aging has obvious characteristics, such as thinning, dryness, fine wrinkles, insufficient sweating, and increased sensitivity to temperature. The thinning of the epidermis leads to a decrease in skin barrier function, in part due to a decrease in the proliferation and renewal ability of keratinocytes and a reduction in the number of epidermal stem cells (Giangreco et al., 2008; Lavker et al., 1989; Rittié and Fisher, 2015).

During the intrinsic aging process, the number of dermal fibroblasts is reduced, and the synthesis ability of collagen and elastin in ECM is decreased, especially for type I and III collagen, which is thought to cause the thinning of dermis, the increase of wrinkles and the loss of elasticity, making the skin fragile. The production of sebum decreases with age, especially in postmenopausal women (Man et al., 2009). In addition, chronic itching is very common in aging skin, suggesting that the loss of age-related Merkel cells causes the sense of touch to turn to itching (Feng et al., 2018).

The ability of all normal dividing cells to replicate decreases over time, a process known as cellular senescence (Yeh, 2016). Senescent cells have a higher proportion in aging skin. Telomere is a special structure consisting of a short, multi-repeat, non-transcribed sequence (TTAGGG) and some binding proteins, which is a prerequisite for the sustained division of cells and is essential for cell replication (Collado et al., 2007; Turner et al., 2019). Telomere protects chromosomes from degradation by nucleases and prevents terminal connections between chromosomes, thereby maintaining the stability of chromosome structure. Each time the cell divides, the telomere at the end of the chromosome is lost by about 30～200 bp. After multiple cell divisions, telomere becomes very short, and important DNA fragments are lost during subsequent division, leading to loss of cellular function.

MMPs expression increased is another factor associated with skin aging. MMPs are involved in cell communication and are responsible for cell-matrix signaling events. As a class of proteolytic enzymes, the main physiological role is to degrade various protein components in ECM. MMPs expression is increased in senescent fibroblasts, while the expression of tissue inhibitor of metalloproteinases (TIMPs) is decreased. Their expression can be activated by oxidative stress and can therefore be reduced by antioxidants such as isoorientin, resveratrol, equol and other polyphenolic compounds (Afaq and Katiyar, 2011; Lephart et al., 2014; Lephart, 2016; Sárdy, 2009; Zheng et al., 2019). In fact, skin aging which is only mediated by intrinsic factors does not exist. Those who have lived strictly indoors for a lifetime may have similar skin condition.

2.3. Photoaging

Photoaging accounts for more than 80 % of facial aging (Friedman, 2005). Long-term exposure to cigarette smoke and UV radiation are independent causes of accelerated skin aging (Morita, 2007; Panich et al., 2016). They exacerbate the intrinsic aging and can be mitigated by behavioral changes in most cases. Among them, UV radiation is the main cause of photoaging (Cavinato and Jansen-Dürr, 2017; Han et al., 2014). UV in sunlight mainly includes three types according to its wavelength, long-wave UV (UVA, 320～400 nm), medium-wave UV (UVB, 280 ～320 nm), and short-wave UV (UVC, 200～280 nm) (Parisi and Turner, 2006). UVC has the strongest mutagenicity, but will be blocked by the ozone layer from reaching the earth's surface. UVA is a weak mutagen, but it has a strong penetrating ability that can affect the dermis and even the subcutaneous tissue area. UVB mutagenesis is strong, can directly interact with DNA to produce thymine dimer photoproduct, resulting in DNA damage (Cavinato and Jansen-Dürr, 2017; Makrantonaki et al., 2013).

UV radiation produces ROS that cause destructive oxidative stress, activate the arachidonic acid pathway, and mediate inflammatory responses (Baumann, 2018). Acute UV radiation can also cause sunburn, abnormal pigmentation, and long-term exposure can lead to malignant tumors (Rittié and Fisher, 2015). The degree of photoaging depends on many factors including the season, altitude, frequency, duration and intensity of the sun's rays. In addition, it is also associated with the natural protection of skin pigmentation (Alexis and Obioha, 2017; Fisher et al., 2002).

Photoaging skin becomes rough, laxity, wrinkled, and the capillaries under the skin surface expand, which is very different from the skin that is mainly intrinsic aging (Farage et al., 2008; Wlaschek et al., 2001). The keratinocyte activity decreases, renewal slows down, barrier function is abated in epidermis layer, bring about skin dryness and desquamate. The number of fibroblasts in the dermis is gradually reduced, collagen and elastin synthesis are slowed down and decomposition is accelerated, usually more severe than intrinsic aging (Farage

Table 1
The different changes between intrinsic and extrinsic aging skin.

	intrinsic aging skin	extrinsic aging skin
Clinical manifestation	Dryness, laxity, fine wrinkles Elasticity decrease, brittleness increase Benign tumor (hemangioma, fibroma mole, seborrheic keratosis)	Pachulosis, thickness, laxity, deep and thick wrinkles Hyperpigmentation, telangiectasis Benign or malignant tumor (solar keratosis, squamous-cell carcinoma, malignant melanoma)
Histology manifestation	The epidermis and dermis become thinner, the epidermal-dermal junction is flattened, and the adhesion between the epidermis and the dermis is reduced. The activity and the ability of proliferation of keratinocytes and fibroblasts decreased, the number of Langerhans cells and melanocytes decreased Elastic fibers become thinner and less numerous Collagen fibers straighten and loose in structure Reduced proteoglycan content Vascular reduction between tissues Hair follicles and glands reduced	The epidermis and dermis become thicken, the epidermal-dermal junction is flattened Dermal fibroblast activity increased, the number of Langerhans cells and melanocytes decreased Elastic fibers degeneration and abnormal deposition Collagen fibers degradation Increased proteoglycan content The vessels dilate and flex, and the walls thicken Hair follicles dilate and sebaceous glands atrophy

et al., 2013). At the same time, Langerhans cells are reduced, resulting in decreased immunity (Watson et al., 2013). An important histological feature of skin photoaging is the accumulation of amorphous elastic fibers, accompanied by disruption and disorder of collagen (Varani et al., 2004; Watson et al., 2013). In addition, UV can stimulate melanocytes to accelerate the synthesis and transfer of melanin to form age spots. Skin appendages also undergo significant changes during photoaging, such as atrophy of the sebaceous glands, reduced sweating and insufficient secretion of emulsion on the surface of the skin (Gilchrest, 2013; Scharffetter-Kochanek et al., 2000) (Table 1).

3. Biomarkers of cellular senescence and skin aging

As schematically proposed in Fig. 1, senescent cells have some common features that allow them to be recognized in vitro and in vivo, although it is induced by different stimuli. Biomarkers of skin aging are increasingly used in clinical practice to evaluate physiological changes in aging skin and aging-related diseases, and to effectively identify the effects of interventions. Therefore, studying the biomarkers is conducive to an in-depth understanding of the phenomenon and mechanism of skin aging.

3.1. Senescence-associated β-galactosidase(SA-β-Gal)

In general, senescent cells appear abnormal morphology, such as a large volume, flattening, and increased particles (Hayflick, 1965). One of the earliest and most widely used senescence biomarkers is SA-β-Gal, which remains the gold standard for identifying senescent cells in vitro and tissues (Dimri et al., 1995; Lee et al., 2006; Tang et al., 2018). But SA-β-Gal has certain limitations, and it can only accurately detect senescence phenomenon at pH 6.0, otherwise it will lead to false positive staining of non-senescent cells. The activity of SA-β-Gal is also increased in quiescent cells or in response to various forms of stress. At the same time, the activity of SA-β-Gal is often lost in fixed or cryopreserved tissues, leading to false negative results (Pati et al., 2014; Wang and Dreesen, 2018; Yang and Hu, 2005). In addition, not all senescent cells express SA-β-Gal. SA-β-Gal is expressed in senescent fibroblasts and keratinocytes, but is absent in quiescent fibroblasts and terminally differentiated keratinocytes (Dimri et al., 1995). And it is also absent from immortal cells, When H_2O_2 is used to induce cellular senescence, SA-β-Gal appeared in normal human epidermal keratinocytes (NHEKs) instead of immortalized keratinocytes (HaCaT) cells (Liu et al., 2012).

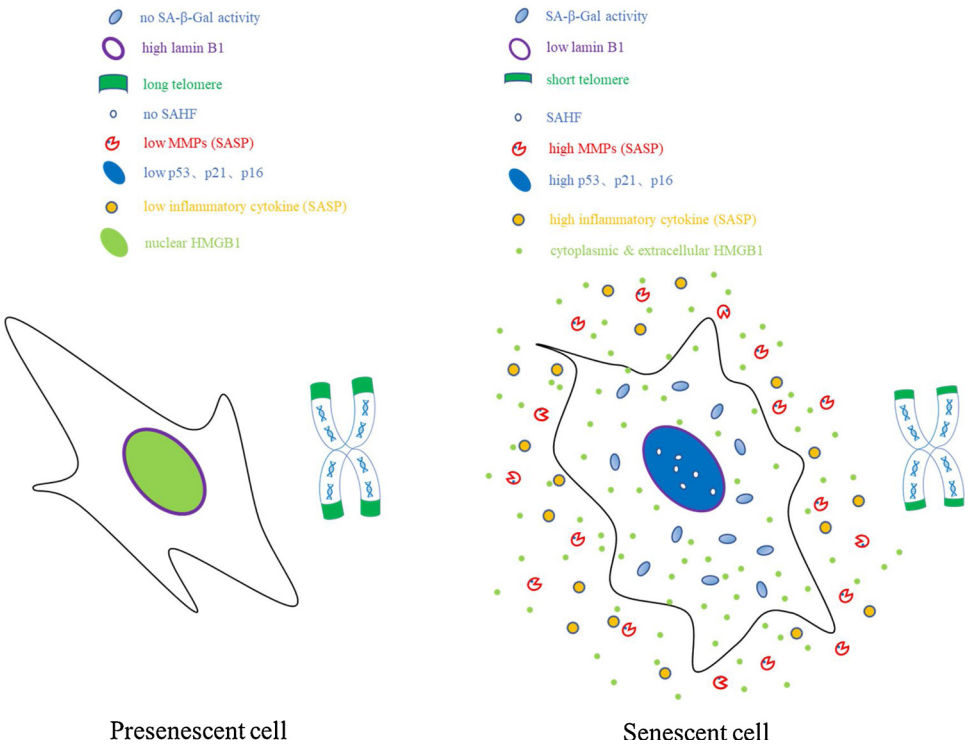

Fig. 1. Presenescent versus senescent cells. Compared to presenescent cells, senescent cells arecharacterized by expanded, flattened cell morphology; increased SA-β-Gal activity; reduced Lamin B1 expression; shorter telomere; occurrence of SAHF; secretion of SASP factors, such as MMPs and inflammatory cytokines; upregulation of p53, p21, p16; and translocation of HMGB1 from nucleus to cytoplasm and extracellular space (improved from Wang and Dreesen, 2018).

3.2. Cell cycle regulators

As a stress response, cellular senescence can force cells out of the cell cycle and loss the ability to cope with growth factors or mitogens (Bhatia-Dey et al., 2016). Cycle arrest is a typical phenomenon of cellular senescence, p53, p21 and p16 as a class of cell cycle regulators are commonly used to detect senescent cells. Human dermal fibroblasts (HDFs) after UV irradiation showed up-regulation of p53, p21 and p16 (Chen et al., 2008). In addition, Mouse embryonic fibroblasts (MEFs) and human melanoma cells also showed the same results (Li et al., 2018).

As an important tumor suppressor gene, p53 maintains genome stability in a variety of cellular damage stress responses. The phosphorylation of p53 at serine 15 is an important change at the molecular level of senescent cells and has been observed in normal HDFs that undergo replicative senescence (RS), oncogene-induced senescence (OIS) and other forms of senescence (Ghosh et al., 2008; Rufini et al., 2013; Webley et al., 2000). p21 is the most classical target gene of p53, and activated p21 specifically binds to the cyclin/cyclin kinase complex of G1 phase and inhibits its kinase activity (Pines, 1994; Qian and Chen, 2013). Knockout p21 in MEFs were unable to complete p53-dependent G1 arrest after DNA damage (Attardi et al., 2004). p21 is significantly up-regulated in RS cells, and knockout of the p21 in human vascular endothelial cells completely blocked rat sarcoma (Ras)-induced cellular senescence (Borgdorff et al., 2010). However, the mechanism of cell senescence induced by p21 is not fully understood. p16 blocks the phosphorylation of retinoblastoma (Rb), forming the E2F complex that blocks cells in the G1 phase, where most senescent cells stop (Nevins, 2001). Overexpression of p16 in young cells showed senescence phenotypes, and the aging delayed after knocking out p16 in mice (Liu et al., 2019). p16 is considered to be one of the universal biomarkers of cellular senescence due to its obvious changes, convenient detection, and its ability to be found in various senescent cells (Baker et al., 2011; Krishnamurthy et al., 2004). p16 can increase the stability of p21 protein, and p21 activates the gene expression of p16 through the transcription factor Sp1. The two pathways synergistically inhibit cell cycle and induce senescence.

However, these genes are not absolute senescence biomarkers. For example, p53 is involved in apoptosis, and mutations may also alter the pattern of p53 activity. Furthermore, the reversible growth arrest state of quiescent cells is also dependent on the cell cycle regulators described above. Thus, analysis based solely on p53 levels can't distinguish between senescent and apoptotic cells (Matjusaitis et al., 2016).

3.3. Senescence-associated heterochromatin foci (SAHF)

Senescent cells often present with punctate heterochromatin structures, a characteristic phenomenon known as SAHF. SAHF is rich in heterochromatin protein 1γ (HP1γ), anti-silencing function 1 (ASF1), histone H3 lysine9 trimethylation (H3K9me3) and Phosphorylated histone H2AX (γH2AX), which isolate cell cycle regulatory genes and potentiate age-related growth stagnation (Swanson et al., 2013). Not only are senescent cells in healthy people, but Hutchinson-Gilford progeria syndrome (HGPS) cells also show severe SAHF. (Chojnowski et al., 2015; Goldman et al., 2004).

Overexpression of p16 can promote the SAHF formation by activating Rb, indicating that the p16/Rb pathway plays an important role in the formation of SAHF. In cells that induced senescence with Ras and inhibit p16 or Rb, the formation of SAHF was significantly attenuated, although the cells still entered the senescence state (Narita et al., 2006). High-mobility group A (HMGA) protein is a non-histone enriched in chromatin, when the expression of HMGA protein is increased, the activity of SA-β-Gal is increased, the formation of SAHF is enhanced, and the growth of cells is obviously inhibited. When HMGA protein is inhibited in senescent cells, the formation of SAHF is weakened, and other signs of aging are also decreased, suggesting that HMGA protein is essential for SAHF formation (Narita et al., 2006). p16 and HMGA can jointly promote SAHF formation in a synergistic manner. MEFs could not form SAHF in response to activation of oncogene Ras (OS) and shorten telomere relative to human embryonic lung fibroblasts IMR90 cells when detected and compared SAHF between them, namely cannot use SAHF marks senescence phenomenon of MEFs (Kennedy et al., 2010). And SAHF cannot be detected in senescent cells of all species. So SAHF has limitations as a senescence biomarker.

3.4. Nuclear lamin B1 (Lamin B1)

Nuclear lamins are the major components of nuclear lamina, which maintain the shape and size of the nucleus and are involved in regulating genomic stability. Defects in nuclear lamins can lead to HGPS, Néstor-Guillermo progeria syndrome (NGPS). Among them, Lamin B1 is closely related to aging(Liu et al., 2011; Shimi et al., 2011). In vitro, Lamin B1 expression decreased in RS and premature senescent cells caused by different factors such as DNA-damaging drugs, UV radiation, and oncogene (Dreesen et al., 2013; Freund et al., 2012; Shimi et al., 2011). In vivo, Lamin B1 is also down-regulated in intrinsic human aging skin, showing the same result in mouse photoaging skin (Freund et al., 2012; Wang et al., 2017).

Meanwhile, Lamin B1 is closely related to autophagy (Jiang and Ji, 2018). During cellular senescence, nuclear autophagy is aberrantly activated, leading to decrease the expression of Lamin B1 (Shimi et al., 2011). Lamin B1 is transported from the nucleus to the cytoplasm by means of vesicles after binding to the autophagy-related protein LC3, and then degraded by lysosomes. Studies have found that inhibiting the interaction between LC3 and Lamin B1 by blocking peptide (Lamin B1 analogue) can slow down cellular senescence (Dou et al., 2015). It should be noted that change in Lamin B1 mRNA level cannot be used as a senescence biomarker.

In addition to Lamin B1, the Lamin B receptor (LBR) and Lamina-associated poly-peptide 2α (LAP2α) were also showed down-regulation (Dreesen et al., 2013; Lukášová et al., 2017). However, the expression of LBR was different in different epidermal layers which may limit the use of LBR as an appropriate biomarker of skin aging (Solovei et al., 2013). The expression of Lamin B1 was found to be stable in quiescent cells, and LAP2α loss occurred not only in senescent cells, but also in quiescent cells. Therefore, the common detection of Lamin B1 and LAP2α can distinguish senescent cells from quiescent cells (Dreesen et al., 2013).

3.5. Telomere

Telomere is considered to be one of the biomarkers of aging (Kanaki et al., 2016; Zietzer and Hillmeister, 2014). The shortening of telomere length was observed in both extrinsic and intrinsic skin aging. DNA double-strand damage is an important factor in triggering cellular senescence. Although DNA damage is not a senescence biomarker, the resulting telomere dysfunction-induced foci (TIF) is often used to detect and quantify senescent cells in vivo and in vitro (Alder et al., 2015; Opresko and Shay, 2017; Zhang et al., 2016). TIF is increased with age in primate dermal fibroblasts (Herbig et al., 2006). Telomerase is activated to add sequences at the ends of telomeres, maintaining the ability to divide continuously. Telomerase activity was not detected in normal skin cells in vivo or in vitro. Therefore, it should be noted that as a biomarker to judge senescence, telomerase detection is only applicable to the research on germ, stem and most cancer cells, and is not suitable in normal cells.

3.6. SASP

Cellular senescence is often accompanied by the production of SASP (Hari and Acosta, 2017; Ito and Igaki, 2016). SASP consist of pro-inflammatory cytokines (IL-1, IL-6 and IL-8, etc.), growth factors (HGF,

Fig. 2. ROS sources and antioxidant system in skin.

GRO and TGF-β, etc.), insulin-like growth factor binding protein 7 (IGFBP-7), and chemokines (such as CXCL-1/3, CXCR2) and MMPs (Waldera Lupa et al., 2015). SASP can change the microenvironment of cells, on the one hand, it can promote the malignant transformation of adjacent recipient cells, leading to the occur of inflammation and diseases. On the other hand, it can activate the immune system to clear senescent cells (Borodkina et al., 2018; Campisi et al., 2011). Nuclear factor kappa-B (NF-κB) is the core regulatory pathway for the secretion of SASP by senescent cells (Ghosh and Capell, 2016).

IL-6 is associated with the senescence of keratinocytes, melanocytes and fibroblasts caused by DNA damage (Ghosh and Capell, 2016; Green, 2008; Lu et al., 2006). IL-1 expression is increased in senescent fibroblasts, epithelial and chemotherapy-induced senescent tumor cells, and it can bind to IL-1 receptor/Toll-like receptors to activate NF-κB, thereby increasing SASP expression (Chang et al., 2002). Ectopic expression of IL-1α regulates the high expression of SASP, leading to the senescence of IMR90 cells, while inhibiting senescence by genetically and pharmacologically inhibiting IL-1 receptor or inflammatory complex, indicating IL-1α can mediate the senescence of surrounding normal cells (Acosta et al., 2013). High expression of MMPs was detected in chronological aging and photoaging skin, and accelerated the degradation of ECM (Quan et al., 2009; Quan and Fisher, 2015). However, SASP may be different due to different cell types and aging degree. IL-6 and IL-8 are also involved in various physiological processes including inflammatory reactions, so SASP as a biomarker of skin aging has certain limitations (Coppé et al., 2010; Rodier et al., 2009). However, other biomarkers can be combined to judge the occurrence of aging in actual research, especially when correlating the effects of aging on the microenvironment of cells or tissues, the study of SASP has important biological significance.

3.7. Other biomarkers of skin aging

Skin aging is accompanied by decreased collagen, hydroxyproline is the highest in collagen, while hydroxyproline is mainly found in skin collagen, and almost no hydroxyproline in other tissues. Therefore, it can be used as an indicator for evaluating skin aging (Kong et al., 2018; Miller et al., 1964). Hyaluronic acid is an acidic mucopolysaccharide which has important water-holding effects secreted by fibroblasts in skin. Hyaluronic acid can improve nutrient metabolism, increase elasticity and prevent skin aging, and its content gradually decreases with the increase of age (Kerscher et al., 2008; Manuskiatti and Maibach, 1996). Halogenated tyrosine increases with age in both photo-exposed and photo-protected skin, suggesting that it may be a useful biomarker of skin aging (Ishitsuka et al., 2012). In senescent cells, high mobility group box-1 (HMGB1) transfers from the nucleus to the cytoplasmic and extracellular spaces, promoting the release of SASP such as IL-1β, IL-6 and MMP-3 (Biran et al., 2017; Davalos et al., 2013). Human keratinocytes release HMGB1, IL-1 and IL-6, and reduce the nuclear expression of HMGB1 in mouse epidermis after UVB irradiation (Johnson et al., 2013).

A useful biomarker can be quantified using existing techniques and must be closely related to specific conditions, although it may not be able to identify all senescent cells and aging skin (Matjusaitis et al., 2016). The ability to accurately detect senescent cells by a single biomarker, especially in vivo, remains challenging. Currently, the identification of aging should be determined by analyzing multiple indicators.

4. Oxidative stress and skin aging

4.1. ROS metabolism

ROS are a class of substances that are composed of oxygen or contain oxygen and are active in nature. Common ROS in the body include superoxide anion (•O_2-), hydrogen peroxide(H_2O_2), highly active hydroxyl radical (•OH), singlet oxygen ($^1O_2$), lipid peroxides, and nitrogen oxides. Molecular oxygen gets unpaired single electron to form $^{\cdot}O_2-$. $O_2^{\cdot}-$ is the first ROS produced in the cell, $O_2^{\cdot}-$ forms H_2O_2 under the catalysis of antioxidant enzymes. Under stress conditions, $O_2^{\cdot}-$ can release ferrous ion from the iron-sulfur center of the protein, participate in the Fenton reaction, and convert H_2O_2 into $O^{\cdot}H$ (Bains and Hall, 2012; Krivoruchko and Storey, 2010). $^{\cdot}OH$ reacts easily with surrounding molecules in the body, with a half-life of only10^{-9} s (Ames et al., 1993).

As shown in Fig. 2, sources of ROS include a wide variety of enzymatic and non-enzymatic substances such as mitochondrial electron transport chain, cyclooxygenase, peroxisome oxidase, NADPH oxidase, and lipoxygenase. Under normal circumstances, ROS production and clearance are in a delicate dynamic balance, in which antioxidant system plays an important role (Mittler, 2002; Obrador et al., 2019). In general, most antioxidants have a higher concentration in epidermal layer than in dermal layer (Rinnerthaler et al., 2015).

4.2. ROS mediate the occurrence of skin aging

The morphological and histological features of chronological skin and photoaged skin are distinct, they involve similar signaling

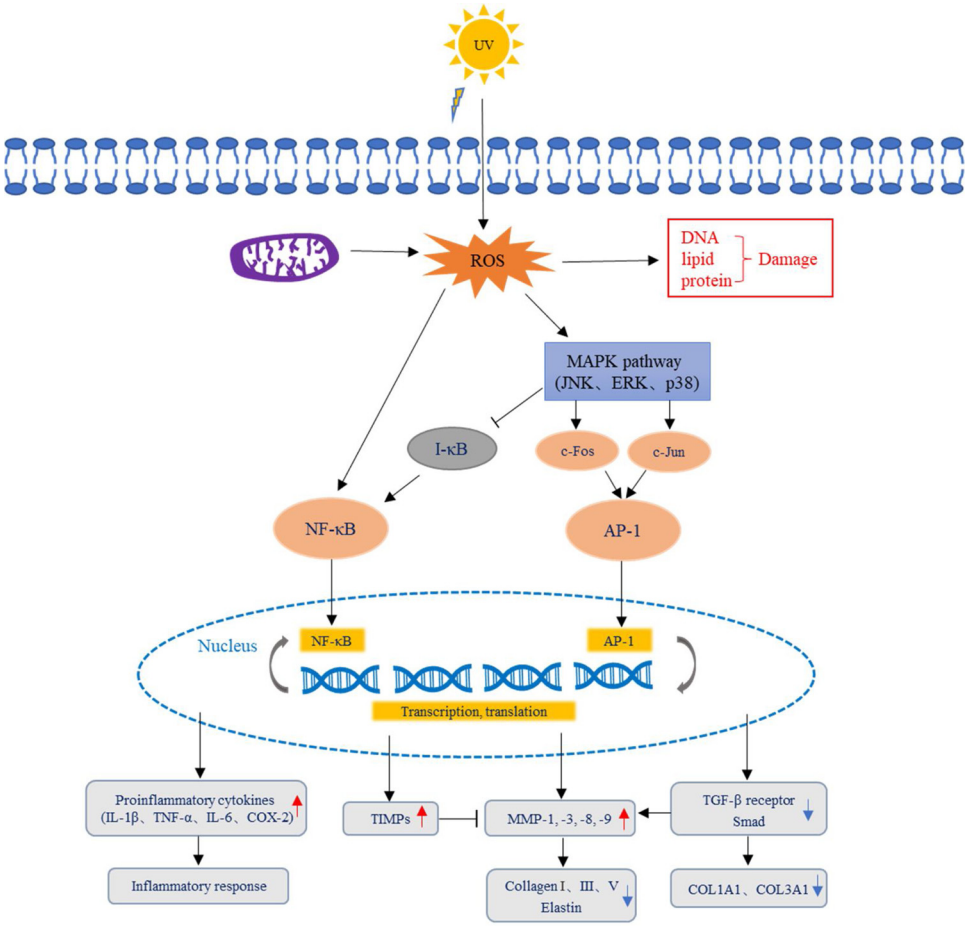

Fig. 3. The schematic diagram of ROS-mediated skin aging. ROS can be generated by mitochondria and external factors such as UV radiation. Excessive ROS activate the MAPK and the NF-κB signaling pathway, leading to the activation of AP-1 and NF-κB. They can increase the expression of proinflammatory cytokines such as IL-1β, TNF-α, IL-6 and COX-2 to regulate the inflammatory response, and make the ratio of MMPs/TIMPs unbalanced by activating MMPs and reducing the expression of TIMPs, thus decompressing ECM. Meanwhile, they can regulate the TGF-β/Smad signaling pathway to reduce collagen production and ultimately accelerate skin aging.

pathways to some extent although induced in a different way (Gilchrest, 1989; Kohl et al., 2011; Rittié and Fisher, 2002). As shown in Fig. 3, ROS mainly derived from cellular oxidative metabolism and UV radiation, play a major role in skin aging according to the free radical aging theory (Rinnerthaler et al., 2015). Excessive ROS can directly cause damage to cells, such as mitochondrial DNA damage, singlet oxygen oxidizes guanine to 8-oxoguanine (8-oxoG), protein carbonylation and 4-hydroxynoncnal production, leading to skin aging (Kammeyer and Luiten, 2015; Marnett, 1999).

ROS can induce the synthesis of MMPs by stimulating mitogen-activated protein kinase (MAPK) and activating the heterodimer activator protein 1 (AP-1) composed of c-Fos and c-Jun (Chen et al., 2016). MMPs can degrade collagen and elastin in the ECM, playing a complex role in skin aging (Pittayapruek et al., 2016). Among them, Collagenase (MMP-1) is the only MMP capable of decomposing intact fibrillar collagen, while other MMP types, such as 92 kDa gelatinase (MMP-2), matrix lysing enzyme (MMP-3) and 72 kDa gelatinase (MMP-9) can further decompose degraded collagen fragments (Krieg et al., 1988). In addition, ROS and activated MAPK signaling pathway can activate NF-κB, which affects the expression of multiple cytokines that mediate inflammation (Bell et al., 2003; Wang et al., 2019). In addition, the activated NF-κB regulates the expression of heme oxygenase-1 (HO-1) indirectly increasing the level of free iron in cells, thereby promoting the further production of ROS through the Fenton reaction (Kammeyer and Luiten, 2015; Whitmarsh and Davis, 1996).

Moreover, NF-κB and AP-1 can reduce the transcription level of TIMPs, activate MMPs better than TIMPs, then further degrade collagen and elastin (Hall et al., 2003). NF-κB also releases MMP-8 to accelerate the degradation of ECM (Sárdy, 2009). AP-1 can down-regulate the expression of transforming growth factor-β (TGF-β) type II receptor, leading to impaired downstream Smad/TGF-β signaling pathway and reduced the transcription of COL3A1 and COL1A1 genes encoding type III and type I collagen precursors, indirectly reducing the biosynthesis of collagen (Kim et al., 2012; Quan et al., 2004; Talwar et al., 1995) (Figure 3). More importantly, AP-1 and NF-κB are involved in the skin carcinogenesis in the elderly by regulating the balance between cell proliferation and apoptosis (Bickers and Athar, 2006; Calcinotto et al., 2019).

5. Autophagy and skin aging

5.1. Autophagy process and function

Autophagy is an evolutionarily conserved decomposition process found in eukaryotes from yeast to mammals (Ravanan et al., 2017; Wen and Klionsky, 2016). Depending on the difference of physiological functions and transport methods, the main types of autophagy include chaperon-mediated autophagy (CMA), micro-autophagy, and macro-autophagy (commonly referred to as autophagy) (Yang and Klionsky, 2010). Autophagy can be divided into three steps: initiation, formation, and degradation. Start-up stage: under the action of stress or some inducing factors, cells begin to undergo autophagy. The key proteins in the initiation phase are serine-threonine protein kinases represented by mammalian target of rapamycin (mTOR). Formation stage: this process requires the coordinated participation of a variety of proteins encoded by autophagy related genes (Atg), including the formation of phagophore, phagophore encapsulating dysfunctional organelles or misfolded proteins, phagophore extension and edge gradual fusion to form autophagosome. Degradation stage: the autophagosome and lysosome fuse to form autolysosome through the transmission of cytoskeletal microtubule network system. The hydrolase in autolysosome degrades the endomembrane of autophagosome and substances encapsulated by

it, the degradation products are released into the cytoplasm by permeases and reused (Abada and Elazar, 2014; Devkota, 2017; Legakis et al., 2007; Mizushima and Komatsu, 2011). Most mammals maintain a basal level of autophagy for normal circulation of intracellular proteins and organelles.

Through autophagy, cells remove unwanted or damaged proteins, lipids or other cellular components, so it is an important mechanism for maintaining organelle stability (Mizushima and Komatsu, 2011). Mitochondria are the energy factories of cells. The ubiquitin Ser65 phosphorylation reaction mediated by PINK1 kinase and E3 ligase Parkin were used to mark the damaged mitochondria with ubiquitin of mitochondrial membrane proteins. Through these markers, autophagy can distinguish between healthy and damaged mitochondria, and recruit mitochondrial autophagy receptors NDP52, P62/SQSTM1, etc., to promote the binding of damaged mitochondria to phagophore (Tang et al., 2011; Song et al., 2016; Yamano et al., 2016). In addition, autophagy can degrade readily aggregated cytoplasmic proteins associated with neurodegenerative diseases, such as a-synuclein associated with Parkinson's disease (PD) (Rubinsztein et al., 2011). In the state of oxidative stress, autophagy plays a role in protecting by degrading oxidized proteins and lipids, alleviating the oxidative damage of cells. Autophagy can also promote the degradation of many bacteria and viruses, and protects against many infectious diseases (Huang and Klionsky, 2007). When cells experience starvation, autophagy provides them with nutrients that maintain their vitality by degrading their own non-essential components. In addition, autophagy affects many physiological and pathological activities of organisms, such as organism development, tumor suppression, antigen presentation, survival, death, and aging (Dikic and Elazar, 2018; Levine and Kroemer, 2019).

5.2. Autophagy participates in the regulation of skin aging

A higher autophagy activity was found in longer-lived species (Pride et al., 2015). Activation of autophagy has been shown to significantly prolong the replication life of cells and inhibit stress-induced cellular senescence in many human and animal cell models, while inhibition of autophagy leads to premature aging. Treatment of primary bronchial epithelial cells with the cigarette smoke extract while adding the autophagy inhibitor 3-MA or knocking down LC-3 and ATG5 results in increased number of senescent cells and SASP accumulation. Conversely, using rapamycin (mTOR inhibitor) to activate autophagy significantly inhibited cigarette smoke extract -induced cellular senescence (Fujii et al., 2012). In addition, inhibition of the autophagy negative regulator TORC1 complex can also prolong the lifespan of yeast and delay the appearance of aging pathology (Rallis et al., 2013). Caloric restriction has a significant anti-aging and life-prolonging effect which is also the most effective physiological autophagy inducer, the anti-aging effect of caloric restriction was blocked after inhibiting autophagy (Levine and Kroemer, 2008). Changes in skin cells can indirectly reflect age-related neurodegenerative diseases (Akerman et al., 2019), HDFs from patients with PD show significant changes in redox balance, mitochondrial function and autophagy (Teves et al., 2018).

However, the potential relationship between autophagy and skin aging is still difficult to determine. Unc-51 like kinase 3 overexpression promotes autophagy but leads to premature aging of HDFs. A significant increase in autophagy vesicles was observed in senescent fibroblasts (Gerland et al., 2003), and which was also evident in senescent keratinocytes induced by ROS (Gosselin et al., 2009). Young et al. showed that oncogene-induced fibroblast senescence is likely to be dependent on previous autophagy, and the occurrence of senescence can be suppressed by using pharmacological and genetic methods to reduce the expression level of autophagy (Young et al., 2009). We need to note that inhibiting autophagy only delays but does not eliminate the occurrence of aging. Some studies support a similar conclusion that although autophagy accelerates aging, aging and autophagy are independent processes (Gewirtz, 2013; Goehe et al., 2012). Overexpression of ATG5 reduced the proliferation of melanoma cells and induced senescence, inhibition of autophagy could delay the occurrence of senescence induced by oncogene (Liu et al., 2013).

At the same time, many studies in recent years hold the opposite view that activation of autophagy delays the occurrence of aging. Human primary fibroblasts prematurely aging in a ROS and p53-dependent manner after knocking out ATG7, ATG12 or lysosomal-associated membrane protein (Lamp2), suggesting that inhibition of autophagy is actually a connivance of aging (Kang et al., 2011). When autophagy-deficient keratinocytes are subjected to oxidative stress, DNA damage and aging are abnormally increased (Song et al., 2017). Overexpression of ATG5 inhibits senescence of MEFs induced by RAS, while ATG5 or ATG3 deficiency is prone to aging (Wang et al., 2012). These studies provide compelling data and inconsistent with the conclusion of Young et al. Activation of autophagy by rapamycin prevents UVB-induced photoaging of MDFs by reducing the production of ROS (Qin et al., 2018). Long-term low-dose UVA exposure results in impaired lysosomal function of dermal fibroblasts, thereby blocking autophagic flux (Lamore and Wondrak, 2013). Therefore, autophagy may be necessary for UV-mediated aging (Cavinato and Jansen-Dürr, 2017), but this assumption requires further validation, such as different UV exposure conditions and different cell types.

Autophagy-deficient melanocytes show significant SASP (Ni et al., 2016). Melanocytes lacking Atg7 undergo premature senescence and exhibit maladjusted antioxidant system (Zhang et al., 2015). In addition, autophagy activation can limit the accumulation of transferred melanin (Katsuyama et al., 2018; Murase et al., 2016). Compared with normal skin, the expression of p62 negatively correlated with autophagy level was up-regulated in human nevus, malignant melanoma and metastatic melanoma, while the incidence of melanoma and nevus formation were generally related to aging (Sample et al., 2018). Fibroblasts from premature aging patients with Cockayne syndrome B protein (CSB) deficiency showed autophagy impaired, restoring autophagy could alleviate premature senescence and photosensitive phenotype in CSB mouse (Majora et al., 2018).

6. MAPK signaling pathway is a potential junction between skin aging and autophagy

MAPK is a highly conserved serine-threonine protein kinase that is activated by a variety of factors including cytokines, neurotransmitters, hormones and cellular stress (Gaestel, 2016). Its signal transduction through mitogen-activated protein 3 kinase (MAPKKK), mitogen-activated protein 2 kinase (MAPKK) and MAPK continuous phosphorylation, together with regulation of cell growth, differentiation, apoptosis, inflammation and other important cellular physiology/pathological process (Burotto et al., 2014; Cuadrado and Nebreda, 2010). Among the pathways of MAPK family, p38 mitogen-activated protein kinase (p38 MAPK), extracellular regulated protein kinase (ERK) and c-Jun N-terminal kinase (JNK) are the most widely studied.

As mentioned earlier, MAPK is important in the process of skin aging. Siegesbeckia glabrescens extract attenuated photoaging of hairless mice and fibroblasts by inhibiting MAPK/NF-κB signaling pathway by increasing collagen synthesis genes (COL1A1, COL3A1, COL4A1, COL7A1) and weakening the expression of MMPs (Kim et al., 2017). Thymus vulgaris can alleviate the damage of UVB-radiated hairless mice and HDFs by activating the antioxidant system and inhibiting the MAPK/AP-1 pathway, thereby reducing the expression of MMPs and increasing collagen synthesis (Sun et al., 2017). Kong et al. demonstrated that icariin inhibited TNF-α/IFN-γ-induced inflammatory response in HaCaT cells by inhibiting p38MAPK rather than ERK or JNK signaling pathway (Kong et al., 2015). Activation of the MAPK signaling pathway promotes senescence of human skin cancer HS-1 cells by affecting the expression of the aging marker p53/p21 (Zhao et al., 2018). Moreover, the MAPK signaling pathway is involved in the regulation of melanin production (Hu et al., 2019). Approximately 60 % of

melanomas have mutation of BRAF that result in abnormal activation of the MAPK signaling pathway (Zhang et al., 2019).

Meanwhile, the MAPK signaling pathway is closely related to autophagy. Chinese poplar propolis exerts anti-inflammatory effects by inhibiting autophagy and MAPK/NF-κB pathway (Xuan et al., 2019). Astragaloside protects rat primary dermal fibroblasts from photoaging induced by UVB radiation, not only by inhibiting ERK and p38 MAPK, but also by activating autophagy (Wen et al., 2018). However, unfortunately these studies did not elaborate the relationship between MAPK signaling pathway and autophagy. The occurrence of mitophagy in mammalian cells requires the regulation of the MAPK1 and MAPK14 (Hirota et al., 2015). JNK can regulate the expression of c-Jun and c-Fos after activated through phosphorylation, thus enhancing the transcriptional activity of Beclin1 which is the first mammalian autophagy protein identified (Dilley et al., 2013; Park et al., 2009; Oberstein et al., 2007). In addition, JNK also can induce nuclear localization of FoxOs and increase its activity to regulate the expression of other ATGs such as Atg7 to affect autophagy (Wong et al., 2010; Zhou et al., 2015). ROS accumulation induced by UVB radiation can mediate the activation of JNK and ERK MAPK in keratinocytes, which in turn regulates the upregulation of adenovirus E1B 19-kDa interacting protein 3 to induce autophagy (Moriyama et al., 2017).

The p38 MAPK pathway is also involved in autophagy regulation. In particular, sustained p38α MAPK activation increases mitochondrial ROS production and further promotes autophagosome formation and enhanced basal autophagic flux (Shen et al., 2019; Slobodnyuk et al., 2019). Inhibition of p38 MAPK expression by SB203580 can reduce autophagy flux and promote inflammatory response by phosphorylating ULK1 (He et al., 2018). As a natural antioxidant and autophagy inducer, resveratrol has a good anti-aging effect, and the induced autophagy by it is associated with the activation of p38 MAPK pathway (Wang et al., 2018). Liu et al. demonstrated that microRNA-181a regulates autophagy of PD by inhibiting the p38/JNK MAPK pathway (Liu et al., 2017). Endoplasmic reticulum stress leads to MKK4 activation and aggregation on lysosomes, which activates the p38 MAPK on lysosomes, and upregulates p38 MAPK induces CMA through direct phosphorylation of the T211 and T213 sites of LAMP2A (CMA receptor) (Li et al., 2017).

In summary, the MAPK signaling pathway may be the potential junction of oxidative stress-induced skin aging and autophagy, but we should note that the above studies did not focus in the field of skin aging when discussing the relationship between MAPK and autophagy, while some studies have reported their interrelationships, further research is urgently needed in this area.

7. Conclusions and prospects

Skin aging is a direct manifestation of the body's aging, which is the result of the joint action of genetic and environmental factors, and delaying skin aging is important in maintaining people's mental health and normal physiological functions of the skin. Chronological aging and photoaging skin show great differences in clinical indicators but involve similar cellular characteristics and regulatory pathways. Thanks to the monitoring of aging biomarkers, it is possible to make qualitative or quantitative analysis of senescent cells in vitro or in vivo, and the functional research of cellular senescence in aging tissue and body has made great progress. At the same time, we should clearly recognize that there are many limitations in current biomarkers, and there is no biomarker that can accurately and stably detect senescence cells. Therefore, it is essential to select appropriate biomarkers for combination in different situations. Improving and discovering new biomarkers and methods to detect skin aging will allow us to better understand the physiological and biochemical changes of aging skin, including wound healing, skin cancer and vascular disease.

Oxidative stress mediates the occurrence of skin aging. The ultimate decline of skin cells or tissues, whether caused by external or internal factors, seems to be caused by endogenous or exogenous ROS. Aging skin has chronic inflammation, and its cell proliferation and waste disposal rate are slow, which are all related to autophagy. Although autophagy can alleviate the oxidative damage of photoaging skin induced by UV radiation, it is unclear whether autophagy activation can effectively prevent photoaging, and the role of autophagy in skin aging remains to be clarified. MAPK signaling pathway is an important signaling pathway in skin aging, especially photoaging, and many studies have shown that MAPK is involved in the regulation of autophagy. Therefore, in the future, it is necessary to study whether the autophagy in aging skin is related to the MAPK pathway and whether it can effectively regulate the inflammatory response, collagen synthesis and decomposition.

Declaration of Competing Interest

The authors declare no competing financial interest.

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References

Abada, A., Elazar, Z., 2014. Getting ready for building: signaling and autophagosome biogenesis. EMBO Rep. 15, 839–852. https://doi.org/10.15252/embr.201439076.

Acosta, J., Banito, A., Wuestefeld, T., Georgilis, A., Janich, P., Morton, J., Athineos, D., Kang, T.-W., Lasitschka, F., Andrulis, M., Angulo, G., Morris, K., Khan, S., Jin, H., Dharmalingam, G., Snijders, B., Carroll, T., Capper, D., Pritchard, C., Gil, J., 2013. A complex secretory program orchestrated by the inflammasome controls paracrine senescence. Nat. Cell Biol. 15. https://doi.org/10.1038/ncb2784.

Afaq, F., Katiyar, S.A., 2011. Polyphenols: skin photoprotection and inhbition of photocarcinogenesis. Mini Rev. Med. Chem. 11, 1200–1215. https://doi.org/10.2174/13895575111091200.

Akerman, C., Hossain, S., Shobo, A., Zhong, Y., Jourdain, R., Hancock, M., George, K., Breton, L., Multhaup, G., 2019. Neurodegenerative disease-related proteins within the epidermal layer of the human skin. J. Alzheimers Dis. 1–16. https://doi.org/10.3233/JAD-181191.

Alder, J.K., Barkauskas, C.E., Limjunyawong, N., Stanley, S.E., Kembou, F., Tuder, R.M., Hogan, B.L.M., Mitzner, W., Armanios, M., 2015. Telomere dysfunction causes alveolar stem cell failure. Proc. Natl. Acad. Sci. U. S. A. 112, 5099–5104. https://doi.org/10.1073/pnas.1504780112.

Alexis, A.F., Obioha, J.O., 2017. Ethnicity and aging skin. J. Drugs Dermatol. 16, s77–s80. https://doi.org/10.1126/science.278.5344.1717b.

Ames, B.N., Shigenaga, M.K., Hagen, T.M., 1993. Oxidants, antioxidants, and the degenerative diseases of aging. Proc. Natl. Acad. Sci. U. S. A. 90, 7915–7922. https://doi.org/10.1073/pnas.90.17.7915.

Arda, O., Göksügür, N., Tüzün, Y., 2014. Basic histological structure and functions of facial skin. Clin. Dermatol. 32, 3–13. https://doi.org/10.1016/j.clindermatol.2013.05.021.

Attardi, L.D., de Vries, A., Jacks, T., 2004. Activation of the p53-dependent G1 checkpoint response in mouse embryo fibroblasts depends on the specific DNA damage inducer. Oncogene 23, 973–980. https://doi.org/10.1038/sj.onc.1207026.

Bains, M., Hall, E.D., 2012. Antioxidant therapies in traumatic brain and spinal cord injury. Biochim. Biophys. Acta 1822, 675–684. https://doi.org/10.1016/j.bbadis.2011.10.017.

Baker, D.J., Wijshake, T., Tchkonia, T., LeBrasseur, N.K., Childs, B.G., van de Sluis, B., Kirkland, J.L., van Deursen, J.M., 2011. Clearance of p16Ink4a-positive senescent cells delays ageing-associated disorders. Nature 479, 232–236. https://doi.org/10.1038/nature10600.

Baumann, L., 2018. How to use oral and topical cosmeceuticals to prevent and treat skin aging. Facial Plast. Surg. Clin. North Am. 26, 407–413. https://doi.org/10.1016/j.fsc.2018.06.002.

Bell, S., Degitz, K., Quirling, M., Jilg, N., Page, S., Brand, K., 2003. Involvement of NF-κB signalling in skin physiology and disease. Cell. Signal. 15, 1–7. https://doi.org/10.1016/S0898-6568(02)00080-3.

Bhatia-Dey, N., Kanherkar, R.R., Stair, S.E., Makarev, E.O., Csoka, A.B., 2016. Cellular senescence as the causal nexus of aging. Front. Genet. 7, 13. https://doi.org/10.3389/fgene.2016.00013.

Bickers, D.R., Athar, M., 2006. Oxidative stress in the pathogenesis of skin disease. J. Invest. Dermatol. 126, 2565–2575. https://doi.org/10.1038/sj.jid.5700340.

Biran, A., Zada, L., Abou Karam, P., Vadai, E., Roitman, L., Ovadya, Y., Porat, Z., Krizhanovsky, V., 2017. Quantitative identification of senescent cells in aging and disease. Aging Cell 16, 661–671. https://doi.org/10.1111/acel.12592.

Birch-Machin, M.A., Bowman, A., 2016. Oxidative stress and ageing. Br. J. Dermatol. 175, 26–29. https://doi.org/10.1111/bjd.14906.

Blume-Peytavi, U., Kottner, J., Sterry, W., Hodin, M.W., Griffiths, T.W., Watson, R.E.B.,

Hay, R.J., Griffiths, C.E.M., 2016. Age-associated skin conditions and diseases: current perspectives and future options. Gerontologist 56, S230–S242. https://doi.org/10.1093/geront/gnw003.
Borgdorff, V., Lleonart, M.E., Bishop, C.L., Fessart, D., Bergin, A.H., Overhoff, M.G., Beach, D.H., 2010. Multiple microRNAs rescue from Ras-induced senescence by inhibiting p21Waf1/Cip1. Oncogene 29, 2262–2271. https://doi.org/10.1038/onc.2009.497.
Borodkina, A.V., Deryabin, P.I., Giukova, A.A., Nikolsky, N.N., 2018. Social life" of senescent cells: what is SASP and why study it? Acta Naturae 10, 4–14.
Briggaman, R.A., Wheeler, C.E., 1975. The epidermal dermal junction. J. Invest. Dermatol. 65, 71–84. https://doi.org/10.1111/1523-1747.ep12598050.
Burotto, M., Chiou, V.L., Lee, J.-M., Kohn, E.C., 2014. The MAPK pathway across different malignancies: a new perspective. Cancer 120, 3446–3456. https://doi.org/10.1002/cncr.28864.
Calcinotto, A., Kohli, J., Zagato, E., Pellegrini, L., Demaria, M., Alimonti, A., 2019. Cellular senescence: aging, Cancer, and injury. Physiol. Rev. 99, 1047–1078. https://doi.org/10.1152/physrev.00020.2018.
Campbell, K.L., Lichtensteiger, C.A., 2004. In: K.L.B.T.-S.A.D.S. Campbell (Ed.), 1 - STRUCTURE AND FUNCTION OF THE SKIN. Hanley & Belfus, Philadelphia, pp. 1–9. https://doi.org/10.1016/B978-1-56053-626-0.50005-7.
Campisi, J., Andersen, J., Kapahi, P., Melov, S., 2011. Cellular senescence: a link between cancer and age-related degenerative disease? Semin. Cancer Biol. 21, 354–359. https://doi.org/10.1016/j.semcancer.2011.09.001.
Cavinato, M., Jansen-Dürr, P., 2017. Molecular mechanisms of UVB-induced senescence of dermal fibroblasts and its relevance for photoaging of the human skin. Exp. Gerontol. 94, 78–82. https://doi.org/10.1016/j.exger.2017.01.009.
Chang, B.-D., Swift, M., Shen, M., Fang, J., Broude, E., Roninson, I., 2002. Molecular determinants of terminal growth arrest induced in tumor cells by a chemotherapeutic agent. Proc. Natl. Acad. Sci. U. S. A. 99, 389–394. https://doi.org/10.1073/pnas.012602599.
Chen, W., Kang, J., Xia, J., Li, Y., Yang, B., Chen, B., Sun, W., Song, X., Xiang, W., Wang, X., Wang, F., Wan, Y., Bi, Z., 2008. p53-related apoptosis resistance and tumor suppression activity in UVB-induced premature senescent human skin fibroblasts. Int. J. Mol. Med. 21, 645–653. https://doi.org/10.3892/ijmm.21.5.645.
Chen, T., Hou, H., Fan, Y., Wang, S., Chen, Q., Si, L., Li, B., 2016. Protective effect of gelatin peptides from pacific cod skin against photoaging by inhibiting the expression of MMPs via MAPK signaling pathway. J. Photochem. Photobiol. B, Biol. 165, 34–41. https://doi.org/10.1016/j.jphotobiol.2016.10.015.
Chojnowski, A., Ong, P.F., Wong, E.S.M., Lim, J.S.Y., Mutalif, R.A., Navasankari, R., Dutta, B., Yang, H., Liow, Y.Y., Sze, S.K., Boudier, T., Wright, G.D., Colman, A., Burke, B., Stewart, C.L., Dreesen, O., 2015. Progerin reduces LAP2α-telomere association in Hutchinson-Gilford progeria. Elife 4, e07759. https://doi.org/10.7554/eLife.07759.
Collado, M., Blasco, M.A., Serrano, M., 2007. Cellular senescence in Cancer and aging. Cell 130, 223–233. https://doi.org/10.1016/j.cell.2007.07.003.
Coppé, J.-P., Desprez, P.-Y., Krtolica, A., Campisi, J., 2010. The senescence-associated secretory phenotype: the dark side of tumor suppression. Annu. Rev. Pathol. 5, 99–118. https://doi.org/10.1146/annurev-pathol-121808-102144.
Cuadrado, A., Nebreda, A.R., 2010. Mechanisms and functions of p38 MAPK signalling. Biochem. J. 429, 403–417. https://doi.org/10.1042/BJ20100323.
Davalos, A.R., Kawahara, M., Malhotra, G.K., Schaum, N., Huang, J., Ved, U., Beausejour, C.M., Coppe, J.-P., Rodier, F., Campisi, J., 2013. p53-dependent release of Alarmin HMGB1 is a central mediator of senescent phenotypes. J. Cell Biol. 201, 613–629. https://doi.org/10.1083/jcb.201206006.
Devkota, S., 2017. The autophagy process. Oncotarget 8, 18623. https://doi.org/10.18632/oncotarget.15951.
Dikic, I., Elazar, Z., 2018. Mechanism and medical implications of mammalian autophagy. Nat. Rev. Mol. Cell Biol. 19, 349–364. https://doi.org/10.1038/s41580-018-0003-4.
Dilley, M.A., Jones, S.M., Scurlock, A.M., Perry, T.T., Pesek, R.D., 2013. Pneumococcal meningitis in a patient with Irak-4 deficiency: a case of failed prophylactic therapy. J. Allergy Clin. Immunol. 131, AB153. https://doi.org/10.1016/j.jaci.2012.12.1207.
Dimri, G.P., Lee, X., Basile, G., Acosta, M., Scott, G., Roskelley, C., Medrano, E.E., Linskens, M., Rubelj, I., Pereira-Smith, O., 1995. A biomarker that identifies senescent human cells in culture and in aging skin in vivo. Proc. Natl. Acad. Sci. 92, 9363 LP–9367. https://doi.org/10.1073/pnas.92.20.9363.
Dou, Z., Xu, C., Donahue, G., Shimi, T., Pan, J.-A., Zhu, J., Ivanov, A., Capell, B.C., Drake, A.M., Shah, P.P., Catanzaro, J.M., Ricketts, M.D., Lamark, T., Adam, S.A., Marmorstein, R., Zong, W.-X., Johansen, T., Goldman, R.D., Adams, P.D., Berger, S.L., 2015. Autophagy mediates degradation of nuclear lamina. Nature 527, 105–109. https://doi.org/10.1038/nature15548.
Dreesen, O., Chojnowski, A., Ong, P.F., Zhao, T.Y., Common, J.E., Lunny, D., Lane, E.B., Lee, S.J., Vardy, L.A., Stewart, C.L., Colman, A., 2013. Lamin B1 fluctuations have differential effects on cellular proliferation and senescence. J. Cell Biol. 200, 605 LP–617. https://doi.org/10.1083/jcb.201206121.
Durai, P.C., Thappa, D.M., Kumari, R., Malathi, M., 2012. Aging in elderly: chronological versus photoaging. Indian J. Dermatol. 57, 343–352. https://doi.org/10.4103/0019-5154.100473.
Eckhart, L., Zeeuwen, P., 2018. The skin barrier: epidermis versus environment. Exp. Dermatol. 27. https://doi.org/10.1111/exd.13731.
Farage, M., Miller, K.W., Elsner, P., Maibach, H., 2008. Intrinsic and extrinsic factors in skin ageing: a review. Int. J. Cosmet. Sci. 30, 87–95. https://doi.org/10.1111/j.1468-2494.2007.00415.x.
Farage, M.A., Miller, K.W., Elsner, P., Maibach, H.I., 2013. Characteristics of the aging skin. Adv. Wound Care (New Rochelle) 2, 5–10. https://doi.org/10.1089/wound.2011.0356.
Feng, J., Luo, J., Yang, P., Du, J., Kim, B., Hu, H., 2018. Piezo2 channel–Merkel cell signaling modulates the conversion of touch to itch. Science (80-.) 360, 530–533. https://doi.org/10.1126/science.aar5703.
Fisher, G.J., Kang, S., Varani, J., Bata-Csorgo, Z., Wan, Y., Datta, S., Voorhees, J.J., 2002. Mechanisms of photoaging and chronological skin aging. Arch. Dermatol. 138, 1462–1470. https://doi.org/10.1001/archderm.138.11.1462.
Freund, A., Laberge, R.-M., Demaria, M., Campisi, J., 2012. Lamin B1 loss is a senescence-associated biomarker. Mol. Biol. Cell 23, 2066–2075. https://doi.org/10.1091/mbc.E11-10-0884.
Friedman, O., 2005. Changes associated with the aging face. Facial Plast. Surg. Clin. North Am. 13, 371–380. https://doi.org/10.1016/j.fsc.2005.04.004.
Fujii, S., Hara, H., Araya, J., Takasaka, N., Kojima, J., Ito, S., Minagawa, S., Yumino, Y., Ishikawa, T., Numata, T., Kawaishi, M., Hirano, J., Odaka, M., Morikawa, T., Nishimura, S., Nakayama, K., Kuwano, K., 2012. Insufficient autophagy promotes bronchial epithelial cell senescence in chronic obstructive pulmonary disease. Oncoimmunology 1, 630–641. https://doi.org/10.4161/onci.20297.
Gaestel, M., 2016. MAPK-activated protein kinases (MKs): novel insights and challenges. Front. Cell Dev. Biol. 3, 88. https://doi.org/10.3389/fcell.2015.00088.
Gerland, L.-M., Peyrol, S., Lallemand, C., Branche, R., Magaud, J.-P., Ffrench, M., 2003. Association of increased autophagic inclusions labeled for β-galactosidase with fibroblastic aging. Exp. Gerontol. 38, 887–895. https://doi.org/10.1016/S0531-5565(03)00132-3.
Gewirtz, D.A., 2013. Autophagy and senescence: a partnership in search of definition. Autophagy 9, 808–812. https://doi.org/10.4161/auto.23922.
Ghosh, K., Capell, B.C., 2016. The senescence-associated secretory phenotype: critical effector in skin Cancer and aging. J. Invest. Dermatol. 136, 2133–2139. https://doi.org/10.1016/j.jid.2016.06.621.
Ghosh, A.K., Kanda, T., Steele, R., Ray, R.B., 2008. Knockdown of MBP-1 in human foreskin fibroblasts induces p53-p21 dependent senescence. PLoS One 3, e3384. https://doi.org/10.1371/journal.pone.0003384.
Giangreco, A., Qin, M., Pintar, J., Watt, F., 2008. Epidermal stem cells are retained in vivo throughout skin aging. Aging Cell 7, 250–259. https://doi.org/10.1111/j.1474-9726.2008.00372.x.
Gilchrest, B., 1989. Skin aging and photoaging: an overview. J. Am. Acad. Dermatol. 21, 610–613. https://doi.org/10.1016/S0190-9622(89)70227-9.
Gilchrest, B., 2013. Photoaging. J. Invest. Dermatol. 133, E2–E6. https://doi.org/10.1038/skinbio.2013.176.
Goehe, R.W., Di, X., Sharma, K., Bristol, M.L., Henderson, S.C., Valerie, K., Rodier, F., Davalos, A.R., Gewirtz, D.A., 2012. The autophagy-senescence connection in chemotherapy: must tumor cells (Self) eat before they sleep? J. Pharmacol. Exp. Ther. 343, 763 LP–778. https://doi.org/10.1124/jpet.112.197590.
Goldman, R.D., Shumaker, D.K., Erdos, M.R., Eriksson, M., Goldman, A.E., Gordon, L.B., Gruenbaum, Y., Khuon, S., Mendez, M., Varga, R., Collins, F.S., 2004. Accumulation of mutant lamin A causes progressive changes in nuclear architecture in Hutchinson-Gilford progeria syndrome. Proc. Natl. Acad. Sci. U. S. A. 101, 8963–8968. https://doi.org/10.1073/pnas.0402943101.
Gosselin, K., Deruy, E., Martien, S., Vercamer, C., Bouali, F., Dujardin, T., Slomianny, C., Houel-Renault, L., Chelli, F., De Launoit, Y., Abbadie, C., 2009. Senescent keratinocytes die by autophagic programmed cell death. Am. J. Pathol. 174, 423–435. https://doi.org/10.2353/ajpath.2009.080332.
Green, M.R., 2008. Senescence: not just for tumor suppression. Cell 134, 562–564. https://doi.org/10.1016/j.cell.2008.08.003.
Hall, M.C., Young, D.A., Waters, J.G., Rowan, A.D., Chantry, A., Edwards, D.R., Clark, I.M., 2003. The comparative role of activator protein 1 and Smad factors in the regulation of Timp-1 and MMP-1 gene expression by transforming growth factor-β1. J. Biol. Chem. 278, 10304–10313. https://doi.org/10.1074/jbc.M212334200.
Han, A., Chien, A.L., Kang, S., 2014. Photoaging. Dermatol. Clin. 32, 291–299. https://doi.org/10.1016/j.det.2014.03.015.
Hari, P., Acosta, J.C., 2017. In: Nikiforov, M.A. (Ed.), Detecting the Senescence-Associated Secretory Phenotype (SASP) by High Content Microscopy Analysis BT - Oncogene-Induced Senescence: Methods and Protocols. Springer, New York, New York, NY, pp. 99–109. https://doi.org/10.1007/978-1-4939-6670-7_9.
Hayflick, L., 1965. The limited in vitro lifetime of human diploid cell strains. Exp. Cell Res. 37, 614–636. https://doi.org/10.1016/0014-4827(65)90211-9.
He, Y., She, H., Zhang, T., Xu, H., Cheng, L., Yepes, M., Zhao, Y., Mao, Z., 2018. p38 MAPK inhibits autophagy and promotes microglial inflammatory responses by phosphorylating ULK1. J. Cell Biol. 217, 315–328. https://doi.org/10.1083/jcb.201701049.
Herbig, U., Ferreira, M., Condel, L., Carey, D., Sedivy, J.M., 2006. Cellular senescence in aging primates. Science 311 (5765). https://doi.org/10.1126/science.1122446.
Hirota, Y., Yamashita, Sichi, Kurihara, Y., Jin, X., Aihara, M., Saigusa, T., Kang, D., Kanki, T., 2015. Mitophagy is primarily due to alternative autophagy and requires the MAPK1 and MAPK14 signaling pathways. Autophagy 11, 332–343. https://doi.org/10.1080/15548627.2015.1023047.
Hu, S., Huang, J., Pei, S., Ouyang, Y., Ding, Y., Jiang, L., Lu, J., Kang, L., Huang, L., Xiang, H., Xiao, R., Zeng, Q., Chen, J., 2019. Ganoderma lucidum polysaccharide inhibits UVB-induced melanogenesis by antagonizing cAMP/PKA and ROS/MAPK signaling pathways. J. Cell. Physiol. 234, 7330–7340. https://doi.org/10.1002/jcp.27492.
Huang, J., Klionsky, D., 2007. Autophagy and human disease. Cell Cycle 6, 1837–1849. https://doi.org/10.4161/cc.6.15.4511.
Ishitsuka, Y., Maniwa, F., Koide, C., Kato, Y., Nakamura, Y., Osawa, T., Tanioka, M., Miyachi, Y., 2012. Increased halogenated tyrosine levels are useful markers of human skin ageing, reflecting proteins denatured by past skin inflammation. Clin. Exp. Dermatol. 37, 252–258. https://doi.org/10.1111/j.1365-2230.2011.04215.x.
Ito, T., Igaki, T., 2016. Dissecting cellular senescence and SASP in Drosophila. Inflamm. Regen. 36, 25. https://doi.org/10.1186/s41232-016-0031-4.

Jabłońska-Trypuć, A., Krętowski, R., Kalinowska, M., Świderski, G., Cechowska-Pasko, M., Lewandowski, W., 2018. Possible mechanisms of the prevention of doxorubicin toxicity by cichoric acid-antioxidant nutrient. Nutrients 10, 44. https://doi.org/10.3390/nu10010044.

Jiang, Y., Ji, J.Y., 2018. Understanding lamin proteins and their roles in aging and cardiovascular diseases. Life Sci. 212, 20–29. https://doi.org/10.1016/j.lfs.2018.09.026.

Johnson, K.E., Wulff, B.C., Oberyszyn, T.M., Wilgus, T.A., 2013. Ultraviolet light exposure stimulates HMGB1 release by keratinocytes. Arch. Dermatol. Res. 305, 805–815. https://doi.org/10.1007/s00403-013-1401-2.

Kammeyer, A., Luiten, R.M., 2015. Oxidation events and skin aging. Ageing Res. Rev. 21, 16–29. https://doi.org/10.1016/j.arr.2015.01.001.

Kanaki, T., Makrantonaki, E., Zouboulis, C., 2016. Biomarkers of skin aging. Rev. Endocr. Metab. Disord. 17. https://doi.org/10.1007/s11154-016-9392-x.

Kang, H.T., Lee, K.B., Kim, S.Y., Choi, H.R., Park, S.C., 2011. Autophagy impairment induces premature senescence in primary human fibroblasts. PLoS One 6, 1–12. https://doi.org/10.1371/journal.pone.0023367.

Katsuyama, Y., Taira, N., Yoshioka, M., Okano, Y., Masaki, H., 2018. 3-O-glyceryl-2-O-hexyl ascorbate suppresses melanogenesis through activation of the autophagy system. Biol. Pharm. Bull. 41, 824–827. https://doi.org/10.1248/bpb.b17-01042.

Kennedy, A., McBryan, T., Enders, G., Johnson, F.B., Zhang, R., Adams, P., 2010. Senescent mouse cells fail to overtly regulate the HIRA histone chaperone and do not form robust Senescence Associated Heterochromatin Foci. Cell Div. 5, 16. https://doi.org/10.1186/1747-1028-5-16.

Kerscher, M., Bayrhammer, J., Reuther, T., 2008. Rejuvenating influence of a stabilized hyaluronic acid-based gel of nonanimal origin on facial skin aging. Dermatologic Surg. 34, 720–726. https://doi.org/10.1111/j.1524-4725.2008.34176.x.

Kim, J.-A., Ahn, B.-N., Kong, C.-S., Kim, S.-K., 2012. Chitooligomers inhibit UV-A-induced photoaging of skin by regulating TGF-β/Smad signaling cascade. Carbohydr. Polym. 88, 490–495. https://doi.org/10.1016/j.carbpol.2011.12.032.

Kim, J., Kim, M.B., Yun, J.G., Hwang, J.K., 2017. Protective effects of standardized siegesbeckia glabrescens extract and its active compound kirenol against UVB-induced photoaging through inhibition of MAPK/NF-κb pathways. J. Microbiol. Biotechnol. 27, 242–250. https://doi.org/10.4014/jmb.1610.10050.

Kohl, E., Steinbauer, J., Landthaler, M., Szeimies, R.-M., 2011. Skin ageing. J. Eur. Acad. Dermatol. Venereol. 25, 873–884. https://doi.org/10.1111/j.1468-3083.2010.03963.x.

Kong, L., Liu, J., Wang, J., Luo, Q., Zhang, H., Liu, B., Xu, F., Pang, Q., Liu, Y., Dong, J., 2015. Icariin inhibits TNF-α/IFN-γ induced inflammatory response via inhibition of the substance P and p38-MAPK signaling pathway in human keratinocytes. Int. Immunopharmacol. 29, 401–407. https://doi.org/10.1016/j.intimp.2015.10.023.

Kong, S.-Z., Li, D.-D., Luo, H., Li, W.-J., Huang, Y.-M., Li, J.-C., Hu, Z., Huang, N., Guo, M.-H., Chen, Y., Li, S.-D., 2018. Anti-photoaging effects of chitosan oligosaccharide in ultraviolet-irradiated hairless mouse skin. Exp. Gerontol. 103, 27–34. https://doi.org/10.1016/j.exger.2017.12.018.

Koohgoli, R., Hudson, L., Naidoo, K., Wilkinson, S., Chavan, B., Birch-Machin, M.A., 2017. Bad air gets under your skin. Exp. Dermatol. 26, 384–387. https://doi.org/10.1111/exd.13257.

Krieg, T., Hein, R., Hatamochi, A., Aumailley, M., 1988. Molecular and Clinical aspects of connective tissue. Eur. J. Clin. Invest. 18, 105–123. https://doi.org/10.1111/j.1365-2362.1988.tb02400.x.

Krishnamurthy, J., Torrice, C., Ramsey, M.R., Kovalev, G.I., Al-Regaiey, K., Su, L., Sharpless, N.E., 2004. Ink4a/Arf expression is a biomarker of aging. J. Clin. Invest. 114, 1299–1307. https://doi.org/10.1172/JCI22475.

Krivoruchko, A., Storey, K.B., 2010. Forever young: mechanisms of natural anoxia tolerance and potential links to longevity. Oxid. Med. Cell. Longev. 3, 186–198. https://doi.org/10.4161/oxim.3.3.12356.

Lamore, S., Wondrak, G., 2013. UVA Causes Dual Inactivation of Cathepsin B and L Underlying Lysosomal Dysfunction in Human Dermal Fibroblasts. J. Photochem. Photobiol. B 123C, 1–12. https://doi.org/10.1016/j.jphotobiol.2013.03.007.

Lavker, R., Zheng, P., Dong, G., 1989. Morphology of aged skin. Clin. Geriatr. Med. 5, 53–67. https://doi.org/10.1016/S0733-8635(18)30801-5.

Lee, B.Y., Han, J.A., Im, J.S., Morrone, A., Johung, K., Goodwin, E.C., Kleijer, W.J., DiMaio, D., Hwang, E.S., 2006. Senescence-associated β-galactosidase is lysosomal β-galactosidase. Aging Cell 5, 187–195. https://doi.org/10.1111/j.1474-9726.2006.00199.x.

Legakis, J., Yen, W.-L., Klionsky, D., 2007. A cycling protein complex required for selective autophagy. Autophagy 3, 422–432. https://doi.org/10.4161/auto.4129.

Leidal, A.M., Levine, B., Debnath, J., 2018. Autophagy and the cell biology of age-related disease. Nat. Cell Biol. 20, 1338–1348. https://doi.org/10.1038/s41556-018-0235-8.

Lephart, E.D., 2016. Skin aging and oxidative stress: equol's anti-aging effects via biochemical and molecular mechanisms. Ageing Res. Rev. 31, 36–54. https://doi.org/10.1016/j.arr.2016.08.001.

Lephart, E.D., Sommerfeldt, J.M., Andrus, M.B., 2014. Resveratrol: influences on gene expression in human skin. J. Funct. Foods 10, 377–384.

Levine, B., Kroemer, G., 2008. Autophagy in the pathogenesis of disease. Cell 132, 27–42. https://doi.org/10.1016/j.cell.2007.12.018.

Levine, B., Kroemer, G., 2019. Biological functions of autophagy genes: a disease perspective. Cell 176, 11–42. https://doi.org/10.1016/j.cell.2018.09.048.

Li, W., Zhu, J., Dou, J., She, H., Tao, K., Xu, H., Yang, Q., Mao, Z., 2017. Phosphorylation of LAMP2A by p38 MAPK couples ER stress to chaperone-mediated autophagy. Nat. Commun. 8, 1–13. https://doi.org/10.1038/s41467-017-01609-x.

Li, Y.F., Ouyang, S.H., Tu, L.F., Wang, X., Yuan, W.L., Wang, G.E., Wu, Y.P., Duan, W.J., Yu, H.M., Fang, Z.Z., Kurihara, H., Zhang, Y., He, R.R., 2018. Caffeine protects skin from oxidative stress-induced senescence through the activation of autophagy. Theranostics 8, 5713–5730. https://doi.org/10.7150/thno.28778.

Liu, G.-H., Barkho, B., Ruiz Macias, S., Diep, D., Qu, J., Yang, S.-L., Panopoulos, A., Suzuki, K., Kurian, L., Walsh, C., Thompson, J., Boue, S., Fung, H., Sancho-Martinez, I., Zhang, K., Yates, J., Izpisua Belmonte, J.C., 2011. Recapitulation of premature aging with iPSCs from Hutchinson-Gilford progeria syndrome. Nature 472, 221–225. https://doi.org/10.1038/nature09879.

Liu, L., Xie, H., Chen, X., Shi, W., Xiao, X., Lei, D., Li, J., 2012. Differential response of normal human epidermal keratinocytes and HaCaT cells to hydrogen peroxide-induced oxidative stress. Clin. Exp. Dermatol. 37, 772–780. https://doi.org/10.1111/j.1365-2230.2011.04315.x.

Liu, H., He, Z., Rütte, T., Yousefi, S., Hunger, R., Simon, H.-U., 2013. Down-regulation of autophagy-related protein 5 (ATG5) contributes to the pathogenesis of early-stage cutaneous melanoma. Sci. Transl. Med. 5, 202ra123. https://doi.org/10.1126/scitranslmed.3005864.

Liu, Y., Song, Y., Zhu, X., 2017. MicroRNA-181a regulates apoptosis and autophagy process in Parkinson's disease by inhibiting p38 mitogen-activated protein kinase (MAPK)/c-Jun N-terminal kinases (JNK) signaling pathways. Med. Sci. Monit. 23, 1597–1606. https://doi.org/10.12659/MSM.900218.

Liu, J.-Y., Souroullas, G., Diekman, B., Krishnamurthy, J., Hall, B., Sorrentino, J., Parker, J., Sessions, G., Gudkov, A., Sharpless, N., 2019. Cells exhibiting strong p16 INK4a promoter activation in vivo display features of senescence. Proc. Natl. Acad. Sci. U. S. A. 116, 201818313. https://doi.org/10.1073/pnas.1818313116.

Lu, S.-Y., Chang, K.-W., Liu, C.-J., Tseng, Y.-H., Lu, H.-H., Lee, S.-Y., Lin, S.-C., 2006. Ripe areca nut extract induces G(1) phase arrests and senescence-associated phenotypes in normal human oral keratinocyte. Carcinogenesis 27, 1273–1284. https://doi.org/10.1093/carcin/bgi357.

Lukášová, E., Kovarˇík, A., Bacˇíková, A., Falk, M., Kozubek, S., 2017. Loss of lamin B receptor is necessary to induce cellular senescence. Biochem. J. 474, 281–300. https://doi.org/10.1042/BCJ20160459.

Majora, M., Sondenheimer, K., Knechten, M., Uthe, I., Esser, C., Schiavi, A., Ventura, N., Krutmann, J., 2018. HDAC inhibition improves autophagic and lysosomal function to prevent loss of subcutaneous fat in a mouse model of Cockayne syndrome. Sci. Transl. Med. 10https://doi.org/10.1126/scitranslmed.aam7510. eaam7510.

Makrantonaki, E., Eckardt, R., Steinhagen-Thiessen, E., Gschnell, M., Zouboulis, C.C., 2013. Skin aging. MMW-Fortschritte der Medizin 17, 50–55.

Man, M.Q., Xin, S.J., Song, S.P., Cho, S., Zhang, X.J., Tu, C.X., Feingold, K.R., Elias, P.M., 2009. Variation of skin surface pH, sebum content and stratum corneum hydration with age and gender in a large chinese population. Skin Pharmacol. Physiol. 22, 190–199. https://doi.org/10.1159/000231524.

Manuskiatti, W., Maibach, H.I., 1996. Hyaluronic acid and skin: wound healing and aging. Int. J. Dermatol. 35, 539–544. https://doi.org/10.1111/j.1365-4362.1996.tb03650.x.

Marnett, L., 1999. Lipid peroxidation-DNA damage by malondialdehyde. Mutat. Res. 424, 83–95. https://doi.org/10.1016/S0027-5107(99)00010-X.

Matjusaitis, M., Chin, G., Sarnoski, E.A., Stolzing, A., 2016. Biomarkers to identify and isolate senescent cells. Ageing Res. Rev. 29, 1–12. https://doi.org/10.1016/j.arr.2016.05.003.

McGlone, F., Reilly, D., 2010. The cutaneous sensory system. Neurosci. Biobehav. Rev. 34, 148–159. https://doi.org/10.1016/j.neubiorev.2009.08.004.

Miller, E.J., Martin, G.R., Piaz, K.A., 1964. The utilization of lysine in the biosynthesis of elastin crosslinks. Biochem. Biophys. Res. Commun. 17, 248–253. https://doi.org/10.1016/0006-291X(64)90392-4.

Mittler, R., 2002. Oxidative stress, antioxidants and stress tolerance. Trends Plant Sci. 7, 405–410. https://doi.org/10.1016/S1360-1385(02)02312-9.

Mizushima, N., 2007. Mizushima NAutophagy: process and function. Genes Dev. 21, 2861–2873. https://doi.org/10.1101/gad.1599207.

Mizushima, N., Komatsu, M., 2011. Autophagy: renovation of cells and tissues. Cell 147, 728–741. https://doi.org/10.1016/j.cell.2011.10.026.

Morita, A., 2007. Tobacco smoke causes premature skin aging. J. Dermatol. Sci. 48, 169–175. https://doi.org/10.1016/j.jdermsci.2007.06.015.

Moriyama, M., Moriyama, H., Uda, J., Kubo, H., Nakajima, Y., Goto, A., Morita, T., Hayakawa, T., 2017. BNIP3 upregulation via stimulation of ERK and JNK activity is required for the protection of keratinocytes from UVB-induced apoptosis. Cell Death Dis. 8, 3–4. https://doi.org/10.1038/cddis.2017.4.

Murase, D., Hachiya, A., Fullenkamp, R., Beck, A., Moriwaki, S., Hase, T., Takema, Y., Manga, P., 2016. Variation in Hsp70-1A expression contributes to skin color diversity. J. Invest. Dermatol. 136, 1681–1691. https://doi.org/10.1016/j.jid.2016.03.038.

Narita, M., Narita, M., Krizhanovsky, V., Nuñez, S., Chicas, A., Hearn, S., Myers, M., Lowe, S., 2006. A novel role for high-mobility group a proteins in cellular senescence and heterochromatin formation. Cell 126, 503–514. https://doi.org/10.1016/j.cell.2006.05.052.

Nevins, J.R., 2001. The Rb/E2F pathway and cancer. Hum. Mol. Genet. 10, 699–703. https://doi.org/10.1093/hmg/10.7.699.

Ni, C., Narzt, M.-S., Nagelreiter, I.-M., Zhang, C.F., Larue, L., Rossiter, H., Grillari, J., Tschachler, E., Gruber, F., 2016. Autophagy deficient melanocytes display a senescence associated secretory phenotype that includes oxidized lipid mediators. Int. J. Biochem. Cell Biol. 81, 375–382. https://doi.org/10.1016/j.biocel.2016.10.006.

Oberstein, A., Jeffrey, P.D., Shi, Y., 2007. Crystal structure of the Bcl-XL-beclin 1 peptide complex: beclin 1 is a novel BH3-only protein. J. Biol. Chem. 282, 13123–13132. https://doi.org/10.1074/jbc.M700492200.

Obrador, E., Liu-Smith, F., Dellinger, R.W., Salvador, R., Meyskens, F.L., Estrela, J.M., 2019. Oxidative stress and antioxidants in the pathophysiology of malignant melanoma. Biol. Chem. 400, 589–612. https://doi.org/10.1515/hsz-2018-0327.

Opresko, P.L., Shay, J.W., 2017. Telomere-associated aging disorders. Ageing Res. Rev. 33, 52–66. https://doi.org/10.1016/j.arr.2016.05.009.

Panich, U., Sittithumcharee, G., Rathviboon, N., Jirawatnotai, S., 2016. Ultraviolet

radiation-induced skin aging: the role of DNA damage and oxidative stress in epidermal stem cell damage mediated skin aging. Stem Cells Int. 2016, 7370642. https://doi.org/10.1155/2016/7370642.
Parisi, A.V., Turner, J., 2006. Variations in the short wavelength cut-off of the solar UV spectra. Photochem. Photobiol. Sci. 5, 331–335. https://doi.org/10.1039/B512029B.
Park, K.-J., Lee, S.-H., Lee, C.-H., Jang, J.-Y., Chung, J., Kwon, M.-H., Kim, Y.-S., 2009. Upregulation of Beclin-1 expression and phosphorylation of Bcl-2 and p53 are involved in the JNK-mediated autophagic cell death. Biochem. Biophys. Res. Commun. 382, 726–729. https://doi.org/10.1016/j.bbrc.2009.03.095.
Pati, S., Jain, S., Behera, M., Acharya, A.P., Panda, S.K., Senapati, S., 2014. X-gal staining of canine skin tissues: a technique with multiple possible applications. J. Nat. Sci. Biol. Med. 5, 245–249.
Petruk, G., Giudice, R.Del, Rigano, M.M., Monti, D.M., 2018. Antioxidants from plants protect against skin photoaging. Oxid. Med. Cell. Longev. 2018. https://doi.org/10.1155/2018/1454936.
Pines, J., 1994. Cell cycle. p21 inhibits cyclin shock. Nature 369, 520–521. https://doi.org/10.1038/369520a0.
Pittayapruek, P., Meephansan, J., Prapapan, O., Komine, M., Ohtsuki, M., 2016. Role of matrix metalloproteinases in photoaging and photocarcinogenesis. Int. J. Mol. Sci. 17, 868. https://doi.org/10.3390/ijms17060868.
Poljšak, B., Dahmane, R., Godic, A., 2012. Intrinsic skin aging: the role of oxidative stress. Acta Dermatovenerol. Alp. Panonica. Adriat. 21 (1-), 1–4. https://doi.org/10.2478/v10162-012-0012-5. 2012.
Pride, H., Yu, Z., Sunchu, B., Mochnick, J., Coles, A., Zhang, Y., Buffenstein, R., Hornsby, P., Austad, S., Pérez, V., 2015. Long-lived species have improved proteostasis compared to phylogenetically-related shorter-lived species. Biochem. Biophys. Res. Commun. 457. https://doi.org/10.1016/j.bbrc.2015.01.046.
Qian, Y., Chen, X., 2013. In: Galluzzi, L., Vitale, I., Kepp, O., Kroemer, G. (Eds.), Senescence Regulation by the p53 Protein Family BT - Cell Senescence: Methods and Protocols. Humana Press, Totowa, NJ, pp. 37–61. https://doi.org/10.1007/978-1-62703-239-1_3.
Qin, D., Ren, R., Jia, C., Lu, Y., Yang, Q., Chen, L., Wu, X., Zhu, J., Guo, Y., Yang, P., Zhou, Y., Zhu, N., Bi, B., Liu, T., 2018. Rapamycin Protects Skin Fibroblasts from Ultraviolet B-Induced Photoaging by Suppressing the Production of Reactive Oxygen Species. Cell. Physiol. Biochem. 46, 1849–1860. https://doi.org/10.1159/000489369.
Quan, T., Fisher, G., 2015. Role of age-associated alterations of the dermal extracellular matrix microenvironment in human skin aging: a mini-review. Gerontology 61. https://doi.org/10.1159/000371708.
Quan, T., He, T., Kang, S., Voorhees, J.J., Fisher, G.J., 2004. Solar ultraviolet irradiation reduces collagen in photoaged human skin by blocking transforming growth factor-beta type II receptor/Smad signaling. Am. J. Pathol. 165, 741–751. https://doi.org/10.1016/s0002-9440(10)63337-8.
Quan, T., Qin, Z., Xia, W., Shao, Y., Voorhees, J., Fisher, G., 2009. Matrix-degrading metalloproteinases in photoaging. J. Investig. Dermatol. Symp. Proc. 14, 20–24. https://doi.org/10.1038/jidsymp.2009.8.
Rallis, C., Codlin, S., Bähler, J., 2013. TORC1 signaling inhibition by rapamycin and caffeine affect lifespan, global gene expression, and cell proliferation of fission yeast. Aging Cell 12. https://doi.org/10.1111/acel.12080.
Ravanan, P., Srikumar, I.F., Talwar, P., 2017. Autophagy: the spotlight for cellular stress responses. Life Sci. 188, 53–67. https://doi.org/10.1016/j.lfs.2017.08.029.
Rinnerthaler, M., Bischof, J., Streubel, M.K., Trost, A., Richter, K., 2015. Oxidative stress in aging human skin. Biomolecules 5, 545–589. https://doi.org/10.3390/biom5020545.
Rittié, L., Fisher, G.J., 2002. UV-light-induced signal cascades and skin aging. Ageing Res. Rev. 1, 705–720. https://doi.org/10.1016/S1568-1637(02)00024-7.
Rittié, L., Fisher, G.J., 2015. Natural and sun-induced aging of human skin. Cold Spring Harb. Perspect. Med. 5, a015370. https://doi.org/10.1101/cshperspect.a015370.
Rodier, F., Coppé, J.-P., Patil, C.K., Hoeijmakers, W.A.M., Muñoz, D.P., Raza, S.R., Freund, A., Campeau, E., Davalos, A.R., Campisi, J., 2009. Persistent DNA damage signalling triggers senescence-associated inflammatory cytokine secretion. Nat. Cell Biol. 11, 973–979. https://doi.org/10.1038/ncb1909.
Rubinsztein, D.C., Mariño, G., Kroemer, G., 2011. Autophagy and aging. Cell 146, 682–695. https://doi.org/10.1016/j.cell.2011.07.030.
Rufini, A., Tucci, P., Celardo, I., Melino, G., 2013. Senescence and aging: the critical roles of p53. Oncogene 32, 5129–5143. https://doi.org/10.1038/onc.2012.640.
Sajo, M.E.J., Kim, C.S., Kim, S.K., Shim, K.Y., Kang, T.Y., Lee, K.J., 2017. Antioxidant and anti-inflammatory effects of shungite against ultraviolet B irradiation-induced skin damage in hairless mice. Oxid. Med. Cell. Longev. 2017. https://doi.org/10.1155/2017/7340143.
Sample, A., Zhao, B., Wu, C., Qian, S., Shi, X., Aplin, A., He, Y.-Y., 2018. The autophagy receptor adaptor p62 is up-regulated by UVA radiation in melanocytes and in melanoma cells. Photochem. Photobiol. 94, 432–437. https://doi.org/10.1111/php.12809.
Sárdy, M., 2009. Role of matrix metalloproteinases in skin ageing. Connect. Tissue Res. 50, 132–138. https://doi.org/10.1080/03008200802585622.
Scharffetter–Kochanek, K., Brenneisen, P., Wenk, J., Herrmann, G., Ma, W., Kuhr, L., Meewes, C., Wlaschek, M., 2000. Photoaging of the skin from phenotype to mechanisms. Exp. Gerontol. 35, 307–316. https://doi.org/10.1016/S0531-5565(00)00098-X.
Shen, T., Miao, Y., Ding, C., Fan, W., Liu, S., Lv, Y., Gao, X., De Boevre, M., Yan, L., Okoth, S., De Saeger, S., Song, S., 2019. Activation of the p38/MAPK pathway regulates autophagy in response to the CYPOR-dependent oxidative stress induced by zearalenone in porcine intestinal epithelial cells. Food Chem. Toxicol. 131, 110527. https://doi.org/10.1016/j.fct.2019.05.035.
Shimi, T., Butin-Israeli, V., Adam, S.A., Hamanaka, R.B., Goldman, A.E., Lucas, C.A., Shumaker, D.K., Kosak, S.T., Chandel, N.S., Goldman, R.D., 2011. The role of nuclear lamin B1 in cell proliferation and senescence. Genes Dev. 25, 2579–2593. https://doi.org/10.1101/gad.179515.111.
Shimizu, H., 2016. Structure and function of the skin. Shimizu's Dermatology, pp. 1–42. https://doi.org/10.1002/9781119099086.ch1.
Slobodnyuk, K., Radic, N., Ivanova, S., Llado, A., Trempolec, N., Zorzano, A., Nebreda, A.R., 2019. Autophagy-induced senescence is regulated by p38α signaling. Cell Death Dis. 10. https://doi.org/10.1038/s41419-019-1607-0.
Solovei, I., Wang, A.S., Thanisch, K., Schmidt, C.S., Krebs, S., Zwerger, M., Cohen, T.V., Devys, D., Foisner, R., Peichl, L., Herrmann, H., Blum, H., Engelkamp, D., Stewart, C.L., Leonhardt, H., Joffe, B., 2013. LBR and lamin A/C sequentially tether peripheral heterochromatin and inversely regulate differentiation. Cell 152, 584–598. https://doi.org/10.1016/j.cell.2013.01.009.
Song, W.-H., Yi, Y.-J., Sutovsky, M., Meyers, S., Sutovsky, P., 2016. Autophagy and ubiquitin-proteasome system contribute to sperm mitophagy after mammalian fertilization. Proc. Natl. Acad. Sci. U. S. A. 113. https://doi.org/10.1073/pnas.1605844113.
Song, X., Narzt, M.S., Nagelreiter, I.M., Hohensinner, P., Terlecki-Zaniewicz, L., Tschachler, E., Grillari, J., Gruber, F., 2017. Autophagy deficient keratinocytes display increased DNA damage, senescence and aberrant lipid composition after oxidative stress in vitro and in vivo. Redox Biol. 11, 219–230. https://doi.org/10.1016/j.redox.2016.12.015.
Sun, Z., Park, S.Y., Hwang, E., Zhang, M., Seo, S.A., Lin, P., Yi, T.H., 2017. Thymus vulgaris alleviates UVB irradiation induced skin damage via inhibition of MAPK/AP-1 and activation of Nrf2-ARE antioxidant system. J. Cell. Mol. Med. 21, 336–348. https://doi.org/10.1111/jcmm.12968.
Swanson, E., Manning, B., Zhang, H., Lawrence, J., 2013. Higher-order unfolding of satellite heterochromatin is a consistent and early event in cell senescence. J. Cell Biol. 203. https://doi.org/10.1083/jcb.201306073.
Talwar, H.S., Griffiths, C.E.M., Fisher, G.J., Hamilton, T.A., Voorhees, J.J., 1995. Reduced type I and type III procollagens in photodamaged adult human skin. J. Invest. Dermatol. 105, 285–290. https://doi.org/10.1111/1523-1747.ep12318471.
Tang, F., Wang, B., Li, N., Wu, Y., Jia, J., Suo, T., Quan, C., Liu, W., Tang, J., 2011. RNF185, a novel mitochondrial ubiquitin E3 ligase, regulates autophagy through interaction with BNIP1. PLoS One 6, e24367. https://doi.org/10.1371/journal.pone.0024367.
Tang, R., Li, Q., Wang, D., Chen, J., Huang, J., Zeng, Q., 2018. Modernization of Traditional Medicine the protective effect of Dendrobium officinale polysaccharides on photoaging fibroblasts by scavenging reactive oxygen species and promoting the expression of TGF-β1. Traditional Medicine Research 3, 131–139. https://doi.org/10.12032/TMR201811071.
Teves, J.M., Bhargava, V., Kirwan, K., Corenblum, M., Justiniano, R., Wondrak, G., Anandhan, A., Flores, A., Schipper, D., Khalpey, Z., Sligh, J., Curiel-Lewandrowski, C., Sherman, S., Madhavan, L., 2018. Parkinson's disease skin fibroblasts display signature alterations in growth, redox homeostasis, mitochondrial function, and autophagy. Front. Neurosci. 11. https://doi.org/10.3389/fnins.2017.00737.
Tobin, D.J., 2017. Introduction to skin aging. J. Tissue Viability 26, 37–46. https://doi.org/10.1016/j.jtv.2016.03.002.
Turner, K.J., Vasu, V., Griffin, D.K., 2019. Telomere biology and human phenotype. Cells 8, 73. https://doi.org/10.3390/cells8010073.
Varani, J., Schuger, L., Dame, M.K., Leonard, C., Fligiel, S.E.G., Kang, S., Fisher, G.J., Voorhees, J.J., 2004. Reduced fibroblast interaction with intact collagen as a mechanism for depressed collagen synthesis in photodamaged skin. J. Invest. Dermatol. 122, 1471–1479. https://doi.org/10.1111/j.0022-202X.2004.22614.x.
Waldera Lupa, D.M., Kalfalah, F., Safferling, K., Boukamp, P., Poschmann, G., Volpi, E., Götz-Rösch, C., Bernerd, F., Haag, L., Huebenthal, U., Fritsche, E., Boege, F., Grabe, N., Tigges, J., Stühler, K., Krutmann, J., 2015. Characterization of skin aging-associated secreted proteins (SAASP) produced by dermal fibroblasts isolated from intrinsically aged human skin. J. Invest. Dermatol. 135, 1954–1968. https://doi.org/10.1038/jid.2015.120.
Wang, A.S., Dreesen, O., 2018. Biomarkers of cellular senescence and skin aging. Front. Genet. 9, 1–14. https://doi.org/10.3389/fgene.2018.00247.
Wang, Y., Wang, X., Lapi, E., Sullivan, A., Jia, W., He, Y.-W., Ratnayaka, I., Zhong, S., Goldin, R., Goemans, C., Tolkovsky, A., Lu, X., 2012. Autophagic activity dictates the cellular response to oncogenic RAS. Proc. Natl. Acad. Sci. U. S. A. 109, 13325–13330. https://doi.org/10.1073/pnas.1120193109.
Wang, A.S., Ong, P.F., Chojnowski, A., Clavel, C., Dreesen, O., 2017. Loss of lamin B1 is a biomarker to quantify cellular senescence in photoaged skin. Sci. Rep. 7, 15678. https://doi.org/10.1038/s41598-017-15901-9.
Wang, J., Li, J., Cao, N., Li, Z., Han, J., Li, L., 2018. Resveratrol, an activator of SIRT1, induces protective autophagy in non-small-cell lung cancer via inhibiting Akt/mTOR and activating p38-MAPK. Onco. Ther. 11, 7777–7786. https://doi.org/10.2147/OTT.S159095.
Wang, Y., Wang, L., Wen, X., Hao, D., Zhang, N., He, G., Jiang, X., 2019. NF-κB signaling in skin aging. Mech. Ageing Dev. 184. https://doi.org/10.1016/j.mad.2019.111160.
Watson, R.E.B., Gibbs, N.K., Griffiths, C.E.M., Sherratt, M.J., 2013. Damage to skin extracellular matrix induced by UV exposure. Antioxid. Redox Signal. 21, 1063–1077. https://doi.org/10.1089/ars.2013.5653.
Webley, K., Bond, J.A., Jones, C.J., Blaydes, J.P., Craig, A., Hupp, T., Wynford-Thomas, D., 2000. Posttranslational modifications of p53 in replicative senescence overlapping but distinct from those induced by DNA damage. Mol. Cell. Biol. 20, 2803–2808. https://doi.org/10.1128/mcb.20.8.2803-2808.2000.
Wen, X., Klionsky, D.J., 2016. An overview of macroautophagy in yeast. J. Mol. Biol. 428, 1681–1699. https://doi.org/10.1016/j.jmb.2016.02.021.
Wen, W., Chen, J., Ding, L., Luo, X., Zheng, X., Dai, Q., Gu, Q., Liu, C., Liang, M., Guo, X., Liu, P., Li, M., 2018. Astragaloside exerts anti-photoaging effects in UVB-induced premature senescence of rat dermal fibroblasts through enhanced autophagy. Arch.

Biochem. Biophys. 657, 31–40. https://doi.org/10.1016/j.abb.2018.09.007.
Whitmarsh, A.J., Davis, R.J., 1996. Transcription factor AP-1 regulation by mitogen-activated protein kinase signal transduction pathways. J. Mol. Med. 74, 589–607. https://doi.org/10.1007/s001090050063.
Wlaschek, M., Tantcheva-Poór, I., Naderi, L., Ma, W., Schneider, L.A., Razi-Wolf, Z., Schüller, J., Scharffetter-Kochanek, K., 2001. Solar UV irradiation and dermal photoaging. J. Photochem. Photobiol. B, Biol. 63, 41–51. https://doi.org/10.1016/S1011-1344(01)00201-9.
Wong, C.H., Iskandar, K.B., Yadav, S.K., Hirpara, J.L., Loh, T., Pervaiz, S., 2010. Simultaneous induction of non-canonical autophagy and apoptosis in cancer cells by ROS-dependent ERK and JNK activation. PLoS One 5, e9996. https://doi.org/10.1371/journal.pone.0009996.
Xuan, H., Yuan, W., Chang, H., Liu, M., Hu, F., 2019. Anti-inflammatory effects of Chinese propolis in lipopolysaccharide-stimulated human umbilical vein endothelial cells by suppressing autophagy and MAPK/NF-κB signaling pathway. Inflammopharmacology 27, 561–571. https://doi.org/10.1007/s10787-018-0533-6.
Yamano, K., Matsuda, N., Tanaka, K., 2016. The ubiquitin signal and autophagy: an orchestrated dance leading to mitochondrial degradation. EMBO Rep. 17. https://doi.org/10.15252/embr.201541486.
Yang, N.-C., Hu, M.-L., 2005. The limitations and validities of senescence associated-β-galactosidase activity as an aging marker for human foreskin fibroblast Hs68 cells. Exp. Gerontol. 40, 813–819. https://doi.org/10.1016/j.exger.2005.07.011.
Yang, Z., Klionsky, D.J., 2010. Eaten alive: a history of macroautophagy. Nat. Cell Biol. 12, 814–822. https://doi.org/10.1038/ncb0910-814.
Yeh, C.-K., 2016. Cellular senescence and aging. Oral Dis. 22, 587–590. https://doi.org/10.1111/odi.12483.
Young, A.R.J., Narita, Masako, Ferreira, M., Kirschner, K., Sadaie, M., Darot, J.F.J., Tavaré, S., Arakawa, S., Shimizu, S., Watt, F.M., Narita, Masashi, 2009. Autophagy mediates the mitotic senescence transition. Genes Dev. 23, 798–803. https://doi.org/10.1101/gad.519709.
Zhang, C.-F., Gruber, F., Ni, C., Mildner, M., Koenig, U., Karner, S., Barresi, C., Rossiter, H., Narzt, M.-S., Nagelreiter, I.M., Larue, L., Tobin, D.J., Eckhart, L., Tschachler, E., 2015. Suppression of autophagy dysregulates the antioxidant response and causes premature senescence of melanocytes. J. Invest. Dermatol. 135, 1348–1357. https://doi.org/10.1038/jid.2014.439.
Zhang, J., Rane, G., Dai, X., Shanmugam, M.K., Arfuso, F., Samy, R.P., Lai, M.K.P., Kappei, D., Kumar, A.P., Sethi, G., 2016. Ageing and the telomere connection: an intimate relationship with inflammation. Ageing Res. Rev. 25, 55–69. https://doi.org/10.1016/j.arr.2015.11.006.
Zhang, X., Cai, L., Zhao, S., Long, J., Li, J., Wu, L., Su, J., Zhang, J.L., Tao, J., Zhou, J., Chen, X., Peng, C., 2019. CX-F9, a novel RSK2 inhibitor, suppresses cutaneous melanoma cells proliferation and metastasis through regulating autophagy. Biochem. Pharmacol. 168, 14–25. https://doi.org/10.1016/j.bcp.2019.06.014.
Zhao, X.D., Huang, C., Wang, R.X., Wang, S.A., 2018. DUSP22 promotes senescence of HS-1 Skin cancer cells through triggering MAPK signaling pathway. Eur. Rev. Med. Pharmacol. Sci. 22, 7819–7825. https://doi.org/10.26355/eurrev-201811-16406.
Zheng, H., Zhang, M., Luo, H., Li, H., 2019. Isoorientin alleviates UVB-induced skin injury by regulating mitochondrial ROS and cellular autophagy. Biochem. Biophys. Res. Commun. 514, 1133–1139. https://doi.org/10.1016/j.bbrc.2019.04.195.
Zhou, Y.Y., Li, Y., Jiang, W.Q., Zhou, L.F., 2015. MAPK/JNK signalling: a potential autophagy regulation pathway. Biosci. Rep. 35, 1–10. https://doi.org/10.1042/BSR20140141.
Zietzer, A., Hillmeister, P., 2014. Leucocyte telomere length as marker for cardiovascular ageing. Acta Physiol. Oxf. (Oxf) 211, 251–256. https://doi.org/10.1111/apha.12284.