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Commentary

The impact of cellular senescence in skin ageing: A notion of mosaic and therapeutic strategies

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ABSTRACT

Cellular senescence is now recognized as one of the nine hallmarks of ageing. Recent data show the involvement of senescent cells in tissue ageing and some age-related diseases. Skin represents an ideal model for the study of ageing. Indeed, skin ageing varies between individuals depending on their chronological age but also on their exposure to various exogenous factors (mainly ultraviolet rays). If senescence traits can be detected with ageing in the skin, the senescent phenotype varies among the various skin cell types. Moreover, the origin of cellular senescence in the skin is still unknown, and multiple origins are possible. This reflects the mosaic of skin ageing. Senescent cells can interfere with their microenvironment, either via the direct secretion of factors (the senescence-associated secretory phenotype) or via other methods of communication, such as extracellular vesicles. Knowledge regarding the impact of cellular senescence on skin ageing could be integrated into dermatology research, especially to limit the appearance of senescent cells after photo(chemo)therapy or in age-related skin diseases. Therapeutic approaches include the clearance of senescent cells via the use of senolytics or via the cooperation with the immune system.

1. Introduction

The ageing of the population is one of the major challenges our society faces, but we are still far from understanding all its underlying mechanisms. Based on the data available on model organisms and humans, nine hallmarks contributing to the ageing process have been described. These include genomic instability, telomere attrition, epigenetic alterations, altered cellular communication, stem cell exhaustion, mitochondrial dysfunction, deregulated nutrient sensing, loss of proteostasis, and cellular senescence [1]. If cellular senescence was first described as associated with the exhaustion of proliferative capacities of the cells and with the critical shortening of telomeres, it was later demonstrated that cellular senescence could also be induced by the expression of oncogenes or by stress exposure [2].

Skin is a model of choice for ageing studies. Indeed, skin ageing is influenced by both intrinsic and extrinsic factors. The presence and accumulation of senescent cells in the skin with age have been highlighted [3]. The skin is composed of several cell types that can undergo senescence, including fibroblasts, keratinocytes, melanocytes, sebocytes and skin stem cells. The study of senescence in these various skin cell types reveals particular features based on cell type.

Senescent cells, although they are unable to divide, remain metabolically active and are able to interfere with their cellular

Abbreviations: 53BP1, 53-binding protein 1; ATM, ataxia telangiectasia mutated; ATR, ataxia telangiectasia mutated and Rad3-related; AURKA, aurora kinase A; CDK, cyclin-dependent kinase; Chk, checkpoint kinase; DDR, DNA damage response; DNA-SCARS, DNA segments with chromatin alterations reinforcing senescence; EV, extracellular vesicle; HGPS, Hutchinson-Gilford progeria syndrome; IGFBP, insulin-like growth factor binding protein; IL, interleukin; MMP, matrix metalloproteinase; mtDNA, mitochondrial DNA; NF-κB, nuclear factor-kappa B; OIS, oncogene-induced senescence; pRb, protein of retinoblastoma; PUVA, psoralen plus UVA; ROS, reactive oxygen species; SA-βgal, senescence-associated beta-galactosidase; SAmiR, senescence-associated microRNA; SASP, senescence-associated secretory phenotype; SIPS, stress-induced premature senescence; WS, Werner syndrome.

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and matrix environments. They can directly secrete specific factors, known as the SASP (senescence-associated secretory phenotype) [4], but other methods of communication, such as secreted extracellular vesicles, are being considered. Communication between senescent cells and their neighbouring cells is associated with both beneficial and detrimental effects. In particular, such communication is suspected to play a role in age-related diseases. Interestingly, some age-related skin diseases have been shown to be associated with an increase in the proportion of senescent cells. Reducing or limiting the presence of senescent cells and their adverse effects on the skin seems to be a promising therapeutic strategy. Various therapeutic approaches will be presented, with a particular focus on the prevention of the appearance of senescent cells and their specific elimination via the use of senolytic agents or the immune system.

2. Skin ageing and senescence

2.1. Intrinsic and extrinsic skin ageing features

Classically, two types of skin ageing have been identified: intrinsic ageing (mainly visible on photo-protected areas) and extrinsic ageing (particularly due to UV exposure and located on photo-exposed areas) [5]. Extrinsic ageing seems to be superimposed on intrinsic ageing and is more or less pronounced depending on the intensity, duration and chronicity of UV exposure and on the skin phototype, according to the Fitzpatrick (or photo-typing) scale. Indeed, individuals with dark skin, which is enriched by photoprotective melanins, show less pronounced photoageing [6]. Furthermore, other environmental factors may also interfere with skin ageing, such as smoking (as shown by prominent facial wrinkles in the skins of heavy cigarette smokers) [7] and air pollution (highlighted in women exposed to high air pollution due to heavy traffic) [8].

Intrinsic and extrinsic skin ageing features are characterized by reduced physiological function and an increased susceptibility to age-related dermatoses, such as dry skin (xerosis cutis), itching (pruritus), ulcers, dyspigmentation, wrinkles, fungal infections and benign or malignant skin cancers (for a review [9]). Intrinsic and extrinsic skin ageing are different at the clinical and histological levels [10]. Clinically, intrinsically aged skin looks thin and dry with fine lines. In contrast, extrinsically aged skin appears thicker (“leathery aspect”) with deep wrinkles and “age spots” (actinic lentigines). The refinement or thickening of the skin reflects variations in the thickness of the dermis and epidermis compartments. Histologically, many changes affect the structural components of the connective tissue, leading to their increased degradation and the accumulation of an unfunctional matrix due to cross-links in collagen fibers (intrinsic) or to the accumulation of partially degraded elastin fibers (extrinsic).

Despite their differences, both types of skin ageing seem to be driven by similar molecular pathways [10]. Indeed, the generation of ROS (reactive oxygen species) and the degradation of the extracellular matrix by overexpressed MMPs (matrix metalloproteinases) are common features of both types of skin ageing [11]. ROS accumulation mainly leads to the activation of receptor tyrosine kinases (RTKs) via the inactivation of protein tyrosine phosphatases (PTPs). This allows the phosphorylation of RTKs and the activation of their downstream signalling pathways, including the three families of MAPKs (mitogen-activated protein kinases): ERK (extracellular signal-regulated kinases), JNK (c-Jun N-terminal kinase) and $p38^{MAPK}$. Downstream of these MAPKs, transcription factor AP-1 (activator protein-1) is activated, inducing the expression of several metalloproteinases (MMP-1, -3 and -9) and preventing the expression of procollagen-1 [11,12] (Fig. 1).

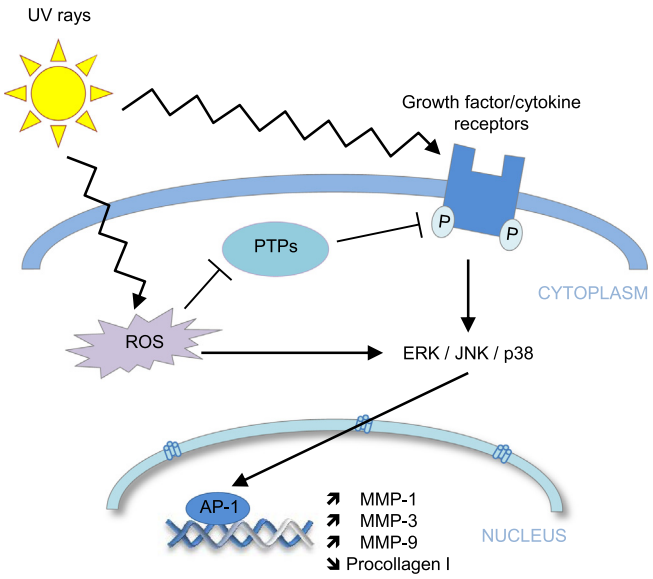

Fig. 1. Major pathways involved in ROS-related skin photoageing. UV rays generate ROS and activate growth factor/cytokine receptors. ROS accumulation leads to the activation of receptor tyrosine kinases via inactivating protein tyrosine phosphatases (PTPs). This allows the phosphorylation of the receptors and the activation of their downstream signalling pathways, including the three families of MAPKs: ERK, JNK and p38. Downstream of these MAPKs, the transcription factor AP-1 is activated, inducing the expression of various MMPs (MMP-1, -3 and -9) and preventing the expression of procollagen I. (Adapted from [12]) AP-1: activator protein-1; ERK: extracellular signal-regulated kinase; JNK: c-Jun N-terminal kinase; MAPKs: mitogen-activated protein kinases; MMP: matrix metalloproteinases; PTPs: protein tyrosine phosphatases; ROS: reactive oxygen species.

In both types of skin ageing, the accumulation of senescent cells is observed in both the epidermis and the dermis [13,14]. The origin of these senescent cells is not yet known. It is likely that several mechanisms are responsible for their appearance, such as an increase in inflammation or the level of oxidative stress.

2.2. General features of cellular senescence

First described in the early 1960s by L. Hayflick in vitro, senescence can be defined as an irreversible growth arrest and a resistance to mitogenic stimuli in a proliferation-competent cell; it was then called “replicative” senescence [15]. This was subsequently associated with the critical shortening of telomeres [16]. Senescence can affect all somatic cells and can be detected by the use of several biomarkers of senescence, such as SA-βgal (senescence-associated beta-galactosidase) activity, the overexpression of cell cycle arrest proteins such as $p16^{Ink4a}$, the common mtDNA (mitochondrial DNA) deletion and senescence-associated microRNAs (SAmiRs).

It was later demonstrated that cellular senescence can also be induced by the expression of oncogenes or by stress exposure [2].

Oncogene expression in normal cells was shown to induce a senescent phenotype named “oncogene-induced senescence” or OIS. This was first reported by the expression of the oncogenic form of *RAS* (*H-Ras*^{V12}) in normal murine and human fibroblasts, leading to irreversible growth arrest and increased SA-βgal activity [17]. OIS is also detected after the expression of other oncogenes, including members of Ras signalling pathway, such as *N-RAS* (neuroblastoma RAS), *RAF* and *BRAF*^{E600}, or after the expression of mutated forms of tumour suppressor genes, such as *PTEN* (phosphatase and tensin homolog), *VHL* (von Hippel-Lindau tumour suppressor), *RB1* (RB transcriptional corepressor 1) and *NF-1* (neurofibromin 1), leading to their inactivation [18].