



# Cellular Senescence as a Barrier to Tissue Engineering

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## EDITORIAL

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*In vitro* tissue regeneration requires the expansion of cells in a monolayer culture over extended periods to obtain sufficient cell numbers. However, prolonged monolayer culture conditions often induce cellular senescence, a state characterized by irreversible cell cycle arrest in response to various stressors such as oxidative damage, telomere shortening, and DNA damage. Cellular senescence was historically regarded as an *in vitro* artifact, it is now recognized as a critical biological process implicated in aging, tissue remodeling, and the pathogenesis of chronic diseases including osteoarthritis, cardiovascular disease, diabetes, and cancer [1]. Senescent cells may play beneficial roles in acute wound healing<sup>3</sup> by modulating inflammation and tissue remodeling, however, their accumulation during *in vitro* expansion is detrimental to tissue engineering applications. This is primarily due to the senescence-associated secretory phenotype (SASP), which involves the release of pro-inflammatory cytokines that can propagate senescence to neighboring cells and compromise regenerative potential [2]. There is growing interest in developing strategies to either prevent the onset of senescence or selectively target and eliminate senescent cells to enhance regenerative outcomes and improve therapeutic efficacy.

During *in vitro* monolayer expansion, cells may undergo senescence via two primary mechanisms: telomerase-dependent and telomerase-independent<sup>8</sup> pathways. Telomerase-dependent senescence is driven by progressive

telomere shortening, ultimately triggering replicative exhaustion and causes cell cycle arrest. In contrast, telomerase-independent senescence arises from extrinsic or intrinsic signals, such as oxidative damage, oncogenic signals, expression of pro-inflammatory cytokines. This form of senescence is predominantly regulated by canonical pathways, including the p53/p21 and p16/Rb pathways, which also enforce irreversible cell cycle arrest [3]. Recent studies have expanded this understanding of senescence by finding additional regulatory factors such as changes in chromatin architecture, mitochondrial dysfunction, and alterations in nuclear structural proteins [4]. Identification of senescent cells remains a major challenge in both research and clinical contexts. Although senescence-associated  $\beta$ -galactosidase (SA- $\beta$ -gal) activity is a commonly used marker, it lacks specificity and is insufficient as a standalone indicator of senescence. Therefore, a combination of markers is recommended to improve diagnostic accuracy. These include increased expression of p16<sup>INK4a</sup>, p21<sup>CIP1</sup>, and p53, as well as changes in chromosomal organization and nuclear components such as nuclear myosin 1 $\beta$  (NM1 $\beta$ ) [5]. The heterogeneity of senescent phenotypes and the absence of universal biomarkers make the selective targeting and elimination of senescent cells particularly complex and technically demanding.

Senescent cells secrete inflammatory cytokines and convert into a senescence-associated secretory phenotype (SASP).

Inflammatory proteins secreted by senescent cells that can damage nearby cells, increase tissue breakdown, and cause chronic inflammation. In addition, these signals promote senescence in the neighbouring healthy cells. This causes an irreversible path and leads to deterioration of the tissues. A variety of strategies are currently being explored to prevent, modulate, or eliminate cellular senescence. These include genetic approaches, such as gene editing aimed at modulating key regulatory genes involved in senescence pathways; senolytic drugs, which selectively induce apoptosis in senescent cells; and senomorphic compounds, which suppress the detrimental effects of the SASP without eliminating the cells themselves [6]. Dasatinib and quercetin are important senolytics and have shown their efficacy in preclinical models and are under evaluation in human clinical trials.<sup>14</sup> Metformin which is a widely used antidiabetic agent, has shown senomorphic properties by attenuating SASP-associated inflammatory responses.<sup>16</sup> Additionally, peptide-based inhibitors that disrupt critical protein-protein interactions within senescent cells are emerging as potential therapeutic tools. Despite promising effects of all these drugs and inhibitors (senotherapeutics), there are still significant limitations because they all have off-target effects, insufficient specificity, and causing cytotoxicity in healthy cells. Therefore, further improvement in drug design and delivery is necessary to enhance therapeutic selectivity and safety.

Senescence is also a major issue in stem cell therapy and tissue engineering. For example, mesenchymal stem cells (MSCs), chondrocytes (cartilage forming cells), nucleus pulposus and annulus fibrosus cells (intervertebral disc forming cells) can become senescent during in vitro monolayer culture. This reduces their ability to form tissues in vitro that resembles the respective native tissue. Strategies to prevent senescence in these cells can result in better tissue formation.

Senescence is a complex but exciting area of research. In the body it plays both helpful and harmful roles. With deeper understanding of pathways that regulate senescence, we can get closer to use senescence-targeting therapies to treat age-related diseases, improve stem cell therapies, and possibly extend healthy lifespan. Still, careful testing is needed to make sure these treatments are safe and effective for people.

### ***Competing interests***

The author declares no competing interests.

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