Review Article

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Cellular senescence and nanoparticle-based therapies: Current developments and perspectives

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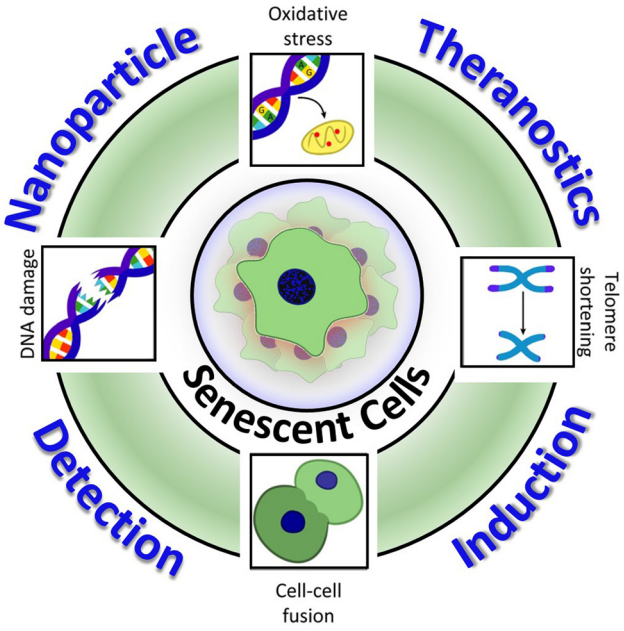
Abstract: The timing and location of senescent cells *in vivo* is a leading candidate explanation for human aging. A rapidly developing scientific field with the potential to slow the aging process is the creation of pharmacologically active medicines that target senescent cells. Senotherapeutics have been developed to selectively or preferentially target and eliminate senescent cells. Senolytic compounds that delay aging in animal models are being explored in humans with great hope. Nanoparticle (NP) drug delivery strategies for targeting senescent cells are in their infancy, but advancements have been made, and preliminary anti-aging applications are promising. However, using nanomedicine effectively requires an understanding of how NPs behave in senescent cells. Senescence theranostics could offer a variety of information, including a prognostic predictor in cancer patients after treatment. The NPs have a much better outlook for translating it to the clinic for aging. Reversing aging pathologies may only require a percentage reduction in senescent cells to achieve therapeutic success, in contrast to cancer, where it is essential to eradicate the tumor. This review provides an overview of the factors that lead to senescence and different therapeutic approaches, focusing on the use of nanocarriers/particles in senotherapy.

Keywords: senescence, cellular senescence induction, nanoparticles



Graphical abstract

1 Introduction

Cellular senescence is a cellular state caused by the natural aging process or environmental stress. Many changes in cellular functions occur as a result of cellular senescence, including the loss of the ability to proliferate, changes in the architecture of the cell nucleus, and morphological changes in the cellular structure [1,2]. Hayflick and Moorhead were the first researchers to study and describe the phenomenon of cellular senescence in 1961, and subsequent research published in 1965 resulted in the later coining of the term “Hayflick limit” to indicate the period at which human fibroblasts cease to divide [3,4]. Apoptosis, also known as programmed cell death, is one way the cells respond to stress and damage [5]. Conversely, cells can age as opposed to dying by activating the senescence pathway, which is triggered by persistent DNA damage and involves a network of proteins that participate in cell cycle arrest [6].

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This review aims to provide a general view of cellular senescence, the factors that lead to senescence, and different therapeutical approaches, focusing on the state-of-the-art nanocarrier (NC)/particle interaction with senescence cells and nanoparticle (NP)-based therapies. This work serves as an introductory compendium of relevant aspects of cell senescence and nanomedicine for senotherapy for the community working on materials science, nanobiotechnology, and nanosciences. We also provide a fresh view of developments in the field and outline some of the perspectives and research opportunities.

2 Senescence

Many changes not observed in young cells can be highlighted during cellular senescence. Depending on the cell line and the way of senescence induction, morphological changes in cells can be enormous or very subtle. The most fundamental changes are shown in Figure 1, compared to a non-senescent cell. Cell enlargement is caused by cell cycle arrest at certain time points during cell growth [7]. For example, the size of cancer cell lines before and after senescence induction was shown by Bojko *et al.*, which was clearly noticeable in fluorescence-stained cells [8]. Nucleus formation changes as the heterochromatin is redistributed and DNA parts are tightly compressed, and as a result, it forms senescent-associated heterochromatin *foci* (SAHF). This specific formation can be seen in a microscope with simple nuclei fluorescence staining, depending on cell lines [9,10]. Interestingly, constitutive heterochromatin regions are not included in SAHF formation. Its role is to separate genes promoting proliferation to successfully arrest the cell cycle and protect cells from going through apoptosis by hiding excessive DNA damage [11]. Mitochondria have reduced mitochondrial membrane potential, increasing proton leakage and generating high reactive oxygen species (ROS). Due to hyper-fusion, the mitochondrial mass of senescent cells is much higher, while that of non-senescent cells is continuously going through fissions and fusions to maintain metabolic balance [12].

Cell metabolism and dynamics change drastically after the induction of cellular senescence. The potential of the mitochondrial membrane is decreased, which consequently compromises the ability to produce ATP, which is highly reduced [13]. Other organelles that are affected by cellular senescence are lysosomes. Their size increases, and as the cell tries to recompensate dysfunctional lysosomes with newer ones, its number also greatly increases. When cells go through cellular senescence, lysosomes start excessive production of β-galactosidase, which will be discussed further in this review.

One of the features of senescent cells is their ability to enhance their microenvironment by producing and secreting multiple cytokines and chemokines, various growth factors,

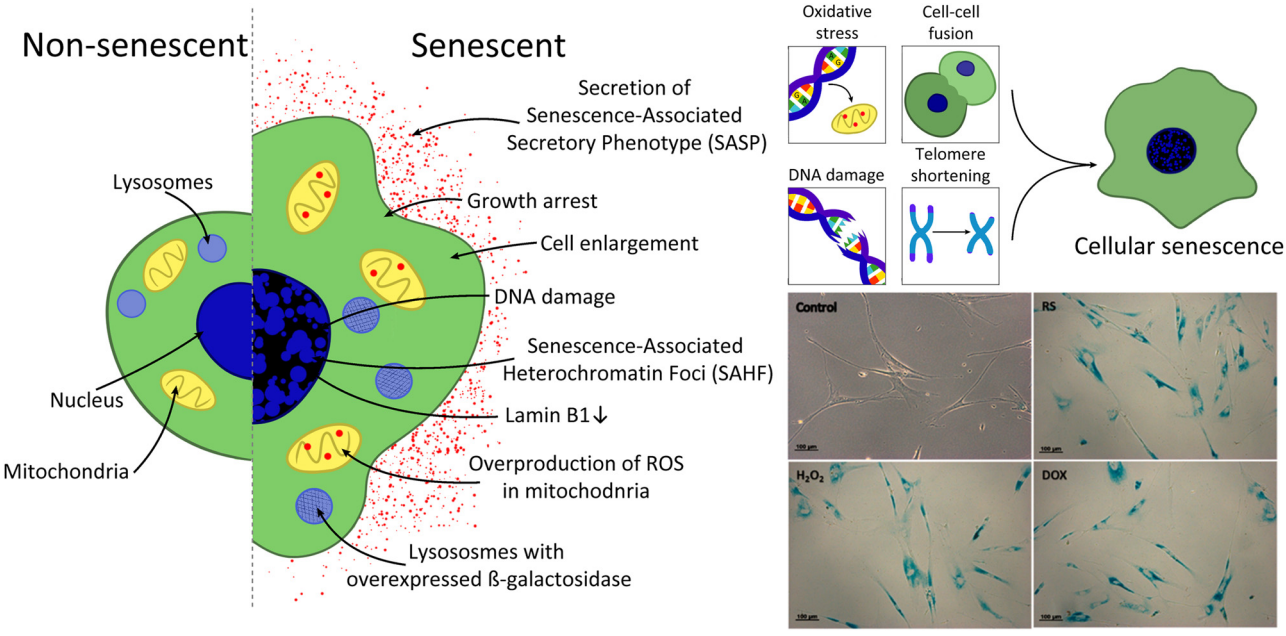

Figure 1: Schematic of the most basic changes between senescent and non-senescent cells, examples of cellular senescence occurring naturally or induced and example of the difference in β-gal expression by Foroozandeh *et al.* [26].

Table 1: SASP components with classification

SASP classification	SASP components [1,13,16,31,176]	Ref.
Chemokines	ENA-78/CXCL5, MCP-1/CCL2, MIP-1 α/CCL3, MIP-3 α/CCL20, CCL-28, GCP-2/CXCL6, I-TAC/CXCL11, MCP-4/CCL13, NAP2/CXCL7, GRO α/CXCL1, GRO β/CXCL2, GRO γ/CXCL3, MCP-2/CCL8, RANTES/CCL5, SDF-1/CXCL12	[35,40,71,86,177–187]
Cytokines and interleukins	MIF, GM-CSF, IL-6, IL-7, IL-8, IL-1 α, IL-1 β, IL-11, IL-13, IL-15, Leptin, I-309	[35,179–189]
Growth factors	HGF, VEGF/VEGFA, bFGF/FGF-2, AREG, KGF/FGF-7, PDGF-BB, SCF, PIGF, GDNF	[35,181–184,186–190]
Proteases	MMP1, MMP2, MMP3, MMP10, MMP13, MMP14, tPA, uPA	[40,180–182,187,191,192]
Receptors	uPAR, sTNF RI, sTNF RII, Axl, GITR/TNFRSF18, TRAIL-R3/TNFRSF10C, Osteoprotegerin, IL-2R α, IL-6R	[35,185–187,193]
Regulators	spg130, STING, SPINK1, TIMP-1, TIMP-2, IGFBP-1, IGFBP-2, IGFBP-3, IGFBP-4, IGFBP-5, IGFBP-6, IGFBP-7, PAI-1/SEPINE1, ICAM-1	[35,178,182–186,190,191,194]
Others	Angiogenin, COX2, ALOX5, SERPINB2/PAI-2, SERPINB4, PGE-2	[35,184,190,191,195–197]

proteases, and many soluble proteins, most of them pro-inflammatory. This heterogeneous mix is called senescent-associated secretory phenotype (SASP), whose compartments are listed in Table 1. SASP composition is not always the same depending on cell line and way of senescence induction, but a few SASP components are very characteristic for induced senescence-like IL-6 and IL-8 [14]. It is known that SASP is crucial in tumorigenesis because it can influence tumor development progression by enhancing the proliferation of cells and immunosuppression or regression, thanks to the proliferation arrest [15,16]. Regulation of secretion of those components is compromised by the dysfunctional activity of mitochondria [13]. In addition, SASP is involved in the pathogenesis of age-related diseases like chronic kidney disease (CKD) [17] or/and cancer [18].

Modulating immune cells with the help of senescent cells becomes a point of interest in biology. Immune checkpoint blockage (ICB) shows beneficial properties in several cancer types, but the majority of cancers show a very low response rate to ICB, like ovarian tumors [19]. Several studies showed the opportunity of using cellular senescence, especially SASP to amplify ICB and make cancer cells more visible to the immune system [19–21]. Marin *et al.* showed that senescent cells and SASP can act as activators for dendritic cells (DC) and CD8+ T cells with very high efficiency, where DC and CD8+ cells are a crucial part of the antitumor immune response [20].

2.1 Biomarkers

To identify and measure biological states, processes, and responses, it is possible to introduce certain biomarkers into the biological model to examine their state. Many known biomarkers can give quantitative and/or qualitative data [22]. Senescent cells have a variety of biomarkers, which can give morphological, genetic, or secretive data. To identify cellular senescence, it is essential to use a few methods, as the use of only one is not sufficient evidence.

One of the most basic known biomarkers for identifying cellular senescence is senescence-associated β-galactosidase (SA-β-gal), whose activity is a very characteristic feature that is common among all senescent cell types. β-Galactosidase is a glycoside hydrolase enzyme, which the senescent cells overexpress in lysosomes. At pH 6.0, β-galactosidase reacts with X-gal (5-bromo-4-chloro-3-indoyl-β-galactopyranoside) and, due to hydrolysis, yields a visible, usually blue product [23,24]. Depending on the SA-β-gal staining kit, the analysis can be performed with a simple optical microscope, an inverted optical microscope [25,26], or can be identified with flow cytometry or confocal microscopy [27,28].

Morphologically, simple fluorescence staining methods can identify many features characteristic of some of the senescent-type cells. The cytoskeleton or membrane staining can highlight the changes in the size of cells [8] while staining the nuclei can show SAHF, as mentioned earlier. However, it is important to remember that those features cannot be taken as biomarkers for certain, as they depend on the cell type and type of induction. Other morphological changes that can be observed are enlargement and an increase in the number of lysosomes, which can also be stained with fluorescence reagents [13]. The stability of the nucleus is dependent on the presence of nuclear laminas. Lamin B1 is one of the filament proteins located on the inner layer of the nucleus. The level of this lamin B1 is a hallmark of cellular senescence because its loss occurs upon activation of either p53 or pRB pathway, which are highly responsible for senescence induction. It was discovered that lamin B1 loss is independent of ROS-induced senescence [29,30].

DNA damage is the main cause of cellular senescence. DNA damage induces the expression of kinases, such as ataxia telangiectasia mutated (ATM), that are recruited to the site of damage and mediator proteins like the phosphorylated form of histone H2AX (γ-H2AX), which is a protein designed to repair damaged DNA [31,32]. As cell cycle arrest is a very characteristic feature of cellular senescence, the use of BrdU (5-bromo-2-deoxyuridine) or EdU (5-ethynyl-2-deoxyuridine) is highly valuable as this assay can be used in cell proliferation analysis. Those two assays use an analogue of thymidine to highlight cells where active DNA synthesis is still present [26,29,33,34].

The presence of SASP components, such as IL-6 or IGFBP7, acts as a marker of cellular senescence, and it can be detected with antibody arrays (*e.g.*, ELISA, western blot) [35–37] or liquid chromatography and mass spectroscopy [38]. Those elements can be analyzed with reversed transcriptome PCR (RT-PCR), which shows the expression level of the analyzed genes, or real-time PCR (RT-PCR), which shows the presence of genes. Both of these assays are common for cellular senescence studies in many articles. It is possible to detect SASP components like IL-1α, IL-1β, and IL-6, and proteins that are responsible for cell cycle arrest, p16, p21, and p53 [39–41]. The previously mentioned lamin B1 can also be analyzed with RT-PCR [40].

2.2 Cellular senescence induction

Cellular senescence can be divided into two main types: natural and induced. One of the naturally occurring types of senescence is replicative senescence, which is caused by natural cell division and telomere shortening. Telomeres are structures at the end of the linear chromosome created with tandem repeated nucleotide sequences $(TTAGGG)_n$, which protect the DNA from degradation or breaking and provide chromosome stability. Due to every cell division, telomeres are subjected to shortening as during DNA replication, telomeres undergo erosion. With continuous erosion with each DNA replication, telomeres are at a point where the cell can no longer pass through division. That is the moment when the cell enters replicative senescence [42–44]. Another natural type is senescence, which occurs during embryonic development and pregnancy to placental syncytiotrophoblasts due to cell–cell fusion during pregnancy and can be beneficial and dangerous in some situations [45]. It supports regulation of the placenta's growth during pregnancy, thanks to cytokines in SASP secreted by senescence cells [11], but diverse increases can lead to many pregnancy pathologies, including stillbirths [47]. Fusion-induced senescence is prompted by fusogenic, like the ERVWE1 protein, which mediates the formation of multinuclear syncytriophoblasts in the placenta. This formation is crucial in the maternal–fetal connection [45]. Other aspects are also wound healing and tissue remodeling, where the role of senescent cells is outstanding. Healing and remodeling are multistage processes involving cytokines, chemokines, and growth factors present in SASP. Experiments on Zebra fish have shown that senescent cells are present during the whole tissue regeneration process after amputating fin and disappear when the process is over, which was confirmed by various markers. Moreover, the regeneration process is hampered after treating them with senolytics, which indicates that cellular senescence is essential in limb regeneration for Zebra fish [48].

Environmental stress caused by a group of many possible stress stimuli is responsible for the activation of stress-induced premature senescence (SIPS), with therapy-induced senescence (TIS) as one of them, which is the subject of many studies [46,49]. Any type of stress causes damage to the cell nucleus and, hence, to the DNA contained in it. DNA damage response is responsible for stress-induced premature cellular aging. As previously mentioned, a few pathways are responsible for cellular senescence, but the most known are tumor suppressor pathways, $p53/p21^{CIP1}$ and $pRB/p16^{INK4a}$ [50,51]. One of many sources of stress that can lead to cellular senescence is ROS derived from O_2-like oxygen-based free radicals. Mitochondrial dysfunction and overproduction of ROS in the cells can be caused by stress sources such as ionizing radiation, chemotherapeutics, or general environmental toxins. This can disrupt homeostasis, lipid peroxidation, and promote DNA damage [52,53]. ROS-induced DNA damage occurs due to guanine, whose oxidation can cause modification and pairing with adenine instead of cytosine, causing DNA mutations [52,54]. Overall, ROS affects the structural integrity of DNA by the breakdown of nitrogen base-pairing and phosphodiester bonds [52]. ROS generation and ROS-induced DNA damage are responsible for cellular senescence, but constitutive production of high ROS levels is crucial for senescent phenotype maintenance, which creates a closed circle. Moreover, SASP promotes ROS generation and induces senescence [52,55].

Many agents can induce cellular senescence, including mustard gas, which causes DNA damage in the form of single- and double-strand breaks and, due to a cascade of reactions, leads to phosphorylation of p53 [56]. Various scientific groups closely investigated cellular senescence induction by mustard gas. Horn *et al.* studied the sensitivity of primary human dermal fibroblasts (HDFs) to sulfur mustard. Their study showed that senescence is triggered after a single administration of sulfur mustard, and

induction highly depends on time and concentration [57]. Soleimani *et al.* investigated the influence of nitrogen mustard on mice's cornea and discovered the connection between cellular senescence after exposure to mustard gas and fibrosis of the cornea. This gave a new insight into the possible therapy with senolytic agents [58].

We can highlight one specific type of stress-induced senescence, TIS, as cellular senescence can be induced by common cancer treatments like radiotherapy or chemotherapy [59].

2.2.1 Chemotherapeutics

Chemotherapeutics are known for their cytotoxic properties toward cancer cells in even very small concentrations. Apoptosis is caused mainly by the inhibition of enzyme topoisomerase II but also by ROS overproduction, which causes genomic damage *via* oxidative stress. It generates free radicals in cells, inducing and increasing DNA double-strand breaks [34,60]. Doxorubicin (DOX) is one of many chemotherapeutics commonly used in biomedicine; due to its extensive use, it is not surprising that it was the first reported chemotherapeutic to induce senescence [24,61]. Although DOX is a well-known chemotherapeutic, it also has an unexpected drawback. It causes a high risk of failure of different organs, not only targeted ones, which can occur even after many years after treatment. Piegari *et al.* confirmed this suspicion *in vitro* using cells isolated from oncologic patients after autopsy. According to their work, the cells they used, human cardiac progenitor cells, are highly sensitive to anthracycline drugs, like DOX, which results in increased apoptosis and decreased growth, and the concentration of DOX is responsible for the cell's viability. It is very interesting to note that DOX did not affect the expression of p21, which may suggest that DNA damage-induced activation of p53 was not followed by p21 [34].

Hu *et al.* studied the time delay effect of DOX on HeLa cell lines, which explains the importance of induction time, especially the time with fresh medium after incubation with DOX [62]. It is important to remark that not all drugs cause cellular senescence. A study by Bojko's team shows that chemotherapeutics have different senescence induction effects on cancer cells. While drugs like DOX, irinotecan, and methotrexate were the strongest inducers, oxaliplatin and 5-fluorouracil did not show any senescence induction effects. These experiments were performed on various cancer cells, and they showed that cells are more or less sensitive to TIS. In this research, SHSY-5Y did not show any signal of classic senescent markers, while MDA-MB-231 was very sensitive to senescence induction [8]. Another type of drug used in chemotherapy is etoposide, which was studied by Bang *et al.* on astrocytes extracted from Rat's brain cortex. This work showed many changes, including induced DNA stress and mitochondrial dysfunction that led to cellular senescence, and was tested by many biomarkers [39]. Interestingly, unknown properties of chemotherapy-induced senescent cells about engulfing neighbor non-treated cells were shown by Tonnessen-Murray *et al.* while performing time-lapse observation *in vitro* on cancer cells 4226 extracted from rats and on cell lines MCF-7 and MPE600 [63].

2.3 Cellular senescence in diseases

There are many known diseases that are connected with age. Here, we describe only a few of the most severe age-related diseases [64–66]. Kidneys undergo structural and functional change with age. Several cell types in kidneys experience cellular senescence and secrete many factors defined by CKD. This is a condition where kidneys are damaged and cannot filter blood as efficiently as they should, which can develop many health problems like cardiovascular pathologies or mineral bone disorders due to waste that should be filtered but remains in the body [67,68]. Chronic inflammation and oxidative stress in CKD lead to the accumulation of senescent cells, but it is hard to determine whether cellular senescence is an after-effect of CKD or, rather, the cause of CKD [69–71]. The presence of senescent cells in CKD tissues was proven by using various senescent markers [72]. Moreover, other research studies showed that renal function in aging mice was restored, thanks to senotherapy and removing senescent cells [73]. Cellular senescence occurs in many known ophthalmology diseases, which are strongly connected with aging. Cataract is the most common disease, which is responsible for causing blindness worldwide. The risk of cataract occurrence increases with age due to the decrease of the lens stem cells (LSC) level. Fu *et al.* showed that patients aged 50 and above demonstrated high levels of senescent LSC, which strongly inclined cataract development [74,75]. Another known ophthalmology disease is glaucoma, which is caused by retinol ganglion cell degeneration (RGC). Cellular senescence of RGC is the main cause of exhaustion of RGC, which is directly connected to glaucoma symptoms. Skowronska-Krawczyk *et al.* studied primary open-angle glaucoma, where gene SIX6 is a strong link to this disease, and its connection with the expression of $p16^{INK4a}$ causing cellular senescence was discovered [75,76]. Many studies

already prove that diseases like Alzheimer's disease and Parkinson's disease (PD) are strongly connected with cellular senescence [77]. Characteristics of PD motor symptoms are the result of progressive degradation of dopamine-producing neurons called dopaminergic neurons in the midbrain with age [78,79]. Patients with PD present high levels of senescent markers in astrocytes in brain tissue. The high number of senescent cells and aged astrocytes in the PD brain suggests senescent-induced neuroinflammation might be an important mechanism for PD neurodegeneration [80,81]. Alzheimer's disease is an age-related progressive degenerative neurological disease [82,83]. It is recognized by certain hallmarks such as accumulation of amyloid β (Aβ) and aggregation of protein tau [84,85]. Multiple studies have shown the presence of many senescence markers, which indicates the connection between senescent cells and the progression of Alzheimer's disease [86,87]. Neuroinflammation in this disease is caused by the overactivation of microglia and the overproduction of proinflammatory cytokines that are part of SASP. In addition, excessive expression of IL-6 causes neurodegeneration. A high level of pro-inflammatory cytokines reduces the ability of the cells to remove Aβ, causing its accumulation [81,88–90]. Senescence-accelerated mice P8 (SAMP8) is a great model for a closer study of Alzheimer's disease, which was described in more detail in the literature [91]. Experiments performed on SAMP8 in general focus on age-related diseases such as sarcopenia, characterized by loss of muscle mass and muscle function, which was studied by Huang *et al.* [92], or age-related changes in the small intestine, which was the subject of the work of Suzuki *et al.* [93].

As mentioned earlier, cellular senescence is a defense mechanism against cancer due to its growth arrest and SASP, which sends signals to neighboring cells to suppress tumor progression. Moreover, interleukins recruit macrophages and immune cells to eliminate cancer cells after entering the state of cellular senescence [94]. However, this is not a flawless mechanism, and what is supposed to protect us from cancer can also be harmful to us. SASP plays a very important role in tumor development by sending signals that directly or indirectly block immune surveillance [95,96]. The most recognized SASP components that can promote cancer cell proliferation are IL-6 and IL-8 [95,97]. Studies have shown that IL-6 recruits myeloid-derived suppressor cells, which results in an immunosuppressive microenvironment [98]. Several studies proved that senescent cancer cells can be highly connected with cancer relapse [40]. Reprogramming caused by SASP signaling might even lead to the development of stemness properties. It is even more important to mention that the generation of highly aggressive tumors is an essential feature of cancer stem cells [99,100].

Another interesting insight in connection of cellular senescence with age-related diseases is the ability to upregulate protein programmed death ligands (PD-L1). Studies showed that PD-L1-positive cells are resistant to the activity of lymphocytes T, which effectively makes our immune system decline as PD-L1 causes the inactivation of immune cells [101–104]. Two groups, Wang *et al.* and Onorati *et al.*, carried out very interesting studies in this aspect and indicated the possibility of creating a therapy to prevent age-related diseases [103,104].

Many diseases are connected with cellular senescence and are age-related. Senotherapies would be a great way to promote healthy aging by eliminating senescent cells in the target area, such as the brain. It is not known if senolytics are able to cross the blood–brain barrier besides fisetin and dasatinib+quercetin (D+Q), which were studied *in vivo* on that matter [105,106]. It is also important to remember that the correct dose of such drugs can help purge senescent cells, but, on the other hand, some senolytics show senescent-inducing properties, like Nutlin-3a [20,107,108].

3 Emerging therapies for cellular senescence: Targeting senescent cells for age-related diseases

There are three main approaches for targeting cellular senescence. The first is killing senescent cells (senolytics), the second is inhibiting the SASP (senomorphics or senostatics), and the last therapy is using the immune system against senescent cells (immunosurveillance) [109]. Senescent cells arise in almost all types of tissues and organs with increasing age [110]. To better understand how cellular senescence contributes to the emergence of disease, research into new indicators or causes is ongoing. Several genetic mouse models allowed for simultaneous tracking and functional studies on senescent cells [111–113]. The overwhelming amount of evidence points to the possibility that the number of senescent cells in mice might affect longevity and that the trajectory of that lifespan is sensitive to treatments that remove senescent cells from the body [114].

Navitoclax is an anti-cancer drug that inhibits the BCL-2 family protein and, together with galacto-conjugation (Nav-Gal) results in a promising senolytic strategy. Muñoz-Espín *et al.* showed that Nav-Gal is activated by increased SA-β-gal activity and can induce programmed cell death. A combination of Nav-Gal and cisplatin (a drug used in senescence-

inducing chemotherapy) results in the elimination of senescent lung cancer cells and inhibition of tumor growth, simultaneously reducing thrombocytopenia, which is one of the limitations of Navitoclax treatment [115]. Another example of a new generation of senolytics is galactose-modified duocarmycin (GMD). Duocarmycin can bind to the minor groove of DNA and alkylate adenine, resulting in cell death [116]. GMD can induce apoptosis in senescent cells in a lysosomal β-galactosidase (GLB1)-dependent manner. Moreover, in the mouse model, this prodrug could reduce β-catenin-positive preneoplastic senescent cells and is considered a new anticancer drug [117]. Cai *et al.* used a similar strategy to develop a specific prodrug. Galactose-modified gemcitabine (SSK1) is commonly used in chemotherapy [118]. SSK1 specifically is cleaved by lysosomal β-gal into gemcitabine and activates p38 to induce apoptosis in senescent cells. In aged mice, SSK1 reduced the number of senescent cells and inhibited senescence-associated signatures in the kidneys and liver. Moreover, this compound decreased senescence-associated gene expression, attenuated low-grade chronic inflammation, and improved physical function compared to the control mice. Recently, the elimination of senescent cells has become a new approach to treating different diseases. It was shown that atherosclerosis is an age-associate disease. Liu *et al.* developed an aptamer-mediated senolytic that can target cells with high lysosomal β-gal activity and induce apoptosis in senescent endothelial cells [119]. Some of the specific-targeting senescent cell senolytic are used in anticancer treatment. For example, Jia *et al.* tested the neddylation (posttranslational modification protein) inhibitor MLN4924 (MLN), which can induce cellular senescence by suppressing p21 degradation in cancer cell lines [120]. The combination of MLN and Navitoclax successfully eliminated MLN-induced senescent A549 cells [121].

With the increasing knowledge about cellular senescence and its impact on the pathogenesis of many different diseases, the local elimination of senescent cells is becoming insufficient [122]. Khosla's team reported a transgenic mouse model p16-LOX-ATTAC to clear senescent osteocytes specifically. Osteocyte senescence is a major factor in age-related bone loss. Local elimination of senescent osteocytes inhibits bone loss in the spine and improves bone formation without impacting osteoclasts or marrow adipocytes. In comparison, systematic senolysis in the p16-LOX-ATTAC mouse model prevents bone loss in the spine and the femur and reduces osteoclasts and marrow adipocytes. Furthermore, results showed that SASP in the peritoneal cavity can induce cellular senescence in distant host osteocytes. Khosla's team highlighted that the therapy may require a more systemic approach [123,124]. It is necessary to distinguish senescent cells from normal cells for better treatment and faster disease detection and/or prevention. However, there is a great need for sensitive assay for the detection of cells causing age-related diseases. Sancenón *et al.* developed a naphthalimide-based two-photon probe (AHGa) in mice tumor xenografts treated with senescence-inducing chemotherapy, palbociclib. In senescent cells, AHGa is a naphthalimide fluorophore, which is transformed into AH, resulting in a 5-fold enhanced fluorescence emission intensity [125]. Chronic renal failure (CRF) is a progressive decline in the renal structure and functions of kidneys. Moreover, oxidative stress and premature cellular senescence are found in patient's kidneys suffering from CRF. Abnormal accumulation of senescent cells damages surrounding cells through high levels of SASP secretion and can lead to organ failure [126]. Li *et al.* reported a new theragnostic–senolytic prodrug (TSPD) to induce senolysis in renal unilateral ischemia-reperfusion injury murine model with a high risk of progression to CRF. This TSPD compound is made of coumarin skeleton as a fluorescence carrier, b-galactosidic bond for selectivity, and gemcitabine as a cytotoxic drug. Theragnostic approach allowed TSPD to detect and induce apoptosis in senescent cells specifically. Furthermore, *in vivo* studies showed that TSPD treatment can improve renal function in the mice model of CRF [127].

Based on extensive preclinical studies revealing the advantages of senotherapy, multiple clinical trials in aging and age-related diseases [128], as well as cancer treatment [129], are developed. Current senotherapeutic strategies include conventional senotherapeutics, prodrugs, protein degraders, immunotherapies, and the use of NCs for the delivery of senolytics. NCs offer a means to transport otherwise insoluble drugs and to specifically target senescent cell populations through the modification of their surface with peptides, antibodies, or other biomolecules that recognize motifs on the membrane of senescent cells. Recent advances in nanoscience have impacted many areas of therapy and can potentially improve present senotherapy approaches. Several NP- and NC-based strategies have been developed in the past few years, aiming to detect senescence *in vivo* or induce the death of senescent cells as a therapeutic approach. However, NPs can induce senescence in certain conditions, which may be undesirable in some therapies employing NPs, *i.e.*, for NPs applied in cancer therapy. While there is a large body of work on NPs for cancer treatment and on the interaction of NPs with cancer cells, and despite the potential of NPs in senotherapy their interaction with senescent cells is practically not considered in the literature on cellular senescence.

3.1 NP-assisted senescence

3.1.1 Induction of senescence by NPs

NPs are small particles with sizes below 100 nm, are widely used in many scientific and technological fields, and can potentially be used in drug delivery, tissue engineering, and sensing [130]. The term NCs refers to NPs when used for drug delivery. In recent years, interest has increased in developing a wide range of medical therapies based on NCs. Delivery systems based on NCs have a significant advantage compared to free drug administration, such as (a) the possibility to deliver otherwise insoluble drugs, (b) selective targeting of the disease cells and tissues, (c) release of the entrapped therapeutics in the desired area, and (d) significant decrease of the necessary drugs' dose.

Only limited intravenously administered NCs could reach clinical trials on humans, and even fewer were approved by the Food and Drug Administration (FDA) or European Medicines Agency (EMA). Among other types of administration, such as oral, local, and topical, there are more examples of already approved nanosystems [131–133]. Among the FDA- and EMA-approved NCs are Doxil®, Merqibo®, Myocet®, or Abreaxane [131–133].

Apart from NPs and NCs, scientists worldwide are also trying to develop nanomaterials for medical therapies. For example, in ophthalmology, such nanomaterials could help with corneal therapies connected to ocular injuries and diseases. Corneal scaffold material could be used instead of donor tissue, but such materials must meet many mechanical and optical criteria to be considered for further use [134,135]. Such information was described in detail by Soleimani *et al.* [136]. Other nanomaterials, such as hydrogel nanocomposites, are widely studied as wound dressings. Li *et al.* studied the antibacterial properties of chitosan, which has great properties that wound dressing requires, such as biocompatibility, biodegradability, water absorption, and more, combined with Au–Ag NPs and discovered that this combination greatly promotes the wound-healing process *in vivo* [137,185] Liang *et al.* [138] greatly elaborated many other discoveries of hydrogel nanocomposites.

Induction of cellular senescence by NPs is a rather new concern for researchers working with NPs. The majority of the groups focus on *in vitro* cytotoxicity of their newly developed systems. However, before NPs become toxic, they may cause stress-induced premature cellular senescence. The accumulation of senescent cells can cause age-related diseases. There is a need to consider the effect of the accumulation of NPs in the environment and their possible negative effect on the human body after prolonged exposure to them. Notably, some groups investigated NPs' possible induction of cellular senescence with confirmed non-toxic concentrations during unintended exposure. It was reported that prolonged exposure to specific NPs could cause senescence of lung cells [139,140]. Senescent lung cells are known to have an effect on the progressions of age-related diseases, such as idiopathic pulmonary fibrosis (IPF) or chronic obstructive pulmonary disease.

Spannbrucker and colleagues reported that repetitive exposure to the non-toxic concentration of carbon NP pollution had an impact on the induction of a senescent-like phenotype on the lung epithelial cells [140]. The group highlighted the difficulties in reproducing human real-life cumulative exposure to NPs. Thus, they proposed the simplified *in vitro* model, where they observed the properties of lung epithelial cells after cumulative exposure to NPs over 14 days. The cellular senescence was confirmed after recognition of several parameters: (a) accumulation of cell clocking proteins p21 and p16; (b) decrease of the redox-sensitive histone deacetylase SIRT1 and Connexin-43 at the plasma membrane; and (c) inability to proliferate [140].

Chen and colleagues have investigated the induction of lung cellular senescence due to prolonged exposure to silver NPs (AgNPs) *via* inhalation [139]. A complete growth arrest was observed after 6 days of exposure of human MRC5 fibroblasts to AgNPs. Other cellular senescence characteristics and markers were observed, such as enlarged cell size, strong SA-β-gal activity, and the presence of SAHF. The cellular senescence was induced *via* the upregulation of the cyclooxygenase-2/prostaglandin E2 (COX2/PEG2) intracrine pathway. Moreover, AgNPs caused upregulation of COX2 and an increase of lung cellular senescence in mice and, consequently, mild fibrosis in the lung tissue [139].

Mytych *et al.* analyzed the effect of silica, silver, and diamond NPs on the induction of cellular senescence [141]. NP treatment increased ROS production and glutathione (GSH) reduction. Induction of oxidative stress caused SIPS. All cell lines exposed to NPs showed a decrease in the level of lamin B1 pools, accompanied by the upregulation of the telomeric repeat binding factors 1 and 2 (TRF1 and TRF2) protein level, which is part of the telomere-focused protective response. In cancer cells, the TFR-based response was independent of the p53 pathway, while in the fibroblast, the p53/p21 signaling was active.

Tian and co-workers investigated the senescence induction pathways using the hydroxyl-modified graphene quantum dots (OH-GQDs) on two lung carcinoma cell lines with or without the presence of p53 (A549, wild-type p53 and H1299, p53-null) [142]. They demonstrated that in both cell lines, the production of ROS was enhanced by OH-GQDs. The

group found that the induction of ROS production led to the activation of the p21 signal pathway in both p53-dependent and -independent manner. However, p21 is one of the p53-activated factors. In p53-null cells, the p21 signal pathway activation was initiated by different factors. The detailed mechanism of p21 activation in p53-null cells needs further investigation, which was highlighted in the work.

Other works also showed that the enhanced production of oxidative stress, induced by NPs, is related to disruption of the levels of p53 and p21 and can lead to premature senescence. Ye and colleagues showed that silica NPs incubated with myocardial H9c2 (2-1) cells led to upregulation of the expression of p53 and p21 and, in fact, to cell cycle arrest at the G1 phase [143]. Roy and colleagues reported that zinc oxide NPs (ZnO NPs) induced macrophage cell death, mostly by increased ROS production. They also observed p53, p21/waf1 signaling [144]. Deylam and co-workers confirmed that the cellular senescence induction by ZnO NPs is dependent on the NP sizes (10–30 and 35–45 nm). Both sizes of NPs led to senescence of the mesenchymal stem cells (MSCs). However, smaller NPs caused the production of larger amounts of senescence cells. Cellular senescence was confirmed with increased lysosomal β-galactosidase activity level and upregulation of NF-kB and p53 (Table 2) [145].

3.2 Targeting and therapy of senescent cells by NPs

Many cancer treatments can effectively kill cancer cells, but sometimes, cells undergo permanent cell growth arrest instead of apoptosis or necrosis. Some groups introduced cellular senescence as a successful cancer treatment [146–149]. In fact, cellular senescence plays both beneficial and detrimental roles in cancer and age-related diseases [150,151]. The SASP, present in senescent cells, participates in the clearance of the senescent cells, tissue regeneration, and repair. However, the SASP can also promote the formation of secondary tumors and cancer relapse by stimulating phenotypes associated with aggressive cancer cells. The accumulation of senescent cells can increase the risk of cancer and age-related diseases. Some groups considered the use of senotherapy in combination with the current cancer treatment to minimize the risk of cancer relapse [40]. There are two strategies to minimize the negative effects of senescence:senolytic induction and SASP neutralization [152,153]. Senolysis initiates the direct elimination of the senescent cells. The drawback of the potential combined cancer and senolysis therapy lies in the current lack of approved senolytic drugs and their high toxicity *in vivo*.

Thus, to bypass the side effects of the double therapy, NPs can be used as NCs to encapsulate senolytic drugs [151,154–156]. Reducing the necessary dose by encapsulating the therapeutics in NPs may greatly decrease the toxicity of the senolytic drugs. Using NCs to deliver drugs may also improve their targeting abilities. Moreover, properly designed NCs can release their drug cargo in the targeted senescent cells.

Agostini and co-workers investigated NC-based systems to deliver cargo and luorophores to the senescent cells (Figure 2) [156]. The group used galacto-oligosaccharide (GOS) capped mesoporous silica NPs (MSNs). SA-β-gal present in senescent cells released the cargo in the senescent cells (aged human fibroblast, DC1787; cells from human Dyskeratosis Congenital patients, X-DC1774 and X-DC4646). β-Galactosidase present in senescent cells digest the sugar coating on the NPs, and cargo can be released from the NCs to the senescent cells (Figure 2). In another work, Muñoz-Espín and colleagues took advantage of the previous findings to encapsulate the therapeutic agent into β(1,4)-galacto-oligosaccharide-coated MSNs (GalNP) and to ensure the release of the cargo within the senescent cells (Figure 2) [155]. This group observed the effect of the senolytic drug navitoclax on human cancer cell lines, which undergo senescence after treatment with palbociclib (human melanoma cells, SK-MEL-103, and human squamous carcinoma cells, NCI-H226). Navitoclax is a drug that strongly and specifically inhibits Bcl-2, Bcl-w, and Bcl-xL, anti-apoptotic proteins, to induce senolysis [151]. The group confirmed their previous results in the *in vivo* experiments. Due to the design of the coated NPs, navitoclax was only released in senescent cells and not in healthy cells. Moreover, the treatment was only effective on tumors formed from senescent cells and not from growing tumors. These results indicate that the selolytic treatment should not be applied together with anticancer treatment but only after cancer cells undergo senescence. In another work, they demonstrated the positive double treatment of another cancer type with an anticancer drug, followed by the administration of the senolytic drug encapsulated in NPs [151]. Galiana *et al.* discovered that mice with aggressive triple-negative breast cancer treated with palbociclib and then navitoclax-encapsulated in β(1,4)-galacto-oligosaccharide-coated MSNs led to inhibition of tumor growth, reduction of the size of metastases, and reduction in the toxicity of navitoclax. A fascinating study was performed by Chibaya *et al.*, where they used NPs to boost the immune system against pancreatic tumors to enhance interactions between immune and tumor cells. Their method included senescence induction using trametinib and palbiciclib combined. They targeted the tumor microenvironment (TME) with NPs loaded with agonists of stimulator of interferon genes (STING) and toll-like receptor 4 (TLR4). Their research shows that the combination of senescence induction and

Table 2: Nanoparticles used in senescence induction or senotherapy and the mechanism of induction or targeting and senolytic release

NP type	Induction/ senolysis	Experimental system	Mechanism	Ref.
AgNP	Induction	*In vitro*: MRC5 *In vivo*: C57BL/6 mice	Senescence induction *via* the COX2/PGE2 pathway	Chen *et al.* 2020 [139]
Carbon NP	Induction	*In vitro*: RLE-6TN	Induction of intracellular oxidative stress	Spannbrucker *et al.* 2019 [140]
Silica NP Silver NP Diamond NP	Induction	*In vitro*: HDFa; HeLa; ACHN; A549; MCF7	Induction of oxidative stress and promotion of DNA DSBs and SSBs	Mytych *et al.* 2015 [141]
OH-GQDs	Induction	*In vitro*: A549; H1299	Overproduction of ROS and activation of p21 expression	Tian *et al.* 2016 [142]
Silica NP	Induction	*In vitro*: H9c2(2-1)	Induction of oxidative stress and upregulation of p21 and p53	Ye *et al.* 2010 [143]
ZnO NPs	Induction	*In vitro*: AMSCs' BMSCs	—	Deylam *et al.* 2021 [145]
SNs-4N1Ks	Senolysis	*In vitro*: MCF7	Peptide is exposed at the surface of the nanoparticle as it is attached by incorporation to the lipidic structure of the nanosystem	Jatal *et al.* 2022 [158]
GalNP	Senolysis	*In vitro*: SK-MEL-103; NCI-H226; Huh7, SAOS-2, UT-SCC-42B *In vivo*: C57BL/6 mice; athymic nude mice	Navitoclax was released due to contact with SA β-gal, which dissolved the coating of NP	Muñoz-Espín *et al.* 2018 [155]
GalNP	Senolysis	*In vitro*: 4 T1; *In vivo*: Balb/cByJ mice	As in the work of Muñoz-Espín *et al.*, NPs were encapsulated with Navitoclax, which was released due to contact of NP coating with SA β-gal	Galiana *et al.* 2020 [151]
ZnO NP	Senolysis	*In vitro*: A549; HuH-7	ZnO NPs display toxic properties to senescent tumor cells —	Wiesmann *et al.* 2021 [150]
NanoMIP	Senolysis	*In vitro*: EJp16 *In vivo*: C57/BL6J mice	Selective binding to senescent cells, thanks to targeting B2MG present of cells' surface Dasatinib as cargo	Ekpenyong-Akiba *et al.* 2019 [154]
MNPQ	Senolysis	*In vitro*: BJ	Quercetin was used to functionalize the surface of NPs	Lewinska *et al.* 2020 [162]
Chiral gold NP	Senolysis	*In vitro*: MA-C; MN9D; BV-2 *In vivo*: PD mice	NPs accumulated mostly in senescent cells due to surface modification with anti-B2MG and anti-DCR2 antibodies. Mechanism of clearance of senescent cells by activation Fas signaling pathway after using 808 nm NIR	Xu *et al.* 2022 [163]
Chiral Cu_xCo_yS NPs	Senolysis	*In vitro*: IMR-90	Using AFM and NIR photon illumination to kill senescent cells, NPs were modified with B2MG to target senescent cells	Li *et al.* 2020 [164]
UAuTe	Senolysis	*In vitro*: IMR-90 *In vivo*: SAMP8 mice; C57BL/6J mice	anti-B2MG conjugated to Au NPs was used to recognize senescent cells, NIR light inducing the disassembly of the NPs and release of apoptosis enzyme Granzyme B	Qu *et al.* 2020 [198]
CSNR	Senolysis	*In vitro*: IMR-90 *In vivo*: C57BL/6 mice	Surface of NPs was modified with anti-B2MG and TPP to target selectively senescent cells' mitochondria. With NIR's irradiation, mitochondrial damage was caused leading to apoptosis	Lu *et al.* 2020 [165]
BBR-LCNs	Senolysis	*In vitro*: 16HBE; RAW264.7	—	Paudel *et al.* 2022 [166]
PARP1@PLS-PT100	Senolysis	*In vitro*: HFF-1; *In vivo*: SD rats	NPs were modified with PT100, a highly selective inhibitor of the DPP4 receptor, whose expression was shown to be on the surface of SFs	Zhao *et al.* 2022 [167]

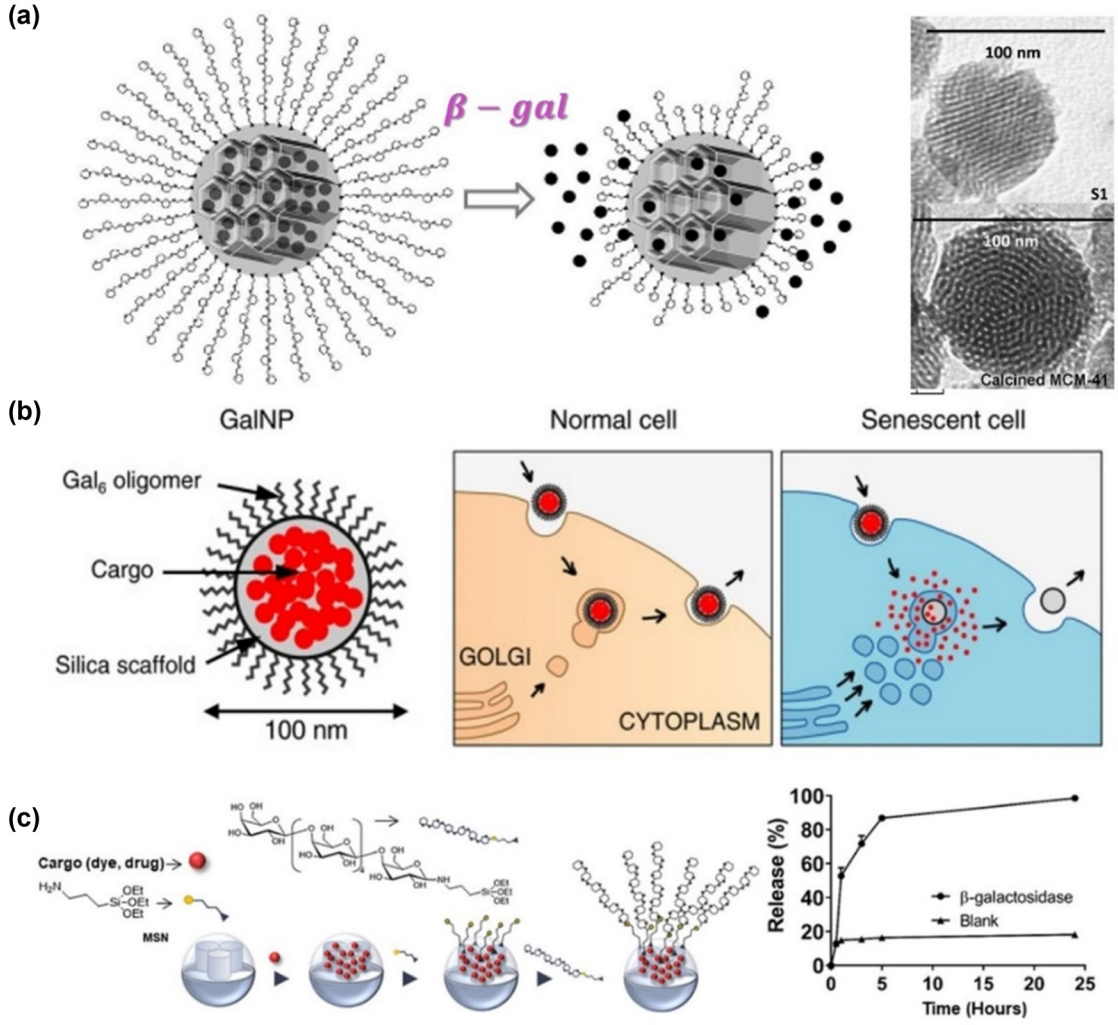

Figure 2: (a) Graphic of material coated with galacto-oligosaccharide (GOS) and schematic of delivery mechanism with beta-gal. Right: Representative TEM images of nanocarriers [156]. (b) Schematic illustration of the release mechanism of drug cargo from MSNs coated with 6-mer β(1,4)-galactooligosaccharides [155]. (c) Schematic of synthesis coated mesoporous silica loaded with dye or drug. Nanoparticles are functionalized on their outer surface so that GOS can be covalently bounded [151].

tumor-targeting therapy significantly enhances the production of IFNβ and promotes activation of NK and T cells in the tumor area due to SASP regulation with STING and TLR4 agonists [157].

Jatal *et al.* successfully prepared a biodegradable and biocompatible vitamin E-sphingomyelin nanosystem (SN) associated with 4N1Ks peptide derived from thrombospondin 1 (TSP1) protein for targeting and eliminating senescent cells in breast cancer [158]. The 4N1Ks peptide combines both properties by targeting the CD47 receptor expressed on the surface of senescent cells and exhibiting senolytic activity. To overcome the problem of short half-life and aggregation tendency of peptide drugs, 4N1Ks peptide was chemically conjugated to a PEGylated hydrophobic chain and attached to the SN. The resulting SNs-4N1Ks (SNs-Ks) demonstrated an improved cytotoxic effect on MCF7 cancer cells, decreasing cancer cells' capacity to form colonies, as compared to free peptides, and higher hemocompatibility. In addition, senescence escape experiments indicated the enhancement of senolytic activity of SNs-Ks in the chemotherapy-induced senescence model of breast cancer cells.

TIS in tumor cells was previously reported to lack permanent cell fate. In fact, senescent tumor cells have the ability to re-enter the cell cycle under some conditions [159–161]. Often, tumors regrown from senescent tumor cells have enhanced resistance toward already used therapy or are more aggressive compared to the original tumor. Wiesmann and co-workers demonstrated that cancer cell lines (non-small cell lung cancer, H549; and hepatocellular carcinoma, HuH-7) treated with the gamma irradiation with 16

Gy resulted in cell death and cell cycle arrest of the remaining tumor cells [150]. Repeating the 16 Gy irradiation on the remaining senescent cells did not lead to further cell death. Moreover, the group demonstrated that senescent cells re-enter the cell cycle within 2 to 4 weeks after irradiation. In addition, post-irradiation treatment of senescent tumor cells with ZnO NPs led to a drastic decrease in the senescent cell population. This showed the significant toxic effect of ZnO NPs on senescent cells.

Ekpenyong-Akiba and colleagues used a different approach to target senescent cells. They designed molecularly imprinted NPs (nanoMIPs), polymeric NPs with one binding site to target the extracellular epitome of one of the senescence markers (β_2 microglobulin, B2M) [154]. The group demonstrated the efficient targeting of the senescent cells *in vitro* and *in vivo*. NanoMIPs loaded with the senolytic drug, dasatinib, has successfully killed senescent cells, while the impact on other cells was minimal. Lewinska and colleagues utilized a natural senolytic compound, quercetin, to functionalize the surface of Fe_3O_4 NPs (MNPQ) against oxidative-stress-induced senescent human fibroblast cells [162]. The group reported eliminating the senescent cells *in vitro* and decreasing the senescence-associated proinflammatory responses. Xu and coworkers investigated the effect of chiral gold NPs illuminated with NIR irradiation at 808 nm on the clearance of senescent microglia cells to minimize the symptoms of PD [163]. The group demonstrated that NPs highly accumulated in the senescent microglia cells in the brains of the mice. Moreover, irradiation led to apoptosis and clearance of the senescent cells. In fact, the mice treated with L-P^+ NPs exhibit a remarkable recovery of some functions previously disturbed by the PD, such as motor abilities, spatial cognition, and memory. Another group also used chiral NPs, chiral Cu_xCo_yS NPs under an alternating magnetic field (AMF), and NIR photon illumination to kill senescent lung fibroblast cells [164]. Both AMF and NIR illumination of senescent cells treated with chiral NPs were effective in killing senescent cells. However, D-CuxCoyS NPs were more efficient than L-NPs. Moreover, a combination of both AMF and photon illumination shortened the treatment time. In addition, the group confirmed positive effects *in vivo* and a lack of toxic effects on normal cells. The application of NIR light in combination with upconversion-NP (UCNP)-centered Au_{20}–Au_{30} NP tetrahedron (UAuTe) was demonstrated to accelerate the clearance of senescent cells [163] selectively. The beta-2-microglobulin antibody (anti-B2MG) conjugated with Au NPs was used to recognize senescent cells, while the NIR light induced the disassembly of the UAuTe. The release of the Granzyme B exposed to UCNPs caused apoptosis in senescent cells. The *in vivo* experiments resulted in the restoration of renal function, tissue homeostasis, fur density, and athletic ability in a senescence mouse model after 30 days of treatment with the NIR-responsive tetrahedron. The anti-B2MG antibody was also used to modify triphenylphosphonium (TPP) conjugated plasmonic core–shell spiky nanorods (CSNRs) [165]. aB2MG-TPP@CSNRs irradiated with NIR light selectively induced mitochondrial damage and apoptosis of senescent cells. In addition, the authors demonstrated the capability of CSNRs to modulate the immune response *in vitro* and *in vivo*. The photo-induced formation of ROS contributed to senescent-cell apoptosis and the clearance of senescent cells in mice related to the adjuvant immune effect.

Chronic exposure to cigarette smoke can cause premature senescence of airway epithelial cells. In the work of Paudel *et al.*, the protective effects of using berberine-loaded liquid crystalline NPs (BBR-LCNs) against cigarette-smoke-induced oxidative stress, inflammation, and senescence were investigated [166]. BBR-LCNs showed potent antioxidant activity by lowering the level of ROS and expression of ROS-associated genes (Gpx2, Nqo1) in both bronchoepithelial cells (16HBE) and macrophages (RAW264.7). The anti-inflammatory effect of BBR-LCNs was caused by the downregulation of IL-1β, IL-6, and TNF-α gene expression. The antisenescence activity of BBR-LCNs was demonstrated by X-gal staining, the gene expression of CDKN1A (p21), and immunofluorescent staining of p21.

Diabetic wounds are highly associated with an increase in cellular senescence. Zhao and co-workers explored targeted therapy based on poly-L-lysine/sodium alginate (PLS) modified with talabostat (PT100) and encapsulating a PARP1 plasmid (PARP1@PLS-PT100) to eliminate senescent fibroblasts (SFs) [167]. PT100 selectively inhibits the dipeptidyl peptidase 4 (DPP4) receptor, which was shown to be commonly expressed on SFs. Treatment with PARP1@PLS-PT100 nanospheres revealed high selectivity for SFs over normal fibroblasts, increased apoptosis of SFs, and the disappearance of cellular senescence, resulting in wound healing with increased M2 macrophages.

Another recent approach that we have proposed suggests that senescent cells, due to their growth arrests and virtual immortality, could play an important role in studying NCs inside the cells [168]. Our previous study used fluorescent Si NPs to track the uptake and retention of proliferation and senescent cells (WI-38 fibroblast). The probes accumulate on senescent cells that reside in the cytoplasm for an extended period (weeks) (Figure 3). Conversely, the probes on proliferating cells get “diluted” during cellular division, and the overall fluorescence of the cells decreases. The study poses significant possibilities as, on the one hand, it allows for an efficient NP-based long-term tracking method for senescent populations. On the other hand, it provides a unique model for studying NP fate in cellular models. Furthermore, we

identified the retention kinetics of NPs, which not only allows suggesting a pathway to address their off-targeting in proliferative cells but also suggests a way of restricting drug toxicity to senescent cells.

4 Perspectives and conclusions

The single most significant risk factor for disease development is aging. The reality that people are now living much longer than ever before represents a significant healthcare challenge. According to estimates, 92% of persons over the age of 65 have one or more chronic conditions and require specialized medical care [169]. For nations across the globe, the increasing proportion of elderly persons in the populace dramatically impacts economic expenditures and social burdens. In the long run, further innovations and technologies are forecasted to treat aging effectively. Several biotech companies, realizing the demand, are involved in the development of such anti-aging therapies [170]. The past few years have been an exciting time for researchers working on cellular senescence, which has yielded an incredible wealth of knowledge on how targeting a unifying aging mechanism is achievable. In order to extend life, modern medicine, which formerly concentrated on treating just one disease at a time, is increasingly focusing on treating the root cause of numerous diseases at once.

Delivering therapeutic medicines based on SA-β-Gal+ shows vast potential. More drug targets may emerge specific to molecular mechanisms driving aging pathologies. Heterogeneity within senescent cell populations was discovered by utilizing techniques to determine gene expression profiles at a single-cell level [171]. As we learn more about senescent cell functions being beneficial or detrimental to health, new approaches will be thought to exploit the differences based on cell surface markers. NP-based systems could be used to target certain organs affected by conditions like Alzheimer's, heart disease, and liver fibrosis.

The development of NPs has a much better outlook for translating it to the clinic for aging. Reversing aging pathologies may only require a percentage reduction in senescent cells to achieve therapeutic success, in contrast to cancer, where it is essential to eradicate all tumor cells. In general, side effects from anti-aging drugs should be easier to deal with than those from cancer drugs. Senolytic and senomorphic medications may rely on

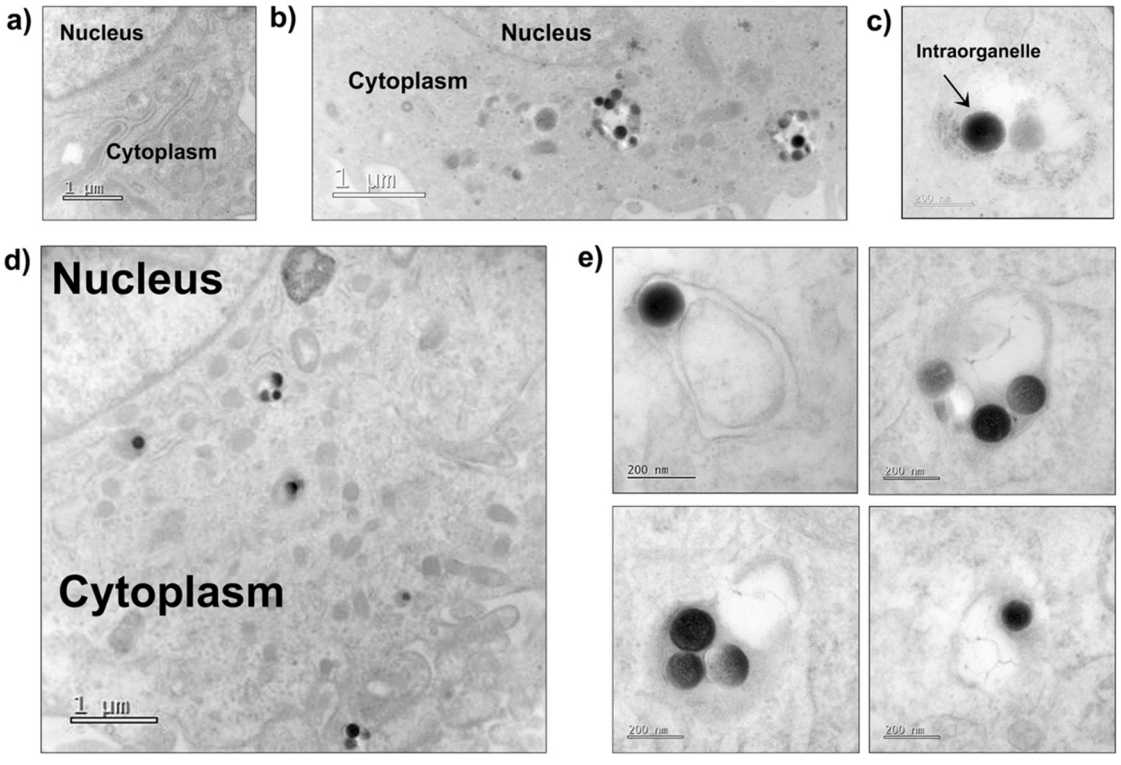

Figure 3: Biological fate of SiNP inside the senescent cells. (a) Senescent cells without SiNP. (b) and (d) SiNP in the cytoplasm of senescent cells. (c) SiNPs show inside the organelle after 24 h and (e) after 12 days [168].

repurposing clinically approved drug delivery technologies to address bioavailability or drug solubility concerns. For various applications, encapsulation techniques for the well-known senolytic drug fisetin have already been described [172]. In recent years, emerging natural compounds from fruits and vegetables have been discovered to be effective senolytic agents [173]. These can be used in conjunction with NPs in food products to take advantage of changing metabolism for obesity and diabetic conditions. Supplementation could come in the form of liposomal supplements that are more absorbable by the body [174,175]. Preventive interventions are the best course of action, and they may be as simple as providing people with nanoformulations that promote healthy aging.

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