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REVIEW

Advanced drug delivery platforms targeting cellular senescence: A promising strategy for cancer therapy

Xue Zhang[a,†], Lingxiao Yang[a,†], Xiaopeng He[a,†], Min Zhao[a], Zaixiang Fang[a], Gang Xu[a,b,*], Zhenyu Duan[a,b,*], Kui Luo[a,b,*]

[a]*Department of Radiology, Huaxi MR Research Center (HMRRC), Institution of Radiology and Medical Imaging, Liver Transplant Center, Organ Transplant Center, Department of General Surgery, Frontiers Science Center for Disease-Related Molecular Network, State Key Laboratory of Biotherapy, West China Hospital, Sichuan University, Chengdu 610041, China*
[b]*Psychoradiology Key Laboratory of Sichuan Province, Key Laboratory of Transplant Engineering and Immunology, NHC, and Research Unit of Psychoradiology, Chinese Academy of Medical Sciences, Chengdu 610041, China*

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Abstract Cellular senescence is a state of cell cycle arrest caused by various types of stress, and it is characterized by morphological changes, metabolic reprogramming, and the release of the senescence-associated secretory phenotype (SASP). In cancer therapy, senescence plays a complex role by inhibiting cancer progression, mediating metabolic imbalance, modulating local immune responses, and restructuring the cancer microenvironment. These mechanisms have been harnessed to develop nano-drug delivery systems (Nano-DDSs)-based combination therapies for cancer. We systematically explain key biological features of cellular senescence and detail recent advances in creating drug delivery systems aimed at targeting cancer senescence through these four mechanisms. Additionally, we discuss the clinical challenges in translating senescence-targeting strategies with Nano-DDSs and propose future directions within an interdisciplinary framework. This review offers valuable insights into designing advanced Nano-DDSs based on the multidimensional regulatory mechanisms of cellular senescence and their application in cancer treatment.

*Corresponding authors.
E-mail addresses: gangxu@wchscu.cn (Gang Xu), duanzhenyu@wchscu.cn (Zhenyu Duan), luokui@scu.edu.cn (Kui Luo).
[†]These authors made equal contributions to this work.

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1. Introduction

In recent years, cellular senescence (SN), a stable state of cell cycle arrest, has gained attention in the context of cancer initiation, progression, and therapy. SN can be induced by various factors, including telomere shortening, deoxyribonucleic acid (DNA) damage, oxidative stress, oncogene activation, and radiotherapy/chemotherapy[1,2]. The core mechanism of SN induction is typically involved in signaling pathways related to the tumor protein p53 (p53), cyclin-dependent kinase inhibitor 1A (p21)-retinoblastoma protein (Rb), and cyclin-dependent kinase inhibitor 2A ($p16^{INK4a}$)-Rb, leading to the inhibition of cyclin-dependent kinase (CDK) activity. After the inhibition, cells are arrested in the gap 1 (G1) or gap 2 (G2)/mitosis (M) phase, while maintaining active metabolism and secretion[3-5]. Notably, these key senescence regulatory pathways are highly conserved throughout evolution. In both mammals, such as humans, and non-mammalian organisms such as *Drosophila*, the p53 homolog participates in DNA damage-induced cell cycle arrest, suggesting that senescence was established early in evolution as a fundamental cell fate determination program[6,7]. In anticancer therapy, this cell cycle blockade directly inhibits abnormal proliferation of cancer cells, which is the biological basis of its anticancer effect[8]. SN has been recognized not only for its role in proliferation suppression but also for its multifaceted regulatory effects on cancer through a series of intracellular and extracellular regulations. Firstly, senescent cells (SNCs) are often subjected to metabolic reprogramming and oxidative stress, thus their metabolic vulnerability can be exploited through certain sensitive metabolic interventions[9]. Secondly, SNCs significantly influence the tumor microenvironment (TME) through their secreted senescence-associated secretory phenotype (SASP)[10]. The SASP can recruit and activate natural killer (NK) cells, cluster of differentiation (CD) 8 positive ($CD8^+$) T lymphocytes, and macrophages to enhance immune clearance of cancer cells[11,12]. In addition, the SASP has been found to promote angiogenesis and matrix remodeling and help recruit regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), thereby undermining anticancer immune responses and facilitating cancer recurrence and metastasis[13].

Based on multifactorial mechanisms of senescence, cancer treatment strategies targeting cellular senescence have transitioned from a single approach of targeting senescence induction to a multi-mechanistic combinatorial approach. This combinational approach encompasses blocking proliferation at the cell cycle level with senescence inducers[14], targeting redox imbalance or metabolic vulnerability of senescent cells for selective killing[15], enhancing immune responses through components of the SASP[16], and modifying the cancer microenvironment by utilizing the regulatory effects of senescence on extracellular matrix remodeling and angiogenesis to improve chemotherapy efficacy[8,17]. Furthermore, a novel therapeutic strategy, the "one-two punch" strategy, has been developed by initially inducing senescence in cancer cells, followed by selective elimination of these senescent cells[2,18]. This approach aims to retard cancer progression while reducing inflammation and recurrence risks associated with long-term accumulation of senescent cells, thereby enhancing the precision of senescence-based anticancer therapies[19]. To apply these strategies of targeting cellular senescence, conventional drug delivery methods become challenging for effective combined or sequential delivery and responsive release of various drug types, such as senescence inducers, senolytics, immunostimulants, and metabolic regulators[20].

The emergence of nano-drug delivery systems (Nano-DDSs) provides a promising platform for addressing this challenge[21]. With excellent biocompatibility, targeted delivery, controllable release, and multifunctional modification, the Nano-DDSs can integrate various drugs with different mechanisms of action in one single platform and control the spatial and temporal release of them to maximize their therapeutic efficacy [22,23]. Recently, Nano-DDSs for targeting senescence have become one of the advanced anticancer drug delivery systems with great potential in precision cancer therapy[24]. In this review, we first examine fundamental biological characteristics of cellular senescence and its multifaceted roles in cancer treatment. We subsequently elaborate on design principles and material types of Nano-DDSs that leverage senescence mechanisms for anticancer applications. The latest research advancements based on their mechanisms of action: cancer progression regulation, metabolic dysregulation, local immune modulation, and TME remodeling, are systematically reviewed with representative examples (Fig. 1). Finally, we analyze the opportunities and challenges in leveraging Nano-DDSs for precise senescence regulation, optimizing combination therapies in Nano-DDSs, and facilitating clinical translation of Nano-DDSs-based combination therapies. These challenges span the entire spectrum from biological research to technological translation, and propose future directions to enhance senescence-based cancer therapies.

2. Overview of cellular senescence in cancers

2.1. Cellular senescence

Research on cellular senescence dates back to the 1960s, when Hayflick and Moorhead proposed that the aging of tissues and organs resulted from the accumulation of non-dividing cells, which are known as SNCs[25]. They described that the cells entered a state of cell cycle arrest after reaching their maximum number of divisions, the "Hayflick limit". In this state, the cells lost their proliferative capacity while they retained their metabolic activity, and this state was referred to as replicative senescence[5]. Subsequent research has elucidated that the molecular basis of the "Hayflick limit" lies in the progressive shortening of telomeres after each cell division[26]. When telomeres are shortened to a critical length, the shortening of telomeres is recognized as one type of DNA damage, thereby activating the DNA damage response (DDR) pathway and ultimately leading to permanent cell cycle arrest[27]. In addition to telomere shortening, various exogenous or endogenous factors, including oxidative stress, ionizing radiation, viral infection, chemical toxicity, and oncogene

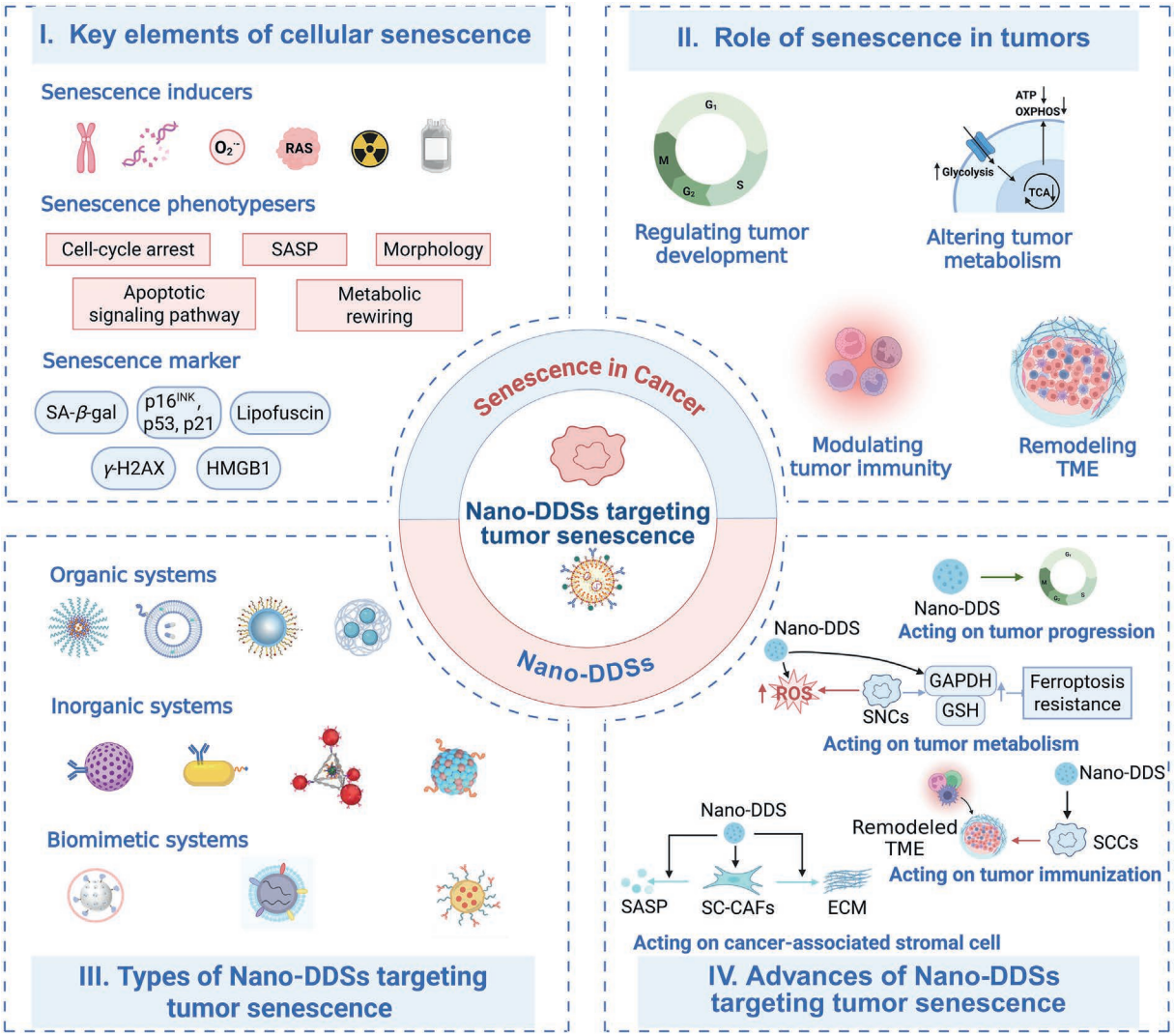

Figure 1 Nano-DDSs targeting cellular senescence for cancer therapy. (I) Key elements of cellular senescence: inducers, phenotypes, and biomarkers; (II) roles of senescence in cancers; (III) classification of Nano-DDSs targeting cancer senescence; and (IV) advances in Nano-DDSs targeting cancer progression, metabolism, immunization, and cancer-associated stromal cells. Rat sarcoma virus (RAS), senescence-associated secretory phenotype (SASP), senescence-associated β-galactosidase (SA-β-Gal), cyclin-dependent kinase inhibitor 2A ($p16^{INK4a}$), tumor protein p53 (p53), cyclin-dependent kinase inhibitor 1A (p21), gamma-H2A histone family member X (γ-H2AX), high mobility group box 1 (HMGB1), adenosine triphosphate (ATP), oxidative phosphorylation (OXPHOS), tricarboxylic acid cycle (TCA), tumor microenvironment (TME), nano-drug delivery systems (Nano-DDSs), reactive oxygen species (ROS), senescent cells (SNCs), glyceraldehyde-3-phosphate dehydrogenase (GAPDH), glutathione (GSH), senescent cancer cells (SCCs), senescent cancer-associated fibroblasts (SC-CAFs), extracellular matrix (ECM). Created with BioRender.com.

activation, can induce broad cellular senescence by triggering DDR or modulating senescence-associated molecular pathways[18]. Gradual elucidation of these mechanisms has enabled the identification of key intervention targets for senescence regulation in cancer therapy[11,28].

2.1.1. Characterization of cellular senescence

SNCs typically do not exist as individual, discrete cells within the body; instead, they are often observed in clusters. They exhibit distinctive morphological alterations, metabolic reprogramming, and anti-apoptosis, and secrete SASPs (Fig. 2)[11,15]. The morphological alterations in SNCs, including an increased cell volume, an irregular shape, and cytoskeletal rearrangement, are primarily driven by the mechanistic target of rapamycin complex 1 intracellular signaling pathway. These structural changes consequently influence critical cellular behaviors such as migration and adhesion[29]. In correspondence with these morphological changes, SNCs develop unique metabolic reprogramming. The upregulation of caveolin-1 in the plasma membrane elevates the cellular cholesterol content, thereby regulating p53 activity and signaling[30,31]. The loss of Lamin B1 compromises the nuclear integrity, accompanied by a decrease in the membrane potential and an increase in the lysosomal activity[32]. Ultimately, metabolic reprogramming leads to a series of metabolic characteristics in SNCs, including mitochondrial dysfunction, enhanced glycolysis, and imbalance of nicotinamide adenine dinucleotide (NAD^+)/nicotinamide adenine dinucleotide H (NADH)[33,34]. These characteristics have been harnessed to develop senescence strategies

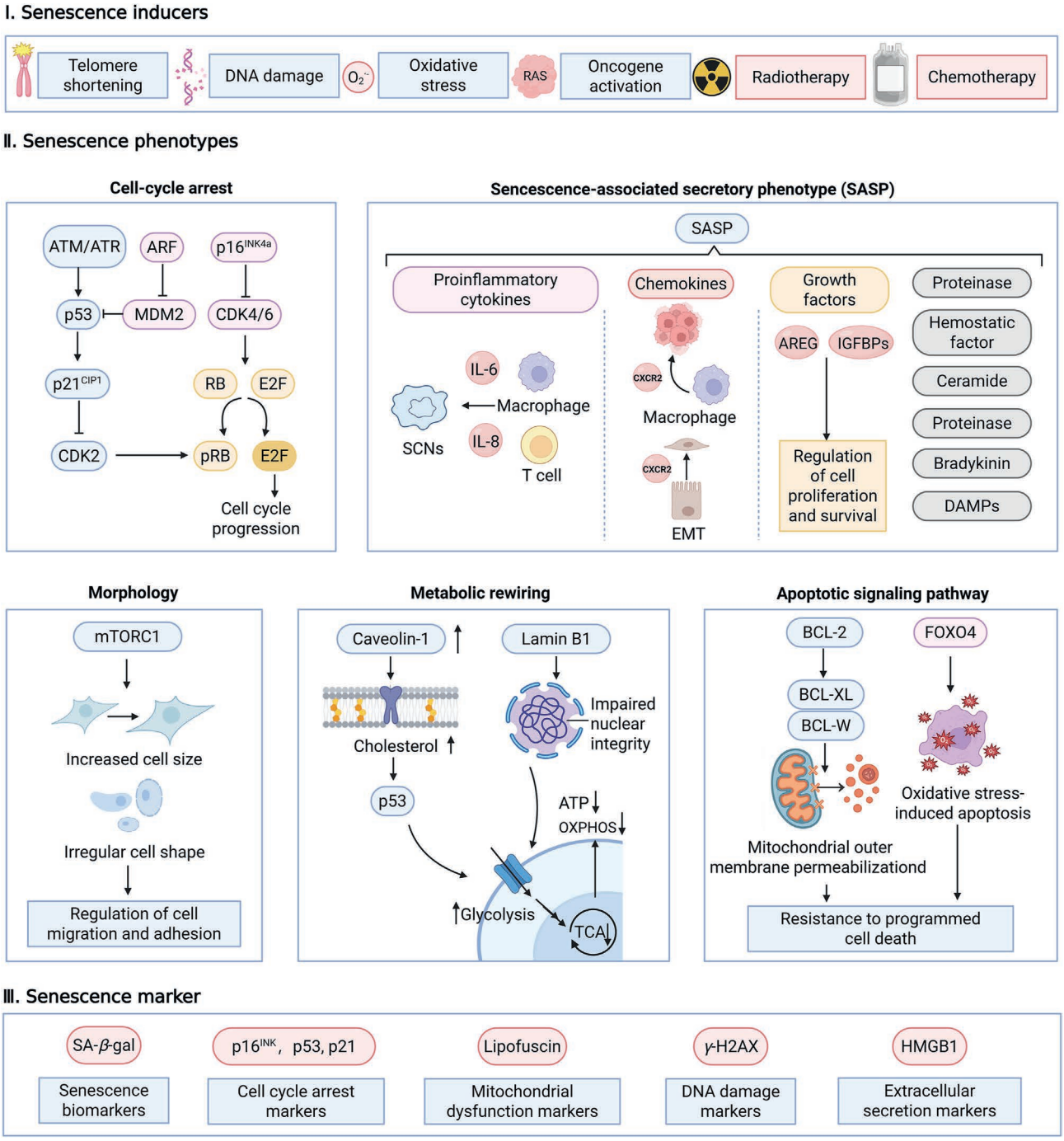

Figure 2 Inducing factors, phenotypes, and biomarkers of cellular senescence. I. Cellular senescence can be induced by various factors, including endogenous factors (highlighted in blue, *e.g.*, telomere shortening, DNA damage, oxidative stress, and oncogene activation) and exogenous factors (highlighted in pink, *e.g.*, radiation therapy and chemotherapy). II. Upon entering the senescent state, cells undergo various phenotypic changes, including 1) cell cycle arrest. DNA damage activates ATM/ATR and p53, inducing the expression of the CDKI p21CIP1; simultaneously, the INK4a/ARF locus derepresses and induces the expression of CDK4/6 inhibitor $p16^{INK4a}$ and MDM2 inhibitor ARF; p53 is activated by inhibiting MDM2; and $p16^{INK4a}$ and p21CIP1 maintain low phosphorylation of retinoblastoma protein RB (the brown intensity for the level of phosphorylation] and bind to E2F to suppress its transcriptional activity; 2) SASP (including pro-inflammatory cytokines, chemokines, growth factors, proteases, hemostatic factors, ceramides, bradykinin, extracellular matrix components, and DAMPs). Pro-inflammatory cytokines (*e.g.*, IL-6 and IL-8) can recruit immune cells to sites of senescent cell accumulation, facilitating immune surveillance and clearance of damaged cells; chemokines (*e.g.*, CXCR2) attract cancer-associated macrophages and promote epithelial−mesenchymal transition, thereby driving cancer progression and metastasis; and growth factors (*e.g.*, AREG and IGFBPs) can influence cell proliferation and survival. 3) Morphological changes. These changes are driven by the mTORC1 intracellular signaling pathway and characterized as an increased cell volume and an irregular shape, which ultimately impact cell migration and adhesiveness; 4) Metabolic reprogramming. In SNCs, the upregulation of caveolin-1 elevates the plasma membrane cholesterol level and regulates p53 activity along with its associated signaling pathways; the loss of Lamin B1 results in

for cancer therapy. Additionally, apoptotic signaling pathways in SNCs are altered, resulting in resistance to programmed cell death. SNCs primarily employ a multi-layered anti-apoptotic mechanism through the B-cell lymphoma (BCL)-2 family and forkhead box protein O4 (FOXO4)[35,36]. Specifically, the transcriptional upregulation of BCL-XL (BCL-2L1) and BCL-W (BCL-2L2) during senescence sequesters pro-apoptotic BCL-2-homology3 (BH3) domain-containing proteins to inhibit mitochondrial outer membrane permeabilization and apoptosis[37]. FOXO4 nuclear localization suppresses oxidative stress-induced apoptosis[38]. Through these elucidated mechanisms, molecular targets have been identified for developing selective senolytic drugs to clear SNCs (*e.g.*, BCL-2-targeting ABT-263), promoting their anti-cancer effects.

Notably, SNCs are characterized not only by a loss of proliferative capacity but also by the secretion of various bioactive molecules, collectively referred to as the SASP[10]. These secreted molecules include cytokines, chemokines, growth factors, and proteases, which can significantly impact the cellular microenvironment and influence various physiological and pathological processes, particularly playing critical roles in aging and cancer[39,40]. The SASP can be categorized into several types based on the nature and function of the secreted molecules[12]. Pro-inflammatory cytokines, such as interleukin-6 (IL-6) and interleukin-8 (IL-8), play crucial roles in mediating immune responses and inducing inflammation [13]. These cytokines recruit immune cells to the sites of senescent cells, aiding in immune surveillance and clearance of damaged cells[41,42]. For instance, interleukin-1β (IL-1β) can induce growth arrest and senescence in proliferative astrocytomas and upregulate the expression of SASP factors[43]. Chemokines (*e.g.*, C−X−C motif chemokine receptor 2 (CXCR2)), another type of the SASP, attract cancer-associated macrophages and promote epithelial−mesenchymal transition (EMT), thereby facilitating cancer progression and metastasis[44]. Growth factors, including amphiregulin (AREG) and insulin-like growth factor binding proteins (IGFBPs), are also an important type of the SASP. They can influence cell proliferation and survival. For example, IGFBP7 has been shown to induce senescence in certain cell types, thereby inhibiting cancer growth[45]. Additionally, there are hundreds of proteins and non-protein signaling molecules in the SASP, such as proteases, coagulation factors, bradykinin, ceramides, extracellular matrix (ECM) constituents, as well as damage-associated molecular patterns (DAMPs)[46].

The role of the SASP in disease progression is multifaceted and context-dependent[47]. In the cancer context, a prevailing hypothesis posits that the SASP from senescent non-cancerous cells may induce cell cycle arrest in adjacent transformed cells. This process, mediated through juxtracrine signaling, is termed as "secondary senescence". The secondary senescence may contribute to cancer suppression in the early stages[12,48]. As the disease progresses, cytokines in the late-stage SASP can promote the clearance of neoplastic cells by recruiting immune cells to the cancer site. However, the pro-inflammatory nature of the SASP can also foster an environment conducive to cancer progression, including enhanced cancer proliferation, angiogenesis, metastasis, and suppression of anti-cancer immunity[49]. Thus, the SASP could exhibit both cancer-suppressive and cancer-promoting effects, depending on the duration and the disease progression stage. An acute, transient SASP may activate immune surveillance to play a protective role in early cancer suppression and tissue repair, whereas a prolonged, persistent SASP may promote cancer progression and impair tissue regeneration[50,51].

2.1.2. Markers of cellular senescence

The main characteristics of SNCs include DDR-mediated proliferative arrest, accompanied by morphological changes, SASP production, and upregulation of anti-apoptotic pathways. Consequently, cell cycle analysis, cyclin detection, and the examination of expression levels of key molecules that trigger proliferative arrest (*e.g.*, $p16^{INK4A}$, p53, and p21) have become standard methods for senescence detection[52,53]. For *in situ* identification and monitoring of SNCs in clinical settings, senescence-associated β-galactosidase (SA-β-Gal) has emerged as a prominent biomarker for identifying and tracking SNCs. Nevertheless, SA-β-Gal is also expressed in many non-SNCs in developing limbs and healthy neurons. Therefore, SA-β-Gal may not be a specific biomarker for SNCs[54]. Additionally, lipofuscin, an indigestible aggregate composed of oxidized proteins, lipids, and metals, accumulates significantly in SNCs due to mitochondrial dysfunction and reactive oxygen species (ROS) buildup, and it has become a novel senescence marker. Evangelou et al. developed a lipophilic, hapten-linked Sudan Black B analogue to target lipofuscin and achieved convenient visualization of SNCs[55]. Moreover, gamma-H2A histone family member X (γ-H2AX) and high mobility group box 1 (HMGB1) serve as biomarkers for DNA damage and nuclear excretion, respectively, and both markers are

compromised nuclear integrity, accompanied by a decrease in the mitochondrial membrane potential and an increase in the lysosomal activity; ultimately, metabolic reprogramming leads to a constellation of features characterized by mitochondrial dysfunction, enhanced glycolysis, reduced oxidative phosphorylation, and a disrupted NAD^+/NADH balance; and 5) altered apoptosis signaling pathways in senescence-associated nuclear changes including the transcriptional upregulation of BCL-XL (BCL2L1) and BCL-W (BCL2L2) during senescence. These upregulated proteins sequester pro-apoptotic BH3-domain-containing proteins to inhibit mitochondrial outer membrane permeabilization and apoptosis; the nuclear localization of FOXO4 suppresses oxidative stress-induced apoptosis; collectively, these changes confer a marked resistance to programmed cell death. III. Biomarkers for cellular senescence, including senescence biological markers, cell cycle arrest markers, mitochondrial dysfunction markers, DNA damage markers, and extracellular secretory biomarkers. Rat sarcoma virus (RAS), ataxia-telangiectasia mutated (ATM), ATM and rad3-related (ATR), tumor protein p53 (p53), cyclin-dependent kinase inhibitor 1A (p21), cyclin-dependent kinase (CDK), alternative reading frame (ARF), mouse double minute 2 (MDM2), cyclin-dependent kinase inhibitor 2A ($p16^{INK4a}$), retinoblastoma protein (RB), E2 factor (E2F), phospho-retinoblastoma protein (pRB), senescent cells (SNCs), interleukin (IL), C−X−C motif chemokine receptor 2 (CXCR2), epithelial−mesenchymal transition (EMT), amphiregulin (AREG), insulin-like growth factor-binding proteins (IGFBPs), damage-associated molecular patterns (DAMPs), mechanistic target of rapamycin complex 1 (mTORC1), adenosine triphosphate (ATP), oxidative phosphorylation (OXPHOS), tricarboxylic acid cycle (TCA), B-cell lymphoma (BCL), forkhead box protein O4 (FOXO4), senescence-associated β-galactosidase (SA-β-Gal), gamma-H2A histone family member X (γ-H2AX), high mobility group box 1 (HMGB1). Created with BioRender.com.

supplementary for SNC identification. The identification of these markers allows for evaluating the level of senescence during the development of Nano-DDSs targeting SNCs for cancer therapies[54].

With advances in technology, the single-cell technique was applied to map the SNCs in both mice and humans, and the technique overcame the limitations of analyzing homogenized tissue samples[56]. This study revealed tissue-specific differences in senescence, indicating that a single biomarker may not be able to accurately identify SNCs. Instead, a comprehensive approach using multiple indicators should be developed to assess cellular senescence[57,58].

2.1.3. Drugs for cellular senescence

The scientific discovery of senescence as a cellular state and a pathological marker has been transformed into a variety of senescence-targeting therapeutic strategies. The characteristics of SNCs have been harnessed for the development of senescence-targeting therapeutic drugs/modalities. These drugs/modalities can be broadly categorized into two main types: inducing cellular senescence and targeting SNCs clearance[59,60].

To explore senescence induction as a therapeutic strategy, therapeutic drugs/modalities have been employed to deliberately induce cellular senescence in a specific pathological context to suppress cancer progression, mitigate fibrosis, and regulate tissue repair[61] (Table 1[62-89]). Notably, therapy-induced senescence (TIS) has emerged as a key anticancer mechanism. Studies have shown that mitogen-activated protein kinase (MEK) inhibitors, cyclin-dependent kinase (CDK) 4/6 inhibitors, chemotherapy, and low-dose radiotherapy can induce irreversible senescence in cancer cells to directly inhibit their proliferation and prevent metastasis[90]. Moreover, senescent cancer cells often exhibit upregulation of characteristic SASP factors, which enhance major histocompatibility complex class I (MHC-I) expression, promote antigen presentation, and recruit and activate immune cells, thus demonstrating synergistic effects in cancer immunotherapy[2]. Additionally, senescent cancer cells exhibit heightened susceptibility to ROS accumulation due to dysregulated redox homeostasis[91]. These findings offer insights for developing combination therapeutic strategies for TIS[92,93].

Meanwhile, SNCs are byproducts of radiotherapy and chemotherapy, and they are generated because of damage to DDR or interference with cell cycle-related proteins to block cell division[38]. Under normal physiological conditions, SNCs in the body are naturally cleared. However, due to immune dysfunction or SNCs accumulation beyond a certain threshold, it becomes challenging to eliminate them from the body[94]. A continuous increase in the SNC burden may lead to tissue damage, contributing to the onset or progression of various diseases, particularly age-related diseases (*e.g.*, cardiac dysfunction, diabetes, osteoarthritis)[95]. Moreover, an elevated level of the local SASP not only mediates a chronic inflammatory microenvironment through pro-inflammatory cytokines such as interleukin-1 (IL-1), IL-6, and IL-8, but also regulates intercellular communication *via* growth factors (*e.g.*, hepatocyte growth factor, transforming growth factor-β (TGF-β), granulocyte-macrophage colony-stimulating factor (GM-CSF)) and modulates extracellular matrix components (*e.g.*, metalloproteinases)[96]. The regulated intercellular communication patterns facilitate the spread of senescence signals within tissues, accelerating tissue aging, a process known as paracrine senescence by the SASP[41]. Consequently, timely clearance of SNCs can prevent or delay tissue dysfunction and extend the lifespan, leading to the development of SNC clearance therapy (SNCCT)[97].

Currently, there are three major types of SNCCT: selective SNC clearance (senolysis), immune-mediated SNC clearance, and SASP neutralization (senomorphics)[98]. Senolytic drugs are SNC-clearing agents, and they selectively eliminate SNCs by inhibiting key survival pathways of SNCs[99]. For instance, ABT-737 induces apoptosis in senescent cells by inhibiting BCL-2 and BCL-xL, and its clinical derivative, Navitoclax (ABT-263), exhibits a broader inhibitory spectrum by additionally targeting BCL-W, thereby more effectively disrupting the survival pathways of senescent cells[37,100]. D-retro-inverso peptide induces SNC apoptosis by disrupting the p53−FOXO4 interaction and blocking p53 nuclear localization[101]. Immune-mediated SNC clearance relies on immune surveillance through robust responses from macrophages, NK cells, and cytotoxic T cells. SNC immune evasion may result from the presence of immune-suppressive factors in the microenvironment or the loss or covering of SNC-specific immune markers, which is akin to the mechanism of evading immune clearance of cancer cells *via* decoy receptors, immune-modulatory cytokines, and checkpoint ligands[25]. To tackle SNC immune evasion, Ming et al. developed a chimeric peptide, E16-uPA24, which targeted SNCs by binding to the urokinase-type plasminogen activator receptor on their surface through the uPA24 domain. The glutamate peptide chain on the other end activated and recruited NK cells through glutamate receptors to clear SNCs. This approach successfully cleared SNCs in mouse models of liver and lung fibrosis and extended the survival of chemotherapy-treated lung adenocarcinoma mice[25]. Additionally, breakthroughs in chimeric antigen receptor T-cell (CAR-T) therapy are promising for SNC immune clearance. By targeting SNC-specific surface markers, patient-derived cytotoxic T cells can achieve highly specific cellular immunity[102]. The immune-mediated SNC clearance strategy also shows promise in the field of liquid tumors. A phase II clinical trial by Wang et al. demonstrated that umbilical cord blood (UCB) infusion potently enhanced anti-cancer immune responses, thereby facilitating the clearance of SNCs. Their study revealed a significant increase in the proportions of cytotoxic $CD8^+$ T cells and NK cells in the peripheral blood of elderly acute myeloid leukemia (AML) patients following UCB infusion, concurrently with an upregulation of anti-aging markers such as telomerase activity. These findings provide compelling clinical evidence to support the strategy of immune-mediated clearance of SNCs[103]. Senomorphics modulates the production of the SASP from SNCs by inhibiting pro-SASP signaling pathways, blocking SASP secretion, or suppressing the activity of SASP components. For example, it has been revealed that silencing epigenetic factors such as mixed lineage leukemia 1 (MLL1, also referred to as KMT2A), bromodomain-containing protein 4 (BRD4), and high mobility group box 2 can block SASP production without triggering SNC replication. Moiseeva et al. demonstrated that metformin, an anti-diabetic drug, reduced the level of the SASP during aging by blocking nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) signaling. However, inhibiting intracellular pro-SASP signaling may increase the cancer risk, and blocking SASP secretion or inhibiting SASP components may have a diminished long-term efficacy[104,105]. Therefore, better delivery systems for delivering senolytic drugs or enhancing immune-based SNC clearance can be developed to minimize off-target effects, mitigate systemic toxicity, and effectively block SASP secretion.

Table 1 Senescence-inducing and senolytic drugs with their mechanisms of action.

Drug category	Mechanism category	Drug name	Brief mechanism of action	Ref.
Senescence-inducing drugs	Deoxyribonucleic acid (DNA) replication stress inducers	Aphidicolin, Thymidine, Hydroxyurea, Bromodeoxyuridine, Gemcitabine, Cyclopentenyl cytosine.	Inhibiting DNA polymerase, reducing deoxycytidine triphosphate synthesis, inhibiting ribonucleotide reductase by exerting DNA replication stress, and activating senescence pathways.	62
	DNA-damaging agents	2a. DNA topoisomerase inhibitors, including Doxorubicin, Etoposide, Daunorubicin, Mitoxantrone, Camptothecin, SN-38.	Inhibiting topoisomerase I/II, inducing DNA double-strand breaks or single-strand breaks, and activating DNA damage response.	63
		2b. DNA cross-linkers, including Cisplatin, Mitomycin C, Busulfan, Cyclophosphamide, Diaziquone.	Inducing intra-strand/inter-strand DNA cross-linking, hindering DNA replication and repair, and triggering senescence.	64,65
		2c. Drugs for complexing DNA to induce damaging effects, including Actinomycin D, Bleomycin, Temozolomide.	Combining DNA intercalation, transcription inhibition, and topoisomerase inhibition to induce DNA damage and DNA damage response activation.	66,67
	Epigenetic modifiers	5-Aza-2'-deoxycytidine, Sodium butyrate, Trichostatin A, MS-275, SAHA (Vorinostat), LBH589 (Pandefinostat), Curcumin, C646.	Inhibiting DNA methyltransferases, histone deacetylases, or histone acetyltransferases, and activating senescence-related genes through epigenetic regulation.	68,69
	Telomerase activity inhibitors	SYUIQ-5, BMVC4, Pyridostatin, Compound 115405, Perylene derivatives, Indole derivatives, Harmine, BIBR1532, Azidothymidine.	Stabilizing telomeric G-quadruplexes, inhibiting telomerase activity, or downregulating its expression, leading to telomere dysfunction and inducing senescence.	70-72
	Cyclin-dependent kinase inhibitors	Palbociclib (PD-0332991), Roscovitine (Seliciclib), Ribociclib (LEE011).	Inhibiting cyclin-dependent kinase 4/6 or cyclin-dependent kinase 2/7/9, arresting cell cycle at the Gap1 phase, activating the phospho-retinoblastoma protein pathway, and inducing senescence.	73-76
	p53 activators	Nutlin-3A, FL118 (Camptothecin analogue).	Inhibiting mouse double minute 2 binding to tumor protein 53 (p53), activating the p53- cyclin-dependent kinase inhibitor 1 (p21) pathway, and inducing cell cycle arrest and senescence.	77,78
	Protein kinase C activators	TPA/PMA (12-*O*-tetradecanoylphorbol-13-acetate), PEP005 (Ingenol-3-angelate), PEP08 (20-*O*-acetyl-ingenol-3-angelate).	Activating protein kinase C, inducing DNA damage, or inhibiting telomerase activity, and triggering senescence.	79,80
	Reactive oxygen species inducers	Hydrogen peroxide, *Tert*-butyl hydroperoxide, Phenyl 2-pyridyl ketoxime, Phenylaminonaphthoquinones, Paraquat.	Increasing intracellular reactive oxygen species levels, exerting oxidative stress, inducing DNA damage, and activating senescence pathways like p53-p21.	81,82
Senolytic drugs	B-cell lymphoma 2 family inhibitors	Navitoclax (ABT-263), ABT-737.	Inhibiting anti-apoptotic proteins of the B-cell lymphoma 2 family induces apoptosis in senescent cells (SNCs).	83,84

(*continued on next page*)

Table 1 (*continued*)

Drug category	Mechanism category	Drug name	Brief mechanism of action	Ref.
	Tyrosine kinase inhibitors	Dasatinib (+ Quercetin).	Multi-target inhibition of anti-apoptotic pathways synergistically eliminates SNCs.	85
	Forkhead box protein O4 (FOXO4)-p53 interaction disruptors	FOXO4-dependent retro-inverso peptide.	Interfering with the interaction between p53 and FOXO4, preventing p53 translocation out of the nucleus, and activating p53-induced apoptosis.	86
	Natural products	Querceti (commonly used in combination with dasatinib), Fisetin.	Multi-target inhibition of anti-apoptotic pathways synergistically eliminates SNCs.	85,87
	Immune-mediated senolytics	Chimeric antigen receptor T-cell therapy.	Engineering T cells to express chimeric antigen receptors that specifically target surface markers on senescent cells, enabling the selective elimination of senescent cells.	87
	Lysosomal inhibitor	Chloroquine.	Inhibiting the lysosomal activity of SNCs and disrupting their autophagy process leads to cell death.	88,89

However, the translation of senescence-targeted therapies into clinical applications faces multiple challenges. Firstly, there are very few specific biomarkers that can be used to accurately quantify the burden of senescent cells *in vivo* and *in situ*, real-time monitor therapeutic responses for precise evaluation of treatment efficacy and dose optimization[106]. Secondly, there are insufficient clinical data for optimal dosage regimens, therapeutic windows, and long-term medication safety, particularly in patient populations with multiple metabolic comorbidities[107]. Additionally, the design of clinical trials should comprehensively cover high heterogeneity of metabolic diseases, common comorbidities, and the selection of clinically relevant endpoint indicators, such as glycated hemoglobin, the hepatic fat content, and systemic inflammatory markers[108,109].

2.2. Impacts of senescence on cancer progression and metastasis

With the increasing focus on cellular senescence as a therapeutic target, its role in oncology has been extensively reported, laying the foundation for developing anticancer therapies from the perspective of senescence. However, research has shown that cellular senescence has a multifaceted impact on cancers, displaying a "double-edged sword" effect[110,111]. In the following sections, we elaborate on the dual effects of cellular senescence on cancer progression, cancer cell metabolism, local cancer immunity, and cancer microenvironment remodeling (Fig. 3).

2.2.1. Regulating cancer development

Although cellular senescence was initially considered an effective mechanism for cancer suppression, recent studies have revealed dual effects of senescence on cancer cells. SNCs undergo cell cycle arrest to inhibit cancer progression, serving as the first line of defense against cancer[112]. Additionally, chemokines and pro-inflammatory factors secreted by senescent cells (*i.e.*, the SASP) help recruit immune cells to clear senescent cells, thereby exerting a broader anti-cancer effect[113,114]. Furthermore, cancer-associated cellular senescence may act as a physiological cancer-suppressive mechanism. Oncogene-induced senescence (OIS) is a critical barrier for cancer progression. For instance, overexpression of Harvey rat sarcoma viral oncogene homolog (HRAS), an oncogene, can induce permanent cell cycle arrest to block cancer cell proliferation. Bennett et al. demonstrated that OIS in melanoma may hinder cancer progression[115]. In multiple myeloma studies, the oncogenic HRAS signaling pathway has been shown to prevent malignant transformation by inducing p21Cip1/Waf1-dependent senescence[116].

Cancer development is a multi-step process involving the normalization of the tissue microenvironment and the accumulation of continuous mutations. New evidence from Schedin et al. suggests that changes in senescence-associated DNA methylation impede somatic reprogramming into induced pluripotent stem cells with unlimited growth and differentiation, thereby halting proliferation of precancerous cells and ultimately inhibiting cancer progression[117,118].

In addition to the positive effects of senescence on inhibiting cancer progression, increasing evidence has suggested that senescence may contribute to enhanced drug resistance of cancer cells[119]. First, the epigenome of senescent cells undergoes extensive changes, known as an "epigenetic drift". This drift may lead to the activation of oncogenes that are originally silenced, or incorrect silencing of cancer suppressor genes, thereby creating favorable conditions for carcinogenesis[119]. Second, clinical studies on breast, ovarian, and lung cancers support that wild-type p53-mediated cell cycle arrest and senescence become barriers to effective chemotherapy and major culprits for relapsing[120,121]. Furthermore, a study on breast cancer progression confirmed that senescent cancer cells in human epidermal growth factor receptor 2-positive cancer exhibited a high metastatic rate, and they drove cancer growth in patient-derived xenograft models[122].

2.2.2. Altering cancer metabolism

Senescent cells exhibit metabolic hyperactivity, which may have a "double-edged sword" effect. Energy production in the senescent

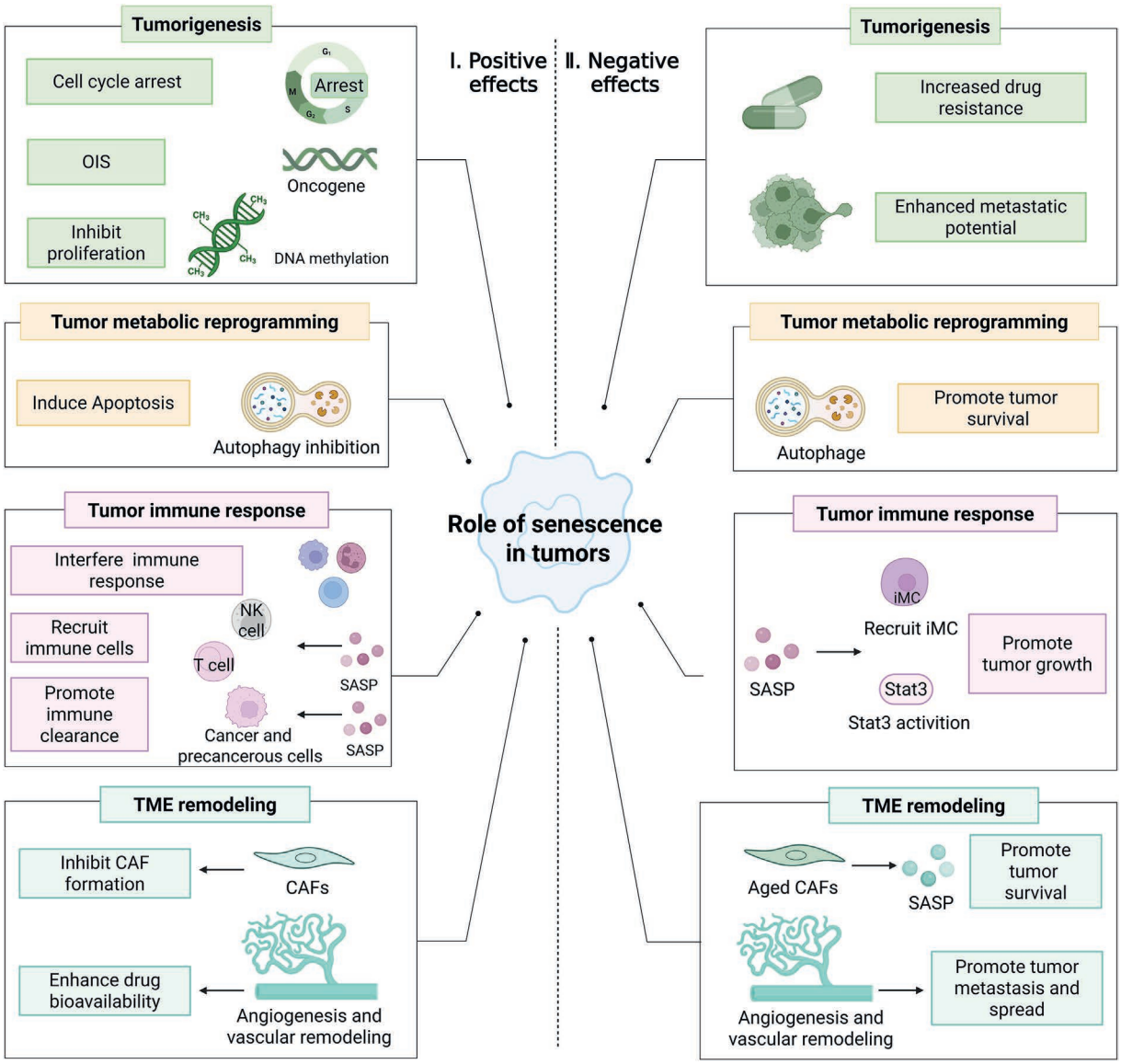

Figure 3 Positive and negative effects of senescent cells on cancer progression, including effects of cellular senescence on cancer development, cancer cell metabolism, local cancer immunity, and cancer microenvironment remodeling. Cellular senescence exerts inhibitory effects on cancer development through multiple mechanisms, including blocking cancer proliferation *via* senescence-induced cell cycle arrest; hindering malignant progression *via* OIS; and inhibiting the reprogramming of somatic cells into induced pluripotent stem cells *via* senescence-associated DNA methylation changes to halt the proliferation of pre-malignant cells. Conversely, senescence may promote cancer progression by enhancing drug resistance and facilitating the metastatic capacity of senescent cancer cells. By regulating cancer cell metabolism, toxic proteins generated during the SASP production process are cleared *via* the autophagy pathway, thus promoting cancer cell survival and growth; in contrast, blocking this metabolic clearance pathway may induce cancer cell apoptosis. In the local cancer immune process, cellular senescence modulates immune responses either by directly acting on immune cells or through the SASP. The SASP promotes immunosuppression by recruiting myeloid cells and regulatory T cells, yet it can activate the immune system to clear cancer cells and pre-malignant cells; in specific contexts such as during liver carcinogenesis, persistent senescent cells recruit $CCR2^{+}$ immature myeloid cells *via* the SASP, inhibiting the natural killer cell function and promoting cancer progression; additionally, SASP factors secreted by senescent cells, including the immunosuppressive cytokines CXCL2 and GM-CSF, exert pro-cancer effects primarily through activation of the STAT3 signaling pathway. Senescence exhibits bidirectional regulatory effects on the remodeling of the cancer microenvironment. Senescence can suppress CAF activation, and senescent CAFs promote cancer cell survival and adaptability by secreting SASP components such as TGF-β, IL-6, and IL-10. Senescent cells release abundant pro-angiogenic SASP factors, including VEGF, PDGF, and FGF, to regulate angiogenesis, which mediate neovascularization and vascular restructuring within cancer tissues. Neovascularization presents a dual effect. The increased vascular density promotes cancer metastasis and spread, and it simultaneously enhances the delivery efficiency of chemotherapeutic agents to cancer tissues, thereby potentially improving chemotherapy efficacy. Oncogene-induced senescence (OIS), senescence-associated secretory phenotype (SASP), immature myeloid cell (iMC), signal transducer and activator of transcription 3 (Stat3), cancer-associated fibroblast (CAF). Created with BioRender.com.

cells is significantly augmented by enhancing glycolysis, fatty acid oxidation, and oxidative phosphorylation, which is manifested as increased glucose uptake and elevated lactate production[123,124]. The metabolic reprogramming in senescent cells, including the aberrant utilization of "aerobic glycolysis", directly provides essential bioenergy and intermediate molecules for the production and maintenance of the SASP[113]. While the metabolic mode of high energy consumption drives the SASP production, this mode constitutes a key pro-cancer risk. The study by Dörr et al. showed that senescent cancer cells harness the high-energy consumption metabolic mode to effectively clear toxic proteins generated during the SASP process *via* the autophagy pathway, thereby maintaining their own survival and evading apoptosis[125]. Furthermore, this metabolic pattern is accompanied by a rapid increase in local lactate concentration within the cancer, leading to microenvironment acidification. This characteristic not only directly promotes cancer invasiveness but also serves as a potential target for the development of targeted and stimuli-responsive drug delivery systems[126]. Blocking the energy support metabolic pathway can effectively induce apoptosis in senescent cells, and it could be a potential therapeutic strategy for targeted cancer elimination.

2.2.3. *Modulation of local cancer immunity*

Cancer tissues are often infiltrated by various immune cells to trigger a range of cancer immune responses[127]. Lymphocytes, including NK cells, $CD8^+$ cytotoxic T cells, and $CD4^+$ helper T cells (Th cells), along with pro-inflammatory macrophages (M1) and dendritic cells (DCs), contribute to anti-cancer immune responses[128,129]. In addition, MDSCs, including activated neutrophils, M2 macrophages, and heterogeneous $Foxp3^+$ Treg populations, play a role in suppressing anti-cancer immunity[130,131].

Cellular senescence modulates cancer immune responses in a complex and bidirectional manner, either through direct interactions with immune cells or the SASP. The specific outcome of the modulation process is highly contingent upon the microenvironmental context and the specific composition of the SASP. Under certain conditions, the SASP can activate potent immune surveillance and clearance mechanisms. For instance, the re-expression of the senescence marker p53 triggers an immune response to recruit various types of immune cells, including natural killer cells, neutrophils, and macrophages, leading to effective elimination of hepatocellular carcinoma (HCC) cells in mouse models[132]. At the clinical level, senescence induction by platinum-derived agents (*e.g.*, cisplatin) promotes the enrichment of T cells and natural killer cells within the cancer microenvironment of ovarian cancer, thereby significantly enhancing anti-cancer immune responses. This promotion effect is particularly pronounced in a specific genetic context, for example, in patients with homologous recombination-deficient ovarian cancer[133].

However, the persistent presence of the SASP exerts significant immunosuppressive effects. Exposure to regulatory T cells and cancer cells can induce senescence in effector T cells, compromising their targeted cancer cell killing function[134]. These senescent effector T cells exhibit reduced surface expression levels of CD27 and CD28, diminish their proliferative capacity upon Toll-like receptor stimulation, and recruit additional myeloid cells and regulatory T cells through SASP factor secretion, thereby establishing a localized immunosuppressive cancer microenvironment[132]. Notably, when senescent cells are persistently present during hepatocarcinogenesis, the SASP recruits $CCR2^+$ immature myeloid cells to promote cancer growth by impairing the natural killer cell function[10,51]. In prostate cancer models, Toso et al. identified that SASP factors produced by senescent prostate cells, including immunosuppressive cytokines (*e.g.*, C-X-C motif chemokine ligand 2 (CXCL2) and GMCSF), primarily exert pro-cancer effects through activation of the Stat3 signaling pathway[135,136]. Furthermore, infiltration of immunosuppressive myeloid-derived suppressor cells into benign prostate cancer not only inhibits the proliferation of natural killer cells and $CD8^+$ T cells but also produces IL-1 receptor antagonists to counteract IL-1 signaling, consequently inducing additional senescence and creating a vicious cycle[135,136]. In a mouse model study on mesenchymal stromal cells with conditional p27 expression-induced senescence, senescence and SASP-related genes were upregulated in p27-induced skin cells, and these cells displayed Stat3 phosphorylation and lymphocytopenia. Concurrently, MDSCs were recruited to infiltrate into the cancer tissue. The SASP-mediated immunosuppressive microenvironment significantly promoted the growth of cancer cells inoculated into immunocompetent homozygous mice[50].

2.2.4. *Cancer microenvironment remodeling*

The TME is a complex microenvironment composed of both cancer cells and various non-neoplastic components. In addition to cancer cells, there are stromal cells (*e.g.*, cancer-associated fibroblasts (CAFs)), endothelial cells, diverse types of immune cell populations, and extracellular matrix (ECM) components, including collagen, hyaluronic acid, and laminin, in this microenvironment[137]. Within this sophisticated microenvironment, cellular senescence exerts dual regulatory effects on cancer progression through its dynamic remodeling of the stromal constituents.

From a cancer-suppressive perspective, senescence may have significant anti-cancer potential[111]. Research indicates that the process of cellular senescence can effectively suppress the formation of CAFs, thereby hampering the development of cancer stroma. More importantly, senescence-mediated vascular remodeling, under specific conditions, enhances the drug delivery efficiency by improving vascular permeability and normalization within cancer, consequently promoting the accumulation of chemotherapeutic agents in cancer tissues and significantly improving treatment outcomes[138,139]. The enhancement in the drug delivery efficiency could overcome cancer therapeutic resistance[111]. Therefore, these mechanisms may be harnessed as a protective barrier against cancer progression within the cancer microenvironment.

Conversely, senescence may promote cancer progression. Senescent CAFs may establish a cancer-favorable microenvironment through the secretion of SASP factors, including TGF-β, IL-6, and IL-10. These factors promote cancer progression through multiple mechanisms, including blocking the infiltration of cytotoxic T cells, inducing stem-like properties in cancer cells to enhance drug resistance, and stimulating the proliferation of pre-malignant and malignant cells[140,141]. Using patient-derived rectal cancer organoids, Nicolas et al. demonstrated that p53-dependent senescence in CAFs underlay resistance to conventional radiotherapy[140]. In addition, Di et al.[142] reported that senescent mesenchymal stem cells promoted the proliferation and migration of breast cancer cells *via* IL-6 secretion. At the endothelial level, senescence induces the secretion of pro-angiogenic SASP factors, such as vascular endothelial growth factor (VEGF), platelet-derived growth factor (PDGF), and fibroblast growth factor (FGF),

which mediate neovascularization and vascular remodeling[111]. While the neovascularization process may enhance the delivery efficiency of chemotherapeutic drugs, it simultaneously facilitates cancer metastasis and dissemination by increasing the vascular density[139].

3. Design and classification of Nano-DDSs for cancer senescence

The primary goal of Nano-DDSs is to deliver drugs to the correct location at the appropriate time, thereby enhancing efficacy and reducing side effects[143,144]. Traditional DDSs are typically constructed from immediate or sustained-release formulations, and they have limited control over the spatial and temporal distribution of drugs released from DDSs. In contrast, advanced Nano-DDSs (*e.g.*, controlled-release, targeted, and stimuli-responsive systems) remarkably enhance the delivery efficiency and accuracy by harnessing precisely controlled release mechanisms, enhancing site-specific targeting, and responding to the *in vivo* environment[145]. These systems can also effectively overcome physiological barriers, such as the blood-brain barrier and the gastrointestinal tract[146]. Commonly used nanocarrier materials for advanced Nano-DDSs include liposomes, polymer nanoparticles, micelles, and hydrogels, and these materials hold unique advantages, including biocompatibility, stability, and controlled drug release. It is projected that Nano-DDSs could become highly personalized, efficient, and patient-friendly therapeutic systems for targeting senescence in the cancer microenvironment[17,147] (Fig. 4).

3.1. Advances in Nano-DDSs for cancer treatment

Nanoparticles, by virtue of a nanoscale dimension, a large surface area, and high tunability, have been widely used to prepare advanced Nano-DDSs[148]. Preclinical studies have demonstrated that nanoparticle carriers can significantly enhance drug accumulation specifically in tumor tissues through passive and/or active targeting strategies[149]. Furthermore, surface functionalization effectively prolongs their circulation half-life and improves pharmacokinetic properties[150]. Collectively, the employment of Nano-DDSs can effectively mitigate systemic toxicity associated with senotherapy, thereby providing crucial technical support for enhanced treatment safety.

The enhanced permeability and retention (EPR) effect, observed in preclinical animal cancer models and clinical studies on cancer patients, is considered a key design principle for Nano-DDSs[151]. This effect is ascribed to abnormal cancer vasculature and obstructed lymphatic drainage; thus, macromolecules or nanoparticles with appropriate physicochemical properties (such as size, shape, surface charge, and biocompatibility) can accumulate more effectively in cancer tissues[152-154]. Specifically, a nanoparticle size between 50 and 150 nm has been demonstrated to be optimal for cancer targeting based on the EPR effect, while particles smaller than 5−6 nm are cleared by the kidneys, and those larger than 200 nm may be eliminated during circulation or retained in the periphery of cancer blood vessels rather than infiltrating in the cancer tissue[155,156]. Additionally, the surface charge of nanoparticles has a great impact on their cancer distribution, and neutral or slightly negative charges are favorable in preventing recognition and phagocytosis by the mononuclear-phagocyte system[153]. Modification of nanoparticle structures with biocompatible polymers, such as *N*-(2-hydroxypropyl) methacrylamide (HPMA) or polyethylene glycol (PEG), has been shown to enhance cancer accumulation[157-159]. Nanoparticles with high aspect ratios and low surface curvature have been demonstrated to improve cancer enrichment[160].

However, the complexity and heterogeneity of the TME have hampered the practical application of passive targeting strategies. The abnormal cancer vasculature, a high interstitial pressure, and heterogeneous blood flow result in pronounced variabilities in the EPR effect between patients, cancer types, and cancer stages (primary versus metastatic); therefore, the therapeutic efficacy of drugs in Nano-DDSs cannot be accurately predicted or translated from animal models into individual patients[161,162]. Active targeting or TME-responsive strategies have been developed for advanced Nano-DDSs. Commonly used active targeting moieties include folic acid, targeting peptides (*e.g.*, arginylglycylaspartic acid (RGD), cyclic RGD peptide (cRGD), internalizing RGD peptide (iRGD)), and hyaluronic acid. Recent advances in biomimetic approaches, primarily based on biological membranes, have also significantly improved the drug delivery efficiency[22,23,163]. For instance, coating of nanoparticles with red blood cell membranes improves their blood half-life, and coating with cancer cell membranes enhances the targeting efficiency *via* their homing effect[164].

"Hitchhiking" strategies have been developed by leveraging inherent physiological characteristics of cells, effectively overcoming limitations of the EPR effect. Stimuli-responsive strategies are developed by exploiting the TME characteristics of cancer tissues compared to normal tissues, and stimuli-responsive Nano-DDSs can respond to the TME characteristics, such as acidic pH, a high glutathione (GSH) level, excess ROS, hypoxia, and overexpressed enzymes, thereby improving drug distribution and controlled release profiles[165]. Strategies of controlled and precise drug release can also be realized through responding to external stimuli such as light, magnetic fields, ultrasound, and electric fields. Beyond controlled release, stimuli-responsive Nano-DDSs can also maximize their intra-cancer distribution *via* light or magnetism-guided delivery, improve cancer penetration *via* responsive charge inversion or size changes, and enhance their cancer retention through responsive *in vivo* assembly[166-168].

Overall, unique characteristics of cancer tissues and their microenvironment are gradually deciphered through advances in biological sciences, and they have been harnessed for the development of potent Nano-DDSs. During the development of Nano-DDSs for cancer treatment, accumulation, penetration, internalization, drug release, retention, and self-degradation should be comprehensively considered. Integration of nanocarrier characteristics with therapeutic needs for simultaneous loading and synergistic treatment *via* multiple drugs could be realized *via* a single Nano-DDS[169-171].

3.2. Classification of Nano-DDSs targeting cancer cell senescence characteristics

In recent years, Nano-DDSs have been developed to target cancer cell senescence characteristics. These nanosystems have demonstrated significant potential in reducing systemic toxicity of traditional senescence-associated drugs, and they provide a new perspective for addressing cancer resistance[172,173]. To systematically elaborate design principles, therapeutic effects, and clinical application of Nano-DDSs targeting cancer cell senescence, we categorize these Nano-DDSs into organic materials, inorganic

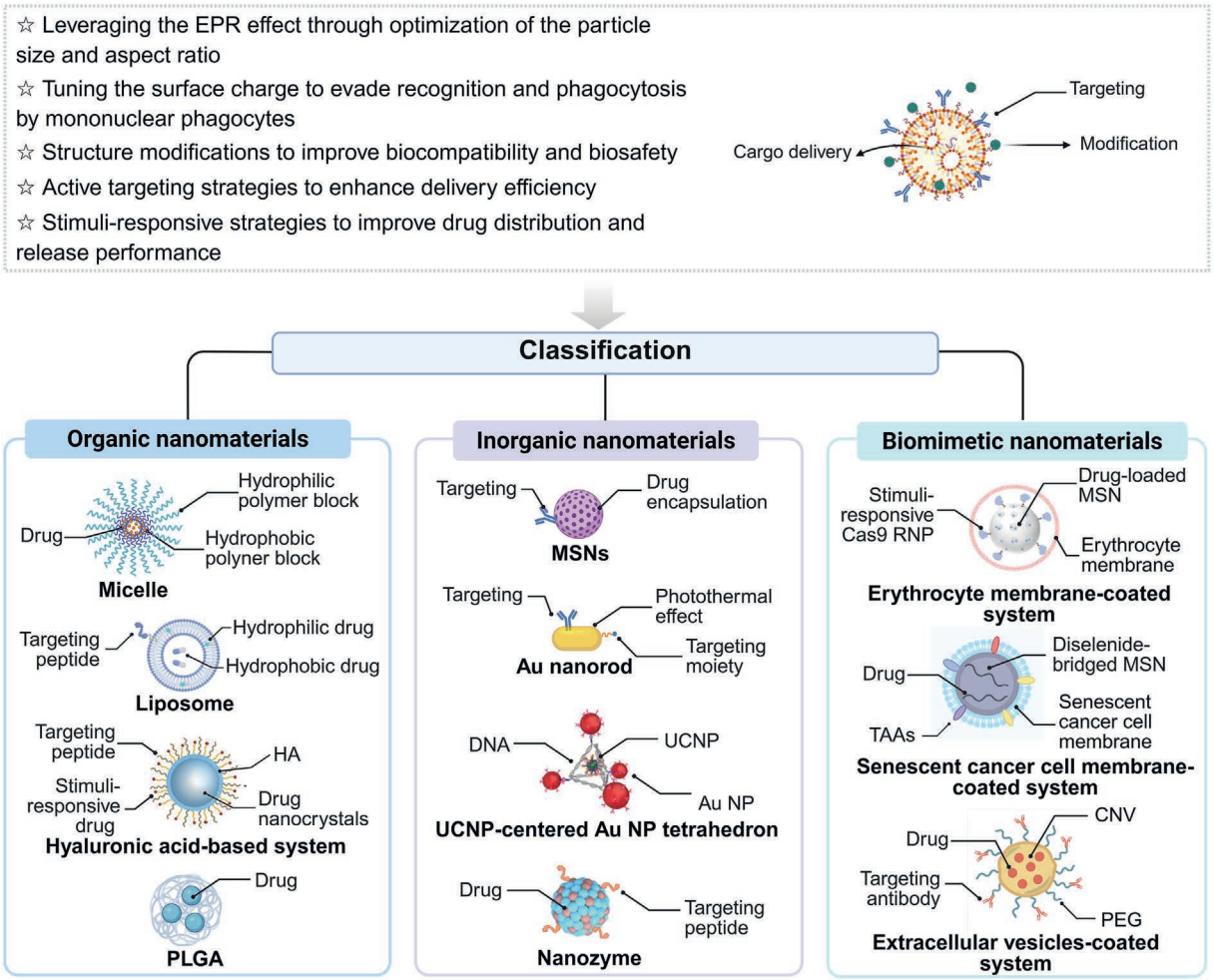

Figure 4 Design principles and classification of Nano-DDSs targeting senescence in the cancer microenvironment. Hyaluronic acid (HA), poly (lactic-*co*-glycolic acid) (PLGA), mesoporous silica nanoparticles (MSNs), upconversion nanoparticles (UCNPs), nanoparticle (NP), Cas9 ribonucleoprotein (Cas9 RNP), tumor-associated antigens (TAAs), curcuma-derived extracellular vesicles (CNVs), polyethylene glycol (PEG). Created with BioRender.com.

materials, and biomimetic materials based on the type of the core nanocarrier material[144].

3.2.1. Organic systems

Organic nanomaterials have exceptional biocompatibility, and they hold distinct drug delivery advantages. Among these organic nanomaterials, polymer micelles, a typical self-assembled organic nanocarrier, are used to load drugs through hydrophobic-hydrophilic interactions of amphiphilic polymers. Covalent bonds are also employed in polymeric micelles to attach functional groups for targeted delivery, rapid drug release, and self-degradation[174]. For example, Magkouta et al. encapsulated dasatinib linked to a lipofuscin-binding domain (LBD) in a polymer micelle (PEO-*b*-PCL), resulting in a nanomedicine, mGL392. In senescent tissues, an acidic environment triggered rapid degradation of mGL392 to expose LBD, which binds to lipofuscin. Meanwhile, through the catalysis of intracellular esterases, dasatinib was released from the polymer micelle, selectively eliminating Palbociclib (Pal)-induced senescent cancer cells in mice[175].

Liposomes (LP) are defined as a closed vesicular system with an aqueous core and a lipid bilayer. They have advantages such as biocompatibility, biodegradability, and pH/enzyme-triggered release; more importantly, they can be used for co-delivery of multiple drugs[176]. For instance, Tang et al. designed a pH-sensitive liposome-based co-delivery system (pSL) to simultaneously deliver Gemcitabine and Zebularine, overcoming cytidine deaminase-dependent drug resistance in pancreatic cancer[177]. In addition, Fan et al. developed a cRGD peptide-modified liposome system, Aur/Pal@LPT, to target $\alpha v\beta 3$ integrin-overexpressing melanoma. Aur/Pal@LPT co-delivered a CDK4/6 inhibitor, Pal, and a ferroptosis inducer, auranofin (Aur), to achieve synergistic ferroptosis through oxidative imbalance following cancer cell senescence induction[178].

Hyaluronic acid (HA), a natural polysaccharide and a key component of the extracellular matrix, offers excellent biocompatibility, non-immunogenicity, and modifiability. It can specifically bind to CD44 on cancer cell surfaces, and it is often employed for cancer targeting. Liang et al. incorporated HA into a micelle loaded with doxorubicin (DOX) and cancer-associated fibroblast (CAF)-sensitive peptides, resulting in HSD-P@V. It was a dual-targeting system for both cancer cells and CAFs. This approach simultaneously targeted cancer-induced senescence and inhibited the accumulation of senescent CAFs (SC CAFs) and their associated detrimental byproducts[179].

Since its approval by the U.S. Food and Drug Administration, poly(lactic-*co*-glycolic acid) (PLGA) has been extensively studied due to its excellent sustained-release property and clinical translatability. It has been used to load a couple of senolytic drugs, such as ABT-263 and $p16^{INK4a}$, and the PLGA-based Nano-DDS has demonstrated prolonged anti-cancer effects in rat models through targeting senescence[180].

Overall, organic nanomaterials exhibit excellent biocompatibility and functionalizability. Standardized production processes and safety evaluation systems could be established for organic Nano-DDSs to accelerate their clinical translation in targeting cellular senescence[181].

3.2.2. Inorganic systems

Inorganic nanomaterials are employed for efficient drug delivery due to their uniform size and stable physicochemical properties. Their poor biocompatibility is often enhanced through functionalization with organic materials, integrating the advantages of both organic and inorganic systems.

Mesoporous silica nanoparticles (MSNs) are the most widely used carriers, and they have a high porosity, a large drug-loading capacity, and facile surface modifiability[182]. They have been employed to construct Nano-DDSs targeting cancer cell senescence. For example, MSNs modified with galactooligosaccharides were used to target senescent cells overexpressing SA-β-Gal and deliver DOX and Navitoclax/ABT-263 (NAV)[183,184]. Shi et al.[185] utilized MSNs to load azidothymidine (AZT) and conjugated Cas9 ribonucleoprotein (RNP) complexes to MSNs to induce senescence and apoptosis in cancer cells *via* CRISPR-mediated gene editing. Functionalized MSNs with a positive charge have also been reported to electrostatically adsorb genetic materials, enabling targeted siRNA delivery for epigenetic regulation and enhancing the efficacy of senescence inducers. For instance, Yang et al.[186] developed HA-modified liposome-coated MSNs (HLMN@DOX/R). The modified MSNs were efficiently loaded with both siRNA and DOX, and achieved cancer-targeting delivery, overcoming DOX resistance in breast cancer[185,186].

In contrast, metal nanoparticles, such as gold nanorods and upconversion materials, possess unique photothermal, electromagnetic properties, broadening the application of inorganic nanomaterials. Lu et al.[187] functionalized gold nanorods with anti-β-2-microglobulin (B2M) antibodies and leveraged surface plasmon resonance effects to specifically target and bind to B2M overexpressed on the surface of SNCs. Additionally, triphenylphosphine was introduced to the gold nanorods to target mitochondria through electrostatic interactions[187,188]. Under near-infrared (NIR) irradiation, photothermal effects were generated by gold nanorods to induce mitochondrial dysfunction and subsequently trigger apoptosis in SNCs. Furthermore, upconversion nanoparticles (UCNPs) converted NIR to high-energy visible/ultraviolet light *via* a multiphoton process, and the visible/ultraviolet light exhibited a deep tissue penetration ability and tunable multicolor properties[189]. Qu et al. self-assembled anti-B2M antibody-modified gold nanoparticles with UCNPs into a stable tetrahedral structure, and loaded senolytic Granzyme B *via* boronate ester linkage onto the tetrahedral structure. This Nano-DDS achieved controlled clearance of DOX-induced senescent IMR-90 cells and real-time monitoring of apoptosis *via* changes in the fluorescence signal[190].

Artificial nanocatalysts are synthetic nanomaterials that have enzyme-like activity or mimic enzymatic functions. DDSs derived from nanocatalysts can activate/inhibit multi-enzyme-mediated pathways for the elimination of senescent cancer cells. For instance, Zhao et al.[191] utilized Mo_4VC_4 nanocatalysts as carriers to load a CDK4/6 inhibitor, Pal, and modified the nanocalysts with Arg-Gly-Asp (RGD) peptides to construct the MVPR system. This system induced GSH depletion and ROS production through peroxidase-like enzymatic activity to exacerbate oxidative stress induced by Pal in senescent cancer cells, ultimately leading to cell apoptosis.

In summary, inorganic nanomaterials, with their unique physicochemical properties, have been extensively explored for drug delivery. Their uniform size, stable characteristics, and multifunctionality have been leveraged for targeted drug delivery, SNC clearance, and photothermal/photodynamic therapy. Functionalization strategies, such as organic material modifications, have significantly improved their biocompatibility and *in vivo* metabolism. However, long-term toxicity, degradation pathways, and clinical translation of inorganic nanomaterials remain to be addressed before they are applied as precision medicine for anti-cancer therapies.

3.2.3. Biomimetic systems

Biomimetic materials are a class of materials that are derived from natural substances or mimic distinct characteristics and functions of biological systems. Currently, biomimetic materials for anti-cancer therapy are primarily created by extracting cell membranes from various cells, such as red blood cells, white blood cells, cancer cells, and platelets, and they are used as a coating layer on different types of nanoparticles. This cell membrane coating strategy preserves natural recognition functions of surface proteins or functional moieties on the membrane, and has advantages such as immune evasion, homologous targeting, and prolonged circulation. This approach has been widely used in the design of nanodrugs for targeting cellular senescence[192].

For example, CD47 on the surface of erythrocyte membranes (EMs) enables evasion of recognition by the reticuloendothelial system (RES)[193]. Shi et al. used EMs to coat MSNs and designed a TME-responsive E@M-A/RNP system for the delivery of adenine nucleotide translocator (ANT) and Cas9 ribonucleoprotein (Cas9 RNP)[185,194]. This Nano-DDS significantly reduced off-target effects of senescence-inducing drugs, prevented their damage to major organs, including the liver, spleen, and kidneys, and mitigated hemolysis observed for uncoated controls. Moreover, genetically engineered cell membranes expressing specific antigens or antibodies can allow dual targeting. For instance, Jian et al.[195] transfected 4T1 breast cancer cells to generate FAP-α, scFv-expressing FAP-CAR-4T1 cells. Membrane vesicles isolated from these cells were used to coat PLGA nanoparticles loaded with nintedanib and ABT-263 to construct a biomimetic nanoplatform, FAP-CAR-CM@PLGA-AB NPs. This platform achieved dual targeting of CAFs and senescent CAFs, remodeled the cancer immune microenvironment, and exhibited promising anti-cancer efficacy when combined with radiotherapy.

Additionally, antigenic properties of cell membranes can be exploited to synthesize immunotherapeutic nanodrugs to activate the immune system for anti-cancer effects. Since senescent cancer cell membranes have abundant tumor-associated antigens (TAAs) and immunogenic SASPs, Yang et al. developed SCCM@NA by coating MSNs with senescent cancer cell membranes and loading them with an immune adjuvant, oligodeoxynucleotide (CpG). Treatment with SCCM@NA significantly increased the expression of co-stimulatory markers, including CD80, CD86, and CD40 on DCs and induced the secretion of cancer necrosis factor-alpha

(TNF-α) and IL-6 at a high level. Moreover, SCCM@NA helped reduce the ratios of M2 macrophages and Tregs in the TME to the lowest level, demonstrating immunostimulatory advantages of senescent cancer cell membranes[196].

Compared to the strategy of engineering cell membranes, extracellular vesicles, natural endogenous nanocarriers, play a crucial role in cell communication and senescence regulation due to their intrinsic bioactive molecules, such as proteins, miRNAs, and lipids. For instance, Guo et al.[197] utilized curcuma-derived extracellular vesicles (CNVs) as nanocarriers, modified them with antibodies targeting death receptor 5 (DR5), and loaded them with DOX to construct DR5-CNV/DOX. This Nano-DDS precisely targeted DR5-overexpressing senescent cancer cells. Additionally, curcumin within the CNVs inhibited the secretion of pro-inflammatory SASPs.

Biomimetic systems constructed through coating biomimetic materials onto nanoparticles can effectively overcome the limitations of biocompatibility and targeting of nanoparticles. The use of senescent cell membrane components and intrinsic extracellular vesicle contents can exert anti-cancer and senescence-regulating effects. Therefore, biomimetic nanoparticles have great potential in therapies targeting cellular senescence characteristics. However, these innovative strategies are in the development and validation stages. To successfully enter clinical settings, developing technologies for large-scale effective extraction and functionalization of cell membranes, enhancing nanoparticle stability and targeting efficiency, maintaining long-term clinical stability, and thoroughly evaluating long-term biosafety should be addressed for the biomimetic system[195,198,199].

4. Advances of anti-cancer Nano-DDSs targeting cellular senescence

Nano-DDSs have been developed and applied in targeting cellular senescence as an anticancer therapeutic approach. We will elaborate on innovative strategies of harnessing cellular senescence characteristics to elegantly design Nano-DDSs and smartly apply them for treating various types of cancer in this section. We review recent advances in using Nano-DDSs to tackle cancer and the TME, including immunity, metabolism, and the extracellular matrix (Table 2[178,179,196,200-208]), by leveraging senescence characteristics. These Nano-DDSs have displayed their anti-cancer effects by precisely targeting and modulating senescence-associated pathways, such as directly inducing cancer cell senescence to prevent cancer progression, eliminating cancers through metabolic disturbances, and regulating immunity and the TME to suppress cancer growth (Fig. 5).

4.1. Nano-DDSs for cellular senescence acting on cancer progression

Inducing senescence can drive cancer cells into cell cycle arrest, thus preventing cancer progression, and the senescence-inducing strategy has been extensively explored for cancer treatment[209]. Conventional radiation or chemotherapy-induced senescence has been shown to be ineffective because these therapeutic modalities can induce senescence of non-target cells and/or yield insufficient senescence in cancer cell populations within the TME[210]. Therefore, targeted Nano-DDSs have been explored to enhance the efficiency of senescence induction.

Telomerase, a ribonucleoprotein complex composed of telomerase reverse transcriptase (TERT) and a telomerase RNA component, plays a crucial role in alleviating replicative senescence by extending telomeres and preventing their shortening[211]. In cancer cells, a high expression level of TERT maintains the telomere length, thereby supporting continuous cell proliferation. It has been discovered that CRISPR-Cas9-mediated TERT gene inactivation can accelerate cancer cell senescence and exhibit distinct anti-cancer effects[212], while there is a low gene-editing efficiency in solid cancer because of delivery barriers[193,213,214]. Shi et al.[185] designed a red blood cell membrane (EM)-coated Nano-DDS (E@M-A/RNP) for controlled release of AZT and Cas9 RNP in the TME. AZT was loaded into mesoporous silica to form M-A nanoparticles, and Cas9 RNP was coupled to M-A *via* a disulfide bond linker, creating an M-A/RNP complex. The outer layer of the M-A/RNP complex was coated with EM to construct E@M-A/RNP nanoparticles. The fluorescence intensity of Cas9 RNP released from E@M-A/RNP was positively correlated with the GSH level. After exposure to a high GSH concentration in the TME, GSH-responsive controlled release of Cas9 RNP was confirmed. AZT released from E@M-A/RNP inhibited telomere replication and enhanced the efficiency of Cas9 RNP gene editing. The gene editing efficiency of the E@M-A/RNP group reached 38.1%, and more than 80% of the telomerase activity was inhibited. The E@M-A/RNP group significantly outperformed single treatment groups (E@M-RNP or E@M-A), and it displayed a synergistic effect of AZT and Cas9 RNP[200].

Additionally, Nano-DDSs for inducing senescence have been demonstrated to overcome limitations of conventional chemotherapy[54]. All-trans retinoic acid (ATRA) induces cancer cell senescence by activating retinoic acid receptors (RAR). ATRA self-assembled into pH-sensitive amphiphilic dextran-retinal (DR) micelles after coupling with dextran *via* hydrazone bonds[215]. Zhang et al.[201] incorporated DOX into the DR micelles to enhance the chemotherapeutic effects of DOX and reduce its side effects by inducing cancer cell senescence. In an acidic endosomal/lysosomal environment, the hydrazone bonds of the micelles were cleaved, leading to micelle disassembly and rapid release of ATRA and DOX. mRNA expression analysis revealed that ATRA upregulated the expression of p21 *via* the RAR signaling pathway to induce cell cycle arrest at the G0/G1 phase, thus promoting cell senescence in MCF-7 breast cancer cells and significantly enhancing DOX-induced cancer cell apoptosis. *In vivo* fluorescence imaging supported that the DOX-loaded DR micelles incorporated with indocyanine green (ICG) exhibited a fluorescence intensity approximately 10 times higher than free ICG at the cancer site. *In vivo* efficacy assessments revealed that, compared to free DOX, the DOX-loaded DR micelle group significantly improved the survival rate up to 3 weeks and had a remarkably shrunk cancer volume. Moreover, damage to heart and kidney tissues in the DOX-loaded DR micelle group was significantly reduced, confirming that this novel nano-delivery platform can enhance the therapeutic efficacy and biosafety of a drug through a synergistic effect of targeted delivery and senescence induction.

The "one-two punch" strategy offers promise for precision cancer therapy through senescence induction. In this strategy, a senescence inducer is initially applied to trigger cancer cell senescence, and a senolytic drug is subsequently used to eliminate senescent cancer cells; therefore, this strategy can mitigate the negative effects of SASP accumulation, such as inflammation and tissue aging. The "one-two punch" strategy has been extensively investigated, and it is currently under clinical investigation.

Table 2 Nano-DDSs targeting cellular senescence for tumor therapy.

Targeting mechanism	Name	Nanomaterial type	Drug loading and release	Cancer model	Efficacy metrics	Ref.
Target tumor progression	E@M-A/RNP	Biomimetic nanomaterial	Drug loading rate: 33.2%; Cumulative rates of drug release: 72.1%	Lung adenocarcinoma	E@MA/RNP achieves 37.0% gene editing efficiency and potent antitumor efficacy with high biosafety through azidothymidine-clustered regularly interspaced short palindromic repeats synergy	200
	DD-micelles	Organic nanomaterial	Encapsulation efficiency: ~73.4%, drug loading rate: 12.4%; Cumulative rates of drug release: 100%	Breast adenocarcinoma	It markedly suppresses tumor growth, extends mouse survival, and synergistically triggers both senescence and apoptosis	201
	Gal-NP	Inorganic nanomaterial	Cumulative rates of drug release: ~100%	Triple-negative breast cancer	Gal-NP enhances senolytic efficacy and reduces systemic toxicity through enzyme-controlled targeted release, effectively inhibiting tumor growth and metastasis	202
	Ba SAzyme	Inorganic nanomaterial	–	Lung adenocarcinoma	The "one-two punch" strategy of Ba SAzyme and anti-programmed cell death ligand 1 enables potent suppression of both primary and distant tumors, leading to extended survival	203
Target tumor metabolism	Aur/Pal@LPT	Organic nanomaterial	Drug loading rate for Aur: 2.5 %, for Pal: 5.8%	Melanoma	Aur/Pal@LPT overcomes melanoma treatment resistance by synergistically enhancing ferroptosis through senescence induction and antioxidant depletion	178
	AZT-P/pyro NCP	Inorganic nanomaterial	Encapsulation efficiency: 50.2%, drug loading rate: 7.1%; Cumulative rates of drug release: 79.2%	Triple-negative breast cancer	AZT-P/pyro NCP achieved tumor growth inhibition values of 98.1% and 96.0% against subcutaneous and orthotopic breast tumors, respectively	204
Target tumor immunization	AX@NPs-FA/ AbCD47	Organic nanomaterial	Encapsulation efficiencies for AZD8055: 83.5%, for XL413: 75.1% Cumulative rates of drug release (Ph = 6): for AZD8055: ~90%, for XL413: ~85%	Liver cancer	AX@NPs-FA/ AbCD47 for synergistic senescence-immunotherapy in hepatocellular carcinoma *via* dual targeting and sequential release	205,206

(*continued on next page*)

Table 2 (*continued*)

Targeting mechanism	Name	Nanomaterial type	Drug loading and release	Cancer model	Efficacy metrics	Ref.
	NPs	Organic nanomaterial	–	Pancreatic cancer	Immuno-NPs drive T cell/interferon-mediated tumor regression and prolonged survival in pancreatic ductal adenocarcinoma models	207
	SCCM@NA	Biomimetic nanomaterial	Drug loading rate: 1%	Melanoma	SCCM@NA potently activates dendritic cells, targets lymph nodes, and enhances antitumor immunity with improved efficacy and reduced toxicity in melanoma	196
Target tumor microenvironment	HSD-P@V	Organic nanomaterial	Drug loading rate for Val: ~57.28%, for Dox: ~2.14%; Cumulative rates of drug release: ~90%	Triple-negative breast cancer	HSD-P@V significantly inhibited tumor growth and lung metastasis, thereby extending the survival of tumor-bearing mice	179
	FAP-CAR-CM@PLGA-AB NPs	Biomimetic nanomaterial	Encapsulation efficiency: ~36.4% for ABT-263 and ~18.2% for nintedanib; Cumulative rates of drug release: ~41.5% for ABT-263 and ~49.0% for nintedanib	Triple-negative breast cancer	The dual clearance of cancer-associated fibroblasts and senescent cancer-associated fibroblasts by FAP-CAR-CM@PLGA-AB NPs reversed radiation resistance and immunosuppression, resulting in 86.7% tumor suppression	208

However, nonspecific distribution of senescence inducers and senolytic drugs may result in moderate cancer cell clearance and strong systemic toxicity due to off-target effects. Nonspecific distribution may be mitigated through the use of precisely targeted Nano-DDSs. Galiana et al. used a CDK4/6 inhibitor (Pal) to induce cancer cell senescence in mice and released navitoclax from a Nano-DDS to SNCs to reduce systemic toxicity[202]. *S*A-β-Gal-responsive mesoporous silica nanoparticles (Gal-NPs) were developed to encapsulate navitoclax. The galactooligosaccharide-terminated structure of Gal-NP was hydrolyzed by highly expressed *S*A-β-Gal in SNCs, triggering specific drug release. Experimental results confirmed that Gal-NPs loaded with ICG abundantly accumulated at the cancer site of Pal-treated mice within 24 h, evidenced by a strong fluorescence signal, while the control group displayed weak fluorescence signal slightly above background noises, confirming the targeting specificity of the Nano-DDS for SNCs. *In vivo* experiments demonstrated that, in the combination therapy group (Pal + Gal-NPs), the cancer volume was significantly reduced, and all mice survived up to the experimental endpoint, while in the Pal + free navitoclax group, early death was noticed. Additionally, mice in the free navitoclax group experienced a significant weight loss and a substantial decrease in the platelet count, while the Gal-NPs group exhibited a slight reduction in the weight and the platelet count, indicating that the Nano-DDS significantly reduced the systemic toxicity of navitoclax. It has been noted that oral administration of Pal may not adequately induce cancer cells into senescence. Smart integration of both senescence inducers and senolytic drugs in one single Nano-DDS and sequential release of them at the cancer site could optimize the senescence induction efficiency and enhance their anti-cancer efficacy.

To address synergistic limitations of the "one-two punch" strategy, Zhang et al.[203] combined α-emitting radionuclide, ^{223}Ra, with Ba, a single-atom nanozyme (SAzyme), creating ^{223}Ra/Ba SAzyme with enzyme-like activities. ^{223}Ra/Ba SAzyme induced DNA damage through localized energy deposition, and it exhibited enzymatic activities, including catalase (CAT) and peroxidase (POD), to regulate the level of ROS. Dual functionalities of ^{223}Ra/Ba SAzyme led to both cancer cell senescence induction and the clearance of SNCs. *In vitro* experiments showed that ^{223}Ra/Ba SAzyme significantly increased the G2 phase population in Lewis lung carcinoma (LLC) cells, confirming effective induction of cell senescence. *In vivo* SPECT/CT imaging and γ-counting analysis revealed that ^{223}Ra/Ba SAzyme maintained a high concentration

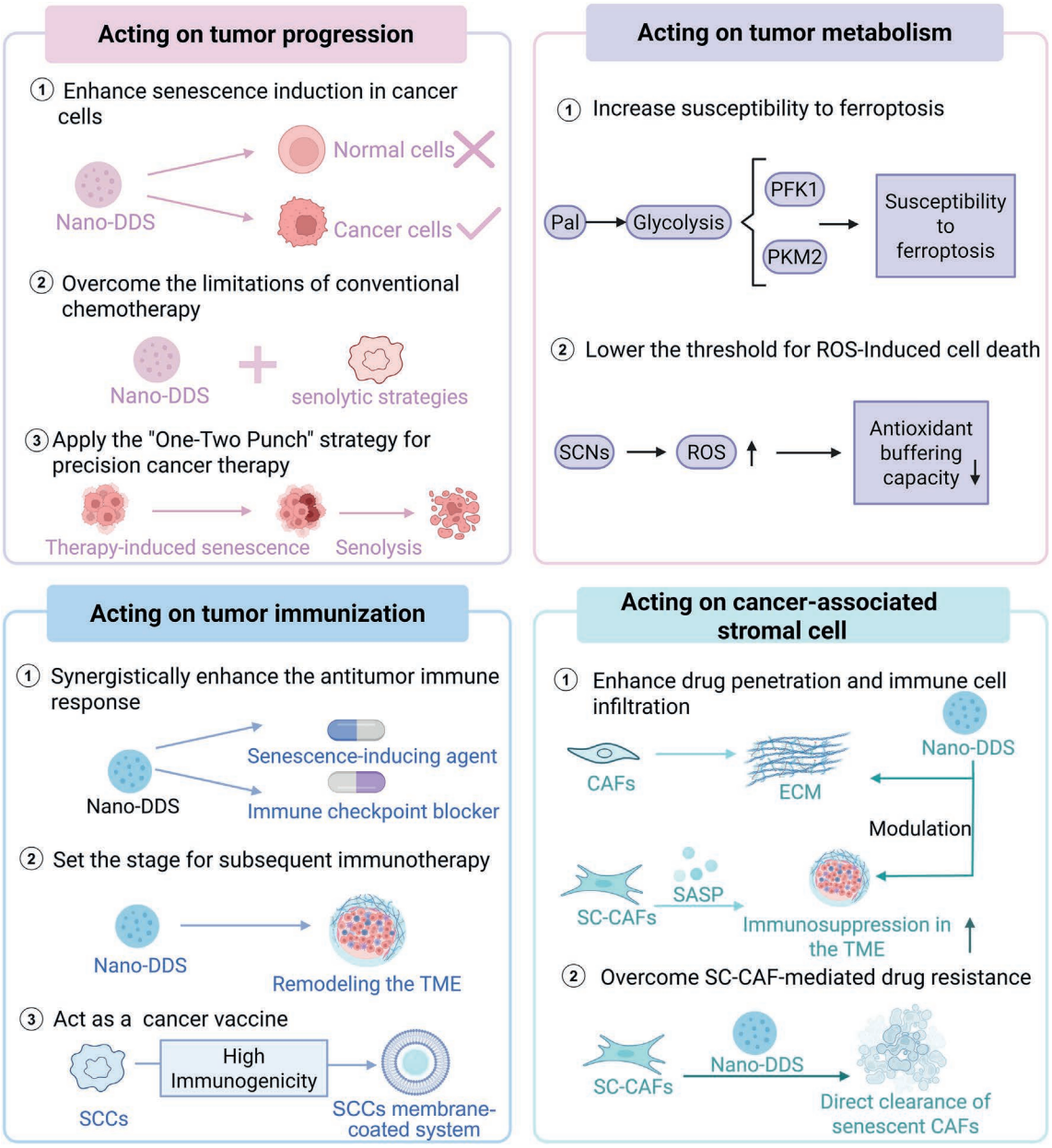

Figure 5 Strategies of nanotechnology-aided targeting of senescence pathways in anti-cancer therapy. Nano-DDSs can specifically target senescence-associated signaling pathways, exerting anti-cancer effects through four core strategies: directly inducing cancer cell senescence, mediating metabolic interventions to eliminate cancer cells, and regulating cancer immunity and the TME. Nano-drug delivery systems (Nano-DDSs), palbociclib (Pal), phosphofructokinase 1 (PFK1), pyruvate kinase M2 (PKM2), senescent cells (SNCs), reactive oxygen species (ROS), senescent cancer cells (SCCs), tumor microenvironment (TME), cancer-associated fibroblast (CAF), extracellular matrix (ECM), senescent cancer-associated fibroblasts (SC-CAFs). Created with BioRender.com.

at the cancer site for up to 4 h, and treatment with ^{223}Ra/Ba SAzyme resulted in dose-dependent inhibition of cancer growth and characteristic apoptosis features, such as nuclear fragmentation and dissolution, indicating ROS-mediated clearance of senescent cancer cells. Furthermore, PD-L1 immune checkpoint blockade therapy was introduced in this study to eliminate SNCs. In a bilateral cancer model, the combination therapy group (^{223}Ra/Ba SAzyme + PD-L1 blockade) significantly inhibited both primary and distant cancer growth, extending mouse survival. This breakthrough study using α-emitting radionuclides could inspire the development of more effective and precise radionuclide-derived nanomedicines for senescence-based cancer therapy (Fig. 6).

4.2. Nano-DDSs for cellular senescence acting on cancer metabolism

Aging leads to metabolic abnormalities in cancer cells, including disruptions in energy metabolism and the redox system. Nano-DDSs have been developed for targeting metabolic vulnerabilities of senescent cancer cells. Ferroptosis, an iron-dependent form of lipid peroxidation-induced cell death, has recently gained

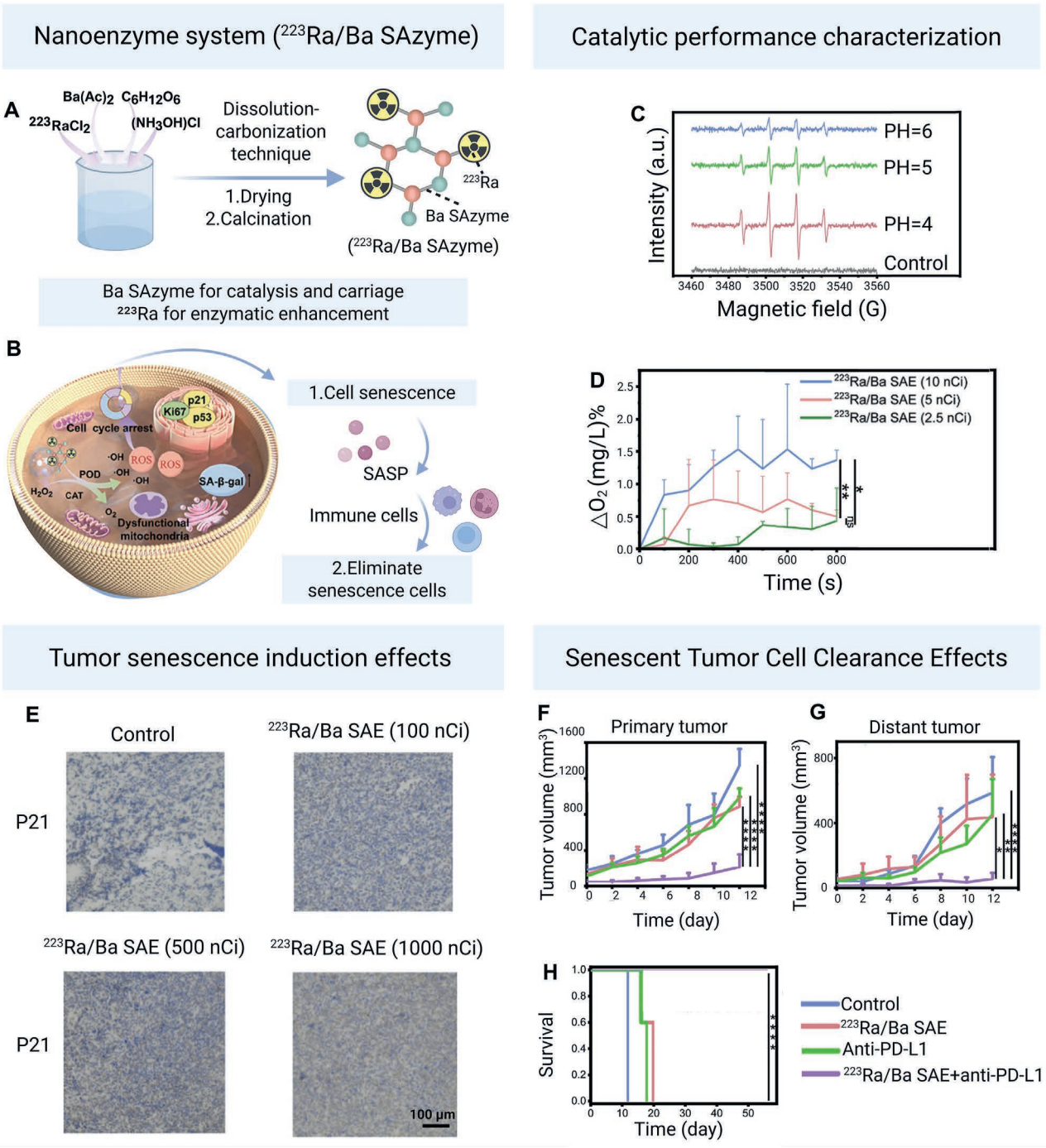

Figure 6 Application of Nano-DDSs in targeting cellular senescence to regulate cancer progression. (A) Schematic diagram of the preparation process of ^{223}Ra/Ba SAzyme. (B) ^{223}Ra/Ba SAzyme exhibited significant POD-like and CAT-like dual enzyme mimicking activities and efficiently catalyzed the generation of ROS, which induced cancer cell senescence and enhanced anti-cancer immune responses, ultimately leading to the clearance of senescent cells. (C) ESR spectra to detect the generation of ·OH free radicals. (D) Oxygen (O_2) production catalyzed by different doses of ^{223}Ra/Ba SAzyme. (E) Qualitative detection results of a senescence marker protein, p21. (F, G) Average growth curves of primary and distal tumors. (H) Kaplan-Meier survival curve analysis of mice in different treatment groups. Single-atom nanozyme (SAzyme), catalase (CAT), peroxidase (POD), senescence-associated β-galactosidase (SA-β-Gal), antigen Kiel-67 (ki67), tunor protein p53 (p53), cyclin-dependent kinase inhibitor 1A (p21), reactive oxygen species (ROS), senescence-associated secretory phenotype (SASP), and electron spin resonance (ESR). Adopted with permission from Ref. 203, copyright © 2024 Elsevier Ltd. All rights are reserved, including those for text and data mining, AI training, and similar technologies.

extensive attention in cancer therapy[216,217]. Unfortunately, GSH and reduced NADPH in the TME remarkably weaken the generation of toxic oxidized lipids and reactive ROS, and they contribute to resistance to ferroptosis in malignant cancers such as melanoma[218]. It has been shown that CDK4/6 inhibitors (*e.g.*, Pal) can enhance the activity of phosphofructokinase 1 (PFK1) and pyruvate kinase M2 (PKM2) in SNCs during glycolysis, accelerating the depletion of GSH and NADPH, thus cells become susceptible to ferroptosis. Fan et al.[178] developed a targeted liposomal nanomedicine, Aur/Pal@LPT, to deliver Pal and a ferroptosis inducer, auranofin (Aur). Aur/Pal@LPT was modified with cRGD peptides, which targeted overexpressed αvβ3 integrins on melanoma cells. Pal and Aur were co-encapsulated in liposomes at a molar ratio of 3.7:1, and Aur/Pal@LPT displayed a synergistic effect with a combination index (CI) < 1. Pal induced cellular senescence, enhanced PFK1 and PKM2 activity to accelerate GSH and NADPH depletion, leading to elevated levels of GSH reduction products (*e.g.*, thioredoxin (Trx)) and lipid peroxidation products (*e.g.*, malondialdehyde (MDA)), thus enhancing Aur-induced ferroptosis[219]. Compared to control groups, Aur/Pal@LPT significantly inhibited cancer growth and extended mouse survival. Histological analysis of cancer sections revealed a marked decrease in the level of antioxidants and a significant increase in lipid peroxidation products, confirming successful induction of redox-based ferroptosis. Combination of a senescence-inducing drug with a ferroptosis inducer in a Nano-DDS in this study overcame ferroptosis resistance due to melanoma heterogeneity, which offers a novel approach to expanding senescence-based therapeutic strategies for anti-cancer treatment (Fig. 7).

SNCs maintain their metabolic activity while they are unable to proliferate. Therefore, an elevated level of accumulated ROS is seen in SNCs, which leads to a reduced antioxidant buffering capacity and a lowered ROS-induced death threshold[220]. To address this issue, Zhen et al. developed a nanoscale coordination polymer particle (AZT-P/pyro NCP) to deliver senescence-inducing azidothymidine monophosphate (AZT-P) and a photosensitizer, pyro, for photodynamic therapy (PDT). To construct AZT-P/pyro, Zn^{2+} was introduced to coordinate with the phosphate group of AZT-P to form a core that was responsive to an acidic TME. Upon 660 nm light irradiation, pyro co-assembled with cholesterol, 1,2-dioleyl-*sn*-glycero-3-phosphocholine (DOPC), and 1,2-distearoyl-*sn*-glycero-3-phosphoethanolamine-*N*-amino (polyethylene glycol)-2000 to form a lipid shell of AZT-P/pyro (pyro NCP), enhancing the passive targeting capacity of the nanoparticle. Under light irradiation, AZT-P/pyro significantly increased the levels of intracellular ROS and singlet oxygen, leading to a marked elevation of senescence markers such as telomere shortening, upregulation of p21, enhanced secretion of IL-6, and potent cytotoxicity to cancer cells. In a 4T1 breast cancer mouse model, AZT-P/pyro significantly promoted the polarization of cancer-associated macrophages toward the M1 phenotype, increased the proportion of mature dendritic cells, decreased the percentage of myeloid-derived suppressor cells (MDSCs), and enhanced the level of infiltration and biological function of cytotoxic T lymphocytes, resulting in effective suppression of both subcutaneous and orthotopic breast cancers with an inhibition rate of 98.1% and 96.0%, respectively. These results indicated that AZT-P/pyro not only significantly enhanced ROS-based anticancer efficacy of the photosensitizer but also remodeled the TME by synergistically inducing cell senescence and exerting photodynamic therapeutic action. This light-responsive Nano-DDS overcomes limitations of traditional PDT in cancer treatment by integrating senescence-induction and anticancer therapy[204].

4.3. Nano-DDSs for cellular senescence acting on cancer immunization

It has been shown that the senescence SASP can influence cancer immune clearance through immune recruitment or suppression. Meanwhile, SNCs can trigger host anticancer immune responses by altering surface receptors to stimulate the immune system. Nano-DDSs have been developed to target immune characteristics of cancer cell senescence to enhance the immune-stimulatory effects of SNCs[221]. Furthermore, targeted immunotherapy carriers have been prepared based on specific biomarkers of senescent cancer cells, which allow precise targeting of senescent cancer cells, enhance local immune cell infiltration, and minimize adverse effects on normal tissues[222]. However, there are challenging issues, including effectively combining immunotherapy with senescence induction and establishing the correlation between these two processes.

To leverage the impact of senescence on cellular immunogenicity, a strategy has been proposed to enhance anticancer immune responses by co-delivering senescence-inducing agents and immune checkpoint inhibitors through Nano-DDSs. For example, in HCC, CD47, an inhibitory immune checkpoint molecule, binds to the N-terminal region of the immune cell surface signal regulatory protein alpha (SIRPα) to transmit a "don't eat me" signal. A high expression level of CD47 in HCC promotes immune evasion[223]. Interestingly, solely blocking CD47 showed disappointing therapeutic effects and posed a risk of anemia[224]. Gong et al. analyzed the data from the TCGA database and identified that CDC7 and CD47 interact synergistically in HCC carcinogenesis. RNA sequencing of Bel-7402 cells and their chemotherapy-resistant cell lines revealed significant downregulation of senescence-associated genes (*e.g.*, TP53 and H2AX) and upregulation of CD47 in resistant cells. The result suggests that combined inhibition of CD47 and induction of senescence may mitigate chemotherapy resistance and improve therapeutic outcomes of CD47 blockade. To achieve combined inhibition of CD47 and induction of senescence, they designed a dual-targeted Nano-DDS, AX@NPs-FA/AbCD47. They prepared calcium phosphate liposomes, incorporated a CD47 inhibitor, AZD8055, on the liposome surface, and encapsulated a senescence inducer, XL413, inside the liposome. After modification with folic acid (FA) and anti-CD47 antibody (AbCD47), AX@NPs-FA/AbCD47 selectively targeted folate receptor 1 (FOLR1) overexpressed on HCC cells and blocked CD47 on cancer cell surfaces. In the acidic TME, XL413 on the surface and AZD8055 inside AX@NPs-FA/AbCD47 were released sequentially to induce cellular senescence and subsequently enhance immune responses. In a mouse HCC model, AX@NPs-FA/AbCD47 successfully downregulated CD47 and CDC7 and induced senescence, significantly inhibiting cancer growth. In chemotherapy-resistant HCC models, the Nano-DDS displayed a remarkable anticancer efficacy, with an inhibition rate of 85.15%. Additionally, in the AX@NPs-FA/AbCD47 group, the proportion of M1 macrophages in tumor-infiltrating lymphocytes (TILs) significantly increased, indicating that the Nano-DDS effectively promoted anticancer immune responses[205,206].

In addition to direct co-delivery of drugs, another strategy is to induce senescence and remodel the TME, creating a favorable microenvironment for subsequent immunotherapy. The STING pathway, a major regulator for type I interferon (IFN-I)

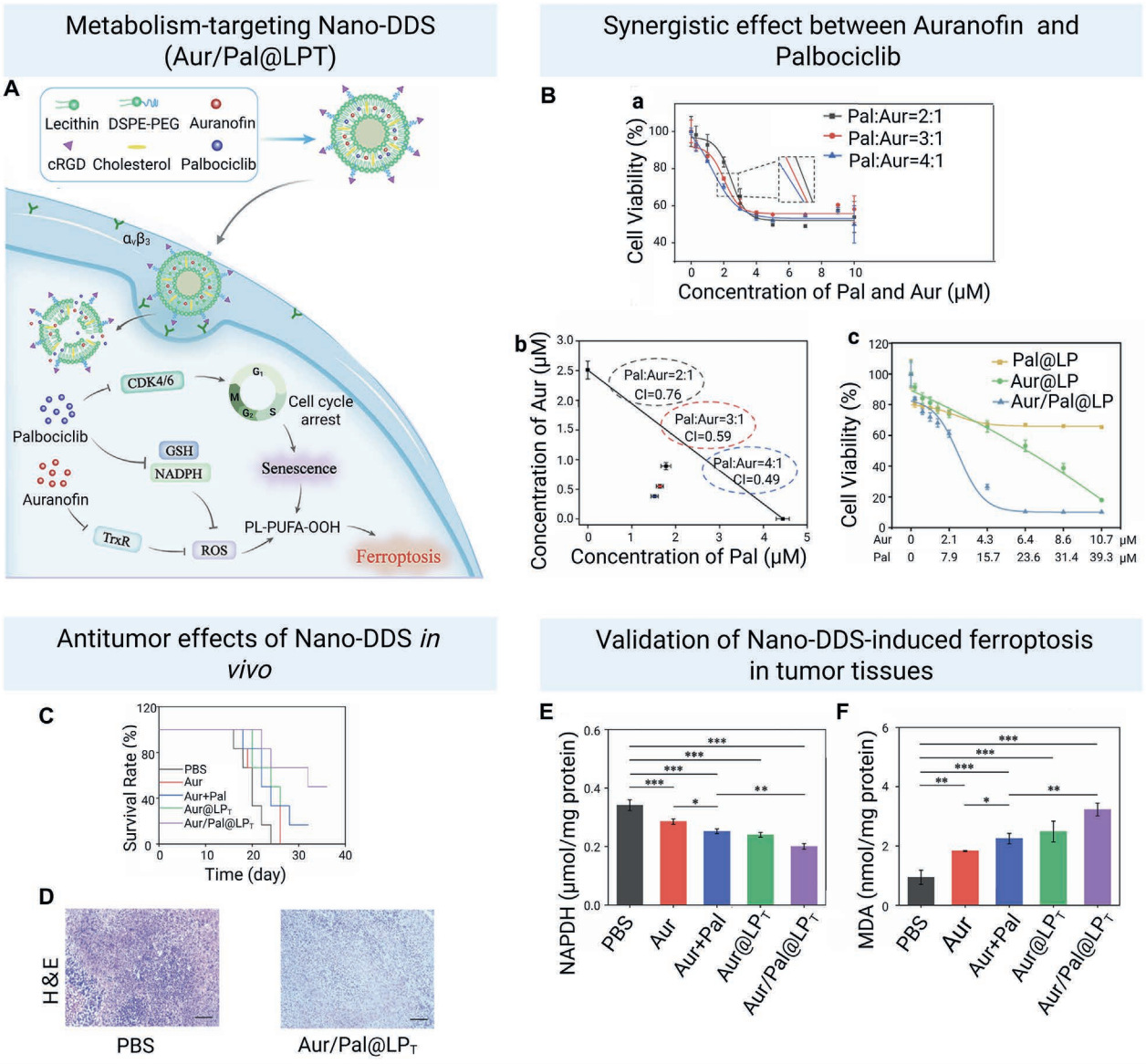

Figure 7 Application of Nano-DDSs in targeting cellular senescence by regulating cancer metabolism. (A) cRGD-modified liposomes co-loaded with a CDK4/6 inhibitor, Pal, and a ferroptosis inducer, finasteride, to generate Aur/Pal@LPT. cRGD with a high affinity to the $\alpha v\beta 3$ integrin on cancer cells was harnessed for active targeting delivery. Pal induced cellular senescence and depleted intracellular coenzymes (GSH and NADPH), and it synergized with finasteride to enhance melanoma cell sensitivity to ferroptosis. (B) a. Cell viability after combined treatment with Aur and Pal; b. CI of Aur and Pal based on IC_{50}, confirming a pronounced synergistic effect; c. Drug-loaded liposomes exhibited enhanced cytotoxicity. (C) Survival curves of mice treated with different formulation groups. (D) Endpoint cancer tissue sections stained with H&E (scale bar: 100 μm) and TUNEL (scale bar: 20 μm), indicating cancer cell apoptosis and tissue morphological changes. (E) Reduced nicotinamide adenine dinucleotide phosphate (NADPH), and (F) MDA in tumor tissues at the end of treatment. 1,2-distearoyl-snglycero-3-phosphoethanolamine-*N*-[methoxy(polyethyleneglycol) 2000] ammonium (DSPE-PEG2000), cyclic arginylglycylaspartic acid (cRGD), cyclin-dependent kinase 4 and 6 (CDK4/6), palbociclib (Pal), glutathione (GSH), nicotinamide adenine dinucleotide phosphate (NADPH), thioredoxin reductase (TrxR), reactive oxygen species (ROS), combined index (CI), malondialdehyde (MDA). Adopted with permission from Ref. 178, Copyright © 2024 American Chemical Society.

production, has become an important target for enhancing anti-cancer immune responses by NK cells and T cells[225]. The Toll-like receptor 4 (TLR4) agonist, monophosphoryl lipid A (MPLA), can activate NF-κB *via* a MyD88-dependent signaling pathway to induce the expression of inflammatory factors such as TNF-α and IL-12. These inflammatory factors amplify IFN-I signaling to promote the activation of dendritic cells (DCs) and macrophages, and IFN-I synergizes with STING agonists to enhance innate immune responses[225]. Chibaya et al.[207] utilized lipid nanoparticles (LNPs) to co-deliver a STING agonist, cyclic dinucleotide monophosphate (cGAMP), and a TLR4 agonist, MPLA. Inspiringly, a cancer cell senescence induction strategy was developed by combining a MEK inhibitor (trametinib (T)) and a CDK4/6 inhibitor Pal (P) into an oral T/P regimen. The oral administration induced cancer cell senescence, triggered SASP secretion, and remodeled the TME in pancreatic ductal

adenocarcinoma (PDAC). This approach improved vascular permeability, thereby overcoming fibrosis barriers and enhancing drug penetration. In addition, upregulation of major histocompatibility complex class I (MHC-I) antigen presentation enhanced anticancer immune responses. Experiments revealed that, after a 4-day T/P oral pre-treatment, PDAC-bearing mice exhibited a pronounced increase in the level of nanoparticle uptake by localized cancer cells, achieving remarkable cancer inhibition and prolonged survival. Furthermore, in a highly fibrotic *Trp53*$^{fl/wt}$ genetically engineered mouse model (GEMM), the T/P treatment improved nanoparticle penetration in the TME, which enhanced $CD8^+$ T cell and NK cell infiltration, supporting that this combined strategy can overcome fibrosis barriers[207].

Finally, senescent cancer cells can be employed as a source for cancer vaccines. Senescent cancer cells (SCCs) exhibit high immunogenicity, but a vaccine formulation from live SCCs contains the immune-suppressive SASP and carries carcinogenic risks[226,227]. To address these issues, Yang et al.[196] induced senescence in B16-OVA melanoma cells using DOX and isolated the SCC cell membrane (SCCM). The SCCM preserved a high expression level of MHC-I and cancer-specific antigens, and it eliminated the immune-suppressive effects of the SASP. The SCCM was used to coat mesoporous silica nanoparticles loaded with an immunoadjuvant, CpG, constructing a biomimetic cell nano-vaccine (SCCM@NA). SCCM@NA selectively retained immunogenic components and diminished SASP interference. Encouragingly, SCCM@NA was combined with the CpG adjuvant to enhance antigen-presenting cell (APC) activation and pro-inflammatory cytokine secretion. The $CD80^+$/$CD86^+$/$CD40^+$ expression increased by 1.5−2 times, and the TNF-α level increased by 50%. It also significantly improved the cytotoxic activity of $CD8^+$ T cells. Compared to the live SCC-based vaccine formulation, SCCM@NA showed a faster accumulation rate in lymph nodes, helped recruit a higher number of antigen-specific $CD8^+$ T cells, and, when combined with αPD-1, significantly prolonged mouse survival. Therefore, senescent cancer cell membrane-based nano-vaccines could be developed as an effective strategy for cancer immunotherapy (Fig. 8)[196].

4.4. Nano-DDSs for cellular senescence acting on cancer-associated stromal cells

In addition to immune cells in the TME, non-cancer cells, especially CAFs, play a critical role in cancer progression and treatment resistance[228,229]. CAFs secrete the ECM components to impair drug penetration and immune cell infiltration. Furthermore, treatment-induced SC-CAFs exacerbate the immunosuppressive TME through their unique SASP[226,230]. Therefore, Nano-DDSs have been employed to target cancer-associated stromal cells to remodel the TME *via* senescence strategies. For example, Liang et al. designed a CAF-triggered, structurally deformable Nano-DDS (HSD-P@V) to target CAFs and deliver valsartan (Val, a CAF modulator) and DOX into the cancer site. In this design, DOX was conjugated to HA *via* diselenide (Se−Se) bonds to form HA−Se−Se−DOX (HSD) micelles. The surface of the micelles was modified with CAF-sensitive peptides to form HSD-P. After grafting CAF-sensitive peptides onto the surface of valsartan nanocrystals (VNs), the HSD-P@V Nano-DDS exhibited enhanced stability and responsive drug release. Upon reaching the TME, HSD-P@V disassembled after exposure to CAFs and released Val to inhibit the CAF activity, resulting in pronounced reductions in TGF-β secretion and collagen expression. The reduction in collagen synthesis enhanced drug penetration. Subsequently, a high concentration of H_2O_2 in cancer cells triggered DOX release to induce cancer cell senescence and promote immune cell recruitment and activation *via* the SASP. The HSD-P@V group exhibited significantly deeper penetration of DOX into the cancer tissue, up to approximately 50 μm, compared to other groups, demonstrating enhanced drug permeability. Additionally, the proportion of $CD8^+$ T cells in the HSD-P@V group increased to 39.8% compared to 10.6% in the control group, and the proportion of NK cells rose from 1.01% to 5.76%, while the proportions of Tregs and MDSCs were significantly reduced. The apoptosis rate of cancer cells in the HSD-P@V group was highest ($45.43 \pm 2.58\%$), with a median survival time of 45 days, which was significantly longer than that of other groups. These results supported that HSD-P@V significantly remodeled the TME and suppressed cancer growth through its triple mechanisms of ECM degradation, senescence induction, and immune modulation (Fig. 9)[179].

More specific Nano-DDSs have been designed to directly eliminate SC CAFs and mitigate therapeutic resistance mediated by them. For example, in breast cancer radioresistance, radiation-induced SC CAFs exacerbate resistance by promoting cancer cell stemness conversion and immune suppression. To address this challenge, Jiang et al. designed a biomimetic core-shell nanoparticle, FAP-CAR-CM@PLGA-AB NP[208]. The nanoparticle consisted of a PLGA core, loaded with ABT-263 that targets Bcl-2 family proteins to selectively clear SC CAFs and Nintedanib that targets VEGFR/PDGFR to inhibit the CAF activity. This Nano-DDS was functionalized with 4T1 cell membranes with FAP-α scFv, which allows homologous targeting of cancer and specific binding to CAFs and SC-CAFs in the TME. *In vivo* experiments showed that the FAP-CAR-CM@PLGA-AB NP combined with radiotherapy achieved a cancer inhibition rate of 86.7%, significantly higher than the monotherapy group (82.3%), the PLGA-AB NP group (63.6%), and the free drug group (39.5%). The FAP-CAR-CM@PLGA-AB NP effectively reduced the number of CAFs and the expression level of senescence markers. Additionally, the FAP-CAR-CM@PLGA-AB NP significantly promoted $CD8^+$ T cell infiltration and successfully remodeled the cancer immune microenvironment[16]. Overall, targeting of CAFs and SC-CAFs and modulation of senescence *via* precise Nano-DDSs can effectively overcome TME barriers, enhance drug penetration, and regulate the immune microenvironment. This combination therapeutic strategy *via* Nano-DDSs could offer a new avenue for anticancer treatment[231].

5. Summary and outlook

In summary, cellular senescence, a distinct biological state, has been extensively explored for cancer therapy through Nano-DDSs. The mechanisms for cancer therapy *via* modulation of cellular senescence include inhibition of cell proliferation, metabolic vulnerability exposure, immune modulation, and TME remodeling. An array of intervention targets has been discovered from these multiple mechanisms, and Nano-DDSs have been developed for these targets or their combination. By combining senescence inducers and/or clearance agents with immune activators and/or metabolic regulators on a single nanoplatform for coordinated, sequential delivery, Nano-DDSs can integrate anticancer mechanisms both spatially and temporally, overcoming limitations of traditional monotherapies[232,233]. These

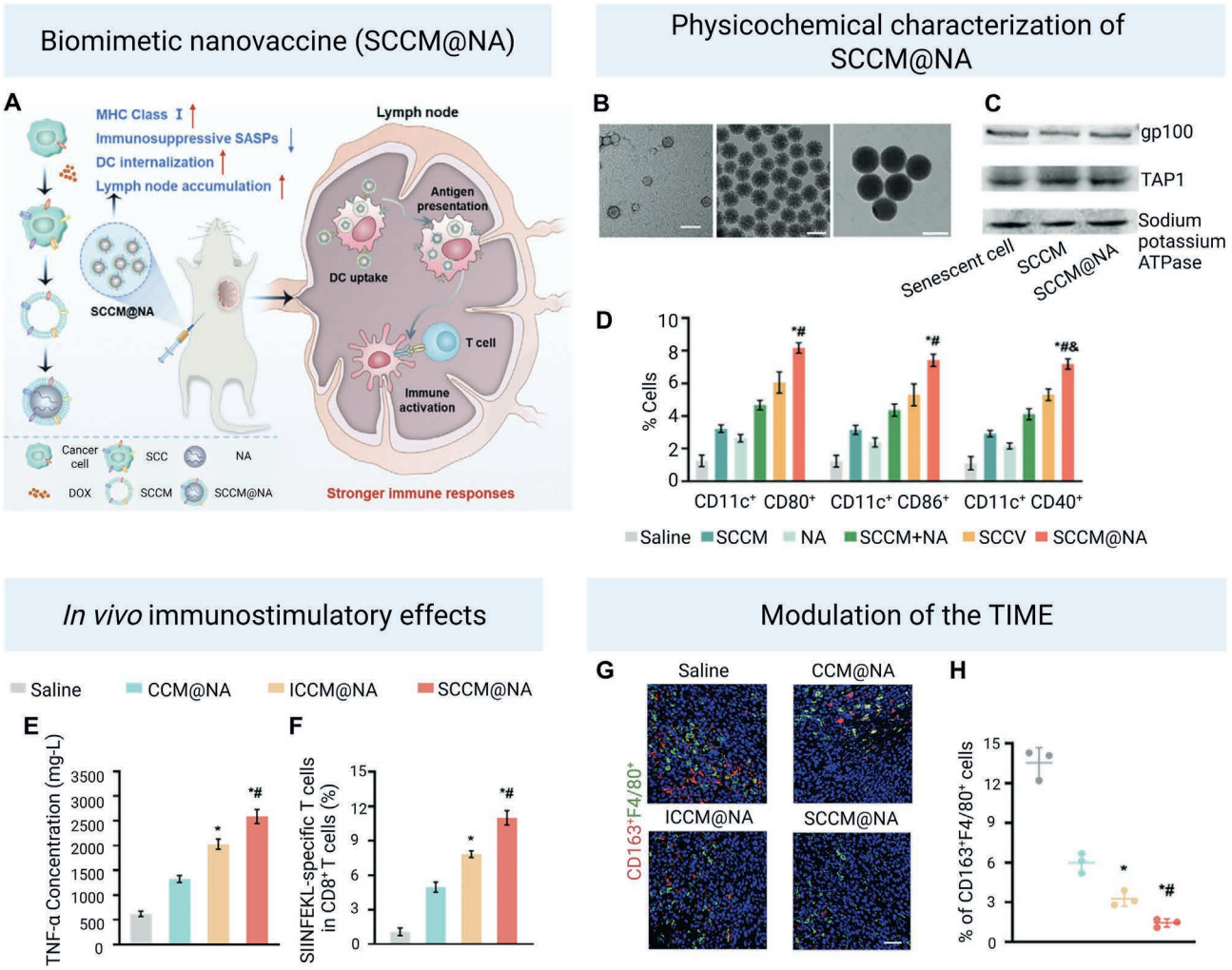

Figure 8 Application of Nano-DDSs targeting cellular senescence to regulate cancer immune response. (A) Schematic diagram of a biomimetic nanovaccine designed to enhance DC internalization, improve lymph node targeting, and strengthen immune responses. (B) Transmission electron microscope images of SCCM vesicles (left), nano-antigens (NA, middle), and SCCM@NA (right), with a scale bar of 200 nm. (C) Expression levels of gp100 and TAP1 in senescent cells, SCCM, and SCCM@NA. (D) Quantitative analysis of the proportion of $CD11c^+CD80^+$, $CD11c^+CD86^+$, and $CD11c^+CD40^+$ cells in different treatment groups. (E) Quantitative analysis of TNF-α secretion. (F) Quantitative analysis of SIINFEKL antigen-specific $CD8^+$ T cells. (G) Immunohistochemical analysis of M2 macrophages in cancer tissues, labeled with CD163 (red) and F4/80 (green). (H) The calculated ratios of M-2 macrophages relative to the whole cells count within the corresponding tissue area. Major histocompatibility complex class I (MHC-I), dendritic cells (DCs), senescent cancer cells (SCCs), SCC membrane (SCCM), nanoadjuvant (NA). Adopted with permission from Ref. 196, copyright © 2024 The Author(s). Advanced Science is published by Wiley-VCH GmbH.

Nano-DDSs-based therapeutic approaches have become refined, systematic, and effective.

The latest advancements in Nano-DDSs targeting cellular senescence characteristics have been covered in this review, and efforts are devoted to Nano-DDSs for inhibiting cancer progression, targeting metabolic vulnerability, modulating immunity, and regulating cancer-associated stromal cells. For example, E@M-A/RNP and ^{223}Ra/Ba SAzyme induced senescence in cancer cells and eliminated SNCs through telomerase targeting or the "one-two punch" strategy, effectively inhibiting cancer proliferation; Aur/Pal@LPT and AZT-P/pyro NCP exploited metabolic imbalances in SNCs, synergizing with ferroptosis or photodynamic therapy to significantly enhance cancer-killing effects; AX@NPs-FA/AbCD47 and SCCM@NA remodeled the TME and boosted anti-cancer immune responses through targeting CD47 and harnessing the immunogenicity of senescent cancer cells and immune modulation of the SASP; and HSD-P@V and FAP-CAR-CM@PLGA-AB NPs targeted CAFs and regulated their senescent state to improve drug penetration and reverse immune suppression. A common feature of these Nano-DDSs is their precise, synergistic targeting, overcoming non-specificity and resistance associated with traditional therapies. Specific mechanisms or their combinations (*e.g.*, senescence induction, metabolic regulation, or immune activation) have been elegantly harnessed for the design and development of multi-functional Nano-DDSs. Integration of senescence induction and clearance of senescent cells in one single Nano-DDS has significantly enhanced therapeutic specificity and efficacy, and these Nano-DDSs have entered different phases of clinical trials. It is noted that the drug delivery efficiency, *in vivo* distribution kinetics, and long-term safety remain

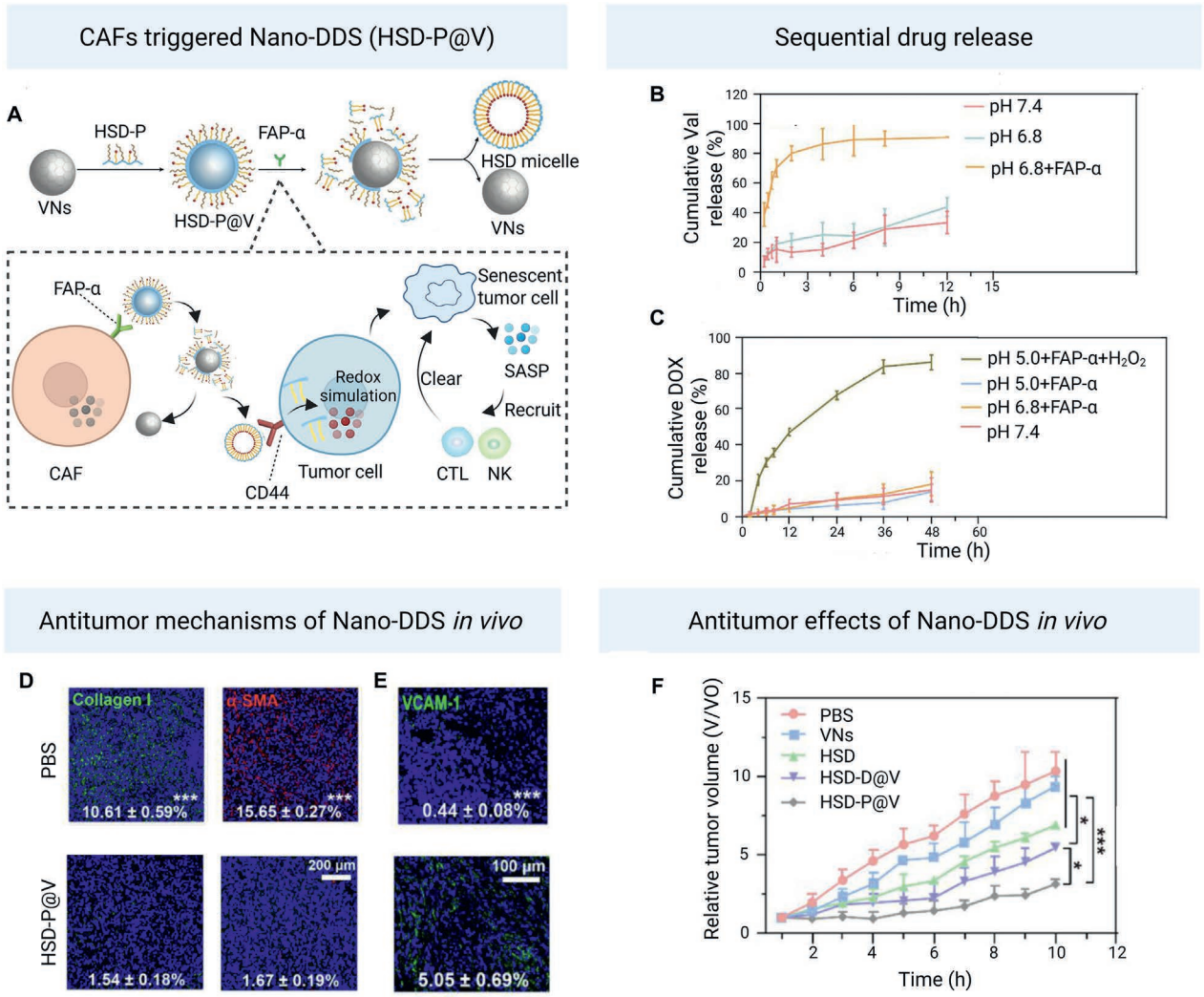

Figure 9 Application of Nano-DDSs targeting cellular senescence to regulate cancer-associated stromal cells. (A) Schematic diagram of the preparation and transformation process of HSD-P@V and its anti-cancer immune mechanism. In response to FAP-α expression on CAFs, the peptide was cleaved to release VNs from HSD. VNs induced inactivation of CAFs to reduce collagen synthesis for the ECM. The dissociated HSD micelles carried DOX deep into the cancer to induce cancer cell senescence and activate anti-cancer immune responses. (B) Release curves of valine under different conditions. (C) Release curves of DOX under different conditions. (D) Immunofluorescence detection of collagen I and α-SMA in cancer tissues. (E) Immunofluorescence detection of VCAM-1 in cancer tissues. (F) Relative tumor volume of 4T1 tumor-bearing mice after intravenous administration. HA-Se-Se-DOX (HSD), fibroblast activation protein-α (FAP-α), valsartan nanocrystals (VNs), cancer-associated fibroblast (CAF), cluster of differentiation 44 (CD44), natural killer cell (NK cell), senescence-associated secretory phenotype (SASP), cytotoxic T lymphocyte (CTL). Adopted with permission from Ref. 179, copyright © 2024 Shenyang Pharmaceutical University. Published by Elsevier B.V.

key challenges. Future efforts should be made to optimize biocompatibility and targeting specificity of Nano-DDSs, develop multifunctional, synergistic therapeutic platforms, and validate their efficacy and feasibility through large-scale preclinical studies, eventually promoting their translation into clinical application[234].

However, translating senescence-targeting strategies into clinical practice faces multiple biological mechanism challenges. Although positive and negative effects of senescence have been identified and reviewed in this article, the dual role of the SASP is insufficiently, non-systematically considered for Nano-DDSs design[235]. Nano-DDSs have been developed to harness the beneficial or detrimental effects of senescence for cancer therapy. Particularly, the SASP-associated strategies by leveraging its immune activation or angiogenesis-promoting properties have been developed to enhance anti-cancer effects. However, the immunosuppressive, pro-angiogenic, and matrix remodeling negative effects of the SASP are rarely explored in the development of Nano-DDSs[178]. For instance, although Chibaya et al. enhanced the efficacy of innate immune activators by inducing senescence, their study did not address the dual nature of the SASP, particularly its immunosuppressive components[207], which may lead to unforeseeable long-term risks. The heterogeneity of the SASP and its temporal dynamics are critical for targeting senescence *via* Nano-DDSs. The SASP components and their functions from different sources of senescent cells exhibit pronounced variations[10,236]. For example, the SASP from senescent cancer cells displays immune-activating effects, while the SASP

from senescent CAFs in the TME may promote strong immune suppression[10,236]. Thus, the negative effects of the SASP from CAFs should also be considered when targeting cancer cell senescence *via* Nano-DDSs. Meanwhile, the SASP composition is dynamically changed during the aging process[237,238]. The early-stage SASP contains a high proportion of anti-cancer components, such as immune activators, while the SASP from late-stage senescent cells often exerts pro-cancer effects[238]. Senomorphics can alleviate the harmful effects of senescent cells on tissues by blocking pro-SASP signaling cascades, disrupting secretion processes, or directly inhibiting specific SASP components[239]. Long-term side effects of the SASP may not pose a major threat when Nano-DDSs clear SNCs rapidly to achieve therapeutic goals, while if elimination of SNCs in the short term is not feasible, SASP neutralization (senomorphics) may be considered for incorporation into Nano-DDSs to mitigate the risks associated with the SASP[68,240]. Senomorphics can alleviate the harmful effects of senescent cells on tissues by blocking pro-SASP signaling cascades, disrupting secretion processes, or directly inhibiting the activity of specific SASP components. Incorporation of senomorphics into Nano-DDSs design for senescence induction could help balance the dual effect of the SASP, enhancing the overall safety and controllability of treatment[241].

Another pivotal challenge lies in the comprehensive assessment of the potential toxicity associated with Nano-DDSs in senescence-targeting therapies. The first concern is the off-target toxicity stemming from insufficient targeting specificity[242]. The non-specific distribution of nano-formulations *in vivo* may inadvertently damage senescent cells within healthy tissues, thereby disrupting the tissue homeostasis maintained by physiological senescence processes[243]. This issue is compounded by the pharmacokinetics and biodistribution of the nanocarriers themselves *in vivo*[244]. It is very challenging to predict long-term accumulation of Nano-DDSs at the tumor sites and their cumulative toxicity due to an inadequate understanding of the absorption, distribution, metabolism, and excretion (ADME) processes of Nano-DDSs within the complex *in vivo* environment[245]. Additionally, it is noted that some senolytics are incorporated into Nano-DDSs (*e.g.*, navitoclax) initially for other therapeutic purposes, rather than acting as selective anti-aging agents. Furthermore, CAR T-cell-based elimination of senescent cells faces significant challenges, including induction of cytokine storms and reliance on SNC markers, which may hamper its application. These challenges may be overcome after comprehensively revealing senescence regulation mechanisms and developing strategies for mitigating risks during senescence clearance following cancer-induced senescence[238].

Beyond the aforementioned challenges at the biological mechanism level, translating senescence-targeting nanomedicines into clinical practice faces a series of practical technological and translational obstacles. The primary bottleneck lies in large-scale production and quality control. The complex synthesis processes of nanocarriers, along with stringent requirements for particle size uniformity and surface modification consistency, contribute to a strenuous transition process from laboratory preparation to industrial large-scale production[246-248]. In addition, the long-term biosafety of nanomaterials themselves should be comprehensively evaluated. Their components and degradation products may accumulate in organs such as the liver and spleen, potentially inducing chronic toxicity or immune reactions, and this is particularly critical for senescence intervention strategies because long-term or repeated administrations are often required[249,250]. Furthermore, the EPR effect of Nano-DDSs is significantly inconsistent among clinical patients[251]. The treatment effect is influenced by factors such as the cancer type, the degree of vascularization, and stromal characteristics, therefore, the treatment efficacy cannot be accurately predicted and standardized[252]. Reliable patient stratification strategies for combination therapies could be developed to enhance the targeting efficiency[252]. Finally, regulatory science faces new challenges, as there is currently no specific review framework for senescence-intervention nanomedicines[253]. Establishing new evaluation standards and guidelines for their unique mechanisms of action (such as sequential induction and clearance), the identification of senescence-specific biomarkers, and dynamic monitoring of the SASP may be achieved through collaborative efforts from industry, research institutes, and regulatory bodies[254].

To systematically overcome these obstacles and expand therapeutic boundaries, interdisciplinary enabling technologies could be integrated for targeting senescence for optimal therapeutic effects. The integration of artificial intelligence (AI) and computational models is emerging as a pivotal breakthrough; however, there are very few reliable models that can be used to accurately predict patient-specific senescent cell heterogeneity and establish dynamic SASP profiles[255,256]. Future efforts should be devoted to the development of AI algorithms to integrate multi-omics and clinicopathological features. By leveraging machine learning to analyze high-throughput data, individual senescence patterns could be forecasted, and the patterns could be harnessed for the design of personalized nanodrugs[257]. Simultaneously, AI-driven simulations of nanocarrier trajectories *in vivo* could help optimize their physicochemical properties to enhance drug accumulation at senescent lesions[258]. Meanwhile, interdisciplinary integration and collaboration could be critical for developing senescence intervention strategies. For instance, combining senescence-targeting strategies with immunotherapy can simultaneously clear senescent cells and activate anti-cancer immunity[259]. The development of nanosystems for co-delivering senolytic agents and immune checkpoint inhibitors not only alleviates the immunosuppressive microenvironment due to senescent cell accumulation but also promotes antigen presentation and T cell activation, thereby generating synergistic anti-cancer effects[175].

In terms of specific technical development, continuous improvement of the intelligent responsiveness of Nano-DDSs is essential. For instance, the majority of current prodrug strategies are developed on the basis of single biomarkers (*e.g.*, SA-β-Gal), while a high heterogeneity level in the expression of this biomarker across different senescent cells and normal tissues leads to inconsistent therapeutic efficacy or nonspecificity[260]. Integrating Nano-DDSs with multi-responsiveness for a prodrug through controlling specific drug release in response to multiple signals in the tumor microenvironment (*e.g.*, pH, enzymes, or redox status) holds great potential in overcoming the limitations of single biomarkers and significantly enhancing both the precision and broad applicability of the Nano-DDSs[261-263].

In terms of platform integration, innovative combinations of Nano-DDSs with emerging treatment modalities should be explored. Taking proteolysis-targeting chimeras (PROTACs) as an example, this technology provides a new approach for degrading traditionally "undruggable" senescence-related proteins[264]. However, systemic administration of PROTACs often carries off-target toxicity risks since the target proteins (*e.g.*, BCL-2/xL and BRD4) perform crucial biological functions in normal cells[14,265].

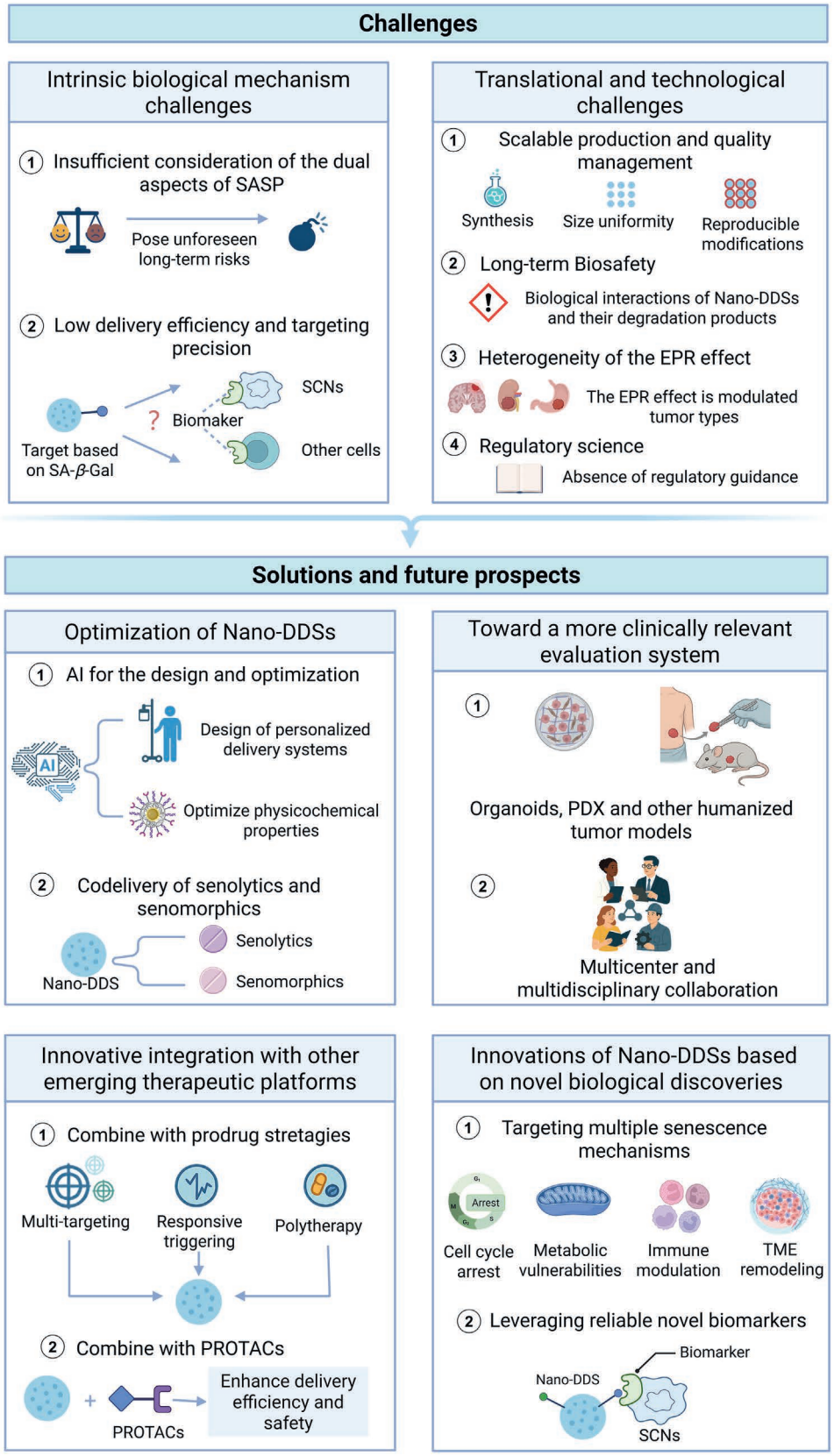

Figure 10 Challenges of Nano-DDSs-based anti-senescence cancer therapies in the clinical translation process, current research strategies, and forward-looking innovative solutions. Senescence-associated secretory phenotype (SASP), senescence-associated β-galactosidase (SA-β-Gal), senescent cells (SNCs), enhanced permeability and retention (EPR), artificial intelligence (AI), patient-derived xenograft (PDX), proteolysis-targeting chimeras (PROTACs), nano-drug delivery systems (Nano-DDSs), tumor microenvironment (TME). Created with BioRender.com.

Leveraging the targeting and controlled-release capabilities of Nano-DDSs can enhance the accumulation of PROTACs in diseased tissues while reducing exposure of them to non-target tissues, thereby improving therapeutic safety and enhancing the degradation efficiency[266].

At the translational validation level, more clinically relevant evaluation systems should be established for assessment of Nano-DDSs-derived senescence-targeting therapies. Organoids, patient-derived xenograft (PDX) models, and humanized cancer models should be employed to systematically evaluate the efficacy, safety, and pharmacokinetic characteristics of Nano-DDSs in different senescence contexts across various cancer types in physiologically relevant environments[267,268]. Meanwhile, within a multicenter, multidisciplinary collaborative framework, early validation of reproducibility and process scalability of a Nano-DDS candidate should be conducted to provide robust data support for its subsequent clinical translation[269-273] (Fig. 10).

In summary, the development of anti-cancer Nano-DDSs strategies based on multiple mechanisms of cellular senescence is gradually transitioning from conceptual exploration to controllable and stratified systems design. Future efforts should be devoted to developing microenvironment-responsive nanocarriers that integrate emerging therapeutic platforms to enhance targeting and safety; creating temporally regulated delivery systems for "induction-clearance" combination therapy; combining SASP modulation with immune microenvironment remodeling to boost immune therapy outcomes; and establishing reliable biomarker evaluation systems to accelerate clinical translation. Nano-DDSs targeting senescence can achieve revolutionary breakthrough to provide precise, efficient, and safe cancer treatment options through interdisciplinary collaboration and synergistic innovation, ultimately benefiting a wide patient population.

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Author contributions

Gang Xu, Zhenyu Duan and Kui Luo conceived the outline of this review. Xue Zhang, Lingxiao Yang, Xiaopeng He and Zhenyu Duan collected papers for writing, drafted the original manuscript, and performed the creation of figures/tables. Min Zhao and Zaixiang Fang helped revise the manuscript and discuss the content. Gang Xu, Zhenyu Duan, Kui Luo supervised this project and finalized this manuscript. All authors have read and approved the final manuscript.

Conflicts of interest

The authors have declared that no competing interest exists.

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