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Nanocarriers targeting senescent cells

A B S T R A C T

Ageing and multiple chronic diseases in humans associate with an aberrant accumulation of senescent cells in a diversity of tissues, which contributes to organ dysfunction and drives their pathological manifestations. It emerges that elimination of senescent cells ameliorates and even reverts the progression of age-related disorders, thereby extending healthspan and lifespan in preclinical mouse models. Development of delivery carriers specifically targeting senescent cells offers innovative therapeutic and diagnostic applications in translational medicine.

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1. Introduction

Severe or unrepairable damage often elicits across vertebrates a cell autonomous response based on a stable cell cycle arrest, known as cellular senescence. This cellular fate involves the upregulation of survival pathways and the acquisition of a senescence-associated secretory phenotype (SASP) that entails a complex mixture of cytokines, proteases and other extracellular matrix remodelling factors. The main role of cellular senescence is to prevent the expansion of damaged cells and to facilitate tissue repair. Senescent cells during ageing, however, accumulate in multiple tissues, probably due to inefficient clearance by immune cells, where they contribute to disease onset and progression through a series of complex cell autonomous and proinflammatory – tissue disruptive – paracrine effects that impact both the surrounding microenvironment and tissue homeostasis. Cellular senescence thus relates to a wide variety of human age-related pathologies including, among others, cancer, fibrosis, cardiovascular diseases, obesity, type 2 diabetes, sarcopenia, osteoarthritis, and neurological disorders [1]. Importantly, genetic ablation of senescent ($p16^{Ink4a}$-positive) cells in mice attenuates tissue dysfunction and symptoms of frailty, leading to an increased healthspan and lifespan [2].

Senescent cells possess distinct molecular vulnerabilities targetable by senolytic drugs (pharmacologically active agents that selectively kill senescent cells) [3,4]. Research over the last few years has produced preclinical proof-of-concept that senotherapies do delay, prevent, or revert multiple age-related phenotypes, chronic disorders, geriatric syndromes and loss of physiological resilience [4,5], while lengthening life in old age mice [6]. Because of the unfortunate presence of undesirable off-target effects is a common feature of these pharmacological interventions that hampers a more effective translation of preclinical studies into early phase clinical trials, many different strategies for optimising selectivity of senolytic drugs are currently under evaluation.

Over the past decades, nanomedicine has been a research area in continuous expansion aimed at impacting broadly on healthcare [7]. The application of gated materials in the biomedical field has been boosted because these systems allow the release of one or several cargoes upon the application of external stimuli [8]. Functionalised nanoparticles (NPs) with a molecular gate are able to efficiently carry and specifically deliver therapeutic agents, imaging probes, or biological materials to targeted sites such as a particular organ, tissue, or even cellular type (Fig. 1A). The first cargo delivery system reported to target senescent cells consisted of mesoporous silica nanoparticles capped with a mixture of galacto-oligosaccharides (GosNPs) of different lengths [9] (Fig. 1B). Cellular uptake of GosNPs occurs via endocytosis and, after fusion with lysosomal vesicles, the cargo is preferentially released in cells with increased endogenous senescence-associated β-galactosidase (SAβ gal) activity, a widely used marker of senescence, which mediates enzymatic hydrolysis of the cap. By using this approach, the authors showed the preferential release of rhodamine in human senescent fibroblasts from dyskeratosis congenita patients.

1.1. Therapeutic nanoparticles

We have improved the former technology by generating silica beads capped with a homogeneous coating consisting mostly of 6-mer galacto-oligosaccharides (GalNPs) (Fig. 1B), which allows for a more specific and controlled β-galactosidase-dependent cargo release when compared to GosNPs. GalNPs were validated in *in vivo* models of damage-induced and chemotherapy-induced senescence [10]. We demonstrated that gal-encapsulated drugs are preferentially released into damaged or pathological tissues containing high levels of senescent cells, such as bleomycin-induced lung fibrosis. Importantly, the release of gal-encapsulated doxorubicin into fibrotic lungs does revert pulmonary fibrosis, in stark contrast to the administration of free doxorubicin, as it results in a

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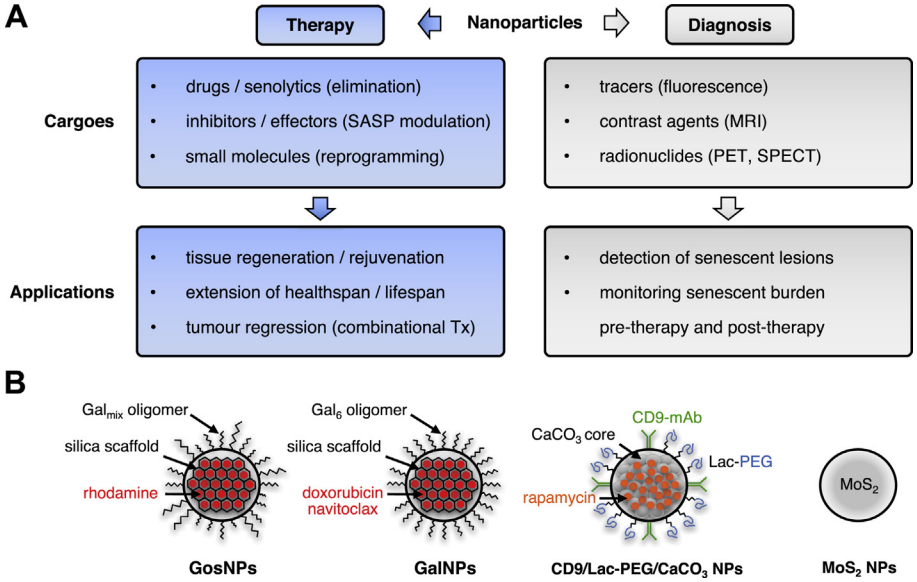


Fig. 1. Therapeutic and diagnostic applications of nanoparticles targeting senescent cells. (A) Nanocarriers can be loaded with multiple cargoes, either for therapeutic or diagnostic applications, as indicated. Nanocarriers can in addition be functionalised with polymers, ligands or antibodies for a selective targeting of senescent cells. SASP, senescence-associated secretory phenotype. MRI, magnetic resonance imaging. PET, positron emission tomography. SPECT, single-photon emission computed tomography. Tx, therapy. **(B)** Different nanodevices to target senescent cells according to their physicochemical properties. GosNPs and GalNPs, galacto-oligosaccharide coated mesoporous silica nanoparticles; CD9-Lac/$CaCO_3$ NPs, CD9 monoclonal antibody-conjugated calcium carbonate nanoparticles wrapped with lactose-polyethylene glycol; MoS_2 NPs, molybdenum disulphide nanoparticles.

remarkable reduction in the abnormal amount of collagen present and in the recovery of respiratory function. Furthermore, chemotherapy treatment of xenograft tumours in mice causes a fraction of tumour cells to undergo senescence, and the concomitant treatment with gal-encapsulated doxorubicin results in full tumour regression. Of note, we found that gal-encapsulation prevents the exposure of non-pathological tissues to drugs, therefore reducing their associated toxicities. Our work obtained for the first-time proof of principle for the *in vivo* biological activity of a vehicle that allows preferential drug delivery into diseased tissues harbouring senescent cells. This may open new therapeutic opportunities for the treatment of multiple senescence-associated disorders and, additionally, targeted-delivery of drugs into senescent cells may improve cancer chemotherapy by eliminating tumour cells undergoing chemotherapy-induced senescence (Fig. 2).

Besides their capability to kill senescent cells, nanocarriers remarkably also have the attractive potential to dampen the detrimental effects of cellular senescence by manipulating the SASP with encapsulated inhibitors, effectors and small molecules, or by reprogramming these cells so they can accomplish their tissue-associated functions. A recent *in vitro* study makes use of porous calcium carbonate nanoparticles (CaCO3) loaded with rapamycin (Rapa, an mTOR inhibitor capable of constraining the secretory phenotype of senescent cells) [11] (Fig. 1B). CaCO3(Rapa) NPs were wrapped with a conjugate of lactose (Lac, galactose/glucose dimers joined in a β-1,4- glycosidic linkage) for a targeted cargo release mediated by SAβgal activity; and with polyethylene glycol, for a conceivable stabilisation in circulating blood and prevention of opsonisation. These NPs were further functionalised with a monoclonal antibody against CD9, a cell surface glycoprotein receptor overexpressed in some cellular types undergoing senescence. CD9-Lac/$CaCO_3$ NPs were thus designed as a targeted delivery system at two levels: (i) by using surface targetable proteins of senescent cells leading to cell specific uptake, (ii) by exploiting an increased lysosomal enzymatic activity of senescent cells for a

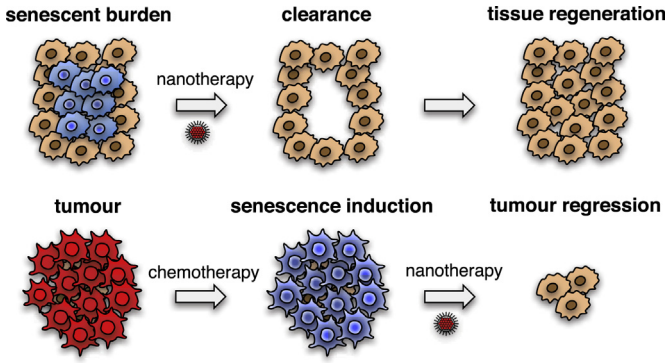


Fig. 2. Rationale of the applications of seno-nanotherapies. Nanotherapies can be used to remove the senescent burden associated with chronic disorders or during ageing, thereby promoting tissue repair and regeneration. Also, an interesting application is the combined use of nanotherapies and senescence-inducing chemotherapies or radiotherapies in so to facilitate tumour regression and the eradication of senescent cells.

preferential cargo release. The authors showed that CD9-Lac/CaCO3(Rapa) exhibited anti-senescence effects in primary human dermal fibroblasts (HDFs), along with a reduced expression of some SASP components, including IL-6 and IL-1β. In another recent study, molybdenum disulphide nanoparticles (MoS_2 NPs, see Fig. 1B) pre-treatment of human aortic endothelial cells succeeded to inhibit H_2O_2-induced senescence by preventing lysosomal and mitochondrial dysfunction, triggering autophagy and resisting impaired autophagic flux, which results in improved endothelial functions [12]. However, MoS_2 nanodevices, differently to GalNPs or CD9-Lac/$CaCO_3$ NPs, were not functionalised for a preferential targeting of senescent cells, thereby limiting their current *in vivo* potential applications to *in situ* preventive treatments for damaged tissues. Despite the aforementioned promising findings, the *in vivo* efficiency of most of these emerging nanovehicles still lack

demonstration in preclinical models.

1.2. Diagnostic nanoparticles

In addition to therapeutic approaches, monitoring senescent lesions in humans remains a formidable challenge in clinical imaging. To date, the list of imaging probes reported to track senescent cells is a short one, these probes are based mainly on fluorescent molecules, only tested in cell cultures in most of the cases. This includes two-photon SG1 [13] and single photon near-infrared Gal-Pro [14] probes assessed in senescent HDFs, and AHGa, a naphthalimide-based probe conjugated with acetylated galactose tested in SK-MEL103 (melanoma) xenografts undergoing chemotherapy-induced senescence [15]. These senoprobes are preferentially activated in cells exhibiting high SAβgal activity and contain fluorescent units conjugated with a galactose residue via a glycosidic bond. Crucially, the conceivable use of current fluorescent probes to detect senescent lesions in humans would require their adaptation to deep tissue penetration bioimaging techniques.

Nanocarriers specifically targeting senescent cells represent an elegant translational option as they can encapsulate tracers, contrast agents, radionuclides, and even senoprobes (Fig. 1A). As an example, diagnostic GalNPs, capable of releasing fluorescent dyes in senescent tumour xenografts [10], could be loaded with gadolinium or with radioactive tracers to track senescent tissues by magnetic resonance imaging (MRI) or positron emission tomography (PET), respectively. It is tempting to speculate that diagnostic nanocarriers could hence be employed in longitudinal studies to monitor the senescent burden in patients subjected to senotherapies, or the response of solid tumours to the administration of senescence-inducing chemotherapies. Moreover, since cellular senescence is a hallmark of numerous human precancerous lesions [16], the hypothetical use of diagnostic nanocarriers for early detection of some cancer types is an exciting possibility that demands to be explored. Furthermore, senescence-activatable NPs could potentially be employed as theranostic tools, aimed at the simultaneous detection and eradication of senescent lesions associated with human chronic disorders or natural ageing.

1.3. Future perspectives: challenges and limitations

A relevant advantage of targeted encapsulation methods (either diagnostic or therapeutic) is the protection of healthy tissues from the exposure to the administered compounds. Accordingly, we found in mice that gal-encapsulation of drugs and senolytics reduced the associated off-target effects of the free compounds, as it is shown for doxorubicin cardiotoxicity and for navitoclax-induced thrombocytopenia [10]. The development of nanotechnologies to target senescent cells is however still in its infancy, and it is the subject of safety concerns and long-term risks. Translation of preclinical studies into early phase clinical trials will imply a better and complete understanding of the cellular uptake and intracellular trafficking of NPs, biocompatibility and biodistribution properties, pharmacokinetics/pharmacodynamics (PK/PD) analyses, and routes of administration/elimination of the core materials in animal models.

In the particular case of mesoporous silica nanoparticles, and other silica formulations of various physicochemical properties, there is solid evidence that NPs accumulate mainly in the lungs of healthy mice at early post-tail vein injection times [17]. NPs are, however, rapidly cleared from the lungs and partially sequestered by the mononuclear phagocytic system (MPS, including liver, spleen and lymph nodes). This is in part due to discontinuous gaps in the endothelium lining the sinusoidal walls of these organs, allowing a passive entrapment of foreign nanoparticles. In addition, resident macrophages can identify nanoparticles as foreign substances that need to be engulfed, degraded and eliminated. This scenario applies not only to silica nanoparticles but also to multiple NPs types, which weights down potential translational applications. In this regard, we found that a substantial number of cells targeted by GalNPs were macrophages, although these levels were reduced in fibrotic lungs when compared to healthy lungs, presumably because of the presence of senescent fibroblasts and alveolar epithelial cells competing for nanoparticles [10]. The possibility that macrophages with a high SAβgal activity [18] can activate GalNPs encapsulating drugs is yet to be tested in our experimental settings. It is however worth mentioning that no evidence of hepatic or renal damage was gathered following daily treatments of GalNPs encapsulating doxorubicin for more than two weeks, as evaluated by serum markers and histology. The absence of altered blood parameters suggests that doxorubicin is not significantly released when GalNPs are taken up by non-senescent cells, being eventually removed by exocytosis [19]. Excretion of silica NPs or their degraded products occurs principally through the urine by renal clearance and, to a lesser extent, in faeces, with a peak at 24 hours post-administration for both routes [17].

A promising clinical application of NPs targeting senescent cells is their use in combination with standard (senescence-inducing) chemotherapies [10] (Fig. 2). This strategy may benefit from the extravasation of NPs from the tumour blood vessels into the tumour microenvironment through gaps between adjacent endothelial cells, an effect known as enhanced permeability and retention (EPR), a product of leaky tumour vasculature and poor lymphatic drainage [20,21]. This potential effect in humans, however, has been hardly explored, and most of the available data have been obtained in preclinical animal models. In this regard, elucidation of whether impaired angiogenesis and endothelial dysfunction in the elderly may reduce the effectiveness of interventions based on systemic administration of NPs is yet to be conducted. For the time being, PK data of nanomaterials on naturally-aged mouse models and vascular disorders are currently limited. Similarly, a potential pitfall in some age-related disorders accumulating senescent cells is the possibility that the senescent secretome, including inflammatory cytokines, growth factors and tissue remodelling proteases, affects the blood supply to the damaged tissue, thereby precluding targeting of nanoparticles and drug delivery. Although this possibility cannot be ruled out in some experimental settings, depending on the particular nanotechnology, organ, and disease model, similar levels of GalNPs encapsulating a fluorescent compound were measured in healthy and bleomycin-treated mouse lungs enriched in senescent cells, indicating that the diffusion of NPs was not altered [10]. Intracellular release of the fluorophore preferentially occurred in fibrotic lungs, remarkably. It is important to recall that intravenous administration of GalNPs in mice results in a preferential lung accumulation due to the anatomic distribution of the blood flow. It seems likely that organs with a relevant blood supply, such as the heart, liver, or kidneys, can be targeted by these or similar nanocarriers. In the particular case of the brain, there are some reported examples of polymeric NPs capable to deliver drugs, but this has posed a big challenge due to the intrinsic limitations associated with the blood brain barrier (BBB), making uncertain the potential use of mesoporous silica nanoparticles [22]. An interesting alternative to systemic injection of GalNPs would be exploring direct routes of administration, such as a transdermal drug delivery system if the target is the skin, or oral uptake when the target is the digestive

system. Addressing the utility of GalNPs to target other organs and tissues containing senescent lesions, especially for those having a reduced blood circulation, will require further work.

Only a few (non-targeted) NPs formulations enjoy at present approval for clinical use (e.g. Abraxane or Doxil) [23], mainly because of the limited information available in the use of nanodevices in *in vivo* and of safety concerns, which underlies the importance of a better understanding and controlled delivery of NPs in live organisms. Physicochemical properties of NPs affect the biological processes involved in the delivery to target tissues, including interactions with serum proteins (such as opsonins), blood circulation, biodistribution, competition with other organs and cells (i.e. MPS, macrophages, or renal clearance), extravasation, and specific cell targeting. Increasing the selectivity of nanocarriers for senescent cells is crucial to improve delivery. In this respect, it is imperative to carry out some fundamental research on the characterisation of more precise markers of senescent cells. As an example, the identification of senescence-specific membrane markers would facilitate the functionalisation of nanodevices with specific antibodies to target senescent cells, such as the recently reported surface targetable protein DPP4, expressed preferentially in senescent but not proliferating human diploid fibroblasts [24]. Despite some other membrane-associated proteins in the surfacesome of senescent cells being found (such as DEP1 or BMG2), a universal marker of cellular senescence is still lacking [25]. Senescent cells accumulate in a broad number of age-related disorders and during ageing and therefore they appear to escape from immunosurveillance and clearance. This could be due to the absence of distinct antigenic determinants in their membranes when compared to normal (healthy) cells, but also to the implementation of detrimental secretory programmes causing immunosuppression, or to a deficient infiltration of cells of the immune system in the “remodelled” microenvironment of senescent cells. Of note, although yet to be tested *in vivo*, the *in vitro* validation of CD9-Lac/$CaCO_3$ NPs targeting a cell surface glycoprotein receptor overexpressed in senescent cells [11] is a promising first step.

2. Conclusions

Altogether, nanotechnologies constitute an innovative strategy to specifically target senescent cells for potential and multiple diagnostic and therapeutic interventions. Vehicles designed for a selective cargo delivery could be used for detection, longitudinal monitoring, elimination and manipulation of senescent cells. Further studies with second generation senescence-specific nanocarriers and a better comprehension of their dynamic behaviour in preclinical models of senescence-associated disorders will be fundamental in providing opportunities for successful translational applications.

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