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Senotherapies: A New Approach to Enhancing the Effectiveness of Anti-Cancer Treatments

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Abstract:

At first, cellular senescence was thought to as a potent anticancer process, and medication that induced senescence was considered adequate. On the other hand, there is growing evidence that persistent senescent cells (SNCs) may thwart cancer therapy. Cancer recurrence is caused by tumour cells undergoing senescence escape and regaining their stem-like properties; Accumulating SNCs have been linked to worsening clinical outcomes, including prognosis, toxicity, and treatment resistance. Senotherapies that target and neutralise SNCs may thus provide a novel strategy for achieving synergistic anticancer treatment. In this paper, we also discuss polyploidy and its connection to senescence, and we emphasise the promise of senotherapies as a new adjuvant antiTUMOR therapeutic method. By focusing on cellular senescence, this approach may open up new possibilities for developing anticancer treatments.

Keywords: Polyploid; Senescence escape; Antitumor therapy; Senotherapy; Cellular senescence; Synergistic

INTRODUCTION:

While most of the early increases were in children's longevity, most current improvements have been in older people's longevity. Life expectancy in the West has doubled over the previous two centuries. According to projections, by 2041, the proportion of the global population aged 65 and over will have climbed from 18% to 26%. Over the same time frame, the expected percentage of the population over 85 rises from 2% to 4%. Despite improvements in longevity, there has been an increase in the incidence of chronic illnesses. The frequency of chronic illnesses among the elderly has increased, which has resulted in life expectancy surpassing health expectancy. This means that more than half of the population over 75 suffers from a combination of two or more chronic illnesses.

Since senescent Cancer cells have a negative effect on tumour development, this article will address the possibility of senotherapies as a novel synergistic anticancer treatment.[1]

CELLULAR SENESCENCE AND THE PROGRESSION OF CANCER: INHIBITOR OR PROMOTER?

Radiation therapy, chemotherapy, and other treatments are beneficial against cancer in several trials. Cancer cells undergo senescence as a quick reaction to therapy in vivo. The emergence of cancer throughout old age is like a double-edged sword. Senescent tumour cells secrete SASP, a pro-inflammatory cytokine that may inhibit growth by attracting immune cells to the tumour microenvironment (TME). Tumours that were previously immunologically "cool" become "hot" when senescent TUMOR cells are present, making them vulnerable to eradication by natural predators (NK cells), T cells or monocytes/macrophages. In contrast, SNC production decreases as time passes [1].

Several of these pathways also play a role in cancer's initiation, maintenance, progression, recurrence, and therapeutic response (Fig. 1). Hence, senescence and cancer interactions are multifaceted and poorly understood[2].

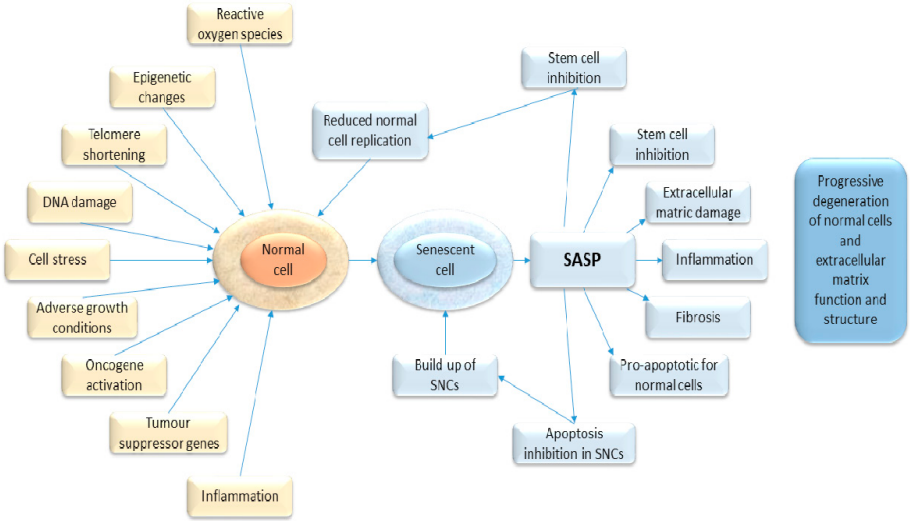

Fig .1. Diagram showing factors that can set off senescence (in yellow) and how it will affect the host tissue (in blue).

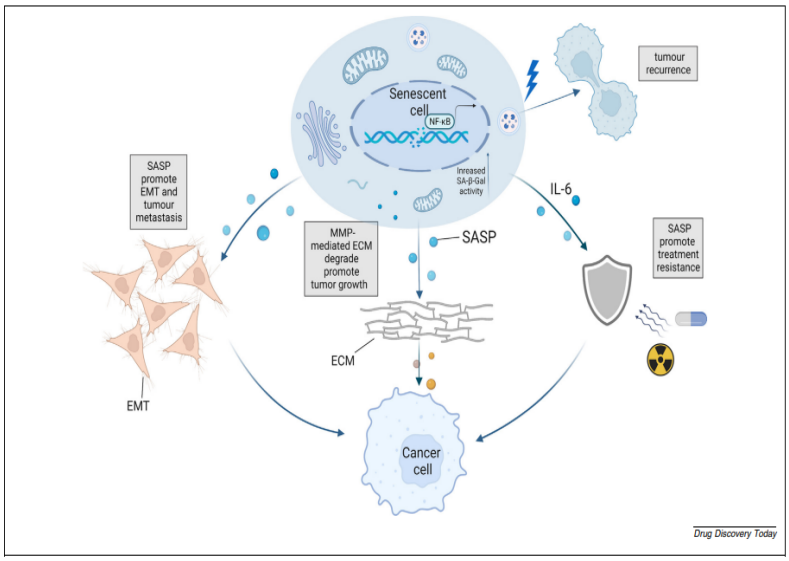

Fig .2

Adaptive immunity, in particular, loses a lot of its effectiveness. An Inability to efficiently eliminate SNCs leads to their accumulation and subsequent degenerative consequences in aged adults, increased incidence of cancer and other age-related illnesses. The key motivation for the push is MNCs' concealed usage of SASP. Interleukin (IL)-6 and other matrix metalloproteinases have been linked to SNC-induced TUMOR development. Extracellular matrix (ECM) degradation and digestion may release TUMOR-promoting cytokines, including growth factors and factors that induce epithelial differentiation. Successful epithelial-mesenchymal transitions (EMT) can be influenced by senescent fibroblasts in breast cancer (Fig. 2). MMPs can suppress the immune system. To promote TUMOR cell growth and immunological suppression, SNCs with elevated MMP levels may cleave the NKG2-D embedded membrane protein (NKG2-D) in NK cells. Like Wnt-16b and soluble frizzled-related protein 2 (sFRP2), IL6 produced by aging mouse endothelium protects lymphocytes against chemotherapy (Fig. 2). IL6 inhibits CD8+ T cells' ability to perform immunosurveillance. IL6 recruits myeloid-derived suppressor cells (MDSCs), and they stymie the IL1a signalling pathway to make the surrounding environment TUMOR-permissive. [1]

In conclusion, these findings support the idea that chronic SNCs significantly reduce medication effectiveness by promoting immune evasion, TUMOR invasion, and proliferation.

ESCAPE OF SENESCENT CELLS: A COMPLICATED SIGN OF TREATMENT FAILURE

Although SASP has a role in promoting TUMOR development, senescence escape might be a fundamental cause of cancer treatment failure, TUMOR recurrence, and even the origin of human cancer. Tumour cells that undergo senescence escape tend to be more aggressive, stemmed, and drug-resistant.

The application of TIS to antitumor therapy is based on the premise that senescence is an irreversible form of growth arrest. However, there is growing evidence that senescent TUMOR cells can escape growth arrest and recover their proliferative capacity, despite preliminary studies of senescent fibroblasts concluding that senescence is an irreversible cell cycle arrest. Senescent TUMOR cells can temporarily enter a dormant state. Given that most cancer therapies target malignantly proliferating TUMOR cells, senescent TUMOR cells can temporarily escape treatment and re-enter the cell cycle when stimulated by different conditions. The TUMOR cells that escape from senescence regain the ability to regenerate themselves and produce progeny with chromosomal instability or a stem cell-like phenotype, driving cancer recurrence and resulting in treatment failure[3].

WHAT IS THE MOLECULAR MECHANISM BEHIND SENESCENCE EVASION?

The mechanisms through which SNCs can evade senescence are as varied as the SNCs themselves, depending on factors of cell type, tissue of origin, senescence induction pathway, and more. Although senescence escape is a relatively new phenomenon, the mechanisms driving it are still poorly understood.

According to new research, epigenetics is significant in the molecular process of senescence escape. By inhibiting the expression of several E2F target genes, tumour suppressor genes like retinoblastoma (RB) and promyelocytic leukaemia (PML) regulate whether or not fibroblasts can leave senescence and enter the cell cycle again. Methylation of lysine 9 on histone H3 is necessary for permanently repressing E2F target genes (H3K9me3). By blocking histone demethylases such as Jumonji domain-containing protein 2C (JMJD2C) and lysine-specific demethylase 1 (LSD1), senescent melanocytes caused by the RAS/BRAF oncogene and senescent lymphoma cells induced by treatment may recover proliferation. SETD1A, an H3K4 methyl transferase, is required for cell division and multiplication. By preventing S-phase kinase-associated protein 2 (SKP2) from degrading p27 and p21, resetting SETD1A kicks off senescent escape. For the senescence phenotype to persist, p21 is required. The re-

expression of polo-like kinase 1 (PLK1) and cyclin D1 after p21WAF1 inactivation may revitalise the proliferative potential of senescent TUMOR cells (CDKN2A). The senescence of colorectal cancer cells is caused by the action of oncogenes (CDC25).

These cancer cells are vulnerable to senolytics because their survival depends on the B cell leukaemia/lymphoma 2 XL (BCL-xL)/myeloid cell leukaemia-1 (MCL1) signalling pathway. Increased synthesis of Myc, which binds to and suppresses the CD47 promoter, is another consequence of p21 repression. Thrombospondin-1 binds to CD47, which is a CD47 receptor (TSP1). Using SWATH quantitative proteomics, we found that TSP1 generated by SNCs inhibits senescence escape in triple-negative breast cancer. In addition, the results demonstrated that TUMOR cells resistant to senescence had decreased levels of TSP1 and CD47.

The method by which SNCs are no longer needed to promote metabolic activity during senescence was also investigated in another research. Overexpression of SLC1A5 (a glutamine transporter) and glutamine synthetase (a glutamine synthetase) was found in clones resistant to therapy-induced senescence. Moreover, human anterior gradient protein 2 (HAGP2) and Olfactomedin 4 (OLFM4) promote senescent cancers in evading detection.[1]

CELLULAR MORPHOLOGY AND THE FLEEING OF SENESCENCE

To learn more about how immortality is acquired by TUMOR cells that suppress senescence, it is necessary to examine how ageing acts as a barrier against the aggressive growth of cancer. Both their invasiveness and their stemminess are unique from their parental plants. Which SNCs are at risk for senescence escape? Polyploidy is fundamental to the investigation of these topics. Both polyploidy and senescence have several standard features, including an initial phase characterised by DNA damage, regulation by the same set of proteins (p21, p53, and Rb), and the potential to avoid apoptosis by producing their own set of anti-apoptotic proteins. Although SNCs formed by treatment are diverse and ever-changing, those induced by DNA-damaging agents all share a common feature: polyploidy. Polyploidy and senescence go hand in hand in H1299 cells. Cancer cells with polyploid chromosomes are often known as Polyploid Giant Cells (PGCCs).

The question then becomes how senescent polyploid cells divide. Erenprecise has shown that SNCs experienced mutations, chromosomal duplications, and continued asexual reproduction after the generation of polyploids. This results in the random dissemination of genetic information through mechanisms like epigenetic control, reprogramming of genes, etc. In the long run, only the descendants who inherit the genetic information required to maintain life will succeed. It has been shown that cells that have undergone survival selection become more aggressive and resistant to genotoxic therapy. About 1%-2% of polyploid cells can replicate outside the tumour, indicating that not all TUMOR cells are regenerative. Clearance by navitoclax and similar drugs seems to be more successful against polyploid SNCs because these cells appear to have a greater need for the BCL-xL protein for survival (Fig. 3)[4]. A similar buildup of SNCs is seen in cancer and ageing. The latter may arise from senescent somatic cells increasing the ploidy of their offspring, giving them malignant traits.

SYNERGISTIC ANTICANCER TREATMENT THROUGH SENOTHERAPIES

As was previously mentioned, it may be harmful for senescent cells to survive following therapy. This supports a method where therapy-induced senescent cells are removed for the greater good, reducing the possibility of TUMOR development and side effects.

Aiming Senolytic Agents At Quiescing Cancer Cells

One defining feature of senescent cells is an alteration in chromatin structure that leads to differential gene expression. These alterations can profoundly impact fundamental processes like apoptosis regulation, developing mutations and vulnerabilities specific to senescent cells and potentially exploitable by medications that could act as senolytic agents. Combining or following senescence-inducing therapies with these chemicals might have medical benefits (Fig. 4; TABLE. 1).[5]

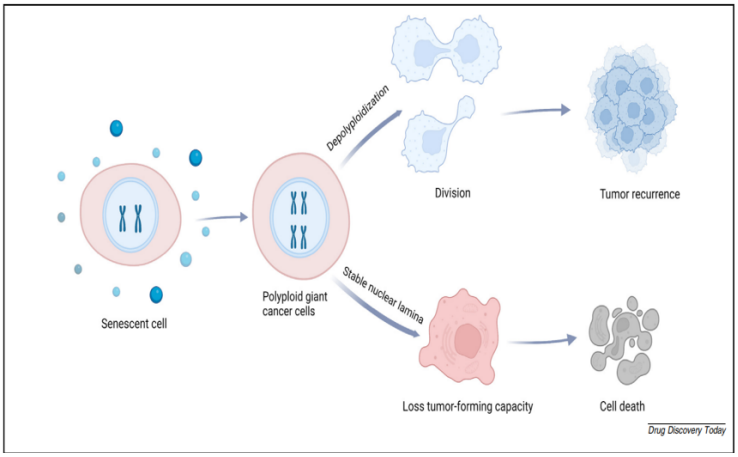

Fig.3: Cellular Morphology and The Fleeing of Senescence

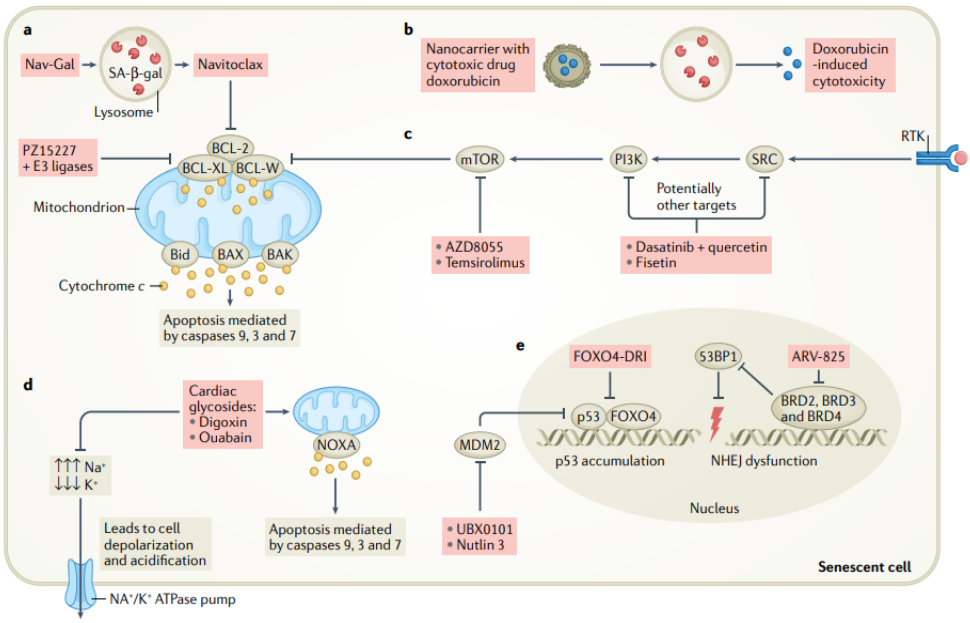

Fig. 4 | Aiming Senolytic Agents at Quiescing Cancer Cells. The alterations that senescent cells undergo make them more amenable to removal by senolytic medicines. a | By increasing their levels of anti-apoptotic proteins, senescent cells become resistant to apoptosis. Anti-apoptotic BCL-2 family inhibitor navitoclax causes cells to undergo intrinsic apoptosis by releasing cytochrome c, which triggers caspases 9, 3, and 7 involved in apoptosis. Senescence-associated —galactosidase (SA—beta-gal) activates galactic-conjugated navitoclax (Nav-Gal) to release it from senescent cells. PZ15227, an XL compound, hijacks the cereblon E3 ligase to hasten the breakdown of BCL. b | With the aid of SA—beta-gal, nanocarriers containing doxorubicin may be released, killing senescent cancer cells. c | The PI3K-AKT and SRC kinase pathways are only two of the many that dasatinib blocks. Both quercetin and fisetin inhibit PI3K and other upstream pathways that regulate the anti-apoptotic BCL-XL protein. Downstream of receptor tyrosine kinases, mTOR inhibition with AZD8055 or temsirolimus may activate apoptosis and cause senolysis (RTKs). d | Digoxin and ouabain are cardiac glycosides that may stimulate intrinsic apoptosis by activating the pro-apoptotic BCL-2 family protein NOXA. Depolarization and acidification of cells result from the inhibition of Na+/K+ pumps caused by cardiac glycosides. It's possible to increase senolysis anyway. e | UBX0101 (also called nutlin 3) may lead to p53 accumulation because it disrupts the MDM2-regulated ubiquitin degradation pathway. Forkhead box protein O4 (FOXO4)-DRI peptide blocks FOXO4's ability to bind to p53, preventing senescent cells from undergoing senolysis. ARV-825, a chimeric medication that targets proteolysis, interferes with 53BP1 recruitment and halts recombinational repair after DNA damage.

TABLE 1 | APPLICATIONS OF SENOLYTIC TREATMENTS IN CANCER

AGENTS	MECHANISMS OF DRUGS OR THEIR TARGETS	PRECLINICAL EVIDENCE	CLINICAL studies
ABT737	Inhibits BCL-2, BCL-W and BCL-XL	using xenografts and cell lines from breast cancer patients[6]; using etoposide treatment on breast cancer cell lines [7]	NA
Navitoclax (ABT263)	Inhibits BCL-2, BCL-W and BCL-XL	B cell CLL cell lines treated with the CD20 antibody rituximab [8]	Chronic lymphocytic leukaemia (CLL) of the B cell: Phase II treatment with Rituximab (NCT01087151) [8]
		Treatment with chemotherapy: etoposide- and doxorubicin-treated cell lines and xenograft models of breast and lung cancer[9,10,11]; cells from breast and lung cancer that were exposed to radiation [11]	Treatment of small cell lung cancer with etoposide in Phase I of a multi-chemotherapy trial (NCT00878449) [12]; etoposide with cisplatin (NCT00878449) or irinotecan (NCT01009073) in various cancers [12]; docetaxel (NCT00888108)[13], paclitaxel (NCT00891605)[12], or gemcitabine (NCT00887757)[14] in solid tumors Platinum-resistant recurrent ovarian cancer: a phase II single-agent trial (NCT02591095) [15]
		Using olaparib (a PARP inhibitor) in established cancer xenograft models and cell lines for lung, ovarian, and breast cancer [16]	NA
		Treatment of cancer cell lines derived from the lung, melanoma, breast, colon, and liver by inhibiting AURK with barasertib or CDK4/6 or alisertib with palbociclib[9,10,17]	NA

AGENTS	MECHANISMS OF DRUGS OR THEIR TARGETS	PRECLINICAL EVIDENCE	CLINICAL studies
Nav-Gal	Inhibits BCL-2, BCL-W and BCL-XL	Using palbociclib in preclinical models of breast and melanoma cancer; using radiation therapy and doxorubicin on cell lines of lung and colon cancer; using cisplatin in xenograft models and cell lines for lung cancer [17]	NA
Nanocarrier-encapsulated doxorubicin	DNA damage	The use of palbociclib in xenografts and cell lines of melanoma and lung cancer [18]	NA
ARV825	Degrades BET family proteins	Using doxorubicin in xenografts and colon cancer cell lines [19]	NA
Digoxin	Inhibits Na+ /K+ pumps	Melanoma, lung, breast, liver, colon, and liver cancer cell lines were treated with barasertib, alisertib, tozasertib (an AURK inhibitor), etoposide, or palbociclib. [20]; in a lung cancer cell line with bleomycin chemotherapy [21]; lung cancer treatment using gemcitabine doxorubicin in xenograft models of breast cancer [21]	NA
Ouabain	Inhibits Na+ /K+ pumps	In cell lines of several cancers (disease of the colon, stomach, oesophagus, lungs, and liver) with barasertib, alisertib, Palbociclib, tozasertib, or etoposide [20]	NA
Temsirolimus	Inhibits mTOR	Docetaxel treatment of Xenografts and Prostate cancer cell lines and; in xenografts and breast cancer cell lines with 5-fluorouracil chemotherapy [22]	Diffuse large B-cell lymphoma, stage II treatment with rituximab (NCT01653067) [23] Capecitabine first-line treatment for recurrent solid cancers in phase I (NCT01050985) [24]
AZD8055	Inhibits mTOR	By treating liver cancer cell lines with TAK931 or XL413 (both CDC7 inhibitors); by using XL413 in xenograft models of liver cancer and a MycOE;Trp53-/- HTVI mouse model of liver cancer [25]	NA
PDL1 blocking or PD1 antibodies	T-cell immune responses	When administered to the KRASG12D, Trp53-/- the syngeneic pancreatic cancer mouse model and pancreatic cancer GEMM, palbociclib, and trametinib significantly improved survival. [26,27]; GEMM with MMTV-rtTA/tetO-HER2 breast cancer and abemaciclib (a CDK4/6 inhibitor) [28]; using CDK4/6 inhibitor trilaciclib in KRASG12D; Trp53-/- palbociclib in syngeneic colon cancer animal models and lung cancer GEMM [29]; genetic deletion of Cdkn1a or Cdkn2a in syngeneic melanoma mice models [31]	Palbociclib with avelumab (anti-PDL1) for breast cancer in phase II (NCT04360941) [30]; In numerous ongoing trials, PD1 or PDL1 antibodies are added to chemotherapy; however, it is not known whether or if this triggers senescence
CAR T cells	T-cell immune responses	Inducing senescence in KRASG12D;Trp53-/- lung cancer GEMMs with palbociclib and trametinib [32]	NA

AURK{Aurora Kinase}; BET{Bromodomain And Extra Terminal Domain}; CAR{Chimeric Antigen Receptor}; CDK{Cyclin-Dependent Kinase}; CLL{Chronic Lymphocytic Leukemia}; GEMM{Genetically Engineered Mouse Model}; HTVI{Hydrodynamic Tail Vein Injection}; PDX{Patient-Derived Xenograft}; MMTV{Mouse Mammary Tumor Virus}; NA{Not Available}; Nav-Gal{Galactic-Conjugated Navitoclax}; OE{Overexpression}; PARP{Poly(ADP-Ribose) Polymerase}

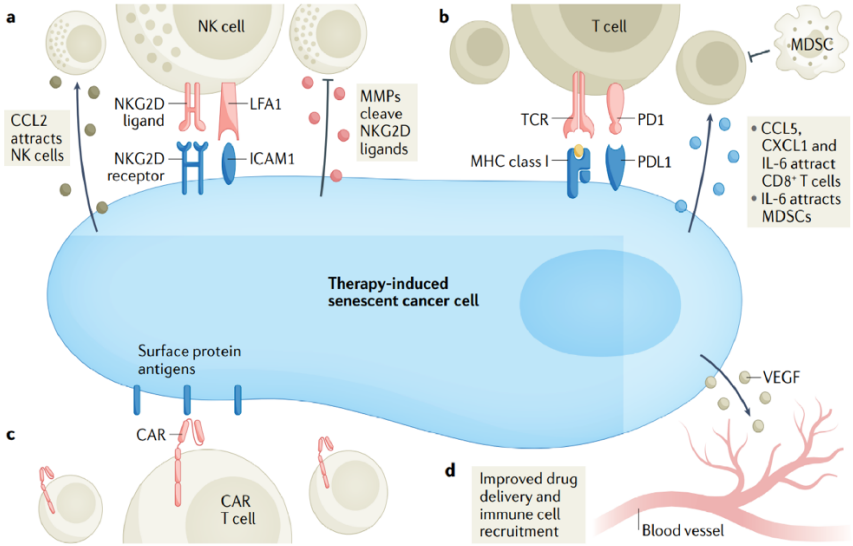

Fig. 5 | Immune response-mediated senolysis.

IMMUNE RESPONSE-MEDIATED SENOLYSIS

Substances that modulate immune cells, such as cytokines, chemokines, and SASPs, can either hasten or slow down the elimination of senescent cells [33] (Fig. 5; Table 1). Initial research on the effect of SASP components on the immune system showed that the SASP promotes the clearance of senescent pre-neoplastic cells, hence maintaining tissue homeostasis. A study on the link between liver fibrosis and cancer provides more proof. In a model of carbon tetrachloride-induced liver fibrosis, treatment with the chemical increases the expression of a ligand for an NK cell activating receptor, NKG2D, therefore facilitating the use of NK cell-mediated cytotoxicity in the elimination of senescent cells. In a mouse model of hepatocellular carcinoma caused by the NrasG12V oncogene, restoring Trp53 expression promoted senescence in cancer cells and CCL2 production. NKG2D overexpression on senescent cells attracts NK cells, which subsequently undergo NK cell-mediated senolysis (Fig. 5a). KRASG12D; Trp53-/- mice are a lung cancer model that has been treated with the MEK inhibitor trametinib and the CDK4/6 inhibitor palbociclib to induce senescence. Tumour necrosis factor (TNF) and intercellular adhesion molecule 1 (ICAM1) were both generated by NF-B-controlled senescent cells in the SASP, activating natural killer (NK) cells and increasing cancer cell eradication. Despite the likelihood that prolonged inflammation caused by the SASP might have harmful consequences under some situations, this work reveals that senescence and the SASP can increase immune system detection and cancer cell killing. In this case, senescence induction may be helpful because NK cells efficiently eliminate senescent cancer cells.

KRAS mutation causes pancreatic ductal adenocarcinoma in a mouse model; researchers have demonstrated that enhancing immune surveillance with drugs that target the immunological barrier PD1 may be senolytic[26]. We found that therapy-induced senescence improved tumour vasculature function via SASP-facilitated vascular remodelling; in addition, when anti-PD1 antibodies are administered with palbociclib and trametinib, senolytic effects are shown directly. Because of this reaction, more of the chemotherapeutic drug gemcitabine can penetrate the cancer cells and have an impact (Fig. 5d). As a result of SASP activation in the tumour microenvironment, endothelial cells produce more of the cell surface protein VCAM1, which promotes lymphocyte adherence and extravasation into tissues [26]. Including the pro-inflammatory cytokines and the pro-angiogenic factor VEGF as well as IL-6, chemokines CCL5 and CXL1 into SASP increases CD8+ T cell infiltration into tumours and improves the effectiveness of checkpoint blockade anti-PD1 treatment [26] (Fig. 5b). These fascinating results raise the possibility that treatment-induced SASP, vascular remodelling, and the development of more effective T cell-based immunotherapies are all interconnected. Immune responses and the effectiveness of anti-PD1 treatment have been demonstrated to be enhanced by pro-senescence therapy in several preclinical investigations across a variety of cancer types. [27] (Table 1). (Table 1).

Neoantigens must be expressed on the surface of a cancer cell for cytotoxic T lymphocytes to target it for destruction. When anti-PD1 treatment demonstrates synergy with pro-senescence therapy, the issue of whether neoantigens are recognised by senescent cancer cells emerges. The ability of T lymphocytes to recognise neo-antigens in senescent cancer cells may be improved by elevating the expression of antigen presentation genes, such as those that create major histocompatibility complex (MHC) class I molecules [26]. Cancer/testis antigens may be re-expressed due to senescence-related epigenetic reprogramming. The finding that introns are present in many mRNA transcripts from senescent cells raises an intriguing new possibility. Synergism between the SASP's recruitment of immune cells and the emergence of such neoantigens is possible; treatments that increase T-cell activity, such as anti-programmed death-1 (anti-PD-1) antibodies, may amplify this effect.

Taken as a whole, these findings suggest that therapeutic efficacy may be enhanced when senescence induction therapies are combined with immunotherapies. However, the effectiveness of immunotherapies may also be affected by the SASP in senescent cancer cells, which may vary by tissue type, senescence cause, time, and hormones. Chimeric antigen receptor (CAR) T-cell therapies that detect cell surface proteins increased in senescence can be developed to alleviate these context-dependency difficulties of immunotherapies. Clearance of senescent cells by uPAR-specific CAR T cells was observed in vitro. A mouse model of lung cancer (Fig. 5c). Notch3, DEP1, B2M, DPP4, NKG2D, and ICAM1 are NOTCH1 (ref. [21]) is only one example of a cell surface protein that is increased in senescence and, as a result, may be targeted by immunotherapies. Unfortunately, while senolytic treatments based on CAR-T cells show promise, they may be out of reach for the average patient due to high costs.

METHODS FOR EXPLORING POSSIBLE NEW SENOTHERAPEUTICS

Inducing SnC death (senolysis), reversing the senescent state (senoreversal), and maybe suppressing the adverse effects of the SASP (senostasis) are only some of the strategies found to combat the harmful effects of SnCs (Fig. 6). Thus, senolytics and other small-molecule senotherapeutics, have attracted much interest from the academic and corporate communities because to their great translational potential. Bioinformatics and selective library screening are the most effective methods for discovering new senotherapeutics. However, new senotherapeutics may be developed thanks to recent advances in drug screening and design (Fig. 7).

DRUG SCREENING. Because SnCs are the focus of senotherapeutics, drug development using this approach relies heavily on in vitro SnC-based screening. Considering the variety of SnCs, it is possible to reproduce the variation by cultivating different cell types and driving them into senescence under varying stress conditions. Senoprobes may be used to detect and study the senotherapeutic effects on SnCs during drug treatment. These senoprobes include cell viability assays and SA—gal-based chemogenic or

fluorogenic dyes. To find senolytics and senomorphics, phenotypic pharmacological screening might be used. Genome-wide screening using CRISPR/Cas9 has been used to find genes like SMARCB1, coagulation factor IX(F9), and KAT7 that may influence cellular senescence. By learning more about the biology of senescence and discovering new senescence targets, we might potentially leverage the essential proteins and pathways that control senescence in structure-based virtual screening. It is possible to supplement senotherapeutic screening with the use of Computer-Aided Drug Design (CADD), Machine Learning (ML), And Artificial Intelligence (AI). Deep learning-based senescence scoring by morphology (DeepSeSMo), built from pre-trained convolutional neural networks, has recently been proven effective in identifying SnCs and quantifying senescence.

DRUG DESIGN. The discovery of new senotherapeutics is aided by drug screening; it creates relatively few new chemical entities because of its heavy reliance on existing chemical libraries. Nonetheless, rational drug design is optimal for developing senotherapeutics, which contain unique chemical structures based on specific molecular processes. In addition, it may be utilised to improve the efficacy of senescence drug screening hits and reported senotherapeutics by iteratively studying their structure-activity relationships to achieve pharmacodynamic and pharmacodynamic properties more typical of pharmaceuticals. CADD, AI, and ML may be used with traditional medicinal chemistry to create novel senotherapeutics. [34]

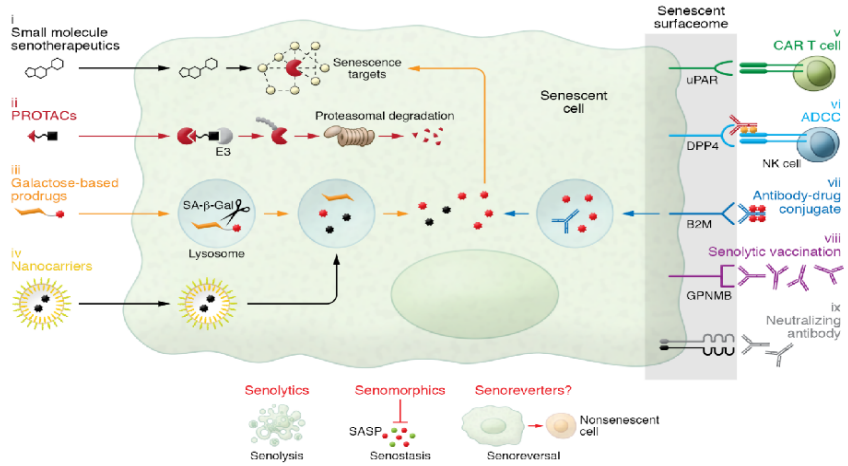

Fig. 6. Targeting senescent cells using current methods.

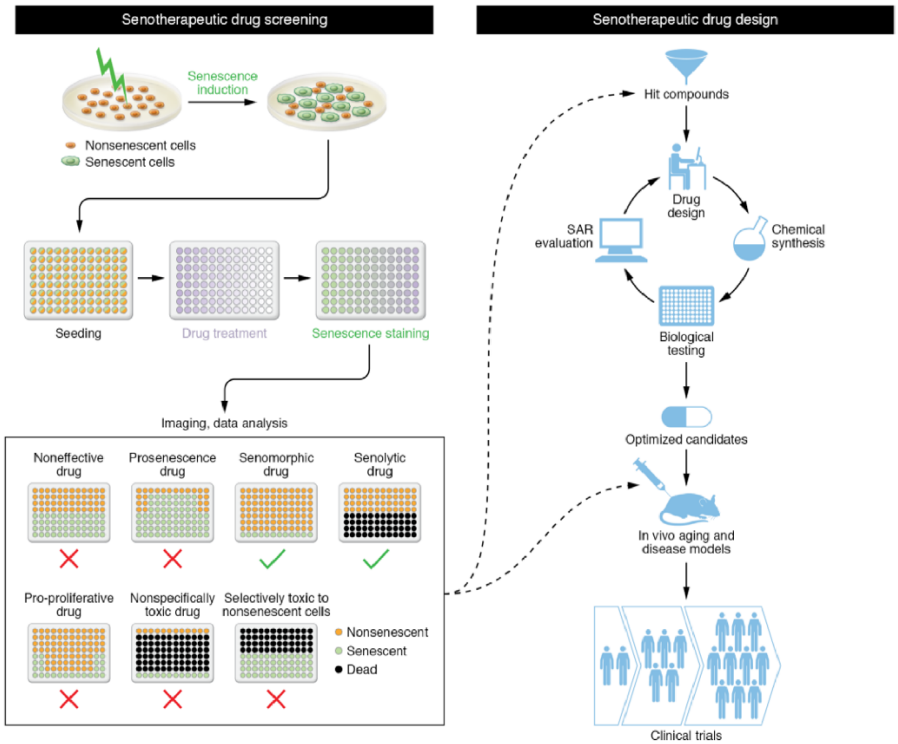

Fig. 7. Drug design and drug screening can aid in developing senotherapeutics for treating age-related diseases and aging.

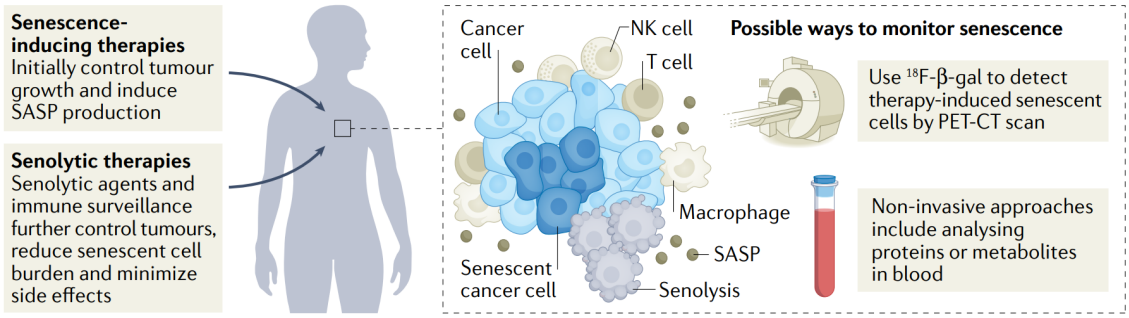

Fig. 8 | Future Perspective For Senescence-Based Therapies

Future Prospects And Obstacles

Combination treatment has been shown to reduce the likelihood of drug resistance developing. Using many therapies simultaneously to combat cancer has been standard practice since 1958. Yet, toxicity is a significant hurdle that prevents pharmaceutical combinations in oncology from being as successful as they may be. As direct combo toxicity may be avoided with sequential pharmaceutical therapy regimens, more therapeutic options should be available. Senescence is a permanent state of cells that persists even after the senescence inducer is eliminated. Sequential treatment, including pro-senescence and senolytic medicines, makes sense[9]. As such, pro-senescence therapy can effectively be included in a treatment timeline. It is possible that genotoxic chemotherapy, which induces senescence in normal tissues, might have undesirable side effects. [35] (Fig. 8).

Another area for improvement is that there are no universally accepted biomarkers for the senescent state. A single marker cannot reliably distinguish between senescence and other growth-arrested states is apparent. Several laboratories have established gene signatures that define primary cell senescence. To find the SENCAN classifier for malignant senescence, for instance, we recently employed a panel of senescent cancerous cells. In models of chemotherapy-induced senescence[31], galactose-conjugated fluorescent nanoparticles showed promise for identifying senescent cells and may prove helpful for this purpose in vivo. It would be ideal to monitor the success of senescence induction in patients' tumors using noninvasive imaging techniques. A radioactive -β-gal PET tracer might be utilised for this purpose, although its research and development are yet in their early stages (Fig. 8). Yet, it is possible that -gal-associated detection methods miss detecting specific senescent cells. It has been found that senescent cells in some kinds of tissue do not trigger SA— β-gal activity. Due to the presence of macrophages with increased SA—β-gal activity, inflammatory tumour tissues may yield false-positive findings. Several noninvasive approaches exist for monitoring senescent cell clearance. Oxylipin production, for instance, skyrockets throughout old age. In particular, senescent cells collect and produce the internal prostaglandin dihomo-15D-PGJ2, which is one kind of oxylipin. Dihomo-15D-PGJ2 may be identified as a significant development in human urine and blood samples. (Fig. 5).

There is also the problem that there need to be senolytic medications that work well for everyone. Due to their intended use in combating the effects of aging, most senolytic medicines have been evaluated in primary cell cultures. Utilizing a collection of old cancer cells, we recently discovered very varied senolytic effectiveness utilizing the most commonly used senolytic drug (navitoclax). Not only is there no gold standard for diagnosing senescence, but there is also a pressing need to find ways to exploit the ubiquitous and druggable susceptibility of senescent cancer cells. We have developed a genetic screening tool based on inducible CRISPR-Cas9, in which gene editing is begun only after cells have been subjected to senescence induction. This paves the way for drop-out screens to be carried out, with the ultimate goal of identifying new senolytic targets throughout the whole genome. If common weaknesses are shared by senescent cancer cells, they should appear in unbiased genomic tests. The wide variety of tumours is another problem that affects all cancer therapies. Tumour heterogeneity may hinder senescence induction, which results in different therapeutic responses in other cancers. Would it be essential to induce senescence in most cancer cells with innate heterogeneity, or do senescent cells kill non-senescent cancer cells through the bystander effect? The ability of senescent cells to sensitise non-senescent cancer cells to senolytic therapy by spreading the senescent phenotype through the SASP to adjacent non-senescent cells in TUMORS is poorly understood. Moreover, the SASP of the senescent cells might form a local TUMOR microenvironment that can amplify such bystander effects. For instance, the bystander effect is thought to be responsible for killing out resistant cancer cell subpopulations, which may explain why immunotherapy is so effective in treating the disease. Bystander effects may offer a way to overcome TUMOR heterogeneity, but their significance in the context of senescence-inducing medications has yet to be understood. Thus, research into senolytic treatment, eliminating normal senescent cells, is essential for older people. Increasing senescent cells in old tissues may threaten the structural integrity of hepatic and perivascular tissues or harm vascular endothelial cells, leading to fibrosis and health failure. The potential for this risk necessitates the research and development of cancer-selective senolytics. The advantages of senescence-based therapeutics, including the potential for sequential therapy and the recruitment of immune cells, make them worthwhile to investigate despite many unanswered concerns.[5]

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