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Senolytic therapies for healthy longevity

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Clearing senescent cells with targeted drugs to combat age-related disease

The estimated “natural” lifespan of humans is approximately 30 years. Improvements in working conditions, housing, sanitation, and medicine have extended life expectancy to nearly 80 years in most developed countries. The downside of longer lifespans is that a significant fraction of the population now experiences aging-related tissue deterioration and diseases of aging. Healthy aging is limited by the fact that natural selection favors genetic programs that confer fitness early in life to maximize reproductive output without consideration as to how these alterations may have late-life detrimental effects. One such program is cellular senescence, which enhances the reproductive success of the young by blocking proliferation of cancerous cells but decreases the health of the old by littering tissues and organs with senescent cells (SNCs). In mice, the selective elimination of SNCs, commonly known as senolysis, extends median lifespan and prevents or attenuates various features of aging and age-related diseases such as osteoarthritis, atherosclerosis and neurodegeneration, without exerting overt adverse side effects (1, 2). These exciting findings have inspired the development of senolytic drugs to safely eliminate the SNCs that drive tissue degeneration and age-associated disease in humans.

Much of our current knowledge about the properties of SNCs is based on experiments in cultured cells, largely because SNCs in tissues and organs are difficult to identify and collect. One key characteristic of SNCs is that they are in a state of permanent cell-cycle arrest, typically initiated and maintained by the p53-p21-RB and p16-RB tumor suppressor pathways (3). Various stresses induce this state, including oxidative and genotoxic stress, telomere shortening, excessive mitogenic signaling, DNA replication errors, mitotic defects, and mitochondrial dysfunction. Furthermore, SNCs produce a bioactive secretome, referred to as the senescence-associated secretory phenotype (SASP) (4), that can disrupt normal tissue architecture and function through diverse mechanisms, including recruitment of inflammatory immune cells, remodeling of the extracellular matrix, induction of fibrosis, and inhibition of stem cell function (3).

How then should researchers identify targets for the development of senolytic drugs, considering that our knowledge of SNCs in vivo is presently limited? One strategy would be to identify vulnerabilities shared by cancer cells and SNCs and then use specifically tailored

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variants of anticancer agents to target such vulnerabilities to trigger the selective elimination of SNCs. Cytotoxic cancer agents have significant limitations, including the emergence of therapy-induced resistance due to the high mutation rate of cancer cells and the need for the complete eradication of cancer cells to achieve disease remission. These same challenges are unlikely to occur with senolytic drugs for several reasons. First, while evidence is emerging that SNCs are subject to genomic instability, SNCs by definition do not proliferate, thereby precluding the propagation of therapy-resistant clones. Second, although rates of senescence increase with aging, the absolute numbers of SNCs that accumulate in tissues remain generally low. Third, while cancer cells need to be entirely eradicated for successful treatment, partial elimination of SNCs can prevent or attenuate age-related disease phenotypes, with beneficial effects of senolysis typically occurring at clearance rates of 60–80% (1, 2). While cancer therapeutics that interfere with cell division are unsuitable as senolytic drugs, agents that block the pathways that cancer cells rely on for survival might be worth pursuing as senolytics, because apoptosis resistance is a feature shared by cancer cells and SNCs.

Proof-of-principle evidence for the effectiveness of the above strategy comes from targeting the B cell lymphoma 2 (Bcl-2) protein family members Bcl-2, Bcl-xL, and Bcl-w, three anti-apoptotic proteins frequently overexpressed in both cancer cells and in SNCs (see the figure). Independent laboratories have shown that two targeted cancer therapeutic agents, ABT-263 and ABT-737, selectively eliminate SNCs by blocking the interaction of Bcl-2, Bcl-xL and Bcl-w binding with BH3 domain-containing pro-apoptotic proteins (5, 6). Remarkably, Bcl-2 inhibitors are senolytic across species, in multiple cell types, and against cells made senescent using multiple senescence-inducing stressors. In mice, pharmacological inhibition of Bcl-2 family members results in the elimination of various kinds of senescent stem cells, including hair follicle, skeletal muscle, and hematopoietic stem cells, in each instance resulting in the rejuvenation of the stem cell populations (5, 6). Importantly, in mouse models for two major age-related human diseases, atherosclerosis and neurodegeneration, ABT-263 cleared SNCs from atherogenic plaques and brain tissue, respectively, substantially attenuating the progression of key disease phenotypes (7, 8). A second example where lessons can be taken from oncology pertains to the p53 pathway. Molecules that interfere with the Mdm2-p53 interaction and thereby increase p53 activity can induce apoptosis in cancer cells that express wild-type p53. Interference with this regulatory mechanism by UBX0101 triggers apoptosis of SNCs that accumulate in articular cartilage and synovium, and these cells are causally implicated in the development of osteoarthritis (9).

In addition to the challenge of drug resistance, most cancer therapies are limited by toxic side effects. This holds true for Bcl-2 inhibitors, which cause unintended neutropenia and thrombocytopenia. These side effects, however, may not be problematic for this class of senolytics. Because SNCs accumulate slowly and are non-proliferative, their abundance could be controlled via intermittent dosing. Like Bcl-2 family inhibitors, drugs that target p53's ability to bind to MDM2 are selective, though not specific for cancer cells and SNCs, and therefore are also likely to affect some normal cell populations. Various other approaches have been reported to trigger the elimination of SNCs, including the treatment of SNCs with a peptide drug designed to interfere with the p53-FOXO4 interaction (10), the

creation of galacto-oligosaccharide-coated nanoparticles to deliver cytotoxic agents into senescence-associated-β-galactosidase-positive SNCs (11), and the use of natural products with anticancer properties, such as quercetin and fisetin, and quercetin in combination with the pan-tyrosine kinase inhibitor dasatinib (12, 13). Although quercetin, fisetin, and dasatinib are often referred to as senolytics, it should be noted that they each act on a myriad of pathways and mechanisms implicated in diverse biological processes, which makes it difficult to decipher how they eliminate or otherwise impact SNCs and to attribute any therapeutic or detrimental effects they may have in clinical trials to senolysis.

Senolytic molecules that inhibit drug targets originally discovered in oncology could yield promising first-generation human drugs. This strategy may not however accomplish the long-term goal of developing the most ideal senolytics that selectively, safely and effectively eliminate detrimental SNCs upon systemic administration (see the figure). Efforts to identify such “next-generation” senolytics could nonetheless greatly benefit from general principles that have been used in the discovery of cancer drugs. For instance, it will be important to focus drug development on age-related degenerative diseases in which SNCs are clear drivers of pathophysiology and in which senolysis could be disease modifying (e.g., osteoarthritis and atherosclerosis). SNCs implicated in conditions that meet these requirements should be characterized for unique vulnerabilities to identify gene products that enable the survival of those particular SNCs. Agents that selectively target such gene products are likely to have the lowest risk of harmful side effects.

Development of such next-generation senolytics will require a richer molecular description of the in vivo properties of SNCs. This includes potentially beneficial SNCs that arise in the context of tissue repair and regeneration to facilitate tissue remodeling and limit excessive fibrosis through the SASP factors they produce (14). One problem in acquiring such information is that SNCspecific markers in vivo are only now being developed. Until such markers are validated, accurate visualization, collection, and tracking of SNCs in tissues and organs and at sites of age-related disease is difficult. The same challenge also applies for experiments designed to determine whether properties of SNCs in vivo are preserved in vitro and to identify which cells become senescent in a particular disease of aging. Another challenge is the increasingly likely possibility that, rather than being a static endpoint, cellular senescence is a series of progressive and phenotypically diverse cellular states acquired after initial growth arrest (3). This SNC evolution is at least partially driven by processes that introduce genomic diversity, such as the formation of micronuclei and activation of retrotransposable elements (15). These findings predict the SNCs are heterogeneous collections of cells with fewer shared core properties than anticipated.

The SASP is considered the driver of tissue deterioration and disease, but due to the challenges above, several fundamental questions regarding the bioactive secretome of SNCs in vivo remain unanswered. For instance, it is unclear to what extent SASP factors systemically drive age-related pathologies by entering the circulation. If this is substantial, local clearance of SNCs at specific disease sites may not provide therapeutic benefit, and systemic senolysis may be required. Additionally, cell culture experiments indicate that the composition of the SASP varies by cell type and senescence-inducing stressor. The extent to which diversity in SASP composition translates into phenotypic heterogeneity in disease and

aging remains to be established. Moreover, the SASP is complex and consists of hundreds of secreted proteins, raising the question as to whether the phenotypes result from the effects of many factors or only a subset.

As knowledge of the fundamental biology and vulnerabilities of SNCs expands, the rational design of senolytics is expected to yield therapies to eliminate SNCs that drive degeneration and disease. This positive outlook is based on successes in oncology and the fact that the main limitation of cancer therapies, the clonal expansion of drug-resistant cells, does not apply to SNCs. Additional confidence comes from the recent progress in bringing senolytic agents into human clinical trials. The first clinical trial is testing the targeted senolytic drug UBX0101 for the treatment of osteoarthritis of the knee, with a second drug, UBX1967, specifically tailored for diseases of the aging eye, advancing to human testing. Multiple clinical trials targeting diverse diseases of aging with senolytic drugs are expected to follow soon.

Although many questions in SNC biology remain unanswered, it is widely recognized that senolysis has the potential to transform the treatment of age-related degenerative disorders. One condition in particular, osteoarthritis, is highly suitable for this purpose because it meets many important criteria that allow for well-designed clinical trials. Key among these are the facts that preclinical studies in mice show that SNCs drive disease pathology, that local SNC senolysis reverses disease pathology and alleviates joint pain, and that limited, intermittent senolytic treatments are sufficient to obtain a therapeutic effect. The ability to administer the senolytic locally is not only critical to control potential side effects, but also to increase the likelihood that any disease modifying benefits are due to senolysis at sites of disease rather than systemic senolysis or off-target, but disease modifying effects. Success in these first clinical studies is the next critical milestone on the road to the development of treatments that can extend healthy longevity in people.

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References

1. Baker DJ et al., Nature 479, 232–236 (2011). [PubMed: 22048312]
2. Baker DJ et al., Nature 530, 184–189 (2016). [PubMed: 26840489]
3. van Deursen JM, Nature 509, 439–446 (2014). [PubMed: 24848057]
4. Coppe JP et al., PLoS Biol 6, 2853–2868 (2008). [PubMed: 19053174]
5. Yosef R et al., Nat Commun 7, 11190 (2016). [PubMed: 27048913]
6. Chang J et al., Nat Med 22, 78–83 (2016). [PubMed: 26657143]
7. Bussian TJ et al., Nature, (2018).
8. Childs BG et al., Science 354, 472–477 (2016). [PubMed: 27789842]
9. Jeon OH et al., Nat Med 23, 775–781 (2017). [PubMed: 28436958]
10. Baar MP et al., Cell 169, 132–147 e116 (2017).
11. Munoz-Espin D et al., EMBO Mol Med 10, (2018).
12. Xu M et al., Nat Med 24, 1246–1256 (2018). [PubMed: 29988130]
13. Yousefzadeh MJ et al., EBioMedicine 36, 18–28 (2018). [PubMed: 30279143]

14. Munoz-Espin D et al., Cell 155, 1104–1118 (2013). [PubMed: 24238962]
15. Dou Z et al., Nature 550, 402–406 (2017). [PubMed: 28976970]

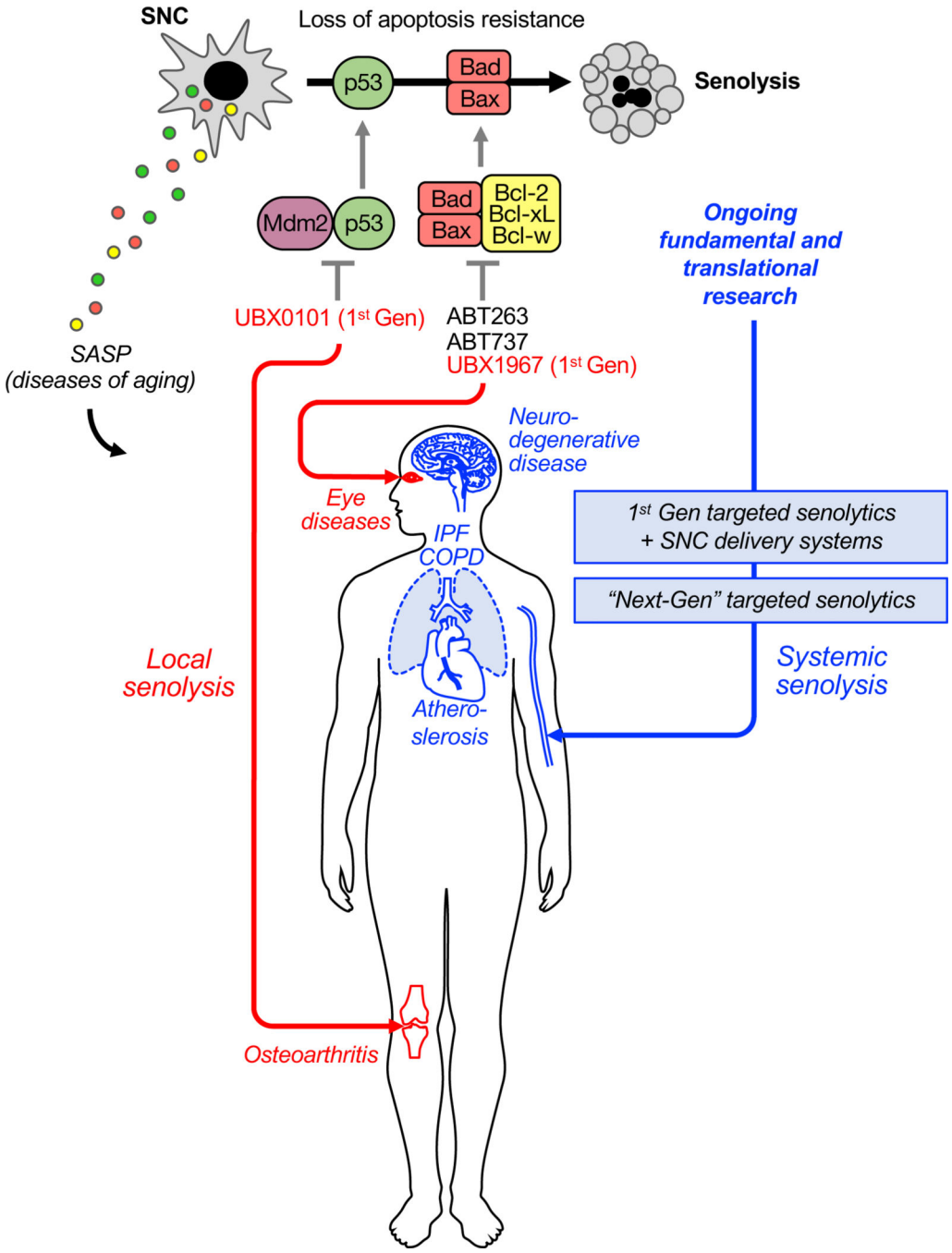

Figure. Senolytic therapies for optimized aging.

SNCs resist cell death by activating prosurvival and inhibiting pro-apoptotic pathways. First generation senolytic drugs developed to effectively target key components of these pathways eliminate SNCs and thereby the SASP that drives diseases of aging. Clinical testing of one such drug, UBX0101, is ongoing for the treatment of osteoarthritis, with a second drug, UBX1967, advancing to human testing for eye diseases. Development of highly selective senolytics that safely and effectively eliminate SNCs upon systemic administration for

treatment of neurodegenerative or cardiovascular diseases, among others, awaits further advancements from fundamental and translational research on SNCs.