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Mechanisms of Ageing and Development

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Senolytic drugs: Beyond the promise and the hype

Cellular senescence was first described by Hayflick and Moorhead in 1961 and since then it has evolved from being often disregarded as an *in vitro* curiosity to more recently being hailed as a common factor driving tissue dysfunction during aging and disease. Cumulative evidence indicates that senescent cells accumulate with age in most tissues and in the context of multiple age-related diseases, making them a promising therapeutic target (Gorgoulis et al., 2019).

Senescent cells have been shown to be resistant to cell-death *via* apoptosis and to up-regulate prosurvival pathways. This led to the proposition that by targeting senescence-associated prosurvival pathways it may be possible to specifically eliminate detrimental senescent cells from tissues. Interventions that target such pathways and specifically kill senescent cells (but not proliferating cells) are commonly known as “senolytics” (Robbins et al., 2021).

In this special issue, we bring together experts in the field of cellular senescence, who have been at the forefront of the identification and development of “senolytic” interventions, as well as its preclinical testing and clinical application.

Two articles by the laboratories of Paul Robbins and Daniel Muñoz-Espín focus on emerging approaches to identifying new senolytic compounds such as the use of high-throughput screens and bioinformatics (Zhang et al., 2021) as well as the application of nanoparticles as possible carriers of drugs targeting specifically senescent cells (Morsli et al., 2022).

Furthermore, a collection of articles from the laboratories of Julie Andersen, Nathan LeBrasseur, Sundeep Khosla, Mikolaj Ogrodnik, Miranda Orr and Gavin Richardson focus on the potential impact of senolytic interventions in different organs such as the brain (Gonzales et al., 2021; Lee et al., 2021), muscle (Englund et al., 2021), bone (Doolittle et al., 2021), skin (Pils et al., 2021), and heart (Pils et al., 2021) in the context of aging and disease. An article by the laboratory of Stefan Tullius proposes the promising application

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of senolytic drugs to improve organ quality and reduce graft immunogenicity during solid organ transplantation (Matsunaga et al., 2021).

Finally, an article by the laboratory of James Kirkland offers strategies to best translate preclinical findings to humans and describes some of the ongoing and planned clinical trials using senolytic drugs (Wissler Gerdes et al., 2021).

While there is a growing excitement in the field, we strongly felt that this special issue should not be a pamphlet solely highlighting the promise of senolytics and we asked authors to discuss critically the challenges and limitations of its application.

As emphasized in several of the articles of this special issue, senescence is a complex and highly heterogenous phenotype and despite tremendous progress in recent years we are still far from fully understanding it. Senescent cells have been shown to have both beneficial and detrimental effects depending on the physiological context, thus there may be pitfalls to their elimination. There is no single, standalone marker that allows the identification of senescent cells, posing a challenge to their identification and targeting. The senescent phenotype as well as the response to senolytic drugs largely depends on the cell-type and inducing stimuli, which poses a challenge to a “one-drug-fits-all” approach. Finally, post-mitotic cells such as neurons (Gonzales et al., 2021; Lee et al., 2021) and cardiomyocytes (Owens et al., 2021) express senescent markers and can be eliminated by senolytic drugs, which may be detrimental to tissue integrity unless these cells are efficiently replaced.

Despite these challenges, it is undeniable that preclinical studies and early clinical trials support that senescent cells are promising therapeutic targets to alleviate, or even reverse, functional chronic disorders in aging. We predict that as our understanding of senescence and its complexity continues to grow, more effective ways to target these cells will likely be developed.

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