Journal of Pharmaceutical Chemistry and Chemical Science

Progress towards development of clinically-relevant senotherapeutics for extending healthspan

Paul D. Robbins

University of Minnesota, USA

Abstract

Cellular senescence is caused by the accumulation of DNA damage and/or other cellular stressors that drives proliferating or terminally differentiated non-dividing cells to a state characterized by replicative arrest, profound chromatin changes, increased expression of the cell cycle inhibitors p16Ink4a and/or p21CIP1 as well as resistance to apoptosis. Some senescent cells can develop a senescence-associated secretory phenotype (SASP), consisting of pro-inflammatory cytokines, chemokines, and extracellular matrix-degrading proteins, which have deleterious paracrine and systemic effect. Cell senescence is one of the hallmarks of aging known to negatively influence a healthy lifespan and thus represents a target for drug development. Drugs able to kill senescent cells specifically in cell culture, termed senolytics, or suppress markers of senescence, termed senomorphics, can reduce the senescent cell burden in vivo and extend healthspan. We have developed a senescent cell culture, C12FDG-based SA-ß-gal assay for screening for agents able to function as senotherapeutics. Using this assay, we identified a number of senotherapeutics including HSP90 inhibitors, Bcl-2 family inhibitors, fisetin and the combination of dasatinib/quercetin as senolytics and IKK/NF-kB inhibitors, mitochondrial targeted free radical scavengers and young stem cell-derived extracellular vesicles as senomorphics. The activity of these senotherapeutics to reduce senescence and extend healthspan has been confirmed in the Ercc1-/Δ mouse model of accelerated aging carrying a p16INK4a-Luciferase reporter and, in some cases, in naturally aged mice. In addition, several of these senotherapeutic compounds currently are in Phase IIb clinical trials for assessing their ability to reduce the senescent cell burden. Progress towards optimizing the activity of these identified senotherapeutics as well as the identification of novel senotherapeutics will be presented.

2nd International Conference on Pharmacology and Pharmaceutical research
Webinar | April 21, 2021

Citation: TPaul D. Robbins, *Progress towards development of clinically-relevant senotherapeutics for extending healthspan,* Euro pharma 2021, 2nd International Conference on Pharmacology and Pharmaceutical research, Webinar, April 21, 2021, 05:02-11