Podcast Episode 22: Current Status of Senolytics

As of 27.9.2021

Episode teaser

Hey everyone! Welcome to the new episode of the Life Extension Podcast – technology & magic, society & business. In this episode I'll discuss the current status of senolytics, new drugs acting against so-called zombie cells, which are thought to be at the origin of Alzheimer, atherosclerosis, cancer, and all the other age-related diseases. Continue listening, if you want to hear more about what we know about cell senescence and its role in aging and potentially in a reversal of aging, about drug research and trials, the business potential of senolytics, and perhaps most importantly about what this could mean for you to delay age-related diseases and to extend your life.

What is cell senescence

The term cell senescence was coined by Leonard Hayflick already in 1961. He found that somatic cells stop dividing after 40 to 60 replications due to a limited number of telomeres in the chromosomes. When cells stop dividing, he called them senescent. Today the use of the term cell senescence has changed, based on new insights gained during the last 10 years.

When cells in adults get old or damaged they normally enter apoptosis – also called programmed cell death. This is a process of cellular self-destruction, during which the cell dissolves itself to make room for new cells. But sometimes damaged cells become senescent instead of entering apoptosis. Senescent cells stop replicating as if they were dead, but they don't self-destruct. In the contrary they develop new activities, which is called SASP, or senescence-associated secretory phenotype. They produce and release signalling molecules which lead to inflammation of neighbouring cells and tissues. Even worse, they can convert other cells to senescent state as well. This creepy behaviour earned senescent cells their nick name "zombie cells". Similarly to the movies, zombie cells are undead, technically dead but behaving as if they were not, and even infecting the living with their undead state of being. The immune system would normally attack and kill these cells, but with increasing age they accumulate in greater numbers, eventually proving too much for the immune system to handle. As a result cell senescence leads to inflammation and disease (Kirkland 2020; MDC). By way of infecting other cells and tissues, they are also thought to be responsible for co-morbidity, the experience that one disease somehow leads to another. For example, in the case of chronic lung disease (COPD) stress caused by smoking is thought to cause senescence in lung cells, which in turn causes chronic lung disease. With senescence spreading to other tissues, the patient could then develop heart disease in addition to his lung disease (King 2020). According to the prevailing geroscience theory, cell senescence is considered today as a root cause contributor to many age-related disease conditions. Cell senescence is one of the hallmarks of aging (Campbell 2020).

But what causes cell senescence? In fact cell senescence is normal to a degree, as it has harmful and beneficial effects. In young and healthy body tissue cell senescence is part of a repair mechanism, when

signalling molecules released by senescent cells call in the immune system to attack and clear cells, which were damaged by external factors like e.g. smoking (King 2020), radiation, or obesity (Conley 2020). Cell senescence is playing a beneficial role in the suppression of tumours, wound healing, and during early development stages of organisms. But when the organism gets older, the immune system weakens and becomes overwhelmed by accumulating senescent cells, leading to age-related diseases like atherosclerosis or osteoarthritis (Scudellari 2017).

The relationship between cell senescence and cancer is a complicated one. Senescent cells act tumour suppressant when they cause inflammation in neighbouring cells and tissues, triggering an immune response to destroy damaged cells. But when senescent cells accumulate beyond a certain threshold, the immune system can't clear them anymore, turning senescent cells themselves into a risk factor for cancer. Therefore the timing of intervening against senescent cells is important, as we want to slow down or reverse the onset of chronic diseases, but without promoting cancer.

The discovery of molecular pathways related to cell senescence and a number of observations in laboratories have led to the idea of creating drugs to remove senescent cells and in turn to achieve an improvement of age-related conditions, or to slow down and possibly reverse aging.

Numerous preclinical trials with mice and human tissues have clearly confirmed the role of senescent cells in causing age-related diseases, frailty, and earlier death. These effects can be demonstrated when transplanting senescent cells into mouse models, and they would be alleviated when senescent cells are removed. Or put in a different way, transplanting zombie cells into mice makes them age faster, reducing them through senolytic drugs makes them younger.

Senolytic drugs

Many senescent cells do not only cause inflammation of other cells and tissues. They also manage to protect themselves against programmed cell death by a defense mechanism called SCAP (senescent cell anti-apoptotic pathways). The pharmacological strategy against senescent cells is to temporarily interrupt this defense mechanism, finally leading to their self-destruction. Several such compounds, called senolytics, have already been confirmed. Administrations of Dasatinib, Quercetin, and Fisetin have been demonstrated to massively reduce the number of senescent cells in mice, monkeys, and in humans, and at the same time leading to improvements of cardiac, vascular, kidney functions, and other benefits with respect to insulin sensitivity, diabetis, bone, brain, and lung disease. Conditions of frailty in mice have improved, health and life spans were extended. At present multiple clinical trials with humans are under way in phase 1 and 2 for kidney, lung, and bone diseases, diabetis, Alzheimer's, and frailty (Kirkland 2020). Another class of drugs, called senostatics, work from the other side by preventing or slowing down cell senescence in the first place. Rapamycin and Metformin are the best-known senostatics. While the apparently best-known group of researchers in the senolytics field around Kirkland in the Mayo Clinic warns against intervening in the formation of senescent cells, others like medical practitioner Alan Green suggest to use senolytics and senostatics at the same time (Green 2021).

While a few senolytic compounds have already been identified, with efficacity well established, they also exhibit side-effects in relation to the tumour suppressant function of senescent cells, which need to be further investigated during clinical trials.

Timing and dosage of senolytic drugs are important and still need to be explored further. E.g. treatment of young mice with Dasatinib and Quercetin has demonstrated beneficial effects when administered in an early stage of invertebrate disk degeneration, but remains useless when disk degeneration is already well established (Novais 2021).

Some researchers suggest to continue searching for further senolytics and senostatics occurring naturally in plants in order to hopefully avoid side-effects (Kaur 2020).

For consumers who can not wait until clinical trials are completed, a few of the senolytic compounds currently under research are easily available. Among them Quercetin or Fisetin are sold as nutritional supplements. Will such supplements really reverse aging as it is hoped for? We don't know yet. Dasatinib on the other hand is not a supplement, but a well-known prescription drug against cancer. Its application as a senolytic drug is therefore called "off-label use", with the major advantage that safety is already well understood.

Business

A number of start-up companies are involved in the race for senolytic drugs. Among them are Calico, a Google subsidiary, as well as Unity Biotechnology, and Oisin Biotechnologies – all being located on the American Westcoast. Investing in the research of senolytic drugs is a very risky game and investors might lose all their money. On the other hand, potential benefits are huge. Cell senescence after all is an important trigger of most if not all age-related disease conditions. Even if senolytic drugs would not be able to completely abolish these diseases, they might nevertheless delay their onset by a few years. Each year of further delaying those diseases would save patients and health insurance companies the cost of treating them, amounting to huge sums of money at the level of countries or the human population. Those risk-taking investors are gambling for a share in what might become the biggest industry which ever was.

Conclusion

So this is the current status of senolytics: a strong geroscience theory has been formulated, biological mechanisms have been identified, benefits on health and life span have been confirmed in experimental trials. Now multiple ongoing clinical trials with humans need to confirm that results can be translated to human applications with acceptable side-effects. There is the hope that a senolytic pill, swallowed every 6 weeks or so, would actually help aging people to live healthier and longer lives, even after they have started to develop serious age-related disease conditions. It will be exciting to look out for results of the ongoing trials, because, if successful, they could lead to the development of such drugs within a few years – in reach for many living humans. Amazing! A human dream come true – if it comes true. Would those pills also be useful as prevention? That is even less clear, as senescent cells also have beneficial effects, and clearing them out too early might be harmful. We will probably need to develop individual

risk-benefit profiles to assess at which stage of life and health senolytic drugs would be more beneficial than harmful. At the moment there is still insufficient data from trials to support administration of senolytic drugs in a safe way (Forever Healthy Foundation 2020, Kirkland 2020). As a consumer, you'd better hold on for a few more years, if you can wait.

Bibliography

Campbell, Molly (2020): Proteomics, "Zombie" Cells and Clinical Biomarkers of Aging. Technology Networks. Available online at https://www.technologynetworks.com/proteomics/articles/proteomics-zombie-cells-and-clinical-biomarkers-of-aging-329469.

Conley, Sabina et al. (2020): Human Obesity Induces Dysfunction and Early Senescence in Adipose Tissue-Derived Mesenchymal Stromal/Stem Cells. In *Front. Cell Dev. Biol,* checked on 10.9.21.

Dolgin, Elie (2020): Send in the Senolytics. In *Nature Biotechnology.* Available online at https://www.nature.com/articles/s41587-020-00750-1.

Forever Healthy Foundation (2021): Dasatinib & Quercetin Senolytic Therapy: Risk-Benefit Analysis. Karlsruhe. Available online at https://brain.forever-healthy.org/display/EN/Dasatinib+and+Quercetin+Senolytic+Therapy, checked on 19.5.21.

Green, Alan (2021): Senolytics Treatment. Available online at https://senolyticstreatment.com/, updated on Feb 2021, checked on 20.9.21.

Kaur, Amanpreet. et al. (2020): An Appraisal on the Value of Using Nutraceutical Based Senolytics and Senostatics in Aging. In *Front. Cell Dev. Biol.* Available online at https://www.frontiersin.org/articles/10.3389/fcell.2020.00218/full.

King, Anthony (2020): Zombie cells hold clues to COPD progression. In *Nature Outlook*. Available online at https://www.nature.com/articles/d41586-020-01374-w.

Kirkland, JL and Tchkonia, T (2020): Senolytic drugs: from discovery to translation. In *Journal of Internal Medicine*. Available online at https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7405395/.

Mayo Clinic (2021): Zombie Cell Edition. Available online at https://discoverysedge.mayo.edu/2020/05/12/mayo-clinic-research-news-zombie-cell-edition/, checked on 8.9.21.

MDC Berlin: When zombie cells attack, senolytics come to the rescue. MDC Berlin. Available online at https://www.mdc-berlin.de/news/news/mdc-lecture-when-zombie-cells-attack-senolytics-come-rescue, checked on 10.9.21.

Novais, Emanuel et al. (2021): Long-term treatment with senolytic drugs Dasatinib and Quercetin ameliorates age-dependent intervertebral disc degeneration in mice. In *Nature Communications* 12 (5213). Available online at https://www.nature.com/articles/s41467-021-25453-2.

Scudellari, Megan (2017): To stay young, kill zombie cells. In *Nature* 550, pp. 448–450. Available online at https://www.nature.com/articles/550448a.

van Deursen, Jan (2014): The role of senescent cells in ageing. In *Nature* 509. Available online at https://www.nature.com/articles/nature13193.pdf.