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Removing zombie (senescent) cells using senolytics slows the aging process

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Abstract

Recent studies have shown a new solution that could delay the aging process, just by removing zombie (senescent cells), all cells in our bodies are at a risk of becoming senescent due to exposure of harmful stimuli that activate a specific signaling pathway. Senescent cells have undergone permanent growth arrest, adopt an altered secretory phenotype, and accumulate in organs with ageing and injury. Recent studies have shown that depletion of senescent cells extends healthy lifespan and delays age-associated disease—proving that senescence and the senescence-associated secretory phenotype are causative agents of organ dysfunction. Great interest is therefore focused on the manipulation of senescence as a novel therapeutic target in many age related disease by using a cocktail of drugs known as senolytics, these reduce the zombie cell count to delay aging by the intermittent administration of the senolytic drug combination, Dasatinib and Quercetin, which transiently disables the pro-survival pathways that defend senescent cells against their own apoptotic environment, selectively eliminates senescent cells in mice and human cell cultures. In the first clinical trial of senolytics, they decreased physical dysfunction in patients with idiopathic pulmonary fibrosis (IPF), a progressive, fatal, cellular senescence-associated disease. In another clinical trials, usage of the senolytic mixture improved the health of patients with diabetic kidney disease, osteoarthritis and age related immunosuppression.

Introduction

Aging is characterized by a gradual functional decline. In mammals, aging occurs across multiple organ systems, causing a progressive deterioration that eventually results in tissue dysfunction. Consequently, age is a risk factor for many diseases, such as cardiovascular disease, dementia, osteoporosis, osteoarthritis, cancer, type 2 diabetes, idiopathic pulmonary fibrosis, and glaucoma. Despite these links with human pathology, the understanding of the aging process remains limited but it has been discussed that zombie cells in our body have an impact in the aging process.(1)

To be more specific zombie cells are a common, non-dividing cell type called Senescent cells (5). The cells in our bodies also have the ability to become senescent at some time or another. DNA damage due to radiation exposure, chemotherapy, telomere shortening and metabolic stress including high fat have been shown to promote a normal cells to enter a senescence phase. Senescence is cellular program that induces a stable growth arrest to ensure that further damage to other cells are not caused. When a cell enters the senescence phase it stops producing copies of itself, begins to release hundreds of proteins, and activates anti-death pathways. This pathway is activated due to persistent DNA damage response due to chronic genomic stress or telomere attrition leads to activation of several signaling pathways that lead to cellular senescence including the p53 and p16 pathway. The p53 activates p21 which deactivates cyclin-dependent kinase 2 (Cdk 2). Without Cdk 2, retinoblastoma protein (pRB) remains in its active, unphosphorylated form which prevents E2F mediated transcription thus preventing genes essential for DNA replication and proliferation. In turn preventing cell cycle progression through the G1 to S phase checkpoint. P16 works in ways similar to p53, but it inactivates cyclin-dependent kinase 4 (Cdk 4) and cyclin-dependent kinase 6 (Cdk 6) instead of Cdk2 thus without cdk4/6, pRB remains active and unphosphorylated. This inhibition of pRB phosphorylation also inhibits E2F transcription therefore leads to inhibition of G1-S progression. Once a cell becomes senescent it starts secreting a complex mixture of factors termed the SASP or Senescence Associated Secretory Phenotype, this secretion stimulates chronic inflammation, destructively remodels nearby tissues and encourages nearby cells to also become senescent leading to its accumulation. This accumulation is known to occur with age, as the immune system can no longer clear

the senescent cells thus leading to aging and has been identified as partially responsible for most age related diseases.(1) Studies of removing senescent cells using senolytics have shown optimum results for keeping young and slowing down the aging process. Senolytics are a cocktail to drugs including both Dasatinib (a leukemia drug) and Quercetin (a natural plant compound) that have been proved to decrease the amount of zombie cells and rejuvenate worn out tissue and organs by selectively inducing apoptosis.(5)

The aim of this study is clarify the association between senescent cells and age related disease and how senolytics may reverse their effects.

The materials and method

Method 1

To determine if senescent cells are linked to aging and whether senolytics are effective, Dr.James L. Kirkland, M.D., Ph.D., of the Mayo Clinic in Rochester, Minnesota used mice in vivo, senescent cells, and injections with senolytic drugs. He first injected young (four-month-old) mice with senescent (SEN) cells.

In addition to young mice injected with senescent cells, the researchers also tested older (20-month-old), non-transplanted mice with Dasatinib and Quercetin intermittently for 4 months.

Finally, they treating very old (27-month-old) mice with Dasatinib and Quercetin biweekly.(2)

Method 2

Recent trails on humans where done to see how senolytics act on different age related diseases.

In Idiopathic pulmonary fibrosis (IPF)

Dr. Musi and his colleagues trailed 14 adults, who were at least 50 years old, with stable mild-to-moderate IPF. Then they measured the patient's physical function through a six-minute walk distance, four-meter gait speed, and sitting-to-standing repetitions test, then they treated them with nine doses of Dasatinib and Quercetin for a period of three weeks.(3)

In Osteoarthritis

They trailed old patients suffering from arthritis using local rather than systemic administration of a small molecule senolytic drug.(1)

In age related immunosuppression

They used senolytic drugs that selectively target senescent hematopoietic stem cells.(1)

In Diabetic kidney disease

For this particular study, nine participants aged 50 to 80 received a dose of Dasatinab, combined with Quercetin (with drug-controlled diabetes) for a period of three days at Mayo Clinic in Rochester, Minnesota. This test was dependent on the expression of p16 and p21 which were both used as markers of senescent cells, along with SAβgal activity.(4)

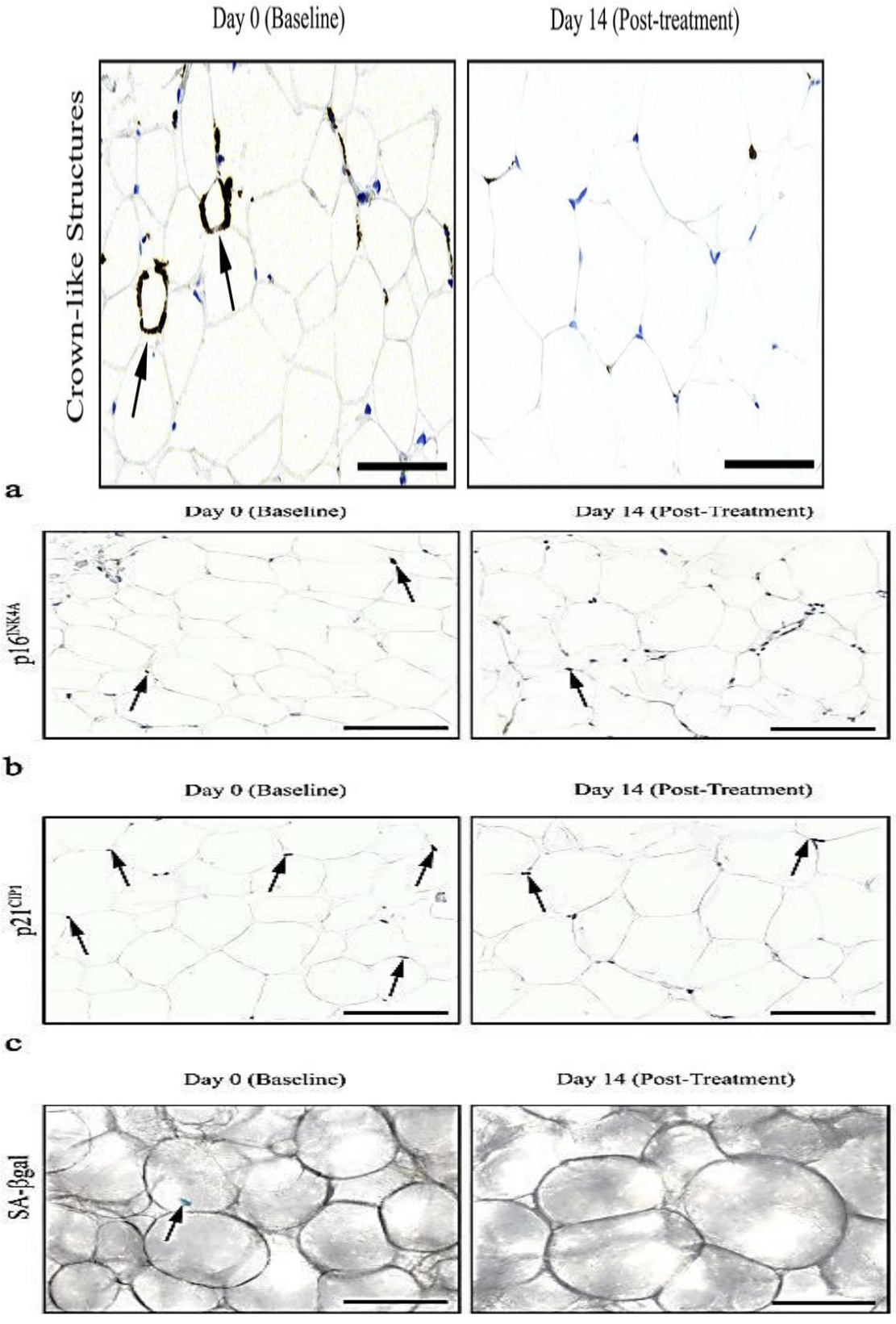
Results 1

The SEN four month old mice showed impaired physical function as determined by maximum walking speed, muscle strength, daily activity, food intake, and body weight. In addition, the researchers saw increased numbers of senescent cells, beyond what was injected, suggesting a propagation of the senescence effect into neighboring cells. They then treated the SEN mice for three days with the senolytics. They found that Dasatinib and Quercetin selectively killed senescent cells and therefore changed the walking speed, endurance, and grip strength in the SEN mice. Lastly the results obtained from the 20 and 27 month-old non-transplanted mice on senolytics showed improvement in normal age-related physical dysfunction, resulting in higher walking speed and grip strength which led to a 36 percent higher average post-treatment life span and lower mortality hazard than control mice.(2)

Results 2

By the end of the first trial of IPF patients, they were reportedly able to walk farther than they could previously in the same amount of time and other physical function gains greater than 5 percent in the majority of the participants after they completed the senolytic treatment, all without any serious side effects.(3) The second trials done on patients suffering from osteoarthritis, using local administration of senolytics improved the ability of chondrocytes to produce cartilage. They also saw that by the removal of senescent hematopoietic stem cells restored the functionality of HSCs and increased myeloid, B, and T cell numbers.(1)Last but not least, administration of senolytics to patients suffering from DKD, showed that by using senolytics, there was a significant reduction in adipose tissue p16 by 35%, Senolytics significantly reduced

adipose tissue p21 cells 17% , D + Q also reduced SAβgal+ (senescence associated beta galactosidase) cells by 62%, crown like structures were also reduced.it was also observed that although the drugs cleared the body in a couple of days, the reduction in adipose tissue senescent cells was evident for at least 11 days. This revealed decrease insulin resistance, cell dysfunction, proteinuria and other processes that cause disease progression and complications. The team also notes that occasional dosing can reduce the risks from having to give the drugs on a regular bases.(4)



Discussion

Aging is a normal process that occurs to every individual in the world, but that doesn't mean that we can't slow down the aging process to enjoy everything the world has to offer. Thus people have been using and doing whatever possible to feel more youthful even in their old age including Botox, Fillers, different types of cosmetic creams, regular exercise and eating more healthy. But even when a person lives a healthy life style its normal that with age due to the accumulation of senescent cells in different parts of the body, a person tends to be at risk of many diseases, this is the point that led to the formation of drugs against aging which are known as senolytic drugs. The intended target of senolytics is senescent cells. There are evidence showing that the drugs D + Q decrease senescent cells in humans. In the first demonstration that health span can be improved by removing senescent cells from naturally-aged mice, we found that clearing senescent cells with D + Q enhances treadmill endurance. Confirming and extending that first study, they subsequently showed that D + Q decreased a range of additional disorders in old mice. These included age-related muscle weakness, reduced daily activity, and decreased running endurance on a treadmill, additionally, in old mice, D + Q delayed age-related diseases and extended their remaining lifespan by 36%. These findings are consisted with the geroscience hypothesis, this hypothesis posits that by targeting a fundamental ageing process such as cellular senescence, multiple age-related disorders can be delayed, or even prevented. It was suggested that oral administration of D + Q decreases overall senescent cell burden, as opposed to targeting senescent cells within a single organ or structure, such as may be the case following local injection of agents into knees or eyes.(4) The first ever human trails were done on patients suffering from idiopathic pulmonary fibrosis, which is a fatal chronic lung disease characterized by progressive scarring of the lung tissue, leading to respiratory failure. There is no cure for IPF, and current anti-fibrotic treatments only arrest its further progression. Mechanistically, senescent cells secrete pro-fibrotic factors that activate scar-forming myofibroblasts which persist in the fibrotic tissue. Therapeutic strategies to treat IPF by targeting cellular senescence with senolytics. After completing the 3 week course of the drugs, they found a significant improvement in participant's mobility, the average increase of 21.5 meters observed in the six-meter walk test, No drug therapies, including the available anti-fibrotic drugs, have ever shown to stop the

decline in, let alone improve, an IPF patient's six-minute walk distance. However, other physical function markers such as lung function, were unchanged. Further studies are still being held at UT Health San Antonio and the South Texas Veterans Health Care system to study DQ effectiveness.(3) Further findings provide support for the likelihood that the administration of D + Q on cellular senescence in illnesses such as DKD, osteoarthritis and age related immunosuppression are beneficial. In case of osteoarthritis lifelong tear on ligaments is a significant risk factor for the development of arthritis. Failure of chondrocytes to produce cartilage results in degradation of joints and immobilization. Expression of p16 in these cells correlates with severity and progression of the disease Moreover, Clearance of these senescent cells using senolytics resulted in the increased functionality of the remaining chondrocytes with rejuvenation of cartilage soon after.(1) As we know one of the primary risk factors for complications in old age is infection. The inability of the body to raise a response to immune offenses is caused by a functional decline in hematopoietic stem cells. The accumulation of senescent HSCs with age contributes to immune decline. Interestingly, the removal of these cells restored the functionality of HSCs and increased myeloid, B, and T cell numbers in transplant experiments.(1) The last proved case of senolytics were done on DKD patients , 11 days after the last dose in subjects with DKD, which is the most common cause of end-stage kidney failure and which is characterized by increased senescent cell burden. They found D + Q decrease insulin resistance, proteinuria, and renal podocyte dysfunction caused by high fat diet-induced or genetic obesity. (4) Although the researches about senescent cells and how they correlate to age and senolytic drugs are still ongoing to provide a more understanding on how they work exactly but the results of many experiments proved that these cells are directly linked to the aging process and that senolytic drugs may after all provide the key to slow down aging in the future.

Conclusion

The past few years have unveiled a key role for senescence in aging, there is evidence that senescent cells accumulate with age in many tissues, mostly at sites afflicted by age associated Pathologies. They actively contribute to the ageing of the organism by producing secretions called the SASP or Senescence Associated Secretory Phenotype, which causes chronic inflammation, destructs nearby tissues and encourages nearby cells to also become senescent. To try and prevent this, senolytics were introduced. It is believed that these drugs reduce the count of senescent cells to improve a patient's wellbeing. The findings reported here are results from an ongoing clinical trial of senolytics for treating dysfunction in patients. Fewer than 150 subjects have been treated with these drugs so far and senolytic agents have still not been used outside the context of clinical trials. But the future of senolytics is promising.

References

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