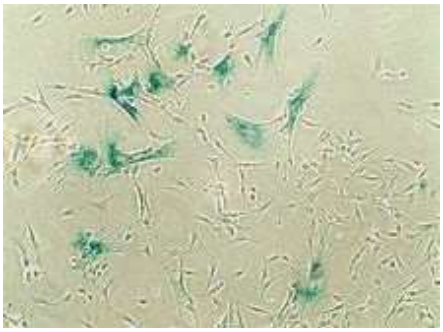
Fighting the Zombies: Imagine if Your Body Kept Functioning No Matter Your Age!

Senescent cells were first described in the late 1950s but remained largely a curiosity until 2008, when their dark nature was revealed by Dr Judith Campisi, a researcher based in California, who found that the cells secrete a cocktail of alarming factors which poison the surrounding tissue. This describes the paradox that even the diseased organs of very old people don't contain high absolute numbers of senescent cells – zombie cells: it doesn't take many.

Experiments in mice made scientists wonder what would happen if we cleared these zombie cells away. In 2011, Prof. Jan van Deursen and colleagues from the Mayo Clinic showed that eliminating senescent cells in mice via a genetic trick delayed some of the ravages of age in prematurely aged mice.

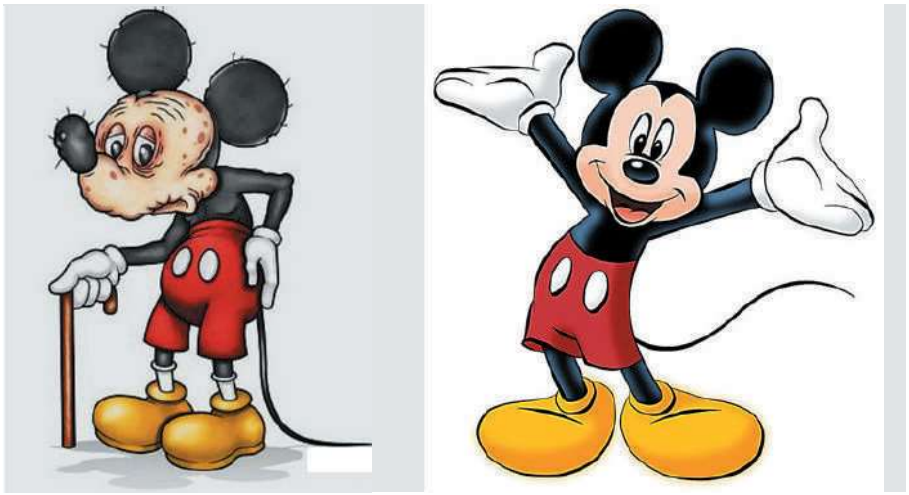


Zombie Cells

When you are young, you have plenty of yellow senescent cells known as zombie cells. These cells keep your body in a healthy state but as you age these cells are damaged and cease to divide – they are also resistant to dying. These cells accumulate with age in your body as the immune system cannot clear them.

Zombie cells are responsible for most age-related diseases since they create inflammation and dysfunction throughout the body as they accumulate and are not destroyed.

Cellular senescence may participate in four complex biological processes which each have opposing effects such as tumour suppression versus tumour promotion; aging versus tissue repair. The challenge therefore now is to understand the senescence response well enough to harness its benefits while suppressing its drawbacks. Old worn-out cells that should have undergone apoptosis are known as senescent cells and these promote disease as you age. Known as zombie cells, they create inflammation and dysfunction throughout the body. Scientists are now investigating ways to eradicate these cells from the body. In recent experiments with elderly mice treated with a senolytic their kidney function improved, their fur regrew, and they were able to run twice as quickly as untreated younger mice. Researchers are hoping that senolytics will do the same for humans in the not too distant future.



Twin mice the same age. The mouse on the right appears younger because researchers have removed the senescent cells. Prof. Jan van Deursen, Mayo Clinic USA.

Compelling evidence that senescent cells can drive degenerative aging pathologies are seen in the phenotypes of transgenic mice with hyperactive p53 seen in mice who were cancer-free, as p53 is a critical tumour suppressor.

These mice showed premature aging, degenerative changes, osteoporosis, sarcopenia, etc. Cells from these mice underwent rapid senescence; moreover, tissues from these mice rapidly accumulated senescent cells, and, in lymphoid tissue, the p53 response shifted from apoptotic to primarily senescent *in vivo*, which is a strong correlation between cellular senescence and premature aging phenotypes (Hinkal *et al.*, 2009).

It should be noted that another mouse model of elevated p53 activity showed unusual cancer resistance but normal longevity, with no signs of premature aging (García-Cao *et al.*, 2002).

Other mouse models also suggest that cellular senescence can drive age-related pathologies other than cancer. In models of both accelerated and normal aging, it is important to note that the crucial roles for the p53 and/or other pathways are not singular. There is mounting evidence that these pathways interact and modulate each other (Zhang *et al.*, 2006; Leong *et al.*, 2009; Su *et al.*, 2009; Yamakoshi *et al.*, 2009). Although these mouse models and other findings indicate a strong association between aging phenotypes and pathologies and cellular senescence, other processes undoubtedly also contribute to aging and age-related disease.

In one of the mouse models of p53 activity, there was also excessive

p53-dependent apoptosis, which was also proposed to contribute to the phenotypes shown by these mice. In addition, some cells in aging organisms simply lose functionality, which certainly contributes aging phenotypes. Neurons, for example, lose the ability to form synapses, despite cell bodies remaining viable, which is an important component of many neurodegenerative pathologies (Esiri, 2007). Likewise, cardiomyocytes lose synchronicity of gene expression, which almost certainly affects heart function (Bahar *et al.*, 2006).

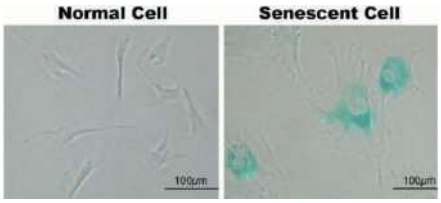
Developing therapies to kill senescent cells is part of the quest to defeat ageing and keep people healthier longer, enjoying a better quality of life. Senescent cells or zombie cells are of interest to investors as it is not just slowing down the clock but actually turning it back and rejuvenating people.

Work is still mainly on mouse models with one clinical trial in humans underway. This field is growing in popularity and scientists who want to study aging. Dr Laura Niedernhofer said *"There is a recognition that there is a potential here to go to the root cause of aging".*

"If chemists can come up with drugs that can kill senescent cells in humans, we think this is going to revolutionise modern medicine." Judith Campisi, *Chemical and Engineering News*, March 2018.

According to Judith Campisi:
"No longer would you have a pill for your blood pressure and a pill for your glaucoma and a pill to stabilise your heart and a pill to improve your kidney function. You'd have a pill that would hit multiple problems that affect the elderly." Campisi concluded, "It is very unlikely that these are drugs that you would have to take every day. Just when enough senescent cells had accumulated again."

As we get older, senescent cells build up in our tissues, where they contribute to conditions such as arthritis, type ll diabetes, and heart disease. Senescent cells are zombie-like damaged cells that stop working. They don't just sit around idly. Instead, they wreak havoc throughout our bodies, causing dysfunction and inflammation.

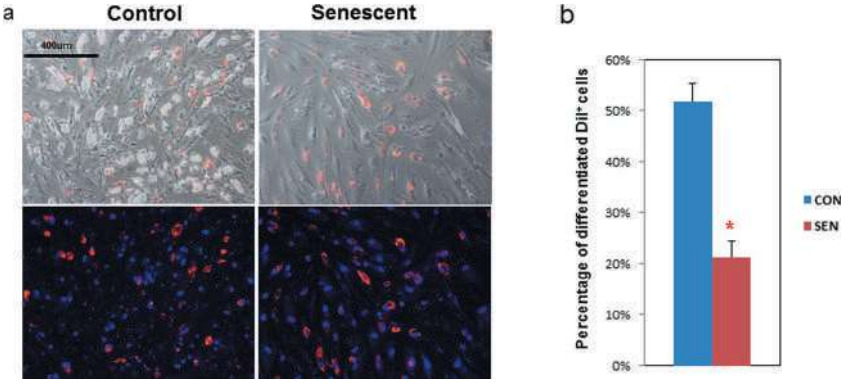


Senescent cells vs. healthy ones. Courtesy of Y.Tambe / CC BY-SA 3.0

By the time individuals reach old age, significant numbers of senescent cells have accumulated in the body. Senescent cells remain metabolically active, the inflammation they produce causing a vast array of problems throughout the body and accelerating the process of aging.

Senolytics destroy these zombie cells, reduce inflammation and improve tissue function. Removing senescent cells not only delays aging, but it also reverses parts of the aging process.

Researchers have used senolytics to clean out the senescent cells in mice, allowing them to live longer and reducing plaque build-up in their arteries, a natural process of aging due to cholesterol in the blood.



Control cells in blue and senescent in red

This process of zombie cells not being dead cells and not working properly is behind many problems related to aging, and when it is your heart, it becomes a major problem.

It is estimated that 920,000 UK citizens are currently living with heart failure, with the majority over the age of 65. This has a real effect on people's quality of life – as most of these people cannot walk upstairs without being out of breath or feeling constantly tired.

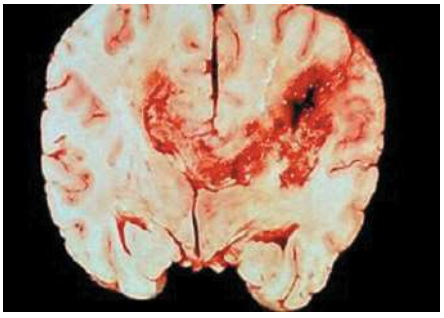
If you are elderly, you will most likely develop heart failure and if you have a heart attack, you are, unfortunately less likely to fully recover.

The answer as to what causes these cells in the heart to become zombies seems to be that it is unique to the way the heart works.

Many of the senolytic compounds are cancer drugs and come with downsides. They also kill some healthy cells or trigger side-effects such as reducing the number of platelets that help our blood clot.

De Keizer and colleagues (Erasmus University) plan to move cautiously with the FOXO4-DRI senolytic. They want to determine whether their peptide kills cancer cells, which share some similarities with senescent cells. They will test the compound in glioblastoma patients. If the FOXO4-DRI senolytic proves safe, they will begin testing the peptide against age-related diseases and even aging itself.

Most senescent cells self-destruct in a process called apoptosis. It's the best thing that can happen to senescent cells. Normally senescent cells have a type of DNA damage that



Glioblastoma multiforme...central area of necrosis & haemorrhage

spurs a protective protein called p53 to eliminate the cell. Instead, the researchers found that a different protein called FOXO4 binds to p53 and prevents it from doing its duty.

FOXO4 is a protein that controls gene expression, a master transcription factor associated with aging and development. When FOXO4 is activated in a cell, it can block apoptosis. p53 is the most common trigger of apoptosis and has multiple functions in the cell nucleus. FOXO4 latches onto p53 and blocks apoptosis.

To counteract this effect, De Keizer's team from Erasmus University designed a molecule, known as a peptide. This custom-designed peptide prevents the FOXO4 and p53 from linking up, prompting the senescent cells to commit suicide. Most notably, the peptide spared healthy cells.

The peptide is an artificially modified FOXO4, a dummy that binds to p53 in place of regular FOXO4. It works just like a senolytic. De Keizer calls it FOXO4-DRI, and it works by crowding out the native FOXO4.

To test the FOXO4-DRI senolytic, De Keizer injected it into normal, elderly mice. In addition to improving their kidneys and fur, the peptide also increased their energy levels. While the senolytic compound did not reduce the number of platelets, it could still have potentially lethal side-effects.

Researchers agreed FOXO4-DRI senolytic is a breakthrough. It vaulted senolytics into the rare class of longevity drugs, such as metformin and rapamycin.

Apoptosis is an important cell function throughout the lifespan of an organism. A cell needs to have good judgment about when to self-destruct; apoptosis can go haywire in either direction.

In the elderly, apoptosis fails to eliminate senescent cells, but sometimes healthy cells undergo apoptosis prematurely, and we lose vital organ tissue as a result. FOXO4 has many roles, including DNA repair. Researchers measure the value of a senolytic by its ability to kill senescent cells without harming healthy cells. Compared to earlier senolytics, the FOXO4-DRI senolytic is more selective. When researchers give an optimal dose of the peptide to mice, more than 80% of their senescent cells succumb to apoptosis, while destroying an undetectable number of healthy cells.

Dr Richardson and colleagues from Newcastle University have discovered that zombie cells are not caused by normal cells dividing or telomeres getting shorter, but by damage to the telomeres, which is linked to aging. Navitoclax can kill zombie cells and reverse the problems of heart and other diseases that occur with aging.

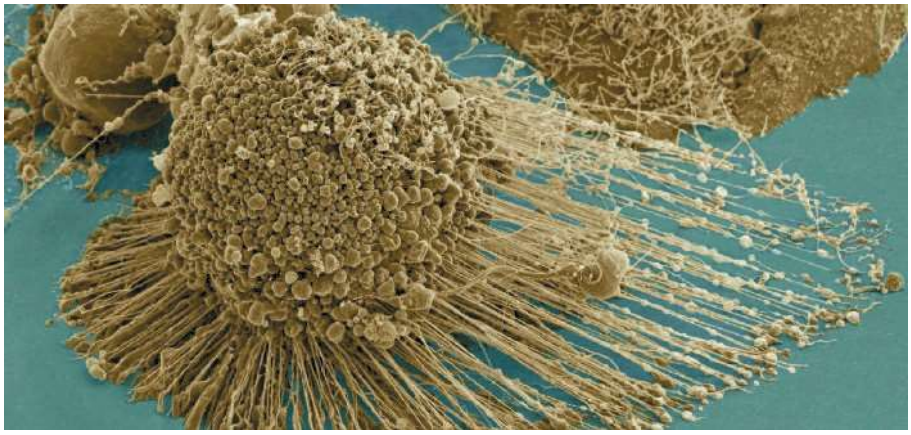
So when you start getting the signs of age-related diseases, *"you could take these drugs"*, suggested Dr Richardson.

"We are not trying to make people live forever but instead give them a better quality of life as they age."

More research is required to make sure the treatment is safe. Senolytic compounds are experimental drugs and have not been proven to be safe and effective in clinical trials.

Research long-term side-effects, as in the short term the treatment helps but in the long term, we may find other problems.

Next: study the cells in organs such as the human heart that has been donated to science. In the UK, if these tests are successful, we could move into clinical trials in humans by 2022 or 2023.



Cell undergoing apoptosis. Image courtesy of Tom Deerinck of NIH

Christene Leiper

Professor Christene Leiper attended Sydney University, RMIT Melbourne and Bond University in Australia, where she achieved Professor of Health Sciences and Medicine. Christene has also undertaken part of her PhD at University of Edinburgh, Scotland. Christene's international experience encompasses many therapeutic areas of medicine. Christene is the Managing Director and Director of five companies, including three CROs and two software / medical applications companies.

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