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What inspired you to rise to the challenge of confronting age-related diseases?

Ageing is arguably the most complex biological process, and is thus an enormous intellectual challenge. When I started my research career, colleagues told me: ‘you suffer from ageing, you don’t study it – this is useless’. I found this a challenge. In less than 30 years, this view has been completely overturned. With biological interventions, we can now extend life in many animals – in some species up to five times their normal lifespan. The goal now is to ensure that those extra years are lived in good health.

In humans, progress in hygiene, lifestyle, food and classical medicine causes a continuous increase in life expectancy of up to three months per year. Healthy life expectancy, however, increases much more slowly. If this discrepancy is not dealt with, quality of life for older people will decline and health service costs will soon spiral out of control. Intervening to slow the ageing process as the common underlying cause of all age-related diseases is the only real hope there is.

The strong link between chronic disease and old age has been widely acknowledged, but research on how to combat this issue is lacking. Why is this?

Primarily because ageing biology is such a young science. With good justification, society is cautious in redirecting funds towards the search for a ‘fountain of youth’, which still does not sound like a safe investment strategy. However, as ageing biology begins to deliver on its promises, the funding situation is improving. For instance, in my native country, Germany, there was not a single chair in ageing in 2000, but now there are three or four institutes devoted to understanding this area of research. Scientists will now need to show that their work can lead to interventions that extend healthy life expectancy in humans, especially in those that are most vulnerable to rapid ageing and the early development of age-related diseases, disabilities and cognitive decline.

What is cellular senescence? How does this mechanism lead to chronic disease, frailty and other age-related health problems?

Cellular senescence is a response to irreparable DNA damage that causes a permanent block in cell division. As long as this block works, a cell with damaged DNA cannot proliferate to generate a tumour. However, cells cannot just stop dividing, so the senescence response also triggers many other changes in the way cells behave. Importantly, they generate free radicals and many other potent signalling molecules, including those that induce inflammation. These signals change the behaviour of surrounding cells, making some of them senescent as well and redirecting the functions of others. Thus, senescence limits tissue regenerative capacity, causes chronic systemic inflammation and changes function in both senescent and non-senescent cells.

Your research group has made world-leading discoveries about telomeres. Can you introduce your studies on this topic?

When telomere shortening became prominent as a cause of cellular senescence it was known that telomeric DNA must be lost with time because of the so-called end replication problem – an intrinsic inability of the DNA replication machinery to copy a DNA strand to its very end. The interpretation was that telomeres would be cellular counters or clocks, stopping cell proliferation after a fixed number of divisions in order to limit the risk of tumour proliferation.

At the time, I wanted to confirm that there were really two different ‘types’ of ageing: stress-induced ageing in non-dividing cells, and inborn and pre-programmed ageing in dividing cells. Much to our surprise, we found that stressed cells lost their telomeres much faster, with the end replication problem being only a minor contribution to total telomere loss. Thus, we showed telomeres to be much more functional than a simple mechanical clock; namely, a ‘sentinel’ measuring the risk of DNA damage and raising the alarm accordingly.

Is there potential for your research to lead to the development of chronic inflammation prevention strategies?

Having shown chronic inflammation to be a causal mechanism for accelerated ageing, we are, of course, thinking about the possibility of anti-inflammatory interventions in fast-ageing humans. It is well established that some of us age more slowly than others. Could anti-inflammatories help those on the ‘fast track’? The problem is that all anti-inflammatories in use have very serious side effects if taken long term. New, safer drugs are needed.

Professor Thomas von Zglinicki discusses how recent strides in biomedical research may improve the health and wellbeing of a global ageing population
TRIMMING TELOMERES

Over time, evidence has emerged pointing toward cellular senescence – a permanent arrest of cell division when a normally replicating cell encounters DNA damage – as a main driver of numerous age-related pathologies. Telomeres are lengths of non-coding DNA found at the end of each chromosome that act as a buffer to protect the integrity of the genetic code during replication. It was originally thought that telomeres are shortened step by step within each cell division by a constant molecular mechanism. When telomeres get too short, they are recognised as damaged DNA by the cell and trigger a signal that induces cell senescence or, in some cases, cell death. It appeared from existing evidence that telomere loss had similar characteristics to a regular clock ticking down to the end of a cell’s ability to replicate.

The results of Zglinicki’s research conflict with this longstanding picture, showing for the first time that DNA replication is not the only determinant of telomere loss. His team assumed, based on current knowledge, that using oxidative stress to induce cellular senescence would cause cell division to stop before telomeres were significantly sheared off.

Although cell division was soon halted, the rate of telomere loss actually increased, thereby indicating that telomere shortening is affected by oxidative damage. In short, DNA repair is less efficient in telomeres than elsewhere in the genome such that oxidative damage speeds up telomere shortening. Rather than a countdown to the end of cell proliferation as previously thought, telomere loss could be viewed as a measuring stick to assess the risk of DNA damage.

Zglinicki’s lab was the first to propose and test the hypothesis that the extent of telomere shortening could be used as a biomarker for ageing and the risk of developing age-related disease. The researchers measured telomere length in people with various age-related conditions, such as cerebrovascular disease and strokes, and compared the results to the lengths of telomeres in healthy individuals. While the results in large cohorts supported the theory, the prognostic power was not significant enough to be used accurately in individuals to define biological age or foretell the outlook of health for the future.

CIRCULUS VITIOSUS

Though telomere shortening may not be the accurate biomarker one might hope for, it provides a key to unlocking the pathology of accelerated ageing. Zglinicki’s lab has found the first evidence of a dynamic feedback loop characterising the relationship between cellular senescence and chronic inflammation.

This circulus vitiosus, or vicious circle, starts when telomeres become too short, triggering a DNA damage response that causes cellular senescence. As a result, a gene known as CDKN1A is activated causing mitochondrial dysfunction and the production of reactive oxygen species and of signalling peptides like IL-1 and IL-6 that cause inflammation. Reactive oxygen species cause more DNA damage which spurs on the damage response, and so the circle continues.

Recently, Zglinicki’s lab investigated the effects of this feedback loop in mice to determine whether chronic low-grade inflammation accelerates the accumulation of senescent...
cells, and if these cells in turn aggravate chronic inflammation. Genetically engineered to produce enhanced inflammatory signals, Zglinicki’s team found that the mice aged faster than their normal counterparts, who lived twice as long. The researchers showed that the inflammation signals trigger the production of oxygen free radicals to induce DNA damage that generated senescence signalling. This signalling led to more inflammatory signals and the increased release of oxygen free radicals.

**INTERVENTION ON THE HORIZON**

Although ageing and age-related conditions in humans have long been associated with chronic inflammation, the research carried out by Zglinicki’s team provides the first mechanistic explanation of this relationship, and has even provided a starting point from which to explore potential interventions. Anti-inflammatories may have had no beneficial effects for healthy mice but, for those with enhanced inflammation, the cellular signs of accelerated ageing came to a halt. Although long-term use of existing anti-inflammatories has serious side effects, they at least provide a crucial platform for the development of interventions for individuals ageing faster than normal. Ageing is an extraordinarily complex process but biomedical research continues to unravel its mysteries, the reality of prolonging lifespans and maintaining quality of life becomes ever nearer.

**TELOMERES AND AGE-RELATED DISEASES**

**OBJECTIVES**

- To uncover the role of telomeres and mitochondria in cellular senescence leading to chronic systemic inflammation
- To improve the healthy life expectancy of older people through ageing biology research

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