Compound found in berries and red wine can rejuvenate cells, suggests new study

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Resveratrol is a powerful antioxidant found in blueberries.

By the middle of this century the over 60s will outnumber the under 18s for the first time in human history. This should be good news, but growing old today also means becoming frail, sick and dependent. A healthy old age is good for you and a remarkably good deal for society. Improving the overall health of older Americans could save the US alone enough money to pay for clean drinking water for everyone on Earth for

the next 30 years.

But if we want people to be healthy in old age we have to understand the mechanisms underlying the deterioration of our bodies over time. Doing so – and learning how we can prevent it – has been the goal of ageing research for more than 60 years.

There has been astonishing progress made over the last decade. In 2009, it was shown that the drug rapamcyin extended the lifespans of mice by 10-15%. Two years later a landmark study showed that experimental clearance of "senescent" cells – dysfunctional cells which build up as we age and cause damage to tissue – improved healthy lifespan in laboratory mice. These results delighted those of us who had argued for decades that senescent cells were a major cause of late life problems and should therefore be therapeutic targets.

Research on both living human cohorts and isolated cells have looked at the types of genes which change in expression levels (the process by which information from a gene is used to make the tens of thousands of proteins needed by a cell during ageing. This has revealed that the largest changes occur in genes which regulate how "messenger RNAs" are made. These transfer the information stored in DNA to the cellular machinery which turns it into proteins.

In the human cell, proteins known as "RNA splicing factors" determine which messenger RNA can be made from RNA building blocks in a process known as RNA splicing. The ability of our cells to do this is restricted with ageing. But it was unclear whether this loss is a result of senescent cells accumulating in ageing tissue or something new, occurring in parallel with senescence until now.

New evidence

Now our latest study, published in BMC Cell Biology shows that a natural substance can actually rejuvenate senescent cells by targeting RNA splicing.

In our experiments, we treated such cells with compounds we synthesised based on resveratrol, a natural product found in red wine, berries and other foods, reported to alter RNA splicing in cancer cells. Resveratrol – which can be found in many natural foods – is a blunt tool that affects multiple cellular pathways. But our synthetic variants are actually much more precise and we picked ones that preferentially affected RNA splicing.

Senescent human cells treated with our products showed remarkable effects, which we called "rejuvenation". RNA splicing patterns were rapidly reset to that seen in young cells and then the senescent cultures began to grow again. Variations of this basic experiment showed that splicing factor restriction is separate from senescence but interacts with it.

Restoring RNA splicing rejuvenates senescent cells in part because our cells are normally rendered senescent through telomere shortening, the gradual loss of the DNA at the ends of chromosomes that occurs with repeated cell division. Some RNA splicing factors that decline with age are capable of helping to repair telomeres and so, if you restore them, they lengthen telomeres back up and stop the cell being senescent.

Restricted splicing has serious implications beyond the capacity of cells to divide and how tissues deal with stress. It limits cell responses, potentially contributing to the increased frailty that is a hallmark of ageing in many organisms including humans.

Following our discoveries the area of RNA splicing is now ripe for detailed study, not least because cells from old individuals that have not

become senescent probably still have compromised splicing. Restricted splicing may prove to be a critical mechanism in the development of a wide range of age-associated diseases.

Drugs and diet

Our compounds have allowed us to begin to identify the key molecular pathways that mediate splicing factor restriction and may have a future as a platform for anti-degenerative drugs. But when only one or two in tens of thousands of compounds become medicines none of us are quitting work just yet.

As resveratrol and similar molecules are found in food, our work may have revealed an unsuspected link between diet and RNA splicing. Many groups have shown the beneficial effects of diets containing these foods – altered splicing may be one, but not the only, way in which they mediate their effects. However you'd need to drink some 30 litres of red wine a day to achieve the doses of analogues of resveratrol we used in tissue culture.

Pure resveratrol already exists as a dietary supplement. However, we do not recommend taking it just yet. One of the reasons we made the novel compounds was that resveratrol, like many natural products, has a whole range of activities, some that appear beneficial and some less so.

Our emphasis on achieving health in later life without undue concern for its extension chimes closely with the popular view. Something in excess of 60% of the population do not want thousand-year lifespans, even when given a guarantee of perfect health.

The challenge now is to convert this basic scientific discovery into the benefits people want, and as quickly as possible. Until then, there's always blueberries.