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Evolution does not care

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Cells form the biological unit of all living organisms. But, like organisms, cells go through a life cycle: new cells emerge after cell division, they live, they age and they die. In some cases cell death is necessary for the organism's development and life. However, many times massive cell death is a sign of some disease. One of the most frequent examples is a set of neurodegenerative diseases - Parkinson's, Alzheimer's, Huntington's - in which people experience progressive loss of certain groups of neurons. Many times the symptoms of these diseases show up, when the person heads towards the late stage of life. In other words, aging of organisms goes hand in hand with aging of their cells.

Aging itself may also be seen from a point of view of evolution. One evolutionary theory of aging was formulated 60 years ago by the American biologist George C. Williams. His theory suggested, that evolution selects genes that are beneficial in the young and reproductive periods, although they have negative effects in old age. This theory is referred to as the *antagonistic pleiotropy* theory of aging or simply the "pay later" theory. Hence, some genes are evolutionarily selected for their fitness promoting effects in early life. But, when old, the organism "pays" for those benefits with bad side effects.

One cellular mechanism to maintain cells in a healthy state and to prevent aging is autophagy. Autophagy, which originates from the Greek term "eating of oneself", digests damaged cellular organelles (the cell's "internal organs") and protein aggregates. It therefore may be regarded a cellular self-cleansing mechanism. Autophagy is generally associated with cell-protection and health-promoting properties. But would autophagy genes also behave according to the evolutionary theory of aging or, in other words, could autophagy be harmful in old animals?

To answer this question we employed the roundworm *Caenorhabditis elegans*, which is a nice aging model due to its short lifespan of around three weeks. By targeted inactivation of gene expression we turned off many hundred genes, one-by-one, in old worms [1]. While we found many genes that behaved according to Williams' aging theory, autophagy genes showed by far the strongest lifespan extending effects when inactivated in old worms. Inactivation of the same autophagy genes in early life, in agreement with the theory, significantly reduced lifespan.

But what happens to the autophagy process during aging? What we saw is that the autophagy process is becoming dysfunctional with increasing age. Cells start to accumulate underdigested autophagy structures and this strongly affects the health of old animals.

It is important to know, if effects that you see are specific to a certain tissue. That's why in a second round of experiments we focused on inactivating autophagy specifically in five different tissues: in the muscles, in the germline, in the gut, in the hypodermis, and in the neurons. Surprisingly, health- and lifespan promoting effects were only mediated through the neurons. This inactivation in the neurons not only extended lifespan by up to 60% but also increased muscle health and neuronal integrity of the tested worms. The tested worms moved better, lived longer and their neurons remained in better shape.

The mechanism of this effect is yet to be revealed. But the result itself is very intriguing. In fact, human neurodegenerative diseases, such as Alzheimer's, Parkinson's, and Huntington's, are often associated with dysfunctional autophagy in neurons. And if inhibition of autophagy is neuroprotective, it may also prove therapeutic in the human disease context. Could downregulation of autophagy in old humans be a means of preventing or soothing such diseases? Imagine you have reached the second half of your life and then taking a pill that helps you to stay fit and to live longer - so it must be for the old worms. By

switching off the autophagic machinery in the neurons the animal slows down its aging process. However, despite the extended life span and health span it is still not known if switching off autophagy may have negative side effects in old worms, not to say in humans.

This study screened only around 4% of all worm genes but discovered not less than 30 new genes essential for regulating the life span of the worm. Hence, the research team is convinced that many more genes remain to be discovered that promote health and lifespan upon their late-life inactivation. These findings clearly illustrate that, in order to understand how genes and gene networks shape the aging process, we must always take the timing of their expression into consideration.

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