Worms may hold the secret to longer life

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Research into the remarkable regenerative powers of worms and the insights they can give into battling diseases could help humans live longer and healthier lives.

Humans have long dreamed of finding the secret to eternal youth, but despite the benefits of better living conditions and modern medicine, time still takes its unrelenting toll on our bodies.

While people today live longer than ever before, age-related diseases such as dementia and other neurodegenerative conditions rob people of the chance of living healthy lives into old age.

But researchers have a secret weapon in the battle with the ageing process – the humble worm. Flatworms have the ability to regrow large parts of their bodies after losing them. Roundworms, meanwhile, may hold the secret to counteracting neurodegenerative scourges like Alzheimer's disease and conditions such as muscular dystrophy.

Scientists see these creatures as a rich source of potential clues about the ageing process and how we too might regenerate tissues.

In a project called MacModel, researchers are using the flatworm *Macrostomum lignano*, which is normally found living in the tidal sands of the Adriatic Sea, to investigate ageing mechanisms. Previous research observed that the animals had a remarkable ability to regenerate, and that the worms tended to live for longer after repeated amputation, suggesting that something about the regeneration process also rejuvenated them.

Professor Eugene Berezikov, principal investigator for MacModel and a stem cell researcher at the University of Groningen in the Netherlands, and his team, tried to investigate further by severing the worms' heads to induce regeneration.

Their findings, however, appeared to contradict the earlier research – after multiple amputations, flatworms had decreased survival compared to intact worms. But there was another major difference with the earlier findings – both worms that underwent amputations and those that did not tended to live longer than the median 200-day lifespan seen in the previous research.

Many of Prof. Berezikov's worms were still alive after a whopping 740 days, including about 70% of the intact worms. This defies the tendency for small organisms to be shorter-lived, explains Prof. Berezikov.

'*Macrostomum* is very small, about 1 millimetre, so for it to live for more than two years makes it a huge outlier,' he said. Often, a creature of this size would be expected to live just a few weeks.

Naturally long-lived

Prof. Berezikov speculates that these worms may be naturally long-lived and parasites may have contaminated the worms used in earlier research. When they were amputated, the worms may have lived longer in the previous research not because they rejuvenated, but because the cutting eradicated their unwanted guests.

To probe deeper, Prof. Berezikov and his colleagues delved into the worm's genome and now believe they have found a possible explanation for its longevity – several genes that were more active in older worms.

These genes, which are also found in humans, are involved in various processes responsible for a cell's wellbeing, and some are already known to benefit lifespan when extremely active in mice and the nematode worm *Caenorhabditis elegans*.

'This is a very good example of where we started with one thing and ended up with something completely different,' said Prof. Berezikov. 'We found something even more remarkable, we think – that the animal is a Methuselah with natural mechanisms to offset ageing.'

The results may also be easier to translate into potential treatments for humans than if the researchers had found that the extended lifespan was indeed down to regeneration. For now, the researchers behind MacModel are still attempting to unravel how these genes lead to longer life in the worms, before they can be used to aid the development of treatments to extend human life.

The MacModel researchers have also produced a high-quality annotated genome sequence for *M. lignano*, along with other genetic modification tools that Prof. Berezikov believes have created a powerful model for further studies into stem cells and ageing.

He warned, however, that it could take a decade before these can be used for applications in humans. First, the team hopes to test the genes they identified in *M. lignano* in model species more relevant to humans, such as the short-lived fish *Nothobranchius furzeri* (killifish) and mice.

But worms do not just have the power to potentially extend human life, they may also hold lessons about how to improve its quality. A research project called REPROWORM is using worms to look at reprogramming cells to regenerate brain and nerve tissues in an attempt to treat conditions like Alzheimer's disease and muscular dystrophy.

The researchers behind the project are using the nematode, or roundworm, *C. elegans*species, which has a similar number of genes to humans – about 20,000 – more than half of which have human equivalents.

Dr. Baris Tursun, principal investigator for REPROWORM and a researcher at the Max Delbrück Center in Berlin, Germany, and his team, screened all 20,000 of the worm's genes. Their aim was to identify specific genes that may have a role in blocking cells from being reprogrammed. They hoped that turning off these genes could then allow cells to be converted into other cell types needed to repair damaged tissues, such as stem cells and neurons.

Overcoming barriers

The analysis identified about 160 genes that seem to play a role in blocking cell fate reprogramming. Subsequent tests of a number of these in a type of human cell known as fibroblasts showed that some of these genes have a role as a barrier for reprogramming cells in both people and *C. elegans*.

The researchers are now planning to test more of the blocking genes they identified in *C. elegans* to see if they too could be applied to human cells.

But there are safety concerns that will need to be investigated, as it is still unknown how well cells that have been reprogrammed in this way will behave once they are transplanted back into humans, said Dr. Tursun. They might replicate uncontrollably to form tumours, for example.

'I think it will take several years before we can approach it,' added Dr. Tursun. But he said it was exciting to see how findings in these tiny creatures can be extended to human cells.

'It is the concept of using this mighty little worm as a strategy to work in vivo (in a living organism) and do a lot with genetics to find mechanisms, principles and concepts that we can also really apply to human cells,' he explained.

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