The accidental discovery of how to stay young for longer

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Credit: Peter Griffin/public domain

Living longer usually means a longer dotage, but wouldn't it be enticing to extend young adulthood instead? It's such an appealing prospect that scientists who are announcing success with roundworms are keen to be clear they are a long way from achieving it in humans.

"We don't want people to get the impression they can take the drug we

used in our study to extend their own teens or early twenties," says lead author Michael Petrascheck from The Scripps Research Institute (TSRI), California.

"We may have done this in worms, but there are millions of years of evolution between worms and humans.

"We think it is exciting to see that extending lifespan by extending young adulthood can be done at all," he says.

In the study to be published in the journal *eLife*, the TSRI-led team administered an antidepressant called mianserin to *Caenorhabditis elegans*, a type of roundworm used frequently in research. In 2007, they discovered that the drug increases the lifespan of roundworms by 30-40 per cent. Their new goal was to investigate how.

The team treated thousands of worms with either water or mianserin and looked at the activity of genes as the worms aged. First, they measured the activity of genes in young adults as a reference point against which to monitor the aging process. Reproductive maturity begins in day-old roundworms and they live for 2-3 weeks on average.

As the worms aged, the team observed dramatic changes in gene expression. However, the changes occurred in a way that came as a complete surprise. Groups of genes that together play a role in the same function were found to change expression in opposing directions.

They have called this newly-discovered phenomenon 'transcriptional drift'. By examining data from mice and from 32 human brains aged 26 to 106 years, they confirmed that it also occurs in mammals.

"The orchestration of gene expression no longer seemed coordinated as the organism aged and the results were confusing because genes related

to the same function were going up and down at the same time," says Petrascheck.

"Transcriptional drift can be used as a new metric for measuring age-associated changes that start in young adulthood," says first author Sunitha Rangaraju.

"Until now we have been dependent on measuring death rates, which are too low in young adults to provide much data. Having a new tool to study aging could help us make new discoveries, for example to treat genetic predispositions where aging starts earlier, such as Hutchinson-Gilford progeria syndrome," she says.

Using this new metric revealed that treatment with mianserin can suppress transcriptional drift, but only when administered at the right time of life. By 10 days old, treated worms still had the gene expression characteristics of a three-day-old—physiologically they were seven days younger. But by 12 days, the physiological changes required to extend lifespan were complete and lifelong exposure to the drug had no additional effect. Mortality rates were shifted parallel by 7-8 days across the treated worms' lifespan, confirming the finding.

Mianserin blocked signals related to the regulation of serotonin and this delayed physiological changes associated with age, including the newly-identified transcriptional drift and degenerative processes that lead to death. The effect only occurred during young adulthood and the duration of this period of life was significantly extended.

"How much of our findings with regards to lifespan extension will spill over to mammals is anyone's guess, for example the extension of lifespan might not be as dramatic," says Petrascheck.

"However, we are already excited about the fact that we observed the

phenomenon of transcriptional drift in species ranging from worms, mice to humans."

The findings have opened up many new avenues of research for the team and are likely to spawn a wealth of research by others. For example, a significant next step for the team will be to test the effect in mice and to investigate whether there are any side effects. Different environments could produce different results and this will need to be explored. They would also like to test whether the impact is different for different organs in the body.

The discovery of 'transcriptional drift' raises the prospect of the phenomenon providing a new general metric for aging, but again this requires further research.

In terms of extending teenage and young adult life in humans, just the idea invites a wealth of questions about the potential social implications and whether this would be as desirable as it first seems.

More information: Sunitha Rangaraju et al. Suppression of transcriptional drift extends lifespan by postponing the onset of mortality , *eLife* (2015). DOI: 10.7554/eLife.08833

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