Live Fast, Die Young?

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In Greek mythology, Tithonus was granted eternal life, but not eternal youth, leading to his prolonged suffering. What we hope in the 21st century is that slowing the rate of the ageing process will extend both life expectancy and healthspan; so a longer life in good health. Limiting daily food consumption, for example, by caloric restriction or intermittent fasting, has been shown to lengthen lifespan and postpone age-associated changes in various animal models. Enhanced lifetime has been observed in mice with an extended daily period of fasting, regardless of diet composition or overall caloric intake (1). This effect was reproduced in rhesus monkeys, an excellent model for human ageing, highlighting a favourable impact on age-related illnesses, in addition to overall survival (2).

An emerging body of evidence suggests that inhibition of the growth hormone/insulin-like growth factor 1 (GH/IGF-1) signalling pathway promotes longevity. First, an inverse correlation has been observed between plasma IGF-1 levels and average lifespan in mice (3). Various models of GH/IGF-1 deficiency (Ames – *Prop1* mutation, Snell – *Pou1f1/*PIT1 mutation, Little – GH deficient or GH-releasing hormone (GHRH) deficient mice – leading to GH/IGF-1 deficiency, as well as a GH receptor knockout model – leading to IGF-1 deficiency), manifest improved insulin sensitivity and live longer than their wild-type littermates (4,5). Conversely, a transgenic mouse model with high circulating GH levels and acromegaly-like phenotype shows substantially reduced lifespan (6). Caloric restriction can further extend lifespan in some, but not all, models of GH/IGF-1 deficiency. However, would caloric restriction in GH excess models extend the shortened lifespan?

Although there is no shortage of molecular theories explaining ageing, a new paper published in *Nature* by Cédric Debès and colleagues (7) widens our scope by revealing a key role for the speed of transcriptional elongation. These authors studied the kinetics of transcription during ageing of five different species: roundworm (*Caenorhabditis elegans*), fruit fly (*Drosophila melanogaster*), mouse (*Mus musculus*), rat (*Rattus norvegicus*) and human (*Homo sapiens*). They observed that the speed of transcriptional elongation (catalysed by DNA-dependent RNA polymerase II) uniformly increased with age. This intriguing finding held for all five species and tissue types investigated, including the brain, hypothalamus, liver, kidney, whole blood, and could be mimicked in senescent (vs. proliferating) human umbilical vein endothelial cells and foetal lung fibroblasts. They recognised that in senescent cells, reduced nucleosome density (i.e., longer distances between DNA wrapped around histones) parallels the increased speed of elongation. Since for active transcription DNA needs to be uncoiled to provide access to transcriptional regulators and RNA polymerase II, the observation of reduced nucleosome density in senescent cells raised the hypothesis that increased inter-nucleosome distances with ageing could be responsible for increased rate of RNA elongation. This idea is consistent with loss of canonical histones and their gradual replacement with histone variants (possessing altered functional properties) with age (8). Overexpression of canonical histone genes in fruit fly indeed reduced entry into senescence and decelerated transcriptional elongation, suggesting a regulatory role for nucleosome density and ensuing chromatin accessibility. Intriguingly, established longevity-promoting interventions (inhibition of insulin/IGF-1 signalling in roundworms and flies, as well as dietary restriction in mice) tended to reduce age-related RNA polymerase II elongation speed. Mechanistically, reduced fidelity of transcription and increased inaccuracy of pre-mRNA splicing events are potential consequences of increased elongation speed. Increased rates of mistakes in transcription and splicing at higher speed of RNA

polymerase II was confirmed by enhanced formation of circular RNAs, retention of introns, erroneous splicing events, as well as increased mismatch occurrence, resulting in an overall decline in the quality of RNA production. All of these molecular proof-of-concept endpoints suggest impaired proofreading capacity of RNA polymerase II at an increased speed of elongation.

The increased elongation speed observed in aging animals and senescent cells along with its reversal through reducing food intake or inhibiting the GH/IGF-1 pathway raises a few points. A particularly pressing question for endocrinologists is about what happens the other way round. Would excessive insulin or GH/IGF-1 signalling lead to increased RNA polymerase elongation speed? In animal models with an acromegaly-like condition, would we observe increased elongation speed, reduced fidelity of transcription and increased rate of impaired splicing events? Could these disease states be interpreted as accelerated ageing bound together through rushed and faulty transcript elongation? Transgenic mice with GH excess have a shorter lifespan (6); is this related to accelerated transcript elongation? Could faster transcription elongation be relevant in cancer, ultimately producing malfunctioning proteins – considering the proteostasis hypothesis of cancer and ageing? Apart from general life-extending interventions (e.g., caloric restriction), are there ways to slow down transcription elongation, or to restore nucleosome density in ageing cells? Should we expect of such interventions to increase not just lifespan but also healthspan, and reduce, or at least delay, age-related pathologic conditions? Would these *in vivo* data from fruit fly and roundworms be true in non-human primates? Finally, would the longer lifespan observed in animal models with reduced GH/IGF-1 signalling and the lack of certain diseases in GH receptor and GHRH receptor deficient mice and patient groups indicate a gain of certain health benefits? And as a corollary, would GH replacement in GH deficient individuals cancel out the health benefits of normalised GH action through increasing transcriptional elongation speed? Further research into this novel and exciting mechanism is likely to shed light on key aspects of healthy aging in humans.

References

1. Green CL, Lamming DW, Fontana L. Molecular mechanisms of dietary restriction promoting health and longevity. *Nat Rev Mol Cell Biol* 2022;23:56-73

2. Mattison JA, Colman RJ, Beasley TM, Allison DB, Kemnitz JW, Roth GS, Ingram DK, Weindruch R, de Cabo R, Anderson RM. Caloric restriction improves health and survival of rhesus monkeys. *Nat Commun* 2017;8:14063

3. Yuan R, Tsaih SW, Petkova SB, Marin de Evsikova C, Xing S, Marion MA, Bogue MA, Mills KD, Peters LL, Bult CJ, Rosen CJ, Sundberg JP, Harrison DE, Churchill GA, Paigen B. Aging in inbred strains of mice: study design and interim report on median lifespans and circulating IGF1 levels. *Aging Cell* 2009;8:277-287

4. Masternak MM, Panici JA, Bonkowski MS, Hughes LF, Bartke A. Insulin sensitivity as a key mediator of growth hormone actions on longevity. *J Gerontol A Biol Sci Med Sci* 2009;64:516-521

5. Junnila RK, Duran-Ortiz S, Suer O, Sustarsic EG, Berryman DE, List EO, Kopchick JJ. Disruption of the GH Receptor Gene in Adult Mice Increases Maximal Lifespan in Females. *Endocrinology* 2016;157:4502-4513

6. Wolf E, Kahnt E, Ehrlein J, Hermanns W, Brem G, Wanke R. Effects of long-term elevated serum levels of growth hormone on life expectancy of mice: lessons from transgenic animal models. *Mech Ageing Dev* 1993;68:71-87

7. Debes C, Papadakis A, Gronke S, Karalay O, Tain LS, Mizi A, Nakamura S, Hahn O, Weigelt C, Josipovic N, Zirkel A, Brusius I, Sofiadis K, Lamprousi M, Lu YX, Huang W, Esmaillie R, Kubacki T, Spath MR, Schermer B, Benzing T, Muller RU, Antebi A, Partridge L, Papantonis A, Beyer A. Ageing-associated changes in transcriptional elongation influence longevity. *Nature* 2023;616:814-821

8. Pal S, Tyler JK. Epigenetics and aging. *Sci Adv* 2016;2:e1600584