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Review

Mechanisms underlying longevity: A genetic switch model of aging

Jeremy M. Van Raamsdonk[1]

Laboratory of Aging and Neurodegenerative Disease (LAND), Center for Neurodegenerative Science, Van Andel Research Institute, Grand Rapids, MI, USA
Department of Neurology and Neurosurgery, McGill University, Montreal, Quebec, Canada
Metabolic Disorders and Complications Program, Brain Repair and Integrative Neuroscience Program, Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada

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ABSTRACT

While the questions of "What causes aging?" and "Why do we age?" and "How can we stop it?" remain unanswered, recent advances in aging research have continued to increase our understanding of the aging process. Until the last couple of decades, aging was viewed as an inevitable process of damage accumulation and not a subject for scientific pursuit. This view changed when it was demonstrated that the aging process is in fact malleable and genetically determined: mutations in single genes can have dramatic effects on longevity. Despite the rapid advancement of our knowledge about aging, the cause of aging remains unclear. In this paper, experiments demonstrating the roles of genetics and epigenetics in modulating longevity are reviewed, concluding with a new model of aging. This genetic switch model of aging proposes that aging is caused by a genetically-programmed turning off of survival and maintenance pathways after reproduction finishes leading to a progressive functional decline. If this model is correct, it may be possible to extend lifespan and healthspan by identifying the molecular pathways involved and simply turning the switch back on.

1. Introduction

One of the major questions in aging research is "what causes aging?" Despite many advances and years of investigation, the answer to this question remains poorly defined. Nonetheless, a number of theories have been proposed. A group of theories, collectively known as damage accumulation hypotheses, suggest that aging is caused by the accumulation of damage with increasing age. The most widely accepted of these theories is the free radical theory of aging (FRTA). The FRTA proposes that reactive oxygen species (ROS) generated by normal metabolism cause oxidative damage that accumulates with age eventually leading to cellular dysfunction, thereby causing aging (Harman, 1956). While it is clear that oxidative damage increases with advancing age, and that high levels of ROS can be toxic, accumulating evidence indicates that oxidative damage can be experimentally dissociated from lifespan (Van Raamsdonk and Hekimi, 2010). It has been shown that increasing oxidative damage does not necessarily decrease lifespan (Yang et al., 2007) and that having increased oxidative damage is compatible with long life (Van Raamsdonk and Hekimi, 2009). In fact, ROS have been shown to act as signaling molecules (Schieber and Chandel, 2014; Shadel and Horvath, 2015) and mild increases in ROS in the right place and at the right time can increase lifespan (Schaar et al., 2015). For example, an increase in ROS has been shown to modify a cysteine residue within IRE-1 kinase, which leads to activation of the SKN-1/NRF2 antioxidant response, and extended longevity (Hourihan et al., 2016). These results suggest that while the accumulation of damage is associated with increased age, it does not cause aging. Moreover, it casts doubt on the FRTA, suggesting the possibility that new theories of aging are needed. In this paper, I review some important experiments on the genetics and epigenetics of aging, and conclude by proposing a new theory of what causes aging.

2. Longevity is a genetically encoded trait

While aging has traditionally been thought of as a stochastic process of damage accumulation, work from the past three decades has demonstrated that aging is a malleable process that can be strongly influenced by genetics. Using the worm *C. elegans*, experiments in the late 1980s and early 1990s demonstrated that mutations in single genes can markedly increase the lifespan of the organism (Friedman and Johnson, 1988; Kenyon et al., 1993; Wong et al., 1995)). In fact, it has been shown that changing just one gene out of 20,000 genes in the worm genome can result in an amazing tenfold increase in lifespan from 20 days to over 200 days (Ayyadevara et al., 2008). Mutations in single

E-mail address: jeremy.vanraamsdonk@vai.org.
[1] Laboratory of Aging and Neurodegenerative Disease, Center for Neurodegenerative Science, Van Andel Research Institute, 333 Bostwick Avenue NE, Grand Rapids, MI 49503, USA.

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genes have also been shown to increase lifespan in other models organisms, including yeast, flies and mice. Importantly, many of the genes that modulate longevity appear to be conserved across species (Bitto et al., 2015) and genetic variation in at least some of these genes has been shown to be associated with longevity in humans (e.g. (Suh et al., 2008)). At present there have been 270, 570, 108, and 50 life-extending genes identified in yeast, worms, flies and mice, respectively ((Tacutu et al., 2013); http://genomics.senescence.info/genes/). While the functions of many of these genes, and their role in determining lifespan, have yet to be defined, the identification of these longevity-modulating genes has permitted the delineation of multiple pathways of lifespan extension, such as the insulin-IGF1 signaling pathway, the dietary restriction pathway, and the mild mitochondrial impairment pathway. The fact that single gene mutations can increase lifespan clearly indicates that organisms have the genetic capacity to live longer.

3. Interventions in adult and aged animals can increase lifespan

After it had been established that genetic pathways can modulate longevity, a key question was to determine when these pathways act to extend lifespan. It was shown that timing requirements for distinct pathways of lifespan extension were different. Decreasing insulin/IGF-1 signaling has been shown to double the lifespan of the worm (Friedman and Johnson, 1988; Kenyon et al., 1993). To determine when decreasing insulin/IGF-1 signaling could increase lifespan, Dillin et al. (2002a) used RNAi to knockdown the expression of the insulin/IGF-1 receptor gene *daf-2* during development only or beginning at different developmental stages and continuing to death. It was found that decreasing *daf-2* expression during development had no effect on lifespan, while decreasing expression throughout adulthood could increase lifespan even if the treatment was begun as late as day 6 of adulthood. This indicates that decreasing insulin-IGF1 signaling acts during adulthood to increase lifespan, and more generally demonstrates that changes taking place in adult organisms can still increase lifespan. As a dramatic example of this, it was shown that treating 600 day old mice with the mTOR inhibitor rapamycin could still significantly increase their lifespan (Harrison et al., 2009). It was subsequently shown that rapamycin could be delivered for just 3 months in 2 year old mice and extend longevity (Bitto et al., 2016). Similarly, it has been shown that methionine restriction beginning at 1 year of age is sufficient to increase lifespan in mice (Sun et al., 2009). In addition, parabiosis experiments, in which the vasculature of an old mouse is connected to a young mouse, have shown that specific circulating factors from young mice are able to increase the lifespan of old mice (Katsimpardi et al., 2014; Sinha et al., 2014; Villeda et al., 2014). Finally, it has been shown that exposing worms to a mild heat stress for just 2 h during the first week of adulthood is sufficient to increase their lifespan by 5–10 days (Dues et al., 2016; Lithgow et al., 1995). Combined, these results show that the lifespan of an organism is still malleable during adulthood as interventions administered throughout adulthood, or for short periods of adulthood, can increase lifespan.

4. Changes during development can affect adult lifespan

Intriguingly, some pathways of lifespan extension affect longevity exclusively during development. It has been shown that mutations (Feng et al., 2001; Lakowski and Hekimi, 1996; Yang and Hekimi, 2010) and RNAi knockdowns (Lee et al., 2003) that mildly affect mitochondrial function cause increased lifespan. To determine whether there is a critical window of time for decreasing mitochondrial function to increase lifespan, Dillin et al. (2002b) used RNAi to knock down subunits of the electron transport chain (ETC) during development only or during adulthood only. They found that decreasing mitochondrial function during development was sufficient to increase lifespan to the same extent as decreasing function throughout development and adulthood, while knocking down the expression of genes encoding subunits of the ETC during adulthood had no effect on lifespan (Dillin et al., 2002b). The fact that maternal expression of CLK-1 is sufficient to revert the lifespan of a homozygous *clk-1* deletion mutant to wild-type also suggests that inhibiting mitochondrial function increases lifespan during development (Wong et al., 1995). The ability of interventions during development to increase adult lifespan is not limited to worms. In mice, it has been shown that decreasing nutrition intake during the first 20 days of life (until weaning) by increasing litter size by 50% (crowded litter) is sufficient to increase mean and maximum lifespan by 100 days (Sun et al., 2009). These results show that interventions administered during development can be sufficient to increase lifespan.

5. Epigenetic changes can extend longevity

Since lifespan can be modulated through changes in gene expression, and interventions administered during development can increase adult lifespan, it is plausible that these interventions induce epigenetic modifications that maintain changes in gene expression throughout adulthood. To determine the extent to which epigenetic modifications could affect longevity, Greer et al. (2010) performed a targeted RNAi screen in *C. elegans* of known modifiers of histone methylation. They found that knocking down expression of multiple members of a H3K4 trimethylation complex resulted in increased lifespan. Intriguingly, they went on to show that deficiencies in the trimethylation complex in the parental generation resulted in increased lifespan in genetically wild-type (+/+) offspring not only in the first generation of progeny but for the first four generations of progeny (Greer et al., 2011).

The fact that overexpression of the histone deacetylase SIRT6 in mice increases lifespan demonstrates that epigenetic modifications can also influence longevity in mammals (Kanfi et al., 2012). Further support for this conclusions comes from the finding that the epigenetic changes induced by cellular reprogramming towards pluripotency increase lifespan in a progeria mouse model (Ocampo et al., 2016). A role for epigenetics in determining lifespan is further supported by observations that biologic age can be estimated using measurements of DNA methylation (cytosine-5 methylation within CpG dinucleotides) in what is known as the epigenetic clock (Horvath, 2013). These results indicate that epigenetic changes can lead to extended longevity.

6. Decline in stress resistance with age can be mediated by epigenetic modifications

As the ability to resist multiple stresses has been proposed to be a key determinant of longevity (Miller, 2009), a number of groups have explored the relationship between stress resistance and aging. In every case, it was found that resistance to stress declines with age (Bansal et al., 2015; Dues et al., 2016; Labbadia and Morimoto, 2015). In these experiments performed in *C. elegans*, the precise timing of the decrease in stress resistance varied somewhat between labs but it was generally observed that stress resistance declined shortly after the peak reproductive period (day 1–3 of adulthood). This suggests that worms maintain their ability to respond to stress until they have successfully passed on their genes to the next generation. Consistent with this conclusion, it was observed that the ability of multiple stress response pathways to be activated by stress is lost with advancing age (Dues et al., 2016).

In exploring the mechanism involved in the decline of one of these stress response pathways (the heat shock response), it was found that the decrease in stress resistance is a genetically-programmed event (Labbadia and Morimoto, 2015). In young adult worms, the H3K27me3 demethylase JMJD-3.1 removes methyl groups from H3K27 thereby allowing the heat shock transcription factor HSF-1 to bind to heat shock elements (HSE) to activate genes involved in the heat shock response. After the peak reproductive period, the expression of JMJD-3.1 decreases, resulting in a failure to demethylate H3K27 surrounding HSEs, thereby blocking the binding of HSF-1 and preventing the upregulation