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Does longer lifespan mean longer healthspan?

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Abstract

Once thought to be impossible, it is now clear that changing the activity of several conserved genetic pathways can lead to lifespan extension in experimental organisms. In humans, the goal is to extend healthspan, the functional and disease-free period of life. Are the current pathways to lifespan extension also improving healthspan?

Keywords

insulin/IGF-1 signaling; TOR signaling; *C. elegans*; mice; longevity; aging

Lifespan vs. Healthspan

It is likely that we will look back on the first half of the 21st century in healthcare as the age of aging. The world is getting older and the numbers are staggering – up to 20% of the globe will be over 60 years in the near future and healthcare costs will rise. Chronic diseases of aging are increasing and are inflicting untold costs on human quality of life, and there is a growing recognition that solutions must be found to keep people healthy longer.

Most medical research is targeted at diseases in isolation and yet evidence is mounting that physiologic changes associated with aging underlie a vast majority of chronic disease states. If this is true, slowing aging might prevent multiple morbidities simultaneously.

The aging research field has undergone dramatic change in the past three decades, evolving from a prevailing view of aging as non-modifiable to demonstrating in experimental organisms that changing the activity of a number of genetic pathways can lead to lifespan extension. Importantly, most of these pathways, including the TOR- and insulin/IGF signaling pathways as well as genes like Sirtuin protein deacetylases, have conserved effects across disparate species, suggesting that they may modulate lifespan in humans.

Lifespan is currently the most used measure of aging, yet it does not provide all of the information necessary to warrant human intervention. For successful implementation in

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humans, interventions need to enhance healthspan, the functional and disease-free period of life. It is worth clarifying the range of possibilities for healthspan extension. Consider an intervention that doubles the lifespan of an organism (**Figure 1**). At the extreme, the intervention may not extend healthspan at all and the period of morbidity would be tripled (although this seems unlikely) (**Figure 1A**). Alternatively, an intervention may stretch survival equally, in which case both healthspan and the period of morbidity would be doubled (**Figure 1B**). It could also result in unaltered (**Figure 1C**) or even compressed morbidity (**Figure 1D**) and healthspan would be disproportionately extended. We describe an intervention as extending healthspan chronologically if the period of functional capacity or disease resistance is enhanced, or as extending healthspan proportionately if these periods are extended relative to the enhanced lifespan of the organism. When considering human interventions, the clear goal is to extend healthspan while not enhancing morbidity. The examples in **Figure 1** are idealized, yet evidence from extensive studies in animal models of lifespan extension for example by mutation of the insulin/IGF receptor, *daf-2*, in the soil nematode *Caenorhabditis elegans* or using the mTOR inhibitor rapamycin in mice suggests that some but not all elements of healthspan can be extended with age. Lifespan extension by dietary restriction has also been studied intensely and readers are directed to a recent review (Solon-Biet et al., 2015).

***daf-2* and *C. elegans* healthspan**

Mutations in one of the first genes associated with aging, the insulin/IGF-1 receptor *daf-2*, were reported more than 20 years ago to lead to a doubling of the lifespan of *C. elegans* (Kenyon et al., 1993). Since then, the insulin/IGF signaling pathway has been studied extensively, with evidence that reduced signaling leads to lifespan extension in organisms ranging from worms to mice (Junnala et al., 2013), and even possibly humans (Milman and Barzilai, 2015). Notably, data from both worm and mouse models of long-lived mutants with reduced insulin/IGF signaling indicate that animals often have delayed onset of diseases, including neurodegenerative disorders (Dillin and Cohen, 2011), although functional metrics of youth have been tested to a lesser extent. Perhaps the best indicator of improved healthspan for this pathway comes from studies of centenarians (i.e., individuals >100 years of age), who are more likely to have IGF-1 receptor genetic variants associated with reduced function, and reduced IGF1 levels are predictive of enhanced survival in female nonagenarians (i.e., women 90-99 years of age) (Milman and Barzilai, 2015).

Despite extensive studies of this pathway, however, recent evidence has called into question whether reduced insulin/IGF signaling confers healthspan extension in *C. elegans*. One report tested several classic long-lived mutants, including *daf-2*, *eat-2*, *ife-2*, and *clk-1* across a range of cellular and behavioral assays, finding no consistent chronological healthspan extension and therefore suggesting that lifespan extension in these mutants was achieved without accompanying healthspan benefits (Bansal et al., 2015). Among the measures tested were resistance to stresses such as heat and oxidative agents, movement and pharyngeal pumping. Although some mutants extended chronological healthspan in a subset of contexts, none of the mutants proportionally extended healthspan, leading the authors to conclude that lifespan and healthspan can be dissociated.

A more recent report also examined the *daf-2* mutant, and measured maximum velocity in a 30 second window longitudinally (Hahm et al., 2015), rather than movement over a five minute period cross-sectionally (Bansal et al., 2015). These maximum-velocity assays were performed on media plates without a bacterial food source since *daf-2* mutants have altered food vs. exploration preferences (Hahm et al., 2015). In this context, the *daf-2* mutant exhibited a proportional increase in their healthspan (**Figure 1C**). The investigators also adapted a human metric to measure quality-adjusted lifespan in *C. elegans* for the first time, and showed that *daf-2* and other long-lived mutants, except *clk-1*, had improved life quality (Hahm et al., 2015). The ultimate utility of this metric for measuring healthspan in invertebrates will require more research.

Together, these studies highlight that the experimental definition of healthspan in non-vertebrates such as *C. elegans* is still being developed, with a need (i) to establish multiple measures of animal function that are likely to be relevant to the human condition, and (ii) for assessments to be performed across a range of interventions that lead to enhanced longevity.

Rapamycin and murine healthspan

Another case where healthspan has been experimentally tested is in the context of lifespan extension by rapamycin, a specific inhibitor of the nutrient responsive TOR kinase. Similar to genetic models of TOR inhibition, rapamycin treatments produce lifespan extension in organisms ranging from yeast to mice, with evidence beginning to accumulate in humans. Most mice studies conducted with rapamycin have shown extension of median lifespan by up to 30%, even when initiated relatively late (20 months of age) (Johnson et al., 2015). Given that rapamycin is clinically approved for use in humans, it is imperative to determine whether the drug improves healthspan.

Several laboratories have assessed healthspan metrics in mice treated with rapamycin. The first comprehensive study concluded that rapamycin slowed several physiologic metrics of aging, including liver degeneration, myocardial abnormalities, endometrial hyperplasia and non-lethal adrenal tumors. Other metrics trended toward significance, while rapamycin had the opposing effect of increasing cataract formation and causing testicular degeneration in male mice (Wilkinson et al., 2012). Furthermore, rapamycin was found to rejuvenate the aging mouse heart (Dai et al., 2014; Flynn et al., 2013). However, not all studies have proved to be so promising, with one report finding more modest healthspan benefits of rapamycin. Here, rapamycin improved a subset of aging phenotypes, including cancer, cardiac and metabolic changes, and learning and memory tasks, but whether the effect was aging specific was called into question because rapamycin improved many of these phenotypes in young animals as well (Neff et al., 2013). Moreover, several other age-related phenotypes were not measurably affected by rapamycin. Another more recent study focused on functional metrics of aging, finding mostly female-specific benefits of rapamycin on a range of (but not all) parameters including grip strength, maintenance of body mass, and sleep quality (Fischer et al., 2015). For these studies, rapamycin was administered in a microencapsulated form in the food at similar doses, suggesting that differences in dosage do not underlie differential effects on healthspan. Rapamycin is also protective in several

mouse models of chronic disease, although many of these have not been assessed in the context of aging (Kennedy and Pennypacker, 2014).

In summary, the murine data regarding rapamycin, while incomplete, suggests that some aspects of healthspan are improved during aging and a subset of chronic diseases is delayed. However, other functional changes are unaffected and a few, such as cataracts may be accelerated. This would put rapamycin in category C of Figure 1 for most pathologies of aging, but also reflects the complexity of the healthspan issue, where some pathologies can be delayed while others are unaffected. Little is known for humans, although a recent study indicated that everolimus, a rapamycin derivative, could ameliorate immunosenescence in the elderly (Mannick et al., 2014).

Concluding Remarks

We now know that life expectancy is a modifiable parameter in animal models, and efforts are ongoing to embark on a path to test interventions in humans. The test parameters will likely be prevention of chronic diseases of aging and/or improvement of age-related functional decline. While there is optimism that this approach could represent a breakthrough in the treatment of chronic diseases of aging, the result is likely to be more complex. Healthspan is not one metric but a compilation of functional measures involving different organs and distinct disease mechanisms that may differ between different organisms. Certainly, more experimental studies are needed to better define the healthspan concept and to identify the best metrics for each aging model organism. Interventions are likely to be effective against a subset of the physiologic changes associated with aging, but perhaps not all. Finding ways to match aging interventions with clinical parameters in humans will not be straightforward, but the data in animal models suggest that there is indeed a unique opportunity to help people enjoy longer, healthier lives.

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Figure 1. Schematic illustrating effects of lifespan extension on healthspan extension

In A-D, lifespan extension is accompanied by differential effects on morbidity onset, thus affecting healthspan in different ways. ‘Chronological’ and ‘Proportional’ are used in the text to describe specific effects of longevity paradigms on healthspan. Evidence from the reduced insulin/IGF-1 and TOR signaling paradigms have provided evidence in support of B and C.