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Review

A brief history of modern aging research

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ABSTRACT

Over the last few decades, aging research has emerged as a vibrant area of rigorous scientific study. With its humble beginnings in yeast and worms, the field has progressed so dramatically that scientists are now able to extend the lifespan of mice with the use of small molecule drugs. However, it was not too long ago that answering the more basic question, whether aging was amenable to scientific study, was itself a topic of contentious debate. To begin to understand how a field that was initially thought of as pseudoscience has come so far, it is instructive to understand its roots in both theory and practice.

1. Is aging amenable to scientific study?

What is aging? The following two scenarios may be illustrative: 1) In the first case, everything that lives, dies; 2) In the second, everything that lives, ages, and then dies. Although they may appear similar, these two concepts differ in one important regard – the rate of death. The latter depicts a mortality rate that increases with age, while the former depicts one in which death can occur with equal probability at any age (Fig. 1). Empirically, we know that death is much more likely with advanced age (and intuitively we all know that our grandparents are more likely to die than our parents). And though it may seem strange to say, old age is the single greatest risk factor for death.

While today we take it for granted that this biological phenomenon, which we call aging, is amenable to scientific study, just thirty years ago this question itself was hotly debated. Pre-existing theories based on evolutionary biology painted a gloomy picture for the early scientists that attempted to develop this nascent field.

Evolutionary theory attributed aging to the concomitant breakdown of multiple biological systems due to the declining influence of natural selection post-reproduction. The theory posited that since most animals in the wild do not survive to old age (instead dying from predation, starvation or other extrinsic factors), there had been little pressure to select for alleles that conferred much benefit later in life (reviewed in Kirkwood, 2005). Consequently, the numerous detrimental phenotypes that we generally associate with aging were attributed to this waning influence of natural selection. It was also postulated that aging may arise as a consequence of antagonistic pleiotropy, in which alleles that provide substantial benefit early in life become detrimental during adulthood (Williams, 1957). For these reasons, evolutionary theory stated that aging was an inevitable byproduct of the rules of natural selection and therefore not a regulated process amenable to scientific study (let alone intervention).

2. The first evidence hinting at the possible regulation of aging

In spite of this skepticism, evidence began to emerge in the late twentieth century that challenged these beliefs (Table 1). First, it appeared that the mortality curves for widely divergent organisms, ranging from single-celled yeast to humans, closely resembled one another (Fig. 2) (Kaeberlein et al., 2001). This hinted at a commonality in the aging process that was potentially amenable to scientific study, particularly in model organisms. Second, it appeared that while aging itself may not be regulated, the rate of aging could be. This was best exemplified by the vastly disparate lifespans of closely related species, such as those in the rodent family: a typical rat lives around 5 years, while the average naked-mole rat lives 30 years. Even within the same species, dramatically different aging rates were observed. Take for example the case of the honey bee - even though the queen and worker bees are genetically identical, the queen lives on average ten times longer (an early insight into the importance of epigenetics in the aging process).

However, the strongest case was made by calorie restriction (CR) (Koubova and Guarente, 2003). CR is simplicity at its best: by reducing food intake by a specific amount (in mice this equates to 30–40% below *ad libitum*), one can extend the average and maximum lifespan of a wide variety of organisms (McCay et al., 1935; Weindruch et al., 1986; Fernandes et al., 1976; Kubo et al., 1984). The fact that CR works in such diverse organisms suggests that it had been selected for early in evolution, possibly as a survival mechanism during times of food scarcity. This idea of hunkering down during harsh times is not just a theory – it is vividly exemplified by organisms such as microbes and worms in which alternate long-lived life forms (such as spores and

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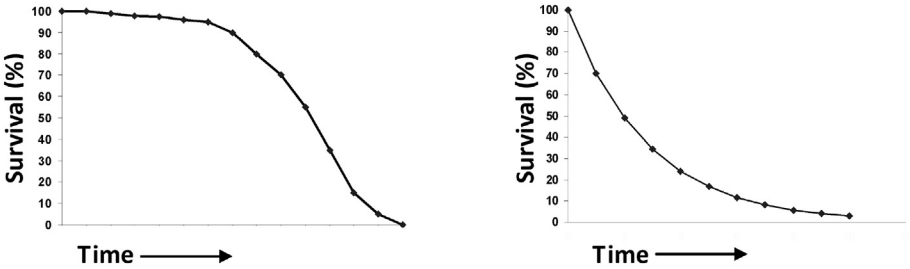

Fig. 1. Increased mortality with age.
Nearly all organisms show higher mortality rates with advanced age (left), as opposed to a fixed mortality rate where death is equally likely at any age (right).

Table 1
A listing of key findings in aging research, with particular focus on insulin-IGF1 and Sirtuin pathways.

Year	Finding	Reference
1935	Report of lifespan extension in rodents with calorie restriction	McCay et al., 1935
1950	Report of a premature aging syndrome in humans (Hutchinson-Gilford)	Thomson and Forfar, 1950
1977	Finding that worm lifespan could be modulated with environmental interventions	Klass, 1977
1980	Report that Snell dwarf mice may live longer than wildtype counterparts	Eicher and Beamer, 1980
1982	Finding that inbred strains of worms can have significantly different lifespans, indicating possible genetic regulation of aging	Johnson and Wood, 1982
1983	First creation of genetic mutants (in worms) that display increased lifespan	Klass, 1983
1988	Identification of the first gene mutation (age-1) that increases lifespan (in worms)	Friedman and Johnson, 1988
1993, 1995	Demonstration that DAF-16 is required for longevity phenotypes of insulin signaling mutant worms, defining the first regulatory network for aging	Kenyon et al., 1993; Larsen et al., 1995
1995	First evidence implicating Sirtuins in aging (in yeast)	Kennedy et al., 1995
1996	First definitive description of a long-lived mouse strain (Ames dwarf mice), indicating genetic regulation of aging in mammals	Brown-Borg et al., 1996
1997	Extrachromosomal rDNA circles identified as a cause of aging in yeast	Sinclair and Guarente, 1997
1999	Identification of SIR2 as the key Sirtuin mediating longevity in yeast	Kaeberlein et al., 1999
1999	Discovery of a non-deacetylase activity (ADP-ribosyltransferase) for Sirtuins, hinting at broader enzymatic functions	Frye, 1999
2000	Discovery of a NAD^+ dependent deacetylase activity for SIR2	Imai et al., 2000
2001	Description of a second long-lived mouse strain (Snell dwarf mice)	Flurkey et al., 2001
2001	Evidence of SIR2 regulation of lifespan in multicellular organisms (worms)	Tissenbaum and Guarente, 2001
2002	Discovery that increased respiration during CR is required for lifespan extension in yeast	Lin et al., 2000
2003	Extension of mouse lifespan via heterozygous deletion of IGF1 receptor or deletion of insulin receptor in white adipose tissue	Holzenberger et al., 2003; Blüher et al., 2003
2003	First evidence indicating a role of TOR in aging (in worms)	Vellai et al., 2003
2003, 2004	The first SIR2 agonist, resveratrol, discovered and shown to extend the lifespan of yeast and later, worms	Howitz et al., 2003; Wood et al., 2004
2004	First evidence that AMP-Kinase regulates aging (in worms)	Apfeld et al., 2004
2007	Two neurons found to be required for lifespan extension via calorie restriction in worms, highlighting the importance of neuronal regulation of aging	Bishop and Guarente, 2007
2007	Extension of mouse lifespan via deletion of insulin receptor in the brain	Taguchi et al., 2007
2008	First evidence that a pharmacological agent (metformin) can extend the lifespan of mice	Anisimov et al., 2008
2009	Association of genetic variants in insulin-IGF1 signaling with human longevity	Pawlikowska et al., 2009
2009	A second pharmacological agent (rapamycin) found to extend the lifespan of mice	Harrison et al., 2009
2010	Association of SIRT1 variants with aging in a Han Chinese Population	Zhang et al., 2010
2011	Discovery of a more general deacylase enzymatic function for mammalian Sirtuins	Du et al., 2011
2012	Mammalian SIRT6 shown to regulate the lifespan of male mice	Kanfi et al., 2012
2013	Brain-specific overexpression of SIRT1 shown to extend lifespan of mice	Satoh et al., 2013
2014	Pharmacological inhibition of glucose digestion and release into the blood (with Acarbose) shown to extend lifespan of mice	Harrison et al., 2014
2014	First evidence that pharmacological activation of SIRT1 extends lifespan in mice	Mitchell et al., 2014; Mercken et al., 2014
2016	Evidence that repletion of NAD^+ levels with use of precursors extends lifespan of mice	Zhang et al., 2016
2016	Demonstration that combination of longevity associated drugs (metformin and rapamycin) can additively extend lifespan in mice	Strong et al., 2016
2017	Association of a variant in human growth hormone receptor with longevity in males	Ben-Avraham et al., 2017

IGF1, insulin-like growth factor 1; rDNA, ribosomal DNA; TOR, target of rapamycin; ADP, adenosine diphosphate; NAD^+, nicotinamide adenine dinucleotide; CR, calorie restriction.

dauer larvae, respectively) can form during times of stress.

On the other end of the spectrum, a series of premature aging diseases began to be identified in humans that appeared to accelerate many aspects of the aging process (Thomson and Forfar, 1950). For instance, individuals suffering from Hutchinson-Guilford Syndrome or Werner Syndrome exhibited classic aging related diseases such as osteoporosis, cataracts, alopecia, skin atrophy (and death) at an inappropriately young age.

Together, these observations strongly suggested that the *rate* of aging was likely a regulated process and thus amenable to scientific inquiry. The race to identify the longevity-associated genes was on.

3. Regulation of aging through the insulin signaling pathway

The initial studies attempting to find a genetic basis for aging were performed in the nematode worm, *Caenorhabditis elegans* (Kenyon, 2011). In 1977, Michael Klass demonstrated that the lifespan of worms could be increased by subtle environmental variations such as growth under low temperature or reduced food availability (Klass, 1977). A few years later, two experiments would provide the first evidence that specific genes may be involved in this process: 1) In 1982, Johnson and Wood reported observing differing lifespans for various inbred strains of worms created in the laboratory (Johnson and Wood, 1982); and 2) One year later, Klass would mutagenize worms and show that several of his mutants lived substantially longer than the wildtype controls (Klass,