

The Fountain of Youth: Exploring the Genetics of Aging

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In 1993, Cynthia Kenyon identified a single gene mutation that doubles the lifespan of the microscopic nematode, *C. elegans* [3]. Even more exciting, the worms not only lived longer, they actually aged slower; it was the human equivalent of a 40-year-old person looking 20. Many other genes have subsequently been found to modulate lifespan, and learning how these genes function at the cellular has provided key insights into the biological mechanisms of aging.

Though the primary cause of aging is still unknown, many factors have been identified in the process. Various types of damages accumulate as an individual ages. This could be due to an increased rate of damage that, over time, outstrips the body's ability for repair. In the 1970s, biogerontologist Denham Harman proposed that mitochondrial production of reactive oxygen species such as hydrogen peroxide (H_2O_2), hydroxyl (OH) and superoxide (O_2^-) during respiration caused oxidative damage to cells; the accumulation of such damage is commonly believed to accelerate the process of aging [4]. From this, the mitochondria is portrayed as a biological "clock," with the impetus of the process being oxidative stressors metabolized in cells. The reactive products created from respiration can damage the mitochondrial inner membrane, creating a positive feedback loop that allows more free radicals to leak out of the mitochondria into the cytoplasm of the cell. Superoxide dismutase is an enzyme that helps mitigate free radical damage. Transgenic mice that lack this enzyme have significantly decreased lifespan (30-40 days for mutants versus 2-3 years for wild-type) and the mutant phenotype can be partially rescued by administration of antioxidants [10, 11]. Thus, the accumulation of oxidative damage seems to be a factor that influences aging. Furthermore, genetic manipulation of lifespan in model organisms has revealed potential therapeutic targets for treating various age-related diseases. One such example involves insulin signaling and the modulation of aging through caloric/dietary restriction.

The insulin-signaling pathway regulates many biological processes, including metabolism, fertility, development, and lifespan [12]. An abundance of research has been done in *C. elegans* to better understand how the insulin pathway affects these processes. In *C. elegans*, DAF-2 functions as an insulin-like receptor and mediates signaling through this pathway. DAF-2 negatively regulates lifespan by repressing a downstream transcription factor, DAF-16. In the presence of insulin, the DAF-2 receptor signals downstream components of the insulin-signaling pathway to inhibit DAF-16. This inhibition prevents the DAF-16 transcription factor from entering the nucleus, and results in a normal lifespan. In the absence of proper insulin signaling (as is the case when *daf-2* is mutated), DAF-16 is no longer inhibited, and it translocates into the nucleus to activate gene expression. Under these conditions, animals live twice as long [12]. It is important to note that the lifespan extension phenotype exhibited by *daf-2* mutants is dependent upon DAF-16 activation—when *daf-16* and *daf-2* are both mutated, the animals have a normal lifespan [12]. What then, does DAF-16 do? We know that *daf-2* mutants live longer because DAF-16 is activated, but how? To answer this question, researchers study gene expression. Since DAF-16 is a transcription factor, identifying which genes it regulates could reveal how these worms live longer.

The ability to survey the entire genome has revolutionized the way scientists can study complex biological phenomena such as aging. Researchers have taken advantage of new genomic and proteomic technologies to simultaneously assay the expression pattern of thousands of genes to identify expression changes that are associated with aging. Application of these new methodologies towards aging research has led to the identification of many genes that are regulated by DAF-16, which has revealed that lifespan extension in *daf-2* mutants arises from altered metabolism, elevated stress response, and improved damage repair/clearance [2]. Thus, studying the

insulin-signaling pathway in *C. elegans* has shed new light on the aging process and provided insight into various age-related diseases.

Another way to increase lifespan is through caloric restriction. In yeast, reducing glucose concentrations increases lifespan [9]. Caloric restriction is a biological stressor that induces various responses, such as cellular defense, damage repair, and energy production, to increase the organism's chance of survival. Lee *et al.* (2002) showed that there is also a shift in the fuel source. Instead of utilizing glucose as an energy source, cells utilize lipids and amino acids. But how does changing the fuel source increase lifespan?

Examining the enzyme complexes of the mitochondrial electron transport chain (ETC), key determinants of aging which are conserved from prokaryotes to mammals, can provide insight into mechanism of this lifespan extension. Mitochondrial complexes I, III, IV and V generate many reactive oxygen species, while complex II produces very few [5, 7, 8]. Under normal conditions, glucose catabolism takes place in complex I, producing reactive oxygen species that damage the cell. However, reduced glucose availability during dietary restriction results in a shift toward lipid catabolism, which occurs in complex II. Increased utilization of complex II over the other enzyme complexes during dietary restriction reduces the production of damaging reactive oxygen species. Animals live longer due to this reduction in free radical creation, which supports the role of oxidative damage in aging.

In addition to the shift in fuel source, caloric restriction activates proteins called sirtuins to extend lifespan [6]. In yeast, caloric restriction activates the Sir2 protein, which is conserved from prokaryotes to mammals. Interestingly, a small molecule found in red wine called resveratrol has been found to increase the lifespan of many organisms, including mammals, by activating this protein. Effectors of this protein have been shown to exert many of the positive consequences of caloric restriction, such as anti-diabetic, anti-cancer, and neuroprotective effects [6]. As a result, sirtuins are receiving focused attention as a potential target for treating diseases of aging.

Indeed, aging is a mystery that affects every organism on this planet. Research has been active in the field for many years on numerous fronts.

Scientists have taken advantage of the wide range of techniques available in model organisms to elucidate the mechanisms of aging. These organisms are ideal for aging research due to their short base lifespan, which allows for quickly quantifiable measurements of longevity. In addition, there is a wealth of information available for these organisms, including completely sequenced genomes and various bioinformatics databases. With these advantages, model organisms are on the forefront of aging research, enabling science to question the various changes that are associated with aging. Furthermore, genetic manipulation of lifespan in model organisms has revealed potential therapeutic targets for treating various age-related diseases, translating research into reality.

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