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The Roles that *age-1* and *daf-2* Genes Play in Aging

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Introduction

The factors that determine the lifespan of an organism have become an increasingly popular area of study in recent years. There are theories like the antagonistic pleiotropy, accumulated mutation, and calorie restriction that explain certain facets of the process of aging. However, a complete explanation of what determines the life of an organism is still unknown. In this article, I discuss the role that genes, especially *age-1* and *daf-2*, play in the process of aging of an organism.

Genes are the basic unit of inheritance. They not only hold the information to build and maintain our cells and tissues but are also responsible for passing genetic information onto future offspring. In this regard, genes hold the information to code for proteins that regulate the biological processes that take place in our body. This makes it very clear that recognizing the role of aging genes like *age-1* and *daf-2* is important in order to understand the process of aging.

In order to study the role of genes, scientists have used techniques by which the concerned genes are mutated and the mutations' effects on the phenotype of the organism are observed. *C. elegans*, a form of microscopic nematode, has been widely used in aging studies to easily obtain a mutant variety of organisms and to more readily control external factors. Many aging genes have been found to prolong the lifespan of *C. elegans* by increasing their resistance to stress and by preventing diseases. Thus, it is believed that aging genes affect limiting biological processes (Johnson et al. 2002).

Age-1 Gene and Aging

There are numerous aging genes that have been found to cause at least a 20% increase in the lifespan of *C. elegans*. *Age-1* is one such example. It is the first gerontogene mutant to be identified based on the organism's phenotype (Johnson et al., 2002). The *age-1* mutation was initially identified in *C. elegans* that lived longer than the wild-type worms. To date, age mutants in *C. elegans* have been divided in different groups: namely, dauer-forming, sterile, clock, etc. According to the study carried out by Johnson et al., *C. elegans* with *age-1* (*hx546*) alleles on an average have a 70% longer lifespan than the wild-type worms. It has also been found that the age mutants have a higher level of metabolic activity throughout their lifespan. In addition to this, *age-1* worms are found to be resistant to oxidative stress by hydrogen peroxide and UV irradiation. One of the most important phenotypes seen in age mutants is the significant reduction in the mutations of mitochondrial DNA in comparison to the naturally found organisms. In addition to their effects in increasing lifespan, it has also been found that the *age-1* mutants do not compromise in their fertility and somatic growth, as these factors have been found to be comparable to those of the wild-type worms.

Daf-2 and Dauer Formation

Another significant aging gene is *daf-2*. This gene is the insulin-like receptor in *C. elegans*, which has also been conserved in human beings. *Daf-2* was isolated by its effects on dauer formation. In normal conditions, the *daf-2* gene acts to negatively regulate *daf-16*, a fork-head transcription factor, by a process of phosphorylation cascade. It was found that some mutation in the *daf-2* gene caused constitutive dauer formation. Dauer is an alternative developmental stage of nematodes, in this case *C. elegans*, where the larvae (specifically in L2 Stage) goes into a static phase and survives harsh conditions like scarcity of food, overcrowding, etc. In order to survive the harsh conditions, dauers have thick cuticles around their body and often remain motionless by using their fat stores for survival (Butcher et al., 2007). Worms in dauer stage are considered non-aging, because they can survive for several months in the same stage, and then, as the conditions improve, worms can progress into the adult stage. In order to get into this stage and escape harsh external conditions, *C. elegans* sense the environmental conditions like overcrowding and possibly scarcity of food, by the level of a small chemical called the dauer pheromone (Butcher et al., 2007). If the concentration of this chemical gets too high, it indicates a higher stress level and induces the worms in an L2 larval stage to enter into a dauer stage. This is because a high level of pheromone inhibits *daf-2* and *age-1* and increases the level of *daf-16*. As a result, this promotes a dauer larval stage and increases the lifespan of the organism (Riddle et al., 2007). Once the conditions get back to normal, the larvae can develop into an L4 stage and become a normal adult. It has been found that the *daf-2* worms that go into dauer stage can have a 100% increase in their lifespan compared to that of the wild-type worms.

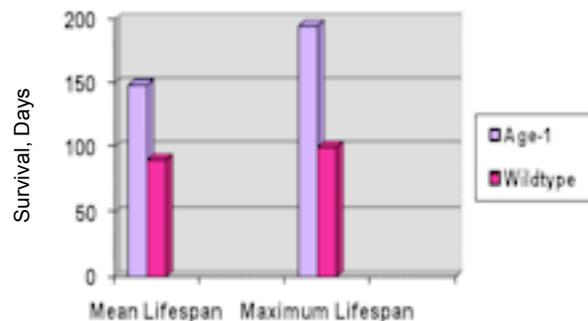


Figure 1. The average life span of *age-1* worms increased by 70% more than the wild type worms, while the maximum lifespan increased by almost 105%.

Daf-2, Calorie Restriction and Aging

The longevity enhanced by the mutation in *daf-2* has also been found to be similar to the effects of calorie restriction. Calorie restriction (CR) is a system of dietary regimen where dietary energy intake is reduced by 10-25% of the normal Western diet. In many studies, including those with human beings, CR has led to a decrease in cellular oxidative stress and reductions in the fasting glucose level, pressure, cholesterol, etc., which lead to an increased lifespan. This

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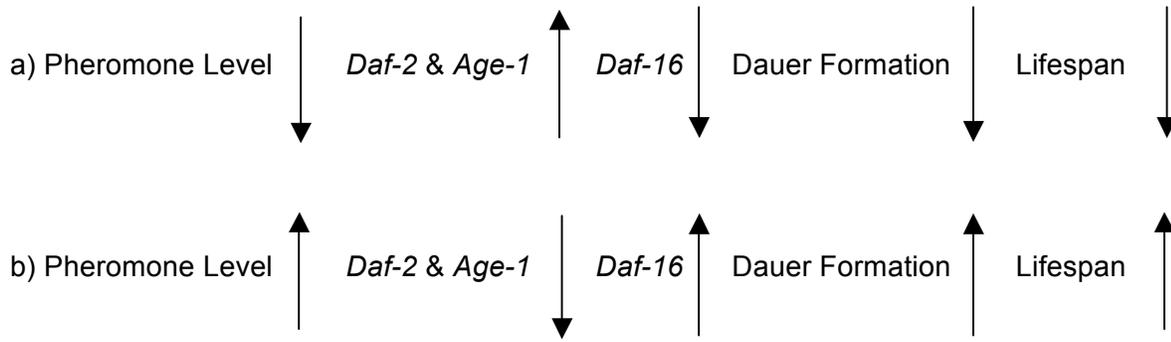


Figure 2a. Inhibitory effects are seen in dauer formation of *C. elegans* when the level of pheromone is low; **Fig. 2b.** Development of L2 stage worms into dauer stage increases in high levels of dauer pheromone.

indicates that the *daf-2* gene might be involved in the process of aging by controlling biological metabolic processes. Studies carried out by Hekimi et. al have shown that the increase in longevity produced by *daf-2* is the longest increase in lifespan produced by a single gene mutation (Hekimi et. al, 2002).

Daf-2, Age-1 and Insulin Signaling Pathway

Daf-2 and *age-1* encode parts of the insulin-like signaling pathway and are found to play a role in the regulation of *daf-16*, a transcription factor that acts in an insulin-mediated pathway to affect dauer formation. It is known that *daf-16* causes a dauer-defective phenotype and extends the lifespan of *daf-2* and *age-1* mutants. It has also been found that mutations in this pathway affect fertility, embryonic development, and viability. This indicates that *age-1* and *daf-2* are involved in biological processes that determine the development of possible progeny in the future. This makes it highly probable that genes like *age-1* might have been selected by evolution for the role they play in reproduction, despite their negative role in aging (Tissenbaum et. al, 1998).

Oxidative Damage Regulation by Age and Daf-2 Genes

Another major component of aging that the aging genes

have been found to affect is oxidative stress, which is a condition where higher levels of free radicals cause an increase in cellular damage. As all organisms need oxygen to survive, oxidative damage to a certain level is a normal phenomenon. However, to prevent this from getting too high, all forms of living beings try to maintain a reducing environment within their cells. One such antioxidant defense system in cells is maintained by enzymes like the super oxide dismutase (SOD) and catalase. SOD is a class of enzymes that catalyze the conversion of harmful super oxide into oxygen and hydrogen peroxide, while catalase helps in decomposing reactive hydrogen peroxide into water and oxygen. As oxidative damage to cells has been known to lead to negative effects in living cells, such as mitochondrial damage and in some cases even telomere shortening, it is clear that these enzymes play an important role in preventing cells from aging too fast. In this regard, it has been found that *age-1* and *daf-2* mutants have higher levels of super oxide dismutase (SOD) and catalase activity in their cells. Studies carried out by Honda et al. have shown that *age-1* and *daf-2* mutations lead to oxidative stress resistance phenotype in *C. elegans* by regulating through the insulin-signaling pathway (Honda et al., 1999). This evidence further substantiates the notion that the *age-1* and *daf-2* genes play an important role in determining the lifespan of an organism.

a) Normal Conditions:



b) Disrupted Daf-2 Pathway:

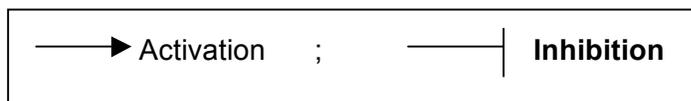


Figure 3. Representation of the Insulin Signaling Pathway.

Aging Genes and Antagonistic Pleiotropy

We have seen a great deal of experimental evidence that verifies that the mutant *age-1* and *daf-2* genes foster an increased lifespan. However, a question remains as to why these mutant genes that confer increased lifespan were not selected over the other genes that did not allow organisms to live as long as possible. This phenomena can be explained by the theory of antagonistic pleiotropy, first proposed by Medawar et al. Antagonistic pleiotropy is the process of expression of a gene that leads to multiple effects, which are beneficial earlier in life but may prove to be detrimental to the organism in the future. Antagonistic pleiotropy explains that animals in the wild generally did not reach an age when senescence started taking place; therefore, the genes that allowed a reproductive advantage early in life — even if they led to more accelerated effects of aging later on — were selected over those genes that did not give much reproductive advantage but helped the organisms live longer. It may also be true that, although some of the organisms might have lived long enough to undergo senescence, negative selection against harmful traits might not have been effective, because the natural selection force decreases with age. Therefore, it is highly likely that these factors lead to the selection of genes that do not help an organism live the longest possible lifespan over mutant forms that do (Kenyon et. al, 1995).

Conclusion

Daf-2 and *age-1* mutants seem to have the same genetic activities for their longevity by activating the same process that involves a common gene: *daf-16*. However, the role that any other unidentified genes play in the extension of lifespan cannot yet be excluded. Studies have indicated that these aging genes are involved in many other biological processes significant in determining the lifespan of an organism, such as reproductive development, resistance to oxidative stress, and resistance to bacterial pathogens, etc. (Tissenbaum et. al., 1997). These findings have greatly helped us to understand not only the role of *daf-2* and *age-1* genes but also the molecular mechanisms and biological processes behind aging.

We now know the role that *daf-2* and *age-1* play in the process of aging of an organism. As seen by the vast number of research being carried out on this issue, it is clear that these genes play an exceedingly significant role in determining the lifespan of an organism. Although none of the explanations have been fully able to pinpoint the exact biological processes behind aging, it is commendable how the rapid pace of development in the field of science and technology has identified new factors and parameters of aging, one such example being the role of *age-1* and *daf-2*. However, taking into account the vastly overreaching causes and effects of aging, it must not be forgotten that aging is a very complicated process, and many more studies need to be done to understand the complete biology behind it. Hence, although numerous studies have helped us understand the role that *age-1* and *daf-2* play in aging, there are various other aspects that are yet to be understood.

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