

Evolutionary theories of aging

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Introduction. Aging, from an evolutionary point of view, can be defined as a progressive decline in fitness (the ability to survive and reproduce) with increasing age (1). Yet, most biomedical researchers studying aging are concerned mainly with determining what causes aging at the molecular and cellular level (the physiological decline in function with age). As Thomas Kirkwood (2) correctly points out however, understanding why aging has evolved may help pinpoint which factors (i.e. genes, intrinsic damage, extrinsic damage) are most likely to be causally involved in aging.

The original theory that aging was an adaptive, genetically programmed event that served to limit population size and thus prevent overcrowding has been largely disregarded (3). Since aging is not normally observed in wild populations due to the high rate of early mortality from extrinsic factors (accident, disease, predation, etc.), aging is not required to prevent overcrowding and there would be little selection pressure for an “aging gene” to have evolved. Furthermore, if there were an aging gene, it would be expected that some individuals would have a mutated gene that allowed them to survive while their counterparts aged and died. This would clearly be advantageous for the individual and thus it is assumed the selection pressure for the mutation would be high, leading to the evolution of immortal individuals. However, this is not the case and therefore three major theories to explain the evolution of aging have emerged. These three theories are: 1) the accumulated mutations theory, 2) the antagonistic pleiotropy theory, and 3) the disposable soma theory.

Accumulated mutations theory. The accumulated mutations theory was first proposed by Medawar in 1952 and central to this theory is the idea that the influence of natural selection diminishes with age (1-5). If a deleterious mutation that manifests itself at a young age exists in a population, there will be strong selection pressure to eliminate that mutation because it will impact the fitness of a large majority of the population. However, if that same mutation does not manifest itself until late in life, many of the individuals carrying the mutation will have died before the mutation is expressed. If the mutation is rarely expressed, there is little opportunity for natural selection to clear this mutation from the genome. Therefore, these late-acting deleterious mutations can be passed from one generation to the next and may accumulate in the genome. If organisms are raised in a protective environment where extrinsic mortality is low, aging could occur as a result of the cumulative action of these late-onset deleterious mutations. Laboratory experiments to test for evidence that such mutations contribute to aging have been performed but the results are not conclusive.

Antagonistic pleiotropy theory. The second evolutionary theory of aging, antagonistic pleiotropy, was formulated by Williams in 1957 and proposes that genes exist which have beneficial effects early in life but harmful effects later in life (3, 5). If these genes confer increased reproductive success early in life, they would be selected for despite the fact that they may later cause senescence. Again, this hinges on the fact that in wild populations, few individuals would live long enough for the harmful effects to exert themselves. Therefore,

in terms of selection, it would be profitable to keep these genes around. The antagonistic pleiotropy theory is often referred to as the trade-off theory for obvious reasons – you may increase reproductive success early in life but the trade-off is that you age quicker.

There is more evidence for the antagonistic pleiotropy theory of aging than for the accumulated mutations theory but it should be noted that most of this evidence comes from experiments using *Drosophila melanogaster*. Whether or not the results are reproducible in other species remains to be seen. In a classic artificial selection experiment (6), fruitflies bred for longevity were found to exhibit decreased fertility in early life (delayed reproduction = increased life span).

Disposable soma theory. The third major theory is the disposable soma theory of aging (2-4). Unlike the previous two theories, it does not implicate genes as being involved in the aging process but focuses on the idea that cell maintenance (DNA repair, protein turnover, antioxidant defenses, etc) is costly. Given the fact that extrinsic mortality is extremely high in the wild - for example, nine out of ten newborn wild mice will die before the age of 10 months (7) – it would make little sense to use precious metabolic resources to maintain the soma beyond the expected lifetime of the organism. Using extra energy to increase reproductive capacity will be more beneficial from an evolutionary standpoint because it will enhance the fitness of that individual. Therefore, organisms have evolved in such a way that the amount of energy invested in maintaining the soma is sufficient to keep the animal alive long enough to reproduce but less than that which would be required to keep it alive indefinitely. The term disposable soma came from the analogy with disposable products (4) – why spend money making something durable if it will only be used for a limited amount of time?

The disposable soma theory also helps to explain why different species have different life spans (3). The higher the extrinsic mortality rate for a species, the less energy should be invested in somatic maintenance. More energy should be directed towards reproducing as often as is possible. Therefore, these species will have shorter life spans if allowed to age since investment in somatic maintenance is minimal. Comparative data exists to support this theory. Animals with adaptations that offer increased protection from extrinsic mortality have longer life spans. Some examples are birds and bats that have wings allowing them to escape dangerous situations and turtles that have sturdy protective shells. Austad (8) found that opossums living on an island where extrinsic mortality was low, aged at a slower rate than opossums living on the mainland where there was significant risk of death by predation. There was no evidence that other environmental factors (i.e. parasitism, disease, decreased food availability) contributed to this difference.

Caloric restriction and evolutionary theories of aging. Caloric restriction (CR) is the only experimental intervention that has consistently been shown to slow the rate of aging and increase mean and maximum life span in a variety of species (9). The exact mechanisms by which CR extends life span are not yet established, a feat complicated by the fact that CR causes numerous physiological changes, making it difficult to determine cause and effect. Is it possible that there is an evolutionary foundation for the life-extending CR effect?

A hypothesis consistent with the disposable soma theory of aging is that CR works by shifting the energy allocated to growth and reproduction towards repair and maintenance of the soma. In the wild, food shortages occur quite frequently and an adaptive response to this situation has likely evolved. In a case where

food was scarce, the probability of successful reproduction and the chance that any offspring conceived would survive would be minimal. In that situation, it would make sense to invest more energy in maintaining the soma so that you could survive until a time when resources were more abundant and reproductive success would be greater.

DNA replication and repair and protein synthesis and turnover are two maintenance systems that are vital to the survival of the organism and require significant amounts of energy. If CR does extend life span by diverting more energy to these maintenance processes, one would expect to see these systems being upregulated with CR. Indeed, results from a recent study in our laboratory show that as little as eight weeks of caloric restriction in young (6-months) rats results in increased 20S proteasome activity compared to ad libitum fed (AD) rats. The 20S proteasome plays a major role in selectively recognizing and degrading oxidized proteins (10), thereby helping to maintain the soma by preventing the accumulation of potentially toxic oxidized proteins. This study also showed that antioxidant potential was significantly higher in the CR animals compared to the AD animals. Antioxidants probably also play a significant role in somatic maintenance in that they can scavenge free radicals before the radicals can damage macromolecules in the cell. There is also evidence that DNA damage is reduced by CR, possibly as a result of increased DNA repair capacity (11). Furthermore, growth is slowed and reproduction is diminished or absent in CR animals (12). If normal feeding is resumed, these animals remain fertile far longer than animals fed ad libitum throughout their lives. I believe this is strong evidence in support of the hypothesis that CR diverts energy from growth and reproduction towards somatic maintenance and thus may explain the life-prolonging effects of CR.

Since the antagonistic pleiotropy and disposable soma theory are not entirely unrelated (both seem to favor the idea that delayed reproduction results in increased longevity), the next hypothesis may be somewhat similar to the previous one. In terms of the antagonistic pleiotropy theory, it could be hypothesized that CR extends life by preventing the expression of pleiotropic genes. Genes that are normally “turned on” to increase early-life fitness, may be suppressed by CR. As mentioned previously, CR does result in diminished reproduction in laboratory animals. The end result is that the animal lives longer but it has sacrificed much of its reproductive potential. Indeed, it is known that CR can alter the expression of many genes (13) so this may be a plausible working hypothesis. However, the fact that single genes have been found that increase life span without causing any identifiable adverse pleiotropic effects weakens this hypothesis (14, 15).

Finally, can the life-prolonging effects of CR be explained in terms of the accumulated mutations theory of aging? Since this theory postulates that it is the accumulation of late-onset deleterious mutations passed from generation to generation that causes aging, I don't see how an intervention that can prolong life in any given individual animal can be relevant to this theory. CR cannot possibly eliminate the mutations from the genome and in fact I would think that there would be an increased chance that these genes would be expressed since the animal is living longer. It's hypothetically possible that breeding CR animals would give natural selection a chance to eliminate these mutations but it still does not explain how CR prolongs the life span of individual animals. The only other possible hypothesis is that CR somehow prevents these late-onset deleterious mutations from manifesting themselves (similar to the previous hypothesis) but I cannot offer any data to support this.

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