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The Origin of Senescence and Death: An Evolutionary Enigma

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Abstract

Aging, or senescence, can be described as a reduction in the chance of survival and/or fertility of an organism over time. Senescence is characterized by a decline in organ functions, ultimately resulting in death. This may be caused by many mechanisms, such as inappropriate redistribution of DNA over daughter cells after cell division and accumulation of damage caused by, for instance, chemical radicals over a lifetime. These mechanisms may indeed explain senescence, but they do not explain the origin of senescence and death. Although many evolutionary theories of aging provide explanations for the life history of an organism, they again do not explain the origin of senescence and death per se. Consequently, senescence remains largely an enigma to evolutionary biology. Complete repair of damage and immortality are not impossible. Indeed the germ-cell line is in essence immortal. The existence of single-cell organisms demonstrates immortality indirectly as they give rise to descendants by splitting into two nearly identical daughter cells, and there are even some multicellular organisms that are allegedly immortal. I argue that senescence and mortality are the result of less-than-optimal circumstances causing immortality to become essentially impossible, because extrinsic (from outside the organism) factors will cause death even in the presence of perfect cellular repair mechanisms.

Introduction

Life is something enigmatic; although we generally can determine easily whether or not something is alive or dead, it is still rather difficult to define life. Nevertheless, some unique characteristics exist that distinguish living from nonliving objects, such as the ability to grow and reproduce. Yet, humans and many other organisms live long after their growth and reproductive period has ended. Thus there must be other important features that distinguish life from non-life. One such feature is metabolism: the continuous, simultaneous occurrence of many tightly controlled chemical reactions in a complex interacting network, in which the rate of each individual reaction is controlled adequately to meet the demands of the cell and the whole organism.

While during the initial stages of life there is a progressive development of structures, and organ and reproductive function, during later stages of life the reproductive capacity and organ functions decrease. This decrease in reproductive capacity and organ function is often referred to as aging, a process that ultimately will result in death.

Strictly speaking, the term "aging" describes the passing of time in the lifetime of an object. A better term for the

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process that will be discussed here would be "senescence." However, the term "aging" is so often used in the literature to describe this process that the terms "aging" and "senescence" will be used interchangeably in this paper.

Causes of Senescence and Death

During discussions of senescence and the maximal life span of an organism, it is important to realize the distinction between the ecological and the potential or physiological life span. The ecological life span is defined as the average life expectancy under normal conditions, while the physiological life span is the maximal life span that can be attained under optimal conditions (Prinzinger, 2005). An obvious question is whether death and aging are necessary and inevitable.

Evolutionists have argued that death and aging are programmed and required for evolution (Prinzinger, 2005; von Weizsacker, 1980). The argument is that because of the occurrence of mutations, new organisms may become better adapted to the environment and thus need to replace the older, less-adapted and less fit organisms. Immortality would prevent the replacement of old organisms by new organisms as the niches would already be filled with the older individuals, hence hampering the progress of evolution (Prinzinger, 2005). Consequently, it is thought, selection will occur for aging and death and against any tendency to immortality (von Weizsacker, 1980).

Irrespective of the question of whether or not aging and death are required for evolution, we are confronted with their occurrence as an inevitable, but intuitively paradoxical, part of life. But what is the mechanism behind aging and death? Many theories of aging exist that are not necessarily exclusive of each other (Prinzinger, 2005; Troen, 2003). A few are discussed in some detail before discussing the evolutionary theories of the origin of aging and death and what they actually do explain or fail to explain.

Theory of maximum metabolic scope

According to the theory of the maximum metabolic scope, the physiological life span of an organism is determined by the absolute amount of energy that can be generated per gram of body mass (Prinzinger, 2005). At first glance this might appear surprising, but the relation between physiological life span and body mass is confirmed in a wide variety of species with widely varying body masses, where species with a low body mass are short-lived and species with a large body mass are long-lived. Indeed, the physiological life span largely can be predicted by the following equation:

$$A = aM^{0.25}$$

where A is the physiological life span; a is a constant and M is body mass. It is intriguing that the mass specific energy metabolism (S) follows the inverse pattern with an identical, but negative, exponent:

$$S = bM^{-0.25}$$

where b is a constant and M again is body mass. This relation indicates that the energy metabolic rate per gram of body mass decreases with increasing body mass (Prinzinger, 2005). Applying the above equations, the shorter life span of the mouse than that of the elephant should be related to a higher mass-specific energy metabolism in the mouse. That this indeed is the case is reflected by the much higher heart rate of the mouse than that of the elephant. Furthermore, if the theory of maximum metabolic scope is true, then animals with a lower metabolic rate should live longer than predicted by the above equation. In line with this suggestion is the observation that tortoises, which have a lower metabolic rate than mammals with a comparable body mass, have a longer physiological life span. Similarly, mammals that hibernate have a longer physiological life span than mammals of comparable body mass that do not hibernate (Prinzinger, 2005). It should be noted, however, that this relation does not always hold. Marsupials with a lower metabolic rate, for instance, have a shorter life span than body mass-matched other mammals (de Magalhaes and Toussaint, 2002). Nevertheless, the generality of the relation between body mass and physiological life span strongly suggests that the maximum metabolic scope is indeed an important determinant of the physiological life span, but it does not provide a mechanism for how the mass-specific energy metabolism, and hence physiological life span, is limited.

Oxidative stress

Oxidative stress is thought to be the main factor contributing to aging (Clark, 2004; Heininger, 2002; Nohl et al., 1997; Troen, 2003). During the generation of adenosine triphosphate (ATP), the mitochondria inevitably form some oxygen free radicals, oxygen molecules with an unpaired, highly reactive electron. These oxygen radicals may affect proteins and DNA, resulting in an impaired cell function and ultimately death. There are also other sources of oxygen radicals, and exercise is associated with a burst in oxidative stress not derived from mitochondria. If oxygen radicals indeed play an important role in aging, then a reduction of their generation should result in an increased life span. Indeed, a significant increase in life span of houseflies reared at lower temperatures, or with reduced activity levels, was related to a lower metabolic rate and diminished formation of reactive oxygen species (Heininger, 2002; Troen, 2003). Finally, the increase in life expectancy of many animals subjected to caloric restriction is associated with a decline in oxidant production and oxidative damage, lending further support to the importance of radicals in the aging process (Dirks and

Leeuwenburgh, 2006; Heininger, 2002). It should be noted that these observations are also in line with the theory of maximum metabolic scope, and it may well be that the formation of reactive oxygen species is the mechanism of the theory discussed above.

Interestingly, UV-induced DNA damage in paramecium resulted in a decreased life span of a clone; the clone ceased to exist earlier than when not exposed to UV-light. If, however, DNA repair was induced by exposure to visible light, photoreactivation, no decrease in clonal life span occurred. Moreover, an increased clonal life span occurred after repetitive UV exposure and photoreactivation, possibly by enhancing DNA repair (Smith-Sonneborn, 1979). The DNA-repair enzyme involved in the photoreactivation is photolyase, which is activated by visible light.

There is no evidence, however, of increased protein miss-synthesis during aging, which corresponds with the absence of a change in the overall DNA repair capacity (Troen, 2003). This might appear at odds with the above statement that reactive oxygen species may cause damage of DNA molecules. It should be noted, however, that in particular, mitochondrial DNA (mtDNA) is vulnerable to oxidative damage, as the mtDNA repair system is less effective than that for nuclear DNA. More importantly, the mtDNA is much closer to the source of the oxygen free radicals than is the nuclear DNA (Heininger, 2002).

The formation of reactive oxygen species may even be aggravated during aging by a kind of positive feedback loop, where the free radicals cause not only mutations in the mtDNA but also oxidative modification of antioxidant and DNA repair enzymes resulting in defective mitochondria. This in turn produces even more reactive oxygen species and an impairment of oxidative damage repair (Heininger, 2002). Over time this oxidative stress may result in an elevated intracellular Ca^{2+} concentration that disrupts the cytoskeleton (Heininger, 2002) and results in an accumulation of inappropriately functioning proteins (Heininger, 2002; Troen, 2003). In this context it is interesting to note that extrapolating the curve of age versus occurrence of mitochondrial DNA deletions in the human heart yields an age of 129 years at which point 100% of the mitochondrial DNA will have deletions (Troen, 2003). Coincidentally, the decline in muscle power and strength during aging also converges to 0 at around 120 years (Degens, 2008). This is close to the maximal life span, if we can apply that text as such, mentioned in Genesis 6:3: "His days will be an hundred and twenty years" (KJV).

Remodeling of DNA

It has been shown in cell culture that cells can undergo a limited number of cell divisions (usually around 50), which is, albeit weakly, inversely related to the age of the donor (Macieira-Coelho, 1993; Troen, 2003). In the human body, old cells are continuously replaced by new cells. In order to do so, progenitor cells divide into two daughter cells such that each daughter cell receives an equal share of DNA. It appears, however, that the DNA is not always distributed evenly to the daughter cells, which could be due, for example, to errors in DNA synthesis (Macieira-Coelho, 1993). This is true particularly with genes coding for proteins in the cytoskeleton.

The cytoskeleton is not only important for maintaining the shape of the cell, but components of the cytoskeleton also play a role in mechano- and signal-transduction, cell division, cell-cell interaction, and gene expression. Clearly, a disturbance in the cytoskeleton may cause a disturbed cell, and even whole body function. One example is Duchenne muscular dystrophy where a mutation in the cytoskeletal protein dystrophin causes disturbed skeletal muscle function resulting in premature death. The unequal distribution of the DNA to the daughter cells may progressively hinder initiation of proliferation (Macieira-Coelho, 1993; Troen, 2003) and thereby provide a possible timer that indicates the age of the cell and hence the organism. Ultimately, the progressive impairment of the initiation of cell division may be such that no further cell divisions are possible.

More recently, there has been an interest in the role of telomeres in the aging process. Telomeres are stretches of DNA at the ends of chromosomes that play an important role in making replication of the DNA possible. The telomere shortens with each cell division, and this may limit the number of divisions a cell can complete. Indeed, elongation of telomeres increases the number of divisions a cell can accomplish, while shortening the telomere diminishes the replicative capacity of the cell. Based on these observations it has been suggested that telomere length may be the cellular "aging clock" (Heininger, 2002; Troen, 2003). The enzyme that accomplishes the lengthening of the telomeres is telomerase, and the activity of this enzyme contributes to the immortality of the germ line. Also the immortality of the HeLa cell line, often used in laboratories, is related to an overexpression of telomerase, preventing the shortening of the telomeres after DNA replication.

Biological clock

As stated above, the number of divisions per cell is limited. In the whole body, however, some cells undergo a much higher rate of replication than other cell types. Theoretically a situation may develop in which the cells that have replicated often cannot replicate further while cells that have been replicating much less have many more replications "available" and are still in the "power of their youth." In other words, there might be an intra-individual variation of the rate of aging (Heininger, 2002). One may wonder whether and, if so, how the aging process is coordinated in

a multicellular organism with different cell types.

It has been proposed that there might be a central timing device that coordinates the aging process of the individual cells in an organism. One such clock or timing device suggested is the pineal gland (Kloeden et al., 1993). This gland produces melatonin, which influences the rhythm of many metabolic processes (Hadorn and Wehner, 1977). During aging the nightly melatonin peak decreases, which may somehow inform all cells about the age of the organism (Kloeden et al., 1993). In support of this theory is the observation that the life span of old mice increased when implanted with a pineal gland from a young mouse. A similar result was obtained when extra melatonin was added to the drinking water during the night (Kloeden et al., 1993). Such suggestions, however, are at best speculative and deserve further study, not in the least to explore the mechanism by which the decline in the nightly melatonin peak may inform cells of the age of the organism.

Longevity genes

Several genes have been associated with longevity, and many of those appear to affect the metabolic rate or the resistance to oxidative stress (Clark, 2004; Kirkwood, 2002; Troen, 2003). Also, mutations in DNA repair genes may impact the life span of an organism (Heininger, 2002; Troen, 2003). One particular example of the effects of a mutation in DNA repair genes is Werner's syndrome, characterized by a form of accelerated aging and early death (Troen, 2003). Extension of the life span in the laboratory resulting from a mutation in a certain gene may come at the cost of fitness and thus be far from beneficial in natural conditions (Walker et al., 2000). Although there seems to be a genetic component of aging, "longevity genes" do not abolish aging; they merely delay the aging process by improving the repair capacity, antioxidative capacity, and survival of the cells (Heininger, 2002; Kirkwood, 2002).

Evolution of Senescence and Death

In the previous section of this paper it was indicated that oxidative stress may be one of the most important causes of aging and ultimately death. Therefore one could ask, "Is the generation of reactive oxygen species a mistake of evolution or the Creator?" This cannot be the case because reactive oxygen species play important roles in cell signaling, function, and cell differentiation (Barja, 1993). To repair the damage caused by reactive oxygen species, the cell contains numerous antioxidant enzymes, a system that continuously checks for mutations making use of the redundancy of the genetic code, and more than 150 DNA repair genes (Bergman, 2006; Wood et al., 2005). The repair machinery is so elaborate that Kirkwood (2002) stated that organisms are "programmed for survival, not death." The continuous repair, however, requires many resources, especially when exposure to a hazardous environment or generation of reactive oxygen species increases in severity. Therefore, it is argued that aging and death are the consequence of the trade-off between the cost of continuous repair and the chance of accidental death on the one hand and the cost of reproduction on the other (Heininger, 2002).

Assuming that, in principle, an organism is immortal, accidental death will cause the proportion of individuals of a certain generation to decrease over time, and death of all is ultimately inevitable (Figure 1). Investment of all resources into damage repair to enhance survival thus may be futile, particularly when one realizes that it occurs at the expense of investment of resources in growth and reproduction (Kirkwood, 2002). Indeed,

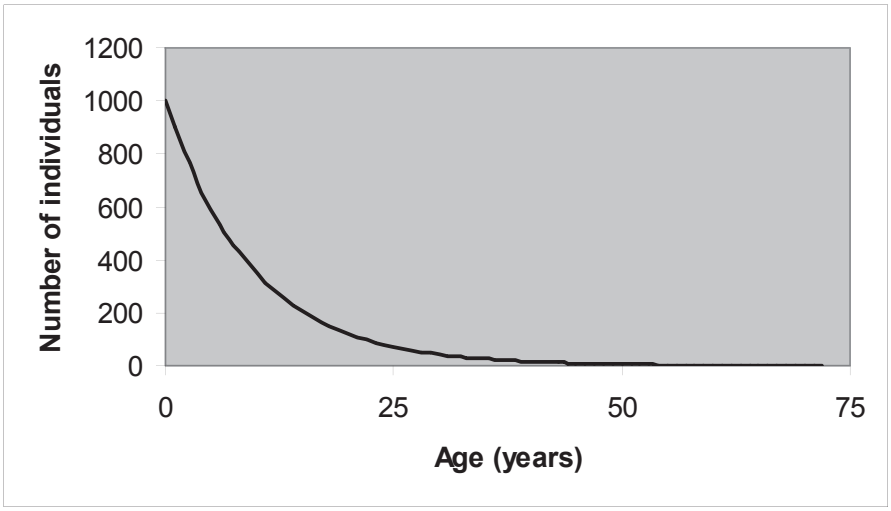

Figure 1. In analogy of the test tube example of Medawar (Medawar, 1952), let us assume that at time 0 years 1000 physiologically immortal individuals were born. They are exposed to extrinsic factors that cause an annual 10% risk of death. It can be seen that despite an unlimited physiological life span, the external factors cause practically all individuals to have died by the age of 55; the ecological life span is 55 years. It can be understood that in a less-than-perfect world it is a waste of energy and resources to spend everything on immortality. It would be better to divide the resources between reproduction and survival. This also has been called the germ-soma conflict for resources (Heininger, 2002).

the rate of aging may well be related to the severity of exposure to hazardous environmental factors, as with increasing hazards the cost for maintenance and repair may become so excessive that reproduction becomes impossible when seeking to maintain survival.

Because of this, von Weizsäcker (1980) suggested that death is an inevitable element in evolution. Individuality (an organism as self-maintaining system) and death are, according to him, inseparable "inventions of nature." Accordingly, somewhere during evolution, aging and death must have come into existence. That death does not need to exist can be seen in single-cell organisms, which essentially have an unlimited life span; they propagate by cell division resulting in two virtually identical daughter cells. It is suggested that only when multicellular organisms, which have both germ cells (eggs and sperms) and somatic cells (such as muscle and nerve cells, etc.), appeared on the stage did aging and death come into existence.

The somatic cells would be specialized to create the optimal conditions for the germ cells. The whole purpose of this division of tasks between the germ line and somatic line was to increase the reproductive success of the species (Cremer, 1980). One thus could say that the soma became disposable and this theory has aptly been called "the disposable soma theory." It is suggested that aging and death resulted from a period of shortage of food, somehow causing the differentiation of a germ line that could survive by extracting nutrients from the dying somatic cells (Heininger, 2002).

But why would evolution favor the germ cell line and not the somatic cells, giving them immortality instead (Cremer, 1980)? Or, formulated differently, why are organisms not immortal (von Weizsacker, 1980) or able to function adequately at old age (Partridge and Barton, 1993)? Could immortal somatic cells not in the same way obtain nutrition from dying germ cells, without the need for differentiation as happens in single-cell organisms? This latter question is not too far-fetched, as there is evidence that immortality of the soma does exist in nature, though not at the expense of the germ line, as for instance in Hydra (Martinez, 1998), the hydrozoa *Turritopsis nutricola* (Gilbert, 2006), the bristle cone tree, and many fungi. Yet, most organisms do indeed suffer from senescence and ultimately death. Thus, the question remains regarding how this differentiation in germ and somatic cell lines occurred in the first place.

Although there is no unequivocal evolutionary explanation for the origin of senescence and death, the observation that most multicellular organisms eventually die suggests that true immortality is impossible (Cremer, 1980). One has to realize that most evolutionary theories about senescence and death do not so much explain their origin, but rather deal with the prediction of life history traits. The two most important current theories on senescence and death or, better, the determination of the optimal life history are:

1. Negative pleiotropy, which states that senescence is due to genes that have a twofold effect: positive at early age and negative at later age.
2. Senescence is the consequence of mutation accumulation (Hughes et al., 2002; Partridge and Barton, 1993).

Assuming that in principle an organism is immortal, accidental death will inevitably cause the proportion of individuals of a certain generation in a population to decrease over time (Figure 1). The theory of antagonistic pleiotropy specifies the optimal life history possible within physiological and ecological constraints. According to this theory, senescence is the cause of genes that have a beneficial effect at young age and a detrimental effect at old age. Because of the decrease in the number of individuals of a certain generation over time, the force of natural selection decreases with age. It is thus possible that some genes that have an advantageous effect at young age and a detrimental effect at old age, being genes that are negative pleiotropic in old age, may be selected (Medawar, 1952; Troen, 2003).

One example of such a gene is p53. It has been shown that overexpression of the p53 gene (producing an abundance of the protein) inhibits the progression of cancer, but at the same time accelerates aging (Troen, 2003). The attenuation of the development of tumors is clearly beneficial early in life, but the acceleration of aging is not advantageous later in life. Genes such as the p53 gene, however, are present in all life-forms and it is thus unlikely that they have evolved. It has, for this and other reasons, been suggested that "the notion of antagonistic pleiotropy be dropped from theories of the evolution of senescence" (Clark, 2004).

The theory of mutation accumulation states that ultimately senescence and death are due to the accumulation of mutations. It is argued that as the influence of natural selection decreases with age, the abundance of mutants that have a detrimental effect at old age will become more abundant in the population (Hughes et al., 2002; Partridge and Barton, 1993; Service, 1993; Stearns and Hoekstra, 2000). Such an accumulation of mutations that have a detrimental effect at old age will eventually cause death. Therefore, after a certain age it might be better, in evolutionary terms, to invest resources in reproduction rather than survival. As a result, over time an optimal life history will eventually emerge. This optimal life history will be an evolutionarily stable strategy (given the circumstances no other life history will result in a better reproductive success) (Partridge and Barton, 1993). If selection occurs for improved fitness at old age, senescence and death will be delayed. This is observed in fruit flies artificially selected for a high fitness

at old age (Service, 1993; Stearns and Hoekstra, 2000).

Von Weizsäcker (1980) suggested that organisms with a short life history will have a higher rate of evolution than those with a long life history. This, he argued, is because organisms with a short life history, or generation time, can "try out" more mutants in a given time than those with a long life history. Furthermore, the old and new generation would need to share resources like food and habitat. Seen in that light, it is better that the old generation quickly disappears to make place for the new generation. The population with the shorter life history, a shorter life span, and more offspring thus may produce more variety than the longer living population and would have an evolutionary advantage.

It is clear, however, that there is quite a large range in the life expectancy of organisms, and there also is a need to explain the existence of relatively long life histories and life spans. One suggestion is that a longer life history and life span could have been brought about by an increase in the brain to body mass ratio during evolution, which was accompanied by a lower selection pressure by predation (Sacher, 1980). With the possible exception of primates, the increase in brain mass also led to an increase in the ability to control the environment. This is something that has to be learned and consequently, it is argued, the pressure for early sexual maturity decreased, and henceforth sexual maturity occurred at a later age (Hart and Stephens, 1980). If the training and care are to be provided to a large extent by the parents, then the life span may also increase even after the reproductive period. The latter, interestingly, also implies the possession of altruistic genes.

Senescence and Death in the Creation Model

In the creation model we would expect that all organisms would originally be immortal and thus be provided with extensive machinery for repair and maintenance. This indeed is the case, as there are at present already at least 150 known DNA repair proteins (Bergman, 2006; Wood et al., 2005). Moreover, there is a fourfold redundancy of the genetic code in diploid organisms (each DNA molecule consists of two strands, two DNA molecules form a chromatide) protecting the cell, and hence the organism, from the detrimental effects of a deleterious mutation in one of the DNA strands.

Finally, multicellular organisms have a mechanism to eliminate damaged cells via programmed cell death, or apoptosis, further protecting the organism from unwanted cell proliferation, as in cancer, and ultimately malfunctioning organs and death (Bergman, 2008). However, after the Fall conditions deteriorated as predation occurred. If we assume that there was some sort of protective vapor canopy around the earth before the Flood, pre-Flood organisms would have been protected more from hazardous radiation from space than contemporary organisms. This might explain the longer life expectancy before the Flood. Further, it might well be that the maintenance and repair machinery in our cells is not adequate to fully reverse damage caused by the present-day environment but is well suited for the conditions before the Flood. Moreover, following the test-tube example by Medawar (1952), it becomes clear that with the exposure to external lethal factors it pays to invest in reproduction rather than longevity. Hence, senescence occurred after the Fall and occurred even earlier in life after the Flood.

Conclusion

Several mechanisms of senescence have been discussed, but ultimately they boil down to the accumulation of damage to proteins and DNA, particularly mitochondrial DNA. In this context, it is interesting to note that extrapolation of the rate of mitochondrial DNA mutations yields an age of 129 years where all mitochondrial DNA will have deletions. This is close to the 120 years mentioned in Genesis 6:3. The evolutionary origin of senescence is thought to have occurred during the differentiation of a germ and somatic line (Heininger, 2002; von Weizsacker, 1980).

Although it is clear that somatic cells die while germ and cancer cells are in principle immortal, the evolutionary-based theories for the origin of senescence and death provide no satisfactory answers and are highly speculative. Most evolutionary theories of senescence and death really do not deal with the origin of senescence and death, but rather with optimal life history. They prove to be quite powerful in explaining the life histories observed in natural populations and have also proved adequate to predict changes in life history when populations of laboratory animals were manipulated. If the pressure on a population of extrinsic lethal factors, such as predation, decreases, the life span of the individuals in the population increases. This is explained by the fact that the contribution of older organisms to the total reproductive success of the population increased and it thus became more profitable to invest in maintenance and repair at the expense of fertility at a young age (Stearns and Hoekstra, 2000).

If we extrapolate this observation, it is tempting to speculate that in the presence of limiting damaging factors and a complete absence of mortality related to external factors, investment in repair and maintenance becomes so profitable that the maintenance and repair mechanisms of the cells are improved to such an extent that ultimately even immortality may be possible. This suggestion is not completely without justification as is indicated by the immortality of the germ cell line, the continued existence of single-cell organisms, and even immortality of multicellular organisms

(Gilbert, 2006; Martinez, 1998). Stated differently, mortality could be the consequence of deteriorated circumstances, making immortality practically impossible because of extrinsic lethal factors. This suggestion then would fit the notion that there probably was no death before the Fall (Henry, 2006).

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