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The disposable soma theory revisited

Time as a resource in the theories of aging

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All life processes are subject to time constraints. At the cellular level, damage repair and cell cycle arrest are interrelated, allowing sufficient time for repair prior to cell cycle progression. Organisms have evolved so that developmental timing is linked to environmental conditions, such as nutrient availability and predation. Recent results in mammals regarding species-specific differences in cell cycle arrest and DNA damage suggest that a stable cell cycle arrest is a feature of longer-lived species. The implication of these results is that longer-lived species delay cell cycle progression to a greater degree than shorter-lived species, allowing for higher fidelity repair. We suggest that the ability to devote longer periods of time to repair and maintenance is a key feature of longer-lived species, and that evolutionary pressure to complete repair and resume cell division is a determinant of species lifespan. Thus, time is a resource that must be managed by the organism to attempt to maximize the fidelity of repair, while completing development and reproduction in the limited window of opportunity afforded by environmental pressures. This viewpoint on time as a resource has implications for theories regarding the aging process and the development of species lifespan.

Key words: aging, theory, genome stability, mTOR, DNA damage, cell cycle

Abbreviations: mTOR, mammalian target of rapamycin

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Remarkable variation exists in the lifespan of species. Very short-lived organisms, such as the fruit fly, survive a matter of days, completing growth, maturation, reproduction and senescence in this time. In contrast, long-lived organisms, such as the blue whale, survive well over a hundred years, completing the same functions in that time. The "disposable soma theory" postulates that an organism divides its energy between maintenance and reproduction in order to match its developmental and reproductive rate to the evolutionary niche in which it has developed.[1,2] This division of labor implies that short-lived organisms direct more resources toward reproduction in order to successfully produce offspring during their lifespan, while long-lived organisms direct more energy toward maintenance in order to ensure function over their lifespan. The disposable soma theory has been broadly cited as an allocation of energy leading to a trade-off between increased lifespan and increased fertility. This trade-off manifests itself as a reduction in the ability to maintain somatic cells when energy is directed toward reproductive fitness. Thus, short-lived animals are expected to be less efficient in the maintenance of somatic cells than long-lived organisms. Given this concept, one would predict that the difference in the efficiency of maintenance would be reflected in differences in the fundamental processes required for highly complex functions such as DNA repair. This seems to be the case. For example, primary cell strains derived from short-lived mammals, such as rodents, routinely overcome the intrinsic growth controls that lead to replicative senescence in cell culture.[3] They eventually transform into cells capable of forming tumors when reintroduced into animals, while primary cells from long-lived species, such as humans, very rarely spontaneously

overcome senescence.[4] These fundamental observations support the concept that genome surveillance is less stringent in cells from short-lived animals. This difference in genome surveillance may represent one aspect of the resource allocation put forth by the disposable soma theory, although other aspects of cellular maintenance, such as the removal of damaged proteins or organelles, may contribute to the increased stability of cells from long-lived animals.[5] A difference in the capacity to remove cellular damage can be found in the difference in sensitivity to oxidative stress between mouse and human cells. The proliferation of primary mouse fibroblasts is greatly enhanced when the cells are maintained under oxygen tensions similar to those found in vivo, while human fibroblast cultures are able to grow and divide under ambient oxygen, which is much higher than the levels found within the organism.[6] Additionally, mouse cells accumulate DNA damage in ambient oxygen, suggesting that DNA repair mechanisms in short-lived animals, such as mice, have lower fidelity than in long-lived species such as humans.[7] Accordingly, proteins central to DNA end joining are closely correlated with species lifespan.[8] The implication of these findings is that DNA repair is more faithful in longer-lived species despite observations that bulk DNA repair occurs at similar rates in human and rodent cells.[8]

The disposable soma theory as originally articulated postulates an energy-saving resource allocation in shorter-lived species that accelerates development at the expense of accurate repair. However, we postulate that time is the most essential resource at both the cellular and organism level. It is well-established that developmental rate and longevity are inversely correlated. Noteworthy are experiments addressing this relationship comparing individuals of the same spices.[9-11] For example, in an interesting reanalysis of published data on the mortality of the fish *Perca fluviatilis*, Metcalfe and Monaghan show that the early growth rate is the strongest predictor of adult mortality rate.[11-13] Our hypothesis to address these observations is that at the cellular level, time is required for accurate repair of DNA damage incurred by random radiation, intracellular free radicals and during normal DNA replication. The amount of time allocated to repair DNA damage can be evaluated by the length of time that the cell cycle is arrested following damage when cells are under conditions that are favorable for growth. As reported in the September 2011 issue of *Aging*, the G_2 checkpoint appears to be inherently less stable in rodent cells than in human cells as assessed by the appearance of micronuclei.[14] Micronuclei are membrane-bound fragments of the nucleus that result from unresolved DNA damage that interferes with chromosome segregation.[15] Decreased genomic stability, as judged by increased formation of micronuclei, correlates well with shorter species lifespan, and destabilization of the G_2 checkpoint dramatically increases the number of micronuclei, suggesting that premature progression through the G_2 checkpoint underlies the formation of micronuclei. The stable G_2 arrest observed in human cells may allow these cells to devote the time required to ensure faithful DNA repair before committing to cell division. These results are consistent with reports that cells derived from naked mole rats (28 y maximum lifespan) are able to achieve a more stable arrest than cells derived from mice (4 y maximum lifespan); observations that the naked mole rat cells are less prone to escape from senescence than mouse cells[16,17] and studies indicating that in mice, lifespan is positively affected by p53 activity[18-21] while negatively related to the fraction of hemopoietic cell cycling.[39] In addition, enhanced stability of cell cycle arrest in mouse cells has been achieved through the introduction of the human MAD2 protein, providing a concrete example of one protein that has diverged between a short-lived and long-lived species that relates directly to the stability of cell cycle arrest.[22] It is now recognized that there is communication between DNA repair complexes and factors required for signaling cell cycle arrest and the completion of DNA repair to allow the resumption of normal cell cycle progression.[23,24] It is this complex interaction that is likely to be at the core of the differences between long-lived and short-lived species in terms of the stability of arrest. It is possible that this critical communication system dictates the fidelity of repair, and the differences in fidelity are reflected in differences in the stability of the arrest. It is this "time for repair" that may well be the critical limiting resource in the trade-off that lies at the center of the disposable soma theory.

The disposable soma theory is based on the viewpoint that aging is not influenced by selective pressure on a species, because selective pressure occurs prior to and during the reproductive period while aging occurs after reproduction has been completed.[25] An alternative view of the aging process has been proposed based on the identification of single gene mutations and specific signaling pathways that can affect the rate of aging in a population, such as the insulin-like growth factor and mTOR pathways. A "quasi programed theory of aging" has been proposed, where a "quasi program" is the unintended continuation of a developmental program.[26-28] This viewpoint argues that the existence of specific intracellular signaling pathways responsive to nutrient sensing or hormonal regulation that can have significant impact on lifespan indicates that a regulatory program to maintain species lifespan within an optimal range exists.[29] Thus, aging is a "quasi" programed process that represents a continuation of developmental processes resulting in a defined lifespan. This is somewhat analogous to the reproductive theory of aging.[30] The postulation is that continued developmental programs induce age-related changes that impact the organism long before the accumulation of damage would induce a loss of function and death. In this paradigm, time is also an essential driver of the process. The external environment impacts upon the nutrient-sensing pathways involving mTOR and the proposed downstream aging processes, which alters the rate of cell proliferation, development and, eventually, aging. The simplest example of a pressure that would alter the aging process is the availability of nutrients, which is known to impact the mTOR pathway critical to aging. Signaling through mTOR is increased under high nutrient conditions and delayed under low nutrient conditions, and the downstream consequence of the changes in mTOR signaling is an alteration in the aging process.

Interestingly, there is an interplay between p53 and the mTOR pathway that dictates the outcome of cellular arrest, driving cells to senescence or maintaining quiescence, which may play a role in this process.[31,32] Whatever the mechanism, the period of high or low nutrient availability is time-dependent, essentially a "window of time" that must be accommodated by the organism to adjust to the changing environment. Thus, time is intimately linked to the process.

Similar arguments can be made for other theoretical approaches to aging, such as the free radical theory of aging. The free radical theory of aging is based on the fact that oxidative processes are essential to life, for example, mitochondrial processes, yet the subsequent generation of free radical damage is inadequately controlled, leading to the accumulation of cellular damage and eventual dysfunction characteristic of the aging process.[33] This theory has been modified over time, encompassing mitochondrial function and disparate findings regarding the association between free radical damage, repair and cellular redox systems, but remains essentially based on an imbalance of damage and repair.[34-36] The concept of time as an essential element in the repair of damage as outlined for the disposable soma theory would hold for the free radical theory of aging. Intracellular redox systems are unable to appropriately clear oxidative damage when metabolism is highly active, such as during times of high nutrients or rapid growth and development. An increase in the amount of time allowed for redox repair prior to subsequent cell division in proliferative cells would improve cellular clearance of oxidative damage, leading to increased function during the aging process and enhanced longevity. Similarly, clearance of damaged proteins and dysfunctional organelles in post-mitotic cells to more accurately balance protein synthesis, degradation and metabolism can be envisioned to provide enhanced function late in life.

It should be noted that the pressure of time limitations impacts both aging and the defined lifespan characteristic of a species. These two aspects of aging should be considered separately, although they are intertwined. The term aging refers to the constellation of changes that occurs during the later stages of the lifespan of any species. Although very broad, one potentially useful description of the phenotypic effects of these changes is that an aging organism shows a reduced capacity to maintain homeostasis. This description encompasses most, if not all, of the characteristics associated with aging, such as reduced functional capacity, increased vulnerability to multiple diseases and a reduction in the ability to respond to stress or injury. Thus, gene mutations or environmental factors, such as caloric restriction, that have been found to delay the aging process provide improvements in a specific set of cellular or physiologic parameters late in life relative to control populations. This aspect of aging is addressed by theories such as the free radical theory and is likely the target of interventions such as caloric restriction.

The term lifespan can be used in several contexts. It can refer to either the lifespan of a given population under study or to the species lifespan. Changes in the rate of aging can affect the lifespan of the study population but may not influence species lifespan. Species lifespan remains fixed within a certain limit, although what this limit may be is a matter of some debate.[37,38] For example, caloric restriction will increase the lifespan of a given population but has not been shown to affect the lifespan of the species. Thus, there are two key questions concerning lifespan, first, what mechanisms influence population lifespan, and, second, what mechanisms determine the lifespan characteristic of a species. These are very different questions but we propose that the allocation of the time available to an organism drives both of these processes.

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