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Opinion

Is mammalian aging genetically controlled?

João Pedro de Magalhães
University of Namur (FUNDP), Unit on Cellular Biology (URBC), Rue de Bruxelles, 61, 5000 Namur, Belgium (e-mail: jpnitya@senescence.info; fax: +32-81-724135)

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Abstract

The rate of aging is species-specific, indicating that aging has a strong genetic component. Amongst mammals, the synchronization of the aging process suggests the presence of genetic determinants. In addition, single gene manipulations can change the rate of aging and demonstrate how a few genetic factors can regulate aging. Therefore, I propose that aging is regulated by a small set of genetic mechanisms, a single clock. If we can find what these regulatory mechanisms are, then instead of trying to delay age-related pathologies one by one we may be able to discover how to delay the entire aging process and most, if not all, of its pathologies.

Aging is an intrinsic process of loss of viability and increase in vulnerability. The most accurate method to measure aging is to calculate the rate at which mortality increases with age, such as the mortality rate doubling time (MRDT). Unlike longevity, which is how long an organism is expected to live under ideal circumstances and can vary due to many factors, the MRDT allows us to detect changes in biological aging. For example, although longevity varies widely between human populations, the rate of aging remains stable with the MRDT between 7.6 and 8.9 years (Finch 1990). Between humans and baboons, despite few changes between populations of the same species, the rate of aging varies about two-fold (MRDT for baboons between 3.5 to 4.8 years, Bronikowski et al. 2002). Since the rate of aging is species-specific, it must be genetically controlled, as there must be genetic differences between humans and baboons to cause a two-fold difference in the rate of aging.

The rate of aging varies much in mammals, yet most age-related changes occur on a time scale in approximate proportion to the lifespan, independently of how long this is. For example, rhesus monkeys have roughly half the age of humans when they display the same age-related patterns (Finch 1990). The synchronization of aging amongst mammals suggests that the changes and deterioration associated with aging are genetically controlled; the aging process is thus timed by the genetic information. Since these are closely related species, the aging process is controlled by a relatively small set of genes. For instance, mice, despite a rate of aging 25–30 times faster than humans, share an estimated 97–98% of our genes (Mural et al. 2002). Therefore, the aging phenotype, although it can be modulated by multiple factors, is timed and controlled by a small set of genetic mechanisms, suggesting the presence of a single clock. Evidently, the genomic information that regulates the rate of aging can involve, for example, genes from defensive or repair mechanisms, and not necessarily genes causing aging purposively (Rattan 1995).

Several evidences suggest that a few genes can regulate the aging process and that there can be a single clock controlling aging. Contrary to previous pessimistic beliefs, one mutation in the more than 17,000 genes of *C. elegans* delays the rate of aging (Johnson 2002). A single mutation can extend average longevity in mice by 30% without noticeable side effects; it also appears to delay the rate of aging (Migliaccio et al. 1999). Selective breeding can substantially delay the aging process in dogs (Miller 1999). Also, results from mice suggest that the

majority of age-related changes are under coordinated genetic control (Miller et al. 2002). In addition, caloric restriction delays age-related changes and slows the rate of aging (Weindruch and Walford 1988). It can be argued, however, that caloric restriction delays the entire genetic program, indirectly retarding the aging process. Nonetheless, caloric restriction shows how age-related changes can be retarded in parallel as if timed by a common clock. Finally, human progeroid syndromes, even if they do not accelerate aging, can accelerate a vast amount of age-related pathologies. For example, Werner's syndrome demonstrates how a single gene can regulate an array of complex age-related phenotypic changes (Goto 1997).

Wide variations in the rate of aging amongst closely related species such as mammals or even primates are difficult to rationalize if aging is caused by a large variety of processes. The idea of multifactorial aging becomes questionable when we compare baboons to humans and witness a two-fold difference in rate of aging between two genetically similar species. Although the aging process maintains the stochastic nature of any biological system, its pace is genetically controlled. That is why, for example, rhesus monkeys display the aging changes and pathologies of old humans at about half the age of an old human. It is unlikely that several mechanisms evolved to change the onset of each age-related pathology (Cutler 1975). Instead, there must be genes, or, more likely, differences in the gene activity of a few crucial genes that act as regulatory nodes of the aging process. Although the exact nature of such a "timekeeper of aging" is unclear at present, transcriptional regulatory proteins, due to their authoritative role in eukaryotic cells (Lee et al. 2002), may be one of the players involved.

In conclusion, the focus of gerontology should be on the unraveling of the genetic mechanisms that determine the rate of aging in mammals, since it will open the possibility for us to delay the aging process in humans. Instead of fighting age-related pathologies one by one, we may be able to postpone the appearance of most, if not all, age-related pathologies.

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