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Genomes Optimize Reproduction: Aging as a Consequence of the Developmental Program

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Natural selection shapes genomes for reproduction, not for postreproductive survival. One hypothesis then is that the developmental program, optimized for reproduction, inadvertently regulates aging in mammals. Herein we review, revive, and refine the developmental theory of aging. Implications and experimental approaches for studying the progressive deterioration of physiological function that we call aging are also discussed.

Among vertebrates there is an immense diversity in the timing of life-history events. By the time a mouse is old, a child is learning to speak. When a dog is at the end of its life span, a teenager is discovering puberty. When a female monkey reaches menopause, a woman is starting her family. When that same woman reaches menopause, a turtle may be more fertile than it ever was. Furthermore, one of the most intriguing aspects of mammalian aging is how its phenotype is remarkably similar across different species, sometimes appearing as the same process timed at different rates (19, 39). Understanding why different species age at different paces is crucial to understanding the progressive deterioration of physiological function we call aging.

Many mechanistic theories of aging argue that age-related decline results from damaging by-products of metabolism and/or inefficient repair mechanisms (27, 32). According to this view, damage—which can take on many forms—accumulates throughout the life span (38). The exponential increase in mortality and the functional decline that characterize aging, however, only begin after sexual maturity, whether this occurs at age 13, as in humans, age 5, as in monkeys, or at less than 2 months, as in mice. Therefore, one alternative view is that aging is perhaps linked to development (11, 30, 38, 54). Life-history traits such as developmental schedules, age at maturity, and life span are associated with one another (8, 24, 30). That accelerated growth negatively affects the longevity and adult-onset pathologies of mammals is suggested by several studies, such as studies in mice and rats (46), squirrels (24), dogs (39), and humans (1, 2). Yet, although a number of theories linking development to aging have been put forward (38), the mechanistic basis of such a link remains largely unknown.

In this work, we review and revive the developmental theory of aging. By incorporating recent findings in the biology of aging, we also propose a series of refinements to this theory. Lastly, a number of experiments for studying the link between development and aging are suggested.

Genomes Optimize Reproduction

According to the evolutionary theory of aging, after reproduction, the force of natural selection declines with age (37, 47). The emphasis of genomes is on reproduction, not postreproductive survival, and therefore in all vertebrates, the genetic program—the genome—is optimized for reproduction. If reproduction, including child rearing, shapes the genetic program responsible for what we are, then subsequent events are irrelevant from an evolutionary perspective. It may even be that early-life processes are harmful at later ages, as predicted by the antagonistic pleiotropy theory (53). This reasoning forms the evolutionary backbone of the developmental theory of aging. The developmental program, in its most simplistic form, can be defined as a genetically determined sequence of cellular and molecular events designed to produce a given adult phenotype optimized for reproduction. One hypothesis then is that this same developmental program inadvertently regulates the pace of aging among mammals and is a cause of age-related physiological degeneration (11, 30, 38, 54).

Our genome and its gene products can be divided into: *1*) information encoding the basic biochemistry of life, including functions such as respiration, DNA replication, and repair mechanisms; and *2*) the developmental program (FIGURE 1). As mentioned in the introduction, a number of mechanistic theories of aging argue that the causes of aging are located within the former. Examples include the free-radical theory of aging, which argues that oxidative damage accumulation causes aging, and theories relating DNA damage to aging (38). Evidence in favor of these theories is mostly indirect, however. Several experiments have been

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conducted in model organisms, such as mice, in which oxidative or DNA damage was altered through genetic interventions. The results have been largely disappointing, and a causal link between oxidative damage and aging has never been shown in mammals (13). Accelerated aging phenotypes in mice and humans suggest that some aspects of DNA metabolism may be linked to aging, but it is not obvious, and it even appears unlikely, that DNA damage accumulation alone drives aging (13). One hypothesis is that metabolic rates may be faster in faster-aging organisms. If cellular biochemical processes occur at a faster pace, then it makes sense that damage also accumulates faster. Some results, however, suggest that metabolic rates, and hence the pace of biochemical processes, do not influence the life spans of mammals (23), and mice with higher metabolic rates have even been reported to live longer (50). Moreover, as argued by others (11, 36), the slow evolution of structural genes cannot account for differences in aging rates among mammals. Therefore, there is no strong reason to suspect that rates of aging are determined by the basic biochemistry of life.

The developmental theory of aging states that the genetic mechanisms regulating the pace of aging are located in the latter; that is, they are part of the developmental program (FIGURE 1). This concept is supported by observations in a number of animals. In organisms such as the salmon or marsupials of the genus *Antechinus*, the neuroendocrine system—triggered by reproduction—directly causes the death of organisms (19). Other authors have argued that a morphogenetic program originates aging in response to reproductive impulses (30, 38). It is dubious, however, that similar mechanisms occur in animals that rear their offspring, such as most mammals and birds. Besides, not only reproduction but a number of developmental processes have the potential to disrupt homeostasis and cause degeneration (see below). Nonetheless, *Antechinus* and, particularly, the remarkable physiological degeneration of the salmon after spawning demonstrate how a developmental program optimized for reproduction can trigger senescence (19).

Many species that appear not to age show indefinite growth and/or increasing reproductive output with age—e.g., bullfrogs, lobsters, certain fishes, and some turtles (19, 26). In fact, development is much more plastic in organisms such as reptiles and amphibians than in mammals. For example, regeneration, which often involves the reactivation of certain phases of the developmental program, is much more advanced in newts than in humans (6, 28). In other amphibians too, development can be delayed—and life span probably extended—depending on environmental conditions (17). Ordinarily, we try to focus on species that are evolutionary and biologically closer to humans, such as mammals or at least vertebrates; however, another classical example in gerontology is the dauer pathway in *Caenorhabditis elegans*. Animals entering this pathway can delay development,

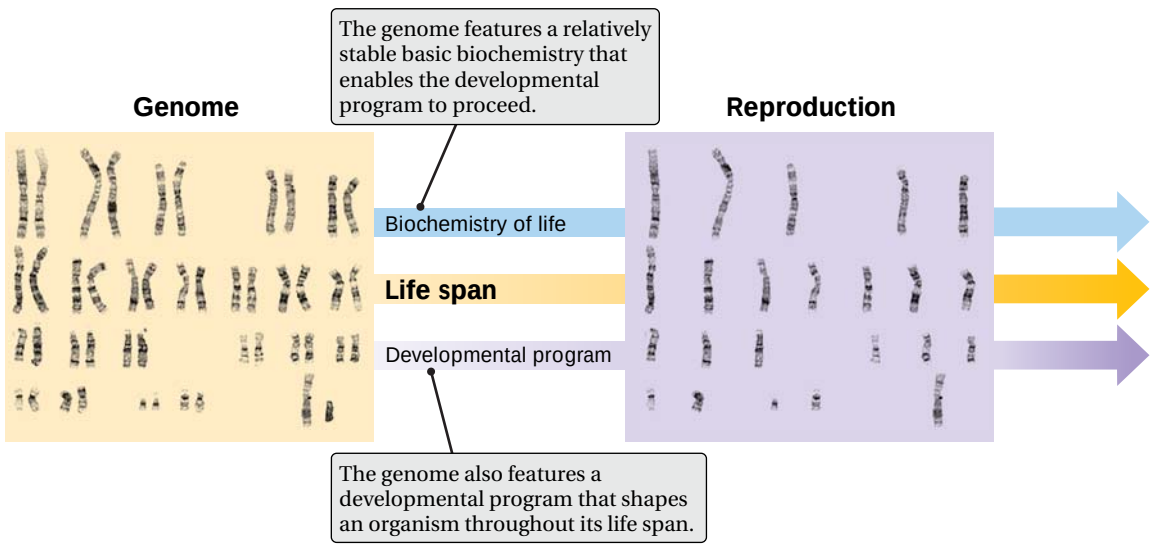

FIGURE 1. **Functions a vertebrate genome must possess for the resulting organism to reproduce**
A genome is a vehicle for reproduction whose information can be divided into 2 parts. On the one hand, the genome must feature the basic biochemistry of life such as repair mechanisms aimed at keeping the organism alive for the completion of the developmental program. On the other hand, the genome must feature a developmental program that establishes a set of higher functions in adulthood optimized for reproduction. The developmental theory of aging states that, contrary to theories of aging based on damage accumulation, the developmental program also regulates changes in adulthood. Although the biochemistry of life remains relatively unchanged, the developmental program shapes an organism throughout its life span. In other words, the causal structure of aging lies in the developmental program. The image represents a karyotype of the human genome.

growth, and aging (5, 33). Other examples exist among invertebrates (5, 19, 38), such as the well-known case of social insects in which queens greatly outlive workers and males, again showing how aging is not determined in the basic biochemistry of life but by developmental pathways.

Further evidence has recently accumulated in favor of the developmental theory of aging. Succinctly, genetic mechanisms regulating aging in mammals were indirectly linked to development (16), and the way that neuroendocrine systems affect aging (13, 40) as well as developmental schedules (3, 41) supports the theory. A similar impact of caloric restriction (CR) on development and aging has been observed (26). Recent results also suggest a link between developmental programs and aging at an epigenetic level (48). Lastly, the self-renewal of stem cell populations has been associated with developmental pathways, such as the Wnt signaling pathway (45). Therefore, the hypothesis we champion in this work is that the developmental program regulates rate of aging in mammals and may be the cause of most, though probably not all (see below), age-related changes.

Aging as an Unintended Outcome of Development

The idea that aging is an extension of development was suggested as early as 1864 (9). Many proposals linking development to aging have been put forward, involving mechanisms such as dysdifferentiation, overdifferentiation, loss of gene repression, increase in gene repression, and deregulation of transcription (38). One possible reason for the lack of acceptance of these theories is their conceptual, even abstract nature. In contrast, theories of aging based on damage accumulation often predict mechanisms that can be used to interpret age-related changes and pathologies; deriving experiments to test such theories has also proven much easier. Herein we wanted to put forward precise mechanisms and derive testable hypotheses from the developmental theory of aging.

The essence of the developmental theory of aging is that some, though not all, developmental mechanisms inadvertently affect postreproductive life, causing what we call aging. Our proposal is that mechanisms regulating development can affect aging according to two general processes (FIGURE 2). On one hand, the developmental program merely exists to optimize fitness at a given time, and so age-related deleterious changes may derive from the continuing actions of that same developmental program. This can be seen as an extension of antagonistic pleiotropy in that genes beneficial in early life are harmful at later stages (14, 53). For example, presbyopia appears to occur because the eye lenses grow continuously, eventually leading to farsightedness (19, 26). Similarly, neurodegeneration has been proposed to represent the continuation of the genetic programs that underlie early life, such as the need to decrease brain plasticity before adulthood (14). These are examples of developmental mechanisms essential for generating an adult organism but whose continued actions after reproduction may result in age-related dysfunction.

Alternatively, and as predicted from the declining force of natural selection with age (37, 47), age-related changes can derive from the fading actions of certain developmental mechanisms (FIGURE 2). One example is muscle loss, which might derive from the cessation of growth as organisms reach adulthood. In contrast, animals that do not cease to grow may avoid this form of degeneration. Another

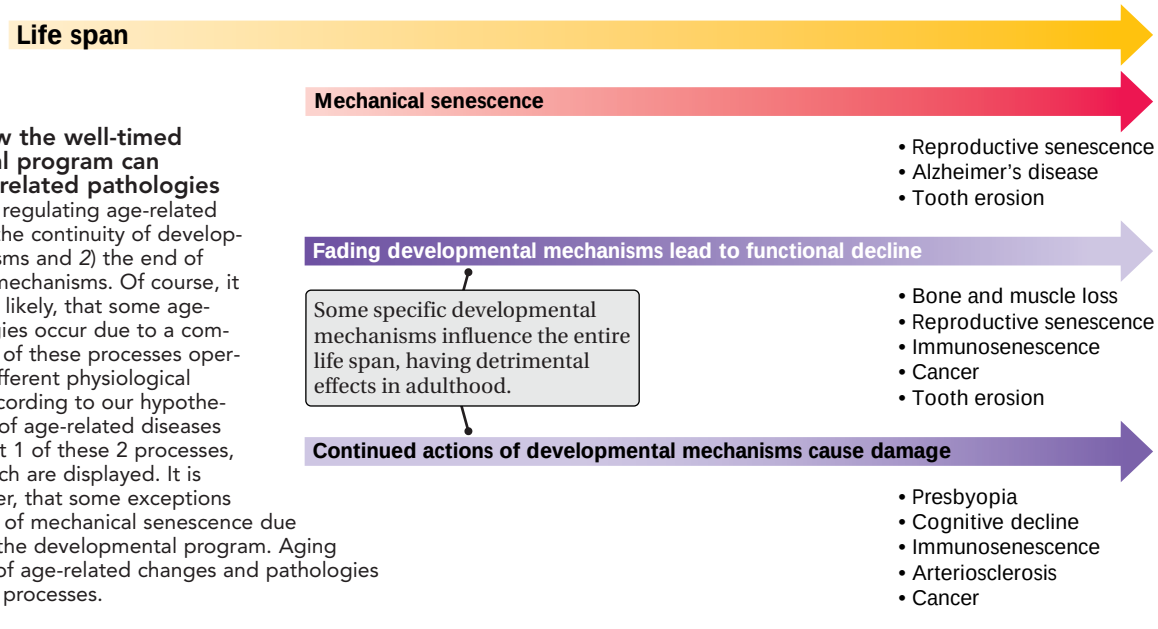

FIGURE 2. **How the well-timed developmental program can influence age-related pathologies**
The 2 processes regulating age-related changes are: *1*) the continuity of developmental mechanisms and *2*) the end of developmental mechanisms. Of course, it is possible, even likely, that some age-related pathologies occur due to a combination of both of these processes operating through different physiological mechanisms. According to our hypothesis, the majority of age-related diseases should fit at least 1 of these 2 processes, a number of which are displayed. It is possible, however, that some exceptions exist in the form of mechanical senescence due to limitations in the developmental program. Aging is then the sum of age-related changes and pathologies caused by these processes.

example may be cancer. Certainly, cancer rates are related to the basic biochemistry of organisms, such as DNA repair mechanisms, but there is also an age-related component: cancer rates increase exponentially with age in many species, including humans (19). Our hypothesis is that the age-related increase in cancer incidence occurs because the developmental program has ceased. Although speculative, this hypothesis is supported by the large number of oncogenes involved in growth and development (41): *HRAS*, *ABL1*, *MYC*, *FOS*, *VEGF*, and *AKT1*, among others. In fact, it has been argued that protooncogenes are controlled by the same molecular mechanisms that underlie normal development (42). Our suggestion is that the end of the developmental program, and consequently the end of the growth period that characterizes preadulthood, indirectly results in cells "losing grip" over these genes. The age-related increase in cancer incidence could then be a result of the end of the developmental program. Indeed, some recent results suggest that growth patterns during childhood are associated with breast cancer in women (1).

There are many developmental mechanisms, and probably only a small percentage of these influence aging. For example, certain developmental mechanisms continue throughout the life span, whereas others are exhausted before reproduction. In FIGURE 3 we present a few different models based on actual physiological processes and their regulation during the life span. *Model A* appears to accurately represent most human functions during the course of the life span in which a rapid increase in functionality occurs before reproduction, followed by a steady decline. This also appears to occur, for example, in the case of insulin-like growth factor-I (IGF-I), whose levels rise before birth, increase greatly in infancy and childhood, and then steadily decline from puberty onward (22). Of course, there are myriad physiological processes that occur during development and change differently with time: certain hormones, like growth hormone (GH), steadily decline throughout the life span (*model B*) whereas others, like IGF-II, and some processes, such as cartilage growth, fully decline until reproduction (*model C*). Alternatively, a steady increase throughout the life span may occur in some processes, as is witnessed in memory T cells (*model D*). Certainly other, more complex models exist: for instance, DHEA levels rise and fall more than once until puberty before steadily declining throughout adulthood. The complexity of the developmental program surpasses this work and even current scientific knowledge (21), and so the models presented herein are only a glimpse of how aging may originate in developmental mechanisms. As we learn more about the regulation of developmental mechanisms during the life span and how they are optimized for reproduction, we will understand how and which of them affect age-related changes.

Age-related changes proportional to the mammalian life span and reproductive schedules are expected to be regulated and timed by development. In mammals these are the majority, and it is remarkable how age-related pathologies tend to occur in synchrony with the total life span of mammals (39). It is possible, however, that some age-related changes are the result of mechanical senescence (9). One example is Alzheimer's disease, which is unique to humans (under natural circumstances) and may be unrelated to normal cognitive aging (49). It appears that the longevity of humans may make us uniquely susceptible to *Abeta* toxicity (20). Consequently, it is possible that Alzheimer's disease is a form of mechanical senescence, despite the fact that some loci that play a role in the disease, such as *APOE*, are also involved in development.

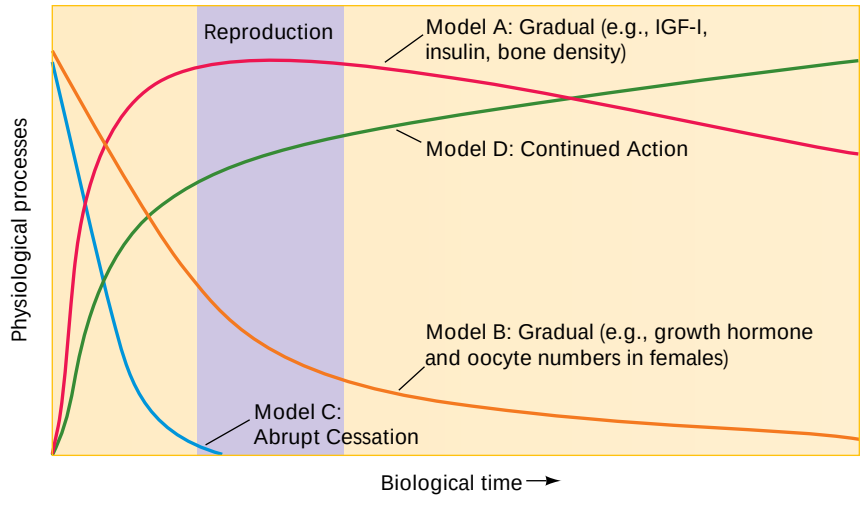

FIGURE 3. **Regulation of developmental mechanisms throughout the life span**
Developmental mechanisms may have unintended consequences for the physiology of adult organisms either through their continued actions (*model D*, green) or due to their gradual (*models A*, red, and *B*, orange) or abrupt (*model C*, blue) cessation. Reproduction represents an organism passing its genes to the next generation. In higher vertebrates this includes a number of life-history events, such as the time it takes to reach sexual maturity, mating, gestation, and child rearing. Physiological levels fitting *model A* include IGF-I, insulin, and bone density; growth hormone and oocyte numbers in females fit *model B*; IGF-II and cartilage growth fit *model C*; and memory T cells fit *model D*.

Other potential examples of mechanical senescence include tooth erosion and oocyte exhaustion in mammals, which may be perceived as caused by intrinsic limitations in the body plan of most mammals. These can also be seen as outcomes, or at least constraints, of the developmental program. Female reproductive senescence results from the age-related loss of ovarian oocytes, the number of which was fixed during development (19). Some reptiles that appear not to age feature oocyte regeneration in adulthood (19). In mammals, however, the program regulating oocyte regeneration is inactive except at early stages of development, and so reproductive senescence can be perceived as an outcome of its blockage. Similarly, tooth erosion can be seen as a limitation in mammalian development, an end of a specific developmental process that results in worn out teeth not being replaced. Many of our evolutionary ancestors—e.g., reptiles—feature continuous tooth replacement, which is rarely observed in mammals (19). Unique evolutionary events may have set up these constraints on mammalian genomes (15). Interestingly, dental development occurs more slowly in humans compared with other primates and extinct hominids, hinting that the pace of dental development affects the onset of tooth erosion (7). Therefore, even in cases of mechanical senescence, the timing of developmental mechanisms may determine the pace of age-related changes among mammals.

Implications and Interventions for Antiaging Medicine

One of the aims of this work is to make others aware that age-related changes and pathologies can derive from early-onset developmental mechanisms, as supported by recent results (1, 2). Hopefully, researchers and clinicians will try to understand age-related pathologies by looking at the physiology and genetics of normal developmental processes. Assuming a link between development and aging also has major implications for how experiments are designed and interpreted in gerontology. If we see aging as triggered by development, rather than a mere accumulation of damage, then to study aging it is necessary to understand the life span as a whole and not merely its last segment. Herein, we offer a few ideas about how this can be achieved, including suggestions for experiments.

Gene-expression studies of aging generally begin in adulthood (52), so in a sense such studies are focusing on the results of aging, not its causes. Hopefully, future studies will consider the entire life span of organisms—or at least postnatal life span—to capture how the genetic program determines development, adulthood, and senescence. In parallel, studies of epigenetic factors such as chromatin structure can also provide clues regarding how the genetic program regulates gene expression during development and aging (48). Lastly, physiological studies should aim to identify how and which developmental mechanisms can affect age-related pathologies using the general models we hypothesized (FIGURES 2 AND 3).

Segmental progeroid syndromes either in humans or mice can be seen as a disruption of a system affecting multiple age-related changes. Linking the systems affected in these diseases to how normal developmental programs regulate such systems may provide clues about aging. Intriguingly, patients suffering from Werner, Cockayne, or Hutchinson-Gilford syndromes appear to have developmental and growth deficiencies (36). Maybe these segmental progeroid syndromes are impairing developmental processes. Many genetic diseases disrupt systems in the human body, but only a few accelerate several age-related changes (36). Therefore, we suggest that perhaps the key to understanding segmental progeroid syndromes is not in their generalized havoc or DNA imbalance but rather in some specific disruption to normal ontogeny. For example, Werner syndrome is primarily a disease affecting connective tissues at the cellular level (31), but we know very little about the normal development of connective tissue and whether it relates to the pathophysiology of Werner syndrome.

Considering aging as a result of the developmental program also has important implications in developing therapies for age-related diseases. Because we suggest two processes for the emergence of age-related diseases (FIGURE 2), the two general ways to delay or prevent age-related changes are: *1*) stop or delay developmental mechanisms that cause age-related diseases; and *2*) restart certain developmental mechanisms. Moreover, a complementary—although at present mostly theoretical—approach is to incorporate mechanisms found in, for instance, reptiles or amphibians in human medicine, as suggested before (15, 25).

Blocking specific genes involved in the temporal regulation of developmental processes may allow a delay of development and aging. In fact, it was suggested by Medvedev (38) that the incomplete repression of the developmental program may be detrimental to organisms. Delaying development, it appears, is already achieved in CR and through manipulations of the GH/IGF-I axis. One can argue that these life-extending interventions delay developmental mechanisms at an organismal, systemic level. Consequently, other growth-control genes may be of interest to gerontologists (18, 41). For

example, like many long-lived mouse strains, *Igf2*-null mice are dwarf throughout their life spans, but since the gene is mostly inactive after weaning, longevity studies have been largely ignored (18). Although there is little information on the timing of development in these animals, we suggest that they could be worthwhile subjects of aging studies. Indeed, it has been argued that neuroendocrine activity, likely driven by reproduction, causes senescence (40). Nonetheless, although hormones are important in modeling life history, blocking their effects will not suffice. Although details regarding the mechanisms regulating rate of development are largely obscure (21), since developmental programs are also expressed on a tissue-specific level, the most likely scenario is that multiple local-level and organismal mechanisms operate in regulating the pace of development and aging. Is there a master clock regulating development and aging? Probably there are some organismal regulators affecting the whole body (10), such as hormones like the GH/IGF-I axis, but there are possibly multiple tissue- and organ-level regulators, making antiaging interventions a difficult, albeit not impossible, task.

If manipulating, in adulthood, the expression of genes responsible for development can ameliorate age-related pathology, then one promising technology is conditional gene expression, which can be applied to mice (4, 34). For example, it would be interesting to study models of accelerated aging in mice using conditional knockouts that preserve normal ontogeny and only disrupt the gene associated with premature aging in adulthood. For instance, disruption of the proliferation-associated SNF2-like gene (PASG), a helicase, causes growth retardation and accelerated aging in mice (51). It would be relevant to know the effects of PASG disruption in adult mice, particularly if coupled with gene expression and physiological studies encompassing the entire postnatal life span. Likewise, experiments in rodents involving alterations of the GH/IGF-I axis or premature-aging genes during development—but not in adulthood—could prove relevant to understanding aging. Lastly, a number of developmental genes have been shown to be underexpressed during the course of adult life (43, 52). It would be interesting to conditionally overexpress such genes in adulthood.

Another idea would be to target all genes exclusively expressed during prenatal development. As mentioned above, many such genes are crucial in cancer development later in life and may become deregulated due to the end of the developmental program. Suppressing prenatal cell proliferation programs in adulthood could lead to a sort of cancer vaccine with potential implications for other diseases that result from abnormal cell proliferation. One potential experiment would be to use RNA technology, such as RNAi, to block the activity of genes crucial in embryonic cell proliferation in adult mice.

To restart developmental processes in adults, there are two promising avenues of research: embryonic stem cells, which have their developmental process restarted and hold great promise for biology and medicine (44), and understanding the plasticity of the developmental process of amphibians and reptiles, which may hold the keys to sprouting regeneration in mammals (6). The use of specific genetic programs from other species in medicine is challenging, however. Certainly implementing oocyte regeneration to, for instance, female mice would be extraordinary, but it would require precise knowledge of the genes involved.

> *"...the most likely scenario is that multiple local-level and organismal mechanisms operate in regulating the pace of development and aging."*

With the current surge in genomic data and high-throughput methods, however, it may soon be possible to identify genes and pathways unique to organisms with regenerative capacities and eventually reconstruct the mechanisms involved.

One system that encompasses our ideas is the regeneration of auditory hair cells (AHCs). Loss of AHCs is a major cause of deafness, and hence regeneration of these cells has considerable medical interest (25). One approach is to employ embryonic stem cells to differentiate AHCs, which can then be inserted into the inner ear (35). In a sense, embryonic stem cells are cells at early states of development that are differentiated into progenitors of a particular developmental program and thus can be used for rejuvenation. It can also be argued, however, that progenitor stem cells are undamaged, and hence their replacement to restore function is in accordance with damage-based mechanistic theories of aging. Recently, regeneration of AHCs was also achieved through gene therapy with *Atho1*, a signaling molecule that orchestrates the development of AHCs in embryos (29). These results show that regeneration and antiaging medicine are to a large degree a matter of transmitting the right information to cells, as debated before (12), rather than just replacing damaged old cells and molecules. Lastly, it is interesting to note that most mammals, unlike most birds and amphibians, lose the capacity to regenerate AHCs early in life. Therefore, a third approach is

to employ genomic tools to understand the basis of this regenerative capacity and eventually apply it to mammals (25).

Concluding Remarks

Rather than expect differences in defensive or protective genes to regulate the pace of aging, which have never been found (13), it appears that the genetic factors that drive development may also regulate aging rates. Looking at aging as the unintended outcome of a programmed, well-orchestrated development explains why adult life span is proportional to developmental time among mammals. This perspective is also consistent with the antagonistic pleiotropy theory (53): alleles that favor early reproduction and a faster development may entail deleterious late-life effects and thus cause a faster senescence. Besides, mammals feature a robust set of developmental strategies, particularly compared with amphibians, and therefore it is not surprising that aging in different species of mammals appears to be the same process only timed at radically different rates.

The fact that CR started in adulthood extends life span in rodents has been hailed as evidence against the developmental theory of aging (46). In our model, however, the developmental program does not cease at the end of the developmental period. Indeed, we argue that fading or excessive actions of developmental mechanisms in adulthood cause aging (FIGURE 2). Consequently, CR started in adulthood will still affect developmental mechanisms, namely those whose unintended actions cause aging. Moreover, the regulatory role of neuroendocrine factors—like the GH/IGF-I axis—in aging and CR fits a link between development, reproduction, and aging (3, 13, 40).

In conclusion, aging may not be primarily due to damage accumulating from the basic biochemical reactions that make up life but rather the result of the developmental program or of changes brought about by it. Our hypothesis is that the timing of development regulates the rate of aging among mammals, with a subset of developmental mechanisms determining the pace and causing most age-related changes. Maybe people change as they grow old due to the same mechanisms that drive changes throughout the earlier stages in life. ■

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References

1. Ahlgren M, Melbye M, Wohlfahrt J, and Sorensen TI. Growth patterns and the risk of breast cancer in women. *N Engl J Med* 351: 1619–1626, 2004.
2. Barker DJ. Fetal programming of coronary heart disease. *Trends Endocrinol Metab* 13: 364–368, 2002.
3. Bartke A, Chandrashekar V, Dominici F, Turyn D, Kinney B, Steger R, and Kopchick JJ. Insulin-like growth factor 1 (IGF-1) and aging: controversies and new insights. *Biogerontology* 4: 1–8, 2003.
4. Bockamp E, Maringer M, Spangenberg C, Fees S, Fraser S, Eshkind L, Oesch F, and Zabel B. Of mice and models: improved animal models for biomedical research. *Physiol Genomics* 11: 115–132, 2002.
5. Brakefield PM, Gems D, Cowen T, Christensen K, Grubeck-Loebenstein B, Keller L, Oeppen J, Rodriguez-Pena A, Stazi MA, Tatar M, and Westendorp RG. What are the effects of maternal and pre-adult environments on ageing in humans, and are there lessons from animal models? *Mech Ageing Dev* 126: 431–438, 2005.
6. Carlson BM. Muscle regeneration in amphibians and mammals: passing the torch. *Dev Dyn* 226: 167–181, 2003.
7. Carroll SB. Genetics and the making of *Homo sapiens*. *Nature* 422: 849–857, 2003.
8. Charnov EL. *Life History Invariants: Some Explorations of Symmetry in Evolutionary Ecology*. Oxford, UK: Oxford University Press, 1993.
9. Comfort A. *Ageing: The Biology of Senescence*. London: Routledge & Kegan Paul, 1964.
10. Conboy IM, Conboy MJ, Wagers AJ, Girma ER, Weissman IL, and Rando TA. Rejuvenation of aged progenitor cells by exposure to a young systemic environment. *Nature* 433: 760–764, 2005.
11. Cutler RG. Evolution of human longevity: a critical overview. *Mech Ageing Dev* 9: 337–354, 1979.
12. De Magalhaes JP. The dream of elixir vitae. In: *The Scientific Conquest of Death: Essays on Infinite Lifespans*, edited by The Immortality Institute. Buenos Aires: Libros En Red, 2004, p. 47–62.
13. De Magalhaes JP. Open-minded scepticism: inferring the causal mechanisms of human ageing from genetic perturbations. *Ageing Res Rev* 4: 1–22, 2005.
14. De Magalhaes JP and Sandberg A. Cognitive aging as an extension of brain development: a model linking learning, brain plasticity, and neurodegeneration. *Mech Ageing Dev* (June 8, 2005); doi:10.1016/j.mad.2005.04.004.
15. De Magalhaes JP and Toussaint O. The evolution of mammalian aging. *Exp Gerontol* 37: 769–775, 2002.
16. De Magalhaes JP and Toussaint O. GenAge: a genomic and proteomic network map of human ageing. *FEBS Lett* 571: 243–247, 2004.
17. Denoel M and Joly P. Neoteny and progenesis as two heterochronic processes involved in paedomorphosis in *Triturus alpestris* (Amphibia: Caudata). *Proc R Soc Lond B Biol Sci* 267: 1481–1485, 2000.
18. Efstratiadis A. Genetics of mouse growth. *Int J Dev Biol* 42: 955–976, 1998.
19. Finch CE. *Longevity, Senescence, and the Genome*. Chicago: University of Chicago Press, 1990.
20. Geula C, Wu CK, Saroff D, Lorenzo A, Yuan M, and Yankner BA. Aging renders the brain vulnerable to amyloid beta-protein neurotoxicity. *Nat Med* 4: 827–831, 1998.
21. Gilbert SF. *Developmental Biology*. Sunderland, MA: Sinauer, 2003.
22. Hammerman MR. Insulin-like growth factors and aging. *Endocrinol Metab Clin North Am* 16: 995–1011, 1987.
23. Harvey PH, Pagel MD, and Rees JA. Mammalian metabolism and life histories. *Am Nat* 137: 556–566, 1991.
24. Harvey PH and Zammuto RM. Patterns of mortality and age at first reproduction in natural populations of mammals. *Nature* 315: 319–320, 1985.

25. Hawkins RD and Lovett M. The developmental genetics of auditory hair cells. *Hum Mol Genet 13 Spec No* 2: R289–R296, 2004.

26. Hayflick L. *How and Why We Age*. New York: Ballantine, 1994.

27. Holliday R. The multiple and irreversible causes of aging. *J Gerontol A Biol Sci Med Sci* 59: B568–B572, 2004.

28. Imokawa Y and Yoshizato K. Expression of *Sonic hedgehog* gene in regenerating newt limb blastemas recapitulates that in developing limb buds. *Proc Natl Acad Sci USA* 94: 9159–9164, 1997.

29. Izumikawa M, Minoda R, Kawamoto K, Abrashkin KA, Swiderski DL, Dolan DF, Brough DE, and Raphael Y. Auditory hair cell replacement and hearing improvement by Atoh1 gene therapy in deaf mammals. *Nat Med* 11: 271–276, 2005.

30. Kanungo MS. *Genes and Aging*. Cambridge, UK: Cambridge University Press, 1994.

31. Kipling D, Davis T, Ostler EL, and Faragher RG. What can progeroid syndromes tell us about human aging? *Science* 305: 1426–1431, 2004.

32. Kirkwood TB. Understanding the odd science of aging. *Cell* 120: 437–447, 2005.

33. Klass M and Hirsh D. Non-ageing developmental variant of *Caenorhabditis elegans*. *Nature* 260: 523–525, 1976.

34. Lewandoski M. Conditional control of gene expression in the mouse. *Nat Rev Genet* 2: 743–755, 2001.

35. Li H, Roblin G, Liu H, and Heller S. Generation of hair cells by stepwise differentiation of embryonic stem cells. *Proc Natl Acad Sci USA* 100: 13495–13500, 2003.

36. Martin GM. Genetic syndromes in man with potential relevance to the pathobiology of aging. *Birth Defects Orig Artic Ser* 14: 5–39, 1978.

37. Medawar PB. *An Unsolved Problem of Biology*. London: H. K. Lewis, 1952.

38. Medvedev ZA. An attempt at a rational classification of theories of ageing. *Biol Rev Camb Philos Soc* 65: 375–398, 1990.

39. Miller RA. Kleemeier award lecture: are there genes for aging? *J Gerontol A Biol Sci Med Sci* 54: B297–B307, 1999.

40. Mobbs CV. Not wisely but too well: aging as a cost of neuroendocrine activity. *Sci Aging Knowledge Environ* 2004: pe33, 2004.

41. Nijhout HF. The control of growth. *Development* 130: 5863–5867, 2003.

42. Pearson RD. The determined embryo: homeodynamics, hormones, and heredity. In: *Environment, Development, and Evolution: Toward a Synthesis*, edited by Hall BK, Pearson RG, and Muller GB. Cambridge, MA: MIT Press, 2003, p. 67–84.

43. Prolla TA. DNA microarray analysis of the aging brain. *Chem Senses* 27: 299–306, 2002.

44. Rao MS and Mattson MP. Stem cells and aging: expanding the possibilities. *Mech Ageing Dev* 122: 713–734, 2001.

45. Reya T. Regulation of hematopoietic stem cell self-renewal. *Recent Prog Horm Res* 58: 283–295, 2003.

46. Rollo CD. Growth negatively impacts the life span of mammals. *Evol Dev* 4: 55–61, 2002.

47. Rose MR. *Evolutionary Biology of Aging*. New York: Oxford University Press, 1991.

48. Russanova VR, Hirai TH, Tchernov AV, and Howard BH. Mapping development-related and age-related chromatin remodeling by a high throughput ChIP-HPLC approach. *J Gerontol A Biol Sci Med Sci* 59: 1234–1243, 2004.

49. Small SA, Chawla MK, Buonocore M, Rapp PR, and Barnes CA. Imaging correlates of brain function in monkeys and rats isolates a hippocampal subregion differentially vulnerable to aging. *Proc Natl Acad Sci USA* 101: 7181–7186, 2004.

50. Speakman JR, Talbot DA, Selman C, Snart S, McLaren JS, Redman P, Krol E, Jackson DM, Johnson MS, and Brand MD. Uncoupled and surviving: individual mice with high metabolism have greater mitochondrial uncoupling and live longer. *Aging Cell* 3: 87–95, 2004.

51. Sun LQ, Lee DW, Zhang Q, Xiao W, Raabe EH, Meeker A, Miao D, Huso DL, and Arceci RJ. Growth retardation and premature aging phenotypes in mice with disruption of the SNF2-like gene, PASG. *Genes Dev* 18: 1035–1046, 2004.

52. Weindruch R, Kayo T, Lee CK, and Prolla TA. Gene expression profiling of aging using DNA microarrays. *Mech Ageing Dev* 123: 177–193, 2002.

53. Williams GC. Pleiotropy, natural selection, and the evolution of senescence. *Evolution* 11: 398–411, 1957.

54. Zwaan BJ. Linking development and aging. *Sci Aging Knowledge Environ* 2003: pe32, 2003.

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