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Mosaic aging

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Summary

Although all multicellular organisms undergo structural and functional deterioration with age, senescence is not a uniform process. Rather, each organism experiences a constellation of changes that reflect the heterogeneous effects of age on molecules, cells, organs and systems, an idiosyncratic pattern that we refer to as *mosaic aging*. Varying genetic, epigenetic and environmental factors (local and extrinsic) contribute to the aging phenotype in a given individual, and these agents influence the type and rate of functional decline, as well as the likelihood of developing age-associated afflictions such as cardiovascular disease, arthritis, cancer, and neurodegenerative disorders. Identifying key factors that drive aging, clarifying their activities in different systems, and in particular understanding how they interact will enhance our comprehension of the aging process, and could yield insights into the permissive role that senescence plays in the emergence of acute and chronic diseases of the elderly.

Introduction

Oliver Wendell Holmes Sr., the 19th century American physician and polymath, once penned a whimsical poem entitled “The Deacon's Masterpiece, or the Wonderful One-Hoss Shay”, in which he describes the consequences of building a horse carriage so well that no single part can fail before another:

> “Now in building of chaises, I tell you what,
>
> There is always *somewhere* a weakest spot, --
>
> In hub, tire, felloe, in spring or thill,
>
> In panel, or crossbar, or floor, or sill,
>
> In screw, bolt, thoroughbrace, -- lurking still,
>
> Find it somewhere you must and will, --
>
> Above or below, or within or without, --
>
> And that's the reason, beyond a doubt,
>
> A chaise *breaks down*, but doesn't *wear out*.”

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In the poem, an imaginary shay (*chaise*) was constructed with uniformly durable materials, and it functioned flawlessly for exactly one hundred years, at which point:

> "You see, of course, if you're not a dunce,
>
> How it went to pieces all at once,--
>
> All at once, and nothing first,--
>
> Just as bubbles do when they burst.
>
> End of the wonderful one-hoss-shay.
>
> Logic is logic. That's all I say."

Lewis Thomas has suggested that Holmes' shay is a metaphor for the aging human body, or, more precisely, for a hypothetical body in which no one system can fail before another [1]. Holmes and Thomas, both physicians, were well aware that a corporeal Deacon's Masterpiece probably does not exist. Senescence is not a uniform process that progresses similarly in all parts of the mammalian body, but rather affects the various systems in different individuals in different ways. Hence, despite diverse signs of senescence throughout the body, it is often the untimely failure of a single feature (the 'weakest spot') that results in debilitation and death. Substantial research has been devoted to the question of which systems are prone to break down, and why. Are there general principles that govern the aging process (as Hayflick has argued [2]), or does each system, each cell, or each molecule succumb to advancing age for different reasons? Or could a single causative factor, acting arbitrarily, engender a wide variety of aging phenotypes? A related question is whether age-associated diseases are separate from senescence *per se*, or whether they simply represent 'weak spots' that arise in the general course of aging in individuals. The close link between aging and such ailments as cardiovascular disease, cancer, arthritis and dementia, to name only a few, suggests that "to consider aging of man in the 'absence of disease' is an abstraction which has little possibility of full attainment" [3].

Mosaic Aging

The quest to identify the factors that regulate vertebrate aging is hampered by the complexity of the aging process [4-6], one manifestation of which is individual variation. This is a particular problem in humans, who are genetically diverse and subject to an especially broad spectrum of environmental influences. While we often tend to refer to 'aging' as a unitary phenomenon, in complex organisms, each individual experiences a temporally and spatially unique constellation of physical and functional decline, a heterogeneity that has been referred to as 'differential aging' [7-9]. Because these changes affect different organic components at different times and rates, we will call them "mosaic aging." The interconnectedness of living systems predicts that mosaic aging will engender a wide array of individual phenotypes.

A robust example of mosaic aging is menopause, one of the most thoroughly studied examples of physiological senescence [10] that occurs across a range of ages in different women [11] and in female nonhuman primates [12]. Menopause is associated with myriad interacting changes in hormones and behavior that are related to the loss of ovarian follicles [12,13]. The age of natural menopause varies over a fairly wide range, and is subject to genetic and extrinsic influences [11,14,15]. Given the far-reaching physiological impact of menopause, it is perhaps not surprising that there is a weak, but statistically significant, positive correlation between early menopause and early mortality due to multiple causes [16-18]. However, the effects of menopause on certain systems may be contradictory. For instance, the extended presence of ovarian hormones in women experiencing later menopause may protect against heart disease [19], but early menopause may be associated with a decrease in breast cancer (see [17]).

From a phylogenetic perspective, it is interesting to note that, although humans and chimpanzees experience ovarian follicular loss and reproductive cessation at remarkably similar rates and ages [20,21], humans have a uniquely extended postmenopausal lifespan [22]. Thus, although early ovarian failure may predict shorter lives in individuals, the relatively early menopause of the human species is associated with the longest lifespan in the primate order. Menopause therefore illustrates an additional feature of mosaic aging: because the rates of aging of the reproductive system can be decoupled from senescence of other systems, it was possible for the human species to extend lifespan well beyond the period of reproduction. This phenomenon has been formalized in evolutionary hypotheses of aging, such as the grandmother hypothesis [23].

The brain presents an edifying paradigm for the spatiotemporal irregularity of senescent decline as well, owing in part to its structural and biochemical complexity. For example, in the medial temporal lobe of humans, the hippocampal formation is more vulnerable to the ravages of time than is the adjacent entorhinal cortex [24]. At the cellular level, advancing age affects specific neuronal types preferentially [25-37]. Molecularly, some proteins are especially prone to age-associated degenerative phenomena such as aberrant glycosylation/glycation, phosphorylation, conformational corruption and aggregation [35,38-42]. In older primates (including humans), the accumulation of Aβ-protein deposits in the brain is highly variable among conspecific animals of the same age [43,44]. Even well-defined human neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease are characterized by a remarkable degree of variability, both clinically and pathologically [45-48].

In addition to certain proteins, DNA also is a macromolecular weak spot, in that it is particularly susceptible to damage and base substitutions whose effects can ramify throughout the system [49]. In addition, epigenetic modifications such as methylation and acetylation can differentially influence the activity of DNA, and indeed may account for some of the phenotypic divergence in aging twins [50]. In adult animals, tissues with continually dividing cells (such as epithelial and hematopoietic cells) are especially prone to neoplasia, whereas those containing a large component of postmitotic or minimally mitotic cells (such as neurons and cardiomyocytes) show a different pattern of senescent changes, including cellular lipofuscinosis, mitochondrial DNA deletions, and protein aggregation [10,51-53]. For the individual organism, the pattern and magnitude of such changes governs the phenotypic deterioration that we broadly refer to as senescence. Because of the mosaic (and to some degree random) nature of the changes, some people advance into their later years with extraordinary success, remaining physically and mentally vigorous into their 80's and 90's, yet others become increasingly impaired in one or more domains (‘successful’ vs. ‘usual’ aging, respectively [54]). In other words, there is no unitary “aging”, but rather, each individual, in time, will experience a multifaceted and distinctive pattern of decline in the functionality of the cells and tissues of the body.

Implications

What are the theoretical and practical implications of mosaic aging? First, although there may turn out to be relatively few mediators of senescence, such as oxidative stress [10,55] or epigenetic factors [50,56], the manifestations of these agents still are, to a considerable extent, stochastic and regional. Hence, even if a single molecular catalyst is found to drive the aging process, this catalyst may not be homogeneously operational throughout all bodily systems, and its effects thus may ramify in intricate and unpredictable ways. For this reason, although we might come to agreement on a particular driver of aging, we should not necessarily expect a uniform *pattern* of aging in complex organisms.

Second, aging mosaicism underscores the value of longitudinal studies of aging, in which the trajectory of changes can be tracked in each individual from a known (and probably unique) biological baseline. In this light, it also will be informative to determine the extent of mosaicism in different species. Although we expect that variability will be most apparent in anatomically and physiologically complex organisms, there are practical and theoretical advantages to analyzing mosaic aging in simpler multicellular creatures such as *Caenorhabditis elegans*, *Drosophila melanogaster*, or *Daphnia magnus*. The first, and most obvious advantage is that these species have short lifespans that can be observed over a brief period of time. In the case of the fruit fly, *Drosophila*, for example, experimental evolution is possible, in which researchers can intentionally select for specific physiological traits and analyze genetic mutations that accompany phenotypic changes (e.g., [57]).

Third, because the potential multiplicity of aging trajectories may be less in simple organisms, more complex species will be required to fully understand mosaic aging as it pertains to humans. Studies of nonhuman primates, for example, are valuable in that they can probe the mechanisms of aging in species that lack the varied and sometimes self-destructive dietary and other behavioral tendencies of humans. Investigations of older rhesus monkeys have begun to determine patterns of senescence in a biologically proximate species maintained in a relatively constant and well-characterized milieu [58-61]. Such analyses are optimized by taking a holistic view of aging [7] to reveal consistent versus idiosyncratic changes in multiple bodily systems.

Finally, it is imperative to recognize the ever-present ‘weak spots’ that can diminish the quality and/or duration of life in a given individual (such as a predisposition to arthritis, dementia, cancer or stroke). In humans, personalized medicine will enable patients to discern, and possibly to manage, genetic and environmental risk factors for premature debility or death.

In this regard, modern computer-based, bioinformatic analyses of multiple endpoints can be helpful in identifying organismic or environmental variables (and their potential interactions) that can accelerate or retard senescence. One such approach is the application of multivariable analyses of complex datasets, which is particularly applicable to large, longitudinal studies in which individuals are closely followed with respect to particular variables of interest. Data obtained from such longitudinal analyses can be extensive, and the value of such studies is widely recognized. Indeed, the National Institute on Aging lists more than 30 such studies currently underway (http://www.nia.nih.gov/ResearchInformation/ScientificResources/LongitudinalStudiesAllCurrent.htm). One longitudinal study of aging, the Framingham Heart study, has been ongoing for more than a half-century [62,63]. The original purpose of the project was to compare those with and those without “signs of arteriosclerotic or hypertensive cardiovascular disease”. Additionally, by waiting until diseases progressed, the study planned to study “differences, at the time of initial examination” between those who remained healthy and those who became ill or died [62]. Data from the Framingham study have now been extensively analyzed, with many endpoints besides cardiovascular disease, yielding about 2,000 publications on important aspects of human aging.

Multivariate analysis also can be useful in separating genetic, epigenetic and non-genetic variability in age-related outcomes in twin studies. One such study, based upon a longitudinal analysis of participants in the Danish Twin Registry, estimates that only about one-fourth of the variation in self-reported health and number of hospitalizations can be attributed to genetic factors *per se* [64], again highlighting the influence of stochastic and environmental factors on health-related outcomes. Future work would benefit from a multivariate analysis of a multiplicity of different aging processes, not necessarily representing diseases, but rather

normal age-related changes, such as loss in skin elasticity, changes in visual acuity, and, of course, changes in cognitive capacity.

Conclusions

The view of aging as a mosaic process can inform the search for specific biomarkers and, paradoxically, might also shed light on general principles of senescence. The application of bioinformatic approaches will help to separate the wheat from the chaff; rather than just seeking biomarkers that correlate with aging (few of which are meaningful on their own), such markers could be evaluated in a matrix that includes as many indices as possible of the functional status of diverse systems, including the immune, endocrine, urogenital, gastrointestinal, respiratory, cardiovascular, nervous and musculoskeletal systems. We may thereby discover that a particular circulating biomarker is not always associated with aging in general, but it *is* linked to age-related changes in a particular system that can have real consequences for the quality and/or length of life in a particular person.

Every human body, like every vehicle (except, of course, Holmes' shay), has components that will fail even while the other parts are still functional. One goal of aging research is to establish the fundamental principles of senescence, but another should be to identify the weak spots that accompany aging in individuals, and to develop the means to shore them up. To some extent this is already happening, two examples being antilipidemic and antihypertensive drugs. Eventually, we humans might reach the point at which we are essentially free of the major catastrophic illnesses of old age, yet estimates are that, if all such ailments were suddenly eliminated, the average human life expectancy would increase by only around 15 years [65]. In other words, even in the absence of age-related diseases, the aging process would persist, and the animate bubble would eventually burst. While this may not be a comforting scenario to those who seek to live indefinitely, the elimination of the dread diseases of old age would be a gift of considerable worth to humanity.

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