ISSN 0006-2979, Biochemistry (Moscow), 2013, Vol. 78, No. 9, pp. 1061-1070. © Pleiades Publishing, Ltd., 2013.
Published in Russian in Biokhimiya, 2013, Vol. 78, No. 9, pp. 1354-1366.

Studies that Shed New Light on Aging

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Received May 16, 2013

Abstract—I will first discuss how all aging models that assume that the aged cell has irreversibly lost its youthful capabilities through such mechanisms as accumulated dysfunction, accumulated damage, and/or accumulation of toxic byproducts of metabolism have been shown to be incorrect. I will then briefly discuss models of aging and propose an experiment that would distinguish between those models and provide a basis for organismic rejuvenation.

DOI: 10.1134/S0006297913090137

Key words: aging, aging mechanisms, theories of aging, parabiosis, cross-age transplantation, rejuvenation, cellular aging, age-dependent transcriptional patterns

By the turn of the 21st century, gerontologists and biologists reached a consensus "evolutionary theory of aging" [1-3], putting aging research into the mainstream of biological research. This so-called theory, simply put, states that because continued selective pressure tends to make the lifespan of a sexually-reproducing organism longer – as a longer-lived organism produces more offspring – it can be assumed that mechanisms retarding aging are insufficient to allow organisms the long lives evolutionary theory predicts. The theory assumes that an aged cell is irreversibly damaged as a result of life's slings and arrows, leading to the currently accepted paradigm of "wear and tear" as the cause of aging.

The "wear and tear" paradigm of aging maintains that as an organism ages, the incidence of cellular damage and toxic metabolic byproducts eventually exceeds the organism's ability to repair or remove them, leading to their accumulation [4]. This, in turn, results in the increase in the number of senescent cells and a decrease in effective stem cell populations, or an alteration of their potency [5]. So aging is characterized as the accumulation of damage leading to dysfunction. Metaphorically, the aging of an organism is like that of an automobile, eventually as parts wear out and malfunction more quickly than they can be repaired or replaced, the automobile becomes a jalopy destined for the junkyard. This is assumed to be the same case regarding cells, even stem cells, and consequently the tissues, organs, organ systems, and the organism whose functioning is based on those cells.

CELLULAR REJUVENATION IMPLIES STOCHASTIC THEORIES OF AGING CONFUSE CAUSE AND EFFECT

In spite of inconsistencies and improper assumptions, these current leading "evolutionary" theories of aging are widely accepted models yet, to call them "theories", is normally a scientific assessment of their proven truth, which is not the case [6]. As this paper will show, the hypothesis that aging at the cellular level is the product of the accumulation of irreparable damage and/or uneliminable toxic substances has been tested and rejected in numerous studies. Simply demonstrating that cells can be rejuvenated by exogenous factors is logically equivalent to demonstrating that cells are not irreparably damaged by aging, in direct contradiction to the assertion that aging is the result of irreparable damage. If cells are not irreparably damaged by aging, then what makes them age and accumulate damage? As we will show, it is becoming clear that the accumulation of damage is an effect of aging and not its cause. This confusion of cause and effect is evinced in many aging "theories" based the many phenomena correlated with aging. So mitochondrial dysfunction, ROS (reactive oxygen species) production, telomere shortening, and DNA damage accumulation – each has been separately regarded as "the cause" of aging [7], yet they are all more properly regarded as effects of aging: the demonstration that each of these "causes" of aging are reversed by cellular rejuvenation shows that those are all processes that are not its cause but are all

consequences of aging, the result of cellular decisions, but decisions that can be, as we shall see, reversed. All stochastic models that assume the hypothesis that aging results from the irreversible loss of information to entropy are shown to be incorrect by the demonstration of cellular rejuvenation: the hypothesis that information is irretrievably lost through aging must be rejected as the information for a total renewal was not lost in the aged or senescent cell: it was demonstrably recovered. As we will show, evidence points to aging being a programmed process controlled, in mammals, through factors present in their blood. The ultimate control of the process is epigenetic, but it is coordinated across the body by soluble factors and juxtacrine interactions. I believe the process is a continuation of the developmental program, with a beginning and an end.

Kirkwood's [8] statement "but, if programmed, the programming is very loose, because there is a large variation in the rates of senescence of individual cells within the population", is close to what we believe to be true, in that an organism's lifespan is governed by a very loose programming with many environmentally-influenced decision pathways that may extend or diminish lifespan, but inevitably (except for organisms showing negligible senescence, or replaying earlier developmental stages like *Turritopsis nutricula*) drives an individual from zygote through reproductive adulthood and to subsequent senescence and death. To suggest that aging changes are to a great degree preordained is to take a position that sounds more hopeless than the various variations of "wear and tear" (stochastic) theories which, at least, grant the possibility of interfering with damage production and/or accumulation. However, as we will show, several studies indicate that the exogenous factors can reset the age phenotype of body cells, tissues, organs, and possibly organisms, this view of aging leads to the possibility of recovering youth – that very "fountain of youth" that Dr. Kirkwood told us was to go the way of the perpetual motion machine – an impossibility [9].

AGE-RELATED TRANSCRIPTION PROFILES AND THE THEORIES OF AGING

The stochastic theories of aging suggest a general decline [2] in all aspects of the organism – it is suggested by all the wear and tear theories that the cell ultimately becomes dysfunctional to the stage where it cannot perform its duties nor even maintain itself and dies. It is expected under such a paradigm that the cell deteriorates with age, much as an automobile does. As opposed to this, an explanation more consistent with observed biology is an epigenetically controlled program that is an approximately life-long extension of the developmental program that begins with fertilization [7]. If that is the case, then aging may be evolutionarily selectable as nature may be selecting a successful program and not a collection of genes, or for that matter individual, "selfish" genes.

Evidence for this view comes from the technological innovation that allows the simultaneous analysis of the rates of transcription of tens of thousands of genes using DNA microarrays [10-12]. These sorts of studies show age-dependent changes in the regulation of thousands of genes. The study of Stuart Chambers [13] shows that there are marked age-dependent, order of magnitude differences in the transcriptional rates of many genes, and of these age-regulated genes, the regulation must be seen as anti-homeostatic. An example of this is the down-regulation of DNA repair genes in mice [13] at ages at which DNA defects show increased frequency and DNA repair becomes inefficient [14]. Other examples will be considered later. One would certainly suspect that down-regulating the transcription rates of repair enzymes at or just prior to the time of increased DNA damage accumulation and the documented decreased ability for DNA repair ("inefficient repair" [14]) must have a causal connection. Yet homeostasis is an active process that at the level of the cell tries to preserve integrity – turning down DNA repair activity at the time of an increase in DNA damage (by ROS, "leaky" mitochondria, etc.) is exactly contrary to the principle of homeostasis (even failing to up-regulate DNA repair when there is DNA damage is at least non-homeostatic) and demands an explanation. The explanation of the hypothesis called "antagonistic pleiotropy" would be that some pleiotropic protein that once acted towards the cell's benefit now operates (at its evolutionarily untouchable post-reproductive stage of deterioration) to its detriment – but what we observe is not a change in the character of genes, but a quantitative change in their appearance in the cell – and that change is opposite to what the principle of homeostasis demands! While Chambers attributes those negative changes, such as genetic dysregulation and the loss of genetic suppression to entire segments of chromosomes, to epigenetic dysregulation, the very specific timings of age-dependent changes in transcription rates of aging-related genes, apparently correlated with developmental stages in the post-adult lifespan, implies a programmatic decision to down-regulate cellular maintenance and repair systems aging damage rather than a stochastic unraveling of epigenetic control. The age-coordinated expression of specific genes appears to result in the very dysfunctions that their lack or excess might reasonably be expected to give rise to: decreased synthesis of DNA repair proteins might be expected to give rise to the accumulation of DNA defects, excesses of proinflammatory cytokines should lead to generalized inflammation, increased production of amyloidogenic proteins ought to produce amyloidoses (including Alzheimer's disease) – processes associated with aging [13].

It may be safely assumed that cellular deficiencies including the progressive loss of proliferative potential and potency in stem cell and progenitor cell populations