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Early-life stress and reproductive cost: A two-hit developmental model of accelerated aging?

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ABSTRACT

Two seemingly independent bodies of research suggest a two-hit model of accelerated aging, one highlighting early-life stress and the other reproduction. The first, informed by *developmental models of early-life stress*, highlights reduced longevity effects of early adversity on telomere erosion, whereas the second, informed by *evolutionary theories of aging*, highlights such effects with regard to reproductive cost (in females). The fact that both early-life adversity and reproductive effort are associated with shorter telomeres and increased oxidative stress raises the prospect, consistent with life-history theory, that these two theoretical frameworks currently informing much research are tapping into the same evolutionary-developmental process of increased senescence and reduced longevity. Here we propose a mechanistic view of a two-hit model of accelerated aging in human females through (a) early-life adversity and (b) early reproduction, via a process of telomere erosion, while highlighting mediating biological embedding mechanisms that might link these two developmental aging processes.

Introduction

Theories of aging have long addressed why and how we age [1], but heterogeneity in the pace of aging continues to raise questions. From a developmental view, as we age, various biological and environmental processes contribute to the functional decline of cells, tissues and organs rendering individuals more susceptible to disease. However, these changes can vary developmentally with age, and importantly, may be amplified by previous adverse environmental exposures early in life, possibly via the programming of cellular-aging processes [2].

Several theoretical perspectives address *the developmental effects of early-life stress*, including the Developmental Origin of Health and Disease (DOHaD) Model [3], the Allostatic Load Model [4], and Predictive Adaptive Response frameworks [5–7]. All share the view that early-life adversity "programs" physiology and behavior to promote survival and/or reproduction, but that such developmental processes carry a cost or have trade-offs in later life involving increased morbidity and reduced longevity. Also important to consider are *evolutionary theories of aging*, including the Mutation Accumulation Theory [8], the Antagonistic Pleiotropy Theory [9], the Disposable Soma Theory [10], and the recent Reproductive-Cell Cycle Theory [11]. These, like the aforementioned perspectives, highlight trade-offs between growth and the ultimate goal of evolution, reproductive success, at the expense of longevity later in life.

The following empirical observations would seem consistent with this claim: (1) perinatal and childhood adversity plays an etiological role in the programming of late-life disease, resulting in increased morbidity and reduced longevity [2,12]; (2) increased fertility coincides with reduced longevity in birds and mammals [13], as well as in primates [14], although this association has not gone unchallenged in the human case [15–17]. From an evolutionary life-history perspective, organisms facing risks that could reduce their chances of surviving to reproductive age should, if possible, accelerate their development and thereby increase their prospects of passing on genes to future generations before becoming unable to do so due to an early death [7,18]. Ultimately, the organism trades-off longer-term health costs involved in accelerating development for increased probability of reproducing before dying. Thus, accelerated aging does not so much represent a disease process, but rather the consequence of a developmental adaptation crafted by natural selection.

Should this analysis prove accurate, questions arise regarding underlying mechanisms linking developmental influences with accelerated aging processes. Recent evidence suggests that telomere erosion may function as one important cellular mediator

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linking early-life stress with later-life morbidity and early mortality [19–21]. And this is because telomere regulation appears receptive and malleable in response to environmental inputs [22], requires energy for its maintenance [23], and is predictive of health [24,25] and early mortality [26]. Several highly energetically costly biochemical processes are implicated in regulating telomeres, including, among others, mitochondrial function, oxidative stress and inflammation [27].

With that in mind, reproduction is considered a highly costly process, one linked to increased levels of oxidative stress and glucocorticoids during pregnancy [28,29], as well as energy demands during lactation [30,31]. Notably, oxidative stress is itself related to reproductive trade-offs [32,33] and aging [34,35], and is considered a main factor influencing the rate of telomere erosion [36]. Thus, theory and evidence raise the possibility that the very developmentally induced accelerated aging processes involving early-life adversity and reproduction may operate at the cellular level via accelerated erosion of telomere length (TL). Moreover, epigenetic programming suggests that the reproduction-related aging process can be *intensified* by stress exposure in early life, mediated by biological embedding mechanisms.

The hypothesis

Here, we borrow a term used in cancer research that describes accumulation of mutations—that is, 'hits' – to the cell's DNA [37], and broadly apply it to human cellular aging. Specifically, we offer a mechanistic analysis of our hypothesized two-hit developmental model of accelerated aging via accelerated telomere erosion. We first provide empirical evidence of the effects of early-life adversity (i.e., prenatal, postnatal and early childhood) on cellular aging processes (i.e., telomere erosion) in support of the first hypothesized "hit" of our model. Thereafter, we discuss the cost of reproduction and its effect on cellular aging in support of our second hypothesized "hit". We then highlight biological embedding mechanisms of early-life adversity and early reproduction that might link these two developmental frameworks to induce accelerate aging via telomere erosion. Before drawing conclusions, we point out limitations of our argument. Finally, we discuss our hypothesized two-hit model of accelerated aging—emphasizing the interaction between early-life stress and early reproduction – based on the mechanistic integration of these two frameworks – and discuss implications for aging research. Fig. 1 schematically illustrates the framework to be developed.

Supporting evidence and evaluation of the hypothesis

We advance our hypothesized two-hit model based on two seemingly independent bodies of research, one highlighting early-life stress and the other reproduction.

Hit one

Early life adversity, then, functions as the first hit in the two-hit model of accelerated aging being developed herein. DOHaD-related research indicates that adverse conditions during prenatal development, resulting, for example, in low birth-weight predict increased risk of cardiovascular disease [38], cognitive problems [39] and early mortality [12]. Such adverse developmental effects are not limited to the pre-/perinatal period, as evidence also indicates that poor family environments early in life are associated with compromised metabolic and immune functioning [40], and adult health more generally [41]. Further, childhood maltreatment, a severe form of toxic stress for young children, is associated with mental and physical health problems [42–44]. Also meriting attention is evidence linking cumulative risk and higher allostatic load among rural children [45] and adolescences [46].

Such early-life-adversity effects on health in later life invite consideration of underlying mediating mechanisms. Recently, the length of telomeres has been posited as a factor regulating aging processes that could mediate such early-adversity effects [47]. Telomeres are DNA-protein repeats at the end of chromosomes that act as a 'cap' to protect chromosomes from deterioration [20]. Telomeres shorten with each cell division and are considered a hallmark for cellular aging [19]. While TL can be maintained in certain cell types by telomerase, most somatic cells lack sufficient telomerase and, as a consequence, telomeres progressively shorten with each cell division [48,49].

Notably, not only is there ever increasing evidence linking age-related TL with a broad range of risk factors that predict disease morbidity and early mortality, such as adult mental disorders and unhealthy behaviors (e.g., smoking, substance use, poor sleep and diet) [21], but the same is true of research chronicling effects of early-life adversity, including prenatal stress and maltreatment, on TL [27,50–54]. The fact that telomeres prove sensitive to adversity and predictive of health, as well as related to known poor-health risk factors, has resulted in them being regarded as a "biological clock" for studying accumulated cellular aging throughout the life course. According to such a medical model, telomere erosion reflects "wear and tear" which eventually compromises well-being, thus proving predictive of increased morbidity and reduced longevity. Here we challenge this prevailing view, as have others [55,56], by casting telomere erosion, a conserved cellular mechanism [57], in evolutionary perspective in order to explain developmental trade-offs in later life involving increased senescence and reduced longevity.

Hit two

While the evidence just summarized is consistent with the claim that early-life adversity programs the organism's physiology to promote survival at the expense of increased morbidity and reduced longevity through faster erosion of telomeres, a separate body of research addresses trades-offs between reproductive success and longevity in later life. The work underscores the second hit of the two-hit model under consideration.

The Disposable Soma Theory suggests that the developing organism, under limited resources, will shift energy allocation to reproductive activities while reducing energy distribution to non-reproductive aspects of somatic maintenance [10]. Thus, even though accelerated development may prove detrimental to health and even longevity in the longer term, such costs are regarded as ones which natural selection would discount, according to life-history theory, given the primacy placed on reproductive success [55,58–60]. Consistent with such a life-history perspective is long-standing evidence that earlier timing of reproduction and shorter lifespans are related across taxa [61], including birds and mammals [13], as well as primates [14] and humans [62,63], although, as noted earlier, inconsistencies exist in the latter case [15–17]. Such data become especially noteworthy if the biological processes involved in linking reproduction and lifespan play a role in regulating developmental rate, reproduction and aging, which is exactly what we are predicting. As telomere length and erosion appear to be adaptive, there is reason to expect they may mediate trade-offs between developmental life-history processes and longevity [64]. Intriguingly, several animal models provide support for this line of thinking [65–70]. In addition, then, to early-life-adversity effects on telomere regulation, the energetically costly process of reproduction can further impact the rate of aging via accelerated telomere erosion, thereby supplying the second hit of our model.