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Development and Longevity: Cellular and Molecular Determinants - A Mini-Review

This is the final peer-reviewed author's accepted manuscript (postprint) of the following publication:

Published Version:

Development and Longevity: Cellular and Molecular Determinants - A Mini-Review / Marchionni S.; Sell C.; Lorenzini A.. - In: GERONTOLOGY. - ISSN 0304-324X. - STAMPA. - 66:3(2020), pp. 223-230. [10.1159/000505327]

Availability:

This version is available at: <https://hdl.handle.net/11585/762797> since: 2020-06-22

Published:

DOI: <http://doi.org/10.1159/000505327>

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(Article begins on next page)

This is the final peer-reviewed accepted manuscript of:

Silvia Marchionni, Christian Sell, Antonello Lorenzini.

Development and Longevity: Cellular and Molecular Determinants - A Mini-Review.

Gerontology 2020, v.66, n.3, pp.223-230.

The final published version is available online at:

<https://doi.org/10.1159/000505327>

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INVITED MINI-REVIEW

TITLE

Development and longevity: cellular and molecular determinants. A mini-review

Silvia Marchionni¹, Christian Sell², Antonello Lorenzini^{1*}

¹ Department of Biomedical and Neuromotor Sciences (DIBINEM), University of Bologna, Bologna, Italy.

² Department of Pathology & Laboratory Medicine, Drexel University College of Medicine, Philadelphia, PA, USA.

Short Title: **Development influences longevity**

*Corresponding Author

Full name: **Antonello Lorenzini**

Department of Biomedical and Neuromotor Sciences (DIBINEM)

University of Bologna

Via Irnerio 48, 40126 Bologna, Italy

Tel: **+39 051 2091208**

Fax: **+39 051 2091208**

E-mail: **antonello.lorenzini@unibo.it**

ABSTRACT

Across species, development and longevity are tightly linked. We discuss the relevant literature and suggest that the root for this stringent relationship is the rate of development. The basis for the relationship between rate of development and longevity lies in adaptations that have occurred through evolution at multiple levels of biological complexity: organism, organ, cellular and molecular. Thus, the analysis of the relationship is of interest for multiple fields of biology.

Keywords: development, growth rate, longevity, aging, senescence, IGF-1, caloric restriction, telomere, DNA damage.

Abbreviations: growth hormone, GH; Insulin-like growth factor type 1, IGF1; mechanistic target of rapamycin, mTOR; stress induced senescence, SIS; telomerase reverse transcriptase, TERT; caloric restriction, CR; DNA double strand breaks, DNA DSB;

Introduction

The trajectory of the aging process seems deeply rooted in the trajectory of development. We will review supporting evidence for this statement obtained through the comparisons between species or comparisons between individuals of the same species. Finally, we will list some research fields that have begun to provide mechanistic explanations.

1. Interspecies comparisons linking development with longevity

There are several lines of evidence linking development and longevity. It is a well-known fact that species with a greater body mass have a tendency to be long-lived. For example the bowhead whale is believed to live over 200 years, while elephants live up to 65 years [*for data referring to species longevity please refer to the AnAge database, unless other ways specified* [1]]. Even stronger facts supporting this link, however, come from less appreciated relationships: for example the relationships between longevity and the time to reach sexual maturity and between longevity and growth rate.

1.1 Interspecies comparisons linking body mass and longevity

Several reports suggest there is a relationship between body dimension of a species and maximum longevity. Body mass is positively linked to longevity among mammals and birds [2]. Similarly, a positive relationship is observed between maximum body length and longevity in fish, snakes, caudatans (salamanders and newts), and anurans (frogs and toads) [3]. Although evident, this relationship is not stringent and several taxa diverge notably from the common trend line.

A prominent evolutionary biology theory predicts that long life spans are selected for, when extrinsic mortality is low [4]. The large brain of primates, for example, is thought to allow life spans longer than that expected based on their body mass. The brown capuchin monkey, a primate living on tall tropical forest trees, has a body mass of only 2.6 Kg but a maximum longevity of 46 years; in comparison, the dog, usually much heavier, has a maximum longevity of 24 years. Despite its mouse-like size, the longevity of the naked mole-rat exceeds 30 years, making it the longest-lived rodent species. This extreme longevity is most likely due to its evolution in an underground environment which minimizes predation. The ability to fly is obviously a characteristic that dramatically changes the biological niche of a species and can reduce extrinsic mortality. Healy and colleagues have proposed that flight has an even stronger influence on life span than body mass in affecting the evolution of longevity [5]. This explains why bats are exceptionally long lived among mammals and birds' longevity exceed that of mammals of similar size. Among fish,

snakes, caudatans and anurans, when statistically controlling for size, the production of venom or becoming poisonous, was correlated with greater longevity, presumably due to the protection provided by these adaptations [3].

Among invertebrates, the relationship between longevity and body mass is not straightforward. Bivalves are highly studied from a gerontology viewpoint due to the wide variation in lifespan. *Arctica islandica* e.g., has been reported to be capable of living past 500 years. Ridgway et al., investigating 56 species, report a weak, although significant, relationship between maximum life span and asymptotic shell length [6], while a larger study involving 297 species reported no relationship [7].

1.2 Interspecies comparisons linking sexual maturity and longevity

De Magalhães and colleagues have defined t_{sex} as the sum of gestation time plus the time to reach sexual maturity from birth, and a relationship between longevity and t_{sex} has been clearly demonstrated, which is independent from body mass [2]. Primates and bats are not an exception in the t_{sex} analysis, although these species fall far from the trend line linking longevity with body mass. For example, t_{sex} for the brown capuchin monkey is 1861 days compared with 573 days for an average dog; t_{sex} for the little brown bat is 265 days, a period much longer than the 61 days needed by the heavier mouse. The naked mole rat also does not fall outside this relationship with its 298 days to reach sexual maturity from the day of its conception.

Female sexual maturity was positively related to lifespan post maturity in a large study examining over 700 species of birds and mammals [8]. Ridgway and colleagues, investigating 35 species of bivalves, reported that, even in this class of mollusks, sexual maturity is significantly related to adult life span [6].

1.3 Interspecies comparisons linking growth rate and longevity

Growth, in vertebrates, generally displays an asymptotic sigmoidal trajectory most often described by logistic, Gompertz or von Bertalanffy functions [9]:

$$\text{Logistic: } weight_{(t)} = A / (1 + Be^{-Kt})$$

$$\text{Gompertz: } weight_{(t)} = Ae^{-Be^{-Kt}}$$

$$\text{von Bertalanffy: } weight_{(t)} = A(1 - Be^{-Kt})^3$$

Where (A) is the asymptotic maximum weight, (B) is a biological constant and (K) is the growth rate.

It is generally observed that species having small body mass tend to have growth rates higher than species having large body mass; in other words, species with small body mass reach their maximum size faster (for mammals see [10]). Rapid growth can have positive effects: it can improve short-term survival and can increase reproductive success. Contrary to expectations, however, growth is not always the maximum possible and it is not simply dictated by resource availability; often animals grow at a lower rate than their theoretical maximum. This discrepancy indicates that rapid growth can be costly [11], and growth rate is, in fact, inversely related to adult life span. We will briefly review supporting data for this relationship looking at prenatal and postnatal growth when applicable.

Concerning prenatal growth, Ricklefs reported a positive relationship between growth rate of the embryo and the rate of aging in mammals and birds [9]; additionally, he reported an inverse relationship between gestation or incubation time and the rate of aging in mammals, birds and reptiles [12].

Regarding postnatal growth, an inverse relationship between postnatal growth rate and life span exists for mammal and birds [2]. Since the statistic assumptions of regression analysis used in these investigations assumes that each data point is independent, an analysis of phylogenetic independence was also necessary.

This scrutiny reinforces the inverse relationship between mammalian postnatal growth rate and longevity but weakens the same relationship in birds [2].

A specific example of the inverse relationship between development and longevity exists for two fish species of the genus *Nothobranchius* which differ greatly in the rate of development but not in maximal size (*N. furzeri* and *N. kunthae*). In these two species, longevity reflects the developmental rate, the slow growing species outlives the rapidly growing species by about 4 fold [13].

Bivalves, which follow a uniform developmental progression from the larval stage, differ from mammals in that growth rate is not related to asymptotic adult size [7]. Nonetheless, there is a robust negative relationship between growth rate and longevity in this class [7][6].

2. Intraspecies comparisons linking development with longevity

2.1 Intraspecies comparisons linking body mass and longevity

When one considers individuals within the same species, the relationship between body mass and longevity, which was positive among species, is now reversed. Within a species, heavier body weights usually correspond to shorter life span. This relationship has been reported in mice [14], [although not in inbred rats [15]] horses [16], dogs [17] and humans [18].

When examining these studies, it is important to note that body weight is influenced by past and present life conditions such as nutritional status and the level of physical activity, while body length is influenced primarily by nutritional conditions during development [19][20].

Several studies have examined the relationship between human stature and longevity, with conflicting results [19][18]. For example, Salaris and colleagues, concluded that a taller 70 year old person is expected to live two years less than a shorter coetaneous individual [21]. Other authors, however, have reported a positive relationship between height and lifespan in humans [22]. There are several factors which may contribute to the differences in these studies. One important parameter is gender: Brandts et al. have reported a positive correlation between height and longevity in woman but not in men [23]. Another factor which may influence the analysis is social status. Muller and Mazur claim that "*tall people, especially men, have an advantage in achieving high social status, leading to fewer health hazards and better medical care.*" [19], recommending that the study of populations in which social status factors are less variable be used for these analyses. An examination of one such cohort, military service man from two class years (1925 and 1950), found an increased mortality associated with taller height. Regarding these populations, it was noted: "*they comprise men highly screened for physical and mental fitness, subject to a healthy lifestyle, and medically well cared for. Height in this population had no effect on rank or income*". The study found that taller service man in the 1950 class showed a higher tumor incidence past 55 years of age. Interestingly, stature seems to impact chronic diseases differently. A large observational study of over one million people found an increased risk for cancer in taller cohorts but a decreased risk for coronary heart disease and stroke [22].

2.2. Intraspecies comparison linking sexual maturity and longevity

The Reproductive-Cell Cycle Theory of Aging suggest that hormones promoting growth and sexual maturity could also be responsible for accelerating aging, an example of antagonistic pleiotropy [24]. When conventional laboratory strains of mice were compared with strains derived from the wild, the wild derived strains tended to be smaller, reach sexual maturity later and generally appeared to be longer lived [25]. In humans, Tabatabaie et al., reported that long lived Ashkenazi Jewish exhibit delayed reproductive maturity [26].

2.3 Intraspecies comparisons linking growth rate and longevity

Rollo analyzed the relationship between maximal longevity and maximum adult mass in laboratory mice and rats, concluding that growth rate was negatively related with longevity in both species [27]. Consistent with this conclusion, mutations or gene deletions that negatively affect GH signaling not only reduced adult body size of mice but also delayed maturation. These animals appeared to be more resistance to stress, were generally healthier and displayed extended longevity. However no consistent effects on life span were observed in an examination of humans with similar mutations [28].

The inverse relationship between growth rate and longevity is well established in dogs. In a review dedicated to dog aging, Selman and colleagues state that “*large dogs grow faster and for longer than small dogs*” and, as mentioned previously, large dogs have shorter lifespans than small dogs [29].

A small number of studies have examined the relationship between developmental rate and longevity in *C. elegans*. Although early fecundity does not appear to impact longevity [30] an inverse relationship between longevity and developmental rate has been reported in a study of 16 wild derived strains. Interestingly, this examination failed to find this correlation also among individuals within a single strain [31].

Using fish, Lee and colleagues were able to artificially manipulate growth rate by controlling ambient temperature early in life. Catch-up growth resulted in a 14.5% reduction in median lifespan while reduced growth resulted in lifespan extension of 30.6% [32].

In humans, the analysis of birth weight in conjunction with adult mortality reveals a U shaped curve. When these data are analyzed separately for causes of death, birth weight appears positively and linearly linked to cancer mortality, while cardiovascular and all other types of death are still linked to birth weight in a U shaped fashion [33].

Low birthweight has been associated with an increased risk of type 2 diabetes mellitus and metabolic syndrome in both human and rodents [34]. In a British cohort of 2,547 girls, a high growth rate during childhood was associated with an increased risk of breast cancer [35].

In conclusion, there is supportive evidence that deviation from the normal growth trajectory, in either a positive or negative manner, can modulate disease susceptibility. Fast intrauterine growth seems to associate with increased cancer risk while slow intrauterine growth seems to associate with endocrine dysfunction. For a possible explanation see [36].

3. Endocrine, tissue, cellular and molecular correlates

In the first two sections of this review we have presented evidence that the relationship between longevity and body mass tends to be positive between species but negative within a species. This puzzling aspect of development is absent when we focus our attention to the speed of development. When considering time to sexual maturity or the growth rate constant K there is no discrepancy between interspecies and intraspecies comparisons. Slow development is consistently linked to greater longevity in both inter and intra species observations. Below we will propose some possible cellular and molecular correlates that may underlie this relationship.

3.1 Endocrine level

3.1.1 GH/IGF-1 and thyroid hormone signaling

The neuroendocrine axis regulates developmental rate, adult body size and is intimately related to longevity. Transgenic mouse studies confirmed that reduced GH signaling extends lifespan and generally support an inverse relationship between body mass and longevity [37], although the complexity of the neuroendocrine signaling axis makes it unclear whether GH, IGF-1 or insulin signaling has the greatest influence on longevity in mammals [38]. The relationship between body mass and longevity has been

explored in studies using mice harboring mutations affecting pituitary development, these studies display impairment in circulating levels of multiple neuroendocrine hormones, including GH and IGF-1. Ames dwarf mice, that harbor a mutation in the *Prop1* gene, are the mutant mice with the longest longevity. When these mice were treated with GH starting at 1 or 2 weeks of age for 6 weeks, their growth trajectory tended towards normal values and they sustained a reduction in their longevity [39].

Insulin-like growth factor type 1 (IGF1), the main effector of GH, is a major determinant of dog size. In order to achieve a greater body weight, large dogs grow faster and for longer periods [29] and a mortality curve analysis in dogs concluded that larger dogs have a shorter lifespan due to a relatively rapid rate of aging [40]. Conversely, a reduction in GH is almost always accompanied by a reduction in IGF-1; this makes it difficult to determine their independent effects on longevity, although there is some indication that GH has an IGF-1 independent role [41].

3.1.2 Nutritional interventions

Nutritional status modifies the endocrine landscape, which impacts cellular bioenergetics through distinct molecular pathways such as the target of rapamycin (TOR) pathway. Thus, the impact of nutritional status extends from the molecular to the endocrine level. The impact of nutrition on longevity will vary based on the timing of the intervention during the lifespan, for example during development or adulthood, and this makes the interpretation of the findings complicated.

In their seminal report, McCay and colleagues applied caloric restriction (CR) either immediately or two weeks after weaning, concluding that partial food deprivation prolongs life span by retarding rat development [42]. This started a prolific research area on the antiaging role of reduced nutrition that has clarified that CR retains antiaging effects also if started in adulthood, i.e. without slowing down development but only affecting thinness. These, mainly rodents, data, cumulatively, seem to suggest that thinness may be an avenue to longevity. We and others, instead, have come to the conclusion that there is now sufficient evidence to suggest the opposite view: it is obesity that directly accelerated the aging process [[43] and reviews cited therein].

3.2 Tissue level

Cortical neurons are post-mitotic cells whose abundance in the tissue seems to be linked to the length of development. In fact, the final number of neurons is significantly related to time of sexual maturity of the species [8]. The total number of cortical neurons declines significantly during aging, beginning in early adulthood [44] and ablation of hypothalamic neurons in young mice accelerated aging; while implantation of hypothalamic progenitor cells in mid-aged animals prolong their lifespan [45]. These observations suggest that tissue functionality is related to the number of functional cells and aging is accompanied by an increasing percentage of damaged and dysfunctional cells. It is possible that, if an extended development leads to a higher number of functional cells in key tissues, such as the cortex and the hypothalamus, there is a greater reserve to preserve function and extend longevity [8].

3.3 Cellular level

3.3.1 Cellular replicative capacity

Cells in different tissues vary in their replicative capacity, some are post-mitotic, many are quiescent, and a small fraction are actively proliferating. The growth characteristics of cells that retain replicative capacity can be compared *in vitro*. While some animal species display indefinite proliferative capacity in these cells, others display a finite replicative potential [46][47].

It has been hypothesized that the limited replicative capacity of cells (termed replicative senescence) may be a manifestation of aging at the cellular level [48]. However two fundamental corollaries of this assumption, the relationship of replicative capacity with 1) donor age and 2) species longevity, did not hold

up experimental validation [49]. For species that display replicative senescence, replicative capacity is positively linked to adult body mass [47] and it seems to be a species distinctive feature. In fact, although these measurements have been conducted only in vitro, in few cell types (mainly skin fibroblasts and muscle cells), using media that are probably non equally optimized for all species, the variability between replicates is small if compared to the variability observed across species [47]. Finally, replicative capacity is higher during development and lower once development is completed [49].

3.3.2 *Stress induced senescence (SIS)*

While the role in aging of the limited replicative capacity of differentiated cells has been questioned (see previous paragraph), much attention has been dedicated to the cellular senescence program itself. Although first identified as a response to telomere shortening, it is now clear that multiple types of stress, including the activation of oncogenes and mitochondrial dysfunctions, can induce senescence [50]. SIS is now considered an important contributing factor to the aging process. Interestingly, species that do not display replicative senescence retain stress induced senescence.

Senescent cells, which resemble oncogene-induced senescence, have been observed during embryonic development in chickens and mice, establishing a physiological role for senescence during development. We have obtained data supporting a role in development also for SIS. We observe that fibroblasts from long-lived species more efficiently activate SIS than shorter-lived species when challenged with equal levels of DNA damage. We have proposed that this represents an advantage during development where rapid cell divisions may increase the burden of DNA damage; see DNA damage paragraph below and [51].

3.4 Molecular level

3.4.1 *Telomeres*

The linear ends of chromosomes represent a fundamental problem for biology due to the inherent asymmetry of the DNA molecule. Telomeres represent a particularly fragile genomic location and tend to accumulate damage during aging. Also, they tend to shorten during chronological aging and their rate of shortening is inversely related to longevity in mammals and birds [52]. Unprotected telomeres trigger a DNA damage response leading to cellular senescence [53], which can accelerate aging.

The activity of the telomerase reverse transcriptase (TERT) responsible for telomere extension, is inversely linked with body mass, and telomere length is also inversely linked to species longevity, an important observation poorly considered in gerontology [54][46]. The above data clearly support a role for short telomeres concomitant with low or absent telomerase activity as an evolutionary strategy for longevity and cancer prevention.

3.4.2 *DNA damage*

A high rate of cellular proliferation requires a high rate of DNA replication. In human cells the accuracy of DNA replication is negatively correlated to the rate of synthesis [55].

Our studies have shown an exponential relationship between the capacity to bind DNA-ends (a measure of the capacity to detect double strand breaks, DSB) and mammalian longevity, which appears to be correlated to the relative abundance of the Ku80 protein [54]. Making these observations particularly relevant in this context is that we did not observe a meaningful relationship of this capacity with adult body mass, despite the fact that the evolution of large body mass would be expected to positively associate with increased genomic stability [reviewed in [56]]. We have also demonstrated, in fact, a relationship between body mass and a more efficient erythropoiesis in mammals [57].

In support of our initial observations on DNA-end binding, we subsequently observed a better capacity to form γ H2AX and 53BP1 foci in long-lived species [58][59]. The γ H2AX and 53BP1 proteins are believed to

represent independent molecular signatures of the presence of a DSB. There is extensive work on the relationship between enhanced DNA repair capacity and species longevity, however not all repair capacity may be equally relevant to longevity. Recent work, for example, shows that in rodents, DSB repair capacity associates with longevity while nucleotide excision repair associates with propensity for sun exposure [60].

We have already discussed the inverse relationship between long-lived species and telomere length, in addition Seluanov and colleagues have suggested that small and long-lived species that retain telomerase activity may have adopted another pro-longevity strategy: slow cellular proliferation [61]. A slow cellular proliferation should facilitate an error-free DNA replication and, in case damage occurs, also allow a better damage-recognition and handling. Handling unreparable damage could be accomplished via induction of apoptosis or senescence (see above paragraph on SIS). Of course, slow cellular proliferation imposes slow development, which is correlated with enhanced longevity as discussed previously.

Summary and Conclusions

We have reviewed the relationship between developmental pace and adult size considering both inter and intra species relationships. Although the interactions are not always straight forward, we believe that a fundamental relationship is quite evident: slow development is associated with longevity.

This notion points to time as a fundamental biological constraint. If we consider the seasonal variations of the environment, one can easily envision the time constraints placed on developmental processes by environmental pressure. The enormous migrations that are among the most spectacular event in biology are driven by the need to be at the appropriate place at the appropriate time. However, even removed from the biological niche, rapid development has a clear beneficial impact on reproductive fitness, creating a trade-off between reproductive fitness and longevity. In a reevaluation of the disposable soma theory of aging, we have proposed that the impact that this “time factor” has at the cellular level is a critical component of the evolution of species lifespan; time is the overlooked resource which must be allocated towards either reproductive fitness or somatic maintenance [62].

Our hypothesis is that a lower rate of development is associated with extended cell cycle time allowing more efficient damage surveillance and repair mechanisms to operate more efficiently. Fast growth carries a fitness benefit but, at the cellular level, it will negatively impinge on the efficiency of these cellular machineries. During development, this causes an accumulation of cells harboring unrepaired damage which will undermine the resilience of the soma and ultimately cause early aging.

In the second part of this review we have provided a list of research fields where this hypothesis can be evaluated and expanded. This list is most probably incomplete and we ask forgiveness to all the relevant literature that we have not included. Our opinion is that this list should and will increase with the understanding of the profound link between development and aging.

Disclosure Statement

The authors have no commercial or financial relationships that could be construed as a potential conflict of interest.

Funding Sources

This work was supported by RFO funding of University of Bologna to AL and National Institutes of Health/National Institute on Aging (Grant AG39799) to CS.

Author Contributions

SM and AL assembled the literature. AL wrote the initial draft of the manuscript. All authors contributed equally in implementing and revising the manuscript.

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