
Historical Aspects and Biology of Aging

Peter M. Nilsson

Department of Clinical Sciences, Lund University, Skåne University Hospital, Malmö, Sweden

Aging is a universal finding in humans, afflicting biological processes as well as maturation and deterioration of organ function. There exist a number of theories on how aging is programmed and develops as presented in gerontology, the science of normal aging. Not only the “wear and tear” hypothesis exists but also aging models dependent on the influence of oxidative stress, metabolic processes, and the accumulation of genetic damage on the DNA and impaired genetic repair functions [1]. Modern discoveries point to the role of longevity-regulating genes, so-called “gerontogenes” [2]. These gerontogenes are classified as lifespan regulators, mediators, effectors, housekeeping genes, genes involved in mitochondrial function linked to metabolism, and genes regulating cellular senescence and programmed cell death (apoptosis) [2]. Intensive research is directed to understand what regulates aging and how to control this, not at least apoptosis, of vital importance to understand organ development and changes in health and disease. The maximum lifespan recorded was 122 years for a French woman (Jean Calment, France, 1875–1977).

Even if it is very hard to disentangle the different influences on the aging process and to judge upon the accuracy of the different hypotheses to explain human aging in general, it comes natural to view aging in its evolutionary context as all aspects of human biology, and even cognitive function, are supposed to be influenced by evolutionary selection mechanisms during millennia perspectives.

EVOLUTIONARY TRAITS, GENES, AND THE ENVIRONMENT INFLUENCING AGING

From an evolutionary perspective the lifespan of mammals has been formed by selective processes based on genetic regulation of survival and reproduction in relation to available nutrition, environmental hazards, and competition for resources. According to the “*disposable soma hypothesis*” by Kirkwood [3] there exists a trade-off between maintenance of bodily functions, depending on energy investments, and the costs of reproduction, especially for women. This is why, according to this hypothesis, women with a higher number of offspring will be at increased risk for a shorter lifespan as compared to women with fewer offspring, if basal health and social conditions tend to be equal, as studied in British noble families over many centuries [4]. This is also influenced by nutritional resources, as reproductive capacity in women tends to cease during periods of famine and starvation.

Behind such traits there must be genetic regulators, as evolution works via genetic adaption and fitness in relation to a changing environment. A further support for the genetic influence on longevity is the family resemblance of longevity as well as risk of some chronic disease conditions that tend to run in families, that is, clusters of cardiovascular disease [5] and metabolic abnormalities. According to a number of studies the genetic explanation of longevity is approximately 25% [6]. This leaves a substantial proportion of longevity to the influence of environmental factors or to epigenetic mechanisms (gene–environmental interactions). It is still unclear if true life-prolonging genes exist in humans as in other less-developed organisms (*Caenorhabditis elegans*), or if a long lifespan is a marker of the less strong impact or lack of disease-related genes in some individuals. According to

environmental factors, there are many such detrimental factors well known to decrease lifespan, for example, smoking, infectious disease, and malnutrition, but the only environmental factor known to prolong life in mammals, at least in rodents and monkeys, is continuous calorie restriction [7]. This is believed to exert similar effects in humans but still not proven. Nevertheless some individuals have adopted a lifestyle based on calorie restriction and balanced physical activity, hoping for a prolonged life.

CHANGES DURING THE TWENTIETH CENTURY IN LIFE EXPECTANCY

There is no doubt that the rapid increase in longevity during the past twentieth century is an indication of the strong influence of environmental factors on human lifespan, reflecting better nutrition and housing, improved hygiene and conditions in early life, as well as the progress of healthcare and improved medical treatment, even if temporary setbacks have also been noticed, for example, in Russia during the 1990s [8]. The negative socioeconomic changes for many citizens in Russia during this period could be one component of the increased cardiovascular risk based on gene–environmental interactions in high-risk populations [9]. On the other hand, it is still necessary to understand the biology (and genetics) behind the aging process, as there are still many examples of differential aging also in developed countries. A proof of the role of genetic influences on aging and shortened lifespan are the rare conditions of Hutchinson–Gilford progeria in children and Werner’s syndrome in middle-aged subjects [10]. Even if these rare conditions are not possible to causally treat today, they represent an opportunity to learn more about biological changes taking place during the aging process, especially when it is upregulated in the progeria syndromes with shortened lifespan.

EARLY LIFE PROGRAMMING EFFECTS

Human life starts at the conception followed by a growth during 9 months in fetal life *in utero* when organs are formed and developed based on numerous cell divisions under genetic regulation. Nutritional factors are of great importance for this process, as mediated by the feto-placental unit and influenced by maternal dietary intakes. For more than 30 years now, researchers have documented the importance of fetal growth and birth weight for bodily development and health also in adult life. Starting with early observations from northern Norway by Forsdahl [11] and by Gennser [12] in Sweden, David Barker and many other colleagues developed a concept based on the detrimental health consequences of fetal growth retardation leading to the small-for-gestational age (SGA) phenotype in newborn babies. This condition in early life was associated with increased levels of cardiovascular risk factors (hypertension, dyslipidemia, and hyperglycemia) and even overt type 2 diabetes in adult life, but also with impaired neurocognitive developments and a number of other adverse health conditions, summarized in the so-called “Barker hypothesis” [13]. In more recent years a new paradigm has evolved with a focus not only on fetal growth and birth weight as outcomes but also on postnatal growth patterns. Of special importance for adult health is the combination of impaired fetal growth, causing SGA at birth, combined with a rapid catch-up growth pattern in the first few years of life. This has been named the “mismatch” growth pattern when different organs are programmed *in utero* for a life with scarce resources and calorie depletion but later on the newborn child will experience the opposite, an environment with a surplus of calories and nutritional abundance. This may negatively impact on organ development and increase the risk of cardiometabolic disturbances in adult life. The most well-known protagonists of the “mismatch” hypothesis today are Peter Gluckman and Mark Hanson, with important reviews on the topic [14]. They are both active in the “Developmental Origins of Health and Disease” (DOHaD) society, to further explore the mismatch hypothesis.

An even more recent hypothesis of early life programming of adult disease risk is linked to the impact on child gut microbiota from the mother during delivery [15], as a detrimental gut microbiota pattern could be one factor increasing the risk of obesity in adult life and adverse health conditions such as cardiovascular disease [16] and type 2 diabetes [17]. It is believed that the mother’s gut bacteria will normally colonize the gastrointestinal system of the newborn child and that this will protect from overgrowth of more deleterious skin bacteria that could be associated with later disease risk [15].

It is likely that such influences in early life from nutrition, growth patterns, and microbiota patterning could also impact on aging in general and/or age-related medical conditions. These include not only defined chronic disease but also the increasing frailty, that is, related to sarcopenia and osteoporosis in old age, as well as cognitive decline [18]. Newer studies on the life of centenarians have also highlighted the role of early life influences, for example, the longevity associated with being born to younger mothers (first-born) when siblings within the same family are compared [19]. There also seem to exist large gender differences found in longevity determinants for males and females, suggesting a higher importance of occupation history for male centenarians as well as a higher importance of home environment history for female centenarians [19].

VASCULAR AGING IN PERSPECTIVE

What implications do these observations have for the concept of early vascular aging (EVA) with increased arterial stiffness as a central characteristic [20]? First of all, EVA is likely to be an expression of biological aging in general and some of the mechanisms regulating aging in other organs must also be applicable to the vascular tissue, especially in the arterial wall. This is believed to be possible to estimate by measuring leukocyte telomere length (LTL), a proposed marker of biological aging as LTL tends to shorten with every cell division. However, in a large population-based study, the Asklepios study in Belgium, no association between pulse wave velocity (PWV), a marker of arterial stiffness as the core characteristic of EVA, and LTL was seen in a cross-sectional analysis [21]. On the other hand, some associations were seen with cardiac function, which is why the authors concluded that in a generally healthy, young to middle-aged population, LTL is not related to left ventricular (LV) mass or systolic function, but might be associated with an altered LV filling pattern, especially in women. The Asklepios study purposefully selected healthy individuals for screening.

The findings of this large and more recent Belgian study contradicts earlier observations from a smaller French study [22], when it was concluded that LTL provides an additional account to chronological age with regard to variations in both pulse pressure and PWV among men, such that men with shorter telomere length are more likely to exhibit high pulse pressure and PWV, which both are indices of large artery stiffness (arteriosclerosis). The longer telomere length in women of that study suggests that for a given chronological age, biological aging of men is more advanced than that of women [22].

How to resolve these contradictory findings? It is believed that cross-sectional analyses of LTL in relation to organ function is probably not enough. Of even greater importance could be to evaluate relationship with telomere attrition rate based on repeated measurements of LTL over a time period. Few studies have applied this more laborious and costly method, and this is why more studies are needed with precise methods for measuring LTL and also attrition rate over time [23]. Before such data are available it is hard to judge on the true relationship between LTL and telomere biology, as a marker of aging, and arterial stiffness representing vascular aging. On the other hand, there are numerous studies to show associations between shorter telomeres and vascular disease based on atherosclerosis, as recently summarized [24].

NEW MODELS AND INTERVENTIONS TO INFLUENCE AGING

If a deeper understanding can be achieved of the aging process in general, with its vascular implications, this could also lead to the establishment of new experimental models to test the reversibility (if any) of these processes. Molecules that suppress these age-related changes would provide an excellent medical intervention target for vascular disorders. Mammalian Sir2 (SIRT1, a NAD⁺-dependent deacetylase), previously shown to extend the lifespan of lower organisms, is a promising target molecule to influence some aspects of vascular aging. The influence of SIRT1 in various pathophysiological processes of vascular aging has been summarized and Wang et al. proposed that SIRT1 and its activators can become novel therapeutic targets for age-related vascular disease [25]. Time will tell if this intervention model will be able to shed new light on the aging process in general and vascular aging in particular (Table 1.1).

TABLE 1.1 Some Factors of Importance to the Shaping of Human Aging and Longevity

Genetic programming, based on evolutionary selection
Epigenetic influences (gene – environmental interaction and imprinting)
Early life programming (nutrition, growth rates, neurocognitive function)
Family patterns (sibling rank, age of parents, shared microbiota)
Adult lifestyle (smoking, nutrition, physical activity)
Telomere biology
Health problems and disease
Medical treatment and interventions
Societal factors and social support
Secular trends

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