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Review Article

Aging Is Selected For, Adaptive and Programmed: The Eco-Evo-Devo Theory of Aging

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Abstract

Immortal, infinitely reproducing organisms, aka Darwinian demons, claiming the majority of resources, would severely undermine the fitness of offspring. Evolution co-selected fertility and longevity, linking births to deaths and creating various trait correlations, e.g., the fast-slow continuum of life history strategies. Importantly, these correlations and trade-offs are modulated by resource availability and acquisition. The ecological conditions-dependent semelparity-iteroparity plasticity and continuum highlights the programmed nature of both reproductive modes and reproduction-related death pathways. Parental effects, as transgenerational indirect genetic effects, and eco-evolutionary feedback underlie the aging-related action of multilevel selection.

Aging trajectories are determined by energy budgets, reproductive activity and stress responses. Evolution "appointed" the germline cells, the prospective individuals of the next generation, as guardians of limited resources and mediators of population regulation. In this capacity, beginning at reproductive maturity, signals of germline cells more or less gradually degenerate parental immune competence, undermine stress response pathways and proteostasis, and derange mitochondrial energy homeostasis. Moreover, the reproductive activity of organisms limits itself, restricting the number of offspring depending on ecological births-deaths balance.

The soma is not defenseless. Longevity is correlated and co-selected with somatic stress response capacity. Aging is a survival program of the soma, resisting germline-imposed death. Throughout phylogeny, metabolically stressed organisms downregulate metabolic rate by means of insulin resistance and store rather than use nutrients. In this legacy, aging organisms activate the metabolic stress program and inflammatory defense. The somatic hypometabolic-hypoxic reprogramming adjusts oxygen supply to metabolic demands. The aging organism downregulates vasorelaxant gasotransmitters, while atrial natriuretic peptide becomes resistant. On the other hand, a variety of vasopressor agents are upregulated including type 5 phosphodiesterases. This results in increased vascular tone, reduced tissue perfusion, tissue hypoxia, and, eventually, hypertension and atherosclerosis. However, the survival factors are incapacitated during the course of aging so that the soma is caught in a dead-end trap.

Introduction

The major goal of ecological evolutionary developmental biology, also known as "eco-evo-devo," is to uncover the rules that underlie the interactions between an organism's environment, genes, and development and to incorporate these rules into evolutionary theory [1].

Aging is one of Michael Brooks' "13 things that don't make sense" [2]. "Why Do We Age?" is one of Sherratt & Wilkinson's "Big questions in ecology and evolution" [3]. And Josh Mitteldorf noted: "...we must acknowledge a crisis for evolutionary theory. There is a deep disconnect between predictions and experiment. [...] This is not an artifact that can be accommodated with a tweak of the theory or a footnote in the textbook. To reconcile the phenomenology of aging within evolutionary theory will require new foundations, new mechanisms, a fundamentally different model." [4].

Evolution is a basic science for medicine [5]. Age is by far the single biggest risk factor for the majority of complex age-related

diseases [6]. For some time, physicians thought that aging looked like being programmed. However, for 70 years, the so-called "evolutionary theories of aging" (ETAs, i.e., mutation accumulation theory [7], antagonistic pleiotropy theory [8], disposable soma theory [9] that are more complementary than mutually exclusive, shaped thinking in evolutionary biology and gerontology. The basic assumption, shared by all three theories, is that aging is caused by the declining strength of natural selection with increasing age. In consequence, aging is considered haphazard, not selected for, maladaptive, and not programmed [10]. Rooted in population genetics, the hypothetico-deductive ETAs were deeply entrenched in theory some time before there was evidence to back them up and "they have been adopted as gerontology's paradigm largely by default (due to the lack of alternatives) rather than for any compelling evidential reasons" [11]. The ETA proponents have made attempts to school the "ignorant" (particularly biologists and medical professionals) in the "odd science of aging" [12-15]. Yet, a systematic survey among participants of a symposium on the Biology of Aging revealed a marked disagreement on the most fundamental questions in the field, and little consensus on anything other than the heterogeneous nature of aging processes [16]. Areas of major disagreement included what participants viewed as the essence of aging, when it begins, whether aging is programmed or not, whether we currently have a good understanding of aging mechanisms, whether aging is or will be quantifiable, whether aging will be treatable, and whether many non-aging species exist [16].

In 2002, I introduced and, in 2012, elaborated on a theory of aging that I called the "germ-soma conflict theory" [17,18]. In a comprehensive approach [19], integrating a huge number of scientific publications on the topic (of which more than 21,000 have been referenced in this series of works), I have extended the concept and present compelling evidence that aging/death is programmed and is co-selected with reproduction in a multilevel-selective, ecological-evolutionary, adaptive process. This is a synopsis of this comprehensive work dubbed the eco-evo-devo theory of aging. Here, I can only give a rather general outline and a minimum of references. For an in-depth understanding of the ecological forcing and evolutionary rationale of aging/death and its co-selection with reproduction the lecture of the series of the other 30 papers is recommended. Due to the biomedical impact of this theory, I address this series of papers to both ecologists, evolutionary biologists, biologists and physicians/gerontologists. Elaborating the eco-evo-devo basis of aging and longevity, I advocate a threefold change of perspective or frame of reference: (1) from a replicator perspective of natural selection to an interactor/replicator perspective; (2) from an evolutionary, autonomous-individual, perspective to an ecological-evolutionary perspective; and (3) from a parent/soma-centered perspective to a transgenerational germline-soma conflict perspective.

The ecological theater and the evolutionary play

The relationship between evolution and ecology is aptly summed up in [20] metaphor 'The ecological theater and the evolutionary play' [21]. The birth and death processes of individuals are a common object of study of both subjects, and there is a wide recognition that a synthesis of the relevant areas of population ecology and evolutionary genetics is needed to inject an ecological basis into evolutionary theory [21]. A logical structure of this article would be to first build the ecological theater and then let the evolutionary play unfold. But since the evolutionary play is perceived as product of evolutionary neglect [22] and is questioned by the ETAs in the first place, I decided to elaborate the signatures of natural selection first and build the ecological theater in a second, the evolutionary play in a third, and the eco-evolutionary feedback in a fourth step.

Evolutionary signatures in aging

The ETAs maintain that aging is not selected for but is rather a product of evolutionary neglect, not evolutionary intent [22]. In this chapter, I present evidence for the action of natural selection in the evolution of aging.

Natural selection is a two-step process

The ETAs are based on a replicator aspect of natural selection. However, decades of scientific work have established that natural selection is a two-step process in which an individual's interaction with its environment occurs in such a way that reproduction becomes differential (the Hull-Dawkins distinction between interactors and replicators) [23]. Due to this dual process, natural selection is both a process and its outcome. Individual organisms are interactors with a stochastic environment, both being affected by, and affecting, their abiotic and biotic environment. In a world of limited resources, evolution by natural selection has zero-sum dynamics, a situation in which one individual's gain is matched by other individuals' loss. For instance, mating success due to competition for limited reproductive resources is a zero-sum game [24].

Signatures of aging-related natural selection

A multitude of genetic and life history characteristics witness the operation of natural selection in the causation of aging [25]. 1. The phylogenetic conservation of genes, noncoding microRNAs, transcription factors and signaling pathways that regulate longevity is a signature of strong negative (purifying) selection. The evolutionary importance of a protein site under purifying selection is typically measured by the degree of conservation of the protein site itself. 2. A multitude of quantitative trait loci studies have identified genomic regions associated with senescence/lifespan regulation in plants, C. *elegans, Drosophila,* mice, and humans. 3. In various *Drosophila melanogaster* populations, the McDonald–Kreitman test suggested adaptive evolution and positive or

balancing selection in protein-coding sequences related to longevity. 4. Linkage disequilibrium for genes linked to longevity has been demonstrated in D. *melanogaster*, mice, and humans. 5. Signatures of positive selection and coevolution suggest reptile (including birds)- and mammal-specific interactions between members of the insulin/insulin-like growth factor-1 and target of rapamycin (TOR) signaling network and other aging-relevant processes, like cellular respiration, metal ion homeostasis, inflammation and the antioxidant defense. 6. The signatures of positive and negative selection with regard to longevity are particularly evident in mitochondrial DNA. 7. If many alternative paths connect a regulator to its target gene, a loss of function in one of the intermediate regulators may be compensated by one of the alternative pathways through the network [26]. This phylogenetically conserved network architecture regulating longevity can only be explained by the workings of natural selection. 8. A multitude of cellular, cell-nonautonomous, apoptosis- and senescence-related transcription factors and mediators control organismal senescence. 9. Senescence is affected by a degenerate system that is both necessary for, and an inevitable outcome of, natural selection. 10. Antagonistic pleiotropy, or fitness component trade-off, is clearly a case of opposing selection. 11. Allometric relationships result from the regulation of scale and proportion by strong natural selection and have a genetic basis. In addition to the allometric relationship of body size to maximum lifespan, life expectancy and age at maturity are correlated. 12. Artificial selection experiments with D. *melanogaster* 1) confirmed the relationship between age at maturity/first reproduction and longevity, 2) demonstrated that delayed reproduction was causally involved in the retardation of aging, and 3) displayed the genetic signatures of longevity selection.

Aging is shaped by the life-long action of natural selection

Life-long environmental interactions impact on aging trajectories irrespective of the pre-or post-reproductive status of an organism [27]. Increased developmental growth rate is often associated with reduced longevity, the "growth-senescence" trade-off. Experiencing adverse conditions during early life is associated with an earlier reproductive aging, reduced adult survival and an increase in morbidity from many different sources, even if the adult environment is benign [28].

Since fitness is a transgenerational concept, the fitness of parents is dependent on the fitness of offspring. The Negative Senescence Theory posits that natural selection forces can be effective in postreproductive individuals when intergenerational transfers take place. Parents can have positive fitness consequences for offspring in terms of parental care and transfer of resources during the period of altriciality and beyond. However, a post-reproductive organism can interact with offspring and conspecifics both ways by transferring and competing for resources. It can be shown that there is no such thing as a post-reproductive "selection shadow". Parental care in semelparous organisms benefits predominantly the fitness of offspring at a cost to the parents but must have been selected for before the transfer of genes in the one-time reproductive event. Thus, the fitness interests of the offspring determine the post-reproductive behavior of parents. Non-feeding adults occur in various groups of animals, most notably holometabolous insects [29]. At any rate, the non-feeding adult phenotype, limiting adult longevity, is selected for at the juvenile, larval stage. Thus, both pre-, peri-, and post-reproductive selective forces shape the life history of individuals.

Natural selection formed the antagonistic pleiotropy in aging and the co-selection of fecundity and longevity

Correlational selection is common in nature and is probably a central force acting on the integration of traits and leading to their coadaptation [30]. Trait correlations, associated with differences in fitness outcomes, can be created and altered in strength and directionality by correlational selection [31]. Pleiotropy is context-dependent, is able to maintain genetic variation in populations, can promote evolvability, and, due to its network architecture, provide robustness. Antagonistically pleiotropic genes are the genetic basis for fitness trade-offs. In its broadest sense, antagonistic pleiotropy can refer to any form of genetic trade-off between fitness components, whether these components are expressed in the same or different individuals within a population. Epigenetics refers to hereditable modifications that are not a result of changes in the DNA sequence. Life-cycle transitions often depend on the pleiotropy of genes that is orchestrated by epigenetic regulation of gene expression. Epigenetics play a major role in the initiation and regulation of reproductive development.

Trade-offs represent the costs paid in the currency of fitness when a beneficial change in one trait is linked to a detrimental change in another [32]. Trade-offs resulting from conflicting selection pressures have played a central role in the development of life history strategies [33]. Survival and reproduction can vary positively, negatively, or not at all, depending on the variation in resources acquired among individuals [34]. Comparative studies of life history traits in a variety of taxa identified various correlations between features of reproductive activity and longevity, the "fast-slow continuum". Reproductive activity and aging trajectories are integrated by huge gene and signaling networks and co-regulated by neuroendocrine mediators. Evidence for a fecundity-longevity trade-off is based on 1) artificial selection for late reproduction causes lifespan extension; 2) reproductive maturation and aging trajectories are accelerated by increased extrinsic mortality; 3) removal of germline cells or inhibition of their signaling extend the somatic lifespan; 4) age at reproductive maturity and adult lifespan are linked by a 'life-history invariant'.

The ecological theater

... for it is evident that when one or more individuals have provided a sufficient number of successors, they themselves, as consumers of

nourishment to a constantly increasing degree, are an injury to those successors. Natural selection therefore weeds them out, and in many cases favors such races as die almost immediately after they have left successors [35].

Discovering the biological basis of aging is one of the greatest remaining challenges for science. Work on the biology of aging has discovered a range of interventions and pathways that control aging rate. A picture is emerging of a signaling network that is sensitive to nutritional status and that controls growth, stress resistance, and aging [36].

Limited resources are the fundamental raison d'être of natural selection and of evolution. Aging/death can only be understood from a joint ecological and evolutionary, an eco-evo, perspective [18]. Populations have the potential to grow exponentially but this is confronted with the limited nature of resources. In fact, that populations outgrow resources was the central idea of Malthus's *An Essay on the Principle of Population* (1798) that led Darwin to the conclusion that this pressure, analogous to breeder's artificial selection, was a natural form of selection. The limitation of resources is a pervasive feature in ecological communities and competition for scarce resources is a source of conflict and strong co-evolutionary force. Natural selection favors those individuals who compete best for scarce resources and can use them most economically [18].

The ecology and genetics of aging-related adaptation

"Gene x environment" interactions determine the structure of longevity patterns [37]. Adaptation has an ecological causation and genetic basis. The costs of adaptation have to be paid because resources allocated to one structure or function are not available for other ones or specialization of a feature leaves it less able to perform a variety of tasks [38]. Long-lived mutant organisms pay a price in terms of fitness costs and are outcompeted by wild-type conspecifics in their natural environment. $p66^{Shc}$, a conserved vertebrate protein, enhances cellular ROS production. Under lab conditions, the deletion of $p66^{Shc}$ in mice prolongs lifespan and induces resistance to obesity, atherosclerosis, ischemic injury, and diabetes. However, under natural conditions, deletion of $p66^{Shc}$ was strongly counterselected, causing defects in fat accumulation, thermoregulation, and reproduction, and suggesting that $p66^{Shc}$ has been evolutionarily selected because of its role in energy metabolism in the wild [39]. The ecological basis of aging and longevity is epitomized by iteroparity-semelparity transitions that depend on genotype x environment interactions. The plasticity of semelparous and iteroparous reproduction strategies that is illustrated by a multitude of examples, suggests that semelparity and iteroparity, rather than representing a simple dichotomy, are opposite ends of a continuum of life history strategies [18].

Ecological-evolutionary population regulation

Exogenous processes are density-independent in that they do not return a population to a stable equilibrium, whereas endogenous processes are density-dependent and promote reduced growth and numerical stationarity around an equilibrium population size [40]. Extrinsic factors such as food, habitat suitability, predation, parasitism, environmental fluctuations, or catastrophes are all potential sources of density limitation [41]. There is overwhelming evidence that intraspecific competition is a strong selective force, giving rise to a variety of innovations. Competition for limited resources may result in disruptive selection that can lead to reciprocal fitness outcomes in a zero-sum game. A multitude of processes target to maintain and economize the population's resource base: (1) The competition between same-species individuals may induce self-thinning that is observed in crowded plant and animal populations as a result of intraspecific competition and plays an important role in determining population dynamics and community structure [42]. (2) Negative feedback can be generated by a variety of mechanisms, including metabolic rate that can vary considerably within an individual or species depending on activity level and resource availability. (3) Site-dependence is a resource-economizing mechanism. (4) Competition for resources generates biodiversity such as heterogeneity, temporal and spatial diversity. (5) Resource partitioning through ontogenetic niche shifts with and without metamorphosis is thought to enable population growth by reducing intraspecific competition between life history stages. (6) Dispersal (immigration, emigration) contributes to the change of population size in open populations [43]. (7) Cannibalism is a well-documented phenomenon in many animal species, is often density- and food-shortage-dependent and is a major cause of mortality in these species.

Population regulation by density-dependent fecundity/longevity trade-offs

When competitive interactions occur, the expression of a resource-dependent phenotype, for example, growth and body size, in any focal individual will depend on the extent to which its resource acquisition is decreased by its competitors [44]. Density-dependent feedback could be important factors in reducing the intensity of conflicts [45]. Population stability is usually thought of as being tightly linked to the persistence of the system. Density-dependent effects that may be masked under benign conditions can become manifest under harsher conditions. The main pathway by which density affects demographic parameters is via individual body mass.

It makes little evolutionary sense to consider aging/death independently of reproductive activity. Density-dependent individual juvenile survival and growth has been demonstrated in a number of invertebrate and vertebrate systems. Populations which undergo high larval/juvenile mortality subsequently may experience higher adult survival than cohorts not subjected to high density-related selection early in life [46]. Fecundity is related to resources, and thus to body size and survival and has been

recognized as a strong determinant of population dynamics for a broad range of taxa [47]. Age at maturity and adult lifespan are closely associated with a population's intrinsic rate of increase. How long an individual life is not as important to a population's demography as the number of years it reproduces. There is strong evidence that age at maturity is density-dependent in a multitude of taxa and is pivotal because individual fitness is often more sensitive to changes in age at maturity than to changes in any other life history trait [48]. Costs of reproduction may be density dependent. Population density and fecundity are inversely correlated in a multitude of animal populations [49]. Population density is an important determinant of reproductive rates including skipped reproduction in many taxa. Population regulation through density-dependent reproductive senescence and somatic senescence is broadly observed in natural and experimental systems across a range of organisms. Factors including lower resource availability, higher consumption, and lower dispersal range are associated with the evolution of shorter lifespans [50]. The reproductive of eusocial insects outlive most solitary insects, and both queens and reproductive workers live much longer than their non-reproducing nestmates. This astounding association of high reproductivity with long lifespan obviously represents a challenge to life history theory that predicts the typical trade-off between fecundity and longevity known from many solitary species of sexually reproducing metazoans [51]. Eusocial insects can decouple the fertility/longevity trade-off due to a different 'wiring', i.e., changes in the regulatory architecture of hormonal networks, probably by means of epigenetic factors. Intriguingly, colony lifespan, as approximated by queen lifespan, scales with colony mass in the same way as lifespan scales with body mass in unitary insects [52].

Intrinsic aging, affecting both reproductive and somatic aging, is a major factor of population regulation. Extrinsic mortality is to a significant extent a sequel of intrinsic aging that renders organisms more vulnerable to predation, immunosenescence-related infection, and harsh weather conditions. According to statistical computations derived from animal demographics, between 2% and 78% of deaths are due to senescent decline, with the higher percentages in long-lived species. Extrinsic mortality does not cause but shapes intrinsic mortality indirectly through its effects on the intensity of competition depending on multiple parameters, including food availability, population density, the type of extrinsic mortality, and, more broadly, ecological conditions.

Eco-evolutionary bottom-up and top-down feedback and feedforward controls

Regardless of their nature and complexity, all control systems ultimately rely on two basic strategies, that is, feedback and feedforward control. [...] While feedback controllers can flexibly respond to disturbances and changes in the system after they have occurred, they are intrinsically unable to anticipate them. When disturbances can be anticipated (or ignored altogether), feedforward or open-loop control becomes an effective option, allowing for improved robustness and the reduction or elimination of response delay [53].

Ecosystem hierarchies are regulated by an array of biotic and abiotic factors that often are classified as either bottom-up or top-down processes: whether the population is regulated from below, by its food supply, or from above, by its enemies [54]. Empirical evidence from a wide range of ecosystems provides unequivocal evidence that both resources and consumers interact in a multilevel 'both way' causation to shape natural populations, communities, and ecosystems. Top-down trophic cascades tend to be stronger in aquatic than terrestrial ecosystems. The strong top-down regulation through extrinsic mortality may be linked to negligible senescence in some aquatic invertebrates (e.g., *Hydra vulgaris* and sea urchin *Strongylocentrotus franciscanus*) and terrestrial plants. In plant communities, the balance of top-down and bottom-up forces varies over environmental or productivity gradients and the context-dependence of herbivore top-down effects [55]. Effects of local density can vary between top-down and bottom-up interactions and among life stages [56]. Genes essential for viability and, particularly, metabolic pathways play a central role in the regulation of aging at any stage in life and are phylogenetically highly conserved. Thus, public (bottom-up) and private (top-down) mechanisms of aging reflect the dual control of aging.

Anticipatory systems in predictable and unpredictable environments

Evolution is 'far-sighted' [57]. Mimicking evolutionary processes by using algorithms, evolutionary computation is able to predict/anticipate the future by learning from the past. In biological systems, memory is deposited in genomes and gene regulation networks that are both the selection-imprinted genetic memory of past environments. Feedforward and feedback mechanisms serve complementary roles; feedback serves to correct for the inevitable uncertainty in feedforward control. In evolution, the feedback loop occurs through Charles Darwin's natural selection-mediated preferential reproduction of the fit and Alfred R. Wallace's elimination of the unfit [58]. Feedforward mechanisms rely on external cues and allow organisms to anticipate, prepare or prime themselves and/or their offspring for environmental change [59].

Anticipatory systems differ in predictable and unpredictable environments. By adaptively adjusting the phenotypes of their offspring to suit future environmental conditions, parents may increase their own and the fitness of their offspring. The natural world is full of rhythms making it predictable. Organisms have evolved to anticipate the environmental changes related to these rhythms. Long-term timing mechanisms that allow organisms to anticipate environmental events months or years in advance and to optimize survival and reproductive success are widespread in nature [60]. When environmental conditions fluctuate, strategies

may be superior that are inferior under constant conditions [58]. It is in the nature of things that unpredictable, stochastic environments should elicit stochastic responses, as predicted by Ross Ashby's "Law of Requisite Variety", even at the risk of being not adaptive in specific cases. Maternal bet-hedging is the anticipatory response to uncertain information and the population-level insurance against idiosyncratic risk. Anticipations may be less accurate in more stochastic environments and the environmental harshness determines whether lotteries may have fewer or more winners. Both theoretical and experimental approaches demonstrated that in the face of variable and unpredictable environments, bet hedging that 'covers all bases' is the evolutionary stable strategy [58]. Conservative diversified or mixed bet-hedging strategies evolved to strike a balance between various ecological, individual and species-specific factors.

Feedforward control and transgenerational transmission of stress-related information

When the phenotype of a focal individual is affected by genes being expressed in another individual with whom it is or has been interacting, for example, when individuals respond to the behavior of another individual by changing their own behavior, these effects are known as indirect genetic effects (IGEs) [61]. In contrast, direct genetic effects (DGEs) reflect the effect of the focal genotype on the expression of traits in the focal phenotype [62]. Because competition is widespread and likely to influence trait expression, it seems probable that an antagonistic relationship between DGEs and IGEs is common [63]. In resource-limited environments, fitness is zero-sum, so that any gain by one individual causes its competitors to lose, hence there is a negative DGE-IGE covariance for fitness [64]. Parental effects are the influence of the parent's genotype or phenotype on their offspring over and above the direct effect of transmitted genes. Transgenerational parental effects use some aspect of phenotypic condition in the parental generation to maximize fitness in the offspring and are likely to evolve if parents can process environmental signals more accurately than the offspring generation [65]. Zaternal genetic effects are a well-known example of IGEs. Conditions of stress, particularly early-life metabolic stress, seem to be important as inducers of parental effects.

Phenotypic plasticity is the ability of a genotype to produce different phenotypes in response to or anticipation of distinct environmental conditions [66]. In most organisms, genetically identical individuals develop markedly different phenotypes when exposed to different environments and such plastic modifications of morphology, physiology, life-history or behavior have been frequently shown to be adaptive, yielding increased fitness returns under specific conditions [67]. Competition and plasticity may interact to pave the way for the evolution of complex, novel phenotypes [68]. The "plasticity-first" hypothesis proposes that novel traits arise initially from variants produced via plasticity in a new environment, which are then subsequently refined by adaptive genetic evolution, with "genes as followers, not leaders, in adaptive evolution".

Epigenetics is closely linked to environmental conditions and mitochondrial bioenergetics and connects the genome to its environment. Environmental information, which is detected and processed through parental sensory systems, can modulate lifespan of offspring by providing information about the presence and quality of food as well as presence and density of conspecifics and enemies [69]. Certain metabolic pathways are epigenetically controlled, revealing a tight crosstalk between metabolism and epigenome. Empirical evidence points to the occurrence of non-genetic mechanisms of inheritance in all taxonomic groups that can modulate a broad range of phenotypic traits, particularly aging trajectories and aging-related disease risk [70]. Alteration of epigenetic states triggered by stressful experience can be transmitted across multiple generations, breaking the Weismann barrier [71]. Particularly, inter- and transgenerational effects of metabolic stress on morbidity and/or lifespan were observed in a variety of taxa. A multitude of mechanisms may convert reversible epigenetic changes into stable epigenetic and genetic transgenerational effects [49].

The evolutionary play

Aging/death trajectories are driven by three axes: metabolism/resource utilization, gonadal signals, and stress response pathways. All three axes converge at the gonadal signaling axis, mediated by the energy-costly reproduction, the germline-signaling induced repression of the stress and immune response, and the self-limited reproductive activity. Importantly, germline cells control the longevity of the soma from 'within' by a variety of signals, e.g., gonadal hormones that limit the reproductive potential and drive a variety of aging pacemakers, particularly the senescence of the immune system and the pineal-hypothalamic-pituitary-gonadal feedback loop [18].

The energy budget of reproduction and aging

Energy is the fuel of life [72]. Life history is largely driven by resource limitations and energy allocation trade-offs. The Darwinian demon concept implies that high reproduction and survival cannot be attained simultaneously – they compete for limited resources and entail direct and indirect costs to each other [18]. The evolutionary signature of resource limitation and its persistent selection pressure for energy-efficient solutions can be found both at the micro- and macro-evolutionary level. Energetic pressures constrain the resource budget within which organisms that compete for limited resources have to reproduce. The Dynamic Energy Budget theory, which characterizes the uptake and use of energy by living organisms, is a useful tool to explain the complex inter-relations between body mass, energy dynamics and life expectancy [73]. The allometry of life history components

constrains an extensive web of scaling relationships, ranging from density, body size, metabolic rates and growth rates to lifespans. It is generally accepted that there is a strong relation between energy metabolism and aging and that many processes regulating energy metabolism also influence the aging process. Dietary restriction, for example, has been reported to increase the lifespan of a wide range of organisms. Such a link is also supported within the main theories for aging: the "free radical theory of aging", for instance, links oxidative damage production directly to energy metabolism [73]. The "rate of living" hypothesis and "pace of life" theory also link metabolic rate and longevity. Individuals that exhibit 'fast' phenotypes are expected to allocate more into current reproduction and acquire more resources to fuel this investment, whereas 'slow' phenotypes are predicted to allocate more into future reproduction [74]. The disposable soma theory postulates that the respective energy allocated to reproduction and somatic maintenance underlies the evolutionary process of aging. Intriguingly, however, the disposable soma theory fails to predict the fecundity-longevity trade-offs under both scarce- and abundant-resource conditions, and the lack of a fecundity-longevity trade-off in eusocial queens.

The germline-soma conflict

No general property of organisms is of value in evolution under all environmental circumstances, everything is context-dependent [75]. Cooperation and competition can be treated not as polar opposites but as points on a continuum of antagonistic-mutualistic interactions. The direction of an interaction may be antagonistic under one set of ecological conditions, yet neutral or beneficial under alternative conditions [76]. The balance between costs and benefits is strongly condition-dependent, with systems potentially shifting back and forth on a mutualism-parasitism continuum [77]. The parent-offspring conflict over the level of parental investment in offspring characterizes the fetal-maternal interactions in viviparity and parental brood care. Parent-offspring co-adaptation occurs because individuals adapt to the parental supply when they are offspring and to the demand they inherit from their own offspring when they are parent [78].

Darwinian principles of variation and selection can be extended to sub-organismal entities. Organisms are coevolutionary battlegrounds with cell competition, mitochondrial selection, mitonuclear coevolution, interlocus contest evolution as genetic signature of sexual conflict, soma-fetus parasitic/symbiotic relationship, and the germline-soma conflict. The ontogeny of most organisms is marked by a series of transitions (life cycle transitions or life-history transitions) between stages (e.g., hatch, metamorphosis, reproductive maturation), each of which can be characterized by the age and size at which they occur and the conflicts they create [79]. Metamorphosis allows insects to develop in separate niches and to partition resources. Resource partitioning mechanisms minimize niche overlap between competitors and may have contributed to the exceptional evolutionary success of holometabolans. Generally, competition in nature is asymmetric, establishing dominance hierarchies.

Germ-soma or reproductive division of labor is a hallmark of complex multicellular organisms such as plants and animals [80]. In all organisms where parents and their offspring are not genetically identical (e.g., in sexually reproducing ones), conflicts of interest will arise between them. Various processes ensure the germline-soma distinction: germ plasma, DNA elimination, meiosis, microsatellite mutability, 5-methylcytosine deamination, and transposable element (TE) mobilization. Importantly, gonads are immune-privileged organs, i.e., they reside in an immunoprotected environment that is provided by structural barriers and secreted factors. Protection of developing germ cells from non-self, autoimmune, reactions is evident in all species. The essential role of this immune privilege is highlighted by the antigenicity of TEs and germ cell cancer genes (GC genes). TEs are mobilized during gametogenesis and, in concert with the germ plasm and GC genes, may be capable of creating or strengthening a germ–soma distinction. During cancerogenesis, TEs are mobilized, and GC genes are expressed, resulting in the identification of cancer cells as non-self by the immune system. The expression of immunogenic TEs and GC genes in a variety of cancers supports the concept of the soma-to-germline transition in cancers and the non-self-identity of germline cells.

The study of coevolution revolves around the premise that selection unfolds in a reciprocal pairwise manner which also applies to the soma-germline dyadic interaction. Like host and parasite, the gene products from the conflicting partners are part of the evolving, biotic environment of one another, and they can potentially coevolve in an antagonistic or correlational fashion. A key characteristic of antagonistic coevolution is that it can lead to a self-reinforcing adaptation/counter-adaptation chain reaction that leads to both a higher mutational robustness and higher evolvability of the genetic network. It can lead to recurrent, even perpetual, gene substitutions at antagonistically interacting loci [18].

Germline signals, reproductive and somatic senescence

Germline cells shape their future environment, anticipating (via parental effects) and preventing a crowded, resource-depleted, environment that would arise in a world of immortal, infinitely reproducing organisms [81]. Importantly, gonadal signals have Janus faces, rendering the organism vital, attractive to potential mates and fecund, while at the same time the same signals exert progeroid effects. Gonadal hormones exert suppressive and progeroid actions on the pineal-hypothalamic-pituitary-gonadal axis. The germline signals are part of a highly integrated signaling network that includes metabolic and stress response pathways. Melatonin as somatic hormone and sex steroids as gonadal hormones epitomize the germline-soma conflict underlying aging. Melatonin and the gonadal steroids antagonistically regulate

seasonal reproductive activity in a multitude of species and are components of a complex feedback mechanism through which the pineal and gonadal hormones each inhibit the secretion of the other. Levels of melatonin, a regulator of both energetic and oxidative stress processes, decline in adult organisms exerting systemic metabolic stress. Sex hormones, like other growth factors, activate the gerontogene $p66^{shc}$ that advances aging and shortens lifespan. Moreover, the collapse of proteostasis is mediated by a concerted action of gonadal- and metabolism-axis-signaling pathways.

The fundamental question "why do we age?" has to be complemented by the, as fundamental, "why does the reproductive activity limit itself?" Importantly, reproductive senescence and somatic aging are tied to each other by shared processes. The reproductive period is self-limited in both females and males due to the multiple detrimental effects of gonadal steroids and the reproductive activity-related oxidative stress on gonadal functioning and the hypothalamic-pituitary-gonadal axis. In humans, the higher female survival probability in older age stands in contrast to the earlier reproductive senescence of females. Both the late-life aging deceleration and mortality plateau and the human gender gap of life expectancies have a shared explanation: both are consequences of the sexually dimorphic, reproductive aging-related, waning of progeroid gonadal hormone signaling. And [82] note "…individuals that can no longer reproduce and that do not provide some form of care to offspring or other relatives are effectively dead" verbalized the evolutionary imperative of reproductive senescence-triggered somatic demise.

The stress axis of aging

Life stress has been associated with accelerated cellular aging and increased risk for developing aging-related diseases [83]. Aging organisms exhibit multiple systemic, cellular and mitochondrial features of a general stress response [18]. Genes involved in a number of stress response pathways are reproducibly upregulated with age across multiple species, tissues, and cell types [84]. Both intrinsic and various extrinsic stressors often strongly interact, and there is cumulative evidence that this may lead to a strong synergism between the two, causing normally non-severe stresses to become harmful when combined. It is one of the paradoxes of aging that, although mediators of stress response are constitutively upregulated, the stress response capacity is impaired. Mechanistically, the collapse of stress response pathways and proteostasis is an organism-level phenomenon in C. *elegans* as animals reach reproductive maturity and is regulated by signals from the germ stem cells [85]. Likewise, a similarly timed collapse of the heat shock response (HSR) occurs in aged flies subjected to hyperthermia, and in the aging rat adrenal cortex (in response to restraint stress) [86], suggesting that the early transcriptional dysregulation of stress responses after reproductive maturation is a conserved event in metazoans.

The metazoan nuclear factor-kappaB (NF-κB) is often referred to as the cellular 'sensor' for oxidative stress and is activated as part of the DNA damage response. NF-κB activation is the motif that is most strongly associated with aging and inflamm-aging, being identified as a candidate activator of aging-related transcriptional changes in multiple tissues [18]. There is a deep connection between adaptation to stress and longevity [87]. In a variety of species, stress resistance has been shown to correlate positively with lifespan but inversely with reproductive performance. Evidence from mutants, artificial selection experiments, genes, transcription factors, and processes such as autophagy, hormesis and mitohormesis, shared by both stress responses and aging pathways, show that stress resistance is linked to, and co-selected with, longevity. Intriguingly, the link between stress response and longevity is modulated context-specifically by signals from germline cells. Moreover, the aging organism is under metabolic stress as displayed by the features of hypometabolism and increased storage of resources.

The ETAs are unable to provide a sound explanation for the stress response phenotype of aging (or have rarely addressed this issue) and the regulation of aging by the stress response network. Why should organisms that have a long evolutionary history of economic use and optimal allocation of resources [88], invest, in the first place, less resources into tissue maintenance (as the Disposable Soma Theory suggests), only to invest much more resources later into stress/inflammatory responses to repair and mitigate the sequelae of ensuing tissue failure? In fact, it should be energetically always worthwhile to prevent rather than to repair and cure.

The pineal-hypothalamic-pituitary-gonadal-immune crosstalk, a primary driver of aging

Dysfunction of the thymus, a key organ in T lymphocyte ontogenesis, plays a prominent role in aging and life expectancy as driver of immunosenescence and inflammaging, both prime pacemakers of organismal aging [88]. The thymus is the primary sex hormone-responsive organ. The involution of the thymus begins in childhood and peaks around puberty, resulting in changes in the architecture of the thymus and in an almost completely non-functional organ at advanced age [89]. Gonadal hormones entail a long-term degeneration of immunocompetence, e.g., by thymus involution and lymphoid organ atrophy that leads to immunosenescence. A causal role of sex steroids is firmly established and supported by findings that peripubertal gonadectomy or chemical castration can considerably postpone age-related thymic atrophy and consequently functional deterioration of the immune system [18]. The hypothalamus-pituitary-gonadal axis provides the proximate mechanisms for reproduction-immune tradeoffs, particularly in seasonal breeders. With its intrinsic susceptibility to oxidative stress, the thymus is the predetermined breaking point that is programmed to become dysfunctional at sexual maturity. In a concerted action, metabolism, sexual maturation and reproductive

activity conveyed by sexual steroids, and stress responses mediated by glucocorticoids impact thymus involution. The involution of the thymus and pineal gland go hand in hand because they mutually influence each other in the context of immune system regulation and act as a functional unit, known as the thymus-pineal axis. The functionality of the immune system is the strongest predictor of human longevity and healthy aging [90].

The crosstalk between the heat shock response and inflammation occurs at several levels (gene level, posttranscriptional and protein level) [91]. Low-grade inflammation is the common pathway of stress- and aging-related diseases. High levels of age-associated pro-inflammatory markers are detected in the majority of older individuals, even in the absence of risk factors and clinically active diseases [92]. The low-grade systemic inflammation, "inflamm-aging", is characterized by primarily innate immunity (e.g., tissue senescent cells and activated macrophages), which, at least in part, is manifested along with the accumulation of dysregulated T cells [89].

The cellular senescence program

Nine major hallmarks of aging have been identified: genomic instability, epigenetic alterations, loss of proteostasis, deregulated nutrient-sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, altered intercellular communication and telomere attrition [93]. The hallmarks can be grouped into three main categories: (i) damage to cellular functions; (ii) antagonistic responses to such damage; and (iii) integrative hallmarks. The hallmarks are interconnected [94]. Particularly, mechanistic target of rapamycin (mTOR) and mitochondrial dysfunction increasingly appear to be common factors linking several, if not all, of these hallmarks. Mitochondria play a key role in inflammation. Pro-inflammatory factors, known as the senescence-associated secretory phenotype, loss of proteostasis and autophagy regulate the aging process in an autocrine, paracrine and endocrine fashion. Importantly, a multitude of cell-autonomous senescence processes have been shown to have cell-nonautonomous effects on metazoan longevity. DNA methylation, referred to as "epigenetic clock" that mainly occurs on sets of cytosine phosphate guanine (CpG)-dinucleotides, allows to develop accurate estimators of chronological age and age acceleration. Epigenetic changes appear to be a driver of aging, are tightly coupled to the metabolic state, and appear to be related to stress exposure. Shortening of telomeres, the repetitive DNA caps at the ends of eukaryotic chromosomes, leads to accelerated aging, and increases the risk of age-related diseases.

Coupling of ecological and evolutionary mechanisms

Interactions between natural selection and environmental change are well recognized and build the core of ecology and evolutionary biology [95]. Reciprocal interactions between ecology and evolution, eco-evolutionary feedbacks, are critical for understanding the evolution of biological diversity, the structure of communities and the function of ecosystems [95].

Tapping the eco-evolutionary "fossil record" of aging

A deeper understanding of biological and pathological processes can be achieved by "unearthing the fossil record" of the genome in physiology and development [96]. In aquatic and terrestrial ecosystems, limitation of nutrients and building blocks, particularly phosphorus and nitrogen, shapes food webs and, in deep evolutionary time, was and still is a pervasive phenomenon in the natural habitat making resource management an evolutionary necessity. Inorganic phosphorus and magnesium/calcium play a fundamental physiological role in energy production, membrane transport, and signal transduction. Endocrine regulation of systemic phosphate homeostasis depends essentially on the interaction between bone-derived FGF23 and kidney-derived klotho. Dysregulation of the FGF23–Klotho system leads to phosphate imbalance and induces a wide range of organ/tissue damage in blood vessels, bone, and kidney [97]. Levels of phosphate are inversely correlated to lifespan among different species. There is multiple crosstalk between phosphate and other nutrient sensing pathways.

A consistent pattern unfolds: Under nutrient depletion, prokaryotes and primitive eukaryotes initiate events at the crossroads of stress responses, differentiation, reproduction, and programmed cell death. Phenotypically, the germline-dependent aging/death is actuated by two mechanisms. In some once-reproducing organisms such as *Bacillus subtilis*, *Myxococcus xanthus, Chlamydomonas reinhardtii, Volvox carteri, Adactylidium* and *Acarophenax tribolii*, the offspring hatch from inside the mother and kill the mother organism during their hatching. In other semelparous and all iteroparous organisms, the germline cells effect the aging/death of the soma by signaling pathways, e.g., by hormones [18].

The eco-evolutionary coupling of stress, sex, and aging/death

Stress-induced mutagenesis—the increase of mutation rates in stressed or maladapted individuals—has been demonstrated in both prokaryotes and eukaryotes [98]. Environmental stress is known to initiate sexual reproduction in a broad range of metazoan species that normally undergo asexual reproduction [49]. Linking stress to sex, condition-dependent sex allows the offspring of maladapted, facultatively sexual, individuals to acquire adaptive alleles [99]. As the final common pathway of stress responses, oxidative stress, creating genetic variation of gametes, has also been linked to sexual reproduction in obligate sexual organisms. Redox regulation, at least in part mediated by gonadal hormones, is a hallmark of gametogenesis and a variety of other sexual reproduction-related events. The heat shock response (HSR) is a conserved stress response that maintains proteostasis within cells and organisms

[100]. Heat shock proteins (Hsps) are the key orchestrators of proteostasis and the HSR. Importantly, reproductive maturation is accompanied by a germline signaling-induced downregulation of the HSR, allowing the oxidative stress-associated gametogenesis. Thus, non-eusocial taxa exhibit an inverse relationship between reproductive potential and HSR function. In a multitude of taxa, the costs of reproduction are, at least in part, paid by an increased susceptibility to stress and oxidative stress. Cellular expression of Hsps (and their reproduction-related decline) can have tissue- and organism-wide systemic effects.

A signaling pathway from gametogenesis-associated metabolic/oxidative stress via activation of 5'AMP-activated protein kinase (AMPK) appears to result in an AMPK-mediated cell-nonautonomous attenuation of the HSR. The "cell cycle and apoptosis regulator" (CCAR) family may be the "missing link" between germline signaling and stress response/proteostasis breakdown. Links between sexual reproduction and aging/death are demonstrated for semelparity, *Hydra* and *Arabidopsis thaliana* reproductive activity. Importantly, semelparous and iteroparous organisms share the same pattern of neuroendocrine changes, in a continuum of chronologies that range from catastrophic to more or less gradual [18].

Genetic assimilation refers to the process of selection by which phenotypes that were originally expressed only after an environmental stimulus become genetically fixed [101]. In higher taxa, e.g., birds and mammals, sexual reproduction became fixed as an assimilated response to environmental stochasticity, generating proactive genetic variation. Likewise, aging/death appear to be genetic assimilations: self-limited reproduction, aging and death of the parent generation are proactive processes avoiding overcrowding with its consequences for future resource limitation and offspring fitness. Gene regulatory networks have been co-opted between development, sexual reproduction and aging. One of these networks is the HSR, engaging various processes to orchestrate life history traits.

Aging is selected for by multilevel selection

Theory holds that when individual and group interests' conflict, individual interests prevail [102]. Cooperative systems give incentives to cheat by selfish individuals that benefit from the common goods without contributing their fair share. Various factors have been suggested to be able to constrain the evolution of over exploitative behavior, and thus reduce the potential for a tragedy of the commons to arise in populations [18]. Certain traits can reconcile individual and group interests by making it individually beneficial to behave in a way that is beneficial to the group [103]. Parental care appears to be one of these traits. In parent-offspring coadaptation, reciprocal altruistic or selfish functions of co expressed gene's fitness loss or gain during one life stage may at least partly be offset by its gain or loss during the other life stage [104]. Like parental care, parental demise may be determined by differential coexpression and reciprocally altruistic or selfish functions underlying parent-offspring coadaptation. Generally, intergenerational conflicts including parental-offspring conflicts in viviparity and parental care favor offspring. Animals seem to prioritize reproduction over adult survival, respectively offspring fitness over parental fitness.

Examples from diverse fields share the common thread that feedback between evolutionary (individual) strategies and the environment fundamentally alter dynamic predictions of models [105]. Importantly, ecological feedback extends the previous dyadic interaction into a triadic relationship. Ecological and evolutionary processes influence all levels of biological organization, but ecology and evolution are inseparable at the population level [106]. In the absence of feedback mechanisms, cooperators are doomed in prisoner's dilemma interactions, but sufficiently strong positive feedback between cooperators and patch quality enables cooperators to persist or even take over the population [107].

Evolutionary theories of cooperation have to grapple with the paradox that in nature cooperation is abundant at all levels of biological organization despite the individual incentive to cheat. One of the central arguments against aging as a phenomenon caused by natural selection has always been that it has to be caused by "group selection". The complete absence of organisms that can cheat their way out of aging (in an otherwise obligatorily aging species) is a strong argument against "aging as the result of group selection". To prevent the rise of a "Darwinian demon", evolution put emphasis on the near universality of aging. To this end, evolution "reined in" any attempt of the soma to gain immortality and infinite reproductive potential. Theoretical evaluations have shown that a Darwinian demon can be prevented, and population stability can evolve as a consequence of selection on individuals. The evolutionary cheater-proof approach was to empower the germline cells as the individuals of the future generation to be the guardians of limited resources by eliminating the parents after they have fulfilled their evolutionary task.

Hamilton's inclusive fitness or kin selection theory suggests that genetic relatedness is a strong selective force explaining the existence of cooperation and altruism. The insight that germline cells eliminate their closely related parents to preserve scarce resources in the "struggle for existence" emphasizes the strength of eco-energetic selection forces and refutes Hamilton's theory.

The eco-evolutionary flow of information in the causation of aging

Correlation does not imply causation. With causation, one event (the cause) brings about another event (the effect) [6]. A causal fallacy, called common cause, fallaciously assumes a spurious relationship when two occurrences have no causal connection, yet it may be inferred that they do, due to a certain third, unseen factor (referred to as a "confounding factor") [18]. Potential biases like confounding and reverse causation may hamper the identification

of causal associations. Darwin's theory of natural selection aimed at supporting the causal efficacy of natural selection by appealing to the known causal efficacy of artificial selection. Importantly, *Drosophila* lines subjected to laboratory evolution for longevity showed genetic signatures of selection, particularly in genes related to lifespan determination such as regulation of metabolism, immune/defense response, stress resistance, reproduction, mitochondrial function, oxidative stress, and DNA repair [37]. Time series analyses to estimate the direction of causal influence are used in Granger's causality, convergent cross mapping, time series in experimental evolution, and phylogenetic path analysis. Time series confirmed the role of environmental factors (e.g., overexploitation, infectious diseases, predation, density) in the causation of life history strategy changes and the fast-slow continuum of life history traits.

The Mendelian randomization (MR) approach takes advantage of the random assignment of an individual's genotype from his or her parental genotypes that occurs before conception [109]. MR studies can reveal causal relationships, being independent of any measured or unmeasured confounders by using genetic variants as instrumental variants. Age is by far the single biggest risk factor for the majority of complex age-related diseases. At least to a large extent, age-related diseases can be characterized as accelerated-aging (AA)-related diseases. Various MR studies based on cross-sectional or longitudinal datasets have identified markers of AA, e.g., body mass index, blood pressure, dyslipidemia and poor glycemic control as causal factors in the manifestation of multiple age-related diseases. The epigenetic clock and its acceleration and the maintenance of telomeres are candidate biomarkers of aging.

Complex traits such as aging are typically affected by a large number of common alleles (over 300 human aging-related genes and >2000 genes associated with aging or longevity in model organisms) [110], each of little predictive value, with small or statistically non-significant effect. The genetic contribution to longevity in humans has been estimated to range from 15% to 40%, with the remainder being under the influence of environmental or stochastic factors. In centenarians, as the best model of healthy aging in humans, longevity genes should be enriched. Population-based genetic association studies, the genome-wide association study (GWAS) and the candidate gene association study (CGAS), are based on genotyping of single nucleotide polymorphisms (SNPs) [111]. In both CGAS and GWAS studies, SNPs of genes coding for ApoE, insulin/IGF1 and TOR signaling pathways, heat shock responses, mitochondrial functions, DNA repair and adiponectin were found enriched in centenarians and long-lived individuals. These studies confirmed that aging pathways that were identified in lower taxa and are phylogenetically conserved are also functional in humans.

An ancient survival response to metabolic stress becomes a dead-end trap in aging

Throughout phylogenesis, organisms whose lifestyle can be described as "feast and famine" cycles respond to or anticipate phases of environmental, particularly metabolic, stress by downregulating anabolic and activating catabolic processes and defenses. In aging, however, these survival factors are incapacitated catching the organisms in a dead-end trap.

Hypometabolism, a survival response to metabolic stress

Metabolic dormancy is a phylogenetically conserved state of reduced metabolic activity adopted by many organisms to overcome conditions of environmental, particularly metabolic, stress [112]. Animals that undergo dauer formation, diapause, hibernation, torpor, and estivation exhibit amazing adaptations that give them the metabolic flexibility to survive in environments not available to most other animals [113,114]. In order to achieve hibernation, animals must 1) increase their metabolic fuel reserve in preparation for hibernation, 2) downregulate carbohydrate metabolism and switch to catabolism of stored lipid reserves as metabolic fuel, and 3) reversibly suppress all non-essential ATP consuming processes [115]. Organisms downregulate the insulin/insulin-like growth factor-1 (IIS) signaling pathway to mediate this metabolic reprogramming. Throughout phylogeny, downregulation of IIS regulates metabolic dormancy, and favors longevity.

Mediators of metabolic rate depression include AMP-activated protein kinase, fork head class O (FoxO) transcription factors, the sirtuin signaling pathways, nuclear factor erythroid 2-related factor 2 (Nrf2) and its invertebrate homologs [114]. All of them are also mediators of longevity. Two major areas of epigenetics—DNA methylation and histone modifications—are known to have profound effects on controlling gene expression [116]. MicroRNAs can negatively control their target gene expression post transcriptionally. Regulatory mechanisms for safe transitions into metabolic dormancy, while stabilizing long-term viability must be rapid, reversible, easily inducible, and have a low energy demand. MicroRNAs possess all of these characteristics, making them excellent candidate regulators of hypometabolism [117].

In hibernating small mammals, the innate and adaptive immune systems are downregulated. Two major types of adipose tissue, brown adipose tissue (BAT) and white adipose tissue (WAT) are both structurally and functionally distinct. While WAT primarily acts as a storage site for lipids, BAT functions as a thermogenic tissue, dissipating energy as heat to mediate non-shivering thermogenesis [118]. BAT has been recognized as an endocrine organ that secretes a myriad of regulatory factors. They exert local autocrine and paracrine effects, as well as endocrine actions, targeting tissues and organs at a distance. The BAT is a natural antagonist of the thymus in cell-mediated immunity. In hibernating animals, thymuses undergo yearly involution in winter and regeneration in summer.

Mitohormesis, turning oxidative stress into a longevity mechanism

Harman's Mitochondrial Free Radical Theory of Aging (MFRTA)

suggests that oxidative damage to cellular macromolecules caused by reactive oxygen species (ROS) from mitochondria accumulates in cells over an animal's lifespan and eventually leads to the dysfunction and failure that characterize aging [119,120]. However, in recent years evidence kept accumulating that questioned the causal effect of ROS in aging [120]. While it is clear that oxidative damage increases with advancing age, and that high levels of ROS can be toxic, it has become increasingly evident that ROS may not cause aging and is even sometimes associated with longevity.

The term "hormesis" is used to describe a dose–response relationship where the response is reversed between low and high doses of a stressor [121]. Various kinds of biphasic or nonlinear dose–response relationships are referred to as hormetic responses. In response to exposure to at least 1000 different chemical and environmental stressors, hormesis has been described across a wide range of organisms [122]. Epigenetic transcriptional reorganization appears to be a common mechanism underlying all hormetic and lifespan-extending effects [123]. In a multitude of taxa following a single stress hormesis, cross-tolerance to multiple stressors has been observed. In aging, several small-dose stressors exert an anti-aging effect, suggesting a cross-tolerance hormesis to the putative stressor that causes aging.

Mitochondrial hormesis occurs in response to any stress that can impinge upon mitochondrial function and stimulates adaptive responses that improve not only mitochondrial function but also global resistance to stress [124]. Mitohormesis is supported by the potential for mtROS to simultaneously induce bioenergetics and antioxidant adaptations through the transcription factor peroxisome proliferator-activated receptor γ coactivator 1α (PGC-1α). Mechanisms of the mitochondrial stress response include the mitochondrial unfolded protein response (UPR^{mt}), a retrograde signaling pathway, the catalytic cycle of peroxiredoxins, mitochondrial uncoupling, and cell-nonautonomous signaling. Mitohormesis is a mediator of longevity in various exceptionally long-lived species.

Aging is a somatic survival program

Scientists have been vexed by findings that the soma presents both pro-aging and anti-aging features and mechanisms. It is becoming increasingly evident that some of the supposedly negative biological consequences of aging may actually be beneficial to health and longevity [125]. Metabolic syndrome can be associated with improved longevity in older people, and the term "reverse metabolic syndrome" has been coined to describe this paradox [125]. Many studies suggest the ambivalence of aging-related processes that is highlighted by the presence of so-called genetic "risk factors" for major diseases in individual genomes that do not always compromise longevity. Intriguingly, the share of such variants among centenarians is sometimes similar to that in a younger population [126]. Germline signals compromise the resilience of their host, the soma, by a) reproductive maturity-related collapse of proteostasis and stress response; b) gonadal hormone-mediated, accelerated thymus involution; c) gonadal signal-associated downregulation of pineal gland-secreted hormones resulting in metabolic stress. Moreover, gonadal hormones are instrumental in reproductive senescence due to a self-limiting feedback control of reproductive activity in both the brain and the gonads [18].

The maintenance programs induced in response to adversity are of two types: metabolic dormancy and defense, respectively. Unfavorable conditions, including nutrient scarcity, require reallocation of available resources into stress-specific catabolic and energy-saving maintenance mechanisms [127]. Shared signaling pathways between metabolic dormancy and aging characterize the latter as somatic survival program in response to metabolic stress. Downregulation of anabolic hormonal systems, including the IIS, regulates metabolic dormancy. Defense processes are characterized by energy consumption and anabolic metabolism. The whole stress response machinery from the heat shock response to mitokines FGF21 and GDF15, the AMPK-FOXO-sirtuin and corticosteroid signaling pathways, adiponectin and Nrf2, antioxidant and inflammatory pathways are available to be engaged in the defense. Inflammation is a physiological defense to tissue damage, promoting cellular repair and restoring homeostatic conditions. However, during aging the stress response systems including the mitohormetic response become increasingly dysfunctional. In short-lived species, proteostasis collapses rapidly at reproductive maturation but declines more gradually in long-lived taxa. The responsiveness of the AMPK-FOXO-sirtuin signaling pathway to activation diminishes with aging. Inflammaging may have a role in the decline of the AMPK activity. The ability to respond to oxidative stress with the activation of Nrf2 signaling and expression of its target antioxidant genes declines with age [128]. Adiponectin has a protective role against age-related diseases, and thus is an excellent candidate gene for longevity [129]. In age, however, adiponectin resistance is thought to be due to downregulation of adiponectin receptors.

The hypometabolic-hypoxic reprogramming of aging

A link between environmental hypoxia and the longevity of populations exposed to hypoxia has been shown in populations in the wild, by experimental studies and in human populations living at high altitudes [130]. Hypoxia adaptation contributes to longevity, although in a complex manner, as observed in the Tibetan population, mole-rats, and various model organisms. Hypometabolism is a key response to reduce energy expenditure and prolong survival under periods of adverse abiotic conditions in a range of taxa [131]. Hypometabolism and both environmental and cellular hypoxia are linked in a reciprocal feedback loop through interconnected signaling networks. The energy savings and substrate conservation required for surviving cold dormancy and hypoxia involve universal mechanisms: downregulation of energy production (supply-side) and of energy consumption (demand-

side) [132]. Thus, oxygen delivery is responsive to the changing metabolic needs [133].

Germline signals put the soma under metabolic stress. The soma responds by downregulating metabolic and adjusting oxygen supply to metabolic demands. The key to the recognition of the hypometabolic-hypoxic (HH) reprogramming in aging is the age-dependent increase of the pulmonary arterial pressure that signifies the reflectory downregulation of global oxygen supply according to the "consumption drives delivery" adjustment. In a coordinated process, the aging organism downregulates vasorelaxant gasotransmitters nitric oxide (NO) and hydrogen sulfide (H_2S), while atrial natriuretic peptide (ANP) becomes resistant. On the other hand, a variety of vasoconstrictor agents are upregulated including type 5 phosphodiesterases, resulting in increased vascular tone, reduced tissue perfusion, tissue hypoxia, and, eventually, hypertension and atherosclerosis. The expression of hypoxamiRs, microRNAs that are expressed under conditions of low oxygen and are involved in overall metabolic regulation [134], ultimately proves that HH reprogramming is activated in aging. However, what is adaptive under ephemeral environmental stress becomes maladaptive under the persistent stress exerted by the germline signals.

Anti-aging approaches related to HH reprogramming aim to increase tissue perfusion that increases peripheral oxygen delivery. Lifestyle measures like aerobic exercise and breathing methods that exploit the Bohr effect result in increased tissue perfusion and oxygen extraction. Exercise training can be regarded as an effective countermeasure against HH maladaptation. Pharmacological interventions may use NO and H_2S donor/prodrugs and phosphodiesterase type 5 inhibitors.

Aging as dead-end trap

The hypothalamus has a central role in aging [135]. The central regulation of energy balance relies on the ability of the brain to promptly and efficiently sense variations of metabolic state [136]. This regulation is based on the central integration and monitoring of peripheral signals circulating in the blood, such as metabolites (glucose, free fatty acids and amino acids) and hormones (mainly leptin, ghrelin and insulin). In many ways insulin resistance appears to start in the hypothalamus [136]. In situations when increased adiposity is adaptive (e.g., under metabolic stress), the hypothalamus becomes resistant to the effects of leptin. Impaired leptin responsiveness is a key characteristic of the metabolic defects that are responsible for disrupted energy control [137]. Both diet-induced and age-associated obesity are directly correlated with leptin resistance. Importantly, leptin resistance during aging is independent of fat mass [138].

Low-grade inflammation is a hallmark of aging; the systemic level of inflammation is negatively correlated with human longevity [139]. In aging, the BAT as anti-inflammatory tissue endures a loss of both mass and activity, and a decrease in white fat browning. Much like in chronic overnutrition, an age-related increase since young adulthood can cause hypothalamic micro-inflammatory changes, albeit in a manner which can be independent of the nutritional status [139]. Hypothalamic inflammation appears to be the pacemaker of hypothalamic and systemic insulin and leptin resistance. Leptin is not only an adipose tissue-derived messenger to the brain, signaling the amount of energy stores, but is also a crucial factor of the innate and adaptive immune system that mediates an inflammatory response by regulating the production of proinflammatory cytokines, favoring the chronic proinflammatory state [140].

Estrogens regulate key features of metabolism, including food intake, body weight, energy expenditure, insulin sensitivity, leptin sensitivity, and body fat distribution. Estrogen-related dysregulation of hypothalamic estradiol feedback mechanisms and hypothalamic-pituitary dysfunction contribute to the onset and progression of reproductive senescence, independent of ovarian failure. Gonadal steroids appear to be degenerative and cytotoxic in a variety of hypothalamic nuclei, incite loss of arcuate nucleus (ARC) synapses, actuate the oxidative stress-mediated degeneration of β-endorphin neurons in the ARC and elicit neuronal and glial stress reactions. Estrogens induce aging-like dysfunctions in the hypothalamic regulation of estrous cycles and estrogen-induced luteinizing hormone surges [18].

Epigenetic changes have a huge influence on the aging process. Aging cells experience alterations in all aspects of the chromatin landscape, DNA accessibility, and noncoding RNA production, until a threshold of altered gene expression and compromised genomic integrity is crossed, and the cells finally succumb to a permanent halt in progression through the cell cycle [141]. Many aging-associated microRNAs seem to interact with genes and pathways that are relevant to aging. Circulating microRNAs appear to be causally involved in the control of aging and age-related diseases, including sirtuin functions, cellular stress regulator Nrf2, metabolic regulation, mitochondrial gene expression and functions, autophagy and Inflammaging.

Organisms use both circadian and circannual rhythms for time measurements [90]. There appear to be two clock pathways that communicate with each other, one involving the pineal gland, which regulates short photoperiodicity, and a second one involving pituitary calendar cells, the latter being more embedded in longer living animals [142]. A temporal program about life, aging and death in the pineal-suprachiasmatic nucleus network of the brain has been repeatedly demonstrated. Pineal gland aging has been considered responsible for promoting aging of the body. Melatonin, a key regulator of energy metabolism, is critical for the synchronization of circadian and seasonal rhythms. The energy budget within which an organism has to grow and reproduce functions as a life-long metabolic clock. In addition, the epigenetic

clock is a biomarker of chronological and biological aging. The circadian and circannual clocks are reciprocally linked to the metabolic rheostat, establishing an integrated life-long measure of resource use and an energy budget-related longevity clock.

The immune system and the stress response system arguably are the most vital defense systems in a stochastic and adverse environment. With its intrinsic susceptibility to oxidative stress, the thymus is the predetermined breaking point that is programmed to become dysfunctional at sexual maturity. In addition, from bacteria to C. *elegans* and humans, proteins are expressed at levels just below their solubility limits, limits that are exceeded following metabolic and oxidative stress. The germline cell signaling attacks these two systems with a low safety margin, assuring the decease of the soma.

Target of rapamycin, the aging ratchet

Target of rapamycin (TOR) is the conductor of the cellular signaling symphony [143]. TOR is an evolutionarily conserved serine/threonine kinase belonging to the phosphoinositide 3-kinase-related kinase family and is present in all eukaryotic species examined to date. The TOR kinase is found in two complexes, TORC1 and TORC2 that can have synergistic or antagonistic effects. Sensing of inputs from nutrients, growth factors, and cellular stress signals uniquely positions the IIS and downstream TOR signaling networks to synchronize growth in tune with a variety of inhibitory and stimulatory environmental signals. All three major axes of lifespan determination, namely metabolism, germline signaling, and stress response [18] converge to the TOR pathway. Lifespan control of translation by phosphate and amino acids is mediated by TOR (see 7.1). A link between TOR signaling and nitrogen metabolism has been established that suggests a crucial role of this pathway in coupling nitrogen availability to continued cell growth and longevity [144]. TOR plays a key role in mitochondrial homeostasis. The three components of basal metabolic rate (BMR), proton leak, maintenance of ionic gradients, and the cost of biosynthesis, comprising ca. 20 % of BMR, are regulated by the signaling rheostat of mechanistic TOR (mTOR). Probably, all nutrient-dependent developmental transitions such as metamorphosis and reproductive maturation are linked to TOR signaling. From worms and flies to mammals, gonadal signals activate TOR and in a reciprocal feedback loop are activated by TOR. mTOR regulates the coordinate expression or nuclear localization of several transcription factors that individually are responsive to internal or external cues of stress [145]. mTORC1 senses stresses, coupling stress to proteostasis. Various stressors induce the activation of an evolutionarily conserved cell protective mechanism, the heat shock response (HSR), to maintain protein homeostasis in virtually all eukaryotic cells [146]. Heat shock factor 1 (HSF1) plays a central role in the HSR and mTORC1 phosphorylates and activates HSF1 in the regulation of stress.

The TOR pathway mediates the link between nutrition and longevity [147]. In mammals, mTORC1 accounts for 60% of inter-species variation in longevity, mTORC1 gene expression, and protein phosphorylation being the strongest longevity predictors [148]. At multiple levels, TOR regulates many aspects of cellular senescence including mitochondrial function, autophagy and protein homeostasis, senescence-associated secretory phenotype, epigenetic clock and telomere length. mTOR activation and inflammation are linked in a reciprocal-causation feedback loop. The mTOR signaling pathway is required in driving immune and inflammatory responses and reciprocally regulates the innate versus adaptive immune responses. Given that mTORC1 is connected to a variety of downstream epigenetic pathways, it is possible that metazoan TORC1 communicates nutrient information directly to chromatin regulators eliciting epigenomic changes and diet-induced transgenerational phenotypes [149]. The regulation of mTOR signaling by miRNAs and control of miRNA biogenesis by mTOR in a reciprocal relationship has also been demonstrated [150].

mTORC1 activity in the mediobasal hypothalamus is critically implicated in the regulation of food intake and body weight and in the central actions of both nutrients and hormones, such as leptin, ghrelin and triiodothyronine [151]. There has been a growing number of reports of aberrant activation of mTOR signaling in both somatic and reproductive aging. A ratchet is a device with angled teeth that allows a bar or cog to move in one direction only [152]. Reproductive maturation and consumption of resources are associated with an imbalance between TORC1 and TORC2 that results in a ratchet-like mitochondrial malfunction that cannot be corrected due to the TOR-related inhibition of auto/mitophagy. The ratchet-like action of mTOR is highlighted by the pulsatile pattern of the menstrual cycle. Both at the ovarian and hypothalamic level, with every menstrual cycle mTOR activation appears to deplete the ovarian reserve and advance reproductive senescence. In aging, an imbalance of mTOR-inhibiting and -activating factors occurs, resulting in the aging-related overactivation of mTOR. Inhibitors of mTOR activation such as AMPK, sirtuins, sestrins, p53, and tuberous sclerosis complex are downregulated, resulting in a general loss of mTOR inhibition. On the other hand, increased oxidative stress, 4-hydroxy-2-nonenal derived from the decomposition of peroxidation products of omega-6 polyunsaturated fatty acids, and advanced glycation end products, the toxic metabolites of glycolysis, all may contribute to the aging-associated overactivation of mTOR.

The flaws of the "evolutionary theories of aging"

After it could no longer be ignored that aging is regulated by genes, several adherents of the ETAs have argued that aging is due, at least in part, to genetic programs that evolved to regulate development but progress into adulthood and gradually cause dysfunction [153]. Various evidence argues against the claim [154] that "aging is an aimless continuation of the developmental program that was not switched off" [155].

Karl Popper stressed that science progresses by rejecting or

modifying causal hypotheses, not by actually proving causation [156]. From the very start, the ETAs suffered from a variety of flaws [10]. With the evidence that aging is regulated by phylogenetically conserved genes and transcription factors, the ETAs should have been abandoned decades ago. The ETA proponents first ignored or denied for a long-time genetic control, then downplayed its importance as a quasi-program, an aimless continuation of the developmental program. The ETAs use circular reasoning, "alternative facts", and pseudo-evolutionary arguments resulting in dozens of inconsistencies, false predictions, and exceptions to their scope (e.g., semelparity, programming of cellular senescence/death mechanisms). On the other hand, they suppressed and censored the mention of programmed aging in publications.

Is there a fountain of youth?

The therapeutic strategies targeting the hallmarks of aging have been broadly grouped into four categories, namely systemic (blood) factors, metabolic manipulation (diet regimens and dietary restriction mimetics), suppression of cellular senescence (senolytics), and cellular reprogramming, which likely have common characteristics and mechanisms of action [157]. Aging is a multifactorial process, and it cannot be expected that a single silver bullet miraculously may significantly slow down the process [158]. A combination of several approaches may bring superior results of slowing aging. Lifestyle-based interventions, particularly physical activity, remain the mainstay approach to minimize the risk for diseases, reduce morbidity and mortality and most importantly, improve healthspan in aging. We can slow down the speed of this ageing but there is no fountain of youth. Growth, reproductive-maturation and -activity, and aging/death are inextricably linked in a huge network of signaling pathways. This network pervades every aspect of life and death and represents an impenetrable wall against immortality (at least for higher taxa that are not controlled by top-down eco-evolutionary feedbacks).

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Conflict of Interest

No Conflict of interest.

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