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Review article

Why we age – Integrating error, program, and selective pressure

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ABSTRACT

Whether aging arises primarily from the progressive accumulation of molecular damage (error-based theories) or from regulated, development-related processes (programmatic theories) has been debated for more than a century. This question is central to aging research and shapes our conceptual understanding of aging. Although the existence of a dedicated aging program and the evolutionary advantage of aging remains controversial, the possibility that aging confers adaptive benefits at the species level should not be dismissed. Age-associated DNA methylation changes, which are enriched in developmental genes, support the hypothesis of an underlying program. However, the functional relevance of these epigenetic modifications remains unproven, and epigenetic clocks exhibit a substantial stochastic component – which is generally the case in epigenetics, also during development. This review argues that aging should not be interpreted exclusively as the result of random molecular damage or the output of a specific genetic program, but rather as a regulated modulation of how organisms acquire defects and epigenetic drift over time – possibly governed by feedback mechanisms of genetic and epigenetic networks – which may ultimately be beneficial to the species.

1. Introduction

Why we age remains subject of lively debate among scientists. Aging is accompanied by numerous molecular changes that are summarized as hallmarks of aging (Lopez-Otin et al., 2023). Although this framework has enabled advances in the field by integrating diverse biological observations, it remains largely descriptive and does not answer the fundamental question of *why* aging occurs. Two seemingly opposing conceptual models dominate the discussion: 1) error-based theories, which assume that aging is the result of progressive accumulation of somatic mutations and other molecular defects, and 2) aging theories, which view aging as a regulated, developmental-like process (de Magalhaes, 2025). Many primary hallmarks – such as genomic instability, telomere shortening, and loss of proteostasis – naturally align with error-based hypotheses, which may be why this view often prevails. On the other hand, the idea that aging resembles a coordinated developmental program is not new and gained new attention due to evidence linking aging to epigenetic modifications – and epigenetics is known to control development (Gems et al., 2024).

The conceptual divide between these models is further deepened by evolutionary considerations. While many researchers reject the possibility that aging might be favored by natural selection (Kirkwood, 2008; Meyer et al., 2025), others have proposed that under certain ecological conditions – particularly in resource-limited environments – aging might confer advantages at the level of species (Rose, 1990; Weismann, 1891). After decades of theoretical analysis, the majority of evolutionary biologists have rejected the idea of programmed aging as incompatible with standard selection theory. The wording is often exclusionary, stating, for example, that "the idea that aging is programmed, in the face of evolutionary logic and experimental evidence is as unpromising as scientific stance as to continue to assert that the sun orbits the earth" (Kirkwood and Melov, 2011). However, an overly dogmatic rejection may be premature.

In this review, I re-examine the possibility that aging may contain adaptive elements and attempt to reconcile programmed and non-programmed perspectives, particularly in light of epigenetic clock biology.

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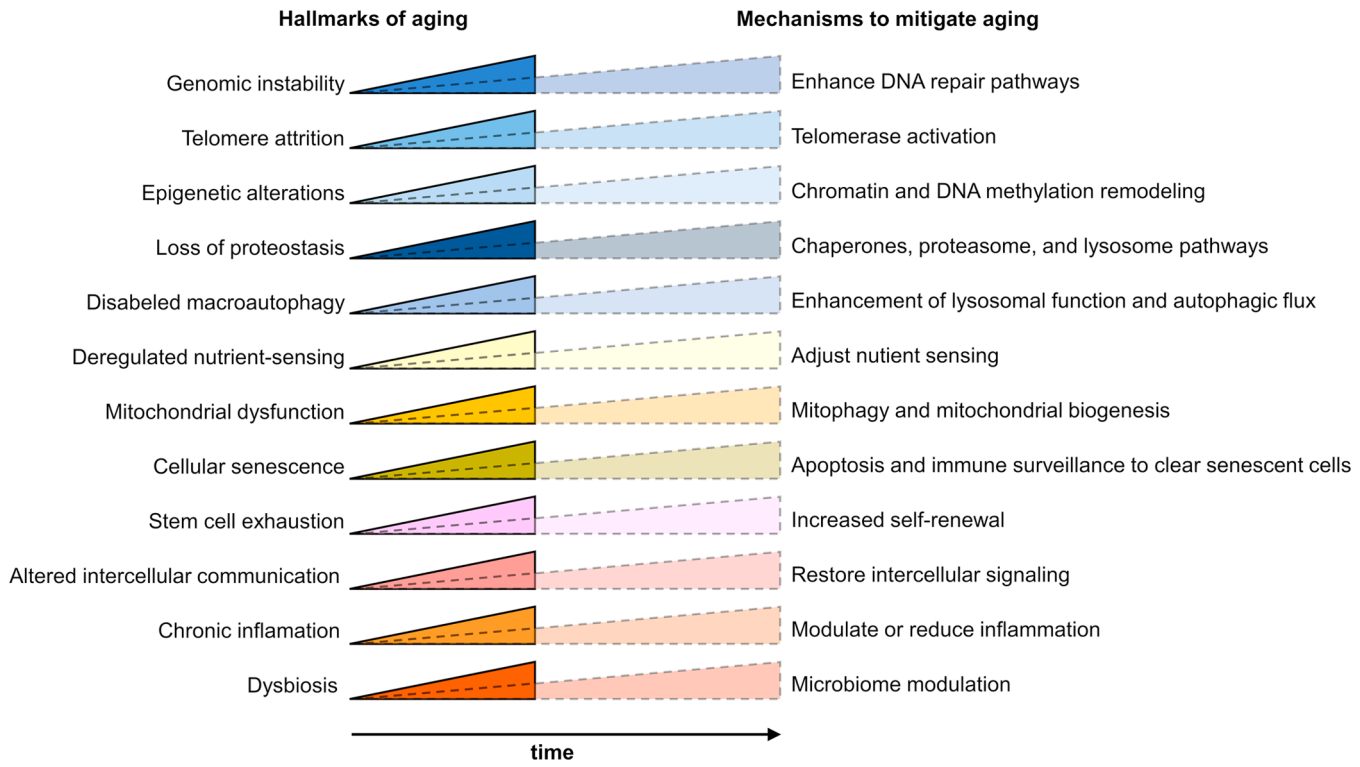

Fig. 1. The hallmarks of aging are subject to modulation. When the famous hallmarks of aging were defined, they were selected for their time-dependent manifestation during aging, but also by the possibility to experimentally accentuate the hallmark, and by the opportunity to decelerate, halt, or reverse aging by therapeutic interventions on the hallmark (Lopez-Otin et al., 2023). In fact, the hallmarks of aging can also be modulated by cellular and molecular means. Mechanisms that mitigate these age-associated changes are depicted.

2. The controversy surrounding programmed aging

As discussed above, several theories have been proposed to explain the evolutionary origins of aging. Classical evolutionary theories include the mutation accumulation theory, which posits that deleterious mutations with effects that manifest late in life can accumulate because the force of natural selection declines with age (Medawar, 1952); the antagonistic pleiotropy theory, which suggests that certain genes confer fitness benefits early in life but have detrimental effects later in life (Williams, 1957); and the disposable soma theory, which argues that organisms face trade-offs in allocating limited resources among growth, reproduction, and somatic maintenance (Kirkwood, 1977). Collectively, these theories explain how aging can arise and persist through evolutionary processes despite its negative effects on survival and function. Importantly, they generally view aging as a by-product of evolutionary trade-offs and constraints rather than as a programmed or adaptive process. Although it is impossible to comprehensively review the extensive literature that has accumulated over the past two centuries, several key arguments help explain why the concept of programmed aging is so controversial.

A central issue concerns the definition of the term ‘programmed’ (Austad, 2004a). In the strictest sense, programmed aging implies the existence of specific genes or signaling cascades whose function directly cause aging (Kirkwood and Melov, 2011). The term ‘program’ may also be interpreted more broadly to refer not to a single dedicated pathway, but to higher-order regulatory architectures that increasingly steer the system toward dysregulation and decline (Austad, 2004b). Even under this expanded interpretation, however, several arguments are commonly raised against the concept of programmed aging (Kirkwood and Melov, 2011).

One frequently cited argument is the apparent rarity of visibly aging animals in the wild (Kirkwood and Melov, 2011). However, this observation might be explained by the fact that natural selection begins long before individuals reach their maximal lifespan. In addition, there may be slight differences in aging processes between laboratory and field studies (Maklakov et al., 2026).

A related evolutionary argument is that if aging was controlled by an independent genetic program, one would expect the existence of inactivating mutations that override or bypass this program. The absence of individuals who completely escape aging is therefore seen as evidence against the existence of specific “aging genes” (Kirkwood and Austad, 2000). In fact, the so far identified genes that seem to be involved in regulating lifespan – such as components of insulin/IGF signaling, mTOR, or sirtuin pathways – play rather broad physiological roles in growth, metabolism, and stress resistance. Their pleiotropic nature and generally moderate effects on lifespan argue against interpreting them as dedicated aging programs.

Perhaps the most common argument against the idea that aging is programmed is the declining force of natural selection after reproductive maturity – the so-called “selection shadow” (Meyer et al., 2025). W. D. Hamilton formalized this principle in 1966, demonstrating mathematically that natural selection against death declines with increasing age because of the higher reproductive potential of younger organisms in the cohort (Hamilton, 1966). The decline in selection with age then allows accumulation of harmful mutations (Medawar, 1952). Yet this reasoning raises further questions. If selection only diminishes after reproduction, why is the reproductive window itself often so limited? In humans, for example, all oocytes are formed before birth, and the ovarian reserve declines largely through atresia – a regulated process sometimes described as “programmed follicle loss” (Wallace and Kelsey, 2010). Theoretically, the human reproductive span could extend well beyond a century. Instead, the developmental mechanisms that govern reproductive timing appear to be linked to the aging of the organism (de Magalhaes, 2023; Kirkwood and Holliday, 1979). Furthermore, in many species, including fish, oocytes are generated throughout life (Nakamura et al., 2010). In such cases, the force of natural selection may not decline

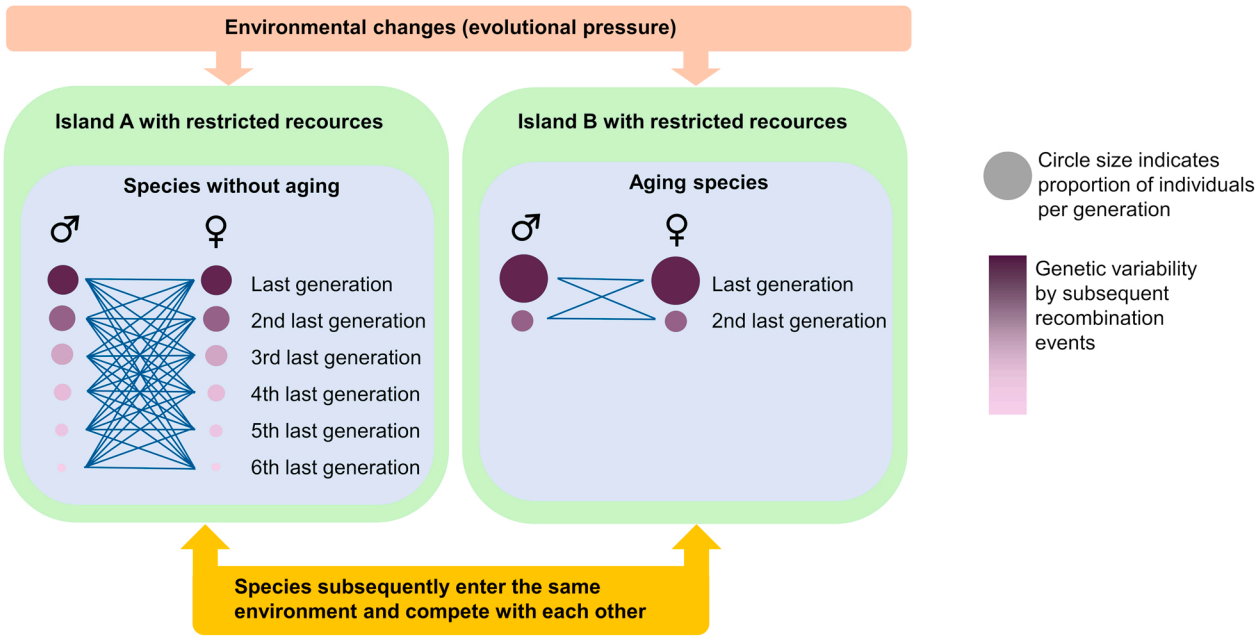

Fig. 2. Competition between aging and non-aging species. The schematic representation as islands is a simplification and can be understood as any form of spatial separation of habitats. In the immortal species, any individual will also occasionally die because of predators, disease and accidents.

as sharply with age – yet these species show clear signs of aging (Vrtílek et al., 2022). Thus, although the decline in selection after the reproductive phase is well documented, from an evolutionary perspective it may not fully explain why aging occurs.

It is important to note that the absence of a clearly defined "aging program" does not mean that there is no regulatory control. Many long-term developmental processes that span over years or decades are based on complex genetic networks that are not yet fully understood. It is well known that the characteristic hallmarks of cellular aging can be mitigated by specific enzymes and pathways (Fig. 1) (Blasco, 2005; Lopez-Otin et al., 2013; Lopez-Otin and Kroemer, 2021). Indeed there is evidence of improved DNA repair and genomic stability in animals with longer lifespan (Vijg and Suh, 2013). Germline cells obviously maintain their continuity across generations, demonstrating that the accumulation of damage is not an inevitable default state for all cell types. Moreover, somatic cells can be rejuvenated through reprogramming into induced pluripotent stem cells (iPSCs), which, despite accumulating somatic mutations, are capable of generating an entirely new, developmentally young organism (Rando and Chang, 2012). Moreover, iPSCs do not show signs of replicative senescence, and characteristics associated with long-term culture are also reversed during reprogramming (Franzen et al., 2021; Frobel et al., 2014). These observations suggest that, at least in pluripotent state, aging can be counteracted and even reset to ground state.

2.1. *Why aging could be selected at species level*

At first glance, it seems counterintuitive that aging – a process characterized by functional decline and increased mortality – could confer an evolutionary advantage. For most biological traits, it is widely accepted that natural selection operates primarily at the level of individuals, rather than at the level of groups or species (Kirkwood and Melov, 2011). Nevertheless, the idea that aging might confer advantages at a higher level of biological organization is not new. Already in 1891, A. Weismann proposed that senescence could be beneficial for the species by removing older individuals, thereby preventing overpopulation and facilitating generational turnover (Weismann, 1891). Although this early group-selection argument was later criticized for lacking mechanistic and theoretical support, it was followed up by many other scientists. The underlying rational can be exemplified by the following scenario:

Imagine two species occupying the same ecological niche on two different islands with limited resources: one species is immortal, the other ages. As environmental conditions change – sometimes gradually, sometimes abruptly – both species must adapt as efficiently as possible. Adaptation is particularly driven by genetic recombination, rather than new mutations, and each reproductive cycle introduces new combinations of genetic information, increasing diversity (de Visser and Elena, 2007). In an immortal species, multiple generations would coexist and compete for limited resources. This ongoing competition would reduce the number of new individuals in the later generation, reducing the overall rate of genetic recombination and slowing the emergence of newly combined variants. In contrast, in an aging species, a programmed life span removes older individuals after successful reproduction. This turnover frees resources for subsequent generations, enabling more frequent recombination events and greater genetic diversity across the population. If these two species were now to enter the same ecosystem, the aging species could therefore hold an adaptive advantage: more generation turnover, greater genetic variation, and ultimately more rapid adaptation to changing environmental conditions (Fig. 2).

With regard to this scenario, it has been argued that such selection at the group level can operate only in geographically isolated subpopulations (Kirkwood and Melov, 2011). However, strict geographic isolation – such as that found on islands – is not necessarily a prerequisite. Spatial structure can emerge in many ecological contexts: distinct valleys, fragmented forest patches, heterogeneous microhabitats, or even socially structured populations without obvious physical barriers. Whenever dispersal is limited and local interactions dominate, distinct sexual productivity and generation turnover can, in principle, generate higher-level selection effects.

Several studies have used computational and spatially explicit simulations to explore whether aging could evolve under such structured conditions (Martins, 2011; Mitteldorf and Martins, 2014; Mitteldorf and Pepper, 2009; Travis, 2004). Some of these models suggested that, under certain assumptions, selection for aging is possible. Nonetheless, critics argue that many of these models rely on restrictive or biologically unrealistic parameters and therefore do not conclusively demonstrate that

adaptive aging is likely to evolve under natural conditions (Kowald and Kirkwood, 2016). It is questionable anyway whether such models correctly take the evolutionary benefit of sexual reproduction into account (Otto and Michalakis, 1998): Recombination provides evolutionary advantages that extend beyond merely reshuffling beneficial and deleterious mutations (Fischer, 1930). Since most phenotypic traits are polygenic and depend on interactions among multiple loci and chromatin regions, recombination enhances the efficiency of selection across the genome. It reduces interference among linked loci, facilitates the assembly of favorable allele combinations, and improves the purging of deleterious variants. These advantages of genomic recombination arise even in the absence of new mutations (Bell, 1982). As exemplified above, aging of the organism can increase the overall frequency of sexual recombination, and hence the benefits to evolution should not be underestimated.

2.2. Evidence that aging is adapted to the species in an evolutionary manner

Although this evolutionary advantage of aging has not yet been proven, it fits well with the patterns observed in the animal kingdom. In mammals, lifespan correlates strongly with age at sexual maturity and gestation period, regardless of metabolic rate or body weight (de Magalhaes, 2023; de Magalhaes et al., 2007). In humans, the relatively long post-reproductive longevity might favor kin-selection, with increased reproductive success of the offspring (Hamilton, 1966).

The remarkable longevity of the naked mole-rat – a rodent capable of living more than 25 years in captivity – could be related to its unusual reproductive system (Horvath et al., 2022; Kim et al., 2011). On a molecular level, exceptional longevity of naked mole-rats may, at least in part, be explained by their highly efficient DNA repair mechanisms (Evdokimov et al., 2018). However, this raises an important question: why have comparable mechanisms not evolved in other rodents, such as mice, which are of similar body size yet exhibit life expectancies that are roughly tenfold shorter? Naked mole-rats live in highly social colonies, sometimes numbering in the hundreds, yet typically only a single female (the queen) reproduces, while the remaining workers are non-reproductive. Since the stability of the colony depends on the longevity of this single female reproductive animal, selection is likely to favor prolonged lifespan in queens. For the non-breeding workers, however, the absence of reproduction means that their aging has little evolutionary impact for the colony and for the species. In fact, the queens of social insects also have a remarkably long life expectancy, which can reach almost 30 years in some ant species (Jemielity et al., 2005; Remolina and Hughes, 2008), whereas the life-expectancy of most other related insects ranges within weeks to months. It has even been suggested that extended lifespan is a necessary prerequisite for the evolution of eusocial species (Carey, 2001).

Another striking example is the hydra, which shows little or no signs of aging. This apparent biological immortality may be due to its primary mode of reproduction – asexual budding (Martinez, 1998). Since there is no frequent sexual recombination, the evolutionary advantage of generational change is reduced, so there is little selection pressure for aging in hydra. However, the few obligately parthenogenetic higher animals – essentially evolutionary side branches – appear to remain subject to aging (Jaron et al., 2021).

Taken together, it appears that aging in species is shaped more by environmental, demographic and life history dynamics – such as when and how often organisms reproduce, survival patterns at different ages, and how natural selection works across life stages – than by the straightforward accumulation of cellular defects. However, this does not rule out the possibility that the evolution of aging and lifespan is closely linked to the evolution of mutation rates and error accumulation (Li et al., 2023).

2.3. Epigenetic clocks point toward a developmental program

A wide range of molecular biomarkers have been developed to estimate the aging process, including transcriptomic, proteomic, and metabolomic signatures (Ibáñez de Opakua et al., 2025; Johnson et al., 2020; Peters et al., 2015). Together, these approaches provide complementary insights into the complex and multifaceted nature of aging and can serve as valuable tools for monitoring age-related biological changes. Among these biomarkers, however, epigenetic clocks have attracted particular attention because they have reinforced the notion that aging may, at least in part, resemble a developmental process. This idea stems from the central role of epigenetic modifications in cellular differentiation and development (de Magalhaes, 2012; Gems et al., 2024). Accordingly, this review focuses primarily on epigenetic clocks and their implications for understanding the relationship between development and aging.

Epigenetic clocks emerged from the observation that DNA methylation levels at specific genomic loci change in a highly reproducible manner throughout life (Bork et al., 2010). The first epigenetic aging markers were described 15 years ago by Bocklandt et al. and our group (Bocklandt et al., 2011; Koch and Wagner, 2011). Two years later, the groundbreaking studies of Hannum et al. (2013) and S. Horvath (2013) have set the stage for epigenetic clocks that can estimate a person's chronological age with unprecedented accuracy. In the following years, a variety of epigenetic age predictors were developed, and it was shown that epigenetic age predictions of several clocks correlate with overall mortality (Lin et al., 2016; Marioni et al., 2015) and are influenced by age-associated diseases or characteristics (Bell et al., 2019; Field et al., 2018; Moqri et al., 2024b). To this end, next-generation epigenetic clocks were developed that are based not only on CpG dinucleotides correlated with chronological age, but also capture specific disease-associated parameters (Johnson and Shokhirev, 2025) – such predictors are even more powerful in estimating biological age, and, therefore, raise high hopes for geroscience and age-adapted personalized medicine (Belsky et al., 2022; Levine et al., 2018; Lu et al., 2019). However, biological age is a complex construct that cannot be captured by a single metric. Therefore, epigenetic clocks should be regarded as valuable biomarkers rather than comprehensive measures of biological aging (Johnson and Shokhirev, 2024). The ultimate clinical utility of epigenetic clocks remains to be proven.

Either way, the finding that aging is associated with epigenetic modifications is intriguing – and this was not only observed on DNA methylation level, but also in the histone code (de Lima Camillo et al., 2025) and chromatin accessibility (Morandini et al., 2024; Ucar et al., 2017). Furthermore, oxidative conversion of guanine to 8-oxoguanine (8-oxoG), a DNA lesion commonly generated by reactive oxygen species (ROS), has emerged as a potential epigenetic-like modification. Beyond serving as a marker of oxidative damage, 8-oxoG may influence gene expression and contribute to redox-dependent adaptive responses ("redoxogenetic adaptation") during aging (Radak et al., 2024).

Epigenetic programs are known to govern developmental processes and hence the regular changes with age appeared indicative for an underlying program. Notably, while age-associated DNA methylation changes occur preferentially at specific sites in the genome, they are enriched at sites that are regulated during development. For example, age-associated DNA methylation is enriched in targets of Polycomb complexes (particularly PRC2), which also play an essential role in development (Moqri et al., 2024a; Teschendorff et al., 2010). Another striking finding is that age-associated DNA methylation is completely reversed upon reprogramming into pluripotent state (Weidner et al., 2014) – so it is clearly possible to reset epigenetic clocks to zero, but it remains unclear whether partial rejuvenation is possible. Attempts of partial rejuvenation remain controversial and it is not clear if a stable state of partial rejuvenation exists (Puri and Wagner, 2023).

With regard to the above considerations on different aging rates in different species, it is noteworthy that epigenetic clocks tick at different

speeds in different species (Lu et al., 2023). DNA methylation-based clocks have been described across mammals and in many vertebrates. Furthermore, the correlation of epigenetic aging progresses with life expectancies has even been observed when comparing two different dog breeds with known differences in lifespan (Lowe et al., 2018). These exciting findings suggest that epigenetic drift may act as the balance spring in the "clockwork" of aging. On the other hand, it is unlikely that mammalian-type epigenetic clocks are applicable to most invertebrates. This is particularly true for dipterans (e.g., flies, mosquitoes), which have lost their DNA methylation tools, as have many insect species of other large orders (Maleszka, 2025). If epigenetic clocks are relevant to the aging of these species, they should therefore be associated with other epigenetic markers, which need to be further investigated in the future (Maleszka, 2025). To date, it has not been proven whether epigenetic clocks are functionally relevant to the aging process or whether they are merely a by-product that can be used as a biomarker.

2.4. The stochastic component of epigenetic clocks

Most epigenetic clocks are based on hundreds or fewer CpGs, often selected by algorithms that favor CpGs with rather linear changes with aging and that work best together to predict chronological age. While relatively few specific regions exhibit such pronounced DNA methylation changes with age, it has been demonstrated that, depending on tissue type, sample number, measurement method and statistical analysis, more than 10% of CpGs across the genome exhibit significant age-related changes (Bernabeu et al., 2023). Not all age-associated CpGs show a linear relationship with chronological age, but especially those selected for epigenetic clocks have either a linear or logarithmic progression (Perez-Correa et al., 2025). Thus, age-related epigenetic changes do not appear to be limited to very specific sites in the genome, but they are clearly enriched at certain regions in the genome: hypomethylated regions are usually in intergenic regions, while hypermethylation is enriched in specific promoter regions (Christensen et al., 2009).

Why are these genomic regions susceptible to age-related changes in DNA methylation, and what drives these changes? During development, DNA methylation appears to be coordinated by DNA methyltransferases (DNMTs) and demethylation complexes (e.g. TETs) that are directed to specific sites in the genome. Albeit age-associated differentially methylated regions often span over several hundred base pairs, there is often not much evidence based on binding motives for such programmatic modulation of an epigenetic aging program. One exception is that age-associated DNA methylation is enriched in PRC2 target genes (Moqri et al., 2024a) and these modifying complexes can interact with DNMTs. However, for most age-associated changes such co-factor recruitment or binding signatures are largely unclear. Furthermore, amplicon sequencing of age-associated regions showed that neighboring CpGs are not regulated together, but rather develop highly dynamic modifications within individual DNA strands (Han et al., 2020). Therefore, it has long been assumed that age-associated DNA methylation is due to epigenetic drift, which can be perceived as an increase in entropy or loss of control (Chan et al., 2025; Teschendorff et al., 2013).

Recently, several studies have further supported the notion that epigenetic clocks have a strong stochastic component (Tarkhov et al., 2024). Mathematical models indicated that even pure stochastic assumptions might explain the epigenetic clockwork – an imperfect maintenance mechanism of DNA methylation might therefore drive DNA methylation levels to an equilibrium state, which is unique for each CpG site and not necessarily close to a 50% DNA methylation level (Meyer and Schumacher, 2024; Tong et al., 2024). This finding is therefore more consistent with the defect accumulation theory – and it is a strong argument for the idea that epigenetic clocks do not have to follow a program. Even if epigenetic clocks should be perceived more as stochastic epigenetic drift, it is unclear why this loss of control is not counteracted at these sites. Furthermore, as indicated above, epigenetic clocks tick at different speeds in different species – so here too, the rate of stochastic accumulation of age-related DNA methylation could well be influenced in terms of evolution.

In contrast to aging, development is widely considered to be orchestrated by specific epigenetic programs (Laird, 2010; Reik et al., 2001). However, it should be noted that it is also largely unclear how developmental epigenetics are regulated across the life-time of the organisms. The DNA methylation landscape is remarkably consistent for certain cell types and developmental stages, and DNA methylation levels can often be determined relatively accurately between 0% and 100% – and since each cell has only two copies of DNA, this means that even such development-associated DNA methylation patterns have a probabilistic component. Furthermore, in analogy to age-related changes, such cell type-specific modifications are not limited to a few functional promoter regions but are observed across the entire genome, where the binding sites for methylating or demethylating complexes are often unknown (Loyfer et al., 2023; Moss et al., 2018; Schmidt et al., 2020). When analyzing DNA methylation patterns associated with specific cell types it becomes again evident that neighboring CpGs on individual strands are not regulated together (Franzen et al., 2021). Obviously, there has to be a coordinating mechanism of developmental epigenetics, but we should accept that epigenetic modulation always has a stochastic component – including processes that are clearly perceived as developmentally regulated (Feinberg and Irizarry, 2010; Pujadas and Feinberg, 2012). Methylation entropy has been suggested to be related to specific DNA binding motifs, regulatory DNA, and CpG density, suggesting a role for epigenetic entropy in developmental plasticity (Fang et al., 2023). Furthermore, many developmental processes unfold at defined stages of the life course – such as sexual maturation, growth cessation, or reproductive senescence – yet the molecular mechanisms that determine the precise timing of these transitions remain incompletely understood. Therefore, we need to better understand the interplay of stochastic and programmed regulation in epigenetics – during aging and development.

2.5. Is epigenetic aging co-regulated within a network?

Although DNA methylation is arguably the best-characterized epigenetic modification, it is surprising how little we understand about how methylation is gained or lost at specific genomic loci. Even less clear is how DNA methylation states are coordinated across the entire genome, and how coordination extends across homologous chromosomes (Bozic et al., 2022). Emerging evidence suggests that age-associated methylation changes do not occur in isolation but may instead be embedded within higher-order regulatory networks (Wagner, 2025a). Even the aberrant DNA methylation patterns associated with malignant transformation and tumor development seem to be co-regulated within highly consistent modules (Varona Baranda et al., 2026).

We recently demonstrated that targeted epigenetic editing of individual age-associated CpG sites induces reproducible "bystander" methylation changes at additional loci across the genome (Liesenfelder et al., 2025). Importantly, these secondary modifications were not attributable to direct off-target effects of genome editing and were significantly enriched at other age-associated CpGs. Notably, the bystander changes occurred at sites that both gain and lose methylation with age. Therefore, targeted manipulation of single CpGs does not currently permit directed resetting of the epigenetic clock. However, these findings point toward the existence of an interconnected epigenetic network that may coordinate age-associated DNA methylation dynamics at the genome-wide level. Although the molecular basis of this co-regulation remains unknown and requires further validation, the observation of structured, reproducible interactions among age-associated CpGs supports the idea that aging-associated methylation patterns may comprise a regulated system-level component rather than purely independent stochastic events (Wagner, 2025a).

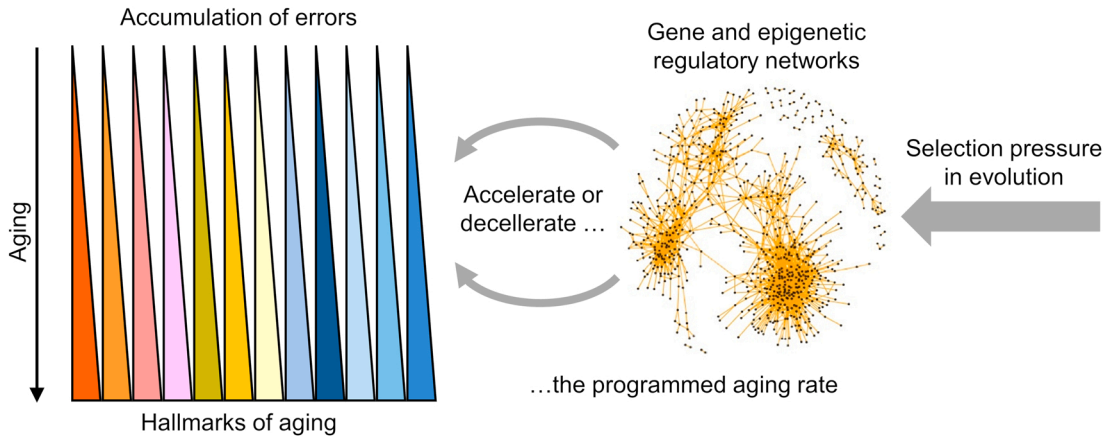

Fig. 3. Integrating Error, Program, and Selective Pressure. If the hallmarks of aging can be modulated through available molecular mechanisms, then error-based and programmatic theories of aging need not be mutually exclusive. The rate of aging may be influenced by genetic and epigenetic regulatory networks that govern the accumulation, repair, and tolerance of molecular damage. In this framework, the pace of aging could be shaped to align with species-specific characteristics, such as generation time, and the impact of the ecological niche.

2.6. Integrating program and error

While many researchers reject the possibility that aging has programmed and evolutionary purposeful components (Meyer et al., 2025), it is important to note that stochastic and programmed components are two sides of the same coin. As explained above, the hallmarks of aging can – at least in principle – be counteracted at the cellular level. Furthermore, there is substantial evidence that the rate of aging can be modulated between species in response to environmental and evolutionary stresses. It is widely accepted that the accumulation of genetic damage contributes to the aging process (Schumacher et al., 2021). For example, mutations in homologous recombination or other DNA repair pathways are associated with progeroid syndromes, and several of these mutations seem to alter the epigenetic clock trajectories (Perez et al., 2024). In addition, it has been shown that genetic perturbations can directly influence DNA methylation patterns over genomic distances of up to several kilobases, thereby affecting epigenetic age estimates (Koch et al., 2025). However, this does not imply that DNA damage is the sole driver of aging (Wagner, 2025b), but rather that genomic instability and epigenetic modulation are mechanistically intertwined. Age-associated epigenetic modifications are likely to have functional relevance, even when their effects are subtle, indirect, or not immediately reflected at the level of steady-state gene expression. Importantly, many of these changes appear to arise in part through stochastic processes, yet they may still follow reproducible patterns.

Assuming that molecular defects accumulate at a species-specific rate, this phenomenon can be interpreted quasi-programmatically – not necessarily as the result of a specific aging process, but as the consequence of regulated biological processes interacting with entropy and cumulative damage (Blagosklonny, 2006). In this broader sense, an ‘aging program’ could be understood as the characteristic pace at which molecular changes accumulate over time. In fact, the timing of many developmental transitions may also be controlled by stochastic but progressively accumulating epigenetic dynamics that function as a kind of biological clockwork unfolding over the entire lifespan (Fig. 3).

3. Conclusion

The long-standing debate about whether aging is primarily due to the gradual accumulation of molecular defects or to an evolutionary development process continues to be actively pursued. However, rather than viewing these perspectives as mutually exclusive, they can be integrated into a unified framework in which the concept of ‘program’ is expanded to include the regulation and modulation of defect accumulation, which occurs at a species-specific rate. To many researchers, it may seem obvious that stochastic and programmed aspects are intertwined, whereas the relatively harsh formulation of other researchers indicating that aging should only be viewed as the ‘chaotic, stochastic reality of biology’ (Kirkwood and Melov, 2011; Meyer et al., 2025) may be misleading. An integrative model of aging does not necessarily require direct selection as a specific program during evolution, but it does not rule out the possibility that aging can be selected for. If aging does indeed resemble a purposeful process in evolution, it could, together with sexual recombination, be one of the most successful strategies in evolution for promoting genomic recombination, as all higher species are bound to aging. Furthermore, the perception that the accumulation of errors, such as mutations or epigenetic drift, ultimately drive aging explains why no individual can easily escape aging. It therefore seems inappropriate to take dogmatic positions that deny the existence of a programmed component in the aging process. Whether epigenetic clocks play a functional role in this process remains unproven, but given the similarities to other developmental processes, it appears likely that aging is at least in part driven by epigenetic changes, which may be coordinated within an epigenetic network across the genome.

Author contributions

W.W. conceived and wrote this commentary.

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