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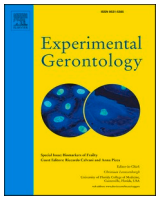

Review

An evolutionary perspective of lifespan and epigenetic inheritance

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ABSTRACT

In the last decade epigenetics has come to the fore as a discipline which is central to biogerontology. Age associated epigenetic changes are routinely linked with pathologies, including cardiovascular disease, cancer, and Alzheimer's disease; moreover, epigenetic clocks are capable of correlating biological age with chronological age in many species including humans. Recent intriguing empirical observations also suggest that inherited epigenetic effects could influence lifespan/longevity in a variety of organisms. If this is the case, an imperative exists to reconcile lifespan/longevity associated inherited epigenetic processes with the evolution of ageing. This review will critically evaluate inherited epigenetic effects from an evolutionary perspective. The overarching aim is to integrate the evidence which suggests epigenetic inheritance modulates lifespan/longevity with the main evolutionary theories of ageing.

1. Introduction

1.1. Epigenetics and ageing

Biogerontology has emerged from a field on the margins of biological research in the 20th century to a mainstream discipline which is now firmly embedded within 21st century biomedical research (García-Peña et al., 2023; Witham et al., 2022). The growing status of biogerontology is brought into sharp focus when its relationship with epigenetics is examined. According to PubMed in 2022, 1076 papers were published which had epigenetics and "ageing"/"aging" in their abstract. The intense focus on ageing and epigenetics has generated intriguing questions about the exact nature of their relationship. DNA methylation (DNAm) is the most extensively studied epigenetic mechanism (Greenberg and Bourc'his, 2019; Mattei et al., 2022). DNAm occurs at cytosines in CpG dinucleotides to form 5-methylcytosine (Hotchkiss, 1948; Moore et al., 2013; Wyatt, 1950). Age related changes to DNAm strongly correlate with health (Cribb et al., 2022; Hata et al., 2023; Mc Auley et al., 2018; Morgan et al., 2018; Morgan et al., 2020; Zagkos et al., 2019). Moreover, methylation clocks are incredibly precise at statistically correlating DNAm levels with chronological age in a wide variety of species (Duan et al., 2022; Horvath, 2013; Horvath et al., 2022; Prado et al., 2021; Stubbs et al., 2017). However, an important caveat exists. To date, no explanation exists which can mechanistically account for the purely correlative predictions generated by methylation clocks. Indeed, it is possible DNAm alterations at particular clusters of CpGs could have a limited, or no role in ageing; and are merely indicative of changes, which are a by-product of this process (Bell et al., 2019; Ying et al., 2022). This is not the only aspect of the epigenetics-ageing nexus which requires further elucidation. Another conundrum centres on how age associated DNAm changes/epigenetic processes more broadly intersect with the evolution of ageing. To appreciate the problem, it is necessary to introduce the main evolutionary theories of ageing.

1.2. Ageing and evolutionary theory

1.2.1. The traditional non-adaptive theories

From an evolutionary standpoint it is broadly acknowledged that ageing is a nonadaptive process which is due to the declining force of natural selection (NS) with age (Charlesworth, 1994; Flatt and Partridge, 2018; Gavrilov and Gavrilova, 2002; Hamilton, 1966; Rose, 1991). This idea is captured in the mutation accumulation theory (MAT) (Medawar, 1952). The MAT postulates that ageing is due to the passive build-up of harmful alleles which are only functionally expressed post reproductively; as recently evidenced by a study which identified a decline in purifying selection with age in humans, mice, and insects (Cheng and Kirkpatrick, 2021). The antagonistic pleiotropy theory (APT) is an extension to the MAT, which posits that ageing is the result of alleles which have opposing effects (Williams, 1957). Certain alleles confer a reproductive advantage in early life but are detrimental in later years. Many genes associated with human disease display these properties (Byars and Voskarides, 2020). The disposable soma theory (DST) also suggests ageing is due to the diminishing capacity of NS (Kirkwood, 1977). Unlike the MAT and the APT, however the DST is a physiological

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interpretation of ageing (Kirkwood, 2005). According to the DST ageing is the result of the strategic partitioning of energy between somatic maintenance and the germ line. The ecological context the organism evolved in underpins how the energy is partitioned. According to this evolutionary model sufficient energy is directed towards somatic preservation for an organism to reach reproductive age. However, the energy allocated towards somatic maintenance and repair is insufficient for indefinite survival. As a result, damage accumulates due to inadequate investment in somatic maintenance and repair. The cornerstone of the DST is the trade-off between reproduction and somatic investment (Kirkwood and Holliday, 1979). As reproduction is costly, according to the DST investing early in this process is essential at the expense of fertility in later life. The trade-off between reproduction and lifespan in turn impacts the rate of ageing; a prediction which is supported by empirical data (Bargas-Galarraga et al., 2023; Lemaître et al., 2015).

1.2.2. Adaptive theories and the evolution of ageing

In addition to the non-adaptive evolutionary theories, there are many ideas which suggest ageing is an adaptive process. Adaptive ageing is discussed in depth in this special issue of Experimental Gerontology (Pamplona et al., 2023). It is also worth briefly discussing adaptive ageing here. The basis of evolutionary thinking around adaptive ageing traces its origins to the work of Weismann, who theorised that ageing evolved as an adaptive process which is essential for removing older members of a species to free up resources for younger individuals (Weismann and Poulton, 1891). Although Weismann did alter his thinking at a later point. Despite this, the conceptual attractiveness of this line of thinking has influenced the development of many ideas which can be categorised broadly as programmed/adaptive ageing. One such idea is that of phenoptosis or programmed organism death (Libertini et al., 2022; Skulachev, 1999, 2012). This notion centres on genes having inherent features which make individuals who possess the genes vulnerable to programmed death. Other ideas have focused on inclusive fitness. Such as the recent "adaptive death" idea which centres on using inclusive fitness and kin selection, as a basis for interpreting the ageing process in *Caenorhabditis elegans* (*C. elegans*). The authors posit that "adaptive death" increases inclusive fitness (Galimov and Gems, 2021).

1.3. Evolution and epigenetics

It remains unknown how the theories outlined above reconcile with age-associated epigenetic changes. Although, recent work did address this puzzle (Mc Auley, 2021). A range of evolutionary concepts were evaluated together with epigenetic data. It was concluded that in humans age associated DNAm changes can align with many evolutionary frameworks. It was also revealed that some recent evolutionary ideas have interesting parallels with the traditional theories. This is exemplified by the epigenetic clock theory (ECT) (Horvath and Raj, 2018). The ECT predicts that ageing is a by-product of development and maintenance programmes, with DNAm clocks the emergent cellular component of the programmes. The ECT overlaps with the APT the DST and programmed ageing. It also synergises with other ideas, for instance, it has similarities with the hyperfunction/development theory of ageing, an idea which suggests certain genes are fine-tuned for elevated biosynthesis in early life, but the declining force of NS results in sub-optimal physiology in later years (Blagosklonny, 2022; de Magalhães and Church, 2005; Gems, 2022). Epigenetics has also been embedded within ideas which centre on programmed ageing. For instance, DNAm has been suggested to be the proximate mechanism which actively controls programmed ageing (Mitteldorf, 2016). While, epigenetics continues to be at the centre of other emerging ideas, including a recently introduced information theory (de Magalhães, 2023).

Given epigenetic ageing intersects with so many different ideas it can be argued that it has yet to be fully reconciled with evolutionary theory. Burgeoning experimental data further emphasizes the conceptual gap between epigenetics and evolutionary theory. The data centres on recent experimental observations which have revealed that certain organisms have the capacity to transmit environmentally induced phenotype alterations to their offspring (Ashapkin et al., 2023; Lee et al., 2023; Santilli and Boskovic, 2023; Wan et al., 2021; Xia and de Belle, 2016). When this process spans one generation it is known as intergenerational epigenetic inheritance (IEI) (Stäubli and Peters, 2021). If the effects extend over multiple generations it is referred to as transgenerational epigenetic inheritance (TEI) (Burton and Greer, 2022; Perez and Lehner, 2019). The extent to which this form of non-genetic inheritance impacts Darwinian fitness is not apparent. Its relevance to the evolution of ageing is also unclear. The next sections will examine IEI and TEI. The aim is to gain a deeper understanding of the intersection between epigenetic inheritance, longevity/lifespan and the evolution of ageing. For conceptual clarity and to aid with our discussion it is important to explicitly define what is meant by the term's lifespan and longevity. Lifespan is defined as the maximum amount of time an organism can live, while longevity is defined as the mean age acquired by individuals of a population at the time of mortality (Brooks-Wilson, 2013).

2. Inherited epigenetic effects which impact lifespan/longevity in canonical organisms

2.1. Worms

Several inherited mechanisms have been identified which impact offspring fitness in canonical organisms (Table 1). *C. elegans* lifespan can be increased by mutating COMPASS (Greer et al., 2010). COMPASS is a multiprotein complex required for the methylation of histone 3 lysine 4 (H3K4) (Shilatifard, 2012). When COMPASS mutants are mated with wild type worms longevity phenotypes are generated (Greer et al., 2011). Offspring do not have the COMPASS mutation, but the long-lived phenotype is transgenerationally inherited (Greer et al., 2011). An epigenetic modification has been identified which explains this phenomenon. It has been found that COMPASS mutants (wdr-5) possess elevated levels of H3K9me2 (Kerr et al., 2014). The wdr-5 mutants can pass on increased longevity to their offspring. This implies that elevated H3K9me2 is responsible for the longevity phenotype. Other lines of evidence support the idea that histone methylation is important for epigenetic inheritance in this organism. For instance, histone H3K4 trimethylation (H3K4me3) has been associated with a multigenerational non-genetic response to obesity (Wan et al., 2022a). This could be due to H3K4me3 acting as a regulator of fat accumulation which directly influences lifespan in worms (Han et al., 2017). However, modification of histones is not the only epigenetic mechanism associated with transgenerational inheritance in worms. Small RNAs (sRNAs) molecules also have the capacity to contribute to inherited transgenerational effects. Starvation-induced developmental arrest results in the synthesis of sRNAs that are transgenerationally inherited in offspring which possess a longevity phenotype (Frolows and Ashe, 2021; Houri-Zeevi and Rechavi, 2017; Rechavi et al., 2014). Experimental observations have been reinforced by theoretical work which suggests sRNAs are pivotal to epigenetic inheritance (Silva et al., 2021).

2.2. The Lansing effect in worms

The Lansing effect is theorised to be a transgenerational signal whereby lifespan is shortened in the offspring of old parents (Lansing, 1947). There is experimental evidence that the Lansing effect exists in many species (Ivimey-Cook et al., 2023; Monaghan et al., 2020; Qazi et al., 2017). In worms dietary restriction (DR) has been shown to enhance the fitness of ageing female *Caenorhabditis remanei* parents, but diminishes the fitness of their offspring (Mautz et al., 2020). In further work it was revealed that worms who underwent temporary fasting (TF) had a reduced risk of mortality and enhanced late-life reproduction (Ivimey-Cook et al., 2021). However, when the F3 descendants

Table 1
Examples of intergenerational/transgenerational inheritance effecting longevity/lifespan.

Organism	Study summary	Observations	Mechanism/key outcome
C. elegans	Drop in the H3K4me3 chromatin modifiers, ASH-2, WDR-5 or SET-2 in parental generation associated with extended lifespan of descendants (Greer et al., 2011)	Altering chromatin modifiers in parents induces an epigenetic 'memory' of longevity in descendants.	Altered histone methylation
C. elegans	Starvation-induced developmental arrest administered (Rechavi et al., 2014)	Offspring of starved *C. elegans* showed increased lifespan	Small RNAs were inherited through three consecutive generations
C. elegans	H3K9me2 protects lifespan against the transgenerational burden of COMPASS activity (Kerr et al., 2014)	Offspring of wdr-5 mutants outcrossed to wild-type worms for many generations lived longer than wild-type organisms, despite normal WDR-5 activity. This was associated with increased H3K9me2 levels.	Elevated levels of H3K9me2
Caenorhabditis remanei	Females used to examine the effect of DR on them and their offspring (Mautz et al., 2020).	Increase in fecundity, survival, and stress resistance after re-exposure to food compared with their counterparts with constant food access. Offspring had reduced early and lifetime fecundity, and were smaller at sexual maturity.	Suggested these observations support direct trade-off between investment in soma and gametes.
C. elegans	Investigated the cumulative effect of parental age on offspring, using three parental age regimes (Travers et al., 2021)	Hermaphrodites increased parental investment with advancing age, resulting in fitter offspring who reach their reproductive peak earlier.	Suggested results inconsistent with the idea that old parents transfer a cumulative detrimental 'ageing factor' to their progeny.
C. elegans	Investigated the effect of temporary fasting on mortality risk, age-specific reproduction and fitness across three generations (Ivimey-Cook et al., 2021).	TF reduced mortality risk and improved late-life reproduction in P0 individuals to TF (P0). TF effected F1-F3 generations both negatively and positively.	Suggested that transgenerational trade-offs accompany the benefits of DR.
C. elegans	*C. elegans* treated with heat shock (Wan et al., 2021).	N6-methyldeoxyadenine (6 mA) mediates the transfer of a transgenerational longevity mechanism. Pro-survival mechanism was passed down to five generation of progeny.	N6-methyldeoxyadenine (6 mA)
C. elegans	This was a mutation accumulation (MA) experiment and downregulated insulin/IGF-1 (IIS) signalling in half of 400 MA lines by silencing daf-2 gene expression using RNA interference (RNAi) across 40 generations (Duxbury et al., 2022).	Identified benefit to fitness from multigenerational reduction of IIS. Enhanced under stress	No specific epigenetic mechanism was implicated
D. melanogaster	Flies subjected to various post-eclosion dietary manipulations (PDM) (Xia and de Belle, 2016)	Low protein (LP) and high protein PDM decreased longevity, while the intermediate protein diet extended longevity up to the F3 generation. No evidence for a trade-off between longevity and reproduction.	No specific epigenetic mechanism was implicated.
D. melanogaster	Post-eclosion dietary manipulation (Xia et al., 2016)	PDM with an LP diet upregulated E(z), an H3K27 specific methyltransferase. This resulted in higher levels of H3K27me3. This was synonymous with shortened longevity of F0 flies and their F2 offspring.	E(z)-mediated H3K27me3 is one epigenetic mechanism which could transgenerationally modify lifespan in *D. melanogaster*
Mus musculus	KDM1 transgenic mice used (Siklenka et al., 2015)	Increased expression of the chroma-tin modifier, KDM1A during spermatogenesis induced significant developmental defects in offspring. Persisted paternally for three generations. Survivability; with each successive generation decreased.	Key event in this mouse model which led to offspring abnormalities was alternations in histone methylation in developing sperm

underwent TF early in life, this reduced their fitness, and increased their risk of mortality. Other work is more equivocal. *C. elegans* hermaphrodites have been observed to increase their investment in offspring as they get older (Travers et al., 2021). Offspring were fitter and reached their reproductive peak sooner. Most recently, in *C. elegans* multigenerational adulthood-only daf-2 RNA interference (RNAi) parents were observed to increase investment in somatic maintenance (Duxbury et al., 2022). This was associated with an increase in lifespan with no survival/reproductive cost for parents or offspring. Because reduced daf-2 expression during development had fitness costs it was posited this could be accounted for from an evolutionary perspective by the development theory of ageing.

2.3. Insects

Drosophila melanogaster (D. melanogaster) has been ubiquitously employed to demonstrate transgenerational inheritance (Fridmann-Sirkis et al., 2014; Karunakar et al., 2019; Mu et al., 2021; Sun et al., 2023). Transgenerational effects in *D. melanogaster* suggest parental diet can affect body size, development time, and egg quality of future generations (Deas et al., 2019). Moreover, when male *D. melanogaster* are exposed to a high population density they have offspring which display an increased competitive ability (Dasgupta et al., 2019). Focusing specifically on lifespan. In recent work the sucrose level of adult *D. melanogaster* was adjusted post mating (Camilleri et al., 2022). It was revealed that parental flies lived longer when sucrose treatments were matched, but they had offspring with shorter lifespans. The mechanism (s) underpinning this are unclear. It was suggested this was due to a trade-off between parental investment in offspring quality versus offspring quantity, which is manifested during certain diets. Non-genetic inheritance in flies could involve histone posttranslational modifications (Sun et al., 2023; Zenk et al., 2017). Diet studies have helped revealed this. In *D. melanogaster* an intermediate protein-carbohydrate diet increased lifespan through to the F3 generation (Xia and de Belle, 2016). The epigenetic mechanism was identified in further work. The level of E (z) was upregulated during a low protein diet. E(z) is a methyltransferase which enhances the levels of H3K27 trimethylation (H3K27me3) (Xia et al., 2016).

2.4. The Lansing effect in insects

The Lansing effect has also been investigated in insects. In the neriid fly *Telostylinus angusticollis* it has been observed that paternal age impacts offspring lifespan in an equivalent manner to maternal age (Wylde et al., 2019). This lasted over two generations. In an intriguing study involving antler flies (Protopiophila litigata) (Angell et al., 2022).

Parental age at reproduction was recorded in a laboratory. Male offspring were then released into the wild. Interestingly, advanced paternal, but not maternal age, increased sons' adult lifespan, while parental age did not impact sons' reproductive ageing.

3. Epigenetic inheritance in mammals

3.1. Rodents

In mammals most studies of TEI have involved rodents (Bohacek and Mansuy, 2015). In fact, experimental strategies involving laboratory rodents have been used extensively to explore transgenerational effects (Anwer et al., 2022; Ben Maamar et al., 2018; Carone et al., 2010; Weaver et al., 2004; Wei et al., 2014). Investigations have revealed that key rodent behavioural phenotypes, including socialization, addictive tendencies, and stress response can be transgenerationally modulated by environmental perturbations (Gapp et al., 2014a; Jawaid and Mansuy, 2019). Diet is also associated with transgenerational effects in rodents. Metabolic disturbances in rat offspring have been observed to correlate with a maternal diet high in fat (Woyames et al., 2022). Time-restricted feeding (TRF) during pregnancy also effects rat offspring (Prates et al., 2022). This was characterised by dysregulated metabolism in later life. It was suggested TRF 'programmed' rat offspring for altered metabolism during adulthood. Parsimonious logic would imply this is an AP effect, whereby offspring are 'programmed' to survive in early life at the expense of survival in later life.

Other forms of dietary manipulation have been associated with transgenerational effects in rats. Interestingly, resveratrol has been suggested as a mediator of non-genetic inheritance (Sharma et al., 2022). A study which intergenerationally treated rats with resveratrol observed that rat offspring had smaller litters and a reduced life expectancy (Sharma et al., 2022). The mechanism(s) underpinning this remain obscure. However, resveratrol effects several epigenetic processes, including the activity of the methyl transfer enzyme, DNMT3b (Fernandes et al., 2017; Qin et al., 2014). Other mechanisms could be involved in TEI in rodents. Some are consistent with those observed in worms and flies. For example, altered H3K4me3 demethylase in mice sperm is thought to be the conduit for paternally inherited transgenerational effects in this rodent (Siklenka et al., 2015). H3K4me3 has also been associated with the transgenerational inheritance of metabolic dysfunction in mice (Macrae et al., 2022).

3.2. Humans

In humans inherited transgenerational effects have been implied for decades (Morgan and Whitelaw, 2008; Pembrey et al., 2006). Indeed, the negative impact of prenatal undernutrition on offspring health has been widely documented (Barker and Osmond, 1986; Heijmans et al., 2008; Roseboom et al., 2006; Schulz, 2010; Shen et al., 2019). Epidemiological data has associated grandparent nutrition to the longevity of their grandchildren (Bygren et al., 2001; Kaati et al., 2007). An obstacle preventing the wide spread acceptance of non-genetic inheritance in humans is the challenge associated with identifying biological mechanisms based on epidemiological observations (Horsthemke, 2018). Despite this, evidence from mammals, has led to speculation that non-genetic transgenerational inheritance is possible in humans. For instance, it has been observed that epigenetic marks are not entirely erased in the zygote and germ cells of mice (Hackett et al., 2013). This provides a route for DNAm changes to be inherited in mammals, including humans. Extremely tentative recent data implies epigenetic inheritance influences human longevity. The GrimAge acceleration epigenetic clock (GrimAA) (Lu et al., 2019), was used to observe that offspring of parents who consumed high levels of alcohol suffered a 4.43-year increase in GrimAA (Carter et al., 2022).

3.3. The Lansing effect in mammals

The Lansing effect has also been suggested to exist in mammals (Péron et al., 2019). Maternal age at reproduction has been shown to influence the healthspan of human offspring (Kenny et al., 2013). Increased maternal age is associated with distinct DNAm changes in human offspring (Markunas et al., 2016). Evidence exists from other mammals that a maternal age effect on offspring is not unique to humans. Maternal age has been shown to modulate offspring longevity in Asian elephants. Offspring of older mothers had reduced survival (longevity) but increased reproductive success (Reichert et al., 2020). Similar observations have been made in bottlenose dolphins were calf survival decreases with maternal age, while calves who have older mothers have lower survival (Karniski et al., 2018). This tacitly suggests maternal age could negatively affect offspring longevity in long lived mammals.

4. Reconciling inherited effects with evolutionary theory

So far, this work has provided some compelling examples of IEI and TEI. It would appear such phenomena are relevant to a variety of 'simple' organisms. In addition, several putative biological mechanisms have been suggested to mediate IEI/TEI in these organisms. Some of these mechanisms effect lifespan/longevity. However, irrespective of the processes which may be involved in IEI/TEI, it is crucial that non-genetic inheritance is reconciled with ageing evolutionary theory. To date, no satisfactory explanation has been posited which firmly integrates ageing evolutionary theory with non-genetic inheritance. As Fig. 1 illustrates it may be the case that a new paradigm is needed to assimilate evolutionary theory with recent experimental findings. In this section I speculate how non-genetic inheritance could potentially be integrated with each of the main non-adaptive evolutionary theories of ageing.

4.1. Mutation accumulation

A way to examine the relationship between the MAT and epigenetic inheritance is to view this theory through a slightly different evolutionary lens. A more nuanced interpretation considers the accumulation of epimutations and genetic mutations with age. It is conceptually plausible this combined mutational load is a significant determining factor of age-associated gene dysregulation (Gentilini et al., 2015; Klironomos et al., 2013). Combining genetic and nongenetic inheritance has been modelled previously using the Price equation (Day and Bonduriansky, 2011). It is possible to adapt this conceptualization in order to have the MAT as its kernel. Under this view a scenario can be explored whereby the effects of accumulated epimutations are inherited. The negative or positive effects of this epimutational load are then carried by the offspring. This is conceivable if a parent has its offspring later in life. In fact, in *Drosophila* Marinkovic and Bajraktari provide evidence for the accumulation over many generations of age related 'micromutations' (Marinkovié and Bajraktari, 1988). The 'micromutations' impacted development time and longevity. Specifically, they found that age-affected events were generated by ontogenetically 'programmed' alterations in genetic loads at specific chromosomes, which were inherited by future generations. Interestingly, Lamb suggests that the changes were not the result of genetic mutations, but were the result of epimutations that were transmitted from parents to offspring (Lamb, 1994). Environmental changes could also result in a build-up of epimutations. Indeed, environmental stress promotes sperm epimutations in rats, which persist for several generations (Anway et al., 2005). It would be worthwhile identifying how a build-up of epimutations impact offspring lifespan/longevity. Deteriorated sperm quality effects reproductive fitness in humans (Aitken, 2017; Jenkins et al., 2016). Although, it is uncertain to what extent impairment of sperm quality determines health in human offspring if at all (Omu, 2013). If it does, the inheritance of

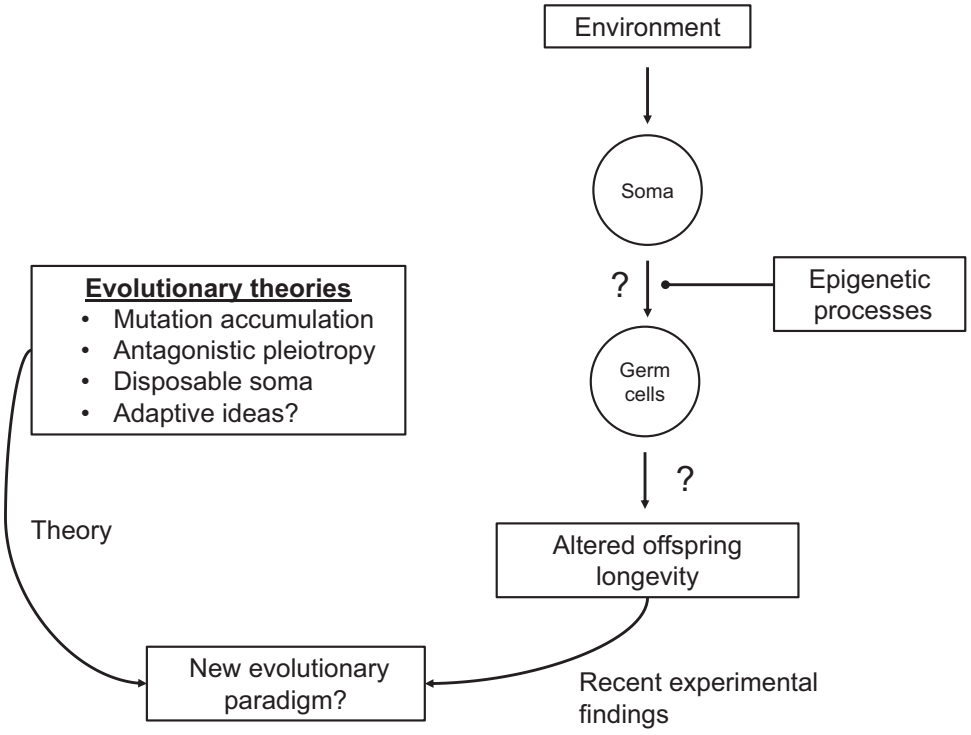

Fig. 1. An illustrative example of the conceptual gat that exists between evolutionary theory and empirical data surrounding non-genetic inheritance and longevity. An alternative paradigm may be needed to reconcile experimental data with evolutionary theory.

accumulated epimutations which affect sperm DNAm could impact the lifespan/longevity of future generations. However, it is likely that only certain types of epimutations are transgenerationally inherited. This view is supported by the observation that transgenerational differential DNAm regions in sperm have unique consensus DNA sequence motifs that are associated with epimutations (Guerrero-Bosagna et al., 2014).

4.2. Antagonistic pleiotropy

It is essential to reiterate that the premise of the APT is that alleles which confer a reproductive advantage have detrimental effects in later life. A plethora of alleles have been identified in humans and other animals which display these properties (Austad and Hoffman, 2018; Bochdanovits and de Jong, 2004; Byars and Voskarides, 2020). Many of these alleles undergo epigenetic changes with age (Mc Auley, 2021). Moreover, epigenetic modulation of gene activity is responsible for a multitude of pleiotropic effects (Mozhui et al., 2023). Putting these observations together, a logically coherent way to integrate the APT with epigenetic inheritance is as follows; fluctuating environments are a threat to the survival of an organism (Lalejini et al., 2021). The solution provided by evolution is phenotypic plasticity (Pigliucci, 2005; Sommer, 2020). Phenotypic plasticity is the functional response of an organism to a specific environmental change (DeWitt et al., 1998; Sultan, 2021). This is an evolved trait which enables animals to buffer the effects of environmental heterogeneity (Price et al., 2003). It is conceivable that within this context pleiotropic alleles can be selected for despite their harmful effects in later life (DeWitt et al., 1998).

Epigenetic modification provides a framework which enables the expression of antagonist alleles to change throughout life. It must be emphasised however, that for the APT to fully fit with ideas which focus on the inheritance of non-genetic effects, a transgenerational epigenetic signal which can modulate gene activity across the life-span is required. A good candidate for this are homeobox genes which upon ageing undergo methylation changes (Bork et al., 2010; Jung and Pfeifer, 2015; Morgan et al., 2018). Other epigenetic mechanisms could also be involved in this process. As previously outlined histone H3K4me3 has been identified as a transgenerational epigenetic signalling mechanism in *C. elegans* (Wan et al., 2022b). Moreover, H3K4me3 plays a significant role in regulating gene expression during early mammalian development (Zhang et al., 2016). In addition, H3K4me3 influences gene expression across the lifespan in *Saccharomyces cerevisiae* and *C. elegans* (Cruz et al., 2018). Although, it is more likely that epigenetic mechanisms are involved in transgenerational epigenetic signalling and its effect on lifespan. In fact, histone H3 lysine 9 mono- or di-methylation (H3K9me1/2) was recently implicated in regulating lifespan in *C. elegans* daf-2-mutants (Huang et al., 2022). It is feasible it is also involved in epigenetic inheritance in this organism.

4.3. The disposable soma theory

Advocates of DST could argue IEI/TEI does not invalidate this theory. Older parents will have accumulated somatic damage. If it is assumed non-genetic changes can pass from a deteriorated soma to the germline. Then it is conceivable these effects can impact offspring fitness. Some evidence does add weight to these arguments. Firstly, increasing age is associated with lower quality oocytes in mammals (Ge et al., 2015; Sher et al., 2007). Secondly, this phenomenon can be accompanied by DNAm changes (Yue et al., 2012). However, due to the contradictory nature of the experimental evidence, the idea that information can pass from soma to the germ line remains speculative in humans at least (Horsthemke, 2018). The DST and non-genetic inheritance can also be examined if longevity is viewed as being moulded by the combined effects of resource availability in a parent and its offspring. This idea has been theoretically examined (Van Den Heuvel et al., 2016). A mathematical model was constructed based on the assumption that mothers encounter a trade-off between investment in their own somatic preservation, and allocation to offspring somatic maintenance. Simulations predicted that the optimal division of resources between maternal somatic maintenance, and investment in offspring somatic preservation, results in old mothers having progeny with reduced lifespan. This finding contradicts

observations from the wild. Older female African elephants invest more resources to their offspring (Lee et al., 2016). It is thought this guarantees offspring survival. This is evidenced by maternal longevity improving daughter survival to reproductive age, and increasing their reproductive rate.

Insights can also be gained when non-genetic inheritance and the DST are examined from the perspective of the intrauterine environment. Using DST logic, it is plausible that the foundations are laid during the intrauterine period which determine the extent to which offspring resources are divided between reproduction and somatic maintenance. A poor intrauterine environment could trigger epigenetic processes that mould development in anticipation of its postnatal environment. This idea is conceptually close to the predictive adaptive response (PAR) hypothesis, which suggests that the foetal milieu provides a forecast of the predicted postnatal environment (Bateson et al., 2014). PAR is in turn closely coupled to the 'thrifty genotype' model, which suggests metabolic programming confers a survival advantage in a postnatal environment of finite resources (Neel, 1962, 1999). The "thrifty phenotype" hypothesis is similar to the DST in that its central idea is that the goal of an organism is to survive to reproductive age, even if this increases the risk of mortality/disease in later life. Accordingly, organisms born into a resource deficient environment will reproduce earlier and have more offspring, at the expense of longevity. Mechanisms which underpin the "thrifty phenotype" remain to be identified. Processes linked to energy metabolism are logical candidates. H3K4me3 has been shown to act as a transgenerational epigenetic signal for regulating genes involved in lipid metabolism in *C. elegans* (Wan et al., 2022b). Epigenetic mechanisms involved in insulin signalling are also reasonable candidates. For instance, individuals who were prenatally exposed to the Dutch Hunger Winter, had, 6 decades later less DNAm on the imprinted insulin-like growth factor 2 gene, when compared to their unexposed siblings (Heijmans et al., 2008).

5. Programmed ageing: is the effect epigenetic inheritance has on lifespan/longevity an adaptive mechanism?

It is clear from this review that the environment an organism inhabits can impact the fitness of its offspring both negatively and positively (Álvarez-Quintero et al., 2021; Goos et al., 2019; Guerrero-Bosagna and Skinner, 2012; Ragsdale et al., 2022). As discussed there is a growing body of empirical data which suggests that environmentally induced inherited epigenetic effects could contribute to variations in lifespan/longevity (Greer et al., 2011; Ivimey-Cook et al., 2021; Jordan et al., 2019; Vaiserman et al., 2017). It could be argued that the impact inherited epigenetic effects have on lifespan/longevity is an evolutionary adaptation, and possibly even act as evidence for programmed ageing. However, this is not the case. In order to appreciate why, it is necessary to understand what defines an adaptation. An adaptive process can be defined in many ways (Reeve and Sherman, 1993). However, an exceptionally well thought out conceptual framework exists which is a powerful tool for determining adaptive processes (Stearns and Ebert, 2001). Four criteria are used (Table 2). In essence, an adaptation is a change in state which increases reproductive success. If an effect does not fit within this definition alternative explanations are essential. For instance, it may be the case that an epigenetic effect is disruptive/maladaptive rather than adaptive (Gapp et al., 2014b). This is the case with an epigenetic trap (ET) (O'Dea et al., 2016). An ET is a fluctuation in the environment which results in an epigenetic change that generates a heritable maladaptive phenotype which is not associated with an increase in phenotypic variance in a population. Given that many inherited non-genetic effects have been linked with a decrease in lifespan in model organisms (Mautz et al., 2020; Nilsson and Skinner, 2015; Rechavi et al., 2014); it is difficult to argue that in all cases the effects epigenetic inheritance has on lifespan is adaptive. In fact, it is more likely that it is maladaptive/disruptive.

Table 2
Criteria needed for an inherited effect to be recognised as adaptive*.

Criteria	Description
1. The selection criterion	Trait manifests as a heritable change correlating with reproductive success
2. The perturbation criterion	If trait optimal state has been predicted by a model and tested experimentally.
3. The functional criteria	Change in a phenotype which is induced within a particular environmental signal which associates with enhanced growth, survival or reproduction.
4. The design criterion	An adaptation is recognised by its complexity.

* Adapted from Stearns and Ebert (2001).

6. Discussion

It has long been viewed that environmental factors which induce epigenetic changes in somatic cells only impact the exposed generation, and that these alterations cannot be transmitted to their offspring. In this review I have highlighted a body of evidence which challenges this notion. Many of the examples explored in this work detail how epigenetic changes impact the lifespan/longevity of future generations. A drawback of these observations however is they have mainly been identified in 'simple' organisms, such as worms and flies. Despite this caveat, it can be broadly concluded that epigenetic inheritance influences lifespan/longevity in organisms with very short lifecycles. Moreover, some of the observations discussed in this review suggest that in mammals, DNAm signatures can be transmitted to gametes from the soma. However, the evidence for this is contradictory and arguments which advocate for epigenetic inheritance need to be subjected to rigorous empirical scrutiny (Perez and Lehner, 2019). It is empirical studies which have identified that adaptive phenotypic plasticity is an evolved trait that enables organisms to respond appropriately when faced with a particular environmental challenge (Acasuso-Rivero et al., 2019; Auld et al., 2010). An adjunct to this is that empirical investigations have revealed that transgenerational environmental effects can be adaptive when parental and offspring environments are the same (Bonduriansky and Day, 2009; Leimar and McNamara, 2015). However, it is inescapably contentious to suggest that lifespan/longevity will consistently be inherited non-genetically as part of an adaptive process when an organism is faced with a particular ecological challenge. A trait will only have an adaptive phenotypic response if it confers a reproductive advantage. It is crucial to acknowledge that NS will only favour an increase in lifespan when living longer is likely to yield a reproductive benefit, something which will lead to a new fitness optimum in the population (Grenier et al., 2016; O'Dea et al., 2016). Thus, to reiterate in the majority of cases where lifespan/longevity is modulated by non-genetic effects this is likely to be maladaptive.

A key goal of this review was to close the conceptual gap between ageing evolutionary theory and non-genetic inheritance. To achieve this the main evolutionary theories of ageing were speculatively reconciled with non-genetic inheritance. What can broadly be concluded as a result of this literature survey is that it is possible to synthesise arguments which mechanistically harmonize each theory with non-genetic inheritance. This is unsurprising because previous work has found that each theory can be used as a theoretical framework to account for other processes, which are synonymous with ageing, such as the effects of DR, epigenetic drift and free radical damage (Golubev et al., 2018; Mc Auley, 2022; Robins et al., 2017; Zagkos et al., 2021). This serves to emphasise that the main evolutionary theories of ageing are not mutually exclusive. This means that a more pluralistic interpretation of ageing and evolutionary theory may be required. A pluralistic approach has successfully been applied to other areas of evolutionary biology. Most notably, it has been used to address phylogenetic questions about different taxa (Doolittle and Bapteste, 2007). Adopting this approach means a uniquely 'correct' way to describe the evolution of ageing may not exist. In fact, when ageing patterns are examined in natural populations its

timing and intensity is context and taxa specific (Gaillard and Lemaître, 2020; Promislow, 1991). Thus, it makes logical sense that several different hypotheses can account for the evolution of ageing, within different ecological contexts. Indeed, how ageing is perceived from an evolutionary perspective depends on the adopted theory (Gladyshev, 2016; Johnson et al., 2019). If ageing is viewed through a purely genetic lens then arguments can be made for MTA or APT; if it is explored from a largely physiological perspective the DST is more appropriate. Based on this reasoning, it is to an extent futile debating which theory is 'correct', when meaningful empirical evidence exists which provides support for each theory (Mc Auley, 2021). Thus, it is my hope that future work in this area will adopt a more pluralistic perspective when examining the intersection between epigenetics, ageing and evolutionary theory. Such an approach will only serve to improve our understanding of epigenetics and where it sits within the evolution of ageing.

References

Acasuso-Rivero, C., Murren, C.J., Schlichting, C.D., Steiner, U.K., 2019. Adaptive phenotypic plasticity for life-history and less fitness-related traits. Proc. R. Soc. B 286, 20190653.

Aitken, R.J., 2017. DNA damage in human spermatozoa; important contributor to mutagenesis in the offspring. Transl. Androl. Urol. 6, S761.

Álvarez-Quintero, N., Velando, A., Noguera, J.C., Kim, S.Y., 2021. Environment-induced changes in reproductive strategies and their transgenerational effects in the three-spined stickleback. Ecol. Evol. 11, 771–783.

Angell, C.S., Janacek, R., Rundle, H.D., 2022. Maternal and paternal age effects on male antler flies: a field experiment. Am. Nat. 199, 436–442.

Anway, M.D., Cupp, A.S., Uzumcu, M., Skinner, M.K., 2005. Epigenetic transgenerational actions of endocrine disruptors and male fertility. Science 308, 1466–1469.

Anwer, H., Morris, M.J., Noble, D.W., Nakagawa, S., Lagisz, M., 2022. Transgenerational effects of obesogenic diets in rodents: a meta-analysis. Obes. Rev. 23, e13342.

Ashapkin, V., Suvorov, A., Pilsner, J.R., Krawetz, S.A., Sergeyev, O., 2023. Age-associated epigenetic changes in mammalian sperm: implications for offspring health and development. Hum. Reprod. Update 29, 24–44.

Auld, J.R., Agrawal, A.A., Relyea, R.A., 2010. Re-evaluating the costs and limits of adaptive phenotypic plasticity. Proc. R. Soc. B Biol. Sci. 277, 503–511.

Austad, S.N., Hoffman, J.M., 2018. Is antagonistic pleiotropy ubiquitous in aging biology? Evol. Med. Public Health 2018, 287–294.

Bargas-Galarraga, I., Vilà, C., Gonzalez-Voyer, A., 2023. High investment in reproduction is associated with reduced life span in dogs. Am. Nat. 201, 163–174.

Barker, D.J., Osmond, C., 1986. Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 327, 1077–1081.

Bateson, P., Gluckman, P., Hanson, M., 2014. The biology of developmental plasticity and the predictive adaptive response hypothesis. J. Physiol. 592, 2357–2368.

Bell, C.G., Lowe, R., Adams, P.D., Baccarelli, A.A., Beck, S., Bell, J.T., Christensen, B.C., Gladyshev, V.N., Heijmans, B.T., Horvath, S., 2019. DNA methylation aging clocks: challenges and recommendations. Genome Biol. 20, 1–24.

Ben Maamar, M., Sadler-Riggleman, I., Beck, D., Skinner, M.K., 2018. Epigenetic transgenerational inheritance of altered sperm histone retention sites. Sci. Rep. 8, 5308.

Blagosklonny, M.V., 2022. As predicted by hyperfunction theory, rapamycin treatment during development extends lifespan. Aging (Albany NY) 14, 2020.

Bochdanovits, Z., de Jong, G., 2004. Antagonistic pleiotropy for life–history traits at the gene expression level. Proc. R. Soc. Lond. B Biol. Sci. 271, S75–S78.

Bohacek, J., Mansuy, I.M., 2015. Molecular insights into transgenerational non-genetic inheritance of acquired behaviours. Nat. Rev. Genet. 16, 641–652.

Bonduriansky, R., Day, T., 2009. Nongenetic inheritance and its evolutionary implications. Annu. Rev. Ecol. Evol. Syst. 40, 103–125.

Bork, S., Pfister, S., Witt, H., Horn, P., Korn, B., Ho, A.D., Wagner, W., 2010. DNA methylation pattern changes upon long-term culture and aging of human mesenchymal stromal cells. Aging Cell 9, 54–63.

Brooks-Wilson, A.R., 2013. Genetics of healthy aging and longevity. Hum. Genet. 132, 1323–1338.

Burton, N.O., Greer, E.L., 2022. Multigenerational Epigenetic Inheritance: Transmitting Information Across Generations, Seminars in Cell & Developmental Biology. Elsevier, pp. 121–132.

Byars, S.G., Voskarides, K., 2020. Antagonistic pleiotropy in human disease. J. Mol. Evol. 88, 12–25.

Bygren, L.O., Kaati, G., Edvinsson, S., 2001. Longevity determined by paternal ancestors' nutrition during their slow growth period. Acta Biotheor. 49, 53–59.

Camilleri, T.L., Piper, M.D., Robker, R.L., Dowling, D.K., 2022. Maternal and paternal sugar consumption interact to modify offspring life history and physiology. Funct. Ecol. 36, 1124–1136.

Carone, B.R., Fauquier, L., Habib, N., Shea, J.M., Hart, C.E., Li, R., Bock, C., Li, C., Gu, H., Zamore, P.D., 2010. Paternally induced transgenerational environmental reprogramming of metabolic gene expression in mammals. Cell 143, 1084–1096.

Carter, A., Bares, C., Lin, L., Reed, B.G., Bowden, M., Zucker, R.A., Zhao, W., Smith, J.A., Becker, J.B., 2022. Sex-specific and generational effects of alcohol and tobacco use on epigenetic age acceleration in the Michigan longitudinal study. Drug Alcohol Depend. Rep. 4, 100077.

Charlesworth, B., 1994. Evolution in Age-Structured Populations. Cambridge University Press Cambridge.

Cheng, C., Kirkpatrick, M., 2021. Molecular evolution and the decline of purifying selection with age. Nat. Commun. 12, 2657.

Cribb, L., Hodge, A.M., Yu, C., Li, S.X., English, D.R., Makalic, E., Southey, M.C., Milne, R.L., Giles, G.G., Dugué, P.-A., 2022. Inflammation and epigenetic aging are largely independent markers of biological aging and mortality. J. Gerontol. A 77, 2378–2386.

Cruz, C., Della Rosa, M., Krueger, C., Gao, Q., Horkai, D., King, M., Field, L., Houseley, J., 2018. Tri-methylation of histone H3 lysine 4 facilitates gene expression in ageing cells. Elife 7, e34081.

Dasgupta, P., Sarkar, S., Das, A.A., Verma, T., Nandy, B., 2019. Intergenerational paternal effect of adult density in Drosophila melanogaster. Ecol. Evol. 9, 3553–3563.

Day, T., Bonduriansky, R., 2011. A unified approach to the evolutionary consequences of genetic and nongenetic inheritance. Am. Nat. 178, E18–E36.

de Magalhães, J.P., 2023. Ageing as a software design flaw. Genome Biol. 24, 1–20.

de Magalhães, J.P., Church, G.M., 2005. Genomes optimize reproduction: aging as a consequence of the developmental program. Physiology 20, 252–259.

Deas, J.B., Blondel, L., Extavour, C.G., 2019. Ancestral and offspring nutrition interact to affect life-history traits in Drosophila melanogaster. Proc. R. Soc. B 286, 20182778.

DeWitt, T.J., Sih, A., Wilson, D.S., 1998. Costs and limits of phenotypic plasticity. Trends Ecol. Evol. 13, 77–81.

Doolittle, W.F., Bapteste, E., 2007. Pattern pluralism and the tree of life hypothesis. Proc. Natl. Acad. Sci. 104, 2043–2049.

Duan, R., Fu, Q., Sun, Y., Li, Q., 2022. Epigenetic clock: a promising biomarker and practical tool in aging. Ageing Res. Rev. 101743.

Duxbury, E.M., Carlsson, H., Sales, K., Sultanova, Z., Immler, S., Chapman, T., Maklakov, A.A., 2022. Multigenerational downregulation of insulin/IGF-1 signaling in adulthood improves lineage survival, reproduction, and fitness in Caenorhabditis elegans supporting the developmental theory of ageing. Evolution 76, 2829–2845.

Fernandes, G.F.S., Silva, G.D.B., Pavan, A.R., Chiba, D.E., Chin, C.M., Dos Santos, J.L., 2017. Epigenetic regulatory mechanisms induced by resveratrol. Nutrients 9, 1201.

Flatt, T., Partridge, L., 2018. Horizons in the evolution of aging. BMC Biol. 16, 1–13.

Fridmann-Sirkis, Y., Stern, S., Elgart, M., Galili, M., Zeisel, A., Shental, N., Soen, Y., 2014. Delayed development induced by toxicity to the host can be inherited by a bacterial-dependent, transgenerational effect. Front. Genet. 5, 27.

Frolows, N., Ashe, A., 2021. Small RNAs and chromatin in the multigenerational epigenetic landscape of Caenorhabditis elegans. Philos. Trans. R. Soc. B 376, 20200112.

Gaillard, J.M., Lemaître, J.F., 2020. An integrative view of senescence in nature. In: Wiley Online Library, pp. 4–16.

Galimov, E.R., Gems, D., 2021. Death happy: adaptive ageing and its evolution by kin selection in organisms with colonial ecology. Philos. Trans. R. Soc. B 376, 20190730.

Gapp, K., Jawaid, A., Sarkies, P., Bohacek, J., Pelczar, P., Prados, J., Farinelli, L., Miska, E., Mansuy, I.M., 2014a. Implication of sperm RNAs in transgenerational inheritance of the effects of early trauma in mice. Nat. Neurosci. 17, 667–669.

Gapp, K., von Ziegler, L., Tweedie-Cullen, R.Y., Mansuy, I.M., 2014b. Early life epigenetic programming and transmission of stress-induced traits in mammals: how and when can environmental factors influence traits and their transgenerational inheritance? Bioessays 36, 491–502.

García-Peña, C., Tella-Vega, P., Medina-Campos, R.H., García-Hernández, H., 2023. Introduction: Historical Development and Progression of Clinical Research on Ageing, Biochemistry and Cell Biology of Ageing: Part IV, Clinical Science. Springer, pp. 1–12.

Gavrilov, L.A., Gavrilova, N.S., 2002. Evolutionary theories of aging and longevity. TheScientificWorldJOURNAL 2, 339–356.

Ge, Z.-J., Schatten, H., Zhang, C.-L., Sun, Q.-Y., 2015. Oocyte ageing and epigenetics. Reproduction (Cambridge, England) 149, R103.

Gems, D., 2022. The hyperfunction theory: an emerging paradigm for the biology of aging. Ageing Res. Rev. 101557.

Gentilini, D., Garagnani, P., Pisoni, S., Bacalini, M.G., Calzari, L., Mari, D., Vitale, G., Franceschi, C., Di Blasio, A.M., 2015. Stochastic epigenetic mutations (DNA methylation) increase exponentially in human aging and correlate with X chromosome inactivation skewing in females. Aging (Albany NY) 7, 568.

Gladyshev, V.N., 2016. Aging: progressive decline in fitness due to the rising deleteriome adjusted by genetic, environmental, and stochastic processes. Aging Cell 15, 594–602.

Golubev, A., Hanson, A.D., Gladyshev, V.N., 2018. A tale of two concepts: harmonizing the free radical and antagonistic pleiotropy theories of aging. Antioxid. Redox Signal. 29, 1003–1017.

Goos, J.M., Swain, C.J., Munch, S.B., Walsh, M.R., 2019. Maternal diet and age alter direct and indirect relationships between life-history traits across multiple generations. Funct. Ecol. 33, 491–502.

Greenberg, M.V., Bourc'his, D., 2019. The diverse roles of DNA methylation in mammalian development and disease. Nat. Rev. Mol. Cell Biol. 20, 590–607.

Greer, E.L., Maures, T.J., Hauswirth, A.G., Green, E.M., Leeman, D.S., Maro, G.S., Han, S., Banko, M.R., Gozani, O., Brunet, A., 2010. Members of the H3K4 trimethylation complex regulate lifespan in a germline-dependent manner in C. elegans. Nature 466, 383–387.

Greer, E.L., Maures, T.J., Ucar, D., Hauswirth, A.G., Mancini, E., Lim, J.P., Benayoun, B. A., Shi, Y., Brunet, A., 2011. Transgenerational epigenetic inheritance of longevity in Caenorhabditis elegans. Nature 479, 365–371.

Grenier, S., Barre, P., Litrico, I., 2016. Phenotypic plasticity and selection: nonexclusive mechanisms of adaptation. Scientifica 2016.

Guerrero-Bosagna, C., Skinner, M.K., 2012. Environmentally induced epigenetic transgenerational inheritance of phenotype and disease. Mol. Cell. Endocrinol. 354, 3–8.
Guerrero-Bosagna, C., Weeks, S., Skinner, M.K., 2014. Identification of genomic features in environmentally induced epigenetic transgenerational inherited sperm epimutations. PLoS One 9, e100194.
Hackett, J.A., Sengupta, R., Zylicz, J.J., Murakami, K., Lee, C., Down, T.A., Surani, M.A., 2013. Germline DNA demethylation dynamics and imprint erasure through 5-hydroxymethylcytosine. Science 339, 448–452.
Hamilton, W.D., 1966. The moulding of senescence by natural selection. J. Theor. Biol. 12, 12–45.
Han, S., Schroeder, E.A., Silva-García, C.G., Hebestreit, K., Mair, W.B., Brunet, A., 2017. Mono-unsaturated fatty acids link H3K4me3 modifiers to C. elegans lifespan. Nature 544, 185–190.
Hata, M., Andriessen, E.M.M.A., Hata, M., Diaz-Marin, R., Fournier, F., Crespo-Garcia, S., Blot, G., Juneau, R., Pilon, F., Dejda, A., Guber, V., Heckel, E., Daneault, C., Calderon, V., Des Rosiers, C., Melichar, H.J., Langmann, T., Joyal, J.-S., Wilson, A. M., Sapieha, P., 2023. Past history of obesity triggers persistent epigenetic changes in innate immunity and exacerbates neuroinflammation. Science 379, 45–62.
Heijmans, B.T., Tobi, E.W., Stein, A.D., Putter, H., Blauw, G.J., Susser, E.S., Slagboom, P. E., Lumey, L., 2008. Persistent epigenetic differences associated with prenatal exposure to famine in humans. Proc. Natl. Acad. Sci. 105, 17046–17049.
Horsthemke, B., 2018. A critical view on transgenerational epigenetic inheritance in humans. Nat. Commun. 9, 2973.
Horvath, S., 2013. DNA methylation age of human tissues and cell types. Genome Biol. 14, 1–20.
Horvath, S., Raj, K., 2018. DNA methylation-based biomarkers and the epigenetic clock theory of ageing. Nat. Rev. Genet. 19, 371–384.
Horvath, S., Lu, A.T., Haghani, A., Zoller, J.A., Li, C.Z., Lim, A.R., Brooke, R.T., Raj, K., Serres-Armero, A., Dreger, D.L., 2022. DNA methylation clocks for dogs and humans. Proc. Natl. Acad. Sci. 119, e2120887119.
Hotchkiss, R.D., 1948. The quantitative separation of purines, pyrimidines, and nucleosides by paper chromatography. J. Biol. Chem. 175, 315–332.
Houri-Zeevi, L., Rechavi, O., 2017. A matter of time: small RNAs regulate the duration of epigenetic inheritance. Trends Genet. 33, 46–57.
Huang, M., Hong, M., Hou, X., Zhu, C., Chen, D., Chen, X., Guang, S., Feng, X., 2022. H3K9me1/2 methylation limits the lifespan of daf-2 mutants in C. elegans. Elife 11, e74812.
Ivimey-Cook, E.R., Sales, K., Carlsson, H., Immler, S., Chapman, T., Maklakov, A.A., 2021. Transgenerational fitness effects of lifespan extension by dietary restriction in Caenorhabditis elegans. Proc. R. Soc. B 288, 20210701.
Ivimey-Cook, E.R., Shorr, S., Moorad, J.A., 2023. The distribution of the Lansing effect across animal species. Evolution 77, 608–615.
Jawaid, A., Mansuy, I.M., 2019. Inter-and transgenerational inheritance of behavioral phenotypes. Curr. Opin. Behav. Sci. 25, 96–101.
Jenkins, T.G., Aston, K.I., Meyer, T.D., Hotaling, J.M., Shamsi, M.B., Johnstone, E.B., Cox, K.J., Stanford, J.B., Porucznik, C.A., Carrell, D.T., 2016. Decreased fecundity and sperm DNA methylation patterns. Fertil. Steril. 105 (51–57), e53.
Johnson, A.A., Shokhirev, M.N., Shoshitaishvili, B., 2019. Revamping the evolutionary theories of aging. Ageing Res. Rev. 55, 100947.
Jordan, J.M., Hibshman, J.D., Webster, A.K., Kaplan, R.E., Leinroth, A., Guzman, R., Maxwell, C.S., Chitrakar, R., Bowman, E.A., Fry, A.L., 2019. Insulin/IGF signaling and vitellogenin provisioning mediate intergenerational adaptation to nutrient stress. Curr. Biol. 29 (2380–2388), e2385.
Jung, M., Pfeifer, G.P., 2015. Aging and DNA methylation. BMC Biol. 13, 1–8.
Kaati, G., Bygren, L.O., Pembrey, M., Sjöström, M., 2007. Transgenerational response to nutrition, early life circumstances and longevity. Eur. J. Hum. Genet. 15, 784–790.
Karniski, C., Krzyszczyk, E., Mann, J., 2018. Senescence impacts reproduction and maternal investment in bottlenose dolphins. Proc. R. Soc. B Biol. Sci. 285, 20181123.
Karunakar, P., Bhalla, A., Sharma, A., 2019. Transgenerational inheritance of cold temperature response in Drosophila. FEBS Lett. 593, 594–600.
Kenny, L.C., Lavender, T., McNamee, R., O'Neill, S.M., Mills, T., Khashan, A.S., 2013. Advanced maternal age and adverse pregnancy outcome: evidence from a large contemporary cohort. PLoS One 8, e56583.
Kerr, S.C., Ruppersburg, C.C., Francis, J.W., Katz, D.J., 2014. SPR-5 and MET-2 function cooperatively to reestablish an epigenetic ground state during passage through the germ line. Proc. Natl. Acad. Sci. 111, 9509–9514.
Kirkwood, T.B., 1977. Evolution of ageing. Nature 270, 301–304.
Kirkwood, T.B., 2005. Understanding the odd science of aging. Cell 120, 437–447.
Kirkwood, T.B., Holliday, R., 1979. The evolution of ageing and longevity. Proc. R. Soc. Lond. B Biol. Sci. 205, 531–546.
Klironomos, F.D., Berg, J., Collins, S., 2013. How epigenetic mutations can affect genetic evolution: model and mechanism. BioEssays 35, 571–578.
Lalejini, A., Ferguson, A.J., Grant, N.A., Ofria, C., 2021. Adaptive phenotypic plasticity stabilizes evolution in fluctuating environments. Front. Ecol. Evol. 550.
Lamb, M.J., 1994. Epigenetic inheritance and aging. Rev. Clin. Gerontol. 4, 97–105.
Lansing, A.I., 1947. A transmissible, cumulative, and reversible factor in aging. J. Gerontol. 2, 228–239.
Lee, P.C., Fishlock, V., Webber, C.E., Moss, C.J., 2016. The reproductive advantages of a long life: longevity and senescence in wild female African elephants. Behav. Ecol. Sociobiol. 70, 337–345.
Lee, H.-Y., Lee, B., Lee, E.-J., Min, K.-J., 2023. Effects of parental dietary restriction on offspring fitness in Drosophila melanogaster. Nutrients 15, 1273.
Leimar, O., McNamara, J.M., 2015. The evolution of transgenerational integration of information in heterogeneous environments. Am. Nat. 185, E55–E69.
Lemaître, J.-F., Berger, V., Bonenfant, C., Douhard, M., Gamelon, M., Plard, F., Gaillard, J.-M., 2015. Early-late life trade-offs and the evolution of ageing in the wild. Proc. R. Soc. B Biol. Sci. 282, 20150209.
Libertini, G., Corbi, G., Shubernetskaya, O., Ferrara, N., 2022. Is human aging a form of phenoptosis? Biochem. Mosc. 87, 1446–1464.
Lu, A.T., Quach, A., Wilson, J.G., Reiner, A.P., Aviv, A., Raj, K., Hou, L., Baccarelli, A.A., Li, Y., Stewart, J.D., 2019. DNA methylation GrimAge strongly predicts lifespan and healthspan. Aging (Albany NY) 11, 303.
Macrae, T.A., Fothergill-Robinson, J., Ramalho-Santos, M., 2022. Regulation, functions and transmission of bivalent chromatin during mammalian development. Nat. Rev. Mol. Cell Biol. 1–21.
Marinkovié, D., Bajraktari, I., 1988. Parental age dependent changes as a source of genetic variation in Drosophila melanogaster. Genetica 77, 113–121.
Markunas, C.A., Wilcox, A.J., Xu, Z., Joubert, B.R., Harlid, S., Panduri, V., Håberg, S.E., Nystad, W., London, S.J., Sandler, D.P., 2016. Maternal age at delivery is associated with an epigenetic signature in both newborns and adults. PLoS One 11, e0156361.
Mattei, A.L., Bailly, N., Meissner, A., 2022. DNA methylation: a historical perspective. Trends Genet. 38, 676–707.
Mautz, B.S., Lind, M.I., Maklakov, A.A., 2020. Dietary restriction improves fitness of aging parents but reduces fitness of their offspring in nematodes. J. Gerontol. A 75, 843–848.
Mc Auley, M.T., 2021. DNA methylation in genes associated with the evolution of ageing and disease: a critical review. Ageing Res. Rev. 72, 101488.
Mc Auley, M.T., 2022. Dietary restriction and ageing: recent evolutionary perspectives. Mech. Ageing Dev. 111741.
Mc Auley, M.T., Mooney, K.M., Salcedo-Sora, J.E., 2018. Computational modelling folate metabolism and DNA methylation: implications for understanding health and ageing. Brief. Bioinform. 19, 303–317.
Medawar, P., 1952. Uniqueness of the individual. In: Medawar, P.B. (Ed.), An Unsolved Problem of Biology. HK Lewis. Citeseer.
Mitteldorf, J., 2016. An epigenetic clock controls aging. Biogerontology 17, 257–265.
Monaghan, P., Maklakov, A.A., Metcalfe, N.B., 2020. Intergenerational transfer of ageing: parental age and offspring lifespan. Trends Ecol. Evol. 35, 927–937.
Moore, L.D., Le, T., Fan, G., 2013. DNA methylation and its basic function. Neuropsychopharmacology 38, 23–38.
Morgan, D.K., Whitelaw, E., 2008. The case for transgenerational epigenetic inheritance in humans. Mamm. Genome 19, 394–397.
Morgan, A., Davies, T.J., Mc Auley, M.T., 2018. The role of DNA methylation in ageing and cancer. Proc. Nutr. Soc. 77, 412–422.
Morgan, A.E., Acutt, K.D., Mc Auley, M.T., 2020. Electrochemically detecting DNA methylation in the EN1 gene promoter: implications for understanding ageing and disease. Biosci. Rep. 40.
Mozhui, K., Kim, H., Villani, F., Haghani, A., Sen, S., Horvath, S., 2023. Pleiotropic influence of DNA methylation QTLs on physiological and aging traits. bioRxiv, 2023.2004. 2012.536608.
Mu, Y., Hu, X., Yang, P., Sun, L., Gu, W., Zhang, M., 2021. The effects of cadmium on the development of Drosophila and its transgenerational inheritance effects. Toxicology 462, 152931.
Neel, J.V., 1962. Diabetes mellitus: a "thrifty" genotype rendered detrimental by "progress"? Am. J. Hum. Genet. 14, 353.
Neel, J.V., 1999. The "Thrifty Genotype" in 1998 1.
Nilsson, E.E., Skinner, M.K., 2015. Environmentally induced epigenetic transgenerational inheritance of disease susceptibility. Transl. Res. 165, 12–17.
O'Dea, R.E., Noble, D.W., Johnson, S.L., Hesselson, D., Nakagawa, S., 2016. The role of non-genetic inheritance in evolutionary rescue: epigenetic buffering, heritable bet hedging and epigenetic traps. Environ. Epigenetics 2, dvv014.
Omu, A.E., 2013. Sperm parameters: paradigmatic index of good health and longevity. Med. Princ. Pract. 22, 30–42.
Pamplona, R., Jové, M., Gómez, J., Barja, G., 2023. Programmed versus non-programmed evolution of aging. What is the evidence? Exp. Gerontol. 175, 112162.
Pembrey, M.E., Bygren, L.O., Kaati, G., Edvinsson, S., Northstone, K., Sjöström, M., Golding, J., 2006. Sex-specific, male-line transgenerational responses in humans. Eur. J. Hum. Genet. 14, 159–166.
Perez, M.F., Lehner, B., 2019. Intergenerational and transgenerational epigenetic inheritance in animals. Nat. Cell Biol. 21, 143–151.
Péron, G., Bonenfant, C., Lemaitre, J.-F., Ronget, V., Tidiere, M., Gaillard, J.-M., 2019. Does grandparental care select for a longer lifespan in non-human mammals? Biol. J. Linn. Soc. 128, 360–372.
Pigliucci, M., 2005. Evolution of phenotypic plasticity: where are we going now? Trends Ecol. Evol. 20, 481–486.
Prado, N.A., Brown, J.L., Zoller, J.A., Haghani, A., Yao, M., Bagryanova, L.R., Campana, M.G., Maldonado, J., E., Raj, K., Schmitt, D., 2021. Epigenetic clock and methylation studies in elephants. Aging Cell 20, e13414.
Prates, K.V., Pavanello, A., Gongora, A.B., Moreira, V.M., de Moraes, A.M.P., Rigo, K.P., Vieira, E., de Freitas Mathias, P.C., 2022. Time-restricted feeding during embryonic development leads to metabolic dysfunction in adult rat offspring. Nutrition 103, 111776.
Price, T.D., Qvarnström, A., Irwin, D.E., 2003. The role of phenotypic plasticity in driving genetic evolution. Proc. R. Soc. Lond. B Biol. Sci. 270, 1433–1440.
Promislow, D.E., 1991. Senescence in natural populations of mammals: a comparative study. Evolution 45, 1869–1887.
Qazi, M.C.B., Miller, P.B., Poeschel, P.M., Phan, M.H., Thayer, J.L., Medrano, C.L., 2017. Transgenerational effects of maternal and grandmaternal age on offspring viability and performance in Drosophila melanogaster. J. Insect Physiol. 100, 43–52.

Qin, W., Zhang, K., Clarke, K., Weiland, T., Sauter, E.R., 2014. Methylation and miRNA effects of resveratrol on mammary tumors vs. normal tissue. Nutr. Cancer 66, 270–277.
Ragsdale, A., Ortega-Recalde, O., Dutoit, L., Besson, A.A., Chia, J.H., King, T., Nakagawa, S., Hickey, A., Gemmell, N.J., Hore, T., 2022. Paternal hypoxia exposure primes offspring for increased hypoxia resistance. BMC Biol. 20, 1–14.
Rechavi, O., Houri-Ze'evi, L., Anava, S., Goh, W.S.S., Kerk, S.Y., Hannon, G.J., Hobert, O., 2014. Starvation-induced transgenerational inheritance of small RNAs in *C. elegans*. Cell 158, 277–287.
Reeve, H.K., Sherman, P.W., 1993. Adaptation and the goals of evolutionary research. Q. Rev. Biol. 68, 1–32.
Reichert, S., Berger, V., Jackson, J., Chapman, S.N., Htut, W., Mar, K.U., Lummaa, V., 2020. Maternal age at birth shapes offspring life-history trajectory across generations in long-lived Asian elephants. J. Anim. Ecol. 89, 996–1007.
Robins, C., McRae, A.F., Powell, J.E., Wiener, H.W., Aslibekyan, S., Kennedy, E.M., Absher, D.M., Arnett, D.K., Montgomery, G.W., Visscher, P.M., 2017. Testing two evolutionary theories of human aging with DNA methylation data. Genetics 207, 1547–1560.
Rose, M.R., 1991. Evolutionary Biology of Aging. Oxford University Press on Demand.
Roseboom, T., de Rooij, S., Painter, R., 2006. The Dutch famine and its long-term consequences for adult health. Early Hum. Dev. 82, 485–491.
Santilli, F., Boskovic, A., 2023. Mechanisms of transgenerational epigenetic inheritance: lessons from animal model organisms. Curr. Opin. Genet. Dev. 79, 102024.
Schulz, L.C., 2010. The Dutch hunger winter and the developmental origins of health and disease. Proc. Natl. Acad. Sci. 107, 16757–16758.
Sharma, A.K., Mukherjee, M., Kumar, A., Sharma, G., Tabassum, F., Akhtar, S., Imam, M. T., Almalki, Z.S., 2022. Preliminary investigation on impact of intergenerational treatment of resveratrol endorses the development of 'super-pups'. Life Sci. 121322.
Shen, L., Li, C., Wang, Z., Zhang, R., Shen, Y., Miles, T., Wei, J., Zou, Z., 2019. Early-life exposure to severe famine is associated with higher methylation level in the IGF2 gene and higher total cholesterol in late adulthood: the Genomic Research of the Chinese Famine (GRECF) study. Clin. Epigenetics 11, 1–9.
Sher, G., Keskintepe, L., Keskintepe, M., Ginsburg, M., Maassarani, G., Yakut, T., Baltaci, V., Kotze, D., Unsal, E., 2007. Oocyte karyotyping by comparative genomic hybrydization provides a highly reliable method for selecting "competent" embryos, markedly improving in vitro fertilization outcome: a multiphase study. Fertil. Steril. 87, 1033–1040.
Shilatifard, A., 2012. The COMPASS family of histone H3K4 methylases: mechanisms of regulation in development and disease pathogenesis. Annu. Rev. Biochem. 81, 65–95.
Siklenka, K., Erkek, S., Godmann, M., Lambrot, R., McGraw, S., Lafleur, C., Cohen, T., Xia, J., Suderman, M., Hallett, M., 2015. Disruption of histone methylation in developing sperm impairs offspring health transgenerationally. Science 350, aab2006.
Silva, W.T., Otto, S.P., Immler, S., 2021. Evolution of plasticity in production and transgenerational inheritance of small RNAs under dynamic environmental conditions. PLoS Genet. 17, e1009581.
Skulachev, V., 1999. Phenoptosis: programmed death of an organism. Biochemistry C/C of Biokhimiia 64, 1418–1426.
Skulachev, V., 2012. What is "phenoptosis" and how to fight it? Biochem. Mosc. 77, 689–706.
Sommer, R.J., 2020. Phenotypic plasticity: from theory and genetics to current and future challenges. Genetics 215, 1–13.
Stäubli, A., Peters, A.H., 2021. Mechanisms of maternal intergenerational epigenetic inheritance. Curr. Opin. Genet. Dev. 67, 151–162.
Stearns, S.C., Ebert, D., 2001. Evolution in health and disease: work in progress. Q. Rev. Biol. 76, 417–432.
Stubbs, T.M., Bonder, M.J., Stark, A.-K., Krueger, F., von Meyenn, F., Stegle, O., Reik, W., 2017. Multi-tissue DNA methylation age predictor in mouse. Genome Biol. 18, 1–14.
Sultan, S.E., 2021. Phenotypic Plasticity as an Intrinsic Property of Organisms, Phenotypic Plasticity & Evolution. CRC Press, pp. 3–24.
Sun, L., Mu, Y., Xu, L., Han, X., Gu, W., Zhang, M., 2023. Transgenerational inheritance of wing development defects in Drosophila melanogaster induced by cadmium. Ecotoxicol. Environ. Saf. 250, 114486.
Travers, L.M., Carlsson, H., Lind, M.I., Maklakov, A.A., 2021. Beneficial cumulative effects of old parental age on offspring fitness. Proc. R. Soc. B 288, 20211843.
Vaiserman, A.M., Koliada, A.K., Jirtle, R.L., 2017. Non-genomic transmission of longevity between generations: potential mechanisms and evidence across species. Epigenetics Chromatin 10, 1–12.
Van Den Heuvel, J., English, S., Uller, T., 2016. Disposable soma theory and the evolution of maternal effects on ageing. PLoS One 11, e0145544.
Wan, Q.-L., Meng, X., Dai, W., Luo, Z., Wang, C., Fu, X., Yang, J., Ye, Q., Zhou, Q., 2021. N6-methyldeoxyadenine and histone methylation mediate transgenerational survival advantages induced by hormetic heat stress. Sci. Adv. 7, eabc3026.
Wan, Q.-L., Meng, X., Wang, C., Dai, W., Luo, Z., Yin, Z., Ju, Z., Fu, X., Yang, J., Ye, Q., 2022a. Histone H3K4me3 modification is a transgenerational epigenetic signal for lipid metabolism in Caenorhabditis elegans. Nat. Commun. 13, 1–14.
Wan, Q.-L., Meng, X., Wang, C., Dai, W., Luo, Z., Yin, Z., Ju, Z., Fu, X., Yang, J., Ye, Q., 2022b. Histone H3K4me3 modification is a transgenerational epigenetic signal for lipid metabolism in Caenorhabditis elegans. Nat. Commun. 13, 768.
Weaver, I.C., Cervoni, N., Champagne, F.A., D'Alessio, A.C., Sharma, S., Seckl, J.R., Dymov, S., Szyf, M., Meaney, M.J., 2004. Epigenetic programming by maternal behavior. Nat. Neurosci. 7, 847–854.
Wei, Y., Yang, C.-R., Wei, Y.-P., Zhao, Z.-A., Hou, Y., Schatten, H., Sun, Q.-Y., 2014. Paternally induced transgenerational inheritance of susceptibility to diabetes in mammals. Proc. Natl. Acad. Sci. 111, 1873–1878.
Weismann, A., Poulton, E.B., 1891. Essays upon Heredity and Kindred Biological Problems. Clarendon press.
Williams, G.C., 1957. Pleiotropy, natural selection, and the evolution of senescence. Evolution 11, 398–411.
Witham, M.D., Cooper, R., Bowden Davies, K.A., Ortega-Martorell, S., Stewart, C.E., Sayer, A.A., 2022. Ageing research translation: a new era for UK Geroscience. Nat. Aging 2, 867–868.
Woyames, J., Souza, A.F.P., Miranda, R.A., Oliveira, L.S., Caetano, B., Andrade, C.B.V., Fortunato, R.S., Atella, G.C., Trevenzoli, I.H., Souza, L.L., 2022. Maternal high-fat diet aggravates fructose-induced mitochondrial damage in skeletal muscles and causes differentiated adaptive responses on lipid metabolism in adult male offspring. J. Nutr. Biochem. 104, 108976.
Wyatt, G., 1950. Occurrence of 5-methyl-cytosine in nucleic acids. Nature 166, 237–238.
Wylde, Z., Spagopoulou, F., Hooper, A.K., Maklakov, A.A., Bonduriansky, R., 2019. Parental breeding age effects on descendants' longevity interact over 2 generations in matrilines and patrilines. PLoS Biol. 17, e3000556.
Xia, B., de Belle, S., 2016. Transgenerational programming of longevity and reproduction by post-eclosion dietary manipulation in Drosophila. Aging (Albany NY) 8, 1115.
Xia, B., Gerstin, E., Schones, D.E., Huang, W., de Belle, J.S., 2016. Transgenerational programming of longevity through E (z)-mediated histone H3K27 trimethylation in Drosophila. Aging (Albany NY) 8, 2988.
Ying, K., Liu, H., Tarkhov, A.E., Lu, A.T., Horvath, S., Kutalik, Z., Shen, X., Gladyshev, V. N., 2022. Causal epigenetic age uncouples damage and adaptation. bioRxiv, 2022.2010. 2007.511382.
Yue, M.-x., Fu, X.-w., Zhou, G.-b., Hou, Y.-p., Du, M., Wang, L., Zhu, S.-e., 2012. Abnormal DNA methylation in oocytes could be associated with a decrease in reproductive potential in old mice. J. Assist. Reprod. Genet. 29, 643–650.
Zagkos, L., Mc Auley, M., Roberts, J., Kavallaris, N.I., 2019. Mathematical models of DNA methylation dynamics: implications for health and ageing. J. Theor. Biol. 462, 184–193.
Zagkos, L., Roberts, J., Mc Auley, M., 2021. A mathematical model which examines age-related stochastic fluctuations in DNA maintenance methylation. Exp. Gerontol. 156, 111623.
Zenk, F., Loeser, E., Schiavo, R., Kilpert, F., Bogdanović, O., Iovino, N., 2017. Germ line–inherited H3K27me3 restricts enhancer function during maternal-to-zygotic transition. Science 357, 212–216.
Zhang, B., Zheng, H., Huang, B., Li, W., Xiang, Y., Peng, X., Ming, J., Wu, X., Zhang, Y., Xu, Q., 2016. Allelic reprogramming of the histone modification H3K4me3 in early mammalian development. Nature 537, 553–557.