

# Chapter 4

## Role of Environmentally Induced Epigenetic Transgenerational Inheritance in Evolutionary Biology



Jennifer L. M. Thorson and Michael K. Skinner

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**Abstract** The mid-twentieth century saw the incorporation of Mendelian genetics into Darwinian theories of evolution. This foundation, termed the modern evolutionary synthesis, has developed into the primary current paradigm of evolutionary biology. However, the current modern synthesis does not include a role for epigenetics in developmental modifications or any mechanisms of non-genetic inheritance. With the recent expansion of epigenetic research into non-genetic mechanisms of adaptation and inheritance, there is a need to expand the modern synthesis into a new extended evolutionary theory. The current chapter presents the role of environmentally induced epigenetic transgenerational inheritance in evolutionary biology.

**Keywords** Epigenetics · Epigenetic transgenerational inheritance · Phenotypic plasticity · Adaptation · Evolution

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J. L. M. Thorson · M. K. Skinner (✉)

Center for Reproductive Biology, School of Biological Sciences, Washington State University, Pullman, WA, USA

e-mail: [skinner@wsu.edu](mailto:skinner@wsu.edu)

## 4.1 The Modern Synthesis

The modern evolutionary synthesis is based on the theories of evolution and natural selection as described by Charles Darwin and Alfred Russel Wallace in the mid-nineteenth centuries (Jablonka 2017). In these theories, adaptive evolution occurs when four proposed postulates are met. These include: (1) variation within a population, (2) variation is heritable, (3) competition occurs between offspring for limited resources, and (4) the survival and reproduction of the offspring are not random but are associated with the heritable variation (i.e., genetic inheritance) (Darwin 1859). With these postulates of evolution by natural selection as a foundation, the discoveries of Mendelian genetics, which described how traits could be inherited as well as the discovery of the genetic materials deoxyribonucleic acid (DNA) and ribonucleic acid, provided the molecular mechanisms of inheritance of adaptive traits and the trajectory of adaptive evolution. The field of population genetics formalized the study of Mendelian genetics and the implications for inheritance and adaptation. All of these developments eventually lead to the development and formalization of the modern evolutionary synthesis in the twentieth century, with the term coined by Julian Huxley in his 1942 book (Huxley 1942).

Ideas of phenotypic plasticity and non-genetic inheritance were not incorporated into the modern synthesis. At the end of the nineteenth century, James Mark Baldwin examined the response of *daphnia* to the presence of predators in their environment. Baldwin published a paper in 1896 proposing a mechanism whereby organisms interact with a changing environment and develop adaptive traits, which were then passed on to their offspring (Baldwin 1896). This phenomenon was termed as the Baldwin effects and was most often incorporated in psychological research, though evidence has accumulated for the Baldwin effect in evolutionary biology (e.g., Crispo 2007). In the early nineteenth century, Paul Kammerer demonstrated in the midwife toad, an environmentally (i.e., arid or aquatic) induced parent-of-origin non-genetic acquired reproductive traits (Vargas et al. 2017). In the mid-nineteenth century, Conrad Waddington pioneered investigations into the phenotypic plasticity with experiments examining the effects of heat shock on *Drosophila* wing shapes in the 1940s (Waddington 1940). Waddington found that after several generations of exposure to heat shock, an adaptive wing shape became “canalized” in the population, by which he meant the trait was retained in a population regardless of the genotype or environment. These results lead Waddington to coin the term “developmental epigenetics” to describe the phenotypic response to the environment (Waddington 1940). The initial genetic terminology used to describe effects such as those observed by Baldwin, Kammerer, and Waddington was genetic assimilation, where heritable changes occur in response to a novel environmental pressure (Crispo 2007). Despite early evidence for these phenomena, interest soon waned in favor of strictly genetic inheritance of traits in the absence of any non-genetic mechanisms. When the modern synthesis was formalized, ideas of soft inheritance, described by Ernst Mayr as “gradual change of the genetic [hereditary] material itself, either by use or disuse, or by some internal progressive tendencies, or through

the direct effect of the environment” (Mayr 1980) were strictly left out of the modern synthesis without a specific molecular mechanism to be considered (Jablonka 2017).

Aside from the evidence supporting the Baldwin effect and genetic assimilation, and epigenetic phenomenon proposed by Waddington, there are other phenomena long accepted by the evolutionary community to serve as mechanisms of inheritance. The first being maternal effects, which have long been documented in both plant and animal breeding and quantitative genetics (Falconer 1996). The maternal environment can affect offspring development and fitness, which can influence adaptation across generations (Mousseau and Fox 1998). Maternal effects on offspring fitness are both non-genetic and heritable, so are a form of adaptive non-genetic (i.e., intergenerational) inheritance. Moreover, epigenetic inheritance is implicated as a part of the parental effects inherited by offspring (Danchin et al. 2019; Skinner 2015). There has been recent interest in two additional non-genetic forms of inheritance. Prions are proteins which have the capacity to incorporate changes that last over many cycles of mitosis and meiosis and thus serve as a non-genetic mechanism of inheritance (i.e., intergenerational) (Harvey et al. 2018). Prions may even serve as facilitators of other forms of epigenetic inheritance, for example, altered chromatin states (Harvey et al. 2020). If prion-mediated alterations lead to adaptive phenotypic change, this is an alternative route to non-genetic inheritance (i.e., intergenerational) of adaptive traits. Finally, horizontal gene transfer is a common phenomenon in bacteria and may even influence eukaryotic organism’s nutrition, protection, and adaptation to extreme environments (Husnik and McCutcheon 2018). While horizontal gene transfer does involve alterations and inheritance of genetic material, it is outside the typical vertical inheritance described in the modern synthesis and is therefore a candidate to be incorporated as a novel mechanism of inheritance (i.e., intergenerational).

The recent research and evidence for the phenomena described above has led to the proposition of an extended evolutionary synthesis (EES) (Pigliucci 2007; Pigliucci and Muller 2010). The EES would take the tenets of the modern synthesis and build upon them, adding what has been demonstrated in evolvability, phenotypic plasticity, epigenetics and epigenetic inheritance, and evolution on adaptive landscapes (Pigliucci 2007). The authors who originally proposed these ideas were careful to argue that this EES would not be a “paradigm shift” as none of the new evidence directly opposes the original modern synthesis, but instead propose a shift from the population genetic-centered view that originally characterized the modern synthesis (Pigliucci and Muller 2010). While this debate continues in the evolutionary biology community (Baedke et al. 2020; Futuyma 2017; Muller 2017), there is sufficient evidence to suggest that non-genetic forms of inheritance are implicated in all aspects of evolution (Adrian-Kalchhauser et al. 2020; Bonduriansky et al. 2012; Richards 2006; Stajic and Jansen 2021; Sultan 2017). In particular, epigenetic inheritance of environmentally influenced alterations is implicated in adaptive evolutionary change (Nicolglou and Merlin 2017; Nilsson et al. 2020; Norouzitallab et al. 2019; Skinner 2015).

## 4.2 Molecular Epigenetic Mechanisms

The regulation of gene expression and genome activity requires a variety of molecular epigenetic mechanisms. The most extensively studied epigenetic mechanism is DNA methylation. DNA methylation involves the attachment of a small methyl group to DNA which produces 5-methylcytosine (5mC). This attachment occurs primarily at the cytosine base when it is adjacent to a guanine residue (Singer et al. 1979). Other chemical modifications of cytosine and adenine bases in DNA can occur and are far less frequent potential mechanisms of non-genetic adaptation.

DNA is wrapped around histone proteins to form the nucleosome, and these histone proteins can be chemically modified to alter gene expression. These histone post-translational modifications act to facilitate downstream functions in chromatin (Rothbart and Strahl 2014). The downstream effects of histone modifications include changing chromatin structure, recruiting transcriptional cofactors to regulate gene expression, and even repressing gene expression in heterochromatin regions of the genome. The variety of forms and effects of histone modifications is extensive and complex (Bartova et al. 2008; Taylor and Young 2021). Additional possible sources of epigenetic variation can be found in the presence of histone variants, in the spacing between nucleosomes and the position of chromatin in the nucleus (Margueron and Reinberg 2010). The modulation of these components is critical for the regulation of gene expression through determination of accessibility and sequential recruitment of regulatory factors to the DNA sequence (Quina et al. 2006). In the male germline, the sperm histone retention is also critical for the early embryo and involved in epigenetic inheritance (Ben Maamar et al. 2021).

The action of non-coding RNA molecules as epigenetic factors has been explored extensively (Huang et al. 2014; Wei et al. 2017). Non-coding RNAs are small and long, and do not code for any protein. They instead function as regulatory toward gene expression (Kornfeld and Bruning 2014). These RNA molecules are considered epigenetic factors as they are not dependent on DNA sequence and do not rely on a complementary nucleotide sequence to function. Epigenetic modifications can occur on RNA molecules, which then affect translation and gene expression (Sibbritt et al. 2013). Methylation of adenosine to form N6-mA is the most common modification to the internal sequence of mRNA, and this reversible modification is associated with post-transcriptional gene expression regulation (Fu et al. 2014; Yue et al. 2015). Sperm ncRNAs are postulated as important molecular mechanisms that can transmit gene regulatory information across generations and in response to environmental pressures (Sharma 2017).

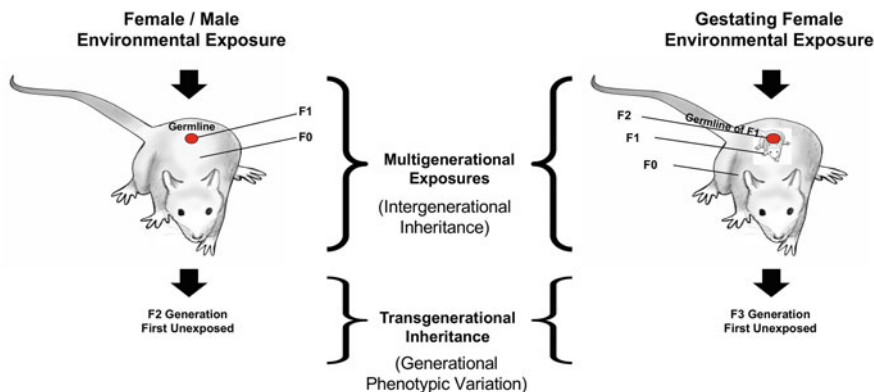
Since all these epigenetic processes can be altered in the germline (i.e., sperm and egg), following fertilization they can impact the early embryo epigenetics and transcriptomes to influence the offspring and subsequent generations. The repeated demonstration of epigenetically facilitated transgenerational inheritance of altered phenotypes suggests that this molecular mechanism plays a significant role in ecology and evolution, and should be included in evolutionary processes and theory (Angers et al. 2020; Herman et al. 2014; Sarkies 2020; Skinner 2015).

Transgenerational inheritance has been repeatedly demonstrated in model organisms in a laboratory setting. Further research is needed among field populations of non-model organisms responding to natural selection pressures (Hu and Barrett 2017; Sarkies 2020; Vogt 2015). For example, observations have been provided in Darwin finches for a role for epigenetic transgenerational inheritance and evolution (McNew et al. 2017; Skinner et al. 2014).

West-Eberhard proposed a process by which environmental pressures result in the selection of novel phenotypic traits which then result in genetic alterations and ultimately speciation (West-Eberhard 2003). This theory has been coined “genes as follower,” and epigenetic variation is a strong candidate to explain the molecular mechanisms at play (Banta and Richards 2018; Jablonka 2006, 2017; Vogt 2021). Interestingly, environmentally induced epigenetic transgenerational inheritance has been shown to increase genetic mutations in the transgenerational generations (Skinner et al. 2015). Therefore, epigenetic inheritance promotes not only adaptive phenotypic variations, but also genetic variation on which the modern synthesis is based (McCarrey et al. 2016).

### 4.3 Epigenetic Transgenerational Inheritance

There are several different types of exposure to selection pressures, an organism can experience that could lead to altered epigenetics and a resultant altered phenotype. Direct exposure to any selection pressure involves the specific organism directly experiencing the exposure (Maynard 2000). An example of direct exposure would include a significant alteration in the seasonal temperature regime, such as that resulting from human-mediated climate change. Multigenerational exposure involves the organism experiencing the exposure and the germ cells that organism carries inside them (Skinner 2008). For example, when an organism is exposed to altered nutrition or a significant increase in temperature outside the normal seasonal regime, their sperm or egg cells are also exposed to that shift (Nilsson et al. 2018). These environmental pressures and exposures can alter the epigenetics to impact the developmental trajectory of the organism and subsequent offspring development due to the exposed germ cells, termed as intergenerational epigenetic inheritance (Skinner 2015). Finally, transgenerational phenomena are those in which an organism does not have continued direct exposure to the environmental stressor, but there is a permanent reprogrammed germ cell epigenetic inheritance of the epigenetic-induced phenotypic alterations resulting from the direct exposure of their ancestors, Fig. 4.1 (Anway et al. 2005; Nilsson et al. 2018; Skinner 2008). An example of environmentally induced epigenetic transgenerational inheritance could involve a single intense episode of heat shock that is experienced by an F0 generation, the F1 germ cells and the F2 germline within the F1 generation fetus. If a phenotypic shift is observed among the F3 generation, a generation that did not directly experience the heat shock, there is an epigenetic transgenerational inheritance phenomenon, Fig. 4.1 (Nilsson et al. 2018; Skinner 2008). Examples of transgenerational



**Fig. 4.1** Environmentally induced transgenerational epigenetic inheritance: schematic of environmental exposure and affected generations for both gestating female and adult male or female. The multigenerational direct exposures are indicated in contrast to the transgenerational generation without direct exposure. Modified from (Nilsson et al. 2018)

inheritance in human and animal models have been reviewed (Aiken and Ozanne 2014; Jirtle and Skinner 2007; Nilsson et al. 2018).

The epigenetically mediated inheritance of an environmental shock or alteration in selection pressures fits well with the original postulates of natural selection. The alteration in selection regime may yield novel variation in the population (postulate 1) (as described by West Eberhard 2003 (West-Eberhard 2003)). The novel phenotypes are heritable (postulate 2) (Anway et al. 2005; Bohacek and Mansuy 2015; Holland and Rakyan 2013; Legoff et al. 2019). Competition between offspring results in differential survival based on the phenotype of individuals (postulate 3), and the differential fitness of phenotypes is not random, but is explained by inheritance of the adaptive phenotype (postulate 4) (Sarkies 2020; Skinner 2015; Sudan et al. 2018; Weyrich et al. 2018). The alternative route to adaptation mediated by epigenetic alterations leading to inherited phenotypes is supported as an important avenue of evolutionary change.

It should be noted that, as a “rapid path” to adaptive change, epigenetic transgenerational inheritance of epigenetically mediated phenotypes may not always be adaptive (Skinner 2015). When the environment is shifting rapidly, an adaptive response may involve phenotypic switching by epigenetic inheritance rather than by genetic mutation (Burggren 2016; Skinner 2015). The capacity for epigenetic changes and resulting phenotypic changes to occur rapidly and even transiently may be the most adaptive path in some circumstances. Whether by transient phenotypic switching in changing environments or long-term alterations in response to phenomena such as climate change, epigenetic transgenerational inheritance provides a pathway toward adaption.

#### 4.4 Examples of Epigenetic Transgenerational Inheritance Impacts on Evolution

The role of heritable epigenetic variation induced by environmental changes has been demonstrated in plant systems (Becker and Weigel 2012; Bossdorf et al. 2008; Cubas et al. 1999; Hirsch et al. 2012; Richards et al. 2010). While plant species are known to exhibit a high level of developmental plasticity in changing environments, heritable epigenetic variation is proposed as a major mechanism influencing this developmental plasticity and ultimately the adaptation and evolution of plant species (Miryeganeh and Saze 2019; Sudan et al. 2018). Plant species may be more prone to epigenetic inheritance through environmentally altered epigenetic states. This may be a result of their modes of reproduction and the lack of a sequestered germ line (Quadrana and Colot 2016). The plant group has served well for initial observations of adaptive epigenetic variation and evolutionary change. Notable examples of environmental-induced adaptive phenotypic change were documented in *Taraxacum officinale* (Ferreira de Carvalho et al. 2016; Wilschut et al. 2016) and *Arabidopsis* (Luo et al. 2020; Schmid et al. 2018).

Heritable epigenetic variation has been demonstrated in many animal species as well (E. Nilsson et al. 2018). *Caenorhabditis elegans* is one of the most studied animal species in the investigation of mechanisms of epigenetic inheritance (Fabrizio et al. 2019; Greer et al. 2011; Rechavi et al. 2011). The inheritance of epigenetic mechanisms, such as histone modifications or heritable small RNAs, can alter adaptive ancestral response among *C. elegans* (Rechavi and Lev 2017).

Empirical tests of the proposed idea that epigenetic mechanisms can contribute to environmental adaptation and evolution have been found in clonal laboratory lineages, monoclonal invasive animal species, and adaptive radiations (Vogt 2017). Natural animal populations have been found in general to contain higher epigenetic variation than genetic variation. The invasive house sparrow (*Passer domesticus*) exemplifies this pattern (Liebl et al. 2013). This example also demonstrates a pattern among invasive animal species whereby the higher amount of epigenetic variation is proposed as a mechanism by which rapid phenotypic change and adaptive evolution are facilitated by the enhanced epigenetic variation (Carneiro and Lyko 2020; Vogt 2017). Animal lineages that are not reliant on genetic variation, such as clonal lineages, are also prime candidates for the investigation of adaptation through environmentally induced epigenetic variation. The asexual clonal snail *Potamopyrgus antipodarum* is a widespread invasive species in the North America. Adaptive phenotypic variation in these invasive populations was found to be associated with epigenetic variation, providing support for the proposed mechanism of adaptation through environmentally induced epigenetic variation (Thorson et al. 2017, 2019). *Chrosomus eos-neogaeus* is a hybrid clonal fish, which inhabits both the predictable (lakes) and unpredictable (intermittent streams) environments. Significant differentiation in epigenetic phenotype has been documented in this hybrid (Massicotte and Angers 2012), and this variation is associated with the divergent environments (Leung et al. 2016). The invasive house sparrow populations exhibit

morphological variation which is associated with epigenetic variation between sub-populations in the Middle East (Riyahi et al. 2017) and among distinct introductions in Australia (Sheldon et al. 2018). These successful invasive species, which exhibit significant epigenetic variation, provide natural empirical investigations into the potential for environmentally induced epigenetic variation and inheritance to act as a source of adaptive phenotypic variation.

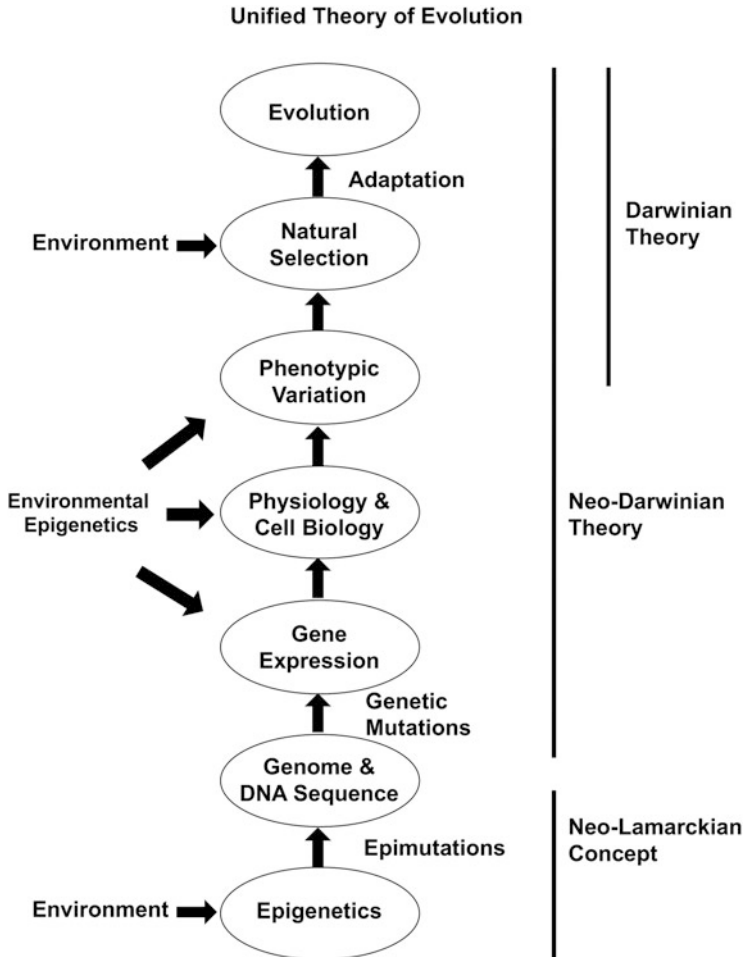
Adaptive radiations provide additional empirical examples of epigenetically mediated evolutionary change. Epigenetic changes were found to be more common than genetic changes among five closely related species of Darwin's finches (Skinner et al. 2014). Moreover, epigenetic variation was correlated with urban and rural populations of two of the Darwin finch species, suggesting environmentally induced epigenetic inheritance in this adaptive radiation (McNew et al. 2017). The examples of *Chrosomus eos-neogaeus*, *Passer domesticus*, and Darwin's finches support the role of epigenetic variation particularly among population with depleted genetic variation which can include invaders, founding populations, clonal lineages, and adaptive radiations (Vogt 2017). From these natural empirical examples, strong support for the proposed "soft inheritance" hypotheses (i.e., epigenetic inheritance) has been developed.

Laboratory populations have also shown significant evidence of induced epigenetic change and transgenerational inheritance of altered phenotypes. The evidence for epigenetic transgenerational inheritance of environmentally induced epigenetic changes in mammalian species has been reviewed (Legoff et al. 2019). Laboratory lineages of *Rattus norvegicus* have demonstrated numerous cases of epigenetic transgenerational inheritance of altered phenotype induced by an environmental perturbation and accompanied by epigenetic alterations and epigenetic transgenerational inheritance (Anway et al. 2005; Nilsson et al. 2018; Nilsson and Skinner 2015). Laboratory manipulations and environmental exposure experiments provide important support for the proposed mechanism of epigenetic inheritance and phenotypic change. Other human-mediated alterations to selection regimes include captive breeding programs and hatcheries. Hatchery and wild populations of Steelhead trout (*Oncorhynchus mykiss*) exhibit extensive phenotypic differences in growth and maturation rates. When examined for epigenetic differences, significant differential methylation was found in somatic and germ cells of these hatchery and wild populations (Nilsson et al. 2021).

#### **4.5 Conclusion: Integration of Epigenetic Transgenerational Inheritance and Evolutionary Biology**

Overall, the evidence for a functional role of epigenetic variation and the various mechanisms of epigenetic variation in all organisms investigated, such as plants (Chang et al. 2020; Hauser et al. 2011; Lamke and Baurle 2017) and animals is





**Fig. 4.2** Schematic of the unified theory of evolution. No dominance is suggested by the appearance of specific circles (e.g., epimutations versus genetics) such that all are equally important components. Modified from (Skinner 2015)

compelling (Nilsson et al. 2018; Skvortsova et al. 2018; van Otterdijk and Michels 2016; Xu and Xie 2018). With a proposed epigenetic mechanism for non-genetic inheritance, there is significant support for the previously discarded ideas of “soft inheritance” (i.e., epigenetic inheritance) from the late nineteenth and early twentieth centuries (Skinner 2015). Epigenetic inheritance has been described as a redemption of the ideas of Jean Baptiste Lamarck, who was the first to suggest the inheritance of acquired characteristics (Nilsson et al. 2020; Skinner 2015; Wang et al. 2017), Fig. 4.2. This new evidence suggests that a revision of the ideas set forth during the establishment of the modern synthesis is required. The impacts of epigenetic transgenerational inheritance and epigenetic variation on the evolutionary and

adaptive trajectory of species are supported as relevant and crucial (Jablonka 2017; Skinner 2015). The four postulates of natural selection are supported by the evidence of epigenetic inheritance and phenotypic change, such that alteration of the modern synthesis need to focus on the integration of the non-genetic and genetic forms of inheritance involved in phenotypic variation, adaptative, and evolution.

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