Epigenetic inheritance in adaptive evolution

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Abstract

Since the Modern Synthesis our ideas of evolution have mostly centered on the information encoded in the DNA molecule and their mechanisms of heredity. Increasing evidence however suggests that epigenetic mechanisms have the potential to perpetuate gene activity states in the context of the same DNA sequence. Here, we discuss recent compelling evidence showing that epigenetic signals triggered by environmental stress can persist over very long timeframes, contributing to phenotypic changes in relevant traits upon which selection could act. We argue that epigenetic inheritance plays an important role in fast phenotypic adaptation to fluctuating environments, ensuring the survival of the organisms of a population under environmental stress in the short term while maintaining a "bet-hedging" strategy of reverting to the original state if the environment returns to standard conditions. These examples call for a reevaluation of the role of non-genetic information in adaptive evolution, raising questions about its broader relevance in nature.

Keywords: Epigenetic inheritance, Waddington, adaptation, environmental change, genetic assimilation.

Graphical Abstract: Figure 1

Introduction

When Charles Darwin published *On the Origin of Species* in 1859 and put forward his ideas on Natural Selection, he did so with no concrete notion of how the traits he examined were passed from one generation to the next. It would take the work of Gregor Mendel and the Modern Synthesis of the early 20th century to bring solid concepts of heredity into evolutionary theory. Finally, the extraordinary advances in molecular biology in the 1950s and 60s cemented these concepts in chemical processes: DNA was the molecule that carried genetic information, which made up genes and accounted for the variation upon which natural selection could act, thus bridging the gap between the microscopic world of Watson and Crick and the zoological observations of Darwin, by way of Mendel.

However, this tidy relationship is complicated by the presence of additional layers of information without which the genetic code alone could not give rise to the diversity of life we observe. The field of "Epigenetics", a term coined in 1942 by Conrad Waddington, is the study of this additional information. Though its definition is somewhat nebulous, today the word generally denotes those regulatory signals peripheral to the DNA, such as DNA methylation or histone modifications, that contribute to the regulation of gene expression and which can be maintained across cell divisions independently of the underlying DNA. To formalize these notions, in this review we will consider epigenetics to denote "the study of molecules and mechanisms that can perpetuate alternative gene activity states in the context of the same DNA sequence"[1].

While the genetic information encoded in the DNA remains the "blueprint" for an individual organism, epigenetic signals have emerged as major factors in development, cognition and phenotypic plasticity, therefore accounting for considerable variation both within and between individuals, including individuals that are genetically identical. While much of this variation is intra-generational, being reset during development, increasing evidence suggests that some of it can be transmitted between generations. Unequivocally demonstrating a case of true Transgenerational Epigenetic Inheritance (TEI) is difficult due to the necessity of proving that an epigenetic signal observed across generations is in fact the carrier of the information and not just a secondary signal. In a first instance, this requires the separation of epigenetic from genetic factors involved in a phenotype, a distinction that is not always possible, especially in natural environments. In addition, the epigenetic signal must be observed to persist beyond any possible direct influence from the environmental factor that stimulated it. This includes influence exerted at the earliest stages of an individual's development, such as on their parents' germ cells or gametes. In organisms with live birth such as mammals, this means persistence beyond the F2 if a male ancestor was exposed or F3 for a female ancestor[1,2].

In some organisms these obstacles have so far proven insurmountable, despite extensive investigation. Interest in vertebrates, and mammals in particular, has been understandably high due to their relevance to humanity. Indeed, given the already well-known role of epigenetics in human diseases, the implications of TEI on medical science alone would be enormous. Despite this, strong evidence for TEI in mammals and mechanistic insight into its potential function are rare, due at least partly to the demanding requirements imposed by rigorous proof just described. Completely excluding any contribution of genetic factors and other confounding parameters in putative TEI phenomena in mammals requires high investment of time, effort and funds [3]. Several instances of epigenetic inheritance across one or two generations exist[4], but in the absence of transmission to further generations, these fall under the category of "intergenerational" epigenetic inheritance, rather than true "transgenerational" inheritance. A few intriguing examples exist with good correlational evidence of TEI in rodents over three or more generations, notably with respect to obesogenic drugs[5]. However, these examples often describe either apparent inheritance of epigenetic marks of unknown function[6], or observation of unexplained phenotype persistence without a molecular underpinning[7,8]. Until molecular mechanisms can be firmly assigned to phenotypic observations in these cases, and ideally exclude any possible genetic influence, an unambiguous and comprehensive example of TEI affecting natural traits in mammals is still lacking. On the other hand, a recent example of induced DNA methylation at regulatory regions of two mouse genes that can be inherited through multiple generations has been published[9], providing a proof-of-concept for the possibility of TEI in mammalian species.

While TEI in mammals is far from understood, recent work has seen several well-described instances of TEI in a variety of other organisms across the kingdoms of life. In some instances, clear molecular mechanisms of action and transmission have been described, testifying to an extremely varied landscape involving a wide range of epigenetic signals (reviewed in [2]). These signals, which frequently interact, include DNA methylation, histone modifications and non-coding RNAs, and by some definitions could be extended to less typical carriers of epigenetic information such as chromatin contacts[10] and 3D protein configuration[11]. The existence of these clear-cut cases of TEI in model organisms bolsters the numerous but necessarily less detailed reports of TEI in wild populations, suggesting a broader relevance of TEI in nature including to species important to the environment as well as human agriculture, industry and health. The phenotypes governed by these cases of TEI often involve traits crucial to the organism's survival, including metabolism[12,13], fertility[13,14] and predator response[15]. If epigenetic signals do indeed represent a source of variation in such important processes, forming "epialleles" that can persist for several generations, we may therefore ask to what extent they, like genetic information, underlie traits upon which natural selection acts.

If epigenetic signals can persist over very long timeframes, these epialleles could behave in a similar fashion to genetic alleles, increasing or decreasing in the population subject to natural selection and (epi)genetic drift. This may be of particular relevance to plants, in which TEI is a much more established phenomenon showing remarkable stability of epialleles[16]. While interesting, such a process represents nothing new, merely swapping epigenetic for genetic information within the framework of well-established evolutionary processes. However, the molecular nature of these epigenetic signals allows for alternative and more unique roles for TEI, complementing rather than replacing genetic information to assist in the organism's survival. Here we will discuss two such roles particular to heritable epigenetic information in shorter evolutionary timescales. We will examine these roles through recently described examples, discussing the interplay between genetic and epigenetic information in the adaptation and survival of an organism and its implications for the course of evolution.

Epigenetic inheritance can be important for fast adaptation to fluctuating environments.

One approach to understanding the relative contribution of epigenetic variation to survival is to consider what advantages epigenetic mechanisms might provide over genetic mutation in nature. One clear benefit would be the rapid adaptability of an epigenetically determined trait, which can be established quickly in response to environmental factors and erased if conditions stably returned to their previous state. One example illustrating the adaptive potential of environmentally-induced epigenetic variation and inheritance in natural populations was recently shown in the crustacean *Daphnia pulex*[17]. The authors analyzed changes in the epigenome in response to three common environmental pollutants (cadmium, glyphosate, 4-nonylphenol) in genetically homogeneous populations. Individuals were exposed for over 15 generations to the pollutants and then either continued for a similar period of time in polluted water or moved to clean water. The authors found that exposure to all three pollutants altered global patterns of DNA methylation compared to individuals maintained throughout in clean water and classified different categories of differentially methylated regions (DMRs) depending on the conditions compared. These were "direct" DMRs (present only under treatment conditions and absent when the pollutant was removed), "persistent" DMRs (present under treatment conditions and maintained in the

absence of pollutant) and "legacy" DMRs (which arose only upon transfer from pollutant to clean conditions).

While they likely contribute to survival, the *direct* sites are unstable, dependent on continuous exposure to the stressors, and are thus not subject to selection. These represent phenotypic plasticity, facilitating adaptation by promoting the resilience of organisms to environmental change[18]. The *persistent* methylated sites on the other hand fulfill the criteria of a stable epigenetic change transmitted by TEI, primarily for two reasons: i. the populations of *Daphnia* were clonal, excluding confounding effects provoked by genetic variation in the population, ii. the epigenetic change is transmitted for numerous generations (>15). Furthermore, the authors demonstrated that different fitness-related traits are compromised in the great grand offspring (F3) of the treated animals after being returned to clean water, suggesting that the transmissible epigenetic information is associated with phenotypic variation in the population. Taken together, these features suggest a strong possibility for a role in short-term adaptive evolution, raising the possibility for TEI to shape the evolutionary trajectory of *Daphnia* in natural populations.

A similar example involving a different epigenetic mark has been described in the fission yeast *Schizosaccharomyces pombe*. In this organism, which lacks DNA methylation, exposure to chemical stressors including caffeine led to novel deposition of the repressive histone mark H3K9me at heterochromatin islands across the genome, some of which repressed genes to confer caffeine resistance. Once again, some of these marks were observed to persist over several generations, providing another case of TEI involving a clearly selectable phenotype[19]. Further observation highlighted the true advantage of heritable epigenetic variation compared to genetic changes. After growth in non-caffeine conditions for many generations the H3K9me, and its associated caffeine resistance phenotype, were gradually lost. Indeed, while such a phenotype provides a clear advantage in the specific case of a caffeine environment, the gene silencing that underlies it is likely to prove deleterious in other conditions. Responding to this pressure with a heritable but erasable epigenetic mark provides the best of both worlds, allowing the organism to survive the stress without resorting to a more permanent mutation which may prove disadvantageous later.

Comparing these two examples can provide insight into the types of organism, trait and condition in which TEI might play an important role. Concerning their differences, their reliance on completely different molecular signals (DNA methylation and histone modification) illustrates how similar instances of TEI can arise independently with different mechanisms in response to comparable environmental pressures. Looking beyond at the mechanisms of establishment and transmission of these signals however might lead us to consider their deeper similarities. In the case of *Daphnia*, the authors showed that the *persistent* DMRs tended to occur at loci with the highest methylation rate in the genome, and that the pollutant exposure provoked a reduction in their methylation deposition. Strikingly, the *legacy* modifications showed an opposite trend, as they increased methylation deposition in sites with initial lower methylation. One possible reading of this is that in the *persistent* sites, the pollutant exposure may impair the DNA methylation reinforcement mechanism that is required to maintain high methylation levels at this site, and prevent DNA replication-dependent dilution over generations. In the *legacy* sites, either a putative overcompensation mechanism caused by secondary effects of the persistent loci or the impairment of the methylation resetting during *Daphnia* asexual reproduction could contribute to methylation accumulation over generations.

In the case of *S. pombe*, a follow up study found that exposure to caffeine and other stressors led to the cleavage of the H3K9 demethylase enzyme Epe1 by the proteasome, regulated by the MAP kinase stress signaling pathway[20]. This resulted in relocalisation of Epe1 from the nucleus to the cytoplasm, allowing spreading of H3K9me to sites where it is normally restricted. Artificial cleavage of Epe1 had similar effects on H3K9me spreading and even led to increased caffeine resistance through the same mechanisms as exposure. This raises the question of the extent to which the changes observed are side-effects of pollutant exposure, possibly by direct action of the chemical agent in question, that persist over generations, or rather are adaptations that have evolved to trigger in response to such stressors in order to temporarily enhance the survival of the organism until such time as conditions return to normal.

While these two fascinating biological examples warrant extensive future investigation of the molecular mechanisms at play, our current understanding indicates that the similarities between them are informative. Firstly, both organisms are relatively short-lived, as are many others in which robust cases of TEI have been described. This bias may result from the fact that short life cycles are also a key trait of model organisms. However, all short-lived organisms face the similar challenge of surviving in an environment that can either remain static for many generations or change significantly and abruptly between generations. Seasonal change alone represents an extreme generational shift for those organisms that live in temperate climates and whose life cycle does not span a full year. In such cases TEI may be an effective means of responding to these changes, as opposed to longer lived organisms in which adaptability within the lifetime of a single individual, by cognitive learning for instance, might be more important. Indeed, mathematical models suggest an advantage for such medium-term, non-genetic inheritance systems in randomly changing environments[21] or periodically fluctuating environments, if the period is longer than the generation time of the organism in question[22].

Secondly, both *Daphnia* and *S. pombe* are clonal organisms, though sexual reproduction is also possible. Not only does this indicate that genetic diversity may be lower than in obligate sexual organisms, but mutations are also slow to spread within a clonal population. Furthermore, organisms that resort to asexual reproduction are often those that frequently colonize new environments with only a few individuals, leading to population bottlenecks and founder effects in which additional variation supplied by epigenetics might be especially advantageous. In these contexts, even more so than in sexual organisms, mutations also represent significant evolutionary dead-ends if deleterious.

In some organisms then, heritable epigenetic change can provide additional phenotypic variation upon which selection can act in the short term while maintaining a “bet-hedging” strategy of possible reversion should conditions return to their previous state (Figure 1). Perhaps more subtly, epigenetic marks can also contribute more permanent evolutionary adaptation by stimulating genetic change, as discussed in the next section.

The role that this epigenetic inheritance plays in adaptation to new environments would be greater the more stable the epigenetic information is. However, what drives the stability of the epigenetic signal’s transmission to the progeny, which can vary considerably, is unclear. Recent evidence indicates that the longer the organisms are exposed to the stressor conditions the higher the probability to induce stable epigenetic transmission to their progeny. For example, in *Drosophila* multiple rounds of restraint stress in fathers provoked stronger transmission of the heterochromatin-associated mark H3K9me2 to their progeny than in fathers that were exposed to restraint stress only once[23]. In the same vein, in the

nematode worm *Caenorhabditis elegans* thermal stress produces embryos with lower deposition of the repressive histone modification H3K9me3 in a gene array[24]. Interestingly, periodic thermal exposure for 5 generations provoked transmission of the epigenetic signal for twice as many generations as a single exposure. The periodicity of exposure over generations might be the reason for the extraordinary numbers of generations that the differentially methylated CpG sites were transmitted in Daphnia populations upon exposure to the stressors[17].

These results suggest that long-term exposure to stressors is important for the stable transmission of the epigenetic status throughout the germ cells. Furthermore, it seems that the exposure periodicity of the stressor can trigger a positive reinforcement loop that maximizes the chances of long-term inheritance of the epigenetic status. Indeed, increasing the number of times an organism is exposed to the stressor strengthens the transgenerational epigenetic transmission, and the more generations the epigenetic inheritance is transmitted maximizes the chances that the epigenetic information will be transmitted to a further generation (see Rule 3: Transgenerational "momentum"[25]). In summary, the burgeoning evidence for transgenerational epigenetic inheritance is bringing us a clearer picture of the stability of epigenetic information over generations, suggesting that populations that face periodic or continuous exposure to alternate environments will have higher chances of accumulating stable epigenetic variation lasting multiple generations on which selection can act. Again, these results match the situations in which models predict epigenetic inheritance to be most advantageous[21,22], increasing the likelihood that these epimutations are programmed responses to environmental stress. In this view, epigenetic inheritance represents a process that has evolved by classical Darwinian processes rooted in genetic variation, but which instigates limited Lamarckian inheritance mechanisms as a temporary measure. These Lamarckian processes may take into account the nature, severity and duration of the environmental stimulus to tailor its response by restricting itself in both genomic context, to target specific relevant loci, and in time, to match the duration of the stress.

The role of epigenetic inheritance in genetic assimilation.

Conrad Hal Waddington's landmark paper "Genetic Assimilation of an Acquired Character" provides for the first time a clear example of how phenotypes originally triggered by environmental stressors can be assimilated in standard conditions[26]. In this work, flies were exposed in their pupal stage to a strong heat shock and in adulthood developed mutant wing vein patterns named "crossveinless". Waddington not only showed that selection for the crossveinless phenotype can increase the penetrance in the population but more importantly he demonstrated that this trait can become independent of the stressor and so be assimilated into the fly population in normal conditions. This seemingly Lamarckian phenomenology was explained by Waddington in fully Darwinian terms through his concept of "genetic assimilation" which he defined as "a process by which a phenotypic character, which initially is produced only in response to some environmental influence, becomes, through a process of selection, taken over by the genotype, so that it is found even in the absence of the environmental influence which had at first been necessary"[27].

Genetic assimilation relies at its core on a certain amount of standing genetic variance in the population to be responsive to selection. Under normal conditions this standing genetic variance is

'cryptic', having no impact on the phenotype because the standard phenotype is canalized towards a norm by minor genetic and environmental variations during development. However, Waddington's genetic assimilation definition was purely hypothetical and lacked clear examples showing the molecular mechanism underlying this process. It was not until the landmark work of Rutherford and Lindquist (1998) that it was proposed that the buffering system that canalized the phenotype could be mediated by the function of the Hsp90 protein[28]. In their work, they elegantly showed that when Hsp90 (Hsp83 in *Drosophila spp*.) function is impaired, different types of fly phenocopies arise as a consequence of the expression of cryptic genetic variants present in the fly population. The authors concluded that Hsp90 could act as a "genetic capacitor", allowing the accumulation of cryptic genetic mutations in the fly population by limiting their impact.

Remarkably, Hsp90 not only releases cryptic genetic variance, but also epigenetic variance that can be assimilated into the population by selection over multiple generations[29]. Sollars et al. showed that drug inactivation of Hsp90 released phenotypic variation associated with a Krüppel genetic allele ($Kr^{lf\text{-}1}$) in fly eyes. Importantly, an eye mutant phenotype induced by the drug inactivation of Hsp90 for a single generation can be stably transmitted for up to 13 generations despite the restoration of Hsp90 function. This result shows that Hsp90 acts not only as a buffering system for genetic variance but also fully epigenetic variance and that the epialleles established upon Hsp90 inactivation can be transmitted for multiple generations. The direct link to the epigenetic role of Hsp90 suggests that epigenetic inheritance may play a role in Waddington's assimilation of an inducible trait, a process proposed as epigenetic assimilation mechanisms[30].

Hsp90, in addition to its more known cytoplasmic chaperone function, also has nuclear functions important for gene regulation. For example, it promotes RNA polymerase II pausing near gene promoters and is necessary for the correct activation of the paused genes in response to environmental stimuli[31]. Furthermore, Hsp90 physically interacts and co-binds chromatin with Trithorax group members, facilitating the correct expression of Hox genes[32]. Of note, genetic alleles in Trithorax group members and chromatin architecture proteins worsen the eye mutant phenotype in the Krüppel sensitized genetic background, as did Hsp90 mutants[29]. Trithorax proteins, and their counterpart Polycomb group proteins, are gene expression modulators that act by depositing activating and repressive histone marks, respectively[33]. It should be noted that both Trithorax and Polycomb members have the potential to drive epigenetic inheritance associated with differential segregation of histone marks and chromosome pairing[10,34,35]. The chromatin-associated role of Hsp90 and its interaction with these molecular partners suggests that Polycomb and Trithorax associated Hsp90 function might be instructive for the establishment and transmission of heritable epigenetic information upon stress.

An expanded view of genetic assimilation includes the concept of "genetic takeover", i.e. the replacement of an epimutation over time by a genetic mutation with an identical or similar effect[36]. Genetic takeover provides an additional role for epigenetic inheritance in adaptation by its influence on genetic variation. Indeed, several epigenetic marks have been observed to have either negative or positive effects on mutation rate[37–42]. While the former effect of decreased mutability has been proposed as a safeguard against deleterious mutation in important genes, the latter has interesting implications for potential targeted acceleration of mutation[36,43]. In the model put forward previously (Figure 1) we discussed the advantage of epimutations as a bet-hedging strategy. However, this only applies if the environmental stress that provoked epimutation is temporary. In the case where it is permanent, the

temporary solution of the epimutation must give way to a more stable genetic mutation if the organism is to survive in the long term. In this case, epimutation serves the alternative function of a "stop-gap" solution. Far from being passive however, inheritance of the epiallele and its spreading through the population can actively promote the appearance of a mutation in two ways: by maintaining a larger population so that such a mutation is more likely to occur than in a depleted population, and by increasing the mutation rate at the epiallelic locus.

This latter effect has the benefit of targeting mutation to the gene or genes in which it is most likely to be of benefit for the situation in which the stressed organism finds itself. Combined with the previously described results indicating that repeated stimulus strengthens the stability of epigenetic response, this suggests a fine-tuning mechanism by which an organism can tailor its response to the severity and duration of an environmental stress. Indeed, the stronger the selective pressure, the longer the epimutation persists and the faster and more completely it will spread in a population, all of which increases the likelihood of a mutation occurring at the epigenetically modified locus, which necessarily is important in the environmental response under selection. Interestingly, it has been suggested that the epigenetic marks that stimulate mutation tend to be those that repress gene expression[37,39,40],although other findings contradict this view[44,45]. Of note, the counterselection of lethal mutations might be biased towards specific chromatin regions. Therefore, precise genome-wide measurements of mutation rates before they can cause cell death and in the same cells in which chromatin marks are measured will be needed before firm conclusions can be drawn. If accurate however, such observations would fit well with a "targeted evolution" model, as mutations, which are far more likely to interfere with the proper function of a gene than to stimulate or modify it, would be far more desirable at a gene whose repression was advantageous.

Combining this process with the limited Lamarckism discussed above provides an integrated view of epigenetic inheritance in short-term survival, providing a dual bet-hedging and stop-gap function to ensure adaptation to situations in which classic Darwinian evolution is too slow to respond. Both processes act concurrently and yet provide alternative strategies for stresses of varying severity and duration, tailoring the organism's response be appropriate to the survival challenge that it faces.

Concluding remarks

This review outlines recent evidence for cases of epigenetic inheritance that can complement genetic variants in the course of adaptations of individuals to novel environments. Through examples of various mechanisms that drive epigenetic inheritance in different animals under stressed developmental conditions, we discussed the putative advantages offered by epigenetic over genetic inheritance variants in fluctuating environments. We posit that the main advantage of epialleles over genetic alleles in short-term evolution is that, while they may be stably inherited for multiple generations, and thus be a target of selection, they nonetheless remain plastic and responsive to future environmental changes allowing the survival and adaptation of individuals of a population in fluctuating environmental conditions. We propose that epigenetic inheritance may thus be particularly relevant in organisms with relatively short life spans because, among other reasons, it is more likely that the progeny will face the same environmental conditions as their ancestors while remaining possible that they will face drastically different conditions to which they must adapt rapidly. Recent work regarding the mechanisms that could

drive the stability of epigenetic information over generations suggests a situation in which long-term exposure to an alternative developmental environment is crucial for the stable transmission of the epigenetic state through the gametes, thus providing a mechanism by which the TEI response can be limited and tailored to the challenge faced by the organism. Finally, we discussed the role of epigenetic inheritance in genetic assimilation and the related concept of genetic takeover. These processes represent a stop-gap solution as an alternative and yet concurrent strategy to bet-hedging, ensuring the best chance of survival for an organism regardless of whether the environmental stimulus that triggered it proves transient or persistent.

Author Contributions

G.S. and M.H.F.-J. conceived and drafted the manuscript and G.C. provided critical editorial input.

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Competing interest statement

The authors declare no competing interests.

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Figure legends

Figure 1. Under standard conditions a given population thrives. Introduction of a stressor provides a challenge for the population which can respond, or not, in different ways. **A**. Failure to adapt to the stressor leads to a decline in the population which, if it persists or is taken to extremes of severity, can eventually lead to its extinction. **B**. While relatively rare, a mutation can arise in the population that provides a resistance to the stressor. This mutation will gradually spread through the population with a speed dependent on the degree of advantage granted by the mutation, which in turn depends on the severity of the stressor. Eventually, if the stressed condition persists, the mutation will completely penetrate the population, reaching fixation. However, if conditions revert back to standard, those individuals bearing the mutation may find themselves at a disadvantage in an environment to which they are now maladaptive, particularly compared to other individuals that were never subject to stressed conditions. **C**. Alternatively, an epimutation conferring a resistance phenotype can arise. While this epigenetic adaptation might be less stable that a genetic one, its advantage is two-fold. Firstly, as the epimutation does not represent an evolutionary dead-end if conditions return to their previous state, it allows for easy re-adaptation and provides a bet-hedging strategy should the stressed conditions prove transient. Secondly, the epimutation can serve as a stop-gap solution, arising rapidly to ensure survival until a more robust mutation arises. This temporary measure not only buys time, but could actually increasing the chances of a relevant mutation arising by maintaining a larger population so that such a mutation is more likely to occur than in a depleted stressed population, and by increasing the mutation rate locally over the epigenetically modified locus, as some epigenetic marks are known to do.