ENVIRONMENTAL EPIGENETICS

Environmental Epigenetics, 2016, 1–12

doi: 10.1093/eep/dvv014
Perspectives

PERSPECTIVES

The role of non-genetic inheritance in evolutionary rescue: epigenetic buffering, heritable bet hedging and epigenetic traps

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Abstract

Rapid environmental change is predicted to compromise population survival, and the resulting strong selective pressure can erode genetic variation, making evolutionary rescue unlikely. Non-genetic inheritance may provide a solution to this problem and help explain the current lack of fit between purely genetic evolutionary models and empirical data. We hypothesize that epigenetic modifications can facilitate evolutionary rescue through 'epigenetic buffering'. By facilitating the inheritance of novel phenotypic variants that are generated by environmental change—a strategy we call 'heritable bet hedging'—epigenetic modifications could maintain and increase the evolutionary potential of a population. This process may facilitate genetic adaptation by preserving existing genetic variation, releasing cryptic genetic variation and/or facilitating mutations in functional loci. Although we show that examples of non-genetic inheritance are often maladaptive in the short term, accounting for phenotypic variance and non-adaptive plasticity may reveal important evolutionary implications over longer time scales. We also discuss the possibility that maladaptive epigenetic responses may be due to 'epigenetic traps', whereby evolutionarily novel factors (e.g. endocrine disruptors) hack into the existing epigenetic machinery. We stress that more ecologically relevant work on transgenerational epigenetic inheritance is required. Researchers conducting studies on transgenerational environmental effects should report measures of phenotypic variance, so that the possibility of both bet hedging and heritable bet hedging can be assessed. Future empirical and theoretical work is required to assess the relative importance of genetic and epigenetic variation, and their interaction, for evolutionary rescue.

Key words: climate change; evolutionary traps; evolutionary tracking; plasticity; epimutation; transgenerational epigenetic inheritance

Received 1 November 2015; **revised** 30 November 2015; **accepted** 9 December 2015

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Introduction

We are living through a period of human-induced rapid environmental change, with a concurrent loss of biodiversity that is of major concern [1–4]. Organisms are adapted to live and reproduce within the range of environmental conditions experienced by their ancestors. If the environment changes outside these conditions, then population fitness (i.e. the average fitness of individuals in the population) is predicted to decline [5, 6]. In the face of such rapid environmental change, populations could go extinct, migrate to more suitable environments or stay and adapt to the novel conditions [7]. Understanding the processes that lead to adaptation in changed environments is vitally important, both for theoretical insights into organismal evolution and practical attempts to conserve biodiversity.

The process by which genetic adaptation saves a population from otherwise inevitable extinction is termed 'evolutionary rescue' (hereafter, for phrases in single inverted commas, see Table 1), and it has received much attention in recent years [7, 18–22]. Evolutionary rescue relies on the traditional tools of evolution: genetic variation that already exists within the population, new mutations and gene flow [7]. Having more genetic variance within a population increases its 'evolutionary potential', making rescue from extinction more likely [23–25]. However, there are few documented examples of evolutionary rescue, and it is unclear whether genetic evolution is sufficient for a population to cope with rapid environmental change [7]. Phenotypic change does not necessarily require changes in gene frequency: it can also be the result of 'phenotypic plasticity', and there is an increasing appreciation of heritable non-genetic sources of phenotypic variation (e.g. parental effects, cultural inheritance and epigenetic variation) [15, 18, 26].

Non-genetic variation is now recognized as an underappreciated component of evolution [27] and there is accumulating evidence that, by altering gene expression, variation in epigenetic marks can cause heritable phenotypic variation that is

Table 1. Glossary of terms

Term	Definition
Adaptive epigenetic response	An adaptive phenotypic response to selection brought about by environmental change that is mediated through epigenetic inheritance, resulting in the population reaching a fitness optimum in the new environment
Cryptic genetic variation	Genetic variability that is not translated into phenotypic variability under normal environmental conditions, but that is exposed under atypical environmental conditions generating heritable phenotypic variation [8]
Epigenetic buffering	Epigenetic modifications which provide phenotypic resilience against fluctuating environmental change, facilitating the persistence of a population through rapid environmental change over ecological timescales
Epigenetic inheritance	Inheritance of phenotypic variations that do not stem from differences in the DNA sequences [9]. With this term, we do not mean cellular epigenetic inheritance (i.e. within-generation maintenance of epigenetic states) but intergenerational or transgenerational epigenetic inheritance (see below)
Epigenetic trap	Any change in the environment which causes the existing epigenetic machinery of an organism to produce a maladapted phenotype, with no increase in phenotypic variance within the population
Evolutionary potential	Ability of a population to respond to future selection pressures, taking into account currently existing (visible and cryptic) genetic variation [10]. Note that Le Rouzic and Carlborg [10] use this definition to describe "evolvability"; however, we use this to describe evolutionary potential of a population
Evolutionary rescue	Genetic adaptation that allows population recovery from environmentally induced demographic effects that would normally cause extinction [7]. Increases in beneficial mutations and/or standing genetic variation may prevent negative population growth and extinction
Genetic assimilation	Process by which selection converts an environmentally responsive phenotype into a phenotype that no longer requires the environmental stimuli for its production [8]
Heritable bet hedging	Process in which phenotypic variation is increased due to environmental factors and importantly, induced phenotypic values are heritable. In contrast, traditional bet hedging is a process in which evolved phenotypic variability buffer unpredictable environmental changes but heritability of phenotypic values are usually not assumed (Fig. 2; see also [11, 12, 13])
Intergenerational (epigenetic) inheritance (i.e. parental effects)	Effect of a parental phenotype on their offspring's phenotype that cannot be attributed to the parental or offspring genome, non-parental components of the environment or their interaction [14]. Effects occur across a single generation (F_0–F_1). See also the definition of 'epigenetic inheritance" above
Non-genetic inheritance	The transmission to offspring of parental phenotypic or environment variation that does not include the inheritance of DNA sequences (i.e. genes) [15]
Phenotypic plasticity	Changed phenotypic expression of a genotype/individual under different environmental conditions. Two forms of plasticity have recently been defined by Snell-Rood [16]: (i) developmental plasticity where a genotype/individual expresses different phenotypes in different environments by taking different developmental trajectories early in life that are often established during a sensitive period and (ii) activational plasticity, which is an immediate phenotypic change by a genotype/individual in response to the environment and can occur throughout an organism's life
Standing genetic variation	Genetic variation that is present in the population as opposed to new mutations [8]
Transgenerational epigenetic inheritance	Transmission from parents to offspring of phenotypic traits resulting from different methylation patterns or chromatin structure that affects gene expression, generally over two or more generations (F_0–F_N, where $N \geq 2$) [15]. See also the definition of 'epigenetic inheritance' above
Transposable elements	Mobile DNA segments in the genome. Two major types exist: (i) DNA transposon that do not use reverse transcriptase to integrate into the genome and (ii) retrotransposon that uses reverse transcriptase to integrate into the genome [17]

independent of genetic variation [28–31]. Interestingly, it appears that epigenetic modifications can also affect the probability that a region of the genome will mutate (e.g., single-base and transposon-mediated mutations and translocation) [32]. Therefore, not only may epigenetic modification promote heritable phenotypic variation, but it could also facilitate genetic evolution by modulating mutation rates across the genome [33]. It is now conceivable that epigenetic variation (and the resulting novel genetic variation) could be a key mechanism by which organisms adapt to rapid environmental change.

In this article, we hypothesize that epigenetic-mediated variation can provide populations with the resilience to persist through periods of environmental change, and we name this phenomena 'epigenetic buffering'. First, we provide a brief overview of epigenetic mechanisms that have so far been discovered, discuss how they may increase heritable phenotypic variance and outline how the interaction between genetic and epigenetic sources can maintain, and possibly increase, a population's evolutionary potential. We then provide an extensive list of examples for both 'intergenerational' and 'transgenerational epigenetic inheritance', and discuss whether, during rapid environmental change, increased phenotypic variance caused by epigenetic mechanisms is likely to be adaptive. We speculate that bet hedging, in combination with transgenerational inheritance (termed 'heritable bet hedging'), may be a common adaptive mechanism in response to rapid environmental change. We also discuss how maladaptive outcomes of transgenerational epigenetic inheritance could occur when organisms fall into an 'epigenetic trap'. However, seemingly maladaptive responses may prove beneficial over a longer time period. We then reach our main thesis: that over ecological timescales, epigenetic change provides populations with the phenotypic and genetic variability required to persist during sudden environmental change, and possibly facilitates genetic adaptation over evolutionary timescales. Finally, we present predictions based on our proposed phenomena, and suggest avenues for future empirical and theoretical research.

Evolution and Epigenetic Inheritance

Evolution and the Epigenetic Mechanisms Underlying Phenotypic Variation

Adaptive phenotypic evolution (or adaptive tracking) relies on selection, variation and heritability, and the properties of these variables will influence evolutionary dynamics [32]. Although genetic mechanisms provide the most faithful mode of phenotypic transmission, less stable epigenetic mechanisms, such as DNA methylation (see below), may be selected to persist if a plastic phenotype is adaptive. The inclusion of 'non-genetic inheritance' mechanisms into evolutionary thinking is a major goal of the extended evolutionary synthesis [34, 35]. Three alternative classes of epigenetic variation have now been recognized [36], each having different and important roles in the evolutionary process. These include (i) obligate epigenetic variation: epigenetic variation is completely associated with genetic variation; (ii) facilitated epigenetic variation: the genotype probabilistically determines the epigenotype and (iii) pure epigenetic variation: epigenetic variation is driven by stochastic events that are independent of the genotype [36]. Importantly, because obligate epigenetic variation is indistinguishable from genetic variation, in this article we exclude it from our discussions of epigenetic variation and evolutionary implications.

The molecular mechanisms underlying epigenetic variation are now beginning to be understood ([9, 37–39]; for an accessible and extensive overview, see [40]) and have been shown to have transgenerational effects on phenotypic development. Three major categories of molecular epigenetic mechanisms are now known to regulate gene expression [41]: (i) DNA methylation (usually methylation of cytosine) which can silence genes by blocking transcription factors from binding to promoter sites; (ii) histone modifications (post-translational modification of histone tails by different chemical compounds) which can up-regulate, down-regulate and silence genes; and (iii) processes mediated by non-coding RNAs (ncRNAs) which can provide sophisticated gene regulation in both plants and animals. For example, mild heat stress in the nematode (*Caenorhabditis elegans*) produces a heritable change in gene expression due to RNA interference from small interference RNA (one type of ncRNA), which may involve interactions with chromatin modifications [42]. DNA methylation, histone modifications and ncRNAs can interact to influence gene regulation in a variety of ways. They can, for example, change chromatin configuration (chromatin remodelling) [43]. These molecular mechanisms contribute substantially to phenotypic development and thus have important consequences that influence phenotypic variation.

Phenotypic plasticity is likely mediated by epigenetic mechanisms, which can lead to permanent or transient changes in the phenotype that can influence the amount of phenotypic variation in a population [16, 44]. Epigenetic processes translate environmental cues to changes in gene expression, leading to both permanent (developmental plasticity, *sensu* [16]) and transient phenotypic effects (activational plasticity, *sensu* [16]). Although phenotypic plasticity is recognized as an intra-generational phenomenon, the recognition that epigenetic processes have the capacity to be transgenerational suggests that epigenetic mechanisms responsible for influencing the development of the phenotype in one generation can affect phenotypic variation in subsequent generations. While theoretical models treat phenotypically plastic responses as a genetic phenomenon [45], it is important to recognize that, for many plastic responses, we lack a good understanding of how genetic and epigenetic mechanisms interact when responding to environmental cues, or how much genetic variation exists in the epigenetic machinery. More empirical work exploring the genetic and epigenetic processes of phenotypically plastic responses will inform our understanding of these important questions.

Increasing Evolutionary Potential: Three Pathways Via Epigenetic Mechanisms

Epigenetic mechanisms can enable heritable changes in gene expression that can increase both phenotypic and genetic variance. Epigenetic mutations, or epimutations, can change gene expression independent of DNA sequence change [43], and heritable epimutations and associated phenotypes can be selected and maintained [46]. Furthermore, an allele carrying an epimutation can be considered an allelic variant that is distinct from other genetic variants at a particular locus, and thus it can promote heterozygosity (or epiheterozygosity) with another allele [30]. A special type of epimutation is paramutation, which is well known in plants and has now been described in animals such as mice [47]. Paramutation at a heterozygous locus causes the other allele to adopt its epigenetic state [30]. Therefore, paramutation, if stable through generations, can quickly spread, changing the epigenetic landscape of a population. Epigenetic changes can also promote genetic mutations, such as when

epigenetic regulation of 'transposable elements' (TEs) is destabilized. It is hypothesized that epigenetic mechanisms originally evolved as a defence mechanism against parasitic viral TEs, but have now been co-opted to regulate gene expression in eukaryotes [48]. For example, small RNAs (which affect gene regulation) probably evolved to disable invading RNAs from retroviruses (by RNA interference) [49, 50]. Now, disruption of TEs by epigenetic changes could dramatically increase the occurrence of genomic mutations and rearrangements [17, 51, 52]. Mutations mediated by TEs are extremely frequent for two reasons. First, TEs constitute a large portion of eukaryote genomes (e.g., half of the human genome and 90% of the maze genome; [53]). Second, TEs can cause numerous types of genetic mutations; TEs can 'jump' around the genome by inserting or copying themselves, and they can also duplicate, translocate and invert a portion of the genome (although these mutations are mostly deleterious) [17, 48, 51].

Although evolutionary change driven by epimutations is probably short lived (due to their transient heritability [54]), their effects on genetic variation could have lasting evolutionary implications. In addition to the aforementioned ability of epigenetic factors to affect TE-mediated mutations, epigenetic changes also affect chromatin structure. Chromatin configuration affects the probability of a region of the genome mutating [55]; epimutations that affect chromatin structure could therefore influence mutation rates at these sites. More directly, there is experimental evidence that epimutations can lead to biased mutation rates [33, 56]. Methylated cytosine, for example, has a higher probability of being replaced by thymine than non-methylated cytosine [56]. Methylated regions have also been associated with mutations involving copy number variation [33]. Far more speculatively, epiheterozygosity could also facilitate mutations, as it has recently been shown that genetic heterozygosity is associated with increased mutation rates [57]. This increased mutation rate is presumably due to mismatches between paternal and maternal alleles. It is unknown if epiheterozygosity similarly facilitates mutations, but it is an intriguing possibility. Indeed most literature on this topic is fairly speculative, and it remains unknown how prevalent epigenetic effects on mutation rates are in nature [9, 58].

In addition to epimutations, epigenetic mechanisms could increase evolutionary potential in response to environmental change via two additional pathways (Fig. 1). First, environmental change can expose 'cryptic genetic variation', which is part of the 'standing genetic variation' [8]. This might occur by demethylation or chromatin remodelling to turn genes 'on' which had previously been unexpressed. Second, environmental stress could create new genetic variation, by inducing random and/or biased genetic mutations (as described above).

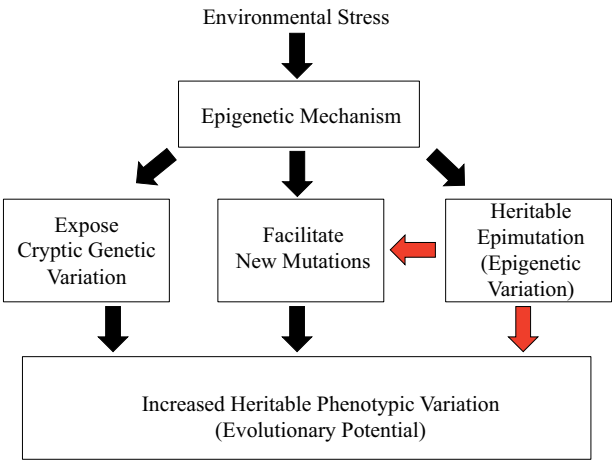

Figure 1. Three different ways in which epigenetic modification can increase heritable phenotypic variation and thus evolutionary potential. Red arrows indicate transient nature of these effects

In summary, we envisage three different ways in which environmental change could increase heritable phenotypic variation: (i) exposing cryptic genetic variation; (ii) generating genetic variation and (iii) creating more heritable epigenetic variation. Each of these paths, which we summarize in Fig. 1, could maintain, and eventually enhance, the evolutionary potential of a population when faced with environmental change. In this article, our focus is on the third pathway, which is the basis of transgenerational epigenetic inheritance.

Adaptive Value of Transgenerational Epigenetic Inheritance

An Overview of Transgenerational Epigenetic Inheritance Examples

There is now growing evidence demonstrating that non-genetically transmitted phenotypes [9, 15, 28, 37, 59] can be generated by diverse environmental effects, affect a wide range of offspring traits (both positively and negatively) and be transmitted by both parental lines for several generations (i.e. transgenerational effects; Table 2). Numerous studies have reported non-genetic inheritance across one (F_0–F_1) generation (i.e. intergenerational effects; see references within Supplementary Table S1), but documenting unequivocal transgenerational effects requires assessing the first generation not directly exposed to the environmental stress. For postnatal or adult F_0 exposure, this requires assessing the F_2 generation. For *in utero* embryonic exposure (i.e. gestating F_0 female exposure), however, assessment of the F_3 generation is required [37, 84]. Currently, transgenerational inheritance research (Table 2) is dominated by studies investigating effects of either nutrition (e.g. altered dietary composition, undernourishment) or pollution (particularly endocrine disrupting chemicals). Most endocrine disrupting chemicals have been documented to have negative effects on offspring reproduction, social behaviours, disease onset and even mate preference (Table 2). At least one study identified a potential positive effect—first generation progeny exposed to bisphenol A *in utero* displayed fewer social interactions as compared with control mice, but increased social interactions and decreased non-social behaviours (grooming and cage exploration) were observed in later generations (F_2 and F_4) [66]. Likewise, parental malnutrition generally has negative effects on size, growth, longevity and disease (Table 2), although one study found that parental habitat quality (i.e. food source quality) positively affects the foraging strategy of F_2 and F_3 generations of a flour beetle [78]. A recent study found that predation pressure results in earlier maturation and larger clutch size in three subsequent generations of *Daphnia* [79]. Finally, studies have documented transgenerational tolerance or increased sensitivity to abiotic factors like heavy metals or odours [72, 73], the latter of which is a stunning example of how learned fear response, through odour fear conditioning in F_0 mice, can be transmitted via sperm [73]. As illustrated in Supplementary Table S1, many more biotic and abiotic effects have been revealed in studies that assess non-genetic inheritance in the first generation; such effects need to be explored in subsequent generations.

Table 2. Examples of environmental factors that can have transgenerational (F_2; F_3 if F_1 offspring were *in utero* during exposure of F_0 mother) effects, the nature of those effects on offspring and their consequences for offspring fitness [15]

Environmental manipulation experienced by parental generation (F_0)[a]	Effect on offspring	Consequences for offspring fitness	Offspring generations affected	Species	Reference
Abiotic					
Chemicals: endocrine disrupters					
Fungicide (vinclozolin)	Behaviour: mate selection	Negative	F_3	*Mus musculus* (mice)	[60]
Fungicide (vinclozolin)	Disease: testicular, prostate, kidney, ovarian	Negative	F_3	*M. musculus* (mice; strain specific)	[61]
Fungicide (vinclozolin) and pesticide (methoxychor)	Male infertility	Negative	F_1–F_4	*Rattus norvegicus* (brown rat)	[62–64]
Hydrocarbons (jet fuel)	Disease: ovarian	Negative	F_1–F_3	*R. norvegicus* (brown rat)	[65]
Plastic (bisphenol A)	Social interaction and social behaviours	Positive or negative	F_1–F_4	*M. musculus* (mice)	[66]
Plastic (DEHP (di-2-ethylhexyl phthalate))	Reproductive: sperm counts, motility and testis organization	Negative	F_1–F_4	*M. musculus* (mice)	[67]
Dioxin (TCDD (2,3,7,8-Tetrachlorodibenzo-p-dioxin))	Sex ratio, skeletal abnormalities, fertility	Negative	F_1–F_2	*Danio rerio* (zebrafish)	[68]
Pesticides, plastics, dioxin, jet fuel	Reproductive: ovarian and spermatogenic	Negative	F_3	*R. norvegicus* (brown rat)	[69]
17α-ethinylestradiol	Fertilization rate, embryo survival	Negative	F_2–F_3	*Oryzias latipes* (medaka)	[70]
Tributyltin	Metabolic: obesity	Negative	F_2–F_3	*M. musculus* (mice)	[71]
Other abiotic					
Heavy metal exposure	Increased tolerance	Positive	F_2	*Oryza sativa* L. (rice)	[72]
Exposure to odour (fear conditioning)	Sensitivity to odour	Positive	F_2	*M. musculus* (mice)	[73]
Biotic					
Nutrition					
Undernourishment	Body weight and obesity	Negative	F_2	*Homo sapiens* (human)	[74]
Dietary composition (food restricted)	Sex ratio and growth	Negative	F_2	*Mesocricetus auratus* (golden hamster)	[75]
Dietary composition (over nutrition)	Longevity, disease	Negative	F_2	*H. sapiens* (human)	[76, 77]
Dietary composition (habitat quality)	Foraging strategy, population growth rate	Positive	F_2–F_3	*Tribolium castaneum* (flour beetle)	[78]
Other biotic					
Predation	Maturation and clutch size	Positive	F_1–F_3	*Daphnia ambigua* (water flea)	[79]
Maternal separation/maternal stress	Depressive-like behaviour, behavioural response to aversive environment	Negative	F_2–F_3	*M. musculus* (mice)	[80]
Traumatic stress (unpredictable maternal separation)	Avoidance and fear, depressive behaviours, abnormal metabolism	Negative and positive	F_1–F_2	*M. musculus* (mice)	[81]

[a]See also tables in these references: Table 1 in [83]; Tables 1 and 2 in [37, 83]; Tables 1 and 3 in [9]; Table 3 in [59].

Adaptive Plasticity: Predictability and Stability

There is scant empirical evidence of an 'adaptive epigenetic response' to environmental change [54]. Two conditions need to be met to demonstrate that an environmentally induced phenotype is adaptive [85]. First, when exposed to the environmental trigger, individuals who express the modified phenotype are fitter than those who do not. Second, when the environmental trigger is absent, individuals who nevertheless express the modified phenotype are less fit than their 'normal' counterparts. Although simple in theory, the empirical reality of demonstrating adaptive plasticity is often cumbersome [26]. Where an adaptive transgenerational plastic response to an environmental trigger has been reported, there has not been a concurrent demonstration that transgenerational epigenetic mechanisms were the cause [54]. Conversely, examples of environmentally induced transgenerational epigenetic inheritance have not been shown to be adaptive [54]. Of course, absence of evidence is not evidence of absence, and examples of adaptive epigenetic transgenerational plasticity may well emerge as research methods improve and interest intensifies.

It is unlikely that novel and rapid environmental change would induce an adaptive phenotypic response. For an organism to exhibit adaptive plasticity in response to an environmental cue it requires pre-existing genetic or epigenetic architecture, presumably selected by evolution during past periods of similar environmental conditions. In the context of human-induced rapid environmental change, it is assumed that population fitness declines because the environmental conditions are beyond those previously experienced. Furthermore, adaptive transgenerational plasticity requires the environment to change predictably (either consistent change in the same direction or periodic fluctuations), so that an environmental cue experienced by one generation predicts the environment of future generations (detection-based effects [86]). For example, models have shown that non-genetic inheritance can be adaptive in fluctuating environments, provided that those fluctuations are predictable [87, 88], and environmental stability can promote the evolution of partial epigenetic inheritance [89]. Therefore, both the instability and unpredictability of the environment during periods of human-induced rapid environmental change render it unlikely that transgenerational epigenetic effects could induce an adaptive phenotypic change. Given that the majority of genetic mutations are inconsequential or deleterious with respect to fitness [33, 90], this will also likely be true for epimutations.

Maladaptive Plasticity: Epigenetic Traps or Adaptively Maladaptive?

Most examples of transgenerational epigenetic inheritance seem to lead to a reduction in fitness (but see Table 2 for a few positive effects); however, if heritable phenotypic variation is increased, then an adaptive response could evolve over time. If there is no increase in evolutionary potential, then negative transgenerational epigenetic inheritance could only be maladaptive, so why do such effects occur? We see similarities to the concept of an 'evolutionary trap', where the environmental cue that an organism uses to assess the quality of a resource becomes inappropriate due to environmental change, causing individuals to make the "wrong decision" [5, 6]. In the case of epigenetic inheritance, the molecular machinery presumably evolved for adaptive purposes [86]. It is only when encountering something recent in evolutionary terms, such as an obesogenic environment or novel toxins, that the pre-existing epigenetic mechanisms produce inappropriate responses that can have maladaptive consequences for average population fitness. It is therefore the environmental mismatch that causes the epigenetic machinery of an organism to produce a heritable maladaptive phenotype—we term this an epigenetic trap. Although we recognize that this term is somewhat synonymous with evolutionary traps, we specifically use this to more effectively define what part of the molecular machinery is being monopolized to lead to maladaptive outcomes. A potential example of an epigenetic trap comes from a series of studies on epimutations in mammalian sperm. Glucocorticoid receptors are induced by stressful experiences, but they are also induced by evolutionarily novel stimuli such as endocrine disruptors and alcohol (presumably by "hacking" into the same or similar epigenetic pathways) [38]. Although epigenetic traps at first seem problematic to our thesis, it is important to recognize that, analogous to most mutations being deleterious, evolutionary rescue only requires a few beneficial mutations to rapidly spread through a population. Similarly, although many epigenetic responses may be maladaptive, the increased phenotypic variation may generate a small frequency of beneficial epimutations, enabling populations to explore new phenotypic space produced by environmental stressors. Furthermore, maladaptive phenotypic plasticity, mediated by epigenetic mechanisms, may itself facilitate adaptive evolutionary responses by increasing the strength of directional selection and allowing populations to reach the phenotypic optimum more quickly. For example, Ghalambor *et al.* [91] showed that the direction of plastic responses in gene expression was opposite to the direction of adaptive evolution, suggesting that adaptive plasticity may constrain evolutionary responses, while maladaptive plasticity allows populations to adapt more quickly to environmental change.

Heritable Bet Hedging

We speculate that where epigenetic mechanisms can provide an adaptive response to novel and unpredictable environmental change, it will most likely be through a random increase in heritable phenotypic variability combined with adaptive evolution (tracking), i.e. heritable bet hedging (Fig. 2; cf. [54]). Bet hedging is often conceptualized as an intergenerational effect (such as a maternal effect on offspring size variation), where responses are driven by plastic allocation strategies in the parents that do not result in heritable effects in subsequent generations (i.e. no shifts in the offspring phenotypic mean values or frequencies; Fig. 2B; Table 1). In fluctuating environments experienced by a population in its evolutionary past, bet hedging strategies can yield greater geometric mean fitness—despite a reduction in arithmetic mean fitness—by reducing the variance in fitness across fluctuating environments [11]. Nonetheless, under environmental conditions not encountered in a species' evolutionary history, directional environmental change may lead to extinction when only bet hedging strategies are relied upon (Fig. 2B). We predict that heritable epigenetic mechanisms can lead to phenotypic variation generated by bet hedging strategies being transgenerationally inherited, facilitating adaptive evolution (i.e. changes in the offspring phenotypic mean values or frequencies; Fig. 2C). When a population has not evolved an adaptive response to a particular environmental change, it is likely to be knocked off its fitness peak, and heritable phenotypic variation is then required for recovery through evolutionary processes [54, 92]. Theoretically, heritable bet hedging could allow populations to move between different peaks in the adaptive landscape [93], which might lead to recovery from rapid (possibly transient) environmental change. To date, heritable

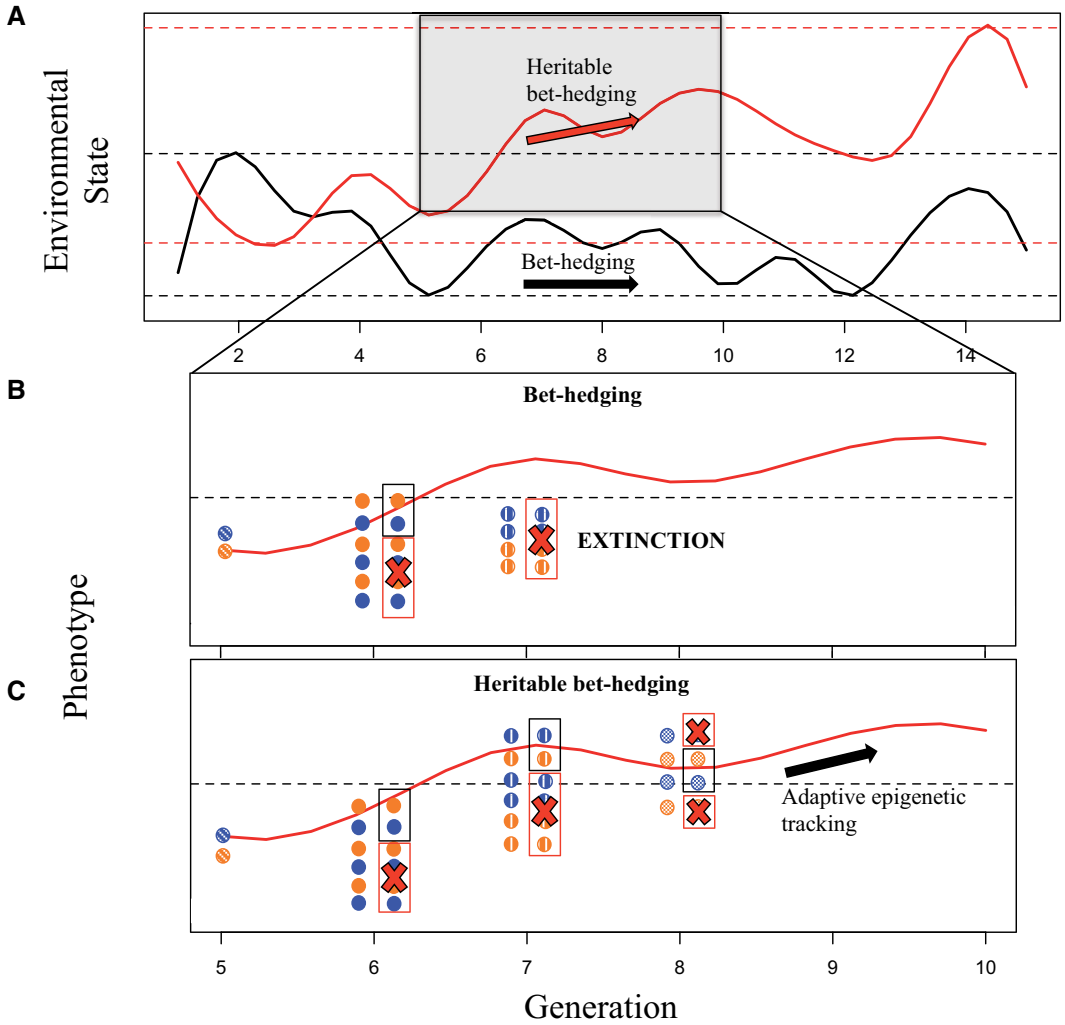

Figure 2. Epigenetic mechanisms can lead to heritable bet hedging that buffers populations from extinction. (**A**) A population experiences stochastic environmental variation across generations (black solid line) that falls within the zone experienced by the population over its evolutionary history (dotted black line). This is contrasted with directional stochastic variation (solid red line) caused by a rapid environmental shift across the generations that drives the population mean environment beyond normal environmental variation. For example, considering temperature, while we might assume that temperature fluctuations remain constant over time (i.e. they vary randomly within $\pm 3^{\circ}$) the mean temperature might move from 23°C to 25°C over 10 years (what we consider directional stochastic variation). Populations can be maintained through bet hedging strategies within the dotted black lines, but require the presence of heritable phenotypic variation to cope with novel directional environmental changes (red dotted lines). (**B**) A bet hedging strategy fails to allow populations to cope with directional stochastic environmental change (red solid line). Bet hedging results in plastic allocation strategies (e.g. maternal effects) in the parental generation that leads to increased phenotypic variation in the subsequent generation. Selection favours individuals most closely matching the environmental optimum at the time of selection (black square) while selecting against individuals too far from the phenotypic optimum (red square with red X). The next generation, however, will on average exhibit similar phenotypes to generation 5, because these plastic responses are not heritable. (**C**) A bet hedging strategy where phenotypic variation is heritable (heritable bet hedging) allows a population to adaptively track an environmental optimum outside the range experienced in its evolutionary history. This is achieved by recruiting epigenetic mechanisms to 'convert' non-heritable phenotypic variability, generated through a bet hedging strategy, to heritable phenotypic variability (i.e. adaptive epigenetic tracking). In both (B) and (C) similar coloured circles (blue or orange) represent the phenotypes of two family lineages while different patterned circles represent each unique generation. Two columns of circles within a given generation represent the phenotypes before selection and the phenotypes left after selection (i.e. circles within the black square). Only 3–4 generations are shown for simplicity

bet hedging has not been demonstrated in multicellular organisms [54], but research that pays heed to phenotypic variance of offspring traits after parental exposure to an environmental change could tell a different story. This will be a necessary first step in assessing the importance of heritable bet hedging in epigenetic buffering [12].

Responding to Rapid Environmental Change

Epigenetic modifications could be the mechanism by which populations buffer against rapid, fluctuating environmental change (Fig. 3)—hereafter we will refer to this process as epigenetic buffering. If organisms depended on genetic adaptation alone, then a shift in the environment would decrease the populations' genetic variance, reducing its future evolutionary potential. By decoupling the relationship between the phenotype under selection and the genotype, epigenetic inheritance could facilitate phenotypic adaptation, while both reducing genetic loss and providing the heritable phenotypic variation necessary for changes in trait distributions across generations. For example, consider a large population that experiences a sharp reduction in fitness due to a rapid environmental change (Fig. 3A).

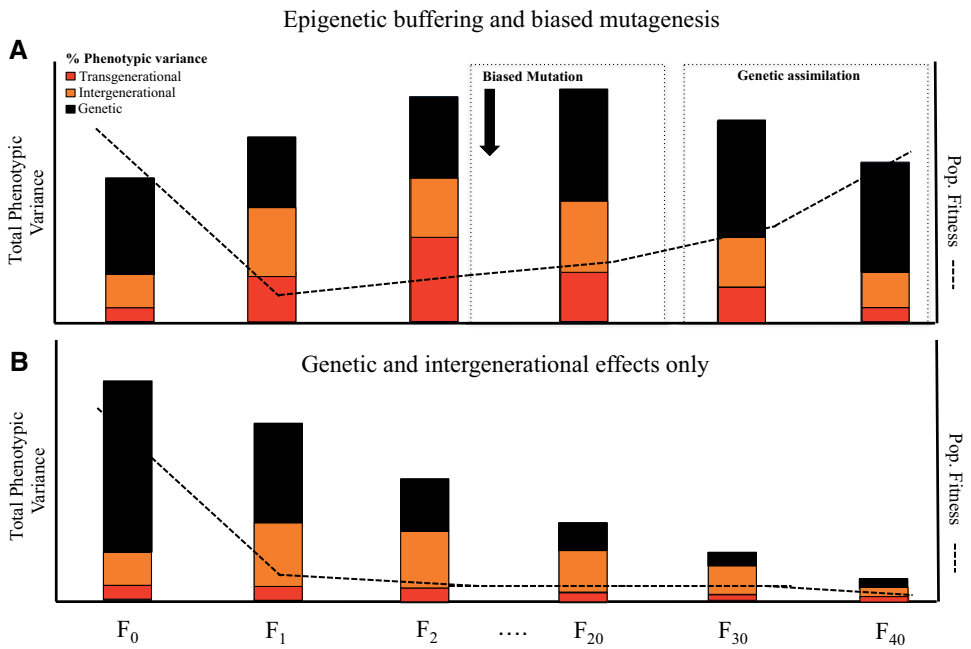

Figure 3. (**A**) Epigenetic buffering helps retain genetic variance in response to a rapid decline in population fitness (dotted line). In response to an environmental stressor, we predict that total phenotypic variance should increase. In F_1, intergenerational non-genetic/epigenetic effects (i.e. bet hedging) initially generate most phenotypic variance (orange bar), which shelters genetic variance (black bar) because this process dissociates the genotype from phenotype. In F_2, phenotypic variation continues to increase, but a larger proportion of variance is attributed to transgenerational epigenetic inheritance, facilitating the heritability of a portion of the phenotypic variants. Over longer time scales, if the population remains in a stressful environment, it might begin to re-acquire genetic variants (replenishing genetic variance) through biased mutation rates (or through increased rates of mutation). Over longer time periods, we may get genetic assimilation as the population converges on the new fitness optima. (**B**) Depletion of genetic variation in a population when transgenerational epigenetic mechanisms (red bar) comprise a very low, non-significant proportion of the total phenotypic variance. In response to an environmental stressor, we see strong selection on phenotypic variation that slowly depletes genetic variation

The environmental change increases genome-wide epigenetic variation causing a random increase in heritable phenotypic variance (i.e. heritable bet hedging). Positive selection increases the proportion of adaptive phenotypes, as well as their epigenetic creators, in subsequent generations. It is possible that epigenetic markers at genomic sites increase the probability of mutations at these locations (e.g. biased mutations—see 'Increasing evolutionary potential: three pathways via epigenetic mechanisms'). When the epigenetic inheritance that promoted the adaptive phenotype degrades, some of these phenotypes may be maintained through the new genetic variants. Evolutionary rescue may then occur. In contrast, if heritable epigenetic mechanisms did not lead to some of the phenotypic variation being transmissible, we would predict a rapid decrease in genetic variation that may lead to population extinction (Fig. 3B). This simplified hypothetical scenario (Fig. 3) necessitates some contentious assumptions based on the extended evolutionary synthesis [34, 35], and whether such processes could actually lead to evolutionary rescue requires much further investigation. Nonetheless, this concept has been suggested in other papers without being directly named. For example, Bonduriansky et al. [15] suggested that non-genetic inheritance might allow the phenotype to match the environment when environmental change is too rapid or stochastic for genetic adaptation to keep up, and Harrisson et al. [24] claimed that "nongenetic inheritance may serve to buffer a population against rapid environmental change".

Epigenetic buffering could occur by influencing each of the three modes of evolutionary potential depicted in Fig. 1, thereby facilitating evolutionary rescue over evolutionary timescales. The scenario of epigenetic buffering we describe above focuses on epigenetic variation because this is a less familiar case, traditionally however, the interaction between epigenetic and genetic variation could also increase evolutionary potential. When a population experiences detrimental environmental change we would expect a reduction in genetic variance—due to negative selection and a declining population size—but epigenetic buffering may reduce this loss. This conservation of a populations' genetic variance would provide greater scope for rescue. Furthermore, epigenetic buffering could increase the probability of new genetic variation. By preventing extinction in the short term, epigenetic buffering buys time for random mutations to occur, which could then aid evolution in the long term. An exciting possibility is that in addition to this random mechanism, epigenetic buffering could also facilitate biased mutations, which might hasten 'genetic assimilation' of the environmentally induced phenotypes. Genetic assimilation of phenotypic variants caused by environmental change is a common idea which is discussed in depth elsewhere [94]. Therefore, epigenetic buffering could provide population resilience to environmental change over ecological timescales, and paths towards population persistence over evolutionary timescales.

In summary, epigenetic buffering could facilitate evolutionary rescue through two basic phenomena which increase evolutionary potential: (i) heritability of environmentally induced phenotypes and (ii) reducing genetic loss and increasing the probability of novel genetic variation.

Outstanding Questions and Future Directions

Many factors should affect the likelihood of a population undergoing evolutionary rescue via epigenetic buffering. Below we

present some outstanding questions. Ultimately, deeper insights into the mechanisms of evolutionary rescue—and the potential importance of epigenetic buffering—could provide creative solutions to conservation problems. However, we also stress the need for more empirical studies on epigenetic inheritance that test for adaptive or maladaptive phenotypic plasticity within the context of ecologically relevant environmental conditions. This will be informative in comparing and contrasting the importance of phenotypic plasticity to adaptive evolution under novel environmental conditions.

Which phyla are more likely to experience epigenetic buffering? We predict that there will be differences between phyla in the importance of epigenetic buffering. For example, there is mounting empirical evidence that plants possess more sophisticated mechanisms for genome evolution via epigenetic mechanisms than animals do [39, 95–97]. There is a simple ecological hypothesis for this: plants are less able to move away from environmental disturbances or exhibit other types of behavioural plasticity, so they are more reliant on genetic adaptation and phenotypic plasticity through epigenetic pathways [51]. Furthermore, there is likely to be within-phyla variation in the magnitude of epigenetic buffering. Mammals, for example, undergo extensive epigenetic reprogramming between generations [98], but in zebrafish (*Danio rerio*) the paternal methylation pattern is faithfully inherited [99, 100]. Studies from a diversity of species will be required to predict ecological impacts of environmental change, and these differences should be taken into account when evaluating empirical evidence.

How does the timing of environmental change affect the likelihood of epigenetic buffering? The life-history stage in which a species experiences an environmental disturbance could affect the likelihood of epigenetic inheritance, and we predict an interaction with taxa. For example, for mammals, an environmental disturbance early in development is far more likely to cause transgenerational inheritance than a disturbance that occurs in adulthood [101]. This is due to gamete differentiation (i.e. the Weismann barrier [102]). For species with different forms of reproduction this variable may be less important. We predict that the length of environmental fluctuations relative to the generation time of a species is another key factor. If the environment fluctuates too rapidly, then epigenetic inheritance might be eroded due to the instability of epigenetic markers. Overall, there will be limits on epigenetic buffering and some types of environmental change will inevitably lead to extinction. These dynamics are undoubtedly complex and require theoretical models.

Does heritable bet hedging occur in response to environmental change, and can bet hedging evolve? We urge empiricists to place greater importance on reporting variance in phenotypic traits. We predict that parental generations encountering environmental stress should produce offspring with more variable phenotypic traits, given the potential role of heritable bet hedging in epigenetic buffering. Understanding the adaptive significance of bet hedging has been difficult and most of the existing evidence is non-rigorous [12]. There are undoubtedly pragmatic reasons for this—measuring geometric mean fitness is difficult and requires multi-generational studies. As a result, environmental effects on trait variation are often unreported, with the focus primarily being on mean phenotypic outcomes. Nevertheless, reporting how phenotypic variance changes in response to environmental stressors will enable future meta-analytic tests of these theoretical ideas, and evaluation of the importance of transgenerational epigenetic inheritance. From a theoretical perspective, it would be interesting to consider the evolution of bet hedging itself. So far we have assumed that each individual in a population will generate the same variance in their offspring's traits in response to environmental change, but this need not be the case. A population could undergo positive selection for increased offspring variance during periods of environmental instability, which may further facilitate rapid shifts across the fitness landscape.

What is the relative importance of genetic variation, new mutations and epigenetic variation for evolutionary rescue? Molecular biology can be used to investigate how evolutionary potential is affected by environmental stress. The three mechanisms shown in Fig. 1—standing genetic variation, new genetic variation created by biased mutation and epigenetic variation—could all be tested empirically. Admittedly, this research will be limited by current knowledge of epigenetic mechanisms, choice of study species, and time and costs. However, there is still potential for important insights. Heritable epigenetic variation may be more important for populations with less standing genetic variation, as these populations will have lower evolutionary potential to begin with. The utility of epigenetic variation in evolutionary rescue may be constrained if epigenetic variation is correlated with genetic variation (of which there is some evidence; see [103]). It is, therefore, worth measuring the correlation between genetic and epigenetic variation to determine how independent these mechanisms are. In other words, it is important to distinguish among obligatory, facilitated and pure epigenetic variation (*sensu* [36]). We would also predict the importance of new genetic variation (both random and biased) to increase with successive generations. Quantifying the magnitude and stability of heritable epigenetic variation is vital. This detail, combined with measurements of biased mutation rates, can inform evolutionary models.

Funding

S.N. is funded by an Australian Research Council Future Fellowship (FT130100268) and D.W.A.N. is funded by an Australian Research Council Discovery Early Career Research Award (DE150101774). D.H. is supported by National Health and Medical Research Council (APP1063981).

Acknowledgements

We thank Losia Lagisz and three anonymous reviewers for commenting on earlier versions of this manuscript.

Supplementary data

Supplementary data are available at *EnvEpig* online.

Conflict of interest: None declared.

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