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HOW STABLE 'SHOULD' EPIGENETIC MODIFICATIONS BE? INSIGHTS FROM ADAPTIVE PLASTICITY AND BET HEDGING

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Although there is keen interest in the potential adaptive value of epigenetic variation, it is unclear what conditions favor the stability of these variants either within or across generations. Because epigenetic modifications can be environmentally sensitive, existing theory on adaptive phenotypic plasticity provides relevant insights. Our consideration of this theory suggests that stable maintenance of environmentally induced epigenetic states over an organism's lifetime is most likely to be favored when the organism accurately responds to a single environmental change that subsequently remains constant, or when the environmental change cues an irreversible developmental transition. Stable transmission of adaptive epigenetic states from parents to offspring may be selectively favored when environments vary across generations and the parental environment predicts the offspring environment. The adaptive value of stability beyond a single generation of parent–offspring transmission likely depends on the costs of epigenetic resetting. Epigenetic stability both within and across generations will also depend on the degree and predictability of environmental variation, dispersal patterns, and the (epi)genetic architecture underlying phenotypic responses to environment. We also discuss conditions that favor stability of random epigenetic variants within the context of bet hedging. We conclude by proposing research directions to clarify the adaptive significance of epigenetic stability.

KEY WORDS: **DNA methylation, environmental cues, maternal effects, transgenerational plasticity.**

The past 20 years of work on epigenetics has altered our understanding of the molecular variation that shapes phenotypes and its patterns of inheritance. (For the purposes of this article, we define *epigenetics* as regulation of gene expression by molecular mechanisms other than DNA sequence change, such as DNA methylation, histone modifications, and small RNA molecules.) In place of fixed Mendelian factors that change in frequency across generations according to consistent selective trajectories, epiallelic variation constitutes reversible, transiently heritable effects on gene expression that can be generated either randomly or in response to cellular or external environmental cues (reviewed by Lemos et al. 2008; Jablonka and Raz 2009; Bollati and Baccarelli 2010). Evolutionary biologists face the task of bringing this aspect of variability to models of adaptive evolution. One major challenge in this effort is to understand the adaptive consequences of epigenetic stability versus instability as a mode of phenotypic variation.

A starting point is provided by existing theoretical approaches to the evolution of environmentally mediated phenotypic expression (i.e., *phenotypic plasticity*), including both individual (*within-generation*) plasticity, and the effects of parental environments on offspring (*transgenerational plasticity* or *parental environmental effects*). Because these aspects of plasticity theory involve the adaptive evolution of induced, transiently heritable

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variation, they provide relevant insights into the evolution of epigenetic changes that are also transmitted with various degrees of stability, both within and across generations. In addition, epiallelic effects on gene expression, such as DNA methylation changes, can be a proximate mechanism for both individual and transgenerational plasticity (well-documented examples include yeast metabolic plasticity [Herrera et al. 2012], *Arabidopsis* flowering time plasticity [Yaish et al. 2011], and inherited effects of diet on mouse development [Cropley et al. 2006]; for further examples, see Jablonka and Raz 2009; Holeski et al. 2012). However, it is not yet known the extent to which epigenetic mechanisms mediate plastic responses, including adaptive plastic responses.[1]

Some epigenetic variants affect ecologically meaningful traits and can be stably inherited for at least several generations (e.g., Johannes et al. 2009), suggesting a potential influence on the process of evolutionary adaptation (Richards 2006; Paszkowski and Grossniklaus 2011). The stability of epigenetic transmission within and across generations in various epialleles, taxa, and environments is not well characterized, but it is known to vary greatly (Gill et al. 2012; Turck and Coupland 2013; Verhoeven and Preite 2013). Given the extreme variability in epigenetic stability, what are the adaptive consequences of the level of stability itself?

We define epigenetic stability as *the persistence of modifications in gene expression and/or epigenetic marks that influence gene expression*. Such stability can exist at different temporal scales. Specifically, two aspects of stability parallel the distinction between within- and transgenerational plasticity: (1) within-generation stability that often entails the transmission of epigenetic modifications across mitotic cell divisions, and (2) transgenerational stability that entails the persistence of epigenetic modifications across parent–offspring generations via stable inheritance of epigenetic marks across meiotic cell divisions and/or other mechanisms (Martin and Zhang 2007).

Here, we examine existing theory on adaptive phenotypic plasticity to ask, *what level of stability would be adaptive for environmentally induced epigenetic changes*? Considering the many empirical questions that remain unanswered, our goal is to generate hypotheses that suggest a research agenda. We first consider the adaptive value of stable versus reversible epigenetic changes within a generation. Next, we examine theoretical predictions regarding adaptive transgenerational environmental effects and consider the implications of their persistence beyond a single offspring generation, interpreting these predictions in terms of epigenetic changes inherited across one or more generations. We also briefly review adaptive arguments regarding randomly generated offspring variation (*bet hedging*) to inform predictions regarding the stability of randomly generated (rather than environmentally cued) heritable, epiallelic variation. We then note how the dynamics of epigenetic variability may instead lead to a nonadaptive scenario in which selection for particular levels of stability is impeded. We close with a discussion of key questions to be resolved to determine the adaptive consequences of epigenetic stability, and we propose research approaches to these unresolved theoretical and empirical questions.

[1] We make no assumptions regarding the prevalence or stability of any particular epigenetic mechanism that may be involved in plastic responses.

Epigenetic Stability Within a Generation: Insights from the Evolution of Within-Generation Adaptive Plasticity

The parallels between plastic responses to environmental cues and environmentally induced epigenetic changes outlined above mean that our theoretical understanding of the former can shed light on the latter. Thus, understanding the conditions under which a stable phenotype that persists over the lifetime of an individual is adaptive leads to predictions about when stable epigenetic modifications might be adaptive. Similarly, understanding when it is adaptive for an organism to respond to an environmental challenge and change its developmental trajectory allows us to deduce conditions under which some degree of epigenetic instability might also be adaptive. It is important to note that, in some cases, transient epigenetic changes may lead to long-lasting phenotypic changes. Plasticity theory will not be useful in predicting the level of epigenetic stability in such cases due to the lack of a correlation between epigenetic and phenotypic stability.

Adaptive plasticity is usually conceived as a specific, functionally appropriate response of an organism to some environmental cue. Under this view, and assuming the presence of genetic variation for the environmental response (i.e., genotype by environment variation), such plasticity is expected to evolve ceteris paribus when the plastic response is indeed appropriate and the selective benefits of the response outweigh the costs of responding (Auld et al. 2010). As many studies have shown, however, these seemingly simple conditions conceal a number of more complex factors. In this section, we outline how our understanding of these factors can inform predictions about the adaptive value and evolution of within-generation epigenetic stability in cases when epigenetic change occurs (like plasticity) as a specific response to some environmental cue. We start by examining the consequences of the cue and its perception by the organism, before discussing the effects of environmental heterogeneity, both temporal and spatial. We then consider the effects of different forms of selection, including the possible costs associated with epigenetic modification and with plastic responses. Finally, we

explore which aspects of genetic architecture might be pertinent to whether epigenetic stability is favored.

ACCURACY OF THE CUE

Perhaps the most critical factor for within-generation epigenetic stability is the nature of the environmental cue that induces the epigenetic change. As is the case for phenotypic plasticity more generally, there are two distinct issues involved: the reliability of the cue in predicting the environment in which the organism will find itself after completing its response, and the exactitude with which the organism perceives the cue. These two issues are sometimes subsumed in a parameter called "accuracy" (e.g., Moran 1992). In general, one would expect that the greater the accuracy of the cue, the more likely an epigenetic response is to evolve; responding to unreliable or poorly perceived cues would seem to be unnecessarily costly. Nevertheless, plasticity can be favored even when accuracy is surprisingly low (Moran 1992; Sultan and Spencer 2002), and epigenetic responses are likely to be similar in this regard.

An appropriate epigenetic response to a cue (i.e., one mediating an adaptive plastic response) has two aspects: the induced change in epigenetic state, and the persistence of this induced state for as long as is needed to alter phenotypic expression. More accurate cues, therefore, should lead to epigenetic switches with sufficient flexibility to respond to the environmental cue, but also with adequate stability to resist spurious cues and ensure the appropriate regulation of gene expression. Less accurate cues might favor unstable epigenetic marks in order for the organisms to be able to respond later on to different, more appropriate cues. Indeed, some occasional instability may be favored as a form of bet hedging (see below).

ENVIRONMENTAL HETEROGENEITY

The degree of environmental heterogeneity, either temporal or spatial, influences the adaptive value of plasticity (Reed et al. 2010), and is therefore also expected to influence the adaptive value of epigenetic stability. Linking the spatial and temporal dimensions of environmental heterogeneity is the relationship between the scale of such heterogeneity and dispersal distances. With fine-grained environmental variation, typical dispersal distances are greater than the distances among sites with different environmental states, so the organism experiences a variable environment; in coarse-grained environments, by contrast, migrants typically disperse to similar environments.

What is critical to the selective outcome is the degree to which individuals experience environmental variation (Baythavong 2011). When environmental changes occur multiple times during an organism's life (either because of temporal changes in the local environment, or because of continued dispersal across a spatially heterogeneous habitat), an irreversible developmental response is likely to be less appropriate than shorter-term behavioral or physiological changes (Gluckman et al. 2005), although in the case of modular organisms, such as plants, short-term developmental responses can also track these changes (de Kroon et al. 2005). Epigenetic marks that are resistant to resetting (i.e., stable) would seem to be disadvantageous in these circumstances. Alternatively, environments may change once within the lifetime of an organism and then remain stable. It is under these circumstances that an environmentally induced epigenetic change that persists at least until the developmental response is initiated (and possibly throughout an individual's lifetime), is expected to be most adaptive. This scenario may occur when an irreversible developmental transition is cued to an environmental (frequently seasonal) factor: the "developmental environment" changes irreversibly, yet this developmental transition occurs in response to an environmental cue that may or may not endure. Thus, we may expect stable, sometimes even irreversible, environmentally induced epigenetic changes when these changes control developmental transitions that are environmentally cued. However, if many generations occur before any environmental change, or if the environmental change occurs very slowly (i.e., over multiple generations), epigenetic responses would seem no more likely to evolve than genetically constitutive adaptation, notably a population-level rather than an individual-level response. This issue has been framed within the context of the evolution of plastic generalists versus specialists (Van Tienderen 1991, Whitlock 1996).

These insights from plasticity theory indicate that there are two fundamentally different aspects of epigenetic stability affecting the organism: resistance to resetting (equivalently, sensitivity to the environmental cue) and persistence of the mark until the phenotypic response is initiated, if not complete. The degree to which environmental sensitivity and persistence of epigenetic marks have independent molecular bases remains to be determined. Nevertheless, assuming that an epigenetic modification leads to a more appropriate phenotype in the cuing environment, a high degree of environmental heterogeneity would thus be expected to select for the easy establishment of the epigenetic mark, followed by the stability of the mark until at least the phenotypic response was underway.

LIFE HISTORY

The ordering of events in the life cycle can be crucial to the evolution of plasticity and this same factor is likely to play a role in the evolution of epigenetic stability. For example, Scheiner and Holt (2012) found that plasticity was more likely to evolve with higher migration rates (conferring a higher degree of environmental heterogeneity experienced by the organism) only when dispersal from the cuing environment occurred after selection. Dispersal before selection means that some plastic types end up in the wrong environmental state even if they have responded in

what would have been the appropriate manner had they not dispersed. This result suggests that plasticity of adult characters that is caused by the induction of epigenetic modifications that persist throughout adult life is more likely in taxa that disperse as either gametes or postselection adults. When dispersal from the cuing environment occurs before selection, some degree of epigenetic instability within a lineage could engender a form of bet hedging (see below) that may be more advantageous than stability.

It is critical, too, that the cue occurs at a time in the organism's lifecycle when it can respond. In vertebrates, for instance, there is often a critical window of time during which some important stimulus must occur for an appropriate plastic response to be made by the developing individual (Gluckman et al. 2005). To some extent, this window itself may be the result of selection to enable a more appropriate or cost-effective response than that resulting from a cue at a different time, although organisms with determinate development are presumably constrained in this respect.

These considerations suggest that epigenetic modifications that regulate plastic responses would occur only at certain times in development, and hence the degree of epigenetic stability may be selected to differ at different stages in the lifecycle. Sensitivity to an environmental cue may be adaptive at some stages, whereas resistance and stability appropriate at others. Moreover, if induced epigenetic changes remain stable through mitotic divisions, gene expression can continue to be appropriately regulated long after the cue has disappeared. Such epigenetic stability would be particularly crucial for plastic responses of which the benefit occurs some time after the cue (Gluckman et al. 2005; e.g., van den Heuvel et al. 2013). Thus, the stability of plasticity-inducing epigenetic marks within a generation that experiences just one environmental change would appear to be adaptive under a wide range of conditions.

SELECTIVE COSTS AND GENETIC ARCHITECTURE

Theoretical considerations regarding the cost of plasticity can also enhance our understanding of the stability of epigenetic marks, because epigenetic responses and/or the ability to respond to an environmental cue may come at a price. Plasticity costs, as reflected in the lower fitness of plastic types of equivalent phenotypes, are potentially critical to the evolution of plasticity (Scheiner 1993; DeWitt et al. 1998), and it is likely the same applies to epigenetic stability. In plasticity theory, it has been important to distinguish between any inherent cost of the ability to mount a plastic response (so-called "global costs") and costs that are specific to a particular environmental state ("local costs" sensu Sultan and Spencer 2002). Global costs stem from the requirement to maintain the machinery necessary to sense the cue and respond developmentally. Empirical attempts to measure such costs have generally discovered them to be lacking or quite small (e.g., Scheiner and Berrigan 1998; Van Buskirk and Steiner 2009; but see Auld et al. 2010). These findings support the view that the machinery for sensing and responding to environmental cues is part of the normal functioning of the cell (Sultan and Stearns 2005). To the extent that epigenetic changes are a widespread feature of gene regulation that provides an efficient trigger for plastic responses, they may constitute a large part of this normal and hence cost-free machinery. Nevertheless, there may be some limits to adaptive epigenetic stability if either stability or resetting is costly. Theoretical studies (e.g., Van Tienderen 1991) have suggested that global costs can severely restrict the range of conditions under which plasticity is favored. By contrast, local costs (for instance, when plastic response to an extreme environment is developmentally expensive or is not completely appropriate) appear to impose a lesser restriction on the evolution of plasticity (Sultan and Spencer 2002).

The form of selection may also influence the evolution of plasticity and hence any underpinning epigenetic modifications. For the sake of simplicity, most modeling has assumed constant viability selection. However, much empirical evidence suggests that frequency- or density-dependent selection is ubiquitous (see examples cited in Asmussen et al. 2004 and Sinervo and Calsbeek 2006). These forms of selection might well favor plastic types that can respond to density or frequency (possibly through some proxy, such as increased contact with conspecifics) because they can develop into alternative phenotypes that are favored at different densities or frequencies. Accordingly, the ease with which an epigenetic mark can be reset may be more important than currently recognized.

The difference between hard and soft selection may also be important in the evolution of plasticity and hence in any underlying epigenetic modifications. This difference is especially crucial in metapopulation models, where hard selection in each site can leave space in harsher sites for migrants from more benign sites, effectively increasing migration rates and hence the apparent degree of spatial heterogeneity. Hard selection may therefore be expected to favor the easy establishment of epigenetic marks and their subsequent stability until the phenotypic response is initiated (or beyond). In his model of the evolution of plastic generalists versus specialists, Van Tienderen (1991) found that the difference between hard and soft selection affected the number of possible evolutionary outcomes and their properties. Indeed, the outcome under hard selection may depend on historical contingency, such that selection may not lead to the globally optimal solution. Hence, whether epigenetic stability is selectively favored may also be historically contingent.

Because genetic architecture plays an important role in the evolution of plasticity (Gomulkiewicz and Kirkpatrick 1992; Scheiner 1993; Engen et al. 2011; Scheiner et al. 2012; Wang et al. 2013), it is likely to influence the evolution of epigenetic

stability as well. For example, if a trait is affected by one gene of large effect, the way in which this gene is most appropriately epigenetically modified is likely to be different from a gene that contributes to a polygenic trait because a change in the expression of the former will have a greater phenotypic consequence than a change in the expression of the latter. A further aspect of genetic architecture is the issue of genetic correlations across environments: are the same genes associated with trait expression in different environments, or do different (possibly unlinked) genes underpin alternative phenotypes in different environments? If different genes are involved, the complete inactivation by epigenetic modification, that is stable long-term, might be appropriate; with the same genes a more subtle alteration of expression is more likely. In short, it matters how epigenetic modification mediates these different possibilities.

Epigenetic Stability Across Generations

EPIGENETIC STABILITY FROM PARENTS TO OFFSPRING: INSIGHTS FROM TRANSGENERATIONAL PLASTICITY

Adaptive effects of parental environment on offspring development (*adaptive transgenerational plasticity*) are increasingly well known in both plants and animals (see, e.g., Donohue and Schmitt 1998; Agrawal et al. 1999; Mondor et al. 2005; Galloway and Etterson 2007; Herman et al. 2012; Salinas and Munch 2012). However, due to experimental limits it is often not known whether these effects persist beyond a single offspring generation. Known mechanisms of adaptive transgenerational plasticity are diverse and include resource or transcript provisioning and hormonal contributions to seeds, eggs, or gestating embryos (Mousseau and Fox 1998; Mao et al. 2010). Because environmentally induced epigenetic modifications can be meiotically transmitted from parent to offspring (examples in Jablonka and Raz 2009; Hauser et al. 2011), epigenetic modifications also appear to be a likely mechanism for adaptive transgenerational effects (Herman and Sultan 2011; Holeski et al. 2012). However, definitive confirmation does not yet exist, because the phenotypic effects of inherited, environmentally induced epigenetic marks generally have not been shown to be adaptive, whereas established cases of adaptive transgenerational plasticity have not identified the underlying mechanism(s) (but see Weaver et al. 2004). Experimental tests of transgenerational effects are complex because distinguishing between the persistence of epigenetic modifications and the reinduction of them in progeny generations requires decoupling of the parent and offspring environments. Moreover, conclusively establishing transgenerational inheritance of epigenetic marks across meiosis is difficult in systems where mothers and developing embryos retain a close physiological and environmental association. Specifically, establishing inheritance in such cases requires progeny individuals to be at least two generations removed from the inducing stimulus, or three generations for mammals, because environments experienced by mothers could directly induce effects in developing embryos and their germ lines (Jirtle and Skinner 2007).

Despite the absence to date of a definitive example of adaptive transgenerational epigenetic inheritance, existing evidence indicates that such modifications can potentially mediate adaptive transgenerational plasticity in at least two ways. First, epigenetic mechanisms could directly mediate this form of plasticity if the environment experienced by parents induces specific epigenetic modifications that pass through the germ line to produce functionally appropriate phenotypes in the offspring (Bossdorf et al. 2008; Angers et al. 2010; Shea et al. 2011). Second, epigenetic modifications that are stable only intragenerationally can have indirect transgenerational effects if they influence phenotypes of parents that in turn influence offspring phenotypes (e.g., epigenetically mediated maternal behavior as in Weaver et al. 2004), or if they result in the inheritance of parental RNAs, hormones, or other substances that affect offspring gene expression and development (Bonduriansky and Day 2009). Such modifications will then be subject to the evolutionary dynamics of transgenerational plasticity. Our discussion of transgenerational epigenetic stability pertains to both categories of heritable epigenetic effect, as both promote the continuity of epigenetic information across generational boundaries.

Many of the same factors that are important for the evolution of within-generation epigenetic stability will also influence the adaptive value of epigenetic stability across generations, including the reliability of cues and the exactitude of responses to those cues, the nature of environmental variation, costs and constraints of environmental response, and patterns of dispersal. Additionally, of course, for epigenetic stability across generations to evolve so as to adaptively track environments, genetic variation for transgenerational stability must be present in populations. Studies of transgenerational plasticity in both plants and animals have identified abundant genotype by environment variation for these inherited effects (e.g., Wulff et al. 1994; Sultan 1996; Stjernman and Little 2011). To the extent that transgenerational plasticity is in fact mediated by epigenetic regulation, this $G \times E$ variation could indicate the existence of genetic variation for inducibility, transgenerational persistence, and/or phenotypic impact of epigenetic modifications.

Arguments regarding the evolution of adaptive transgenerational plasticity (e.g., Donohue and Schmitt 1998; Galloway 2005; Uller 2008) can be extended to suggest that epigenetic stability from parents to offspring will be favored when four general conditions are satisfied: environments vary spatially and/or temporally;

parental environments predict, to some degree at least, offspring environments; transgenerational effects enhance the product of parental and offspring fitness; and costs associated with transgenerational response are low. Although several authors have modeled the effects of nongenetic inheritance on adaptive evolution (e.g., Lachmann and Jablonka 1996; Pal and Miklos 1999; Day and Bonduriansky 2011; and Klironomos et al. 2013), few models have formally investigated the influence of these latter factors on the evolution of adaptive transgenerational plasticity itself. An exception is the model of Uller and Pen (2011), which verifies the importance of environmental variation and predictability across generations for the evolution of adaptive transgenerational effects on offspring phenotypes, and recognizes three additional factors as follows: parent–offspring conflict over the optimal offspring phenotype; costs associated with maternal versus offspring control of the phenotype; and constraints on the offspring's ability to respond to its own environment or to appropriately modulate maternally transmitted developmental cues. This model illustrates the rich complexity of interacting factors that can influence the evolution of adaptive transgenerational effects, and hence of the stability of the epigenetic mechanisms that may underlie this mode of adaptation.

Patterns of environmental variation are a critical factor that influences the evolution of adaptive transgenerational plasticity. In particular, the spatial scales of gene flow and offspring dispersal influence whether adaptive transgenerational plasticity will evolve (Galloway 2005). For example, in outcrossing plants, the scale of seed dispersal can be smaller than the scales of both environmental heterogeneity and pollen dispersal, resulting in similarity in the environments experienced by mothers and offspring, but not fathers and offspring. In outcrossing populations of animals as well as plants, extensive gamete exchange among ecologically distinct habitat patches may preclude genetically based specialization to local environments. Under these conditions and when offspring experience the same environment as one parent but not the other, adaptive transgenerational effects may evolve in lieu of local genetic adaptation (Galloway 2005; Spencer and Clark 2006). This scenario was elegantly demonstrated in a woodland plant system in which transgenerational plasticity provided an adaptive match between offspring light acquisition traits and open versus shaded microsites (Galloway and Etterson 2007, 2009). In such cases, stable transmission from parent to offspring of any epigenetic changes that mediate such plasticity will be favored.

The degree of temporal environmental change from one generation to another also influences the adaptive value of epigenetic stability across this time scale. This issue has been investigated within the context of "positive" and "negative" maternal effects (Hoyle and Ezard 2012). A "positive" maternal effect occurs when maternal and offspring phenotypes positively covary (e.g., when large mothers produce large offspring), whereas a "negative" effect occurs when maternal and offspring phenotypes are negatively correlated (e.g., when large mothers produce many small offspring, which in turn produce few large offspring, see Falconer 1965; Kirkpatrick and Lande 1989). When the environment suddenly undergoes an extreme and lasting change, then "positive" maternal effects, if favorable, can enable more rapid adaptation to the new environment than would be possible by Mendelian inheritance alone (Hoyle and Ezard 2012). If such a maternal effect is implemented by means of a stable epigenetic modification, then the stability from one generation to the next would promote this adaptive response. By contrast, in relatively invariant environments with stabilizing selection, slightly negative maternal effects are favored when they maintain a phenotypic mean that oscillates close to the optimum (Hoyle and Ezard 2012). In that restrictive case, epigenetic resetting every generation, rather than stability, would be favored.

The evolution of adaptive transgenerational plasticity is also favored when a lag time exists between perceiving an environmental cue and mounting an appropriate phenotypic response, because transgenerational effects can preinduce the required offspring phenotype (Sultan 1996; Agrawal et al. 1999). Transgenerationally induced individuals thus have an early growth advantage, because they are adaptively matched to their environment from the outset. Because lag times will vary for different types of traits, transgenerational plasticity may be particularly advantageous for developmental traits that are expressed slowly. Consequently, epigenetic modifications that regulate such traits may selectively evolve to be stably transmitted from parent to offspring.

WHEN WILL MULTIGENERATIONAL EPIGENETIC STABILITY BE ADAPTIVE?

Although stable, multigenerational epigenetic transmission has been documented in a number of cases (e.g., at least 40 generations in *Caenorhabditis elegans*, Vastenhouw et al. 2006; and eight generations in *Arabidopsis thaliana*, Johannes et al. 2009), none of these cases involves a phenotypic effect that is known to be adaptive, nor is it known whether such long-term stability is rare or widespread. Only a few models examine the conditions that would favor the persistence of epigenetically inherited variation across more than a single offspring generation.

However, current theory does suggest that stable, multigenerational epigenetic inheritance can be advantageous, depending on temporal patterns of environmental variation. For instance, selection strongly favors high rates of random switching between epigenetic states in rapidly fluctuating environments, and longer-term epigenetic stability when environments change less frequently (Lachmann and Jablonka 1996; Kussell and Leibler 2005). Adaptation to fluctuating environments can therefore be attained by selectively tuning the periodicity of random switching between alternative epigenetic states to the periodicity of

environmental change. Critically, these models show that this temporal matching is even more advantageous when environments directly induce adaptive epigenetic states (Furrow and Feldman 2013), but this benefit may hold only when costs of maintaining an environmental sensor are relatively low (Kussell and Leibler 2005).

Epigenetic stability on the scale of several generations can be interpreted as an evolutionary "strategy" that maintains adaptive phenotype-environment matching at an intermediate temporal scale, between short-term, within-generation plastic responses, and long-term, genetically based adaptations (Lachmann and Jablonka 1996, Klironomos et al. 2013). Consequently, rates of both random and environmentally induced epigenetic change could be expected to evolve to match patterns of environmental variability across generations. Experimental results to date have generally borne out this prediction (e.g., Acar et al. 2008). A new model by Furrow and Feldman (2013) corroborates the expected finding that environmentally sensitive epigenetic changes are more advantageous than random epimutation under fluctuating environments, and shows that multigenerational epigenetic stability is favored under a broad range of conditions. Importantly, this model also shows that low genetic variation at target sites for epigenetic regulation, high-recombination rates between epigenetic regulators and target loci, and potential costs of epigenetic regulation will all impede the evolution of epigenetic stability across generations.

One pressing question is whether epigenetic stability across multiple generations can be more beneficial than stability across a single parent–offspring transition. In cases where epigenetic marks are adaptive and relatively insensitive to the environment, the marks could be inherited for multiple generations in a manner analogous to the inheritance of adaptive genetic alleles. Such long-term epigenetic inheritance could be favorable if environments are stable, perhaps even more favorable than single parent–offspring transgenerational plasticity if such plasticity carries a cost. It is also possible that adaptive epigenetic inheritance in the form of transgenerational plasticity could operate over multiple generations (see Shea et al. 2011 for a theoretical comparison of these modes of epigenetic inheritance). At present, adaptive multigenerational epigenetic inheritance in this context seems unlikely: stable transmission across a single generation would provide the early growth advantage described above through early matching of progeny phenotype to environment, while preserving the ability to respond to subsequent environmental changes that may occur during the lifetime of the progeny. For multigenerational epigenetic stability to be more adaptively favorable than single-generational stability in this context, previous generations would have to predict the offspring's environmental conditions more accurately than parental ones, which seems highly implausible, or lag times for appropriate phenotypic response must last longer than a generation, which also seems unlikely. Accordingly, environmentally induced epigenetic modifications that persist beyond parent–offspring transmission may be no more favorable, and possibly less favorable, than single-transgenerational stability. The observation that parental environmental effects on offspring are ubiquitous, but that epigenetic stability is only rarely multigenerational, is consistent with this hypothesis. Nevertheless, the prevalence in natural systems of stable epigenetic transmission across multiple generations is an empirical question that remains to be determined.

If environmentally induced epigenetic changes can indeed be stable for more than one episode of meiotic transmission, despite the lack of an adaptive benefit to such prolonged stability, the question arises whether reversing epigenetic marks entails significant costs. For instance, is it biochemically difficult and/or expensive to demethylate a site once methylation has occurred, or expensive to maintain the machinery required to do so? If so, are these costs consistent or taxon-, locus-, or environmentally dependent? Perhaps it is the cost of resetting epigenetic changes that shapes selection on their stability, rather than patterns of stable persistence per se in relation to environmental cues and variability. The cost of epigenetic reversibility is a distinct question to be considered, especially in circumstances in which epigenetic marks are stable for more than one generation.

TRANSGENERATIONAL STABILITY OF RANDOMLY GENERATED EPIALLELIC VARIANTS: INSIGHTS FROM BET HEDGING

The evolutionary matching of levels of epigenetic stability to patterns of environmental change requires that those patterns occur consistently enough to effect natural selection. However, this kind of consistent variability may be absent from many natural systems. Under unpredictable conditions, the production of phenotypically diverse offspring should be favorable, because, in principle, it would cause at least some individuals within each generation to be suited to whatever conditions prevail. Such a strategy of enhanced variability is termed *bet hedging* (reviewed by Simons 2011). Although in many instances, bet hedging is understood to consist of random variation, it can also entail random alternation between particular phenotypes (Veening et al. 2008a).

Bet hedging may lead to lower arithmetic mean fitness within any particular generation, but, because it minimizes fitness variance across generations, it results in higher geometric mean fitness over the long term (Philippi and Seger 1989) and consequently a greater total number of descendants compared to nonbet-hedging strategies (Cohen 1966; Lewontin and Cohen 1969; Gillespie 1974). Evidence for bet hedging in natural systems comes from a wide array of taxa (Hairston and Munns 1984; Marshall et al. 2008; Veening et al. 2008b; see references in Simons 2011). For instance, certain plants produce seeds that vary in size,

dispersal ability, and dormancy behavior, resulting in germination in different environments (Evans et al. 2007; Venable 2007).

In theory, epigenetic processes could lead to this kind of offspring variability if changes to offspring are random and/or spontaneous, or if epiallelic stability from parent to offspring is inconsistent—that is, if some progeny individuals inherit particular epigenetic marks while reversal occurs in other individuals at some or all affected loci. It is not yet known to what extent epigenetic mechanisms can give rise to bet-hedging variability. In several bacterial systems, the production of alternative cellular states by a single genotype enhances population viability in unpredictable environments (Veening et al. 2008a; Beaumont et al. 2009). These cellular states are each stably transmitted across several generations, but intermittently subject to spontaneous switching among states. In one case, epigenetic inheritance is a mechanism for this kind of bet hedging: in *Bacillus subtilis*, alternative cellular states that are inherited epigenetically result in the persistence of phenotypically distinct subpopulations of bacteria, each suited to a different environment (e.g., conditions favorable for growth vs. unpredictable periods of stress, Veening et al. 2008b). These subpopulations can coexist indefinitely so long as environments continue to vary. Although epigenetic inheritance was found to be stable for at least two generations in this system, it is unclear precisely what level of stability contributes to adaptive bet hedging in this scenario.

To our knowledge, such a direct connection between epigenetic regulation and bet hedging has not been confirmed in multicellular organisms. In Dandelion (*Taraxacum*), several controlled environmental stresses were found to increase epiallelic variability within genetically uniform seed families (Verhoeven et al. 2010). This result is consistent with bet-hedging via random epigenetic changes, although it is not conclusive because it remains to be determined whether this enhanced epigenetic variability causes phenotypic differences in offspring individuals.

Modeling results support a plausible role for epigenetic variation and inheritance in bet hedging. Jablonka et al. (1995) found that the most advantageous strategy under random or nearly random temporal environmental variation consisted of conditional bet hedging coupled with stable epigenetic inheritance. Under this strategy, offspring of different epigenetically based phenotypes were produced in a ratio that depended on the current environment. Long-term stability of induced epigenetic variants effectively averaged reproductive output over many generations and environments, resulting in reduced fitness variance and hence greater population growth compared to both a fixed genetic strategy (i.e., insensitive to environment), and an adaptive plastic strategy without the capacity for epigenetic inheritance (Jablonka et al. 1995). Here, the advantage of a conditional bet-hedging strategy arose from the production of variable offspring coupled with multigenerational epigenetic transmission of that variation, because each of these components reduced variance in fitness.

Stable inheritance of environmentally induced epigenetic variation that is random with respect to adaptation can be advantageous when the phenotype is far from its optimal state (Pal 1998; Pal and Miklos 1999). In this case, nonadaptive plasticity allows for the exploration of phenotypic space, increasing the probability of producing a phenotype that is closer to the optimum. Stable inheritance of such randomly induced epigenetic states over many generations increases the frequency of rare adaptive variants by retaining them across generations. Such retention enhances the efficiency of selection and hence the rate of adaptive evolution compared to unstable epigenetic changes. In contrast, once the character is close to its optimal value, genetically fixed adaptations are favored, as continued production of random epigenetic states moves the average phenotype away from the optimum (Pal 1998; Pal and Miklos 1999).

Potential Nonadaptive Consequences of Variation in Epigenetic Stability

If genetic variation exists for the stability of epigenetic marks, it is possible that the stability itself can evolve adaptively. An alternative evolutionary scenario is one in which, due to its lability, epigenetic variation contributes primarily to noise in the system rather than to adaptive outcomes, including favorable levels of stability itself. Despite initial expectations, epigenetic marks appear to be remarkably widespread in genomes across the phylogenetic spectrum (Jablonka and Raz 2009). Because many of these alternative states are not reset every generation, natural populations are likely to contain high levels of epiallelic variation, with corresponding heterogeneity in phenotypic expression (Geoghegan and Spencer 2012, 2013). Very high levels of epigenetic variation indeed appear to be the case in natural systems examined to date (e.g., Herrera and Bazaga 2010; Lira-Medeiros et al. 2010; Richards et al. 2012). If loci that control epigenetic stability themselves exhibit high levels of epigenetic variation, such variation could act to obstruct selection for particular levels or patterns of stability.

In general, phenotypic variation unconnected to allelic differences can render selection inefficient, whether such variation arises from immediate plastic responses to microenvironmental variation or from heterogeneous epigenetic states unrelated to such plasticity (Sultan 2003). The biochemical reactions that govern epigenetic changes and their resetting may be sensitive to multiple environmental factors and factor states, rather than precisely regulated by specific cues. If this is the case, in natural habitats these variants are likely to blink on and off irregularly both

within and across generations, as myriad environmental signals are received. Indeed, environmental stresses can induce random methylation changes as well as consistent, putatively adaptive ones (Verhoeven et al. 2010). Such a scenario would generate enormous amounts of variation at the individual level that did not constitute adaptive environment-phenotype matching. The irregular regeneration of this variation in successive generations would impede selection for particular epialleles in particular conditions, leading instead to the maintenance of epiallelic and consequently phenotypic variation. This prediction is consistent with the results of population-epigenetic models by Geoghegan and Spencer (2012; 2013), which showed that strong viability selection did not lead to epiallelic fixation, but rather to persistent epigenetic variation and, in some cases, to stable polymorphisms (as long as alternative inducing environments were relatively common). Their models further show that even if natural selection leads to the fixation of DNA sequence variants that influence fitness traits, epiallelic switching can cause phenotypic variation to be maintained in populations.

Proposed Research Directions

Despite intense interest in the subject, the adaptive significance of epigenetic stability is currently unclear. Progress on this issue will require integrative studies that examine the source and stability of epigenetic variation over a range of timescales and environmental conditions, as well as the adaptive value of its phenotypic effects. Below, we outline three broad questions critical to addressing these evolutionary issues.

Are epigenetic changes a major regulatory mechanism of adaptive plasticity, either within or across generations, and if so, which epigenetic mechanisms? This question can be addressed by combining studies of adaptive plasticity with molecular analysis of environmentally induced epigenetic variation. There are numerous experimental tools for testing whether within- or transgenerational plastic responses to specific environments are adaptive, including phenotypic selection analysis and comparisons of individual performance in experiments that manipulate environments, genotypes, or phenotypic states (reviewed by Schmitt et al. 1999; Dorn et al. 2000; Herman and Sultan 2011). The general approach is to raise genetically uniform replicate individuals of lines of interest in a range of ecologically relevant environments for one or more generations, and measure functionally important traits as well as components of fitness expressed in each environment. These data can be used to estimate selection on the measured traits, or to test whether the phenotype expressed in each environment meets functional predictions and/or has higher fitness than alternative phenotypes. Epigenetic analysis can be directly incorporated into plasticity studies by testing for statistical associations between induced phenotypic variation and the presence of specific induced epialleles. Such a correlational approach can be combined with manipulation of epigenetic variation (e.g., demethylation using 5-azacytidine treatment or use of methylation-deficient mutants) to causally test the phenotypic and fitness consequences of alternative epigenetic states in specific environments (e.g., Herrera et al. 2012).

Empirical studies can help to resolve several key factors regarding the adaptive value of epigenetic stability. Based on the above consideration of plasticity theory, adaptive environmentally induced epigenetic changes are predicted to occur when environments vary in space and time, and when environmental cues reliably predict selective environments. The adaptive stability of these changes will depend on the temporal environmental variability experienced by organisms: epigenetic changes should be less stable in situations when the environment changes repeatedly within a lifetime, and more stable when the environment changes only once during the lifetime. Epigenetic changes that are stable within a generation are predicted when dispersal occurs at the gamete or early zygote stage, or when epigenetic changes control irreversible, environmentally cued developmental transitions. Costs of epigenetic stability or reversibility could alter the adaptive value of epigenetic modifications and of their stable transmission. Investigating the causes and magnitudes of these potential costs is necessary to predict the adaptive value of stable epigenetic modifications.

These predictions can be tested by measuring and/or manipulating spatial and temporal environmental variation or dispersal, and the accuracy, timing, and duration of environmental cues, as well as by comparative studies. Broad-sense costs of stability or reversibility can be assessed in a similar manner as costs of plasticity by comparing the fitness of individuals with similar phenotypes, but different epigenetic stability; ideally, actual biochemical costs could become more well understood with continued studies of the molecular mechanisms of epigenetic marking.

What are the inducing cues, patterns of stable transmission, and phenotypic effects of epigenetic modifications in natural systems, and do different types of epigenetic modification differ in their stability? Many studies have demonstrated inheritance of induced DNA methylation changes (reviewed by Jablonka and Raz 2009), but it is not yet known whether these changes are commonly transmitted across multiple generations, or if other epigenetic alterations (e.g., histone modifications or small RNAs) are commonly induced by environmental cues and inherited. Furthermore, in most known cases, the inducing stimulus is highly artificial, and phenotypic effects are unclear. Studies are needed to clarify the extent to which epigenetic modifications are inherited over multiple generations under ecologically realistic conditions, and to characterize their effects on phenotypes, including components of fitness. Such studies can test the degree to which

randomly or environmentally induced epigenetic modifications continue to be stably transmitted in the face of new environmental cues. Theoretical investigations of such epigenetic stability can make progress by incorporating parameters known to influence the evolution of adaptive within- and transgenerational plasticity, in addition to parameters unique to epigenetic models, such as rates of epigenetic resetting. Comparative studies could resolve the extent to which ecologically distinct species or populations differ in patterns of induction, stability of transmission, and phenotypic effects of epigenetic changes. Empirical studies are also needed to determine whether genotypes in natural populations differ in epigenetic stability so as to provide material for evolutionary change in epigenetic stability.

Is the production of epigenetic variation a common mechanism for bet hedging, and if so, what is the optimal level of epigenetic stability for such a strategy? Because the fitness benefits of bet-hedging strategies are manifest only over the long term, progress on this issue will require multigenerational studies focused on the fitness effects of epialleles of a range of stabilities in unpredictable environments. Conclusive evidence for a role of epigenetic variation in bet hedging would consist of: identification of a putative bet-hedging trait (Simons 2011), demonstration that epigenetic variation underlies variation in the trait, and demonstration that variation in the trait confers a fitness advantage in unpredictable environments. Experimental manipulations of environmental variability and predictability could be used to test whether epigenetic variation is effective in bet hedging. Genetic manipulations of epigenetic stability under diverse regimes of environmental variation would be especially effective for such studies.

Conclusion

Surveys of epigenetic variation in natural animal and plant populations (e.g., Herrera and Bazaga 2010; Richards et al. 2012; Schrey et al. 2012) have shown that such variation is extensive—often even more so than genetic variation. Evolutionary biologists must incorporate this dimension of molecular diversity into our understanding of adaptation (e.g., Day and Bonduriansky 2011). Here, we addressed one aspect of this broad task by evaluating the potential adaptive role of epigenetic stability. Previous work on the evolution of adaptive phenotypic plasticity and bet hedging points to a number of salient factors to investigate, including environmental cues and patterns of environmental variation, response lag times, and possible costs of epigenetic changes and reversals. However, the applicability of these insights rests on the answer to a fundamental and as yet open question—are epigenetic changes a major regulatory mechanism of these two well-known modes of adaptation? If the answer is affirmative, existing theory can provide a major head start on integrating epigenetic dynamics into evolutionary theory.

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