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Epigenetic inheritance and plasticity: The responsive germline

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ABSTRACT

Developmental plasticity, the capacity of a single genotype to give rise to different phenotypes, affects evolutionary dynamics by influencing the rate and direction of phenotypic change. It is based on regulatory changes in gene expression and gene products, which are partially controlled by epigenetic mechanisms. Plasticity involves not just epigenetic changes in somatic cells and tissues; it can also involve changes in germline cells. Germline epigenetic plasticity increases evolvability, the capacity to generate heritable, selectable, phenotypic variations, including variations that lead to novel functions. I discuss studies that show that some complex adaptive responses to new challenges are mediated by germline epigenetic processes, which can be transmitted over variable number of generations, and argue that the heritable variations that are generated epigenetically have an impact on both small-scale and large-scale aspects of evolution. First, I review some recent ecological studies and models that show that germline (gametic) epigenetic inheritance can lead to cumulative micro-evolutionary changes that are rapid and semi-directional. I suggest that "priming" and "epigenetic learning" may be of special importance in generating heritable, fine-tuned adaptive responses in populations. Second, I consider work showing how genomic and environmental stresses can also lead to epigenome repatterning, and produce changes that are saltational.

1. Introduction

In multicellular organisms, developmental plasticity, the capacity of a single genotype to give rise to different phenotypes, depends on the regulatory modulation of genes and gene products. At the molecular level, most of these regulatory changes lead to stable alterations in transcription, RNA processing, and protein structure, which can all be inherited in cell lineages; in some tissues, they also lead to changes in DNA base sequence (e.g., in mammals, DNA sequences change in the immune system, and possibly also in the nervous system). The molecular processes that underlie persistent developmental changes are known as epigenetic mechanisms. They include mechanisms that lead to DNA base modifications (e.g., cytosine methylation) and their perpetuation; mechanisms that lead to histone modifications and their perpetuation; the recruitment and maintenance of histone variants at specific DNA sites; the recruitment and maintenance of non-histone DNA-binding proteins; several RNA-associated regulatory systems that have transmissible effects; mechanisms that lead to changes in the three-dimensional templating of proteins and cell structures; and switches between alternative self-sustaining, regulatory, metabolic feedback-loops (Jablonka and Lamb, 2005, 2010). Some of the epigenetic variations that are transmitted by these mechanisms are carried on nuclear chromosomes (epigenetic marks in DNA methylation, histone modifications, non-histone binding proteins), some have both nuclear and cytoplasmic components (regulatory small RNAs) while others are transmitted through the cytoplasm (e.g., prions and self-sustaining metabolic loops). These epigenetic control and memory mechanisms are commonly interconnected, forming persistent, self-maintaining, cellular networks. They are also important in the recruitment and regulation of the natural cellular engineering processes that are involved in DNA repair and the control of transposition and recombination.

In the last two decades, biologists have become increasingly aware that epigenetic mechanisms can lead to phenotypic changes in the next generation through gametic transmission of epigenetic variations (Jablonka and Raz, 2009; Jablonka, in press). The consequences of this for evolutionary thinking are profound, and the view of evolution that is now emerging is significantly different from the neo-Darwinian view that dominated evolutionary thought in the second half of the 20th century (Jablonka and Lamb, 2010; Bonduriansky, 2012).

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2. Epigenetic variations in gametes

It is impossible to review here all of the already substantial and rapidly growing data on gametic epigenetic inheritance – the inheritance via the germline of variations that do not depend on differences in DNA base sequence (see Jablonka and Raz, 2009; for a general review; for wild plants, see Richards, 2011; for mammals, see Daxinger and Whitelaw, 2012; for a review of genomic imprinting, mainly in mammals, see Ferguson-Smith, 2011). I shall therefore describe some representative results from recent studies in plants, ciliates, nematodes and mammals that show that gametic epigenetic inheritance occurs in both multicellular and unicellular organisms, that heritable epigenetic variation can be extensive, and that it can sometimes be adaptive.

Some of the most telling evidence for the occurrence and transgenerational inheritance of epigenetic variants has come from work with the plant *Arabidopsis thaliana*. Two large-scale studies have been made of inbred lines that were derived from a common ancestor and were propagated in a greenhouse for 30 generations. Using methylation-sensitive sequencing techniques, the methylation patterns of lines from the 3rd generation were compared to those of lines from the 30th generation (Becker et al., 2011; Schmitz et al., 2011). Since the lines all had the same DNA (barring a few possible mutations and rare transpositions), and since there had been no change in the environment in which the plants lived, the results tell us about the frequency with which inherited variations in methylation occur in an undisturbed line of plants. The authors of one of the studies summarized their results and conclusions in this way: "We examined spontaneously occurring variation in DNA methylation in *Arabidopsis thaliana* plants propagated by single-seed descent for 30 generations. 114,287 CG single methylation polymorphisms (SMPs) and 2485 CG differentially methylated regions (DMRs) were identified, both of which show patterns of divergence compared to the ancestral state. Thus, transgenerational epigenetic variation in DNA methylation may generate new allelic states that alter transcription, providing a mechanism for phenotypic diversity in the absence of genetic mutation" (Schmitz et al., 2011, p. 369). The lower bound of the epimutation rate found was 4.46×10^{-4} per CG per generation, which is several orders of magnitude higher than the classical mutation rate, which in these lines is 7×10^{-9} base substitutions per site per generation. There were many other interesting findings in both studies: the variations in DNA methylation were sometimes correlated with changes in gene expression, and DMRs were more stable than single site changes, with some variants reverting frequently and other being stable. The overall conclusion is that methylation variants at many sites are stably inherited through meiosis, and may therefore affect evolutionary change in populations, although the effect of frequent reversions has to be taken into account when considering their evolutionary significance.

Further information about the stability and phenotypic effects of epigenetic variants in *Arabidopsis* has come from investigations using epiRILs (epigenetic Recombinant Inbred Lines). These epiRILs were constructed by using mutants in the methylation pathway to produce a series of lineages that are genetically nearly identical, but differ in their patterns of wild type and methylation-deficient loci, i.e., the lineages carry different epialleles (Johannes et al., 2009; Reinders et al., 2009; Teixeira et al., 2009). Many epialleles have been found to be stably inherited, some for 14 generations (so far, the experiment is on-going; Colot, personal communication). Moreover, some epiallelic variations are associated with differences in phenotypic characters such as time to flowering and plant height, which can be adaptive, and the heritabilities of these traits is similar to those found in genetic studies (Johannes et al., 2009).

We know far more about epigenetic inheritance involving DNA methylation in *Arabidopsis* than we do about this type of inheritance in most other organisms. Nevertheless, we do know that heritable epigenetic variations, not only variations in cytosine methylation, but epigenetic variations involving all the different epigenetic inheritance systems enumerated, are ubiquitous: epigenetic inheritance has been found in every organism in which it has been sought (Jablonka and Raz, 2009).

Some of the most remarkable examples of epigenetic inheritance have been found in ciliates. These unicellular organisms have two types of nuclei: a diploid, germline micronucleus, and a DNA-rich macronucleus, which has somatic functions. Following sexual reproduction, the old macronucleus is destroyed, and a dedicated epigenomic and genetic engineering system rearranges the nuclear genome through regulated deletions, inversions, fragmentations, and amplifications to form a new, gene-rich macronucleus. The process is guided by RNA templates from the parental macronucleus, and artificially altering these can lead to the inheritance of changes in the macronucleus of subsequent generations (Nowacki and Landweber, 2009). Ciliates can also transmit acquired or induced structural changes to the cortex (Beisson and Sonneborn, 1965; Grimes and Aufderheide, 1991), although the mechanisms through which they do so are not understood. In the yeast *Saccharomyces cerevisiae*, another unicellular organism, the inheritance of prion proteins is common, and in some environments the effects of these structural variants are adaptive (Halfmann et al., 2012).

Several types of epigenetic inheritance have been found in the nematode worm *Caenorhabditis elegans*, one of the organisms in which transmissible RNAi-mediated gene silencing was first recognized. It has now been discovered that the RNAi system of this animal enables the transmission of resistance to *any* invading virus, whatever its sequence (Rechavi et al., 2011). Whether the RNAi system is also involved in the epigenetic inheritance of the nematode's olfactory memory (Remy, 2010), or in the inheritance of longevity modifications produced by manipulating its chromatin marks (Greer et al., 2011), remains to be investigated. However, recent studies showing the role of piRNA in the surveillance of the nematode genome and the transmission of new variations (reviewed in Baumann, 2012), and the availability of mutants defective in the RNAi system, provide the incentive and the methodology to test the possibility that these traits are epigenetically transmitted through the RNAi system.

In mammals, too, there is evidence that epigenetic inheritance is widespread, and that new variation can arise in response to environmental changes (Guerrero-Bosagna and Skinner, 2011; Daxinger and Whitelaw, 2012). For example, Suter and her colleagues found that methylation variability among isogenic mice that had received a diet supplemented with methyl-donors (such as folic acid) for six generations progressively increased, suggesting that some of the induced epigenetic changes were heritable (Li et al., 2011). In another study using inbred mice, Suter's group found that the penetrance of an epigenetically-controlled coat-color phenotype progressively, but reversibly, increased when methyl-donor supplementation of the diet was coupled with selection for high penetrance (Cropley et al., 2012). Rassoulzadegan (2011) has used a very different approach to manipulating epigenetic states in mice: she found that injecting specific small RNAs into fertilized eggs led to the heritable silencing of various target genes. Psychological stress also seems to heritably alter mouse phenotypes: separating mice from their mothers for an unpredictable few hours during each of the first 14 days after birth induced heritable, depressive-like adult behaviors, and altered their responses to novel and aversive environments; the early stress also altered the methylation profile of specific germline genes (Franklin et al., 2010). The

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methylation status of thousands of loci in the developing germline of male rat fetuses was changed when their gestating mothers were exposed to the fungicide vinclozolin, an androgen suppressor, and the disease phenotypes induced by the chemical, as well as the epigenetic profile it induced, were inherited for four generations (Skinner et al., 2008, 2010).

There are two general features of the studies just described that are of particular interest from an evolutionary perspective. The first is that in most of the cases discussed, epigenetic alterations involved a large number of loci, and this could increase the number of phenotypic attributes that can be screened by selection; the second is that frequently the inducing agent was some kind of environmental stress. It has become increasingly clear that ecological stresses, such as changes in temperature or exposure to toxins, and also genomic stresses, such as those that follow hybridization lead to wide-ranging epigenetic changes (the evolutionary effects of these stresses are discussed in Section 6).

3. Epigenetic accommodation through exploration and stabilization

The evidence presented in the previous section shows that epigenetic processes generate a large amount of developmental variability, especially in stressful conditions, and that some epigenetic variations are transmitted to subsequent generations. What still needs to be explained, however, is how this conditions-sensitive ability to create diversity is related to both ontogenetic adaptive plasticity and to evolutionary adaptation.

Recent years have seen a substantial increase in the role of developmental plasticity in evolution, which is reflected in important books such as *Developmental Plasticity and Evolution* by West-Eberhard (2003) and *Plasticity, Robustness, Development and Evolution* by Bateson and Gluckman (2011). West-Eberhard (2003) started her analysis with the developmental systems' responses to a challenge – to a challenge imposed by the conditions of life, or to a genetic challenge (e.g., a mutation). She called the systemic developmental response which leads to an organism's adjustment to this challenge *phenotypic accommodation*. One example that she used to explain this concept was Slijper's goat, which was born without proper front legs but, initially with human help, learnt to walk and run on its hind legs. Following the goat's untimely death in an accident after a year of bipedal life, the post-mortem examination found many changes in its skeleton, musculature, and innervation. West-Eberhard reviewed and discussed the mechanisms behind such correlated changes in various aspects of the phenotype, especially mechanical flexibility, new regulatory interactions, and exploratory processes followed by stabilization at the cellular, physiological and behavioral levels. At the molecular level, accommodation can involve epigenetic changes in regulatory systems (and sometimes also genomic changes; see Shapiro, 2011). For example, the plasticity of the flower-living yeast *Metschnikowia reukaufii*, which can exploit a very wide range of plant nectars, is associated with induced epigenetic changes (Herrera et al., 2012). Insect pollinators spread this yeast to flowers of many different individuals and species, which differ in the composition and concentration of sugars in their nectar. The rapid accommodation necessary for the yeast to exploit this constantly varying resource is correlated with changes in DNA methylation, and is impaired when the cells are treated with the DNA methylation inhibitor 5-azacytidine.

Phenotypic adjustments of the types seen in Slijper's goat or nectar-exploiting yeast occur within a single generation, but as Waddington argued many years ago and has shown experimentally, when environmental challenges persist for generations, phenotypic adjustments can be followed by genetic assimilation that leads to the stabilization of conditional ontogenetic responsiveness, and in some cases, even to unconditional expression (Waddington, 1957). Through selection, the frequencies of alleles that influence the likelihood of producing the phenotypic features that enable the organisms to cope with the challenge are altered. West-Eberhard extended Waddington's framework to include not only genetic changes that lead to increased stabilization of the accommodated phenotype, but also to changes that increase responsiveness and that ameliorate detrimental side-effects. The evolutionary process that she envisages starts with phenotypic rather than genotypic change. As West-Eberhard sees it "genes are followers, not leaders, in adaptive evolution" (West-Eberhard, 2003, p. 20).

Bateson and Gluckman (2011), who adopt this phenotype-first approach, discuss additional aspects of genetic accommodation, stressing the role of epigenetic mechanisms in the process. First, they focus on the mutational biases introduced by epigenetic chromatin marks, which alter the probability of mutation, recombination and transposition, and thus bias, and can accelerate, genetic accommodation processes. Second they argue that genetic accommodation processes may have played a particularly important role in the evolution of animal behavior. Since behavioral accommodation processes are likely to lead to adaptive and persistent learnt responses, they lead to the construction of stable and reproducible developmental niches employing epigenetic mechanisms, and to directional selection for developmental robustness. The effects of the exploration and stabilization mechanisms that allow an animal to learn and improve new adaptive behaviors unmask variations in genes that enable a more efficient response to the new conditions, without undermining the generative exploration-stabilization strategy and without compromising plasticity (Bateson and Gluckman, 2011; Bateson, in press).

The examples discussed in this and the previous section show that the challenges that an organism faces can be of very different kinds: they can be predictable (recurring during the individual's lifespan or the lineages' phylogenetic history) or novel (never before encountered); they can be mild or they can be drastic. It is likely that the response to each type of challenge will employ different coping-strategies: highly predictable challenges will mobilize existing regulatory networks, which have evolved to deal with exactly these challenges, whereas unpredictable challenges may require extensive (behavioral, neural, epigenomic or genomic) rejigging (Jablonka and Lamb, 1995, 2005). In all cases, but especially in the case of unpredictable and drastic challenges, the process is likely to entail the generation and exploration of multiple states, followed by the stabilization of those states that lead to the resolution of the problems caused by the challenge. This type of process has been found in many other biological systems that deal with challenges that are not entirely (or not at all) predictable. Classic examples of exploration and selective stabilization mechanisms are those employed by the adaptive immune system when responding to a new kind of antigen, or by the nervous system when responding adaptively to developmental cues, which are never entirely identical, or by trial-and error learning. The dynamic processes that lead to cellular spindle formation, root elongation toward water, and the amazing feat of food-finding by the fungus *Physarum* (Tero et al., 2010), are among many other similar examples of the use of exploration and selective stabilization processes to solve problems (for more examples and discussions see Kirschner and Gerhart, 2010 pp. 262–264 West-Eberhard, 2003 pp. 37–44).

Studies by Braun and his colleagues have shed some light on the strategies that enable one organisms, the yeast *S. cerevisiae*, to survive in novel and severely challenging conditions (Braun and David, 2011; David et al., 2010; Stern et al., 2007; Stolovicki and Braun, 2011; Stolovicki et al., 2006). These workers used

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a genetically-engineered haploid strain in which the essential gene *HIS3*, which codes for an enzyme from the histidine biosynthesis pathway, was deleted from its normal chromosomal location. The gene was re-introduced into the cell on a plasmid under the promoter of *GAL1*, a gene from the galactose utilization system. The GAL system, and with it the essential *HIS3*, are strongly repressed in glucose medium, so in these conditions the engineered cells cannot produce histidine, and significant adaptation is required for their survival. Such adaptation is not part of the evolved response-repertoire of the yeast cells, so there are no pre-existing, evolved "programs" or "procedures" that can deal with it. What Braun and his colleagues found was remarkable: after a lag period of 6–20 days, 50% of the cells maintained on glucose without histidine started to multiply. In these cells, the regulation of the GAL1 promoter was altered, and this altered regulation was inherited for hundreds of generations. The basis of the altered regulation seems to have involved complex re-wiring ("promoter scrambling"), with different cells finding different adaptive solutions. Some of these solutions were associated with genetic mutations (e.g., in the repressor or in the promoter of the GAL system) and some seem to have involved epimutations. However, even when a mutation was involved, the mutation alone could not explain the propagation of the adapted phenotype. It seems that multiple changes are required to generate a stably adapted lineage.

Comparable experiments, in which developing larvae of the fruit fly *Drosophila melanogaster* were exposed to a challenge that the species can never before have encountered, have been carried out by Seon, Braun and colleagues (Stern et al., 2012). They created lines of flies in which a drug resistance gene was linked to various different tissue-specific promoters, and consequently was expressed in some tissues but not others. The fly larvae were then fed with food containing a toxic concentration of the drug. To accommodate to this challenge, the gene would need to be expressed in additional tissues. What they found was that, after a developmental delay, the promoter activity had been broadened, and the resistance gene was expressed in the gut and elsewhere, thus enabling the larvae to tolerate the otherwise lethal conditions. They identified part of the mechanism that is responsible for this adaptive response: it involved the suppression of Polycomb group genes, which affect chromatin structure and maintain the repressed state of many developmental regulators. Amazingly, the accommodated phenotype was inherited, sometimes for as many as 24 generations.

The results of these experiments with yeast and *Drosophila* draw attention to three principal questions about the molecular accommodation process. First, what is the nature of the process of molecular exploration, and how is it induced? (Are there changes in DNA sequence? in the RNA system? in chromatin? in the conformation of proteins? How are new regulatory networks formed?). Second, what leads to stabilization, once a stable functional state is reached? Third, what is the nature of this dynamically stable state, and how is it recognized? In the *Drosophila* case, we also need to ask how germline cells recognize and respond to a systemic (whole organism) somatic stable state.

We do not have complete answers to any of these questions. The detailed studies made by the Braun and Soen groups show that as result of a challenge there are wide-ranging changes in gene expression: there are many new and different patterns of transcription. It seems that a subset of these – those that provide an adaptive response allowing the organism to survive and reproduce – are stabilized. Similar conclusions can be drawn from the work of Adam and his colleagues on adaptation in an isogenic population of *Escherichia coli* exposed to increasing concentrations of various antibiotics (Adam et al., 2008). In all cases, it appears that there are several "solutions" to the problem.

We still need to know how an adaptive stable state is found, and how it is stabilized. In the case of a single cell, the ability of the cell to divide, or to continue to perform a vital function, is a good indicator of an adaptive state, and it is likely that molecules produced when the cell is in this state act as signals that directly or indirectly lead to its stabilization through some form of autocatalysis. The nature of these signals is not known, nor is it known what stabilization entails, although there is little doubt that epigenetic control mechanisms and natural genetic engineering systems are involved. The problem is even more difficult with multicellular organisms. Not only must there be a signal that leads to the stabilization of the state of the whole organism, but this signal must also reach the germline and modify it in a way that leads to the persistence of the adapted state in subsequent generations. How do such signals reach the germline and how does it respond?

4. An epigenetically responsive germline?

The germline is not a safe in which genomes are stored passively, secure and inviolate unless some rare, unavoidable, random hit occurs and causes a mutation. The germline has evolved to be a particularly active cell type with mechanisms that ensure genome functionality and variability. On the one hand there are many dedicated repair and elimination mechanisms that ensure that detrimental lesions are unlikely to be perpetuated in their harmful state (e.g., transposable elements and unpaired chromosome regions can be silenced), and on the other hand there are mechanisms that generate variations (genetic recombination is the most well-known example). During mild genomic or environmental challenges, mechanisms of coping with problems in the germline are mobilized. For example, when meiotic pairing is compromised, unpaired regions are transcriptionally inactivated through modifications of the chromatin conformation, or they are excised (reviewed in Kelly and Aramayo, 2007; Kota and Feil, 2010). Similarly, the movement of transposable elements is normally restrained by epigenetic mechanisms involving small RNAs (Saito and Siomi, 2010). However, in catastrophic, unpredictable conditions, for which the organism is not prepared, release from transposon silencing can be a way of responding to the challenge.

As Barbara McClintock suggested many years ago, transposition may lead to new types of individuals, whose changed genomic organization increases the "exploration space" of the offspring (McClintock, 1984; Jorgensen, 2004). As well as being instrumental in effecting gross chromosomal changes, transposable elements can have more subtle effects. By carrying new regulatory sequences to their sites of insertion, they affect the expression of neighboring genes. These inserted elements seem to be particularly prone to epigenetic meta-stability (Chong and Whitelaw, 2004), with internal and external conditions modifying gene expression in ways that are inherited, although in mammals, usually not with high fidelity. Germline transposition can thus increase the range of inducible, selectable, epigenetic variations in descendants.

In challenging conditions, even when parent organisms do not themselves respond phenotypically, epigenetic events in the germline can lead to responses in their offspring. An example of such *direct induction* (or *gametic induction*) of epigenetic changes in germline cells is seen following the transient administration of an androgen inhibitor, the fungicide vinclozolin, to pregnant female rats: the parent females themselves are unaffected, but their male offspring have reduced fertility and testes diseases that are inherited through the male line for at least 4 generations (Anway et al., 2005; Skinner et al., 2010). The induced diseases are correlated with changed methylation patterns. As might be expected with the generation of epigenetic variations in the germline, where both nuclear and cytoplasmic elements undergo massive

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restructuring prior to gamete formation, the induction of the diseases depends on the stage at which treatment is given: in the rat, the period of gonadal sex determination, when the germ cells undergo re-methylation, is particularly sensitive to the endocrine disrupters that lead to heritable epigenetic variations.

If an environmental challenge induces in a parent a trait that is transmitted gametically to offspring, it can (at least in theory) be the result of either of two processes: *parallel induction* or *somatic induction*. *Parallel induction* would occur if the same factor independently induced epigenetic changes in both the soma and germline; in other words, the germline change is induced directly, without somatic mediation, so similar somatic phenotypes are apparent in both the induced individual and its descendants. A possible example of parallel induction has been investigated in the flour moth *Ephestia kuehniella*. Subjecting a short antennae mutant of this insect to a slightly higher than normal temperature during the last larval instar and early pupal stages of development, or adding lithium ions to the larval food, results in the suppression of the mutant antenna phenotype in the treated generation and in five subsequent generations (Pavelka and Koudelová, 2001). The molecular mechanisms behind this are unknown, and the findings are open to several interpretations, one being that the treatment modifies the epigenetic state of the mutant gene in the same way in both the germline and the primordial somatic antennal cells of the treated ancestors. *Somatic induction* is different: a change is first induced in the soma, and this somatic effect is then transmitted to the germline; in other words, the germline change is not direct, but is mediated through the soma. Like parallel induction, somatic induction leads to similarity between the induced ancestor and its descendants. A clear example of this type of induction is seen following the ingestion by *C. elegans* of bacteria with DNA sequences coding for double-stranded RNA. The RNAs that are produced from this DNA in the soma migrate to its germ cells, and hence affect subsequent generations (Vastenhouw et al., 2006; see Jablonka and Lamb, 2010 for a discussion of the epigenetic inheritance mechanisms, and Baumann, 2012 for recent insights in *C. elegans*). A less direct route between the soma and germline would be one mediated by hormones: hormonal changes may affect not only somatic tissues, but also germ cells, which are rich in hormone receptors (see discussion in Jablonka and Raz, 2009).

In plants, where there is no sequestered germline, an epigenetic change that is induced in the relatively undifferentiated meristem cells, which give rise to both vegetative structures and the germ cell lineage, could result in similar phenotypes in both parents and offspring. This has the interesting consequence that long-lived perennial plants may be able to pass to their offspring, through their germ cells, epigenetic variations that were induced years earlier and have already been somatically tested.

Whatever the route by which epigenetic variations are acquired by germline cells, if they are to be transmitted to future generations, they have to survive the dramatic nuclear and cytoplasmic processes that take place during gamete production. To understand how this is possible, it is important to recognize that gametic epigenetic inheritance is a *reconstruction not a replication process*. Although the epigenome of both male and female germlines is reset during gametogenesis – in mammals, for example, most DNA methylation and histone marks are erased – erasure is not total, and there are differences between males and females. Some traces of past chromatin structure may be retained, possibly in the form of partial methylation marks, or partial histone modifications, and these are sufficient for the reconstruction of the ancestral epigenetic patterns in the offspring (Margueron and Reinberg, 2010). Hence, for variant epigenetic states to be inherited, we must assume that the "default state", which is required for the totipotency of cells in the embryo, is not the same in all individuals. There is no "delete button" that makes every reset individual gamete or embryo epigenetically identical. Traces of epigenetic variations in the form of variant small RNAs, variant templating proteins, or variant methylation or histone traces, which are determined by the parental germline, enable the *reconstitution* (probabilistically) of the parental variant state (e.g., of DNA methylation).

5. Population epigenetics

As knowledge about epigenetic inheritance has grown, so has the recognition that it must influence evolutionary changes in populations. However, compared to the extensive information we have on other kinds of developmental and genetic diversity in populations, the data we have on ecological and population epigenetics is scarce, although relevant studies are underway (reviewed by Bossdorf et al., 2008; Ledón-Rettig et al., in press; Richards, 2011). Some generalizations that provide an empirical basis and a theoretical framework for population epigenetics are already emerging. The first is that the amount of epigenetic variability in populations of genetically similar organisms can be enormous (see for example Lira-Medeiros et al., 2010; Gao et al., 2010; Herrera et al., 2012). In general, there is far more epigenetic variation than genetic variation, although how much of the epigenetic variation is heritable is as yet unknown. The data from the study of *Arabidopsis* inbred lines that was discussed in Section 2 suggest that the amount of heritable variation is likely to be substantial. Second, there is a relationship between stress and the induction of epigenetic heritable variation, and both genomic shocks and environmental or experimental stresses can induce variation (Bossdorf et al., 2010; He et al., 2010; Whittle et al., 2009). Third, some of the heritable epigenetic variations have phenotypic effects, and some of those effects are adaptive (such adaptive epigenetic variations are described by Johannes et al., 2009; Rasmann et al., 2012; Scoville et al., 2011). There are still many open questions, however. For example, the probability that induced variations are adaptive is unknown, nor is it known what affects the transmission fidelity of epigenetic variants. It is also not know to what extent adaptation involves the kind of exploratory mechanisms envisaged by Braun, Soen and their colleagues, although some observations on the evolutionary dynamics of interspecific hybrids suggest that such processes do take place (see next section).

When modeling the consequences of epigenetic inheritance for population change, factors additional to those included in classical population genetics models (selection, drift, migration and random mutations) need to be taken into account. Even in highly inbred lines, where we may assume that genetic variation is minimal, the following properties of epigenetic variants have to be considered: (i) *Inducibility* – we need to know how easy it is to induce the variant, how extensive the change is, what the cost of inducing it is, and whether its retention depends on the continued presence of the inducer; (ii) *Paramutability* – we need to know whether the epigenetic state of one locus can be transferred to homologous loci (Erhard and Hollick, 2011), thus biasing the transmission of the variant (the epigenetic equivalent of gene conversion); (iii) *Transmissibility* – we need information about the fidelity of transmission of different variants, and how long epigenetic memory lasts.

Models incorporating epigenetics-specific factors have been constructed since the 1990s (Jablonka et al., 1992; Lachmann and Jablonka, 1996; Masel and Bergman, 2003; Pál, 1998; Pál and Miklós, 1999), but recently modeling of epigenetic evolution has begun to accelerate. The most general model is that constructed by Day and Bonduriansky (2011), who extended the Price equation (the broadest formalization describing evolutionary change through selection), and showed that substantial changes in

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evolutionary population dynamics occur once epigenetic variations are incorporated (see also Helanterä and Uller, 2010). Other theoreticians have adapted classical population genetic equations to include epigenetic variations, and investigated the resulting population dynamics, finding, in all cases, significant effects (Geoghegan and Spencer, 2011; Johannes and Colomé-Tatché, 2011). Those models that incorporated selection showed that adaptation can be very rapid because, in contrast to classical gene mutations, each of which is assumed to be a unique event, the same epigenetic variant can be induced in many individuals at the same time (Jablonka and Lamb, 1995; West-Eberhard, 2003).

What we know about the ways in which epigenetic variations can be induced and transmitted between generations suggests that persistent exposure to a new environment can have cumulative effects (Cropley et al., 2012; Li et al., 2011; Remy, 2010). Consequently, the accumulation and decay dynamics of epigenetic states over several generations may have important effects on the response of individuals and populations to changed conditions. Consider, for example, a new, challenging environment that causes a gene to become epigenetically marked in a way that affects the phenotype; if the environment does not persist, it is likely that the mark will be erased, and the phenotype will be lost in the next generation (Fig. 1a). Occasionally, the mark and the associated phenotype may be inherited (Fig. 1b). Another possibility is that the mark is only partially erased. Although the phenotype is not expressed in the next generation, because some trace of the mark remains, when exposed to a challenge of the same type it either takes less of a challenge to elicit the phenotypic response, or the response is produced more rapidly. This kind of "learning through sensitization" is illustrated in Fig. 1c. Ginsburg and Jablonka (2009) have described and discussed the implications of this and other cases of "epigenetic learning" through the accumulation, consolidation or decay of epigenetic marks. They argue that often epigenetic learning may be selectively superior to perfect inheritance, because if conditions change, a perfectly "memorized" response will no longer be adequate, and if conditions remain the same, a partial memory is better than having to develop the phenotype from scratch, which would be necessary if "forgetting" or "resetting" was complete. Since the epigenetic mechanisms that underlie such cellular learning are ubiquitous, and the fitness benefits are obvious, it is plausible that, through selection, small modulations in the sensitivity of the epigenetic systems to the conditions in which they operate could lead to complex, plastic, heritable, adaptive dispositions to respond.

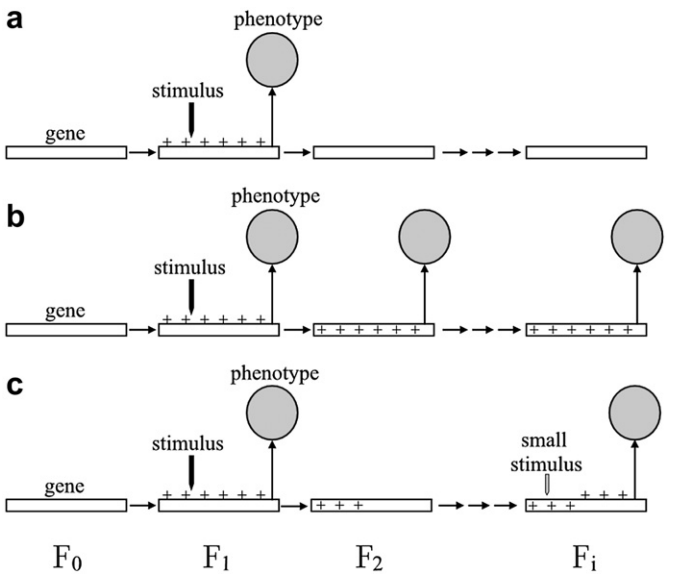

Fig. 1. Epigenetic inheritance and epigenetic sensitization. (a) An environmental stimulus alters a chromatin mark (represented by six plus signs), and this leads to a phenotypic change; the chromatin mark is not inherited (total erasure), so future generations do not show the phenotype. (b) The induced mark is inherited (indicated by the encapsulation of the plus signs), so the next generations have the same phenotype, even in the absence of the stimulus. (c) The induced mark is partially erased (three plus signs remain), so the phenotypic change is not seen in the next generation; in a later generation, because traces of the mark remain, a smaller stimulus is sufficient to produce the phenotype.

The models just described are speculative, but point to areas in which empirical and theoretical studies may be worthwhile. The same is true of models of the evolution of epigenetic strategies, and of the genetics of epigenetics (Lachmann and Jablonka, 1996; Masel and Bergman, 2003). Of more immediate practical importance is the extension of the classical quantitative genetic models to include epigenetic inheritance, since these enable rough estimates to be made of the contribution of heritable epigenetic variation to total phenotypic variance (Tal et al., 2010). The inter-relations between genetic and epigenetic systems of inheritance are going to be some of the most important problems that applied biologists, as well as evolutionary biologists, have to tackle.

6. Systemic changes

One of the problems that evolutionary biologists have been debating for years is the extent to which the population genetics models that were the basis of the mid-20th century Modern Synthesis could account not only for adaptive evolution, but also for the sometime rapid origin of major novelties and new species (see Gould, 2002; Pigliucci and Müller, 2010; Shapiro, 2011). To some extent, with our better understanding of the modularity of development, epigenetic regulation, plasticity and genetic accommodation, the gap between these two aspects of evolution (sometimes referred to as micro- and macro-evolution) has closed, but not completely. Increasingly it looks as if the key missing element has been what Shapiro (2011; this volume) has called natural engineering processes. These are necessary for survival and reproduction in normal circumstances (e.g., they are essential for DNA repair, genetic recombination, constraining transposon activity, mammalian immunity, etc.), but they are also the basis of the complex genomic and epigenomic reorganization that occurs as a consequence of severe stress. Following extraordinary ecological or genomic challenges, such as exposure to very high temperatures, extreme pathogen attacks, or hybridization, the mechanisms that control natural genetic engineering systems are activated, leading to wide-ranging changes in epigenomic and genomic states. Jablonka and Lamb (1995, 2008, Table 1), Richards (2011) and Shapiro (2011, Table 2.10) provide many examples of the types of mechanisms that are induced by unusual stresses.

Stresses that occur within the genome may well prove to be one of the most significant factors in the generation of novel phenotypes and new species. Even in the heyday of the Modern Synthesis, when speciation was seen primarily as the outcome of adaptation through the slow and gradual selective accumulation of small genetic variants in geographically isolated populations, the most enthusiastic proponents of this view conceded that speciation might be "facilitated" by chromosomal reorganization, and that instantaneous speciation could occur through polyploidy (Mayr, 1963, p. 439; these issues are discussed at book-length by Stebbins, 1971; and by White, 1973).

Today it looks as if rather than merely "facilitating" the changes that are associated with the production of new species and new adaptations, chromosomal reorganization plays a key role. This is most evident with interspecific or intraspecific hybridization, which is often associated with polyploidization (allopolyploidization).

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Hybridization and polyploidization have been particularly important in the evolution of angiosperm plants, but they are not uncommon in animal groups such as insects, fish and amphibians (Leitch and Leitch, 2008; Mable, 2004). The presence of two, often very different, genomes in the same nucleus creates a host of problems, ranging from the disruption of the usual patterns of gene expression control, to the failure of chromosome to pair properly during meiosis. Remarkably, the hybrids sometimes cope with these difficulties. They respond to the challenge with widespread, extremely rapid, reproducible, targeted, genetic and epigenetic modifications.

Investigations comparing natural and experimentally constructed plant hybrids and polyploids with their parent species have shown that there are wide-ranging alterations in DNA methylation patterns, in siRNAs and miRNAs, and in gene expression profiles (e.g., Ha et al., 2009; Kenan-Eichler et al., 2011; Shivaprasad et al., 2012). For example, with bread wheat allopolyploids, in which DNA elimination is a major response to hybridization, Levy and Feldman (2004) showed that particular chromosomal regions and sequences are targeted, and that immediately following allopolyploidization there is a burst of methylation modification, associated with changes in the activation and silencing of genes. In *Arabidopsis*, too, the epigenetic changes that follow hybridization seem to be targeted: comparison of natural and newly formed allopolyploid lines with the parental species showed that some genes in the hybrids were more susceptible to epigenetic change than others were, but there were differences between genetically similar lines and between generations (Wang et al., 2004). Small RNAs were found to be associated with both the maintenance of stability (siRNAs) and the generation of diversity (miRNAs) (Ha et al., 2009). The observation that several generations are required to establish stable expression patterns is reminiscent of the kind of searching process that has been suggested to explain adaptation to novel environments in yeast (see Section 3). Over a period of several generations, the genomes of allopolyploid individuals seem to be "searching" for a stable state.

Hybridization and polyploidy are not the only types of genomic mixing likely to produce system-wide variation that could lead to novel phenotypes and speciation. In addition to sexual hybridization, it is now recognized that more limited genome intermingling comes about through horizontal gene transfer (reviewed in Ryan, 2006; Shapiro, 2011). In addition, genomes constantly have to cope with the accidents of maintenance and repair that produce duplications, deletions and rearrangements of chromosomes, some of which survive.

Environmental stresses can also affect genomic and epigenomic stability. For example, the progeny of tobacco plants infected by TMV virus show marked changes in methylation and a higher frequency of small rearrangements in several regions with homology to a resistance gene (Boyko et al., 2007). Another environmental factor with genomic effects is the endosymbiont *Wolbachia*, which is maternally inherited in strains of many arthropod species, and can feminize genetic males by altering their genomic imprints (Negri et al., 2009). However, perhaps the most intriguing hints of the type of large-scale reorganization of the epigenome that may occur when organisms find themselves in new and challenging environments has come from studies of domestication. Over a 50 year period, selection for domestication in silver foxes led not only to rapid evolution of docility, but also to changes in pigmentation, modifications in skeletal morphology and hormonal profiles, altered vocalization, more frequent presence of B chromosomes, and some non-Mendelian patterns of inheritances (reviewed in Markel and Trut, 2011). Although for these animals the molecular epigenetic basis of the changes has not yet been investigated, studies of chickens show that their domestication involved massive, genome-wide, heritable changes in methylation (Nätt et al., 2012). It would be especially satisfying to have a fuller understanding of the genetics and epigenetics of domestication, because of Darwin's use of it as a model for his theory of evolution. Darwin certainly recognized the role the environment played in generating variation in domestic species, writing "As almost every part of the organization becomes highly variable under domestication, and as variations are easily selected both consciously and unconsciously, it is very difficult to distinguish between the effects of the selection of indefinite variations and the direct action of the conditions of life" (Darwin, 1875, p. 414). May be molecular studies of epigenetic systems will help solve the problem that Darwin recognized, and give us a better understanding of plasticity and the role of the environment in producing evolutionary change.

7. Conclusions and future directions

The existing knowledge of epigenetic systems leaves little doubt that non-genetic information can be transmitted through the germline to the next generation, and that internal and external conditions influence what is transmitted and for how long. The stress-induced mechanisms that lead to wide-ranging genetic and epigenetic modifications are of obvious importance in both adaptive evolution and in speciation: environmentally induced changes often begin as matched to conditions in which they may prove advantageous, unlike mutations, which begin as random with respect to environment. These epigenetic mechanisms increase the range of heritable variations, and they can result in substantial phenotypic changes because they involve multiple genomic and cellular elements. These are important discoveries, which form robust links between development and evolution and deepen our understanding of both. However, this body of knowledge also raises many questions: What are the differences (if any) between the responses to genomic and to environmental stresses? Can we find methods to identify the epigenetic re-patterning processes that took place in recent speciation events? Do the epigenomic accommodation mechanisms demonstrated in model organisms in the laboratory operate in natural conditions? Can we construct models for the emergence of novel phenotypes that are informed by epigenetic mechanisms? These are just a few of the many tantalizing questions whose answers await new experiments and new conceptualizations.

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