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Introduction

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How does epigenetics influence the course of evolution?

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Epigenetics is the study of changes in gene activity that can be transmitted through cell divisions but cannot be explained by changes in the DNA sequence. Epigenetic mechanisms are central to gene regulation, phenotypic plasticity, development and the preservation of genome integrity. Epigenetic mechanisms are often held to make a minor contribution to evolutionary change because epigenetic states are typically erased and reset at every generation, and are therefore, not heritable. Nonetheless, there is growing appreciation that epigenetic variation makes direct and indirect contributions to evolutionary processes. First, some epigenetic states are transmitted intergenerationally and affect the phenotype of offspring. Moreover, *bona fide* heritable 'epialleles' exist and are quite common in plants. Such epialleles could, therefore, be subject to natural selection in the same way as conventional DNA sequence-based alleles. Second, epigenetic variation enhances phenotypic plasticity and phenotypic variance and thus can modulate the effect of natural selection on sequence-based genetic variation. Third, given that phenotypic plasticity is central to the adaptability of organisms, epigenetic mechanisms that generate plasticity and acclimation are important to consider in evolutionary theory. Fourth, some genes are under selection to be 'imprinted' identifying the sex of the parent from which they were derived, leading to parent-of-origin-dependent gene expression and effects. These effects can generate hybrid disfunction and contribute to speciation. Finally, epigenetic processes, particularly DNA methylation, contribute directly to DNA sequence evolution, because they act as mutagens on the one hand and modulate genome stability on the other by keeping transposable elements in check.

This article is part of the theme issue 'How does epigenetics influence the course of evolution?'

1. Introduction

In this theme issue of the *Transactions*, we have drawn together a selection of papers that address a common question: how is the newish field of epigenetics impacting the now mature field of evolutionary biology? Much of our contemporary understanding of how evolution works is captured in a body of theory that developed in the 1940s known as the 'Modern Synthesis' (MS) [1,2]. The MS was pivotal because it reconciled Mendel's demonstration that inheritance is particulate with Darwin's theory of natural selection on continuous variation, and incorporated Fisher's [3] contributions to population genetics. The MS view of evolution can be summarized by the statement that evolution proceeds by changes in allele frequencies within and between populations as a consequence of natural selection, population subdivision and genetic drift [4]. The MS explicitly rejects the possibility of inheritance of acquired characteristics [5]. This assumption was later reinforced by Crick's 'Central Dogma' of molecular biology, the idea that information held in DNA is transcribed into messenger RNAs that are then translated into an amino acid sequence in a protein, with

no possibility of feedback of information from protein to the DNA [6]. Furthermore, while quantitative geneticists and animal breeders have always recognized the importance of parental (typically maternal) effects in determining the phenotype of offspring [7,8], parental effects were regarded as having little or no consequence for evolution because they lasted one or two generations at most, and had a negligible bearing on allele frequencies.

Despite the contemporary ascendence of the MS view of evolution, especially among field-based evolutionary biologists, there has been, ever since its inception, an alternative narrative [5]. In the same year that Huxley's [1] book promoting the MS was published, Conrad Waddington sent a letter to *Nature* that has the following passage:

> The battle, which raged so long, between the theories of evolution supported by geneticists on one hand and naturalists on the other, has in recent years gone strongly in favour of the former … The classical 'naturalist' theory—the inheritance of acquired characteristics—has been very generally relegated to the background … [because] it has required a type of heredity … for the existence of which there was no adequate evidence. Naturalists cannot fail to be continually and deeply impressed by the adaptation of the organism to its surroundings … These adaptive characters are inherited and some explanation must be provided. If we are deprived of the hypothesis of the inheritance of … [acquired characteristics], we seem thrown back on an exclusive reliance on the natural selection of merely chance mutations. It is doubtful, however, whether even the most statistically minded geneticists are entirely satisfied that nothing more is involved than sorting out of random mutations by the natural selective filter [9, p. 563].

Waddington goes on to postulate an evolutionary mechanism that acts in concert with natural selection that he termed 'genetic assimilation'. The essence of the genetic assimilation argument is based on another of Waddington's ideas: 'canalization'. Waddington argued that while the genotypes of a population tend to be highly variable, the phenotypes are not. Therefore, despite a variable environment and the interactions of dozens or hundreds of highly variable genes contributing to a phenotype, their sum tends to lead to a remarkably similar phenotypic outcome [9,10]. Waddington proposed that natural selection acts on the regulation of gene networks so that the networks canalize 'normal' development to what he called 'wild-type', the common phenotype in the wild. Our modern understanding of the way gene networks work tends to endorse Waddington's view, in that there is enormous redundancy, buffering and feedback within them [11,12]. Both empirical and theoretical studies show that this redundancy tends to produce the same phenotypic outcome, even if one or two genes within the network are significantly over or under expressed as a result of mutation, or if an organism is subjected to an extreme environmental challenge [11,13,14].

But what does canalization have to do with genetic assimilation? Waddington's argument, which in our view is persuasive, was that the expression of any extreme phenotype that has been observed in nature must be genotypically possible. That is, the *possibility* of extreme phenotypes must lurk within the normal genome. These extreme phenotypes are only expressed when an environmental or genetic challenge is sufficient to reveal them. Therefore, the selection on the *regulation* of a gene network alone should be sufficient to produce the same extreme phenotype *without change in the average genotype* of the genes that directly contribute to a trait [5,15–17].

This brings us to epigenetics. The term 'epigenetics' was also coined by Waddington [18] to mean the processes whereby the 'genes of the genotype bring about phenotypic effects'. But this definition has evolved and multiplied [19]. Today it is typically used to mean the transfer of information beyond DNA sequence between cell divisions, that influences gene regulation [20–24]. Epigenetic processes are central to embryogenesis, helping to guide the development of a fertilized egg into a mature organism with specialist cells, tissues and organs, all of which express different sets of genes in different cell lineages. Epigenetic states are of three main kinds, which we briefly describe below. More detailed reviews of the molecular mechanisms underlying the maintenance and transmission of epigenetic states within and across generations are provided in this issue [25,26] and particularly [27].

(a) Chromatin modification

In eukaryotic cells, DNA is packed into chromatin, the basic unit of which is the nucleosome. A nucleosome is made of 147 nucleotides (nt) of DNA wrapped around a multiprotein core made up of two copies of each of the four histones H2A H2B, H3 and H4. Nucleosomes limit access to the DNA, and must be loosened up to allow transcription. This loosening is favoured or hampered depending, notably, on post-translation modifications to histones such as acetylation, methylation or phosphorylation of specific amino acid residues. Chromatin states can be retained across cell divisions and in part, this unifies the genes that are switched on and off in different cell lineages and, eventually, tissues and organs [20,28].

(b) DNA methylation

DNA methylation is the addition of a methyl group to specific nucleotides, mainly cytosines (Cs), in eukaryotes. In mammals and insects, the vast majority of DNA methylation is at symmetric CG sites (where G is guanosine). Plants exhibit in addition methylation at CHG and CHH sites (where H is any base but G, see [26]). Note that the opposite strand of DNA to a C-G is a complementary G-C. In large measure, this complementarity explains why DNA methylation states are reliably propagated across cell divisions.

In insects, DNA methylation is mostly within gene bodies, whereas in mammals and plants it is most prevalent in transposable elements (TEs) and other repeat sequences [29]. In mammals, methylation of regulatory sequences within promoters and enhancers is often associated with gene silencing and may prevent the binding of transcription factors [28]. The function of methylation is less clear in insects, but it is highly heritable and widespread in bees wasps and ants, suggesting that it has function [29].

(c) Small interfering RNA molecules

Cells contain a plethora of small non-coding RNA molecules (18–50 nt long), some produced transiently with as-yet unknown roles, while others are tightly regulated and have important and well-characterized roles in gene regulation. Here, we concern ourselves with the most well understood that are known or thought to contribute to gene regulation: (i) small interfering RNAs (siRNAs) are usually produced in response to the presence of a double-stranded RNA (dsRNA)

in the cell (e.g. from an infecting virus), and cause the dsRNA's degradation, thereby suppressing translation, or guide DNA methylation and other chromatin modifications over TE sequences [30]; (ii) microRNAs (miRNAs) are 21–23 nt long RNAs, produced from longer, genome-encoded precursors. They bind to complementary target messenger RNAs and either degrade them or inhibit translation at the ribosome [31,32]. miRNAs are often thought to have a fine-tuning role on gene expression; (iii) PIWI-interacting RNAs (piRNAs) interact with PIWI proteins to suppress transcription of TEs during meiosis in animal gonads [33–35]; and (iv) tRNA-derived fragments (tRFs) are short fragments of a transfer RNA molecule. The precise biogenesis, regulation and function of tRFs is still not well understood, but of relevance to our theme issue is that their prevalence changes in mammalian semen in response to changing environmental conditions [36–38].

2. Multigenerational epigenetic inheritance

One of the ways an organism responds to its environment is by tweaking its gene expression to make the best use of the prevailing conditions. This process often contributes to 'phenotypic plasticity', the ability of an organism to develop in different ways depending on the environment [39,40]. The transfer of epigenetic information relevant to gene regulation between mitotic cell divisions leaves open the possibility that such information is also transferred from parents to offspring via gametes. If so, parents can potentially contribute their epigenetic states to their offspring [26], and thereby help guide the offspring's development towards a phenotype that is pre-adapted to current conditions [24,41,42]. In some circumstances, parents may even manipulate gene expression in offspring in ways that benefit the parent [43].

Despite the plausibility of multigenerational epigenetic inheritance [24] there are several major impediments, especially in mammals [22]. In animals, the production of gametes is confined to specialized tissues: the testis and the ovaries. This sets up a significant obstacle to the inheritance of epigenetic states known as the 'Weismann Barrier' [44,45]. In mammals, egg production is completed within the female fetus very early in its gestation. This precludes any directed alterations to the DNA sequence. Nonetheless, it is likely that mothers can influence the epigenetic state of a fetus via factors transferred across the placenta. Thus, because of the auto-propagation of epigenetic states, it is not unreasonable to suggest that mammalian mothers could influence the development of their offspring and even the developing eggs within female fetuses. If so, and there is some evidence, this could potentially influence the epigenetic state of grand-offspring [23,46].

Mammalian fathers are different. In males, spermatogenesis is an ongoing process throughout life. Therefore, fathers have the possibility of affecting gene expression in offspring in ways that benefit offspring. The fact that mammalian semen is packed with small RNA molecules provides a highly plausible mechanism by which they might achieve this [24,47,48].

The importance of small RNA molecules in epigenetic inheritance is perhaps best characterized in *Caenorhabditis elegans*. Examples of transgenerational inheritance include responses to pathogens such as *Pseudomonas* [49] and possibly viruses [50,51] that are propagated over generations. These mechanisms and the overwhelming evidence for intergenerational epigenetic inheritance in *C. elegans* are reviewed by Frolows & Ashe [25]. They emphasize that many small RNA molecules aggregate in perinuclear granules. It is becoming clear that perinuclear granules are intimately involved in the production of heritable small RNAs. A single generation of dysfunctional perinuclear granules leads to the creation of aberrant siRNA molecules that incorrectly silence genes for multiple generations, even after functional perinuclear granules are restored [25].

In plants, there is more scope for transgenerational epigenetic inheritance and because the Weissmann's Barrier is more of a picket fence, there are also more possibilities for parents to provide information that can benefit their propagules than in animals. Indeed, flowers are formed on the apical meristem from a lineage of cells that has experienced everything that the plant has ever seen since it was a seed [52]. Furthermore, reprogramming of DNA methylation states between generations appears to be much more limited in plants than it is in mammals. Thus, like DNA mutations, alteration in DNA methylation patterns in the apical meristems of a parent plant can potentially be transferred to offspring [53].

Phenomenologically, radish plants that experience heavy insect attack appear to ready their propagules to ramp up the production of spines and toxins [54,55]. Although it is important to note that effect sizes were small, this may be an example of adaptive transgenerational epigenetic inheritance [54,55]. Epigenetic inheritance may be particularly important in spreading adapted traits in species and strains that propagate clonally [56]. Without any genetic variation, the only way a clonally propagated plant can achieve heritable adaptation to new environments is via new mutations or transgenerational epigenetic inheritance.

3. A discussion about terms

As a field, epigenetics and its role in evolution is young, and for this reason, there is a lack of consensus on terms, especially across the sub-disciplines of biology. These differences became abundantly apparent as we edited the papers contributed to this issue. While we have not attempted to harmonize the terms used by the authors of the different papers, below we discuss how some terms are used fluidly, and how this can sometimes lead to ambiguity and confusion [57].

(a) Epigenetic inheritance, transgenerational epigenetic inheritance and cultural inheritance

There is a general consensus that 'epigenetic inheritance' refers to the transfer of epigenetic information across mitotic cell divisions [20–23] and transgenerational epigenetic inheritance is the transfer of epigenetic information across multiple generations [47,58]. We think these are useful definitions. However, some authors take a much broader view of 'epigenetic inheritance' [59–61], and include notions like intergenerational cultural transmission. For example, the language spoken at home is typically transmitted from parent to offspring and in this sense is a heritable phenotype despite an absence of any genetic basis.

While we acknowledge the importance of cultural inheritance, particularly in the evolution of human societies, the papers in this issue are mostly confined to questions where the basis of inheritance rests on information passed through

gametes in addition to DNA sequence. Nonetheless, we acknowledge that this distinction is leaky. For example in rats, mothers that lick and groom their pups transmit this behavioural trait to their offspring when they nurture their own babies. While this may or may not be learned behaviour, there is an interesting element of epigenetic inheritance involved. Pups that are groomed and nurtured by their mothers show increased acetylation and decreased methylation in the promotor region of a glucocortoid receptor gene that promotes responsiveness to serotonin and decreased stress levels [62]. For this reason, offspring that have benefited from motherly grooming are likely to grow up to be more attentive mothers in a virtuous cycle [23].

Another instructive case is adult lactose tolerance in milk-drinking human societies [63]. Changes in the frequency of mutants of the *MCM6* gene that promote the synthesis of lactase in adult humans are an example of *bona fide* evolutionary change brought about by the culturally transmitted practice of dairying. Here, a change in cultural practices (in this case adult milk drinking) has brought about genetic change at the population level mediated by natural selection on genes that confer lactose tolerance. This is an example of 'niche construction' elaborated in Loison's article in this issue [5].

(b) Parent-specific gene expression and genomic imprinting

The kinship theory of genomic imprinting proposes that a gene which is involved in regulating the amount of resources received by an embryo or juvenile from its mother can be under divergent selection in its patrigenic (derived from the father) or matrigenic (derived from the mother) form [64–66]. This is because matrigenes are in every one of the mother's offspring at equal frequency but an offspring's patrigenes are only present in siblings that were sired by the same father. Under these circumstances, a gene can evolve to be expressed at a level that draws extra maternal resources in its patrigene form, and to compensate, to be downregulated or completely switched off in its matrigene form [64,65], see Oldroyd & Yagound [43].

The mechanism by which a gene is distinguished in its patrigene or matrigene form is called 'genomic imprinting'. In mammals and plants, 'imprints' typically involve sex-specific DNA methylation of the promoter regions of the relevant genes [67,68]. In insects, parent-specific allele expression levels are repeatedly observed [69–72]. However, the underlying molecular mechanisms of the imprinting that cause parent-specific gene expression (PSGE) in insects have not been conclusively established [43].

The term 'genomic imprinting' means many different things to different people [57]. The original paper discussing the theoretical possibility of imprinting [65] does not use the term at all. Instead, this paper refers only to PSGE. Some authors are using 'imprinting' synonymously with PSGE, or parent-of-origin (PoO) effects on phenotype. To these authors if a gene shows parentally biased expression, or if reciprocal crosses show a direction-of-crossing effect, there must be imprinting in play. However, this is by no means necessarily true, especially when hybrids between species or subspecies are involved. Here, interactions between maternally derived mitochondria and paternally derived nuclear genomes can have significant consequences for gene expression and phenotype [73,74]. Straight-up maternal effects arising, for example, from the physical size of the mother are also likely. Consider, for example, the likely PoO effects of reciprocal crosses between great danes and chihuahuas.

(c) Parent-of-origin effects

A PoO effect occurs when the offspring of reciprocal crosses are phenotypically different or if there is PSGE. As noted above it is important to interpret PoE carefully, because it can also arise from cyto-nuclear interactions. Nevertheless, strong PoO effects across multiple genes and phenotypes related to embryogenesis or reproductive capacity is strong evidence for genomic imprinting, even when an association with methylation or other epigenetic modifications cannot be demonstrated.

(d) Parental manipulation

As argued by Oldroyd & Yagound [43] there is a theoretical possibility that parents directly manipulate gene expression in embryos. Like genomic imprinting, this could occur as a consequence of sexual selection on males to compete with other males to extract additional resources for their offspring from mothers. The fact that mammalian and insect semen carries large amounts of small RNAs gives some weight to this hypothesis.

4. Phenotypic plasticity and its role in genetic assimilation and evolutionary change

Recall that canalization is Waddington's idea that distinct genotypes can result in the same phenotype and that phenotype is robust to environmental perturbations (see above) [17]. Phenotypic plasticity is the flip side of canalization: the ability of some genotypes to significantly modify their phenotype to compensate for environmental heterogeneity [41,75]. For example, animals and plants may tune their physiology to accommodate unusually high or low temperatures [42]. The significance of phenotypic plasticity to evolutionary processes is much debated, and a great deal of this debate hinges on divergent interpretations of its meaning. de Jong [76] takes the view that phenotypic plasticity is an adaptive trait, subject to the natural section, that allows organisms of similar genotypes to develop different and appropriate phenotypes without change to genotype. The allegedly alternative view is that phenotypic plasticity is a strong driver of rapid adaptation and evolution [15,39] that proceeds as follows. First, there must be a significant environmental change that causes a significant plastic response in the average phenotype of a population. The changed phenotype is called a 'phenotypic accommodation' and is independent of any genetic change [15,77]. If the phenotypic accommodation becomes widespread and is maintained over generations because of a permanent change in the environment, then 'genetic accommodation' can ensue, which may involve changed allele frequencies and/or adjustments to gene regulatory networks [78,79].

In an important contribution on how parental effects may evolve, Kuijper & Johnstone [80] develop a mathematical model that predicts the likelihood that paternal effects will emerge under alternative scenarios of selection favouring high parent fecundity (expected in spatially structured populations) versus high parent viability (expected in stable

environments). In populations that experience fecundity selection, high-fidelity inheritance is favoured and parental effects are unlikely to evolve. By contrast, in populations subject to viability selection, there can be benefits to offspring mimicking parents, and parental effects are more likely to evolve. The authors develop some testable predictions suggested by their model [80].

In another example of phenotypic plasticity, Chen *et al.* [81] study phenotypic traits related to pathogenicity in clinical isolates of the recently evolved fungal pathogen *Saccharomyces cerevisiae*. They show that prions—misfolded protein aggregates that can often catalyse the conversion of correctly folded proteins to other forms—are involved in the gain of pathogenic traits such as drug resistance. Changes to protein function and subsequently organism phenotype for multiple generations owing to non-DNA encoded alterations in protein structure is an important form of plasticity and epigenetic adaptation.

5. Epigenetic adaptation in inbred and clonal species

Experimental studies on plants provide some of the best-known examples of epigenetic variants that are inherited across multiple generations [26]. However, it is still unclear to what extent transgenerational epigenetic inheritance occurs in plants in nature. Mounger *et al*. [56] provide observations and theoretical evidence that transgenerational epigenetic inheritance could underlie much of the rapid adaptation that characterizes invasive plant populations. Mounger *et al*. acknowledge, however, that detailed genome-wide surveys are still lacking, especially for clonal plants, where epigenetic mechanisms could play an even more important function. They also stress the need to measure somatic mutation rates in invasive clonal lineages, as these could be sufficient to generate or maintain abundant genetic variation, notably through TE mobilization, which tends to generate large-effect mutations [26]. Hybridization and polyploidization affect DNA methylation patterns and are thought to be important for the invasive success of some plant species, but here again, the authors stress the need to monitor TE mobilization before concluding that DNA variation plays any role in this success, either directly or indirectly through increased transposition.

An unfortunately iconic non-plant invasive species is the cane toad *Rhinella marina*. Cane toads were introduced to Australia in 1935 in an ill-conceived attempt at biological control of insect pests in Queensland sugar cane crops [82]. From an initial population of about 100 individuals, cane toads have successfully colonized the wet tropics of northern Queensland through to extremely arid regions in Western Australia, with disastrous ecological consequences. Using a complex experimental design involving laboratory and semi-natural field trials, Sarma *et al.* [83] set out to determine whether chemically induced DNA methylation alterations or alarm cues perceived during the larval stage influence offspring defences. Although responses and epigenetic effects were observed in G2 progeny, suggesting intergenerational transmission, few were consistent between populations. Nonetheless, the authors identified several inherited differentially methylated regions (DMRs) in genes that are important for the response to alarm clues, suggesting a causal role. Whether these DMRs can be transmitted across multiple generations and whether they are responsible for the changes in gene expression observed are important questions for the future.

6. Epigenetics, conflict and speciation

For the most part, the interests of parents, offspring and individual genes are completely aligned: building lots of high-quality offspring [84]. Conflict theory examines what happens when the interests of interacting relatives are not completely aligned, usually because of asymmetries in relatedness [84–90]. As discussed above, genomic imprinting can evolve when the selective pressures on a gene differ depending on whether it was inherited from a mother or a father. But in polyandrous species it may also be possible for direct parental manipulation of offspring gene expression to evolve, a possibility explored for social insects in [43].

The original proposal for the evolution of PSGE (and by extension genomic imprinting) is based on the potential for genomic conflict in the endosperm, the nourishing tissue that surrounds the embryo in the seeds of flowering plants [65]. The endosperm acquires nutrients from the mother plant, which are then used to nourish the embryo in the seed. Haig & Westoby [65] argued that PSGE evolved in flowering plants as a consequence of conflict between the optimal expression levels of genes involved in furnishing the endosperm with resources. The double dosage of maternal genes relative to paternal genes in the endosperm allows maternally derived genes greater control over the amount of maternal resources that are provided to the endosperm [91]. If this hypothesis is correct then the ploidy level of the endosperm is central to seed viability. As reviewed by Köhler *et al.* [92], inappropriate gene expression levels underpin the seed arrest observed when plants of different polyploidy levels are crossed. Remarkably, the so-called 'triploid block' suggests that gene dosage in the endosperm often causes post-zygotic reproductive isolation, and thereby reinforces reproductive isolation. However, an important challenge for the future will be to identify the genes involved as well as their mode of action, as it is unclear if endosperm-based hybridization barriers have a common genetic basis.

7. Epigenetics, phenotypic plasticity and adaptation

Transgenerational epigenetic inheritance can either facilitate or impede the pace of adaptation of a population. In our current period of rapid environmental change, there is an urgent need to better understand the evolutionary basis of phenotypic plasticity and adaptation, and the ability of populations to survive and thrive under the novel conditions under which they increasingly find themselves [93–95]. It is generally held that epigenetic processes may allow more rapid adaptation than DNA-based changes [96], but this may be a naive hope. Three papers in this issue consider the adaptive value of epigenetic inheritance and parental effects.

First, Baduel & Colot [26] analyse the types, sources and consequences of TE-associated epivariation in plants, in which most DNA methylation is associated with TEs. In *Arabidopsis*, around one-third of TE-sequences maintain differences in DNA methylation states over at least eight

and presumably many more generations. Intriguingly, many of these differences overlap with epialleles found in nature. Despite this overlap, the frequency of epialleles in nature appears similar to levels of sequence-based genetic variation, suggesting that, in *Arabidopsis* at least, epiallelic variation is unlikely to allow for rapid adaptation. However, Baduel and Colot then point out that additional epigenetic variation at TEs can also be induced by environmental stressors, and that such changes probably do contribute significantly to evolvability by generating rapid and transient phenotypic plasticity. This review canvases work performed in species other than *Arabidopsis* and it becomes clear that plant species differ so widely in their TE content and life history, that these differences must influence the impact that TE-associated epivariation has within a particular species. The second half of Baduel and Colot's review considers the evolutionary significance of TE-associated epiallelic variation. They conclude that such variation comes in different flavours, and that each flavour has a unique potential for contributing to adaptation and evolution. They suggest that the mobilization of TEs owing to environmentally induced epigenetic changes probably provides plants with a powerful means of phenotypic exploration and adaptation.

Second, McGuigan *et al.* [93] consider the possible role that epigenetic processes may play in rapid responses to climate change. A few instances of the strong correlation between the frequency of epialleles and environmental differentiation have been reported, even where genetic differentiation is weak. However, the authors strongly caution that there are very few convincing cases where measures of epigenetic variation have been linked to fitness. This may be because in variable environments, epigenetic settings inherited from parents may not be appropriate for the conditions being experienced by offspring, and are just as likely to detract from offspring fitness as they are to enhance it [80,93].

Third, Crean & Immler [97] examine the impact that environmental changes can have on gametes, particularly but not exclusively, the male gametes of external fertilizers. These changes, which can be genetic or epigenetic, can influence future generations both directly and indirectly and be adaptive (e.g. better resilience to higher salinity) or maladaptive (e.g. stress transmission). Crean and Immler also consider the importance of the gametic environment in the context of human assisted reproductive technology (ART), and in agriculture and fisheries. Owing to perturbations in the gametic environment, ART techniques may cause unanticipated and under-appreciated changes to population traits that are only now starting to come to light.

8. Direct effects of epigenetics on genome evolution

Thus far we have focused on the effects of epigenetic inheritance and transgenerational epigenetic inheritance on phenotypic plasticity and adaptation and how these may help drive evolution. However, it is also important to note that DNA methylation and other chromatin modifications directly affect the rate of mutation in DNA. Hence epigenetic mechanisms directly affect genome evolution.

It is now 40 years since it was shown in bacteria that 5-methylcytosines (5 mC) are mutation hotspots. This situation is caused by the less efficient repair of thymine compared to uracil, respectively, produced by the spontaneous deamination of methylated cytosines and unmethylated cytosines [98,99]. In eukaryotes, CpG dinucleotides are the main targets of C methylation and the higher mutability of 5 mC results in a general depletion of CpG dinucleotides relative to the local density of Cs and Gs in the genomes of any organism subject to DNA methylation in the germ line, as reviewed by Yi & Goodisman [100]. However, as alluded to by the authors, beyond this direct and striking effect of DNA methylation on the mutation rate, there are also indirect effects mediated by chromatin, stemming from the fact that it modulates the exposure of DNA to insults, as well its accessibility to repair activities.

The study of epigenetic mechanisms and sex chromosome evolution and regulation have a rich shared history. In mammals, inactivation of the X chromosome via heterochromatinization is necessary to achieve appropriate gene dosage between the sex chromosomes. Less known is how epigenetics affects the evolution of sex chromosomes, which has been mainly viewed as the succession of mutational events that enable autosomes to differentiate each other. As reviewed by Muyle *et al.* [101], findings from a wide range of plant and animal species provide clear evidence that epigenetic processes play important causal roles in the evolution of sex chromosomes as well as in the regulation of sexual phenotypes. They describe how the Y chromosome accumulates sequence repeats and TEs that must be epigenetically silenced. TE suppression on the Y chromosome can impede the expression of Y-linked genes, a process that could accelerate Y chromosome degeneration. Epigenetics also serves to modulate hard-wired sex determination, and thereby enable sex reversal or lability in response to environmental cues. Such sex phenotype leakiness is probably adaptive as it can have profound effects on demography. For example, it can be advantageous for dioecious plants (i.e. plants with distinct male and female individuals) to switch to hermaphroditism during a period of rapid range expansion.

9. Epigenetics and the development of castes in social insects

One of the most striking examples of phenotypic plasticity are the morphologically and/or behaviourally distinct castes (think worker honeybees compared to queen bees) of social insects (see the cover picture of this issue for a striking example). How are these castes formed from identical genomes? Oldroyd & Yagound [29] take us through the evidence that epigenetic changes are functionally responsible for caste formation and leave us with the take-home message that the jury is still out: changes to DNA methylation, small RNAs and chromatin have been observed between individuals from different castes, but it is far from certain whether these are functional changes.

10. Concluding remarks

There are growing calls for an extended evolutionary synthesis that incorporates all forms of inheritance: DNA, epigenetic and cultural [59,102,103,60] into one overarching view of how evolution proceeds. The field of evolutionary

epigenetics has been characterized by evidence for fascinating phenomena like an apparent rapid adaptation by a population in response to a predator or temperature change, and a corresponding reduction in phenotypic plasticity [104]. Such experiments clearly support the hypothesis of phenotypic assimilation as a mechanism of rapid adaptation, but do not prove it. To do so needs a multilevel approach: identification (or better, experimental introduction) of an environmental challenge, identification of a phenotypic response that is mediated by epigenetic changes, and then evidence of selection as demonstrated by non-synonymous changes in DNA that compensate for or complement epigenetic changes. This is a tall order, especially for wild populations. However, we now have the opportunity to make these connections using epigenomic methodologies. Endler [105,106] pioneered studies of experimental evolution in wild fish populations, and was able to show rapid phenotypic adaptation: toning down of sexual signalling in populations exposed to predators. Such systems can be manipulated by experimental addition or removal of predators in different subpopulations [107] and provide the opportunity to relate environmental change, corresponding changes in epigenotype, the transmission of changed epigenetic states through gametes, corresponding changes in gene expression in offspring, and changes in genotype across longer time scales. Experiments such as these (which could include cultural perturbations) will undoubtedly expand our understanding of how evolution works.

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