OPINION

Inherited epigenetic variation — revisiting soft inheritance

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Abstract | Phenotypic variation is traditionally parsed into components that are directed by genetic and environmental variation. The line between these two components is blurred by inherited epigenetic variation, which is potentially sensitive to environmental inputs. Chromatin and DNA methylation-based mechanisms mediate a semi-independent epigenetic inheritance system at the interface between genetic control and the environment. Should the existence of inherited epigenetic variation alter our thinking about evolutionary change?

A unifying theme in biology is that the characteristics displayed by organisms are controlled — ultimately — by the nucleotide sequence of their genome. Another cornerstone of modern biology is that inherited information that is transmitted on the chromosomes changes only at random, without direction from the environment towards particular phenotypic outcomes. These elements of our current biological thinking are being tested by recent work in the field of epigenetics.

Here I expore the interplay between genetic and epigenetic variation before considering the potential implications of inherited epigenetic variation for our current conceptions of inheritance and evolutionary change.

Epigenetic marks and codes

Over the past 10 years, the study of epigenetics (BOX 1) has navigated its way through the fascinating layers of non-Mendelian inheritance and metastable genetic characters (BOX 2) to reach a foundation of biochemical mechanisms that alter inherited information without changing the primary nucleotide sequence. From our present day vantage point, several core components of the epigenetic machinery can be discerned. One fundamental layer of epigenetic genome modification involves direct covalent modification of nucleotides — for example, methylation at the fifth position of cytosine (5mC), the most common DNA modification used in eukaryotes. Curiously, although 5mC is not present in all eukaryotic species, cytosine methylation is an ancient mechanism that has been lost relatively recently in some eukaryotic lineages[1] — perhaps having been made redundant and supplanted by other epigenetic marks. When present, 5mC serves as a guide for the placement and maintenance of other epigenetic codes, such as the repertoire of post-translational modifications of the core histone proteins that package DNA into nucleosomal particles[2,3]. For example, cytosine methylation in mammalian cells alters local chromatin structure by recruiting histone deacetylases through 5mC-binding proteins. Histone modifications, in turn, alter the binding affinity of proteins that mediate transcriptional activity and might also affect higher-order interactions between nucleosomes and chromatin fibre organization. Epigenetic modifications at the DNA, nucleosomal and chromosomal level affect gene expression, and ultimately phenotypes, by providing differential access to the underlying genetic information.

The molecular specifics of epigenetic modifications might be dismissed as minutiae of little importance to researchers who are focused on more synthetic issues at the evolutionary and population level, except for the potential autonomy of epigenetic modifications from their genotypic context. This autonomy, coupled with the stability and persistence of epigenetic marks, provides an alternative inheritance system, operating at the interface of the familiar stable genetic system that is encoded in primary nucleotide sequence and the transient protein–DNA interactions that mediate gene-expression changes in response to developmental signals and environmental stimuli.

Epigenetic inheritance

The molecular pathways that initiate different epigenetic states on identical DNA sequences are now coming into focus through recent studies demonstrating that small RNA molecules, generated by the RNA interference machinery (BOX 3), can direct cytosine methylation and histone modification marks that are associated with transcriptional quiescence to particular genomic regions (reviewed in REFS 4–6). In addition, epigenetic silencing machinery can be recruited to specific genomic regions by transcription factors[7–11]. Once the epigenetic marks that are characteristic of silent chromatin are acquired, they are propagated through several mechanisms. One of the best-understood mechanisms is the clonal propagation of 5mC patterns by the action of 'maintenance' cytosine-DNA-methyltransferases, which recognize hemimethylated CpG (5mCpG/CpG) and add a methyl group to the unmethylated cytosine[12]. By using cytosine methylation on the template strand as a guide, maintenance methyltransferases restore full methylation on the appropriate residues after the passage of the DNA replication fork. Experimental evidence indicates that the fidelity of maintenance methylation is in the range of 95–99% (REFS 13,14). Although this figure is several orders of magnitude lower than the fidelity of DNA polymerases that propagate genetic information, there is evidence to indicate that the precise cytosine methylation pattern matters less than the density of 5mC (REFS 15,16). A similar strategy of using pre-existing marks to guide the addition of new marks also applies to the histone modification machinery. For example, histone H3

Box 1 | **Defining epigenetics**

Application of the term 'epigenetics' has shifted over time and it is useful to consider how its historical origins relate to current usage. The term was coined by Conrad H. Waddington to refer to the execution of the phenotype starting from genotypic potential[61], something that could be roughly equated with developmental gene-expression programmes and developmental signalling pathways. Indeed, Waddington explicitly aligned the new term to the concept of epigenesis (the unfolding of developmental programmes from an undifferentiated zygote), thereby firmly grounding epigenetics in a developmental context. Inherent in the word's original usage was the view that epigenetic mechanisms are reset (that is, erased and re-established) at one point in the lifecycle of an organism. Indeed, some researchers continue to use the term epigenetic to refer only to mechanisms that are wiped clean and reset once every developmental cycle.

The current use of the term epigenetics emphasizes heritable changes in gene expression that cannot be tied to genetic variation. The original connotations of the word are retained in that the central focus is alternative gene-expression states, but emphasis is now placed on gene-expression states that are stable and transmitted through cell divisions — (meta)stable states, not simply reversible gene-expression programmes that respond nimbly to the controls exerted by *trans*-acting factors orchestrating development. The difference accommodates the inertia of epigenetic gene-expression states, which can be perpetuated in the absence of the conditions that established them. The distinction between the original and current uses of the term becomes apparent when one considers that stable alternative gene-expression states that are superimposed on identical gene sequences can be transmitted through meiosis in some cases. This expands the original view of epigenetics because these alternative gene-expression states can escape an obligatory resetting step during the developmental life cycle.

Today's use of the term epigenetics often relies on a negative operational definition, which is invoked when an alternative gene-expression state is uncovered but no underlying genetic alteration is found. In response, a positive definition has been proposed that equates epigenetic regulation with the active perpetuation of local chromatin states[1]. This definition reflects an emphasis on our growing understanding of the molecular mechanisms that underlie epigenetic phenomena.

isoforms that are methylated on lysine 9, a hallmark of silent chromatin, recruit histone lysine 9 methyltransferases through intermediary proteins, such as heterochromatin protein 1 (HP1) (REF. 17). This mechanism ensures that the appropriate histone marks are added to newly assembled nucleosomes that are distributed with parental nucleosomes on the replicated daughter strands left in the wake of DNA replication-fork passage. Self-reinforcing signalling among the major biochemical marks that characterize transcriptionally silent chromatin[2,3,18], such as the pathway described above that connects 5mC and histone deacetylation, also contribute to the propagation and stability of epigenetic states. The stability of silent epigenetic states is bolstered by repairing the effects of lapses in the propagation of epigenetic marks through the reiterative action of *de novo* cytosine methyltransferases[12,19] and by histone modification machinery that is guided by continual input from small RNA molecules[20] and recruitment from sequence-specific binding factors.

These mechanisms, working together to buffer epigenetic states, explain how transcriptionally silent epigenetic states are propagated through mitotic divisions. Mitotic epigenetic inheritance leads to clonal sectors of gene silencing, giving rise to the familiar and striking examples of variegation that initially drew the attention of scientists to several epigenetic phenomena (BOX 2). The fidelity of the mitotic transmission of epigenetic states can be remarkably precise, with reversion frequencies in the 10^{-6} range (events per cell division) for some epigenetic states, such as the mitotic propagation of X-chromosome inactivation[21].

For epigenetic variation to affect inheritance, mitotic propagation is not sufficient — transmission through meiosis is essential. There are two general arguments against the meiotic transmission of epigenetic states. The first is the widespread evidence for erasure of epigenetic marks in a developmental context[22]. For example, most DNA methylation marks are removed during the early cleavages of mammalian development. The model of epigenetic resetting in early development fits comfortably with the original concept of epigenetics and reinforces the widely held view that epigenetic information is confined to a single organismal generation. The resetting of mono-allelic expression states that are established by parental imprinting in mammals is another example of epigenetic erasure, but in this case, the epigenetic marks are transmitted stably through meiosis and are reset at a later stage of development. The second consideration supporting the view that epigenetic information is limited to a single generation is a theoretical one: the erasure of epigenetic marks that are specific to independent cell lineages has been proposed to be essential for effective coordination between different cell types during development[23]. In other words, the epigenetic meandering of different cell lineages needs to be erased to bring these lineages back to the same ground

Box 2 | **Epigenetic phenomena**

The fundamental characteristic of epigenetic phenomena is that one genotype can show alternative phenotypes, which are based on the epigenetic state of one or more loci within the genome. Many of the classic epigenetic experimental systems were discovered because of apparent genetic instability or deviations from expected Mendelian inheritance patterns. Some of the best-studied epigenetic phenomena are listed below:

Transposon activity 'changes in phase'. Originally defined and articulated by McClintock; an alteration in transposition rate or the expression of a nearby gene correlated with a change in the epigenetic state of the transposon

Position-effect variegation. Caused by the reversible inactivation of a gene that is due to a change in genomic environment, usually because of moving a euchromatic gene close to a domain of heterochromatin

X-chromosome inactivation. A sex-chromosome dosage-compensation mechanism in mammals that leads to the transcriptional silencing of a large percentage of genes on one X-chromosome in XX females

Paramutation. An allelic interaction that leads to heritable changes in one allele's gene-expression state

Parental imprinting. Parent-of-origin specific gene expression, whereby a single allele is differentially expressed depending on the sex of the parent transmitting the allele

Transgene silencing. Can occur at the transcriptional or post-transcriptional level; post-transcriptional gene silencing was discovered in early plant transgenesis experiments and was later found to be mediated by RNA interference pathways.

Box 3 | **RNA interference and epigenetics**

RNA interference (RNAi) should be considered as an epigenetic mechanism that falls under the umbrella of steady-state metabolic states. Initiation of RNAi leads to production of small RNA molecules, which mediate the downregulation of gene expression through post-transcriptional mechanisms (that is, sequence-specific transcript degradation and/or translational repression)[62,63]. These small RNA species, which direct the action of RNases that carry out transcript turnover, can also serve as primers for the production of dsRNA precursors that are used in the production of more small RNAs (through RNA-dependent RNA polymerase action in plants and fungi). Therefore, RNAi represents a type of self-reinforcing feed-forward metabolic state that can affect gene-expression states without changing nucleotide sequence. Post-transcriptional silencing states that are mediated by RNAi are not stably inherited through meiosis, and are therefore not, by themselves, an important mechanism for inherited epigenetic variation. However, small RNAs that are generated by RNAi pathways can target DNA methylation (in plants) and chromatin-level silencing (in fungi and plants), which can be transmitted stably through meiosis in certain circumstances[4–6].

state that is represented by the genotype, thereby eliminating the developmental noise that might result from a mismatched assemblage of different epigenotypes.

Despite the experimental evidence from mammals and theoretical considerations, the erasure of epigenetic marks is not a universal feature in the life cycle of multicellular organisms. For example, DNA methylation levels are not reset in early development in the zebrafish[24], calling into question whether the mammalian example is a good model for epigenetic dynamics in other vertebrates. Even in mammals the erasure of 5mC marks is not absolute[25,26].

That epigenetic erasure is incomplete is demonstrated by the number of meiotically transmitted epigenetic alleles (epialleles) that are observed in a wide variety of eukaryotes[27] (TABLE 1). The variant epialleles that have been studied so far arose in several different genomic contexts; transgenic reporters and systems were excluded in TABLE 1. These epialleles show a range of stabilities — one of the most stable being the B′ epiallele in maize for which a germinal revertant has never been recovered, despite the examination of several hundred thousand seeds (V. Chandler, personal communication).

Autonomy of epigenetic marks

The significance of meiotic transmission of differential epigenetic states depends on the relationship between epigenetic states and their genotypic context. Three classes of epigenetic variation are illustrated in FIG. 1.

Obligatory epigenetic variation is completely dependent on genetic variation and there is a strict one-to-one correspondence between the epigenotype and either *cis*- or *trans*-acting genetic variation. In this case, epigenetic variation can be viewed as a

Table 1 | **Examples of meiotically transmitted epialleles**

Locus/ epiallele	Organism	Mechanism	Stability	Phenotype	References
a-m2-7991A1	Maize	Transposon-associated; the *Spm* element is inserted upstream of the *a* pigmentation gene; the epigenetic state of the transposon is associated with DNA methylation	Metastable	Pigmentation and transposition	67
A^{vy}	Mouse	Transposon-associated; the IAP element is inserted upstream; loss of the silent epigenetic state is associated with overexpression	Metastable	Yellow coat colour; obesity	31
$Axin^{Fu}$	Mouse	Transposon-associated; intronic IAP element; loss of the silent epigenetic state of the transposon is associated with overexpression of a partial *Axin* coding sequence	Metastable	Kinked tail	68
B′	Maize	The epigenetic state of the short tandem repeat block 100 kb upstream of the coding sequencing is associated with transcriptional inactivity; generated by paramutation	Stable	Reduced pigmentation	69
b2	*Ascobolus immersus*	Induced by gene duplication (methylation is induced premeiotically); DNA hypermethylation is associated with gene silencing	Metastable	Reduced pigmentation	70
bal	*Arabidopsis thaliana*	Loss of gene silencing of an array of pathogen resistance genes leads to overexpression	Metastable	Dwarfism; elevated disease resistance	41
fwa	*Arabidopsis thaliana*	Transposon-associated; the SINE element is upstream of the coding sequence; loss of the silent epigenetic state on SINE-associated repeats is associated with ectopic expression	Stable	Delayed flowering	28,43
Lcyc	*Linaria vulgaris* (toadflax)	DNA hypermethylation of coding sequence is associated with gene silencing	Metastable	Radially symmetrical flowers	51
MLH1	Human	DNA hypermethylation of upstream region is associated with gene silencing	Metastable	Predisposition to tumour formation	71
P-pr	Maize	Elevated cytosine methylation of coding sequence is associated with gene silencing	Stable	Reduced pigmentation	72
pai2	*Arabidopsis thaliana*	Repeat-associated; RNA-directed DNA hypermethylation of coding sequence is associated with gene silencing	Metastable	Metabolic	73,74
sup	*Arabidopsis thaliana*	DNA hypermethylation of coding sequence is associated with gene silencing	Metastable	Abnormal floral organ number	42

IAP, intracisternal A-particle; SINE, short interspersed nuclear element; *Spm*, suppressor-mutator.

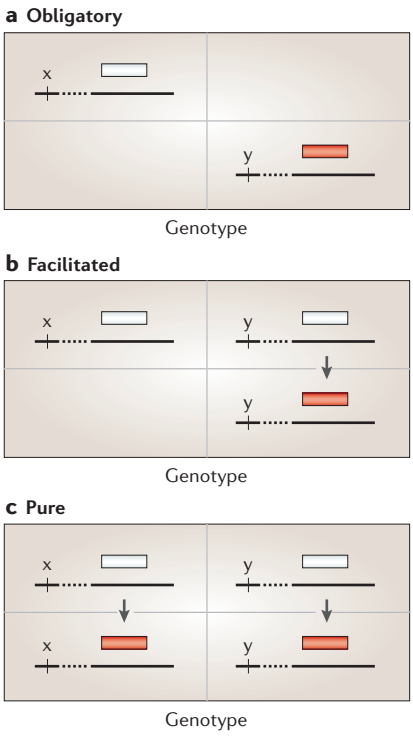

Figure 1 | **Three classes of epigenetic variation.** The range of autonomy of epigenetic variation in relationship to genotypic context is expressed in three genotype × epigenotype matrices. The horizontal axis distinguishes between two genotypes that are represented by alleles x and y. At a genomic location either in *cis* or in *trans* (dashed line), two alternative epigenetic states are depicted as either open or filled red boxes. **a** | In this scenario, the epigenotype of the locus is strictly determined by genotype; so, the epigenotype is an obligatory phenotype of the alternative genotypes. **b** | The matrix illustrates facilitated epigenetic variation (epiallele formation: open box–red box) that can occur, in a probabilistic manner, only in the context of genotype y. **c** | In this matrix, stochastic events generate alternative epialleles at some finite frequency regardless of the genotype.

phenotypic read-out downstream of the genotype. Although the epigenetic states that are dictated by the genotype might be responsible for important changes in gene activity, the epigenotype is the proximate cause of these changes, not the ultimate cause. Several examples that fit the obligatory epigenetic variation category have been described in the literature, including transposon-associated alleles where the presence of the transposon is strictly associated with epigenetic silencing of the nearby coding sequence[28,29].

A second category is facilitated epigenetic variation, in which the genotype directs or potentiates the epigenotype in a probabilistic but not strictly deterministic manner. The mouse *Agouti* viable yellow (A^{vy}) and A^{iapy} epialleles provide examples of facilitated epigenetic variation[30,31]. Genetic variation in the form of a transposon (an intracisternal A-particle (IAP) retroelement) that is inserted upstream of the *Agouti* coding sequence leads to overexpression of the *Agouti* gene, depending on the epigenetic state of the IAP element. In the absence of the transposon there is no epigenetic variation at the *Agouti* locus. In this case, the epigenetic variation at the transposon determines the phenotype; the genotype by itself cannot explain the phenotype. Other examples of facilitated epigenetic variation include the many examples of epiallele formation in DNA methylation mutant backgrounds in *Arabidopsis thaliana*[32–34]. In these cases, *trans*-acting genetic variation potentiates the formation of meiotically transmissible epialleles at unlinked loci that are stable in the absence of the original DNA methylation mutations. The important distinction is that facilitated epigenetic variation represents a breakdown in the strict link between genetic and epigenetic variation.

The third class of epigenetic variation effectively severs this link — pure epigenetic variation is generated by stochastic events that are largely independent of genetic variation. Such stochastic events include random errors in propagating silent genetic states after DNA replication and the targeting of silent chromatin to ectopic genomic locations. Striking examples that are consistent with stochastic alterations in epigenetic information have been described in somatic cell lineages in humans, including the recent report of a growing divergence in epigenotype during ageing in monozygotic twins[35], as well as the genomic redistribution of cytosine methylation and the formation of aberrant tumour-suppressor epialleles that are frequently observed in cancers[36]. In practice, it is difficult to distinguish between pure and facilitated epigenetic variation because the aetiology of a discovered epigenetic allele is often unclear and possible genetic changes that might influence the adoption of a particular epigenotype could go undetected. Despite these practical limitations, it is important to realize that pure epigenetic variation represents an extreme end point of a gradient towards the increasing independence of epigenetic variation from its genotypic context.

Epigenetics and soft inheritance

Does the existence of inherited epigenetic alleles that are to some degree independent of genetic variation necessitate a modification of our models of evolutionary change? The neo-Darwinian concept of inheritance posits that the hereditary material is 'hard' and impervious to environmental influences. If the formation of epialleles is random and not initiated or guided by the environment, the generation of epigenetic variation could be equated with random genetic mutation without otherwise altering our current view of evolutionary mechanisms. On the other hand, if the physical or behavioural environment of the cell or organism influences epiallele formation, a mechanistic foundation for soft inheritance exists in which the environment could mould a malleable hereditary material (BOXES 4,5).

A growing body of evidence indicates that epigenetic states can be influenced by the environment. For example, prolonged cold-temperature treatments in plants can lead to both chromatin[37] and DNA methylation changes at specific genomic loci[38]. Treatment with DNA damaging agents that are used in traditional chemical mutagenesis protocols can also change epigenetic states[39–41]. Indeed, some of the best-studied inherited epialleles in plants were derived originally from chemical mutagenesis experiments[42,43]. Some of the most striking examples of environmental modulation of epigenetic states are derived from the recent animal literature. One class of examples involves the alteration of DNA methylation through dietary regimes that alter single carbon metabolism in rodents. In the case of the mouse A^{vy} epiallele (TABLE 1), dietary supplements (for example, folic acid and vitamin B_{12}) that increase the abundance of the central methyl donor metabolite *S*-adenosylmethionine elevate DNA methylation of the upstream IAP element and suppress *Agouti* overexpression[44–46]. Another intriguing example of an environmentally induced, mitotically stable epiallele was recently described in rats: nurturing maternal behaviour leads to postnatal remodelling of the epigenetic state of the hippocampal glucocorticoid receptor gene (*GR*; also known as nuclear receptor subfamily 3, group C, member 1 (*NR3C1*)), creating a hypomethylated epiallele that persists into adulthood[47]. Mothers that show poor nurturing behaviour rear individuals with an alternative silent *GR* gene epiallele. The preceding examples show that epigenotypes can respond to an organism's physical, nutritional and even behavioural environment. Although these examples do not involve meiotic

Box 4 | **Types of soft inheritance**

The term soft inheritance was proposed by Mayr[64,65] to contrast with hard inheritance, the latter being characterized by an hereditary material that remains constant, except by stochastic and random mutation, in transit from one generation to the next. Mayr's definition of soft inheritance was tied to the belief that "the genetic basis of characters could be modified either by direct induction by the environment, or by use and disuse, or by an intrinsic failure of constancy, and that this modified genotype was then transmitted to the next generation."[64] This definition encompasses a range of hypotheses, including the familiar theory of neo-Lamarckian evolution by the environmental or behavioural induction of adaptive somatic traits and their subsequent transmission to the following generation (BOX 5).

Less controversial forms of soft inheritance also need to be recognized. Environmental induction of inherited variation that does not necessarily lead to adaptive changes, whether induced exclusively in the reproductive lineages or in both the somatic and reproductive lineages (when separated), also qualifies as soft inheritance, although it is not neo-Lamarckian. Where to draw the line on what constitutes hard versus soft hereditary material is open to interpretation, but the metastability of many epigenetic states fits well with the "intrinsic failure of constancy" component of Mayr's definition.

transmission of the environmentally induced epialleles, this is not always the case. A recent publication reported that treatment of gestating female rats with industrial chemicals that disrupt endocrine function can lead to male fertility defects in subsequent generations (F1 to F4), which are correlated with widespread alterations in DNA methylation[48]. This study resembles an earlier report demonstrating transgenerational effects on gene expression, DNA methylation and growth efficiency that is induced by nuclear transplantation in mice[49].

All the elements are in place to allow a type of soft inheritance that is based on DNA methylation and chromatin-level silencing: the creation of alternative epigenetic alleles that are biased by environmental inputs; the stability and mitotic propagation of epialleles; absent or incomplete epiallele erasure; and meiotic transmission. There is no reason on mechanistic grounds to reject the possibility that environmentally induced or modified epialleles can be inherited. It might be more meaningful to ask why we are not constantly confronted with the inheritance of environmentally induced phenotypic variation. In the case of mammals, the answer probably lies in a reasonably comprehensive erasure of epigenetic marks and the early germ–soma divergence that ensures that epigenetic alterations in somatic lineages are not transmitted through the germ line. The germ–soma division formed the core of Weismann's rejection in the late nineteenth century of neo-Lamarckian inheritance. These considerations indicate that epigenetic inheritance is unlikely to mediate in mammals the most extreme form of soft inheritance that involves the transmission of adaptive acquired characters (BOX 4). However, a less extreme form of soft inheritance is possible that might be based on the transmission of environmentally induced or influenced epialleles that are generated in the germ line. In this case, there is no reason to propose that these epialleles will have any adaptive significance, without resorting to the contortion of invoking a parallel induction of epigenetic changes in reproductive and somatic lineages. However, in organisms in which reproductive lineages or germ lines are derived from vegetative or somatic lineages late in development and epiallele erasure is less extensive, such as plants, both forms of soft inheritance could operate through epigenetic mechanisms.

Even if it is conceded that the molecular mechanisms are present to mediate soft inheritance through epigenetic mechanisms, the significance of such mechanisms must be questioned. The variation that has been shown to underlie the developmental and phenotypic differences between species occurs at the genetic rather than the epigenetic level. Among individuals in a population, however, epigenetic variation might have a significant role in controlling phenotypic variation[50,51]. In addition, epigenetic variation might have a role as a bridge towards genetic end points by facilitating genetic assimilation of characters (for example, accelerated genetic decay of hypermethylated epialleles)[52–54].

Future directions

There are many questions to address about the mechanistic aspects of epigenetic inheritance and the significance of inherited epialleles. Several continuing lines of enquiry will be important in resolving these questions. First, it is necessary to continue to flesh out our knowledge of the machinery that orchestrates epigenetic regulation through biochemical and genetic dissection approaches. Second, studies that parallel Johanssen's pure line experiments[55] should continue to determine whether alternative epigenetic alleles can be detected or selected in inbred backgrounds with limited genetic variation[56–59]. Third, the meiotic behaviour of epigenetic alleles that are created or manipulated by environmental regimes needs to

Box 5 | **Lamarck and his Legacy**

The more extreme model of soft inheritance, referred to as neo-Lamarckian in BOX 4, derives its name from the pre-Darwinian evolutionist Jean-Baptiste Lamarck (1744–1829) (REF. 66) who proposed a mechanism for the transformation of species through the inheritance of characters that are acquired during an organism's lifetime. He proposed that the use or disuse of an organ or appendage led to either its amplification or atrophy, respectively. The progeny of the organism were then postulated to express the modified phenotype through inheritance of the acquired character. According to Lamarck, the environment and behaviour direct organic change in an organism's form and therefore the direction of adaptations. In building his evolutionary theory, Lamarck adopted and elaborated a mechanism of variation and inheritance that was commonly accepted in the nineteenth century and influenced generations of biologists, stretching into the early twentieth century. For example, in *On The Origin of Species*, Darwin repeatedly used the phrase 'conditions of life' and referred to the effects of use and disuse to explain the source of variation on which natural selection acts.

The modern synthesis of evolutionary genetics in the 1930s–1940s dispensed with soft inheritance models, establishing the view that genetic variation is random and stochastic, not moulded by the environment. Through the remainder of the twentieth century, inheritance of acquired characters has re-emerged sporadically, most famously and tragically in the case of T. D. Lysenko, who built an early career as an agronomist on a verifiable epigenetic phenomenon ('vernalization' or cold-induced flowering in certain plant varieties). He later fused this observation with unsupported claims of inheritance of environmentally induced variation and an escalating political ruthlessness, which eventually led to the evisceration of genetics in the Soviet Union in the period between the 1930s and early 1960s. The devastation wrought by Lysenkoism in the relatively recent past has added to the stigma of neo-Lamarckian hypotheses.

be examined, starting with the better-understood epialleles. For example, do dietary supplements in mice that carry the A^{vy} allele alter the epigenetic state of the epiallele in untreated progeny, as well as the somatic tissue of the individuals that are treated *in utero*[44–46]? Fourth, several epigenomics projects that are currently underway to chart the epigenetic landscape of large eukaryotic genomes will pinpoint new loci that are sensitive to epigenetic modification and variation[60]. This information will inform systematic efforts to monitor the stability, environmental sensitivity and meiotic behaviour of many epigenetic alleles in different experimental models. Finally, it will be necessary to extend these findings to natural populations to evaluate the role of inherited epigenetic variation in a real-world context.

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SERIES ON HISTORICAL PROFILES — TIMELINE

D'Arcy Thompson and the theory of transformations

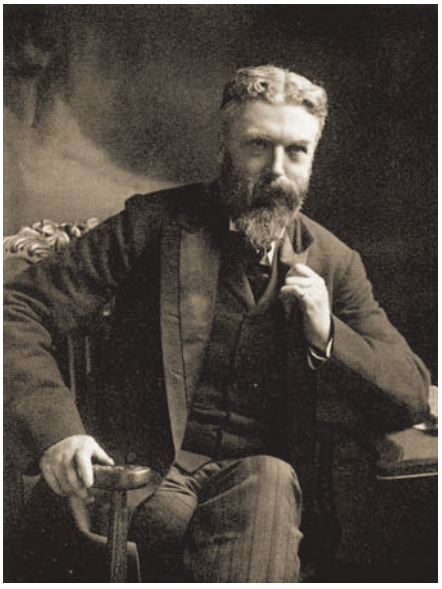
Wallace Arthur

Abstract | D'Arcy Thompson was a biologist, a mathematician and a classicist. His writing was great literature as well as great science. He is primarily known for a single book — *On Growth and Form* — and indeed for a single chapter within it, on his 'theory of transformations', which shows how the differences between the forms of related species can be represented geometrically. This theory cries out for causal explanation, which is something the great man eschewed. Perhaps the time is close when comparative developmental genetics will be able to provide such an explanation.

Evolutionary and developmental biology parted company from each other around 1900 and remained largely separate for about three-quarters of the twentieth century. They only began to reintegrate in the late 1970s and early 1980s, eventually producing the interdisciplinary endeavour that we now know as evolutionary developmental biology or 'evo–devo'[1–6]. The two main catalysts of reintegration were a series of books, most notably Stephen Jay Gould's *Ontogeny and Phylogeny* in 1977 (REF. 7), and the advances in developmental genetics that were made possible by the discovery of the homeobox in the early 1980s (REFS 8,9). In the period between 1900 and 1975, only a few lone voices had intermittently reminded biologists that the two great processes of biological creation — evolution and development — were deeply intertwined. D'Arcy Thompson (1860–1948) was one of them[10] (FIG. 1). Others included the neo-Darwinians Huxley[11] and de Beer[12], the mutationist Goldschmidt[13], and the hard-to-classify Waddington[14].

D'Arcy Thompson was unique; no one before him had attempted the kind of geometrical approach to development and evolution that he did. His entirely novel theory of transformations has, for nearly a century, been an inspiration to biologists who are interested in how development and morphology evolve. The esteem in which D'Arcy Thompson is held by those who are interested in furthering the reintegration of theories of evolution and development can be gauged from the dedication at the front of Gould's *Ontogeny and Phylogeny*: "To the philomorphs of Cambridge, the world, and beyond, where D'Arcy Thompson must lie in the bosom of Abraham."[7]

For those unfamiliar with the theory of transformations, here is a brief overview. You take either the outline of an entire animal or plant, or the outline of one of its component parts such as a bone or a leaf, and draw this against the background of a Cartesian grid (for example, ordinary graph paper). Then you submit the grid to some systematic mathematical transformation, such as stretching it in one dimension or distorting it so that its squares become rhombuses. You inspect the transformed outline of the animal that you drew faithfully on the original grid, and in many cases note that, far from being just a weird shape, the transformed outline corresponds closely to the shape of another related animal. Clearly, this intriguing finding is telling us something about how evolution works — but what? This is the key question.



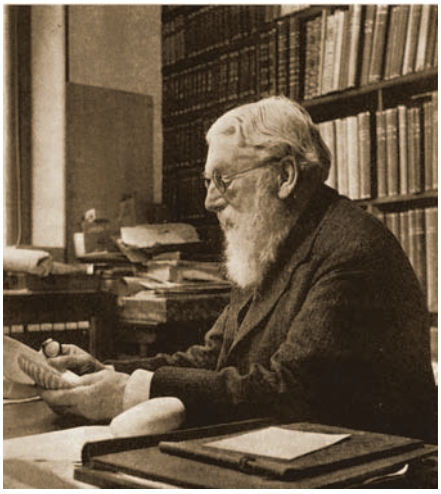


Figure 1 | **D'Arcy Thompson in the early 1900s and in the 1940s.** Reproduced with permission from REF. 15 © (1958) Oxford University Press.

Author biography

Eric Richards completed his graduate training in Fred Ausubel's laboratory in the Department of Molecular Biology at Massachusetts General Hospital (Department of Genetics, Harvard Medical School, USA) and later moved to Cold Spring Harbor Laboratory, USA, as a Fellow, where he began working on DNA methylation mutants in the flowering plant *Arabidopsis thaliana*. In 1992, Eric joined the faculty of Washington University, USA, where he is currently Professor of Biology. His laboratory continues to study the regulation of cytosine methylation using genetic approaches, with a focus on understanding stable epigenetic variation that is generated in DNA methylation mutant backgrounds, and the epigenetic component of natural variation.

Toc blurb

A growing body of evidence indicates that epigenetic states can be influenced by the environment. Considering that erasure of epigenetic marks between generations is not universal among multicellular organisms, what are the potential implications of inherited epigenetic variation for current theories of inheritance and evolutionary change?

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