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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 Whitlelaw, 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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