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Epigenetics and Evolution: An Overview

Abstract - After many years of neglect, the developmental aspect of heredity and its place in evolution are now receiving attention. In this overview, I discuss the relationship between epigenetic inheritance (mainly cellular epigenetic inheritance) and biological evolution. I point to six effects and implications of epigenetic inheritance that are important for evolutionary studies: (i) evolution can occur along the epigenetic axis without changes in DNA base sequence; (ii) epigenetic inheritance can affect the stability of the selective environment and speed up genetic accommodation; (iii) epigenetic variations can bias and target changes in DNA base sequence, leading to both micro- and macro-evolutionary changes; (iv) epigenetic inheritance constrains and channels the evolution of ontogeny; (v) epigenetic variations and epigenetic inheritance systems were important during the major evolutionary transitions; (vi) the genetic evolution of epigenetic inheritance systems is an important part of evolutionary history. Since epigenetic inheritance is ubiquitous and has far-reaching implications for evolutionary studies, I conclude that the present concepts of heredity and evolution need to be extended.

Epigenetic Inheritance

The term 'epigenetic inheritance' refers to the transmission across generations of phenotypic variations that do not depend on variations in DNA sequences or on the persistence of inducing signals. Hence, functional and structural phenotypic variations can persist when a cell or a multicellular organism reproduces, even if the stimulus that induced the phenotypic variation is no longer present. Genetically identical cells or organisms, living in identical conditions, can therefore display different heritable phenotypes because the developmental histories of their lineages were, at some point in the past, different. The term "epigenetic inheritance" is used

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to describe both non-genetic inheritance in cell lineages, and the transmission across generations of more general, whole-organism, physiological, behavioral and cultural non-genetic variations.

Epigenetic inheritance systems

At the cellular level, there are several kinds of molecular processes that maintain different cell phenotypes and enable their transmission to daughter cells through mitosis, and sometimes also through meiosis. Four broad types of epigenetic inheritance system (EIS) have been characterized (see Jablonka and Lamb, 2005):

1. *Self-sustaining metabolic loops*. When gene products act as positive regulators that maintain the transcriptional activity of genes in regulatory networks, the transmission of these products can lead to the same states of gene activity being reconstructed in daughter cells. Such gene products act as epigenetic switches, enabling heritable phenotypic modifications that do not require DNA sequence changes. A well-characterized example of such a system has recently been described in the fungal pathogen *Candida albicans*. In this pathogen the epigenetic switch that underlies the transition between white and opaque cells, two states that are heritable for many generations, has been identified and shown to operate through the formation of a self-sustaining stable feedback loop (Zordan *et al*., 2006).

2. *Structural inheritance*. Pre-existing cellular structures act as templates for the production of similar structures, which become components of daughter cells. Examples are prions in fungi (Wickner *et al*., 2004; Shorter and Lindquist, 2005), cortical structures in ciliates (Grimes and Aufderheide, 1991), and genetic membranes (Cavalier-Smith, 2004).

3. *Chromatin marking systems*. Chromatin marks are the variant, modifiable, histone and non-histone proteins and RNA molecules that are non-covalently bound to DNA, as well as small chemical groups (such as methyls) that are covalently bound directly to the DNA. Chromatin marks influence gene activity and may segregate with the DNA strands during replication, nucleating the reconstruction of similar marks in daughter cells (Henikoff *et al*., 2004).

4. *Heritable RNA-mediated variation in gene expression, such as gene silencing through RNA interference*. Silent transcriptional states are actively maintained through repressive interactions between small RNA molecules and the mRNAs to which they are partially complementary (Meister and Tuschl, 2004). RNA interference may not be the only type of RNA-mediated inheritance of variations. RNA-DNA and RNA-RNA interactions may lead not only to silencing, but also to the recruitment of mechanisms that lead to gene deletions and gene amplifications (Mochizuki and Gorovsky, 2004). Small heritable RNAs also seem to be involved in processes of paramutation (Rassoulzadegan *et al*., 2006).

These four types of EIS are often interrelated and interact in various ways. Nucleic-acid base-pairing, either DNA-DNA, DNA-RNA, or RNA-RNA, seems to be involved in the establishment of at least some DNA methylation and histone modifications, which are processes that have been described as constituting the chromatin marking EIS (Bernstein and Allis, 2005), and pairing is always involved in RNA-mediated inheritance.

What is passed on to the next generation through EISs depends on the conditions that a reproducing entity (a cell or a multicellular organism) and its ancestors experienced. For all EISs there is good evidence that some induced variations can be transmitted through both asexual and sexual reproduction, and the number and variety of cases of such inheritance is increasing rapidly, as the conditions for intergenerational induction and transmission are identified. For example, a series of experiments with rats has shown how some industrially important compounds, which are endocrine disruptors, can cause epigenetic changes in germline cells that are associated with testis disease states; these changes are inherited for at least four generations (Anway *et al.*, 2005, 2006).

Many of the best examples of transgenerational epigenetic inheritance are found in plants (for reviews see Grant-Downton and Dickinson 2005, 2006; Takeda and Paszkowski, 2006; Zilberman and Henikoff, 2005). This is probably related to the reproductive and developmental strategies of plants. In plants, the germline is repeatedly derived from somatic cells, so the developmentally established epigenetic states of somatic cells may sometimes persist when they become germ cells. In general, therefore, although there are some good examples of transgenerational epigenetic inheritance in sexually reproducing organisms that have early germline segregation, such as mammals (Chong and Whitelaw, 2004), epigenetic inheritance is likely to play a much larger role in the adaptive evolution of the many groups in which there is no distinct and permanent germline, or where germline-soma segregation occurs late in development (Jablonka and Lamb, 1995).

At the level of the whole organism, ancestral states can be transmitted through the creation of conditions that induce or positively bias the reconstruction of the same states in descendants, thus bypassing the germ line. For example, rat mothers nurse their pups during the first week of life, and the amount of licking and grooming they give have long-lasting effects on the offspring's ability to withstand stress and approach novelty: well-licked offspring are less sensitive to stress and more adventurous than poorly licked offspring (reviewed by Meany, 2001). Crucially, because highly-licked female offspring become good lickers when they become mothers, and under-licked female offspring become under-licking mothers, maternal behavior (it makes no difference whether the mother is the genetic or the adoptive mother) is reconstructed. In this way, variations in the sensitivity to stress are inherited through the maternal lineage. Changed environmental conditions can alter maternal behavior, and, when it does, the altered behavior and the far-reaching developmental effects that it triggers are transmitted within the lineage. The

hormonal and developmental conditions that create this self-sustaining developmental/behavioral loop have been partially characterized. The differences in the amount of nursing and licking that the offspring receive are reflected in changes in the epigenetic state (DNA methylation and histone acetylation) of certain key genes in the brain (Weaver *et al.*, 2004). Unless specifically reversed, these remain stable throughout life, have stable effects, and lead to the reconstruction of the same behavioral development through maternal behavior. Hence, it seems that in this case at least, self-sustaining physiological loops at the level of the whole organism are associated with cellular epigenetic inheritance.

There are many other examples of the transmission of behavior from parents or "tutors" to offspring or "trainees" that lead to the reconstruction of the same trajectories of development in the offspring. Although most such developmental reconstructions are not as well characterized at the physiological and molecular levels as in the case just described, they are probably very common. They underlie the many cases of non-genetic behavioral transmission in vertebrate groups that provide the basis for animal traditions (Avital and Jablonka, 2000).

The evolutionary importance of epigenetic inheritance

EISs can affect various aspects of adaptive evolution, speciation, and macroevolution, and because of this their own evolution is also of obvious significance. Some of the effects that EISs have are direct: the epigenetic variations are induced and then selected, so their frequency in the population changes. Other effects are indirect consequences of the biases (or targeting) that EISs introduce into the generation of genetic variants, and the effects of heritable epigenetic variations on the selection of genetic variants.

1. *Selection acting on heritable epigenetic variants can lead to medium-term and long-term adaptations, and initiate speciation.*

Epigenetic inheritance provides a new source of selectable variation, which may be crucial if populations are small and lack genetic variability. The best understood examples of evolution through the selection of heritable non-genetic variation are human cultural traditions and the many traditions in non-human animals that are the result of the transmission and stabilization of behavioral differences (Avital and Jablonka, 2000). Cellular epigenetic variations can also provide material for selection, as the *Drosophila* experiments of Sollars and his colleagues have clearly shown (Sollars *et al.*, 2003). Because induced epigenetic variants often arise when environmental conditions change, which is exactly the time when new phenotypes are likely to have a selective advantage, and because many individuals in the population may acquire similar modifications at the same time, adaptation can be very rapid.

The stability of the phenotypes that are transmitted across generations varies, but this stability may itself evolve both genetically and epigenetically. Theoretical models have shown that epigenetic inheritance, for which stability is generally lower than with DNA inheritance, can have a selective advantage when the environment changes at medium rates (every 2-100 generations), and when it changes stochastically (Jablonka *et al.*, 1995; Lachmann and Jablonka, 1996).

Epigenetic changes can lead to long-term effects by initiating speciation. Reproductive isolation may begin when non-genetic behavioral differences prevent mating taking place (Avital and Jablonka, 2000), or when differences in chromatin structure result in hybrid offspring either failing to develop normally or being sterile because the two sets of parental chromosomes carry incompatible chromatin marks (Jablonka and Lamb, 1995). For example, incompatibility between parental imprints is thought to be the reason why the development of hybrids between species of the mouse genus *Mus* is abnormal (Shi *et al.*, 2005). Epigenetic inheritance may have also been important at the initial stages of the evolution of dosage compensation and the morphological divergence of sex chromosomes in mammals (Jablonka, 2004).

2. *Cellular epigenetic variations can affect the rate of genetic evolution by affecting selection.*

Epigenetic changes that occur during development because of altered environmental conditions can unmask hidden genetic variation, and therefore affect which alleles are selected (West Eberhard, 2003). If such epigenetic changes are themselves inherited, adaptive evolution may be speeded up. For example, even in absence of genetic variation, adaptation can occur through the selection of heritable "epialleles", i.e., differences in the chromatin structure of a locus. Although epialleles may not be as stable as genetic alleles, adaptations based on such variation may be able to do a "holding job" that allows a population to survive until genetic accommodation occurs. Similarly, work on yeast has shown how a heritable epigenetic change in the three-dimensional structure of a protein that is involved in translation can generate new variations (Shorter and Lindquist, 2005). The spectrum of phenotypes that is induced when the altered protein is present enables some cells to survive stressful conditions. In nature, its presence in the population would therefore probably allow time for the selection of more stable genetic variants. In other words, the epigenetic inheritance of the altered form of the protein would result in more rapid genetic accommodation.

3. *Epigenetic variations can affect the production of genetic changes, and lead to both micro and macro evolutionary changes.*

Heritable variations in chromatin can affect genetic variation by influencing rates of mutation, transposition, and recombination (Jablonka and Lamb, 1995,

2005). For example, highly methylated transposable elements in plants rarely move, whereas when the same elements are demethylated they are usually very mobile (Fedoroff and Botstein, 1992). When transposable elements move to new locations they can introduce changes in coding or regulatory sequences, and they are regarded as a major source of mutations (Kidwell and Lisch, 1997), so the chromatin marks they carry (e.g. the extent to which they are methylated) affect the rate at which mutations are generated. Sometimes even a small insertion can lead to a gross phenotypic change – a "macromutation", a "hopeful monster". The notion that these hopeful monsters have a role in evolution used to be derided, but it is becoming clear that there are circumstances in which they can be honed by natural selection into adapted organisms (Bateman and Di Michele, 2002). Since the movement of some transposable elements is known to be markedly influenced by various types of internal (genetic) and external (environmental) stress, hopeful monsters may be more common in circumstances in which the survival of existing forms is threatened.

The relationship between genetic and epigenetic variation in repeated sequences seems to be both intimate and evolutionarily significant. Sequence studies have shown how, during plant and animal phylogeny, developmental genes have been duplicated and re-used (Garcia-Fernandez, 2005). Rodin *et al.*, (2005) have suggested that epigenetic silencing following gene duplication and repositioning can play an important role in the re-usage of the duplicated genes, making the genetic degeneration of the duplicates less likely.

Probably of more significance than single gene epimutations with major effects are the systemic genomic changes that are mediated through epigenetic control mechanisms and re-pattern the genome. The extent and sophistication of the interactions between epigenetic and genetic variations are being revealed by studies of cases of non-Mendelian inheritance in ciliates (Preer, 2000, 2006). Recent studies of evolution during conditions of genomic and ecological stress suggest that developmentally-induced variations in DNA are often (if not invariably) mediated by chromatin marking or RNA-mediated EISs. Genomic stresses such as hybridization and polyploidization induce massive epigenetic and genetic reorganization in plants (see Adams *et al.*, 2003, and papers in the Biological Journal of the Linnean Society 82(4) 2004, a special issue devoted to the subject). Ecological stresses such as nutritional changes can induce significant variations in repeated sequences in plants (Cullis, 2005), probably via epigenetic mechanisms, and hormonal stresses may be responsible for the appearance of micro-chromosomes in silver foxes (Belyaev *et al.*, 1981).

Epigenetic inheritance probably plays a significant role in speciation through polyploidization and hybridization, which are of central importance in plant evolution (Rapp and Wendel, 2005). In many naturally occurring and experimentally induced polyploids and hybrids, DNA methylation patterns are dramatically altered, and genes in some of the duplicated chromosomes are heritably silenced. Following polyploidization and hybridization there is a very rapid enhancement of

selectable variation, with all the opportunities for adaptation that this provides. The epigenetic events occurring during homoploid hybridization have not yet been sufficiently studied, but it is likely that in these cases epigenetically regulates heritable changes will be found to play a role in the divergence process. In general, it seems that heritable epigenetic variations may play a large role in initiating the divergence between population that leads to reproductive isolation, both by increasing selectable variation and by reorganizing genomes.

4. *Cellular epigenetic inheritance acts as a powerful constraint on the evolution of development.*

Reliable cellular EISs were a pre-condition for the evolution of complex multicellular organisms with specialized cell lineages, because cells in such lineages have to maintain their determined state and transmit it to daughter cells, even when the conditions that initiated it are no longer present. However, the cells that give rise to the next generation of organisms need to have an uncommitted state, and efficient EISs could jeopardize this. Natural selection should therefore favor mechanisms that counter the possibility of epigenetic variations being transmitted through the germ cells. EISs therefore impose a strong constraint on the evolution of ontogeny.

There are several features of development that may be outcomes of selection to prevent cells with inappropriate epigenetic legacies from founding the next generation. First, it may be one of the evolutionary reasons why many epigenetic states are so difficult to reverse in somatic cells, because irreversibility prevents a rogue somatic cell from becoming a germ cell and carrying its inappropriate epigenetic marks to the next generation. Second, the early segregation and quiescent state of the germline, which is seen in many different animal groups, may be the result of selection against acquiring the epigenetic "memories" associated with somatic cell determination and the chance epimutations that occur during cellular activities. Third, the massive changes in chromatin structure that occur during meiosis and gamete production may in part be the outcome of selection against the transmission of epigenetic variations that would prevent a zygote from starting its development with a clean epigenetic slate.

5. *Non-genetic inheritance plays a central role in major evolutionary transitions.*

We believe (Jablonka and Lamb, 2006) that non-genetic inheritance systems played an important role in all the major evolutionary transitions enumerated by Maynard Smith and Szathmáry (1995). For example, cellular epigenetic inheritance was crucial for the evolution of long nuclear chromosomes that maintain their patterns of gene activity following replication, as well as for the transition to eukaryotic cells and to multicellularity. Similarly, non-genetic behavioral transmission was instrumental in forming cohesive social units in animals, and cultural transmission though symbols was central to the social and cognitive evolution of humans.

6. *The genetic evolution of EISs.*

Once it is recognized that epigenetic inheritance has had a substantial role in evolution, the genetic evolution of epigenetic inheritance systems becomes an important topic. There are a few theoretical and comparative studies that have addressed the evolution of EISs, but the subject is still understudied. Genomic imprinting and X-chromosome inactivation have been important subject of evolutionary study for some time, but other epigenetic processes that are based on EISs (paramutation and stress-induced epigenomic alterations) have not received as much attention. With the exception of DNA methylation (Bestor, 1990; Bird, 1995; Regev e*t al*., 1998; Colot and Rossignol, 1999; Mandrioli, 2004) there has been little discussion of the evolution of the EISs and the ecological and developmental contexts in which this evolution occurred, although the situation is beginning to change. There are now a few comparative studies of histone evolution (Sandman *et al*., 1998, Felsenfeld and Groudine, 2003) and of the RNAi systems (Cerutti and Casa-Mollano, 2006).

General theoretical implications

Incorporating epigenetic inheritance into the framework of evolutionary theory, and focusing on the interactions between epigenetic variations and genetic modifications has important implications for evolutionary theory. The emerging picture is that the evolutionary effects of non-genetic inheritance are manifold and significant, although their importance and the type employed varies between taxa.

Evolutionary thinking is still lagging behind events in developmental biology and molecular biology, but I believe it is already clear that an extension of the basic definitions of evolution and heredity is unavoidable. If heredity involves the inheritance of developmental variations, evolution cannot be defined in terms of changes in gene frequency alone, which is how Dobzhansky (1937) suggested it should be defined. Dobzhansky's classical definition has to be extended. Marion Lamb and I have suggested that evolution can be said to occur through *the set of processes that lead to a change in the nature and frequency of heritable types in a population.* Heredity, too, needs to be redefined to incorporate processes beyond DNA replication, and we suggested that heredity should be defined as *the developmental reconstruction processes that link ancestors and descendants and lead to similarity between them* (Jablonka and Lamb *in press*). Evolutionary change can be based on epigenetic, behavioral and symbol-based cultural heritable variations, as well as genetic differences (Jablonka and Lamb, 2005).

The new data do more than expand the basic concepts of heredity and evolution. They also alter the theoretical edifice of evolutionary theory provided by the Modern Synthesis. Although there is no doubt that the cumulative selection of small random genetic variations plays an important role in evolution, Lamarckian

processes are also significant, and under certain conditions can lead to both targeted and stochastic saltational changes. Since the exclusion of Lamarckian and saltational changes was one of the defining features of the Modern Synthesis, a new theoretical evolutionary framework that goes beyond this synthesis needs to be constructed.

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REFERENCES

Adams K.L., Cronn R., Percifield R. and Wendel J.F. 2003. Genes duplicated by polyploidy show unequal contributions to the transcriptome and organ-specific reciprocal silencing. *Proceedings of the National Academy of Science*s, *USA* 100: 4649-4654.

Anway M.D., Cupp A.S., Uzumcu M. and Skinner M.K. 2005. Epigenetic transgenerational actions of endocrine disruptors and male fertility. *Science* 308: 1466-1469.

Anway M.D., Memon M.A., Uzumcu M. and Skinner M.K. 2006. Transgenerational effect of the endocrine disruptor vinclozolin on male spermatogenesis. *Journal of Andrology* 27: 868-879.

Avital E. and Jablonka E. 2000. *Animal Traditions: Behavioural Inheritance in Evolution.* Cambridge University Press, Cambridge.

Bateman R.M. and DiMichele W.A. 2002. Generating and filtering major phenotypic novelties: neoGoldschmidtian saltation revisited. In Q.C.B.Cronk, R.M. Bateman and J.A. Hawkins (eds), *Developmental Genetics and Plant Evolution*. Taylor & Francis, London, pp. 109-159.

Belyaev D.K., Ruvinsky A.O. and Trut L.N. 1981. Inherited activation-inactivation of the star gene in foxes. *Journal of Heredity* 72: 267-274.

Bernstein E. and Allis C.D. 2005. RNA meets chromatin. *Genes and Development* 19: 1635-1655.

Bestor T.H. 1990. DNA methylation: evolution of a bacterial immune function into a regulator of gene expression and genome structure in higher eukaryotes. *Philosophical Transactions of the Royal Society of London B* 326: 179-187.

Bird A.P. 1995. Gene number, noise reduction and biological complexity. *Trends in Genetics* 11: 94-100.

Cavalier-Smith T. 2004. The membranome and membrane heredity in development and evolution. In R. P. Hirt and D. S. Horner (eds), *Organelles, Genomes and Eukaryote Phylogeny: An Evolutionary Synthesis in the Age of Genomics*. CRC Press, Broca Raton, pp. 335-351.

Cerutti H. and Casas-Mollano J.A. 2006. On the origin and functions of RNA-mediated silencing: from protists to man. *Current Genetics* 50: 81-99.

Chong S. and Whitelaw E. 2004. Epigenetic germline inheritance. *Current Opinion in Genetics and Development* 14: 692-696.

Colot V. and Rossignol J.L. 1999. Eukaryotic DNA methylation as an evolutionary device. *BioEssays* 21: 402-411.

Cullis C.A. 2005. Mechanisms and control of rapid genomic changes in Flax. *Annals of Botany* 95: 201-206.

Dobzhansky, T. 1937. *Genetics and the Origin of Species.* Columbia University Press, New York.

Fedoroff N. and Botstein D., (eds) 1992. *The Dynamic Genome: Barbara McClintock's Ideas in the Century of Genetics*. Cold Spring Harbor Laboratory Press, Plainview NY.

Felsenfeld G. and Groudine M. 2003. Controlling the double helix. *Nature* 421: 448-453.
Garcia-Fernàndez J. 2005. The genesis and evolution of homeobox gene clusters. *Nature Reviews Genetics* 6: 881-892.
Grant-Downton R.T. and Dickinson H.G. 2005. Epigenetics and its implications for plant biology. 1. The epigenetic network in plants. *Annals of Botany* 96: 1143-1164.
Grant-Downton R.T. and Dickinson H.G. 2006. Epigenetics and its implications for plant biology. 2. The 'epigenetic epiphany': epigenetics, evolution and beyond. *Annals of Botany* 97: 11-27.
Grimes, G. W., and K. J. Aufderheide. 1991. *Cellular Aspects of Pattern Formation: TheProblem of Assembly*. *Monographs in Developmental Biology*, vol. 22. Karger, Basel.
Henikoff S. McKittrick E. and Ahmad K. 2004. Epigenetics, histone H3 variants, and the inheritance of chromatin states. *Cold Spring Harbor Symposia on Quantitative Biology* 69: 235-244.
Jablonka E. 2004. The evolution of the peculiarities of mammalian sex chromosomes: an epigenetic view. *BioEssay*s, 26: 127-132.
Jablonka E. and Lamb M.J. 1995. *Epigenetic Inheritance and Evolution: The Lamarckian Dimension.* Oxford University Press, Oxford.
Jablonka E. and Lamb M.J. 2005. *Evolution in Four Dimensions: Genetic, Epigenetic, Behavioral and Symbolic Variation in the Evolution of Life*. MIT Press, Cambridge MA.
Jablonka E. and Lamb M.J. 2006. The evolution of information in the major transitions. *Journal of Theoretical Biology* 239: 236-246.
Jablonka E. and Lamb M.J. (in press) The expanded evolutionary synthesis – a response to Godfrey-Smith, Haig, and West-Eberhard. *Biology and Philosophy.*
Jablonka, E., Oborny B., Molnár I., Kisdi E., Hofbauer J., and Czárán T. 1995.The adaptive advantage of phenotypic memory. *Philosophical Transactions of the Royal Society of London B* 350:133-141.
Kidwell M.G. and Lisch D. 1997. Transposable elements as sources of variation in animals and plants. *Proceedings of the National Academy of Sciences*, USA 94: 7704-7711.
Lachmann M. and Jablonka E. 1996. The inheritance of phenotypes: an adaptation to fluctuating environments. *Journal of Theoretical Biology* 181: 1-9.
Mandrioli M. 2004. Epigenetic tinkering and evolution: is there any continuity in the role of cytosine methylation from invertebrates to vertebrates? *Cellular and Molecular Life Sciences* 61: 2425-2427.
Maynard Smith J. and Szathmáry E. 1995. *The Major Transitions in Evolution*. Freeman, Oxford.
Meaney M.J. 2001. Maternal care, gene expression, and the transmission of individual differences in stress reactivity across generations. *Annual Review of Neuroscience* 24: 1161-1192.
Meister G. and Tuschl T. 2004. Mechanisms of gene silencing by double-stranded RNA. *Nature* 431: 343-349.
Mochizuki, K. and Gorovsky M.A. 2004. Small RNAs in genome rearrangements in *Tetrahymena*. *Current Opinion in Genetics and Development* 14: 181-187.
Preer, J. R. Jr. 2000. Epigenetic mechanisms affecting macronuclear development in *Paramecium* and *Tetrahymena*. *Journal of Eukaryotic Microbiology* 47: 515-524.
Preer, J. R. Jr. 2006. Sonneborn and the cytoplasm. *Genetics* 172: 1373-1377.
Rapp R.A. and Wendel J.F. 2005. Epigenetics and plant evolution. *New Phytologist* 168: 81-91.
Rassoulzadegan M., Grandjean V., Gounon P., Vincent S., Gillot I. and Cuzin F. 2006. RNA-mediated non-mendelian inheritance of an epigenetic change in the mouse. *Nature* 441: 469-474.
Regev A., Lamb, M.J. and Jablonka E. 1998. The role of DNA methylation in invertebrates: developmental regulation or genome defense? *Molecular Biology and Evolution* 15: 880-891.
Rodin S.N., Parkhomchuk D.V. and Riggs A.D. 2005. Epigenetic changes and repositioning determine the evolutionary fate of duplicated genes. *Biochemistry (Moscow)* 70: 559-567.
Sandman K., Pereira S.L. and Reeve J.N. 1998. Diversity of prokaryotic chromosomal proteins and the origin of the nucleosome. *Cellular and Molecular Life Sciences* 54: 1350-1364.

Shi W., Krella A., Orth A., Yu Y. and Fundele R. 2005. Widespread disruption of genomic imprinting in adult interspecies mouse (*Mus*) hybrids. *Genesis* 43: 100-108.

Shorter J. and Lindquist S. 2005. Prions as adaptive conduits of memory and inheritance. *Nature Reviews Genetics* 6: 435-450.

Sollars V., Lu X., Xiao L., Wang X., Garfinkel M.D. and Ruden D.M. 2003. Evidence for an epigenetic mechanism by which Hsp90 acts as a capacitor for morphological evolution. *Nature Genetics* 33: 70-74.

Takeda S. and Paszkowski J. 2006. DNA methylation and epigenetic inheritance during plant gametogenesis. *Chromosoma* 115: 27-35.

Weaver I.C.G., Cervoni N., Champagne F.A., D'Alessio A.C., Sharma S., Seckl J.R., Dymov S., Szyf M.and Meaney M.J. 2004. Epigenetic programming by maternal behaviour. *Nature Neuroscience* 7: 847-854.

West-Eberhard M.J. 2003. *Developmental Plasticity and Evolution*. Oxford University Press, New York.

Wickner R.B., Edskes H.K., Ross E.D., Pierce M.M., Baxa U., Brachmann A. and Shewmaker F. 2004. Prion genetics: new rules for a new kind of gene. *Annual Review of Genetics* 38: 681-707.

Zilberman D. and Henikoff S. 2005. Epigenetic inheritance in *Arabidopsis*: selective silence. *Current Opinion in Genetics and Development* 15: 557-562.

Zordan R.E., Galgoczy D.J. and Johnson A.D. 2006. Epigenetic properties of white–opaque switching in *Candida albicans* are based on a self-sustaining transcriptional feedback loop. *Proceedings of the National Academy of Science*s, *USA* 103: 12807-12812.

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