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Epigenetics: The origins and evolution of a fashionable topic

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ABSTRACT

The term "epigenetics" was introduced in 1942 by embryologist Conrad Waddington, who, relating it to the 17th century concept of "epigenesis", defined it as the complex of developmental processes between the genotype and phenotype. While in the years that followed, these processes – in particular gene regulation – were tackled, not in the frame of epigenetics but of genetics, research labelled "epigenetics" rose strongly only in the 21st century. Then it consisted of research on chromatin modifications, i.e. chemical modifications of DNA or histone proteins around DNA that do not change the base sequence. This rise was accompanied by far-reaching claims, such as that epigenetics provides a mechanism for "Lamarckian" inheritance. This article highlights the origin of epigenetics, the major phases of epigenetic research, and the changes in the meaning of the term. It also calls into question some of the far-reaching claims that have accompanied the recent rise of epigenetics.

1. Introduction

Looking at the growing calls among evolutionary biologists for a major revision of neo-Darwinism (though for very different reasons), paleobiologist Erwin (2007) concluded that "there is nothing scientists enjoy more than the prospect of a good paradigm shift", referring to the concept of paradigm shifts by historian/philosopher of science Kuhn (1962). Erwin's observation is strongly supported by the development of epigenetics, a fashionable subject which is not only a fast-growing scientific field, but also widely attended to in the popular literature. Scientists and commentators of science enjoy the prospect that epigenetics is leading to a "paradigm shift" in many fields of biological and medical research, such as genetics, development, evolution, cancer, nutrition, and Alzheimer's disease. Assertions that epigenetics regulates gene-expression or that it relativizes the causal role of genes in development and heredity are widespread, as is the use of epigenetics as a major explanatory concept in the fast rising neo-Lamarckism.

This article presents an overview of the history, current research, and changing meanings of "epigenetics" in the context of development and genetics. It also deals with some of the far-reaching claims and revolutionary aspirations of some epigeneticists, emphasizing instead that epigenetic changes do not relativize the importance of genes but are part of the mechanisms for the regulation of gene expression controlled by the genome.

2. From epigenesis to epigenetics: epigenetics as development

Despite epigenetics being a recent fashion, the term is old; it has drastically changed its meaning over time, with many changes occurring particularly after 2000 (for details see Bird (2007), Felsenfeld (2014), Haig (2011), and Morange (2013)). The adjective "epigenetic" existed many centuries before the noun "epigenetics"; it was, however, related, to "epigenesis" and not "epigenetics." The term "epigenesis" was coined by the physician and physiologist William Harvey around 1650 for the conception of development as a gradual process of increasing complexity from initially homogeneous material in the egg, an idea that was originally proposed by Aristotle. Epigenesis contrasted with preformation, according to which the embryo or parts of it are preformed from origination. The term *genesis* (gr.) can be translated as origin, and *epi* as on or after.

In 1942 embryologist Conrad Waddington introduced the term "epigenetics" into modern biology, emphasizing its relationship to the classical concept of "epigenesis". Waddington defined "epigenetics" as the "whole complex of developmental processes" that lie between "genotype and phenotype". In his characterization of the "epigenotype" he speculated about a biological system in which "concatenations of processes [are] linked together in a network, so that a disturbance at an early stage may gradually cause more and more far-reaching abnormalities in many different organs and tissues" (Waddington, 1942, p. 10). His often-cited model of an "epigenetic landscape", illustrating the various developmental pathways a cell might take during differentiation, attributes a major role to the genes which underlie the landscape, acting to

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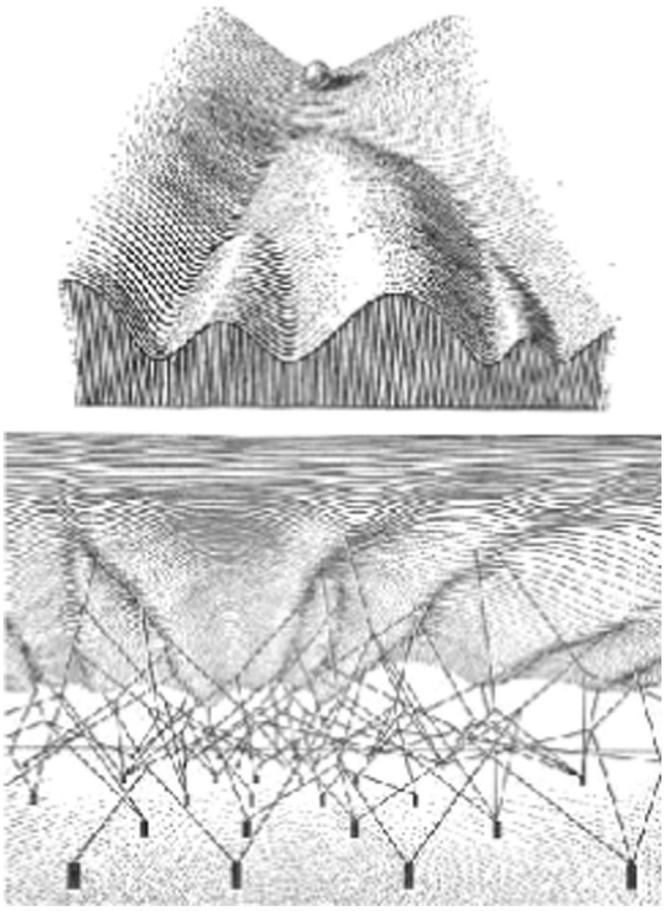

Fig. 1. The "epigenetic landscape" as proposed by Conrad Waddington shows a ball rolling down on an inclined surface with a cascade of branching ridges and valleys. It is used as a visual metaphor for the branching pathways of cell fate determination, representing the series of either/or decisions of the developing cell. The underlying genes act to structure the "landscape"; the presence or absence of particular genes determines which path shall be followed from a certain point of divergence (Waddington, 1957).

structure it (Fig. 1). That is to say, according to Waddington, the presence or absence of particular genes determines which path the cell will follow from a certain point of divergence (Waddington, 1957, pp. 19 and 26).

Another conception of "epigenetics" was suggested by microbiologist Nanney (1958). He distinguished two cellular control systems: first, a "library of specificities" accomplished by template replicating mechanisms based on DNA sequences, the "genetic system", and, second, "auxiliatory mechanisms" which were involved in determining which specificities were to be expressed in a particular cell, i.e., the control of gene expressions. Referring to Waddington's (1942) paper, he called these auxiliatory mechanisms "epigenetic" to "emphasize the reliance of these systems on the genetic systems and to underscore their significance in developmental processes" (Nanney, 1958, p. 712). Most of his examples were phenomena in micro-organisms, including biochemical processes such as environmentally-induced enzyme synthesis.

Research labelled "epigenetics" remained marginal until the end of the millennium (see below). In modern terms, Waddington's understanding of epigenetics can be regarded as mechanism for the regulation of gene expression. But research that could have been labelled so according to the definitions above, did take place: The operon model of gene regulation in bacteria by Jacob and Monod (1961) provided the first comprehensive model of such a regulation. It would also fit Nanney's concept of epigenetics. However, from the outset, this research had been part of (molecular) genetic, not epigenetic, research. Moreover, Waddington (in line with all his colleagues) would not have conceived of prokaryotes as organisms which might be relevant for the study of either genetics or development.

Subsequent research on the regulation of gene expression in the development of higher organisms likewise was not labelled epigenetic. It began in the 1960s, carried out by molecular biologists whose focus was on development, most vigorously Davidson (Davidson, 1968, 2014; Morange, 2002, 2013; Deichmann, 2016a). Convinced that models based on specific repressors, which were developed in bacteria, were not applicable to higher organisms, he postulated non-specific inhibition of gene expression in eukaryotes by histones combined with selective activators (Davidson, 1968, pp. 315–323). In a theoretical model proposed by Britten and Davidson (1969), various types of genes at different hierarchical levels of regulation interact to control the fates of cells in development through differential gene expression. This theory not only contained the first detailed model of gene regulation in higher organisms, but also predicted wide evolutionary implications: Fundamental changes in the regulatory regions, which lead to changes in the process of transcription, may result in stable systems of genes that could enable evolutionary novelties. The model, in which the concept of genetic information in the form of DNA sequences was central, was further developed by experimental research on gene regulation in development and by the study of evolutionary mechanisms for the changes of body plans (Davidson, 2006; Peter and Davidson, 2015; an assessment is in Morange (2009); see also Wolter (2013)).

3. From chromatin to epigenetic marks: epigenetics as biochemistry: DNA methylation and histone marks

Many epigenetic phenomena today relate to chemical or structural modifications of chromatin, i.e. complexes of DNA and proteins into which the genomes of higher organisms are packaged. The term chromatin was introduced by cytologist Walther Flemming in 1879 for the stainable structures in the cell nucleus visible during cell division, which were later called "chromosomes". Flemming predicted that the term 'chromatin' would disappear when the chemical nature of chromatin would be discerned. However, 'chromatin' did not disappear once its molecular composition was resolved, but continued to be used for the complex of DNA with basic proteins, mainly histones. Research into chemical chromatin modifications, in particular histone and DNA marks originated in the 1960s. Interestingly, research on DNA methylation and histone modifications developed separately from one another for about two decades. Only from the 1990s onward did this research begin to be labelled "epigenetics".

3.1. Histone modifications

The pioneers of modern chromatin research were Vincent Allfrey and Alfred Mirsky, who confirmed the inhibitory effect of histones on transcription and showed that their acetylation and methylation alleviated the inhibition. Mirsky was one of the major proponents of the inhibitory effect of histones on transcription as a means of gene regulation. In contrast, as mentioned above, his former Ph.D. student Eric Davidson considered selective activation as a major mechanism of gene regulation in higher organisms. Allfrey's and Mirsky's work on histone acetylation did not have much impact, in part, because it was not clear whether these modifications caused inhibition or just correlated with it (Morange, 2013).

The discovery of nucleosomes in 1973–4 formed the structural origin of modern chromatin research (see e.g. Morange, 2013; Olins and Olins, 2003). Nucleosomes are basic units of the eukaryotic chromatin structure; they consist of approx. 150 bp DNA wrapped around a protein core that is formed by eight histone proteins. However, these first structural studies did not reveal an obvious effect of histone modifications on the overall structure of the nucleosome (Morange, 2013).

New research on chromatin structure modification started in the 1990s Felsenfeld (2014) summarized this research: Research in yeast showed the connection between chromatin structure and its function. David Allis identified an enzyme in Tetrahymena similar to a protein in yeast that acetylated histones. A mutation of the gene for this protein in yeast had effects on growth. Stuart Schreiber discovered an enzyme in mammalian cells that removed histone acetylation marks and was related to a yeast gene known to regulate transcription. This was followed by the discovery of enzymes that move the nucleosomes around on DNA, which also had significant phenotypes detected through yeast genetics—chromatin remodeling enzymes.

It was shown that the enzymes attaching methyl and acetyl groups to the histone tails of nucleosomes are not DNA sequence-specific, but need a sequence-specific protein factor (for example a transcription factor) to find the right place. In some cases the modifications were shown to be transmitted by cell division, and in rare cases also the germ line.

The question of how to interpret the patterns of histone marks in terms of active state has not yet been answered in a conclusive way. Allis's suggestion of a histone code—a system in which different combinations of histone modification patterns regulate specific and distinct functional outputs of eukaryotic genomes (Jenuwein and Allis, 2001)—has met with skepticism (Felsenfeld, 2014; Deichmann, 2013). The histone modifications are not stable and not faithfully copied, and they disappear after a few cell generations. Assumptions that these modifications affect gene activity led to their designation as epigenetic marks. But so far, there are only correlations. What has been shown is the opposite: namely, that histone acetylation was generated as a consequence of transcription (see Fig. 2). Whether they precede or follow transcription, histone modifications play an important role in transcription mechanisms, and interference with the modification process has multiple effects on the phenotype (Felsenfeld, 2014).

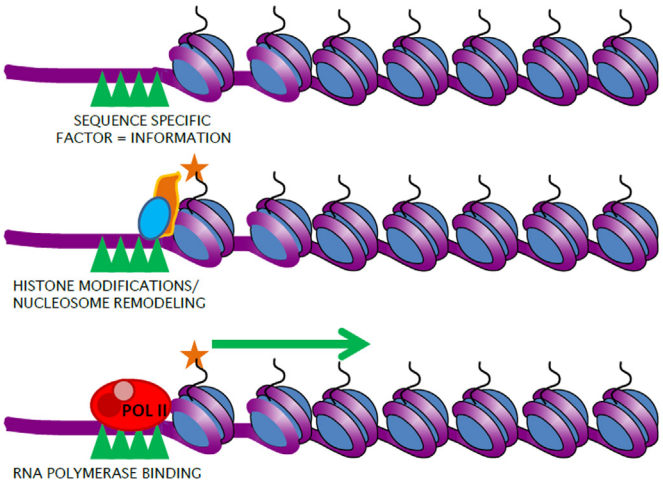

Fig. 2. A simplified description of steps that may be associated with activation of gene transcription. The initial step (top) must involve recognition of DNA sites (nucleotide sequences) near the gene by one or more specific regulatory proteins that target that gene. That is the signal that allows the remaining steps (below) to prepare the chromatin to accommodate RNA polymerase and transcription. Source: Reprinted from Felsenfeld (2014), with kind permission of the author.

3.2. DNA methylation

Starting in the mid-1970s, a correlation between the lack of DNA-methylation and gene activity was reported by, among others, Adrian Bird, Frank Grossveld, Robin Holliday, and A.D. Riggs. In 1975 Holliday and Riggs proposed in 1975 the hypothesis that DNA methylation might play a role in the regulation of gene expression (Holliday and Pugh, 1975; Riggs, 1975, see also the overview in Holliday (2006)).

In the late 1970s Howard Cedar and Aharon Razin began to work on DNA methylation in the context of gene regulation in eukaryotes; Razin had previously worked on DNA methylation in bacteria which use it as a restriction modification system to selectively cut entering phage DNA. Cedar and Razin conducted key experiments in which they showed that in in vitro experiments methylation can indeed cause gene repression. Through transfection experiments of naked and methylated DNA into animal cells in culture they provided clear evidence that "there is a pattern of methylation, and that pattern is maintained from generation to generation" of cells (Naveh-Many and Cedar, 1981; Stein et al., 1982a, 1982b; Deichmann, 2014).

DNA methylation plays a crucial role in early mammalian development. At an early stage (before the blastocyst stage) massive DNA demethylation erases almost every methyl group of the DNA (which had been copied from the methylation patterns of the egg and sperm) so that the cells become pluripotent. Only a few especially marked genes, such as imprinted genes, are not demethylated (except for those cells that are destined to make gametes). Subsequently, de novo methylation affects almost the whole genome, except for sequences called CpG islands that are protected (Deaton and Bird, 2011).

Unlike the early erasure of methyl groups and subsequent *de novo* methylation, which affect nearly all genes, all changes in methylation from the time of implantation are specific changes, directed by transcription factors or repressors, i.e. DNA sequence specific proteins. An example is the turning off of pluripotency genes, such as Oct-4, Nanog and Sox-2, as a pre-requisite for differentiation. Cedar emphasizes that DNA methylation occurs only after genes have been turned off by a sequence-specific repressor protein (Deichmann, 2014).

The methylation itself does not turn off a gene, because it is not an active repressor, but it renders the repression permanent. Methylation patterns are not inherited from parents, because their methylation patterns are erased. In the same way that DNA methylation does not turn off genes, the demethylation itself does not turn them on: "Basically in almost every case, you first turn on transcription and then you get demethylation. The change in methylation is not meant to turn on the gene; it's meant to make the decision to turn on the gene permanently" (Deichmann, 2014). The process is initiated by a specific transcription factor. As soon as it touches down on the gene, the machinery to open the chromatin and do demethylation is brought about to this place. "Most people misunderstand the role of methylation" (Deichmann, 2014). In both cases the specific changes of gene expression have to be targeted by something that recognizes the DNA sequence. These changes, though minor, are very important for these tissues.

3.3. DNA methylation and histone modifications as epigenetics; new definitions

Following the discovery of imprinted genes in mice and men in the 1990s, epigenetics became closely associated with DNA methylation (Haig, 2011). Robin Holliday, who in the 1980s and 90s proposed several extended definitions of epigenetics and was in part responsible for the plurality of meanings of the term (Morange, 2013), proposed that changes in gene expression through

(de-)methylation of DNA be called. In addition, he strongly promoted the idea that epigenetic defects in germ line cells could be inherited by offspring (Haig, 2011). Contrary to what Waddington believed, intergenerational heritability was increasingly considered to be a basic property of phenomena of epigenetics.

A few years later modifications of histone proteins were considered to be another mechanism of "epigenetic inheritance" (Haig, 2011), a fact which led Kevin Struhl, himself studying chromatin modifications, to remark that "people decided that if they call them that it makes them interesting" (Pearson, 2008). Epigenetics was now concerned with the transmission of phenotype through mitosis or the germ line by mechanisms that did not involve changes in the DNA sequence. A new definition of epigenetics as "the study of mitotically and meiotically heritable changes in gene function that cannot be explained by changes in DNA sequences" was proposed (Riggs et al., 1996), followed by many others. In 2007, Adrian Bird proposed as definition of epigenetics "the structural adaptation of chromosomal regions so as to register, signal or perpetuate altered activity states" (Bird, 2007, 398). According to Felsenfeld (2014), most of these definitions do not distinguish between situations in which the modifications may be propagated through cell division, thus helping to maintain a pattern of gene expression, and other cases in which the modifications are simply part of the transcriptional apparatus.

Epigenetics, meanwhile, means very different things to different researchers. Large parts of epigenetic research, in particular in medical epigenetics, consist of studies on correlations, not causation. Other studies examine the involvement of epigenetic factors in gene regulation processes, with the genome as first cause. Molecular immunologist Ellen Rothenberg holds that "the major players driving changes in the epigenetic landscape (histone marks, chromatin compaction and looping, etc.)" are sequence-specific transcription factors, "as part of the mechanism of their roles in controlling gene expression". She thinks that "the transcription factors are critical for setting initial positions for histone marks, and then as development proceeds, determining where the patterns of histone marks must change." In the post-embryonic cells she studies, "these positionings of histone marks as a result of prior differentiation events sit at the crossroads between regulatory past and regulatory future. By affecting DNA accessibility, they create an inertial resistance to change. But when transcription factor ensembles cross the threshold to cause further differentiation, they change the histone mark distribution, reshaping the epigenetic landscape" (personal communication to the author, 19 August 2015).

Research labelled epigenetics was marginal until 2000. It increased rapidly after studies in DNA methylation and histone modification were conducted under this label. This increase can be demonstrated quantitatively, using a citation analysis: I compared the number of citations of articles with "epigenetic" in the title in 1990 and 2013 in the Science Citation Index Expanded of the Web of Science, and found an increase by a factor of 66.5. This Citation Index covers over 8500 major journals across 150 disciplines. To find out whether this increase is specific to "epigenetic", I compared it with that of the number of papers with genetics in the title in this period of time and thereby showed that the increase of "epigenetic" compared to "genetic" is higher by a factor of 15.8. Interestingly, in the same period of time, there is also a significantly stronger increase in papers with "epigenetic" in the title compared to genetics in the Social Science Citation Index.

The increase is not linear: While there is hardly any increase between 1990 and 2000, the number of papers in the sciences and (to a lesser extent) social sciences with "epigenetic" in the title (measured by the ratio of epigenetic/genetic) rises drastically only starting in 2000 (Fig. 3).

The figure illustrates that although the term "epigenetics" had already been proposed in 1942 and research on DNA methylation and histone modification had been conducted since the 1960s, the term was rarely used. In contrast, the number of articles with "chromatin" in the title did not increase more than that with genetics in it (both by a factor of 4.2) during the same period of time (Deichmann, 2015). We can assume, first, that the strong increase of "epigenetics" after 2000 means that the term was increasingly used for research formerly called chromatin research, and second, that the term was applied in a large variety of research formerly not related to chromatin.

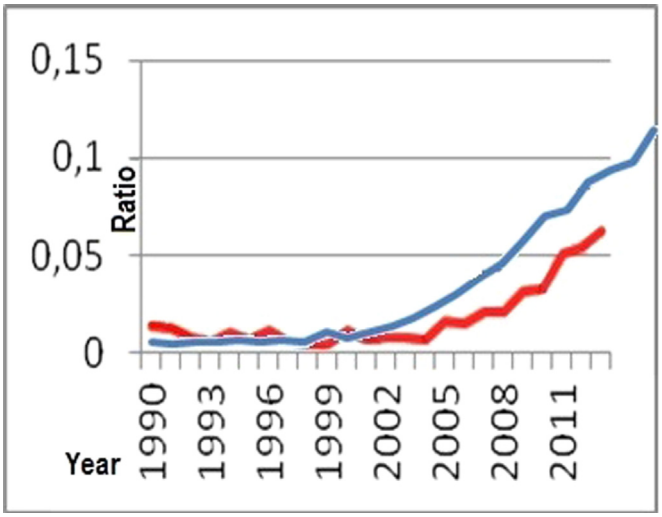

Fig. 3. Ratio of "epigenetic" to "genetic" in titles of papers in the Science Citation Index Expanded (of the Web of Science) between 1990 and 2013 (in blue), and in titles of papers in the Social Sciences Citation Index of the Web of Science between 1990 and 2013 (in red).

According to Howard Cedar, epigenetics all of a sudden appeared as a solution for many problems for which there were no solution in sight: "If you don't know the cause, you say it's epigenetic" (Deichmann, 2014). Similarly, Bird (2010) holds: "Epigenetics is a useful word if you don't know what's going on—if you do, you use something else." Third, the strong rise of "epigenetics" in titles might be explained by the phenomenon of "Epigenetic Hype."

4. Extended epigenetics or the "Epigenetics Hype"

The term "hype about epigenetics" was introduced by Maderspacher (2010) to describe the widespread claims of victory over genes by epigenetics in scientific and popular literature. Similarly, "Epigenetics Hype" here is used for an extended version of epigenetics, i.e. the far-reaching, revolutionary claims of having discovered entirely new mechanisms of heredity and evolution which are supposed to replace older concepts. The claim that "DNA Is Not Destiny… The new science of epigenetics rewrites the rules of disease, heredity, and identity" (http://discovermagazine.com/2006/nov/cover) is an example of Epigenetics Hype as is the unwarranted claim in a Nature Editorial (2010), in which the explanation for the diversity of life is expected from epigenetics because, allegedly, "genome sequences, within and across species, were too similar to be able to explain [it]." In his article on epigenetics in The New Yorker, prize-winning author and cancer researcher Mukherjee (2016) does not even mention transcription factors and repressors when dealing with the question of what puts a gene on and off in development, but invokes epigenetics instead.

Most frequently, epigenetics is used to support the claim of a

comprehensive paradigm shift in evolutionary biology, namely the justification of the idea of soft inheritance, often equated with "Lamarckian inheritance." This question has been dealt with in greater detail elsewhere (Deichmann, 2016b) and will be summarized here only briefly.

Statements that epigenetics rehabilitates so-called Lamarckian inheritance have been made in scientific publications, those of the history and philosophy of science, and the popular press, see for example Vargas (2009), Gissis and Jablonka (2011), Lindquist (2011), Biopro (2014), and Mukherjee (2016). It should be emphasized, however, that even if there were clear evidence of soft inheritance, the term "Lamarckian inheritance" would be inappropriate for most of the examples presented. Jean-Baptiste Lamarck (1744–1829), a renowned French naturalist, put forward the first comprehensive theory of organic evolution around 1800. It included the notion of progress, i.e. evolution towards higher perfection and complexity, not driven by chance. Consequently, the old idea of the spontaneous generation of lower organisms from non-living material was included as well because it had to account for the continued existence of primitive organisms. In this evolutionary theory Lamarck proposed mechanisms for the transformation of species through the inheritance of characteristics that were actively acquired during an organism's lifetime and led to better adaptation: The use or disuse of an organ would lead to its amplification or atrophy, and both would be inherited.

The idea of the inheritance of acquired characteristics was not invented by Lamarck, but existed already in Greek antiquity, where it was supported, for example, by Aristotle. It was adopted by most naturalists before and after Lamarck until the early 20th century, including by Charles Darwin, who amended, not replaced it, with the concept of natural selection (though Darwin did not share Lamarck's conviction of evolution being directed towards greater perfection). The idea of the inheritance of actively acquired characteristics as a means for adaptation was abandoned by most biologists in the West in the 1920s and 30s with the advent of population genetics, a synthesis of Mendelian genetics and a Darwinian evolutionary theory that was stripped of Lamarckism, generated by Ronald Fisher, JBS Haldane, and Sewall Wright.

Phenomena of inherited variation related to epigenetic marks are supported by very few data (Bird, 2007). But even if there was clear evidence, these phenomena would not be Lamarckian, because: a) They are not actively acquired; b) they are not adaptive (except by chance) and in many cases are even detrimental to the organisms, such as alleged long term detrimental effects of starvation; c) histone modifications are not stable over many generations, DNA methylation patterns are not as faithfully replicated as the DNA sequence; both modifications thus do not have a long-lasting impact on evolution.

According to Bird (2013), there is no hard evidence for the influence of the environment on inherited epigenetic marks: "Because this is something that's talked about an awful lot, there is the view that the environment influences our epigenome. And I have a skeptical stance on that. Not because I will never believe it no matter what anybody says, but just because I feel there is a great tendency to want it to be true. And I much prefer to see some hard data on that". Similarly, Howard Cedar points out: "First of all, we don't know if the environment affects DNA methylation or how it affects it. But there are lots of problems with this idea. The biggest problem is the one of inheritance. The fact that methylation patterns are erased in the early embryo makes it very difficult to explain how an environmental effect could then be inherited to later generations" (Deichmann, 2014). In addition to this erasure, the early divergence of germ line and soma cells, as first suggested by Weismann in late 19th century, would prevent the transmission of epigenetic changes in somatic cells through the germ line.

In plants the situation is different. Future germ cells arise from somatic cells and epigenetic silencing mechanisms play a big role in development (Henderson and Jacobsen, 2007). These phenomena are not examined in the present paper.

The most distorted version of Epigenetics Hype is currently developing in Russia, where epigenetics is used to rehabilitate Trofim Lysenko, a Soviet agronomist, who gained political power under Stalin and came to rule Soviet biology for decades in which the flourishing genetics and population genetics in the Soviet Union were destroyed (Medvedev, 1969; Joravsky, 1970; Graham, 1993). Recent years have seen a rebirth of Lysenkoism in Russia. Today an increasing number of Russian scientists try to rehabilitate Lysenko's pseudo-scientific work by relating it to epigenetics. According to Graham (2014), some of these Russian scientists praise Lysenko (who rejected any kind of molecular explanations) as "an outstanding natural scientist" who anticipated epigenetics. According to Graham, the trend to rehabilitate Lysenko is supported by "Putin's revival of Soviet attitudes" (Graham, 2014). A new biology textbook with Lysenko's views has been produced by nationalists who are pushing for its adoption in local schools.

5. Outlook – epigenetics is not a scientific revolution but a set of new mechanisms related to the old concept of gene regulation

While many scientists and science commentators enjoy, as stated by Erwin in the beginning, the far-reaching revolutionary claims of epigeneticists to have found new principles of hereditary transmission, development, and evolution, others are concerned about the disregard of "principles of gene regulation and of evolutionary and developmental biology that have been established during the past 50 years" (Ptashne et al., 2010). They point out that "chromatin 'marks' and local chemical modifications of DNA are the consequences of DNA-sequence-specific interactions of proteins (and RNA) that recruit modifying enzymes to specific targets." Investigators of "epigenomics" themselves expressed their concern about scientists' attributing to the "epigenome" the same value as the genome. They, too, criticize the non-consideration of established knowledge concerning the importance of sequence-specific DNA recognition events and transcriptional networks in controlling epigenetic changes (Madhani et al., 2008). Felsenfeld (2014) expressed the opinion of many that "there is no question that the initial signals to determine the activity state of a gene during development have to come from DNA sequence-specific transcription factors that recognize the regulatory elements associated with the gene".

The term epigenetics in its modern definition is highly problematic because many of the so-called epigenetic marks are not transmitted through cell division or the germ line: "Whatever you call them, they are mechanisms for the regulation of gene expression, and that's what you have to study". Similarly, Bird (2013) believes that the layers of genetics and epigenetics will be dissolved: "So the way in which genetics and epigenetics interact, I think, is dissolving the distinctiveness of epigenetics. And I think that's a good thing".

The recent rise of epigenetics is not, in the sense of Thomas Kuhn, a revolution, because research in chromatin modification, DNA methylation, etc. did not replace genetic and genomic research, but opened up new areas of research related to the old question of gene regulation in the development of higher organisms and to medical and other applications. Research called epigenetics does not call into question the paradigm of genomic information as a major cause of heredity and development. Concerning the longing for an overturning of this paradigm through new paradigms brought about by epigenetics, it may be useful to remember another idea of Kuhn, namely: "We have to relinquish

the notion, explicit or implicit, that changes of paradigm carry scientists and those who learn from them closer and closer to the truth" (Kuhn, 1962).

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