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Epigenetics: A way to bridge the gap between biological fields

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ABSTRACT

The concept of epigenetics has evolved since Waddington defined it from the late 1930s as the study of the causal mechanisms at work in development. It has become a multi-faceted notion with different meanings, depending on the disciplinary context it is used. In this article, we first analyse the transformations of the concept of epigenetics, from Waddington to contemporary accounts, in order to identify its different meanings and traditions, and to come up with a typology of epigenetics throughout its history. Second, we show on this basis that epigenetics has progressively turned its main focus from biological problems regarding development, toward issues concerning evolution. Yet, both these different epistemological aspects of epigenetics still coexist. Third, we claim that the classical opposition between epigenesis and preformationism as ways of thinking about the developmental process is part of the history of epigenetics and has contributed to its current various meanings. With these objectives in mind, we first show how Waddington introduced the term "epigenetics" in a biological context in order to solve a developmental problem, and we then build on this by presenting Nanney's, Riggs' and Holliday's definitions, which form the basis for the current conception of "molecular epigenetics". Then, we show that the evo-devo research field is where some particular uses of epigenetics have started shifting from developmental issues to evolutionary problems. We also show that epigenetics has progressively focused on the issue of epigenetic inheritance within the Extended Evolutionary Synthesis' framework. Finally, we conclude by presenting a typology of the different conceptions of epigenetics throughout time, and analyse the connections between them. We argue that, since Waddington, epigenetics, as an integrative research area, has been used to bridge the gap between different biological fields.

Epigenetics is currently one of the most active research domains in biology. It involves the study of a wide variety of biological phenomena such as cellular differentiation and development, metabolism, diseases, phenotypic variability, inheritance, evolution, behaviours, and even culture. The understanding of what epigenetics is has evolved since Conrad H. Waddington defined it from the late 1930s as a kind of conceptual tool that allowed him to integrate data in genetics and embryology. During its history throughout the advances of molecular, developmental, and evolutionary biology, epigenetics has become a multi-faceted notion with different meanings, depending on the biological discipline in which it is used.

The conceptual history of epigenetics has been the subject of several publications since 2000 (in particular, see Deichmann, 2016; Felsenfeld, 2014a, 2014b; Haig, 2004, 2012; Morange, 2013). Each of these historical reviews assesses the research advances, which have contributed to the rise of epigenetics. Some of them also highlight how the meaning of "epigenetics" has changed. The present article examines this general history of epigenetics, and, by drawing on some of these analyses (but without necessarily assessing each singular historical episode), re-examines how various meanings and uses of epigenetics have risen and changed over time. Our review work allows to emphasize some aspects of the recent history of epigenetics that most of the available studies have neglected: we do not focus only on developmental biology and molecular genetics, but expand our analysis to the way epigenetics has been conceived in evolutionary-oriented research areas (e.g., evolutionary developmental biology). The evolutionary implications of epigenetics represent today one of the major topics that leads the debate in this research area.[1] Moreover, evolutionary biology has recently widely referred to the term "epigenetics" while evolutionary biologists remain sometimes quite unaware of the historical

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[1] For a recent review, see Verhoeven, Vonholdt, & Sork, 2016, which introduces the special issue "Epigenetic Studies In Ecology and Evolution" of the journal Molecular Biology.

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uses of epigenetics in other fields of biology (e.g, embryology, genetics, developmental biology, and molecular biology).[2]

The aim of this article is many-fold. First, we analyse the transformations of the concept of epigenetics, from Waddington to contemporary accounts, in order to identify its different meanings and traditions, and to come up with a typology of epigenetics throughout its history. Second, we show on this basis that epigenetics has progressively turned its main focus from biological problems regarding development, toward issues concerning evolution (i.e. from understanding the underlying processes of differentiation to understanding also the mechanisms of epigenetic inheritance). Yet, both these different epistemological aspects of epigenetics still coexist. Third, we claim that the classical opposition between epigenesis and preformationism as ways of thinking about the developmental process is part of the history of epigenetics and has contributed to its current various meanings. Finally, we argue that epigenetics is from the beginning an integrative research area that, despite its various conceptions and practices, in each of its particular uses plays the role of an epistemological bridge between different biological fields.[3] Even though it is not central in our analysis, we also offer in the conclusion a definition of epigenetics, which is meant to be a useful working tool for those who want to stick to Waddington's project.

With these objectives in mind, we divide the article into two main parts, followed by a conclusion. The first part concerns the link between epigenetics and the problem of development. We introduce Waddington's initial uses of the term in a biological context, and explain what he had in mind when he first defined the term. Then, we present David L. Nanney's, Arthur D. Riggs and Robin Holliday's respective later definitions of epigenetics. A comparative analysis of these three conceptions enables us to reveal their differences as well as their connections in term of filiation. The second part concerns the link between epigenetics and the problem of the origin of phenotypic variation and evolution. We consider that an additional focus on evolutionary problems is to be seen in the context of the rising field of evo-devo studies. We explain how discussions about epigenetics have progressively paid attention to the question of (transgenerational) epigenetic inheritance in connection with discussions concerning a new extended (or expanded; cf. Gould, 2002, p. 3) evolutionary synthesis. We conclude by presenting a typology of the different conceptions of epigenetics throughout time, and tackle in which ways they are connected. We argue that, since Waddington, epigenetics has been used to bridge the gap between different biological fields.

1. Epigenetics and the problem of development

1.1. Waddington's epigenetics (W-epi)

Since the late 1930s, Waddington had been interested in the development of the embryo and, more particularly, in the way genes have an effect on this process. In his first reference book *An Introduction to Modern Genetics* (1939), he declared that both experimental embryology and genetics (also referred to as phaenogenetics) were essential to investigate "how an adult organism arises from the individuals of the previous generation" (p. 137). While experimental embryology investigated development by performing "experiments on its mechanisms", genetics examined "the changes produced in developing organisms by gene-changes" (p. 137). Thus, going against the traditional separation – which was artificial, according to Waddington – between genetics and other biological fields of that time, Waddington's project was to connect the data of embryology and of genetics, in other terms, to integrate the research results of Hans Spemann's school and of Thomas H. Morgan's school, in order to answer to the problem of development. In particular, he argued that "the general mechanism of the development of animals and the ways in which genes may act to control the course of the reactions" both "fall into the general investigation of how an adult organism arises from the individuals of the previous generation" (p. 137).[4]

In his 1939 book, Waddington offered for the first time a view of "development as an epigenetic process": he argued that the constituents of the fertilized egg, interacting, give rise to new types of tissues and organs which were not previously present. Waddington's main concern was to understand how this happens, in other words, how the genotype (usually defined as the sum of the genes contained in the fertilized egg; cf. Johannsen, 1911) can bring about phenotypic effects. Note that, in Waddington's view, the genotype is more than the sum of the genes: it is "the whole genetic system of the zygote considered both as a set of potentialities for developmental reactions and as a set of heritable units" (p. 155). The phenotype as well is not simply conceived as the final result of the developmental process, but rather as "the whole set of characters of an organism, considered as a developing entity" (p. 155). Waddington wanted to investigate the relation between the genotype and the phenotype thus conceived. By addressing the question "what does lie between the two?" he was taking into consideration "the development of differences within a single organism" rather than the differences between whole organisms at the genotype and phenotype level. He conceived of individual development as a whole complex network of processes which dynamically organize and construct tissues, organs – the entire organism – by interacting with the genotype and reacting to the external environment: the "epigenetic constitution" or the "epigenotype", as he called it (p. 156).

One year later, in *Organisers and Genes* (1940) Waddington both summarized the then available theoretical and experimental research regarding the developing embryo, and then discussed how genes act on a developing system. This book is where Waddington first introduced his idea of the "epigenetic landscape", as well as its representation, based on a drawing of his friend and artiste John Piper. He argued that "a fuller picture would be given by a system of valleys diverging down an inclined plane. The inclined plane symbolizes the tendency for a developing piece of tissue to move towards a more adult state. The sides of the valleys symbolize the fact that developmental tracks are, in some sense, equilibrium states" (p. 92). The interactions of genes with one another, and with the environment, come to define a developmental pathway. In this way, Waddington tried to condense two different views of two processes described differently but which are similar in his opinion. The first is the analysis of the sequence of reactions in response to diffusible substances, leading from the gene to the adult character (e.g., those depicted by Beadle, 1939; Ephrussi, 1938, 1939; see Waddington 1940, p. 77). The second is his branching-track system, where the presence or absence of particular genes acts by determining which developmental path shall be followed from a certain point of divergence (Waddington 1940, p. 83).[5]

It was not until his 1942 article, "The Epigenotype", that Waddington explicitly defined epigenetics as an investigation regarding the relation between phenotypes and genotypes. He conceived it as the study of the causal mechanisms at work in development by which "the

[2] In this paper, we have chosen to left aside other research areas in biology such as biomedical research. Despite the fact that epigenetics seems to play an increasing role in this context, it has appeared to us that the study of epigenetics in biomedicine raises conceptual issues but also, and above all, ethical and societal issues that, we claim, deserved to be fully addressed in a separate article.

[3] This argument is reminiscent of Star and Griesemer's work on "boundary concepts" (1989) and Löwy's considerations on the "strength of loose concepts" (1992). While not incompatible with these claims about the usefulness of flexible terms for the construction of scientific knowledge and for cooperation between different professional domains ("social worlds", in Star & Griesemer's words), we will show later that our claim, however, is different.

[4] The title of Waddington's 1940 book, *Organisers and Genes*, is meaningful in this respect. For further details, see Waddington's review (1935) of Morgan's book *Embryology and Genetics* (1934).

[5] For a detailed analysis of Waddington's representations of the epigenetic landscape, see Baedke, 2013.

genes of the genotype bring about phenotypic effects" (p. 18). In other terms, epigenetics is the study of the epigenotype, the whole complex of developmental processes that both sit between the genotype and the phenotype, and dynamically connect them. In this context, Waddington assumed that this sort of study required the integration of "what can be seen of the developmental process" – the phenotypes, from which geneticists reached conclusions about the mechanisms of inheritance and the hereditary units – and "what experimental embryology has already revealed of the mechanics of development". Thus, epigenetics was the accomplishment of his attempt to merge experimental embryology and genetics, development and inheritance, in order to explain the construction of organisms in terms of the action of both organisers[6] and genes. Actually, Waddington explicitly used the term "epigenetics" in this context because he wanted to focus on the classical theory of epigenesis, and so to stress the idea that an organism is not pre-formed in the zygote and just unfolds during ontogenesis. Rather, he argued, it is progressively constructed during the developmental process from the interactions of the original constituents of the fertilized egg (see also Waddington 1939, pp. 154–155; [1940] 1947, p. 91–93).

In order to precise and further develop his conception of epigenetics one could look at Waddington's later publications, such as *Principle of Embryology* (1956) and *The Strategy of the Genes* (1957). However, the bibliographical references used above provide enough information for the aim of this article. Actually, most of the authors who refer to Waddington to justify their own definition of epigenetics mainly quote his 1942 definition. Waddington's later work does not seem to have influenced their conception, at least not explicitly. This is why we have decided to focus our analysis, in this paper, on the assumed influences of Waddington.

1.2. The problem of development

This short presentation of the key ideas that Waddington started to introduce and discuss in the late 1930s and early 1940s shows that his principal concern was "the problem of development": how an adult organism is progressively constructed from a fertilized egg. This issue includes the central question of how cell differentiation occurs via the regulation of the action of genes (i.e., gene expression). In other words, closer to a more contemporary vocabulary: how cells of the same genotype do express differently their genes and so acquire distinct phenotypic features, giving rise to different types of cells, and then to different tissues and organs. These were Waddington's main worries and epigenetics was his tentative answer to them.

Other solutions to "the problem of development" were offered in the decades following Waddington's earlier publications regarding epigenetics.[7] After discovering genetic transposition in maize in the 1940s, Barbara McClintock formulated the hypothesis of "coordinated transposition" in order to account for gene expression during cell differentiation and development. She suggested that, in each cell nucleus, transposable elements could change their location along the chromosome, thus controlling the differential expression of genes. Her hypothesis was met with scepticism from the beginning. Moreover, over the decades that followed, several sets of experimental data discarded McClintock's hypothesis, in particular cloning experiments performed in the 1960s which showed the developmental capacity of nuclei of differentiated cells (Gurdon, 1962; Gurdon & Uehlinger, 1966). However, this should not detract from the recognition her work found later and still finds today: transposable elements and their epigenetic states (in particular, their methylation profiles) play a significant role in the regulation of downstream gene expression, as exemplified by the way the A^{vy} at the agouti locus in the mouse (Morgan, Sutherland, Martin, & Whitelaw, 1999) and the murine *axin-fused* allele (Rakyan et al., 2003) have been shown to be differentially expressed due to the DNA methylation state of a retrotransposon within them. Moreover, in her 1951 paper on the link between chromosome organization and genic expression, McClintock suggested that "chromatin that functions to control how the genic material may operate in the nuclear system" (1951: p. 29), in other words, that differential gene action depends on the chromatin conformation of alleles with no need of any change in the genes themselves. This idea has turned out to be fundamental for the understanding of cellular differentiation and development.

Around two decades later, in 1961, François Jacob and Jacques Monod introduced the operon model in order to explain the regulation of gene expressions in prokaryotes. In this model, a set of structural genes are under the control of adjacent regulatory genes, as in the case of the lactose operon in bacteria, where the expression of structural genes is negatively regulated by regulatory genes. More precisely, in the absence of lactose in the cell, a repressor factor produced by the regulatory gene *lac I* can link itself at the level of the operator (a regulatory region of the operon lactose), and thus represses the transcription of the structural genes *lac Z*, *lac Y*, and *lac A*, usually involved in lactose metabolism. Despite its tremendous impact on gene regulation research, many of Jacob and Monod's contemporaries, especially embryologists, were not happy with the operon model (see Morange, 2002, 2013). In fact, while the model explained gene regulation in prokaryotes, and in particular the progressive modification of gene activity via a cascade of regulatory genes, it couldn't explain global changes in gene expression and genetic regulation in eukaryotes. This was one of the strongest objections addressed by researchers outside microbiology, who did not believe at all that mechanisms described in bacteria could account for cell differentiation and for the development of multicellular organisms. As shown by Morange (forthcoming), this objection was more specifically motivated by the refusal of three essential features of the operon model: the mechanism of negative regulation (and thus gene activation as the result of a double inhibition), the existence of operons (i.e. sets of genes whose transcription is controlled by the same repressor), and the limited number of co-regulated genes.

Britten and Davidson (1969) proposed several years later an alternative theoretical model for the regulation of gene expression, namely the gene-battery model (also called Britten-Davidson model). The regulatory role of non-coding repetitive sequences, observed by molecular hybridization in the 1960s, and of their products (what they called "activator RNAs") are at its core. Moreover, the organization of the regulatory system in gene networks is also a fundamental feature of this model: it allows the simultaneous activation of a huge number of non-contiguous genes. Such an organization also accounts for evolutionary modifications, which are not due to the acquisition of new elements, but to new combinations of pre-existing parts of the system (i.e., by evolutionary tinkering). By proposing their model, Britten and Davidson addressed the shortcomings of the operon model, which they harshly criticized, by accounting for global changes of gene expression in a cell. As noticed by Morange (forthcoming), they did not explicitly build on the operon model to elaborate their own model, which they conceived as radically different and new. It should be noted, however, that both models of gene regulation have several similarities (e.g., the relations between different sorts of genes, the role of signals in gene activation, etc.) that their respective authors themselves did not acknowledge.[8]

Launched by the Britten-Davidson model, whose main molecular

[6] Since the experimental work of Hans Spemann and Hilda Mangold in the 1920s, the term "organizer" referred to a particular region of the embryo inducing morphological differentiation through chemical signals.

[7] Note that no mention of the term "epigenetics" can be found in these other solutions, even though they all looked for an answer to the problem of development as Waddington tried to do.

[8] For more details about the reasons why Britten and Davidson rejected the operon model see Davidson's 1968 book, *Gene Activity In Early Development*. About this issue, see also Morange, 2013 and Deichmann, 2016. For an insightful comparison of the two models, see Morange forthcoming.

features have since been abandoned because of their speculative nature (e.g., the existence of activator RNAs or the link between the abundance of repetitive sequences and their role in gene regulation), theoretical research on gene regulatory networks has expanded rapidly, especially thanks to Davidson himself (see, Davidson & Erwin, 2006; Davidson, 2006). It has proven to be a fruitful research strategy to identify the causal mechanisms involved in the developmental process.

1.3. Nanney's epigenetics (N-epi)

Back to the end of the 1950s another biologist – more precisely, a ciliatologist – was also both concerned with the problem of development, and used the expression "epigenetic" to talk about it. Nanney suggested introducing the distinction between two complementary, genetic and epigenetic control systems, both involved in the process of cell differentiation during development. The hypothesis of genetic control systems was consistent at that time with the recent research in chemical genetics, in particular with the discovery of the physico-chemical nature of the genetic material by James D. Watson and Francis H. C. Crick. The DNA sequence was considered as the depositary of the encoded information, which was preserved through cell division in virtue of a semi-conservative mechanism of copy and reconstruction of daughter strands from the parental DNA molecule. Template replicating mechanisms had been shown to maintain the "library of specificities", no matter whether they were expressed or not: they allowed the faithful conservation of the primary genetic material along cell lineages. But other mechanisms were needed in order to decode these specificities and to determine which of them should be expressed and when. Nanney called these auxiliary mechanisms "epigenetic control systems". He argued that they had different principles of operation than genetic control systems, and that their function was to regulate the expression of genetic potentialities. Despite their differences as regards to their role and operation mode, according to Nanney, both genetic and epigenetic control systems were involved in determining cellular characteristics.

It is worth asking why Nanney specifically used the expression "epigenetic control systems" rather than another subsidiary control system to genetic systems. In an insightful paper on the history of epigenetics, David Haig (2004) explains that the term "epigenetic" was not Nanney's first choice. Nanney initially contrasted genetic and paragenetic systems and, after presenting his ideas at a conference on extrachromosomal inheritance at Gif-sur-Yvettes (France), he changed the term "paragenetic" for "epigenetic". In his 1958 paper, he claimed that "the term 'epigenetic' was chosen to emphasize the reliance of these systems on the genetic systems and to underscore their significance in developmental processes" (1958, p. 712). He also made a reference to Waddington's *Principles of Embryology*, which had been published two years previously. On this basis, Haig argues that Nanney's hypothesis regarding what he came to call epigenetic control systems was at first independent of Waddington's works. But Haig also stresses that Nanney thought that the two meanings of "epigenetics", his own and Waddington's, were compatible. Following Haig, we argue that the overlap between these two uses of the term is significant. Both Nanney and Waddington aimed to solve the same problem, i.e., those of development and its associated processes. According to Nanney, cells with the same genotype can have different phenotypes because of the activity of epigenetic control systems, which "regulate the expression of genetically determined potentialities" (1958, p. 713). How could these differences in the activity of genes be maintained during the construction of the developing organism? For Nanney, the answer regarded a striking feature of epigenetic control systems: they are *mitotically stable*, i.e., differences in gene expression among cells are maintained during cell division. Such "cellular memory", as he called it, allows lineages of cells to maintain their differences so that they can participate to the construction of different parts (tissues and organs) in the developing organism.

What is the difference between Nanney's and Waddington's answers to the problem of development? We have just argued above that they had the same research interest[9]: both of them aimed at integrating genetics with the study of development. But genetics had experienced an important change at the beginning of the 1950s: it had become molecular since the discovery of the chemical nature of genetic material in 1953. Therefore, whilst Waddington's project was to merge classical (Mendelian) genetics and experimental embryology in order to find a solution to the problem of development, and thus contributing to the rise of developmental biology, Nanney looked for an answer to the same problem but with the advances of molecular genetics of his time. In other words, they did not look at the developmental process at the same level: Waddington investigated the relationship between the genotype and the phenotype at the level of the whole developing (multicellular) organism, and so conceived a large and inclusive notion of what epigenetics should study; whereas Nanney investigated the very same problem as Waddington's but he focused his attention on the intracellular level[10].

Nanney was a partisan of extra-chromosomal inheritance and was convinced that the majority of epigenetic control systems were situated in the cytoplasm, rather than in the nucleus (Haig, 2004). He was thus far away from the current idea that gene expression depends on epigenetic factors in the nucleus, such as DNA methylation, transcription factors or repressors, histone modifications and, more generally, chromatin structure. One of his contemporaries, Joshua Lederberg, had suggested that we should talk of "epinucleic information" in order to account for Nanney's epigenetic control systems. Lederberg's expression is closer to the current concept of epigenetic modification in molecular and cellular biology because it refers to "an aspect of the nucleic acid configuration other than the nucleotide sequence or in polypeptide or polyamine adjuncts to the polynucleotide" (1958, p. 385). Despite his accuracy, Lederberg's terminology (i.e. "epinucleic information") did not catch on amongst researchers, contrary to Nanney's (i.e., "epigenetic control systems"), which remained. Indeed, it actually turns out that Nanney's terminology and his definition of epigenetics is at the origin of the modern conception of molecular and cellular epigenetics, as we will show later.

1.4. Riggs' and Holliday's epigenetics (RH-epi)

The current conception of epigenetics in molecular and cellular biology finds its roots in the 1960s and the 1970s when a set of research advances, both theoretical and experimental, happened in molecular genetics.[11] Two of these advances are particularly significant: the discovery that the chromatin state may influence gene activity— hypothesis which already figured in McClintock's work on chromosome conformation in the 1950s and was then further established by Mary Lyon's work on X chromosome activity in mammals (1961, 1974); the discovery that DNA structure is structured in nucleosomes (which are complexes of DNA and histones). These two findings had been the result of a growing interest in genome complexity and organization, in eukaryotes, which triggered research on chromatin states (heterochromatin and euchromatin, which respectively refer to the condensed inactive and non-condensed active chromatin structure), and on the molecular structure of nucleosomes (e.g., the investigation of chemical

[9] This is true despite the fact that Nanney was a protozoologist, more precisely a ciliatologist, and was not dealing with multicellular organisms. As a matter of fact, in his 1958 paper, for instance, he explicitly and repeatedly refers to multicellular organisms when discussing his theoretical work on the main features of epigenetic control systems.

[10] Based on this difference, Haig (2004) argues that each of them – Waddington and Nanney – are at the origin of two specific meaning of epigenetics. We will show later that this is one of the possible readings of the conceptual history of epigenetics (the second, in section 3).

[11] For more details about all these research advances in the 1960s and 1970s, see Morange, 2013 and Deichmann, 2015, 2016.

modifications at the level of histones).[12] From this moment, the problem of development was open to receiving an answer at the molecular level.

In 1975, Riggs and Holliday, independently from one another, first offered a molecular solution to the problem of development with their pioneering works. They both had the same hypothesis: DNA methylation (i.e., a chemical modification of the DNA sequence) influences gene expression, while its mitotic stability explains cell differentiation and development.[13] But none of them used the term "epigenetic" to talk about DNA methylation. The term appeared some years later, in Holliday's 1979 paper about the theory of carcinogenesis, and then in many of his successive papers.

Both Riggs and Holliday focused on what Nanney had called "cellular memory". They saw it as the central feature to account for cell differentiation and development. As in the case of Nanney's epigenetic control systems, the stability of DNA methylation patterns during cell division – the fact that these patterns are "somatically heritable" from cell to cell in Holliday's terms – allows an explanation of how cell lineages maintain their differentiated state and so enable the process of development. More precisely, both Riggs and Holliday predicted the existence of specific enzymes that add methyl groups to the DNA sequence, either in a region-specific manner, or by interacting with other proteins. Note that, at that time, they also both considered DNA methylation patterns as "heritable" through mitotic cell divisions. However, they did not say anything about the possibility that such DNA methylation patterns could be "heritable" (i.e., stable) through meiosis too – which implies inheritance at the organism level from one generation to the next.[14]

It was only from the 1990s that such a molecular, and even intranucleic, conception of epigenetics started being used more and more in molecular and cellular biology. At that time, experimental arguments in favour of DNA methylation as a mechanism controlling gene activity had accumulated since the initial, independent, suggestions by Riggs (1975) and by Holliday and Pugh (1975) (see Morange, 2013). Moreover, as noticed by Deichmann (2015), the study of DNA methylation and of the mechanism of histone modifications started to converge in the 1990s, whereas they had developed separately from one another before. It was indeed in the 1990s that Holliday provided a more precise definition of what he called epigenetics: "the study of the changes in gene expression which occur in organisms with differentiated cells, and the mitotic inheritance of given patterns of gene expression" (Holliday, 1994, p. 453). And he clarified what he meant by "to be *somatically heritable through cellular mitotic division*" (i.e., "nuclear inheritance which is not based on differences in DNA sequence", Holliday, 1994, p. 454). His hypothesis regarding DNA methylation as an epigenetic process, as well as Riggs', have thus represented a decisive step towards the current view of what epigenetics is – both at the molecular and cellular level. In 1996, Russo, Martienssen and Riggs finally defined epigenetics as: "the study of mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence" (Russo, Martienssen, & Riggs, 1996, p. 1). What has become one of the most quoted and commonly used definitions of epigenetics in molecular and cellular biology points at three specific and defining features: 1) the cellular stability or the 'memory' of epigenetic changes (which is often expressed, improperly[15], by the term "heritable[16]"); 2) the impact of epigenetic changes on gene expression/gene function[17]; and 3) the fact that whatever the changes are, they do not involve modifications of the DNA sequence. These three features were already present in Nanney's conception of epigenetic control systems, but in looser terms and as theoretical hypotheses because of the great difficulties, at his time, regarding experimentally testing them. As mentioned previously, Haig claims that this puts Nanney at the origin of a specific tradition in epigenetics, which is now represented by the current use of the expression "molecular epigenetics".

But what is the relationship between such a tradition and Waddington's conception of epigenetics? Even though, as has already been shown, both Nanney and Waddington had in common the problem of development, we will also argue that Waddington's view is at the root of another tradition in epigenetics, which coexists today with molecular epigenetics, and whose field of research is evolutionary developmental biology (also called "evo-devo"). Therefore, molecular epigenetics can be linked to Waddington's epigenetics through his interest in the problem of development. But Waddington's epigenetics, through the recent extension of his general project which aimed at bridging the gap between embryology and genetics, and later with evolution too, is also linked to another research domain (i.e., the evo-devo). Before coming back to this other tradition, let's look more precisely to what molecular epigenetics is today.

1.5. Molecular epigenetics today (M-epi)

We have argued previously that one of the currently most popular views regarding epigenetics in molecular and cellular biology corresponds to Riggs' and Holliday's conception. Their conception has, however, received a number of more or less equivalent reformulations during the past two decades. Russo et al.'s formulation in 1996 (quoted above) is a paradigm example, among others (see, for instance, Bird, 2007; Egger, Liang, Aparicio, & Jones, 2004; Pembrey et al., 2005; Richards, 2006; Skinner, Manikkam, & Guerrero-Bosagna, 2010; Weigel & Colot, 2012), of the current understanding of the notion. However, we would agree with Haig (2012) that the label "epigenetic" is now also used to refer to any chromatin modification affecting gene expression, whether it is mitotically and/or meiotically stable *or not*. Such conceptual loosening has happened by the turn of the century with the inclusion among epigenetic mechanisms of histone modifications, and later on of the action of non-coding RNAs, before knowing whether they are heritable or not.[18] Recent researches have indeed progressively relaxed one of the main conditions – and even a *conditio* sine *qua non* – of Nanney's conception of epigenetics, this being the stability (or heritability) of epigenetic changes. While still coexisting with it, a looser and more inclusive meaning of what epigenetics is, at the molecular level, has thus emerged: it applies to the alterations of

[12] About the study of chromatin, its history, its current research and the philosophical questions it raises, see Deichmann, 2015.

[13] There is no apparent link between research results about chromatin effects and Riggs' and Holliday & Pugh's hypothesis of DNA methylation. As suggested by Morange (personal communication), if there is a direct route it rather lies between chromatin effects and the discovery that histones can have an inhibitory role (Allfrey, Faulkner, & Mirsky, 1964).

[14] Holliday considered such a possibility in his 1987 paper, "The Inheritance of Epigenetic Defects" where he mentioned and discussed the evidence, new at that time, of transmission of altered methylation patterns through the germline.

[15] See Skinner (2011) for a critical discussion of the distinction between "mitotic stability" and "inheritance".

[16] Note that meiotic heritability of epigenetic changes is now explicitly mentioned as a possible mechanism of epigenetic stability at the cellular level. Anyway, in the 1990s, only a few uncontroversial cases of transgenerational inheritance, from one generation of multicellular organisms to the next, had already been observed, in particular in plants (for a review, see Jablonka & Raz, 2009). We will come back later to this additional feature of epigenetics and its link with current debates about transgenerational epigenetic inheritance.

[17] Note that talking about « the impact of epigenetic changes on gene expression » or « on gene function » involves a different experimental quantification of this impact. In the first case, one looks at the RNA transcripts, on the second case one looks at the proteins products. This illustrates how definitions can have consequences on experimental practices (Christoph Grunau, personal communication).

[18] For instance, see the definition of epigenetics by the journal *Nature*: "Epigenetics is the study of molecular processes that influence the flow of information between constant DNA sequence and variable gene expression patterns. This includes investigation of nuclear organization, DNA methylation, histone modification and RNA transcription. Epigenetic processes *can* result in intergenerational (heritable) effects as well as clonal propagation of cell identity without any mutation change in DNA sequence" (emphasis added), (https://www.nature.com/subjects/epigenetics).

gene activity that are not due to changes in the DNA sequence but are due to other molecular mechanisms such as histone chemical modifications, changes of the chromatin structure, and actions of non-coding RNAs. Some of these mechanisms have not been shown (at least, not yet) to be preserved through cell division and proliferation, and still they are qualified, in the literature, as "epigenetic mechanisms": their stability/heritability is no more a *conditio* sine *qua non* of epigenetics. Consequently, any phenotypic variation that is not attributable to genetic (DNA sequence) variation but to any other molecular modification of the chromatin could actually be considered, broadly speaking, as epigenetic.[19] This broader definition tends to be adopted by those researchers who study how cellular differentiation and embryogenesis are epigenetically regulated, and who are not particularly concerned by the question of heritability and, more broadly, by evolutionary issues.

2. Epigenetics and the problem of phenotypic variation and evolution

2.1. Evo Devo epigenetics (ED-epi)

Throughout the 1990s and 2000s, various independent definitions of epigenetics have been used in the context of the emerging field of evolutionary developmental biology (evo-devo), which in the 1980s had seized upon the developmental question in order to investigate the relationship between development and evolution, and, if possible, formulate a new theoretical synthesis between them (Coleman, 1980; Gould, 1977; Hamburger 1980; Lauder, 1982; Wallace, 1986)[20]. Despite its internal diversity in terms of epistemological and methodological strategies, research in evo-devo is generally focused on the study of the genotype-phenotype map: it studies the role of developmental mechanisms on the origin of phenotypic variation and its evolution. Other core problems also include species specificity of development in different environments over evolutionary time, and the question of evolution of new body plans characterized by different patterns of development. In this research context, evo-devo biologists often refer to Waddington's notion of epigenetics, to his metaphor of the epigenetic landscape, and sometimes to his work on genetic assimilation: they see him as the first author who tried to open the developmental blackbox and to disentangle the complex relationship and processes between the genotype and the phenotype.

All definitions of epigenetics that have been proposed in the evo-devo literature during the last twenty years see Waddington as their source of inspiration. Some of them are, however, closer to the current view of molecular epigenetics (having its origin in Nanney's work, see part 1): they focus on intracellular mechanisms that cause phenotypic variation by gene expression's modification. Gilbert and Epel (2009), for instance, define "epigenetics" as the study of "those genetic mechanisms that create phenotypic variation without altering the base-pair nucleotide sequence of the genes." They add, more specifically, that they "use this term [epigenetics] to refer to those mechanisms that cause variation by altering the *expression* of genes rather than their sequence" (p.12). They explicitly refer to the idea of change in gene expression, which contributes towards focusing their definition of epigenetics on the developmental process, and therefore at the level of the whole individual organism. However, it seems that their definition sheds some of the traditional key features of the epigenetic mechanisms – namely their stability/heritability, which is a central feature in order to account for how cell differentiation can take place. Development, in particular the genotype-phenotype map, is still considered a problem, as attested by the large number of references to Waddington. However, the meaning of epigenetics, with these authors, seems to shift towards another issue, i.e., those of the origin of phenotypic variation during the developmental process.

Most of the time, though, very broad definitions of epigenetics appear in the evo-devo literature: they cover many levels of biological organization (from the molecular to the species level), and they apply to a huge diversity of mechanisms at different spatial and temporal scales (such as gene expression, phenotypic plasticity, developmental canalization and developmental stability, morphological integration, ecological interactions, etc.). For instance, Benedikt Hallgrimsson and Brian K. Hall define epigenetics as "the study of emergent properties in the origin of the phenotype in development and in modification of phenotypes in evolution." Consequently, they consider that "[f]eatures, characters, and developmental mechanisms and processes are epigenetic if they can be understood only in terms of interactions that arise above the level of the gene as a sequence of DNA" (2011, p.1). They add that "[e]xplanations of development and evolution that focus on properties of processes or pathways […] are epigenetic explanations. [And] the relevant part of the explanations for phenotypic variation are at the level of the interactions among gene products, among cell populations, and among the processes generated that link the two levels [genotypic and phenotypic]" (2011, p. 1–2). Their definition is particularly broad because it includes disparate phenomena, documented in the book edited by Hallgrimsson and Hall, pertaining to individual organisms but also to natural populations and even to biological species[21]: molecular phenomena, such as modifications of DNA methylation, and other chromatin chemical changes affecting the structure and function of genes (see chapter 5); phenomena at the level of cells and tissues, for instance, inductive interactions between two cellular populations and creating a third one (see chapter 9 & 11), interactions between the activity of muscles and bones which can affect the morphology of the latter (see chapter 13); and phenomena at the populations and species level such as phenotypic changes of preys (for instance, in plankton) due to chemical elements coming from predators (see chapter 19). Therefore, any interaction above the level of the DNA sequence, and which has an impact on phenotypic variation is "epigenetic" according to their definition, no matter whether or not it is stable (or heritable), and whether or not it produces phenotypic change by directly affecting gene expression. It is, however, clear that, in this case, the developmental process is part of the issue at stake even if it is only one issue among others: the main problem being rather the origin of phenotypic variation through the interactions at various levels of biological organization and the modification of the phenotype over evolutionary time.

If the purpose of evo-devo was from its origin to gather different fields, data, and problems of biology within a same general framework, it has probably succeeded, albeit to the detriment of certain notions, which had precise definitions in some fields and lost them through the connection of different fields (e.g. molecular epigenetics from molecular biology, or phenotypic plasticity from quantitative genetics, are becoming fuzzier within evo-devo, as shown with the broad definition of epigenetics above). Maybe, this is the price to pay for gathering different research fields. As shown by Star and Griesemer (1989) and by Löwy (1992) amongst others, the use of loose concepts can have a heuristic value: their "boundary" nature can facilitate contact and

[19] For a critical view on such loose and more inclusive molecular definition of epigenetics, see Ptashne, 2007.

[20] Various sub-traditions or research programs coexist in evo-devo (see Müller et Newman 2005). Two of them are particularly apparent: studies in developmental genetics about the origin of morphological diversity (Carroll, 2008) and studies looking for developmental solutions to unexplained evolutionary issues, such as the origin of phenotypic novelty/innovation (Hall et al., 2003; Müller & Newman, 2003). One of the main difference between the two resides in the different way they provide an answer to Wallace's challenge, to wit, the idea that developmental and evolutionary explanations are incommensurable (Nicoglou, 2011; Wallace, 1986; see): the first sub-tradition is on Wallace's side and considers that developmental and evolutionary explanations cannot be unified; the other, on the contrary, suggests that the distance between development and evolution can be overcome by looking into the developmental blackbox.

[21] See chapter 23 of *Epigenetics: Linking Genotype and Phenotype in Development and Evolution* (2011) for a synthetic summary of the book, its main objectives and results.

interactions between different domains, and allow common and federative research strategies.

Epigenetic inheritance is an example of such loose notions that do not just have one precise meaning because they are used throughout a set of different biological fields. At the same time, it can be seen as a "boundary concept", in Star and Griesemer's words: its nature, both "plastic" and "robust", allows it to inhabit interacting research fields (namely, developmental biology, evolutionary biology, systems biology). Let's now look at the appearance of this notion.

2.2. From mitotic stability to transgenerational inheritance

What if the stability/heritability of epigenetic modifications was not limited to intra-generational transmission, from cell-to-cell in a developing organism, but also applied to transmission from one generation of organisms to the next? What would be the consequence of this for epigenetics and its scope? In the previous section, we mentioned that current definitions of epigenetics in molecular and cellular biology refer to mitotic and meiotic stability of chromatin modifications affecting gene expression. This means that epigenetic modifications could be passed on across generations of organisms too: through mitotic cell divisions in unicellulars and in asexual organisms, and through meiotic cell divisions in the germline in sexually reproducing organisms. On such a view, epigenetic inter- (and even *trans*-) generational inheritance[22] becomes more than a mere hypothesis. The possibility of transmission between generations of epigenetic variation could have an important impact on the evolutionary process, and this precisely in virtue of its heritability. Therefore, the theory of evolution should take it into account when trying to better predict and explain the evolution of natural populations.

The next section regards another conception of epigenetics that we call "Extended Synthesis epigenetics" (ES-epi) because its partisans were motivated by the project of integrating epigenetics, and in particular epigenetic inheritance, into evolutionary theory. This conception springs out from evo-devo but, because of its focus on the heritability aspect of epigenetics, it has defined its own meaning of "epigenetics". Regarding this meaning, we show that, from Nanney's cellular memory of epigenetic changes, through Riggs' and Holliday's idea of mitotic and meiotic heritability, through to the very possibility of epigenetic transgenerational inheritance, the way some biologists understand epigenetics has progressively changed from a developmental centred view to an evolutionary one.

2.3. Extended Synthesis epigenetics (ES-epi)

Eva Jablonka's works with various collaborators (in particular, Lamb, Lamm, and Raz) provide a good case for presenting the latter meaning of epigenetics we analyse in this paper. She adopts a definition of epigenetics which synthetizes some aspects of Nanney's tradition (namely, epigenetic mechanisms as control systems involved in cell determination and differentiation by regulating gene activities without altering the DNA sequence) with Waddington's view (epigenetics as the study of the epigenotype, i.e. the complex network of developmental mechanisms between the genotype and the phenotype, underpinning developmental plasticity and canalization, and producing persistent phenotypic effects).[23] In a 2011 paper Jablonka and Lamm argue that today epigenetics "has become a more specific term": it currently refers to "the study of the mechanisms that lead to persistent developmental changes in gene activities and effects, but do not involve altered DNA base sequences" (p. 4). They recognize that cellular stability or memory is central for development to take place and, at the same time, they recall that Waddington did not focus his work on cell heredity, or indeed even mention it. However, they then claim that "cellular epigenetic inheritance […] fits beautifully into his [Waddington's] view of the epigenotype with its myriad of stabilizing mechanisms" (p. 4). In a way, Jablonka and Lamm acknowledge that the notion of epigenetics has changed since Waddington's formulation; but, at the same time, argue that his more general understanding of epigenetics is still relevant, in as far as it includes and applies to all epigenomic factors that we know today and which are part of "the great developmental-heredity-evolution entangled web" (p. 4).

Particularly devoted, over many years, to emphasize the role of developmental processes and non-genetic forms of transmission in evolution (Jablonka & Lamb, 1995, 2005), Jablonka has focused her theoretical research on one component of epigenetics – epigenetic inheritance – that she also calls "epigenetic memory" (Jablonka, 2013). This refers to "when phenotypic variations in DNA base sequences are transmitted to subsequent generations of cells or organisms" (p.132). She distinguishes between a broad and a narrow sense of epigenetic inheritance (Jablonka & Raz, 2009), and concentrates her investigation on the latter, to wit, cellular transgenerational epigenetic inheritance, which "refers to epigenetic transmission in sexual or asexual cell lineages, and the unit of this transmission is the cell" (p.132). In other words, she focuses on epigenetic inheritance through cell divisions, rather than through developmental interactions between organisms (mother-offspring interactions, social learning, symbolic communication, etc.). In particular, her focus lies in between-generation epigenetic transmission that, in sexually reproducing organisms, goes through the germline and so involves a single-cell "bottleneck" (a gamete or a spore).[24] Why so? Because, she argues, the consequences of transgenerational epigenetic inheritance through gametes "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" (2013, p.99). Jablonka's purpose is to show that the traditional theory of evolution, the Modern Synthesis, should be revisited in favour of a new Extended Evolutionary Synthesis (see also Pigliucci & Müller, 2010), which would integrate, among other things, non-genetic forms of transmission. Epigenetics, and especially transgenerational epigenetic inheritance, should thus be taken seriously in order to gain new insights into the evolutionary thinking (see for instance Danchin & Pocheville, 2014). On this view, focused on the heritability aspect of epigenetics, the problem of development merges with evolutionary issues. Even more than that, the answer to the problem of development becomes one means to challenge the traditional view of evolution, addressing the question of how it should change, and profoundly rethinking it with a view to ensure an Extended Evolutionary Synthesis.[25]

To sum up, the work of Jablonka and colleagues is a paradigmatic case of an evolutionary centred view of epigenetics. It combines two different views (Waddington's and Nanney's), which belong to two different research areas (developmental biology and molecular

[22] We use the expressions "intergenerational inheritance" to refer to the transmission from one generation of organisms to the next and "transgenerational inheritance" for the transmission over more than one generation of organisms.

[23] See, in particular, Jablonka & Raz, 2009, Jablonka & Lamm, 2011.

[24] Note that transgenerational epigenetic inheritance is far from being uncontroversial. While it is accepted on an experimental base for many unicellular organisms (for instance, ciliates; Nowacki & Landweber, 2009) and for plants (several studies have been done with *Arabidopsis thaliana*; Johannes et al., 2009, Becker et al., 2011, Schmitz et al., 2011), it is still an open issue in the case of mammals because of the series of reset mechanisms taking place in the germline at each generation. This is not, by the way, our concern here. For a critical discussion on gametic transgenerational inheritance of epigenetic modifications, and in particular about its differential significance in different kingdoms, see Heard & Martienssen, 2014.

[25] We have chosen to discuss Jablonka's work because it is particularly representative of this view of epigenetics and its scope. Several other authors are on the same line as hers and conduct their research with a view to an Extended or Expanded Evolutionary Synthesis: for instance, see Bonduriansky & Day, 2009, Pigliucci & Müller, 2010, Heläntera & Uller, 2010, Bonduriansky, Crean, & Day, 2012, Danchin et al., 2011, Mesoudi et al., 2013, Laland et al., 2015.

Table 1
Summary of the different conceptions of epigenetics, their definitions of the term (or what they intend to study), the fields concerned and the problems they try to solve.

Conception	Definition The study of	Fields	Problem
W-epi (*Waddington's epigenetics*) 1940s	Causal mechanisms at work in development, by which the genes of the genotype bring about phenotypic effects. (1940s)	Classical genetics and experimental embryology → developmental biology	Development (at the organismal level)
N-epi (*Nanney's epigenetics*) 1950s-60s	Auxiliary integrative systems regulating the expression of genetic potentialities.	Chemical (molecular) genetics and developmental biology	Development (at the cellular level)
RH-epi (Rigg's and Holliday's epigenetics) 1970s → 1990s-2000s **&** **M-epi** (Molecular epigenetics) 2000s-10s	Mitotically and/or meiotically heritable changes in gene function that cannot be explained by changes in DNA sequence. Any chromatin modification affecting gene expression, whether it is heritable or not.	Molecular genetics and epigenetics	Development (at the molecular level)
ED-epi (Evo-Devo epigenetics)	Developmental mechanisms (above the level of DNA sequence) at the origin of the phenotype and its modification across evolution (1990s-2010s).	Developmental genetics Evo-devo biology Systems biology	The origin of phenotypic variation and the interplay between development and evolution
ES-epi (Extended Synthesis epigenetics)	Mix of N-epi & ED-epi; Focus on transgenerational epigenetic inheritance (2000s- 2010s).	Evo-devo biology Evolutionary biology Systems Biology	The origin of phenotypic variation and evolution → Towards an extended (or expanded) synthesis

biology), with the objective of solving open evolutionary issues.

3. Conclusion

In this paper we have identified and analysed different ways in which epigenetics has been conceived and defined historically, from Waddington's initial introduction of the term to its current and evolving various uses in biology. This allows us to establish the following typology (of conceptions of epigenetics) represented in Table 1.

There are two possible ways to understand this table.[26] One of them follows the structure of the present article and corresponds to the first main result of our analysis. There are two different approaches concerning epigenetics, which differ with respect to the problem they address: those who raise the problem of development (including Waddington's, Nanney's, Riggs' and Holliday's works until current studies in molecular and cellular biology); those who raise the problem of the origin of phenotypic variation and its evolution (including the studies in Evo-Devo and its recent discussions concerning the possibility of an Extended Evolutionary Synthesis). Thanks to this first reading, we have shown that there has been a change in the focus of epigenetics during its history, from issues focusing on development (embryology) to issues directed towards evolution. These two ways of conceiving the explanatory target of epigenetics still coexist today but are often located in different research areas in biology (i.e., respectively, cell differentiation studies, and evolutionary studies). The other possible way to understand the table covers and enriches Haig's reconstruction of the dual origin of epigenetics (2004). It brings to light two different epistemological traditions, which rely respectively on Waddington's and Nanney's work. Evo-Devo epigenetics (*ED-epi*) and Extended Synthesis epigenetics (*ES-epi*) both belong to Waddington's tradition, whereas Riggs' and Holliday's epigenetics (*RH-epi*) and current molecular epigenetics (*M-epi*) belong to Nanney's tradition. Our contribution to Haig's analysis consists in stressing that these two co-existing traditions of epigenetics reflect the classical opposition between epigenesis and preformationism as two ways to conceive and account for development. Waddington's tradition includes the idea that organisms are progressively constructed throughout time due to various kinds of developmental interactions, i.e., development as epigenesis. This has led to the emergence of developmental genetics to be later integrated into evolutionary studies. Nanney's tradition includes the idea of a preformationism, according to which auxiliary molecular factors and mechanisms are needed in order to read/decode DNA sequence information. This tradition succeeded in promoting molecular genetics, including all its recent "epigenetic" developments.

It is useful to understand these distinctions and so recognize that to the diversity of meanings, uses, and practices of epigenetics respond the plurality of research interests, the various key issues biologists address, and their different epistemological stances and commitments. Despite the diversity we highlight, epigenetics appears as an important research area in biology; it has already received a certain recognition within the scientific community (as meetings, labs, and journals attest). Therefore, it becomes urgent to have a clear view of the history of the different research projects embedded into the label "epigenetics". Notably, Waddington's project was to merge experimental embryology and genetics; Nanney attempted to bring together developmental biology and molecular genetics with molecular and cellular biology; and some Evo-Devo studies look towards an Extended Synthesis connecting developmental and evolutionary biology. Throughout its history, as well as today, and irrespective of its specific conception and definition, epigenetics has proved to be an integrative research field, an epistemological bridge, which allows combining different fields in biology. In other words, despite its multi-faceted nature, each particular use of the notion of epigenetics has been shown to be a way, or at least an attempt, to integrate research results from different biological fields, thus participating to the construction of further knowledge.[27] As already mentioned above (see footnote 3), such a claim may sound like Löwy's or Star and Griesemer's works on the role of boundary concepts. While compatible with the considerations of these authors, our claim is different: we less focus on the loose nature of the concept of epigenetics than on what is common to its different conceptions and characterizes each of them, even when they are defined in precise terms: to be an epistemological bridge between biological fields.

The results of our analysis does not forbid us to offer a definition of epigenetics in light of how we have offered a clarification of its different

[26] This table is not meant to be exhaustive but it attempts to give the key features of the different meanings of epigenetics where it is commonly and mainly invoked. As we announced in the introduction (footnote 2), we decided to exclude, for instance, physiology, immunology and biomedicine from our study; one of the next steps would be to integrate these fields too in our historical and epistemological analysis.

[27] On could also argue that the notion of epigenetics sometimes tends to cause confusion in the study of living organisms because the fundamental differences between epigenetic systems in different species are often neglected (e.g., the distinct influence of epigenetic inheritance in plants and in animals). Indeed, this can lead to careless extrapolation of experimental results and global interpretations across different kingdoms. We thank an anonymous referee for this insightful remark.

domain of research throughout its history. We argue that our definition could be a useful working tool for biologists who want to stick to Waddington's view (since most of them continue to quote Waddington's 1942 article): in providing an answer to the problem of development, in mapping what lies between the genotype and the phenotype, and in line with more recent molecular results in developmental biology.

We thus propose the following definition of epigenetics: Epigenetics is *the study of various intracellular factors that have an effect on the stability of developmental processes through their action on genome potentialities (i.e., the genome susceptibility to be differentially expressed)*[28]. This definition contains two cores features of one of the currently most popular view of epigenetics in molecular and cellular biology (Russo et al., 1996): 1) factors and mechanisms which remain stable throughout development (cellular memory of epigenetic changes), 2) which affect the genome expression. But our definition explicitly leaves aside the claim that epigenetic changes do not involve modifications of the DNA sequence. Of course we agree with this claim, which is motivated by the methodology used by biologists to study the phenotypic effects of epigenetic phenomena (when they try to keep stable DNA sequence); however, we think that such a claim does not allow to grasp the interdependence between epigenetic factors and the genome along the developmental process.

As regards to the other conceptions of epigenetics, our definition does not mention evolution as it is focused on the problem of development but it doesn't mean that it is at odds with the idea of epigenetic inheritance. Indeed, one could conceive it as a starting point to further study the stability of development across generations. Furthermore, our definition could be useful for those who want to avoid overly broad definitions of epigenetics – as we find sometimes in Evo-Devo studies (e.g. see section 2.1). It would also help to avoid misuses and confusions about "epigenetics" as it appears in the media, where it is often presented as providing the answers that genetics has failed to provide: in particular, epigenetics would reveal how to control the expression of our genes (e.g., by changing our dietary and lifestyle conditions), and thus build a better future for us, and for our children and grandchildren.[29]

Finally, we conclude that in line with our definition, epigenetics should not be understood as "epi-genetics" (i.e. what is above or upon genetics). The term "epigenetics" in Waddington's view did not refer to an additional layer above the genes and of different nature; he rather meant that development is a genetic process during which genes are differentially and selectively expressed, and thus progressively construct the individual organism: development was an epigenesis for Waddington (see Gilbert, 1991; Speybroeck, 2002; Peterson, 2017a, 2017b). Indeed, those who would like to define epigenetics should keep in mind the nature of his initial project: to bridge the gap between development (understood as epigenesis) and genetic mechanisms. The current challenge for biologists today will, then, be to assess how they understand each of these two poles before trying to bridge them.

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[28] Note that this definition applies to DNA methylation as well as other chemical changes (acetylation, phosphorylation, etc.), histone modifications, changes of chromatin structure, transcription factors as well as small (non coding) RNAs.

[29] For instance, in an article published in *Time Magazine* (January 6, 2010) epigenetics is depicted as a new science revealing "how the choices you make can change your genes—and those of your kids". Actually, the title of this article is "Why your DNA isn't your destiny". See also Mukherjee's epigenetics article "Same But Different", published in the 2 May issue of *The New Yorker*, and the paper two researchers, Ptashne and Greally (2016), posted to criticize the inaccurate way Mukherjee (2016) presented gene regulation processes. (https://whyevolutionistrue.wordpress.com/2016/05/06/researchers-criticize-the-mukherjee-piece-on-epigenetics-part-2/).

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