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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.