Part I
General Introduction

Epigenetics and Human Health
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The Research Program in Epigenetics: The Birth of a New Paradigm

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Abstract

This introductory chapter sketches a short history of the concept of epigenetics, from Waddington to today. The chapter outlines the promises associated with the development of epigenetic research, particularly in the field of cancer, and the still unmet challenges, with several examples.

The recent discovery that humans and chimpanzees have essentially the same DNA sequence is simply revolutionary. The obvious question is "why then do they differ so widely"? Obviously, there is something else other than the DNA sequence that explains differences among species. An even more revolutionary advancement could then be the discovery that what makes the difference is a certain pattern of methylation of CpG islands in key genes, for example for the olfactory receptors in chimpanzees (unmethylated) and for brain development in humans. Though this is still speculation, there are great expectations from epigenetics/omics to fill the gaps left by genetics/omics.

If we consider Thomas Kuhn's description of the advancement of science through a sequence of revolutions (leading to paradigmatic leaps), we can probably conclude that epigenetics is definitely a new paradigm. According to Kuhn there are several ways in which a new paradigm arises. Usually this implies a more or less profound crisis of the existing theory, the development of alternative theories – without sound observations yet – and possibly a technological leap forward. These three conditions hold for the shift from genetics to epigenetics, though not necessarily in the order I have suggested.

In a way, a theoretical model for epigenetics (the one by Waddington, who coined the term) came first historically, when genetics was still flourishing. Then several signs of crisis emerged, and now the technological developments allow one to study epigenetic changes properly. To be clear, when I say that the genetic paradigm is in a crisis, this may seem at odds with the successes of genome-wide association studies (GWAS) in 2007–2008. In fact, by crisis I mean (i) the obvious

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gap – referred to above – between DNA sequencing and the ability to explain, for example, differences between species; and (ii) the emerging failures of the paradigm that until very recently strictly separated genes from the environment, according to the neo-Darwinian view. On the one hand we had the environmental exposures, that could cause somatic mutations, or cause chronic diseases by several mechanisms not involving DNA. On the other hand, we had inherited variation, but the link between the two was not straightforward. Recently, to fill the gap the theory of gene–environment interactions (GEI) was coined, with not much success, or at least not the kind of success that was expected. Not many good examples of *bona fide* GEI are available today. Ten years ago, for example, people expected that variants in DNA repair could explain much of cancer variation, in particular in relation to exposure to carcinogens, but a recent synopsis on DNA repair variants in cancer done by us [1] showed surprisingly few associations. Also GWAS led to the discovery of not many variants strongly associated with cancer (with relative risks usually lower than 1.5). In addition, the patterns of association were rather unusual with some regions or SNP associated with several cancers or several diseases, like in the case of 5p15 [2]. Ironically, for 8q24 not only have multiple associations been found, but also the implicated regions are non-coding regions, shedding light probably on some regulatory mechanisms involved, that is, exactly epigenetics.

Well before the gene–environment divide fell into a crisis, Waddington coined his theory of phenotypic plasticity and epigenetics. Waddington referred to epigenetics as an amalgam between genetics and epigenesis, where the latter is the progressive development of new structures. Waddington related epigenetics very much to embryonic development, and put forward the idea that the latter is not entirely due to the "program" encoded in DNA, but depends on environmental influences [3]. His definition of epigenetics is extremely modern: "the causal interactions between genes and their products, which bring the phenotype into being", that echoes a contemporary definition: "the inheritance of DNA activity that does not depend on the naked DNA sequence" [4].

Coming to the present time, the study of epigenetics has definitely been enabled by recent technological advancements, that allow us to investigate DNA methylation, histone acetylation, RNA interference, chromatine formation and other signs of epigenetic events.

What is new in this paradigm? First, it refers not to structural but to functional changes in DNA (gene regulation). Second, we are observing continuous quantitative changes, that is, nature seems to work in degrees, not according to leaps like mutations: the ratio between hypo- and hyper-methylation, for example, seems to be very relevant to cancer. Third, epigenetic changes are reversible: as some chapters in this book show, nice animal experiments have been conducted with dietary supplements that were able to reverse methylation patterns. Fourth, epigenetic patterns seem to be heritable (though this may be the weakest part, since the evidence is not entirely persuasive). Fifth, epigenetic changes fill the gap between genes and the environment: the mysterious relationships between (spontaneous)

heritable mutations and selection in neo-Darwinian theory may be overcome by a more sophisticated paradigm that resembles Lamarck's research program – but of course we have to be cautious. Sixth, a successful new theory according to Popper, Lakatos and Kuhn is one that explains unexplained findings in the previous theory and is able to predict new findings.

Are we already in the position to say that the epigenetic theory is able to overcome the old divide between genetics and the environment? I am not aware of any prediction made by epigenetics on theoretical grounds that was subsequently verified, but we can wait. One good candidate is what I said at the start about humans and chimpanzees.

To be sure, some recent research involving epigenetics is extremely promising [5]. In addition to the studies mentioned above, it is worth mentioning the fact that Inuit populations exposed to persistent organic pollutants (POPs) also had detectable hypomethylation of their DNA [6]; this kind of investigation can prove very effective in finding a link between low-level environmental exposures and the risk of disease, through the investigation of sensitive intermediate markers. Exposures that have been found to interact with "metastable epialleles" are, for example, genistein, a component of diet that seems to protect from epigenetic damage, the drug valproic acid, arsenic, and of course vinclozoline (see the current book). But the research is just in its infancy, and many more examples are likely to follow.

In addition to clarifying the relationships between genes and the environment, there is a further dimension in epigenetics, that is the fact that it may explain a feature of evolution that has been slightly neglected, except in developmental studies: self-organization of the living being. In fact a modern theory of evolution should encompass two big chapters, both the selection–adaptation component, and the self-organization component (the latter very often overlooked). This is in fact a promising component of the new revolutionary paradigm of epigenetics; for example, one might speculate that cancer is explained by a Darwinian paradigm (since it is due to selective advantage of mutated/epimutated cells) [7] but without the self-organization element that has characterized the evolution of organisms and species.

The next years will probably show the ability of the new paradigm to explain unexplained findings, and to make correct predictions.

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