

Editorial

Epigenetics: A New Peek into the Black Box of Behavior

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INTRODUCTION

The term “epigenesis” was suggested by Waddington [1] in his attempt to explain why embryonic cells develop into vastly diverse cell types, both in morphology and function, despite the fact that they all share the same set of genes encoded in their DNA. To address this puzzle he envisioned a regulatory system that works on the DNA and controls the timing and levels of expression of different genes. That is, the development of different cell phenotypes is controlled by programmable mechanisms that governs the pattern of gene expression in the cell. These mechanisms are referred to now as epigenetic and they are defined as heritable modifications to the DNA and its associated proteins that do not involve changing the underlying nucleotide sequence that codes the genetic information [2]. In this context, epigenetic information can be considered as a specific plan that guides cell differentiation and development. However, new evidence suggests that epigenetic mechanisms not only are involved in cell development and maturation, but they also mediate the effect of environmental factors on the physiology and behavior of the organism [3].

There are several epigenetic mechanisms that have been identified to date, but the two most studied and understood are DNA methylation; the addition of a methyl group to cytosine in cytosine-guanine dinucleotide (CpG) sites, and post-translational histone modifications; the acetylation, methylation, phosphorylation and ubiquitination of the N-terminal of histone proteins (protein units which constitute the core structure around which the DNA is wrapped to form chromatin particles). Both mechanisms essentially alter the availability of the DNA to the cellular transcriptional apparatus leading, thereby, to overexpression, underexpression, or silencing of certain genes this not only determines the phenotype of the cell, but also its physiology, which could ultimately affect the susceptibility of the individual to disease.

EPIGENETICS AND HUMAN BEHAVIOR

Although epigenetic programs are stable and typically are maintained throughout the lifetime of the individual during somatic cell (mitotic) divisions, and can be passed down to the next generation via germ-line (meiotic) transfer [4,5], they are potentially reversible and modifiable [6]. Alterations induced in the epigenome by environmental factors, therefore, could mediate the interaction between environmental effects and the

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biological and behavioral responses of the organism. This notion is especially important in the context of perinatal exposures, when most physiological and behavioral traits develop according to the hypothesis of early origins of disease risk [7]. The realization of the important role played by epigenetic processes in mediating the effect of environmental factors on the physiology and behavior of the offspring originated from two lines of evidence: 1) findings from many studies of associations between prenatal exposures and an altered patterns of DNA methylations in the offspring and, 2) studies that demonstrated the effect of epigenetic modifications on brain development and behavior. Examples of the first are well-established associations of gestational smoking and maternal stress during pregnancy with methylation patterns of the DNA both in childhood and adulthood [8,9]. Examples of the second are extensive data from animal experiments illustrating the role of epigenetic mechanisms in shaping early brain development and, consequently, behavioral patterns of the offspring [10,11].

The ability of the epigenome to reprogram in response to environmental stimuli made it a plausible candidate mechanism for explaining brain plasticity, especially at early stages of life when brain plasticity is at its maximum and when most of epigenetic modifications take place. An important factor in this context is the early postnatal mother-infant interaction. For example, convincing evidence from animal and human studies has accumulated showing a profound effect of maternal distress and depression on infant's behavior [12-14]. Strong evidence also suggest a significant role of epigenetic mechanisms in mediating these effects [15,16]. A related issue to this line of evidence is the fact that epigenetic processes have been shown to underlie developmental pathways that are involved in higher functions related to learning and memory [17], which provide the basic steps in developing experience-related behavioral phenotype. In other words, acute changes in the physiology of the neuron during the process of learning or forming long memories, for example, are governed by environmentally-induced epigenetic alterations which, consequently, modify the patterns of gene expression in the neuron.

FUTURE DIRECTIONS

Most data on the interplay of perinatal environmental

exposures and epigenetic alterations in shaping the behavioral patterns of the offspring come from animal studies. Unlike animal models, the long rearing period in humans and the strong dependence of the infant on his/her mother implies a central role of the mother-infant interaction in shaping the environmental milieu within which the child's behavioral phenotype develops. Identifying and characterizing epigenetic dysfunctions caused by the disruption of this relationship, therefore, will improve our understanding of the origins of many behavioral and psychological disorders and potentially provide novel targets for intervention. Continuous research concentrating on discovering new epigenetic mechanisms involved in cognition and memory formation will not only help understanding the mechanisms underlying impaired cognition and learning disorders in childhood, but also those implicated in later neurodegenerative diseases such as Alzheimer's [18].

Drug addiction and substance abuse is also an important field where epigenetic research could provide insightful information since all addictions involve structural and functional modifications in the reward system of the brain, indicating a role of epigenetic mechanisms in maintaining the addiction [18]. A related question in this context is how much of the addiction is due to contextual vs. epigenetic factors. For example, in an alcoholic descendant of an alcoholic parent, is the addictive behavior of the descendent caused by factors such as imitation and social influence, for example? Or is it determined by abnormal epigenetic alterations caused by the addiction of the parent? And what is the relative role of each—especially in the case of an alcoholic mother who consumed alcohol during pregnancy?

Addressing these questions requires extensive, multidisciplinary research using longitudinal design and well-established cohorts. Studies that investigate the mediating role of epigenetic alterations in the effect of early environmental exposures on later behavioral traits, especially studies spanning more than one generation, are needed. Identifying specific epigenetic alterations that translate into increased susceptibility to behavioral disorders underlying physical and psychological diseases, such as obesity, drug abuse and depression is very important. Such studies are very expensive but they could identify novel targets for preventive interventions and effective treatments for severely disabling diseases such as drug addiction, Alzheimer's, and certain types of mental retardation.

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