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Epigenetics and the Human Brain: Where Nurture Meets Nature

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Editor's note: While our genetic code determines a great deal of who and what we are, it does not act alone. It depends heavily on the epigenome, an elaborate marking of the DNA that controls the genome's functions. Because it is sensitive to the environment, the epigenome is a powerful link and relay between our genes and our surroundings. Epigenetic marks drive biological functions and features as diverse as memory, development, and disease susceptibility; thus, the nurture aspect of the nature/nurture interaction makes essential contributions to our body and behaviors. As scientists have learned more about how the epigenome works, they have begun to develop therapies that may lead to new approaches to treating common human conditions.

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Since the discovery of DNA in the 1950s, one of the primary goals of geneticists has been to understand how differences in the DNA sequence can influence human health and lead to diseases. After several decades of intense research, two conclusions are clear: (1) in most cases, it is difficult to establish a direct link between any specific gene(s) and specific biological processes or diseases, and (2) most traits and pathologies are associated with more than just one gene and have complex mechanisms. Discovering that such complexity is at play led researchers to acknowledge that the genome on its own is likely not sufficient to sustain all biological functions, and that another level of regulation is contributing. They proposed the epigenome as one of these additional levels.

Tightly associated with the genome, the epigenome represents an ensemble of biochemical marks present on the DNA itself. These marks modulate the DNA's activity and functions, but occur without any change in the DNA sequence. Instead, various enzymes add epigenetic marks to the DNA. The marks stamp genes with a unique signature that signals the gene to be active or silent.

Unlike the DNA sequence, epigenetic processes are dynamic and not fixed, although some can persist for long periods of time, up to several years or a lifetime. Further, they are strongly influenced by the environment and by exposure to external factors like diet, living conditions, exercise, stress, chemicals, drugs, and toxins. Both positive and negative factors can modulate the epigenome. For instance, positive factors such as enriched living conditions, like social interactions, physical activity, and changing surroundings, can promote beneficial epigenetic marks, while severe stress or agricultural chemicals can permanently alter some marks.[1,2] These modifications can impact various aspects of an organism's life during any phase of development, and can increase the susceptibility to diseases. For example, traumatic events and severe chronic stress in early life can alter the epigenome in a persistent and sometimes heritable fashion.[3-5] Many cancers are also associated with epigenetic alterations induced by factors such as poor diet and toxins.[6,7]

Although the concept of epigenetics has had a revival in the past decade, it was first discovered in the 18th century. About 50 years before Charles Darwin published his famous book *On the Origin of Species*, French naturalist Jean-Baptiste Lamarck was the first to propose that surrounding conditions can modify characteristics acquired during a person's lifetime, and those characteristics can be passed on to the offspring.[8] According to Lamarck's theory—which his contemporaries largely overlooked and even criticized—a person's make-up can change within a generation depending on environmental factors. As it turns out, this

postulate forms the basis of the underlying principles of epigenetics and provides a conceptual framework for the question of how the environment impacts an organism and its offspring. Because this concept is so fundamental to the understanding of biological functions, some scientists proposed that Lamarckian principles be integrated into evolutionary theory. This remains a disputed issue, however.

Epigenetics provides support for another longstanding unresolved question: the contribution of nature versus nurture. Since epigenetics acts as a conduit through which environmental factors elicit lifelong biological changes, it provides a molecular basis to suggest that nurture has a strong impact on biological functions and behavior, in some cases, perhaps a stronger impact than nature (genes). The concept of epigenetics further offers an explanation for individual differences resulting from life experiences, one of the most striking examples being of identical twins who have exactly the same genotype but different physiological or behavioral responses or disease susceptibility. It substantiates the proposal that both nature and nurture are essential contributors to our selves and our bodies, but that their respective contribution varies.

We and others in the field believe that the study of the epigenome warrants as much research as the study of the genome. We are convinced that the field of epigenetics has an immense potential for new discoveries that will help us better understand human diseases and possibly provide new approaches to curing them. Several aspects of epigenetic marks are of particular interest to researchers: (1) they are gene specific, (2) they are influenced by the environment, (3) they are dynamic and reversible, but (4) they can nonetheless remain stable across generations.

Epigenetic Processes

In a broad sense, epigenetics is the ensemble of processes that link a person's genotype, or the genetic information, to its phenotype, the physical and biological expression of this genetic information. These processes regulate gene activity. They can activate or inactivate genes, alter the amount of protein synthesized or expressed by a gene, and determine when a gene is expressed throughout the course of a lifetime. By implementing such changes, epigenetic processes regulate gene activity in a dynamic way.

Further, epigenetic processes can produce local changes within specific tissues or cells in the body. For instance, the epigenetic signature of each cell type has the potential to be distinct. Since the same DNA is present in every cell of an organism, epigenetic processes

provide a means to create and maintain diversity between and within cell types. Thus, while neuronal and epithelial cells in a given person contain exactly the same DNA, epigenetic processes can modulate gene activity in each cell type differently, and thus activate or silence specific cellular functions or features. They may also do so within similar cells in the same organ—whether brain, liver, or kidney. Epigenetics, therefore, largely accounts for the uniqueness of each organ or cell, while also regulating the organ's maintenance, health, and aging.

The epigenome regulates gene expression in several ways. One of the best-studied forms of epigenetic regulation involves DNA methylation, in which molecules of carbon and hydrogen (methyl groups) chemically bind to cytosine, one of the four nucleotide bases in DNA. One consequence of DNA methylation is the silencing of gene expression. If certain regions of the DNA around genes are methylated—that is, if all cytosines carry methyl groups—their activity is diminished.

Another type of epigenetic regulation involves modifications of histone proteins, which are linked closely to the DNA and help organize its structure. Within the cell nucleus, the DNA is packaged around histone proteins, and it forms nucleosomes, similar to beads on a necklace (see Figure 1, page 9). Although fairly compact, histone proteins have small tails that project from the coils they form with the DNA. These tails are accessible to local enzymes that can easily modify some of the amino acids in these tails. Histone modifications result from biochemical processes leading to the addition of specific marks on individual amino acids. There can be hundreds of modifications on a given histone, and the ensemble of these modifications forms a unique combination or code that modulates the way the DNA is structured. Thus, depending on which histone modifications are present together at a certain time and place, they can change the way the DNA is packaged. They can tighten the packaging, thus making DNA inaccessible to the machinery needed to read and express its genes. They can also loosen the packaging and open access to the DNA for gene expression. Histone modifications are therefore crucial determinants of gene activity.

Researchers also recently discovered an additional epigenetic process involving noncoding RNAs, or ribonucleic acids. Unlike most messenger RNAs (mRNAs) that result from DNA transcription and are translated into proteins and enzymes, noncoding RNAs are not used to produce proteins. But they play an extremely important role in the regulation of gene activity because they can target specific mRNAs (owing to the fact that they have the same sequence) and prevent their translation into proteins. They therefore provide an

additional level of regulation not on the DNA itself, but rather on the intermediate RNA molecule resulting from the initial phase of gene expression (DNA transcription). Scientists have suggested the existence of other epigenetic processes, but further research is needed to identify and understand them.

Epigenetics and Memory

Recent work in the field of neurobiology has revealed that epigenetic processes are essential for complex brain functions. For example, recent studies showed that several enzymes that modify DNA or histone proteins are essential elements of signaling pathways, allowing proper neuronal signaling for learning and memory.[9] This is because the formation of long-term memory requires that epigenetic processes induce lasting changes in gene expression in brain cells. Mice with dysfunctions in any of the epigenetic components that contribute to these changes can have impaired long-term memory.[10,11] Interestingly, some of the cognitive impairments can be reversed by the administration of drugs acting on the defective epigenetic components. Mice with more components favorable to some epigenetic marks have improved memory and better cognitive performance.[12-14] These findings suggest that memory performance can easily be modulated, whether impaired or improved, by epigenetic processes.

Because of this modulation, scientists are exploring the possibility of using epigenetic therapies to treat memory and cognitive function disorders.[15-18] For instance, drugs that modulate histone-modifying enzymes such as inhibitors of histone deacetylases (HDACs) could benefit people with memory impairment, age-related cognitive decline, or even Alzheimer's disease.[19] Epigenetic marks may also be used for diagnostic purposes. This will require the detection of overlapping marks in the brain and in peripheral tissue, such as blood or plasma. If a blood test can detect such marks, they may serve as early biological markers, or biomarkers, signaling a particular biological state that may be pathological.

Epigenetics and Development

Epigenetic processes are also fundamental for cellular development. During the successive phases of prenatal and postnatal development, rapid changes occur in the organization of the nervous system and the body. Molecular processes influenced by environmental conditions influence these changes. Thus in these processes, both innate genetic programs and sensory experiences regulate brain development and control the

establishment of functional neuronal circuits. Researchers have examined the influence of environmental conditions, in particular the effect of mother-infant interactions, to examine long-lasting consequences of early-life experiences. In rat and mouse models, researchers have examined how the natural variability in the quality and quantity of interactions between moms and their pups impacts behavior. These interactions modulate the pups' response to living conditions later in life, and can alter their reaction to stress and aversive conditions. An alteration of these reactions has been linked to the development of anxiety and depression.[20] Further, variability in maternal care can translate into stable epigenetic modifications that remain beyond the period of maternal care.[21]

In experiments on mice, our group demonstrated that severe chronic stress experienced during early life not only alters adult behavior in the animals subjected to the stress, but also impacts the behavior of the offspring across several generations. This model is based on chronic and unpredictable maternal separation combined with maternal stress. The study showed that such separation, experienced daily for most of the postnatal life, induces depressive and impulsive behaviors and alters social skills in the separated offspring when adult.[4,5] Strikingly, the offspring of the animals directly subjected to the stress manifested similar behavioral alterations, despite the fact that they were raised without the same type of stress. Both female and male mice transmitted the behavioral symptoms, independent of the maternal care they received. Researchers linked the behavioral alterations with alterations in epigenetic processes—in particular, changes in DNA methylation in several genes in the brains of the stressed animals and their offspring, as well as in the germ line (in particular, spermatozoa). This indicates that early stress can persistently alter the epigenome in multiple tissues and cells, and that the alterations occurring in germ cells can be maintained and passed on to subsequent generations.

The correlation among early childhood experience, behavioral symptoms, and epigenetic alterations demonstrated in rodent models has also been observed in humans. For instance, researchers observed striking differences in epigenetic profiles when comparing the brains of people who experienced childhood abuse and committed suicide later in life with the brains of people who did not experience such childhood trauma and later committed suicide.[22] The people who had been abused exhibited changes in the methylation profile of several stress-related genes. Early childhood experiences can influence the brain for a lifetime, but exposure to detrimental stimuli even earlier—particularly in the womb and shortly after birth—can also increase susceptibility to diseases.

Several studies also showed that a poor or high-fat diet is detrimental to health across several generations.[23] Epigenetic factors have also been implicated in the transgenerational effects of such inappropriate diet. Such effects, which arise through both paternal and maternal transmission, may have negative consequences for the offspring. In rats, for example, males fed a high-fat diet generated female offspring with a diabetes-like condition manifested by impaired glucose tolerance and insulin secretion, although these offspring received a normal diet. This condition was associated with abnormal gene expression in pancreatic cells of the offspring.[24]

Experiences during adulthood can also dynamically and persistently modify the epigenome. One of the most striking examples occurs in identical (monozygotic) twins, who have the same genome but often vary greatly in their susceptibility to disease. Manel Esteller and colleagues at the Centro Nacional de Investigaciones Oncológicas showed that twins are indistinguishable in their gene expression profile early in life. Sets of older twins, however, have significant differences in their epigenetic profiles.[25]

Although Esteller's study was not longitudinal, it showed that twins who grew up in different environments had more epigenetic differences and more divergent medical histories than twins who remained in similar conditions. This highlights the influence of a person's surroundings and living environment on the epigenome. The authors did suggest that the divergence in medical histories was related purely to age, suggesting a random epigenetic divergence called an epigenetic drift. In other words, epigenetics can change with or without environmental influence.

Epigenetic Interventions

In light of the significant and lasting effects of environmental factors on biological functions, behavior, and diseases, it now appears essential to gain a better understanding of the processes that regulate the epigenome. It is equally important to identify the factors that lead to permanent alterations of these mechanisms and might therefore protect or endanger public health. Then we must find new ways to prevent or treat both negative and positive consequences of such alterations.

Unlike genes, which can be altered only through complex gene therapies, epigenetic marks are reversible and therefore amenable to environmental or drug treatment approaches. First, the avoidance of certain chemicals and toxic agents, or better lifestyle and diet choices, may prevent alterations of the epigenome. Since studies have shown that some compounds

used in agriculture have strong and lasting effects on the epigenome, preventing their use would be beneficial. A better knowledge of nutrition would help us both avoid negative epigenome alterations and optimize a diet's potential to prevent or protect people from diseases. For instance, perhaps a single dietary intervention could reduce the risk of metabolic diseases across generations.

For the time being, therapeutic interventions based on drugs appear to be the most direct and rapid treatment strategies. Doctors are already using inhibitors of enzymes that drive epigenetic processes, such as DNA methyl transferase inhibitors or HDACs inhibitors, in the treatment of cancers like leukemia and lymphoma.[26] These treatments could be exploited for other conditions. Prompted by the growing interest in diseases of the central nervous system, such as neurodegenerative and psychiatric diseases, mental retardation, and drug addiction, more epigenetic therapies are under development.[27]

Another avenue related to diseases is the potential to diagnose people who are at risk by determining their epigenetic profile. Aberrant epigenetic changes may provide unique biological markers for specific diseases.[28] In cancer research, scientists are developing quantitative techniques for detecting and analyzing DNA methylation to diagnose and classify diseases. Finally, a better understanding of epigenetic processes would be of great importance for the field of assisted reproduction technology, since this technology has been associated with a higher risk for epigenetic defects correlated to chronic disorders.[29]

We have witnessed a recent burst of research efforts, discussions, and debates on epigenetics. The enthusiasm in this area reflects the realization that these processes form a fundamental biological basis for the interplay among environmental signals, the genome, and heritability. Researchers have begun to determine the normal profile of epigenetic marks in various tissues and body fluids, and in the future they will systematically analyze epigenetic alterations and their links with pathologies. Scientists will need to address many additional issues, such as what controls the propagation of epigenetic information throughout developmental stages and how changes in the epigenome are inherited. Continued research will hopefully yield great discoveries in the next decade. Revealing how epigenetic marks work and what they do will surely open important new chapters in genetics and human health.

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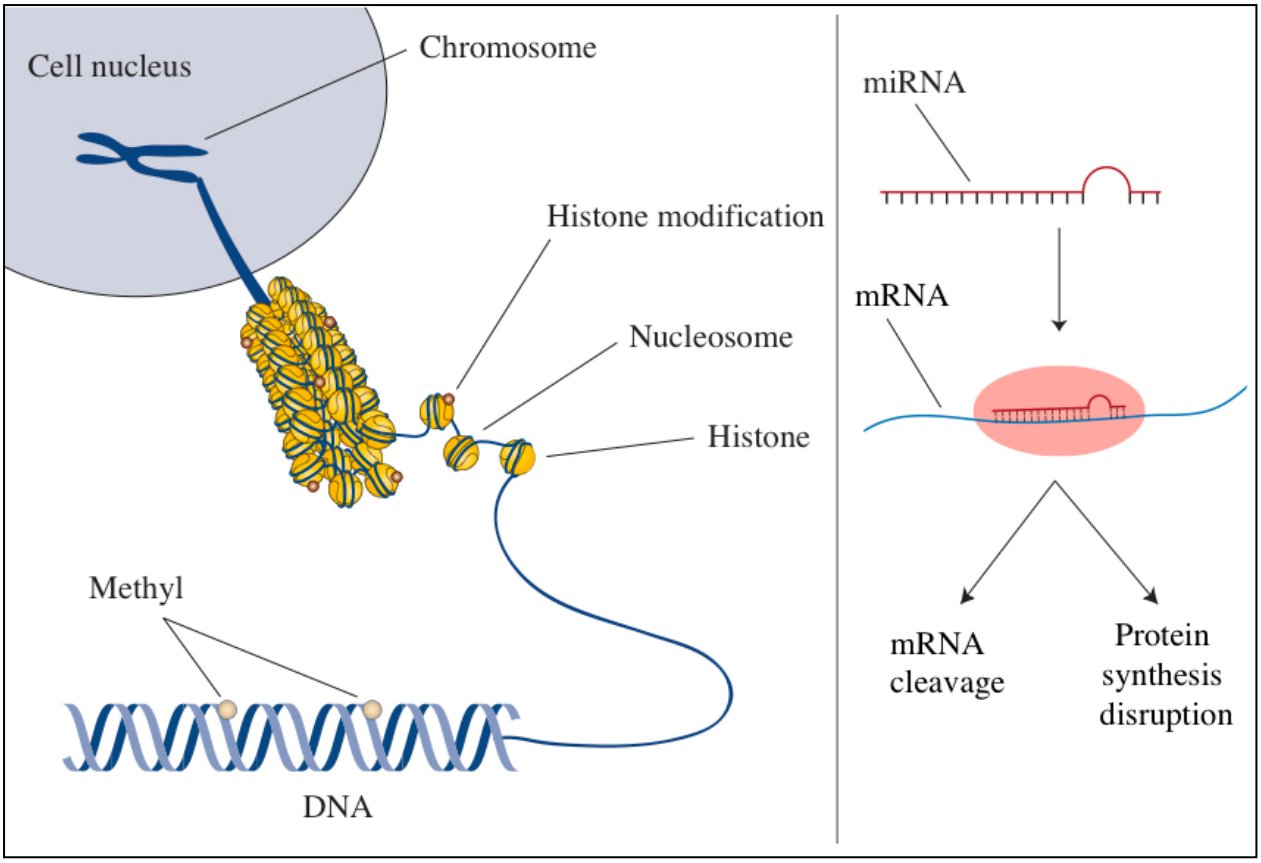
Figure 1



Most common epigenetic processes. Left: Schematic representation of DNA and its packaging with histone proteins in chromosomes, and of epigenetic modifications on the DNA and histones. Right: Scheme representing how microRNAs, one form of small noncoding RNAs, recognize a cognate mRNA by sequence homology, leading to its cleavage and to the blockade of its translation into a protein.

Isabelle M. Mansuy, Ph.D., is associate professor in molecular cognition at the Medical Faculty of the University Zürich, and in the Biology Department of the Swiss Federal Institute of Technology (ETH) Zürich. She completed her Ph.D. in developmental neurobiology at the Friedrich Miescher Institute in Basel, Switzerland, and at the Université Louis Pasteur, Strasbourg, France, and then was a postdoctoral fellow in the lab of Eric Kandel at the Center for Learning and Memory of Columbia University in New York. She was appointed assistant professor in neurobiology at ETH Zürich in December 1998.

Dr. Mansuy's research examines the molecular mechanisms and epigenetic basis of complex brain functions, and focuses on cognitive functions and behavior in mammals. Her research in the past decade revealed the existence of molecular suppressors of learning and memory in the mammalian brain, and identified the Ser/Thr protein phosphatases calcineurin and PP1 as such suppressors. She is currently examining the importance of protein phosphatases in chromatin remodeling in the adult brain, and in the epigenetic control of memory formation. Dr. Mansuy also studies the epigenetic basis of the influence of detrimental environmental factors on behavior, and of its inheritance across generations. This work recently demonstrated that early trauma in mice induces depression, impulsiveness, and impaired social skills, and that these behavioral symptoms are transmitted across several generations. Her team is currently examining the molecular and cellular mechanisms potentially involved. Research in the Mansuy lab combines genetic and environmental animal models; epigenetic approaches; and molecular, behavioral, electrophysiological, proteomic, and imaging techniques.

Safa Mohanna is a Ph.D. student in the lab of Isabelle M. Mansuy at the Brain Research Institute at the University Zürich (UZH) and the Swiss Federal Institute of Technology Zürich (ETH Zürich). He holds an M.Sc. in life science and technology from the Swiss Institute of Technology in Lausanne (EPFL). Mr. Mohanna is interested in the molecular mechanisms of memory formation and in the potential implications of a better understanding of these mechanisms to clinical practice. His current research focuses on the role of a novel memory-associated protein in learning, memory, and synaptic plasticity. He investigates the potential interaction between this novel protein and epigenetic mechanisms, and its implication in brain diseases characterized by memory deficits, such as Alzheimer's disease.

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