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Epigenetics and the nervous system: epiphenomenon or missing piece of the neurotherapeutic puzzle?

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In today's *Lancet Neurology*, Esteller and colleagues present a thorough overview of epigenetics for clinical neuroscientists.[1] While the term does have broader definitions, epigenetics essentially refers to heritable changes in gene expression that cannot be attributed to differences in genetic code.[2] In a recent landmark paper, Fraga, Esteller, and colleagues[3] showed that genetically identical monozygotic twins have similar epigenetic profiles early in life but, as they age, several epigenetic signatures—including DNA methylation and histone acetylation patterns—diverge. The findings provided an elegant explanation for why monozygotic twins are discordant in their susceptibility to disease.

The implications of these findings for the study of phenotypic variation in physiology and disease, otherwise known as the "nature versus nurture" debate, are enormous. The ambitious but now tangible goals of the Human Genome Project were to define the boundaries of the human genome as a scaffold on which to understand human phenotypic variation. A much more complete picture of differences between physiology and disease will require a comprehensive understanding of how epigenetics interfaces with genetics to modulate distinct human phenotypes. This knowledge will be achieved only by a dedicated study of the epigenome similar to that initiated for the genome in the early 1990s—thus, the time seems ripe for the Human Epigenome Project.

Evidence in favour of a major role for epigenetic modifications in neurological disease has come from three converging lines of enquiry. First, histone residues that are targets for epigenetic modifications have shown a high conservation throughout evolution—indirect evidence of their essential roles.[4] Evolutionary conserved mechanisms control gene expression in the embryonic brain and plastic changes in the postnatal brain in response to environmental and social cues. Second, mutations in epigenetic components are associated with multisystem disease syndromes in human beings, all of which involve the nervous system. Some illustrative examples are outlined in the Review by Esteller and co-workers, and include Rett syndrome (caused by mutations in the methylated DNA binding protein, MecP2), Rubinstein-Taybi syndrome (by mutations in the histone acetyltransferase, CBP), and Coffin-Lowry syndrome (by mutations in histone phosphorylase). Third, and most exciting from a therapeutic perspective, small-molecule epigenetic modulators, specifically

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For more on the Human Genome Project see http://www.ornl.gov/sci/techresources/Human_Genome/home.shtml

related to histone acetylation and commonly referred to as histone deacetylase (HDAC) inhibitors, have shown broad efficacy in many disease models, including those for stroke, Huntington's disease, Friedreich's ataxia, Parkinson's disease, spinal muscular atrophy, amyotrophic lateral sclerosis, and Alzheimer's disease.[5]

In certain sporadic diseases (eg, stroke), HDAC inhibitors seem to upregulate genes such as *PRDX* (which encodes the peroxiredoxin family, known scavengers of toxic hydrogen peroxide) and thus provide homeostatic compensation for the increased free radicals produced during and after stroke.[6] Furthermore, HDAC inhibitors are appealing candidates for the treatment of chronic neurodegenerative disorders because, as described in this Review, they are also being studied in the clinic for the treatment of cancer. Therefore, these inhibitors might have the potential to treat chronic neurodegeneration without increasing the risk of cancer, a major concern for many therapies based on cytotoxicity. Moreover, their neuroprotective effects and anticancer properties offer the opportunity to minimise the neurotoxic effects of chemotherapeutic drugs without affecting their efficacy.

Why could HDAC inhibitors succeed where other drugs have failed? Esteller and colleagues allude to some of the putative advantages of HDAC inhibitors. Another important aspect of these intriguing small molecules is their ability to induce the expression of several hundred genes without lethal toxicity in multiple cell types. Most acute or chronic neurological disorders involve complex pathophysiological changes in several cell types; as a single drug, HDAC inhibitors might achieve what could only be previously achieved with drug combinations. Although combination therapies have been the hallmark of therapeutic success for cancer, AIDS, and tuberculosis, a combination trial is, however, an expensive and challenging regulatory endeavour. As well as their effects on neuronal survival, there is growing awareness of the role of HDAC inhibitors in plasticity, neurogenesis, and regeneration, suggesting that they could ameliorate disease by both preventing neuronal death and enhancing brain repair.[7] Together, these features make HDAC inhibition a leading prospect for neurotherapeutics. Encouragingly, small molecules that can modulate the function of other epigenetic modifiers are being developed (eg, DNA methyltransferase inhibitors) and these might also soon find their way to neurology clinics.

The excitement over epigenetics and neurological therapeutics is building, but a few important points of caution are worth noting. First, most of the small-molecule inhibitors of HDACs used in preclinical studies to date, such as trichostatin A and suberoylanilide hydroxamic acid (SAHA; also known as vorinostat), are based on hydroxamic acid. The hydroxamate moiety allows these drugs to bind and neutralise the zinc hydrolase activity at the end of a tubular pocket in the core of the HDAC protein. However, as with all small molecules, these drugs have off-target effects (hydroxamic acids can bind to zinc, iron, and other trace metals that are free or bound to proteins). Thus, it is important to show that the effects of hydroxamate-based HDAC inhibitors are due to zinc binding in the tubular pocket of the HDAC and not due to binding of free or bound zinc or iron. Additional experimental controls needed to provide confidence that HDACs are the target of action for HDAC inhibitors should involve the molecular deletion of one or more HDAC isoforms, using RNA interference or conditional knockout, to occlude the effects of HDAC inhibitors in vitro and in vivo.[8]

This Review sets the framework for a series of exciting investigations that evaluate epigenetic modifications at specific genes and at genome level in the aetiology of inherited and sporadic neurological diseases. These investigations will provide a clear picture of whether or not epigenetics is the crucial missing piece to the neurotherapeutic puzzle. Solving this puzzle has important consequences, as it promises not only to give therapeutic benefit to patients but also to provide new insights into the mysteries of brain function.[9]

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