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Epigenetics: An Expanding New Piece of the Stroke Puzzle

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Completion of the Human Genome Project in 2003 ushered in a wave of optimism and anticipation that new therapies and even cures for many diseases would soon be forthcoming [1]. Aside from impressive progress in reducing the costs of genotyping [2], the promise offered by the Human Genome Project has been largely unrealized, particularly in relation to stroke [3]. More than 100 Genome-Wide Association studies [4] made possible with the new information provided by the Human Genome Project have yielded many interesting findings about the genetics of stroke-related brain injury, but all have generally fallen far short of identifying a genetic basis for vulnerability to cerebral ischemia [5]. With the notable exception of monogenic diseases, Genome-Wide Association studies have generally not been an efficient strategy to elucidate the genetic mechanisms of disease, particularly in complex pathologies such as ischemic cerebral injury [6]. These studies have taught us that most disease pathologies, including those associated with cerebral ischemia, are polygenic and involve highly variable contributions from the genes involved. Such findings raise the important question: why are the genetic components of complex diseases so variable?

The Three Categories of Epigenetic Mechanisms

Long before the Human Genome Project was completed, it was recognized that genetic factors were not the only, or perhaps even not the most important, determinants of responses to some diseases. Indeed, in the same issue of Nature Genetics that was dedicated to completion of the Human Genome Project, it was already recognized that “epigenetic” factors were major players in the etiology and progression of many diseases [7]. Following completion of the Human Genome Project, understanding of epigenetic mechanisms has expanded rapidly and it is now recognized that epigenetic regulation involves three main categories of mechanisms [8, 9], as summarized in Figure 1.

The most widely studied category of epigenetic mechanisms includes the enzymes that mediate DNA methylation. These reactions are catalyzed by DNA Methyltransferases [10], which play a critical role in many cancers [11]. DNA methylation occurs most often on cytosine residues in promoter regions of regulated genes, and can greatly attenuate gene expression. Many DNA methylation reactions exhibit specific developmental timing and require methyl donors, such as folic acid, for their function. This is one reason why dietary folic acid is so important during pregnancy [12]. Work with DNA Methyltransferases has helped identify multiple inhibitors of DNA methylation, many of which have found use in clinical studies of cancer [13]. DNA demethylation reactions have been proposed, but clear evidence for enzymes reversing DNA methylation, in vivo, is not yet well established [14].

A second category of epigenetic mechanisms involves the enzymes that reversibly acetylate and methylate the histone proteins that tightly bind DNA. This large and diverse group of enzymes plays a key role chromatin structure and gene expression [15, 16], although the basis for their gene-specificity remains unclear [17]. As a general mechanism, acetylation of the lysine residues on histone proteins adds negative charge, which in turn promotes their dissociation from DNA; deacetylation reverses this process and promotes gene “silencing” [18]. Studies of histone acetyltransferases and deacetylases have also helped identify a broad variety of selective inhibitors, many of which are in clinical trials [19, 20].

The third and most recently recognized category of epigenetic mechanisms includes the pathways involved in the transcription, processing, and action of a class of short (≈20–25 nucleotides) RNA molecules identified as micro-RNAs (miRNAs) [21]. In contrast to DNA methylation and histone modification, the main function of miRNAs is involved much more with message translation than with gene transcription. The miRNA molecules directly bind mRNA and either retard or accelerate its degradation. In addition, miRNA binding to mRNA can block message translation [22]. The sequences coding for miRNAs often arise from intronic DNA, and regulate the gene products coded by adjacent exons. More than 1000 unique sequences of miRNA have been identified, and together these regulate approximately 30% of all mammalian genes [22]. A single miRNA can help regulate multiple different gene products, and a single gene product can be regulated by multiple different miRNAs. As such, miRNAs play key roles in many cellular functions and are particularly important in cardiovascular biology [23–28]. Expression and action of miRNAs change with development and in response to nutritional stress [29]. The actions of specific miRNA molecules can be inhibited by reverse-sense antagomirs, and these have proven useful in many studies of miRNA function [30, 31].

Epigenetic Mechanisms in Physiological Regulation

Apart from the molecular mechanisms responsible for epigenetic regulation, a broad variety of evidence has implicated epigenetic regulation in long-term environmental influences on gene regulation. One of the best-known such examples is the epidemiological work of Barker, who identified a cohort of Dutch individuals with a uniquely elevated risk of coronary artery disease [32, 33]. The common feature among this cohort was maternal food restriction during the Dutch famine in World War II. These early studies established that fetal nutritional stress could produce life-long changes in the vulnerability to cardiovascular disease, and subsequent work has further established the epigenetic basis of such “vascular programming” [34]. Similarly, other studies have implicated epigenetic mechanisms in long-term responses to hypoxia [35–38] and ischemia [39–41]. Of particular relevance to stroke are findings that miRNA is involved in ischemic preconditioning [42–48] and may even play a role in ischemic postconditioning [49]. Together, these results emphasize that environmental influences can produce long-term changes in physiological patterns of gene expression through epigenetic mechanisms.

Epigenetic Mechanisms in Stroke

Appreciation of the potential involvement of epigenetic mechanisms in the incidences and outcomes of stroke has begun to motivate studies of these mechanisms in relation to cerebral ischemia and stroke [50]. DNA methylation has been suggested to contribute to delayed ischemic brain injury in mice [51] and has been correlated with stroke risk in humans [52, 53]. Histone modifications have been implicated in LPS-induced cerebral inflammation [54] and oxidative neuronal injury [55], and may be neuroprotective following ischemia [56] in rodent brains. Correspondingly, inhibitors of histone modification have been suggested to be neuroprotective in animal models of cerebral ischemia [57–61] and intracranial hemorrhage [62]. In turn, miRNAs have been shown to play diverse roles in neuronal [63–66], glial [67] and endothelial [68, 69] responses to stroke. In addition, miRNAs have been suggested to regulate the effects of ischemia on aquaporin expression and function [70] and in some cases may be neuroprotective [71]. miRNAs may also help explain gender-based differences in responses to cerebral ischemia [72]. Although studies of epigenetic mechanisms in stroke are still in the early stages, the data accumulated to date strongly suggest that further studies of these mechanisms are well justified and that future publications resulting from these studies are worthy of careful attention.

Epigenetic Mechanisms and Cell-Based Therapies

Outside the brain, epigenetic mechanisms may contribute to the cerebral vulnerability to ischemia through many different pathways. Epigenetic mechanisms appear to play a major role in the development and progression of diabetes [73–75], and are intimately involved in regulation of angiogenesis [30, 76–83] and growth factor function [84]. Correspondingly, epigenetic mechanisms can play key roles in cell proliferation and differention [85–93]. These diverse findings suggest that the success of cell-based therapies, such as those discussed in this issue of Translational Stroke Research, may also depend, at least in part, on epigenetic mechanisms. Without doubt, studies of epigenetics are expanding rapidly and offer great promise for improved understanding of stroke pathology. Translational Stroke Research has already included two manuscripts on this topic [94–95], and another by Baltan appears in this issue. More are sure to come.

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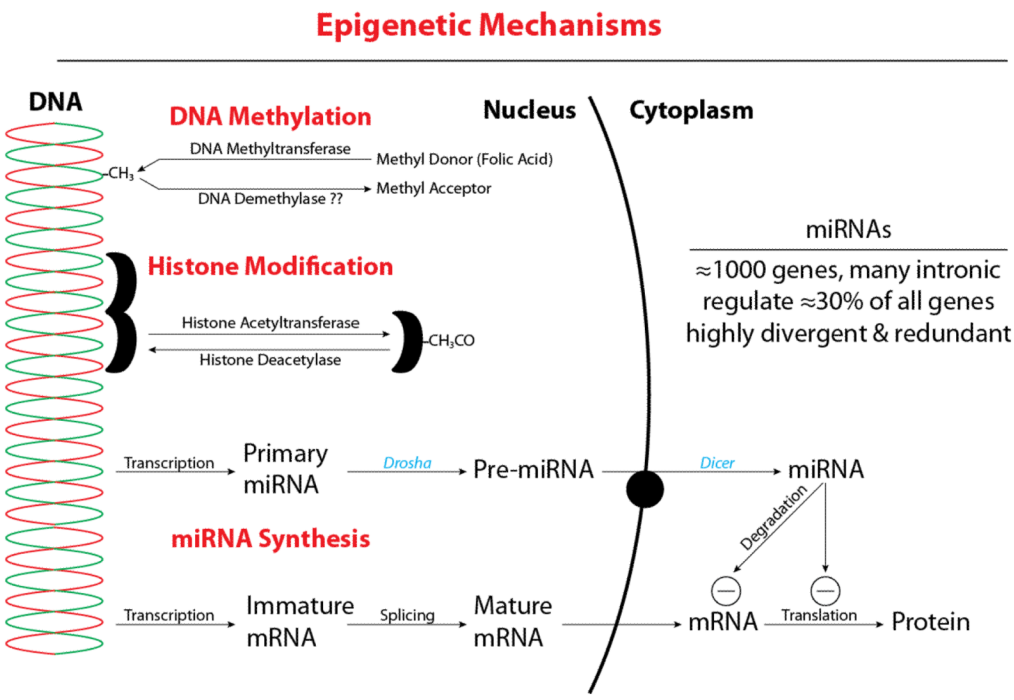

Figure 1.

Epigenetic mechanisms can be divided into three main categories. The first includes the mechanisms mediating DNA methylation, typically at cytosine residues in gene promoter regions. These reactions attenuate gene expression and are catalyzed by multiple different isoforms of DNA Methyltransferases. An important requirement for these reactions is a methyl donor, typically folic acid supplied through the diet. DNA demethylation has been proposed, but has not yet been demonstrated in vivo. The second epigenetic category of mechanisms includes the enzymes that acetylate and deacetylate lysine residues on histone proteins. These enzymes regulate chromatin structure and include Histone Acetyltransferases and Histone Deacetylases. In general, histone acetylation promotes dissociation from DNA and facilitates gene expression, whereas deacetylation promotes reassociation and reduced gene expression. The third epigenetic category includes the pathways that transcribe, process, and transport miRNA, which arises from more than 1000 genes. In many cases, miRNA is coded by intronic regions of DNA, and regulates the gene coded by adjacent exons. In general, miRNAs are highly divergent, such that one miRNA can bind multiple different mRNAs. In addition, miRNAs are also highly redundant; many different miRNAs can regulate a single gene mRNA. Overall, approximately 30% of all genes are regulated by miRNAs.