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Point of View

DNA methylation changes in schizophrenia and bipolar disorder

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The etiology of the major psychotic disorders, including schizophrenia and bipolar disorder, remains poorly understood. Postmortem brain studies have revealed altered expression of multiple mRNAs, affecting neurotransmission, metabolism, myelination and other functions. Epigenetic mechanisms could be involved, because for a limited number of genes, the alterations of mRNA levels have been linked to inverse DNA methylation changes at sites of the corresponding promoters. However, results from independent studies have been inconsistent, and when expressed in quantitative terms, disease-related methylation changes appear to be comparatively subtle. A recent study identified approximately 100 loci with altered CpG methylation in schizophrenia or bipolar disorder, the majority of which were gender-specific. Additional work will be necessary to clarify the origin and timing of these methylation changes in psychosis and to determine the specific cell types affected in the diseased brain.

Aberrations in DNA methylation have been implicated in a wide variety of brain disorders. Examples include (1) mental retardation syndromes resulting from certain imprinting disorders (example: Angelman and Prader-Willi syndromes),[1,2] triplet repeat expansions (fragile X syndrome),[3,4] mutations in DNA methyltransferase encoding genes (ICF syndrome)[5] and (2) a subset of gliomas[6-9] and neuroectodermal[6,10,11] tumors which show promoter hypermethylation of tumor suppressor genes. More recently, however, DNA methylation has been studied in the context of a very different category of brain malady: the major psychotic disorders, including schizophrenia and bipolar disorder, which are defined by delusions, hallucinations and mood alterations. While a variety of radiological, histological and molecular alterations have been observed in schizophrenic[12] and bipolar brain,[13] a definitive diagnostic neuropathology or molecular phenotype is lacking. The etiologies of these disorders are complex, demonstrating concordance rates of less than 70% in monozygotic twins, non-Mendelian inheritance patterns and sexual dimorphism;[14] these features, obviously, provide fertile ground for "epigenetic" disease models. Of note, the molecular pathology of the major psychotic disorders is thought to involve alterations in gene expression, including a downregulation of transcripts involved in cellular metabolism,[15-17] inhibitory neurotransmission[18] and myelination and other oligodendrocyte functions.[19,20] Therefore, it is tempting to speculate that at least some of these transcriptional defects could be due to aberrant increases in CpG methylation and repressive chromatin remodeling at 5' regulatory sequences. However, to date, DNA methylation has only been assayed for a small number of genes (namely, *REELIN*,[21-24] *COMT*,[25-27] *DRD2*[28] and *SOX10*[29]) in postmortem brain of subjects diagnosed with schizophrenia or other major psychoses.

Recently, Mill and colleagues published the first comprehensive methylation study of major psychosis,[30] in which they assayed methylation at approximately 7,800 loci—primarily within CpG islands of gene promoter regions—in frontal cortex of a comparatively large set of postmortem brain samples (35 schizophrenia, 35 bipolar and 35 control subjects). Based on Figure 2 of Mill et al., approximately 100 loci demonstrated significant disease-related methylation changes. Interestingly, a subset of the loci that were hypermethylated showed altered gene expression in previous studies employing some of the same brain samples studied by Mill et al., with approximately an equal portion of up and downregulated transcripts. That schizophrenia and bipolar disorder showed methylation changes of similar magnitude and direction for a number of loci resonates with some of the clinical, genetic and neurochemical features common to both disorders.[31] Strikingly, the list of genes showing altered methylation in Mill et al., includes at least one locus, *DYSBINDIN*, which confers genetic risk for psychosis.[32-34] This is interesting, because information regarding interactions between sequence polymorphisms and epigenetic modifications in human brain is available only for very few psychosis genes, including *BDNF*,[30] *GAD1*[35] and *5-HT2A*.[36]

Perhaps one of the most intriguing discoveries by Mill et al.,[30] was the finding that the vast majority of disease-related DNA methylation changes differentially affected male and female patients. At present, straightforward explanations for this puzzling phenomenon are lacking because the genes involved are located on autosomes and, until now, not known to show sex-specific regulation. It remains to be determined whether or not these loci are differentially methylated or show monoallelic expression in normal brain and which, if any, of the corresponding gene transcripts are differentially expressed in female and male brain. Sex steroids may play a role; estrogen, for example, is an important modulator of frontal lobe function in females,[37,38] and there is ample evidence that the hormone is involved in the regulation of chromatin structures, including DNA

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and histone methylation, at a number of gene promoters.[14,39,40] Furthermore, gender-specific chromatin alterations in schizophrenia may extend beyond the level of DNA methylation—both androgens and estrogens are known to interact with chromatin remodeling complexes[14,41-43] and recent evidence suggests that promoter-associated histone methylation changes at select GABAergic gene loci may be more prominent in female schizophrenia subjects, compared to their male counterparts.[35] Given the sexual dimorphism of schizophrenia and bipolar disorder—including differences in rate of occurrence, symptoms and time course—the differential methylation changes observed in male and female patients should not come as a surprise.

It is noteworthy that absolute methylation differences between psychosis and control samples were relatively small in the Mill et al. study,[30] even for some of the more significant loci (for example, 17% vs. 25% for *WDR18*). Therefore, DNA methylation changes in psychosis appear to be more subtle compared to those observed in brain neoplasia or some of the above-mentioned mental retardation syndromes. These features emphasize that DNA methylation analysis in psychosis samples is best approached by quantitative methodology, for which bisulfite sequencing remains the gold standard.[44] Given this lack of dramatic methylation changes in schizophrenia or bipolar brain, it comes as no surprise that earlier studies reporting positive findings (*REELIN*,[21,22] *COMT*[25]) were not consistently replicated in subsequent work.[23,24,26,27,30] Some of these inconsistencies may be due differences in methodology, the specific CpG dinucleotides assayed, brain regions examined and clinical populations from which the postmortem specimens were obtained. Furthermore, it must be noted that for these genes, the degree of DNA methylation may not necessarily correlate with functional consequences (i.e., decrease in mRNA transcript levels); rather, the specific location of the methylated CpG dinucleotide—for example, within a transcription factor binding site—may be more critical for mediating transcriptional repression.

In addition to the overall subtle nature of these psychosis-related alterations, the interpretation of DNA methylation studies on postmortem brain is complicated by additional factors:

(1) To date, most methylation studies in brain have utilized DNA extracted from whole tissue homogenates. This represents a major confound, as different cell types are known to possess unique methylation patterns and brain tissue is comprised of multiple types of neurons, glia and other cells. Moreover, specific sub-populations of cells within specific brain regions are thought to be affected in the psychotic disorders, such as parvalbumin-immunoreactive neurons,[45-49] oligodendrocytes[50-53] and astrocytes.[54-56] Thus, if alterations in DNA methylation within specific cell populations do indeed play a role in the pathoetiology of psychosis, some methylation changes may be "diluted"—or even undetectable—due to the averaging of methylation signals from a heterogeneous pool of cells. Furthermore, neuron-to-glia ratios show considerable variation during the course of normal maturation and aging.[57] This is not a trivial point, because there is evidence that, for select gene loci, the DNA methylation signal from postmitotic neurons differs considerably from tissue homogenate. Specifically, when DNA methylation was selectively assayed for neuronal nuclei obtained from postmortem human brain, 4/10 loci showed age-related

methylation changes similar to DNA from tissue homogenate, but 6/10 loci did not.[58]

(2) In addition, in vitro studies in cell culture suggest that DNA methylation is dynamically regulated—on the scale of minutes to hours—in response to DNA methyltransferase inhibitors[59,60] and depolarization.[61] Thus, it will be important to more fully elucidate how diverse environmental stimuli impact the regulation of DNA methylation in human brain, as these factors could potentially result in methylation changes unrelated to disease etiology. Indeed, recent studies have demonstrated that the DNA methyltransferases and methylation patterns in a variety of tissues, including CNS, are influenced by a variety of factors, including social environment,[62,63] ischemia,[64] environmental toxins,[65-67] nicotine,[68] alcohol,[69] psychostimulants[70,71] and antipsychotic drugs.[30,72,73]

However, the above-mentioned factors could also play a role in the pathogenesis of schizophrenia and bipolar disorder. Thus, it will be important to explore both the origin and timing of DNA methylation changes in psychosis whether they arise from stochastic events during embryogenesis, are secondary effects of psychosis in the patient (or even in an affected parent), or reflect exposure to different environmental stimuli during subsequent development, maturation and aging remains to be determined. The latter hypothesis gains credence from work by Fraga et al., (2005)[74] which shows that methylation patterns of monozygotic twins become increasingly different with age; furthermore, twins who were raised apart demonstrated greater differences in DNA methylation patterns than those raised together. In addition to environmental influences, accumulating evidence suggests that epigenetic marks can be inherited across multiple generations,[75-77] providing an alternative explanation for the aggregation of schizophrenia and bipolar disorder in families. However, to date, evidence for DNA methylation changes in germ cells of individuals diagnosed with major psychosis is lacking.[30]

Therefore, while important issues remain to be resolved, including the origin of methylation changes in schizophrenia and bipolar disorder, ante- and postmortem confounds, and cellular heterogeneity of brain tissue, one can expect that epigenetic studies on human brain, such as the one undertaken by Mill et al.,[30] will significantly advance our understanding of the molecular pathology underlying complex psychiatric disorders.

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