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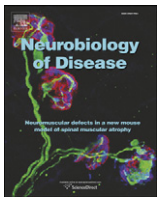

Review

The epigenetics of social adversity in early life: Implications for mental health outcomes

Patrick O. McGowan [a,b], Moshe Szyf [b,c,*]

[a] Department of Psychiatry, McGill University, Montreal, Quebec, Canada H3G 1Y6
[b] Sackler Program for Epigenetics and Psychobiology at McGill University, McGill University, Montreal, Quebec, Canada H3G 1Y6
[c] Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada H3G 1Y6

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ABSTRACT

An organism's behavioral and physiological and social milieu influence and are influenced by the epigenome, which is composed predominantly of chromatin and the covalent modification of DNA by methylation. Epigenetic patterns are sculpted during development to shape the diversity of gene expression programs in the organism. In contrast to the genetic sequence, which is determined by inheritance and is virtually identical in all tissues, the epigenetic pattern varies from cell type to cell type and is potentially dynamic throughout life. It is postulated here that different environmental exposures, including early parental care, could impact epigenetic patterns, with important implications for mental health in humans. Because epigenetic programming defines the state of expression of genes, epigenetic differences could have the same consequences as genetic polymorphisms. Yet in contrast to genetic sequence differences, epigenetic alterations are potentially reversible. This review will discuss basic epigenetic mechanisms and how epigenetic processes early in life might play a role in defining inter-individual trajectories of human behavior. In this regard, we will examine evidence for the possibility that epigenetic mechanisms can contribute to later-onset neurological dysfunction and disease.

* Corresponding author. Department of Pharmacology and Therapeutics, McGill University, Montreal, Quebec, Canada H3G 1Y6.
E-mail address: moshe.szyf@mcgill.ca (M. Szyf).
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Contents

Introduction

Different cell types execute distinctive programs of gene expression that are highly responsive to developmental, physiological, pathological and environmental cues. The combination of mechanisms that confer long-term programming to genes and could bring about a change in gene function without changing gene sequence is herein termed epigenetic changes. We propose a definition of epigenetics that includes any long-term change in gene function that persists even when the initial trigger is long gone that does not involve a change in gene sequence or structure. Thus, a change in chromatin or DNA methylation in a postmitotic neuron that lasts for a long period of time would be considered an epigenetic change even in the absence of cell division. This definition stands in contrast to some classical definitions of epigenetics that require heritability in dividing somatic cells or even through germ line transmission across generations. The less strict definition of epigenetics proposed here is especially important in understanding long-term changes in gene function in the brain. Stable changes in chromatin or DNA modification in postmitotic neurons or dividing cells could be environmentally driven, may occur in response to triggers at different points in life and are potentially reversible, whereas genetic differences are germ line transmitted, virtually fixed and irreversible.

Much of the phenotypic variation seen in human populations might be caused by differences in long-term programming of gene function rather than the sequence per se, and any future study of the basis for inter-individual phenotypic diversity should consider epigenetic variations in addition to genetic sequence polymorphisms (Meaney and Szyf, 2005). In effect, epigenetic silencing and genetic silencing could have similar phenotypic consequences. Therefore, mapping the epigenome is potentially as important as the mapping of the genome in our quest to understand phenotypic differences in humans.

By extension, identifying epigenetic differences that are associated with behavioral pathologies has important implications for human health because they are potentially reversible and amenable to therapeutic intervention (Szyf, 2001; Szyf, 2009). Drugs targeting epigenetic mechanisms are currently being tested in clinical trials in psychiatric disorders (Simonini et al., 2006). It is our view that once we understand the rules through which different environmental exposures modify epigenetic processes, we may also be able to design behavioral strategies to prevent and reverse deleterious environmentally driven epigenetic alterations. The dynamic nature of epigenetic regulation, in contrast to the virtually static nature of the gene sequence, provides a mechanism for reprogramming gene function in response to changes in life style trajectories. In this way, epigenetics may provide explanations for well defined environmental effects on phenotypes. Epigenetic changes have now been associated with a number of paradigms involving social behavior in animal models—for example stress (Fuchikami et al., 2009), animal models of PTSD (Chertkow-Deutsher et al., 2009), chronic social defeat (Tsankova et al., 2006) and extinction of conditioned fear (Bredy et al., 2007). Rather than to attempt an exhaustive review of what is currently a somewhat disparate literature, our focus on early life adversity will serve as a platform to discuss the basic mechanisms involved in epigenetic programming and our studies of epigenetic differences associated with early life social adversity in humans.

The epigenome

Chromatin and the histone code

The epigenome consists of the chromatin, a protein-based structure around which the DNA is wrapped, as well as a covalent modification of the DNA itself by the methylation of cytosine rings found at CG dinucleotides (Razin, 1998). The epigenome determines the accessibility of the DNA to the transcription machinery, which converts genetic information into the messenger RNA necessary for gene function. Inaccessible genes are therefore relatively silent whereas accessible genes are actively transcribed. Densely packaged chromatin can be visualized microscopically and is termed heterochromatin while open accessible chromatin is termed euchromatin. Recently, another new level of epigenetic regulation by small non-coding RNAs termed microRNA has been discovered (Bergmann and Lane, 2003), which has already been suggested to play an important role in behavioral pathologies in humans (Vo et al., 2005), as has been reviewed elsewhere (Mehler and Mattick 2006; Mehler and Mattick, 2007; Qureshi and Mehler, 2009).

The basic building block of chromatin is the nucleosome, which is made up of an octamer of histone proteins. The N-terminal tails of these histones are extensively modified by methylation, phosphorylation, acetylation and ubiquitination. The state of modification of these tails plays an important role in defining the accessibility of the DNA wrapped around the nucleosome core. It was proposed that the amino terminal tails of H3 and H4 histones that are positively charged form tight interactions with the negatively charged DNA backbone, thus blocking the interaction of transcription factors with the DNA. Modifications of the tails neutralize the charge on the tails, thus relaxing the tight grip of the histone tails. Different histone variants, which replace the standard isoforms also play a regulatory role and serve to mark active genes in some instances (Henikoff et al., 2004). The specific pattern of histone modifications was proposed to form a "histone code," that delineates the parts of the genome to be expressed at a given point in time in a given cell type (Jenuwein and Allis, 2001).

Histone modifying enzymes and chromatin remodeling

The most investigated histone modifying enzymes are histone acetyltransferases (HAT), which acetylate histone H3 and H4 at different residues as well as other histone deacetylases (HDAC), which deacetylate histone tails (Kuo and Allis, 1998). Histone acetylation is believed to be a predominant signal for an active

chromatin configuration (Perry and Chalkley, 1982; Lee et al., 1993). Deacetylated histones are characteristic of chromatin associated with inactive genes. Histone tail acetylation is believed to enhance the accessibility of a gene to the transcription machinery whereas deacetylated tails are highly charged and believed to be tightly associated with the DNA backbone and thus limiting accessibility of genes to transcription factors (Kuo and Allis, 1998).

Some specific histone methylation events are associated with gene silencing and some with gene activation (Lachner et al., 2001). Particular factors recognize histone modifications and further stabilize an inactive state. Recently described histone demethylases remove the methylation mark causing either activation or repression of gene expression (Shi et al., 2004; Tsukada et al., 2006). Chromatin remodeling complexes, which are ATP dependent, alter the position of nucleosomes around the transcription initiation site and define accessibility of regulatory regions to the transcription machinery. It is becoming clear now that there is an interrelationship between chromatin modification and chromatin remodeling (Bultman et al., 2005).

A basic principle in epigenetic regulation is targeting. Histone modifying enzymes are generally not gene specific. Specific transcription factors and transcription repressors recruit histone-modifying enzymes to specific genes and thus define the gene-specific profile of histone modification (Jenuwein and Allis, 2001). Transcription factors and repressor recognize specific *cis*-acing sequences in genes, bind to these sequences and attract the specific chromatin modifying enzymes to these genes through protein-protein interactions. Signal transduction pathways, which are activated by cell-surface receptors, could serve as conduits for epigenetic change linking environmental triggers at cell surface receptors with gene-specific chromatin alterations, leading to the reprogramming of gene activity.

DNA methylation and gene expression silencing

The DNA molecule itself can be chemically modified by methyl residues at the 5′ position of the cytosine rings in the dinucleotide sequence CG in vertebrates (Razin, 1998) (Fig. 1). What distinguishes DNA methylation in vertebrate genomes is the fact that not all CGs are methylated in any given cell type (Razin, 1998), resulting in cell type specific patterns of methylation. Thus, the DNA methylation pattern confers upon the genome its cell type identity. Since DNA methylation is part of the chemical structure of the DNA itself, it is more stable than other epigenetic marks and thus it has extremely important diagnostic potential in humans (Beck et al., 1999).

A growing line of evidence supports the idea that, similar to chromatin modification, DNA methylation is also potentially reversible (Ramchandani et al., 1999) even in predominantly post mitotic tissues such as the brain (Weaver et al., 2004). The DNA methylation pattern is not copied by the DNA replication machinery, but by an independent enzymatic machinery (Razin and Cedar, 1977) termed DNA methyltransferase(s) (DNMTs; Fig. 2). DNA methylation patterns in vertebrates are distinguished by their correlation with chromatin structure. Active regions of the chromatin, which enable gene expression, are associated with hypomethylated DNA whereas hypermethylated DNA is packaged in inactive chromatin (Razin and Cedar, 1977; Razin, 1998).

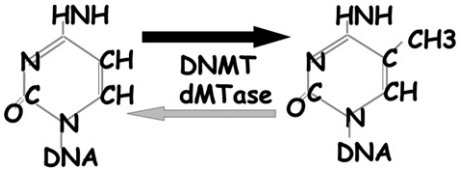

Fig. 1. The reversible DNA methylation reaction. DNA methyltransferases (DNMT) catalyze the transfer of methyl groups from the methyl donor S-adenosylmethionine to DNA releasing S-adenosylhomocysteine. Demethylases release the methyl group from methylated DNA.

DNA methylation in critical regulatory regions, including gene promoters and enhancers, serves as a signal to silence gene expression by two main mechanisms (Fig. 3). The first mechanism involves direct interference of the methyl residue with the binding of a transcription factor to its recognition element in the gene. The interaction of transcription factors with genes is required for activation of the gene; lack of binding of a transcription factor would result in silencing of gene expression. This form of inhibition of transcription by methylation requires that the methylation event occur within the recognition sequence of the transcription factor. The second mechanism is indirect. A certain density of DNA methylation in the region of the gene attracts the binding of methylated-DNA binding proteins such as MeCP2 (Nan et al., 1997). MeCP2 recruits other proteins such as SIN3A and histone modifying enzymes, which lead to the formation of a "closed" chromatin configuration and the silencing of gene expression (Nan et al., 1997). Thus, aberrant methylation will silence a gene, resulting in loss of function, which will have a similar consequence to a loss of function by genetic mechanism such as mutation, deletion or rearrangement.

Although much of our current knowledge of the role of DNA methylation in gene regulation derives from studies of effects in promoter regions, it is becoming clear that DNA methylation in other gene elements plays important roles in regulating gene function. For example, increased DNA methylation within the body of genes is typically associated with active transcription (ref). However, the function of gene body methylation remains elusive. First elucidated in plants by high-throughput sequencing methods, it has been suggested that gene body methylation might help to inhibit cryptic transcription initiation (Zilberman et al., 2007) or suppress recombination or transposon insertion within genes (Zhu, 2008). Other recent data indicate that DNA methylation at the 3′ ends of genes, as well as intragenic DNA methylation may play distinct roles on regulating gene expression (Suzuki and Bird, 2008). For example, DNA methylation within intronic regions may regulate the activity of intragenic non-coding RNAs that may be involved in regulating RNA splice variation, silencing of chromatin, degradation of mRNA and blocking translation (Mattick and Makunin, 2006). As briefly mentioned above, epigenetic regulation by small non-coding RNAs termed microRNA could potentially play an important role in behavioral pathologies in humans as well, as has been reviewed elsewhere (Mehler and Mattick 2006; Mehler and Mattick, 2007; Qureshi and Mehler, 2009).

The roles of the DNA methylation machinery and the reversibility of DNA methylation patterns

The DNA methylation machinery in vertebrates has two main roles. First, it has to establish new cell-type specific DNA methylation patterns during development and possibly during adulthood in response to new signals. Second, it has to maintain these patterns during downstream cell divisions and after DNA repair. The different enzymes and proteins of the DNA methylation machinery must address these different tasks. The methylation of DNA occurs immediately after replication by a transfer of a methyl moiety from the donor *S*-adenosyl-L-methionine (AdoMet) in a reaction catalyzed by DNMTs (Fig. 2). Three distinct phylogenic DNA methyltransferases were identified in mammals. DNMT1 shows preference for hemimethylated DNA *in vitro*, which is consistent with its role as a maintenance DNMT (Fig. 2), whereas DNMT3a and DNMT3b methylate unmethylated and methylated DNA at an equal rate which is consistent with a *de novo* DNMT role (Okano et al., 1998).

We have proposed that the DNA methylation pattern is a balance of methylation and demethylation reactions that are responsive to physiological and environmental signals and thus forms a platform for gene-environment interactions (Ramchandani et al., 1999) (Fig. 1). There are now convincing examples of active, replication independent DNA demethylation during development as well as in somatic tissues

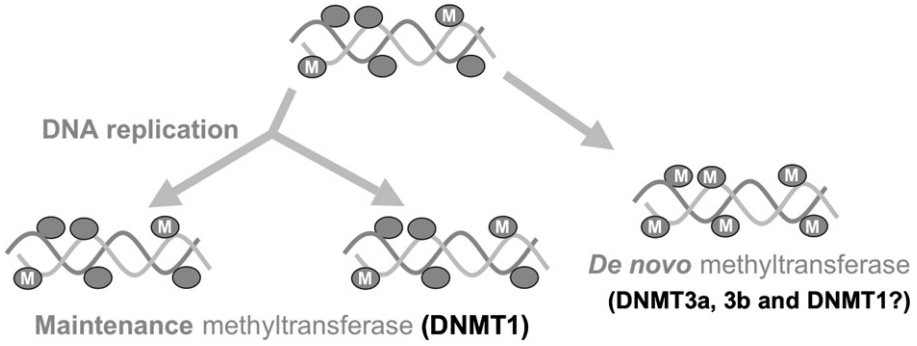

Fig. 2. DNA methylation reactions. Early after fertilization many of the methylation marks are removed by demethylases. De novo DNA methyltransferases (DNMT) add methyl groups. Once a pattern is generated it is inherited by maintenance DNMTs that copy the methylation pattern. Methyl groups are indicated by M, potential methylatable sites are indicated by an open circle.

(Lucarelli et al., 2001; Kersh et al., 2006). One example from our laboratory is that of the glucocorticoid receptor gene promoter in the brains of adult rats upon treatment with the HDAC inhibitor TSA (Weaver et al., 2004), and which has been reviewed elsewhere (e.g., see (Meaney and Szyf, 2005; McGowan and Kato, 2008a; McGowan et al., 2008b).

We also propose that the direction of the DNA methylation reaction is defined by the state of chromatin. The gene-specificity of the state of chromatin is defined by sequence-specific *trans*-acting factors that recruit chromatin-modifying enzymes to specific genes. Chromatin configuration then gates the accessibility of genes to either DNA methylation or demethylation machineries. We propose the following model: Factors that target specific chromatin modification events to genes are good candidates to define the direction of the DNA methylation equilibrium by either recruiting DNA methylation enzymes or by facilitating demethylation (D'Alessio and Szyf, 2006; Shilatifard, 2006; Berger, 2007; Suzuki and Bird, 2008).

Epigenetic contributions to mental health

Influence of DNA methylation on mental health

Genetic defects in genes encoding the DNA methylation and chromatin machinery exhibit profound effects on mental health in humans. A classic example is RETT syndrome, a progressive neurodevelopmental disorder and one of the most common causes of mental retardation in females, which is caused by mutations in the methylated DNA binding protein MeCP2 (Amir et al., 1999). Mutations in MeCP2 and reduced MeCP2 expression have widespread neurological effects, being also associated with autism (Nagarajan et al., 2006; Ben Zeev Ghidoni, 2007; Herman et al., 2007; Lasalle, 2007). ATRX, a severe X-linked form of syndromal mental retardation associated with alpha thalassaemia (ATR-X syndrome) is caused by a mutation in a gene encoding a member of the SNF2 subgroup of a superfamily of proteins with similar ATPase and helicase domains involved in chromatin remodeling (Picketts et al., 1996). The ATRX mutation is associated with aberrant DNA methylation (Gibbons et al., 2000). Although these genetic lesions in the methylation machinery were present through development and are thus fundamentally different from methylation changes after birth, these data nevertheless support the hypothesis that DNA methylation defects could lead to mental pathologies. Thus, it is conceivable that environmental exposures affecting the activity of the methylation machinery would also lead to behavioral and mental pathologies.

There are some data indicating aberrant methylation in mental pathologies later in life in humans, although it is unclear whether these changes in DNA methylation originated during embryogenesis

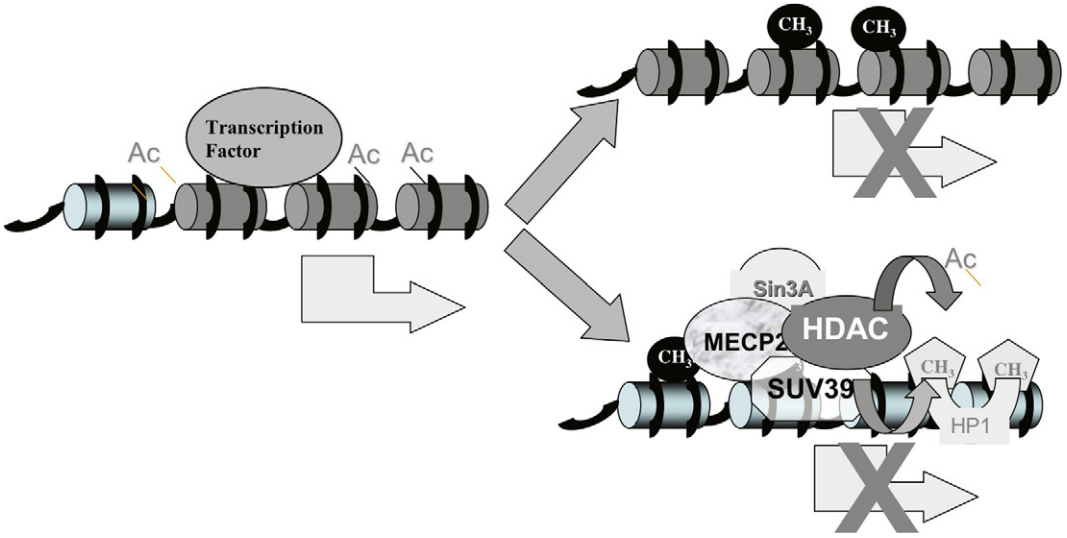

Fig. 3. Two mechanisms of silencing gene expression by DNA methylation. An expressed gene (transcription indicated by a horizontal arrow) is usually associated with acetylated histones and is unmethylated. A methylation event would lead to methylation by two different mechanisms. The methyl group (CH3) interferes with the binding of a transcription factor that is required for gene expression, resulting in blocking of transcription. The second mechanism shown in the bottom right is indirect. Methylated DNA attracts methylated DNA binding proteins such as MeCP2, which in turn recruits co-repressors such as SIN3A, histone methyltransferases such as SUV39 that methylates histones and histone deacetylases (HDAC), which remove the acetyl groups from histone tails. Methylated histones (K9 residue of histone tails) recruit heterochromatin proteins such as HP1, which contributes to a closed chromatin configuration and silencing of the gene.

or later in life as a response to an environmental exposure. For example, the gene encoding *REELIN*, a protein involved in neuronal development and synaptogenesis and implicated in long-term memory, was found to be hypermethylated in the brains of schizophrenia patients, and the methylation of the *REELIN* gene promoter was correlated with its reduced expression and increased DNMT1 expression in GABAergic interneurons in the prefrontal cortex (Chen et al., 2002; Costa et al., 2002; Costa et al., 2003; Grayson et al., 2005; Veldic et al., 2007).

Another example is the association between the DNA methylation status of the promoter of membrane-bound catechol-*O*-methyltransferase (COMT) (Abdolmaleky et al., 2006), an enzyme regulating the level of dopamine, with schizophrenia and bipolar disorder. The COMT gene has two promoters, each generating its own mRNA isoform: the membrane-bound isoform (MBCOMT) and the soluble isoform (S-COMT), respectively. One study examined the methylation status of the MB-COMT promoter in the prefrontal cortex (Brodmann's area 46) by means of a methylation-specific PCR analysis (Abdolmaleky et al., 2006). While 60% of 35 controls showed some PCR product obtained from the methylated allele, only 29% of 35 patients with bipolar disorder and 26% of 35 patients with schizophrenia showed a methylation signal. Subjects with a methylation signal showed significantly lower expression levels of MBCOMT than those not showing a methylation signal in postmortem brain samples. This study suggested the possible role of hypomethylation of the promoter of MB-COMT in both bipolar disorder and schizophrenia. These results suggest that gene-specific DNA methylation changes may be associated with increased risk of multiple forms of psychopathology.

We have described in a first published report of aberrant methylation associated with suicide that promoters of the genes encoding ribosomal RNA (rRNA) are heavily methylated in hippocampi from subjects who committed suicide relative to controls (McGowan et al., 2008c). Methylation of rRNA defines the fraction of rRNA molecules that are active in a cell, and the output of rRNA transcription defines to a large extent the protein synthesis capacity of a cell. Protein synthesis is critical for learning and memory. We found that the genetic sequence of rRNA was identical in all subjects, and there was no difference in methylation between suicide victims and controls in the cerebellum, a brain region that is not normally associated with psychopathology. These data imply that epigenetic effects that influence psychopathology likely target particular neural pathways. A reduced capacity for protein synthesis in the hippocampus of suicide victims could be epigenetically regulated, and may be involved in the pathology leading to suicide.

Thus, evidence is emerging that aberrant DNA methylation is involved in psychopathologies. Standardized forensic psychiatry methods had been used to ascertain that all of the suicide victims in our study had a history of severe abuse or neglect during childhood, which is common among suicide victims. Thus, the data suggest that severe adversity during early childhood may have been a contributing factor to the observed epigenetic pathology. It was unclear whether the observed abnormalities were a result of early adversity or whether they had emerged during adulthood as a result of the mental disorders associated with suicide. We undertook another study to address this question.

In a subsequent study, we examined the glucocorticoid receptor gene promoter in the hippocampus of human suicide victims and controls (McGowan et al., 2009). We showed previously that the epigenetic status of the glucocorticoid receptor gene promoter is regulated by parental care during early postnatal development in rats and amenable to pharmacological interventions later in life (for reviews, see (Meaney and Szyf, 2005; McGowan et al., 2008b). In our recent study, all of the suicide victims and none of the controls had a history of childhood abuse or severe neglect. A third group was composed of suicide victims with a history that was negative for childhood abuse or neglect. We found that, as in the animal model, the glucocorticoid receptor was epigenetically regulated in the human brain, and associated with altered glucocorticoid receptor gene expression. Hypermethylation of the glucocorticoid receptor gene was found among suicide victims with a history of abuse in childhood, but not among controls or suicide victims with a negative history of childhood abuse. The data are consistent with other data from the literature suggesting that suicide has a developmental origin. They suggest that epigenetic processes might mediate the effects of the social environment during childhood on hippocampal gene expression and that stable epigenetic marks such as DNA methylation might then persist into adulthood and influence vulnerability for psychopathology through effects on intermediate levels of function such as activity of the hypothalamic–adrenal–pituitary (HPA) axis that regulates the stress response. However, it remains unclear whether the epigenetic aberrations documented in brain pathologies were present in the germ line, whether they were introduced during embryogenesis, or whether they were truly changes occurring during early childhood.

There has been considerable interest in the DNA methylation changes in monozygotic twins discordant for mental disorders. Monozygotic twin pairs share a virtually identical genome but not the same pre- and post-natal environments, and frequently differ in their prevalence of mental disorders (e.g., see Petronis, 2006). Differences in DNA methylation were observed between monozygotic twins discordant for schizophrenia (Tsujita et al., 1998; McDonald et al., 2003; Petronis et al., 2003). Another case control analysis also found that a decreased methylation status of PPIEL (peptidylprolyl isomerase E-like) in the affected twin and in patients with bipolar II disorder was significantly correlated with its mRNA expression level, and also with the DNA methylation levels in peripheral leukocytes (Kuratomi et al., 2007). A case study of monozygotic twins discordant for Alzheimer's disease found substantially lower overall levels of DNA methylation in the temporal cortex of the affected twin (Mastroeni et al., 2009). Recently, a large-scale study of methylation discordance in monozygotic twins using whole-genome microarray methods found substantial variability across the genome in DNA methylation between twins (Kaminsky et al., 2009). These data suggest that widespread differences in DNA methylation between twins may underlie some of the variability associated with divergent incidences of mental disorders. However, caution is perhaps warranted in the interpretation of such results. For example, DNA methylation differences between monozygotic twins were reported to increase with age (Fraga et al., 2005). Consequently, it is possible that the differences in DNA methylation in discordant twins may not always be related to the pathophysiology of the illness in question.

Chromatin modifications and their roles in mental health

The fact that histone methylation is reversible provides a wide platform for pharmacological and therapeutic manipulations of the state of histone methylation in both directions. Both histone demethylases and histone methyltransferase are excellent candidates for new drug discovery. Understanding the intricate details of their genomic targets will allow the design of targeted and specific therapeutics.

The epigenetic effects of current clinically used monoamine oxidase inhibitors provide leads for the further development of therapies targeting the epigenome. For example, H3K4Me2 is a hallmark of active genes and the target of the histone demethylase LSD1, which demethylates H3-K4Me2. Interestingly, certain non-selective monoamine oxidase inhibitors used as antidepressants such as Tranylcypromine that were clinically used for some time and believed to be acting on monoamine oxidases also appear to inhibit LSD1 demethylase (Lee et al., 2006). It is possible that inhibition of LSD1 is part of the mechanism of action of these antidepressants

through activation of critical genes suppressed by the H3-K4me2 demethylating activity of LSD1 in the brain (Shi et al., 2004) or by repressing genes activated by the H3-K9Me2 demethylation activity of LSD1 (Metzger et al., 2005). Thus, it is possible that LSD1 inhibition is involved in the mechanism of action of antidepressive agents. It is tempting to speculate that selective inhibitors of LSD1 might be effective as antidepressants. This is an idea that might be pursued in the future.

Valproic acid, a long established antiepileptic and mood stabilizer, is also an HDACi (Phiel et al., 2001), suggesting a possible role for HDACi in treating mental disorders such as schizophrenia and bipolar disorder. Valproic acid has some effect in alleviating psychotic agitation as an adjunct to antipsychotics in schizophrenia (Bowden, 2007; Yoshimura et al., 2007). One recent study found that valproate, when used during pregnancy, was associated with a 6–9 point lower average IQ in offspring at 3 years of age (Meador et al., 2009). Although biological and behavioral effects of HDACi in the brain are somewhat characterized, the specific gene targets of HDACi in the brain and their function in mental pathologies are not well delineated. Nevertheless, the limited clinical data suggest a potentially important role for HDACi in treatment of mental disorders. Several clinical trials have tested valproate as an adjunctive therapy to antipsychotics in schizophrenia. There are indications that valproate might improve violent episodes in a subset of schizophrenia patients (Basan and Leucht, 2004) and might have an effect on euphoric mania in combination with antipsychotics (Bowden, 2007), as well as, features of manic symptomatology in bipolar disorders (Bowden, 2007). It should be noted that many of these trials were of small size and that further clinical trials are needed with valproate and with more potent and selective HDACi to methodically test the therapeutic potential of HDACi.

One question that needs to be addressed is whether the observed defects in histone acetylation in mental pathologies are a consequence of aberrant deregulation of the overall levels of certain HDAC isotypes or HATs, or whether it involves the aberrant targeting of HDAC to a selection of promoters. The fact that inhibition of a general enzyme such as HDAC results in exquisite positive changes in the brain implies some specificity, even for a general inhibitor of a specific class of HDACs as discussed above. It will be important to delineate the response of the transcriptomes of different brain regions to HDACi and to map the genes that are critically involved in the molecular pathology of the disease. It will also be important to characterize the critical isoforms of HDAC for regulation of these genes. The advent of isotypic specific HDACi might enhance the efficacy and potency of the treatment and reduce its toxicity.

As noted in the examples provided above, HDACi used in the treatment of psychiatric disorders, either in combination with other psychiatric drugs or alone, lack specificity for particular genes or neural networks. In much same manner as for classical drugs used in psychiatric therapy, then, it is unlikely that any epigenetic drug by itself will be entirely effective in treating mental disorders. It must also be noted that the HDACi activity of the aforementioned valproate is not the only action of this drug. As such, at present the putative direct epigenetic effects of these drugs on the symptomatology associated with mental disorders are not well understood. Thus, it will be important to develop HDACi that are specific for particular chromatin modifications as well as animal models lacking particular HDAC activities in order to directly test evidence for their molecular and behavioral mechanisms (Tsankova et al., 2007).

Summary and prospective

We propose that epigenetic mechanisms serve as an interface between the environment and the genome, and that enzymes that sculpt chromatin states and DNA methylation patterns are responsive to cellular signaling activated in the brain in response to adversity early in life. We hypothesize that the social environment early in life has a long-lasting impact on mental and physical health trajectories via epigenetic marking of specific genes. However, one important aspect of the basic epigenetic mechanisms reviewed here is that although the epigenetic markings are long-lasting they are nevertheless potentially reversible. Such data suggest, therefore, that appropriate social and pharmacological interventions could reverse deleterious epigenetic markings sculpted by negative social exposures early in life. In this review, we have focused on the epigenetic consequences of social adversity early in life and its association with clear deleterious behavioral outcomes such as suicide in humans. However, although much work remains to be done, there is some indication that positive early social experience can have a mitigating effect on stress responses later in life via epigenetic mechanisms, suggesting a protective role for positive early parental care (Weaver et al., 2004). Taken together, these data suggest that social and pharmacological interventions might activate signaling pathways in the brain that would result in a change in either the targeting or activity of the epigenetic machinery and thus a change in epigenetic markings. Epigenetic drugs are now in use in cancer and psychiatric therapy, and it is anticipated that the future will see increased use of epigenetic drugs and interventions in several other health conditions. Thus, understanding the epigenetic consequences of social exposures stands not only to revolutionize medicine but also to transform social sciences and humanities as well. Epigenetics could serve as a bridge between the social sciences and the biological sciences, allowing a truly integrated understanding of human health and behavior.

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