



DNA Methylation: The Essential Link between Environmental Adversities and Major Depressive Disorder



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Abstract

Major depressive disorder has been a major public health problem. Multiple evidences suggests that epigenetic modification is essential in biological processes of depression. In recent times, DNA methylation has been regarded as a potential link between environment stress and depression. The genetic vulnerability is not able to explain by itself the development of major depression as it is a complex disorder where no single gene is sufficient to cause this disease. Probably each susceptibility gene contributes to a small fraction of the total genetic risk. In this present review an attempt has been made to elucidate the contribution of genetic and epigenetic factors and environment in the pathogenesis of major depressive disorder.

Keywords: Stress; Methylation; 5-HT; Glucocorticoid; DNA methyl transferases

Introduction

Major depressive disorder (MDD) is a common psychiatric problem characterized by sadness, loss of interest or pleasure, guilt feelings, cognitive deficiencies etc. that impair an individual's ability to function properly in daily works deteriorating the quality of his life. Depression is considered as the psychiatric diagnosis most commonly associated with suicide. A number of brain regions responsible for higher cognitive functions undergo alteration or deterioration in depression patients [1]. It has been recognized that chronic environmental stresses play critical role in the etiology of MDD [2]. Individuals may respond to environmental stresses by heritable changes in their genome that involve alterations in the expression of the genes without any changes in gene sequence [3]. Such modifications can be brought about by linking DNA with methyl groups and this epigenetic modification has been regarded as a potential link between environment and major depression [4,5]. DNA methylation is the key mechanism that regulate many vital developmental processes like genome imprinting, X-chromosome inactivation, transposon silencing, gene regulations etc [6]. Regulation of gene activity is extremely important for normal functioning of the genome. Cells can perform their functions normally only if both DNA sequences and epigenetic components of the genome operate properly. Thus the abnormalities in the DNA methylation are responsible for human diseases in which diseased tissue exhibit different DNA methylation pattern from normal counterparts [7]. An

increasing number of human diseases have been associated with aberrant DNA methylation that includes cardiovascular diseases, neurological disorders, cancer [8] and major depression [9]. Various experimental and epidemiological evidences suggest that stress can cause the methylation of selected genes / promoters that influence the expressions of genes relevant to the risk for the development of depression [10-12]. Although it is generally believed that the interplay of genetic polymorphism and environmental stresses increase the susceptibility of the MDD, many peculiarities associated with this disease make it difficult to explain the aetiology of this disorder only in terms of such association. DNA methylation, a kind of epigenetic mechanism which is acquired and heritable offers new insight into the pathogenesis of MDD [13]. In this present article an attempt has been made to elucidate how adverse environmental factors can activate the DNA methylation and negatively regulate the expression of genes related to depression. Before that a brief discussion will be made on why interactions between genetic polymorphism and environmental factors are not sufficient to explain the complex etiology of MDD.

Controversies Over the Etiology of Depression due to Gene-Environment Interactions

Since the heritability of depression is approximately 40% it is considered that in addition to genetic factors, environmental factors should also be considered as the important factor for the

etiology of the MDD [14]. In spite of a number of genome-wide association studies (GWAS) very few genetic variants have been implicated in the depressive disorder. For example Wray et al. [15] by investigating 5763 cases and 6901 controls could only correlate the polymorphism of two genes namely, galanin and adenylyl cyclase with MDD. In another very large GWAS comprising 9240 MDD subjects and 9519 controls failed to correlate any single nucleotide polymorphism (SNP) with MDD [16]. It has been suggested that dysregulation of central serotonergic system plays a major role in the pathogenesis of major depression [17]. Thus in search of candidate genes for MDD, researches have been mainly focused on genes associated with serotonergic system [13]. The Serotonin (5-HT) transporter gene SLC6A4 is widely distributed both in central and peripheral nervous system. The major function of the SLC6A4 gene product i.e. serotonin transporter (SERT) is to reuptake of 5-HT from the synaptic cleft. This reuptake of 5-HT is important for the modulation of strength and duration of 5-HT mediated neurotransmission. Furthermore, transport of 5-HT from the synaptic cleft to the presynaptic neuron also assists in its reutilization [18]. There are two polymorphic regions in SLC6A4 gene. One of them called serotonin transporter linked polymorphic region (5-HTTLPR) lies 1400bp upstream of the transcription start site of SLC6A4 and contains repeated copies of 20-23bp. The most common forms include 14 and 16 repeats called short(s) and long(l) alleles respectively. The 's' allele possesses lower transcriptional activity than 'l' allele. 5-HTTLPR has been reported to be associated with many psychiatric disorders like anxiety, bipolar disorder, schizophrenia, depression in the presence of adversities [19]. However, a meta-analysis of the interaction of serotonin transporter gene 5-HTTLPR and stressful life events on depression revealed that neither 5-HTTLPR polymorphism nor the interaction of life stresses with the 5-HTTLPR genotype contributed to depression [20]. Recurrences of depressive episode are very common in MDD patients [21]. Recently one study [22], that was conducted on 1000 MDD patients, revealed that glucocorticoid receptor (GR) and mineralocorticoid receptor (MR) gene polymorphism were not associated with the recurrence of depression. Overall this study could not establish any consistent association between GR and MR gene polymorphism, interaction between GR and MR haplotypes and stressful conditions and recurrence of MDD. Possibly these polymorphisms might be associated with onset of MDD. Out of several thousands of genes expressed in brain, candidate gene studies provided little convincing support for the involvement of any candidate gene in MDD [23]. It is possible that numerous loci with small effects can interact epistatically with each other and with environmental factors in the etiology of depression. Some important genes in this respect are the genes for serotonin transporter, angiotensin-converting enzyme, 10-methylenetetrahydrofolate reductase, tryptophan hydroxylase, brain-derived neurotrophic factor (BDNF), catechol-O-methyl transferase, phospholipase A2, glucocorticoid receptor (GR) etc. [13,23].

Gene Silencing by DNA Methylation and its Induction by Stress

DNA methylation involves the transfer of a methyl group in the 5- position of the cytosine residue in a CpG dinucleotide. The reaction is catalyzed by a group of enzymes called DNA methyl transferases (DNMTs). In mammals out of three enzymatically active forms of DNMTs, DNMT1 is required for maintaining methylation after each cell division; while DNMT3a and DNMT3b are responsible for de novo methylation during development and differentiation [24]. In case of mammals, methylation at promoter and enhancer genes cause the silencing of gene expressions in two ways. In the first mechanism, methyl groups interfere the binding of transcription factors in the regulatory regions and block the transcription of a gene thereby. In the second mechanism, methyl CpG binding protein 2 (MeCP2) can recognize and bind to methylated DNA in promoter and suppress the transcription [19]. Although for some genes DNA methylation is tissue specific, there are many genes which showed similar DNA methylation pattern in peripheral cells and brain [19]. Since it is nearly impossible to study the brain epigenetic pattern by using brain tissues, from living subjects peripheral epigenetic patterns using blood, buccal tissue, saliva samples have been used to correlate the epigenetic pattern of the brain [25]. The methylation process may begin with an 'epigenator' that may include a cascade of events in which release of glucocorticoid in response to environmental stress via an intracellular signaling pathway can recruit an 'epigenetic initiator' such as a DNA binding factor. Example of such an epigenetic initiator is REST protein which is neuron specific and contains a zinc domain that recognizes a specific DNA sequence for the establishment of the epigenetic pathway. The epigenetic initiator also recruits an 'epigenetic maintainer' such as DNMT for the methylation of DNA [26].

Multiple Evidences Link Depression with DNA Methylation of Genes Induced by Adverse Environmental Exposures

Stressful or traumatic life events, especially in the early phases of life are strongly associated with the development of many psychiatric illnesses including depression [27]. Recent evidences suggest that social psychological stresses may cause the methylation of selected genes or their promoters and alter the gene expressions relevant to diseases [10-12]. It had been observed that low level of maternal licking and grooming in rats led to higher cytosine methylation in the promoter of glucocorticoid receptor gene NR3C1 in the hippocampal neurons causing the reduced synthesis of GR. As GR causes the feed-back inhibition hypothalamic-pituitary-adrenal (HPA) axis, reduced synthesis of this steroid receptor cause the hyperactivation of this axis leading to depression [28,29]. In case of human, postmortem brain samples of suicide victims with the history of childhood abuses exhibited enhanced DNA methylation in promoter of NR3C1 exon accompanied by lower expression of the GR in hippocampus [30].

Bipolar disorder, in which patients exhibit depression and manic episodes also display aberrant methylation in the promoters of the genes relevant to depression. For example, in one study methylation status of NR3C1 gene promoter was assessed in patients with bipolar disorder having the history of childhood traumatic experiences such as sexual, physical and emotional. It was revealed that increase in traumatic events were associated with higher percent of NR3C1 methylation in blood leucocytes in these patients. Among the various maltreatments, emotional abuse was most significantly associated with methylation [31]. Brain-derived neurotrophic factor (BDNF) plays an important role in the survival and maintenance of the neurons of the central nervous system (CNS) [32]. BDNF binds to specific tyrosine kinase receptor namely, tropomyosin-related kinase B receptor (trkB) and initiates signaling cascade to regulate many aspects of neuron developments such as neurite outgrowth, synthesis of differentiating factors and morphological plasticity. In adults, BDNF maintains neural homeostasis and is involved in neuronal plasticity as well as learning and memory [33]. Thus lack of BDNF may impair cognitive function leading to depression. Recently many studies have revealed that DNA methylation of BDNF gene is linked to pathogenesis of depression as this epigenetic change reduces the synthesis of BDNF. It has been seen that adverse environmental circumstances can downregulate BDNF expression by the methylation of BDNF exon. For example, traumatic stress experiences such as continuous psychological stresses caused the hypermethylation of the BDNF exon IV and reduced the expression of this neurotropic factor in the CA1 region of hippocampus in post-traumatic stress disorder (PTSD)-like rats [34]. Furthermore, increased DNA methylation at the BDNF promoter IV in the hippocampus of adult mice had been associated with depression like behaviors [35]. In one study comparison of BDNF promoter methylation and cortical thickness was made between the patients with recurrent MDD and healthy controls. It was revealed that compared to controls, various regions of prefrontal cortex (PFC) such as orbitofrontal cortex, middle frontal cortex etc. were thinner in MDD patients accompanied by higher methylation in BDNF promoter [36]. Since PFC is associated with higher cognitive functions like encoding memory, intelligence, language, planning, decision making, prefrontal dysfunction due to its thinning might be responsible for depression [1]. In addition to the negative regulation of GR and BDNF expression by DNA methylation, this epigenetic mechanism also sheds light on its association with SLC6A4 gene expression that probably predisposes depression. It has been reported that lymphoblast cells exhibited increased methylation in the CpG island of the SLC6A4 gene promoter with reduced synthesis of SLC6A4 mRNA in the subjects with the history of depression [37]. In addition it had been found that depressive symptoms were more common among the adolescents with elevated buccal cell 5HTT methylation who carried 5HTTLPR short-allele [38]. In another study methylation status in the promoter of the gene SLC6A4 was measured in more than hundred patients with MDD. This study showed that

childhood adversities was significantly associated with higher SLC6A4 promoter methylation [39].

Monozygotic (MZ) twins are assumed to be genetically identical and match exactly on age, and sex which eliminate their confounding effects in biological analysis. In addition, identical twins generally share common raising environment which also limit the confounding effects of early life experiences [40]. It has been suggested that some of the observed phenotypic differences between MZ twins may be the result of epigenetic factors [41,42]. In fact substantial epigenetic differences occur in the genome during the lifetime of MZ twins, due to dynamic nature of epigenetic processes. Differences in epigenetic patterns in genetically identical individuals could occur by the influence of many factors such as smoking habits, physical activity, or diet, that have been proposed to have a long-term influence on epigenetic modifications [43]. Such random epigenetic alterations may accumulate during the lifetime of two MZ twins, and could lead to profound changes in gene expression if the alterations present in regulatory regions of the genome [13]. In fact many differences in the methylation have been found in CpG sites of a number of genes in MZ twins such as dopamine D2 receptors, catechol-o-methyl –transferase genes etc. that are associated with psychiatric illness [44,45]. In a recent study association between SLC6A4 promoter methylation variation and variation in depressive symptoms was measured in many monozygotic twin pairs by using peripheral blood leucocytes. This study that revealed the variation in the methylation level within the promoter region of the SLC6A4 gene was associated with the variations of depressive symptoms in a large number of MZ twin pairs. Furthermore this relationship was not confounded by genetics and shared environment [40]. Thus the discordances of the depression phenotypes in MZ twins reflect that epigenetic modifications are of substantial importance in producing depression phenotypes.

Discussion

Genetic analysis of MDD is recognized as one of the greatest challenging task confronted by the biologists (Figure 1). For some complex traits such as in schizophrenia a number of genetic loci have been detected [23]. However, many GWAS studies have failed to correlate significant association of any candidate genetic polymorphism and stressful life events with the MDD. Rather, it has been suggested that many small genetic loci can interact with each other and environment in the etiology of depression. Recently epigenetics has emerged as a candidate mechanism by which environmental cues can be translated into stable alterations in chromatin structure that ultimately lead to the persistent expression of altered gene program. There are some genes like 5-HT receptor, BDNF, GR whose repression can give rise to depression. A plethora of recent researches deciphered that environmental adversities may cause the methylation of the gene promoters/genes leading to depression. A number of experimental and postmortem studies using brain

samples, as well as studies using peripheral tissues of have confirmed this association. In our speculation complex etiology of MDD probably involves many phenomena of which epigenetic change in the form of DNA methylation plays a major role. In essence, pathogenesis of MDD can be viewed as combined effects

of adverse environmental conditions, epistatic interactions of many genes with small effects and DNA methylation at a large scale.

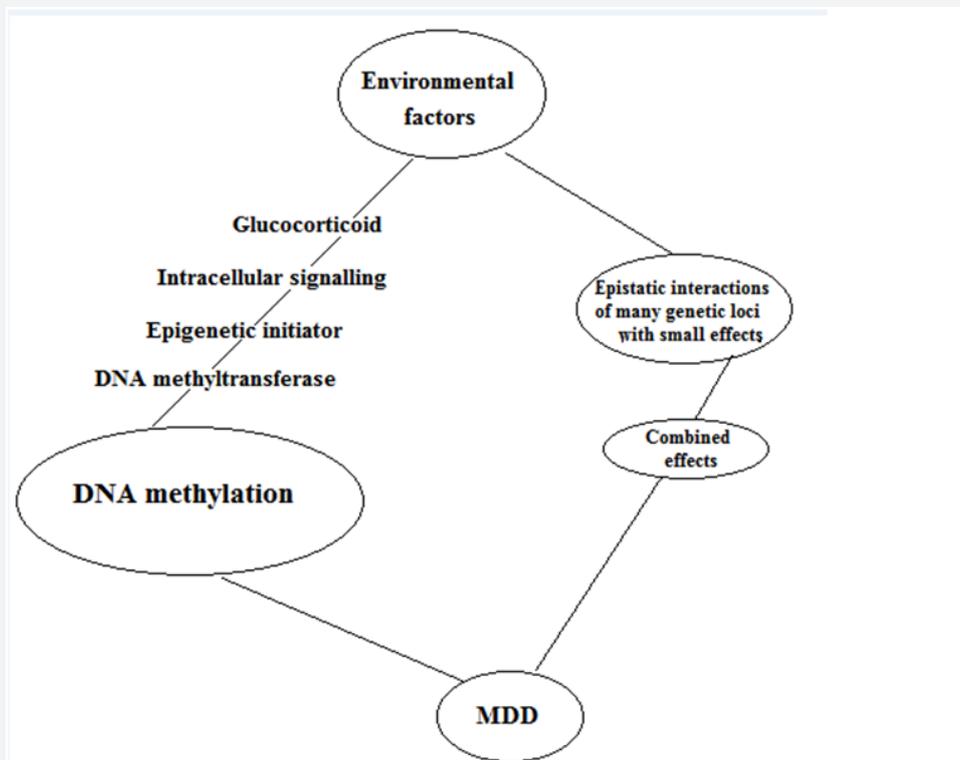


Figure 1: Complex etiology of MDD in which DNA methylation plays a vital role.

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