

EDITORIAL:**MAJOR DEPRESSIVE DISORDER, ENVIRONMENTAL FACTORS AND EPIGENETICS.**

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ABSTRACT

New insights in epigenetics have declared depression a genetic malady. For psychiatric disorders, the evaluation of the epigenetic basis influenced by environmental insults showed a deeper understanding of complex multifactorial psychiatric disorders like Major depressive disorder (MDD). The WHO 2008 report has ranked MDD globally as the third leading cause of burden of diseases and predicted it to be the number one by 2030. Eight hallmarks of insults that lead to MDD are contaminated air, soil, food/water, ecological stressors, chemicals in households, occupational hazards, and food or diet linked to the absence of essential nutrients. Epigenetics, according to the National Human Genome Research Institute, refers to changes in gene function causing their activation or deactivation without any alteration in DNA sequence. Epigenetics include histone modifications, DNA methylations, miRNAs and lncRNAs. Hypermethylation of the serotonin transporter gene has been consistently found in loci encoding Brain-derived neurotrophic factors (BDNF) and SLC6A4. During pregnancy, fetal epigenetic reprogramming may occur due to maternal stress and nutritional restriction. Increased cortisol or malnutrition in mothers, down-regulate the cortisol enzyme, decreasing its expression in the fetal cortex, making these children four times more at risk of stress later in life. Histone modifications, including methylation and acetylation at the lysine moiety during posttranslational modifications, affect neurons in the CNS significantly, leading to the pathophysiology of MDD. Dysregulation of miRNAs and lncRNAs cause negative neural plasticity, stress responses, neurotrophic factors expression, neuroinflammation, neurotransmission, the hypothalamic-pituitary-adrenal axis (HPA axis), neurogenesis and gliogenesis and neural stem cell maintenance. Among epigenetic multifactorial disorders, psychiatric ailments have received more prominence in etiology than other diseases.

KEYWORDS

Brain-Derived Neurotrophic Factor; Depressive Disorder, Major; Epigenesis, Genetic; Histones; Neuroinflammatory Diseases; Serotonin Plasma Membrane Transport Proteins.

Major Depressive Disorder MDD, is determined by environmental and genetic factors is now well established. The World Health Organization in their 2008 report has ranked MDD globally as the, “third cause of the burden of diseases”. Currently almost, 280 million people are suffering from it and WHO predicts that by 2030 it will be the number one disease. It is a multifactorial and a complex disorder and is a major cause of disability, worldwide.

DNA is replicating every second, but the integrity of DNA is always under attack from environmental insults. There are eight hallmarks of insults, such as contaminated air, soil, food and water, as well as exposure of humans to environmental stressors, chemicals in household settings, and occupational hazards. Recent research has revealed that food or diet is also the most important environmental factor, which is linked to the deficiency of essential nutrients leading to

MDD. Unbalanced intake, diets low in micronutrients, or eating disorders starve the DNA of essential nutrients, leaving epigenetic marks that compromise the DNA machinery for expression and signalling. Epigenetics do not cause changes in the DNA sequence, but refer to gene expression processes affecting translation. It also includes histone modifications, microRNAs (miRNAs), and above all, DNA methylation (DNAm). (1)

Environmental Basis of MDD

During development, stressful events may produce altered neural circuits and maladaptive responsiveness in the regions of the brain that regulate emotions and the intervention of responses to stress. As the action of multiple loci of small effect combines with a diversity of environmentally imposed insults, resulting in MDD. Among the factors contributing to depression are those that start influencing the foetus. Affecting the intrauterine life are perinatal complications, maternal stress, a lack of nutrients, exposure to infection, and social drawbacks. For growing ups and grownups are bullying, childhood maltreatment, traumatic events, urban upbringing, ethnic minority status, drug abuse, and exposure to stress. Traumatic life experiences early in life, during the growing years especially, were found to cause a deep impression on the development of the brain, particularly on regions involved in the mediation and regulation of stress response and emotions, which may be permanent or lifelong for mental health outcomes.(2) Thus, it has been observed that childhood adversities lead to depressive episodes or lifetime chronic depression, with an increased risk of suicide attempts in different periods of life. Other than that adverse family environment, poor parental relationship, parental loss, or maltreatment add to psychopathology.(3)

Although these studies prove that adversities during early life have an impact on the vulnerability of MDD, they may not lead to psychopathology in all exposed persons. This is because the stressful stimuli are regulated by the genetic makeup of the individual, which helps them cope with untoward situations. Studies, however, also suggest that because of the interaction between genes and the environment in the uterus, the foetus is exposed to environmental challenges during the pre-perinatal period, which can trigger psychopathology.

Epigenetic Basis of MDD

The stressful childhood experience significantly weakens the developing adaptive mechanisms required later in adulthood to deal with challenges, contributing to poor health outcomes, negative interpersonal relationships, and unhealthy lifestyles. (4) In the development of depression, the interaction between gene and environment was first observed by Caspi et al.(5) They studied polymorphism in serotonin transporter (5-HT T) gene and concluded that gene-by-environment interaction may lead to depressive symptoms in some individual's response to environment. The recent researchers use the term epigenetics for this phenomenon. According to the National Human Genome Research Institute, epigenetics refers to "the changes in gene function that cause their activation or deactivation without any alteration in the DNA sequence." (6), These processes that are mediated by epigenetic alteration are histone modifications, DNA methylations, coding by microRNAs (miRNAs) and noncoding RNAs (lncRNAs) (7). Among the resultant stress-related epigenetic multifactorial disorders, psychiatric ailments received more prominence in the etiology than genetic diseases.

Epigenetic Marks in MDD Patients

DNA Methylation

The process of methylation in DNA adds 5' cytosine at position cytosine phosphate guanine dinucleotide (CpGs), which is generally associated with repression of transcriptional. Most studies on MDD patients have consistently found the serotonin transporter gene hypermethylated in the loci encoding Brain-derived neurotrophic factor (BDNF) and SLC6A4. (8) During pregnancy, maternal stress and nutritional restriction have been found to be the cause of fetal epigenetic reprogramming. Increased cortisol in stressed mothers can pass on to the foetus and, after a cascade of reactions, consequently down-regulate the cortisol enzyme HSD11B2 (11 β -hydroxysteroid dehydrogenase type 2), and so does malnutrition, decreasing the expression of this enzyme in the fetal cortex. This makes these children in later life 4 times more at risk to stress (9) The researchers coined the term “foetal origin of psychopathology” to describe it.

Thus, the pathophysiology is that the regulation of those genes that are required for emotional control, stress response, and brain development are altered due to the high methylation of DNA. Events that happen, either early or later in our lives, may impart a long-term impact on behaviour, consequently leading to changes in the limbic regions, such as the hippocampus and amygdala, as a result of maladaptation.

Histone Modifications

Histones and non-histone proteins are key elements of structural organisation of DNA. The histones are classified into five major groups, namely: H2A, H2B, H3, H4, and H1/H5, involved in linking nucleosomes and further DNA packaging. Animal studies have revealed that besides the structural significance, dynamics, and expression of DNA, histones also play a role in the pathogenesis of MDD through their variant H3.3. In response to chronic social defeat, that is in a depressed human nucleus accumbens (NAc), the dynamics of the H3.3 histone variant are activated. NAc plays a crucial role in motivation, reward, aversion, etc. This occurs due to high acetylation of H3 and down-regulation of histone deacetyltransferases (HDACs), enzymes required for the addition and removal of acetyl groups from histone tails, respectively. However, its negative effects can be limited with the use of antidepressants, which prevent H3.3 dynamics. (10) A large number of data is available on histones modifications, but posttranslational modifications of histone methylation and acetylation at the lysine moiety, which affect the neurons of CNS (central nervous system), play a significant role in the pathophysiology of MDD.

Noncoding RNAs

Non-coding RNAs, another novel epigenetic regulator, includes miRNAs and lncRNAs. MicroRNAs (miRNA) are of many types of non-coding RNAs and are of a 20–25-nucleotides in length that can bind to the 3'UTR (3'-untranslated region) of target mRNAs for cleavage or translational repression. Several miRNAs involved in MDD pathogenesis have been identified, which cause circadian disruption, altered cell signalling, worse stress response and sensitivity altered neurotransmission, microglial apoptosis, endotoxemia and neuroinflammation. miRNAs represent a potential hope for therapeutic targets implicated in MDD pathogenesis. (11)

Similarly, Long non-coding RNAs (LncRNA) are of many types with more than 200 nucleotide bp in size. lncRNAs execute important signalling and epigenetic actions, pretty alike to non-coding RNAs, playing a synergistic effect with miRNAs. lncRNAs being richly expressed in the brain, their dysregulation formulate negatively neural plasticity, stress responses, neurotrophic factors expression, neuroinflammation, neurotransmission, HPA axis, neurogenesis and gliogenesis and neural stem cell maintenance.

Depression has been declared epigenetic malady and now for psychiatric disorders epigenetic basis is being evaluated to understand not only the multifactorial complexity of these disorders as well as to provide epigenetic markers for the better management of the major depressive disorder (MDD).

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