EDITORIAL

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MAJOR DEPRESSIVE DISORDER, ENVIRONMENTAL FACTORS, EPIGENETICS

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ABSTRACT

New insights in epigenetics have declared depression a genetic malady. For psychiatric disorders, the study of the epigenetic basis influenced by environmental insults gave a deeper understanding of complex multifactorial psychiatric disorders like the 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 first 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 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 the DNA sequence. Epigenetics includes 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 gene (serotonin transporter gene). During pregnancy, fetal epigenetic reprogramming may occur due to maternal stress and nutritional restriction. Increased cortisol or malnutrition in mothers, down-regulates 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 post-translational modifications, significantly affect neurons in the CNS, leading to the pathophysiology of MDD. Dysregulation of miRNAs and lncRNAs causes negatively altered 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, has now been established to be caused by environmental and genetic factors. The World Health Organization in the 2008 report has ranked MDD as the, "third cause of the burden of diseases" globally. Currently almost, 280 million people are suffering from MDD 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, micronutrients, 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. An imbalanced 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 signaling. Epigenetic factors 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 defects combines with a diversity of environmentally imposed insults, it results in MDD. Among the factors contributing to depression are those that start influencing the foetus. The factors affecting intrauterine life are prenatal complications, maternal stress, a lack of nutrients, exposure to infection, and social drawbacks. For those growing up and grownups social impediments 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 resultantly impact mental health outcomes permanently (lifelong).[2] Thus, it has been observed that childhood adversities lead to depressive episodes or a lifetime of chronic depression, with an increased risk of suicide attempts in different periods of life. Other than that adverse family environment, poor parental relationships, parental loss, or maltreatment add to psychopathology.[3]

Although these studies prove that adversities during early life have an impact on the vulnerability to 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 to 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 prenatal period, which can trigger psychopathology.

Epigenetic Basis of Mdd

Stressful childhood experiences significantly weaken 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-HTT) gene and concluded that gene-by-environment interaction may lead to depressive symptoms in some individual's response to the environment. Currently 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 non-coding RNAs (lncRNAs).[7] Among the resultant stress-related epigenetic multifactorial disorders, psychiatric ailments have received more prominence in their 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 ability. Most studies on MDD patients have consistently found the serotonin transporter gene hypermethylated in the loci encoding Brain-derived neurotrophic factor (BDNF) and SLC6A4 gene (serotonin transporter gene).[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 be passed on to the foetus and, after a cascade of reactions, consequently down-regulate the cortisol enzyme HSD11B2 (11β-hydroxysteroid dehydrogenase type 2), and so does malnutrition, by 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] 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 behavior, 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 in the structural organization 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.

The Nucleus Accumbens (NAc) plays a crucial role in motivation, reward, aversion, etc. This occurs due to high acetylation of H3 and down-regulation of histone deacetyl transferases (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 amount of data are available on histone modifications, but posttranslational modifications of histone methylation and acetylation at the lysine moiety, which affect the neurons of CNS (central nervous system), plays a significant role in the pathophysiology of MDD.

Noncoding RNAs

Non-coding RNAs, are another novel epigenetic regulator, includes miRNAs and lncRNAs. MicroRNAs (miRNA) constitute many types of non-coding RNAs and are 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 signaling, degraded stress response and sensitivity. altered neurotrans mission, microglial apoptosis, endotoxemia and neuroinflammation. The miRNAs represent a hope as potential therapeutic targets in altering 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, very similar to non-coding RNAs, playing a synergistic effect with miRNAs. lncRNAs being richly expressed in the brain, their dysregulation impacts negatively neural plasticity, stress responses, neurotrophic factors expression, neuroinflammation, neurotransmission, HPA axis, neurogenesis and gliogenesis and neural stem cell maintenance.

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

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