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TARGETING DNA METHYLATION ON TRANSGENERATIONAL CONSEQUENCES OF PRENATAL STRESS-INDUCED DEPRESSION

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REVIEW **OPEN ACCESS**

ABSTRACT

Background: Depression is a common mental disorder with disabilities and mortalities burden. Maternal stress during pregnancy has a strong correlation with the depression of children event in their adulthood phase. Abundant maternal cortisol transfer to the fetus generates blunted hypothalamus-pituitary-adrenal axis response.
Objective: To understand the mechanism of targeting DNA methylation on transgenerational consequences of prenatal stress-induced depression.
Methods: This review provides a comprehensive explanation of the DNA methylation changes as well as the occasion of new potential therapy that focused on DNA methylation inhibitors in depression from 33 trusted sources.
Results: Higher fetal circulation of cortisol led to epigenetic changes during fetal development in an antenatal stress situation. DNA methylation of crucial genes such as brain-derived neurotrophic factor (BDNF) and nuclear receptor subfamily 3 group C member 1 (NR3C1) are responsible for the molecular mechanism of depression progression into the next generation through transcriptional inhibition.
Conclusion: Demethylation is becoming a potential target to reduce the risk of depression in children who has a risk of prenatal stress mother. The role of plant bioactive compound as demethylation agent is promising and need further exploration.

Keywords: depression, DNA methylation, prenatal stress.

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INTRODUCTION

The prevalence of depression is higher than other psychiatric disorders. Approximately, more than 300 million people are living with depression in the past years.[1] This number is increasing by about 50 million people during the global pandemic situation.[2] Depression is a mood disorder which are characterized by sadness, anhedonia, and somatic or cognitive symptoms such as appetite disorder, sleep disturbances, lethargy, and decrease in concentration.[3] Thereupon, people with depression suffer from a decline in psychosocial function that adverse daily work activities. The long-term financial impact could rise from disability problems in depression. Severe depression relates to premature mortality in according to suicide behavior.[4–7] Consequently, depression is remaining as a public health issue that needs further attention.[2]

The persistence of higher stress thorough pregnancy has a significant effect on psychopathological disorders involving depression.[8] Maternal stress during pregnancy is a great risk factor for depression development in the later life of children.[8] Despite those associations remain not clearly explained, many molecular mechanisms are proposed as a possible pathway other of transgenerational effect of maternal stress to their children.[9]

Fetal epigenetic changes in maternal stress during pregnancy is highlighted by recent studies.[10] Epigenetic refers to the genomic transcriptional modification that potentially heritable into future generation as response to environmental stimulation independently from DNA sequences.[11] Further, epigenetic alters the expression of regulatory protein that normally necessary for brain plasticity and neuronal survival. Among several epigenetic changes, DNA methylation of several gene is well characterized in depression such as *BDNF* and *NR3C1*.[12]

Animal study was reported the favourable behaviour outcome of DNA methylation inhibitor in prenatally-stressed offspring mice.[13] The DNA methylation is suggested as both target and predictor of treatment response in depression.[14] The use of plant metabolite compound is potentially predicted has reversing effect on DNA methylation thus arising new insight

of depression treatment and management in the future.[15]

METHOD

This review provides the comprehensive explanation about the DNA methylation changes as well as the occasion of new potential therapy that focused on DNA methylation inhibitor in depression from 33 trusted sources.

DISCUSS AND RESULTS

The mechanism of DNA methylation

DNA methylation is one of the most studied about epigenetic inherited. Methylation of DNA is initiates by methyl group transfer from S-adenylyl methionine (SAM) as donor to the fifth carbon position of cytosine residue that linked to guanine via phosphate molecule (CpG).[16]

This mechanism is catalysed by family of enzyme DNA-methyltransferases (DNMTs). Methylation of DNA in brain are tightly regulated in normal process. However, the increase of DNA methylation leads to gene silencing by transcriptional inhibition.[17] Methylation inhibits the attachment of transcription factor in promoter and recruit methyl-binding proteins (MBPs) that induce chromatin remodelling.[16,18]

Three types of DNMTs enzyme are modulates DNA methylation as passive or active pathway namely DNMT1, DNMT3a, and DNMT3b. The DNMT1 is major enzyme that play a role as maintenance of DNA methylation. This enzyme located in replication fork during DNA replication thus methylation is persisted in new replicated DNA. Methylation copy of parental DNA into daughter strand of DNA is determined by the function of DNMT1.[19]

Other two enzymes, the DNMT3a and DNMT3b are responsible to novel methylation (*de novo*) process of naked DNA.[19] Distinct expression between DNMT3a and DNMT3b are shown in different stage of development. DNMT3a is more frequent in mature differentiated cells or late embryonic phase, whereas DNMT3b in early embryonic phase.[20]

DNA methylation in depression

DNA methylation in several genes are strongly correlates with depression such as *BDNF* and *NRC3C1*. Those genes are essential to encode the synthesis of BDNF and glucocorticoid receptor respectively.[21]

Protein of BDNF is member of brain growth factor to promotes neuronal plasticity and communication.[22] Level of BDNF decline both in depression patient and brain post-mortem study from suicide victim. Antidepressant treatment is associated with the increase of serum BDNF mRNA level in several brain areas. Conversely, animal model of BDNF knockout demonstrates depressive-like behaviour. Numerous studies are consistently support the role of BDNF deficiencies in depression disorder development.[23]

BDNF is a stress sensitive gene which is susceptible to adverse stressful environment.[24] Early life stress well established affect methylation on *BDNF*.[25] Either environmental toxicant or psychological stress are related to BDNF methylation.[26,27] Maternal bisphenol exposure during pregnancy was correlated with BDNF methylation in hippocampal tissue of adolescent offspring.[26] Physical and psychological stress exposure in half-late pregnancy induce low expression of BDNF and increase BDNF methylation in exon IV either in post-weaning or adult offspring.[27] This supports the long-lasting effect of maternal stress during pregnancy on BDNF expression thorough life of the offspring.

Uterine environment is important for foetal well-being.[28] Typically, cortisol as stress hormone is inactivated by 1ß-hydroxydehydrogenase type 2 (11ß-HSD-2) enzyme then prevent transplacental shift of cortisol. However, chronic maternal stress in pregnancy over activates hypothalamic-pituitary-adrenal (HPA) axis subsequently increase the level of maternal cortisol. Additionally, prenatal stress downregulates the function of 11ß-HSD-2 enzyme thus permits abundant feto-maternal transfer of cortisol then reach the foetus.[29]

Excess of cortisol in foetal circulation dysregulates the negative feedback set point in hypothalamus and prolonged the hormonal effect of cortisol on neuronal and endocrine developmental of foetus.[29] Stress induces rapid downregulation of glucocorticoid receptor (GR) mRNA as well as DNA methylation of *NR3C1* gene.[30–32] DNMT3a is strongly linked to those mechanism since DNMT3a expression are significantly increase after stress exposure. The increase of DNA methylation in *NR3C1* gens is found in patient with depression that associate with HPA-axis activation.[30]

DNA demethylation as potential target therapy: role of plant metabolite compound?

Enzyme of ten eleven translocation (TET) play a major role in demethylation process. First, TET enzyme inhibits the activity of DNMT. Second, TET enzyme oxidized the 5-methyl-cytosine into another form.[33]

Previous study reported the reduction of DNA methylation, suppression of DNMT1 and DNMT3b activity by raspberry anthocyanin administration in vitro.[34] The application of ascorbic acid was demonstrated reduces DNA methylation by activate TET-oxygenase enzyme. Other animal study showed admiring effect of genipin as plant terpenoid compound in reducing the methylation of *BDNF* and normalized the depressive-like behaviour of prenatally stressed offspring through inhibition of DNMT1.[35] The behavioural effect of plant anthocyanin from purple sweet potatoes was reported modifying the offspring behaviour from prenatal stress dam.[36]

Limited studies are exploring the benefit of plant metabolite compound towards DNA methylation in depression model. This arising new potential research field for overcome the effect of prenatal stress to depression development in thorough life of children

CONCLUSION

DNA methylation is the key factor of foetal programming of depression development in children from prenatal stressed mother. New insight of the utility of plant metabolite compound is promising to reverse the methylation process.

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