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Epigenetics in Suicide and Depression

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Underlying causes of Major Depressive Disorder (MDD) remain an enigma. A major gain of uncovering mechanisms leading to this devastating disorder will be the prevention of suicide, the worst outcome of MDD. In the search to understand the neurobiology of MDD several promising hypotheses have been formulated. These hypotheses are largely focused on alterations in monoaminergic neurotransmission, trophic factor signaling, neurogenesis, and glial development and transport. However, a recent proposal may potentially bring together all of these hypotheses and offer a basis for understanding the complexity of MDD. This proposal involves epigenetic gene regulation and provides a nexus for gene/environment interaction, both of which are known to increase the risk for MDD. In addition, epigenetic mechanisms are accessible therapeutic targets that are already in development for many diverse diseases including certain types of cancer and neurodegenerative disorders.

The term epigenetics, meaning 'beyond' genetics, was coined by C.H. Waddington to refer to phenotypic changes not coded by DNA (1). Epigenetics refers to a heritable but mutable set of processes that regulate the expression of particular genes in certain cell types and/or at specific developmental time points. These processes regulate the access of transcription factors and enhancers to gene promoters, either by acting on the promoter sequence itself or by remodeling chromatin structure at a tertiary structure level. Chromatin is composed of DNA wound around a core of proteins known as histones, which associate with each other to pack DNA into the nucleus. Epigenetic mechanisms that can impact gene expression include molecular modifications of the DNA (e.g. DNA methylation) or the histones (e.g. acetylation, deacetylation, phosphorylation, and methylation). DNA methylation occurs at specific CpG residues within promoter regions of genes, which allows the recruitment of methyl-CpG binding proteins such as methyl-CpG binding protein 2 (MeCP2) to directly bind to the methylated DNA and further recruit other components of a large repressor complex to suppress gene expression. While there are several molecular modifications that can occur on histone tails to impact gene expression, histone acetylation and deacetylation are two of the most studied. Specific histone residues can be acetylated by histone acetyltransferases (HATs) which results in increased gene expression while the deacetylation of histones by histone deacetylases (HDACs) results in repressed gene expression.

Recent studies have reported alterations in epigenetic markers in suicide victims suggesting a link between mechanisms that regulate gene expression and MDD. Poulter *et al.* demonstrated that DNA methyltransferase (DNMT) 3b expression, an enzyme that *de novo* methylates CpG islands, is increased in suicide completers compared to controls in frontopolar cortex (2).

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Additionally, this increase was more pronounced in female versus male postmortem tissue; such sexual dimorphism is of note since MDD is twice as prevalent in women. The study further revealed that DNMT 3b up-regulation may contribute to hypermethylation of the GABA-A receptor promoter, thereby potentially explaining the down-regulation of GABA-A expression in suicide completers.

Another recent study focusing on tropomysin related kinase B (TrkB), the receptor for brain derived neurotrophic factor (BDNF), has linked alterations in TrkB expression to epigenetic processes in suicide. Previous studies have shown that BDNF as well as TrkB levels are decreased in suicide victims (3) as well as serum of depressed patients (4). Ernst *et al.* focus on the reduction of the TrkB.T1 variant found in glia and have reported its decreased expression in cortical areas (primarily Brodmann areas 8 and 9) (5). They show that both mRNA and protein for this splice variant are decreased in the brains' of suicide victims. Promoter sequencing revealed that Trk.T1 promoter regions were hypermethylated compared to controls indicating the potential involvement of altered DNA methylation contributing to decreased gene expression. These clinical studies highlight not only the importance of epigenetic mechanisms that regulate gene expression in suicide completers, but also suggest that the process is mutable in the disease state.

Preclinical studies have corroborated the idea that epigenetic changes may underlie altered levels of MDD-related target genes and might be experience-dependent. In rats, acute immobilization stress decreased acetylation of histones at BDNF exons that correlated to decreases in BDNF transcript levels (6). This finding has been replicated in mice using chronic stress. Tsankova *et al.* demonstrated that 10 days of chronic social defeat stress is associated with decreases in BDNF mRNA as well as histone methylation, a marker for gene repression (7). This study further revealed that stress-related gene repression and decreased BDNF levels are both reversed by chronic antidepressant treatment. These studies strengthen the hypothesis that epigenetic modifications contribute to the etiology of MDD, particularly major depressive episodes that result from chronic stress. Moreover, antidepressant treatments are capable of reversing the epigenetic changes associated with MDD.

Given that many genes have altered expression levels in depression, it is worth looking at the data related to serotonin and depression from a fresh perspective. Several clinical studies have focused on the serotonergic system in relation to mood disorders and particularly with MDD. Many of these have reported decreases in elements of the serotonin signaling pathway including serotonin, serotonin receptors such as 5HT1a and 5HT2a, serotonin transporter, and tryptophan (and by association tryptophan hydroxylase) (8). These targets are of great interest given their relevance to classical antidepressant medications, however it has been difficult to show by what mechanism these alterations may be related to MDD with the exception of a few known polymorphisms (9). An examination of epigenetic changes with respect to promoter regions of serotonergic target genes may reveal new insights on how this system may be susceptible to these mechanisms.

These studies lay the groundwork for future consideration of epigenetic mechanisms in clinical studies of depression and suicide. While it is tempting to assign an epigenetic change as a mechanism of the disease state, it is crucial to delve further into how these alterations themselves are mediated in order to distinguish those which are coincidental versus instrumental in causing MDD. Recent studies have shown that epigenetic modifications can occur in response to drug abuse, stress, learning, and early life experience. However, it is unclear how these experiences govern the activity of enzymes that trigger epigenetic modifications and result in changes in gene expression. Additionally, new techniques that are sensitive to modifications at the chromatin or histone level may contribute valuable insights into how epigenetic mechanisms may be involved in MDD pathology. Knowledge of how

epigenetics are influenced by life experience can further our understanding of the etiology of MDD and hopefully reveal new therapeutic avenues toward suicide prevention.

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