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OPINION
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DNA Methylation as a Therapeutic and Diagnostic Target in Major Depressive Disorder

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Major Depressive Disorder (MDD) is a widespread debilitating neuropsychiatric disorder. While a broad range of drugs to treat MDD are available, a large portion of the patients fail to achieve a complete and sustained remission. It is estimated that only about half of the patients will be responsive to currently available antidepressant treatment (Rush et al., 2006), while others will be only partly responsive, and some will develop a treatment-resistant MDD (Akil et al., 2018).

The etiology of MDD is not clear and considering the large heterogeneity of symptoms and pathophysiologies it is likely to arise from a complex integration of genetic risk factors (Flint and Kendler, 2014; Geschwind and Flint, 2015) and environmental influences, mostly adverse life experiences (Gourion et al., 2008; LeMoult et al., 2020).

Adverse experiences such as early-life stress and poor maternal care are associated with increased risk for MDD in humans (Heim et al., 2010; Lippard and Nemeroff, 2020) and these findings were recapitulated in rodent models (Liu et al., 1997; Caldji et al., 1998) and non-human primates (Champoux et al., 2002; Barr et al., 2003). Maternal behavior and environmental stress alter the development of the hypothalamic–pituitary–adrenal (HPA) axis stress response leading to a stress susceptible phenotype associated with a greater risk for depression later in life (Liu et al., 1997; Anacker et al., 2014). Early-life stress effects can further interact with genetic factors that predispose individuals to depression (Heim and Binder, 2012).

The genome can integrate environmental signals through epigenetic mechanisms such as DNA methylation of CpG dinucleotides and histone modifications. Indeed, ample evidence has linked environmental stress to epigenetic alterations. Increased DNA methylation of the glucocorticoid receptor (GR) promoter was found in the hippocampus of rat pups with poor maternal care (Weaver et al., 2004) and in the post-mortem human brains of individuals who suffered childhood abuse (McGowan et al., 2009). Similar findings suggested conserved epigenetic signature of early life stress in rats and humans (Suderman et al., 2012). It was also demonstrated that peripheral tissues (including blood, saliva and buccal cells) can be used as surrogates for measuring epigenetic changes in the brain across many neuropsychiatric disorders (Fuchikami et al., 2011; Unternaehrer et al., 2012; Lax et al., 2018; McEwen et al., 2020). In addition, many CpGs show correlation of DNA methylation levels between blood and several brain regions, and hence can serve as disease biomarkers (Hannon et al., 2015; Edgar et al., 2017).

The observations that environmental factors, such as early-life stress, that make individuals prone to MDD, also modulate the epigenetic signals to ultimately reprogram brain gene-expression patterns encouraged studies that seek direct associations between MDD and DNA methylation. For example, a genome-wide DNA methylation study in post-mortem brain samples from MDD patients who died during a depressive episode and matched controls found more than a hundred differentially methylated regions between the groups (Nagy et al., 2015). Recently, a large-scale genome-wide study directly compared brain and blood DNA methylation patterns in MDD

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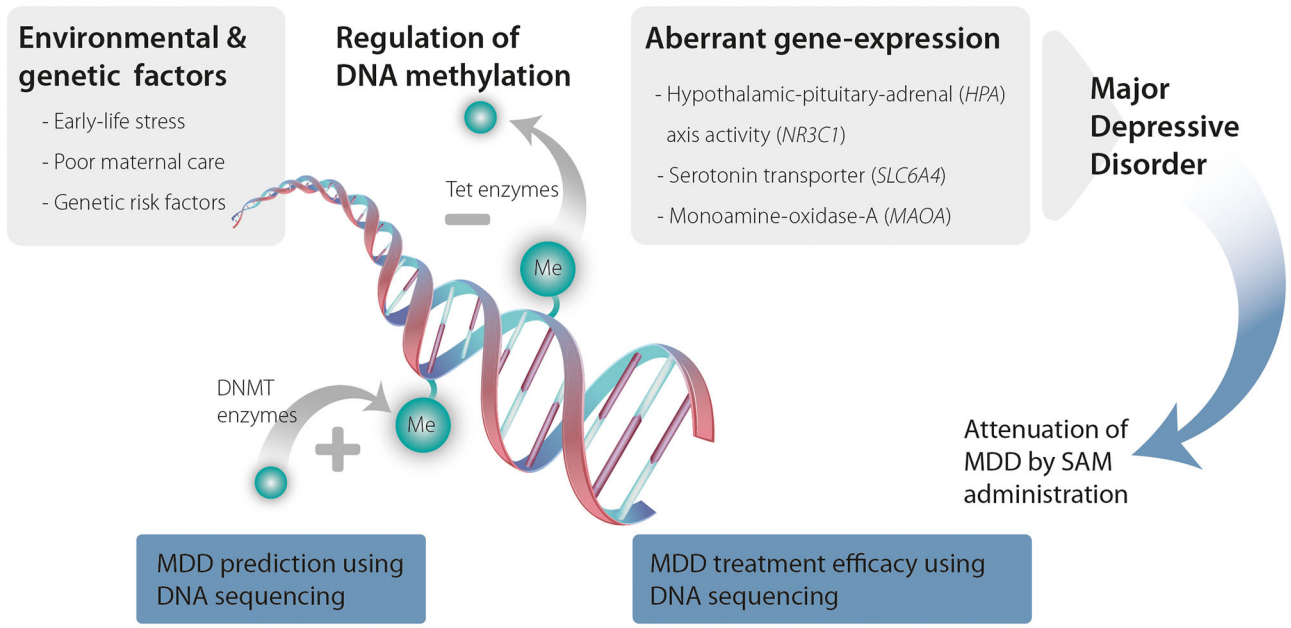

FIGURE 1 | Environmental and genetic risk factors promote changes in DNA methyltransferases (DNMTs) and ten-eleven translocation methylcytosine dioxygenases (TET) activity that increase DNA methylation and demethylation, respectively. Changes in DNA methylation lead to aberrant expression of genes that are associated with MDD ultimately causing MDD. SAM administration can attenuate these changes in DNA methylation. Further, genomic sequencing to detect changes in DNA methylation can serve as a predictive tool for MDD as well as a tool to predict treatment efficacy and responsiveness.

patients including replication cohorts and found differentially methylated sites in MDD patients (Aberg et al., 2020). Other researchers used a candidate gene approach and found changes in DNA methylation levels for the genes *MAOA* (encoding the monoamine-oxidase-A enzyme) and *NR3C1* (encoding the glucocorticoid-receptor) in individuals with MDD and childhood adversities (Melas et al., 2013).

Other studies aimed to assess DNA methylation levels of the promoter of *SLC6A4*, the gene that encodes the serotonin transporter, a major target of many antidepressant drugs. Kang et al. (2013) found an association between childhood adversity and worse clinical presentation of MDD and higher methylation levels of the *SLC6A4* promoter with no effect of antidepressant treatment on methylation levels of this region. Using the same approach, Okada et al. (2014) did not find a significant difference between DNA methylation levels of the *SLC6A4* promoter in healthy controls and MDD patients before antidepressant treatment. However, they found significantly increased methylation in some CpGs following a 6-week treatment. Similar findings were also found in additional studies (Vijayendran et al., 2012; Zhao et al., 2013; Domschke et al., 2014). Furthermore, several studies linked peripheral measures of *SLC6A4* promoter DNA methylation to brain connectivity in MDD (Chiarella et al., 2020), brain functions involved in emotional stimuli (Frodl et al., 2015), and hippocampal volume in MDD (Booij et al., 2015). Notably, heterogeneity in DNA methylation changes in MDD across experiments is to be expected due to factors such as genomic heterogeneity and the parameters of the sampled population. For example, a distinct DNA methylation signature was found for adult-onset and late-onset MDD (Yamagata et al., 2021). On the other hand, parameters such as ethnicity might have smaller effects. A meta-analysis of multiethnic epigenome-wide studies for depressive symptoms found DNA methylation signatures of depression which were robust across ethnicities (Story Jovanova et al., 2018).

Taken together, the findings that DNA methylation changes were observed in MDD led to efforts to pharmacologically manipulate DNA methylation levels as a potential antidepressant treatment. Administration of S-adenosyl methionine (SAM), a methyl donor that is used by DNA methyltransferases (DNMTs) to catalyze DNA methylation, can increase global DNA methylation. Therefore, many studies examined the effect of SAM administration as a monotherapy or an add-on to antidepressant treatment. The overall effects of SAM administration in MDD were analyzed in several thorough systemic reviews, which concluded that SAM shows promising results although additional larger randomized double-blind studies with long-term follow-up are required (Galizia et al., 2016; Sarris et al., 2016; Sharma et al., 2017; Cuomo et al., 2020). Animal models suggested some mechanistic insight into the beneficial effects of SAM. Saunderson et al. (2016) demonstrated that SAM administration attenuated stress-induced c-Fos and Egr-1 gene-promoter demethylation and protein expression in the dentate gyrus of stressed rats. Intracerebroventricular

infusion of methionine (SAM precursor) reversed stress response and DNA methylation levels of the GR promoter in rat offspring from poor maternal care dams (Weaver et al., 2005) and systemic methionine injections in the same animal model altered gene-expression of over 300 genes in the hippocampus (Weaver et al., 2006). Notably, *Dnmt3a* over-expression (which increases global methylation) specifically in the nucleus accumbens increased depressive-like behaviors, while DNMT inhibition with RG-108 decreased depressive-like behaviors in mice (LaPlant et al., 2010). Also, forebrain deletion of *Dnmt1*, but not *Dnmt3a*, showed anti-depressive effects (Morris et al., 2016).

In naïve newborn and adult rodents, systematic administration of the DNMT inhibitors 5-aza-2-deoxycytidine or 5-azacytidine reduced depressive-like behaviors through demethylation of the *Bdnf* gene promoter leading to increased brain Bdnf mRNA and protein levels (Sales et al., 2011; Li et al., 2017). While the findings of pharmacological inhibition of DNA methylation might be seen as contradictory to the beneficial effects of SAM observed in preclinical and clinical studies, it is important to note that different models, species, and administration routes were used, making it hard to directly compare these results. Also, while SAM treatment is a promising add-on MDD therapy, it increases DNA methylation globally and can potentially reprogram gene-expression beyond those that are causative for MDD. However, many human studies on the effects of SAM administration on MDD showed beneficial effects for this treatment with no major adverse side-effects reported. Currently, there are not pharmacological interventions that can manipulate DNA methylation levels of specific genomic loci. Novel technologies might allow this in the future, for example by targeting a catalytically inactive CRISPR/deadCAS9 protein fused to DNMT3a (dCAS9-DNMT3a) to loci of interest as was shown experimentally (Liu et al., 2016; Vojta et al., 2016; Xu and Heller, 2019).

Disentangling whether changes in DNA methylation are the cause or result of MMD is very difficult in human studies which can measure mostly associations. However, several studies found that DNA methylation can predict behavioral outcomes, including major depression, in humans (Ursini et al., 2011; Guintivano et al., 2014; Humphreys et al., 2019). In addition, studies in animal models for MDD showed that manipulating the methyl donor availability, DNMTs levels and DNMTs activity can induce MDD-like behavioral phenotypes (LaPlant et al., 2010; Sales et al., 2011; Morris et al., 2016; Li et al., 2017). Therefore, it is prudent to assume that alterations in DNA methylation, as a result to external stressful stimuli, are at least partly causative of MDD, although it is likely that some methylation alterations are secondary to MDD (and yet can serve as potential biomarkers).

The notion that manipulating DNA methylation has an impact on MDD encouraged studies measuring DNA methylation levels as potential biomarkers to predict MDD and its severity in vulnerable populations as well as treatment outcomes. For example, blood methylation levels were measured in several cohorts to successfully predict antenatal and postpartum depression (Guintivano et al., 2014; Payne et al., 2020). Some of these studies focused on one or a few candidate genes as potential MDD predictors, mostly the *BDNF* and *SLC6A4* genes (Booij et al., 2015; Kleimann et al., 2015), while others used genome-wide methods (Barbu et al., 2020).

A recent systematic review on DNA methylation in depression and the effects of MDD treatment on DNA methylation concluded that findings from studies that aimed to search for biomarkers for MDD treatment outcome are inconsistent; with some studies showing significant results while others had mixed findings. This is most likely due to larger heterogeneity compared to other studies, types and stages of treatment and small sample sizes in some of the studies. Overall, the most consistent effects were increased methylation of the *BDNF* and *SLC6A4* genes in MDD patients (Li et al., 2019).

Taken as a whole, a growing body of evidence support a role for DNA methylation in MDD (see summary in **Figure 1**). Drugs that modify DNA methylation are available and demonstrate significant effects across both preclinical and clinical studies. These drugs (mostly methionine and SAM) have the potential to be used as adjuvants increasing the efficacy of classic antidepressant treatments. Further, peripheral DNA methylation has the potential to become a non-invasive method for assessing MDD risk and treatment-efficacy estimation. Future large-scale research on MDD patients is needed for further study and validation to establish these approaches.

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The author confirms being the sole contributor of this work and has approved it for publication.

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