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The effects of DNA methylation on human psychology

Farzeen Kader, Meenu Ghai*, Leah Maharaj

School of Life Sciences, University of KwaZulu-Natal, Westville Campus, Durban 4000 South Africa

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ABSTRACT

DNA methylation is a fundamental epigenetic modification in the human genome; pivotal in development, genomic imprinting, X inactivation, chromosome stability, gene expression and methylation aberrations are involved in an array of human diseases. Methylation at promoters is associated with transcriptional repression, whereas gene body methylation is generally associated with gene expression. Extrinsic factors such as age, diets and lifestyle affect DNA methylation which consequently alters gene expression. Stress, anxiety, depression, life satisfaction, emotion among numerous other psychological factors also modify DNA methylation patterns. This correlation is frequently investigated in four candidate genes; *NR3C1, SLC6A4, BDNF* and *OXTR,* since regulation of these genes directly impact responses to social situations, stress, threats, behaviour and neural functions. Such studies underpin the hypothesis that DNA methylation is involved in deviant human behaviour, psychological and psychiatric conditions. These candidate genes may be targeted in future to assess the correlation between methylation, social experiences and long-term behavioural phenotypes in humans; and may potentially serve as biomarkers for therapeutic intervention.

1. Introduction

1.1. Epigenetics and DNA methylation

Several decades have passed since epigenetics was described as 'the branch of biology which studies the casual interactions between genes and their products, which brings the phenotype into being' [1]. Now, epigenetics is more commonly understood as heritable changes in gene function or cell type that cannot be attributed to modifications of the DNA sequence [2,3]. Epigenetic patterns are heritable and preserved during cell division; however extrinsic and environmental factors contribute to epigenetic modifications during an individual's lifetime [3–5]. Epigenetic modifications comprise of nucleosomal remodelling, histone modification, chromatin looping, non-coding RNAs and the most well explored, DNA methylation [5–8].

DNA methylation is described as the covalent attachment of a methyl group onto the cytosine residue of DNA, primarily occurring on CpG dinucleotides. However, non-CpG methylation occurring in human embryonic stem cells has been previously documented [9,10]. CpGs in human DNA may be intermittent but highly methylated, or CpG-rich but mostly lacking in methylation. The latter segment, consisting of a GC content of more than 50% is known as a CpG Island (CGI) and is roughly 200–3000 bp long [11,12].

The methylation reaction is catalysed by DNA methyltransferases (DNMTs). DNMT1, DNMT3a, and DNMT3b catalyse the addition of methyl groups particularly at CpG dinucleotides. DNA methylation is crucial to the developing embryo, differentiation [13], as well as numerous subsequent processes; including genomic imprinting [14], X chromosome inactivation [15], conservation of chromosome stability, repression of repeat and viral sequences [16].

The effect of DNA methylation on gene expression is known to be a function of the methylation site [16–18]. Promoter methylation has been researched in vast detail and the popular notion is that it leads to repression of transcription, however elongation remains unaffected [18–20]. Conversely, in most cases methylation within the gene body tends to positively correlate with gene expression [8,11,21]. Such contradictory roles of DNA methylation in the promoter and gene body regions has been labelled a methylation paradox [22].

Aberrant DNA methylation is also associated with numerous diseases [23]. This includes, but is certainly not restricted to cancers [24–27], autoimmune diseases including systemic lupus erythematosus [28,29], rheumatoid arthritis [30,31], and diabetes [32–34], neurodegenerative diseases including Alzheimer's, Parkinsons and Huntington's disease [35]. The scientific community has been inundated with reports of these diseases, and therapies involving the manipulation of DNA methylation are now well under way [36,37]. However, recent findings show that psychological factors such as anxiety, hostility, depression, happiness and life satisfaction also initiate anomalous DNA methylation patterns, and as a result leads to several psychological diseases [38–41]. Despite these findings, the exact mechanisms underlying the links

* Corresponding author.
E-mail addresses: farzeenkader68@gmail.com (F. Kader), ghai@ukzn.ac.za (M. Ghai), leahmaharaj@gmail.com (L. Maharaj).

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between the human DNA methylation/gene expression paradox with psychological diseases remains to be elucidated.

The present review discusses DNA methylation; from establishment of gene- and site-specific DNA methylation patterns, to the effects on gene expression; and thereafter outlines the current status of research linking gene- and site-specific methylation to psychological diseases to understand whether aberrant DNA methylation is a repercussion, or rather a cause of psychological anomalies.

1.2. Establishment of DNA methylation

DNA methyltransferases (DNMTs) DNMT1, DNMT3a and DNMT3b are enzymes that establish methylation patterns in humans during early embryogenesis [42,43]. These enzymes may be classified as being maintenance or *de novo* DNMTs [44–47]. During DNA replication, DNMT1 localizes to the replication fork, binds to DNA and preferentially methylates hemi-methylated DNA. Additionally, DNMT1 serves the role of repairing DNA methylation. Hence, DNMT1 is referred to as the 'maintenance DNMT' [11,48,49]. DNMT3a and DNMT3b introduce methylation at CpG sites that were previously completely unmethylated i.e. sites that were 'naked' [50], hence these enzymes are referred to as '*de novo* DNMTs'. DNMT3a is necessary during cellular differentiation, whereas DNMT3b is central in maintaining chromosomal stability during early development [51,52]. DNMT3L lacks catalytic activity of its own, however it interacts with DNMT3a and DNMT3b and increases their activities [52–54]. DNMT3L is also fundamental to establish maternal and paternal imprinting, methylation of retrotransposons, as well as compaction of the X chromosome [11,15,55].

1.3. DNA demethylation

Removal of DNA methylation; or DNA demethylation, has been observed particularly in the germline and early embryogenesis [56]. Erasure of methylation patterns allows the chromatin template to revert to a less differentiated state, characterised by low levels of DNA methylation which is necessary in cellular reprogramming [57,58]. DNA demethylation is key for development of mammalian primordial germ cells as it is an important component of parental imprint erasure [59]. The process of DNA demethylation may occur by either active or passive mechanisms [60].

Active DNA demethylation is an enzymatic process that can occur in both dividing and non-dividing cells. It is part of the epigenetic remodelling process, being responsible for a global loss of DNA methylation in the paternal genome [61]. This is usually within 6–8 h of fertilization, prior to DNA replication [62]. Active demethylation may occur by deamination of the amine to a carbonyl group by activation-induced cytidine deaminase/apolipoprotein B mRNA-editing enzyme complex (AID/APOBEC). The deamination reaction converts methyl-cytosine to thymine, resulting in T:G mismatches. Base excision repair mechanisms cleave the thymine residue using thymine DNA glycosylase (TDG), and replace it with an unmethylated cytosine [63–65]. Alternatively, active demethylation can involve oxidation of the methyl group by Ten-Eleven Translocation (TET) enzymes TET1, 2 and 3. A hydroxyl group is added onto the methyl group, thereby forming hydroxymethyl-cytosine (hmC, discussed later). Two mechanisms can convert hmC back into cytosine; iterative oxidation by TET enzymes which continuously oxidise hmC, and deamination by AID/APOBEC [66,67].

Passive DNA methylation occurs in dividing cells, and is believed to be a feature of mammalian development in the maternal genome prior to pre-implantation growth [62,68]. Since DNMT1 actively maintains DNA methylation during replication, downregulation or exclusion of DNMT1 or its recruitment factors from the nucleus leaves newly incorporated cytosines to remain unmethylated. This reduces overall methylation after each round of division [61,63]. The passive demethylation mechanism is efficient for global demethylation, preventing locus-specific removal of methylation from regions of DNA [63].

1.4. Site-specific DNA methylation and gene expression

1.4.1. Promoter methylation

To gain insight into the effects or functions of human DNA methylation in gene expression and regulation, one must consider the uneven distribution of CpG dinucleotides across the genome. The human genome holds approximately 30 million CpG dinucleotides, which exist in either an unmethylated, hemi-methylated or completely methylated state [69,70]. These dinucleotides cluster to form CGIs that are typically located in the promoter region, where methylation is generally associated with transcriptional silencing [70–74]. Two highly accepted mechanisms for which this silencing occurs exist. One, it is mediated by proteins that house a methyl-CpG binding domain (MBD). The MBD binds to methylated CGIs, which is followed by recruitment of histone deacetylases, chromatin compaction and gene repression [18,44,75]. The next mechanism involves methylation-dependent transcription factors which bind to their respective target sites, thereby blocking transcription factors from binding to promoter regions. Hence, the gene is rendered inactive [18,76]. Methylation at non-CGI promoters play a role in establishing and maintenance of cell identity. These promoters tend to be restricted in their expression [77,78].

1.4.2. Gene body methylation

CGIs and methylation are not exclusive to promoter regions; they can also be found in gene bodies, which are the transcribed portion of genes. Gene body methylation profiles are conserved among both vertebrates and invertebrates [79–81]. In contrast to promoter methylation, most gene bodies are CpG-poor and extensively methylated [16,44]. Furthermore, while promoter methylation drives transcriptional silencing, studies have shown that methylation of the gene body correlates to high gene expression in actively dividing cells [81–83]. Positive correlations between gene body methylation and gene expression has been observed in B-lymphocyte cell lines, placenta, peripheral white blood cells, fibroblasts and embryonic stem cells [81,84].

The exact role of methylation in transcribed regions/gene body methylation has yet to be completely deciphered [8,18,85]. However, reports state that it does facilitate efficient transcriptional elongation; via the control of spurious intragenic transcription, potential silencing of alternate promoters, regulation of intragenic non-coding RNAs present in intronic regions, and alternative splicing [18,86–91]. Alternative splicing is said to create diversity in regulation and expression of main transcripts which enhance protein diversity [92–95]. Yet another function of gene body methylation is the repression of harmful genetic elements, such as transposable and viral elements [11,96,97].

1.5. Genetic variants, DNA methylation and gene expression

Genetic variants in an individuals' DNA sequence modifies the epigenetic state, particularly DNA methylation [98]. It is believed that genetic variants such as single nucleotide polymorphisms (SNPs), especially when located in close proximity or in *cis* change the methylation status at a CpG site [99–102]. A single SNP can influence the fate of more than one nearby CpG sites methylation. Correlations between SNPs and methylation are now frequently referred to as methylation quantitative trait loci (mQTLs) [99,100,103]. However, variable methylation is not always explained by a nearby SNP; as a previous study by Gibbs et al. [100] showed that SNPs were accountable for over 90% variation of methylation at associated CpG sites; whereas research by van Dongen et al. [104] showed that genetic variants could account for only about 7% of observed variable DNA methylation patterns. SNPs affect both gene expression (eQTLs) and methylation independently; the influence on gene expression may be by multiple mechanisms