Folate and DNA methylation during \textit{in utero} development and aging

J.A. McKay, E.A. Williams and J.C. Mathers

\textsuperscript{1}Human Nutrition Research Centre, School of Clinical Medical Sciences, University of Newcastle upon Tyne, NE1 7RU, U.K., and \textsuperscript{†}Human Nutrition Unit, University of Sheffield, Northern General Hospital, Sheffield S5 7AU, U.K.

Abstract

DNA methylation is one of several epigenetic mechanisms that play a regulatory role in genome programming and imprinting during embryogenesis. Aberrant DNA methylation has been implicated in the pathogenesis of a number of diseases associated with aging, including cancer and cardiovascular and neurological diseases. Evidence is accumulating that dietary factors \emph{in utero} modulate disease risk in later life. Although folic acid is a key component of DNA methylation, the impact of folic acid availability \emph{in utero} on DNA methylation patterns and disease risk in adulthood is at present poorly characterized. This review describes the relationship between folic acid and DNA methylation, and the association between DNA methylation during \emph{in utero} development and aging.

Introduction

Nutritional insults during foetal and neonatal development are hypothesized to have a detrimental impact on adult morbidity and mortality \cite{1}, but the underlying mechanisms are poorly understood. Folate insufficiency in pregnancy is well recognized as a risk factor for NTDs (neural tube defects), but may also influence NCD (non-communicable disease) risk in later life by the critical role of folate in DNA methylation and synthesis of purines and pyrimidines. This review focuses on the interaction between folate and DNA methylation during \emph{in utero} development and aging.

DNA methylation

DNA methylation is the addition of a methyl group to a cytosine residue present in a CpG dinucleotide \cite{2}. CpG dinucleotides occur at low abundance throughout the human DNA genome and tend to concentrate in regions known as CpG islands found in the promoter regions of genes. A CpG island is a region of DNA with more than 200 bp, a high G-C content and an observed/expected ratio of CpGs greater than 0.6 \cite{2}. CpG dinucleotides are typically methylated in non-promotor regions and unmethylated in promoter regions. Methylation within the promoter region correlates with transcriptional silencing and the methylation status of CpG islands is believed to regulate gene transcription through the inhibition of transcription factor binding either directly or via altered histone acetylation \cite{3}. This regulatory function is consistent with the role DNA methylation plays in silencing genes on the inactive X chromosome, in imprinted genes and parasitic DNA \cite{2}.

Changes in DNA methylation through \emph{in utero} development and aging

DNA methylation is critical to mammalian development. Methylation patterns are established during embryogenesis and remain largely unchanged in adult cells \cite{4}. Genome-wide demethylation occurs before embryo implantation followed by \textit{de novo} global remethylation after implantation in advance of organ development, allowing gene-specific methylation patterns to develop, which determine tissue-specific transcription \cite{5}. DNA methylation is also involved in the repression of either the maternal or paternal allele of imprinted genes. Incorrect development of DNA methylation patterns can lead to embryonic lethality \cite{6} and developmental malformations \cite{7}.

Although methylation patterns are established during early life, these are not fixed. Gradual hypomethylation of the vertebrate genome occurs with age in most tissues (reviewed in \cite{8}) accompanied by aberrant hypermethylation in the promoter regions of genes, e.g. \textit{ER}, \textit{IGF2} and \textit{c-myc} (reviewed in \cite{8}). Such age-related methylation has been implicated as an early step in carcinogenesis \cite{9}. Therefore, not only is it vital that DNA methylation patterns develop correctly during early life, but the preservation of these patterns may be beneficial to long-term health.

Folate, DNA methylation and \emph{in utero} development

Folate, a water-soluble vitamin B, is essential for the transfer of one-carbon units \cite{10}. It is indispensable in the methionine cycle and, therefore, for the synthesis of S-adenosylmethionine, the common methyl donor for DNA methylation. Folate deficiency leads to a decrease in S-adenosylmethionine and an increase in homocysteine. Dietary deficiencies in folate have been observed to decrease genome-wide methylation both in humans and in animal models, and...
methylation is corrected when a folate-replete diet is restored (reviewed in [11]).

The importance of folate in pregnancy for the prevention of NTDs has been well documented [10] and is further demonstrated in the Folbp1 (folate-binding protein 1) knockout mouse. Matings of heterozygous parents produced only Folbp+/- and Folbp+/+ offspring, indicating that complete inactivation of the gene required for cellular uptake of folate was embryo-lethal [12].

The agouti mouse model provides a more subtle demonstration of the importance of methyl donors, including folate, in DNA methylation and embryonic development [13]. Methyl donor supplementation of agouti dams during pregnancy causes the agouti gene to be silenced by methylation, altering the coat colour of the offspring. The present study suggests that maternal diet can have a significant effect on DNA methylation of the offspring.

Folate, DNA methylation and NCD risk

There are several genetic and acquired NCDs associated with abnormal DNA methylation (reviewed in [10]). Prader–Willi, Angelman’s and Beckwith–Wiedemann syndromes all result from abnormal demethylation of the silenced allele of imprinted genes causing biallelic expression. Abnormalities in folate metabolism and DNA methylation have been associated with Down’s syndrome, and aberrant DNA methylation has been implicated in the pathogenesis of neurological disorders including Alzheimer’s, Parkinson’s and Huntington’s diseases [14]. Altered DNA methylation has been extensively documented in tumorigenesis [10]. Genome-wide hypomethylation is associated with malignancy, which may cause chromosomal translocations and may lead to genetic mutations via cytosine to thymine transitions. Aberrant promoter region methylation, accompanied by altered gene expression for several proto-oncogenes and tumour suppressor genes, has been observed in a range of cancers and is probably an early event in carcinogenesis.

Future studies will provide insight into how folate supply during development affects methylation status and chronic disease risk in later life.

Implications for public health

The roles played by folate in nucleotide synthesis and in methylation of cell macromolecules explain the vital role of this vitamin during development in utero. Folate supplements in early pregnancy reduce the risk of NTDs and, possibly, other birth defects. Aberrant methylation patterns appear to be important components of the aetiology of cancers [10] and cardiovascular and neurological diseases. This result suggests that extra folate may be beneficial; however, since excess folate may mask the early symptoms of vitamin B12 deficiency, the risk/benefit ratio for food fortification by folate remains uncertain.

J.A.M. holds a BBSRC studentship.

References


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