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Review of Epigenetics of Folate and Associated Derangements

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Abstract

Folate, a vital water-soluble B vitamin, plays a central role in one-carbon metabolism, serving as a key donor of methyl groups necessary for DNA methylation—an essential epigenetic mechanism regulating gene expression. This review synthesizes current evidence on folate's role in epigenetic modulation, drawing from PubMed, Google Scholar, and other reputable sources. Particular attention is given to folate's inverse association with cancer risk, especially colorectal cancer, and its influence on epigenetic processes such as DNA methylation and histone modifications. Dysregulation of these mechanisms is closely linked to carcinogenesis and other chronic non-communicable diseases. Moreover, mutations or deficiencies in folate-related proteins may result in aberrant epigenetic reprogramming, leading to altered transcriptional activity and increased disease susceptibility. This review underscores the critical importance of adequate folate status in maintaining epigenetic homeostasis and preventing the onset of various malignancies and chronic conditions.

Keywords: Epigenetics; DNA Methylation; Histone Modifications; Malignancies; Transcription; Non-Communicable Chronic Diseases

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Introduction

Epigenetics encompasses heritable changes in gene expression or phenotype without alterations to the DNA sequence (Aswathy and VR, 2025; Emre *et al.*, 2025; Khatami *et al.*, 2025). In mammals, key epigenetic mechanisms include DNA methylation, histone modifications, chromatin remodeling, and non-coding RNA-mediated regulation, such as microRNAs and long non-coding RNAs (Ali and Tang, 2025; Costa *et al.*, 2025; Yildiz, 2025).

The epigenetic regulatory mechanisms modulate chromatin structure and also contribute to the regulation of the major molecular processes in the nucleus including transcription, replication, repair, and RNA processing (Song *et al.*, 2025; Zhang *et al.*, 2025). DNA methylation involves the covalent modification of genomic DNA which modifies gene expression and also provides the mechanism for transmitting and perpetuating epigenetic information through DNA replication and cell division (Pignataro *et al.*, 2025; Triantaphyllopoulos *et al.*, 2025; Zhou and Reizel, 2025). The role of DNA methylation in gene cellular regulation has also provided the potential for a new paradigm of disease intervention and treatment (L. Liu et al., 2025; Williams et al., 2025; Zhang et al., 2025). The development of various DNA methylation inhibitors that alter the methylation patterns within mammalian cells has led to the clinical use of the inhibitors in experimental therapies for human diseases such as hematological malignancies (Abdar Esfahani *et al.*, 2025; Rehman *et al.*, 2025) and myelodysplastic disorders (Smith *et al.*, 2025).

These processes modulate chromatin structure, influencing nuclear activities such as transcription, replication, DNA repair, and RNA processing (Ambrosio *et al.*, 2025). DNA methylation, a covalent modification, regulates gene expression and preserves epigenetic information through DNA replication and cell division, offering novel therapeutic targets, particularly for hematological malignancies and myelodysplastic syndromes via methylation inhibitors (Maher *et al.*, 2025; Yusoff *et al.*, 2025).

Folate, alongside other B vitamins, plays a critical role in epigenetic regulation through one-carbon metabolism, which supplies methyl groups for DNA, RNA, and protein methylation (Liang et al., 2025; C. Yan et al., 2025). These epigenetic marks are implicated in conditions such as neural tube defects (NTDs), asthma, cardio metabolic disorders, and cancer (Li *et al.*, 2025; Maj and Upadhya, 2025). While folate's role in preventing NTDs is well-established, its impact on other conditions remains inconsistent

due to challenges in identifying affected genomic loci, the direction of methylation changes, and their timing across the lifespan (Araszkiewicz *et al.*, 2025; Brown *et al.*, 2025). This review examines folate's role in epigenetic regulation and the health consequences of its deficiency, drawing on current literature to provide a comprehensive analysis.

Molecular Bases of Epigenetic Modifications

Epigenetics refers to heritable changes in gene expression independent of DNA sequence alterations, encompassing DNA methylation, histone post-translational modifications, chromatin remodeling, and non-coding RNA-mediated gene silencing (Engin and Engin, 2025; Kaya and Adamakis, 2025; Yildiz, 2025). This review focuses on folate's contributions to DNA methylation, histone modifications, chromatin remodeling, and their implications for disease.

DNA Methylation

DNA methylation involves the addition of a methyl group to the 5th carbon of cytosine, forming 5-methylcytosine, predominantly at CpG-rich regions known as CpG islands, typically located near gene promoters (Du et al., 2025; Williams et al., 2025; C. Yan et al., 2025). This modification occurs symmetrically on both DNA strands and is associated with gene silencing when present at promoter CpG islands, whereas hypomethylation correlates with active transcription(Marei, 2025). In mammals, DNA methylation supports long-term gene silencing mechanisms, including X-chromosome inactivation, genomic imprinting, and suppression of repetitive DNA elements (Montano and Timp, 2025; Smith *et al.*, 2025). The role of methylation at enhancers is less defined, with increased methylation often reducing transcription factor binding, though its impact on transcription varies by sequence context (Ragusa *et al.*, 2025; Van Dijck *et al.*, 2025).

Histone post-translational modification and chromatin remodeling

Histone post-translational modifications occur on specific amino acids, primarily lysine and arginine, at the N-terminal tails of histones (Y. Liu and Wang, 2025; Tang *et al.*, 2025; Xiao *et al.*, 2025). These modifications alter DNA-histone interactions, modulating chromatin accessibility to transcription machinery and serving as binding sites for proteins that recruit chromatin-modifying enzymes (Michael, 2025a; Vickram et al., 2025; Zhang et al., 2025). Histones, positively charged proteins, form the chromatin core (H2A, H2B, H3,

H4), around which DNA wraps to form nucleosomes, linked by histone H1 (Davie *et al.*, 2025; Dutta *et al.*, 2025). Chromatin exists as tightly packed heterochromatin (transcriptionally inactive) or loosely structured euchromatin (transcriptionally active) (Paggi and Zhang, 2025; Rodenburg *et al.*, 2025). Histone modifications regulate gene expression by facilitating transitions between chromatin states or acting as scaffolds for reader proteins, with specific modifications either activating or repressing gene expression (Michael, 2025b; Roy, 2025).

miRNA-mediated gene silencing

MicroRNAs (miRNAs) are short (~22 nucleotides), evolutionarily conserved non-coding RNAs that regulate gene expression in eukaryotic cells. Transcribed by RNA polymerase II as primary miRNAs (pri-miRNAs), they are processed by Drosha and DGCR8 into precursor miRNAs (Gogineni *et al.*, 2025; Singh *et al.*, 2025). In the cytoplasm, miRNAs mediate post-transcriptional gene silencing by binding to the 3'-untranslated region of target mRNAs, with perfect complementarity inducing mRNA cleavage and partial matches leading to translational repression (Paris *et al.*, 2025; Powell *et al.*, 2025). The precise mechanisms of miRNA action warrant further investigation.

Molecular Bases of Epigenome Regulation Associated with folate

Folate is indispensable in one-carbon metabolism, supporting nucleotide biosynthesis, the methionine cycle, and methylation reactions (Liang et al., 2025; E. H. Reynolds, 2025; C. Yan et al., 2025). It facilitates DNA synthesis, stability, and repair, and through 5-methyltetrahydrofolate (5-methylTHF), it supplies methyl groups for homocysteine remethylation to methionine, catalyzed by methionine synthase (Cerreto *et al.*, 2025; Tian *et al.*, 2025). This process generates S-adenosylmethionine (SAM), the primary methyl donor for methylation reactions (Nishikawa *et al.*, 2025; Xing and Tu, 2025). Folate metabolism involves conversions such as 5, 10-methylenetetrahydrofolate (5, 10-methyleneTHF) to 5-methylTHF by Methylenetetrahydrofolate reductase (MTHFR), balancing nucleotide synthesis and methylation requirements (Castillo *et al.*, 2025).

Role of folate in DNA Methylation

Folate's role in 1-carbon metabolism related to DNA methylation.

Dietary folate is metabolized to 5-methylTHF in the intestine or liver, where it is polyglutamated for cellular retention and one-carbon cycle functionality (Sangha, 2025). Folic acid from supplements or fortified foods is reduced to dihydrofolate, then tetrahydrofolate (THF), by dihydrofolate reductase, entering the folate pool (Megala and Kavitha, 2025; Puspitasari *et al.*, 2025). THF is converted to 5, 10-methyleneTHF by serine hydroxymethyltransferase, then to 5-methylTHF by MTHFR, supporting homocysteine remethylation to methionine and SAM production (Castillo *et al.*, 2025; Sangha, 2025). Other nutrients, including vitamins B6, B12, riboflavin, and choline, support this pathway (Pannia, 2021). SAM regulates MTHFR activity, inhibiting it at high concentrations to balance methyl group availability (Blomgren, 2025; Xing and Tu, 2025). The MTHFR 677C→T variant reduces enzyme activity, potentially diverting methyl groups from DNA methylation to synthesis pathways (Araszkiewicz *et al.*, 2025). S-adenosylhomocysteine (SAH) inhibits SAM-dependent methyltransferases, and its hydrolysis to homocysteine is essential for maintaining DNA methylation (Liang *et al.*, 2025; Tian *et al.*, 2025).

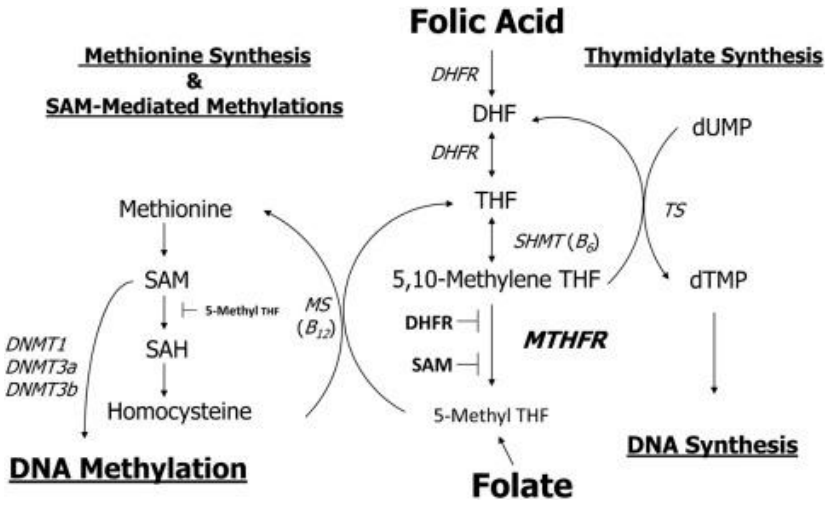

Figure 1. Folic acid metabolism. This schematic diagram shows the process by which folate/folic acid are being used for DNA methylation. The *MTHFR* 677C→T variant reduces enzyme activity (Frosst *et al.*, 1995) which may help to divert the available methyl groups from the DNA methylation pathway toward the DNA synthesis pathway (R. Green and Miller, 1999; Hoffbrand and Jackson, 1993; Quinlivan et al., 2005). The pathway is complex and it is highly regulated, with feedback loops and interactions not shown in the schematic figure. Gene names for enzymes are in italics and cofactors are in parentheses.

DHF, dihydrofolate; DHFR**,** dihydrofolate reductase; DNMT, DNA methyltransferase; dTMP, thymidylate; dUMP, deoxyuridine monophosphate; MS, methionine synthase; MTHFR, Methylenetetrahydrofolate reductase; SAH, S-adenosylhomocysteine; SAM, S-adenosylmethionine; SHMT, serine hydroxy methyltransferase; THF, tetrahydrofolate; TS, thymidylate synthase(Crider *et al*., 2012).

Low folate status and DNA methylation.

Low folate levels, indicated by reduced dietary intake or blood concentrations, are associated with cardiovascular disease, cancers, and NTDs (Ayoub, 2025; Gunnala *et al*., 2025). During cell division, folate deficiency impairs thymidine synthesis, leading to uracil misincorporation in DNA, increasing chromosomal breaks and micronuclei formation, particularly in individuals with the MTHFR TT genotype (J. Li et al., 2025; Zhang et al., 2025). These effects destabilize the genome, elevating disease risk.

DNA methylation, cancer, and folate.

Cancer is characterized by global DNA hypomethylation and targeted hypermethylation, resulting in tumor suppressor gene silencing and chromosomal instability (Imran *et al*., 2025; Vaidya *et al*., 2025). Hypomethylation of repetitive elements may predict cancer risk and mortality. Large-scale studies reveal tumor-specific methylation patterns distinct from normal tissues, with progressive methylation changes as tumors advance (Mäki-Nevala *et al*., 2025; Saha *et al*., 2025). Folic acid supplementation may prevent tumor suppressor gene loss of heterozygosity, but its role in healthy tissues and cancer predisposition remains unclear (Mellor *et al*., 2025; R. Zhou *et al*., 2025). *In vitro* folate depletion studies demonstrate both global hypomethylation and targeted hypermethylation, complicating its role in carcinogenesis (Sun *et al*., 2025; Verma and Lindroth, 2025).

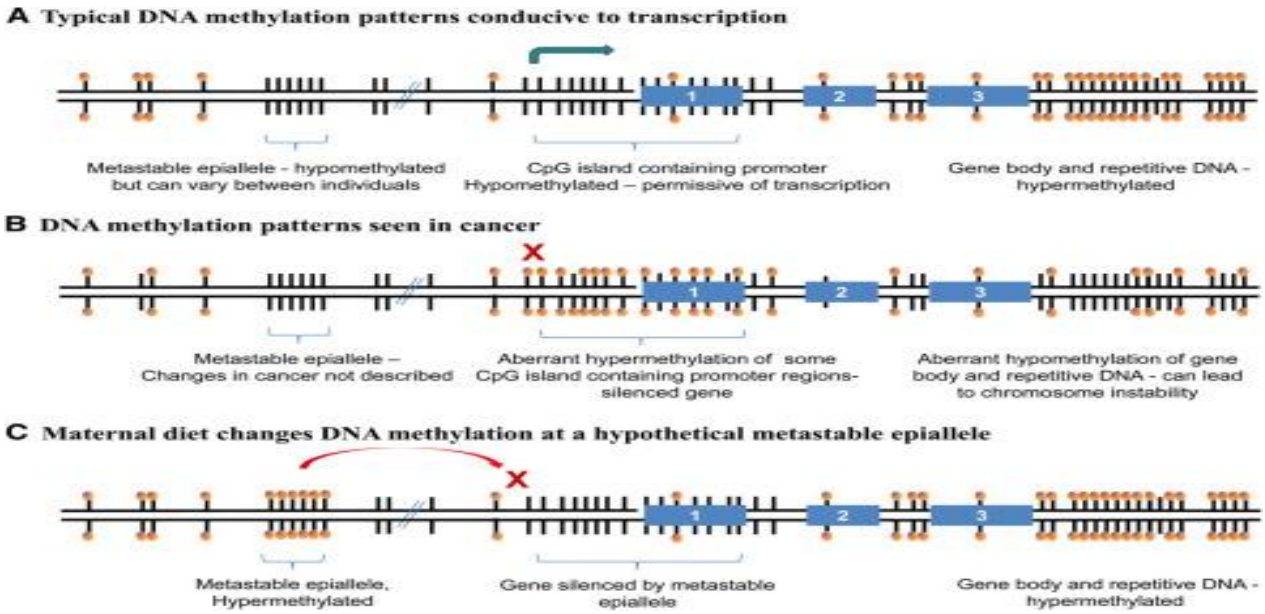

Figure 2 DNA methylation patterns at different types of genetic loci and how the patterns change in cancer and response to maternal diet. This is a cartoon of a hypothetical single section of double-stranded DNA. Each bar represents a 59-CpG -39 site. Methylated CpG is indicated by bars with balls at the end. The green arrow indicates transcription start and active transcription. The red X equals gene silencing. The numbered blue rectangles are exons. (A) DNA methylation patterns conducive to transcription: – patterns set during development. CpGs throughout the genome are targeted for methylation by DNA methyltransferases (DNMT1, DNMT3a, DNMT3b). CpG islands are regions with a concentration of CpGs often (but not always) associated with the promoter regions of genes(Crider *et al.*, 2012). CpG islands generally are thought to be actively protected from DNA methylation to allow for appropriate regulation of transcription (Stimson and Vertino, 2002). (B) Dysregulation of DNA methylation seen in cancer post-transformation. Cancer cells have aberrant DNA methylation patterns. Overall DNA methylation levels are reduced (Feinberg and Vogelstein, 1983),(Frigola *et al.*, 2005; Jackson *et al.*, 2004; Narayan *et al.,* 1998). A subset of genetic sites is hypermethylated, including some tumor suppressor genes; the specific loci hypermethylated vary among types of tumors (Christensen *et al.,* 2010; Y.-H. Kim *et al.*, 2011). (C) Maternal diet epigenetically changes methylation levels at the metastable epiallele, which can change the transcription of a neighboring region. Metastable epialleles are regions of the genome that have a variable methylation pattern that is semi-heritable across generations, illustrated by the Agouti mouse model (Waterland and Jirtle, 2003). In mice, a maternal diet that includes additional methyl donors can lead to increased methylation at the metastable epiallele (the intracisternal a particle

retrotransposon), a change in expression at nearby genetic loci, and permanent changes in the phenotype distribution of the offspring (Waterland and Jirtle, 2003). The sequence of the retrotransposon is a candidate for methylation in the early embryo; however, the extent to which it becomes methylated varies in genetically identical individuals based on maternal diet (methyl donors as well as other dietary factors) (Dolinoy *et al.*, 2006; Waterland, 2003). However, a study has found candidate loci in the human genome that show differential methylation dependent on the season of birth (Waterland *et al.*, 2010).

Studies of cancer patients and folate status and global DNA methylation.

Site-Specific DNA Methylation in Cancer.

A clinical trial of folic acid supplementation (1 mg/day for 3 years) in colon adenoma patients observed modest increases in methylation at specific loci with higher red blood cell folate, though functional impacts were unclear (Ly *et al.*, 2012). Observational studies indicate high plasma folate is associated with increased methylation at certain loci, but results are inconsistent (Bartak et al., 2025; Clement et al., 2025; J. Li et al., 2025). Comprehensive studies analyzing thousands of loci suggest complex interactions between folate and DNA methylation, necessitating advanced analytical approaches (Alemu *et al.*, 2025; Cohen *et al.*, 2025).

Folate Status in Healthy Adults.

In healthy adults, folate depletion in rapidly dividing tissues, such as blood and gut mucosa, may reduce global DNA methylation, particularly in older women or those with the MTHFR TT genotype (Bidoli, 2025; Hamdani et al., 2025; J. Li et al., 2025; Tang et al., 2025; R. Zhou et al., 2025). Repletion studies demonstrate increased methylation (Bartak *et al.*, 2025; Moghadamnia *et al.*, 2025; Parkes, 2025; Salavoura, 2025), but results vary due to small sample sizes, age differences, and intervention durations. Observational data suggest genotype-dependent methylation responses to folate status (Popa et al., 2025; Song et al., 2025; Wallace et al., 2025; C. Yan et al., 2025)

Epigenetic Responses to Environmental and Dietary Factors: The Role of Developmental Timing

There is considerable focus on reversing epigenetic changes, such as global DNA hypomethylation, seen in early tumorigenesis, as rapidly dividing tumor tissues may be particularly vulnerable to low folate levels, resulting in hypomethylation (Bakrim *et al.*, 2025;

Li *et al.*, 2025; Marei, 2025; Verma and Lindroth, 2025; Zhang *et al.*, 2025). Three clinical trials evaluated the impact of folic acid supplementation (0.4–10 mg/day) on global DNA methylation in patients with colon cancer (Fatima *et al.*, 2025; Flori *et al.*, 2025; Kapała *et al.*, 2025; T. Li *et al.*, 2025). Prior research has indicated that DNA methylation may act as a biomarker for colorectal cancer, with folic acid supplementation potentially increasing methylation in the colon and leukocytes of patients (Ediriweera and Sandamalika, 2025; Zwart *et al.*, 2025). Observational studies, including cohort and case-control designs, investigated the connection between folate status (assessed via folate/folic acid intake or blood folate levels) and cancer, with five studies specifically analyzing global DNA methylation (Ayoub, 2025; Frost *et al.*, 2025; Ledowsky *et al.*, 2025; T. Li *et al.*, 2025; Naderi *et al.*, 2025). These studies found a link between cancer and global DNA hypomethylation in blood and/or tumor tissue, but the association between folate status and global methylation was inconsistent. Such inconsistencies may arise from limited sample sizes or assay imprecision. Global hypomethylation was detected in tumors, as well as in normal colon cells and blood of cancer patients

The relationship between global hypomethylation and folate status (e.g., intake or blood folate levels) varies across cancer patient studies, likely due to differences in study designs, methylation assays, and tissues examined (Ahmad *et al.*, 2025; IKE *et al.*, 2025; Zwart *et al.*, 2025). Multiple techniques measure "global" DNA methylation, such as those targeting repetitive elements (LINE, SINE, Alu) or genomic restriction sites, yet these measures often show low correlation (Arachchillage and Udomsinprasert, 2025; Prabsattru *et al.*, 2025; Youngson *et al.*, 2025). This is because they assess distinct DNA sequence subsets in different genomic regions, which may be regulated differently. Recent studies suggest that methylation changes differ by tumor type and the repetitive DNA elements used as proxies for global methylation (Vlasac *et al.*, 2025). Early colon cancer trials used the methyl acceptance assay to estimate global DNA methylation (Günçer *et al.*, 2025; J. S. Li *et al.*, 2025; Yun *et al.*, 2025). This method, which involves enzymatic methylation of purified genomic DNA with radiolabeled tritium, has limited precision and requires intact DNA. Damaged DNA, whether from the condition under study or sample handling, can skew results. Therefore, selecting appropriate assay methods is critical for study design to ensure reliable and reproducible data (J. S. Li *et al.*, 2025; Yun *et al.*, 2025).

Folate, Fetal Development, and DNA Methylation

Early development is highly sensitive to folate levels due to rapid growth and epigenetic reprogramming (Ménézo et al., 2025; C. Yan et al., 2025). Studies of famine-exposed individuals show methylation changes at growth-related loci, such as IGF2 (Pidsley *et al.*, 2012; Plunk and Richards, 2020; C. M. Reynolds and Vickers, 2019). Maternal folic acid supplementation is associated with slight increases in offspring IGF2 methylation, inversely correlated with birth weight (B. Li et al., 2025; Shokrollahi *et al.*, 2025). NTD-affected fetuses exhibit brain hypomethylation and lower maternal folate levels (Chen *et al.*, 2025; Nie *et al.*, 2025). Cord blood studies show inconsistent associations between folate status and methylation, with some links to homocysteine levels and birth weight (Avram *et al.*, 2025; González-Ludlow *et al.*, 2025; Madiwale *et al.*, 2025)

High Folate Intake and DNA Methylation

High folate intake, often investigated to reverse cancer-related methylation changes, shows no consistent association with aberrant methylation or increased disease risk (Fernández-Ramos *et al.*, 2025; Fernandez *et al.*, 2012; Wang *et al.*, 2025). DNA methylation is highly context-specific, varying by tissue, genomic region, and developmental stage (Brethouwer *et al.*, 2025; Smith *et al.*, 2025). Some studies suggest high maternal folic acid intake may reduce methylation at specific loci, such as H19 (Jiao *et al.*, 2025), but broader impacts remain unclear

Folate in Histone Methylation

Histone methylation involves the addition of methyl groups to lysine or arginine residues on histone tails, catalyzed by histone methyltransferases (HMTs) using SAM as a methyl donor (Souza et al., 2025; Vickram et al., 2025; C. Yan et al., 2025). Folate supports SAM production via one-carbon metabolism, enabling histone methylation (Souza *et al.*, 2025; Xing and Tu, 2025; Yan *et al.*, 2025). Deficiency reduces SAM levels, impairing methylation and disrupting gene expression, chromatin structure, and cellular differentiation, contributing to diseases such as cancer and neurological disorders (Souza et al., 2025; C. Yan et al., 2025; Zainuddin et al., 2025).

Folate in Histone Acetylation

Histone acetylation, catalyzed by histone acetyltransferases (HATs), uses acetyl-CoA to add acetyl groups to lysine residues, promoting euchromatin formation and gene

expression (Mai *et al*., 2025; Sadia *et al*., 2025). Folate supports acetyl-CoA production, and its deficiency reduces acetyl-CoA levels, impairing acetylation and altering gene expression (Singh *et al*., 2025; Verma and Lindroth, 2025). High folic acid intake may influence acetylation, with rodent studies suggesting behavioral and gene expression changes, though human studies, particularly on autism, remain inconclusive (Fang *et al*., 2025; Rondanelli *et al*., 2025; Theis *et al*., 2025)

Folate in Histone Deacetylation

Histone deacetylation, catalyzed by histone deacetylases (HDACs), removes acetyl groups, promoting chromatin compaction and gene silencing (Bakrim *et al*., 2025; Jang *et al*., 2025; Vickram *et al*., 2025). Folate supports NAD+ production, a cofactor for NAD+-dependent HDACs (sirtuins). Deficiency reduces NAD+ levels, impairing deacetylation and affecting gene expression (Shadfar, 2025). HDACs interact with DNA methylation machinery, and combined HDAC and DNA methyltransferase inhibitors exhibit synergistic effects in cancer therapy, reactivating silenced genes (Imran *et al*., 2025; Kumar *et al*., 2025).

Synergetic Regulation of HDACs

HDACs interact with other epigenetic modifiers, such as lysine demethylases and methyltransferases, to coordinate chromatin remodeling and gene repression (Kim, 2025; Marei, 2025; Zhang *et al*., 2025). These interactions highlight the potential for combined epigenetic therapies in cancer treatment.

Folate in Histone Ubiquitination

Histone ubiquitination, primarily mono-ubiquitination of H2A and H2B, regulates transcription and DNA repair by altering chromatin structure or recruiting remodeling proteins (Davie *et al*., 2025; Shu *et al*., 2025). Folate's role in one-carbon metabolism supports neural tube closure, and its deficiency is linked to NTDs (Bhasker and Veleri, 2025; Nie *et al*., 2025; Pacoıta *et al*., 2025). Studies suggest folate influences histone ubiquitination, particularly H2AK119ub1, critical for developmental gene silencing (An *et a*l., 2025; Aquilino *et al*., 2025). Folate supplementation may mitigate NTD risk by modulating these epigenetic marks, though mechanisms require further exploration (Gunnala et al., 2025; J. Li et al., 2025; C. Yan et al., 2025).

Role of folate in Histone Deubiquitination

Histone deubiquitination, catalyzed by enzymes such as USP7, removes ubiquitin from histones, regulating gene expression (Bakkar et al., 2025; Jiao *et al.*, 2025; Roy, 2025; Roy and Ghosh, 2025). Folate enhances USP7 activity, supporting chromatin structure and cellular homeostasis. This role underscores folate's importance in epigenetic regulation (Krekora *et al.*, 2025; X. Yan and Liu, 2025)

Conclusion and future perspectives

This review underscores folate's pivotal role in epigenetic regulation through DNA methylation, histone modifications, and chromatin remodeling. Aberrant epigenetic patterns are implicated in diseases, including cancer, imprinting disorders, and developmental defects. Unlike genetic alterations, epigenetic changes are gradual, dose-dependent, and potentially reversible, offering opportunities for dietary and therapeutic interventions. Folate's inverse association with cancer risk and its modulation of DNA methylation highlight its therapeutic potential. However, its effects are complex, varying by cell type, organ, developmental stage, and genetic factors. While animal models provide valuable insights, differences in folate metabolism necessitate cautious extrapolation to humans. Future research should investigate folate's long-term epigenetic effects across life stages, its interactions with other nutrients, and its potential in modulating disease risk through targeted epigenetic therapies.

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