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# DNA Methylation: Its Role and Interaction with Epigenetic Modifications in Cancer

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**Abstract:** DNA methylation is an epigenetic mark involving the addition of a methyl group to DNA, particularly at cytosine residues. This methylation plays an important role in

regulating gene expression through direct gene repression or through the control of other epigenetic modifications such as histone modification or chromatin remodeling. DNA methylation is catalyzed by *de novo* and maintenance DNMT methyltransferase type enzymes and requires the transfer of a methyl group to cytosine to transform it into 5-methyl-cytosine. Currently, several investigations have highlighted the involvement of aberrant DNA methylation with certain tumors. Indeed, the methylation of antioncogenes and/or the demethylation of oncogenes are the major alterations that are strongly linked to human cancers. DNMTs play a central role in the epigenetic regulation of the human genome, both in normal and pathological processes. Recent discoveries on the differentiated roles of DNMTs in DNA methylation, and their implication in various cancers, open the way to new therapeutic approaches targeting these enzymes to treat epigenetic diseases. It is essential to continue exploring the roles of DNMTs to better understand their implication in tumorigenesis mechanisms and to develop more effective treatment strategies.

**Keywords:** DNA methylation; oncology; genotoxicity; gene expression; cancer; tumor

## 1. Introduction

Cancer is a complex disease that affects cells, tissues, and even entire organs. This disease arises from various risk factors, including environmental factors (smoking, exposure to genotoxic substances, diet, lifestyle, psychological stress, etc.), as well as genetic, hormonal, microbial, and epigenetic factors [1]. The fundamental mechanisms underlying tumor transformation involve interdependent elements that often lead to chromosomal, genetic, and epigenetic instability [2, 3]. This instability disrupts cellular functions such as DNA repair and metabolism, resulting in the loss of cellular memory and the definitive transformation of cells into clones that form metastases [4].

With advancements in molecular biology, studies in molecular oncology have precisely dissected the major events leading to tumor transformation [5]. Recent research indicates that disruption of transcriptional control is frequently linked to tumor transformation in the majority of human cancers [3]. This transcriptional control is finely regulated at the level of gene promoters by regulatory elements (transcription factors) that bind to promoters depending on the chromatin context [1]. Gene expression regulation can be influenced by various epigenetic marks, including DNA methylation [5]. DNA methylation is a chemical mark (the addition of a methyl group to the nitrogenous cytosine base) that influences other molecular factors, thereby preventing the transcriptional machinery from accessing the DNA [4].

Recent studies, such as the comprehensive analysis of solute carrier genes in colorectal cancer, have explored the role of DNA methylation in the regulation of these genes, highlighting its influence on tumor progression [6–9]. DNA methylation is a major indicator that determines whether certain genes are expressed, playing a key role in various human diseases, including cancers [1]. In addition, liquid biopsy, leveraging DNA methylation biomarkers, is emerging as a powerful non-invasive tool for cancer detection and monitoring, offering significant advantages in precision medicine [10]. This methylation occurs through specific enzymes called DNA methyltransferases (DNMTs), which have the ability to add the methyl group specifically to cytosines of gene promoters, thus controlling their expression (gene activation or repression) [5]. In mammals, five members of the DNMT family have been identified, namely *DNMT1*, *DNMT2*, *DNMT3a*, *DNMT3b*, and *DNMT3L* [3, 11]. Moreover, current research into epigenetic drug interventions has focused on targeting aberrant DNA methylation patterns in cancers such as breast cancer, with promising therapeutic directions emerging from this approach [12].

Notably, several recent studies have demonstrated a close relationship between disturbances in DNA methylation and the development of certain cancers, such as breast, colon, and prostate cancers [4]. Specifically, in colorectal cancer, alterations in the methylation landscape of *HOXA* genes have been linked to tumorigenesis, suggesting that specific methylation patterns could serve as potential biomarkers for diagnosis and prognosis [7]. In cancer, although global hypomethylation is observed, some genes become inactivated due tohypermethylation of CpG islands in regulatory regions, which remain unmethylated in non-malignant tissues [3].

In this review, we will highlight the major implication of DNA methylation in the onset of human cancers and propose key therapeutic strategies targeting DNA methylation as a promising approach against cancer [5]. This review distinguishes itself by integrating the latest discoveries on DNMTs and their role in tumorigenesis, while also offering perspectives for future research and demonstrating innovative strategies for cancer treatment through epigenetic modulation [1, 3, 4].

## 2. DNA Methyltransferases

DNMTs are a group of enzymes involved in DNA methylation. Normally, the human genome regroups many genes encoding five DNMTs (Table 1); *DNMT1*, *DNMT2*, *DNMT3A*, *DNMT3B*, and *DNMT3L* [3, 13].

**Table 1.** Types, protein lengths and function of Human DNMTs.

| DNMT type | Protein length | Function | NCBI Reference Sequence | Associated Cancers |
|---|---|---|---|---|
| ***DNMT1*** | 1616 amino acids | Maintenance of DNA methylation | CAA45219.1 | Colorectal, lung, breast cancer |
| ***DNMT2*** | 391 amino acids | tRNA methylation (not a cytosine DNA methyltransferase) | CAG29312.1 | Not directly linked to DNA methylation in cancer, but involved in RNA modification |
| ***DNMT3A*** | 912 amino acids | *De novo* DNA methylation | Q9Y6K1.4 | Acute Myeloid Leukemia (AML) |
| ***DNMT3B*** | 853 amino acids | *De novo* DNA methylation | Q9UBC3 | Breast, lung cancer |
| ***DNMT3L*** | 386 amino acids | Regulatory factor, stimulates DNMT3A and DNMT3B activity (lacks catalytic activity) | NP_787063.1 | Testicular cancer |

Together, DNMT enzymes lead directly and indirectly to the *de novo* establishment, maintenance and modification of DNA methylation at different levels [14, 15]. These activities are of crucial importance in the stability of DNA and the regulation of gene expression. Furthermore, DNA methylation occurs when DNMTs transfer a methyl group from S-adenosylmethionine (SAM), a methyl group donor, to the carbon-5 position of cytosine residues, which acts as the methyl acceptor [3, 16, 17]. This reaction forms 5-methylcytosine (5mC), frequently found within CpG islands, which are common targets of epigenetic DNA methylation, particularly in gene promoter regions. Notably, approximately 70% of gene promoter regions are located in CpG islands [18].

The catalytic activity of DNMTs in the human genome is primarily mediated by *DNMT1*, *DNMT3A*, and *DNMT3B* [14, 19, 20]. *DNMT3A* and *DNMT3B* are responsible for establishing *de novo* methylation, which is generally considered non-CpG-specific (Figure 1.b), where other sites like CpA and CpT are targeted by DNMT3 at lower levels compared to CpG islands [3, 15, 19]. Meanwhile, *DNMT1* is the most highly expressed DNMT in normal

cell tissues [21] and is largely responsible for maintaining existing methylation patterns by methylating the unmethylated strand of hemimethylated DNA during replication, ensuring the transmission of epigenetic information from mother cells to daughter cells (Figure 1.c) [20, 22]. The maintenance of methylation by *DNMT1* is CpG sites specific, while methylation of non-CpG sites is not restored by *DNMT1* during replication [14, 15]. *DNMT2* and *DNMT3L* are not believed to function as cytosine methyltransferases. However, *DNMT3L* plays an important role in DNA methylation without exerting direct catalytic activity on DNA. Numerous studies showed that *DNMT3L* acts as a potent cofactor, physically interacting with *DNMT3A* and *DNMT3B*, thereby enhancing their catalytic activities [23–25]. *DNMT3L* could also induce transcriptional repression through interaction with histone deacetylase 1 (HDAC1) [22]. On the other hand, despite the high phylogenetic similarity between *DNMT2* and other DNMTs, studies have revealed that *DNMT2* lacks catalytic activity in DNA methylation and instead serves as a tRNA methyltransferase that catalyzes tRNA methylation at a single specific site, highlighting its post-transcriptional regulatory function [3, 17, 26, 27].

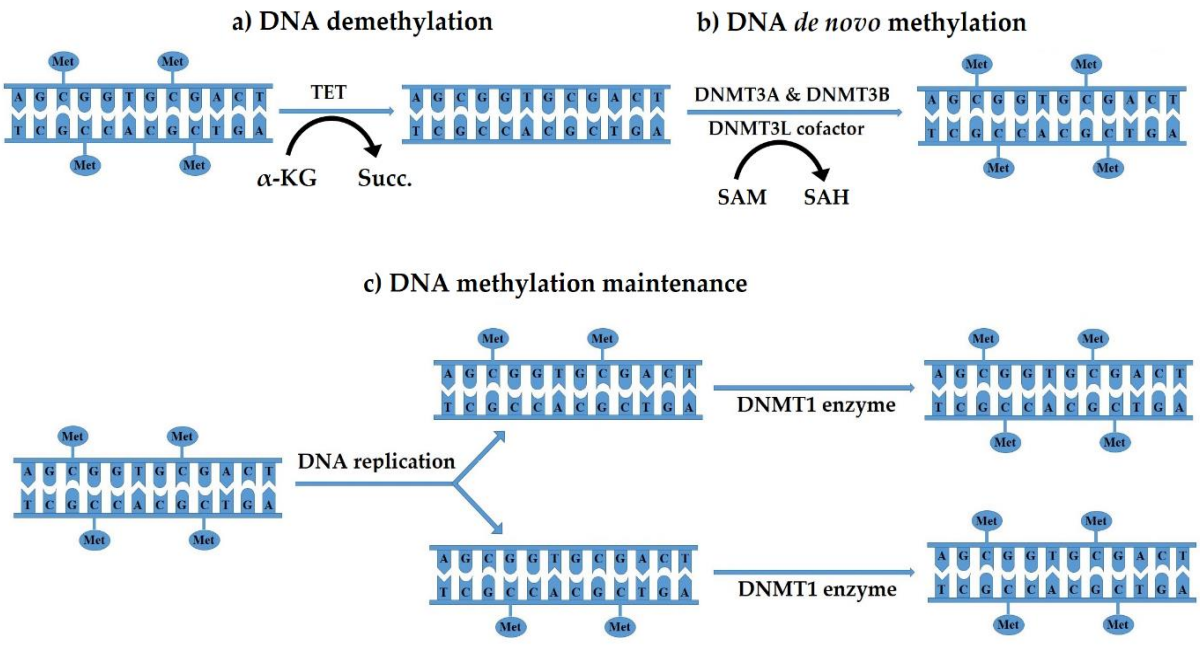


**Figure 1:** Processes of DNA Methylation. **a)** DNA demethylation mediated by TET enzymes, **b)** DNA *de novo* methylation by DNMT3 and **c)** DNA methylation maintenance by DNMT1 (α-KG: α-ketoglutarate) SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine, Succ: Succinate).

DNA methylation can inhibit transcriptional activation by interfering with the propagation of active chromatin marks. Chromatin is prepared for transcriptional activation through the methylation of H3K4 (lysine 4 of histone H3), a process mediated by a family of H3K4 methyltransferases [28]. Initial reports indicated that DNA methylation was broadly

associated with a decline in gene expression. However, this inverse correlation between DNA methylation and gene expression has since been shown to be specific to cases where methylation occurs in gene promoter regions. Originally, it was thought that this process was driven solely by the physical impact of the methyl group extending from the DNA and interacting with the transcription machinery [29].

DNA methylation plays a key biological role in embryonic development by restoring DNA methylation that was globally erased after fertilization through a process of demethylation, notably by Ten-Eleven Translocation (TET) methylcytosine dioxygenases (Figure 1.a) [30, 31]. DNA demethylation, regulated by the TET family of proteins (TET1, TET2, and TET3), involves the elimination of the 5-mC methyl group in different oxidation steps using the α-KG (ketoglutarate) cofactor, with the generation of succinate and $CO_2$ (Figure 1.a). TETs oxidize 5-mC and catalyze the conversion of 5-mC to 5 hydroxymethylcytosine (5-hmC). The latter is a comparatively more stable intermediate substrate and is less prone to further oxidation by TET proteins than 5-mC. Its oxidation can lead to two products: 5-formylcytosine (5-fC) and 5-carboxylcytosine (5-caC). Both of these molecules can be cleaved by thymine-DNA glycosylase (TDG) and ultimately repaired to unmodified cytosine [32]. Additionally, epigenetic therapy, targeting the dysregulated DNA methylation patterns in cancer, holds promise for reversing abnormal gene silencing and offers a novel approach to cancer treatment[33].

DNA methylation establishment in germ cells and after fertilization, mainly mediated by *de novo* methylation, represents an important step in epigenetic programming through chromatin remodeling during embryonic development [34, 35]. The epigenetic reprogramming by the *de novo* methylation plays a key role in the formation of pluripotent and differentiated cells from the zygote, which represents a totipotent cell, where each cell type will be the subject of a specific methylation pattern [14, 15]. This process explains the role of DNMTs in cells differentiation and development.

DNMTs are also involved in gene regulation, mostly in gene expression repression through the methylation of gene promoter regions [3]. The methylated cytosines in a promoter region recruit gene suppressor proteins and reduce the interplay between DNA and transcription factors [36]. In addition, CpG islands methylation is transcriptionally regressive and is extensively monitored by several synergistic and/or inducible pathways [37]. The effects of gene repression mediated by DNMTs could be partly explained by the recruitment of methyl-CpG binding proteins, such as MECP2, methyl-CpG binding domain 1 (MBD1), and MBD2 proteins that act as a transcriptional repressors by binding to the methyl-CpG site [38, 39]. Moreover, this repressive effect is associated with the recruitment of HDAC activity

leading to chromatin state modification [20, 40–42]. The DNMT proteins include a transcriptional repression domain (TRD), which forms a complex with several corepressor molecules (e.g. mSin3A) and histone deacetylase proteins (e.g. HDAC1, HDAC2) [29, 42, 43]. Furthermore, the role of DNMTs in transcriptional silencing could be mediated *via* retrotransposon methylation. *De novo* methylation of retrotransposon by the DNMT3 group is specifically regulated by the PIWI protein family [44, 45].

The role of DNMTs has been tested through gene knock-out studies. For instance, loss of *DNMT1* and *DNMT3B* results in embryonic lethality in mice, while the loss of *DNMT3A* negatively affects postnatal development [46]. Inactivation of DNMTs in human embryonic stem cells (ESCs) by CRISPR/Cas9 showed that deletion of *DNMT3A* and *DNMT3B* results in viable and pluripotent cell lines, whereas deletion of *DNMT1* resulted in rapid cell death of human ESCs [47]. In addition, many diseases have been discovered based on DNMT mutations. Centromeric instability and facial anomalies (ICF) syndrome is an example of a disease related to *DNMT3B* mutations [48, 49]. Mutations in *DNMT1* were found to cause hereditary sensory and autonomic neuropathy type 1E (HSAN1E) [50, 51]. Additionally, Tatton-Brown–Rahman syndrome results from mutations in *DNMT3A* genes [52, 53]. However, the hypothesis has been proposed that severe mutations of DNMTs could result in embryonic lethality [46, 54].

## 3. Involvement of DNMT Alterations in Cancer

Epigenetic modifications (e.g., DNA methylation, mRNA methylation, histone modification, chromatin remodeling, and RNA modification) play critical roles in tissue differentiation, embryonic development, and disease onset by regulating gene expression [55, 56]. These are heritable changes in gene expression patterns that occur independently of primary DNA sequence changes and alter the outcome at a locus or chromosome level while maintaining the fundamental DNA sequence. Environmental influences such as pollution, food, toxic chemicals, and inflammation can trigger epigenetic modifications to a locus or chromosome. These epigenetic alterations can be responsible for a wide range of diseases, including cancers [57].

Moreover, the relationship between DNMTs and cancer can be understood through two primary mechanisms that disrupt epigenetic regulation. First, mutations in genes encoding DNMTs, such as *DNMT3a* and *DNMT3b*, can lead to dysfunction in DNA methylation [46, 52, 58]. This dysfunction results in abnormal methylation patterns, leading to either global hypomethylation or localized hypermethylation, particularly in tumor suppressor gene promoters [59, 60]. These epigenetic disruptions cause aberrant gene expression, where genes normally repressed may become activated, and vice versa,

promoting uncontrolled cell proliferation and tumorigenesis [61, 62]. Second, even in the absence of mutations, DNMTs can become dysfunctional due to various factors. These enzymes, although not mutated, may be impaired by external influences such as post-translational modifications, oxidative cellular environments, or interactions with regulatory proteins [36, 48]. Dysfunctional DNMTs may cause aberrant DNA methylation, disturbing the expression of genes crucial for cell regulation, leading to abnormal cell growth and cancer progression [55, 63].

Overall, whether DNMTs are mutated or not, their dysfunction can significantly impact DNA methylation, resulting in gene expression alterations that favor the development of various cancers [43, 57]. Understanding these underlying mechanisms is crucial for developing effective therapeutic strategies targeting DNMTs and associated epigenetic processes [64].

On the other hand, the data presented in Table 1 highlight the specific roles that different DNMTs play in cancer, illustrating how mutations and dysregulations of these enzymes contribute to oncogenesis. *DNMT1* is primarily responsible for maintaining DNA methylation patterns during cell division. Its overexpression has been linked to poor prognosis in colorectal cancer, where it is associated with global DNA hypomethylation and localized hypermethylation of tumor suppressor genes [44, 55]. This duality in function—where both hypo- and hypermethylation can drive cancer progression—underscores the complexity of DNMT1's role in cancer [56]. In addition, DNMT3A and DNMT3B are key players in *de novo* DNA methylation, establishing new methylation patterns during development and in response to cellular stress [29, 57]. Mutations in *DNMT3A* are particularly prevalent in acute myeloid leukemia (AML), where they lead to aberrant hypermethylation and are correlated with poor patient outcomes [63, 65]. Similarly, DNMT3B mutations have been associated with aggressive breast and lung cancers, where they contribute to the hypermethylation of genes that regulate cell growth and apoptosis, promoting tumorigenesis [66]. DNMT2, while primarily involved in tRNA methylation, has recently been implicated in broader epigenetic regulation and cancer progression [67]. Although not directly linked to DNA methylation in cancer, DNMT2's role in RNA modification and its potential impact on gene expression and cellular stress responses warrant further investigation. This suggests that DNMT2 might contribute to tumorigenesis through mechanisms that are not yet fully understood but are promising in the context of cancer biology [68]. DNMT3L acts as a regulatory factor, enhancing the activity of DNMT3A and DNMT3B. Although DNMT3L itself lacks catalytic activity, its role in stimulating *de novo* methylation is essential, particularly in germ cell development [69]. Dysregulation of DNMT3L has been linked to the development of germ

cell tumors, illustrating its importance in maintaining epigenetic stability in specific cell types [61]. The misregulation of DNMT3L in cancers such as testicular cancer further highlights the intricate interplay between epigenetic regulators and tumorigenesis [62].

These findings underscore the importance of understanding the specific roles of DNMTs in different cancers. The ability of DNMTs to influence gene expression through methylation patterns makes them potential targets for therapeutic interventions [70]. As our understanding of the molecular mechanisms underlying DNMT-related dysregulation in cancer deepens, it may lead to the development of more precise and effective treatments that target these enzymes or their downstream effects [59]. The therapeutic implications of DNMT dysregulation in cancer are profound, as targeting these enzymes could potentially restore normal gene expression patterns and improve treatment efficacy [71].

### *3.1. DNA Methylation and Cancer*

The DNA of cancer cells is known to exhibit altered methylation patterns. There are two different models that have been identified; broad regions of global hypomethylation that spread throughout the genome and then localized regions of hypermethylation at specific sites, called CpG islands, in the promoter regions of genes [29]. Both are involved in tumor carcinogenesis [65]. This epigenetic mechanism also has a significant effect on the regulation of genomic imprinting, chromosome stability, transposable element repression, X-chromosome inactivation, and tissue-specific genes [36].

As an epigenetic mark, DNA methylation is influenced by environmental factors that could interrupt or enhance the activity of DNMTs and subsequently alter the levels of DNA methylation [63, 67, 72]. High levels of DNMT activity lead to hypermethylation and consequent gene repression [68]. In contrast, low DNMT activities are often associated with hypomethylation and gene expression activation [69]. Both up- and down-regulation of DNMT activities have been implicated in the development of several diseases, including cancer, without altering DNA sequence composition [22, 41, 61]. The link between DNMT activities and cancer development may be due either to tumor suppressor genes silencing by hypermethylation [41, 67], or to the activation of oncogenes *via* hypomethylation [62, 69]. However, the particularity of epigenetic marks, including DNA methylation, lies in their reversible nature. Tis reversibility of epigenetic marks prompts scientists to search for compounds that could positively affect the DNMT activity and thus be used as epidrugs in the treatment of diseases caused by DNMT disorders, such certain cancer types. Among the most well-known compounds, 5-azacytidine and 2′-deoxy-5-azacytidine are widely used in the combinatorial treatment of many cancers due to their inhibitory effects on DNMTs [59, 70]. In addition, a considerable number of bioactive compounds are characterized by their potent

ability to modulate the DNMT activities [60, 73]. For instance, Mirza et al. [41] revealed that natural compounds such as EGCG, genistein, curcumin, resveratrol, withaferin A, and guggulsterone can decrease DNMT activities *via* the down-regulation of DNMT gene transcription and the decrease of DNMT1, HDAC1, and MeCP2 protein levels, resulting in hypomethylation and the reactivation of tumor suppressor genes.

In cancer, although there is global hypomethylation, certain genes become inactivated due to hypermethylation of CpG islands in regulatory regions, which remain unmethylated in non-malignant tissues. This type of epigenetic silencing was initially identified in studies of retinoblastoma tumors, which revealed that the retinoblastoma gene (RB1), a tumor suppressor gene that regulates the cell cycle, was inactivated by hypermethylation [74]. Therefore, a significant number of tumor suppressor genes silenced by DNA hypermethylation in tumor tissues have been recognized. Undoubtedly, silencing associated with DNA methylation is pivotal in the process of tumorigenesis and is a prominent feature of all kinds of human malignancies [64]. Genes that undergo hypermethylation in regulatory regions are implicated in a range of critical cell signaling pathways [22]. For example, several cell cycle-related genes, namely *p15INK4a* (CDKN2B) and *p16INK4a* (CDKN2A), undergo DNA methylation-mediated silencing in several types of cancer. Both proteins are involved in controlling G1 progression, functioning as cyclin-dependent kinase inhibitors, and are major tumor suppressors [75]. Additionally, there is evidence that different genes are hypermethylated in cancers, including *p16INKa*, *RB1*, and *VHL1* in renal cell carcinoma [11]; *CDKN2A*, *hMLH1*, and *APC* in colorectal cancer (CRC); *MGMT* in colon, lung, lymph, and other tumors [76], and *DNMT3B*, *TET2*, *BRAF*, *IDH1*, and *MYC* in prostate cancer [77]. Further research has pointed to promoter hypermethylation of various breast cancer genes involved in the regulation of cellular transcription (e.g., *HOXA5*), apoptosis (e.g., *BCL2*), DNA repair (e.g., *BRCA1*), metastasis (e.g., *TWIST*), hormone-mediated cell signaling (e.g., *ERα/β*), and cell adhesion (e.g., *CDH1*) [78]. Some of the hypermethylated genes in cancer are related to cancer cell survival as they have pro-apoptotic functions, e.g., *death-associated protein kinase 1* (*DAPK1*), which mediates interferon-γ-induced apoptosis, or *TMS1*, which activates apoptotic signaling pathways [79]. It has also been established that DNA hypermethylation leads to the alteration of genes encoding upstream regulators of several cellular mechanisms. These include transcription factors (e.g., *GATA4* and *GATA5*) or genes implicated in different receptor-mediated signaling pathways (e.g., *ESR1*, *RARB2*, and *CRBP1*) which are frequently hypermethylated in cancer [22]. The methylation profile of *BRCA1*, which is responsible for the repair, transcription, and recombination of DNA double-strand breaks, has also been well-explored in breast and ovarian cancer [80]. Moreover, DNMT1 has been proven to be a key factor in the aggressiveness of triple-negative breast cancer (TNBC). In fact, it causes

hypermethylation in the estrogen receptor (ER) promoter regions, tumor suppressor genes, microRNAs, and epithelial markers implicated in the suppression of the epithelial-mesenchymal transition, leading to metastasis and cancer proliferation [81]. In addition, overexpression of DNMT1 or DNMT3A potentially leads to global DNA hypermethylation and silencing of DNA repair genes like *hOGG1*, *ERCC1*, *hMSH2*, and *XRCC1* inducing impaired DNA repair and resulting in genome instability [82]. Inhibition by DNA hypermethylation of genes involved in cell adhesion can lead to invasion and/or metastasis, and thus to tumor progression, e.g., *CDH1* (E-cadherin) and *CDH13* (H-cadherin) [83]. Increased DNMT1 protein expression was significantly associated with poorer gastric cancer differentiation by immunohistochemical examination, whereas no DNMT1 immunoreactivity was found in any of the non-cancerous gastric epithelia examined (except in the proliferative areas). Another confirmation of the significant relationship between DNMT1 and CIMP overexpression in gastric cancers was provided by protein-level analysis using immunohistochemistry. The genes *hMLH1*, *THBS-1*, and *E-cadherin* could be targets for DNMT1 overexpressed in gastric cancers [84]. It should also be noted that overexpression of DNMT1 is not consistently a side effect of enhanced cell proliferative ability, but it is strongly related to regional DNA hypermethylation [85]. The occurrence of increased DNMT1 protein expression in hepatocellular carcinoma (HCC) is clearly associated with impaired tumor differentiation and portal vein involvement. Moreover, HCC patients with elevated DNMT1 protein expression have substantially lower overall and recurrence-free survival rates than patients without DNMT1 expression [86].

Overexpression of TET1 or TET2 can cause an overall decrease in 5- mC [32], and TET2 enzyme mutation are considered important in the progression of tumors, and especially in chronic myelomonocytic leukemia [87]. Different DNA repair genes are also hypermethylated in tumor tissues, reinforcing the evidence that classical genetic damage like mutations can be promoted by epigenetic events [22]. This is exemplified by MGMT (O-6-methylguanine-DNMT), which prevents the negative impact of DNA alkylation occurring in healthy tissues and has been found to be silenced in many different kinds of carcinomas [88]. A malfunction in DNA mismatch repair is seen in a considerable fraction of gastric neoplasia and is linked to hypermethylation of *hMLH1* gene promoter [89].

Integrative multi-omic approaches have provided deeper insights into the role of DNA methylation in cancer, highlighting the importance of comprehensive profiling in the development of targeted therapies [90]. DNA methylation changes the metabolism of cancer cells. In fact, metabolic reprogramming is now considered one of the most important characteristics of cancer cells, as they must adapt their metabolism to meet energy and

biosynthetic needs and ensure their proliferation [91]. Many tumor-related genes, including *hMLH1*, *p16*, *BRCA1*, *MGMT*, *GSTP1*, *DAPK-1* and *TIMP-3*, undergo suppression in human cancers by regional DNA hypermethylation around their promoter regions [92]. Indeed, *IDH1/2* isocitrate dehydrogenase mutations have been documented to promote a loss of their normal catalytic capacity, which is the generation of α-KG by isocitrate decarboxylation, and an increase in their ability to act as a catalyst for the conversion of α-KG to 2-hydroxyglutarate (2-HG), which in turn suppresses the action of the α-KG-dependent histone demethylases and TET 5-methylcytosine hydroxylases. Changes in intermediate and energy metabolism are also a key feature of a pattern of epigenetic instability that is typical of a variety of malignancies, such as AML, myelodysplastic syndrome, and gliomas [93, 94]. It has become known that many tumor-related genes, including *hMLH1*, *p16*, *BRCA1*, *MGMT*, *GSTP1*, *DAPK-1*, and *TIMP-3* are suppressed in human cancers by regional DNA hypermethylation around their promoter regions [92].

DNA hypomethylation was the initial epigenetic abnormality recognized in human tumors. Chromosomal instability and gene activation are triggered by hypomethylation. It can also promote abnormal expression of certain proto-oncogenes and reactivation of retroviruses, DNA repeats (e.g., *Alu*, *LINE*, satellite DNA, epicentromeric, and centromeric tandem repeats), and transposable elements (TEs) [62].

In cancer cells, DNA hypomethylation of single genes is relatively rare. Most of the promoters involved in the loss of DNA methylation are tissue-specific genes [22]. In this sense, it has been found that *MAGE* (*MAGE-A1* and *MAGE-A3*) gene promoter hypomethylation enhances its expression in colorectal carcinomas (CRCs) as well as in gastric cancers and may be involved in the early stages of human CRC development and progression [95]. The cancer/testis antigen (CT) family, which is confined to adult testicular germ cells under normal circumstances, has been recorded to be aberrantly activated in different types of human cancer [96].

Depending on the roles of genes impacted by hypomethylation, this process may be correlated with different levels of tumorigenesis. DNA methylation loss in the *CDH3* gene promoter resulted in P-cadherin overexpression in both breast and CRCs. As a result, decreased cell polarity enhances cell invasion, motility, and migration, which in turn are linked to impaired patient survival [97, 98]. Loss of DNA methylation could also activate latent viral sequences embedded in the genome, potentially leading to tumor progression. An example is the human genital papillomavirus (HPV) genomes that are potently suppressed by CpG methylation after infection. DNA hypomethylation phenomena allow HPV re-expression, which can be associated with cervical cancer progression [99]. DNA

hypomethylation may also act as a tumor suppressor. For instance, TE hypomethylation (LINE1 and endogenous retrovirus "ERV") has been recorded to promote activation of their anti-viral expression and signaling, leading to an intensified response to immune checkpoint blockade in kidney cancer cell lines [100]. In addition, hypomethylation was identified in oncogene promoters such as *MN/CA9* in human renal cell carcinoma [101]. It has also been identified in *IL-10* CpG islands, a cytokine that aids in the oncogenic promotion and suppression of tumor suppressor genes in gastric cancer [102].

The issue of the underlying pathway of hypomethylation phenomena in cancer has been challenged by a number of proposals concerning the possible role of DNMT3B in this process. Recent hypotheses suggest a potential role for catalytically inactive variants of DNMT3B in this event. In several cancer cell lines, over 20 variants of this enzyme, which code for truncated proteins lacking a catalytic domain, have been discovered [103]. Inactive DNMT3B variants have been suggested to negatively control DNMT function. They have the potential to abrogate the DNA methylation machinery through the ability to titrate DNMT3B binding partners, thereby interacting with the DNA methylation machinery, or by competing with the active form to bind to target DNA sequences. In fact, increased levels of DNMT3B4 in chronic myeloid leukemia are linked to DNA hypomethylation of LINE1. Moreover, HEK293 cell lines that stably overexpress DNMT3B4 demonstrate demethylation of satellite 2 after multiple passages. This suggests that overexpression of DNMT3B4 in any way causes a loss of DNA methylation [103].

Hypermethylation of CpG islands in the promoter region of a tumor suppressor or other cancer-related gene is often associated with transcriptional silencing of the associated gene. The number of gene-associated promoters that are known to become hypermethylated during carcinogenesis is rapidly growing. Genes of numerous pathways involved in DNA repair (*MGMT*, *MLH1*, *BRCA1*), signal transduction (*APC*), differentiation (*MYOD1*), angiogenesis (*THBS1*, *VHL*), carcinogen-metabolism (*GSTP1*), cell adherence (*CDH1*, *CDH13*), cell cycle regulation (*p15*, *p16*, *RB*, *p16INK4a*, *p15INK4b*, *p14ARF*), apoptosis (*Caspases*, *p14*, *DAPK*), and detoxification (*GSTP1*) are often inappropriately inactivated by DNA methylation [104]. In addition, tumor suppressor genes (*p16INK4a*, *p14ARF*, *p15INK4b*, *MGMT*, *hMLH1*, *BRCA1*, *GSTP1*, *DAPK*, *CDH1*, *p73*, and *APC*) are commonly affected according to the most common types of human tumors [105].

DNA methylation alters the metabolism of cancer cells and vice versa. However, the metabolic routes in which DNA methylation is implicated principally concern glycolysis, the methionine cycle, and the tricarboxylic acid (TCA) cycle. Furthermore, demethylation of the promoter is linked to *HK2* and *PKM2* overexpression, both of which promote enhanced

glycolysis. Conversely, hypermethylation of the promoter results in the gene silencing of *FBP-1* and *FBP-2*, both of which identify the rate-limiting enzymes of glucogenesis. *FBP-1* and *FBP-2* silencing may inhibit gluconeogenesis but enhance glycolysis, thereby benefiting tumor cell proliferation [106].

Global changes mediated by DNA hypo- and hypermethylation are of biological importance in cancer. Indeed, they play an important role in tumorigenesis and have also been shown to be involved in chromosomal instability, chemoresistance, metastasis, tumor invasion, proliferation, and survival of cancer cells. These changes also result in decreased immune responsiveness, apoptosis, and sensitivity to chemotherapy. In relation to inflammation, chronic inflammation is known to induce global DNA hypomethylation [107]. DNA hypomethylation can lead to loss of imprinting (LOI) in tumors and activation of growth promoting genes, such as R-Ras and MAPSIN in gastric cancer and S-100 in colon cancer. Hypomethylation specific to genes in prostate cancer has been reported, including *CYP1B1*, *HPSE*, *PLAU*, as well as for *CRIP1*, *S100P*, and *WNT5A*. Increased expression of *HPSE*, which encodes heparanase, an extracellular matrix degradation protein that degrades heparan sulfate, has been implicated in tumor invasion and metastasis [108].

Proper DNA methylation is fundamental for proper cell function and development. Therefore, any defect or abnormality in this reorganization process can be linked to a wide range of disorders, especially cancer. In fact, tumor cells are distinguished by the presence of a distinct methylome from that of normal cells. It is noteworthy that both hypo- and hypermethylation events can be identified in cancer. Typically, there is an overall reduction in the level of methylated CpGs. This process is responsible for contributing to genome instability and, less commonly, promoting silenced oncogenes [22].

### *3.2. Histone Modification and Cancer*

Although epigenetics is the epi-information that extends DNA pattern that can be transmitted from parents to offspring, years of investigation have revealed that histone modifications are among the most important mechanisms through which epigenetic control is achieved [109]. Histones represent a group of structural proteins that cooperate with DNA to provide a miraculous topology for DNA packaging into the nucleus as chromatin. This chromatin is organized into repeating units called nucleosomes, each consisting of an octamer of histone proteins formed by two copies of the four histone proteins (*H2A*, *H2B*, *H3*, and *H4*) surrounded by 147 bp of DNA, and interconnected by a short DNA linker [110]. A histone linker H1 binds to DNA input/output sites on the nucleosomal core to enhance nucleosome binding to DNA and ensure the stability of higher-order chromatin architecture [111]. This

complex is designed to monitor DNA accessibility and therefore regulate its replication, transcription, recombination, and repair [110]. Histone modifications can occur in the N- and C-terminal tails as well as the core domain of these histone proteins due to a variety of extrinsic and intrinsic alterations that can occur throughout the life cycle. They can be modified post-transcriptionally, such as acetylation, phosphorylation of serines (S) and threonines (T), methylation of lysines (K) and arginines (R), sumoylation of lysines, and ubiquitination [112].

### *3.3. Histone Methylation and Cancer*

Histone methylation involves three different constituents; readers (histone methylation recognition proteins), writers (histone methyltransferases: *HMTs*), and erasers (histone demethylases: *HDMs*) [32]. Histone methylation, which usually occurs on the lysine (K) and arginine (R) residues of *histones H3* and *H4* by the addition of methyl groups, is one of the most prominent post-transcriptional modifications [113]. This methylation is mediated by histone methyltransferase (HMT), which uses S-adenosyl methionine (SAM) as a substrate to transfer methyl groups to lysine and arginine residues of histones [114]. Histone lysine residues can be mono-, di-, and trimethylated (me1, me2, and me3, respectively) to function as active or repressive marks on gene expression. Overall, H3K4, H3K36, and H3K79 are considered active marks occupying regions of actively transcribed genes in chromatin. However, H3K9, H3K27, and H4K20 are recognized as repressive marks generally associated with gene expression silencing and chromatin condensation [115]. Histone demethylation is mediated by two HDMs; histone demethylases containing the Jumonji C domain (JMJC) that demethylate tri-methyl states in lysine and arginine residues, and lysine-specific demethylases of the amine oxidase type (LSD or KDM) that remove the methyl group only from mono- and di-methylated lysines [116]. Recurrent histone mutations, which interfere with histone methylation and are involved in oncogenesis, are recognized in several malignancies and are described as oncohistones. The latter can induce epigenomic and transcriptomic reprogramming, eventually leading to oncogenesis. Well-documented oncohistones, which include mutations in both *H3.1* and *H3.3*, include H3K27M in glioma, H3K36M in chondroblastoma, and the H3G34 mutations that occur in bone cancer and glioma [114]. Furthermore, altered histone methylation can initiate disruption of gene expression, potentially contributing to the emergence of cancer. For example, mutations in EZH2, a histone methyltransferase that suppresses gene transcription *via* H3K27, have been linked to diffuse large B-cell lymphoma (DLBCL) [117].

### *3.4. Histone Acetylation and Cancer*

Histone acetylation and acetylation are critical processes that are mediated by the balance between two families; HDACs and histone acetyltransferases (HATs). Acetylation can decrease the positive charge of lysine residues, which prevents histone tails from binding to negatively charged DNA, potentially exposing the underlying DNA [118]. HATs are divided into three groups; p300/CREB binding protein (CBP), GCN5-related N-acetyl transferases (GNAT), and MYST HATs. They act as catalysts for the removal of an acetyl group from the acetyl-CoA cofactor to the ε-amino group of the lysine residues of histone proteins to neutralize their base charge [118]. There are 18 HDACs belonging to four classes in humans; class I proteins of type Rpd3 (HDAC1-3 and HDAC8), class II proteins of type Hda1 (HDAC4-7, HDAC9, and HDAC10), class III proteins of type Sir2 (SIRT1, SIRT2, SIRT3, SIRT4, SIRT5, SIRT6, and SIRT7), and the class IV protein (HDAC11). The class I and class II HDACs, which catalyze the metal-dependent hydrolysis of acetylated histones, share a conserved group of amino acid residues at their active sites [119]. On the other hand, histone-lysine acetylated residues are recognized by Bromodomain and extra terminal domain (BET) proteins, particularly BRD2, BRD3, and BRD4, which in turn recruit HDAC proteins. These deacetylases induce DNA compaction and transcriptional repression and increase the interaction between histones and DNA [116]. Both HDACs and HATs are involved in the preservation of chromatin accessibility and gene expression control. Nevertheless, impairment of this process can contribute to the development of several disorders, such as cancer. Different investigations have demonstrated the association of these enzymes with cancer promotion and progression, and many inhibitory drugs (HDACi and HATi) have been used as therapeutic agents to block the activity of these enzymes and consequently treat cancer. HAT gene mutations have been linked to a variety of different cancers, whereas HDAC mutations have so far been associated with some leukemia cancers [120].

The cyclic AMP response element-binding protein (CBP) and p300 HATs were first discovered by two independent groups in 1996. CBP frequently interacts with p300 to form a CBP/p300 complex, which can subsequently engage other HATs like PCAF (p300/CBP-associated factor). Both CBP and p300 biallelic mutations have been observed in a number of cancers, most notably gastric, breast, and colon cancers [114]. HDAC1 has been reported to be involved in promoting cell proliferation in gastric cancer through upregulation of long non-coding RNAs BC01600 and AF116637 [121], and is also overexpressed in prostate cancer cells [122]. HDAC2, on the other hand, is consistently overexpressed in human gastric carcinoma [123] and breast cancer [124, 125]. It is also significantly overexpressed in human lung cancer cells and deregulates the expression of apoptotic and cell cycle proteins [126].

Additionally, BET proteins function as a platform to recruit RNA polymerase II and other transcription factors to drive gene expression. BET protein overexpression and translocation mutations are recognized in cancer tumorigenesis [127]. Blocking BRD4 binding to chromatin by BET inhibitors, JQ1, has been shown to induce an anticancer effect and differentiation in BRD4-dependent tumors [128].

### *3.5. Chromatin remodeling and Cancer*

Chromatin remodeling is a vital process involving dynamic modifications in chromatin structure and is evolutionarily conserved from yeast to humans. High-order chromatin structures are uneven, with some areas relaxed and others condensed. In the relaxed chromatin areas, DNA is in an "open" state and is accessible by additional proteins regulating gene expression, namely transcription factors and RNA polymerases [129]. Indeed, this process regulates the accessibility of DNA regulatory elements that control chromosomal processes (enhancers, promoters, replication origins) to regulate gene transcription, DNA replication, repair, and recombination. Thus, it allows for the packaging and unpackaging of the genome [130]. Chromatin remodeling is achieved *via* chromatin remodeling complexes. ATP-dependent chromatin remodeling complexes use the energy of ATP hydrolysis to disrupt the binding between DNA and histones, resulting in positional changes of nucleosomes [131, 132].

Families of chromatin remodeling complexes can be divided into the imitation switch (ISWI) family, chromodomain, helicase, DNA binding (CHD) family, switching defective/sucrose non-fermenting (SWI/SNF) family, and Inositol requiring 80 (INO80) family. Each of these families uses the energy of ATP hydrolysis to change the structure of chromatin and control the proteins of the transcription mechanism by rearranging the nucleosomes [114]. The INO80 family of chromatin remodelers, INO80 and SWR1, are involved in nucleosome editing by exchanging histone variants. ISWI remodelers, Isw1a, Isw1b, and Isw2 complexes, as well as CHD, are implicated in nucleosome maturation and spacing to create fixed-distance nucleosome arrays [133]. There are a number of chromatin remodeling family members known to be mutated in malignancies, including SNF5, BRG1 and MTA1, indicating that they may be effective tumor suppressors. There is now strong support for this assertion through the sequencing of cancer genomes, which identified high-frequency mutations in several members of the SWI/SNF complex in a range of solid and hematological malignancies [133]. Evidence from mouse models has demonstrated that impaired expression of these so-called tumor suppressors can enhance the susceptibility to cancer development. In BRG1, even haploinsufficiency causes an increase in tumors [134]. Nevertheless, despite the abundance of data linking SWI/SNF complexes to cancer, no

mechanistic evidence is available to demonstrate that altered chromatin remodeling resulting from aberrant chromatin binding or loss of ATPase activity is required [133]. Chromatin remodeling mutations have been proven to be key catalysts for a range of diseases, especially cancers [135, 136]. Numerous BAF proteins can function as cancer suppressors, in which their loss or decrease in expression is reported to produce dysregulation of both gene expression and tumorigenesis [137]. SWI/SNF, which is considered a core tumor suppressor complex, is one of the main mutation hotspots found in pancreatic carcinoma [138]. Furthermore, SNF5 is a cancer-associated remodeler that exhibits mutations causing increased chromosomal instability, leading to tumorigenesis [139]. INO80 dysfunction can dysregulate gene expression, DNA synthesis, and DNA repair, potentially contributing to tumorigenesis and genome instability. In fact, there are reports that INO80 is effective in establishing and preserving the chromatin open state at enhancers to promote oncogene expression and tumor growth in non-small cell lung cancers (NSCLCs) [140].

### *3.6. Interplay Between DNMTs and Other Epigenetic Mechanisms*

As highlighted by Liu et al. (2022) [4], DNMT alterations in cancer are not isolated events but part of a complex network of epigenetic changes that collectively drive tumorigenesis. These include interactions between DNMTs and histone modifications, such as histone methylation and acetylation, as well as chromatin remodeling. This interconnectedness suggests that DNMTs may influence cancer progression not only through direct DNA methylation but also by modifying the chromatin landscape, thus affecting the accessibility of transcription factors and other regulatory proteins to DNA. Furthermore, Liu et al. (2022) [4]have compiled extensive data on the expression of DNMTs in various cancers [4]. Building on this foundation, it is crucial to explore how DNMT interactions with these other epigenetic mechanisms contribute to the heterogeneity observed in tumor behavior and patient outcomes. In fact, recent studies suggest that DNMT3B may interact with PRC2 (Polycomb Repressive Complex 2) [141–143], enhancing its ability to maintain repressive histone marks at certain loci, which could be pivotal in sustaining the malignant phenotype in certain cancers. While Liu et al. (2022) provide a comprehensive overview of DNMT expression and downstream effects [4], there is a need to investigate how these enzymes interact with other molecular pathways unique to specific cancer types. For example, the role of DNMTs in regulating non-coding RNAs and their subsequent impact on chromatin structure and gene expression is an emerging field that remains underexplored. Additionally, understanding the crosstalk between DNMTs and the immune system could unveil new therapeutic targets, particularly in cancers where immune evasion plays a critical role.

## 4. Future Directions

Although DNA methylation is often acknowledged as a characteristic of gene repression, recent findings indicate that its function in gene regulation is more intricate and contextually sensitive than previously comprehended [144–146]. Gene repression facilitated by DNA methylation does not consistently correspond directly with methylation levels. Various elements, including DNA-bending proteins, engage with methylated sites to affect gene silence. These proteins are essential for the structural conformation of chromatin, influencing the efficacy of methylation in repressing transcription [147]. The control of these DNA-bending factors is extremely stochastic, indicating that their impact on gene expression may fluctuate based on cellular context, environmental conditions, or other epigenetic modifications. In some instances, these variables may augment gene repression, but in others, they may not obstruct gene expression whatsoever. The unpredictability presents considerable difficulties in analyzing methylation data, especially in cancer research, where epigenetic alterations often exhibit intricate patterns.

To tackle these obstacles, modern methods like single-cell epigenomics provide exciting opportunities for a more profound investigation of DNA methylation variability in tumor tissues. Single-cell methodologies allow researchers to analyze the epigenetic landscape with unparalleled precision, revealing cell-to-cell heterogeneity that is obscured in bulk analysis [148]. This heterogeneity significantly impacts cancer development, since several cell types within a single tumor may have unique methylation patterns that affect treatment resistance or metastatic capability.

Future research should concentrate on using these advanced technologies to elucidate the stochastic mechanisms associated with DNA methylation, explaining the interaction of this epigenetic mark with chromatin architecture in various cancer cell types. These researches will be essential for elucidating the specific processes by which DNA methylation facilitates oncogenesis and for developing more effective, focused medicines that tackle this complexity.

## 5. Conclusion

In this review, the involvement of DNA methylation in human cancers was described and discussed. It is clear that alterations in this epigenetic modification play a key role in cellular transformation and promotion. Specifically, these alterations can inhibit the expression of tumor suppressor genes and lead to the overexpression of oncogenes, thereby promoting cellular proliferation. Moreover, changes in DNA methylation can cause

disruptions in other epigenetic pathways, further contributing to the development of human cancers.

It is also evident that DNMTs play a multifaceted role in cancer progression. However, the interaction between DNMTs and other epigenetic regulators, such as histone modifiers and chromatin remodelers, represents a particularly promising area for future research. These studies should aim to deepen our understanding of these complex interactions, especially in the context of personalized medicine, where a better understanding of the epigenetic landscape of individual tumors could lead to more targeted and effective therapies. Furthermore, the potential of DNMTs as biomarkers for cancer diagnosis and prognosis merits further investigation. Their use in combination with other molecular markers could enhance the precision and effectiveness of cancer detection and treatment strategies. Continued investigation in this area is essential for the development of innovative diagnostic and therapeutic tools that could transform the management of cancer patients.

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## References

1. Zhang J, Yang C, Wu C, et al. DNA methyltransferases in cancer: biology, paradox, aberrations, and targeted therapy. Cancers 2020; 12(8): 2123.
2. Fouad YA, Aanei C. Revisiting the hallmarks of cancer. Am J Cancer Res 2017; 7(5): 1016.
3. Lyko F. The DNA methyltransferase family: a versatile toolkit for epigenetic regulation. Nat Rev Genet 2018; 19(2): 81-92.
4. Liu P, Yang F, Zhang L, et al. Emerging role of different DNA methyltransferases in the pathogenesis of cancer. Front Pharmacol 2022; 13: 958146.
5. Zhang W, Xu J. DNA methyltransferases and their roles in tumorigenesis. Biomark Res 2017; 5(1): 1.
6. Zabidi NAN, Baharudin R, Bakarurraini NQR, et al. Investigating DNA methylation of solute carrier genes in colorectal cancer: a comprehensive analysis using microarray and bioinformatics tools. Prog Microbes Mol Biol 2023; 6(1).

7. Ishak M, Baharudin R, Tan LTH, et al. Landscape of HOXA genes methylation in colorectal cancer. Prog Microbes Mol Biol 2020; 3(1).

8. Ab Mutalib NS, Ismail I, Abdullah Zawawi MR, et al. Comprehensive analysis of microRNA methylation profiles and determination of their functional significance in colorectal cancer: a study protocol. Prog Microbes Mol Biol 2023; 6(1).

9. Norhisan NN, Baharudin R, Rus Bakarurraini NQ, et al. Decoding the methylation patterns of ABC transporters in colorectal cancer. Prog Microbes Mol Biol 2024;7 (1).

10. Geissler F, Nesic K, Kondrashova O, et al. The role of aberrant DNA methylation in cancer initiation and clinical impacts. Ther Adv Med Oncol 2024; 16.

11. Reyngold M, Chan TA. Molecular oncology: causes of cancer and targets for treatment. Published online 2018.

12. Mungly SB, Peter EP, Hii LW, et al. Epigenetic drug interventions in breast cancer: a narrative review of current research and future directions. Prog Microbes Mol Biol 2024; 7(1).

13. Tiedemann RL, Putiri EL, Lee JH, et al. Acute depletion redefines the division of labour among DNA methyltransferases in methylating the human genome. Cell Rep 2014; 9(4): 1554-1566.

14. Gruenbaum Y, Cedar H, Razin A. Substrate and sequence specificity of a eukaryotic DNA methylase. Nature 1982; 295(5850): 620-622.

15. Smallwood SA, Kelsey G. De novo DNA methylation: a germ cell perspective. Trends Genet 2012; 28(1): 33-42.

16. Du Q, Wang Z, Schramm VL. Human DNMT1 transition state structure. Proc Natl Acad Sci 2016; 113(11): 2916-2921.

17. Jeltsch A, Ehrenhofer-Murray A, Jurkowski TP, et al. Mechanism and biological role of Dnmt2 in nucleic acid methylation. RNA Biol 2017; 14(9): 1108-1123.

18. Saxonov S, Berg P, Brutlag DL. A genome-wide analysis of CpG dinucleotides in the human genome distinguishes two distinct classes of promoters. Proc Natl Acad Sci 2006; 103(5): 1412-1417.

19. Chédin F. The DNMT3 family of mammalian de novo DNA methyltransferases. Prog Mol Biol Transl Sci 2011; 101: 255-285.

20. Fuks F, Burgers WA, Brehm A, et al. DNA methyltransferase Dnmt1 associates with histone deacetylase activity. Nat Genet 2000; 24(1): 88-91.

21. Robertson KD, Uzvolgyi E, Liang G, et al. The human DNA methyltransferases (DNMTs) 1, 3a and 3b: coordinate mRNA expression in normal tissues and overexpression in tumours. Nucleic Acids Res 1999; 27(11): 2291-2298.

22. Kulis M, Esteller M. DNA methylation and cancer. Adv Genet 2010; 70: 27-56.

23. Aapola U, Mäenpää K, Kaipia A, et al. Epigenetic modifications affect Dnmt3L expression. Biochem J 2004; 380(3): 705-713.

24. Chedin F, Lieber MR, Hsieh CL. The DNA methyltransferase-like protein DNMT3L stimulates de novo methylation by Dnmt3a. Proc Natl Acad Sci 2002; 99(26): 16916-16921.

25. Hata K, Okano M, Lei H, et al. Dnmt3L cooperates with the Dnmt3 family of de novo DNA methyltransferases to establish maternal imprints in mice. Published online 2002.

26. Goll MG, Kirpekar F, Maggert KA, et al. Methylation of tRNAAsp by the DNA methyltransferase homolog Dnmt2. Science 2006; 311(5759): 395-398.

27. Jurkowski TP, Jeltsch A. On the evolutionary origin of eukaryotic DNA methyltransferases and Dnmt2. PLoS One 2011; 6(11): e28104.

28. Ruthenburg AJ, Allis CD, Wysocka J. Methylation of lysine 4 on histone H3: intricacy of writing and reading a single epigenetic mark. Mol Cell 2007; 25(1): 15-30.

29. Wajed SA, Laird PW, DeMeester TR. DNA methylation: an alternative pathway to cancer. Ann Surg 2001; 234(1): 10.

30. Hackett JA, Sengupta R, Zylicz JJ, et al. Germline DNA demethylation dynamics and imprint erasure through 5-hydroxymethylcytosine. Science 2013; 339(6118): 448-452.

31. Ross SE, Bogdanovic O. TET enzymes, DNA demethylation and pluripotency. Biochem Soc Trans 2019; 47(3): 875-885.

32. Cheng Y, He C, Wang M, et al. Targeting epigenetic regulators for cancer therapy: mechanisms and advances in clinical trials. Signal Transduct Target Ther 2019; 4(1): 1-39.

33. Liu J, Huang B, Ding F, et al. Environment factors, DNA methylation, and cancer. Environ Geochem Health 2023; 45(11): 7543-7568.

34. Geiman TM, Robertson KD. Chromatin remodeling, histone modifications, and DNA methylation—how does it all fit together? J Cell Biochem 2002; 87(2): 117-125.

35. Sasaki H, Matsui Y. Epigenetic events in mammalian germ-cell development: reprogramming and beyond. Nat Rev Genet 2008; 9(2): 129-140.

36. Moore LD, Le T, Fan G. DNA methylation and its basic function. Neuropsychopharmacology 2013; 38(1): 23-38.

37. Parle-McDermott A, Ozaki M. The impact of nutrition on differential methylated regions of the genome. Adv Nutr 2011; 2(6): 463-471.

38. Fuks F, Hurd PJ, Wolf D, et al. The methyl-CpG-binding protein MeCP2 links DNA methylation to histone methylation. J Biol Chem 2003; 278(6): 4035-4040.

39. Martín Caballero I, Hansen J, Leaford D, et al. The methyl-CpG binding proteins Mecp2, Mbd2 and Kaiso are dispensable for mouse embryogenesis, but play a redundant function in neural differentiation. PLoS One 2009; 4(1): e4315.

40. Jones PL, Veenstra GJC, Wade PA, et al. Methylated DNA and MeCP2 recruit histone deacetylase to repress transcription. Nat Genet 1998; 19(2): 187-191.

41. Mirza S, Sharma G, Parshad R, et al. Expression of DNA methyltransferases in breast cancer patients and to analyse the effect of natural compounds on DNA methyltransferases and associated proteins. J Breast Cancer 2013; 16(1): 23.

42. Nan X, Ng HH, Johnson CA, et al. Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. Nature 1998; 393(6683): 386-389.

43. Bird A. DNA methylation patterns and epigenetic memory. Genes Dev 2002; 16(1): 6-21.

44. Aravin AA, Sachidanandam R, Bourc'his D, et al. A piRNA pathway primed by individual transposons is linked to de novo DNA methylation in mice. Mol Cell 2008; 31(6): 785-799.

45. Kuramochi-Miyagawa S, Watanabe T, Gotoh K, et al. DNA methylation of retrotransposon genes is regulated by Piwi family members MILI and MIWI2 in murine fetal testes. Genes Dev 2008; 22(7): 908-917.

46. Li E, Bestor TH, Jaenisch R. Targeted mutation of the DNA methyltransferase gene results in embryonic lethality. Cell 1992; 69(6): 915-926.

47. Liao J, Karnik R, Gu H, et al. Targeted disruption of DNMT1, DNMT3A and DNMT3B in human embryonic stem cells. Nat Genet 2015; 47(5): 469-478.

48. Hansen RS, Wijmenga C, Luo P, et al. The DNMT3B DNA methyltransferase gene is mutated in the ICF immunodeficiency syndrome. Proc Natl Acad Sci 1999; 96(25): 14412-14417.

49. Xu GL, Bestor TH, Bourc'his D, et al. Chromosome instability and immunodeficiency syndrome caused by mutations in a DNA methyltransferase gene. Nature 1999; 402(6758): 187-191.

50. Smets M, Link S, Wolf P, et al. DNMT1 mutations found in HSANIE patients affect interaction with UHRF1 and neuronal differentiation. Hum Mol Genet 2017; 26(8): 1522-1534.

51. Sun Z, Wu Y, Ordog T, et al. Aberrant signature methylome by DNMT1 hot spot mutation in hereditary sensory and autonomic neuropathy 1E. Epigenetics 2014; 9(8): 1184-1193.

52. Tatton-Brown K, Zachariou A, Loveday C, et al. The Tatton-Brown-Rahman syndrome: a clinical study of 55 individuals with de novo constitutive DNMT3A variants. Wellcome Open Res 2018; 3.

53. Tatton-Brown K, Seal S, Ruark E, et al. Mutations in the DNA methyltransferase gene DNMT3A cause an overgrowth syndrome with intellectual disability. Nat Genet 2014; 46(4): 385-388.

54. Greenberg MV, Bourc'his D. The diverse roles of DNA methylation in mammalian development and disease. Nat Rev Mol Cell Biol 2019; 20(10): 590-607.

55. Al Aboud NM, Tupper C, Jialal I. Genetics, epigenetic mechanism. 2018.

56. Bailey KA, Fry RC. Environmental toxicant exposure and the epigenome. In: Advances in Molecular Toxicology. Vol 6. Elsevier; 2012: 129-162.

57. Zhou Z, Rajasingh S, Barani B, et al. Therapy of infectious diseases using epigenetic approaches. Epigenetics Hum Dis 2018: 689-715.

58. Heydari Z, Moeinvaziri F, Mirazimi SMA, et al. Alteration in DNA methylation patterns: epigenetic signatures in gastrointestinal cancers. Eur J Pharmacol 2024; 973: 176563.

59. Jones PA, Taylor SM, Wilson VL. Inhibition of DNA methylation by 5-azacytidine. In: Modified Nucleosides and Cancer. Springer; 1983: 202-211.

60. El Omari N, Bakha M, Imtara H, et al. Anticancer mechanisms of phytochemical compounds: focusing on epigenetic targets. Environ Sci Pollut Res 2021; 28(35): 47869-47903.

61. Lyko F, Brown R. DNA methyltransferase inhibitors and the development of epigenetic cancer therapies. J Natl Cancer Inst 2005; 97(20): 1498-1506.

62. Ehrlich M. DNA hypomethylation in cancer cells. Epigenomics 2009; 1(2): 239-259.

63. Bird A. Perceptions of epigenetics. Nature 2007; 447(7143): 396.

64. Esteller M. Epigenetics in cancer. N Engl J Med 2008; 358(11): 1148-1159.

65. McMahon KW, Karunasena E, Ahuja N. The roles of DNA methylation in the stages of cancer. Cancer J 2017; 23(5): 257.

66. Lee AV, Nestler KA, Chiappinelli KB. Therapeutic targeting of DNA methylation alterations in cancer. Pharmacol Ther 2024; 258: 108640.

67. Jin Z, Liu Y. DNA methylation in human diseases. Genes Dis 2018; 5(1): 1-8.

68. Rinaldi L, Datta D, Serrat J, et al. Dnmt3a and Dnmt3b associate with enhancers to regulate human epidermal stem cell homeostasis. Cell Stem Cell 2016; 19(4): 491-501.

69. Van Tongelen A, Loriot A, De Smet C. Oncogenic roles of DNA hypomethylation through the activation of cancer-germline genes. Cancer Lett 2017; 396: 130-137.

70. Christman JK. 5-Azacytidine and 5-aza-2′-deoxycytidine as inhibitors of DNA methylation: mechanistic studies and their implications for cancer therapy. Oncogene 2002; 21(35): 5483-5495.

71. Sergeeva A, Davydova K, Perenkov A, et al. Mechanisms of human DNA methylation, alteration of methylation patterns in physiological processes and oncology. Gene 2023; 875: 147487.

72. Cao JX, Zhang HP, Du LX. Influence of environmental factors on DNA methylation. Yi Chuan Hered 2013; 35(7): 839-846.

73. El Omari N, Bakrim S, Bakha M, et al. Natural bioactive compounds targeting epigenetic pathways in cancer: a review on alkaloids, terpenoids, quinones, and isothiocyanates. Nutrients 2021; 13(11): 3714.

74. Greger V, Passarge E, Höpping W, et al. Epigenetic changes may contribute to the formation and spontaneous regression of retinoblastoma. Hum Genet 1989; 83(2): 155-158.

75. Drexler HG. Review of alterations of the cyclin-dependent kinase inhibitor INK4 family genes p15, p16, p18 and p19 in human leukaemia–lymphoma cells. Leukemia 1998; 12(6): 845-859.

76. Arantes L, De Carvalho AC, Melendez ME, et al. Methylation as a biomarker for head and neck cancer. Oral Oncol 2014; 50(6): 587-592.

77. Zhao SG, Chen WS, Li H, et al. The DNA methylation landscape of advanced prostate cancer. Nat Genet 2020; 52(8): 778-789.

78. Pasculli B, Barbano R, Parrella P. Epigenetics of breast cancer: biology and clinical implication in the era of precision medicine. Semin Cancer Biol 2018; 51: 22-35.

79. Michie AM, McCaig AM, Nakagawa R, et al. Death-associated protein kinase (DAPK) and signal transduction: regulation in cancer. FEBS J 2010; 277(1): 74-80.

80. Catteau A, Morris JR. BRCA1 methylation: a significant role in tumour development? Semin Cancer Biol 2002; 12: 359-371.

81. Wong KK. DNMT1: a key drug target in triple-negative breast cancer. Semin Cancer Biol 2021; 72: 198-213.

82. Zhou Z, Lei Y, Wang C. Analysis of aberrant methylation in DNA repair genes during malignant transformation of human bronchial epithelial cells induced by cadmium. Toxicol Sci 2012; 125(2): 412-417.

83. Katoh M. Epithelial-mesenchymal transition in gastric cancer. Int J Oncol 2005; 27(6): 1677-1683.

84. Etoh T, Kanai Y, Ushijima S, et al. Increased DNA methyltransferase 1 (DNMT1) protein expression correlates significantly with poorer tumour differentiation and frequent DNA hypermethylation of multiple CpG islands in gastric cancers. Am J Pathol 2004; 164(2): 689-699.

85. Kanai Y, Hirohashi S. Alterations of DNA methylation associated with abnormalities of DNA methyltransferases in human cancers during transition from a precancerous to a malignant state. Carcinogenesis 2007; 28(12): 2434-2442.

86. Saito Y, Kanai Y, Nakagawa T, et al. Increased protein expression of DNA methyltransferase (DNMT) 1 is significantly correlated with the malignant potential and poor prognosis of human hepatocellular carcinomas. Int J Cancer 2003; 105(4): 527-532.

87. Yamazaki J, Taby R, Vasanthakumar A, et al. Effects of TET2 mutations on DNA methylation in chronic myelomonocytic leukaemia. Epigenetics 2012; 7(2): 201-207.

88. Weller M, Stupp R, Reifenberger G, et al. MGMT promoter methylation in malignant gliomas: ready for personalized medicine? Nat Rev Neurol 2010; 6(1): 39-51.

89. Fleisher AS, Esteller M, Tamura G, et al. Hypermethylation of the hMLH1 gene promoter is associated with microsatellite instability in early human gastric neoplasia. Oncogene 2001; 20(3): 329-335.

90. Zhu J, Yang Y, Li L, et al. DNA methylation profiles in cancer: functions, therapy, and beyond. Cancer Biol Med 2023: 1-6.

91. Stuani L, Recher C, Portais JC, et al. Utilization of α-ketoglutarate for synthesis of 2-hydroxyglutarate oncometabolite promotes catabolic flexibility, redox perturbation and mitochondrial activity that supports chemoresistance in IDH1 mutant acute myeloid leukaemia. Blood 2017; 130: 5080.

92. Baylin SB, Ohm JE. Epigenetic gene silencing in cancer—a mechanism for early oncogenic pathway addiction? Nat Rev Cancer 2006; 6(2): 107-116.

93. Kosmider O, Gelsi-Boyer V, Slama L, et al. Mutations of IDH1 and IDH2 genes in early and accelerated phases of myelodysplastic syndromes and MDS/myeloproliferative neoplasms. Leukemia 2010; 24(5): 1094-1096.

94. Lin J, Yao D, Qian J, et al. IDH1 and IDH2 mutation analysis in Chinese patients with acute myeloid leukaemia and myelodysplastic syndrome. Ann Hematol 2012; 91(4): 519-525.

95. Kim KH, Choi JS, Kim IJ, et al. Promoter hypomethylation and reactivation of MAGE-A1 and MAGE-A3 genes in colorectal cancer cell lines and cancer tissues. World J Gastroenterol 2006; 12(35): 5651.

96. Caballero OL, Chen YT. Cancer/testis antigens: potential targets for immunotherapy. Innate Immune Regul Cancer Immunother Published online 2012: 347-369.

97. Milicic A, Harrison LA, Goodlad RA, et al. Ectopic expression of P-cadherin correlates with promoter hypomethylation early in colorectal carcinogenesis and enhanced intestinal crypt fission in vivo. Cancer Res 2008; 68(19): 7760-7768.

98. Ribeiro AS, Albergaria A, Sousa B, et al. Extracellular cleavage and shedding of P-cadherin: a mechanism underlying the invasive behaviour of breast cancer cells. Oncogene 2010; 29(3): 392-402.

99. Badal RM, Badal D, Badal P, et al. Pharmacological action of Mentha piperita on lipid profile in fructose-fed rats. Iran J Pharm Res 2011; 10(4): 843.

100. de Cubas AA, Dunker W, Zaninovich A, et al. DNA hypomethylation promotes transposable element expression and activation of immune signalling in renal cell cancer. JCI Insight 2020; 5(11).

101. Cho M, Uemura H, Kim SC, et al. Hypomethylation of the MN/CA9 promoter and upregulated MN/CA9 expression in human renal cell carcinoma. Br J Cancer 2001; 85(4): 563-567.

102. Tang J, Pan R, Xu L, et al. IL10 hypomethylation is associated with the risk of gastric cancer. Oncol Lett 2021; 21(4): 1-1.

103. Ostler KR, Davis EM, Payne SL, et al. Cancer cells express aberrant DNMT3B transcripts encoding truncated proteins. Oncogene 2007; 26(38): 5553-5563.

104. Tost J. DNA methylation: an introduction to the biology and the disease-associated changes of a promising biomarker. Mol Biotechnol 2010; 44: 71-81.

105. Esteller M. CpG island hypermethylation and tumour suppressor genes: a booming present, a brighter future. Oncogene 2002; 21(35): 5427-5440.

106. Chen C, Wang Z, Ding Y, et al. DNA methylation: from cancer biology to clinical perspectives. Front Biosci-Landmark 2022; 27(12): 326.

107. Watanabe Y, Maekawa M. Methylation of DNA in cancer. Adv Clin Chem 2010; 52: 145-167.

108. Ramalho-Carvalho J, Henrique R, Jerónimo C. DNA methylation alterations as biomarkers for prostate cancer. In: Epigenetic Biomarkers and Diagnostics. Elsevier; 2016: 275-296.

109. Zhang Y, Sun Z, Jia J, et al. Overview of histone modification. Histone Mutat Cancer Published online 2021: 1-16.

110. Kouzarides T. Chromatin modifications and their function. Cell 2007; 128(4): 693-705.

111. Hergeth SP, Schneider R. The H1 linker histones: multifunctional proteins beyond the nucleosomal core particle. EMBO Rep 2015; 16(11): 1439-1453.

112. Strahl BD, Allis CD. The language of covalent histone modifications. Nature 2000; 403(6765): 41-45.

113. Greer EL, Shi Y. Histone methylation: a dynamic mark in health, disease and inheritance. Nat Rev Genet 2012; 13(5): 343-357.

114. Fang D, Han J. Histone mutations and cancer. Springer 2021.

115. Bowman GD, Poirier MG. Post-translational modifications of histones that influence nucleosome dynamics. Chem Rev 2014; 115(6): 2274-2295.

116. Castelli G, Pelosi E, Testa U. Targeting histone methyltransferase and demethylase in acute myeloid leukaemia therapy. OncoTargets Ther 2018; 11:131.

117. Martinez-Garcia E, Licht JD. Deregulation of H3K27 methylation in cancer. Nat Genet 2010; 42(2): 100-101.

118. Luan Y, Ngo L, Han Z, et al. Histone acetyltransferases: enzymes, assays, and inhibitors. In: Epigenetic Technological Applications. Elsevier 2015: 291-317.

119. Seto E, Yoshida M. Histone deacetylase inhibitors and their biological effects. Cold Spring Harb Perspect Biol 2014; 6:a018713.

120. Figueroa ME, Chen SC, Andersson AK, et al. Integrated genetic and epigenetic analysis of childhood acute lymphoblastic leukaemia. J Clin Invest 2013; 123(7): 3099-3111.

121. Yu H, Li SB. Role of LINC00152 in non-small cell lung cancer. J Zhejiang Univ-Sci B 2020; 21(3): 179-191.

122. Halkidou K, Gaughan L, Cook S, et al. Upregulation and nuclear recruitment of HDAC1 in hormone refractory prostate cancer. Prostate 2004; 59(2): 177-189.

123. Song Y, Manson JE, Buring JE, et al. Associations of dietary flavonoids with risk of type 2 diabetes, and markers of insulin resistance and systemic inflammation in women: a prospective study and cross-sectional analysis. J Am Coll Nutr 2005; 24(5): 376-384.

124. Shan W, Jiang Y, Yu H, et al. HDAC2 overexpression correlates with aggressive clinicopathological features and DNA-damage response pathway of breast cancer. Am J Cancer Res 2017; 7(5): 1213.

125. Zhao H, Yu Z, Zhao L, et al. HDAC2 overexpression is a poor prognostic factor of breast cancer patients with increased multidrug resistance-associated protein expression who received anthracyclines therapy. Jpn J Clin Oncol 2016; 46(10): 893-902.

126. Jung KH, Noh JH, Kim JK, et al. HDAC2 overexpression confers oncogenic potential to human lung cancer cells by deregulating expression of apoptosis and cell cycle proteins. J Cell Biochem 2012; 113(6): 2167-2177.

127. Subramanian C, Jarzembowski JA, Opipari AW, et al. CREB-binding protein is a mediator of neuroblastoma cell death induced by the histone deacetylase inhibitor trichostatin A. Neoplasia 2007; 9(6): 495-503.

128. Filippakopoulos P, Qi J, Picaud S, et al. Selective inhibition of BET bromodomains. Nature 2010; 468(7327): 1067-1073.

129. Wegel E, Shaw P. Gene activation and deactivation related changes in the three-dimensional structure of chromatin. Chromosoma 2005; 114(5): 331-337.

130. Clapier CR, Cairns BR. The biology of chromatin remodelling complexes. Annu Rev Biochem 2009; 78(1): 273-304.

131. Burns LG, Peterson CL. Protein complexes for remodelling chromatin. Biochim Biophys Acta Gene Struct Expr 1997; 1350(2): 159-168.

132. Zhou CY, Johnson SL, Gamarra NI, et al. Mechanisms of ATP-dependent chromatin remodelling motors. Annu Rev Biophys 2016; 45: 153.

133. Reyes AA, Marcum RD, He Y. Structure and function of chromatin remodellers. J Mol Biol 2021; 433(14): 166929.

134. Wilson BG, Roberts CW. SWI/SNF nucleosome remodellers and cancer. Nat Rev Cancer 2011; 11(7): 481-492.

135. Cui K, Tailor P, Liu H, et al. The chromatin-remodelling BAF complex mediates cellular antiviral activities by promoter priming. Mol Cell Biol 2004; 24(10): 4476-4486.

136. García-Pedrero JM, Kiskinis E, Parker MG, et al. The SWI/SNF chromatin remodelling subunit BAF57 is a critical regulator of oestrogen receptor function in breast cancer cells. J Biol Chem 2006; 281(32): 22656-22664.

137. Hodges C, Kirkland JG, Crabtree GR. The many roles of BAF (mSWI/SNF) and PBAF complexes in cancer. Cold Spring Harb Perspect Med 2016; 6(8): a026930.

138. Shain AH, Giacomini CP, Matsukuma K, et al. Convergent structural alterations define SWItch/Sucrose NonFermentable (SWI/SNF) chromatin remodeler as a central tumour suppressive complex in pancreatic cancer. Proc Natl Acad Sci 2012; 109(5): E252-E258.

139. Vries RG, Bezrookove V, Zuijderduijn LM, et al. Cancer-associated mutations in chromatin remodeler hSNF5 promote chromosomal instability by compromising the mitotic checkpoint. Genes Dev 2005; 19(6): 665-670.

140. Zhang S, Zhou B, Wang L, et al. INO80 is required for oncogenic transcription and tumour growth in non-small cell lung cancer. Oncogene 2017; 36(10): 1430-1439.

141. Dar MS, Mensah IK, He M, et al. Dnmt3bas coordinates transcriptional induction and alternative exon inclusion to promote catalytically active Dnmt3b expression. Cell Rep 2023; 42(6): 112587.

142. Tibben BM, Rothbart SB. Mechanisms of DNA methylation regulatory function and crosstalk with histone lysine methylation. J Mol Biol 2024; 436(7): 168394.

143. Shi TH, Sugishita H, Gotoh Y. Crosstalk within and beyond the Polycomb repressive system. J Cell Biol 2024; 223(5): e202311021.

144. Fuso A, Raia T, Orticello M, et al. The complex interplay between DNA methylation and miRNAs in gene expression regulation. Biochimie 2020; 173: 12-16.

145. Dhar GA, Saha S, Mitra P, et al. DNA methylation and regulation of gene expression: guardian of our health. Nucleus 2021; 64(3): 259-270.

146. Oliva M, Demanelis K, Lu Y, et al. DNA methylation QTL mapping across diverse human tissues provides molecular links between genetic variation and complex traits. Nat Genet 2023; 55(1): 112-122.

147. Lee DY, Teyssier C, Strahl BD, et al. Role of protein methylation in regulation of transcription. Endocr Rev 2005; 26(2): 147-170.

148. Schwartzman O, Tanay A. Single-cell epigenomics: techniques and emerging applications. Nat Rev Genet 2015; 16(12): 716-726.