# *DNMT3A*: A Multifunctional Mediator of Cancer Progression

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**Abstract** The advances in the research on the structure and function of *DNMT3A* and the role of *DNMT3A* in tumorigenesis and development were reviewed, including gynecologic cancers, hematologic tumors, melanoma, amelanoma, colorectal cancer and other cancers, to provide new ideas for the treatment of cancer.

**Key words** *DNMT3A*, Cancer, Methylation

## 1 Introduction

The pathogenesis of cancer is complex, the degree of invasion of surrounding tissues and organs is large, and it is very easy to metastasize and poses a great threat to human health. At present, the discovery of some biomarkers has made great achievements in the prediction and treatment of cancer, and it is of great significance to summarize the existing research results and limitations in a timely manner for better treatment of cancer. DNA methylation can add a methyl group to the promoter region of a gene, resulting in silencing or mutation of the gene, and aberrant methylation of pro- and tumor-suppressor genes is an important cause of cancer development and mutation[1-2]. *DNMT3A* is an important isoform of DNA methyltransferases that has been shown to promote or inhibit the occurrence and progression of a variety of cancers by regulating related genes, and can predict the occurrence of cancer[3]. However, the specific mechanism of *DNMT3A* in regulating cancer progression is still unclear, so exploring the relationship between *DNMT3A* and a variety of cancers is helpful to find suitable biomarkers for the treatment of recalcitrant cancers.

## 2 Structure and function of *DNMT3A*

*DNMT3A*, also known as DNA methyltransferase 3A, belongs to the highly conserved DNA methyltransferase family, DNA methylation plays a crucial role in mammalian development, and the two families of DNMT3 and DNMT1 are responsible for the establishment and maintenance of methylation, respectively, and *DNMT3A*, as a member of the DNMT3 family, is the main enzyme that establishes DNA methylation during ontogeny[4]. It is composed of three parts: the N-terminal regulatory domain, the C-terminal MTase (methyltransferase catalytic domain) domain, and the GK repeat[5]. Among them, the N-terminal regulatory domain includes the ADD (ATRXDNMT3-DNMT3L) domain and the PWWP (Pro-Trp-Trp-Pro) domain, and it has been confirmed that the ADD domain can specifically bind to unmethylated H3K4 (H3K4me0) to reduce the DNA affinity of the catalytic domain and inhibit *DNMT3A* enzyme activity[6]. The PWWP domain is able to recognize the H3K36me3 region to avoid causing accidental gene methylation[7], and mice with mutations and deletions in the PWWP domain will exhibit abnormal hypermethylation and growth delay. The C-terminal MTase domain is the core region of DNMTs-catalyzed methyl transfer[8]. GK repeats, on the other hand, are able to link the N-terminal regulatory domain with the C-terminal MTase domain[5]. Relevant studies have shown that gametes that lack *DNMT3A* will lose their methylation imprint, resulting in hypomethylation of the entire genome[9]. Other researchers have found that *DNMT3A* knockout mice have learning deficits in some associative memory and episodic memory tasks[10]. These studies suggest that the unique molecular structure of *DNMT3A* makes it play an important role in germ cytogenesis, early embryonic development, learning and memory, and carcinogenesis[8].

## 3 Research progress on the role of *DNMT3A* in the occurrence and development of tumors

**3.1 *DNMT3A* and gynecologic cancers** Breast cancer is the most common cancer in women worldwide, with an increase in incidence in recent years[11]. *DNMT3A* plays an important role in the occurrence and progression of breast cancer. Triple negative breast cancer (TNBC) is a common subtype of breast cancer with a poor prognosis. The results of RNA sequencing and immunohistochemistry of TCGA showed that *DNMT3A* was significantly overexpressed in TNBC, and then *DNMT3A* was shown to interact with MYC to induce promoter methylation and inhibit the expression of miR-200b to promote TNBC progression[12]. In most subtypes of breast cancer, *DNMT3A* can also promote breast cancer growth and invasion by mediating the downregulation of cutaneous torpen protein (DPT) expression, which in turn interferes with the interaction between DPT and YAP[13]. The results of pathway analysis showed that *DNMT3A* was mainly involved in the P53 signaling pathway to affect the progression of breast cancer, which showed the significance of *DNMT3A* in the treatment of breast cancer[14]. In summary, *DNMT3A* is highly expressed in breast cancer, and can be used as a potential marker for breast cancer and can be used to treat breast cancer by targeting *DNMT3A*.

Cervical cancer, the fourth most common cancer among

Received: February 21, 2024 Accepted: May 26, 2024

Supported by the Student Innovation and Entrepreneurship Training Program of Chengde Medical University (2023023); the Natural Science Fund of Hebei Province (H2022406025); the Science and Technology Project of Hebei Provincial Department of Education (BJK2023001); the High-level Talents Research Startup Fund of Chengde Medical University (202201); Discipline Construction Funds of Chengde Medical University.

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women worldwide, seriously affects women's physical and mental health[15]. A controlled analysis of cancer and normal cervical tissue samples showed that *DNMT3A* was expressed at high levels in cancer tissues[16], suggesting that *DNMT3A* may promote the development of cervical cancer. One study found that the SUV39H1 regulation of the promoter of *DNMT3A* led to the increased expression of *DNMT3A* in cervical cancer, which in turn inhibited the expression of cervical cancer costimulatory factors Tim-3 and galectin-9 to affect the occurrence and progression of cervical cancer[17]. In addition, it has been found that *DNMT3A* is regulated by miR-182, which affects the growth of cervical cancer cells, which shows significance for targeted therapy of cervical cancer[18].

In summary, *DNMT3A* is able to affect the growth, migration and invasion of gynecologic cancers. Moreover, the down-regulation of *DNMT3A* is related to the impact on its priming region, and further study of the relationship between *DNMT3A* and other gynecologic cancers is helpful to obtain new therapeutic targets.

**3.2 *DNMT3A* and hematologic tumors** Acute myeloid leukemia (AML) is a highly heterogeneous leukemia[19], and mutations in the *DNMT3A* gene are widely believed to be closely related to the development and progression of AML. Large-scale parallel DNA sequencing results have shown that *DNMT3A* mutations can lead to aberrant DNA methylation patterns that affect the expression of key genes, including genes related to hematopoietic cell differentiation and proliferation, which in turn affect the pathophysiological processes of AML[20]. In addition, the results of cell experiments suggest that *DNMT3A* mutations often lead to poor prognosis and treatment responsiveness in patients[21].

Non-Hodgkin lymphoma is another common hematologic tumor that is relatively difficult to diagnose early and has also been shown to be associated with aberrant expression or mutations in *DNMT3A*[22]. Studies have shown that abnormalities in *DNMT3A* can alter the DNA methylation status of B cells, affecting the proliferation, apoptosis, and self-renewal of a variety of cells, thereby promoting or inhibiting the development of non-Hodgkin lymphoma[23]. In addition, studies on the link between *DNMT3A* and angioimmunoblastic T-cell lymphoma (AITL) have found that mutations in *DNMT3A* affect the status of Tfh cells and B cells, which in turn affects tumor progression[24].

In conclusion, the role of *DNMT3A* in a variety of hematologic malignancies is crucial. By affecting DNA methylation levels, *DNMT3A* mutations can cause a range of abnormal gene expression, which in turn affects cell function and drives cancer progression. An in-depth understanding of the mechanism of action of *DNMT3A* in hematological malignancies is expected to provide important guidance and enlightenment for the development of future therapeutic strategies and targeted therapies.

**3.3 *DNMT3A* and melanoma** Melanoma is the deadliest form of skin cancer, with a mortality rate of up to 80%, and only 14% of patients with metastatic melanoma survive for five years or more[25]. Aberrant DNA methylation in melanoma plays a complex role in regulating tumor cell suppressor genes as well as gene expression that regulates homeostatic processes, including cell proliferation, metabolism, and immune responses[26], and its identification and classification is an important step in understanding the human melanoma methylation landscape and using it clinically[27]. Parmanand *et al.* investigated the epidermal chromosomal landscape of melanoma using various publicly available databases and found that *DNMT3A* was significantly overexpressed in melanoma samples compared to normal skin samples, and matched the results of the Human Protein Atlas data. The simultaneous use of shRNA mediated was found to lead to growth inhibition of melanoma cells by its elimination in melanoma cells, suggesting that *DNMT3A* is a potential regulator of melanoma growth[28]. Wang *et al.* demonstrated that inhibition of *DNMT3A* in mouse B16 melanoma cells significantly inhibited tumor growth and metastasis in a xenograft mouse model, further validating that *DNMT3A* is required to maintain tumor stemness of B16 cells, and its presence contributes to the *in vitro* pluripotent differentiation ability of melanoma cells[29]. Pooneh *et al.* demonstrated that potent DNA methyltransferase inhibitors appear to reduce methylation processes in cancer cells such as melanoma and re-express silent genes in malignancies through studies of epigenetically modifying drugs for uveal melanoma[30-31]. David *et al.* proposed the first patient with *DNMT3A* overgrowth syndrome with early-stage melanoma, and found another acquired erroneous *DNMT3A* dominant tumor clone by exome sequencing of the primary tumor, demonstrating that the loss of *DNMT3A* function is related to the development of melanoma[27]. These studies show that *DNMT3A* is involved in the development of melanoma through a variety of mechanisms, and has great potential for early diagnosis and treatment of melanoma.

**3.4 *DNMT3A* and colorectal cancer** Colorectal cancer (CRC) is one of the most common gastrointestinal malignancies in the world. Its incidence and mortality are increasing year by year and are now considered the third most commonly diagnosed cancer worldwide and the second leading cause of cancer-related death[32]. The results of the UALCAN website and the Human Protein Atlas (HPA) database showed that the expression of *DNMT3A* in colorectal cancer tissues was significantly increased [33], suggesting that *DNMT3A* plays an important role in the proliferation and expression of colorectal cancer cells. *DNMT3A* SNP-448A >was confirmed in a controlled trial evaluating genomic DNA extracted from colorectal cancer patients and healthy human samples using polymerase chain reaction-restriction fragment length polymorphism analysisG is able to promote genetic susceptibility to CRC[34]. In addition, *DNMT3A* has been shown to promote the proliferation of CRCs by regulating DAB2IP-mediated MEK/ERK activation [35]. It has also been shown that when *DNMT3A* is suppressed, Doxinduced cell growth hormone (DOX) can treat HCT116 colorectal cancer cells, and the mechanism may be that *DNMT3A* affects the expression of P21 and plays a role in the senescence and apoptosis of HCT116 cells[36]. In addition, some researchers have found that TDG can inhibit the migration and invasion of human colorectal cancer cells in vitro and in vivo through tumor metastasis experiments in nude mice, and further chromatin immunoprecipitation analysis shows that TDG can accelerate *DNMT3A* interpretation and significantly down-regulate *DNMT3A* expression levels, thereby inhibiting colorectal cancer cells [37].

In summary, *DNMT3A* can affect the aging and proliferation of colorectal cancer cells through a variety of mechanisms, and further research will help to understand the occurrence and development mechanism of colorectal cancer and provide new targets for

colorectal cancer treatment.

**3.5 *DNMT3A* with other cancers** In liver cancer research, it has been shown that aberrant methylation of DNA contributes to the occurrence of liver cancer and microRNA-639 expression is down-regulated in liver cancer tissues and cells. Inhibition of miR-639 expression is attributed to hypermethylation of its promoter region, and *DNMT3A* has been found to mediate this hypermethylation. Therefore, *DNMT3A*-mediated hypermethylation inhibited the expression of miR-639 and inhibited the expression of MSYT2 and ZEB1, thereby promoting tumorigenesis of hepatocellular carcinoma. These findings reveal the mechanism by which *DNMT3A* is involved in the aberrant expression of miRNAs in liver cancer malignancies and provide new biomarkers for liver cancer[38]. In clinical trials of liver cancer, high mRNA levels of *DNMT3A* significantly reduced the survival rate of patients[39]. These results suggest that the expression of *DNMT3A* gene has a great impact on the prognostic process of liver cancer patients. In related cell experiments, miR-4270 successfully inhibited the progression of hepatocellular carcinoma by inhibiting *DNMT3A*-mediated methylation of the HGFAC promoter, indicating that the high expression of *DNMT3A* gene exerts a crucial effect on hepatocellular carcinogenesis, and proving the importance of *DNMT3A* for targeted therapy of clinical hepatocellular carcinoma[40].

In gastric adenocarcinoma tissues, the expression levels of *DNMT3A* and *HDAC2* were significantly up-regulated in gastric adenocarcinoma tissues compared with healthy gastric adenocarcinoma tissues. Immunohistochemistry confirmed that *DNMT3A* was highly expressed in gastric adenocarcinoma tissues[41]. Studies have shown that the high expression of *DNMT3A* gene in gastric adenocarcinoma is usually associated with the high expression of *HDAC2*, and the interaction between the two promotes the progression of gastric cancer[42], suggesting that we can treat some clinical gastric adenocarcinoma diseases by inhibiting *HDAC2* gene and thus affecting *DNMT3A* expression. In some specific gastric adenocarcinoma subtypes, such as gastric adenocarcinoma with enteroblastic differentiation, morphological and immunohistochemical studies support *DNMT3A* as a potential therapeutic target for such specific gastric adenocarcinoma[43].

In lung cancer, the pathophysiological processes of many types of lung cancer cells are affected by the degree of DNA methylation mediated by the *DNMT3A* gene. miR-708-5p has been shown to inhibit the initiation, development, and stemness of non-small cell lung cancer (NSCLC) by interfering with *DNMT3A*-dependent DNA methylation[39]. These results indicated that *DNMT3A* gene expression plays an important role in the differentiation of lung cancer stem cells. In clinical trials, non-small cell lung cancer patients often develop resistance when treated with tyrosine kinase inhibitors (TKIs), in part because high *DNMT3A* levels reduce the TKI susceptibility of NSCLC cells by upregulating apoptotic protein (IAP) inhibitors, and cells with high *DNMT3A* expression regain their proliferative profile in the absence of TKIs, leading to subsequent tumor recurrence and growth[44]. In addition, studies on animal models of early metastasis of small cell lung cancer have revealed that *DNMT3A* is able to interact with KMT2C to lead to histone and DNA hypomethylation, which in turn promotes the metastasis of small cell lung cancer, opening up new horizons for targeted therapies for small cell lung cancer[45].

In conclusion, the aberrant expression of *DNMT3A* gene plays a regulatory role in a variety of cancers, and is involved in the pathophysiological processes of a variety of cancers by affecting DNA methylation levels and gene expression.

## 4 Problems and prospects

As a classic proto-oncogene, *DNMT3A* is up-regulated in most cancers, affecting the expression of key genes by leading to aberrant DNA methylation patterns, thereby promoting cell carcinogenesis and accelerating tumor progression. *DNMT3A* expression is also down-regulated in a small number of cancers, such as small cell lung cancer cells, where *DNMT3A* expression down-regulation promotes cancer cell metastasis. In addition, low expression of the *DNMT3A* gene may affect gene expression and cell differentiation, leading to some diseases and developmental abnormalities.

Some studies have observed a correlation between increased *DNMT3A* expression and DNA methylation in melanoma, breast cancer, liver cancer, and gastric cancer. DNA methyltransferases that have been able to determine *DNMT3A* gene expression add methyl groups to specific locations in DNA to regulate gene expression. However, there are still major research loopholes in the mechanism and exact function of *DNMT3A* expression in the pathophysiological processes of various cancers, including the activators that cause the abnormal expression of *DNMT3A* in some cancers have not yet been clarified, and the role and mechanism of *DNMT3A* in some tumors and how to affect tumor progression through DNA methylation still need to be further studied and explored.

These studies further affirm the important role of *DNMT3A* in promoting the occurrence and development of certain cancers, and provide a new target for the treatment of multiple cancers. In future studies, further exploration of the role of *DNMT3A* in the initiation, progression, migration and immune response of cancer will help to better understand the pathogenesis of cancer and develop new treatments, which are expected to address drug resistance in some cancer treatments through such studies.

In conclusion, the study of *DNMT3A* gene has great research prospects for exploring the expression mode of cell genes, preventing and treating cell cancer, and solving the problems of drug resistance in cancer treatment.

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