LncRNA-mediated DNA methylation: an emerging mechanism in cancer and beyond

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Abstract
DNA methylation is one of the most important epigenetic mechanisms to regulate gene expression, which is highly dynamic during development and specifically maintained in somatic cells. Aberrant DNA methylation patterns are strongly associated with human diseases including cancer. How are the cell-specific DNA methylation patterns established or disturbed is a pivotal question in developmental biology and cancer epigenetics. Currently, compelling evidence has emerged that long non-coding RNA (lncRNA) mediates DNA methylation in both physiological and pathological conditions. In this review, we provide an overview of the current understanding of lncRNA-mediated DNA methylation, with emphasis on the roles of this mechanism in cancer, which to the best of our knowledge, has not been systematically summarized. In addition, we also discuss the potential clinical applications of this mechanism in RNA-targeting drug development.

Keywords: lncRNA, DNA methylation, Non-coding RNA, DNMT, TET, Cancer

Background
DNA methylation is the methyl modification on the fifth carbon of cytosines (5-methylcytosine, 5mC) typically found in the context of symmetrical CpG dinucleotides in mammals [1, 2]. It is estimated that 70–80% of CpG sites in the mammalian genome are methylated [3], excluding specific regions called CpG islands (CGIs). CGIs are CpG-rich sequences of about 1 kilo-base (kb) in length that mostly exist in gene promoters [4]. Approximately 60% of human gene promoters contain CGIs [5].

DNA methylation is established by DNA methyltransferases (DNMTs). In the simplified but widely accepted ‘division of labor’ model, it is proposed that DNMT3A and DNMT3B are essential for de novo DNA methylation, while DNMT1 is for methylation maintenance during DNA replication [6]. Ten-eleven translocation (TET) family of enzymes (TET1, TET2, and TET3) oppose the actions of the DNMT family by oxidation of 5mC, followed by replication-dependent dilution or thymine DNA glycosylase (TDG)-dependent base excision repair, leading to active DNA demethylation [7–9].

Genome-scale analysis revealed distinct DNA methylation patterns across different cell types, developmental stages, and in response to different stimuli [3, 10, 11]. Aberrant DNA methylation pattern is associated with diseases, including cancer [12–15]. In cancer cells, whereas the general DNA methylation levels are reduced, the CGIs are hypermethylated in a cancer-specific manner [16, 17]. These observations raised a fundamental question: how does the cell type-specific DNA methylation pattern established across the genome? It is well-demonstrated that histone modification and chromosome remodeling [18], as well as transcriptional factors, play key roles in the regulation of DNA methylation genome-wide and in site-specific manner [19–22].
another important regulator of DNA methylation, especially in cancer.

While less than 2% of the human genome encodes proteins, nearly three-quarters can be actively transcribed into non-coding RNAs [23], amongst the ones typically with length more than 200 nucleotides are cataloged as lncRNAs. According to a current statistical analysis, there are more than 173,112 annotated lncRNAs transcribed from 96,411 genomic loci [24]. It is demonstrated that lncRNAs play versatile roles in development and diseases including cancer [25–27]. In the nucleus, lncRNAs regulate chromatin remodeling and transcription; In the cytoplasm, lncRNAs regulate translation and mRNA turnover (reviewed in ref. [27]). There is accumulating evidence up to date showing that lncRNAs mediate DNA methylation via multiple manners, thereby regulating target gene expression in diverse physiological and pathological processes. In this review, we summarize our current understanding of lncRNA-mediated DNA methylation, with emphasis on the functions of this mechanism in cancer. The future direction and potential clinical application are also discussed.

**LncRNAs recruit DNA methyltransferases**

More than a decade ago, it was discovered that lncRNAs transcribed from the promoter of rRNA genes (rDNA) regulate DNA methylation and transcription of rDNA [28]. Later, it was demonstrated that this kind of lncRNA interacts with rDNA promoter and forms a DNA:RNA triplex, which is recognized by DNMT3B to epigenetically regulate rDNA expression [29, 30]. Although it is still unclear if this is a common model nowadays, a variety of lncRNAs have been reported to recruit DNMTs and regulate target gene expression, playing key roles in mesoderm commitment [31], muscle regeneration [32, 33], neural differentiation [34], adipogenesis [35], mental disorder [36], cardiovascular diseases [37–40], osteoarthritis [41], as well as types of cancer (Table 1).

Using an optimized RIP-seq method, Merry et al. identified 148 lncRNAs interacting with DNMT1 in colon cancer cells [56], and the following investigation showed that one of these lncRNAs, DACOR1, could recruit DNMT1 and reprogram genome-wide DNA methylation [57]. Currently, a growing number of studies suggest that lncRNA might recruit DNMTs directly to specific targets (Fig. 1a), including both protein-coding genes [43, 44, 46–50, 54, 55, 58] and non-coding genes such as miRNA [42, 51, 88]. For instance, in esophageal cancer (EC), lncRNA ADAMTS9-AS2 was reported to recruit DNMT1/3 to CDH3 promoter, inhibiting the cancer cell proliferation, invasion, and migration [49]. Two other lncRNAs, HOTAIR and LINC01270 might recruit DNMTs to the promoters of MTHFR and GSTP1 respectively, leading to chemoresistance in EC [47, 48]. In lung adenocarcinoma (LUAD), lncRNA HAGLR was identified as a tumor suppressor by recruiting DNMT1 to the promoter of E2F1 to inhibit tumor growth [55]. A recent study revealed a more complex scenario, in which the authors identified two novel variants of lncRNA LINCO0887, and showed that the short form variant suppressed Carbonic Anhydrase IX (CA9) by recruiting DNMT1 to its promoter, while the long-form variant activated CA9’s transcription via interacting with HIF1α [45]. The two variants were supposed to differentially respond to hypoxia and oppositely control the progression of tongue squamous carcinoma [45].

Meanwhile, several groups also proposed that lncRNAs could recruit DNMT indirectly through the mediation of other factors (Fig. 1b). It was previously proposed that the polycomb group (PcG) protein EZH2 (Enhancer of Zeste homolog 2) interacts with DNMT and associates with DNMT activity [89]. Studies in recent years demonstrated in diverse cancers that lncRNAs might regulate DNA methylation of target genes via association with EZH2, promoting tumor growth [75, 77], metastasis [74, 76, 78] and radio-resistance [79]. Alternatively, EZH2 might regulate DNA methylation by the formation of H3K27me3 histone modification [73], while the molecular mechanism involved in H3K27me3-induced DNA methylation is unclear. Apart from histone modifier EZH2, two transcriptional regulators, NF-κB and PHB2 were also reported to interact with DNMT3A [80, 90]. LncRNA NKILA was identified as a suppressor of NF-κB by sequestering NF-κB in cytoplasm [91]. Upon proinflammatory stimuli, NF-κB is released from the sequestration and translocated into the nucleus (Fig. 2). DNMT3A is then recruited to the promoter of KLF4 by NF-κB, repressing KLF4 transcription by DNA methylation [90]. Another study by Wang et al. reported a lncRNA called Lnc34a, which could interact with Prohibitin 2 (PHB2) and then recruit DNMT3A to miR-34a promoter, silencing miR-34a expression and promoting colorectal cancer growth [80]. PHB2 is a multi-functional protein that can shuttle between nucleus and mitochondria [92]. Interestingly, the nuclear-encoded lncRNA MALAT1 was recently discovered to be transported into mitochondria and to regulate the methylation status of mitochondrial DNA in hepatocellular carcinoma [59], yet the detailed mechanism is unclear.

While most of the reported function of lncRNA recruitment of DNMT is to target DNMT to specific genomic sites or regions, recent work from Jones et al. proposed a different model, in which the lncRNA CCDC26 specifically interacts with DNMT1 and promote its localization from the cytosol to nucleus (Fig. 2), while removal
Table 1  LncRNAs mediate DNA methylation in cancer

| lncRNA          | Role            | Factor       | Target       | Function                                      | Cancer      | Ref |
|-----------------|-----------------|--------------|--------------|-----------------------------------------------|-------------|-----|
| TINCR           | Recruit         | DNMT1        | miR-503-5p   | Regulate EGFR expression                       | BC          | [42]|
| MROS-1          | Recruit         | DNMT3A       | PRUNE2       | Nodal metastases                              | OC          | [43]|
| HOTAIR          | Recruit         | DNMT1        | PTEN         | Cell proliferation, invasion and migration    | CML         | [44]|
| LINC00887       | Recruit         | DNMT1        | CA9          | Suppress oncogenic CA9                         | TNCC         | [45]|
| LINC0472        | Recruit         | DNMTs        | MCM6         | Inhibited tumor growth and metastasis         | TSCC        | [46]|
| LINC01270       | Recruit         | DNMTs        | GSTP1        | Promote tumorigenesis and drug resistance      | EC          | [47]|
| HOTAIR          | Recruit         | DNMTs        | MTHFR        | Chemosensitivity                               | EC          | [48]|
| ADAMTS9-AS2     | Recruit         | DNMT1/3      | CDH3         | Inhibits proliferation, invasion, and migration| EC          | [49]|
| IRAIN           | Recruit         | DNMT1/3      | VEGFA        | Suppresses tumor growth                        | RC          | [50]|
| PVT1            | Recruit         | DNMT1        | miR-18b-5p   | Promotes proliferation                         | GBC         | [51]|
| B2RAP1-AS1      | Recruit         | DNMT3b       | THBS1        | Promotes angiogenesis                          | HCC         | [52]|
| PYCARD-AS1      | Recruit         | DNMT1, 9a    | PYCARD       | Regulates apoptosis                            | BC          | [53]|
| MIR210HG        | Recruit         | DNMT1        | CACNA2D2     | Promotes proliferation and invasion           | NSCLC       | [54]|
| HAGLR           | Recruit         | DNMT1        | E2F1         | Suppresses tumor growth                        | LUAD        | [55]|
| DACOR1          | Recruit         | DNMT1        | Genome-wide  | Promotes cell proliferation                    | GC          | [56, 57]|
| PVT1            | Recruit         | DNMT1        | BNIP3        | Control metabolic Reprogramming                | HCC         | [58]|
| MALAT1          | Recruit         | DNMT1/3      | Mitochondrial DNA |                                    | HCC         | [59]|
| HOTAIR          | Upregulate      | DNMT3b       | PTEN         | Doxorubicin resistance                         | AML         | [60]|
| RP11-159K7.2    | Upregulate      | DNMT3A       |              | Promotes cell growth and invasion              | LSCC        | [61]|
| GASS            | Down-regulate   | DNMTs        | miR-424      | Suppresses multiple malignant phenotypes       | Glioma      | [62]|
| Inc-OIP5-AS1    | Upregulate      | DNMT1        | pre-miR-218–1| Promote cell motility and proliferation        | KS          | [63]|
| Linc-GALH       | Ubiquitinate    | DNMT1        | Gankyrin     | Promotes metastasis                            | HCC         | [64]|
| LUCAT1          | Inhibits ubiquitination | DNMT1 | tumor-suppressor genes | Promotes tumor formation and metastasis | ESCC        | [65]|
| HOTAIR          | Upregulate (via EZH2) | DNMT3A | miR-122     | Activate Cyclin G1 and promote tumorigenicity  | HCC         | [66]|
| HOTAIR          | Upregulate      | DNMT1/3B     | HOXA1        | Multidrug resistance                           | SCLC        | [67]|
| H19             | Upregulate      | TET3         | MED12        | Promotes cell proliferation                    | UL          | [68]|
| DBCCR1-003      | Sequestrate     | DNMT1        | DBCCR1       | Inhibits cell growth                           | BCa         | [69]|
| TTTY15          | Sequestrate     | DNMT3A       | TBX4         | Suppresses metastasis                          | NSCLC       | [70]|
| HOTAIRM1        | Sequestrate     | G9a/EZH2/DNMTs | HOXA1      | Promotes tumor growth and invasion             | GBM         | [71]|
| 91H             | Repel           | DNMTs        | H19/IGF2 locus |                                    | BC          | [72]|
| HOTAIR          | Recruit (via EZH2) | HOXA1     |              | Promotes cell migration and invasion           | SCLC        | [73]|
| SNHG3           | Recruit (via EZH2) | MED18     |              | Promotes cell migration and invasion           | GC          | [74]|
| HOXB13-AS1      | Recruit (via EZH2) | DNMT3B | HOXB13       | Promotes cell proliferation                    | Glioma      | [75]|
| Lnc-LALC        | Recruit (via EZH2) | DNMTs      | LZTS1        | Liver metastasis                               | CRC         | [76]|
| HOTAIR          | Recruit (via EZH2) | DNMT1      | miR-454-3p   | Promotes tumor growth                          | CS          | [77]|
| GIHCG           | Recruit (via EZH2) | DNMT1      | miR-200b/a/429|                                    | HCC         | [78]|
| LINC00630       | Restrict (via EZH2) | DNMT3B | BEX1         | Suppresses cell apoptosis and promotes radio-resistance | CRC         | [79]|
| Lnc34a          | Recruit (via PHB2) | DNMT3A | miR-34a      | Promotes cell proliferation                    | CRC         | [80]|


of CCDC26 leads to genome-wide hypomethylation, increasing double-stranded DNA breaks and inducing cell death [93]. More investigation is needed to confirm if the interaction is direct and to reveal the detailed mechanisms.
to interact with TETs and regulate DNA methylation (Table 1).

In some cases, lncRNA directly interacts with TETs and recruits them to specific targets (Fig. 1a). It was demonstrated that lncRNA Oplr16 binds to the Oct4 promoter, orchestrating the promoter-enhancer loops and then interacts with TET2 by the 3’ region of Oplr16 [95]. Similarly, Du et al. identified two motifs in lncRNA Platr10 that interact with Oct4 promoter and TET1 respectively, thus inducing TET1-mediated DNA demethylation at specific site [96]. A research by Zhou et al. suggested that lncRNA TETILA regulates TET2 subcellular localization and enzymatic activity by binding to the DSBH (double-stranded β-helix) domain of TET2 [97]. In acute myeloid leukemia, lncRNA MAGI2-AS3 recruits TET2 to LRIG1 promoter, inducing up-regulation of LRIG1 and inhibition of leukemic stem cell self-renewal [85]. Interestingly, using RNA reverse transcription-associated trap sequencing (RAT-seq) approach to profile genome-wide interaction targets for lncRNAs in mice, a recent study reported that lncRNA Pblr20 recruits TET2 to the enhancer of Pou5F1 and activates the enhancer-transcribed RNAs [98]. Whether a similar mechanism exists in humans especially in cancer development remains uninvestigated.

There is also evidence supporting an indirect model (Fig. 1c), in which lncRNAs recruit TET via GADD45A. It was first reported by Arab et al. that an antisense lncRNA from TCF21 gene locus termed TARID might recruit GADD45A (growth arrest and DNA-damage-inducible, alpha), and GADD45A then recruits TET to the promoter of its partner gene and induce its activation by DNA demethylation [99]. In the following work, the authors further showed that TARID forms an R-loop at the TCF21 promoter to recruit GADD45A [100]. It was speculated that lncRNA PCDHa-AS might function in a similar mechanism to recruit TET3 via GADD45A, driving stochastic promoter choice to establish a neuronal surface identity code for circuit assembly [101]. In colorectal cancer (CRC), lncRNA SATB2-AS1 directly recruits WDR5 and GADD45A, promoting SATB2 transcription by histone modification, as well as DNA demethylation [87], which inhibits cell metastasis and regulates the immune response in CRC. Recently, a database was created, with a comprehensive list of R-loops and their respective regulatory proteins [102], which might serve as a useful resource to identify novel lncRNAs with the potential to recruit GADD45A via formation of R-loops.

**LncRNAs repel/ sequester DNA methyltransferases**

While most of the current reports suggest the DNMT-recruiting role of lncRNAs, some lncRNAs are also shown to repel or sequester DNMT to negatively regulate DNA methylation (Fig. 1d and Table 1).

It was first reported by Di Ruscio et al. that a lncRNA arising from the CEBPA gene locus binds to DNMT1 and prevents CEBPA promoter methylation [103]. The lncRNA DBCCR1-003 was reported to function similarly
to suppress DBCCR1 promoter methylation by sequestering DNMT1 and eventually to inhibit cell growth in bladder cancer [69]. In non-small cell lung cancer, lncRNA TTTY15 interacts with DNMT3A and inhibits the binding of DNMT3A to TBX4 promoter, while the lower expression level of TTTY15 is associated with tumor metastasis [70]. In glioblastoma, lncRNA HOTAIRM1 was suggested to interact with several epigenetic factors including DNMT1/3A/3B to sequester them away from HOXA1 promoter [71]. In breast cancer, it was discovered that lncRNA 91H, which is transcribed from the antisense orientation of H19, promotes oncogenesis by masking methylation site on the H19 promoter, inducing the oncogenic H19 overexpression [72].

LncRNAs control SAM/SAH level to regulate DNMT activity

DNMT catalyzes transmethylation reactions using S-adenosylmethionine (SAM) as the methyl group donor, yielding S-adenosylhomocysteine (SAH) as a by-product, which is also a strong feedback inhibitor of DNMT [6]. In mammals, SAM is biosynthesized by methionine adenosyltransferase (MAT) from ATP and methionine [104], while SAH is reversibly cleaved into adenosine and homocysteine by S-adenosylhomocysteine hydrolase (SAHH, also known as AdoHcy hydrolase, AHCY), which is essential to prevent accumulation of SAH [104], thereby relieving its inhibition to DNMT (Fig. 3).

It was proposed that lncRNA H19 binds to and inhibits SAHH, leading to genome-wide methylation changes at numerous gene loci [105]. Afterward, this mechanism was verified in embryonic hematopoietic stem cell development [106], odontogenic differentiation [107], metabolic abnormality [108] and neurodegenerative diseases [109].

In breast cancer, it was demonstrated that H19 inhibits SAHH, resulting in the accumulation of SAH, which restricts DNMT3B from methylating Beclin1 promoter and inducing the upregulation of Beclin1 and subsequently initiates autophagy, contributing to tamoxifen resistance [81]. Interestingly, the interaction of H19 and SAHH might be enhanced by Benzo [α]pyrene (BaP), which is a potent carcinogen, especially in lung cancer [84].

Other than the SAH level regulated by SAHH, the SAM level regulated by MAT is another factor affecting DNMT activity (Fig. 3). MAT has several homologs and isoenzymes, among which, MAT1A is mainly expressed in adulthood, serving as a marker for the normal differentiated liver. While MAT2A is a marker for rapid liver growth and dedifferentiation, which is transcriptionally induced in hepatocellular carcinoma (HCC) [104]. It was reported that the oncogenic lncRNA SNHG6 upregulates MAT2A expression as a competitive endogenous RNA (ceRNA) to sponge miR-1297, while down-regulates MAT1A translation by suppressing nucleocytoplasmic shuttling of MAT1A mRNA, thereby causing genome-wide hypomethylation and promoting HCC [83]. Recently, the same group of investigators identified a novel lncRNA named LINC00662 that was shown to decay MAT1A mRNA by RNA–RNA interactions and degrades SAHH protein by ubiquitination [82]. These studies revealed a pathway regulating the level of SAM/SAH to further control DNMT activity, with broad functions in cancer and other diseases.

LncRNAs regulate the expression of DNMTs/TETs

There is compelling evidence showing that lncRNAs control the expression of DNMTs and TETs at diverse levels.
to regulate DNA methylation (Table 1 and Fig. 4). It was reported that lncRNAs promote or suppress DNMT expression, playing key roles in osteogenesis [110], macrophage polarization [111], as well as cell invasion in Kaposi's sarcoma [63] and chemoresistance in small cell lung cancer [67] and acute myeloid leukemia [60]. Several molecular mechanisms of lncRNA's regulatory effect on DNMTs or TETs have been elucidated (Fig. 4).

The first mechanism is to regulate the transcription, as demonstrated in malignant glioma, where IncRNA GAS5 directly interacts with EZH2 and stimulates the formation of polycomb repressive complex 2 (PRC2), thereby transcriptionally suppressing DNMT [62]. There is also a report suggesting that EZH2 is recruited by IncRNA HOTAIR to upregulate DNMT, while the mechanism is unclear [66].

The second mechanism is to regulate the stability of DNMT mRNA, where IncRNA functions as a mediator to upregulating DNMT by interaction with the stabilizing factor HuR [112], or as a ceRNA to sponge specific miRNA, thereby upregulating DNMT [61]. The latter mechanism was also discovered in TET regulation, where estradiol and progesterone upregulate IncRNA H19 to suppress miRNA Let-7 and stabilize TET3 mRNA, activating key fibroid-promoting genes in uterine leiomyomas [68]. LncRNA might also exert this effect via a more indirect manner, as demonstrated for LINC1281, which stabilizes the expression of Let-7 miRNA, thus down-regulating its targets DNMT3A/B [113].

The third mechanism is to regulate DNMT at the protein level. Current studies mainly focus on protein degradation by ubiquitination (Fig. 4). It was reported by several groups that lncRNAs serve as a protein-binding scaffold and induce ubiquitin-mediated DNMT protein degradation, epigenetically regulating target gene expression in obesity-mediated beta cell dysfunction [114], polycystic ovary syndrome [115] and hepatocellular carcinoma (HCC) [64]. The detailed mechanism involving the role of IncRNA in DNMT ubiquitination is largely unknown and warrant more deep investigation. In esophageal squamous cell carcinoma, a distinct model was proposed, in which, the IncRNA LUCAT1 binds DNMT1 to protect it from ubiquitination, while LUCAT1 knockdown promotes ubiquitination of DNMT1 through UHRF1 (Ubiquitin-Like PHD and RING Finger Domain-Containing Protein 1) [65]. However, it is well established that UHRF1 deposits dual mono- ubiquitination on the H3 histone tail and PCNA-associated factor 15 (PAF15) for direct DNMT1 recruitment and DNA methylation maintenance [116–118], while its roles in the mediation of DNMT1 ubiquitination need further validation and investigation.

**Conclusions and discussions**

Studies in recent years have revealed the multi-faceted role of IncRNA in regulating DNA methylation. Firstly, IncRNAs can recruit or repel DNA modifiers (DNMTs/
TETs) to specific gene targets (Fig. 1; Fig. 2); Secondly, lncRNAs can regulate DNMT activity by controlling the level of DNMT cofactor SAM/SAH (Fig. 3); Lastly, lncRNAs can regulate the expression of DNMTs/TETs per se at multiple levels (Fig. 4). All these mechanisms have been investigated in development and disease, with emphasized roles in cancer.

While most of the studies focused on the DNA methylation of the gene promoters, there is also a recent report highlighting the gene-body methylation mediated by a lncRNA by recruiting DNMT3A, which facilitates transcription of CTSG in dermamatomyositis myoideum [119]. Whether this mechanism exists in cancer needs further investigation.

Although this review mainly discussed the lncRNA function in mediating DNA methylation, another two issues should be noted. The first is that lncRNAs are in turn regulated targets of DNA methylation [120–123]; The second is that lncRNAs also mediate other epigenetic alterations such as histone modification and chromosome remodeling [124–131]. These issues provide an additional layer of gene expression regulation to form complex cross-talk between lncRNA, transcriptional factors, and various epigenetic modifications. More elaborate investigations are warranted to reveal the common mechanisms.

**Perspectives**

The emerging roles of lncRNAs in cancer through the mediation of DNA methylation suggest novel applications in drug development. While there are currently no drugs targeting lncRNA based exactly on this mechanism, relevant studies shed light on this field (Fig. 5).

One direction is to design lncRNA mimics to regulate the activity of their target proteins, which was recently applied in treating a rare disease of phenylketonuria, where a lncRNA HULC was identified to interact with phenylalanine hydroxylase (PAH) and to modulate the enzymatic activities of PAH. In their work, the authors constructed a lncRNA mimic that rescues PAH enzymatic activity in HULC-deficient cells and mouse models, which showed the therapeutic potential for phenylketonuria [132].

Another direction is to design small molecules directly targeting lncRNA-protein interactions [133–136]. Based on the structural insight of the interaction between lncRNA HOTAIR and EZH2, Ren et al. conducted a high-throughput virtual screening and identified a compound that selectively interrupts the lncRNA-protein interaction and inhibits cancer cell invasion and migration [137].

Owing to the fast progress of RNA structural biology and screening technologies, as well as the in-depth mechanistic studies and drug delivery technologies, it is reasonable to expect that RNA-targeting will emerge as a growing therapeutic strategy for human disorders, especially cancer.

**Abbreviations**

lncRNA: Long non-coding RNA; CGIs: CpG islands; DNMTs: DNA methyltransferases; TET: Ten-eleven translocation; TDG: Thymine DNA glycosylase; Pcg: Polycomb group; PRC2: Polycomb repressive complex 2; EZH2: Enhancer of Zeste homolog 2; GADD45A: Growth arrest and DNA-damage-inducible alpha; SAM: S-adenosylmethionine; SAH: S-adenosylhomocysteine; MAT: Methionine adenosyltransferase; SAHH: S-adenosylhomocysteine hydrolase; ceRNA: Competitive endogenous RNA; BC: Breast cancer; OC: Oral cancer; CML: Chronic myeloid leukemia; TSCC: Tongue squamous cell carcinoma; TNBC: Triple-negative breast cancer; EC: Esophageal cancer; PCa: Prostate cancer; RC: Renal carcinoma; GBC: Gallbladder cancer; HCC: Hepatocellular carcinoma; OSA: Osteosarcoma; NSCLC: Non-small cell lung cancer; LUAD: Lung adenocarcinoma; CRC: Colorectal cancer; GC: Gastric cancer; AML: Acute myeloid leukemia; UL: Uterine leiomyomas; GBM: Glioblastoma multiforme; CS: Chondrosarcoma.

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