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Roles of m⁶A RNA Methylation Modification in Cancer Stem Cells: New Opportunities for Cancer Suppression

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ABSTRACT

As a reversible post-transcriptional modification, N⁶-methyladeno sine is the most common form of RNA modification in eukaryotic mRNA. Cancer stem cells (CSCs), which are a subpopulation of cells with self-renewal ability and differentiation potential, have been regarded to one of the roots of tumor occurrence, recurrence, and metastasis. Currently, numerous studies have demonstrated that m⁶A RNA modification is critically implicated in the regulation of CSCs stemness or the CSC-like traits of cancer cells. This review summarized the effects of m⁶A RNA modification-related enzymes and underlying mechanisms contributing to CSCs or cancer cell stemness, which may provide novel targets and research directions for the specifically elimination of CSCs or cancer cells with stemness.

KEYWORDS: Cancer stem cells; m⁶A RNA modification; Post-transcriptional modification; Stemness; CSC-like traits

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1. Introduction

Since the discovery of N^6-methyladenosine (m^{6}A) in 1974, m^{6}A has been an unknown field due to the technical bottleneck [1]. M^{6}A refers to the methylation modification process on the sixth nitrogen atom of RNA adenine catalyzed by methyltransferase, which is reversible [2]. In recent years, with the breakthrough of detection technology and the deepening of scientists' understanding of m^{6}A, m^{6}A-RNA modification has become numerous dynamically regulated modifications in the entire transcriptome. It has been found that m^{6}A is the most common form of RNA modification in eukaryotic mRNA. There are three types of enzymes involved in the process of RNA methylation modification: Methyltransferases, also known as "writers", including methyltransferase like protein (METTL) 3, METTL14, and WT1 Associated Protein (WTAP); Demethylase is called "eraser", including Fat mass and obesity-associated protein (FTO) and alkylation repair homolog protein 5 (ALKBH5); The m6A recognition protein is called "reader", including the protein family of the YTH domain (YTHDFQ, YTHDF2, YTHDC1, YTHDC2, etc.) and the hnRNP protein family (hnRNPA2B1). M^{6}A-RNA modification is tightly involved in transcriptional regulation and participates in almost every stage of RNA metabolism, including RNA processing, nuclear output, translation, and RNA degradation [3] (**Figure 1**).

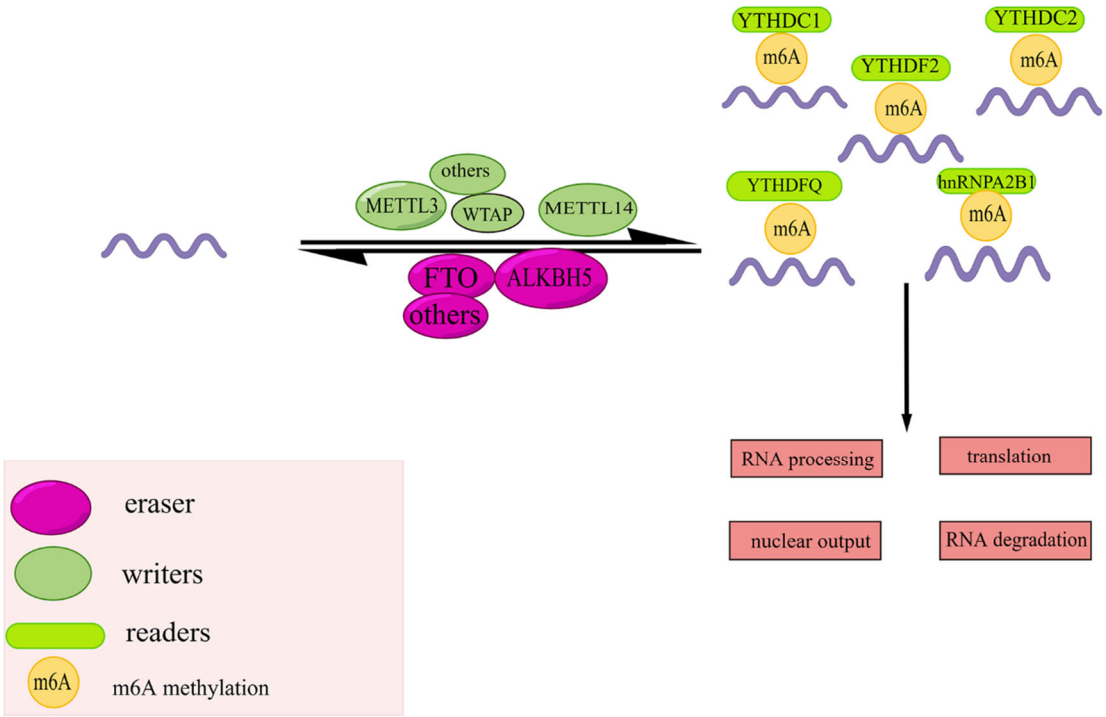

Figure 1. The process of m^{6}A RNA methylation modification.

There are three types of enzymes involved in the process of RNA methylation modification.

Methyltransferases including METTL3, METTL14, and WTAP; Demethylase including FTO and ALKBH5; The m6A recognition protein including the protein family of the YTH domain (YTHDFQ, YTHDF2, YTHDC1, YTHDC2, etc.) and the hnRNP protein family (hnRNPA2B1). M^{6}A-RNA modification is tightly involved in transcriptional regulation and participates in almost every stage of RNA metabolism, including RNA processing, nuclear output, translation, and RNA degradation.

Cancer stem cells (CSC) are a kind of cells with self-renewal ability and differentiation potential, these two specific traits of CSCs have been demonstrated to result in the tumor resistance to standard treatment methods [4]. Therefore, CSCs have long been regarded as the source of drug resistance, tumor relapse, and metastasis (**Figure 2**). Emerging evidences have revealed the critical roles of on m^{6}A-RNA modification in CSCs progression [5]. This review has made a further understanding of the function of m^{6}A-RNA modification, and summarized the relationship between m^{6}A and CSCs and its potential applications.

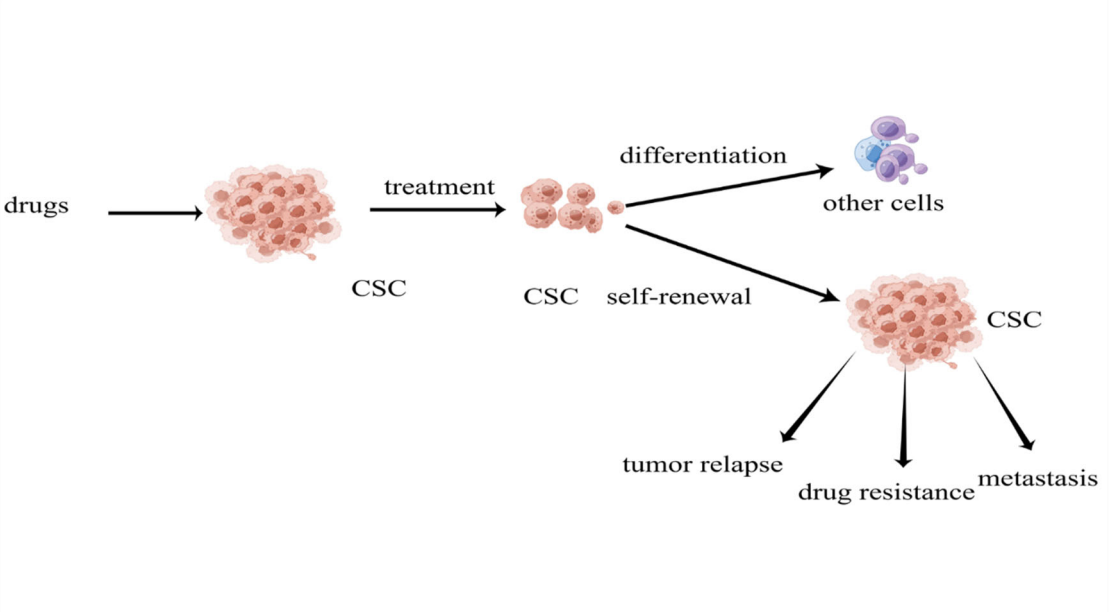

Figure 2. The functions of CSCs during tumor progression.

CSCs hold the self-renewal and differentiation ability resulting tumor relapse, drug resistance, and metastasis.

2. The constitutes of m^{6}A-RNA modification and their emerging roles

Currently, more than 100 chemical modifications have been found in coding and non-coding RNA (ncRNA) [6]. M^{6}A-RNA modification is the most common and abundant post-transcriptional RNA modification in eukaryotic cells. M^{6}A methyltransferase and demethylase are involved in the dynamic and reversible regulation of the level of m^{6}A modification. It is usually found that the m^{6}A-RNA modification is concentrated

around the termination codon, which implies its role in translation control, or in the 3-'untranslated regions (3'-UTR), which affects the affinity of specific RNA binding proteins (RBPs) to their target mRNA [7]. The m^{6}A modification is not random, but mainly occurs in adenine with RRACH (R: A/G, H: A/C/U) conservative structure [8]. The m^{6}A modification recognition protein specifically recognizes m^{6}A modification and regulates RNA splicing, transport, stability and translation [9]. Although RNA methylation does not affect base pairing and gene coding, emerging studies have shown that m^{6}A is widely involved in the regulation of biological processes, including stem cell renewal and differentiation, tissue development, heat shock response, tumor invasion and other processes [10, 11]. M^{6}A RNA modification is involved in almost all major biological processes from normal development to disease through m^{6}A methyltransferase, m^{6}A demethylase, and m^{6}A recognition protein.

2.1 M^{6}A methyltransferase

M^{6}A methyltransferase, also known as "writer", is responsible for promoting RNA methylation during the post-transcriptional modification of RNA, that is, the m^{6}A process [12]. Currently, the “writer” contains three enzymes, namely METTL3, METTL14, and WTAP. Methyltransferase plays an important role in regulating biological phenomena such as biological clock, immunity, reproduction, and the occurrence and development of various diseases [13]. In the process of RNA methylation, METTL3, METTL14, and WTAP form a special complex, called WMM complex. A recent study proposed the following model: WTAP firstly binds to mRNA, and then recruits METTL3 and METTL14 complexes to catalyze the methylation of the sixth nitrogen atom on RNA adenine [14]. This WMM complex mediates methylation process and thereby regulates tissue differentiation, cell apoptosis and cell cycle, and plays critical roles in tissue formation and embryonic development (**Figure 3**).

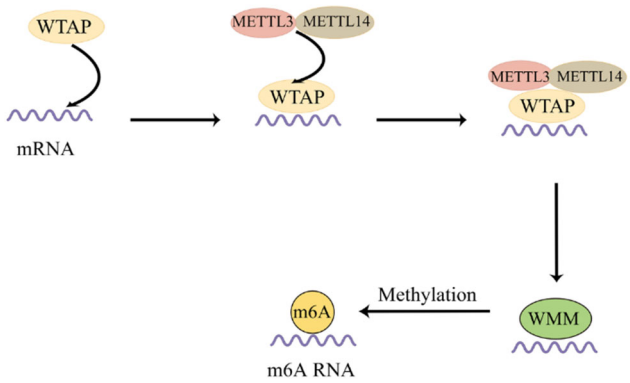

Figure 3. METTL3, METTL14, and WTAP form a special complex, called WMM complex, to mediate RNA methylation.

WTAP firstly binds to mRNA, and then recruits METTL3 and METTL14 complexes to catalyze the methylation of the sixth nitrogen atom on RNA adenine.

2.2 M^{6}A demethylase

In 2011, the first m^{6}A demethylase FTO was found, proving that m^{6}A is a reversible and controllable process, which triggered a boom in m^{6}A research [15]. In eukaryotic cells, "erasers" include FTO and ALKBH5, both of which belong to AlkB α-Glutaric acid dependent dioxygenase [16]. Before 2011, most studies focused on the relationship between FTO and obesity and eating [17]. Thus, FTO is also called obesity gene. With the function of FTO as a demethylase widely known, research on FTO-mediated m^{6}A-RNA regulation and thus affecting the occurrence and progress of diseases (especially cancer) began to boom [18]. Knockout of FTO or ALKBH5 in human cells resulted in an overall upregulation of m^{6}A levels. FTO contains a special carboxyl terminal domain and N-terminal Alk like domain [19]. These structures can identify the common sequence GGACU or RRACU in the target sequence. FTO catalyzes the oxidation of m^{6}A to form N^6-hydroxymethyl adenine and N^6-aldehyde adenine, and specifically catalyzes the decomposition of intermediates into adenosine and formaldehyde in a concentration dependent manner to achieve m^{6}A demethylation. FTO targets multiple RNA substrates and has different functions for different tissues and biological systems. Another RNA demethylase, ALKBH5, widely exists in human tissues and is mainly localized in the nucleus, especially abundant in mouse testes [20]. It is essential for spermatogenesis and mouse reproduction, and functionally contributes to the normal splicing of mRNA and the formation of longer 3'-UTR mRNA. In addition, ALKBH5 can promote the demethylation of m^{6}A and affect the metabolism, stability, nuclear output, splicing and translation efficiency of mRNA [21]. Knockout or overexpression of ALKBH5 will affect the expression level of mRNA methylation and cause many diseases. Downregulation of ALKBH5 can accelerate the nuclear output of mRNA and is closely related to reproductive system diseases and various cancers through m^{6}A-dependent modification (**Figure 4**).

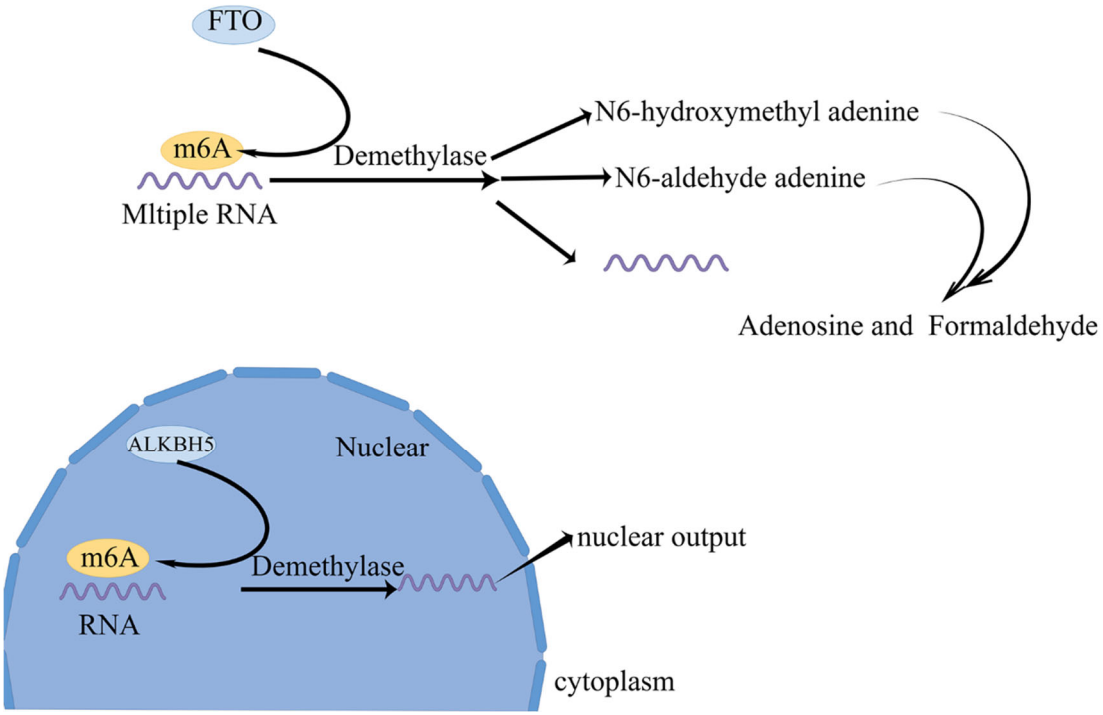

Figure 4. The process of M^{6}A demethylase-mediated RNA demethylation. FTO catalyzes the oxidation of m6A to form N6-hydroxymethyl adenine and N6-aldehyde adenine, and specifically catalyzes the decomposition of intermediates into adenosine and formaldehyde in a concentration dependent manner to achieve m6A demethylation. ALKBH5 is mainly localized in the nucleus and functionally promotes the demethylation of m6A and affect the metabolism, stability, nuclear output, splicing and translation efficiency of mRNA.

2.3 M^{6}A recognition protein

The m^{6}A recognition protein is called "reader", which regulates the interaction between RNA and protein to enable the m^{6}A-modified RNA to perform specific biological functions [22]. It mainly recognizes m^{6}A modification in RNA and regulates downstream molecular mechanisms. "Readers" mainly include: YTHDFs and YTHDCs subtypes; HNRNPs, IGF2BPs et al [23]. Methylated-reading proteins can selectively recognize and bind to m^{6}A-modified mRNA to regulate downstream pathways. Functionally, YTHDF2 can recruit mRNA containing m^{6}A modification to the mRNA decay point, and reduce the stability of RNA through transcription complex subunit 4 (CCR4-NOT)-mediated adenosine acidification, thus mediating the degradation of transcripts [24]. YTHDF1 interacts with translation initiation factors to promote the translation of target mRNA [25]. YTHDF1 interacts with YTHDF3 to enhance the translation effect and affect YTHDF2-mediated RNA degradation [26]. It has been shown that YTHDF1-3 interacts with each other to

jointly regulate RNA metabolism. IGF2BP1-3 increases the stability of mRNA containing m^{6}A modification to protect RNA in cells [27]. In the mouse lung cancer model, IGF2BP1 can cooperate with kirsten rat sarcoma viral oncogene (KRAS) to promote tumor progression [28]. In animal models, YTHDF1 can affect the function of tumor antigen presenting CD8+T cells in mice [29]. Additionally, YTHDF1 may be a potential therapeutic target to enhance the efficacy of PD-L1 [30]. YTHDF2 affects all aspects of RNA metabolism and plays an important role in many biological processes, such as migration, invasion, metastasis, proliferation, apoptosis, cell cycle, cell vitality, cell adhesion, differentiation and inflammation of human cancer [31]. The consumption of all three YTHDF analogues can promote the differentiation of leukemia cells. Notably, all YTHDF proteins have the same m^{6}A binding site on mRNA (**Figure 5**).

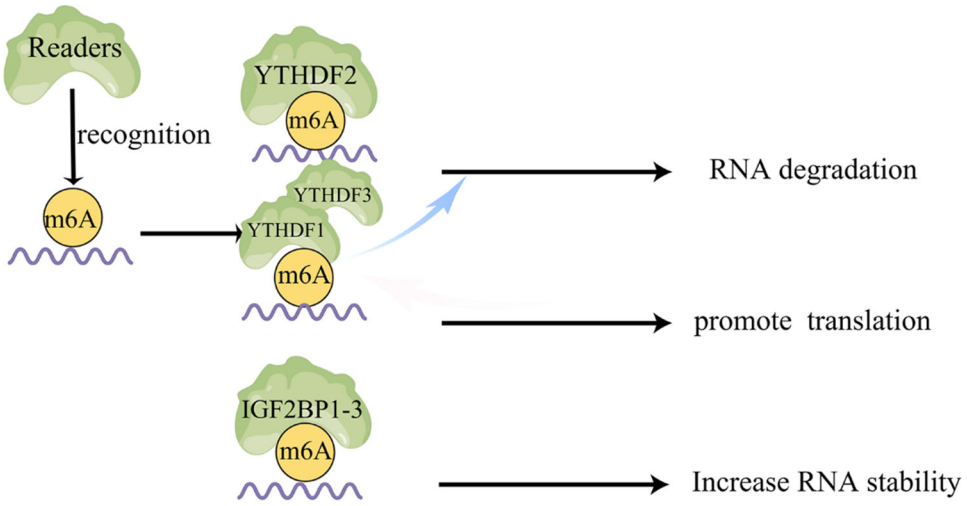

Figure 5. The process of m^{6}A RNA methylation mediated by M^{6}A recognition protein. YTHDF1 interacts with translation initiation factors or YTHDF3 to promote the translation of target mRNA and affect YTHDF2-mediated RNA degradation. Additionally, YTHDF1-3 interacts with each other to jointly regulate RNA metabolism. Furthermore, IGF2BP1-3 increases the stability of mRNA containing m6A modification to protect RNA in cells.

Through the action of the above three enzymes, m^{6}A becomes a dynamic and reversible process, and participates in RNA metabolism through methylation, affecting upstream and downstream genes.

3. The effects of m^{6}A-RNA modification on CSC progression

CSCs are a group of cells with self-renewal and multi-directional differentiation potential. It is generally believed that the basic characteristics of CSCs are self-replication and multi-lineage differentiation and cloning *in vitro* and *in vivo*, which can produce cancer cells. Therefore, CSCs not only play an important role in cancer progression and maintaining the homeostasis of cancer cells, but also have broad application prospects in the treatment of different kinds of tumors. Experiments showed that CSCs have higher proliferative capacity than ordinary cancer cells. They can divide and proliferate continuously for many times, which is the primary condition to maintain the stability of cancer cell characteristics. Additionally, the differentiation potential, that is, CSCs derived from a single cell can produce and differentiate into cancer cells. Furthermore, CSCs have been found to have immunomodulatory activity as CSCs have been shown to exhibit the immunotherapeutic resistance. According to these characteristics, CSCs play an irreplaceable role in the treatment of malignant tumors as our previous studies have shown targeting CSCs can significantly suppress tumor migration, invasion, and drug resistance [32-34]. Epigenetics plays an important role in maintaining the above biological characteristics of CSCs, which refers to the phenomenon that the DNA sequence has not changed but the traits have heritable changes. In recent years, with the rapid development of high-throughput sequencing technology, epigenetic modification, especially epigenetic post-transcriptional modification, has gradually become one of the important hotpots in disease occurrence and development. Among them, m^{6}A is the most abundant type of apparent post-transcriptional modification in eukaryotic mRNA. The methylation modification of m^{6}A targets downstream molecules through its corresponding methylase molecules, and is widely involved in CSC proliferation and self-renewal, targeted differentiation, immune regulation and other biological processes [35]. Recent studies have shown that the occurrence and development of many malignant tumors involve the modification of corresponding CSCs by m^{6}A RNA modification. Through the regulation of corresponding m^{6}A-RNA modification, including the regulation of RNA splicing, exonuclear transport, translation and stability, cells can respond quickly to external stimuli, which can achieve the treatment of malignant tumors and remission of cancers. With the continuous development of epigenetics and the in-depth study of tumor treatment, m^{6}A RNA modification plays a very important role in regulating the occurrence and development of CSCs-related malignant tumors.

3.1 The effects of m^{6}A methyltransferase on CSC progression

METTL3 can regulate mouse embryonic stem-cell heterochromatin, the integrity of which is critical for

silencing retroviral elements and for mammalian development [36]. Since normal stem cells and CSCs share numerous common traits during their progression [37], it has been shown that knockdown of METTL3 or METTL14, the key components of the RNA methyltransferase complex, dramatically promotes human glioma stem cell growth, self-renewal, and tumorigenesis [38]. And an integrated analysis of m^6A-RIP (RNA immunoprecipitation) and total RNA-Seq of METTL3-silenced glioma stem cells identified that m^6A modification in glioma stem cells is principally carried out by METTL3 [39]. Consistently, Visvanathan et al. found that silencing METTL3 in glioma stem-like cells can inhibit the growth of intracranial glioma in situ and prolong the survival period of mice [40]; Yu-Zhou Chang et al. demonstrated that METTL3 promotes the stem cell maintenance and thus facilitates the malignant progression of glioma through the upregulation of metastasis - associated lung adenocarcinoma tran 1 (MALAT1) expression by enhancing its stability via m^6A modification [41]. Meanwhile, silencing METTL3 could enhance the sensitivity of γ radiation in glioma stem cells. Additionally, the critical roles of METTL3 in the progression of other types of CSCs also have been largely revealed, for example, Ting Li et al. found that METTL3 significantly inhibited cell self-renewal, the frequency and migration of CSCs, and the occurrence and metastasis of colorectal cancer by targeting IGF2BP2 *in vitro* and *in vivo* [42]; A recent study confirmed that METTL3-mediated m^6A-RNA modification is necessary to activate the TEK-VEGF-A-mediated tumor progression and angiogenesis in bladder CSCs [43]. Similarly, GAO et al. proved that m^6A-RNA modification played a key role in self-renewal and tumorigenicity of bladder CSCs through the METTL3-AFF4-SOX2/MYC signal axis, and promoted the progress of bladder CSCs [44]; METTL3 can also promote the stemness and malignant progression of breast cancer [45], kidney cancer [46], and gastric cancer [47]. Furthermore, METTL14, another key component of the RNA methyltransferase, is indicated to be implicated in CSC progression, like WENG et al. found that METTL14, is highly expressed in normal hematopoietic stem/progenitor cells (HSPCs) and acute myeloid leukemia (AML) cells carrying t(11q23), t(15;17), or t(8;21), and METTL14 is required for development and maintenance of AML and self-renewal of leukemia stem/initiation cells through by regulating its mRNA targets (e.g., MYB and MYC) through m^6A modification [48]; Zhenchuan Liu el al. demonstrated that METTL14 expression was downregulated in esophageal squamous cell carcinoma, suppressed TRIB2 expression via miR-99a-5p-mediated degradation of TRIB2 mRNA by targeting its 3'-UTR, this is responsible for the enhanced CSC properties and radiotherapeutic resistance [49]; And METTL14 knockout promotes the proliferation, self-renewal, metastasis and tumor initiating capacity of bladder CSCs via regulating the

stability of Notch1 mRNA through m^{6}A modification [50]. Notably, hexavalent chromium [Cr(VI)] is a common environmental carcinogen causing lung cancer in humans, a recent study indicated that and chronic Cr(VI) exposure could alter cellular epitranscriptome by increasing the m^{6}A RNA modification via upregulating METTL3 expression, which plays an important role in Cr(VI)-induced cell transformation, CSC-like property, and tumorigenesis [51]. Besides, WTAP-mediated m^{6}A methylation of Bcl-2 mRNA is shown to be necessary for recombinant neuropilin 1 (NRP1)-induced stemness and radiotherapeutic resistance in breast cancer [52].

3.2 The effects of m^{6}A demethylase on CSC progression

Shen et al. confirmed that targeting m^{6}A-RNA demethylase ALKBH5 can effectively inhibit the development and maintenance of AML, inhibit the self-renewal of leukemia stem cells, and retain normal hematopoietic function, highlighting the potential of targeting the LKBH5-ACC3 axis to treat leukemia [53]. Zhang et al. revealed that the increase of ALKBH5 in glioma stem cell-like cells promoted the self-renewal and tumorigenesis by regulating the ALKBH5-FOXM1 pathway [54]. In consistent, Kowalski et al. proved that the high expression of ALKBH5 increased the radiation resistance of glioma stem cells by regulating homologous recombination (HR). Interestingly, they also found that ALKBH5 promoted the invasion of glioblastoma by promoting the invasion of glioblastoma [55]. Additionally, the previous studies have shown that hypoxia induces the phenotype of breast CSCs by promoting HIF-dependent and ALKBH5-mediated Nanog mRNA demethylation [56]; Yu et al. have demonstrated that ALKBH5 can promote the tumorigenicity of multiple myeloma by increasing the proportion of side population (SP) cells and CD138-/CD34 myeloma stem cells by activating the Hippo signal pathway related to CSCs and promoting the expression of multifunctional factors NANOG, SOX2 and OCT4 [57]. Furthermore, ALKBH5 was found to be highly expressed in CSCs derived from non-small cell lung cancer (NSCLC) and could suppress lung cancer progression by regulating epithelial-mesenchymal transition (EMT) and stemness via modulating p53 gene transcriptional activity [58]. These data indicate that ALKBH5 plays a key role in the maintenance of multiple myeloma stem cells.

FTO, another important m^{6}A demethylase, also has been found to be involved in CSC progression, such as Huang et al. found that FTO enhanced the second messenger cAMP signal, inhibited the self-renewal of ovarian CSCs, and thus suppressed the occurrence of tumors by exerting the activity of demethylase [59]. Similarly, Sébastien Relier et al. demonstrated that FTO impedes CSC abilities in colorectal cancer through its

N^6,2'-O-dimethyladenosine (m^6A_m) demethylase activity [60]. In addition, FTO was found to be highly expressed in esophageal cancer stem-like cells, and that its level was also substantially increased in esophageal cancer tissues, which was closely correlated with a poor prognosis in esophageal cancer patients; Functional experiments indicated that FTO knockdown significantly suppressed the proliferation, invasion, stemness, and tumorigenicity of esophageal cancer cells via promoting the formation of lipid droplets in esophageal cancer cells by enhancing HSD17B11 expression [61].

3.3 The effects of M^{6}A recognition protein on CSC progression

As one of distinct family members of m(6)A readers, IGF2BP1 promotes the stability of MGAT5 mRNA by upregulating the m^6A-RNA modification of MGAT5 mRNA, thus promoting the formation of the phenotype of liver CSCs [45]. Additionally, IGF2BP1 can bind to other transcripts to regulate CSC activity, such as Irina A Elcheva et al. reported that genetic or chemical inhibition of IGF2BP1 decreases leukemia cells tumorigenicity and sensitizes leukemia cells to chemotherapeutic drugs through critical regulators of self-renewal (HOXB4, MYB, ALDH1A1) [62]. IGF2BP1 can also bind to and stabilize m^6A-modified IQGAP3 transcript, which is an important stem cell factor in rapidly proliferating isthmus stem cells in the stomach, to sustain stem cell potential in cancer [63].

As another “readers”, YTHDF2 can target the YTHDF2-MYC-IDFBP3 axis to link RNA endonucleating transcriptome modification and maintain the expression of oncogenes, thus promoting the growth of glioma stem cells, this indicates that YTHDF2 is a potential target in glioblastoma [64]. Similarly, Zhang et al. confirmed that YTHDF2 can promote the phenotype of liver CSCs and tumor metastasis by promoting the m^6A-RNA modification of OCT4 mRNA, leading to the enhanced expression of OCT4 protein, which is also a critical stemness regulatory master [65]. In addition, targeting YTHDFs can also regulate CSC activity or tumor cell stemness, like TRIM29, as an oncogene, promotes the stem cell-like phenotype of cisplatin-resistant ovarian cancer cells in a m^6A-YTHDF1 dependent manner [66]; Targeting YTHDF2 can selectively compromise CSCs in AML with enhancing hematopoietic stem cells activity [67]. Furthermore, heterogeneous nuclear ribonucleoprotein A2B1 (hnRNPA2B1), which is a known m^6A “reader” and reported to implicated in lung adenocarcinoma progression via reading the m^6A site on primary microRNA-106b (pri-miR-106b) to facilitate the maturing of miR-106b-5p, thus activating the Wnt/β-catenin signaling to aggravate stemness [68]; In melanoma stem cells, Mengqi Chu et al. also revealed that hnRNPA2B1 level was significantly upregulated in melanoma stem cells compared with non-stem cells and facilitated the

tumorigenesis by affecting the splicing of TPPP3, EIF3H, DOCK2, DAPK1, RNF128, and SYT7 [69]. These above results indicate that m^{6}A-related enzymes are inextricably linked with CSCs by mediating post-transcriptional m^{6}A modification of RNA, and m^{6}A regulatory factors hold the potential as therapeutic targets.

4. The application prospect of targeting m^{6}A-RNA modification in CSCs-targeted therapy

Targeting FTO has been demonstrated to hold promising therapeutic significance via suppressing tumor growth, potentiating immunotherapy, and attenuating drug resistance [18], for example, Rui Su et al. reported two potent small-molecule FTO inhibitors (FB23 and FB23-2) that exhibit strong anti-tumor effects in multiple types of cancers by dramatically attenuating leukemia stem cell self-renewal and reprogram immune response [70, 71]; Sarah Huff et al. further demonstrated that described the structure-based design, synthesis, and biochemical evaluation of a new class of FTO inhibitors (FTO-02 and FTO-04), which could attenuate neurosphere formation in patient-derived glioblastoma stem cells without affecting the growth of healthy neural stem cell-derived neurospheres [72]. Moreover, Kunxia Cao et al. revealed that FTO inhibitor-loaded GSH-bioimprinted nanocomposites (GNPIPP12MA) can selectively target leukemia blasts, especially leukemia stem cells, and induce ferroptosis by disrupting intracellular redox status [73]. In addition, FTO makes leukemia cells sensitive to the cytotoxicity of T cells and overcomes the immune escape induced by HMA [71]. In the mouse acute myeloid leukemia model, 50 nmol of CS1 can almost completely inhibit the regeneration of leukemia cells, highlighting the strong role of FTO inhibitors in inhibiting the self-renewal of cancer cells. Interestingly, using FTO inhibitors as cancer drugs has many advantages. FTO inhibitors can prevent or treat obesity and overweight concomitantly. FTO inhibitors R-2HG, MA, FB23 and FB23-2 have been proved to inhibit the activity of FTO or the process of FTO-mediated demethylation, and thus have anti-tumor effects [16, 74]. Two compounds were identified in a high-throughput virtual screening library of 144000 pre-selected compounds, which inhibited the proliferation of three leukemia cell lines [75]. Eliza Yankova et al. carried out high-throughput screening on 250000 different drug-like compounds and finally developed the METTL3 small molecule inhibitor STM2457 [76]. They further proved its inhibition on leukemia through *in vitro* and *in vivo* experiments. Similarly, a recent study also reported two novel FTO inhibitors using virtual screening, structural optimization, and bioassay, namely 18077 and 18097 exhibiting the activity of suppressing breast cancer [77]. Furthermore, some clinically-approved drugs or natural compounds also have been indicated to improve chemoresistance and CSC progression via targeting m^{6}A

RNA modification, such as omeprazole [78], Saikosaponin D [79], Simvastatin [80], and Berberine [81]. Although m^{6}A-related enzyme inhibitors are currently in the experimental stage, the development of inhibitors and the success of various experiments undoubtedly suggest a new way to treat cancer. It is believed that more m^{6}A-related enzyme inhibitors can be used in tumor research and treatment in the near future, and we will be closer to cancer cure.

5. Discussion and conclusion

M^{6}A refers to the methylation modification process on the sixth nitrogen atom of RNA adenine catalyzed by methyltransferase, which is reversible. M^{6}A is involved in many processes such as tumorigenesis, development and drug resistance, and plays a role in promoting most tumors. CSCs are cells with self-renewal ability and differentiation potential, which play a key role in tumor drug resistance, recurrence and distant metastasis. In recent years, the research on the influence of m^{6}A modification and abnormal expression of m^{6}A regulatory protein on the stemness of CSCs is increasing. M^{6}A regulatory protein can affect various CSCs-related cancers by regulating the epitope transcriptome of cancer, thereby promoting or inhibiting the CSCs stemness, drug and radiotherapeutic resistance. This suggests that m^{6}A is closely related to the occurrence and development of cancer, the generation of drug resistance and prognosis. Although some studies have shown that m^{6}A-related enzymes regulate the stemness of a variety of CSCs by mediating, inhibiting or reading m^{6}A, targeting numerous signal pathways, the specific regulatory mechanisms are still fragmentary, which requires in-depth research. Currently, there is no detection and sequencing technology for RNA modification types, and many theoretical and basic technical problems need to be solved. Improving the RNA epigenetic regulation theory is the research basis for further analyzing epigenetics and precise treatment of diseases. Meanwhile, m^{6}A level in CSCs can be used to predict cancer risk, achieve early diagnosis, predict patient prognosis, and provide new treatment methods, which has practical significance.

6. Competing interests

The authors declare that they have no competing interests.

7. Acknowledgements

The pictures in this article are drawn by Figdraw.

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