



Surmounting cancer drug resistance: New insights from the perspective of N⁶-methyladenosine RNA modification

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ABSTRACT

Despite the development of targeted therapy, drug resistance remains a primary hindrance to curative treatment of various cancers. Among several novel approaches to overcome drug resistance, modulating N⁶-methyladenosine (m⁶A) RNA modification was found to be an important strategy in various types of cancer cells. Considered as one of the most common epigenetic RNA modifications, m⁶A regulates multiple biological processes including cellular proliferation, metabolism, and metastasis through modulation of RNA splicing, degradation, and translation, leading to anticancer drug resistance. This regulatory network is orchestrated mainly by several m⁶A regulators, including “writers”, “readers”, and “erasers”. It is encouraging that several small molecules targeting m⁶A regulators have shown great potential in overcoming drug resistance in different cancer cell types, two of which entacapone and meclofenamate, are currently undergoing evaluation. However, the m⁶A modification participates in complex biological processes and its functions are context-dependent, which has challenged the clinical application of targeting the m⁶A modification in cancer therapy.

In this review, we discuss the molecular mechanisms underlying the m⁶A modification in regulating anticancer drug resistance through modulation of drug-target interaction and drug-mediated cell death signaling. Alteration of the m⁶A modification interferes with drug efficacy through modulation of the expression of multidrug efflux transporters (e.g., ABCG2, ABCC9, ABCC10), drug metabolizing enzymes (e.g., CYP2C8), and drug targets (e.g., p53 R273 H). Furthermore, alterations of the m⁶A modification may protect cells from drug-mediated cell death by regulating DNA damage repair (e.g., p53, BRCA1, Pol κ, UBE2B, and ERCC1), downstream adaptive response (e.g., critical regulators of apoptosis, autophagy, pro-survival signaling, and oncogenic bypass signaling), cell stemness, and tumor microenvironment (e.g., ITGA6, ITGB3, and PD-1). We particularly highlight recent advances in therapeutic strategies targeting the m⁶A modification with the aim to surmount chemoresistance. The comprehensive understanding of the role of the m⁶A modification integrated with combined therapeutic strategies, should facilitate the development of future therapeutic strategies to circumvent or surmount drug resistance, thus enhancing therapeutic efficacy.

1. Introduction

Conventional chemotherapy as well as targeted therapy constitute a pivotal arm of first-line treatment in cancer management. Most patients with early-stage tumors gain a complete or partial response after

chemotherapy and targeted therapy, whereas patients with late-stage tumors often display dismal therapeutic outcomes (Miller et al., 2019). Tumor cells escape the cytotoxicity of chemotherapy and targeted therapy through multifactorial intrinsic and acquired drug resistance mechanisms (Assaraf, 2006; Assaraf et al., 2019; Bar-Zeev et al.,

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2017; Cui et al., 2018; Gacche and Assaraf, 2018; Gonen and Assaraf, 2012; Li et al., 2016; Livney and Assaraf, 2013; Milman et al., 2019; Niederer et al., 2015; Shapira et al., 2011; Vasconcelos et al., 2019; Wijdeven et al., 2016; Zhitomirsky and Assaraf, 2016; Zhong and Virshup, 2020). Tumor cells with intrinsic resistance exhibit molecular heterogeneity prior to drug treatment due to genetic and/or epigenetic alterations, via the survival of an antiapoptotic subpopulation(s) during drug treatment. In contrast, acquired chemoresistance results from the selective pressure of drug treatment, which endows tumor cells with newly acquired genetic and/or epigenetic features that enhance tumor cell survival and clonal expansion (Abbosh et al., 2017; Assaraf et al., 2019; Bailey et al., 2020; Caswell and Swanton, 2017; Jiang et al., 2020; Kamranvar and Masucci, 2011; Leonetti et al., 2019a; Long et al., 2020; McGranahan and Swanton, 2017; Mudduluru et al., 2016; Qazi et al., 2017; Raz et al., 2016; Wijdeven et al., 2016). Multiple mechanisms, including altered drug metabolism, deregulated drug transport, and altered target proteins/receptors, are involved in disruption efficient binding of drugs to their targets. Altered drug metabolism, deregulated drug transport, mutation or altered expression of target proteins are the leading causes responsible for diminished anticancer drug efficacy (Bivona and Doebele, 2016; Chen et al., 2016; Joyce et al., 2015; Wang et al., 2020b; Zhitomirsky and Assaraf, 2016). For instance, the anti-cancer effect of chemotherapeutic agents that induce DNA damage-mediated cell death can be abolished by enhanced DNA damage repair or adaptive responses including activation of redundant pro-survival pathways, acquisition of stemness and alteration of the inflammatory response and T cell homeostasis (Chang, 2016; Cheng et al., 2020; Erin et al., 2020; Nickoloff et al., 2017; O'Donnell et al., 2019). Targeting these mechanisms may readily overcome cancer drug resistance (Fig. 1).

Epigenetic alterations have been intensively studied to uncover the driving force of intrinsic or acquired drug resistance since the discovery of methylation of DNA repair gene O⁶-methylguanine-DNA methyltransferase (MGMT), which sensitizes glioblastoma multiforme (GBM) cells to the anchor alkylating agent temozolomide (Berdasco and Esteller, 2019; Hegi et al., 2005). Epigenetic modifications include covalent modifications (e.g., phosphorylation, methylation, acetylation, propionylation, ubiquitination, sumoylation, GlcNAcylation, citrullination, and crotonylation) on DNA, RNA, and histones (Audia and Campbell, 2016; Valencia and Kadoc, 2019). Epigenetic modifications provide a possible explanation to connect genome and environmental factors (Berdasco and Esteller, 2019). Although discovered decades ago,

studies on RNA methylation have long been overlooked until the identification of fat mass and obesity-associated protein (FTO) as an RNA demethylase (Jia et al., 2011). RNA methylation occurs on several sites, including 7-methylguanosine (m^7G), 5-methylcytosine (m^5C), N¹-methyladenosine (m^1A) and m^6A (Michalak et al., 2019). The pan-cancer analysis demonstrates that mutations in m^6A modification sites are significantly correlated with tumor development, which attracted the attention of scholars interested in this most common RNA methylation (Zuo et al., 2018). The m^6A modification can be modulated by “writers” (i.e., m^6A methyltransferases), “readers” (i.e., m^6A -binding proteins), and “erasers” (i.e., m^6A demethylases) in eukaryotes (Shi et al., 2019a). The “writer” complex contains methyltransferase-like 3/14 (METTL3/14), Wilms tumor 1-associated protein (WTAP), RNA-binding motif protein (RBM) 15/15B, zinc finger CCCH-type containing 13 (ZC3H13), Casitas B-lineage lymphoma-transforming sequence-like protein 1 (CBLL1) (also known as HAKAI), and Vir-like m^6A methyltransferase associated (VIRMA) (also known as KIAA1429) (Zaccara et al., 2019). Furthermore, METTL16 has been identified as a new member of the group of “writer” proteins (Warda et al., 2017). The “eraser” proteins FTO and α -ketoglutarate-dependent dioxygenase alkB homolog 5 (ALKBH5) remove the m^6A RNA modification (Jia et al., 2011; Zheng et al., 2013). The “reader” proteins include YT521-B homology (YTH) proteins, insulin-like growth factor 2 mRNA binding proteins (IGF2BPs), eukaryotic initiation factor 3 (eIF3), heterogeneous nuclear ribonucleoproteins (HNRNPs), and fragile X mental retardation proteins (FMRPs), which recognize the m^6A RNA modification and trigger downstream signaling (Zaccara et al., 2019). YTH domain containing 1 (YTHDC1) participates in pre-mRNA splicing and RNA exportation (Roundtree et al., 2017; Xiao et al., 2016), while the same family members YTHDC2 and YTH domain family 2/3 (YTHDF2/3) induce intracellular RNA degradation (Kretschmer et al., 2018; Shi et al., 2017; Wang et al., 2014). Besides, IGF2BP family proteins sustain RNA stability (Huang et al., 2018), yet YTHDF1/3 and YTHDC2 facilitate RNA translation (Bailey et al., 2017; Wang et al., 2015). In addition, eIF3 binds to the m^6A site in the 5' UTR region, leading to mRNA translation (Lee et al., 2015). HNRNPC and HNRNPG participate in pre-mRNA processing as well as structure switching (Liu et al., 2015; Zhou et al., 2019a), while HNRNPA2B1 facilitates primary miRNA processing (Wu et al., 2018). Moreover, FMRP binds to YTHDF2, thus promoting the stability of mRNA (Zhang et al., 2018a). Therefore, the m^6A modification can affect the abundance of mRNA, microRNA (Roignant and Soller, 2017), long non-coding RNA (lncRNA) (Jin et al., 2019a), and circular

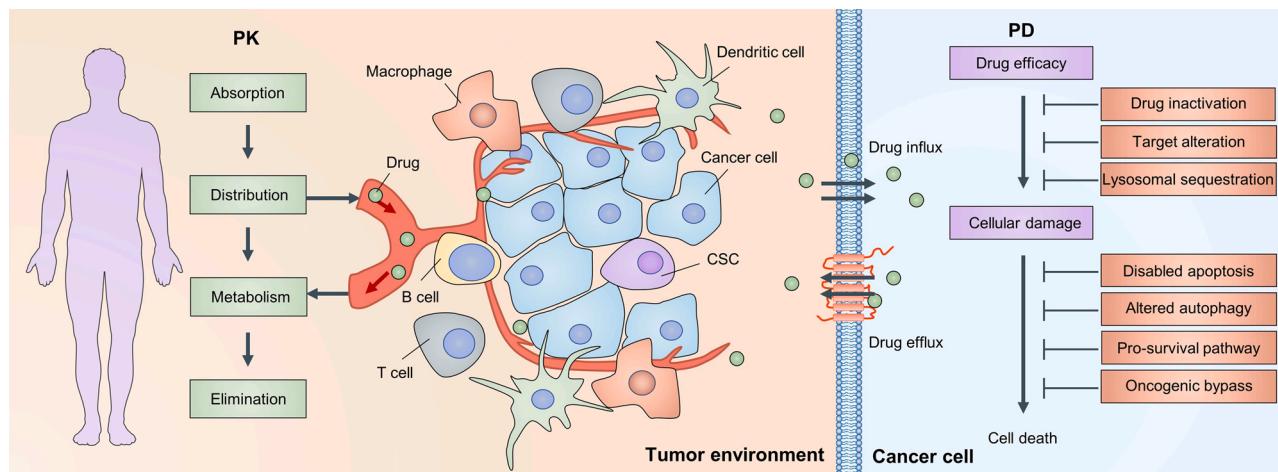


Fig. 1. Molecular mechanisms of anticancer drug resistance. Pharmacokinetic (PK) factors (e.g., drug absorption, distribution, metabolism, and elimination) limit the amount of drug that reaches the TME. Quantitative and qualitative alterations in drug influx and efflux system impact the intracellular accumulation of anticancer drugs in tumor cells. The drug efficacy is determined by its pharmacodynamics (PD) properties. Inactivation of drugs, altered target proteins, or intracellular drug sequestration impact drug efficacy. Disabled apoptosis, altered autophagy, activation of pro-survival pathways, or oncogenic bypass, are the leading determinants of drug resistance. Besides, the presence of cancer stem cells and altered TME also contribute to drug resistance.

RNA (circRNA) (Zhou et al., 2017a), suggesting an extensive role of the m⁶A modification in global epigenetic remodeling (Fig. 2). Emerging evidences indicate that m⁶A modification is strongly associated with drug resistance. In the current review, we focus on the mechanisms of RNA m⁶A modification-associated drug resistance, as well as strategies targeting the m⁶A modification to overcome chemoresistance.

2. m⁶A-mediated aberrant drug transport and metabolism

Adequate intracellular drug concentration in cancer cells is a prerequisite for effective cytotoxic drug treatment, which is orchestrated by drug influx and efflux transporters as well as metabolism. The drug influx rate is determined by the concentration gradient of the drug and the number of drug transporters present on the cell surface (Mandal et al., 2017). The expression of drug efflux transporters is negatively correlated with intracellular drug retention (Joyce et al., 2015). Besides, enzyme-mediated drug metabolism affects drug distribution, thus controlling drug efficacy (Ingelman-Sundberg and Lauschke, 2020).

2.1. Multidrug-resistance efflux transporters

Drug transporters determine the efficacy of drug delivery into cancer cells by manipulating anticancer drug efflux (Dallavalle et al., 2020). Studies on drug efflux mainly focus on the impact of ATP-binding cassette (ABC) transporter family proteins, of which several ABC transporters mediate multidrug resistance (MDR) including ABCB1 (P-gp/MDR1), ABCG2 (BCRP/MXR), ABCC1 (MRP1) and ABCC10 (MRP7) (Kathawala et al., 2015; Li et al., 2016). Interestingly, recent studies indicate that the expression of ABC family proteins can be regulated by RNA m⁶A modification, directly on their transcripts or indirectly via upstream signaling pathways, thus influencing the drug efflux and drug resistance of tumors. For example, ABCG2-dependent multidrug resistance is correlated with the expression of METTL3. METTL3-induced RNA m⁶A modification upregulates ABCG2 transcripts and modulates the Hippo pathway in non-small cell lung cancer (NSCLC) that can be abrogated by YTHDF3 depletion (Jin et al., 2019a). Besides, a microarray assay analysis revealed that the m⁶A modification is significantly enriched upon ABCC10 gene expression in drug-resistant NSCLC cells, while ABCC10-mediated drug efflux is associated with

paclitaxel- and gefitinib-resistance in NSCLC cells (Kathawala et al., 2014a, b; Zhao et al., 2018). Apart from direct regulation, enrichment of RNA m⁶A modification on tripartite motif containing 11 (*TRIM11*) transcripts, induces cisplatin-resistance through positively regulating the Dishevelled-Associating Protein with a high frequency of LE ucinines (Daple)/β-catenin/ABCC9 pathway in nasopharyngeal carcinoma cells (Zhang et al., 2020a). It is noteworthy that ABC transporters also participate in intracellular drug sequestration (Englinger et al., 2018; Zhitomirsky and Assaraf, 2016). For instance, ABCG2-rich extracellular vesicles sequester drugs away from their drug targets, thus leading to MDR (Goler-Baron and Assaraf, 2012). The regulatory role of the m⁶A modification on ABCG2 indicates another novel strategy on targeting intracellular drug sequestration to surmount drug resistance (Jin et al., 2019a). These studies indicate that the m⁶A modification confers cancer cells with drug-resistant capacity through regulating ABC-mediated drug efflux, hence highlighting the potential of targeting the m⁶A modification to enhance the intake of drug and thus facilitate drug efficacy.

2.2. Drug metabolism

Drug metabolism governs drug bioactivation, catabolism, conjugation as well as elimination, thus determining the efficacy of the chemotherapeutic drug treatment (Ingelman-Sundberg and Lauschke, 2020; Joyce et al., 2015; Noll et al., 2016). Studies have demonstrated that the m⁶A modification participates in the regulation of the cytochrome P450 (CYP) family of enzymes, the most studied drug-metabolizing enzymes, modulating the metabolism of various anticancer drugs. For instance, the expression of cytochrome P450 family member CYP2C8 is upregulated upon METTL3/14 depletion but downregulated by FTO depletion, indicating that the m⁶A modification may impact drug metabolism via downregulating CYP2C8 (Backman et al., 2016; Nakano et al., 2020). Thus, the RNA m⁶A modification may attenuate the activity of antimetabolites (e.g., Tegafur-Uracil, Tegafur-Gimeracil-Oteracil) and alkylating agents (e.g., cyclophosphamide) which are prodrugs that rely on bioactivation, while activating camptothecin alkaloids (e.g., irinotecan), anti-mitotic natural products (e.g., paclitaxel) and molecular targeted agents (e.g., gefitinib, erlotinib) (Oyama et al., 2012). Whether other drug-metabolizing enzymes are

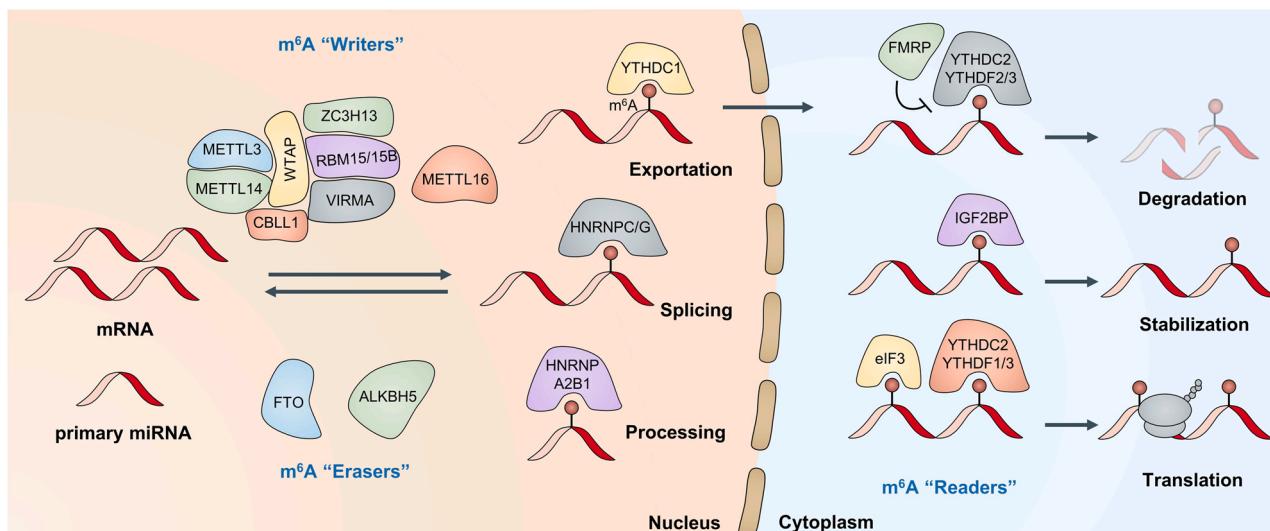


Fig. 2. Molecular composition of the m⁶A modification. The m⁶A modification is regulated by “writers,” “readers,” and “erasers.” The m⁶A “writer” complex, consisting of METTL3, METTL14, WTAP, RBM15/15B, ZC3H13, CBLL1, and VIRMA, together with METTL16 can catalyze the m⁶A modification. m⁶A “eraser” proteins FTO and ALKBH5, facilitate demethylation on m⁶A site. m⁶A “reader” proteins conduct their biological functions by binding to the m⁶A modification. YTHDC1 participates in pre-mRNA splicing and RNA exportation, whereas YTHDC2 and YTHDF2/3 induce intracellular RNA degradation. IGF2BP family proteins sustain RNA stability. YTHDF1/3, YTHDC2 and eIF3 facilitate RNA translation. HNRNPG and HNRNPA2B1 participate in pre-mRNA processing as well as structure switching, while HNRNPA2B1 promotes primary miRNA processing. FMRP binds with YTHDF2 to stabilize mRNA.

regulated by the m⁶A modification needs further elucidation.

3. m⁶A-mediated alteration of drug targets

Quantitative and qualitative alterations in drug target proteins resulting in altered protein expression and function are critical impediments to anticancer drug efficacy (Minari et al., 2018; Nayar et al., 2019; Wang et al., 2017a). A comparative study revealed a significant overlap between resistance-driving m⁶A modified transcripts and FDA approved drug targets in NSCLCs ($p < 0.05$), indicating that the global scale alterations of the m⁶A modification in drug targets exist ubiquitously (Meng et al., 2020). A typical example is p53 (encoded by the TP53 gene), the mutations of which trigger tumorigenesis through gain-of-function activities in 42 % of human tumors (Cao et al., 2020; Frezza and Martins, 2012; Kandoth et al., 2013; Stiewe and Haran, 2018). Of note, METTL3 depletion suppressed the expression of mutant p53 and sensitized colorectal cells to doxorubicin (Uddin et al., 2019). Recent studies reveal more precise insights into the regulatory role of m⁶A on the expression of mutant p53; unlike other mutated genes, mutations in TP53 typically cluster on specific amino acids (e.g., R175H, R273H), leading to abnormal folding of p53 (Green et al., 2018). m⁶A modification at the point-mutated 273 codon (G > A) of TP53 pre-mRNA preferentially promoted the splicing of mutant pre-mRNA and subsequently enhanced the expression of p53 protein (R273 H) in cancer cells (Uddin et al., 2019). Hence, targeting the m⁶A modification may serve as a complementary approach for small molecules directly targeting mutant p53 (e.g., APR-246 and PRIMA-1) to reverse cancer cell resistance (Rangel et al., 2019; Zhang et al., 2018b). Intensive studies on m⁶A-mediated alterations in drug targets other than the p53 protein may deepen our understanding as to the development of potential strategies to reverse drug target alterations.

4. m⁶A modulates DNA damage repair

Most chemotherapeutic agents induce cell death via apoptosis due to DNA damage (Brinkman et al., 2020; Carneiro and El-Deiry, 2020; Gourley et al., 2019). Eukaryotic cells treated with cytotoxic agents, are usually arrested in cell cycle to allow for damage repair or undertake apoptotic decision when unrepairable DNA damage occurs. Failure to achieve a cell cycle arrest or DNA damage repair, results in cancer cell resistance to DNA-damaging drugs (Dekanty et al., 2015; Gobin et al., 2019). The regulatory role of RNA m⁶A on TP53, indicating that targeting m⁶A could be a potential therapeutic strategy to impede or overcome drug resistance by regulating downstream pathways to induce cell cycle arrest and DNA damage repair (Uddin et al., 2019; Williams and Schumacher, 2016). Besides, the m⁶A modification also regulates recruitment or expression of key enzymes in eukaryotic DNA damage repair, including nucleotide excision repair (NER) and homologous recombination (HR). For example, the m⁶A modification directly facilitates the recruitment of DNA polymerase κ (Pol κ) to the UV-induced DNA damage site, thus initiating NER in A375 melanoma and HeLa cells (Xiang et al., 2017). Additionally, METTL3 upregulates the expression of ubiquitin-conjugating enzyme E2B (UBE2B) (also known as Rad6B), a critical enzyme that activates DNA damage repair through monoubiquitination of FANCD2, PCNA, and γ-H2AX, thus leading to drug resistance to 5-fluorouracil (5-FU), cisplatin, and gemcitabine (Narayanan et al., 2020; Somasagara et al., 2017; Taketo et al., 2018). Moreover, METTL3-mediated upregulation of yes-associated protein (YAP) leads to NER by upregulating the expression of downstream excision repair cross-complementing 1 (ERCC1) in NSCLC (Jin et al., 2019a). Notably, m⁶A modulated the essential HR factor BRC-1/BRCA1 in colorectal cancer cells by upregulating the expression of its cooperator ankyrin repeat and LEM-domain containing protein 1 (ANKLE1), suggesting that the m⁶A modification facilitates DNA repair (Hong et al., 2018; Tian et al., 2020). Consistently, circMORC3-mediated m⁶A modification on DNA damage repair-associated transcripts, lead to

cisplatin-resistance in bladder cancer cells (Su and Lin, 2020). However, the m⁶A modification in other types of tumors may result in the opposite effect on DNA damage repair; a typical example is that FTO-mediated β-catenin upregulation, lead to increased expression of ERCC1 and subsequently activation of NER, which is responsible for the resistance to cisplatin and radiotherapy in cervical squamous cell carcinoma (CSCC) (Zhou et al., 2018). Together, unveiling the determinants of m⁶A function in DNA damage repair may facilitate the development of new strategies to sensitize cancer cells to DNA-damaging agents.

5. m⁶A activates downstream adaptive responses

After binding to their cellular targets, anticancer drugs can subsequently induce cell death. However, multiple cellular adaptive responses regulated by the m⁶A modification, such as disruption of apoptosis, initiation of autophagy, and activation of pro-survival signaling, are evoked to support cancer cell survival, which is a major concern in current cancer therapy (Fig. 3) (Roos et al., 2016; Sabnis and Bivona, 2019).

5.1. Apoptosis

Cancer cells endowed with enhanced DNA repair capacity can survive drug-induced DNA damage upon drug treatment. Upregulation of anti-apoptotic proteins, including B-cell lymphoma 2 (BCL-2), inhibitor of apoptosis proteins (IAPs), and FLICE inhibitory protein (FLIP), play critical roles in determining cell sensitivity to anti-cancer agents (Allen et al., 2015; Carneiro and El-Deiry, 2020). Notably, the m⁶A modification affects the expression of BCL-2 with variable outcomes depending on the specific cancer context. In a recent study, increased FTO levels upregulated BCL-2 expression resulting in resistance to tyrosine kinase inhibitors (TKIs) in leukemia cells, *in vitro* and *in vivo* (Yan et al., 2018). Specifically, cells with mRNA m⁶A hypomethylation and thus upregulation of FTO, displayed increased resistance to TKIs and enhanced K562 leukemia growth rates in mice. Consistently, genetic or pharmacological restoration of m⁶A methylation through FTO deactivation, restored cancer cell sensitivity to TKIs. Thus, from a mechanistic perspective, FTO-dependent RNA m⁶A demethylation enhanced mRNA stability of proliferation/survival transcripts bearing m⁶A and subsequently led to increased protein synthesis (Yan et al., 2018). These findings identify a novel function for the RNA m⁶A methylation in regulating cell fate decisions and thus demonstrate that a dynamic m⁶A methylome is an additional epigenetic driver of resistance to TKIs, providing a mechanistic basis for cancer drug resistance towards TKIs, the resistance of which is known to be multifactorial (Adar et al., 2012; Gotink et al., 2011; Leonetti et al., 2019a, b; Zhitomirsky and Assaraf, 2015, 2016).

Moreover, these results are consistent with the finding that overexpression of ALKBH5 stabilizes BCL-2 transcription in epithelial ovarian cancer cells (Zhu et al., 2019), suggesting that the RNA m⁶A modification is negatively correlated with BCL-2 expression and resistance to apoptosis. However, different results are found with other tumors, implying that the m⁶A modification can also be positively correlated with the expression of anti-apoptotic proteins and thus apoptosis resistance. For example, METTL3-mediated m⁶A modification increased the levels of BCL-2 at both the mRNA and protein levels in breast cancer (Wang et al., 2020a). Moreover, ALKBH5 depletion-induced m⁶A modification facilitated the degradation of lncRNA H19, leading to the release of miR-29b-3p from the 3'UTR of IAPs transcription, thus inhibiting the expression of IAPs (Zhang et al., 2020b). Overall, the m⁶A modification modulates cell apoptosis in a cancer context-dependent manner.

5.2. Autophagy

Autophagy is a lysogenic process by which damaged organelles and aggregated proteins are degraded, allowing cells to cope with stress.

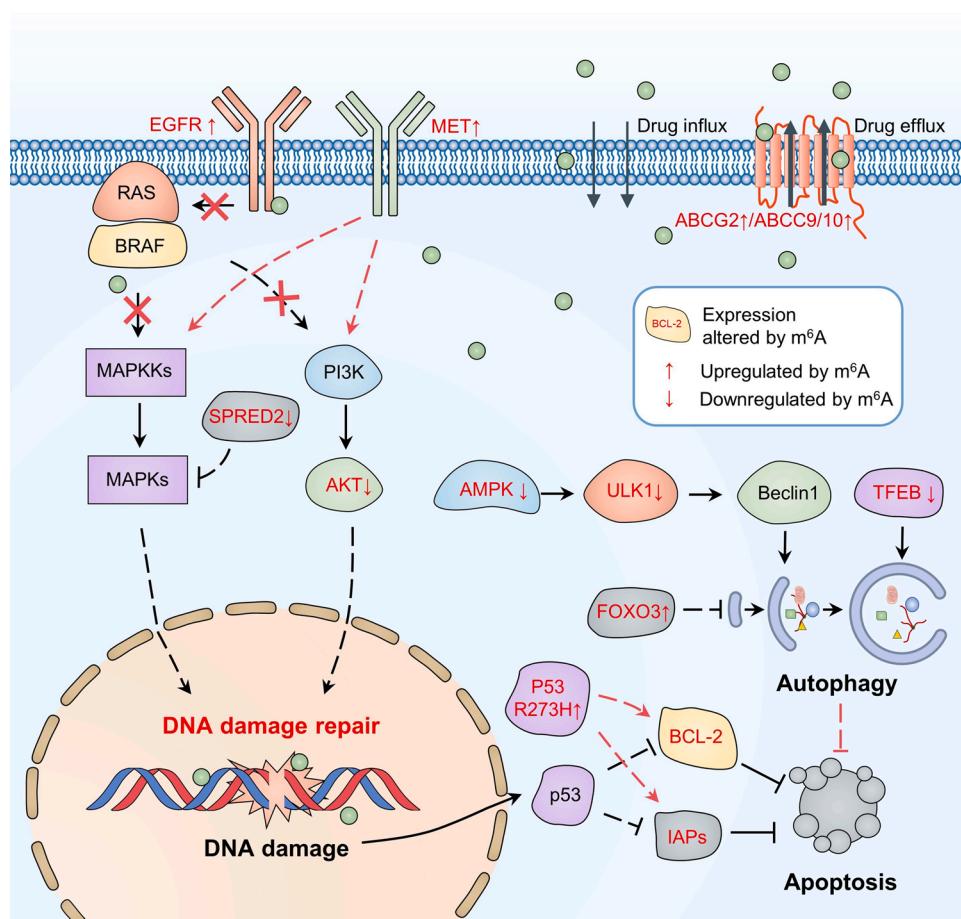


Fig. 3. Regulatory functions of m⁶A in drug efficacy. m⁶A modification upregulates drug transporters (e.g., ABCG2, ABCC9, ABCC10), facilitating ATP-driven drug efflux. Chemotherapeutic agents can induce genomic DNA damage, leading to p53-induced apoptosis. m⁶A could selectively upregulate the p53 (R273 H) protein, releasing prohibited antiapoptotic proteins (e.g., BCL-2, IAPs). m⁶A impacts autophagy through altering the expression of key regulators (e.g., AMPK, ULK1, TFEB, FOXO3), determining the survival of tumor cells. Targeted agents can preferentially bind to EGFR T790 or BRAF V600E proteins, impeding continuous activation of pro-survival signaling (e.g., MAPK, AKT). While the m⁶A alteration reactivates pro-survival signaling through upregulating redundant pathways (e.g., MET, MAPK cascades, and PI3K-AKT). Activation of pro-survival signaling and altered DNA damage repair contribute to tumor chemoresistance upon drug treatment.

Therefore, this process may result in the survival of cancer cells which are undergoing anticancer drug treatment (Adar et al., 2012; Gotink et al., 2011; Piya et al., 2017; Zhitomirsky and Assaraf, 2016). Recent advances provide an insight into the initiation of m⁶A modification-regulated autophagy as well as the formation of autophagosomes. In some cases, the RNA m⁶A modification impedes autophagy. For example, depletion of METTL14 stabilized CAMKK2 transcript, thus initiating autophagy through activation of adenosine 5'-monophosphate-activated protein kinase (AMPK) and downstream Unc-51-like kinase 1 (ULK1) complex (Chen et al., 2020). Besides, FTO-mediated demethylation separates ULK1 transcription from YTHDF2, leading to increased ULK1 expression and autophagy initiation (Jin et al., 2018). Consistently, depletion of METTL14 enhanced autophagy that was provoked by cisplatin treatment in pancreatic cancer cells through the mTOR signaling axis (Kong et al., 2020). Moreover, FTO depletion-mediated m⁶A modification of autophagy-related gene-5 (*ATG5*) and *ATG7* transcripts recruited the reader protein YTHDF2, leading to facilitated degradation and impaired autophagosome formation (Wang et al., 2019c). Intriguingly, METTL3 can sensitize liver cancer cells to sorafenib through stabilizing forkhead box class O3 (FOXO3) in a YTHDF1-dependent manner, thus inhibiting the transcription of autophagy-related genes, including *ATG3*, *ATG5*, *ATG7*, *ATG12*, and *ATG16L1* (Lin et al., 2020). Furthermore, METTL3 impaired autophagic flux through mRNA methylation of the transcript of transcription factor EB (TFEB), a master transcription factor, regulating autophagy and lysosomal biogenesis; this lead to the recruitment of the “reader” protein HNRNPD to downregulate TFEB expression (Puer-tollano et al., 2018; Zhitomirsky and Assaraf, 2015; Zhitomirsky et al., 2018). METTL3-mediated downregulation of TFEB can be reversed by ALKBH5 overexpression (Song et al., 2019). Conversely, m⁶A modification can promote autophagy in some cases; a typical example is that

depletion of ALKBH5 facilitated the degradation of *BCL-2* transcript in ovarian cancer cells, thereby initiating autophagy through disruption of the *BCL-2*-Beclin1 complex (Zhu et al., 2019). Taken together, the RNA m⁶A modification plays orchestrated roles in regulating autophagy, and the effect of the m⁶A modification on autophagy is cancer context-dependent. However, whether other autophagy-associated proteins could undergo m⁶A modification too, remains to be determined. Further studies are needed to elucidate other determinants of m⁶A-associated autophagy regulation.

5.3. Pro-survival signaling

Epidermal growth factor receptor (EGFR) and AKT (also known as protein kinase B) signaling pathways determine cell survival and cell death through modulation of HR and non-homologous end-joining (NHEJ) (Castejón-Grinán et al., 2018; Hawkins et al., 2011; Zhou et al., 2019b). Altered m⁶A modification levels can induce activation of EGFR and AKT, which may contribute to chemoresistance in cancer treatment. METTL3-mediated upregulation of *EGFR* mRNA may promote downstream mitogen-activated protein kinase (MAPK) signaling and lead to DNA damage repair and cell survival, which is considered a major molecular determinant of acquired drug resistance (Lin et al., 2016; Ohm et al., 2019). However, overexpression of YTHDF2 enhanced the degradation of *EGFR* mRNA, thus suppressing the survival of hepatocellular carcinoma cells which rely on EGFR signaling (Zhong et al., 2019). These findings indicate that both the level of the m⁶A modification as well as m⁶A “reader” protein expression, converge to determine the stability of targeted mRNA. Unlike EGFR, the m⁶A modification negatively correlates with AKT activation (Liu et al., 2018). Downregulation of m⁶A modification in endometrial cancer down-regulated pleckstrin homology domain leucine-rich repeat protein

phosphatase 2 (PHLPP2) and upregulated mammalian target of rapamycin complex 2 (mTORC2) expression; this contributed to the increased phosphorylation on AKT (S473), and promoted DNA-protein kinase catalytic subunit (DNA-PKcs)-dependent DNA damage repair (Liu et al., 2018; Toulany et al., 2012). Therefore, targeting the m⁶A modification has the potential to become an effective strategy to sensitize tumor cells to DNA-damaging agents.

5.4. Oncogenic bypass signaling

Although combined targeted therapies sensitize cancer cells to chemotherapy through targeting oncogenic signaling, drug resistance continues to be a primary impediment due to activation of oncogenic bypass signaling pathways (e.g., MAPK, c-MET, or PI3K/AKT signaling) (Assaraf et al., 2019; Leonetti et al., 2019a; Pagliarini et al., 2015). Multiple evidences indicate that m⁶A modification may participate in the reactivation of mutant v-raf murine sarcoma viral oncogene homolog B1 (BRAF) (V600E) downstream effectors of the MAPK pathways (Andrulis et al., 2013). For example, METTL3 promoted the maturation of *pri-miR1246* and subsequently decreased downstream Sprout-related proteins with Ena/vasodilator-stimulated phosphoprotein homology-1 domain 2 (SPRED2) expression, which reactivated the MAPK pathway in colorectal cancer cells (Peng et al., 2019b). Microarray analysis revealed that the MAPK cascade is significantly enriched in METTL3-mediated chemo- and radio-resistant pancreatic cancer cells (Taketo et al., 2018), indicating that METTL3-mediated chemoresistance and radioresistance may result from the activation of the MAPK cascade. Additionally, m⁶A-mediated reactivation of phosphatidylinositol 3-kinase (PI3K)/AKT signaling is another cause of acquired resistance in the treatment with BRAF (V600E) inhibitor (Shi et al., 2014). Inhibition of m⁶A lead to enhanced activation of PI3K/AKT signaling in gastric cancer and endometrial cancer, suggesting that the m⁶A modification is a possible bypass mechanism (Liu et al., 2018; Zhang et al., 2019b). Apart from BRAF (V600E), EGFR (T790) is another well-studied mutated drug target (Oxnard et al., 2018). Ample evidences indicate that reactivation of downstream c-MET is responsible for the resistance to EGFR inhibitors (Nanjo et al., 2017; Ortiz-Cuaron et al., 2016; Xu and Yao, 2020). Notably, chidamide-mediated downregulation of METTL3 and WTAP facilitated the degradation of *MET* mRNA, resulting in the restoration of NSCLC cell sensitivity to crizotinib treatment (Ding et al., 2020). It is important to note that chidamide, a histone deacetylase inhibitor, was approved by the Chinese FDA for the treatment of relapsed or refractory peripheral T-cell lymphoma. Consistently, METTL3 depletion down-regulated c-MET expression in uveal melanoma cells (Luo et al., 2020), suggesting that the RNA m⁶A modification may be a potential therapeutic target in EGFR-resistant patients. Overall, the m⁶A modification activated downstream signaling pathways, hence bypassing the canonical drug targets, which may be taken into consideration for targeted therapy in order to evade or overcome drug resistance.

6. m⁶A plays a dual role in maintaining cancer stem cells

Cancer stem cells (CSCs) constitute a small population of tumors, which sustain pluripotency, promote tumor progression and drug resistance (Ayob and Ramasamy, 2018; Steinbichler et al., 2018). The epithelial to mesenchymal transition (EMT) triggers the acquisition of stemness, in which the epithelial cells transform into mesenchymal-like cells with an increased ability of migration, invasion, and resistance to cell death. Besides, sustained pluripotency of CSCs contributes to tumor survival and recurrence due to its self-renewal ability (Chang, 2016). Recent studies indicate that the m⁶A modification is involved in the maintenance of CSCs in tumors, leading to drug resistance and cancer recurrence even after cancer treatment (Fig. 4).

6.1. Initiating CSCs

Evolutionary conserved EMT triggers phenotype transformation in cancer cells, resulting in the initiation of CSCs and tumor invasion (Li et al., 2017b; Wilson et al., 2020; Zhou et al., 2017b). The transforming growth factor-β (TGF-β) pathway promotes EMT mainly through activation of downstream transcription factors and TGF-β secretion into the tumor microenvironment (TME) (Li et al., 2017b; Su et al., 2020). Notably, the m⁶A modification regulates the TGF-β signaling pathway in a context-dependent manner. Recently, the m⁶A RNA modification was shown to facilitate the degradation of *TGFB1* mRNA and its downstream transcription factor matrix metalloprotease 13 (MMP13) in HeLa cells (Li et al., 2020). FTO overexpression was shown to promote tumor metastasis through upregulation of MMP13 in esophageal squamous cell carcinoma (Liu et al., 2020). Moreover, the m⁶A modification could further inhibit the TGF-β autocrine loop through disruption of TGF-β dimerization, leading to inhibition of TGF-β receptor-mediated cell signaling (Li et al., 2020). Whereas, different results from other laboratories indicate that the m⁶A modification is positively correlated with TGF-β and EMT. For instance, METTL3 depletion significantly blocked TGF-β activation and contributed to the attenuation of EMT in Hela cells, lung cancer cells, melanoma cells, and colorectal cancer cells, revealing an indispensable role of METTL3 in the EMT process (Dahal et al., 2019; Li et al., 2018; Wanna-Udom et al., 2020). Consistently, reduced m⁶A modification attenuated metastasis in multiple tumors, including colon cancer and pancreatic cancer (Xia et al., 2019; Yang et al., 2019a). The expression of downstream transcription factors of TGF-β signaling pathway, including JUNB, SRY-related HMG-box 2 (SOX2), and MMP2, was activated by the m⁶A modification, resulting in the upregulation of EMT markers (e.g., FN1/Fibronectin and VIM/Vimentin) (Dahal et al., 2019; Li et al., 2018; Wanna-Udom et al., 2020). The distinct functions of the m⁶A modification in regulating cancer metastasis may be due to various m⁶A “reader” proteins, which warrants further studies.

6.2. Sustaining CSCs

CSCs share numerous similarities with embryonic stem cells (ESCs), both of which require the activation of pluripotent transcription factors (e.g., OCT4, SOX2, KLF4, NANOG, and MYC) as well as certain signaling pathways (e.g., Hedgehog, Hippo, NF-κB, Notch, Wnt/β-catenin, and Keap1/Nrf2 signaling) to sustain self-renewal ability (Wu et al., 2016; Yang et al., 2020; Zhong and Virshup, 2020). The regulatory role of the m⁶A modification includes two aspects: managing transcription factors and signaling pathways.

The m⁶A modification exhibits distinct effects in regulating pluripotent transcription factors, thus affecting the sustainment of stemness. On the one hand, METTL3 promotes pluripotency through regulating m⁶A modulation of transcription factors (e.g., OCT4, SOX2, KLF4, NANOG, and MYC) in ESCs (Batista et al., 2014; Chen et al., 2015; Cheng et al., 2019; Cui et al., 2017; Geula et al., 2015; Visvanathan et al., 2018). This process can be abrogated by zinc finger protein 217 (ZFP217), which binds to METTL3 and forms an inactivated complex (Aguilo et al., 2015). Additionally, METTL14 retains the pluripotency of hematopoietic stem/progenitor cells (HSPCs) by stabilizing MYB/MYC, which can be negatively regulated by salmonella pathogenicity island 1 (SPI1) (Weng et al., 2018). It is consistent that other components of m⁶A “writer” complex, including WTAP and VIRMA, can be recruited by zinc finger protein Zc3h13 and promote the maintenance of stemness in mouse ESCs (Wen et al., 2018). On the other hand, the m⁶A modification negatively correlates with the pluripotency of cancer cells in some cases. For instance, overexpression of the m⁶A “eraser” protein ALKBH5 decreased the m⁶A modification and subsequently increased NANOG expression, resulting in an increased number of stem cells in breast cancer (Zhang et al., 2016). Similarly, overexpression of FTO lead to activation of MYC signaling, thereby conferring drug resistance upon leukemia cells, which can be reversed by inhibiting MYC signaling (Su

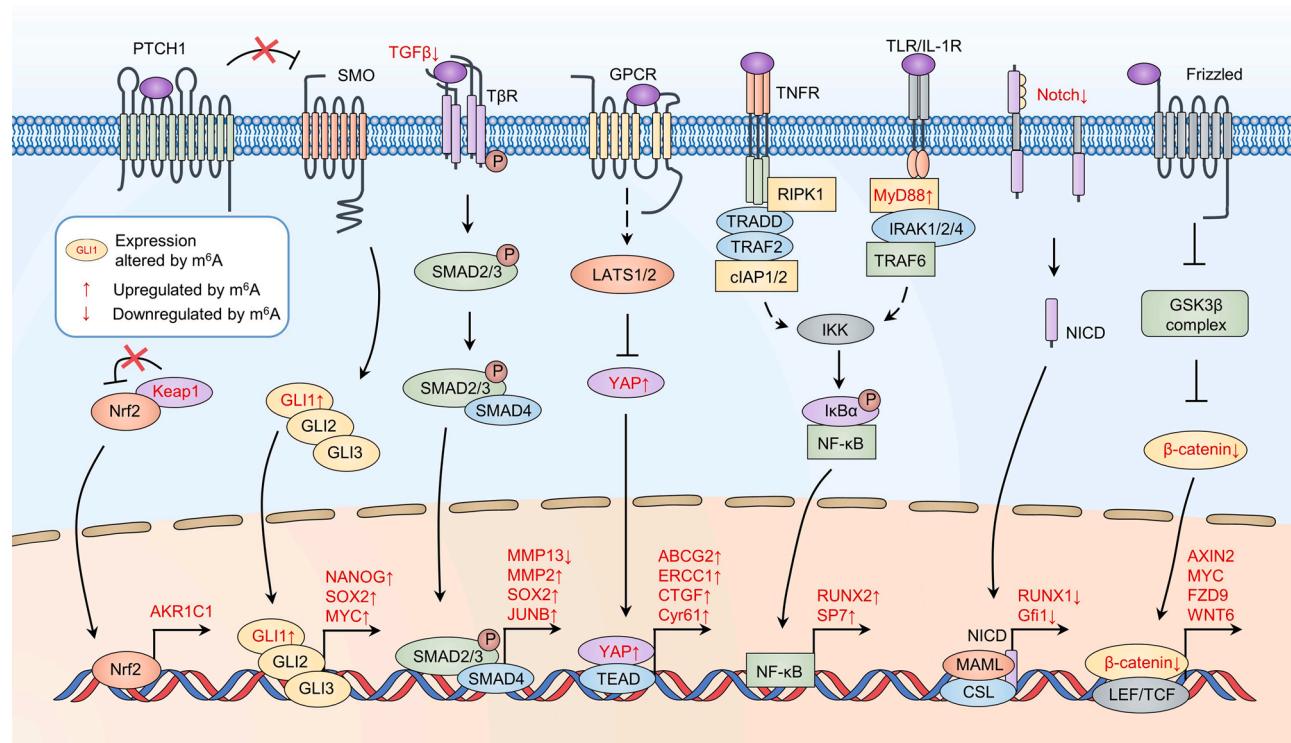


Fig. 4. m⁶A-mediated alteration of pathways in cancer stem cells. Keap1 binds to the Nrf2 protein, leading to proteasome-mediated degradation. Alterations of the m⁶A modification on Keap1 mRNA modulate its translation, affecting translocation of Nrf2 into nucleus and expression of its downstream transcription factors including aldo-keto reductase 1C1 (AKR1C1). Hedgehog ligands release Smoothened (SMO) from inhibition of Patched 1 (PTCH1), activating glioma-associated oncogene homolog 1-3 (GLI1-3), and downstream factors. m⁶A upregulates expression of GLI1 and downstream factors (e.g., NANOG, SOX2, MYC). TGF-β activates its receptor, leading to phosphorylation of SMAD2/3. SMAD4 binds to SMAD2/3, thereby activating transcription of downstream factors (e.g., MMP13, MMP2, SOX2, JUNB). Ligands of the Hippo pathway activate G protein-coupled receptors (GPCR, some of which are transcription factors). Downstream Large Tumor Suppressor 1/2 (LATS1/2) is phosphorylated, resulting in the inactivation of YAP. m⁶A upregulates YAP and its downstream factors (e.g., ABCG2, ERCC1, CTGF, and Cyr61). Tumor necrosis factor receptor (TNFR) and Toll-like receptor/interleukin-1 receptor (TLR/IL-1R) can activate inhibitor of NF-κB kinase (IKK), releasing NF-κB from IκBα. This results in translocation of NF-κB transfer into nucleus and activation of downstream effectors. m⁶A increases the expression of MYD88, subsequently activating transcriptional factors (e.g., RUNX2, SP7). After detachment of ligands, Notch receptor proteins are cleaved. Thus, Notch intracellular domain (NICD) translocates to the nucleus, eliciting its transcriptional functions. m⁶A downregulates the expression of Notch and its downstream factors (e.g., RUNX1, Gfi1). Wnt ligands bind to the Frizzled receptor, abolishing the formation of the glycogen synthase kinase-3 (GSK3β) complex. β-catenin is stabilized from GSK3β complex-induced degradation, leading to the activation of downstream effectors. m⁶A downregulates β-catenin, and impacts the expression of its transcriptional factors (e.g., AXIN2, MYC, FZD9, and WNT6). CTGF, Connective-tissue growth factor; Cyr61, cysteine-rich protein 61; RUNX, Runt-related transcription factor gene; SP7, transcription factor Osterix; Gfi1, growth factor independent 1.

et al., 2018). To gain a systematic understanding on dual roles of the m⁶A modification in regulating transcription factors, further studies on the expression level of “reader” proteins in different tissues and specificity of “reader” proteins binding to different transcripts, are urgently needed.

Intriguingly, the m⁶A modification plays different roles in modulating stemness-related intracellular signaling pathways. Studies show a positive correlation between the m⁶A modification and several signaling pathways including Hedgehog, Hippo, and nuclear factor kappa B (NF-κB) pathways (Cai et al., 2019; Jin et al., 2019a; Yu et al., 2020). METTL3 increases the m⁶A modification and thus promotes the expression of glioma-associated oncogene homolog 1 (GLI1), leading to the activation of the Hedgehog pathway in prostate cancer (Cai et al., 2019). Additionally, overexpression of METTL3 promotes the translation of YAP and transcriptional coactivator with PDZ-binding motif (TAZ) by upregulating m⁶A modification on their mRNAs, suggesting a critical role for METTL3 in regulating the Hippo pathway in therapy-refractory patients. Consistently, METTL3 depletion decreased YAP activity via inactivating metastasis-associated lung adenocarcinoma transcript 1 (MALAT1)-miR-1914-3p-YAP axis, which sensitized NSCLC cells to cisplatin (Jin et al., 2019a; Lin et al., 2016). Furthermore, METTL3 inhibits osteogenic differentiation through activation of the

NF-κB pathway in mesenchymal stem cells, which can be rescued by ALKBH5 activation (Yu et al., 2020). Whereas, the m⁶A modification is negatively correlated with the activation of the Notch signaling pathway. METTL3 was shown to increase the m⁶A modification of *Notch1* mRNA and lead to repression of Notch signaling through YTHDF2-mediated mRNA degradation in mouse hematopoietic stem cells and progenitor cells (Lv et al., 2018). As for the Wnt/β-catenin pathway, the expression of m⁶A “reader” proteins YTHDF1 and YTHDF2 governs the different roles of m⁶A modification in regulating the Wnt/β-catenin pathway. FTO upregulated β-catenin by downregulating its m⁶A modification in CSCC, resulting in cisplatin resistance and radioresistance (Zhou et al., 2018). Moreover, YTHDF1 depletion inhibited cell pluripotency through downregulating frizzled-9 (FZD9) and Wingless-type MMTV integration site family member 6 (WNT6) in colorectal cancer cells, and downregulated transcription factor 4 (TCF4) in intestinal stem cells (Bai et al., 2019; Liu and Qian, 2020). However, the positive correlation between the m⁶A modification and the Wnt/β-catenin pathway could be reversed by YTHDF2. Studies on hematopoietic stem cells indicated that YTHDF2 depletion upregulated Axin2 and c-Myc, resulting in inactivation of the Wnt/β-catenin pathway (Wang et al., 2018a). Notably, it has been previously observed that CSCs exhibit low levels of reactive oxygen species (ROS) through managing

redox signaling including Keap1/Nrf2 pathway, leading to drug resistance to conventional chemotherapy (Cui et al., 2018; Dai et al., 2020). YTHDF1 deficiency in NSCLC cells downregulated *Keap1* mRNA translation, leading to cisplatin resistance through activating Nrf2 signaling (Shi et al., 2019b). Intriguingly, METTL3 has been reported to facilitate the maturation process of *miR-873-5p*, which is negatively correlated with *Keap1* translation, leading to activation of Nrf2 signaling (Wang et al., 2019b). Overall, the m⁶A modification is closely linked to the maintenance of stemness in CSCs through regulating specific transcription factors and signaling pathways.

7. Tumor microenvironment and the m⁶A RNA modification

Intrinsic factors, including gene alterations and pathway reactivation, have been studied in multiple aspects, while the extrinsic factors were usually overlooked. TME modulates tumor progression and drug resistance through alternating cell-cell and cell-extracellular matrix (ECM) adhesion as well as deregulation of immune responses (Binnewies et al., 2018; Qu et al., 2019; Sidaway, 2019; Sun, 2016), in which the m⁶A modification plays an essential role (Fig. 5).

7.1. Integrins

Integrins mediate signaling transduction between the ECM and intracellular pathways, thus affecting tumor initiation and progression (Cooper and Giancotti, 2019; Kechagia et al., 2019). Recent studies indicate that m⁶A-mediated alteration of integrin expression affects the sensitivity of tumor cells to integrin-targeted therapeutic agents (Seguin et al., 2015). METTL3 upregulated the m⁶A modification of integrin α6 (*ITGA6*) in the 3'UTR region, thus promoting the translation of *ITGA6* mRNA (Jin et al., 2019b). Additionally, m⁶A is highly enriched in lncRNA *FAM225A*, which acts as a competing endogenous RNA (ceRNA) for sponging *miR-1275* and *miR590-3p*, leading to increased expression of integrin β3 (*ITGB3*) in nasopharyngeal carcinoma cells (Zheng et al., 2019). These evidences indicate that the m⁶A modification may facilitate the expression of integrins, which activate downstream pro-survival signaling pathways and control ECM remodeling, thus promoting drug resistance in cancer cells.

7.2. Immune response

Deregulation of immune response caused by altered expression of

cytokines, inflammatory response, or activation of immune cells may cause cancer cells to evade from immunogenic cancer cell death (Melgar et al., 2019; Pérez-Ruiz et al., 2020; Schoenfeld and Hellmann, 2020). Cytokines participate in the activation of non-specific innate immune responses and antigen-induced adaptive immune responses, that are the key factor in oncogenic infiltration of immune cells (Tucci et al., 2019; West et al., 2015). Abundant evidences suggest that the m⁶A modification may regulate “cytokine storm”, the prompt release of abundant cytokines to the microenvironment after recognition of antigens, which cannot be well explained by *de novo* gene transcription (Chang et al., 2019; Tisoncik et al., 2012). During the innate viral response, the m⁶A modification stabilizes selective transcripts, including tumor necrosis factor beta (*TNFB*) mRNA, to activate type I interferon response (Winkler et al., 2019), which can be disrupted by m⁶A depletion (Zheng et al., 2017). Besides, the m⁶A modification influences immune response through modulation of the inflammatory response. Activation of inflammatory pathways by autocrine, paracrine, endocrine, cytokines or other soluble factors [e.g., lipopolysaccharide (LPS) and growth factors] is involved in acquired drug resistance (Zhang et al., 2019a). YTHDF2 plays a crucial role in controlling LPS-induced inflammatory response by downregulating the MAPK and NF-κB pathways, indicating a possible oncogenic bypass of chemoresistance (Yu et al., 2019). Apart from promoting secretion of cytokines and inflammatory response, the m⁶A modification also activates various immune cells during innate and adaptive immune responses. It was recently shown that FTO depletion inhibited the activity of the NF-κB pathway and stability of signal transducer and activator of transcription (*STAT1*) and peroxisome proliferator-activated receptor-γ (*PPAR-γ*) mRNA as a result of YTHDF2 recognition, leading to macrophage inactivation (Gu et al., 2020). Furthermore, YTHDF1 activates dendritic cells (DC) through promoting the translation of CD40, CD80, and Toll/interleukin-1 receptor domain-containing adaptor protein (TIRAP), leading to T cell activation (Wang et al., 2019a). In addition, m⁶A-mediated degradation of suppressor of cytokine signaling (*SOCS*) family mRNA abrogated the inhibition of interleukin-7 (IL-7) signaling in naïve T cells, thus triggering the initiation of the adaptive immune response *in vivo* (Li et al., 2017a). Moreover, the m⁶A modification sustained the inactivation of CD4⁺D4⁺ regulatory T cells (Tregs) through activating the IL-2-STAT5 signaling pathway (Tong et al., 2018). Therefore, the m⁶A modification modulates T cell homeostasis by activating naïve T cells and Treg cells. Recent studies indicate that the binding of programmed cell death ligand 1 (PD-L1) on the surface of cancer cells with programmed cell death

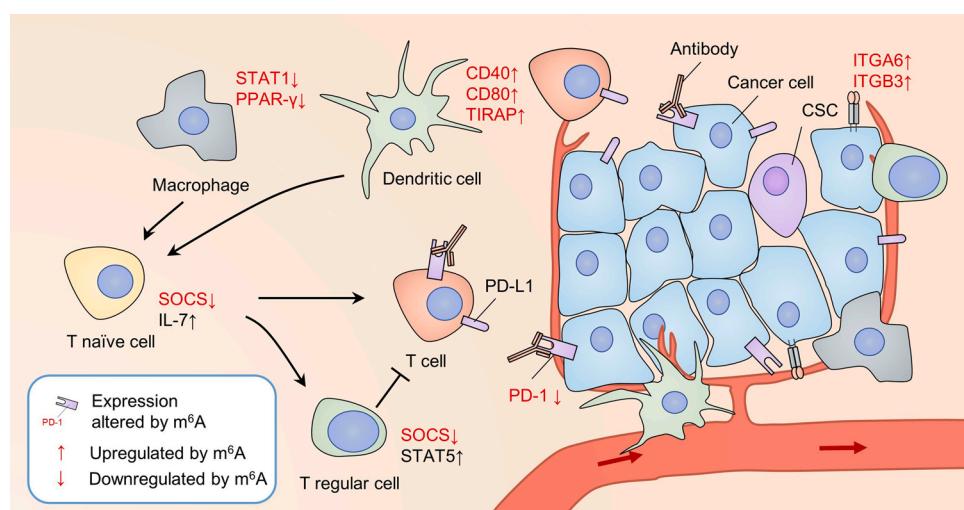


Fig. 5. m⁶A-mediated alterations in the tumor microenvironment. m⁶A downregulates the expression of signal transducer and activator of transcription 1 (STAT1) and peroxisome proliferator-activated receptor (PPAR-γ) in macrophages, their inhibiting its activation. In dendritic cells, the m⁶A modification increases the expression of CD40, CD80, and TIR domain-containing adaptor protein (TIRAP), resulting in the activation of dendritic cells. In naïve T cells, m⁶A decreases the expression of Suppressor of cytokine signaling (SOCS) family proteins, hence activating naïve T cells. Naïve T cells differentiated into activated T cells and T regulatory cells. m⁶A could decrease the expression of SOCS family proteins and lead to upregulation STAT5 in T regulatory cells, leading to inhibition of T cells. Tumor cells can upregulate the expression of PD-1, which inactivates T cells through binding to PD-L1 on T cells. m⁶A inhibits the expression of PD-1 in tumor cells, whose downregulation may serve as an important mechanism of resistance to PD-1 blockade therapy.

protein 1 (PD-1) on T cells inhibited T cell-mediated elimination of cancer cells (Restrepo et al., 2020). Anti-PD-1 checkpoint blockade has been considered as an efficient and low-toxicity strategy for cancer therapy (Diesendruck and Benhar, 2017; Kon and Benhar, 2019; Leonetti et al., 2019b). Emerging evidences have demonstrated that FTO regulates YTHDF2-mediated mRNA decay of *PD-1* (*PDCD1*), CXC chemokine receptor 4 (CXCR4), and *SOX10*, indicating that FTO inhibition may reverse the resistance to anti-PD-1 treatment (Yang et al., 2019b).

8. Targeting the m⁶A modification to surmount anticancer drug resistance

8.1. Targeting m⁶A regulators

As discussed above, the m⁶A modification plays a double-edged sword role in driving drug resistance, with yet unclear underlying molecular mechanisms (Table 1). It has been reported that a higher enrichment score of the m⁶A modification was observed in afatinib (an irreversible TKI of Her2 and EGFR kinases)-resistant cells compared with afatinib-sensitive cells (Meng et al., 2020). In contrast, the m⁶A modification is downregulated during the development of TKI resistance in multiple leukemia cell lines, indicating the context-dependent feature of the m⁶A modification (Yan et al., 2018). Apart from the global m⁶A alterations, the function of m⁶A regulators also varies in different tumors (Huang et al., 2020), which attracts researchers' attention to study the

molecular regulation of m⁶A modulators for therapeutic targeting.

8.1.1. Targeting METTL3

METTL3 has been considered a drug resistance determinant in pancreatic cancer, NSCLC, and colon cancer (Ding et al., 2020; Jin et al., 2019a; Taketo et al., 2018; Uddin et al., 2019). Conversely, several studies reported that METTL3 depletion facilitated oncogenic processes in glioblastoma stem cells, cervical cancer cells, and renal cell carcinoma cells (Cui et al., 2017; Li et al., 2017c; Wang et al., 2017b). Notably, m⁶A targeted transcription factors varied in different tumor types. The context-dependent function of METTL3 suggests that further investigation of modalities of m⁶A modulation are needed to develop METTL3-targeted treatments.

8.1.2. Targeting FTO and ALKBH5

Downregulation of FTO or ALKBH5 promotes drug resistance to Poly (ADP-ribose) polymerase (PARP) inhibitors in epithelial ovarian cancer cells by activating the Wnt/β-catenin pathway (Fukumoto et al., 2019). Besides, FTO overexpression-dependent m⁶A deregulation, lead to TKI resistance in leukemia, cisplatin and radiotherapy resistance in CSCC cells, and immune checkpoint inhibitor resistance in melanoma (Yan et al., 2018; Yang et al., 2019b; Zhou et al., 2018). Similar to FTO, ALKBH5 leads to cisplatin resistance in oral squamous cell carcinoma (OCSS) cells (Shriwas et al., 2020), suggesting that FTO and ALKBH5 may function differently in distinct tumors. Therefore, clinical selection

Table 1
Studies on m⁶A alteration in drug-resistant cancer cells.

Cancer type	Therapeutic agents	Role of m ⁶ A	Critical m ⁶ A regulators	Targeted mRNA / pathways	Refs
bladder cancer	cisplatin	pro-resistant	VIRMA	DNA repair	(Su and Lin, 2020)
cervical squamous cell carcinoma	cisplatin, irradiation	anti-resistant	FTO↑	β-catenin↑ / DNA repair	(Zhou et al., 2018)
colon cancer	doxorubicin	pro-resistant	METTL3↑	TP53 R273H↑	(Uddin et al., 2019)
epithelial ovarian cancer	PARP inhibitor	pro-resistant	FTO↓, ALKBH5↓	FZD10↑ / Wnt pathway	(Fukumoto et al., 2019)
glioma	γ-irradiation	pro-resistant	METTL3 ↑	SOX2↑	(Visvanathan et al., 2018)
hepatocellular carcinoma	sorafenib	anti-resistant	METTL3 ↓	FOXO3↓ / autophagy	(Lin et al., 2020)
leukemia	R-2HG	pro-resistant	FTO ↓	MYC/CEBPA↑	(Su et al., 2018)
leukemia	tyrosine kinase inhibitors	anti-resistant	FTO↑	MERTK↑, BCL-2↑	(Yan et al., 2018)
melanoma	anti-PD-1 blockade	anti-resistant	FTO↑, YTHDF2	PD-1 (PDCD1)↓, CXCR4↓, and SOX10↓	(Yang et al., 2019b)
nasopharyngeal carcinoma	cisplatin	pro-resistant	METTL3↑	TRIM11↑	(Zhang et al., 2020a)
non-small cell lung cancer	afatinib	pro-resistant	m ⁶ A ↑	AURKB, CDK2, CDK4, CDC20, ABCC10 / NF-κB, cell cycle	(Meng et al., 2020)
non-small cell lung cancer	cisplatin	pro-resistant	METTL3↑	YAP↑ / Hippo pathway	(Jin et al., 2019a)
non-small cell lung cancer	cisplatin	anti-resistant	YTHDF1↓	Keap1↓ / Nrf2↑	(Shi et al., 2019b)
non-small cell lung cancer	crizotinib	pro-resistant	METTL3↑, WTAP↑	c-MET↑ / ERK, EGFR signaling	(Ding et al., 2020)
oral squamous cell carcinoma	cisplatin	anti-resistant	ALKBH5↑	FOXM1↑, NANOG↑	(Shriwas et al., 2020)
osteosarcoma	doxorubicin		METTL3↑, ALKBH5↑, (FTO↓, METTL14↓)*		(Wang et al., 2019d)
pancreatic cancer	5-FU, cisplatin, gemcitabine	pro-resistant	METTL3	MAPK pathway, ubiquitin-dependent process, RNA splicing	(Taketo et al., 2018)

5-FU, 5-fluorouracil; ABCC10, ATP-binding cassette, subfamily C 10; ALKBH5, AlkB homolog 5; AURKB, aurora B kinase; BCL-2, B cell CLL/lymphoma-2; CDK2, cyclin-dependent kinase-2; CEBPA, CCAAT/enhancer-binding protein alpha; CXCR4, CXC chemokine receptor 4; EGFR, epidermal growth factor receptor; ERK, The extracellular signal-regulated kinase; FOXM1, Forkhead Box M1; FOXO3, Forkhead Box Class O3; FTO, fat mass and obesity-associated protein; FZD10, Frizzled-10; Gy, gray; MAPK, mitogen-activated protein kinase.; MERTK, Mer tyrosine kinase; METTL3, methyltransferase-like 3; NF-κB, nuclear factor kappa B/inhibitor; PARP, Poly (ADP-ribose) polymerase; PD-1, programmed cell death 1; R-2HG, R-2-hydroxyglutarate; SOX2, SRY-related HMG-box 2; TRIM11, Tripartite Motif Containing 11; VIRMA, Vir like m6A methyltransferase associated; WTAP, Wilms tumor 1-associated protein; YAP, Yes-associated protein; YTHDF, YT521-B homology domain family.

* Downregulation of FTO and METTL14 were not significant.

of m⁶A demethylase inhibitors should be cancer context-dependent.

8.1.3. Targeting other m⁶A regulators

To date, strategies targeting m⁶A are mainly dependent on the regulation of METTL3, FTO, and ALKBH5. However, multiple lines of evidence indicate that other m⁶A regulators also hold great potential to become druggable therapeutic targets. For example, YTHDF1 depletion-mediated degradation of Keap1 facilitated the activation of Nrf2 signaling in NSCLC cells, resulting in cisplatin resistance (Shi et al., 2019b). YTHDF2 is reported to play an oncogenic role in hepatocellular carcinoma HepG2 cells, which can be abrogated by microRNA-145 (Yang et al., 2017). Moreover, WTAP promoted cisplatin resistance through upregulating c-MET in NSCLC cells (Ding et al., 2020). In addition, depletion of m⁶A reader protein HNRNPC sensitized gastric cancer cells to 5-fluorouracil (5-FU), paclitaxel and cisplatin, indicating that HNRNPC could be a potential biomarker for chemoresistance (Huang et al., 2016). However, whether or not the m⁶A modification is involved in HNRNPC-mediated drug resistance requires further investigation.

8.2. Candidate m⁶A-targeted compounds

Since FTO is the first identified m⁶A modification regulator, its targeting is the most studied m⁶A modulation strategy (Table 2). FTO and ALKBH5 are both Fe(II)/2-oxoglutarate-dependent oxygenases (2OGX), which require 2-oxoglutarate (2OG) and Fe(II) to catalyze the demethylated reaction. Therefore, 2OG analogs and iron-chelating agents may competitively inhibit the activation of FTO and function as positive regulators of m⁶A modification. R(-)-2-hydroxyglutarate (R-2HG), a 2OG analog, competitively binds to FTO, leading to inhibition of the enzymatic activity of the latter (Su et al., 2018). However, other 2OGXs including m¹A demethylase ALKBH3 also require 2OG as a cofactor for its catalytic activity. Competitive inhibitors of 2OG may inhibit unexpected 2OGXs and thus induce undesirable side-effects (Herr and Haussinger, 2018; Niu et al., 2018; Toh et al., 2015). To reduce unexpected side-effects during treatment, drugs with higher specificity are urgently needed. High-throughput screening of small molecule library identified

several potent candidates, which may need further investigations to verify their anticancer effects *in vivo*. Rhein is the first identified competitive inhibitor that binds to the active site of FTO and disrupts its cofactors and substrate complex (Chen et al., 2012). Several compounds (e.g., MO-I-500, citrate, N-CDPCB, CHTB, radicicol, CS1, CS2) are found to inactivate FTO or ALKBH5 by disrupting the interaction between FTO/ALKBH5 and their cofactors or substrates (He et al., 2015; Qiao et al., 2016; Su et al., 2019; Wang et al., 2018b; Xu et al., 2014; Zheng et al., 2014). Notably, the anti-inflammatory drug meclofenamic acid (MA) and its derivative FB23-2 can bind to the nucleotide recognition lid (NRL) region of FTO, thus exhibiting a highly selective inhibitory effect on FTO (Huang et al., 2019, 2015). Multiple lines of evidences validated the anticancer effect of MA in different cancer types including prostate cancer and uterine cervical cancer (Soriano-Hernandez et al., 2012, 2015). It is encouraging that a pilot clinical study of meclofenamate in subjects with progressive or recurrent brain metastasis (NCT02429570) started recently, which may provide new strategies for the treatment of late-stage cancers. A screening study of U.S. FDA-approved drugs indicated that entacapone (previously used in combination with levodopa for the treatment of Parkinson's disease), is as a potent FTO inhibitor (Peng et al., 2019a; Senek et al., 2017). Entacapone directly binds to FTO on its cofactor- and substrate-binding sites, leading to the inactivation of FTO (Peng et al., 2019a). Moreover, entacapone-mediated m⁶A modification may downregulate TKI-targeted kinases, suggesting that the entacapone with TKI combination may benefit TKI-resistant cancer cells. Indeed, entacapone in combination with imatinib is currently under early phase I clinical study for the treatment of gastrointestinal stromal tumors (NCT04006769). Moreover, 3D proteome-wide scale screening identified MV1035 as an effective ALKBH5 inhibitor, which shows favorable anticancer efficacy in glioblastoma cells (Malacrida et al., 2020). Moreover, several compounds are identified as activators or inhibitors of METTL3, however, the anticancer effect of these compounds remains largely unknown and requires further study (Selberg et al., 2019; Tzelepis et al., 2019). Taken together, although multiple m⁶A regulator-targeted compounds may hold promise to enhance cancer treatment efficacy and improve the

Table 2
Identified FTO and ALKBH5 inhibitors.

Molecule	Validated cancer type	Target	IC ₅₀ (of target) (μM)	Mechanism	Identified year	References
Rhein	glioblastoma	FTO, ALKBH2, ALKBH3	21 (FTO)	disrupting cofactor and substrates binding	2012	(Chen et al., 2012)
MO-I-500	HeLa cell	FTO	8.7	chelating the active site Fe2, competitively binding to substrate recognition lid	2014	(Zheng et al., 2014)
citrate		ALKBH5, FTO	488 (ALKBH5)	competitively with Fe2 and 2OG, binds to the ALKBH5	2014	(Xu et al., 2014)
compound 12	Hela cell	FTO, ALKBH5	0.81 (FTO)	disrupting substrates binding	2015	(Toh et al., 2015)
Meclofenamic acid	HeLa cell, prostate cancer, uterine cervical cancer	FTO	7	disrupting cofactor and substrates binding, and specific binding to NLS	2015	(Huang et al., 2015)
N-CDPCB		FTO	4.95	disrupting cofactor and substrates binding	2015	(He et al., 2015)
CHTB		FTO, ALKBH2	39.24 (FTO)	disrupting cofactor and substrates binding	2016	(Qiao et al., 2016)
R-2HG	acute myeloid leukemia	FTO	133.3	competitive substrate to 2OG	2018	(Su et al., 2018)
Radicicol	acute myeloid leukemia, epithelial ovarian carcinoma	FTO, HSP90	16.04 (FTO)	disrupting cofactor and substrates binding	2018	(Wang et al., 2018b)
FB23-2	acute myeloid leukemia	FTO	0.06	disrupting cofactor and substrates binding, and specific binding to NLS	2019	(Huang et al., 2019)
CS1	acute myeloid leukemia	FTO	0.143	inhibiting the binding of FTO to its target mRNAs	2019	(Su et al., 2019)
CS2	acute myeloid leukemia	FTO	0.713	inhibiting the binding of FTO to its target mRNAs	2019	(Su et al., 2019)
Entacapone	liver cancer	FTO, COMT	3.5 (FTO)	disrupting cofactor and substrates binding	2019	(Peng et al., 2019a)
MV1035	glioblastoma	ALKBH5, Na ⁺ channel		inhibition of the catalytic activity	2020	(Malacrida et al., 2020)

2OG, 2-oxoglutarate; ALKBH, AlkB homolog; CHTB, 4-chloro-6-(6'-chloro-7'-hydroxy-2',4',4'-trimethyl-chroman-2'-yl)benzene-1,3-diol; COMT, catechol-O-methyltransferase.; FTO, fat mass and obesity-associated protein; HSP90, Heat shock protein 90; N-CDPCB, N-(5-chloro-2,4-dihydroxyphenyl)-1-phenylcyclobutane carboxamide; NLS, nuclear location signal; R-2HG, R-2-hydroxyglutarate.

outcome in clinical practice, related studies are still rare. Promoting clinical trials of novel compounds as well as developing strategies for targeting other m⁶A modification modulators are urgently needed.

9. Conclusions

In the review, we summarized the recent studies on m⁶A RNA modification in regulating cancer drug resistance. Notably, m⁶A displays distinct roles in different tumor types, suggesting the complexity of m⁶A modification in drug resistance. The RNA m⁶A modification exhibits pro-drug resistance functions in both cisplatin- and afatinib-resistant NSCLC cells, indicating that typical modulatory patterns may exist in specific drug-resistant tumor cells. In addition, R-2HG-resistant leukemia cells exhibit upregulated FTO levels, while TKI-resistant leukemia cells downregulate FTO. The distinct roles of FTO in leukemia emphasize the necessity to clarify the molecular mechanisms underlying the m⁶A modification-dependent drug resistance in the clinical setting. The m⁶A modification not only contributes to intrinsic drug resistance through heterogeneous RNA methylome in different types of cancer cells but also promotes acquired resistance by altering the transcription of key regulators in various signaling pathways. Further studies on the m⁶A RNA modification at multiple levels of drug resistance are required in order to develop of combinational strategies to overcome therapy resistance.

Although promising in promoting novel therapeutic strategies to circumvent drug resistance, our molecular understanding of the m⁶A modification is still in infancy. Notably, the main impediment in targeting the m⁶A modification is its dual function in regulating drug resistance, resulting in intangible therapeutic efficacy in different tumors. As mentioned above, the heterogeneity of the RNA methylome and m⁶A “reader” protein expression in different tumors can be a possible explanation. m⁶A “reader” proteins exhibit a dominant role in the regulation of mRNA stability, while studies on its functions are sometimes overlooked. This evidence underlines the necessity to study the regulatory networks of the m⁶A RNA modification. It is encouraging that increasing studies on m⁶A regulatory mechanisms and pharmacologic approaches are emerging, which may shed light on the clinical strategies to surmount drug resistance.

10. Future perspectives

With the development of high-throughput screening technologies and increased understanding of the molecular basis underlying the m⁶A modification, several novel compounds targeting m⁶A regulators including FTO, ALKBH5, and METTL3 have been considered as potential therapeutic agents for future cancer therapy. Multiple evidences indicate that targeting the m⁶A modification can sensitize cancer cells to anti-cancer agents in various types of cancer cells, indicating that m⁶A-targeted compounds could be effective combinational agents. Notably, several m⁶A-targeted molecules including meclofenamate and entacapone are now under early phases of clinical evaluation for late-stage cancer treatment, that highlights the positive perspective in targeting the m⁶A modification. However, some impediments should be taken into consideration when using m⁶A-targeted compounds in future studies. Firstly, further investigation is needed to determine the efficacy and safety of m⁶A-targeted compounds before their clinical use. Secondly, the number of selective or specific inhibitors of m⁶A regulators is limited and efforts to screen for effective inhibitors targeting the m⁶A modification are urgently needed. Furthermore, since the effect of the m⁶A modification is context-dependent, intensive studies on RNA methylome and regulatory network of m⁶A modification in different organs or individuals should be considered. With the advances in managing drug resistance due to m⁶A modification, combinational strategies using m⁶A-targeted agents with chemotherapeutic or targeted molecules may shed new light on evading drug resistance in clinical practice.

Declaration of Competing Interest

The authors report no declarations of interest.

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