RNA m⁶A甲基化修饰及其在肝癌中的作用

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摘要: N⁶-甲基腺苷（m⁶A）是真核生物中最丰富的RNA内部转录后修饰，这种类型的修饰是由甲基转移酶、去甲基化酶和识别m⁶A修饰的蛋白质协同调控的动态可逆的表观遗传修饰。m⁶A修饰在基因表达的转录后调节起着至关重要的作用，其通过影响RNA代谢的各个过程，例如RNA的加工、核输出和翻译等，参与多种细胞功能、代谢和疾病过程。肝癌是最常见的恶性肿瘤之一，其发病率和死亡率在全球均位居前列。已有的研究结果表明m⁶A修饰参与了肝癌的发生发展，但具体的分子机制以及作用未得到充分阐明。本文介绍了目前已知的m⁶A修饰因子在肝癌中的作用，归纳总结了m⁶A修饰在肝癌中的最新研究进展。此外，本文还阐述了针对m⁶A修饰参与的肝癌治疗策略，为进一步探索m⁶A修饰在肝癌的作用，寻找肝癌治疗靶点提供参考。

关键词: N⁶-甲基腺苷，肝癌，研究进展，治疗策略

Methylation modification of RNA m⁶A and its role in hepatocellular carcinoma

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Abstract: N⁶-methyladenosine (m⁶A) is the most prevalent internal RNA post-transcriptional modification in eukaryotes. This type of modification is dynamically reversible and epigenetically regulated by a collaborative interplay of methyltransferases, demethylases, and m⁶A-binding proteins. Modification of m⁶A plays a critical role in post-transcriptional regulation of gene expression, involving various processes in RNA metabolism, such as RNA processing, nuclear export, and translation, thereby participating in diverse cellular functions, metabolism, and disease processes. Hepatocellular carcinoma (HCC) is one of the most common malignant tumors, ranking high in both incidence and mortality globally. Existing research indicates that m⁶A modification is involved in the development and progression of HCC. However, its specific molecular mechanisms and functions have not been fully elucidated. This review describes the current understanding of the roles of known m⁶A modification factors in HCC and it summarizes the latest advances in research on m⁶A modification in HCC. This review also discusses therapeutic strategies targeting m⁶A modification involvement in HCC, providing a valuable reference to further explore the role of m⁶A modification as a potential therapeutic target in HCC.

Keywords: N⁶-methyladenosine, hepatocellular carcinoma, research progress, therapeutic strategies

1. 引言

肝脏是人体的重要器官，具有代谢、免疫等多种功能[1]。但各种肝脏疾病威胁着人类健康，例如肝炎、肝硬化和肿瘤[2]，酒精、肥胖和病毒感染等都是导致肝脏疾病发生发展的危险因素，肝癌是全球第六大常见癌症和第二大癌症相关死亡原因[3]。目前肝癌的治疗手段包括手术、放化疗、分子靶向治疗和免疫检查点治疗[4]，它们在提高患者生存率和减少肿瘤复发等方面发挥了重要作用，尽管如此，治疗的效果仍不理想。因此，深入研究肝癌发生发展的分子机制，寻找新的治疗靶点以及有效的治疗手段，是当前肝癌研究过程中亟待解决的问题。新的证据显示m⁶A修饰在肝癌的发生发展中扮演着重要角色。N⁶-甲基腺苷（m⁶A）是指在腺苷酸的N⁶位置上添加一个甲基基团，主要在终止密码子区和3'非编码区（3'UTR）附近富集，发生在DRACH或RRACH固定基团中（D代表A、G或U，R代表A或G，H代表A、C或U）。m⁶A是真核生物mRNA中最丰富的mRNA修饰之一，它几乎影响mRNA生命周期的每个阶段[5]。m⁶A是通过甲基转移酶、去甲基化酶和结合蛋白完成动态可逆的修饰过程，这使得其在细胞通讯间起到关键作用，对于调节RNA代谢、mRNA稳定性和剪切翻

医学新视角 2024年4月第1卷第2期:82-88
The New Perspectives Journal of Medicine. 2024; 1(2): 62-88.

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译等方面发挥重要作用[6,7]。同时，异常的m⁶A修饰会导致细胞的恶性增殖，从而促进肿瘤发生。由于m⁶A修饰在基因调控方面有着重要作用，对m⁶A修饰在肝癌中研究进展的归纳总结有助于全面揭示肝癌的分子机制。本文将介绍目前已知的m⁶A修饰因子在肝癌中的作用以及最新的研究进展，为寻找肝癌治疗靶点提供参考。

2. m⁶A甲基化过程的修饰因子

m⁶A修饰过程中的参与者可以根据其功能分为"书写器（writers）"、"擦除器（erasers）"和"阅读器（readers）"三种类型。其中"书写器（writers）"即甲基转移酶，功能是催化形成m⁶A修饰，"擦除器（erasers）"即去甲基化酶，功能是消除m⁶A修饰，而"阅读器（readers）"即结合蛋白，负责识别已经形成的m⁶A修饰。三种参与者在m⁶A修饰过程中建立动态可逆的信号调节网络。33个m⁶A RNA甲基化调节因子如表1所示。

2.1. m⁶A甲基转移酶（writers）

甲基转移酶是以S-腺苷甲硫氨酸（S-adenosylmethionine，SAM）作为甲基供体参与催化RNA的甲基化修饰过程。这些甲基转移酶包括METTL3 、METTL14 、WTAP、RBM15 /RBM15B、ZC3H13 、KIAA1429、CBLL1、

ZCCHC4、METTL16 、METTL5、PCIF1[8-10]。METTL3是最早被证明具有m⁶A催化作用的酶，近些年来发现METTL3与另一活性成分METTL14可以组合成为异二聚体核心，并与其他分子形成甲基转移酶复合物（MTC）[11]，如WTAP、RBM15 /RBM15B、ZC3H13、KIAA1429、CBLL1。在复合物结构中METTL3是主要的催化因子，而METTL14则是重要的支撑结构。在细胞核中，METTL3与调节因子WTAP（Wilms Tumor 1 associated protein）结合，该蛋白将整个METTL3:METTL14:WTAP 三元复合物重新定位到核斑点[12]，而核斑点是丰富的mRNA底物，最终使WTAP在体内发挥作用，目前在哺乳动物、苍蝇、酵母和植物中都发现了这三种蛋白的同源物[13]。该复合体中其他研究较少的亚基包括病毒样m⁶A甲基转移酶相关蛋白（KIAA1429，也称VIRMA）、RNA 结合基序蛋白15/15B（RBM15/15B）和锌指 CCCH 型含13 蛋白（ZC3H13）。与 WTAP 一样，这些辅助蛋白也能调节体内细胞的m⁶A水平。除了MTC外，还确定了其他的m⁶A修饰因子，METTL16负责对U6 snRNA、lncRNA 和pre-mRNA 的内含子进行m⁶A修饰，METTL5负责 18S rRNA 的m⁶A修饰，ZCCHC4负责 28S rRNA 的m⁶A修饰[14]。PCIF1（一种与RNA 聚合酶II的丝氨酸-5-磷酸化羧基末端结构域相互作用的因子）是一种帽特异性腺苷甲基转移酶（CAPAM），目前被鉴定出负责m⁶Am（N⁶、2'-O-二甲基腺苷）的N⁶甲基化[15]。

表1 33个m⁶A RNA甲基化调节因子列表

m⁶A-related Molecule	Full name	type
METTL3	Methyltransferase like 3	"writers"
METTL14	Methyltransferase like 14	"writers"
WTAP	WT1 associated protein	"writers"
RBM15	RNA binding motif protein 15	"writers"
RBM15B	RNA binding motif protein 15B	"writers"
ZC3H13	Zinc finger CCCH-type containing 13	"writers"
KIAA1429	Vir like m⁶A methyltransferase associated	"writers"
CBLL1	Cbl proto-oncogene like 1	"writers"
ZCCHC4	Zinc finger CCHC-type containing 4	"writers"
METTL16	Methyltransferase like 16	"writers"
METTL5	Methyltransferase like 5	"writers"
PCIF1	Phosphorylated CTD interacting factor 1	"writers"
FTO	Fat mass and obesity-associated protein	"erasers"
ALKBH5	α-ketoglutarate-dependent dioxygenase AlkB homolog 5	"erasers"
ALKBH3	α-ketoglutarate-dependent dioxygenase AlkB homolog 3	"erasers"
YTHDF1	YTH N⁶-methyladenosine RNA binding protein 1	"readers"
YTHDF2	YTH N⁶-methyladenosine RNA binding protein 2	"readers"
YTHDF3	YTH N⁶-methyladenosine RNA binding protein 3	"readers"
YTHDC1	YTH N⁶-methyladenosine RNA binding protein C1	"readers"
YTHDC2	YTH N⁶-methyladenosine RNA binding protein C2	"readers"
EIF3A	Eukaryotic translation initiation factor 3 subunit A	"readers"
EIF3H	Eukaryotic translation initiation factor 3 subunit H	"readers"
IGF2BP1	IGF2 mRNA-binding protein 1	"readers"
IGF2BP2	IGF2 mRNA-binding protein 2	"readers"
IGF2BP3	IGF2 mRNA-binding protein 3	"readers"
HNRNPA2B1	Heterogeneous nuclear ribonucleoprotein A2B1	"readers"
HNRNPC	Heterogeneous nuclear ribonucleoprotein C	"readers"
HNRNPG	RNA binding motif protein X-linked	"readers"
LRPPRC	leucine rich pentatricopeptide repeat containing	"readers"
ELAVL1	ELAV like RNA binding protein 1	"readers"
PRRC2A	The proline-rich coiled-coil 2A	"readers"
FMR1	Fragile X messenger ribonucleoprotein 1	"readers"
SND1	Staphylococcal nuclease and tudor domain containing 1	"readers"

医学新视角 2024年4月第1卷第2期:82-88
The New Perspectives Journal of Medicine. 2024; 1(2): 62-88.

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2.2. m6A去甲基化酶（erasers）

这类酶的作用与甲基转移酶的作用相反，通过去除RNA中的N6-甲基腺苷使m6A修饰过程保持动态可逆，被称为"erasers"。目前被发现的有FTO、ALKBH5、ALKBH3[16,17]。FTO（脂肪量和肥胖相关蛋白）是第一个被鉴定出具有去除甲基化修饰作用的蛋白，对体外RNA中的N6-甲基腺苷残基具有高效的去甲基化活性[18]。ALKBH5是第二种被确定的去甲基化酶，其具有催化结构域，能够使单链RNA（ssRNA）和单链DNA（ssDNA）去甲基化，特别是催化ssRNA中m6A的去甲基化[19]。ALKBH5的去甲基化酶活性显著影响核斑点中mRNA的输出、RNA代谢和mRNA加工因子的组装[20]。ALKBH3可以去甲基化RNA中的1-meA和3-meC以及tRNA中的N6-meA，并且ALKBH3修饰的tRNA可以提高蛋白质翻译效率[21]。

2.3. m6A结合蛋白（readers）

要实现下游生物学功能的调节作用，m6A修饰信息需要被具有解析功能的蛋白质识别。m6A结合蛋白（readers）通过与m6A修饰区域特异性结合或改变RNA二级结构使蛋白质更容易与RNA结合等方式完成对m6A修饰信息的识别[22]。"readers"包括YT521-B同源结构域家族蛋白1、2和3（分别为YTHDF1、YTHDF2、YTHDF3），YT521-B同源结构域包含1和2（分别为YTHDC1和YTHDC2），真核翻译起始因子3（EIF3A/H），胰岛素样生长因子2 mRNA结合蛋白（IGF2BP，包括IGF2BP1/2/3），和异质核糖核蛋白（HNRNPs，包括HNRNPA2B1、HNRNPC/G）[23]。富含亮氨酸的五肽重复序列(PPR) 基序蛋白(LRPPRC)、ELAV样RNA结合蛋白1（ELAVL1）、PRRC2A（The proline-rich coiled-coil 2A）[24]。脆弱 X 信使核糖核蛋白1（FMR1，也称FMRP）、含有葡萄球菌核酸酶结构域的蛋白1（SND1）[25]。这些结合蛋白的功能丰富多样，负责识别不同位点的m6A修饰。在YTH域家族中，YTHDF1通过与起始因子相互作用来增强mRNA翻译效率和蛋白质合成[26]。YTHDF2通过识别m6A修饰，将mRNA募集到衰变位点来诱导其降解[27]。YTHDF3与YTHDF1协同作用促进mRNA的翻译[28]。YTHDC1和YTHDC2主要在核内实现甲基化识别功能，分别起到调节mRNA剪切[29]和刺激mRNA翻译的功能。EIF3蛋白可以和mRNA的5'UTR端的m6A修饰位点结合促进翻译效率[30]。IGF2BP1/2/ 3被认为能结合 m6A修饰位点，并通过增强mRNA稳定性的方式促进mRNA表达[31]。HNRNP家族成员也可以识别m6A修饰，HNRNPA2B1具有调节转录本交替剪接的能力，它通过与DGCR8蛋白相互作用，以m6A依赖性方式加速初级miRNA（pri-miRNA）的处理过程[32,33]，而HNRNPC/G识别m6A后可以调控mRNA的丰度和剪接。IGF2BP1/2/3被认为可以增强m6A修饰的mRNA稳定性和翻译效率[34]。LRPPRC是由大量的PPR蛋白构成，PPR蛋白与RNA结合可以调节RNA的转录加工等过程[35]。ELAVL1是一种RNA结合蛋白，优先与3'UTR中富含AU或U的元素结合[36]，参与多种肿瘤生物过程。PRRC2A可以特异性结合甲基化RNA，类似于IGF2BPs的RNA结合结构域（RBD）的情况，它可以识别m6A的转录本并

调节mRNA稳定性[37]。FMR1是一种与临床相关的、依赖于RNA序列的m6A结合蛋白，FMR1通过与核糖体结合，抑制目标mRNA的翻译[38]。SND1 是一种多功能蛋白质，具有在转录后水平调节基因表达的作用，SND1还可以结合m6A修饰的mRNA并保持mRNA稳定性[39]。总的来说，m6A修饰对RNA代谢的各个方面都有重要影响，但具体的作用取决于不同m6A修饰因子的功能。

3. m6A修饰在肝癌发生发展中的双重作用

3.1. "writers"在肝癌发生发展中的作用

m6A修饰通过多种方式调节RNA的剪切、翻译和降解，对肝癌的发育和转移都有着不同的影响（促癌或抑癌）。METTL3和METTL14作为甲基转移酶复合物的关键组分在肝细胞癌中的表达作用恰恰相反，单独对METTL3或METTL14敲低，肝细胞癌中所表现出的mRNA表达以及各种生物过程均不相同，这表明二者之间可能存在相反的调节作用[40]。事实上，METTL3通过m6A-YTHDF2依赖性方式抑制肝细胞癌中SOCS2的表达，将METTL3敲除后，SOCS2 mRNA的表达增加，并且大大减少了肝细胞癌的增殖和迁移[41]。而缺氧导致的METTL14抑制导致了YTHDF2依赖性SLC7A11沉默，防止肝细胞癌铁死亡，促进肝细胞癌发展[42]。此外，METTL14还通过介导lncRNA和circRNA的m6A修饰来参与肝细胞癌的进展[43,44]。WTAP是甲基转移酶的另一关键组分，在肝癌中显著上调。WTAP的敲低提高了肝细胞癌的自噬水平，抑制肝细胞癌的增殖，而WTAP的过表达抑制肝细胞癌的自噬并促进肝癌发展[45]。RBM15/15B的上调也与肝癌的不良预后相关，有研究表明RBM15B可以被YY1转录激活，通过m6A依赖方式调节TRAM2 mRNA的稳定性，促进肝细胞癌的侵袭和增殖，同时也提高了肝细胞癌的索拉非尼耐药性[46]。ZC3H13在肝癌中起到抑制作用，有研究证实ZC3H13在肝细胞癌中的表达显著降低，其上调抑制了肝细胞癌（HCC）的生长和增殖[47]。KIAA1429被认为是最大的m6A甲基转移酶，在大多数癌症中都具有致癌作用。KIAA1429可以通过上调ID2 mRNA的m6A修饰水平来抑制ID2表达，促进肝细胞癌的侵袭与增殖[48]。ZCCHC4主要作用于人28S rRNA，同时其在肝癌中高表达，ZCCHC4能够促进28S rRNA中的m6A修饰，促进肝癌细胞生长[49]。甲基转移酶METTL16也在肝癌中起着关键的作用，其可以通过m6A依赖性方式下调lncRNA RAB11B-AS1，抑制肝细胞癌凋亡[50]。CBLL1也称为HAKAI，是负责稳定甲基转移酶复合物的关键成分[51]，在结直肠癌（CRC）中，其过表达会带动上皮细胞向间充质细胞的转化，随着E-钙粘蛋白的下调和N-钙粘蛋白的上调，使肿瘤细胞更具侵袭性[52]。此外，CBLL1过表达会引起体内肿瘤细胞的非微转移[53]。在肝癌中，HAKAI在HCC细胞中的过表达显著增加了锚定依赖性生长、球形细胞形成能力和异种移植中的肿瘤生长，而HAKAI缺失会导致相反的效果，表明其在HCC中的致癌作用[54]。METTL5是一种修饰特定位点的甲基转移酶，可增加癌症中的蛋白质翻译效率，据最新的研究报道，METTL5的上调可以促进c-Myc的稳定性，激活其下游的糖酵解基因，驱动葡萄糖的代谢重编程信号通路，从而

医学新视角 2024年4月第1卷第2期:82-88
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促进HCC的增殖和转移[55]。PCIF1是催化mRNA 5'端2'-O-甲基化腺苷的m⁶A甲基化的酶，有实验揭示了PCIF1在调节VSV发病机制方面的作用[56]，最新的研究表明PCIF1表达在CRC中上调并与患者生存呈负相关，具体来讲，PCIF1通过m⁶A修饰靶向作用于FOS、IFITM3和STAT1，以一种环境依赖性机制调节CRC的生存以及对抗病毒药物PD-1的反应[57]。目前关于PCIF1的研究较为不足，在肝癌中的促癌或抑癌机制还需进一步探索。

3.2. "erasers"在肝癌发生发展中的作用

与其他的有明确促癌或抑癌作用的m⁶A修饰因子不同，FTO和ALKBH5在肝癌中的作用并不固定。一方面，FTO过表达与HCC的不良结局相关，其可以通过介导PKM2 mRNA的去甲基化，加速翻译进程，从而促进HCC[58]。同时，有研究表明，AMD1在人HCC中富集提示预后不良，而高水平的AMD1增强了IQGAP1与FTO之间的相互作用，提高FTO表达并增加HCC干性[59]。另一方面，FTO在HCC中也可以起到保护作用，在HCC起始过程中Cul4a的FTO依赖性动态mRNA去甲基化有助于抑制HCC的发展[60]。其他实验也证明了这一现象，目前新鉴定出一种circGPR137B，其能够通过circGPR137B/miR-4739/FTO反馈回路抑制HCC肿瘤发生和转移[61]。另一个去甲基化因子ALKBH5也在HCC发挥双重作用，具体来说，LINC02551是HCC生长和转移所必须的lncRNA，而ALKBH5对LINC02551的m⁶A修饰增强了DDX24的稳定性，促进HCC的发展[62]。但ALKBH5介导的m⁶A去甲基化还会导致LYPD1的转录后抑制，进而抑制HCC进展[63]。可能是由于这些蛋白质结构存在差异导致其底物具有特异性，通过作用不同的靶点使得在肿瘤中具有不同的促癌抑癌作用，但具体的双重作用机制还有待进一步探索。与前两个去甲基化因子不同的是，ALKBH3过表达在肝癌中具有促癌作用[64]，HIF-1α激活的lncRNA ALKBH3-AS1可以增强ALKBH3 mRNA的稳定性，从而促进肝癌细胞的增殖与侵袭[65]。

3.3. "readers"在肝癌发生发展中的作用

结合蛋白主要通过识别和结合RNA的m⁶A修饰位点来参与RNA的各种进程。最近的研究表明，YTHDF1过表达与HCC不良预后、T细胞浸润低密切相关[66]。具体来讲，YTHDF1可以通过激活PI3K／AKT／mTOR信号通路并诱导EMT来促进HCC的进展[67]。乙型肝炎病毒（HBV）感染是HCC的主要危险因素，YTHDF2介导的m⁶A修饰稳定了MCM2和MCM5的mRNA，从而促进细胞周期进展和HBV相关的HCC进展[68]。与同家族的酶一样，HCC中的YTHDF3表达显著，其通过促进磷酸果糖激酶PFKL的表达来促进HCC的有氧糖酵解[69]。YTHDC1/2也在HCC起到重要作用，据研究报道YTHDC1/2都是疾病治疗的靶点[70]，m⁶A修饰的FAM111A-DT/YTHDC1/KDM3B/FAM111A调控通路促进了HCC的生长[71]。目前关于EIF3A/H在肝癌中的研究较少，但YTHDF3可以招募EIF3A促进靶基因翻译，引起结直肠癌（CRC）的化学耐药性[72]。METTL3也可以与EIF3H相互作用增强翻译、形成密集堆积的多核糖体和致癌转化[73]。

IGF2BP1/2/3是作用于关键靶RNA的翻译和稳定性的转录后调节。其中IGF2BP1不仅调节c-Myc/p16轴促进肝内胆管癌（ICCA）生长和抑制衰老，还激活ZIC2/PAK4/AKT/MMP2通路诱导肿瘤转移[74]；新发现的一种癌症睾丸相关lncRNA（LINC01977）与IGF2BP2相关，IGF2BP2介导的m⁶A修饰增强了LINC01977的稳定性，数据表明LINC01977与RBM39相互作用，通过抑制Notch2泛素化和降解促进肝细胞癌的进展[75]。同样的，敲低IGF2BP3可显著抑制HCC中的细胞增殖和迁移[76]。CHD1L是HCC的驱动基因，而最新的研究表明，CHD1L可以通过激活HNRNP A2／B1-nmMYLK通路预防LPS诱导的HCC细胞死亡[77]。另外，HNRNPC/G参与着核酸代谢，从机制上来讲，HNRNPC下调通过降低 HIF6A表达来抑制IL-3/STAT1介导的HCC转移[78]。LRPPRC是最新发现的m⁶A修饰因子，有研究证明了其在肝癌中的促癌作用。LRPPRC在人肝癌组织中表现出显著的上调，同时LRPPRC与PD-L1呈正相互作用，与CD8+、CD4+T细胞浸润和趋化因子CXCL9和CXCL10呈负相关，此外，LRPPRC抑制减轻了小鼠模型中的肿瘤生长，并改善了肿瘤的抗肿瘤免疫和免疫浸润[79]。ELAVL1也被称为HuR，其可以通过与miR-122的3'末端强结合而对miR-122生物发生至关重要，同时，有实验证明了PLK1-ELAVL1／HuR-miR-122信号传导促进了HCV的增殖[80]。PRRC2A在肿瘤发生和免疫调节中起着至关重要的作用，在肝癌中的PRRC2A表达上调，体外实验证实沉默PRRC2A可以抑制HCC细胞的增殖和转移能力[81]。FMR1也称为FMRP，其可以调节STAT3 mRNA的定位和翻译，最新的研究显示，FMRP在HCC组织中高表达，FMRP敲低在体外和体内有效抑制HCC转移[82]。SND1是miRNA调节复合物RISC的一个亚基，已被列为HCC的癌基因。具体来讲，SND1与磷酸甘油酸变位酶5（PGAM5）相互作用促进线粒体自噬以及肝癌进展[83]。

4. m⁶A在肝癌临床治疗中的作用

4.1. m⁶A在肝癌化疗中的作用

化疗是最有效的临床治疗方式之一，在很多恶性疾病中都取得了显著的效果，但耐药性是降低化疗效果的主要障碍。中晚期肝癌有局部的经肝动脉插管化疗栓塞术、经肝动脉持续灌注化疗以及全身静脉化疗等治疗方式，常用的有铂类、阿霉素类、紫杉醇、氟尿嘧啶等化疗药物。目前，尽管在RNA表观遗传修饰的研究中，m⁶A在肝癌治疗中的研究较少，但m⁶A修饰在其它多个癌种的化疗中都发挥了一定作用。铂（Pt）药物是使用最广泛的抗癌药物之一[84]，有研究报道m⁶A甲基转移酶有助于肿瘤对顺铂（首个获批的铂类药物）的耐药性。METTL3介导睾丸生殖细胞肿瘤（TFAP2C）mRNA上的m⁶A修饰，并通过招募IGF2BP1促进其稳定性，从而增强顺铂抗性[85]。METTL3还在非小细胞肺癌（NSCLC）中促进FSP1的表达，增强顺铂治疗诱导的FSP1介导的铁死亡[86]。紫杉醇（Taxol）和蒽环类药物也在癌症治疗中起重要作用，METTL3可以通过m⁶A修饰方式调节ERRγ的剪切，促进ERRγ的表达决定紫杉醇耐药性[87]。METTL3还通过加速pri-microRNA-7-221p成熟来促进MCF-3乳腺癌细胞的阿霉素耐药性[88]。

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4.2. m⁶A在肝癌免疫治疗中的作用

免疫治疗是通过诱导、增强或是抑制免疫应答来治疗疾病。PD-1是众所周知的免疫抑制分子，可以通过抑制T细胞活性来抑制免疫反应，促进肿瘤的免疫耐受。有研究报道，甲基转移酶WTAP介导的m⁶A修饰通过与结合蛋白IDF2BP3共同作用增强了外泌体circCCAR1的稳定性，而circCCAR1被CD8+ T细胞吸收，并通过稳定PD-1蛋白导致CD8+ T细胞功能障碍[89]。IDO1通过调节T细胞相关免疫应答和促进免疫抑制的活化来负责肿瘤免疫逃逸，而Abrine是一种IDO1抑制剂，与抗PD-1抗体对肝癌的治疗具有协同作用[90]。在非酒精性脂肪性肝炎相关HCC（NASH-HCC）中YTHDF1高表达，同时通过EZH2-IL-6信号传导促进NASH-HCC肿瘤发生，其招募并激活髓源性抑制细胞（MDSCs）导致细胞毒性CD8 T细胞功能障碍[91]。免疫检查点阻断（ICB）这种治疗方法已显示出抑制复发和转移的潜力，有实验将ICB和热消融（TA）联合起来对HCC进行治疗，将肿瘤相关抗原（TAAs）和去甲基化酶FTO共同递送到肿瘤浸润树突状细胞（TIDC）中，结果显示，可以改善效应T细胞的肿瘤浸润并产生免疫记忆，与ICB治疗协同作用，抑制远处HCC生长和肺转移[92]。这些研究揭示了m⁶A修饰因子在免疫治疗中的新功能，此外，其他的m⁶A修饰因子在肝癌的免疫治疗中的作用仍有待确定。

4.3. m⁶A在肝癌靶向治疗中的作用

在肝癌中，索拉非尼和仑伐替尼是常用的治疗药物，有研究证明FOXO3是METTL3的关键下游靶标，同时METTL3消耗可通过取消已确定的METTL3介导的FOXO3 mRNA稳定作用而显著增强索拉非尼对HCC的耐药性，而过表达FOXO3则可恢复m⁶A依赖性索拉非尼敏感性[93]。此外，沉默circRNA-SORE显著的提高了索拉非尼诱导HCC凋亡的功效[94]。FZD10在肝脏干细胞中的激活是由FZD10 mRNA的METTL3依赖性N⁶-甲基腺苷甲基化介导的，而FZD10/β-连环蛋白/c-Jun/MEK/ERK信号通路决定了肝癌细胞对仑伐替尼治疗的反应[95]。另一种甲基转移酶KIAA1429通过介导m⁶A甲基化来促进索拉非尼耐药的肝细胞癌侵袭、迁移和上皮间充质转化（EMT）[96]。总的来说，m⁶A修饰在靶向耐药性中的作用逐渐被识别，这促进了未来肝癌的靶向治疗，但还需探索m⁶A修饰因子在耐药中的具体作用。

5. 总结与展望

m⁶A修饰在肝癌的发生发展以及耐药性中起着重要作用，关于m⁶A修饰因子的研究结果不断增加，揭示了在肿瘤中m⁶A修饰的功能，但目前很多研究专注于甲基转移酶复合体的功能以及酶的催化活性上，其他的m⁶A修饰因子的机制研究却很少涉及。因此，本文总结了m⁶A修饰在肝癌中的机制、作用和治疗耐药性等方面的最新进展，探索m⁶A修饰因子的确切功能，为开发药物的关键靶点提供参考。

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