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RNA m⁶A修饰在肿瘤发展及免疫治疗中的研究进展

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摘要 N6-甲基腺嘌呤(N6-methyladenosine, m⁶A)是指在腺苷的N6位置发生的甲基化修饰, 是真核mRNA中最常见的表观遗传修饰方式。m⁶A甲基化的紊乱会导致基因转录和翻译过程异常, 从而促进癌症的发生和发展。最近的研究表明, m⁶A甲基化不仅可以影响肿瘤的细胞增殖和抑制信号网络, 还能调节肿瘤免疫原性。该研究聚焦于探讨m⁶A调节因子在调控肿瘤关键信号通路中的相关机制, 并阐述了m⁶A表观遗传修饰调节免疫检查点的表达方式。这将为理解m⁶A表观遗传修饰在调节肿瘤免疫逃逸中的作用和机制提供一个新思路。此外, 该文还强调了基于m⁶A修饰的靶向联合免疫治疗策略的前景和发展方向, 这有望提高免疫检查点抑制剂的治疗效果。

关键词 m⁶A甲基化; 肿瘤发展; 肿瘤免疫; 免疫治疗

Research Progress on RNA m⁶A Modification in Tumor Development and Immunotherapy

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Abstract m⁶A (N6-methyladenosine) refers to the methylation modification that is observed at the N6 position of adenosine and is the most prevalent epigenetic modification seen in eukaryotic mRNA. Disruptions in

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m⁶A methylation can result in aberrant gene transcription and translation procedures, thereby facilitating the onset and progression of cancer. Recent investigations have indicated that m⁶A methylation not only impacts tumor cell proliferation and inhibitory networks but also regulates tumor immunogenicity. The objective of this analysis is to investigate the pertinent mechanisms of m⁶A regulatory factors in governing vital signaling pathways in tumors and elucidate how m⁶A epigenetic modification controls the expression of immune checkpoints. By undertaking this, this study offers a fresh perspective on the role and mechanism of m⁶A epigenetic modification in regulating tumor immune escape. Furthermore, the article emphasizes the potential and future direction of targeted combination immunotherapy strategies based on m⁶A modification, which could enhance the effectiveness of immune checkpoint inhibitors.

Keywords m⁶A methylation; tumorigenesis; tumor immunity; immunotherapy

化学修饰是一种高度特异性和有效的方法,用于调节生物大分子的功能。所有生物大分子(如蛋白质、RNA、DNA、糖和脂质)都会受到合成后的共价修饰的影响。最近的研究表明, RNA不仅在蛋白质合成的中间体中发挥作用,而且在转录后的调控中扮演重要角色,可直接影响基因的表达。RNA甲基化修饰是一种重要的RNA修饰形式,包括N6-甲基腺嘌呤(m⁶A)、N1-甲基腺嘌呤(N1-methyladenosine, m¹A)、5-甲基胞嘧啶(5-methylcytidine, m⁵C)、假尿嘧啶(pseudouridine, Ψ)和5-羟甲基胞嘧啶(5-hydroxymethylcytosine, hm⁵C)^[1], 均已被报道影响多种生物过程。在各种表观遗传修饰中, m⁶A是真核细胞中最丰富和保守的内部修饰形式^[2], 存在于mRNA、长非编码RNA(long non-coding RNA, lncRNA)、miRNA(microRNA)等^[3-6], m⁶A通过在RNA的第六个含氮碱基上添加甲基的形式, 影响修饰RNA的稳定性和翻译。此外, RNA甲基化修饰也参与了疾病进展等多种生物过程, 成为肿瘤发生发展中的重要调节因子。

m⁶A甲基化修饰是通过甲基转移酶、去甲基化酶和m⁶A识别蛋白的调控实现的。它们分别负责添加、去除或识别m⁶A修饰, 影响含有m⁶A RNA的多种代谢, 并保持m⁶A修饰的动态平衡(图1)^[7]。m⁶A修饰可以通过改变目标基因的表达水平, 进而影响相关细胞过程和生理功能。在分子机制上, m⁶A参与RNA代谢的各个步骤, 包括mRNA翻译、降解、剪接和折叠^[8-9]。最近的研究表明, m⁶A修饰还调控了免疫细胞活化并使得免疫细胞浸润到肿瘤微环境(tumor microenvironment, TME)中, 因此可能影响免疫治疗的疗效^[10-11]。本综述重点介绍了m⁶A调节因子的最新研究进展, 包括m⁶A在肿瘤发生和癌症进

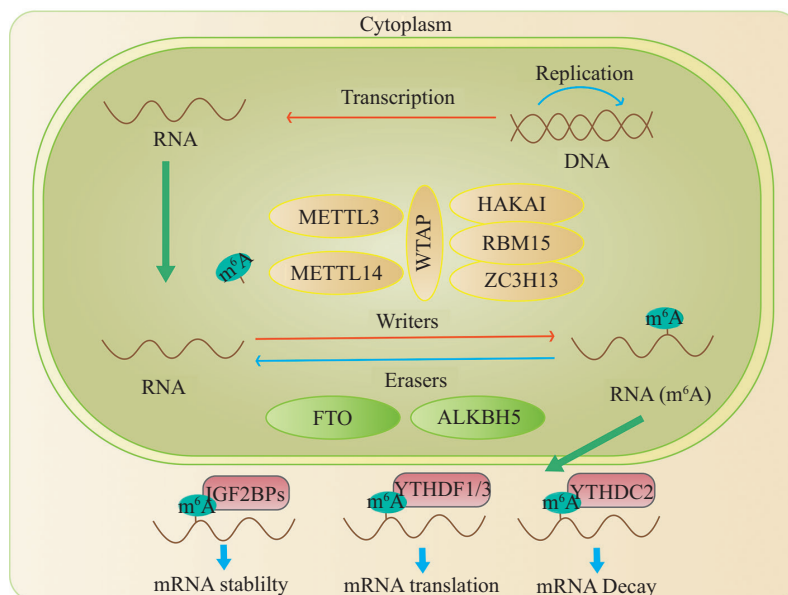
展中的功能及m⁶A表观遗传修饰如何调节免疫检查点的表达, 从而为基于m⁶A甲基化修饰的肿瘤免疫治疗提供了新的思路。

1 m⁶A调节器及其在肿瘤中的作用

1.1 m⁶A写入器

m⁶A写入器(writers)是一类催化m⁶A形成的甲基转移酶, 它通过复合物将m⁶A组装到靶RNA上。m⁶A甲基转移酶复合物(methyltransferase complex, MTC)由甲基转移酶样蛋白3-甲基转移酶样蛋白14(methyltransferase like 3 - methyltransferase like 14, METTL3-METTL14)异二聚体、Wilms肿瘤1相关蛋白(Wilms tumor 1-associated protein, WTAP)、RNA结合基序蛋白15(RNA binding motif protein 15, RBM15)、RNA结合基序蛋白15B(RNA binding motif protein 15B, RBM15B)、Cbl原癌基因样1(Cbl proto oncogene like 1, CBLL1也被称作HAKAI)、病毒样m⁶A甲基转移酶相关蛋白(Vir-like m⁶A methyltransferase associated, VIRMA也称作KIAA1429)和含锌指CCCH型13(zinc finger CCCH-type containing 13, ZC3H13)组成^[12-14]。

其中, METTL3是m⁶A MTC的催化核心, 利用S-腺苷甲硫氨酸(S-adenosyl methionine, SAM)作为甲基供体^[15]。而METTL14为METTL3提供结构支撑, 并与其形成稳定的异源二聚体核心复合物, 对于底物的识别至关重要^[16-17]。METTL3-METTL14二聚体介导m⁶A在哺乳动物RNA上的沉积^[18], 在不同的肿瘤或某些情况下的同一肿瘤中发挥癌基因和抑癌基因的双重作用^[13]。细胞质METTL3直接促进数种癌基因包括表皮生长因子受体(epidermal growth factor receptor, EGFR)和Hippo通路效应物TAZ等的翻译, 但尚

图1 m⁶A RNA修饰机制及其生物学功能Fig.1 m⁶A RNA modification machinery and its biological functions

不清楚这一功能是否由其催化活性介导^[19]。在急性髓系白血病 (acute myeloid leukemia, AML) 中, METTL3 表达水平高, 在 AML 细胞增殖中扮演必需的角色, 并对维持 AML 细胞未分化表型及在小鼠异种移植模型 AML 的发生过程至关重要^[20-21]。在分子水平上, METTL3 通过促进致癌靶基因的翻译发挥作用, 例如修饰编码致癌转录因子 MYC37 的 mRNA。在免疫缺陷小鼠中, METTL3 的下调会导致细胞周期停滞、白血病细胞分化及无法建立白血病模型^[20]。尽管 METTL14 在白血病中没有显著表达, 但其在 AML 中也是一种癌基因, 通过 myc 依赖方式发挥作用^[22]。ZHOU 等^[23]发现, 在肾透明细胞癌 (clear cell renal carcinoma, ccRCC) 中, m⁶A 调节因子的改变导致了 m⁶A 水平与包括生存期在内的临床参数恶化之间的显著关联。VHL-HIF-METTL3/14 通路可能参与了 ccRCC 中 m⁶A 的调控, PI3K-mTOR 和 p53 信号通路可能是 ccRCC 中 m⁶A 的下游靶点^[23]。此外, METTL14 参与肾癌中 m⁶A 修饰和嘌呤受体 P2RX6 (purinergic receptor P2X, P2RX6) 蛋白翻译的下调^[24]。在肝癌中, METTL3 过表达导致细胞因子信号转导抑制因子 2 (Suppressors of cytokine signalling 2, SOCS2) mRNA 降解, 从而驱动肿瘤生长^[25], 并导致 SNAIL 翻译上调, 从而使癌细胞发生上皮-间充质转化。而 METTL14 蛋白低表达, 被证明具有与 METTL3 相反的作用并通过与微处理器复合物 DGCR8 相互作用和促

进 miRNA 成熟来降低肝癌细胞的转移潜能^[26]。在肺癌中 METTL3 的致癌作用也有报道。与正常组织相比, METTL3 在人肺癌组织中过表达^[19], METTL14 蛋白和转录本表达丰度也均增高。

WTAP 不具有甲基化活性, 是复合物的调节亚基, 其通过招募 METTL3-METTL14 复合物形成催化核心, 作用于靶 RNA^[27]。METTL3 的敲除和过表达均导致 WTAP 蛋白表达上调, 提示 METTL3 水平在 WTAP 蛋白稳态中起关键作用。然而, 仅上调 WTAP 而没有功能性 METTL3 不足以促进细胞增殖。因此, WTAP 的致癌功能与功能性 m⁶A 甲基化复合物密切相关。研究表明, WTAP 影响 MAPK (mitogen-activated protein kinase)^[28]、AKT^[14]、Wnt^[29] 和 NF-κB^[30] 信号通路, 通过调控下游靶点 EGR3^[31]、HK2^[32]、ETS1^[33] 和 CAV-1^[30] 促进肿瘤进展。

RBM15 是 SPEN (split-end) 家族成员。位于染色体 1p13.3。它能够编码 RNA 结合蛋白 RBM15/RBM15B 的蛋白同源物。RBM15/RBM15B 是 WTAP 的互作伴侣, 通过结合富含 U 的 RNA 共识序列将其招募到 RNA 的特定位点^[20], 从而在 XIST 和细胞 mRNA 中介导 m⁶A 形成^[34]。研究表明, 敲低 RBM15/15B 的表达显著降低 m⁶A 的总体水平, 表明 RBM15/15B 在 MTC 中发挥重要作用^[34]。在肿瘤进展方面, RBM15 在 MTC 中发挥的作用仅在白血病、肝癌和喉癌中有报道。

KIAA1429(VIRMA)是MTC的重要亚单位,它在MTC中发挥支架作用。KIAA1429通过招募MTC到3'-UTR和接近终止密码子的位置^[14],有选择地介导甲基化。研究发现,KIAA1429能诱导*GATA3*前体mRNA 3'-UTR上m⁶A甲基化,导致*GATA3*前体mRNA降解,从而促进肝癌的进展和转移。此外,KIAA1429在肝癌组织中显著上调,并通过提高DNA结合抑制因子2(inhibitor of DNA binding 2, *ID2*) mRNA中的m⁶A水平来抑制*ID2*表达,从而促进肝癌细胞的迁移和侵袭^[35]。

最新研究发现,ZC3H13是一种具有保守锌指结构的转录因子,它在RNA m⁶A甲基化中扮演关键角色,通过介导ZC3H13-WTAP复合体的核内定位发挥作用^[13,36]。该因子在多种癌症中高表达,并与预后相关^[37]。锌指CCCH结构域蛋白13(zinc finger CCCH-type containing 13, ZC3H13)主要促进MTC与RNA的结合^[38]。此外,已证明ZC3H13具有肿瘤抑制作用,分别通过调节Ras-ERK和Wnt信号通路抑制结直肠癌和乳腺癌的进展和转移^[39-40]。

另外,研究发现甲基转移酶样蛋白16(METTL16)^[41]是U6剪接体小核RNA(snRNA)的甲基转移酶,并通过“UACAGAGAA”序列的催化底物来调节SAM的稳态。在SAM缺失条件下,METTL16诱导剪接一个保留内含子,从而促进*MAT2A*的表达和提高SAM的水平。然而,METTL16在癌症中的作用需要进一步研究。

1.2 m⁶A擦除器

2011年,JIA等^[42]首次在体内证明脂肪量和肥胖相关蛋白(fat mass and obesity-associated protein, FTO)可以逆转m⁶A。这意味着FTO是第一个被发现的m⁶A去甲基化酶^[42]。2017年首次报道*FTO*基因对肿瘤进展的影响^[43]。研究表明,FTO可以降低*ASB2*和*RARA* mRNA转录本上的m⁶A水平,并调节这些靶点的表达,从而促进AML进展。此外,FTO也在肝癌、肺癌、乳腺癌、宫颈癌和结直肠癌的肿瘤进展中起到促进作用^[44-46]。而在肾癌、胰腺癌、甲状腺癌和胆管癌中,FTO具有肿瘤抑制作用^[47-48]。

在FTO之后,发现了第二个m⁶A去甲基化酶,即ALKBH5。ALKBH5参与多种癌症的生物学进展,并发挥着致癌和抑癌的双重作用。在乳腺癌中,ALKBH5的表达受到缺氧诱导因子1 α (hypoxic inducible factor 1 α , HIF1 α)和HIF1 β 诱导,过表达ALKBH5可以在无氧低氧暴露情况下降低*NANOG* mRNA的甲基

化水平,并增加乳腺癌干细胞的数目^[49]。

1.3 m⁶A甲基读取器

m⁶A写入器和擦除器的相互作用对m⁶A修饰的动态可逆调节起着决定性作用。不同种类m⁶A甲基读取器丰富了m⁶A生物功能的多样性。m⁶A读取器包括YTH结构域(YTH N6-methyladenosine RNA binding protein F1, YTHDF)家族蛋白和胰岛素样生长因子-2 mRNA结合蛋白(insulin growth factor 2 mRNA binding protein, IGF2BP)家族蛋白。

位于细胞质中的YTHDF家族成员包括YTHDF1、YTHDF2和YTHDF3。报道显示这三种读取器表现出不同的功能。YTHDF1促进mRNA的翻译,YTHDF2促进mRNA的降解,YTHDF3促进mRNA的翻译和降解,但对于这三种读取器发挥不同功能的机制尚不清楚^[50]。研究表明,YTHDF1/3在癌症中只表现出致癌作用^[51],TCGA数据库分析显示,YTHDF1在肝细胞癌(hepatocellular carcinoma, HCC)中的表达显著上调,并且与病理分期呈正相关。Kaplan-Meier分析显示,YTHDF1低水平表达与HCC患者更好的生存率相关。此外,*YTHDF1*共表达基因的GO和KEGG通路分析表明,YTHDF1在调节HCC细胞的细胞周期和代谢中发挥重要作用。YTHDF2在肺癌组织中上调,促进肺癌细胞生长,并与6-磷酸葡萄糖酸脱氢酶(glucose-6-phosphate dehydrogenase, G6PD) 3'-UTR上的m⁶A修饰位点结合。这样促进了肺癌细胞中*G6PD* mRNA的翻译,增强了磷酸戊糖途径(pentose phosphate pathway, PPP)通量,从而推动了肿瘤生长^[52]。在结直肠癌(colorectal cancer, CRC)中,lncRNA-GAS5(long noncoding RNA GAS5)与Yes相关蛋白(Yes-associated protein, YAP)的WW结构域直接结合,并促进其磷酸化和泛素介导的降解,这减弱了YAP介导的*YTHDF3*转录作用。研究显示YTHDF3能选择性地与m⁶A甲基化的GAS5结合并且是可逆的,触发其降解并形成GAS5-YA-YTHDF3负反馈回路,从而促进CRC的发展^[53]。

与YTH结构域家族蛋白不同,IGF2BP家族蛋白通过KH结构域特异性识别m⁶A修饰的RNA,不促进mRNA降解而是稳定mRNA。IGF2BP家族包括IGF2BP1、IGF2BP2和IGF2BP3。这些蛋白在多种癌症类型中高度表达,并参与许多不同的分子机制。IGF2BP1和IGF2BP3是由肿瘤和胎儿组织产生的癌胚蛋白,但在成人组织^[54]中表达下调。最近研究发

现, IGF2BP1能与SOX2 mRNA的3'-UTR m⁶A位点结合, 抑制SOX2 mRNA的降解, 从而促进子宫内膜癌细胞的增殖和转移^[55]。此外, METTL3依赖IGF2BP1延长色素盒8(chromobox 8, *CBX8*)mRNA的半衰期, CBX8募集赖氨酸甲基转移酶2B(lysine methyltransferase 2B, *KMT2B*)和Pol-II到富含亮氨酸重复序列的G蛋白偶联受体5(leucine rich repeat containing G protein-coupled receptor 5, *LGR5*)的启动子并维持H3K4me3状态。这些因素共同促进LGR5的表达, 最终维持CRC细胞的干性并增强其化疗耐药性^[56]。

综上所述, m⁶A RNA修饰的各个组成部分与癌症密切相关, 它们普遍具有促进癌症的作用。然而, 它们的作用机制以及特定靶RNA似乎与癌症类型有关。

2 m⁶A修饰与抗肿瘤免疫

肿瘤免疫治疗现已成为癌症治疗的主流方法之一, 并取得了显著的成功。免疫检查点抑制剂(immune checkpoint inhibitors, ICIs)是重要的免疫治疗药物, 主要靶向细胞毒性T淋巴细胞相关蛋白4(cytotoxic T-lymphocyte-associated protein 4, CTLA4)、程序性死亡受体1(programmed cell death-1, PD-1)和程序性死亡受体-配体1(programmed cell death-ligand 1, PD-L1), 在过去几十年中取得了显著的成功, 改善了晚期癌症患者的预后。尽管ICIs联合其他疗法取得了一定效果, 但许多患者可能对治疗无反应或反应低, 因此耐药和复发问题成为了当前的治疗难题^[57]。近年来, 多项研究表明m⁶A修饰在调节肿瘤免疫逃逸过程中发挥了重要作用, m⁶A修饰可以通过直接或间接影响ICIs靶点(包括PD-1、PD-L1、CTLA4等检查点)或一些关键信号通路的表达水平, 从而极大地影响ICIs疗效。

2.1 m⁶A与PD-1

最近的研究越来越多地证明了m⁶A调控因子的改变与PD-1的表达水平之间存在显著关联。YANG等^[58]发现, 高表达的FTO通过去除RNA m⁶A修饰在黑色素瘤生长中发挥致癌作用, 并降低对抗PD-1阻断免疫治疗的反应。而FTO下调会增加关键的致瘤性黑色素瘤细胞内在基因*PD-1*、*CXCR4*和*SOX10*的m⁶A甲基化水平, 导致通过m⁶A读取器YTHDF2的RNA衰变增加, 从而增强了小鼠对抗PD-1治疗的反应, 表明FTO作为一种m⁶A去甲基化酶在促进黑色素瘤肿瘤

发生和抗PD-1耐药性中起着至关重要的作用^[58]。另一项研究发现, IGF2BP的表达与PD-1表达呈正相关, 表明IGF2BP家族调控的m⁶A修饰可能对接受ICIs治疗的胰腺癌患者有潜在益处^[59]。有研究建立m⁶A分数预后模型发现, 高风险评分是胰腺癌的独立预后指标, 高风险评分越高, 胰腺癌患者的总生存期越低; 低m⁶A评分与PD-1和CTLA-4的低丰度相关, 提示m⁶A在预测胰腺癌患者ICIs疗效的临床应用中具有关键作用^[60]。

2.2 m⁶A与PD-L1

作为PD-1配体, PD-L1是另一种关键的免疫检查点蛋白, 其与PD-1结合, 可促进癌细胞的免疫逃逸。研究表明, m⁶A相关调节因子的失调严重影响PD-L1的表达。在乳腺癌中, METTL3的表达水平与患者的生存及CD8⁺、CD4⁺ T细胞的浸润呈负相关。敲低METTL3可显著减少*PD-L1* mRNA的m⁶A修饰, 使得IGF2BP3对m⁶A的识别减少从而促进*PD-L1* mRNA的降解^[61]。在膀胱癌中, JNK信号通路促进METTL3的表达, 进而抑制TME中CD8⁺ T细胞功能。抑制JNK/METTL3信号轴后恢复CD8⁺ T细胞的杀伤功能, 从而抑制肿瘤的发生发展。METTL3的高表达增强了*PD-L1* mRNA 3'-UTR区域的m⁶A修饰, IGF2BP1与mRNA结合后介导PD-L1的表达, 抑制了CD8⁺ T细胞的功能^[62]。此外, 在非小细胞肺癌(non-small cell lung carcinoma, NSCLC)中METTL3还可以通过影响环状IGF2BP3的代谢来调控PD-L1的表达。环状IGF2BP3通过PKP3依赖的方式稳定*OTUB1* mRNA, 从而降低NSCLC细胞中PD-L1的泛素化水平, 导致PD-L1表达水平升高, 最终介导免疫逃逸^[63]。与NSCLC相似, 胆管癌(cholangiocarcinoma, CCA)中的METTL14通过在3'-UTR区结合*Siah2*(Seven in absentia homolog 2) mRNA触发m⁶A修饰, 以YTHDF2依赖的方式促进其降解。当去除*Siah2*后, METTL14增加了PD-L1的蛋白稳定性, 然后抑制了T细胞增殖和T细胞介导的抗肿瘤活性, 表明METTL14-*Siah2*-PD-L1调节轴在CCA免疫治疗中的临床潜力^[64]。在肝内胆管癌(intrahepatic cholangiocarcinoma, ICC)中, ALKBH5的缺失以YTHDF2依赖的方式增加了*PD-L1* 转录本3'-UTR区的m⁶A丰度^[65]并下调了PD-L1表达。在乳腺癌中PD-L1的表达与METTL3和IGF2BP3的表达呈正相关, METTL3通过m⁶A-IGF2BP3依赖的方式促进*PD-L1* mRNA的稳定, 从而上调PD-L1的表

达^[61]。除此之外, m⁶A调节因子也调控了其他类型癌症中PD-L1的表达, 例如敲低*IGF2BP1*下调PD-L1表达并激活免疫细胞浸润, 从而抑制肝细胞癌的进展^[66]。这些研究结果为乳腺癌和肝细胞癌等癌症的免疫治疗提供了新的方向。

2.3 m⁶A与其他免疫检查点

m⁶A不仅影响PD-1和PD-L1, 还调控其他检查点如CD80、ICOS和VISTA(V-type immunoglobulin domain-containing suppressor of T cell activation)。与PD-1和PD-L1类似, 研究发现METTL3能够促进CD80的翻译表达, 通过m⁶A依赖的方式促进树突状细胞的活化和成熟^[67]。此外, METTL3还通过m⁶A修饰促进滤泡辅助性T细胞(follicular helper T cell, TFH)分化。在METTL3缺陷的TFH细胞中, m⁶A水平和可诱导共刺激分子(inducible synergistic co-stimulation molecules, ICOS)的表达水平均降低, 表明m⁶A修饰可以调节ICOS的表达^[68]。同样, YTHDF1在CRC中以m⁶A依赖的方式增强PD-L1和VISTA的蛋白水平^[69]。一些研究通过生信分析发现, m⁶A甲基化修饰与免疫治疗靶点PD-1、PD-L1、CTLA4、TIGIT和LAG3表达的关系, 揭示了m⁶A修饰在多种癌症抗肿瘤免疫治疗策略中的重要作用。例如, 基于m⁶A甲基化相关基因表达的m⁶A评分或m⁶A相关的高/低风险亚组是根据PD-1、PD-L1和CTLA-4等多个免疫检查点的差异表达区分的, 包括在小细胞肺癌、膀胱癌、头颈部鳞状细胞癌和胃癌^[70-72]等中。研究结果表明, 这些免疫检查点的异常表达对肿瘤的疗效有重要影响。

3 靶向m⁶A调节器在癌症免疫治疗中的潜在应用

尽管免疫疗法取得了显著进展, 但其低反应性仍然存在。综上, m⁶A修饰在肿瘤免疫治疗中发挥重要作用, 参与介导免疫检查点的表达。因此, 开发m⁶A调节因子的抑制剂/激动剂可能是改善肿瘤免疫应答一种有前景的治疗策略, 与ICIs联用可能会使肿瘤细胞对抗癌药物重新增敏。虽然抑制剂/激动剂尚未广泛应用于临床实践, 但在癌症动物模型中已显现出抑制肿瘤生长的潜力。

其中, FTO是目前最有希望开发抑制剂的m⁶A调节因子靶点。迄今为止, 已发现超过10种FTO抑制剂, 并且治疗效果在不同模型中已经验证^[73]。其

中大黄酸是第一个FTO抑制剂, 通过与FTO的催化结构域可逆性结合, 抑制FTO调控的m⁶A去甲基化, 并且具有较低的细胞毒性。YAN等^[74]发现, 大黄酸和酪氨酸激酶抑制剂(tyrosine kinase inhibitors, TKI)联合治疗对白血病细胞具有较好的抑制效果, 耐药细胞对TKI更敏感并抑制了集落形成。然而, 目前尚未有关于大黄酸与免疫治疗联合应用对肿瘤影响的研究报道。另外, GNPIPP12MA是一种负载FTO抑制剂和非甾体抗炎药甲氯芬那酸(meclofenamic acid, MA)的GSH生物印迹纳米复合材料。还原型谷胱甘肽(glutathione, GSH)耗竭可降低细胞内GSH水平, 诱导铁死亡。AML细胞和白血病干细胞(leukemia stem cells, LSCs)摄取GNPIPP12MA, GNPIPP12MA通过促进T细胞浸润和IFN- γ 分泌来增强抗PD-L1治疗的疗效^[75]。最近的研究报道缺失FTO可以促进肿瘤中CD8⁺T细胞的浸润, 从而抑制肿瘤的生长并阻断FTO介导的免疫逃逸。新型FTO抑制剂Dac51通过促进T细胞浸润来增强PD-L1阻断治疗的效果, 从而起到抑制肿瘤的作用, 体现一种协同改善黑色素瘤和NSCLC免疫应答的有效策略^[76]。

STM2457作为一种METTL3抑制剂, 靶向AML的关键干细胞群, 逆转AML的恶性表型, 具有治疗AML的潜力^[77]。在宫颈鳞状细胞癌(cervical squamous cell carcinoma, CESC)中, 免疫激活分子ICOS、KIR2DL4、TNFSF9、CD86与METTL3表达呈负相关。同时METTL3在M1型巨噬细胞、树突状细胞和M2型巨噬细胞等免疫细胞的浸润中发挥作用。STM2457联合PD-1阻断在体内抑制CSEC的进展^[78]。

研究人员在CRC中发现, 携带YTHDF1敲低的CT26和MC38肿瘤细胞的小鼠显示出肿瘤生长速度和重量明显下降的现象。与单一治疗组相比, 接受联合治疗的小鼠的总生存期显著延长^[69]。由此可见, YTHDF1缺失可能增强抗PD-L1免疫疗法的疗效。遗憾的是, 迄今为止尚未开发出相应的YTHDF1抑制剂并应用于临床。

综合而言, 这些研究发现GNPIPP12MA、Dac51和STM2457等药物在免疫治疗中具有协同抗肿瘤作用, 并有望进入临床试验。

4 总结与展望

本文综述了m⁶A写入器、擦除器和读取器在肿瘤中的生物学特性及其对肿瘤免疫的调控。m⁶A写

入器催化RNA上m⁶A修饰,擦除器则去除m⁶A。读取器通过识别m⁶A甲基化影响RNA的生物学过程。研究发现,这些m⁶A调控因子在肿瘤的发生、发展、转移和耐药等生物学过程中起重要作用。m⁶A在肿瘤治疗中显示出潜在的应用前景,可作为新的靶点。目前已开发出多种靶向m⁶A调节剂的抑制剂,并且多项临床前研究显示其具有良好的抗肿瘤活性,并可与免疫检查点协同抑制肿瘤。m⁶A抑制剂联合免疫检查点阻断疗法有潜在的应用,可增强m⁶A修饰在肿瘤免疫治疗中的作用,弥补免疫治疗的局限性。尽管m⁶A抑制剂尚未应用于临床试验,但为发现新型癌症治疗方法指明了方向。然而,m⁶A的研究在各种类型肿瘤中仍处于起步阶段,深入了解m⁶A修饰的分子机制将为患者进行个体化治疗提供重要信息。

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