综述

m^{6}A甲基化修饰调控肿瘤免疫的研究进展

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［摘要］N^6-甲基腺苷（N^6-methyladenosine，m^{6}A）是一种调控真核细胞基因表达最常见的修饰方式，影响RNA的剪接、降解、稳定性以及蛋白翻译等过程。研究表明m^{6}A甲基化修饰与肿瘤发生发展密切相关，在肿瘤免疫应答的相关过程中也发挥着重要的调控作用。m^{6}A修饰参与调节免疫细胞的分化、成熟过程以及相关的抗肿瘤免疫反应。在肿瘤微环境中，m^{6}A修饰也可影响免疫细胞的募集、活化和极化等，从而促进或抑制肿瘤细胞的增殖与转移，起到重塑肿瘤免疫微环境的重要作用。近年来肿瘤的免疫治疗逐渐应用于临床，如免疫检查点抑制剂治疗、过继性细胞免疫治疗等，都取得了较好的临床效果。通过靶向m^{6}A修饰来干预机体免疫系统，如通过小分子抑制剂靶向失调的m^{6}A调控因子、诱导免疫细胞重编程等，可提高抗肿瘤免疫反应，加强免疫细胞对肿瘤细胞的识别和杀伤能力。m^{6}A修饰是肿瘤免疫治疗的一个新方向，具有潜在的临床应用价值。该文围绕m^{6}A甲基化修饰对免疫细胞及肿瘤免疫应答的调控作用进行综述，探讨其免疫治疗的新思路。
［关键词］m^{6}A甲基化；肿瘤免疫；免疫治疗
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Research progress of m^{6}A methylation modification in regulating tumor immunity

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[Abstract] N^6-methyladenosine (m^{6}A) is the most prevalent modification that regulates gene expression in eukaryotes. It regulates splicing, degradation, stability, and translation of RNA. Numerous studies have demonstrated the close association between m^{6}A methylation and tumor development, highlighting its crucial role in regulating tumor immune response. The m^{6}A modification actively participates in governing immune cell differentiation and maturation as well as modulating anti-tumor immune responses. Within the tumor microenvironment, m^{6}A modification can also impact the recruitment, activation, and polarization of immune cells, thereby either promoting or inhibiting tumor cell proliferation and metastasis. Consequently, it plays a pivotal role in reshaping the tumor immune microenvironment. In recent years, immunotherapy for tumors has been increasingly applied to clinical practice with notable success achieved through approaches such as immune checkpoint inhibitor therapy and adoptive cell immunotherapy. Targeting m^{6}A modifications to interfere with the immune system, such as targeting dysregulated m^{6}A regulators through small molecule inhibitors and inducing immune cell reprogramming, can improve anti-tumor immune response and strengthen immune cells′ ability to recognize and kill tumor cells. The m^{6}A modification represents a novel avenue for potential clinical application within tumor immunotherapy. This review provides a comprehensive summary of the regulatory impact of m^{6}A methylation modification on immune cells in the context of cancer, while also delving into novel targets for tumor immunotherapy.
[Key words] m^{6}A methylation; tumor immunity; immunotherapy

N^6-甲基腺苷（N^6-methyladenosine，m^{6}A）是一种广泛存在于真核细胞RNA上的碱基修饰行为。研究[1]表明，m^{6}A甲基化参与调控多种细胞分子通路，与肿瘤发生、侵袭以及肿瘤微环境形成密切相关。m^{6}A修饰在免疫系统的发育和免疫应答的诱导过程中也发挥重要作用[2]。免疫细胞参与肿瘤微环境的形成，通过m^{6}A修饰调控免疫细胞效应功能，从而发挥抗肿瘤作用，有望成为肿瘤免疫治疗新靶标。

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1 m^{6}A甲基化修饰成员及其功能

m^{6}A修饰，即腺苷位于第6位的氮原子（nitrogen，N）发生甲基化，是真核生物mRNA最丰富的内部修饰，主要调节RNA的稳定性、剪接、降解、翻译等过程[3-5]。m^{6}A修饰主要由三类酶参与完成——甲基转移酶（writers）、去甲基化酶（erasers）和甲基化识别酶（readers），分别调控m^{6}A的催化、去除和识别。m^{6}A甲基转移酶复合物，包括核心组分甲基转移酶样3（methyltransferase like 3，METTL3）、甲基转移酶样14（methyltransferase like 14，METTL14）和其他调控因子如Wilms′肿瘤蛋白1相关蛋白（Wilms′ tumor 1-associating protein，WTAP）、病毒样m^{6}A甲基转移酶相关蛋白（vir like m^{6}A methyltransferase associated protein，VIRMA/KIAA1429）、RNA结合基序蛋白15/15B（RNA binding motif protein 15/15B，RBM15/15B）、Cbl原癌基因样1（Cbl proto-oncogene like 1，HAKAI）、锌指CCCH类包含蛋白13（zinc finger CCCH-type containing 13，ZC3H13），此外还有甲基转移酶样16（methyltransferase like 16，METTL16）等单一的甲基转移酶[6]。去甲基化酶可以逆转m^{6}A修饰，主要包括脂肪和肥胖相关蛋白（fat mass and obesity associated protein，FTO）、AlkB同源蛋白5（AlkB homolog 5，ALKBH5）[6]。甲基化识别酶主要包括YTH结构域蛋白家族，如YTH结构域m^{6}A RNA结合蛋白1/2/3（YTH N^6-methyladenosine RNA binding protein 1/2/3，YTHDF1/2/3）、YTH结构域包含蛋白1/2（YTH domain containing 1/2，YTHDC1/2），以及胰岛素样生长因子2 mRNA结合蛋白1/2/3（insulin-like growth factor 2 mRNA-binding protein 1/2/3，IGF2BP1/2/3）等[6]。这三类酶共同调控m^{6}A动态平衡，对于细胞的生长发育和功能发挥至关重要[7-8]。

2 m^{6}A修饰与肿瘤固有免疫

固有免疫是机体发育过程中形成的非特异性防御功能，发挥抗原提呈、吞噬等作用，是抗肿瘤免疫的第一道防线。固有免疫细胞包括树突状细胞（dendritic cell，DC）、自然杀伤细胞（natural killer cell，NK细胞）、肿瘤相关巨噬细胞（tumor-associated macrophages，TAM）、单核细胞（monocyte）、中性粒细胞（neutrophil）、骨髓源性抑制细胞（myeloid-derived suppressor cell，MDSC）、γδT细胞、肥大细胞（mast cell）等。

2.1 m^{6}A与DC

DC是功能最强的抗原提呈细胞（antigen presenting cell，APC），能有效激活初始T细胞，在免疫应答起始阶段发挥重要作用[9]。DC的功能障碍可导致免疫逃逸，促进肿瘤的发生[10]。研究[11]显示，METTL3介导m^{6}A修饰增强CD40、CD80和Toll样受体4（Toll-like receptor 4，TLR4）信号适配器Toll/白细胞介素-1β（interleukin-1β，IL-1β）受体结构域衔接蛋白（TIR domain-containing adapter protein，TIRAP）在DC的翻译，以刺激T细胞激活，增强TLR4/NF-κB信号诱导的细胞因子产生。m^{6}A甲基化也可影响DC迁移。通过去除DC中非编码RNA lnc-Dpf3的m^{6}A修饰，降低YTHDF2介导的lnc-Dpf3降解，可阻碍DC迁移，影响免疫应答启动[12]。此外HAN等[13]发现，YTHDF1可以识别m^{6}A标记的编码溶酶体蛋白酶的转录本，增加其在DC中的翻译，降解DC摄取的抗原。而YTHDF1的缺失则可下调溶酶体蛋白酶的表达，增强DC对肿瘤抗原的提呈能力，从而有效地激活T细胞的抗肿瘤反应。

2.2 m^{6}A与NK细胞

NK细胞是固有免疫系统中具有直接杀伤效应的细胞毒性淋巴细胞，与抗肿瘤、抗病毒感染和免疫调节有关。NK细胞具有强大的抗肿瘤能力，被认为是目前除T细胞以外，最有潜力的肿瘤杀伤效应细胞[14]。研究发现m^{6}A修饰在维持NK细胞稳态和功能效应中起到重要作用。在黑色素瘤中，NK细胞中METTL3的蛋白表达水平与效应分子呈正相关，METTL3的缺失会改变NK细胞的动态平衡，抑制NK细胞在肿瘤微环境中的杀伤功能[15]。YTHDF2也在维持NK细胞稳态和终末成熟中发挥作用。YTHDF2在活化的NK细胞中表达增加，通过形成信号转导和转录激活因子5（signal transducer and activator of transcription 5，STAT5）-YTHDF2正反馈环，促进NK细胞的效应功能；也可通过降低*Tardb*基因转录RNA的稳定性，调节NK细胞增殖和存活[16]。

2.3　m⁶A与TAM

TAM是浸润在肿瘤组织中的巨噬细胞，在肿瘤微环境的形成等方面发挥重要作用。在肿瘤微环境和刺激因子的作用下，巨噬细胞可以向不同的方向极化，M1型巨噬细胞可以促进免疫反应、抗肿瘤，M2型巨噬细胞则表现为免疫抑制、促进肿瘤进展[17-19]。METTL3可通过介导*STAT1* mRNA的甲基化修饰，增强其稳定性，从而上调*STAT1*表达，促进M1极化[20]。YIN等[21]也证明了METTL3对TAM的调控作用。在黑色素瘤或肺癌的小鼠模型中，METTL3缺陷小鼠TAM在肿瘤中的浸润程度增加，METTL3缺失降低YTHDF1介导SPRED2翻译，通过ERK途径增强NF-κB/STAT3激活，导致肿瘤生长和转移。研究[22]发现，YTHDF2也可调节TAM抗肿瘤功能，TAM中YTHDF2缺失通过靶向γ干扰素（interferon-γ，IFN-γ）-STAT1信号通路，将TAM重新编程为抗肿瘤表型并增强其抗原交叉提呈能力，进而增强细胞毒性T细胞介导的抗肿瘤免疫。

2.4　m⁶A与单核细胞

单核细胞在血液循环中能吞噬、清除受伤或衰老的细胞及其碎片，并可迁移到组织分化为巨噬细胞[23]。在结直肠癌患者的外周血免疫细胞中，单核细胞中的m⁶A水平与单核细胞免疫反应呈负相关[24]。另外，ZHANG等[25]发现METTL3介导的m⁶A修饰和YTHDF2介导的识别可促进*PGC-1α* mRNA降解，诱导单核细胞分化为M1型和M2型巨噬细胞，从而发挥调节肿瘤免疫作用。

2.5　m⁶A与中性粒细胞

中性粒细胞在肿瘤微环境中发挥双重作用，可以直接杀伤肿瘤细胞或与其他免疫成分相互作用介导抗肿瘤反应，也可通过促血管生成、细胞外基质重塑、免疫抑制等促进肿瘤进展[26]。OU等人[27]发现，C5aR1⁺中性粒细胞亚群通过WTAP介导的m⁶A甲基化上调*ENO1*诱导乳腺癌细胞糖酵解，与肿瘤进展和患者不良预后有关。衰老的中性粒细胞分泌的外泌体piRNA-17560可增强乳腺癌细胞中FTO表达。FTO通过减少m⁶A甲基化增强锌指E盒结合蛋白1（zinc finger E-box binding homeobox 1，*ZEB1*）基因稳定性，从而导致肿瘤细胞的化学治疗耐药和上皮间质转化。衰老中性粒细胞可作为乳腺癌潜在治疗靶点[28]。

2.6　m⁶A与MDSC

MDSC是由未成熟的前体单核细胞和中性粒细胞组成的骨髓细胞群，具有较强的免疫抑制活性，它们与许多病理条件下的免疫反应调节和肿瘤不良预后密切相关[29]。METTL3通过碱性螺旋-环-螺旋转录因子家族成员E41（basic helix-loop-helix family member e41，*BHLHE41*）-C-X-C模体趋化因子配体1（C-X-C motif chemokine ligand 1，*CXCL1*）/C-X-C模体趋化因子受体2（C-X-C motif chemokine receptor 2，*CXCR2*）信号通路促进MDSC迁移，促进结直肠癌进展[30]。在非酒精性脂肪性肝炎相关的肝癌中，YTHDF1在肿瘤组织过表达，诱导IL-6分泌及MDSC募集和激活，抑制抗肿瘤免疫[31]。

2.7　m⁶A与γδT细胞

γδT细胞是一种执行固有免疫功能的T细胞，其TCR由γ和δ链组成，分布于肠道、呼吸道以及泌尿生殖道等黏膜和皮下组织。γδT细胞既能杀伤肿瘤细胞，又能识别某些肿瘤抗原，参与抗肿瘤免疫应答[32]。研究表明，m⁶A去甲基化酶ALKBH5调节γδT细胞发育，胸腺细胞中ALKBH5缺失使*Jagged1/Notch2*信号转导受损，有助于增强γδ T细胞前体的增殖和分化[33]。METTL3介导的m⁶A甲基化则可调节mRNA稳定性和双链RNA（double-stranded RNA，dsRNA）含量，以平衡γδ T1和γδ T17这两个主要功能不同的亚群细胞[34]。

2.8　m⁶A与肥大细胞

肥大细胞通过分泌多种细胞因子，参与免疫调节。肥大细胞在肿瘤组织中浸润，分泌组胺、血管内皮生长因子等，可刺激肿瘤血管新生，促进肿瘤生长及转移，还可调控T细胞等免疫细胞的招募和活性，影响抗肿瘤免疫[35]。研究[36-37]发现，在食管鳞状细胞癌和胃癌中，METTL3、WTAP等高表达，并且肥大细胞等免疫细胞在肿瘤中浸润增加，提示肥大细胞的浸润受到m⁶A甲基化影响。m⁶A甲基化修饰与肥大细胞功能也密切相关。m⁶A甲基转移酶复合体参与调节肥大细胞的生长增殖，并可影响细胞因子mRNA的稳定性，抑制肥大细胞介导的炎症反应[38]。

m⁶A修饰对固有免疫细胞的调控作用见表1。

表1 m^{6}A修饰对固有免疫细胞的调控作用

Tab 1 Role of m^{6}A modifications in innate immune cells

Immune cell	m^{6}A regulator	Type	Related factor	Function	Reference
DC	METTL3	Writer	CD40, CD80 and Tirap	Positively correlates with DC maturation and function in promoting T-cell activation	[11]
	YTHDF1	Reader	Lysosomal proteases	Negatively correlates with cross-presentation of engulfed tumour neoantigens	[13]
	YTHDF2	Reader	lnc-Dpf3	Positively correlates with DC migration	[12]
NK	METTL3	Writer	SHP-2	Positively correlates antitumor immunity of NK cells	[15]
	YTHDF2	Reader	Tardb	Positively correlates with NK cell antitumor activity as well as NK cell homeostasis and maturation	[16]
TAM	METTL3	Writer	STAT1, STAT3	Positively correlates with M1 macrophage polarization	[20-21]
	YTHDF2	Reader	STAT1	Negatively correlates with macrophage reprogramming and antitumor immunity	[22]
Monocyte	METTL3	Writer	PGC-1α	Positively correlates with monocyte differentiation into different types of macrophages	[25]
Neutrophil	WTAP	Writer	ENO1	Positively correlates with tumor glycolysis mediated by C5aR1-positive neutrophils	[27]
	FTO	Eraser	ZEB1	Positively correlates with senescent neutrophils-mediated chemoresistance in breast cancer	[28]
MDSC	METTL3	Writer	BHLHE41	Positively correlates with MDSC migration	[30]
	YTHDF1	Reader	EZH2	Positively correlates with MDSC recruitment and activation	[31]
γδ T cell	METTL3	Writer	STAT1	Positively correlates with equilibrate γδ T1 and γδ T17 cells	[34]
	ALKBH5	Eraser	Jagged1/Notch2	Negatively correlates with proliferation and differentiation of γδ T cell precursors	[33]
Mast cell	METTL3	Writer	IL-13	Negatively correlates with inflammatory responses of mast cells	[38]

3 m^{6}A修饰与肿瘤适应性免疫

适应性免疫又称特异性免疫，是机体在抗原刺激下产生的免疫应答。肿瘤相关抗原被APC识别摄取后提呈给效应细胞，包括T细胞和B细胞，从而启动抗肿瘤免疫应答。

3.1 m^{6}A与T细胞

T淋巴细胞来源于骨髓干细胞，在胸腺中分化成熟后迁移至外周完成免疫功能。T细胞具有多种生物学功能，如直接杀伤靶细胞、调控或辅助其他免疫细胞发挥功能，以及产生细胞因子等，在抗肿瘤免疫中占主导地位[39-40]。T细胞按照功能和表面标志主要可分成以下亚群。

3.1.1 m^{6}A与CD4$^+$辅助性T细胞 未激活的初始CD4$^+$T细胞在各种抗原和细胞因子的刺激和调控下，分化为不同类型的辅助性T细胞（helper T cell，Th细胞）。其中Th1亚型通过协助细胞毒性CD8$^+$T细胞和B细胞发挥抗肿瘤功能，也可产生IFN-γ和TNF-α等直接作用于肿瘤细胞；Th2亚型主要分泌IL-4、IL-13等细胞因子，可抑制细胞毒性T细胞的杀伤作用[41]。研究[42]发现m^{6}A影响初始CD4$^+$T细胞的分化，METTL3缺陷的初始T细胞表现出Th1细胞减少，而Th2细胞增加。初始T细胞中*METTL3*基因敲除导致细胞因子信号家族细胞因子信号抑制因子1（suppressor of cytokine signaling1，SOCS1）、SOCS3和CISH蛋白水平抑制，从而抑制IL-7/STAT5信号通路，影响T细胞稳态和分化[42]。m^{6}A甲基化也影响CD4$^+$T细胞的功能。去甲基化酶ALKBH5通过降低*CXCL2*和*IFN-γ* mRNA中m^{6}A水平，增强其mRNA稳定性和翻译，促进Th1细胞功能[43]。

3.1.2 m^{6}A与调节性T细胞 调节性T细胞（regulatory T cell，Treg细胞）是CD4$^+$T细胞分化的一个亚群，可介导对免疫细胞功能的负调节。研究表明m^{6}A甲基化同样在Treg细胞的分化和效应功能中发挥关键作用。METTL14缺失可导致初始T细胞无法维持向诱导Treg细胞的分化[44]。METTL3介导m^{6}A甲基化是维持Treg抑制功能所必需的，而Treg细胞中METTL3缺失增加*Socs* mRNA水平，引起IL-2/STAT5信号通路失活，导致Treg细胞功能和稳定性受到破坏[45]。

3.1.3 m^{6}A与CD8$^+$T细胞 CD8$^+$T细胞为细胞毒性T细胞，其激活后可释放穿孔素、颗粒酶等杀伤肿瘤细胞。多项研究表明，m^{6}A甲基化修饰与CD8$^+$T细胞肿瘤浸润密切相关。在结肠癌间质细胞中，METTL14表达与m^{6}A水平和CD8$^+$T细胞浸润程度呈正相关[46]；在非小细胞肺癌中，YTHDF1和YTHDF2高表达导致肿瘤间质中包括CD8$^+$T细胞在

内淋巴细胞亚群浸润程度均显著增加[47]。同样在非小细胞肺癌中，LIU等[48]发现METTL3可介导环状RNA circIGF2BP3的m⁶A修饰促进其环化，circIGF2BP3通过miR-328-3p和miR-3173-5p竞争性上调PKP3，使$CD8^+$ T细胞浸润减少，抑制肿瘤免疫反应。此外，小鼠黑色素瘤细胞可通过FTO介导糖酵解途径，抑制$CD8^+$ T细胞激活，逃避免疫监视；而*FTO*基因敲除后，肿瘤细胞糖酵解活性下降，$CD8^+$ T细胞功能恢复[49]。

3.2　m⁶A与B细胞

B细胞在抗原刺激下可分化为浆细胞，产生抗体介导体液免疫应答。在肿瘤免疫中，B细胞主要依赖分泌抗肿瘤相关抗原抗体，活化的B细胞还可通过抗原提呈促进T细胞激活，发挥抗肿瘤作用[50]。研究[51]发现m⁶A修饰参与调节早期B细胞发育，如METTL14的缺失会阻断幼稚B细胞从前B期（pro-B cell）向大前B期（large pre-B cell）的转变，影响B细胞成熟。另一项研究[52]表明METTL14介导的m⁶A修饰促进负免疫调节因子（如*Lax1*和*Tipe2*）的mRNA衰变，从而影响生发中心B细胞的阳性选择和增殖。另一方面，B细胞中异常m⁶A修饰调节肿瘤发生发展。多发性骨髓瘤患者浆细胞中FTO上调，m⁶A甲基化水平显著降低，促进多发性骨髓瘤细胞增殖、迁移和侵袭[53]。

m⁶A修饰对适应性免疫细胞的调控及在肿瘤免疫中的作用见表2和图1。

表2　m⁶A修饰对适应性免疫细胞的调控作用

Tab 2　Role of m⁶A modifications in adaptive immune cells

Immune cell	m⁶A regulator	Type	Related factor	Function	Reference
$CD4^+$ T cell	METTL3	Writer	SOCS	Positively correlates with proliferation and differentiation of T cells	[42]
	ALKBH5	Eraser	IFN-γ, CXCL2	Positively correlates with Th1 cell activation	[43]
Treg cell	METTL3	Writer	SOCS	Positively correlates with sustaining Treg suppressive functions	[45]
	METTL14	Writer	RORγt	Positively correlates with Tregs differentiation	[44]
$CD8^+$ T cell	METTL3	Writer	circIGF2BP3	Negatively correlates with $CD8^+$T cell responses and facilitates tumor immune	[48]
	METTL14	Writer	Ebi3	Negatively correlates with dysfunctional $CD8^+$T cell levels in patients with colorectal cancer	[46]
	YTHDF1/2	Reader	unkown	Positively correlates with tumor-infiltrating lymphocytes, including $CD8^+$ T cells	[47]
	FTO	Eraser	c-Jun, JunB, and C/EBPβ	Positively correlates with glycolytic metabolism of tumor cells; negatively correlates with $CD8^+$T cell responses	[49]
B cell	METTL14	Writer	Lax1, Tipe2	Positively correlates with B cell maturation	[52]
	FTO	Eraser	HSF1	Positively correlates with tumor-promoting and pro-metastatic in multiple myeloma	[53]

4　m⁶A甲基化修饰在肿瘤免疫治疗中的应用

肿瘤免疫治疗旨在外源干预机体免疫系统，恢复、提高机体的抗肿瘤免疫反应，加强对肿瘤细胞的识别和杀伤能力。目前临床上已应用的肿瘤免疫治疗方法主要包括免疫检查点抑制剂治疗、过继性细胞免疫治疗等；而将m⁶A作为靶点来调控机体免疫系统的抗肿瘤应答，可能是免疫治疗新的方向。

4.1　靶向m⁶A修饰辅助免疫检查点治疗

免疫检查点在调节免疫激活程度、维持免疫稳态方面发挥着关键作用。肿瘤细胞可表达某些物质来激活免疫检查点，逃避免疫监视，抑制抗肿瘤免疫反应。以程序性死亡受体1（programmed cell death-1，PD-1）抗体为代表的免疫检查点抑制剂类药物可解除这种抑制作用，重新激活免疫细胞。目前m⁶A修饰对免疫检查点的影响也得到了广泛研究。结直肠癌中，敲除*METTL3*或*METTL14*可通过*YTHDF2*稳定*Stat1*和*Irf1* mRNA，促进IFN-γ-Stat1-Irf1信号通路，进而增强结直肠癌抗PD-1治疗中的免疫应答[54]。研究[55]发现，YTHDF1通过m⁶A-p65-CXCL1/CXCR2轴抑制抗肿瘤免疫以促进结直肠癌进展，也可作为免疫检查点阻断疗法的治疗靶点。

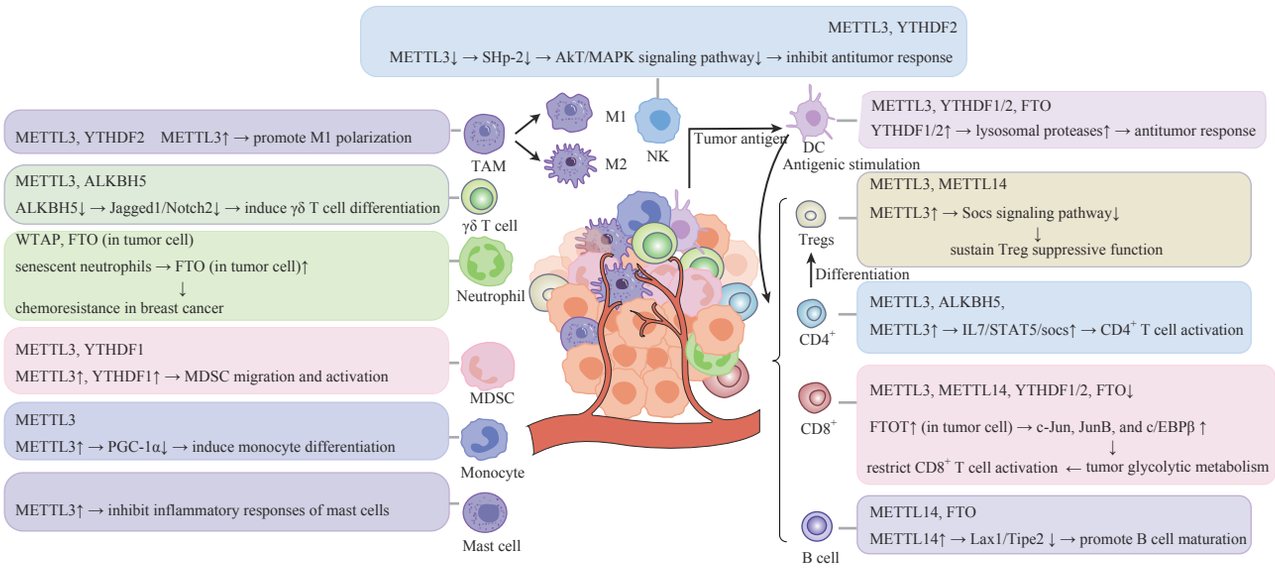

图 1　m^{6}A 修饰对免疫细胞及肿瘤免疫应答的调控作用

Fig 1　Modification of m^{6}A in immune cells and antitumor immune response

4.2　靶向 m^{6}A 调节因子增强免疫应答

m^{6}A 甲基化在肿瘤的发生发展以及抗肿瘤免疫中起到重要作用，靶向调控失调的 m^{6}A 修饰成为免疫治疗的新策略。目前已经开发出一系列 m^{6}A 调节因子的抑制剂，并且研究验证了 m^{6}A 抑制剂可增强抗肿瘤反应。如 FTO 抑制剂 Dac51 可恢复肿瘤组织中 CD8$^+$T 细胞免疫监视功能，抑制肿瘤生长[49]。FB23 和 FB23-2 也可直接与 FTO 结合，抑制其去甲基化酶活性，在控制急性髓系白血病（acute myeloid leukemia，AML）进展中发挥作用[56]。研究也报道了 METTL3 抑制剂 STM2457 在抗 AML 中具有较好疗效[57]。通过小分子抑制剂靶向失调的 m^{6}A 调控因子具有临床应用潜力，但仍需深入研究其作用机制并验证其安全性。

4.3　调节免疫细胞重编程

通过干扰免疫细胞中发挥特定功能所必需的 m^{6}A 位点，可诱导免疫细胞重编程从而发挥抗肿瘤作用。鉴于 T 细胞在肿瘤免疫中的主导地位，大多数肿瘤免疫疗法和对抗免疫逃逸集中在 T 细胞重编程。例如，肿瘤微环境中 Treg 抑制 CD8$^+$T 细胞的肿瘤杀伤功能，通过干扰 m^{6}A 修饰选择性去除肿瘤浸润性 Treg 可能具有一定疗效[45]。此外，在 TAM 中，TLR9 激动剂结合小干扰 RNA 靶向 YTHDF2，可使 TAM 重新编程为抗肿瘤表型，提高抗肿瘤作用[22]。

4.4　预测临床预后

m^{6}A 修饰也可以作为某些肿瘤早期诊断、预后预测和风险分层的生物标志物。ZHANG 等[58]建立了一套评分系统（m^{6}Ascore）来量化胃癌中 m^{6}A 修饰模式，并与肿瘤微环境中免疫细胞浸润特征相联系；他们发现 m^{6}A 甲基化修饰模式与肿瘤免疫表型和抗 PD-1/程序性死亡因子配体 1（programmed cell death ligand 1，PD-L1）免疫治疗应答显著相关；结果表明 m^{6}Ascore 有助于预测抗 PD-1/L1 免疫治疗应答，是一种可靠的免疫治疗预后和临床评估的生物标志物。

5　总结与展望

m^{6}A 甲基化修饰参与调控多种免疫细胞的发生、稳态和功能，在重塑肿瘤免疫微环境过程中发挥重要作用。其表达可能影响免疫细胞在某些肿瘤中的浸润程度，也可能成为肿瘤进展过程中的促进或抑制因素。因此，在肿瘤免疫治疗领域，m^{6}A 修饰是一个重要的潜在靶标。但结合现有研究，还有较多问题有待进一步深入，如 m^{6}A 对肿瘤免疫的调节可以促进或抑制，需要探索更精准的调控方式；是否存在肿瘤特异性 m^{6}A 靶点或调控因子；靶向 m^{6}A 调节机体免疫系统的安全性还需进一步验证等。m^{6}A 甲基化修饰与肿瘤免疫应用于临床尚有许多问题亟待解决，但其对肿瘤免疫治疗提供了新思路，具有重要的应用意义和前景。

利益冲突声明/Conflict of Interests

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作者贡献/Authors′ Contributions

周海霞与张靖共同构思文章框架，周海霞负责文献整理、撰写初稿并完成修改，张靖提出写作思路并修改、审阅全文。两位作者均阅读并同意了最终稿件的提交。

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