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· 综述 ·

m5C 甲基化修饰及其在肿瘤免疫治疗中的研究进展

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【摘要】 表观遗传修饰在真核细胞生物学过程中有重要的调节作用。肿瘤免疫疗法是治疗癌症的重要手段和临床策略。5-甲基胞嘧啶(5-methylcytosine, m5C)是继N6甲基腺苷(N6-methyladenosine, m6A)之后发现的表观遗传调控网络的重要组成部分。RNA的m5C甲基化修饰能影响被修饰RNA分子的命运,并在包括RNA稳定性、蛋白质合成和转录调控在内的各种生物学过程中发挥重要作用。最近研究表明,m5C甲基转移酶、去甲基化酶、甲基化识别蛋白与多种细胞生物学过程和系统性疾病有关,包括肿瘤的发生、转移和肿瘤免疫微环境等。m5C甲基化修饰可在多个水平上广泛影响基因表达和肿瘤发生发展的生物学过程,但其具体机制及与其他表观遗传修饰的相互作用尚未阐明,其在恶性肿瘤中的调控机制、风险评估和靶向治疗的研究有待深入。本文将从m5C的动态调节网络、m5C修饰在实体瘤中的生物学作用及在肿瘤免疫治疗中的潜在靶点等进行综述。

【关键词】 肿瘤; 表观遗传修饰; 甲基化修饰; 5-甲基胞嘧啶; N6甲基腺苷; RNA甲基化; 免疫治疗; 肿瘤微环境; m5C调节蛋白

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Research progress on m5C methylation and its prospects in tumor immunotherapy LU Yunyang, DU Weidong, YU Dongsheng. Hospital of Stomatology, Guanghua School of Stomatology & Sun Yat-sen University & Guangdong Provincial Key Laboratory of Stomatology, Guangzhou 510055, China

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【Abstract】 Epigenetic modification plays an important role in the biological regulatory process of eukaryotic cells. Tumor immunotherapy is an important means and clinical strategy for the treatment of some cancers. 5-Methylcytosine (m5C) is an important component of the epigenetic regulatory network discovered after m6A and has become a new topic for life science research in recent years. The m5C methylation of RNA can affect the fate of the modified RNA molecules and play an important role in various biological processes, including RNA stability, protein synthesis and transcriptional regulation. Recent studies have shown that m5C writers, erasers and readers are related to a variety of cellular biological processes and systemic diseases, including the occurrence, metastasis and tumor immune microenvironment. m5C methylation can widely affect gene expression and the biological process of tumorigenesis and development at multiple levels, but its specific mechanism and potential interaction with other epigenetic modifications in tumor immunotherapy are still unclear, and its regulatory mechanism, risk assessment and role in targeted therapy for malignant tumors need to be further studied. This article will review the dynamic regulatory network of m5C, the biological role of m5C modification in solid tumors and potential targets in tumor immunotherapy.

【Key words】 tumor; epigenetics; methylation; 5-methylcytosine; N6-methyladenosine; RNA methylation;

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目前已鉴定出RNA中170多种甲基化修饰,包括N6-甲基腺苷(N6-methyladenosine, m6A)、5-甲基胞嘧啶(5-methylcytosine, m5C)和7-甲基鸟苷酸(7-methylguanylate, m7G)等^[1]。它们通过作用于RNA的三级结构、生物发生、定位和功能来增加RNA种类的复杂性,对细胞生物学过程和癌症发生至关重要^[2]。m5C甲基化修饰指DNA或RNA胞嘧啶环第5位碳上连接甲基,是一种高度集中的可逆的表观遗传修饰。这种修饰首先在DNA^[3],随后在RNA上被发现^[4]。RNA m5C修饰存在广泛的靶位点,包括信使RNA(messenger RNA, mRNA)和非编码RNA(non-coding RNA, ncRNA),例如转运RNA(transfer RNA, tRNA)、核糖体RNA(ribosomal RNA, rRNA)、微小RNA(micro RNA, miRNA)、小核RNA(small nuclear RNA, snRNA)和增强子RNA(enhancer RNA, eRNA)等^[5]。随着甲基化RNA免疫沉淀测序和液相色谱质谱仪等技术鉴定方法研究的不断改进^[6],mRNA m5C修饰已被发现影响多种生物学过程,如mRNA的稳定、剪接和核质穿梭^[7];DNA损伤修复^[8];细胞增殖和迁移^[9];干细胞的发育、分化和重编程^[10]。

mRNA的m5C甲基化状态与癌症的发生、转移、复发及耐药密切相关,也与肿瘤免疫微环境和免疫治疗有关。本文将从m5C的动态调节网络、m5C修饰在实体瘤中的生物学作用及在肿瘤免疫治疗中的潜在分子机制等作一综述。

1 m5C的动态调节网络

动态的m5C甲基化和去甲基化修饰主要由3种蛋白介导,分别是甲基转移酶(writer)、去甲基化酶(eraser)和m5C识别蛋白(reader)(图1)。m5C甲基转移酶以S-腺苷甲硫氨酸(S-adenosylmethionine, SAM)作为甲基供体,将甲基转移到胞嘧啶的第五位碳原子形成m5C甲基化修饰。在m5C修饰RNA后,m5C识别蛋白会特异性地与修饰位点结合,通过识别和结合m5C位点发挥生物学效应。去甲基化酶介导RNA的去甲基化,TET诱导的去甲基化

的本质是通过促进后续的氧化来取代修饰。总之,通过以上3种蛋白相互作用,m5C甲基化修饰在多个水平上广泛影响基因表达和多种生物学过程,但其具体机制尚未完善。

2 m5C修饰在肿瘤中的作用

目前,许多m5C相关蛋白在肿瘤发生发展中起着重要的调节作用,同一修饰在不同肿瘤中可能发挥不同的功能。

2.1 m5C与肝细胞癌

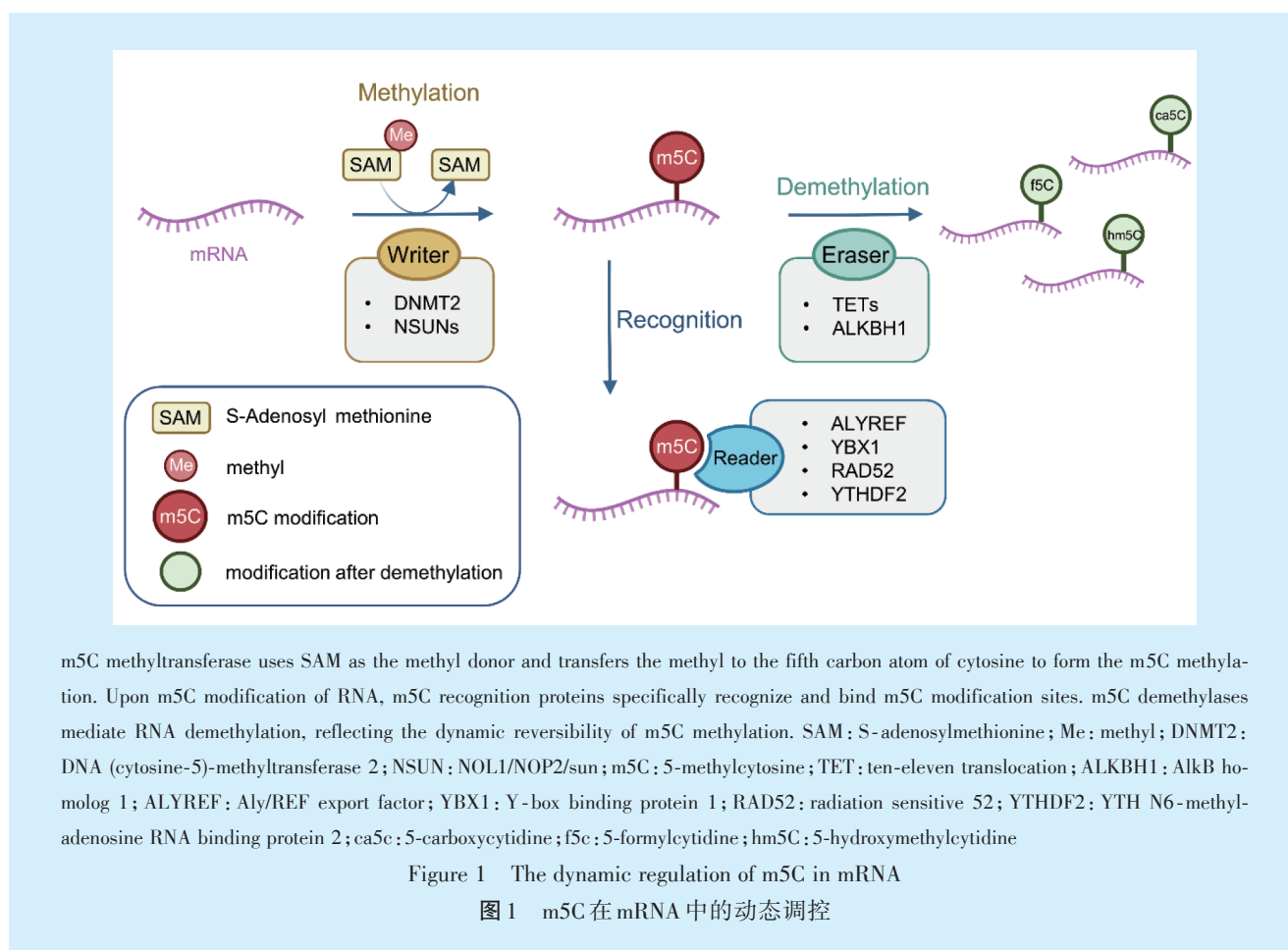
肝细胞癌中m5C调控基因的突变频率较高,且m5C相关基因的调控异常与肝细胞癌的高分期相关^[11]。m5C调控基因可能是具有肝细胞癌治疗潜力的新靶点。

在肝细胞癌细胞中,NOL1/NOP2/sun结构域家族成员1(NOL1/NOP2/sun family member 1, NSUN1)与长链非编码RNA(long non-coding RNA, lncRNA)-PVT1结合,促进肿瘤发生、细胞增殖和干细胞样特性^[12]。NSUN2也在肝细胞癌细胞中上调表达,NSUN2沉默通过下调Fizzy相关蛋白1(Fizzy/cell division cycle 20 related 1, FZR1),增加肝细胞癌细胞自噬^[13]。此外,NSUN4和Aly/REF输出因子(Aly/REF export factor, ALYREF)在肝细胞癌中上调,与细胞周期调节和有丝分裂明显相关,并与预后不良有关^[11]。

2.2 m5C与胃肠道癌

除NSUN6外,m5C所有调控基因的表达在胃肠道癌的病理I期至IV期均显著上调。在胃肠道癌中,NSUN2的突变率最高^[14]。NSUN2可通过m5C依赖性和非依赖性途径促进肿瘤进展。

在胃癌细胞中,NSUN2以m5C依赖的方式修饰叉头框蛋白C2(forkhead box C2, FOXC2) mRNA。m5C结合Y-box结合蛋白1(Y-box binding protein 1, YBX1)与甲基化FOXC2 mRNA结合增强其稳定性,从而促进胃癌细胞增殖、迁移和侵袭^[15]。NSUN2通过在p57^{Kip2} mRNA的3'非编码区(3' untranslated Region, 3'UTR)中引入m5C来破坏p57Kip2



稳定性,促进胃癌细胞增殖^[16]。

2.3 m5C与结直肠癌

在结直肠癌中,NSUN2抑制miR-125b表达,增强Grb相关结合蛋白2(Grb-associated binding protein 2, Gab2)的表达,进而促进细胞迁移^[17]。另外,NSUN5也在结直肠癌组织和细胞中上调,NSUN5-KO小鼠的细胞增殖显著降低,细胞周期停滞。NSUN5可能通过视网膜母细胞瘤基因(Retinoblastoma, Rb)-周期蛋白依赖性激酶(cyclin-dependent kinase, CDK)通路调节结直肠癌细胞增殖^[18]。

2.4 m5C与乳腺癌

在三阴乳腺癌中,NSUN2过表达通过Myc促进癌细胞增殖、迁移、侵袭^[19]。NSUN6调节Yes相关蛋白(Yes associated protein 1, YAP1)靶基因的哺乳动物STE20样激酶1(Mammalian Sterile 20-like Kinase 1, MST1),引发破骨细胞分化和乳腺癌骨转移^[20]。

2.5 m5C与头颈部鳞状细胞癌

在头颈部鳞状细胞癌中,NSUN2表达显著上调,可能与线粒体功能及细胞周期检查点相关基因有关^[21]。此外,头颈部鳞状细胞癌中DNA甲基

化转移酶1(DNA cytosine-5-methyltransferase 1, DNMT1)下调,可能与肽交联和体液免疫有关^[22]。NSUN2表达与T细胞激活评分呈负相关^[23]。另外,在下咽鳞癌中,NSUN3水平升高,增强肿瘤增殖和侵袭^[24]。

2.6 m5C与泌尿系统肿瘤

在前列腺癌中,NSUN1表达升高,通过上皮间质转化(epithelial-mesenchymal transition, EMT)通路促进转移和侵袭^[25]。

在膀胱癌中,ALYREF稳定丙酮酸激酶M2(pyruvate kinase M2, PKM2) mRNA,通过PKM2介导的糖酵解促进膀胱癌细胞增殖^[26]。

在尿路上皮性膀胱癌中,NSUN2和YBX1上调,YBX1与胚胎致死性异常视觉类蛋白1(embryonic lethal abnormal vision like protein 1, ELAVL1)结合,促进侵袭和转移,与T、N分期、肿瘤分级呈正相关^[27]。

在透明细胞肾细胞癌组织中NSUN1和NSUN4的mRNA水平高于正常组织,而NSUN6和10-11易位家族蛋白酶2(ten-eleven translocation 2, TET2)的

mRNA水平较低,透明细胞肾细胞癌中NSUN1高表达与不良总生存期相关^[28]。

3 m5C在肿瘤免疫微环境中的意义

肿瘤免疫微环境(tumor immune microenvironment, TIME)与肿瘤进展和免疫治疗反应密切相关。最近研究发现,m5C修饰能调控肿瘤中浸润的免疫细胞。TET2和10-11易位家族蛋白酶3(ten-eleven translocation 3, TET3)在Treg细胞免疫稳态中起重要作用^[29]。与此同时,TIME中多种m5C调节蛋白可作为癌症预后和诊断标志物。在肺腺癌中,m5C评分高的患者预后更好,且不同m5C修饰模式提示不同的免疫浸润模式^[30]。研究表明,m5C风险评分与肺鳞癌内中性粒细胞、静息CD4⁺记忆T细胞和M2巨噬细胞呈正相关,与滤泡辅助T细胞、CD8⁺T细胞和活化NK细胞呈负相关^[31]。m5C对TIME的影响也逐渐被证实存在于其他肿瘤中。

多项研究表明,m5C修饰参与了头颈鳞状细胞癌TIME的调控。NSUN3的敲低被证明能调控头颈鳞状细胞癌中巨噬细胞M1/M2极化,增加M1型巨噬细胞的浸润,并且在体内和体外抑制头颈鳞状细胞癌的生长^[32]。研究发现,低风险组的静息NK细胞、M2型巨噬细胞和中性粒细胞的含量显著低于高风险组,m6A/m5C/m1A相关lncRNA与头颈鳞状细胞癌的免疫微环境、肿瘤突变负荷有关,可用于预测头颈鳞状细胞癌免疫治疗的预后^[33]。

4 m5C与肿瘤免疫治疗

m5C相关肿瘤免疫治疗的基础和临床研究已取得重大进展^[34]。一方面,Segovia等^[35]联合使用m5C抑制剂和免疫检查点抑制剂,成功诱导癌细胞发生凋亡和免疫原性细胞死亡,这些效应与内源性抗肿瘤免疫反应和冷免疫肿瘤转热相关。另一方面,m5C甲基化修饰机制被用于提高mRNA免疫治疗的疗效。有研究发现m5C甲基化修饰降低了RNA的抗原性并抑制了免疫反应。甲基化修饰后,RNA的免疫原性减弱或消失,不再触发先天免疫。这是利用RNA进行免疫治疗方向的新突破^[36]。基于此,m5C/m1C组合修饰被用于提高外源mRNA逃避体内Toll样受体激活和下游先天免疫信号转导,进而提高mRNA表达蛋白质的能力^[37]。有生物团队设计材料递送m5C修饰的mRNA来重编程肿瘤相关巨噬细胞或抗癌T细胞,诱导抗肿瘤免疫并促进肿瘤消退^[38]。

在头颈鳞状细胞癌中,NSUN2与M2型巨噬细胞转化、T细胞活化呈负相关^[21]。因此,NSUN2被认为是头颈鳞状细胞癌免疫检查点阻断的潜在靶点。此外,NSUN2负向调控鼻咽癌肿瘤微环境中的免疫细胞浸润,提示NSUN2可能与免疫治疗和化疗的敏感性呈负相关。NSUN2可能是参与鼻咽癌进展的重要癌基因^[39]。

m5C调节蛋白及lncRNA相关风险模型的构建也为癌症治疗和疗效预测提供了新思路,可以用于指导更准确和个性化的免疫治疗方案。m5C相关风险评分是结肠癌患者的独立预后因素,低评分组对免疫治疗更敏感,而高评分组对化疗药物更敏感,该评分可用于预测结肠癌患者的预后、免疫治疗反应和药物敏感性^[40]。这些免疫治疗预测手段也被应用于其他肿瘤中。

5 小结

虽然有研究对m5C表观遗传修饰为癌症生物学和免疫反应的分子作用提供了新的见解,但对于其在恶性肿瘤中的调控机制、风险评估和靶向治疗的研究仍不够深入。首先,目前还没开发出靶向调节m5C的特异性小分子抑制剂;其次,大多数研究都集中在mRNA,部分最新研究提示了m5C对非编码RNA的修饰也在癌症发生发展中起重要作用。未来,RNA m5C在调控免疫系统和肿瘤免疫微环境中的作用将是研究的重要方向。值得注意的是,部分m6A甲基化调节基因也参与了m5C的催化,m6A与m5C的组合效应有待进一步探索。

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