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·综 述·

DNA甲基化与肿瘤免疫逃逸：作用机制与治疗研究现状

DNA methylation and tumor immune evasion: mechanism and current status of therapeutic research

任绍欣[a]综述；任伟宏[b]，王钰娜[a]审阅（河南中医药大学 a. 第一临床医学院；b. 第一附属医院 检验科，河南 郑州 450000）

[摘 要] 肿瘤免疫逃逸是肿瘤恶性进展的关键阶段，也是肿瘤免疫治疗所面临的一个主要挑战。研究表明，DNA甲基化可通过影响肿瘤抗原、MHC Ⅰ类分子、免疫检查点分子和免疫基因的表达，以及巨噬细胞的募集和极化介导肿瘤免疫逃逸的发生与进展，是肿瘤有前途的治疗靶点。目前，DNA去甲基化药物在肿瘤治疗领域的应用取得了新的进展，包括与免疫检查点抑制剂（ICI）、其他免疫药物和化疗药物等的联合应用，以及纳米药物和肿瘤疫苗等多种新型药物的开发等。为促进DNA去甲基化药物作为抗肿瘤药物的发展，本文探讨了DNA甲基化在肿瘤免疫逃逸中的作用机制及DNA去甲基化药物在实验室与临床相关试验研究现状，提出了改进措施和可能的研究方向。

[关键词] DNA甲基化；肿瘤免疫逃逸；DNA去甲基化药物；免疫检查点抑制剂
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在全球范围内，恶性肿瘤的发病率和死亡率正在逐年增长，癌症已经成为导致死亡的主要原因[1]。肿瘤细胞通过肿瘤免疫编辑过程[2]逃避免疫系统的监视，从而引发免疫逃逸而致肿瘤进展[3]。因此，肿瘤免疫逃逸是肿瘤恶性进展的关键步骤，也是免疫治疗的主要障碍之一[4]。表观遗传修饰在肿瘤免疫逃逸中起着关键作用[5]。DNA甲基化是通过影响DNA转录以控制基因表达的表观遗传修饰之一，其主要涉及由DNA甲基转移酶（DNA methyltransferase, DNMT）催化将甲基团（-CH3）从供体S-腺苷甲硫氨酸转移到DNA链胞嘧啶残基的5'碳原子上，尤其是胞嘧啶-磷酸-鸟嘌呤（cytosine-phosphate-guanine, CpG）岛区域[6]。近年来，DNA甲基化在肿瘤免疫逃逸中的调节作用得到了很好的表征，其能够使快速分裂和高度突变的肿瘤逃避免疫反应和抵抗免疫治疗[7]。DNA去甲基化药物在肿瘤治疗中也展现出显著的潜力，与其他抗肿瘤药物的联合治疗表现出更高的疗效，但仍需深入研究以优化治疗方案[8]。本文通过从肿瘤免疫逃逸的角度分析DNA去甲基化药物的治疗机制，深入讨论DNA去甲基化药物及联合其他药物治疗的研究进展，旨在为未来靶向DNA甲基化开展肿瘤治疗提供新的策略。

1 DNA甲基化在肿瘤免疫逃逸中的作用机制

肿瘤细胞通过产生对免疫效应具有抗性的肿瘤变异和在肿瘤内逐渐形成免疫抑制微环境来逃避免疫攻击[9]，限制癌症免疫循环[10]的各个环节，影响固有免疫应答和适应性免疫应答过程，从而实现肿瘤免疫逃逸。DNA甲基化则通过调控基因表达直接或间接地促使这些改变的形成而介导肿瘤免疫逃逸的发生与进展（图1）。

1.1 通过影响抗原提呈介导肿瘤免疫逃逸

肿瘤细胞表达的肿瘤抗原减少或缺失，其将不能被有效识别[11-12]。DNA甲基化可促使肿瘤抗原表达下降以促进肿瘤免疫逃逸。研究显示，携带新抗原基因的启动子高甲基化可致使新抗原耗竭[13]，这表明DNA甲基化对肿瘤抗原表达的直接影响。此外，DNA甲基化在缺氧反应元件位点排斥缺氧诱导转录因子的结合，进而阻断缺氧诱导的免疫冷肿瘤中隐匿转录物的表达，使用去甲基化药物后以缺氧诱导转录因子依赖性方式增加了隐匿转录、增强了免疫原性并减少了肿瘤生长[14]。环状GMP-AMP合酶（cyclic GMP-AMP synthase, cGAS）和干扰素基因刺激因子（stimulator of interferon gene, STING）的启动子高甲基化导致其转录沉默，进而导致STING信号通路转导功能障碍。使用去甲基化药物5-氮杂-2'-脱氧胞苷介导STING信号的恢复增强了黑色素瘤细胞亚群的抗原性和主要组织相容性复合体（MHC）Ⅰ类分子的表达[15]。DNA甲基化也可直接作用于HLA-A启动子导致其表达减少[16]。肿瘤细胞表面MHC Ⅰ分子的表达下调将使其提呈肿瘤抗原的能力减弱，阻碍效应T细胞的杀伤[17-21]。

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[作者简介] 任绍欣（1998—），女，硕士生，主要从事肿瘤分子检测技术研究。E-mail: renshaoxin0620@163.com
[通信作者] 任伟宏，E-mail: ren_weihong@163.com

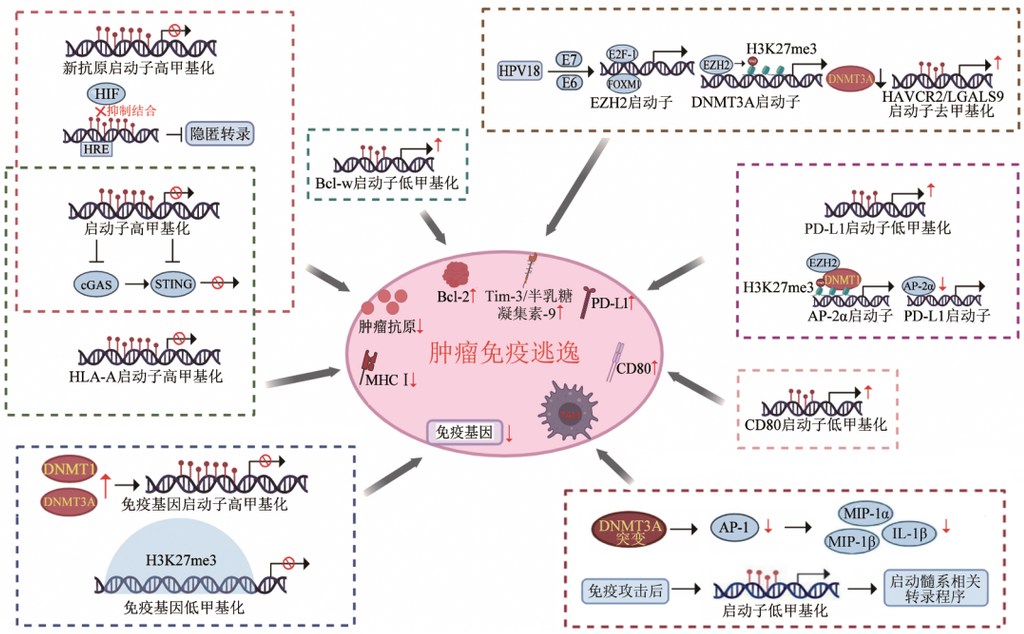

图1　DNA甲基化在肿瘤免疫逃逸中的作用机制（使用BioRender.com创建）

1.2　通过调节免疫检查点分子表达介导肿瘤免疫逃逸

肿瘤细胞可表达、分泌或驱动多种免疫抑制分子来抑制机体的抗肿瘤免疫，其中免疫检查点分子与其配体相互作用可抑制T细胞的活化和效应，促进肿瘤免疫逃逸[22-31]。在神经胶质瘤中，zeste同源物增强子2（enhancer of zeste homolog 2, EZH2）/组蛋白H3第27位赖氨酸的三甲基化（tri-methylation of histone H3 lysine 27, H3K27me3）/DNMT1复合物增强转录因子AP-2α（transcription factor AP-2-alpha）的甲基化导致AP-2α低表达，进而导致AP-2α对PD-L1的转录抑制活性和内吞降解作用下降，使PD-L1表达增高，促进了胶质瘤的免疫逃逸[32]。敌草隆暴露和Akt过表达通过DNA低甲基化促进神经胶质瘤形成及介导PD-L1与Bcl-w的过表达[33]，肿瘤细胞高表达Bcl-2家族抗凋亡蛋白可抵抗效应T细胞等诱导的凋亡，逃避杀伤效应[34-37]。另外，在牙龈-颊口腔鳞状细胞癌中发现DNMT3B（上调）和甲基胞嘧啶双加氧酶1（下调）的表观遗传修饰引起的显著失调，以及由于显著启动子低甲基化驱动的PD-L1和CD80上调[38]。人乳头瘤病毒18型（HPV18）癌蛋白E6和E7介导的转录因子E2F-1和叉头框蛋白M1（forkhead box M1, FOXM1）通过EZH2-H3K27me3-DNMT3A调控HAVCR2/LGALS9启动子区域的去甲基化，导致宫颈癌共刺激分子Tim-3/半乳糖凝集素-9（galectin-9）的表达上调，Tim-3/galectin-9的结合引起免疫耐受，在致癌过程中导致免疫逃逸[39]。

1.3　通过抑制免疫基因的表达介导肿瘤免疫逃逸

CpG岛甲基化表型（CpG island methylator phenotype, CIMP）在多种肿瘤类型中可见[40]，其特征为基因启动子区域CpG岛的高甲基化。在肾上腺皮质癌中，由于基因组畸变和过度增殖，DNMT1和DNMT3A的表达增加，导致数百个基因的启动子DNA甲基化增加，CIMP直接引起了免疫相关基因的抑制及肿瘤浸润免疫细胞的减少，从而促进肿瘤免疫逃逸和侵袭，用DNA去甲基化药物5-氮杂胞苷处理则重新激活了免疫相关基因[41]。还有研究[42]发现，在早期前列腺癌中部分DNA低甲基化结构域富集H3K27me3，导致免疫相关基因的沉默。

1.4　通过影响巨噬细胞的募集和极化介导肿瘤免疫逃逸

DNA甲基化可介导肿瘤相关巨噬细胞的极化和功能重塑，进而促进肿瘤的恶性进展，易化肿瘤的免疫逃逸[43]。DNMT3A突变的急性髓系白血病（acute myeloid leukemia, AML）预后不良。研究[44]显示，DNMT3A突变的AML细胞通过AP-1位点抑制炎症因子MIP-1α、MIP-1β和IL-1β的表达进而减弱M1巨噬细胞极化并抵抗其杀伤作用，实现免疫逃逸。5-氮杂-2'-脱氧胞苷可以刺激巨噬细胞向M1样表型的活化[45]。胶质母细胞瘤干细胞（glioblastoma stem cell, GSC）在暴露于体内环境和随后的免疫攻击之后，GSC经历位点特异性DNA甲基化变化以及伴随的转录变化，这些变化启动了髓系相关的转录程序，导致肿瘤相关巨噬细胞的募集增加[46]。

2 DNA去甲基化药物的相关实验室研究

2.1 与免疫检查点抑制剂（immune checkpoint inhibitor, ICI）联用

DNA去甲基化药物与ICI联合用药的策略是一种创新的肿瘤治疗方法，它结合了两种不同机制的药物以期增强治疗效果。研究[47]显示，地西他滨（decitabine, DAC）治疗可使结直肠癌细胞中干性标志物和PD-L1表达上调，这可能会诱导免疫逃逸，但其诱导癌症睾丸抗原NY-ESO-1的高表达可增强免疫应答，因此DAC联合抗PD-1/抗PD-L1抗体治疗是潜在的治疗措施。另一项研究结果[32]表明，使用DAC与抗PD-1免疫疗法相结合治疗，可有效抑制GL261神经胶质瘤细胞的进展。DNA甲基转移酶抑制剂guadecitabine是DAC的二核苷酸前药，通过抑制DNMT1引起非特异性低甲基化，与ICI或guadecitabine单独治疗相比，与ICI联合使用可显著减少皮下黑色素瘤的生长和转移形成；尤其是guadecitabine通过增加效应记忆$CD8^+$T细胞、诱导脾中效应NK细胞、减少肿瘤微环境中的肿瘤浸润性Treg细胞和髓源性抑制细胞，大大提高了联合ICI的疗效[48]。

另外，还有基于这两种药物联合用药的新形式。一种新型纳米调节剂采用“双向调控”的表观遗传治疗策略，利用DNMT抑制剂泽布拉林（zebularine, Zeb）上调肿瘤相关抗原的表达而提高免疫原性，溴结构域蛋白4抑制剂JQ1下调PD-L1表达以阻断PD-1/PD-L1的结合，toll样受体9（toll-like receptor 9, TLR9）激动剂CpG可以促进DC成熟，从而与Zeb共同促进T细胞的活化；将Zeb和JQ1通过静电相互作用与缩合的CpG共同加载到阳离子脂质体中，以获得G-J/ZL，然后，将天冬酰胺-甘氨酸-精氨酸（asparagine-glycine-arginine, NGR）修饰材料羧甲基壳聚糖涂覆在G-J/ZL的表面，构建核壳结构CG-J/ZL；在NGR的介导下，CG-J/ZL可以靶向肿瘤组织并在酸性肿瘤微环境下触发分解[49]。PPD（mPEG-b-PLG/PEI-RT3/DNA）通过引入多种相互作用和聚脯氨酸Ⅱ（polyproline Ⅱ, PPⅡ）-螺旋构象介导编码shPD-L1的质粒递送，从而下调肿瘤细胞上PD-L1的表达以缓解T细胞的免疫抑制，Zeb是一种DNMT抑制剂，诱导DC成熟和MHC Ⅰ分子表达以增强抗原提呈，PPD与Zeb联合治疗启动全身抗肿瘤免疫反应，通过产生持久的免疫记忆来有效防止肿瘤复发和转移[50]。

2.2 其他新型药物联用

一种基于双金属有机骨架的仿生纳米平台[a bimetallic metal-organic framework（MOF）-based biomimetic nanoplatform, AFMMB]，由DNA去甲基化药物、白血病干细胞膜和促自噬肽组成，自噬触发的AFMMB溶解释放出活性成分，通过抑制DNA甲基化、上调MHC Ⅰ类分子和诱导RNA甲基化介导的PD-L1转录物的衰变，从而恢复干扰素基因通路的刺激因子，增强T细胞介导的免疫反应，抑制实体瘤的生长和转移[51]。一种新型药物采用六聚组氨酸（hexahistidine, His6）-金属组装体（metal assembly, HmA）作为递送载体，装载尼日利亚菌素（nigericin, Nig）和DAC，形成双重药物递送系统（Nig+DAC）@HmA，Gasdermin D（GSDMD）是一种由胱天蛋白酶-1（caspase-1）介导的细胞焦亡过程中的关键蛋白，在大多数肿瘤细胞中表达较低，DAC通过DNA去甲基化上调GSDMD的表达，GSDMD随后被Nig激活的核苷酸结合寡聚化结构域样受体蛋白3炎性体和caspase-1蛋白切割，实现了有效的肿瘤细胞焦亡，并诱导显著的全身抗肿瘤免疫反应[52]。TLR7激动剂SZU-106与去甲基化药物DAC偶联，处理AML细胞以构建肿瘤疫苗，DAC治疗增加AML细胞中肿瘤抗原表达，SZU-106-DAC-AML增强了DC和T细胞在体内外的活化，显著抑制肿瘤生长，延长动物生存期[53]。

3 DNA去甲基化药物的临床试验研究

目前有一些临床试验正在研究DNA去甲基化药物与ICI联合治疗肿瘤的效果（表1），大多数研究结果表明，联合治疗是安全可耐受的，且部分研究显示其具有良好的免疫调节和抗肿瘤活性，但也有一些研究未能证明其在提高临床疗效方面取得显著进展。

还有一些联合用药研究展现出抗肿瘤活性。用阿扎胞苷和卡铂联合治疗可以诱导转移性黑色素瘤的疾病稳定和对ICI的再敏感，在阿扎胞苷和卡铂治疗后，HLA-A普遍升高，HLA-A位点上增加的平均甲基化降低，T细胞（尤其是$CD8^+$T细胞）浸润幅度增大[62]。口服5-氮杂胞苷和组蛋白脱乙酰酶抑制剂罗米地辛（romidepsin）联合治疗外周T细胞淋巴瘤安全、有效，且具有高度活性，可获得高缓解率并延长缓解期[63]。Guadecitabine和顺铂的组合是可耐受的，在铂难治性生殖细胞癌患者中显示出活性[64]。此外，一些研究未观察到明显的临床治疗效果。可切除胰腺导管腺癌患者辅助治疗后使用CC-486（口服DNMT抑制剂阿扎胞苷）治疗并未延长复发时间和总生存期，也未改善一线转移性治疗的疾病反应[65]。Guadecitabine与结直肠癌疫苗（GVAX）联合治疗可耐受，但在结直肠癌患者中无明显的免疫活性[66]。

表1 DNA去甲基化药物与ICI的临床试验研究

DNA去甲基化药物	ICI	ICI靶点	肿瘤类型	临床效果	文 献
Guadecitabine	伊匹木单抗	CTLA-4	黑色素瘤	安全、可耐受；良好的免疫调节和抗肿瘤活性	[54]
Guadecitabine	阿替利珠单抗	PD-L1	转移性尿路上皮癌	诱导少数患者的免疫激活；未达到预期效果	[55]
Guadecitabine	帕博利珠单抗	PD-1	实体瘤	安全、可耐受；具有抗肿瘤活性	[56]
Guadecitabine	帕博利珠单抗	PD-1	卵巢癌	可行；产生了与免疫反应相关的临床益处	[57]
阿扎胞苷	帕博利珠单抗	PD-1	骨髓增生异常综合征	安全，毒性可控；在部分患者中有抗肿瘤活性	[58]
阿扎胞苷	帕博利珠单抗	PD-1	转移性结直肠癌	安全，可耐受；临床活性适中	[59]
阿扎胞苷	度伐利尤单抗	PD-L1	AML	可行；未提高临床疗效	[60]
CC-486	度伐利尤单抗	PD-L1	实体瘤	未见强大的药效学或临床活性	[61]

4 结　语

DNA甲基化在肿瘤免疫逃逸中扮演了重要的角色，靶向DNA甲基化的肿瘤治疗具有巨大的潜力与挑战。尽管一些临床试验显示DNA去甲基化药物的应用具有抗肿瘤与免疫调节作用，但治疗效果仍未达到预期标准。由于肿瘤表观遗传学和肿瘤免疫学之间相互作用的复杂性，在未来的临床试验中，应优化表观免疫疗法的剂量、计划和组合[67]。通过精准医学方法，利用特定生物标志物选定患者群体，设计临床试验来优化这些药物组合的开发和使用，并注重预测性生物标志物的识别、药物给药策略的调整，以及临床试验设计和反应标准方面的研究[68]。另外，这些措施需要综合考虑肿瘤的生物学特征、患者的个体差异以及治疗方法的复杂性。特别地，鉴于纳米调节剂等新型药物的良好实验效果，应积极推进其进一步的开发和深入研究，以便加速其从实验成果向临床应用的转化过程。未来的研究和临床实践将不断为提高DNA去甲基化药物治疗肿瘤效果提供新的认识和方法。

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