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·专家论坛·

基于B7H3促瘤机制的靶向抗肿瘤策略：机遇与挑战

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［摘　要］ 以靶向PD-1/PD-L1和CTLA-4为代表的免疫检查点阻断治疗在实体瘤的治疗中取得了不俗疗效，但仅有不到30%的患者能够从中受益的现实表明，还存在其他免疫检查点分子介导的免疫抑制。B7H3属于免疫球蛋白超家族B7家族成员，与CTLA-4/PD-1主要表达在T细胞并介导后者的免疫抑制或耗竭不同，B7H3蛋白不仅诱导性表达在免疫细胞，还组成性高表达在多种肿瘤细胞和肿瘤相关脉管系统。B7H3不仅能够激活多条信号通路直接促进肿瘤细胞恶性表型，还可以通过重塑肿瘤免疫抑制微环境间接促进肿瘤的进展、转移和耐药。因此，基于B7H3的多项靶向抗肿瘤策略，包括特异性抗体、抗体偶联药物及CAR-T细胞等均已进入临床试验并展示出较好的应用前景。但总体而言，该领域的研究依然处于探索阶段，在相互作用受体的鉴定、降低毒性、打破耐药及联合用药策略优化等方面还面临着许多问题和挑战亟待突破。

［关键词］ B7H3；免疫检查点；免疫逃逸；肿瘤免疫；靶向治疗
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Targeted anti-tumor strategies based on the tumor-promoting mechanisms of B7H3: opportunities and challenges

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[Abstract] Immune checkpoint blockade (ICB) therapy, represented by PD-1/PD-L1 and CTLA-4, has achieved remarkable efficacy in the treatment of solid tumors; However, only less than 30% of the patients benefit from it, suggesting that there still exists other immune checkpoints molecule-mediated immunosuppression. B7H3 is a member of the B7 immunoglobulin superfamily. Unlike CTLA-4 or PD-1 which is mainly expressed in T cells to mediate their immunosuppression or depletion, B7H3 is not only inducibly expressed in immune cells, but also constitutively highly expressed in various tumor cells and tumor-associated vascular systems. B7H3 not only directly promotes the malignant biological phenotypes of tumor cells by activating multiple signaling pathways, but also indirectly promotes tumor progression, metastasis and drug resistance by remodeling tumor immunosuppressive microenvironment. Therefore, several targeted anti-tumor strategies targeting B7H3, including specific antibodies, antibody-drug conjugation (ADC) and CAR-T, have entered clinical trials and shown promising application prospects. However, in general, the research of B7H3 is still in the exploratory stage. There are still many bottlenecks and challenges to be overcome in the identification of reciprocal receptors, reduction of toxicity, breaking drug resistance, and optimization of combination drug therapy, *etc*.

[Key words] B7H3; immune checkpoint; immune escape; tumor immunity; targeted therapy
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B7H3(CD276)是一种穿膜糖蛋白,属于免疫球蛋白超家族B7家族成员。B7H3 mRNA在组织细胞广泛表达,但其蛋白表达极为严格,主要组成性表达在肿瘤细胞和肿瘤相关脉管系统,诱导性表达在某些免疫细胞;而在正常组织细胞不表达或低水平表达[1]。B7H3在mRNA和蛋白水平上的表达差异与miRNA和甲基化修饰等转录后调控相关[2-5]。除了胞膜表达,在血清和外泌体中亦检测到可溶性B7H3(soluble B7H3,sB7H3)的存在[6]。遗憾的是,至今尚未鉴定出其特异性受体,这为靶向B7H3的研究带来许多不确定性甚至正反两面性。随着研究的深入,B7H3的促瘤机制逐渐清晰,可概括为两个方面:一是直接促进肿瘤细胞恶性表型的改变;二是通过调控肿瘤免疫微环境抑制抗肿瘤免疫应答,进而促进肿瘤进展。基于B7H3的促肿瘤效应,靶向B7H3的抗肿瘤策略应运而生,单克隆抗体、双特异性抗体、抗体-药物偶联物(antibody-drug conjugation,ADC)及CAR-T细胞等疗法已在临床前及临床试验中进行安全性和有效性评估,为靶向B7H3生物药的临床应用提供了广阔的发展前景。

1　B7H3直接促肿瘤进展的机制

B7H3在肿瘤组织及肿瘤相关脉管系统高表达与肿瘤患者的临床病理和预后呈显著负相关。B7H3通过激活多条信号通路直接提升肿瘤细胞的增殖和侵袭能力;通过促进EMT、肿瘤干性、新生血管生成及有氧糖酵解等机制促进肿瘤的进展、转移和耐药。

1.1　B7H3诱导肿瘤细胞恶性表型

B7H3蛋白在多种肿瘤组织中组成性上调表达,尤其高表达于明显缺乏炎性浸润和PD-1、PD-L1及CTLA-4表达低下的转移灶中[7];且与患者的临床分期、肿瘤体积及淋巴血管转移等临床病理显著相关[8-9],提示B7H3可作为肿瘤预后不良的指标。在骨髓瘤中,B7H3诱导ROS增加导致Src激活和负调控因子SHP-1(Src homology 2 domain containing phosphatase 1)失活,介导细胞因子信号转导抑制因子3(suppressor of cytokine signaling 3,SOCS3)蛋白酶体降解并促进STAT3活化,激活下游靶基因转录,从而促进肿瘤细胞生长、存活和化疗耐药[10]。B7H3高表达的肿瘤细胞通过促进己糖激酶2(hexokinase-2,HK2)表达,或通过ROS介导HIF-α稳定重塑葡萄糖代谢,提高肿瘤葡萄糖摄取和乳酸生成能力,促进肿瘤进展[11-12]。此外,与正常细胞相比,口腔癌细胞的B7H3 N-聚糖末端α-半乳糖具有高度多样的岩藻糖基化修饰,这些修饰能够增强其与免疫细胞DC-SIGN和CD207的作用,提示聚糖修饰在B7H3介导的直接促瘤中发挥重要作用[8]。

1.2　B7H3促进肿瘤转移相关因子的表达

B7H3可通过激活PI3K/Akt/mTOR、NF-κB及JAK2/STAT3/Slug等多条信号途径调控肿瘤转移相关细胞因子或金属蛋白酶如IL-8、MMP-2/-9及TIMP1/2的表达,促进肿瘤的侵袭和转移[13-14];阻断JAK2/STAT3信号或采用shRNA沉默B7H3表达能够显著抑制结直肠癌或黑色素瘤的侵袭能力[1]。肿瘤血管生成是肿瘤转移的一个重要指标,B7H3蛋白表达与血管内皮细胞标志蛋白CD31表达水平呈显著正相关;B7H3通过激活NF-κB通路上调VEGF表达,进而促进肿瘤血管的生成和肿瘤的侵袭、转移[15-17]。

1.3　B7H3促进肿瘤耐药发生

肿瘤干细胞(cancer stem cell,CSC)是肿瘤化疗耐药发生的重要因素。B7H3能够促进结直肠癌对奥沙利铂/5-FU或多柔比星的化疗耐药,增强肿瘤细胞抗辐射能力[18-20];用shRNA沉默肿瘤细胞B7H3的表达能够显著增强细胞对化疗药物的敏感性[21]。B7H3通过激活MAPK激酶信号增加CSC数量,或上调HK2提升结直肠癌有氧糖酵解效能进而促进肿瘤的进展和化疗抵抗[12,22]。B7H3中和性抗体可有效清除CSC,抑制人头颈鳞状细胞癌模型小鼠肿瘤的生长和淋巴结转移[23]。此外,B7H3通过激活NF-κB/ERK1/2通路和调节自噬基线水平增强结直肠癌的抗辐射能力,B7H3特异性抗体3E8能够显著提升结直肠癌对辐射的敏感性[19,24]。

2　B7H3间接促肿瘤机制

除了直接促进肿瘤细胞的恶性表型,B7H3还可以通过抑制免疫细胞如T细胞和NK细胞的抗肿瘤效能,增强免疫抑制性细胞亚群如肿瘤相关巨噬细胞(tumor-associated macrophage,TAM)及Treg细胞的促瘤能力,营造适宜肿瘤生长和转移的免疫微环境,从而发挥间接促瘤作用。

2.1　B7H3抑制T细胞介导的抗肿瘤效应

来自TCGA肿瘤数据库11 060例不同类型肿瘤患者的数据分析结果显示,B7H3与mTORC1的高表达与肿瘤免疫抑制表型及患者预后不良呈显著正相关;抑制B7H3能够通过增强细胞毒性T细胞(cytotoxic T cell,CTL)活性、IFN-γ效应及上调肿瘤细胞表面MHC-Ⅱ类分子表达从而削弱mTORC1活化介导的促肿瘤作用;B7H3缺失的肿瘤组织中$CD4^+CD38^+CD39^+$CTL数量显著增加[25]。应用B7H3缺陷小鼠或B7H3中和性抗体治疗,荷瘤小鼠CTL抗肿瘤效能显著增强,肿瘤生长明显抑制[26]。B7H3糖基化异常是导致其蛋白稳定性下调和三阴性乳腺癌免疫

抑制的主要原因。糖基化异常的B7H3通过限制T细胞的瘤内浸润、增殖和活化进而抑制CTL对肿瘤细胞的杀伤;岩藻糖基转移酶FUT8通过催化N-聚糖上的核心岩藻糖基化以维持B7H3高表达,敲除FUT8能够恢复CTL抗肿瘤效能从而抑制肿瘤进展[27]。

2.2 B7H3增强免疫抑制细胞亚群功能

肿瘤组织B7H3高表达与M2型巨噬细胞和静息$CD4^+$记忆性T细胞数量以及与$FOXP3^+$ Treg细胞的浸润呈显著正相关[2,28]。有学者分析了纤维板层癌组织微环境中各种免疫检查点分子的表达,发现在适应性免疫应答抵抗患者的肿瘤组织中B7H3、PD-1、PD-L1和IDO表达显著提高;在40%患者的肿瘤组织检查到B7H3高表达;在91%患者肿瘤组织的肿瘤浸润淋巴细胞(tumor infiltrating lymphocyte,TIL)和TAM中检测到B7H3的表达[29]。B7H3通过CCL2-CCR2-M2巨噬细胞轴介导的免疫抑制促进肿瘤进展[30];通过m^6A依赖的免疫微环境重塑促进Treg细胞在瘤内募集进而导致肿瘤免疫逃逸[2]。

2.3 B7H3抑制固有免疫介导的抗肿瘤效应

非小细胞肺癌患者B7H3高表达的肿瘤组织中$CD8^+$ T细胞、NK细胞和浆细胞样DC数量均显著增加[31];抑制急性髓系白血病(AML)细胞中B7H3的表达显著增强NK细胞的杀伤作用[32]。此外,B7H3高表达可上调IL-10,抑制IL-12、IFN-γ及TNF-α等炎症细胞因子的产生进而促进肿瘤的免疫逃避[33-35]。

3 靶向B7H3的抗肿瘤策略

肿瘤表达的B7H3不仅能够直接促进肿瘤细胞自身的增殖、侵袭、EMT或干性等恶性表型,还通过重塑肿瘤免疫微环境间接促进肿瘤的进展和转移。因此,基于B7H3的抗肿瘤策略不仅能直接靶向肿瘤本身,还能解除肿瘤微环境免疫抑制,达到一箭双雕的效果。

3.1 基于B7H3抗体的治疗方案

3.1.1 靶向B7H3的抗体阻断疗法 大量临床前研究表明,B7H3中和性抗体能够显著增加肿瘤微环境中$CD8^+$ T细胞和NK细胞浸润,抑制肿瘤生长,延长卵巢癌[36]、黑色素瘤[26]和结肠癌[37]等模型小鼠生存期。在近期一项Ⅱ期临床试验(NCT02923180)中,SHENDEROV等[38]将Fc增强型B7H3单抗依诺布利妥单抗(enoblituzumab/MGA271)用于侵袭性前列腺癌患者术前的新辅助治疗,结果显示,入组的32例患者中有21例(66%)术后12个月未检测到前列腺特异性抗原PSA,耐受性良好;治疗后患者肿瘤组织中CTL的数量显著提升,推测该抗体通过解除B7H3介导的免疫抑制从而激活患者机体的抗肿瘤免疫应答,抑制肿瘤的进展。

3.1.2 基于B7H3抗体的放射免疫疗法 抗B7H3单克隆抗体常被用作载体与放射性核素偶联以特异性靶向肿瘤组织,实现对肿瘤的特异性杀伤,减轻放化疗的不良反应和并发症。B7H3单克隆抗体376.96偶联^{212}Pb显著抑制胰腺癌异种移植小鼠的肿瘤生长,延长荷瘤小鼠的生存期[39]。放射性核素I标记的人源化B7H3单克隆抗体8H9(^{131}I-8H9),在多个中枢神经系统转移瘤患者临床试验(NCT00089245、NCT01502917和NCT01099644)中均显示患者的生存期显著延长,表明B7H3是放免治疗有希望的靶点[40]。

3.1.3 靶向B7H3的ADC ADC由抗体通过连接子结合细胞毒性药物组成,兼具抗体药的特异性和细胞毒性药物的强杀伤作用,是当前肿瘤治疗领域发展迅速的一类药物。MGC018是一种偶联多卡霉素(duocarmycin)的人源化B7H3单抗药物,可将多卡霉素定向输送到肿瘤组织。在乳腺癌、卵巢癌、肺癌以及黑色素瘤的临床前肿瘤模型中,MGC018均显示出强大的抗肿瘤活性,在食蟹猴体内也表现出良好的药代动力学和安全性[41]。吡咯苯唑氮偶联的B7H3抗体药物可同时靶向$B7H3^+$肿瘤和肿瘤脉管系统,在多种实体瘤临床前模型中展现出良好的抗肿瘤活性[42]。此外,拓扑异构酶Ⅰ抑制剂偶联的B7H3单克隆抗体DS-7300a已经进入Ⅰ期/Ⅱ期临床试验(NCT04145622)[1]。

3.1.4 靶向B7H3的双/三特异性抗体 双特异性抗体(bispecific antibodies,BsAb)是由两种不同单克隆抗体的片段人工合成的抗体,具有增强肿瘤特异性杀伤的同时减少脱靶效应的优势。靶向B7H3双特异性抗体由抗CD3单链抗体与B7H3单链抗体连接构建,可同时靶向T细胞表面的CD3分子及肿瘤细胞表达的B7H3,招募并激活T细胞进入肿瘤组织发挥抗肿瘤效能[43]。一种基于BsAb mRNA的治疗方法,即将编码B7H3×CD3-BsAb的mRNA封装到脂质纳米颗粒中,可显著延长BsAb的半衰期,对血液系统恶性肿瘤和黑色素瘤显示出持久的抗肿瘤效能[44]。然而,一项CD3×B7H3人源化BsAb(obrindamab)在治疗$B7H3^+$晚期肿瘤的Ⅰ期临床试验(NCT02628535)中,由于入组患者发生肝不良反应,试验被提前终止[1]。

三特异性杀伤细胞接合器(tri-specific killer engager,TriKE)由3个具有不同特异性的单链抗体或2个单链抗体(CD16特异性和目标抗原特异性)和一种细胞因子(最常见的是IL-15)组成,可在NK细胞和肿瘤细胞之间形成抗原特异性免疫突触,从而触发NK细胞介导的肿瘤细胞裂解[45]。VALLERA等[46-47]将B7H3的单链抗体和CD16单链抗体通过交联

人IL-15构建了第一代和第二代B7H3/IL-15/CD16 TriKE，该TriKE通过促进NK细胞的增殖和活化增强对肿瘤细胞的杀伤活性，显著降低肿瘤荷载量。表1汇总了目前在研的基于B7H3抗体的临床试验项目。

表1　基于B7H3抗体的抗肿瘤研发项目

药名/代码	研发阶段	机 构	治疗领域/适应证	靶 点	药物类型
Omburtamab/131-I-8H9	申请上市	Y-Mabs（赛生药业公司大中华权利）	神经母细胞瘤，转移癌，腹膜癌	B7H3	放射性单抗
Enoblituzumab/TJ271	临床Ⅱ期	Macrogenics（天境生物公司大中华权利）	实体瘤：头颈癌，非小细胞肺癌，尿路上皮癌	B7H3	单抗
MGC-018	临床Ⅱ期	Macrogenics公司	肝癌，黑色素瘤，卵巢上皮癌，去势抗性前列腺肿瘤，肾细胞癌，胰腺导管腺癌	B7H3	ADC
DS-7300	临床Ⅱ期	第一三共公司	实体瘤	B7H3	ADC
Mirzotamab clezutoclax; ABBV-155	临床Ⅰ期	艾伯维公司	血液肿瘤，实体瘤	B7H3	ADC
BAT8009	临床Ⅰ期	百奥泰公司	实体瘤	B7H3	ADC
XmAb-808	临床前	Xencor公司	肾细胞癌	B7H3×CD28	BsAb
LVGN-5596	临床前	礼进生物公司	实体瘤	B7H3×CD40	BsAb
ATG-027	临床前	德琪医药公司	实体瘤，血液肿瘤	B7H3×PD-L1	BsAb
GTB-5550	临床前	明尼苏达大学；GT Biopharma公司	实体瘤	B7H3×CD16×IL15	三特异性抗体
MIL-108	临床前	天广实生物公司、百奥赛图公司	实体瘤	B7H3	单抗
SHR-1812	临床前	恒瑞医药公司	肿瘤	CD3×B7H3	双抗

注：数据来自https://clinicaltrials.gov/

3.2　靶向B7H3的CAR-T细胞抗肿瘤策略

B7H3蛋白在肿瘤组织及肿瘤相关脉管组织高表达而在正常组织低表达或不表达的特性，使其成为CAR-T细胞设计的理想肿瘤抗原靶标，表2汇总了目前在研的靶向B7H3的CAR-T细胞临床试验项目。靶向B7H3的CAR-T细胞在多种实体瘤和血液瘤中显示出强大的抗肿瘤活性，且未检测到明显毒性，其中一种B7H3-CAR-T细胞（TAA-06）已经获得FDA治疗神经母细胞瘤孤儿药资格认定[48]。但TANG等[49]报道了一例B7H3-CAR-T细胞治疗复发性胶质母细胞瘤患者的临床试验，该CAR-T细胞仅能在治疗早期（＜50 d）发挥抗肿瘤功效，随后会产生耐药，即使增加细胞用量亦无法打破耐药。为进一步提高CAR-T细胞的抗肿瘤效果，YANG等[50]通过构建B7H3和CD70串联的CAR-T细胞以提高其抗肿瘤活性；LEI等[51]用泛组蛋白脱乙酰酶抑制剂SAHA增强B7H3特异性CAR-T细胞在实体瘤中的抗肿瘤活性；LI等[52]在B7H3-CAR-T细胞中共表达T细胞趋化因子CCL2受体（CCL2b）以促进CAR-T细胞通过血脑屏障，显著提高了非小细胞肺癌脑转移患者的治疗效果。

3.3　靶向B7H3的联合治疗

抗肿瘤免疫涉及多种途径，通过合理组合可有效增强抗肿瘤免疫治疗潜力，如联合阻断B7H3和PD-L1可显著增加肿瘤抗原特异性$CD8^+$ T细胞抗肿瘤效应[53]。Ⅰ期临床试验结果显示，依诺布利妥单抗联合CTLA-4抗体[54]或PD-1抗体[55]治疗较单独任何一种抗体药物都更有效，两者联合治疗显著提升TIL的瘤内募集和抗肿瘤活性，且未见剂量依赖毒性和严重不良反应。依诺布利妥单抗联合帕博利珠单抗在初发性/转移性非小细胞肺癌和复发性/转移性头颈鳞状细胞癌患者中的总反应率分别可达36%和33%[56]。靶向B7H3×CD3的BsAb联合索拉非尼在卵巢癌模型中展现出协同抗肿瘤作用，有望成为卵巢癌患者治疗的新选择[57]。除上述联合治疗方案外，B7H3抑制剂联合外科治疗[58]、射频消融[59]、介入治疗、电场治疗[60]等也逐渐受到关注。ZHANG等[61]在前列腺癌异种移植鼠模型中证实，B7H3-CAR-T细胞联合分次辐照（fractionated radiation，FIR）治疗比单独治疗更有效。

表2 靶向B7H3的CAR-T细胞治疗研发项目

药名/代码	研发阶段	机 构	治疗领域/适应证	靶 点	药物类型
TAA-06	FDA孤儿药认定/临床Ⅰ期	博生吉公司	肺癌,黑色素瘤,结直肠癌,神经母细胞瘤等实体瘤	B7H3	CAR-T细胞
KT-032	临床前	南京卡提公司	间皮组织肿瘤,卵巢癌,三阴性乳腺肿瘤,胰腺癌	Mesothelin;B7H3	CAR-T细胞
fhB7H3.CAR-Ts	临床Ⅱ期	徐州医科大学附属医院	转移性卵巢癌	B7H3	CAR-T细胞
EGFR/B7H3 CAR-T	临床前	广州医科大学附属第二医院	转移性乳腺癌;转移性肺癌	EGFR;B7H3	CAR-T细胞
CAR.B7-H3	临床Ⅰ期	UNC Lineberger综合癌症中心	输卵管癌,胶质母细胞瘤,神经母细胞瘤,卵巢肿瘤,胰腺导管腺癌,腹膜肿瘤	B7H3	CAR-T细胞
SCRI-CARB7H3(s)	临床Ⅰ期	西雅图儿童医院	肾上腺皮质癌,晚期实体瘤,尤因肉瘤,生殖细胞和胚胎癌,肝母细胞瘤,黑色素瘤,肾母细胞瘤,神经母细胞瘤,骨肉瘤,横纹肌肉瘤,软组织肉瘤	B7H3	CAR-T细胞
B7H3-CAR-T cell	临床Ⅰ期	圣裘德儿童研究医院	骨肉瘤,横纹肌肉瘤,神经母细胞瘤,尤因肉瘤,肝母细胞瘤,黑色素瘤,恶性上皮肿瘤,软组织肉瘤	B7H3	CAR-T细胞
4SCAR-276	临床Ⅱ期	深圳市免疫基因治疗研究院	神经母细胞瘤,实体瘤	B7H3	CAR-T细胞

注:数据来自https://clinicaltrials.gov/

4 存在问题与解决思路

鉴于B7H3蛋白在肿瘤中表达的特异性,靶向B7H3的抗肿瘤策略终将发展得丰富多彩。尽管靶向B7H3的临床前及临床试验已显示出较好的临床应用前景,但总体而言,该领域的研究依然处于探索阶段,距离真正的临床应用还面临着许多挑战亟待突破,当然其中也蕴藏着更多的发现和机遇。

4.1 B7H3受体未明使基于B7H3的靶向治疗受限

至今为止B7H3的受体仍未明确,使得靶向B7H3的免疫治疗不能像PD-1/PD-L1抑制剂那样双管齐下靶向配体和受体。尽管在小鼠中发现了TLT-2可与B7H3结合,但是人类中未发现类似的相互作用[62]。HUSAIN等[63]利用自行开发的高通量高灵敏配体-受体互作平台检测技术,鉴定出IL-20RA可能是B7H3受体,但尚未得到业界公认。因此,B7H3受体的鉴定和验证工作是该领域研究的热点和重点。相信随着鉴定技术平台的进步和研究的深入,B7H3受体分子的阐明能够极大促进基于B7H3相关生物药的开发。

4.2 靶向B7H3免疫治疗尚处于临床试验阶段

尽管大部分基于B7H3的免疫治疗或联合治疗试验结果较为乐观,但大多处于临床试验的早期阶段,亦有部分试验因未达到预期或毒性较大而终止。学者们推测,临床疗效有限可能与B7H3的表达分布及表观遗传修饰等相关。一方面,肿瘤的异质性导致低表达或不表达B7H3的肿瘤细胞能够逃避免疫系统的识别与杀伤;另一方面,B7H3不仅在肿瘤细胞表达,在肿瘤浸润的DC和巨噬细胞中也表达,这些$B7H3^{+}$免疫细胞在治疗中也会被无差别杀伤,导致其抗肿瘤效能被削弱,进而降低了靶向B7H3免疫治疗的效果。因此,寻找和鉴定调控B7H3蛋白表达的关键分子能够为基于B7H3的临床治疗提供新的解决方案。

4.3 靶向B7H3药物的不良反应影响其临床应用

靶向B7H3生物药引发的不良反应与当前大多数靶向药物类似,如BsAb治疗因激活大量T细胞产生细胞因子而引发过度炎症反应。CAR-T细胞可诱发致命的细胞因子释放综合征,而局部区域CAR-T细胞治疗可能削弱这种不良反应。有研究[64]发现在非典型畸胎样/横纹肌样肿瘤中,于侧脑室内或瘤内注射B7H3.BB.z-CAR-T细胞可有效抑制肿瘤进展,与静脉注射相比,其动力学更快、效果更好,且全身炎症细胞因子水平显著降低。此外,MURTY等[65]构建了一种携带自杀开关报告基因HSV1-tk的CAR-T细胞基因工程系统,可通过前药更昔洛韦诱导B7H3 CAR-T细胞发生可控凋亡,以此限制CAR-T细胞的潜在毒性。

4.4 靶向B7H3的联合治疗策略有待进一步优化

靶向B7H3生物药的不良反应和继发性耐药严重限制了其临床应用,如何在提升肿瘤特异性抗肿瘤效应的同时减少不良反应是当前靶向B7H3治疗策略研发的难点和重点。与趋化因子或细胞因子偶联、提高CAR-T细胞的代谢适应性或联合其他免疫检查

点抑制剂及放化疗等策略已初见成效[66]。NK细胞因无MHC的限制性且来源广泛，成为CAR-T细胞领域新的生长点。B7H3 CAR-NK细胞治疗在非小细胞肺癌异种移植鼠模型中显著抑制肿瘤生长，延长荷瘤小鼠的存活期[67]。此外，与抗体相比，小分子抑制剂因成本低、分子小、半衰期短且口服给药方便而受到临床青睐。研究[68]发现，B7H3 IgV结构域的FG环对B7H3介导的免疫抑制功能十分重要，根据FG环与活化的T细胞结合特性设计的小分子抑制剂，能够阻断B7H3与受体结合，从而阻止肿瘤免疫逃逸。

5 展　望

肿瘤的精准治疗或肿瘤患者的个体化治疗是肿瘤免疫治疗未来的发展目标和方向，基因编辑、转录组学、单细胞测序及空间蛋白组学等新技术的发展和运用，对肿瘤细胞特性和肿瘤免疫微环境特征及各种组分间时空关联的认知得到了空前的深化和扩展。

基于B7H3蛋白在肿瘤和肿瘤脉管系统特异性组成性高表达的特征，靶向B7H3的各种治疗方案及联合治疗策略的优化是未来研发的热点；肿瘤B7H3的表达水平和/或血清中sB7H3含量是否可以作为肿瘤特异性标志物用于肿瘤患者分层诊治、疗效监测和预后评估的指标还有待更广泛的验证。尽管已发现B7H3表达能够活化多条信号转导通路，在调控肿瘤生长、侵袭、转移和免疫逃逸中发挥多种效能，但其特异性互作受体及精确的表达调控和转录后表观遗传修饰机制等均尚未明晰，亟待进一步深入研究。相信随着研究的进展和深入，B7H3在肿瘤及肿瘤免疫中扮演的角色会更加清晰，基于B7H3的抗肿瘤诊治策略会越发精准，期待不久的将来能够为肿瘤患者带来巨大福音。

[参 考 文 献]

[1] KONTOS F, MICHELAKOS T, KUROKAWA T, *et al*. B7-H3: an attractive target for antibody-based immunotherapy[J]. Clin Cancer Res, 2021, 27(5): 1227-1235. DOI: 10.1158/1078-0432.CCR-20-2584.

[2] ZHOU Y R, ZHOU H D, SHI J L, *et al*. Decreased m^6A modification of CD34/CD276(B7-H3) leads to immune escape in colon cancer[J/OL]. Front Cell Dev Biol, 2021, 9: 715674[2023-03-10]. https://pubmed.ncbi.nlm.nih.gov/34307389/. DOI: 10.3389/fcell.2021.715674.

[3] KANCHAN R K, PERUMAL N, ATRI P, *et al*. miR-1253 exerts tumor-suppressive effects in medulloblastoma *via* inhibition of CDK6 and CD276 (B7-H3)[J]. Brain Pathol, 2020, 30(4): 732-745. DOI: 10.1111/bpa.12829.

[4] YANG X, FENG K X, LI H, *et al*. MicroRNA-199a inhibits cell proliferation, migration, and invasion and activates AKT/mTOR signaling pathway by targeting B7-H3 in cervical cancer[J/OL]. Technol Cancer Res Treat, 2020, 19: 1533033820942245[2023-03-10]. https://pubmed. ncbi. nlm. nih. gov/32856542/. DOI: 10.1177/1533033820942245.

[5] XU H, CHEUNG I Y, GUO H F, *et al*. MicroRNA miR-29 modulates expression of immunoinhibitory molecule B7-H3: potential implications for immune based therapy of human solid tumors[J]. Cancer Res, 2009, 69(15): 6275-6281. DOI: 10.1158/0008-5472.CAN-08-4517.

[6] NAKASHIMA T, OMORI K, NAMBA M, *et al*. Serum and bronchoalveolar lavage fluid levels of soluble B7H3 in patients with interstitial lung diseases[J/OL]. Respir Med, 2023, 212: 107224[2023-03-10]. https://pubmed. ncbi. nlm. nih. gov/37003499/. DOI: 10.1016/j.rmed.2023.107224.

[7] BRADY L, KRINER M, COLEMAN I, *et al*. Inter- and intra-tumor heterogeneity of metastatic prostate cancer determined by digital spatial gene expression profiling[J/OL]. Nat Commun, 2021, 12(1): 1426 [2023-03-10]. https://pubmed. ncbi. nlm. nih. gov/33658518/. DOI: 10.1038/s41467-021-21615-4.

[8] CHEN J T, CHEN C H, KU K L, *et al*. Glycoprotein B7-H3 overexpression and aberrant glycosylation in oral cancer and immune response[J]. Proc Natl Acad Sci U S A, 2015, 112(42): 13057-13062. DOI: 10.1073/pnas.1516991112.

[9] AUNG P P, PARRA E R, BARUA S, *et al*. B7-H3 expression in merkel cell carcinoma-associated endothelial cells correlates with locally aggressive primary tumor features and increased vascular density[J]. Clin Cancer Res, 2019, 25(11): 3455-3467. DOI: 10.1158/1078-0432.CCR-18-2355.

[10] LIN L, CAO L, LIU Y, *et al*. B7-H3 promotes multiple myeloma cell survival and proliferation by ROS-dependent activation of Src/STAT3 and c-Cbl-mediated degradation of SOCS3[J]. Leukemia, 2019, 33(6): 1475-1486. DOI: 10.1038/s41375-018-0331-6.

[11] LIM S, LIU H, DA SILVA L M, *et al*. Immunoregulatory protein B7-H3 reprograms glucose metabolism in cancer cells by ROS-mediated stabilization of HIF1α[J]. Cancer Res, 2016, 76(8): 2231-2242. DOI: 10.1158/0008-5472.can-15-1538.

[12] SHI T G, MA Y C, CAO L, *et al*. B7-H3 promotes aerobic glycolysis and chemoresistance in colorectal cancer cells by regulating HK2 [J/OL]. Cell Death Dis, 2019, 10(4): 308[2023-03-10]. https://doi.org/10.1038/s41419-019-1549-6. DOI: 10.1038/s41419-019-1549-6.

[13] TEKLE C, NYGREN M K, CHEN Y W, *et al*. B7-H3 contributes to the metastatic capacity of melanoma cells by modulation of known metastasis-associated genes[J]. Int J Cancer, 2012, 130(10): 2282-2290. DOI: 10.1002/ijc.26238.

[14] ZHONG C H, TAO B, CHEN Y T, *et al*. B7-H3 regulates glioma growth and cell invasion through a JAK2/STAT3/slug-dependent signaling pathway[J]. Oncotargets Ther, 2020, 13: 2215-2224. DOI: 10.2147/ott.s237841.

[15] SEAMAN S, ZHU Z Y, SAHA S, *et al*. Eradication of tumors through simultaneous ablation of CD276/B7-H3-positive tumor cells and tumor vasculature[J]. Cancer Cell, 2017, 31(4): 501-515. DOI: 10.1016/j.ccell.2017.03.005.

[16] WANG R Q, MA Y C, ZHAN S H, *et al*. B7-H3 promotes colorectal cancer angiogenesis through activating the NF-κB pathway to induce VEGFA expression[J/OL]. Cell Death Dis, 2020, 11: 55[2023-03-10]. https://doi.org/10.1038/s41419-020-2252-3. DOI: 10.1038/s41419-020-2252-3.

[17] FERRARA N. VEGF and the quest for tumour angiogenesis factors [J]. Nat Rev Cancer, 2002, 2(10): 795-803. DOI: 10.1038/nrc909.

[18] MA Y C, WANG R Q, LU H M, *et al*. B7-H3 promotes the cell cycle-

mediated chemoresistance of colorectal cancer cells by regulating CDC25A: Erratum[J/OL]. J Cancer, 2020, 11(22): 6703[2023-03-10]. https://doi.org/10.7150/jca.53041. DOI: 10.7150/jca.53041.

[19] MA Y C, ZHAN S H, LU H M, *et al.* B7-H3 regulates KIF15-activated ERK1/2 pathway and contributes to radioresistance in colorectal cancer[J/OL]. Cell Death Dis, 2020, 11(10): 824[2023-03-10]. https://doi.org/10.1038/s41419-020-03041-4. DOI: 10.1038/s41419-020-03041-4.

[20] WANG R Q, SUN L Q, XIA S H, *et al*. B7-H3 suppresses doxorubicin-induced senescence-like growth arrest in colorectal cancer through the AKT/TM4SF1/SIRT1 pathway[J/OL]. Cell Death Dis, 2021, 12(5): 453[2023-03-10]. https://doi. org/10.1038/s41419-021-03736-2. DOI: 10.1038/s41419-021-03736-2.

[21] ZHANG W, WANG J, WANG Y F, *et al*. B7-H3 silencing by RNAi inhibits tumor progression and enhances chemosensitivity in U937 cells [J]. Onco Targets Ther, 2015, 8: 1721-1733. DOI: 10.2147/OTT.S85272.

[22] LIU Z X, ZHANG W L, PHILLIPS J B, *et al*. Immunoregulatory protein B7-H3 regulates cancer stem cell enrichment and drug resistance through MVP-mediated MEK activation[J]. Oncogene, 2019, 38(1): 88-102. DOI: 10.1038/s41388-018-0407-9.

[23] WANG C, LI Y, JIA L F, *et al.* CD276 expression enables squamous cell carcinoma stem cells to evade immune surveillance[J]. Cell Stem Cell, 2021, 28(9): 1597-1613. DOI: 10.1016/j.stem.2021.04.011.

[24] LI Y C, YANG X D, YAO P G, *et al.* B7-H3 increases the radioresistance of gastric cancer cells through regulating baseline levels of cell autophagy[J/OL]. Am J Transl Res, 2019, 11(7): 4438-4449[2023-03-10]. https://www. ncbi. nlm. nih. gov/pmc/articles/PMC6684931/.

[25] LIU H J, DU H, KHABIBULLIN D, *et al.* mTORC1 upregulates B7-H3/CD276 to inhibit antitumor T cells and drive tumor immune evasion[J/OL]. Nat Commun, 2023, 14: 1214[2023-03-10]. https://doi. org/10.1038/s41467-023-36881-7. DOI: 10.1038/s41467-023-36881-7.

[26] LEE Y H, MARTIN-OROZCO N, ZHENG P L, *et al.* Inhibition of the B7-H3 immune checkpoint limits tumor growth by enhancing cytotoxic lymphocyte function[J]. Cell Res, 2017, 27(8): 1034-1045. DOI: 10.1038/cr.2017.90.

[27] HUANG Y, ZHANG H L, LI Z L, *et al*. FUT8-mediated aberrant N-glycosylation of B7H3 suppresses the immune response in triple-negative breast cancer[J/OL]. Nat Commun, 2021, 12(1): 2672 [2023-03-10]. https://pubmed. ncbi. nlm. nih. gov/PMC8113546/. DOI: 10.1038/s41467-021-22618-x.

[28] LIN W Z, XU Y Y, GAO J, *et al*. Multi-omics data analyses identify B7-H3 as a novel prognostic biomarker and predict response to immune checkpoint blockade in head and neck squamous cell carcinoma[J/OL]. Front Immunol, 2021, 12: 757047[2023-03-10]. https://doi.org/10.3389/fimmu.2021.757047. DOI: 10.3389/fimmu.2021.757047.

[29] KIM A K, GANI F, LAYMAN A J, *et al*. Multiple immune-suppressive mechanisms in fibrolamellar carcinoma[J]. Cancer Immunol Res, 2019, 7(5): 805-812. DOI: 10.1158/2326-6066.cir-18-0499.

[30] MIYAMOTO T, MURAKAMI R, HAMANISHI J, *et al*. B7-H3 suppresses antitumor immunity *via* the CCL2-CCR2-M2 macrophage axis and contributes to ovarian cancer progression[J]. Cancer Immunol Res, 2022, 10(1): 56-69. DOI: 10.1158/2326-6066.CIR-21-0407.

[31] YIM J, KOH J, KIM S, *et al*. Effects of B7-H3 expression on tumour-infiltrating immune cells and clinicopathological characteristics in non-small-cell lung cancer[J]. Eur J Cancer, 2020, 133: 74-85. DOI: 10.1016/j.ejca.2020.03.033.

[32] TYAGI A, LY S, EL-DANA F, *et al*. Evidence supporting a role for the immune checkpoint protein B7-H3 in NK cell-mediated cytotoxicity against AML[J]. Blood, 2022, 139(18): 2782-2796. DOI: 10.1182/blood.2021014671.

[33] SUH W K, GAJEWSKA B U, OKADA H, *et al*. The B7 family member B7-H3 preferentially down-regulates T helper type 1-mediated immune responses[J]. Nat Immunol, 2003, 4(9): 899-906. DOI: 10.1038/ni967.

[34] FASSBENDER M, GERLITZKI B, ULLRICH N, *et al*. Cyclic adenosine monophosphate and IL-10 coordinately contribute to nTreg cell-mediated suppression of dendritic cell activation[J]. Cell Immunol, 2010, 265(2): 91-96. DOI: 10.1016/j.cellimm.2010.07.007.

[35] MENG F Y, YANG M, CHEN Y S, *et al*. miR-34a induces immunosuppression in colorectal carcinoma through modulating a SIRT1/NF-κB/B7-H3/TNF-α axis[J].Cancer Immunol Immunother, 2021, 70(8): 2247-2259. DOI: 10.1007/s00262-021-02862-2.

[36] CAI D L, LI J M, LIU D F, *et al*. Tumor-expressed B7-H3 mediates the inhibition of antitumor T-cell functions in ovarian cancer insensitive to PD-1 blockade therapy[J]. Cell Mol Immunol, 2020, 17(3): 227-236. DOI: 10.1038/s41423-019-0305-2.

[37] LU H M, SHI T G, WANG M Y, *et al*. B7-H3 inhibits the IFN-γ-dependent cytotoxicity of Vγ9Vδ2 T cells against colon cancer cells [J/OL]. OncoImmunology, 2020, 9(1): 1748991[2023-03-10]. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7185217/. DOI: 10.1080/2162402x.2020.1748991.

[38] SHENDEROV E, DE MARZO A M, LOTAN T L, *et al*. Neoadjuvant enoblituzumab in localized prostate cancer: a single-arm, phase 2 trial[J]. Nat Med, 2023, 29(4): 888-897. DOI: 10.1038/s41591-023-02284-w.

[39] KASTEN B B, GANGRADE A, KIM H, *et al*. ^{212}Pb-labeled B7-H3-targeting antibody for pancreatic cancer therapy in mouse models [J]. Nucl Med Biol, 2018, 58: 67-73. DOI: 10.1016/j.nucmedbio.2017.12.004.

[40] BAILEY K, PANDIT-TASKAR N, HUMM J L, *et al*. Targeted radioimmunotherapy for embryonal tumor with multilayered rosettes[J]. J Neuro Oncol, 2019, 143(1): 101-106. DOI: 10.1007/s11060-019-03139-6.

[41] SCRIBNER J A, BROWN J G, SON T, *et al*. Preclinical development of MGC018, a duocarmycin-based antibody-drug conjugate targeting B7-H3 for solid cancer[J]. Mol Cancer Ther, 2020, 19(11): 2235-2244. DOI: 10.1158/1535-7163.mct-20-0116.

[42] KENDSERSKY N M, LINDSAY J, KOLB E A, *et al*. The B7-H3-targeting antibody-drug conjugate m276-SL-PBD is potently effective against pediatric cancer preclinical solid tumor models[J]. Clin Cancer Res, 2021, 27(10): 2938-2946. DOI: 10.1158/1078-0432.CCR-20-4221.

[43] WEIDLE U H, KONTERMANN R E, BRINKMANN U. Tumor-antigen-binding bispecific antibodies for cancer treatment[J]. Semin Oncol, 2014, 41(5): 653-660. DOI: 10.1053/j.seminoncol.2014.08.004.

[44] HUANG C, DUAN X, WANG J C, *et al.* Lipid nanoparticle delivery system for mRNA encoding B7H3-redirected bispecific antibody displays potent antitumor effects on malignant tumors [J/OL]. Adv Sci, 2023, 10(3): 2205532[2023-03-10]. http://dx. doi.

org/10.1002/advs.202205532. DOI: 10.1002/advs.202205532.

[45] DAVIS Z B, VALLERA D A, MILLER J S, *et al*. Natural killer cells unleashed: Checkpoint receptor blockade and BiKE/TriKE utilization in NK-mediated anti-tumor immunotherapy[J]. Semin Immunol, 2017, 31: 64-75. DOI: 10.1016/j.smim.2017.07.011.

[46] VALLERA D A, FERRONE S, KODAL B, *et al.* NK-cell-mediated targeting of various solid tumors using a B7-H3 tri-specific killer engager *in vitro* and *in vivo*[J/OL]. Cancers, 2020, 12(9): 2659[2023-03-10]. https://doi. org/10.3390/cancers12092659. DOI: 10.3390/cancers12092659.

[47] KONTOS F, KUROKAWA T, VALLERA D A, *et al.* IL-15/B7-H3 TriKEs-based immunotherapy for pancreatic ductal adenocarcinoma[J/OL]. J Am Coll Surg, 2019, 229(4): S176 [2023-03-10]. https://doi.org/10.1016/j. jamcollsurg. 2019.08.388. DOI: 10.1016/j. jamcollsurg. 2019.08.388.

[48] ZHANG Z L, JIANG C Y, LIU Z Y, *et al.* B7-H3-targeted CAR-T cells exhibit potent antitumor effects on hematologic and solid tumors[J]. Mol Ther Oncolytics, 2020, 17: 180-189. DOI: 10.1016/j.omto.2020.03.019.

[49] TANG X, WANG Y L, HUANG J H, *et al.* Administration of B7-H3 targeted chimeric antigen receptor-T cells induce regression of glioblastoma[J/OL]. Sig Transduct Target Ther, 2021, 6: 125[2023-03-10]. https://doi.org/10.1038/s41392-021-00505-7. DOI: 10.1038/s41392-021-00505-7.

[50] YANG M J, TANG X, ZHANG Z L, *et al.* Tandem CAR-T cells targeting CD70 and B7-H3 exhibit potent preclinical activity against multiple solid tumors[J]. Theranostics, 2020, 10(17): 7622-7634. DOI: 10.7150/thno.43991.

[51] LEI X, OU Z, YANG Z, *et al.* A pan-histone deacetylase inhibitor enhances the antitumor activity of B7-H3-specific CAR T cells in solid tumors[J]. Clin Cancer Res, 2021. 27(13): 3757-3771. DOI: 10.1158/1078-0432.CCR-20-2487.

[52] LI H X, HARRISON E B, LI H Z, *et al.* Targeting brain lesions of non-small cell lung cancer by enhancing CCL2-mediated CAR-T cell migration[J/OL]. Nat Commun, 2022, 13: 2154[2023-03-10]. https://doi. org/10.1038/s41467-022-29647-0. DOI: 10.1038/s41467-022-29647-0.

[53] YONESAKA K, HARATANI K, TAKAMURA S, *et al*. B7-H3 negatively modulates CTL-mediated cancer immunity[J]. Clin Cancer Res, 2018, 24(11): 2653-2664. DOI: 10.1158/1078-0432.ccr-17-2852.

[54] LARKIN J, CHIARION-SILENI V, GONZALEZ R, *et al*. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma[J]. N Engl J Med, 2015, 373(13): 1270-1271. DOI: 10.1056/nejmc1509660.

[55] FOUNTZILAS C, JAVLE M, TAN W, *et al.* A phase 1, open-label, dose escalation study of intravenous paricalcitol in combination with gemcitabine in patients with advanced malignancies[J]. Cancer, 2018, 124(19): 3890-3899. DOI: 10.1002/cncr.31676.

[56] AGGARWAL C, PRAWIRA A, ANTONIA S, *et al.* Dual checkpoint targeting of B7-H3 and PD-1 with enoblituzumab and pembrolizumab in advanced solid tumors: interim results from a multicenter phase Ⅰ/Ⅱ trial[J/OL]. J Immunother Cancer, 2022, 10(4): e004424[2023-03-10]. https://doi.org/10.1136/jitc-2021-004424. DOI: 10.1136/jitc-2021-004424.

[57] HUANG C, LI H J, FENG Y Y, *et al.* Combination therapy with B7H3-redirected bispecific antibody and Sorafenib elicits enhanced synergistic antitumor efficacy[J]. Theranostics, 2020, 10(23): 10498-10512. DOI: 10.7150/thno.49480.

[58] WHITE A A, LEE D N, MAZZOLA E, *et al.* Adjuvant therapy following induction therapy and surgery improves survival in N2-positive non-small cell lung cancer[J]. J Surg Oncol, 2021, 123(2): 579-586. DOI: 10.1002/jso.26305.

[59] MINAMI Y, NISHIDA N, KUDO M. Radiofrequency ablation of liver metastasis: potential impact on immune checkpoint inhibitor therapy[J]. Eur Radiol, 2019, 29(9): 5045-5051. DOI: 10.1007/s00330-019-06189-6.

[60] LEI K F, JI W W, GOH A, *et al.* Investigation of uniform sized multicellular spheroids raised by microwell arrays after the combined treatment of electric field and anti-cancer drug[J].Biomed Microdevices, 2019, 21(4): 1-9. DOI: 10.1007/s10544-019-0442-5.

[61] ZHANG Y D, HE L L, SADAGOPAN A, *et al.* Targeting radiation-resistant prostate cancer stem cells by B7-H3 CAR T cells[J]. Mol Cancer Ther, 2021, 20(3): 577-588. DOI: 10.1158/1535-7163. mct-20-0446.

[62] HASHIGUCHI M, KOBORI H, RITPRAJAK P, *et al.* Triggering receptor expressed on myeloid cell-like transcript 2 (TLT-2) is a counter-receptor for B7-H3 and enhances T cell responses[J]. Proc Natl Acad Sci U S A, 2008, 105(30): 10495-10500. DOI: 10.1073/pnas.0802423105.

[63] BUSHRA H, RAMANI S, CHIANG E, *et al.* A platform for extracellular interactome discovery identifies novel functional binding partners for the immune receptors B7-H3/CD276 and PVR/CD155[J]. Mol Cell Proteom, 2019, 18(11): 2310-2323. DOI: 10.1074/mcp.TIR119.001433.

[64] THERUVATH J, SOTILLO E, MOUNT C W, *et al.* Locoregionally administered B7-H3-targeted CAR T cells for treatment of atypical teratoid/rhabdoid tumors[J]. Nat Med, 2020, 26(5): 712-719. DOI: 10.1038/s41591-020-0821-8.

[65] MURTY S, LABANIEH L, MURTY T, *et al*. PET reporter gene imaging and ganciclovir-mediated ablation of chimeric antigen receptor T cells in solid tumors[J]. Cancer Res, 2020, 80(21): 4731-4740. DOI: 10.1158/0008-5472.can-19-3579.

[66] MARTINEZ M, MOON E K. CAR T cells for solid tumors: new strategies for finding, infiltrating, and surviving in the tumor microenvironment[J/OL]. Front Immunol, 2019, 10: 128[2023-03-10]. https://doi. org/10.3389/fimmu. 2019.00128. DOI: 10.3389/fimmu. 2019.00128.

[67] YANG S, CAO B H, ZHOU G Y, *et al*. Targeting B7-H3 immune checkpoint with chimeric antigen receptor-engineered natural killer cells exhibits potent cytotoxicity against non-small cell lung cancer [J/OL]. Front Pharmacol, 2020, 11: 1089 [2023-03-10]. https://doi.org/10.3389/fphar.2020.01089. DOI: 10.3389/fphar.2020.01089.

[68] VIGDOROVICH V, RAMAGOPAL U A, LÁZÁR-MOLNÁR E, *et al*. Structure and T cell inhibition properties of B7 family member, B7-H3 [J]. Structure, 2013, 21(5): 707-717. DOI: 10.1016/j.str.2013.03.003.

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