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肿瘤微环境多胺抑制T细胞抗肿瘤活性*

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摘要 肿瘤免疫治疗是继手术、放疗、化疗之后的第四大肿瘤治疗技术，克服肿瘤免疫微环境（tumor microenvironment，TME）的免疫抑制作用已成为当前研究的核心问题。多胺作为重要的免疫调节因子，在TME中异常积聚，对肿瘤浸润性T细胞具有严重的抑制作用。因此，系统探讨多胺对T细胞功能的调控，对提升免疫治疗效果和解决免疫耐药问题具有重要意义。多胺阻断治疗（polyamine blocking therapy，PBT）作为新型辅助肿瘤免疫治疗策略，通过降低TME多胺水平恢复T细胞功能，并且联合免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）治疗时展现出克服耐药的潜力。尽管已有研究揭示多胺对T细胞免疫功能具有抑制作用，但其中的调控机制仍有待进一步阐明。此外，考虑到肿瘤细胞存在多胺代偿机制，PBT应采用多重机制抑制策略，以提高治疗的有效性和安全性。未来，PBT的临床转化可联合多组学技术，以及结合纳米递药系统，提升PBT在肿瘤免疫治疗中的应用潜力。本文阐述了TME中多胺对T细胞免疫功能的调控作用，旨在为肿瘤免疫治疗提供参考。

关键词 多胺，免疫治疗，肿瘤微环境，多胺阻断疗法，免疫检查点抑制剂
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多胺（Polyamines），包括腐胺（Putrescine）、亚精胺（Spermidine）和精胺（Spermine），是细胞增殖和分化的重要调节因子。它们通过与核酸和蛋白质相互作用，精确调控基因表达、蛋白质合成及修饰[1-2]。细胞主要通过自身合成和依靠膜转运蛋白从外界摄取多胺。在正常细胞中，多胺代谢受到严格调控，以维持细胞稳态，其含量通常维持在毫摩尔水平[3-4]。然而，为满足快速增殖的需求，肿瘤细胞常通过上调*c-MYC*基因[5-6]的表达，以激活多胺合成和多胺转运[7-8]。恶性程度和侵袭性较高的肿瘤通常伴有更高水平的多胺积累[9]，且不同肿瘤分型在多胺代谢调控方面也存在明显差异。例如，肝细胞癌（hepatocellular carcinoma，HCC）中亚精胺合酶（spermidine synthase，SRM）[10]和精胺合酶（spermine synthase，SMS）的表达[11]与癌症分期呈正相关，并且高水平的多胺还会降低肝癌免疫疗法的敏感性[12]；胰腺导管腺癌（pancreatic ductal adenocarcinomas，PDAC）可通过突变Kirsten大鼠肉瘤病毒癌基因同源物（Kirsten rat sarcoma viral oncogene homolog，KRAS）驱动鸟氨酸氨基转移酶（ornithine aminotransferase，OAT）和多胺合成酶的表达，支持癌细胞增殖[13]。此外，不同乳腺癌分型（激素受体阳性、人类表皮生长因子受体阳性及三阴性）在多胺合成与代谢调控上存在明显差异，多胺代谢紊乱不仅影响乳腺癌肿瘤微环境（tumor

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microenvironment，TME）的异质性，而且与癌症不良预后相关[14]。其中，雌激素受体阳性（estrogen receptor-positive，ER+）乳腺癌对靶向多胺代谢治疗更为敏感[15]。

肿瘤治疗一直是医学领域的重大挑战，而免疫治疗作为新兴策略，展现出巨大潜力。在肿瘤免疫治疗中，克服TME的免疫抑制作用是关键环节之一[16-18]。TME由免疫细胞、肿瘤相关成纤维细胞（cancer-associated fibroblasts，CAFs）、内皮细胞和细胞外基质（extracellular matrix，ECM）等多种组分构成。在肿瘤细胞凋亡过程中，会释放大量多胺到TME中，而这些多胺对肿瘤浸润性免疫细胞的活性具有重要调控作用[19]，具体机制包括调控巨噬细胞分化[20]、抑制树突状细胞（dendritic cell，DC）的抗原呈递功能[21-22]，以及影响CD8+ T细胞活性[23]。近年来，在多种肿瘤模型中表明，靶向干预多胺代谢能有效抑制肿瘤生长、重塑TME

并恢复抗肿瘤免疫细胞的功能[24-26]。

T细胞作为重要的抗肿瘤免疫细胞，研究多胺对其功能的调节具有重要意义。本综述将总结近年来关于多胺如何影响肿瘤浸润性T细胞抗肿瘤活性的研究进展，重点分析其在调控CD4+ T细胞分化、CD8+ T细胞功能以及免疫检查点分子方面的作用机制。本文旨在深入剖析多胺代谢在T细胞免疫应答调节的核心作用，并评估其作为新型肿瘤免疫治疗靶点的潜在应用前景。

1　多胺的代谢过程

L-精氨酸（L-arginine，L-Arg）作为多胺合成的重要前体，在精氨酸酶-I（arginase-I，Arg-I）的催化下转化为鸟氨酸，后者在鸟氨酸脱羧酶（ornithine decarboxylase，ODC）作用下生成腐胺。当细胞内的多胺水平过高时，鸟氨酸脱羧酶抗酶1（ornithine decarboxylase antizyme 1，OAZ1）与ODC单体结合，形成无活性的ODC-OAZ1异二聚体，从而抑制ODC以同源二聚体形式发挥正常功能。ODC-OAZ1异二聚体随后被26S蛋白酶体识别并降解[27]，以此来维持细胞内多胺水平的稳态。不同于正常细胞，肿瘤细胞中抗酶抑制剂1（antizyme inhibitor 1，AZIN1）的过表达，能竞争性结合ODC-OAZ1异二聚体，恢复ODC活性，并促进多胺合成[28]。腺苷甲硫氨酸脱羧酶1（adenosylmethionine decarboxylase 1，AMD1）是多胺合成的另一关键酶，负责提供亚精胺和精胺合成所需的氨丙基。此外，多胺的分解代谢同样重要。在亚精胺/精胺乙酰转移酶1（spermidine/spermine N1-acetyltransferase 1，SAT1）、多胺氧化酶（polyamine oxidase，PAOX）和精胺氧化酶（spermine oxidase，SMOX）等酶类操控多胺之间的相互转化和氧化分解，最终生成较小的代谢产物排出细胞[29]。而在分解过程中，释放的活性氧类（reactive oxygen species，ROS）可能会引起细胞氧化损伤[30]（图1）。多胺代谢失调与肿瘤化疗和

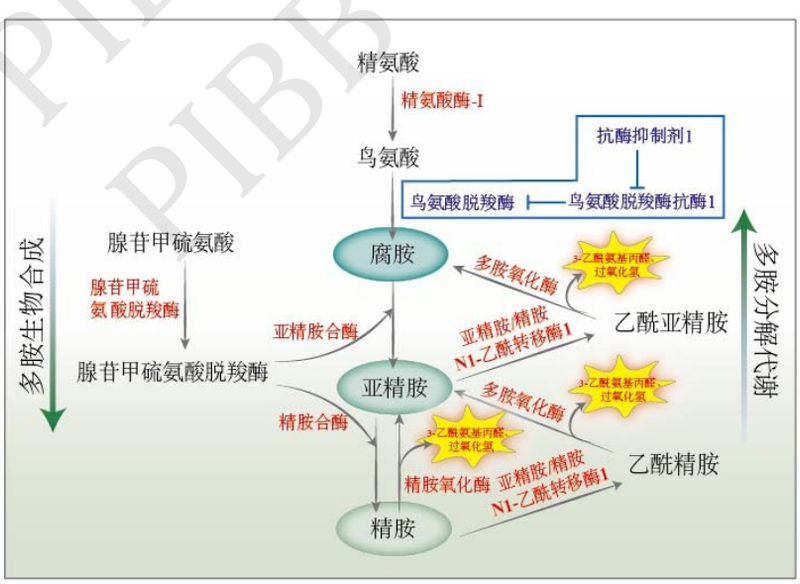

Fig.1　Polyamine metabolic pathway

图1　多胺代谢途径

放疗后的不良预后相关联[31]，并与其他疾病（如衰老、Bachmann-Bupp综合征及Snyder-Robinson综合征等）也存在一定关联[32]。

2　T细胞内多胺促进细胞增殖和功能

T细胞增殖和活化均依赖于细胞内多胺的水平。Wu等[33]研究发现，当多胺合成受阻时（如缺乏ODC酶活性），T细胞从G_0/G_1期进入S期的过程明显延迟，导致整体增殖能力降低；而通过补充外源性多胺能有效恢复细胞周期进程和增殖能力，表明多胺在维持T细胞增殖中具有关键作用。

在T细胞功能调控方面，亚精胺同样发挥着重要的调节作用。亚精胺能通过自噬依赖性机制逆转老年免疫细胞衰退，促进记忆性CD8+ T细胞的形成[34]，并增强γ干扰素（IFN-γ）的合成[35]。此外，亚精胺还通过与线粒体三功能蛋白（mitochondrial trifunctional protein，MTP）结合，促进三磷酸腺苷（adenosine triphosphate，ATP）生成，提高老年小鼠CD8+ T细胞的抗肿瘤免疫能力[36]。

3　TME多胺抑制肿瘤浸润性T细胞功能

多胺是调控T细胞增殖和功能的关键因子，T细胞内正常水平的多胺对其细胞扩增及效应功能具有重要保障。然而，TME中异常积累的多胺对肿瘤浸润性T细胞的功能产生严重的抑制作用[37]，具体表现为抑制T细胞的分化与活化，干扰其代谢途径等。尽管T细胞可能在一定程度上会利用TME中的多胺作为代谢底物，但整体而言，多胺的积聚仍不利于其有效发挥抗肿瘤效应。

3.1　TME多胺调控CD4+ T细胞分化

CD4+ T细胞激活后可通过分泌IFN-γ、肿瘤坏死因子-α（tumor necrosis factor α，TNF-α）和白介素（interleukin，IL）-2直接杀伤肿瘤细胞，并协助CD8+ T细胞发挥抗肿瘤作用[38-39]。CD4+ T细胞在TME中的细胞因子调控下，能分化成辅助性T细胞（T helper，Th）1型（Th1）、Th2、Th17及调节性T细胞（regulatory T cell，Treg）等亚群[40-41]。值得注意的是，Treg细胞会释放IL-10和转化生长因子-β（transforming growth factor-β，TGF-β）来抑制免疫反应，促进肿瘤免疫逃逸[42]。多胺能对CD4+ T细胞的分化和活化有重要的调控作用，如亚精胺能通过自噬途径增加Treg细胞的数量[43]。精胺通过抑制CD4+ T细胞中胞外信号调节激酶（extracellular signal-regulated kinase，ERK）的磷酸化，从而调控促分裂原活化的蛋白质激酶（mitogen-activated protein kinase，MAPK）/ERK信号通路，以剂量依赖性的方式抑制CD4+ T细胞的增殖和活化，并阻止向Th1和T17细胞分化[44]。Carr等[45]研究指出，活化的T细胞会增强对谷氨酰胺的摄取以满足能量需求，而这一过程是由ERK信号通路调控的。因此，精胺可能通过抑制ERK蛋白的活性，干扰了T细胞活化过程中的能量代谢，导致能量供应不足，从而抑制T细胞的增殖能力及细胞因子IL-2和IFN-γ的合成。

肿瘤细胞通过激活关键信号分子c-Myc，增强对TME中L-Arg及其他氨基酸的摄取和消耗，导致局部氨基酸浓度降低。由于肿瘤浸润性T细胞无法摄取足够的氨基酸，进而激活氨基酸饥饿反应（amino acid response，AAR）并通过激活非抑制蛋白激酶-2（general control nonderepressible 2，GCN2）通路来调整细胞代谢状态，减少精氨酸的消耗。GCN2的激活上调了转录因子叉头框蛋白质3（forkhead box protein 3，Foxp3）的表达，促进Treg细胞的分化和成熟[46]；并且氨基酸耗竭可导致细胞程序性死亡受体-配体1（programmed death-ligand 1，PD-L1）和程序性死亡受体1（programmed death-1，PD-1）上调，抑制抗肿瘤免疫[47]。此外，Sun等[48]发现，肝癌细胞上调了精胺合成，并通过激活PI3K-Akt-mTOR-S6K信号通路诱导肿瘤相关巨噬细胞向M2型肿瘤相关巨噬细胞（M2-polarized tumor-associated macrophages，M2-TAMs）极化。同时，多胺还通过激活骨髓来源的抑制性细胞（myeloid-derived suppressor cells，MDSCs）的信号转导及转录激活蛋白3（signal transducer and activator of transcription 3，STAT3）信号通路，驱动其扩增[49]。M2-TAMs和MDSCs也会通过上调表达Arg-I [50-51]加剧局部精氨酸匮乏，并促进多胺合成。多胺还上调DC中吲哚胺2，3-双加氧酶1（Indoleamine 2，3-dioxygenase 1，IDO1）的表达。IDO1是一种将色氨酸转化成犬尿氨酸的酶，色氨酸的减少和全尿氨酸的积累会抑制T细胞增殖并促进Treg细胞的分化[52-54]，加剧TME免疫抑制。

3.2　TME多胺抑制T细胞激活

3.2.1　TME多胺抑制T细胞受体信号转导

T细胞活化是一个复杂且有序的过程。首先，抗原呈递细胞（antigen presenting cells，APC）通

过其表面的主要组织相容性复合物（major histocompatibility complex，MHC）将抗原肽精确地呈递给T细胞。随后，T细胞受体（T cell receptor，TCR）特异性地识别抗原肽，并与MHC分子共同形成稳定的TCR-MHC-抗原肽三元复合物。最终，在共刺激信号作用下（T细胞表面CD28分子与APC表面CD80/86配体结合）T细胞被完全激活，并通过释放穿孔素、颗粒酶和颗粒溶血素等细胞毒性效应分子，杀伤肿瘤细胞[55-56]。TCR复合物由TCR-α和TCR-β链组成，通过与CD3复合物（包括CD3γ、CD3δ、CD3ε和CD3ζ四个亚单位）协同作用，传递抗原识别信号。CD3复合物将激活信号传递至T细胞内，激活下游信号通路，辅助T细胞执行免疫功能[57]。

亚精胺具有抑制TCR信号转导的显著效应。研究表明，在CD8+T细胞培养体系中加入亚精胺后，细胞DNA复制过程明显延长。同时，胆固醇生物合成相关基因，如3-羟基-3-甲基戊二酰辅酶A还原酶（3-hydroxy-3-methylglutaryl-CoA reductase，*Hmgcr*）、角鲨烯单加氧酶（squalene monooxygenase，Sqle）以及调控胆固醇内流的低密度脂蛋白受体基因（low density lipoprotein receptor，Ldlr）均受到显著抑制。亚精胺通过降低细胞质膜中的胆固醇含量直接抑制CD3ε聚集簇的形成，进而阻碍TCR的聚集过程，并阻断了T细胞激活信号的转导[58]（图2a）。L-Arg作为多胺生物合成的重要前体物质，同时也是T细胞增殖和活化的必需氨基酸[59]。然而，TME中的免疫抑制细胞产生的Arg-I[60]和肿瘤细胞对营养的摄入会大量消耗L-Arg，导致T细胞活性降低[61]。L-Arg耗竭或缺乏会导致TCR-CD3ζ蛋白表达水平下降[62]，而CD3ζ链是TCR信号转导的核心组件（图2a）。尽管导致这一现象的机制尚未明确，但可能与CD3ζ mRNA的半衰期缩短密切相关[63]。此外，多胺还可能阻碍DC有效呈递抗原，从而削弱T细胞对特异性抗原的免疫应答。如腐胺可显著增加缺乏抗原呈递能力的人类白细胞抗原DR阴性、谱系标志物阴性（HLA-DR negative，lineage negative，HLA-DR$^-$Lin$^-$）阴性表型DC数量[64]，并且亚精胺和精胺通过抑制DC表面共刺激分子CD80/CD86的表达[65]，抑制T细胞激活。

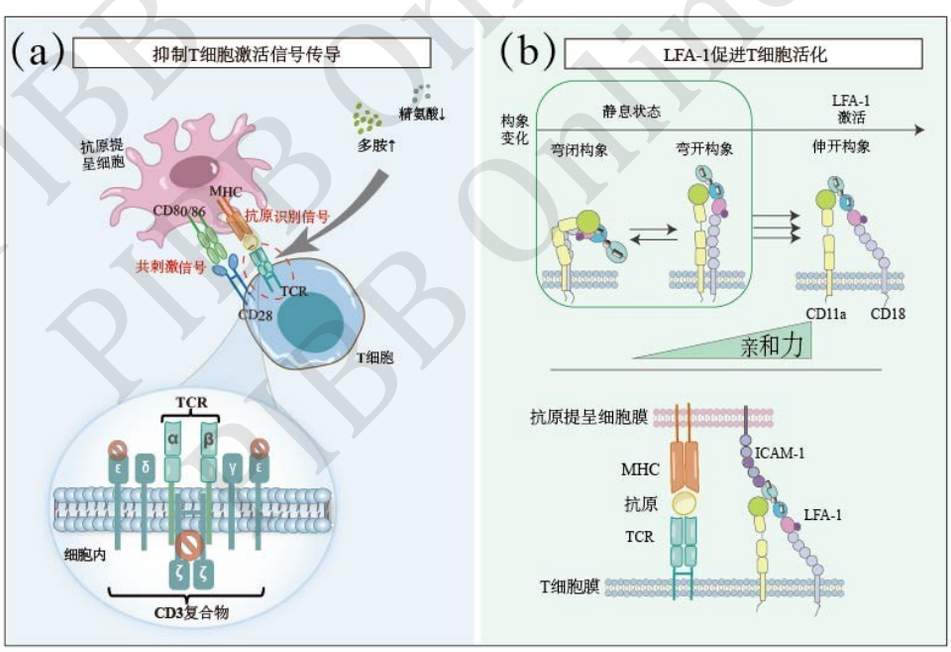

Fig.2　Polyamine metabolism inhibits t cell activation signaling

图2　多胺代谢抑制T细胞激活信号传导

（a）TME中M2型巨噬细胞和肿瘤细胞消耗L-Arg合成多胺，抑制CD3复合体的CD3ε聚集簇的形成和CD3ζ蛋白表达，从而阻断TCR激活信号的传导。（b）LFA-1受到TCR刺激信号被激活，由闭合型构象转化为开放型，并与APC表面细胞间黏附分子-1（Intercellular cell adhesion molecule-1，ICAM-1）结合，增加APC与T细胞之间的结合，促进激活信号传递。MHC：主要组织相容性复合体（major histocompatibility complex）；CD80/86：分化簇，又称白细胞分化抗原（cluster of differentiation）；TCR：T细胞受体（T cell receptor）；LFA-1：淋巴细胞功能相关抗原-1（lymphocyte function-associated antigen 1）；ICAM-1：表面细胞间黏附分子-1（intercellular cell adhesion molecule 1）；CD11a/CD18：整合素家族分子（integrin）。

T细胞发挥效应功能高度依赖于TCR和淋巴细胞功能相关抗原-1（lymphocyte function-associated antigen 1， LFA-1）的协同作用[66-67]。TCR在受到抗原刺激后通过传递信号，促使LFA-1从闭合性构象转变为激活状态的开放性构象[68]。这种构象的转变确保了T细胞和APC之间发生紧密接触，形成“免疫突触”，促进了信号传递和细胞间的相互作用（图2b）。然而，精胺能下调LFA-1重要组成分子（CD11a分子和CD18分子）的表达水平[69]，导致T细胞的激活受到抑制。

3.2.2　TME多胺促进肿瘤细胞PD-L1的表达

肿瘤细胞通过上调PD-L1表达，并与T细胞表面PD-1结合，抑制T细胞活化来逃避免疫监视[70-72]。研究表明，精胺能诱导HCC的PD-L1表达，减少CD8+ T细胞的数量并促进肿瘤转移。其机制主要涉及精胺与HCC细胞表面钙敏感受体（calcium sensing receptor， CaSR）第552位丝氨酸发生结合，触发Ca^{2+}内流[73]，进而激活Akt/β-catenin通路，促进PD-L1的表达[74]。此外，Akt/β-catenin通路的激活显著上调了N-寡糖转移酶复合物的催化亚基A（STT3 oligosaccharyltransferase complex catalytic subunit A， STT3A）的表达，而STT3A参与PD-L1蛋白的N-糖基化修饰过程，这一修饰对PD-L1蛋白的稳定性有增强作用（图3）。

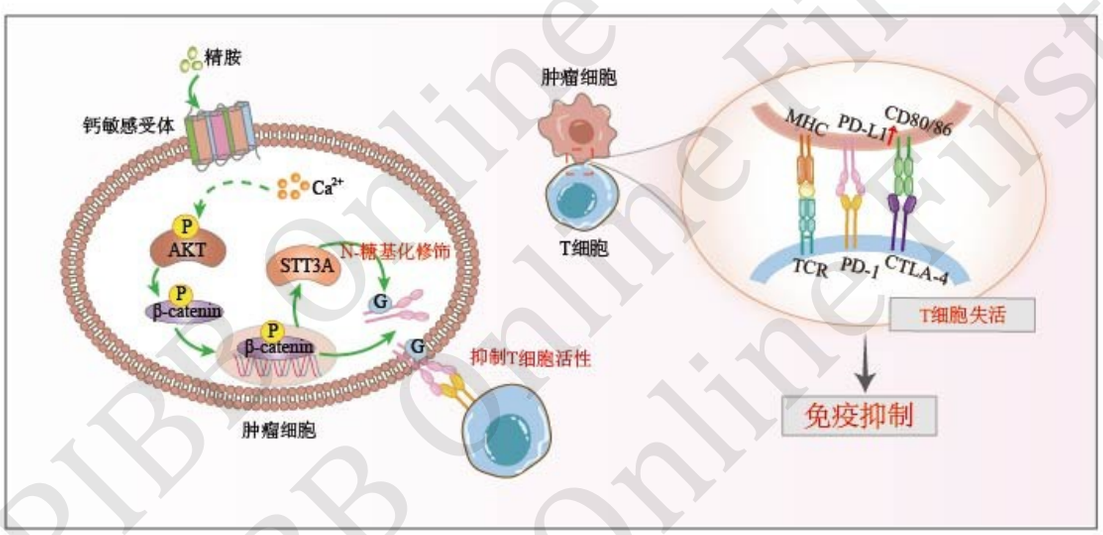

Fig.3　Polyamines in the TME promote the expression of PD−L1 in tumor cells

图3　TME多胺促进肿瘤细胞PD−L1的表达

精胺作用于肿瘤细胞膜表面的钙敏感受体，胞内钙离子浓度升高，激活Akt/β-catenin通路以促进PD-L1蛋白表达，并上调STT3A的表达，促进的PD-L1蛋白N-糖基化修饰，最终通过PD-1/PD-L1轴抑制T细胞的免疫活性。AKT：蛋白激酶B（protein kinase B）；β-catenin：β联蛋白；STT3A：N-寡糖转移酶复合物催化亚基A（STT3 oligosaccharyltransferase complex catalytic subunit A）；MHC：主要组织相容性复合体（major histocompatibility complex）；PD-L1：程序性死亡受体-配体1（programmed death-ligand 1）；CD80/86：分化簇（cluster of differentiation）；TCR：T细胞受体（T cell receptor）；PD-1：程序性死亡受体-1（programmed death-1）；CTLA-4：细胞毒性T淋巴细胞相关蛋白-4（cytotoxic T-lymphocyte-associated protein 4）。

4　多胺阻断疗法在抗肿瘤免疫的应用

多胺的合成和分解代谢在肿瘤增殖、分化和转移过程中发挥关键作用，因此，靶向多胺代谢的新型治疗策略对肿瘤治疗具有重要意义。目前，研究主要集中于抑制多胺生物合成、激活多胺分解代谢及阻断多胺转运等[75]。多胺阻断疗法（polyamine blocking therapy， PBT）作为新兴的抗肿瘤策略，主要通过阻断多胺的合成和转运来抑制肿瘤细胞的生长和转移。其中，ODC和AMD1是多胺生物合成过程的关键酶，抑制其活性可有效降低肿瘤细胞内多胺水平。ODC抑制剂二氟甲基鸟氨酸（difluoromethylornithine， DFMO）已获批用于治疗非洲锥虫病，并在肿瘤治疗研究中展现出潜力[76]。已知的AMD1酶抑制剂可分为三代，其中第一代米托胍腙（Mitoguazone， MGBG）和第二

代SAM486A（CGP-48664）因毒性和疗效问题临床应用受限，而第三代AbeAdo及其他抑制剂仍处于研究阶段[77-78]。DFMO在破坏肿瘤进展、调节肿瘤微环境以及辅助免疫检查点抑制剂（immune checkpoint inhibitors，ICIs）治疗中展现了显著的抗肿瘤效果。值得注意的是，由于肿瘤细胞会通过代偿性增加多胺代谢酶和多胺摄取，单独地使用DFMO并不能完全耗尽细胞内的多胺[79]。如神经母细胞瘤会通过上调多胺转运ATP酶13A3来增加摄取外源性多胺[80-81]，而通过联合多胺转运蛋白抑制剂（AMXT 1501）可明显抑制神经母细胞瘤细胞的生长。此外，多胺是调控机体重要生理功能的物质之一，在使用PBT治疗肿瘤过程中应关注到对正常生理功能的影响（表1）。因此，联合多重机制或提高抑制剂靶向性来抑制多胺代谢，以降低药物毒副作用及耐药性，成为未来的研究重点。本团队基于计算机分子对接技术与实验验证，成功发现了针对ODC[82]和AMD1[83]的小分子共价抑制剂。这些共价抑制剂在抑制酶活性方面表现出显著效果。特别是针对ODC的小分子抑制剂ODC-MPI-1，其在A549肺癌细胞中显著抑制了多胺的合成，并在体外细胞增殖实验及小鼠肿瘤模型中均表现出显著的抑制癌细胞增殖的效果，展现了其作为候选药物分子的巨大潜力。

表1 多胺阻断疗法治疗风险及解决策略

Table 1 Risks and solutions of polyamine blockade therapy

风险	具体问题	解决策略
全身副作用	多胺在机体各组织中均发挥生理功能，系统阻断可能会影响正常组织正常功能[84]，如DFMO的耳毒性[85]	结合纳米递药系统，实现肿瘤特异性释放； 开发其他途径的多胺抑制剂
耐药性	肿瘤细胞代偿性增加多胺合成酶或上调多胺转运蛋白[86]	联合多途径的多胺代谢抑制剂[8]
肠道影响	肠道中的多胺有助于维持肠粘膜上皮的完整性，防止肠道菌群失调[87-88]	联合益生菌或膳食干预维持菌群平衡

亚精胺在胶质母细胞瘤（glioblastoma multiforme，GBM）小鼠模型中显著升高。Kay等[89]发现，外源性补充亚精胺削弱了TME中的细胞毒性免疫反应，具体表现为肿瘤浸润性CD8+ T细胞数量减少、IFN-γ、TNF-α和颗粒酶分泌降低，同时Treg细胞的比例增加。相反，敲低多胺合成限速酶ODC1明显改善CD8+ T细胞的数量和功能，并延长鼠生存期。这表明GBM细胞通过上调ODC1表达，增加亚精胺合成，从而抑制T细胞的增殖和功能，促进肿瘤生长。临床上，GBM的化疗疗效往往不佳且复发率较高，这与其免疫微环境的高度免疫抑制状态密切相关。因此，联合阻断多胺合成途径的疗法可能为改善GBM的治疗效果提供一种有前景的策略。

研究发现，PBT在PDAC小鼠模型中有效增加了肿瘤浸润性T细胞共刺激标志物（CD86分子）的表达，从而增强T细胞活化[90]。多胺合成酶抑制剂DFMO还能促进T细胞活化，增加CD8+ T细胞中的IFN-γ和TNF-α等细胞杀伤因子的合成[23]，并通过减少TME中$Foxp3^+$ Treg细胞的分化及MDSCs的扩增减轻免疫抑制[91]。DFMO与抗PD-1治疗的联合应用已被证明能够有效解除肿瘤细胞对CD8+ T细胞的免疫抑制，增强抗肿瘤效果[25]。Alexander等[92]利用DFMO和多胺转运体抑制剂（Trimer44NMe）共同阻断多胺，并联合抗PD-1抗体应用于对抗PD-1单一疗法耐药的乳腺癌（4T1）和黑色素瘤（B16F10）小鼠模型中。研究结果显示，PBT不仅成功逆转了肿瘤对抗PD-1疗法的耐药性，还显著延长了小鼠的生存期。并且，PBT治疗后4T1小鼠的M2-TAMs明显减少，并通过抑制MDSCs的转录因子STAT3的激活，促进向抗肿瘤的M1型肿瘤相关巨噬细胞（M1-polarized tumor-associated macrophages，M1-TAMs）分化。此外，通过靶向递送药物抑制多胺代谢，在抗肿瘤中也具有明显效果。Wang[93]设计了一种携带他达拉非（Tadalafil，TA）和抗PD-1抗体的肿瘤靶向纳米药物，其中TA是一种5型磷酸二酯酶（phosphodiesterase type 5 inhibitor，PDE5）选择性抑制剂，能使Arg-I失活，从而抑制MDSCs和M2-TAMs细胞内多胺代谢[50]，该新型纳米药物的

设计明显改善了HCC对ICIs的耐药性，并且副作用小。Cu-Pic/HA NPs是由铜离子、皮克酸（Piceatannol，Pic）和透明质酸（hyaluronic acid，HA）共同组成的一种纳米颗粒，能通过消耗、减少摄取和抑制合成三重机制来阻断多胺代谢，能成功逆转肿瘤免疫微环境的免疫抑制状态并激活了T细胞的抗肿瘤效应，在肿瘤免疫治疗的辅助应用中展现出一定的前景[94]（图4）。

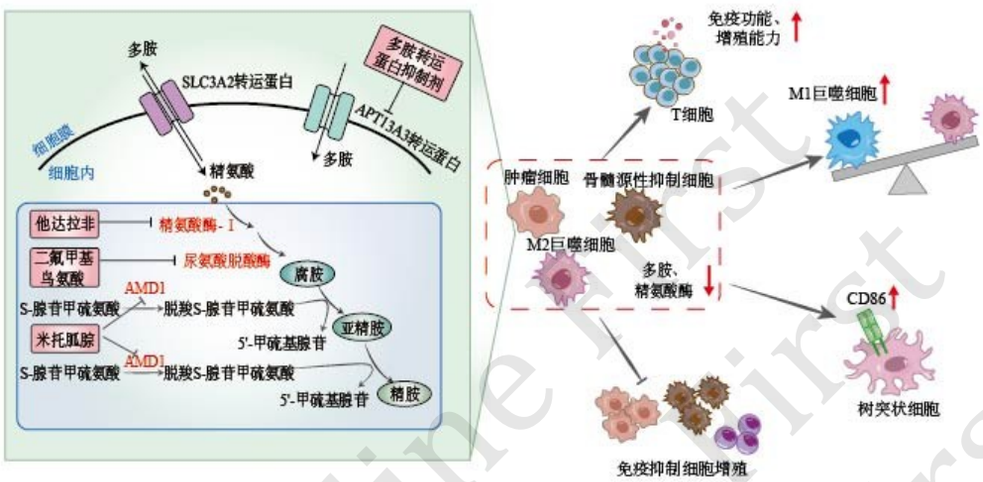

Fig.4　Polyamine blockade therapy improves tumor immune microenvironment

图4　多胺阻断疗法改善肿瘤免疫微环境

SLC3A2：溶质载体家族3成员2（solute carrier family 3 member 2）；APT13A3：多胺转运ATP酶13A3（polyamine-transporting ATPase 13A3）；AMD1：腺苷甲硫氨酸脱羧酶1（adenosylmethionine decarboxylase 1）；CD86：分化簇（cluster of differentiation）。多胺阻断疗法抑制肿瘤细胞、M2-TAMs和MDSCs内的多胺合成和摄取，使肿瘤免疫微环境得以改善，具体表现为：恢复T细胞增殖和功能，增加M1-TAMs数量，恢复抗原呈递细胞的抗原呈递功能，降低免疫抑制细胞数量。

5　总结与展望

多胺在TME中对T细胞功能起到广泛调控，显著影响其抗肿瘤免疫。尤其在T细胞的激活和分化过程中发挥重要作用，并且还通过促进免疫抑制型细胞（如MDSCs、M2-TAMs和Treg细胞等）扩增，抑制DC的抗原呈递功能以及上调肿瘤细胞表面PD-L1表达等，加剧对T细胞的免疫抑制。多胺合成酶抑制剂DFMO在改善TME免疫抑制发挥着重要作用，其中在与ICIs联合治疗肿瘤时，有效地提高了耐药肿瘤的敏感性。然而，针对多胺代谢的研究仍面临诸多挑战。一方面，多胺如何精准调控T细胞分化及功能还尚未完全阐明；本团队[31]基于乳腺癌RNA-seq数据分析，发现原癌基因*SPI1*和干扰素调节因子1（interferon regulatory factor，*IRF1*）基因与多胺代谢调控密切相关，并且这些转录因子参与了细胞免疫过程，对肿瘤免疫具有重要影响。未来，将进一步探讨*SPI1*和*IRF1*是否通过导致多胺代谢失调进而影响T细胞活性。另一方面，PBT策略需要考虑到肿瘤细胞的代偿性补充多胺问题，单一机制阻断多胺合成或摄取可能难以取得明显疗效。因此，通过多重机制阻断多胺代谢（如DFMO联合多胺转运蛋白抑制剂）是降低TME多胺水平和预防耐药的有效方案之一。然而，需要注意的是，DFMO作用靶点ODC1的半衰期较短（约20 min），易在体内被快速清除，导致药效维持时间有限。有研究指出，OAT可能会成为一个理想的PBT靶点，其抑制剂不仅能有效抑制多胺合成，而且不会产生对正常细胞的毒副作用[13]。

未来，PBT的临床转化需考虑到不同肿瘤类型对其敏感性的差异，通过联合多组学技术（转录组、代谢组等）解析不同类型肿瘤中的多胺代谢特征，开发精准的靶向策略。同时，PBT应结合纳米递送系统，提高药物的稳定性和靶向性，优化治疗效果。随着对多胺代谢在TME中作用机制的不断深入，PBT与免疫治疗联合策略有望为抗肿瘤免疫提供新突破。

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Tumor Microenvironment Polyamines Inhibit T Cell Antitumor Activity*

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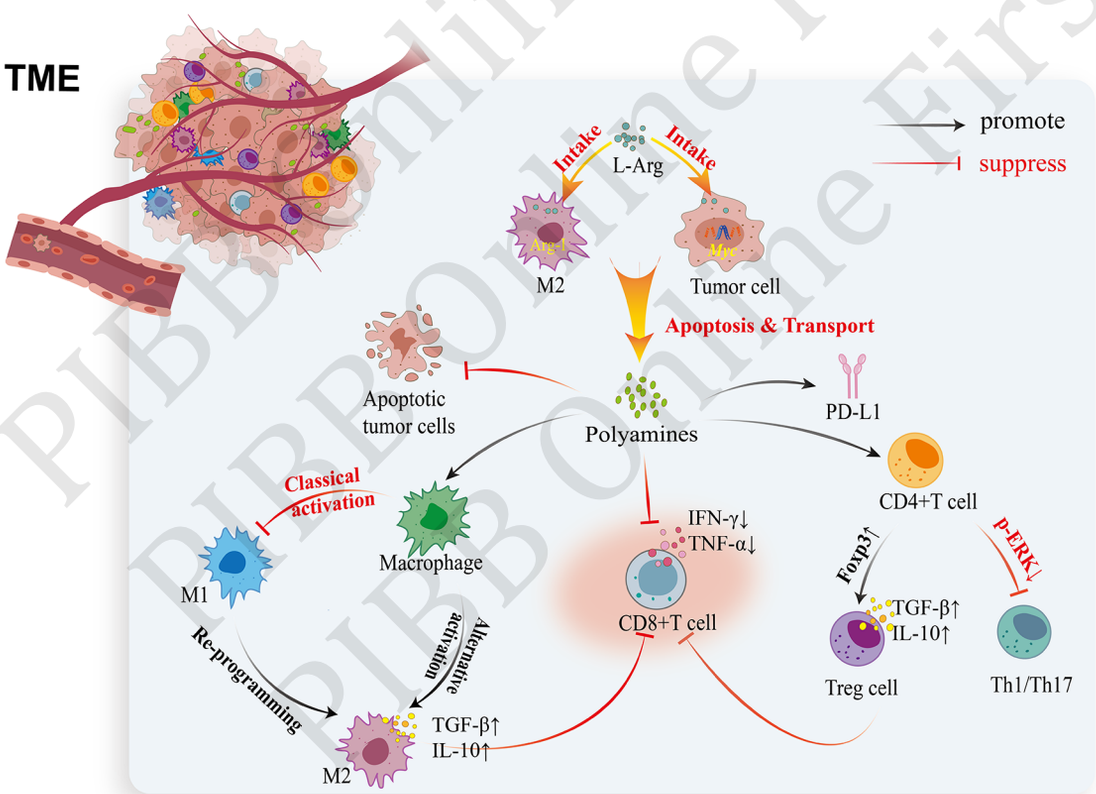
Graphical abstract



Abstract　Tumor immunotherapy has emerged as the fourth major therapeutic modality, following surgery, radiotherapy, and chemotherapy. Unlike traditional treatments that primarily target tumor cells directly, immunotherapy harnesses the body's immune system to recognize and eliminate cancer cells. Over the past decade, various immunotherapeutic strategies have been developed, including immune checkpoint inhibitors (ICIs), chimeric antigen receptor (CAR) T cell therapy, cancer vaccines, and cytokine-based therapies. However, the immunosuppressive tumor microenvironment (TME) poses a significant obstacle to the effectiveness of these treatments. Polyamines—including putrescine, spermidine, and spermine—are polycationic metabolites that often

accumulate abnormally in the TME and act as critical immunoregulatory molecules. T cells play a central role in antitumor immunity, yet their function is frequently influenced by immunoregulatory factors within the TME. Elevated polyamine levels in the TME have been implicated in dampening antitumor T cell responses, thereby facilitating tumor immune evasion. Polyamines in the TME originate from both tumor cells and tumor-associated immune cells. Tumor cells often overexpress the oncogene *MYC*, which drives the upregulation of polyamine biosynthetic enzymes, resulting in excessive intracellular polyamine production. Additionally, M2-polarized tumor-associated macrophages (M2-TAMs) contribute to polyamine accumulation by upregulating arginase-I (Arg-I), an enzyme that catalyzes the conversion of arginine into ornithine—a key precursor in the polyamine biosynthetic pathway. These combined sources lead to sustained polyamine enrichment in the TME, contributing to immune dysfunction and supporting tumor progression. Moreover, polyamines indirectly affect T cell activity by modulating macrophage polarization and directly suppress tumor cell apoptosis, further promoting an immunosuppressive environment. This review highlights the multifaceted roles of polyamines in modulating tumor-infiltrating T cell function, with a particular focus on their influence on $CD4^+$ T cell differentiation, $CD8^+$ T cell cytotoxicity, and immune checkpoint molecule expression. Recent studies suggest that polyamines suppress $CD4^+$ T cell activation and differentiation by modulating the MAPK/ERK signaling pathway. Additionally, polyamines can impair T cell receptor (TCR) signaling and promote immune evasion through the upregulation of PD-L1 expression on tumor cells. These effects collectively contribute to weakened antitumor T cell responses. Polyamine blocking therapy (PBT), which primarily targets polyamine biosynthesis and transport, has emerged as a novel adjunctive immunotherapeutic strategy in cancer treatment. By reducing polyamine levels in the TME, PBT restores T cell effector functions and alleviates immunosuppression. Notably, studies have demonstrated that combining PBT with ICIs produces synergistic antitumor effects and may overcome resistance to ICI monotherapy. Although research has revealed the inhibitory effects of polyamines on T cell immune function, the underlying regulatory mechanisms remain to be fully elucidated. Moreover, due to compensatory mechanisms employed by tumor cells to maintain polyamine homeostasis, multi-targeted approaches may be necessary to achieve safe and effective therapeutic outcomes. Future PBT strategies may benefit from the integration of multi-omics technologies and the development of nanocarrier-based drug delivery systems, which could collectively enhance their specificity, efficacy, and applicability in cancer immunotherapy. This review systematically elucidates the immunomodulatory effects of polyamines on T cell function within the TME and provides theoretical support and novel insights for the advancement of tumor immunotherapeutic strategies.

Key words polyamines, immunotherapy, tumor microenvironment, polyamine blockade therapy, immune checkpoint inhibitors

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