·综　述·

T细胞免疫代谢调控与免疫检查点抑制剂联合应用的现状及研究进展

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［**摘要**］ 近年来免疫检查点抑制剂（immune checkpoint inhibitor，ICI）已广泛应用于多种恶性肿瘤的治疗，但由于其单药客观缓解率较低，部分瘤种仅10%~20%，因此ICI联合用药成为近期研究热点。研究表明，肿瘤特殊的代谢方式及产物可以调控T细胞的分化和功能，而细胞代谢调节药物可以使T细胞在肿瘤微环境（tumor microenvironment，TME）中寿命延长及功能增强，联合ICI提高其治疗效果。拟对T细胞免疫代谢调控机制，TME和ICI对T细胞免疫代谢的影响，以及细胞代谢药物联合ICI的研究进展进行综述。

［**关键词**］ T细胞；免疫代谢；免疫检查点抑制剂；肿瘤微环境；联合治疗

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Research status and progress of mechanism of T cell immune metabolism and its application combined with immune checkpoint inhibitor

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［**Abstract**］ Cancer immunotherapy based on immune checkpoint inhibitor (ICI) has been widely developed. However, due to the low objective response rate of ICI monotherapy, only 10%-20% in some tumors, ICI combination therapy has become a research highlight recently. Studies have shown that cancer metabolism and its products can regulate the differentiation and function of T cells. Regulating cell metabolism can prolong the longevity and enhance the function of T cells in the tumor microenvironment (TME), and the combination of ICI can improve its therapeutic effect. Here, we summarized the differentiation of T cells regulated by immune metabolism, the effects of TME and ICI on T cell immune metabolism, and research progresses on the role of combination of cell metabolism drugs and ICI in cancer immunotherapy.

［**Key words**］ T lymphocytes; Immune metabolism; Immune checkpoint inhibitor; Tumor microenvironment; Combination therapy

在免疫检查点抑制剂（immune checkpoint inhibitor，ICI）成功用于多种癌症并带来肿瘤治疗领域的变革之前，手术、放疗、化疗和分子靶向治疗几乎是所有癌症的主要治疗方式[1]。既往对放疗、化疗及分子靶向治疗效果和耐药的研究主要集中在肿瘤细胞自身遗传或突变的内在因素上[2]，而很少关注肿瘤的外部因素，即肿瘤微环境（tumor microenvironment，TME）。TME主要由肿瘤细胞及其周围的免疫细胞、炎症细胞、肿瘤相关成纤维细胞、间质组织、微血管、各种细胞因子和趋化因子构成[3]。在实体瘤患者中，肿瘤免疫应答表现不佳，主要是由于TME中存在一些抑制性信号，抑制效应T细胞（effector T cell，

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Teff）的免疫功能[4]。抑制性信号包括肿瘤细胞产生的一系列免疫抑制性因子，如转化生长因子β、白细胞介素（interleukin，IL）-10等，以及T细胞表面免疫抑制性分子如程序性死亡［蛋白］-1（programmed death-1，PD-1）、溶细胞性T淋巴细胞相关抗原4（cytolytic T lymphocyte-associated antigen-4，CTLA-4）等[5]。阻断CTLA-4或PD-1均可解除对T细胞的抑制作用，产生持久的激活效应，且毒性较低。靶向CTLA-4的伊匹单抗是第一个被批准用于癌症临床治疗的ICI，PD-1/程序性死亡［蛋白］配体-1（programmed death ligand-1，PD-L1）单抗在肺癌、肝癌、结直肠癌等多种恶性肿瘤中疗效显著，使免疫疗法逐渐成为癌症治疗的成熟手段[6-8]。但从大型临床试验及治疗中可以清楚地看到，只有小部分患者对免疫治疗产生应答，仍存在大量无或低免疫应答及复发患者。

研究[9]显示，肿瘤细胞为维持庞大的合成代谢需求，采用与普通细胞代谢方式不同的有氧糖酵解方式，即Warburg效应，该效应消耗1分子葡萄糖，只产生2分子腺苷三磷酸（adenosine triphosphate，ATP），效率低下，但反应速度快，可为高速增殖的癌细胞提供必需的能量。癌细胞的高代谢和TME紊乱的脉管系统都可以导致营养物质缺乏，使癌细胞与浸润的免疫细胞之间存在代谢竞争[10]。癌细胞的高代谢导致低氧和酸性TME，其代谢产物等都是造成免疫抑制的重要因素。因此，细胞代谢已成为癌细胞和免疫细胞维持生命力和功能的关键。通过对癌细胞和免疫细胞代谢的深入研究可以揭示两者代谢的机制及异质性，发现可能的治疗窗口并进行干预。通过联合治疗策略，提高ICI的临床反应。要实现这一目标首先要了解T细胞参与癌症免疫应答的过程中，不同细胞亚群的分化与代谢方式的关系；其次需要了解这些代谢方式在TME中及ICI应用后如何受到干扰；最后再尝试通过不同的代谢干预措施来增强ICI抗肿瘤免疫反应，从而找到有望应用到肿瘤临床治疗的ICI联合治疗方案。

1 T细胞增殖分化过程中的代谢方式

T细胞是介导抗肿瘤免疫的核心[11-12]。其抗肿瘤免疫反应依赖于$CD4^+$和$CD8^+$ T细胞与肿瘤抗原的相互作用。接受抗原刺激后的T细胞在增殖分化过程中，必须保持基本营养物质供给和能量需求之间的平衡。不同T细胞亚群采用相应的代谢途径如糖酵解、氧化磷酸化（oxidative phosphorylation，OXPHOS）和脂肪酸氧化（fatty acid oxidation，FAO），以适应TME的营养物质水平及能量需求[13]。而这些代谢途径反过来不仅可以控制T细胞激活和效应功能，也决定T细胞的分化方向。幼稚或静息的T细胞主要依赖OXPHOS途径生成ATP。一旦T细胞激活，代谢方式就切换到糖酵解、谷氨酰胺和支链氨基酸的分解代谢，导致葡萄糖和氨基酸的摄取增加[14]。激活的T细胞也会增加对脂肪酸的摄取，但抑制FAO并促进脂类合成，OXPHOS也相应增加[15]。除了增强糖酵解外，磷酸戊糖途径也会增强葡萄糖代谢，再加上谷氨酰胺分解，共同促进基本生物分子合成代谢[16-17]。这些代谢变化是由T细胞受体和CD28，以及细胞因子受体激活的下游信号通路如磷脂酰肌醇-3-激酶（phosphatidylinositol-3-kinase，PI3K）/蛋白激酶B（protein kinase B，Akt）/哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）调控的。mTOR是T细胞分化的关键调控因子，由两种不同的复合物mTORC1和mTORC2组成，协调细胞对营养水平和能量状态变化的反应[18]。mTOR诱导转录因子缺氧诱导因子-1α（hypoxia-inducible factor-1α，HIF-1α）和c-Myc表达，而HIF-1α和c-Myc都负反馈调控mTOR复合物。C-Myc促进有氧糖酵解和谷氨酰胺分解代谢酶的表达，并微调这些代谢途径来进行生物合成脂类、氨基酸和核酸[19]。HIF-1α介导T细胞对氧气水平的反应也会促进葡萄糖的摄取和分解[20]，并合成Teff分泌的细胞因子，有利于Teff的有效激活和克隆增殖。同时通过调节脂类代谢基因表达抑制调节性T细胞（regulatory T cell，Treg）的分化和功能[21]。当抗原被清除后，一部分Teff分化成持续存在的记忆性T细胞（memory T cell，Tmem），代谢方式也由糖酵解转变为OXPHOS介导的分解代谢[22]。

2 TME和ICI对T细胞代谢的影响

癌细胞为营养物质的摄取创造了一个葡萄糖、脂质、氨基酸及氧气均有限的TME。mTOR和磷酸腺苷活化蛋白激酶（adenosine monophosphate-activated protein kinase，AMPK）分别调控T细胞合成和分解代谢[23]。当营养物质和能量充分时，mTOR被激活并诱导以糖酵解为基础的合成代谢反应[24]。而当营养物质和能量匮乏时，AMPK途径激活并抑制mTOR，诱导细胞代谢转为以线粒体OXPHOS和FAO为基础的分解代谢[25]，但mTOR和AMPK之间相互作用的机制尚不明确。Warburg效应使癌细胞消耗葡萄糖并增加乳酸，乳酸可以抑制PI3K/Akt/mTOR通路，从而抑制T细胞糖酵解并增强FAO[26]。因为Teff通过糖酵解获得能量，而Treg则依靠FAO，因此该过程抑制幼稚T细胞向Teff的分化，并促进$CD8^+$肿瘤浸润淋巴细胞凋亡。乳酸还可以通过乳酸脱氢酶B生成丙酮酸和还原型烟酰胺腺嘌呤二核苷酸（reduced nicotinamide adenine dinucleotide，NADH），导致丙酮酸生成不平衡和NADH/烟酰胺腺嘌呤二核苷酸（nicotinamide adenine dinucleotide，NAD）比例升高，通过阻碍有氧糖酵解，减弱T细胞增殖和效应功能[27]。

此外，肿瘤细胞的特殊生化代谢产物也会抑制肿瘤浸润淋巴细胞的功能。色氨酸可以激活T细胞并促进其增殖。癌细胞通过吲哚胺-2,3-双加氧酶（indoleamine 2,3-dioxygenase，IDO）和色氨酸-2,3-双加氧酶（tryptophan-2,3-dioxygenase，TDO）将色氨酸代谢为犬尿氨酸（kynurenine，KYN）[28]，KYN可抑制Teff活性[29]。KYN结合于芳香烃受体，激活细胞质中的转录因子[30]并诱导$CD4^+$ T细胞转化为$Foxp3^+$ Treg[31]。KYN也可诱导肿瘤浸润淋巴细胞活性氧（reactive oxygen species，ROS）产生，抑制IL-2信号通路并削弱Tmem的功能[32]。T细胞激活后，可消耗L-精氨酸进行合成代谢并快速增殖。精氨酸是蛋白质合成的基本氨基酸，提高精氨酸水平可诱导全面代谢变化，由糖酵解向OXPHOS转变，维持Tmem的生存[33]。在TME中，骨髓来源的抑制细胞（myeloid-derived suppressor cell，MDSC）分泌精氨酸酶，降解精氨酸，导致T细胞缺乏精氨酸[34]。靶向精氨酸酶或补充L-精氨酸可提高ICI治疗效果[35-37]。另一种具有免疫抑制作用的代谢产物是腺苷，由具有酶活性的CD38、CD39和CD73产生[38]。腺苷通过结合A2A受体产生环磷酸腺苷（cyclic adenosine monophosphate，cAMP），cAMP激活蛋白激酶A（protein kinase A，PKA），PKA介导Akt抑制信号转导和转录激活因子5（signal transducer and activator of transcription 5，STAT5）磷酸化，抑制T细胞功能[39-40]。另外，PKA使转录因子cAMP反应元件结合蛋白（cAMP response element-binding protein，CREB）磷酸化，诱导Treg产生[41]。因为瘤细胞、巨噬细胞高表达CD38、CD39和CD73，因此TME富含腺苷，维持了TME的抑制性。前列腺素E2（prostaglandin E2，PGE2）是一种小分子脂质介质，由花生四烯酸通过环氧合酶（cyclooxygenase，COX）-2和微粒体前列腺素E合酶（microsomal prostaglandin E synthase，mPGES）-1合成。PGE2抑制Th1分化、B细胞功能和T细胞活化[42-43]。PGE2通过两种机制抑制T细胞的增殖：抑制IL-2的产生以及通过cAMP信号途径下调转铁蛋白受体水平[44]。

最新证据表明，ICI也影响T细胞的代谢，PD-1/PD-L1配对后PD-1分子细胞内区招募磷酸酶SHP-2，使TCR和CD28下游信号去磷酸化[45]，抑制TCR信号通路介导的T细胞激活。PD-1信号通路也影响线粒体超微结构，降低Mic19和Mic14这两种重要的构成线粒体嵴组织蛋白的表达，减少T细胞线粒体嵴生成，减弱其去极化，导致线粒体功能障碍[47]。PD-1/PD-L1结合，使T细胞代谢重编程，增强内源性脂质的FAO限速酶基因肉毒碱棕榈酰基转移酶1A（carnitine palmitoyltransferase 1A，CPT1A）的表达，增强FAO，削弱T细胞的糖酵解、谷氨酰胺分解和支链氨基酸代谢，抑制T细胞活化所需的能量和物质合成[46]，但可拯救Teff由糖酵解引起的快速

死亡和细胞终末分化，将代谢平衡向以脂肪为基础的代谢模式倾斜，使T细胞寿命得以延长。因此，阻断PD-1信号最终会触发Teff糖酵解，导致其终末分化，通过细胞凋亡造成克隆缺失[48]，结果Teff的可用性减少。这很可能是抗PD-1单抗单药治疗过程中，部分患者最初有反应，但后来无反应的原因。

3 调节细胞代谢联合ICI抗肿瘤免疫治疗的探索

3.1 AMPK/mTOR

AMPK和mTOR之间的平衡调节T细胞命运。Teff依赖mTOR通路，而Tmem更依赖AMPK。治疗2型糖尿病的二甲双胍具有抗癌作用，二甲双胍使pAMPK的水平升高，mTOR下游蛋白pS6水平下降，延长Tmem寿命。mTOR抑制剂雷帕霉素可增强PD-L1单抗对口腔癌细胞系MOC1的抑制作用，扩增肿瘤浸润Tmem，增强干扰素-γ分泌，促进瘤细胞主要组织相容性复合体-Ⅰ（major histocompatibility complex-Ⅰ，MHC-Ⅰ）类分子表达。Vistusetib（AZD2014）是mTORC1/2双激酶抑制剂，可促进Th1分化，增强Tmem功能和寿命。与CTLA-4、PD-1、PD-L1单抗联合应用，可抑制肿瘤浸润淋巴细胞的功能耗竭，延长MC-38和CT-26移植瘤动物的生存期[49]。另一种mTOR抑制剂依维莫司可上调肾癌细胞系PD-L1的表达，与PD-L1单抗联合应用，可抑制动物模型中肾癌细胞系786-O和RENCA的生长。TWS119是糖原合酶激酶-3β（glycogen synthase kinase-3β，GSK-3β）的类似物，可上调Wnt/β-catenin信号通路，从而抑制mTOR信号，诱导干细胞样Tmem分化，并促进FAO，增强PD-L1单抗的抗肿瘤作用[50]。

3.2 FAO

脂肪酸生物合成及FAO与T细胞分化密切相关。Teff增强脂类生物合成，而Tmem降低脂类合成，增强FAO。苯扎贝特是PPAR-1α激动剂，促进PGC-1α、Cpt1α和LCAD表达，增强FAO和肿瘤浸润淋巴细胞的ROS，维持其功能，与PD-L1单抗联用对肺癌具有明显的抑制作用[51]。GW501516是PPARα和PPARδ/β激动剂，在$CD8^+$ T细胞过继免疫治疗中，可增强其CPT1α表达，促进FAO，促进Teff分化，与PD-1单抗联用对黑色素瘤动物模型具有显著疗效[52]。

3.3 IDO/TDO

干扰素-γ诱导IDO1的上调和TDO的肿瘤异位表达，使色氨酸分解代谢产物KYN升高，介导免疫抑制。BGB-5777是IDO1抑制剂，通过拮抗IDO1，抑制色氨酸分解代谢，从而减少KYN的产生，增强Teff功能。与PD-1单抗联合可持续提升进展期胶质母细胞瘤患者的生存获益[53]。PEG-KYNase是一种药物分解酶，可将KYN降解为免疫惰性、无毒、易清除的代谢产物，逆转IDO1/TDO上调的免疫抑制作用，抑制肿瘤生长。在小鼠移植瘤模型中，PEG-KYNase与PD-L1联合治疗B16-F10黑色素瘤、4T1乳腺癌及CT26结肠癌效果显著[54]。

3.4 精氨酸

L-精氨酸可以促进免疫细胞功能，特别是T细胞的增殖、分化和体内活性。He等[37]建立了带有原位和转移性骨肉瘤的BALB/c小鼠移植瘤模型，结果发现，L-精氨酸显著升高小鼠脾脏$CD8^+$ T细胞数量、血清干扰素-γ水平，与PD-L1单抗联用保护扩增的$CD8^+$ T细胞免于耗竭，并加强这些T细胞分泌干扰素-γ、颗粒酶B和穿孔素的能力。这种联合治疗策略可显著延长骨肉瘤小鼠的生存时间，提示补充L-精氨酸结合PD-L1单抗可能是治疗骨肉瘤患者的一种有效方法。CB-1158是精氨酸酶抑制剂。Steggerda等[35]研究发现，CB-1158可缓解MDSC在体内外对T细胞增殖的抑制，与ICI联用可提高肿瘤浸润$CD8^+$ T细胞和自然杀伤（natural killer，NK）细胞数量，以及炎性细胞因子、干扰素诱导的基因表达如*INFA*1、*ISG*15、*USP*18、*IRF*5等，对肿瘤细胞系CT26、B16、4T1体内外模型具有明显的杀伤效果。

3.5 腺苷

腺苷由CD39和CD73活性胞外酶产生，参与TME的免疫抑制。为了阻断腺苷途径，Perrot等[55]制备了IPH5201和IPH5301两种抗体，分别靶向人细胞膜表面和可溶性CD39和CD73，并有效地阻断ATP水解为腺苷，这些抗体通过刺激树突状细

胞、巨噬细胞及肿瘤特异性T细胞，促进抗肿瘤免疫，将CD39敲入小鼠模型中，IPH5201可增加ATP诱导化疗药物奥沙利铂的抗肿瘤活性。CPI-444和PBF509是一种有效的、选择性的A2A受体拮抗剂[56-57]。用二者阻断A2A受体可以恢复T细胞由腺苷引起的信号转导抑制，促进IL-2和干扰素-γ的产生。体外研究[56]发现，CPI-444联合PD-L1单抗或CTLA-4单抗可消除高达90%的小鼠肿瘤，包括恢复对PD-L1单抗或CTLA-4单抗单药治疗的不完全免疫应答，肿瘤痊愈的小鼠再次接种肿瘤后，生长完全受到抑制，表明CPI-444和PBF509可抑制$CD8^+$ Tmem的免疫删除，延长其寿命。

3.6 COX

黄酮类化合物melafolone和asprin均是COX-2的抑制剂。通过抑制COX-2，抑制PGE2生成，从而抑制肿瘤细胞分泌肿瘤坏死因子-β、血管内皮生长因子，下调其表达PD-L1，抑制下游PI3K/Akt活性，有助于激活Teff，增加颗粒酶B、IL-2、干扰素-γ分泌。与PD-L1单抗联用可增强对肺癌、黑色素瘤细胞的杀伤作用[58-59]。

3.7 线粒体解偶联/ROS生成

Chamoto等[60]研究发现，在小鼠PD-1单抗治疗模型中，引流淋巴结中肿瘤特异性$CD8^+$ T细胞存在更多的线粒体和ROS。Teff和Tmem的ROS与PD-1单抗对瘤细胞具有协同抑制作用。羰基-氰-对-三氟甲氧基苯肼是线粒体解耦联剂，可降低T细胞线粒体膜电位，Luperox是H_2O_2前体，二者均可促进ROS生成，激活PGC-1α及下游信号，增强Teff功能[60]。

3.8 糖酵解/谷氨酰胺

Sukumar等[61]研究发现，激活的$CD8^+$ T细胞应用糖酵解抑制剂2-脱氧葡萄糖，可提高Teff生成。Leone等[62]研究指出，谷氨酰胺拮抗剂6-diazo-5-oxo-L-norleucine可抑制瘤细胞OXPHOS和糖酵解，提高TME氧含量，降低酸性，并提高Teff OXPHOS代谢，促进Teff分化。二者与PD-1单抗联用可提高T细胞抗肿瘤活性。

4 总结

随着ICI被广泛应用于多种实体瘤免疫治疗中，低应答率机制及可能的改善方案是亟待解决的问题。癌细胞通过其代谢方式形成免疫抑制性的TME，导致T细胞代谢失衡，造成其功能障碍或耗竭，有利于癌细胞的生存。通过调控代谢方式可以帮助T细胞建立新的代谢平衡并克服功能障碍。本文总结了免疫代谢对T细胞的分化，肿瘤免疫监视和免疫抑制的调节机制，以及联合调节细胞代谢药物和ICI在癌症免疫治疗中的作用。深入研究肿瘤和T细胞代谢方式和精确调控途径，并以此为靶点，能够提高抗肿瘤治疗的持续性和有效性，并提高以免疫治疗为基础的抗肿瘤治疗的适用性和疗效。

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