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·综 述·

基于PD-1/PD-L1抑制剂的肺癌免疫治疗预测标志物的研究进展

Research progress on PD-1 / PD-L1 inhibitor-based immunotherapy predictive marker in lung cancer

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[摘 要] 近年来,免疫检查点抑制剂在肺癌治疗中取得突破性进展,正迅速改变着肺癌的治疗模式,也标志着免疫治疗2.0时代的到来。新的肿瘤治疗模式对精准医学提出更高要求,对程序性死亡受体1(programmed death 1, PD-1)/程序性死亡配体1(programmed death ligand 1, PD-L1)抑制剂预后生物标志物也在不断地探索之中,主要包括以下几个方面:PD-L1表达水平、肿瘤基因组异质性与肿瘤新抗原、T细胞特点、肿瘤微环境以及机体整体状态等。本文将针对目前PD-1/PD-L1抑制剂在肺癌免疫治疗中的潜在生物标志物最新临床研究进展及其研究前景进行综述。

[关键词] 肺癌;免疫治疗;免疫检查点抑制剂;生物标志物;程序性死亡受体1;程序性死亡配体1
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目前,肺癌的治疗已进入免疫治疗时代,程序性死亡受体1(programmed death 1, PD-1)及程序性死亡配体1(programmed death ligand 1, PD-L1)抑制剂与传统化疗相比疗效和生存质量均显示出卓越的优越性,在未经选择的肺癌患者有效率约为20%,已成为部分肺癌患者一线、二线治疗的推荐选择[1-3]。但抗肿瘤免疫应答过程中受到肿瘤内环境及整体多种因素的影响,如肿瘤细胞的基因突变较少而不易被免疫系统识别、肿瘤中原本存在的免疫细胞过少、肿瘤微环境不适宜免疫细胞浸润或生存等因素,均会限制PD-1/PD-L1抑制剂对免疫细胞的激活。PD-1/PD-L1抑制剂的临床应用中表现出的特殊缓解模式如延迟有效、假性进展等,也对疗效判断和预测产生巨大困扰。因此,开发预测疗效的生物标志物,以进一步实现获益人群的筛选和疗效的评估,是实现PD-1/PD-L1抑制剂一线治疗肺癌的关键,也是精准免疫治疗的核心。基于PD-1/PD-L1抑制剂的肺癌免疫治疗预测标志物的研究迅猛发展,这些生物标志物在具有一定疗效预测价值的同时仍存在许多局限性,面临着免疫系统的适应性和动态变化的挑战,多种生物标志物联合应用与动态监测成为未来发展趋势。

1 PD-1/PD-L1表达水平

作为PD-1/PD-L1信号通路的重要组成部分,肿瘤细胞的PD-L1表达水平是免疫检查点抑制疗法的潜在生物标志物。在PD-1抑制剂派姆单抗(pembrolizumab)治疗非小细胞肺癌(non small-cell lung cancer, NSCLC)患者的KEYNOTE系列研究[4-6]中,随着PD-L1表达水平的提高,患者对派姆单抗的客观有效率(ORR)、中位无进展生存(PFS)和总生存期(OS)均明显提高;尤在KEYNOTE-001临床研究中,PD-L1表达>50%的患者ORR达45.3%,而PD-L1表达<1%的患者ORR只有10.7%。在PD-1抑制剂纳武单抗(nivolumab)治疗NSCLC患者的CheckMate-017和CheckMate-057临床研究中,肺鳞癌患者PD-L1表达与纳武单抗疗效无明显相关性[7];在肺腺癌中,PD-L1表达>5%的患者,ORR和中位数OS分别是36%和18.1个月,而PD-L1表达<5%的患者,ORR和中位数OS分别只有10%和9.7个月[8]。PD-L1抗体阿特朱单抗(atezolizumab)治疗NSCLC的Ⅱ期临床试验POPLAR[9]中,PD-L1表达状况定义为PD-L1阳性的浸润

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免疫细胞（immune cell, IC）所占据的肿瘤细胞面积百分比，肿瘤细胞表明的PD-L1不参与评分。IC0为PD-L1阴性，IC1/2/3代表PD-L1表达的强度递增，其中IC0的患者ORR仅8%，而IC3的患者ORR达38%；IC0的患者PFS和中位OS分别是1.7个月和9.7个月，IC3的患者分别为7.8个月和15.5个月。在组织标本来源方面，REHMAN等[10]评估了从35例NSCLC肿瘤样本不同部位组织块上的PD-L1表达水平，提示肿瘤细胞PD-L1水平相似，但免疫细胞的一致性较差，仅为75%。ILIE等[11]研究结果显示，活检标本与手术标本PD-L1染色存在明显差异。在既往NSCLC研究中，KEYNOTE-001采用新鲜手术标本[11]，CheckMate-057主要使用库存的标本[7]，结果均显示PD-L1检测对疗效的预测作用相似。

目前，美国国立综合癌症网络（NCCN）指南推荐一线治疗前检测PD-L1状态，派姆单抗二线治疗和一线治疗只能分别用于PD-L1≥1%和PD-L1>50%的NSCLC患者；纳武单抗和阿特朱单抗二线治疗不需要PD-L1表达检测。但将其作为肿瘤标志物尚存在争议：（1）检测试剂盒及抗体不同，所规定的PD-L1阳性定义标准亦不相同[12-13]，目前国际上有4种抗体，其中SP142抗体与其他3种抗体（22C3、28-8和SP263）的一致性较差；（2）不同的肿瘤类型之间PD-L1表达存在较大差异[14]，肿瘤内PD-L1表达的异质性[15]、判读的主观性等都可导致PD-L1表达水平测定的误差；（3）肿瘤浸润淋巴细胞（tumor infiltrating lymphocyte, TIL）上亦可检测出PD-L1，样本细胞的细化排除干扰仍需探索[4]。蓝图项目1（Blueprint 1）[5]对PD-L1免疫组织化学染色法对22C3、28-8、SP263和SP142抗体进行了比较，结果发现前3种抗体一致性较好，而SP142抗体肿瘤细胞染色相对较少；4种抗体对免疫细胞染色的一致性较差。但由于该研究仅采用手术标本，参与评阅的病理专家相对较少，其结果存在局限性。在蓝图项目1的基础上，蓝图项目2也在进行之中，该研究分析5种抗体（28-8、22C3、SP142、SP263和73-10）对肿瘤细胞和免疫细胞PD-L1表达染色的一致性，将纳入更多的临床肺癌样本类型，包括手术组织和粗针穿刺、细针穿刺样本等；并比较普通光学显微镜阅片和数字扫描成像阅片的差异；参与评阅的病理专家更多并将评审者统一培训。此外，PD-L1也受样本采集部位、采集时间（治疗前或治疗后）、治疗方案等因素发生动态变化[6]，在治疗中动态监测PD-L1表达水平可能对预测微小残留病灶（minimal residual disease, MRD）转化及免疫治疗时机的选择有指导意义[16]。

2 肿瘤新抗原

肿瘤基因组突变是一个动态连续的过程，包括DNA修复酶失活、抑癌基因失活、癌基因激活等改变。基因组倍增及动态变化的染色体不稳定性与瘤内异质性相关，并导致驱动体细胞拷贝数变异演化，促进肿瘤复发和转移[17-18]。

EGFR、*MET*、*BRAF*和*P53*突变通常是肺癌早期克隆驱动事件，特定的基因型的患者包括*EGFR*突变和*ALK*重排患者均对PD-1/PD-L1抑制剂反应性较差。最近发表的一项回顾性分析28例PD-1/PD-L1抑制剂治疗晚期肺腺癌的临床研究[19]显示，伴*EGFR*突变（n=22）或*ALK*重排（n=6）的患者缓解率（response rate, RR）分别为5%和0%。2017年美国临床肿瘤学会（ASCO）报道的一项在*EGFR*突变人群中的研究[20]发现，CD73表达增高和IFN-γ表达下调及*EGFR*突变人群对免疫治疗的无应答有关。肿瘤*PTEN*基因失活导致JAK/STAT信号通路上调，VEGF等免疫抑制细胞因子在免疫微环境中表达增加，可减弱PD-L1免疫抑制剂药物效果，进而促进药物耐药。

肺癌相比于其他类型肿瘤拥有更高的突变负荷[21]，研究较多的潜在生物标志物有肿瘤突变负荷（tumor mutation burden, TMB）、微卫星高度不稳定（microsatellite instability-high, MSI-H）和错配基因修复缺失（mismatch-repair deficiency, dMMR），这些潜在的生物标志物都具有一个共同点：突变相关新抗原（mutation-associated neo-antigen）。基于临床研究，2018年5月派姆单抗被美国FDA批准用于MSI-H或dMMR的成人和儿童实体瘤患者。这是FDA批准的首款不依据肿瘤来源，而是依据生物标志物进行区分的抗肿瘤疗法，标志着肿瘤免疫治疗进入了一个全新的时代。利用癌症基因组图谱对患者的基因数据分析结果[19]显示，患者对PD-1和CTLA-4药物的敏感性在新抗原丰富的肿瘤中会增强，该研究相关临床试验（NCT01876511）也得出相似结论。目前研究[22-23]显示，TMB越高，肿瘤产生的新抗原越多，越容易被免疫细胞识别，免疫治疗响应程度也越高，并且在多种肿瘤中趋势一致。在CheckMate-026研究[24]中，高TMB组（＞200个非同义突变）的中位PFS和ORR分别为9.7个月和47%，相比低TMB组4.2个月和28%明显增高。KETNOTE-001研究[4]中，派姆单抗在PD-L1未选择人群的应用中，高TMB的患者也显示出更持久临床获益。进一步的肺癌治疗研究[25-26]显示，高PD-L1表达与高TMB群人并不重合，两者并无相关性。使用血浆游离DNA检测TMB可使更多无法获得肿瘤组织患者获益。最近欧洲临床

肿瘤学会（ESMO）会议上公布的二线及以上NSCLC治疗（POPLAR和OAK研究）血液肿瘤突变负荷（blood-tumor mutational burden，bTMB）与阿特朱单抗疗效提高的相关性研究数据[27]显示，bTMB高的患者在使用阿特朱单抗治疗后，PFS和OS体现出更多获益。但由于肿瘤的异质性、取样时机和计算方法的不同，组织样本与血液样本两者测定TMB结果的一致性、TMB检测的可行性及有效界值的选择仍需要进一步的临床数据验证。

近年来相关研究[28]也证明，两种DNA聚合酶POLε、POLδ的突变可导致TMB水平增高，从而促进肿瘤的发生。有研究[27]表明，在子宫内膜癌中，对比其他亚型患者，DNA聚合酶POLε突变患者$CD4^+$/$CD8^+$TIL和PD-L1均表达增加，并且预后更好，因此推测其突变可能与PD-1/PD-L1抑制剂疗效相关，有望成为一种预后生物标记物。

3　T细胞库检测

T细胞活化需要T细胞受体（T cell receptor, TCR）信号和共刺激因子（如CD28）两种信号同时作用，而T细胞表面的共抑制因子（如PD-1）作为免疫检查点，维持着机体免疫稳态。目前普遍认为，PD-1/PD-L1阻断主要通过抑制TCR信号转导来逆转T细胞衰竭，肿瘤内基因组异质性可生成新抗原，通过T细胞应答来改变肿瘤免疫原性。对11例局限性肺腺癌患者进行多区TCR测序发现，浸润性T细胞密度和克隆性方面存在着显著的瘤内异质性（intra-tumor heterogeneity, ITH），TCR ITH与预测的新抗原ITH呈正相关[30]。进一步研究[31]发现，TCR异质性的程度与患者的复发风险相关，这意味着T细胞库的异质性可能对于肺癌患者疗效预测有潜在的临床意义。使用免疫检查点抑制剂后，肿瘤内及外周血TCR克隆性扩增或多样性增加可通过TCR互补决定区（complementarity determining region 3, CDR3）序列的扩增检测。在多种实体肿瘤中研究[32]显示，TCR扩增状态可能是预测PD-1/PD-L1抑制剂疗效及免疫毒性潜在的生物标志物，但T细胞库检测时机及检测方法仍是目前研究所要探寻的问题。

PD-1与PD-L1的结合可使PD-1胞质结构域中的两种酪氨酸（Y224和Y248）在激酶LCK的作用下磷酸化，进而募集了细胞质内酪氨酸磷酸酶SHP2，使PD-1本身以及CD28去磷酸化，从而终止CD28信号传递，产生免疫抑制。CD28在PD-1活化后优先发生去磷酸化，PD-1可直接靶向CD28的胞质区域，提示PD-1主要通过灭活CD28信号来抑制T细胞的功能[33-34]。因此，患者T细胞CD28表达情况可作为预测PD1/PD-L1疗效的潜在生物标志物，仍需进一步临床研究的验证。

4　肿瘤微环境

在肿瘤微环境（tumor microenvironment, TME）中，浸润的淋巴细胞和炎性细胞[35]已证实与多种实体肿瘤类型包括肺癌的生存率相关[36-37]。在一项797例I-IIIA期NSCLC患者的回顾性研究[38]中，基质$CD8^+$淋巴细胞密度为疾病特异性生存率、PFS和OS的独立预后因素（均$P<0.01$）。多重免疫组化（multiplex immunochemistry）可充分利用有限的肿瘤活检标本进行TME的评价，真实反映免疫细胞的时空特异性和功能蛋白的表达情况。一项II期临床试验评估纳武单抗作为IB-IIIA期高危NSCLC患者术前新辅助治疗的初步研究结果[39]显示，在18例患者中，通过利用多重免疫组化技术发现7例患者切除后肿瘤残留率低于10%，1例完全缓解。

由于PD-L1表达的异质性，PD-1表达阴性效应T细胞（Teff signature）提供了一个免疫豁免的肿瘤微环境，对免疫治疗疗效产生影响[38]。免疫评分（immunoscore）通过分析TIL在肿瘤核心和边缘两种区域的分布对免疫细胞浸润进行系统性评估[41-42]，TIL的三分法[43]和四分法基于PD-L1表达水平描述肿瘤免疫微环境中的免疫结构。TENG等[44]根据肿瘤微环境中TIL与PD-L1的表达与否将肿瘤分为4种类型：I型：PD-L1（+），有TIL浸润；II型：PD-L1（-），无TIL浸润；III型：PD-L1（+），无TIL浸润；IV型：PD-L1（-），有TIL浸润。因此，为了进一步提高抗PD-1通路疗法的有效性，其中II型肿瘤由于不能在肿瘤微环境中引起抗肿瘤免疫反应，疗效和预后差，必须采取新的治疗策略。III型肿瘤通过预先招募T细胞可增强其对免疫检查点抑制剂疗法的反应性。

使用基因芯片技术可同时检测多个基因以评估基因特征。既往研究[45]显示，多种基因表达特征与NSCLC的预后相关，对于免疫相关基因特征与PD-1/PD-L1抑制剂临床获益的联系也在探索之中[46-47]。世界肺癌大会（WCLC）上发表的OAK回顾性III期临床研究[48]中，效应T细胞特征定义为*PDL1*、*CXCL9*和*IFNG*这3个基因的mRNA表达情况，在高Teff人群中观察到PFS更显著获益（*HR*=0.73）。但是，研究发现部分基因突变与肺癌不良预后相关。

对肿瘤微环境的分类研究可为免疫检查点抑制剂的疗效预测和实现精准治疗提供策略[49-50]。

5　机体整体状态

炎症细胞可促进肿瘤发生发展及转移[51-52]，故监

测炎症和免疫状态可预测肿瘤免疫治疗的疗效，利用外周血细胞计数检查监测和预测免疫状态是一个有前景的研究领域。肿瘤微环境中浸润的中性粒细胞被认为具有免疫抑制作用，而淋巴细胞通常是反应机体免疫状态的指标，中性粒细胞与淋巴细胞比值（neutrophil lymphocyte ratio, NLR）可综合反映肿瘤患者机体炎症及免疫状态。现有研究[53-55]证实，治疗前高NLR肺癌患者应用免疫检查点抑制剂反应性较差。

外周血细胞因子是接受免疫抑制剂检查的肺癌患者的另一种潜在生物标志物[56]。在一项纳入63例接受PD-1抗体治疗的晚期恶性黑色素瘤或者晚期肺癌患者的研究[57]中，通过对比PD-1抗体使用前和使用2~4周后血液中IL-8的变化，可以较早地预测PD-1抗体的疗效，甚至可以辅助判断“假进展”，该研究界定浓度变化阈值为9.2%。另一项研究[58]发现，血浆IL-6和吲哚胺2,3-双加氧酶（indoleamine 2,3-dioxygenase, IDO）在有明显炎症状态的TME中升高，提示其可能具有潜在的疗效预测价值。

现有研究[59]显示，抗生素可能会影响PD-1/PD-L1的疗效，提示机体肠道微生物群的组成可影响其对免疫检查点抑制剂的疗效反应。对接受过PD-1抑制剂治疗的不同癌症类型的患者进行大规模分析的研究[60-61]显示，肠道微生物种类多样化的患者更可能响应抗PD-1免疫疗法；微生物的类型也与不同患者对治疗的响应差异有关：肠道中含有大量梭菌目细菌的患者更有可能对治疗做出响应，而那些肠道内具有更多拟杆菌目细菌的患者对治疗响应度差。另一项同类研究[62]中，学者们调查了来自249例肺癌、肾癌和膀胱癌患者的数据，研究结果显示，接受抗生素（破坏了肠道微生物组）治疗的患者PFS及OS均明显缩短。多项前瞻性研究正在探索肠道微生态与免疫检查点阻断剂相互作用的机制。

6 展 望

PD-1/PD-L1检查点抑制剂在肺癌中的应用取得了前所未有的成功，但获益人群较少，并且考虑到成本较高、存在免疫相关不良反应等风险，寻找有效的预测指标刻不容缓。目前，PD-L1单抗一线的应用以PD-L1表达是疗效预测的主要生物标志物，但检测技术的差异性及PD-L1表达的异质性、动态性，使得单独使用PD-L1表达水平预测有效性的结果不尽人意。随着研究的不断深入，肿瘤TMB及肿瘤新抗原、TIL、T细胞库特征、外周血细胞因子以及机体整体状态等在预测疗效方面都被认为具有一定潜力，值得进一步探究确证。在未来，将各项生物标志物统一和标准化，深入研究各项标志物之间的联系，探索多种标志物联合检测及动态监测的可行性，计算机与医学数据库的应用，有望建立一个新的预后模型，以最大限度地提高免疫治疗效果。相信随着肿瘤免疫机制研究的深入，技术手段的不断丰富，基于PD-1/PD-L1抑制剂的肺癌免疫治疗预测标志物的研究将会更加精准完善，推动肺癌的精准治疗的进程。

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