综 述

PD-1/PD-L1 抑制剂疗效相关生物预测标记物的研究进展

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摘要：PD-1/PD-L1 检查点抑制剂疗法在癌症治疗中取得了里程碑式的突破，但疗效差异很大。因此，能够用于疗效评价的生物学标记物的研究对于 PD-1/PD-L1 抗体药物的应用很重要。本文讨论了 PD-1/PD-L1 抗体疗效相关生物预测标记物的研究进展。PD-L1 表达是对 PD-1/PD-L1 抗体疗效预测的逻辑生物标记，然而 PD-L1 表达对该药物的预测价值目前有很大争论。一些其他生物标记也陆续得到关注，如 TIL、错配修复基因 (MMR)、肿瘤基因突变负荷 (TMB)、癌基因突变 (EGFR、ALK、KRAS)，需要达成共识和标准化，以便在未来的研究中广泛应用。

关键词：免疫检查点抑制剂；程序性死亡受体 -1；程序性死亡配体 -1；生物预测标记物
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Research advances in predictive biomarkers of anti PD-1/PD-L1 immunotherapy

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Abstract: Despite the marked success of applications of PD-1/PD-L1 checkpoint blockades in clinical practice, the efficacy and responsiveness of these agents varies greatly among different tumor types and across individual patients. Therefore, establishment of predictive biomarkers for checkpoint blockades is of great importance to maximize the therapeutic benefits. In this review, we discuss the current progress and challenges of developing predictive biomarkers of immunotherapy responsiveness, aiming to provide directions for future studies. PD-L1 expression is a logical biomarker for the prediction of response to anti-PD-(L)1 immunotherapies. However, the predictive values of PD-L1 expressions for immunotherapy still remain controversial. Multiplex detecting methods and combined biomarkers may provide new strategies, including tumor mutation burden, some oncogene mutations, like EGFR, ALK, KRAS and STK11. As current evidence of those potential predictors, a consensus and standardization is needed to be established for popularization in future studies.

Keywords: immune-checkpoint inhibitor; programmed death 1; programmed death ligand 1; biomarker

程序性死亡受体-1(PD-1)/程序性死亡配体-1(PD-L1)抑制剂在抗肿瘤治疗中取得显著的临床获益，开启了肿瘤免疫治疗的新纪元。其具有特异性强、不良反应小、作用时间持久等优点，已广范应用于黑色素瘤、非小细胞肺癌、尿路上皮癌、头颈鳞癌、结直肠癌、肾细胞癌和胃癌等各种实体瘤中。但临床数据表明，PD-1/PD-L1 抑制剂的疗效差异很大，在黑色素瘤患者中，Nivolumab 或 Pembrolizumab 的客观缓解率(objective response rate，ORR)是 40% 左右；在 NSCLC 患者中，Nivolumab 或 Pembrolizumab 的 ORR 是 20% 左右[1-3]。鉴于此，有效预测疗效的生物标记物对于更高效、更精准地使用 PD-1/PD-L1 抑制剂意义重大。

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1 PD-1/PD-L1 信号通路及 PD-1/PD-L1 抑制剂

免疫检查点是免疫细胞具有的一组调节和控制免疫应答的信号通路分子，可以是刺激性或抑制性的，免疫应答的功效由共刺激信号和共抑制信号之间的微妙平衡决定，PD-1/PD-L1 是一组抑制性免疫检查点分子[4]。PD-1 在激活的 T 细胞、B 细胞、单核细胞和树突状细胞表面广泛表达；PD-1 有两种结合配体，PD-L1 和 PD-L2，PD-L2 主要表达在活化的巨噬细胞、树突状细胞和少数肿瘤中，而 PD-L1 则在活化的 T 细胞、B 细胞、巨噬细胞、树突状细胞和肿瘤细胞广泛表达，同时在机体一些免疫屏蔽部位如胎盘、眼及其上皮、肌肉等组织表达，PD-L1 在体内的作用远远超过 PD-L2[5-7]。

肿瘤细胞及肿瘤微环境通过上调 PD-L1 表达并与肿瘤特异的 $CD8^+$ T 细胞表面的 PD-1 结合，来抑制 T 细胞的免疫反应；还可以通过激活 EGFR、MAPK 或 PI3K-Akt 通路，高表达 STAT3 蛋白和 HIF-1 转录因子等上调 PD-L1 的表达，也能扩增 PD-L1 基因上调 PD-L1 表达，而且 EB 病毒也能诱导 PD-L1 高表达。另外，活化肿瘤浸润性 T 淋巴细胞 (TIL) 产

生的γ-干扰素也可以诱导PD-L1的表达[8-9]。

PD-1/PD-L1抑制剂竞争性结合T细胞中PD-1或肿瘤细胞中PD-L1，断开肿瘤细胞与T细胞PD-1/PD-L1通路的链接，恢复T细胞的抗肿瘤活性，从而改善抗肿瘤效应。目前已经上市的PD-1/PD-L1抑制剂有5种，其中2种是PD-1抑制剂，3种是PD-L1抑制剂。

PD-1抑制剂：Nivolumab和Pembrolizumab都是通过基因工程改造的，抗PD-1的完全人源化IgG4型单克隆抗体，Nivolumab是百时美施贵宝公司生产，商品名为Opidivo，简称O药，Pembrolizumab是美国默沙东公司生产的，商品名为Keytruda，简称K药。这两种药被美国FDA陆续批准用于治疗不可切除或转移性黑色素瘤、NSCLC、肾细胞癌、经典型霍奇金淋巴瘤、头颈部鳞癌、尿路上皮癌、转移性结直肠癌和肝癌[1,10-17]。

PD-L1抑制剂：Atezolizumab(商品名Tecentriq，简称T药)、Avelumab(商品名Bavencio，简称B药)、Durvalumab(商品名Imfinzi，简称I药)，这3种药是一种人源化抗PD-L1的IgG4型单克隆抗体。目前，FDA批准的适应证为尿路上皮癌和NSCLC。

2 PD-1/PD-L1抑制剂潜在的疗效预测因子

2.1 PD-L1 2015年，FDA批准对于PD-L1表达≥50%且无明确驱动基因突变的初诊晚期NSCLC患者可以一线选择Pembrolizumab，PD-L1检测也写进了肺癌NCCN指南[18]。将5%肿瘤细胞表达PD-L1作为阈值，PD-L1阳性肿瘤患者的客观缓解率高于PD-L1阴性肿瘤患者[19]。这强调了PD-L1的表达对晚期NSCLC患者抗PD-1/PD-L1治疗的预测价值。然而，后期试验表明PD-L1阴性的患者使用PD-1/PD-L1抑制剂也获得很好疗效[20-21]。在一项Atezolizumab治疗NSCLC的试验中，发现无论PD-L1的表达水平如何，OS都得到了改善[22]。因此，单纯检测PD-L1的表达情况并不一定能精确预测PD-1/PD-L1抑制剂的疗效。

目前，PD-L1检测存在一些不确定性。首先，肿瘤组织中PD-L1表达存在异质性，同一肿瘤不同病灶中PD-L1表达不一致；穿刺标本和手术切除标本PD-L1表达不一致[23-26]；肿瘤在治疗过程中，PD-L1的表达也发生动态改变[27-28]。PD-L1表达的多变性和异质性限制了其检测的可靠性和可重复性。另外，检测PD-L1表达的免疫组织化学方法(IHC)所用染色抗体有很多种(IHC28-8、IHC22C3、E1L3N、SP412和SP263)[1,12,22,29-32]，标本处理强度(固定和包埋)和染色技术(人工和自动化)存在很大差异[33-35]，诊断性检测中阳性结果或评分系统的Cut-off值不统一，以上使得PD-L1检测结果难以达到一致。

2.2 肿瘤浸润淋巴细胞(tumor infiltrating lymphocytes，TIL)的数量 研究发现，TIL的数量与肿瘤患者的生存时间密切相关[36-38]。肿瘤组织中的TIL代表了机体的“免疫预存”状态。有研究发现，TIL阳性+PD-L1阳性组对PD-1/PD-L1抑制剂有很好的应答，而TIL阴性+PD-L1阳性组几乎对PD-1/PD-L1抑制剂无应答[39]。说明TIL的数量在一定程度上具有疗效预测的潜质。TIL主要浸润在肿瘤组织的癌巢、肿瘤基质和肿瘤侵入性边缘，不同部位与疗效的相关性不同，其中癌巢中TIL的数量与PD-1/PD-L1抑制剂疗效相关性最高[40]。但也有研究显示，存在于肿瘤微环境的TIL均与预后密切相关[41]。

2.3 肿瘤微环境中抗原提呈细胞和分子 在机体的抗肿瘤免疫反应过程中，T细胞、B细胞的激活需要有抗原提呈细胞的参与，体内抗原提呈细胞主要为树突状细胞和巨噬细胞。T细胞识别树突状细胞MHC分子递呈的抗原，引起活化。在一项肾癌患者接受PD-1/PD-L1抑制剂治疗的临床试验中发现，低应答组的肿瘤组织中存在大量失去抗原提呈功能的DC(dendritic cells)细胞，研究者推测不成熟DC与PD-1/PD-L1抑制剂疗效有相关性[42-44]。目前，检测不成熟DC的抗体已得到临床应用[42-43]。另外，免疫细胞通过对肿瘤细胞上MHC Ⅰ/Ⅱ分子进行识别，启动抗肿瘤免疫程序，而肿瘤特异性抗原提呈分子会减少或消失，从而导致免疫逃逸。Johnson等[45]发现免疫组化显示肿瘤组织上MHC Ⅱ类分子阳性率与应答和临床获益相关。

2.4 DNA错配修复基因(mismatch-repair，MMR) 2015年6月的美国临床肿瘤学会(American Society of Clinical Oncology，ASCO)年会公布了一项抗PD-1免疫治疗的研究结果，探索错配修复(MMR)基因状态指导下的抗PD-1免疫治疗晚期癌症的价值。该Ⅱ期临床研究纳入既往标准治疗失败的晚期病例41例，根据MMR状态将患者分为3组：MMR突变的结直肠癌、MMR正常的结直肠癌和MMR突变的其他肿瘤，3组均给予抗PD-1药物Pembrolizumab治疗。主要研究终点是20周时的免疫相关的客观反应率(irORR，也可称为有效率)和免疫相关的无进展生存(irPFS)期。大肠癌突变组的客观缓解率和无进展生存率分别是40%和78%，大肠癌无突变组分别为0和11%[46]。有错配修复基因突变的肿瘤在PD-1/PD-L1抑制剂治疗中更容易获益。MMR是在遗传性非息肉性大肠癌中分离得到的一组遗传易感基因，该基因突变会导致错配修复功能缺失，进而出现微卫星不稳定(microsatellite instability，MSI)，从而容易发生肿瘤。Diaz和Li[47]认为d-MMR肿瘤中出现更多的肿瘤新抗原增强机体抗肿瘤免疫反应，而应用PD-1抗体治疗纠正免疫抑制，恢复抗肿瘤免疫，可达到较好疗效。

2.5 肿瘤基因突变负荷(tumor mutation burden，TMB)肿瘤突变负荷是一份肿瘤样本中，所评估基因的外显子编码区每兆碱基中发生置换和插入/缺失突变的总数。TMB高表达肿瘤细胞的新抗原水平更高，有助于激发更强抗肿瘤免疫应答。2018年百时美公司公布的一项随机Ⅲ期临床试验CheckMate-227[48]，旨在对比Nivolumab单用或联合Ipilimumab与化疗初治晚期NSCLC患者的疗效及安全性，发现TMB高表达的NSCLC患者中，Nivolumab和Ipilimumab联合治疗组的PFS显著长于其他3组。该试验表明TMB是一种重要且独立的预测性生物标记物，可以鉴定可能受益于一线Nivolumab+Ipilimumab组合疗法的NSCLC患者群体[49]。

2.6 肿瘤驱动基因突变 目前尚未发现与免疫抑制剂疗效相关的癌基因，但有些癌基因突变能够使PD-L1的表达

上调。EGFR基因突变或ALK基因融合均能上调PD-L1表达[50-51]。在一项使用Atezolizumab治疗晚期NSCLC的临床试验中，EGFR突变且PD-L1阳性的患者ORR为31%，EGFR野生型且PD-L1阳性的患者ORR为22%[33]。有数据显示，高水平PD-L1表达在EGFR突变的患者中并不常见，阳性率在3%～5%[52]。另一个肺癌常见驱动基因是KRAS，突变率为25%～30%。Meta分析纳入NSCLC的3个著名试验：Checkmate 057、OAK和POPLAR，旨在研究KRAS基因与免疫抑制剂疗效的关系[53]。KRAS突变组使用免疫抑制剂较使用多西他赛更能延长OS[54]。以上提示，癌基因突变与免疫抑制剂的疗效有一定的相关性。

3 PD-1/PD-L1抑制剂疗效与临床指标的关系

年龄、性别、病理类型、吸烟史及紫外线照射史等与免疫抑制剂疗效的关系近期也有所报道。有研究显示，NSCLC患者年龄越高，PD-1/PD-L1抑制剂疗效越好，但年龄＞75岁的患者疗效较差[55-56]。鳞NSCLC对免疫抑制剂疗效好，而非鳞NSCLC疗效不统一。吸烟史和紫外线照射史可能会导致机体癌基因突变增加，从而增加对PD-1/PD-L1抑制剂的敏感性。有报道外周血循环标记物与PD-1/PD-L1抑制剂疗效有相关性。如在治疗过程中，嗜酸性粒细胞和淋巴细胞计数增加，则提示抗PD-L1药物(Ipilimumab)疗效好[57-58]。在一项大样本616例黑色素瘤患者的研究中，发现淋巴细胞计数升高，嗜酸性粒细胞增加，LDH降低、没有实质器官转移(除了肺和软组织)这4项因素与PD-1/PD-L1抑制剂疗效相关[59]。

4 结语

临床尚缺少PD-1/PD-L1抑制剂的有效预测指标。PD-L1检测目前应用较广，但临床应用存在问题很多。TIL需要有效的检测方法，肿瘤细胞和TIL相互作用的过程中，涉及到的细胞因子和受体配体机制还需要深入研究。癌基因如MMR、EGFR、ALK、KRAS突变与PD-1/PD-L1抑制剂疗效的相关性还需要大样本的数据验证。其中PD-L1、TMB和MMR是最有前景、关注度最高的潜在预测因子，值得进一步深入研究。

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