

免疫检查点抑制剂抗肿瘤免疫治疗的相关预测标志物研究进展

冀寿健¹, 徐建明²

¹联勤保障部队第960医院消化内科, 山东济南 250031; ²解放军总医院第五医学中心消化肿瘤内科, 北京 100853

摘要:以免疫检查点抑制剂为代表的免疫疗法开创了肿瘤治疗的新途径, 已在泛癌种患者中展现了持久的临床获益, 但仅有一小部分患者治疗有效, 且特异性的免疫相关不良事件和肿瘤超进展限制了其应用。因此开发预测性生物标志物, 以筛选获益人群、最大程度降低毒性风险是目前的研究热点。本文综述了免疫检查点抑制剂抗肿瘤免疫治疗的相关预测标志物研究进展, 并展望了其在精准免疫治疗方面的未来方向。

关键词:免疫检查点抑制剂; 生物标志物; 预后; 药物不良事件; 超进展

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Research advances in predictive biomarkers for immune checkpoint inhibitors in cancer immunotherapy

Ji Shoujian¹, Xu Jianming²

¹Department of Gastroenterology, the 960th Hospital of the PLA, Jinan 250031, Shandong Province, China; ²Department of Gastrointestinal Oncology, the Fifth Medical Center of PLA General Hospital, Beijing 100853, China

Corresponding author: XU Jianming. Email: jmxu2003@163.com

Abstract: Immune checkpoint inhibitors (ICIs)-based immunotherapy has created a new era of anti-cancer therapy and has shown durable clinical benefits in pan-cancer patients. Unfortunately, only a fraction of patients can response to ICIs. Moreover, specific immune-related adverse events and hyperprogressive diseases limit its application. Thus, it is imperative to identify valid biomarkers in optimizing patient selection for maximizing the clinical benefits and minimizing the risk of toxicity. The current progress of predictive biomarkers for ICIs are comprehensively summarized and their future directions in achieving precision immuno-oncology are discussed in this review.

Keywords: immune checkpoint inhibitors; biomarker; prognosis; adverse drug event; hyperprogression

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近年来, 免疫疗法开创了抗肿瘤治疗的新途径, 尤其是免疫检查点抑制剂 (immune checkpoint inhibitors, ICIs) 在多瘤种中均展现了良好的疗效和生存获益^[1]。抗 PD-1/PD-L1 抗体作为主要代表, 已获批应用于泛癌种的治疗, 颠覆了传统的抗肿瘤治疗模式^[2]。但单药治疗有效率在大多数瘤种中仅 20%~30%, 多数患者仍难以获益^[3]。抗 PD-1/PD-L1 抗体并非均安全低毒, 部分患者还可能发生有别于传统治疗的特异性免疫相关不良事件 (immune-related adverse events, irAEs), 严重时可能

危及生命^[4]。此外, 有患者接受治疗后不但无效, 而且可能会出现疾病超进展, 生存期显著缩短, 对临床决策提出挑战^[5]。探索 ICIs 治疗的预测性生物标志物是当前的研究热点。随着多重荧光免疫组化、多组学、高通量测序、深度学习等技术的不断发展完善, 多维度下各种新型预测生物标志物应运而生^[6]。本文综述了抗 PD-1/PD-L1 抗体治疗疗效、irAEs、超进展等预测性生物标志物的研究进展, 以期为肿瘤医师的免疫治疗临床与科研工作提供参考。

1 ICIs 治疗效果的预测标志物

1.1 PD-L1 表达

PD-L1 表达是目前国际上认可度最高的 ICIs 治疗预测生物标志物之一。一项研究纳入了黑色素

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第一作者: 冀寿健, 博士, 主治医师。Email: 18766179211@163.com

通信作者: 徐建明, 博士, 主任医师。Email: jmxu2003@163.com

瘤、非小细胞肺癌(non-small cell lung cancer, NSCLC)、前列腺癌和结直肠癌等多瘤种的患者接受抗PD-1抗体治疗,其中17例PD-L1阴性患者均无效,而25例PD-L1阳性患者客观缓解率(objective response rate, ORR)高达36%,提示PD-L1阳性患者似乎对ICIs治疗更为敏感^[7]。然而,部分PD-L1阴性患者接受抗PD-1抗体治疗时依然有效。CheckMate-040研究显示PD-L1阳性患者ORR达26%,而PD-L1阴性患者ORR也有19%^[8]。这或许与组织PD-L1表达时间与空间上的异质性有关。因为有研究指出PD-L1在不同解剖部位间差异较大,不同活检部位的PD-L1表达也可能预测价值不同。而且PD-L1表达在治疗过程会发生变化,一定程度上影响了结果判定^[9]。另外由于瘤种之间生物学特点各异,最佳Cut-off值难以统一,而检测抗体也尚未标准化,这些均限制了PD-L1表达预测的准确性^[10]。

基于组织PD-L1检测的缺陷,有研究着眼于从外周血中检测PD-L1的表达情况。Yue等^[11]研究发现治疗前基线外周血中存在高PD-L1表达循环肿瘤细胞的患者无进展生存期显著延长。此外,PD-L1不仅以细胞膜型形式存在,还能够表现为可溶性形式。Hayashi等^[12]发现在NSCLC中,接受PD-1抑制剂治疗持久获益的患者治疗前可溶性PD-L1水平低于无临床获益的患者,并提出可溶性PD-L1可能作为组织PD-L1预测能力的补充。因此,需进一步优化PD-L1检测及与其他标志物的联合以提升PD-L1在ICIs治疗中的预测价值。

1.2 DNA损伤修复

DNA损伤修复(repair of DNA damage, DDR)系统对于保持基因组完整性至关重要。DDR通路包括错配修复、同源重组、非同源末端连接等多种方式。而DDR缺陷是肿瘤免疫原性的重要决定因素,更强的免疫原性意味着被免疫系统识别的概率增加。有研究指出,错配修复缺陷(mismatch repair deficiency, dMMR)/微卫星高度不稳定(microsatellite instability-high, MSI-H)的患者肿瘤微环境中更多的T淋巴细胞浸润,提示对ICIs治疗敏感^[13]。而后续研究也证实了这一假设,dMMR患者接受ICIs后表现出持久的临床获益,而且不受肿瘤类型限制^[14]。但遗憾的是晚期患者dMMR发生率仅5%左右^[14]。而编码DNA聚合酶(POLE)和Delta1(POLD1)的基因对于DNA损伤修复同样具有重要的作用。POLE突变的患者,类似

于dMMR,CD8⁺T细胞局部浸润增加,而细胞毒性T淋巴细胞标志物和效应因子的表达也同样增加^[15]。Wang等^[16]发现调整MSI状态后POLE/POLD1突变依然是ICIs患者的独立预后因素。另一项研究评估了53个DDR基因,结果发现DDR突变与预后明显改善有关^[17]。

1.3 肿瘤突变负荷和新抗原负荷

肿瘤突变负荷(tumor mutation burden, TMB)指在肿瘤组织内每兆碱基发生基因突变的总数。很多研究已报道TMB与ICIs疗效和预后之间存在显著相关性^[18-19]。而KEYNOTE-158研究前瞻性探索TMB与抗PD-1抗体治疗疗效和预后的关系^[20]。高TMB定义为每兆碱基 ≥ 10 个突变。结果发现,高TMB组ORR显著高于低TMB组(29% vs 6%)。基于此,美国FDA批准Pembrolizumab单药可作为标准治疗失败的高TMB晚期肿瘤患者的治疗选择。但值得注意的是,该研究仅纳入了小细胞肺癌、肛门癌、唾液腺癌等10个较为罕见的瘤种,却并未纳入NSCLC、消化道肿瘤等,指导临床应用还需慎重;而且近年来TMB在泛瘤种免疫治疗中的预测价值也备受质疑。一项研究发现仅在CD8⁺T细胞与新抗原负荷呈正相关的瘤种中,高TMB可预测ICIs疗效。而在上述两者无显著相关性的瘤种中则不然,相反,这部分患者中高TMB的预后更差^[21]。此外,不同瘤种间TMB最佳Cut-off值差异较大,选择单一值指导泛瘤种治疗可能不是最佳方法^[19]。因此,区分瘤种以评估TMB的预测价值是必要的。

另外,许多研究也探索了血液TMB(blood TMB, bTMB)预测ICIs治疗疗效的价值。一项临床研究首次前瞻性验证了bTMB可预测NSCLC免疫治疗的临床结局^[22]。然而,也有研究发现bTMB越高,无进展生存期和总生存期(overall survival, OS)反而越短^[23]。提示可能存在混杂因素影响了bTMB的预测能力。有项研究即指出等位基因频率(allelic frequency, AF)对bTMB有影响,高AF bTMB与循环肿瘤DNA的数量密切相关,而低AF bTMB则不然。经调整AF后的低AF且bTMB-H与预后显著改善相关^[24]。优化bTMB是预测免疫治疗结局的一个潜在方向。

肿瘤新抗原是肿瘤细胞产生的突变肽段被主要组织相容性复合体I呈递到细胞表面而形成的新的抗原,识别这种肿瘤特异性抗原是激活免疫应答的关键因素^[25]。新抗原负荷,即T细胞实际靶向

的突变数量,与免疫治疗结局直接相关。有研究指出,新抗原负荷高的肺腺癌患者接受ICIs治疗表现出更长的OS^[26]。理论上讲,TMB越高新抗原产生则越多,更有可能诱导有效的抗肿瘤免疫应答。但国内一项针对NSCLC的研究发现,约50%的致癌突变没有产生新抗原,这意味着新抗原负荷一定程度上比TMB能够更精准地预测免疫治疗结局^[27]。

1.4 免疫细胞亚群

肿瘤中存在免疫细胞浸润是免疫治疗起效的关键前提。效应T细胞是识别肿瘤新抗原的主力军,T细胞浸润与免疫治疗结局关系密切^[28]。而T细胞受体作为T细胞识别肿瘤抗原肽的结构基础,其多样性在抗肿瘤免疫中至关重要。研究指出,ICIs治疗有效的患者在基线时表现出更高的T细胞受体多样性^[29]。也有研究发现T细胞并非唯一杀伤肿瘤的免疫细胞,B细胞浸润与患者预后及对免疫治疗的疗效呈正相关^[30]。相反,调节性T细胞可通过分泌免疫抑制性细胞因子等多种机制阻碍抗肿瘤免疫反应。Oweida等^[31]发现应用抗PD-L1抗体治疗的小鼠模型中,调节性T细胞的聚集可以促进免疫治疗耐药。髓源性抑制细胞同样作为一类负性免疫细胞,一方面可直接诱导T细胞耗竭,另一方面也可以分泌如IL-10之类的免疫抑制细胞因子诱导调节性T细胞等负性免疫细胞扩增,塑造抑制性免疫微环境,加剧免疫治疗耐药^[32]。肿瘤微环境是由众多细胞类型和分子构成的复杂结构,多维度评估免疫细胞亚群的浸润分布特征可更全面地反映免疫治疗结局。一项研究通过分析14种免疫生物标志物表达特征,发现肿瘤不同区域中浸润的免疫细胞分布不同。进一步分析发现肿瘤浸润免疫细胞对患者预后的影响不仅取决于其数量,与肿瘤细胞的空间距离也密切相关^[33]。

1.5 细胞因子

在肿瘤抗原提呈、T细胞活化、浸润至肿瘤局部、杀伤肿瘤等抗肿瘤免疫循环中的每一步中都需要细胞因子的参与^[34]。细胞因子水平应该能反映免疫治疗的效果。一项研究在接受抗PD-1/PD-L1治疗的NSCLC队列中,识别出14种特征性细胞因子构建了OS预测模型,将患者区分为高低风险组,发现高风险组患者预后显著差于低风险组^[35]。高龄或体力状况评分差的患者应用ICIs疗效不确切,而有研究指出这类患者在接受抗PD-1抗体治疗时,血清血管内皮生长因子水平可能是

负性预测标志物,有助于筛选获益人群^[36]。另外,外周血取样的便捷有助于ICIs治疗的监测。一项研究表明,在接受抗PD-1抗体治疗有效的患者中,外周血IL-8水平在最佳评效时相比于基线显著降低,并在疾病进展时显著升高。而在治疗无效的患者中,IL-8水平相比基线显著升高,提示血清IL-8水平的动态变化与免疫治疗效果密切相关^[37]。有研究揭示了IL-8主要在髓样细胞中表达,其高表达与抗原呈递能力下调相关,也可促进肿瘤内中性粒细胞浸润^[38-39]。这些均可导致ICIs治疗预后不佳。

1.6 宿主特征与血液学指标

多数标志物的检测通常要求复杂严格的实验流程,费用较为昂贵。由此很多研究意图从简单易得的临床指标中寻找潜在的预测标志物。有研究表明,接受抗PD-L1抗体治疗患者的体质量指数(body mass index, BMI)与OS存在线性关系,高BMI与OS显著改善有关^[40]。也有研究发现基线肿瘤病灶数量与ICIs治疗预后相关,病灶数量少的患者生存期显著延长^[41]。远处器官转移也可以影响ICIs治疗结局。合并肝转移或骨转移的患者接受ICIs治疗预后不良^[42]。另外,体力状态较差,如东部肿瘤协作组评分为2分的患者很难从ICIs治疗中获益^[43]。

许多血液学指标也能预测ICIs疗效。中性粒细胞与淋巴细胞比值、C-反应蛋白(C-reactive protein, CRP)等指标可反映机体的炎性状态。治疗前基线低中性粒细胞与淋巴细胞比值的患者接受PD-1抑制剂治疗生存时间显著延长^[44]。CRP的动态变化可预测NSCLC患者免疫治疗结局。有研究将CRP突发反应者定义为ICIs治疗后1个月内CRP水平升高超过基线至少1倍,而在随后3个月内下降至基线水平以下,CRP反应者定义为CRP水平在3个月内下降超过30%,其余为CRP无反应者。相较于CRP无反应者,前两组更容易从ICIs治疗中获益^[45]。白蛋白水平可一定程度上反映机体的营养状况。有研究显示血清白蛋白水平低(<3.5 g/dL)的患者从ICIs治疗中获益减少^[46]。血液学化验指标简单易得,有必要在进一步的前瞻性研究中验证其预测价值。

1.7 其他预测标志物

影像组学的发展为探索肿瘤免疫治疗预测标志物提供了无创性的监测手段^[47]。一项研究基于294例接受PD-1/PD-L1抑制剂治疗的胃癌患者,

从治疗前增强CT的肿瘤图像中提取肿瘤特征数据, 其中最具预测性的特征构建影像组学评分, 低评分的患者无进展生存期显著延长^[48]。也有研究针对肝细胞癌患者磁共振检查的肿瘤图像进行特征提取以构建预测模型, 发现其与患者接受免疫治疗的预后显著相关^[49]。PET-CT目前在肿瘤治疗评估中的应用愈发普及。有研究发现, 在接受免疫治疗后1年经PET-CT评估为完全代谢反应的黑色素瘤患者, 在后续长达5年的随访中仍具有良好预后^[50]。ICIs治疗中的合并用药也会影响其疗效。有研究指出, 在ICIs治疗前1个月使用过抗生素的患者, 相比未使用过抗生素的患者OS显著缩短(2个月 vs 26个月)^[51]。另外, 合并使用质子泵抑制剂的患者同样预后不良^[52]。这可能与肠道菌群失调有关。因为研究发现肠道菌群对免疫治疗具有非常重要的影响, 特定的肠道微生物构成确实能显著延长患者的生存期。而抗生素和质子泵抑制剂均可影响肠道菌群微环境^[53-54]。循环肿瘤DNA的动态监测可以预测接受抗PD-1抗体治疗患者的预后。在转移性黑色素瘤患者中, 基线可检测到循环肿瘤DNA且治疗期间持续升高的患者预后较差^[55]。

1.8 预测标志物的联合应用

从抗肿瘤免疫循环可以看出ICIs的免疫应答影响因素繁多, 单一标志物可能很难全面评估, 而标志物的联合应用可能更有效地预测ICIs治疗结局。研究表明, PD-L1表达与TMB无显著相关性^[56]。而CheckMate-568研究显示, PD-L1表达<1%且TMB<10的患者的ORR仅为5%, 这表明联合PD-L1和TMB可筛选出难以获益的人群^[57]。此外, 随着多组学及机器学习技术的迅速发展, 其在推动肿瘤精准个体化诊疗方面发挥了关键作用。一项研究纳入77例接受ICIs治疗的晚期黑色素瘤患者, 对基线肿瘤进行全基因组、转录组、甲基化及免疫细胞浸润等检测, 发现高TMB、新抗原负荷、干扰素- γ 相关基因的表达、低PSMB8甲基化以及肿瘤微环境中T细胞含量与治疗结局相关。结合TMB与干扰素- γ 6的预测模型预测效能最高, 高TMB+高干扰素- γ 6特征的肿瘤对免疫疗法最敏感^[58]。也有研究基于外周血进行蛋白质组检测, 从92个肿瘤免疫相关蛋白中确定了3种与食管癌患者免疫治疗预后相关的标志物——IL-8、酪氨酸激酶受体TIE2和肝细胞生长因子, 利用三者建立了血管生成相关风险评分, 可以反映免疫抑制

状态, 更好地预测ICIs治疗疗效^[59]。病理组学同样也可以用于预测肿瘤免疫治疗结局。一项研究利用深度学习技术从胃癌全视野病理切片图像中提取3类病理组学特征, 涵盖单个细胞形态、细胞空间分布和整体微环境信息, 建立了病理组学特征驱动的综合预测模型, 能有效识别从免疫治疗中获益的潜在人群, 并且预测性能优于PD-L1评分^[60]。此外, 一项研究基于TMB、MSI、BMI、肿瘤分期等16项因素开发了一种机器学习模型, 在泛癌种中对于患者免疫治疗疗效和预后的预测价值远超TMB^[61]。

2 ICIs治疗下irAEs的预测标志物

ICIs虽然为肿瘤治疗带来了全新理念和突破性疗效, 但irAEs也不容忽视。不同于传统治疗的毒性反应, irAEs通常认为是免疫系统过度激活而产生的“脱靶效应”, 是阻碍ICIs应用的一大障碍^[62]。如果可以预估患者接受ICIs治疗过程中irAEs的发生发展模式, 对于患者生活质量的提高和治疗的持久性都有很好的保证。目前已有一些研究探索了针对irAEs的预测性标志物。

细胞因子被认为是一类irAEs的预测标志物。有研究表明irAE的发生IL-1 β 的基线高水平有关^[63]。也有研究发现, 接受ICIs治疗后高IL-6水平与irAEs密切相关, 如克罗恩病或银屑病样皮炎。这或许与IL-6在肿瘤相关的全身炎症反应中发挥的重要作用有关^[64]。而在小鼠模型中, 联合使用IL-6阻滞剂和ICIs不仅增强了抗肿瘤效果, 还减轻了自身免疫性脑脊髓炎症状^[65]。另外, CRP作为一项可反映人体炎症状态的指标, 也被认为与irAEs有关。一项回顾性研究发现, 接受ICIs治疗发生irAEs的患者, 其CRP水平显著升高, 且通常早于症状出现^[66]。irAEs的出现也与不同的肠道菌群组成有关。一项研究在接受PD-1抑制剂治疗的黑色素瘤患者队列中鉴定出了与irAEs相关的两种微生物特征。他们发现7种链球菌累积丰度最高的8例患者均出现了irAEs^[67]; 还有些指标是与器官特异性irAEs相关的, 比如有研究显示抗甲状腺抗体阳性的患者更容易发生甲状腺功能障碍^[68]。

但irAEs并非百害而无一利。已有研究表明irAEs与ICIs治疗预后相关, 发生irAEs的患者生存期显著延长^[69-70]。还有研究指出irAEs恢复后, 重新引入ICIs治疗的风险-回报比似乎是可以接受的^[71]。因此在irAEs的临床诊疗过程中, 既要及时

发现、合理处置，又要综合评估、全面考量 ICIs 的后续应用，力争最大程度上使患者获益。

3 ICIs 治疗下超进展的预测标志物

在目前的认知中，超进展是肿瘤在某些情况下表现出的一种异常的加速性生长现象，但迄今为止无统一标准化的定义。多数文献中将其定义为治疗失败时间 < 2 个月，或肿瘤负荷相比治疗前增加超过 50%，肿瘤增长速度增加超过 2 倍^[72]。超进展在 ICIs 治疗中的发生率为 4% ~ 29%，严重妨碍到患者后续治疗的选择及临床预后^[73]。如何预测超进展发生是目前的研究热点。有研究指出鼠双微基因 2 及鼠双微基因 4 的基因扩增和表皮生长因子受体突变的患者接受 ICIs 治疗疗效较差，肿瘤增长速度显著增加^[74]。这也是目前认可度较高的预测超进展的有效标志物。也有研究指出 CD8⁺/CD4⁺ T 细胞的表型可以预测超进展，因为肿瘤免疫微环境中 T 细胞的耗竭是触发 ICIs 治疗下肿瘤生长加速的潜在机制之一^[73]。国内一项回顾性研究发现低 BMI、贫血、非引流区淋巴结或胰腺转移以及抗 PD-1 单药治疗与超进展发生密切相关，且基于上述风险因素构建了一个可视化的列线图预测模型^[75]。另外一项研究基于血浆蛋白质组学发现血清淀粉样蛋白 A1 在超进展患者 ICIs 治疗整个过程中呈上升趋势。而且在验证队列中发现血清淀粉样蛋白 A1 在多癌种超进展患者中高表达，83.3% 的血清淀粉样蛋白 A1 高表达患者最终均发生了超进展^[76]。另外，部分常规血液学指标，如中性粒细胞计数、CRP、乳酸脱氢酶等动态变化，以及转移器官个数、年龄等患者特征也与超进展有关^[77]。当然，这些结论还需要进一步的验证。

4 结语与展望

我们分析了在抗肿瘤免疫治疗中 ICIs 相关预测标志物的研究进展，这些标志物的开发涉及肿瘤微环境中各种分子和细胞的表达、外周血及宿主特征等，并实现了从单一标志物到多因素联合预测的进阶。然而肿瘤的发生发展以及对机体免疫系统网络的影响，ICIs 的应用对肿瘤微环境和全身免疫系统的影响都极为复杂，现有的标志物研究仍无法满足临床所需。因此，一方面需要加强对如 PD-L1、TMB 等传统标志物的认识，进一步完善和优化其检测方法；另一方面也需要在现有基础上更深入理解肿瘤免疫治疗的内在机制，充

分考虑固有免疫与获得性免疫的特征与结合点，基于机器学习、人工智能等前沿技术继续探索具有科学性、创新性的预测标志物，并通过前瞻性的临床研究验证其有效性。此外，还要充分认识各类标志物的优势所在，以期建立多组学、多维度的联合预测模型，推动肿瘤免疫治疗的精准个体化发展，最大限度地提高患者生存获益。

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