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·综 述·

以肿瘤相关免疫细胞为标志物预测和评估抗PD-1/PD-L1疗效的研究进展

Research progress on tumor-associated immunocytes as markers for predicting and assessing the efficacy of anti-PD-1/PD-L1 therapy

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[摘 要] 研发生物标志物以准确预测或评估抗PD-1/PD-L1治疗的疗效具有重要意义。T细胞、B细胞、巨噬细胞、DC、中性粒细胞、NK细胞和髓源性抑制细胞等肿瘤相关免疫细胞通过多种途径影响肿瘤免疫治疗的疗效。近年来的研究发现,有些免疫细胞可以作为预测指标,在治疗前预判肿瘤患者能否对抗PD-1/PD-L1治疗产生应答;有些免疫细胞可以作为疗效评估指标,在治疗早期判断患者从长期治疗中获益的可能性。本文主要就上述肿瘤相关免疫细胞对于肿瘤免疫治疗的影响以及预测作用进行综述。

[关键词] 肿瘤;免疫治疗;免疫检查点;肿瘤相关免疫细胞;生物标志物
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以抗PD-1/PD-L1为代表的肿瘤免疫疗法给肿瘤治疗带来了重大变革。目前国内外已有多种抗PD-1/PD-L1药物应用于临床,从总体上看肿瘤患者对抗PD-1/PD-L1治疗的有效率只有20%左右[1-2],急需研发有效的生物标志物以预测抗PD-1/PD-L1治疗的疗效。目前,美国食品药品监督管理局(Food and Drug Administration,FDA)已经批准PD-L1表达、肿瘤突变负荷(tumor mutation burden,TMB)和高微卫星不稳定/错配修复缺陷(microsatellite instability-high/mismatch repair-deficient,MSI-H/dMMR)用于预测肿瘤患者的疗效[3-4]。然而,上述指标仍需进一步完善,主要原因是:PD-L1检测抗体以及检测平台缺乏统一标准,PD-L1表达的动态性和异质性等;TMB检测需要进行全外显子测序,其成本高,耗时长,适用范围窄[5-6];MSI-H/dMMR在胃肠肿瘤中多见,在黑色素瘤、非小细胞肺癌(non-small cell lung carcinoma,NSCLC)等肿瘤中相对较少[7]。以获得性免疫细胞和先天免疫细胞为标志物预测或评估抗PD-1/PD-L1治疗疗效逐渐成为肿瘤免疫治疗的研究热点之一。本文将对这一领域近年来的相关研究进展进行综述,以期为研发精准预测和评价抗PD-1/PD-L1治疗疗效的生物标志物提供参考。

1 获得性免疫细胞

1.1 肿瘤浸润T细胞(tumor infiltrating T cell, TIL)

T细胞是适应性免疫的重要组成部分,是抗PD-1/PD-L1治疗激活的主要细胞组分。TUMEH等[8]研究了46例接受派姆单抗(pembrolizumab)治疗的转移性黑色素瘤患者,在治疗后的不同时间对患者的肿瘤组织进行连续活检显示,与治疗无效的患者相比,对抗PD-1治疗产生应答的患者的肿瘤组织边缘和内部浸润的$CD8^+$ T细胞数量显著增加;肿瘤组织中$CD8^+$T细胞数量与肿瘤缩小直接相关。URYVAEV等[9]检测了接受抗PD-1抗体治疗的30例黑色素瘤患者和26例NSCLC患者的组织标本。在黑色素瘤样本中,$CD8^+$T细胞数量<1 900/mm^{2}时,患者应答率小于33.3%;$CD8^+$T数量>1 900/mm^{2}时,患者应答率为90.9%。在NSCLC标本中,$CD8^+$T细胞数量<886/mm^{2}时应答率只有16.7%;$CD8^+$T细胞数量在886~1 899/mm^{2}范围内时,应答率为60%。这些研究结果提示了以TIL为标志物评估或预测抗PD-1/PD-L1治疗疗效的可行性。

亦有研究[10]发现,TIL是一个异质群体(图1),各个亚群的分布密度以及表型存在差异,一些TIL并不能对抗PD-1/PD-L1治疗产生应答。如果仅以CD3或CD8为指标测定肿瘤组织中TIL的数量,难以精准预测患者能否从治疗中获益[11]。

1.1.1 T细胞因子-1(T cell factor-1, TCF-1)$^+$T细胞 研究[12]表明,TCF-1^+T细胞具有记忆性T细胞的特征,而且部分TCF-1^+T细胞可能成为预测抗PD-1/PD-L1治疗疗效的生物标志物,主要包括:耗竭性前体T细胞(precursor exhausted T cell,T_{pex})和记忆前体样T细胞。

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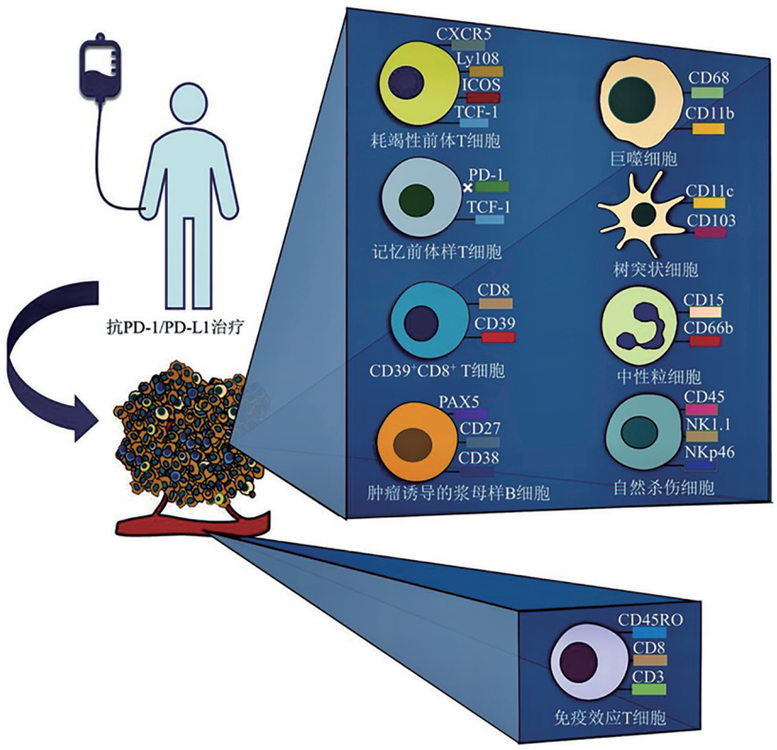

图1 多种调控抗PD-1/PD-L1治疗疗效的免疫细胞

初始T细胞在接受抗原刺激后，能够分化成效应T细胞和记忆T细胞。如果抗原持续存在，初始T细胞便会分化为耗竭性T细胞[12-13]。耗竭性T细胞高表达PD-1等负性免疫检查点分子。抗PD-1抗体可以激活耗竭性T细胞的效应状态，增加其杀伤肿瘤的活性。但是，耗竭性T细胞存在异质性，并非所有耗竭性T细胞都可以对抗PD-1治疗产生响应。TCF-1$^+$ T_{pex}可以响应抗PD-1治疗[14-15]。抗PD-1治疗一方面促进TCF-1$^+$ T_{pex}的自我更新，另一方面诱导其向具有肿瘤杀伤功能的TCF-1$^-$ T细胞分化[16]。除TCF-1外，T_{pex}的标志物还包括Ly108[16]、CXCR5[17]和ICOS[18]等，而终末分化的耗竭性T细胞表面表达TIM-3和CD244等[19-20]抑制性分子。这些标志物有助于准确检测肿瘤组织中T_{pex}的数量（图2）。MILLER等[13]以25例接受抗PD-1治疗的黑色素瘤患者接受治疗前的肿瘤标本为研究对象，评估T_{pex}在疗效预测中的价值。结果显示，T_{pex}丰度与患者的持续反应时间正相关；与T_{pex}低丰度的患者相比，T_{pex}高丰度患者的疾病无进展生存期由392 d延长至681 d。

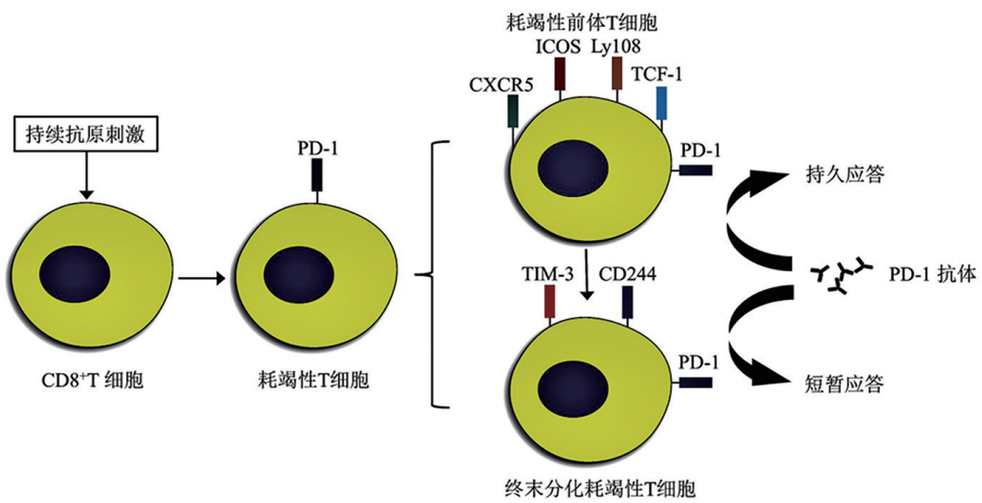

图2 耗竭性前体T细胞和终末分化耗竭性T细胞

有研究[21]显示，TCF-1$^+$记忆前体样T细胞可能成为预测抗PD-1治疗疗效的标志物。经典的观点认为抗PD-1治疗主要的靶细胞是PD-1$^+$ CD8$^+$T细胞[22]。在结肠癌移植瘤小鼠模型的研究[21]中发现，部分PD-1$^-$T细胞会对抗PD-1治疗产生响应，抗PD-1治疗诱导CD62L^{hi}Slamf7$^-$CX3CR1$^-$幼稚样T细胞向CD62L$^-$Slamf7^{hi}CX3CR1$^+$记忆前体样和CD62L$^-$Slamf7^{hi}CX3CR1$^-$效应样T细胞顺序分化。在T细胞中敲除TCF1，记忆前体样T细胞的数量和功能均会受损，抗PD-1治疗的疗效大打折扣。研究者[21]检测了36例NSCLC患者的癌组织标本，通过基因集富分析发现，记忆前体样T细胞（CD62L$^-$Slamf7^{hi}CX3CR1$^+$PD-1$^-$TCF$^+$CD8$^+$）会在预后较好的患者肿瘤组织中富集。在治疗早期，这群T细胞可能成为预判抗PD-1治疗长期疗效的指标。

1.1.2　“旁观者”T细胞　近来，以肿瘤浸润淋巴细胞数量的多少划分“热肿瘤”和“冷肿瘤”的观点[11]受到一些学者的质疑。在肿瘤组织中，并不是所有浸润T细胞都能够识别并杀伤肿瘤细胞，大部分只是“旁观者”。SCHEPER等[10]报道，在卵巢癌和结直肠癌组织中能识别肿瘤的T细胞仅占T细胞总数的10%。SIMONI等[23]报道，在肺癌和结直肠癌患者癌组织中仅有一小部分的CD8$^+$T细胞可以识别肿瘤相关抗原，大部分CD8$^+$T细胞是“旁观者”，主要识别人巨细胞病毒和EB病毒等其他抗原。具有识别肿瘤潜能的T细胞是抗PD-1/PD-L1治疗的主要靶细胞。因此，发现特异性标志物以准确指示具有肿瘤反应性T细胞具有重要意义。有研究[22,24-25]显示，患者肿瘤组织或外周血中PD-1$^+$T细胞可能是肿瘤抗原特异性的T细胞。最近也有研究发现，CD39可能成为鉴定肿瘤特异性T细胞的良好标志物。CD39为细胞表面的一种酶，可催化ATP转化为腺苷。KORTEKAAS等[26]分别从宫颈、外阴及口咽鳞状细胞癌组织中分选出CD39$^+$和CD39$^-$T细胞，体外扩增后发现对肿瘤产生特异性反应的T细胞几乎仅存在于CD39$^+$T细胞群。亦有研究者[10,23,27-28]在卵巢癌、结肠癌、皮肤癌和肺癌等多种肿瘤组织中发现，CD39$^+$T细胞是肿瘤反应性T细胞，提示该细胞群可能是预测抗PD-1/PD-L1治疗疗效的理想指标。最近的研究[29]发现，在经抗PD-1抗体治疗的NSCLC患者中，高水平CD39^{high}T细胞和髓源性抑制细胞（myeloid-derived suppressor cell，MDSC）与患者总生存期和无进展生存期下降密切相关。CD39$^+$T细胞能否成为预测患者疗效的生物标志物，仍需更多的研究加以证实。开发精准、可靠的生物学标志物用于区分“旁观者”T细胞和肿瘤抗原特异性T细胞是该领域的发展方向之一。

1.2　外周血T细胞

YOST等[28]对接受抗PD-1治疗的基底细胞癌和鳞状细胞癌患者外周血T细胞进行研究。在治疗前，患者外周血中检测到11.8%的具有肿瘤反应潜能的克隆性T细胞；抗PD-1抗体治疗后使这一数值升高至35.5%。该研究提示，外周血中存在肿瘤反应性T细胞，抗PD-1/PD-L1治疗可引起外周血T细胞的变化。通过检测特异性标志物或T细胞克隆性扩增、定性或定量分析外周血中肿瘤反应性T细胞，将可能使外周血T细胞成为预测抗PD-1/PD-L1治疗疗效的标志物。KAMPHORST等[22]检测了接受抗PD-1抗体治疗的NSCLC患者血液样本。治疗4周后，在80%治疗有效患者的外周血中出现Ki67$^+$PD-1$^+$CD8$^+$T细胞的明显增殖，而在大部分治疗无效的患者中并未观察到这种现象。该研究结果提示，在接受第一或第二周期治疗后，患者外周血中是否出现Ki67$^+$PD-1$^+$CD8$^+$T细胞可能成为疗效评估的指标。VALPIONE等[30]在黑色素瘤患者的外周血中发现，免疫效应T细胞（immune-effector T cell，T_{IE}）CD8$^+$CD45RA$^-$CD45RO^{high}T细胞可预测免疫检查点抑制剂（immune checkpoint inhibitor，ICI）的疗效。T_{IE}≥0.8%患者的总生存期相较于T_{IE}<0.8%的患者显著增加，预测准确度为85%~92%。T_{IE}检测在患者使用抗PD-1抗体3周后进行，可以根据检测结果调整后续用药方案。FAIRFAX等[31]通过转移性黑色素瘤患者外周血T细胞测序分析发现，在治疗有效的患者出现了T细胞克隆性扩增。治疗3周后出现优势克隆（单个克隆在T细胞总数中占比超过0.5%）的数量与治疗后6个月的疗效密切相关，提示通过分析外周血T细胞克隆性分布特点来评估患者从抗PD-1/PD-L1长期治疗中获益的可能性。

1.3　B细胞

在肿瘤发生发展的过程中，肿瘤组织中会形成异位淋巴器官，即三级淋巴结构（tertiary lymphoid structure，TLS）。肿瘤组织中的TLS呈现不同的成熟状态，最高级可以形成生发中心结构。TLS由多种免疫细胞和基质细胞组成，B细胞在TLS形成中发挥重要作用[32]。最近的研究发现，肿瘤浸润B细胞和TLS对于抗PD-1/PD-L1治疗疗效产生重要影响。HOLLERN等[33]通过三阴性乳腺癌的小鼠模型发现，肿瘤浸润B细胞通过分泌抗体和激活T细胞提高ICI的疗效。2020年1月*Nature*杂志同时发表3篇文章，报道了B细胞以及TLS在预测抗PD-1/PD-L1治疗疗效中的重要作用。HELMINK等[34]通过对黑色素瘤和肾细胞癌患者治疗前以及治疗中肿瘤组织样本进行RNA测序分析，发现MZB1、IGLL等B细胞相关基因在应答患者组织中显著富集。免疫组化染色结果显示，应答患者肿瘤组织中CD20$^+$B细胞和TLS的密

度都高于非应答者，B细胞和TLS数量与患者良好预后正相关。CABRITA等[35]通过分析转移性黑色素瘤患者肿瘤组织中免疫细胞的组成也得到了相似的结论。PETITPREZ等[36]对软组织肉瘤患者的研究发现，抗PD-1/PD-L1治疗应答者的治疗前肿瘤组织中会存在次级淋巴滤泡样TLS，在肿瘤组织切片中TLS的判读标准为出现T细胞、B细胞和DC共同聚集的区域，该区域的面积超过60 000 μm^2，包含>700个细胞，其中CD20$^+$B细胞至少350个。这些研究为以B细胞和TLS为标志物预测或评估抗PD-1/PD-L1治疗疗效提供了新方向。

需要指出的是，亦有研究认为B细胞在肿瘤恶性进展中发挥促进作用，例如促进肿瘤淋巴结转移[37]、肿瘤血管生成[38]，抑制抗肿瘤免疫反应等[39-40]。以B细胞为标志物准确预测抗PD-1治疗的疗效，可能还需要进一步确认具体的B细胞亚群与抗PD-1/PD-L1治疗疗效间的关系。例如GRISS等[41]报道的CD27$^+$CD38$^+$PAX5$^+$B细胞亚群的数量与抗PD-1治疗效果呈正相关。

2 先天免疫细胞

肿瘤微环境中的巨噬细胞、DC、中性粒细胞、MDSC和NK细胞等均可影响抗PD-1/PD-L1治疗的疗效[42]。这些细胞亦可能成为预测或评估抗PD-1/PD-L1治疗疗效的生物标志物。

2.1 巨噬细胞

研究者[43-45]在接受抗PD-1/PD-L1治疗的成胶质细胞瘤、肺癌等多种肿瘤患者的肿瘤组织中发现，巨噬细胞的数量与不良预后正相关。近年来，巨噬细胞影响抗PD-1/PD-L1治疗疗效的机制逐步得到揭示。(1)有研究者[46]利用亚细胞水平的体内成像技术发现，F4/80$^+$巨噬细胞吞噬抗PD-1抗体，其机制是巨噬细胞通过其表面的Fcγ受体介导了抗PD-1抗体的内吞。在结肠癌小鼠模型中阻断Fcγ受体，肿瘤重新对抗PD-1抗体治疗产生应答。(2)CD11c$^+$/CD206$^+$巨噬细胞抑制CD8$^+$T细胞在肿瘤组织中的浸润[47]。PERANZONI等[48]在卵巢癌小鼠模型中发现，清除巨噬细胞可促进CD8$^+$T细胞向肿瘤组织迁移和浸润，并且显著增强抗PD-1抗体治疗疗效。(3)CD68$^+$巨噬细胞可诱导肿瘤细胞对免疫治疗产生抗性。巨噬细胞可以通过激活肿瘤细胞的NF-κB信号通路诱导PD-L1的表达[49]。该通路诱导的PD-L1$^+$肿瘤细胞与活化T细胞释放IFN-γ诱导的PD-L1$^+$肿瘤细胞具有不同的生物学性状，可导致肿瘤细胞对抗PD-1/PD-L1治疗产生抗性。

上述研究未对特定巨噬细胞亚群(如M1或M2型)与抗PD-1/PD-L1治疗疗效的关系进行研究，通过大量样本定性或定量分析以特定巨噬细胞亚群为标志物预测抗PD-1/PD-L1治疗疗效的可行性将是该领域未来的发展方向之一。

2.2 DC

MAYOUX等[50]报道，在接受抗PD-L1抗体治疗的肾细胞癌和NSCLC患者肿瘤组织中DC丰度高的患者死亡风险较丰度低的患者分别降低了62%和46%。这提示了以DC为标志物预测抗PD-1/PD-L1治疗疗效的可行性。近来，DC在抗PD-1/PD-L1治疗发挥疗效过程中的关键作用及其机制被逐步揭示。GARRIS等[51]在小鼠结肠癌移植瘤模型中发现，清除DC导致抗PD-1抗体的疗效显著下降。抗PD-1抗体发挥疗效需要DC感知T细胞释放的IFN-γ并释放IL-12以增强T细胞的抗肿瘤活性。SALMON等[52]在黑色素瘤小鼠模型中发现，CD103$^+$DC是唯一能够将完整肿瘤抗原运送到淋巴结并活化CD8$^+$T细胞的抗原提呈细胞。CD103$^+$DC是抗PD-L1抗体发挥疗效的必要条件。特异性删除DC中的PD-L1可显著增强CD8$^+$T细胞的抗肿瘤作用[53]。此外，有研究者报道了抗PD-L1抗体发挥疗效的新机制。表达于DC表面的PD-L1和CD80可发生顺式相互作用，从而抑制了CD80与表达于T细胞表面的CD28相互作用，CD80与PD-L1是其与CD28的结合力的3倍。而且，在肿瘤相关DC中PD-L1的表达水平远高于CD80，这使得DC表达的CD80难以与T细胞表达的CD28结合并辅助T细胞活化。抗PD-L1抗体可解除PD-L1对CD80的封闭作用，促进DC对肿瘤特异性T细胞的活化[50,54-55]。

2.3 中性粒细胞

中性粒细胞在肿瘤细胞外基质重塑、血管生成以及肿瘤转移中发挥重要作用[56]。研究者[57-58]在多种肿瘤的动物模型中发现，肿瘤组织中高丰度的中性粒细胞可以显著减弱抗PD-1/PD-L1治疗的疗效。阐明中性粒细胞影响免疫治疗疗效的机制有助于提高抗PD-1/PD-L1治疗疗效。近期有研究者[59-60]报道了CXCR1或CXCR2激动剂、IL-17可以诱导中性粒细胞产生细胞外捕获网络(neutrophil extracellular trap, NET)。NET可抑制CD8$^+$T细胞对肿瘤细胞的杀伤，使肿瘤对抗PD-1/PD-L1治疗产生抗性。靶向IL-17或NET可以增强ICI的疗效。KARGL等[61]在NSCLC患者的组织中按照T细胞/中性粒细胞比值(derive neutrophil-to-lymphocyte ratio，dNLR)的最低四分位数和最高四分位数，将患者分为CD8/CD66S-low和CD8/CD66S-high两组。CD8/CD66S-low组的生存率明显低于CD8/CD66S-high组。有研究[62-63]证实，

dNLR与接受抗PD-1/PD-L1治疗的NSCLC患者的预后具有相关性，dNLR=中性粒细胞数/（白细胞数−中性粒细胞数）。dNLR>3的患者预后最差。在黑色素瘤、胰腺癌、膀胱癌和肾癌中，较高的dNLR也预示更短的生存期。

2.4　MDSC

MDSC是DC、巨噬细胞和粒细胞的前体，其本身可以通过表达精氨酸酶1、吲哚胺2,3-双加氧酶和诱导型一氧化氮合酶抑制$CD8^+$ T细胞介导的抗肿瘤免疫反应[64-65]。在结肠癌小鼠移植瘤模型中，使用组胺抑制MDSC的NADPH氧化酶，可提高抗PD-1/PD-L1治疗的疗效[66]。使用c-Rel抑制剂R96A，可降低MDSC的数量、增强抗PD-1抗体的疗效[67]。通过抑制源细胞的受体酪氨酸激酶，限制MDSC的分化和增殖，可以增加黑色素瘤患者组织中$CD8^+$ T细胞浸润，增强抗PD-1治疗效果[68]。MDSC的数量与接受抗PD-1/PD-L1治疗患者的不良预后具有相关性，通过流式细胞术对$CD14^+CD11b^+HLA\ DR^{low}$ MDSC进行检测，MDSC数量高于中位数的患者接受治疗的有效率为70%，而MDSC数量低于中位数的患者的有效率为32%[69]。

2.5　NK细胞

NK细胞是机体抵抗肿瘤的重要免疫细胞类型[70-71]。经典的观点认为抗PD-1/PD-L1治疗主要通过激活肿瘤特异性$CD8^+$ T细胞来发挥抗肿瘤效应。研究[72-73]发现，肿瘤组织中的NK细胞也可以表达PD-1。$PD\text{-}L1^+$肿瘤细胞抑制$PD\text{-}1^+$ NK细胞的功能，并诱导PD-1在NK细胞与肿瘤细胞的免疫突触处聚集，抗PD-1/PD-L1治疗可以激活NK细胞的抗肿瘤活性。亦有研究发现，NK细胞可表达PD-L1[74]，抗PD-L1治疗能够直接激活NK细胞的抗肿瘤功能[75]。而且NK细胞的数量和亚群分布与抗PD-1/PD-L1治疗的疗效具有相关性[76-77]。通过对接受抗PD-1治疗的转移性黑色素瘤患者的肿瘤组织进行分析发现，对治疗产生应答患者的肿瘤组织中NK细胞的丰度显著升高[78-79]。一项对NSCLC的前瞻性研究[77]发现，与无应答组相比，在临床受益组患者接受治疗前所取的组织样本中含有更多表型活跃的NK细胞。在另一项霍奇金淋巴瘤的研究[76]中发现，应答组患者外周血中存在大量活化的NK细胞。

3　结　语

综上所述，肿瘤相关免疫细胞可能成为预测或评估抗PD-1/PD-L1治疗疗效的理想标志物。经典的免疫评分是利用数字病理学方法对肿瘤组织中$CD3^+$和$CD8^+$淋巴细胞进行定量分析。近年来研究发现，以多种免疫细胞为参数进行综合免疫评分可以提高其评价肿瘤ICI疗法疗效的准确性[80]。深入研究各种肿瘤相关免疫细胞与抗PD-1/PD-L1治疗疗效的关系，将有助于进一步提高综合免疫评分的效能。然而，评分指标过多也会降低临床实践的可行性。目前快速发展的包括单细胞测序技术和多组学技术[81-84]，为准确检测肿瘤相关免疫细胞及细胞亚群提供了强大的技术手段。此外，无创检测将是该领域未来发展的重要方向。例如，结合患者治疗前循环肿瘤DNA（circulating tumor DNA，ctDNA）、外周血$CD8^+$ T细胞特征以及治疗早期ctDNA动态变化等参数，实现了以外周血为检测样本准确预测抗PD-1/PD-L1治疗对NSCLC患者的长期疗效[85]。相信随着相关技术的逐步完善以及抗PD-1/PD-L1治疗相关生物标志物研究的不断深入，疗效预测方法将更加简便、精准。

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