

PD-1/PD-L1抑制剂在胃癌的临床应用与耐药性挑战

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摘要

胃癌的发病率在东亚地区呈现显著地域聚集性, 是欧美国家的2~3倍。虽然根治性手术联合辅助化疗让早期患者的5年生存率提升至70%以上, 但晚期的预后仍不容乐观。近年来, 免疫检查点抑制剂的兴起, 特别是针对PD-1及其配体PD-L1, 通过阻断相关通路, 成功唤醒T细胞的抗肿瘤免疫作用, 逐步在临床中显现出治疗潜力。本文系统综述了PD-1/PD-L1抑制剂在胃癌中的表达特性、临床意义及其抑制剂的临床应用, 并探讨了免疫治疗的耐药机制、潜在生物标志物以及联合治疗策略的最新进展, 目的是为胃癌临床决策提供循证依据。

关键词

胃癌, PD-1, PD-L1, 免疫检查点抑制剂, 耐药机制, 生物标志物, 联合治疗

Clinical Applications and Resistance Challenges of PD-1/PD-L1 Inhibitors in Gastric Cancer

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Abstract

The incidence of gastric cancer exhibits significant regional clustering in East Asia, where rates are

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2 to 3 times higher than in Western countries. Although radical surgery combined with adjuvant chemotherapy has improved 5-year survival rates to over 70% in early-stage patients, outcomes for advanced-stage disease remain poor. In recent years, immune checkpoint inhibitors—particularly those targeting PD-1 and its ligand PD-L1—have demonstrated therapeutic promise by reactivating antitumor T-cell responses through pathway blockade. This review provides a comprehensive overview of PD-1/PD-L1 expression patterns in gastric cancer, their clinical significance, and the application of corresponding inhibitors. It also discusses mechanisms of resistance, emerging biomarkers, and advancements in combination therapy strategies, aiming to inform evidence-based clinical decision-making in the treatment of gastric cancer.

Keywords

Gastric Cancer, PD-1, PD-L1, Immune Checkpoint Inhibitors, Resistance Mechanisms, Biomarkers, Combination Therapy

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1. 引言

胃癌(Gastric cancer, GC)是一种胃黏膜上皮细胞恶性变异引起的肿瘤。越来越多的证据表明,幽门螺旋杆菌感染、EB病毒(Epstein-Barr virus, EBV)、肥胖等因素会显著增加胃癌的风险[1]。最新全球癌症统计显示,胃癌的发病率为每年约100万例,位列全球第五;死亡率为78万例,居全球第四位,仅次于肺癌、肝癌和结直肠癌[2]。尽管手术切除联合围手术期化疗可改善早期患者的预后,但约有70%的病例在确诊时已进展至局部晚期或转移阶段,其5年生存率不足10%[3]。传统化疗方案虽能延长总生存期(Overall survival, OS),但受限于肿瘤异质性和药物耐药性,治疗效果有限[4]。此外,晚期患者常伴体能状态下降或脏器功能不全,难以耐受高强度及长时期的化疗。

近年来,免疫检查点抑制剂通过多种途径来阻断程序性死亡受体-1 (Programmed death protein 1, PD-1)及程序性死亡配体-1 (Programmed death ligand 1, PD-L1)的相互作用,重塑肿瘤免疫微环境(Tumor immune microenvironment, TME),在晚期胃癌的治疗中展现出显著临床获益[5]。关键III期临床试验CHECKMATE-649证实[6],纳武利尤单抗(nivolumab)联合化疗可显著延长中位总生存期(Median overall survival, mOS),并为其作为一线治疗新标准提供了坚实依据。然而临床实践中仍面临显著挑战,约50%~70%的晚期肿瘤患者对免疫检查点抑制剂(Immune checkpoint inhibitors, ICIs)原发性耐药,且最初有反应的肿瘤常随着时间的推移产生适应性或获得性耐药[7]。

本研究系统总结了PD-1/PD-L1检查点抑制剂在胃癌免疫治疗中的作用机制与应用模式,并深入分析了治疗过程中出现的耐药性及副作用问题,旨在为未来联合疗法的设计与优化提供理论依据,进一步提升PD-1/PD-L1通路在胃癌治疗中的疗效。

2. PD-1/PD-L1 在胃癌中的表达及临床意义

2.1. PD-1/PD-L1 在胃癌组织及微环境中的表达特点

PD-1作为T细胞反应的关键抑制剂,主要在活化的T细胞、B细胞、和髓样细胞上表达,通过与PD-L1结合调节免疫反应[8]。在肿瘤细胞中,PD-1的显著表达可能是其逃避免疫监视的一种策略。PD-L1和PD-L2是PD-1受体的天然配体,通过向表达PD-1的免疫细胞传递抑制信号,发挥重要的免疫检查点

作用。

PD-1/PD-L1 信号通路在胃癌中的表达具有显著的异质性,其模式受 TME 和分子亚型的影响。PD-L1 的表达在胃癌患者中呈现出显著的差异性,其中肿瘤细胞的表达率为 19%~63%,肿瘤浸润淋巴细胞(Tumor-infiltrating lymphocytes, TILs)的表达率为 34%~53%,而通过综合阳性评分(Combined positive score, CPS)评估,大约 63%的患者呈现 PD-L1 的阳性表达[9]。PD-L1 表达与特定分子亚型密切相关,例如微卫星不稳定性高(Microsatellite Instability-High, MSI-H)和 EBV 胃癌中 PD-L1 表达显著上调,而 HER2 高表达或 ATM 基因低表达的亚型中,免疫浸润水平较低[10][11]。

2.2. PD-1/PD-L1 通路在胃癌免疫逃逸中的分子机制

PD-1/PD-L1 信号通路的激活是胃癌逃避免疫系统识别和清除的关键分子机制。肿瘤细胞通过上调 PD-L1 的表达水平,与 T 细胞表面的 PD-1 受体发生特异性结合。此一结合不仅抑制了 T 细胞的活化和增殖,还显著降低了其细胞毒性 T 细胞(Cytotoxic T Lymphocytes, CTLs)的功能。同时,这一交互作用还引发 T 细胞程序性死亡和功能性耗竭,从而突破免疫系统的抗肿瘤防御机制,促进肿瘤的疾进。这种免疫逃逸现象在肿瘤微环境的免疫抑制条件下尤为明显[12]。

2.2.1. PD-L1 的基因调控和表观调控机制

遗传和表观遗传等多层次调控 PD-L1 的表达。PD-L1 的基因扩增或重排可直接上调其表达,这一机制在血液肿瘤中尤为显著。在胃癌中,PD-L1 3'非翻译区(3'UTR)的突变或结构破坏也可增强 mRNA 稳定性,例如 RNA 结合蛋白 TTP (Tristetraprolin)调控缺失减少 mRNA 降解,从而促进表达[13]。DNA 甲基化和组蛋白修饰也至关重要,TET3 功能缺失导致 PD-L1 启动子区域的甲基化,抑制转录,而 KMT2 家族突变则与低表达相关[14]。转录后,miR-105-5p 和 EBV 相关的 miR-BART5-5p 抑制 PD-L1 翻译,而 lncRNA PROX1-AS1 通过 miR-877-5p/PD-L1 轴促进表达[15]。

2.2.2. 关键信号通路在 PD-L1 表达调控中的作用

多种致癌信号通路调控 PD-L1 的表达。MYC 基因通过上调 CD47 影响其表达,而 EGFR 或 ALK 的激活可通过 STAT3 及 PI3K/Akt 信号通路诱导的表达,而肿瘤抑制蛋白(Phosphatase and Tensin Homolog, PTEN)基因缺失则通过激活 PI3K/Akt/mTOR 信号通路来增强免疫抑制[16]。缺氧环境下,缺氧诱导因子-1 (HIF-1)促进 PD-L1 转录。此外,泛素特异性蛋白酶(Ubiquitin-Specific Protease 7, USP7)通过去泛素化,导致其蛋白质水平的显著提升,从而增强免疫逃逸能力,进而与患者的不良预后相关[17]。

2.2.3. 肿瘤微环境对 PD-L1 表达的调控

肿瘤微环境中的细胞因子和炎症介质也促进 PD-L1 的表达。胃癌细胞可分泌粒细胞-巨噬细胞集落刺激因子(GM-CSF)致 JAK/STAT3 信号通路上调中性粒细胞和巨噬细胞表面的 PD-L1 表达。干扰素- γ (Interferon- γ , IFN- γ)通过 JAK2/STAT3 轴促进 PD-L1 转录,抑制自噬降解,并募集髓源性抑制细胞(Myeloid-derived suppressor cells, MDSC)从而抑制 CD8+ T 细胞功能[18]。

2.2.4. 分子分型与 PD-L1 的异常表达

不同分子分型的胃癌在 PD-L1 表达上存在显著差异。EBV 阳性胃癌中,IFN- γ /IRF3/CD274 轴被激活,进而使 PD-L1 以组成型显著上调[18]。MSI-H 型胃癌因高突变负荷产生新抗原,诱导 CD8+ T 细胞浸润及 IFN- γ 释放,激活适应性免疫逃逸[19]。

2.2.5. 免疫治疗的联合应用影响 PD-L1 的表达

化疗和靶向治疗影响 PD-L1 表达及免疫治疗效果。5-氟尿嘧啶(5-Fluorouracil, 5-FU)诱导 PD-L1 上调,

但与 PD-1 抑制剂联合可增强抗肿瘤效应[20]。雷帕霉素通过抑制 Gli 信号阻断 PD-L1 转录, 提示 mTOR 抑制剂可改善免疫治疗耐受性[21]。

3. PD-1/PD-L1 抑制剂在胃癌中的临床应用

3.1. GC 中的 PD-1/PD-L1 抑制剂单药治疗

作为一种免疫检查点抑制的治疗手段, PD-1/PD-L1 抑制剂在胃癌治疗中已经展示出一定的临床效益, 尤其适用于多线治疗失败的晚期或复发性患者。代表性药物包括纳武利尤单抗(Nivolumab)和帕博利珠单抗(Pembrolizumab), 多项临床试验验证了其疗效。其中帕博利珠单抗和纳武利尤单抗已在多项关键 III 期临床试验中展示出改善生存和客观缓解率的潜力。例如, KEYNOTE-061 研究表明, 对于 CPS ≥ 1 的患者, 帕博利珠单抗单药治疗的 mOS 达 9.1 个月[22]。ATTRACTION-2 研究了纳武利尤单抗与安慰剂三线治疗晚期胃癌疗效, 纳武利尤单抗治疗延长了患者的 mOS (5.26 个月比 4.14 个月)、mPFS (1.61 个月比 1.45 个月)和提高了 ORR 至 11.2% [23]。

3.2. GC 中的 PD-1/PD-L1 抑制剂联合治疗

考虑到许多患者的 PD-L1 阴性状态和单药免疫治疗的局限性[24], 目前的研究越来越多地聚焦于探索与其他治疗手段的联合应用。现有研究表明, PD-1/PD-L1 抑制剂与化疗、放疗、靶向药物和其他 ICI 联合使用可增强抗肿瘤效果。

3.2.1. PD-1/PD-L1 抑制剂联合手术治疗

在局部晚期胃癌中, PD-1/PD-L1 抑制剂与手术结合显著改善预后。术前免疫治疗联合化疗可提高病理反应率, 并优化淋巴结清扫效果, 及减少手术并发症[25][26]。术后辅助免疫治疗通过清除微小残留病灶降低复发风险, 初步研究显示其耐受性良好并具潜在生存获益[27]。尽管围手术期综合策略在胃癌个体化治疗中优势明显, 但不可忽略术前样本获取有限, 其预后评估仍存在局限[28]。

3.2.2. PD-1/PD-L1 抑制剂联合化学治疗

PD-1/PD-L1 抑制剂与化疗联合表现出显著协同效应。化疗通过诱导免疫原性细胞死亡(ICD)、释放损伤相关分子模式(DAMP)及重塑肿瘤微环境(TME), 增强肿瘤免疫原性和 T 细胞活化, 同时缓解免疫抑制状态[29]。临床试验进一步验证其疗效。例如: NEOSUMMIT-01 研究表明, 围手术期使用特瑞普利单抗(toripalimab)联合替吉奥 + 奥沙利铂(SOX)或卡培他滨 + 奥沙利铂(XELOX)治疗的局部晚期胃癌患者中, 病理完全缓解高达 44.4%, 显著高于单纯化疗组的 20.4% [26]。Tang 等人的研究显示, PD-1 抑制剂联合阿帕替尼(apatinib)及 SOX 新辅助化学治疗在局部晚期胃癌患者中获得 71.5%的客观缓解率(ORR)及 94.5%的疾病控制率(DCR), 其中 R0 切除率高达 96.1%, 且病理完全缓解率(pCR)为 21.6% [30]。值得注意的是, RATIONALE-305 研究是一项涵盖全球多中心的重要研究, 其结果表明卡瑞利珠单抗联合化疗对晚期胃癌患者具有显著的临床益处, 中位总生存期(OS)可达 15 个月, 其中近三分之一的患者实现了持续 2 年以上的持久反应[31]。这些数据凸显联合化疗在提升反应率和手术可行性方面的优势。然而, 化疗的毒性和患者耐受性问题仍不可忽视。

3.2.3. PD-1/PD-L1 抑制剂联合放疗

放疗通过释放肿瘤抗原、上调 PD-L1 表达及减少 TME 中免疫抑制细胞, 与 PD-1/PD-L1 抑制剂协同增强抗肿瘤免疫反应[32]。SHARED 研究显示, 信迪利单抗联合同步放化疗在局部晚期胃癌中的病理完全缓解率高于单纯放化疗[33]。正在进行的 RACING III 期试验将进一步评估联合放化疗加 PD-1 抑制剂

的长期获益[34]。

3.2.4. PD-1/PD-L1 抑制剂联合靶向治疗

在晚期胃癌(GC)的治疗中, PD-1/PD-L1 抑制剂与靶向药物(如抗 VEGF 和 HER2 靶向药物)的联合应用已成为提升疗效的重要策略。抗 VEGF 药物, 如贝伐珠单抗(bevacizumab)和雷莫芦单抗(ramucirumab), 能通过抑制肿瘤血管生成改善肿瘤微环境(TME), 从而显著增强免疫效应细胞的浸润, 并与 PD-1 抑制剂协同作用[35]。KEYNOTE-811 研究评估了帕博利珠单抗联合曲妥珠单抗和化疗在 HER2 阳性晚期胃癌中的一线治疗方案的效果, 结果显示 mOS 达 20 个月, mPFS 为 10 个月, ORR 显著提高至 74.4%, 较单独化疗组有呈现显著改善[36]。但该方案在非 HER2 阳性患者中的适用性和耐药问题仍需进一步验证。针对 HER2 过表达的胃癌患者, HER2 靶向药物如曲妥珠单抗(trastuzumab)和曲妥珠单抗德鲁特康(Trastuzumab deruxtecan, T-DXd), 与 PD-1 抑制剂联合可通过增强抗肿瘤免疫反应和直接细胞毒性双重机制发挥作用[37]。作为 HER-2 阳性胃癌的一线治疗, 帕博利珠单抗联合曲妥珠单抗联合化疗的 ORR 为 74.4%, 与对照组相比增加了 22.7%, 完全缓解率为 11%, 显著优于对照组的 3% [38]。这些联合策略旨在克服单一疗法的局限性, 如 PD-1 抑制剂单药治疗的有效率通常低于 20%~30%。通过这种方式, 为 HER2 阳性或阴性的晚期胃癌患者提供更个性化的治疗选择。

3.2.5. PD-1/PD-L1 抑制剂联合其他 ICIs

除 PD-1 外, 细胞毒性 T 淋巴细胞抗原 4 (Cytotoxic T-Lymphocyte Antigen 4, CTLA-4)和淋巴细胞活化基因 3 (Lymphocyte-Activation Gene 3, LAG-3)等免疫抑制分子同样受到广泛关注, 并已在临床实践中得到应用。CTLA-4 抑制剂则通过抑制 CTLA-4 与 B7 分子的结合, 主要增强 T 细胞在早期活化和增殖阶段的功能[39]。由于 PD-1 主要作用于效应 T 细胞阶段, 而 CTLA-4 则在 T 细胞活化初期发挥抑制作用, 因此联合阻断这两种检查点能够更全面地解除免疫抑制, 显著增强抗肿瘤免疫反应。例如, CheckMate-032 试验评估了 Nivolumab 联合伊匹木单抗(ipilimumab)在晚期胃癌患者中的疗效, 结果显示联合治疗组的客观缓解率(ORR)达 24%, 中位无进展生存期(mPFS)为 1.4 个月, 中位总生存期(mOS)则达到 6.9 个月[40]。另一项研究表明, pembrolizumab 联合替西木单抗(tremelimumab)在晚期胃癌患者中亦展现出一定疗效, 但同时伴一定概率的不良反应[41]。这些研究结果提示, 联合治疗在提高疗效方面具有潜力, 尤其对部分难治性胃癌患者。然而, 挑战依然存在, 首要问题是联合治疗显著增加了免疫相关不良事件(irAEs)的发生率, 如皮疹、腹泻和肝炎, 且严重 irAEs 发生率可超过 30% [42]。未来研究需致力于优化治疗方案, 并探索可预测疗效及安全性的生物标志物, 以提高临床获益。

4. PD-1/PD-L1 抑制剂耐药的关键机制

4.1. 肿瘤细胞内在机制相关耐药性

各种原因引起肿瘤细胞表面缺乏 PD-L1 表达时, 阻断 T 细胞的抗肿瘤作用, 导致治疗效果显著下降[43]。如在微卫星不稳定性高的胃癌中, JAK1 的移码突变或功能丧失会导致 PD-L1 表达显著降低。TCGA 数据库显示, 15%的 MSI-H 胃癌患者存在 JAK1 功能丧失, 导致 IFN- γ 诱导的 PD-L1 表达减少, 引发对 PD-1 抗体的原发性耐药[44]。在部分转移性结直肠癌患者中, K162fs 和 L88S 基因突变通过无义介导的 RNA 衰变或蛋白质降解机制, 使 PD-L1 表达缺失, 进而引起对 PD-L1 抗体治疗的耐药[45]。信号通路异常同样可以干扰 PD-L1 的正常表达。例如, JAK1/2 功能丧失通过抑制 PD-L1 的转录, 使肿瘤细胞无法响应 PD-1/PD-L1 抑制剂[46]。研究发现, 在非小细胞肺癌中, KRAS 突变通过增强 ERK 信号诱导 PD-L1 表达, 导致对 PD-1 阻断的初始抵抗[47]。这些证据表明, PD-L1 表达缺失以及信号通路异常通过削弱免

疫检查点抑制剂的作用靶点, 直接导致胃癌中的耐药性。

4.2. T 细胞功能障碍相关耐药性

在抗肿瘤免疫应答过程中, T 细胞需依次经历抗原识别、活化、克隆增殖与功能特化, 并通过趋化迁移与肿瘤浸润实现免疫清除。然而, 胃肿瘤细胞通过多种途径破坏抗原呈递系统, 从而导致 T 细胞功能障碍。肿瘤细胞中的 B2M 基因突变或 HLA-I 表达下调会削弱肿瘤抗原的呈递, 从而阻碍 T 细胞对抗原的识别, 进一步影响 CD8⁺ T 细胞的激活[48]。PD-1 阻断虽可短暂逆转 T 细胞耗竭, 但往往诱导 T 细胞免疫球蛋白黏蛋白分子-3 (T-cell Immunoglobulin and Mucin-domain containing-3, TIM-3)等替代性检查点代偿性上调, 进而抑制细胞毒性 T 细胞(CTL)和 Th1 细胞的功能[49]。肿瘤微环境中乳酸水平的升高及调节性 T 细胞(Tregs)的增殖也会加剧 T 细胞耗竭, 使其难以有效杀伤肿瘤细胞[50]。研究结果表明, CD38 的过表达通过调控腺苷受体通路, 显著抑制了 T 细胞的增殖能力和细胞因子的分泌过程, 这一机制已成为肿瘤获得性耐药的重要驱动因素之一[51]。T 细胞对肿瘤组织的有效浸润, 是触发和维持抗肿瘤免疫反应的关键环节[52]。在胃癌等“免疫冷”肿瘤中, 由于特异性基因突变和多条信号通路的异常, 呈现出 T 细胞浸润不足的特征[53]。WNT/ β -catenin 信号通路的异常激活也减少了 T 细胞浸润, 并通过干扰树突状细胞(DC)的募集, 进一步阻碍抗肿瘤免疫反应的启动和维持[54]。

4.3. 免疫检查点相关耐药性

PD-1/PD-L1 抑制剂在肿瘤治疗中的耐药性也有部分源于肿瘤微环境中其他免疫检查点的存在, 如 CTLA-4、TIM-3 和 LAG-3, 这些检查点在调节 T 细胞功能中起重要作用。CTLA-4 作为一种抑制性受体, 阻断 T 细胞的共刺激通路, 从而抑制其活化, 导致 T 细胞活化阈值升高, 与不良预后密切相关[55]。研究显示:胃癌组织中 CTLA-4⁺ Tregs 浸润水平与患者生存期成负相关($P < 0.01$), 而阻断 CTLA-4 可加强树突状细胞的免疫激活能力, 为联合治疗提供机制支撑[56]。在 PD-1 阻断微环境下, TIM-3 表达呈现补偿性上调, 其通过与磷脂酰丝氨酸或半乳糖凝集素-9 交联, 抑制 IFN- γ 与 TNF- α 产生, 并诱导 CD8⁺ TILs 凋亡[57]。Klapholz 等人发现, MSS 型胃肠肿瘤中 TIM-3 及 PD-1 双阳性 TILs 比例超过 30% 的患者, 对 PD-1 抑制剂无应答率提高 4.2 倍[58]。LAG-3 则通过调节效应 T 细胞(Teff)的功能, 增强调节性 T 细胞的作用, 维持免疫耐受, 在胃癌患者中其高表达与肿瘤进展密切相关[59]。

4.4. 肿瘤微环境(TME)相关耐药性

胃癌 TME 中免疫抑制细胞的增加导致免疫细胞功能障碍和免疫抑制细胞扩增, 从而形成免疫抑制环境[60]。调节性 T 细胞(Tregs)、髓源性抑制细胞(MDSCs)和肿瘤相关巨噬细胞(Tumor-associated macrophages, TAMs)通过多种机制削弱抗肿瘤免疫反应。Tregs 可通过分泌 IL-10 和 TGF- β 等抑制性细胞因子, 耗竭效应 T 细胞的 IL-2, 或通过细胞接触直接抑制 T 细胞活性, 从而构建免疫抑制性微环境[61]。M2 型 TAMs 通过分泌 IL-10 和募集 Tregs 加剧免疫抑制, 并在 TME 中形成正反馈循环[62]。

细胞外基质(Extracellular Matrix, ECM)的化学特性在对 PD-1/PD-L1 抑制剂耐药性的形成具有重要影响。TME 中硬化的 ECM 通过阻碍免疫细胞和药物的渗透, 降低了抗肿瘤免疫反应和药物递送效率[63]。而癌细胞和癌症相关成纤维细胞(Cancer-Associated Fibroblasts, CAFs)分泌的 TGF- β 既促进 ECM 硬化, 又诱导 CAFs 形成, 进一步加剧免疫抑制环境[64]。ECM 重塑还与新生血管的异常形成相关, 由 M2 型 TAMs 分泌的血管内皮生长因子(Vascular Endothelial Growth Factor, VEGF)等因子驱动, 导致药物分布不均和肿瘤缺氧, 肿瘤缺氧状态触发 HIF-1 的表达, 调节 MDSCs 的功能, 并促进外泌体中 PD-L1 的释放, 从而加强免疫逃逸[65]。

4.5. 代谢介导的耐药性

肿瘤细胞的代谢重编程与 PD-1/PD-L1 抑制剂的耐药密切相关, 主要表现为葡萄糖、脂质与氨基酸代谢的协同异常[66]。肿瘤细胞微环境中乳酸浓度升高, 直接抑制细胞毒性 T 淋巴细胞(CTL)分泌 IFN- γ , 导致 PD-L1 表达下降[67]。在胃癌中这一过程被进一步放大, 如己糖激酶-2 (HK2)过表达通过 NF- κ B 通路诱导 PD-L1 转录激活, 而靶向 HK2 可使 PD-1 单药治疗的小鼠模型肿瘤体积缩减 78% [68]。

胃癌细胞通过 SCD1 介导的脂肪酸去饱和化增强膜脂筏形成, 导致 CD8+ T 细胞免疫突触结构完整性破坏, 进而降低 TCR 信号转导效率[69]。肿瘤细胞通过 ASCT2 转运体摄取微环境中 80%以上的谷氨酰胺, 导致 CTL 线粒体氧化磷酸化受阻, ATP 产量下降 55%。在胃癌中, 谷氨酰胺缺乏激活 Ca²⁺/NF- κ B 信号轴, 促使 PD-L1 表达上调并抑制 T 细胞颗粒酶 B 释放[70]。

4.6. 表观遗传学介导的耐药性

肿瘤细胞的表观遗传改变通过重塑肿瘤微环境和调控免疫应答导致治疗抵抗。相关研究显示: IL-1 β 通过烟酰胺核苷酸转氢酶(Nicotinamide Nucleotide Transhydrogenase, NNT)的乙酰化修饰, 干扰铁硫簇的稳定性, 最终导致胃癌对 ICI 的原发耐药。阻断 IL-1 β 信号可恢复 T 细胞功能, 并增强抗 PD-1 疗法的疗效, 提示靶向 NNT 乙酰化可能是克服耐药的新策略[71]。组蛋白修饰的异常通过调节 TME 的免疫抑制状态参与其中。例如, 组蛋白脱乙酰酶 8 (HDAC8)的过表达已被证实促进肝细胞癌的 ICI 耐药, 而类似机制可能在胃癌中通过表观遗传重塑影响免疫细胞浸润[72]。

DNA 甲基化在表观遗传调控中发挥着重要的作用, 直接影响 TME 与 ICI 疗效。DNA 甲基转移酶 1 (DNA-methyltransferase 1, DNMT1)作为维持 DNA 甲基化的核心酶, 其活性异常可导致 PD-L1 基因的低甲基化, 从而上调肿瘤细胞表面 PD-L1 表达, 形成适应性免疫逃逸[73]。研究发现, 使用表观遗传药物 5-氮杂胞苷(5-AZA)可逆转趋化因子 CXCL9 和 CXCL10 启动子的甲基化, 恢复其在肝细胞癌(HCC)中的表达, 从而增强 T 细胞浸润并降低 ICI 耐药风险[74]。

5. PD-L1/PD-1 抑制剂在胃癌的潜在疗效生物标志物

PD-L1 免疫组化是目前用于免疫治疗疗效预测的生物标志物之一, 其中 Dako22C3 和 Dako28-8 抗体是最常用于临床的检测方法。Dako28-8 抗体主要采用肿瘤比例评分(TPS)进行评估, 而 Dako22C3 抗体主要采用 CPS 评分进行评估, 与 TPS 不同, CPS 同时量化了肿瘤细胞及浸润免疫细胞的 PD-L1 表达, 从而更全面地反映了肿瘤微环境的免疫抑制状态。在临床实践中通常采用 CPS ≥ 1 、 ≥ 5 或 ≥ 10 等阈值来筛选潜在获益人群[75]。例如, KEYNOTE-062 试验结果, 在 CPS 评分 ≥ 10 的患者中, 帕博利珠单抗单药治疗使 OS 显著延长(17.4 个月 vs 10.6 个月), 证实了高 PD-L1 表达的预测价值[76]。但是 PD-L1 临床应用仍面临显著挑战。如同一患者原发灶与转移灶间, 甚至同一标本不同区域的 PD-L1 表达均可能存在显著差异, 使得单次活检样本难以准确反映整体免疫特征[77]。不同检测抗体(如 22C3 vs 28-8)和评分系统(CPS vs TPS)之间缺乏统一标准, 增加了判断的主观性与可重复性问题。PD-L1 表达具有动态变化特性, 可能受治疗影响而上下波动, 其阳性状态并非恒定。这些问题限制了 PD-L1 作为独立预测指标的可靠性。更加值得注意的是部分 PD-L1 阴性患者在临床试验中仍对免疫治疗产生缓解反应, 提示其阴性预测价值有限, 不能作为排除治疗资格的唯一标准。

微卫星不稳定性高(MSI-H)主要是在 DNA 复制过程中引发微卫星序列高频率插入/缺失突变。KEYNOTE 系列研究的汇总分析显示, 接受帕博利珠单抗治疗的 MSI-H 胃癌患者 ORR 达到 57%, 显著高于 MSS 型患者的 9%~15% [78]。但在微卫星稳定的患者中亦存在一定比例的免疫应答者, 说明 MSI-H

的阴性预测价值仍不绝对。

肿瘤突变负荷是肿瘤基因组中每百万碱基对的非同义突变数, 其中高 TMB 提示肿瘤可能产生更多新抗原, 从而激活抗肿瘤免疫应答。KEYNOTE-158 试验的突破性发现显示, 在泛癌种 TMB-H 患者中, 帕博利珠单抗治疗的 ORR 高达 29% [79]。但在胃癌中, TMB 中位数显著低于黑色素瘤等免疫治疗敏感瘤种, 且部分低 TMB 患者亦能产生应答, TMB 的阴性预测价值尚存不确定性, 需与肿瘤免疫浸润情况共同评估[80]。

高密度肿瘤浸润淋巴细胞(TILs)通常说明有较为活跃的抗肿瘤效应, 如 CD8+细胞毒性 T 细胞通过识别肿瘤抗原释放颗粒酶和穿孔素介导肿瘤杀伤。例如, 一项针对胃癌免疫治疗的前瞻性研究显示, TILs 密度 $\geq 100/\text{mm}^2$ 的患者接受 PD-1 抑制剂治疗时, 其 ORR 高达 52.3%, 显著高于 TILs 低密度组的 15.7% [81]。但是 TILs 密度较低并不完全等同于免疫治疗无效, 部分低密度患者亦显示一定程度的治疗反应, 提示其阴性筛选能力有限。

微生物多样性与稳定性的降低会削弱肠粘膜局部免疫力, 并通过免疫细胞激活触发全身免疫反应。幽门螺杆菌的存在与胃癌发生密切相关, 并在调控免疫系统及改变免疫微环境方面发挥作用, 从而可能影响免疫治疗效果。相关研究显示, 乳酸杆菌相对丰度超过 3% 的患者中位 PFS 达 9.2 个月, 显著高于低丰度组的 4.1 个月($p = 0.006$) [82]。微生态组成因个体差异大而具有不确定性, 其负面预测能力仍待进一步明确。

EBV 相关胃癌(EBVaGC)作为独特的分子亚型, 对免疫治疗显示出超常敏感性。III 期临床试验数据显示, EBVaGC 患者接受帕博利珠单抗一线治疗的 ORR 高达 100% [83]。然而, 一项前瞻性临床研究, 6 例接受卡瑞利珠单抗治疗的 EBV 阳性 mGC 患者, 均未达到客观缓解, 这让人怀疑 EBV 阳性是否是 mGC 免疫治疗反应的可靠预测指标[84]。当前证据存在明显不一致, 提示 EBV 状态虽具潜在预测价值, 但其阴性表达并不能完全排除治疗反应, 仍需更大样本验证。

液体活检技术凭借其无创、动态监测优势, 已成为预测胃癌 PD-1/PD-L1 抑制剂疗效的重要研究方向。循环肿瘤细胞(Circulating tumor cells, CTC)、循环肿瘤 DNA (Circulating tumor DNA, ctDNA)和细胞外囊泡(Extracellular vesicles, EVs)为主要关注的生物标志物。研究显示, ctDNA 丰度降低与肿瘤退缩呈正相关, 且基因谱分析揭示相关通路变异可预测疗效差异[85]。基线 CTC 携带 PD-L1 高表达提示更优应答, 治疗后 PD-L1 + CTC 丰度升高往往预示耐药进展[86]。在 EV 生物标志物的开发方面, 基于 PD-L1、PD-L2 和 CD3 表达构建的 EV 评分模型, 已将免疫治疗的客观缓解率提升至 42.9%, 且与中位无进展生存期的延长显著相关[87]。

6. 结论

PD-1/PD-L1 抑制剂在胃癌治疗中展现出显著进展, 主要通过联合化疗或靶向的方案提高了晚期患者的客观缓解率与生存期。但是仍面临重重挑战, 部分患者的免疫系统难以被有效激活, 或深陷于肿瘤微环境的强抑制状态, 导致治疗反应迟钝甚至完全无效。与此同时, 免疫检查点抑制剂也可能唤醒系统性的免疫反应, 引发多器官毒性, 治疗风险陡然增加。在此背景下, 现有的 CPS 评分和 MSI-H/dMMR 等生物标志物在不同人群中表现出明显的预测效能差异, 难以满足精准筛选与广泛适用的需求。为走出这一困境, 我们应推动基于肿瘤免疫表型和微环境特征的分型策略, 明确肿瘤的免疫状态, 进而制定差异化的治疗组合方案。并发展基于多组学特征的不良反应预测模型, 以实现毒性事件的早期预警与分层管理, 从而提高治疗安全性。我们更应该突破单一指标的局限, 构建多维数据的复合预测模型, 并结合人工智能算法优化。在适应性临床试验的支持下, 疗效与毒性的实时反馈将直接反哺治疗决策, 使每一步都更贴近患者真实反应。

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