Advances in Clinical Medicine 临床医学进展, 2023, 13(10), 16766-16771
Published Online October 2023 in Hans. https://www.hanspub.org/journal/acm
https://doi.org/10.12677/acm.2023.13102347

Hans汉斯

PD-1/PD-L1信号通路在食管鳞状细胞癌中的研究进展

图荪阿依·吾麦尔，苏晓梅，马晓梅*

新疆医科大学第三临床医学院(附属肿瘤医院)病理科，新疆 乌鲁木齐

收稿日期：2023年9月25日；录用日期：2023年10月19日；发布日期：2023年10月24日

摘　要

程序性细胞死亡-1 (PD-1)和程序性死亡配体1 (PD-L1)是维持免疫稳态的重要蛋白，在生理情况下，PD-1/PD-L1信号通路介导且参与外周自身耐受性的维持和自身免疫性疾病的预防，在肿瘤微环境(TME)中，肿瘤细胞可以通过在细胞表面表达PD-L1并与PD-1受体阳性的免疫效应细胞结合，使PD-L1表达水平向上调节，致肿瘤细胞能够躲避被免疫识别与攻击。PD-1/PD-L1信号通路抑制剂可以特异性阻断PD-1与PD-L1之间结合，激活T细胞活性，对肿瘤细胞产生杀伤力。本文的目的是阐述PD-1/PD-L1信号通路在食管鳞状细胞癌中的研究成果及临床意义，回顾现有的临床证据，为食管鳞状细胞癌的治疗提供最新知识。

关键词

食管鳞状细胞癌，免疫治疗，PD-1，PD-L1

Research Progress of PD-1/PD-L1 Signaling Pathway in Esophageal Squamous Cell Carcinoma

Tusunayi·Wumaier, Xiaomei Su, Xiaomei Ma*

Department of Pathology, The Third Clinical Medical College (Affiliated Cancer Hospital) of Xinjiang Medical University, Urumqi Xinjiang

Received: Sep. 25th, 2023; accepted: Oct. 19th, 2023; published: Oct. 24th, 2023

Abstract

Programmed cell death-1 (PD-1) and programmed death ligand 1 (PD-L1) are important proteins

*通讯作者。

文章引用: 图荪阿依·吾麦尔, 苏晓梅, 马晓梅. PD-1/PD-L1 信号通路在食管鳞状细胞癌中的研究进展[J]. 临床医学进展, 2023, 13(10): 16766-16771. DOI: 10.12677/acm.2023.13102347

in the maintenance of immune homeostasis. Under physiological conditions, PD-1/PD-L1 signaling pathway mediates and participates in the maintenance of peripheral autotolerance and the prevention of autoimmune diseases. Tumor cells can express PD-L1 on the cell surface and bind to PD-1 receptor-positive immune effector cells, so that the expression level of PD-L1 can be adjusted upward, so that tumor cells can avoid immune recognition and attack. PD-1/PD-L1 signaling pathway inhibitors can specifically block the binding between PD-1 and PD-L1, activate T cell activity, and cause damage to tumor cells. The purpose of this paper is to expound the research results and clinical significance of PD-1/PD-L1 signaling pathway in esophageal squamous cell carcinoma, and review the existing clinical evidence, to provide the latest knowledge in the treatment of esophageal squamous cell carcinoma.

Keywords

Esophageal Squamous Cell Carcinoma, Immunotherapy, PD-1, PD-L1

1. 引言

食管癌是世界第六大癌症相关死亡的主要原因之一[1]，食管鳞状细胞癌(Esophageal squamous cell carcinoma, ESCC)在亚洲是最常见的类型。中国 ESCC 的 5 年总生存率为 15%~25% [2]，预后差，这是由于早期阶段未发现明显症状，导致众多患者在出现症状时已处于晚期或终末期以及 ESCC 具有较高的复发和转移倾向有关[3]。ESCC 的标准治疗方法包括手术、放疗、化疗等，最近几年，随着对肿瘤免疫调节机制的认识增加，许多免疫治疗药物正式在临床上应用[4] [5]。

程序性细胞凋亡-1 (Programmed cell dead-1, PD-1)和程序性凋亡配体 1 (Programmed cell dead-ligand-1, PD-L1)是免疫稳态维持的重要蛋白，PD-1/PD-L1 信号通路抑制免疫细胞的过度活化，预防自身免疫性疾病[6]。PD-1/PD-L1 信号通路已被发现在多种肿瘤中表达，并且与患者的预后密切相关。许多临床试验表明，PD-1/PD-L1 信号阻断剂在包括 ESCC 在内的多种恶性肿瘤患者中显示出显著的抗肿瘤疗效[7] [8] [9] [10]，为肿瘤免疫治疗带来了新的时代，也为 ESCC 的治疗提供了新的治疗策略。然而，只有 20%~40% 的患者将受益于肿瘤免疫治疗，少数的患者获得长期的疾病控制[11] [12]。总之阻断 PD-1/PD-L1 信号给我们提供了新的抗癌思路，本文的目的是阐述 PD-1/PD-L1 信号通路在 ESCC 中的研究成果及临床意义，回顾现有的临床证据，为 ESCC 的治疗提供最新知识。

2. PD-1/PD-L1 信号通路概述及肿瘤组织中的表达关系

2.1. PD-1/PD-L1 信号通路概述

PD-1，也称为 CD279，首次与 1992 年在 2B4-11 (小鼠 T 细胞杂交瘤)和白细胞介素-3 (IL-3)缺失的 LyD9 (小鼠造血祖细胞系)中被人们发现[13]。PD-1 是 B7-CD28 家族的成员之一，其氨基酸序列中有 15% 与 CD28 相似，有 20%与细胞毒性 T 淋巴细胞相关抗原-4 (Cytotoxic T lymphocyte associated antigen 4, CTLA4)相似，与诱导型 T 细胞共刺激剂的相似性为 13% [14]。PD-1 是一种 55 kDa 的跨膜蛋白[15]，含有 288 个氨基酸，细胞外 N 端结构域(IgV-Like)、膜渗透结构域和细胞质尾部分别位于 N 端和 C 端，具有两个酪氨酸碱基[16]。PD-1 是适应性和先天免疫反应的抑制剂，在 T 细胞、B 细胞、巨噬细胞和树突

细胞(dc)等细胞上表达。值得注意的是，PD-1 在肿瘤特异性 T 细胞上高度表达[17]。

PD-1 与其配体结合后，活性免疫细胞受到抑制。PD-1 有两个已被发现的配分别为 PD-L1 和 PD-L2，它们均是 B7 家族成员[18]。PD-L1 是一种 33 kDa 的 1 型跨膜糖蛋白，其胞外区含有 290 个氨基酸，Ig-和 IgC 结构域[16]。PD-L1 广泛表达于多类免疫细胞中。此外，PD-L1 作为一种逃避抗肿瘤反应的“适应性免疫机制”在肿瘤细胞中表达[19]。PD-L1 与 CD8 T 细胞丰富的免疫环境、Th1 细胞因子和化学因子的生成以及干扰素和特异性遗传因子表达特征有关[20]。

2.2. PD-1/PD-L1 信号通路在肿瘤组织中的表达

PD-1/PD-L1 信号通路在肿瘤免疫治疗中是必不可少的[21]。在生理情况下，PD-1/PD-L1 信号通路介导且参与外周自身耐受性的维持和自身免疫性疾病的预防。然而，在肿瘤微环境(tumor microenvironment, TME)中，肿瘤细胞可以通过在细胞表面表达 PD-L1 并与 PD-1 受体阳性的免疫效应细胞结合，PD-1 将通过其细胞内信号传导结构域启动抑制性信号传导级联，使 PD-L1 的表达水平向上调节，致肿瘤细胞能够躲避被免疫识别与攻击，进而促进肿瘤发展[22]，机制如下：1) 使 T 细胞活化被抑制并介导其凋亡；2) 抑制细胞毒性 T 细胞产生颗粒酶和穿孔素；3) 抑制如 IFN-γ、IL-2、TNF-α 等炎症细胞因子的分泌，并促进 IL-10，一种免疫抑制细胞因子的分泌；4) 使 T 细胞周期被阻滞，导致细胞在 G_0/G_1 期停止运作；5) 促肿瘤细胞转移和浸润速度加速[23] [24] [25] [26] [27]。基于以上分子机制，抑制 PD-1/PD-L1 信号是使失调的 TME 正常化的可行策略[28]，PD-1/PD-L1 信号通路抑制剂可以特异性阻断 PD-1 与 PD-L1 之间结合，激活 T 细胞活性，对肿瘤细胞产生杀伤力[29]。

3. PD-1/PD-L1 信号通路与食管鳞状细胞癌

3.1. PD-1/PD-L1 信号通路在食管鳞状细胞癌中的表达及其预后

免疫检查点(Immune checkpoints, ICs)是通常在多种免疫细胞表面表达的免疫抑制分子，在防止自身免疫和长期炎症的发生中起着重要作用[30]。目前，PD-1 和 PD-L1 是 ESCC 中研究最多的 ICs。Chen K [31]等：应用免疫组化技术对 536 例原发性 ESCC 患者的组织微阵列检测 PD-1 和 PD-L1 的表达，结果显示 PD-1 和 PD-L1 在 ESCC 中的表达率分别为 33.5% (117/349)和 41.4% (222/536)。PD-L1 的表达因肿瘤部位、分级、淋巴结转移和疾病分期而有显著差异($P < 0.05$)。此外，其表达与无病生存(DFS)相关。PD-L1 表达阳性的患者与 PD-L1 未表达的患者相比，疾病复发的风险降低(风险比[HR] = 0.75，95%可信区间[CI]：0.56~1.00，$P = 0.048$)。Kaplan-Meier 曲线显示了相似的结果，$P = 0.047$。然而，在 ESCC 中，PD-1 的表达与临床病理因素或转归无显著相关性，研究者得出结论：PD-L1 可能是 ESCC 预后的一个有利指标。

Liu Z 等[32]对 PubMed、Embase、Cochrane 图书馆和科学网数据库进行了系统搜索，并采用随机效应模型评估了 PD-L1 表达与 ESCC 临床病理特征以及预后之间的相关性，研究者共纳入 31 项回顾性研究中的 5368 名患者。结果显示 PD-L1 的过度表达与淋巴结转移(OR: 1.342, 95%CI: 0.995~1.809, $P = 0.050$)和远处转移(OR: 1.516, 95%CI: 1.001~2.294, $P = 0.050$)显著相关。合并 HR 显示，PD-L1 过表达与 ESCC 患者总生存期(Overall survival, OS)差显著相关(HR: 1.306, 95%CI: 1.108~1.539, $P < 0.010$)，但与无病生存期(Disease-free survival, DFS)无关(HR: 1.180, 95%CI: 0.937~1.487, $P = 0.160$)。在亚组分析中，异质性显著降低。PD-L1 过度表达与截断点≥1%时 DFS 差相关(HR: 1.642, 95%CI: 1.367~1.973, $P < 0.010$, $I^2 = 0\%$)，截断点 ≥10%时 OS 更差(HR: 1.575, 95%CI: 1.175~2.111, $P < 0.010$, $I^2 = 0\%$)。研究者得出结论：PD-L1 的过表达与 ESCC 的淋巴结转移和远处转移以及低生存率相关。

多数研究者认为 PD-1、PD-L1 的过表达给 ESCC 带来了不良的预后，但也有研究者认为 PD-1、PD-L1 的过表达是 ESCC 预后良好的指标[33] [34]。

3.2. PD-1/PD-L1 信号通路抑制剂与食管鳞状细胞癌

PD-1/PD-L1 信号通路抑制剂通过阻断 PD-1/PD-L1 信号通路致使肿瘤细胞死亡，并且在肿瘤免疫治疗中取得了较好的进展，也从根本上改变了恶性黑色素瘤的治疗方法，由于在肿瘤免疫逃避中 PD-1/PD-L1 起重要作用，因此针对 PD-1/PD-L1 信号通路抑制剂的治疗疗效成了近期研究热点。

Nivolumab 是一种针对 PD-1 的人源化 IgG4 kappa 单克隆抗体，可阻断 PD-1 与其配体 PD-L1 之间的相互作用[35]。CheckMate-648 是一项开放性 III 期试验，研究结果显示在肿瘤细胞 PD-L1 表达为 1%或更高的患者中，Nivolumab 加化疗比单独化疗有显著的无进展生存获益(疾病进展或死亡的风险比，0.65；98.5%CI：0.46~0.92；P = 0.002)。研究者得出结论：一线纳武单抗联合化疗和一线纳武单抗联合伊匹单抗治疗晚期 ESCC 患者的总生存期均明显长于单独化疗，且未发现新的安全性信号[36]。ATTRACTION-3 是一项多中心、随机、开放的 III 期研究，研究结果显示与化疗组相比，nivolumab 组的总生存率显著提高(中位数为 10.9 个月，95%CI 为 9.2~13.3 对 8.4 个月，7.2~9.9；死亡风险比为 0.77，95%可信区间为 0.62~0.96；P = 0.019)。研究者得出结论：在先前接受治疗的晚期 ESCC 患者中，与化疗相比，Nivolumab 与总生存率的显著改善和良好的安全性相关，并且可能代表这些患者的新的标准二线治疗选择[37]。

Pembrolizumab 一种人源化 IgG4 单克隆抗体，旨在阻断 PD-1 与其配体 PD-L1 之间的相互作用[35]。KEYNOTE-180 是一项开放、全球性的 II 期研究，Pembrolizumab 作为三线或后期治疗的 ESCC 患者的客观缓解率为 14.3% (95%CI: 6.7%~25.4%)，腺癌患者的客观缓解率为 5.2% (95%CI: 1.1%~14.4%)，PD-L1 阳性肿瘤患者的客观缓解率为 13.8% (95%CI: 6.1%~25.4%)，PD-L1 阴性肿瘤患者的客观缓解率为 6.3% (95%CI: 1.8%~15.5%)。研究者得出结论：这些数据支持 Pembrolizumab 作为一种有价值的治疗选择，对经过 2 个或更多疗程后疾病进展的晚期转移性食管癌患者具有持久的益处[38]。KEYNOTE-181 是一项随机、开放、全球性的 III 期研究，此研究中 Pembrolizumab 单一治疗的中位总生存期为 10.3 个月，而化疗为 6.7 个月(风险比[HR] 0.64 [95%CI: 0.46~0.90])。研究者得出结论：在 PD-L1 CPS ≥ 10 的晚期食管癌患者中，Pembrolizumab 与化疗组相比，能延长患者的 OS，治疗相关不良事件较少，尤其是 ESCC 患者[39]。KEYNOT-590 是一项随机、安慰剂对照、双盲、III 期研究，结果显示 Pembrolizumab 联合化疗较安慰剂加化疗相比可显著提高先前未经治疗的晚期 ESCC 和 PD-L1 CPS ≥ 10 的患者的总生存率，改善了 ESCC，PD-L1 CPS ≥ 10 的患者的总生存期和无进展生存期，并且在所有随机分组的患者中，无论组织学如何，在总治疗人群中具有可控的安全性[40]。

4. 展望

免疫疗法是当前新兴肿瘤疗法的研究热点，并且给 ESCC 带来了新的治疗方式，免疫治疗的深入研究可以显著改善 ESCC 患者预后，使患者生存率提高。相比于其他抗肿瘤药物，目前免疫治疗在 ESCC 还是在研究阶段。PD-1/PD-L1 在 ESCC 中存在较高的阳性表达率，但其表达与预后的关系仍存在争议。PD-1/PD-L1 信号通路抑制剂虽然在 ESCC 治疗方面取得了一些进展，疗效及用药安全性仍需大量临床探究来进一步确认，并存在一定的不足，如疗效的预测、制定最佳治疗策略、克服免疫治疗方案耐药等将是该领域未来需要解决的问题。除此之外，对于临床工作者而言，应重视通过为患者设计个性化治疗方案，使免疫治疗疗法与其他治疗的优势互补，从而提高 ESCC 患者的生存率，带来更多的生存获益。

参考文献

[1] Bray, F., Ferlay, J., Soerjomataram, I., *et al*. (2018) Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **68**, 394-424. https://doi.org/10.3322/caac.21492

[2] Liang, M.-Q., Yu, F.-Q. and Chen, C. (2020) C-Myc Regulates PD-L1 Expression in Esophageal Squamous Cell Car-

cinoma. *American Journal of Translational Research*, **12**, 379-388.

[3] Lu, D., Liu, X., Feng, S., *et al*. (2019) The Current Situation of Esophageal Cancer Staging and Perioperative Strategies Determination in Central and Southern China: A Cross Sectional Survey. *Frontiers in Oncology*, **9**, Article No. 1098. https://doi.org/10.3389/fonc.2019.01098

[4] Liu, W., Huo, G. and Chen, P. (2023) Efficacy of PD-1/PD-L1 Inhibitors in Advanced Gastroesophageal Cancer Based on Characteristics: A Meta-Analysis. *Immunotherapy*, **15**, 751-771. https://doi.org/10.2217/imt-2022-0305

[5] Dedecker, H., Teuwen, L.-A., Vandamme, T., *et al*. (2023) The Role of Immunotherapy in Esophageal and Gastric Cancer. *Clinical Colorectal Cancer*, **22**, 175-182. https://doi.org/10.1016/j.clcc.2023.03.001

[6] Yi, M., Niu, M., Xu, L., *et al*. (2021) Regulation of PD-L1 Expression in the Tumor Microenvironment. *Journal of Hematology & Oncology*, **14**, Article No. 10. https://doi.org/10.1186/s13045-020-01027-5

[7] Wolchok, J.D., Chiarion-Sileni, V., Gonzalez, R., *et al*. (2017) Overall Survival with Combined Nivolumab and Ipilimumab in Advanced Melanoma. *New England Journal of Medicine*, **377**, 1345-1356. https://doi.org/10.1056/NEJMoa1709684

[8] Kudo, T., Hamamoto, Y., Kato, K., *et al*. (2017) Nivolumab Treatment for Oesophageal Squamous-Cell Carcinoma: An Open-Label, Multicentre, Phase 2 Trial. *The Lancet Oncology*, **18**, 631-639. https://doi.org/10.1016/S1470-2045(17)30181-X

[9] Janjigian, Y.Y., Bendell, J., Calvo, E., *et al*. (2018) CheckMate-032 Study: Efficacy and Safety of Nivolumab and Nivolumab plus Ipilimumab in Patients with Metastatic Esophagogastric Cancer. *Journal of Clinical Oncology*, **36**, 2836-2844. https://doi.org/10.1200/JCO.2017.76.6212

[10] Kojima, T., Muro, K., Francois, E., *et al*. (2019) Pembrolizumab versus Chemotherapy as Second-Line Therapy for Advanced Esophageal Cancer: Phase III KEYNOTE-181 Study. *Journal of Clinical Oncology*, **37**, 2. https://doi.org/10.1200/JCO.2019.37.4_suppl.2

[11] Garon, E.B., Hellmann, M.D., Rizvi, N.A., *et al*. (2019) Five-Year Overall Survival for Patients with Advanced Non–Small-Cell Lung Cancer Treated with Pembrolizumab: Results from the Phase I KEYNOTE-001 Study. *Journal of Clinical Oncology*, **37**, 2518-2527. https://doi.org/10.1200/JCO.19.00934

[12] Hamid, O., Robert, C., Daud, A., *et al*. (2019) Five-Year Survival Outcomes for Patients with Advanced Melanoma Treated with Pembrolizumab in KEYNOTE-001. *Annals of Oncology*, **30**, 582-588. https://doi.org/10.1093/annonc/mdz011

[13] Ishida, Y., Agata, Y., Shibahara, K., *et al*. (1992) Induced Expression of PD-1, a Novel Member of the Immunoglobulin Gene Superfamily, upon Programmed Cell Death. *The EMBO Journal*, **11**, 3887-3895. https://doi.org/10.1002/j.1460-2075.1992.tb05481.x

[14] Carreno, B.M. and Collins, M. (2002) The B7 Family of Ligands and Its Receptors: New Pathways for Costimulation and Inhibition of Immune Responses. *Annual Review of Immunology*, **20**, 29-53. https://doi.org/10.1146/annurev.immunol.20.091101.091806

[15] Ratajczak, K., Grel, H., Olejnik, P., *et al*. (2023) Current Progress, Strategy, and Prospects of PD-1/PDL-1 Immune Checkpoint Biosensing Platforms for Cancer Diagnostics, Therapy Monitoring, and Drug Screening. *Biosensors and Bioelectronics*, **240**, Article ID: 115644. https://doi.org/10.1016/j.bios.2023.115644

[16] Han, Y., Liu, D. and Li, L. (2020) PD-1/PD-L1 Pathway: Current Researches in Cancer. *American Journal of Cancer Research*, **10**, 727-742.

[17] Yang, Q., Shi, G., Chen, X., *et al*. (2020) Nanomicelle Protects the Immune Activation Effects of Paclitaxel and Sensitizes Tumors to Anti-PD-1 Immunotherapy. *Theranostics*, **10**, 8382-8399. https://doi.org/10.7150/thno.45391

[18] Sudo, S., Kajiya, H., Okano, S., *et al*. (2020) Cisplatin-Induced Programmed Cell Death Ligand-2 Expression Is Associated with Metastasis Ability in Oral Squamous Cell Carcinoma. *Cancer Science*, **111**, 1113-1123. https://doi.org/10.1111/cas.14336

[19] Wu, X., Ke, X., Ni, Y., *et al*. (2020) Tumor-Infiltrating Immune Cells and PD-L1 as Prognostic Biomarkers in Primary Esophageal Small Cell Carcinoma. *Journal of Immunology Research*, **2020**, Article ID: 8884683. https://doi.org/10.1155/2020/8884683

[20] Lantuejoul, S., Damotte, D., Hofman, V., *et al*. (2019) Programmed Death Ligand 1 Immunohistochemistry in Non-Small Cell Lung Carcinoma. *Journal of Thoracic Disease*, **11**, S89-S101. https://doi.org/10.21037/jtd.2018.12.103

[21] Cui, Y., Shi, J., Cui, Y., *et al*. (2023) The Relationship between Autophagy and PD-L1 and Their Role in Antitumor Therapy. *Frontiers in Immunology*, **14**, Article ID: 1093558. https://doi.org/10.3389/fimmu.2023.1093558

[22] Lv, G., Sun, X., Qiu, L., *et al*. (2020) PET Imaging of Tumor PD-L1 Expression with a Highly Specific Nonblocking Single-Domain Antibody. *Journal of Nuclear Medicine*, **61**, 117-122. https://doi.org/10.2967/jnumed.119.226712

[23] Shi, F., Shi, M., Zeng, Z., *et al*. (2011) PD-1 and PD-L1 Upregulation Promotes CD8+ T-Cell Apoptosis and Postoper-

ative Recurrence in Hepatocellular Carcinoma Patients. *International Journal of Cancer*, **128**, 887-896. https://doi.org/10.1002/ijc.25397

[24] Patsoukis, N., Sari, D. and Boussiotis, V.A. (2012) PD-1 Inhibits T Cell Proliferation by Upregulating p27 and p15 and Suppressing Cdc25A. *Cell Cycle*, **11**, 4305-4309. https://doi.org/10.1002/ijc.25397

[25] Mansfield, A.S., Aubry, M.C., Moser, J.C., *et al*. (2016) Temporal and Spatial Discordance of Programmed Cell Death-Ligand 1 Expression and Lymphocyte Tumor Infiltration between Paired Primary Lesions and Brain Metastases in Lung Cancer. *Annals of Oncology*, **27**, 1953-1958. https://doi.org/10.1093/annonc/mdw289

[26] Velcheti, V., Rimm, D.L. and Schalper, K.A. (2013) Sarcomatoid Lung Carcinomas Show High Levels of Programmed Death Ligand-1 (PD-L1). *Journal of Thoracic Oncology*, **8**, 803-805. https://doi.org/10.1097/JTO.0b013e318292be18

[27] Rollins, M.R. and Gibbons Johnson, R.M. (2017) CD80 Expressed by $CD8^+$ T Cells Contributes to PD-L1-Induced Apoptosis of Activated $CD8^+$ T Cells. *Journal of Immunology Research*, **2017**, e7659462. https://doi.org/10.1155/2017/7659462

[28] Sanmamed, M.F. and Chen, L. (2018) A Paradigm Shift in Cancer Immunotherapy: From Enhancement to Normalization. *Cell*, **175**, 313-326. https://doi.org/10.1155/2017/7659462

[29] Cheng, C., Zhuge, L., Xiao, X., *et al*. (2022) Overcoming Resistance to PD-1/PD-L1 Inhibitors in Esophageal Cancer. *Frontiers in Oncology*, **12**, Article No. 955163. https://doi.org/10.3389/fonc.2022.955163

[30] Hu, C., Meiners, S., Lukas, C., *et al*. (2020) Role of Exosomal microRNAs in Lung Cancer Biology and Clinical Applications. *Cell Proliferation*, **53**, e12828. https://doi.org/10.1111/cpr.12828

[31] Chen, K., Cheng, G., Zhang, F., *et al*. (2016) Prognostic Significance of Programmed Death-1 and Programmed Death-Ligand 1 Expression in Patients with Esophageal Squamous Cell Carcinoma. *Oncotarget*, **7**, 30772-30780. https://doi.org/10.18632/oncotarget.8956

[32] Liu, Z., Sun, L., Cai, L., *et al*. (2022) Clinicopathological and Prognostic Values of PD-L1 Expression in Oesophageal Squamous Cell Carcinoma: A Meta-Analysis of 31 Studies with 5368 Patients. *Postgraduate Medical Journal*, **98**, 948-957. https://doi.org/10.18632/oncotarget.8956

[33] Jesinghaus, M., Steiger, K., Slotta-Huspenina, J., *et al*. (2017) Increased Intraepithelial CD3+ T-Lymphocytes and High PD-L1 Expression on Tumor Cells Are Associated with a Favorable Prognosis in Esophageal Squamous Cell Carcinoma and Allow Prognostic Immunogenic Subgrouping. *Oncotarget*, **8**, 46756-46768. https://doi.org/10.18632/oncotarget.18606

[34] Zhang, W., Pang, Q., Zhang, X., *et al*. (2017) Programmed Death-Ligand 1 Is Prognostic Factor in Esophageal Squamous Cell Carcinoma and Is Associated with Epidermal Growth Factor Receptor. *Cancer Science*, **108**, 590-597. https://doi.org/10.1111/cas.13197

[35] Jiang, Y., Chen, M., Nie, H., *et al*. (2019) PD-1 and PD-L1 in Cancer Immunotherapy: Clinical Implications and Future Considerations. *Human Vaccines & Immunotherapeutics*, **15**, 1111-1122. https://doi.org/10.1080/21645515.2019.1571892

[36] Doki, Y., Ajani, J.A., Kato, K., *et al*. (2022) Nivolumab Combination Therapy in Advanced Esophageal Squamous-Cell Carcinoma. *New England Journal of Medicine*, **386**, 449-462. https://doi.org/10.1080/21645515.2019.1571892

[37] Kato, K., Cho, B.C., Takahashi, M., *et al*. (2019) Nivolumab versus Chemotherapy in Patients with Advanced Oesophageal Squamous Cell Carcinoma Refractory or Intolerant to Previous Chemotherapy (ATTRACTION-3): A Multicentre, Randomised, Open-Label, Phase 3 Trial. *The Lancet Oncology*, **20**, 1506-1517. https://doi.org/10.1016/S1470-2045(19)30626-6

[38] Shah, M.A., Kojima, T., Hochhauser, D., *et al*. (2019) Efficacy and Safety of Pembrolizumab for Heavily Pretreated Patients with Advanced, Metastatic Adenocarcinoma or Squamous Cell Carcinoma of the Esophagus: The Phase 2 KEYNOTE-180 Study. *JAMA Oncology*, **5**, 546-550. https://doi.org/10.1001/jamaoncol.2018.5441

[39] Kojima, T., Shah, M.A., Muro, K., *et al*. (2020) Randomized Phase III KEYNOTE-181 Study of Pembrolizumab versus Chemotherapy in Advanced Esophageal Cancer. *Journal of Clinical Oncology*: *Official Journal of the American Society of Clinical Oncology*, **38**, 4138-4148. https://doi.org/10.1200/JCO.20.01888

[40] Sun, J.-M., Shen, L., Shah, M.A., *et al*. (2021) Pembrolizumab plus Chemotherapy versus Chemotherapy Alone for First-Line Treatment of Advanced Oesophageal Cancer (KEYNOTE-590): A Randomised, Placebo-Controlled, Phase 3 Study. *The Lancet*, **398**, 759-771. https://doi.org/10.1016/S0140-6736(21)01234-4