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炎症细胞及乳酸在结直肠癌肝转移中的作用机制

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摘　要

结直肠癌(Colorectal cancer, CRC)是全球第三大最常见的恶性肿瘤，大约50%的患者在随访期间发生结直肠癌肝转移(Colorectal cancer liver metastasis, CRLM)，肝转移是其最常见的远处转移部位；并且肝转移是结直肠癌患者死亡的主要原因。CRLM的管理最好通过多学科方法实现，诊断和治疗决策过程很复杂。为了优化患者的生存和生活质量，必须克服几个未解决的挑战。这些主要包括及时诊断和确定可靠的预后因素。早期识别结直肠癌肝转移的危险因素可能是降低肝转移发生率的有效策略。炎症细胞及乳酸在肿瘤微环境中发挥着重要作用，对肿瘤细胞转移机制至关重要。本文将探讨炎症细胞及乳酸在结直肠癌异时性肝转移中的作用，这是对手术后发生异时性肝转移的结直肠癌患者进行有效干预的前提，对改善患者生活质量、延长患者生命具有重要意义。

关键词

炎症细胞，乳酸，结直肠癌，肝转移

The Role and Mechanism of Inflammatory Cells and Lactic Acid in Colorectal Cancer Liver Metastasis

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Abstract

Colorectal cancer (CRC) is the third most common malignant tumor worldwide, and approximately 50% of patients develop colorectal cancer liver metastasis (CRLM) during follow-up, making it the most common distant metastatic site. Liver metastasis is the main cause of death in patients with CRC. The management of CRLM is best achieved through a multidisciplinary approach, and the process of diagnosis and treatment decision-making is complex. To optimize patient survival and quality of life, several unresolved challenges must be overcome. These include the timely diagnosis and the identification of reliable prognostic factors. Early identification of risk factors for CRLM may be an effective strategy to reduce the incidence of liver metastasis. Inflammatory cells and lactic acid play a significant role in the tumor microenvironment and are crucial for the metastatic mechanism of tumor cells. This paper will explore the role of inflammatory cells and lactic acid in the metachronous liver metastasis of colorectal cancer, which is a prerequisite for effective intervention in patients with metachronous liver metastasis of colorectal cancer after surgery, and has important significance for improving patient quality of life and extending patient life.

Keywords

Inflammatory Cells, Lactic Acid, Colorectal Cancer, Liver Metastasis

1. 引言

结直肠癌(CRC)是全球第三大最常见的恶性肿瘤，据估计，2022 年发生超过 190 万例新发结直肠癌(包括肛门癌)病例和 90.4 万例死亡，占癌症病例和死亡人数的近十分之一，发病率排名第三，但死亡率排名第二[1]；在中国结直肠癌发病率排名第二，而死亡率排名第四[2]。肝转移是其最常见的远处转移部位；并且肝转移是结直肠癌患者死亡的主要原因。初诊时同时性肝转移约占所有结直肠癌患者 15%~25%。同时，即使原发病灶根治性切除后，异时性肝转移仍占 10%~25% [3]。未经治疗的肝转移患者的中位生存期仅 6.9 个月，无法切除患者的 5 年生存率低于 5% [4]。一旦发生肝转移，治疗变得更加复杂，需要综合应用手术、化疗、放疗以及靶向治疗等多种手段。而这些治疗方式不仅增加了医疗费用，也给患者带来了更多的副作用和生活质量下降的风险。

鉴于结直肠癌术后肝转移对预后的显著影响，识别和理解其危险因素对于改善患者预后至关重要。肿瘤微环境(tumor microenvironment, TME)在肿瘤的发生、发展和侵袭中起着至关重要的作用[5]。肿瘤微环境的主要成分是微血管(微血管和淋巴管)、炎性反应细胞和癌症相关成纤维细胞。炎症细胞通过释放活性氧(reactive oxygen species, ROS)、活性氮(reactive nitrogen species, RNS)或蛋白酶以及促进循环生长因子如白细胞介素-1、白细胞介素-6 和血管内皮生长因子的分泌，参与肿瘤的起始、生长、增殖或转移扩散等多个过程[6]-[8]。乳酸及其产生的酸性肿瘤微环境可以通过对相关的免疫细胞，如单核/巨噬细胞，自然杀伤(NK)细胞，中性粒细胞和树突状细胞，抑制其增殖和存活[9]，诱导免疫细胞去分化[10]，调节下游过程的信号传导抑制免疫细胞抗癌作用[11] [12]。本综述旨在系统总结和分析炎症细胞及乳酸在结直肠癌根治术后发生肝转移的机制及相关临床预测模型，为临床实践提供参考依据，并为未来研究提供方向。

肝脏是结直肠癌最常见的转移部位。肝脏的独特结构和以下特征使其本质上容易发生血源性转移。(1) 肝门静脉和肝动脉的双重供血，为循环癌细胞侵入肝脏提供了更多的机会。这一现象是大多数原发肿瘤向特定继发器官转移的基础[13] [14]。(2) 肝窦内皮细胞(liver sinusoidal endothelial cells, LSECs)的血流缓慢和高通透性促进了播散性癌细胞的侵袭能力[15]。(3) 肝脏的免疫耐受能力形成免疫抑制微环境，防止抗原进入肝脏后过度反应造成损伤[16]。

CRLM 的发病发展主要分为四个相互重叠的阶段[17] [18]。(1) 微血管期：被困在窦状血管中的肝浸润性结直肠癌细胞通过枯否细胞(Kupffer cells, KCs)和自然杀伤细胞介导的抗肿瘤细胞毒性吞噬而被杀死[19] [20]；它们也可能通过逃避细胞毒性作用并粘附在 LSECs [18]上而存活，这有助于癌细胞迁移到疾病空间以避免免疫杀伤。(2) 外渗和血管生成前期：CRC 细胞迁移到窦周间隙，招募基质细胞，包括负责纤维连接蛋白和胶原分泌的肝星状细胞(hepatic stellate cells, HSCs)，形成新生血管的框架[21] [22]，和门静脉成纤维细胞负责产生 IL-8 促进侵袭和血管生生成[23]。(3) 血管生成期：在 LSECs 被激活并被肿瘤-肝脏界面增选后，激活的肝星状细胞来源的血管内皮生长因子(vascular endothelial growth factor, VEGF)诱导转移内血管的形成，这些血管与窦状血管[24]呈连续性。多种免疫抑制细胞，如免疫抑制调节性 T-(Treg)细胞、髓源性抑制细胞(myeloid-derived suppressor cells, MDSCs)和巨噬细胞被激活形成免疫抑制微环境，促进 CRLM 的发展。(4) 生长期：CRC 细胞获得充足的血液供应，在肝脏固有免疫耐受和免疫抑制微环境的“保护”下迅速增殖，最终形成可检测的转移性肿瘤[25]。

2. 炎症细胞在结直肠癌肝转移中作用

肿瘤微环境中各种各样的先天免疫细胞在结直肠癌肝转移中起着至关重要的作用。这些细胞包括单核/巨噬细胞、自然杀伤(NK)细胞、中性粒细胞和树突状细胞。越来越多的证据表明，炎症细胞可产生可溶性细胞因子，避开宿主防御机制的作用，帮助癌细胞存活和生长[26]。

1) 中性粒细胞(Neutrophils)

中性粒细胞是先天免疫系统的重要组成部分，在结直肠癌肝转移中发挥双重作用，既促进又抑制肿瘤的生长和转移。浸润恶性组织的中性粒细胞被称为肿瘤相关中性粒细胞(tumour-associated Neutrophils, TANs)，TANs 通过呈递抗原并释放 IL-18 诱导 NK 细胞活化，从而促进活化的 t 细胞免疫反应，从而抑制肿瘤生长及转移。在促进肿瘤生长和转移方面，TANs 释放 CCL2 和 CCL17，募集-ccr2 + M2 巨噬细胞和-ccr4+ T-reg 细胞，在肝脏形成抑制性肿瘤微环境，从而促进癌症的进展和转移[27]。此外，TANs 产生 MMP-9 和中性粒细胞弹性酶，促进癌细胞外渗，并驱动弥散性癌细胞转移[28]。而且 TANs 挤压染色质纤维，形成中性粒细胞细胞外陷阱(NETs)，将 CRC 细胞困在肝脏中，最终促进其侵袭和转移能力，促进其在肝脏定植[29]。

2) 巨噬细胞(Macrophages)

巨噬细胞作为多功能抗原提呈细胞，是肿瘤免疫的重要介质。巨噬细胞通过 MHC-I 和 MHCII 向 T 细胞呈递外源抗原，并辅之以共刺激信号、抑制信号或其他细胞因子信号，调节 T 细胞活化[30]。浸润恶性组织的巨噬细胞被称为肿瘤相关巨噬细胞(tumour-associated macrophages, TAMs)。巨噬细胞具有固有的可塑性和极化特性，通常被分为两种亚型：M1 和 M2 巨噬细胞。M1 巨噬细胞通过释放细胞毒性活性氧(ROS)、NO 和 IL-12，直接杀伤癌细胞，从而抑制肿瘤生长[31]。然而，M2 巨噬细胞通过分泌 IL-10、TGF-β、CCL17 和 CCL22 等细胞因子诱导免疫抑制性肿瘤微环境的形成[32] [33]。由于 M2 巨噬细胞呈递肿瘤抗原的能力较差，因此会破坏 Th1 适应性免疫[34]。此外，M2 巨噬细胞产生 MMPs 调节基质重塑，从而促进肿瘤的侵袭和转移[35]。在结直肠癌中，不断扩大的肝转移肿瘤中富含 tam (主要是 M2 巨噬细胞)，在 CRLM 中起着重要的作用。有报道称，细胞外基质糖蛋白 spondin 2 (SPON2)重塑细胞骨架，

激活整合素β1/PYK2 信号，促进 tam 的迁移，从而增加 tam 的浸润，促进 CRC 的转移[36]。此外，CRC 衍生的脂质在 CD36 的帮助下重塑 tam 的代谢，从而诱导 tam M2 极化，推动肝转移的发展。肝转移细胞通过 CCL2/CCR2 趋化因子轴募集 tam 形成免疫抑制微环境[37]，该微环境受 CRC 细胞中 TCF4 表达的调控，促进肿瘤转移。

总之，作为肿瘤微环境中主要的肿瘤浸润免疫细胞，tam 在结直肠癌的进展和转移中起着关键作用，其高比例与预后不良密切相关[38]。

3) T 细胞和 B 细胞

T 细胞在结直肠癌发生肝转移中发挥着重要作用。CD4+ T 细胞通过调控 CD8+ T 细胞活性和影响抗肿瘤反应结果，在抵抗肿瘤方面起着关键作用。不同的 CD4+ T 辅助细胞亚群(如 Th1、Th2、Th9、Th17 和 FOXP3+ Treg 细胞)会产生不同的细胞因子和调节抗肿瘤免疫应答[39]。特别是 FOXP3+ Treg 细胞在肝转移组织中的高比例与较差的预后相关[40]。这些 Treg 细胞通过与抗原呈递细胞相互作用、使用免疫抑制代谢物、产生细胞因子等途径，抑制效应 T 细胞的活化。此外，CD8+ T 细胞作为抗肿瘤的关键细胞，在对抗癌细胞时促进细胞毒杀，并通过不同机制如细胞因子释放和抑制受体的调节，影响肿瘤的生长和转移[41]-[43]。因此，激活 CD8+ T 细胞以及减少 Treg 细胞在肿瘤微环境中的影响，可能是治疗肝转移结直肠癌的有益途径。

B 细胞通过分化为浆细胞产生特异性抗体，对抗肿瘤抗原。抗体依赖的细胞介导毒性(ADCC)：抗体可以标记肿瘤细胞，使其成为自然杀伤(NK)细胞等效应细胞的靶标。补体激活：抗体可以激活补体系统，导致肿瘤细胞溶解和死亡。与 T 细胞相比，B 细胞的浸润数量较少，但最近的研究表明，B 细胞在向 T 细胞呈递肿瘤抗原、分泌促进细胞毒性免疫反应的细胞因子、促进免疫浸润性肿瘤微环境的形成和对抗免疫编辑等方面发挥着积极作用[44] [45]。此外，B 细胞还有助于肿瘤相关的三级淋巴结构(TLS)的形成，该结构支持肿瘤特异性 B 细胞的成熟和亚型转换，以及肿瘤特异性 T 细胞反应的发展[46]。B 细胞可以集中在肿瘤边缘或形成各种复杂的肿瘤相关免疫聚集体，从小簇到结构化的 TLS。特别是，T 细胞和 B 细胞之间的抗原特异性相互作用似乎在 TLS 和肿瘤浸润淋巴细胞群中至关重要，而肿瘤微环境的抗肿瘤作用通常取决于 T 细胞和 B 细胞的合作[47]。

4) 树突状细胞(Dendritic cells)

树突状细胞(dc)是典型的抗原提呈细胞，在触发抗原特异性免疫反应和诱导免疫耐受方面具有相当大的影响。常规 dc (cdc)的抗原提呈功能对于效应 T 细胞的抗肿瘤反应很重要。有效的抗原呈递增加了-CD4+ Th1 细胞的极化和-CD8+ T 细胞的活化[48] [49]。从骨髓来源的祖细胞分化而来的肝驻留调节性 dc 分泌高水平的 IL-10 而低水平的 IL-12，从而抑制有效的 t 细胞功能来维持肝脏耐受[50]。CRLM 中被鉴定为 DC3s 的一组 cdc 可诱导促炎表型，并与不良预后相关[51]。DC3s 可能被认为是改善 CRLM 免疫治疗效果的一个有希望的靶点。需要进一步的研究来阐明 DC3s 促进 CRLM 的机制。研究发现，结直肠癌患者肝转移灶中树突状细胞的数量和功能常被抑制，这与较差的预后相关。增强树突状细胞功能或采用树突状细胞疫苗策略，被认为是潜在的治疗途径[52]。

3. 乳酸在结直肠癌肝转移中的作用

乳酸是细胞代谢过程中通过糖酵解产生的代谢产物。正常细胞在有氧条件下主要通过氧化磷酸化生成能量，而缺氧条件下通过糖酵解生成乳酸。癌细胞即使在有氧条件下也倾向于通过糖酵解产生能量，这一现象称为 Warburg 效应。Warburg 效应导致乳酸的大量积累，是肿瘤细胞代谢重编程的标志之一[53]。在实体瘤的生长过程中，快速增殖的细胞需要更持续的能量来生长和存活[54]。为了支持这种高代谢需求，糖酵解在各种肿瘤组织中都非常活跃[55]。因此，糖酵解状态被认为对预测患者预后有潜在价值。通过有

氧糖酵解和谷氨酰胺水解产生大量乳酸，并随后排放到癌细胞之间的细胞外空间(即肿瘤微环境)。这种过量和持续产生乳酸导致酸性肿瘤微环境[56]，抑制抗癌免疫反应，进而促进肿瘤的生长和转移[57]。

乳酸及其形成的酸性肿瘤微环境与炎症细胞密切相关。乳酸的积累不仅直接改变了炎症细胞的代谢和功能，还通过调控其分泌的炎症因子和趋化因子，进一步建立了一个免疫抑制且支持结直肠癌肝转移的复杂网络。

T 细胞与乳酸：乳酸通过降低 T 细胞的 pH 值，抑制了 T 细胞的增殖和生存，导致效应 T 细胞的功能受到抑制。此外，乳酸还减少了 T 细胞对趋化因子的响应，降低了它们的迁移能力[58]。调节性 T 细胞(Tregs)：在酸性 TME 中，Tregs 的活性和招募增加，这进一步抑制了抗癌免疫反应。酸性环境还有助于 Treg 的诱导，增加了 Treg 活性，从而减少了抗癌免疫反应[59]。吲哚胺 2,3-双加氧酶是 Treg 表达的一种免疫调节酶，可将色氨酸转化为犬尿氨酸。酸性 TME 水平升高会降低色氨酸水平，进而激活维持 Treg 抑制功能的应激反应途径[60] [61]。

树突细胞(DC)与乳酸：树突状细胞作为经典的抗原提呈细胞，其功能在乳酸丰富的肿瘤微环境中被显著抑制。乳酸通过干扰树突状细胞成熟过程，降低其抗原提呈能力，使其难以有效激活 CD8+ T 细胞[62] [63]。当与不同肿瘤细胞系分泌的 IL-4 和 GM-CSF 一起培养时，DC 前体不表达 CD1a，不能分化为 DC [64]。因此，乳酸诱导的酸中毒会损害单核细胞向 DC 的分化。增强 DC 功能是克服肿瘤免疫抑制进行肿瘤免疫治疗的途径之一。在这方面，IDO 和 STAT3 的抑制作用正在小鼠和临床试验中进行探索[65]。

中性粒细胞与乳酸：在乳酸积累导致的酸性微环境中，中性粒细胞的凋亡被延迟，同时其向 N2 表型的分化增加[66]，这一表型具有强烈的促肿瘤功能。N2 型中性粒细胞通过释放 MMP-9 和中性粒细胞弹性酶，促进基质降解以及癌细胞侵袭和转移[67]。

自然杀伤细胞(NK 细胞)与乳酸：虽然在某些情况下，NK 细胞在酸性环境中的激活和脱颗粒能力得到增强，但乳酸通常抑制 NK 细胞的效应功能。在黑素瘤小鼠模型中的研究表明，将肿瘤微环境 pH 值降低到 5.8~7.0 会减少溶解颗粒含量的释放，如穿孔素和颗粒酶。它还能降低 IFN-γ 和 TNF-α 的分泌，从而降低对肿瘤细胞的细胞毒性反应[68]。

乳酸不仅作为代谢产物，还作为信号分子，通过与 G 蛋白偶联受体 GPR81 结合，促进肿瘤细胞的增殖、药物抗性和 PD-L1 的表达增加[69] [70]。

乳酸和酸性肿瘤微环境通过多种机制抑制抗癌免疫反应，促进肿瘤的生长和转移。这些机制包括抑制免疫细胞的增殖和生存、诱导免疫细胞的去分化、以及通过信号传导影响下游过程。这些发现为开发新的抗癌治疗策略提供了潜在的靶点。

炎症细胞和乳酸在结直肠癌肝转移中的协同效应显著影响了肿瘤微环境的形成与发展。通过深入研究两者之间复杂的相互作用，可以揭示新的治疗靶点，为开发个体化治疗方案提供科学依据。未来的研究或许可以集中在以下几个方面。深入机制研究：利用先进的单细胞技术和基因编辑工具，解析乳酸和炎症细胞相互作用的具体机制，为新药开发提供基础数据。临床转化研究：通过多中心、大规模的临床试验验证潜在治疗靶点和联合治疗策略的有效性，并开发精准的生物标志物，用于个体化治疗方案的优化。动态监测与调整：结合液体活检等前沿技术，实现对患者治疗反应的动态监测，并根据实时数据调整治疗方案，提高治疗效果。

这些方向的深入研究将有助于提高结直肠癌肝转移患者的生存率和生活质量，为实现精准医疗提供新的契机。

参考文献

[1] Bray, F., Laversanne, M., Sung, H., Ferlay, J., Siegel, R.L., Soerjomataram, I., *et al*. (2024) Global Cancer Statistics

2022: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA*: *A Cancer Journal for Clinicians*, **74**, 229-263. https://doi.org/10.3322/caac.21834

[2] 郑荣寿, 陈茹, 韩冰峰, 等. 2022 年中国恶性肿瘤流行情况分析[J]. 中华肿瘤杂志, 2024, 46(3): 221-231.

[3] 中国医师协会外科医师分会, 中华医学会外科分会胃肠外科学组, 中华医学会外科分会结直肠外科学组, 等. 中国结直肠癌肝转移诊断和综合治疗指南(V2023) [J]. 中华胃肠外科杂志, 2023, 26(1): 1-15.

[4] Stewart, C.L., Warner, S., Ito, K., Raoof, M., Wu, G.X., Kessler, J., *et al*. (2018) Cytoreduction for Colorectal Metastases: Liver, Lung, Peritoneum, Lymph Nodes, Bone, Brain. When Does It Palliate, Prolong Survival, and Potentially Cure? *Current Problems in Surgery*, **55**, 330-379. https://doi.org/10.1067/j.cpsurg.2018.08.004

[5] Wikman, H., Vessella, R. and Pantel, K. (2008) Cancer Micrometastasis and Tumour Dormancy. *APMIS*, **116**, 754-770. https://doi.org/10.1111/j.1600-0463.2008.01033.x

[6] Ocana, A., Nieto-Jiménez, C., Pandiella, A. and Templeton, A.J. (2017) Neutrophils in Cancer: Prognostic Role and Therapeutic Strategies. *Molecular Cancer*, **16**, Article No. 137. https://doi.org/10.1186/s12943-017-0707-7

[7] Bhat, A.A., Nisar, S., Singh, M., Ashraf, B., Masoodi, T., Prasad, C.P., *et al*. (2022) Cytokine- and Chemokine-Induced Inflammatory Colorectal Tumor Microenvironment: Emerging Avenue for Targeted Therapy. *Cancer Communications*, **42**, 689-715. https://doi.org/10.1002/cac2.12295

[8] Chen, A., Huang, H., Fang, S. and Hang, Q. (2024) ROS: A "Booster" for Chronic Inflammation and Tumor Metastasis. *Biochimica et Biophysica Acta* (*BBA*)-*Reviews on Cancer*, **1879**, Article 189175. https://doi.org/10.1016/j.bbcan.2024.189175

[9] Huber, V., Camisaschi, C., Berzi, A., Ferro, S., Lugini, L., Triulzi, T., *et al*. (2017) Cancer Acidity: An Ultimate Frontier of Tumor Immune Escape and a Novel Target of Immunomodulation. *Seminars in Cancer Biology*, **43**, 74-89. https://doi.org/10.1016/j.semcancer.2017.03.001

[10] Zhang, D., Tang, Z., Huang, H., Zhou, G., Cui, C., Weng, Y., *et al*. (2019) Metabolic Regulation of Gene Expression by Histone Lactylation. *Nature*, **574**, 575-580. https://doi.org/10.1038/s41586-019-1678-1

[11] Choi, S.Y.C., Collins, C.C., Gout, P.W. and Wang, Y. (2013) Cancer-Generated Lactic Acid: A Regulatory, Immunosuppressive Metabolite? *The Journal of Pathology*, **230**, 350-355. https://doi.org/10.1002/path.4218

[12] Feichtinger, R.G. and Lang, R. (2019) Targeting L-Lactate Metabolism to Overcome Resistance to Immune Therapy of Melanoma and Other Tumor Entities. *Journal of Oncology*, **2019**, Article 2084195. https://doi.org/10.1155/2019/2084195

[13] Chambers, A.F., Groom, A.C. and MacDonald, I.C. (2002) Dissemination and Growth of Cancer Cells in Metastatic Sites. *Nature Reviews Cancer*, **2**, 563-572. https://doi.org/10.1038/nrc865

[14] Lake-Bakaar, G., Ahmed, M., Evenson, A., Bonder, A., Faintuch, S. and Sundaram, V. (2014) Management of Hepatocellular Carcinoma in Cirrhotic Patients with Portal Hypertension: Relevance of Hagen-Poiseuille's Law. *Liver Cancer*, **3**, 428-438. https://doi.org/10.1159/000343871

[15] Poisson, J., Lemoinne, S., Boulanger, C., Durand, F., Moreau, R., Valla, D., *et al*. (2017) Liver Sinusoidal Endothelial Cells: Physiology and Role in Liver Diseases. *Journal of Hepatology*, **66**, 212-227. https://doi.org/10.1016/j.jhep.2016.07.009

[16] Zheng, M. and Tian, Z. (2019) Liver-Mediated Adaptive Immune Tolerance. *Frontiers in Immunology*, **10**, Article 2525. https://doi.org/10.3389/fimmu.2019.02525

[17] Wang, Y., Zhong, X., He, X., Hu, Z., Huang, H., Chen, J., *et al*. (2023) Liver Metastasis from Colorectal Cancer: Pathogenetic Development, Immune Landscape of the Tumour Microenvironment and Therapeutic Approaches. *Journal of Experimental & Clinical Cancer Research*, **42**, Article No. 177. https://doi.org/10.1186/s13046-023-02729-7

[18] Brodt, P. (2016) Role of the Microenvironment in Liver Metastasis: From Pre-To Prometastatic Niches. *Clinical Cancer Research*, **22**, 5971-5982. https://doi.org/10.1158/1078-0432.ccr-16-0460

[19] Timmers, M., Vekemans, K., Vermijlen, D., Asosingh, K., Kuppen, P., Bouwens, L., *et al*. (2004) Interactions between Rat Colon Carcinoma Cells and Kupffer Cells during the Onset of Hepatic Metastasis. *International Journal of Cancer*, **112**, 793-802. https://doi.org/10.1002/ijc.20481

[20] Piñeiro Fernández, J., Luddy, K.A., Harmon, C. and O'Farrelly, C. (2019) Hepatic Tumor Microenvironments and Effects on NK Cell Phenotype and Function. *International Journal of Molecular Sciences*, **20**, Article 4131. https://doi.org/10.3390/ijms20174131

[21] Liu, X., Xu, J., Rosenthal, S., Zhang, L., McCubbin, R., Meshgin, N., *et al*. (2020) Identification of Lineage-Specific Transcription Factors That Prevent Activation of Hepatic Stellate Cells and Promote Fibrosis Resolution. *Gastroenterology*, **158**, 1728-1744.e14. https://doi.org/10.1053/j.gastro.2020.01.027

[22] Lee, J., Ung, A., Kim, H., Lee, K., Cho, H., Bandaru, P., *et al*. (2021) Engineering Liver Microtissues to Study the Fusion of HepG2 with Mesenchymal Stem Cells and Invasive Potential of Fused Cells. *Biofabrication*, **14**, Article 014104.

https://doi.org/10.1088/1758-5090/ac36de

[23] Mueller, L., Goumas, F.A., Affeldt, M., Sandtner, S., Gehling, U.M., Brilloff, S., *et al*. (2007) Stromal Fibroblasts in Colorectal Liver Metastases Originate from Resident Fibroblasts and Generate an Inflammatory Microenvironment. *The American Journal of Pathology*, **171**, 1608-1618. https://doi.org/10.2353/ajpath.2007.060661

[24] Taura, K., De Minicis, S., Seki, E., Hatano, E., Iwaisako, K., Osterreicher, C.H., *et al*. (2008) Hepatic Stellate Cells Secrete Angiopoietin 1 That Induces Angiogenesis in Liver Fibrosis. *Gastroenterology*, **135**, 1729-1738. https://doi.org/10.1053/j.gastro.2008.07.065

[25] Milette, S., Sicklick, J.K., Lowy, A.M. and Brodt, P. (2017) Molecular Pathways: Targeting the Microenvironment of Liver Metastases. *Clinical Cancer Research*, **23**, 6390-6399. https://doi.org/10.1158/1078-0432.ccr-15-1636

[26] Goodla, L. and Xue, X. (2022) The Role of Inflammatory Mediators in Colorectal Cancer Hepatic Metastasis. *Cells*, **11**, Article 2313. https://doi.org/10.3390/cells11152313

[27] Zhou, S., Zhou, Z., Hu, Z., Huang, X., Wang, Z., Chen, E., *et al*. (2016) Tumor-Associated Neutrophils Recruit Macrophages and T-Regulatory Cells to Promote Progression of Hepatocellular Carcinoma and Resistance to Sorafenib. *Gastroenterology*, **150**, 1646-1658.e17. https://doi.org/10.1053/j.gastro.2016.02.040

[28] Zhu, K., Li, P., Mo, Y., Wang, J., Jiang, X., Ge, J., *et al*. (2020) Neutrophils: Accomplices in Metastasis. *Cancer Letters*, **492**, 11-20. https://doi.org/10.1016/j.canlet.2020.07.028

[29] Yang, L., Liu, L., Zhang, R., Hong, J., Wang, Y., Wang, J., *et al*. (2020) IL-8 Mediates a Positive Loop Connecting Increased Neutrophil Extracellular Traps (Nets) and Colorectal Cancer Liver Metastasis. *Journal of Cancer*, **11**, 4384-4396. https://doi.org/10.7150/jca.44215

[30] Guerriero, J.L. (2019) Macrophages: Their Untold Story in T Cell Activation and Function. *International Review of Cell and Molecular Biology*, **342**, 73-93. https://doi.org/10.1016/bs.ircmb.2018.07.001

[31] Zhang, Y., Han, G., Gu, J., Chen, Z. and Wu, J. (2024) Role of Tumor-Associated Macrophages in Hepatocellular Carcinoma: Impact, Mechanism, and Therapy. *Frontiers in Immunology*, **15**, Article 1429812. https://doi.org/10.3389/fimmu.2024.1429812

[32] Komohara, Y., Fujiwara, Y., Ohnishi, K. and Takeya, M. (2016) Tumor-Associated Macrophages: Potential Therapeutic Targets for Anti-Cancer Therapy. *Advanced Drug Delivery Reviews*, **99**, 180-185. https://doi.org/10.1016/j.addr.2015.11.009

[33] Huang, Y., Snuderl, M. and Jain, R.K. (2011) Polarization of Tumor-Associated Macrophages: A Novel Strategy for Vascular Normalization and Antitumor Immunity. *Cancer Cell*, **19**, 1-2. https://doi.org/10.1016/j.ccr.2011.01.005

[34] Allavena, P., Sica, A., Solinas, G., Porta, C. and Mantovani, A. (2008) The Inflammatory Micro-Environment in Tumor Progression: The Role of Tumor-Associated Macrophages. *Critical Reviews in Oncology/Hematology*, **66**, 1-9. https://doi.org/10.1016/j.critrevonc.2007.07.004

[35] Boutilier, A.J. and Elsawa, S.F. (2021) Macrophage Polarization States in the Tumor Microenvironment. *International Journal of Molecular Sciences*, **22**, Article 6995. https://doi.org/10.3390/ijms22136995

[36] Huang, C., Ou, R., Chen, X., Zhang, Y., Li, J., Liang, Y., *et al*. (2021) Tumor Cell-Derived SPON2 Promotes M2-Polarized Tumor-Associated Macrophage Infiltration and Cancer Progression by Activating PYK2 in CRC. *Journal of Experimental & Clinical Cancer Research*, **40**, Article No. 304. https://doi.org/10.1186/s13046-021-02108-0

[37] Grossman, J.G., Nywening, T.M., Belt, B.A., Panni, R.Z., Krasnick, B.A., DeNardo, D.G., *et al*. (2018) Recruitment of $CCR2^+$ Tumor Associated Macrophage to Sites of Liver Metastasis Confers a Poor Prognosis in Human Colorectal Cancer. *OncoImmunology*, **7**, e1470729. https://doi.org/10.1080/2162402x.2018.1470729

[38] Donadon, M., Torzilli, G., Cortese, N., Soldani, C., Di Tommaso, L., Franceschini, B., *et al*. (2020) Macrophage Morphology Correlates with Single-Cell Diversity and Prognosis in Colorectal Liver Metastasis. *Journal of Experimental Medicine*, **217**, e20191847. https://doi.org/10.1084/jem.20191847

[39] Tosolini, M., Kirilovsky, A., Mlecnik, B., Fredriksen, T., Mauger, S., Bindea, G., *et al*. (2011) Clinical Impact of Different Classes of Infiltrating T Cytotoxic and Helper Cells (Th1, Th2, Treg, Th17) in Patients with Colorectal Cancer. *Cancer Research*, **71**, 1263-1271. https://doi.org/10.1158/0008-5472.can-10-2907

[40] Koyama, S. and Nishikawa, H. (2021) Mechanisms of Regulatory T Cell Infiltration in Tumors: Implications for Innovative Immune Precision Therapies. *Journal for ImmunoTherapy of Cancer*, **9**, e002591. https://doi.org/10.1136/jitc-2021-002591

[41] Qureshi, O.S., Zheng, Y., Nakamura, K., Attridge, K., Manzotti, C., Schmidt, E.M., *et al*. (2011) Trans-Endocytosis of CD80 and CD86: A Molecular Basis for the Cell-Extrinsic Function of CTLA-4. *Science*, **332**, 600-603. https://doi.org/10.1126/science.1202947

[42] Setoguchi, R., Hori, S., Takahashi, T. and Sakaguchi, S. (2005) Homeostatic Maintenance of Natural *Foxp*3^+ $CD25^+$ $CD4^+$ Regulatory T Cells by Interleukin (IL)-2 and Induction of Autoimmune Disease by IL-2 Neutralization. *The*

Journal of Experimental Medicine, **201**, 723-735. https://doi.org/10.1084/jem.20041982

[43] Masuda, K., Kornberg, A., Miller, J., Lin, S., Suek, N., Botella, T., *et al*. (2022) Multiplexed Single-Cell Analysis Reveals Prognostic and Nonprognostic T Cell Types in Human Colorectal Cancer. *JCI Insight*, **7**, e154646. https://doi.org/10.1172/jci.insight.154646

[44] Phanthunane, C., Wijers, R., De Herdt, M., Koljenović, S., Sleijfer, S., Baatenburg de Jong, R., *et al*. (2022) Intratumoral Niches of B Cells and Follicular Helper T Cells, and the Absence of Regulatory T Cells, Associate with Longer Survival in Early-Stage Oral Tongue Cancer Patients. *Cancers*, **14**, Article 4298. https://doi.org/10.3390/cancers14174298

[45] Liu, H., Li, Z., Han, X., Li, Z., Zhao, Y., Liu, F., *et al*. (2023) The Prognostic Impact of Tumor-Infiltrating B Lymphocytes in Patients with Solid Malignancies: A Systematic Review and Meta-Analysis. *Critical Reviews in Oncology/Hematology*, **181**, Article 103893. https://doi.org/10.1016/j.critrevonc.2022.103893

[46] Anderson, N.M. and Simon, M.C. (2020) The Tumor Microenvironment. *Current Biology*, **30**, R921-R925. https://doi.org/10.1016/j.cub.2020.06.081

[47] Fridman, W.H., Meylan, M., Petitprez, F., Sun, C., Italiano, A. and Sautès-Fridman, C. (2022) B Cells and Tertiary Lymphoid Structures as Determinants of Tumour Immune Contexture and Clinical Outcome. *Nature Reviews Clinical Oncology*, **19**, 441-457. https://doi.org/10.1038/s41571-022-00619-z

[48] Salmon, H., Idoyaga, J., Rahman, A., Leboeuf, M., Remark, R., Jordan, S., *et al*. (2016) Expansion and Activation of $CD103^+$ Dendritic Cell Progenitors at the Tumor Site Enhances Tumor Responses to Therapeutic PD-L1 and BRAF Inhibition. *Immunity*, **44**, 924-938. https://doi.org/10.1016/j.immuni.2016.03.012

[49] Merad, M., Sathe, P., Helft, J., Miller, J. and Mortha, A. (2013) The Dendritic Cell Lineage: Ontogeny and Function of Dendritic Cells and Their Subsets in the Steady State and the Inflamed Setting. *Annual Review of Immunology*, **31**, 563-604. https://doi.org/10.1146/annurev-immunol-020711-074950

[50] Xia, S., Guo, Z., Xu, X., Yi, H., Wang, Q. and Cao, X. (2008) Hepatic Microenvironment Programs Hematopoietic Progenitor Differentiation into Regulatory Dendritic Cells, Maintaining Liver Tolerance. *Blood*, **112**, 3175-3185. https://doi.org/10.1182/blood-2008-05-159921

[51] Liu, Y., Zhang, Q., Xing, B., Luo, N., Gao, R., Yu, K., *et al*. (2022) Immune Phenotypic Linkage between Colorectal Cancer and Liver Metastasis. *Cancer Cell*, **40**, 424-437.e5. https://doi.org/10.1016/j.ccell.2022.02.013

[52] Palucka, K. and Banchereau, J. (2012) Cancer Immunotherapy via Dendritic Cells. *Nature Reviews Cancer*, **12**, 265-277. https://doi.org/10.1038/nrc3258

[53] Vander Heiden, M.G., Cantley, L.C. and Thompson, C.B. (2009) Understanding the Warburg Effect: The Metabolic Requirements of Cell Proliferation. *Science*, **324**, 1029-1033. https://doi.org/10.1126/science.1160809

[54] Nieman, K.M., Kenny, H.A., Penicka, C.V., Ladanyi, A., Buell-Gutbrod, R., Zillhardt, M.R., *et al*. (2011) Adipocytes Promote Ovarian Cancer Metastasis and Provide Energy for Rapid Tumor Growth. *Nature Medicine*, **17**, 1498-1503. https://doi.org/10.1038/nm.2492

[55] Weinhouse, S. (1956) On Respiratory Impairment in Cancer Cells. *Science*, **124**, 267-269. https://doi.org/10.1126/science.124.3215.267

[56] Warburg, O., Wind, F. and Negelein, E. (1927) The Metabolism of Tumors in the Body. *Journal of General Physiology*, **8**, 519-530. https://doi.org/10.1085/jgp.8.6.519

[57] Wang, J.X., Choi, S.Y.C., Niu, X., Kang, N., Xue, H., Killam, J., *et al*. (2020) Lactic Acid and an Acidic Tumor Microenvironment Suppress Anticancer Immunity. *International Journal of Molecular Sciences*, **21**, Article 8363. https://doi.org/10.3390/ijms21218363

[58] Pucino, V., Certo, M., Bulusu, V., Cucchi, D., Goldmann, K., Pontarini, E., *et al*. (2019) Lactate Buildup at the Site of Chronic Inflammation Promotes Disease by Inducing $CD4^+$ T Cell Metabolic Rewiring. *Cell Metabolism*, **30**, 1055-1074.e8. https://doi.org/10.1016/j.cmet.2019.10.004

[59] Tanaka, A. and Sakaguchi, S. (2019) Targeting Treg Cells in Cancer Immunotherapy. *European Journal of Immunology*, **49**, 1140-1146. https://doi.org/10.1002/eji.201847659

[60] Sharma, M.D., Shinde, R., McGaha, T.L., Huang, L., Holmgaard, R.B., Wolchok, J.D., *et al*. (2015) The PTEN Pathway in T_{regs} Is a Critical Driver of the Suppressive Tumor Microenvironment. *Science Advances*, **1**, e1500845. https://doi.org/10.1126/sciadv.1500845

[61] Nakamura, T., Shima, T., Saeki, A., Hidaka, T., Nakashima, A., Takikawa, O., *et al*. (2007) Expression of Indoleamine 2, 3-Dioxygenase and the Recruitment of Foxp3-Expressing Regulatory T Cells in the Development and Progression of Uterine Cervical Cancer. *Cancer Science*, **98**, 874-881. https://doi.org/10.1111/j.1349-7006.2007.00470.x

[62] Hinshaw, D.C. and Shevde, L.A. (2019) The Tumor Microenvironment Innately Modulates Cancer Progression. *Cancer Research*, **79**, 4557-4566. https://doi.org/10.1158/0008-5472.can-18-3962

[63] Liu, H., Pan, M., Liu, M., Zeng, L., Li, Y., Huang, Z., *et al*. (2024) Lactate: A Rising Star in Tumors and Inflammation.

Frontiers in Immunology, **15**, Article 1496390. https://doi.org/10.3389/fimmu.2024.1496390

[64] Gottfried, E., Kunz-Schughart, L.A., Ebner, S., Mueller-Klieser, W., Hoves, S., Andreesen, R., *et al*. (2006) Tumor-derived Lactic Acid Modulates Dendritic Cell Activation and Antigen Expression. *Blood*, **107**, 2013-2021. https://doi.org/10.1182/blood-2005-05-1795

[65] Wculek, S.K., Cueto, F.J., Mujal, A.M., Melero, I., Krummel, M.F. and Sancho, D. (2019) Dendritic Cells in Cancer Immunology and Immunotherapy. *Nature Reviews Immunology*, **20**, 7-24. https://doi.org/10.1038/s41577-019-0210-z

[66] Cao, S., Liu, P., Zhu, H., Gong, H., Yao, J., Sun, Y., *et al*. (2015) Extracellular Acidification Acts as a Key Modulator of Neutrophil Apoptosis and Functions. *PLOS ONE*, **10**, e0137221. https://doi.org/10.1371/journal.pone.0137221

[67] Díaz, F.E., Dantas, E., Cabrera, M., Benítez, C.A., Delpino, M.V., Duette, G., *et al*. (2016) Fever-Range Hyperthermia Improves the Anti-Apoptotic Effect Induced by Low Ph on Human Neutrophils Promoting a Proangiogenic Profile. *Cell Death & Disease*, **7**, e2437. https://doi.org/10.1038/cddis.2016.337

[68] Brand, A., Singer, K., Koehl, G.E., Kolitzus, M., Schoenhammer, G., Thiel, A., *et al*. (2016) LDHA-Associated Lactic Acid Production Blunts Tumor Immunosurveillance by T and NK Cells. *Cell Metabolism*, **24**, 657-671. https://doi.org/10.1016/j.cmet.2016.08.011

[69] Mathew, M., Nguyen, N., Bhutia, Y., Sivaprakasam, S. and Ganapathy, V. (2024) Metabolic Signature of Warburg Effect in Cancer: An Effective and Obligatory Interplay between Nutrient Transporters and Catabolic/Anabolic Pathways to Promote Tumor Growth. *Cancers*, **16**, Article 504. https://doi.org/10.3390/cancers16030504

[70] Wagner, W., Kania, K.D., Blauz, A. and Ciszewski, W.M. (2017) The Lactate Receptor (HCAR1/GPR81) Contributes to Doxorubicin Chemoresistance via ABCB1 Transporter Up-Regulation in Human Cervical Cancer HeLa Cells. *Journal of Physiology and Pharmacology*, **68**, 555-564.