

肿瘤微环境对肿瘤代谢的影响及研究进展

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摘 要: 肿瘤能量代谢的重要特征为其主要通过糖酵解供能, 即众所周知的 Warburg 效应。肿瘤微环境不仅为肿瘤生长提供能量支持, 而且调控肿瘤信号通路, 促进肿瘤细胞的增殖、侵袭和转移。全文就肿瘤微环境及其对肿瘤代谢的调控作用进行综述。

关键词: 恶性肿瘤; 肿瘤微环境; 肿瘤代谢; Warburg 效应

中图分类号: R730.231 **文献标识码:** A **文章编号:** 1671-170X(2020)01-0047-06

doi: 10.11735/j.issn.1671-170X.2020.01.B011

Research Progress on Effect of Tumor Environment in Tumor Metabolic

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Abstract: Aerobic glycolysis is considered as a key feature of cancer metabolism, which is known as Warburg effect. The tumor environment supplies energy and also modulates signaling pathways in tumor cells and stimulate proliferation, invasion and metastasis. In recent years, tumor microenvironment and metabolism have become a hot spot in tumor research. The role of tumor environment in the tumor metabolism is reviewed in this article.

Subject words: malignant tumors; tumor environment; tumor metabolic; Warburg effect

1 肿瘤代谢生物学特性

正常情况下, 细胞将葡萄糖转化为丙酮酸, 然后进入三羧酸循环, 进行氧化磷酸化, 然而 Warburg 观察到, 与正常细胞相比, 肿瘤细胞即使在氧气供应充分的条件下, 也主要依靠糖酵解获取能量, 被称为 Warburg 效应^[1]。虽然糖酵解效率较低, 仅能产生 2 个 ATP, 氧化磷酸化可产生 36 个 ATP, 但显然对于肿瘤细胞, 糖酵解具有更明显的生存优势。首先, 糖酵解产生 ATP 的速度比氧化磷酸化快一百倍, 有利于肿瘤细胞竞争葡萄糖满足其代谢需求^[2-3]; 其次, 肿瘤细胞有氧糖酵解可再生还原分子 NAD⁺, 循环进入糖酵解或其他细胞必需的代谢途径; 第三, 糖酵

解有助于线粒体进行其他合成代谢: 产生细胞生长、有丝分裂必需的脂质, 氨基酸和核苷酸^[4]。此外, 肿瘤细胞糖酵解产生代谢废物乳酸, 使肿瘤微环境具有低葡萄糖、低氧和低酸碱度的特点。低氧环境有利于肿瘤血管生成, 也有助于通过提高 HIF-1 α 进一步诱导糖酵解^[5]。酸性肿瘤微环境(tumor microenvironment, TME)诱导肿瘤恶性表型, 用酸性培养基处理小鼠黑色素瘤细胞可以增加黑色素瘤细胞的肺部转移^[6]。因此, 以 Warburg 效应为基础的肿瘤能量代谢是肿瘤细胞与肿瘤微环境共同作用的结果。

2 肿瘤微环境生物学特性

在过去 20 年中, 一系列研究揭示了肿瘤微环境在调节肿瘤进程中的关键作用^[7]。目前观点认为, 肿瘤不仅仅是一种不受控制的细胞增殖疾病, 也是微环境失调导致的疾病。在肿瘤进展的各个阶段均能

基金项目: 浙江省卫生厅项目(2017RC001; 2018257154; 2018KY148)
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收稿日期: 2019-05-07; **修回日期:** 2019-09-18

发现肿瘤微环境参与肿瘤重塑的“踪迹”。例如,胰腺癌患者通常出现与肿瘤进展相关的恶性结缔组织化,提示肿瘤不良预后^[8]。肿瘤基质重塑基因如基质金属蛋白酶(matrix metalloproteinase, MMPs)和胶原蛋白的异常高表达是乳腺癌患者不良预后因子^[9]。组织纤维化也可以使患恶性肿瘤风险增加,肝硬化患者以胶原蛋白的积累异常为特征患肝癌的风险升高^[10]。研究肿瘤微环境的作用机制,探索肿瘤微环境与肿瘤细胞的相互作用是未来癌症研究的一个重要领域。肿瘤微环境组成复杂,包括成纤维细胞、免疫细胞、脂肪细胞、血管内皮细胞及细胞外基质等。

2.1 肿瘤相关成纤维细胞

肿瘤相关成纤维细胞(cancer-associated fibroblast, CAFs)是肿瘤微环境的主要成分,与正常成纤维细胞相比,CAFs是体积较大的纺锤形间充质细胞,参与肿瘤的发生、发展和转移^[11]。CAFs活性受肿瘤细胞分泌的生长因子调控,如转化生长因子 β 1(transforming growth factor beta 1, TGF- β 1)和血小板衍生生长因子(platelet-derived growth factor, PDGF)。另一方面,CAFs自身可以分泌成纤维细胞生长因子(fibroblast growth factor, FGF)、基质细胞衍生因子1(stromal cell derived factor 1, SDF1)、MMPs和胰岛素样生长因子1(insulin-like growth factor 1, IGF1)等,进一步促进肿瘤生长、血管生成和转移^[12]。此外,CAF激活后可以分泌趋化因子,诱导细胞外基质各细胞类型的募集,构成细胞外基质成分,促进肿瘤血管生成^[13]。

2.2 肿瘤相关免疫细胞

肿瘤相关免疫细胞包括巨噬细胞、T细胞、B细胞、自然杀伤细胞(natural killer cells, NK cells)和肿瘤相关中性粒细胞(tumor-associated neutral granule cells, TAN cells)等,参与肿瘤免疫反应,影响肿瘤微环境,调控肿瘤生长、转移。巨噬细胞是肿瘤微环境中含量最丰富的免疫细胞,位于肿瘤基质实体区域,根据其M1和M2亚型,对肿瘤进展(例如细胞增殖、转移和侵袭)发挥促进或抑制作用^[14]。此外,巨噬细胞可分泌血管内皮细胞生长因子(vascular endothelial cell growth factor, VEGF),促进肿瘤血管新生^[15];T细胞包括细胞杀伤性T细胞, $\alpha\beta$ -T细胞和 $\gamma\delta$ -T细胞,CD8+T细胞可以杀伤肿瘤细胞,CD4+T细胞在肿瘤免疫反应中发挥重要作用^[16]。树突细胞

可以激活B细胞,NK细胞和NK-T细胞,诱导、维持肿瘤免疫反应,广泛用于癌症免疫治疗^[17];B细胞可以分泌IL10和IgG等细胞因子影响肿瘤和微环境中其他细胞的功能^[18];TAN细胞在促血管新生中发挥重要作用,还可以释放基质金属蛋白酶9(matrix metalloproteinase 9, MMP9)影响肿瘤迁移^[19]。

2.3 肿瘤相关脂肪细胞

脂肪组织通常被认为主要用于能量存储,自1994年发现瘦素后,陆续发现脂肪细胞能够调节全身能量和代谢稳态。脂肪细胞通过分泌脂质、脂肪因子和细胞因子等共同参与构成肿瘤微环境,如肝细胞生长因子和脂联素,促进肿瘤细胞的粘附、迁移和侵袭,调控炎症反应,影响肿瘤恶性进展和增殖^[20]。脂肪细胞因子影响多种生物学过程,包括葡萄糖和脂肪酸代谢、脂肪细胞分化、免疫反应^[21]。脂肪细胞释放的游离脂肪酸一方面可以作为肿瘤细胞代谢的能量来源,另外,游离脂肪酸可以激活微环境中的巨噬细胞和血管内皮细胞,维持肿瘤微环境的功能稳定^[22]。此外,脂肪细胞可以分泌炎症细胞因子,如TNF- α , IL-6, IL-1 β 和CCL2,调控肿瘤免疫反应^[23]。

2.4 肿瘤血管内皮细胞

1971年Judah Folkman提出所有肿瘤都依赖于血管生成,血管不仅为肿瘤提供生长所需的氧气和营养,也为肿瘤转移提供途径,其通过激活VEGF信号轴,诱导肿瘤细胞渗入肿瘤血管,促进肿瘤转移^[24-25]。肿瘤血管内皮细胞受到肿瘤细胞分泌的多种细胞因子及信号通路的调控。例如,肿瘤细胞通过分泌VEGF作用于血管内皮细胞,使肿瘤血管通透性升高,增加肿瘤组织间隙液压,细胞增殖、转移异常活跃,血管生成相关基因异常高表达等促血管生成特性^[26]。

2.5 肿瘤细胞外基质

肿瘤细胞外基质(tumor extracellular matrix, ECM)是指在肿瘤微环境中,为肿瘤细胞提供生化成分和基本结构支持的非细胞成分。ECM不只用作细胞间填充物,是负责细胞间通讯,参与细胞增殖和粘附的活性物质^[27]。ECM由胶原蛋白、蛋白多糖、层粘连蛋白和网络连接蛋白等组成。胶原蛋白是ECM中最重要的成分,分为I型、II型、III型、V型和XI型胶原;可通过重塑、降解影响肿瘤细胞粘附,促进基底

膜损伤,诱导肿瘤血管新生,促进肿瘤恶性进展^[28];蛋白多糖一方面能够隔离水和阳离子,保证肿瘤微环境的空间和结构稳定。另一方面,介导了粘附、转移、血管新生等肿瘤恶性进程^[29];黏连蛋白是由 α 、 β 、 γ 链组成的三聚糖蛋白,除了可以影响细胞分化、迁移、凋亡外,还能够通过整合素调控肿瘤细胞与ECM之间的动态联系^[30];纤连蛋白是一种多结构域蛋白质,与ECM中其他蛋白存在多个结合位点,影响胶原蛋白的组装。研究表明,在ECM中缺乏纤连蛋白时胶原纤维无法积聚^[31]。

2.6 针对肿瘤微环境的治疗方法

肿瘤微环境作为肿瘤赖以生存的基础,为肿瘤的增殖、转移、侵袭提供物质基础。目前针对肿瘤微环境的治疗方法包括靶向肿瘤新生血管、肿瘤微环境基质细胞、抑制肿瘤免疫逃逸等^[32]。靶向抑制VEGF的贝伐珠单抗是第一个也是目前为止最成功的针对肿瘤微环境的靶向药,可提高非小细胞肺癌及转移性结直肠癌患者生存率^[33]。尽管肿瘤新生血管靶向药层出不穷,但其仅能针对部分肿瘤类型,且用药后极易产生药物耐受。通过调控肿瘤微环境中的各类基质细胞(如肿瘤相关脂肪细胞)以及细胞因子(如IL-6,IL-12)影响肿瘤微环境性质,逆转低氧、偏酸性环境,一方面可抑制肿瘤细胞生存,另外也可以影响肿瘤微环境中免疫抑制因子的释放,从而达到清除肿瘤细胞,逆转药物耐受的作用^[34-35]。由于肿瘤微环境的复杂性,考虑到其与肿瘤免疫系统以及肿瘤代谢之间密切的相互作用,联合治疗将是未来肿瘤治疗的发展方向,进一步提高对肿瘤微环境调控机制的了解,将有助于开发更加具有针对性的治疗方案。

3 肿瘤微环境与肿瘤代谢相互作用

3.1 CAFs 与肿瘤代谢

CAFs是肿瘤微环境中的主要组分,越来越多的证据表明,CAFs可通过调控信号通路,影响肿瘤代谢途径,在肿瘤生长、转移中发挥作用^[36]。研究发现,CAFs细胞中也存在Warburg效应,为与癌细胞区分,将其命名为逆向Warburg效应^[37]。微囊蛋白1(caveolin-1,Cav-1)通过降低TGF- β 抑制CAF的活性,蛋白质组学研究发现,Cav-1敲除时糖酵解相关酶

显著性上调,包括丙酮酸激酶和乳酸脱氢酶A等^[38]。另外Cav-1敲除的成纤维细胞在常氧条件下,通过升高细胞中活性氧(reactive oxygen species,ROS),稳定HIF-1 α 。HIF-1 α 通过以下途径促进肿瘤糖酵解^[39]:①介导葡萄糖转运蛋白过表达,增加葡萄糖摄取,激活糖酵解;②活化糖酵解酶如Glut,HK-2,PKM-2,LDH-A;增加LDH-A表达,促进乳酸生成;③通过上调PDK-1降低丙酮酸转化为乙酰-CoA。当用CAF条件培养基刺激胰腺癌细胞时,肿瘤糖酵解增强,细胞中单羧酸转运蛋白1(mono-carboxylate transporter 1,MCT1)等表达显著性增加^[40],证明肿瘤相关成纤维细胞对肿瘤代谢的关键调控作用。

3.2 肿瘤相关免疫细胞与肿瘤代谢

当T细胞进入肿瘤微环境杀伤肿瘤细胞时,代谢调控信号通路会抑制其正常功能,称为代谢检查点。例如葡萄糖含量降低可以下调IFN- γ 转录,抑制T细胞增殖^[41],肿瘤细胞通过竞争葡萄糖摄入,调控T细胞代谢,进而抑制T细胞活化,实现免疫逃逸^[42-43]。此外,低氧对T细胞的合成和功能至关重要,在细胞和动物模型中发现,低氧可以抑制T细胞增殖。通过给荷瘤小鼠补充氧气,缓解微环境缺氧后,T细胞浸润增加,促炎细胞因子表达上调,肿瘤生长受到抑制,小鼠存活率升高^[44]。因此,肿瘤糖酵解诱导的低氧、酸性微环境,会引起代谢介导的T细胞功能障碍,这可能是肿瘤细胞代谢重编程介导免疫逃逸的机制之一。

3.3 肿瘤相关脂肪细胞与肿瘤代谢

肿瘤微环境中的脂肪细胞主要参与调控肿瘤的能量稳态。成熟的脂肪细胞能够产生ROS,诱导肿瘤细胞有丝分裂^[45]。距离肿瘤血管较远的脂肪细胞会发生局部缺氧,激活HIF-1 α ,激活肿瘤相关巨噬细胞和单核细胞^[46]。脂肪细胞可以通过AMPK信号通路,促进肿瘤细胞增殖、转移,诱导血管新生^[47]。研究发现线粒体损伤可能是导致脂肪细胞代谢失调的关键原因,确切的分子机制还有待研究,目前发现可能与激活AKT信号通路,抑制p53和PTEN的正常功能有关^[48]。进一步了解脂肪细胞的代谢特征将有助于针对肿瘤代谢重编程设计新的治疗策略。

3.4 肿瘤血管内皮细胞与肿瘤代谢

肿瘤血管内皮细胞的代谢与正常内皮细胞不同,主要依靠糖酵解供能^[49]。可能原因包括:首先,肿

瘤血管内皮细胞需要优先保证向组织细胞运输足量氧气;其次,糖酵解产生 ATP 更快,更能满足 EC 的增殖和迁移需要;另外,糖酵解途径不依赖氧气,有利于肿瘤通过新生血管向缺氧区域的迁移,无需调整代谢方式。VEGF 可以激活糖酵解限速酶:6 磷酸果糖 2 激酶/果糖-2,6-二磷酸酶 3(6-phosphofructo-2-kinase/fructose-2,6-biphosphatase 3,PFKFB3)表达上调,增强内皮细胞糖酵解。PFKFB3 可通过调节 CD163+肿瘤相关巨噬细胞在口腔鳞状细胞癌中的渗透,促进肿瘤转移、血管生成^[50]。上述研究说明同时靶向肿瘤血管新生和肿瘤代谢可能具有协同抗肿瘤作用,但是目前针对肿瘤相关血管内皮细胞的代谢研究仍处于起步阶段,PFKFB3 阻断剂在减少血管生成的同时会引发严重的全身不良反应。因此,需要更深入地研究肿瘤血管内皮细胞的代谢调控网络,以实现抗肿瘤疗效与不良反应之间的平衡。

3.5 ECM 与肿瘤代谢

ECM 对于肿瘤细胞摄取微环境中的营养成分以及生成功能性 ATP 至关重要。纤连蛋白作为 ECM 蛋白,其 EDA 片段可以刺激葡萄糖转运蛋白 GLUT1 的转录及表达,增加肿瘤的葡萄糖摄取率^[51]。黏着斑信号传导途径介导 ECM 信号传递反过来激活肿瘤细胞 PI3K 信号通路,促进 GLUT1 和 GLUT4 蛋白过表达以及胞内葡萄糖的摄入,诱导肿瘤糖酵解^[52]。Ras 和 Myc 等致癌基因促进谷氨酸转化为谷氨酰胺,增强蛋白质生物合成,维持肿瘤细胞恶性增殖^[53]。反过来,肿瘤糖酵解诱导的低氧微环境激活 HIF-1 α ,导致 C-MET 过表达,引起肿瘤外基质降解,进一步导致肿瘤侵袭、转移^[54]。说明肿瘤外基质与肿瘤细胞通过代谢相互作用,共同促进了肿瘤的恶性演进。

越来越多的数据表明,肿瘤细胞不仅依靠葡萄糖供能,肿瘤微环境为肿瘤生长提供了巨大的能量支持。针对肿瘤代谢功能的研究初步揭示了肿瘤进展和转移性扩散的能量来源,但是调控肿瘤代谢的分子机制仍然没有完全阐明。在未来的研究中,我们需要更为深入地研究肿瘤微环境,特别是肿瘤相关成纤维细胞和肿瘤免疫细胞如何具体参与肿瘤细胞的能量代谢。深入研究肿瘤细胞以及肿瘤微环境的能量代谢作用网络,将有助于更好地理解肿瘤恶性演进。

参考文献:

- [1] Warburg O, Wind F, Negelstein E. The metabolism of tumors in the body[J]. *J Gen Physiol*, 1927, 8(6):519-530.
- [2] Pfeiffer T, Schuster S, Bonhoeffer S. Cooperation and competition in the evolution of ATP-producing pathways [J]. *Science*, 2001, 292(5516):504-507.
- [3] Martinez-Outschoorn UE, Peiris-Pagés, Pestell RG, et al. Cancer metabolism: a therapeutic perspective[J]. *Nat Rev Clin Oncol*, 2017, 14(1):11-31.
- [4] Icard P, Shulman S, Farhat D, et al. How the Warburg effect supports aggressiveness and drug resistance of cancer cells[J]. *Drug Resist Update*, 2018, 5(38):1-11.
- [5] Hu L, Rui C, Liu H, et al. Emodin and rhein decrease levels of hypoxia-inducible factor-1 α in human pancreatic cancer cells and attenuate cancer cachexia in athymic mice carrying these cells[J]. *Oncotarget*, 2017, 8(50):88008-88020.
- [6] Zhang T, Suo C, Zheng C. Hypoxia and metabolism in metastasis[J]. *Adv Exp Med Biol*, 2019, 1136:87-95.
- [7] Walker C, Mojares E, Del Río Hernández A. Role of extracellular matrix in development and cancer progression [J]. *Int J Mol Sci*, 2018, 19(10):pii:E3028.
- [8] Mayerle J, Kaltho H, Reszka R, et al. Metabolic biomarker signature to differentiate pancreatic ductal adenocarcinoma from chronic pancreatitis [J]. *Gut*, 2017, 67 (1):128-137.
- [9] Pally D, Pramanik D, Bhat R. An interplay between reaction-diffusion and cell-matrix adhesion regulates multi-scale invasion in early breast carcinomatosis [J]. *Front Physiol*, 2019, 10:790.
- [10] Primac I, Maquoi E, Blacher S, et al. Stromal integrin $\alpha 11$ regulates PDGFR- β signaling and promotes breast cancer progression[J]. *J Clin Invest*, 2019, 130:4609-4628.
- [11] Fiori ME, Franco SD, Villanova L, et al. Cancer-associated fibroblasts as abettors of tumor progression at the crossroads of EMT and therapy resistance [J]. *Mol Cancer*, 2019, 18(1):70.
- [12] Shiga K, Hara M, Nagasaki T, et al. Cancer-associated fibroblasts: their characteristics and their roles in tumor growth[J]. *Cancers (Basel)*, 2015, 7(4):2443-2458.
- [13] Kim BG, Sung JS, Jang Y, et al. Compression-induced expression of glycolysis genes in CAFs correlates with EMT and angiogenesis gene expression in breast cancer [J]. *Commun Biol*, 2019, 2:313.
- [14] Mahlbacher G, Curtis LT, Lowengrub J, et al. Mathematical modeling of tumor-associated macrophage interactions with the cancer microenvironment [J]. *J Immunother Can-*

- cer, 2018, 6(1): 10.
- [15] Ando N, Hara M, Shiga K, et al. Eicosapentaenoic acid suppresses angiogenesis via reducing secretion of IL-6 and VEGF from colon cancer-associated fibroblasts [J]. *Oncol Rep*, 2019, 42(1): 339–349.
 - [16] Gorchakov AA, Kulemzin SV, Kochneva GV, et al. Challenges and prospects of chimeric antigen receptor T-cell therapy for metastatic prostate cancer [J]. *Eur Urol*, 2019, S0302–2838(19)30658–X.
 - [17] Garofano F, Gonzalez-Carmona MA, Skowasch D, et al. Clinical trials with combination of cytokine-induced killer cells and dendritic cells for cancer therapy [J]. *Int J Mol Sci*, 2019, 20(17): 4307.
 - [18] Wennhold K, Shimabukuro-Vornhagen A, von Bergwelt-Baildon M. B cell-based cancer immunotherapy [J]. *Transfus Med Hemother*, 2019, 46(1): 36–46.
 - [19] Granot Z. Neutrophils as a therapeutic target in cancer [J]. *Front Immunol*, 2019, 10: 1710.
 - [20] Allegra A, Innao V, Gerace D, et al. The adipose organ and multiple myeloma: impact of adipokines on tumor growth and potential sites for therapeutic intervention [J]. *Eur J Intern Med*, 2018, 53: 12–20.
 - [21] Dirat B, Bochet L, Escourrou G, et al. Unraveling the obesity and breast cancer links: a role for cancer-associated adipocytes? [J]. *Endocr Dev*, 2010, 19: 45–52.
 - [22] Liang P, Henning SM, Guan J, et al. Effect of dietary omega-3 fatty acids on castrate-resistant prostate cancer and tumor-associated macrophages [J]. *Prostate Cancer Prostatic Dis*, 2019, Aug 22. [Epub ahead of print]
 - [23] Springer NL, Iyengar NM, Bareja R, et al. Obesity-associated extracellular matrix remodeling promotes a macrophage phenotype similar to tumor-associated macrophages [J]. *Am J Pathol*, 2019, 16 (18): 30607–30612.
 - [24] Hida K, Maishi N, Annan DA, et al. Contribution of tumor endothelial cells in cancer progression [J]. *Int J Mol Sci*, 2018, 19(5): pii: E1272.
 - [25] Li B, Hong J, Hong M, et al. piRNA-823 delivered by multiple myeloma-derived extracellular vesicles promoted tumorigenesis through re-educating endothelial cells in the tumor environment [J]. *Oncogene*, 2019, 38(26): 5227–5238.
 - [26] Schaaf MB, Houbaert D, Meçe O, et al. Lysosomal pathways and autophagy distinctively control endothelial cell behavior to affect tumor vasculature [J]. *Front Oncol*, 2019, 9: 171.
 - [27] Niklason LE. Understanding the extracellular matrix to enhance stem cell-based tissue regeneration [J]. *Cell Stem Cell*, 2018, 22(3): 302–305.
 - [28] Zhang R, Ma M, Lin XH, et al. Extracellular matrix collagen I promotes the tumor progression of residual hepatocellular carcinoma after heat treatment [J]. *BMC Cancer*, 2018, 18(1): 901.
 - [29] Cerezo-Magaña M, Bång-Rudensam A, Belting M. The pleiotropic role of proteoglycans in extracellular vesicle mediated communication in the tumor microenvironment [J]. *Semin Cancer Biol*, 2019, Jul 2. [Epub ahead of print]
 - [30] Sun T, Patil R, Galstyan A, et al. Blockade of a laminin-411-notch axis with CRISPR/Cas9 or a nanobioconjugate inhibits glioblastoma growth through tumor-microenvironment cross-talk [J]. *Cancer Res*, 2019, 79(6): 1239–1251.
 - [31] Xiaodi T, Hayat M, Celia ML, et al. Connective tissue growth factor contributes to joint homeostasis and osteoarthritis severity by controlling the matrix sequestration and activation of latent TGFβ [J]. *Ann Rheum Dis*, 2018, 77(9): 1372–1380.
 - [32] Bian X, Xiao YT, Wu T, et al. Microvesicles and chemokines in tumor microenvironment: mediators of intercellular communications in tumor progression [J]. *Molecular Cancer*, 2019, 18(1): 50.
 - [33] Kabbinavar F, Hurwitz HI, Fehrenbacher L, et al. Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer [J]. *J Clin Oncol*, 2003, 21(1): 60–65.
 - [34] Li I, Nabet BY. Exosomes in the tumor microenvironment as mediators of cancer therapy resistance [J]. *Molecular Cancer*, 2019, 18(1): 32.
 - [35] Hanoteau A, Newton JM, Krupar R, et al. Tumor microenvironment modulation enhances immunologic benefit of chemoradiotherapy [J]. *J Immunotherapy Cancer*, 2019, 7(1): 10.
 - [36] Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression [J]. *Cancer Res*, 2019, 79(18): 4557–4566.
 - [37] Lee M, Yoon JH. Metabolic interplay between glycolysis and mitochondrial oxidation: the reverse Warburg effect and its therapeutic implication [J]. *World J Biol Chemistry*, 2015, 6(3): 148–161.
 - [38] Sotgia F, Martinez Outschoorn UE, Howell A, et al. Caveolin-1 and cancer metabolism in the tumor microenvironment: markers, models, and mechanisms [J]. *Annu Rev Pathol*, 2012, 7: 423–467.
 - [39] Ngwa VM, Edwards DN, Philip M, et al. Microenviron-

- mental metabolism regulates antitumor Immunity[J]. *Cancer Res*, 2019, 79(16):4003–4008.
- [40] Hong CS, Graham NA, Gu W, et al. MCT1 modulates cancer cell pyruvate export and growth of tumors that co-express MCT1 and MCT4[J]. *Cell Rep*, 2016, 14(7):1590–1601.
- [41] Agrawal B. New therapeutic targets for cancer; the interplay between immune and metabolic checkpoints and gut microbiota[J]. *Clin Transl Med*, 2019, 8(1):23.
- [42] Chang CH, Qiu J, O'Sullivan D, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression [J]. *Cell*, 2015, 162(6):1229–1241.
- [43] Ho PC, Bihuniak JD, Macintyre AN, et al. Phosphoenolpyruvate is a metabolic checkpoint of antitumor T cell responses [J]. *Cell*, 2015, 162(6):1217–1228.
- [44] Hatfield SM, Kjaergaard J, Lukashev D, et al. Immunological mechanisms of the antitumor effects of supplemental oxygenation[J]. *Sci Transl Med*, 2015, 7(277):277ra30.
- [45] Wang C, Shao L, Pan C, et al. Elevated level of mitochondrial reactive oxygen species via fatty acid β -oxidation in cancer stem cells promotes cancer metastasis by inducing epithelial-mesenchymal transition[J]. *Stem Cell Res Ther*, 2019, 10(1):175.
- [46] Wakui M, Kawai K, Mizushima T, et al. Fatty Acid β -Oxidation-dependent and -independent responses and tumor aggressiveness acquired under mild hypoxia[J]. *Anticancer Res*, 2019, 39(1):191–200.
- [47] Lu T, Sun L, Wang Z, et al. Fatty acid synthase enhances colorectal cancer cell proliferation and metastasis via regulating AMPK/mTOR pathway[J]. *Onco Targets Ther*, 2019, 12:3339–3347.
- [48] Kim WY. Therapeutic targeting of lipid synthesis metabolism for selective elimination of cancer stem cells[J]. *Arch Pharm Res*, 2019, 42(1):25–39.
- [49] Ranieri G. Biological basis of tumor angiogenesis and therapeutic intervention: past, present, and future [J]. *Int J Mol Sci*, 2018, 19(6):1655–1658.
- [50] Li JJ, Mao XH, Tian T, et al. Role of PFKFB3 and CD163 in oral squamous cell carcinoma angiogenesis [J]. *Curr Med Sci*, 2019, 39(3):410–414.
- [51] Rick JW, Chandra A, Dalle Ore C. Fibronectin in malignancy: cancer-specific alterations, protumoral effects, and therapeutic implications[J]. *Semin Oncol*, 2019, 7754(18):30272–30280.
- [52] Romani P, Brian I, Santinon G, et al. Extracellular matrix mechanical cues regulate lipid metabolism through lipin-1 and SREBP[J]. *Nat Cell Biol*, 2019, 21(3):338–347.
- [53] Zhang J, Hochwald SN. The role of FAK in tumor metabolism and therapy [J]. *Pharmacol Ther*, 2014, 142(2):154–163.
- [54] Ni WD, Yang ZT, Cui CA, et al. Tenascin-C is a potential cancer-associated fibroblasts marker and predicts poor prognosis in prostate cancer [J]. *Biochem Biophys Res Commun*, 2017, 486(3):607–612.