

单羧酸转运蛋白的肿瘤临床应用进展

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摘要: 肿瘤细胞由于存在代谢重编程的特性表现出高糖酵解率, 导致乳酸过量产生以及细胞外酸度增加。单羧酸转运蛋白(monocarboxylate transporter, MCT)通过介导跨细胞膜的质子耦合乳酸转运, 对维持这种代谢表型至关重要, 也有助于肿瘤细胞 pH 值调节。溶质载体 16 (solute carrier 16, SLC16) 基因家族编码的蛋白质 MCT1 和 MCT4 亚型在实体瘤和血液恶性肿瘤等多种肿瘤中过度表达。与特定生理环境中发生的情况类似, MCT1 和 MCT4 能够介导肿瘤细胞之间以及肿瘤微环境中的肿瘤和基质细胞之间的乳酸穿梭。这种形式的代谢合作方式是引起多种重要的肿瘤侵袭性特征的原因, 包括细胞增殖、存活、血管生成、迁移、侵袭、转移、免疫耐受和治疗抵抗。对 MCT 功能调节了解的日益深入为临床实践中可预见的新型抑制剂的设计提供了新途径。全文概述 MCT 亚型在肿瘤中的作用, 总结其药理学靶向的最新进展, 以及新型有效的选择性 MCT1 和/或 MCT4 抑制剂在肿瘤治疗中的潜力。

关键词: 糖酵解; 乳酸; 单羧酸转运蛋白; 肿瘤治疗

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Progress in Clinical Application of Monocarboxylate Transporters in Tumors

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Abstract: Tumor cells exhibit high rates of glycolysis due to the presence of metabolic reprogramming, resulting in excessive lactate production as well as increased extracellular acidity. Proton-linked monocarboxylate transporter (MCT) are essential for maintaining this metabolic phenotype by mediating proton-coupled lactate transport across cell membranes and also contribute to tumor cell pH regulation. Among the proteins encoded by the SLC16 gene family, the MCT1 and MCT4 subtypes are the most studied in tumors, and they are overexpressed in a variety of tumor types, such as solid tumors and hematologic malignancies. Similar to what occurs in specific physiological environments, MCT1 and MCT4 are able to mediate lactate shuttling between tumor cells and between tumor and stromal cells in the tumor microenvironment. This form of metabolic cooperative mode is responsible for important tumor aggressive features, including cell proliferation, survival, angiogenesis, migration, invasion, metastasis, immune tolerance, and treatment resistance. The growing understanding of the functional regulation of MCTs provides a new avenue for the design of novel inhibitors that are foreseeable in clinical practice. This review provides an overview of the role of MCT subtypes in tumors, summarizes recent advances in their pharmacological targeting, and summarizes the potential of novel potent and selective MCT1 and/or MCT4 inhibitors in cancer therapy.

Subject words: glycolysis; lactic acid; monocarboxylate transporter; oncology treatment

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在复杂的肿瘤微环境 (tumour microenvironment, TME) 中, 大多数肿瘤细胞的代谢模式转变为糖酵解速率升高, 从而产生乳酸增加, 这是一个公认的肿瘤代谢特征^[1]。对于每个葡萄糖分子而言, 糖酵解较氧化磷酸化在能量产生方面产能效率低, 但是肿瘤细胞仍然倾向于优先依赖糖酵解^[2]。葡萄糖转化为乳酸是由乳酸脱氢酶 (lactate dehydrogenase, LDH) 催化的^[3]。在实体瘤的进展和转移过程中, 肿瘤细胞适应重新编程的糖酵解、氧化应激和缺氧, 这是一种由缺氧诱导因子 (hypoxia-inducible factor, HIF)、髓细胞增生原癌基因 (c-Myc)、RAS 和其他因子控制的生存机制^[4-5]。在这些压力条件下, 肿瘤细胞通过葡萄糖发酵产生的乳酸可以被氧化肿瘤细胞用作氧化磷酸化的燃料, 而不是将葡萄糖作为燃料 (Figure 1)^[6]。肿瘤糖酵解产生的过量乳酸引起细胞外酸化, 其形成过程是通过单羧酸转运蛋白 (monocarboxylate transporter, MCT) 将其转运到细胞外部 (当发生代谢共生时也可以转运到细胞内部)^[7]。综上, 乳酸不仅为一种代谢废物, 而且还是肿瘤和其他一些疾病中的必需代谢物, 在生理条件下也发挥着重要作用^[8]。

MCT 由溶质载体 16 (solute carrier 16, SLC16) 基因家族编码, 参与立体选择性和双向 (细胞内和细胞外) 质子连接的乳酸运输^[9-10]。该基因家族由 14 个成员 (SLC16A1 至 SLC16A14) 组成, 编码 14 个跨膜相应蛋白 (MCT1~14), 参与跨生物膜运输各种营

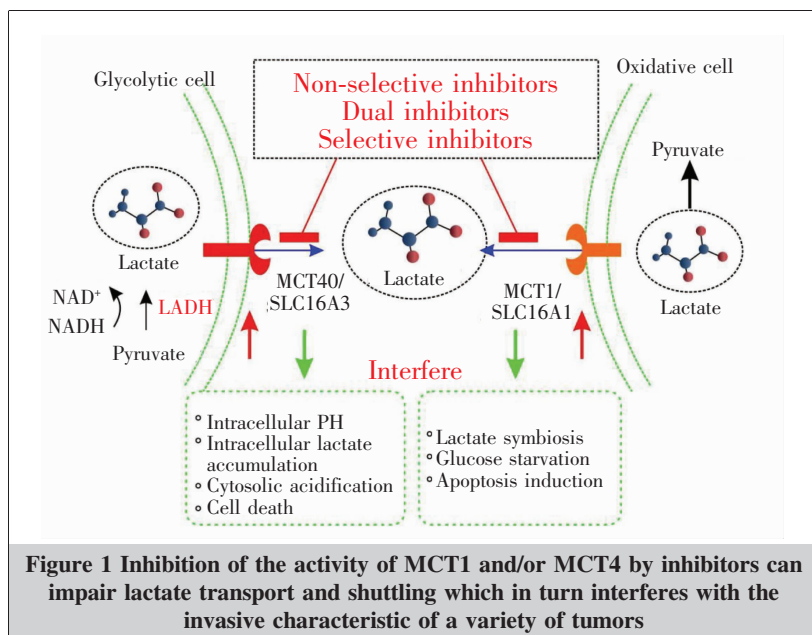
养物质、质子和代谢物^[11]。编码 MCT1~4 的 4 个基因已得到表征并得到广泛探索^[12]。MCT1~4 具有共同的单羧酸底物, 例如乳酸盐、丙酮酸盐、d-β-羟基丁酸盐和乙酰乙酸盐。这些必需代谢物的运输是细胞基本生物过程的重要需求^[10, 13]。在哺乳动物中, MCT1~4 是唯一通过质子同向机制转运单羧酸盐的成员^[10, 14]。这些 MCT 具有组织和底物特异性表达模式, 它们在生物过程中发挥着至关重要的作用^[15]。

1 MCT1~4 的表达和底物亲和力

MCT1 在多种组织中普遍表达, 而 MCT2 主要在肝脏、肾脏、睾丸和大脑中表达。MCT3 主要在视网膜色素脉络丛上皮细胞中表达, 并将乳酸转运到这些细胞外, MCT4 主要在糖酵解组织中表达, 包括白色骨骼肌、星形胶质细胞和白细胞^[10, 16-17]。

MCT1 对单羧酸盐表现出中等亲和力, 通常使用 Michaelis-Menten constant (Km 值) 来衡量, 它是酶促反应动力学中的一个关键参数, 反映了酶与底物的亲和力, 并且受到多种因素的影响。通过测定 Km 值, 可以更深入地理解酶的催化特性及其在生物体内的生理功能。而 MCT1 对单羧酸盐的 Km 值在 1.0~12.5 mmol/L 范围内, 而对乳酸的 Km 值则为 3.5~10.0 mmol/L。MCT2 在 Km 值 0.1~1.2 mmol/L 范围内对单羧酸盐表现出最高的亲和力, 对 L-乳酸的亲和力为 0.5~0.7 mmol/L。MCT3 对乳酸的亲和力与

MCT1 相当, 但比 MCT4 更高, 其对单羧酸盐的 Km 值在 5~6 mmol/L 范围内, 对乳酸的 Km 值在 22~28 mmol/L 范围内。MCT4 对 L-乳酸和丙酮酸的 Km 值分别确定为 28 mmol/L 和 150 mmol/L。MCT4 对乳酸的亲和力高于丙酮酸, 有助于了解 MCT4 在高度糖酵解组织中的优先表达, 因为这些亲和力差异使 MCT4 表达细胞能够在富含乳酸的环境中输出乳酸; 通过这种方式, 丙酮酸向乳酸的转化和 NAD⁺ 的恢复得以维持, 这是连续糖酵解通量所必需的。表达 MCT1 的细胞无法避免丙酮酸损失, 因为丙酮酸 Km 水平 (0.7 mmol/L) 高于乳酸^[11, 17-18]。



2 正常组织和癌组织中 MCT 表达的调控

正常组织中的 MCT 表达以不同的方式进行调节,发生在转录和转录后水平。运动促进骨骼肌中 *MCT1/SLC16A1* 和 *MCT4/SLC16A3* 基因表达的上调,其上调是通过增加钙和 1-磷酸腺苷(adenosine monophosphate, AMP)介导的,从而激活 AMP 激活蛋白激酶(AMP-activated protein kinase, AMPK)和过氧化物酶体增殖物激活受体 γ 共激活剂 1- α (PGC-1 α)途径。另一方面,AMPK 激活导致支持细胞中这些转运蛋白基因的下调^[18-20]。缺氧是 MCT4 表达的主要调节因子,通过与基因启动子区域的缺氧反应元件(hypoxia response elements, HRE)相互作用,从而稳定 HIF-1 α 转录因子来介导^[21]。

关于 MCT 的翻译控制的证据知之甚少,除了 MCT1 中半胱氨酸残基的抑制性 S-亚硝化外,对 MCT 翻译后修饰的研究仍然缺乏;然而,这种修饰是通过药理学诱导的,其在正常和病理条件下的相关性仍有待阐明。MCT1~4 在质膜上的稳定性、定位和功能需要与 CD147/basigin(一种高度糖基化的单次跨膜蛋白)和 gp70/embigin 等蛋白质伴侣相互作用^[22]。MCT 和分子伴侣之间的相互作用促进乳酸跨膜转运,并且在功能上相互依赖,因此其中一种分子的沉默通常会下调另一种分子的表达。功能活跃的 MCT1 形成二聚体,与细胞膜上的 CD147 相互作用,进一步招募其他蛋白质并形成超级复合物。例如, MCT1 和 MCT4 与碳酸酐酶相互作用^[23], MCT4 与上皮细胞中的 β 1-整合素相互作用^[24]。

MCT 在肿瘤中表达的调节机制尚不完全清楚,但其机制与正常组织相似。P53 肿瘤抑制基因直接与 *MCT1* 的启动子区域结合,并改变 *MCT1* mRNA 的稳定性以抑制转录。体外和体内研究表明, P53 基因的缺失增强了 MCT1 的表达,同时通过高糖酵解通量导致乳酸流出^[25]。c-Myc 癌蛋白可控制 *SLC16A1/MCT1* 的转录^[26]。涉及 *MCT1* 作为直接靶基因的信号通路,例如 Wnt、NF- κ B 和转移相关结肠癌 1 (metastasis-associated colon cancer-1, MACC1),通过触发 *SLC16A1* 转录来加速乳酸输出^[27-28]。此外,在结肠癌中, Wnt 驱动的 Warburg 代谢得到 MCT1 的支持,并且通过显性失活 LEF-1 表达的 Wnt 抑制

是由近端 *SLC16A1* 启动子中的 Wnt 反应元件介导的;这证实了 MCT1 在 Wnt 信号通路中发挥重要作用^[27]。另一方面, MCT4 受 HIF-1 α 的直接调节, HIF-1 α 是参与缺氧适应的主要转录因子^[21]。谷氨酰胺激活 HIF-1 并支持 MCT-4 表达^[29]。缺氧也调节 MCT1 表达,但其机制尚未明确。细胞外酸中毒可以启动 HIF-2 和 Myc 激活,导致 MCT1 和 MCT4 转录,细胞外乳酸通过环磷酸腺苷(cyclic adenosine monophosphate, c-AMP)和 c-AMP 反应元件结合蛋白(c-AMP response element-binding protein, CREB)信号通路刺激乳酸受体,触发 MCTs 的表达^[30]。

目前也有在肿瘤中 MCT 与蛋白质伴侣相互作用依赖性的报道。因此,靶向 CD147 来抑制 MCT 似乎是一种合理的方法,并且已经测试了几种抑制剂。除了 CD147 之外,还报道了与其他质膜相关蛋白的共表达,包括不同肿瘤中的透明质酸受体 CD44 和碳酸酐酶(例如 CAIX)^[31]。在葡萄糖剥夺环境中观察到涉及线粒体活性氧(mitochondrial reactive oxygen species, mt ROS)依赖性机制的翻译后稳定。在同一细胞系中,葡萄糖剥夺通过诱导肝肿瘤细胞自噬来降低 MCT1 表达^[32]。

3 乳酸转运在肿瘤中的作用

如前所述, MCT1 和 MCT4 在肿瘤进展和侵袭性中发挥着至关重要的作用,因为它们主要参与乳酸转运和穿梭。乳酸穿梭主要发生在含氧量正常的氧化肿瘤细胞和缺氧糖酵解肿瘤细胞之间,以及氧化肿瘤细胞和糖酵解基质细胞之间^[33]。为了肿瘤糖酵解的进行并避免细胞内酸化,高度糖酵解的肿瘤细胞或基质细胞表现出乳酸外流。反过来,细胞外乳酸可以充当氧化细胞的燃料,而 MCT1~4 是这种转运的重要介质,有助于形成酸性肿瘤微环境(Figure 1)。与 MCT4 相比, MCT1 对作为优选底物的丙酮酸盐和乳酸盐显示出更高的亲和力,而 MCT4 显示出对乳酸盐的偏好。在恶性肿瘤中, MCT1 与乳酸输入更相关, MCT4 与乳酸输出更相关,与特定生理环境中发生的情况类似^[34-36]。值得注意的是 MCT 转运活性是组织 and 环境依赖性的,并且 MCT1 也可能代替 MCT4 介导糖酵解细胞中的乳酸流出^[19]。通过为肿瘤细胞提供合成代谢支持、充当能量来源以及介导

细胞外和细胞内信号传导功能,乳酸在恶性肿瘤中的作用远非仅仅是一种废弃的肿瘤代谢物^[37](Figure 1)。

3.1 MCT1 和 MCT4 介导的乳酸穿梭

如前所述,由于 TME 的代谢异质性和肿瘤细胞持续的能量需求,乳酸穿梭可发生在 TME 内。Sonveaux 等^[38]和 Martinez-Outschoorn 等^[39]的研究最初描述了糖酵解肿瘤细胞或肿瘤相关成纤维细胞(cancer-associated fibroblasts, CAF)与氧化肿瘤细胞之间建立的共生关系。无论哪种方式, MCT1 和 MCT4 都会介导这种代谢合作, 因为它们通过细胞膜输出(MCT1)或输入(MCT4)乳酸方面具有优先功能。这种“反向 Warburg”表型后来扩展到三室环境^[40]。这种形式涉及与肿瘤相关的基质细胞,如免疫细胞和内皮细胞(endothelial cells, EC)^[41]。

成纤维细胞的细胞可塑性是指他们的糖酵解代谢模式可以在乳酸饱和的静息状态微环境下快速进行葡萄糖完全氧化^[42]。即使在生理自我维持修复过程(如伤口愈合)下,成纤维细胞也能够改变其形态和代谢程序以应对炎症反应的需求^[43]。因此, CAF 从最初阶段起就是恶性肿瘤的主要参与者,参与细胞外基质重塑、促进肿瘤的炎症和营养生物合成^[44-45]。由于 CAF 被认为参与乳酸穿梭, 因此在其他肿瘤模型中报道 CAF 中乳酸产量增加^[46]和 MCT4 高表达^[47-48], 以及它们与恶性潜能增强、治疗耐药性增强以及患者预后不佳的相关性^[49-50]。因此, 针对肿瘤细胞和 CAF 之间的代谢共生已被提出可作为一种治疗选择靶点^[51]。

静息态的免疫细胞(immune cells, IC)通常利用氧化磷酸化或脂肪酸氧化来产生能量, 但当其生物合成需求增加时, 它们可以采用糖酵解代谢^[52]。在恶性肿瘤中, 效应 CD8⁺T 细胞主要参与肿瘤杀伤, 而有效免疫反应的在生物能量上需求增加^[53]。活化 T 细胞数量的扩增必然涉及代谢转变, 从而帮助 T 细胞适应缺氧等其他微环境限制^[54]。因此, 与肿瘤细胞的代谢竞争发生在 TME 内。肿瘤细胞不仅在这种竞争中取得胜利, 而且还通过 MCT 利用代谢物与 IC 的穿梭来逃避免疫系统^[55]。IC 在酸性 TME 下阻断乳酸输, 或由于乳酸摄取和信号传导, 导致糖酵解通量受损^[56]。肿瘤来源的乳酸通常被描述为糖酵解肿瘤中的免疫抑制代谢物, 也与免疫治疗(immune therapy, IT)失败有关^[57]。有研究已提出以葡萄糖代

谢和乳酸分泌为靶点来提高 IT 功效的策略^[58]。然而, 最近的一项研究调查了乳酸钠(不考虑乳酸的酸性对应物)对效应 T 细胞功能的影响, 结果表明乳酸钠具有促进干性的作用, 并能改善抗肿瘤免疫力, 揭示了除 pH 值之外乳酸的免疫保护特性^[59]。

当肿瘤学血管生成发生时, EC 变为糖酵解主导型^[60]。与生理状态下血管网络相反, 肿瘤血管生成存在血管渗漏和紊乱的特点, 导致氧气和营养输送不良, 最终导致缺氧。在恶性循环中, 缺氧是糖酵解开关(在肿瘤细胞和 EC 中)和血管生成的主要触发开关因素^[61]。乳酸分泌直接或间接(通过 HIF 诱导)诱导血管内皮生长因子(vascular endothelial growth factor, VEGF)的产生和活性, 因此乳酸穿梭在其中发挥着重要作用。此外, ECs 可以通过 MCT1 从 TME 摄取乳酸, 在其中充当细胞内信号传导介质或代谢燃料, 并被完全氧化为丙酮酸。以上方式都会促进血管生成, 为靶向内皮细胞中的代谢途径以诱导血管正常化和改善药物输送提供了理论基础^[62-63]。

3.2 MCT1 和 MCT4 在肿瘤中的靶向作用

抑制 MCT1 会导致细胞内乳酸积累, 从而导致糖酵解流量、肿瘤细胞生长(通过减少糖酵解中间体的产生)以及三磷酸腺苷和烟酰胺腺嘌呤二核苷酸磷酸水平下降^[26]。在胶质母细胞瘤模型中, MCT1 基因下调或药理学抑制与 U251 细胞系中糖酵解代谢、迁移和侵袭率降低以及诱导细胞死亡有关^[64]。AZD3965 特异性抑制 MCT1 还导致细胞内乳酸积累和体内肿瘤生长减少^[65]。AZD3965 的活性也在 Burkitt 淋巴瘤模型中与阿霉素或利妥昔单抗联合使用的方案中进行了评估, 提示该模型诱导肿瘤生长减少^[66]。

一种新型 MCT1/MCT4 双重抑制剂能够通过改变糖酵解和线粒体代谢来损害猫口腔鳞状细胞癌(oral squamous cell carcinoma, OSCC)和人头颈肿瘤细胞系的活力。此外, 该抑制剂的使用导致皮下异种移植肿瘤模型的生长显著减少, 并延长了猫 OSCC 原位模型的总生存期。该项研究假设 MCT1/MCT4 的双重抑制可能是治疗猫口腔癌的有效疗法^[67]。肾癌细胞株(786-O)和人脐静脉内皮细胞(HUVEC)共培养细胞表现为过度表达 MCT1 和 MCT4, 小分子抑制剂抑制 MCT1 和 MCT4 活性可减弱共培养细胞的迁移和侵袭^[68]。当使用小干扰 RNA(siRNA)和

miR-124 等非编码 RNA 对 MCT1 和 MCT4 进行基因沉默时,肿瘤细胞生长减少^[69]。siRNA 介导的两种 MCT 基因沉默通过抑制乳酸转运降低了恶性胶质瘤 U-87 细胞的活力^[70]。胰腺肿瘤细胞中 miR-124 靶向 MCT1 显示细胞内 pH 值增加和细胞增殖减少,这意味着 miR-124 抑制 PANC-1 细胞的糖酵解活性^[71]。鉴于 MCT1 和 MCT4 的活性对 CD147 的依赖性,靶向该辅助蛋白概括了 MCT 抑制的代谢效应^[72]。

肿瘤细胞中的 MCT 抑制可能会破坏已建立的代谢与基质细胞共生。例如,通过基因沉默或药理抑制来抑制内皮细胞和肿瘤细胞中的 MCT1 会损害体外和体内乳酸诱导的血管生成^[62]。同样,MCT1 抑制破坏了肿瘤细胞和成纤维细胞之间的共生关系,损害了肿瘤细胞增殖^[73]。

4 MCT 抑制剂

小分子以其生物学、药理学和临床潜力而闻名。天然和合成小分子已被确定为 MCT 抑制剂,表现出非选择性和/或选择性 MCT 抑制能力^[74-75]。一些具有显著 MCT1 和 MCT4 抑制活性的小分子已在临床前试验中得到探索,其中一种抑制剂已进入高级临床试验。大多数 MCT 抑制剂都在于芳香族或脂肪族核心上具有羧酸功能部分。部分 MCT 选择性抑制剂已在体内得到验证^[76-77]。

一些研究报道多种抗糖酵解化合物在肿瘤抑制和免疫监视促进方面发挥作用,即通过促进记忆 T 细胞的形成^[78],这些细胞比糖酵解效应 T 细胞具有更高的代谢可塑性、扩张潜力和持久性^[79]。在此背景下,强效 MCT4 抑制剂 VB124 改善了肝细胞癌 (hepatocellular carcinoma, HCC) 异种移植瘤中的抗 PD-1 治疗,IT 耐药患者的 MCT4 表达高于应答者^[80]。在另一项关于 HCC 的研究中,在 IT 耐药患者的肿瘤浸润调节性 T 细胞中也发现了较高的 MCT1 表达水平^[81]。联合使用 MCT1 抑制剂 (AR-C155858) 和抗 PD1 抗体可有效降低 HCC 异种移植瘤中的肿瘤生长^[82]。小分子双重抑制剂 NGY-B 通过阻断乳酸分泌到 TME 中来激活抗肿瘤免疫,并在三阴性乳腺癌中与抗 PD-L1 IT 协同作用^[83]。另一方面,非甾体类抗炎药双氯芬酸以不依赖于环氧化酶的方式阻断 MCT1 和 MCT4^[84],且不损害 T 细胞,保留其激活状

态、活力和效应功能,同时延缓肿瘤生长并增强 IT^[85]。Huang 等^[86]的研究中,AZD3965 被封装在 pH 可激活的纳米颗粒中,以产生一种抑制 MCT1 的肿瘤靶向方法,使用纳米颗粒与 PD-1 抑制剂联合治疗可显著减少肿瘤生长,提高荷瘤小鼠的存活率,同时降低毒性。

5 小 结

MCT1 和 MCT4 在肿瘤细胞进展和存活中发挥着重要作用,并且在许多肿瘤中过度表达。MCT 有助于肿瘤微环境的酸度并与治疗耐药性相关,成为潜在的治疗靶点。在多种人类实体瘤中,MCT 表达已被证明与预后相关。因此,更好地了解 MCT1 和 MCT4 过度表达及其致癌参与作用,可为开发新的 MCT 靶向疗法提供希望。简而言之,可以通过针对 MCT1 和 MCT4 开发具有可接受药代动力学和安全特性的潜在选择性 MCT 抑制剂,最终可能应用于临床实践。

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