ISSN 1007-7626 中国生物化学与分子生物学报 http://cjbmb.bjmu.edu.cn 2020 年 9 月
CN 11-3870/Q Chinese Journal of Biochemistry and Molecular Biology 36(9):1041~1047

·综述·

DOI:10.13865/j.cnki.cjbmb.2020.07.1115

肿瘤干细胞的代谢

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摘要 肿瘤干细胞(cancer stem cells, CSCs)又称为肿瘤起始细胞(tumor initiating cells, TICs),是一类具有干细胞样特性的细胞群,能够起始肿瘤发生并具有自我更新和分化能力,是导致肿瘤异质性的主要原因之一,且呈现高度的化疗不敏感性和化疗耐药性,对于肿瘤的发生发展以及肿瘤复发至关重要。近年来,肿瘤代谢在肿瘤发生发展中的重要地位日益凸显,虽然分化的肿瘤细胞与肿瘤干细胞都呈现出适应性的代谢重编程(metabolic reprogramming),但是目前观点认为,肿瘤干细胞的代谢特征具有其特异性,从而满足其生存需求,并维持其干性和自我更新。关于肿瘤干细胞的特异性代谢特征至今并未达成共识。一些研究发现,肿瘤干细胞主要依赖有氧糖酵解供能。但也有研究指出,线粒体代谢是其主要能量来源。肿瘤干细胞似乎表现出更好的代谢适应性,能够转变其代谢偏好以更好的适应其生存环境的改变。关注肿瘤干细胞代谢异常和通路的改变,将有望为肿瘤治疗寻找代谢弱点(vulnerability)和作用靶标。基于现有的肿瘤干细胞相关研究,本文综述了有关肿瘤干细胞鉴别和分离培养的方法,着重介绍了肿瘤干细胞的糖代谢、脂肪酸代谢和氨基酸代谢特征,也讨论了肿瘤微环境对肿瘤干细胞代谢的影响,强调了靶向肿瘤干细胞代谢结合化疗药物的治疗策略,从而有助于临床寻找更为有效的肿瘤治疗手段。

关键词 肿瘤干细胞;干性;代谢;微环境;肿瘤治疗

中图分类号 Q291

Metabolism of Cancer Stem Cells

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Abstract Cancer stem cells (CSCs), also called tumor initiating cells (TICs), are cell populations harboring stem cell-like properties of initiating tumorigenesis as well as self-renewal. They are essential for tumorigenesis, tumor progression, and recurrence, which are highly resistant to chemotherapy. Cancer stem cells are one of the main causes of tumor heterogeneity. Tumor metabolism is emerged play an important role in tumorigenesis and progression. Although both differentiated tumor bulk cells and cancer stem cells show adaptive metabolic reprogramming, the metabolic characteristics of cancer stem cells are now considered specific to meet their survival demands and to maintain their stemness. To date, consensus has not yet been reached on the metabolic characteristics on cancer stem cells. Some studies have shown that cancer stem cells mainly rely on aerobic glycolysis for energy supply whereas some studies have pointed out that mitochondrial metabolism is their main source of energy, either. In addition, cancer stem cells can change their metabolic preference to better adaptation to tumor microenvironment.

收稿日期: 2020-03-12; 修回日期: 2020-05-13; 接受日期: 2020-05-26

上海市卫生和计划生育委员会青年课题(No. 20174Y0092)资助

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Received: March 12, 2020; Revised: May 13, 2020; Accepted: May 26, 2020

Supported by Shanghai Municipal Commission of Health, and Family Planning (20174Y0092 to Q.J. Fan)

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To explore the specific metabolic pathways in cancer stem cells may lay the foundation for tumor therapy. Here we review the identification and isolation methods of cancer stem cells, especially focus on the metabolic pathways, including glucose, fatty acid and amino acid metabolism, in cancer stem cells. We also discuss the influence of microenvironment on cancer stem cell metabolism, and emphasize the therapeutic strategies that target cancer stem cell metabolism combined with chemotherapeutic drugs, which might help to find more efficient means of tumor treatment in the clinic.

Key words cancer stem cells (CSCs); stemness; metabolism; microenvironment; tumor therapy

1 引言

肿瘤是具有高度异质性(heterogeneity)的组织,其中并非所有肿瘤细胞都能够无限生长和分化成大块的肿瘤组织(bulk tumor)[1,2]。肿瘤干细胞假说认为,肿瘤的发生发展是由肿瘤中少量的肿瘤干细胞(cancer stem cells,CSCs)推动的,解释了肿瘤在常规手术及放化疗成功后容易复发和转移的原因[3]。肿瘤干细胞模型的提出,首先是基于急性粒细胞白血病中的发现[4]。之后多个研究报道了肿瘤干细胞在实体肿瘤中的存在,包括乳腺癌、肺癌、胰腺癌、前列腺癌和脑癌等[5-9]。肿瘤干细胞与成体干细胞一样,保持未分化的状态,具有自我更新和多向分化的潜能。但是,肿瘤干细胞基因组发生多种突变,导致多种蛋白质功能异常,不具有形成正常个体或组织细胞的能力。肿瘤组织具有异质性和层次性。肿瘤干细胞是肿瘤组织内能够自我更新并有肿瘤再生能力的细胞。肿瘤干细胞是肿瘤细胞中数量很少的一个亚群,能够分化产生异质性的肿瘤细胞,建立肿瘤组织的层次性;相较于分化的肿瘤细胞,其代谢可塑性(plasticity)和适应性更强,从而决定了其对营养缺乏的高度适应能力和对化疗药物的高度耐受性。

代谢适应(metabolic adaptation)和代谢重编程(metabolic reprogramming)被认为是肿瘤细胞的十大标志之一[10]。虽然代谢在肿瘤中的作用正在被广泛研究,但是大多数的研究主要集中在肿瘤群体层面,对分化的肿瘤细胞研究较多,而忽略了肿瘤的层次性和异质性。目前,众多抗肿瘤药物在临床前实验中对肿瘤细胞具有良好的杀伤作用,但是大多在实际临床应用中很难达到理想的效果。Table 1 列出抗肿瘤药物或小分子化合物在临床试验中的应用。随着肿瘤干细胞研究的进展,特别是对肿瘤干细胞代谢特征的认知,寻找肿瘤干细胞代谢脆性(vulnerality)从而靶向肿瘤干细胞特征性的代谢途径,研发新型靶向药物结合化疗药物,有望成为肿瘤临床治疗的有效途径。本文将主要围绕近年来肿瘤干细胞代谢研究领域的进展做一综述。

Table 1 Antineoplastic drugs or small molecular compounds in clinic trials

Drug	Target	Indication	phase	ORR (%)	PFS(Month)
FT-2102	IDH	Hepatobiliary tumors	1b/2		
CB-839	Glutaminase 1	Non-small cell lung cancer	1/2		
Aspirin	COX2	Colorectal cancer	2	25	
Osimertinib	EGFR	Non-small cell lung cancer	3	80	18.9
Napabucasin	STAT3	Pancreatic cancer	2	59	6.0
Metformin+Gefitinib	Glucose metabolism	Non-small cell lung cancer	2	71	13.1
Epacadostat+Keytruda	IDO	Melanoma	1/2	55	12.4
Indoximod+Keytruda	IDO	Melanoma	2	61	12.9

IDH: isocitrate dehydrogenase; IDO: indoleamine 2, 3-dioxygenase; COX2: cyclooxygenase 2; EGFR: epidermal growth factor receptor; STAT3: signal transducer and activator of transcription 3; ORR: Objective Response Rate; PFS: Disease free survival

2 肿瘤干细胞的鉴别和分离培养

目前,鉴别肿瘤干细胞的常规方法,是根据肿瘤细胞是否为高表达特异性的干细胞标志物,并根据这些标志物分离出肿瘤干细胞。在实体瘤中常用并且得到公认的肿瘤干细胞标志物,主要包括 CD133、CD44、CD166、CD90、Nestin、Sox2 和 Nanog 等。肿瘤干细胞的标志物种类复杂,通常包括表面标志物和转录因子两类,但一种标志物通常不足以鉴定肿瘤干细胞。Table 2 列出肿瘤干细胞的特异性标记物。例如,研究表明,乳腺癌干细胞除了表达 CD44 还需要表达乙醛脱氢酶 ALDH 才具有明显的干细胞性质[11]。前列腺癌肿瘤干细胞的标志是 $CD133^+/CD44^+/A2131^{hi}$[8]。在肺癌中,部分学者认为,

$CD133^+/ALDH^+$ 的细胞具有肿瘤干细胞特性[12]。但也有人认为,$CD166^+$细胞干细胞特性更明显[13]。

Table 2　Specific markers of tumor stem cells

Tumor	CD34	CD44	CD90	CD96	CD117	CD133	CD166	Lgr5	EpCAM	ALDH1	ABCG2	A2131
Leukemia	+			+								
Breast cancer		+				+				+		
Lung cancer		+	+				+			+	+	
Pancreatic cancer		+				+	+			+		+
Brain cancer			+			+						
Colorectal cancer		+				+		+	+	+		
Ovarian cancer		+				+						
Osteosarcoma					+	+					+	

+: positive

目前,分离肿瘤干细胞主要采用以下方法:第 1 种是利用细胞表面的蛋白质标志物及特异抗体进行免疫磁珠分选或流式分选;第 2 种是利用筛选侧群细胞(side population, SP)的策略,用结合 DNA 的荧光燃料 Hoechst33342 处理细胞,利用肿瘤干细胞可将染料泵出细胞的性质,筛选出未染色或低染色的侧群细胞,即为肿瘤干细胞;第 3 种是从细胞系和肿瘤活检物中分离肿瘤干细胞的策略。在非黏附条件下,将肿瘤细胞系培养在干细胞培养基(即添加 EGF、βFGF、胰岛素和 B27 等的无血清 DMEM/F12 培养基)中体外成球,即为肿瘤干细胞球(tumor sphere)。

3　肿瘤干细胞的代谢

早期研究认为,肿瘤干细胞类似成体干细胞的休眠状态,代谢缓慢,由于其线粒体小且不成熟,处于低氧环境,导致其代谢主要依赖糖酵解(glycolysis)而不是氧化磷酸化(oxidative phosphorylation, OXPHOS)提供能量[14]。但是,近年来的研究发现,肿瘤干细胞与分化的肿瘤细胞一样,也依赖于功能活跃的线粒体进行三羧酸循环(tricarboxylic acid cycle,TAC)和脂肪酸 β 氧化(fatty acid oxidation, FAO)等。同时,其氨基酸代谢和核苷酸代谢也明显改变。但是,相较于正常成体干细胞和分化的肿瘤细胞,肿瘤干细胞的代谢表型呈现出特征性的差异[6]。Fig.1 介绍肿瘤干细胞的主要代谢途径。下文将就肿瘤干细胞的糖、脂和氨基酸代谢特点进行详细介绍。

3.1　肿瘤干细胞糖代谢的异质性

葡萄糖是肿瘤细胞的主要能量来源。20 世纪初,Otto Warburg 发现,即便在氧气充足的情况下,肿瘤细胞依旧采取有氧糖酵解的方式代谢葡萄糖,即 Warburg 效应。研究发现,葡萄糖同样是肿瘤干细胞所必需的营养物质。肿瘤干细胞生存环境中,

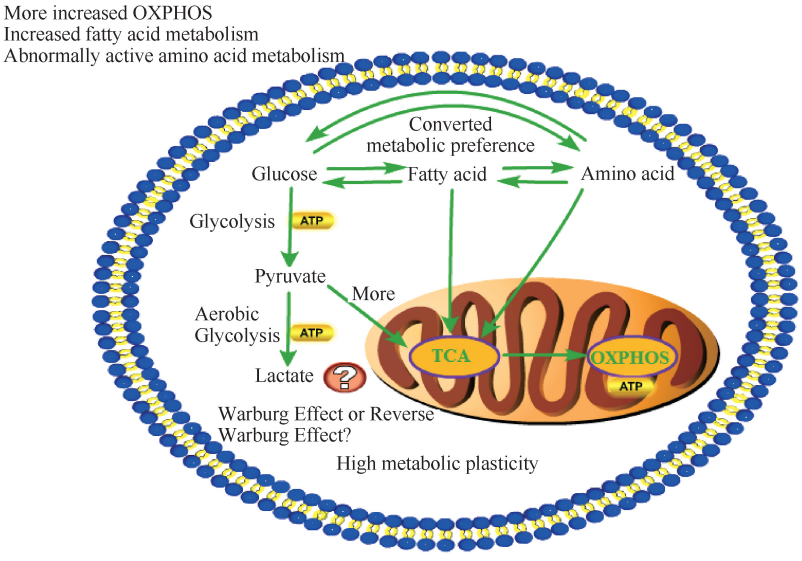

Fig.1　Main metabolic pathways of cancer stem cells　CSCs appear to be metabolically plastic and rely on multiple metabolic pathways for their energy production

葡萄糖的含量直接影响肿瘤干细胞的存活[15]。但是其糖代谢类型多变,具体是否符合 Warburg 效应与肿瘤类型及其生存环境密切有关。研究已经发现了许多与肿瘤干细胞糖代谢相关的关键分子。例如,己糖激酶-1(hexokinase-1, HK-1)、己糖激酶-2(hexokinase-2, HK-2)、丙酮酸脱氢酶激酶-1(pyruvate dehydrogenase kinase-1, PDK-1)、甘油醛-3-磷酸脱氢酶(glyceraldehyde-3- phosphate dehydrogenase, GAPDH)等,使得肿瘤干细胞的糖代谢存在明显的异质性,尚未得到统一结论,仍待进一步探索。

早期研究表明,在多种肿瘤中,肿瘤干细胞相较于分化的肿瘤细胞,糖酵解水平更高,包括脑胶质母细胞瘤、结直肠、乳腺癌、肺癌、卵巢癌和骨肉瘤等[6, 16-20]。与分化的肿瘤细胞相比,肿瘤干细胞的葡萄糖摄取、糖酵解酶的表达、乳酸生成量以及 ATP 含量显著增加,进行高水平的糖酵解以降低 ROS 水平,从而维持肿瘤干细胞的稳态,因此这种糖酵解代谢表型的升高,可能与降低线粒体氧化应激有关[6, 16-21]。肺癌、急性粒细胞白血病和乳腺癌等多种肿瘤干细胞中,PDK-1 水平明显升高,PDK-1 能够抑制丙酮酸向乙酰辅酶 A 的转化,诱导丙酮酸在细胞质中转化乳酸[6, 22, 23]。肿瘤干细胞中,HK-1 和 HK-2 水平都相对较高,HK-1 和 HK-2 能够催化糖酵解过程中葡萄糖向 6-磷酸葡萄糖的转化,维持肿瘤干细胞中糖酵解活性[6, 24]。研究发现,体外抑制糖酵解过程能够显著降低肿瘤干细胞的生存能力。同时,糖酵解抑制剂与传统放化疗联用一定程度上增加了抗肿瘤效果[16, 20, 23]。

但随着研究的进展,大量的证据表明,部分肿瘤干细胞更偏向于氧化磷酸化而不是糖酵解。近期的这些研究发现,相较于分化的肿瘤细胞,肿瘤干细胞具有更低的葡萄糖消耗速率和乳酸产生,但产生更多的 ATP。此外,研究还发现,与分化的肿瘤细胞相比,大部分肿瘤干细胞的线粒体质量更好,膜电位更高[25-27],这可能是导致线粒体氧耗和 ROS 水平高的原因。而且研究表明,抑制氧化磷酸化能够影响肿瘤干细胞的生存和致瘤能力[27-30]。例如,使用电子传递链抑制剂抗霉素 A,能够抑制肺癌侧群细胞的成球能力和肿瘤干细胞标志物的表达[31]。使用氧化磷酸化复合物 I 的抑制剂二甲双胍治疗,在一定程度上能够抑制肿瘤干细胞的干性以及体内的致瘤能力,但是发现在治疗中会产生耐药性。有趣的是,使用线粒体 ROS 诱导剂甲萘醌治疗,则不会产生耐药性,而且通过抑制 MYC 能够预防/逆转二甲双胍的耐药性[27, 32, 33]。在黑色素瘤干细胞中,过氧化物酶体增殖物激活受体 γ 共激活因子 1α(peroxisome proliferator-activated receptor γ coactivator-1α, PGC-1α)表达增加,从而提高线粒体代谢以增加其生存所需的能量需求[34]。此外,在乳腺癌中抑制 PGC-1α 的表达,会降低乳腺癌干细胞的干性[35]。因此,线粒体功能正常和代谢特征旺盛,可能是肿瘤干细胞维持干性的基础,也是肿瘤治疗的潜在靶点。

肿瘤干细胞的生存,主要依赖糖酵解还是氧化磷酸化,在不同的肿瘤中并不确定,而且在不同的生存环境中代谢模式也会相互转换,体现了肿瘤干细胞广泛的代谢适应性[36-38]。有研究表明,甚至肿瘤干细胞不同亚群的代谢模式也不同,与上皮样的肿瘤干细胞相比,间充质样的肿瘤干细胞更倾向于糖酵解[39, 40]。部分依赖氧化磷酸化的肿瘤干细胞,在氧化磷酸化被抑制时会向糖酵解转变[26, 41-43]。肿瘤干细胞在饥饿和缺氧的条件下能够上调葡萄糖转运蛋白来提高糖酵解水平,以缓解生存压力[42, 44]。另有研究表明,同时抑制糖酵解和氧化磷酸化,能够有效抑制肿瘤干细胞的能量生成从而抑制其生存[41, 45]。上述这种代谢适应能力,能够帮助肿瘤干细胞在肿瘤发生发展过程中更好地适应环境变化,更有利于肿瘤干细胞的生存。

3.2 肿瘤干细胞脂肪酸代谢异常活跃

近年来,肿瘤干细胞中脂肪酸代谢逐渐成为研究的热点。有报道显示,肿瘤干细胞中脂肪酸代谢相关酶类的表达和活性明显上调[46-49],高脂饮食能够增强肿瘤干细胞的致瘤能力和恶性转化[50, 51],而抑制脂肪酸合成以及甲羟戊酸途径能够显著降低肿瘤干细胞的生存能力[49]。肿瘤干细胞增加脂肪酸代谢,能够降低 ROS 水平,增加乙酰辅酶 A 的含量。肉碱棕榈酰转移酶(carnitine palmitoyl transferase 1, CPT1)是脂肪酸氧化的关键酶,JAK/STAT3 信号通路能够提高 CPT1 活性和脂肪酸氧化,抑制 STAT3 则显著降低乳腺癌干细胞的自我更新能力[52]。在神经胶质瘤干细胞中,一种多不饱和脂肪酸合成酶-长链脂肪酸延长酶 2(elongation of very long chain fatty acids protein 2, ELOVL2)表达明显上调,促进多不饱和脂肪酸的合成和细胞膜磷脂的合成,维持其自我更新和致瘤能力[53]。在卵巢癌干细胞中,NF-κB 能够直接调节脂质去饱和酶的表达,增加细胞内不饱和脂质的含量[54]。多不饱和脂肪酸的增加会增加细胞膜的流动性,膜流动性的增加对细胞

极性和细胞迁移等具有重要作用,这可能是导致肿瘤干细胞分化形成的肿瘤细胞,具有更强的迁移和侵袭能力强的原因。在肝细胞癌干细胞中,Nanog 能够上调脂肪酸代谢,抑制葡萄糖氧化磷酸化从而降低氧耗和 ROS 水平,来维持自身干性和化学耐药性[55]。在一些肿瘤干细胞中,抑制线粒体丙酮酸载体(mitochondrial pyruvate carreier, MPC)能够诱导 Nanog、ALDH1 和 HIF-1α 的增加[56]。因此,Nanog 可能是肿瘤干细胞脂肪酸代谢的关键调控因子之一。

肥胖引发的炎症以及相关的脂质因子被认为是肿瘤驱动的重要因素。其中,瘦素(leptin)就能够上调 STAT3,诱导肿瘤干细胞中的 CPT1B 表达并提高其脂肪酸氧化活性,从而促进肿瘤干细胞的干性和耐药性[57],提示了肥胖与肿瘤发生发展的重要关联。但是,肿瘤干细胞为何脂肪酸代谢如此活跃的机制尚不完全清楚,除了维持低 ROS 水平外,其如何调节肿瘤干细胞干性维持和自我更新的关系,仍有待深入探究。

3.3　肿瘤干细胞潜在致命弱点:独特的氨基酸代谢

最近的研究发现,肿瘤干细胞还有第 3 种活跃的代谢途径-氨基酸代谢。部分肿瘤干细胞会从葡萄糖代谢转换为主要依赖甚至完全依赖氨基酸代谢获取能量,当他们摄取氨基酸的能力被干扰时,这些肿瘤干细胞就会死亡[58]。胰腺癌干细胞依赖谷氨酰胺代谢,通过靶向谷氨酰胺酶(glutaminase)或谷氨酰胺草酰乙酸转氨酶(glutamic-oxaloacetic transaminase, GOT)抑制谷氨酰胺代谢,可减少肿瘤干细胞标志物的表达,抑制其自我更新,并通过积累 ROS 提高对化疗药物的敏感性[59],同时头颈癌干细胞的干性维持也需要谷氨酰胺[60]。结直肠癌干细胞中赖氨酸代谢增加,ROS 水平降低,从而激活 Wnt 信号通路以维持自身干性[61]。色氨酸的代谢产物 ITE[2-(1' H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester]能够激活芳香烃受体(aryl hydrocarbon receptor,AhR)进入细胞核后,精准结合到 OCT4 基因的启动子区,抑制 OCT4 的表达从而抑制肿瘤干细胞的增殖[62]。非小细胞肺癌干细胞对氨基酸中的甲硫氨酸尤为依赖,抑制甲硫氨酸循环(methionine cycle)能够显著抑制其增殖和转移[63]。虽然目前关于肿瘤干细胞氨基酸代谢的研究不多,但这些有限的研究已经表明,氨基酸代谢在肿瘤干细胞代谢重编程中占了重要地位。

此外,另有研究发现,在肿瘤干细胞中,一些原本与代谢调控无关的蛋白质,例如节律基因 CLOCK 功能发生改变,发挥调节肿瘤干细胞代谢的作用[64]。还有研究报道,肿瘤干细胞也存在核酸代谢相关酶及其代谢产物的显著改变[63]。这些结果均提示我们,肿瘤干细胞具有广泛的代谢适应性,单一靶向的代谢疗法可能很难彻底治愈肿瘤。

4　肿瘤干细胞的微环境

肿瘤微环境(microenvironment)对于肿瘤干细胞的影响非常重要,主要涉及缺氧、营养素缺乏以及微环境中的免疫细胞及其分泌的细胞因子、生长因子和激素等[65]。缺氧微环境能够促进乳腺癌干细胞标志物的表达,激活 JAK2/STAT3 信号通路提高脂肪酸氧化水平,以维持其干性[66]。除了缺氧,肿瘤干细胞在实体瘤中还面临着营养素缺乏的困境。缺氧以及葡萄糖缺乏会诱导微环境中免疫细胞发展为免疫抑制表型,改变肿瘤干细胞与免疫细胞的相互作用关系,从而促进肿瘤的发生发展[67-70]。与正常组织相比,肿瘤微环境酸性程度更高,从而触发血管生成和提高运动特性,以增加肿瘤干细胞的浸润能力[71-73]。另外,细胞因子 IL-8 能够上调葡萄糖转运体 3(glucose transporter 3,GLUT3)表达,提高葡萄糖摄取以及己糖胺生物合成,调控肿瘤干细胞的发展[72];乳腺脂肪细胞来源的瘦素,能够维持乳腺癌干细胞的干性和化疗耐药性[57];转化生长因子 β(transforming growth factor-β, TGF-β)和细胞毒性 T 淋巴细胞抗原 4(cytotoxic T lymphocyte associated antigen-4, CTLA4)能够帮助肿瘤干细胞逃逸免疫监控[74]。总体来说,微环境对于肿瘤干细胞的影响仍有许多未解之谜。

5　问题与展望

肿瘤干细胞假说认为,肿瘤内只有一小部分细胞可以产生肿瘤并维持肿瘤生长,是导致肿瘤的发生、转移、复发和耐药的主要原因。肿瘤干细胞独特的代谢特征,将它们与分化的肿瘤细胞区分开来,使其抵抗传统的治疗方式,并导致肿瘤复发。靶向肿瘤干细胞代谢已成为肿瘤治疗的新思路,为治愈肿瘤或者让患者长期带病生存带来了希望。

但是,针对肿瘤干细胞的治疗仍面临许多问题与挑战。首先,需要更加明确地定义肿瘤干细胞,因为到目前为止很多肿瘤干细胞的标志物均存在争议;第 2,肿瘤干细胞的生存微环境尚不明确,肿瘤干细胞是否是根据微环境的改变来进行代谢适应,

也需要进一步验证研究;第 3,肿瘤干细胞的代谢网络极其复杂,而且肿瘤干细胞的代谢适应与其存活的因果关系也不清楚。在肿瘤发生过程中,肿瘤干细胞的代谢特征会发生改变,出现不同的肿瘤干细胞亚群,为靶向治疗增加了难度,未来通过靶向肿瘤干细胞代谢疗法,可能需要同时靶向线粒体呼吸和糖酵解两条途径[58]。尽管对于肿瘤干细胞代谢领域的研究仍有待拓宽和加深,但是靶向肿瘤干细胞代谢治疗策略,在肿瘤治疗方面已经展现出了巨大的潜力和应用价值。

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