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肿瘤细胞与肿瘤相关巨噬细胞之间的代谢串扰

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摘要 在肿瘤微环境(tumor microenvironment, TME)中, 肿瘤相关巨噬细胞(tumor associated-macrophages, TAMs)是最丰富的细胞群之一, 在肿瘤发生、化疗耐药、免疫逃避和转移中起着关键作用。TAMs与肿瘤细胞之间存在重要的相互作用: 代谢重编程可以赋予肿瘤细胞在TME中的生存优势, 相应的代谢副产物可以影响TAMs的功能。此外, TAMs响应TME中存在的信号进行代谢重编程, 这会影响其功能和癌症进展。确定影响肿瘤细胞与TAMs之间复杂相互作用的代谢变化是探索新的治疗方法的重要一步, 从而增强其抗肿瘤活性。该文综述了肿瘤细胞与TAMs相互作用过程中的代谢变化, 为抗肿瘤治疗提供新的靶点。

关键词 肿瘤细胞; 肿瘤相关巨噬细胞; 代谢; 串扰; 靶向治疗

Metabolic Crosstalk between Tumor Cells and Tumor-Associated Macrophages

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Abstract TAMs (tumor-associated macrophages) are one of the most abundant cell populations in the TME (tumor microenvironment) and play a key role in tumorigenesis, chemoresistance, immune evasion, and metastasis. There is an important interaction between TAMs and tumor cells: metabolic reprogramming can confer a survival advantage on tumor cells in TME, and corresponding metabolic by-products can affect the function of TAMs. In addition, TAMs undergo metabolic reprogramming in response to signals present in the TME, which can affect their function and cancer progression. Identifying metabolic changes that affect the complex interactions between tumor cells and TAMs is an important step in the exploration of new treatments that enhance their tumoricidal potential. This article summarizes the metabolic alterations during tumor cell-TAM interactions, highlighting potential targets for cancer treatment.

Keywords tumor cells; tumor-associated macrophages; metabolism; crosstalk; targeted therapy

巨噬细胞在组织稳态维持和宿主防御方面起着重要作用, 主要通过吞噬作用、外源性抗原呈递以及分泌细胞因子和生长因子进行免疫调节[1]。在肿瘤微环境(tumor microenvironment, TME)中, 巨噬细胞是一种重要的基质成分, 通常被称为肿瘤相关巨噬细胞(tumor-associated macrophages, TAMs)。当受到不同因素的刺激时, 巨噬细胞表现出不同的表型和功能, 称为TAMs的极化。TAMs的可塑性使它

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们能动态响应TME的变化并呈现不同的激活状态。一般来说, TAMs分为两种类型: 经典M1巨噬细胞和替代M2巨噬细胞。M1巨噬细胞参与免疫反应、病原体清除和抗肿瘤免疫。相反, M2巨噬细胞与抗炎反应、伤口愈合和致瘤特性有关。通常情况下, 我们所说的TAMs表现为促进肿瘤恶化的M2表型。M2型TAMs具有免疫抑制特性, 能够分泌免疫抑制性细胞因子(如IL-10、TGF-β), 抑制T细胞的抗肿瘤活性, 并促进肿瘤的免疫逃逸和进展[2]。而肿瘤细胞作为TME的主要成分, 是肿瘤发生发展的核心驱动因素。在肿瘤细胞中, 代谢重编程不仅赋予肿瘤细胞生长优势, 而且还能影响免疫细胞分化和功能, 从而促进癌症进展[3]。同样, TME中TAMs的代谢重编程可以通过不同的途径影响其功能[4]。肿瘤细胞与免疫细胞之间的相互作用塑造了肿瘤免疫微环境中的代谢竞争, 通过限制营养物质的正常代谢及形成酸性环境, 削弱抗肿瘤免疫反应, 最终形成免疫抑制微环境[5]。因此, 从免疫和代谢的角度推进肿瘤治疗, 深入了解肿瘤细胞和TAMs的代谢重编程, 以及它们之间的代谢串扰, 有望取得肿瘤研究的关键突破, 并为开发创新疗法铺平道路。尽管已有研究涉及肿瘤细胞与TAMs各自代谢重编程的基本特征以及二者在TME中的相互作用, 但目前关于肿瘤细胞与TAMs代谢调节串扰的分子信号通路研究仍较为有限。因此本文综述了肿瘤细胞和TAMs之间的代谢串扰在癌症生物学进展中的重要性, 并概述了当前靶向肿瘤细胞和TAMs的代谢药物, 从而为肿瘤治疗提供了新靶点。

1 肿瘤细胞的代谢重编程

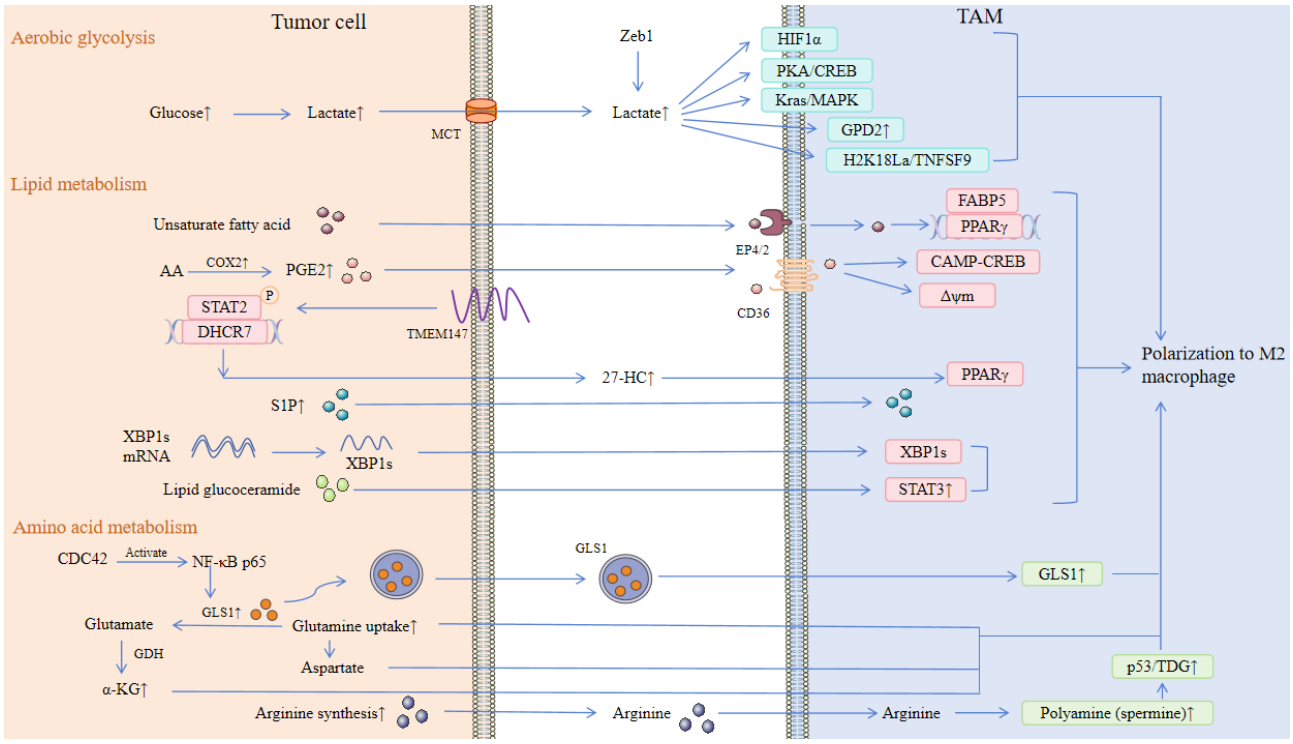
肿瘤细胞中的代谢重编程是癌症生物学的核心, 并且是肿瘤发生的重要基础。与正常细胞不同, 癌细胞表现出独特的代谢表型, 特别是通过改变葡萄糖、氨基酸和脂质代谢途径来满足其增加的能量和生物合成需求[6]。“Warburg效应”, 是癌症中葡萄糖代谢重编程的典型状态[7]。具体来说, “Warburg效应”是指肿瘤细胞即便在氧充足条件下仍优先选择糖酵解功能的现象。因此, 肿瘤细胞通过有氧糖酵解产生大量乳酸, 并通过单羧酸转运蛋白4将多余的乳酸释放到细胞外形成酸性TME[8]。糖酵解和乳酸在诱导TAMs免疫抑制表型中起着极为关键的作用[9]。在肿瘤细胞生长过程中, 除了葡萄糖代谢和能量供应外, 细胞还需要大量的脂质来合成脂肪、构建生物膜和维持其功能[10]。脂质相关代谢网络主要包括脂肪酸、花生四烯酸、胆固醇/鞘脂代谢网络等[11]。研究表明, 肿瘤细胞与肿瘤浸润免疫细胞通过脂质代谢交互作用及其代谢产物的动态调控, 在塑造免疫抑制微环境中发挥关键作用[12-15]。此外, 肿瘤细胞的氨基酸代谢呈现异常活跃状态, 其中精氨酸、谷氨酰胺及色氨酸作为关键代谢节点, 在肿瘤细胞与TAMs的代谢重编程中发挥核心调控作用。总之, 肿瘤细胞的代谢重编程与TAMs有着密切联系。

2 肿瘤细胞代谢重编程影响TAMs极化

肿瘤细胞的代谢重编程不仅支持其快速增殖, 还通过代谢产物调节TME中免疫细胞功能, 尤其是促进TAMs的极化, 进而影响肿瘤免疫逃逸、血管生成及肿瘤进展。下文将探讨乳酸、脂质和氨基酸这三类代谢产物影响TAMs极化的机制, 以及靶向该过程的潜在治疗价值(图1)。

2.1 乳酸

在癌症中, 肿瘤细胞糖酵解的高通量, 以及三羧酸循环或氧化磷酸化(oxidative phosphorylation, OXPHOS)的抑制, 可以诱导肿瘤细胞与TAMs之间的营养竞争, 最终促使TAMs向M2表型极化[16]。同时, 肿瘤细胞有氧糖酵解产生的乳酸是癌症进展的有利因素[17]。乳酸积累通过抑制肿瘤浸润免疫细胞的杀瘤作用来促进TME中的免疫抑制[18]。肿瘤细胞分泌的乳酸则会驱动TAMs的M2极化, 并以缺氧诱导因子-1α依赖性方式诱导血管内皮生长因子表达[19]。锌指E盒结合同源框1(zinc finger E-box binding homeobox 1, Zeb1)是一种转录因子, 其在酸性TME中异位表达产生的乳酸通过刺激PKA/CREB信号通路诱导TAMs极化为M2型, 从而在体外和体内促进“Warburg效应”, 并促进乳腺癌细胞的增殖、迁移及提高其化学耐药性[20]。乳酸等代谢产物还可通过形成浓度梯度指导巨噬细胞极化, 进而调控TAMs的功能表型。这种代谢物梯度还诱导TAMs中信号通路(包括Kras/MAPK通路)的差异激活[21]。此外, 宫颈癌细胞分泌的乳酸通过组蛋白乳酸化上调GPD2表达, 从而促进宫颈癌中的M2巨噬细胞极化[22]。而胶质瘤细胞中的乳酸通过MCT1/H3K18La/TNFSF9轴导致巨噬细胞的M2极化, 最终显著促进胶质瘤细胞的恶性进展[23]。综



肿瘤细胞代谢重编程通过释放代谢物、信号介质以及影响TME的代谢景观, 从而驱动TAMs的极化。

Tumor cell metabolic reprogramming drives the polarization of TAMs by releasing metabolites, signaling mediators, and influencing the metabolic landscape of the TME.

图1 肿瘤细胞代谢重编程影响TAMs极化

Fig.1 Metabolic reprogramming of tumor cells affects the polarization of TAMs

上所述, TME中的乳酸水平与巨噬细胞的信号转导功能和极化息息相关。因此, 靶向肿瘤细胞的乳酸代谢通路, 干扰乳酸的生成、转运及其信号转导, 是未来癌症治疗的重要潜在策略。

2.2 脂质

肿瘤组织脂质丰富, 这些脂质主要来源于癌细胞的脂肪从头合成、癌症相关成纤维细胞和脂肪细胞的脂质供应, 且在TME中对TAMs的产生、分化和功能具有重要影响[24-25]。而来自肿瘤细胞的不饱和脂肪酸被TAMs吸收后, 会促进FABP5与过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor gamma, PPARγ)的结合, 增强PPARγ在巨噬细胞中的转录活性, 从而促使TAMs向免疫抑制型表型转变[26]。前列腺素是花生四烯酸(arachidonic acid, AA)经环氧合酶-2(cyclooxygenase-2, COX-2)催化所产生的代谢产物, 通过EP4/2受体双重调控TAMs功能: 一方面通过下调M1型TAMs中*c-Myc*和OXPHOS相关基因表达削弱抗肿瘤免疫反应[27]; 另一方面通过cAMP-CREB信号通路及线粒体膜电位(Δψm)调控机制诱导TAMs向M2样表型极化[28-30]。此外, PGE2还可通过调控程序性死亡配体1(programmed cell death ligand 1, PD-L1)的表达进一步促进免疫抑制微环境的形成[31]。这些机制共同介导了PGE2依赖的肿瘤免疫逃逸。另一项研究表明, 肝细胞癌(hepatocellular carcinoma, HCC)细胞中TMEM147信号通路通过激活STAT2增加*DHCR7*的转录, 进而改变细胞胆固醇平衡, 使细胞外27-羟基胆固醇(27-hydroxycholesterol, 27HC)水平升高。这些细胞分泌的27HC从而增强巨噬细胞的脂质代谢, 并激活PPARγ信号通路, 驱动M2型巨噬细胞极化[32]。鞘脂代谢对肿瘤细胞中的脂质代谢也至关重要。肿瘤凋亡衍生的鞘氨醇-1-磷酸(sphingosine-1-phosphate, S1P)是一种鞘脂, 通过促进血管生成参与肿瘤进展, 并且可促进巨噬细胞极化为TAMs样表型[33]。同样, 肿瘤细胞衍生的脂质葡萄糖神经酰胺通过诱导巨噬细胞中的内质网(endoplasmic reticulum, ER)应激反应, 促使巨噬细胞极化为促肿瘤表型。在此过程中, STAT3的激活以及IRE1剪接介导的XBP1产生共同发挥作用, 两者协同诱导巨噬细胞向促肿瘤表型的极化[34]。故使用相关的脂质代谢抑制剂抑制肿瘤细胞的脂质代谢并诱

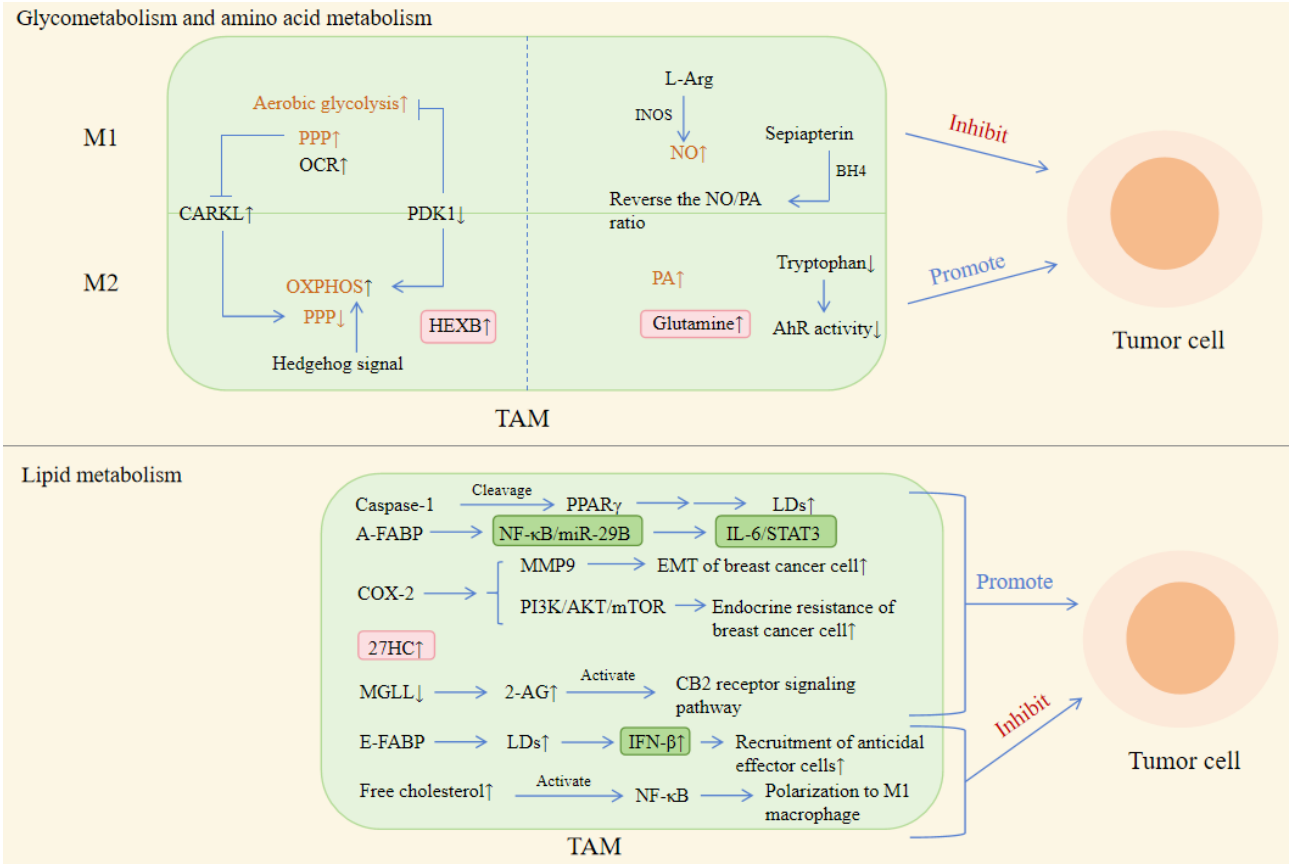
导巨噬细胞向抗肿瘤表型极化是一种重要的治疗策略。

2.3 氨基酸

多种氨基酸参与TAMs极化和活化的调节。肿瘤细胞通过代谢重编程劫持微环境氨基酸资源以维持增殖，其中谷氨酰胺的异常消耗尤为显著[35]。这种代谢竞争导致TME中谷氨酰胺水平失衡：一方面，谷氨酰胺剥夺削弱M2型TAMs极化，并减少趋化因子CCL22的产生[36]；另一方面，其分解产物α-酮戊二酸(alpha-ketoglutarate, α-KG)又可反向激活M2极化相关通路[37]，凸显氨基酸代谢对TAMs表型调控的双向性。而在HER2阳性胃癌中，肿瘤细胞通过CDC42-NF-κB信号轴上调谷氨酰胺酶1(glutaminase 1, GLS1)表达，加速谷氨酰胺分解代谢。GLS1过表达促使肿瘤细胞释放含GLS1的微囊泡，这些微囊泡被TAMs摄取后，通过增强其谷氨酰胺代谢活性驱动M2型极化[38]。同样，谷氨酰胺的衍生物天冬氨酸可直接诱导TAMs向M2表型极化[39]，表明肿瘤代谢产物可通过多途径塑造免疫抑制微环境。而精氨酸代谢作为肿瘤细胞代谢重编程调控TAMs极化的核心机制之一，在乳腺癌中，肿瘤细胞通过产生精氨酸，促进TAMs中的多胺合成，进而通过表观遗传机制(p53/TDG介导的DNA去甲基化)驱动TAMs的M2极化，抑制$CD8^+$ T细胞功能，从而促进免疫抑制和肿瘤进展[40]。因此，肿瘤细胞代谢重编程释放的谷氨酰胺、精氨酸等氨基酸，通过调控TAMs的代谢通路、表观遗传修饰及免疫信号网络，多维度驱动其向M2型极化并增强其免疫抑制功能。

3 TAMs的代谢重编程影响癌症

为了在复杂恶劣的TME中生存，TAMs通过代谢重编程影响肿瘤细胞生长及癌症发展，主要体现在糖代谢、脂质代谢和氨基酸代谢三大关键途径，下文将分别阐述其机制与影响(图2)。



为了适应TME，TAMs的代谢被重新编程，其通过释放细胞因子和代谢物对肿瘤发展产生直接或间接的影响。

To adapt to the TME, TAMs undergo metabolic reprogramming, which allows them to exert direct or indirect effects on tumor development through the release of cytokines and metabolites.

图2 TAMs的代谢重编程与肿瘤发展

Fig.2 Metabolic reprogramming of TAMs and tumor development

3.1 TAMs的糖代谢重编程与肿瘤发展

TAMs中葡萄糖代谢模式的改变可导致免疫抑制, 促进肿瘤生长和转移[41]。不同极化状态下的TAMs代谢模式各异, 对肿瘤的发生、进展、血管生成和转移影响不同[42]。通常, M1 TAMs主要依赖有氧糖酵解, 并且其磷酸戊糖途径(pentose phosphate pathway, PPP)因NADPH的增加而增强。相比之下, M2 TAMs更侧重于高水平的OXPHOS, PPP活性较低。M2 TAMs能产生IL-10和VEGF, 进而促进肿瘤生长、血管生成和肿瘤转移[36,43-44]。此外, 不同极化状态的巨噬细胞通过调节景天庚酮糖激酶(sedoheptulokinase, SHK)的表达来调控PPP。M1型巨噬细胞通过抑制SHK的表达, 以提高PPP通量和耗氧率, 从而有助于其执行免疫杀伤功能; 而M2型巨噬细胞的SHK高表达降低了PPP通量, 这导致糖酵解过程受限, 而这一代谢模式更倾向于支持肿瘤的免疫逃逸与组织修复过程[45]。参与巨噬细胞糖代谢的关键调节酶在癌症中也发挥关键作用。例如, 丙酮酸脱氢酶激酶1(pyruvate dehydrogenase kinase 1, PDK1)可以调节巨噬细胞极化。PDK1的敲低可减弱M1巨噬细胞中的有氧糖酵解并增强M2巨噬细胞中的OXPHOS[46]。综上所述, 葡萄糖代谢调控着巨噬细胞的差异化激活, 从而影响癌症进展。己糖胺酶B(hexosaminidase subunit beta, HEXB)是胶质母细胞瘤(glioblastoma, GBM)中糖酵解的关键调节因子, TAMs分泌的HEXB可通过结合肿瘤细胞表面的ITGB1/ILK受体复合物, 激活YAP1信号通路, 进而稳定HIF1α蛋白, 上调糖酵解基因(如*PKM2*、*HK2*)的表达[47]。

TAMs还可以根据氧气的可用性调整其细胞内代谢。研究表明, 缺氧可抑制TAMs对葡萄糖的摄取, 从而增加TME中的葡萄糖含量, 进一步促进肿瘤细胞的葡萄糖摄取。故在缺氧条件下降低TAMs的糖酵解活性有利于乳腺癌的生长和转移[48]。最近的研究表明, 抑制TME中异常激活的Hedgehog信号通路, 可通过逆转其驱动的、依赖OXPHOS的M2型TAMs极化, 将TME重编程为免疫激活状态[49]。

综上所述, TAMs可根据不同的信号或相互作用动态调整其代谢模式, 并维持相应的极化表型。因此, 选择性靶向TAMs的代谢对于进一步改善肿瘤的免疫治疗效果是至关重要的。

3.2 TAMs的脂质代谢重编程与肿瘤发展

TAMs可通过重编程脂质代谢来影响癌症进展, 涉及脂肪酸(fatty acid, FA)、AA和胆固醇(cholesterol, CHOL)代谢途径。与肿瘤细胞相比, TAMs的脂质代谢可发挥促肿瘤和抗肿瘤作用。TAMs的特点之一是脂质积累。研究表明, caspase-1裂解PPARγ可使脂滴在TAMs中积累, 促进肿瘤生长[50]。而脂肪酸结合蛋白(fatty acid-binding protein, FABP)作为脂质代谢的关键调控因子, 不同形式的FABP对癌症生长和转移的影响不同。表皮脂肪酸结合蛋白(epidermal fatty acid-binding protein, E-FABP)在TAMs中高表达, 通过上调脂滴形成来促进IFN-β的产生, 从而有助于NK细胞的募集以杀死肿瘤[51]。相反, 脂肪细胞脂肪酸结合蛋白(adipocyte fatty acid-binding protein, A-FABP)在乳腺癌TAMs中高表达, 通过NF-κB/miR-29B/IL-6/STAT3通路促进乳腺癌的增殖和转移[52]。

除了脂质积累外, TAMs中AA代谢的改变对肿瘤发展也有重大影响。AA是类花生酸的关键前体, 类花生酸包括PGE2、白三烯等, 它们由AA通过脂氧合酶(lipoxygenase, LOX)和环氧合酶(cyclooxygenase, COX)等代谢途径产生[53]。表达COX-2的TAMs可广泛地调节肿瘤细胞侵袭、生存和转移等特性影响肿瘤发生。研究表明, TAMs中的COX-2不仅通过触发MMP-9表达促进乳腺癌细胞的上皮–间质转化, 还可以增加癌细胞中的Bcl-2水平以及降低Bax水平来促进乳腺癌细胞增殖和存活[54-55]。此外, TAMs中COX-2/PGE2的高表达通过激活乳腺癌细胞中的PI3K/AKT/mTOR通路从而增强乳腺癌的内分泌抵抗[56]。

ABCG1是ABC转运蛋白超家族的一员, 调节细胞内胆固醇稳态[57], 然而当TAMs中缺乏ABCG1表达时, 细胞中游离胆固醇的积累会导致NF-κB激活使TAMs极化为M1型, 从而增强TAMs对肿瘤细胞的毒性作用, 抑制肿瘤增殖[58]。此外, TAMs产生的胆固醇代谢物27HC可促进乳腺癌细胞的增殖[59]。

更有趣的是, 肿瘤细胞与TAMs在脂质代谢中存在差异且相互影响: 肿瘤细胞通过上调单酰基甘油脂肪酶(monoacylglycerol lipase, MGLL)驱动脂质合成, 从而促进自身的增殖和转移; 而TAMs中MGLL的缺失导致2-花生四烯酸甘油(2-arachidonoylglycerol, 2-AG)累积, 通过激活CB2大麻素受体信号通路, 驱动TAMs向促肿瘤M2表型极化[60-61]。综上所述, 对不同细胞实施脂质代谢干预可产生不同的效果, 故靶向TAMs与肿瘤细胞间的代谢互作, 对癌

症治疗具有重要意义。

3.3 TAMs的氨基酸代谢重编程与肿瘤发展

诱导型一氧化氮合酶(inducible nitric oxide synthase, iNOS)/精氨酸酶1(arginase 1, ARG1)轴是TAMs免疫代谢的核心调控节点。而精氨酸代谢对于TAMs和肿瘤细胞之间的串扰很重要。在精氨酸代谢过程中, 肿瘤细胞倾向于从iNOS介导的一氧化氮(nitric oxide, NO)合成途径转变为ARG1依赖的多胺(polyamine, PA)合成途径, 以满足其生长和增殖需求[62]。而在TAMs中, PA提高M2型TAMs的活性, 而NO提高M1型TAMs的活性, 这两种代谢途径相互抑制[63]。研究发现, SEP(sepiapterin)是一氧化氮合酶辅因子BH4的内源性生物合成前体, 补充SEP可以在HER2阳性乳腺癌细胞和TAMs中将精氨酸代谢从PA合成转变为NO合成, 从而抑制乳腺肿瘤细胞的生长[64]。因此, 靶向调控精氨酸代谢可能会提高机体的抗肿瘤免疫力。谷氨酰胺是TAMs的重要能量来源, 对其生理功能至关重要[65]。TAMs可通过谷氨酰胺合成酶(glutamine synthetase, GS)利用氨和谷氨酸自主合成谷氨酰胺。在TME中, TAMs内GS活性受到抑制时, 其诱导T细胞募集的能力增强, 促进癌细胞运动的能力减弱。这表明, 抑制TAMs中的GS活性可增强其抗肿瘤功能。因此, 靶向GS以重编程TAMs的谷氨酰胺代谢, 是治疗癌症的潜在策略[66]。此外, TAMs中的芳香烃受体(aryl hydrocarbon receptor, AhR)作为色氨酸代谢产物的关键受体, 可通过控制膳食色氨酸摄入或抑制肠道菌群的色氨酸代谢, 降低其活性, 从而增强机体的抗肿瘤免疫力[67]。靶向氨基酸代谢已被证明可以推动癌症相关疗法的发展, 然而目前有关氨基酸代谢机制的研究较为缺乏, 探索其代谢机制对于治疗癌症是极其必要的。

4 靶向代谢的药物和策略

TAMs和肿瘤细胞的代谢在肿瘤的发生和发展中起着关键作用。近年来, 越来越多的研究表明, 靶向肿瘤和免疫细胞的代谢与常规靶向治疗相结合, 可能是协同提高疗效的新方法, 具有重要的治疗意义。以下将分别探讨靶向肿瘤细胞代谢和靶向TAMs代谢的药物和策略(表1和表2)。

4.1 靶向肿瘤细胞代谢

尽管微环境中肿瘤细胞和TAMs代谢的某些潜在机制仍不清楚, 但研究表明, 抑制相关代谢酶的功能可能是治疗肿瘤的合理方法。乳酸脱氢酶A(lactate dehydrogenase A, LDHA)是肿瘤细胞糖酵解的关键酶, 马其林A(machilin A)通过抑制该酶减少乳酸产生, 从而抑制癌症进展[68]。此外, LDHA抑制剂草氨酸预处理MDA-MB-231细胞也可抑制乳酸的产生, 使TAMs极化为M1型[69]。草氨酸对宿主细胞没有显著毒性, 在卵巢癌中联合PARP抑制剂可增强对肿瘤的抑制作用[70]。而PFKFB3作为糖酵解的关键调节因子, 也已成为肿瘤治疗靶点。例如, PFK158可减少肿瘤细胞的葡萄糖摄取、ATP产生和乳酸释放, 并诱导细胞凋亡[71]。紫草素(shikonin)通过诱导细胞坏死性凋亡或减少M2-型丙酮酸激酶(pyruvate kinase M2, PKM2)通过外泌体的分泌, 有望逆转癌症中的顺铂耐药[72-73]。己糖激酶(hexokinase 2, HK2)作为糖酵解的限速酶, 与癌细胞的不良预后密切相关。苄丝肼(benserazide)通过直接结合HK2并降低其活性, 阻断葡萄糖代谢, 导致ATP水平降低; 同时它也能诱导细胞凋亡。当采用纳米脂质体改良后, 其靶向性增强, 抑瘤效果提升[74]。而近期研究发现, 利用蛋白质降解靶向嵌合物(proteolysis-targeting chimera, PROTAC)技术设计合成的新型HK2降解剂C-02可有效地降解HK2蛋白和降低乳腺癌细胞的活性, 克服传统抑制剂的耐药性问题[75]。单羧酸转运蛋白1(monocarboxylate transporter 1, MCT1)是乳酸外排的关键转运蛋白之一, 其抑制剂AZD3965可有效阻断乳酸的外排、减少肿瘤细胞对葡萄糖的摄取, 从而抑制肿瘤细胞的增殖, 并且其与放疗联合使用可增强抗肿瘤效果[76]。然而当使用AZD3965治疗时, 肿瘤细胞可通过上调MCT4表达, 维持乳酸外排和细胞内pH稳态, 从而逃逸药物抑制。临床前研究显示, AZD3965仅在MCT4低表达或缺失的肿瘤模型中有效。这一机制性耐药是临床转化的重要障碍[77]。此外, Olutasidenib(FT-2102)和Vorasidenib(AG-881)可抑制异柠檬酸脱氢酶(isocitrate dehydrogenase, IDH)突变引起的代谢产物 2-羟基戊二酸(2-hydroxyglutaric acid, 2-HG)的积累, 从而恢复细胞的正常代谢和基因表达[78-79]。CPI-613作为一种有效的线粒体功能抑制剂, 可通过抑制丙酮酸进入线粒体, 从而阻断TCA循环, 导致ATP产生量减少和细胞凋亡[80]。氯尼达明(lonidamine)则是一种复合体II抑制剂, 通过靶向复合体II, 阻断线粒体呼吸链, 从而减少肿瘤细胞的能量供应, 抑制肿瘤细胞的生长和增殖[81]。

最近研究表明, 脂肪酸合成酶(fatty acid synthase, FASN)抑制剂TVB-2640在乳腺癌临床前模型中具有显著的抗肿瘤潜力[82]。目前, 它处于临床试验中, 在与紫杉醇和曲妥珠单抗联合治疗三阴性乳腺癌的临床试验(NCT03179904)中进行测试。而表没食子儿茶素没食子酸酯(epigallocatechin gallate, EGCG)通过降低FASN表达水平, 提高放射抗性鼻咽癌对治疗的敏感性, 从而改善疗效[83]。 此外, 研究发现用特比萘芬(terbinafine)靶向合成胆固醇生物合成的关键酶SQLE也可能是预防和治疗肿瘤(包括肝癌和乳腺癌)的有效途径[84-85]。甾醇调节元件结合蛋白(sterol regulatory element-binding protein, SREBP)是脂质代谢的关键调节因子, 通过转录调节下游基因进而维持脂肪酸和胆固醇代谢平衡, 法托司他汀(fatostatin)通过阻断SREBP通路而达到抗肿瘤的作用[86]。 GLS1抑制剂, 如BPTES、CB-839, 已被证明可以通过改变谷氨酰胺代谢和破坏ROS清除系统来抑制癌细胞的增殖和迁移[87-88]。WANG等[89]还开发了ROS响应型纳米粒(PD-G@BC), 共载代谢调节剂BPTES和CPI-613, 协同阻断肿瘤细胞中的糖酵解和谷氨酰胺代谢, 从而剥夺肿瘤增殖所需的营养/能量供应, 引发免疫反应。而小分子DFMO(一种已获批用于临床的多胺合成抑制剂)可以有效阻断肿瘤细胞与TAMs之间的精氨酸–多胺代谢轴, 从而抑制肿瘤生长。这一发现不仅解释了以往关于精氨酸功能异质性的争议, 也为开发新的抗癌疗法提供了新的思路[40]。

4.2 靶向TAMs代谢

TAMs作为TME中的主要免疫细胞群, 在各种癌症的发展中发挥着重要作用, 使其成为极具潜力的治疗靶点[91]。脂质稳态与癌症密切相关。ARBU(arenobufagin), 源自蟾蜍毒液的天然化合物, 通过抑制TAMs的LOX-1受体功能和上调ABCA1的表达, 诱导TAMs向抗肿瘤M1型极化, 可显著抑制肿瘤

表1 靶向肿瘤细胞代谢的药物

Table 1 Drugs targeting tumor cell metabolism

靶向代谢类型 Targeted metabolic type	名称 Name	癌症类型 Types of cancer	机制 Mechanism	临床分期 Clinical stages	参考文献 References
Glycometabolism	Machilin A	Colon, breast, lung, and liver cancers	Inhibit LDHA	Preclinical tests	[68]
	Oxamic acid	Breast cancer	Inhibit LDHA	Preclinical tests	[69]
	PFK158	Ovarian cancer, cervical cancer	Inhibit glycolysis	Preclinical tests	[71]
	Shikonin	Bladder cancer, non-small cell lung cancer	Inhibit PKM2	Preclinical tests	[72-73]
	Benserazide	Colorectal cancer	Inhibit HK2	Preclinical tests	[74]
	C-02	Breast cancer	Induction of HK2 degradation	Preclinical tests	[75]
	AZD3965	Lymphoma	Inhibit MCT1	Phase I	[76]
	Olutasidenib (FT-2102)	Glioma	Inhibit mutant IDH1	Phase II	[78]
	Vorasidenib (AG-881)	Glioma	Inhibit mutant IDH1/2	Phase III	[79]
	CPI-613	Pancreatic cancer	Inhibit PDH	Phase III	[80]
	Lonidamine	Lung cancer	Inhibition of complex II	Phase III	[81]
Lipid metabolism	TVB-2640	Breast cancer	Inhibit FASN	Phase II	[82,90]
	EGCG	Esophageal carcinoma	Inhibit FASN	Phase I/II	[83]
	Terbinafine	Liver cancer, breast cancer	Target SQLE to synthesize cholesterol	Phase I/II/III	[84-85]
	Fatostatin	Endometrial cancer	Target SREBP	Preclinical tests	[86]
Amino acid metabolism	BPTES	Colorectal cancer	Inhibit GLS1	Preclinical tests	[87]
	CB-839	Colorectal cancer	Inhibit GLS1	Phase II	[88]
	DFMO	Breast cancer	Block the arginine-polyamine metabolic axis	Phase II	[40]

表2 靶向TAMs代谢的药物

Table 2 Drugs that target the metabolism of TAMs

靶向代谢类型 Targeted metabolic type	名称 Name	癌症类型 Types of cancer	机制 Mechanism	临床分期 Clinical stages	参考文献 References
Lipid metabolism	ARBU (arenobufagin)	Hepatocellular carcinoma	Inhibit LOX-1 receptor and up-regulate ABCA1	Preclinical tests	[92]
	Celecoxib	Colon cancer	Upregulate interferon γ to alter the TAMs phenotype	Phase III	[95]
	Metformin	Prostate cancer	Suppress COX-2/PGE2 axis	Phase II/III	[96]
	EI-05	Breast cancer	Promote lipid droplet formation of TAMs	Preclinical tests	[97]
	Etomoxir	Hepatocellular carcinoma	Inhibition of FAO	Preclinical tests	[98]
	Decitabine	Hepatocellular carcinoma	Inhibit FAO oxidation and reverse TAMs polarization	Preclinical tests	[99]
Amino acid metabolism	Glufosinate	Lung, skin, and breast cancers	Lower glutamine levels	Preclinical tests	[100-101]
	SRX3207	Lung cancer, melanoma, colorectal cancer	Inhibit ARG1 expression and increase INOS	Preclinical tests	[102]
	PEG-BCT-100	Advanced solid tumors	Induce arginine depletion	Phase II	[103]
	Epacadostat	Melanoma	Inhibit tryptophan metabolism	Phase II	[104]
Glycometabolism	Chloroquine	Liver cancer, melanoma	Reprogram the metabolism of TAMs, from oxidative phosphorylation to glycolysis	Phase I/II	[105]
	2-DG	Pancreatic cancer	Inhibit glycolysis	Phase I	[106]

进展, 联用PD-1抗体可克服肿瘤的免疫治疗耐药[92]。值得注意的是, 过量的细胞内游离胆固醇可通过增加内质网应激引起细胞毒性, 从而导致细胞凋亡。因此, 抑制胆固醇酯化被认为是转移性癌症的一种新的治疗策略[93]。

TAMs通过过表达COX-2和mPGES1, 促进AA代谢以生成PGE2; 而PGE2能够直接上调PD-L1的表达。研究表明, COX-2抑制剂塞来昔布(celecoxib)除了能联合抗PD-1治疗抑制B16-F10黑色素瘤和4T1乳腺癌模型中的PD-L1表达外, 还可以促进干扰素γ的产生, 将TAMs的表型从M2逆转为M1[94-95]。一项针对前列腺癌小鼠模型的研究也表明, 二甲双胍(metformin)抑制COX-2/PGE2轴, 并通过减少免疫抑制TAMs的浸润进一步抑制肿瘤进展[96]。此外, EI-05作为E-FABP的新型激活剂, 可刺激TAMs促进脂滴形成和IFNβ产生, 以及增强TAMs的抗肿瘤活性, 从而抑制乳腺肿瘤生长。然而, EI-05作为一种单靶点E-FABP激活剂, 其作用可能因FASN等酶的表达下调(尤其在III级癌中)而失效[97]。FAO对于维持TAMs促肿瘤表型至关重要, 依托莫西(etomoxir)可抑制FAO, 从而减少IL-1β的分泌, 并抑制肿瘤细胞的迁移[98]。地西他滨(decitabine)通过其去甲基化作用, 逆转*RIPK3*基因的高甲基化状态, 从而抑制FAO并逆转TAMs的M2极化[99]。这些结果表明, TAMs的脂代谢通路中存在多个潜在的治疗靶点, 针对这些靶点开发药物, 可以为肿瘤治疗提供新的策略和手段。

IL-10通过激活GS促进巨噬细胞向促肿瘤的M2表型极化。研究发现, GS特异性抑制剂草铵膦(glufosinate)可通过降低细胞内谷氨酰胺水平、增加琥珀酸积累并增强糖酵解代谢, 从而逆转M2型巨噬细胞的免疫抑制特性, 提升机体抗肿瘤免疫应答能力[100-101]。此外, TAMs可通过PI3K/AKT/mTOR通路促进ARG1表达, 增强L-精氨酸代谢并诱导免疫抑制; 而抑制PI3Kγ表达可通过下调ARG1并上调iNOS的表达水平, 从而增加细胞内L-精氨酸的蓄积, 最终激活抗肿瘤免疫[102]。PEG-BCT-100则是通过诱导TAMs中的精氨酸耗竭, 去抑制TAMs的生长和增殖[103]。但精氨酸在体内参与多种生理过程, 如蛋白质合成、一氧化氮合成等。因此, PEG-BCT-100可能会对正常细胞产生一定的影响, 尤其是那些对精氨酸需求较高的细胞。抑制TAMs中的色氨酸代谢对于增强机体的抗肿瘤免疫力具有重要意义,

Epacadostat是一种高效的免疫抑制性吲哚胺2,3-双加氧酶1(indoleamine 2,3-dioxygenase 1, IDO1)抑制剂, 并与免疫检查点存在协同作用[104]。IDO1被抑制后, 会代偿性激活其他酶(如TDO), 导致犬尿氨酸通路功能得以维持, 从而使肿瘤产生耐药性, 未来应开发IDO1/TDO双靶点药物阻断代偿性免疫抑制。

更有趣的是, 氯喹(chloroquine)在先前研究中是一种抗疟药, 而目前研究发现氯喹将TAMs极化为M1型, 具体机制是通过激活转录因子EB(transcription factor EB, TFEB)将TAMs的代谢从OXPHOS重新编程为糖酵解, 从而增强机体的抗肿瘤免疫力[105]。作为HK2的竞争性抑制剂, 2-脱氧葡萄糖(2-deoxyglucose, 2-DG)通过抑制TAMs中的糖酵解, 有效抑制肿瘤细胞的EMT, 是一种很有前景的糖酵解抑制剂[106]。

4.3 其他治疗策略

肿瘤细胞与TAMs在TME中相互依存、相互影响, 仅针对单一目标的治疗策略存在局限性。因此, 开发共同靶向肿瘤细胞和TAMs代谢的药物能更有效地发挥治疗作用, 开启肿瘤治疗的新纪元。作为阻断谷氨酰胺代谢的前体药物, JHU083不仅对癌细胞有影响, 而且对TME的免疫成分也有作用。它通过增加抗肿瘤炎性TAMs的产生来改善抗肿瘤免疫疗效, 并降低肿瘤的转移潜力[107]。辛伐他汀则通过破坏脂筏, 阻断整合素β3/FAK信号通路, 使耐药癌细胞对紫杉醇重新敏感, 同时通过调节胆固醇相关的肝脏X受体/ATP结合盒转运蛋白A1轴来促进M2型TAMs向M1表型转换, 这使得TGF-β分泌减少, 从而抑制TGF-β引起的上皮–间质转化。而基于辛伐他汀的纳米药物可以提高药物的靶向性、稳定性和疗效[108]。这些联合靶向肿瘤细胞和TAMs代谢的药物有望克服单一治疗的局限性, 提高治疗效果, 故开发共同靶向药物是未来有必要进一步研究的。

研究表明, 巨噬细胞通过各种机制影响肿瘤细胞, 已成为免疫系统的新关注点和靶点。巨噬细胞在TME中含量丰富且具有高度表型可塑性, 并在免疫调节中起关键作用, 这促使人们开发了基于CAR巨噬细胞的治疗方案。KLICHINSKY等[109]利用复制缺陷型腺病毒载体, 开发出基于CD3ζ的抗HER2 CAR巨噬细胞, 实现高效CAR递送。而腺病毒感染诱导CAR巨噬细胞中的M1分化, 使TME从抗炎转变为促炎状态。在体内, 这些CAR巨噬细胞显著延长了肿瘤植入小鼠的生存期并减少了肺转移[109]。此外, 抗Dectin-1抗体可逆转TAMs的免疫抑制效应并恢复T细胞效应器功能, 与抗PD-L1抗体组合治疗时对肿瘤细胞凋亡方面产生协同作用, 表明Dectin-1$^+$ TAMs有望成为免疫治疗靶点并增强ICIs的抗肿瘤作用[110]。这种联合治疗策略在癌症研究中被广泛探讨和应用, 为提高癌症治疗效果提供了新的可能性。

5 小结与展望

肿瘤细胞与TAMs的代谢相互作用共同促进了肿瘤细胞的存活与免疫逃逸, 其中代谢调控在此过程中发挥着关键作用。改变肿瘤细胞的代谢不仅能影响其自身生长, 还能改变TAMs的代谢状态和表型。当TAMs的代谢被重新编程时, 会形成一个反馈回路, 进而影响癌症的发展。而目前TAMs如何影响肿瘤细胞代谢的研究相对较少, 仍需深入探索。本文总结了目前靶向肿瘤细胞和TAMs代谢的药物和相关的治疗方法, 以及这两种细胞通过代谢重编程相互作用的具体机制, 为高效的肿瘤治疗提供了良好的切入点。然而, 精确靶向TAMs和肿瘤细胞的代谢靶点仍存在诸多挑战与未解之谜。首先, 肿瘤细胞和TAMs在代谢上具有异质性, 当使用专门针对脂质代谢的药物治疗时, 可能表现出相同或相反的效果。其次, 我们发现部分靶向代谢药物的作用途径在肿瘤细胞与正常细胞间存在共享。在开发靶向代谢药物时, 确保靶向TAMs或肿瘤细胞代谢的特异性也是值得考虑的。除了已关注的代谢物(如乳酸、脂肪酸等)外, 微环境中的衣康酸、亚精胺、肌酸等介质同样调控免疫代谢串扰, 其作为治疗靶点的潜力亟待探索。再次, 在现有研究中, 关于TAMs代谢的探索存在明显局限, 多数研究依赖体外模型, 或仅聚焦于基因表达层面, 而对体内TAMs代谢的直接测量严重不足, 这使得我们对TAMs代谢本质的理解还不够深入, 也难以明确其代谢改变是直接由肿瘤诱导的, 还是细胞自身的一种代偿反应。因此, 深入解析免疫细胞与肿瘤细胞之间的代谢相互作用, 将推动癌症免疫代谢治疗的发展, 为肿瘤防治提供更有价值的理论依据与实践策略。

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