•综述•

鞘氨醇激酶和1-磷酸鞘氨醇及其受体信号在肿瘤微环境中的研究进展

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摘要: 鞘氨醇激酶 (SphK)、1-磷酸鞘氨醇 (S1P) 及其受体 (S1PR) 参与肿瘤细胞增殖、迁移等生物学过程, 在癌症的发生发展中起重要作用。近年来, 研究者日益关注癌细胞与肿瘤微环境之间的相互作用, 肿瘤微环境具有遗传稳定性并且能够被诱导为抗肿瘤表型, 具有显著的治疗优势。研究显示, SphK/S1P/S1PR能够调节肿瘤微环境的多个方面。本文从肿瘤免疫微环境、癌症相关成纤维细胞、肿瘤血管生成、肿瘤缺氧微环境4个角度对SphK和S1P/S1PR信号对肿瘤微环境的影响进行综述, 并简要概述相关药物研究情况, 旨在阐明SphK/S1P/S1PR在癌症中的作用及为抗肿瘤药物的研究提供新思路。

关键词: 肿瘤微环境; 鞘氨醇激酶; 1-磷酸鞘氨醇; 1-磷酸鞘氨醇受体; 抗肿瘤药物

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Research progress of sphingosine kinase and sphingosine-1-phosphate (S1P) /S1P receptor signaling in tumor microenvironment

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Abstract: Sphingosine kinase (SphK), sphingosine-1-phosphate (S1P) and S1P receptor (S1PR) are involved in the tumor biological processes such as tumor cell proliferation and migration, and play an important role in the development of cancer. In recent years, researchers have increasingly focused on the interaction between cancer cells and the tumor microenvironment. The tumor microenvironment is genetically stable and can be induced to an antitumor phenotype, which has significant therapeutic advantages. Studies have shown that SphK/S1P/S1PR can regulate multiple aspects of the tumor microenvironment. This review summarizes the effects of SphK and S1P/S1PR signaling on the tumor microenvironment from four perspectives: tumor immune microenvironment, cancer associated fibroblasts, tumor angiogenesis and tumor hypoxic microenvironment, and also outlines potential drug research related to these signal molecules, aiming to elucidate the role of SphK/S1P/S1PR in tumor occurrence and development and provide new ideas for the research of anti-tumor drugs.

Key words: tumor microenvironment; sphingosine kinase; sphingosine-1-phosphate; sphingosine 1-phosphate receptor; anti-tumor drug

近年来, 人们认识到癌细胞与肿瘤微环境之间的相互作用是癌症发生发展的重要因素, 肿瘤微环境包括肿瘤中的所有非癌宿主细胞及其非细胞成分。肿瘤微环境参与癌细胞增殖、抗凋亡、诱导血管生成、启动肿瘤侵袭和转移及肿瘤免疫逃逸[1,2]。癌细胞易发生突变而产生耐药性, 而肿瘤微环境中的非癌细胞在遗传上更具有稳定性, 并且可以通过药物诱导其转化为抗肿瘤表型, 因此, 了解肿瘤微环境, 靶向肿瘤微环境的治疗具有显著的优势[3]。

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1-磷酸鞘氨醇 (sphingosine-1-phosphate, S1P) 是一种重要的鞘脂代谢物, 来源于细胞内的神经酰胺, 神经酰胺酶将神经酰胺转化为鞘氨醇, 随后, 鞘氨醇被鞘氨醇激酶 (sphingosine kinase, SphK) 磷酸化而产生S1P[4]。SphK 有两种同工酶 SphK1 和 SphK2, 它们催化相同的生化反应, 但底物亲和力和亚细胞定位不同, 从而对细胞功能产生不同的影响[5]。SphK1 主要促进细胞增殖、抑制细胞凋亡, 而 SphK2 则具有促凋亡作用[6], 也有研究表明 SphK2 能够促进癌细胞增殖[7]。SphK1 主要位于细胞质中, 其被磷酸化激活后转移到质膜上, 催化 S1P 生成, 其产生的 S1P 通过转运体转移到细胞外以发出信号[8] , SphK1 在多种癌组织中过表达, 能够促进肿瘤的发生发展[9], 其表达增加与预后不良高度相关[10]。SphK2 在细胞核、内质网、线粒体中均有分布, 其产生的 S1P 可以调节基因的表达及线粒体呼吸[11-13], SphK2 核定位减少及质膜定位增加与肿瘤发展有关, 其同样在多种癌组织中过表达, 具有促肿瘤作用[14]。

S1P 以自分泌或旁分泌的方式作用于其特异性 G 蛋白偶联受体 1-磷酸鞘氨醇受体 (sphingosine-1-phosphate receptors, S1PRs)[15], 调节细胞增殖、细胞迁移、血管生成及免疫细胞运输等生物学过程[16]。在心血管系统中, S1P/S1PR1 信号在血管发育中起重要作用, 并且能够促进肌动蛋白细胞骨架的动态重塑和加强细胞间连接, 迅速改善内皮屏障功能, 动脉粥样硬化疾病模型中亦观察到血管内皮细胞 S1P 水平降低及 S1PR1 损伤[17,18]。S1P/S1PR 信号参与 T 细胞、B 细胞、树突状细胞等免疫细胞的迁移和分化, 是免疫介导性疾病如类风湿关节炎、系统性红斑狼疮、特应性皮炎及炎症性肠病的潜在治疗靶点[19]。在神经系统疾病中, 组织中 S1P 水平降低与神经退行性疾病的发生高度相关, S1P/S1PR 轴也通过调节淋巴细胞运输参与多发性硬化症等神经炎性疾病的进展[20]。在癌症中, S1PR 可以与 G 蛋白特异性结合, 当 S1P 与 S1PR 结合时激活多种信号通路如 PI3K/AKT、STAT3 等, 促进肿瘤的迁移、侵袭、增殖和血管生成[21]。目前, 多项研究发现 S1P 作为信号分子参与调节肿瘤微环境, 包括肿瘤免疫微环境、肿瘤相关成纤维细胞、内皮细胞和氧气供应等 (图 1)。

1 SphK 和 S1P/S1PR 信号与肿瘤免疫微环境的关系

免疫细胞是肿瘤微环境的重要组成部分, 其浸润的密度因肿瘤而异, 所有免疫细胞在肿瘤组织中的密度均高于非癌组织[22]。肿瘤细胞可以通过抑制各种效应免疫细胞或刺激免疫抑制细胞来实现肿瘤免疫逃逸[23]。研究已经证明, S1P 在多种类型免疫细胞的运输和活化中发挥重要作用[24,25], 在癌症中, S1P 能够调控肿瘤微环境中的免疫细胞, 进而影响肿瘤的发生发展。

1.1 巨噬细胞

巨噬细胞是存在于所有组织中的固

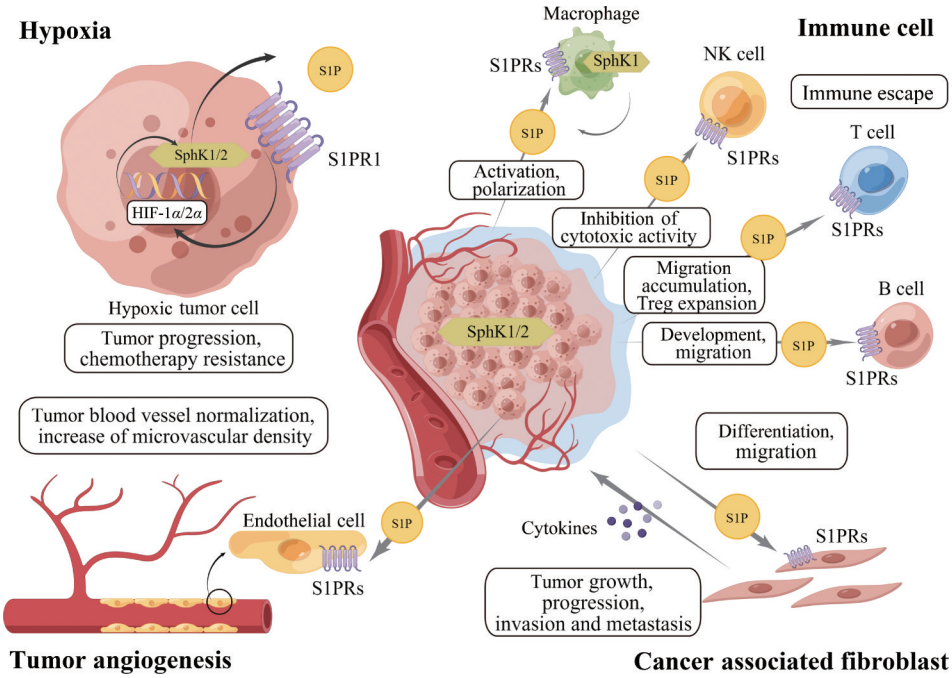

Figure 1 SphK and S1P/S1PR signaling regulate tumor microenvironment (By Figdraw). In the tumor microenvironment, SphK1 and S1P/S1PR signaling can regulate the migration and activation of a variety of immune cells, promote the differentiation and migration of fibroblasts, increase angiogenesis, and make tumor cells adapt to the hypoxic microenvironment. NK cell: Natural killer cell; HIF-1α: Hypoxia-inducible factor-1α

有免疫细胞, 具有强大的吞噬和分泌功能[26]。巨噬细胞不是均一的细胞群, 其表型和功能表现出高度异质性, 根据巨噬细胞活化方式、表面分子、分泌细胞因子及生物学功能不同将其分为经典活化的M1型与可选择活化的M2型[27], M1型巨噬细胞参与抗原呈递、具有抗肿瘤作用, M2型巨噬细胞促进抗炎反应、具有促肿瘤作用[28]。在肿瘤微环境中的巨噬细胞被称为肿瘤相关巨噬细胞 (tumor associated macrophages, TAM), TAM是支持肿瘤发生发展的重要因素[29], 与患者预后不良有关[30]。S1P能够调节巨噬细胞迁移、存活、极化及吞噬作用[31], 在肿瘤微环境中, SphK/S1P/S1PR轴在巨噬细胞活化和极化中发挥重要作用。

癌细胞能够分泌S1P使肿瘤微环境中的巨噬细胞发挥支持作用。在急性T细胞白血病中, 凋亡的Jurkat细胞分泌的S1P不仅可以作为单核细胞和巨噬细胞有效的趋化剂[32], 也能够促进巨噬细胞存活[33]并且通过上调巨噬细胞内缺氧诱导因子 (hypoxia-inducible factor, HIF) 1α转录促进其向M2表型转化[34]。S1P的促极化作用在乳腺癌模型[34,35]和黑色素瘤模型[36]中得到验证。进一步的研究表明, S1P-S1PR4信号介导了凋亡肿瘤细胞活化人巨噬细胞产生免疫抑制因子IL-10的过程[37]。SphK1和SphK2也参与了S1P的促极化作用, 二者下调都能使巨噬细胞转化为抗肿瘤的M1表型[36,38]。此外, 凋亡的Jurkat细胞分泌的S1P还能刺激巨噬细胞释放更多前列腺素E_2 (prostaglandin E_2, PGE_2) 刺激内皮细胞的迁移和增殖, 从而促进血管生成[39]。

SphK、S1P、S1PR通过活化巨噬细胞在肿瘤进展中发挥重要作用。当巨噬细胞中SphK1上调时, 其白介素-6 (interleukin-6, IL-6)、环氧化酶-2 (cyclooxygenase-2, COX-2) 和肿瘤坏死因子-α (tumor necrosis factor-α, TNF-α) 表达水平显著增加, 在结肠癌变的早期及结肠炎相关癌症的进展中起关键作用[40,41]。在肥胖依赖性乳腺癌小鼠模型中, SphK1/S1P/S1PR1轴是连接肥胖、慢性炎症和乳腺癌的关键因素, 可以促进促炎细胞因子表达和TAM浸润, S1PR1信号传导通过上调TAM中NLRP3炎症小体表达和IL-1β产生促进肿瘤淋巴管生成和转移, 从而有利于乳腺癌进展和肺部转移[42,43]。

1.2 自然杀伤细胞 自然杀伤细胞 (natural killer cell, NK cell) 也是一种固有免疫细胞, 对肿瘤细胞具有很强的溶细胞作用, 基于NK细胞的免疫治疗已应用于血液系统恶性肿瘤中[44]。研究发现, S1P在NK细胞增殖、迁移[45]和细胞毒性抑制[46]中起关键作用。在肿瘤微环境中, S1P可以作为抗炎因子, 显著减少NK细胞释放IL-17A和γ干扰素 (interferon-γ, IFN-γ)[47]。同时, S1P/S1PR1信号保护人髓白血病K562细胞免受NK细胞诱导的裂解。S1P还可以上调树突状细胞 (dendritic cell, DC) 表面的人类白细胞抗原 (human leukocyte antigen, HLA) 的HLA-I和HLA-E, 从而调节NK细胞与DC的相互作用[47]。SphK1在自然杀伤细胞型大颗粒淋巴细胞白血病患者的外周血单个核细胞中过度表达, 导致血清中S1P升高, 使用SphK1抑制剂能够诱导异常NK细胞凋亡[48]。

1.3 T细胞 不同T细胞亚型在肿瘤微环境中的比例与患者预后和免疫治疗反应密切相关。$CD8^+$ T细胞在抗肿瘤免疫中起核心作用, 而调节性T细胞 (regulator T cell, Treg) 抑制肿瘤相关抗原呈递, 干扰$CD8^+$ T细胞的细胞毒性作用[22,49]。SphK/S1P/S1PRs信号在T淋巴细胞运输、活化与亚群分化发挥重要作用[50,51]。

S1PR1在T细胞迁移中发挥重要作用[50], 在肿瘤微环境中, S1PR1同样能够介导乳腺癌患者骨髓中肿瘤特异性Treg选择性动员并易位到肿瘤组织中[52]。然而, 靶向此诱导迁移作用可能并不能解除免疫抑制效应, 在胶质母细胞瘤中, 表面S1PR1缺失的幼稚T细胞大量滞留在骨髓中, 而外周血中T细胞数量严重减少, 淋巴器官收缩, 从而导致肿瘤免疫逃逸[53]。S1PR1和S1PR4信号在T淋巴细胞活化及亚群分化中的作用值得关注, 二者可以调节$CD8^+$ T/Treg比例以促进肿瘤免疫逃逸。在黑色素瘤、膀胱癌和乳腺癌的小鼠模型中, S1PR1能够通过JAK/STAT3信号介导肿瘤中的Treg细胞积累, 限制$CD8^+$ T细胞的募集与活化, 促进肿瘤生长[54]。凋亡的乳腺癌细胞释放S1P, 作用于树突状细胞表面的S1PR4诱导IL-27分泌, 激活Treg细胞并抑制$CD8^+$ T细胞的细胞毒性[55]。膀胱癌中S1PR1的上调激活了肿瘤生长因子-β (tumor growth factor-β, TGF-β) 信号通路, 促进肿瘤中Treg扩增[56]。在乳腺癌和结肠炎相关癌症的小鼠模型中, 敲除$CD8^+$ T细胞表面S1PR4可以增加肿瘤组织中$CD8^+$ T细胞丰度, 抑制肿瘤进展[57]。在$CD8^{Low}$ T细胞中, 抑制S1PR4能够增加趋化因子受体CXCR4的表达, 这表明调节S1PR4信号可能是抗CXCR4免疫治疗的潜在联合方法[58]。

近年研究发现, 靶向SphK1能够减少肿瘤微环境中Treg浸润, 增强免疫检查点抑制剂疗效。在黑色素瘤模型中, SphK1缺陷的T细胞维持中枢记忆表型, SphK1/S1P信号通过激活过氧化物酶体增殖物活化受体γ (peroxisome proliferators activated receptor γ, PPARγ) 调节Treg/Th17平衡[59], 沉默SphK1可以观察到肿瘤微环境中的$CD8^+$ T/Treg比例增加[60]。进一步, 有研究者

发现卵巢癌细胞能够释放包裹SphK1的细胞外囊泡以上调微环境中的S1P水平, 通过增加卵巢癌细胞表面程序性死亡配体1 (programmed cell death 1 ligand 1, PD-L1) 表达及促进T细胞耗竭而增强免疫抑制效应[61]。SphK1抑制剂联合免疫检查点抑制剂疗效增强在黑色素瘤、乳腺癌、结肠癌、卵巢癌模型中均得到验证[60,61]。

1.4 B细胞 在肿瘤微环境中, B细胞除了分泌抗体和促炎细胞因子外, 还具有识别抗原、调节抗原加工和呈递以及启动、调节T细胞效应的作用[62]。S1P/S1PRs信号对于B细胞的生长发育和迁移是必需的[51]。目前, 关于肿瘤微环境中S1P信号对B细胞影响的研究主要集中在血液肿瘤领域。在B细胞型慢性淋巴细胞白血病 (B-cell chronic lymphocytic leukemia, B-CLL) 中, 不同的B细胞群表达不同的S1PR组合, S1PR1促进B细胞迁移, 而S1PR4调节、S1PR2抑制S1PR1的促迁移信号[63], S1PR1表达障碍可以延长B-CLL细胞在外周淋巴器官中的滞留时间, 有助于B-CLL细胞生存[64], 上调S1PR1可以促进CLL细胞从淋巴结重新分布到血液中[65]。在弥漫性大B细胞淋巴瘤中, 抑制S1PR1能够下调STAT3活性并导致体外和体内淋巴瘤肿瘤细胞生长抑制[66], S1PR2与致癌转录因子FOXP1的转录水平呈负相关, S1PR2过表达的肿瘤细胞生长受抑制[67]。

1.5 其他免疫细胞 已有研究表明, STAT3是S1PR1基因的转录因子, 同时, S1P/S1PR1信号能够激活STAT3, 二者形成的正反馈环路能够持续活化肿瘤细胞中STAT3信号, 促进肿瘤的恶性进展, 抑制肿瘤细胞或基质髓样细胞的S1PR1表达能够抑制肿瘤生长[68]。髓样细胞中S1PR1-STAT3信号轴对于塑造肿瘤转移前微环境十分重要, 靶向该信号可以抑制肿瘤转移[69]。

在套细胞淋巴瘤中, S1P/S1PR1信号途径影响CD1d依赖性抗原的处理和呈递, S1P含量增加会导致NKT细胞抗肿瘤效应减弱, 而通过敲降SphK减少胞内S1P含量则会增强NKT细胞对套细胞淋巴瘤的杀伤[70]。

2 与癌症相关成纤维细胞的关系

癌症相关成纤维细胞 (cancer associated fibroblast, CAF) 是一组活化的纤维母细胞, 属于间充质细胞谱系, 在肿瘤微环境中具有异质性, 在肿瘤细胞增殖、浸润、转移、上皮间充质转换和耐药中发挥作用[71]。S1P/S1PRs信号能够以浓度依赖性方式诱导成纤维细胞迁移[72], 同时通过反式激活TGF-β信号通路诱导肌成纤维细胞表型[73], 参与多种纤维化疾病的发展[74]。

在肿瘤微环境中, SphK/S1P/S1PR信号能够促进成纤维细胞对癌细胞的支持作用。过表达SphK1的黑色素瘤细胞促使成纤维细胞转分化, 上调成纤维细胞中SphK1表达及S1P分泌, 相应地, 成纤维细胞分泌的S1P通过S1PR1/S1PR3促进黑色素瘤细胞迁移[75]。在高级别浆液性卵巢癌中, SphK1-S1P-S1PR2/S1PR3轴激活TGF-β信号通路, 诱导卵巢成纤维细胞转化为CAF, 促进卵巢癌细胞迁移和侵袭[76]。胰腺癌细胞产生S1P作用于胰腺星状细胞上的S1PR2, 使其分泌包括基质金属蛋白酶-9 (matrix metalloproteinase-9, MMP-9) 在内的旁分泌因子, 促进肿瘤细胞生长和迁移[77]。S1PR也能独立影响成纤维细胞, 有研究发现乳腺癌细胞以外泌体的形式分泌的S1PR2可以被成纤维细胞吸收、加工, 加工后的蛋白能够激活成纤维细胞的ERK1/2途径促进细胞增殖[78]。

3 与肿瘤血管生成的关系

血管生成对肿瘤的生长和转移至关重要, 肿瘤微环境中血管内皮细胞、周细胞及骨髓衍生的前体细胞参与肿瘤血管生成, 其中, 血管生成因子、细胞因子和游离非编码RNA可以促进肿瘤血管生成[79,80]。已有研究显示, SphK/S1P/S1PR能够调节上述细胞的增殖、迁移和血管管腔形成, 从而在血管生成中发挥重要作用[81]。

有研究表明, 在肾透明细胞癌中敲低SphK1使得肿瘤血管生成减少[82]。一项基于基因集变异分析评分系统的研究显示, 在乳腺癌中, 高血管生成评分与SphK1高表达及SphK2低表达相关[83]。SphK1产生S1P是乳腺癌诱导的血管生成和淋巴管生成的关键介质[84]。S1P单克隆抗体在多种肿瘤模型中抑制血管生成因子, 减少肿瘤血管生成, 从而减少肿瘤血流[85,86], 也有研究者进一步观察到了抗S1P单抗能促进肿瘤血管重塑, 在后期增加肿瘤血流量[87]。S1PRs在血管生成中具有重要作用。有研究表明, 肿瘤血管内皮细胞上S1PR1的表达对于内皮细胞迁移和肿瘤血管的生成是必需的[88]。S1P通过内皮S1PR1 (及S1PR2/3) 信号传导稳定肿瘤相关血管, 决定了肿瘤血管表型和成熟度[89]。癌细胞诱导内皮细胞中S1PR1活性, 进一步通过血管内皮生长因子 (vascular endothelial growth factor, VEGF) 及其受体VEGFR2信号促进肿瘤血管生成[90]。S1PRs抑制剂FTY720能够减少肾透明细胞癌 (clear cell renal cell carcinoma, ccRCC) 小鼠肿瘤微血管密度并诱导肿瘤血管正常化[91]。不过, 也有研究表明S1PR2对血管生成具有负向调控作用, 在小鼠Lewis肺癌和B16黑色素瘤模型中, 内皮细胞和骨髓来源树突状细胞上的S1PR2缺失导致肿瘤血管生成和肿

瘤生长加速[92]。有研究完整地显示了SphK/S1P/S1PRs信号在肿瘤血管生成中的作用。在胶质瘤细胞缺氧应激期间, 其SphK1表达和酶活性增加, 细胞内S1P产生和释放增加, 作用于人脐静脉内皮细胞上的S1PR, 介导血管新生[93]。在卵巢癌中, SphK1表达水平与卵巢癌组织的微血管密度密切相关, S1P通过S1PR1和S1PR3诱导血管生成因子分泌从而促进血管生成[94]。总而言之, SphK/S1P/S1PRs信号能够促进肿瘤血管生成, 但仍需关注其对血管重塑的调控以综合评估其对肿瘤发展的影响。

4 与肿瘤缺氧微环境的关系

在肿瘤微环境中, 癌细胞的迅速增殖和肿瘤血管的异常生长导致肿瘤组织氧气供应不足[95]。SphK1和SphK2在缺氧条件下上调能够促进肿瘤进展。在缺氧条件下, SphK1通过激活ERK通路促进胶质瘤细胞增殖[96], A549细胞系中SphK2表达上调、增加S1P分泌并且诱导S1PR1/S1PR3介导的化疗耐药性[97]。

HIF是信号通路的关键分子, 在维持缺氧状态和促进肿瘤进展中起关键作用[98]。有研究者发现, 在胶质母细胞瘤中采用氯化钴诱导的缺氧能够诱导SphK1表达及S1P分泌增加, 沉默HIF-2α会消除该诱导作用, 而沉默HIF-1α则会上调HIF-2α与SphK1的表达。进一步, 研究者发现SphK1启动子具有两个HIF靶向的缺氧反应元件 (hypoxia response element, HRE)[93]。在卵巢癌细胞系中, HIF-1α或HIF-2α的上调显著诱导SphK1蛋白表达增加[99]。这似乎表明HIF-1α与HIF-2α在上游调控SphK1相关信号, 但亦有多项研究发现, SphK1/S1P/S1PR1信号也能够调节HIF信号。在几种癌细胞系 (前列腺癌、胶质母细胞瘤、乳腺癌、肾细胞癌和肺癌) 中, 缺氧条件下SphK1活性显著上调, 通过AKT/GSK-3β信号途径上调细胞中HIF-1α水平[100]。ccRCC中SphK1/S1P信号传导通过磷脂酶D驱动的机制控制HIF-2α的表达和转录活性[101], 在ccRCC中使用FTY720能够拮抗S1PR1并且抑制SphK1, 显著下调癌细胞内HIF-1α和HIF-2α表达[91]。细胞外S1P调节几种癌细胞系 (前列腺癌、肺腺癌、胶质母细胞瘤) 缺氧条件下的HIF-1α水平, 使用S1P单克隆抗体可以下调癌细胞内HIF-1α的表达和活性[87]。在缺氧处理的骨肉瘤细胞系中, SphK1/S1P/S1PR1信号传导促进HIF-1α积累[102], SphK1通过调节HIF-1α表达促进骨肉瘤细胞的糖酵解以及对多柔比星的抗性[103]。

5 靶向SphK/S1P/S1PR信号的化合物的抗肿瘤作用

鉴于SphK/S1P/S1PR在癌症的发生发展中具有重要作用, SphK抑制剂、S1P抗体和S1PR拮抗剂作为癌症治疗的潜在药物被广泛研究 (表1)。

Table 1 Compounds targeting SphK/S1P/S1PR signaling. S1P: Sphingosine-1-phosphate; S1PRs: Sphingosine-1-phosphate receptors; SphK: Sphingosine kinase

Drug name	Target	Selective	Clinical information
SKI-I	SphK1	Yes	Preclinical
SKI-II	SphKs	No	Preclinical
PF543	SphK1	Yes	Preclinical
ABC294640	SphK2	Yes	Phase II
			NCT02229981
			NCT02939807
			NCT02757326
			NCT03377179
FTY720	SphKs	No	Preclinical
Sonepcizumab	S1P	Yes	Phase I
			NCT00661414
Suramin	S1PR3	Yes	Phase II
			NCT00054028
			NCT01038752
			NCT01671332

5.1 靶向SphK的抑制剂 SKI-(I-IV)是非脂质小分子SphK抑制剂, 其中研究最充分的是SKI-II及SKI-I。SKI-II是一种非选择性的SphKs抑制剂, 可以竞争性结合SphKs但不影响ATP结合[104]。研究表明, SKI-II在异种移植小鼠肿瘤模型中抑制肿瘤发生, 抑制乳腺癌、前列腺癌、急性髓系白血病细胞等肿瘤细胞增殖、诱导细胞凋亡[105,106]。SKI-I是SphK1的选择性抑制剂, 比SKI-II更有效, 可抑制ERK2, 但二者的溶解度和生物利用度都较低, 限制了其进一步应用于临床[107]。

PF543是一种新型的SphK1选择性抑制剂, 作为一种鞘氨醇的竞争性抑制剂, 对SphK1的选择性比SphK2及S1P受体高100倍, 能够显著下调SphK1和内源性S1P水平[108]。研究显示, PF543在不同癌细胞系中的细胞毒性存在差异, PF543对结直肠癌肿瘤细胞和头颈部鳞状细胞癌肿瘤细胞具有抑制增殖和促进凋亡、坏死和自噬的作用[109,110], 而在头颈癌细胞系1483中, PF543对肿瘤细胞的生存和增殖没有显著抑制作用[108]。

ABC294640是特异的竞争性SphK2抑制剂[111], 能够降低细胞内S1P水平, 抑制pERK和AKT信号传导[112], 促进肿瘤细胞凋亡和自噬, 降低癌细胞内c-Myc水平[113,114], 研究表明, ABC294640能够下调胰腺癌细胞内c-Myc水平, 从而增强其对吉西他滨的敏感性[115], 通过干扰STAT3通路与索拉非尼发挥协同作用[114]。临床前研究表明, ABC294640有良好的口服生物利用度和安全性[112]。目前已开展包括弥漫性大B细胞淋巴瘤 (NCT02229981)、肝细胞癌 (NCT02939807)、多发性骨髓瘤 (NCT02757326) 和胆管癌 (NCT03377179)

临床试验[116]。

FTY720是一种鞘氨醇类似物, 目前已作为免疫抑制剂治疗多发性硬化, 其被磷酸化后可以诱导S1PR内化从而发挥免疫抑制作用[117]。FTY720的抗肿瘤细胞增殖作用在多种癌症中均有报道, 包括肝癌、乳腺癌、前列腺癌、卵巢癌等。其抗癌机制包括抑制或降解SphK1、重新激活蛋白磷酸酶2A、诱导细胞凋亡、抑制SphK1或PI3K/AKT/mTOR信号传导等, 但很大程度上独立于其对S1PRs的作用[118]。此外, FTY720的免疫抑制作用是其产生药物不良反应的主要原因, 目前已开发其类似物如OSU-2S以减少免疫方面不良反应[119]。

5.2 S1P阻断抗体 Sonepcizumab是靶向S1P的单克隆抗体, 在多种肿瘤的异种移植肿瘤模型中具有抑制肿瘤血管生成和肿瘤生长、转移的作用[86], 但其在实体瘤患者的临床试验 (NCT00661414) 未达到无进展生存期的主要终点, 并且可诱发外周淋巴细胞减少[120], 这可能导致肿瘤免疫抑制, 从而限制其临床应用。

5.3 S1PR拮抗剂 Suramin是尿素衍生物, 可以拮抗S1PR3, 在转移性乳腺癌的I/II期临床试验 (NCT00054028) 中, 非细胞毒性剂量的suramin联合紫杉醇具有良好的抗肿瘤作用[121]。Suramin在非小细胞肺癌中亦与多西紫杉醇联合进行 (NCT01038752、NCT01671332) II期临床试验, 但未观察到对多西紫杉醇疗效的显著改善作用。

6 总结与展望

综上, SphK/S1P/S1PR信号在肿瘤微环境的调节中起重要作用。肿瘤细胞能够通过该通路调节微环境中的非癌细胞发挥促肿瘤作用, 实现免疫逃逸, 增加血管生成, 适应缺氧环境。相对地, 肿瘤微环境中受该信号刺激的非癌细胞也能够通过分泌细胞因子等各种方式, 塑造有利于肿瘤的微环境, 促进肿瘤发生发展和耐药。但是, 目前的研究结果仍有矛盾与不足之处, 如有研究表明S1PR2信号传导能够稳定肿瘤相关血管[89], 但另一项研究却发现S1PR2对血管生成具有负向调控作用[92]。多项研究表明, HIF-1α与HIF-2α在上游调控SphK1相关信号[93,99], 但亦有一些研究发现, SphK1/S1P/S1PR1信号也能够调节HIF信号[91,100]。这表明研究者还需要更全面、更深入的研究以阐明SphK/S1P/S1PR信号在肿瘤微环境中的调节机制。

从现有的研究结果来看, SphK/S1P/S1PR是针对肿瘤微环境的有希望的治疗靶点, 在最近的研究中也有学者在动物实验中发现靶向SphK1能够增强肿瘤免疫检查点抑制剂的疗效[60,61]。但正如前文所言, 目前仍没有有效的调节剂应用于临床治疗, 与肿瘤微环境治疗相结合的研究也比较少见, 未来还需要开发高亲和力和高特异性的治疗药物, 并且注意考察其对肿瘤微环境的影响。随着相关研究的日益深入, 靶向SphK/S1P/S1PR信号轴将成为一种具有应用前景的癌症治疗方式。

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