•综述•

LSD1促进肿瘤发生发展的机制和靶向治疗研究进展

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摘要: 赖氨酸特异性去甲基化酶1 (lysine-specific demethylase 1, LSD1) 是黄素腺嘌呤二核苷酸依赖型单胺氧化酶家族的成员之一, 在多种肿瘤细胞中均高表达。LSD1参与肿瘤细胞增殖、侵袭、分化及免疫细胞杀伤等多种进程, 在肿瘤进展中起到关键作用。研究发现, LSD1不仅通过去甲基化组蛋白和非组蛋白底物发挥作用, 同样也可以通过不依赖去甲基化酶活性的蛋白−蛋白相互作用多样化地发挥促肿瘤功能。随着对LSD1促肿瘤机制研究的日益深入, 靶向LSD1治疗肿瘤已经成为领域研究热点。本文对LSD1作用于不同蛋白所发挥的促癌功能进行综述, 同时对进入临床阶段的LSD1抑制剂进行了整理。对LSD1在肿瘤中功能的全面理解将为开发更有效及更具特异性的LSD1抑制剂提供理论支撑, 为靶向LSD1发挥更好的抗肿瘤治疗指明方向。

关键词: 赖氨酸特异性去甲基化酶1; 肿瘤; 组蛋白; 蛋白−蛋白相互作用; 肿瘤免疫微环境

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Advances in the study of tumorigenesis and progression mechanism of LSD1 and its targeting strategies

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Abstract: Lysine-specific demethylase 1 (LSD1) is a member of the flavin adenine dinucleotide (FAD)-dependent monoamine oxidase family and is highly expressed in various tumor cells. LSD1 plays a crucial role in tumor progression by participating in multiple processes such as tumor cell proliferation, invasion, differentiation, and immune cell killing. Studies have shown that LSD1 exerts its oncogenic functions not only by demethylating histone and non-histone substrates but also through demethylase activity-independent protein-protein interactions, thereby diversifying its mechanisms of action. With the increasing depth of research into the tumor-promoting mechanisms of LSD1, targeting LSD1 for cancer therapy has become a major focus in the field. This review summarizes the oncogenic functions of LSD1 through its interactions with different proteins and provides an overview of LSD1 inhibitors that have entered clinical stages. A comprehensive understanding of the roles of LSD1

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in tumors will offer theoretical support for developing more effective and specific LSD1 inhibitors, thereby guiding future directions for enhanced anti-tumor therapies targeting LSD1.

Key words: lysine-specific demethylase 1; tumor; histone; protein-protein interaction; tumor immune microenvironment

赖氨酸特异性去甲基化酶 1 (lysine-specific demethylase 1, LSD1) 是黄素腺嘌呤二核苷酸 (flavin adenine dinucleotide, FAD) 依赖型单胺氧化酶家族的成员之一。LSD1 在 2004 年作为第一个组蛋白去甲基化酶被发现, 证明了组蛋白的甲基化修饰和其他的组蛋白修饰一样, 是一个可逆的过程[1]。LSD1 的底物特异性、功能多样性、与多种疾病的强关联性, 一直受到研究人员的广泛关注。

LSD1 在多种血液系统恶性肿瘤和实体瘤中均高表达。LSD1 在急性髓系细胞白血病 (acute myelocytic leukemia, AML) 和急性淋巴细胞白血病 (T-cell acute lymphoblastic leukemia, T-ALL) 中 LSD1 表达增加[2-7]。同时, 它在包括非小细胞肺癌 (non-small cell lung cancer, NSCLC)、小细胞肺癌 (small-cell lung carcinoma, SCLC)、前列腺癌 (prostate cancer, PCa)、肝癌 (liver cancer)、结直肠癌 (colorectal cancer, CRC)、胃癌 (gastric cancer, GC)、乳腺癌 (breast cancer, BC) 和神经母细胞瘤 (neuroblastoma, NB) 中表达量升高[8-17]。LSD1 在不同肿瘤中拥有不同的突变偏好。其中, 丧失胺氧化酶样结构域 (AOL domain) 和塔结构域 (TOWER domain) 的截短型突变 LSD1 转录功能发生改变, 从转录水平提高促癌基因细胞周期蛋白 D2 (cyclin D2, CCND2) 的表达, 同时从转录水平抑制了抑癌基因 Krüppel 样因子 4 (Krüppel-like factor 4, KLF4) 和 PR/SET 结构域 11 (PR/SET domain 11, PRDM11) 的表达, 从而促进了多发性骨髓瘤的进展[18]。而 LSD1 的 251 位精氨酸突变为谷氨酰胺通过破坏 LSD1/CoREST/HDAC 复合物的形成, 使 LSD1 功能下降, 逆转了 LSD1 对乳腺癌细胞的抑癌作用, 从而促进乳腺癌细胞的侵袭和迁移[19]。LSD1 的广泛高表达凸显了其作为泛癌靶点的价值, 而其癌种特异性突变则强调了开发突变选择性药物及个体化治疗的必要性, 为实现精准肿瘤治疗提供依据。

LSD1 高表达促进癌症的发展、转移和耐药, 其主要作用包括维持肿瘤细胞的干性、促进细胞上皮间质转化 (epithelial-mesenchymal transition, EMT) 与侵袭和抑制细胞凋亡。LSD1 对组蛋白去甲基化的作用一直受到研究人员的关注, LSD1 可特异性去除组蛋白 H3 第 4 位赖氨酸 (H3K4) 和组蛋白 H3 第 9 位赖氨酸 (H3K9) 的单甲基化与二甲基化修饰, 从而对转录产生调控作用进而影响基因的表达。近些年的研究发现, 除组蛋白外, LSD1 还可调节诸多癌症相关非组蛋白底物的甲基化, 同时也可通过与多种蛋白相互作用, 从而影响癌症进程。基于其在多种肿瘤进展过程中发挥的关键作用, LSD1 愈发成为药物开发的热门靶点。目前尚未有以 LSD1 为靶点设计的已上市抗肿瘤药物, 但大量 LSD1 抑制剂正处于临床开发阶段与临床前研究阶段。然而, 目前对于 LSD1 的机制研究尚不够系统和透彻, 以 LSD1 为靶点开发的抗肿瘤药物也面临存在血液、肾脏等毒性, 单药易耐药, 生物标志物缺失等问题。因此, 系统性地总结目前对于 LSD1 相关促癌机制的研究及相关抗癌药物的开发情况, 并将它们进行有机的串联组合, 赋予药物更充分的机制背景, 赋予机制以药物验证, 这对于提高人们对 LSD1 的整体了解、促进 LSD1 抑制剂的开发十分有益。相较于既往综述, 本文系统梳理了与 LSD1 相互作用的蛋白质, 并构建了“LSD1-互作蛋白−作用机制−靶向化合物−生物学功能”的关联框架, 从而清晰串联起从基础机制到药物发现的完整逻辑链条, 为开发更高选择性与效力的 LSD1 靶向药物提供新的思路与参考。

1 LSD1 发现及结构

1.1 LSD1 的发现 2001 年, Howard 课题组[20]在组蛋白去乙酰基酶 1 (histone deacetylase 1, HDAC1) 复合物中发现了 FAD 依赖型单胺氧化酶家族的蛋白质 KIAA061。2004 年, Shi 课题组[1]鉴定出 KIAA061 即第一个被发现的组蛋白去甲基化酶, 并将其命名为 LSD1。

1.2 LSD1 的结构与功能 LSD1 的蛋白结构具有高度保守性, 由 852 个氨基酸组成, 包括 3 个主要的结构域: N 端的 SWIRM 结构域 (Swi3p, RSC8p, and Moira domain)、AOL 结构域和两段 TOWER domain 结构域[21]。SWIRM 结构域起到稳定 LSD1 蛋白结构的作用, 两段 AOL 结构域段共同形成 LSD1 的酶活核心结构, 该区段可以非共价的形式结合 FAD; TOWER 结构域为 LSD1 与作用于核小体所需的 REST 辅助抑制因子 (corepressor of REST, CoREST) 结合提供平台 (图 1A、B)[21,22]。

由于 LSD1 的催化结构域与胺氧化酶的催化结构

域不论在结构还是催化机制方面都具有很强的相似性, 因此基于“老药新用”的思路, 单胺氧化酶 (monoamine oxidase, MAO) 抑制剂——反苯环丙胺 (tranylcypromine, TCP) 被作为LSD1的抑制剂展开了研究。目前一系列以TCP结构为基础的LSD1抑制剂已进入临床试验阶段, 包括ORY-1001、GSK-2879552、INCB059872、IMG-7289和ORY-2001等[23]。

作用机制方面, LSD1对组蛋白H3K4去甲基化的功能依赖于FAD, 通过氧化反应催化单甲基化或二甲基化的H3K4去甲基化, 但无法对三甲基化的H3K4去甲基化。LSD1对组蛋白H3K4的去甲基化过程主要包含以下几个步骤: 首先, LSD1与组蛋白H3结合, 随后其FAD辅基将第4位赖氨酸上的甲基氧化, 生成亚胺中间体, 同时氧气被还原为过氧化氢。接着, 该亚胺中间体经水解释放出甲醛, 并产生去甲基化的赖氨酸。若底物为二甲基化赖氨酸, 则上述步骤需重复进行一次 (图1C)[24,25]。当LSD1与CoREST、C末端结合蛋白1 (C-terminal-binding protein 1, CtBP1) 及核小体重塑和去乙酰化酶 (nucleosome remodeling and deacetylase, NuRD) 复合物相互作用时, LSD1使H3K4去甲基化, 对转录起到抑制作用[1,26-29]。

LSD1对组蛋白H3K9去甲基化的过程同样依赖于FAD。不同的是LSD1与雄激素受体 (androgen receptor, AR) 或雌激素受体 (estrogen receptor, ER) 相互作用, 使其不再作用于单甲基或二甲基化的H3K4而是作用于单甲基或二甲基化的H3K9, 从而促进转录[30-32]。LSD1可与含有Jumonji结构域的赖氨酸去甲基酶4C (lysine demethylase 4C, JMJD2C) 去甲基化酶产生协作, 刺激雄激素靶基因的转录, 从而使肿瘤细胞增长速度加快[31,33,34]。使用LSD1抑制剂对LSD1进行抑制, 可降低肾癌细胞中的AR活性, 减缓异种移植瘤小鼠模型中的体内肿瘤生长[35]。有报道表明因LSD1具有去甲基化反应释放H_2O_2的特点, ER在结合的靶点上募集LSD1, 进而募集碱基切除修复酶并引起DNA氧化, 进而促进转录[32]。在雌激素刺激下, LSD1与雌激素相关受体α (estrogen-related receptor-alpha, ERRα) 相互作用, 使启动子和增强子对LSD1的募集增加, 随后激活转录并刺激肿瘤细胞增殖和侵袭, 引起肿瘤生长 (图1D)[30,36,37]。

综上所述, LSD1与特定蛋白的相互作用决定了其特异性作用于的组蛋白底物。

2 LSD1通过组蛋白修饰促进肿瘤进展

如前文所述, LSD1在调节组蛋白H3K4、H3K9的甲基化状态中起重要作用。具体到肿瘤生物学领域, 目前已有诸多研究表明LSD1通过对肿瘤细胞组蛋白中单甲基化及双甲基化的H3K4和H3K9去甲基化, 起到了促进癌症进展的作用。

LSD1除与上文提到的CoREST具有相互作用外, 还可与其他蛋白, 如与SNAG家族的蛋白相互作用, 作用于组蛋白从而对转录产生调控作用。具有SNAG结构域的多种蛋白质均已被报道与LSD1具有相互作用, 其中包括Snail家族转录抑制子1 (Snail family transcriptional repressor 1, Snail1) 和Snail家族转录抑制子2 (Snail family transcriptional repressor 2, Snail2)[38]。有研究表明, LSD1与Snail1或Snail2存在相互作用, Snail1或Snail2募集LSD1, 起到抑制转录的作用。且使用抑制剂parnate或多肽TAT-SNAG抑制LSD1与Snail1或Snail2间的相互作用可抑制肿瘤细胞的侵袭性, 从而抑制转移[38]。有文献[38,39]报道, E钙黏蛋白 (epithelial cadherin, E-cadherin) 是一种与EMT密切相关的蛋白, 据报道Snail1和Snail2等转录因子可以通过抑制E-cadherin表达来促进EMT, 从而导致癌症的转移, 但Snail1和Snail2的作用依赖于LSD1, 在抑制LSD1表达后, Snail1和Snail2不再对E-cadherin产生抑制作用。据报道在结直肠癌中LSD1与E-cadherin启动子发生物理相互作用, 降低该区域的二甲基H3K4, 下调E-cadherin表达, 从而促进结肠癌转移 (图2A)[40]。有趣的是, 除与Snail1和Snail2相互作用抑制E-cadherin表达外, LSD1还可在ASXL1等基因的启动子区去除H3K4me2, 抑制其转录, 促进EMT发生[41]。这些均体现了LSD1可通过组蛋白修饰促进EMT从而促进肿瘤转移。

除了促进肿瘤细胞的生长和侵袭, LSD1还可作用于组蛋白影响肿瘤细胞免疫应答。在三阴性乳腺癌中, 使用LSD1抑制剂SP-2509后, 上调相关基因启动子区域的H3K4双甲基化, 增加肿瘤细胞释放C-X-C基序趋化因子5 (C-X-C motif chemokine 5, CXCL5)、C-X-C基序趋化因子9 (C-X-C motif chemokine 9, CXCL9) 和C-X-C基序趋化因子10 (C-X-C motif chemokine 10, CXCL10) 等趋化因子, 使肿瘤部位的$CD8^+$ T浸润增加。在三阴性乳腺癌的异种移植瘤小鼠中, 使用LSD1抑制剂和抗程序性死亡受体1 (programmed death-1, PD-1) 抗体, 可增强PD-1阻断抑制肿瘤生长和肺转移的效果[42]。除乳腺癌外, 抑制LSD1可通过Janus激酶 (Janus kinase, JAK) 通路下调肺腺癌细胞中的细胞程序性死亡配体1 (programmed death ligand 1, PD-L1) 表达来阻止肿瘤生长和转移[43,44]。使用抑制剂抑制小细胞肺癌中的LSD1可恢复MHC I类抗原呈递, 并缓解PD-L1检查点疗法耐药[45]。通过LSD1抑制剂靶向LSD1可抑制干细胞样

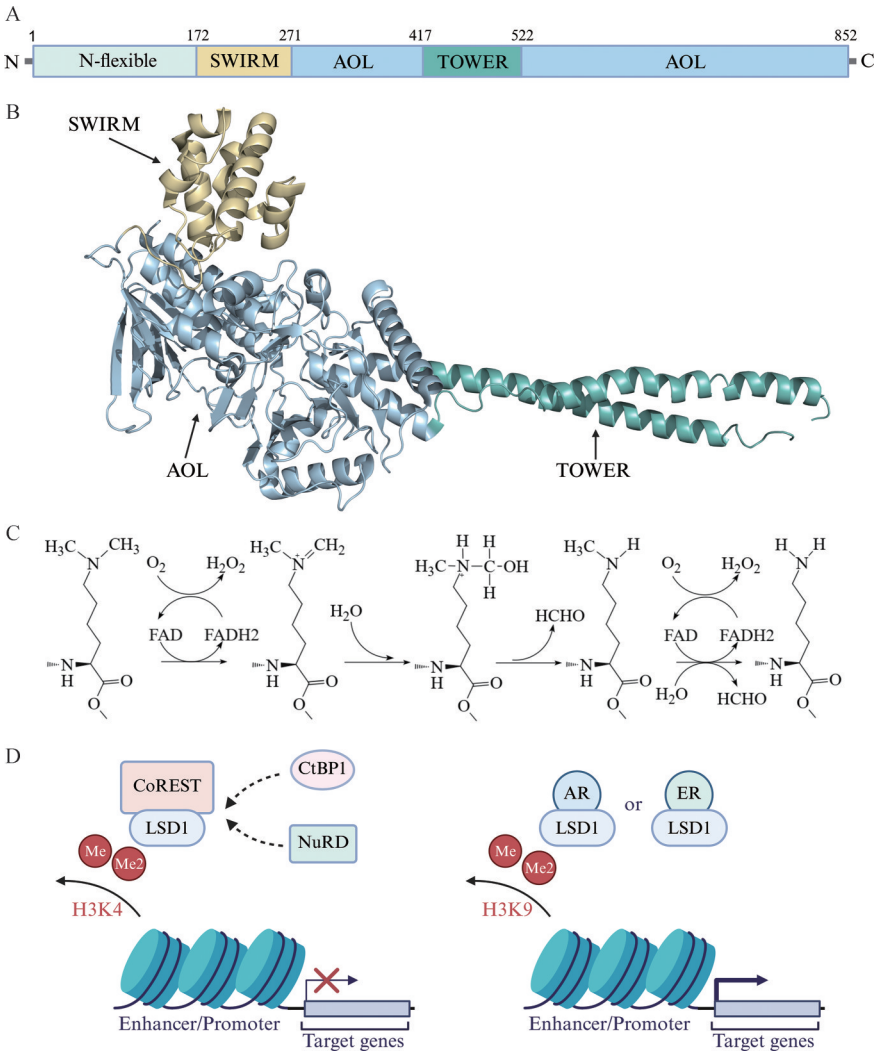


Figure 1 The structure and function of LSD1. A: The protein sequence of LSD1; B: The three-dimensional protein structure of LSD1 (the structure is obtained from PDB ID: 3ABT); C: The molecular mechanism by which LSD1 performs demethylase function; D: The basic function of LSD1. Figure created with BioRender (biorender.com). CoREST: Corepressor of REST; LSD1: Lysine-specific demethylase 1; CtBP1: C-terminal-binding protein 1; NuRD: Nucleosome remodeling and deacetylase; AR: Androgen receptor; ER: Estrogen receptor

特性, 并使头颈部鳞状细胞癌对 PD-1 阻断敏感 (图 2B)[46]。这提示研究者, 抑制 LSD1 能够增强免疫细胞浸润并克服肿瘤免疫逃逸, 为后续 LSD1 抑制剂的开发和使用提供了新的思路。

除影响肿瘤细胞自身外, LSD1 也通过外泌体发挥作用。在 PDX 模型中 LSD1 通过诱导外泌体中 PD-L1 的积累来抑制胃癌微环境中 T 细胞的应答[43,44,47]。这提示 LSD1 与 PD-L1 具有广泛的相互作用, 其机制也值得进一步进行探索。

3 LSD1 作用于非组蛋白促进肿瘤进展

LSD1 对组蛋白的去甲基化功能已经被大家所熟知, 但除此之外, 大量的非组蛋白已被鉴定为 LSD1 的底物。

肿瘤抑制因子 P53 (tumor protein 53, P53) 是第一个被发现的 LSD1 非组蛋白底物。LSD1 催化 P53 的第 370 位赖氨酸位点发生去甲基化, 从而抑制 P53 的转录功能并促进癌症的发展[48]。LSD1 还可催化叉头盒蛋白 A1 (forkhead box A1, FOXA1) 的第 270 位赖氨酸位点去甲基化, 抑制 LSD1 会影响 FOXA1 的转录活性, 从而降低其下游的干性蛋白 MYC 的信号转导功能, 抑制去势抵抗性前列腺癌 (castration-resistant PCa, CRPC) 生长[49]。

除了影响蛋白功能外, LSD1 还会去甲基化多种非组蛋白, 通过影响这些蛋白的稳定性, 从而影响癌症的进展。LSD1 可与肌球蛋白磷酸酶靶向亚基 1 (myosin phosphatase target subunit 1, MYPT1) 相互作用, 通过去甲基化 MYPT1 的 442 位赖氨酸位点, 使其无法进入泛素蛋白酶体途径降解, 降低其蛋白质稳定性[50]。已

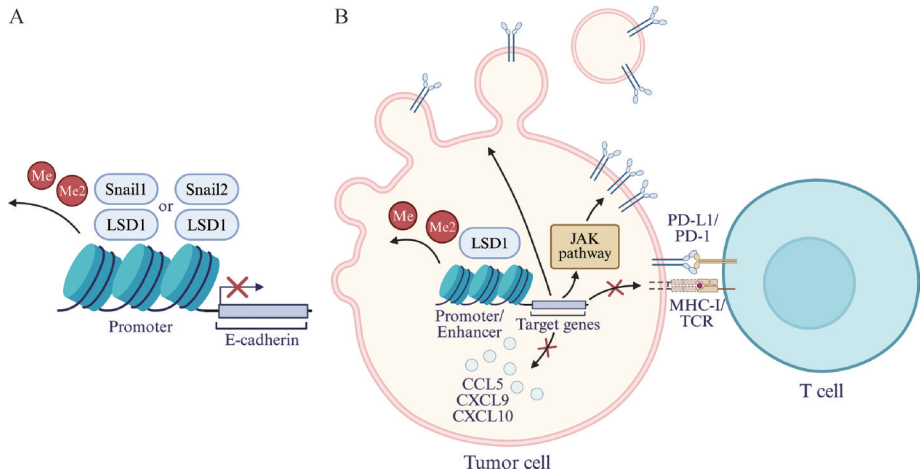


Figure 2 LSD1 targets histones to promote cancer progression. A: LSD1 acts on cancer cells to enhance invasion, metastasis, and other malignant behaviors; B: LSD1 targets the tumor microenvironment to facilitate immune evasion by cancer cells. Figure created with BioRender (biorender.com). Snail1: Snail family transcriptional repressor 1; Snail2: Snail family transcriptional repressor 2; E-cadherin: Epithelial cadherin; JAK: Janus kinase; PD-1: Programmed death-1; PD-L1: Programmed death ligand 1; CXCL5: C-X-C motif chemokine 5; CXCL9: C-X-C motif chemokine 9; CXCL10: C-X-C motif chemokine 10

有多篇文章报道MYPT1的稳定性下调与肿瘤的发展和耐药密切相关[51,52]。LSD1可去甲基化E2F转录因子1 (E2F transcription factor 1, E2F1)的第185位赖氨酸位点, 使E2F1无法进入泛素蛋白酶体途径降解, 从而使静止期肿瘤细胞进入S期, 诱导肿瘤细胞增殖[53,54]。除E2F1外, LSD1也可去甲基化缺氧诱导因子1α (hypoxia-inducible factor 1-alpha, HIF-1α)的第391位赖氨酸位点, 从而使HIF-1α无法进入泛素−蛋白酶体途径降解。由LSD1稳定的HIF1α, 激活对血管内皮生长因子(vascular endothelial growth factor, VEGF)的转录, 使其表达上调, 从而增强肿瘤血管生成, 促进肿瘤进展[55]。除此之外, LSD1还可作用于黑色素瘤(melanoma, MEL)中的argonaute蛋白家族催化成分2 (argonaute RISC catalytic component 2, AGO2)的第726位赖氨酸位点, 通过去甲基化该位点提高AGO2的稳定性, 抑制双链RNA (double-stranded RNA, dsRNA)的异常积累和1型干扰素的活化, 降低肿瘤免疫原性和T细胞的功能, 进而加速肿瘤的发展(图3A)[56]。这些研究均指出, LSD1对非组蛋白的去甲基化作用可以正向或负向调节蛋白质的转录活性和稳定性, 从而影响癌症的进展。除此以外, LSD1也可以不依赖于去甲基化酶的活性, 通过作为支架蛋白或变构调节因子调节蛋白质的功能和稳定性。近期报道称LSD1可以作为变构调节因子通过非酶功能调节蛋白质F-box和WD重复域蛋白7 (F-box and WD repeat domain-containing 7, FBXW7)的稳定性。FBXW7发挥E3泛素连接酶的活性需要发生二聚化, 而FBXW7单体则倾向于自我泛素化[57,58]。LSD1作为伪底物结合FBXW7, 使其无法二聚化, 引发FBXW7的泛素−蛋白酶体途径和自噬溶酶体途径降解, 进而促进肿瘤细胞的增殖[59]。LSD1能够独立于其去甲基化酶活性, 通过使雌激素相关受体α (estrogen-related receptor α, ERRα)不进入蛋白酶体途径降解以稳定ERRα, 促进了癌症的侵袭性, 但具体机制尚待阐明。最近有研究表明, LSD1可通过C末端AOL结构域直接与泛素结合蛋白p62 (sequestosome 1, p62)的N末端PB1 (Phox and Bem1)结构域结合, 作为支架蛋白不依赖去甲基化酶活性促进p62的泛素化和随后的蛋白酶体途径的降解, 从而加速癌症的进展[60]。有部分LSD1新型抑制剂的设计思路为打断LSD1与其互作蛋白的相互作用, 从而抑制肿瘤进展。如具有SNAG结构域的GFI-1和GFI-1B可与LSD1发生相互作用且与白血病分化密切相关[61,62]。研究人员发现使用药物OG86破坏LSD1与GFI-1相互作用后诱导AML细胞的分化[63]。使用新型LSD1抑制剂T-3775440打断LSD1与GFI-1B相互作用, 可诱导AML细胞分化, 从而抑制肿瘤的生长(图3B)[4]。

综上所述, LSD1主要通过两种方式作用于非组蛋白影响癌症进程: ① 依赖于LSD1去甲基化酶活性, 催化非组蛋白去甲基化; ② 不依赖于去甲基化酶活性, 通过蛋白−蛋白相互作用影响蛋白质稳定性。

4 靶向LSD1的抗肿瘤药物研发进程

鉴于LSD1在肿瘤进展中的病理作用已被诸多研究证实, 且其高表达被证明与各种癌症的不良预后相关[28,47,64-66], 基于靶向LSD1的治疗策略已经成为肿瘤学的研究热点。近年出现了一系列的LSD1抑制剂,

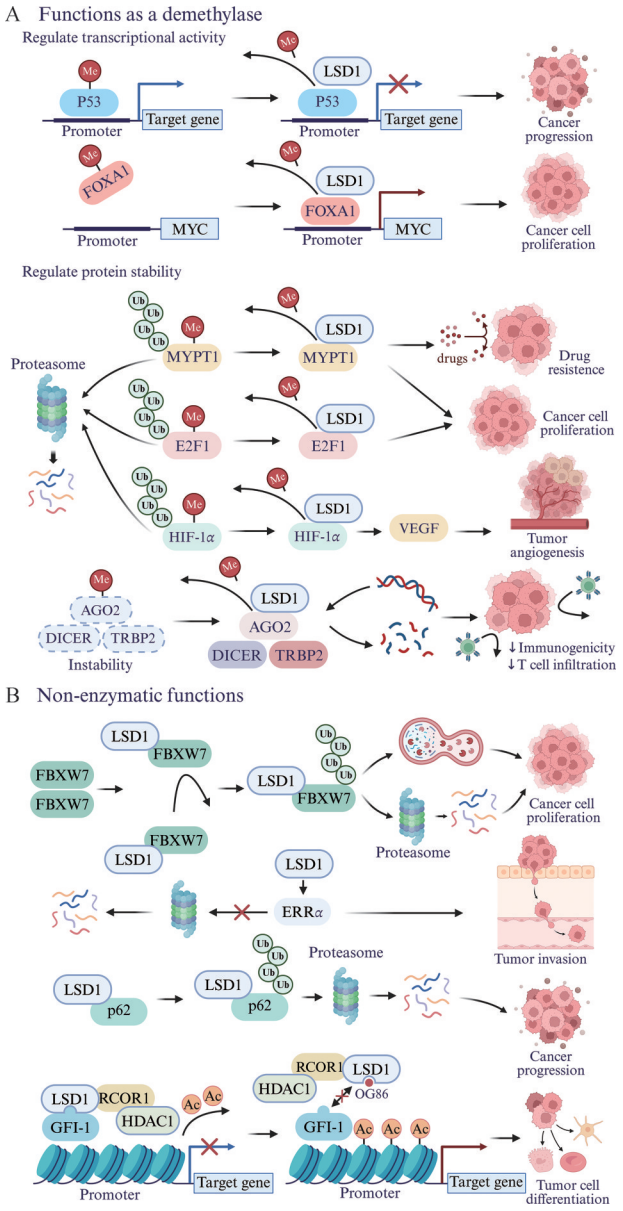


Figure 3 LSD1 promotes tumor progression by targeting non-histone proteins. A: Through its demethylase activity, LSD1 acts on non-histone substrates, modulating their transcriptional activity or stability, thereby promoting tumor progression *via* multiple mechanisms; B: Independent of its enzymatic activity, LSD1 interacts with other proteins to exert tumor-promoting effects. Figure created with BioRender (biorender. com). P53: Tumor protein 53; FOXA1: Forkhead box A1; MYC: Myelocytomatosis oncogene; MYPT1: Myosin phosphatase target subunit 1; E2F1: E2F transcription factor 1; HIF-1*α*: Hypoxia-inducible factor 1-alpha; VEGF: Vascular endothelial growth factor; AGO2: Argonaute RISC catalytic component 2; TRBP2: Transactivation response element RNA-binding protein; FBXW7: F-box and WD repeat domain-containing 7; ERR*α*: Estrogen-related receptor *α*; p62: Sequestosome 1; GFI-1: Growth factor independent 1 transcriptional repressor; HDAC1: Histone deacetylase 1; RCOR1: REST corepressor 1

目前有14种抑制剂已进入临床试验, 包括7种不可逆抑制剂GSK-2879552 (临床均已终止)、IMG-7289 (bomedemstat)、ORY-1001 (iadademstat)、ORY-2001、INCB059872、TAK-418和LH-1802, 2种可逆抑制剂CC-90011 (pulrodemstat)和SP-2577 (seclidemstat mesylate), 以及2种双重LSD1/HDAC抑制剂4SC-202和JBI-802和3种新型LSD1抑制剂SYHA1807 (结构未公布)、ET-1002 (结构未公布)、HE-006 (中国申请临床, 结构未公布)。

已有大量文献表明LSD1抑制剂除自身发挥抗肿瘤作用外, 还可通过联用增强抗肿瘤作用, 具体包括: ① 使耐药癌细胞保持对化疗药物的敏感性; ② 增强免疫细胞浸润, 克服肿瘤免疫逃逸; ③ 与其他表观遗传调控相关蛋白 (如HDAC) 抑制剂相互作用延长治疗窗口期。

4.1 靶向LSD1的不可逆抑制剂 首先应用于抑制LSD1的药物是TCP。LSD1是单胺氧化酶的同源物, 研究人员根据药物再利用策略通过实验证明TCP为一种不可逆的LSD1抑制剂。其具有LSD1抑制活性, 但拥有较差的选择性[38,67,68]。后期的研究发现, 相比于单胺氧化酶MAO-A和MAO-B, LSD1具有更大、更亲水的活性口袋。这为研究人员改造TCP提供了思路[69]。改造的产物主要分为5种, 包括氨基取代的TCP化合物、苯基取代的TCP化合物、环丙基基团取代的TCP化合物、其他基团取代的TCP化合物和限定构象的TCP化合物。大量研究以TCP为模板, 旨在开发更有效的TCP抑制剂, 提高疗效和选择性。目前已进入临床试验的基于TCP改造的化合物均为氨基取代的TCP化合物。

IMG-7289又称为bomedemstat, 是一种口服LSD1抑制剂。作为LSD1靶点目前唯一进入III期临床研究的抑制剂, 它由Imago BioSciences公司开发, 目前有共计15项临床研究正在进行中。其中总计9项临床研究适应症包含原发性血小板增多症, 4项临床研究适应症包含骨髓纤维化, 3项适应症包含真性红细胞增多症, 2项适应症包含AML, 分别有1项适应症包含肝功能衰退、骨髓增生异常综合征和小细胞肺癌。Bomedemstat在骨髓增生性肿瘤 (myeloproliferative neoplasms, MPN) 中具有正常化或增加血细胞计数、减少脾脏体积、恢复正常脾脏结构、减轻骨髓纤维化和提高生存率的潜力[70]。Bomedemstat还增加SCLC模型鼠免疫检查点阻断治疗的敏感度, 增强T细胞杀伤[71]。在临床上, bomedemstat已通过临床试验证实其在原发性血小板增多症、骨髓纤维化、真性红细胞增多症、肝功能衰退和AML中均可起到治疗效果。然而临床试

验显示其具有较高毒性, 多个试验指出其在治疗过程中具有一定的全因死亡率。同时其会产生多种严重不良反应, 包括贫血、血小板减少症、中性粒细胞减少、恶心和肺炎等, 临床安全性相对较低。

目前已进入II期临床研究的基于TCP的化合物包括ORY-1001和INCB059872。ORY-1001又称iadademstat, 由Oryzon Genomics公司开发, 是一种安全性良好且无明显血液学毒性的强效AML治疗药物[72,73]。研究表明, ORY-1001可显著抑制AML和肺癌异种移植模型的生长, 提高T-ALL异种移植模型的存活率[74-76]。关于ORY-1001抑制癌症的机制也有诸多文献进行了报道, 包括ORY-1001会导致LSD1目标基因启动子区的H3K4me2积累; ORY-1001抑制己糖激酶2 (hexokinases 2, HK2)介导的Warburg效应, 抑制肿瘤的发展; ORY-1001诱导Notch信号通路激活, 抑制肿瘤发生; ORY-1001特异性抑制乳腺癌中SOX2驱动的癌症干细胞 (cancer stem cell, CSC)成球能力[72,73,77]。同公司研发的另一款LSD1/MAO-B双重抑制剂ORY-2001, 又称vafidemstat。ORY-2001可在口服的情况下穿透血脑屏障, 进入大脑, 主要用于治疗神经系统疾病, 包括阿尔茨海默病 (Alzheimer's disease, AD)和神经炎症[78]。INCB059872由Incyte Corporation开发, 是一种靶向LSD1的强效、选择性、口服抑制剂。一项研究表明, 在临床AML患者的骨髓样本中使用INCB059872可增强白细胞祖细胞被诱导向髓系分化[79,80]。

不可逆的LSD1抑制剂往往通过占据LSD1和GFI-1B或GFI-1的作用位点来抑制两者之间的相互作用, 从而抑制GFI-1B或GFI-1对下游靶基因的转录调控, 从而导致血小板减少等体内不良反应[11,81,82]。由武田制药公司开发的TAK-418不抑制LSD1-GFI-1B相互作用, 避免了血液学不良反应, 从而更安全地发挥缓解神经发育障碍动物模型的社交障碍和减弱因年龄增长或淀粉样蛋白前体上调引起的记忆力缺陷的功能[83-85]。LH-1802由中国科学院上海药物研究所柳红和李佳团队合作研发, 具有优异的LSD1抑制作用以及选择性, 在大鼠和狗中表现出良好的PK和安全性。

4.2 靶向LSD1的可逆抑制剂 为了减少TCP类不可逆抑制剂可能产生的各种不良反应, 研究人员尝试了各种方法来筛选可逆抑制剂。两种可逆抑制剂CC-90011和SP-2577, 目前均已进入II期临床阶段。CC-90011是第一个进入临床试验的可逆性LSD1抑制剂, 由Celgene公司通过对化合物库进行高通量筛选, 发现先导化合物, 并通过一系列改造后获得[86]。该化合物可促进AML细胞分化, 同时在SCLC的PDX模型中表现出抗肿瘤效果[87]。SP-2577是Salarius Pharmaceuticals开发的另一种可逆性LSD1抑制剂。与CC-90011类似, SP-2577也是通过对化合物库高通量筛选后, 进行改造所得[88]。

4.3 靶向LSD1和HDAC的双重抑制剂 LSD1的单靶点抑制剂虽有一定治疗作用, 但也面临长期给药易耐药等困境。HDAC与LSD1均作为CoREST复合物的组成部分, 最近研究表明两者协同发挥生物学功能, 同时抑制两者的功能可能起到更好的抗肿瘤效果。基于此研究思路, 研究人员对靶向LSD1和HDAC的双重抑制剂进行了开发, 其中4SC-202进入临床I期, JBI-802进入临床II期。

4SC-202又称domatinostat, 是一种新型口服LSD1和I类HDAC (HDAC1/2/3)双重抑制剂。4SC-202对多种实体瘤和非实体瘤细胞均有抑制生长的效果[89,90]。临床研究证实4SC-202通过调节肿瘤免疫微环境增强免疫治疗反应, 提示4SC-202有作为免疫治疗增敏剂的可能性[91]。

JBI-802是首个处于临床试验阶段的LSD1和HDAC6双重抑制剂, 由Jubilant Therapeutics Inc.于2020年报道发现。JBI-802在AML模型中疗效优于LSD1或HDAC6选择性抑制剂。同时, JBI-802以剂量依赖性方式抑制LSD1和HDAC6, 表现出对多种实体瘤和非实体瘤细胞增殖的强效抑制活性, 并可增敏免疫检查点抑制剂治疗[92]。

4.4 其他LSD1抑制剂 除上述药物外, 还有一些新型的LSD1抑制剂正在开发。由石药集团开发的新型LSD1抑制剂SYHA 1807 (结构未公布, 已进入I期临床)具有特异性分布于肺部的特点, 近期发布的其用于治疗SCLC的临床前评估结果显示, 该候选药物在肺组织中的存在量几乎是骨髓中的4倍[93,94]。

由Epiaxis Therapeutics Pty Ltd研发的ET-1002 (结构未公布)和由南昌弘益研发的HE-006 (结构未公布)作为处于临床I期的LSD1抑制剂, 目前相关报道较少 (表1)。

4.5 LSD1抑制剂与其他疗法联用 多项研究表明LSD1抑制剂可与多种化疗联用从而起到更好的抗肿瘤作用。

维生素A衍生物全反式维甲酸 (all-*trans* retinoic acid, ATRA)可促进白血病细胞分化, 其在急性早幼粒细胞白血病 (acute promyelocytic leukemia, APL)患者中表现出显著疗效[95]。TCP可与诱导分化的药物ATRA联用, 从而提高肿瘤效果。使用TCP抑制LSD1能够增强AML细胞对ATRA的响应性, 使AML细胞分化比例增加[96]。它还能恢复AML和骨髓增生异常

综合征 (myelodysplastic syndrome, MDS) 患者对ATRA的敏感性。同时, ATRA与GSK2879552的联用也在不同亚型的AML中表现出抑制增殖和促进分化的协同作用[97]。

除ATRA外, LSD1抑制剂ORY-1001联合DNA甲基转移酶1 (DNA methyltransferase 1, DNMT1) 抑制剂阿扎胞苷治疗老年AML患者的临床研究取得了显著的治疗成果[98]。

除了上文提到的研究外, 多个研究LSD1抑制剂与化疗药物联用疗效的临床研究正在进行中。此外还有研究指出LSD1抑制剂与免疫检查点抑制剂 (immune checkpoint blockade, ICB) PD-1抗体联用, 从而增强PD-1抗体对黑色素瘤或SCLC抑制作用[56, 71]。这些发现提示, LSD1抑制剂的临床价值不仅在于其单药活性, 更在于广阔的联合治疗潜力。因此, 相关研发应从两方面展开: 一方面开发新型抑制剂, 另一方面大力探索已知抑制剂与标准疗法的联合用药方案。

4.6 LSD1抑制剂临床应用中面临的挑战与解决策略 LSD1抑制剂在临床应用中面临着毒性、耐药、生物标志物缺失等挑战, 这在上文中亦有所提及, 此处进行扩展归纳。

LSD1在临床试验中常表现出一些典型的不良反应, 尤以不可逆LSD1抑制剂为甚。如经典的TCP改造化合物, 可能会引起粒细胞减少、肾功能异常、低血压、造血干细胞功能改变等[61,81,99]。血小板减少也较常见, 如ORY-1001的首次人体I期研究中血小板减少症就是主要的不良反应类型, INCB059872的临床前研究亦有此问题发生[73]。可逆LSD1抑制剂不良反应相对有限, 但也可能存在意外毒性。

LSD1抑制剂普遍存在单药耐药问题, 如GSK-2879552在AML和SCLC临床试验中因“风险−获益比欠佳”与耐药而终止, IMG-7289在单药AML/SCLC治疗中耐药发生率也较高[99,100]。这种耐药的发生可能是由于补偿通路的激活造成的。

缺乏可靠的生物标志物是LSD1抑制剂开发的重要障碍, 目前大多临床试验并未建立明确的分子标志物, 主要依赖简单的LSD1表达及组蛋白甲基化情况等作为参考指标。这可能是LSD1在不同肿瘤、不同个体中的异质性表达与调控导致的, 也可能源于其深度参与CoREST复合物等的组装和功能, 从而具有复杂的多靶标交互。目前亦有探索特定抑制剂的生物标志物的尝试, 如一些研究提示分化标志 (如CD11b) 可作为反应性指标, 但仍缺乏广泛的验证[100]。

为了减少LSD1抑制剂的毒性, 可提高可逆抑制剂的研发投入比重, 并优化其药代动力学特性, 降低长期不可逆结合引发的脱靶风险; 也可尝试引入靶向递送系统。针对耐药问题, 前文所述的联用策略及多靶点策略均颇有前景。开发生物标志物方面, 则需要更加深入、全面的药物疗效−个体基因与肿瘤微环境特征的联合监测。

4.7 靶向LSD1药物的未来发展方向 如上所述, LSD1具有独立于其去甲基化酶活性的非经典功能。研究者有理由期待靶向LSD1参与的蛋白质相互作用可以为基于LSD1的药物设计提供新的方向和潜在位点, 而不仅限于目前常见的对其去甲基化酶活性的限制。如对于那些LSD1高表达的癌症, 可通过蛋白降解靶向嵌合体 (proteolysis targeting chimera, PROTAC) 技术或其他技术靶向LSD1蛋白降解, 其中研究人员偶然发现小分子化合物UM171具有在造血干细胞 (hematopoietic stem cells, HSC) 和AML细胞中降解LSD1的能力, 从而抑制白血病的进展[101-104]。这提示一方面可以筛选已知化合物库获得新颖结构的LSD1降解剂, 另一方面可以基于UM171的结构进行改造以获得特异性更好, 更适合成药的化合物。同时, 研究人员可通过变构抑制剂阻断LSD1的非经典功能和寻找破坏LSD1与互作蛋白相互作用的化合物或多肽, 从而抑制LSD1的功能。这些策略均为靶向LSD1药物研发提供了具有潜力的方向。

Table 1 LSD1 inhibitors in clinical trials (only display clinical trials related to tumor). MPN: Myeloproliferative neoplasm; AML: Acute myeloid leukemia; R/R AML: Relapsed/refractory acute myeloid leukemia; ATRA: All-*trans* retinoic acid; MDS: Myelodysplastic syndrome; SCLC: Small cell lung carcinoma; SCCOHT: Small cell carcinoma of the ovary, hypercalcemic type; OCCC: Ovarian clear cell tumor; EC: Endometrial cancer; MLS: Myxoid liposarcoma; DSRCT: Desmoplastic small round cell tumor; EMC: Extraskeletal myxoid chondrosarcoma; AFH: Angiomatoid fibrous histiocytoma; CCS: Clear cell sarcoma; LGFMS: Low grade fibromyxoid sarcoma; SEF: Sclerosing epithelioid fibrosarcoma; PPMS: Primary pulmonary myxoid sarcoma; CMML: Chronic myelomonocytic leukemia; GI: Gastrointestinal; MCC: Merkel cell carcinoma; NSCLC: Non-small cell lung cancer

Title	Status	Condition	Intervention	Registration number
Irreversible inhibitor				
An extension study of bomedemstat (IMG-7289/MK-3543) in participants with myeloproliferative neoplasms (IMG-7289-CTP-202/MK-3543-005)	Completed	• MPN	Drug: Bomedemstat	NCT05223920

Continued

Title	Status	Condition	Intervention	Registration number
Venetoclax and bomedemstat in patients with R/R AML (VenBom)	Suspended	• AML • Refractory AML • AML, in relapse	Drug: Bomedemstat Drug: Venetoclax	NCT05597306
A study of bomedemstat (IMG-7289/MK-3543) with and without ATRA, in participants with advanced myeloid malignancies (IMG-7289-CTP-101/MK-3543-001)	Completed	• AML • MDS	Drug: Bomedemstat Drug: Tretinoin	NCT02842827
Bomedemstat and maintenance immunotherapy for treatment of newly diagnosed extensive stage SCLC	Terminated	• Extensive stage SCLC • Limited stage SCLC	Drug: Bomedemstat Biological: Atezolizumab	NCT05191797
Iadademstat in combination with azacitidine and venetoclax in treating newly diagnosed AML	Recruiting	• AML • MDS/AML	Drug: Azacitidine Procedure: Biospecimen collection Procedure: Bone marrow biopsy Procedure: Echocardiography test Drug: Iadademstat Procedure: Multigated acquisition scan Other: Questionnaire administration Drug: Venetoclax	NCT06357182
Study of iadademstat and gilteritinib in patients with R/R AML with FMS-like tyrosine kinase mutation (FLT3 mut+) (FRIDA)	Recruiting	• AML, in relapse • AML refractory	Drug: Iadademstat Drug: Gilteritinib oral tablet	NCT05546580
A randomized study of ASTX727 with or without iadademstat in advanced MPNs	Recruiting	• Accelerated phase MPN • Blast phase MPN • Essential thrombocythemia myelodysplastic/MPNs • MPN, not otherwise specified • Polycythemia vera • Primary myelofibrosis • Secondary myelofibrosis	Procedure: Biospecimen collection Procedure: Bone marrow aspiration Procedure: Bone marrow biopsy Drug: Decitabine and cedazuridine Drug: Iadademstat	NCT06661915
Testing the combination of an anti-cancer drug, iadademstat, with other anti-cancer drugs (venetoclax and azacitidine) for treating AML	Recruiting	• AML	Drug: Azacitidine Procedure: Biospecimen collection Procedure: Biospecimen collection Procedure: Bone marrow aspiration Procedure: Buccal swab Drug: Iadademstat Drug: Venetoclax	NCT06514261
Testing the combination of an anti-cancer drug, iadademstat, with other anti-cancer drugs (atezolizumab or durvalumab) at improving outcomes for SCLC	Recruiting	• Extensive stage SCLC • Stage IV lung cancer AJCC v8	Biological: Atezolizumab Procedure: Biopsy procedure Procedure: Biospecimen collection Procedure: Computed tomography Biological: Durvalumab Procedure: Echocardiography test Drug: Iadademstat Procedure: Magnetic resonance imaging Procedure: Multigated acquisition scan	NCT06287775
A study of INCB059872 in relapsed or refractory Ewing sarcoma	Terminated	• Relapsed Ewing sarcoma	Drug: INCB059872	NCT03514407
An open-label, dose-escalation/dose-expansion safety study of INCB059872 in subjects with advanced malignancies	Terminated	• Solid tumors and hematologic malignancy	Drug: INCB059872 Drug: ATRA Drug: Azacitidine Drug: Nivolumab	NCT02712905

Continued

Title	Status	Condition	Intervention	Registration number
Azacitidine combined with pembrolizumab and epacadostat in subjects with advanced solid tumors (ECHO-206)	Terminated	• Solid tumors • Advanced malignancies • Metastatic cancer	Drug: Azacitidine Drug: Pembrolizumab Drug: Epacadostat Drug: INCB057643 Drug: Pembrolizumab Drug: Epacadostat Drug: INCB059872	NCT02959437
Phase I clinical study to evaluate the safety, tolerability, pharmacokinetics/ pharmacodynamics, and preliminary efficacy of LH-1802 Capsules Reversible inhibitor	Recruiting	• R/R AML • MDS	Drug: LH-1802	CTR20222026
A study of CC-90011 and comparators in participants with prostate cancer	Completed	• Prostatic neoplasms	Drug: CC-90011 Drug: Abiraterone Drug: Prednisone	NCT04628988
A safety, tolerability and preliminary efficacy evaluation of CC-90011 given in combination with cisplatin and etoposide in subjects with first line, extensive stage SCLC	Completed	• SCLC	Drug: CC-90011 Drug: Cisplatin Drug: Carboplatin Drug: Etoposide Drug: Nivolumab	NCT03850067
A safety, tolerability and preliminary efficacy study of CC-90011 in combination with venetoclax and azacitidine in R/R acute myeloid leukemia and treatment-naïve participants not eligible for intensive therapy	Terminated	• Leukemia, myeloid	Drug: CC-90011 Drug: Venetoclax Drug: Azacitidine Drug: Venetoclax Drug: CC-90011	NCT04748848
A safety and efficacy study of CC-90011 in participants with relapsed and/or refractory solid tumors and non-Hodgkin's lymphomas	Terminated	• Lymphoma, non-Hodgkin • Neoplasms	Drug: CC-90011 Drug: Rifampicin Drug: Itraconazole	NCT02875223
A safety and efficacy study of CC-90011 in combination with nivolumab in subjects with advanced cancers	Completed	• Neoplasms	Drug: CC-90011 Drug: Nivolumab	NCT04350463
Phase I trial of the LSD1 inhibitor SP-2577 (seclidemstat) in patients with advanced solid tumors	Completed	• Advanced solid tumors	Drug: SP-2577 seclidemstat	NCT03895684
Pilot trial of SP-2577 plus pembrolizumab in select gynecologic cancers	Withdrawn	• SCCOHT • OCCC • Ovarian endometrioid adenocarcinoma • EC	Drug: SP-2577 Drug: Pembrolizumab	NCT04611139
A rollover protocol to allow for continued access to the LSD1 inhibitor seclidemstat (SP-2577)	Enrolling by invitation	• Ewing sarcoma • MLS • DSRCT • EMC • AFH • CCS • Myoepithelial tumor • LGFMS • SEF	Drug: Seclidemstat	NCT05266196
Clinical trial of SP-2577 (seclidemstat) in patients with relapsed or refractory Ewing or Ewing-related sarcomas	Active, not recruiting	• Ewing sarcoma • MLS • Sarcoma, soft tissue • DSRCT • EMC • AFH • CCS • PPMS • Myoepithelial tumor • SEF • Fibromyxoid tumor	Drug: Seclidemstat Drug: Cyclophosphamide Drug: Topotecan	NCT03600649

Continued

Title	Status	Condition	Intervention	Registration number
Seclidemstat and azacitidine for the treatment of myelodysplastic syndrome or CMML	Recruiting	• CMML-0 • CMML-1 • CMML-2 • MDS • Recurrent CMML • Recurrent MDS	Drug: Azacitidine Drug: Seclidemstat	NCT04734990
Dual inhibitor of LSD1 and HADC				
Oral histone deacetylase inhibitor 4SC-202 in patients with advanced hematologic malignancies (TOPAS)	Completed	• Advanced hematologic malignancies	Drug: 4SC-202	NCT01344707
4SC-202 in combination with pembrolizumab in patients primary refractory/non-responding to prior anti-PD-1 therapy (SENSITIZE)	Completed	• Malignant melanoma	Drug: 4SC-202 in combination with pembrolizumab	NCT03278665
Epigenetic modulation of the immune response in GI cancers (EMERGE)	Unknown status	• Cancer • GI cancer	Drug: Domatinostat Drug: Avelumab	NCT03812796
Domatinostat in combination with avelumab in patients with treatment-naïve metastatic MCC (MERKLIN 1)	Withdrawn	• MCC	Drug: Domatinostat in combination with avelumab	NCT04874831
Domatinostat in combination with avelumab in patients with advanced MCC progressing on anti-PD- (l) 1 (MERKLIN2)	Completed	• MCC	Drug: Domatinostat in combination with avelumab	NCT04393753
A study of orally administered JBI-802, an LSD1/HDAC6 inhibitor, in patients with advanced solid tumors	Unknown status	• Locally advanced solid tumor • Metastatic solid tumor	Drug: JBI-802	NCT05268666
A study of orally administered JBI-802 alone or in combination with pembrolizumab for patients with NSCLC with an STK11 mutation	Recruiting	• NSCLC	Drug: JBI-802 Drug: Pembrolizumab	NCT07207395
New type of LSD1 inhibitor				
A study of SYHA1807 in subjects with extensive-stage SCLC	Unknown status	• Extensive-stage SCLC	Drug: SYHA1807 Drug: SYHA1807	NCT04404543
An open, multicenter, phase I clinical study to evaluate the safety, efficacy and pharmacokinetics of HE006 tablets in the treatment of R/R AML patients	Recruiting	• R/R AML	Drug: HE006	ChiCTR22000663 64/CTR20221763

5 总结与展望

大量的研究证明, LSD1在多种癌症中高表达, 且与维持肿瘤细胞的干性、促进肿瘤细胞增殖、抑制肿瘤细胞凋亡和促进肿瘤免疫抑制性微环境形成等促癌因素密切相关。这些研究结果证明LSD1是治疗多种癌症的良好靶点。因此, LSD1抑制剂的研发对于肿瘤的治疗具有重要意义。LSD1既可以通过作用于组蛋白, 特异性地通过癌细胞中单甲基化和双甲基化的组蛋白H3K4或H3K9去甲基化以调控转录, 从而产生促肿瘤作用; 也可以通过去甲基化癌细胞非组蛋白赖氨酸位点, 影响蛋白功能或稳定性, 从而影响肿瘤进程; 同时可以通过不依赖于去甲基化酶活性的蛋白–蛋白相互作用影响蛋白质功能或稳定性, 以发挥促癌功能。

因为LSD1在肿瘤中具有多样化的作用, 以下靶向LSD1治疗癌症相关问题值得思考: ① 使用LSD1酶活性抑制剂是否可以抑制LSD1独立于其去甲基化酶活性的非经典功能; ② 可阻断LSD1非经典功能的变构抑制剂是否可以一定程度上抑制LSD1的去甲基化酶活性; ③ LSD1具有多样化促肿瘤作用, 开发LSD1降解剂, 如PROTAC, 促进LSD1的降解, 可否作为一种更有效而全面的治疗策略。众多研究表明, LSD1在不同癌症类型中具有不同的作用, 如何明确LSD1的功能, 更精确和差异化地使用LSD1抑制剂从而靶向LSD1进行治疗, 还亟待研究人员进一步研究。

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