TRAIL基因修饰间充质干细胞治疗恶性肿瘤研究进展

刘广洋[1, 2]，张晨亮[1, 2]，李 欣[1, 2]，苗 丽[1, 2]，徐立强[1, 2]，米 一[1, 2]，陈瑶瑶[1, 2]，刘拥军[1, 2*]

1. 北京贝来生物科技有限公司，北京 100176

2. 北京市亦创生物技术产业研究院 干细胞与再生医学研究所，北京 100176

摘 要：间充质干细胞（mesenchymal stem cells，MSCs）是一种具有自我更新及多向分化潜能的干细胞。MSCs具有对多种肿瘤组织归巢及定向迁移的特性，可以将其作为治疗肿瘤药物的载体，用来治疗无法通过手术去除的肿瘤；同时，MSCs自身参与重塑肿瘤微环境，影响其侵袭、增殖和转移等生物学行为，并且具有抗炎及损伤组织修复的能力。肿瘤坏死因子相关凋亡配体（TRAIL/Apo2L）作为诱导细胞凋亡的肿瘤坏死因子家族成员之一，可通过结合肿瘤细胞表面两个特异性死亡受体（DR4、DR5），特异激活肿瘤细胞凋亡。TRAIL基因修饰的MSCs（TRAIL-MSCs）可定位至肿瘤组织并抑制原发肿瘤及转移瘤的增殖、促进其凋亡，有望用于多种实体肿瘤及血液肿瘤的靶向治疗。综述了TRAIL-MSCs治疗肿瘤的研究进展，并讨论了TRAIL-MSCs联合放化疗对肿瘤的治疗效果，为该疗法在肿瘤治疗领域的应用提供理论依据。

关键词：间充质干细胞；基因修饰；TRAIL；细胞凋亡；死亡受体；放化疗；耐药性

中图分类号：R979.1 **文献标志码：**A **文章编号：**1674-6376（2021）10-2058-07

DOI：10.7501/j.issn.1674-6376.2021.10.002

Research progress of TRAIL gene modified mesenchymal stem cells in treatment of malignant tumors

LIU Guangyang[1, 2], ZHANG Chenliang[1, 2], LI Xin[1, 2], MIAO Li[1, 2], XU Liqiang[1, 2], MI Yi[1, 2], CHEN Yaoyao[1, 2], LIU Yongjun[1, 2]

1. Beijing Baylx Biotech Co., Ltd., Beijing 100176, China

2. Stem Cell Biology and Regenerative Medicine Institution, Yi-Chuang Institute of Bio-Industry, Beijing 100176, China

Abstract: Mesenchymal stem cells (MSCs) is one of adult stem cells with self-renewal and multi-differentiation potential. MSCs also possess other characteristics including homing and directional migration to a variety of tumor tissues, which can be used as a vehicle for anti-tumor drug to treat the tumors which cannot be removed by surgery. Meanwhile, MSCs participate in reshaping the tumor microenvironment, affecting their biological behaviors such as invasion, proliferation and metastasis, and have the ability to anti inflammation and repair damaged tissues, thus laying the foundation for development of tumor drug. Tumor necrosis factor-related apoptosis ligand (TRAIL/Apo2L), as one of the tumor necrosis factor family, which can specifically induces tumor cells apoptosis by binding with two specific death receptors (DR4, DR5) on the surface of tumor cells. Studies have found that engineered mesenchymal stem cells over-expressing TRAIL (TRAIL-MSCs) migrate to tumor tissue to reduce the growth of primary cancers and metastases, and promote the tumor cells apoptosis. So TRAIL-MSCs can be used as to treat a variety of solid tumors and hematological tumors. This paper reviewed the research progress of TRAIL-MSCs in the treatment of tumor, and discussed the therapeutic effect of TRAIL-MSCs combined with radiotherapy and chemotherapy on tumor, providing theoretical basis for the application of trail-MSCs in the field of tumor treatment.

Key words: mesenchymal stem cells; gene modification; TRAIL; apoptosis; death receptor; radiation and chemotherapy; drug resistance

世界卫生组织国际癌症研究机构（IARC）发布的Global Cancer Statistics 2020报告估计，2020年全球新发癌症病例1 929万例，癌症死亡病例996万例[1]。尽管在癌症治疗方面的知识和经验有了长足

收稿日期：2021-08-01

基金项目：北京市科技计划课题（Z211100002521006）

第一作者：刘广洋，研究方向为干细胞新药开发与转化医学研究。E-mail：liugy04@163.com

***通信作者：**刘拥军 E-mail：liu.yongjun@vip.163.com

的进步，但有效对抗和治疗恶性肿瘤的能力仍然有限[2]，需要更有效和创新的方法来提高癌症的治疗效果。间充质干细胞（MSCs）可以定位至肿瘤部位，作为载体提供靶向治疗，通过基因工程方法体外基因修饰MSCs，使其表达如肿瘤坏死因子（TNF）相关的凋亡诱导配体（TRAIL）等抗肿瘤蛋白，已成为恶性肿瘤的细胞治疗途径之一。此外，使用小分子抑制剂来增强肿瘤细胞对TRAIL或TRAIL基因修饰MSCs（TRAIL-MSCs）的敏感性，可以获得更好的治疗效果。本文综述了TRAIL-MSCs治疗肿瘤的研究进展，并讨论了TRAIL-MSCs联合放化疗对肿瘤的治疗效果，为该疗法在肿瘤治疗领域的应用提供理论依据。

1 MSCs及其向肿瘤趋化作用

MSCs是一种具有自我更新及多向分化潜能的干细胞，与其他潜在的细胞疗法相比，MSCs低表达MHC-I类分子，不表达Fas基因蛋白配体（FasL）和MHC-II类分子及其共刺激分子（CD86、CD40等），从而降低移植风险，并克服了移植细胞引起的免疫排斥，已成为最具临床前景的细胞治疗产品[3-5]。

MSCs可以作为治疗肿瘤的药物载体，通过插入治疗基因，可以追踪、归巢至肿瘤组织中，用来治疗无法通过手术去除的肿瘤[6]。大量报告表明，MSCs能够渗透至肿瘤基质及其微环境中，并有助于基质组织损伤修复[7]。MSCs迁移到肿瘤微环境的确切机制尚不完全清楚，研究普遍认为，肿瘤微环境中大量分泌的趋化因子和炎症细胞因子充当了MSCs表面趋化因子受体的配体，从而招募MSCs迁移至肿瘤部位。研究发现，肿瘤细胞可通过分泌趋化因子CXCL-12[基质细胞衍生因子（SDF-1）]，结合MSCs细胞表面受体CXCR-4，驱动MSCs的肿瘤归巢作用[8]；CXCL12/CXCR4通路在血管生成和造血干细胞动员过程发挥重要作用[9]，并在MSCs迁移的信号传导与肿瘤归巢能力之间存在很强的联系，加入CXCR4的阻断剂后，MSCs的迁移能力较对照组显著降低[10]。另外，血管黏附因子及肿瘤组织分泌的炎症因子也对MSCs的归巢存在重要介导作用[11]。多项研究表明改变骨形态发生蛋白2（BMP-2）、B细胞淋巴瘤2（BCL-2）和促红细胞生成素（EPO）等基因的外源表达可增强MSCs在目标部位的归巢及治疗效果[12-13]。以上结果为MSCs作为载体直接递送抗肿瘤剂至肿瘤微环境提供了充分的理论依据。

MSCs通过多种因素趋化进入肿瘤间质后，与肿瘤细胞交互作用，通过分泌多种细胞因子、生长因子、免疫调节因子调节肿瘤的生物学行为[14]，MSCs一方面可抑制肿瘤局部炎症反应、并促进血管和脉管组织形成，另一方面则通过抑制靶细胞PI3K/Akt信号通路中Akt蛋白激酶活性，改变肿瘤细胞周期，抑制肿瘤细胞的生长[15-16]。

综上所述，MSCs可趋化至肿瘤组织并发挥复杂的生物学功能，其对肿瘤生物学行为还有待深入研究及确证。

2 TRAIL及其受体

TRAIL，也称凋亡素2配体（Apo2L），是TNF超家族的成员，通过与其受体结合介导肿瘤细胞的凋亡，而对正常细胞没有毒性。人TRAIL基因定位在染色体3q26，该蛋白是一种II型跨膜蛋白，其胞外域与FasL（28%）和TNF-α（23%）具有最高的序列同源性[17]。TRAIL的主要生理功能表现为参与T细胞及NK细胞介导的因病毒感染或转染、肿瘤恶变等导致的细胞凋亡[18-19]。TRAIL的受体主要包括4种：TRAIL-R1[也称死亡受体4（DR4）]、TRAIL-R2[也称死亡受体5（DR5）]、TRAIL-R3（DcR1）和TRAIL-R4（DcR2）[20-21]。其中DR4和DR5都包含1个保留的死亡域（DD）序列，并在信号凋亡传导中发挥重要作用[22-23]。TRAIL-R3/DcR1和TRAIL-R4/DcR2与DR4和DR5细胞外域具有同源性，可作为诱饵与TRAIL结合并抑制其对细胞凋亡的诱导作用[24]。

当TRAIL与DR5或DR4的受体分子结合形成三聚体时，与带有死亡受体的Fas相关蛋白（FADD）和caspase-8结合形成称为死亡诱导信号复合物的功能性凋亡介导信号复合物（DISC）[25]。接头分子FADD被募集后，结合并激活caspase-8和caspase-10，而活化的caspase-8和10激活天冬氨酸蛋白水解酶并促进pro-caspase-3转化为其活性形式，从而导致死亡底物的裂解并最终导致细胞凋亡[25-26]。另一方面，Caspase-8的裂解及活化可激活BH-3依赖蛋白Bid（促凋亡Bcl-2家族的一个成员），该蛋白与线粒体中的Bax和Bak相互作用以破坏线粒体外膜的稳定性及通透性，从而释放细胞色素-C[27]。在细胞质中，细胞色素-C与接头蛋白APAF-1以及pro-caspase-9等结合形成凋亡体，从而激活caspase-9，并活化caspase-3、6和7等“凋亡执行者”蛋白酶，引起细胞凋亡[28]。

3 TRAIL-MSCs治疗恶性肿瘤

3.1 TRAIL-MSCs对恶性实体肿瘤的治疗作用

多项研究已经证明，TRAIL可单独作为一种有

效的抗肿瘤药物[29]，TRAIL对结直肠癌、乳腺癌、胶质母细胞瘤和非小细胞肺癌等多种实体肿瘤均具有抑制肿瘤细胞增殖和诱导细胞凋亡的作用[30-31]。然而，TRAIL在动物体内半衰期短，可被肾脏快速清除，最终导致其生物利用度较差[32]。因此，利用MSCs向肿瘤的归巢作用，采用分子生物学手段基因修饰MSCs使其在肿瘤病灶部位持续表达TRAIL，从而定向杀伤肿瘤细胞已成为具有临床前景的肿瘤细胞疗法。

研究证实，表达分泌TRAIL的基因修饰MSCs有抑制肿瘤生长的特性[33-36]，并且这种治疗优于重组TRAIL蛋白及抗DR5抗体等传统治疗方法[37-40]；体外迁移实验证实，TRAIL-MSCs能够向肿瘤迁移，而瘤内注射及颅内对侧注射2×10^5个TRAIL-MSCs均表现出显著抑制小鼠颅内肿瘤的生长及显著延长荷瘤小鼠生存时间的作用，其治疗效果明显优于腺病毒介导的胶质瘤原位TRAIL基因治疗[41]。此外，研究证明表达TRAIL的骨髓来源的MSCs通过iv可归巢至乳腺癌肺转移的小鼠模型的肿瘤组织中，通过连续4周给予TRAIL-MSCs（7.5×10^5/周）可发挥显著的治疗肺转移癌的作用[42]；最近的研究发现，过表达TRAIL的基因修饰脂肪来源MSCs同样可定位于肿瘤组织，通过iv可抑制人肺癌H460细胞异种移植小鼠模型的肿瘤细胞增殖，而对正常组织没有明显的毒副作用[35]。MSCs表达的TRAIL可显著抑制非小细胞肺癌来源的$CD133^+$肿瘤干细胞增殖，并促进细胞凋亡[43]。这些研究表明，TRAIL-MSCs可以选择性地定位至肿瘤组织中并对肿瘤细胞起到抑制增殖、促进凋亡的作用。

3.2 TRAIL-MSCs对血液系统恶性肿瘤的治疗作用

血液系统恶性肿瘤（hematological malignancies，又称血液肿瘤）包括各种类型的白血病、淋巴瘤和骨髓瘤等；血液肿瘤细胞对TRAIL的敏感性存在较大差异：一方面，不同血液肿瘤细胞DR4/DR5受体表达水平不同；另一方面，异常的骨髓微环境为部分肿瘤细胞提供了一个保护环境，能够降低血液肿瘤细胞对化疗的敏感性[44]。研究发现，TRAIL对T细胞淋巴白血病有显著的杀伤作用，而对其他血液肿瘤细胞杀伤效果不显著[45]。而针对复发惰性B细胞滤泡性非霍奇金淋巴瘤患者的Ib/II期临床试验研究发现，将TRAIL添加到标准治疗中时并没有更好的有效性结果[46]。

将TRAIL基因修饰MSCs后，对部分血液系统肿瘤具有较为显著的治疗作用。1项研究表明携带TRAIL的脂肪来源MSCs（AD-MSCs）在体外具有迁移到多发性骨髓瘤（MM）细胞并杀死MM细胞的作用，发现尽管MM细胞对rhTRAIL具有中等敏感性，但TRAIL-MSCs仍可显著诱导MM细胞死亡，值得注意的是，该作用与caspase-8激活有关，并被capsase抑制剂消除[47]。本课题组的研究也发现，经TRAIL基因修饰的脐带来源MSCs对B、T细胞淋巴白血病均具有显著的细胞增殖抑制及促进凋亡作用，且该效应与肿瘤细胞分泌的DR4/DR5密切相关。

4 放化疗提高TRAIL-MSCs抗肿瘤效果

尽管TRAIL在某些肿瘤细胞类型中是一种有效的凋亡诱导剂，然而，肿瘤干细胞（CSC）可通过诱饵受体DcR1、DcR2和细胞凋亡抑制剂（如cFLIP）的过度表达，增强对TRAIL的耐药性或抗性[48]；同时，肿瘤细胞可通过细胞保护性自噬等方式阻断TRAIL介导的细胞死亡[49]；而外周血中的循环肿瘤细胞（CTC）可能通过下调DR4、DR5的表达进一步降低对TRAIL的敏感性[50]。

研究发现，联合放化疗等肿瘤常规治疗可能克服TRAIL的耐药性，并可能增强TRAIL/Apo2L在各种肿瘤中的凋亡活性[50]。放射疗法可显著上调神经胶质瘤细胞的DR-5表达水平并诱导capsase激活，协调增强肿瘤细胞对TRAIL敏感性，增强TRAIL-MSCs杀伤肿瘤细胞的能力，同时放射疗法还可增加IL-8表达，从而提高TRAIL-MSC的迁移能力[51]。

而顺铂、硼替佐米等化疗药物或辛二酰苯胺异羟肟酸（SAHA）、AT406、MK886等小分子抑制剂对肿瘤细胞的预处理已被证明可以增加TRAIL诱导细胞凋亡的敏感性[47,52-55]。硼替佐米等化疗药物可显著增强胶质瘤细胞对TRAIL的敏感性，从而对TRAIL基因修饰的神经干细胞（NSC）治疗脑胶质瘤小鼠具有协同或敏化作用[56]。凋亡抑制因子（inhibitor of apoptosis proteins，IAPs）抑制剂AT406和c-FLIP表达抑制剂rocaglamide分别通过克服IAP对caspase-3/6/7/9竞争抑制和阻断c-FLIP对procaspase-8竞争抑制增强肿瘤细胞对TRAIL的敏感性；体外研究发现，TRAIL、AT406和rocaglamide的三联组合，通过激活外在细胞凋亡途径，显著改善17种不同实体癌细胞系中TRAIL诱导的细胞凋亡作用[55]。对于神经胶质瘤细胞，研究发现脂氧合酶抑制剂MK886可通过上调DR5的表

达、下调抗凋亡蛋白 Survivin、显著增强 caspases 活性，从而增强恶性神经胶质瘤细胞对 TRAIL-MSCs 的敏感性而诱导细胞凋亡[53]。小剂量顺铂能够增加 DR4/DR5 的表达，增强 TRAIL-MSCs 的疗效，进而抑制多形性胶质母细胞的生长[57]；在 1 项使用小鼠恶性胶质瘤异种移植模型的研究中也观察到了类似的结果，小剂量顺铂通过增加 DR5 的表达，提高了肿瘤对 TRAIL-MSCs 的敏感性[54]。而硼替佐米同样可增强多发性骨髓瘤细胞对 TRAIL 的敏感性，增强 TRAIL-MSCs 对 MM 细胞的杀伤作用[47]。本课题组研究也发现，地塞米松等可显著增强急性淋巴白血病细胞表达 DR4/DR5，从而增强 TRAIL-MSC 杀伤 B 及 T 急性淋巴细胞白血病肿瘤细胞的能力[58-59]。而 5-氟尿嘧啶（5-FU）等可增强肺腺癌、脑胶质瘤等实体肿瘤细胞对 TRAIL 的敏感性，从而可协同 TRAIL-MSC 治疗上述恶性肿瘤[60]。

另外，MSC 可以显著上调肿瘤细胞中的 TRAIL 蛋白的表达，说明 MSC 分泌某些细胞因子和转录因子，导致肿瘤微环境中 TRAIL 基因转录和后续相应蛋白的表达量增加[61]。这与本课题组的实验结果相类似，使用 MSCs 条件培养上清液处理肿瘤细胞后，胶质瘤细胞 U87MG、U251 等膜表面 TRAIL 受体 DR5 蛋白的表达量升高，虽然不能直接诱导肿瘤细胞的凋亡，但可以间接诱导凋亡相关蛋白的大量表达，进而增强 TRAIL-MSCs 对肿瘤细胞增殖抑制的作用[62]。

5 结语

MSCs 因其低免疫原性、较高的安全性及肿瘤靶向和归巢作用，已成为具有潜力的肿瘤治疗药物载体。TRAIL-MSCs 对于恶性实体肿瘤及血液肿瘤均具有一定的杀伤作用，已成为具有临床前景的肿瘤细胞疗法，然而肿瘤细胞通过各种调节和保护机制可增强其对 TRAIL 的耐药性（图 1），为该疗法提出了挑战。大量体内外研究表明放疗、化疗等传统疗法与 TRAIL-MSCs 联用可发挥协同效应，为增强肿瘤细胞对 TRAIL 的敏感性提供理论依据，并为 TRAIL-MSC 疗法在肿瘤治疗领域的应用奠定基础。

利益冲突 所有作者均声明不存在利益冲突

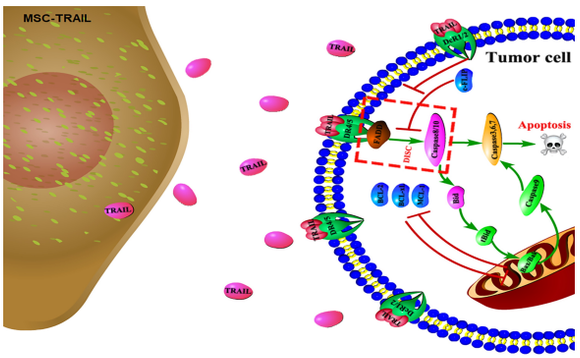

图 1 TRAIL-MSCs 诱导肿瘤细胞凋亡作用及肿瘤细胞对 TRAIL 信号通路的耐药机制

Fig. 1 TRAIL-MSCs induces tumor cells apoptosis and drug resistance mechanism of tumor cells to TRAIL signaling pathways

参考文献

[1] Clinton S K, Giovannucci E L, Hursting S D. The world cancer research fund/American institute for cancer research third expert report on diet, nutrition, physical activity, and cancer: impact and future directions [J]. J Nutr, 2020, 150(4): 663-671.

[2] Sonnenschein C, Soto A M. The aging of the 2000 and 2011 hallmarks of cancer reviews: A critique [J]. J Biosci, 2013, 38(3): 651-663.

[3] Lopez-Santalla M, Fernandez-Perez R, Garin M I. Mesenchymal stem/stromal cells for rheumatoid arthritis treatment: an update on clinical applications [J]. Cells, 2020, 9(8): E1852.

[4] Markov A, Thangavelu L, Aravindhan S, et al. Mesenchymal stem/stromal cells as a valuable source for the treatment of immune-mediated disorders [J]. Stem Cell Res Ther, 2021, 12(1): 192.

[5] Lin W, Huang L, Li Y, et al. Mesenchymal stem cells and cancer: Clinical challenges and opportunities [J]. Biomed Res Int, 2019, doi: 10.1155/2019/2820853.

[6] D'Souza N, Burns J S, Grisendi G, et al. MSC and tumors: homing, differentiation, and secretion influence therapeutic potential [J]. Adv Biochem Eng Biotechnol, 2013, 130: 209-266.

[7] Wang H, Cao F, De A, et al. Trafficking mesenchymal stem cell engraftment and differentiation in tumor-bearing mice by bioluminescence imaging [J]. Stem Cells, 2009, 27(7): 1548-1558.

[8] Hu C J, Yong X, Li C Z, et al. CXCL12/CXCR4 axis promotes mesenchymal stem cell mobilization to burn wounds and contributes to wound repair [J]. J Surg Res, 2013, 183(1): 427-434.

[9] Yellowley C. CXCL12/CXCR4 signaling and other recruitment and homing pathways in fracture repair [J]. Bonekey Rep, 2013, 2: 300.

[10] Orimo A, Gupta P B, Sgroi D C, et al. Stromal fibroblasts present in invasive human breast carcinomas promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion [J]. Cell, 2005, 121(3): 335-348.

[11] Al-Kharboosh R, ReFaey K, Lara-Velazquez M, et al. Inflammatory mediators in glioma microenvironment play a dual role in gliomagenesis and mesenchymal stem cell homing: implication for cellular therapy [J]. Mayo Clin Proc Innov Qual Outcomes, 2020, 4(4): 443-459.

[12] Campeau P M, Rafei M, François M, et al. Mesenchymal stromal cells engineered to express erythropoietin induce anti-erythropoietin antibodies and anemia in allorecipients [J]. Mol Ther, 2009, 17(2): 369-372.

[13] Jin S, Li H, Han M, et al. Mesenchymal stem cells with enhanced bcl-2 expression promote liver recovery in a rat model of hepatic cirrhosis [J]. Cell Physiol Biochem, 2016, 40(5): 1117-1128.

[14] Zhang W. Mesenchymal stem cells in cancer: friends or foes [J]. Cancer Biol Ther, 2008, 7(2): 252-254.

[15] Khakoo A Y, Pati S, Anderson S A, et al. Human mesenchymal stem cells exert potent antitumorigenic effects in a model of Kaposi's sarcoma [J]. J Exp Med, 2006, 203(5): 1235-1247.

[16] Qiao L, Xu Z, Zhao T, et al. Suppression of tumorigenesis by human mesenchymal stem cells in a hepatoma model [J]. Cell Res, 2008, 18(4): 500-507.

[17] Walczak H, Krammer P H. The CD95 (APO-1/fas) and the TRAIL (APO-2L) apoptosis systems [J]. Exp Cell Res, 2000, 256(1): 58-66.

[18] Martínez-Lorenzo M J, Alava M A, Gamen S, et al. Involvement of APO_2 ligand/TRAIL in activation-induced death of Jurkat and human peripheral blood T cells [J]. Eur J Immunol, 1998, 28(9): 2714-2725.

[19] Kayagaki N, Yamaguchi N, Nakayama M, et al. Involvement of TNF-related apoptosis-inducing ligand in human $CD4^+$ T cell-mediated cytotoxicity [J]. J Immunol, 1999, 162(5): 2639-2647.

[20] Pan G. An antagonist decoy receptor and a death domain-containing receptor for TRAIL [J]. Science, 1997, 277 (5327): 815-818.

[21] Pan G, O'Rourke K, Chinnaiyan A M, et al. The receptor for the cytotoxic ligand TRAIL [J]. Science, 1997, 276 (5309): 111-113.

[22] Marsters S A, Sheridan J P, Pitti R M, et al. A novel receptor for Apo2L/TRAIL contains a truncated death domain [J]. Curr Biol, 1997, 7(12): 1003-1006.

[23] Wu G S, Burns T F, McDonald E R, et al. KILLER/DR5 is a DNA damage-inducible p53-regulated death receptor gene [J]. Nat Genet, 1997, 17(2): 141-143.

[24] Almasan A, Ashkenazi A. Apo2L/TRAIL: apoptosis signaling, biology, and potential for cancer therapy [J]. Cytokine Growth Factor Rev, 2003, 14(3/4): 337-348.

[25] Bodmer J L, Holler N, Reynard S, et al. TRAIL receptor-2 signals apoptosis through FADD and caspase-8 [J]. Nat Cell Biol, 2000, 2(4): 241-243.

[26] Kuijlen J M A, Bremer E, Mooij J J A, et al. Review: On TRAIL for malignant glioma therapy ? [J]. Neuropathol Appl Neurobiol, 2010, 36(3): 168-182.

[27] Gao X, Deeb D, Jiang H, et al. Curcumin differentially sensitizes malignant glioma cells to TRAIL/Apo2L-mediated apoptosis through activation of procaspases and release of cytochrome c from mitochondria [J]. J Exp Ther Oncol, 2005, 5(1): 39-48.

[28] Röhn T A, Wagenknecht B, Roth W, et al. CCNU-dependent potentiation of TRAIL/Apo2L-induced apoptosis in human glioma cells is p53-independent but may involve enhanced cytochrome c release [J]. Oncogene, 2001, 20(31): 4128-4137.

[29] Younes A, Kadin M E. Emerging applications of the tumor necrosis factor family of ligands and receptors in cancer therapy [J]. J Clin Oncol, 2003, 21(18): 3526-3534.

[30] Ehrhardt H, Fulda S, Schmid I, et al. TRAIL induced survival and proliferation in cancer cells resistant towards TRAIL-induced apoptosis mediated by NF-kappaB [J]. Oncogene, 2003, 22(25): 3842-3852.

[31] Baader E, Toloczko A, Fuchs U, et al. Tumor necrosis factor-related apoptosis-inducing ligand-mediated proliferation of tumor cells with receptor-proximal apoptosis defects [J]. Cancer Res, 2005, 65(17): 7888-7895.

[32] Kelley S K, Harris L A, Xie D, et al. Preclinical studies to predict the disposition of Apo2L/tumor necrosis factor-related apoptosis-inducing ligand in humans: characterization of *in vivo* efficacy, pharmacokinetics, and safety [J]. J Pharmacol Exp Ther, 2001, 299(1): 31-38.

[33] Bagci-Onder T, Wakimoto H, Anderegg M, et al. A dual PI3K/mTOR inhibitor, PI-103, cooperates with stem cell-delivered TRAIL in experimental glioma models [J]. Cancer Res, 2011, 71(1): 154-163.

[34] Sasportas L S, Kasmieh R, Wakimoto H, et al. Assessment of therapeutic efficacy and fate of engineered human mesenchymal stem cells for cancer therapy [J]. PNAS, 2009, 106(12): 4822-4827.

[35] Un Choi Y, Yoon Y, Jung P Y, et al. TRAIL-overexpressing adipose tissue-derived mesenchymal stem cells efficiently inhibit tumor growth in an H460 xenograft model [J]. Cancer Genomics Proteomics, 2021, 18(4): 569-578.

[36] Deng L, Wang C, He C, et al. Bone mesenchymal stem cells derived extracellular vesicles promote TRAIL-

related apoptosis of hepatocellular carcinoma cells via the delivery of microRNA-20a-3p [J]. Cancer Biomark, 2021, 30(2): 223-235.

[37] Soria J C, Smit E, Khayat D, et al. Phase 1b study of dulanermin (recombinant human Apo2L/TRAIL) in combination with paclitaxel, carboplatin, and bevacizumab in patients with advanced non-squamous non-small-cell lung cancer [J]. J Clin Oncol, 2010, 28(9): 1527-1533.

[38] Camidge D R, Herbst R S, Gordon M S, et al. A phase I safety and pharmacokinetic study of the death receptor 5 agonistic antibody PRO95780 in patients with advanced malignancies [J]. Clin Cancer Res, 2010, 16(4): 1256-1263.

[39] Yenilmez E N, Genc D, Farooqi A A, et al. Mesenchymal stem cells combined with IFNγ induce apoptosis of breast cancer cells partially through TRAIL [J]. Anticancer Res, 2020, 40(10): 5641-5647.

[40] Jung P Y, Ryu H, Rhee K J, et al. Adipose tissue-derived mesenchymal stem cells cultured at high density express IFN-β and TRAIL and suppress the growth of H460 human lung cancer cells [J]. Cancer Lett, 2019, 440/441: 202-210.

[41] Kim S M, Lim J Y, Park S I, et al. Gene therapy using TRAIL-secreting human umbilical cord blood-derived mesenchymal stem cells against intracranial glioma [J]. Cancer Res, 2008, 68(23): 9614-9623.

[42] Loebinger M R, Eddaoudi A, Davies D, et al. Mesenchymal stem cell delivery of TRAIL can eliminate metastatic cancer [J]. Cancer Res, 2009, 69(10): 4134-4142.

[43] Fakiruddin K S, Lim M N, Nordin M, et al. Targeting of $CD133^{+}$ cancer stem cells by mesenchymal stem cell expressing TRAIL reveals a prospective role of apoptotic gene regulation in non-small cell lung cancer [J]. Cancers (Basel), 2019, 11(9): 1261.

[44] Williams D A. A new mechanism of leukemia drug resistance? [J]. N Engl J Med, 2007, 357(1): 77-78.

[45] Snell V, Clodi K, Zhao S, et al. Activity of TNF-related apoptosis-inducing ligand (TRAIL) in haematological malignancies [J]. Br J Haematol, 1997, 99(3): 618-624.

[46] Cheah C Y, Belada D, Fanale M A, et al. Dulanermin with rituximab in patients with relapsed indolent B-cell lymphoma: an open-label phase 1b/2 randomised study [J]. Lancet Haematol, 2015, 2(4): e166-e174.

[47] Ciavarella S, Grisendi G, Dominici M, et al. *In vitro* anti-myeloma activity of TRAIL-expressing adipose-derived mesenchymal stem cells [J]. Br J Haematol, 2012, 157 (5): 586-598.

[48] Garza E, Delgado P, Quiroz A G, et al. Behind the adaptive and resistance mechanisms of cancer stem cells to TRAIL [J]. Pharmaceutics, 2021, 13(7): 1-18.

[49] Han J, Hou W, Goldstein L A, et al. Involvement of protective autophagy in TRAIL resistance of apoptosis-defective tumor cells [J]. J Biol Chem, 2008, 283(28): 19665-19677.

[50] Twomey J D, Zhang B L. Circulating tumor cells develop resistance to TRAIL-induced apoptosis through autophagic removal of death receptor 5: evidence from an *in vitro* model [J]. Cancers, 2019, 11(1): 1-16.

[51] Kim S M, Oh J H, Park S A, et al. Irradiation enhances the tumor tropism and therapeutic potential of tumor necrosis factor-related apoptosis-inducing ligand-secreting human umbilical cord blood-derived mesenchymal stem cells in glioma therapy [J]. Stem Cells, 2010, 28(12): 2217-2228.

[52] Butler L M, Liapis V, Bouralexis S, et al. The histone deacetylase inhibitor, suberoylanilide hydroxamic acid, overcomes resistance of human breast cancer cells to Apo2L/TRAIL [J]. Int J Cancer, 2006, 119(4): 944-954.

[53] Kim S M, Woo J S, Jeong C H, et al. Effective combination therapy for malignant glioma with TRAIL-secreting mesenchymal stem cells and lipoxygenase inhibitor MK886 [J]. Cancer Res, 2012, 72(18): 4807-4817.

[54] Kim S M, Woo J S, Jeong C H, et al. Potential application of temozolomide in mesenchymal stem cell-based TRAIL gene therapy against malignant glioma [J]. Stem Cells Transl Med, 2014, 3(2): 172-182.

[55] Huang Y, Yang X, Xu T R, et al. Overcoming resistance to TRAIL-induced apoptosis in solid tumor cells by simultaneously targeting death receptors, c-FLIP and IAPs [J]. Int J Oncol, 2016, 49(1): 153-163.

[56] Balyasnikova I V, Ferguson S D, Han Y, et al. Therapeutic effect of neural stem cells expressing TRAIL and bortezomib in mice with glioma xenografts [J]. Cancer Lett, 2011, 310(2): 148-159.

[57] Redjal N, Zhu Y N, Shah K. Combination of systemic chemotherapy with local stem cell delivered S-TRAIL in resected brain tumors [J]. Stem Cells, 2015, 33(1): 101-110.

[58] 王立华, 李 欣, 徐立强, 等. 地塞米松提高TRAIL基因修饰的脐带间充质干细胞对急性B淋巴细胞白血病细胞的杀伤作用及机制研究 [J]. 药物评价研究, 2021, 44 (8): 1653-1659.

Wang L H, Li X, Xu L Q, et al. Killing effect of TRAIL gene-modified umbilical cord mesenchymal stem cells enhanced by dexamethasone and its mechanism [J]. Drug Eval Res, 2021, 44(8): 1653-1659.

[59] 李 欣, 王立华, 米 一, 等. 地塞米松提高 TRAIL 基因修饰脐带间充质干细胞对急性 T 淋巴细胞白血病细胞的杀伤作用及机制研究 [J]. 药物评价研究, 2021, 44(10): 2074-2080.
Li X, Wang L H, Mi Y, et al. Killing effect of TRAIL gene-modified umbilical cord mesenchymal stem cells enhanced by dexamethasone and its mechanism on acute T lymphoblastic leukemia [J]. Drug Eval Res, 2021, 44 (10): 2074-2080.

[60] 苗 丽, 李 欣, 米 一, 等. TRAIL 基因修饰脐带间充质干细胞联合 5-氟尿嘧啶对 U-87MG、A549 及 HeLa 细胞杀伤作用研究 [J]. 药物评价研究, 2021, 44(10): 2065-2073.
Miao L, Li X, Mi Y, et al. Therapeutic Effect of TRAIL gene-modified stem cells combined with fluorouracil on solid tumor cells [J]. Drug Eval Res, 2021, 44(10): 2065-2073.

[61] Hardiany N S, Yo E C, Ngadiono E, et al. Gene expression of molecules regulating apoptotic pathways in glioblastoma multiforme treated with umbilical cord stem cell conditioned medium [J]. Malays J Med Sci, 2019, 26 (6): 35-45.

[62] 李 欣, 徐立强, 米 一, 等. TRAIL 基因修饰间充质干细胞对神经胶质瘤细胞的杀伤作用的研究 [J]. 药物评价研究, 2021, 44(10): 2081-2087.
Li X, Xu L Q, Mi Y, et al. Killing effect of TRAIL gene-modified umbilical cord mesenchymal stem cells enhanced by dexamethasone and its mechanism on acute T lymphoblastic leukemia [J]. Drug Eval Res, 2021, 44 (10): 2081-2087.

[责任编辑 兰新新]