



doi:10.3978/j.issn.1005-6947.2017.10.007  
http://dx.doi.org/10.3978/j.issn.1005-6947.2017.10.007  
Chinese Journal of General Surgery, 2017, 26(10):1265-1271.

· 基础研究 ·

# 巨噬细胞移动抑制因子促进有氧糖酵解与直肠癌细胞耐药性的关系

黄荣, 汪泓, 陈保华, 樊明湖

(中国人民解放军第一八四医院 普通外科, 江西 鹰潭 335000)

## 摘要

**目的:** 探讨巨噬细胞移动抑制因子(MIF)在结直肠癌细胞耐药中的作用和机制。

**方法:** 用5-氟尿嘧啶(5-FU)药物浓度持续递增法诱导人结直肠癌细胞株LoVo细胞构建5-FU耐药的人结肠癌LoVo/5-FU细胞。检测指标包括细胞对5-FU的敏感性(IC<sub>50</sub>)、细胞MIF蛋白表达、细胞葡萄糖摄取水平、细胞中乳酸脱氢酶(LDH)活性、细胞培养基上清中乳酸水平,分别用CCK-8法、Western blot、2-NBDG法、微孔法、试剂盒法检测。比较LoVo/5-FU细胞与亲本LoVo细胞间上述指标的差异,并检测用siRNA或慢病毒技术干扰或过表达MIF蛋白,或用PFKFB3抑制剂PFK-15抑制有氧糖酵解后,LoVo/5-FU细胞上述指标的变化。

**结果:** 成功构建LoVo/5-FU细胞,该细胞的MIF蛋白表达、对5-FU的IC<sub>50</sub>、葡萄糖摄取、LDH活性和乳酸生成水平都较其亲本LoVo细胞明显升高(均P<0.05);在LoVo/5-FU细胞上,siRNA干扰MIF后表现为MIF蛋白表达、对5-FU的IC<sub>50</sub>、葡萄糖摄取、LDH活性和乳酸生成水平均明显减少,而MIF蛋白过表达后表现为上述指标的明显升高(均P<0.05);用PFK-15抑制有氧糖酵解后,LoVo/5-FU细胞对5-FU的IC<sub>50</sub>、葡萄糖摄取、乳酸水平均明显降低(均P<0.05),但LDH活性无明显变化(P>0.05),PFK-15对MIF过表达的LoVo/5-FU细胞也有同样作用(均P<0.05)。

**结论:** MIF通过上调LoVo细胞有氧糖酵解,诱导其对5-FU耐药能力的增加。

## 关键词

结直肠肿瘤; 抗药性, 肿瘤; 巨噬细胞游走抑制因子; 糖酵解  
中图分类号: R735.3

## Relationship of macrophage migration inhibition factor enhancing aerobic glycolysis to drug resistance of colorectal cancer cells

HUANG Rong, WANG Hong, CHEN Baohua, FAN Minghu

(Department of General Surgery, the 184 Hospital of People's Liberation Army, Yingtan, Jiangxi 335000, China)

## Abstract

**Objective:** To investigate the action and mechanism of macrophage migration inhibition factor (MIF) in drug resistance of colorectal cancer.

**Methods:** The 5-fluorouracil (5-FU)-resistant human colon cancer LoVo/5-FU cells were established by stepwise exposure of human colon cancer LoVo cells to increasing concentrations of 5-FU. The studied parameters included the sensitivity of cells to 5-FU (IC<sub>50</sub>), MIF protein expression, glucose uptake ability of cells, lactic

收稿日期: 2017-05-13; 修订日期: 2017-09-17。

作者简介: 黄荣, 中国人民解放军第一八四医院主治医师, 主要从事结直肠癌方面的研究。

通信作者: 汪泓, Email: a13667010409@163.com

dehydrogenase (LDH) activity of cells and lactate production from cultured cells supernatant, which were detected by CCK-8 assay, Western blot analysis, 2-NBDG method, microporous assay and kit assay, respectively. The differences in above parameters between LoVo/5-FU cells and their parent LoVo cells were compared, and changes in these parameters in LoVo/5-FU cells before and after MIF interference and overexpression by siRNA and lentivirus transfection, or inhibition of aerobic glycolysis by PFKFB3 inhibitor PFK-15 were examined.

**Results:** The LoVo/5-FU cells were successfully constructed, which showed significantly increased MIF protein expression,  $IC_{50}$  to 5-FU, glucose uptake, LDH activity and lactate production level compared with their parent LoVo cells (all  $P < 0.05$ ). In LoVo/5-FU cells, the  $IC_{50}$  to 5-FU, glucose uptake, LDH activity and lactate production level were significantly decreased after MIF interference by siRNA, while those above parameters were significantly increased after MIF overexpression (all  $P < 0.05$ ). After inhibition of aerobic glycolysis by PFK-15, the  $IC_{50}$  to 5-FU, glucose uptake and lactate production level in LoVo/5-FU cells were significantly decreased (all  $P < 0.05$ ), but the LDH activity showed no significant change ( $P > 0.05$ ), and the same effects were exerted by PFK-15 in LoVo/5-FU cells with MIF overexpression (all  $P < 0.05$ ).

**Conclusion:** MIF enhanced the resistance of LoVo cells to 5-FU by increasing the aerobic glycolysis.

#### Key words

Colorectal Neoplasms; Drug Resistance, Neoplasm; Macrophage Migration-Inhibitory Factors; Glycolysis

CLC number: R735.3

近年来,随着人们健康意识的提高,结直肠癌的诊断和治疗有显著的提高<sup>[1]</sup>。但随着治疗进展,结直肠癌耐药的发生率也越来越高。结直肠癌耐药的发生严重影响了治疗效果,严重威胁患者的生存率<sup>[2-3]</sup>。因此,进一步阐明结直肠癌的耐药机制,寻找新的治疗靶点是目前研究的热点。巨噬细胞移动抑制因子(macrophage migration inhibition factor, MIF)在肿瘤的发生、发展和转移中发挥重要的促进作用<sup>[4-6]</sup>。新近的研究<sup>[8]</sup>表明, MIF与乳腺癌<sup>[7]</sup>、骨肿瘤等耐药相关,但其是否参与结直肠癌耐药的发生及具体机制鲜有报道。因此,本研究进一步探讨MIF在结直肠癌耐药的作用和机制。

## 1 材料与方法

### 1.1 材料

人结直肠癌细胞株LoVo来源本实验室。DMEM培养基(life公司,美国),胎牛血清(Gibco公司,美国);5-氟尿嘧啶(5-FU)(Sigma公司,美国);6-磷酸果糖激酶-2/果糖双磷酸酶-2(6-phosphofructo-2-kinase, PFKFB3)抑制剂PFK-15(Selleck公司,中国);荧光标记的葡萄糖类似物2-NBDG(Thermo公司,美国);乳酸脱氢酶(lactate

dehydrogenase, LDH)活性检测试剂盒和乳酸(lactate)含量检测试剂盒(Sigma公司,美国);CCK-8试剂盒(Dojindo公司,日本);MIF抗体(CST公司,美国); $\beta$ -actin(proteintech公司,中国);嘌呤霉素(和元生物,上海),Lipofectamine™ 2000 Transfection Reagent(lip-2000, invitrogen, 美国)。

### 1.2 方法

**1.2.1 耐药结直肠癌细胞LoVo(LoVo/5-FU)构建** 耐药株的构建参考文献<sup>[9-11]</sup>报道的方法。用含5-FU的培养基(DMEM,含10%胎牛血清)培养LoVo,从5  $\mu\text{mol/L}$ 开始,溶度逐渐递增,每2周增加5  $\mu\text{mol/L}$ ,持续24周。可见LoVo在15  $\mu\text{mol/L}$ 保持稳定生长。

**1.2.2 5-FU对结直肠癌细胞LoVo生长抑制曲线建立** 参考Wei等<sup>[12]</sup>方法构建生长抑制曲线。1  $\times 10^4$ 个/孔的结直肠癌细胞LoVo种于96孔板中,12 h后,加入不同溶度的5-FU(10  $\mu\text{mol/L}$ ~1 mmol/L)。孵育72 h后,加入CCK-8 10  $\mu\text{L}$ /孔孵育2 h,酶标仪检测吸光度,描绘生长抑制曲线,计算 $IC_{50}$ 。

**1.2.3 干预处理** (1) MIF的siRNA干扰: si-RNA由上海吉玛生物公司帮忙设计及合成,阴性对照序列: GGC TAC GTC CAG GAG CGC ACC, si-MIF: ACA GGG UCU ACA UCA AUA dTdT。将20  $\mu\text{mol}$

si-RNA 和 5  $\mu$ L lip-2000 混合于 100  $\mu$ L 无血清的 DMEM 中静置 15 min 后, 加入细胞长至 70% 的 6 孔板中。12 h 后更换含 10% 胎牛血清的新鲜 DMEM, 继续培养 48 h, Western blot 检测 MIF 蛋白水平。(2) PFKFB3 抑制剂 PFK-15 处理: PFK-15 按终浓度 10  $\mu$ mol/L 预处理细胞 1 h 后, 再与相应处理。(3) MIF 过表达: 过表达 MIF 蛋白的慢病毒由上海和元生物予构建及合成。1  $\times$  10<sup>5</sup>/孔细胞种于 6 孔板中, 24 h 后加入终滴度为 5  $\times$  10<sup>6</sup> 的慢病毒, 12 h 后更换继续含 10% 胎牛血清的新鲜 DMEM, 继续培养 48 h, 荧光显微镜下观察转染情况。同时给予终浓度为 800  $\mu$ g/L 的嘌呤霉素培养 1 周, 观察细胞再无死亡, 并荧光显微镜下 95% 细胞带绿色应该后 Western blot 检测 MIF 蛋白表达。

**1.2.4 Western blot 检测 MIF 表达** 提取全细胞胞浆蛋白, 加入 5 $\times$  上样缓冲液, 沸水煮 10 min 后 -20  $^{\circ}$ C 保存。SDS-PAGE 胶分离蛋白(90 V, 1.5 h), 转膜(冰浴, 90 V, 2 h), 封闭(5% 脱脂奶粉, 常温, 2 h), 一抗(1:1 000) 4  $^{\circ}$ C 过夜孵育, 二抗(1:5 000) 常温 1 h, TBST 5min/次  $\times$  3 次洗膜后 ECL 显影。

**1.2.5 葡萄糖摄取率检测** 参考 Fischer 等<sup>[13]</sup>的方法, 葡萄糖的摄取率通过细胞对 2-NBDG 摄取量来反映。细胞在无血清条件下培养 24 h 后更换为含 37 kBq/mL 2-NBDG 的低糖 DMEM 继续培养 24 h。消化细胞后留小部分细胞计数, 其他用 0.5 mol/L 氢氧化钠裂解细胞 15 min 后, 加入同体积 0.5 mol/L 盐酸中和。用液体闪烁计数仪(HIDEX 300SL, 芬兰)检测细胞裂解液的 dpm 值。(LoVo 总放射性 - 非特异性结合的放射性)/(细胞数  $\cdot$  24 h) 即得出 LoVo 葡萄糖摄取量。

**1.2.6 微孔法检测 LDH 活性** LDH 活性检测根据产品说明书(Sigma-Aldrich, MAK066)进行。收集各组细胞 1  $\times$  10<sup>6</sup>, 加入 100  $\mu$ L 细胞裂解液孵育冰上 10 min 后, 13 000 r/min 离心 10 min 去除杂质, 收集上清。乳酸溶液、1 $\times$  的 INT 溶液、酶溶液等体积混合为工作液。50  $\mu$ L 标准版品(10 milliunits/mL)或样品和 50  $\mu$ L 工作液等体积混合后加入 96 孔板中, 室温避光孵育 30 min, 酶标仪 490 nm 测量样品吸光度。LDH 活性 = (样品孔吸光度 - 背景空白对照孔吸光度)/(标准管吸光度 - 标准空白管吸光度)  $\times$  标准品浓度。

**1.2.7 微孔法检测乳酸水平** 乳酸水平检测根据试剂盒说明书(Sigma-Aldrich, MAK064)进行。各组细胞按 1  $\times$  10<sup>6</sup>/孔种于 6 孔版中, 12 h 后更换 1 mL/孔无血清培养基培养 24 h。收集细胞培养基, 13 000 r/min 离心 10 min 去除杂质。将 20  $\mu$ L 样品、26  $\mu$ L 乳酸盐测定缓冲液、2  $\mu$ L 乳酸酶混合物和 2  $\mu$ L 乳酸盐探针混合, 在室温下孵育 30 min。酶标仪 570 nm 测量样品吸光度。用溶度微 1 mmol/L 的乳酸盐标准物 0、2、4、6、8、10  $\mu$ L 分别加入由 26  $\mu$ L 乳酸盐测定缓冲液、2  $\mu$ L 乳酸酶混合物和 2  $\mu$ L 乳酸盐探针混合物中建立标准曲线。

### 1.3 统计学处理

应用 SPSS 19.0 统计学软件, 计量资料以均数  $\pm$  标准差( $\bar{x} \pm s$ )表示, 采用 *t* 检验或方差分析, 两两比较用 LSD-*t* 检验。P < 0.05 为差异有统计学意义。

## 2 结果

### 2.1 耐药结直肠癌细胞 LoVo 中 MIF 表达和有氧糖酵解的变化

通过用 5-FU 培养 LoVo 6 个月, 成功构建对 5-FU 耐药的结直肠癌 LoVo/5-FU 细胞, LoVo 和 LoVo/5-FU 对 5-FU 的 IC<sub>50</sub> 分别为 0.220 和 5.600  $\mu$ mol/L。同时进一步检测 MIF 蛋白表达和有氧糖酵解情况, 结果显示 LoVo/5-FU 细胞 MIF 蛋白表达、葡萄糖摄取率、LDH 活性、乳酸产生都较 LoVo 细胞明显升高(均 P < 0.05)(图 1)。

### 2.2 下调 MIF 对 LoVo/5-FU 耐药和有氧糖酵解的影响

为了解 MIF 高表达介与 LoVo 耐药及有氧糖酵解的关系, 通过 siRNA 下调 LoVo/5-FU 中 MIF 蛋白表达进一步观察上述指标的变化。结果显示 siRNA 干扰后, LoVo/5-FU 细胞 MIF 蛋白表达、葡萄糖摄取率、LDH 活性、乳酸水平以及对 5-FU IC<sub>50</sub> 均明显下降(图 2)。

### 2.3 抑制有氧糖酵解对 LoVo/5-FU 对 5-FU 耐药的影响

进一步用 PFK-15 抑制有氧糖酵解, 观察 LoVo/5-FU 对 5-FU 耐药的变化。结果显示, PFK-15 可减少 LoVo/5-FU 葡萄糖摄取和乳酸水平(均 P < 0.05), 但对 LDH 活性影响不大(P > 0.05); 同时, 明显减少 LoVo/5-FU 对 5-FU 耐药(图 3)。

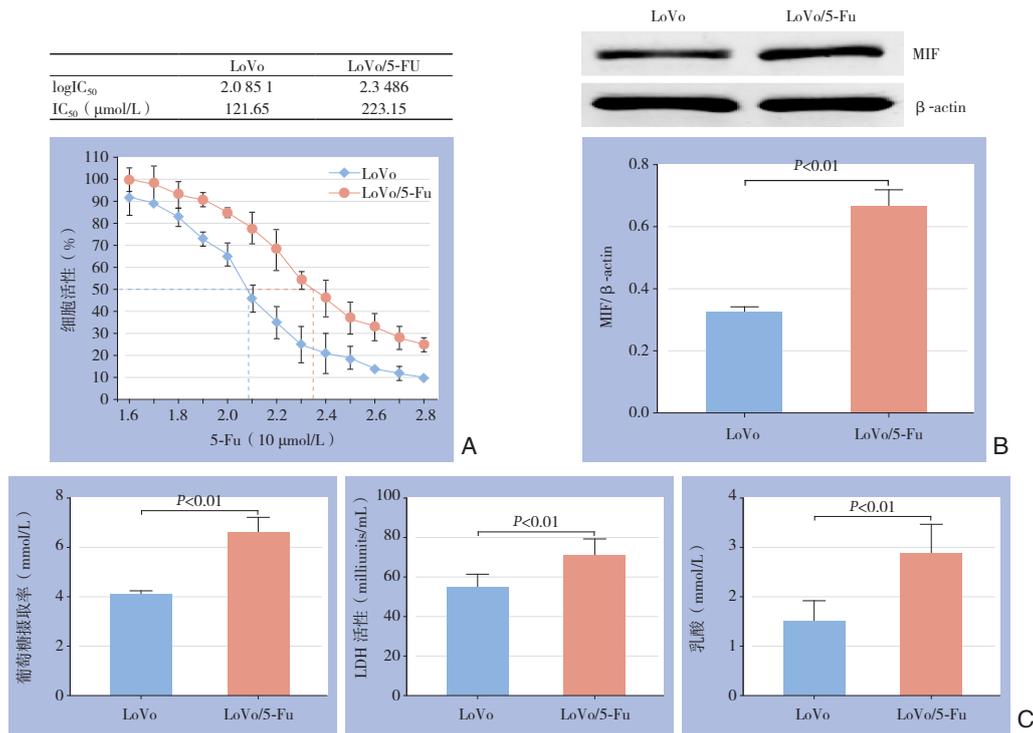


图 1 LoVo/5-FU 细胞 MIF 表达和有氧糖酵解的变化 A: 细胞生长抑制曲线及细胞对 5-FU 的 IC<sub>50</sub>; B: Western blot 检测 MIF 蛋白表达及灰度值分析结果; C: 糖酵解相关指标检测结果

Figure 1 Changes in MIF expression and aerobic glycolysis in LoVo/5-FU cells A: Cell growth inhibition curves and IC<sub>50</sub> values of cells; B: Western blot analysis for MIF protein expressions and results of grayscale intensity analysis; C: Results of detection of glycolysis related markers

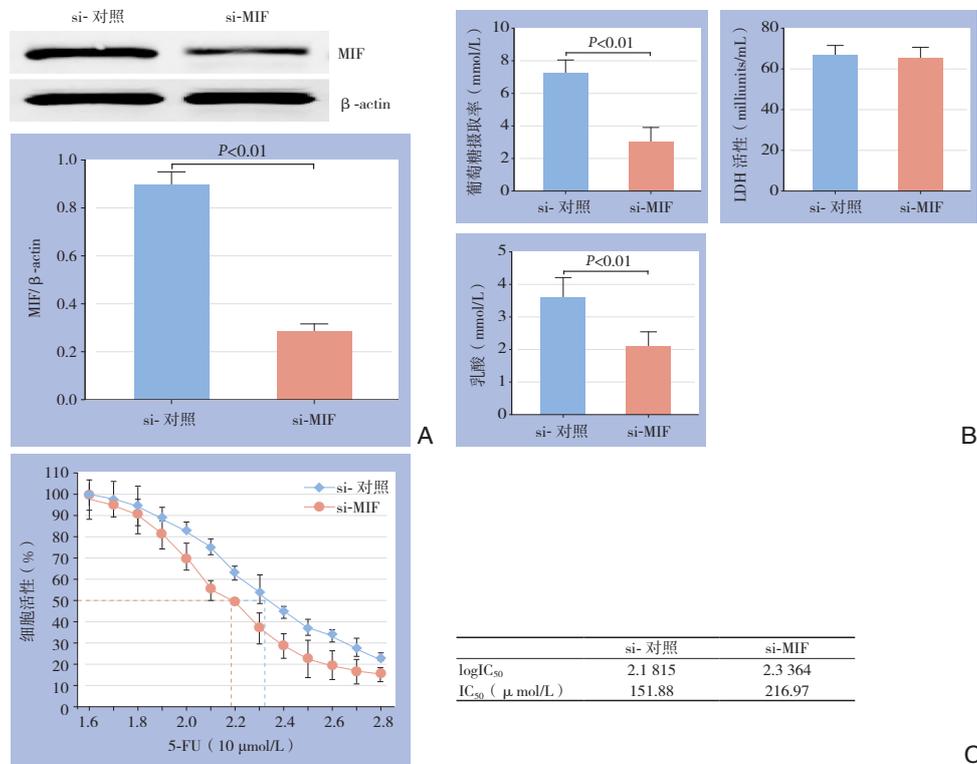


图 2 下调 MIF 对 LoVo/5-FU 耐药和糖酵解的影响 A: Western blot 检测 MIF 蛋白表达与灰度分析结果; B: 糖酵解相关指标检测结果; C: 细胞生长抑制曲线与 IC<sub>50</sub>

Figure 2 Effects of MIF knockdown on drug resistance and aerobic glycolysis in LoVo/5-FU cells A: Western blot analysis for MIF protein expressions and results of grayscale intensity analysis; B: Results of detection of glycolysis related markers; C: Cell growth inhibition curves and IC<sub>50</sub> values

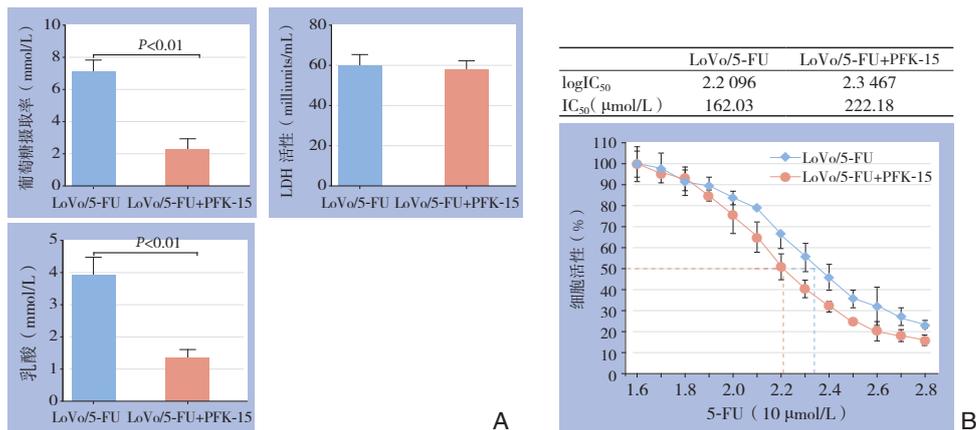


图 3 抑制糖酵解对 LoVo/5-FU 耐药的影响 A: 糖酵解相关指标检测结果; B: 细胞生长抑制曲线与 IC<sub>50</sub>

Figure 3 Effects of inhibition of aerobic glycolysis on drug resistance of LoVo/5-FU cells A: Results of detection of glycolysis related markers; B: Cell growth inhibition curves and IC<sub>50</sub> values

### 2.4 MIF 过表达对 LoVo 对 5-FU 耐药的影响及抑制有氧糖酵解的干预作用

为进一步探讨三者的关系, 在过表达 MIF 的 LoVo/5-FU 细胞上观察以上指标的变化。结果显示, 过表达 MIF 后, LoVo/5-FU 细胞 MIF 蛋白表

达、葡萄糖摄取率、LDH 活性、乳酸水平和 5-FU 的 IC<sub>50</sub> 均明显增加 (均  $P < 0.05$ ) ; 加用有氧糖酵解抑制剂 PFK-15 后, MIF 过表达的上述作用除了 LDH 活性无明显有下降外, 其他作用被明显抑制 (均  $P < 0.05$ ) (图 4)。

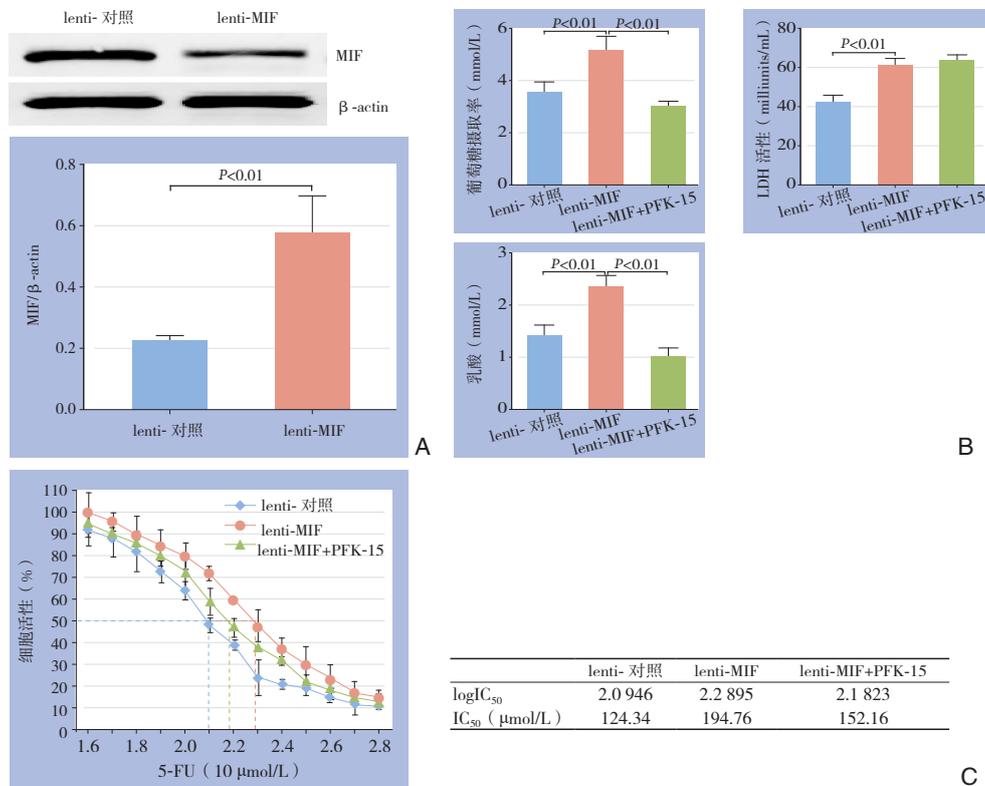


图 4 MIF 过表达影响 LoVo 对 5-FU 耐药的影响及同时抑制有氧糖酵解的干预作用 A: Western blot 检测 MIF 蛋白表达与灰度分析结果; B: 糖酵解相关指标检测结果; C: 细胞生长抑制曲线与 IC<sub>50</sub>

Figure 4 Effects of MIF overexpression on drug resistance of LoVo cells and interventional effects of inhibition of aerobic glycolysis A: Western blot analysis for MIF protein expressions and results of grayscale intensity analysis; B: Results of detection of glycolysis related markers; C: Cell growth inhibition curves and IC<sub>50</sub> values

### 3 讨论

化疗是结直肠癌治疗的重要手段之一，如何提高化疗疗效和减少肿瘤耐药的能力是目前研究的热点<sup>[14-15]</sup>。本研究通过5-FU构建耐药的结直肠癌细胞LoVo(LoVo/5-FU)，发现其MIF蛋白表达和有氧糖酵解水平都明显增加；而抑制MIF蛋白表达或有氧糖酵解，能显著减少LoVo/5-FU的耐药能力。另一方面，本研究也发现MIF可增加LoVo的有氧糖酵解和对5-FU的耐药能力。

MIF因能抑制单核和巨噬细胞移动而得名。近年来研究<sup>[16-18]</sup>发现，MIF在肿瘤组织中高表达，其通过促进细胞增殖、抑制凋亡发生和促进血管生成等参与肿瘤的发生发展。进一步的研究<sup>[7-8]</sup>发现，MIF在肿瘤耐药中也发挥重要作用，MIF可抑制自噬诱导的细胞死亡，进而增加乳腺癌和骨肉瘤等肿瘤的耐药能力。在本研究中发现，在LoVo/5-FU中，MIF的表达较LoVo显著增加；在LoVo中过表达MIF可以增加LoVo对5-FU的耐药；而敲低MIF表达后，LoVo/5-FU的耐药能力被显著抑制。由此说明，MIF是调控结直肠癌耐药的一个重要因子。

MIF是如何调控结直肠癌耐药能力增加的？现有研究<sup>[19-21]</sup>表明，肿瘤细胞的有氧糖酵解是肿瘤发生发展的重要机制。Ge等<sup>[22]</sup>发现，有氧糖酵解的关键酶之一PFKFB3可以通过上调乳酸的生成，激活TLR4信号通路，诱导乳腺癌耐药能力增加；而抑制有氧糖酵解也成为减少肿瘤耐药能力的重要手段<sup>[23-25]</sup>。本研究运用PFKFB3的抑制剂PFK-15处理LoVo/5-FU，减少有氧糖酵解后，发现LoVo/5-FU的耐药能力被明显抑制。同时，本研究也发现，过表达MIF所诱导的LoVo耐药能力的增加可以被PFK-15所抑制。提示，MIF介导的结直肠癌耐药能力增加可能是通过上调结直肠癌有氧糖酵解。

综上所述，MIF介导的有氧糖酵解可能是结直肠癌耐药能力增加的重要机制，是减少直肠癌耐药能力的一个靶点。

#### 参考文献

- Aarons CB, Mahmoud NN. 现代结直肠癌外科治疗的思考[J]. 中国普通外科杂志, 2015, 24(4):459-466. doi:10.3978/j.issn.1005-6947.2015.04.001.
- Aarons CB, Mahmoud NN. Current surgical considerations for colorectal cancer[J]. Chinese Journal of General Surgery, 2015, 24(4):459-466. doi:10.3978/j.issn.1005-6947.2015.04.001.
- Wu DW, Huang CC, Chang SW, et al. Bcl-2 stabilization by paxillin confers 5-fluorouracil resistance in colorectal cancer[J]. Cell Death Differ, 2015, 22(5):779-789. doi: 10.1038/cdd.2014.170.
- Arena S, Siravegna G, Mussolin B, et al. MM-151 overcomes acquired resistance to cetuximab and panitumumab in colorectal cancers harboring EGFR extracellular domain mutations[J]. Sci Transl Med, 2016, 8(324):324ra14. doi: 10.1126/scitranslmed.aad5640.
- Hu CT, Guo LL, Feng N, et al. MIF, secreted by human hepatic sinusoidal endothelial cells, promotes chemotaxis and outgrowth of colorectal cancer in liver prometastasis[J]. Oncotarget, 2015, 6(26):22410-22423.
- Abdul-Aziz AM, Shafat MS, Mehta TK, et al. MIF-Induced Stromal PKCbeta/IL8 Is Essential in Human Acute Myeloid Leukemia[J]. Cancer Res, 2017, 77(2):303-311. doi: 10.1158/0008-5472.CAN-16-1095.
- Dessein AF, Stechly L, Jonckheere N, et al. Autocrine induction of invasive and metastatic phenotypes by the MIF-CXCR4 axis in drug-resistant human colon cancer cells[J]. Cancer Res, 2010, 70(11):4644-4654. doi: 10.1158/0008-5472.CAN-09-3828.
- Wu MY, Fu J, Xu J, et al. Steroid receptor coactivator 3 regulates autophagy in breast cancer cells through macrophage migration inhibitory factor[J]. Cell Res, 2012, 22(6):1003-1021. doi: 10.1038/cr.2012.44.
- Liu Y, Zhao L, Ju Y, et al. A novel androstenedione derivative induces ROS-mediated autophagy and attenuates drug resistance in osteosarcoma by inhibiting macrophage migration inhibitory factor (MIF)[J]. Cell Death Dis, 2014, 5:e1361. doi: 10.1038/cddis.2014.300.
- Sun L, Ke J, He Z, et al. HES1 Promotes Colorectal Cancer Cell Resistance To 5-FU by Inducing Of EMT and ABC Transporter Proteins[J]. J Cancer, 2017, 8(14): 2802-2808. doi: 10.7150/jca.19142.
- 颜畅, 胡艺冰, 穆磊, 等. BMP4增强结直肠癌耐药细胞化疗敏感性的作用及机制[J]. 华中科技大学学报:医学版, 2015, 44(3):281-284. doi:10.3870/j.issn.1672-0741.2015.03.008.
- Yan C, Hu YB, Mu L, et al. BMP4 Enhances the Chemosensitivity of Drug-resistant Colorectal Cancer Cells[J]. Acta Medicinæ Universitatis Scientiæ et Technologiæ Huazhong, 2015, 44(3):281-284. doi:10.3870/j.issn.1672-0741.2015.03.008.
- 文俏程, 陈志康, 陈子华, 等. 胃癌细胞奥沙利铂耐药与上皮-间质转化关系研究[J]. 中国普通外科杂志, 2015, 24(9):1269-1274. doi:10.3978/j.issn.1005-6947.2015.09.012.
- Wen QC, Chen ZK, Chen ZH, et al. Relationship between epithelial

- mesenchymal transition and oxaliplatin-resistance in gastric cancer cells[J]. Chinese Journal of General Surgery, 2015, 24(9):1269–1274. doi:10.3978/j.issn.1005-6947.2015.09.012.
- [12] Wei X, Wang W, Wang L, et al. MicroRNA-21 induces 5-fluorouracil resistance in human pancreatic cancer cells by regulating PTEN and PDCD4[J]. Cancer Med, 2016, 5(4):693–702. doi: 10.1002/cam4.626.
- [13] Fischer Y, Thomas J, Sevilla L, et al. Insulin-induced recruitment of glucose transporter 4 (GLUT4) and GLUT1 in isolated rat cardiac myocytes. Evidence of the existence of different intracellular GLUT4 vesicle populations[J]. J Biol Chem, 1997, 272(11):7085–7092.
- [14] 屈雁玲, 马俊丽, 邓甘露, 等. 甲基莲心碱逆转人结肠癌细胞奥沙利铂耐药的体外研究[J]. 中国普通外科杂志, 2017, 26(3):325–332. doi:10.3978/j.issn.1005-6947.2017.03.009.
- Qu YL, Ma JL, Deng GL, et al. Reversal effect of neferine on oxaliplatin-resistance in human colon cancer cells in vitro[J]. Chinese Journal of General Surgery, 2017, 26(3):325–332. doi:10.3978/j.issn.1005-6947.2017.03.009.
- [15] Yu T, Guo F, Yu Y, et al. Fusobacterium nucleatum Promotes Chemoresistance to Colorectal Cancer by Modulating Autophagy[J]. Cell, 2017, 170(3):548–563. doi: 10.1016/j.cell.2017.07.008.
- [16] Liu W, Liu SY, He YB, et al. MiR-451 suppresses proliferation, migration and promotes apoptosis of the human osteosarcoma by targeting macrophage migration inhibitory factor[J]. Biomed Pharmacother, 2017, 87:621–627. doi: 10.1016/j.biopha.2016.12.121.
- [17] D'Amato-Brito C, Cipriano D, Colin DJ, et al. Role of MIF/CD74 signaling pathway in the development of pleural mesothelioma[J]. Oncotarget. 2016, 7(10):11512–11525. doi: 10.18632/oncotarget.7314.
- [18] Chesney JA, Mitchell RA. 25 Years On: A Retrospective on Migration Inhibitory Factor in Tumor Angiogenesis[J]. Mol Med, 2015, 21(Suppl 1):S19–24. doi: 10.2119/molmed.2015.00055.
- [19] Shang Y, He J, Wang Y, et al. CHIP/Stub1 regulates the Warburg effect by promoting degradation of PKM2 in ovarian carcinoma[J]. Oncogene, 2017, 36(29):4191–4200. doi: 10.1038/ncr.2017.31.
- [20] Jiang SH, Li J, Dong FY, et al. Increased Serotonin Signaling Contributes to the Warburg Effect in Pancreatic Tumor Cells under Metabolic Stress and Promotes Growth of Pancreatic Tumors in Mice[J]. Gastroenterology, 2017, 153(1):277–291. doi: 10.1053/j.gastro.2017.03.008.
- [21] Jin L, Chun J, Pan C, et al. Phosphorylation-mediated activation of LDHA promotes cancer cell invasion and tumour metastasis[J]. Oncogene, 2017, 36(27):3797–3806. doi: 10.1038/ncr.2017.6.
- [22] Ge X, Cao Z, Gu Y, et al. PFKFB3 potentially contributes to paclitaxel resistance in breast cancer cells through TLR4 activation by stimulating lactate production[J]. Cell Mol Biol (Noisy-le-grand), 2016, 62(6):119–125.
- [23] Harada K, Ferdous T, Harada T, et al. Metformin in combination with 5-fluorouracil suppresses tumor growth by inhibiting the Warburg effect in human oral squamous cell carcinoma[J]. Int J Oncol, 2016, 49(1):276–284. doi: 10.3892/ijo.2016.3523.
- [24] Taniguchi K, Sakai M, Sugito N, et al. PKM1 is involved in resistance to anti-cancer drugs[J]. Biochem Biophys Res Commun, 2016, 473(1):174–180. doi: 10.1016/j.bbrc.2016.03.074.
- [25] Jin Y, Cai Q, Shenoy AK, et al. Src drives the Warburg effect and therapy resistance by inactivating pyruvate dehydrogenase through tyrosine-289 phosphorylation[J]. Oncotarget, 2016, 7(18):25113–25124. doi: 10.18632/oncotarget.7159.

( 本文编辑 宋涛 )

本文引用格式: 黄荣, 汪泓, 陈保华, 等. 巨噬细胞移动抑制因子促进有氧糖酵解与直肠癌细胞耐药性的关系[J]. 中国普通外科杂志, 2017, 26(10):1265–1271. doi:10.3978/j.issn.1005-6947.2017.10.007

Cite this article as: Huang R, Wang H, Chen BH, et al. Relationship of macrophage migration inhibition factor enhancing aerobic glycolysis to drug resistance of colorectal cancer cells[J]. Chin J Gen Surg, 2017, 26(10):1265–1271. doi:10.3978/j.issn.1005-6947.2017.10.007