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· 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

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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_{50})、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_{50} 、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_{50} 、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_{50} 、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
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Relationship of macrophage migration inhibition factor enhancing aerobic glycolysis to drug resistance of colorectal cancer cells

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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_{50}), MIF protein expression, glucose uptake ability of cells, lactic

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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^[1]。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^[2-3]。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^[4-6]。新近的研究^[8]表明, MIF与乳腺癌^[7]、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); β -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^[9-11]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^[12]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 μL /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 μmol

si-RNA 和 5 μ L lip-2000 混合于 100 μ 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 μ 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 10⁵/孔细胞种于 6 孔板中, 24 h 后加入终滴度为 5 \times 10⁶ 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 μ 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^[13]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 10⁶, 加入 100 μ 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 μ L 标准版品(10 milliunits/mL)或样品和 50 μ 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 10⁶/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 μ L 样品、26 μ L 乳酸盐测定缓冲液、2 μ L 乳酸酶混合物和 2 μ 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 μ L 分别加入由 26 μ L 乳酸盐测定缓冲液、2 μ L 乳酸酶混合物和 2 μ 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 IC₅₀ 分别为 0.220 和 5.600 μ 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 IC₅₀ 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)。

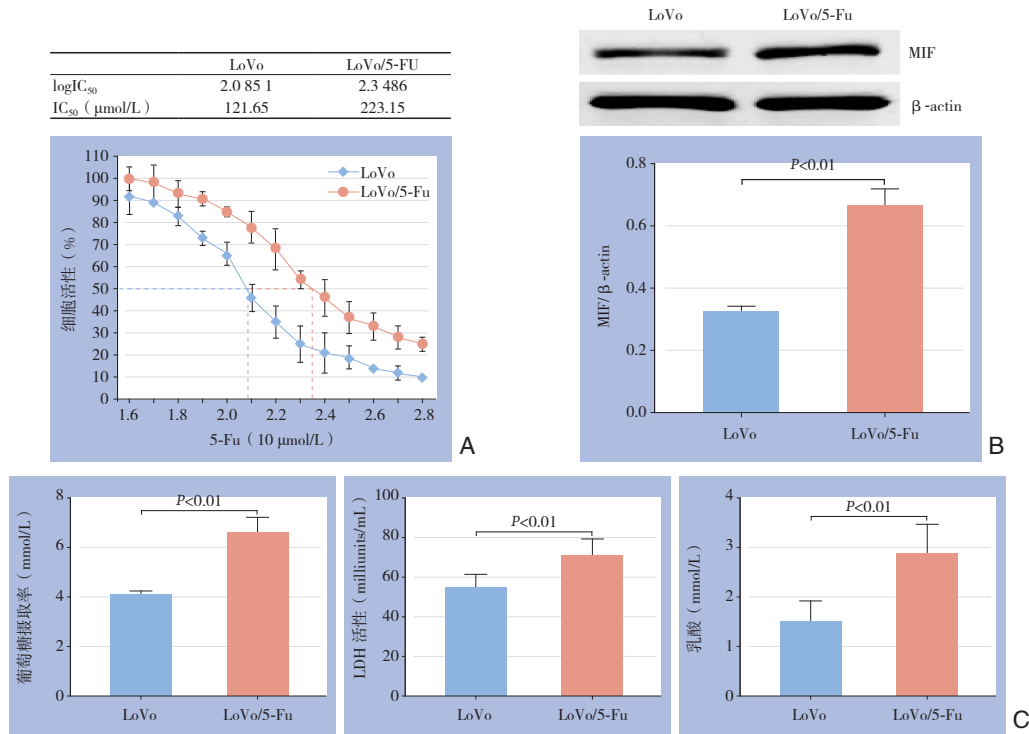


图 1 LoVo/5-FU 细胞 MIF 表达和有氧糖酵解的变化 A: 细胞生长抑制曲线及细胞对 5-FU 的 IC₅₀; B: Western blot 检测 MIF 蛋白表达及灰度值分析结果; C: 糖酵解相关指标检测结果

Figure 1 Changes in MIF expression and aerobic glycolysis in LoVo/5-FU cells A: Cell growth inhibition curves and IC₅₀ 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

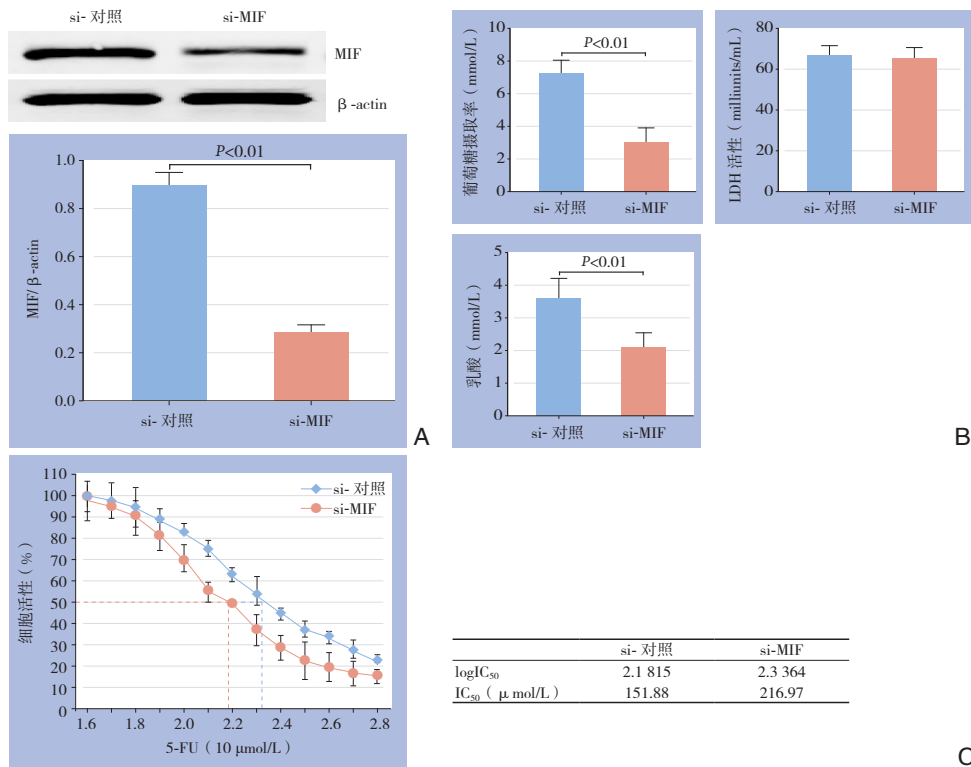


图 2 下调 MIF 对 LoVo/5-FU 耐药和糖酵解的影响 A: Western blot 检测 MIF 蛋白表达与灰度分析结果; B: 糖酵解相关指标检测结果; C: 细胞生长抑制曲线与 IC₅₀

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 IC₅₀ values

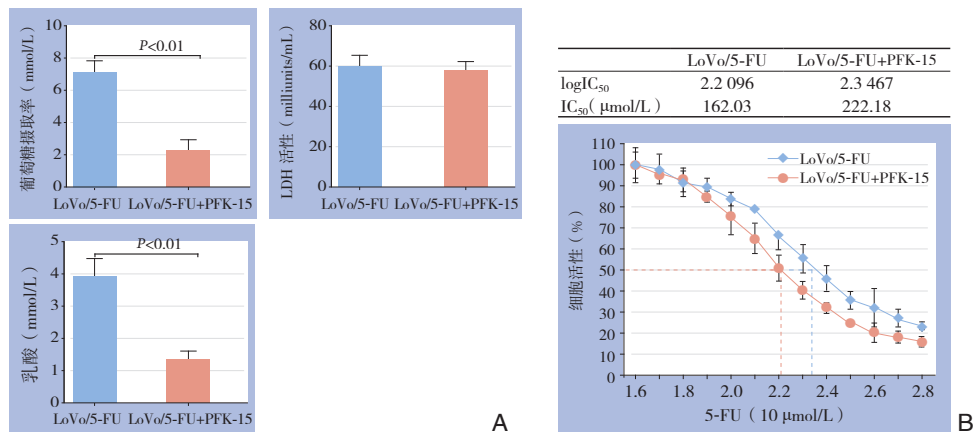


图 3 抑制糖酵解对 LoVo/5-FU 耐药的影响 A: 糖酵解相关指标检测结果; B: 细胞生长抑制曲线与 IC₅₀

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 IC₅₀ 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 IC₅₀ 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)。

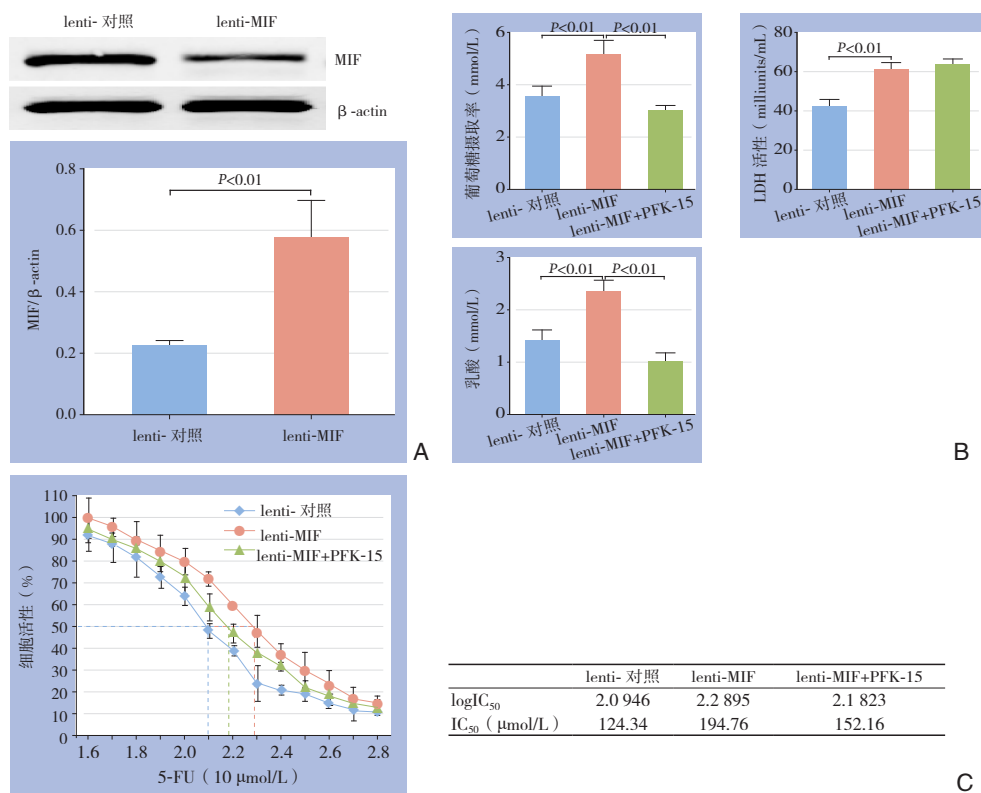


图 4 MIF 过表达对 LoVo 对 5-FU 耐药的影响及同时抑制有氧糖酵解的干预作用 A: Western blot 检测 MIF 蛋白表达与灰度分析结果; B: 糖酵解相关指标检测结果; C: 细胞生长抑制曲线与 IC₅₀

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 IC₅₀ 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^[14-15]。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蛋白表达和在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^[16-18]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^[7-8]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^[19-21]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^[22]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^[23-25]。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。

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