·论著·

UFM1通过激活Wnt/β-catenin信号通路增加三阴性乳腺癌细胞顺铂耐药

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摘要 **目的** 探究泛素折叠修饰因子1(UFM1)对三阴性乳腺癌(TNBC)细胞顺铂敏感性的影响及作用机制。**方法** 将TNBC细胞系MDA-MB-231分为ov-NC、ov-UFM1组、ov-UFM1+sh-NC组和ov-UFM1+sh-ESM1组; MDA-MB-231顺铂耐药(MDA-MB-231/DDP)细胞分为sh-NC组、sh-UFM1组、sh-UFM1+ov-NC组和sh-UFM1+ov-ESM1组。用CCK-8和流式细胞术检测各组细胞对放疗的敏感性; 实时定量PCR检测各组细胞中*UFM1*和内皮细胞特异性分子1(*ESM1*)mRNA表达; Western blotting检测各组细胞中UFM1、ESM1和β-联蛋白(β-catenin)表达。**结果** MDA-MB-231/DDP细胞中*UFM1*表达较MDA-MB-231细胞显著上调($P<0.05$)。过表达*UFM1*升高顺铂处理的MDA-MB-231/DDP细胞的存活率,降低凋亡率,增加细胞中ESM1和β-catenin表达; 敲减*UFM1*则作用效果逆转。敲减*ESM1*降低顺铂处理的过表达*UFM1*的MDA-MB-231/DDP细胞的存活率并增加细胞的凋亡率,降低细胞中β-catenin表达。过表达*ESM1*增加顺铂处理的敲减*UFM1*的MDA-MB-231/DDP细胞的存活率并降低细胞的凋亡率,增加细胞中β-catenin表达。**结论** UFM1通过上调ESM1表达降低TNBC细胞对顺铂的敏感性,其机制可能与诱导Wnt/β-catenin信号通路激活有关。

关键词 三阴性乳腺癌; 泛素折叠修饰因子1; 内皮细胞特异性分子1; 顺铂耐药; Wnt/β-catenin信号通路
中图分类号 R737.9 **文献标志码** A **文章编号** 0258-4646(2026)06-0496-06
网络出版地址 https://link.cnki.net/urlid/21.1227.r.20260605.1331.002
DOI: 10.12007/j.issn.0258-4646.2026.06.003

UFM1 enhances cisplatin resistance in triple-negative breast cancer cells via activation of the Wnt/β-catenin signaling pathway

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Abstract **Objective** To analyze the effects and mechanisms of action of ubiquitin-fold modifier 1 (UFM1) on the sensitivity of triple-negative breast cancer (TNBC) cells to cisplatin. **Methods** MDA-MB-231 cells were divided into ov-NC, ov-UFM1, ov-UFM1+sh-NC, and ov-UFM1+sh-ESM1 groups. MDA-MB-231/DDP cells were divided into sh-NC, sh-UFM1, sh-UFM1+ov-NC, and sh-UFM1+ov-ESM1 groups. CCK-8 and flow cytometry were used to detect the sensitivity of cells to radiotherapy. Real-time quantitative PCR was used to detect the expression of *UFM1* and endothelial cell-specific molecule 1 (*ESM1*) mRNA in the cells. Western blotting was used to detect the expression of UFM1, ESM1 and β-catenin. **Results** *UFM1* mRNA expression was significantly upregulated in MDA-MB-231/DDP cells compared with that in MDA-MB-231 cells ($P<0.05$). Overexpression of *UFM1* increased the survival rate of MDA-MB-231/DDP cells treated with cisplatin, decreased the apoptosis rate, and increased the expression of ESM1 and β-catenin in the cells; in contrast, knockdown of *UFM1* reversed the effects. Knockdown of *ESM1* reduced the survival rate of cisplatin-treated MDA-MB-231/DDP cells with overexpressed *UFM1*, increased the apoptosis rate, and decreased the expression of β-catenin in the cells. Overexpression of *ESM1* increased the survival rate of MDA-MB-231/DDP cells treated with cisplatin while knocking down *UFM1*, reduced the apoptosis rate of the cells, and increased the expression of β-catenin in the cells. **Conclusion** UFM1 reduced the sensitivity of TNBC cells to cisplatin by upregulating ESM1 expression, and its mechanism may be related to activation of the Wnt/β-catenin signaling pathway.

Keywords triple-negative breast cancer; ubiquitin-fold modifier 1; endothelial cell-specific molecule 1; cisplatin resistance; Wnt/β-catenin signaling pathway

三阴性乳腺癌(triple-negative breast cancer, TNBC)是乳腺癌中最致命的亚型[1]。TNBC缺乏雌激素受体、孕激素受体和人表皮生长因子受体2表达,患者无法使用这些受体的靶向药物进行治疗,

基金项目:超声医学工程国家重点实验室项目(2021KFKT014)
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收稿日期:2025-07-09
网络出版时间:2026-06-08 11:37:23

导致其侵袭性更强、复发风险更高且预后更差[2]。目前，化疗是TNBC患者治疗的主要手段。然而，部分患者产生化疗耐药，最终导致治疗失败[3]。因此，明确TNBC化疗耐药的分子机制具有重要意义。

泛素折叠修饰因子1（ubiquitin-fold modifier 1，UFM1）是一种泛素样蛋白家族的泛素折叠修饰因子，它通过三步酶促级联反应共价连接至靶蛋白的赖氨酸残基维持细胞稳态、内质网稳态、蛋白质稳态和囊泡运输，调节DNA损伤修复与自噬[4]。已有研究[5]发现UFM1在TNBC患者肿瘤组织中表达上调，且其高表达的患者总生存期较低。UFM1还参与TNBC的关键生物学过程。研究[6]表明，UFM1通过翻译后修饰促进胎盘特异性蛋白8稳定并上调其表达，抑制程序性死亡受体配体1（programmed death-ligand 1，PD-L1）泛素化，促进TNBC细胞增殖和免疫逃逸。然而，UFM1对TNBC顺铂耐药的影响及机制尚不明确。基于生物信息学的研究[7]发现，敲减*UFM1*降低了TNBC细胞中内皮细胞特异性分子1（endothelial cell-specific molecule 1，ESM1）表达。ESM1又称内皮素，是一种可溶性硫酸皮肤素蛋白聚糖，在子宫内膜癌、结直肠癌、宫颈癌和胃癌等多种恶性肿瘤组织中高表达[8]。研究[9]表明，ESM1在TNBC组织和细胞中表达上调，促进TNBC细胞增殖、迁移和侵袭；ESM1高表达与TNBC患者不良预后有关。还有研究[10]发现ESM1诱导卵巢癌顺铂耐药。然而，UFM1是否介导ESM1影响TNBC细胞顺铂耐药及其作用机制目前尚无报道。本研究探讨UFM1对TNBC细胞顺铂敏感性的影响及作用机制，旨在为UFM1作为TNBC化疗耐药治疗的潜在靶点提供理论依据。

1　材料与方法

1.1　实验细胞和主要试剂、仪器

TNBC细胞系MDA-MB-231购自武汉普诺赛生命科技有限公司；慢病毒购自苏州吉玛基因股份有限公司；细胞培养基和胎牛血清购自美国Gibco公司；CCK-8试剂盒、细胞凋亡检测试剂盒和Western blotting相关试剂购自上海碧云天生物技术有限公司；实时定量PCR相关试剂购自日本TaKaRa公司；Western blotting相关抗体购自英国abcam公司；荧光定量PCR仪购自美国ABI公司；流式细胞仪购自美国ThermoFisher Sciencific公司；酶标仪购自美国BioTek公司；凝胶扫描成像系统购自美国Bio-Rad公司。

1.2　方法

1.2.1　细胞培养：MDA-MB-231细胞用含10%胎牛血清和1%青链霉素的DMEM培养基培养于37 ℃含5%CO_2的细胞培养箱中。

1.2.2　顺铂耐药MDA-MB-231（MDA-MB-231/DDP）细胞建立：向对数生长期的MDA-MB-231细胞中加入0.5 μmol/L顺铂，继续培养细胞至其能在0.5 μmol/L顺铂浓度下稳定生长，然后将顺铂浓度增加0.5 μmol/L，继续培养细胞。逐渐增加顺铂浓度，至细胞在10 μmol/L顺铂浓度下稳定生长，即获得MDA-MB-231/DDP细胞。

1.2.3　细胞转染和分组：取对数生长期的细胞，待其融合度达50%，MDA-MB-231细胞分为转染过表达对照慢病毒（ov-NC）组、转染过表达*UFM1*慢病毒（ov-UFM1）组、转染过表达*UFM1*+敲减对照慢病毒（ov-UFM1+sh-NC）组和转染过表达*UFM1*+敲减*ESM1*慢病毒（ov-UFM1+sh-ESM1）组；MDA-MB-231/DDP细胞分为转染敲减对照慢病毒（sh-NC）组、转染敲减*UFM1*慢病毒（sh-UFM1）组、转染敲减*UFM1*+过表达对照慢病毒（sh-UFM1+ov-NC）组和转染敲减*UFM1*+过表达*ESM1*慢病毒（sh-UFM1+ov-ESM1）组。待细胞稳定生长后用嘌呤霉素筛选稳定转染的细胞并验证。

1.2.4　CCK-8：取对数生长期的细胞均匀铺于96孔板中。用0、2.5、5、10、20、40、80、160、320、640 μmol/L顺铂处理细胞48 h后，用含10% CCK-8的无血清培养基孵育细胞，酶标仪检测450 nm处吸光度值。细胞存活率（%）=顺铂处理的细胞吸光度值/未处理的细胞吸光度值×100。

1.2.5　Western blotting：各组细胞裂解后离心收集蛋白，定量并配置样品（2 μg/μL）。取30 μg蛋白样品，电泳分离后湿转法转移蛋白至PVDF膜。经封闭、一抗、二抗孵育和ECL发光后，用ImageJ软件分析电泳条带吸光度值。

1.2.6　实时定量PCR：将各组细胞用TRIzol法提取的RNA逆转录为cDNA，并以其为模板进行扩增。引物序列如下：*UFM1*，正向5'-TCGGAAGTGCTGATGAGTT-3'，反向5'-CCTCCTTAATAGAAGCCTGGT-3'；*ESM1*，正向5'-ATTATGCGGTGGACTGCCC-3'，反向

5'-GCCATGTCATGCTCTTTGCAG-3'；*β-actin*，正向5'-ACCCTGAAGTACCCCATCGAG-3'，反向5'-AGCACAGCCTGGATAGCAAC-3'。以*β-actin*为内参，采用$2^{-\Delta\Delta Ct}$法计算目的基因的相对表达量。

1.2.7　流式细胞术：取对数生长期的细胞均匀铺于6孔板中。用200 μmol/L顺铂处理48 h后，依次用膜联蛋白-V-氟洛雷素异硫氰酸酯和碘化丙啶染色液孵育，流式细胞仪检测，并采用FlowJo（7.6.5）软件分析细胞凋亡率。

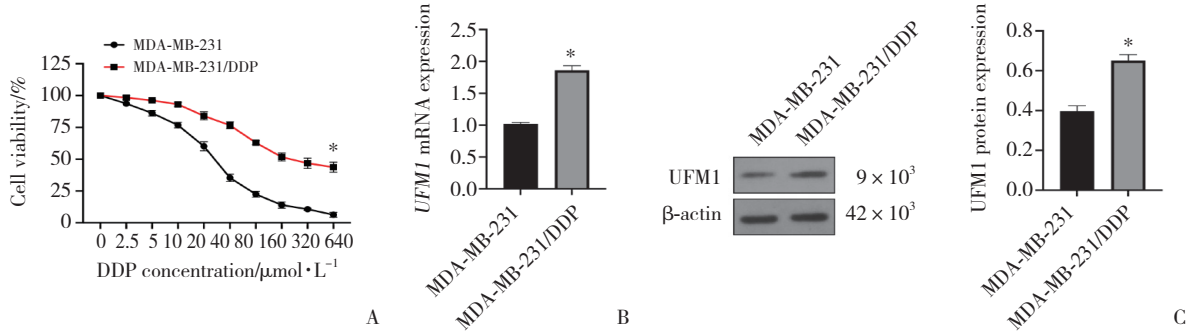
1.3　统计学分析

采用SPSS 22.0进行统计分析，计量资料采用$\bar{x} \pm s$表示，多组间比较采用单因素方差分析，数据均符合方差齐性，组间两两比较采用Tukey事后检验，$P<0.05$为差异有统计学意义。

2　结果

2.1　UFM1在MDA-MB-231和MDA-MB-231/DDP细胞中表达水平比较

CCK-8检测结果显示，与MDA-MB-231细胞相比，MDA-MB-231/DDP细胞存活率明显升高（$P<0.05$）。见图1A。实时定量PCR与Western blotting检测结果显示，与MDA-MB-231细胞相比，MDA-MB-231/DDP细胞中*UFM1* mRNA及蛋白表达均明显上调（$P<0.05$）。见图1B、1C。



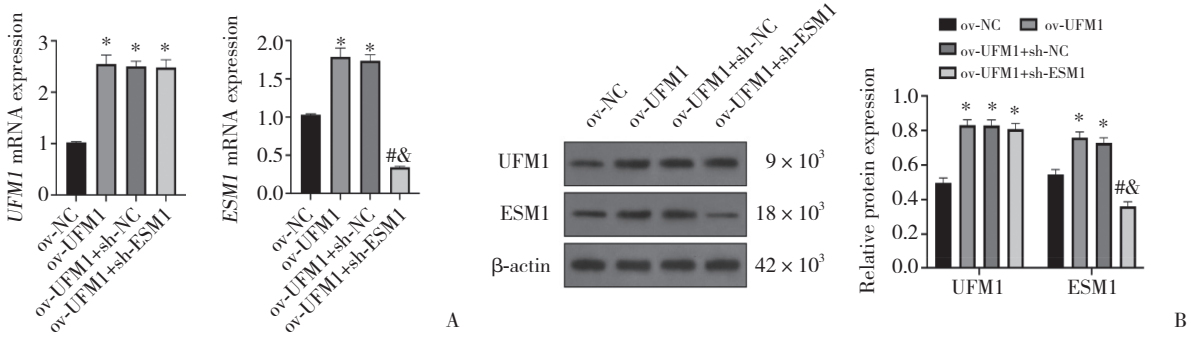
A，cell survival rate（$n=3$）；B，expression of *UFM1* mRNA（$n=3$）；C，expression of UFM1 protein（$n=3$）. * $P<0.05$ vs. MDA-MB-231cells.

图1　UFM1在MDA-MB-231和MDA-MB-231/DDP细胞中的表达

Fig.1　Expression of UFM1 in MDA-MB-231 and MDA-MB-231/DDP cells

2.2　敲减*ESM1*对过表达*UFM1*的MDA-MB-231细胞中ESM1表达的影响

结果显示，与ov-NC组相比，ov-UFM1组、ov-UFM1+sh-NC组和ov-UFM1+sh-ESM1组细胞中*UFM1* mRNA和蛋白表达明显上调（$P<0.05$）。与ov-NC组相比，ov-UFM1组和ov-UFM1+sh-NC组MDA-MB-231细胞中*ESM1* mRNA和蛋白表达明显上调（$P<0.05$）；与ov-UFM1组和ov-UFM1+sh-NC组相比，ov-UFM1+sh-ESM1组MDA-MB-231细胞中*ESM1* mRNA和蛋白表达明显下调（$P<0.05$）。见图2。



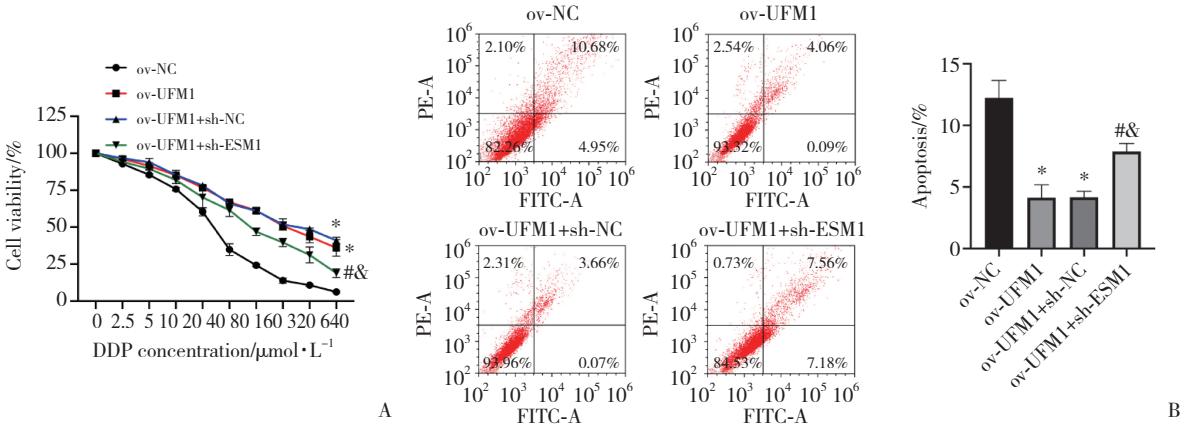
A，expression of *UFM1* and *ESM1* mRNA（$n=3$）；B，expression of UFM1 and ESM1 proteins（$n=3$）. * $P<0.05$ vs. ov-NC group；# $P<0.05$ vs. ov-UFM1 group；& $P<0.05$ vs. ov-UFM1+sh-NC group.

图2　敲减*ESM1*对过表达*UFM1*的MDA-MB-231细胞中ESM1表达的影响

Fig.2　Effect of *ESM1* knockdown on ESM1 expression in MDA-MB-231 cells with *UFM1* overexpression

2.3　敲减*ESM1*对过表达*UFM1*的MDA-MB-231细胞顺铂敏感性的影响

CCK-8结果显示，与ov-NC组相比，ov-UFM1组和ov-UFM1+sh-NC组顺铂处理后细胞存活率明显升高（$P < 0.05$）；与ov-UFM1组和ov-UFM1+sh-NC组相比，ov-UFM1+sh-ESM1组顺铂处理后细胞存活率明显降低（$P < 0.05$）。见图3A。流式细胞术检测结果显示，与ov-NC组相比，ov-UFM1组和ov-UFM1+sh-NC组顺铂处理后细胞凋亡率明显降低（$P < 0.05$）；与ov-UFM1组和ov-UFM1+sh-NC组相比，ov-UFM1+sh-ESM1组顺铂处理后细胞凋亡率明显升高（$P < 0.05$）。见图3B。



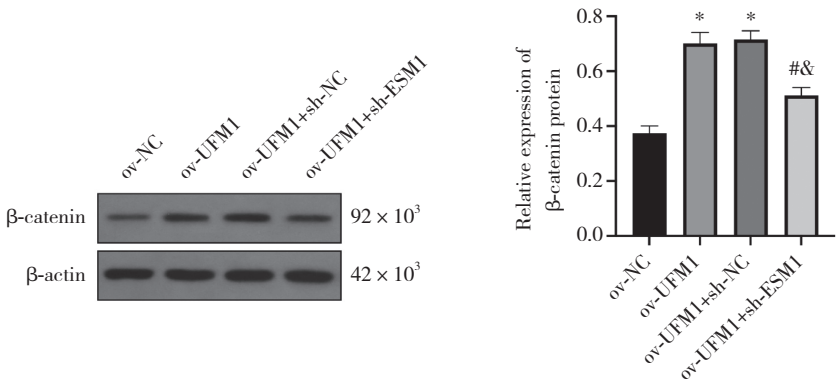
A，cell survival rate detected by CCK-8（$n = 3$）；B，cell apoptosis rate detected by flow cytometry（$n = 3$）. * $P < 0.05$ vs. ov-NC group；# $P < 0.05$ vs. ov-UFM1 group；& $P < 0.05$ vs. ov-UFM1+sh-NC group.

图3　敲减*ESM1*对过表达*UFM1*的MDA-MB-231细胞顺铂敏感性的影响

Fig.3　Effect of *ESM1* knockdown on the sensitivity to cisplatin in MDA-MB-231 cells with *UFM1* overexpression

2.4　敲减*ESM1*对过表达*UFM1*的MDA-MB-231细胞中β-catenin蛋白表达的影响

Western blotting检测结果显示，与ov-NC组相比，ov-UFM1组和ov-UFM1+sh-NC组MDA-MB-231细胞中β-catenin蛋白表达水平明显上调（$P < 0.05$）；与ov-UFM1组和ov-UFM1+sh-NC组相比，ov-UFM1+sh-ESM1组MDA-MB-231细胞中β-catenin蛋白表达水平明显下调（$P < 0.05$）。见图4。



* $P < 0.05$ vs. ov-NC group；# $P < 0.05$ vs. ov-UFM1 group；& $P < 0.05$ vs. ov-UFM1+sh-NC group.

图4　敲减*ESM1*对过表达*UFM1*的MDA-MB-231细胞中β-catenin蛋白表达的影响

Fig.4　Effect of *ESM1* knockdown on β-catenin protein expression in MDA-MB-231 cells with *UFM1* overexpression

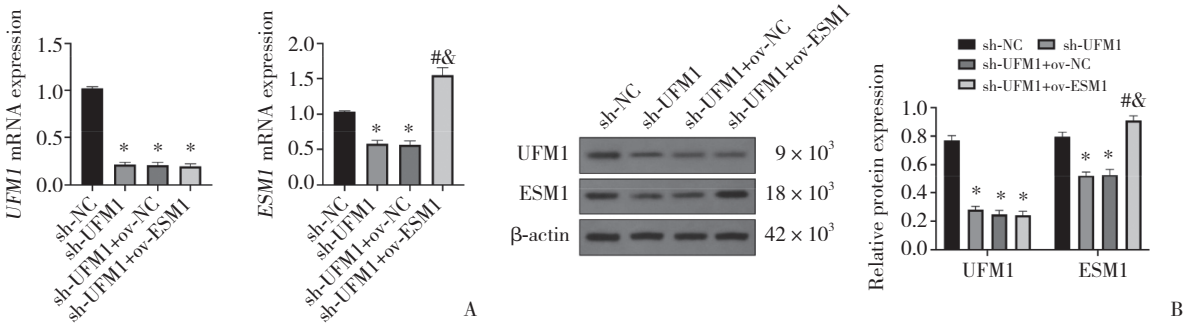
2.5　过表达*ESM1*对敲减*UFM1*的MDA-MB-231/DDP细胞中ESM1表达的影响

与sh-NC组相比，sh-UFM1组、sh-UFM1+ov-NC组和sh-UFM1+ov-ESM1组MDA-MB-231/DDP细胞中*UFM1* mRNA和蛋白表达明显下调（$P < 0.05$）。与sh-NC组相比，sh-UFM1组和sh-UFM1+ov-NC组MDA-

MB-231/DDP细胞中*ESM1* mRNA和蛋白表达明显下调（$P < 0.05$）；与sh-UFM1组和sh-UFM1+ov-NC组相比，sh-UFM1+ov-ESM1组MDA-MB-231/DDP细胞中*ESM1* mRNA和蛋白表达明显上调（$P < 0.05$）。见图5。

2.6　过表达*ESM1*对敲减*UFM1*的MDA-MB-231/DDP细胞顺铂敏感性的影响

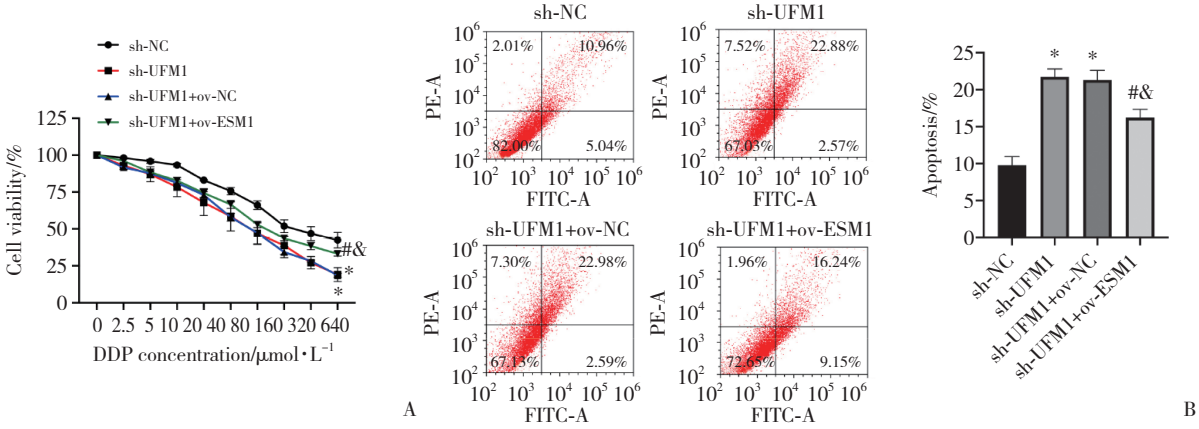
CCK-8结果显示，与sh-NC组相比，sh-UFM1组和sh-UFM1+ov-NC组顺铂处理的MDA-MB-231/DDP细胞的存活率明显降低（$P < 0.05$）；与sh-UFM1组和sh-UFM1+ov-NC组相比，sh-UFM1+ov-ESM1组顺铂处理的MDA-MB-231/DDP细胞的存活率明显升高（$P < 0.05$）。见图6A。流式细胞术检测结果显示，与sh-NC组相比，sh-UFM1组和sh-UFM1+ov-NC组顺铂处理的MDA-MB-231/DDP细胞的凋亡率明显升高（$P < 0.05$）；与sh-UFM1组和sh-UFM1+ov-NC组相比，sh-UFM1+ov-ESM1组顺铂处理的MDA-MB-231/DDP细胞的凋亡率明显降低（$P < 0.05$）。见图6B。



A，expression of *UFM1* and *ESM1* mRNA；B，expression of UFM1 and ESM1 proteins. * $P < 0.05$ vs. sh-NC group；# $P < 0.05$ vs. sh-UFM1 group；& $P < 0.05$ vs. sh-UFM1+ov-NC group.

图5　过表达*ESM1*对敲减*UFM1*的MDA-MB-231/DDP细胞中ESM1表达的影响

Fig.5　Effect of overexpression of *ESM1* on ESM1 expression in MDA-MB-231/DDP cells with *UFM1* knockdown



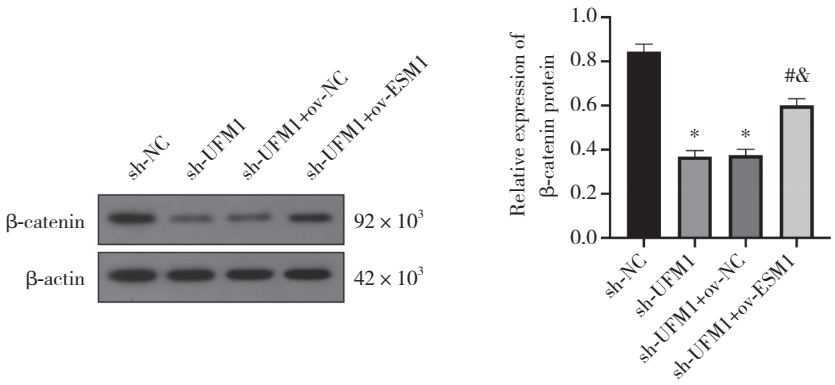
A，cell survival rate detected by CCK-8 ($n = 3$)；B，cell apoptosis rate detected by flow cytometry ($n = 3$). * $P < 0.05$ vs. sh-NC group；# $P < 0.05$ vs. sh-UFM1 group；& $P < 0.05$ vs. sh-UFM1+ov-NC group.

图6　过表达*ESM1*对敲减*UFM1*的MDA-MB-231/DDP细胞顺铂敏感性的影响

Fig.6　Effect of overexpression of *ESM1* on the sensitivity to cisplatin of MDA-MB-231/DDP cells with *UFM1* knockdown

2.7　过表达*ESM1*对敲减*UFM1*的MDA-MB-231/DDP细胞中β-catenin表达的影响

Western blotting检测结果显示，与sh-NC组相比，sh-UFM1组和sh-UFM1+ov-NC组MDA-MB-231/DDP细胞中β-catenin蛋白表达水平明显下调（$P < 0.05$）；与sh-UFM1组和sh-UFM1+ov-NC组相比，sh-UFM1+ov-ESM1组MDA-MB-231/DDP细胞中β-catenin蛋白表达水平明显上调（$P < 0.05$）。见图7。



* $P < 0.05$ vs. sh-NC group; # $P < 0.05$ vs. sh-UFM1 group; & $P < 0.05$ vs. sh-UFM1+ov-NC group.

图7　过表达*ESM1*对敲减*UFM1*的MDA-MB-231/DDP细胞中β-catenin表达的影响

Fig.7　Effect of overexpression of *ESM1* on β-catenin protein expression in MDA-MB-231/DDP cells with *UFM1* knockdown

3　讨论

UFM1在肿瘤中具有双重作用。在口腔鳞状细胞癌组织中UFM1高表达，促进口腔鳞状细胞癌细胞增殖、迁移和侵袭[11]。然而，UFM1下调又与胃癌患者不良预后有关[12]。UFM1还通过促进核因子E2相关因子2的蛋白酶体降解增加胃癌细胞对化疗的敏感性[13]。在TNBC中，UFM1通过上调胎盘特异性蛋白8促进PD-L1表达，从而促进TNBC细胞增殖和免疫逃逸[6]。PD-L1过表达降低TNBC细胞对顺铂的敏感性[14]。本研究发现UFM1在顺铂耐药的MDA-MB-231/DDP细胞中表达较MDA-MB-231细胞显著上调，过表达*UFM1*增加顺铂处理的MDA-MB-231细胞的存活率并降低细胞的凋亡率，而敲减*UFM1*则效果逆转，表明*UFM1*可降低TNBC细胞对顺铂的敏感性。

已有研究[7]表明，敲减*UFM1*后TNBC细胞中ESM1表达显著下调。ESM1通过激活蛋白激酶B依赖的核因子κB/细胞周期蛋白D1信号通路促进TNBC细胞增殖、迁移和侵袭，并在体内水平促进TNBC细胞移植瘤生长[9]。ESM1通过诱导硬脂酰辅酶A去饱和酶1上调P-糖蛋白表达，促进卵巢癌细胞顺铂耐药[10]。此外，ESM1还通过上调缺氧诱导因子-1α促进非小细胞肺癌细胞干性，从而间接诱导肿瘤细胞顺铂耐药[15-16]。本研究发现敲减*UFM1*降低TNBC细胞中ESM1表达，而过表达*UFM1*则效果逆转。本研究还发现，敲减*ESM1*降低顺铂处理的过表达*UFM1*的MDA-MB-231细胞的存活率，增加细胞的凋亡率，而过表达*ESM1*则效果逆转，表明UFM1通过上调ESM1表达降低TNBC细胞对顺铂的敏感性。

已有研究[17]表明，ESM1通过直接结合β-catenin的ARM结构域，稳定β-catenin-转录因子4转录复合体并激活Wnt/β-catenin信号通路。Wnt/β-catenin信号通路在TNBC中的异常活化与患者不良预后和总生存期降低有关，并促进肿瘤细胞上皮-间质转化和炎症[18-19]。Wnt/β-catenin信号通路的激活通过促进TNBC细胞干性诱导细胞对铂类药物耐药。本研究发现，过表达*UFM1*可增加MDA-MB-231细胞中β-catenin蛋白表达，而敲减*UFM1*则降低MDA-MB-231/DDP细胞中β-catenin蛋白表达。敲减*ESM1*降低过表达*UFM1*的MDA-MB-231细胞中β-catenin蛋白表达，而过表达*ESM1*增加敲减*UFM1*的MDA-MB-231/DDP细胞中β-catenin蛋白表达，提示UFM1通过上调ESM1诱导Wnt/β-catenin信号通路激活。

综上所述，UFM1通过上调ESM1表达降低TNBC细胞对顺铂的敏感性，其机制可能与诱导Wnt/β-catenin信号通路激活有关。UFM1可能成为TNBC化疗耐药的治疗靶点。然而，本研究仅进行了细胞实验，后续将进行动物实验进一步论证。

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（编辑　王又冬）

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（编辑　武玉欣）