

子宫内膜异位症患者血清 miR-455 和 FABP4 表达水平及临床意义

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摘要: **目的** 检测子宫内膜异位症 (endometriosis, EMT) 患者血清微小核糖核酸 (miRNA, miR) -455 和脂肪酸结合蛋白 4 (fatty acid binding protein 4, FABP4) 水平, 并探讨二者的相关性及其临床意义。**方法** 选择 2018 年 6 月 ~ 2021 年 3 月苏州高新区人民医院妇产科收治的 73 例 EMT 患者作为观察对象 (EMT 组), 另选取同期健康体检人员 75 例作为对照组, 采用实时荧光定量 PCR (qRT-PCR) 检测两组血清 miR-455 水平, ELISA 法检测血清 FABP4 水平, Pearson 法分析 EMT 患者血清 miR-455 和 FABP4 表达水平相关性, ROC 曲线分析血清 miR-455, FABP4 表达水平对 EMT 的诊断价值。**结果** 与对照组相比, EMT 组患者血清 FABP4 水平 ($17.34 \pm 4.25 \text{ ng/ml}$ vs $8.56 \pm 2.74 \text{ ng/ml}$) 显著增高, miR-455 水平显著降低 (0.67 ± 0.08 vs 1.05 ± 0.19), 差异均有统计学意义 ($t=14.977, 15.780$, 均 $P < 0.001$)。随着 EMT 分期的升高, EMT 患者血清 FABP4 表达水平显著升高, 血清 miR-455 表达水平显著降低, 差异均有统计学意义 ($F=31.108, 160.947$, 均 $P < 0.001$)。相关性分析显示, EMT 患者血清 miR-455 表达水平与 FABP4 呈负相关 ($r=-0.482, P < 0.05$)。血清 miR-455 和 FABP4 联合诊断 EMT 的曲线下面积为 0.922, 敏感度和特异度分别为 87.67% 和 81.33%。**结论** EMT 患者血清中 miR-455 低表达, FABP4 水平较高, 与患者病情严重程度相关, 可能成为 EMT 早期诊断的分子标志物。

关键词: 微小 RNA-455; 脂肪酸结合蛋白 4; 子宫内膜异位症

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Expression Level and Clinical Significance of Serum miR-455 and FABP4 in Patients with Endometriosis

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Abstract: **Objective** To detect the levels of serum microRNA-455 (miR-455) and fatty acid binding protein 4 (FABP4) in patients with endometriosis (EMT), and explore the correlation between the two and clinical significance. **Methods** 73 EMT patients admitted to Department of Obstetrics and Gynecology, People's Hospital of Suzhou High-tech Zone from June 2018 to March 2021 were selected as the observation objects (EMT group), and 75 healthy physical examinee during the same period were selected as the control group. Real-time fluorescent quantitative PCR (qRT-PCR) was used to detect the level of serum miR-455 of subjects in the two groups, ELISA method was used to detect the levels of serum FABP4, Pearson method was used to analyze the correlation between miR-455 and FABP4 in EMT patients, ROC curve was used to analyze the diagnostic value of serum miR-455 and FABP4 expression for EMT. **Results** Compared with the control group, the serum FABP4 ($17.34 \pm 4.25 \text{ ng/ml}$ vs $8.56 \pm 2.74 \text{ ng/ml}$) level of patients in the EMT group was significantly increased, and the level of miR-455 (0.67 ± 0.08 vs 1.05 ± 0.19) was significantly decreased, the differences were statistically significant ($t=14.977, 15.780$, all $P < 0.001$). With the increase of EMT staging, the expression level of serum FABP4 in EMT patients increased significantly, and the expression level of serum miR-455 decreased significantly, the differences were statistically significant ($F=31.108, 160.947$, all $P < 0.001$). Correlation analysis showed that serum miR-455 expression level of EMT patients was negatively correlated with FABP4 ($r=-0.482, P < 0.05$). The area under the curve for the combined diagnosis of serum miR-455 and FABP4 for EMT was 0.922, the sensitivity and the specificity were 87.67% and 81.33%, respectively. **Conclusion** The expression of miR-455 was low in the serum of EMT patients and the level of FABP4 is high, they were related to the severity of the disease, and may become molecular markers for the early diagnosis of EMT.

Keywords: microRNA-455; fatty acid binding protein 4; endometriosis

子宫内膜异位症 (endometriosis, EMT) 是生育年龄妇女常见良性疾病, 临床症状主要表现为月

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经异常、性交痛、不孕不育等,好发于25~45岁育龄女性,发病率为10%~15%,不孕率可达40%,严重影响妇女身心健康^[1-2]。EMT的发病机制尚不清楚,有多种因素参与EMT的发病和进展过程^[3-4]。微小核糖核酸(miRNA)为非编码小分子RNA,与EMT的发生发展有关,miR-455为miRNA的一种,研究表明,miR-455可靶向抑制基质金属蛋白酶2(matrix metalloproteinase 2, MMP2)和MMP9表达,从而降低子宫内层的血管通透性^[5-6]。脂肪酸结合蛋白4(fatty acid binding protein 4, FABP4)是一种脂肪细胞因子,研究表明,FABP4在子宫内层组织和子宫内层上皮细胞系中有表达,参与调控子宫内层上皮细胞系的增殖、迁移和侵袭^[7]。目前EMT患者血清miR-455与FABP4的水平变化尚缺乏研究,本研究回顾性分析EMT患者血清miR-455, FABP4的表达情况,探讨miR-455, FABP4表达水平与EMT发生发展的关系。

1 材料与方法

1.1 研究对象 选择2018年6月~2021年3月苏州高新区人民医院妇产科收治的73例EMT患者作为观察对象(EMT组),年龄20~45(32.40 ± 4.70)岁。纳入标准:①符合EMT诊断标准^[8],经腹腔镜手术及病理检测确诊为EMT;②年龄>18岁,且月经规律;③近3个月内未服用对子宫内层增殖有影响的药物或激素类药物;④患者临床资料完整。排除标准:①卵巢肿瘤、子宫腺肌病、多囊卵巢综合征等疾病患者;②子宫发育异常者;③自身免疫系统疾病患者;④心、肝、肺、肾等重要脏器功能异常者。

根据美国生育协会修订EMT评分标准分期,其中I期患者29例,II期患者16例,III期患者15例,IV期患者13例。

另选取同期女性健康体检人员75例作为对照组,所有体检人员体检无疾病,年龄21~47(32.60 ± 5.00)岁。EMT组与对照组平均年龄比较,差异无统计学意义($P > 0.05$)。

研究样本采集均经过本院伦理委员会批准,患者均知情同意并签署知情同意书。

1.2 仪器与试剂 人FABP4 ELISA试剂盒(美国R&D公司);TRIzol试剂[赛默飞世尔科技(中国)有限公司];逆转录试剂盒、实时荧光定量PCR(quantitative real-time PCR, qRT-PCR)试剂盒(日本TAKARA公司);miR-455及U6引物由上海生工生物工程公司设计与合成。ABI 7900型qRT-PCR仪(美国ABI公司),DU 640紫外分光光度计(BECKMAN公司),Multiskan MK3型全自动酶标仪(芬兰Labsystem公司)。

1.3 方法

1.3.1 样品采集及保存:抽取两组观察对象空腹静脉血5ml,室温静置30min,2000r/min离心15min,取上层血清,于-80℃冰箱保存。

1.3.2 qRT-PCR检测两组血清miR-455的表达:采用qRT-PCR检测两组观察对象血清miR-455水平。TRIzol试剂提取血清总RNA,紫外分光光度计检测RNA的纯度与浓度,逆转录试剂盒合成cDNA,以cDNA为模板进行qRT-PCR扩增。总反应体系15μl,其中SYBR Green Mix 6μl,上下游引物各0.5μl, cDNA 2μl, ddH₂O 6μl。反应条件:95℃预变性60s;95℃变性15s,65℃退火45s,72℃延伸30s,共35个循环。每个样品设置3个复孔。反应结束后,以U6作为内参,采用2^{-ΔΔCt}分析法计算miR-455表达水平。miR-455上游引物序列:5' GTGCCTTTGGACTACATC 3',下游引物序列:5' GAACATGTCTGCGTATCTC 3'; U6上游引物序列:5' CTCGCTTCGGCAGCACCA 3',下游引物序列:5' AACGCTTCACGAATTTGCGT 3'。

1.3.3 ELISA法检测血清FABP4水平:采用ELISA法检测观察对象血清FABP4,按照试剂盒说明书进行操作。

1.4 统计学分析 利用SPSS 22.0进行统计学分析,计量资料以均数±标准差($\bar{x} \pm s$)表示,两组间比较采用t检验;Pearson法分析EMT患者血清miR-455, FABP4表达水平相关性,ROC曲线分析血清miR-455, FABP4表达对EMT的诊断价值。 $P < 0.05$ 为差异有统计学意义。

2 结果

2.1 两组观察对象血清miR-455, FABP4表达水平比较 与对照组比较,EMT组患者血清FABP4水平显著升高(17.34 ± 4.25 ng/ml vs 8.56 ± 2.74 ng/ml), miR-455水平显著降低(0.67 ± 0.08 vs 1.05 ± 0.19),差异均有统计学意义($t=14.977, 15.780$, 均 $P < 0.05$)。

2.2 不同分期EMT患者血清miR-455, FABP4表达水平比较 随着EMT分期的升高,EMT I~IV期患者血清FABP4表达水平显著升高(12.65 ± 3.74 ng/ml, 16.43 ± 4.54 ng/ml, 20.65 ± 4.04 ng/ml, 24.83 ± 4.21 ng/ml),血清miR-455表达水平显著降低($0.87 \pm 0.08, 0.72 \pm 0.06, 0.59 \pm 0.06, 0.41 \pm 0.04$),差异均有统计学意义($F=31.108, 160.947$, 均 $P < 0.05$)。

2.3 EMT患者血清miR-455与FABP4相关性 见图1。相关性分析显示,EMT患者血清miR-455表达水平与FABP4呈负相关($r=-0.482, P<0.05$)。

2.4 血清miR-455, FABP4对EMT的诊断价值 见

图2和表1。血清miR-455诊断EMT的曲线下面积为0.879,截断值为0.79,敏感度和特异度分别为83.56%,78.67%。血清FABP4诊断EMT的曲线下面积为0.882,截断值为12.51 ng/ml,敏感度

和特异度分别为86.42%,79.23%。血清miR-455和FABP4联合诊断EMT的曲线下面积为0.922,敏感度和特异度分别为87.67%,81.33%。

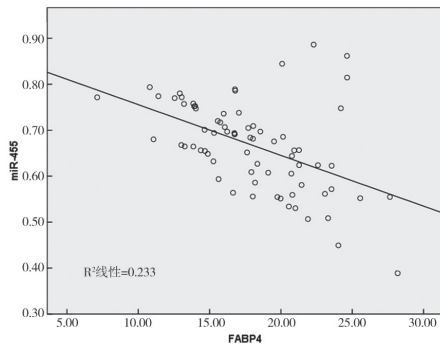


图1 EMT患者血清miR-455与FABP4的相关性分析散点图

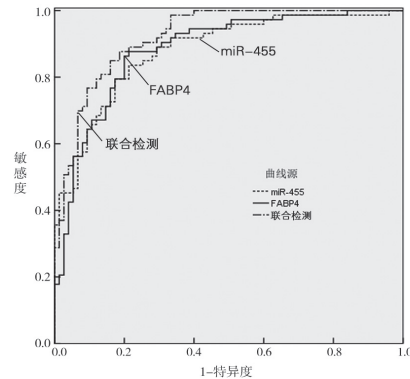


图2 ROC曲线分析血清miR-455, FABP4对EMT的诊断价值

表1

联合检测 Logistic 分析

指标	B	SE	Wald	df	sig	OR
miR-455	0.425	0.100	18.049	1	0.000	1.529
FABP4	0.625	0.064	17.253	1	0.000	1.303
常量	-8.880	1.393	40.644	1	0.000	0.000

3 讨论

子宫内膜异位症(EMT)的发病率呈逐年升高趋势,70%~80%的患者有不同程度的盆腔疼痛,严重影响妇女身心健康,目前腹腔镜检查是诊断EMT的金标准,但其具有有创性,因此寻找有效标志物对EMT的诊断具有重要意义^[9]。

miRNA在多种疾病的病理生理过程中发挥重要作用,可通过调控靶基因表达,调控细胞增殖侵袭而参与EMT的发生发展^[10]。多项报道显示,miRNA在EMT患者血清中异常表达,刘玉瑰等^[11]研究表明,EMT患者血清miR-1304-3p水平升高,miR-17-5p水平降低,且与患者病情严重程度和不孕症有关。赵喜艳等^[12]研究表明,EMT患者血清miR-494-5p与miR-1304-3p表达水平升高,且随病情进展而逐渐增加,对EMT的病情进展评估具有一定意义。miR-455为miRNA的一种,与慢性乙型肝炎、肺炎、肿瘤等多种疾病有关^[13-14]。本研究结果显示,miR-455在EMT患者血清中表达水平显著低于健康人群,提示miR-455可能与EMT的发生有关;另外III~IV期EMT患者血清miR-455表达水平显著低于I~II期患者,提示miR-455与EMT的病情严重程度有关。研究显示^[15],miR-455可以通过激活Nrf2信号通路保护成骨细胞免受氧化应激,EMT的发生机制涉及氧化应激病

例过程,本研究推测EMT患者血清miR-455水平异常表达,可能与子宫内膜的氧化应激有关。

FABP4是脂肪因子,调控脂类生成及降解、参与细胞内脂肪酸的转运和代谢,FABP4还可调控肿瘤细胞脂肪酸代谢,参与调控肿瘤细胞的增殖与迁移^[16]。研究表明^[17],FABP4与胚胎植入有关,抑制子宫内膜上皮细胞中FABP4可消除雌激素和孕激素联合诱导的子宫受体的表达,并减少黏附在子宫内膜细胞上的滋养细胞球体的数量。miR-455可通过调节FABP4来保护人类子宫内膜基质细胞免受氧化应激损伤^[18]。本研究结果显示,与对照组比较,FABP4在EMT组患者血清中水平升高,提示FABP4可能促进细胞增殖,与EMT发生发展过程有关。

目前EMT的病因及发病机制尚不完全清楚,多项报道显示,异位内膜细胞的黏附、侵袭、氧化应激、血管生成是主要病理生理过程^[19]。虽然EMT为良性疾病,但也具有侵袭性、易转移和复发等与肿瘤类似的生物学特性,EMT还与卵巢癌发生、发展具有密切的关系^[20]。本研究推测miR-455,FABP4参与EMT的发展可能与miR-455,FABP4参与血管生成、细胞增殖与侵袭有关。本研究还发现,EMT患者血清miR-455表达水平与FABP4呈负相关,表明二者可能存在负向调控关

系。唐文波等^[21]研究表明, miR-455 可通过靶向调控 FABP4 而保护过氧化氢诱导的人子宫内膜间质细胞氧化应激损伤。本研究推测 miR-455 可能通过靶向调控 FABP4 的表达参与 EMT 的发生与发展。进一步分析发现, 血清 miR-455, FABP4 联合诊断 EMT 的曲线下面积为 0.922, 敏感度和特异度分别为 87.67%, 81.33%, 提示 miR-455 和 FABP4 联合检测对于早期诊断 EMT 具有一定价值, 有一定临床应用意义^[22]。

综上所述, 血清 miR-455, FABP4 在 EMT 患者中分别呈低、高表达, 均与患者病情相关, 可能作为 EMT 早期诊断的分子标志物。但由于本研究临床样本数据少, 结果可能存在一定偏倚, 后续仍需扩大样本量做进一步研究。

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