

# 子宫内膜异位症相关卵巢癌的临床特点及 miRNA 表达的研究进展

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基金项目: 国家自然科学基金青年基金(项目编号: 81701444); 中华医学会临床医学科研专项资金课题(项目编号: 17020380707)

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【关键词】 子宫内膜异位症相关卵巢癌; 临床特点; miRNA

【中图分类号】R 711.71, R 737.31

【文献标志码】A

【文章编号】1674-4020(2021)06-014-05

doi:10.3969/j.issn.1674-4020.2021.06.04

子宫内膜异位症(以下简称内异症)在生育年龄妇女中的发病率为5%~10%, 它的特点为子宫内膜组织生长在子宫腔以外的部位, 主要包括盆腔腹膜、卵巢、直肠阴道隔等。患者可出现盆腔疼痛、不规则阴道出血、不孕等症状<sup>[1]</sup>, 其中疼痛和不孕的发生率高达30%~50%<sup>[2]</sup>, 腹腔镜手术及组织病理学检查是诊断内异症的金标准。内异症虽然是良性疾病, 但有0.5%~1%的概率发展为卵巢癌<sup>[3]</sup>。国外学者将伴随内异症发生的卵巢癌命名为子宫内膜异位症相关卵巢癌(endometriosis associated ovarian cancer, EAOC), 主要病理类型为卵巢透明细胞癌和子宫内膜样癌<sup>[4]</sup>。目前没有较好的预测指标对内异症癌变的风险进行评估。微小RNA(microRNA, miRNA)是一类由内源基因编码的长度约22个核苷酸的非编码RNA序列, 根据其高度相似的同源序列分为不同的miRNA家族, 其在真核基因表达调控中起广泛作用, 可以调控基因的表达和生物功能<sup>[5]</sup>, 与肿瘤的增殖、转移等密切相关, 研究证实miRNA的异常表达在卵巢癌的发生中扮演重要作用<sup>[6]</sup>。现对EAOC的临床特点及miRNA的表达进行综述。

## 1 子宫内膜异位症相关卵巢癌的临床特点

### 1.1 子宫内膜异位症相关卵巢癌的流行病学特点及发病机制

EAOC有两个主要特点: ①内异症与卵巢癌共存并具有相同的危险因素: 例如不孕症和晚绝经是两者发病

的危险因素, 而子宫切除术、口服避孕药及输卵管切除术为两者发病的保护因素<sup>[7]</sup>; ②子宫内膜异位细胞可以逐渐转化为癌细胞<sup>[8]</sup>。目前许多流行病学研究显示内异症和卵巢癌之间有相关性, 1项针对28个研究的荟萃分析显示, 经手术或组织学证实的内异症患者中, 上皮性卵巢癌的标准发病率(standardized incidence ratio, SIR)为1.43-8.95, 比值比(odds ratio, OR)为1.34, 而上皮性卵巢癌患者中同时合并内异症的概率为3.4%~52.6%<sup>[9]</sup>。Lee等<sup>[10]</sup>研究发现内异症患者发生卵巢癌的风险比(hazard ratio, HR)为2.59-24.04。Pearce等<sup>[11]</sup>对关于卵巢癌的13个病例对照研究进行了荟萃分析, 其中包含了13226例内异症患者, 7911例卵巢癌患者, 显示EAOC主要包括透明细胞癌(OR 3.05)、低级别浆液性癌(OR 2.11)、子宫内膜样癌(OR 2.04), 而内异症与黏液性癌和高级别浆液性癌无明显相关性。丹麦1项纳入了45790例内异症患者的研究显示, EAOC的SIR为1.34, 其中, 子宫内膜样癌和透明细胞癌的SIR为1.64和3.64<sup>[12]</sup>。许多研究发现以手术病理为诊断金标准时, EAOC的主要病理类型为子宫内膜样癌和透明细胞癌<sup>[13]</sup>。另一些研究也显示, 患内异症的女性, 不仅卵巢癌的发病风险增加, 乳腺癌、直肠癌、子宫内膜癌、非霍奇金淋巴瘤及脑肿瘤的风险也有所增加<sup>[12,14]</sup>。EAOC的发生机制不完全明确, 可能与内异症的独特肿瘤微环境有关, 它由上皮细胞、基质细胞和免疫细胞组成, 这些细胞能在低氧条件下存活有赖于内异症微环境中高水

平铁、雌激素、炎性细胞因子和趋化因子的影响,氧化剂和内源性抗氧化剂的失衡也在内异症癌变中发挥一定作用<sup>[15]</sup>。另外,不仅在透明细胞和子宫内膜样卵巢肿瘤中发现了抑癌基因如磷脂酰肌醇-3-激酶催化亚单位  $\alpha$  (phosphatidylinositol 3-kinase catalytic  $\alpha$ , PIK3CA)、磷酸酶与张力蛋白同源因子 (phosphatase and tensin homolog, PTEN)、钙黏蛋白相关蛋白 (catenin protein beta 1, CTNNB1)、丰富的互动结构蛋白 1A (at-rich interaction domain-containing protein 1A, ARID1A)、p53 等的频繁突变,在并发子宫内膜异位和非典型子宫内膜异位病变中也发现了这种突变,提示这些抑癌基因的功能丧失是内异症向 EAOC 转化的早期步骤<sup>[8]</sup>。

### 1.2 子宫内膜异位症相关卵巢癌的风险因素及预测指标

年龄增加是 EAOC 的主要风险因素,研究显示:年龄  $\geq 50$  岁的内异症患者患卵巢上皮性癌的风险明显增加,校正后的 HR 为 9.63,而  $< 30$  岁的内异症患者,校正后的 HR 为 4.97<sup>[14]</sup>。另 1 项病例对照研究包含 42 例 EAOC 和 96 例卵巢子宫内膜异位囊肿的患者,发现年龄是内异症恶性转化的重要预测指标,患者年龄增加 5 岁后患 EAOC 的 OR 为 2.17,年龄  $> 49$  岁以后内异症恶性转化的风险明显增高<sup>[16]</sup>。Murakami 等<sup>[17]</sup> 的荟萃分析主要研究卵巢子宫内膜异位囊肿进展为卵巢癌的时间,发现从诊断卵巢子宫内膜异位囊肿进展为癌的中位时间为 36 个月,约 75% 的患者为 60 个月,25% 的患者为 120 个月。内异症患者多有不孕症,关于不孕和上皮性卵巢癌的相关性也有研究,澳大利亚 1 项含 21 646 例不孕症患者的研究中,内异症引起的不孕症患者患卵巢上皮性癌的风险增加了 3 倍,但进行促排卵治疗并未增加卵巢癌的发生风险<sup>[18]</sup>。目前无特异性的预测方法能早期识别 EAOC,超声检查是临床常用鉴别卵巢良恶性肿瘤的方法,AliFehmi 等<sup>[19]</sup> 对 73 例内异症相关卵巢透明细胞癌或混合性子宫内膜样-透明细胞瘤的患者进行了研究,发现多数肿瘤为单侧受累,超声提示为囊性回声,较少合并腹水。对比良性卵巢子宫内膜异位囊肿,EAOC 肿瘤直径更大 (14 cm vs 7.5 cm),多为多房 (45.7% vs 12.2%),多含实性成分 (77.1% vs 14.5%),影像学上的实性成分显示为恶性肿瘤的独立 OR 为 23.7<sup>[16]</sup>。血清 CA 125 水平对预测 EAOC 无明显特异性,Kadan<sup>[16]</sup> 报道和良性卵巢子宫内膜异位囊肿相比,EAOC 患者 CA 125 有所升高,但并不明显 (中位值为 204.9 U/mL vs 66.9 U/mL,  $P = 0.1$ )。Wang<sup>[13]</sup> 关于 EAOC 的报道也显示 CA 125 水平与疾病的恶性转化并无明显相关性。另 1 项研究也发现,EAOC 对比非 EAOC,CA 125 中位值为 122.9 U/mL vs 377.5 U/mL<sup>[20]</sup>。Emanuela 等<sup>[21]</sup> 对肿瘤标志物 CA 72-4 的研究显示,EAOC 组 CA 72-4 升高占 71%,而卵巢子宫内膜异位囊肿组升高占 13.8%,因此,CA 72-4 可能是鉴别 EAOC 更敏感的指标。将 CA 125 做为早期识别 EAOC 的敏感性较差,但人附睾蛋

白-4 (human epididymal protein 4, HE 4) 及 CA 72-4 在鉴别 EAOC 中有更高的特异性,优于 CA 125<sup>[22]</sup>。

总之,合并不孕症、年龄较大、患内异症时间较长的患者进展为卵巢癌的可能性更大;而对于单侧肿瘤、体积较大、多房、伴有实性成分、生长速度较快、相关肿瘤标志物升高的患者,应警惕恶性变的可能。

### 1.3 子宫内膜异位症相关卵巢癌的生存结局

多个研究发现和卵巢上皮性癌相比,EAOC 患者更年轻、多数诊断年龄为绝经前、多为低级别病变或交界性肿瘤,尽管也可能合并子宫内膜癌,但总体预后更好,生存期更长<sup>[23-24]</sup>。Dinkelspiel 等<sup>[25]</sup> 研究了 139 例卵巢上皮性癌患者,其中合并内异症 49 例,未合并内异症 90 例,显示和非 EAOC 相比,EAOC 患者更年轻,病灶更多局限在盆腔 (54% vs 9%),更多为低级别病变 (51% vs 29%)。另 1 项荟萃分析包含了 20 个病例对照研究和 15 个队列研究,共包含 444 255 例患者,EAOC 和非 EAOC 两组患者的无进展生存期无明显差异 (HR, 1.023),但总生存期 EAOC 组略优 (HR, 0.778)<sup>[26]</sup>。Li 等<sup>[24]</sup> 对比了 34 例 EAOC 患者及 94 例非 EAOC 患者,两组患者的中位诊断年龄为 48.65 岁 vs 54.39 岁,EAOC 组不孕症发生率更高 (26.47% vs 10.64%),多为早期病变 (I-II 期: 91.18% vs 73.40%),总生存期更长 (109.8 月 vs 47.4 月)。在 1 项 EAOC 不同病理类型的研究中,46% 为卵巢透明细胞癌,54% 为卵巢子宫内膜样癌,其中 80% 的患者经组织病理学证实合并内异症,42% 的患者未生育,42% 的患者发病年龄在绝经前期。早期卵巢透明细胞癌、子宫内膜样癌及进展期子宫内膜样癌有较好的预后,而进展期卵巢透明细胞癌更容易复发,总生存期更短<sup>[27]</sup>。EAOC 通常和子宫内膜癌也有一定相关性,研究显示,在内异症相关卵巢子宫内膜样癌患者中,同时发生子宫内膜癌的概率较高,但在卵巢透明细胞癌中并未发现有明显相关性<sup>[24]</sup>。

## 2 子宫内膜异位症相关卵巢癌患者 miRNA 的表达

内异症进展为卵巢癌没有一个相对比较敏感和特异的预测指标<sup>[28]</sup>。近年来,学者们致力于寻找更有意义的生物标记。miRNA 的发现为肿瘤的研究带来了更多启示,做为生命活动的重要调控分子,miRNA 参与癌细胞增殖、自主生长信号的产生、迁移、凋亡和新生血管的调节。不同于 mRNA 容易被降解,miRNA 非常稳定,在循环系统中能快速并容易被识别,因此,可以检测血液和组织中的 miRNA 用于癌症的诊断及预后判断<sup>[29]</sup>。最近研究显示,miRNA 表达水平在 EAOC 中扮演重要角色,多种 miRNA 调控失常 (上调或下调) 参与了内异症的形成、生存和对周围组织的侵袭过程<sup>[6]</sup>。Wu 等<sup>[30]</sup> 对 EAOC 患者的 miRNA 表达进行了分析,与良性内异症相比,卵巢癌患者的 miR-1, miR-133a 和 miR-451 的表达明显降低,而 miR-141, miR-200a, miR-200c 和 miR-3613 的

表达均有显著升高 ( $P < 0.05$ )。多个研究证实 miRNA 通过影响不同的基因参与内异症恶性转变, Eggers 等<sup>[31]</sup>观察到内异症进展为卵巢癌的过程中 miR-200b 表达下调, 其通过增强上皮间充质细胞的转化 (epithelial-to-mesenchymal transition, EMT) 来驱动肿瘤细胞进入侵袭状态, 而上调 miR-200b 的表达可逆转 EMT, 成为抑制子宫内膜异位细胞侵袭性的潜在治疗方法。miR-183 通过调控  $\beta 1$  整合素 ( $\beta 1$  integrin, ITGB1) 参与内异症的癌变过程<sup>[32]</sup>, miR-210 通过激活活化转录因子 3 (signal transducer and activator of transcription 3, STAT3) 来诱导内异症细胞增殖、促进血管内皮细胞生长因子产生、抑制细胞凋亡, 从而促进子宫内膜异位细胞的恶性转化<sup>[33]</sup>。miR-2861 通过靶向 STAT3 和基质金属蛋白酶-2 (matrix metalloproteinase-2, MMP2) 来调节子宫内膜异位细胞的增殖和凋亡<sup>[34]</sup>。在内异症癌变过程中也发现 miR-195、miR-196b 表达下调, miR-195 通过调控不规则趋化因子 (fractalkine, FKN)、miR-196b 通过调控人髓细胞增生原癌基因 (myelocytomatosis oncogene, c-Myc) 和 Bcl-2 相关永生基因 3 (Bcl-2-associated athanogene, BAG3) 表达来抑制细胞增殖及诱导细胞凋亡<sup>[35-36]</sup>。miR-181c、miR-141-3p 也参与到调控子宫内膜异位细胞逃避凋亡的过程中<sup>[37-38]</sup>。研究也发现卵巢子宫内膜囊肿内出血可增加氧化应激水平, 使多种 miRNA 表达失调, 促进 EAO 的发展<sup>[39]</sup>。在鉴别良性内异症、EAO 和卵巢高级别浆液性乳头状癌方面, 学者们也进行了很多研究, 在内异症患者的腹腔冲洗液中发现 miR-106b-3p、miR-451a、miR-486-5p 表达上调<sup>[40]</sup>, 在 EAO 患者中 miR-15b、miR-16、miR-21、miR-195 表达上调<sup>[41]</sup>, 而卵巢高级别浆液性乳头状癌患者的血清中 miR-1290 表达明显升高, 可作为鉴别其他卵巢癌类别的生物标记物之一<sup>[42]</sup>。也有研究显示卵巢高级别浆液性乳头状癌患者血清 miR-375 表达下调同时伴有 CA 125 水平明显升高<sup>[43]</sup>。另 1 项研究选择 23 种不同的 miRNA 来鉴别健康人群、内异症和 EAO 患者, 发现有 4 种 miRNA (miR-15b、miR-16、miR-21 和 miR-195) 在 EAO 患者中与健康人群表达有明显差异, 同时在 EAO 的临床小鼠模型中得到了相同的验证。另外关于 EAO 亚型的鉴别, 发现 miR (9、96、182、183、196a、196b、205、375) 等在子宫内膜样癌组织中上调, 而 miR-30a、miR-486-5p 在卵巢透明细胞癌组织中上调<sup>[44]</sup>。和卵巢高级别浆液性乳头状囊腺癌不同, EAO 是以 ARID1A、PTEN、PIK3CA 等基因突变为特点, miRNA 表达失衡可能是促进这些重要的抑癌基因失去功能的原因<sup>[45]</sup>。紫杉醇和铂类联合化疗是 EAO 患者的一线化疗方案, 化疗药物耐药是部分患者预后差的原因, 研究发现 miRNA 的异常表达与化疗耐药有一定关系, 可能将其做为化疗耐药的靶点, Sugio 等<sup>[46]</sup>发现 EAO 患者中 miR-29b 水平升高与无进展生存期相关, BAG3 的下调可能诱导了 miR-29b 表达,

使癌细胞对紫杉醇更敏感, 另外也有研究通过细胞转染 miRNA 来调控各种癌症相关基因或因子的表达, 从而抑制内异症的癌变过程, 可能做为未来治疗 EAO 的一个方向。总之, miRNA 的表达在 EAO 的早期诊断、治疗、预后等各个方面均开展了多项研究, 为我们更深入了解 EAO 提供了帮助<sup>[47]</sup>。

综上所述, 目前已有许多研究证实内异症有较高风险发展为卵巢癌, 内异症多发生在年轻女性, 为其恶性转化提供了一个很长的窗口期, 在临床工作中, 我们应该对 EAO 的相关临床特点做到充分了解, 识别可能出现的早期癌变, 做到早期干预。目前 EAO 的发病机制仍不明确, miRNA 的表达失调可能扮演一个重要角色, 进一步开展 miRNA 方面的研究可能为 EAO 的早期诊断及治疗提供更多的思路。

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(收稿日期:2020-08-04 编辑:向晓莉)

(上接第6页)

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(收稿日期:2021-05-07 编辑:向晓莉)