·综述·

# 外泌体在妇科恶性肿瘤中的作用及临床应用进展

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**摘　要：**外泌体是具有脂质双层膜结构的小囊泡，因其非侵入性、高可及性和稳定性应用于精准医学中，在肿瘤的转移、侵袭和血管生成等过程中发挥重要作用。妇科恶性肿瘤主要包括宫颈癌、卵巢癌和子宫内膜癌，其早期诊断和治疗一直是研究的热点和难点。外泌体作为新型的生物学标志物，具有高度特异性，能够有效阻断妇科恶性肿瘤的发生和发展。本文详细探讨了外泌体在宫颈癌、卵巢癌和子宫内膜癌中的诊断和治疗应用。在宫颈癌中，外泌体参与HPV感染、血管生成和免疫逃逸等过程，其携带的特定miRNA（如miR-30d-5p、let-7d-3p）可作为诊断标志物。此外，外泌体还可作为靶向药物递送载体和疫苗研发平台。在卵巢癌中，外泌体携带的miRNA（如miR-21、miR-200家族）对早期诊断具有参考价值，且外泌体在化疗耐药和肿瘤进展中扮演重要角色。对于子宫内膜癌，外泌体中的miRNA（如miR-15a-5p、miR-106b-5p）可作为早期检测的生物标志物。此外，本文还指出了外泌体在临床应用中面临的挑战，如分离提取的复杂性和细胞来源的识别等，并强调了进一步的基础研究和临床试验的必要性。本文为妇科恶性肿瘤的早期诊断和精准治疗提供了新的思路和方法，具有重要的理论和临床意义。

**关键词：**外泌体；妇科恶性肿瘤；宫颈癌；卵巢癌；子宫内膜癌；临床应用
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# The Role and Clinical Application Progress of Exosomes in Gynecological Malignancies

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**Abstract：**Exosomes are small vesicles with a lipid bilayer membrane structure that have applied in precision medicine due to their non-invasive nature，high accessibility，and stability. Exosomes play a crucial role in processes such as tumor metastasis，invasion，and angiogenesis. Gynecological malignancies primarily include cervical cancer，ovarian cancer，and endometrial cancer，and their early diagnosis and treatment have long been a focus of research. As novel biological markers，exosomes exhibit high specificity and can effectively block the occurrence and progression of gynecological malignancies. This article explores the diagnostic and therapeutic applications of exosomes in cervical cancer，ovarian cancer，and endometrial cancer in detail. In cervical cancer，exosomes are involved in processes such as HPV infection，angiogenesis，and immune evasion，with specific miRNAs（such as miR-30d-5p and let-7d-3p）serving as diagnostic markers. Furthermore，exosomes can act as targeted drug delivery vehicles and vaccine development platforms. In ovarian cancer，the miRNAs carried by exosomes（such as miR-21 and the miR-200 family）have reference value for early diagnosis，and exosomes play an important role in chemotherapy resistance and tumor progression. For endometrial cancer，miRNAs in exosomes（such as miR-15a-5p and miR-106b-5p）can serve as biomarkers for early

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detection. Additionally, this article highlights the challenges faced by exosomes in clinical applications, such as the complexity of isolation and extraction and the identification of cell sources, and emphasizes the necessity for further basic research and clinical trials. This study provides new ideas and methods for the early diagnosis and precision treatment of gynecological malignancies, holding significant theoretical and clinical importance.

**Key words:** exosomes; gynecological malignancies; cervical cancer; ovarian cancer; endometrial cancer; clinical application

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妇科恶性肿瘤是女性中较为常见的疾病之一，预防对限制其发病率和死亡率至关重要。但目前并非所有恶性肿瘤都有有效的筛查方法，因此医学界正开发新的生物标志物和方法来进行及时有效的早期诊断及治疗。最常见的妇科恶性肿瘤包括宫颈癌、卵巢癌和子宫内膜癌。2022年全球癌症统计数据，宫颈癌发病率排名第8位，全球有661 021例新发病例，死亡率排名第9位，有348 189例死亡病例；卵巢癌发病率排名第18位，全球有324 398例新发病例，死亡率排名第14位，有206 839例死亡病例；子宫内膜癌发病率排名第15位，全球有420 242例新发病例，死亡率排名第19位，有97 704例死亡病例[1]。预防妇科恶性肿瘤是降低女性生殖系统患癌症风险的根本途径[2]。新型生物学标志物的发现可以有效预防癌症的发生。外泌体标志物在恶性肿瘤中明显升高，具有高度特异性，因此外泌体的研究有助于癌症的早期发现与预防[3]。

## 1　外泌体概述

外泌体最早由Bonucci和Anderson在1960年代后期首次报道，随后发现它们存在于绵羊网织红细胞中[4]。外泌体是由多种细胞类型产生的细胞外囊泡，包括免疫细胞（巨噬细胞、NK细胞、树突状细胞、T细胞、B细胞）、干细胞和癌细胞，其结构与细胞相似，呈凹面半球形，直径范围为30~150 nm[5]。发现初期，它们的作用被忽视，随着分子生物学的发展，现发现外泌体具有高含量细胞骨架蛋白、MHCI类和Ⅱ类蛋白、黏附蛋白（如四聚体、整合素）以及包封的核酸，携带DNA、RNA、蛋白质等重要物质，充当细胞间通讯调节因子[6]，促进细胞间的物质交换及信息传递。细胞的来源决定了它们的功能和组成成分[7]，因此，明确外泌体的细胞来源是近年来的研究热点及难点。目前，国内外的研究均表明，外泌体在肿瘤领域扮演着至关重要的角色，它们不仅参与肿瘤的形成，还在其发展的多个关键阶段发挥着重要作用[8]。

## 2　外泌体与宫颈癌

宫颈癌是严重威胁女性健康疾病之一[9]，是女性常见的生殖系统疾病，其发病率远超于卵巢癌、子宫内膜癌。最新数据显示，宫颈癌在全球女性癌症中发病率与死亡率均排名第四位[10]，在中国，新发病例和死亡病例为15.1万例和5.6万例，标化发病率和标化死亡率世界排名分别位于第95和126位。据估计，2020年有100万儿童成为孤儿，因他们的母亲均死于癌症，其中有近一半孤儿是因母亲死于宫颈癌的结果。近几年来，宫颈癌逐渐呈现出年轻化趋势，虽然总体发病率逐渐减少[11-12]，存活率仍然很低，在癌症中仍位居前列。据估计，到2030年，全球宫颈癌病例数量将增加约50%[13]。因此宫颈癌的早期诊断显得格外重要。

### 2.1　外泌体在宫颈癌诊断中的作用与应用

宫颈癌是病毒感染性疾病，主要以人乳头瘤病毒（human papillomavirus，HPV）持续感染为主，临床主要的检测方法也是主要针对HPV为主，前期筛查主要是高危型HPV和/或新柏氏液基细胞学检测，因经济、地域、文化水平等影响因素[14]，筛检率较低且无性生活者不建议检测，筛检阳性者需进一步行阴道镜检查，必要者取宫颈活检组织，进行病理学检查，患者体验感差，且易感染及出血，不免造成心理阴影。液体活检是一种无创、准确性高和易操作方式，具有明显的独特性，可以追踪癌症的进展，具有症状出现前检测出癌症的优势[15]。外泌体是液体活检的关键对象之一。Peng等[16]研究发现，外泌体参与宫颈癌的HPV感染、血管生成、免疫逃

逸及癌细胞的增殖、侵袭过程[17-21]。此外,外泌体在宫颈癌的治疗领域展现出巨大的应用前景,如靶向药物的输运、疫苗的研发以及液体活检生物标志物等[22]。因外泌体自身结构的独特性,可成为靶向药物递送的理想载体[23]。Liang[24]等发现载有紫杉醇(paclitaxel, PTX)的AS1411-chol外泌体(通过化学修饰的生物纳米载体)可以被有效地递送至靶癌细胞,为癌症治疗提供有前途的递送平台。Hao等[25-26]研究团队在DC疫苗(sipuleucel-T)的研发方面,进一步用外泌体为载体负载HPV16E7蛋白作为宫颈癌疫苗的研发。Zheng等[27]对121份血浆样本(23例对照样本、5例CINⅠ、59例CINⅡ-Ⅲ、21例宫颈鳞状细胞癌和13例腺癌)进行了外泌体miRNA的研究,通过测序、qRT-PCR、ddPCR等方法,得出结论,外泌体miRNA-30d-5p和let-7d-3p是宫颈癌有价值的诊断生物标志物。目前大多数外泌体是从细胞培养上清液和复杂的生物体液(如血浆)中分离出来的,因此,外泌体的产量和纯度是有限的。当使用外泌体作为免疫疗法或其他方法时,必须实现大规模稳定的制备方法[28-30]。外泌体在如何进一步提升其靶向性、提高药物载装效率以及控制药物释放都是亟须解决的技术瓶颈。目前尚缺乏大规模临床试验的数据支持其安全性和疗效。尽管一些研究报道了外泌体大规模生产和生物相容性改进的方案,但还需要进一步的临床前和临床研究进行验证。

### 2.2 外泌体在宫颈癌靶向治疗中的作用

外泌体miRNA在宫颈癌的靶向治疗方面也表现出独有的优势性,因自身具有独特的结构及稳定性[31-34]。Zhu等[35]研究癌症来源的外泌体miR-651抑制了顺铂耐药性并直接靶向自噬相关基因3(autophagy-related 3, ATG3),验证外泌体miR-651可能是一种治疗剂,用于寻找预测化疗敏感性的特定治疗靶点。Konishi等[36]证实外泌体miR-22可能成为宫颈癌放射治疗的一种有前途的药物递送系统。

还有研究发现在早期进展的宫颈癌患者中,miRNA-1228-5p、miRNA-33a-5p、miRNA-3200-3p和miRNA-6815-5p水平降低,miRNA-146a-3p水平升高,而在中晚期miRNA-605-5p、miRNA-6791-5p、miRNA-6780a-5p和miRNA-6826-5p水平升高和miRNA-16-1-3p(或15a-3p)水平降低,因此可以作为宫颈癌预后的检测指标[37]。外泌体在宫颈癌诊断及治疗中的作用和临床应用详见表1[38-49]。

## 3 外泌体与卵巢癌

卵巢癌在全球女性癌症中发病率与死亡率均排名第8位,是妇科恶性肿瘤相关的死亡的主要原因[50]。任何年龄段均可发病,大多数隐匿性发作,通常诊断出来即是晚期,恶性程度极高,并且与预后不良有关[51]。尽管卵巢癌的诊治方法日趋成熟,70%的患者在确诊时已属于晚期,5年生存率不足50%[52]。卵巢癌作为一种常见的妇科肿瘤,有许多不同的组织类型。其中90%为上皮细胞型,其余为非上皮性卵巢癌。还有一些罕见的病理类型,如小细胞癌和癌肉瘤。不同组织类型的卵巢癌具有不同的分子变化、临床行为和治疗效果[53-54]。

### 3.1 外泌体在卵巢癌诊断中的作用与应用

因卵巢恶性肿瘤自身独特性,发病年龄广、病情隐匿、盆腹腔位置深,造成了极高的死亡率,预后极差[55]。现临床上关于卵巢癌的诊断方法,主要是影像学检查和肿瘤标志物检测(如AFP、CEA、CA199、CA125、HE4),特异性低,不灵敏[56],因此急需新型标志物的出现。外泌体结构稳定,广泛存在于血液、腹水、脑脊液等体液中,可成为卵巢癌未来诊断、治疗和预后的生物标志物之一[57]。Ho等[58]研究发现,Ⅵ型胶原α3(collagen type Ⅵ alpha 3, COL6A3)在促进肿瘤进展和转移中至关重要,可作为一种有价值的生物标志物,用于化疗耐药、转移、复发的早期诊断,以及通过检查上皮性卵巢癌(epithelial ovarian cancer, EOC)患者血液、腹水或组织中COL6A3外泌体来预测生存结局,探索可能相关的信号介导,在未来有望为EOC患者开发治疗靶向COL6的偶联抗体或疫苗。卵巢癌细胞衍生的外泌体被证明对卵巢癌的早期诊断有很高的参考价值,研究证实,miRNA-21、miRNA-141、miRNA-200a、miRNA-200b、miRNA-200c、miRNA-203在卵巢癌外泌体中明显升高[59]。

### 3.2 外泌体在卵巢癌治疗中的作用与应用

卵巢癌的治疗也是难点,早期主要以手术为主,晚期主要是肿瘤细胞减灭术和联合化疗,以及近年来靶向和免疫治疗,大部分患者经过规范化治疗可获得缓解,但卵巢癌复发率较高,70%患者在2~3年内存在复发情况。因此探索新的治疗方法是近年来卵巢癌研究的热点和难点[60]。Cao等[61]发现miR-30a-5p过表达可显著增强HO8910和

表1　外泌体在宫颈癌诊断及治疗中的作用及临床应用

Table 1　The role and clinical application of exosomes in the diagnosis and treatment of cervical cancer

| Content | Molecules | Function | Targets | Expression level | Clinical value | References |
|---|---|---|---|---|---|---|
| cricRNA | CircSLC26A4 | cancer-causing gene | / | upregulated | Biomarker | [38] |
| miRNA | miR-30d-5p | inhibit cervical cancer cells | / | upregulated | diagnosis/treatment | [39] |
| miRNA | miR-30a-5p | tumor suppressor | / | upregulated | treatment | [40] |
| miRNA | miRNA-10a-5p | tumor suppressor | UBE2I | upregulated | treatment | [41] |
| lncRNA | lncRNA TINCR | oncogene | miRNA-7/mTOR | knockdown | prognosis | [42] |
| microRNAs | miR-21 | tumor suppressor gene | RECK | upregulated | therapy | [43] |
| microRNAs | miR-379/miR-656 | tumor suppressor. | C14MC | downregulation | diagnostic and prognostic | [44] |
| miRNA | miR-195-5p | cancer suppressor gene | ATG9A | upregulated | targeted therapy | [45] |
| circRNA | circ_0039787 | oncogene | miR-877-5p/ KRAS | knockdown | biomarker/therapeutic target | [46] |
| lncRNAs | LINC00324 | oncogene | miR-195-5p | upregulated | prognostic molecular marker | [47] |
| miRNA | miR-34b-3p | tumor suppressor | STC2/ FN1 | upregulated | therapeutic | [48] |
| miRNA | miR-141 | oncogene | Ceacam/KLRC | upregulated | therapeutic target | [49] |

HO8910PM细胞的增殖、迁移和侵袭能力,而miR-30a-5p抑制则相反($P$均<0.05)。此外,miR-30a-5p可能通过上调ZEB2和LDH2参与这些致癌过程,miRNA-30a-5p促进了卵巢癌细胞的恶性行为,这可能作为OC患者的一种有前途的诊断和预后标志物。Wang等[62]研究发现circRAD23B通过吸附miR-1287-5p消除了其对Y-box结合蛋白1的抑制作用,促进卵巢癌的进展并诱导细胞卡铂耐药,结论circRAD23B在卵巢癌细胞的细胞质中稳定表达,在耐药组织中显著增加,并与不良预后相关。外泌体在卵巢癌诊断及治疗中的作用及临床应用详见表2[63-69]。

## 4　外泌体与子宫内膜癌

子宫内膜癌是雌激素密切相关的妇科肿瘤[70],在全球女性癌症中发病率排名第6位,虽然67%的患者表现为早期疾病,5年总生存率(overall survival, OS)为81%,但IVA期和IVB期EC的5年OS分别仅为17%和15%[71]。临床症状不典型,无特异性标志物。因此需要新型标志物的出现,提高早期诊断及治疗。

Zhou等[72]研究人员发现,通过候选miRNA液滴数字PCR(droplet digital PCR, ddPCR)在202份独立血浆样本中进一步验证,通过qRT-PCR在32对子宫内膜肿瘤和邻近正常组织中进行验证,并通过ddPCR对12例患者术前和术后匹配的血浆样本进行验证。与健康受试者相比,从子宫内膜癌患者血浆样本中分离的外显子组中miR-15a-5p、miR-106b-5p和miR107显著上调。特别是,单独的miR-15a-5p产生的AUC值为0.813,以区分Ⅰ期子宫内膜癌患者和健康受试者。miR-15a-5p与血清肿瘤标志物(CEA和CA125)的整合达到了更高的AUC值0.899。因此miR-15a-5p可作为子宫内膜癌早期检测的有前途的诊断生物标志物。miR-142-3p、miR-146a-5p和miR-151a-5p在子宫内膜癌患者血浆中显著过表达[73]。miR-143-3p、miR-195-5p、miR-20b-5p、miR-204-5p、miR-423-3p和

表2 外泌体在卵巢癌诊断及治疗中的作用及临床应用

Table 2 The role and clinical application of exosomes in the diagnosis and treatment of ovarian cancer

| Content | Molecules | Function | Targets | Expression level | Clinical value | References |
|---|---|---|---|---|---|---|
| lncRNA | SNHG17 | carcinogenesis | FOXA1/ miR-485-5p/ AKT1 | upregulated | biomarker and therapeutic target | [63] |
| circRNA | circTMCO3 | oncogene | miR-515-5p/ITGA8 | upregulated | therapeutic | [64] |
| Protein | USP43 | carcinogenic | HDAC2 | upregulated | prognosis | [65] |
| miRNA | miR-223 | tumor suppressor | / | upregulated | diagnostic | [66] |
| miRNA | miR-296-3p | tumor suppressor | PTEN/AKT/SOCS6/STAT3 | upregulated | biomarker and therapeutic target | [67] |
| lncRNA | LncRNA IL21-AS1 | oncogene | CD24 | upregulated | therapeutic | [68] |
| circRNAs | circDENND4C | tumor suppressor | miR-200b/c | downregulation | tumor marker | [69] |

miR-484在EC患者血清中显著过表达[74]。此外,来自子宫内膜癌患者尿液来源的外泌体显示miR-200c-3p显著升高[75]。miR-133a在子宫内膜癌细胞和源自子宫内膜癌细胞的外泌体中高度表达,可被正常子宫内膜细胞吸收[76]。外泌体在子宫内膜癌诊断及治疗中的作用及临床应用详见表3[77-82]。

表3 外泌体在子宫内膜癌诊断及治疗中的作用及临床应用

Table 3 The role and clinical application of exosomes in the diagnosis and treatment of endometrial cancer

| Content | Molecules | Function | Targets | Expression level | Clinical value | References |
|---|---|---|---|---|---|---|
| lncRNA | lncRNA DLEU1 | oncogenes | microRNA-E2F3 | upregulated | therapeutic target | [77] |
| miRNA | miR-26a-5p | oncogenes | / | downexpression | treatment | [78] |
| circRNA | hsa_circ_0001610 | / | miR-139-5p/ B1 | overexpression | target | [79] |
| lncRNA | lncRNA NEAT1 | regulators | miR-26a/b-5p-STAT3-YKL-40 | up-regulation | treating | [80] |
| lncRNA | LncRNA FIRRE | / | miR-199b-5p/SIRT1/BECN1 | up-regulation | treatment | [81] |
| lncRNA | LncRNA TRPM2-AS | / | miR-497-5p/SPP1 | upregulated | treatment. | [82] |

## 5 总结与展望

外泌体是一种新型的癌症生物标志物来源,因为它们:①从活的癌细胞中主动分泌;②包含有关肿瘤状况的信息;③可以很容易地从生物体液中提取;④提供易于从高丰度蛋白质中提取的信息;⑤非常稳定。重要的是,外泌体是由活跃增殖的肿瘤细胞分泌的,与凋亡细胞体不同[83]。外泌体携带细胞类型特异性RNA和蛋白质分子,它们还可以揭示很多关于肿瘤标志的信息。已确定外泌体包含许多不同的细胞表面受体和蛋白质(热休克蛋白、黏附分子、细胞骨架蛋白以及与融合和膜运动相关的蛋白质)。此外,外泌体含有miRNA分子,这可能会影响供体细胞和受体细胞之间的相互作用。但是,外泌体在实际临床操作中仍存在可能面临的挑战:外泌体的标准分离、提取耗时,对技术及

仪器设备条件要求较高，因外泌体来源于细胞，具体细胞来源难以识别，目前临床应用仍然处于探索阶段，只有少量外泌体基础的治疗方法进入临床试验，如本文2.1提到靶向药物的输运[84]、疫苗的研发[85]、液体活检生物标志物[86]等治疗方法进入临床试验阶段，如治疗妇科恶性肿瘤小分子或核酸药物，可以掺入外泌体中，然后递送到特定类型的细胞或组织中，实现靶向药物递送，在疫苗研发方面对外泌体进行工程化修饰，增加在肿瘤免疫治疗中的应用[87-88]。目前尚不完全清楚外泌体是如何促进癌症的发展和转移。因此关于外泌体在妇科恶性肿瘤中如何具体的影响肿瘤的分子机制，还需要我们大量基础研究及临床试验。

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