

细胞外囊泡外泌体在上皮性卵巢癌的应用

韩佳楠*, 杨晓玲

内蒙古妇幼保健院, 妇科, 内蒙古 呼和浩特

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摘要

在我国, 卵巢癌年发病率居女性生殖系统肿瘤第3位, 位于子宫颈癌和子宫体恶性肿瘤之后, 呈逐年上升的趋势, 而病死率位于女性生殖道恶性肿瘤之首, 是严重威胁女性健康的恶性肿瘤。已有研究表明, EVs 介导物质运输到近邻和远处细胞影响肿瘤发展的许多过程, 包括促进血管生成, 逃避免疫监视, 侵袭转移, 耐药等。外泌体已成为人类生物流体非侵入性液体活检中早期癌症诊断的新的候选者。本文将对细胞外囊泡外泌体在上皮性卵巢癌的诊断、治疗及预后方面的研究进展进行综述, 以期望在上皮性卵巢癌患者的诊疗中提供参考。

关键词

上皮性卵巢癌, 外泌体, 诊断, 治疗, 复发及预后

Application of Extracellular Vesicle Exosomes in Epithelial Ovarian Cancer

Jianan Han*, Xiaoling Yang

Department of Gynecology, Inner Mongolia Maternal and Child Health Care Hospital, Hohhot Inner Mongolia

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Abstract

In China, the annual incidence rate of ovarian cancer ranks third in female reproductive system tumors, after cervical cancer and uterine body malignancies, showing a rising trend year by year, while the mortality rate ranks first in female reproductive tract malignancies, which is a serious threat to women's health. Previous studies have shown that EVs mediate the transport of substances to neighboring and distant cells, affecting many processes of tumor development, including promoting angiogenesis, evading immune surveillance, invasion and metastasis, drug resistance, etc.

*通讯作者。

Extracellular vesicles have emerged as a new candidate for early cancer diagnosis in non-invasive liquid biopsy of human biological fluids. This article will review the research progress of extracellular vesicle exosomes in the diagnosis, treatment, and prognosis of epithelial ovarian cancer, in order to provide reference for the diagnosis and treatment of epithelial ovarian cancer patients.

Keywords

Epithelial Ovarian Cancer, Exosomes, Diagnosis, Treatment, Recurrence and Prognosis

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1. 上皮性卵巢癌

据 2020 年统计, 中国每年新发病例约 5.5 万例, 且逐年增加, 死亡病例约 3.8 万例。卵巢恶性肿瘤包括多种病理类型, 其中最常见的是上皮性癌(EOC), 约占卵巢恶性肿瘤的 80 [1], 其次是恶性生殖细胞肿瘤和性索间质肿瘤, 各约占 10%和 5% [2]。上皮性卵巢癌早期患者预后良好(FIGO I、II 期患者 5 年生存率分别为 81.3%、66.9%, FIGO III、IV 期患者 5 年生存率分别仅为 41.3%、31.3%) [3]。卵巢癌发病隐匿, 被明确诊断的患者 70%~90%为 III 或 IV 期。上皮性卵巢癌(EOC)的高死亡率可以归因于大多数患者发现时就被诊断为晚期[4]。因此, 在早期、局部和可治愈的阶段识别 EOC 的方法可以显著降低死亡率。

基于普通人群的研究资料显示, 无论是糖类抗原(carbohydrate antigen, CA) 125、HE4 或者经阴道超声, 均不能达到满意的筛查效果[5]-[8]。50%至 90%的早期 EOC 患者表现出 CA-125 水平升高, 但许多其他情况 CA-125 水平会升高[9] [10]。血清人附睾蛋白 4 (HE4)在鉴别卵巢癌患者和妇科良性疾病患者时比 CA-125 的敏感性更高[11]。然而, HE4 因多种非卵巢疾病而有所不同, 如怀孕、绝经状态[12]-[14]。ROMA 指数是将 CA-125 和 HE4 的血清浓度与患者绝经状态相结合的一个评估模型, 其值取决于 CA-125、HE4 的血清浓度、激素和绝经状态[1]。有研究表明恶性肿瘤细胞分泌的蛋白质可以更早地被检测到; 然而, 这些信号往往被血液中的各种蛋白质(如白蛋白、免疫球蛋白)所掩盖[15]。妇产科超声诊断方法包括经腹和经阴道超声, 现阶段, 超声标准评分已经开发出了多种类型, 如: 恶性肿瘤风险指数等等[16]。但卵巢癌的超声检查有一定的假阴性率, 只有少部分卵巢癌患者在转移前包块可能达到超声可测量的大小, 并且早期癌症和良性卵巢肿瘤之间的表现有重叠部分。此外, 超声诊断的操作者间存在个体差异, 需要检查者有足够的妇科超声诊断经验及对卵巢生理解剖结构的理解[17]。其他检查如增强 CT 和磁共振等价格昂贵, 组织活检因系有创操作, 一般不用于卵巢癌的初筛。

2. 细胞外囊泡分泌体

在 1983 年, Pan 和 Johnstone 在研究转铁蛋白受体的释放实验中意外发现, 在绵羊网织红细胞成熟过程中, 有一种细胞外囊泡(extracellular vesicles, EVs)的参与[18]。EVs 是由细胞分泌的具有磷脂双分子层结构的囊泡, 能够通过其携带的生物大分子, 调节受体细胞的生物学特性, 参与细胞的生理学和病理生理学过程[19]。根据其直径大小、形状、来源等不同可以分为外泌体、微囊泡、癌小体等[20]。EVs 几乎可以由所有类型的细胞释放, 内含有许多功能活性物质, 如蛋白质、脂质、mRNA、microRNA (miRNA)等, 能通过水平转移或细胞-受体相互作用来进行内容物的传递, 在局部和远处细胞间的信号交流中发挥重要的作用[21]。并且, 在正常人群和癌症患者如卵巢癌患者中, EVs 的数量及其内容物的组成和含量均有所不同。

细胞之间可以通过释放蛋白质、核酸以及脂质等分子到胞外,与受体结合从而介导细胞间的信号转导。除了这些单分子以外,细胞还可以释放 EVs,通过水平转移功能性 miRNA 和蛋白质等物质到受体细胞,改变受体细胞的功能[21]。EVs 与靶细胞联系的机制目前公认的有以下 3 种:① 直接与靶细胞膜融合,释放内容物到靶细胞中;② 通过内吞作用被靶细胞摄取;③ 识别并结合靶细胞表面的特异性受体[22]。EVs 中含有许多功能活性物质,如蛋白质、脂质、核酸,这些物质能随 EVs 一起出现在大多数循环体液中,而且其内容物的组成及含量与起源细胞、产生方式、细胞状态以及所处的环境相关。EVs 的功能取决于其所含有的内容物,而内容物取决于它们的起源细胞[23]。已有研究表明, EVs 介导物质运输到近邻和远处细胞影响肿瘤发展的许多过程,包括促进血管生成,逃避免疫监视,侵袭转移,耐药等[24]。

外泌体的生物发生始于质膜向内出芽,从而形成早期核内体。早期核内体然后成熟为晚期核内体。晚期核内体膜内陷导致在核内体内形成腔内囊泡,称为多泡体。多泡体要么与溶酶体融合导致降解,要么与细胞质膜融合导致外泌体释放[25]-[27]。电镜观察,完整的孤立外泌体的直径应该在 30~100 nm 范围内,或者可能稍微大一点(最大 150 nm)。从细胞的质膜(PM)出芽的 EV,或由死亡细胞的碎片引起的 EV,不显示这种大小限制,因此可以大到 1 μm 或几微米,或小到,甚至比外泌体更小。外泌体的分子组成也可能更接近于核内体的组成,而不是 PM 的组成。最后,分泌细胞中多泡核内体(MVBs)的存在与 PM 融合。普遍认为外泌体与 MVBs 的腔内囊泡(ILVs)相对应,因为外泌体的起源往往缺乏可靠的证据,因此,在许多研究中 EVs 被命名为外泌体[28]。

3. 细胞外囊泡外泌体在上皮性卵巢癌疾病中的应用价值

3.1. 细胞外囊泡外泌体与肿瘤发生发展

外泌体在肿瘤的发生发展中扮演着重要角色。肿瘤细胞及其周围的肿瘤微环境(TME)共同决定了肿瘤的恶性表型,而外泌体作为细胞间交流的重要媒介,在肿瘤细胞及其微环境之间的信息传递中发挥着关键作用。

1) 促进肿瘤生长:肿瘤源性外泌体(TDEs)通过多种途径促进肿瘤的生长,如携带促进细胞增殖的信号分子,诱导血管生成,以及调节巨噬细胞极化等。此外,外泌体还能将侵袭能力转移到非侵袭性细胞中,促进肿瘤的恶性进展。

来源于肿瘤细胞的外泌体,可以通过多种方式诱导正常细胞发生变化。例如在乳腺癌中,肿瘤来源的外泌体,已经被证明会高表达特异性的 miRNA,可以促进非肿瘤来源的乳腺细胞转化为肿瘤细胞[29]。因此,外泌体可能参与肿瘤的发展过程。肿瘤细胞可以摄取富含热休克蛋白和生存素的外泌体,以抑制或阻碍细胞凋亡、促进细胞的增殖分化,表明外泌体在肿瘤生长中发挥重要的作用。

2) 诱导免疫逃逸:外泌体帮助肿瘤细胞逃脱免疫系统的监视,进行免疫逃逸。它们能够抑制 T 细胞的活化,降低 NK 细胞的功能,改变单核细胞的分化等,从而消除针对肿瘤细胞的先天和适应性免疫反应。

此外,已有研究表明,肿瘤来源的外泌体可以通过向免疫细胞传递蛋白质、DNA、miRNA 等物质,影响免疫细胞的抗肿瘤功能,协助和促进肿瘤免疫逃逸[30] [31]。

3) 促进肿瘤转移:外泌体在肿瘤转移过程中也发挥着重要作用。它们能够促进肿瘤细胞上皮-间充质转化(EMT),降解细胞外基质,促进局部浸润和直接蔓延。此外,外泌体还能将转移能力传递到非转移性细胞上,促进肿瘤的远处转移。与大多数实体瘤不同的是,卵巢癌很少通过血管传播,但在腹膜内有较高的转移倾向,因此直接接触人腹膜间皮细胞(human peritoneal mesothelial cells, HPMC)是转移的起始步骤。在这个“潘多拉的盒子”中,外泌体是一种新的强有力的信号介质,它清除了间皮屏障,促进了癌细胞的侵袭[32] [33]。

3.2. 细胞外囊泡外泌体在上皮性卵巢癌疾病中的应用

3.2.1. 外泌体与上皮性卵巢癌的早期诊断

EOC 的生存率与诊断阶段密切相关, 早期诊断的患者生存率较高[34]。血清 CA-125 和 HE4 水平都是卵巢癌公认的生物标志物。到目前为止, 这两种标志物仅用于监测 EOC 进展和评估治疗效果。目前在临床上对卵巢癌的诊断主要依靠影像学检查和肿瘤标志物, 但这些检查难以发现早期病变并且特异性和灵敏度欠佳。与血清/血浆相比, sEV 样本: 在标志物发现与验证过程中, 降低高丰度蛋白干扰; 外泌体内含物受到磷脂双分子膜保护, 稳定性提高, 减少标志物的降解; 有更好的灵敏度和特异性。因此, 外泌体作为肿瘤诊断和预后评估的生物标志物逐渐成为研究热点[23]。在之前的 EVs 蛋白质组学研究中, 补体系统被报道为 EOC 患者 EVs 中最过表达的途径之一[35]。补体成分 5a (C5a) 是补体系统的核心蛋白, 与 EOC 的病理状态有关[36]。在一项 EVs-蛋白质组学研究中检测到, EVs 水平的 C5a 可能被用作 EOC 患者的一种潜在标志物[37]。有研究在指南建议的 CA-125、HE4 基础上加入了新的标志物 C5a; 选择 EVs 中的上述标志物进行综合分析打分, 对肿瘤的辅助诊断有着更高的临床价值。

3.2.2. 外泌体与上皮性卵巢癌的治疗

据统计卵巢癌患者 5 年内复发率为 50%, 卵巢癌是与化疗耐药相关的复发率最高的肿瘤之一, 卵巢癌如此高的复发率对化疗的效果提出了巨大的挑战[38]。顺铂耐药细胞常见于溶酶体的形态及分泌表型异常[39]。在一项研究中, 将卵巢癌 2008/C13*5.25 细胞反复暴露于顺铂环境中, 筛选出获得性耐药的卵巢癌细胞, 提取活细胞中释放出具有抗性的高质量外泌体, 接着用外泌体染料 PKH67 Green 标记并重新与原始细胞孵育。该研究证实, 外泌体可以重新进入起源细胞, 耐药组外泌体含有显著增多单克隆抗体 LAMP1、转运蛋白 ATP7A、转运蛋白 MRP2 和转运蛋白 ATP7B 等蛋白质, 这可能与耐药时溶酶体的降解受损、细胞内蛋白质的运输异常从而替代有关。因此可以推测检测外泌体蛋白质或许可以早期发现耐药或预测治疗反应。另一项研究表明, 过表达的外泌体 miR-433 通过影响肿瘤微环境驱动细胞衰老, 影响细胞内信号转导, 以促进上皮性卵巢癌细胞对紫杉醇的耐药性[40]。膜联蛋白 A3 的表达增加是卵巢癌细胞铂类耐药的一种机制, Yin 等[41]一项研究发现, 通过免疫印迹和免疫电镜可以在从顺铂耐药细胞释放的外泌体中检测到膜联蛋白 A3, 外泌体的含量、外泌体与生物活性蛋白相互作用及其转移可能影响细胞抗性表型。还有研究表明, 在 Th 低氧诱导条件下培养的腹水卵巢癌细胞系的外泌体携带更有效的致癌蛋白 STAT3 和 FAS, 可以形成更具侵袭性、化学耐药性的卵巢癌表型[42]。通过以上研究推测, 检测外泌体可以预测其抗癌药物的疗效。

靶向治疗恶性肿瘤细胞是一种高效治疗方式, 很多医学研究就是为了找出癌症的“靶点”, 使其能精准治疗, 并减少治疗中的毒副作用等。目前被美国批准用于治疗卵巢癌有四种靶向药物: 奥拉帕尼尼拉帕尼、聚腺苷酸二磷酸核糖基聚合酶(poly ADP-ribose polymerase, PARP)、瑞卡帕尼和贝伐单抗[43][44]。目前外泌体和外泌体模拟物在靶向药物的治疗剂递送中的作用已得到广泛认可[45]。外泌体作为理想的天然纳米载体, 具有的优点: 膜穿透性、生物相容性、无不良免疫原性, 它参与遗传物质和蛋白质在细胞之间的水平转移, 使其在药物蛋白及核酸传递占据独特优势[46]。有研究发现, 卵泡刺激素受体- β (follicle stimulating hormone receptor, FSH β) 链上特定的氨基酸片段能够特异性识别 FSH β 阳性的卵巢癌细胞[47], 锚定 FSH β 的外泌体通过其特异表达分子诱导外周血 T 淋巴细胞的增殖, 从而激发其抗肿瘤效应; 在该研究四个对照组中, 负载 Exosome/FSH β 的树突状细胞能显著激活 T 细胞杀死卵巢癌细胞[48]。这项研究表明了外泌体具有装载靶向肽的潜力。

3.3.3. 外泌体与上皮性卵巢癌的复发检测及预后评估。

复发率高是卵巢癌疾病的一大特点, 也是卵巢癌治疗过程中亟待解决的一大难题。如果能找到监测

卵巢癌复发的有效指标,则能有效改善患者的预后。目前关于 miRNA 在卵巢癌复发监测中的作用也受到越来越多的重视。有研究表明 5 种血清 miRNAs (miR-200c-3p, miR-346, miR-127-3p, miR-143-3p 和 miR-205-5p)可作为 OC 非侵袭性诊断生物标志物。该标志物组水平可反映 OC 的进展和预后[49]。意大利的学者 Bagnoli [50]及其团队最新发表的文章中将该模型应用于晚期诊断的上皮性卵巢癌的早期复发预测中,也取得了较好的预测效果[51]。也有研究[52]表明卵巢癌复发患者与健康人群的外周血标本中 miRNA 的表达差异,发现 miRNA 在早期识别、诊断复发性上皮性卵巢癌患者有着较大的预测价值。Alharbi 有研究[53]同样发现在 Has-miR-1273g-3p 在肿瘤坏死因子- α (TNF- α)、COL1A1、基质金属蛋白酶-2 (MMP-2)、基质金属蛋白酶-9 (MMP-9)等相关基因调控中发挥重要作用,与上皮性卵巢癌复发有关,因此可作为卵巢癌者治疗后复发的监测手段。以上均说明外泌体 miRNA 对卵巢癌的复发检测有较大潜力,可为临床卵巢癌的复发检测提供新思路。

越来越多的研究表明外泌体 miRNA 可作为卵巢癌预后评估的生物标志物。Meng 等人[54]在 163 名 EOC 患者血清外泌体中发现 miR373, miR200a, miR200b 和 miR200c 水平相比健康对照组显著升高,其中 miR200b 和 miR200c 升高的水平与平均生存期呈负相关,提示血清外泌体中的 microRNA 具有预测 EOC 病情进展及患者预后的潜力。美国德克萨斯大学安德森癌症中心实验室的一项研究在卵巢癌细胞中发现 miR940 在卵巢癌细胞来源的外泌体中含量相比正常卵巢上皮细胞丰富,提示 miR940 的高表达与卵巢浆液性囊腺癌患者较高的总体存活率有关,因此预测外泌体 miR940 也可作为一项预测 EOC 预后的无创且便捷的标志物[55]。此外,还有研究指出,卵巢癌患者腹水来源外泌体(ADEs)可以将 miR-6780b-5p 转移至卵巢癌细胞,促进卵巢癌细胞的上皮间质转化(EMT),提示了较差的预后[56]。也有研究者中从腹腔转移的 EOC 患者腹膜外泌体中鉴定出了差异表达的 miRNA,提示 miR149-3p 和 miR222-5p 作为 EOC 患者预后评估标志物具有良好的应用前景[57]。

综上所述,上皮性卵巢癌的诊断现状呈现出多样化、综合化的特点。通过综合运用多种医学检查手段和技术,结合患者的临床表现和病史资料,可以实现对上皮性卵巢癌的准确诊断,为患者的治疗和预后提供有力的支持。

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