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·综 述·

环状RNA参与卵巢癌铂耐药相关机制的研究进展

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[摘 要] 卵巢癌因早期诊断困难、确诊时多为晚期以及高复发率,成为致死率最高的妇科肿瘤。卵巢癌不良预后的重要原因是对铂类抗肿瘤化疗药物的耐药。环状RNA(circRNA)因其特殊的结构在细胞中较mRNA更稳定,参与调控多种肿瘤的发生、发展及化疗耐药。circRNA可作为miRNA的竞争性内源性RNA(ceRNA)与蛋白结合,可通过调控巨噬细胞表型极化,和作为外泌体circRNA参与调控卵巢癌铂耐药的敏感性。circRNA有望成为新的铂耐药标志物及耐药治疗新靶点。为了进一步探讨circRNA与卵巢癌铂耐药的关系,本文对近年来有关circRNA与卵巢癌铂耐药相关研究的文献进行总结。

[关键词] 环状RNA;卵巢癌;铂耐药;机制;综述

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Research progress on the mechanism of circular RNA involved in platinum resistance in ovarian cancer

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Abstract: Ovarian cancer has become the most lethal gynecological tumor due to the difficulty in early diagnosis, the late stage when diagnosed and the high recurrence rate. Resistance to platinum-based anti-tumor chemotherapy drugs is an important reason for the poor prognosis of ovarian cancer. circular RNA (circRNA) is more stable than mRNA in cells due to its special structure, and it is involved in the regulation of the occurrence, development and chemotherapy resistance of a variety of tumors. circRNA can be used as a competing endogenous RNA (ceRNA) of miRNA to bind to proteins, and regulates the phenotypic polarization of macrophages, it can also be used as an exosomal circRNA to regulate the sensitivity of platinum resistance in ovarian cancer. circRNA is expected to be a new marker of platinum resistance and a new target for the treatment of platinum resistance. In order to further explore the relationship between circRNA and platinum resistance in ovarian cancer, this article summarizes the recent literature related to circRNA and platinum resistance in ovarian cancer.

Keywords: circular RNA; ovarian cancer; platinum resistance; mechanism; review

卵巢癌是女性生殖系统中常见的恶性肿瘤,具有病理组织学复杂、恶性程度高、复发率高、预后差等特点,是致死率最高的妇科肿瘤[1-2]。2020年中国卵巢癌新发55 342例,死亡37 519例[3]。因卵巢癌患者早期无明显症状,当患者出现如腹痛、腹大或下腹部包块等明显症状时,多数已是晚期[4]。针对晚期卵巢癌患者最常见的治疗方式为手术结合化疗,但由于晚期卵巢癌易发生转移和侵袭,很难通过手术完全切除病灶,即使经过综合治疗,由于对化疗药耐药,仍有约70%的患者3年内复发[5],因此患者5年生存率仅约40%[6]。目前卵巢癌患者的化疗方案多采用以铂类为基础的联合化疗[7-8],但反复化疗可导致化疗耐药,是卵巢癌患者治疗失败及生存率低的主要原因,因此,探寻卵巢癌的耐药机制十分必要。铂类抗肿瘤药物属于细胞周期非特异药物,主要作用机制是铂进入肿瘤细胞与其DNA结合,形成Pt-DNA加合物,影响DNA的转录和复制,从而介导细胞坏死与凋亡。铂类药物在卵巢癌[9]、宫颈癌[10]、睾丸癌[11]、肺癌[12]、膀胱癌[13]、结直肠癌[14]等治疗中均被广泛应用。

环状RNA(circular RNA,circRNA)是由RNA转录酶Ⅱ转录而来的前体mRNA,是一类不具有5′末端帽子和3′末端poly(A)尾巴的特殊非编码RNA,并以共价键形成环形结构,客观存在于生物体内。circRNA根据来源主要分为4类:由单个或多个外显子衍生的外显子circRNA(ecRNA),由外显子和内含子组成的circRNA(eIciRNA),由内含子衍生的内含子circRNA(ciRNA),以及基因间circRNA[15]。circRNA分布广泛,且种类众多,主要存在于真核细胞的胞质中,且比mRNA丰度更高,某些circRNA丰度甚至是相关线性mRNA的10倍以上[16]。circRNA结构特殊,对RNA外切酶有抗性,所以其在细胞中非常稳定,在大多数物种中其半衰期比mRNA更长[16-17],但由于血清中含有RNase A家族核糖核酸酶,所以circRNA在血清中并不稳定。circRNA的表达水平在不同的种属、组织、细胞

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中具有特异性,在组织器官的不同发育阶段及疾病的不同发展阶段也存在一定的差异,并具有一定序列保守性[18]。circRNA作为非编码RNA之一,因其环状结构在细胞中表达稳定,且在细胞中有重要的作用,能够调控肿瘤的发生、发展,是目前RNA研究领域的热点。近几年研究发现,在卵巢癌中circRNA不仅能够调控卵巢癌细胞的增殖、侵袭、凋亡[19-22],也能够调控卵巢癌的化疗耐药性[23-26],有望成为铂耐药的耐药标志物及耐药治疗新靶点。本文主要就circRNA参与卵巢癌铂耐药调控的机制进行综述。

1 miRNA的竞争性内源性RNA(competing endogenous RNA,ceRNA)

circRNA可以通过miRNA发挥ceRNA作用。miRNA是一类由18~25个核苷酸组成的内源性、非编码单链RNA,可以通过结合mRNA导致基因沉默,而circRNA含有大量的miRNA结合位点,可以通过应答元件与miRNA结合,使miRNA无法与靶基因mRNA结合,消除miRNA对其相应的靶基因mRNA的调控,进而共同参与调控miRNA下游靶基因的表达[27]。目前,在卵巢癌的铂耐药机制方面,ceRNA机制是研究的热点。circRNA能通过ceRNA机制调控铂类抗肿瘤药物在卵巢癌治疗中的耐药。circ Cdr1as能通过ceRNA机制影响卵巢癌铂耐药。mi-1270在卵巢癌中起抑癌作用,可降低顺铂的化疗敏感性。circCdr1as在顺铂耐药卵巢癌患者组织及细胞中明显下调,其能通过海绵吸附mi-1270,上调SCAI表达,进而增加卵巢癌对顺铂的敏感性[28]。Feng等[29]的研究发现,敲低CHTOP的表达,可促进顺铂诱导的卵巢癌细胞凋亡,降低耐药细胞的干性及其转移潜能。Cao等[30]的研究发现,在对顺铂耐药的卵巢癌细胞与组织中,circHIPK2、CHTOP均高表达,miR-338-3P低表达,敲低circHIPK2可抑制对顺铂耐药的卵巢癌细胞的增殖、迁移和侵袭,促进其凋亡,并将细胞周期阻滞在G_0/G_1期,使进入S期的细胞减少;miR-338-3p是circHIPK2的靶点,也是CHTOP的靶点,而降低miR-338-3p的表达可抵消敲低circHIPK2的作用,上调CHTOP可抵消过表达miR-338-3p的作用。因此,沉默circHIPK2可能通过调控miR-338-3p/CHTOP轴抑制对顺铂耐药的卵巢癌细胞的增殖、迁移和侵袭[30]。研究显示,circLPAR3在对顺铂耐药的卵巢癌细胞中显著上调,沉默circLPAR3可增强卵巢癌细胞对顺铂的敏感性;miR634可与circLPAR3相互作用,其抑制剂逆转了敲低circLPAR3对细胞顺铂耐药的调控;PDK1与miR634结合,其过表达逆转了miR634对细胞顺铂耐药的作用;因此,circLPAR3可能通过miR634/PDK1轴参与卵巢癌的顺铂耐药[31]。circSnx12是miR-194-5p的ceRNA,在卵巢组织及对顺铂耐药的细胞中表达均明显升高,敲低circSnx12的表达可降低细胞活力,增强铁死亡,使卵巢癌细胞恢复对顺铂的敏感性,上调circSnx12可通过miR-194-5p/SLC7A11通路抑制铁死亡来增强卵巢癌对顺铂的耐药性[32]。

2 circRNA与蛋白结合

RBPs是一类广泛参与基因表达的蛋白质,如AGO、HuR、AUF1、TTP、CUGBP2、KHSRP等2 000多种。尽管与线性RNA相比,circRNA的RBPs结合位点非常少,但是由于circRNA存在独特的三级结构,决定了蛋白质与circRNA结合比线性RNA更复杂。RBPs与蛋白质相互作用,能够影响蛋白质的表达和功能,调节circRNA的合成、降解、翻译等[33]。ATP7A是重金属转运p型ATP酶的成员,被称为铜转运蛋白,负责将铜离子转运出细胞。研究发现,铂耐药细胞中ATP7A的水平远高于铂敏感细胞,敲低ATP7A可部分逆转对铂类药物的耐药[34]。ATP7A对顺铂、卡铂、奥沙利铂、长春新碱、紫杉醇、SN-38、依托泊苷、阿霉素和米托蒽醌等多种抗癌药物产生耐药性[35]。有研究通过对顺铂耐药细胞株OV90、skov3进行测序,发现hsa_circ_0004804(又称为circPBX3)显著上调且对顺铂耐药性最强,且在体内、外实验中均发现,过表达circPBX3可促进卵巢癌细胞对顺铂的耐受性,敲低circPBX3的表达可增加耐药卵巢癌细胞对顺铂的敏感性,因此circPRKD3能与RNA结合蛋白IGF2BP2相互作用,增加ATP7A mRNA的稳定性,提高ATP7A蛋白表达,敲低ATP7A可消除circPBX3过表达对卵巢癌细胞顺铂耐药性的影响[36]。

3 circRNA与巨噬细胞

巨噬细胞是一种重要的免疫细胞,参与去除细胞碎片,清除凋亡细胞,组织再生与修复,释放炎症因子及生长因子。巨噬细胞主要分为2类:M1型巨噬细胞,具有促炎、抑制肿瘤作用,又称为经典活化型巨噬细胞;M2型巨噬细胞,具有抗炎、组织修复及重塑作用,又称为替代活化型巨噬细胞。巨噬细胞参与多种肿瘤耐药过程,如在结肠癌、多发性骨髓瘤、肺癌、卵巢癌等癌症中均有重要作用[37-40]。有研究发现,在M2型巨噬细胞及与M2型巨噬细胞共同培养的卵巢癌细胞中miR-21呈高表达,且M2型巨噬细胞可显著促进卵巢癌细胞的耐药;将M2型巨噬细胞转染miR-21 mimic后与卵巢癌细胞共培养,不仅促进卵巢癌细胞中

miR-21高表达,还增强了卵巢癌细胞的耐药,其凋亡率也下降,而转染miR-21 inhibitor则出现相反的生物学行为;更重要的是,miR-21可诱导M1型巨噬细胞向M2型巨噬细胞极化,M2型巨噬细胞及经miR-21处理的M2型巨噬细胞可调控卵巢癌细胞中PI3K/AKT信号通路,从而调控卵巢癌细胞的耐药性[41]。Li等[42]的研究发现,circITGB6在铂类耐药卵巢癌患者的肿瘤组织及血清中表达均显著上调,且与不良预后相关,其通过形成circITGB6/IGF2BP2/FGF9三元复合物,稳定FGF9 mRNA,进而诱导肿瘤相关巨噬细胞向M2表型极化,从而促进卵巢癌的铂耐药;而circITGB6反义寡核苷酸阻断M2型巨噬细胞极化后,能显著逆转circITGB6诱导的卵巢癌对顺铂的耐药性。表明circITGB6可通过调节肿瘤微环境,在卵巢癌的化疗耐药中发挥重要作用。

4 外泌体circRNA

外泌体是由细胞产生的胞外小囊泡,可携带特定的蛋白质、核酸、脂类、碳水化合物等生物活性分子由一个细胞传递到另一个细胞,进行细胞间通讯,在肿瘤细胞中可调节肿瘤微环境,并影响肿瘤的发生、发展。circRNA可通过外泌体的携带,在细胞间相互传递,影响肿瘤的侵袭、转移及耐药等过程。在肿瘤耐药方面,外泌体circRNA参与多种肿瘤的化疗耐药、放疗耐药、靶向耐药,有望成为预测肿瘤耐药的标志物[43]。研究发现,在卵巢癌患者的血清中可检测到circRNA Cdr1a表达,且顺铂耐药组中其表达量低,并与miR-1270的表达量呈负相关[28]。外泌体circFoxp1在顺铂耐药的卵巢癌患者中高表达,且其表达与国际妇产科联盟分期、原发肿瘤大小、淋巴转移、远处转移、残留肿瘤直径和临床疗效呈正相关,是预测卵巢癌患者生存和疾病复发的独立因素;高表达circFoxp1可促进细胞增殖,并增强顺铂耐药性,低表达circFoxp1则出现相反的生物学行为[44]。王娟娟等[45]的研究发现,血清外泌体hsa_circ_0004390是影响上皮性卵巢癌患者铂类化疗反应的独立因素,卵巢癌耐药组患者血清外泌体hsa_circ_0004390表达显著高于敏感组患者,血清外泌体hsa_circ_0004390表达低水平组患者总生存期较高水平组患者更长。因此,外泌体circRNA在卵巢癌耐药中发挥了重要作用,是潜在的治疗靶标及耐药标志物。

5 结语与展望

目前,卵巢癌仍是女性生殖系统致死率最高的妇科肿瘤,对于卵巢癌病因、早期筛查手段、治疗方案的相关研究仍然未取得重大突破。卵巢癌一线化疗“金标准”方案仍然是铂类联合紫杉醇,然而铂耐药是导致卵巢癌治疗失败的重要原因。circRNA可通过ceRNA机制、与蛋白结合、巨噬细胞、外泌体来调控卵巢癌对铂的耐药性。在与circRNA有关的卵巢癌铂耐药机制中,研究最广泛、最热门的是circRNA-miRNA-mRNA调控机制,但对于circRNA通过其他机制影响卵巢癌耐药的研究并不多见,仍需进行大量且深入的研究,以探讨circRNA是否能成为卵巢癌铂耐药标志物及耐药治疗新靶点。

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