综述

环状 RNA 在恶性肿瘤耐药中的研究进展

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摘　要:环状 RNA 作为体内稳定存在的一种非编码 RNA 广受关注,其不仅参与肿瘤发生发展,也与化疗耐药密切相关。全文主要关注环状 RNA 在恶性肿瘤化疗耐药中的作用,旨在深入探究耐药可能的分子机制,为临床肿瘤治疗提供有希望的潜在靶点。
主题词:环状 RNA;癌症;耐药;药物疗法
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Progress on CircularRNA in Drug Resistance of Malignant Tumors

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Abstract: Chemotherapy is one of the most effective methods for treatment of malignant tumors, but tumor cells can develop resistance to multiple drugs during the therapy, leading to treatment failure. In recent years, circular RNA has attracted much attention as a non-coding RNA stably present in vivo. Accumulating evidences suggest that circRNAs play a critical role in the occurrence and development of various types of cancer, as well as in chemotherapy resistance. In this review, we summarize the role of circRNAs in the resistance of tumors to chemotherapy, aiming to explore the specific molecular mechanisms and to provide potential targets for drug resistance in cancer treatment.
Subject words: circRNA; cancer; resistant; drug therapy

非编码 RNA(non-coding RNA,ncRNAs)是一类不具有翻译成蛋白质能力的 RNA 序列，包括微小 RNA(miRNA)、长链非编码 RNA(lncRNA)、PIWI 相互作用 RNA(piRNA)、转移 RNA(tRNA)、小核 RNA(snoRNA)和环状 RNAs(circRNAs)等多种 ncRNA 家族[1],其中 miRNA 和 lncRNA 是研究最广泛且作用较明确的两种 RNA,与肿瘤的发生发展及药物耐药密切相关[2-4]。近来,随着对 circRNA 不断探索,使其成为继 miRNA 和 lncRNA 后的又一研究热点。

环状 RNA 是由前 mRNA 的反向剪接产生,并形成一个新的环结构,在 5′和 3′末端不具有自由末端而是由磷酸二酯共价键衔接[5],大多数 circRNAs 的表达低于对应的线性物[6]。大量研究结果已经揭示了 circRNA 在癌症中具有特异性功能，其既可作为肿瘤抑制因子又能以癌基因的形式发挥作用。此外,circRNA 特殊的环形结构赋予了其固有的稳定性,使其稳定存在于血浆、唾液和其他外周组织中,其可能成为癌症诊断和治疗的新型生物标志物和新靶点[7-8]。最近研究表明,circRNA 在多种肿瘤,如血液系统疾病、骨肉瘤、乳腺癌、消化系统肿瘤、肺癌、泌尿系统肿瘤和妇科肿瘤等中发挥重要作用,circRNA 主要通过与微小 RNA 或其他分子结合，抑制其功能,在转录或转录后水平调控基因的表达，从而介导药物耐药。

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1 CircRNA 与骨肉瘤

骨肉瘤(osteosarcoma,OS)主要发生于儿童和青少年,发病率低,侵袭性和转移率高[9]。目前骨肉瘤患者的主要治疗方法是新辅助化疗,其次是手术切除联合其他化学治疗[10]。然而,OS 患者在治疗一段时间后化疗耐药性也是不可避免的。过表达的 hsa_circ_0081001 不仅是 OS 分期及肺转移的独立预后因素,还在化疗耐药中发挥作用,但分子机制尚不清楚[11]。circRNA(circPVT1)高表达与 OS 的肺转移和化疗耐药密切相关,敲低其表达可部分逆转 OS 细胞对多柔比星和顺铂的耐药性,其机制可能是通过靶向多药耐药蛋白(ATP-binding cassette subfamily B member 1,ABCB1),下调其表达,使OS 细胞恢复化疗敏感性[12]。circRNA 也可以充当miRNA 海绵,调控 OS 细胞的化疗耐药,如上调 hsa_circ_0004674 靶向 miR-490-3p/ABCC2 或 miR-1254/EGFR 途径介导顺铂、阿霉素耐药[13],高表达 hsa_circ_001569 则能通过激活 Wnt /β-catenin 途径增加 OS 细胞增殖并介导顺铂耐药[14]。

2 CircRNA 与乳腺癌

阿霉素是治疗乳腺癌的常用化疗药物之一[15]。Gao 等[16]研究表明,与 MCF-7 细胞系相比,MCF-7 / 阿霉素(adriamycin,ADM)耐药细胞系中circ_0006528 显著性上调,而降低其表达可靶向 miR-7-5p-Raf1 信号通路恢复抗性细胞系对 ADM 的敏感性。Liu 等[17]在乳腺癌 Monastrol 耐药细胞系中鉴定出 398 个失调的 circRNAs,其中过表达 circRNA-MTO1 可通过充当竞争性内源 RNA 与肿瘤坏死因子受体 4(tumor necrosis factor receptor,TRAF4)相互作用并抑制驱动(kinesin-5 motor protein,Eg5)蛋白水平发挥逆转 Monastrol 耐药的功能。最新研究发现,环状 RNA-CDR1as 参与了乳腺癌细胞氟尿嘧啶的耐药,且 CDR1as-miR-7-CCNE1 信号通路在该耐药过程中发挥了重要作用[18]。因此,circRNA 可能是未来克服乳腺癌化疗耐药的有希望的潜在治疗靶点。

3 CircRNA 与肺癌

药物耐药的发生是造成肺癌患者 5 年生存率不乐观的一大主要因素。lncRNA 和 miRNA 介导肺癌化疗耐药的研究较多[19],而环状 RNA 在肺癌化疗耐药中的研究较少报道。徐等[20]使用高通量微阵列测定法在紫杉醇耐药肺癌细胞系 A549/Taxol 和亲本 A549 中发现了多种异常表达的 circRNA,他们发现上调的 hsa_circ_0071799 主要针对 miR-141;下调的 hsa_circ_0091931 主要与 miR-34c-5p 结合,是引起 NSCLC 患者紫杉醇耐药最可能的两种 circRNA。既往报道显示,miR-141[21]和 miR-34c-5p[22]不仅参与了多种癌症的发生发展,也与化疗耐药息息相关。近来,多项研究发现 circRNA 在肺癌顺铂耐药中具有调控作用,hsa_circ_0001946 下调既能影响肺癌细胞的增殖、迁移和侵袭,还能通过调节核苷酸切除修复信号通路导致耐药[23];circ_0076305 上调可通过靶向 miR-296-5p 调节信号转导及转录活化因子 3(signal transducer and activator of transcription 3,STAT3)的表达从而介导耐药[24]。综上,circRNA 在肺癌化疗耐药中的重要作用值得深入探究。

4 CircRNA 与卵巢癌

耐药仍是卵巢癌治疗的一大障碍[25]。近来,赵等[26]研究发现 Cdr1as 下调可能是造成卵巢癌顺铂耐药的关键调节基因,其过表达主要通过分子海绵的作用,下调 miR-1270 表达,部分恢复癌细胞侵袭抑制因子(suppressor of cancer cell invasion,SCAI)表达,从而促使卵巢癌细胞对顺铂敏感。因此,探索新的耐药靶点在阐明卵巢癌化疗抵抗及进一步治疗中也是尤为关键的。

5 CircRNA 与血液系统疾病

急性髓性白血病(acute myeloid leukemia,AML)是一种相对罕见的癌症,AML 患者预后不良,5 年生存率仅 27.4%。目前,包括 ADM 在内的化疗是 AML 的主要治疗方法,但长期使用不可避免地会出现耐药性[27]。Shang 等[28]发现阿霉素耐药 AML 细胞系中 circPAN3 上调,且 circPAN3-miR-153-5p / miR-183-5p-XIAP 轴是调控耐药的可能机制。此研究发现了化学敏感和耐药 AML 细胞之间的差异 circRNA,其可能对 AML 患者化疗耐药有指示作用,甚至成为潜在的临床治疗靶点。

6 CircRNA 与消化系统肿瘤

消化系统肿瘤对化疗的耐药性强。因此,寻找新的耐药机制对治疗消化系统肿瘤患者十分紧要。Shao 等[29]的测序结果发现了与胰腺癌吉西他滨耐药最相关的两种 circRNAs (chr14:101402109-101464448+,chr4:52729603-52780244+),并在胰腺癌细胞中证实过表达的 circRNAs 可导致 miR-145 表达不同程度地降低介导胰腺癌细胞吉西他滨的耐药[29],但具体机制仍不清楚。熊等[30]在氟尿嘧啶耐药的结直肠癌细胞中发现了数种异常表达的 circRNA,进一步研究显示明显上调的 hsa_circ_0007031 和 hsa_circ_0000504 分别通过调控 miR-885-3p/AKT3 和 miR-485-5p/STAT3/AKT3 信号通路来促进氟尿嘧啶耐药,而下调的 hsa_circ_0048234 则介导了 miR-671-5p/EGFR 轴的表达从而导致了耐药。另一研究显示,circRNA_101505 在顺铂耐药的肝癌组织和细胞中低表达,而将其上调后,则能使 miR-103 海绵化,进一步促进含氧化硝基域的蛋白 1(NOR1)表达恢复肝癌细胞对顺铂的敏感性[31]。同样,在顺铂耐药的胃癌中发现了高表达的 circAKT3,它不仅可以通过 circRNA 作用于 miR-198 靶向 PI3K/AKT 信号通路,也可介导 DNA 损伤反应致使耐药的发生[32],但两种途径之间是否有关联还有待进一步研究。总之,这些研究为消化系统肿瘤化疗耐药提供了新的 circRNA 生物标志物,而具体的潜在机制还有待新的研究阐释。

7 CircRNA 与泌尿系统肿瘤

目前晚期膀胱癌的主要化疗药物是顺铂,其可用作新辅助治疗联合根治性膀胱切除术,或作为单一药物或转移性膀胱癌治疗的关键成分[33]。但顺铂治疗膀胱癌患者在最后阶段仍会产生耐药性,导致治疗失败和疾病进展[34]。最近,Chi 等[35]发现 circRNA_000285 在顺铂耐药膀胱癌中的表达较相应对照组下调,且其高表达与 miR-124 和 miR-558 表达显著性相关,另外 Su 等[36]研究显示缺氧诱导的 circELP3 高表达可通过靶向癌症干细胞促进膀胱癌细胞对顺铂耐药。恩杂鲁胺是去势抵抗型前列腺癌患者的有效治疗药物[37],但耐药仍是患者终将面临的问题。John 等[38]报道了与前列腺癌恩杂鲁胺耐药相关的 circRNA 表达谱。随后,吴等[39]研究发现 circRNA17 在恩杂鲁胺耐药的前列腺癌中低表达,且上调其表达可通过靶向 miRNA-181c-5p/ARv7 信号轴增强癌细胞对恩杂鲁胺的敏感性。因此,环状 RNA 可能为逆转泌尿系统恶性肿瘤化疗耐药提供新的治疗方式。

目前大量研究已证实,circRNA 异常表达与癌症的临床病理特征密切相关,如肿瘤大小、分化程度、淋巴结及远处转移和预后,然而关于 circRNA 在化疗耐药中的作用及机制尚未完全阐明。circRNA 主要通过调控 circRNA 网络、药物运输、肿瘤干细胞等途径介导耐药,但毫无疑问,仍有许多未知的信号通路或调控方式参与了耐药,值得深入探究。

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