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外泌体非编码RNA在胰腺癌化疗耐药中的潜在作用

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Potential roles of exosomal non-coding RNAs in chemoresistance in pancreatic cancer

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Abstract

Pancreatic cancer (PC) is one of the deadliest digestive system tumors in the world, primarily attributed to

difficulty in early diagnosis, early metastasis, and insensitivity to chemotherapy. The survival of advanced PC patients can be improved by chemotherapy, including gemcitabine, platinum drugs, and 5-fluorouracil, and targeted therapy such as PARP inhibitors. Nevertheless, primary or acquired drug resistance ultimately leads to treatment failure and poor prognosis in patients with PC. The mechanism underlying drug resistance in PC is complex and has not been fully elucidated. Recent studies have indicated that exosomes are the best natural carrier of non-coding RNAs (ncRNAs). They can regulate drug resistance by transporting ncRNAs. Accumulating evidence has demonstrated that exosomal ncRNAs, including microRNAs (miRNAs), long noncoding RNAs (lncRNAs), and circular RNAs (circRNAs), play an crucial role in regulating resistance to chemotherapy drugs in PC. In this review, we systematically focus on the emerging role and regulatory mechanisms of exosomal ncRNAs in influencing chemotherapy resistance in PC. We believe that exosomal ncRNAs can be considered as potential biomarkers for the diagnosis and prognosis of PC as well as new therapeutic targets.

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Key Words: Pancreatic cancer; Exosome; MicroRNAs; LncRNAs; CircRNAs; Chemoresistance

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摘要

胰腺癌是世界上最致命的消化道肿瘤之一, 主要与其早期诊断困难、早期发生转移以及对化疗反应不敏感有关。晚期胰腺癌患者可通过化疗提高生存率,

包括吉西他滨、铂类药物、5-氟尿嘧啶以及PARP抑制剂等靶向治疗药物。然而, 原发性耐药或获得性耐药最终导致胰腺癌患者治疗失败和预后不良。胰腺癌耐药的潜在机制复杂且尚未定论。最近的研究表明, 外泌体是ncRNA的最佳天然载体, 他们可以通过运输ncRNA调节耐药性。越来越多的证据表明, 外泌体非编码RNA, 包括microRNA(miRNAs)、长非编码RNA(lncRNAs)、环状RNA(circRNAs), 在胰腺癌对化疗药物的耐药性中起着重要的调节作用。在这篇综述中, 我们系统地强调了外泌体ncRNAs影响胰腺癌化疗耐药中的新角色和调控机制。此外, 我们认为外泌体ncRNAs可以被认为是诊断和预后的潜在生物标志物, 以及胰腺癌新的治疗靶点。

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关键词: 胰腺癌; 外泌体; 微小RNA; 长链非编码RNA; 环状RNA; 化疗耐药

核心提要: 胰腺癌是世界上最致命的消化道肿瘤之一, 具有发病隐匿, 侵袭性强, 预后差, 死亡率高等特点, 本文主要概述了ncRNAs通过外泌体介导在胰腺癌化疗耐药中的重要作用, 并可作为胰腺癌新的治疗靶点。

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0 引言

胰腺癌是世界上最致命的消化道肿瘤之一, 它是2021年全球第七大常见恶性肿瘤, 也是癌症相关死亡的第四大原因^[1]。胰腺癌最常见的类型是胰腺导管腺癌(PDAC)^[2]。由于早期诊断困难、早期转移、以及对化疗反应不敏感, 胰腺癌患者的五年存活率仅为3%^[3]。手术是彻底治愈胰腺癌的唯一办法, 然而由于早期临床症状不典型, 大多数胰腺癌患者确诊时已经进入了晚期, 错过最佳手术时机。晚期胰腺癌患者可通过化疗提高生存率, 包括吉西他滨(gemcitabine, GEM)、铂类药物、5-氟尿嘧啶以及PARP抑制剂等靶向治疗药物^[4,5]。然而, 对化疗产生多药耐药(multiple drug resistance, MDR)是临床肿瘤学的主要障碍, 可能导致预后不良。胰腺癌的耐药机制很复杂, 包括细胞内药物摄取减少、药物外排增加、药物代谢加速、对药物诱导的凋亡的抵抗、DNA损伤修复、影响药物靶点的突变、癌症干细胞的激活以及上皮-间充质转化(epithelial-mesenchymal transition, EMT)改变药物转运^[6-9]。因此, 进一步了解耐药的潜在分子机制对于更

有效的胰腺癌治疗是十分必要的。

外泌体是由多种细胞释放的内体多囊泡体形成的双层纳米级膜泡, 与肿瘤生长、转移和化疗耐药有关^[10-12]。外泌体可以携带各种生物成分, 包括: 蛋白质、脂质和遗传物质等, 可经邻近细胞摄取需传递的“信息”, 实现细胞与细胞之间的物质交换, 并诱导其表型变化^[13,14]。越来越多的证据表明, 外泌体介导的细胞通讯是一种新发现的耐药机制。通过直接输出药物, 诱导药物失活, 并传递功能蛋白和ncRNAs, 对PDAC耐药起着重要作用^[15-17]。

非编码RNA(ncRNAs)是一种不能被编码成蛋白质的DNA转录产物^[18]。根据长度、形状和功能, ncRNAs可细分为以下几种类型: tiny/short ncRNAs, 大于200个核苷酸的long ncRNA (lncRNAs)和环状RNA(circRNAs), 小的ncRNA, 如microRNAs(miRNAs)、小核仁RNA(snoRNAs)和小核RNAs(snRNAs)^[19]。ncRNAs已被证明是基因表达的关键调控因子, 而不仅仅是基因转录过程中的“副产品”^[20,21]。大量研究表明, ncRNAs参与许多生物学功能, 如细胞增殖、细胞周期进展、细胞凋亡等, 并且在胰腺不同的发育阶段和肿瘤等病理条件下表达存在差异, 与胰腺癌细胞的侵袭、转移、放化疗耐药有关。ncRNAs也可以作为分子信号, 利用外泌体在不同的细胞和组织之间传递^[22-28]。在这些异常表达的ncRNAs中, 各种miRNAs和lncRNAs已被发现在PDAC化疗耐药中发挥重要作用。

本文主要综述了外泌体的生物学, 外泌体ncRNAs调控胰腺癌耐药的机制, 从而为外泌体ncRNAs作为未来可能的胰腺癌生物标志物或治疗靶点的作用提供了新的思路。

1 外泌体: 起源、生物学功能

外泌体是在1981年由Trams等人^[29]在绵羊网织红细胞体外培养液中分离得到被双层膜包围的小囊泡。1987年, Johnstone^[30]将这些细胞外小泡命名为Exosomes。外泌体主要在胞外刺激、微生物攻击或者其他应激条件等的诱导下生成^[31]。外泌体是由晚期的核内体发育而来的, 核内体是由质膜内陷产生的。与内质网融合后, 在高尔基体中加工, 产生多泡小体(multivesicular bodies, MVB)。然后, 成熟的MVB与质膜结合, 以外体的形式将其内容物释放到细胞外空间^[32,33]。由于外泌体的结构很小, 通常采用超速离心法进行分离, 从血液或细胞培养液中提取外泌体^[34]。简而言之, 血浆或血清被稀释(1:1), 在2000转的4℃下离心30 min, 收集的沉淀物用PBS洗涤, 在11万转的4℃下离心70 min, 得到的沉淀物含有外泌体。虽然有不同的方法来分离外泌体, 包括免疫分离、沉淀和

密度梯度离心法, 但到目前为止, 还没有分离外泌体的金标准. 因此, 分离方法应根据具体实验的要求和问题而定^[35,36].

外泌体(Exosome)由多种细胞类型释放, 包括肿瘤细胞、免疫细胞、成纤维细胞、脂肪细胞和神经细胞, 并发现各种体液中富集, 包括血液、唾液、母乳、尿液和脑脊液^[37,38]. 最初外泌体被认为是清除细胞中降解的或不需要的细胞成分的“垃圾桶”, 随着对外泌体研究的不断深入, 发现这些囊泡是有功能的, 外泌体可以介导大量生理或病理条件下的细胞间通讯^[39], 将DNA、RNA(编码和非编码)、脂质和蛋白质等活性成分从供体细胞转移到受体细胞, 也可以通过配体-受体相互作用激活受体细胞的下游信号通路^[40], 同时外泌体的双层膜可以保护这些成分免受蛋白酶、核酸酶和其他环境影响^[41], 从而参与抗原提呈、细胞分化、生长、肿瘤的免疫反应、肿瘤细胞的迁移和侵袭^[42-44]. 越来越多的研究发现, 与健康人相比, 肿瘤患者血液循环中的外泌体数量增加了^[45], 这表明癌症与外泌体分泌增加有关^[46]. 据报道^[47,48], 癌症中的外泌体被关键地释放到癌症微环境和循环系统中, 这些证据表明包括ncRNAs在内的外泌体成分被认为是一种很有前途的筛查工具, 它们可以用来增强早期胰腺癌检测的响应性和可靠性. 同时, 肿瘤来源的外泌体可能与肿瘤的发生、转移、肿瘤微环境和化疗耐药有关^[44,49]. 然而, 外泌体在肿瘤中的确切作用机制还需要进一步的研究.

2 外泌体中的非编码RNA

非编码RNA约占人类基因组的98%, 是一类不能编码蛋白质的RNA, 可以与DNA、RNA或蛋白质相互作用, 在转录、转录后、表观遗传水平上调节基因表达, 并调节细胞过程^[50]. 广泛的研究表明, ncRNAs可调节各种分子过程和人类疾病. 越来越多的研究表明: 外泌体中富含ncRNAs, 包括microRNA(MiRNAs)、长非编码RNA(LncRNAs)、环状RNA(CircRNAs)等, 外泌体作为细胞沟通的媒介, 可以将ncRNAs选择性地包装、分泌和在细胞间转移, 影响肿瘤发生、转移、免疫调节和耐药性等肿瘤发展的关键过程^[28]. 随着对外泌体中的ncRNAs的发现和进一步研究, 出现了许多新的功能和应用, 从细胞间通讯工具到有前途的疾病生物标志物, 可能还存在新的治疗应用. 本文主要对外泌体miRNAs、lncRNAs和CircRNAs在胰腺癌的化疗耐药中的潜在机制进行综述.

2.1 MicroRNA(微小RNA) MiRNAs是由外泌体传递的重要货物, 通常由大约21-25个核苷酸组成的小ncRNA, 通过与靶mRNA的3'非翻译区(UTR)互补结合来调节基

因表达, 从而降低或抑制靶基因的稳定性^[51]. 大多数成熟的miRNA序列位于非编码RNA的内含子或外显子以及Pre-mRNA的内含子中^[52,53]. MiRNA的生物发生始于将miRNA基因转录成大的初级转录本(pri-miRNA), 其中含有一个或几个茎环结构, 每个茎环结构由大约70个核苷酸组成. 然后被包括RNase-III型酶Drosha和RNA结合蛋白Dgcr8的微处理器复合体切割成一个约85个核苷酸的茎环结构, 称为前体miRNA(pre-miRNA). 通过Exportin 5和Ran-GTP复合物将pre-miRNA输出到细胞质后, 它们在环附近被Dicer切割成小的双链RNA(DsRNAs). 这些miRNA双链是不稳定的, 很快就会被切割成单链成熟的miRNA. 成熟的miRNA被装载到Argonaute蛋白(AGO)上, 形成RNA诱导沉默复合物(RISC), 然后与靶mRNA结合, 进行转录后基因沉默^[54,55]. 大量研究表明, 在许多癌症中, 包括胰腺癌, miRNA表达异常在癌症的发生、发展和转移中起着关键作用. 此外, miRNAs被选择性地包裹在参与肿瘤微环境中细胞间通讯的外泌体, 并在肿瘤耐药中发挥重要作用^[56,57].

2.2 长链非编码RNA 长链非编码RNA(long non-coding RNA, LncRNAs)是另一类长度超过200个核苷酸的非编码RNA转录本, 没有或具有有限的蛋白质编码能力^[58]. 与mRNAs一样, 它们也是由RNA聚合酶II(RNA Pol II)从独立启动子转录而来. LncRNAs既存在于细胞核中, 也存在于细胞质中, 并根据其亚细胞定位而发挥不同的功能. 在细胞核内, LncRNAs可能参与基因表达的转录调控和mRNA的剪接. 而在细胞质中, 它们可以影响mRNA的稳定性并调节蛋白质功能^[59]. 越来越多的研究表明, 包括胰腺癌在内的许多癌症中都观察到了LncRNAs表达的失调, 并通过其作为肿瘤抑制因子或癌基因的双重作用与癌症的分期和分级密切相关^[60]. 有趣的是, LncRNA也可以选择性地包裹在外泌体内, 从而保护LncRNA免受降解, 并有助于肿瘤微环境中的细胞间通讯^[61]. 外泌体LncRNA可参与胰腺癌的发生和发展, 如增殖、侵袭、血管生成和耐药, 可能成为有吸引力的治疗靶点^[60].

2.3 环状RNA 环状RNA(circular RNA, CircRNA)是一种新的非编码RNA分子亚型, 它在5'端和聚(A)尾部之间的3'端形成具有共价键的环状结构. 主要是由外显子的pre-mRNA通过反向剪接产生的^[62]. CircRNA是一种长度超过200个核苷酸的长转录本, 它们高度稳定, 进化保守, 在特定组织中广泛分布^[63]. CircRNA最初被认为是RNA拼接的副产品^[64]. 随着高通量RNA测序(RNA-seq)和CircRNA特异的生物信息学的广泛应用, 已经在人类和其他真核生物中鉴定出了数以千计的CircRNA, 并在最近几年逐渐揭示了CircRNA的特征和行为^[65,66]. 虽然

CircRNA不编码已知的蛋白质,但它们广泛参与人类生物过程的调节。许多研究证实, CircRNA在包括胰腺癌在内的肿瘤中高度表达,在肿瘤的发生发展中发挥重要作用^[67,68]。目前对于外泌体circRNA的研究仍处于初级阶段,但少数研究表明^[69,70], CircRNA富含在外泌体中, CircRNA通过外泌体开始循环并到达受体细胞,从而实现其各种生物学功能。与线性RNA不同,具有环状结构的CircRNA不易被核酸外切酶消化,更稳定,半衰期更长,因此它们可以被认为大量癌症诊断和预后的有前途的生物标志物^[71]。

3 外泌体ncRNAs与胰腺癌耐药

越来越多的证据表明,外泌体ncRNAs在促进胰腺癌化疗耐药中发挥了重要的作用,找出其中涉及的机制有助于抑制危及生命的胰腺癌^[28,72]。GEM是胰腺癌化疗中使用最广泛的药物,GEM是一种DNA核苷类似物,它不可逆地抑制核苷酸还原酶的活性,阻止DNA复制和修复所需的双氧核糖核苷酸的合成,可以导致DNA损伤,最终导致癌细胞死亡^[73,74]。尽管如此,大量临床试验表明GEM对胰腺癌患者的疗效较低。肿瘤细胞在首次接触GEM后表现出抗药性^[75,76]。因此,了解GEM耐药的潜在分子机制对于克服GEM耐药和开发胰腺癌新的治疗策略具有重要意义。

外泌体MiRNAs在诸如PDAC等不同恶性肿瘤的进展中发挥着关键作用。几乎所有提到的miRNA都能够在耐药细胞及反应性细胞之间转移,以携带耐药特性,反之亦然。例如:癌相关成纤维细胞(carcinoma-associated fibroblasts, CAFs)是PDAC肿瘤的主要组成部分,对GEM具有本质耐药性,而GEM是PDAC的化疗治疗标准^[6]。然而,GEM治疗的胰腺癌(pancreatic cancer, PC)细胞将外泌体传递的miR-155转移到受体细胞,通过下调GEM代谢基因(DCK)导致胰腺癌细胞耐药^[77]。同时,也有研究发现胰腺癌细胞中miR-155表达的增加具有抗凋亡作用,并导致细胞释放外泌体。外泌体随后将与化疗耐药相关的物质,包括miR-155,传递给其他癌细胞,受体细胞随后产生化疗耐药并显示出外泌体合成的增加^[7]。此外,有研究发现,miR-365可以通过上调癌细胞中三磷酸核苷酸库和诱导胞苷脱氨酶抑制GEM的激活,后者使GEM失活,巨噬细胞来源的外泌体可以通过转移miR-365诱导胰腺癌细胞对GEM的耐药性^[72]。更有研究发现^[78],来自GEM耐药胰腺癌干细胞的外泌体通过传递miR-210介导耐药性状向GEM敏感胰腺癌细胞的水平转移,并抑制GEM诱导的细胞周期阻滞,拮抗GEM诱导的细胞凋亡,促进胰腺癌细胞的管形成和细胞迁移。此外,研究发现^[79],miR-106b通过癌症相关成纤维细胞(CAFs)来源

的外泌体传播,并通过直接靶向TP53INP1促进胰腺癌细胞对GEM的耐药性。因此, CAFs来源的外泌体miR-106b在导致胰腺癌GEM耐药性中发挥了重要作用,从而为胰腺癌细胞对GEM敏感提供了一个新的靶点^[79]。综上所述,外泌体MiRNAs是一种潜在的非侵入性生物标志物和新的抗癌治疗靶点。外泌体MiRNAs作为抗化疗耐药性靶点的价值值得进一步研究。

同时,大量研究表明外泌体LncRNA在胰腺癌发展过程及化疗耐药起着关键作用。例如:外泌体可以介导LncRNA SNHG11通过海绵覆盖miR-324-3p调控VEGFA的表达,促进胰腺癌细胞增殖、迁移和血管生成^[80]。也有研究表明^[81],外泌体LncRNA Sox2ot,作为一种竞争性内源性RNA(ceRNA),可以竞争性地结合miR-200家族上调Sox2,从而诱导EMT和干细胞样特征,促进PDAC的侵袭和转移。此外,有研究表明,在缺氧条件下,缺氧诱导的胰腺星形细胞(pancreatic stellate cells, PSCs)分泌的外泌体将lncRNA UCA1传递到胰腺癌细胞中,lncRNA UCA1通过招募EZH2调控SOCS3蛋白的甲基化,降低SOCS3的表达,促进胰腺癌的GEM耐药性^[82]。因此,外泌体介导的LncRNA可以在胰腺癌发生发展及化疗耐药中发挥重要作用。

并且,有研究发现,外泌体circRNA在胰腺癌发展过程中及化疗耐药中起着重要作用。例如:研究发现^[83]circ-PDE8A可以通过miR-338/MACC1/MET/AKT或ERK通路促进胰腺癌侵袭能力,并且circ-PDE8A可以通过肿瘤分泌的外泌体释放到血液循环中。因此,外泌体circ-PDE8A可能是PDAC诊断或进展的有用标志物。同时,也有研究发现,来自骨髓间充质干细胞(BM-MSCs)的外泌体circ-0030167通过海绵吸收miR-338-5p和靶向Wif1/Wnt8/β-catenin轴,从而抑制胰腺癌细胞的侵袭、迁移、增殖和干细胞性^[84]。同时,研究发现外泌体circZNF91可以作为一种载体,介导低氧和常氧肿瘤细胞之间的信号传输,可以竞争性地结合miR-23b-3p并上调去乙酰化酶Sirtuin1(SIRT1)导致受体胰腺癌细胞的糖酵解和对GEM化疗耐药性,并可能作为一个潜在的治疗靶点^[85]。

4 结论

综上所述,外泌体ncRNAs在胰腺癌化疗耐药中的作用已逐渐被揭示。外泌体作为天然载体,转移参与耐药的ncRNAs和蛋白质。靶向外泌体ncRNAs,结合传统化疗或靶向治疗,可能是治疗晚期胰腺癌耐药性的一个有希望的选择。本文综述了外泌体ncRNAs影响胰腺癌化疗耐药的多种机制,包括:通过调节不同的信号通路、影响EMT、细胞凋亡、自噬、细胞周期失调、靶向ABC药物转运体以及相互调节来发挥作用。例如,一些环状

RNA可以充当miRNA海绵. 外泌体ncRNAs能够在不同细胞之间传递, 使它们对化疗药物敏感或耐药. 本文还讨论了外泌体ncRNAs作为生物标志物的潜在治疗价值. 然而外泌体ncRNAs在化疗耐药中的潜在作用目前尚不清楚. 迄今为止, 将有希望的细胞水平的实验结果转化为临床试验仍然是最困难的挑战. 因此, 了解外泌体ncRNAs调节胰腺癌耐药的机制将有助于改善胰腺癌治疗. 因此, 在这个领域进行全面的临床研究是有必要的.

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