·综述·

DOI：10.12449/JCH240928

外泌体在肝衰竭中的调控机制及其在临床诊疗中的应用价值

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摘要：外泌体是介导细胞间物质与信息传递的重要媒介，源自肝细胞、肝干细胞或肝外间充质干细胞等的外泌体通过抑制免疫炎症反应、拮抗氧化应激与凋亡、诱导自噬等多种方式促进损伤肝细胞的修复与再生，发挥对肝衰竭的保护作用。本文综述外泌体在肝衰竭发病中的分子调控机制及其对肝衰竭发生发展与预后转归的影响，旨在评价其作为肝衰竭诊断标志物与治疗靶点的潜在价值。

关键词：肝功能衰竭；外泌体；间充质干细胞；肝细胞

基金项目：河北省自然科学基金（H2023206042）；河北省政府资助临床医学优秀人才项目（ZF2023082）

Regulatory mechanism of exosomes in liver failure and the application value in diagnosis and treatment

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Abstract: Exosomes are an important vehicle for mediating material transportation and information transmission between cells, and the exosomes derived from hepatocytes, liver stem cells or extrahepatic mesenchymal stem cells promote the recovery and regeneration of damaged hepatocytes by inhibiting immune inflammatory response, antagonizing against oxidative stress and apoptosis, and inducing autophagy, thereby exerting a protective effect against liver failure. This article reviews the molecular mechanism of exosomes in regulating the pathogenesis of liver failure and its effect on the development, progression, and prognosis of liver failure, in order to assess the potential value of exosomes as a diagnostic marker and a therapeutic target.

Key words: Liver Failure; Exosomes; Mesenchymal Stem Cells; Hepatocytes

Research funding: Natural Science Foundation of Hebei Province (H2023206042); Government Funding for Excellent Clinical Medicine Talent Program (ZF2023082)

肝衰竭是以肝细胞凋亡、坏死为特点的严重临床病理综合征。病情进展迅速、预后极差，短期病死率高达50%～90%。外泌体作为细胞间物质与信息传递的重要方式，负责将源细胞中特异性信息介质递送至靶细胞并调控其功能[1]，参与多种肝脏疾病的发病机制[2-6]，成为当前肝细胞再生医学领域研究的焦点。越来越多证据显示，源自肝细胞或肝外间充质干细胞（mesenchymal stem cell，MSC）的外泌体通过调节受损肝脏微环境抑制肝衰竭发生发展、促进损伤肝细胞的修复与再生。因此，外泌体及其成分有望成为肝衰竭诊断的血清生物标志物以及细胞再生治疗新策略[7]。本文将对外泌体调控肝衰竭发病的机制及其在肝衰竭诊断、治疗等方面应用价值的最新研究进展进行综述，探讨外泌体作为肝衰竭诊断标志物与治疗靶点的意义和前景。

1　外泌体生物发生与功能

外泌体是一类源自细胞内多囊泡体的直径为30～100 nm的圆盘或杯形纳米级细胞外囊泡，具有重要的物质与信息传递功能，以及独特的生物学特征。外泌体功能取决于源细胞类型和所携带的生物活性物质，包括蛋

白质、DNA分子（dsDNA、ssDNA、mtDNA等）、RNA分子［mRNA、miRNA（miR）、lncRNA等］和脂质等。这些源细胞成分借助外泌体的保护和输送，完成向靶细胞的物质交换与信号传递，参与调控靶细胞基因编码和蛋白质表达，还能靶向触发靶细胞内转导信号，改变细胞因子水平，发挥抑制炎症、抗凋亡、促进细胞修复与再生等功能[1]。最新研究[8]证实，肝功能障碍程度影响循环外泌体中miRNA谱的变化，在慢加急性肝衰竭（acute-on-chronic liver failure，ACLF）患者中鉴定出miR-320e、miR-374-5p、miR-202-3p和miR-1910-5p四种特征性异常的miR，尤其miR-320e升高与患者90天不良生存率相关。肝细胞、肝干细胞和MSC来源的外泌体均被证实参与抑制肝脏免疫炎症反应，促进肝细胞再生与损伤修复[9-10]。不仅如此，外泌体还被设计为药物递送载体，用于输送药物至目标区域，为药物靶向治疗提供了新的策略[11-12]。因此，评估外泌体数量、功能与其成分变化在肝衰竭生物诊断、靶向治疗和预后预测方面有重要意义。

2 外泌体在肝衰竭中的调控机制

2.1 *抑制免疫炎症损伤* 免疫炎症损伤介导肝细胞坏死是肝衰竭发生的重要机制。Zhang等[13]发现脐带间充质干细胞衍生外泌体（umbilical cord mesenchymal stem cell-derived exosome，UCMSC-Exo）通过抑制急性肝衰竭（acute liver failure，ALF）小鼠肝内巨噬细胞反面高尔基网结构解体，抑制Nod样受体热蛋白结构域相关蛋白3（Nod-like receptor pyrin domain-containing protein 3，NLRP3）炎症通路激活，缓解肝损伤程度。此作用与UCMSC中miR-299-3p表达上调并经外泌体转移至巨噬细胞发挥作用有关。不仅如此，UCMSC-Exo还可降低RAW 264.7巨噬细胞和ALF小鼠肝脏NLRP3、Caspase-3、IL-1β和IL-6表达，通过调节IL-6/STAT3信号通路抑制TNF-α、IL-1β和IL-6水平，减轻ALF小鼠肝损伤[14]。除UCMSC-Exo外，来源于脂肪间充质干细胞的外泌体（（adipose mesenchymal stem cell-derived exosome，AMSC-Exo）中富含的miR-17作用于硫氧还蛋白相互作用蛋白（thioredoxin interacting protein，TXNIP）抑制肝巨噬细胞NLRP3炎症小体活化，改善ALF小鼠肝组织损伤，证实外泌体传递的miR-17在介导AMSC-Exo改善ALF过程中也发挥重要作用[15]。Chen等[16]鉴定不同来源血清外泌体成分与功能发现，健康小鼠血清来源外泌体中miR-34c、miR-151-3p、miR-483-5p、miR-532-5p和miR-687水平均高于纤维化小鼠，证实外泌体在抑制肝细胞坏死、肝星状细胞活化、促炎因子与纤维化相关分子表达等方面发挥重要作用，参与改善肝组织炎症和纤维化。综上，外泌体通过抑制免疫炎症反应、修复受损细胞、阻止肝星状细胞活化等机制发挥肝脏保护效应并参与受损肝脏修复。

2.2 *拮抗氧化应激与细胞凋亡* ERK1/2、PI3K/AKT、谷胱甘肽过氧化物酶（glutathione peroxidase，GPX）信号通路等是调节肝细胞氧化应激、凋亡的重要信号通路，已被证实在多种原因诱导的肝损伤发病机制中发挥作用。Wu等[17]研究发现UCMSC-Exo通过抑制谷胱甘肽（glutathione，GSH）和超氧化物歧化酶（superoxide dismutase，SOD）清除、丙二醛（malondialdehyde，MDA）生成以及细胞色素P450过量产生等多条途径减少氧化应激相关肝细胞凋亡，从而改善肝功能，提高ALF小鼠存活率。机制在于UCMSC-Exo通过促进L0-2细胞中ERK1/2和IGF-1R/PI3K/AKT信号通路活化上调Bcl-2、Nrf-2蛋白和下调Bax蛋白表达，抑制氧化应激相关凋亡机制发挥肝细胞保护作用。SOD和GPX1是机体重要的内源性抗氧化酶。应用UCMSC-Exo干预经CCl_4作用的L0-2细胞后，GPX1活性呈剂量依赖性增加，伴随ROS和MDA水平降低，细胞存活率提高，说明UCMSC-Exo通过促进GPX1活性有效逆转氧化应激相关肝细胞凋亡[18]，GPX1也因此成为抗氧化损伤治疗中的一个新靶位。值得注意的是，UCMSC-Exo调控氧化应激发挥肝脏保护效应并不是通过调控基因表达，而是通过上调GPX等氧化应激相关分子活性、促进ERK1/2磷酸化等机制抑制氧化应激相关肝细胞凋亡。

2.3 *激活细胞自噬* 外泌体生成与自噬之间存在共同的分子机制与实质性交互通讯，由外泌体介导的自噬激活可以有效缓解肝细胞损伤，发挥对肝衰竭的保护作用。Zhao等[19]证实骨髓间充质干细胞来源的外泌体（bone marrow stromal cell-derived exosome，BMSC-Exo）被肝细胞吸收后增加自噬标记蛋白LC3和Beclin-1表达，促进自噬小体的形成。同时，肝细胞中促凋亡蛋白Bax和cleaved-aspase-3表达降低，抗凋亡蛋白Bcl-2上调。应用自噬抑制剂3MA干预后细胞凋亡明显增加，说明BMSC-Exo可能通过激活自噬抑制肝细胞凋亡机制发挥对肝细胞保护效应。MSC衍生外泌体中富集let-7a-5p，后者通过靶向MAP4K3减少转录因子EB磷酸化以激活自噬，阻断MAP4K3通路可削弱let-7a-5p对自噬的激活效应，证实MSC的肝脏保护作用可能部分得益于外泌体中let-7a-5p介导的自噬修复[20]。提取MSC诱导分化的类肝细胞中的外泌体（MSC-Heps-Exo），并将其注入缺血/再灌注（ischemia/reperfusion，I/R）肝损伤小鼠模型，结果显示MSC-Heps-Exo能通过增强自噬、抑制肝细胞凋亡，减

轻I/R相关肝损伤[21]。Zhang等[22]研究也证实，在12个候选miRNA中，miR-486、miR-25、miR-24、miR-20a、miR-466和miR-433-3p在I/R肝损伤中表达显著下调。UCMSC-Exo通过携带miR-20a抑制Beclin-1和Fas减轻I/R肝损伤中细胞凋亡和mTOR、P62、LC3Ⅱ等自噬相关基因的异常表达，证实外泌体通过调控自噬发挥对肝衰竭的保护效应。

3 外泌体作为肝衰竭诊断与预后评估血清生物标志物的潜在价值

外泌体携带的miRNA和蛋白等成分的特异性决定其有望成为预测肝衰竭诊断和进展转归的动态“指纹”，而且血液外泌体检测兼有肝活检的特异性和非侵入操作等优点，又被称为“液体活检”[4,23]。早在2012年，美国学者Bala等[24]就发现在不同肝损伤类型中外泌体富集的miR-122和miR-155变化规律不同，这种特征性改变有助于判定是否存在肝损伤以及诱发肝损伤的病因，因此提出外泌体所含miRNA作为多种生物反应的精细调节者，有望成为评估肝损伤程度与病因的生物标志物。为开发基于血浆外泌体的人类ACLF诊断生物标志物，Xu等[25]对HBV-ACLF患者血浆外泌体中非编码小RNA（small noncanonical RNA，sncRNA）进行测序鉴定，结果发现miR-23b-3p、miR-223-3p、miR-339-5p，tsRNA-20、tsRNA-46和rsRNA-249在HBV-ACLF患者血浆外泌体中存在特征性差异表达，基于此构建的Logistic预测模型对HBV-ACLF早期诊断的特异度和敏感度分别为71.67%和74.29%。Chen等[26]则利用RNA测序技术分析HBV-ACLF患者循环外泌体中差异表达的mRNA和非编码RNA水平，鉴定出的16 784个HBV-ACLF编码基因表达差异性分析结果显示，相比健康人群，HBV-ACLF存在25个上调基因和34个下调基因；而相比慢性乙型肝炎（CHB）患者，HBV-ACLF存在12个上调基因和12个下调基因，佐证了外泌体作为肝衰竭诊断血清生物标志物的潜在可能。

基于肝衰竭血清外泌体相关成分的差异表达，Chen等[26]进一步对ACLF患者上调基因NADPH氧化酶1（NADPH oxidase 1，NOX1）mRNA和lncRNA ZSCAN16-AS1进行qRT-PCR验证，发现NOX1与Alb、PLT负相关，与ALT、TBil和MELD正相关，而ZSCANA16-AS1与Alb负相关，与ALT正相关，提示外泌体的差异表达不仅与肝衰竭的发生有关，其表达定量还影响肝细胞损伤程度与患者预后转归。一项评估血清外泌体lncRNA核富含丰富转录本1（nuclear-enriched abundant transcript 1，NEAT1）预测HBV-ACLF患者90天死亡风险的临床队列研究证实，死亡组患者lncRNA NEAT1水平明显高于存活组，其受试者工作特征曲线下面积高于MELD评分，提示血清外泌体lncRNA NEAT1可能较MELD评分能更好的预测患者90天死亡风险[27]。同样，血清外泌体lncRNA生长阻滞特异性转录因子5（growth arrest-specific 5，GAS5）也被证实对HBV-ACLF患者90天死亡率预测价值优于MELD评分[28]。除RNA外，Jiao等[7]通过流式细胞学检测发现，HBV-ACLF患者较CHB和健康对照人群肝细胞来源外泌体存在116个差异蛋白，其中上调54个，下调62个，同时表达Alb、CD63和血管内皮生长因子的外泌体在存活组患者显著高于死亡组，其对ACLF患者预后评估的敏感度和特异度亦优于AFP等传统的肝再生和预后评估标志物。HEV相关ALF（HEV-ALF）患者也被证实血清外泌体源性氨甲酰磷酸合成酶1（carbamoyl phosphate synthetase 1，CPS1）水平与器官衰竭和预后正相关，预测30天死亡率效能显著高于Child-Pugh、KCH和MELD模型。因此，外泌体及其相关成分检测有望作为肝衰竭患者预后评估的重要生物标志物[29]。

4 外泌体在肝衰竭治疗中的应用价值

MSC来源的Exo不仅将参与调节肝细胞存活、氧化应激，免疫细胞活化、迁移和表型转化等的成分输送到靶细胞发挥MSC移植替代功能，还专门与靶细胞交换mRNA和miRNA，触发下游信号，有效缓解免疫炎症介导的肝损伤，因此成为肝衰竭治疗极具潜力的新策略[30-31]。UCMSC-Exo被证实通过抑制Caspase-3和Bcl-2相关X蛋白驱动的肝细胞凋亡发挥肝脏保护作用，其富集的miR-455-3p靶向PI3K信号，抑制巨噬细胞活化和IL-6、IL-17、G-CSF、IP-10等细胞因子产生，改善肝组织损伤和全身炎症反应[32]。来源于人经血源性干细胞的外泌体（MenSC-Exo）内富含细胞间黏附分子-1、IL-6和IL-8等免疫抑制分子与细胞因子，当外泌体及其内容物被同步传递至肝脏时，可通过阻止肝细胞凋亡缓解肝衰竭的严重程度[33]。Zhang等[34]系统检测了受MSC调控的肝细胞外泌体中miRNA表达，并分析差异表达基因的生物学功能和信号通路，结果发现BMSC-Exo及与BMSC共培养的肝细胞中miR-20a-5p表达上调，但肝细胞IL-8表达下调，提示外泌体miR-20a-5p/肝细胞IL-8轴在BMSC-Exo缓解ACLF治疗中可能发挥重要作用。除MSC外，Zheng等[35]通过共聚焦成像发现骨髓来源的树突状细胞分泌的外泌体与初始T淋巴细胞联合培养时，通过刺激初始T淋巴细胞PI3K/mTOR轴，调节辅助性T淋巴细胞和调节性T淋巴细胞分

化平衡，保护肝脏免受I/R损伤。肝细胞（尤其肝干细胞）来源的外泌体不仅呈剂量依赖方式抑制TNF-α、CCL-2和CXCL-10等炎症介质、趋化因子表达与释放[36]，还可直接向靶肝细胞传递中性神经酰胺酶和鞘氨醇激酶2，导致靶肝细胞内鞘氨醇-1-磷酸合成增加，诱导肝细胞增殖和肝脏再生，为外泌体治疗肝衰竭提供了新的证据支撑[37]。

5　小结与展望

过去十年，基础与临床研究均显示MSC以其多向分化、免疫调控和自我复制等优势作为理想的“种子”细胞在多种疾病治疗方面极具潜力，但MSC临床应用的伦理与安全性仍是再生医学领域关注的焦点。MSC可大量产生外泌体，且外泌体参与介导MSC作用的机制正被广泛关注和研究。作为介导细胞间物质与信息传递的重要媒介，外泌体通过抑制炎症反应、拮抗氧化应激与凋亡、诱导自噬等多种方式改变细胞或组织代谢，影响机体的损伤修复，逐渐被用于包括肝衰竭在内的多种疾病的诊断及治疗（图1）。MSC-Exo不仅具有与其来源MSC相近的效能，相比MSC尤其具有免疫反应小、安全性高、易于存储、运输和管理等独特优势，能够克服MSC治疗中的诸多风险和困难，逐渐成为替代MSC治疗的新策略。越来越多证据显示外泌体及其携带物质不仅可以用作肝衰竭早期预警、诊断和预后评估的理想生物标志物，还可以作为肝衰竭患者细胞再生治疗的理想策略[38]。未来，揭示外泌体最佳细胞来源（包括永生化细胞系构建[39]），内容物分选精准调控、定量释放、靶向传递，全面分析外泌体的生物学特性与功能等将成为其在肝衰竭治疗领域应用的重要前提。当然，如何分离足量高纯度外泌体、开发符合医疗规范标准的外泌体载体、明确最佳给药剂量和频次也是外泌体应用于临床治疗的重要保障。尽管如此，外泌体仍为肝衰竭等肝脏疾病分子诊断与治疗提供了新的策略和希望。

利益冲突声明：本文不存在任何利益冲突。

作者贡献声明：童话、罗越负责查阅文献，撰写文章；王亚东负责指导立题，文章修改与审校。

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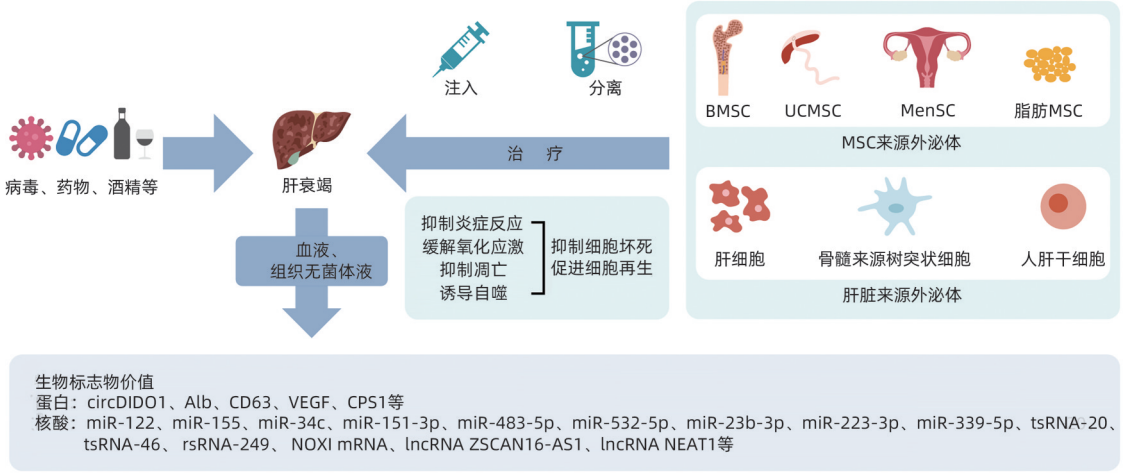

图1　外泌体的来源及其用于肝衰竭诊断与治疗的潜在价值

Figure 1　Origin of exosomes and the potential value to diagnosis and treatment of liver failure

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收稿日期：2023-12-28；**录用日期：**2024-02-08
本文编辑：刘晓红

引证本文： TONG H, LUO Y, WANG YD. Regulatory mechanism of exosomes in liver failure and the application value in diagnosis and treatment[J]. J Clin Hepatol, 2024, 40(9): 1897-1901.
童话，罗越，王亚东．外泌体在肝衰竭中的调控机制及其在临床诊疗中的应用价值[J]．临床肝胆病杂志，2024，40(9)：1897-1901.