

• 综述 •

免疫细胞来源外泌体在肝脏疾病中作用研究进展

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摘要:肝脏疾病是一组常见、病因复杂的消化系统疾病。外泌体是细胞释放的细胞外囊泡,通过其携带的蛋白质、核酸和脂质介导细胞间通信,调节受体细胞生物活性。免疫细胞来源外泌体在病毒性肝炎、肝纤维化、肝细胞癌等多种肝脏疾病的发生、发展中发挥重要作用,可能为肝脏疾病的治疗提供新途径,近年来已成为研究热点。本文就免疫细胞来源外泌体在肝脏疾病中作用的研究进展作一综述。

关键词:肝脏疾病;外泌体;免疫细胞;miRNA

引文格式:

周雯雯,戴胜兰.免疫细胞来源外泌体在肝脏疾病中作用研究进展[J].中华实用诊断与治疗杂志,2023,37(12):1294-1296.

ZHOU W W, DAI S L. Research progress of the role of immune cell-derived exosomes in liver diseases[J]. J Chin Pract Diagn Ther, 2023, 37(12): 1294-1296.

Research progress of the role of immune cell-derived exosomes in liver diseases

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Abstract: Liver diseases are a group of common digestive disorders with complex etiologies. Exosomes are extracellular membrane vesicles released by cells, they mediate intercellular communication by their proteins, nucleic acids and lipids, and regulate the biological activity of recipient cells. Immune cell-derived exosomes play an important role in the occurrence and development of various liver diseases as viral hepatitis, liver fibrosis and hepatocellular carcinoma. Being a potential new way for the treatment of liver diseases, immune cell-derived exosomes have become a research hotspot in recent years. This paper reviews the research progress on the role of immune cell-derived exosomes in liver diseases.

Keywords: liver diseases; exosome; immune cell; miRNA

肝脏疾病影响着全球数百万人,其中病毒性肝炎占主导地位,代谢性肝病发病率逐年上升,导致终末期肝病患者数量不断增加。终末期肝病的治疗方法有限,探讨肝脏疾病的发病机制、寻求新的治疗方法对改善患者预后有重要意义。外泌体是细胞分泌的细胞外囊泡,其携带蛋白质、核酸、脂质等,可介导细胞间通信^[1]。免疫细胞来源外泌体(immune cell-derived exosomes, IEXs)作为活跃的细胞间通信因子,参与病毒性肝炎、肝纤维化、肝细胞癌等多种肝脏疾病的发生、发展。本文就免疫细胞来源外泌体在肝脏疾病中作用的研究进展综述如下。

1 IEXs

1.1 自然杀伤(natural killer, NK)细胞来源外泌体 NK细胞是天然免疫效应细胞,在人体器官免疫监测、肿瘤或病原体清除中发挥重要作用。NK细胞来源外泌体表达典型的NK细胞表面受体(CD56、自然杀伤细胞2族成员D、自然细胞毒性受体等)和细胞毒性蛋白(穿孔素、Fas-L),其功能与亲代细胞相似。

NK细胞分泌的外泌体运载细胞毒性蛋白,通过直接杀伤途径破坏靶细胞引起细胞凋亡^[2]。

1.2 巨噬细胞来源外泌体 巨噬细胞可分为经典活化(M1型)巨噬细胞和替代活化(M2型)巨噬细胞^[3]。M1型巨噬细胞来源外泌体表面存在主要组织相容性复合体(major histocompatibility complex, MHC)和细胞间黏附分子,可刺激T淋巴细胞活化、促进肿瘤细胞凋亡,外泌体携带的miRNA和lncRNA在此过程中起协同作用^[3]。M2型巨噬细胞来源外泌体携带的miRNA和lncRNA可调控侵袭相关蛋白,促进肿瘤侵袭和转移^[4]。来自不同表型巨噬细胞外泌体携带的非编码RNA表达水平不同,可反映亲代细胞特性。

1.3 树突状细胞来源外泌体(dendritic cells-derived exosomes, DEXs) 树突状细胞是一种抗原提呈细胞,通过先天免疫功能启动适应性免疫应答。DEXs表面携带功能性抗原肽/MHC复合物、共刺激分子及与免疫细胞相互作用的其他表面成分。DEXs经MHC提呈抗原肽,通过直接或间接途径刺激T淋巴细胞诱导细胞毒性T淋巴细胞反应。树突状细胞和旁观T淋巴细胞间通过外泌体调节抗原特异性T淋巴细胞免疫反应相互作用,此过程与外泌体携带的miRNA密切相关^[5]。DEXs表面表达Fas-L,通过

MHCⅡ类依赖性途径抑制抗原特异性免疫应答,临床可用于治疗自身免疫性疾病^[4]。DEXs有自然杀伤细胞2族成员D-L、白细胞介素-15/白细胞介素-15受体α复合物等,可促使NK细胞活化^[6]。

1.4 T淋巴细胞来源外泌体 T淋巴细胞也可释放外泌体,靶向不同种类免疫细胞并调控其功能。T淋巴细胞来源外泌体携带T细胞受体/分化簇复合物,使其向具备被T细胞受体识别的MHC多肽的细胞传递信号;还含有促凋亡分子如穿孔素/颗粒酶、Fas-L和Apo2L,表明T淋巴细胞来源外泌体有抗原特异性和细胞毒性^[7-8]。含Fas-L的T淋巴细胞来源外泌体激活诱导多囊泡体与质膜融合,清除过度活化的T淋巴细胞,进而阻止潜在的自身免疫损伤^[9]。携带Fas-L的外泌体在清除肝细胞死亡碎片及抑制肝缺血再灌注相关炎症中发挥保护作用。

1.5 B淋巴细胞来源外泌体 B淋巴细胞来源外泌体也可携带抗原肽/MHCⅡ复合物、共刺激分子和黏附分子,有诱导MHCⅡ多肽限制性T淋巴细胞反应和抗原提呈能力^[10]。B淋巴细胞来源外泌体有酶活性,有助于抑制细胞毒性T淋巴细胞反应,起免疫调节作用。B淋巴细胞来源外泌体富含CD39和CD73,可抑制细胞毒性T淋巴细胞反应,减弱肿瘤化疗疗效^[11]。*Rab27a*基因缺失的B淋巴细胞外泌体产生被抑制,进而提高化疗的抗肿瘤效果^[11]。因此,特异性减少B淋巴细胞来源外泌体可作为肿瘤治疗的途径。但目前关于B淋巴细胞来源外泌体在肝脏疾病方面的临床研究较少。

2 IEXs在肝脏疾病中作用

2.1 IEXs在病毒性肝炎中作用

2.1.1 IEXs与乙型肝炎病毒 乙型肝炎病毒感染期间,巨噬细胞来源外泌体可利用甲型肝炎病毒受体进入肝细胞;随后外泌体利用网格蛋白介导的内吞作用和巨噬细胞吞噬作用有效传递α-干扰素,发挥抗乙型肝炎病毒活性^[12]。慢性乙型肝炎患者外周血中树突状细胞发育不成熟、数量减少和功能障碍,无法有效提呈乙型肝炎病毒相关抗原给T/B淋巴细胞,导致病毒清除障碍,可能是乙型肝炎慢性化的原因^[13]。DEXs可在体内触发和增加抗原特异性T淋巴细胞反应。过表达Tapasin的DEXs可促进T淋巴细胞增殖、Th1型细胞因子(γ-干扰素、白细胞介素-2)分泌,增强免疫应答^[14]。慢病毒负载泛素化乙型肝炎核心抗原的DEXs可在体外有效刺激T淋巴细胞增殖,并诱导激活抗原特异性细胞毒性T淋巴细胞免疫应答,为未来根治乙型肝炎提供了途径^[13]。

2.1.2 IEXs与丙型肝炎病毒 丙型肝炎病毒感染期间,巨噬细胞来源外泌体可为感染肝细胞提供免疫保护。Zhou等^[15]从Toll样受体3激活的巨噬细胞上清液中分离出外泌体,发现其可将I型干扰素和miR-29递送至感染肝细胞,以抑制丙型肝炎病毒感染。经干扰素刺激的巨噬细胞产生的外泌体可抑制丙型肝炎病毒复制并参与抗病毒免疫反应^[16]。

2.1.3 IEXs与丁型肝炎病毒 Yao等^[17]将慢病毒

负载泛素化丁型肝炎抗原的DEXs接种至丁型肝炎小鼠模型,发现抗原修饰的DEXs通过JAK/STAT信号通路激活适应性免疫应答,促进丁型肝炎病毒清除。2.2 IEXs在肝纤维化中的作用 细菌脂多糖作为炎症诱导因子,已被证实与肝纤维化有关。经脂多糖处理的巨噬细胞来源外泌体表达水平升高^[18]。脂多糖处理的巨噬细胞来源外泌体内miRNA(如miR-500)可激活肝星状细胞,促进肝纤维化^[18]。白细胞介素-6诱导巨噬细胞和中性粒细胞释放携带miR-223的外泌体,从而抑制肝纤维化^[19]。自噬是一种促进纤维化的机制,抑制自噬可减轻肝星状细胞活化和肝纤维化。NK细胞来源外泌体携带miR-223靶向自噬相关基因7而抑制自噬,从而抑制转化生长因子-β1诱导的肝星状细胞活化^[20]。NK细胞来源外泌体高表达miR-79抑制自噬,从而抑制肝星状细胞活化,减轻肝纤维化^[21]。表明调控NK细胞来源外泌体内miRNA可能通过调控自噬改善肝纤维化。

2.3 IEXs在肝细胞癌中的作用 巨噬细胞来源外泌体参与肿瘤发生、进展,但其在肝细胞癌中的调控机制尚不清晰。Li等^[22]研究发现,M2型巨噬细胞来源外泌体内miR-27a-3p通过下调硫氧还蛋白相互作用蛋白促进肝癌细胞增殖、迁移、侵袭和耐药性。Zhang等^[23]研究发现,重组信号序列结合蛋白J过表达的巨噬细胞来源外泌体携带的hsa_circ_0004658通过miR-499b-5p/JAM3通路抑制肿瘤进展。以上研究有助于开发新的肝细胞癌治疗药物靶点。

DEXs可通过直接和间接方式克服肿瘤诱导的免疫抑制。Lu等^[24]研究发现,富含甲胎蛋白的DEXs可触发有效的抗原特异性抗肿瘤免疫反应并重塑肝细胞癌小鼠肿瘤微环境,介导细胞毒性T淋巴细胞免疫杀伤作用,抑制肿瘤生长。经Alarmin修饰的肿瘤细胞来源外泌体可增强树突状细胞的免疫原性,促进长效记忆T淋巴细胞形成,抑制原发性肝细胞癌^[25]。Zhong等^[26]通过微波消融联合DEXs疫苗注射可明显抑制肝癌细胞生长并改善免疫微环境。

2.4 IEXs在非酒精性脂肪性肝病中作用 研究^[27]发现,肥胖和消瘦小鼠脂肪组织来源的巨噬细胞(adipose tissue macrophage, ATM)外泌体中存在20种丰度差异明显的miRNA;将肥胖小鼠ATM来源外泌体注射至消瘦小鼠可引起糖耐量减低和胰岛素抵抗;而将消瘦小鼠ATM来源外泌体注射至肥胖小鼠可改善胰岛素抵抗;表明ATM分泌的外泌体参与调控胰岛素抵抗。M2型巨噬细胞分泌的含miR-690外泌体注射至肥胖小鼠时其葡萄糖耐量和胰岛素抵抗改善^[28]。非酒精性脂肪性肝病是一种与胰岛素抵抗密切相关的代谢性应激性肝损伤,推测不同组织来源的巨噬细胞外泌体与非酒精性脂肪性肝病的发生、发展有关,但目前尚无相关研究。

2.5 IEXs在肝缺血再灌注损伤中作用 关于DEXs涉及肝缺血再灌注损伤的研究较少。Zheng等^[29]研究发现,骨髓来源DEXs通过热休克蛋白70调节PI70K/mTOR信号通路,维持Treg分化与Th17细胞间平衡,从而减轻肝缺血再灌注损伤。

3 结语

IEXs 参与病毒性肝炎、肝纤维化、肝细胞癌、非酒精性脂肪性肝病及肝缺血再灌注损伤的发生、发展。IEXs 具备生物相容性、低免疫原性、高负载能力及免疫调节等潜在的治疗特性。关于 IEXs 的研究多处于基础实验阶段, 尚未大量开展临床试验, IEXs 在肝脏疾病治疗中的效果和安全性尚不明确。随着 IEXs 在肝脏疾病中的作用逐渐被阐明, 可为肝脏疾病的治疗提供新思路和新途径。

利益冲突:所有作者声明无利益冲突。

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