巨噬细胞相关的外泌体在心血管疾病中的作用研究进展

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【摘要】外泌体是细胞分泌的具有双层磷脂膜结构的囊泡样物质,内部包含蛋白质、核酸等多种物质,介导炎症反应、免疫应答、物质交换及清除等多种机体生理过程,是细胞间通讯的关键介质。近年的研究表明,外泌体参与不同功能表型的巨噬细胞上游或下游水平调控,在心血管疾病发生发展过程中发挥着重要作用。现对巨噬细胞相关的外泌体在心血管疾病发生和发展中的作用及机制进行综述,为心血管疾病的诊断及治疗提供新的靶点和思路。

【关键词】外泌体;巨噬细胞;心血管疾病
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Role of Macrophage-related Exosomes in Cardiovascular Diseases

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【**Abstract**】Exosomes are one kind of extracellular vesicles with bilayer phospholipid membrane structure secreted by a variety of cells, which contain many constituents of a cell, including proteins, nucleic acids and other substance. Exosomes are the key mediators for regulating inter-cellular communication, mediating various physiological processes such as inflammatory response, immune response, substance exchange and clearance. Recent studies demonstrated that exosomes participate in upstream and downstream regulation of macrophages of different functional phenotypes, and play an important role in the development of cardiovascular diseases. This article reviews the biomedical function and mechanism of macrophage-related exosomes in the occurrence and development of cardiovascular diseases, providing new targets and ideas for future diagnosis and therapeutic strategies.

【**Key words**】Exosome; Macrophage; Cardiovascular disease

心血管疾病是对人类健康与生命构成威胁最大的一组疾病。巨噬细胞在不同微环境中的极化及功能转换,被认为是多种心血管疾病的发生和发展过程中的重要环节。外泌体是细胞衍生的囊泡,内部包含蛋白质、核酸等多种物质,参与细胞间通讯、物质转运和交换等生理过程。近年的研究表明,外泌体参与不同功能表型的巨噬细胞上游或下游水平调控,在心血管疾病相关的病理生理过程中发挥着重要作用。本文对巨噬细胞相关的外泌体在心血管疾病发生和发展中的作用及机制进行综述,为心血管疾病的诊断及治疗提供新的靶点和思路。

1 巨噬细胞与心血管疾病

巨噬细胞是机体固有免疫的重要组成细胞,在机体的炎症反应、免疫调节和损伤修复等过程中起着关键的作用。巨噬细胞活化后可极化为不同的功能亚型:M1 型巨噬细胞(经典活化型)和 M2 型巨噬细胞(选择性活化型)。M1 型巨噬细胞由细菌代谢产物或促炎细胞因子刺激产生,如脂多糖、Toll 样受体、肿瘤坏死因子和 γ 干扰素等,分泌大量促炎细胞因子[肿瘤坏死因子-α、白介素(IL)-1β 和 IL-6 等]、NO 及活性氧中间产物[1-2],引起 Th1 型免疫应答,发挥杀菌、吞噬和促进炎症反应等作用。M2 型巨噬细胞由 IL-4、IL-10 和 IL-13 等激活,通过分泌一系列抗炎细胞因子(IL-10、转化生长因子-β 和精氨酸酶-1 等)、生长因子和血管生成因子而发挥抑制炎症、组织重构和促血管生成等作用[3-5]。根据不同的诱导方式,M2 型巨噬细胞可进一步分为 3 个亚群:IL-4/IL-13 诱导的 M2a,引起Ⅱ型炎症;免疫复合物结合 Toll 样受体诱导的

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M2b,引起 Th2 型免疫应答;IL-10、转化生长因子-β 和糖皮质激素诱导的 M2c,引起免疫抑制、基质重构和组织修复[5]。

巨噬细胞在不同微环境中的极化及功能转换,在动脉粥样硬化(atherosclerosis,AS)、心肌梗死、高血压和肺动脉高压等心血管疾病的发生和发展过程中扮演着关键的角色,逐渐成为了新的治疗靶点[6-10]。外泌体参与了巨噬细胞的上游或下游水平调控,在炎症反应、内皮损伤、组织修复、血管重构和脂质代谢等过程中发挥着重要作用[11-15],一定程度上影响了疾病的发展与转归。

2 外泌体与心血管疾病

细胞外囊泡(extracellular vesicles,EVs)是由多种细胞分泌的、携带了不同种类分子货物(如核酸、蛋白质、脂质和代谢产物等)的膜结合细胞器[16],根据大小及产生机制不同,大致分为三个亚群,包括外泌体、微囊泡和凋亡小体。外泌体是一种直径为 40 ~ 160 nm、密度为 1.09 ~ 1.18 g/mL 的具有双层磷脂膜结构的囊泡样物质,由胞内多胞体与胞膜融合后分泌到细胞外环境,可持续存在于血液、乳汁、唾液、尿液和脑脊液中[16]。外泌体携带供体细胞分泌产生的多种信号分子,运输至受体细胞而实现体内细胞之间的信号沟通,参与机体废弃物质清除、免疫应答和血管生成等多个病理生理过程。由外泌体运载的蛋白质包括 MHC-Ⅰ、MHC-Ⅱ、脂质阀、RNA 结合蛋白、热休克蛋白和细胞因子等,核酸包括 mRNA、DNA、微小 RNA(miRNA)及其他非编码 RNA(circRNA,lncRNA 和 Y-RNA)等[16-18]。这些生物学活性分子不仅在细胞通讯中扮演着重要角色,还有可能成为疾病进展及疗效评估的靶向标志物[19]。

越来越多的研究表明,外泌体通过介导心脏不同细胞类型之间、心脏与外周组织/器官之间的细胞通讯,参与心血管疾病的发生发展过程[20]。Zheng 等[21]研究显示,过表达 Krüppel 样因子 5 的血管平滑肌细胞(vascular smooth muscle cell,VSMC)分泌的外泌体通过 miRNA-155 靶向抑制内皮细胞增殖、迁移及复内皮化,导致内皮细胞通透性增加,促进 AS 进展。Li 等[22]研究表明,心肌缺血患者冠状动脉血清外泌体通过 miRNA-939-iNOS-NO 信号通路促进内皮细胞增殖和血管生成。近年研究显示,球形结构干细胞(cardiosphere-derived cell,CDC)、间充质干细胞(mesenchymal stem cell,MSC)和心脏祖细胞(cardiac progenitor cell,CPC)等产生的外源性外泌体可发挥心脏保护及促进心脏组织修复的作用,是十分具有潜力的治疗方向[23-25]。在上述过程中,巨噬细胞接受外泌体传递的信号分子后极化为不同功能表型,或巨噬细胞在不同微环境中产生不同功能的外泌体作用于下游通路,调控心血管疾病相关病理生理机制的发生和发展。

3 巨噬细胞相关的外泌体与心血管疾病

3.1 内源性外泌体通过调节巨噬细胞极化对心血管疾病的作用

研究发现内源性外泌体通过调节巨噬细胞的极化及功能,从而调控炎症反应和脂质代谢等心血管疾病相关的病理生理机制。Chang 等[26]研究发现,在促粥样硬化微环境下,内皮细胞分泌富集 miR-92a 的外泌体,促进巨噬细胞表现为 M1 型巨噬细胞的功能,并促进巨噬细胞摄取低密度脂蛋白(low density lipoprotein,LDL);敲除 miR-92a 的内皮细胞可抑制共培养的巨噬细胞促炎因子的表达,并抑制巨噬细胞摄取 LDL;体外实验进一步证实,外泌体携带的 miR-92a 通过靶向调控巨噬细胞 Krüppel 样因子 4 而调节巨噬细胞的极化,影响巨噬细胞的脂质代谢功能。Pan 等[15]研究显示,成熟脂肪细胞分泌的外泌体携带的 miR-34a 表达升高与胰岛素抵抗及代谢性炎症呈正相关;外泌体运送 miR-34a 至巨噬细胞,通过抑制 Krüppel 样因子 4 表达而抑制 M2 型巨噬细胞极化,加剧肥胖诱导的全身炎症和代谢失调。

利用内源性外泌体传递 miRNA 调节巨噬细胞极化的作用特点,研究者将外泌体用作靶向调控巨噬细胞的基因治疗载体。供体细胞通过转染 miRNA 激动剂或抑制剂,使分泌的外泌体携带特异性 miRNA 与巨噬细胞结合,实现精准治疗的同时,还可避免免疫排斥。研究显示 miR-33 拮抗剂通过促进 M2 型巨噬细胞极化、促进斑块中 Foxp3 + 表达而发挥 AS 保护作用[27]。Stamatikos 等[28]通过构建特异性表达 miR-33a-5p 拮抗剂的腺病毒载体(HDAdXMoAntimiR33a5p)并转染入内皮细胞中,诱导内皮细胞分泌的外泌体携带高表达的 anti-miR-33a-5p。这些外泌体将 anti-miR-33a-5p 转运至共培养的巨噬细胞或 VSMC 中,可促进胆固醇外流,增强胆固醇逆转运而起到抗 AS 的作用。

3.2 外源性外泌体通过调节巨噬细胞极化对心血管疾病的作用

外源性外泌体通过调节巨噬细胞极化而促进心脏损伤修复和组织再生是干细胞治疗研究热点之一,目前的研究主要集中在 CDC、MSC、CPC、胚胎干细胞(embryonic stem cell,ESC)等产生的外泌体的调控作用及机制。外泌体通过携带干细胞分泌的非编码 RNA(miRNA 和 Y-RNA 等)调控巨噬细胞极化及功

能,被认为是干细胞来源外泌体发挥心脏保护作用的主要机制。

de Couto 等[29]研究发现,将 CDC 分泌的外泌体(CDC-Exo)经冠状动脉输入大鼠和猪的心肌缺血再灌注损伤模型中,可显著减少梗死区域面积;体外试验表明,CDC-Exo 促进骨髓来源巨噬细胞向 M2 型巨噬细胞极化,其富含的 miR-181b 通过抑制巨噬细胞的蛋白激酶 δ 表达而起到心脏保护作用。Cambier 等[30]研究发现,CDC-Exo 中富含的 Y-RNA 片段 EV-YF1 具有心脏保护作用,其主要机制可能是 EV-YF1 促进巨噬细胞极化为心脏保护功能的亚型,从而减少缺血再灌注损伤大鼠模型的梗死区域面积、减少心肌细胞凋亡比例。进一步研究显示[31],CDC-Exo 及其携带的 EV-YF1 可减轻血管紧张素Ⅱ诱导的高血压小鼠的心肌肥厚、心肌纤维化及心脏组织炎症反应;体外试验中,过表达 EV-YF1 的骨髓来源巨噬细胞通过分泌抑炎因子 IL-10 减轻血管紧张素Ⅱ对新生小鼠心室心肌细胞的作用,并相对抑制了血管紧张素Ⅱ刺激心脏成纤维细胞分泌促炎因子 IL-6 的水平,提示 CDC-Exo 携带的 EV-YF1 通过调节巨噬细胞极化及功能,间接调控心脏损伤过程中不同细胞发生的病理生理变化。

研究显示,MSC 来源的外泌体(MSC-Exo)通过调节巨噬极化及功能,有效地减轻炎症反应和心肌损伤。Xu 等[11]研究发现,低剂量脂多糖刺激的骨髓间充质干细胞分泌的外泌体(L-Exo)可显著抑制脂多糖依赖的核因子 κB(NF-κB)信号通路,同时部分激活 AKT1/AKT2 信号通路,促进小鼠缺血心肌中巨噬细胞由 M1 型向 M2 型极化,显著减少心肌梗死后心肌炎症反应及心肌细胞凋亡。Deng 等[12]研究发现,1-磷酸神经鞘氨醇/鞘氨醇激酶-1/1-磷酸神经鞘氨醇受体 1 信号通路是脂肪来源的间充质干细胞分泌的外泌体(ADSC-Exo)促进 M2 型巨噬细胞极化、发挥心脏保护作用的重要下游通路;ADSC-Exo 通过激活 1-磷酸神经鞘氨醇/鞘氨醇激酶-1/1-磷酸神经鞘氨醇受体 1 信号通路,抑制巨噬细胞中 NF-κB p65 及转化生长因子-β1 的表达,促进 M2 型细胞极化,从而抑制炎症反应及心肌纤维化。近期有研究表明 MSC-Exo 携带的 miRNA 是参与巨噬细胞介导的心脏损伤修复的重要信号分子。MSC-Exo 携带的 miR-182 等可通过靶向调控巨噬细胞上的 Toll 样受体 4,促进 M1 型巨噬细胞向 M2 型转化,减少心肌缺血再灌注损伤[32]。$ApoE^{-/-}$ AS 小鼠模型中,MSC-Exo 携带的 miR-let7 通过上调 miR-let7/HMGA2/NF-κB 通路,促进粥样斑块中 M2 型巨噬细胞极化,延缓 AS 进展[33]。

此外,CPC 来源的外泌体(CPC-Exo)和 ESC 来源的外泌体(ESC-Exo)在心血管疾病中对巨噬细胞极化的调节作用逐步被人们所认识。Harane 等[34]将 CPC-Exo 直接经心脏注射入小鼠心肌梗死模型,2 d 后可观察到心肌组织中 M1 型巨噬细胞极化及促炎因子表达水平下调,M2 型巨噬细胞极化及抑炎因子表达水平上调。Singla 等[35]研究发现,阿霉素诱导的心肌病小鼠模型中,外源性给予 ESC-Exo 可促进 M1 型巨噬细胞向 M2 型转化,显著抑制胞质空泡化、肌原纤维减少及心肌肥厚,有效改善心脏功能。基于此,研究者尝试利用静脉输注 MSC-Exo 的方式治疗扩张型心肌病[36],动物试验效果令人鼓舞,在心肌病治疗方面具有良好的发展前景。

3.3 巨噬细胞源性外泌体对心血管疾病的作用

巨噬细胞在不同微环境中表达特异的功能表型,通过外泌体调节细胞间通讯,在 AS 病理生理机制中扮演着重要的角色。巨噬细胞源性泡沫细胞分泌的外泌体通过与 VSMC 整合,调节 VSMC 肌动蛋白细胞骨架及局部黏附信号通路,激活 ERK 及 Akt 磷酸化进程,促进 VSMC 迁移和黏附[37]。进一步研究表明,从氧化型 LDL 培养的巨噬细胞中提取的外泌体携带的多种 miRNA(尤其是 miR-146a)可抑制巨噬细胞迁移、促进巨噬细胞停留在血管壁,加速 AS 发展[38]。此外,Zhu 等[39]研究发现,尼古丁诱导的巨噬细胞可显著增加 VSMC 增殖与迁移能力,导致 $ApoE^{-/-}$ AS 小鼠模型的粥样斑块面积明显增加;其机制被认为是巨噬细胞分泌的外泌体携带的 miR-21-3p 通过靶向抑制人第 10 号染色体缺失的磷酸酶及张力蛋白同源基因而促进 AS 进展。

研究者利用巨噬细胞表型及功能的可塑性,对巨噬细胞分泌的外泌体进行工程化改造,为延缓 AS 进展提供了新的思路。Wu 等[40]应用分子工程技术将 5-氨基酮戊酸己酯盐酸盐导入 M2 型巨噬细胞分泌的外泌体(M2-Exo),5-氨基酮戊酸己酯盐酸盐可诱导抗炎型 CO 及胆红素生成,进一步增强改造后的 M2-Exo 的抑炎作用;体外实验证实改造后的 M2-Exo 可显著增加泡沫细胞的胆固醇外流,减少泡沫细胞内氧化型 LDL 含量,有效地发挥抗 AS 的作用。

4 结语

外泌体作为细胞间通讯的重要介质,通过调节巨噬细胞上游或下游信号通路,介导心血管疾病发生发展的相关机制逐渐被探明。目前的研究主要着眼于抑炎型巨噬细胞(M2 型巨噬细胞)相关的外泌体,外泌体主要发挥心脏保护作用,因而成为心血管疾病的研究热点及新的治疗靶点,但巨噬细胞相关的外泌体在心血管领域的研究刚刚起步,目前研究均处于体外

试验或动物实验阶段,其靶向调控机制有待阐明。M2 型细胞相关的外泌体在肿瘤领域倾向于负面角色,肿瘤相关巨噬细胞主要表现类似 M2 型巨噬细胞的功能,相关的外泌体主要起促进肿瘤增殖侵袭作用。如何做到精准调控外泌体对靶细胞的作用,避免对其他细胞产生负面作用,是未来研究中亟待解决的问题。

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