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干细胞衍生外泌体：再生医学的治疗新策略

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摘　要

外泌体源自内吞膜，是纳米级的囊泡，含有核酸、蛋白质、脂质等生物分子，是原核生物和真核生物中细胞间通讯的有效载体，参与了多种病理生理过程的调节。当前研究发现，干细胞来源的外泌体具有促进细胞增殖、迁移、免疫调节等多种功能，可作为无细胞治疗剂应用于再生医学领域，包括急慢性肾损伤、缺血－再灌注损伤，肝脏、皮肤、角膜损伤等。本综述主要聚焦外泌体的促增殖作用，概述其未来可能的应用方向。

关键词

外泌体，增殖，干细胞，再生医学

Stem Cell-Derived Exosomes: A New Therapeutic Strategy in Regenerative Medicine

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Abstract

Exosomes (EXOs), derived from endocytic membranes, are nanoscale vesicles containing biomolecules such as nucleic acids, proteins and lipids. They work as effective carriers of intercellular

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communication in prokaryotic and eukaryotic organisms, and play significant roles in the regulation of both physiological and pathological processes. Current studies suggest that stem cell-derived exosomes can promote cell proliferation, migration and immune regulation. They can be utilized as cell-free therapeutic agents in the field of regenerative medicine, including acute/chronic renal injury, ischemia reperfusion injury, liver regeneration, skin regeneration, corneal regeneration. This review focuses on the ability of exosomes in promoting cell proliferation and summarizes their possible future application directions.

Keywords

Exosomes, Proliferation, Stem Cell, Regenerative Medicine

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1. 简介

细胞外囊泡(Extracellular Vesicles, EVs)是细胞以胞吞、胞吐等方式释放的膜性囊泡，其发现可以追溯到 1940 年代，最初由 Chargaff 和 West 于 1946 年报道[1]，广泛存在于原核生物、真核生物。这些 EV 中含有脂质、蛋白、RNA、DNA，可通过体液运输到远隔部位，发挥细胞间通讯的作用，影响靶细胞的代谢、增殖。根据 EVs 释放机制及大小可分为三类：1) 细胞凋亡过程中由膜起泡形成的大于 1000 nm 的凋亡小体；2) 由细胞出芽形成的 100~1000 nm 的微囊泡；3) 多泡体与质膜融合后释放的小于 150 nm 的外泌体[2]。

近年来，干细胞疗法因其多能性、自我更新和促进再生细胞因子分泌的能力而蓬勃发展[3]，多项研究已经提出干细胞的治疗作用主要是通过分泌可溶性因子以旁分泌的作用形式介导的，其中在干细胞的部分分泌组中，外泌体在旁分泌作用中起主要作用[4]。外泌体稳定、易于储存，可以通过过滤灭菌并作为现成产品生产，且无免疫排斥，具有归巢效应[5]，剂量易于控制，避免了干细胞的许多缺点，因此，事实上，间充质干细胞(mesenchymal stem cell, MSC)外泌体已被用作 MSCs 的替代品，用于各种疾病模型中的无细胞治疗新策略，包括神经、心血管、免疫、肾脏、肌肉骨骼、肝脏、呼吸、眼科、皮肤病以及癌症[6]-[12]。

2. 外泌体的生物学特性

(一) 生物发生和释放

外泌体的生物发生和释放机制如下：1) 吞噬体与质膜产生的早期内体经历一系列成熟步骤形成晚期内体，即多泡体(Multivesicular Bodies, MVB)，在此过程中，腔内囊泡(intraluminal vesicles, ILVs)积聚在其管腔，而货物分拣到 ILVs 是由内体分选复合物(endosomal sorting complex required for transport, ESCRT)依赖和 ESCRT 独立机制所需的内体分拣复合物介导的[13]；2) 内体衍生的 MVB 部分进入溶酶体被降解，部分与细胞膜融合；3) MVB 通过胞吐作用释放外泌体，进入细胞外环境[14]。此外，有研究表明，外泌体也可由质膜直接出芽释放或通过在细胞内质膜连接隔室(intracellular plasma membrane-connected compartments, IPMCs)出芽延迟释放[15]，在后者的情形中，这些 IPMCs 通过颈部与细胞外环境相连接，其中囊泡可以以脉冲形式储存和释放[16]。

MVB 的运输与细胞膜的融合受到 Rab 鸟苷三磷酸酶(GTPase)蛋白如 Rab27、Rab11、Rab2B、Rab5A、Rab9A、Rab27A、Rab27B 的调节[17]，同时与细胞骨架的运动相协调。最近的研究发现，肌动蛋白细胞骨架调节蛋白 cortactin 在调节外泌体分泌中起重要作用。研究发现 cortactin、Rab27a 和 coronin 1b 协同控制多泡晚期内体中皮质肌动蛋白对接位点的稳定性，从而促进外泌体分泌[18]。此外，液泡蛋白分选因子 4 (vacuolar protein sorting 4, Vps4)和转运所需的 ESCRT 与泛素化蛋白的结合可促进外泌体的释放，小 GTPase 的 Ral 家族也对外泌体的生物发生起到调节作用。紫外线辐射、氧自由基刺激、钙水平或胆固醇含量的变化都可能导致外泌体分泌的变化[15]。

(二) 组成

外泌体包含许多分子，包括蛋白质、脂质、代谢物、mRNA、线粒体 DNA、miRNA 和许多其他非编码 RNA 等。目前，已证实外泌体可从各种细胞中分泌，包括 B 细胞[19]、T 细胞[20]、树突细胞[21]、血小板[22]、施万细胞[23]、肿瘤细胞[24]、心肌细胞[25]、内皮细胞[26]、干细胞[27]等。外泌体的大小和货物是异质的，即使来自同一个细胞也是如此。但在不同的外泌体中，存在部分共同的货物。

外泌体中含有丰富的四跨膜蛋白，如 CD9、CD81、CD82、CD37 和 CD63 [28]，这些蛋白质对细胞靶向和黏附至关重要。此外，Rab GTPase、膜联蛋白和筏蛋白对膜融合很重要，热休克蛋白(heat shock protein, HSP) 70 和 HSP90 是分子伴侣，肿瘤易感基因 101 (tumor susceptibility gene, TSG101)蛋白参与 MVB 生物发生。外泌体还含有细胞因子、转录因子受体、生长因子受体和其他生物活性分子[13]。

外泌体中存在 microRNA、核糖体 RNA 和长链非编码 RNA，这些 mRNA 以主动的方式被分选到外泌体。一个被广泛接受的假设是，microRNA 可以通过外泌体直接递送至靶细胞，从而对其 mRNA 靶标进行功能调节。然而仍缺乏对细胞外囊泡介导的 miRNA 转移功能的直接证明[29]。据报道，EV 中富集了 3’UTR mRNA 片段，而不是完整的 mRNA 分子。由于 3'UTR 包含多个调节 miRNA 结合位点，这表明 EV 的 RNA 可能与细胞 RNA 竞争结合受体细胞中的 miRNA 或 RNA 结合蛋白，从而调节稳定性和翻译[30]。含有 mRNA 的 EV 也已被证明可以在各种压力条件下增强细胞存活能力和组织修复，研究发现人间充质干细胞衍生的 EV 含有 239 个 mRNA，其中大部分参与细胞分化、转录、细胞增殖和免疫调节[31]。同时，其 mRNA 含量受细胞生理状态和应激条件的调节，可能在维持组织稳态和同步细胞功能状态中发挥作用[32]。

(三) 作用机制

EV 主要通过调节细胞内的信号通路来促进细胞增殖和减少细胞凋亡，其治疗作用主要由治疗性蛋白质与 miRNA 介导。

1) 基于蛋白质的作用机制

Zhang 等人[33]研究发现，在大鼠皮肤烧伤模型中，EV 携带的 Wnt4 促进 β-catenin 核转位和活性以增强皮肤细胞的增殖和迁移。Katsuda 等人[34]发现，脂肪组织来源的间充质干细胞(adipose-derived mesenchymal stem cells, ADSC)衍生的 EV 含有酶活性中性溶酶(也称为 CD10)，是大脑中的限速淀粉样蛋白 β (Aβ)降解酶，共培养实验中，ADSC-EV 被转移到过表达淀粉样前体蛋白的 Neuro-2a 细胞中，从而降低了细胞外和细胞内的 Aβ 水平。另一项研究[35]也发现，骨髓(bone marrow, BM)-MSC 衍生的 EV 携带具有酶功能的 CD73 (也称为 ecto-5’-核苷酸酶)，可将 AMP 代谢为腺苷，通过一系列信号传导，表达 A2AR 的 1 型辅助 T (Th1)细胞会导致细胞凋亡。

2) 基于 RNA 的作用机制

miRNA 也被认为是介导 MSC-EV 治疗潜力的关键分子。MSC 衍生的外泌体 miRNA 不仅可以减少受损神经细胞的凋亡，还可以通过改善神经可塑性来增强大脑功能[36] [37]。不同的作者已经报道了不同的外泌体 miRNA，如 miR-22、miR-19a、miR-223 和 miR-132 发挥心脏保护作用，他们提出了各种相关

基因和信号通路作为机制解释[38]。

3. 基本功能

外泌体参与免疫调节、神经细胞之间的信号传递、生殖与发育、肿瘤、神经退行性疾病、感染等多种生理、病理过程[13]。其中，具有与增强细胞增殖有关的功能的外泌体大多来源于干细胞[39]，其功能主要由 miRNA 介导。因此，外泌体可以充当干细胞的替代介质。

下面主要讨论干细胞衍生外泌体在不同疾病中的促增殖与再生作用。

(一) 肾脏疾病

外泌体对于急性肾损伤(AKI)、肾移植的调理、慢性肾脏病(CKD)均有一定功效。

一些临床前研究表明，干细胞衍生的 EV 在不同的 AKI 模型中具有促进组织修复和减少炎症的功能，这在其他综述中已有总结。AKI 的标志是肾功能迅速下降，同时肾小管细胞丢失，导致血尿素氮(blood urea nitrogen, BUN)和血浆肌酐升高，2009 年，布鲁诺等人[31]证明，在甘油注射诱导的 AKI 模型中，BMMSC-EVs 加速受损肾小管细胞的恢复，促进细胞增殖并保护细胞免于凋亡，BM MSC-EV 携带特定的 mRNA，进而刺激受体受损细胞重新进入细胞周期。

对于肾移植患者，用间充质干细胞(MSC)和 MSC-EV 对肾脏进行预处理可限制由于缺血再灌注损伤和慢性同种异体移植肾病引起的组织损伤[40]。MSCs 和 MSC-EVs 在心脏死亡后器官捐献(Donation after Cardiac Death, DCD)的肾脏的大鼠模型中进行了测试。在器官冷灌注(4 小时)期间用 MSC-EV 处理的 DCD 肾脏显示出显着降低的肾损伤迹象[41]。

终末期 CKD 患者肾功能不全的主要原因为肾小球、肾小管纤维化。最近，从 BM MSCs 和肝脏 MSCs 分离的 EV 已被证明在已经建立的糖尿病肾病模型中可有效逆转肾纤维化[42]。MSC-EV 和 HLSC-EV 包含一系列能够下调促纤维化基因、恢复正常肾功能的抗纤维化 miRNA。

目前，Nassar 等人[10]发表了他们使用脐带组织 MSC 衍生的 EV 来改善 CKD 进展的 II/III 期临床试验结果，在该研究中，20 名被诊断患有 CKD (eGFR 15~60 mg/ml)超过 6 个月的患者接受了两剂(间隔 1 周) MSC-EV (100 μg/kg/剂)的治疗。1 年后患者表现出 eGFR 和尿白蛋白肌酐比值的改善，以及 BUN 和肌酐的显着降低，同时血浆中 TGF-β 和 IL-10 水平显着升高，而 TNF-α 持续显着降低。

(二) 肝脏疾病

MSCs 可改善肝硬化患者的疾病进展，而 MSC 来源的外泌体具有类似的效果。Li 等人[43]在昆明小鼠中使用四氯化碳(CCl_4)诱导的肝损伤模型。发现源自人脐带间充质干细胞的外泌体通过抑制肝细胞的上皮－间质转化和胶原蛋白的产生来改善肝纤维化。另外，研究[44]表明，来自接受免疫抑制治疗或经过修饰以表达免疫抑制细胞因子的小鼠的 DC 衍生外泌体促进耐受性免疫反应，mRNA-155 和 miRNA-125b 富集的外泌体促进 M1 的分化巨噬细胞超过 M2 巨噬细胞，从而改善小鼠的炎症反应。人羊膜上皮细胞衍生的外泌体显着减少肝纤维化期间巨噬细胞的数量和巨噬细胞浸润[45]。肝细胞来源的外泌体可以转移鞘氨醇激酶 2，在靶肝细胞中形成 1-磷酸鞘氨醇，从而引起细胞增殖和肝脏再生[46]。

迄今为止，只有少数几组研究了 MSC 外泌体在急性肝损伤中的治疗作用。一些研究表明，MSC-EVs 可以抑制促炎性巨噬细胞的增殖和活化，进而减少白细胞介素(interleukin, IL)-1β、IL-6、IL-18 和肿瘤坏死因子-α (tumor necrosis factor α, TNF-α)等细胞因子的分泌，从而显着改善急性肝衰竭(acute liver failure, ALF)，该机制可能与 MSC-EV 抑制 NOD 样受体热蛋白结构域相关蛋白 3 (NOD-like receptor thermal protein domain associated protein 3, NLRP3)通路有关[47] [48] [49]。Lou 等人[8]发现，脂肪组织来源的 MSCs 可以显着降低升高的血清丙氨酸氨基转移酶和天冬氨酸氨基转移酶水平，及血清促炎因子水平。因此，有理由相信，MSC 衍生的外泌体的移植可能是一种治疗各种类型急性肝损伤的新治疗方法。

(三) 心血管疾病

外泌体对心脏的有益作用包括抗凋亡、抗炎、抗心脏重塑、心脏再生[50]。外泌体中的 miR-22 和 miR-221 分别靶向甲基 CpG 结合蛋白 2 (Mecp2) [51]和 PUMA [52] (Bcl-2 蛋白家族的一个亚类)，降低其表达，从而发挥抗凋亡作用，改善心肌梗死区域的心肌细胞丢失。将 MSC 外泌体直接注射到心肌梗塞的边界区域可减少动物模型中的纤维化和炎症。对靶基因和通路的分析表明，PI3k-Akt-mTOR 通路可能是造成这些现象的主要机制，因为 miR-29、miR-24 表达上调，而 miR-34、miR-130，miR-378 表达[53]。miR-24 的上调限制了主动脉血管炎症。重要的是，miR-24 在小鼠心肌梗死模型中的体内表达可抑制心肌细胞凋亡、缩小梗死面积并减少心源性死亡[54]。心肌祖细胞(cardiac progenitor cell, CPC)来源的外泌体可促进内皮细胞迁移、血管内皮生长因子分泌[55]来诱导心脏再生并改善心脏功能。

外泌体还可促进新生血管的形成，这与内皮细胞和血管平滑肌细胞的增殖、迁移、分化有关[50]。同时，MSCs 衍生的外泌体最近已被证明可上调 wnt5a，通过稳定细胞连接处的纽蛋白以帮助细胞一起移动，在内皮细胞迁移中发挥重要作用，从而增强血管形成与迁移能力[56]。

(四) 皮肤再生

脂肪干细胞来源的外泌体(ADSCs-EXOs)富含 miRNA-125a 和 miRNA-31，可转移至血管内皮细胞以刺激增殖和促进血管生成[57] [58]。在皮肤愈合的增殖期，成纤维细胞增殖产生细胞外基质(extracellular matrix, ECM)，而上皮细胞增殖并向伤口中心迁移以促进伤口愈合。因此，皮肤细胞的增殖和再上皮化对皮肤再生很重要。ADSCs-EXO 被成纤维细胞内化，并以剂量依赖性方式刺激增殖、迁移和胶原合成[59]。最后，ADSCs-EXOs 可以通过调节成纤维细胞分化和基因表达来刺激细胞外基质的重建，从而促进伤口愈合和防止瘢痕增殖。王等人[60]发现 ADSCs-EXOs 阻止了成纤维细胞向肌成纤维细胞的分化，但增加了体内转化生长因子-β3 (transforming growth factor-β3, TGF-β3)与 TGF-β1 的比率，同时增加了皮肤真皮成纤维细胞中基质金属蛋白酶-3 (matrix metalloproteinase 3, MMP3)的表达，导致 MMP3 与基质金属蛋白酶-1 组织抑制剂(TIMP1)的比例很高，有利于细胞外基质(ECM)的重塑，减少疤痕。

(五) 角膜再生

角膜覆盖眼球总表面的前 1/6，表面为非角化复层鳞状上皮，神经支配丰富。角膜的其他细胞成分是角膜基质细胞和内皮细胞。角膜损伤触发修复途径，愈合过程中的瘢痕形成会损害角膜的透明度，并可能致盲[61]。

角膜内皮营养不良是导致视力丧失和角膜移植的原因之一，Buono 等人[62]研究发现，在角膜营养不良体外模型中，MSC-EV 能够诱导人角膜内皮细胞中大部分内质网应激相关基因的显着下调。同时，它们上调了 Akt 通路并限制了 caspase-3 的激活和细胞凋亡。Shang [63]等人发现，用脂肪间充质干细胞衍生的外泌体处理兔角膜基质细胞可使细胞增殖增加、细胞凋亡减少，同时细胞外基质沉积，证明外泌体可能为角膜再生的重要介质。

Han 等人[64]已经证明，上皮衍生的外泌体介导角膜上皮细胞、角膜基质细胞和血管内皮细胞之间的通讯。此外，角膜缘基质细胞衍生的外泌体有助于角膜缘上皮细胞(limbal epithelial cell, LEC)的增殖和伤口愈合[65]，人角膜间充质基质细胞(corneal mesenchymal stem cell, cMSC)外泌体也可加速角膜上皮伤口愈合。Shojaati 等人[66]的研究证明，在角膜清创小鼠模型中，来自角膜基质干细胞的 EV 可以减少炎症、瘢痕和纤维化，从而提高角膜透明度。

Samaeekia 等人的研究表明，角膜间充质干细胞衍生的外泌体可以增加角膜损伤的伤口愈合[67]在损伤的角膜中，外泌体上调抗血管生成因子的表达，如血小板反应蛋白 1 (thrombospondin 1, TSP-1)和抗炎细胞因子，包括 IL-10、TGF-β1 和 IL-6，同时下调促炎因子的表达，如 IL-2、干扰素-γ (interferon-γ, IFN-γ)、巨噬细胞炎症蛋白-1α 和血管内皮生长因子(vascular endothelial growth factor, VEGF) [68]。Leszczynska 等

人研究发现，角膜缘角质细胞衍生的外泌体激活 Akt 信号传导并促进角膜缘上皮细胞的伤口愈合[65]。目前，使用 EV 治疗眼部疾病仍处于临床前实验阶段。

(六) 神经系统疾病

外泌体对于神经系统疾病具有潜在的治疗效果。Xin [69]等人研究发现，富含 miR-133b 的星形胶质细胞来源的外泌体中的氧－葡萄糖消耗(OGD)介导中风后神经元的生长和伸长。星形胶质细胞来源的外泌体也转运 miR-190b 以防止 OGD 诱导的自噬和抑制神经元凋亡[70]。同时，MSC 外泌体中包含的 miR-17-92 簇可介导信号通路 PI3K/Akt/mTOR 的激活，导致脑卒中啮齿动物模型中的神经元重塑和神经发生[71]。

一项研究[72]表明，暴露于 β-淀粉样蛋白的星形胶质细胞衍生的外泌体中存在过量的阿尔兹海默症(AD)的生物标志物磷酸化 Tau 蛋白。另一项研究[73]表明，根据动物实验，释放到血清中的 β-淀粉样蛋白和 tau 最有可能来自大脑中星形胶质细胞衍生的外泌体。星形胶质细胞衍生的 EV 在 AD 患者中的强大作用也可以显示星形胶质细胞衍生的 EV 在脑靶向治疗中有较好的开发前景[74]。

4. 结语

外泌体通过运输核酸、蛋白质、脂质在细胞间通讯发挥重要的作用，参与多种生理、病理过程，其主要功能可能与由传递的 RNA 介导。尽管自外泌体发现以来，人们就对外泌体研究产生了浓厚的兴趣，然而，对于外泌体形成、蛋白质与 RNA 的分选、货物的释放等机制仍不清楚。但是，其促进细胞增殖与再生的治疗作用是毋庸置疑的。未来，外泌体将是心血管、肾脏、肝脏、神经、眼科等疾病的一种较有前景的治疗方式。

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