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内皮/内皮祖细胞来源的细胞外囊泡在再生医学中的应用*

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【摘要】 细胞外囊泡可由几乎所有细胞类型释放，是细胞间信号传递的重要介质。细胞外囊泡通过传递蛋白质、核酸等生物活性分子来调节靶细胞的功能与活性，在组织修复再生中具有重要意义。众多研究表明，内皮/内皮祖细胞来源的细胞外囊泡可促进细胞增殖分化、抑制细胞凋亡以及促进血管生成，在再生医学中发挥着越来越重要的作用。本综述介绍了内皮/内皮祖细胞来源的细胞外囊泡在组织再生修复中的研究进展，并探讨其在再生医学领域应用中所面临的挑战及未来发展方向。

【关键词】 内皮/内皮祖细胞 细胞外囊泡 再生医学

Application of Extracellular Vesicles Derived from Vascular Endothelial/Endothelial Progenitor Cells in Tissue Regeneration and Repair

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【**Abstract**】 Extracellular vesicles can be released by almost all types of cells and are important mediators of intercellular signal transmssion. Extracellular vesicles regulate the function and activity of recipient cells by delivering biologically active molecules such as proteins and nucleic acids, which is of great significance in tissue repair and regeneration. According to numerous studies, extracellular vesicles derived from endothelial/endothelial progenitor cells can induce cell proliferation and differentiation, inhibit cell apoptosis, and promote angiogenesis, playing an increasingly important role in regenerative medicine. We reported in this review the latest findings on applying extracellular vesicles derived from endothelial/endothelial progenitor cells in tissue regeneration and repair, and discussed the challenges and future development directions of their application in the field of regenerative medicine.

【**Key words**】 Endothelial/endothelial progenitor cells Extracellular vesicles Regenerative medicine

细胞外囊泡（extracellular vesicles, EVs）是由细胞分泌的直径为30～1 000 nm的脂质双分子层及其内容物组成的膜性结构[1-2]，根据其生物学发生方式和粒径大小，主要分为3种：外泌体、微囊泡（或微颗粒）和凋亡小体[3-4]。几乎所有细胞都分泌EVs，包括内皮/内皮祖细胞（endothelial cells/endothelial progenitor cells, ECs/EPCs）[5]、间充质干细胞[6]、神经细胞[7]、上皮细胞[8]和肌细胞[9]等。EVs在病理生理调节过程中起着至关重要的作用，REVENFELD等[10]发现细胞释放到体液循环的EVs显示出不同的蛋白质和RNA含量，因此可作为疾病诊断和预后的潜在标志物；TANG等[11]将EVs作为药物递送载体用于小鼠肿瘤模型，结果显示与单纯使用化疗药物相比，使用EVs装载的化疗药物能更有效地杀伤肿瘤细胞，并减少不良反应；随后的研究证明EVs可促进血管化，在心肌梗死、急性肾损伤、创伤性脑病等血管生成相关性疾病及组织再生中有着广阔的应用前景[12]。上述研究表明，EVs具有良好的生物相容性、可避免被巨噬细胞吞噬、可跨越生物屏障等优点，在多种疾病的诊断、治疗、预后、组织再生和修复等方面发挥着重要作用[4]。

近年来EVs已成为再生医学领域的研究热点，大量研究表明，作为一种重要的旁分泌形式，EVs可通过传递信号分子完成细胞间通讯，从而促进修复过程并有利于相关组织再生，有望成为潜在的治疗药物，具有广泛的应用前景[2-3, 13]。EVs在再生医学中的应用主要包括ECs/EPCs、间充质干细胞、脂肪组织等来源的EVs[14-17]，其中ECs/EPCs来源的EVs是目前学者们最关注的研究方向。血管化是决定组织工程和再生医学成败的关键问题[18]。以往学者们主要采用ECs/EPCs与种子细胞共培养等方法来促进血管化[19-20]，而细胞疗法存在以下问题：移植后细胞存活率较低；有发生肿瘤或恶变的风险；可能导致移植免疫排斥反应等[21]。随着EVs研究的不断深入，学者们发现ECs/EPCs来源的EVs可发挥与ECs/EPCs相似的生物学效应[22-30]，且EVs治疗有以下突出优势：其囊泡结构可保护其内容物在传递过程中免受降解；与细胞治疗相比，去除了引起机体免疫排斥反应的抗原物质；非自我复制，降低了医源性肿瘤形成的风险；可跨越生物屏障，治疗难治性疾

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病,如血脑屏障等;可与多种生物材料联合应用以利于其更好地发挥修复再生作用[4, 21, 31]。因此,ECs/EPCs来源的EVs在再生医学领域具有广阔的临床应用前景。本文就近年来ECs/EPCs来源的EVs在组织再生修复中的研究进展以及在再生医学领域中应用所面临的挑战进行综述,并对未来发展方向提出展望。

1 ECs/EPCs来源的EVs与组织修复再生

ECs/EPCs来源的EVs可以分为内皮祖细胞来源细胞外囊泡(EPC-EVs)和内皮细胞来源细胞外囊泡(EC-EVs),二者来源不同,但具有相似的促血管化效应。EPC-EVs具有与EPCs相似的生物学特性,可表达EPCs的特异性标志物(如CD31、CD34和血管内皮生长因子受体2等),以及富集EPCs中与血管生成相关mRNAs和miRNAs[22-29]。EC-EVs含有细胞膜蛋白和参与细胞信号转导的细胞内成分,与ECs具有相似特征[30]。

1.1 骨再生与修复

ECs/EPCs来源的EVs在骨组织的修复和再生领域中已取得了重要的研究进展。有大量研究表明,ECs/EPCs来源的EVs通过促进成骨相关细胞的增殖和迁移,减少细胞凋亡,或者增强细胞功能,诱导细胞成骨向分化,进而促使骨组织的修复重建。

QIN等[32]采用梯度离心法和超离法分离EPC-EVs,并观察到EPC-EVs在体外通过抑制成骨基因的表达和促进成骨细胞增殖来调控骨髓间充质干细胞的成骨分化。CHEN等[33]发现EPC-EVs可以通过Erk1/2-Bcl-2通路促进MC3T3-E1细胞的增殖和迁移,减少细胞凋亡,促进骨组织再生。在牵张成骨(DO)过程中,EPC-EVs增强内皮细胞的增殖、迁移和血管生成能力,可加速DO过程中的骨组织再生,缩短DO治疗时间[34]。骨修复的起始还涉及破骨介导的适当骨吸收。EPC-EVs可以促进破骨细胞前体细胞的募集和分化,从而增强体内骨组织的修复[35]。

ECs/EPCs来源的EVs很大程度上是通过miRNAs调控骨组织的修复与再生。张根生等[36]将miR-27a加载于EC-EVs,实验结果显示过表达miR-27a的EC-EVs可以促进骨组织再生,并可在一定程度上缓解糖皮质激素诱导的股骨头坏死。miR-126可进一步增强EPC-EVs对MC3T3-E1细胞的作用。因此,EPC-EVs和miR-126的联合应用可能通过调控成骨细胞,从而有利于骨再生和骨折愈合[33]。

1.2 神经再生与修复

近年来,ECs/EPCs来源的EVs在神经再生与修复领域同样取得了丰富的研究成果。EVs可以穿过血脑屏障,而且具有低免疫原性、先天稳定性和高传递效率等特点,在治疗脑缺血损伤中具有广阔的应用前景[37-40]。此外,颅内立体定向注射可减少外周循环中EVs的损失,是EVs产生中枢神经系统修复功能的一种重要途径[41]。

ZHANG等[42]首先证明了EC-EVs可被远端轴突迅速内吞并达到达胞体,通过改变受体神经元中的miRNAs及其靶蛋白谱来促进轴突的生长。此外,有研究表明,在2型糖尿病性脑卒中小鼠中,EC-EVs可增加缺血脑的轴突密度、髓鞘密度、血管密度和动脉直径,并诱导缺血边界区M2巨噬细胞极化,有助于改善神经功能。在此过程中,EC-EVs的神经修复作用可能主要是通过miR-126途径介导的[43]。

ECs/EPCs来源的EVs主要通过促进细胞增殖和迁移,减少细胞凋亡,从而发挥神经修复再生作用。已有研究表明,EC-EVs能够激活神经祖细胞的增殖和迁移,抑制细胞凋亡,促进神经再生。但目前的研究还无法确定EC-EVs发挥此作用的具体分子机制[41]。EC-EVs可以促进神经干细胞增殖,抑制细胞凋亡[44]。与EC-EVs共培养时,神经干细胞可保持其多向分化潜能,干性相关基因表达上调[45]。EC-EVs还可通过促进神经细胞增殖、迁移和侵袭,减少细胞凋亡,直接保护神经细胞免受缺血再灌注损伤[46]。ECs经缺氧/复氧处理后,其外泌体中miRNA表达谱发生明显变化,其中miR-21-3p变化最为显著。通过抑制miR-21-3p,EC-EVs可减轻缺氧/复氧诱导的神经细胞凋亡[47]。EC-EVs可以促进少突胶质前体细胞(oligodendrocyte precursor cells, OPCs)的存活、增殖和迁移[48-49]。EC-EVs表面存在大量的纤维连接蛋白,通过与OPCs上的硫酸乙酰肝素蛋白聚糖结合从而介导OPCs内吞EVs,这一过程不依赖于整合素信号通路[49]。

1.3 皮肤再生与修复

大量研究表明,ECs/EPCs在皮肤创面修复中有着极其重要的意义[50],而ECs/EPCs来源的EVs作为旁分泌途径的重要介质,广泛应用于皮肤再生与伤口愈合中。

与生物材料的联合应用,往往有利于EVs更好地发挥组织再生与修复作用。ZHAO等[51]将甲基丙烯酰明胶水凝胶作为伤口敷料与EC-EVs结合,并将其应用于全层皮肤伤口。结果发现,该复合支架能够实现外泌体缓释,加速伤口愈合,为修复皮肤创面缺损和皮肤再生提供了一种新的思路。

细胞间信号交流是ECs/EPCs来源的EVs发挥作用的重要途径。EPC-EVs可增强内皮细胞的血管生成反应,最终促进皮肤创伤修复和再生,在这一过程中,Erk1/2信号通路可能发挥着关键作用[52]。EC-EVs还可促进角质形

成细胞和成纤维细胞的增殖与迁移活性。除了作为细胞间通讯的重要媒介外, ECs/EPCs来源的EVs还含有多种能够与细胞外基质(extracellular matrix, ECM)相互作用的成分。有文献指出, 赖氨酸氧化酶家族成员赖氨酸氧化酶类2存在于EC-EVs膜的外侧, 可与ECM直接接触并相互作用。在低氧刺激下, 酶活性增加, 并催化ECM中的胶原交联。这说明了EC-EVs处于低氧条件下时对局部ECM重构和伤口愈合有着重要作用[53]。

1.4　肾损伤修复

ECs/EPCs来源的EVs在肾损伤修复领域中的应用也已取得初步的研究进展。已有研究表明, EPC可以通过旁分泌机制逆转急性肾损伤, 而EVs是EPCs介导ECs免受凋亡的主要介质, 使用人类EPCs或EPC-EVs以保护急性肾损伤中的缺血性内皮损伤, 或许能成为一种有效的治疗策略[54-55]。

ECs/EPCs来源的EVs在缺血性急性肾损伤中的修复作用主要是通过miRNAs介导的。BITZER等的研究表明, EPC-EVs含有内皮保护性miRNAs, 如miR-126。在大鼠急性肾缺血再灌注过程中, 输送EPC-EVs可改善肾功能障碍。静脉注射后, EPC-EVs通过激活内皮细胞中的血管生成程序, 以及增强肾小管细胞增殖、减少细胞凋亡和白细胞浸润, 在功能和形态上对急性肾损伤具有保护作用[27]。在脂多糖诱导的脓毒血症性急性肾损伤小鼠模型中, EPCs分泌的携带miR-93-5p的EVs可以作用于人肾皮质近曲小管上皮细胞(HK2细胞)。在HK2细胞中, EVs通过靶向赖氨酸特异性去甲基化酶6B以下调TNF-α水平, 从而减少血管渗漏、器官损伤、炎症和细胞凋亡。这提示EPCs分泌的携带miR-93-5p的EVs可作为脓毒血症性急性肾损伤的一个新型治疗工具。VINAS等[56-57]的研究表明, EPC-EVs通过转移microRNA-(miR)-486-5p, 选择性地靶向作用于缺血后的肾脏。miR-486-5p可转移至ECs, 调控磷酸酶张力蛋白同源物/蛋白激酶B信号通路, 通过降低磷酸酶张力蛋白同源物水平, 阻断细胞凋亡, 并刺激蛋白激酶B磷酸化, 以发挥保护作用。进一步研究表明, EVs的靶向作用可能涉及趋化因子受体4与内皮细胞基质细胞衍生因子SDF-1α的相互作用。

1.5　心肌损伤修复

近年来, 已有研究者将ECs/EPCs来源的EVs应用于缺血后心肌损伤修复中, 并在与生物材料联合应用过程中, 取得了良好的治疗效果。

CHUNG等[58]将EPC-EVs与可注射剪切稀化水凝胶联合应用, 发现其可以改善血流动力学、增加血管生成以及保存心室构型。然而, 在体内实际应用过程中, ECs/EPCs来源的EVs治疗效果会受到多种因素影响。血管疾病通常伴随着缺血、缺氧以及强烈的炎症反应, 这可能会极大地损害外泌体的心脏修复功能。心肌梗死后全身炎症状态下, IL-10缺乏会上调外泌体中整合素链接激酶(ILK)并激活ILK介导的NFκB通路, 导致EPC-EVs在促进细胞存活、迁移和血管生成等方面功能发生障碍[59]。此外, 不同给药方式也对ECs/EPCs来源的EVs在心肌梗死治疗效果上产生影响。例如, ANGULSKI等[60]的研究表明, 全身应用EPC-EVs对心肌梗死后的心功能恢复并未产生实质性的有益作用, 这可能是因为EVs倾向于在受损肾脏中特异性分布而对心脏的定位能力较差。这表明在全身应用途径中, 如何让EVs特异性定位于靶组织和靶器官, 可能成为EVs在再生医学领域中的研究热点。

2　挑战与展望

EVs治疗相较于一些传统治疗方法具有诸多优势: 良好的生物相容性和生物稳定性; 降低医源性肿瘤形成的风险; 可跨越生物屏障, 治疗难治性疾病; 可与多种生物材料联合应用。然而, EVs的应用仍有不少问题亟待解决: 在全身应用途径中, 如何让EVs特异性定位于靶组织和靶器官; 不同组织器官的修复再生涉及复杂的分子机制, EVs中是何种分子参与此过程以及如何发挥作用尚未得到确切解释。随着精准医学概念的提出, 向缺血部位和损伤部位靶向递送EVs可能会成为未来再生医学的重要发展方向。

综上所述, ECs/EPCs来源的EVs在促进细胞增殖分化、抑制细胞凋亡以及促进血管生成等方面具有调控功能, 在骨再生与修复、神经再生与修复、皮肤再生与修复、肾损伤修复及心肌损伤修复等方面能发挥重要作用, 在再生医学领域具有广阔的临床应用前景。

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利益冲突　所有作者均声明不存在利益冲突

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