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评 述

间充质干细胞衍生的外泌体在女性生殖功能障碍中的研究进展

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摘要 不孕症是一种影响广泛的生殖健康问题. 尽管传统辅助生殖技术(assisted reproductive technology, ART)已被广泛应用, 但仍有许多不孕症病例无法获得有效治疗效果. 因此, 近年来涌现出许多针对不孕症的新型疗法. 间充质干细胞(mesenchymal stem cell, MSC)衍生的外泌体(mesenchymal stem cell-exosomes, MSC-EXOs)因其旁分泌活性, 在改善不孕症治疗和妊娠结局方面显示出很大潜力. 本文综述了MSC及MSC-EXOs在不同类型女性生殖疾病中的应用, 重点探讨其在治疗女性不孕症中的重要作用及机制.

关键词 间充质干细胞, 外泌体, 生殖, 不孕, 子宫内膜

不孕不育已成为全球生殖健康领域的重大问题, 严重影响育龄患者的生活质量与心理健康[1]. 世界卫生组织数据显示, 全球有约4800万对育龄夫妇正面临不孕不育的困扰. 该病症可细分为原发性与继发性不孕症, 前者指从未受孕, 后者为成功受孕后再次遭遇受孕困难的情况[2]. 女性生殖系统疾病是导致不孕症的主因, 包括卵巢功能不全(premature ovarian insufficiency, POI)、Asherman综合征和多囊卵巢综合征(polycystic ovary syndrome, PCOS)等. 传统辅助生殖技术(assisted reproductive technology, ART)如外科手术、药物治疗、宫腔内人工授精(intrauterine insemination, IUI)和体外受精(*in vitro* fertilization, IVF)虽为常用手段[3], 但伴随的风险如异位妊娠、高发病率和死亡率相关的并发症不容忽视[4]. 科研领域正积极探索更高效且低风险的治疗方法[5]. 近年来, 间充质干细胞(mesenchymal stem cell, MSC)因其多能性及自我更新能力备受关注[6]. MSC可分化为多种细胞类型, 并通过调控关键分子与生物途径对女性生殖障碍产生积极影响. 然而, 其治疗机制可能更多依赖于旁分泌作用而非直接分化[7]. 在干细胞治疗应用中, 需全面考虑移植排斥、运输储存及安全问题. 外泌体(exosomes, EXOs)作为30~160 nm的细胞外囊泡, 可高效转运多种

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生物分子，并在细胞间通讯、生理调节及行为重编程中发挥核心作用. 间充质干细胞衍生的外泌体(mesenchymal stem cell-exosomes, MSC-EXOs)因其在再生医学中的潜力而受重视，已被证明可通过其再生能力改善卵巢和子宫环境，逆转女性不孕症，有望为未来临床治疗带来新的突破[8]. 外泌体是微小半透性膜囊泡，直径介于30~150 nm，密度约为1.13~1.19 g/mL，具有磷脂双分子层结构, 是细胞间通讯的关键介质. 它们通过精细的细胞内吞途径形成并释放，携带丰富的生物活性分子，包括细胞质蛋白、脂质、DNA及多种类型的RNA, 这些分子在正常和病理条件下均有分泌.

1 外泌体概述

外泌体属磷脂双分子层细胞分泌囊泡，直径30~150 nm、密度约1.13~1.19 g/mL. 其生成过程涉及: (ⅰ) 质膜自内吞囊泡渗透, (ⅱ) 由内体膜出芽形成多泡体(multivesicular bodies, MVBs), (ⅲ) MVBs与质膜融合以释放形成外泌体[9,10]. 外泌体结构稳定易获取，且具有独特的可靶向性，其膜表面的受体和黏附分子能够与特定细胞或组织发生特异性相互作用，为实现疾病的靶向治疗提供可能[11]. 在妇科疾病治疗中，不同干细胞来源的外泌体(如骨髓间充质干细胞外泌体、人羊膜间充质干细胞外泌体等)具有不同的功能和应用潜力. 其可通过传递生物活性物质, 如蛋白质和微小RNA (microRNA, miRNA)等, 调控细胞的生物学过程，包括增殖、分化和凋亡等. 外泌体广泛存在于血液、尿液、唾液、羊水、支气管肺泡液和母乳等各种细胞体液中，携带细胞质蛋白、脂质、DNA、不同类型RNA和代谢物等多种生物活性分子，跟随外泌体分泌通过循环系统到达其他细胞和组织，从而参与细胞通讯的远程调控[12]. 外泌体中共有9769种蛋白质，主要包括内吞体运输必需分选复合物(endosomal sorting complex required for transport, ESCRT)蛋白与四跨膜蛋白. ESCRT蛋白是由大约30种蛋白质组成的蛋白质家族，可参与外泌体的形成和分泌，而四跨膜蛋白(如CD63，CD9和CD81)可参与外泌体生物发生、分离和纯化. 外泌体内还包含多种磷脂，外泌体的释放与其内所含胆固醇的程度有关，富含胆固醇的外泌体可被分泌释放，而胆固醇少或无胆固醇的外泌体则被引导至溶酶体消化. 外泌体还包含多种核酸物质，其可通过直接作用于细胞来进行细胞间通信和信息传递[13]. 外泌体还参与机体代谢调节、细胞增殖和凋亡、血管生成、免疫调节、肿瘤发生、组织修复等多种生物学过程. 近些年发现外泌体在女性生殖系统中亦发挥着重要调控作用[14].

2 外泌体对导致妊娠障碍因素的治疗干预

2.1 多囊卵巢综合征(PCOS)

约40%的不孕女性患有排卵障碍, 其中PCOS是引发排卵功能下降的最常见病因，其特征包括不孕、慢性炎症及高雄激素血症[15,16].

近年来，MSC及其衍生外泌体因其在再生医学中的应用潜力而成为治疗PCOS的新兴策略. 研究表明, MSC通过旁分泌机制能够显著增强和恢复卵巢功能，尤其是通过调节Ras相关蛋白1 (Ras-proximate-1, RAP1)/核因子κB (nuclear factor kappa-B, NF-κB)信号通路(RAP1/NF-κB)，影响免疫及炎症反应，从而对卵巢健康产生积极影响. MSC能够下调促炎细胞因子, 如肿瘤坏死因子-α (TNF-α)、白细胞介素-1β (IL-1β)和干扰素-γ (IFN-γ), 同时降低与纤维化相关的基因(如结缔组织生长因子, CTGF)的表达, 促进卵巢功能的恢复[17].

另外，脂肪组织来源的间充质干细胞衍生的外泌体(adipose-derived mesenchymal stem cell-exosomes, AMSC-EXOs)也发挥独特的作用. 研究表明, 其可通过微小RNA-21-5p (miR-21-5p)激活胰岛素受体底物1 (insulin receptor substrate 1)/Akt通路(IRS1/Akt通路), 改善大鼠(rat; *Rattus norregicus*)模型中的代谢紊乱[18], 同时抑制B细胞易位基因2 (B-cell translocation gene 2, BTG 2)的表达，改变肝细胞葡萄糖稳态，从而改善PCOS相关的代谢紊乱和不孕症. 此外，PCOS患者卵丘细胞增殖与凋亡受外泌体miR-323-3p调控，其通过靶向抑制PDCD4表达改善细胞存活状态，缓解PCOS症状[19].

MSC及MSC-EXOs为PCOS的治疗提供一种新的生物制药策略，研究者期待更多针对其疗效的临床应用进展和报道.

2.2 早发型卵巢功能不全与卵巢早衰

早发型卵巢功能不全(premature ovarian insuffi-

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ciency, POI), 又称卵巢功能低下, 指女性在40岁前出现的卵巢功能衰退, 若持续恶化可导致卵巢早衰(premature ovarian failure, POF)[20], 均属复杂内分泌疾病, 导致约1%的女性不孕[21]. 症状包括闭经、雌激素缺乏及促性腺激素提升. 现行主流治疗为激素替代疗法(hormone replacement therapy, HRT), 但仅缓解症状, 无法根治, 且长期使用可能引发心脑血管疾病[22]. 因此, 急需创新高效治法. 研究显示, 干细胞可能通过旁分泌机制, 利用周边细胞分泌的生长因子、细胞因子等生物活性分子, 改善卵巢损伤.

MSC-EXOs可通过靶细胞内化等方式实现细胞间的信息交流, 进而触发修复与再生过程以复原细胞功能[23]. 在动物模型研究中, 外泌体携带高度选择性的miRNA (如miR-126-3p, miR-22-3p, miR-21, miR-29a等)与环状RNA (circularRNA, circRNA)生物活性因子, 定向高效调控卵巢功能[24~28]. 通过促进血管生成、减轻卵巢颗粒细胞(ovarian granulosa cell, OGCs)凋亡、恢复性激素水平、促进卵泡发育等途径提升卵巢性能[29,30].

在分子层面, 外泌体携带的活性分子可精确调控Notch, ATF4-ATF3-CHOP, Wnt/β-catenin等多条关键信号通路[25,26,28], 对卵巢细胞的增殖、分化、激素合成与分泌, 以及应激响应至关重要. 外泌体的介入促使关联通路高效协同, 推动卵巢组织的再生与功能重塑[31]. 此外, MSC和外泌体治疗均显著提升POI的SD大鼠(*Rattus norvegicus* Sprague-Dawley)的妊娠率及生育能力, 且外泌体治疗在安全性与生物相容性上表现更优[32].

尽管其长期疗效与机制仍需深入研究, 但外泌体在卵巢功能保护与恢复中的巨大潜力已备受瞩目[33,34]. 未来研究应聚焦于临床治疗的进一步开发、方案优化及副作用评估, 以实现临床应用的有效转化.

2.3 子宫腔粘连

子宫腔粘连(intrauterine adhesions, IUA), 一种以子宫内膜纤维化和瘢痕形成为特征的妇科疾病, 严重影响女性生殖健康. 传统手术复发率高且修复能力有限, 干细胞治疗虽有潜力, 但仍受限于细胞分化的复杂性与致瘤风险.

MSC-exosomes作为细胞通讯媒介, 在IUA治疗中表现出潜力. 研究显示, 不同来源的外泌体均对IUA有显著疗效. 例如, 胎盘间充质干细胞(placenta mesenchymal stem cell, PMSC)的外泌体通过特定microRNAs (诸如miR-125b-5p, miR-30c-5p及miR-23a-3p)调节转化生长因子β (TGF-β)/Smad信号通路, 促进子宫内膜修复与再生[35]. 蜕膜基质细胞(decidual stromal cell, DSC)的外泌体与海藻酸钠水凝胶(sodium alginate hydrogel, SAH)结合, 在ICR小鼠(*Mus musculus* ICR)模型中显著促进子宫内膜修复与生育功能恢复. 通过诱导子宫血管生成、触发上皮-间充质转化(epithelial-mesenchymal transition, EMT)、助推胶原纤维的重塑与溶解, 推动子宫内膜再生进程[36].

机制上, RNA测序和生物信息学分析揭示, 外泌体中的miRNAs精确调控Hippo, Smad等信号通路, 影响子宫内膜细胞的生物学过程[37,38]. 另外, 胸腺间充质干细胞(thymic mesenchymal stem cells, TMSC)衍生的外泌体中的半乳糖凝集素-1 (galectin-1)亦可通过激活Jak-TAT通路, 促进子宫内膜巨噬细胞向M2表型极化, 揭示外泌体在免疫调节中的重要作用[39]. 此外, 抗纤维化方面, 脐带间充质干细胞(umbilical cord mesenchymal stem cell, UCMSC)衍生的外泌体中miR-140-3p通过调节Smad信号通路, 在子宫内膜基质细胞(human endometrial stromal cell, HESC)中发挥抗纤维化作用. 封装于肝素-洛沙姆水凝胶中的间充质干细胞衍生的外泌体(exosomes-poloxamer hydrogel, EXOs-HP), 亦通过降低纤维化标志物表达, 有效改善IUA症状. 另外, 通过应用血小板源性生长因子BB (platelet-derived growth factor-BB, PDGFBB)来增强月经源干细胞(menstrual blood-derived stromal cells, MenSCs)的生物学特性(如细胞活力、迁移和干性维持能力等)后, 其衍生的外泌体在抗子宫内膜纤维化方面展现出显著优势, 为改进IUA疗效开辟新途径[38,40,41].

2.4 子宫内膜损伤

子宫内膜是子宫的重要组成部分之一, 是子宫体最内层的黏膜层, 为胚胎植入和维持妊娠提供必要的“土壤”. 子宫腔操作、感染和炎症很容易对子宫内膜造成严重损害, 使其难以再生和修复, 直接导致闭经、不孕、流产或其他严重症状[42]. 目前, 临床上主要使用仿生电刺激、复方短期口服避孕药、雌激素和孕激素药物、中药等促进子宫内膜修复[43], 均疗效欠佳. 而MSC衍生的外泌体miRNAs在损伤修复中扮演关键

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角色[44,45]. 研究表明, 通过调节特定的miRNA, 如miR-145-5p, miR-424-5p和miR-202-3p, 可有效促进子宫内膜损伤的修复, 逆转子宫内膜基质细胞纤维化、促进血管生成、调节细胞外基质积累等[46~48]. 在薄型子宫内膜的治疗方面, 外泌体同样展现出巨大的潜力. 研究发现, 骨髓间充质干细胞来源的外泌体(bone marrow stromal cells-derived eosomes, BMSC-EXOs)结合特定miRNA如miR-99b-5p, 通过靶向PCSK9等分子, 不仅能促进子宫内膜增殖, 还能抑制细胞凋亡, 为治疗提供新的方向[49]. 此外, 人脐带间充质干细胞外泌体凝胶技术的开发, 通过同时抑制子宫内膜纤维化和促进微血管生成, 显著提高子宫内膜的容受性和妊娠率[50]. 另外, 结合植物雌激素和外泌体的人工黏液系统, 亦可提供卓越的协同治疗效果和良好的生物安全特性, 为其治疗提供潜在临床方案[51]. 对于慢性子宫内膜炎的治疗, 外泌体也取得令人瞩目的成果. 利用多肽水凝胶作为载体, 实现IL-1β激活的骨髓MSC外泌体(β-exo)的缓释, 通过调节NF-κB信号通路等机制, 展现出强大的抗炎与再生能力[52]. 同时, 其他外泌体疗法如BMSC/anti-miR-124-3p Exo和ADSC-Exo也通过不同的信号通路为子宫内膜炎的治疗提供新的可能[53,54].

3 讨论

本文深入探讨间充质干细胞(MSC)及其外泌体(MSC-EXOs)在女性生殖功能障碍治疗中的作用机制及潜在应用价值. MSC和MSC-EXOs通过旁分泌机制和细胞间通讯, 在改善卵巢功能、促进子宫内膜修

表 1 间充质干细胞衍生的外泌体在不同女性生殖功能障碍中的作用机制及作用结局

Table 1 Mechanisms and therapeutic outcomes of mesenchymal stem cell-derived exosomes in various female reproductive disorders

疾病	现有疗法及不足	外泌体释放分子	调控机制	调控结局
PCOS	药物治疗长期可能增加血栓和脑膜瘤风险; 手术治疗易复发	未提及	RAP1/NF-κB通路[17]	调控免疫及炎症反应, 改善卵巢功能
		miR-21-5P	激活IRS1/Akt通路[18]	改善代谢
		miR-323-3P	下调促炎细胞因子(TNF-α, IL-1β, INF-γ, CTGF); 调控PDCD4表达[19]	调控卵丘细胞增殖与凋亡, 改善卵巢功能
POI&POF	HRT仅缓解症状, 无法根治, 且长期使用可能引发心脑血管疾病	miR-21	通过介导MSX1调节Notch信号通路[26]	促血管生成, 减轻卵巢细胞凋亡, 恢复性激素水平, 促进卵泡发育, 提升卵巢性能[29,30]
		miR-22-3p	靶向KLF6和ATF4-ATF3-CHOP通路[25]	
		miR-29a	靶向HBP1并激活Wnt/β-catenin通路[28]	
		miR-126-3p	靶向PIK3R2序列与PI3K/AKT/mTOR信号通路[24]	
		circRNA	作为miR-125a-5p的竞争性吸附剂, 调节CDK6的表达[27]	
IUA	传统手术复发率高且修复能力有限	miR-23a-3p, miR-30c-5p, miR-125b-5p	通过靶向smad2和smad3的3′-非翻译区来抑制它们的表达, 导致TGF-β/smad信号通路的下调和纤维化的逆转[35]	修复受伤动物的子宫内膜损伤并提高生育能力
		miR-140-3p	调控FOXP1/Smad通路[38]	抗纤维化
		miR-195-5p	通过调节Hippo信号通路中的YAP-Smad7途径减少细胞外基质沉积和肌成纤维细胞转分化[37]	改善子宫内膜纤维化
		Galectin-1	激活Jak-TAT通路[39]	介导巨噬细胞M2型极化, 调节免疫功能
		EXOs-HP	下调纤维化进展标志物: 波形蛋白、COL5A2和COL1A1[40]	显著恢复IUA模型中受损子宫内膜的功能和结构
子宫内膜损伤	仿生电刺激、复方短期口服避孕药、雌激素和孕激素药物、中药等, 均疗效欠佳	miR-99b-5p	靶向PCSK9等分子[49]	促进子宫内膜增殖, 还能抑制细胞凋亡
		miR-145-5p	改善TGFβ1诱导的子宫内膜纤维化[46]	促进子宫内膜损伤的修复, 逆转子宫内膜基质细胞纤维化
		miR-202-3p	靶向MMP11, 显著上调FN和胶原蛋白[48]	修复子宫内膜损伤
		miR-424-5p	通过DLL4/Notch信号通路[47]	调节IUAs血管生成

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复、治疗多囊卵巢综合征(PCOS)、卵巢功能不全(POI)、子宫腔粘连(IUA)以及子宫内膜损伤等方面展现出显著的治疗潜力. 如在子宫内膜异位症的治疗探索中, 外泌体通过下调一系列与疾病进展相关的标志物表达水平, 显示出显著的治疗效果[55]. 这些研究不仅推动对不孕症治疗机制的深入理解, 也为开发新的治疗策略提供科学依据(表1). 随着干细胞研究的深入, 正从动物实验阶段过渡到临床研究阶段. 目前, MSC的应用尚存在一些难点, 例如给药方式无法保证有效药物浓度等. 目前针对提高干细胞功能效率方面, 研究热点主要聚焦在将干细胞与三维模型、生物支架、干细胞载体微球等组成的生物复合材料. 而外泌体作为载体, 能够精准转运MSC中的蛋白质、RNA等信息物质至受体细胞内, 参与信号转导通路, 从而有效发挥MSC的效能. 目前尚无FDA批准的临床外泌体产品, 然而, 基于外泌体治疗的临床试验数量正在增加, 显示了其在临床应用中的巨大潜力.

目前外泌体的生产过程工作量大且产量低, 且外泌体的浓度、纯度和大小可受到不同分离方法的影响. 基于纳米生物技术的人工外泌体的出现, 克服了天然外泌体的局限性, 提供了更高的产量和保留了天然外泌体的生物相容性, 同时表现出新的生物学功能. 然而, 仿生外泌体的长期稳定性、体内分布的安全性以及临床转化中的质量控制等问题还需进一步研究. 未来不仅需要进一步验证外泌体的具体作用机制、长期安全性和治疗效果, 还需建立外泌体培养条件、修饰、生产、纯化、表征和精细储存的标准系统.

总之, MSC和MSC-EXOs在女性生殖功能障碍治疗中展现出巨大潜力. 未来的研究应聚焦于深入探索其机制, 优化生产和应用策略, 并建立严格的质量控制标准, 以实现这些治疗方法的临床转化, 为不孕症患者提供更安全、更有效的治疗选择.

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Research progress of mesenchymal stem cell-derived exosomes in female reproductive dysfunction

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Infertility is a critical reproductive health issue affecting both male and female reproductive systems. Despite the widespread application of traditional assisted reproductive technologies (ART), many cases of infertility remain unresolved. Therefore, clinical researchers are exploring more efficient and non-invasive new therapies to address this challenge. In recent years, mesenchymal stem cell (MSC)-derived exosomes (MSC-EXOs) have shown significant potential in improving the treatment of infertility and pregnancy outcomes due to their paracrine activity. This article reviews the application of MSC and MSC-EXOs in various types of female reproductive diseases, with a focus on their important role and mechanism in treating female infertility.

mesenchymal stem cells, exosomes, reproduction, infertility, endometrium

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