·综述·

间充质干细胞外泌体在骨关节炎再生康复中应用和研究进展

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【摘要】 骨关节炎是临床常见疾病之一,也是最常见的关节炎形式,是导致老年人残疾的主要原因。间充质干细胞疗法已在动物研究和临床试验中证明了其对于软骨修复的有效性,且间充质干细胞的治疗作用被越来越多地归因于旁分泌和外泌体。关节腔内注射间充质干细胞分泌的外泌体作为一种新的骨关节炎治疗方式,具有促进软骨修复和再生、减轻炎症反应和免疫调节的作用,已经成为了治疗骨关节炎的新热点。现有研究证明,间充质干细胞的外泌体在骨关节炎动物模型中普遍具有促进软骨修复、缓解炎症、减轻疼痛以及延缓骨关节炎进展的作用。本综述旨在总结间充质干细胞产生的外泌体在骨关节炎再生康复中的应用与研究进展,为其未来的研究提供参考。

【关键词】 骨关节炎;　间充质干细胞;　外泌体;　再生康复

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骨关节炎(osteoarthritis, OA)是临床常见疾病之一,也是最常见的关节炎形式,是导致老年人残疾的主要原因[1-3]。OA 的病变累及整个关节,可引起软骨退化、骨重塑、骨赘形成和滑膜炎症,导致疼痛、僵硬、肿胀和正常关节功能的丧失[4-5]。2019 年,美国风湿病学院/关节炎基金会关于手部、臀部和膝盖的 OA 管理指南罗列了多种治疗方法,虽然大多治疗方法可以缓解临床症状,且有少部分具有修复软骨损伤的作用,但均无法完全修复受损的关节软骨,且远期疗效均欠佳[4]。关节腔内注射间充质干细胞(mesenchymal stem cells, MSCs)的外泌体作为一种新的 OA 治疗方式,具有促进软骨修复和再生、减轻炎症反应和免疫调节的作用[6-10],现已经成为 OA 治疗的新热点。本综述旨在总结 MSCs 外泌体在 OA 再生康复中的应用和研究进展,以期为其未来的研究提供参考。

MSCs 外泌体

MSCs 是一种具有自我更新和分化能力的多向细胞,在组织愈合和再生医学中发挥着重要作用。研究表明,在组织修复过程中,被招募的 MSCs 分泌化学因子,如趋化因子、细胞因子和生长因子,这些被称为旁分泌,是促进损伤组织修复、再生和分化所必需的[11]。值得注意的是,与 MSCs 的直接分化相比,旁分泌功能在 MSCs 组织修复中的作用最近得到了更广泛的认可,即 MSCs 释放的大量外泌体可通过向受损细胞或组织传递信息参与组织再生,并发挥类似于 MSCs 的生物活性[12]。由于 MSCs 的作用机制以及外泌体具有易保存性(可在-80 ℃环境保存而不损失生物活性)、安全性(比细胞更安全)、可控性(作为非永久性的治疗方式在治疗过程中易被阻止、且其质量和数量可控)等优点[13],研究者们逐渐将研究的靶点转移到 MSCs 外泌体治疗上。MSCs 外泌体是细胞外囊泡的一个亚群,是一类直径为 50~130 nm 的膜囊泡[7],作为细胞间通信的载体,在细胞间转移具有生物活性的脂质、蛋白质和核酸[包括信使核糖核酸(messenger RNAs, mRNAs)、微小核糖核酸(microRNAs,miRNA)和长链非编码核糖核酸(long non-coding RNAs, lncRNAs)],从而在受体细胞中引发生物反应[10]。MSCs 外泌体的蛋白和核酸功能复杂,涉及许多不同的生化过程,如细胞通信、炎症、组织的修复、再生和代谢等。这种生物活性的广泛分布使 MSCs 外泌体可能引发不同的细胞反应,并与多种细胞类型相互作用[7]。MSCs 外泌体的治疗机制包括调节免疫反应性、促进血管生成,以及通过细胞信号通路调控加速细胞增殖和迁移等[8]。

MSCs 外泌体在骨关节炎再生康复中的应用

OA 并不是单一的关节软骨退变疾病,而是影响整个关节相关组织的疾病。以膝关节 OA 为例,它的病理变化包括软骨退变、滑膜炎症、软骨下骨硬化和骨赘形成以及软骨细胞外基质合成代谢和分解代谢的不平衡[13-14]。大多数的 OA 治疗方法基本都是针对疼痛、僵硬和肿胀的对症治疗[7]。MSCs 疗法已在动物研究和临床试验中证明了软骨修复的有效性,但目前 MSCs 的治疗作用被越来越多地归因于旁分泌和 MSCs 外泌体[15]。尽管 MSCs 外泌体治疗 OA 的临床研究较少,但多项动物实验证明,相较于安慰剂或透明质酸等,MSCs 外泌体治疗对于 OA 动物模型关节软骨的软骨损伤(histological-histochemical grading system for osteoarthritis, Mankin)评分、苏木精-伊红(hematoxylin-eosin, HE)染色后的形态、滑膜组织的炎症、氧化应激指标、软骨细胞的合成和降解的调控、基质的合成和再生免疫的表达以及步态异常等均有更好的效果[16-36]。单独的 MSCs 外泌体关节腔注射治疗对于 OA 虽然有较好的治疗效果,但 MSCs 外泌体对损伤部位的靶向治疗效果仍待提高。将 MSCs 外泌体与 3D 打印的定向支架结合起来治疗 OA 的研究证明,此类支架可增强 OA 动物模型骨和软骨的修复[37-43]。

MSCs 外泌体对 OA 再生康复的作用机制

已有证据表明,MSCs 外泌体的多种核酸通过调节 OA 相关信号通路、软骨细胞增殖、细胞外基质沉淀和炎症介质参与 OA 的发展,这些都与 OA 的发病机制有关[19,22-29]。MSCs 外泌体对 OA 的作用机制在体外研究中包括抑制炎症、软骨修复、免疫调节和抑制凋亡几个方向。对此研究者从 miRNA、lncRNA、线粒体、蛋白表达等层面进行了深入的机制探索。miRNA 通过与靶信使核糖核酸(messenger RNA,mRNA)的 3′末端非翻译区(3′-untranslated regio,3′-UTR 区)结合,转录后调节基因表达,会导致翻译抑制或靶降解[15]。除此之外,MSCs 外泌体中lncRNAs的转移也在细胞间通讯中发挥重要作用[17,44-45]。

一、MSCs 外泌体促进软骨修复的作用机制

软骨细胞的迁移是骨、软骨缺损愈合过程中的一个重要因素[37-40],并且在一些细胞工程支架如水凝胶的辅助下,MSCs 外泌体的释放和软骨细胞的迁移会进一步增强[37,41-43,46]。研究证明,MSCs 外泌体可通过多种 RNA 通过不同通路促进软骨细胞的增殖、迁移和软骨细胞基质蛋白的合成等例如其通过抑制 miR-195 靶向 G 蛋白偶联受体激酶 2 相互作用蛋白-1(G protein coupled receptor kinase interacting protein 1, GIT1)的作用促进软骨细胞的增殖和迁移[15];通过 miR-140-5p 可以上调关节软骨细胞的体外增殖和迁移,促进软骨细胞基质蛋白的合成[47-49];通过 miR-92a-3p 靶向无翅型 MMTV 整合位点家族成员 5A(wingless-type MMTV integration site family, member 5A,Wnt5a)的信号通路可抑制软骨降解,并促进 OA 的软骨形成[19,22];通过 lncRNA KLF3-AS1(KLF3 antisense RNA 1, 锌指蛋白 3 反义 RNA1)激活 miR-206 可促进 GIT1 蛋白的表达,从而促进软骨细胞增殖和迁移、抑制软骨细胞凋亡[15,46]。以上研究表明,MSCs 外泌体可通过上述信号通路的调控促进 OA 软骨的修复。

线粒体功能障碍和氧化应激损伤也是 OA 的一个标志。在退行性 OA 软骨中发现,线粒体结构、动力学和基因组稳定性改变,可导致线粒体呼吸减少和过度的活性氧产生[37]。研究表明,MSCs 外泌体可恢复线粒体功能障碍,从而修复受损软骨中的氧化应激损伤,其机制可能与 MSCs 外泌体中 10.3%的线粒体相关蛋白有关,但线粒体功能障碍恢复过程中最相关的蛋白质仍需进一步研究[47,50]。

二、MSCs 的抑制炎症的作用机制

MSCs 外泌体内的营养因子和抗凋亡分子将损伤部位的微环境从促炎状态转变为抗炎状态[31]。OA 患者和动物模型中均可见大量炎症细胞浸润滑膜组织,在这些炎症细胞中,滑膜巨噬细胞是重要的组成部分[51]。巨噬细胞可分化为两种类型,即经典活化(M1 Polarized,M1)和替代性活化(M2 Polarized,M2)巨噬细胞,这两种巨噬细胞在炎症发生发展中有相反的作用,其中 M1 巨噬细胞为促炎细胞,M2 巨噬细胞为抗炎细胞[51-54]。MSCs 外泌体通过高表达的 miR-135b 可抑制丝裂原活化蛋白激酶 6(mitogen-activated protein kinase 6,MAPK6)的表达,促进滑膜巨噬细胞的 M2 极化,从而减轻软骨损伤[51]。

研究证实,靶向抑制核因子 κB(nuclear factor kappa-B, NF-κB)可能有助于 OA 炎症的治疗[55]。当被炎症因子如白细胞介素-1β(interleukin-1 beta, IL-1β)激活时,NF-κB 转移到细胞核,上调炎症相关基因如基质金属蛋白酶(matrix metalloproteinases, MMPs)、前列腺素 E2 类激素脂质化合物 prostaglandin E2(PGE2)、环氧合酶-2(cyclooxygenase-2, COX-2)、一氧化氮合酶(诱导酶)[inducible nitric oxide synthase (enzyme), iNOS]和一氧化氮(Nitric Oxide, NO)的表达,从而导致 OA 炎症因子的产生和软骨细胞的死亡。IkBα(IkappaB-alpha)的磷酸化和降解是 NF-kB 途径激活的关键步骤,MSCs 外泌体可通过高表达的 miR-147b 抑制 IL-1β 和肿瘤坏死因子 α(tumor necrosis factor α, TNF-α)介导的炎症介质表达和 IkBα 降解[31]。

MSCs 外泌体内的多种 RNA 可靶向调节炎症因子的表达从而抑制 OA 的炎症进展。例如其通过 miR-222 靶向组蛋白去乙酰化酶 4(histone deacetylase 4, HDAC4)从而降低基质金属蛋白酶 13(recombinant matrix metalloproteinase 13,MMP13)的蛋白表达;通过 miR-199a-5p 降低白细胞介素-6(interleukin-6, IL-6)和 TNF-α 的蛋白表达可抑制 OA 的炎症和软骨破坏;通过 miR-140-5p 靶向 Toll 样受体 4(toll-like receptor 4, TLR4)抑制滑膜成纤维细胞增殖和炎症因子 IL-6 和白细胞介素-8(Interleukin-8, IL-8)的分泌,从而促进软骨组织再生[22,26-29];通过 miR-9-5p 下调多配体蛋白聚糖-1(syndecan proteoglycan 1, SDC1)降低 IL-1、IL-6、TNF-α、MMP-13、碱性磷酸酶(alkaline phosphatase,AKP)、软骨寡聚基质蛋白(cartilage oligomeric matrix protein, COMP)和 C-反应蛋白(C-reactive protein,CRP)等炎症因子的表达,以增加超氧化物歧化酶(superoxide dismutase, SOD)、NO、丙二醛(malondialdehyde, MDA)、iNOS 和 COX-2 的表达量,从而减轻软骨损伤并抑制炎症和氧化应激损伤[30];通过 lncRNA 人类肺腺癌转移相关转录本 1(metastasis associated lung adenocarcinoma transcript 1, MALAT1)经由 Wnt/β-catenin 信号通路和 NF-kB 途径上调 miR-19b 基因的表达,从而减轻脂多糖(lipopolysaccharide, LPS)诱导的软骨细胞炎症损伤[17];除以上研究较明确的作用通路外,MSCs 外泌体还可以通过 miRNA21,miRNA-146a 和 miRNA181c 这三种特异性miRNA逆转 OA 导致的病理性的炎症状态[49,56]。

三、MSCs 外泌体抑制凋亡的作用机制

多项研究证明,MSCs 外泌体内不仅有调控软骨细胞增殖和炎症反应的 RNA,还有多种 RNA 可靶向调控 B 淋巴细胞瘤-2 基因(B-cell lymphoma-2,Bcl-2)、MAPK、哺乳动物雷帕霉素靶蛋白(mammalian target of rapamycin,mTOR)等与 OA 进展中细胞凋亡过程密切相关的基因与信号通路,从而抑制骨与软骨细胞的凋亡[22,25]。例如有学者证明,其通过 miR-26a-5p 下调前列腺素内过氧化物酶 2(prostaglandin-endoperoxide synthase 2, PTGS2)的表达,可抑制 Bcl-2 基因的表达,影响 OA 的进展[23];通过 lncRNA MEG3 调节 miR-16 和白细胞抑制因子 7(mothers against decapentaplegic homolog 7, SMAD7),发挥其在 OA 进展中的抗增殖和促凋亡作用;通过 lncRNA PVT1(浆细胞瘤多样异位基因 1, plasmacytoma variant translocation 1)上调 miR-488-3p 的表达从而促进软骨细胞的凋亡[17];通过低表达的 C-myc(cellular-myelocytomatosis viral oncogene)基因来调节 MAPK 信号通路,影响软骨细胞的凋亡、增殖和细胞因子表达[46];通过 miR-100-5p 靶向 mTOR 的 3′-UTR 调控蛋白激酶 B(protein kinase B,PKB)/mTOR 信号通路来抑制 mTOR 自噬途径,平衡合成和分解代谢过程从而抑制软骨细胞凋亡[16,48-49];通过 miR-140-5p 和 miR-135b 下调转录因子 Sp1(phospho thr739)的表达

来调节软骨细胞的凋亡和增殖[18,57]。

四、MSCs 外泌体参与免疫调节的作用机制

MSCs 外泌体不仅参与 OA 软骨的修复、抑制炎症反应和凋亡,还会通过干扰素、转化生长因子、肝细胞生长因子、血红素加氧酶 1、IL-6、前列腺素 E2 等分泌因子的协同作用来诱导免疫相关的细胞功能变化,发挥免疫调节活性,它们直接抑制 T 淋巴细胞、B 淋巴细胞、自然杀伤细胞和树突状细胞的细胞因子分泌谱,并抑制抗原呈递细胞的分化和成熟[7,31-32,58-59],且 MSCs 外泌体可通过分泌细胞因子来促进细胞迁移、增殖和基质合成,从而调节软骨细胞的代谢活性[46]。

不同手段调控下的 MSCs 外泌体对 OA 的疗效和作用机制

MSCs 及其外泌体的治疗潜力可通过不同的预处理进行调控,包括物理和生物材料类的干预手段。生物材料类如透明质酸、海藻酸钠 Janus 微球等以载体形式增强 MSCs 对软骨的附着能力,通过靶向递送促进软骨修复[60-62]。物理调控如低强度脉冲超声(low intensity pulsed ultrasound, LIPUS)、冲击波以及脉冲电磁场(pulsed electromagnetic fields, PEMFs)均已被证明能够促进 MSCs 对于软骨损伤的修复作用[63-70]。研究证明,低强度脉冲超声可通过增强基质细胞衍生因子-1(stromal cell-derived factor, SDF-1)和 C-X-C 基趋化因子受体 4(C-X-C motif chemokine receptor 4, CXCR-4)的表达促进 MSCs 向软骨损伤部位的迁移[67];通过抑制 IL-1β 诱导的 NF-kB 通路的激活来增加软骨细胞增殖和细胞外基质合成,从而抑制炎症的发展[68];与 MSCs 联合治疗,可通过抑制治疗后期碱性磷酸酶的表达来促进和维持钙化软骨区的形成,从而加速软骨下骨重建[70]。冲击波预调控 MSCs 的试验发现冲击波通过增加自我更新基因 Nanog、Oct-4(octamer-binding transcription factor-4)和 SOX-2 的 mRNA 表达水平促进 MSCs 的增殖,并且能够增强 MSCs 的成软骨分化,从而促进体内软骨修复[66]。

小结

综上所述,MSCs 外泌体对于软骨细胞炎症反应、增殖、凋亡等作用存在多条通路,其在 OA 动物模型中具有促进软骨修复、缓解炎症、减轻疼痛和延缓 OA 进展的作用。通过体外实验进行的机制研究,研究者们从基因组学、代谢组学到蛋白组学链条式地阐述了 MSCs 外泌体对软骨细胞和 MSCs 的作用通路,并验证了生物或物理性的调控手段可以增强 MSCs 外泌体促进软骨细胞增殖、抑制炎症和凋亡等方面的作用,且进行了相关的通路研究,证明了调控的有效性和可信度。目前,MSCs 外泌体治疗 OA 的研究仍存在许多缺陷,如:MSCs 外泌体最佳剂量的确定,不同大小的软骨病变与其相关的最佳 MSCs 外泌体剂量的相关性,注射到缺陷部位的 MSCs 外泌体的稳定性等问题,均缺乏针对性的研究去阐明和证实;而针对 MSCs 外泌体作用机制的研究方面,现有的证据更多地集中在 MSCs 外泌体促进软骨的修复和抑制炎症的作用机制上,对于 MSCs 外泌体抑制软骨细胞凋亡和参与免疫调节的机制研究相对较少,涉及到的通路也较为单一,特别是对于 MSCs 外泌体缓解 OA 疼痛的作用机制,鲜见系统深入的研究。这些都是今后的研究需要重视的方向。

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