·综　述·

间充质干细胞来源外泌体在骨组织修复中的应用

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［摘　要］　间充质干细胞（mesenchymal stem cell，MSC）是骨组织修复中细胞治疗的重要来源之一，研究表明，MSC衍生的外泌体可以规避干细胞移植的局限性。在骨微环境中，外泌体已被证明在体内外均能促进成骨和成骨分化。外泌体携带DNA、mRNA、miRNA、蛋白质和脂质，在细胞间交流中发挥重要作用，直接在转录水平调节其靶细胞。其中，miRNA在分化的各个阶段都是主要调节因子，通过降解mRNA或阻断翻译来调节生理和病理过程。最近，MSC衍生的外泌体在骨修复和再生中取得重大进展，文章讨论MSC衍生的外泌体的形成以及其在骨组织缺损修复中的应用与潜在治疗机制。

［关键词］　间充质干细胞；外泌体；miRNA；免疫调节；骨修复

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Application of mesenchymal stem cell-derived exosomes in bone tissure repair

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［**Abstract**］　Mesenchymal stem cell（MSC）is one of the most significant sources of cell-based therapeutics for bone tissue regeneration. Investigations have demonstrated that MSC-derived exosomes can get beyond the restrictions of stem cell transplantation. Exosomes have been demonstrated to stimulate osteogenesis and osteogenic differentiation in the bone microenvironment both *in vivo* and *in vitro*. Exosomes play as a crucial role in intercellular communication by directly influencing the transcriptional level of their target cells. They carry DNA，mRNA，miRNA，protein，and lipids. The miRNAs are major regulators at various stages of cell differentiation，and modulate physiological and pathological processes through mRNA degradation or translation blockade. MSC-derived exosomes have advanced significantly in bone regeneration and repair recently. This article addresses the formation of MSC-derived exosomes，their application，and possible therapeutic procedures in the restoration of bone tissue defects.

［**Key words**］　mesenchymal stem cell；exosomes；miRNA；immunomodulation；bone repair

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由于严重创伤、肿瘤切除、手术、炎症性疾病和先天性缺损引起的骨缺损，其修复治疗一直是临床骨科面临的巨大挑战。传统骨缺损生物治疗方法包括自体骨移植、骨移植替代物和细胞治疗等，其中自体骨移植是修复骨缺损的金标准[1-3]，但因其来源有限且存在供区并发症等问题，极大限制了其临床应用。

将干细胞作为种子细胞并联合骨移植材料，是骨组织修复领域中提高骨移植材料疗效的重要手段之一。间充质干细胞（mesenchymal stem cell，MSC）已广泛用于多种组织损伤修复的基础研究与临床试验[4-5]。MSC可从许多不同组织中获得，包括骨髓、脐带血、胚胎、胎膜和脂肪，或是通过各种培养方法进行诱导，分化为成骨细胞、软骨细胞和脂肪细胞，产生骨、软骨、脂肪组织和其他胚胎谱系细

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胞，是具有自我更新能力的多能前体细胞[1,6]。虽然MSC具有免疫调节性和低免疫原性，但其在循环中易被快速清除，且只有1%的MSC可定位于靶组织[7-9]。最近研究表明，MSC通过旁分泌机制发挥治疗作用，而外泌体（exosome，Exo）是重要的旁分泌介质，可将某些生物活性分子转移到靶细胞以调节细胞活动[6,10]。MSC来源外泌体（MSC-Exo）与亲本细胞具有相似的生物学特征，其再生效应在肾损伤[11]、肺损伤[12]、心肌梗死[13]和肝脏损伤[14]的临床前模型中有广泛报道。Exo的具体数量和含量会随微环境信号的不同而不同[15]，较亲本细胞更稳定，与MSC移植相比，Exo具备安全性更高，更易储存、输送和管理的优势[16]。当机体存在临界大小组织缺损时，可以直接将Exo注射到缺损组织中[4,17-18]。因此，MSC-Exo可能是MSC治疗的潜在替代方案。

1 Exo的定义与形成

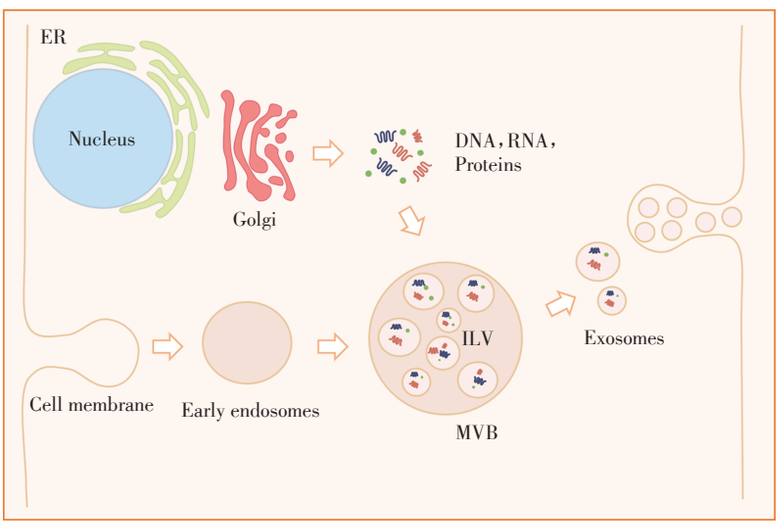
Exo是由不同细胞释放的双层脂膜胞外小泡，直径为30~150 nm。1981年，Trams等[19]首次提出“外泌体”的概念，于1983年首次在绵羊网织红细胞中发现，为了与其他类型的细胞外囊泡区分开，将其命名为Exo[20]。由内体囊泡通过质膜内陷形成，释放到细胞外[21-22]。多囊泡体（multivesicular body，MVB）与质膜融合并释放腔内小泡（intraluminal vesicle，ILV）、Exo或经溶酶体降解[23-24]（图1）。MSC-Exo由多种分子组成，包括微小RNA（microRNA，miRNA）、DNA、mRNA、蛋白质等。Exo的双层膜结构可以保持其内容物稳定，并允许它们在组织和局部细胞内移动[25]。Exo膜上富含表面蛋白，如ALG-2相互作用蛋白X（ALG-2-interacting protein X，Alix）、肿瘤易感基因101（tumor susceptibility gene 101，TSG101）和跨膜蛋白，包括白细胞分化抗原9（cluster of differentiation 9，CD9）、CD63和CD81等[26-27]。MSC-Exo可通过表面的配体/受体分子进行信号传递，或通过网状蛋白和脂筏介导的内吞、巨胞饮和吞噬与细胞膜融合，将内容物释放到靶细胞[10,28]，充当细胞外信使，调节细胞间通讯。

2 MSC-Exo与骨修复

骨缺损修复过程可分为3个阶段：血肿形成、纤维愈伤组织形成和骨重塑。许多研究表明，骨再生的启动依赖于炎症反应和新血管的生成[29-30]。近来，MSC-Exo已被确定为用于组织再生的新兴纳米级无细胞治疗剂，常被用于皮肤伤口愈合、缺血性脑损伤、肾损伤、骨关节炎、骨折愈合和退行性骨病等[31-32]。Exo可以从不同来源的细胞中分离出来，Exo的内容物已被证实反映其亲代细胞的功能，MSC-Exo在骨修复中的作用见表1。

2.1 骨髓间充质干细胞（bone marrow mesenchymal stem cell，BMSC）源性Exo与骨修复

BMSC是骨髓中含量最丰富的细胞，其分泌的Exo已在各种实验模型中验证[33]。应用BMSC来源的Exo（BMSC-Exo）治疗，可使成骨生长因子和骨相关蛋白，如骨桥蛋白（osteopontin，OPN）、Runt相关转录因子2（Runt-related transcription factor 2，RUNX2）、Ⅰ型胶原蛋白（collagen Ⅰ，COLⅠ）、转化



ER：endoplasmic reticulum；ILV：intraluminal vesicle；MVB：multivesicular body.

图1 外泌体生物形成示意图

Figure 1 Schematic of the biogenesis of exosomes

生长因子(transforming growth factor,TGF)-β1等表达水平增加,还可增加体外钙沉积和基质矿化[16,34-35]。体外实验中,BMSC-Exo可促进靶细胞的增殖和迁移。Zhang等[3]每周往大鼠关节内注射人BMSC(hBMSC)-Exo,可有效修复大鼠临界大小的软骨缺损。另外,在股骨头坏死[35]、放射性骨丢失[16]、股骨骨折模型中[36],植入BMSC-Exo后,骨形成和成骨标志物水平增加。骨愈合是个漫长的过程,常规的递送Exo策略无法持续到骨损伤后的血管生成阶段。Yang等[37]通过制备基质金属蛋白酶-1敏感的可注射微球,实现Exo的有效控释,以响应新生血管形成并加速骨愈合早期的组织再生。此外,研究者们通过化学修饰或工程化来增强BMSC及其Exo的治疗效果,如镁可通过调节巨噬细胞的免疫反应来增强BMSC的成骨作用[38];在磁性纳米颗粒和静态磁场的刺激下,BMSC-Exo表现出更强的成骨和血管生成作用[39];以及锂可刺激BMSC-Exo增强成骨作用等[40]。

2.2　脂肪间充质干细胞(adipose-derived stem cell,ASC)源性Exo与骨修复

脂肪相比胎盘、羊膜、骨髓等组织来源更丰富,便于提取且供体创伤小、可自体移植、安全性高,被认为是MSC临床应用的理想来源[41]。ASC可以在体外和体内进行快速有效的成骨分化,最近研究表明人ASC(hASC)衍生的Exo(hASC-Exo)可以发挥与hASC相似的生物学功能,并在血管生成和愈合中起重要作用[42-43]。Zhu等[44]用成骨诱导后的hASC分泌的Exo培养hASC,发现该Exo可以促进hASC的增殖和迁移,且成骨相关蛋白表达与对照组相比显著上调。Li等[45]用含有hASC-Exo的聚乳酸-羟基乙酸共聚物支架治疗小鼠颅骨缺损,该无细胞纳米载体具有骨诱导作用,通过促进MSC在新形成的骨组织中迁移和归巢来显著增强骨再生。缺氧预处理ASC所衍生的外泌体(hypo-ASC-Exo)可能在骨质疏松性骨质愈合过程中起着更重要的促血管生成作用。Li等[46]将hypo-ASC-Exo负载于甲基丙烯酰化明胶中,证实其相比ASC-Exo,血管容积和新骨形成量显著增加。上述研究表明ASC-Exo在骨修复中具有相当大的应用潜力。

2.3　脐带间充质干细胞(umbilical mesenchymal stem cell,uMSC)源性外泌体与骨修复

在现有MSC来源中,脐带来源安全且多产。与其他MSC相比,uMSC促血管生成能力更强,这些特点有助于骨再生过程中的快速组织重建[47-48]。最近一项研究表明,uMSC来源Exo(uMSC-Exo)可加速内皮细胞增殖、迁移和管状细胞形成,进一步促进血管生成,移植uMSC-Exo显著促进股骨骨折大鼠模型的血管生成和骨愈合,因此,Exo可能通过促进血管生成来加速骨折愈合[25]。Hu等[49]用人uMSC(huMSC)-Exo处理软骨细胞与BMSC,发现其促进细胞迁移、增殖和分化,将huMSC-Exo包覆在水凝胶中,可持续释放Exo治疗软骨缺损。分别采用增殖培养基(proliferation medium,PM)和成骨诱导培养基(osteogenic induction medium,OM)培养huMSC以获取Exo。体外结果显示,PM-huMSC-Exo和OM-huMSC-Exo均显著促进hBMSC的增殖与迁移。将Exo掺入3D打印磷酸三钙支架中,OM-huMSC-Exo在修复颅颌面骨缺损方面效果更为明显[50]。因此,功能化Exo在骨修复方面也具有广阔的应用潜力。

2.4　其他MSC源性Exo与骨修复

人牙髓干细胞分泌多种生长因子,据报道这些生长因子参与MSC的成骨。Jin等[51]将人牙髓干细胞外泌体与hASC共培养,促进hASC的成骨分化;在下颌骨缺损大鼠模型中,该Exo可促进骨缺损修复。另外,牙周韧带干细胞衍生的Exo可以在炎症环境下挽救内源性干细胞的成骨能力,促进牙槽骨的再生。Lei等[52]证实牙周韧带干细胞衍生的Exo可在体外显著增强炎症性牙周韧带干细胞的成骨分化能力;在体内促进牙周炎大鼠骨缺损的修复。胎盘间充质干细胞(placental mesenchymal stem cell,PMSC)具有强分化潜力和免疫调节特性,且可以诱导脊髓、心脏和骨骼等各种组织再生。PMSC来源的Exo已被证明可改善心肌纤维化、抑制炎症反应以及加速伤口瘢痕愈合等[53]。其在骨缺损修复方面的治疗作用有待进一步探索。

综上,MSC-Exo主要通过增强靶细胞的增殖与迁移能力,促进成骨或血管生成,为Exo应用于骨缺损组织修复与再生提供了新方向。但不同MSC-Exo在促成骨或成血管能力上差异较大,将来需要投入更多的时间去探索最适合骨组织再生的Exo来源。

3　MSC-Exo在骨修复中的作用机制

MSC-Exo促成骨作用可能由于:①调节免疫功能,改善微环境;②刺激血管生成,优化微环境;③直接调节邻近靶细胞成骨分化过程,为骨再生创造理想条件(图2)。

3.1　调节免疫功能,改善微环境

骨再生和愈合是一个复杂的过程,免疫细胞的持续或异常激活、促炎因子的分泌都不利于骨再

表1 干细胞衍生的外泌体在骨修复中的功能

Table 1 The function of stem cell derived exosomes in bone tissue repair

Parent cell	Target cell	Advantage	*In vitro*	Model	*In vivo*	Reference
BM-MSC	BM-MSC	Reduced oxidative stress, and prevented bone loss	Rescued proliferation inhibition, and reduced related aging protein expression	Radiation-induced bone loss in rats	Mitigated radiation-induced bone loss	[16]
hMSC	hMSC	Osteoinduction	Upregulated osteogenic genes	Calvarial defect in rats	Enhanced osteogenesis	[33]
BMSC	Osteoblast	Delayed/avoided collapse of femoral head	Increased proliferation, and enhanced osteogenic differentiation	Femoral necrosis in rabbits	Promoted local angiogenesis, and prevented bone loss	[34]
mBMSC	Osteoblast	Regenerated defected tissue	Enhanced osteogenic differentiation	Fracture in mice	Promoted fracture recovery	[35]
BMSC	BMSC	Recruited stem cells	Increased migration, and enhanced osteogenic differentiation	Calvarial defect in rats	Promoted angiogenesis	[37]
hASC	hBMSC	Promoted angiogenesis and wound healing	Increased proliferation, increased migration, and enhanced osteogenic differentiation	Calvarial defect in mice	Increased bone formation	[42]
hASC	hASC	Rich source, obtained easily, ideal cell source	Increased proliferation, increased migration, and upregulated osteogenic protein/gene	-	-	[44]
hASC	U937	High yield, low invasion rate	Inhibited M1 marker expression, and upregulated M2 marker expression	Calvarial defect in rats	Increased bone formation	[45]
huMSC	hBMSC	Higher pluripotency potential of bone tissue engineering	Upregulated osteogenic genes	Calvarial defect in rats	Increased bone formation	[47]
huMSC	HUVEC	Obtained easily, excellent proliferation and differentiation ability	Increased migration and proliferation, and promoted angiogenesis	Femoral fracture in rats	Increased angiogenesis, and accelerated bone healing	[25]
huMSC	hBMSC	Rich source of tissues, and painless collection	Increased migration and proliferation, and enhanced differentiation	Knee cartilage defect in rats	Promoted cartilage regeneration	[49]
huMSC	hBMSC	High cell yield	Increased migration and proliferation	Critical-sized calvarial bone defect in rats	Enhanced osteogenesis	[50]
hDPSC	hADSC	Secreted multiple growth factors	Enhanced osteogenic differentiation, and increased migration	Mandibular defect in rats	Increased bone formation	[51]

BM-MSC: bone marrow derived-mesenchymal stem cells; hMSC: human mesenchymal stem cells; BMSC: bone marrow mesenchymal stem cells; mBMSC: mouse bone marrow mesenchymal stem cells; U937: human monocyte cell line; hASC: human adipose derived stem cells; huMSC: human umbilical cord mesenchymal stem cells; HUVEC: human umbilical vein endothelial cells; hDPSC: human dental pulp stem cells.

生。免疫细胞包括T细胞、B细胞、巨噬细胞和中性粒细胞，在骨缺损中起着重要作用[54]。研究表明，MSC-Exo具有持续的炎症调节能力，可降低白介素（interleukin，IL）-1β、IL-6和肿瘤坏死因子（tumor necrosis factor，TNF）-α的表达，并抑制炎症中巨噬细胞的M1表型标志物mRNA的表达[55-57]。其中，Exo的miRNA146、miRNA-34和miRNA-181a可以通过促进巨噬细胞的M2极化来减少M1相关细胞因

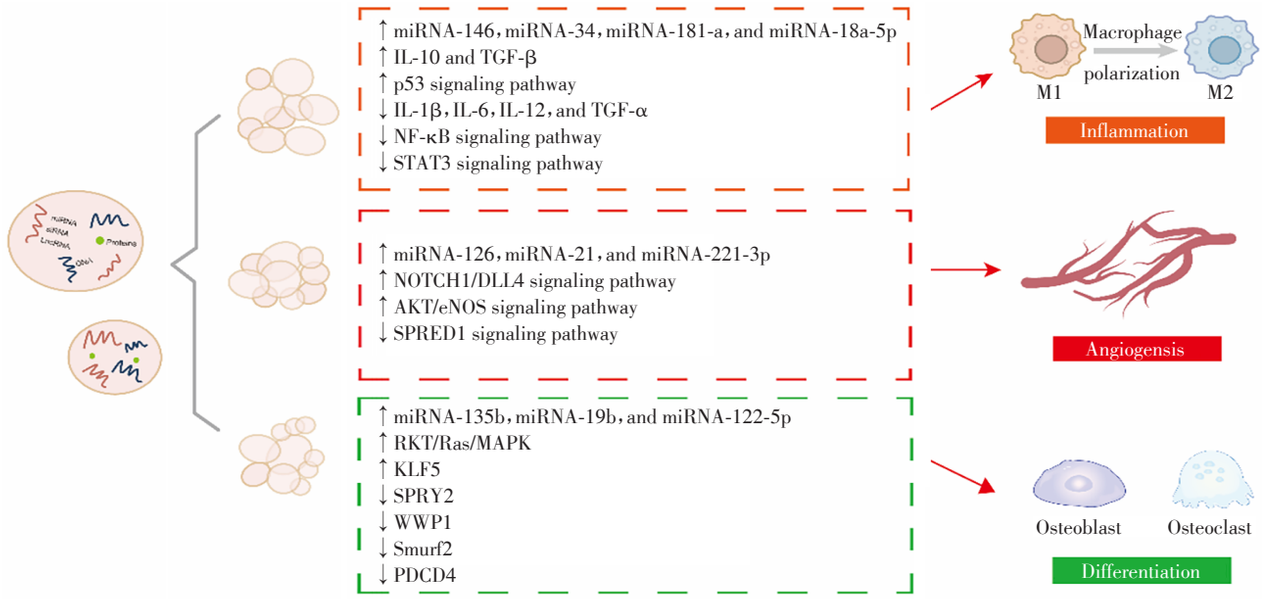


图2　外泌体在骨修复中的主要机制

Figure 2　The mechanisms of exosomes in bone repair

子，如IL-6、IL-12和TNF-α，增强M2相关细胞因子，如IL-10和TGF-β[58-60]。Li等[61]证明MSC-Exo中的miRNA-18a-5p通过靶向共济失调毛细血管扩张突变基因激活p53信号通路，并诱导巨噬细胞M2表型极化。此外，MSC-Exo可以通过NF-κB和STAT3通路诱导巨噬细胞M2极化诱导骨再生[62]。因此，MSC-Exo的免疫调节潜力可用于骨缺损修复。

3.2　刺激血管生成，优化微环境

血管生成与复杂的骨修复和再生密切相关，血管可将营养物质和氧气带到高度代谢活跃区域[63-64]。Liu等[65]证实低氧条件可通过缺氧诱导因子（hypoxia inducible factor，HIF）-1α介导hBMSC-Exo中的miRNA-126增加，miRNA-126可抑制靶基因SPRED1（Sprouty相关蛋白家族，调控造血）表达，促进HUVEC的增殖和迁移。多项研究表明，MSC-Exo通过加速血管生成促进骨愈合和修复。Zhang等[66]从uMSC中分离出Exo并封装在水凝胶中，该复合材料在体外能促进内皮祖细胞的增殖、迁移和血管生成，在体内能促进临界大小骨缺损模型的血管生成与成骨。机制研究表明，Exo所含的miRNA-21是潜在的细胞间信使，通过上调NOTCH1/DLL4通路促进血管生成。此外，AKT磷酸化在血管生成中起重要作用，miRNA-221的直接靶点PTEN是AKT的抑制剂，而miRNA-221的下调会显著抑制HUVEC的功能，进一步损害血管生成。Yu等[67]用阿托伐他汀（atorvastation，ATV）预处理BMSC获取ATV-Exo，结果显示该Exo可通过上调miRNA-221-3p激活AKT/eNOS通路促进血管生成。因此，Exo中miRNA通过激活或去激活不同细胞信号通路来调节成骨分化与血管生成，从而调节其靶蛋白的基因转录和表达。

3.3　直接调节靶细胞成骨分化过程

Xu等[9]发现BMSC-Exo在成骨诱导过程中有9个miRNA显著上调，5个miRNA显著下调，在调控靶细胞MSC成骨过程中起重要作用。其中miRNA-135b通过抑制程序性细胞死亡因子4（programmed cell death factor 4，PDCD4）表达来增强MSC-Exo的作用，从而减轻大鼠股骨坏死症状[68]。BMSC-Exo可促进骨折愈合，在亲本细胞中过表达miRNA-19b的体内外实验中，骨折愈合增加。miRNA-19b通过Wnt/β-catenin信号通路抑制含有WW结构域的E3泛素蛋白连接酶1（WW domain-containing E3 ubiquitin protein ligase 1，WWP1）或Smad泛素调节因子2（Smad ubiquitin regulatory factor 2，Smurf2）表达，并上调Kruppel样因子5（Kruppel-liked factor 5，KLF5）表达来促进hBMSC向成骨细胞分化[69]。恢复Wnt/β-catenin信号有助于BMSC成脂和成骨分化之间的平衡[16]，携带miRNA的Exo选择性调节成骨细胞活性影响骨质疏松过程。Liao等[35]通过功能获得性实验，研究miRNA-122-5p对成骨细胞和BMSC的影响以及含miRNA-122-5p的Exo对股骨头坏死的影响。结果显示miRNA-122-5p负调控发芽的RTK信号拮抗因子2（sprouty RTK signaling antagonist 2，

SPRY2）并提高RTK的活性，从而促进成骨细胞的增殖和分化。另外，在Exo内过表达miRNA-122-5p后，股骨头的骨矿物质密度、骨小梁体积和平均小梁板厚度增加，且观察到坏死股骨头明显愈合。携带miRNA-122-5p的Exo可能通过RTK/Ras/MAPK信号通路下调SPRY2以减轻股骨头坏死症状。这些发现表明相关miRNA与Exo的结合可成为促进骨再生的有前景的策略之一。

Exo通过释放特定成骨蛋白、细胞外基质蛋白或骨相关miRNA，调节靶细胞基因表达[70]。因此，可对亲本细胞进行预处理或修饰亲本细胞以表达特定蛋白质，有针对性地将刺激因子输送到邻近细胞。

4 结论与展望

肿瘤、创伤、手术或炎症性疾病可能会导致临界大小骨缺损，骨缺损及外科重建已成为全球卫生保健系统的主要财务负担之一[71]。骨缺损修复涉及骨组织再生与血管生成，骨环境中的MSC通过分泌Exo参与骨修复调节[72]。与细胞治疗相比，Exo治疗具有安全性高、易于储存运输、免疫原性低、可作为药物载体和治疗效率高等优势，可规避细胞疗法的局限性[16,73]。许多研究已证明不同MSC-Exo可促进成骨或成血管[74]以及免疫调节[75]，在骨缺损和其他疾病（如骨坏死、骨折和骨质疏松症）动物模型中有助于骨再生，这可能与Exo的内容物miRNA有关[76-77]。由于Exo中生物活性分子的复杂性，多数研究仅限于Exo中的单一功能分子。因此，需要更多探索以深入了解Exo参与旁分泌的治疗机制，以便选择适当的细胞源。Exo治疗虽是一种新型且具有前景的骨修复治疗策略，但在将其安全应用于人体之前，还需进行大量研究，尤其是Exo的临床疗效和生产效率方面。

[参考文献]

[1] QI X，ZHANG J Y，YUAN H，et al. Exosomes secreted by human-induced pluripotent stem cell-derived mesenchymal stem cells repair critical-sized bone defects through enhanced angiogenesis and osteogenesis in osteoporotic rats[J]. Int J Biol Sci，2016，12（7）：836-849

[2] ZHANG J Y，LIU X L，LI H Y，et al. Exosomes/tricalcium phosphate combination scaffolds can enhance bone regeneration by activating the PI3K/Akt signaling pathway[J]. Stem Cell Res Ther，2016，7（1）：136

[3] ZHANG S，CHU W C，LAI R C，et al. Exosomes derived from human embryonic mesenchymal stem cells promote osteochondral regeneration [J]. Osteoarthritis Cartilage，2016，24（12）：2135-2140

[4] AL-SOWAYAN B，ALAMMARI F，ALSHAREEDA A. Preparing the bone tissue regeneration ground by exosomes：from diagnosis to therapy[J]. Molecules，2020，25（18）：4205

[5] KUMAR S. Bone defect repair in mice by mesenchymal stem cells[J]. Methods Mol Biol，2014，1213：193-207

[6] LU J，WANG Q Y，SHENG J G. Exosomes in the repair of bone defects：next-generation therapeutic tools for the treatment of nonunion[J]. Biomed Res Int，2019，2019：1983131

[7] HELDRING N，MÄGER I，WOOD M J A，et al. Therapeutic potential of multipotent mesenchymal stromal cells and their extracellular vesicles [J]. Hum Gene Ther，2015，26（8）：506-517

[8] MCBRIDE J D，RODRIGUEZ-MENOCAL L，GUZMAN W，et al. Bone marrow mesenchymal stem cell-derived $CD63^+$ exosomes transport Wnt3a exteriorly and enhance dermal fibroblast proliferation，migration，and angiogenesis *in vitro*[J]. Stem Cells Dev，2017，26（19）：1384-1398

[9] XU J F，YANG G H，PAN X H，et al. Altered microRNA expression profile in exosomes during osteogenic differentiation of human bone marrow-derived mesenchymal stem cells[J]. PLoS One，2014，9（12）：e114627

[10] BJØRGE I M，KIM S Y，MANO J F，et al. Extracellular vesicles，exosomes and shedding vesicles in regenerative medicine - a new paradigm for tissue repair[J]. Biomater Sci，2017，6（1）：60-78

[11] LV L L，FENG Y，WU M，et al. Exosomal miRNA-19b-3p of tubular epithelial cells promotes M1 macrophage activation in kidney injury[J]. Cell Death Differ，2020，27（1）：210-226

[12] JIAO Y，ZHANG T，ZHANG C M，et al. Exosomal miR-30d-5p of neutrophils induces M1 macrophage polarization and primes macrophage pyroptosis in sepsis-related acute lung injury[J]. Crit Care，2021，25（1）：356

[13] DENG J Y，ZHANG N，WANG Y，et al. FNDC5/irisin improves the therapeutic efficacy of bone marrow-derived mesenchymal stem cells for myocardial infarction [J]. Stem Cell Res Ther，2020，11（1）：228

[14] LIN F Y，CHEN W Y，ZHOU J H，et al. Mesenchymal stem cells protect against ferroptosis *via* exosome-mediated stabilization of SLC7A11 in acute liver injury [J]. Cell Death Dis，2022，13（3）：271

[15] ELTOUKHY H S，SINHA G，MOORE C A，et al. Secretome within the bone marrow microenvironment：a basis for mesenchymal stem cell treatment and role in cancer dormancy[J]. Biochimie，2018，155：92-103

[16] ZUO R，LIU M H，WANG Y Q，et al. BM-MSC-derived

exosomes alleviate radiation-induced bone loss by restoring the function of recipient BM-MSCs and activating Wnt/β-catenin signaling[J]. Stem Cell Res Ther, 2019, 10(1): 30

[17] HAO Z C, LU J, WANG S Z, et al. Stem cell-derived exosomes: a promising strategy for fracture healing[J]. Cell Prolif, 2017, 50(5): e12359

[18] SICCO C L, REVERBERI D, BALBI C, et al. Mesenchymal stem cell-derived extracellular vesicles as mediators of anti-inflammatory effects: endorsement of macrophage polarization[J]. Stem Cells Transl Med, 2017, 6(3): 1018-1028

[19] TRAMS E G, LAUTER C J, SALEM N, et al. Exfoliation of membrane ecto-enzymes in the form of micro-vesicles[J]. Biochim Biophys Acta, 1981, 645(1): 63-70

[20] JOHNSTONE R M. The Jeanne Manery-Fisher memorial lecture 1991. Maturation of reticulocytes: formation of exosomes as a mechanism for shedding membrane proteins[J]. Biochem Cell Biol, 1992, 70(3/4): 179-190

[21] MALEKPOUR K, HAZRATI A, ZAHAR M, et al. The potential use of mesenchymal stem cells and their derived exosomes for orthopedic diseases treatment[J]. Stem Cell Rev Rep, 2022, 18(3): 933-951

[22] POURAKBARI R, KHODADADI M, AGHEBATI-MALEKI A, et al. The potential of exosomes in the therapy of the cartilage and bone complications; emphasis on osteoarthritis[J]. Life Sci, 2019, 236: 116861

[23] HUBER J, GRIFFIN M F, LONGAKER M T, et al. Exosomes: a tool for bone tissue engineering[J]. Tissue Eng Part B Rev, 2022, 28(1): 101-113

[24] ZHANG R, MA J, HAN J, et al. Mesenchymal stem cell related therapies for cartilage lesions and osteoarthritis[J]. Am J Transl Res, 2019, 11(10): 6275-6289

[25] ZHANG Y T, HAO Z C, WANG P F, et al. Exosomes from human umbilical cord mesenchymal stem cells enhance fracture healing through HIF-1α-mediated promotion of angiogenesis in a rat model of stabilized fracture[J]. Cell Prolif, 2019, 52(2): e12570

[26] MAQSOOD M, KANG M Z, WU X T, et al. Adult mesenchymal stem cells and their exosomes: sources, characteristics, and application in regenerative medicine[J]. Life Sci, 2020, 256: 118002

[27] DISTEFANO T J, VASO K, DANIAS G, et al. Extracellular vesicles as an emerging treatment option for intervertebral disc degeneration: therapeutic potential, translational pathways, and regulatory considerations[J]. Adv Healthc Mater, 2022, 11(5): e2100596

[28] SONG H, ZHAO J S, CHENG J, et al. Extracellular vesicles in chondrogenesis and cartilage regeneration[J]. J Cell Mol Med, 2021, 25(11): 4883-4892

[29] ZHANG J K, PAN J, JING W. Motivating role of type H vessels in bone regeneration[J]. Cell Prolif, 2020, 53(9): e12874

[30] LU W, ZHOU C, MA Y, et al. Improved osseointegration of strontium-modified titanium implants by regulating angiogenesis and macrophage polarization[J]. Biomater Sci, 2022, 10(9): 2198-2214

[31] BRUNO S, TAPPARO M, COLLINO F, et al. Renal regenerative potential of different extracellular vesicle populations derived from bone marrow mesenchymal stromal cells[J]. Tissue Eng Part A, 2017, 23(21/22): 1262-1273

[32] PAN Q W, KUANG X L, CAI S Y, et al. MiR-132-3p priming enhances the effects of mesenchymal stromal cell-derived exosomes on ameliorating brain ischemic injury[J]. Stem Cell Res Ther, 2020, 11(1): 260

[33] GUAN P F, LIU C, XIE D H, et al. Exosome-loaded extracellular matrix-mimic hydrogel with anti-inflammatory property facilitates/promotes growth plate injury repair[J]. Bioact Mater, 2022, 10: 145-158

[34] HUANG C C, KANG M Y, LU Y, et al. Functionally engineered extracellular vesicles improve bone regeneration[J]. Acta Biomater, 2020, 109: 182-194

[35] LIAO W, NING Y, XU H J, et al. BMSC-derived exosomes carrying microRNA-122-5p promote proliferation of osteoblasts in osteonecrosis of the femoral head[J]. Clin Sci, 2019, 133(18): 1955-1975

[36] HU H F, WANG D, LI L H, et al. Role of microRNA-335 carried by bone marrow mesenchymal stem cells-derived extracellular vesicles in bone fracture recovery[J]. Cell Death Dis, 2021, 12(2): 156

[37] YANG Y, ZHENG W H, TAN W, et al. Injectable MMP1-sensitive microspheres with spatiotemporally controlled exosome release promote neovascularized bone healing[J]. Acta Biomater, 2023, 157: 321-336

[38] ZHANG X F, CHEN Q P, MAO X L. Magnesium enhances osteogenesis of BMSCs by tuning osteoimmunomodulation[J]. Biomed Res Int, 2019, 2019: 7908205

[39] WU D, CHANG X, TIAN J J, et al. Bone mesenchymal stem cells stimulation by magnetic nanoparticles and a static magnetic field: release of exosomal miR-1260a improves osteogenesis and angiogenesis[J]. J Nanobiotechnology, 2021, 19(1): 209

[40] CHEN C J, WANG B N, ZHAO X, et al. Lithium promotes osteogenesis *via* Rab11a-facilitated exosomal Wnt10a secretion and β-catenin signaling activation[J]. ACS Appl Mater Interfaces, 2024, 16(24): 30793-30809

[41] 王扶凝，代会博，唐　蕾，等. 脂肪间充质干细胞在纤维

化疾病治疗中的作用[J]. 南京医科大学学报（自然科学版），2024，44（3）：429-434

[42] LI W Y，LIU Y S，ZHANG P，et al. Tissue-engineered bone immobilized with human adipose stem cells-derived exosomes promotes bone regeneration[J]. ACS Appl Mater Interfaces，2018，10（6）：5240-5254

[43] DONG X，SHEN L H，YI Z，et al. Exosomes from adipose-derived stem cells can prevent medication-related osteonecrosis of the jaw[J]. Med Sci Monit，2021，27：e929684

[44] ZHU M R，LIU Y，QIN H Z，et al. Osteogenically-induced exosomes stimulate osteogenesis of human adipose-derived stem cells[J]. Cell Tissue Bank，2021，22（1）：77-91

[45] LI R，LI D Z，WANG H N，et al. Exosomes from adipose-derived stem cells regulate M1/M2 macrophage phenotypic polarization to promote bone healing *via* miR-451a/MIF[J]. Stem Cell Res Ther，2022，13（1）：149

[46] LI X Q，FANG S，WANG S H，et al. Hypoxia preconditioning of adipose stem cell-derived exosomes loaded in gelatin methacryloyl（GelMA）promote type H angiogenesis and osteoporotic fracture repair[J]. J Nanobiotechnology，2024，22（1）：112

[47] WANG K X，XU L L，RUI Y F，et al. The effects of secretion factors from umbilical cord derived mesenchymal stem cells on osteogenic differentiation of mesenchymal stem cells[J]. PLoS One，2015，10（3）：e0120593

[48] YAO H，CAO Z D，WU W Y. Human umbilical cord mesenchymal stromal cells promotes the proliferation and osteogenic differentiation of autologous bone marrow stem cells by secreting exosomes[J]. Bioengineered，2022，13（4）：9901-9915

[49] HU H X，DONG L L，BU Z H，et al. MiR-23a-3p-abundant small extracellular vesicles released from Gelma/nanoclay hydrogel for cartilage regeneration[J]. J Extracell Vesicles，2020，9（1）：1778883

[50] LI S Y，RONG Q，ZHOU Y，et al. Osteogenically committed hUCMSCs-derived exosomes promote the recovery of critical-sized bone defects with enhanced osteogenic properties[J]. APL Bioeng，2024，8（1）：016107

[51] JIN Q Q，LI P L，YUAN K Y，et al. Extracellular vesicles derived from human dental pulp stem cells promote osteogenesis of adipose-derived stem cells *via* the MAPK pathway[J]. J Tissue Eng，2020，11：2041731420975569

[52] LEI F Z，LI M J，LIN T T，et al. Treatment of inflammatory bone loss in periodontitis by stem cell-derived exosomes[J]. Acta Biomater，2022，141：333-343

[53] LIU H D，ZHANG X，ZHANG M T，et al. Mesenchymal stem cell derived exosomes repair uterine injury by targeting transforming growth factor-β signaling[J]. ACS Nano，2024，18（4）：3509-3519

[54] LOI F，CÓRDOVA L A，PAJARINEN J，et al. Inflammation，fracture and bone repair[J]. Bone，2016，86：119-130

[55] LIU J Y，CHEN B，BAO J，et al. Macrophage polarization in periodontal ligament stem cells enhanced periodontal regeneration[J]. Stem Cell Res Ther，2019，10（1）：320

[56] WEI F，LI Z M，CRAWFORD R，et al. Immunoregulatory role of exosomes derived from differentiating mesenchymal stromal cells on inflammation and osteogenesis[J]. J Tissue Eng Regen Med，2019，13（11）：1978-1991

[57] 高倩茜，程 锐. 间充质干细胞外泌体的生物学功能及其治疗支气管肺发育不良研究进展[J]. 南京医科大学学报（自然科学版），2022，42（2）：286-290，305

[58] DOMENIS R，CIFÙ A，QUAGLIA S，et al. Pro inflammatory stimuli enhance the immunosuppressive functions of adipose mesenchymal stem cells-derived exosomes[J]. Sci Rep，2018，8（1）：13325

[59] JIANG P，LIU R H，ZHENG Y J，et al. MiR-34a inhibits lipopolysaccharide-induced inflammatory response through targeting Notch1 in murine macrophages[J]. Exp Cell Res，2012，318（10）：1175-1184

[60] WEI Z L，QIAO S H，ZHAO J X，et al. miRNA-181a overexpression in mesenchymal stem cell-derived exosomes influenced inflammatory response after myocardial ischemia-reperfusion injury[J]. Life Sci，2019，232：116632

[61] LI X R，SI Y H，LIANG J X，et al. Enhancing bone regeneration and immunomodulation *via* gelatin methacryloyl hydrogel-encapsulated exosomes from osteogenic pre-differentiated mesenchymal stem cells[J]. J Colloid Interface Sci，2024，672：179-199

[62] GAO S，MAO F，ZHANG B，et al. Mouse bone marrow-derived mesenchymal stem cells induce macrophage M2 polarization through the nuclear factor-κB and signal transducer and activator of transcription 3 pathways[J]. Exp Biol Med，2014，239（3）：366-375

[63] WU J Y，CHEN L L，WANG R F，et al. Exosomes secreted by stem cells from human exfoliated deciduous teeth promote alveolar bone defect repair through the regulation of angiogenesis and osteogenesis[J]. ACS Biomater Sci Eng，2019，5（7）：3561-3571

[64] CHENG P Z，CAO T Q，ZHAO X Y，et al. Nidogen1-enriched extracellular vesicles accelerate angiogenesis and bone regeneration by targeting Myosin-10 to regulate endothelial cell adhesion[J]. Bioact Mater，2022，12：185-197

[65] LIU W，LI L W，RONG Y L，et al. Hypoxic mesenchymal stem cell-derived exosomes promote bone fracture healing by the transfer of miR-126[J]. Acta Biomater，2020，103：

196-212
[66] ZHANG Y T, XIE Y, HAO Z C, et al. Umbilical mesenchymal stem cell-derived exosome-encapsulated hydrogels accelerate bone repair by enhancing angiogenesis[J]. ACS Appl Mater Interfaces, 2021, 13(16): 18472-18487
[67] YU M Y, LIU W, LI J X, et al. Exosomes derived from atorvastatin-pretreated MSC accelerate diabetic wound repair by enhancing angiogenesis *via* AKT/eNOS pathway[J]. Stem Cell Res Ther, 2020, 11(1): 350
[68] NOROUZI-BAROUGH L, SHIRIAN S, GORJI A, et al. Therapeutic potential of mesenchymal stem cell-derived exosomes as a cell-free therapy approach for the treatment of skin, bone, and cartilage defects[J]. Connect Tissue Res, 2022, 63(2): 83-96
[69] ZHANG X, YOU J M, DONG X J, et al. Administration of mircoRNA-135b-reinforced exosomes derived from MSCs ameliorates glucocorticoid-induced osteonecrosis of femoral head (ONFH) in rats[J]. J Cell Mol Med, 2020, 24(23): 13973-13983
[70] HUANG Y, XU Y Q, FENG S Y, et al. MiR-19b enhances osteogenic differentiation of mesenchymal stem cells and promotes fracture healing through the WWP1/Smurf2-mediated KLF5/β-catenin signaling pathway[J]. Exp Mol Med, 2021, 53(5): 973-985
[71] MAN K, BARROSO I A, BRUNET M Y, et al. Controlled release of epigenetically-enhanced extracellular vesicles from a GelMA/nanoclay composite hydrogel to promote bone repair[J]. Int J Mol Sci, 2022, 23(2): 832
[72] RAGHAV P K, MANN Z, AHLAWAT S, et al. Mesenchymal stem cell-based nanoparticles and scaffolds in regenerative medicine[J]. Eur J Pharmacol, 2022, 918: 174657
[73] TAGHIYAR L, JAHANGIR S, KHOZAEI R M, et al. Cartilage repair by mesenchymal stem cell-derived exosomes: preclinical and clinical trial update and perspectives[J]. Adv Exp Med Biol, 2021, 1326: 73-93
[74] MATHEW S A, NAIK C, CAHILL P A, et al. Placental mesenchymal stromal cells as an alternative tool for therapeutic angiogenesis[J]. Cell Mol Life Sci, 2020, 77(2): 253-265
[75] KUSHIOKA J, CHOW S K, TOYA M, et al. Bone regeneration in inflammation with aging and cell-based immunomodulatory therapy[J]. Inflamm Regen, 2023, 43(1): 29
[76] ZHANG L, OUYANG P R, HE G L, et al. Exosomes from microRNA-126 overexpressing mesenchymal stem cells promote angiogenesis by targeting the PIK3R2-mediated PI3K/Akt signalling pathway[J]. J Cell Mol Med, 2021, 25(4): 2148-2162
[77] WU J Y, KUANG L, CHEN C, et al. MiR-100-5p-abundant exosomes derived from infrapatellar fat pad MSCs protect articular cartilage and ameliorate gait abnormalities *via* inhibition of mTOR in osteoarthritis[J]. Biomaterials, 2019, 206: 87-100

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报(自然科学版), 2020, 40(9): 1313-1318
[10] 周　瑾, 马红霞. 食管癌术后颈部吻合口瘘危险因素分析及预测模型的建立[J]. 南京医科大学学报(自然科学版), 2023, 43(2): 268-296
[11] TAKEUCHI H, MIYATA H, GOTOH M, et al. A risk model for esophagectomy using data of 5354 patients included in a Japanese nationwide web-based database[J]. Ann Surg, 2014, 260: 259-266
[12] WANG S F, HUANG Y L, XIE J T, et al. Does delayed esophagectomy after endoscopic resection affect outcomes in patients with stage T1 esophageal cancer? A propensity score-based analysis[J]. Surg Endosc, 2018, 32(3): 1441-1448
[13] NAKO Y, SHIOZAKI A, FUJIWARA H, et al. Esophagectomy after endoscopic submucosal dissection(ESD)[J]. Gan To Kagaku Ryoho, 2014, 41(12): 1997-1999
[14] WANG W P, GAO Q, WANG K N, et al. A prospective randomized controlled trial of semi-mechanical versus handsewn or circular stapled esophagogastrostomy for prevention of anastomotic stricture[J]. World J Surg, 2013, 37(5): 1043-1050
[15] HIRASAWA K, KOKAWA A, OKA H, et al. Superficial adenocarcinoma of the esophagogastric junction: longterm results of endoscopic submucosal dissection[J]. Gastrointest Endosc, 2010, 72(5): 960-966

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