

骨髓间充质干细胞来源外泌体在成骨过程中的调控机制及临床应用前景

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摘要

骨形成是一个由多种细胞及生物大分子共同参与、复杂而精细的生物学过程, 这一过程包含了软骨模板形成、成骨分化、成骨细胞活动, 以及骨重建等一系列步骤。在骨髓的复杂微环境中, 骨髓间充质干细胞(BMSCs)作为一类独特的细胞群体, 凭借其多向分化能力而备受瞩目。这类细胞不仅能在特定条件下转化为成骨细胞、脂肪细胞和软骨细胞, 还在组织修复与再生领域发挥重要作用。尤其在骨折愈合、骨质疏松治疗及软骨损伤修复等方面, BMSCs展现出巨大的应用潜力。与此同时, 细胞分泌的微小囊泡——外泌体(exosomes), 正逐渐成为科研领域的热点。这些直径为30~150纳米的囊泡, 富含蛋白质、核酸和脂质等生物活性分子, 是细胞间通讯的重要媒介, 能够调控免疫反应、细胞增殖与分化等关键生命过程。值得注意的是, 从骨髓间充质干细胞中提取的外泌体(BMSCs-Exos), 相较于其母细胞, 具有稳定性高、易保存、免疫原性低和易控制的优点。近年来, BMSCs-Exos在骨质疏松、骨折愈合、软骨修复及关节疾病等方面的治疗潜力日益受到重视。通过深入研究外泌体在成骨过程中的调控机制, 有望为开发新的骨科治疗策略和生物材料提供重要启示。总体而言, BMSCs-Exos对成骨分化起着关键的调节作用, 有望为骨缺损的防治提供新思路。

关键词

骨髓间充质干细胞, 外泌体, 成骨, 调控机制, 临床应用

Exosomes from Bone Marrow Mesenchymal Stem Cells: Regulatory Mechanisms and Clinical Application Prospects in Osteogenesis

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Abstract

Bone formation is a complex and precise biological process involving various cells and biomacromolecules. It encompasses a series of steps, including cartilage template formation, osteogenic differentiation, osteoblast activity, and bone remodeling. Within the intricate microenvironment of the bone marrow, bone marrow mesenchymal stem cells (BMSCs), as a unique cell population, have attracted considerable attention due to their multi-directional differentiation potential. These cells can not only differentiate into osteoblasts, adipocytes, and chondrocytes under specific conditions but also play a significant role in tissue repair and regeneration. Particularly in fracture healing, osteoporosis treatment, and cartilage injury repair, BMSCs demonstrate substantial application potential. At the same time, exosomes—tiny vesicles secreted by cells—are increasingly becoming a research focus. These vesicles, with diameters ranging from 30 to 150 nanometers, are rich in bioactive molecules such as proteins, nucleic acids, and lipids. They serve as important mediators of intercellular communication, regulating key biological processes including immune responses, cell proliferation, and differentiation. Notably, exosomes derived from bone marrow mesenchymal stem cells (BMSCs-Exos) offer advantages over their parental cells, such as high stability, ease of storage, low immunogenicity, and controllability. In recent years, the therapeutic potential of BMSCs-Exos in osteoporosis, fracture healing, cartilage repair, and joint diseases has gained growing recognition. In-depth research into the regulatory mechanisms of exosomes in osteogenesis may provide important insights for developing novel orthopedic therapeutic strategies and biomaterials. Overall, BMSCs-Exos play a key regulatory role in osteogenic differentiation and hold promise for offering new approaches to the prevention and treatment of bone defects.

Keywords

Bone Marrow Mesenchymal Stem Cells, Exosomes, Osteogenesis, Regulatory Mechanisms, Clinical Applications

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1. 引言

骨缺损是一个常见且严重的健康问题，可由外伤、疾病或其他因素引起，造成骨组织的丧失或破坏。目前，骨缺损的治疗手段包括植骨、骨填充材料植入和使用生物活性材料等[1]。但是，目前已有的几种治疗方式均存在着不足，如：骨移植技术虽能解决上述问题，但仍存在供需失衡、移植后易发生排异等问题。现有骨缺损修复材料种类繁多，如人工骨、生物陶瓷等，但在生物相容性及促骨再生方面尚需进一步提高；另外，部分材料可能引起机体的排斥和感染；生长因子、细胞因子等生物活性物质虽然可以促进骨组织再生，但在使用时，需要控制用量及释放速度，以免产生副作用及过度生长[2][3]。目前临床上对骨缺损的修复手段还存在很多问题。因此，如何提高临床治疗效果，提高患者的生活质量是一个亟

待解决的问题。

1.1. 外泌体和成骨的关系

外泌体是由细胞分泌的一种直径约为 30 至 150 纳米(平均约为 100 纳米)的胞外囊泡, 包含 DNA、RNA、脂质、代谢物、细胞浆和细胞膜蛋白等多种生命活性物质[4]。骨髓间充质干细胞(BMSCs)、脂肪干细胞(ADSCs)、免疫细胞等多种细胞均可分泌外泌体。外泌体是一种重要的生物活性物质, 可作用于靶细胞, 参与调控骨稳态、细胞间通讯、细胞分化和增殖、血管生成、应激反应和免疫信号等一系列细胞活动[5]-[9]。

外泌体在成骨分化中发挥重要作用。研究表明, 外泌体可以通过多种途径影响成骨细胞的行为和功能[10]-[15]。例如, 骨髓间充质干细胞来源外泌体可以介导 Angpt1/Tie2-NO 信号传导, 从而促进血管内皮生成和成骨[10]。此外, 外泌体还能通过抑制 IL-6/JAK2/STAT3 信号通路来调节炎症, 使巨噬细胞从 M1 表型极化到 M2 表型, 从而有效减少牙周炎大鼠牙槽骨丢失[11]。在股骨骨不连大鼠模型中, BMSCs-Exos 可以通过激活 BMP-2/Smad1/RUNX2 和 HIF-1 α /VEGF 信号通路明显促进成骨、血管生成和骨愈合过程[12]。此外, 在大鼠股骨缺损模型中, 鼻窦粘膜源性细胞(SMCs)和骨膜源性细胞(PCs)的来源外泌体也能在体内促进骨形成[14]。另外, BMSCs-Exos 中高水平表达 MiRNA-29a, 在体内表现出强大的促进血管生成和成骨的能力[15]。

1.2. 骨髓间充质干细胞来源外泌体的特征及意义

骨髓间充质干细胞是一类分布于骨髓中的多能干细胞, 具有自我更新和多向分化能力, 能够向成骨细胞、脂肪细胞及软骨细胞等方向分化, 是再生医学领域的研究热点[16]。

骨髓间充质干细胞分泌的外泌体是其最主要的胞外囊泡。外泌体中含有多种生物活性成分, 能够通过细胞之间的信息交流来调节组织损伤的修复与再生。

近年来研究发现, BMSCs 除了直接分化为功能细胞外, 还可通过旁分泌机制参与组织损伤修复与再生。有学者指出, 骨髓间充质干细胞的旁分泌信号可能是组织再生的关键, 而不是细胞本身[17][18]。外泌体是骨髓间充质干细胞分泌的主要胞外囊泡之一, 富含蛋白质、核酸和脂质等生物活性分子, 在细胞间通讯中发挥重要作用, 能够传递信号并调控周围细胞的功能与代谢[19]。研究表明, BMSCs 来源的外泌体可被成骨细胞内吞, 进而促进成骨细胞增殖、提高碱性磷酸酶活性并增强钙化结节形成, 从而调控骨再生过程[20][21]。进一步的研究支持旁分泌机制在骨再生中的重要性。例如, 人源骨髓间充质干细胞条件培养基能够增强大鼠骨髓间充质干细胞的迁移、增殖能力, 并上调成骨相关基因(如骨钙素、Runx2)的表达, 其效果优于直接应用细胞。该条件培养基还可通过动员内源性干细胞促进成骨分化, 为旁分泌机制在骨修复中的作用提供了实验依据[22]。

BMSC 来源外泌体的特点包括:

1) 多功能性: BMSCs-Exos 是一种富含多种生物活性分子的细胞外囊泡, 具有显著的多功能性。它们能够参与调控细胞代谢、增殖、凋亡及炎症反应等多个关键生物学过程。在代谢方面, BMSCs-Exos 不仅可以抑制糖酵解过程[23], 还能通过激活 AMPK/PGC-1 α 信号通路, 减轻心肌细胞的氧化应激和线粒体功能障碍, 从而保护心脏免受缺血再灌注损伤[24]; 进一步研究表明, 经 EMPA 增强分泌的外泌体可通过上调 ATAD3A 促进 PINK1/PARKIN 依赖的线粒体自噬, 在减轻心肌缺血再灌注损伤方面效果尤为显著, 为缺血性心脏病的治疗提供了新思路[25]。此外, BMSCs-Exos 还能够调节细胞的增殖活动, 促进组织修复和再生[20][23][26]-[29], 并参与调控细胞凋亡过程, 维持细胞内稳态和平衡[27][30]-[36]。BMSCs-Exos 中的成分还具有调节炎症反应的功能, 可以影响炎症程度和进程, 对维持组织健康具有重要作用[19]

[37]-[39]。此外, BMSCs-Exos 可通过 LNCNA SNHG12 抑制巨噬细胞铁死亡, 从而缓解败血症引起的肺损伤并提高生存率[40]。综上所述, BMSCs-Exos 凭借其内含分子的多样性与功能多重性, 在细胞间通讯与疾病调控中扮演关键角色, 为细胞治疗及多种疾病的干预提供了具有广阔前景的应用途径。

2) 稳定性: 与移植细胞在体内存活时间有限相比, 外泌体在适宜的体内外环境中表现出较强的稳定性[41]。其内部的生物活性分子受到脂质双层膜的保护, 能够在一定程度上抵抗外界环境的影响, 从而在储存和递送过程中较好地保持活性[42]-[44]。这一特点这使得它们在医学领域中具有较好的应用前景, 尤其在无细胞疗法方面[45] [46]。

3) 低免疫原性: 与传统的细胞疗法相比, 外泌体的免疫原性更小, 可以降低免疫排斥的发生。有研究发现, 注射 BMSCs-Exos 处理的树突状细胞(dc)的小鼠能明显延长同种异体皮肤移植后的生存期[47]。

4) 可渗透性: BMSCs-Exos 小巧且具备穿透细胞膜的特性, 可轻易地进入靶细胞, 进行信号传输与调控。可以包被治疗性化合物, 穿过屏障并实现靶向投送, 这种优秀的可渗透性的特点使外泌体成为一种理想的细胞间信息传递媒介, 为在细胞治疗[48]-[50]、疾病和肿瘤的靶向抑制[34] [51]-[53]、药物传递[54]-[56]等领域的广泛应用提供了可靠的基础。

2. 外泌体对成骨过程的调控机制

2.1. 外泌体介导的信号通路

外泌体中富含蛋白、miRNAs、细胞因子等多种生物活性物质, 能够通过细胞间信息传递, 对成骨细胞的增殖、分化与功能发挥重要的调控作用, 进而影响骨形成过程。该作用涉及多种信号通路, 包括 Wnt/ β -catenin、BMP-Smad、PI3K/Akt 等。研究表明, 骨髓间充质干细胞来源的外泌体可通过上调 Bmp2、Bmp6、Bmpr1b、Mmp9 和 Sox9 等成骨相关基因的表达, 从而促进激素性股骨头坏死的成骨修复过程[57]。在骨不连模型中, 移植 BMSC-Exos 能够通过激活 BMP-2/Smad1/RUNX2 和 HIF-1 α /VEGF 信号通路, 促进成骨与血管生成, 加速愈合[12]。此外, 外泌体也通过 MAPK 通路促进成骨细胞增殖, 改善骨质疏松症[58]。在分子机制层面, BMSCs 来源的外泌体通过调节 KLF3-AS1/miR-338-3p 的表达, 促进成骨细胞增殖、迁移, 并抑制细胞凋亡[27]。体外研究进一步显示, BMSCs-Exos 中的长链非编码 RNA H19 和 TUG1 在促进内皮血管生成及骨折修复过程中具有重要作用[10] [59]。

2.2. 调节成骨细胞分化的作用

外泌体可通过携带特异的生物活性物质调控成骨细胞的分化进程, 从而实现促进骨形成与血管生成的目的[60]。例如, 外泌体中的 miRNA 能够靶向调控 Runx2、Osterix 等关键转录因子与调节因子的表达, 进而促进成骨细胞分化。动物实验进一步表明, 年轻 BMSCs 来源的外泌体能够增强老年大鼠在牵张成骨过程中的新骨形成。前期研究也发现, BMSCs-Exos 可通过提升 BMSCs 的增殖与成骨分化能力, 进而改善老龄大鼠牵张成骨模型中的骨组织修复效果[61]。此外, 骨髓间充质干细胞外泌体可促进成骨细胞增殖与分化, 并抑制其凋亡; 其中外泌体 miR-150-3p 水平的升高能够增强该作用, 而抑制 miR-150-3p 则会削弱该作用[62]。

2.3. 生长因子和 miRNA 在调控过程中的作用

外泌体所携带的多种生长因子和 miRNAs 对成骨分化具有重要的调节作用。这些活性分子可以直接或间接影响成骨相关基因的表达, 进而调节骨形成。例如 BMPs 可通过激活 Smad 信号途径促进成骨分化, 而 miR-29 则通过抑制成骨抑制因子的表达, 间接地促进成骨分化[20]。此外, 骨髓间充质干细胞来源的外泌体 miR-206 通过下调 E1f3 的表达, 促进骨关节炎的成骨细胞增殖与分化[23]。同时, 骨髓间充

质干细胞来源的外泌体 miR-29a 也被证明在调控血管生成与成骨过程中具有重要功能, 负载 miR-29a 的 BMSCs-Exos 可能成为治疗骨质疏松症的潜在靶点[15]。

总之, 外泌体可介导多种信号通路, 调控成骨细胞的分化, 并可运载多种生长因子及 miRNAs, 参与成骨进程的调节。这些发现不仅增进了对骨骼生物学的理解, 也为骨相关疾病的治疗提供了新的思路和策略。

3. 骨髓间充质干细胞来源外泌体用于骨组织工程研究

3.1. 骨再生材料的开发与应用

外泌体作为一种细胞外囊泡, 携带有生物活性分子, 如蛋白质、miRNA 等, 具有促进骨再生的潜力。研究表明, 骨髓间充质干细胞来源的外泌体可以通过携带生长因子、调节信号通路等方式, 促进骨组织的修复和再生[63]。然而, 未经修饰的外泌体在体内应用中存在靶向性差、易被快速清除、生物活性难以持久维持等局限性, 这为开发新型的骨再生材料提供了新思路, 可以通过将外泌体应用于生物支架或生物材料中, 实现更有效的骨组织修复

1) 水凝胶类载体: 实现可注射与智能响应释放

水凝胶凭借高含水量、良好的生物相容性及可调节的理化性质, 成为负载外泌体的理想载体。通过分子设计, 可赋予其智能响应特性, 实现精准递送。

① 温敏水凝胶(如 PLGA-PEG-PLGA)在体温下发生可逆的溶胶-凝胶转变, 可通过注射原位成型, 将外泌体固定于缺损部位并实现长效缓释, 有效延长其局部滞留与作用时间[64]。其模块化设计便于整合如携氧组分等功能单元, 以改善局部微环境, 协同增强促血管生成与成骨作用[65]。

② 光交联水凝胶(如甲基丙烯酰化明胶 GelMA)通过光照快速固化, 其交联密度、力学强度及降解速率可通过光照参数精确调控[66][67], 从而实现释放动力学的精准控制。将成骨活性肽(如胸腺素 β 4)与之结合, 可与 BMSCs-Exos 协同, 强化干细胞募集、血管生成与神经长入, 通过多机制耦合促进骨再生[66]。

③ pH 响应性水凝胶可感知骨缺损局部炎症所致的弱酸性微环境, 通过动态共价键(如席夫碱键)的断裂实现靶向释药[68]-[70], 特别适用于伴有感染或慢性炎症的复杂骨缺损修复[68]。

2) 三维多孔支架: 提供结构性支撑与生物活性界面

相较于水凝胶, 三维支架旨在为临界尺寸骨缺损提供稳定的结构性修复。

① 功能化复合支架: 通过将 BMSCs-Exos 负载于 3D 打印的分层多孔支架[71]、金属有机框架(MOF)[72]或明胶基双层支架[73]中, 可在缓释外泌体的同时引导细胞定向行为。例如, 复合镁离子(Mg^{2+})或工程化外泌体, 可协同促进成骨、血管化与神经支配, 启动一体化再生程序[71][72]。

② 仿生界面支架: 通过对支架表面进行功能化修饰(如静电吸附), 可高效捕获并缓释外泌体, 持续激活内源性修复通路(如通过特定 miRNA 促进血管生成), 从而加速骨缺损的内源性再生[74]。

不同生物材料的理化特性精准调控着 BMSCs-Exos 的递送与效能。水凝胶通过可调的孔径、交联度及降解行为管理外泌体的封装与缓释, 其可注射与智能响应性实现了微创精准给药。三维支架则依赖孔隙结构、表面化学与力学性能主导外泌体负载、细胞招募与组织长入。两者的结合, 推动骨修复从被动填充迈向能动态响应微环境、时序释放活性因子的智能化“活性”修复体系。

3.2. 临床治疗中的潜在应用

骨髓间充质干细胞来源的外泌体凭借其独特的生物学特性, 在多种疾病的治疗中展现出广阔的应用前景。在骨骼系统疾病治疗中展现出广阔前景, 其作用机制与应用研究已在多个领域取得进展。

1) 在骨折愈合与骨不连方面, BMSCs-Exos 能通过代谢重编程激活 HIF-1 等关键通路以优化修复微环境[75], 并通过递送甲基转移酶 METTL14 以 m6A 依赖的方式稳定 BMP2 mRNA, 从而促进成骨分化与骨折愈合[76], 将其与生物材料结合可进一步增强疗效, 例如, 负载于 RGD 修饰的水凝胶微粒中可协同促进成骨与血管生成[77], 而具有微/纳米层级结构的钛合金植入体表面则能促进 BMSCs 分泌外泌体, 从而增强骨整合[78]。

2) 在骨缺损修复领域, BMSCs-Exos 与先进生物材料结合构建的递送系统表现突出。例如, 负载经 Yoda1 预处理的外泌体的复合水凝胶能有效激活成骨信号, 促进颅骨缺损修复[79]; 基于脱细胞鱼鳞的仿生支架能缓释外泌体并引导骨再生[80]; 而 T β 4 功能化的光交联水凝胶则可协同促进血管生成、神经发生与成骨, 从而在大鼠模型中实现多机制协同的骨缺损修复[81]。

3) 在骨关节炎与软骨修复中, BMSCs-Exos 主要通过调控免疫微环境和直接保护软骨细胞发挥作用。其可促进巨噬细胞向抗炎 M2 表型极化, 减轻滑膜炎[82]; 所携带的 lncRNA MEG-3 能抑制软骨细胞老化与凋亡[82] [83]。经甲状旁腺激素 PTH 预处理后产生的外泌体可通过 let-7a-5p 抑制 IL-6/STAT3 通路, 促进软骨细胞增殖迁移, 最终延缓骨关节炎进展[84], 此外, BMSCs-Exos 中所富集的 lncRNA SNHG7, 可通过海绵吸附 miR-485-5p 上调铁死亡抑制蛋白 FSP1 的表达, 从而抑制 IL-1 β 诱导的软骨细胞炎症与铁死亡, 为骨关节炎治疗提供了新靶点[85]。

4) 在骨质疏松治疗方面, BMSCs-Exos 通过调控骨代谢平衡发挥作用。其携带的 miR-29a 是调控成骨与血管生成的关键因子[15]。此外, 它还能通过上调 TRIM25 介导促炎受体 TREM1 降解, 进而促进巨噬细胞向 M2 表型极化及成骨分化[86], 所携带的 lncRNA SNHG14, 可通过吸附 miR-27a-3p 上调其靶基因 LMNB1 的表达, 从而调控骨髓间充质干细胞成骨与成脂分化的平衡, 为骨质疏松治疗提供了新思路[87]。

5) 在椎间盘退变的治疗中, 缺氧预处理 BMSCs-Exos 能通过递送 BNIP3 激活线粒体自噬, 延缓髓核细胞衰老并缓解椎间盘变性[88], 作为细胞通讯的功能性载体, BMSCs-Exos 可介导细胞间通讯, 有效抑制髓核细胞凋亡并延缓椎间盘退变, 同时规避了直接细胞移植面临的免疫排斥等临床挑战, 是一种具有前景的无细胞治疗策略[89]。

临床转化方面, 外泌体制剂(如 ExoFlo™)已在部分领域进入临床探索阶段, 初步显示了其安全性与免疫调节潜力[90]。综上, BMSCs 来源的外泌体作为一种多效性、低免疫原性的无细胞治疗策略, 为骨折、骨缺损、骨关节炎、骨质疏松等多种骨骼系统疾病的干预提供了新颖且富有前景的研究方向。

3.3. 挑战和未来发展方向

尽管骨髓间充质干细胞来源的外泌体在骨组织工程中展现出巨大的潜力, 但仍面临着一些挑战。例如, 外泌体的提取和纯化技术仍需进一步优化, 生产成本较高, 临床应用的标准化和规范化亟待建立。此外, 外泌体的长期安全性和稳定性还需要深入研究。未来的发展方向包括优化外泌体的制备工艺、探索新型的外泌体载体和传递系统、建立临床应用的规范和指南, 以及加强外泌体的长期安全性评估等。

综上所述, 骨髓间充质干细胞来源的外泌体在骨组织工程中具有重要的应用前景, 可以作为新型的骨再生材料和临床治疗手段, 为骨损伤修复和骨相关疾病的治疗带来新的希望和机遇。

4. 结论

4.1. 对外泌体在成骨过程中调控机制的总结

在骨组织的再生和修复过程中, 外泌体扮演了重要的角色。研究表明, 外泌体源于间充质干细胞, 通过激活 Wnt/ β -catenin 信号通路和参与免疫调节等机制, 可以促进成骨细胞的活性, 影响破骨细胞的分

化,促进血管新生,从而调节骨组织再生修复过程。此外,外泌体通过转移 miRNA 影响受体细胞的分化,进而影响骨形成。

4.2. 对未来研究和临床应用的展望

外泌体作为一种新型的再生医学技术和给药载体,在骨相关疾病的治疗中具有巨大的潜力。未来的研究应重点聚焦外泌体在骨组织再生修复中的调控机制,进一步探索其与骨细胞间的相互作用,以优化外泌体的生产和应用。同时,临床应用方面需要加强临床试验的设计和管理,建立规范化的临床应用指南,推动外泌体技术在骨科疾病治疗中的临床转化和实际应用。

外泌体(exosome)是一种新型的可再生医疗及给药载体,有望用于骨相关疾病的治疗。因此,本课题将聚焦于 exosome 对骨组织再生修复的调节,并深入探讨 exosomes 与骨细胞之间的交互作用,为优化 exosomes 的制备及使用提供理论依据。

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参考文献

- [1] Wu, X., Yang, H., Liu, G., Sun, W., Li, J., Zhao, Y., *et al.* (2025) Osteomimix: A Multidimensional Biomimetic Cascade Strategy for Bone Defect Repair. *Advanced Materials*, **37**, Article ID: 2416715. <https://doi.org/10.1002/adma.202416715>
- [2] Vermeulen, S., Tahmasebi Birgani, Z. and Habibovic, P. (2022) Biomaterial-Induced Pathway Modulation for Bone Regeneration. *Biomaterials*, **283**, Article ID: 121431. <https://doi.org/10.1016/j.biomaterials.2022.121431>
- [3] Niu, Z., Fan, Y., Yin, L., Tong, Y., Yao, L., Ding, S., *et al.* (2025) Advancing Nanomedicine: For Bone Defect Repair and Regeneration. *International Journal of Nanomedicine*, **20**, 15043-15062. <https://doi.org/10.2147/ijn.s545353>
- [4] Ge, W., Mu, Z., Yang, S., Zeng, Y., Deng, Y., Lin, Y., *et al.* (2025) Biosensor-Based Methods for Exosome Detection with Applications to Disease Diagnosis. *Biosensors and Bioelectronics*, **279**, Article ID: 117362. <https://doi.org/10.1016/j.bios.2025.117362>
- [5] Hade, M.D., Suire, C.N. and Suo, Z. (2021) Mesenchymal Stem Cell-Derived Exosomes: Applications in Regenerative Medicine. *Cells*, **10**, Article 1959. <https://doi.org/10.3390/cells10081959>
- [6] Zhao, M., Li, Q., Chai, Y., Rong, R., He, L., Zhang, Y., *et al.* (2025) An Anti-CD19-Exosome Delivery System Navigates the Blood-Brain Barrier for Targeting of Central Nervous System Lymphoma. *Journal of Nanobiotechnology*, **23**, Article No. 173. <https://doi.org/10.1186/s12951-025-03238-9>
- [7] Zhang, M., Wan, L., Zhang, X., Wang, S., Li, F. and Yan, D. (2025) Exosome Circ-CBLB Promotes M1 Macrophage Polarization in Rheumatoid Arthritis through the TLR3/TRAF3 Signaling Axis. *Frontiers in Immunology*, **16**, Article 1627389. <https://doi.org/10.3389/fimmu.2025.1627389>
- [8] Huang, B., Zhang, Y., Chen, Z., Yuan, Y. and Lin, J. (2025) Exosome-Delivered METTL14 Drives Hypoxia-Induced Proliferation, Metastasis, and Glycolysis of Breast Cancer Cells through Regulating TRIM16-Mediated FGF7 Ubiquitination. *Breast Cancer Research*, **27**, Article No. 145. <https://doi.org/10.1186/s13058-025-02099-2>
- [9] Yang, C., Chen, J., Zhao, Y., Xu, Y., Wu, J., Xu, J., *et al.* (2025) Identification of Salivary Exosome-Derived miRNAs as Potential Biomarkers for Non-Invasive Diagnosis and Proactive Monitoring of Inflammatory Bowel Disease. *International Journal of Molecular Sciences*, **26**, Article 7750. <https://doi.org/10.3390/ijms26167750>
- [10] Behera, J., Kumar, A., Voor, M.J. and Tyagi, N. (2021) Exosomal lncRNA-H19 Promotes Osteogenesis and Angiogenesis through Mediating ANGPT1/Tie2-NO Signaling in CBS-Heterozygous Mice. *Theranostics*, **11**, 7715-7734. <https://doi.org/10.7150/thno.58410>
- [11] Qiao, X., Tang, J., Dou, L., Yang, S., Sun, Y., Mao, H., *et al.* (2023) Dental Pulp Stem Cell-Derived Exosomes Regulate Anti-Inflammatory and Osteogenesis in Periodontal Ligament Stem Cells and Promote the Repair of Experimental Periodontitis in Rats. *International Journal of Nanomedicine*, **18**, 4683-4703. <https://doi.org/10.2147/ijn.s420967>
- [12] Zhang, L., Jiao, G., Ren, S., Zhang, X., Li, C., Wu, W., *et al.* (2020) Exosomes from Bone Marrow Mesenchymal Stem Cells Enhance Fracture Healing through the Promotion of Osteogenesis and Angiogenesis in a Rat Model of Nonunion. *Stem Cell Research & Therapy*, **11**, Article No. 38. <https://doi.org/10.1186/s13287-020-1562-9>
- [13] Zha, Y., Li, Y., Lin, T., Chen, J., Zhang, S. and Wang, J. (2021) Progenitor Cell-Derived Exosomes Endowed with VEGF

- Plasmids Enhance Osteogenic Induction and Vascular Remodeling in Large Segmental Bone Defects. *Theranostics*, **11**, 397-409. <https://doi.org/10.7150/thno.50741>
- [14] Sun, R., Xu, S. and Wang, Z. (2019) Rat Sinus Mucosa- and Periosteum-Derived Exosomes Accelerate Osteogenesis. *Journal of Cellular Physiology*, **234**, 21947-21961. <https://doi.org/10.1002/jcp.28758>
- [15] Lu, G., Cheng, P., Liu, T. and Wang, Z. (2020) BMSC-Derived Exosomal miR-29a Promotes Angiogenesis and Osteogenesis. *Frontiers in Cell and Developmental Biology*, **8**, Article 608521. <https://doi.org/10.3389/fcell.2020.608521>
- [16] Pei, L., Wang, Y., Ye, M., Sun, W., Zhang, J., Gao, P., *et al.* (2025) Exosome-Functionalized Hydrogels Improve Cartilage Repair by Modulating BMSCs Migration and Differentiation. *ACS Applied Materials & Interfaces*, **17**, 41729-41746. <https://doi.org/10.1021/acsami.5c07676>
- [17] Tan, S.H.S., Wong, J.R.Y., Sim, S.J.Y., Tjio, C.K.E., Wong, K.L., Chew, J.R.J., *et al.* (2020) Mesenchymal Stem Cell Exosomes in Bone Regenerative Strategies—A Systematic Review of Preclinical Studies. *Materials Today Bio*, **7**, Article ID: 100067. <https://doi.org/10.1016/j.mtbio.2020.100067>
- [18] Huber, J., Griffin, M.F., Longaker, M.T. and Quarto, N. (2022) Exosomes: A Tool for Bone Tissue Engineering. *Tissue Engineering Part B: Reviews*, **28**, 101-113. <https://doi.org/10.1089/ten.teb.2020.0246>
- [19] Peng, X., Cui, H., Tan, S., Wen, B., Luo, X., Chen, S., *et al.* (2025) The Engineered Bone Marrow Mesenchymal Stem Cell-Derived Exosome: A New Strategy for the Treatment of Inflammatory Diseases. *International Immunopharmacology*, **162**, Article ID: 115136. <https://doi.org/10.1016/j.intimp.2025.115136>
- [20] Zhang, Y., Cao, X., Li, P., Fan, Y., Zhang, L., Ma, X., *et al.* (2021) MicroRNA-935-Modified Bone Marrow Mesenchymal Stem Cells-Derived Exosomes Enhance Osteoblast Proliferation and Differentiation in Osteoporotic Rats. *Life Sciences*, **272**, Article ID: 119204. <https://doi.org/10.1016/j.lfs.2021.119204>
- [21] Yang, X., Yang, J., Lei, P. and Wen, T. (2019) LncRNA MALAT1 Shuttled by Bone Marrow-Derived Mesenchymal Stem Cells-Secreted Exosomes Alleviates Osteoporosis through Mediating MicroRNA-34c/SATB2 Axis. *Aging*, **11**, 8777-8791. <https://doi.org/10.18632/aging.102264>
- [22] Osugi, M., Katagiri, W., Yoshimi, R., Inukai, T., Hibi, H. and Ueda, M. (2012) Conditioned Media from Mesenchymal Stem Cells Enhanced Bone Regeneration in Rat Calvarial Bone Defects. *Tissue Engineering Part A*, **18**, 1479-1489. <https://doi.org/10.1089/ten.tea.2011.0325>
- [23] Huang, Y., Zhang, X., Zhan, J., Yan, Z., Chen, D., Xue, X., *et al.* (2021) Bone Marrow Mesenchymal Stem Cell-Derived Exosomal miR-206 Promotes Osteoblast Proliferation and Differentiation in Osteoarthritis by Reducing Elf3. *Journal of Cellular and Molecular Medicine*, **25**, 7734-7745. <https://doi.org/10.1111/jcmm.16654>
- [24] Zhuang, Y., Wang, Y., Tang, X., Zheng, N., Lin, S., Ke, J., *et al.* (2025) Exosomes Generated from Bone Marrow Mesenchymal Stem Cells Limit the Damage Caused by Myocardial Ischemia-Reperfusion via Controlling the AMPK/PGC-1 α Signaling Pathway. *Biochimica et Biophysica Acta (BBA)—Molecular Basis of Disease*, **1871**, Article ID: 167890. <https://doi.org/10.1016/j.bbadis.2025.167890>
- [25] Jing, Y., Cai, Y., Li, Q., Zheng, Z., Yang, H., Yu, Y., *et al.* (2025) Empagliflozin-Pretreated BMSC Exosomes Attenuate Myocardial Ischemia-Reperfusion Injury by Enhancing Atad3a/Pink1-Dependent Mitophagy. *Stem Cell Research & Therapy*, **16**, Article No. 595. <https://doi.org/10.1186/s13287-025-04715-6>
- [26] Yang, H. and Chen, J. (2022) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Carrying Long Noncoding RNA ZFAS1 Alleviate Oxidative Stress and Inflammation in Ischemic Stroke by Inhibiting MicroRNA-15a-5p. *Metabolic Brain Disease*, **37**, 2545-2557. <https://doi.org/10.1007/s11011-022-00997-4>
- [27] Liu, D., Zhao, X., Zhang, Q., Zhou, F. and Tong, X. (2024) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Promote Osteoblast Proliferation, Migration and Inhibit Apoptosis by Regulating KLF3-AS1/miR-338-3p. *BMC Musculoskeletal Disorders*, **25**, Article No. 122. <https://doi.org/10.1186/s12891-024-07236-0>
- [28] Yu, H., Cheng, J., Shi, W., Ren, B., Zhao, F., Shi, Y., *et al.* (2020) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Promote Tendon Regeneration by Facilitating the Proliferation and Migration of Endogenous Tendon Stem/Progenitor Cells. *Acta Biomaterialia*, **106**, 328-341. <https://doi.org/10.1016/j.actbio.2020.01.051>
- [29] Zhang, M., Johnson-Stephenson, T.K., Wang, W., Wang, Y., Li, J., Li, L., *et al.* (2022) Mesenchymal Stem Cell-Derived Exosome-Educated Macrophages Alleviate Systemic Lupus Erythematosus by Promoting Efferocytosis and Recruitment of IL-17⁺ Regulatory T Cell. *Stem Cell Research & Therapy*, **13**, Article No. 484. <https://doi.org/10.1186/s13287-022-03174-7>
- [30] Liu, L., Zhou, Y., Zhao, X., Yang, X., Wan, X., An, Z., *et al.* (2023) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Alleviate Diabetic Kidney Disease in Rats by Inhibiting Apoptosis and Inflammation. *Frontiers in Bioscience-Landmark*, **28**, Article 203. <https://doi.org/10.31083/j.fbl2809203>
- [31] Tang, S., Tang, T., Gao, G., Wei, Q., Sun, K. and Huang, W. (2021) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Inhibit Chondrocyte Apoptosis and the Expression of MMPs by Regulating DRP1-Mediated Mitophagy. *Acta Histochemica*, **123**, Article ID: 151796. <https://doi.org/10.1016/j.acthis.2021.151796>

- [32] Liu, Y., Guo, Y., Bao, S., Huang, H., Liu, W. and Guo, W. (2022) Bone Marrow Mesenchymal Stem Cell-Derived Exosomal MicroRNA-381-3p Alleviates Vascular Calcification in Chronic Kidney Disease by Targeting NFAT5. *Cell Death & Disease*, **13**, Article No. 278. <https://doi.org/10.1038/s41419-022-04703-1>
- [33] Shen, X., Qin, J., Wei, Z. and Liu, F. (2023) Bone Marrow Mesenchymal Stem Cell Exosome-Derived lncRNA TUC339 Influences the Progression of Osteoarthritis by Regulating Synovial Macrophage Polarization and Chondrocyte Apoptosis. *Biomedicine & Pharmacotherapy*, **167**, Article ID: 115488. <https://doi.org/10.1016/j.biopha.2023.115488>
- [34] Li, S., Huang, C., Tu, C., Chen, R., Ren, X., Qi, L., et al. (2022) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Shuttling miR-150-5p Alleviates Mechanical Allodynia in Rats by Targeting NOTCH2 in Microglia. *Molecular Medicine*, **28**, Article No. 133. <https://doi.org/10.1186/s10020-022-00561-x>
- [35] Chu, S., Yu, T., Wang, W., Wu, H., Zhu, F., Wei, C., et al. (2023) Exosomes Derived from EPHB2-Overexpressing Bone Marrow Mesenchymal Stem Cells Regulate Immune Balance and Repair Barrier Function. *Biotechnology Letters*, **45**, 601-617. <https://doi.org/10.1007/s10529-023-03358-y>
- [36] Li, X., Hu, X., Chen, Q. and Jiang, T. (2023) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Carrying E3 Ubiquitin Ligase ITCH Attenuated Cardiomyocyte Apoptosis by Mediating Apoptosis Signal-Regulated Kinase-1. *Pharmacogenetics and Genomics*, **33**, 117-125. <https://doi.org/10.1097/fpc.0000000000000499>
- [37] Xu, C., Wang, H., Dong, W., Cheng, W., Su, Y., Yang, Q., et al. (2025) Exosomes from LPS-Pretreated BMSCs Treated Periodontitis via Improving Oxidative Stress. *Stem Cell Research & Therapy*. <https://doi.org/10.1186/s13287-025-04860-y>
- [38] Wang, W. and Yin, J. (2025) Exosomal miR-203 from Bone Marrow Stem Cells Targets the SOCS3/NF- κ B Pathway to Regulate Neuroinflammation in Temporal Lobe Epilepsy. *World Journal of Stem Cells*, **17**, Article ID: 101395. <https://doi.org/10.4252/wjsc.v17.i2.101395>
- [39] Liang, W., Li, Y., Ji, Y., Kang, R., Zhang, K., Su, X., et al. (2024) Exosomes Derived from Bone Marrow Mesenchymal Stem Cells Induce the Proliferation and Osteogenic Differentiation and Regulate the Inflammatory State in Osteomyelitis *In Vitro* Model. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **398**, 1695-1705. <https://doi.org/10.1007/s00210-024-03357-4>
- [40] Deng, H., Zhou, W., Wei, J., Jin, T., Chen, Y., Zhu, L., et al. (2025) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Alleviating Sepsis-Induced Lung Injury by Inhibiting Ferroptosis of Macrophages. *International Immunopharmacology*, **158**, Article ID: 114789. <https://doi.org/10.1016/j.intimp.2025.114789>
- [41] Tandon, R. and Srivastava, N. (2025) Unravelling Exosome Paradigm: Therapeutic, Diagnostic and Theranostics Application and Regulatory Consideration. *Life Sciences*, **366**, Article ID: 123472. <https://doi.org/10.1016/j.lfs.2025.123472>
- [42] Zhang, J., Li, S., Li, L., Li, M., Guo, C., Yao, J., et al. (2015) Exosome and Exosomal MicroRNA: Trafficking, Sorting, and Function. *Genomics, Proteomics & Bioinformatics*, **13**, 17-24. <https://doi.org/10.1016/j.gpb.2015.02.001>
- [43] Kalluri, R. and LeBleu, V.S. (2020) The Biology, Function, and Biomedical Applications of Exosomes. *Science*, **367**, eaau6977. <https://doi.org/10.1126/science.aau6977>
- [44] Pegtel, D.M. and Gould, S.J. (2019) Exosomes. *Annual Review of Biochemistry*, **88**, 487-514. <https://doi.org/10.1146/annurev-biochem-013118-111902>
- [45] Phinney, D.G. and Pittenger, M.F. (2017) Concise Review: MSC-Derived Exosomes for Cell-Free Therapy. *Stem Cells*, **35**, 851-858. <https://doi.org/10.1002/stem.2575>
- [46] Vizoso, F., Eiro, N., Cid, S., Schneider, J. and Perez-Fernandez, R. (2017) Mesenchymal Stem Cell Secretome: Toward Cell-Free Therapeutic Strategies in Regenerative Medicine. *International Journal of Molecular Sciences*, **18**, Article 1852. <https://doi.org/10.3390/ijms18091852>
- [47] Sang, H., Zhao, R., Lai, G., Deng, Z., Zhuang, W., Wu, M., et al. (2023) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Attenuate the Maturation of Dendritic Cells and Reduce the Rejection of Allogeneic Transplantation. *Advances in Clinical and Experimental Medicine*, **32**, 551-561. <https://doi.org/10.17219/acem/156643>
- [48] Yang, Y., Li, Y., Zhang, S., Cao, L., Zhang, Y. and Fang, B. (2023) MiR-199a-5p from Bone Marrow Mesenchymal Stem Cell Exosomes Promotes the Proliferation of Neural Stem Cells by Targeting GSK-3 β . *Acta Biochimica et Biophysica Sinica*, **55**, 783-794. <https://doi.org/10.3724/abbs.2023024>
- [49] Mead, B. and Tomarev, S. (2017) Bone Marrow-Derived Mesenchymal Stem Cells-Derived Exosomes Promote Survival of Retinal Ganglion Cells through Mirna-Dependent Mechanisms. *Stem Cells Translational Medicine*, **6**, 1273-1285. <https://doi.org/10.1002/sctm.16-0428>
- [50] Zhang, F., Lu, Y., Wang, M., Zhu, J., Li, J., Zhang, P., et al. (2020) Exosomes Derived from Human Bone Marrow Mesenchymal Stem Cells Transfer miR-222-3p to Suppress Acute Myeloid Leukemia Cell Proliferation by Targeting IRF2/INPP4B. *Molecular and Cellular Probes*, **51**, Article ID: 101513. <https://doi.org/10.1016/j.mcp.2020.101513>
- [51] Zhang, F., Guo, J., Zhang, Z., Qian, Y., Wang, G., Duan, M., et al. (2022) Mesenchymal Stem Cell-Derived Exosome: A Tumor Regulator and Carrier for Targeted Tumor Therapy. *Cancer Letters*, **526**, 29-40.

- <https://doi.org/10.1016/j.canlet.2021.11.015>
- [52] Zhang, H., Wang, J., Ren, T., Huang, Y., Liang, X., Yu, Y., *et al.* (2020) Bone Marrow Mesenchymal Stem Cell-Derived Exosomal miR-206 Inhibits Osteosarcoma Progression by Targeting TRA2B. *Cancer Letters*, **490**, 54-65. <https://doi.org/10.1016/j.canlet.2020.07.008>
- [53] Li, Y.H. (2021) Bone Marrow Mesenchymal Stem Cell-Derived Exosomal miR-338-3p Represses Progression of Hepatocellular Carcinoma by Targeting ETS1. MicroRNA-338-3p Inhibits the Progression of Bladder Cancer through Regulating ETS1 Expression. *Journal of Biological Regulators and Homeostatic Agents*, **35**, 617-627. <https://doi.org/10.23812/20-638-a>
- [54] He, C., Zheng, S., Luo, Y. and Wang, B. (2018) Exosome Theranostics: Biology and Translational Medicine. *Theranostics*, **8**, 237-255. <https://doi.org/10.7150/thno.21945>
- [55] Wei, H., Chen, J., Wang, S., Fu, F., Zhu, X., Wu, C., *et al.* (2019) A Nanodrug Consisting of Doxorubicin and Exosome Derived from Mesenchymal Stem Cells for Osteosarcoma Treatment *In Vitro*. *International Journal of Nanomedicine*, **14**, 8603-8610. <https://doi.org/10.2147/ijn.s218988>
- [56] Guo, J., Wang, F., Hu, Y., Luo, Y., Wei, Y., Xu, K., *et al.* (2023) Exosome-Based Bone-Targeting Drug Delivery Alleviates Impaired Osteoblastic Bone Formation and Bone Loss in Inflammatory Bowel Diseases. *Cell Reports Medicine*, **4**, Article ID: 100881. <https://doi.org/10.1016/j.xcrm.2022.100881>
- [57] Fang, S., Li, Y. and Chen, P. (2018) Osteogenic Effect of Bone Marrow Mesenchymal Stem Cell-Derived Exosomes on Steroid-Induced Osteonecrosis of the Femoral Head. *Drug Design, Development and Therapy*, **13**, 45-55. <https://doi.org/10.2147/dddt.s178698>
- [58] Zhao, P., Xiao, L., Peng, J., *et al.* (2018) Exosomes Derived from Bone Marrow Mesenchymal Stem Cells Improve Osteoporosis through Promoting Osteoblast Proliferation via MAPK Pathway. *European Review for Medical and Pharmacological Sciences*, **22**, 3962-3970.
- [59] Li, W., Li, L., Cui, R., Chen, X., Hu, H. and Qiu, Y. (2023) Bone Marrow Mesenchymal Stem Cells Derived Exosomal Lnc TUG1 Promotes Bone Fracture Recovery via miR-22-5p/Anxa8 Axis. *Human Cell*, **36**, 1041-1053. <https://doi.org/10.1007/s13577-023-00881-y>
- [60] Zhang, B., Huang, J., Liu, J., Lin, F., Ding, Z. and Xu, J. (2021) Injectable Composite Hydrogel Promotes Osteogenesis and Angiogenesis in Spinal Fusion by Optimizing the Bone Marrow Mesenchymal Stem Cell Microenvironment and Exosomes Secretion. *Materials Science and Engineering: C*, **123**, Article ID: 111782. <https://doi.org/10.1016/j.msec.2020.111782>
- [61] Jia, Y., Qiu, S., Xu, J., Kang, Q. and Chai, Y. (2020) Exosomes Secreted by Young Mesenchymal Stem Cells Promote New Bone Formation during Distraction Osteogenesis in Older Rats. *Calcified Tissue International*, **106**, 509-517. <https://doi.org/10.1007/s00223-019-00656-4>
- [62] Qiu, M., Zhai, S., Fu, Q. and Liu, D. (2021) Bone Marrow Mesenchymal Stem Cells-Derived Exosomal MicroRNA-150-3p Promotes Osteoblast Proliferation and Differentiation in Osteoporosis. *Human Gene Therapy*, **32**, 717-729. <https://doi.org/10.1089/hum.2020.005>
- [63] Xiang, K., Hao, M., Zhang, Z., Zhang, K., Sun, H. and Zhang, L. (2025) Engineering 3D-BMSC Exosome-Based Hydrogels That Collaboratively Regulate Bone Microenvironment and Promote Osteogenesis for Enhanced Cell-Free Bone Regeneration. *Materials Today Bio*, **32**, Article ID: 101881. <https://doi.org/10.1016/j.mtbio.2025.101881>
- [64] Wang, B., Ren, Y., Xiao, X., Liu, X., Wang, Y. and Wang, Y. (2026) An Emerging MSC-Exosome Delivery Strategy: Injectable Temperature-Sensitive Hydrogels Encapsulate Exosomes for Enhanced Therapeutic Efficacy. *Drug Discovery Today*, **31**, Article ID: 104586. <https://doi.org/10.1016/j.drudis.2025.104586>
- [65] Wei, Z., Ren, J., Hu, J. and Wei, H. (2025) Polyethylene Glycol-Polyester Based Temperature-Sensitive Hydrogel Delivering Mesenchymal Stem Cell-Derived Exosomes Enhances Acute Skin Wound Healing. *Frontiers in Bioengineering and Biotechnology*, **13**, Article 1730631. <https://doi.org/10.3389/fbioe.2025.1730631>
- [66] Liu, B., Chen, L., Huang, C., Zhang, H., Zhou, H., Chen, Y., *et al.* (2025) A Sprayable Exosome-Loaded Hydrogel with Controlled Release and Multifunctional Synergistic Effects for Diabetic Wound Healing. *Materials Today Bio*, **34**, Article ID: 102159. <https://doi.org/10.1016/j.mtbio.2025.102159>
- [67] Li, L., Ye, C., Wu, Z. and Wu, R. (2025) Plant Exosome-Loaded Intelligent Hydrogels for Osteoporotic Bone Regeneration: Mechanisms and Applications. *International Journal of Nanomedicine*, **20**, 15863-15881. <https://doi.org/10.2147/ijn.s567471>
- [68] Li, S., Li, Y., Chen, Y., Guo, J., Zou, Q. and Ding, Q. (2025) pH-Responsive Hydrogel System Loaded with Curcumin-Preconditioned Mesenchymal Stem Cell Exosomes for Enhanced Diabetic Wound Healing in Orthopedic Applications. *Frontiers in Bioengineering and Biotechnology*, **13**, Article 1688905. <https://doi.org/10.3389/fbioe.2025.1688905>
- [69] Yang, P., Ju, Y., Shen, N., Zhu, S., He, J., Yang, L., *et al.* (2024) Exo-Loaded Gox-Modified Smart-Response Self-Healing Hydrogel Improves the Microenvironment and Promotes Wound Healing in Diabetic Wounds. *Advanced Healthcare Materials*, **14**, Article ID: 2403304. <https://doi.org/10.1002/adhm.202403304>

- [70] Cheng, N., Luo, Q., Yang, Y., Shao, N., Nie, T., Deng, X., *et al.* (2025) Injectable pH Responsive Conductive Hydrogel for Intelligent Delivery of Metformin and Exosomes to Enhance Cardiac Repair after Myocardial Ischemia-Reperfusion Injury. *Advanced Science*, **12**, Article ID: 2410590. <https://doi.org/10.1002/advs.202410590>
- [71] Sun, T., Feng, Z., He, W., Li, C., Han, S., Li, Z., *et al.* (2023) Novel 3D-Printing Bilayer Gelma-Based Hydrogel Containing BP, β -TCP and Exosomes for Cartilage-Bone Integrated Repair. *Biofabrication*, **16**, Article ID: 015008. <https://doi.org/10.1088/1758-5090/ad04fe>
- [72] Kang, Y., Xu, C., Meng, L., Dong, X., Qi, M. and Jiang, D. (2022) Exosome-Functionalized Magnesium-Organic Framework-Based Scaffolds with Osteogenic, Angiogenic and Anti-Inflammatory Properties for Accelerated Bone Regeneration. *Bioactive Materials*, **18**, 26-41. <https://doi.org/10.1016/j.bioactmat.2022.02.012>
- [73] Lian, M., Qiao, Z., Qiao, S., Zhang, X., Lin, J., Xu, R., *et al.* (2024) Nerve Growth Factor-Preconditioned Mesenchymal Stem Cell-Derived Exosome-Functionalized 3D-Printed Hierarchical Porous Scaffolds with Neuro-Promotive Properties for Enhancing Innervated Bone Regeneration. *ACS Nano*, **18**, 7504-7520. <https://doi.org/10.1021/acsnano.3c11890>
- [74] Wang, L., Yang, L., Tian, L., Guo, B., Dai, T., Lv, Q., *et al.* (2025) Exosome-Capturing Scaffold Promotes Endogenous Bone Regeneration through Neutrophil-Derived Exosomes by Enhancing Fast Vascularization. *Biomaterials*, **319**, Article ID: 123215. <https://doi.org/10.1016/j.biomaterials.2025.123215>
- [75] Li, C., Chen, M., Guo, L., Yu, D., Xu, Z., Chen, B., *et al.* (2025) Bone Marrow Mesenchymal Stem Cell Exosomes Improve Fracture Union via Remodeling Metabolism in Nonunion Rat Model. *Journal of Orthopaedic Surgery and Research*, **20**, Article No. 308. <https://doi.org/10.1186/s13018-025-05721-3>
- [76] Liu, M., Guo, Z., Shi, X., Dong, Z., Qiao, H., Wang, D., *et al.* (2025) Bone Marrow Mesenchymal Stem Cell-Derived Exosomal METTL14 Promotes the Osteogenic Differentiation of MC3T3-E1 Cells by Regulating BMP2 in Bone Fracture Recovery. *Human Cell*, **38**, Article No. 141. <https://doi.org/10.1007/s13577-025-01271-2>
- [77] Pan, S., Yin, Z., Shi, C., Xiu, H., Wu, G., Heng, Y., *et al.* (2023) Multifunctional Injectable Hydrogel Microparticles Loaded with miR-29a Abundant BMSCs Derived Exosomes Enhanced Bone Regeneration by Regulating Osteogenesis and Angiogenesis. *Small*, **20**, Article ID: 2306721. <https://doi.org/10.1002/smll.202306721>
- [78] Zhang, Z., Xu, R., Yang, Y., Liang, C., Yu, X., Liu, Y., *et al.* (2021) Micro/Nano-Textured Hierarchical Titanium Topography Promotes Exosome Biogenesis and Secretion to Improve Osseointegration. *Journal of Nanobiotechnology*, **19**, Article No. 78. <https://doi.org/10.1186/s12951-021-00826-3>
- [79] He, X., Liu, Y., Dai, Z., Chen, Y., Liu, W., Dai, H., *et al.* (2024) Yoda1 Pretreated BMSC Derived Exosomes Accelerate Osteogenesis by Activating Phospho-Erk Signaling via Yoda1-Mediated Signal Transmission. *Journal of Nanobiotechnology*, **22**, Article No. 407. <https://doi.org/10.1186/s12951-024-02669-0>
- [80] Wang, Y., Kong, B., Chen, X., Liu, R., Zhao, Y., Gu, Z., *et al.* (2022) BMSC Exosome-Enriched Acellular Fish Scale Scaffolds Promote Bone Regeneration. *Journal of Nanobiotechnology*, **20**, Article No. 444. <https://doi.org/10.1186/s12951-022-01646-9>
- [81] Xi, Y., Zhang, Z., Zhao, Z., Qiu, B., Wang, W., Xu, G., *et al.* (2025) Injectable Thymosin B4-Modified Hyaluronic Acid Hydrogel with Exosomes for Stem Cell Homing and Neuronic-Angiogenic-Osteogenic Coupled Cranial Repair. *ACS Nano*, **19**, 22710-22724. <https://doi.org/10.1021/acsnano.4c10386>
- [82] Jin, Y., Xu, M., Zhu, H., Dong, C., Ji, J., Liu, Y., *et al.* (2021) Therapeutic Effects of Bone Marrow Mesenchymal Stem Cells-Derived Exosomes on Osteoarthritis. *Journal of Cellular and Molecular Medicine*, **25**, 9281-9294. <https://doi.org/10.1111/jcmm.16860>
- [83] He, L., He, T., Xing, J., Zhou, Q., Fan, L., Liu, C., *et al.* (2020) Bone Marrow Mesenchymal Stem Cell-Derived Exosomes Protect Cartilage Damage and Relieve Knee Osteoarthritis Pain in a Rat Model of Osteoarthritis. *Stem Cell Research & Therapy*, **11**, Article No. 276. <https://doi.org/10.1186/s13287-020-01781-w>
- [84] Shao, L., Ding, L., Li, W., Zhang, C., Xia, Y., Zeng, M., *et al.* (2025) Let-7a-5p Derived from Parathyroid Hormone (1-34)-Preconditioned BMSCs Exosomes Delays the Progression of Osteoarthritis by Promoting Chondrocyte Proliferation and Migration. *Stem Cell Research & Therapy*, **16**, Article No. 299. <https://doi.org/10.1186/s13287-025-04416-0>
- [85] Wang, Y., Hu, K., Liao, C., Han, T., Jiang, F., Gao, Z., *et al.* (2024) Exosomes-Shuttled LncRNA SNHG7 by Bone Marrow Mesenchymal Stem Cells Alleviates Osteoarthritis through Targeting miR-485-5p/FSP1 Axis-Mediated Chondrocytes Ferroptosis and Inflammation. *Tissue Engineering and Regenerative Medicine*, **21**, 1203-1216. <https://doi.org/10.1007/s13770-024-00668-8>
- [86] Zhang, Y., Bai, J., Xiao, B. and Li, C. (2024) BMSC-Derived Exosomes Promote Osteoporosis Alleviation via M2 Macrophage Polarization. *Molecular Medicine*, **30**, Article No. 220. <https://doi.org/10.1186/s10020-024-00904-w>
- [87] Tang, J., Yu, H., Ruan, R., Chen, R. and Zhu, Z. (2025) lncRNA SNHG14 Delivered by Bone Marrow Mesenchymal Stem Cells-Secreted Exosomes Regulates Osteogenesis and Adipogenesis in Osteoporosis by Mediating the miR-27a-3p/LMNB1 Axis. *The Kaohsiung Journal of Medical Sciences*, **41**, e70004. <https://doi.org/10.1002/kjm2.70004>
- [88] Jin, Y., Wu, O., Chen, Q., Chen, L., Zhang, Z., Tian, H., *et al.* (2024) Hypoxia-Preconditioned BMSC-Derived Exosomes

Induce Mitophagy via the BNIP3-ANAX2 Axis to Alleviate Intervertebral Disc Degeneration. *Advanced Science*, **11**, Article ID: 2404275. <https://doi.org/10.1002/advs.202404275>

- [89] Zhang, X., Chen, X., Qi, J., Zhou, H., Zhao, X., Hu, Y., *et al.* (2022) New Hope for Intervertebral Disc Degeneration: Bone Marrow Mesenchymal Stem Cells and Exosomes Derived from Bone Marrow Mesenchymal Stem Cell Transplantation. *Current Gene Therapy*, **22**, 291-302. <https://doi.org/10.2174/1566523221666211012092855>
- [90] Sengupta, V., Sengupta, S., Lazo, A., Woods, P., Nolan, A. and Bremer, N. (2020) Exosomes Derived from Bone Marrow Mesenchymal Stem Cells as Treatment for Severe Covid-19. *Stem Cells and Development*, **29**, 747-754. <https://doi.org/10.1089/scd.2020.0080>