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综 述

中药调控外泌体miRNA治疗股骨头坏死研究进展*

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[摘要] 综述外泌体miRNA在股骨头坏死中的研究现状,总结中医药调控外泌体miRNA治疗股骨头坏死的研究进展。外泌体miRNA通过促进成骨、抑制破骨、促进血管生成、调节炎症及调控信号通路,在股骨头坏死的治疗中显示出巨大的潜力,同时外泌体miRNA有助于股骨头坏死的早期诊断。中医药在股骨头坏死的治疗中具有独特的优势,能够通过调控外泌体miRNA的分泌和功能来发挥治疗作用。

[关键词] 股骨头坏死;外泌体;miRNA;中药;综述
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Research Progress on the Regulation of Exosomal miRNA by Traditional Chinese Medicine in the Treatment of Femoral Head Necrosis

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[Abstract] This paper reviews the research status of exosomal miRNAs in femoral head necrosis, and summarizes the research progress of traditional Chinese medicine in treating femoral head necrosis by regulating exosomal miRNAs. Exosomal miRNAs show great potential in the treatment of femoral head necrosis by promoting osteogenesis, inhibiting osteoclastogenesis, promoting angiogenesis, regulating inflammation, and controlling signaling pathways. Meanwhile, exosomal miRNAs are helpful for the early diagnosis of femoral head necrosis. Traditional Chinese medicine has unique advantages in the treatment of femoral head necrosis, and can exert therapeutic effects by regulating the secretion and function of exosomal miRNAs.

[Keywords] femoral head necrosis; exosomes; miRNA; Chinese medicine; review

股骨头坏死(osteonecrosis of the femoral head,ONFH)是一种由于股骨头局部静脉淤滞,动脉血液供应受损,导致骨细胞死亡和骨组织结构破坏的疾病。ONFH是一种临床常见的难治性疾病。其病因复杂多样,主要分为创伤性股骨头坏死和非创伤性股骨头坏死两大类。在中国,ONFH主要风险因素包括长期使用糖皮质激素、酗酒、吸烟、创伤、血液疾病、某些免疫系统疾病等。尽管日益成熟的髋关节置换术能够帮助患者减轻疼痛,改善功能,提高生活质量,但仍面临着使用年限、感染风险、术后并发症、活动受限、费用较高等问题,给患者及社会带来沉重的负担。因此,早期诊断并使用合适的保髋治疗方法能够减轻患者所遭受的痛苦和伤害。

外泌体(exosome,Exos)的内部包裹了多种生物活性物

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质，包括蛋白质、脂质、mRNA、miRNA等。外泌体miRNA可参与细胞间通信，进入靶细胞调控基因表达。在生理状态下，外泌体miRNA能调节细胞增殖、分化、凋亡，而在病理状态时，外泌体miRNA则与肿瘤转移、神经退行性疾病进程相关[1-2]。在骨相关疾病中，外泌体miRNA可以有效促进骨组织修复与再生，改善微环境，调节细胞凋亡，同时外泌体miRNA能调节骨稳态，为ONFH的治疗打开了全新的局面。本文综述了当前外泌体miRNA在治疗股骨头坏死领域的研究现状和进展，并总结了中药调控外泌体miRNA治疗股骨头坏死的研究进展。

1 外泌体概述

外泌体是一种通过连续的内吞-排泄过程形成的直径为40~150 nm的微囊泡，其具有脂质双层膜结构，源自细胞分泌的内体囊泡[3]。外泌体的形成过程主要涉及以下步骤：首先，内体膜通过向内出芽的方式产生多泡体；然后，多泡体与质膜融合，管腔囊泡得以释放，最终形成外泌体[4]。多种细胞都可以分泌外泌体，如脂肪细胞、内皮细胞、血液细胞、肿瘤细胞、间充质干细胞等[5]。外泌体miRNA作为一种生物标志物，可以用于多种疾病的诊断、治疗及预测治疗效果。同时，外泌体发挥治疗效果的途径是通过转运小分子、生物活性分子及核酸药物到相应靶点[6]。因此，作为一种载体，外泌体miRNA可用于疾病的治疗和药物的递送[7-8]。外泌体miRNA与骨质疏松症、骨关节炎、骨折等骨关节疾病密切相关，可通过促进血管内皮细胞的增殖、迁移及成骨细胞的增殖、分化，从而在骨代谢相关疾病中发挥血管生成和成骨调节的重要作用[9-12]。

2 外泌体miRNA在ONFH中的诊断价值

早期诊断和干预不仅在保护股骨头塌陷方面起着至关重要的作用，而且也是成功治疗ONFH的必要条件[13]。目前，ONFH的诊断方式主要为磁共振成像（MRI），但MRI的成本和不便给患者和医疗保健系统带来了沉重的负担。同时早期ONFH通常无症状，并且没有敏感或特异性的血液学指标。因此，有必要找到一种方便的实验室检查，以便及早预测ONFH的发生和发展。外泌体广泛存在于在血液、尿液和唾液等生物体液中，同时与传统的循环标志物相比，外泌体稳定，且在体液中的半衰期更长。此外，与组织病理学检查所需的样本相比，体液样本不仅易获取，还可重复获得，而且获取方式侵入性更小[14]。外泌体在ONFH的诊断当中具有巨大的应用潜力。miR-135b-5p靶向骨钙素（osteocalcin，OCN）、骨唾液蛋白（bonesialoprotein，BSP）、Runt相关转录因子2（runt-related transcription factor-2，RUNX2）和成骨细胞特异性转录因子（osterix，Osx）可影响骨髓间充质干细胞（bone marrow derived mesenchymal stem cells，BMSC）分化为成骨细胞，因此miR-135b-5p可能代表一种有前途的无创生物标志物，用于诊断ONFH[15]。特异性尿外泌体miR-200b-3p和miR-206在ONFH中差异表达，可作为ONFH早期诊断的生物标志物[16]。定量实时聚合酶链反应结果表明，ONFH患者血清中miR-93-5p和miR-320a的表达升高，这些循环miRNAs可作为ONFH的候选早期诊断标志物和潜在的治疗靶点[17]。尿液miR-144可通过促进破骨细胞的形成和增殖来抑制骨组织矿化，其表达水平随ONFH病灶扩大而降低，因此miR-144有助于诊断和监测特发性ONFH进展[18]。

3 外泌体miRNA在ONFH中的治疗作用

3.1 *促进血管生成* 血管生成对于ONFH的治疗至关重要。外泌体miRNA可通过促进血管生成相关因子的表达、影响内皮细胞功能，促进骨坏死区域修复。含有miRNA-210的骨髓间充质干细胞来源的外泌体（BMSC-Exos），能增强糖皮质激素处理的骨微血管内皮细胞（bovine mammary epithelial cells，BMECs）的增殖、迁移和血管生成能力，从而增加微血管密度并增强股骨头的骨重塑[19]。过表达miRNA-378后，脂肪干细胞来源的外泌体可通过下调丝氨酸/苏氨酸激酶Fused抑制物和激活Sonic Hedgehog信号通路的活性，增加人脐静脉内皮细胞（human umbilical vein endothelial cells，HUVECs）的迁移、增殖和血管生成能力，促进骨形态发生蛋白2（recombinant human bone morphogenetic protein 2，BMP2）和RUNX2等成骨相关因子的表达，从而促进血管生成和成骨，抑制糖皮质激素诱导的ONFH的进展[20]。与常氧条件下培养的BMSC-Exos比较，缺氧预处理的BMSC-Exos能促进HUVEC的增殖、迁移、血管内皮生长因子（vascular endothelial growth factor，VEGF）表达和管形成，从而发挥促血管生成和骨保护作用[21]。含有miR-21-5p的人脐带间充质干细胞（human umbilical cord mesenchymal stem cells，hUCMSCs）来源的外泌体（hUCMSC-Exos）可通过抑制SRY-box转录因子5和Zeste增强子同源物2的表达，增加HUVECs迁移数量，增强管形成能力，促进成骨相关标志物OCN、Runx2和胶原蛋白Ⅰ的表达，从而增强血管生成和成骨[22]。诱导多能干细胞（induced pluripotent stem cells，iPSCs）来源的外泌体（iPSC-Exos）可通过激活内皮细胞中的磷脂酰肌醇-3-激酶（phosphatidylin-ositol-3-kinase，PI3K）/蛋白激酶B（protein kinase B，Akt）信号通路，促进HUVECs的增殖、迁移和管形成，改善糖皮质激素引起的骨小梁的破坏，从而促进股骨头局部血管的生成，防止骨质流失[23]。iPSC-Exo能促进去卵巢大鼠成骨标志物RUNX2、Ⅰ型胶原（collagen type Ⅰ，COL1）、碱性磷酸酶（alkaline phosphatase，ALP）和血管生成标志物CD31的表达，从而增强血管生成和成骨细胞的增殖分化，促进大鼠模型临界颅骨缺损的骨再生[24]。

3.2 *促进成骨* 成骨细胞是负责骨形成的主要细胞，破骨细胞主要负责骨组织的重吸收。在正常生理状态下，成骨和破骨过程是耦联的，即骨形成和骨吸收在时间和空间上紧密相连，形成一个连续的循环过程[25]。然而，激素等因素能够引起骨形成与骨吸收失衡，导致骨质流失和骨密度下降，进而导致股骨头的结构异常。外泌体作为细胞间通信的介质，可通过携带特定的生物分子，影响成骨细胞和破骨细胞的功能，从而在骨代谢疾病的治疗中发挥重要作用[26]。

研究[27]表明，来源于BMSC的外泌体过表达miR-27a后，成骨相关基因Runx2、ALP的表达增加，脂肪生成相关基因过氧化物酶体增殖物激活受体γ（peroxisome proliferator-activated receptor γ，PPARγ）和载脂蛋白A5的表达水平下降。同时miR-27a能通过促进BMSC成骨分化，抑制其脂肪分化，从而减轻类固醇诱导ONFH中的骨质流失[27]。miR-26a在$CD34^+$干细胞衍生的外泌体中过表达后，可增加HUVECs的血管生成

和迁移活性，提高BMSCs的增殖率，上调成骨活性，从而抑制糖皮质激素造成的大鼠股骨头损害[28]。miR-155-5p可通过抑制糖原合成酶激酶-3β活性，促进β-catenin的核易位，增加成骨相关基因的表达，从而促进BMSCs的增殖和成骨分化[29]。来源于BMSCs的外泌体miR-150能通过调节Gremlin-1蛋白/核因子κB（NF-κB）轴，抑制肿瘤坏死因子-α（tumor necrosis factor-α，TNF-α）诱导的成骨细胞凋亡，促进成骨分化和自噬[30]。来源于BMSC的外泌体miR-148a-3p能通过抑制Smad泛素化调节因子1表达，促进SMAD7-BCL2轴来促进OCN的表达，从而增加BMSCs的增殖和成骨分化，阻止ONFH的进展[31]。miR-217可通过靶向DKK1并抑制其表达，促进β-catenin的核转位，增加RUNX2、COL1A1的表达，促进BMSCs的增殖和成骨分化[32]。研究表明，200 kD的黏着斑激酶家族相互作用蛋白（FIP200）过表达能够促进血管生成，下调源自骨髓间充质干细胞的外泌体miR-224-3p的表达，上调FIP200的表达，从而促进HUVECs的增殖、迁移、侵袭能力及血管生成[33]。携带过表达miR-122-5p的BMSC-Exo，可通过负调控SPRY2，提高受体酪氨酸激酶的活性，从而促进成骨细胞的增殖和分化，缓解ONFH发展[34]。

然而，部分外泌体miRNA会抑制成骨分化。BMSCs-Exo可通过miR-532-5p，抑制核受体共激活因子3的表达，从而抑制成骨细胞活力并促进细胞凋亡，促进ONFH的发展[35]。脂肪细胞来源的外泌体miR-148a可通过调节Wnt5a/酪氨酸激酶样孤儿受体2通路，增加脂联素、酸结合蛋白2和过氧化物酶体增殖物激活受体γ的表达水平，促进成脂分化，同时脂肪细胞来源的外泌体miR-148a能通过降低ARS染色阳性细胞、ALP、RUNX2和OCN水平，抑制BMSCs的成骨分化[36]。研究[37]表明，miR-214在参与Bio-Oss联合BMSCs治疗ONFH过程中，能抑制成骨细胞的增殖与活性，抑制骨形成。miR-708能通过靶向Smad3的3′-UTR，抑制RUNX2的表达，从而抑制BMSC的成骨分化，促进其成脂分化[38]。miR-144-3p能通过靶向FZD4减少β-catenin核转位、RUNX2和COL1A1的转录，从而抑制BMSC的增殖和成骨分化[39]。研究[40]表明，miR-224-5p在糖皮质激素处理的BMSCs中上调，同时miR-224-5p可通过靶向Smad4抑制成骨，促进BMSCs的成脂分化。miR-141可通过靶向E2F3抑制ONFH大鼠BMSCs的成骨分化，从而促进ONFH的进展[41]。

3.3 减轻炎症反应、维持内环境稳定 维持内环境稳定对于骨组织的健康至关重要。调节内环境中的各种因素可以预防和治疗许多骨骼疾病，保持骨骼的正常功能和结构。富含miR-326的BMSC-Exos，可通过靶向HDAC3，下调炎症细胞因子水平、Caspase-1活性、细胞凋亡相关蛋白的水平，促进软骨细胞中信号转导和转录激活因子1（signal transducerand activator of transcription 1，STAT1）、乙酰化STAT1和乙酰化NF-κB p65的表达，从而抑制软骨细胞的凋亡[42]。滑膜间充质干细胞来源外泌体（exosomesderived from SMSCs，SMSC-Exos）可通过递送Matrilin-3，抑制白细胞介素（IL）-17A诱导的PI3K/Akt/哺乳动物雷帕霉素靶蛋白（mammalian target of rapamycin，mTOR）信号转导轴的激活，从而抑制炎症细胞因子的释放、细胞外基质（Extracellular matrix，ECM）的降解和自噬缺陷[43]。SMSC-Exos中miR-320c能通过靶向ADAM19依赖性Wnt信号传导，抑制ECM降解和软骨细胞凋亡，从而促进软骨损伤修复[44]。SMSC-Exo过表达miR-212-5p后，能靶向74样ETS转录因子3（E74 Like ETS Transcription Factor 3，ELF3），抑制软骨细胞中IL-1β诱导的ELF3表达，从而通过免疫调节的方式，减弱IL-1β诱导的软骨细胞变性和降解[45]。ZENG ZH等[46]采用IL-1β处理软骨细胞，在体外诱导骨关节炎性疾病，同时采用SMSC-Exo进行干预。结果表明，干预后软骨细胞中的miR-130b-3p显著升高，同时SMSC-Exo能通过激活LDL受体相关蛋白12/Akt/β-catenin信号通路，减少软骨细胞凋亡、ECM降解和促炎性细胞因子的分泌。滑膜成纤维细胞（synovial fibroblasts，SFs）具有MSCs的特征，可在骨与软骨的关节破坏和再生中发挥双相作用。$CD34^+$干细胞是SF家族中的亚群之一。$CD34^+THY1$亚群的成骨和软骨形成潜力相对较高，同时THY1还可通过内皮细胞分化参与血管生成，这一研究为骨与软骨的再生提供了新的治疗策略[47]。

3.4 调控信号通路 在外泌体miRNA发挥骨修复作用的过程中，有多个相关的信号通路参与，其中起主要作用的是Wnt/β-catenin及PI3K/Akt等信号通路。抑制miR-139-5p表达，可激活Wnt/β-catenin信号通路，促进BMSCs成骨分化[48]；下调miR-146a表达，能够激活Wnt/β-catenin信号通路，促进成骨，抑制破骨[49]；抑制miR-98-5p表达，可能激活PI3K/Akt/糖原合成酶激酶-3β（glycogen synthase kinase-3β，GSK-3β）信号通路，从而通过靶向BMP2，促进成骨前细胞的活力和分化[50]；抑制miR-212和miR-384表达，可上调RUNX2和激活骨保护素（osteoprotegerin，OPG）/核因子κB受体活化因子配体（receptor activator of NF-κB ligand，RANKL）通路，促进成骨分化[51]。miR-655-3p可通过抑制赖氨酸特异性组蛋白去甲基化酶1的表达，激活BMP-2/Smad信号通路，从而促进MC3T3-E1细胞的成骨分化并抑制其凋亡[52]。miR-195-5p可通过靶向SMURF1，激活BMP-2/Smad/Akt/RUNX2通路，从而促进MC3T3-E1细胞成骨分化并抑制其凋亡[53]。

4 中医药通过调控外泌体miRNA的表达治疗ONFH

中医学虽然没有ONFH明确的病名，但根据其发病机制、症状等，ONFH属于“骨痿”“骨痹”等范畴。肾主骨生髓、藏精，肝藏血、主筋，筋骨的强弱与肝肾精血密切相关。筋骨、关节的功能活动依赖于气血的温煦濡养，气血不足会导致股骨头得不到充分的血供而痿软疏松。总之，中医学认为股骨头坏死的病因主要是肝肾虚衰，气血不足，气滞血瘀，血行不畅，骨失濡养[54]。其中，“血不荣骨”是导致ONFH的直接原因[55]。中医药可以调控miRNA，促进成骨及血管生成与修复，从而发挥治疗ONFH的作用[56]。

4.1 中药单体及中药复方调控miRNA促进骨形成

4.1.1 促进成骨细胞增殖与分化 淫羊藿苷是中药淫羊藿的主要活性成分。钛颗粒能抑制成骨细胞的增殖并促进其凋亡，而淫羊藿苷可能通过上调miR-21-5p阻断钛颗粒的作用，同时淫羊藿苷能增加ALP活性，加速基质矿化并上调BMP2、Runx2、OCN的表达，促进成骨细胞增殖与分化[57]。仙鹤草多糖及其硫酸化衍生物可通过靶向miR-107，升高成骨细胞中

ALP活性、胶原蛋白含量，促进BMP2、Runx2、OSX和OCN蛋白表达，从而促进成骨细胞的增殖和分化[58]。京尼平苷是中药栀子的主要药效成分，可通过靶向miR-214，激活Wnt/β-catenin信号通路，促进成骨细胞活力和CyclinD1、Runx2、Osx、Ocn、ALP的表达，从而促进成骨细胞的增殖和分化[59]。从生姜中分离的姜油酮能通过靶向miR-200c-3p，下调smad7的表达，促进BMSCs中ALP、OC、OSX和RUNX2的表达，加速成骨细胞的分化[60]。王海珍等[61]研究发现，葛根素能提高大鼠成骨细胞增殖活性，降低成骨细胞中miR-196a-3p表达，促进Runx2、OPN、ALP蛋白表达，表明葛根素能通过靶向Runx2，抑制miR-196a-3p的表达，促进成骨细胞的增殖与分化。体外实验表明，经三七总皂苷处理后，成骨细胞MC3T3-E1中成骨标志基因OCN、ALP、骨钙素（BGP）、COL1的表达升高，miR-204的表达下降，同时Runx2、p-PI3K、p-Akt的表达升高，表明三七总皂苷能通过抑制miR-204的表达，激活PI3K/Akt/Runx2通路，促进成骨细胞增殖并抑制其凋亡[62]。金丝桃苷是一种来源于杜仲的黄酮类化合物，可通过靶向miRNA-19a-5p，抑制IL-17A mRNA和蛋白表达，从而升高绝经后骨质疏松症小鼠模型的骨量，发挥骨保护的作用[63]。ZHU W等[64]使用类固醇激素建立ONFH小鼠模型，并采用加味青娥丸干预。结果表明，加味青娥丸可通过上调miR-185-3p的表达，下调miR-129b-5p的表达，调节PI3K/Akt信号通路，促进成骨细胞存活与分化，抑制破骨细胞生成，维持骨稳态，从而参与骨代谢与骨重塑过程。生骨再造丸可通过抑制BMSCs和成骨细胞中miRNA-708的表达，改善ONFH大鼠的血脂水平、骨代谢水平，抑制炎症细胞因子，改善股骨头骨小梁密度水平及骨矿物含量，从而延缓ONFH的进展[65]。补骨脂素是补骨脂中的活性成分之一，能下调miR-125b-5p，促进ALP、OCN和RUNX2等成骨因子的表达，从而促进牙周干细胞的成骨分化[66]。

4.1.2 促进BMSCs成骨分化 巴戟天具有补肾阳、强筋骨的作用。巴戟天多糖是从巴戟天根中提取的生物活性成分，可通过上调miR-21，激活PI3K/Akt通路，促进成骨标志物RUNX2和BMP2表达，抑制成脂标志物CEBPα和PPARγ表达，从而促进BMSCs的成骨分化[67]。此外，巴戟天多糖能通过抑制miR-210-3p表达，上调SCARA3表达，从而促进BMSCs的活力和成骨分化，抑制细胞凋亡和成脂分化[68]。淫羊藿苷能通过下调miR-23a，激活Wnt/β-catenin信号通路，提高ALP活性，促进骨唾液蛋白Ⅱ、Runx2表达，减少脂滴形成和细胞甘油三酯水平，同时淫羊藿苷能下调过氧化物酶体增殖物激活受体-γ和CCAAT增强子结合蛋白-α的表达，从而促进BMSC的成骨分化，抑制脂肪生成[69]。研究[70]表明，淫羊藿苷能通过上调miR-335-5p的表达，抑制PTEN的表达，从而促进BMSC的成骨分化。此外，淫羊藿苷能上调miR-335-5p表达，促进成骨标志基因RUNX2、OPN的表达，增加骨质疏松症大鼠模型骨小梁数量，促进新生骨组织形成以及BMSCs的成骨分化[71]。miR-488在补骨脂素诱导下，能通过靶向Runx2，增加Osx和ALP表达，从而促进BMSCs的成骨分化[72]。槲皮素可通过抑制miR-206，上调连接蛋白43的表达，增加Runx2、OSX、OCN和骨桥蛋白（OPN）表达，从而促进BMSCs增殖和成骨分化[73]。龟甲提取物能通过抑制miRNA-351表达，促进维生素D受体表达，从而促进BMSCs的增殖与成骨分化[74]。活骨灌注液能通过下调miR-34c-5p表达，去除miR-34c-5p对MDM4的抑制，并抑制骨组织中C/EBPα和PPARγ的表达，从而通过抑制BMSCs的成脂分化来缓解ONFH[75]。左归丸能降低大鼠BMSCs中同源异型结构域蛋白转化生长因子2（TGIF2）的表达，促进Runx2、ALP的表达，上调miR-34a的表达，抑制TGIF2的表达，从而促进BMSCs成骨分化，并抑制其成脂分化[76]。温肾通络方能通过靶向miR-122-5p，抑制SPRY2的表达，升高成骨分化相关因子Runx2和Osterix的转录水平，降低脂肪生成相关因子PPARγ2和CEBP-α水平，从而促进BMSCs的成骨分化，并抑制其成脂分化[77]。

4.1.3 抑制成骨细胞凋亡 黄芪多糖是中药黄芪的主要活性成分，可通过抑制SP1/miR-200b-3p轴，激活Wnt/β-catenin信号通路，降低ONFH小鼠促凋亡蛋白Bax、胱天蛋白酶-3（cysteine aspartic acid specific protease 3，Caspase-3）和胱天蛋白酶-9（cysteine aspartic acid specific protease 9，Caspase-9）表达，促进抗凋亡蛋白Bcl-2表达，从而诱导骨细胞自噬，减少成骨细胞凋亡，改善ONFH[78]。研究[79]表明，黄芪多糖能通过下调miR-206，激活HIF-1α/BNIP3轴，从而促进骨细胞自噬，抑制成骨细胞凋亡，进而改善ONFH。黄精的主要成分黄精多糖可通过下调miR-1224的表达，调节Hippo信号通路，抑制破骨细胞增殖，抑制成骨细胞凋亡[80]。补肾健脾活血方能通过抑制miR-140-5p的表达，靶向BMP2，促进OCN、OPC、RUNX2、TGF-β的表达，从而抑制成骨细胞的凋亡[81]。

4.2 中药单体及中药复方调控miRNA促进血管生成 淫羊藿苷可以调节糖皮质激素诱导的miRNA-335过表达，并减少糖皮质激素诱导的ONFH大鼠血清中血栓调节蛋白和VEGF的含量，从而提高BMECs迁移能力和血管成形能力[82]。骨碎补总黄酮能通过抑制MiR-18a-5p的表达，激活HIF1α/VEGF信号通路，促进大鼠骨髓来源内皮祖细胞的增殖、迁移和成管能力，从而促进血管生成及其介导的成骨能力[83]。补肾生骨汤可抑制ONFH大鼠股骨头组织中miR-135b-5p表达，促进RUNX2表达，降低血浆纤维蛋白原水平，提高血浆VEGF、一氧化氮合酶、BGP水平，从而促进ONFH大鼠股骨头组织修复[84]。

5 总结与展望

外泌体miRNA可以通过影响成骨细胞和破骨细胞的分化、功能和活性来调节骨代谢，同时外泌体miRNA能通过调节炎症反应和血管生成，促进骨修复。外泌体miRNA在信号通路的调节中扮演着重要的角色，不仅有助于更好地理解细胞通信机制，还能为疾病的诊断和治疗提供新的策略和靶点。多种来源的外泌体可能通过相关的信号通路治疗ONFH，尽管这些潜在的作用机制为外泌体在ONFH治疗中的应用提供了希望，但目前对这些机制的理解仍然有限。未来的研究需要深入探讨外泌体的生物学特性、来源细胞类型、携带的生物分子及其在骨稳态调控中的具体作用，以便为外泌体促进组织损伤修复的临床应用提供坚实的理论基础。此外，还需要开展更多的临床前和临床研究来验证外泌体治疗ONFH的安全性和有效性。中医药在治疗ONFH方面具有独特的优势和广阔的发展前景。中药能通过调控miRNA，促进成骨、促进

血管生成、减轻炎症反应和改善骨微环境等途径治疗股骨头坏死。然而目前仍存在调控miRNA的特异性和精确性不足、研究方法局限、临床转化困难等问题，未来仍需进一步加强研究和实践，利用系统生物学的方法整合中医药、miRNA和股骨头坏死的研究，不断提高中医药治疗ONFH的科学性与有效性。

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