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在线全文

# circRNA-miRNA网络调控骨重塑的研究进展*

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【摘要】 骨形成与骨吸收的动态平衡是骨重塑的重要过程。骨形成和骨吸收的失调与多种骨相关疾病的发生发展密切相关。非编码RNA（noncoding RNA, ncRNA）通过抑制mRNA翻译或降解mRNA，在生理和病理条件下对蛋白质的表达起调控作用。环状RNA（circular RNA, circRNA）是一种非线性ncRNA，能抵御RNA外切酶的降解作用。circRNA和微RNA（microRNA, miRNA）可直接或间接调控成骨相关基因的表达，从而在骨重塑过程中发挥重要作用。研究证实circRNA-miRNA网络参与间充质干细胞（mesenchymal stem cells, MSCs）向成骨细胞（osteoblasts, OB）谱系分化过程，也参与了骨髓来源巨噬细胞（bone marrow-derived macrophages, BMDM）向破骨细胞（osteoclasts, OC）分化的过程，在骨重塑的成骨-破骨平衡中起重要调节作用。因此，充分了解circRNA-miRNA调控网络将有助于理解骨重塑过程中的成、破骨平衡的调节机制和相关疾病的诊断和治疗。本文就circRNA、microRNA的功能及其作为circRNA-miRNA调控网络机制在骨重塑过程中作用进行综述，以期为今后深入理解骨重塑调控机制和相关疾病的研究和防治提供参考和思路。

【关键词】 环状RNA 微小RNA 成骨分化 破骨分化 骨重塑 综述

**Research Progress in the Regulatory Role of circRNA-miRNA Network in Bone Remodeling**

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【Abstract】 The dynamic balance between bone formation and bone resorption is a critical process of bone remodeling. The imbalance of bone formation and bone resorption is closely associated with the occurrence and development of various bone-related diseases. Under both physiological and pathological conditions, non-coding RNAs (ncRNAs) play a crucial regulatory role in protein expression through either inhibiting mRNAs translation or promoting mRNAs degradation. Circular RNAs (circRNAs) are a type of non-linear ncRNAs that can resist the degradation of RNA exonucleases. There is accumulating evidence suggesting that circRNAs and microRNAs (miRNAs) serve as critical regulators of bone remodeling through their direct or indirect regulation of the expression of osteogenesis-related genes. Additionally, recent studies have revealed the involvement of the circRNAs-miRNAs regulatory network in the process by which mesenchymal stem cells (MSCs) differentiate towards the osteoblasts (OB) lineage and the process by which bone marrow-derived macrophages (BMDM) differentiate towards osteoclasts (OC). The circRNA-miRNA network plays an important regulatory role in the osteoblastic-osteoclastic balance of bone remodeling. Therefore, a thorough understanding of the circRNA-miRNA regulatory mechanisms will contribute to a better understanding of the regulatory mechanisms of the balance between osteoblastic and osteoclastic activities in the process of bone remodeling and the diagnosis and treatment of related diseases. Herein, we reviewed the functions of circRNA and microRNA. We also reviewed their roles in and the mechanisms of the circRNA-miRNA regulatory network in the process of bone remodeling. This review provides references and ideas for further research on the regulation of bone remodeling and the prevention and treatment of bone-related diseases.

【Key words】 Circular RNA microRNA Osteogenic differentiation Osteoclastic differentiation Bone remodeling Review

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在骨重塑的过程中,骨形成与骨吸收之间的动态平衡维持着整体骨量的稳定[1]。负责骨形成的细胞主要源于骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMSCs),而调控骨吸收的OC来源于骨髓单核巨噬细胞(bone marrow-derived macrophage, BMDM)[2]。在骨重塑的过程中,特定部位的骨吸收被激活,在开始阶段,破骨细胞前体细胞被募集至重塑部位,附着于骨基质,随后分化为破骨细胞(osteoclasts, OC),消化骨基质,形成骨陷窝。同时间充质干细胞和骨祖细胞被募集至骨形成部位,随后间充质干细胞和骨祖细胞向成骨细胞(osteoblasts, OB)分化,并行使OB的功能,即合成类骨质。OB逐渐成熟,通过调节钙磷代谢,使类骨质进一步矿化,最终完成骨重塑[3]。骨骼的重塑需要复杂的机制来精细调控骨吸收和骨形成之间的动态平衡,从而维持骨量稳定[4-5]。成骨-破骨活动的失衡与多种骨相关疾病的发生发展密切相关,如骨吸收持续大于骨形成活动,会导致机体无法维持正常的骨量,最终可能发展为骨质减少从而形成骨质疏松症[6]。而骨硬化病则是由于OC功能缺失或者OC数量缺乏,使得骨形成持续大于骨吸收,最终导致机体骨量、骨质密度异常增加,使骨骼脆性增加,易发骨折[7]。

传统的遗传学认为,遗传信息储存于DNA的碱基序列中,亲代与子代间的可遗传变异由碱基序列改变产生[8]。随着生物学的不断发展,研究人员发现许多生命现象与孟德尔遗传学遗传法则不符,在DNA序列未变化的情况下,遗传信息能通过某些机制或途径使保存并传递给子代的基因表达或细胞表型改变,使得亲代与子代之间虽然遗传信息一致,但是表型不一致的现象,这种现象被称为表观遗传[9]。现代的表观遗传主要涉及两方面内容:一是基因转录水平选择性表达的调控,如组蛋白修饰、DNA甲基化、染色质重构等;二是基因的转录后调控,如非编码RNA(noncoding RNA, ncRNA),包括微小RNA、反义RNA、内含子及核糖开关等[10]。在众多的表观遗传机制中,ncRNA调控机制是研究较深入的部分[11]。

越来越多的研究证实ncRNA通过调节骨重塑相关细胞的分化、增殖、凋亡和自噬,在骨代谢过程中发挥重要作用[12]。随着高通量测序技术的发展,研究人员在骨重塑相关的成骨-破骨活动中检测出大量表达异常的ncRNA,包括环状RNA(circular RNA, circRNA)和微小RNA(microRNA, miRNA)[12]。数据表明circRNA、miRNA的相互作用调控了遗传信息的表达,从而决定干细胞的分化方向,在维持成骨-破骨的平衡中发挥重要作用[13-14]。本文就circRNA-miRNA调控网络在骨重塑和骨相关疾病中的研究进展做一综述。

## 1 circRNA-miRNA调控网络

ncRNA依照各自特殊的二级结构和三级结构分为短链非编码RNA(short non-coding RNA, sncRNA)、长链非编码RNA(long non-coding RNA, lnRNA)和环状RNA(circular non-coding RNA, circRNA)。sncRNA是指核苷酸数量在200以下的链状非编码RNA,包括miRNA、小核仁RNA(small nucleolar RNA, snoRNA)、小细胞核RNA(small nuclear RNA, snRNA)、PIWI蛋白相互作用RNA(PIWI-interacting RNA, piRNA)、小干扰RNA(small interacting RNA, siRNA)、转运RNA(transfer RNA, tRNA)、tRNA衍生片段(tRNA fragments, tRFs)、Y RNA衍生片段(Y RNA fragments, YRFs)。其中miRNA受到广泛研究,能够通过促进mRNA降解和抑制mRNA翻译从而抑制目的基因的表达。第二类为长链非编码RNA(long non-coding RNA, lncRNA),其含有的核苷酸数量在200个以上。第三类则为circRNA,与链状ncRNA不同,其结构呈环状[15]。诸多研究发现,在ncRNA中circRNA与miRNA存在密切的相互作用关系,形成了circRNA-miRNA的调节网络。

### 1.1 miRNA

miRNA是一种内源性非编码小RNA分子,由约22个核苷酸组成,存在所有真核细胞中[16]。miRNA基因首先在细胞核中转录成pri-miRNA,然后经Drosha酶修剪成pre-miRNA[17]。通过转运蛋白的传递,pre-miRNA从细胞核转移到细胞质。最后在Dicer酶的加工下形成成熟的miRNA[18]。

关于miRNA的功能已经有许多明确的研究。在细胞质中,Dicer酶与成熟miRNA、AGO蛋白等组装成RNA诱导沉默复合体(RNA-induced silencing complex, RISC)[19]。RISC复合体中的miRNA能够合成和指导RISC通过参与mRNA的降解或翻译抑制在转录后水平下调基因的表达。miRISC能通过干扰eIF4E-cap的识别和40S小核糖体亚基的招募或者通过拮抗60S亚基连接、防止80S核糖体复合物形成来抑制翻译起始过程,RISC也能通过抑制核糖体延伸来抑制起始后步骤的翻译[20]。其次miRISC能与CCR4-NOT和PAN2-PAN3去腺苷酸酶复合物相互作用,促进mRNA的PolyA尾部去腺苷化,随后mRNA的5'帽端(m7G)通过DCP1-DCP2复合物的脱帽作用被去除,最终由XRN-1核酸外切酶介导mRNA发生降解[21]。

miRNA的表达在发育过程中具有组织特异性,参与了许多重要的生物学过程,如发育、增殖、细胞分化、干细胞特性的维持、凋亡和应激反应等[22]。研究表明诸多

miRNA的上调或下调可直接引起靶基因的表达水平改变, 同时由于miRNA与靶mRNA之间不完全配对机制使得一个miRNA能够作用于多个靶基因。越来越多的研究表明, miRNA在骨稳态中起到重要的作用, 能够调节骨重塑活动中成骨活动和破骨活动, 关于miRNA调控OB和OC分化的总结如表1。

### 1.2　circRNA

20世纪70年代, 学者们首次在植物病毒中发现circRNA, 认为其是异常剪接反应的副产物, 没有重要的生物学功能[52]。随着高通量转录组学技术的发展, 人们越来越认识到它们在基因调控中的重要功能[53]。与线性RNA不同, circRNA是由一个或两个外显子通过3'和5'端

**表 1　miRNA调控成、破骨分化过程**

**Table 1　miRNAs regulate the osteoblastic and osteoclastic differentiation processes**

| miRNA | Target gene | Pathway | Sample | Function | Ref. |
|---|---|---|---|---|---|
| *miR*-139-5*p* | *CTNNB*1, *FZD*4 | WNT/β-catenin | hBMSCs | Inhibiting osteogenic differentiation | [23] |
| *miR*-145 | *SEMA*3*A* | WNT/β-catenin | JBMMSCs | Inhibiting osteogenic differentiation | [24] |
| *miR*-145-5*p* | *SEMA*3*A* | WNT/β-catenin | ADSCs | Inhibiting osteogenic differentiation | [25] |
| *miR*-126*a*-3*p* | *LRP*6, *CTNNB*1 | WNT | ADSCs | Inhibiting osteogenic differentiation | [26] |
| *miR*-21 | *HIF*-1*α*, *PTEN* | PI3K/AKT | BMSCs | Enhancing osteogenic differentiation | [27] |
| *miR*-200*b* | *VEGF-A*, *ZEB*2, *EST*1, *KDR*, *GATA*2 | TGF-β, ERK1/2 | rBMSCs, HUVECs | Inhibiting osteogenic differentiation and vasculogenesis | [28] |
| *miR*-765 | *BMP*6 | BMP/Smad | hBMSCs | Inhibiting osteogenic differentiation | [29] |
| *miR*-494 | *RUNX*2, *BMPR*2, *MYOD* | BMP/Smad | C2C12 | Inhibiting osteogenic differentiation | [30] |
| *miR*-1323 | *BMP*4, *SMAD*4 | BMP/Smad | hBMSCs | Inhibiting osteogenic differentiation | [31] |
| *miR*-100-5*p* | *FGF*21, *BMPR*2 | BMP/Smad | mBMSCs | Inhibiting osteogenic differentiation | [32] |
| *miR*-199*b*-5*p* | *GSK-3β* | GSK3β/β-catenin | hBMSCs | Enhancing osteogenic differentiation | [33] |
| *miR*-193*a*-3*p* | *MAP*3*k*3 | MAPK | hBMSCs | Enhancing osteogenic differentiation | [34] |
| *miR*-146*a* | *NF*2, *Smad*4 | TGF-β | BMSCs, HUVECs | Enhancing osteogenic differentiation and vasculogenesis | [35] |
| *miR*-1224-5*p* | *ADCY*2 | Rap1 | BMSCs | Enhancing osteogenic differentiation and inhibiting osteoclastic differentiation | [36] |
| *miR*-199*a*-5*p* | *HIF*1*α* | HIFa/Twist1 | hMSCs | Enhancing osteogenic differentiation | [37] |
| *miR*-130*a* | *Smurf*2, *PPARγ* | – | BMSCs | Enhancing osteogenic differentiation and inhibiting adipogenesis | [38] |
| *miR*-143 | *HDAC*7 | – | mBMSCs | Enhancing osteogenic differentiation | [39] |
| *miR*-384-5*p* | *Gli*2 | – | rBMSCs | Inhibiting osteogenic differentiation and accelerating cell senescence | [40] |
| *miR*-206 | *CX*43 | – | hDPSCs | Inhibiting osteogenic differentiation | [41] |
| *miR*-31 | *SATB*2 | – | hMSCs | Inhibiting osteogenic differentiation | [42] |
| *miR*-138-5*p* | *MACF*1 | – | mBMSCs | Inhibiting osteogenic differentiation | [43] |
| *miR*-214 | *ATF*4 | – | mBMSCs | Inhibiting osteogenic differentiation | [44] |
| *miR*-182 | *PKR* | PKR-IFNβ | mBMMs | Enhancing osteoclastic differentiation | [45] |
| *miR*-29*a* | *SOCS*2 | TNF SF3b | BMMs | Inhibiting osteoclastic differentiation | [46] |
| *miR*-125*a*-5*p* | *TNFRSF*1*B* | – | RAW264.7 | Enhancing osteoclastic differentiation | [47] |
| *miR*-25-3*p* | *NFIX* | – | RAW 264.7 | Enhancing osteoclastic differentiation | [48] |
| *miR*-338-3*p* | *MafB* | – | RAW264.7 | Enhancing osteoclastic differentiation | [49] |
| *miR*-27*a* | *PPARγ*/*APC* | – | mBMMs | Inhibiting osteoclastic differentiation | [50] |
| *miR*-20*a* | *PPARγ* | – | THP-1 | Inhibiting osteoclastic differentiation | [51] |

–: unknown or not mentioned in the literture; hBMSCs: human bone marrow mesenchymal stem cells; JBMMSCs: jaw bone marrow mesenchymal stem cells; ADSCs: adipose-derived stem cells; rBMSCs: rat bone marrow mesenchymal stem cells; HUVECs: human umbilical vein endothelial cells; mBMSCs: mouse bone marrow mesenchymal stem cells; hMSCs: human mesenchymal stem cells; hDPSCs: human dental pulp stromal cells; mBMMs: mouse bone marrow macrophages.

共价结合,从而建立一个闭合环状结构。因此,circRNA能抵御RNA外切酶的降解作用,比线性RNA更稳定,在细胞质中数量丰富且稳定性高[54]。

circRNA可作为内源mRNA的竞争者,是miRNA 的海绵吸附体。circRNA最先被发现的功能就是作为海绵吸附体调控miRNA与mRNA结合,研究显示circRNA上的结合位点能使其与miRNA相互结合,从而提高或降低miRNA的表达水平[55]。

circRNA能够调控转录过程。外显子-内含子环状RNA(exonic-intronic circRNA, EIciRNA)主要存在于细胞核内,EIciRNA在成环时同时包含了RNA中的外显子和内含子。EIciRNA的内含子序列能与U1小核糖体核蛋白(U1 small nuclear ribonucleoproteins, U1 snRNPs)相互作用形成EIciRNA-U1 snRNPs复合体,该复合体能调节RNA聚合酶的活性从而调控转录活动[56]。

另有一小部分circRNA可以被翻译合成蛋白质。目前有两种方式开始circRNA的翻译活动,最主要方式是由真核生物翻译起始因子(eukaryotic translation initiation factor 4 gamma 2, EIF4G2)通过识别和结合circRNA含有IRES序列从而开始翻译过程[57]。而一些没有IRES序列的circRNA进行翻译活动则需要一个RRACH结构域,这个结构域经过m6A修饰之后,YTH结构域家族蛋白3(YTH domain family 3, YTHDF3)则会识别m6A从而募集EIF4G2从而开始翻译过程[58]。

诸多研究发现circRNA能够参与调控干细胞的成骨分化和破骨分化过程。*circ*-0066523在BMSCs成骨诱导过程中上调,通过PI3K/AKT通路促进BMSCs成骨分化[59]。在骨质疏松患者外周血单核细胞中*circ*-0000885的表达升高。进一步研究发现*circ*-0000885能够抑制BMSCs增殖和成骨分化,并具有促进BMSCs凋亡的能力[60]。通过对BMSCs成骨分化过程中差异性表达的circRNA进行鉴定,通过对BMSCs成骨分化过程中差异性表达的circRNA进行鉴定,发现*circFKBP5*出现了统计学显著的上调。circRNA在指导干细胞向OC分化过程中也起到重要作用,*circ*-0008542能够促进RANKL介导的OC分化,而*circ-Hmbox1*则具有相反的生物学效应,起到抑制OC分化的作用[14, 61]。以上研究说明circRNA在干细胞的成骨和破骨分化过程中起到重要的作用,但是目前对circRNA的功能和作用的认识仍处于起步阶段,现有的研究提出,由于circRNA上存在miRNA响应元件(miRNA response elements, MRE),circRNA可作为miRNA海绵从而发挥调控作用,这一调控机制在OB和OC分化方面的研究将在后文中进行阐述。

### 1.3 circRNA-miRNA网络调控下的骨重塑

研究发现一些RNA包括circRNA和mRNA含有MRE[62]。circRNA和mRNA的MRE可以竞争性地结合miRNA,这也被称为miRNA海绵或竞争性内源RNA(competing endogenous RNA, ceRNA)。circRNA与miRNA的相互作用主要依赖于MRE,通过与mRNA竞争性地结合miRNA,从而限制或调节miRNA与靶mRNA的相互作用,最终调节靶mRNA的翻译[63]。

目前,越来越多的证据表明circRNA作为ceRNA与miRNA之间的相互作用是OB和OC分化、成熟过程中重要的调节机制。CHEN等[64]通过circRNA表达谱筛选出调控干细胞成骨分化的关键circRNA——*CDR1as*。通过靶基因预测及验证实验证实了*miR-7-5p*存在于*CDR1as*和*WNT5B*的结合域。*CDR1as*与*miR-7-5p*竞争性结合,解除*miR-7-5p*对下游靶基因*WNT5B*表达的抑制。而*WNT5B*能够抑制*β-catenin*的表达,最终削弱BMSCs的成骨分化能力。另外,在褪黑素(melatonin, MEL)诱导BMSCs成骨分化的研究中,*circ*-0003865的表达降低,研究发现*circ*-003865能与*miR*-3653-3*p*相互结合。*miR*-3653-3*p*能通过抑制*GAS1*表达从而促进干细胞向OB分化。最终研究发现*circ*-0003865能发挥*miR*-3653-3*p*海绵作用进而削弱*miR*-3653-3*p*促进干细胞成骨分化的能力[65]。*circ*-0006859能直接与*miR*-431-5*p*相结合,而*ROCK1*是*miR*-431-5*p*的目的基因,因此*circ*-0006859通过与*miR*-413-5*p*相互结合,促进*ROCK1*的表达,从而发挥对干细胞成骨分化的抑制作用和成脂分化的促进作用[66]。此外,*circRNA*-28313能够竞争性结合*miR*-195*a*,解除*miR*-195*a*对CSF1表达的抑制作用,促进骨髓单核/巨噬细胞向OC分化[67]。并且张力刺激下的MC3T3E1细胞系分泌的外泌体中含有*circ*-008542,作为*miR*-185-5*p*的海绵,也能够促进*RANK*基因表达,促进OC分化和骨吸收[14]。这些研究说明circRNA能通过ceRNA机制,即作为miRNA海绵参与调节OB、OC的分化,并在骨相关疾病的发生发展过程中起到重要作用。见表2。

## 2 circRNA-miRNA网络与骨相关疾病

### 2.1 circRNA-miRNA网络与骨质疏松

骨质疏松是常见的代谢性骨相关疾病,其特征包括骨密度降低和骨脆性增加,就遗传因素而言,目前的研究尚未发现任何一个基因能够决定个体是否发生骨质疏松的表型,但是一些信号通路在骨质疏松的病理过程中发挥了关键作用,例如RNAK/RANL信号通路介导了OC分化及骨质吸收过程[86],研究表明这些病理过程受到

**表 2　circRNA-miRNA网络调控成、破骨分化过程**

**Table 2　The circRNA-miRNA network regulates the osteoblastic and osteoclastic differentiation processes**

| circRNA | Sample | Target gene | Pathway | Function | Ref. |
|---|---|---|---|---|---|
| *circ*-0016624 | hBMSCs | *miR*-98 | BMP2 | Enhancing osteogenic differentiation | [68] |
| *circ*-0000020 | BMSCs | *miR*-142-5*p* | BMP2 | Enhancing osteogenic differentiation | [69] |
| *circ*-0048211 | hBMSCs | *miR*-93-5*p* | BMP2 | Enhancing osteogenic differentiation | [70] |
| *circ*-0007059 | hBMSCs | *miR*-378 | BMP2 | Enhancing osteogenic differentiation | [71] |
| *circ*-0006215 | hBMSCs | *miR*-942-5*p* | RUNX2, VEGF | Enhancing osteogenic differentiation | [72] |
| *circRNA*-23525 | ADSCs | *miR*-30a-3*p* | RUNX2 | Enhancing osteogenic differentiation | [73] |
| *circRNA*-0001795 | hBMSCs | *miR*-339-5*p* | YAP1 | Enhancing osteogenic differentiation | [74] |
| *circ-ITCH* | hBMSCs | *miR*-214 | YAP1 | Enhancing osteogenic differentiation | [75] |
| *circRNA-Smg*5 | BMSCs | *miR*-194-5*p* | β-catenin | Enhancing osteogenic differentiation | [76] |
| *circRNA*-124534 | hDPSCs | *miR*-496 | β-catenin | Enhancing osteogenic differentiation | [77] |
| *circRNA-AFF*4 | BMSCs | *miR*-7723-5*p* | PIK3R1 | Enhancing osteogenic differentiation | [78] |
| *circ*-0026827 | hDPSCs | *miR*-188-3*p* | Beclin1, RUNX1 | Mediating cellular autophagy and enhancing osteogenic differentiation | [79] |
| *circRNA-vgll*3 | ADSCs | *miR*-326-5*p* | Integrinα5 | Enhancing osteogenic differentiation and bone mineralization | [13] |
| *circRNA-SIPA*1*L*1 | DPSCs | *miR*-617 | Smad3 | Enhancing osteogenic differentiation | [80] |
| *circRNA*-0062582 | hBMSCs | *miR*-145 | CBFB | Enhancing osteogenic differentiation | [81] |
| *circRNA*-0006766 | hBMSCs | *miR*-4739 | Notch2 | Enhancing osteogenic differentiation | [82] |
| *circRNA*-0074834 | BMSCs | *miR*-942-5*p* | ZEB1, VEGF | Enhancing osteogenic differentiation and vascularization | [83] |
| *circ*-0006859 | hBMSCs | *miR*-431-5*p* | ROCK1 | Inhibiting osteogenic differentiation | [66] |
| *circRNA*-006873 | hBMSCs | *miR*-142-5*p* | PTEN/Akt | Inhibiting osteogenic differentiation | [84] |
| *circRNA*-0003865 | BMSCs | *miR*-3653-3*p* | GAS1 | Inhibiting osteogenic differentiation | [65] |
| *circRNA-CDR*1*as* | hBMSCs | *miR*-7-5*p* | WNT5B | Inhibiting osteogenic differentiation | [64] |
| *circRNA*-28313 | BMMCs | *miR*-195*a* | RANKL, CSF1 | Promoting osteoclastic differentiation and relieving the inhibition of CSF1 expression | [67] |
| *circ*-0008542 | RAW264.7 | *miR*1-185-5*p* | RNAKL | Enhancing osteoclastic differentiation and bone resorption | [14] |
| *circ-Hmbox*1 | mBMMs | *miR*-1247-5 | RANKL | Inhibiting osteoclastic differentiation | [61] |
| *circRNA*-009934 | Raw264.7 | *miR*-5107 | TRAF6 | Enhancing osteoclastic differentiation | [85] |

rDFCs: rat dental follicle stem cells; the other abbreviations are explained in the footnote to Table 1.

circRNA-miRNA网络的调控。

在骨质疏松疾病中, 干细胞的成骨分化能力被削弱, circRNA-miRNA网络在其中起到重要的调节作用[87]。YIN等[88]发现*circ*-0006859在骨质疏松小鼠的BMSCs中表达升高, 并且高表达*circ*-0006859能够抑制小鼠干细胞的成骨分化。通过免疫共沉淀确认了*circ*-0006859能与*miR*-642*b*-5*p*和*miR*-483-3*p*直接作用, *circ*-0006859分别与*miR*-642*b*-5*p*和*miR*-483-3*p*的直接结合能够促进*EFNA*2和*DOCK*3的表达, 进而抑制Wnt信号通路, 削弱了干细胞成骨分化能力。YU等[68]的研究指出在骨质疏松患者中, *circ*-0016624的下调导致*miR*-98的表达水平升高, 抑制了骨形态发生蛋白(bone morphorgenic protein-2, BMP2)的表达, 抑制了干细胞成骨分化的能力。在一项最近的研究中, MI等[78]发现circRNA *AFF*4能够与*miR*-7723-5*p*结合, 抑制OB凋亡进而促进骨生成活动。这些研究结果表明*circ*-0006859、*circ*-0016624、*circ* RNA *AFF*4等circRNA可能成为治疗骨质疏松的潜在靶点。

同时, 在骨质疏松的病理过程中, OC的分化得到加强, 研究发现*miR*-506-3*p*能够抑制活化T细胞核因子1的表达(nuclear factor of activated T-cells 1, NFATc1), 而*NFATc*1能够介导干细胞向OC分化。同时*circ-UBAP*2能够发挥miR-506-3p海绵的作用, 抑制miR-506-3p的生物学效应[89]。因此*circ-UBAP*2能够解除*miR*-506-3*p*对OC分化的抑制并促进骨质吸收, 加速骨质疏松发展进

程。同样的,*miR*-195*a*能介导对*CSF*-1的抑制,而*CSF*-1是刺激骨髓单核巨噬细胞向OC分化的重要细胞因子,而*circRNA*-28313能作为ceRNA与*miR*-195*a*相互结合,解除*miR*-195*a*对*CSF*-1的抑制,促进*CSF*-1的表达和OC分化,加速骨质吸收进程[67]。利用微阵列芯片检测RAW264.7细胞在被诱导向破骨细胞分化过程中的circRNA和miRNA的表达谱,并基于差异表达RNA之间的相关性分析构建了circRNA-miRNA的共表达网络,结果显示circRNA-007873、circRNA-010763、circRNA-015622与miR-103之间的表达相关,虽然结果有待进一步验证,但也初步显示circRNA-miRNA调控网络在破骨细胞分化以及以及骨质疏松病理进程中的重要作用[90]。

越来越多的高通量RNA测序和circRNA微阵列研究数据表明,大量的circRNA和对应的miRNA在骨质疏松疾病的发生和发展过程中出现差异性表达,目前已有许多研究证明了部分circRNA和miRNA在骨质疏松疾病中存在调控作用,但是还有大量的circRNA和miRNA的研究还停留在发现其差异性表达的阶段,他们的作用及其调控机制还有待进一步验证。并且针对这些circRNA-miRNA的调控网络作用的研究能够帮助我们开发骨质疏松早期诊断的生物标志物,尽早识别骨质疏松疾病的危险因素,提高预防和治疗骨质疏松疾病的效率。

### 2.2 circRNA-miRNA与骨硬化病

骨硬化病是一组罕见的遗传性骨病,由于OC分化和功能障碍,导致成骨-破骨活动失衡,骨重塑效率降低,同时骨量增加、骨脆性增高,使得其临床表现为生长抑制、容易骨折,严重者其骨代谢障碍累及神经系统和血液系统,引起脑神经受压和贫血等症状[91]。严重的骨硬化病需要通过骨髓移植进行治疗,但是这种疗法对于由于缺乏促进OC分化的细胞因子的患者来说并不适用,因此深入了解骨硬化病的发生发展和OC分化和行使功能的调节机制对于骨硬化病的治疗具有重要意义[7]。

一些研究表明miRNA和骨硬化病之间存在关联,通过在体外实验中沉默*DGCR*8和*Dicer*酶或者*AGO*2蛋白等对miRNA的形成、稳定和行使功能至关重要的基因会导致OC分化能力受损。这种效应在转基因小鼠中进一步得到验证,敲除了*Dicer*基因的小鼠显示出了轻度的骨硬化病[92]。对健康人群和骨硬化病患者的外周单核细胞(peripheral blood mononuclear cell, PBMC)的深度测序和蛋白组相对和绝对定量同位素标记分析(isobaric tags for relative and quantitation, iTRAQ)结果显示123种miRNA和173种蛋白发生了差异性表达[93]。因此miRNA在骨硬化病中起到了重要作用,同时鉴于circRNA与miRNA之间密切的调控关系,这些在骨硬化病发生发展过程中的miRNA可能受到circRNA介导的调控作用。研究显示在骨硬化病患者中转录因子*PU*.1的表达降低,*PU*.1能够通过募集增强子上调H3K27乙酰化同时下调H3K4甲基化,促进*NFATc*1的表达,促进单核细胞分化成为OC[94]。而已有研究显示*PU*.1的表达和活性受到相应的circRNA的调控,一方面*circ-SPI*1能够与翻译起始因子eIF4AⅢ相互作用从而拮抗*PU*.1的表达[95],另一方面*circ-Snx*5可以作为*miR*-544的海绵减弱miRNA介导的细胞因子信号传导抑制因子1对*PU*.1活性的抑制[96]。

目前针对骨硬化病这一罕见的基因遗传骨病的研究尚处在起步阶段,由于这一疾病能够严重影响患者生长发育,因此其早期诊断对于疾病的治疗和预后十分重要。在骨硬化病患者中针对circRNA-miRNA网络的研究能够帮助我们开发其早期诊断的分子标志物并判断其严重程度和预后,也能揭示对其进行治疗和干预的新靶点。

## 3 总结与展望

本文综述了circRNA、miRNA在表观遗传中的作用,同时重点介绍了circRNA作为miRNA海绵的表观遗传调控机制和circRNA-miRNA网络在调节骨重塑过程中成骨-破骨活动平衡。骨重塑过程中的成骨活动与破骨活动的平衡对骨重塑的正常进行、骨骼功能的维持具有至关重要的意义,成骨活动与破骨活动的失衡会引发骨质疏松、骨硬化病等疾病。随着高通量测序技术的发展,大量的circRNA和miRNA作为细胞生理活动的调节因子被发掘出来,并逐渐被证实在骨重塑活动中起到重要的调节作用。由骨重塑活动异常引发的骨质疏松和骨硬化病等疾病中检测出众多circRNA和miRNA的差异性表达,同时circRNA可通过与miRNA相互结合,从而发挥对相关信号通路的调控作用。通过预测潜在circRNA-miRNA调节网络有助于研究者深入认识相关疾病的发生发展过程及机制,同时对于疾病的风险及预后加以预判,在疾病的防治中起到指导作用。因此针对circRNA-miRNA调节网络设计的治疗方案有希望提供更有效、更安全的治疗效果。总之,全面了解参与骨重塑过程中的circRNA-miRNA调节网络有助于相关疾病的诊断,对疾病的治疗和预后具有重要意义。

* * *

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