综　述

NFATc 1参与microRNAs调控骨代谢研究进展

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【摘　要】骨骼正常的新陈代谢是维持骨骼健康的重要生物过程，需要破骨细胞与成骨细胞及其他重要因子参与。实验证明，microRNAs作为一种内源性非编码RNA，在调控骨代谢方面发挥重要作用。随着研究的深入，活化T细胞核因子1（nuclear factor of activated T cell cytoplasmic 1，NFATc 1）在骨代谢中的作用也逐渐被发现并成为近些年的研究热点。然而，在不同miRNAs调控下，NFATc 1最终发挥的生物学功能也大不相同。本文主要综述NFATc 1与miRNAs调控骨代谢相关实验研究进展，为骨代谢疾病的诊断及治疗提供理论依据。

【关键词】NFATc 1；microRNAs；骨代谢；破骨细胞；成骨细胞
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NFATc 1 is involved in the regulation of bone metabolism by microRNAs

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【**Abstract**】Normal bone metabolism is an important biological process to maintain bone health，which requires the participation of Osteoclasts，Osteoblast and other important factors. Experiments showed that microRNAs，as an endogenous non coding RNA，played an important role in regulating bone metabolism. With the deepening of researches，the role of nuclear factor of activated T cell cytoplasmic 1（NFATc 1）in bone metabolism has been gradually found and has become a research hotspot in recent years. However，under the regulation of different miRNAs，the final biological functions of NFATc 1 were also very different. This paper mainly reviewed the experimental research progress of NFATc 1 and miRNAs regulating bone metabolism，so as to provide a theoretical basis for the diagnosis and treatment of bone metabolic diseases.

【**Key words**】NFATc 1；microRNAs；Bone metabolism；Osteoclasts；Osteoblast

活化T细胞核因子1（nuclear factor of activated T cell cytoplasmic 1，NFATc 1）是破骨细胞分化的主调控因子[1]，启动子或上游因子通过调控*NFATc 1*基因转录控制骨吸收[2-3]。microRNAs作为一种内源性非编码RNA，参与成骨细胞和破骨细胞代谢过程，miR-100-5p[4]、miR-92a-1-5p[5]等可以负调控破骨细胞分化，而miR-331-3p[6]等可以积极调控骨形成。因此，本文就miRNAs和NFATc 1在骨重塑方面的最新研究进展做一综述，旨在为骨代谢疾病的防治奠定理论基础。

1　NFATc 1在骨代谢中的作用

1.1　NFATc 1生物学功能

NFATc 1来源于活化T细胞核因子家族（nuclear factor of activated T cell，NFAT）[7]，20世纪80年代，JP Shaw等[8]在激活的T细胞中首次发现NFATc 1，随后NFATc 2（NFATc 1 and NFATc）、NFATc 3（NFATc4）、NFATc 4（NFATc3 and NFATx）、NFATc 5（TonEBP and OREBP）也相继被发现[9]，共同组成NFAT转录因子家族。NFAT蛋白发挥调控等生物学功能具有一定差异性，可能与T细胞发育、激活和分化及钙与其他繁多复杂的信号通路整合有关[9-10]。NFATc 1作为NFAT家族核心成员常驻于细胞质中，Ca^{2+}是NFATc 1发挥生物学功能的主要激动剂，胞质钙与钙调素结合激活钙调神经磷酸酶，钙调神经磷酸酶磷酸化激活NFATc 1并进行自扩增，同时易位到细胞核中，完成靶基因转录激活，随着Ca^{2+}内流增加，NFATc 1表达也逐渐上升[10-14]。研究表明，NFATc 1在免疫系统、骨代谢、心脏瓣膜和间隔的形成、动脉粥样硬化及慢性肾功能衰竭中发挥重要作用，如通过协助T细胞提高炎性因子释放和核转录因子-κB受体活化因子配体（RANKL）的表达侵蚀

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类风湿性关节炎骨免疫系统；通过RANKL等其他信号轴调控骨代谢；通过提高心脏瓣膜间质细胞（valve interstitial cell，VIC）前体募集和增殖、建立VIC和有序排列心脏瓣膜细胞外基质（extracellular matrix，ECM），防止心功能障碍[15-18]。

1.2 NFATc 1调控骨代谢

成骨和破骨细胞之间的动态平衡维持骨骼正常代谢，当破骨细胞激活、分化过度时，易导致骨溶解，如骨质疏松症、类风湿性关节炎等骨破坏性疾病[19-20]。破骨细胞的来源和分化受肿瘤坏死因子（tumor necrosis factor，TNF）和巨噬细胞集落刺激因子（macrophage colony - stimulating factor，M-CSF）、RANKL、Ca^{2+}、NFATc 1、Irf 8等因子调控[20-24]。RANKL诱导激活TNF受体相关因子6（TNF receptor-associated factor 6，TRAF6）和c-Fos信号通路后，NFATc 1发生自扩增[25]，NFATc 1被认为是破骨分化的重要特异性调节器，常参与RANKL、MAPK、Ca^{2+}等信号通路下游调控骨吸收过程[12,14,26-27]。

RANKL/NFATc 1信号通路是介导骨吸收的经典通路，在RANKL刺激下，钙转导通路被激活引发钙振荡，诱导NFATc 1自扩增和核易位，促进破骨细胞分化[28]。体外研究证明，RANKL诱导骨髓巨噬细胞48 h后，NFATc 1、c-Fos mRNA和蛋白水平显著提高[29-30]。反之，条件性敲除*NFATc 1*的小鼠，其破骨细胞的发生、激活和分化障碍，导致破骨细胞大量凋亡，发生骨石化症，股骨远端和胫骨近端呈现短的棒状较高密度放射区域，抗酒石酸酸性磷酸酶（tartrate-resistant acid phosphatase，TRACP）阳性率低[22]。在RAW264.7细胞中条件性敲低*NFATc 1*，与破骨细胞分化相关的转录因子如小眼畸形相关转录因子（microphthalmia-associated transeription，MITF）、耐酒石酸酸性磷酸酶（tartrate-resistant acid phosphatase 5，ACP5）、组织蛋白酶K（cathepsin K，CtsK）活性也随之下降[31]，以上实验结果均提示NFATc 1在破骨细胞的分化中发挥着不可或缺的作用，而且NFATc 1的改变还会影响其他破骨相关因子活性。随着研究的深入，越来越多转录因子被发现在RANKL/NFATc 1信号通路中发挥作用。P38MAPK调控GSK-3β/β-catenin信号通路激活和分化破骨细胞[32]。进一步研究发现，P38MAPK是经RANKL介导从而激活下游c-Fos、NFATc 1等与破骨细胞分化相关因子[33]。最近一项研究发现，降低或者沉默醛脱氢酶1A1（aldehyde dehydrogenase 1A1，ALDH1A1）均会导致NFATc 1表达下调，说明ALDH1A1作为NFATc 1上游，促进了RANKL诱导的破骨细胞分化[26]。

然而，也有少数学者发现NFATc 1在某些转录因子的调控下对骨代谢也具有一定有益作用。LUO等人发现G蛋白偶联受体-4（G-protein-coupled receptor 4，LGR4）可以与RANK竞争性结合RANKL激活Gaq和GSK3-β信号通路，而该信号通路抑制NFATc 1发挥破骨作用，进而可以抑制RANKL/NFATc 1介导的破骨细胞分化[34]。流体剪切力（fluid shear stress，FSS）作用于MC3T3-E1细胞45 min时，NFATc 1被激活，活化的NFATc 1转移到细胞核中同时加速ERK5磷酸化，磷酸化的ERK5是成骨细胞增殖分化的重要调节器，从而促进成骨细胞增殖[35]。NFATc 1和NFATc 2灭活的雄性小鼠，骨组织形态学显示第三椎体成骨细胞数量、成骨细胞表面和类骨表面较对照组显著减少[36]，证明了NFATc 1和NFATc 2在某些情况下也有利益于体外成骨分化。低渗透压力通过瞬时受体电位通道3（transient receptor potential melastatin 3，TRPM3）和瞬时感受器电位通道香草素受体4（transient receptor potential channel vanillin receptor 4，TRPV4）诱导小鼠成骨细胞中Ca^{2+}的增加和RANKL介导的NFATc 1的表达[37]。这也对骨重塑受损引起的骨质疾病的防治有广泛的影响。

综合各项在体及离体实验结果，NFATc 1在多数情况下积极参与破骨细胞分化生物过程，有时也会间接影响其它破骨相关基因或蛋白的表达促进骨吸收。随着研究的不断深入，NFATc 1在某些特殊外力刺激下促进成骨细胞分化这一生物作用逐渐被发现。

2 microRNAs在骨代谢中的作用

2.1 microRNAs生物学功能

microRNAs（miRNAs）是一种大约含有19～25个核苷酸、21～23个碱基对的双链内源性非编码RNA[38-39]，由RNA聚合酶Ⅱ（RNAPⅡ）从独立基因转录或者蛋白质编码基因的内含子加工而来，细胞质中RNaseⅢ型家族中Dicer酶或TAR RNA结合蛋白（TAR RNA binding protein，TRBP）识别Drosha/DGCR8在细胞核中处理miRNA产生具有3'悬垂的前体miRNA（pri-miRNA），通过分裂前体形式得到成熟miRNA[40]，转录后调控基因层面的表达。miRNAs作为miRNA诱导沉默复合物（miRSIC）的一部分，miRNA靶向数十个甚至几百个信使RNAs（messager RNA，mRNA），诱导mRNAs降解或者抑制其翻译[7]。此外，当miRISC中的蛋白质AGO2（argonaute proteins 2）与miRNA完全互补的mRNAs相遇时，mRNAs在核内裂解使基因水平表达发生变化[41]。启动子的选择[38]、转录[41]等都会影响miRNAs对下游基因的调控，对靶基因的调控作用广泛参与各类细胞及组织生长、发育等生物学过程。

2.2 microRNAs调控骨重塑

2.2.1 miRNAs积极调控骨形成　miRNA-19a-3p通过抑制组蛋白去乙酰化酶4（histone deacetylase，HDAC4）

的表达，促进hMSCs的成骨分化，缓解骨质疏松症的进展[42]；磷酸化的STAT3直接调控miR-7-5p，miR-7-5p抑制下游靶点-CRY2表达从而上调CLOCK/BMAL1/P300，促进成骨分化[43]。miR-26b通过直接靶向GSK3β/β-catenin激活典型的Wnt信号通路来促进体外诱导骨髓间充质干细胞（bone marrow mesenchymal stem cells，BMSC）的成骨[44]。miR-150-3p[45]、miR-497[46]、miR-135-5p[47]、miR-106b-5p[48]等都可以正向调控骨形成。

2.2.2 miRNAs负向调控成骨细胞分化　另一类miRNAs可以负向调控成骨细胞，促进破骨细胞增殖、分化。miR-224抑制SMAD4的表达及其相关信号通路，抑制成骨细胞的分化[49]。*miR-320a*通过直接靶向CTNNB1和抑制Wnt/β-连环蛋白信号通路，负调控体外BMSCs的成骨分化[50]。*miR-23a*敲除小鼠与对照组相比，骨体积、骨小梁数目等骨参数定量显示明显增多[51]。miR409-5p靶向Lrp8抑制骨发生，而Lrp8作为Wnt信号的正效应因子，Wnt信号通路也因此得到抑制，促进破骨细胞分化导致骨量丢失[52]。miR-124[53-55]、miR-146a[56]在骨质疏松等骨破坏性疾病中发挥一定作用。

此外，同一个信号通路可能受多个因子、miRNA的调控，所以在骨代谢中也会发挥不同的作用，如Wnt信号通路。同样，同一个因子或miRNA可能调控多个信号通路影响骨代谢发展，如miR-214[57]通过靶向Pten/PI3k/Akt通路促进破骨细胞的发生，此外，miR-214[58]过表达还可以通过抑制转录激活因子4（activating transcription factor 4，ATF4）、成骨细胞特异性转录因子转录（osterix，Osx）、碱性磷酸酶和β-catenin等成骨相关因子表达减弱机械应变带来的成骨增强效应。

3 NFATc 1参与microRNAs调控骨代谢

NFATc 1同时存在于成骨细胞和破骨细胞中[59]，参与miRNAs调控骨代谢的机制已成为近几年相关研究领域的焦点。相关研究多集中在近10年，见表1。

表1 NFATc 1参与microRNAs调控骨代谢

Table 1 NFATc 1 is involved in microRNAs regulating bone metabolism

miRNAs	样本名称	概　述
miR-214	RAW 264.7 macrophages	NFATc 1↑，promote osteoclast differentiation
miR-133a	human monocytic cell line THP-1 and murine macrophage cell line RAW264.7	NFATc 1↑，promoted RANKL-induced differentiation of RAW264.7 and THP-1 cells into osteoclasts.
miR-182	BMMs	NFATc 1↑，increase osteoclastogenesis
miR-21	murine macrophage cell line RAW264.7	NFATc 1↑，promote osteoclastogenesis
miR-301-b	BMMs	NFATc 1 ↑，promote osteoclastogenesis
miR-151a-3p	The murine macrophage cell-line RAW264.7 and the human monocyte cell-line THP-1	NFATc 1 ↑，promote osteoclast differentiation
miR-124	mouse BMMs	NFATc 1 translation ↓，Suppress osteoclastogenesis
miR-125a	peripheral blood mononuclear cell，PBMCs	NFATc 1↓，inhibit osteoclasts differentiation
miR-29b	PBMCs	NFATc 1 ↓，impair osteoclasts differentiation
miR-146a	Sprague-dawley OVX rats jawbone	NFATc 1 ↓，relieve relieved the effects of osteoporosis
miR-22-3p	PBMCs	NFATc 1 ↓，reduce the osteoclastic proliferation and differentiation
miR-30a	BMMs	NFATc 1 ↓，inhibited the formation and function of osteoclasts
miR-139-5p	BMMs	NFATc 1 ↓，impair osteoclastogenesis
miR-29a	BMMs	NFATc 1 ↓，downregulated osteoclast formation
miR-506-3p	BMMs	NFATc 1 ↓，attenuate osteoclast formation
miR-143	Mice macrophage lines RAW264.7 cells	NFATc 1 ↓，inhibit osteoclast formation
miR-664-3p	BMSCs	NFATc 1↓，inhibits osteoblast apoptosis
miR-134-5p	BMMs	NFATc 1↓，attenuate osteoclast formation
miR-25	RAW264.7 cells	NFATc 1↓，inhibit osteoclast formation

3.1 NFATc 1和miRNAs正向调控骨形成

研究发现，miR-124过表达可以降低RANKL诱导BMMs（bone marrow-derived macrophages，BMMs）破骨细胞中*NFATc 1*基因表达，对NFκB、p65和c-Fos等调控破骨细胞发生因子的表达则微乎其微。为了证实NFATc 1在miR-124调控破骨细胞分化中的关键作用，研究者引入含有NFATc 1构成型活性形式的逆转录病毒，过量的NFATc 1不仅诱导了大量破骨细胞的形成，而且还阻止了miR-124预处理对破骨细胞生成的抑制，miR-124可能通过降低RhoA和Rac1的表达来抑制破骨细胞前体增殖、迁移和运动，抑制破骨细胞发生[53]。国内学者以C3H10T1细胞进行软骨诱导分化，

过表达miR-124能降低NFATc 1表达水平促进C3H10T1细胞软骨分化[60]。在不同诱导环境下，miR-214对*NFATc 1*的基因表达具有差异性。OHNUMA K等[54]发现在TNF-α和促骨吸收细胞因子IL-6[61]诱导的破骨细胞中，miR-214过表达可以使*CtsK*、*ACP5*、*DC-stamp*和*Itgb3*等破骨相关基因表达水平显著下降，而*NFATc 1*基因的表达水平和其它组相似，蛋白水平表达却发生下降，这也说明miR-214通过抑制NFATc 1翻译参与骨代谢。在对小鼠BMMs细胞研究中发现，过表达miR-134-5p降低NFATc 1表达，使破骨细胞数目降低[62]。体外培养RAW264.7细胞系研究发现，miR-25过表达后Ca^{2+}/NFATc 1信号通路中NFATc 1 mRNA表达减少，抑制破骨细胞的生成[63]。

3.2 NFATc 1和miRNAs负向调控骨吸收

条件性敲除*miR-301-b*[64]小鼠BMMS中，miR-301-b表达和NFATc 1表达呈正相关，其他骨吸收促进因子表达也显著下降。该研究还发现，在敲除*miR-301-b*的BMMS中肿瘤抑制因子圆柱瘤基因（cylindroma，CYLD）表达显著上调，p-NF-κB表达显著降低，miR-301-b靶向CYLD/NF-κB信号通路调节破骨细胞的发生。破骨特异性因子NFATc 1与其他转录因子协作并触发下游调节环路启动破骨细胞特异性基因表达，增强破骨细胞分化[65-66]。miR-506-3p[67]通过靶向抑制RANKL诱导的BMMs中NFATc 1转录，从而下调NFATc 1介导的相关促骨吸收因子金属蛋白酶9（metalloproteinase 9，P9）、Ctsk的表达。已知Pten促进T细胞和肿瘤细胞的增殖，并在RANKL诱导的破骨细胞分化中起关键作用，WANG等[68]通过*Targetscan*基因预测软件发现Pten在其3'UTR中包含miR-21结合位点，是miR-21的靶基因之一，miR-21在翻译水平上负调控Pten，提高Akt和NFATc 1蛋白表达水平，这说明miR-21通过调控Pten激活PI3K/Akt信号通路促进破骨细胞的发生和骨吸收。LI等[69]在绝经后骨质疏松病人血清中发现miR-133a显著上调，并与腰椎骨密度呈负相关，进一步研究发现敲低miR-133a可以降低NFATc 1，c-Fos和TRAP翻译水平，抑制了RANKL诱导的RAW264.7和THP-1细胞向破骨细胞的分化。动物实验发现[70]，miR-146a表达下调与Wnt/β-catenin信号通路Wnt2激活协同减弱NFATc 1、c-Fos and CTK蛋白表达从而抑制去卵巢大鼠颌骨骨质疏松病理改变。miRNAs可以在破骨分化末端发挥抑制破骨细胞的作用。ROSSI等[71]发现稳定表达miR-29b的破骨细胞分化第7 d和分化第18 d时NAFTc-1、Ctsk、MMP9蛋白表达均下降，且呈现无序结节性肌动蛋白点。该研究还证实miR-29b在破骨细胞中靶向抑制C-FOS和金属蛋白酶2（metalloproteinase 2，MMP2），而c-FOS常作为NFATc 1上游的激发点，因此，miR-29b损害末端分化的破骨细胞中NAFTc-1、Ctsk、MMP9的表达和肌动蛋白环的形成抑制骨吸收。

正常小鼠经糖皮质激素诱导后，NFATc 1表达下降，骨量丢失，而miR-29a转基因小鼠在经糖皮质激素诱导28 d后，可以逆转糖皮质激素提高NFATc 1表达，miR-29a可以抑制糖皮质激素诱导的破骨细胞侵蚀骨组织[72]。多数情况下NFATc 1常作为miRNAs下游靶点，发挥调控骨代谢作用。近期一项研究利用钙调神经磷酸酶抑制剂FK506抑制NFATc 1的激活，发现miR-182的表达也受到抑制[73]，NFATc 1作为miR-182诱导的关键上游调控因子，其机制尚不清楚。研究发现去卵巢骨质疏松大鼠模型miR-664-3p沉默后，NFATc 1作为PI3K/Akt/GSK3β/NFATc 1通路下游靶基因表达受到抑制，抑制成骨细胞凋亡，促进BMSCs增殖[74]。

4 microRNAs靶向调控NFATc 1参与骨代谢相关预测

课题组通过基因预测数据库Home - miRWalk（uni-heidelberg.de）预测来源于人和大鼠的NFATc 1的miRNAs，并运用VENNY2.1（http://bioinfogp.cnb.csic.es/tools/venny/）作交集图（图1），发现miR-297和miR-487b-5p可能靶向调控NFATc 1参与骨代谢，具体调控机制有待研究。骨代谢网络是一个在通路、因子及各种各样的微生物调控下运行的复杂而精密网络，因此，关于NFATc 1参与骨代谢的分子调节机制需要进一步研究。

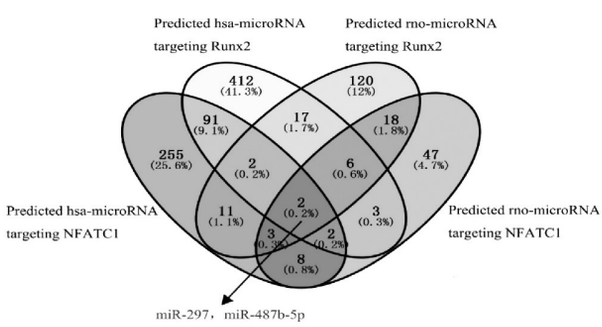


图1 成骨相关蛋白NFATc、Runx2（CBFa1）预测的共同调控miRNAs（miR-297、miR-4p）

Figure 1 Co-regulatory miRNAs (miR-297, miR-4p) predicted by the osteogenesis-related proteins NFATc and Runx2 (CBFa1)

5 小结与展望

NFATc 1广泛参与免疫系统、骨代谢、心脏瓣膜和间隔的形成等生物代谢过程。在骨代谢方面，骨吸收与骨形成过程失调极易导致骨代谢性疾病的发生[75]。NFATc 1常作为破骨细胞相关特异性因子在miRNAs/NFATc 1通路最下游发挥作用，直接或间接调控破骨过程。而在不同miRNAs调控下NFATc 1也可以抑制

破骨细胞增殖和分化，骨代谢发展也有着不同的结局。在某些特殊情况下，*NFATc 1*基因及蛋白的表达差异也会影响miRNA表达，或许是某些miRNA和NFATc 1之间存在反馈调节机制，有待进一步研究。目前关于NFATc 1和miRNA调控骨代谢的研究报道多指向骨代谢中破骨细胞的发生、分化，正向调控骨形成相关报道较少，这也为今后进一步探索NFATc 1在骨代谢方面的作用提供了研究方向。

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