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·综述·

MicroRNA-21调控破骨和成骨分化作用在正畸治疗中的研究进展

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【摘要】 在正畸矫治过程中，牙槽骨塑建与矫治器施加的机械应力的平衡是正畸牙有效移动的关键。牙槽骨塑建涉及众多调控因素，microRNAs(miRNAs)作为转录后调控因子，对骨塑建的发生起着重要的作用。作为miRNAs家族中的一个重要成员，研究证明miRNA-21可促进牙周膜干细胞向成骨细胞分化，同时作为破骨细胞生成的调节剂和破骨细胞分化的启动子，miRNA-21在维持骨平衡、防止骨吸收中发挥重要作用。文献复习结果表明，miRNA-21通过调控程序性细胞死亡蛋白4(programmed cell death 4，PDCD4)、蛋白酪氨酸磷酸酶(phosphate and tension homology deleted on chromsome ten，PTEN)、核因子κB受体活化因子配体(receptor activator of nuclear factor-κB ligand，RANKL)和骨骼保护因子(osteoprotegerin，OPG)等因子调节破骨细胞功能，促进体内骨吸收。miRNA-21在正畸牙移动过程中对外界机械应力高度敏感，在施加正畸力后，miRNA-21可促进破骨细胞生成从而加快正畸移动速度；通过靶向调节牙周膜相关蛋白1(periodontal ligament associated protein-1，PLAP-1)在牙齿移动后期调控牙周膜重塑，改善牙齿移动的潜能。另外，miRNA-21在牙周炎性微环境下同时介导正畸牙移动(orthodontic tooth movement，OTM)和牙槽骨重塑；在缺氧环境中可上调牙周膜干细胞(periodontal ligament stem cells，PDLCs)中的缺氧诱导因子-1α(Hypoxia-inducible factor-1α，HIF-1α)的表达；促进成骨标志物如骨桥蛋白(osteopontin，OPN)、骨钙素(Osteocalcin，OCN)和碱性磷酸酶(alkaline phosphatase，ALP)与Runt相关转录因子2(runt-related transcription factor 2，Runx2)的表达；在正畸牙移动过程中促进成骨分化。

【关键词】 microRNAs；　microRNA-21；　正畸治疗；　正畸牙移动；　成骨分化；　破骨分化；　骨塑建；　牙周组织
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Research progress on microRNA-21 in regulating osteoclast and osteogenic differentiation in orthodontic treatment

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【Abstract】 In the process of orthodontic treatment, the balance between the modeling of alveolar bone and the mechanical stress exerted by the appliance is key to the effective movement of orthodontic teeth. Alveolar bone modeling involves many regulatory factors, and microRNAs (miRNAs), as posttranscriptional regulatory factors, play an important role in the occurrence of bone modeling. As an important member of the miRNA family, miRNA-21 promotes the differ-

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entiation of periodontal ligament stem cells into osteoblasts and plays an important role in maintaining bone balance and preventing bone resorption as a regulator of osteoclast formation and a promoter of osteoclast differentiation. A literature review showed that miRNA-21 can regulate osteoclast function and promote bone resorption through programmed cell death 4 (PDCD4), phosphate and tension homology deleted on chromosome ten (PTEN), receptor activator of nuclear factor-κB ligand (RANKL) and osteoprotegerin (OPG). MiRNA-21 is highly sensitive to external mechanical stress in the process of orthodontic tooth movement. After orthodontic force is applied, miRNA-21 can promote osteoclast formation and accelerate orthodontic movement; through targeted regulation of periodontal ligament associated protein-1 (PLAP-1), it can regulate periodontal ligament remodeling in the late stage of tooth movement and improve the potential of tooth movement. In addition, miRNA-21 mediates orthodontic tooth movement (OTM) and alveolar bone remodeling in the periodontal inflammatory microenvironment. miRNA-21 can upregulate the expression of hypoxia-inducible factor-1α (HIF-1α) in periodontal ligament stem cells in a hypoxic environment. It can promote the expression of osteogenic markers, such as osteopontin (OPN), osteocalcin (OCN), alkaline phosphatase (ALP) and runt-related transcription factor 2 (Runx2), and promote osteogenic differentiation during orthodontic tooth movement.

【Key words】 microRNAs; microRNA-21; orthodontic treatment; orthodontic tooth movement; osteogenic differentiation; osteoclast differentiation; bone modeling; periodontal tissue

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在正畸矫治的牙齿移动过程中，牙齿与颌骨以及其周围组织受到机械力作用，由于张力侧和压力侧受力不同，骨吸收和骨形成的活性空间分离，在骨表面旧骨吸收、新骨形成发生适应性骨塑建（bone modeling）[1]。骨塑建是由成骨细胞和破骨细胞功能平衡介导的；破骨细胞或成骨细胞分化的失调可导致骨平衡失调和骨质疏松症。在正畸治疗中，成骨细胞和破骨细胞的平衡介导着有效的牙齿移动，骨平衡失调会减缓牙齿移动速度。现有研究证明microRNAs（miRNAs）具有调控成骨细胞和破骨细胞的分化和生物学功能的作用；而且在正常和炎症微环境中均可调节正畸牙移动（orthodontic tooth movement，OTM）和牙槽骨重塑[2]。本文就miRNA-21调控成骨细胞与破骨细胞分化作用在正畸治疗中的应用研究进展作一综述。

1　miRNAs的结构及特性

miRNAs作为一种小的非编码RNA，主要存在于细胞核中；由RNA聚合酶Ⅱ转录为长链的初级转录本，随后被Drosha裂解，产生长度约为70个核苷酸的茎环结构前体分子（pre-miRNAs）。它最终被运送到细胞质中，并被RNase Ⅲ酶Dicer进一步加工成成熟的miRNA。miRNAs可以通过抑制信使RNA（messenger RNA，mRNA）的翻译或通过结合其3′-未翻译区（3’- untranslation region，3’UTR）来降解mRNA分子，从而沉默同源靶基因；miRNAs之间靶向目标可能会重叠。miRNAs可以通过DNA或组蛋白修饰对表观遗传产生影响，并在转录水平上调节基因表达。研究表明，miRNAs在破骨细胞、成骨细胞和其他类型细胞的增殖和分化中发挥重要作用[3]；此外，miRNAs可能具有机械敏感性，并在骨塑建过程中成为关键的转录后调节因子[4]。

2　miRNA-21的生物学特性

miRNA-21是定位于染色体17q23.2上的miRNA，其与人类和大鼠空泡膜蛋白的同源物——编码液泡膜蛋白1（vacuole membrane protein 1，VMP1）的基因重叠。miRNA-21被鉴定为一种致癌miRNA；其在大多数人类恶性肿瘤中过表达并作为肿瘤抑制因子；在肿瘤细胞增殖、凋亡和侵袭中发挥重要作用[5]。miRNA-21调节多种肿瘤相关靶基因的表达，如蛋白酪氨酸磷酸酶（phosphate and tension homology deleted on chromsome ten，PTEN）[5]、原肌球蛋白1（tropomyosin 1，TPM1）[6]、

程序性细胞死亡蛋白4(programmed cell death 4, PDCD4)[7]、叉头框蛋白O1(forkhead box O1, FOXO1)[8]及Cdc25a[9]等。在免疫系统中,miRNA-21能够调节T细胞免疫。研究发现,miRNA-21在效应T细胞中的表达频率最高;表明miRNA-21在维持T细胞效应状态中可能起着重要作用。同时,Chen等[10]在斑马鱼胚胎的早期发育阶段(12 h)可以检测到miRNA-21的表达,发现其在成纤维细胞中的表达约占40%。另外,有研究显示miRNA-21在分支形态的发生过程中起着重要作用。Hayashi等[11]的研究发现,miRNA-21的上调可以促进分支形态的发生;抑制miRNA-21的表达则可以引起上皮芽数量的减少,但miRNA-21在生长发育中的作用还有待进一步研究。

miRNA-21除了在肿瘤、免疫和发育中发挥作用外,在促进破骨细胞生成和成骨分化中也起着不可或缺的作用。miRNA-21可以调节成骨细胞和破骨细胞生成以防止骨吸收[12]。Sun等[13]发现上调miRNA-21可显著增加了成骨相关基因标志物骨桥蛋白(osteopontin, OPN)、骨钙素(osteocalcin, OCN)和碱性磷酸酶(alkaline phosphatase, ALP)的表达水平;表明miRNA-21促进了骨髓间充质干细胞(bone marrow mesenchymal stem cells, BMMSCs)在体外的成骨分化;micro-CT显示,miRNA-21过表达可以增加新骨的形成和矿化,促进大鼠体内骨折愈合。miRNA-21对机械刺激产生反应而调节成骨分化,在牙齿移动过程中可以调节OTM和牙槽骨重塑[2]。相反,Wei等[14]验证了Smad5是miRNA-21的一个潜在下游靶点,抑制miRNA-21可以通过靶向Smad5减少人牙周膜干细胞(human periodontal ligament stem cells, hPDLSCs)的成骨分化。miRNA-21在成骨细胞和破骨细胞中具有双重作用,其既可以促进成骨分化,也可以抑制成骨分化;但是miRNA-21在骨形成和骨吸收中的具体作用机制尚未阐明。

3　miRNA-21调控破骨分化对正畸治疗的影响

在正畸牙移动过程中,压力和缺氧均可能启动破骨细胞生成;miRNA在正畸牙移动中过程中对外界机械应力高度敏感,是维持骨骼内环境稳定的关键转录后调节因子[15]。miRNA-21被认为是破骨细胞生成的调节剂和破骨细胞分化的启动子。体外研究发现miRNA-21通过调节PDCD4或通过靶向Fas配体(Fas ligand, FasL)促进破骨作用[16]。另外,miRNA-21可以调节核因子κB受体活化因子配体(receptor activator of nuclear factor-κB ligand, RANKL)和骨骼保护因子(osteoprotegerin, OPG),它们在调节破骨细胞分化和骨吸收功能中起着关键作用[17]。有研究者将敲除OPG小鼠与敲除RANKL小鼠作对比,两组小鼠均发生严重骨质疏松和骨坏死,证明了平衡的RANKL/OPG比例是维持局部骨形成和骨吸收平衡的关键,对骨塑建至关重要[18]。RANKL的产生与miRNA-21、白细胞介素-6(interleukin-6, IL-6)和靶向信号转导子和转录激活因子3(signal transducer and activator of transcription 3, STAT3)通路的调节反馈回路相关,而miRNA-21的表达是由IL-6诱导的,需要STAT3通路的激活[19]。相反,miRNA-21通过抑制PIAS3(protein inhibitor of activated STAT3)来增强STAT3依赖信号通路,而OPG属于肿瘤坏死因子(tumor necrosis factor, TNF)受体配体超家族,是正常骨代谢中TNF受体的关键成员,OPG能拮抗RANKL与核因子κB受体活化因子(receptor activator of nuclear factor-κB, RANK)的结合,从而保持骨量的完整性。

在多发性骨髓瘤来源的BMMSCs中,miRNA-21通过靶向STAT3通路激活因子直接靶向抑制OPG,间接促进RANKL表达,提示miRNA-21能促进破骨细胞发生[20]。敲除小鼠miRNA-21基因后可观察到破骨细胞的增殖受到抑制,干扰miRNA-21后在促进骨形成的同时抑制了BMMSCs的集落形成和增殖[21]。有学者认为,PDCD4是miRNA-21支持破骨细胞功能的功能靶点,可通过靶向PDCD4抑制破骨细胞功能来阻断雌激素减少后诱导的骨质减少,证明miRNA-21通过靶向PDCD4直接控制破骨细胞功能,促进体内骨吸收[12]。Wang等[22]发现miRNA-21可在翻译水平上负调控PTEN,miRNA-21在破骨细胞形成过程中表达上调,促进成骨细胞分化和骨吸收;另外,miRNA-21还可能通过靶向PTEN激活PI3K/AKT信号通路促进破骨细胞生成和骨吸收。C-Fos上调了miRNA-21的表达,而miRNA-21通过下调PDCD4蛋白的表达,减少了C-Fos在RANKL诱导的破骨细胞形成过程中的抑制作用。还有研究发现抑制miRNA-21的表达可能与肿瘤坏死因子-α(tumor necrosis factor-α, TNF-α)抑制雌激素缺乏性骨质疏松症的骨形成有关。许诺等[23]通过细胞学实验证明miRNA-21可以促进破骨细胞的增殖,骨破坏标志因子端

粒酶调节蛋白(target of RNA Ⅲ activating protein, TRAP)与组织蛋白酶K(cathepsin K, CTSK)的表达在慢性牙周炎组织中明显增高,并且miRNA-21的表达与骨破坏标志因子间有明显相关性,提出miRNA-21可以作为治疗牙周炎骨破坏的靶点。

研究表明OTM也受免疫系统的控制,T细胞通过Th1相关细胞因子促进OTM。Wu等[24]发现miRNA-21结构缺失会减缓牙齿移动速度、抑制破骨细胞生成数量;通过向小鼠体内注入活化的T细胞,观察到小鼠的破骨细胞数量明显升高,牙齿移动距离增加,意味着破骨细胞通过T细胞增加了RANKL/OPG的表达,从而促进了OTM。李梦莹等[25]报道在无机械力刺激的情况下,miRNA-21-/-小鼠上颌腭中缝组织的破骨细胞生成和骨吸收受到抑制。Zhang等[26]首次探讨miRNA-21在牙周加速成骨正畸(periodontal accelerate osteogenesis orthodontics, PAOO)中成骨和破骨分化中的调控作用,发现miRNA-21过表达后负调控靶基因PDCD4的表达,导致破骨细胞相关转录因子C-Fos的表达水平升高,破骨细胞增加,牙槽骨发生塑建,正畸牙齿移动量增加。综上,miRNA-21可以调节破骨细胞的分化,影响骨组织的塑建,在施加正畸力后,miRNA-21可促进破骨细胞生成从而加快正畸移动速度,但其具体的作用机制还有待进一步研究。

4　miRNA-21调控成骨分化对正畸治疗的影响

研究发现,miRNA-21不仅影响骨吸收,还影响骨形成和骨分化;并且miRNA-21的缺乏会影响骨重塑的发生,这与促进破骨细胞生成的研究结果相反[27]。miRNA-21在成骨细胞-破骨细胞偶联过程中的双重作用,可能是与其靶点在成骨过程中的动态调节有关。Smieszek等[28]建立了稳定的小鼠成骨前细胞(MC3T3)与破骨细胞前体细胞系(4B12)的间接共培养体系,探讨抑制miRNA-21对成骨和破骨相互作用的影响;发现在体外成骨的第7天和第15天,MC3T3细胞中miRNA-21表达上调,而OPN水平下降;然而MC3T3与4B12细胞共培养时,OPN水平升高,在MC3T3inh21/4B12共培养中其表达水平显著降低;表明成骨细胞产生的OPN可以激活破骨细胞的骨吸收,在调节破骨细胞-成骨细胞偶联中起着关键作用。Zhang等[29]建立大鼠正畸牙移动模型,在缺氧环境中,缺氧诱导因子-1α(Hypoxia-inducible factor-1α, HIF-1α)和miRNA-21的表达显著上调,miRNA-21模拟物增加了HIF-1α的表达,促进成骨分化,成骨标志物OPN、Runt相关转录因子2(runt-related transcription factor 2, Runx2)、ALP的表达均上调;表明miRNA-21对低氧下牙周膜干细胞(periodontal ligament stem cells, PDLCs)中HIF-1的表达有促进作用,并且在正畸牙移动过程中促进成骨分化。

与静态PDLSCs相比,拉伸PDLSCs过程中,miRNA-21的表达水平明显升高,证实了miRNA-21与机械力诱导的PDLSCs成骨分化有关[30]。激活素受体2B(activin receptor type ⅡB, ACVR2B)是成骨分化的关键调控因子;ACVR2B功能的获得或者缺失均会对PDLSCs成骨分化产生影响;miRNA-21通过靶向ACVR2B调控PDLSCs的牵张成骨分化。王红等[31]通过敲除miRNA-21基因的小鼠成功建立了上颌骨缺损模型,发现敲除miRNA-21基因的小鼠的ALP和OCN的表达明显减少,成骨能力减弱,表明miRNA-21具有促进骨重塑的作用,并且敲除 miRNA-21基因抑制了骨缺损的愈合;注射miRNA-21的过表达试剂可以提高敲除miRNA-21基因小鼠的骨愈合能力,加速新骨生成及矿化。Hong等[32]研究发现miRNA-21参与了正畸牙齿移动,是牙周膜组织重塑的重要调节因子。当施加牵引力时,上调的miRNA-21促进了PDLSCs的成骨分化,miRNA-21在压力侧和张力侧均过表达;miRNA-21在矿化早期高表达,在成骨晚期表达降低;提示miRNA-21可能通过靶向调节牙周膜相关蛋白1(periodontal ligament associated protein-1, PLAP-1)在牙齿移动后期调控牙周膜重塑,改善牙齿移动的潜能。

正畸牙移动的早期阶段,是一种炎症阶段,压力和缺氧通过诱导无菌性炎症反应,协同促进骨组织和牙周组织的重塑。TNF-α是一种由巨噬细胞释放的炎性细胞因子,可诱导骨吸收,被认为是参与牙周病发病的主要细胞因子,TNF-α可以抑制PDLSCs的成脂和成骨分化。在炎症微环境中,TNF-α抑制了miRNA-21的表达。上调miRNA-21可通过抑制靶基因Spry1部分减少TNF-α损伤的成脂和成骨作用,提示miRNA-21/Spry1功能轴在炎症微环境下对PDLSC分化中起关键作用,有修复牙周炎损伤的牙周组织的潜力[33]。Chen等[2]报道,通过注射脂多糖(lipopolysaccharide, LPS)诱导小鼠牙周炎症,miRNA-21在炎症中上调,牙齿移动速度与miRNA-21低表达小鼠相比显著增加;同时

下调miRNA-21也导致上颌骨骨量的减少，因此认为miRNA-21在牙周炎症微环境下同时介导OTM和牙槽骨重塑。miRNA-21的缺乏导致压力侧与张力侧牙槽骨破骨细胞生成被抑制；牙齿移动的模型中可以观察到，miRNA-21基因敲除后小鼠牙齿移动距离显著小于野生型小鼠。

5　小　结

miRNA-21可以在正畸治疗中调节成骨细胞和破骨细胞生成以防止骨吸收，并且在破骨细胞和成骨细胞中的双重作用，使骨重塑过程加快，但其具体作用机制尚未完全阐明，有待进一步的研究探讨，以期成为正畸矫治中促进和控制正畸牙移动速度的新靶点。

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