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在线全文

·综　述·

miRNA通过靶向骨保护素参与多种疾病的发病机制*

周　铎[1, 2, 3]，杨德琴[1, 2, 3△]

1. 重庆医科大学附属口腔医院 牙体牙髓科（重庆 401147）；2. 口腔疾病与生物医学重庆市重点实验室（重庆 401147）；
3. 重庆市高校市级口腔生物医学工程重点实验室（重庆 401147）

【摘要】 骨保护素（osteoprotegerin, OPG）是肿瘤坏死因子受体家族中的一员，在成人肺、心脏、肾脏、肝脏、脾脏、胸腺、前列腺、卵巢、小肠、甲状腺、淋巴结、气管、肾上腺、睾丸和骨髓中都有高度的表达，与核因子κB受体激活剂（receptor activator of nuclear factor-κB, RANK）及核因子κB受体激活剂配体（receptor activator of nuclear factor-κB ligand, RANKL）共同组成RANK/RANKL/OPG途径，在多种疾病发展的分子机制中起着重要的作用。微小RNAs（microRNAs, miRNA）是在真核生物中的一类内源性的具有调控功能的非编码RNA，其大小约20～25个核苷酸。miRNA基因被RNA聚合酶转录成初级转录物，与RNA诱导的沉默复合体结合，通过碱基互补配对的方式识别靶mRNA，单个miRNA可以靶向数百个mRNA，并通过参与功能相互作用的途径影响许多基因的表达。近年来大量研究通过miRNA分离、miRNA定量、miRNA谱分析、miRNA靶点检测、体外和体内调节miRNA水平等技术探究了miRNA在疾病中的作用机制，并发现miRNA可通过靶向OPG在骨质疏松症、类风湿关节炎等多种疾病发病中发挥关键作用。本综述旨在探讨各种疾病中miRNA与OPG的相互作用，为研究OPG在疾病中的作用机制提出新的思路。

【关键词】 骨保护素　微小RNA　骨质疏松　类风湿性关节炎　动脉粥样硬化　肿瘤　综述

miRNA Is Involved in the Pathogenesis of Multiple Diseases by Targeting Osteoprotegerin

ZHOU Duo[1, 2, 3], *YANG Deqin*[1, 2, 3△]. 1. *Department of Endodontics, Stomatological Hospital of Chongqing Medical University*, Chongqing 401147, China; 2. *Chongqing Key Laboratory of Oral Diseases and Biomedical Sciences*, Chongqing 401147, China; 3. *Chongqing Municipal Key Laboratory of Oral Biomedical Engineering of Higher Education*, Chongqing 401147, China

△ Corresponding author, E-mail: yangdeqin@hospital.cqmu.edu.cn

【Abstract】 As a member of the tumor necrosis factor receptor family, osteoprotegerin (OPG) is highly expressed in adults in the lung, heart, kidney, liver, spleen, thymus, prostate, ovary, small intestines, thyroid gland, lymph nodes, trachea, adrenal gland, the testis, and bone marrow. Together with the receptor activator of nuclear factor-κB (RANK) and the receptor activator of nuclear factor-κB ligand (RANKL), it forms the RANK/RANKL/OPG pathway, which plays an important role in the molecular mechanism of the development of various diseases. MicroRNAs (miRNAs) are a class of endogenous non-coding RNAs performing regulatory functions in eukaryotes, with a size of about 20-25 nucleotides. miRNA genes are transcribed into primary transcripts by RNA polymerase, bind to RNA-induced silencing complexes, identify target mRNAs through complementary base pairing, with a single miRNA being capable of targeting hundreds of mRNAs, and influence the expression of many genes through pathways involved in functional interactions. In recent years, a large number of studies have been done to explore the mechanism of action of miRNA in diseases through miRNA isolation, miRNA quantification, miRNA spectrum analysis, miRNA target detection, *in vitro* and *in vivo* regulation of miRNA levels, and other technologies. It was found that miRNA can play a key role in the pathogenesis of osteoporosis, rheumatoid arthritis, and other diseases by targeting OPG. The purpose of this review is to explore the interaction between miRNA and OPG in various diseases, and to propose new ideas for studying the mechanism of action of OPG in diseases.

【Key words】 Osteoprotegerin　microRNA　Osteoporosis　Rheumatoid arthritis　Atherosclerosis　Tumor　Review

微小RNAs（microRNA, miRNA）是在真核生物中的一类内源性的具有调控功能的非编码RNA，其大小长约20～25个核苷酸。成熟的miRNA由初级转录物经过一系列的剪切加工而成，随后组装进RNA诱导的沉默复合体，通过碱基互补配对的方式识别靶mRNA[1]。miRNA在靶基因表达的转录后调控中起作用。一个miRNA可以同时靶向位于同一细胞信号通路内的多个基因[2-4]。miRNA的

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△ 通信作者，E-mail: yangdeqin@hospital.cqmu.edu.cn

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靶基因不仅包括mRNA，还包括长链非编码RNA(long noncoding RNA, lncRNA)、假基因和环状RNA(circRNA)。竞争内源性RNA(competing endogenous RNA, ceRNA)也可通过竞争共享miRNA来调节其他RNA转录物[5]。miRNA具有与多个靶基因相互作用的能力，已被证明能够影响许多重要的生物学过程，如细胞生长、组织分化、细胞增殖、胚胎发育和凋亡。miRNA失调在衰老、心血管疾病、癌症等多种疾病的进展中同样起着至关重要的作用[6]。在动物中，miRNA还可以被包装到外泌体或微囊中，并分泌到细胞外环境中，包括各种生物体液，因此可以进行长距离的细胞间通信[7]。

1997年骨保护素(osteoprotegerin, OPG)被发现，作为肿瘤坏死因子(tumor necrosis factor, TNF)受体家族的新成员，也被称为破骨细胞形成抑制因子(ostelclastogenesis inhibitory factor, OCIF)，在我们对破骨细胞的认识中是一个重大的突破。骨保护素是一种可溶性蛋白，可阻止体内破骨细胞生成和骨吸收，调节动物骨量和骨密度[8]。OPG由*TNFRSF11B*基因编码，与核因子κB受体激活剂(receptor activator of nuclear factor-κB, RANK)及核因子κB受体激活剂配体(receptor activator of nuclear factor-κB ligand, RANKL)组成TNF受体超家族的受体-配体对，共同构成骨代谢的关键分子途径RANK/RANKL/OPG途径[9]。破骨细胞前体(osteoclast precursors, OCPs)向破骨细胞分化过程中巨噬细胞集落刺激因子和RANKL作用于OCPs，使其核融合成多核细胞，细胞膜表面的核因子κβ受体活化因子继续与RANKL结合形成成熟破骨细胞[10]，OPG作为诱饵受体，可以与RANKL结合，阻断其结合和激活。

对OPG的研究除了对其在骨代谢中的作用机制深度认识外，还发现其在动脉粥样硬化、糖尿病、类风湿性关节炎、骨质疏松、免疫系统疾病和肿瘤等疾病中起着不同的作用[11]。OPG还在成人肺、心脏、肾脏、肝脏、脾脏、胸腺、前列腺、卵巢、小肠、甲状腺、淋巴结、气管、肾上腺、睾丸和骨髓中都有高度的表达[12]。近年来大量的研究发现，miRNA通过多种不同的方式在疾病发展过程中参与调控OPG，这些调控方式通过抑制或增加OPG的表达水平影响疾病的发展和预后。

1 miRNA在骨质疏松中调控OPG

骨重塑受到成骨细胞和破骨细胞之间的相互作用的严格调节。成骨细胞和破骨细胞通过直接的细胞间接触或分泌蛋白相互交流以调节细胞行为、凋亡和分化。破骨细胞形成的过程中成骨细胞产生巨噬细胞集落刺激因子(macrophage colony-stimulating factor, M-CSF)[13]，其细胞膜表达RANKL[14]，破骨细胞前体细胞表达RANK(RANKL受体)，通过细胞间相互作用识别成骨细胞表达的RANKL，并在M-CSF诱导下分化为破骨细胞[15]。OPG作为一种可溶性RANKL受体，主要由成骨细胞产生，通过抑制RANKL-RANK相互作用抑制破骨细胞形成和破骨细胞骨吸收功能。相反，骨吸收相关的刺激因子和细胞因子增强成骨细胞中RANKL的表达。成熟的破骨细胞也表达RANK和RANKL，两者都支持破骨细胞的存活并刺激破骨细胞的骨吸收活性。

早在20多年前，OPG就已经被发现为骨质疏松发病过程中一个重要的因子，抑制骨中RANKL–RANK信号可通过防止破骨细胞骨吸收增加骨量。RANKL和RANK缺陷小鼠表现出严重的骨质疏松症，伴有破骨细胞分化不足[16]。大量研究表明不同来源的多种miRNA可以通过调控OPG的途径来影响骨质疏松的发展(表1)。在骨质疏松中通过下调骨髓间充质干细胞中的miR-19b-3p可增加OPG的表达，减轻骨质疏松的症状，提高骨密度、矿化程度、胶原含量等[17]。miRNA除了通过调控细胞中的OPG表达来影响成骨细胞和破骨细胞的增殖分化以外，也有报道miRNA通过促进旁分泌作用来抑制破骨细胞分化。转染miR-99a-5p抑制剂后的人骨髓间充质干细胞培养上清液中的OPG表达量上升从而减少多核细胞数量和降低破骨标志物的表达来破坏骨髓细胞的破骨细胞分化潜能[18]。脂肪来源的干细胞外膜囊泡中miR-21-5p和let-7a通过降低破骨细胞相关基因的表达和增加OPG的表达来抑制破骨细胞的分化[19]。在两项基因敲除实验中，miRNA同样被证实通过调控OPG来影响骨质疏松的发展。miR-146a敲除小鼠骨质疏松模型的骨微环境中OPG的表达水平提升，RANKL/OPG以及M-CSF水平受到抑制从而减少骨量散失[20]。相反，在miR-21敲除小鼠中miR-21通过靶向Spry1表现出RANKL的升高和OPG的降

表1 骨质疏松中miRNA对OPG表达的影响

Table 1 Effect of miRNA on OPG expression in osteoporosis

miRNAs	Disease	miRNA expression	OPG expression	References
miR-19b-3p	Osteoporosis	↓	↑	[17]
miR-99a-5p	Osteoporosis	↓	↑	[18]
miR-21-5p, let-7a	Osteoporosis	↑	↑	[19]
miR-146a	Osteoporosis	↓	↑	[20]
miR-21	Osteoporosis	↓	↓	[21]
miR-483-3p	Osteoporosis	↑	↓	[22]
miR-155	Osteoporosis	↓	↑	[23]

↓: Downregulated; ↑: upregulated.

低, 然而miR-21敲除小鼠的骨质疏松模型与正常小鼠骨质疏松模型相比RANKL/OPG比值无明显差异, 破骨细胞的分化和骨吸收能力却都受到了影响, 这是因为miR-21可同时靶向PDCD4抑制破骨细胞功能来阻断骨质减少[21], 这项研究也充分证明了miRNA在调控OPG的过程中同时有可能靶向多个基因, 最终影响疾病的发展。

绝经后骨质疏松患者组织中miR-483-5p 上调, 过表达miR-483-5p可显著抑制细胞活力以及OPG、RUNX2和BMP2的表达[22]。miR-155在骨质疏松中高表达, 阿仑膦酸治疗骨质疏松过程中通过下调miR-155可上调LEPR、AMPK、OPG的表达, 降低RANKL、M-CSF、RANK的表达, 抑制破骨细胞的细胞增殖和骨吸收[23]。这些研究都阐述了OPG在骨质疏松疾病发病和治疗过程中的作用, 并且验证了miRNA在其中扮演的重要角色。

2　miRNA在免疫系统疾病中调控OPG

免疫系统和骨骼系统共享多种分子, 包括细胞因子、趋化因子、激素、受体和转录因子等[24]。在生理和病理条件下, 骨细胞与免疫细胞相互作用, RANK、RANKL、OPG作为重要的因素通过调控破骨细胞的功能和分化影响免疫系统疾病的进展。

近年来研究发现多种miRNA通过直接或间接的方式在免疫系统疾病包括类风湿性关节炎、痛风、强直性脊柱炎等疾病中调控OPG的水平从而改变疾病的发生。miR-145-5p可以通过靶向Wnt1/β-catenin通路来调控OPG, 将miR-145-5p模拟物转染到类风湿性关节炎成纤维细胞样滑膜细胞中, 可引起Wnt1/β-catenin信号传导的各种因子的表达水平降低来导致OPG水平降低[25]。miR-23a同样可通过降低类风湿性关节炎成纤维细胞样滑膜细胞中LRP5、β-catenin的表达水平影响OPG的表达, 导致骨质流失和钙潴留[26]。此外, 抑制miR-106b的表达可提高类风湿性关节炎小鼠OPG表达水平, 降低RANKL/OPG比值, 减少破骨细胞的数量[27], miR-106b还可以通过外泌体从滑膜成纤维细胞传递到软骨细胞, 抑制软骨细胞增殖和迁移, 加速细胞凋亡, 并通过下调PDK4影响RANKL/RANK/OPG系统[28]。

强直性脊柱炎也是一类类风湿炎症性疾病, 抑制成骨细胞let-7i-3p的表达可增加强直性脊柱炎小鼠骨密度、胫骨最大负荷和弯曲弹性模量, 降低TNF-α、MMP-3和RANKL含量, 减轻滑膜组织病理状况, 提高OPG表达量[29]。如表2所示, miRNA在免疫系统疾病中通过不同的方式来直接或间接引起OPG表达水平的变化, 通过改变OPG的表达来使疾病的预后和归转发生变化, 这些研究进一步提示miRNA在探究OPG对免疫系统疾病影响的重要性。

表 2　免疫系统疾病中miRNA对OPG表达的影响

Table 2　Effect of miRNA on OPG expression in immune system diseases

miRNAs	Disease	miRNA expression	OPG expression	References
miR-145-5p	Rheumatoid arthritis	↑	↓	[27]
miR-23a	Rheumatoid arthritis	↓	↑	[26]
miR-106b	Rheumatoid arthritis	↓	↑	[27]
let-7i-3p	Ankylosing spondylitis	↓	↑	[29]

↓: Downregulated; ↑: upregulated.

3　miRNA在心血管疾病和糖尿病中调控OPG

骨调节蛋白与血管生物学的关系早在多年前就备受关注, 有学者提出OPG可能介导血管钙化和心脏代谢疾病。OPG响应炎症刺激而稳定地从血管内皮细胞中释放出来, 这表明它在血管损伤、炎症和动脉粥样硬化中起调节作用。OPG通过抑制RANKL与RANK的结合, 中和RANKL对血管平滑肌细胞MMP活性诱导的影响, 降低心血管疾病的风险[30]。研究发现, miR-30c-5p在人动脉粥样硬化动脉中的表达明显低于正常动脉, 过表达miR-30c-5p可抑制OPG的表达, miR-30c-5p通过直接靶向OPG抑制血管平滑肌细胞的分化导致血管钙化[31]。相反过表达miR-26a可促进CTGF、OPG、RANKL、ALP的表达, 抑制β-GP诱导的血管平滑肌细胞钙化, 降低血管钙化发生的风险[32]。

在过去的研究中糖尿病被认为与心血管疾病互为危险因素, 糖尿病患者的心血管疾病发病风险明显上升, 无论1型糖尿病还是2型糖尿病动脉粥样硬化的过程都更活跃[33]。OPG作为心血管疾病中一个重要的因子, 在心血管疾病与糖尿病相关的研究中同样有着重要的地位。糖尿病主动脉中OPG表达和OPG/TRAIL比值显著增加[34], 循环OPG水平还有可能与胰岛素水平相关[35]。近年来有许多研究从miRNA水平探究了OPG在其中的作用。糖尿病患者miR-433-3p的表达水平明显降低, 其中糖尿病合并血管系统疾病患者的表达水平最低。此外, DKK1和OPG水平降低, Runx2、β-catenin和RANKL水平在两组糖尿病患者中均显著升高, miR-433-3p的下调通过激活RANKL/RANK/OPG和WNT/β-catenin信号通路促进血管疾病的发展[36]。2型糖尿病患者外周血单核细胞miR-145水平降低, miR-145通过靶向OPG抑制细胞增殖和诱导细胞凋亡[37]。还有研究发现血液循环中的miR-23a-

3p、miR-23b-3p、miR-24-3p、miR-27a-3p和miR-27b-3p在1型糖尿病时成簇上调,且与OPG的表达呈正相关,提供了新的糖尿病预测标记[38]。这些研究表明不同miRNA在心血管系统疾病和糖尿病中对OPG表达水平起着不同的作用(表3),是研究心血管疾病和糖尿病疾病发展过程的重要因子。

表3 心血管系统疾病和糖尿病中miRNA对OPG表达的影响

Table 3 Effect of miRNA on OPG expression in cardiovascular system diseases and diabetes mellitus

miRNAs	Disease	miRNA expression	OPG expression	References
miR-30c-5p	Atherosclerosis	↑	↓	[31]
miR-26a	Atherosclerosis	↑	↑	[32]
miR-433-3p	Diabetes	↓	↓	[36]
miR-145	Diabetes	↓	↓	[37]
miR-23a-3p, miR-23b-3p, miR-24-3p, miR-27a-3p, miR-27b-3	Diabetes	↑	↑	[38]

↓: Downregulated; ↑: upregulated.

4 miRNA在癌症中调控OPG

近年来大量的研究证明OPG参与调控癌症的发生和转移,并可作为各种类型癌症的预后标志物,包括骨髓瘤、乳腺癌和前列腺癌等,但其作用的机制尚未明确[39]。OPG及其相关分子在癌症发展中的作用十分复杂,受到多种因子的调控,miRNA作为近年来一个研究热点也被发现在癌症的骨转移中参与调控OPG[40](表4)。有研究发现在肺癌中过表达miR-33a可通过靶向甲状旁腺激素相关蛋白降低其对OPG的抑制活性,从而减少破骨细胞的分化[41]。在非小细胞肺癌中,发生远处转移患者血清中OPG水平显著高于无转移患者,同时非小细胞肺癌细胞中的miR-20a表达显著提高,抑制miR-20a的表达降低了血清中OPG水平,减少了OPG对非小细胞肺癌细胞的侵蚀作用,抑制癌细胞的远处转移[42]。

表4 癌症中miRNA对OPG表达的影响

Table 4 Effect of miRNA on OPG expression in cancer

miRNAs	Disease	miRNA expression	OPG expression	References
miR-33a	Lung cancer	↑	↑	[41]
miR-20a	Lung cancer	↓	↓	[42]
miR-877-5p	Breast cancer	↑	↓	[43]
miR-1273g-3p	Breast cancer	↑	↑	[44]
miR-217	Giant cell tumor	↑	↓	[45]
miR-21	Multiple myeloma	↑	↓	[46]

↓: Downregulated; ↑: upregulated.

在乳腺癌中miR-877-5p过表达降低骨髓细胞中OPG、Runx2和Bglap2的表达,提高RANKL和破骨细胞相关因子的表达,促进亲代乳腺癌细胞的增殖和侵袭。而内源性RNA TRG-AS1通过与miR-877-5p竞争性结合上调WISP2表达起到与过表达miR-877-5p相反的效果,抑制乳腺癌骨转移[43]。乳腺癌细胞系中lncRNA-SNHG3通过靶向miR-1273g-3p来影响骨转移微环境中OPG的表达,调控细胞的成骨分化[44]。另外也有研究报道乳腺癌外泌体miRNA通过RANK-OPG-RANKL轴来增加或减少破骨细胞/成骨细胞的比例破坏骨吸收平衡,影响癌细胞对骨骼的侵袭作用[47]。

此外,一些恶性肿瘤中也有报道miRNA调控OPG的水平。巨细胞瘤中miR-217表达水平显著降低,过表达miR-217可在体外和体内通过抑制OPG/RANKL/RANK信号通路抑制巨细胞瘤的发展[45]。多发性骨髓瘤的骨髓间充质细胞中miR-21的表达显著增强,而OPG显著降低。miR-21通过直接靶向OPG来调控其水平,抑制miR-21可恢复OPG的表达和分泌,减少了骨髓间充质干细胞产生RANKL,影响微环境中的骨吸收平衡,抑制多发性骨髓瘤相关的骨质吸收[46]。

5 总结与展望

过去20多年以来,OPG作为一个关键的因子在对疾病发生的分子机制层面的研究中占据着重要的地位,OPG的研究未限于骨骼中,其通过RANK/OPG/RANKL轴或与其他分子的作用等多种方式贯穿于不同的身体器官的功能与作用中,包括与免疫系统互相作用诞生的“骨免疫学”[48],通过影响炎症因子参与心血管疾病和内分泌系统疾病[49],通过调控破骨细胞或抑制TNF凋亡配体等复杂的方式参与肿瘤的发生和转移[39]等。OPG作为治疗靶点在多种疾病的研究中也较为广泛,如:骨质疏松和心血管系统疾病中通过调节OPG的表达水平来改善发病过程中骨质流失和炎症水平达到治疗疾病的作用;在糖尿病和肿瘤等疾病的发生过程中,OPG在体内或肿瘤细胞的表达水平又可作为预测疾病预后的关键因素。对OPG的上下游调控网络的研究也开始由浅入深,很多调控OPG的激素、生长因子、细胞因子等逐渐浮出水面,其中miRNA作为近年来的一项研究热点,也被大量报道通过间接调控或直接靶向等方式来调控OPG,miRNA特殊的性质为研究OPG在各种疾病中作用机制打开了一扇新的大门,本综述旨在通过讨论近年来不同疾病中miRNA对OPG的调控作用,对疾病的治疗和预后的评估提供新的思路,同时期望miRNA可以作为理解

OPG作用的桥梁, 为探究OPG在疾病中的作用提供新的思路。

*　　*　　*

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