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FOXK1对骨代谢及多种骨性疾病的调控作用

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摘要 随着社会老龄化和人们生活方式的改变, 骨质疏松症及其他骨性疾病的患病率逐年升高。目前骨性疾病的治疗方法以药物治疗为主, 但是药物常常伴随副作用, 可能导致继发性疾病的发生, 因此探寻新的治疗靶点是当前医学领域的研究热点之一。叉头盒蛋白K1(Forkhead box K1, FOXK1)是FOX家族中的重要成员, 它包含DNA结合域和FOX相关域(Forkhead-associated domain, FHA), 通过FHA与其他蛋白的相互作用特异性激活转录程序控制细胞增殖和存活, 但其对骨代谢和骨性疾病的调节作用研究较少。该综述系统性地探讨了FOXK1在骨代谢中的调控作用, 揭示了其通过调节骨细胞状态进而影响骨形成与骨吸收平衡的分子机制, 并探讨了其在骨相关疾病中的潜在作用。通过综述发现, FOXK1可以诱导有氧糖酵解过程来促进成骨细胞的生成, 此外一些microRNA(miR-187-3p和miR-186-5p)可通过靶向调控FOXK1的表达, 继而调控Wnt/β-catenin、HIF-1α和mTOR等一些信号通路。这些信号通路与骨质疏松症、类风湿性关节炎和骨肉瘤等多种骨疾病的发生发展密切相关。该研究聚焦于FOXK1, 为治疗多种骨性疾病开辟了新途径, 同时为深入探究骨性疾病的发生机制及临床治疗策略提供了坚实的理论支持。

关键词 FOXK1; 骨代谢; 骨性疾病

Regulation of Bone Metabolism and Multiple Bone Diseases by FOXK1

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Abstract With the aging population and changes in lifestyle, the prevalence of osteoporosis and other bone-related diseases has been steadily increasing. Currently, the treatment for bone diseases primarily relies on pharmacological approaches. However, medications often come with side effects, which can lead to secondary diseases. Therefore, exploring new therapeutic targets has become one of the hot research topics in the medical field. FOXK1 (Forkhead box K1) is an important member of the FOX family. It contains a DNA-binding domain and a FHA (Forkhead-associated domain), which interacts specifically with other proteins to activate transcriptional programs that regulate cell proliferation and survival. However, its role in bone metabolism and bone-related diseases has been less explored. This review systematically discusses the regulatory role of FOXK1 in bone metabolism, revealing its molecular mechanisms in modulating osteoblast and osteoclast activity, thereby affecting the balance between bone formation and resorption. Furthermore, the review explores its potential involvement in bone-related diseases. The findings suggest that FOXK1 can promote osteoblast differentiation by inducing aerobic glycolysis.

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Additionally, certain microRNAs (miR-187-3p and miR-186-5p) can regulate FOXK1 expression, thereby influencing signaling pathways such as Wnt/β-catenin, HIF-1α, and mTOR. These pathways are closely associated with the pathogenesis of osteoporosis, rheumatoid arthritis, osteosarcoma, and other bone diseases. This study focuses on FOXK1, offering new avenues for treating various bone-related diseases and providing a solid theoretical foundation for further investigation into the pathogenesis and clinical treatment strategies of bone diseases.

Keywords FOXK1; bone metabolism; bone disease

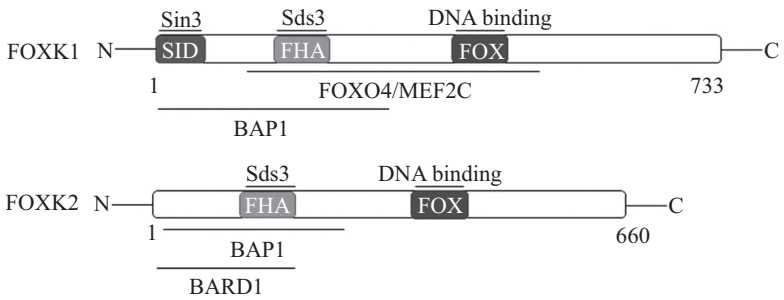
随着人口老龄化，骨质疏松症、类风湿关节炎等骨性疾病的发病率急剧升高[1]。骨是一个会发生连续动态改变的代谢类器官，其通过成骨细胞的骨重建和破骨细胞的骨吸收达到平衡而维持正常的骨结构。研究表明，成骨细胞和破骨细胞的生成异常会破坏骨代谢平衡，从而诱发许多骨代谢性疾病，如骨质疏松症(osteoporosis, OP)、类风湿关节炎(rheumatoid arthritis, RA)和骨肉瘤(osteosarcoma, OS)等[2]。成骨细胞通过分泌多种信号分子来调控自身的生成，这些信号包括前列腺素E2、生长因子、Runx2、糖蛋白、性激素、胰岛素样生长因子、降钙素、骨形态发生蛋白以及Wnt/β-catenin信号通路等[2-5]。此外，过氧化物酶体增殖物激活受体γ(peroxisome proliferator-activated receptor gamma, PPARγ)信号通路在成骨细胞的分化和脂肪细胞的分化中起对立作用，PPARγ可在刺激脂肪生成的同时抑制成骨细胞分化[6]。同样，破骨细胞对维持骨骼正常状态也起着非常重要的作用，我们在对骨性疾病治疗的时候，也可以通过对信号通路(如RANK/RANKL信号通路)、激素(如甲状旁腺激素、1,25-二羟维生素D3、雌激素)等进行干预来调节骨稳态[2,7]。

在众多转录因子中，叉头盒蛋白(Forkhead box, FOX)是近年来研究的热点之一。作为人体最大的基因家族之一，其显著特征在于其“叉头”或“翼螺旋”DNA结合域，它能够特异性地识别并结合一个高度保守的DNA序列，即5′-TTGTTTAC-3′[8-15]。目前，在人类基因组中发现了超过50个FOX家族成员[16-17]。依据序列的相似性，FOX家族被细分为19个不同的亚家族(编号从FOXA到FOXS)[17-21]。它们通过调节基因的表达来控制多种细胞功能，包括细胞周期、细胞生长、增殖、凋亡、自噬、应激抗性、代谢、DNA损伤、耐药性、血管生成和致癌作用等[11]。

1 FOXK家族介绍

叉头盒蛋白K(Forkhead box K, FOXK)转录因子在高等生物的各种组织和器官中具有普遍表达，它在调节细胞分化、细胞周期控制、胚胎发育、新陈代谢等多个生物过程中发挥着重要作用[22]。FOXK家族包括FOXK1和FOXK2两个成员，它们具有相似的结构。FOXK1和FOXK2包含两个结构域，一个是叉头翼螺旋–转螺旋DNA结合结构域，另一个是FHA相关结构域，FHA相关结构域介导其与其他蛋白的相互作用并调节细胞周期动力学(图1)。FOXK1最初由Richard S. WILLIAMS研究团队[23]通过多项分子克隆和基因表达分析实验发现并命名为肌细胞核因子(myocyte nuclear factor, MNF)，该研究团队基于小鼠胚胎发生过程中肌源性谱系的限制性表达模式，发现FOXK1包含两个高度保守结构域，一个DNA结合域和一个FHA结合域，前者主要与FOXK1和DNA的直接相互作用有关，后者负责介导FOXK1与缺陷沉默抑制因子3的相互作用[24]。FOXK1通过DNA和FHA这两个结合域介导其与其他蛋白的相互作用，进而调控细胞功能[25]。与FOXK1类似，FOXK2的FOX结构域介导其与DNA的相互作用，而FOXK2的1—128氨基酸区域由FHA结构域组成，FHA结构域是FOXK2与BRCA1相关环结构域1相互作用所必需的[26]。129—153氨基酸区域的FOX 结构域介导FOXK2与雌激素受体α的相互作用，而FHA 结构域的54—171氨基酸区域介导FOXK2与dishevelled和缺陷沉默抑制因子3的相互作用。它们的转录后水平和活性受到细胞周期、细胞状态、磷酸化、mRNA特异性结合以及蛋白质之间相互作用的影响[27-30]。FOXK家族已经被证实能通过特异性激活相应的转录程序来控制细胞增殖、存活和凋亡、骨骼肌的再生、肌细胞的分化以及肿瘤的发生[31-34]。

FOXK1作为FOXK家族关键的转录因子之一，还参与饥饿诱导的细胞或组织的萎缩过程、自噬程序以及有氧糖酵解等多种生物过程[11]。在饥饿状态下，FOXK1蛋白会从细胞核转移到细胞质，上调相关基因的表达[31]。此外，FOXK1通过提高关键



FOXK家族包含两个成员, 图中用不同字母代表各个域, 以展示其域结构。在上方图中, 已经标出了与FOXK1和FOXK2相互作用的已知蛋白质, 这些蛋白质的标注方式与其特定的域相关联。FOX域: 叉头翼状螺旋–转角–螺旋DNA结合域; FHA域: 叉头相关域; SID域: 与Sin3b相互作用的域; Sds3: 缺陷性沉默抑制因子3; FOXO4/MEF2C: 叉头盒类O4/肌球蛋白增强因子-2C; BAP1: BRCA相关蛋白1; BARD1: BRCA1相关环状域1。
The FOXK family consists of two members. In the diagram, different letters represent various domains to showcase their domain structures. In the upper figure, known proteins that interact with FOXK1 and FOXK2 have been labeled, with the labeling method associated with their specific domains. FOX: Forkhead winged helix-turn-helix; FHA: Forkhead-associated domain; SID: Sin3 interaction domain; Sds3: defective in silent chromatin 3; FOXO4/MEF2C : Forkhead box O4/myocyte enhancer factor 2C; BAP1: BRCA1 associated protein 1; BARD1: BRCA1 associated RING domain 1.

图1 FOXK1、FOXK2结构图(根据参考文献[22]修改)

Fig.1 FOXK1 and FOXK2 structure diagrams (modified from the reference [22])

靶标蛋白(例如己糖激酶-2、磷酸果糖激酶、丙酮酸激酶和乳酸脱氢酶)的表达水平, 促进有氧糖酵解的进行。这一发现表明, FOXK1是糖酵解过程的关键调节因子, 它们可以重新编程细胞代谢[35]。因此, FOXK1家族成员自身的功能变化可能会影响细胞的正常运作。

2 FOXK1对骨代谢的调控作用

在骨骼形成过程中, 骨祖细胞、成熟成骨细胞、骨细胞和破骨细胞之间存在复杂的细胞间信号交流, 这些信号在骨骼的重塑和生长过程中调节骨细胞的活动[4]。在青年期, 骨形成大于骨吸收, 骨骼呈增长状态, 但随着年龄的增长达到老年时, 骨骼会出现净流失。骨骼的总体机械性能是由骨转换率、胶原基质以及骨的大小、结构、几何形态和密度等参数共同决定的, 这些参数的异常可能导致骨质疏松症、成骨不全症等骨骼疾病[4,36]。

根据研究, FOXK1能够调节细胞增殖、分化、代谢, 在成骨细胞中缺乏FOXK1会导致有氧糖酵解的减少[37]。通过CUT&Tag分析, 研究人员发现FOXK1能够靶向多个糖酵解酶(包括己糖激酶-2、磷酸果糖激酶、丙酮酸激酶和烯醇酶1)基因的启动子区域。FOXK1能够增强这些基因的表达, 从而促进糖酵解过程; 此外, 成骨细胞分化过程中糖酵解活动增加, 使用2-脱氧-*D*-葡萄糖抑制糖酵解可以抑制成骨细胞的分化和增殖, 这表明糖酵解对于成骨细胞的功能至关重要[38]。FOXK1作为胰岛素的下游靶标, 在胰岛素刺激后转移到细胞核, 与染色质相互作用, 从而影响细胞的增殖、凋亡、脂肪酸氧化、线粒体生物合成等[37], 并且FOXK1在骨形成的过程中通过调节骨髓间充质干细胞(mesenchymal stem cells, MSCs)的增殖、分化以及自我更新, 影响成骨和成脂分化, 进而在维持干细胞库和促进组织再生中发挥关键作用[38-39]。

FOXK1可以诱导糖酵解和调节糖酵解酶基因, 以此来促进骨形成过程, 也可以直接作用于成骨细胞和影响骨形成标志物如Runx2和Osterix的表达, 这些标志物在成骨细胞分化和骨形成中起关键作用[38]。同样地, FOXK1可对能影响破骨细胞的miR-187-3p产生调节作用[40], 也可能通过与miRNA(如miR-646)的相互作用来调控其下游基因, 如FGF2, 进而影响骨细胞的迁移和侵袭[41]。此外, FOXK1可能通过影响Wnt/β-catenin信号通路来调节骨代谢[19], 这一信号通路在促进骨形成和维持骨稳态中起着核心作用。综上得出, FOXK1在骨细胞代谢中发挥着至关重要的作用。

3 FOXK1对骨性疾病的调节作用

3.1 FOXK1与骨质疏松症

OP是一种代谢性骨疾病, 其特征是由于成骨细胞和破骨细胞的平衡失调而导致骨组织加速退化。骨质疏松症的核心病理改变为破骨细胞量超过骨重建所需, 或成骨细胞量不足以修复空洞[42]。PENG等[38]通过敲除原代鼠颅骨中的FOXK1并进行研究

发现, 在患有骨质疏松症小鼠的骨组织中FOXK1的表达水平降低, 敲除FOXK1会抑制成骨细胞的分化和增殖, 导致骨量和机械强度下降, 所以FOXK1能够通过增加成骨细胞的分化和增殖来促进骨形成。此外, PENG等[38]还发现FOXK1的活性与破骨细胞的活性相关, 通过调节FOXK1能够抑制过度的骨吸收, 而过度的骨吸收是骨质疏松症的特征之一。另外, 张涛等[40]通过实时荧光定量聚合酶链反应(RT-qPCR)和蛋白印迹技术分别检测了OP患者血清和破骨细胞中miR-187-3p及FOXK1的表达量, 报告基因实验结果进一步证实了miR-187-3p与FOXK1之间存在负相关关系, 这种关系可以引伸到OP的治疗当中。此外FOXK1也可能通过影响Wnt/β-catenin[43]、PI3K/AKT[37]、AMPK/ERK[44]等骨代谢相关的信号通路来调节成骨和破骨细胞的功能。

在骨质疏松症治疗中, 提高成骨细胞的活性是关键, 这有助于增加骨密度和改善骨质量。FOXK1具有巨大的潜力, 可能成为治疗骨质疏松症的新药物靶点。通过药物控制FOXK1的活性, 可以调节骨细胞的分化、增殖和凋亡。综上研究发现, FOXK1可能通过干预Wnt/β-catenin、AMPK/ERK、PI3K/AKT等与骨代谢相关的信号通路来调控成骨细胞和破骨细胞的活动。此外, FOXK1还与miR-187-3p之间存在负相关关系。这些发现对治疗OP有着重要的影响。

3.2 FOXK1与类风湿性关节炎

RA是一种以滑膜炎为主要病理改变的慢性全身性炎症性疾病, RA患者的炎症反应依赖于不同的免疫细胞亚群, 其中每个免疫细胞具有独特的代谢需求[44]。例如, 3-羟基丙酸(3-hydroxypropionate, THP)通过线粒体β-氧化和氧化磷酸化(oxidative phosphorylation, OXPHOS)产生ATP, 但是效应T细胞的发育和效应作用依赖于糖酵解代谢[45]。有研究发现, FOXK1在类风湿性关节炎的成纤维细胞样滑膜细胞(rheumatoid arthritis fibroblast-like synoviocytes, RA-FLSs)中起着关键作用[46]。通过分析发现, 在RA-FLSs中, FOXK1的表达水平增加, 组蛋白去乙酰化酶3(histone deacetylase 3, HDAC3)通过去乙酰化FOXK1来增加其蛋白稳定性, 从而促进干扰素信号通路的激活, 导致RA-FLSs增殖、迁移、侵袭能力的增强以及抗凋亡能力的提高, 进而导致RA-FLSs的病理性转化[46]。综上发现使用丙酸处理RA-FLSs, 能阻断HDAC3与FOXK1的相互作用, 增加FOXK1的乙酰化水平, 说明FOXK1在RA的发病机制中扮演着重要的作用, 可以作为一个新的药物靶点来治疗RA。

3.3 FOXK1与骨肉瘤

OS是一种常见的恶性骨癌, 骨肉瘤细胞来源于间充质干细胞[47]。对于骨肉瘤晚期的患者, 应同时进行放化疗[48]。尽管OS患者可以接受切除手术, 但由于OS细胞经常转移到其他器官, 因此亟需开发一种新的治疗手段[49]。ZHANG等[50]在实验中发现miR-186-5p直接靶向FOXK1的3′-非翻译区(3′ untranslated region, 3′-UTR), 并通过负向调节其表达来抑制骨肉瘤细胞的增生。Spearman相关性分析进一步证明, 在OS组织中miR-186-5p与FOXK1蛋白表达之间呈负相关性[50]。miR-186-5p在OS患者的骨组织中表达减少, 并直接作用于FOXK1从而抑制骨肉瘤细胞的增殖、转移和侵袭。目前已经确定了miR-186-5p参与肿瘤的发生与发展[51-54], FOXK1也被证实能对癌细胞增生、转移和代谢产生重要的作用[55]。因此, 探究miR-186-5p及其靶基因*FOXK1*在OS中的表达情况和功能可能有助于了解肿瘤发生的分子机制, 并为OS患者提供治疗靶点[50]。

3.4 FOXK1与其他骨疾病

除了上述骨疾病外, 这些作用原理对其他骨疾病的治疗也有一定的参考意义。例如: 在成骨不全症中, FOXK1可能影响成骨细胞的功能, 导致骨质脆弱和易碎, FOXK1的异常调节可能影响骨骼的正常矿化和强度; FOXK1可能参与骨折愈合过程, 包括成骨细胞的增殖和分化, 以及骨基质的合成, FOXK1的失调可能影响骨折后的骨组织修复等[4]。FOXK1在其他典型骨疾病中的影响尚未被充分研究, 其广泛的生物学特性是研究进一步发展的主要障碍。

4 总结与展望

综述表明, FOXK1对骨代谢起着重要的作用, 作用机制详见表1和图2。FOXK1在胰岛素信号转导中发挥着关键作用, 影响细胞的能量代谢和线粒体功能[37]。此外, FOXK1在骨骼肌和成骨细胞中的功能也逐渐被认识, FOXK1通过诱导有氧糖酵解促进骨形成[38], 表明其在骨代谢中的重要性; FOXK1在脂肪生成处理后诱导小鼠BMSCs增殖[39]。miRNA作为调节基因表达的重要分子, 也在肿瘤发生和发展中发挥着重要作用。研究发现, miR-186-5p通过靶向*FOXK1*抑制骨肉瘤细胞的增殖和转移[50], 揭示了

表1 FOXK1通过各种信号通路对骨疾病的干预作用

Table 1 The interventional effects of FOXK1 on bone diseases through various signaling pathways

骨疾病 Bone diseases	FOXK1表达量 FOXK1 expression levels	信号通路 Signaling pathway	干预作用 Intervention effect	参考文献 Reference
Osteoporosis	High expression	NF-κB	Overexpression of miR-187-3p negatively regulates the FOXK1/NF-κB signaling pathway, thereby inhibiting osteoclast differentiation	[40]
	High expression	Wnt/β-catenin	FOXK1 may influence the proliferation and differentiation of osteoblasts through the Wnt/β-catenin signaling pathway, thereby regulating bone formation	[43]
	High expression	HIF-1α/glycolysis	FOXK1 may promote osteoblast metabolism and bone formation by enhancing the expression of HIF-1α and upregulating the transcription of glycolytic genes	[38]
Rheumatoid arthritis	High expression	HDAC3-FOXK interferon axis	Highly expressed FOXK1 can strengthen the interconnection between HDAC3 and FOXK1, decrease the acetylation level of FOXK1, thereby enhancing the protein stability of FOXK1, and subsequently activating the interferon signaling pathway, which stimulates the pathological transformation of RA-FLSs	[46]
Osteosarcoma	High expression	MAPK/ERK	FOXK1 may regulate the proliferation and migration of osteosarcoma cells through the MAPK/ERK signaling pathway	[44]
	High expression	mTOR	FOXK1 may promote the proliferation and survival of osteosarcoma cells through the mTOR signaling pathway, where miR-186-5p can inhibit the interaction between the mTOR signaling pathway and FOXK1 by targeting FOXK1	[50]

miRNA与转录因子之间的复杂相互作用。这种相互作用不仅影响了肿瘤细胞的生物学特性, 也为肿瘤的治疗提供了新的思路。

*FOXK1*的发现对于治疗骨疾病是一个重大的突破, 作为一个影响骨疾病的基因, 可以被开发成新型药物, 这些药物可以抑制和刺激FOXK1的表达来治疗骨性疾病。同样, 针对一些遗传性的骨疾病, 科学家们可以利用基因编辑技术, 比如CRISPR-Cas9, 来精确地调控*FOXK1*这个基因的表达。通过这种方式, 他们可能能够为这些疾病提供新的治疗方法。另外, FOXK1还可以与其他治疗骨疾病的药物(如双膦酸盐、激素等)相结合, 提高治疗效果。尽管*FOXK1*基因在某些骨疾病中扮演着关键角色, 但目前对于FOXK1的研究还不够全面, 特别是它在不同骨疾病中的应用。此外, FOXK1的特异性问题也尚未得到充分研究, 调节FOXK1可能会对其他器官产生影响, 引起非预期的副作用。目前面临的最大挑战是, 针对FOXK1的治疗方法还没有经过广泛的临床测试验证, 其具体的可操作性和效果还有待进一步的考察和证实。尽管如此, 对FOXK1的研究仍在积极进行中, 研究者们正在努力探索, 旨在能够为骨疾病患者带来新的治疗希望。

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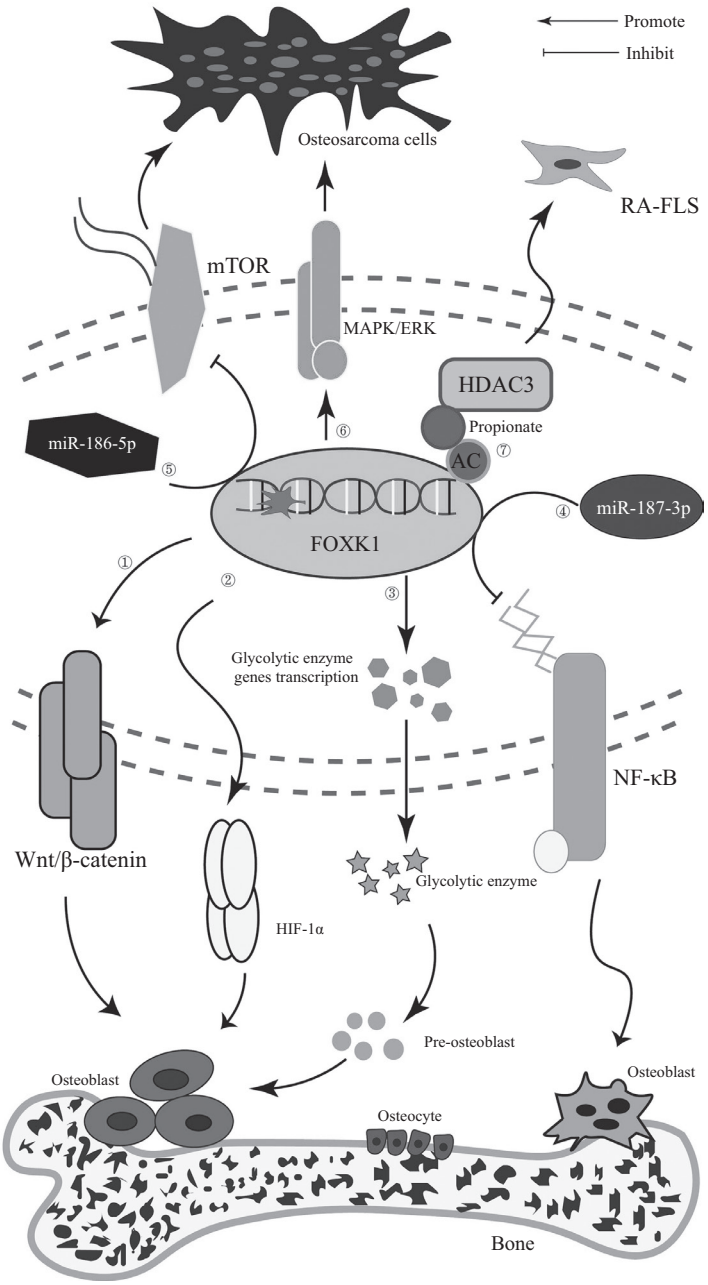

①FOXK1可能影响成骨细胞的增殖和分化, 并通过Wnt/β-catenin信号通路调节骨形成; ②FOXK1可以通过促进HIF-1α的表达从而促进成骨细胞的代谢和骨形成; ③FOXK1可以通过增强糖酵解基因的转录, 促进前成骨细胞向成骨细胞的分化; ④miR-187-3p的过表达会负向调控FOXK1与NF-κB信号通路之间的相互作用, 从而抑制成骨细胞分化; ⑤FOXK1可能通过mTOR信号通路促进骨肉瘤细胞的增殖和存活, 其中miR-186-5p可以通过靶向FOXK1抑制FOXK1与mTOR信号通路之间的相互作用; ⑥FOXK1可以通过MAPK/ERK信号通路调节成骨细胞的增殖和迁移; ⑦高表达的FOXK1增强了HDAC3与FOXK1之间的相互作用, 降低了FOXK1的乙酰化水平, 从而增强了FOXK1蛋白的稳定性, 进而激活了干扰素信号通路, 刺激了RA-FLSs的病理转化。

① FOXK1 may affect the proliferation and differentiation of osteoblasts and regulate bone formation through the Wnt/β-catenin signaling pathway; ② FOXK1 may promote osteoblast metabolism and bone formation by promoting the expression of HIF-1α; ③ FOXK1 can promote the differentiation of pre-osteoblasts into osteoblasts by enhancing the transcription of glycolysis genes; ④ overexpression of miR-187-3p negatively regulates the interaction between FOXK1 and the NF-κB signaling pathway, thereby inhibiting osteoblast differentiation; ⑤ FOXK1 may promote the proliferation and survival of osteosarcoma cells through the mTOR signaling pathway, where miR-186-5p can inhibit the interaction between FOXK1 and the mTOR signaling pathway by targeting FOXK1; ⑥ FOXK1 may regulate the proliferation and migration of osteoblasts through the MAPK/ERK signaling pathway; ⑦ highly expressed FOXK1 enhances the interconnection between HDAC3 and FOXK1 and reduces the acetylation level of FOXK1, thereby enhancing FOXK1 protein stability, which in turn activates the interferon signaling pathway and stimulates pathological transformation of RA-FLSs.

图2 FOXK1对骨代谢和骨性疾病的调节机制

Fig.2 The regulation mechanism of FOXK1 in bone metabolism and bone diseases

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