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◇综述◇

长链非编码RNA HOX转录反义RNA对成骨分化及骨性疾病影响的研究进展

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摘要: 干细胞的成骨分化需要转录因子、信号通路和生物学信号的紧密协调。这种交互网络的失调会影响干细胞和成骨细胞的增殖和凋亡,从而破坏骨代谢和稳态。lncRNAs广泛参与干细胞的成骨分化过程,从而在骨关节炎、骨肿瘤等骨疾病的发生、发展和进展中发挥重要作用。长链非编码RNA HOX转录反义RNA(HOX transcript antisense RNA,HOTAIR)调节干细胞的成骨分化,并在骨形成和相关疾病的发展中起重要的中介作用。现就lncRNA HOTAIR在成骨分化及骨病中的具体作用和机制的相关研究作一综述,以期为未来骨与关节疾病的防治提供新的思路。

关键词: RNA,长链非编码; 肌骨骼疾病; 骨疾病; 间质干细胞; 骨生成; HOX转录反义RNA; 骨与关节疾病; 分子机制; 综述

Research progress on the effects of long noncoding RNA HOX transcription of antisense RNA on osteogenic differentiation and bone diseases

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Abstract: Osteogenic differentiation of stem cells requires the close coordination of transcription factors, signal pathways and biological signals. The disorder of this interactive network will affect the proliferation and apoptosis of stem cells and osteoblasts, thereby destroying bone metabolism and homeostasis. In recent years, studies have shown that lncRNAs are widely involved in the osteogenic differentiation process of stem cells, thereby playing an important role in the occurrence, development and progression of bone diseases such as osteoarthritis and bone tumors. Long non-coding RNA HOX transcript antisense RNA (lncRNA HOTAIR) regulates the osteogenic differentiation of stem cells, and plays an important mediating role in the development of bone formation and related diseases. The specific role and mechanism of lncRNA HOTAIR in osteogenic differentiation and bone diseases are reviewed, in order to provide new ideas for the prevention and treatment of bone and joint diseases in the future.

Key words: RNA, long noncoding; Musculoskeletal diseases; Bone diseases; Mesenchymal stem cells; Osteogenesis; HOX transcript antisense RNA; Bone and joint diseases; Molecular mechanisms; Review

随着全基因组和转录组测序技术的发展,长链非编码RNAs(lncRNAs)受到了越来越多的关注[1]。lncRNAs是一类被定义为转录本长度超过200 nt的非编码RNA,是一种没有或具有低的蛋白质编码潜力的一种RNA[2]。它在包括但不限于细胞增殖、凋亡、分化和迁移在内的许多生物学过程中发挥着重要作用[3]。也可以通过组蛋白修饰、染色质甲基化、与转录因子结合等表观遗传、转录水平、转录后机制来调控这些许多重要的生物过程[4-5]。

HOX转录反义RNA(HOX transcript antisense RNA,HOTAIR)是在RNA聚合酶Ⅱ的作用下生成有2 158个核苷酸的非编码RNA,定位于12号染色体,包含6 232个碱基对[6]。人类的HOX基因家族分为四个亚家族:HOXA、HOXB、HOXC、HOXD,分别成簇分布于染色体。HOX基因家族编码的蛋白均具有一个由61个氨基酸组成的保守的同源结构域,它

们不仅与人类的胚胎发育密切相关,而且在成人器官和组织中起着关键的调节作用[7]。根据相关研究,HOTAIR是癌症生物学中一种特征明确的致癌基因[8],能通过抑制细胞增殖、促进细胞凋亡而在参与乳腺癌[9]、卵巢癌[10]、结肠癌[11]、肝细胞癌[12]、胃癌[13]等多种癌症的发生发展中发挥重要作用。而HOTAIR在骨性疾病中的功能与作用机制的研究尚处于初步阶段,但现在已经发现HOTAIR表达的上升或下降可以调控干细胞成骨分化[14-15],也可以参与如骨关节炎、骨肉瘤、椎间盘退变等多种骨性疾病的发生和发展,这可能与Wnt/β-catenin,HOTAIR/miR-17-5p/SMAD7等多种通路有关。

因此,本研究就HOTAIR对成骨分化及骨性疾病影响的研究进展作一综述,以期为未来骨与关节疾病的防治提供新的思路。

1 lncRNA HOTAIR在成骨分化中的作用

间充质干细胞中的骨髓间充质干细胞是一组位于中胚层的多能干细胞,能在不同条件下可分化为脂肪细胞、成骨细胞、软骨细胞和肌细胞等多种细胞[16-17],参与生理变化,其中成骨细胞、软骨细胞参与骨性疾病的发生与发展,因此,骨髓间充质干细胞被认为是治疗一系列人体骨骼疾病理想的种子细胞[18-19]。

Shen等[20]研究表明HOTAIR在骨质疏松症病人中高表达,过表达HOTAIR后可增减少碱性磷酸酶活性,并通过抑制Wnt通路相关蛋白的表达来抑制骨髓间充质干细胞向成骨细胞的分化。Wang等[21]研究表明骨质疏松症病人中HOTAIR的表达上调,靶向抑制miR-378g,从而抑制骨髓间充质干细胞的成骨分化。毕凤江等[22]研究表明过表达lncRNA HOTAIR能降低骨髓间充质干细胞中成骨相关基因的表达,降低成脂相关基因的表达,与骨质疏松的发病机制有一定关系。毕凤江等人研究表明过表达lncRNA HOTAIR能降低骨髓间充质干细胞中成骨相关基因的表达,降低成脂相关基因的表达,与骨质疏松的发病机制有一定关系[22]。因此,对HOTAIR的研究有望成为改善骨质疏松的新靶点。

lncRNA在间充质干细胞成骨分化过程中起表观遗传调控作用[23],黄涛等[14]通过基础实验表明lncRNA HOTAIR可以抑制脂肪间充质干细胞的成骨分化能力,抑制脂肪间充质干细胞的成骨分化能力。Yuan等[24]研究表明HOTAIR过表达可抑制骨髓间充质干细胞成骨分化及成骨相关基因RUNX2、OCN、ALP的表达,而增加成脂分化的表达。HOTAIR的过表达能促进脂质积累,减少成骨分化,进而影响骨缺损的修复。Wei等[25]研究表明HOTAIR在非创伤性股骨头坏死病人中表达增加,抑制HOTAIR表达导致miR-17-5p表达增加,miR-17-5p的靶基因SMAD7的表达也同步降低,同时成骨分化标志物RUNX2和COL1A1的表达均提高,证实了HOTAIR抑制miR-17-5p在非创伤性股骨头坏死中发挥成骨分化和增殖的作用。其次,miRNAs是调节基因表达的小的非编码内源性核糖核酸。LncRNAs可以通过多种机制调节微小核糖核酸,主要是通过作为竞争性内源性微小核糖核酸海绵发挥作用,降低细胞内可利用的微小核糖核酸水平,从而负面调节靶基因表达[26]。以上的研究表明,HOTAIR能通过多种途径调控成骨分化过程,进而调节骨代谢平衡,影响骨性疾病。

2 HOTAIR在骨性疾病中的作用

随着老龄化的发展,骨性关节炎(OA)、类风湿性关节炎(RA)以及椎间盘退变(IDD)等骨性疾病的防治已成为目前世界卫生组织亟待解决的难题之一[27-29]。近年来,已有许多研究证实lncRNAs通过多种途径及机制参与骨性疾病的发生、发展[5,30]。随着lncRNAs作用于骨代谢性疾病的深入研究,HOTAIR受到了国内外学者的广泛关注。最新的研究表明,HOTAIR在干细胞的成骨分化及肿瘤细胞的生长中异常表达,进而参与OA、骨肉瘤(OS)、RA及IDD等疾病进程[31-33]。

2.1 HOTAIR与OA的关系 OA是一种常见的与年龄相关的退行性疾病,涉及整个关节及关节周围结构,包括软骨、滑膜和软骨下骨等[27]。其特征是关节间隙变窄,肌肉力量减弱,活动受限,甚至引起残疾[34]。OA主要影响50岁以上的病人,在年龄大于65岁的人群中发病率更高[35]。目前,OA已经成为一个重大的公共卫生问题[36]。OA的发生和发展与关节软骨分子水平炎症引起的软骨损伤密切相关,近年来,已有许多研究表明lncRNAs在OA的发生和发展中起重要作用[37-39]。与软骨细胞炎症相关的lncRNA PACER在OA中表达下调,lncRNA PACER可通过下调促进OA的HOTAIR来抑制软骨细胞凋亡,从而改善OA[40]。增加我们对骨关节炎发病机制的理解可能是识别新的疾病生物标志物或治疗靶点以帮助治疗骨关节炎的关键。

HOTAIR在OA中的过表达介导软骨细胞的凋亡[31],加速OA的发生与发展。Yang等[41]证明了与正常软骨细胞相比,OA中HOTAIR的表达显著升高,在OA软骨细胞中HOTAIR通过抑制Wnt抑制因子1(WIF-1)激活了Wnt/β-连环蛋白增加软骨细胞的分解代谢基因表达,最终促进软骨降解,加重OA。有研究证实脂多糖(LPS)是与OA发病相关的

关键促炎性因子,暴露的LPS可以诱导软骨细胞活力降低,导致软骨细胞凋亡增加[42]。Chen等[43]证明HOTAIR的过表达可负调控表达miR-17-3p,导致促进成红细胞转化特异性易位变体1(ETV1)的过表达,导致软骨细胞的细胞活力降低、细胞凋亡和炎性细胞因子内流,而抑制了HOTAIR后则减轻了软骨细胞的损伤。

在另一方面,HOTAIR在促进软骨细胞凋亡的同时也可以促进ECM降解进而加重OA。Hu等[44]研究表明在骨关节炎中,miR-17-5p的表达下调,而FUT2基因的表达增加,HOTAIR和FUT2的表达通过调节Wnt/β-连环蛋白途径的活性可加重ECM降解和软骨细胞凋亡,这种作用可被miR-17-5p逆转,表明HOTAIR/miR-17-5p/FUT2轴通过Wnt/β-连环蛋白途径促进骨关节炎的进展。Mao等[45]研究表明沉默HOTAIR后可以通过抑制Wnt/β-catenin途径的激活从而降低骨关节炎大鼠的滑膜炎症和滑膜细胞增殖,并抑制细胞凋亡。HOTAIR在软骨细胞和关节软骨组织中上调,并伴随miR-20b的下调以及PTEN基因的表达增加。HOTAIR的过表达抑制了软骨细胞的增殖,并促进了细胞凋亡和ECM降解,HOTAIR可以负调控miR-20b,PTEN是miR-20b的靶基因。HOTAIR可能通过miR-20b/PTEN轴参与通过促进软骨细胞凋亡和ECM降解而影响骨关节炎的发生与发展[46]。

HOTAIR在骨关节炎中上调,并且上调了MMP家族包括MMP-1、MMP-3、MMP-9的表达,并促进软骨细胞的凋亡加速OA的恶化[47]。HOTAIR的过度表达可以激活miR-130a-3p,miR-130a-3p可抑制软骨细胞自噬来诱导软骨细胞凋亡进而加重膝关节OA,抑制HOTAIR过表达介导的软骨细胞凋亡可能是膝关节OA基因治疗的潜在机制[48]。孙强等[49]证明了HOTAIR在OA软骨组织和软骨细胞中明显高表达,并能够通过靶向结合miR-130a-3p抑制OA中软骨细胞的增殖和分化而导致骨关节炎的加重。

同时,HOTAIR还可通过促进软骨降解加重OA。证据表明,聚蛋白多糖酶5(ADAMTS-5)的降低可以改善软骨退化、软骨降解,HOTAIR可通过增强肿瘤坏死因子-α促进ADAMTS-5的表达,进而加速软骨退化、软骨降解,进一步恶化OA,表明抑制HOTAIR、ADAMTS-5可能是OA治疗的有效靶点[50-53]。

综上所述,研究表明HOTAIR促进了软骨细胞的凋亡、软骨降解,加速了OA的发生与发展。因此,HOTAIR可能成为OA的潜在治疗靶点。

2.2 HOTAIR在OS中的作用 HOTAIR作为致癌基因,主要可通过调节染色质动力学和癌细胞行为参与癌症的发展[8],例如卵巢癌[9]、结肠癌[10]、肝细胞癌[11]、乳腺癌[12]、胃癌[13]以及人类其他肿瘤。病人存活率低,进一步明确HOTAIR在肿瘤中的作用尤为重要。骨肉瘤是常见的原发性恶性骨肿瘤之一,在青少年生长突增期显示出较高的发病率,严重影响[54-55]。常用的治疗方法是手术联合多种药物化疗,如顺铂、异环磷酰胺、阿霉素、甲氨蝶呤等。已有不少证据表明,多种遗传和环境因素在OS的发生、发展中起着关键作用[56-57]。Guo等[58]研究表明,HOTAIR在对顺铂耐药OS组织和OS细胞中上调。该研究证实了HOTAIR通过miR-106a-5p/STAT3轴影响OS细胞细胞增殖、侵袭和凋亡,增强了Saos2/DDP、MG-63/DDP和U2OS/DDP细胞的耐药性。有研究通过体外研究发现HOTAIR作为一种致癌lncRNA,可以促进OS细胞的增殖和抑制OS细胞的凋亡[32]。

Li等[59]发现HOTAIR在OS细胞中高表达,敲除HOTAIR后,miR-126表达增加,DNA甲基转移酶1(DDNMT1)下调,以致DNA甲基化水平整体下降,增强了CDKN2A基因的表达,HOTAIR通过HOTAIR-miR-126-DNMT1-CDKN2A轴调控OS细胞存活和凋亡,增加OS细胞对DNMT1抑制剂的敏感性。

Zhou等[60]在研究中发现,HOTAIR rs7958904的C等位基因可以降低OS风险,同时也可降低HOTAIR的表达水平。此外,体内研究发现HOTAIR在OS组织中的表达明显高于邻近的正常组织,而rs7958904 CC基因型的受试者HOTAIR RNA水平明显低于其他基因型。相关研究表明HOTAIR通过表观遗传抑制组织非特异性碱性磷酸酶(ALPL),敲除HOTAIR可增加ALPL启动子区组蛋白H3K4甲基化水平,进而抑制成骨细胞的骨肉瘤细胞矿化[61],这项研究支持了生理骨形成是由lncRNA表观遗传调控的观点。

Li等[62]发现HOTAIR在OS组织中的表达较正常组织显著上调。使用特异性小干扰RNA(siRNA/siR)沉默HOTAIR,siR-HOTAIR可抑制人骨肉瘤细胞的增殖,抑制人骨肉瘤细胞中的HOTAIR可以显著减少骨肉瘤细胞的迁移和侵袭。同时表明在沉默HOTAIR之后,OS细胞中的AKT/mTOR信号通路及其多个下游信号被抑制,骨肉瘤的发生被抑制。Wang等[63]研究表明脂多糖可通过TLR4受体介导的HOTAIR表达促进骨肉瘤发生与发展。Wang等[64]表明HOTAIR在骨肉瘤中普遍过度表达,敲除HOTAIR能明显抑制骨肉瘤细胞的增殖,并且抑制骨肉瘤细胞侵袭,降低MMP-2和MMP-9的分泌,与肿瘤高组织学分级和不良预后显著相关。综上所述,HOTAIR可能通过多种途径与骨肉瘤的发生、发展及转归均有关,因此lncRNA HOTAIR可能成为OS

的潜在治疗靶点。

2.3 HOTAIR在RA中的作用 类风湿性关节炎(rheumatoid arthritis,RA)是一种严重影响人类健康的全身性自身免疫性慢性多滑膜关节炎及关节病变[29]。其特征是全身炎症、滑膜炎、炎性关节液、关节软骨破坏、关节损伤和骨侵蚀,常导致关节畸形和功能丧失[65]。Shaker等[66]通过实时定量聚合酶链反应检测血清中HOTAIR的表达水平后发现,与健康对照组相比,RA病人血清中HOTAIR的表达显著上调,认为HOTAIR血清表达水平可作为诊断的无创生物标志物。Song等[67]研究表明类风湿性关节炎病人外周血单个核细胞和血清中HOTAIR的表达水平显著升高,导致巨噬细胞迁移进一步加速了RA的发展,HOTAIR可以通过激活RA滑膜细胞中的MMP-2和MMP-13促进RA的发生。Zhang等[68]证明了HOTAIR的过度表达通过增加细胞增殖和抑制体内外炎症来发挥保护软骨细胞的作用,HOTAIR可以靶向抑制miR-138表达,miR-138过表达可部分逆转HOTAIR过表达对软骨细胞的保护作用,这可能与miR-138表达和NF-kB信号通路的调节有关。综上所述,大多数研究表明HOTAIR影响着类风湿性关节炎的发生与发展。

2.4 HOTAIR在IDD中的作用 椎间盘退变(intervertebral disc degeneration,IDD)是慢性下腰背部疼痛的主要原因。这种情况对病人生活质量有严重的负面影响,同时也带来严重的经济负担[29]。椎间盘退变是一种涉及椎间盘细胞的细胞衰老与细胞凋亡[69]。椎间盘组织包括中央髓核、外纤维环和软骨终板[70]。Yu等[33]通过实验表明lncRNA HOTAIR通过调节miR-34a/Bcl-2轴,抑制IDD病人的NP细胞凋亡,进而延缓、抑制椎间盘的退变。Shao等[71]研究表明HOTAIR可以靶向抑制miRNA-34a-5p通过靶向Notch1基因降解来延缓NP细胞凋亡。

但是Zhan等[72]通过体内及体外实验证明了HOTAIR促进NP细胞凋亡、衰老和ECM分解代谢。有研究通过基础实验证明了HOTAIR的过表达通过激活Wnt/β-连环蛋白通路,可促进NP细胞的衰老、凋亡和ECM的降解加速IDD[73]。Hiyama等[74]证明了MMP-3、MMP-9和MMP-10的表达随着Wnt/β-连环蛋白途径的激活而增加,并促进NP细胞的衰老,加速IDD。综上所述,进一步明确HOTAIR在椎间盘退变中的作用,HOTAIR可能成为IDD的潜在治疗靶点。

3 结论

大量研究表明,lncRNAs是参与多种基因表达的新型调控因子。HOTAIR参与干细胞的成骨分化过程,并与OA、OS、RA、IDD等骨与关节疾病关系密切,对其的研究为骨与关节疾病的靶向治疗提供新的可能。HOTAIR主要通过与转录因子结合、与miRNAs相互作用以及参与染色质修饰等调控干细胞的成骨分化过程。研究者们已证实HOTAIR在OA、OS等骨性疾病的发病过程中呈现差异性表达。但目前关于HOTAIR在骨相关疾病中的作用机制研究较少,仍需更深入的研究来进一步阐明HOTAIR在骨与关节疾病中所参与的分子生物调控网络。这也有助于临床工作者对其在骨与关节疾病的发生与发展中所起的作用有更准确的认识,可以更好地指导HOTAIR的临床应用和科学研究。

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