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Mini Review

The role of long non-coding RNAs in bone diseases

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Abstract

Long non-coding RNAs (lncRNAs) have gained great attention in recent years as critical players in bone biology and bone diseases. A growing number of studies have demonstrated that lncRNAs are involved in osteogenic differentiation and thus serve a pivotal role in the process of occurrence and progression of bone-related diseases. Dysregulation of their expression seem to be implicated in skeletal tissue abnormalities, This article reviews the importance of lncRNAs in the cellular and molecular mechanisms of bone development, their regulatory role in tissue differentiation and in bone cells and we will highlight potential biomarkers and therapeutic targets for the treatment of bone diseases.

Keywords: Bone, Long Noncoding RNAs, Osteoporosis, Osteoarthritis, Rheumatoid arthritis

Introduction

During the past couple of decades, research on non–coding RNAs (ncRNA) has attracted overwhelming interest. This field of study was boosted by epigenetic breakthroughs and transcriptomics approaches and was enhanced by bioinformatics and next-generation laboratory techniques. A vast amount of research indicates that even though only 5% of the genome is translated, up to 80% is transcribed[1]. Strong evidence supports the notion that non-coding RNA molecules play a significant role in regulating vital cell functions. Further, the utilization of the newly identified RNAs for therapeutic and/or prognostic purposes has advanced into a strategic theme in confronting disease. The apparent involvement of RNAs in cell regulation, beyond serving as blueprints for protein production, created a breakthrough in redefining molecular genetics and has expanded the importance of the genetic dogma, but on the other hand, questioned the simplicity of DNA ->RNA ->Protein ->function, by the insertion of parallel, antiparallel, and feedback pathways. In essence, it was a message for going back into the drawing table and redefining molecular genetics.

As revealed by experimental laboratory studies, the biogenesis of ncRNAs adds an intriguing question as to how many more secrets the DNA molecule hides. These RNA molecules can be transcribed from exonic and intronic regions of a gene, within a gene, or neighboring to a gene. Further, their varying processes into functional maturation reveal new mechanisms linking the mode of transcription and maturation pathway with a functional destination[2,3].

The ncRNAs are distinguished based on their lengths into long non-coding RNAs (lncRNAs) with base pair (bp) length >200 and small RNAs (miRNAs) with length <200 bps[4]. Supportive evidence indicates that lncRNA and miRNA may exhibit a further regulatory affair amongst them[5].

During bone development, different lncRNAs seem to have a pivotal role, and pathogenesis may implicate qualitatively or quantitatively these molecules. This perception gives ground into research for utilizing lncRNAs as biomarkers and treatment agents. In this mini-review, lncRNAs and their role in the pathogenesis of bone diseases will be examined, emphasizing the prospective prognostic, diagnostic, and even therapeutic contribution.

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LncRNAs	Mode of action	Reference
PCAT1	Sponges miR-106a-5p upregulates *BMP2*	Jia et al. 2019[12]
PGC1b-OT1	Sponges miR-148a-3p upregulates *KDM6B*	Yuan et al. 2019[13]
OGRU	Sponges miR-320-3p upregulates *Hoxa10*	Wang et al. 2020[14]
LINC02349	Sponges miR-25-3p & miR-33b-5p upregulates *SMAD5* & *Wnt10b*	Cao et al 2020[15]
KCNQ1OT1	Sponges miR-701-3p upregulates *FGFR3*	Chen et al. 2020[16]
TUG1	Sponges miR-545-3p upregulates *CNR2*	Hao et al. 2020[17]
GAS5	Sponges miR-135a-3p upregulates *FOXO1*	Wang X et al. 2019[18]
MALAT1	Sponges miR-30 increases *RUNX2* expression	Yi et al. 2019[19]

Table 1. LncRNAs identified as positive regulators of osteoblastogenesis. PCAT1 prostate cancer-associated ncRNA transcript – 1. PGC1b-OT1 peroxisome proliferator activated receptor γ coactivator-1β-OT1. TUG1 lncRNA Taurine Upregulated Gene 1. GAS5 lncRNA growth arrest-specific transcript 5. MALAT1 metastasis-associated lung adenocarcinoma transcript 1.

LncRNA

According to the Functional Annotation of Mammalian cDNA (FANTOM) 3 project, more than 35,000 lncRNA molecules have been defined[6], most of them specific for certain tissues and in different stages of differentiation. Since in any mature cell type, not more than 25,000 proteins are expressed at any instance, the larger number of lncRNAs indicates significant role(s) in cell regulation[7].

The biogenesis of lncRNA, which is the molecule's transcription mechanisms and their way to functional maturation, further points to a highly regulated and diverse set of activities. Based on their biogenetic mechanism of transcription, lncRNAs can be classified in the following six categories[8]:

1. Intergenic (intergenic expressing regions)
2. Intronic (intronic regions)
3. Bidirectional (either direction of promoter regions)
4. Sense (exon regions)
5. Antisense (opposing direction of transcription)
6. Enhanced (derived from enhancer DNA regions)

In terms of functions assigned to lncRNA (9), they can be divided into:

A. Direct action at the molecular level:
   1. Sponging of miRNAs
   2. Modification of gene expression through chromatin regulation
   3. Regulation of transcription factors and translation outcome

B. Indirectly by affecting critical biochemical pathways:
   4. Angiogenesis
   5. Cell autophagy
   6. Immune regulations
   7. Extracellular matrix (EMT) degradation

The most well-described role is the sponging effect of lncRNA on miRNAs. Since miRNAs bind to specific mRNA regions inhibiting their further processing into protein products, a perplexing double regulatory mechanism exists regarding protein synthesis. In any case, identified and characterized lncRNAs associated with specific cellular functions could be utilized as essential biomarkers, depending on their overexpression or downregulation in disorders, and even be helpful in therapeutic approaches.

LncRNAs and Bone Cells

LncRNAs and Osteoblasts

Osteoblasts are derived from osteoprogenitor cells and are of particular importance for bone formation and remodeling. Key transcription factors such as runt-related transcription factor 2 (RUNX2) and Osterix (OSX) regulate the differentiation of mesenchymal stem cells into osteoblasts[10]. Osteoblast differentiation is regulated through pathways that involve the transforming Growth Factor – b1 as well as the activation of histone deacetylases. The activity of osteoblasts is under the control of extensive regulatory mechanisms that include hormones and growth factors as initiators. These pathways seem to be affected by several miRNAs, which in turn are sponged by lncRNA H19, thus allowing the progression of cell dedication. In addition, several other non-coding RNAs appear to be involved in feedback mechanisms of these crucial pathways, thus regulating the differentiation process[11]. In osteoblastogenesis, lncRNAs have either a positive or negative regulatory mode of action. PCAT1 (prostate cancer-associated ncRNA transcript – 1) sponges the specific microRNA-106a-5p (miR-106a-5p), thus inducing upregulation of gene *Bone Morphogenetic Protein 2 (BMP2)* and osteogenic differentiation, whereas the knockdown of PCAT1 decreased bone formation[12]. The most studied positive regulators lncRNAs are shown in Table 1.

Osteoblast formation relies on several biochemical pathways, well-coordinated and stimulated by extracellular

signals, and key genes such *RUNX, FOX,* and *BMP* seem to be regulated epigenetically by lncRNA molecules which in turn neutralize miRNAs in order to maintain gene overexpression. Therefore, the lncRNAs can be utilized as reliable biomarkers.

Yet lncRNAs not only contribute to the overexpression of key genes but also function as inhibitory factors. Chen et al.[20] has shown that lncRNA XIST overexpression promotes osteoporosis by inhibiting mesenchymal cell differentiation. siRNAs against XIST seem to restore normalization and bone formation in the *in vitro* study, thus indicating a useful therapeutic method. Similar observations pertain to the lncRNA HOTAIR and several others such as osteogenic differentiation inhibitory regulator 1 (ODIR1), small nucleolar RNA host gene 1 (SNHG1), Urothelial Carcinoma Associated 1 (UCA1)[21].

LncRNAs and Osteoclasts

Osteoclasts are responsible for bone resorption and are derived from monocytes. A well-regulated balance should exist between resorption and formation to maintain a stable bone mass[22]. During the osteoclastogenesis, the regulation of mRNA expression seems to implicate directly or indirectly several target-specific lncRNAs that can act either as inhibitory or activating factors. Osteoclast differentiation appears to be upregulated by lncRNA AK077216 via the expression of key transcription factors[23]. Similarly, more than 20 lncRNAs have been reported to either upregulate or downregulate osteoclast formation and function[11] hence exhibiting positive or negative effects in bone diseases. A well-studied osteoclast formation pathway involves exosomal release from endothelial progenitor cells (EPCs) regulated by miR-124 miRNA sponging, of which by lncRNA metastasis-associated lung adenocarcinoma transcript (MALAT)-1 increases osteoclast differentiation[24]. Several other studies for lncRNA MALAT-1 reveal a significant regulatory effect on several cases involving pathogenesis of bone tissue and indicate that the increased level of this molecule in body fluids could be a valuable indicator of bone disease and that MALAT-1 may be sponging a number of miRNAs[21]. LncRNA colorectal neoplasia differentially expressed (CRNDE) overexpression in osteoclasts in osteoporosis strongly suggests targeting therapeutic purposes[25].

LncRNAs and Osteocytes

Bone tissue contains three types of cells: osteoblasts, osteoclasts, and osteocytes. The latter are assigned the mechanosensing mechanisms of the skeletal framework. The role of lncRNAs during the osteoblast to osteocyte conversion is the least studied. Yet, a study using an animal mouse model with tibial fracture indicates that lncRNA H19 may have a regulatory role in the proliferation of osteocytes in reverse relationship with the p53 protein expression, which may be downregulated by H19[26]. Furthermore, an earlier holistic study has shown across the board transcriptome changes in osteoblast to osteocyte conversion *in vitro* and implicated epigenetic mechanisms as regulators by influencing RUNX2, OSX, and several other pathways discussed herein to be controlled by lncRNAs. Therefore, osteocyte formation could also be directly or indirectly regulated by lncRNA, yet this notion has to be further investigated.

LncRNA in Chondrocytes

Chondrocytes are originally derived from mesenchymal stem cells, and are the responsible cells that generate and maintain the cartilaginous matrix in cartilage[27]. Recent evidence supports the notion that several lncRNAs exhibit a significant regulatory role in cellular processing mechanisms and differentiation steps during the various stages of cartilage development. LncRNA differentiation antagonizing nonprotein coding RNA (DANCR) has been shown to have a SOX4 transcription factor binding site. SOX4 promotes chondrogenesis, and interestingly DANCR inhibition by siRNA suppressed the SOX4 effect in an *in vitro* system[28]. Regulation of chondrogenic differentiation has also been reported to be altered by lncRNA DA125942 by downregulating the SOX9 transcription factor among other skeletal patterning involved factors[27]. The already described lncRNA HOX Transcript Antisense RNA (HOTAIR) and others have been reported in the same review study to affect specific bone formation and elongation via several pathways (HOXD genes and other calcification promoting genes).

LncRNAs and Bone Diseases

LncRNAs and Osteoporosis

Osteoporosis is a systemic skeletal disorder characterized by low bone mass, microarchitectural deterioration of bone tissue leading to bone fragility, and consequent increase in fracture risk[29].

Although, it is widely known that lncRNAs could play vital role in the development of osteoporosis, the molecular mechanism of osteoporosis is still not completely understood. Evidence indicates that their function can be distinguished in gene activation, gene silencing (siRNA), and/or involvement in scaffold epigenetic mechanisms inducing modification[30]. Some well-examined lncRNAs are:

- lncRNA – ANCR or DANCR (anti – differentiation non-coding RNA), which had been observed to promote osteoporosis, showed increased levels in osteoblasts of mice, and when silenced same cells exhibited lower levels for apoptosis and higher levels of proliferation[31,32].
- lncRNA BMNCR (Bone Marrow associated), on the contrary, seems to aid against an osteoporotic change since decreased levels of it has been shown in a mouse animal model to promote disease during osteoclast differentiation[33].
- lncRNA GAS5 (growth arrest-specific 5) has been shown to play an essential role in postmenopausal osteoporosis by regulating pathways that lead to osteogenic differentiation[34].
- lncRNA XIST (X – inactive specific transcript) overexpression

has been shown to have an adverse role on alkaline phosphatase activity, which is an essential factor in the calcification process of the bone marrow mesenchymal cells[20].

- On the contrary, lncRNA Bmcob when overexpressed, seems to enhance the transport rate of SBPs (Selenocysteine binding proteins) and increase osteogenesis[35].
- Further, lncRNA UCA1, when inhibited *in vitro* cell lines, was correlated with increased proliferation and differentiation of osteoblasts and the stimulation of bone morphogenic protein – 2 (BMP-2)[36].
- MALAT – 1 regulates Osx expression and can also promote osteogenic differentiation.

Several other lncRNAs have been studied to a great extent and have been suggested for their utilization as biomarkers[30], and further, they are implicated with the pathogenesis of osteoporosis[11]. Multiomics analysis of the prescribed lncRNAs clearly shows their significance in establishing reliable biomarkers. Furthermore, extensive research at the molecular level implicates these lncRNAs as important factors in several growth and differentiation biochemical pathways, and overexpression or underexpression of the lncRNAs may provide pivotal leads as to the pathogenesis of osteoporosis and other bone-related disorders, thus their possible use as therapeutic agents[29].

LncRNAs and Osteoarthritis

Osteoarthritis (OA) is the most common form of arthritis worldwide. While OA is: related to ageing, it is also associated with a variety of both modifiable and non-modifiable risk factors, including: obesity, lack of exercise, genetics, bone density, excessive joint activity, injury, and gender[37]. It is well recognized that, autophagy[38], chondrocyte apoptosis[39], ECM degradation[40] and inflammation[41] are associated with OA whilst the molecular mechanism of lncRNAs regulating OA has not yet been clearly elucidated. Several lncRNAs have been reported to be involved in the pathogenesis of the disease if deregulated such as HOTAIR and GAS5. Jiang S-d et al.[42] developed a working hypothesis for the progression of OA, with overexpressed lncRNAs leading to Matrix metalloproteinases (MMPs) overproduction with the effect of ECM (extracellular matrix) degradation in chondrocytes, which in turn leads to inhibition of collagen-binding integrin proteins, thus weakening the cartilage and enhancing its degradation mechanisms. This approach, if confirmed, could lead to the development of a therapeutic approach via the inhibition of specific lncRNAs.

In the same line of thought, Abbasifard et al.[43] performed an extensive review of clinical studies concerning the role of lncRNAs in OA pathology, verifying with broader evidence the Jiang hypothesis and concluding that lncRNAs can be a key component in therapeutic strategies. Two recently identified lncRNAs, CIR and AMSR, seem to promote the chondrocyte ECM degradation and OA development. CIR lncRNA has been shown to upregulate pathways leading to cell autophagy, cell proliferation, and degradation of ECM in cartilage tissue[44].

Notably, MCM3AP-AS1 lncRNA has been shown to have a specific dual role and act as an upregulator in synovial fluid and chondrocytes and as a down regulator in cartilage tissue affecting two different miRNAs in each case[44]. In OA more than 900 lncRNAs in chondrocytes have been detected in higher or lower levels compared to controls.

MALAT-1 already discussed in OP also seems to be significant for OA, and its levels in OA seem to be reciprocal to miR-150-5p, and its overexpression inhibits apoptosis and ECM degradation. On the contrary, action lncRNA H19 seems to induce chondrocyte destruction by inhibiting the activity of at least one miRNA[45].

LncRNAs and Rheumatoid arthritis

Rheumatoid arthritis (RA) is a long-term condition that causes pain, swelling and stiffness in the joints. The upsurge of the immune system mechanisms seems to be regulated in its various facets by the action of lncRNAs. Most notably:

- The well-known due to its implication in other diseases such as lung cancer HOTAIR (Homeobox antisense intergenic RNA) seems to be over-expressed in RA compared to normal tissue as reported in osteoclasts among different cell types[46]. Since HOTAIR is shown to have a role in chromatin structure and unfolding properties due to histone regulation, it is possible to impose epigenetic mechanisms in gene control[47].
- The previously discussed lncRNA H19 is shown to be expressed at higher levels in RA, and it has been suggested that H19 may be critical in promoting RA through the ERK-1/2 and P13K pathways[48].
- Several other lncRNAs have been identified, including seven in a microarray analysis study in patients with RA, that may be implicated in functions related to the disease process and at significantly differentiated levels of expression in RA that could be utilized as biomarkers[47]. In addition, the well-documented function of lncRNAs in T cell regulation and autoimmune response may indirectly affect RA conditions. Serum samples from RA patients show significant elevation of various lncRNAs such as RNA143598, RNA143596, HIX0032090, IGHCγ1, and XLOC-002730, that seem to be related to the disease course[49]. Therefore, a panel of the above set of lncRNAs could be useful biomarkers for the diagnosis and the progression prediction of the disorder.

Mechanisms of LncRNAs in Bone Diseases

Two types of mechanisms can be distinguished concerning lncRNA activities. The direct qualitative effect by binding and altering the action of other molecules might be it other RNA molecules, mostly miRNAs, or even proteins where they can act as a scaffold or induce enzymatic changes, or by directly binding to DNA regions such as promoter and enhancer regions. The indirect quantitative mode of action

is related to the levels of specific lncRNAs as compared to the alteration of specific critical cellular pathways such as apoptosis, autophagy, epithelial-to-mesenchymal transition (EMT) degradation, immune regulation, differentiation leading pathways.

The best-studied direct effect with regards to the skeletal tissue is the sponging of miRNAs, thus regulating the corresponding mRNA expression and production of critical proteins. miRNAs, in general, have been shown to compete with mRNA translation by directly binding to mRNAs and inhibiting their further translation into protein products. In this sense, lncRNAs, by directly binding to miRNAs act as antagonists of miRNAs and indirectly as synergists of mRNAs. This mechanism allows essential proteins to be expressed differentially and depending on the mode of action of these proteins. The lncRNA could be an up or down mediator of cellular activities, as seems to be the case for many observed cases, such as the dual role of HOTAIR and many other lncRNAs.

It is worth noting that in order for lncRNAs to act as sponges to miRNAs they need to contain a complementary sequence to them. And in cases where it has been observed that one lncRNA sponges more than one different miRNA – as with the case of HOTAIR, than one lncRNA might contain complementary sequences for more than one miRNA or that different miRNAs might contain a short identical fragment. Therefore, to further elucidate the concept of the therapeutic use of lncRNAs, their biogenesis and their complementarity to described miRNAs should be enlightened.

Conclusion and Perspectives

The numerous studies performed in recent years, aided by the advent of transcriptomics and bioinformatics approaches that can process vast amounts of data and evaluate their significance, have shown that lncRNAs are critical in the regulation of gene expression as modifiers at the RNA level. The fact is that in number, lncRNAs exceed by far the number of functional proteins, and their over or under expression is directly correlated with the growth and differentiation state of a cell. Therefore, increased interest has been raised in the utilization of specific well studied lncRNAs not only as biomarkers in the prognosis and diagnosis of disease but also as therapeutic agents in personalized treatment approaches. Yet still, several parameters have to be addressed, such as lncRNA specificity to avoid adverse effects, carrier and vector efficacy, tissue prevailance of abnormally expressed target molecules, followed by clinical studies to determine the toxicity.

Disclaimer

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