Am J Transl Res 2019;11(1):16-30
www.ajtr.org /ISSN:1943-8141/AJTR0087270

Review Article

Emerging roles of long noncoding RNA in chondrogenesis, osteogenesis, and osteoarthritis

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Received October 24, 2018; Accepted December 18, 2018; Epub January 15, 2019; Published January 30, 2019

Abstract: Osteoarthritis (OA) is the most prevalent age-related debilitating joint disease, and is characterized primarily by articular cartilage degradation and subchondral bone lesions. It is also the leading cause of chronic morbidity in older populations. The etiology of OA is multifactorial, with the underlying regulatory mechanisms remaining largely unknown. Long noncoding RNA (lncRNA) is a group of noncoding RNAs defined as being >200 nucleotides in length. Increasing evidence demonstrates that many lncRNAs serve as critical regulators of chondrogenesis and bone and cartilage homeostasis, thereby influencing OA development. In this review, we highlight the current understanding concerning lncRNAs, including their physical features, biological functions, and potential roles in chondrogenesis, osteogenesis, and OA. This information may shed new light on the epigenetic regulation of cartilage and substantiate lncRNAs as novel therapeutic targets in OA.

Keywords: Long noncoding RNA, chondrogenesis, osteogenesis, osteoarthritis, cartilage, chondrocyte

Introduction

Osteoarthritis (OA), a common degenerative joint disorder predominantly occurring in elderly adults, is primarily characterized by destruction of the articular cartilage, presence of subchondral bone lesions, and associated synovitis [1]. The major symptoms of OA include joint pain, joint stiffness, and reduced range of motion [2]. Several risk factors are relevant to the initiation and development of OA, including aging [3], obesity [4], inflammation [5], trauma [6], genetics [7], and abnormal biomechanics [8]. It has been shown that chondrocytes, osteocytes, osteoclasts, and osteoblasts are indispensable for whole-joint homeostasis and defects in these cells and their functions can lead to OA [9].

Long noncoding RNAs (lncRNAs) are defined as RNA species >200 nucleotides long, with little or no protein-coding potential, derived from both intergenic and overlapping protein-coding regions of genes and transcribed by Polymerase II [10]. Based on their structural features and cellular location, lncRNAs can be divided into five sub-categories: antisense, long intergenic noncoding RNA (lincRNA), sense-overlapping, sense intronic, and processed transcripts [11]. Owing to the flexibility of RNAs, lncRNAs are able to fold into unique secondary conformations including DNA-binding domains, RNA-binding domains, and protein-binding domains, which enable them to form broad regulatory networks with DNA, RNA particles, and protein complexes [12]. LncRNAs have been confirmed to influence gene expression both transcriptionally and post-transcriptionally through multiple mechanisms such as chromatin remodeling, competing endogenous RNAs (ceRNAs), mRNA stabilization, and recruitment of scaffolding proteins [10, 11, 13]. This information has helped elucidate their crucial roles in normal and disease development.

Compelling evidence is well documented that lncRNAs alterations are involved in regulating chondrogenesis [14] and osteogenesis [15], and eventually affect the homeostasis of cartilage and bone [16-19]. It is believed that lncRNAs may be beneficial in the prediction of development and diagnosis of OA and may

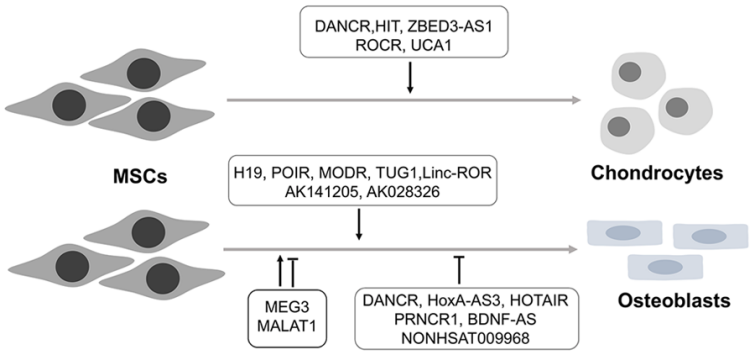

Figure 1. Chondrocytes and osteoblasts are the main lineages that differentiate from MSCs. The main lncRNAs, which are tightly regulated during these differentiation pathways, are represented. Some lncRNAs (MEG3 and MALAT1) are reported showing dual roles in osteogenic differentiation.

serve as potential candidate targets in OA treatment. In this review, we focus on the current literature available regarding lncRNAs, and attempt to clarify the underlying mechanisms of epigenetic and lncRNA regulation of OA onset and progression.

Role of lncRNAs in chondrogenesis

Chondrocytes are the only type of cell in cartilage and are responsible for preserving the homeostasis of synovial joints [20]. Chondrocytes are produced through the process of chondrogenesis, which begins with the condensation of mesenchymal stem cells (MSCs) [21]. MSCs are characterized by their unique features of being undifferentiated and having the abilities for self-renewal and multipotency, and exist in a variety of adult and neonatal tissues, such as bone marrow, adipose tissue, peripheral blood, and specific regions of the placenta and umbilical cord [22, 23]. Therefore, MSC-directed chondrogenic differentiation appears to be an attractive OA treatment strategy for cartilage repair and regeneration [24, 25].

During the past decades, much work has been devoted to understanding the intrinsic mechanisms initiating chondrogenic differentiation by MSCs. Chondrogenic differentiation includes the following stages: mesenchymal cells, prechondrocytes, differentiated chondrocytes, hypertrophic chondrocyte, and endochondral ossification [26]. Numerous transcription factors, cytokines, and growth factors are recruited and involved during chondrogenic differentiation of MSCs into chondrocytes [27]. Members of the SOX family [28], Smads family [29], and bone morphogenetic proteins (BMPs) family [30, 31] are all believed to act as key regulators of chondrogenesis. Moreover, chondrogenesis is accompanied by complex signaling pathways, including Wnt signaling [32], fibroblast growth factor signaling [33], Indian hedgehog signaling [34], and parathyroid hormone-related peptide signaling [35].

Increasing evidence indicates that lncRNAs are also engaged in the development and progression of chondrogenesis [14, 36-39], as summarized in **Figure 1** and **Table 2**. It is known that lncRNA-HIT is expressed in breast cancer and non-small cell lung cancer [40, 41]. Carlson et al. showed that lncRNA-HIT also exists in E11 mouse embryos and is associated with p100 protein and CREB-binding protein (CBP) to form lncRNA-HIT-p100/CBP regulatory complexes during chondrogenic differentiation [42]. Interfering with lncRNA-HIT expression impedes mesenchymal cell condensation and the formation of cartilage nodules by reducing the activity of histone 3K27 acetylation (H3K27ac) or p100. Therefore, lncRNA-HIT is indispensable for chondrogenic differentiation in the limb mesenchyme.

LncRNA LOC102723505, also called the regulator of chondrogenesis RNA (ROCR), is upregulated during chondrogenic differentiation of human bone marrow MSCs (hBMSCs) [43]. Depletion of ROCR impacts SOX9 expression and the production of matrix components, which ultimately disrupts MSC chondrogenesis. The lncRNA urothelial cancer-associated 1 (UCA1) is associated with several human malignancies [44]. Ishikawa et al. demonstrated that UCA1 is expressed in human primary chondrocytes and chondrocytic cell lines, whereas it is not detected in hBMSCs [45]. However, UCA1 expression is markedly induced during chondrocyte differentiation and forced expression of UCA1 in murine chondrocyte precursors expedites their differentiation into chondrocytes, indicating that UCA1 plays a crucial role in chondrogenesis.

The study by Wang and colleagues [39] was the first to elucidate altered expression of the

Table 1. LncRNAs profiles in chondrogenesis, osteogenesis, and osteoarthritis

	Authors/(Refs.)	Study models	Expression profiles
Chondrogenesis			
	Wang et al. 2015 [39]	hBMSCs	2166 upregulated, 1472 downregulated
	Cao et al. 2017 [38]	C3H10T1/2	1669 upregulated, 1945 downregulated
Osteogenesis			
	Zuo et al. 2013 [105]	C3H10T1/2	59 upregulated, 57 downregulated
	Song et al. 2015 [106]	iMSC#3	574 differentially expressed
	Wang et al. 2015 [54]	hBMSCs	687 upregulated, 519 downregulated
	Cui et al. 2016 [67]	hBMSCs	641 downregulated, 1392 upregulated
	Qu et al. 2016 [107]	hPDLSCs	994 upregulated, 1177 downregulated
	Wang et al. 2016 [59]	hPDLSCs	89 differentially expressed
	Gu et al. 2017 [108]	hPDLSCs	777 upregulated, 183 downregulated
	Qiu et al. 2017 [109]	hBMSCs	433 upregulated, 232 downregulated
	Zhang et al. 2017 [110]	hBMSCs	785 upregulated, 623 downregulated
	Huang et al. 2017 [15]	hASCs	1460 upregulated, 1112 downregulated
	Tye et al. 2018 [111]	mBMSCs	462 differentially expressed
	Kim et al. 2018 [112]	Mouse calvarial preosteoclast-like cells	3948 differentially expressed
Osteoarthritis			
	Xing et al. 2014 [79]	Knee cartilage	73 upregulated, 48 downregulated
	Liu et al. 2014 [82]	Knee cartilage	82 upregulated, 70 downregulated
	Fu et al. 2015 [16]	Knee cartilage	3007 upregulated, 1707 downregulated
	Pearson et al. 2016 [17]	Hip cartilage	983 differentially expressed
	Xie et al. 2016 [113]	Ankylosing spondylitis MSCs	184 upregulated, 336 downregulated
	Kang et al. 2016 [99]	Knee synoviocyte	38 downregulated, 14 upregulated
	LV et al. 2017 [114]	Chondrocytes from knee joint and proximal interphalangeal joints	534 upregulated, 638 downregulated
	Liu et al. 2017 [78]	Knee cartilage	51 upregulated, 56 downregulated
	Xiao et al.2018 [115]	Knee cartilage	580 differentially expressed

Table 2. Summary of lncRNAs in chondrogenesis

lncRNAs	Targets	Study models	Cellular process	Reference
DANCR	-	SMSCs	Proliferation and chondrogenesis (+)	Zhang et al. 2015 [48]
	myc, Smad3, STAT3	SMSCs	Proliferation and chondrogenesis (+)	Zhang et al. 2017 [49]
	miR-1305, Smad 4	SMSCs	Proliferation and chondrogenesis (+)	Zhang et al. 2017 [50]
HIT	p100, CBP	mouse embryos	Cartilage formation (+)	Carlson et al. 2015 [42]
ZBED3-AS1	zbed3	SFMSCs	Chondrogenesis (+)	Ou et al. 2017 [46]
ROCR	SOX9	hBMSCs	Chondrogenic differentiation (+)	Barter et al. 2017 [43]
UCA1	-	hBMSCs	Chondrogenic differentiation (+)	Ishikawa et al. 2018 [45]

ZBED3-AS1 gene during hBMSCs chondrogenic differentiation. In a later study, Ou et al. confirmed that ZBED3-AS1 expression changes during the chondrogenic differentiation of human synovial fluid-derived MSCs (SFMSCs) [46]. Additional studies have verified that overexpression of ZBED3-AS1 promotes the chondrogenic potential by regulating the Wnt/β-catenin signaling pathway via the upregulation of *zbed3*. Similarly, the synovium is also a reservoir of MSCs called synovium-derived MSCs (SMSCs), which also demonstrate excellent chondrogenic potential [47]. More recently, Zhang and colleagues found that the transcription factor SOX4 enhances proliferation and chondrogenesis of SMSCs by directly binding to the promoter of lncRNA DANCR (differentiation antagonizing non-protein coding RNA) and increasing its expression [48]. Furthermore, they reported that the upregulation of DANCR activates the expression of myc, Smad3, and STAT3 by directly interacting with their mRNAs, ultimately facilitating proliferation and chondrogenesis of SMSCs [49]. In addition, the upregulation of DANCR attenuates expression of the downstream target miR-1305 and increases

Table 3. Summary of lncRNAs in osteogenesis

lncRNAs	Targets	Study models	Cellular process	Reference
H19	TGF-β1, HDAC4/5	hMSCs, 293T cells	Osteogenic differentiation (+)	Huang et al. 2015 [56]
	miR-141, miR-22	hMSCs, HEK293 cells	Osteoblast differentiation (+)	Liang et al. 2016 [57]
	miR-188, LCoR	mBMSCs	Balance between osteogenic and adipogenic differentiation (+)	Wang et al. 2018 [58]
POIR	miR-182	hPDLSCs	Osteogenic differentiation (+)	Wang et al. 2016 [59]
MODR	miR-454	MSMSCs	Osteogenic differentiation (+)	Weng et al. 2017 [61]
AK141205	CXCL13	mBMSCs	Osteogenic differentiation (+)	Li et al. 2015 [52]
AK028326	CXCL13	mBMSCs	Osteogenic differentiation (+)	Cao et al. [62]
MEG3	BMP4	hBMSCs	Osteogenic differentiation (+)	Zhuang et al. 2015 [70]
	miR-133a-3p	hBMSCs	Osteogenic differentiation (-)	Wang et al. 2017 [59]
	BMP2	hPDLSCs	Osteogenic differentiation (-)	Liu et al. 2018 [116]
MALAT1	miR-204	hAVICs	Osteoblast differentiation (+)	Xiao et al. 2017 [72]
	-	hFOB 1.19 cell	Osteoblast proliferation (-)	Che et al. 2015 [51]
DANCR	EZH2	hFOB1.19 cell	Osteoblast differentiation (-)	Zhu et al. 2013 [63]
	WNT signal pathway	hPDLSCs	Proliferation and cell differentiation (-)	Jia et al. 2015 [64]
	p38 MAPK pathway	hBMSCs	Proliferation and osteogenic differentiation (-)	Zhang et al. 2018 [65]
NONHSAT009968	-	hBMSCs	Osteoblastic differentiation in inflammation (-)	Cui et al. 2016 [67]
HoxA-AS3	EZH2	hBMSCs	Osteogenesis and osteogenic markers (-)	Zhu et al. 2016 [68]
HOTAIR	miR-17-5p	hBMSCs	Osteogenic differentiation and proliferation (-)	Wei et al. 2017 [69]
TUG1	Lin28A	hPDLSCs	Osteogenic differentiation (+)	He et al. 2018 [74]
Linc-ROR	miR-138 and miR-145	hBMSCs	Osteogenic differentiation (+)	Feng et al. 2018 [117]
PRNCR1	miR-211-5p, CXCR4	hMSCs	Osteogenic differentiation (-)	Gong et al. 2018 [118]
BDNF-AS	-	hBMSCs	Osteogenic differentiation (-)	Feng et al. 2017 [119]

the level of Smad4. The crosstalk among DANCR, miR-1305, and Smad4 plays an essential role in SMSC proliferation and differentiation [50].

Role of lncRNAs in osteogenesis

While the underlying mechanisms of OA remain largely unknown, growing evidence suggests that osteoblast dysfunction is involved in the pathogenesis of OA. Ectopic expression of multiple genes during osteoblast differentiation is responsible for aberrant bone remodeling and decreased mineralization, which leads to the development of OA [51, 52]. Furthermore, clinical and experimental studies imply that subchondral bone sclerosis, which results from the disfunction of osteoblasts, is critical to the onset and progression of OA [53]. Recently, multiple altered expression profiles of lncRNAs during osteogenesis have been identified by microarray analyses and are summarized in **Table 1**. Some lncRNAs play important roles in osteogenic differentiation and bone formation, as shown in **Figure 1** and **Table 3**. Defining the regulation of lncRNAs during osteogenic differentiation may help identify new therapeutic targets for OA.

LncRNAs that facilitate osteogenesis

The lncRNA H19, which belongs to the imprinted H19-insulin growth factor 2 (IGF2) locus, is associated with musculoskeletal development and is upregulated during osteogenic differentiation of hBMSCs [14, 54-56]. Huang et al. [56] showed that H19 and its encoded miR-675 not only downregulate TGF-β-mediated phosphorylation of Smad3 but also suppresses HDAC4/5 expression and thereby reduces the recruitment of HDAC4/5 to Runx2. This ultimately enhances the osteogenic differentiation of hMSCs and local bone formation. In contrast, both miR-141 and miR-22 are negative factors for osteogenic differentiation and Wnt/β-catenin. Liang et al. [57] demonstrated that H19 functions as a ceRNA and directly binds to miR-141 and miR-22, antagonizing their inhibition of β-catenin and promoting osteogenesis by activating the Wnt/β-catenin pathway. Moreover, H19 combines directly with miR-188 and prevents the inhibition of LCoR by miR-188, thereby tipping the balance from adipogenesis to osteogenesis [58].

Osteogenesis impairment-related lncRNA of human periodontal mesenchymal stem cells

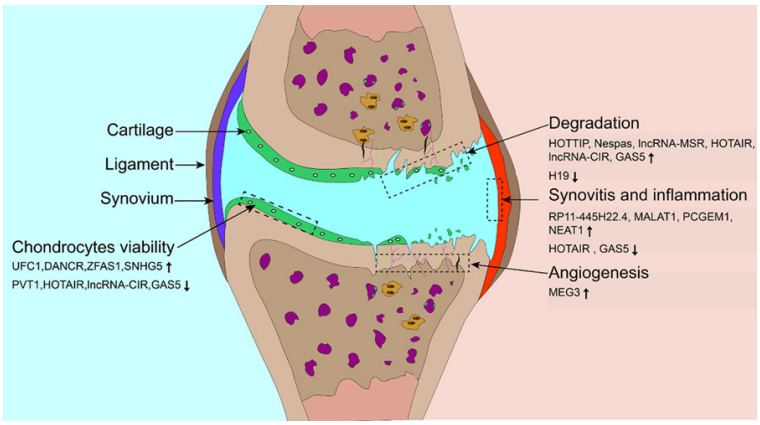

Figure 2. Ectopic expression of lncRNAs between normal and osteoarthritic joints. ECM degradation, chondrocytes viability, immune response and angiogenesis are critical to OA progression. HOTAIR and GAS5 are associated with chondrocytes viability, ECM degradation and immune response.

(lncRNA-POIR) was isolated and identified from periodontitis patient [59]. Wang et al. confirmed that lncRNA-POIR interacts with miR-182 and forms a network to regulate FoxO1. Overexpression of lncRNA-POIR suppresses miR-182 expression and prompts osteogenic differentiation of human periodontal mesenchymal stem cells (hPDLSCs) by upregulating the FoxO1-induced inhibition of the Wnt pathway. Taurine upregulated gene 1 (TUG1), another lncRNA identified from hPDLSCs, is positively associated with osteogenic gene expression, including alkaline phosphatase (ALP), OCN, and Runx2 [60]. Using bioinformatics analysis, lin-28 homolog A (Lin28A) was found to be a downstream target of TUG1 and both involved in the regulation of osteogenic differentiation. A novel osteogenesis differentiation-related lncRNA of maxillary sinus membrane stem cells (lncRNA-MODR) is gradually upregulated during osteogenic differentiation of maxillary sinus membrane stem cells (MSMSCs). Further investigation demonstrated that overexpression of lncRNA-MODR results in an imbalance in the crosstalk in the lncRNA-MODR/miR-454 network, leading to increased RUNX2 expression and thus the promotion of MSMSC osteogenesis [61].

Simulated with osteogenic growth peptide (OGP), lncRNA AK141205 and CXC chemokine ligand-13 (CXCL13) are characterized as positive regulators of osteogenic differentiation. AK141205 promotes osteogenic differentiation by increasing CXCL13 expression through the acetylation of histone H4 in the CXCL13 gene promoter [52]. In addition, CXCL13 expression may be positively regulated by lncRNA AK028326. AK028326 and CXCL13 appear to work together to reverse the high-glucose-mediated suppression of osteogenic differentiation [62].

LncRNAs that attenuate osteogenesis

DANCR, also known as anti-differentiation non-coding RNA (ANCR), functions as a negative regulator of cell differentiation. LncRNA ANCR is significantly decreased during differentiation of the human fetal osteoblastic cell line (hFOB1.19) and the knockdown of ANCR boosts osteoblast differentiation by regulating EZH2/Runx2 [63]. Further studies have shown that ANCR retards the proliferation of hPDLSCs and downregulates osteogenic differentiation via inhibiting the Wnt pathway [64]. Moreover, a recent study has confirmed that DANCR inhibits the proliferation and osteogenic differentiation of hBMSCs by repression of the p38 MAPK pathway [65]. These data suggest that ANCR (DANCR) is a novel mediator of osteogenic differentiation.

Osteogenic differentiation and bone formation is suppressed under inflammatory conditions. Knockdown of the lncRNA MIR31HG may antagonize the inflammation-induced inhibition of osteogenesis in human adipose-derived stem cells (hASCs).

Furthermore, the NF-κB subunit p65 is able to interact with the MIR31HG promoter, with MIR31HG subsequently binding directly to IκBα, which forms a positive feedback loop in the osteogenic differentiation of hASCs [66]. LncRNA NONHSAT009968 was isolated from hBMSCs treated with Staphylococcal protein A (SpA). Silencing of NONHSAT009968 ameliorates the SpA-inhibited osteogenic differentiation of hBMSCs [67]. Therefore, MIR31HG and NONHSAT009968 may be essential targets for promoting osteoblast formation.

It has been reported that lncRNA HoxA-AS3 decreases the lineage specificity of hMSCs and

Table 4. Summary of lncRNAs in osteoarthritis

lncRNAs	Targets	Study models	Cellular process	Reference
H19	-	Human chondrocytes	ECM anabolism and regeneration (+)	Steck et al. 2012 [74]
HOTTIP	HoxA13	MSCs from chicken eggs	OA pathogenesis (+)	Kim et al. 2013 [75]
Nespas	mir-291a-3p, -196a-5p; miR-23a-3p, -24-3p, let-7a-5p	Human chondrocytes	Abnormal lipid metabolism (+)	Park et al. 2017 [76]
lncRNA-MSR	miRNA-152	Human chondrocytes	ECM degradation (+)	Liu et al. 2016 [78]
HOTAIR	-	Rabbit TMJ chondrocytes	ECM degradation and apoptosis (+)	Zhang et al. 2016 [80]
	ADAMTS-5	Human chondrocytes	ECM degradation (+)	Dou et al. 2017 [81]
	miR-138	Rat chondrocytes	Inflammatory injury (-)	Zhang et al. 2017 [97]
	miR-17-5p	Human chondrocytes	ECM degradation and apoptosis (+)	Hu et al. 2018 [120]
lncRNA-CIR	-	Human chondrocytes	ECM degradation (+)	Liu et al. 2014 [82]
	miR-27	Human chondrocytes	ECM degradation (+)	Li et al. 2017 [83]
	-	Human chondrocytes and rat cartilage	ECM degradation and autophagy (+)	Wang et al. 2018 [121]
GAS5	miR-21	Human chondrocytes	ECM degradation and apoptosis (+)	Song et al. 2014 [85]
	KLF2	ATDC5 cells	Inflammatory injury (-)	Li et al. 2018 [94]
PVT1	miR-488-3p	Human chondrocytes	Apoptosis (+)	Li et al. 2017 [86]
UFC1	miR-34a	Human chondrocytes	Proliferation (+), apoptosis (-)	Zhang et al. 2016 [88]
DANCR	miR-577	Human chondrocytes	Proliferation (+), apoptosis (-)	Fan et al. 2018 [89]
ZFAS1	Wnt3a factors	Human chondrocytes	Proliferation (+), apoptosis (-)	Ye et al. 2018 [90]
SNHG5	miR-26a	Human chondrocytes	Proliferation and migration (+)	Shen et al. 2018 [122]
RP11-445H22.4	miR-301a	ATDC5 cells	Inflammatory injury (+)	Sun et al. 2018 [96]
MALAT1	miR-19b	ATDC5 cells	Inflammatory injury (+)	Pan et al. 2018 [123]
PCGEM1	miR-770	Human synoviocytes	Proliferation (+)	Kang et al. 2016 [99]
NEAT1	miR-181c	Human synoviocytes	Proliferation (+)	Wang et al. 2017 [100]
MEG3	VEGF	Knee cartilage	Angiogenesis (+)	Su et al. 2015 [104]

mouse MSCs (mMSCs) into osteoblasts. Similar to ANCR, HoxA-AS3 is able to physically interact with enhancer of Zeste 2 (EZH2) and to increase the level of H3K27me3 at the Runx2 promoter region, ultimately inhibiting Runx2 transcription [68]. The expression of HOX transcript antisense RNA (HOTAIR) is enhanced in hBMSCs isolated from patients with non-traumatic osteonecrosis of femoral head (ONFH) compared to that of patients with OA, but decreases during the process of osteogenic differentiation. Wei et al. [69] determined that HOTAIR represses osteogenic differentiation by modulating miR-17-5p and its target gene SMAD7.

LncRNAs that play dual roles in osteogenesis

It has been shown that knockdown of lncRNA maternally expressed gene 3 (MEG3) attenuates the expression of osteogenic markers such as RUNX2, Osterix, and osteocalcin. Mechanistically, MEG3 located near the BMP4 gene may dissociate SOX2 from the BMP4 promoter and thereby activate BMP4 transcription, leading to osteogenesis development [70]. The lncRNA MALAT1, a highly abundant imprinted gene in multiple cancers [71], is also correlated with osteogenic differentiation [51, 72]. MALAT1 upregulates the expression of Smad4 through the sponging of miR-204 and reinforces the osteogenic differentiation of human aortic valve interstitial cells (hAVICs) [72].

It appears that MEG3 and MALAT1 act as positive modulators of osteogenic differentiation. However, results from two studies are contradictory to this and support the opposite possibility [51, 73]. Wang et al. [73] showed that levels of MEG3 decline during osteogenic differentiation and that expression of the osteogenesis-related gene SLC39A1 is reduced by elevated miR-133a-3p expression and thus inhibit osteogenic differentiation of hBMSCs. Moreover, MALAT1 induction by receptor activator of NF-κB ligand (RANKL), a negative regulator of bone metabolism, promotes RANKL-induced hFOB 1.19 growth inhibition and cell cycle arrest. In consideration of tissue-specific expression, their precise functions need to be further evaluated.

Role of lncRNAs in OA

OA is one of the most common degenerative dysfunctions in synovial joints. It is commonly known that the chondrocyte phenotype and cartilage homeostasis are altered in OA. In addition to extracellular matrix (ECM) degradation, chondrocyte apoptosis, aberrant changes in subchondral bones, inflammatory responses, and angiogenesis are also involved in the development of OA [2]. Recently, results from several expression profiling studies have suggested a correlation between lncRNAs and perturbed articular cartilage. This is summarized in **Figure 2** and **Table 4**. The determination of which lncRNAs are differentially expressed may provide additional opportunities to identify new mechanisms and therapeutic targets [18, 19].

LncRNAs that regulate the proteolytic degradation of ECM

OA is characterized by articular cartilage degradation attributed to a disturbed balance between catabolic and anabolic processes regulating ECM composition. Matrix metabolic enzymes such as matrix metalloproteinases (MMPs) and a disintegrin and metalloproteinase with thrombospondin motifs (ADAMTS) play essential roles in cartilage destruction. Many lncRNAs have been verified as crucial regulators for maintenance or degradation of ECM.

Steck et al. [74] first focused on the correlation between imprinted gene H19, its encoded microRNA-675, and COL2A1 under anabolic and catabolic conditions, suggested that lncRNA H19 serves as a metabolic mediator in cartilage tissues and cultured chondrocytes. Expression of HOTTIP, a modulator for HoxA genes, was found to be increased more than 10-fold in OA chondrocytes. It has been reported that HOTTIP increases cartilage destruction by downregulating the levels of HoxA13 and its downstream target integrin-α1 [75]. LncRNA Nespas is also associated with OA progression. Inducing Nespas expression not only decreases type II collagen expression but also dramatically increases the expression of MMP2 and MMP13. Nespas proved to be a potential new prognostic biomarker for the development of OA [76].

Mechanical stress is an essential component for the development of cartilage degradation in OA [77]. LncRNAs profiling of knee cartilages under mechanical stress of cyclic tensile strain (CTS) identified 107 lncRNAs that are different-

ly expressed in the damaged cartilage compared to that in intact cartilage [78]. A specific thymosin beta-4 (TMSB4) pseudogene lncRNA related to mechanical stress called lncRNA-MSR is present at higher levels in damaged cartilage and is induced in chondrocytes exposed to mechanical stress. Further investigations demonstrated that lncRNA-MSR overexpression significantly disturbs the expression of COL2A1 and ACAN and accelerates the expression of MMP13 and ADAMTS5 by acting as a ceRNA to sequester miR-15, and therefore contributes to cartilage degradation.

Using microarray analysis, Xing el al. [79] determined that HOTAIR is expressed at levels more than 20-fold higher in knee cartilage of OA patients compared to that in normal knee cartilage. Moreover, HOTAIR is also upregulated in the synovial fluid of the temporomandibular joint (TMJ) of OA patients and the TMJ of rab bits with OA. Downregulation of HOTAIR rescues the IL-1β induced expressions of MMP1, MMP3, and MMP9 *in vitro* [80]. In addition, the increased expression of HOTAIR has positive effects on the ADAMTS-5 gene promoter, maintains the stability of ADAMTS-5 mRNA, and causes the upregulation of ADAMTS-5 in OA articular chondrocytes [81]. In contrast, the above situations do not occur in normal articular chondrocytes.

Microarray analyses identified cartilage-injury related lncRNAs (lncRNA-CIRs) that are highly expressed in OA cartilage and chondrocytes. Silencing the lncRNA-CIRs inhibits the degradation of collagen and aggrecan that is induced by IL-1β and TNF-α, and impedes the expression of matrix degrading enzymes such as MMP13 and ADAMTS5 [82]. Mechanistically, lncRNA-CIRs may directly interact with miR-27b and the overexpression of miR-27b may effectively reverse the upregulation of MMP-13 induced by lncRNA-CIRs. Study results indicate that lncRNA-CIRs may be potential targets in OA therapy [83].

LncRNAs that regulate chondrocyte proliferation or apoptosis

It has been established that the primary function of articular chondrocytes is for the maintenance of cartilage homeostasis. The dysregulation of cell phenotypes and a reduction in the number of chondrocytes occur in OA pathogenesis. It is well known that apoptosis is the main cause of chondrocyte consumption when articular cartilages suffer from inflammation, abnormal mechanical stress, injury, or aging [9, 84]. Several studies have recognized the vital roles of lncRNAs in chondrocyte apoptosis.

Growth arrest-specific 5 (GAS5), a known negative regular of cell survival, is upregulated in OA chondrocytes compared with that in non-OA and normal chondrocytes. Overexpression of GAS5 stimulates chondrocyte apoptosis, reduces chondrocyte autophagy, and increases the expression of proteolytic enzymes, including MMP-2, MMP-3, MMP-9, MMP-13, and ADAMTS-4 [85]. Song et al. further explored the underlying mechanism and found that GAS5 regulates the fate of cells by sponging up miR-21. As with GAS5, HOTAIR is not only associated with ECM degradation, but also significantly increases the rate of apoptosis for rabbit condylar chondrocytes induced by IL-1β [80]. That study explored the biological role and underlying mechanisms of lncRNA plasmacytoma variant translocation 1 (PVT1) during OA development. It is reported that PVT1 in OA chondrocytes is upregulated and that the knockdown of PVT1 ameliorates chondrocyte apoptosis. Further investigations revealed that PVT1 exacerbates chondrocytes apoptosis by acting as a sponge for its target gene miR-488-3p [86].

In contrast, some lncRNAs have emerged as positive regulators of cell viability and chondrocyte proliferation. The presence of lincRNA UFC1 has been reported to correlate with the proliferation and migration of hepatocellular carcinoma cells [87]. Zhang et al. [88] showed that UFC1 levels significantly decline in OA chondrocytes but that it facilitates chondrocyte proliferation and inhibits chondrocytes apoptosis. Importantly, they demonstrated that UFC1 regulates chondrocytes survival through physically combining with miR-34a. LncRNA DANCR is considered to have multiple functions in chondrogenesis, osteogenic differentiation, and OA [49, 50, 65, 89]. DANCR is strongly expressed in OA cartilage compared to that of normal cartilage and its overexpression can reverse the inhibition of SphK2 that is modulated by miR-577. Therefore, DANCR activates proliferation and inhibits apoptosis of OA chondrocytes through the miR-577/SphK2 axis [89]. LncRNA ZFAS1, a tumor suppressor gene, has

been reported to be involved in the proliferation and migration of chondrocytes [90]. Overexpression of ZFAS1 not only strengthens the viability, proliferation, and migration of OA chondrocytes but also attenuates OA chondrocyte apoptosis. Along with the overexpression of ZFAS1, the expression of Wnt3a signaling factors, including Wnt3a, β-catenin, and p53, were suppressed. Hence, ZFAS1 might facilitate chondrocyte proliferation and migration and reduce apoptosis by targeting Wnt3a signaling.

LncRNAs that regulate inflammatory responses

OA has been considered as noninflammatory arthritis. However, increasing evidence show that OA progression is associated with inflammation, which leads to articular cartilage loss and symptoms in synovial joints [91]. Like rheumatoid arthritis (RA), high levels of inflammatory mediators are also found in the synovial fluid and sera of OA patients, indicating that OA is by no means a localized noninflammatory lesion [92]. Synovitis involving hyperplasia of synoviocytes and the production of proinflammatory mediators is present during the pathological process of OA. Interestingly, the regulation of lncRNAs during inflammatory changes has also been explored.

An RNAseq transcriptome profiling study of IL-1β stimulation of primary hip OA chondrocytes identified 125 lincRNAs that are differentially expressed [17]. The lincRNA p50-associated cyclooxygenase 2-extragenic RNA (PACER) and two chondrocyte inflammation-associated lincRNAs (CILinc01 and CILinc01) are significantly downregulated in both knee and hip OA cartilage and also rapidly and transiently induced by multiple proinflammatory cytokines. PACER localizes to the upstream region of the COX-2 promoter and directly interacts with the repressive NF-κB subunit p50 to occlude it from the promoter, thereby promoting transcription of the COX-2 gene [93]. Silencing CILinc01 and CILinc02 stimulates the IL-1β-mediated secretion of proinflammatory cytokines.

GAS5 is believed to be upregulated in OA chondrocytes [85]. However, Li et al. [94] demonstrated that GAS5 levels are significantly decreased in lipopolysaccharide (LPS)-induced ATDC5 chondrocytes and that GAS5 overexpression is able to ameliorate the facilitation of inflammatory responses triggered by LPS. Kruppel-like factor 2 (KLF2), a target of GAS5, has been shown to correlate with the modulation of inflammatory processes [95]. Interestingly, overexpression of GAS5 appears to reverse the LPS-induced injury by upregulating KLF2 and consequently inhibiting the NF-κB and Notch signaling pathways. LncRNA RP11-445H22.4 has also been implicated in the cell viability and apoptosis of LPS-induced ADTC5 chondrocytes [96]. Knockdown of RP11-445-H22.4, and thus the promotion of expression of its target miR-301a, ameliorates LPS-induced inflammatory injury of ADTC5 chondrocytes. Mechanistically, RP11-445H22.4 enhances the inflammatory response by abolishing the inhibition of CXCR4 that is directed by miR-301a and therefore positively regulates LPS-activated NF-κB and MAPK/ERK pathways. Zhang et al. showed that HOTAIR is decreased in LPS-induced chondrocytes isolated from SD rats and the overexpression of HOTAIR prevents the release of pro-inflammatory cytokines and reduces cell apoptosis [97]. HOTAIR might function as a protective modulator in LPS-induced inflammatory responses by inhibiting miR-138 and its downstream NF-κB pathway. Interestingly, this conclusion is contradictory to those by previous results obtained using the TMJ OA model [80].

Synovitis is a common feature of OA and primarily characterized by synoviocyte hyperplasia [98]. Ectopic proliferation of synoviocytes results in the secretion of numerous pro-inflammatory cytokines leading to deterioration of the articular cartilage integrity. It is reported that 14 upregulated lncRNAs and 38 downregulated lncRNAs are detected in human OA synoviocytes compared to that of normal synoviocytes [99]. Among the upregulated lncRNAs, prostate cancer gene expression marker 1 (PCGEM1) is found to promote synoviocyte proliferation and autophagy and suppress apoptosis. The PCGEM1 target miR-770 is inhibited in OA synoviocytes and overexpression of miR-770 is able to reverse the PCGEM1-triggered proliferation of synoviocytes.

Crosstalk among lncRNA NEAT1, miR-181c, and osteopontin (OPN) occurs during synoviocyte proliferation [100]. Wang et al. revealed that synoviocyte proliferation is reduced when NEAT1 lncRNA is knocked down and this effect

can be partially reversed by inhibition of its target miR-181c. OPN was shown to positively correlate with NEAT1 and inversely correlate with miR-181c. Therefore, NEAT1 promotes synoviocytes proliferation by sponging with miR-181c so to rescue the expression of OPN.

LncRNAs that regulate angiogenesis of synovial joints

Angiogenesis is closely integrated with inflammation and a critical initiator of OA. During OA development, angiogenesis is stimulated in osteophytes, menisci, and synovium, thereby leading to the formation of osteophytes and destruction of articular cartilage [101]. Moreover, innervation is usually accompanied with vascularization of the articular cartilage, contributing to synovial joint pain. Vascular endothelial growth factor (VEGF), one of the angiogenic factors, is upregulated in OA chondrocytes and may decrease the synthesis and exprression of aggrecan and type II collagen [102]. Targeting VEGF-mediated angiogenesis with antibodies may be a potential therapeutic approach to alleviate the severity of OA [103]. It is reported that lncRNA MEG3 levels are reduced and VEGF levels are upregulated in OA samples compared to those in normal samples. Pearson's correlation coefficient analysis revealed that MEG3 levels are significantly and inversely associated with VEGF levels in OA. In addition, knockdown of MEG3 is able to impair VEGF-mediated endothelial angiogenesis [104]. This suggests that MEG3 may be implicated in the development of OA by modulating angiogenesis.

Conclusions and future directions

Growing evidence indicates that lncRNAs are novel regulators of gene expression. In this context, we reviewed the important roles of lncRNAs in chondrogenesis, osteogenesis, and cartilage homeostasis. While OA is a multi-factorial disease, lncRNAs are shown to have profound effects on OA development and progression. More and more lncRNAs have been identified as being involved in chondrogenic and osteogenic differentiation, providing hope for the establishment of potential OA therapeutic strategies based on tissue engineering. The fact that altered expression of lncRNAs is recognized at different stages of OA progression indicates that lncRNAs may be developed as biomarkers and therapeutic targets. However, research on chondrogenesis, osteogenesis, and OA pathogenesis is still in its infancy and more in-depth studies are need.

Despite large numbers of lncRNAs determined to be differentially expressed during these pathogenic processes, only a small portion of the lncRNAs has been elucidated. It is unlikely that a single lncRNA could be responsible for the cartilage destruction or clinical symptoms observed in synovial joints. Rather, a combination of lncRNAs and their targets are probably required. Therefore, it is important to validate additional lncRNAs involved in the development of OA. Importantly, a variety of studies have confirmed that altered expression of lncRNAs is implicated in tumorigenesis, a fact that should be kept in mind when considering potential side effects of lncRNAs therapy. Studies focusing on these topics will provide additional insight to allow for a better understanding of the roles of lncRNAs in the pathology of OA.

Acknowledgements

We thank Prof. Chuan Ye and Xianwen Shang at Guizhou Medical University (Guizhou, China) and Dr. Guping Mao at Sun Yat-sen University (Guangzhou, China) for valuable assistance. The study was funded by the National Natural Science Foundation of China (NO. 81772403 and NO. 81660317).

Disclosure of conflict of interest

None.

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