

Long noncoding RNAs in mesenchymal stromal/stem cells osteogenic differentiation: Implications in osteoarthritis pathogenesis

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Abstract

This letter focuses on a recently published article that provided an exceptional description of the effect of epigenetic modifications on gene expression patterns related to skeletal system remodeling. Specifically, it discusses a novel modality of epigenetic regulation, the long noncoding RNAs (lncRNAs), and provides evidence of their involvement in mesenchymal stromal/stem cells osteo-/adipogenic differentiation balance. Despite focus on lncRNAs, there is an emerging cross talk between lncRNAs and miRNAs interaction as a novel mechanism in the regulation of the function of the musculoskeletal system, by controlling bone homeostasis and bone regeneration, as well as the osteogenic differentiation of stem cells. Thus, we touched on some examples to demonstrate this interaction. In addition, we believe there is still much to discover from the effects of lncRNAs on progenitor and non-progenitor cell differentiation. We incorporated data from other published articles to review lncRNAs in normal progenitor cell osteogenic differentiation, determined lncRNAs involved in osteoarthritis pathogenesis in progenitor cells, and provided a review of lncRNAs in non-progenitor cells that are differentially regulated in osteoarthritis. In conclusion, we really enjoyed reading this article and with this information we hope to further our under-

standing of lncRNAs and mesenchymal stromal/stem cells regulation.

Key Words: Long noncoding RNAs; Epigenetics; Mesenchymal stromal/stem cells; Degenerative bone diseases; Osteoarthritis; Osteoporosis

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Core Tip: This letter summarizes that long noncoding RNAs (lncRNAs) are involved in mesenchymal stromal/stem cells (MSCs) osteo-/adipo-genic differentiation balance. We added that the interaction between lncRNAs and miRNAs is strongly involved in the regulation of the function of the musculo-skeletal system, by controlling bone homeostasis and bone regeneration, as well as the osteogenic differentiation of stem cells. Additionally, MSCs/progenitor cells lncRNAs are involved in osteogenic differentiation, osteoarthritis pathogenesis, and lncRNAs in non-progenitor cells are differentially regulated in osteoarthritis.

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TO THE EDITOR

We read with great interest the review article by Xia *et al*[1], titled “Epigenetic regulation by long noncoding RNAs in osteo-/adipo-genic differentiation of mesenchymal stromal cells and degenerative bone diseases”. We believe the article provides an exceptional description of the effect of epigenetic modifications on gene expression patterns related to skeletal system remodeling. Specifically, it discusses a novel modality of epigenetic regulation, the long noncoding RNAs (lncRNAs), and provides evidence of their involvement in mesenchymal stromal/stem cells (MSCs) osteo-/adipo-genic differentiation balance. We agree with the authors’ insight that lncRNAs are relevant to clinical practice as altered MSCs differentiation status can be implicated in the initiation/progression of various musculo-skeletal pathologies such as osteoarthritis and osteoporosis. We do, however, have several clarifications we wish to provide.

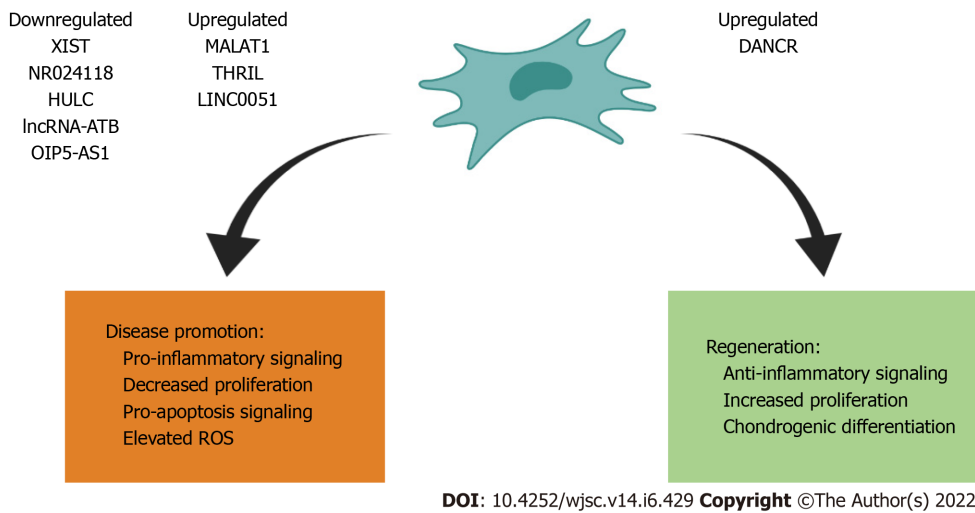
In the introduction, MSCs are defined as “a heterogenous population of cells which include fibroblast, myofibroblast and progenitor cells”[1]. Even though this definition was previously introduced by International Society for Cell & Gene Therapy Mesenchymal Stromal Cell Committee[2], it can be misleading within the present article as authors evaluate the effect of lncRNAs on cells that possess differentiation capacity and not fully differentiated cells (such as fibroblasts). Instead, authors could introduce MSCs as mesenchymal stromal/stem cells are fibroblast-like cells capable of multilineage differentiation at least *in vitro* that possess strong paracrine and immunomodulatory properties *in vivo*. Additionally, even though MSCs are originated from a single cell population during embryogenesis, authors should acknowledge that MSCs show intrinsic propensities to osteo-/adipo-genic differentiation strongly related to their tissue of origin and functional MSC subset heterogeneity[3]. This may significantly affect the role of specific lncRNAs on the overall epigenetic regulation of MSCs differentiation.

In the present article authors have nicely presented the interactions between lncRNAs and epigenetic modifiers during osteo-/adipo-genic MSCs’ differentiation. However, in recent years the crosstalk between lncRNAs and miRNAs interaction has emerged as a novel mechanism in the regulation of the function of the musculoskeletal system, by controlling bone homeostasis and bone regeneration, as well as the osteogenic differentiation of stem cells[4]. We totally acknowledge that the topic of the present article is not miRNAs, however authors could elaborate more on this significant interaction. For example, ANRIL lncRNA was correlated with increased MSCs osteogenic differentiation in the present article. According to recent studies, the molecular mechanism of ANRIL lncRNA effects is based on its direct binding to circulating miR-7a involved in activating the NFκB signaling pathway[5]. Other lncRNAs that exert their osteoinductive activities on progenitor cells *via* binding to miRNAs are MALAT1 and PGC1β-OT1[6,7]. Similarly, HOTAIR lncRNA *via* miR-17-5p interaction inhibits osteogenic differentiation in individuals with a traumatic osteonecrosis of the femoral head. This is in relation to a variable activation of SMAD7 which directly influences osteoblastic differentiation[8]. On this basis of lncRNAs and miRNAs interactions, it seems that H19 lncRNA is a major regulator of MSCs osteogenic differentiation. Specifically, H19 lncRNA act *via* three modes of action: (1) Up-regulate miR-

Table 1 Supplementary information to Figure 1 detailing source and mechanism of activity associated with modified long noncoding RNAs

Upregulated			Downregulated		
lncRNAs	Function	Ref.	lncRNAs	Function	Ref.
DANCR	Increased proliferation and chondrogenesis	Wang <i>et al</i> [12], 2020	XIST	Increased inflammation and apoptotic rate	Lian <i>et al</i> [13], 2020
MALAT1	Decreased rate of synovial fibroblast proliferation	Nanus <i>et al</i> [14], 2020	NR024118	Inflammation, apoptosis, and ROS elevation	Mei <i>et al</i> [15], 2019
THRIL	Upregulated inflammatory injury and apoptosis	Liu <i>et al</i> [16], 2019	HULC	Increased inflammation	Chu <i>et al</i> [17], 2019
LINC0051	Results in anti-proliferative actions	Zhang <i>et al</i> [18], 2020	lncRNA-ATB	Increased inflammation	Ying <i>et al</i> [19], 2019
			OIP5-AS1	Decreased cell proliferation and migration, decreased cell anti-inflammatory mediator secretion	Zhi <i>et al</i> [20], 2020

lncRNAs: Long noncoding RNAs.



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Figure 1 Effects of various long noncoding RNAs on mesenchymal stromal/stem cells/progenitor cells for disease promotion and regeneration.

675 expression and inhibit the phosphorylation of TGF-β1 and Smad3; (2) inhibit the expression of miR-141 and miR-22 and promote Wnt/β-catenin signal transduction pathway; and (3) inhibit the expression of miR-107, miR-27b, miR-106b, miR-125a, and miR-17 resulting in Notch signaling pathway regulation [9-11].

Pathological mechanisms of osteoarthritis (OA) development involve the interplay of different OA symptoms, including inflammatory and degenerative changes that lead to destruction of articular cartilage, deranged chondrocyte regeneration, osteophyte formation, subchondral sclerosis and hyperplasia of synovial tissue. Yet, we must make a distinction between lncRNAs expression in progenitor cells and lncRNAs expression changes in terminally differentiated cells such as chondrocytes as their implication on cell differentiation and protein expression are remarkably different. Herein, in addition to the present article data we incorporated data from other literature to: (1) Review MSCs/progenitor cells lncRNAs involved in osteogenic differentiation; (2) determine MSCs/progenitor cells lncRNAs involved in OA pathogenesis; and (3) provide a review of lncRNAs in non-progenitor cells that are differentially regulated in OA.

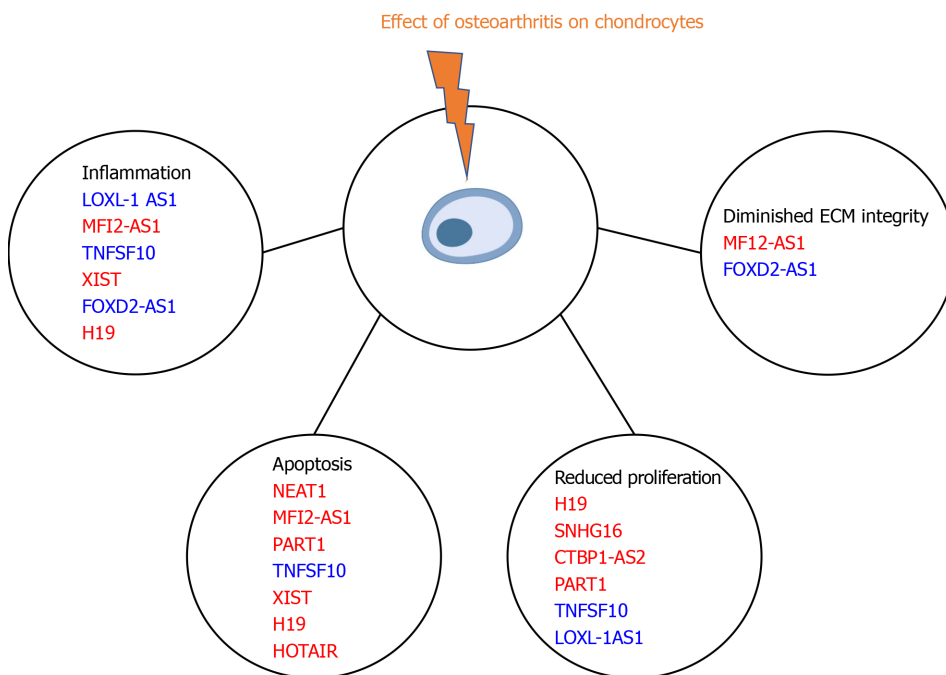
On this basis, we identified four lncRNAs that are upregulated in MSCs/progenitor cells: DANCR, MALAT1, THRIL and LINC0051; and five lncRNAs are downregulated in MSCs/progenitor cells, specifically chondrogenic cell line ATDC5: XIST, NR024118, HULC, lncRNA-ATB, OIP5-AS1. A summary of these findings is featured in Figure 1 and Table 1[12-20].

lncRNAs strongly regulate chondrocytes expression patterns in both physiological and pathological conditions. Twelve different lncRNAs were upregulated in terminally differentiated chondrocytes. We summarize these findings in Figure 2 and Table 2[21-32].

Table 2 Supplementary information to Figure 2 detailing source and mechanism of activity associated with modified long noncoding RNAs

lncRNAs	Function	Ref.
ARFRP1	Increased apoptosis related proteins	Zhang <i>et al</i> [21], 2020
LOXL-1 AS1	Improved inflammation and proliferation rate	Chen <i>et al</i> [22], 2020
NEAT 1	Increases apoptosis, decreases autophagy, decreases viability	Liu <i>et al</i> [23], 2020
MFI2-AS1	Increases inflammation, ECM degradation, and apoptosis	Luo <i>et al</i> [24], 2020
PART1	Low cell proliferation and increased cellular apoptosis	Zhu <i>et al</i> [25], 2019
TNFSF10	Improves cellular proliferation, anti-apoptotic, and anti-inflammatory actions	Huang <i>et al</i> [26], 2019
XIST	Increases inflammation and apoptosis	Wang <i>et al</i> [27], 2019
FOXD2-AS1	Decreases inflammation, decreases ECM degradation	Wang <i>et al</i> [28], 2019
H19	Decreases proliferation, increases apoptosis, increases inflammation	Hu <i>et al</i> [29], 2019
SNHG16	Decreases proliferation	Fan <i>et al</i> [30], 2020
CTBP1-AS2	Decreases proliferation	Zhang <i>et al</i> [31], 2020
HOTAIR	Increases apoptosis	He <i>et al</i> [32], 2020

ECM: Extracellular matrix; lncRNAs: Long noncoding RNAs.



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Figure 2 Effects of various long noncoding RNAs on chondrocytes in osteoarthritis. Red text indicates promotion of pathogenesis, while blue text indicated regeneration by opposing pathogenic signaling. ECM: Extracellular matrix.

In conclusion, we believe there is still much to discover from the effects of lncRNAs on progenitor and non-progenitor cell differentiation. We incorporated data from a recent review article by Ghafouri-Fard *et al*[33] among other articles to: (1) Review lncRNAs in normal progenitor cell osteogenic differentiation; (2) determine lncRNAs involved in OA pathogenesis in progenitor cells; and (3) provide a review of lncRNAs in non-progenitor cells that are differentially regulated in OA. We provided a superficial review of lncRNAs expression and osteoarthritis to clarify what was mentioned and separated the regulation in progenitor and non-progenitor cells, which was not previously published. Again, we really enjoyed the reading by Xia *et al*[1] and with this information we hope to further our understanding of lncRNAs and mesenchymal stromal/stem cells regulation.

FOOTNOTES

Author contributions: Gupta A and Kouroupis D conceptualized the study; Quintero D, Rodriguez HC, Potty AG, Kouroupis D, and Gupta A outlined and designed the manuscript; Quintero D, Rodriguez HC, Kouroupis D and Gupta A drafted the manuscript; Potty AG, Kouroupis D and Gupta A critically reviewed and edited the manuscript; all authors approved the final version of the article for publication.

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