LETTER TO THE EDITOR

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

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Specialty type: Orthopedics
Provenance and peer review: Invited article; Externally peer reviewed.
Peer-review model: Single blind
Peer-review report’s scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): 0
Grade C (Good): 0
Grade D (Fair): 0
Grade E (Poor): 0
P-Reviewer: He BC, China; Niu ZS, China; Yao J, China
A-Editor: Soriano-Ursúa MA, Mexico
Received: March 26, 2022
Peer-review started: March 26, 2022
First decision: April 25, 2022
Revised: April 27, 2022
Accepted: May 21, 2022
Article in press: May 21, 2022
Published online: June 26, 2022

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 musculoskeletal 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.

Citation: Quintero D, Rodriguez HC, Potty AG, Kouroupis D, Gupta A. Long noncoding RNAs in mesenchymal stromal/stem cells osteogenic differentiation: Implications in osteoarthritis pathogenesis. World J Stem Cells 2022; 14(6): 429-434
URL: https://www.wjgnet.com/1948-0210/full/v14/i6/429.htm
DOI: https://dx.doi.org/10.4252/wjsc.v14.i6.429

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 musculoskeletal 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 NFKB signaling pathway[5]. Other lncRNAs that exert their osteoinductive activities on progenitor cells via binding to miRNAs are MALAT1 and PGC1α-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 | Function | Ref. | Downregulated | Function | Ref. |
|-------------|----------|------|---------------|----------|------|
| lncRNAs     |          |      | lncRNAs       |          |      |
| DANCR       | Increased proliferation and chondrogenesis | Wang et al [12], 2020 | XIST | Increased inflammation and apoptotic rate | Lian et al [13], 2020 |
| MALAT1      | Decreased rate of synovial fibroblast proliferation | Nanus et al [14], 2020 | NR024118 | Inflammation, apoptosis, and ROS elevation | Mei et al [15], 2019 |
| THRIL       | Upreregulated inflammatory injury and apoptosis | Liu et al [16], 2019 | HULC | Increased inflammation | Chu et al [17], 2019 |
| LINCO051    | Results in anti-proliferative actions | Zhang et al [18], 2020 | IncRNA-ATB | Increased inflammation | Ying et al [19], 2019 |
|             |          |      | OIP5-AS1      | Decreased cell proliferation and migration, decreased cell anti-inflammatory mediator secretion | Zhi et al [20], 2020 |

lncRNAs: Long noncoding RNAs.

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 LINCO051; 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 Table 2[21-32].
Table 2 Supplementary information to Figure 2 detailing source and mechanism of activity associated with modified long noncoding RNAs

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

ECM: Extracellular matrix; lncRNAs: Long noncoding RNAs.

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.

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.
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.

Conflict-of-interest statement: All the authors report no relevant conflicts of interest for this article.

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S-Editor: Gong ZM
L-Editor: A
P-Editor: Gong ZM

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