Joint Bone Spine 84 (2017) 553–556

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

Review

Long noncoding RNAs in osteoarthritis

Shi-de Jiang [a,b], Jian Lu [a], Zhen-han Deng [b], Yu-sheng Li [b], Guang-hua Lei [b,*]

[a] Department of Orthopaedics, The Central Hospital of Yongzhou, Yongzhou 425000, China
[b] Department of Orthopaedics, Xiangya Hospital of Central South University, Changsha 410008, China

ARTICLE INFO

Article history:
Accepted 7 September 2016
Available online 3 December 2016

Keywords:
Osteoarthritis
Cartilage destruction
Joint pain
Long noncoding RNAs
Disease marker

ABSTRACT

Osteoarthritis (OA) is the most common form of arthritis that may affect all joint tissues. Unfortunately, the pathogenesis of OA is not fully understood yet and it cannot be cured totally. Long noncoding RNA (lncRNA) is a type of RNA molecule greater than 200 nucleotides, and deregulated expression of lncRNAs plays an important role in many types of inflammation-related diseases. In this review, we have focused on the association of lncRNAs in the development and progression of OA and the possibility of lncRNAs as a therapeutic agent for the treatment of OA. Some lncRNAs are up-regulated in OA cartilage, and plays a critical role in the degradation of chondrocyte extracellular matrix, consequently weakening the integrity of the articular cartilage. Therapeutic targeting of these lncRNAs has shown significant influence on controlling OA progression. More clinical studies are in focus for OA treatment strategy by targeting lncRNAs.

1. Introduction

Osteoarthritis (OA) is a chronic degenerative joint disease, which is the most common form of arthritis, mainly characterized by the degradation of articular cartilage, alterations of the underlying subchondral bone, and extensive remodeling of adjacent bone with new bone leading to synovitis as well as osteophyte formation [1,2]. OA is more frequent among the older people in both sexes, commonly affecting knee, neck, lower back, hips, near the ends of the fingers and at the base of the thumb, and is a leading cause of pain, joint dysfunction, physical disability, substantial morbidity and reduced quality of life throughout the world [3–8]. In 1990, OA was estimated as the eighth leading non-fatal burden of life all over the world, while in 2000 it became the sixth [9,10]. The etiology of OA remains mostly unclear, as the pathogenesis of OA is complex and is thought to be associated with a variety of risk factors including genetic factors, constitutional factors (such as age, sex, obesity, gender, and high bone density) and several biochemical and biomechanical factors [11,12]. Diagnosis of OA is typically based on history and clinical examination of patients, and there is no approved treatment for OA, but only some management is supportive to control the symptoms [13,14]. The conventional management includes exercise, lifestyle changes, physical therapy and pain medications, for example: simple analgesics, nonsteroidal anti-inflammatory drugs (NSAIDs), corticosteroid injections and hyaluronic acid (HA) injections. In severe cases of OA, joint replacement surgery such as, arthroscopic surgery, osteotomy, arthrodesis are recommended [15,16]. However, the functional and clinical outcomes of conventional management are poor with large risk of side effects [17]. To overcome these problems, development of potential alternative therapeutics is urgently needed. Elucidation of the pathological mechanisms of OA may help to identify the more effective targets to control the symptoms of OA. The discovery of new and specific biomarkers may help to facilitate an early diagnosis and may help to develop effective therapeutic approaches in the treatment of OA [3,18,19].

It is estimated that the whole human genome contains only 2% of protein-coding RNAs, while the vast majority (about 98%) is non-protein coding RNA [20,21]. According to their size, ncRNAs can be classified into two major groups: (1) small noncoding RNAs, such as microRNAs (miRNAs) and short interfering RNAs (siRNAs), Piwi-interacting RNAs (piRNAs) and small nucleolar RNAs (snoRNAs), and (2) long noncoding RNAs (lncRNAs) [22,23]. Long noncoding RNA (lncRNA) is a type of RNA molecule greater than 200 nucleotides in length (while miRNAs are of 20–22 nt in size) and lacks an open reading frame of significant length and is not translated into a protein [21,24]. The greatest amount of lncRNAs is expressed in the brain and central nervous system in a large diversity of species, including animals, plants, yeast, prokaryotes and even viruses [25,26]. Advances in RNA sequencing (RNAseq) and array technologies have now identified multiple families of

* Corresponding author at: Department of Orthopaedics, Xiangya Hospital of Central South University, Changsha 410008, China.
E-mail address: lgh9640@sina.cn (G.-h. Lei).

http://dx.doi.org/10.1016/j.jbspin.2016.09.006
1297-319X/

lncRNAs including antisense RNAs, intronic lncRNA, pseudogenes and long intergenic noncoding RNAs (lincRNAs). Many lncRNA are named according to their neighboring protein-coding genes. In humans, lncRNAs have been shown to be spliced, 3′ polyadenylated, 5′ capped, and their spliced transcripts are multi-exonic and exhibit transcriptional activation activity like mRNAs [25,27]. LncRNAs have been found to involve in a wide variety of important biological processes including embryonic development, cell growth, cell proliferation, cell cycle progression, transcription, splicing, translation, cellular structure integrity, imprinting, chromatin remodeling, apoptosis, immune responses and heat shock responses [25,28]. It has been reported that deregulated expression of lncRNAs could play an important role in many types of cancer and inflammation-related diseases [29,30]. LncRNAs play an important role in the development of bone and cartilage. LncRNAs are aberrantly expressed in OA cartilage contributing to the degeneration of chondrocyte extracellular matrix. LncRNAs is suggested to be used as a new diagnostic and therapeutic biomarker for progression and prognosis of OA [31,32].

It is reported that epigenetic effects including histone modifications, DNA methylation, and noncoding RNAs may contribute to OA [33]. In this review study, we have focused on the association of lncRNAs in the development and progression of OA and the potential effects of lncRNAs as a therapeutic agent for the treatment of OA.

2. Deregulated expression of lncRNA in OA progression

The lncRNAs are reported to be associated with many human diseases such as cancer, metabolic disease, cardiovascular disease, neurodegenerative disease, and psychiatric disease; however, the involvement of lncRNAs remains largely unknown in the pathogenesis of OA [34,35]. Some researchers reported that lncRNAs are aberrantly expressed in OA. In a study, Xing et al. [36] found that the expression of six lncRNAs (HOTAIR, GAS5, PMS2L2, RP11-445H22.4, H19 and CTD-2574D22.4) was up-regulated in OA cartilage that might be associated with the pathogenesis of OA by increasing the expression of mRNA for MMP-9, MMP-13, BMP-2, and ADAMTS5 [36]. Upregulation of HOTAIR has also been reported by Zhang et al. [37] to contribute OA by inducing IL-1β-induced MMP overexpression and chondrocytes apoptosis. A recent study by Chang et al. [38] identified 18 lncRNAs, which are differentially expressed in injured joints of post-traumatic osteoarthritis. Cartilage injury-related lncRNA (lncRNA-CIR, a pseudogene transcript of vimentin) is aberrantly expressed in OA cartilage. The expression of lncRNA-CIR is increased in the damaged region of tissue lncRNA-CIR and up-regulation of lncRNA-CIR plays a critical role in the degradation of chondrocyte extracellular matrix (ECM) [31,32,34]. This lncRNA may act as a siRNA itself or may induce the mRNA to form endogenous siRNAs to suppress the expression of vimentin. Down-regulation of vimentin promotes ECM degradation and weakens the integrity of the articular cartilage by decreasing the expression of COL2 and aggrecan at the transcriptional and translational levels, leading to the development of OA [31]. Su et al. [19] examined the expression of maternally expressed gene 3 (MEG3, a tumor suppressor) in cartilage samples from OA patients and healthy subjects. They also investigated the potential relationship of MEG3 expression and vascular endothelial cell growth factor (VEGF) level in OA. They demonstrated that MEG3 expression was significantly decreased while the expression of VEGF isoforms is significantly increased in OA patients. VEGF has been shown to regulate hypertrophic cartilage remodeling, ossification, and vascular invasion of growth plate cartilage. Their study suggested that MEG3 expression is inversely correlated with VEGF expression in OA and up-regulation of VEGF results enhanced angiogenesis by which inactivation of MEG3 contributes to OA development [19]. Kang et al. [39] demonstrated a mutual inhibitory control relationship between prostate cancer gene expression marker 1 (PCGEM) and miR-145. They investigated that PCGEM1 stimulates proliferation of OA synoviocytes by acting as a sponge for miR-770. In their study, they found the over-expression of PCGEM and suppressed levels of miR-770 in OA synoviocytes. In another study, Pearson et al. [34] identified a lincRNA, known as p50-associated COX-2-extragenic RNA (PACER) which is increased in OA and thought to be a putative mediator of inflammation and pain in OA cartilage tissue. Song et al. [22] found that growth arrest-specific 5 (GAS5, a tumor suppressor) is up-regulated in OA chondrocytes. Up-regulation of GAS5 increases the expression levels of several MMPs (such as MMP-2, MMP-3, MMP-9, MMP-13, and ADAMTS-4), which are the key factors in cartilage degradation and OA progression. Kim et al. [40] reported miR-101 and HOTTIP as a novel regulatory factor in the pathogenesis of OA. They identified up-regulation of lncRNA, HOTTIP (a known regulator for HoxA genes) and down-regulation of mR-101 in the processes of endochondral ossification and OA progression. Down-regulation of miR-101 causes down-regulation of the collagen-binding integrins expressed on articular chondrocytes including integrin-α1 and resulted in cartilage destruction in OA. Fig. 1 represents the schematic presentation of the functional role of lncRNAs in OA progression.

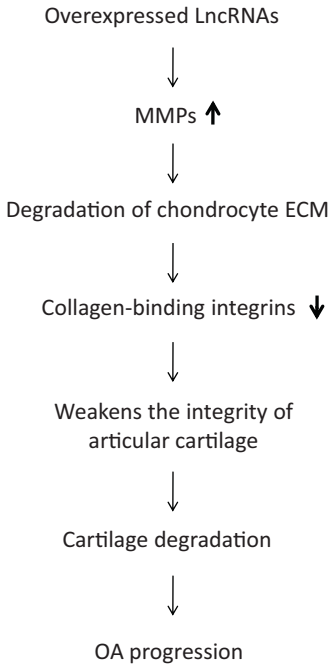

Fig. 1. Role of lncRNAs in OA progression. LncRNAs are up-regulated in OA cartilage, and associated with increased MMPs. When MMP are upregulated then, there is degradation of chondrocyte extracellular matrix (ECM). Degradation of ECM weakens the integrity of the articular cartilage by reducing the level of collagen-binding integrins resulting in cartilage destruction in OA [22,31,36].

3. LncRNA-targeted treatment approach in OA

OA is the most common form of arthritis and has become a major public health problem for normal healthy life. The causes of OA remain unclear and the conventional therapy of OA is still unsatisfactory. Identification of new biomarkers may facilitate the development of effective therapeutic approaches against OA and reduction of disease symptoms [41,42]. Recent reports suggested that aberrant expression of lncRNAs contributes to OA progression and the lncRNAs could be a potent predictive biomarker as well