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Review

The role and function of long non-coding RNAs in osteoarthritis

Mitra Abbasifard[a], Zahra Kamiab[b,c], Zahra Bagheri-Hosseinabadi[d,**], Iman Sadeghi[e,f,*]

[a] Department of Internal Medicine, Ali-Ibn Abi-Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[b] Department of Family Medicine, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[c] Clinical Research Development Unit, Ali Ibn Abi Talib Hospital, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[d] Department of Clinical Biochemistry, School of Medicine, Rafsanjan University of Medical Sciences, Rafsanjan, Iran
[e] Centre for Genomic Regulation (CRG), The Barcelona Institute for Science and Technology, Dr. Aiguader 88, Barcelona, E-08003 Catalonia, Spain
[f] CEINGE-biotecnologie avanzate, Naples, Italy

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ABSTRACT

Osteoarthiritis (OA) is the most prevalent disease of articulating joints in human that frequently results in joint pain, movement limitations, inflammation, and progressive degradation of articular cartilage. The etiology of OA is not completely clear and there is no full treatment for this disease. Molecular investigations have revealed the involvement of non-coding RNAs such as Long non-coding RNAs (lncRNAs) in OA pathogenesis. LncRNAs play roles in multiple cellular and biological processes. Moreover, numerous lncRNAs are differentially expressed in human OA cartilage. In this review, we underlie the increasing evidence for the critical role of lncRNAs in OA pathogenesis reviewing the latest researches.

1. Introduction

Osteoarthritis (OA), the most common type of joint disease, is a chronic degenerative arthritis which is identified by articular cartilage degeneration, changes of the underlying subchondral bone, and widespread remodeling of surrounding bone with new bone resulting in osteophyte formation and synovitis (Cheng et al., 2015; Varela-Eirin et al., 2018). The occurrence of OA is observed more in older people, generally affecting knee, neck, lower back, hips, and fingers. It is a primary cause of pain, disability, considerable morbidity, faulty joints and dropped quality of life all over the world (Manheimer et al., 2018; Eaton et al., 2019). OA affects 250 million people worldwide, about 11% of men and 19% of women over 60 years old (Nelson, 2018). There is not much known about the etiology of OA, as it's pathogenesis is multifaceted and is apparently associated with a wide range of risk factors including such as genetic and environmental factors (Mas, 2014; Brandt et al., 2008). OA is usually diagnosed based on clinical inspection and history of patients. However, no approved treatment exists for OA and the symptoms are controlled only through some managements including exercise, habits changes and physiotherapy, and some medications such as anti-inflammatory drugs (NSAIDs), corticosteroid injections and hyaluronic acid (HA) injections (Loeser Jr, 2000; Poole, 2012). Clarification of pathogenesis of OA could aid in the determination of effective and specific targets to develop diagnostic and therapeutic approaches in the treatment of OA (Johnston, 1997; Murphy et al., 2016).

Remarkably, an attractive field of particular interest which has taken the focus of current research is the study of non-coding RNAs (ncRNAs), as most of the annotated loci in the human genome are non-coding (Morris and Mattick, 2014). In general, ncRNAs are categorized into small ncRNAs and long ncRNAs (lncRNAs) according to their sequence length (Elling et al., 2016). Small ncRNAs are generally known as regulatory RNAs classified into different types, such as microRNAs (miRNAs), ribosomal RNAs (rRNAs), small nuclear RNAs (snRNAs), piwi-interacting RNAs (piRNAs), transfer RNAs (tRNAs), and small interfering RNAs (siRNAs) (Consortium, 2001; Costa, 2005; Sosińska et al., 2015). The regulatory roles of small ncRNAs, particularly miRNAs, are well-determined in the gene expression modulation. Although lncRNAs have been first proposed as the precursor transcripts for small ncRNAs such as miRNAs and snRNAs (Aschrafi et al., 2005; Zadehbagheri et al., 2019), further research has revealed their overlapping with mRNAs as well (Wang et al., 2010). Many lncRNAs are transcribed from genomic loci exhibiting chromatin signatures that indicate their transcription is dynamically regulated in a cell type-specific manner (Guttman and Rinn, 2012; Greco et al., 2017).

Notably, increasing evidence suggests that lncRNAs are important

* Corresponding author at:Centre for Genomic Regulation (CRG), The Barcelona Institute for Science and Technology, Dr. Aiguader 88, Barcelona, E-08003 Catalonia, Spain.
** Corresponding author.
E-mail addresses: baghery.zahra@yahoo.com (Z. Bagheri-Hosseinabadi), iman.sadeghi@crg.eu (I. Sadeghi).

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regulators of pathologic and physiologic processes, and evidence is now emerging to suggest that lncRNAs are central regulators of the inflammatory response. Numbers of lncRNAs are differentially expressed in human OA cartilage. Moreover, some lncRNAs have been shown to be involved in multiple pathological processes during OA, including extracellular matrix (ECM) degradation, inflammatory responses, apoptosis and angiogenesis. In this review, we summarize current knowledge concerning lncRNAs, from their biogenesis, classification and biological functions to molecular mechanisms and therapeutic potential in OA. Therefore, we examined evidence for the role of lncRNAs as regulators of inflammatory joint disease, by highlighting studies that have demonstrated differential expression of lncRNAs in the inflamed joint tissue of patients with RA and those with OA, as well as studies in which lncRNAs have been implicated as regulators of known inflammatory pathways relevant to joint pathology. LncRNAs are poorly conserved across species, which has been a limitation of studies performed to determine their function. This poor conservation places great importance on the requirement to validate the function of lncRNAs in disease-relevant human cells and tissues (Warner and Valdes, 2016). For this reason, our review focuses on lncRNA data generated from analysis of human cells and tissues.

2. Methods

We performed this narrative review as stated in a prospective protocol following the PRISMA Statement guidelines (Moher et al., 2009).

This review of clinical studies was conducted to evaluate lncRNAs in osteoarthritis studies. The studies were identified by searching the PubMed/MEDLINE, Google Scholar, and Sciencedirect databases for peer-reviewed journal articles that were published by September 2019. To identify additional relevant citations, we conducted forward searches in the Web of Science database. The abovementioned databases were searched with the following combinations of keywords: ("long non-coding RNA" OR "lncRNA") AND ("osteoarthrithis" OR "joint disease" OR "inflammatory disease" OR "bone formation" OR "rheumatoid arthritis") AND ("inflammation" OR "neuroinflammation" OR "cytokines" OR "chemokines").

3. Eligibility criteria

We included original peer-reviewed articles and abstracts with no language and year restriction to identify lncRNAs in osteoarthritis. We omitted review articles, in vitro studies, animal studies, and studies that did not present lncRNAs in osteoarthritis.

4. Classification of LncRNAs

LncRNAs contain heterogeneous genomic structure, modulation, function and expressional profiles (Geisler and Coller, 2013). A major function of lncRNAs is modulating the epigenetic status of proximal and distal protein-coding genes via *cis*- and *trans*-acting mechanisms including the recruitment of chromatin remodeling complexes to particular chromosomal regions thereby regulating chromatin status over a single gene promoter, a gene cluster, or an entire chromosome (Mercer et al., 2009; Eddy, 2001; Mercer et al., 2008; Mattick, 2001)(Fig. 1). According to the positional relationship between lncRNAs and their associated protein-coding genes, lncRNAs can be grouped in several classes: (1) long intergenic noncoding RNAs (lincRNAs) with a position between protein-coding genes that are at least 1 kb away from the nearest protein-coding genes.; (2) intronic transcripts that are expressed from intronic parts of protein-coding genes. Most of them show the same tissue expression patterns as the host genes, and may stabilize the host transcripts or regulate their alternative splicing; (3) overlapping lncRNAs that can be considered transcript isoforms of protein-coding mRNAs when they are transcribed from the same genomic strand. The majority of these lncRNAs are without open reading frames (ORFs) for protein translation. Other lncRNAs from this group are transcribed from the opposite strand of the protein-coding genes; and (4) bidirectional ncRNAs (BincRNAs) which have an orientation of head to head with a protein-coding gene within 1 kb (Guttman and Rinn, 2012; Li and Ramchandran, 2010; Mattick and Rinn, 2015). A bidirectional lncRNA transcript exhibits an expression pattern similar to its host gene, suggesting that they may be subject to shared regulatory pressures (Mattick and Makunin, 2006). In addition, some lncRNAs exhibit mixed characteristics, such as macroRNAs, which encompass huge genomic distances and multi-gene transcripts or even the whole chromosome (Mercer et al., 2009).

Intriguingly, mitochondrial lncRNAs have been identified by deep-sequencing techniques and verified by Northern blotting and qRT-PCR (Dorn, 2014). Moreover, the circular RNAs (circRNAs) have been discovered lately as a novel class of lncRNAs that are evolutionary conserved and highly abundant in mammals (Jeck and Sharpless, 2014). They are mainly produced from the transcripts spliced out from the exons or introns during splicing (Memczak et al., 2013).

5. Role of LncRNAs in OA

Although the fundamental molecular mechanisms involved in the pathogenesis of OA are still unknown, the role of some processes such as ECM disruption, angiogenesis, inflammatory response, and cell death in the incidence and progress of OA is clear (Findlay and Atkins, 2014; Greene and Loeser, 2015). In these events, plentiful lncRNAs have shown differential expression in human OA cartilage tissue, by disturbing the molecular mechanisms involved in the pathological processes (Chen et al., 2015). LncRNAs have demonstrated a contribution to a large number of vital biological processes such as cell growth, cell proliferation, regulation of transcription and translation, structural integrity, and cellular responses to environmental stimuli (Ma et al., 2013; Ponting et al., 2009). Previous studies revealed that the disturbance of the lncRNAs mechanism contributes to several forms of cancer and inflammatory diseases (Marques-Rocha et al., 2015). LncRNAs are normally involved in the formation of bone and cartilage. The expression of LncRNAs is disturbed in OA cartilage leading to the degeneration of chondrocyte extracellular matrix (Song et al., 2015) (Fig. 2). Accordingly, they are considered as potential biomarkers for the diagnosis and treatment of OA (Fu et al., 2015).

6. Dysregulation of LncRNAs in OA

Many investigations have reported the involvement of lncRNAs in many human illnesses such as cancer, metabolic disease, cardiovascular disease, neurodegenerative disease, and psychiatric disease; however, the contribution of lncRNAs remains largely unidentified in the pathogenesis of OA (Pearson et al., 2016; Wapinski and Chang, 2011) (Table 1). They have revealed that lncRNAs are aberrantly expressed in OA. In a study, Xing et al. observed 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 (Xing et al., 2014a). Recently, Chang et al. recognized 18 differentially expressed lncRNAs in injured joints of post-traumatic osteoarthritis (Chang et al., 2017). In another study, microarray analysis was exploited to detect a lncRNA with a specific role in the degradation of the cartilage matrix, named cartilage injury–related lncRNA (lncRNA-CIR) (Liu et al., 2014). LncRNA-CIR, a pseudogene transcript of vimentin, is dysregulated in OA cartilage. The expression of lncRNA-CIR is elevated in the damaged region of tissue lncRNA-CIR and the increase of lncRNA-CIR plays a critical role in the degradation of chondrocyte extracellular matrix (ECM) (Liu et al., 2014; Zhang et al., 2016). 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

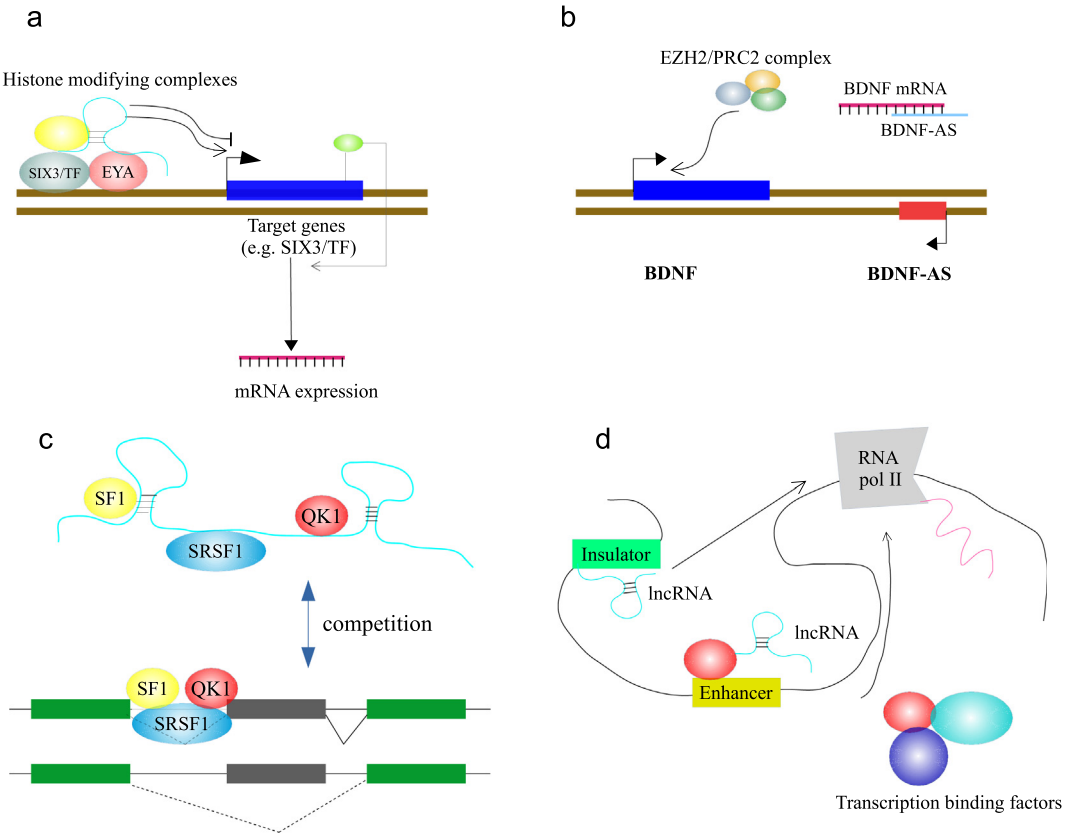

Fig. 1. Examples of functional diversity attributed to long noncoding RNAs (lncRNAs). a, LncRNAs can act as scaffolds for the assembly of protein complexes that epigenetically modify the DNA (e.g., histone acetylation and methylation), leading to modulation of transcription. b, LncRNAs can bind to target mRNA and mediate the assembly of transcription initiation complexes, leading to modulation of transcription. c, LncRNAs can bind different splicing factors and modulate the splicing processes. d, LncRNAs are also involved in a special chromatin modulation names "chromosomal looping" which brings seemingly distance chromosomal regions into proximity for transcriptional regulation in a *cis*-regulatory interactions.

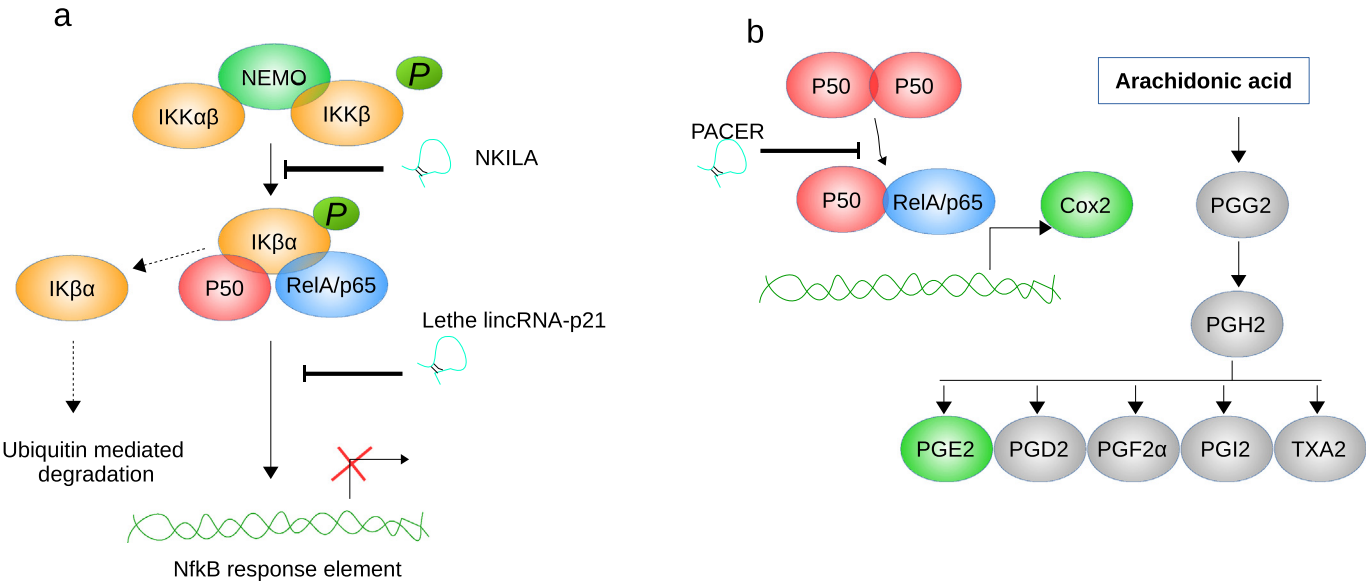

Fig. 2. Functional long noncoding RNAs (lncRNAs) in inflammatory pathways. a, Canonical NF-kB signaling. The lncRNA NKILA (NFkB–interacting lncRNA) blocks the Ikba phosphorylation site, preventing its activation. The lncRNAs Lethe and long intergenic noncoding RNA p21 (lincRNA-p21) both bind to RelA and prevent NF-kB binding to NF-kB response elements. B, Arachidonic acid pathway. The lncRNA p50-associated cyclooxygenase 2 (COX-2)–extragenic RNA (PACER) binds to and removes the repressive action of the p50 homodimer at the COX-2 promoter, leading to activation of COX-2 gene expression.

Table 1
Differentially expressed lncRNAs in osteoarthritis and rheumatoid arthritis joint tissues.

Disease	LncRNA	Tissue/Cell	Expression	Function	Reference
Osteoarthritis	Hivep2-AS (CILinc01)	Chondrocytes	Upregulated	Suppresses IL-6, IL-8, TNF, G-CSF, MIP-1B	(Pearson et al., 2016)
	IL-7AS (CILinc02)	Chondrocytes	Upregulated	Suppresses IL-6	(Pearson et al., 2016)
	H19	Chondrocytes	Upregulated	Anabolic functions	(Steck et al., 2012)
	LncRNA-CIR	Chondrocytes	Upregulated	Promotes expression of MMP-13 and ADAMTS-5	(Liu et al., 2014)
	MEG3	Cartilage	Downregulated	Negatively correlated with VEGF	(Su et al., 2015)
	HOTAIR	Cartilage	Downregulated	Unknown	(Xing et al., 2014b)
	GAS-5	Cartilage	Downregulated	Increases expression of MMPs; induces apoptosis	(Song et al., 2014)
	LnCRNA uc.343	Cartilage	Upregulated	Regulation of HOXC8	(Fu et al., 2015)
Rheumatoid arthritis	H19	Synovium	Upregulated	Increases expression of NfkB, IL-6, TNF	(Stuhlmüller et al., 2003)
	HOTAIR	Synovial fibroblasts, osteoclasts	Downregulated	Increases expression of MMPs	(Song et al., 2015)
	HOTAIR	Bone mononuclear cells	Upregulated	Migration and activation of macrophages	(Song et al., 2015)
	LincRNA-p21	T ells	Downregulated	Inhibition of NfkB following methotrexate treatment	(Spurlock III et al., 2014)

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 (Liu et al., 2014). Another study demonstrated that the upregulation of HOTAIR contributes to OA by inducing IL-1-induced MMP overexpression and chondrocytes apoptosis (Zhang et al., 2016). Su et al. investigated the expression of maternally expressed gene 3 (MEG3, a tumor suppressor) in cartilage samples from OA patients and healthy individuals (Su et al., 2015). Moreover, they assessed the potential relationship of MEG3 expression and vascular endothelial cell growth factor (VEGF) level in OA. It was revealed that MEG3 expression had a lower level while the expression of VEGF isoforms is significantly increased in OA patients (Su et al., 2015). VEGF has been shown to regulate hypertrophic cartilage remodeling, ossification, and vascular invasion of growth plate cartilage (Song et al., 2014). Their study suggested that MEG3 expression is negatively correlated with VEGF expression level in OA and upregulation of VEGF leads to enhanced angiogenesis which in turn inactivation of MEG3 contributes to OA development (Su et al., 2015).

Fu and colleagues performed microarray analysis and identified 4714 lncRNAs that were differentially expressed in OA cartilage compared with non-OA cartilage (Fu et al., 2015). This analysis highlighted lncRNA uc.343, which was up-regulated in OA cartilage, as regulating in cis the expression of homeobox C8, and that many of the differentially expressed lncRNAs function in concert with the transcription factor Sp1 to regulate the expression of *trans* target genes. Furthermore, several lncRNAs were recently showed association with the IL-1b–mediated inflammatory response in primary human OA chondrocytes that were also aberrantly expressed in diseased OA cartilage. Of particular note were human immunodeficiency virus type I enhancer binding protein 2S (Hive2pAS) and IL-7AS, 2 intergenic lncRNAs proximal to the Hivep2 and IL-7 protein-coding genes, respectively (Pearson et al., 2016). These two genes were observed to be upregulated in both knee OA and hip OA cartilage compared with non-OA control cartilage (Pearson et al., 2016; Khaled, 2016). Additionally, locked nucleic acid (LNA)–mediated knockdown of Hive2pAS and IL-7AS gene expression in human chondrocytes lead to enhanced production of proinflammatory cytokines, such as IL-6 telling that these lncRNAs may play role in the regulation of aberrant joint inflammation (Pearson et al., 2016; Liu et al., 2014).

7. Therapeutic approaches for targeting LncRNAs in OA

OA is the most common form of arthritis and has become a major public health problem for a normal healthy life. The causes of OA remain unclear and the conventional therapeutic approaches of OA are still unsatisfactory. Identification of new biomarkers may facilitate the development of effective therapeutic approaches against OA and reduction of disease symptoms (Bijlsma et al., 2011; Henrotin et al., 2014).

In a study, Kang et al. found that over-expression of PCGEM1 inhibited apoptosis, induced autophagy and stimulated the proliferation of human synoviocytes (Kang et al., 2016). They suggested PCGEM1 as a possible target for OA therapy. They transfected miR-770 precursor with pMIR-REPORT vector-PCGEM1 and observed a significant reduction in the proliferation and induction of apoptosis in human synoviocytes. Song et al. reported that GAS5 plays a critical role in the regulation of miR-21 and the over-expression of GAS5 is capable of suppressing miR-21 induction during OA (Song et al., 2014). They investigated that the infection of mice with miR-21-expressing lentiviruses significantly reduced the GAS5 level and stimulated the apoptosis of chondrocytes as well as reduced cartilage destruction and the expression level of MMP-13 RNA. Liu et al. suggested lncRNA-CIR as a potential target in OA therapy (Li and Ramchandran, 2010). They reported that silencing of lncRNA-CIR by small interfering RNA promoted the formation of collagen and aggrecan and reduced the expression of matrix-degrading enzymes, such as MMP13 and ADAMTS5, and thereby reduced cartilage degradation. Kim et al. (Kim et al., 2013) suggested that two non-coding RNAs, miR-101 and HOTTIP could be a potential predictive biomarker as well as a therapeutic target for OA. In their research, they recognized significant downregulation of mR-101 and upregulation of HOTTIP in OA. They demonstrated that upregulation of miR-101 by TGF-3 treatment repressed integrin-1 methylation, stimulated the chondrogenic differentiation of limb mesenchymal cells and repressed the cartilage degradation. Steck et al. showed that H19 could be a potential target for stimulating cartilage recovery by (Steck et al., 2012). However, there is a lack of enough evidence which may support that targeting lncRNA is successful in OA treatment. More investigations are necessary to support lncRNA as a potential therapeutic target to treat OA. Currently, there is still a lack of effectively biological therapy for OA patients, highlighting the need to search for novel therapeutic approaches. As mentioned above, many lncRNAs are aberrantly expressed in human degenerative OA cartilage tissue and some lncRNAs have been shown to involve multiple pathological processes of OA development, suggesting lncRNAs as novel contributors to both diseases. Accordingly, lncRNA targeting therapy is anticipated to open new hope for the management of OA.

8. Conclusions

LncRNA research in inflammatory OA is a blossoming field. However, several lncRNAs have now been detected as being either differentially expressed in diseased joint tissue or as candidate central regulators of inflammatory pathways relevant to joint pathology. Therefore, future studies to determine the functional role and mode of action of these disease-associated lncRNAs will be insightful, as will joint tissue expression profiling of lncRNAs for which functional roles

within key inflammatory pathways have been determined. To this end, it will be important to conduct further transcriptomic analysis of joint tissues (including subchondral bone, cartilage, and synovium) in which diseased joint tissues are compared with age-matched noninflammatory control joint tissue and to conduct functional mode-of-action studies in disease-relevant cells. Several approaches to target lncRNAs for therapeutic purposes can be considered once key disease-relevant contributions of these genes have been identified. A major challenge of all of these approaches is to accomplish target-specific delivery. Recently, several novel delivery strategies have been developed to reduce off-target effects, especially nanoparticles that are characteristic by improved stability, extremely small size, biocompatibility and self-assembly. As the pace of research in lncRNAs progresses, addressing these issues will provide opportunities for the development of novel therapeutic strategies based on targeting lncRNAs for OA. Despite the investigations of lcnRNAs remaining in their infancy, they have been suggested as new contributors to OA. This provides novel insight into the pathogenesis of OA. With continued efforts, some dysregulated lncRNAs may be used as valuable diagnostic biomarkers and therapeutic targets.

Declaration of Competing Interest

None.

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