Interactions Among lncRNA/circRNA, miRNA, and mRNA in Musculoskeletal Degenerative Diseases

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Musculoskeletal degenerative diseases (MSDDs) are pathological conditions that affect muscle, bone, cartilage, joint and connective tissue, leading to physical and functional impairments in patients, mainly consist of osteoarthritis (OA), intervertebral disc degeneration (IDD), rheumatoid arthritis (RA) and ankylosing spondylitis (AS). Long non-coding RNAs (lncRNAs) and circular RNAs (circRNAs) are novel regulators of gene expression that play an important role in biological regulation, involving in chondrocyte proliferation and apoptosis, extracellular matrix degradation and peripheral blood mononuclear cell inflammation. Research on MSDD pathogenesis, especially on RA and AS, is still in its infancy and major knowledge gaps remain to be filled. The effects of lncRNA/circRNA-miRNA-mRNA axis on MSDD progression help us to fully understand their contribution to the dynamic cellular processes, provide the potential OA, IDD, RA and AS therapeutic strategies. Further studies are needed to explore the mutual regulatory mechanisms between lncRNA/circRNA regulation and effective therapeutic interventions in the pathology of MSDD.

Keywords: degenerative musculoskeletal disorders, aging, age-related disease, non-coding RNAs, miRNA, circRNA, lncRNA

INTRODUCTION

Musculoskeletal degenerative diseases (MSDDs) are pathological conditions that affect muscle, bone, cartilage, joint and connective tissue, leading to physical and functional impairment in patients (Chen Y. et al., 2017; Huo et al., 2018). With the acceleration of the global aging process, the prevalence of MSDD is increasing. This is a huge challenge for patients and healthcare workers, and adds to the global healthcare burden (Li and Chen, 2019). The main MSDD consists of osteoarthritis (OA), intervertebral disc degeneration (IDD), rheumatoid arthritis (RA), and ankylosing spondylitis (AS) (Vinatier et al., 2016; Huo et al., 2018; Loef et al., 2018). OA is a chronic age-related MSDD, featuring for subchondral bone thickening, articular cartilage degradation, and osteophyte formation (Loeser et al., 2012; Hunter and Biema-Zeinstra, 2019). IDD is also age-related and is caused by progressive degeneration of the disk (Yang S. et al., 2020), causing loss of disk height, reduced hydration and decreased potential to absorb load (Samartzis et al., 2011; Cooper et al., 2016). RA is an autoimmune disease characterized by aggressive arthritis that can...
lead to joint deformities and loss of function (Smolen et al., 2016). AS, a rare but clear cause of chronic back pain, is an inflammatory disease involving the spine, sacroiliac joints and other joints (Taurog et al., 2016). OA and IDD became mainly responsible for MSDD. Their common character is the broken dynamic equilibrium between catabolism and anabolism in the extracellular matrix (ECM). On the one hand, chondrocytes is only resident cells in the articular system, the ECM degeneration in OA is led by chondrocytes' catabolic and abnormal differentiation (Zhou Z.B. et al., 2019). Cartilage cellularity is reduced in OA because of chondrocyte death. On the other hand, ECM breakdown and abnormal matrix synthesis in IDD is responsible by nucleus pulposus (NP) cells, which are predominant cells in the NP tissue (Fontana et al., 2015). Excessive apoptosis of NP cells could accelerate IDD progression (Zhao et al., 2006). Meanwhile, endplate cartilage degeneration is another risk factor of IDD (Iwakura et al., 2013) due to its irreplaceable nutrition supplement of intervertebral disk (Yuan et al., 2015). Although multiple factors are involved in the pathogenesis of MSDD (Li and Chen, 2019), the development of molecular mechanism of MSDD is still poor. Thus, it is urgent to discover new biomarkers to optimize MSDD early diagnosis and treatment.

With the development of sequencing technology, recent advances have shown that about 98% of the human genome is composed of non-coding RNAs (ncRNAs). In the past, ncRNAs were thought to act as ‘evolutionary junk.’ However, an increasing amount of evidence reported that ncRNAs play an important role in biological regulation (Beermann et al., 2016; Vieira et al., 2018). The main types of ncRNAs include long non-coding RNA (lncRNA), circular RNA (circRNA) and microRNA (miRNA) (Beermann et al., 2016). Recently, extensive evidence suggested that ncRNAs play a vital role in the development of MSDD (Chen W.K. et al., 2017; Yu and Sun, 2018; Wang J. et al., 2019). Moreover, circRNA and lncRNA can interact with miRNA to further regulate downstream target mRNA in the MSDD and play regulatory roles in numerous biological functions, such as proliferation, apoptosis and inflammation. In this review, we focused on the role of lncRNA/circRNA-miRNA-mRNA axis in the development of MSDD and further explored related molecular mechanism of MSDD.

INTERACTIONS BETWEEN IncRNA/circRNA and miRNA

Interactions Between IncRNA and miRNA

MicroRNAs are encoded by endogenous genes, are approximately 20 nucleotides in length and are non-coding single-stranded RNA molecules (Beermann et al., 2016). Since they were first described in Caenorhabditis elegans, the number of miRNAs that have been found in mammals increased (Lee et al., 1993). miRNA is evolutionarily conserved and regulates gene expression at the post-transcriptional level by interfering with mRNA translation and degradation (Zhang et al., 2020b). With

Interactions Between circRNA and miRNA

As endogenous RNAs, circRNAs are characterized by covalent loop structures without 5′–3′ polarity nor a polya-adenylated tail (Zhou et al., 2018). Different from linear RNA, circRNAs are inherently conserved due to their closed covalent structure and resistance to exonucleases; they are considered to be stable in exosomes (Haque and Harries, 2017). circRNAs are classified into four...
types according to their origin, namely, exonic circRNAs, exon-intron circRNAs, intronic circRNAs and intergenic circRNAs (Deng et al., 2016). A growing number of studies indicate that circRNAs exist miRNA complementary binding sites to interact with miRNAs, thereby playing regulatory roles in diseases and effecting in many biological processes, such as inflammation, apoptosis and ECM degradation, by participating in the modulation of transcriptional and post-transcriptional levels (Rong et al., 2017; Verduci et al., 2019). The mechanisms included circRNAs acting as miRNAs sponges and miRNAs regulating circRNAs (Kulcheski et al., 2016). For instance, the circAnks1a could regulate VEGFB (vascular endothelial growth factor-B) expression to suppress the excitability of spinal cord by sponging miR-324-3p in neuropathic pain (Zhang S.B. et al., 2019). Pan et al. (2019) elucidated that the miR-1224 could mediate circRNA-Filip1 expression through regulating Ubr5 in the spinal cord of chronic inflammatory pain mice. Although circRNAs are generally considered as ncRNAs because of non-linear structure, several circRNAs, such as CircFBXW7 (Ye et al., 2019) and Circ-EGFR (Liu et al., 2021), are proved to have translation functions due to its translatable open reading frame containing a start codon. The cap-independent translation pathway is thought to be the main mechanism of circRNA translation to encode protein (He et al., 2021). Combined with the above explanation, currently known that circRNAs can interact with proteins or act as miRNA sponges and regulate the expression of upstream gene to participate in the process of diseases development. In recent years, circRNAs have become a research hotspot in MSDD and showed great potential as biomarkers and therapeutic targets (Li H.Z. et al., 2018; Lei B. et al., 2019; Wu et al., 2019).

INTERACTIONS AMONG IncRNA, miRNA, AND mRNA IN DEGENERATIVE MUSCULOSKELETAL DISEASES

Osteoarthritis

In the past decade, quite number of studies have shown that the interaction between lncRNAs and miRNAs is involved in the multiple biological processes of OA, such as inflammation, proliferation, apoptosis, autophagy, cell viability and ECM degradation (Table 1). The major interaction mechanism between IncRNA and miRNA in OA was that IncRNAs as ciRNAs acts as miRNAs sponges. Wang Q. et al. (2017) reported that the expressions of IncRNA OPN and NEAT1 significantly increased, whereas that of miR-181c decreased. According to luciferase assays, mir-181c could combine with NEAT1 and 3'UTR of OPN in synoviocytes, leading to NEAT1 competing with OPN for binding with miR-181c and further enhancing the level of OPN. Chen Y. et al. (2020) showed that IncRNA HOTAIR (HOX transcript antisense intergenic RNA) and mRNA PTEN (phosphatase and tensin homolog) was significantly increased in the OA mice, whereas miR-20b decreased. HOTAIR was involved in the process of apoptosis and ECM degradation by sponging miR-20b and regulating the downstream target PTEN. Lu and Zhou (2020) revealed that IncRNA00662 was downregulated in the cartilage of OA rats. The expression of miR-15b-5p was negative with IncRNA00662, whereas the expression of GPR120 was positively correlated with IncRNA00662. IncRNA00662 regulated GPR120 in apoptosis by serving as a sponge for miR-15b-5p. Sun P. et al. (2020) also studied the effect of XIST on OA patients and showed that XIST upregulated SGTB and inhibited the depression on SGTB induced by miR-142-5p through sponging miR-142-5p. Another study reported that the level of Inc00623 and HRAS was downregulated, whereas miR-101 was increased in OA tissues compared with normal tissues (Lü et al., 2020). Based on luciferase reporter, miR-101 could combine with Inc00623 and HRAS. Inc00623 sponges miR-101 through competing with HRAS, thereby preventing the miR-101-induced depression on HRAS. Some other IncRNAs act as miRNA sponges in OA and more detailed information is presented in Table 1.

Intervertebral Disk Degeneration

The mechanism by which IncRNA and miRNA act on IDD that has been most studied is as follows: IncRNA acts as the sponge of miRNA to modulate target genes (Figure 1). Xi et al. (2017) demonstrated that IncRNA HCG18 was upregulated in the IDD and plays the sponge roles of miR-146a-5p in NP cells. HCG18 is involved in the progression of cell proliferation and apoptosis in NP cells via the miR-146a-5p/TARF6/NF-kB axis. Compared with normal NP tissues, IncRNA SNHG1 (small nucleolar RNA host gene 1) expression was boosted and miR-326, a target gene of SNHG1, was reduced in IDD samples (Tan et al., 2018). Moreover, miR-326 could directly bind with Cyclin D1 (CCND1), and the level of CCND1 in the NP cells markedly increased. Thus, Tan et al. (2018) observed that SNHG1 modulates NP cells proliferation via sponging miR-326 and further regulating CCND1. Another study reported that IncRNA H19 was upregulated in the IDD tissues and could activate Wnt/β-catenin signaling pathway (Wang et al., 2018d). Moreover, miR-326 could directly bind with Cyclin D1 (CCND1), and the level of CCND1 in the NP cells markedly increased. Thus, Tan et al. (2018) observed that SNHG1 modulates NP cells proliferation via sponging miR-326 and further regulating CCND1. Another study reported that IncRNA H19 was upregulated in the IDD tissues and could activate Wnt/β-catenin signaling pathway (Shao et al., 2019). Another research suggested that LINC00641 level increased in NP tissues, whereas miR-153-3p level decreased. ATG5 (autophagy-related gene 5) was a downstream gene of miR-153-3p and upregulated in NP cells (Wang J. et al., 2019). Moreover, LINC00641 could sponge miR-153-3p, and thereby regulate the level of ATG5, cell death and the progression of IDD. Yang Y. et al. (2019) elucidated that IncRNA lincRNA-SLC20A1 (SLC20A1) was overexpressed in IDD patients, and SLC20A1 could induce ECM degradation via sponging miR-31-5p and further modulating the downstream target gene MMP3. Another study established that the level of IncRNA PART1 and mRNA matrix metallopeptidase 2 (MMP2) in NP tissues were significantly higher than those in the control groups, whereas
TABLE 1 | lncRNA/miRNA/mRNA networks in osteoarthritis.

| Species      | Diseases          | Region                    | InCRNA       | Change | miRNA    | Expression | Target gene | Change | Functions                      | References          |
|--------------|-------------------|---------------------------|--------------|--------|----------|------------|-------------|--------|--------------------------------|---------------------|
| Human        | OA                | Cartilage                 | H19          | Up     | miR-675  | Up         | COL2A1      | Up     | Inflammation                    | Steck et al., 2012  |
| Human, mice  | OA                | Cartilage, chondrocyte    | GAS5         | Up     | miR-21   | Down       | MMPs, ADAMTS-4 | Up     | Cell apoptosis and autophagy    | Song et al., 2014   |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA-MSR   | Up     | miRNA-152| Down       | TMSB4       | Up     | ECM degradation                 | Liu et al., 2016a   |
| Human        | OA                | Cartilage, chondrocyte    | UFC1         | Down   | miR-34a  | Up –       | –           | –      | Cell proliferation and apoptosis| Zhang et al., 2016  |
| Human        | OA, C28/I2 cells | Cartilage                 | HOTAIR       | Up     | miR-17-3p| Down       | ETV1        | Up     | Cell apoptosis and inflammation| Chen H. et al., 2017|
| Human        | OA                | Cartilage                 | IncRNA PVT1  | Up     | miR-488-3p| Down       | –           | –      | Cell apoptosis                   | Li Y. et al., 2017  |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA CiR   | Up     | miR-27   | Down       | MMP13       | Up     | ECM degradation                 | Li Y.F. et al., 2017|
| Human        | OA                | Cartilage, chondrocyte    | IncRNA -UCA1 | Up     | miR-204-5p| Down       | MMP13       | Up     | Cell proliferation              | Wang G. et al., 2017|
| Human        | Synovium tissues  | synoviocytes              | NEAT1        | Up     | miR-181c | Down       | OPN         | Up     | Cell proliferation              | Wang Q. et al., 2017|
| Rats         | OA                | Cartilage, chondrocyte    | IncRNA MEG3  | Down   | miR-16   | Up         | SMAD7       | Down   | Cell proliferation and apoptosis| Xu and Xu, 2017     |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA FOXD2-AS1 | Up     | miR-206 | Down       | CCND1       | Up     | Cell proliferation and apoptosis| Cao et al., 2018    |
| Human        | OA                | Cartilage, chondrocyte    | DANCR        | Up     | miR-577  | Down       | SphK2       | Up     | Cell proliferation and apoptosis| Fan et al., 2018    |
| Human        | OA, C28/I2 cells | Cartilage                 | HOTAIR       | Up     | miR-17-5p| Down       | FUT2        | Up     | Cell proliferation, apoptosis and ECM degradation | Hu et al., 2018    |
| Human        | OA                | Cartilage, chondrocyte    | XIST         | Up     | miR-211  | Down       | CXCR4       | Up     | Cell proliferation and apoptosis| Mohammad et al., 2018|
| Human        | OA                | Cartilage, chondrocyte    | MALAT1       | Up     | miR-127-5p| Down       | P38K/Akt    | Up     | Cell proliferation              | Liang et al., 2018  |
| Mice         | OA                | Cartilage, chondrocyte    | IncRNA-KLF3-AS1 | Up     | miR-206 | Down       | Git1        | Up     | Cell proliferation and apoptosis| Liu et al., 2018    |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA CiR   | Up     | miR-130a | Down       | Bim         | Up     | Cell apoptosis and inflammation| Lu Z. et al., 2019  |
| Murine       | OA, Chondrogenic ATDC5 cells | Chondrocyte | MALAT1       | Up     | miR-19b  | Down       | Wnt/b-catenin and NF-kB pathways | Up | Cell apoptosis and inflammation | Pan et al., 2018    |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA SNHG5 | Down   | miR-26a  | Up         | SOX2        | Down   | Cell proliferation              | Shen et al., 2018   |
| Human        | OA, cartilage ATDCS cells | Cartilage | IncRNA RP11-445H22.4 | Up     | miR-301a | Down       | CXCR4       | Up     | Cell viability, apoptosis and inflammation | Sun et al., 2018    |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA -p21  | Up     | miR-451  | Down –     | –           | –      | Cell apoptosis                   | Tang L. et al., 2018|
| Human        | OA, ATDCS cell   | Cartilage                 | IncRNA TUG3  | Up     | miR-195  | Down       | MMP13       | Up     | ECM degradation                 | Tang L.P. et al., 2018|
| Human        | OA                | Cartilage, chondrocyte    | MEG3         | Down   | miR-203  | Up         | Sirt1       | Up     | Cell viability, apoptosis and inflammation | Wang et al., 2018e   |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA DANCR | Up     | miR-216a-5p| Down       | JAK2/STAT3 signal pathway | Up | Cell proliferation, apoptosis and inflammation | Zhang et al., 2018  |
| Human        | OA                | Cartilage, chondrocyte    | PVT1         | Up     | miR-149  | Down –     | –           | –      | Inflammation                     | Zhao et al., 2018   |
| Human        | OA                | Cartilage, chondrocyte    | IncRNA DNM3OS | Down   | miR-126  | Up         | IGF1        | Down   | Cell proliferation and apoptosis| Ai and Yu, 2019     |
| Rats         | OA                | Cartilage, chondrocyte    | MEG3         | Down   | miR-93   | Up         | TGFBR2      | Down   | Cell proliferation, apoptosis and ECM degradation | Chen et al., 2019   |

(Continued)
| Species | Diseases | Region | IncRNA | Change | miRNA | Expression | Target gene | Change | Functions | References |
|---------|----------|--------|--------|--------|-------|------------|-------------|--------|-----------|------------|
| Human   | OA       | Cartilage, ATDCS cells | lncRNA-HULC | Down | miR-101 | Up | NF-κB and p38MAPK signaling pathways | Down | Inflammation | Chu et al., 2019 |
| Human   | OA       | Synovial fluid, chondrocytes | MCM3AP-AS1 | Up | miR-142-3p | Down | HMG1B | Up | Cell apoptosis | Gao et al., 2019 |
| Human   | OA       | LPS-treated C28/I2 cells | H19 | Up | miR-130a | Down | – | – | Cell viability, apoptosis, and inflammation | Hu et al., 2019 |
| Human   | OA       | Cartilage, chondrocyte | TNFSF10 | Up | miR-376-3p | Down | FGFR1 | Up | Cell proliferation, apoptosis, and inflammation | Huang et al., 2019 |
| Human   | OA       | Cartilage, chondrocyte | IncRNA SNHG1 | Down | miR-16-5p | Up | p38MAPK and NF-κB signaling pathways | Down | Inflammation | Lei J. et al., 2019 |
| Human   | OA       | LPS-treated ATDCS cells | MIAT | Up | miR-132 | Down | NF-κB and JNK pathways | Up | Cell apoptosis and inflammation | Li et al., 2019a |
| Rats    | OA       | LPS-treated chondrocytes | MALAT1 | Down | miR-146a | Up | PI3K | Down | ECM degradation, inflammation and apoptosis | Li et al., 2019b |
| Human   | OA       | Cartilage, synoviocytes | IncRNA-ANRIL | Up | miR-122-5p | Down | DUSP4 | Up | Cell proliferation and apoptosis | Li et al., 2019c |
| Human   | OA       | LPS-treated ATDCS cells | PMS2L2 | Down | miR-203 | Up | MCL-1 | Down | Cell viability, apoptosis, and inflammation | Li et al., 2019d |
| Human   | OA       | Cartilage, chondrocyte | IncRNA-TM1P3 | Down | miR-22 | Up | ALK1 | Up | ECM degradation | Li et al., 2019e |
| Human   | OA       | IL-1β-induced chondrocytes | MALAT1 | Up | miR-145 | Down | ADAMTS5 | Up | ECM degradation | Liu C. et al., 2019 |
| Murine  | OA       | LPS-induced ATDCS cells | THRIL | Up | miR-125b | Down | JAK1/STAT3 and NF-κB pathways | Up | Inflammation | Liu G. et al., 2019 |
| Human   | OA       | Cartilages, chondrocytes | PART-1 | Down | miR-590-3p | Up | TGFBR2, Smad3 | Down | Cell viability and apoptosis | Lu C. et al., 2019 |
| Human   | OA       | hMSC, cartilage, chondrocytes | HOTTIP | Up | miR-455-3p | Down | CCL3 | Up | Cartilage degradation | Mao et al., 2019 |
| Human   | OA       | Chondrocytes | Nespas | Up | miR-291a-3p, miR-196a-5p, miR-23a-3p, miR-24-3p, miR-let-7a-5p | Down | ACSL6 | Up | Lipid metabolism | Park et al., 2019 |
| Human   | OA       | Synovial fluid, chondrogenic cell line ChOND-001 | CAIF | Down | miR-1246 | Up | IL-6 | Up | Cell apoptosis | Qi et al., 2019 |
| Human   | OA       | Cartilage, chondrocyte | MEG3 | Down | miR-361-5p | Up | FOXO1 | Down | Cell proliferation, apoptosis and ECM degradation | Wang A. et al., 2019 |
| Human, rats | OA | Chondrocyte (Human) cartilage (rat) | XIST | Up | miR-1277-5p | Down | MMP-13, ADAMTS5 | Up | ECM degradation | Wang T. et al., 2019 |
| Human   | OA       | Cartilage, chondrocyte | FOXD2-A31 | Up | miR-27a-3p | Down | TLR4 | Up | Cell proliferation, inflammation and ECM degradation | Wang Y. et al., 2019 |
| Human   | OA       | Synovium, chondrocyte | NEAT1 | Down | miR-181a | Up | GPD1L | Down | Cell proliferation, apoptosis and inflammation | Wang Z. et al., 2019 |
| Human   | OA       | Cartilages, mesenchymal stem cells (MSCs) | HOTAIRM1-1 | Down | miR-125b | Up | BMPR2 | Down | Cell viability, apoptosis and differentiation | Xiao et al., 2019 |
| Species | Diseases | Region | IncRNA | Change | miRNA | Expression | Target gene | Change | Functions | References |
|---------|----------|--------|--------|--------|--------|------------|-------------|--------|-----------|------------|
| (49) Human | OA Cartilages, chondrocyte | LINC00341 | Down | miR-141 | Up | YAF2 | Down | Cell apoptosis | Yang Q. et al., 2019 |
| (50) Murine | OA LPS-induced ATDC5 cells | IncRNA-ATB | Down | miR-223 | Up | MyD88/NF-kB and p38 MAPK pathways | Up | Cell viability, apoptosis and inflammation | Ying et al., 2019 |
| (51) Mice | OA IL-6-induced ATDC5 cells | CHRF | Up | miR-146a | Down | / | / | Cell viability, apoptosis and inflammation | Yu et al., 2019 |
| (52) Human | OA Cartilage, chondrocyte | H19 | Up | miR-106a-5p | Down | / | / | Cell proliferation and apoptosis | Zhang X. et al., 2019 |
| (53) Human | OA Cartilage, chondrocyte | MALAT1 | Up | miR-150-5p | Down | AKT3 | Up | Cell proliferation, apoptosis and ECM degradation | Zhang Y. et al., 2019 |
| (54) Human | OA Cartilage, chondrocyte | PART1 | Up | miR-373-3p | Down | SOX4 | Up | Cell proliferation, apoptosis and ECM degradation | Zhu and Jiang, 2019 |
| (55) Mice | OA Cartilage, chondrocytes | HOTAIR | Up | miR-20b | Down | PTEN | Up | Cell apoptosis and ECM degradation | Chen Y. et al., 2020 |
| (56) Human | OA Cartilage, chondrocytes | HOTAIR | Up | miR-130A-3p | Down | – | – | Cell apoptosis | He and Jiang, 2020 |
| (57) Human | OA Cartilage, chondrocyte | GAS5 | Up | miR-34a | Down | Bcl-2 | Up | Cell apoptosis | Ji Q. et al., 2020 |
| (58) Rat | OA BMSCs | BLACAT1 | Up | miR-142-5p | Down | – | – | Cell proliferation and differentiation | Ji Y. et al., 2020 |
| (59) Human | OA Cartilage, chondrocyte | NEAT1 | Up | miR-16-5p | Down | – | – | Cell proliferation and apoptosis | Li D. et al., 2020 |
| (60) Human | OA Cartilage, chondrocyte | XIST | Up | miR-376c-5p | Down | OPN | Up | Cell apoptosis | Li L. et al., 2020 |
| (61) Human | OA Cartilage, chondrocyte | NEAT1 | Up | miR-193a-3p | Down | SOX5 | Up | Cell apoptosis, inflammation and ECM degradation | Liu et al., 2020 |
| (62) Human | OA Cartilage, chondrocyte | LINC00623 | Down | miR-101 | Up | HRAS | Down | Cell apoptosis, senescence and ECM degradation | Lü et al., 2020 |
| (63) Rat | OA Cartilage, chondrocyte | LINC00662 | Down | miR-15b-5p | Up | GPR120 | Down | Cell apoptosis | Lu and Zhou, 2020 |
| (64) Human | OA Cartilage, LPS-treated C28/I2 cells | MIR2-AS1 | Up | miR-130a-3p | Down | TCF4 | Up | Cell viability, apoptosis, inflammation and ECM degradation | Luo et al., 2020 |
| (65) Human | OA Cartilage, chondrocyte | XIST | Up | miR-142-5p | Down | SGTB | Up | Cell growth, proliferation and apoptosis | Sun P. et al., 2020 |
| (66) Human | OA Synovial fluid, chondrocyte | CASC2 | Up | miR-93-5p | Down | – | – | Cell apoptosis | Sun Y. et al., 2020 |
| (67) Human, Rats | OA Cartilage (human), chondrocyte (rats) | H19 | Down | miR-100b-5p | Up | TIMP2 | Down | Cell proliferation, migration and ECM degradation | Tan et al., 2020 |
| (68) Human | OA Cartilage, chondrocyte | SNHG7 | Down | miR-34a-5p | Up | SYVN1 | Down | Cell proliferation, apoptosis and autophagy | Tian et al., 2020 |
| (69) Human | OA Cartilage, chondrocyte | NIKILA | Down | miR-145 | Up | SP1 | Down | Cell proliferation, apoptosis and inflammation | Xue et al., 2020 |
| (70) Human | OA Synovial fluid, chondrocytes | CTBP1-AS2 | Up | miR-130A | Down | – | – | Cell proliferation | Zhang et al., 2020a |
| (71) Human | OA Peripheral Blood, THP-1 cell | IGHCy1 | Up | miR-6891-3p | Down | TLR4 | Up | Inflammation | Zhang et al., 2020c |
TABLE 1 (Continued)

| Species | Diseases | Region | lncRNA | Change | miRNA | Expression | Target gene | Change | Functions | References |
|---------|----------|--------|--------|--------|--------|------------|------------|--------|-----------|------------|
| Human   | OA       | Cartilage, chondrocyte | SNHG15 | Down   | miR-141-3p | Up | BCL2L13 | Down | Cell proliferation, apoptosis and ECM degradation | Zhang et al., 2020e |
| Human   | OA       | Cartilage, chondrocyte | LINC00461 | Up | miR-30a-5p | Down | – | – | Cell proliferation, cell cycle progression, inflammation, and ECM degradation | Zhang et al., 2020g |
| Human   | OA       | Cartilage, chondrocyte | OIP5-AS1 | Down | miR-29b-3p | Up | PGRN | Down | Cell proliferation, migration, apoptosis and inflammation | Zhi et al., 2020 |

ACSLS6, acyl-CoA synthetase 6; ADAMTSs, a disintegrin and metalloprotease with thrombospondin motifs; ALK1, activin receptor-like kinase 1; ANRIL, antisense non-coding RNA in the INK4 locus; ATB, activated by transforming growth factor beta; BCL2L13, Bcl2-like 13; Bim, B-cell lymphoma 2 interacting mediators of cell death; BMPR2, bone morphogenetic protein receptor 2; BMSCs, bone marrow stromal stem cells; CASC2, Cancer Susceptibility 2; CCND1, Cyclin D1; CHRF, cardiac hypertrophy-related factor; CIR, cartilage injury-related; CXCR4, C-X-C chemokine receptor-4; DANCER, differentiation antagonizing non-protein coding RNA; DNM3OS, dynamin 3 opposite strand; ECM, extracellular matrix; ET1, Erythropoiesis transformation-specific translocation variant 1; FGFR1, fibroblast growth factor receptor 1; FUT2, fucosyltransferase 2; GASS, Growth Arrest-Specific 5; G1T1, G-protein- coupled receptor kinase interacting protein-1; GP1D1L, glycerol-3-phosphate dehydrogenase 1-like; GPR120, G protein-coupled receptor 120; HMGB1, high mobility group protein B1; hMSC, human mesenchymal stem cell; HOTAIR1, HOX antisense intergenic RNA myeloid 1 variant 1; HULC, highly up-regulated in liver cancer; IGFI, insulin-like growth factor-1; JAK1, J- Jun-N terminal kinase 1; LPS, lipopolysaccharide; MALAT1, metastasis associated lung adenocarcinoma transcript 1; MCM3AP1-S1, Minichromosome Maintenance Complex Component 3 Associated Protein Antisense RNA 1; MECS, maternally expressed gene 3; MEG3, maternally expressed gene 3; MEG3, maternally expressed gene 3; MPF21, MAPK-associated protein 2; MEG3, maternally expressed gene 3; MEG3, maternally expressed gene 3; MEG3, maternally expressed gene 3; MEG3, maternally expressed gene 3; MEG3, maternally expressed gene 3; MMP, matrix metalloproteinase; MSCs, mesenchymal stem cells; mSR, mechanical stress; NEAT1, nuclear enriched abundant transcript 1; NF-κB, nuclear factor kappa B; OA, osteoarthritis; OPN, osteoponitin; PART1, prostate androgen-regulated transcript-1; PGRN, progranulin; PI3K, Phosphoinositide 3-kinase; PMS2L2, PMS1 Homolog 2, Mismatch Repair System Component Pseudogene 2; PTEN, phosphatase and tensin homolog; PVT1, plasmacytoma variant translocation 1; SGTB, small glutamine rich tetratricopeptide repeat containing beta; SNHG, small nucleolar RNA host gene; SOX4, SRY-related high-mobility group box 4; SOX5, Sex-determining region Y-box protein 5; STAT3, signal transducer and activator of transcription 3; TCF4, transcription factor 4; TGFB2, Transforming growth factor-beta receptor type 2; THRL, TNF and hnrRNP related immune-regulatory IncRNA; TMSB4, Thymosin 6-4; TUG1, taurine upregulated gene 1; UCA1, urothelial carcinoma associated 1; XIST, X-inactive-specific transcript; YAF2, YY1-Associated factor 2.

FIGURE 1 | Example of altered lncRNA expression patterns and their biological effects in intervertebral disk degeneration. lncRNA, long non-coding RNA; ECM, extracellular matrix; MMP, matrix metalloproteinase; MAPK, mitogen-activated protein kinase; SMAD3, SMAD family member 3; LEF1, lymphoid enhancing factor-1; CCND1, cyclin D1; ADAMTS4, a disintegrin and metalloproteinase with thrombospondin motifs 4; TRAF6, tumor necrosis factor receptor-associated factor 6; Notch1, Notch Receptor 1; Bcl-2, B cell lymphoma 2; ATG5, autophagy-related gene 5.

the levels of miR-93 were lower (Gao et al., 2020). Through dual-luciferase reporter assay, they proved that PART1 acts as miR-93 sponge in NP tissues and cells to suppress the expression of miR-93 and to further regulate MMP2. Zheng et al. (2020) showed that MALAT1 was reduced in NP cells, and upregulation of MALAT1 could relieve cell proliferation and apoptosis in vitro and inhibit the degree of INN in vivo. Moreover, they found that MALAT1 plays pivotal roles in IDD through sponging miR-503, and thereby modulate downstream MAPK signaling pathways.
Several studies indicated that IncRNAs plays roles in IDD by modulating miRNA and their target genes. Wang et al. (2018b) showed that the level of IncRNA-RMRP in degenerated NP tissues was higher than that in normal NP tissues, whereas the expression of miR-206 was lower. They indicated that IncRNA-RMRP could promote cell proliferation via modulating miR-206, thereby regulating downstream target gene MMP13 and ADAMTS4. IncRNA HOTAIR was downregulated in NP tissues and cells, whereas miR-34a expression was negatively correlated with HOTAIR and the expression of Bcl-2 was positively connected with HOTAIR (Yu et al., 2018). HOTAIR could inhibit NP cell apoptosis through regulating miR-34a/Bcl-2 axis. A study found that LINCO0958 and mRNA SMAD3 were upregulated in NP tissues, whereas miR-203 was downregulated. Ectopic expression of miR-203 could suppress cell growth and ECM degradation (Zhao et al., 2019). Therefore, LINCO0958 participates in the cell process by regulating miR-203 and SMAD3. Another study reported that the expression levels of LINCO1121 and MMP-16 significantly increased in NP cells, whereas the level of miR-150-5p decreased (Chen X. et al., 2020). They demonstrated that LINCO1121 could enhance the cell process of IDD, such as cell growth, ECM degradation and inflammation by regulating miR-150-5p and MMP-16.

Rheumatoid Arthritis
In RA disease, the most studied mechanism of IncRNA and miRNA is that IncRNA acts as the miRNA sponge to modulate downstream genes (Table 2). IncRNA PVT1 (plasmacytoma variant translocation 1) and SCUBE2 (signal peptide-CUB-EGF-like containing protein 2) were upregulated, whereas miR-543 was downregulated in synovial tissues of RA rats and patients (Wang et al., 2020). Wang et al. (2020) found that the overexpression of PVT1 or the suppression of miR-543 elevated the level of SCUBE2. Moreover, the knockdown of PVT1 could suppress proliferation and induce apoptosis of RA through hindering the expression of SCUBE2 by sponging miR-543 (Wang et al., 2020). IncRNA LINC-PINT (long intergenic non-protein encoding long-chain RNA p53-induced transcript) was reduced in RA tissues and cells (Wang and Zhao, 2020). Through bioinformatics techniques and RNA Binding Protein Immunoprecipitation (RIP) assay, they found that miR-155-5p could interact with LINC-PINT, and SOCS1 was the target mRNA of miR-155-5p. LINC-PINT could inhibit cell proliferation and invasion via sponging miR-155-5p and regulating the level of SOCS1. Yan et al. (2019) revealed that the level of IncRNA HIX003209 in the peripheral blood mononuclear cells (PBMCs) and macrophages of RA samples and the expression of TLR4 was positively correlated with HIX003209. IncRNA HIX003209 directly targeted miR-6089 and was involved in the regulation of inflammation through acting as miR-6089 sponge via the TLR4/NF-κB signaling pathway.

Ankylosing Spondylitis
That IncRNA acts as the sponge of miRNA to modulate target genes is the most studied mechanism of IncRNA and miRNA acting on AS (Table 2). Li Y. et al. (2020) reported the role of MEG3 (maternally expressed gene 3) in the inflammation of AS. They observed that the expression level of MEG3 in the serum of AS patients was significantly downregulated compared with that in normal people, and MEG3 could inhibit inflammatory responses. However, the expression of miR-146a was upregulated in the AS patients and miR-146a could directly bind with MEG3 (Li Y. et al., 2020). Li Y. et al. (2020) assumed that MEG3 may played a vital role in the repression of inflammation factors in AS through sponging miR-146a, thereby exploring a novel potential treatment target for AS patients. Zhang et al. (2020f) found that IncRNA H19 was highly expressed in the AS patients and elevated the expression level of IL-17A and IL-23 inflammation factors. H19 could directly modulate miR-22-5p and miR-675-5p, and VDR (vitamin D receptor) was the target miRNAs of these two miRNAs. Among them, the level of miR-22-5p was negatively correlated with H19, while miR-675-5p and VDR was positively with H19 in AS patients. H19 plays regulatory roles in inflammatory reaction in AS through binding with VDR by sponging miR-22-5p and interacting with miR-675-5p (Zhang et al., 2020f).

INTERACTIONS AMONG circRNA, miRNA, AND mRNA IN DEGENERATIVE MUSCULOSKELETAL DISEASES
Osteoarthritis
Circular RNAs acting as miRNA sponges is the one of the most studied mechanisms (Figure 2). Compared with normal cartilage, circRNA-CER (circRNA_100876) was overexpressed and increased with IL-1 (interleukin-1) and TNF-α (tumor necrosis factor-alpha) in OA chondrocytes. circRNA-CER regulated matrix-degrading matrix metalloproteinase (MMP)-13 expression to participated in the process of chondrocyte ECM degradation by sponging miR-136 (Liu et al., 2016b). According to the research of Zhou et al. (2018), overexpressed circRNA_Atp9b sponge miR-138-5p and then mediate ECM catabolism and inflammation to regulates OA progression in chondrocytes by targeting MMP13. circ_0136474 was also verified by the research of Li et al. (2019f) to sponging miR-127-5p to regulate MMP13 in human OA chondrocytes, then, it suppressed cell proliferation and enhanced cell apoptosis during OA progression. The results were in line with those obtained in a study performed by Zhou Z.B. et al. (2019), who found that circRNA_33186/miR-127-5p/MMP13 axis contributes to OA pathogenesis. Furthermore, circSERPINE2 overexpression could slow down the pace of human chondrocytes apoptosis and promote ECM anabolism by sponging miR-1271-5p and thereby targeting ERG (E26 transformation-specific-related gene) to alleviate OA (Shen et al., 2019). In OA blood samples, the downregulation of ciRS-7 and the upregulation of miR-7 were observed (Zhou X. et al., 2019). ciRS-7 was verified to act as a miR-7 sponge to mediate OA progression. Increased circM3 expression in OA cartilage tissue and cells could serve as a sponge of miR-296-5p to slow down the proliferation and differentiation of OA chondrocytes, thus involving in regulating the occurrence
TABLE 2 | lncRNA/miRNA/mRNA networks in rheumatoid arthritis and ankylosing spondylitis.

| Species | Diseases | Region | lncRNA | Change | miRNA | Expression | Target gene | Change | Functions | References |
|---------|----------|--------|--------|--------|--------|------------|-------------|--------|-----------|------------|
| Human   | RA       | Synovial tissues | LINC-PINT | Down | miR-155-5p | Up | SOCS1 | Down | Cell proliferation and invasion | Wang and Zhao, 2020 |
| Human   | AS       | Synovial tissues | IncRNA MEG3 | Down | miR-6089 | Up | TLR4 | Up | Inflammation | Yan et al., 2019 |
| Human   | AS       | Serum, fibroblast-like synovial cells | H19 | Up | miR675-5p/miR22-5p | miR675-5p up; miR22-5p down | VDR | Up | Inflammation | Li Y. et al., 2020f |

AS, ankylosing spondylitis; MEG3, maternally expressed gene 3; PINT, p53-induced transcript; PVT1, plasmacytoma variant translocation 1; RA, rheumatoid arthritis; SCUBE2, signal peptide-CUB-EGF-like containing protein 2; SOCS1, cytokine signaling 1.

FIGURE 2 | Example of altered circRNA expression patterns and their biological effects in osteoarthritis. circRNA, circular RNA; ECM, extracellular matrix; MMP, matrix metallopeptidase; NAMPT, Nicotinamide phosphoribosyltransferase; COX-2, cyclooxygenase-2; IL-6, interleukin-6; Col II, type II collagen; ERG, E26 transformation-specific-related gene; BAX, BCL2 associated X, apoptosis regulator; Bcl-2, B cell lymphoma 2; IGF1R, insulin-like growth factor 1 receptor; HIF, hypoxia inducible factor; BMP, bone morphogenetic protein.

and development of OA chondrocytes (Ni et al., 2020). The overexpression of circRNA-CDR1as regulated OA progression via reducing Col II level but increased IL-6 and MMP13 contents to modulate inflammation and ECM metabolism by sponging miR-641 (Zhang et al., 2020d).

Several circRNA studies showed that circRNAs act as ceRNAs to competitively bind to miRNAs in OA. Hsa_circ_0045714 expression was downregulated (Liu et al., 2016b; Li B.F. et al., 2017). Furthermore, Li B.F. et al. (2017) determined that hsa_circ_0045714 promoted the expression of miR-193b target gene IGF1R (insulin-like growth factor 1 receptor) to regulate chondrocytes proliferation, apoptosis and ECM synthesis. Otherwise, hsa_circ_0005105 expression is significantly enhanced in OA chondrocytes and can promote ECM degradation by mediating the expression of miR-26a target NAMPT (Nicotinamide phosphoribosyltransferase) (Wu et al., 2017). In the lipopolysaccharide (LPS)-induced OA cell model, the expression levels of circRNA-UBE2G1 was significantly increased and bound to miR-373 as ceRNAs to aggravate the OA progression by targeting hypoxia-inducible factor (HIF)-1a (Chen G. et al., 2020).

Intervertebral Disk Degeneration

Over the past years, some circRNAs have merged as molecular drivers to serve as miRNA sponges or ceRNAs in circRNA/miRNA/mRNA networks in the pathogenesis of IDD (Figure 3). Compared with normal NP tissues, circVMA21 (hsa_circ_0091702) was downregulated in NP tissues and NP
cells in IDD and alleviated NP cell apoptosis by targeting miR-200c and XIAP (X linked inhibitor-of-apoptosis protein) (Cheng et al., 2018). Similarly, circ-GRB10 was downregulated during IDD progression, and competitively bound to miR-328-5p to regulate NP cell apoptosis by targeting erb-b2 receptor tyrosine kinase 2 (ERBB2) in the ErbB signaling pathway (Guo et al., 2018). circRNA_104670 was selected via microarray analysis because of its large multiplier expression in IDD tissues (Song et al., 2018). A study reported that circRNA_104670 acted as a ceRNA that binds to miR-17-3p, downregulated circRNA_104670-suppressed MMP-2 expression through circRNA_104670/miR-17-3p/MMP-2 axis, reduced cell apoptosis.
and increased ECM formation. According to another microarray assay made by Wang et al. (2018a), they selected circ-4099 among 72 upregulated circRNAs in degenerated NP tissues for further analysis. They demonstrated that circ-4099 competitively sponged miR-616-5p, which reversed the suppression of Sox9 by miR-616-5p. Wang et al. (2018c) verified that circSEMA4B was downregulated in IDD specimens, and circSEMA4B served as a miR-431 sponge to compete with SFRP1 or GSK-3β. Wang et al. (2018c) verified that circSEMA4B.

further analysis. They demonstrated that circ-4099 competitively sponged miR-616-5p, which reversed the suppression of Sox9 by miR-616-5p. Wang et al. (2018c) verified that circSEMA4B was downregulated in IDD specimens, and circSEMA4B served as a miR-431 sponge to compete with SFRP1 or GSK-3β.

RA was conducted by Yang J. et al. (2020), They reported that circRNA_09505 is upregulated in PBMCs from RA patients and mice. The knockdown of circRNA_09505 inhibits macrophage proliferation and alleviates arthritis and inflammation. miR-6089 functions as a ceRNA that is being competitively sponged by circRNA_09505 to regulated macrophage inflammatory response. Furthermore, circRNA_09505 was detected to promote AKT1 expression, which is a direct target of miR-6089, to mediate 1kBa/NF-κB signaling pathway. To sum up, circRNA_09505 can sponge miR-6089 and regulate inflammation via miR-6089/AKT1/NF-κB axis in arthritis mice model. Combined with RNA-seq data and RT-qPCR validation of PBMCs from RA patients, the results of Ouyang et al. (2017) showed several upregulated circRNAs (circRNA_101873, circRNA_003524, circRNA_104871, and circRNA_103047), and Wen et al. (2020) proved three upregulated hsa-circRNAs (hsa_circ_0001200, hsa_circ_0001566, and hsa_circ_0003972) and one downregulated hsa_circRNAs (hsa_circ_0008360), but without downstream gene detection to establish circRNA/miRNA/mRNA networks.

At present, studies on circRNA and miRNA interaction mechanism on AS are lacking. The roles of circRNAs in AS remain unclear. Only one profiling and bioinformatics analysis showed differentially expressed circRNAs in AS patients (sampled form spinal ligament tissues), reported the presence of 57 upregulated circRNAs and 66 downregulated circRNAs in AS spinal ligament tissues (Kou et al., 2020).

Taken together, the study about the interactions among circRNA, miRNA and mRNA in RA and AS may have a great clinical prospect.

**CONCLUSION AND FUTURE PROSPECT**

Recent advances in gene expression of lncRNAs and circRNAs, coupled with the ability to interact with the miRNA, mRNA or signaling pathway, have started to expose the different molecular consequence associated with RNA transcriptions and the roles they play in the development of MSDDs (including OA, IDD, RA, and AS) that involve chondrocyte proliferation and apoptosis, ECM degradation and PBMCs inflammation. The effects of ncRNA/circRNA-miRNA-mRNA axis on MSDD progression elucidated their contribution to the dynamic cellular processes and provided the potential OA, IDD, RA and AS therapeutic strategies. The altered expression of IncRNAs or circRNAs refers to diverse biological processes of MSDD, thereby indicating that IncRNAs/circRNAs may be developed as biomarkers and therapeutic targets. Despite the large numbers of ncRNAs, including IncRNAs and circRNAs, determined to be differentially expressed during these pathogenic processes, only a small portion of them has been elucidated. Research on MSDD pathogenesis, especially on RA and AS, is still in its infancy and major knowledge gaps remain to be filled. Therefore, the interactions among IncRNA/circRNA, miRNA and mRNA in MSDD to present the potential pathogenesis is required. Further studies are needed to explore the mutual regulatory mechanisms...
between lncRNA/circRNA regulation and effective therapeutic interventions in the pathology of MSDD.

AUTHOR CONTRIBUTIONS

X-QW and P-JC: conceptualization and methodology. J-BG, XS, Y-MC, and ZY: investigation. Y-LZ and GS: writing – original draft preparation and writing – review and editing. All authors contributed to the article and approved the submitted version.

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