Long non-coding RNAs in rheumatology

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Long non-coding RNAs in Rheumatology

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1. Overview

The last decade has seen an enormous increase in long non-coding RNA (lncRNA) research within rheumatology. LncRNAs are arbitrarily classed as non-protein encoding RNA transcripts that exceed 200 nucleotides in length. These transcripts have tissue and cell specific patterns of expression and are implicated in a variety of biological processes. Unsurprisingly, numerous lncRNAs are dysregulated in rheumatoid conditions, correlating with disease activity and cited as potential biomarkers and targets for therapeutic intervention. In this chapter, following an introduction into each condition, we discuss the lncRNAs involved in rheumatoid arthritis, osteoarthritis and systemic lupus erythematosus. These inflammatory joint conditions share several inflammatory signalling pathways and therefore not surprisingly many commonly dysregulated lncRNAs are shared across these conditions. In the interest of translational research only those lncRNAs which are strongly conserved have been addressed. The lncRNAs discussed here have diverse roles in regulating inflammation, proliferation, migration, invasion and apoptosis. Understanding the molecular basis of lncRNA function in rheumatology will be crucial in fully determining the inflammatory mechanisms that drive these conditions.

2. Arthritic Diseases

2.1 Rheumatoid arthritis

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune condition resulting in progressive disability and premature death in older adults.[1] It is a lifelong condition mainly effecting the lining of the synovial joint causing pain, stiffness and swelling in and around the effected joints. Unfortunately, up to 1% of the world's population suffer with this debilitating condition, for which there is no cure. Additionally, with a third of patients unable to work within 2 years of diagnosis, there is a substantial socioeconomic burden. RA affects more women than men, with women having a 3.6% lifetime risk of developing RA compared to 1.7% in men.[2] Although the aetiology is not fully clear, a combination of genetic, environmental and lifestyle factors are all associated with RA. Aside from gender, additional RA risk factors include age with a peak disease onset in the 60s, obesity, diabetes, osteoporosis and smoking.[3]

Following immune activation, inflammation of the synovial membrane (synovitis) is an initial characteristic presentation of RA. Synovial fibroblasts also termed fibroblast-like synoviocytes (FLS), within the synovial joint membrane, become dysfunctional and hyperplastic forming the pannus. The synovial joint is infiltrated with leukocytes, which interact with FLS inundating the synovial fluid with pro-inflammatory factors.[1] Cells of both the innate and adaptive immune system are thought to be central in RA pathogenesis. Monocytes and macrophages are commonly found to infiltrate the synovium with a polarisation towards the pro-inflammatory (M1) versus anti-inflammatory (M2) macrophage.[4] These cells contribute to a sustained chronic

inflammatory state within the joint by releasing pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNFα) and interleukin 6 (IL-6).[5]

The pro-inflammatory microenvironment within the synovial joint results in cartilage degradation and bone loss. Synovial hyperplasia causes elevated matrix metalloproteinases (MMPs) and tissue inhibitors of metalloproteinases (TIMPs), which drive joint destruction.[1] Proteoglycans and extracellular matrix (ECM) binding soluble factors are released from damaged cartilage further activating FLS and resulting in a tumour like transformation.[6] These activated FLS express matrix-degrading enzymes such as MMPs, ADAMTs and cathepsin, and activate signalling pathways that regulate growth and apoptosis.[6] Activated FLS together with pro-inflammatory cytokines with pro-osteogenic effects facilitate the differentiation of infiltrating macrophages into osteoclasts, which result in inflammatory cysts, bone resorption, erosion and loss.[1, 7]

Synovitis, cartilage damage and bone loss are all detected by radiographs, ultrasonography and magnetic resonance imagining (MRI).[7] Another early inflammatory marker detected by MRI is seen in the subchondral bone marrow. Like synovitis, the bone marrow is infiltrated by a host of immune cells including macrophages, T lymphocytes, B lymphocytes and osteoclasts.[8] The resulting inflammation is detected by MRI, presenting as bone marrow edema (BME). BME is correlated with disease severity and joint destruction and may develop independently of synovitis. As such, detection of BME in MRIs has 100% accuracy in predicting rapid

RA onset.[7, 8] The first joints to be affected by synovitis and BME are the symmetrical joints of the hand and feet, with other joints subsequently becoming diseased.[1]

Pro-inflammatory cytokines released by the tissues and cells described above result in dysfunctional intracellular signalling responsible for inflammation, cell survival and apoptosis. Pathways involved in RA include the Janus Kinase/ Signal Transducers and Activators of Transcription (JAK/STAT), the Mitogen-Activated Protein Kinase (MAPK), and the Phosphatidylinositide-3-Kinase/AKT/mammalian Target of Rapamycin (PI3K/AKT/mTOR), all of which have been previously reviewed.[9] Notably, elevated interleukins in synovial fluid activates the JAK/STAT signalling pathway, which results in the transcriptional expression of STAT-responsive genes including IL-6, IL-10, interferon gamma (INFγ), Oncostatin M (OSM) and TNFA, which contributes to ECM degradation and joint degeneration.[9] The MAPK signalling pathway consisting of p38 MAP kinases, extracellular signal-regulated protein kinases (ERKs) and C-Jun-N-terminal kinases (JNKs) is involved in cytokine responses, NF-kB activation, cell survival and apoptosis. Immune cell and synoviocyte proliferation, apoptosis and survival are regulated by the PI3K/AKT/mTOR pathway.[9]

IL-6 has a fundamental immunoregulatory role in RA pathogenesis, regulating inflammatory pathways in immune cells, synoviocytes and osteoclasts. Elevated IL-6 in RA patient synovial fluid correlates with disease activity and joint destruction.[10, 11] IL-6 binds the soluble IL-6 receptor (sIL-6R) in the synovial fluid and couples with gp130 subunit in synoviocytes or directly binds the IL-6R on leukocytes and macrophages, which activates the JAK/STAT and Ras-MAPK pathways. In

synoviocytes this results in hyperplasia and increased IL-6, IL-1 and Toll-like receptors (TLRs), which promotes a perpetual cycle of inflammation, inducing osteoblasts to produce RANKL, leading to osteoclastogenesis, pro-inflammatory cytokine and MMP production and ultimately bone and cartilage destruction.[11, 12] Synoviocyte secreted RANKL binds RANK receptors on activated macrophages activating the NF-kB, MAPK, NFATc1 and Src signalling pathways and promoting bone resorption. Similarly, TNFα is another important cytokine produced by macrophages, which binds TNF receptors (TNFRs) to activate NF-kB, MAPK and protein kinase B (PKB/AKT) inducing inflammation, tissue degeneration and cell proliferation.[11]

2.2 Osteoarthritis

Globally, osteoarthritis (OA) is the most prevalent degenerative joint disorder affecting 303 million people.[13] In the United States, whilst RA effects 1.3 million adults, OA affects 27 million adults, making OA a significant public health challenge.[14] The debilitating condition affects the entire joint causing loss of articular cartilage mass, subchondral bone sclerosis, joint space narrowing and inflamed synovium.[15, 16] The resulting pain and stiffness of the synovial joints leads to progressive disability and reduced quality of life, amounting to a huge socioeconomic burden costing billions. The Global Burden of Diseases, Injuries and Risk Factors Study (2017) found that incidence and prevalence of OA was up by 8-9% since 1990 and that prevalence not only increased with age but was significantly higher in women.[17] Since age is a significant OA risk factor, with an ageing global population coupled with increased life expectancy, OA prevalence is set to keep increasing.[17] Other risk factors include sex (female), obesity, history of joint injury, abnormal loading, diet and genetics.[18] OA in both weight-bearing and non-weight bearing joints has been linked to obesity,

suggesting the impact goes beyond increased biomechanical loading.[16, 19] Adipose tissue is an endocrine organ, which in obesity has increased infiltration of macrophages and secretion of pro-inflammatory cytokines known as adipokines, which are likely to have systemic effects on joint integrity.[16] Additionally, central adiposity is strongly associated with OA in women, particularly affecting the knee and hand joints.[20] Menopausal women in particular are at greater of risk of developing hip, knee and hand OA due to hormonal factors.[18]

Historically, osteoarthritis was considered a 'wear and tear' condition due to ageing. However, it is now known that joint inflammation plays a central role in both the incidence and progression of OA disease. OA pathogenesis involves the degradation of cartilage and remodelling of subchondral bone. This is driven in part by chondrocytes in the articular cartilage that secrete IL-6 into the synovial fluid, where it binds soluble IL-6 receptor (sIL-6R) and couples with membrane bound gp130 on fibroblasts thereby promoting additional FLS IL-6 secretion.[16] This chondrocyte-fibroblast crosstalk is further exacerbated in obese patients with OA, where the adipokine leptin stimulates greater IL-6 secretion from articular chondrocytes.[16] OA chondrocytes also secrete PGE2, MMP3 and MMP13 leading to further articular cartilage degradation.[21] Increased MMPs and aggrecanases ADMATS4 and ADMATS5 contribute to catabolism of integral cartilage matric components including collagen type II resulting in destabilised mechanical properties and structural integrity of both cartilage and bone.[22] Additionally, loading in knee OA increases joint space narrowing resulting in severe mechanical degradation exposing the underlying subchondral bone.[22] OA subchondral bone is hypoxic, which inhibits osteoblast mineralization and bone formation further contributing to joint damage.[23] Synovial

immune cells such as IFNy and TNF producing T-cells and synovial derived macrophages which differentiate into osteoclasts are also thought to induce ostoclastogenesis and bone remodelling.[24]

Similar to RA, synovitis is now more widely recognised to play a significant role in OA joint pathology. Synovitis in OA is evidenced by increased infiltration of activated B- and T- cells and synovial hypertrophy.[25] Cartilage damage is facilitated by the synovium through secreted cytokines, growth factors, matrix metalloproteases and aggrecanases into the synovial fluid.[19, 24] FLS from OA patients are more inflammatory compared to non-diseased patient controls with femoral neck fracture, and interestingly those that are isolated from obese patients with OA have an increased inflammatory phenotype. Inflammatory OA-FLS are also reported to secret greater levels of pro-inflammatory cytokine IL-6 and chemokine CXCL8.[19] Interestingly, transcriptionally distinct FLS subsets are identified in early and late-stage knee OA patients and parapatellar synovitis has been associated with increased pain.[26] Obese OA patients also exhibit a FLS subset with gene signatures related to immune cell regulation and inflammatory signalling.[27]

Many of the major signalling pathways which govern joint inflammation in RA are shared with OA, such as the IL-6 mediated JAK/STAT and Ras/MAPK pathways discussed earlier. Similarly, the NF-kB signalling pathway is described as the master regulator of inflammation and as such regulates pro-inflammatory cytokines including IL-1β, IL-6, IL-17 and TNFα in both OA and RA, as well as aggrecanases and MMPs which induce cartilage degradation in OA.[28, 29] In bone homeostasis, receptor activator

of nuclear factor kappa B (RANK)/ RANKL pathway activates NF-kB induced transcription factors that balance bone resorption and formation which is deregulated in OA. Additionally, an NF-kB transcriptional target is the hypoxia-inducible factor 2 alpha (HIF-2α) which is elevated in hypoxic OA subchondral bone and OA articular cartilage.[29] In OA activated chondrocytes, NF-kB signalling regulates ECM remodelling and the production of catabolic enzymes and pro-inflammatory factors.[30]Additionally, NF-kB mediated signalling in synovial cells may drive synovial/ cartilage crosstalk resulting in cartilage degradation.[31]

Cartilage degradation results in the accumulation of damage-associated molecular patterns (DAMPs) in the synovial joint, which are recognised by pattern recognition receptors (PRRs) such as TLRs in surrounding tissue leading to activation of a localised innate immune response. TLR1-7 and TLR9 are all upregulated in OA synovium, whilst the soluble TLR4 is recognised as an OA severity biomarker in synovial fluid.[32] TLR4 is also expressed by osteoblasts and may be involved in reduced bone mineralisation in OA. Activated TLRs, through the NF-kB-mediated chemokine release, promote macrophage and lymphocyte infiltration into OA synovium. OA damaged articular cartilage and OA chondrocytes express increased levels of TLRs, which stimulate secretion of catabolic factors including IL-6, cyclo-oxygense 2 (COX-2) and MMP13.[25, 32] COX-2 is differentially expressed in OA joints and regulates the arachidonic inflammatory response pathways.[28] In brief, pro-inflammatory cytokines induce COX-2, which catalyses arachidonic acid into an unstable eicosanoid precursor, PGH2. PGH2 is then converted into the major pro-inflammatory and pain mediating prostaglandin PGE2, which is significantly elevated in OA cartilage.[33]

Nitric oxide (NO) and inducible NO synthase (iNOS) are also key mediators of OA cartilage destruction and chondrocyte apoptosis.[25] Both NO and iNOS are elevated in OA cartilage and patient serum. The pathogenic effects of IL-1β and TNFα are mediated by NO activation. However, conversely some reports suggest innate immune suppression in the early stages of OA is NO-associated.[34] In OA, the p38 MAPK pathway mediates pro-inflammatory cytokine signal transduction. DAMPS, IL-1β and TNFα are all involved in p38 phosphorylation, which is detected in OA chondrocytes and OA articular cartilage to drive OA pathogenesis.[25] p38 MAPK in OA chondrocytes selectively activates MAPK-activated protein kinase 2 (MK2), which regulates TNF stability and IL-1β induced production of catabolic factors MMP3, MMP13 and PGE2.[21, 25] Bioinformatics analysis also finds that MAPK signal transduction pathway is influential in OA synovitis.[35] Additionally, the MAPK signalling transduction pathways are utilised by many adipokines to elicit pro- and anti-inflammatory responses. Through MAPK and PI3K pathways, leptin induces naive T-cell proliferation and IL-2 production.[36], whilst the anti-inflammatory adiponectin through binding to adiponectin receptors attenuates IL-6 and TNFα production by affecting p38-MAPK, JNK and NF-kB signalling pathways.[36]

2.3 Long non-coding RNAs in the pathogenesis of arthritis

2.3.1 Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1)

The highly-conserved 8.5kb Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1) was amongst the first cancer-associated lncRNAs to be discovered.[37] MALAT1 is nuclear RNA localized in nuclear speckles along with pre-mRNA splicing

234 factors and thought to regulate alternative splicing by modulating serine/arginine
235 splicing factors.[38] Several cancer studies have identified MALAT1 involvement in
236 molecular signalling pathways including NF-kB, PI3K/AKT, WNT/β-catenin and
237 MAPK/ERK associated with proliferation, apoptosis and inflammation.[28, 39]

238 MALAT1 studies in OA have largely focused on articular cartilage tissue or articular
239 chondrocytes and to a lesser extent in synovium or FLS. However, the expression of
240 MALAT1 is significantly increased in both OA cartilage and synovium tissue, as well
241 as in isolated chondrocytes and FLS. MALAT1 expression was found to increase in
242 response to LPS stimulation in the murine ATDC5 chondrogenic cell line.[40] Pan et al.[40]
243 report protective effects of MALAT1, since overexpression reversed LPS-induced
244 inflammatory injury. LPS induced expression and secretion of apoptotic and pro-
245 inflammatory factors including Bax, caspase 3 and 9, IL-1B, IL-6, IL-8 and TNFα were
246 all suppressed by MALAT1 overexpression. MALAT1 alleviated LPS-induced cell
247 injury through upregulation of miR-19b and suppressing the Wnt/β-catenin and NF-kB
248 pathways.[40] Chondroprotective effects of MALAT1 was also reported in primary rat
249 chondrocytes treated with IL-1β to mimic OA inflammation. Gao et al.[41] report
250 overexpression of MALAT1 promotes proliferation and inhibits apoptosis and ECM
251 degradation through the suppression of the JNK signalling pathway.

252

253 In contrast, MALAT1 is reported to contribute to OA pathogenesis in several patient
254 studies through its actions on chondrocyte proliferation which is likely due to
255 differences in study context than species dependent functionality. Indeed, as reviewed
256 by Arun et al, MALAT1 has numerous context-dependent molecular mechanisms
257 influencing a myriad of physiological conditions.[42] In human OA chondrocytes,
258 MALAT1 can sponge and inhibit miR-127-5p expression leading to increased

osteopontin (OPN) expression and activation of the PI3K/Akt pathway, which in turn results in increased chondrocyte proliferation.[43] Also, MALAT1 competitively binds miR-150-5p, indirectly promoting AKT3 expression and resulting in increased proliferation, ECM degradation and suppressed apoptosis in primary chondrocytes. [44] Similarly, MALAT1 directly binds and inhibits miR-145, which can no longer suppress ADAMTS5 expression thus promoting ECM degradation and reduced cell viability in IL-1β treated primary chondrocytes.[45] Li et al.[46] found through regulation of miR-146a that MALAT1 indirectly activated the PI3K/AKT pathway, regulating proliferation of LPS treated chondrocytes isolated from the Sprague Dawley (SD) rat model. Additionally, siRNA mediated MALAT1 knockdown in human primary OA chondrocytes silenced IL-6, COX-2 and MMP13 and promoted collagen type II expression (COL2A1) suggesting MALAT1 is pro-inflammatory and pro-degradative.[46] These inflammatory mechanisms have also been identified in OA patient FLS. MALAT1 expression is elevated in OA synovial tissue compared to non-OA patient tissue, and even more so in OA patients who are obese. This increase was correlated with pro-inflammatory cytokine levels including IL-6 and CXCL8. Similar to findings in chondrocytes, LNA-Gapmer silencing of MALAT1 in OA-FLS supressed pro-inflammatory cytokine expression and inhibited their proliferation.[19]

Interestingly, in RA, MALAT1 expression is significantly reduced in synovium tissue and in RA-FLS. Furthermore, it is one of six lncRNA down-regulated in RA serum exosomes.[47-50] LncRNA screening following treatment with the dietary anti-oxidant quercetin, identified MALAT1 to be upregulated during quercetin-induced apoptosis in immortalised RA-FLS.[50] MALAT1 knockdown reversed quercetin-induced apoptosis, reduced caspase-3 and caspase-9 expression and activated the PI3K/AKT pathway,

enhancing cell proliferation.[50] Li et al.[48] reported that MALAT1 was fundamental in suppressing the Wnt signalling pathway by recruiting methyltransferases to the promoter of the CTNNB1 gene, which encodes the β-catenin protein. Silencing of MALAT1 to mimic low expression levels in RA-synovial tissue resulted in activation of the Wnt/β-atenin signalling pathway, increased primary RA-FLS proliferation and the secretion of pro-inflammatory cytokines IL-6, IL-10 and TNFα.[48] This in contrast to MALAT1 silencing in OA-FLS where pro-inflammatory factors and proliferation are inhibited.[19] It is evident that MALAT1 has a significant role in inflammation and cell proliferation in both conditions, although the disease specific mechanisms of action and the differences noted here leave much to be considered.

2.3.2 HOX Transcript Antisense RNA (HOTAIR)

HOX transcript antisense RNA (HOTAIR) was discovered in 2007 by Rin et al,[51] as a 2158-nucleotide containing long intergenic non-coding RNA (lincRNA). HOTAIR is expressed from the antisense strand of the HOXC genes located on chromosome 12.[52] This lincRNA is an important epigenetic regulator, which selectively binds components of the PRC2 complex including Suz12 and the histone methyltransferase EZH2.[52, 53] Whilst the 5' region of HOTAIR associates with PRC2 proteins, the 3' domain interacts with the histone demethylase complex LSD1/CoREST/REST.[54]

Recent studies indicate that HOTAIR lncRNA may have a significant role in the pathogenesis of both OA and RA. The differential expression of HOTAIR has been reported in rheumatic conditions particularly in the cartilage tissue of both OA and RA patients. Gain (GOF) and loss (LOF) of function studies find HOTAIR to be involved

in cell proliferation, apoptosis and inflammation. Chen et al,[55] reported an increase in HOTAIR expression in response to LPS induction in C28/I2 chondrocytes, which correlated with elevated pro-inflammatory cytokine profiles of IL-6, IL-8 and TNFα and cell injury. Suppression of HOTAIR reduced cell proliferation, apoptosis and cytokine expression of C28/I2 articular chondrocytes cells.[55] Mechanistically, this study found that inflammatory injury was regulated through HOTAIR mediated down-regulation of miR-17-5p which lead to an increase in ETV1. Through activation of MAPK/c-Jun and NF-kB pathways, ETV1 regulated inflammatory damage and cell injury.[55] More recently, the HOTAIR/ miR-17-5p axis has also been described in primary human chondrocytes isolated from OA patient articular cartilage tissue. Hu et al.,[56] reported increased HOTAIR and reduced miR-17-5p expression in human OA diseased cartilage, which correlated with chondrocyte apoptosis and extracellular matrix (ECM) degradation in C28/I2 chondrocyte cell line. RNA immunoprecipitation assays confirmed HOTAIR could bind miR-17-5p, which resulted in the indirect upregulation of FUT2 protein. Additionally, FUT2 was found to aggravate ECM degradation and chondrocyte apoptosis through the Wnt/B-catenin pathway.[56] Interestingly, in chondrosarcoma SW1353 cells, HOTAIR can directly activate the Wnt/β-catenin pathway through increased H3K27 trimethylation at the promoter of the Wnt inhibitory factor 1 (WIF-1).[57] Other miRNAs that are regulated by HOTAIR in OA include miR-130a-3p and miR-20b.[58, 59] Upregulated HOTAIR expression is reported in knee OA patients with radiographic evidence of articular cartilage degradation.[58] Increased HOTAIR was found to sponge miR-130a-3p in primary knee OA chondrocytes, reducing miR-130a-3p levels and resulting in repressed autophagy and cell growth leading to chondrocyte apoptosis.[58]

In the destabilization of the medial meniscus (DMM) OA mouse model, silencing of HOTAIR reversed cartilage degradation, repressed MMP13 and ADAMTS-5 and activated aggrecan and collagen type II production in cartilage.[59] HOTAIR was identified as a competing endogenous RNA (ceRNA), which sponged miR-20b resulting in the upregulation of PTEN, a negative regulator of the PI3K/AKT signalling pathway.[59] These findings support a previous study where HOTAIR was also found to strongly promote ADAMTS-5 expression in human OA articular chondrocytes. Dou et al.,[60] found overexpression of HOTAIR stabilized ADAMTS-5 mRNA, which could be through miR-20b sponging as described by Chen at el.[59] HOTAIR lncRNA has similar pro-inflammatory functionalities in OA synovium tissue. HOTAIR expression has been significantly noted in the synovial fluid of temporomandibular joint OA (TMJ-OA) patients. This correlated with increased MMP1, MMP3, MMP9 and HOTAIR in rabbit condylar chondrocytes, a temporomandibular OA model.[61] Additionally, in the ACLT rat model of OA, silencing HOTAIR inhibited the Wnt/β-catenin pathway resulting in reduced synovial inflammation.[62]

HOTAIR is also described to a lesser extent in RA. Song et al.[47] isolated RA patient peripheral blood mononuclear cells (PBMCs) and serum exosomes to find HOTAIR expression was increased by four-fold in these patients. However, in RA patient FLS, HOTAIR was significantly decreased by threefold. Lentiviral overexpression of HOTAIR in FLS and osteoclasts significantly reduced activation of MMP2 and MMP13. Song et al.[47] found that LPS-activated monocytic cells actively migrated towards RA serum exosomes containing high levels of HOTAIR. This suggests *in vivo* circulating HOTAIR-containing exosomes may attract and activate macrophages inducing immune responses in RA. More recently, in LPS-stimulated rat chondrocytes

overexpression of HOTAIR suppressed LPS-induced inflammation. HOTAIR was found to directly target and inhibit miR-138-mediated activation of NF-kB signalling *in vivo*, resulting in the suppression of IL-1β and TNFα.[63] Interestingly, in RA studies overexpression of HOTAIR is recognised to be protective, reducing catabolic MMPs and inflammatory cytokines, whilst the opposite is true in OA where HOTAIR expression promotes cartilage degradation. These opposing mechanisms of HOTAIR in OA and RA suggests there may be condition specific mechanisms coordinated by other regulators which are yet to be determined.

2.3.3 Growth Arrest-Specific 5 (GAS5)

The growth arrest-specific 5 (GAS5) gene encodes several non-coding RNAs including a lncRNA. Although the molecular mechanisms are largely unclear, GAS5 is known to regulate apoptosis, proliferation, invasion and metastasis.[64] Interestingly, its secondary structure forms a stem loop that competitively binds and inhibits glucocorticoid receptors, which may be of functional relevance in rheumatic conditions.[65]

GAS5 expression in OA cartilage tissue and chondrocytes is reported to be significantly upregulated.[66, 67] Lentiviral overexpression of GAS5 in primary human OA chondrocytes inhibited autophagic responses whilst activating apoptosis and up-regulating expression of several MMPs.[67] Song et al.[67] identified a mechanism of reciprocal repression between GAS5 and miR-21, where exogenous GAS5 suppressed miR-21 resulting in apoptosis and increased expression of cartilage MMP13. Lentiviral miR-21 injected into mice significantly reduced GAS5 mRNA levels,

DMM-induced cartilage destruction and MMP13 expression. The conditions that regulate this reciprocal inter-regulator repression between GAS5 and miR-21 requires further study. More recently, silencing of GAS5 in primary chondrocytes promoted proliferation, inhibited apoptosis and reduced expression of pro-inflammatory factors IL-6 and TNFA.[68] Double luciferase reporter assays confirmed the regulatory mechanism of GAS5 lay in the suppression of miR-34a and the subsequent upregulation of the apoptotic regulatory protein Bcl-2. In contrast, effects reported in mouse chondrogenic ATDC5 cells found LPS-induced inflammation suppressed GAS5 mRNA levels, which promoted apoptosis.[69] Arguably LPS may promote apoptosis independently of GAS5, however GAS5 overexpression also alleviated LPS-induced inflammation suggesting lncRNA mechanisms may differ between mice and human. Mechanistically, Li et al.[69] found GAS5 positively regulated the KLF2 transcription factor which in turn suppressed the NF-kB and Notch signalling pathways.

In RA, GAS5 is significantly upregulated in peripheral blood but down regulated in RA synovial tissue and primary RA-FLS.[47, 70-72] Profiling of blood samples from RA patients found GAS5 to be one of several lncRNAs to be significantly upregulated in RA blood monocyte cells.[47] Treatment of primary RA-FLS with the cytotoxic, anti-inflammatory antioxidant Tanshinone IIA (Tan IIA) induced apoptosis and significantly up-regulated GAS5 expression. Silencing of GAS5 reversed these effects of Tan IIA by down-regulating the expression of pro-apoptotic caspases 3 and 9 and activating the PI3K/AKT signalling pathway.[70] In RA patient plasma, GAS5 expression was found to be inversely correlated to concentrations of IL-18, a pro-inflammatory cytokine known to contribute to RA pathogenesis.[71] Overexpression of GAS5 in primary FLS

was found to downregulate IL-18 expression and promote apoptosis. Anti-inflammatory effects of GAS5 in RA were echoed in reports that found the GAS5 promoter to be hypermethylated in RA synovial tissue and patient RA-FLS.[72] GAS5 promoter methylation was inhibited with 5-aza-2-deoxycytidine which increased the expression of GAS5 and decreased the expression of the apoptotic regulator HIPK2 and pro-inflammatory cytokines TNFA and IL-6. Collectively, these multiple studies suggest GAS5 has a significant role in regulating apoptosis and inflammation in both RA and OA.

2.3.4 H19 imprinted maternally expressed transcript (H19)

The highly evolutionary conserved H19 gene is an imprinted gene which encodes a 2.3kb lncRNA. H19 is known for its tumour suppressive effects in cancer where it is associated with cell viability, migration and invasion.[73] Upregulated H19 expression is observed in RA synovial tissue and OA cartilage. Microarray analysis of OA cartilage found H19 was one of 21 up-regulated lncRNAs.[66] Steck et al.[74] found H19 was induced under hypoxic conditions in primary OA chondrocytes and was silenced when stimulated with pro-inflammatory cytokines IL-1β and TNFα. In the human chondrogenic cell line C28/I2, elevated H19 was found to sponge miR-130a resulting in LPS-induced apoptosis and inflammation.[75] Similarly, elevated H19 in primary human chondrocytes stimulated by IL-1β, inhibited proliferation and induced apoptosis. RNA-immunoprecipitation (RIP) assays confirmed H19 sponging of miR-106a-5p, whose overexpression reversed H19 effects.[76] In HC-A cells, silencing H19 not only facilitated proliferation but also suppressed MMP1 and MMP13 whilst upregulating COL2A1 levels. Yang et al.[77] found H19, through suppression of miR-140-5p, could regulate cartilage degradation and calcification in OA. In contrast, Tan

et al.[78] found primary OA-FLS exosomes containing H19 were responsible for cartilage repair through targeting of miR-106b-5p. They also reported decreased H19 expression in OA cartilage as well as a silencing of H19 in OA chondrocytes in response to IL-1β stimulation.[78] In primary RA-FLS stimulated with IL-1β, H19 was significantly elevated, which was also demonstrated to a lesser extent in primary OA-FLS.[79] Stuhlmuller et al.[79] found H19 expression also responded to serum starvation, TNFα and platlet-derived growth factor-BB (PDGF-BB) stimulation and was significantly higher in RA isolated synovial macrophages. Inhibitor assays showed that H19 RNA expression was under the control of the MAPK/ ERK1-2 signalling pathway. Similarly, pro-inflammatory stimulation of RA-FLS MH7A cell line with TNFα increased H19 expression, increased IL-6, IL-8 and IL-1β production and increased apoptosis.[80] Through LOF and GOF studies it was determined that H19 promoted the phosphorylation of TAK1, a MAP3 kinase known to activate the JNK/p38MAPK and NF-kB pathway in RA resulting in cellular inflammation of RA synovial MH7A cells.

2.3.5 Nuclear Enriched Abundant Transcript 1 (NEAT1)

The Nuclear Enriched Abundant Transcript 1, NEAT1, is found in neighbouring regions of MALAT1 on chromosome 11 and shares several similarities with MALAT1 which was previously known as NEAT2.[53] Like MALAT1, NEAT1 is found mainly localised in the nucleus and is necessary for the formation of the nuclear paraspeckles, which are ribonucleoprotein (RNP) bodies thought to regulate gene expression. NEAT1 lncRNA is fundamental for maintaining the paraspeckle architecture, where it also influences splicing factors. This lncRNA enables the expression of cytokines and antiviral genes including IL-8 by binding to the SFPG (splicing factor proline/glutamine-rich) RNA-

binding protein and sequestering it within the paraspeckles. Removal of SFPG from the IL-8 promoter alleviates repression at this locus allowing IL-8 to be transcribed.[54]

NEAT1 expression in OA cartilage tissue and chondrocytes is upregulated and has been described to regulate several miRNAs. Lui et al.[81] found NEAT1 sponged miR-193-3p activating SOX5, resulting in elevated IL-6, IL-1B, TNFA and IL-8 expression, increased apoptosis and promotion of ECM degradation in primary chondrocytes. Similarly, miR-377-3p was also silenced by NEAT1 sponging in IL-1β stimulated primary chondrocytes resulting in increased inflammation, apoptosis and cartilage degradation through elevated ITGA6 expression.[82] Additionally, NEAT1 was identified as a ceRNA silencer of miR-16-5p. However, in mouse ATDC5 chondrocyte cells, this inhibited apoptosis.[83] Similarly, Wang et al.[84] also report NEAT1 to be anti-apoptotic ceRNA of miR-181a in human chondrocytes suggesting there may be miRNA specific regulatory mechanisms. Interestingly, NEAT1 expression is down-regulated in synovial tissue.[84] In RA, NEAT1 expression is reportedly upregulated in RA blood exosomes, RA PBMCs, and in Th17 cells induced from RA CD4+ T-cells.[47, 85] RA pathogenesis is correlated with elevated levels of pro-inflammatory T-helper cells (Th17s) in PBMCs. Shui et al.[85] found NEAT1 knockdown prevented CD4+ T-cells from differentiating into Th17 cells suggesting NEAT1 is involved in RA development.

2.3.6 X-Inactive Specific Transcript (XIST)

One of the first lncRNAs to be as characterised as many protein-coding transcripts was X-Inactive Specific Transcript (XIST) lncRNA.[86] The X-chromosome consists of numerous immune genes that are silenced through mechanisms of X chromosome inactivation (Xi). Xi is essential for dosage compensation of the X chromosome in

female mammals. LncRNA XIST is fundamental in recruiting the PRC2 complex for chromosome wide silencing through H3K27me3.[87] More recently, XIST has been reported as a microRNA sponge in numerous conditions, although this may very well be a sex-specific regulatory mechanism considering XIST is nearly exclusively expressed in females.[88] Certainly rheumatic conditions are highly prevalent in females possibly due to differential levels of hormones, the ability of women to get pregnant, the health consequences that can manifest as a result of pregnancy and giving birth, as well as the number of X chromosomes present in female cells.[89] Interestingly, Xi-skewing is reported in RA, where three times as many women are affected.[90] Although the functions of XIST lncRNA in RA is poorly defined, YY1 expression and protein levels are elevated. The YY1 transcription factor is fundamental in bridging XIST lncRNA to the inactive X chromosome for silencing. Additionally, inhibition of YY1 reduced IL-6 expression and inflammation in collagen-induced mouse arthritis model.[91]

Reports suggest twice as many women as men develop OA of the knee, although there is little differences in the incidence of OA reported in other joints between males and females. [92, 93] As such, in recent years few mechanistic studies have explored these sex specific effects. However, cartilage tissue, chondrocytes and synovium from OA patients all highly express XIST lncRNA and studies largely report an XIST/miRNA regulatory function.[94] OA pathogenesis is characterised by cartilage degeneration, which involves chondrocyte apoptosis. Through regulation of the chondrocyte apoptosis contributor CXCR4 and downstream MAPK signalling, the XIST/ miR-211 axis was found to regulate proliferation and apoptosis in primary chondrocytes.[95] Similarly, the miR-142-5p/SGTB/XIST axis was described in IL-1β treated SW1353

chondrocytes to impact on cell growth and apoptosis.[96] Although, one study in CHON-001 and ATDC5 chondrocyte cell lines found overexpression of XIST to inhibit apoptosis through the miR-653-5p/SIRT1 axis.[97] XIST could also promote MMP-13 and ADAMTS5 mediated ECM degradation by functioning as a ceRNA of miR-1277-5p. This was validated in the DMM OA rat model, where downregulation of XIST proved to be protective against ECM degradation.[98] Additionally, by sponging of miR-149-5p, XIST was found to enhance DNMT3A expression supressing collagen type II and aggrecan production, inhibiting proliferation and promoting apoptosis of IL-1β treated CHON-001 chondrocyte cell line.[99] Interestingly, collagen degradation in primary OA chondrocytes is reportedly regulated by MMP inhibitor TIMP-3. XIST was found to recruit DNMT1, DNMT3A and DNMT3B to increase TIMP-3 promoter methylation, thereby silencing TIMP-3 and promoting collagen degradation.[100] OA chondrocyte apoptosis is also regulated by M1 macrophages via the XIST/ miR-376c-5p/OPN axis in co-culture studies.[101] XIST was identified as a ceRNA of miR376c-5p, which was essential for silencing osteopontin (OPN) known to regulate pro-inflammatory cytokines within M1 macrophages, which in turn promoted apoptosis in primary chondrocytes.

2.3.7 Maternally Expressed Gene 3 (MEG3)

The maternally expressed gene 3 (MEG3) lncRNA is a chromatin binding transcript known to interact with the PRC2 complex.[102] MEG3 recognises GA-rich DNA regions within promoter regions of common EZH2 target genes. In this way, it functions as a guide lncRNA for PRC2 and binds chromatin through a RNA-DNA triple helix conformation.[102, 103] MEG3 expression is downregulated across cancers and similar observations are also reported in rheumatic conditions. Functionally, MEG3 is involved

530 in apoptosis and proliferation through modulating the TGFβ and Wnt/β-catenin
531 signalling pathways and the regulation of p53.[102]

532

533 MEG3 down regulation is observed in OA cartilage tissue and chondrocytes, although
534 there are some conflicting reports.[104-106] In ATDC5 cells, MEG3 functioned as a ceRNA
535 of miR-203 whose downstream target, SIRT1, could alleviate LPS-induced
536 inflammatory injury through the PI3K/AKT and NF-kB pathways in the absence of
537 MEG3.[107] Interestingly, treatment of rabbit joints with the pain eliminating nerve
538 inhibitor methylene blue elevated MEG3 expression. Here, MEG3 overexpression was
539 found to relieve OA-associated pain through suppression of pro-inflammatory
540 cytokines IL-6, TNFA, IL-1B and IL-8.[108] Overexpressed MEG3 was found to be anti-
541 proliferation and pro-apoptotic through the miR-16/SMAD axis in IL-1β treated SD rat
542 chondrocytes.[105] In line with this, a more recent study, using the same IL-1β treated
543 rat OA chondrocytes, also reported MEG3 to be downregulated. However, here
544 overexpression of MEG3 resulted in increased proliferation, suppressed apoptosis
545 and alleviated ECM degradation. Chen et al.[106] found MEG3 to disrupt the miR-
546 93/TGFBR2 axis thus activating the TGFβ signalling pathway which regulates ECM
547 degradation. Although similar findings have been reported in primary chondrocytes
548 isolated from OA patient tissue. Wang et al.[109] reported MEG3 targeting of miR-
549 361/FOXO1 regulatory axis, which promoted proliferation whilst suppressing
550 apoptosis and ECM degradation. Interestingly, MEG3 is highly expressed in RA
551 synovial tissue and RA-FLS, and *in vivo* studies in SD rats found this overexpression
552 facilitates cell proliferation and inhibited inflammation by downregulating miR-141 and
553 inactivating the AKT/mTOR pathway.[110] However in a contradictory study, primary RA-
554 FLS MEG3 expression was found to be down regulated and further suppression

promoted proliferation and invasion, stimulating the STAT3 and PI3K/AKT pathways.[111] The handful of studies mentioned here utilise various models from primary human FLS to immortalised cell lines as well as several animal models. Lu et al. 2019, cited trauma patients undergoing joint placement as appropriate controls however on average these patients were 10 years younger than the OA patients.[111] Whilst another study failed to describe the designation of 'healthy' control.[110] The many contradictions stipulated here may be attributed to these differences in controls used, studies being underpowered or choice of study model.

2.3.8 HOXA Transcript at the Distal Tip (HOTTIP)

The HOXA transcript at the distal tip (HOTTIP) transcript is a ~3.8 kb lncRNA that is highly expressed across many cancers and is known to regulate the HOXA locus. Through binding of WDR5 protein and recruitment of the histone methyltransferase protein MLL, HOTTIP drives activation of the HOXA genes through H3K4 methylation.[112] Reports also find HOTTIP can enhance IL-6 expression in ovarian cancer tissue through binding of c-jun. Additionally, HOTTIP enhanced IL-6 secretion in ovarian cancer tissue promoted neutrophil induced inhibition of T-cell activity.[113, 114] These findings may also be functionally relevant in RA and OA where HOTTIP expression is similarly increased in RA-FLS, OA cartilage and chondrocytes and patients present with elevated IL-6 levels. HOTTIP has been linked to the progression of OA through suppression of HoxA13 in chondrogenic mouse mesenchymal stem cells (MSC), which modulated integrin-α1 expression and cartilage maintenance.[115] Additionally in human chondrogenic MSC, HOTTIP targets the miR-455-3p/CCL3 pathway in OA inducing cartilage degradation.[116] In primary RA-FLS, HOTTIP is thought to recruit DNA methyltransferase Dnmt3b to silence SFRP1.[117] Through

Dnmt3b HOTTIP could also activate the Wnt signalling pathway leading to inflammation. Overexpression of HOTTIP in the rat adjuvant-induced RA model resulted in synovial tissue hyperplasia, increased infiltration of inflammatory cells and elevated IL-6 and IL-8 production and MMP3 expression.[117]

2.3.9 Plasmacytoma Variant Translocation 1 (PVT1)

Plasmacytoma variant translocation 1 (PVT1) is a highly conserved lncRNA transcribed from a prominent cancer-associated region on chromosome 8. PVT1 is a multifaceted lncRNA whose function includes miRNA regulation, epigenetic coordination involving PRC2, cell cycle modulation as well as numerous other signalling pathways.[118] As in cancerous tissues, PVT1 is upregulated in the rheumatic conditions discussed.[66]

In OA, PVT1 is largely described as a sponging ceRNA facilitating apoptosis, inflammation and cartilage degradation. Overexpression of PVT1 in OA primary chondrocytes induced apoptosis through sponging of miR-488-3p.[119] Through sponging of miR-149, PVT1 mediates cartilage degradation.[120] PVT1 silencing suppressed primary chondrocyte catabolism and inflammation, where IL-1β induced production of IL-6, IL-8 and TNFα and expression of MMP3, MMP9 and MMP13 were all downregulated, whilst production of anabolic factors, collagen type II and aggrecan, were increased. Similarly, the PVT1/miR-27b-3p/TRAF3 axis promoted apoptosis and inflammation in C28/I2 cells, whilst the PVT1/miR-26b/CTGF/TGF-B1 axis enhanced cartilage degradation in primary chondrocytes.[121, 122] Interestingly, PVT1 was also found to induce TNFA expression and secretion through miR-211-3p sponging in TMJ-

OA FLS, which in turn facilitated SW982 chondrocyte apoptosis.[123] Although elevated PVT1 expression was found to promote proliferation in RA-FLS through the miR-543/SCUBE2 axis, knockdown resulted in apoptosis and supressed inflammation suggesting tissue specific mechanisms of action.[124, 125] In RA-FLS isolated from Lewis rats injected with complete Freund's adjuvant, evidence suggests PVT1 facilitated promoter methylation of SIRT6, a stress responsive protein known to supress inflammation and bone destruction in arthritic mice.[125]

2.3.10 Taurine Up-regulated 1 (TUG1)

The 7.6 kb Taurine up-regulated 1 (TUG1) transcript is a fundamental cancer regulatory lncRNA involved in a variety of biological processes. Mechanistically, TUG1 regulates transcriptional activity of target genes through its ability to sponge miRNAs and by interacting with the PRC2 compelx.[126] TUG1 is overexpressed in RA patient PBMCs, RA patient serum exosomes and OA patient cartilage.[47, 127] TUG1 overexpression was found to regulate ECM degradation in OA through the miR-195/MMP-13 axis in primary chondrocytes.[127] Interestingly emodin-induced TUG1 expression in ATDC5 chondrogenic cells attenuated apoptosis and inflammation by inactivating the Notch and NF-kB signalling pathways.[128]

2.3.11 Urothelial Carcinoma-Associated 1 (UCA1)

The urothelial carcinoma-associated 1 (UCA1) lncRNA was initially identified as upregulated in bladder cancer and subsequently across other cancers. UCA1 gene encodes three variants ranging from 1.4kb to 2.7kb although the smallest is the most recognised and well-studied as a miRNA sponge.[129] UCA1 is overexpressed in OA

cartilage tissue and through miR-204-5p/MMP-13 axis, suppresses type II and type IV collagen and promotes C28/I2 chondrocyte cell proliferation and MMP13 expression.[130] In RA-FLS cell line, UCA1 expression is significantly reduced and thought to induce apoptosis through Wnt6 expression modulation although the exact mechanism remains to be described.[131]

2.3.12 Cancer Susceptibility Candidate 2 (CASC2)

The cancer susceptibility candidate 2 (CASC2) lncRNA was first recognised in 2004 as an onco-suppressor in endometrial cancer cells.[132] CASC2 is a ~3.3kb lncRNA with three alternative transcripts but no putative protein. In cancer, CASC2 has been identified to regulate proliferation through epigenetic actions and by influencing miRNAs and other regulatory pathways such as STAT3, PI3K/AKT, NF-kB and MAPK.[133] CASC2 is reportedly upregulated in OA chondrocytes and patient plasma.[134, 135] Upregulated CASC2 promoted HC-OA chondrocyte cell apoptosis but was found to be targeted by miR-93-5p for degradation, which reversed these effects.[134] Overexpression of CASC2 in human CHON-001 cells upregulated IL-17 expression, enhanced apoptosis and suppressed cell proliferation.[135] Whilst in OA chondrocytes CASC2 and IL17 expression were positively correlated, in RA patient plasma CASC2 expression was downregulated whilst IL-17 was upregulated.[136] Additionally, in primary RA-FLS, overexpression of CASC2 suppressed IL-17 which promoted apoptosis. These results suggest CASC2 may have disease and tissue specific regulatory mechanisms, which require further investigation.

2.3.13 Antisense Non-coding RNA in the INK4 Locus (ANRIL)

ANRIL is the antisense non-coding RNA in the INK4 locus on chromosome 9 whose transcript is ~38kb in length.[137] ANRIL epigenetically regulates gene expression by forming a RNP complex with polycomb repressive complexes that regulate mono- and tri-methylation of H3K27.[138, 139] ANRIL is known to regulate many biological processes including proliferation and apoptosis. In OA cartilage, ANRIL expression is significantly elevated and downregulation with siRNAs in primary OA-FLS results in cell cycle arrest at GO/G1, inhibited proliferation and enhanced apoptosis.[140] ANRIL is able to sponge miR-122-5p resulting in increased DUSP4 expression and the subsequent regulation of proliferation and apoptosis.[140] In RA, there are few functional studies of note although in RA patient PBMCs ANRIL expression is reportedly decreased.[47, 141] Interestingly the ANRIL/miR-125a axis has been shown to exacerbate disease severity and inflammation in bronchial asthma, which could be functionally relevant in RA and SLE where miR-125a expression is similarly downregulated.[142]

2.3.14 LncRNA Downregulated in Liver Cancer (Lnc-DILC)

The lncRNA downregulated in liver cancer stem cells (lnc-DILC) mediates crosstalk between TNFA/NF-kB signalling and IL-6/STAT3 cascade.[143] Lnc-DILC binding sites were also confirmed at the IL-6 promoter in liver cancer stem cells which through lnc-DILC binding blocks IL-6 expression.[143, 144] In both OA and RA patient plasma the lnc-DILC expression is low whilst IL-6 is elevated.[145] In primary RA-FLS, overexpression of lnc-DILC was found to induce apoptosis and supress IL-6 but only at the protein level.[145] Similar overexpression in CHON-001 chondrocytes also inhibited IL-6 production, although had no significant effects on proliferation and apoptosis.[144] In both studies, IL-6 inhibition occurs at the protein rather than mRNA level suggesting lnc-DILC mechanisms effect IL-6 translation. Although the full regulatory mechanisms

are poorly defined in RA and OA, lnc-DILC has great therapeutic potential in reducing IL-6 driven inflammation.

2.3.15 IGHC gamma 1 (IGHCy1)

IGHCgamma1 (IGHCy1) is a lncRNA transcript significantly upregulated in RA clinical samples and positively correlated with erythrocyte sedimentation rate.[146] IGHCy1 is highly expressed in OA patient PBMCs and in PMA-induced THP-1 macrophages activated with LPS.[147] Silencing with siRNA reduced macrophage cell proliferation. IGHCy1 was identified as a ceRNA of miR-6891-3p resulting in increased TLR4 and NF-kB activity which promoted IL-6 and TNFα production.[147]

2.3.16 Long Intergenic ncRNA p21 (lincRNA-p21)

The long intergenic ncRNA p21 (lincRNA-p21) is p53-activated lncRNA that is well characterised in cancer.[148] Modulated by p53, lincRNA-p21 is a transcriptional repressor involved in triggering apoptosis. Studies also report functions involving protein binding and localisation to chromatin, suppression of targeted mRNA translation as well as cis p21 activation regulating cell cycle.[148] LncRNA-p21 is significantly upregulated in OA patient cartilage tissue.[149] Silencing lncRNA-p21 in primary OA chondrocytes increased cell viability and reduced apoptosis which was reversed by miR-451 overexpression. Tang et al.[149] found that lncRNA-p21 sponged miR-451 and in this way promoted chondrocyte apoptosis. In RA whole blood, lincRNA-p21 levels were significantly reduced whilst the NF-kB activator p65 was increased.[150] Spurlock et al.[150] found those patients not treated with methotrexate had even lower levels of lincRNA-p21. Methotrexate was found to induce lincRNA-p21

expression through DNA-protein kinase catalytic subunit and contributed to NF-kB activation in THP-1 monocytes.

2.3.17 Small Nucleolar RNA Host Gene 1 (SNHG1)

The small nucleolar RNA host gene 1 (SNHG1) is an lncRNA transcript that can be alternatively spiced into eight snoRNAs.[151] SNGH1 is largely reported as a ceRNA which sponges miRNAs and contributes to cell proliferation, migration and metastasis in cancer. [152] SNHG1 is downregulated in RA patient serum exosomes and in RA patient PBMCs although the biological significance of this in RA is yet to be determined.[47] However, in an IL-1β-induced OA chondrocyte model cell line, SNHG1 overexpression inhibited catabolic and inflammatory factors MMPs, ADMATs, collagen, aggrecans, IL-6, TNFA, COX-2 and PGE2.[153] SNGH1 was found to sponge miR-16-5p to inhibit ERK1/2, phosphorylated p38 and phosphorylated p65 factors involved in p38/MAPK and NF-kB signalling pathways.

2.3.18 TNF and HNRNPL Related Immunoregulatory LncRNA (THRIL)

The THRIL lncRNA was identified in THP-1 macrophages in an RNP-complex with hnRNPL which bind to and suppressed the TNFA promoter, hence its namesake TNF- and HNRNPL-related immunoregulatory lncRNA.[154] This lncRNA is reported to also regulate IL-8, CSF1, CCL1 and CXCL10 expression. Interestingly, THRIL expression is elevated in RA and OA patients and in preclinical *in vivo* models. Pro-inflammatory roles are reported in an OA model using ATDC5 cells, where THRIL sponges miR-125b activating the JAK1/STAT3 and NF-kB signalling pathways which induced inflammatory cell injury.[155] Increased THRIL expression is also reported in RA patient

T-cells and in primary RA-FLS where THRIL activated the PI3K/AKT signalling pathway modulating cell growth and inflammation.[156, 157]

2.3.19 ZNFX1 Anti-Sense 1 (ZFAS1)

ZNFX1 antisense RNA1 (ZFAS1) is overexpressed in many cancers and hosts three snoRNAs. ZFAS1 is involved in many cancer-associated biological process, which include increased proliferation, migration, invasion and suppressed apoptosis.[158] Similarly in RA, ZFAS1 is reported to promote cell migration and invasion of patient isolated RA-FLS. ZFAS1 is highly expressed in RA synovial tissue as well as in primary RA-FLS and regulates migration and invasion through sponging of miR-27a.[159] In primary OA chondrocytes, ZFAS1 is downregulated, but its overexpression is reported to promote proliferation and cell migration whilst inhibiting apoptosis and matrix synthesis. Mechanistically, ZFAS1 overexpression was found to significantly suppress Wnt3a, β-catenin and p53.[159]

3. Systemic Lupus Erythematosus

Systemic lupus erythematosus (SLE) is another chronic autoimmune disease which leads to inflammation in various parts of the body including the skin causing rashes, internal organs such as the heart, lungs and kidneys as well as painful and swollen lymph nodes and joints.[160] SLE has an estimated prevalence of 80-100 per 100,000 adults with significant phenotypic heterogeneity. It is one of the leading causes of death in women with a female to male ratio of up to 15:1.[161] Women also have an earlier peak in disease onset, usually in their 30s-50s, although males with later onset develop more severe comorbidities such as nephritis.[160] Depending on race and

749 ethnicity, those of Black, South/ East Asian and Hispanic decent have significantly
750 increased SLE prevalence with more sever disease activity.[162] Although the cause of
751 SLE is unknown, studies find that SLE heritability is less than 40%. Additionally,
752 several environmental and lifestyle factors are also heavily associated with SLE
753 including smoking, obesity, alcohol consumption, diet and air pollution.[160]

754

755 The heterogeneity of SLE is such that almost any organ or tissue in the body may be
756 affected with a variety of clinical presentations. In SLE, defective clearance of
757 apoptotic cells and material is central to loss of immune tolerance resulting in the
758 release of nuclear antigens which provoke a cascade of immune responses resulting
759 in auto-reactivity.[163] The pathophysiology is characterised by aberrant immune
760 responses which sustain the production of autoantibodies, driving chronic
761 inflammation.[163] Several effector cells are involved in SLE, including dendritic cells
762 (DCs), T-cells, B-cells, neutrophils, and monocytes. Plasmacytoid dendritic cells
763 (pDC) are activated by neutrophils which undergo a cell death mechanism known as
764 NETosis forming autoantigen containing neutrophil extracellular traps (NETs).[164]
765 These NETs trigger type-1 IFN production by stimulating TLRs on pDCs, which
766 sustains a positive feedback cycle promoting more NETosis, further pDC activation
767 and enhanced type-1 IFN release. Neutrophils in lupus patients have reduced
768 phagocytic activity, are more apoptotic and prone to NETosis which together
769 stimulates immune activation and tissue damage.[164] SLE myeloid DCs (mDCs),
770 activated by pDC, released IFN-α, secrete pro-inflammatory cytokines and activate
771 autoreactive CD8+ T-cells which differentiate into CD4+ T helper cells.[165] Activated
772 pDCs also produce chemokines (CXCL9, CXCL10, CCL3-5), which attract activated
773 T-lymphocytes to sites of inflammation.[165] In SLE, B-cells are influenced by DCs and

T-cells to differentiate and produce autoantibodies as a result of failed tolerance checkpoints.[166]

More than half of SLE patients present with kidney injury which is a significant contributor to SLE morbidity. The kidney is infiltrated by IL-17 producing T-cells and autoantibody producing B-cells which activate the complement system causing kidney inflammation known as nephritis.[167] Other infiltrating immune cells include pDCS, monocytes, macrophages and platelet aggregates, which bind CD40 on pDCs and monocytes stimulating IFN secretion which facilitates NETosis and further renal tissue damage.[163] The complement system also disrupts the blood-brain barrier resulting in neuronal injury, microglial activation and the infiltration of T-cells.[167, 168] Another common presentation in SLE patients is skin lesions and although not deemed life threatening, cutaneous lupus has a significant contribution in propagating autoimmunity. SLE skin biopsies are abundant in IL-17 secreting T-cells and pDCs, which produce large amounts of IFN-α.[167]

SLE shares many of the key inflammatory pathways described in RA and OA including chemokine signalling, T-cell receptor signalling pathway and TLR pathway. As previously mentioned, TLRs, specifically TLR7 and TLR9, trigger type I IFN production in pDCs.[169] TLR signalling stimulates pro-inflammatory cytokine production through MyD88 or IFN-B and IFN-inducible genes which act on the NF-kB and MAPK signalling pathways.[170] The IFN signalling pathway is a prominent feature of SLE, which has a central role in SLE pathophysiology. The IFN system consists of ubiquitously expressed IFNα/β receptors (IFNAR) and IFNy (IFNGR) and IFNλ (IFNLR) receptors

which are bound by type I, II and III IFN subtypes, respectively, that regulate the expression of 200-2000 genes.[169] A network of cells are involved in the production of IFNs, although the most prolific producer of type I IFN are pDCs.[163, 169] IFN can also act on T-cells to modulate activation, proliferation, differentiation and survival as well as on B-cells to regulate migration, survival, cytokine production and antigen recognition and presentation.[171]

T-cells are drawn to sites of inflammation by pDC cytokine production. Pro-inflammatory cytokines such as IL-6, IL-21 and IL-23 activate STAT3, which suppresses IL-2 whilst enhancing transcription of IL-17 and BCL6, which facilitate inflammation and B-cell antibody production.[171] IL-6 can stimulate CD4 T-cells to differentiate into IL-17 producing T-helper cells (Th17). Th17 cells are initiated by IL-21 to produce IL-17 whilst IL-23 maintains sustained expression of IL-17 through the JAK-STAT signalling pathway.[172] SLE T-cells also have elevated serine/threonine protein phosphatase 2A (PP2A), which regulates DNA hypomethylation of IFN-regulated loci by suppressing the ERK/DNMT1 pathway.[171, 173] Notably the IL-17 promoter is hypomethylated whilst IL-2 remains methylated and silenced due to a failure in histone deacetylase 1 (HDAC1) recruitment.[171] IL-17 is thought to be a fundamental driver in local tissue damage in SLE patients. Additionally, in SLE, T-cells, macrophages and monocytes secrete TNFα, which acts through TNFR1 and TNFR2 receptors triggering the caspase cascade associated with apoptosis or the activation of NF-kB, JNK and MAPK pro-inflammatory pathways, respectively.[172]

3.1 Evidence for the role of lncRNAs in the pathogenesis of SLE

Several lncRNAs have been identified through whole transcriptome profiling of SLE patient samples and many differentially expressed lncRNAs have been validated in SLE patient PBMCs.[174-176] One computational study has used co-expression analysis and ceRNA networks to predict biological significance of some lesser known lncRNAs. Wu et al.[177] found co-expression of GAS5, lnc0640 and lnc5150 may modulate the MAPK and PPAR signalling pathways, contributing to SLE pathogenesis. Additionally, GAS5, lnc0640, lnc3643, lnc7074 and lnc6655 were found to bind miRNAs that targeted genes involved in lncRNA-mRNA co-expression networks.[177] These network predictions have yet to be functionally validated in SLE. MIAT lncRNA is also upregulated in SLE patient serums, although mechanisms have not been established in SLE.[178] However, there are some indications in OA ATDC5 cells where MIAT sponges miR-132 leading to activation of NF-kB and JNK pathways and induction of apoptosis and cytokine release, which may also be functionally relevant in SLE.[179] FAS-AS1 is another lncRNA upregulated in SLE where mechanisms are yet to be determined but its expression is correlated with nephritis and positively correlated with anti-dsDNA antibody levels.[180] Fittingly, in primary OA chondrocytes functional studies find silencing of FAS-AS1 inhibits apoptosis and promotes cell proliferation.[181] Many SLE specific lncRNAs have been correlated with clinical markers such as erythrocyte sedimentation rate (ESR), C reactive protein (CRP), antinuclear antibodies (ANA) and falling complement factors C3 and C4.[182-186] Despite identifying these lncRNAs very few have been functionally investigated in SLE to date. Those for which mechanisms have been determined include MALAT1, GAS5, NEAT1, XIST, TUG1, UCA1 and THRIL are all discussed in more detail below.

3.1.1 Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1)

Similarly to arthritis, elevated MALAT1 expression is also reported in peripheral blood monocytes (PBMCs), CD19+ B-cells and CD4+ T-cells of SLE patients.[187, 188] Silencing of MALAT1 in primary human monocytes reduced expression of IL-21, an important cytokine in the pathogenesis of SLE. MALAT1 silencing also suppressed expression of the deacetylase SIRT1.[187] In another study, MALAT1 expression was positively correlated with type I IFN downstream effectors oligoadenylate synthase (OAS) proteins. OAS proteins were differentially expressed in SLE patients with renal disorders (PBMCs: OAS2 and OASL, CD19+ B-cells: OAS3 and OASL, CD4+ T-cells: OAS3) and those with arthritis symptoms (PBMCs and CD19+ B-cells: OAS2 and OAS3, CD4+ T-cells: OAS2). Silencing of MALAT1 repressed all OAS proteins as well as TNFA and IL-1B expression in IFNα-2a treated immune cells. By computation, this study determined that MALAT1 may function as a ceRNA of six miRNAs that all target OAS proteins, although functional validation is required.[188]

3.1.2 Growth Arrest-Specific 5 (GAS5)

In contrast to RA, expression of GAS5 is down regulated in SLE patient plasma.[176, 177, 189, 190] GAS5 was found to be significantly lower in active SLE, which highlighted its potential as a diagnostic marker.[189] LncRNA screening of 240 SLE patients also found GAS5 to be significantly decreased in plasma.[177] GAS5 was one of five proposed lncRNAs that together presented high diagnostic accuracy for SLE. KEGG pathway analysis of mRNAs associated with SLE found MAPK signalling to be enriched, which correlated with GAS5 lncRNA-mRNA co-expression networks as well as ceRNA networks. These predictions together suggest there may be a GAS5/miRNA/MAPK regulatory axis in SLE yet to be characterised. Interestingly, in CD4+ T-cells isolated

from SLE patients, GAS5 expression was significantly elevated and presented as a diagnostic marker for SLE patients with ulceration.[190]

3.1.3 Nuclear Enriched Abundant Transcript 1 (NEAT1)

Whole blood microarrays and qPCR validation find NEAT1 upregulated in SLE patients.[178] Abnormally high levels of NEAT1 lncRNA is also detected in monocytes isolated from SLE patients.[191] Silencing NEAT1 in LPS-induced THP-1 cells down-regulated inflammatory cytokines IL-6, CXCL10 and CCL8. Zhang et al.[191] determined NEAT1 as an early response gene which selectively regulated TLR4-mediated inflammatory genes through the MAPK pathway. Expansion of myeloid-derived suppressor cells (MDSCs) drives SLE pathogenesis. Through co-culture experiments Dong et al.[192] found NEAT1 expression in granulocyte MDSCs induced the secretion of B-cell activating factor (BAFF), which promoted IFN-signalling activation of B-cells. Furthermore, silencing of NEAT1 alleviated lupus symptoms in lupus-prone MRL/lpr mouse model. An additional complication of SLE is kidney inflammation known as lupus nephritis effecting ~60% of patients. Elevated NEAT1 in SLE kidney tissues contributed to inflammatory cell injury, which included elevated IL-1β, IL-6, TNFα and IFN-y production as well as increased apoptosis.[193] Mechanistically, it was determined that NEAT1 sponging of miR-146b allowed increased TRAF6 expression and activation of the NF-kB signalling resulting in accelerated cell injury in human renal mesangial cells.

3.1.4 X-Inactive Specific Transcript (XIST)

There is considerable evidence for the role of XIST in the pathogenesis of SLE. Sex bias strongly drives risk of SLE, with nine times as many woman developing the autoimmune condition.[194] In SLE female patient lymphocytes, XIST localisation patterns are disrupted and the inactive X chromosome becomes partially reactivated leading to the over expression of immunity related genes.[195] In the NZB/W F1 SLE mouse model with female bias, YY1 expression was reduced resulting in poor localisation of XIST lncRNA to the Xi and increased expression of immune regulatory factors TLR7 and CXCR3 in B-cells.[196] Similar disruptions to X-chromosome maintenance is also reported in SLE patient T-cells.[197] Additionally, skewed allelic expression of X-linked genes has also been attributed to high variability of DNA methylation levels in SLE patients, which has been reversed in SLE mouse models by XIST knockdown.[198] Finally, TSIX is the XIST antisense lncRNA which protects the active X chromosome from silencing during X-inactivation of the second X chromosome in females.[199] TSIX inhibits XIST function by complementary binding of XIST forming a double-stranded RNA complex which is targeted for degradation by the endoribonuclease Dicer. Thus, upregulation of TSIX could be therapeutically protective against the Xi skewing reported in SLE and in tackling cartilage degradation and inflammation in OA as previously described. Intriguingly, the expression levels of TSIX has also been reported to be significantly higher in SLE patients compared to healthy donors and found to be highly expressed in female SLE patients compared with males which may be a protective response against elevated XIST.[174] Although the ratio of XIST to TSIX expression levels in SLE has not been determined. As such endogenous TSIX levels may not be sufficient to reverse the effects of XIST which is also known to act locally to repress TSIX on both inactive and active X-chromosomes.[200]

3.1.5 Taurine Up-regulated 1 (TUG1)

TUG1 expression is significantly reduced in SLE patient whole blood and may be a clinically relevant biomarker.[201] Xu et al.[201] determined the protective effects of TUG1 in HK-2 renal tubular epithelial cells, to understand lupus nephritis in SLE patients. Overexpression of TUG1 targeted the miR-223/SIRT1 axis activating the PI3K/AKT signalling whilst suppressing NF-kB pathway, increasing cell viability and supressing inflammation.[202] With SLE mice, inhibition of the NF-kB signalling pathway with PDTC drug mitigated SLE progression and resulted in the up-regulation of TUG1 lncRNA expression.[203]

3.1.6 Urothelial Carcinoma-Associated 1 (UCA1)

UCA1 levels in SLE patient plasma was significantly increased along with AKT, particularly in females.[204] Jiang and Li found high UCA1 expression correlated with those patients with evidence of organ involvement suggesting UCA1 could be a biomarker for stratifying SLE patients to distinguish those with and without organ involvement. Gain of function investigations found that UCA1 overexpression increased cell proliferation through activation of the PI3K/AKT pathway.[204]

3.1.7 TNF and HNRNPL Related Immunoregulatory LncRNA (THRIL)

THRIL expression is elevated in SLE patients and preclinical models. THRIL overexpression in LPS-induced HK2, a SLE model, increased apoptosis and the expression of pro-inflammatory cytokines IL-1B, IL-6, IL-8 and TNFA. THRIL was identified as a ceRNA of miR-34a which targeted MCP-1, thus THRIL activated the

JNK and Wnt/β-catenin signalling pathways which may be crucial in SLE pathogenesis.[205]

4. Conclusions and Perspectives

The evidence of lncRNA mediated roles in rheumatic conditions has been mounting in recent years and researchers are finally uncovering the diagnostic and therapeutic value of lncRNAs. Numerous lncRNAs have now been identified as central regulators of inflammatory pathways that are relevant to chronic inflammatory rheumatological conditions. This chapter illustrates the diverse role of lncRNAs in regulating inflammation, proliferation, migration, invasion and apoptosis in RA, OA and SLE. Unsurprisingly, since inflammatory diseases share several common pathways, studies have identified lncRNAs that are dysregulated across all three conditions. Although there are still gaps in our knowledge, lncRNA functional characterisation has been best explored in RA and OA and to a lesser extent in SLE, where lncRNAs are still a nascent field. However as inflammatory pathways are shared between conditions it is likely that there will be shared lncRNA functionality amongst respective conditions. These findings will not only add to our understanding of the dysregulation in chronic disease and the involvement of commonly dysregulated pathways, but will also be insightful in identifying therapeutic interventions and at-risk patient populations across these rheumatological conditions.

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LncRNA	Expression (Up '+' /Down '-')	Model	Function	Ref.
MALAT1	+	Human primary FLS	Knockdown reduces expression and protein secretion of CXCL8 and IL6 and inhibits the proliferation of FLS	19
	+	Mouse chondrocyte cell line	Upregulates miR-19b suppressing Wnt/β-catenin and NF-kB pathways and pro-inflammatory factors IL-1β, IL-6, IL-8 and TNFα	40
	+	Rat primary chondrocytes	Prevents activation of JNK signalling pathway supressing IL-1β-induced chondrocyte inflammation, apoptosis and extracellular matrix degradation	41
	+	Human primary chondrocytes	Acts as a molecular sponge to inhibit miR-127-5p, activating the PI3K/Akt pathway and increasing osteopontin (OPN) expression resulting in increased chondrocyte proliferation	43
	+	Human primary chondrocytes	Competitively binds miR-150-5p and indirectly promotes AKT3 expression resulting in increased proliferation, ECM degradation and suppressed apoptosis	44
	+	Human primary chondrocytes	Acts as a molecular sponge to inhibit miR-145, which can no longer suppress ADAMTS5 thus promoting ECM degradation and reduced cell viability	45
	+	Rat primary chondrocytes	Regulates miR-146a which activates the PI3K/AKT pathway, regulating proliferation and expression of IL-6, COX-2 and MMP13 and COL2A1	46
HOTAIR	+	Human chondrocyte cell line	Inhibits miR-17-5p mediated suppression of ETV1 which elevates pro-inflammatory cytokines IL-6, IL-8 and TNFα through activation of MAPK/c-Jun and NF-kB pathways	55
	+	Human primary chondrocytes	Sponging of miR-17-5p upregulates FUT2 increasing ECM degradation and apoptosis through the Wnt/β-catenin pathway	56
	+	Human chondrocyte cell line	Directly activates the Wnt/β-catenin pathway through increased H3K27 trimethylation at the promoter of the Wnt inhibitory factor 1	57
	+	Human primary chondrocytes	Sponges miR-130a-3p reducing miR-130a-3p levels resulting in repressed autophagy and cell growth leading to chondrocyte apoptosis	58

	+	Mouse primary chondrocytes	By sponging miR-20b upregulates PTEN, a negative regulator of the PI3K/AKT signalling pathway causing ECM degradation and chondrocyte apoptosis	59
	+	Human chondrocyte cell line	Stabilizes ADAMTS-5 mRNA through miR-20b sponging in chondrocytes	60
	+	Rabbit primary chondrocytes	Knockdown reverses IL-1β-stimulated expressions of MMP1, MMP3 and MMP9 and significantly decrease apoptosis	61
	+	Rat primary synoviocytes	Silencing inhibits Wnt/β-catenin pathway and reduced inflammation and promoted synoviocytes apoptosis	62
	+	Human primary chondrocytes	Exogenous GAS5 suppresses miR-21 resulting in apoptosis and increased expression of cartilage MMP13 whilst lentiviral miR-21 represses GAS5, MMP13 and cartilage destruction	67
GAS5	+	Human primary chondrocytes	Suppresses miR-34a upregulating apoptotic regulatory protein Bcl-2 increasing apoptosis and expression of pro-inflammatory factors IL-6 and TNFA.	68
	-	Mouse chondrocyte cell line	Positively regulates KLF2 which suppresses the NF-kB and Notch signalling pathway alleviating LPS-induced inflammation	69
	+	Human primary chondrocytes	Induced under hypoxic conditions and silenced when stimulated with pro-inflammatory cytokines IL-1β and TNFα	74
		Human chondrocyte cell line	Found to sponge miR-130a resulting in LPS-induced apoptosis and inflammation	75
H19	+	Human primary chondrocytes	Increased H19 stimulated by IL-1β, inhibits proliferation and induces apoptosis through sponging of miR-106a-5p	76
	+	Human chondrocyte cell line	Suppresses miR-140-5p to regulate cartilage degradation and calcification, increasing MMP1 and MMP13	77
	-	Rat primary FLS and chondrocytes	FLS exosomes containing H19 were responsible for cartilage repair through targeting of miR-106b-5p	78
	+	Human primary chondrocytes	Sponges miR-193-3p activating SOX5, resulting in elevated IL-6, IL-1B, TNFA and IL-8 expression, increased apoptosis and ECM degradation	81
NEAT1	+	Human primary chondrocytes	miR-377-3p sponging by NEAT1 in IL-1β stimulates chondrocytes, increases inflammation, apoptosis and cartilage degradation through elevated ITGA6 expression	82
	+	Mouse and Human	A ceRNA silencer of miR-16-5p inhibits apoptosis whilst reducing expression of	83

		chondrocyte cell line	NEAT1 increased apoptosis and inflammatory cytokines	
	-	Human primary chondrocytes	Anti-apoptotic and inflammatory ceRNA of miR-181a which regulates GPD1L	84
	+	Human primary chondrocytes	Regulates CXCR4 and downstream MAPK signalling to regulate proliferation and apoptosis through the XIST/ miR-211 axis	95
	+	Human chondrocyte cell line	miR-142-5p/SGTB/XIST axis described to impact on cell growth and apoptosis resulting in increased MMP13 and Bax and suppressed Bcl-2	96
	-	Human and Mouse chondrocyte cell lines	Overexpression inhibits apoptosis through the miR-653-5p/SIRT1 axis	97
	+	Human primary chondrocytes	Promotes MMP-13 and ADAMTS5 mediated ECM degradation by functioning as a ceRNA of miR-1277-5p.	98
XIST	+	Human chondrocyte cell line	By sponging miR-149-5p, XIST enhanced DNMT3A expression supressing collagen type II and aggrecan production, inhibiting proliferation and promoting apoptosis	99
	+	Human primary chondrocytes	Recruits DNMT1, DNMT3A and DNMT3B to increase TIMP-3 promoter methylation, thereby silencing TIMP-3 and promoting collagen degradation	100
	+	Human primary chondrocytes	A ceRNA of miR376c-5p, which is essential for silencing osteopontin known to regulate pro-inflammatory cytokines within M1 macrophages, which in turn promotes chondrocyte apoptosis	101
	-	Rat primary chondrocytes	Overexpression is anti-proliferation and pro-apoptotic through the miR-16/SMAD axis	105
	-	Rat primary chondrocytes	Disrupts the miR-93/TGFBR2 axis activating the TGFβ signalling pathway which regulates ECM degradation	106
MEG3	-	Mouse chondrocyte cell line	A ceRNA of miR-203 whose downstream target, SIRT1, alleviates LPS-induced inflammatory injury through the PI3K/AKT and NF-kB pathways in the absence of MEG3	107
	-	Rabbit and Human chondrocyte cell line	Overexpression relieves OA-associated pain through suppression of pro-inflammatory cytokines IL-6, TNFA, IL-1B and IL-8	108
	-	Human primary chondrocytes	Targets the miR-361/FOXO1 regulatory axis, which promotes proliferation whilst suppressing apoptosis and ECM degradation	109

HOTIP	+	Mouse primary chondrocytes	Suppresses HoxA13 which regulates integrin-α1 expression and cartilage maintenance	115
	+	Human primary chondrocytes	HOTTIP targets the miR-455-3p/CCL3 pathway in OA inducing cartilage degradation	116
PVT1	+	Human primary chondrocytes	Overexpression of induces apoptosis through sponging of miR-488-3p	119
	+	Human primary chondrocytes	Silenced IL-1β induced secretion of IL-6, IL-8 and TNFα and expression of MMP3, MMP9 and MMP13 through sponging of miR-149	120
	+	Human chondrocyte cell line	Knockdown inhibits apoptosis and inflammatory response to IL-1β treatment via up-regulated miR-27b-3p targeting TRAF3	121
	+	Human primary chondrocytes	Sponging of miR-26b facilitates CTGF expression enhanced cartilage degradation and increases TGF-β1, SMAD3, and MMP-13	122
	+	Human chondrocyte cell line	Induces TNFA expression and secretion through miR-211-3p sponging facilitating apoptosis	123
TUG1	+	Human primary chondrocytes	Overexpression regulates ECM degradation through the miR-195 suppression and increased MMP-13 expression	127
	+	Mouse chondrocyte cell line	Upregulation attenuated apoptosis and inflammation by inactivating the Notch and NF-kB signalling pathways	128
UCA1	+	Human chondrocyte cell line	Regulates cell survival and matrix synthesis by suppressing the miR-204-5p expression and increasing MMP-13 expression	130
CASC2	+	Human chondrocyte cell line	Upregulation promotes apoptosis but is targeted by miR-93-5p for degradation which reverses these effects	134
	+	Human chondrocyte cell line	Overexpression upregulates IL-17 expression, enhances apoptosis and suppresses cell proliferation	135
ANRIL	+	Human primary FLS	By sponging miR-122-5p increases DUSP4 expression and regulates proliferation and apoptosis	140
Lnc-DILC	-	Human chondrocyte cell line	Overexpression supresses IL-6 at the protein level	144
IGHCy1	+	Human THP-1 cell line	ceRNA of miR-6891-3p resulting in increased TLR4 and NF-kB activity promoting IL-6 and TNFα production	147
lincRNA-p21	+	Human primary chondrocyte	Sponges and represses miR-451 promoting the apoptosis	149

SNHG1		Human chondrocyte cell line	Acts as a molecular sponge of miR-16-5p to inhibit ERK1/2 and phosphorylated p38 and p65 involved in p38/MAPK and NF-kB signalling pathways	153
THRIL	+	Mouse chondrocyte cell line	Overexpression promotes LPS-induced inflammatory injury by supressing miR-125b thus activating JAK1/STAT3 and NF-kB pathways.	155
ZFAS1	-	Human primary chondrocytes	Overexpression promotes proliferation and cell migration whilst inhibiting apoptosis and matrix synthesis through suppression of Wnt3a, β-catenin and p53	159
MIAT		Mouse chondrocyte cell line	Silencing attenuates LPS-induced apoptosis and cytokines release by regulating miR-132 expression which inhibits NF-kB and JNK pathways	179
FAS-AS1	+	Human primary chondrocytes	Low expression decreases expression of MMP1 and MMP13, but increases COL2A1 expression, inhibiting cell apoptosis and promote cell proliferation	181

Table 2. Summary of functional lncRNAs in Rheumatoid Arthritis

LncRNA	Expression (Up '+' /Down '-')	Model	Function	Ref.
MALAT1	-	Human primary FLS	Silencing stimulates β-catenin nucleation, secretion of pro-inflammatory cytokines IL-1, IL-10, and TNFα, elevated proliferation and suppressed apoptosis of FLS	48
	-	Human FLS cell line	Knockdown reversed quercetin-induced apoptosis, reduced caspase-3 and caspase-9 expression and activated the PI3K/AKT pathway, enhancing cell proliferation	50
HOTAIR	+	Human whole blood	HOTAIR-containing exosomes attract and activate macrophages inducing immune responses suppressing activation of MMP2 and MMP13	47
	-	Human primary chondrocytes	Targets and inhibits miR-138-mediated activation of NF-kB signalling in vivo, resulting in increased cell proliferation and suppressed IL-1β and TNFα	63
GAS5	-	Human primary FLS	Silencing reversed Tan IIA effects by down-regulating expression of pro-apoptotic caspases 3 and 9 and activating the PI3K/AKT pathway	70
	-	Human primary FLS	Overexpression downregulated IL-18 expression and promoted apoptosis	71
	-	Human primary FLS	Inhibiting GAS5 promoter methylation increased GAS5 expression supressing apoptotic regulator HIPK2 and pro-inflammatory cytokines TNFA and IL-6	72
H19	+	Human primary FLS and macrophages	Expression responds to serum starvation, IL-1β, TNFα and PDGF-BB stimulation and is regulated by the MAPK/ ERK1-2 signalling pathway	79
	+	Human FLS cell line	Promotes phosphorylation of TAK1, a MAP3 kinase known to activate the JNK/p38MAPK and NF-kB pathway, resulting in increased IL-6, IL-8 and IL-1β production and increased apoptosis	80
NEAT1	+	Human whole blood	Knockdown prevents CD4+ T-cells from differentiating into pro-inflammatory Th17 cells correlated with RA pathogenesis	85
MEG3	-	Human primary FLS	Suppression promotes proliferation, secretion of inflammatory cytokines IL-6 and IL-8 and invasion, stimulating the STAT3 and PI3K/AKT pathways	111
	-	Human primary chondrocytes and FLS	Overexpression facilitates cell proliferation and inhibited inflammation by downregulating miR-141 and inactivating the AKT/mTOR pathway	110
HOTIP	+	Human primary FLS	Recruits Dnmt3b to facilitate SFRP1 promoter methylation which activates the Wnt signalling pathway,	117

			proliferation, invasion, and migration, while supressing apoptosis	
PVT1	+	Human FLS cell line	Promotes proliferation through the miR-543/SCUBE2 axis whilst PVT1 knockdown results in apoptosis and supressed inflammation	124
	+	Rat primary FLS	Knockdown restores sirt6 expression through decreasing sirt6 methylation thereby alleviating RA	125
UCA1	-	Human FLS cell line	Regulates expression of Wnt6 and induces apoptosis	131
CASC2	-	Human primary FLS	Overexpression suppresses IL-17 which promotes apoptosis	136
Lnc-DILC	-	Human primary FLS	Overexpression induces apoptosis and supresses IL-6 at the protein level	145
lincRNA-p21	-	Human THP-1 cell line	Induced by methotrexate through DNA-protein kinase catalytic subunit dependent mechanisms contributing to NF-kB activation	150
THRIL	+	Human primary FLS	Regulates cell growth and inflammatory response by activating the PI3K/AKT signalling pathway	157
ZFAS1	+	Human primary FLS	Promotes cell migration and invasion through sponging of miR-27a	159

Table 3. Summary of lncRNAs in Systemic Lupus Erythematosus

LncRNA	Expression (Up '+' /Down '-')	Model	Function	Ref.
FAS-AS1	+	Human whole blood	Expression is correlated with nephritis and positively correlated with anti-dsDNA antibody levels	180
MALAT1	+	Human whole blood	Silencing reduced expression of IL-21 and SIRT1	187
	+	Human whole blood	Silencing represses all OAS proteins as well as TNFA and IL-1B expression in IFNα-2a treated immune cells. May function as a ceRNA of six miRNAs which target OAS proteins	188
GAS5	-	Human whole blood	co-expression of GAS5, lnc0640 and lnc5150 may modulate the MAPK and PPAR signalling pathways	177
	+	Human whole blood	Elevated in CD4+ T cells of patients with SLE may serve as potential biomarker for diagnosis	190
		Human whole blood	upregulated in SLE patients identified on whole blood microarray and validated in patient samples	178
NEAT1	+	Human whole blood	an early response lncRNA which selectively regulates TLR4-mediated inflammatory genes through the MAPK pathway	191
	+	Human whole blood	Expression in granulocyte MDSCs induces secretion of B-cell activating factor (BAFF), which promoted IFN-signalling activation of B-cells. Silencing alleviates lupus symptoms	192
	+	Human renal cell line	Contributes to inflammatory cell injury, elevated IL-1β, IL-6, TNFα and IFN-y production and increased apoptosis by sponging of miR-146b and increasing TRAF6 expression which activates NF-kB signalling	193
XIST	+	Human whole blood	RNA localization patterns disrupted, evidence of bi-allelic expression and increased transcription of immunity-related genes in SLE lymphocytes	195
	+	Mouse primary B-cells	B cells of late stage SLE NZB/W F1 mice have decreased localization of Xist RNA to the Xi and increased expression of x-linked genes TLR7 and CXCR3	196
	+	Human whole blood	X-chromosome inactivation maintenance is altered in T cells of SLE patients thus X-linked genes are abnormally upregulated	197
	+	Human whole blood	Skewed allelic expression of X-linked genes attributed to high variability of DNA methylation levels which was reversed by XIST knockdown	198

TUG1	-	Human kidney cell line	Overexpression targeted the miR-223/SIRT1 axis activating the PI3K/AKT signalling whilst suppressing NF-kB pathway, increasing cell viability and supressing inflammation	202
	-	Mouse whole kidney	Inhibition of the NF-kB signalling pathway with PDTC drug mitigated SLE progression and resulted in the up-regulation of TUG1 lncRNA	203
UCA1	+	Mouse B-cell cell line	Expression correlated with evidence of active stage and pathological lesions. Overexpression increased B-cell proliferation through activation of the PI3K/AKT pathway	204
THRIL	+	Human kidney cell line	Overexpression increases apoptosis and expression of pro-inflammatory cytokines IL-1B, IL-6, IL-8 and TNFA. Identified as a ceRNA of miR-34a which targets MCP-1 activating the JNK and Wnt/β-catenin signalling pathways	205

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