

## Long non-coding RNAs in rheumatology

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1 **Long non-coding RNAs in**  
2 **Rheumatology**

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17 **1. Overview**

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

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## 41 **2. Arthritic Diseases**

### 42 **2.1 Rheumatoid arthritis**

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

54

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

64 inflammatory state within the joint by releasing pro-inflammatory cytokines, such as  
65 tumour necrosis factor alpha (TNF $\alpha$ ) and interleukin 6 (IL-6).<sup>5</sup>

66

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

78

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

87 RA onset.<sup>7, 8</sup> The first joints to be affected by synovitis and BME are the symmetrical  
88 joints of the hand and feet, with other joints subsequently becoming diseased.<sup>1</sup>

89

90 Pro-inflammatory cytokines released by the tissues and cells described above result  
91 in dysfunctional intracellular signalling responsible for inflammation, cell survival and  
92 apoptosis. Pathways involved in RA include the Janus Kinase/ Signal Transducers  
93 and Activators of Transcription (JAK/STAT), the Mitogen-Activated Protein Kinase  
94 (MAPK), and the Phosphatidylinositide-3-Kinase/AKT/mammalian Target of  
95 Rapamycin (PI3K/AKT/mTOR), all of which have been previously reviewed.<sup>9</sup> Notably,  
96 elevated interleukins in synovial fluid activates the JAK/STAT signalling pathway,  
97 which results in the transcriptional expression of STAT-responsive genes including IL-  
98 6, IL-10, interferon gamma (INF $\gamma$ ), Oncostatin M (OSM) and TNFA, which contributes  
99 to ECM degradation and joint degeneration.<sup>9</sup> The MAPK signalling pathway consisting  
100 of p38 MAP kinases, extracellular signal-regulated protein kinases (ERKs) and C-Jun-  
101 N-terminal kinases (JNKs) is involved in cytokine responses, NF-kB activation, cell  
102 survival and apoptosis. Immune cell and synoviocyte proliferation, apoptosis and  
103 survival are regulated by the PI3K/AKT/mTOR pathway.<sup>9</sup>

104

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

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

120

## 121 **2.2 Osteoarthritis**

122 Globally, osteoarthritis (OA) is the most prevalent degenerative joint disorder affecting  
123 303 million people.<sup>13</sup> In the United States, whilst RA affects 1.3 million adults, OA  
124 affects 27 million adults, making OA a significant public health challenge.<sup>14</sup> The  
125 debilitating condition affects the entire joint causing loss of articular cartilage mass,  
126 subchondral bone sclerosis, joint space narrowing and inflamed synovium.<sup>15, 16</sup> The  
127 resulting pain and stiffness of the synovial joints leads to progressive disability and  
128 reduced quality of life, amounting to a huge socioeconomic burden costing billions.  
129 The Global Burden of Diseases, Injuries and Risk Factors Study (2017) found that  
130 incidence and prevalence of OA was up by 8-9% since 1990 and that prevalence not  
131 only increased with age but was significantly higher in women.<sup>17</sup> Since age is a  
132 significant OA risk factor, with an ageing global population coupled with increased life  
133 expectancy, OA prevalence is set to keep increasing.<sup>17</sup> Other risk factors include sex  
134 (female), obesity, history of joint injury, abnormal loading, diet and genetics.<sup>18</sup> OA in  
135 both weight-bearing and non-weight bearing joints has been linked to obesity,

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

143

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



161 immune cells such as IFN $\gamma$  and TNF producing T-cells and synovial derived  
162 macrophages which differentiate into osteoclasts are also thought to induce  
163 osteoclastogenesis and bone remodelling.<sup>24</sup>

164

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

178

179 Many of the major signalling pathways which govern joint inflammation in RA are  
180 shared with OA, such as the IL-6 mediated JAK/STAT and Ras/MAPK pathways  
181 discussed earlier. Similarly, the NF- $\kappa$ B signalling pathway is described as the master  
182 regulator of inflammation and as such regulates pro-inflammatory cytokines including  
183 IL-1 $\beta$ , IL-6, IL-17 and TNF $\alpha$  in both OA and RA, as well as aggrecanases and MMPs  
184 which induce cartilage degradation in OA.<sup>28, 29</sup> In bone homeostasis, receptor activator

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

193

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

210

211 Nitric oxide (NO) and inducible NO synthase (iNOS) are also key mediators of OA  
212 cartilage destruction and chondrocyte apoptosis.<sup>25</sup> Both NO and iNOS are elevated in  
213 OA cartilage and patient serum. The pathogenic effects of IL-1 $\beta$  and TNF $\alpha$  are  
214 mediated by NO activation. However, conversely some reports suggest innate  
215 immune suppression in the early stages of OA is NO-associated.<sup>34</sup> In OA, the p38  
216 MAPK pathway mediates pro-inflammatory cytokine signal transduction. DAMPS, IL-  
217 1 $\beta$  and TNF $\alpha$  are all involved in p38 phosphorylation, which is detected in OA  
218 chondrocytes and OA articular cartilage to drive OA pathogenesis.<sup>25</sup> p38 MAPK in OA  
219 chondrocytes selectively activates MAPK-activated protein kinase 2 (MK2), which  
220 regulates TNF stability and IL-1 $\beta$  induced production of catabolic factors MMP3,  
221 MMP13 and PGE2.<sup>21, 25</sup> Bioinformatics analysis also finds that MAPK signal  
222 transduction pathway is influential in OA synovitis.<sup>35</sup> Additionally, the MAPK signalling  
223 transduction pathways are utilised by many adipokines to elicit pro- and anti-  
224 inflammatory responses. Through MAPK and PI3K pathways, leptin induces naive T-  
225 cell proliferation and IL-2 production.<sup>36</sup>, whilst the anti-inflammatory adiponectin  
226 through binding to adiponectin receptors attenuates IL-6 and TNF $\alpha$  production by  
227 affecting p38-MAPK, JNK and NF-kB signalling pathways.<sup>36</sup>

228

## 229 **2.3 Long non-coding RNAs in the pathogenesis of arthritis**

### 230 ***2.3.1 Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1)***

231 The highly-conserved 8.5kb Metastasis-Associated Lung Adenocarcinoma Transcript  
232 1 (MALAT1) was amongst the first cancer-associated lncRNAs to be discovered.<sup>37</sup>  
233 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.<sup>38</sup> Several cancer studies have identified MALAT1 involvement in  
236 molecular signalling pathways including NF- $\kappa$ B, PI3K/AKT, WNT/ $\beta$ -catenin and  
237 MAPK/ERK associated with proliferation, apoptosis and inflammation.<sup>28, 39</sup>

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.<sup>40</sup> Pan et al.<sup>40</sup>  
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 TNF $\alpha$  were  
246 all suppressed by MALAT1 overexpression. MALAT1 alleviated LPS-induced cell  
247 injury through upregulation of miR-19b and suppressing the Wnt/ $\beta$ -catenin and NF- $\kappa$ B  
248 pathways.<sup>40</sup> Chondroprotective effects of MALAT1 was also reported in primary rat  
249 chondrocytes treated with IL-1 $\beta$  to mimic OA inflammation. Gao et al.<sup>41</sup> 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.<sup>42</sup> In human OA chondrocytes,  
258 MALAT1 can sponge and inhibit miR-127-5p expression leading to increased

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

277

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

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

294

### 295 **2.3.2 HOX Transcript Antisense RNA (HOTAIR)**

296 HOX transcript antisense RNA (HOTAIR) was discovered in 2007 by Rin et al,<sup>51</sup> as a  
297 2158-nucleotide containing long intergenic non-coding RNA (lincRNA). HOTAIR is  
298 expressed from the antisense strand of the HOXC genes located on chromosome  
299 12.<sup>52</sup> This lincRNA is an important epigenetic regulator, which selectively binds  
300 components of the PRC2 complex including Suz12 and the histone methyltransferase  
301 EZH2.<sup>52, 53</sup> Whilst the 5' region of HOTAIR associates with PRC2 proteins, the 3'  
302 domain interacts with the histone demethylase complex LSD1/CoREST/REST.<sup>54</sup>

303

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

308 in cell proliferation, apoptosis and inflammation. Chen et al,<sup>55</sup> reported an increase in  
309 HOTAIR expression in response to LPS induction in C28/I2 chondrocytes, which  
310 correlated with elevated pro-inflammatory cytokine profiles of IL-6, IL-8 and TNF $\alpha$  and  
311 cell injury. Suppression of HOTAIR reduced cell proliferation, apoptosis and cytokine  
312 expression of C28/I2 articular chondrocytes cells.<sup>55</sup> Mechanistically, this study found  
313 that inflammatory injury was regulated through HOTAIR mediated down-regulation of  
314 miR-17-5p which lead to an increase in ETV1. Through activation of MAPK/c-Jun and  
315 NF-kB pathways, ETV1 regulated inflammatory damage and cell injury.<sup>55</sup> More  
316 recently, the HOTAIR/ miR-17-5p axis has also been described in primary human  
317 chondrocytes isolated from OA patient articular cartilage tissue. Hu et al.,<sup>56</sup> reported  
318 increased HOTAIR and reduced miR-17-5p expression in human OA diseased  
319 cartilage, which correlated with chondrocyte apoptosis and extracellular matrix (ECM)  
320 degradation in C28/I2 chondrocyte cell line. RNA immunoprecipitation assays  
321 confirmed HOTAIR could bind miR-17-5p, which resulted in the indirect upregulation  
322 of FUT2 protein. Additionally, FUT2 was found to aggravate ECM degradation and  
323 chondrocyte apoptosis through the Wnt/B-catenin pathway.<sup>56</sup> Interestingly, in  
324 chondrosarcoma SW1353 cells, HOTAIR can directly activate the Wnt/ $\beta$ -catenin  
325 pathway through increased H3K27 trimethylation at the promoter of the Wnt inhibitory  
326 factor 1 (WIF-1).<sup>57</sup> Other miRNAs that are regulated by HOTAIR in OA include miR-  
327 130a-3p and miR-20b.<sup>58, 59</sup> Upregulated HOTAIR expression is reported in knee OA  
328 patients with radiographic evidence of articular cartilage degradation.<sup>58</sup> Increased  
329 HOTAIR was found to sponge miR-130a-3p in primary knee OA chondrocytes,  
330 reducing miR-130a-3p levels and resulting in repressed autophagy and cell growth  
331 leading to chondrocyte apoptosis.<sup>58</sup>

332

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

348

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



358 overexpression of HOTAIR suppressed LPS-induced inflammation. HOTAIR was  
359 found to directly target and inhibit miR-138-mediated activation of NF- $\kappa$ B signalling *in*  
360 *vivo*, resulting in the suppression of IL-1 $\beta$  and TNF $\alpha$ .<sup>63</sup> Interestingly, in RA studies  
361 overexpression of HOTAIR is recognised to be protective, reducing catabolic MMPs  
362 and inflammatory cytokines, whilst the opposite is true in OA where HOTAIR  
363 expression promotes cartilage degradation. These opposing mechanisms of HOTAIR  
364 in OA and RA suggests there may be condition specific mechanisms coordinated by  
365 other regulators which are yet to be determined.

366

### 367 **2.3.3 Growth Arrest-Specific 5 (GAS5)**

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

374

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

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

396

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

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

415

#### 416 ***2.3.4 H19 imprinted maternally expressed transcript (H19)***

417 The highly evolutionary conserved H19 gene is an imprinted gene which encodes a  
418 2.3kb lncRNA. H19 is known for its tumour suppressive effects in cancer where it is  
419 associated with cell viability, migration and invasion.<sup>73</sup> Upregulated H19 expression is  
420 observed in RA synovial tissue and OA cartilage. Microarray analysis of OA cartilage  
421 found H19 was one of 21 up-regulated lncRNAs.<sup>66</sup> Steck et al.<sup>74</sup> found H19 was  
422 induced under hypoxic conditions in primary OA chondrocytes and was silenced when  
423 stimulated with pro-inflammatory cytokines IL-1 $\beta$  and TNF $\alpha$ . In the human  
424 chondrogenic cell line C28/I2, elevated H19 was found to sponge miR-130a resulting  
425 in LPS-induced apoptosis and inflammation.<sup>75</sup> Similarly, elevated H19 in primary  
426 human chondrocytes stimulated by IL-1 $\beta$ , inhibited proliferation and induced  
427 apoptosis. RNA-immunoprecipitation (RIP) assays confirmed H19 sponging of miR-  
428 106a-5p, whose overexpression reversed H19 effects.<sup>76</sup> In HC-A cells, silencing H19  
429 not only facilitated proliferation but also suppressed MMP1 and MMP13 whilst  
430 upregulating COL2A1 levels. Yang et al.<sup>77</sup> found H19, through suppression of miR-  
431 140-5p, could regulate cartilage degradation and calcification in OA. In contrast, Tan

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

446

#### 447 **2.3.5 Nuclear Enriched Abundant Transcript 1 (NEAT1)**

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

456 binding protein and sequestering it within the paraspeckles. Removal of SFPG from  
457 the IL-8 promoter alleviates repression at this locus allowing IL-8 to be transcribed.<sup>54</sup>  
458 NEAT1 expression in OA cartilage tissue and chondrocytes is upregulated and has  
459 been described to regulate several miRNAs. Lui et al.<sup>81</sup> found NEAT1 sponged miR-  
460 193-3p activating SOX5, resulting in elevated IL-6, IL-1B, TNFA and IL-8 expression,  
461 increased apoptosis and promotion of ECM degradation in primary chondrocytes.  
462 Similarly, miR-377-3p was also silenced by NEAT1 sponging in IL-1 $\beta$  stimulated  
463 primary chondrocytes resulting in increased inflammation, apoptosis and cartilage  
464 degradation through elevated ITGA6 expression.<sup>82</sup> Additionally, NEAT1 was identified  
465 as a ceRNA silencer of miR-16-5p. However, in mouse ATDC5 chondrocyte cells, this  
466 inhibited apoptosis.<sup>83</sup> Similarly, Wang et al.<sup>84</sup> also report NEAT1 to be anti-apoptotic  
467 ceRNA of miR-181a in human chondrocytes suggesting there may be miRNA specific  
468 regulatory mechanisms. Interestingly, NEAT1 expression is down-regulated in  
469 synovial tissue.<sup>84</sup> In RA, NEAT1 expression is reportedly upregulated in RA blood  
470 exosomes, RA PBMCs, and in Th17 cells induced from RA CD4+ T-cells.<sup>47, 85</sup> RA  
471 pathogenesis is correlated with elevated levels of pro-inflammatory T-helper cells  
472 (Th17s) in PBMCs. Shui et al.<sup>85</sup> found NEAT1 knockdown prevented CD4+ T-cells  
473 from differentiating into Th17 cells suggesting NEAT1 is involved in RA development.

474

### 475 **2.3.6 X-Inactive Specific Transcript (XIST)**

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

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

494

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

505 chondrocytes to impact on cell growth and apoptosis.<sup>96</sup> Although, one study in CHON-  
506 001 and ATDC5 chondrocyte cell lines found overexpression of XIST to inhibit  
507 apoptosis through the miR-653-5p/SIRT1 axis.<sup>97</sup> XIST could also promote MMP-13  
508 and ADAMTS5 mediated ECM degradation by functioning as a ceRNA of miR-1277-  
509 5p. This was validated in the DMM OA rat model, where downregulation of XIST  
510 proved to be protective against ECM degradation.<sup>98</sup> Additionally, by sponging of miR-  
511 149-5p, XIST was found to enhance DNMT3A expression suppressing collagen type II  
512 and aggrecan production, inhibiting proliferation and promoting apoptosis of IL-1 $\beta$   
513 treated CHON-001 chondrocyte cell line.<sup>99</sup> Interestingly, collagen degradation in  
514 primary OA chondrocytes is reportedly regulated by MMP inhibitor TIMP-3. XIST was  
515 found to recruit DNMT1, DNMT3A and DNMT3B to increase TIMP-3 promoter  
516 methylation, thereby silencing TIMP-3 and promoting collagen degradation.<sup>100</sup> OA  
517 chondrocyte apoptosis is also regulated by M1 macrophages via the XIST/ miR-376c-  
518 5p/OPN axis in co-culture studies.<sup>101</sup> XIST was identified as a ceRNA of miR376c-5p,  
519 which was essential for silencing osteopontin (OPN) known to regulate pro-  
520 inflammatory cytokines within M1 macrophages, which in turn promoted apoptosis in  
521 primary chondrocytes.

522

### 523 ***2.3.7 Maternally Expressed Gene 3 (MEG3)***

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

530 in apoptosis and proliferation through modulating the TGF $\beta$  and Wnt/ $\beta$ -catenin  
531 signalling pathways and the regulation of p53.<sup>102</sup>

532

533 MEG3 down regulation is observed in OA cartilage tissue and chondrocytes, although  
534 there are some conflicting reports.<sup>104-106</sup> 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.<sup>107</sup> 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.<sup>108</sup> Overexpressed MEG3 was found to be anti-  
541 proliferation and pro-apoptotic through the miR-16/SMAD axis in IL-1 $\beta$  treated SD rat  
542 chondrocytes.<sup>105</sup> In line with this, a more recent study, using the same IL-1 $\beta$  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.<sup>106</sup> found MEG3 to disrupt the miR-  
546 93/TGFBR2 axis thus activating the TGF $\beta$  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.<sup>109</sup> 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.<sup>110</sup> However in a contradictory study, primary RA-  
554 FLS MEG3 expression was found to be down regulated and further suppression



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

563

### 564 ***2.3.8 HOXA Transcript at the Distal Tip (HOTTIP)***

565 The HOXA transcript at the distal tip (HOTTIP) transcript is a ~3.8 kb lncRNA that is  
566 highly expressed across many cancers and is known to regulate the HOXA locus.  
567 Through binding of WDR5 protein and recruitment of the histone methyltransferase  
568 protein MLL, HOTTIP drives activation of the HOXA genes through H3K4  
569 methylation.<sup>112</sup> Reports also find HOTTIP can enhance IL-6 expression in ovarian  
570 cancer tissue through binding of c-jun. Additionally, HOTTIP enhanced IL-6 secretion  
571 in ovarian cancer tissue promoted neutrophil induced inhibition of T-cell activity.<sup>113, 114</sup>  
572 These findings may also be functionally relevant in RA and OA where HOTTIP  
573 expression is similarly increased in RA-FLS, OA cartilage and chondrocytes and  
574 patients present with elevated IL-6 levels. HOTTIP has been linked to the progression  
575 of OA through suppression of HoxA13 in chondrogenic mouse mesenchymal stem  
576 cells (MSC), which modulated integrin- $\alpha$ 1 expression and cartilage maintenance.<sup>115</sup>  
577 Additionally in human chondrogenic MSC, HOTTIP targets the miR-455-3p/CCL3  
578 pathway in OA inducing cartilage degradation.<sup>116</sup> In primary RA-FLS, HOTTIP is  
579 thought to recruit DNA methyltransferase Dnmt3b to silence SFRP1.<sup>117</sup> Through

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

584

### 585 **2.3.9 Plasmacytoma Variant Translocation 1 (PVT1)**

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

592

593 In OA, PVT1 is largely described as a sponging ceRNA facilitating apoptosis,  
594 inflammation and cartilage degradation. Overexpression of PVT1 in OA primary  
595 chondrocytes induced apoptosis through sponging of miR-488-3p.<sup>119</sup> Through  
596 sponging of miR-149, PVT1 mediates cartilage degradation.<sup>120</sup> PVT1 silencing  
597 suppressed primary chondrocyte catabolism and inflammation, where IL-1 $\beta$  induced  
598 production of IL-6, IL-8 and TNF $\alpha$  and expression of MMP3, MMP9 and MMP13 were  
599 all downregulated, whilst production of anabolic factors, collagen type II and aggrecan,  
600 were increased. Similarly, the PVT1/miR-27b-3p/TRAF3 axis promoted apoptosis and  
601 inflammation in C28/I2 cells, whilst the PVT1/miR-26b/CTGF/TGF-B1 axis enhanced  
602 cartilage degradation in primary chondrocytes.<sup>121, 122</sup> Interestingly, PVT1 was also  
603 found to induce TNFA expression and secretion through miR-211-3p sponging in TMJ-

604 OA FLS, which in turn facilitated SW982 chondrocyte apoptosis.<sup>123</sup> Although elevated  
605 PVT1 expression was found to promote proliferation in RA-FLS through the miR-  
606 543/SCUBE2 axis, knockdown resulted in apoptosis and suppressed inflammation  
607 suggesting tissue specific mechanisms of action.<sup>124, 125</sup> In RA-FLS isolated from Lewis  
608 rats injected with complete Freund's adjuvant, evidence suggests PVT1 facilitated  
609 promoter methylation of SIRT6, a stress responsive protein known to suppress  
610 inflammation and bone destruction in arthritic mice.<sup>125</sup>

611

### 612 **2.3.10 Taurine Up-regulated 1 (TUG1)**

613 The 7.6 kb Taurine up-regulated 1 (TUG1) transcript is a fundamental cancer  
614 regulatory lncRNA involved in a variety of biological processes. Mechanistically, TUG1  
615 regulates transcriptional activity of target genes through its ability to sponge miRNAs  
616 and by interacting with the PRC2 complex.<sup>126</sup> TUG1 is overexpressed in RA patient  
617 PBMCs, RA patient serum exosomes and OA patient cartilage.<sup>47, 127</sup> TUG1  
618 overexpression was found to regulate ECM degradation in OA through the miR-  
619 195/MMP-13 axis in primary chondrocytes.<sup>127</sup> Interestingly emodin-induced TUG1  
620 expression in ATDC5 chondrogenic cells attenuated apoptosis and inflammation by  
621 inactivating the Notch and NF-κB signalling pathways.<sup>128</sup>

622

### 623 **2.3.11 Urothelial Carcinoma-Associated 1 (UCA1)**

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

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

633

### 634 ***2.3.12 Cancer Susceptibility Candidate 2 (CASC2)***

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

650

### 651 ***2.3.13 Antisense Non-coding RNA in the INK4 Locus (ANRIL)***

652 ANRIL is the antisense non-coding RNA in the INK4 locus on chromosome 9 whose  
653 transcript is ~38kb in length.<sup>137</sup> ANRIL epigenetically regulates gene expression by  
654 forming a RNP complex with polycomb repressive complexes that regulate mono- and  
655 tri-methylation of H3K27.<sup>138, 139</sup> ANRIL is known to regulate many biological processes  
656 including proliferation and apoptosis. In OA cartilage, ANRIL expression is significantly  
657 elevated and downregulation with siRNAs in primary OA-FLS results in cell cycle  
658 arrest at G0/G1, inhibited proliferation and enhanced apoptosis.<sup>140</sup> ANRIL is able to  
659 sponge miR-122-5p resulting in increased DUSP4 expression and the subsequent  
660 regulation of proliferation and apoptosis.<sup>140</sup> In RA, there are few functional studies of  
661 note although in RA patient PBMCs ANRIL expression is reportedly decreased.<sup>47, 141</sup>  
662 Interestingly the ANRIL/miR-125a axis has been shown to exacerbate disease  
663 severity and inflammation in bronchial asthma, which could be functionally relevant in  
664 RA and SLE where miR-125a expression is similarly downregulated.<sup>142</sup>

665

#### 666 **2.3.14 LncRNA Downregulated in Liver Cancer (Lnc-DILC)**

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

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

679

### 680 **2.3.15 IGHC gamma 1 (IGHCy1)**

681 IGHCgamma1 (IGHCy1) is a lncRNA transcript significantly upregulated in RA clinical  
682 samples and positively correlated with erythrocyte sedimentation rate.<sup>146</sup> IGHCy1 is  
683 highly expressed in OA patient PBMCs and in PMA-induced THP-1 macrophages  
684 activated with LPS.<sup>147</sup> Silencing with siRNA reduced macrophage cell proliferation.  
685 IGHCy1 was identified as a ceRNA of miR-6891-3p resulting in increased TLR4 and  
686 NF-kB activity which promoted IL-6 and TNF $\alpha$  production.<sup>147</sup>

687

### 688 **2.3.16 Long Intergenic ncRNA p21 (lincRNA-p21)**

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

701 expression through DNA-protein kinase catalytic subunit and contributed to NF- $\kappa$ B  
702 activation in THP-1 monocytes.

703

#### 704 **2.3.17 Small Nucleolar RNA Host Gene 1 (SNHG1)**

705 The small nucleolar RNA host gene 1 (SNHG1) is an lncRNA transcript that can be  
706 alternatively spliced into eight snoRNAs.<sup>151</sup> SNHG1 is largely reported as a ceRNA  
707 which sponges miRNAs and contributes to cell proliferation, migration and metastasis  
708 in cancer.<sup>152</sup> SNHG1 is downregulated in RA patient serum exosomes and in RA  
709 patient PBMCs although the biological significance of this in RA is yet to be  
710 determined.<sup>47</sup> However, in an IL-1 $\beta$ -induced OA chondrocyte model cell line, SNHG1  
711 overexpression inhibited catabolic and inflammatory factors MMPs, ADAMTs,  
712 collagen, aggrecans, IL-6, TNFA, COX-2 and PGE2.<sup>153</sup> SNHG1 was found to sponge  
713 miR-16-5p to inhibit ERK1/2, phosphorylated p38 and phosphorylated p65 factors  
714 involved in p38/MAPK and NF- $\kappa$ B signalling pathways.

715

#### 716 **2.3.18 TNF and HNRNPL Related Immunoregulatory LncRNA (THRIL)**

717 The THRIL lncRNA was identified in THP-1 macrophages in an RNP-complex with  
718 hnRNPL which bind to and suppressed the TNFA promoter, hence its namesake TNF-  
719 and HNRNPL-related immunoregulatory lncRNA.<sup>154</sup> This lncRNA is reported to also  
720 regulate IL-8, CSF1, CCL1 and CXCL10 expression. Interestingly, THRIL expression  
721 is elevated in RA and OA patients and in preclinical *in vivo* models. Pro-inflammatory  
722 roles are reported in an OA model using ATDC5 cells, where THRIL sponges miR-  
723 125b activating the JAK1/STAT3 and NF- $\kappa$ B signalling pathways which induced  
724 inflammatory cell injury.<sup>155</sup> Increased THRIL expression is also reported in RA patient

725 T-cells and in primary RA-FLS where THRIL activated the PI3K/AKT signalling  
726 pathway modulating cell growth and inflammation.<sup>156, 157</sup>

727

### 728 **2.3.19 ZNFX1 Anti-Sense 1 (ZFAS1)**

729 ZNFX1 antisense RNA1 (ZFAS1) is overexpressed in many cancers and hosts three  
730 snoRNAs. ZFAS1 is involved in many cancer-associated biological process, which  
731 include increased proliferation, migration, invasion and suppressed apoptosis.<sup>158</sup>  
732 Similarly in RA, ZFAS1 is reported to promote cell migration and invasion of patient  
733 isolated RA-FLS. ZFAS1 is highly expressed in RA synovial tissue as well as in  
734 primary RA-FLS and regulates migration and invasion through sponging of miR-  
735 27a.<sup>159</sup> In primary OA chondrocytes, ZFAS1 is downregulated, but its overexpression  
736 is reported to promote proliferation and cell migration whilst inhibiting apoptosis and  
737 matrix synthesis. Mechanistically, ZFAS1 overexpression was found to significantly  
738 suppress Wnt3a,  $\beta$ -catenin and p53.<sup>159</sup>

739

## 740 **3. Systemic Lupus Erythematosus**

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



749 ethnicity, those of Black, South/ East Asian and Hispanic decent have significantly  
750 increased SLE prevalence with more severe disease activity.<sup>162</sup> 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.<sup>160</sup>

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.<sup>163</sup> The pathophysiology is characterised by aberrant immune  
760 responses which sustain the production of autoantibodies, driving chronic  
761 inflammation.<sup>163</sup> 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).<sup>164</sup>  
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.<sup>164</sup> SLE myeloid DCs (mDCs),  
770 activated by pDC, release IFN- $\alpha$ , secrete pro-inflammatory cytokines and activate  
771 autoreactive CD8+ T-cells which differentiate into CD4+ T helper cells.<sup>165</sup> Activated  
772 pDCs also produce chemokines (CXCL9, CXCL10, CCL3-5), which attract activated  
773 T-lymphocytes to sites of inflammation.<sup>165</sup> In SLE, B-cells are influenced by DCs and

774 T-cells to differentiate and produce autoantibodies as a result of failed tolerance  
775 checkpoints.<sup>166</sup>

776

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

789

790 SLE shares many of the key inflammatory pathways described in RA and OA including  
791 chemokine signalling, T-cell receptor signalling pathway and TLR pathway. As  
792 previously mentioned, TLRs, specifically TLR7 and TLR9, trigger type I IFN production  
793 in pDCs.<sup>169</sup> TLR signalling stimulates pro-inflammatory cytokine production through  
794 MyD88 or IFN-B and IFN-inducible genes which act on the NF-kB and MAPK signalling  
795 pathways.<sup>170</sup> The IFN signalling pathway is a prominent feature of SLE, which has a  
796 central role in SLE pathophysiology. The IFN system consists of ubiquitously  
797 expressed IFN $\alpha/\beta$  receptors (IFNAR) and IFN $\gamma$  (IFNGR) and IFN $\lambda$  (IFNLR) receptors

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

804

805 T-cells are drawn to sites of inflammation by pDC cytokine production. Pro-  
806 inflammatory cytokines such as IL-6, IL-21 and IL-23 activate STAT3, which  
807 suppresses IL-2 whilst enhancing transcription of IL-17 and BCL6, which facilitate  
808 inflammation and B-cell antibody production.<sup>171</sup> IL-6 can stimulate CD4 T-cells to  
809 differentiate into IL-17 producing T-helper cells (Th17). Th17 cells are initiated by IL-  
810 21 to produce IL-17 whilst IL-23 maintains sustained expression of IL-17 through the  
811 JAK-STAT signalling pathway.<sup>172</sup> SLE T-cells also have elevated serine/threonine  
812 protein phosphatase 2A (PP2A), which regulates DNA hypomethylation of IFN-  
813 regulated loci by suppressing the ERK/DNMT1 pathway.<sup>171, 173</sup> Notably the IL-17  
814 promoter is hypomethylated whilst IL-2 remains methylated and silenced due to a  
815 failure in histone deacetylase 1 (HDAC1) recruitment.<sup>171</sup> IL-17 is thought to be a  
816 fundamental driver in local tissue damage in SLE patients. Additionally, in SLE, T-  
817 cells, macrophages and monocytes secrete TNF $\alpha$ , which acts through TNFR1 and  
818 TNFR2 receptors triggering the caspase cascade associated with apoptosis or the  
819 activation of NF-kB, JNK and MAPK pro-inflammatory pathways, respectively.<sup>172</sup>

820

### 821 ***3.1 Evidence for the role of lncRNAs in the pathogenesis of SLE***

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

845

### 846 **3.1.1 Metastasis-Associated Lung Adenocarcinoma Transcript 1 (MALAT1)**

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

860

### 861 **3.1.2 Growth Arrest-Specific 5 (GAS5)**

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

871 from SLE patients, GAS5 expression was significantly elevated and presented as a  
872 diagnostic marker for SLE patients with ulceration.<sup>190</sup>

873

### 874 **3.1.3 Nuclear Enriched Abundant Transcript 1 (NEAT1)**

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

892

### 893 **3.1.4 X-Inactive Specific Transcript (XIST)**

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

919

### 920 **3.1.5 Taurine Up-regulated 1 (TUG1)**

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

929

### 930 **3.1.6 Urothelial Carcinoma-Associated 1 (UCA1)**

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

937

### 938 **3.1.7 TNF and HNRNPL Related Immunoregulatory LncRNA (THRIL)**

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



943 JNK and Wnt/ $\beta$ -catenin signalling pathways which may be crucial in SLE  
944 pathogenesis.<sup>205</sup>

945

#### 946 **4. Conclusions and Perspectives**

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

963

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965

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1594 **Table 1. Summary of functional lncRNAs in Osteoarthritis**

LncRNA	Expression (Up '+' /Down '-')	Model	Function	Ref.
	+	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/ $\beta$ -catenin and NF- $\kappa$ B pathways and pro-inflammatory factors IL-1 $\beta$ , IL-6, IL-8 and TNF $\alpha$	40
	+	Rat primary chondrocytes	Prevents activation of JNK signalling pathway suppressing IL-1 $\beta$ -induced chondrocyte inflammation, apoptosis and extracellular matrix degradation	41
<b>MALAT 1</b>	+	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
	+	Human chondrocyte cell line	Inhibits miR-17-5p mediated suppression of ETV1 which elevates pro-inflammatory cytokines IL-6, IL-8 and TNF $\alpha$ through activation of MAPK/c-Jun and NF- $\kappa$ B pathways	55
<b>HOTAIR</b>	+	Human primary chondrocytes	Sponging of miR-17-5p upregulates FUT2 increasing ECM degradation and apoptosis through the Wnt/ $\beta$ -catenin pathway	56
	+	Human chondrocyte cell line	Directly activates the Wnt/ $\beta$ -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-1 $\beta$ -stimulated expressions of MMP1, MMP3 and MMP9 and significantly decrease apoptosis	61
	+	Rat primary synoviocytes	Silencing inhibits Wnt/ $\beta$ -catenin pathway and reduced inflammation and promoted synoviocytes apoptosis	62
<b>GAS5</b>	+	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
	+	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-1 $\beta$ and TNF $\alpha$	74
			Human chondrocyte cell line	Found to sponge miR-130a resulting in LPS-induced apoptosis and inflammation
<b>H19</b>	+	Human primary chondrocytes	Increased H19 stimulated by IL-1 $\beta$ , 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
<b>NEAT1</b>	+	Human primary chondrocytes	miR-377-3p sponging by NEAT1 in IL-1 $\beta$ 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. By sponging miR-149-5p, XIST enhanced DNMT3A expression	98
	+	Human chondrocyte cell line	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 TGF $\beta$ signalling pathway which regulates ECM degradation	106
	-	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

<b>HOTIP</b>	+	Mouse primary chondrocytes	Suppresses HoxA13 which regulates integrin- $\alpha$ 1 expression and cartilage maintenance	115
	+	Human primary chondrocytes	HOTTIP targets the miR-455-3p/CCL3 pathway in OA inducing cartilage degradation	116
	+	Human primary chondrocytes	Overexpression of induces apoptosis through sponging of miR-488-3p	119
	+	Human primary chondrocytes	Silenced IL-1 $\beta$ induced secretion of IL-6, IL-8 and TNF $\alpha$ and expression of MMP3, MMP9 and MMP13 through sponging of miR-149	120
<b>PVT1</b>	+	Human chondrocyte cell line	Knockdown inhibits apoptosis and inflammatory response to IL-1 $\beta$ 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- $\beta$ 1, SMAD3, and MMP-13	122
	+	Human chondrocyte cell line	Induces TNFA expression and secretion through miR-211-3p sponging facilitating apoptosis	123
<b>TUG1</b>	+	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
<b>UCA1</b>	+	Human chondrocyte cell line	Regulates cell survival and matrix synthesis by suppressing the miR-204-5p expression and increasing MMP-13 expression	130
<b>CASC2</b>	+	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
<b>ANRIL</b>	+	Human primary FLS	By sponging miR-122-5p increases DUSP4 expression and regulates proliferation and apoptosis	140
<b>Lnc-DILC</b>	-	Human chondrocyte cell line	Overexpression supresses IL-6 at the protein level	144
<b>IGHCy1</b>	+	Human THP-1 cell line	ceRNA of miR-6891-3p resulting in increased TLR4 and NF-kB activity promoting IL-6 and TNF $\alpha$ production	147
<b>lincRNA-p21</b>	+	Human primary chondrocyte	Sponges and represses miR-451 promoting the apoptosis	149

<b>SNHG1</b>		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
<b>THRIL</b>	+	Mouse chondrocyte cell line	Overexpression promotes LPS-induced inflammatory injury by suppressing miR-125b thus activating JAK1/STAT3 and NF-kB pathways.	155
<b>ZFAS1</b>	-	Human primary chondrocytes	Overexpression promotes proliferation and cell migration whilst inhibiting apoptosis and matrix synthesis through suppression of Wnt3a, $\beta$ -catenin and p53	159
<b>MIAT</b>		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
<b>FAS-AS1</b>	+	Human primary chondrocytes	Low expression decreases expression of MMP1 and MMP13, but increases COL2A1 expression, inhibiting cell apoptosis and promote cell proliferation	181

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**Table 2. Summary of functional lncRNAs in Rheumatoid Arthritis**

LncRNA	Expression (Up '+' /Down '-')	Model	Function	Ref.
MALAT1	-	Human primary FLS	Silencing stimulates $\beta$ -catenin nucleation, secretion of pro-inflammatory cytokines IL-1, IL-10, and TNF $\alpha$ , 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- $\kappa$ B signalling in vivo, resulting in increased cell proliferation and suppressed IL-1 $\beta$ and TNF $\alpha$	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 suppressing apoptotic regulator HIPK2 and pro-inflammatory cytokines TNF $\alpha$ and IL-6	72
H19	+	Human primary FLS and macrophages	Expression responds to serum starvation, IL-1 $\beta$ , TNF $\alpha$ 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- $\kappa$ B pathway, resulting in increased IL-6, IL-8 and IL-1 $\beta$ production and increased apoptosis	80
NEAT1	+	Human whole blood	Knockdown prevents CD4 <sup>+</sup> 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 suppressing apoptosis	
PVT1	+	Human FLS cell line	Promotes proliferation through the miR-543/SCUBE2 axis whilst PVT1 knockdown results in apoptosis and suppressed 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 suppresses 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-κB 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

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**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
	+	Human whole blood	Silencing reduced expression of IL-21 and SIRT1	187
MALAT1	+	Human whole blood	Silencing represses all OAS proteins as well as TNFA and IL-1B expression in IFN $\alpha$ -2a treated immune cells. May function as a ceRNA of six miRNAs which target OAS proteins	188
	-	Human whole blood	co-expression of GAS5, Inc0640 and Inc5150 may modulate the MAPK and PPAR signalling pathways	177
GAS5	+	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
	+	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
NEAT1	+	Human whole blood	Contributes to inflammatory cell injury, elevated IL-1 $\beta$ , IL-6, TNF $\alpha$ and IFN- $\gamma$ production and increased apoptosis by sponging of miR-146b and increasing TRAF6 expression which activates NF- $\kappa$ B signalling	193
	+	Human whole blood	RNA localization patterns disrupted, evidence of bi-allelic expression and increased transcription of immunity-related genes in SLE lymphocytes	195
XIST	+	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 suppressing 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/ $\beta$ -catenin signalling pathways	205

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