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SASP Regulation by Noncoding RNA

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Abstract

Noncoding RNAs (ncRNAs), including micro (mi)RNAs, long noncoding (lnc)RNAs, and circular (circ)RNAs, control specific gene expression programs by regulating transcriptional, post-transcriptional, and post-translational processes. Through their broad influence on protein expression and function, ncRNAs have been implicated in virtually all cellular processes such as proliferation, senescence, quiescence, differentiation, apoptosis, and the stress and immune responses. Senescence is a cellular phenotype associated with the physiologic decline of aging and with age-related pathologies. Besides their characteristic terminal growth arrest and differential gene expression programs, senescent cells are known to secrete potent pro-inflammatory, angiogenic, and tissue-remodeling factors. This important trait, known as the senescence-associated secretory phenotype (SASP), influences many biological processes such as tissue repair and regeneration, tumorigenesis, and the aging-associated pro-inflammatory state. Here, we review the microRNAs, lncRNAs, and circRNAs that influence the production of SASP factors and discuss the rising interest in SASP-regulatory ncRNAs as diagnostic and therapeutic targets.

1. Introduction

Cellular senescence is a state of terminal growth arrest in which cells are unresponsive to growth factor stimulation. This phenotype was initially described by Hayflick as the end of the lifespan of primary fibroblasts maintained in culture [1]. The senescence program is triggered when cells encounter stress conditions such as critically short telomeres, DNA damage, oncogenic activation, hypoxia, and oxidative stress [2]. Although senescent cells do not divide, they are metabolically active and exibit a distinct metabolic profile. They display a flattened and enlarged morphology, altered gene expression patterns, increased activity of a neutral β-galactosidase, and senescence-associated heterochromatic foci [3–7]. Another major feature of senescent cells is the senescence-associated secretory phenotype (SASP) [8], characterized by the production and secretion of regulatory factors including interleukins, cytokines, growth factors, angiogenic factors, and matrix metalloproteases [8,

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9]. SASP affects the function of tissues and organs by attracting immune cells, enhancing angiogenesis, and remodeling the extracellular matrix [10, 11].

Cell senescence has numerous and complex effects on tissue homeostasis and health. It is necessary for tissue sculpting during development, enhances wound healing, and suppresses detrimental tissue fibrosis in response to damage to the liver, the pancreas, and the skin [12–17]. In addition, in young individuals, senescence has been shown to suppress tumor progression [18, 19]. However, senescence can also have detrimental effects. In older individuals, the accumulation of senescent cells during aging alters the physiologic function of tissues and organs leading to age-related diseases like cancer, cataracts, and atherosclerosis [20, 21]. The accumulation of senescent cells during aging has also been linked to the excessive production of SASP factors, which facilitate chronic inflammation and age-related diseases such as arthritis [15, 22, 23]. In addition, the inflammatory cytokines and growth factors secreted from senescent cells may promote tumor growth in old age by inducing angiogenesis and tumor cell proliferation [24–26].

Given that SASP is such a critical trait of senescent cells, understanding the regulation of SASP factor production provides direct insight into the mechanisms of aging. In this review, we discuss the regulatory RNAs that impact upon the SASP phenotype at all levels – transcriptional, post-transcriptional, and post-translational (Figure 1). We focus on specific noncoding (nc)RNAs that affect subsets of SASP factors, including microRNAs (miRNAs), long ncRNAs (lncRNAs), and circular RNAs (circRNAs).

2. MicroRNAs

MicroRNAs (miRNAs) are small ncRNAs spanning ~22 nucleotides. They are generated from primary transcripts (pri-miRNAs) transcribed from the genome by RNA polymerase II. Pri-miRNAs are processed in the nucleus by a complex comprising the ribonuclease DROSHA (HGNC) and DiGeorge critical region 8 (DGCR8) to generate microRNA precursors (pre-miRNAs) [27–31]. Pre-miRNAs are exported to the cytoplasm by Exportin 5 for further processing [32] and are cleaved in the cytoplasm by ribonuclease DICER1 to produce mature microRNAs [33], which are loaded into the RNA-induced silencing complex (RISC) [34]. Argonaute (AGO) proteins in the RISC direct microRNAs to specific mRNAs, typically forming partial complementarity between the microRNAs and segments of the mRNA 3′-untranslated region (UTR), which in turn lower the stability and/or translation of the target mRNA [35–38]. A few reports suggest that some microRNAs may instead upregulate the expression of target genes by competing with a translation suppressor or by other mechanisms [39, 40].

A single microRNA can target multiple mRNAs most human mRNAs are believed to be regulated by microRNAs [37]. Through this broad impact on gene expression, microRNAs can regulate diverse physiologic processes such as embryonic development and cell proliferation, differentiation, and apoptosis [41–45]. Many microRNAs have also been implicated in pathological conditions including cancer, diabetes, cardiovascular disease, neurodegeneration, and immune diseases [46–48]. Since identification of the first microRNA, lin-4, reported to regulate the lifespan of *C. elegans* [49], many studies have

established that microRNAs are among the key regulators of cell senescence and aging [50, 51] in many species including humans.

2.1. MicroRNAs and SASP

Senescent cells are characterized by profound changes in metabolic and protein expression profiles, including SASP. As described above, SASP is characterized by increased production and secretion of various cytokines, growth factors and matrix metalloproteases [24]. Recently, several microRNAs have been shown to regulate the production and secretion of these factors in senescent cells, as discussed in this section (Table 1).

miR-146a/b—miR-146a and miR-146b were found to be more highly abundant in senescent than in quiescent fibroblasts. In primary human fibroblasts, miR-146a/b inhibit the secretion of SASP factors interleukin (IL)6 and IL8 by acting upon *IRAK1* mRNA and lowering the production of IRAK1, a key factor of the IL-1α (IL1A) receptor signaling pathway [52]. Increased miR-146a/b expression in response to high levels of IL1A was proposed to function as a negative feedback loop to prevent excessive SASP activity [52]. However, miR-146a was induced in human diploid BJ fibroblasts immortalized by overexpression of telomerase, suggesting that in some cases, miR-146a might regulate SASP independently of senescence [53]. In trophoblasts, miR-146a-3p expression was elevated by antiphospholipid antibody (aPL) treatment through the activation of Toll-like receptor 4 (TLR4). This upregulation of miR-146a induced IL8 secretion by activating TLR8 [54].

miR-335—A recent report indicated that miR-335 was upregulated in normal senescent cells and cancer-associated senescent fibroblasts (CAF). Higher levels of miR-335 lowered the abundance of phosphatase and tensin homologue (PTEN), in turn causing a rise in SASP factors like MMP2 and IL6 [55]. Senescent cells showed increased secretion of the protein cyclooxygenase 2 (PTGS2/COX2) and the signaling lipid prostaglandin E2 (PGE2). The levels of miR-335 were downregulated by inhibition of PTSG2/COX2 using celecoxib, which restored PTEN expression and decreased SASP [55].

miR-15b—Sirtuin 4 (SIRT4) is implicated in senescence-associated mitochondrial dysfunction and SASP. Its high expression in human dermal fibroblasts undergoing replicative or stress-induced senescence was associated to decreased levels of miR-15b [56].

miR-187—IL10 is a potent anti-inflammatory molecule that suppresses cytokine expression both transcriptionally and post-transcriptionally. Activation of primary human monocytes with IL10 induced the expression of miR-187, which in turn suppressed production of two major SASP factors, TNF and IL6 [57].

miR-9—The tumor suppressor miR-9, downregulated in cervical adenocarcinoma, was found to inhibit the expression of several targets, including the SASP factor IL6 [58].

miR-21—miR-21 is secreted by cancer cells and acts as a ligand for TLR8 in immune cells, triggering the secretion of pro-inflammatory cytokines TNF and IL6 [59]. While programmed cell death protein 4 (PDCD4), a direct target of miR-21, activates NF-κB and suppresses IL10 production, upregulation of miR-21 in human peripheral blood

mononuclear cells in response to lipopolysaccharide (LPS) suppressed PDCD4 production leading to lower NF-κB activity and greater IL10 production [60].

miR-222—miR-222 is upregulated in less aggressive metastatic cells of oral tongue squamous cell carcinoma (OTSCC). Functional analyses suggested that overexpression of miR-222 inhibited OTSCC cell invasion by inhibiting the SASP factor matrix metalloproteinase 1 (MMP1) [61]. Further analysis revealed that miR-222 inhibited the expression of MMP1 by directly targeting the 3′UTR of *MMP1* mRNA as well as by inhibiting expression of manganese superoxide dismutase 2 (SOD2), an inducer of MMP1 production.

miR-34—Expression of the longevity-associated protein SIRT1 is repressed by miR-34a. An elevation in miR-34a abundance in human aortic smooth muscle cells led to significant downregulation of SIRT1 and caused higher production of pro-inflammatory SASP molecules, although the secretion of SASP factors did not appear to be influenced directly by SIRT1 [62].

miR-125b—Treatment of RAW 264.7 macrophages with LPS reduced the levels of miR-125b, a microRNA that targets *TNF* mRNA and reduces TNF levels [63]. These data suggest that the LPS-dependent decrease in miR-125b may contribute to the LPS-triggered increase in TNF and SASP. The tumor suppressor miR-125b was less abundant in cutaneous squamous cell carcinoma (cSCC) than in healthy skin, leading to higher production of the SASP factor MMP13 in cSCCs [64].

miR-152—miR-152 inhibits the expression of the SASP factor MMP3 by binding to the 3′UTR of *MMP3* mRNA. *In vitro* invasion assays suggested that miR-152 significantly reduced the invasiveness of glioma cells, possibly by inhibiting MMP3 production [65].

miR-147—LPS also induced the expression of miR-147 in mouse macrophages via the TLR4–NF-κB axis. Overexpression of miR-147 was found to suppress the expression of pro-inflammatory cytokines TNF and IL6 in macrophages stimulated with TLR2/TLR3/TLR4 ligands. These findings reveal the existence of a negative feedback loop through which TLR stimulation increases miR-147 levels, in turn suppressing the excessive production of inflammatory cytokines [66].

miR-199a—Activation NF-κB requires a kinase IκB kinase-β (IKBKB), a crucial factor for the activation of TLR–MyD88–NF-κB pathway in ovarian cancer. Recent reports suggest that miR-199a was capable of suppressing the production of IKBKB, which led to the reduced secretion of SASP factors IL6, IL8, and MCP1, and suppressed tumor progression [67].

3. Long-noncoding RNAs (lncRNAs)

Recent advances in high-throughput transcriptome sequencing revealed that the human genome encodes thousands of long noncoding RNAs (lncRNAs) [68]. LncRNAs are defined as transcripts longer than 200 nucleotides that generally lack protein-coding capacity but are

transcribed and processed like mRNAs [69]. LncRNAs can be classified based on their genomic origin into pseudogene-encoded lncRNAs, long intergenic RNAs, antisense lncRNAs, long intronic ncRNAs, etc [69]. LncRNAs have been implicated in the regulation of gene expression by controlling several key processes such as chromatin remodeling, transcription, mRNA stability, translation, and protein stability [70–75]. Recent reports indicate that lncRNAs are critical regulators of physiological processes such as cell division and differentiation, and numerous human diseases including cancer and neurodegeneration [76–78]. Recently, we screened for senescence-associated lncRNAs in human diploid fibroblasts and found that the expression of several lncRNAs was altered in senescent cells [79, 80]. In this section, we will discuss the role of lncRNAs in SASP.

3.1. LncRNAs and SASP

LncRNA-LET—*lncRNA-LET* (low expression in tumor) is less abundant in cancers including hepatocellular carcinoma, colorectal cancer, and squamous-cell lung carcinoma. Silencing of *lncRNA-LET* stabilizes and thereby allows the accumulation of nuclear factor 90 (NF90) [81]. Senescent cells express reduced levels of NF90, an RNA-binding protein (RBP) that suppresses the translation of several SASP factors including MCP1 (CCL2), GROa (CXCL1), and IL6 [82]. Thus, the reduction of NF90 levels in senescent cells is linked to the enhanced production of several SASP factors. Accordingly, NF90 appears to function as an effector of *lncRNA-LET* actions to maintain low levels of SASP factors.

LincRNA-Cox2—*LincRNA-Cox2* expression is induced in mouse upon activation of TLRs through the TLR–MyD88–NF-κB pathway. *LincRNA-Cox2* suppresses the transcription of different sets of proinflammatory genes by interacting with heterogeneous nuclear ribonucleoprotein (HNRNP) A/B and A2/B1. Silencing *LincRNA-Cox2* upregulated chemokines CCL5 and CX3CL1 as well as chemokine receptor 1 (CCRl), while it downregulated other proteins including IL6 following treatment with the TLR activator Pam3CSK4 [83].

NEAT1—The lncRNA nuclear-enriched abundant transcript 1 (*NEAT1*) is required for the formation nuclear paraspeckles [84]. Induction of *NEAT1* expression by viral infection or treatment with poly(I:C), a TLR3 agonist, enhanced the formation of paraspeckles. The splicing factor proline/glutamine-rich (SFPQ) inhibits IL8 transcription. Interestingly, *NEAT1* facilitates the transcription of *IL8* mRNA by relocating SFPQ to nuclear paraspeckles [85].

Lnc-IL7R—The levels of *lnc-IL7R* were elevated upregulated in response to treatment with LPS. Silencing of *lnc-IL7R* reduced trimethylation of histone H3 at lysine 27 (H3K27me3) leading to a decrease in the levels of the inflammatory mediators E-selectin (SELE), VCAM1, IL6, and IL8 [86]. These findings suggest that *Lnc-IL7R* might contribute to regulating SASP factor production [87].

Lethe—The pseudogene lncRNA *Lethe* was shown to be downregulated in aging tissues. It was also reported that aging tissues have highly active NF-κB which could induce several pro-inflammatory genes [88]. *Lethe* interacts with the NF-κB subunit RelA to inhibit the

DNA-binding activity of NF-κB, leading to less production of pro-inflammatory cytokines [89]. The age-associated reduction in *Lethe* may be one of the reasons for the increased NF-κB activity in older individuals.

THRIL—In THP1 macrophages, the lncRNA *THRIL* (TNF- and hnRNPL-related immunoregulatory lincRNA) interacts with the RBP hnRNP L to form a ribonucleoprotein complex that promotes TNF transcription through binding to the *TNF* gene promoter [90].

4. CircRNAs

Circular RNAs (circRNAs) have attracted much interest in recent years. Although circRNAs were first identified decades earlier, extensive investigation was not performed due to poor knowledge of their function and rudimentary detection techniques [91–93]. Recent work has uncovered that thousands of circRNAs are expressed in mammalian cells [94, 95], generally arising from the joining of 5′ and 3′ ends of exonic or intronic sequences during splicing, a process known as 'backsplicing'. Due to the lack of free ends, circRNAs are resistant to cellular exonucleases. Recent studies have described various functions of circRNA in cells including sponging of microRNAs and RBPs, as reviewed recently [96]. Although knowledge of circRNAs in SASP is still at early stages, we anticipate that their contribution to SASP will become more apparent as our understanding of circRNAs progresses.

Circ-Foxo3

Highly expressed in old organs (heart, intestines, lung, and skin) relative to young organs, *Circ-Foxo3* is predominantly localized in the cytoplasm and interacts with senescence-associated proteins FAK, HIF1A, ID1, and E2F1, helping to elicit senescence [97]. In turn, *Circ-Foxo3* increases the production of SASP factors, likely through indirect mechanisms.

CircPVT1

Hundreds of senescence-associated circRNAs (SAC-RNAs) differentially expressed in senescent WI-38 human diploid fibroblasts were recently reported [98]. *CircPVT1*, a SAC-RNA generated from the lncRNA *PVT1*, was identified as being markedly reduced in senescent fibroblasts. The high levels of *CircPVT1* in dividing cells resulted in the sequestration of let-7 and enabling of a proliferative phenotype [98], suppressing senescence and SASP.

5. Concluding remarks and perspectives

We have discussed the current knowledge and possible roles of ncRNAs (microRNAs, lncRNAs, circRNAs) in one of the major facets of senescence, SASP. As in other areas of senescence-associated gene regulation [6, 7], it is interesting that the various levels of control of SASP protein production rely on the actions of ncRNAs of all types. We propose that this extensive network of regulatory mechanisms underscores the critical role of SASP in senescence, and highlight the joint roles of RNA regulators in conjunction with protein and DNA to elicit a highly precise control of the SASP program. The reliance on regulatory ncRNA for the control of cellular processes may be particularly important in processes such as senescence and SASP in which cells experience cumulative damage to protein and DNA

and thus transcriptional regulation alone may not control gene expression patterns with sufficient accuracy. Alternatively, ncRNAs may provide the ‘checks and balances’ that characterize gene regulation driving critical cellular processes. One additional possibility is that SASP-regulatory ncRNAs might be shared between cells via extracellular vesicles originating from neighboring cells or from distant tissues [99, 100] to ensure that this important phenotype is maintained even if cells have impaired transcriptional programs.

As discussed, mounting evidence supports functions for ncRNAs as regulators of the production and secretion of SASP factors by modulating the transcription of SASP genes, the stability of SASP mRNAs, and the translation and/or secretion of SASP proteins. microRNAs target large fractions of mRNAs, and each microRNA can influence hundreds of target mRNAs [101]. Given their pleiotropic actions, inhibition of one microRNA using a stable antisense RNA molecule (an ‘antagomiR’) that binds to the mature microRNA of interest and inhibits its function [102] could have a broad clinical impact. Such approaches have been successfully used in cancer therapy [103–105]. In a similar way, microRNA-based therapeutics can be used to inhibit SASP-associated microRNAs in senescent cells. LncRNAs can interact with DNA, RNA, and protein to alter the expression of specific set of genes implicated in various diseases [106, 107]. Accordingly, lncRNAs are also emerging as therapeutic targets; an interfering lncRNA was recently shown to suppress carcinogenesis by blocking multiple oncogenic microRNAs [108] and might similarly be envisioned to affect SASP. Nonetheless, our knowledge of the roles of lncRNAs in cellular senescence is still very limited, and this knowledge is even more limited for circRNAs. As our understanding of ncRNAs regulating SASP expands and deepens, their potential therapeutic value in age-associated diseases will come into view.

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Abbreviations

TNF	Tumor necrosis factor alpha
IL	Interleukin
LPS	lipopolysaccharide
SASP	Senescence-associated secretory phenotype
TLR	Toll-like receptors
NF-κB	nuclear factor-κB
lncRNA	long noncoding RNA
miRNA	microRNA
UTR	untranslated region

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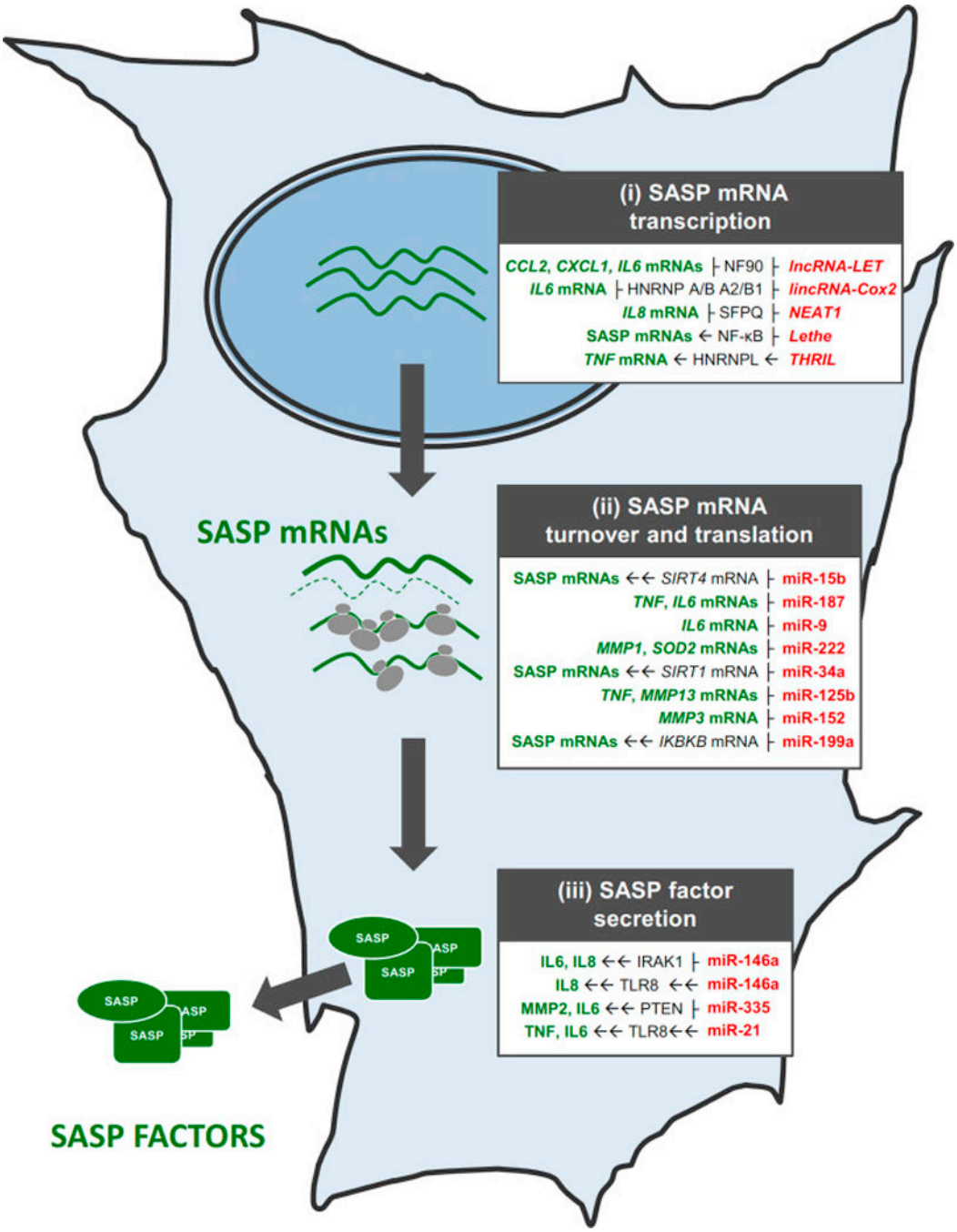

Figure 1. Levels of SASP gene regulation by different ncRNAs

ncRNAs affecting SASP factor production and secretion in a senescent cell by influencing the transcription of SASP genes (i), the post-transcriptional fate of SASP mRNAs (ii), and the secretion of SASP factors (iii), indicated in gray boxes. Red, ncRNAs; green, SASP factors; black, mediators through which some ncRNAs affect SASP factor expression. ├, inhibition/repression, → direct induction/activation, →→ indirect induction/activation.

Table 1
ncRNAs affecting SASP factor production

MicroRNAs, lncRNAs, and circRNAs implicated in regulating SASP factors. The specific ‘Target SASP factors’ affected by the regulatory ncRNAs are listed; ‘[SASP mRNAs]’ denotes general regulation of the SASP phenotype by a given ncRNA. ‘Effector molecules’ are proteins and microRNAs through which some ncRNAs affect SASP gene expression programs.

	ncRNA	Target SASP factor	Effector molecules	References
microRNAs	miR-146a/b	IL6, IL8	IRAK1, TLR8	[52–54]
	miR-335	MMP2, IL6	PTEN	[55]
	miR-15b	[SASP mRNAs]	SIRT4	[56]
	miR-187	*IL6*, *TNF* mRNAs		[57]
	miR-9	*IL6* mRNA		[58]
	miR-21	IL6, TNF, IL10	TLR8, PDCD4	[59, 60]
	miR-222	*MMP1*, *SOD1* mRNAs		[61]
	miR-34a	[SASP mRNAs]	SIRT1	[62]
	miR-125b	*TNF*, *MMP13* mRNAs		[63, 64]
	miR-152	*MMP3* mRNA		[65]
	miR-147	TNF, IL6	(negative feedback?)	[66]
	miR-199a	[SASP mRNAs]	IKBKB	[67]
lncRNAs	*lncRNA-LET*	*CCL2*, *CXCL1*, *IL6* mRNAs	NF90	[81, 82]
	LincRNA-Cox2	*IL6* mRNA	HNRNPA/B, HNRNPA2/B1	[83]
	NEAT1	*IL8* mRNA	SFPQ	[85]
	lnc-IL7R	SELE, VCAM1, IL6, IL8	(negative feedback?)	[86, 87]
	Lethe	[SASP mRNAs]	NF-κB	[88, 89]
	THRIL	*TNF* mRNA	HNRNPL	[90]
circRNA	*Circ-Foxo3*	[SASP mRNAs]	FAK, HIF1A, ID1, E2F1	[97]
	CircPVT1	[SASP mRNAs]	Let-7 sequestration	[98]