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The crosstalk between microRNAs and NF-κB signaling pathway in the induction of senescence-associated secretory phenotype

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Abstract

MicroRNAs (miRNAs), one of non-coding RNAs, play an important role in regulating the expression of target genes at the post-transcriptional level. In the biological process of cellular senescence, there is a bilateral regulating relationship exists between miRNAs and NF-κB signaling pathway. Senescence-associated secretory phenotype (SASP), mainly induced by NF-κB signaling pathway, is also constituted a complex crosstalk with miRNAs. In the present study, we aim to investigate the interactions between miRNAs and NF-κB signaling pathway and their roles in inducing SASP.

Keywords

MiRNA; NF-κB signaling; cellular senescence; SASP.

1. Introduction

1.1. microRNA biogenesis

MicroRNAs (miRNAs) are endogenous single-stranded 18~23nt non-protein-coding RNAs which regulate the expression of genes in animals, nematodes, plants, and viruses[1, 2]. The mature of miRNA is a multi-step process. First of all, the primary miRNAs (pri-miRNA) are transcribed in the cell nucleus with length of 1-3 kb by RNA polymerase II or III [3]. Then the pri-miRNAs are cleaved into roughly 70-90 nucleotide-long stem-loop structures, named pre-miRNAs, in the nucleus by the nuclear endoribonuclease Drosha ribonuclease III and DiGeorge Syndrome Critical Region 8 protein (DGCR8) [3]. These pre-miRNAs are transported to the cytoplasm by Ran/GTP/XPO5 complex and further cleaved by the RNase III Dicer and TAR RNA binding protein (TRBP) into the 18~23 double-stranded oligonucleotides. Next, the miRNA duplexes are incorporated into the RNA-induced silencing complex (RISC) and the Argonaute (AGO) family of proteins, concomitant with several cofactors[4]. After separation, one of the miRNA double strands is loaded onto mature RISC complex to recognize the target mRNA[5]. By perfectly or imperfectly interacting with the 3′ UTR or other regions, including the 5′ UTR, gene promoters, and coding sequence of its complementary target mRNA sites, the RISC complex containing mature miRNA could lead to the target mRNA degradation or translational repression or activate translation under certain conditions [6] (Figure 1).

Enriched in extensively connected genetic networks, miRNAs participate in various biological processes or pathways to exert their regulatory function in a sequence-specific manner. Mounting evidences indicate that a complicated interaction exists between the regulators of signaling pathways and miRNAs precisely modulates the body metabolism and affect the occurrence and development of diseases such as cancer, cardiovascular disease, chronic kidney disease, diabetes, inflammation and neurodegeneration. [4, 7, 8].

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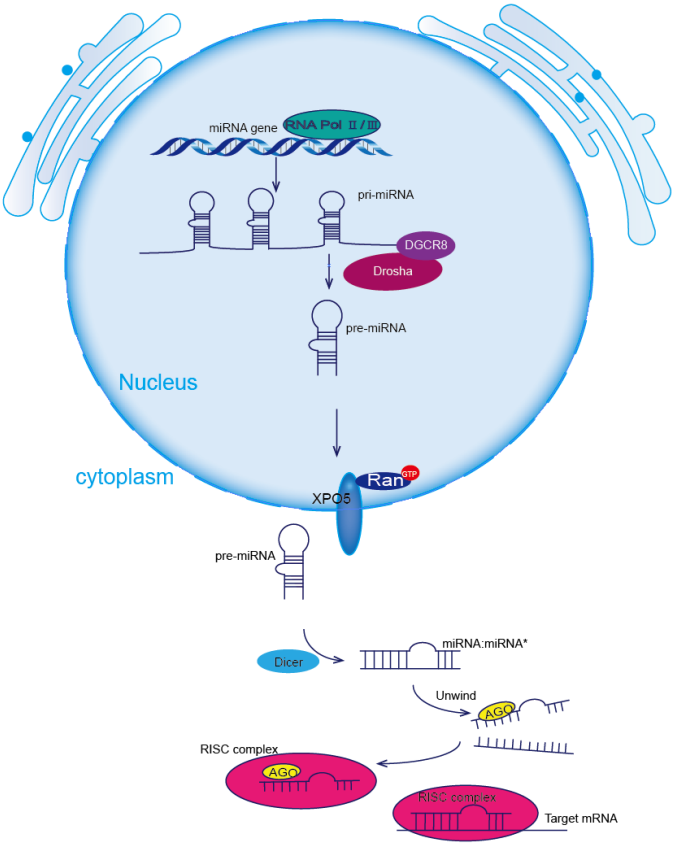

Figure 1. The schematic diagram of canonical biogenetic process of miRNA.

1.2. NF-κB signaling pathway

The NF-kappa-B (NF-κB) family proteins which are evolutionarily conserved master regulators play a critical role in cell survival, proliferation, differentiation, senescence, immunity and inflammatory responses in almost all multicellular beings[9]. In mammalian, NF-κB family proteins consist of five numbers, namely p105/p50 (NF-κB1), p100/p52 (NF-κB2), p65 (RelA), RelB and c-Rel[10]. Generally, the NF-κB signaling is composed of activators, receptors and its proximal pathway adaptor molecules, the IKK complex, the IκB proteins and NF-κB homodimers or heterodimers[11].

The activation of NF-κB signaling pathway consists of two different pathways, the canonical pathway and the noncanonical pathway. In the canonical pathway, a large cytoplasmic IκB kinase complex, which phosphorylates IκBα upon upstream kinase activation, leads to its degradation and subsequent release of the p65/p50 heterodimer. The released p65/p50 heterodimer promptly transfers into the nucleus and then activates the transcription of assorted inflammatory mediators and the signals of antigen/immune stimulation [12]. Compared to the canonical pathway, the alternative pathway entails the protein hydrolysis of p100 by the NF-κB-inducible kinase complex, generating p52 and exposing its nuclear localization sequence to form a heterodimer with RelB [13]. At last, by recruiting the co-activators or interact with other transcription regulators, NF-κB dimers regulate extensive gene expression programs in response to various stimuli in a receptor-specific manner [14].

It is noteworthy that the NF-κB complex initiating the transcription of the target gene is also regulated by post-translational modifications [10]. Furthermore, the deubiquitination of proteins and the acetylation of p65 also play key roles in NF-κB-mediated transcriptional activities which form a feedback circuit aims to regulate the cellular homeostasis [2].

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1.3. Senescence-associated secretory phenotype (SASP)

As a complicated stress response, cellular senescence is an adaptive-activation program with the functions of delaying age-related dysfunction and forming a potent anticancer mechanism [15]. However, the accumulation of senescent cells also result in a low-grade and chronic pro-inflammatory status via the secretion of a multi-component senescence-associated secretory phenotype (SASP), and the occurrence of tissue dysfunction and diverse age-related diseases[16, 17]. The SASP includes various pro-inflammatory cytokines and chemokines, such as IL-1β, IL-6, IL-8, TNF-α, CCL2, CSF3, CCL5 and CXCL1, growth modulators including TGF-β, growth/differentiation factors (GDFs), insulin-like growth factor binding proteins (IGFBPs). It is also comprised multiple signaling molecules, such as ROS, matrix metalloproteases (MMPs), hemostatic factors, extracellular matrix (ECM) components, and damage-associated molecular patterns (DAMPs) [16, 18, 19].

Extracellular vesicles (EVs) such as exosomes are released by all living cells and contain diverse bioactive molecules, including nucleic acids, proteins, lipids, and metabolites. Recently, the EVs have been proved the constituents of the SASP[20]. Importantly, as the essential mediators for intercellular message communication, he EVs secreted from senescent cells (called senescence-associated EVs) are newly SASP factors [27].

SASP can be stimulated by mRNA synthesis, post-transcriptional modification, translation and cellular secretory activity. Moreover, the formation of SASP is also involved in the influence of autocrine and paracrine feedback loops. Notably, SASP expression is regulated to a large extent by epigenetic mechanisms. For example, in carcinogen-induced senescence model, the increase of the H3K79 methyltransferase DOT1L expression promotes H3K79me2/3 at the IL1α locus and drives full expression of SASP factors. On the other hand, the protein, High mobility group box 2 (HMGB2), is able to promote the expression of SASP genes by binding to their central loci and prevent their incorporation into transcriptionally repressive heterochromatin regions[21].

2. miRNAs interaction with NF-κB signaling pathway

2.1. miRNAs regulate the NF-κB signaling circuits

miRNAs are able to regulate the NF-κB signaling circuits via direct or indirect patterns. Table 1 lists the miRNAs, targeted genes on the NF-κB pathway and the related diseases. Let-7 family, which composes of ten members including let-7a, b, c, d, e, f, g, i, miR-98 and miR-202, is evolutionarily conserved among diverse animal species[22]. Let-7a is capable of decreasing NF-κB activity by directly inhibiting the IL-6 expression [23]. Let-7c-5p was shown to protect dental pulp cells from inflammatory disorders by restraining dentin matrix protein-1 (DMP1)-mediated NF-κB pathway activation [24].

In astrocytes, miR-155 and miR-146a, targeting IRAK1 and TRAF6 respectively, adjusted TLR-mediated NF-κB signaling to protect organism from the Escherichia coli infection-mediated neuroinflammatory responses [25]. In addition, miR-146a, as an entitled biomarker of inflammaging, can downregulate canonical NF-κB pathway and modulate the non-canonical NF-κB pathway simultaneously [26, 27].

In indirectly regulation, miRNAs affect the NF-κB signaling pathway by mediating the expression of other molecules. For example, miR-138-5p was found to target the 3′-URT of SIRT1 and then downregulate the expression of inflammatory proteins[28].

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Table 1 The list of miRNAs, target genes, cell types, and the related diseases

miRNAs	Target genes	Related diseases	Ref
let-7a, e, g, i	TLR4; IL-6; NF-κB1; IκBβ	Endotoxin tolerance; Lung cancer; Stroke; Atherosclerosis	[29]
miR-9	NF-κB1	Melanoma; Lung cancer; Ovarian cancer;	[29, 30]
miR-18a	TLR8; TNFAIP-3	Cerebral I/R injury; RASFs	[31]
miR-21	TRIF; TNFAIP-3	Viral infection	[32]
miR-26b	p65	Breast cancer	[33]
miR-30e*	IκBα	Glioma	[34]
miR-98	TRAF1; TAB2; TLR8; NF-κB2	Sepsis; HBV-HCC; Glioma; Atherosclerosis	[35]
miR-99b/ miR-205	TRAF2	Breast cancer	[36]
miR-124	TRAF6; p65	NSCLC	[37]
miR-140	TLR4	KOA; ICH	[38]
miR-143	TNF-α; TAK1	PDA	[39]
miR-146a	TLR4; MyD88; IRAK1; TRAF2; TRAF6; RelB	Lupus nephritis; Myocardial I/R; AD	[27, 40, 41]
miR-150	NF-κB1	Sepsis	[42]
miR-155	TLR4; MyD88	Atherosclerosis; Sepsis	[40]
miR-182	RELA; IKKβ	Endometriosis; SCI	[43, 44]
miR-199a	IKKβ	Ovarian cancer	[45]
miR-200c	p65	Autoimmune diseases	[46]
miR-205	TLR4; IRAK2	Hereditary breast cancer; Cardiac dysfunction	[36]
miR-224	TLR4	AR	[47]
miR-520a	RELA	Cervical cancer	[48]
miR-562	NF-κB1	Breast cancer	[33]
miR-892b	TRAF2; TAK1; TAB2/3	Breast cancer	[49]

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TNFAIP-3, TNFα-induced protein 3; I/R, Ischemia-reperfusion; RASFs, Rheumatoid arthritis synovial fibroblasts; ATL, Adult T cell leukemia; HBV-HCC, hepatitis B virus-related hepatocellular carcinoma; NSCLC ,Non-small cell lung cancer; KOA, Knee osteoarthritis; DPSCs, Dental pulp stem cells; TAK1, TGF-β-activated kinase 1; ICH, intracerebral hemorrhage; PDA, Pancreatic ductal adenocarcinoma; IGRAK1, IL-1 receptor-associated kinase 1; AD, Alzheimer's disease; RIPerC, Remote ischemic preconditioning; SCI, Spinal cord injury; AR, Allergic rhinitis

2.2. miRNAs which are regulated by NF-κB pathway

The mature process of miRNAs is also regulated by NF-κB pathway, especially in the phase of primary miRNA [50]. Table 2 shows the miRNAs regulated by NF-κB and the related biological processes. miR-146a, the first identified NF-κB-dependent miRNA, was upregulated in response to various proinflammatory factors including LPS, IL-1β, IL-6 and TNF-α[51]. The heterodimer p50/p65 was able to promote the transcriptional activity of several miRNA families, such as miRNA-9, miRNA-30b, miRNA-34a, miRNA-146a and miRNA-155[52]. Interestingly, inhibition of NF-κB complex translocation blocks miRNA-149-5p transcription in human airway epithelial cells [53].

Table 2 The miRNAs regulated by NF-κB pathway and the related biological processes.

miRNAs	Biological process	Ref
let-7	Progenitor differentiation; Neuroplastic responses	[50]
miR-9	Differential regulation	[54]
miR-16/21	Cell proliferation	[55]
miR-24-3p	Vascular endothelial cell proliferation	[56]
miR-29b	Leukemia growth	[57]
miR-30b	Synaptic signaling	[52]
miRNA-125b	Sstrogliosis and glial cell proliferation	[52]
miR-130a	Lung microvascular remodeling	[58]
miR-146a	Immune mediation	[59]
miR-149-5p	Epithelial cell inflammation	[53]
miR-155	Induces functional impairment of VSMCs	[60]
miR-181a	Tumor promotion	[61]
miR-198	Pancreatic cancer pathogenesis	[62]
miR-200c	Biogenesis of leiomyoma	[63]
miR-204	Biosynthesis of sulfated proteoglycan	[64]
miR-221/222	Oncogenesis	[65]
miR-224	Inflammatory response	[66]
miR-335-3p	Modulate PAH	[67]
miR-448	EMT	[68]
miR-650	Glioma development	[69]
let-7	Progenitor differentiation; Neuroplastic responses	[50]
miR-9	Differential regulation	[54]
miR-16/21	Cell proliferation	[55]
miR-24-3p	Vascular endothelial cell proliferation	[56]
miR-29b	Leukemia growth	[57]
miR-30b	Synaptic signaling	[52]
miRNA-125b	Sstrogliosis and glial cell proliferation	[52]
miR-130a	Lung microvascular remodeling	[58]
miR-146a	Immune mediation	[59]
miR-149-5p	Epithelial cell inflammation	[53]
miR-155	Induces functional impairment of VSMCs	[60]
miR-181a	Tumor promotion	[61]
miR-198	Pancreatic cancer pathogenesis	[62]
miR-200c	Biogenesis of leiomyoma	[63]
miR-204	Biosynthesis of sulfated proteoglycan	[64]
miR-221/222	Oncogenesis	[65]
miR-224	Inflammatory response	[66]
miR-335-3p	Modulate PAH	[67]

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miR-448	EMT	[68]
miR-650	Glioma development	[69]

VSMCs, vascular smooth muscle cells; PAH, Pulmonary arterial hypertension; EMT, Epithelial-mesenchymal transition

2.3. The role of NF-κB signaling in the secretion of SASP

Inflammatory infections induce cells and organs experiencing detrimental response. DNA damage response (DDR), p38MAPK signaling activation, ROS creation and cGAS-STING axis transduction are capable of activating NF-κB signaling pathway. In senescent cells, the activated NF-κB signaling pathway results in the formation of a large number of age-related pathological processes and diseases, such as cancer, type 2 diabetes, neurodegeneration, age-related macular degeneration, metabolic diseases, autoimmune diseases, and cardiovascular diseases [33]. For senescent cells, the most obvious biochemical feature is the secretion of SASP factors. It is well documented that the secretion of SASP factors is regulated by p53, mTOR, TGF-β, Wnt and NF-KB signaling pathways. However, the transcription factors, which ultimately regulate SASP factor expression at the mRNA level, mainly include NF-κB and CCAAT/enhancer binding protein β (C/EBPβ) [18]. The putative physiological mechanisms that provoke SASP in senescent cells by stimulating the NF-κB signaling cascade response was summarized in Figure 2.

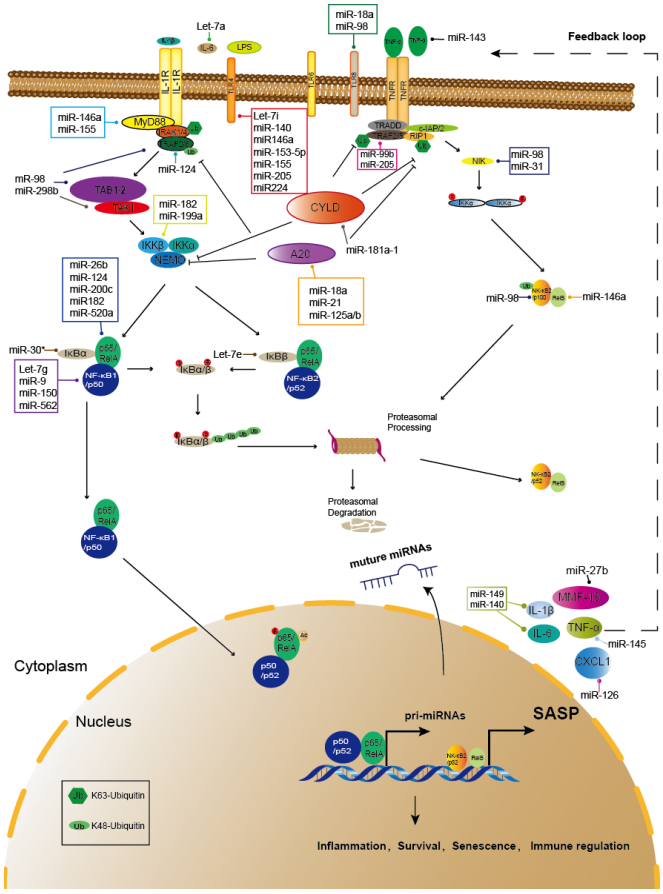

Figure 2 The crosstalk between miRNA and NF-κB signaling.

3. miRNAs and SASP factors

3.1. Regulatory relationship between miRNAs and SASP

miRNAs are first identified to regulate cell cycle regulators involved in the occurrence of pathological changes or senescence process in mammalian cells. Therefore, the dysfunction of

miRNAs plays detrimental roles in organ aging process and cause many age-related diseases [70]. Table 3 summarizes the miRNAs that regulate the production and secretion of SASP. It is well documented that the increase of miR-3150a-3p expression, targeting the PI3K/AKT, ERK, NF-κB signaling pathways, results in the production of TNF-α and IL-1β[71]. Moreover, miR-34a could induce IL-6 expression and participate in the formation of senescent phenotype in endothelial or endothelial progenitor cells (EPC) through downregulating SIRT1 expression [36].

Importantly, miRNA can also be regulated by SASP factors [72]. TNF-α, a member of SASPs, is reported to enhance with aging by activating NF-κB signaling and thus, promoting translocation of the p65 (RelA) together with other DNA-binding factors to stimulate the expression of regulatory miRNAs[73]. Similarly, COX-2-stimulated miR-335 can also target PTEN and promote aging-related phenotypes[74].

Table 3 miRNAs identified as regulator of senescence-associated molecular.

miRNAs	Target gene	Effect on aging	Ref
Let-7	HMGA2; IGF2BP1; KRAS	Targets proliferative proteins that prevent senescence	[75]
miR-9	OPTN; MMP-14	Suppresses autophagy to promote progression of aging	[76]
miR-17-3p	PAR4	Inhibits the transcription of CEBPB and resulting in cellular senescence	[77]
miR-15b	SIRT4	Accelerates the production of mitochondrial ROS	[78]
miR-22	HSP47	Reduces aging-associated tissue fibrosis	[79]
miR-27b	MMP-13	Cartilage degradation in OA joints	[80]
miR-31	MyD88	Relieves neurocyte cell inflammatory	[81]
miR-34a	SIRT1	Impairment of SIRT1 may be related to EPC senescence	[82]
miR-140	IL6; IL1B; SDC4	Inhibits inflammation and stimulates Chondrogenesis in OA	[83]
miR-146a	TRAF6	Regulates mesenchymal stem cells senescence	[84]
MiR-149	TNFA; IL6; IL1B	Suppresses pro-inflammatory cytokines signaling	[85]
miR-181a	NLK; BCL2; MAPK1	Promotes NK cells development and function with aging	[86]
miR-199b-5p	GSK-3β	Inhibits wnt/β catenin and differentiation	[87]
miR-204	SLC35D1	Affects the structure of the cartilage matrix and accelerates the degenerative process	[64]
miR-216a-5p	TGFBR2	Restrains inflammation in bronchopneumonia.	[88]
miR-331-3p	SQSTM1	Affects the selective autophagy pathway during AD process	[76]
miR-335	ROCK1; PTEN	Angiogenesis and inflammation	[74, 89]
miR-623	CXCL12	Affect NPC apoptosis and senescence, and inflammatory factor levels	[90]

HMGA2, High-mobility group AT-hook 2; IGF2BP1, Insulin growth factor 2 mRNA-binding protein 1; OPTN, Optineurin; Hsp47, Heat-shock protein 47; SDC4, syndecan 4; NLK, Nemo-like kinase; SLC35D1, chondroitin sulfate disaccharide repeats; TGFBR2, Transforming growth factor-beta receptor 2; SQSTM1, Sequestosome 1; ROCK1, Rho-associated coiled-coil containing protein kinase 1; NPC, Nucleus pulposus cell

4. Conclusion

As a pivotal transcription factor generally entangled in numerous signaling pathways, NF-κB regulates the systematic expression of many genes mainly associated with immune and inflammatory responses, cell growth, differentiation, cellular senescence and tumorigenesis[23, 25]. In the activation of NF-κB signaling, IκB is phosphorylated and then ubiquitin-labeled to be degraded by proteasomes Therefore, miRNAs that involved in the ubiquitination and proteasomal degradation pathways are also essential in modulating NF-κB activity, and then regulating the secretion of SASP factors [27]. Furthermore, NF-κB activation is able to initiate the expression of miRNAs strengthening the complexity of signaling regulatory networks and forming a feedback loop between NF-κB and miRNAs. Meanwhile, many studies have shown that SASP factors, such as IL-1β, TNF-α and IL-6, are associated with miRNA biogenesis and these synthetic miRNAs can target matrix metalloproteinases and senescence-related genes which in turn regulate the expression of senescence-related proteins.

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