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MiR-147: functions and implications in inflammation and diseases

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Abstract

MicroRNAs (miRNAs) are small non-coding RNAs (19~25 nucleotides) that regulate gene expression at a post-transcriptional level through repression of mRNA translation or mRNA decay. miR-147, which was initially discovered in mouse spleen and macrophages, has been shown to correlate with coronary atherogenesis and inflammatory bowel disease, and modulate macrophage functions and inflammation through TLR-4. Altered miR-147 level has been shown in various human diseases including infectious disease, cancer, cardiovascular disease, neurodegenerative disorder, etc. This review will focus on the current understanding regarding the role of miR-147 in inflammation and diseases.

Keywords

miR-147; infectious disease; cancer; cardiovascular disease; neurodegenerative disorder

Introduction

MicroRNAs (miRNAs) are highly conserved short noncoding RNAs with 19 to 25 nucleotides in size. MicroRNAs act as imperfect sequence guides to recruit a ribonucleoprotein (RNP) complex to the complementary RNAs, leading to the mRNAs or other noncoding RNAs cleavage and degradation, resulting in the reduction of targets expression. A single miRNA can target hundreds of mRNAs and influence the expression of many genes often involved in a functional interacting pathway(1, 2). Since the first miRNA, lin-4, was found in 1993, over 1000 mammalian miRNAs have been identified(3, 4).

miR-147 was first identified in mice spleen tissue in 2002(5). Liu and colleagues found that murine miR-147 was derived from the transcripts of the normal mucosa esophagus specific 1 (NMES1) gene, a potential tumor suppressor. miR-147 was induced in murine macrophages after stimulation of multiple toll-like receptors (TLR2,TLR3 and TLR4) and in the lungs of LPS-treated mice. miR-147 was reported to be a part of a negative feedback loop inhibiting LPS-induced proinflammatory response in macrophages(6, 7). Given its

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Conflicts of Interest

The authors declare no conflicts of interest.

roles in the inflammatory regulation, miR-147 has been widely studied in different diseases including infectious disease, cancer, and cardiovascular disease.

miR-147 and infectious disease

miRNAs bind target mRNAs, typically within the 3′ untranslated region (UTR), to cause their degradation or translational inhibition and thereby regulate various biological processes(8). Mounting miRNAs have been studied in various pathogenic diseases and host immunity(9, 10). Recently studies even implicated complicated roles of miRNAs in viral replication that they can both inhibit and promote viral infections(11, 12).

Altered expression of miR-147 was found through miRNA profiling between healthy and diseased individuals. Yeruva and colleagues compared the expression pattern of 134 miRNAs in mice infected with two Chlamydia muridarum variants (C. muridarum Var001 [CmVar001] and CmVar004). They found that in the mice infected with CmVar004, which grows slower *in vitro* and elicits lower rate of upper genital tract pathology, there is lower expression of inflammatory chemokines and cytokines, and higher expression of miR-147–3p together with 11 other miRNAs. Since the samples were collected within 24 hours of infection, the changes of these 12 miRNAs, including increased miR147 expression, could become a potential predictor in the individuals infected with C. muridarum for their risk to develop pelvic inflammatory disease(13).

Increased sputum miR-147 expression was found in the patients with active pulmonary tuberculosis(14). *In vitro* study showed that miR-147–3p expression was upregulated in murine RAW264.7 macrophages infected with *Mycobacterium marinmu*, which inhibited the production of IL-6 and IL-10 and significantly reduced *Mycobacterium marinum* intracellular survival(15).

The nucleotide-binding oligomerization domain-containing proteins (NOD) 1 and 2 are mammalian cytosolic pattern recognition receptors, which sense bacterial peptidoglycan fragments and initiate cytokine expression and host defense. Intriguingly, activation of NOD inhibited miR-147–3p expression in murine pulmonary endothelial cells, causing upregulation of cytokines such as TNF-α and IL-6. Further investigation revealed that the 3’ UTR of the murine TNF-α and IL-6 mRNA contains the predicted binding site of miR-147(16).

miR-147 expression was also found upregulated in the fresh liver biopsies collected from patients diagnosed with chronic hepatitis C virus infection comparing to normal controls(17). However, miR-147 was downregulated in the infection of Porcine Reproductive and Respiratory Syndrome Virus (PRRSV). PRRSV infection causes Porcine Reproductive and Respiratory Syndrome (PRRS), which is characterized by late term abortions and respiratory disease. Decreased miR-147 was found in the PRRSV-infected porcine alveolar macrophages and miR-147 mimic was confirmed to suppress PRRSV replication(9). Limthongkul and colleagues found that one of the insect cell-derived anionic septapeptides inhibited the multiplication of dengue viruses (DENV-1 16007, DENV-3 16562, and DENV-4 1036) in primary human monocytes. miR-147 expression, together

with other miRNAs such as miR-133a and cytokines such as IFN-I, was upregulated and may mediate the anti-DENV activity of the septapeptides in the DENVs infected primary human monocytes(18).

To study miRNAs roles in the influenza virus infection, host miRNAs expression were investigated and compared in the mice infected with two different influenza A viruses (virus with low pathogenicity or high virulent virus), or in two different susceptible strain mice infected with the same influenza A virus. miR-147 is among the miRNA profiles which display significant difference between groups in both studies. These results suggest that miR-147 may play some role in the influenza A virus infection and host response(12, 19).

miR-147 and cancer

Through RNA silencing and post-transcriptional regulation of different target genes expression, miR-147 participates in various biological processes, including cell proliferation, apoptosis and migration and is considered as a potential candidate for cancer biomarker or even therapeutic target.

The expression of miR-147 has been shown to be upregulated in different samples from individuals with various cancers or carcinomas. In laser microdissected cells from tongue squamous cell carcinomas, miR-147 expression was dramatically increased in comparison to the paired normal tissues(20). Expression of miR-147b in esophageal squamous cell carcinoma (ESCC) tissues and cells were also found to be significantly higher than that in para-carcinoma tissues and normal esophageal epithelial cell. Its expression was closely associated with ESCC clinical staging, invasion depth, histological grading and lymph node metastasis. *In vitro* study showed that miR147 inhibitor suppressed cell proliferation and reduced ESCC cells invasion through upregulating NDUF4, its direct target gene(21). miR-147 was significantly upregulated in gastric cancer tissues and cell lines. miR-147 inhibitor decreased cancer cell proliferation and enhanced the chemosensitivity of gastric cancer cells to 5-fluorouracil (5-FU) by promoting cell apoptosis. Phosphatase and tensin homolog (PTEN) was the direct target of miR-147 and mediated its role in the PI3K/AKT signaling pathway (22, 23). In contrast to other GI tumors, lower miR-147 expression was found in several colon cancer cell lines. *In vitro* study in colon cancer cell lines HCT116 and SW480 confirmed that miR-147 reduced the expression of cancer stem cell markers such as OCT4 and SOX2 and inhibited cell epithelial-to-mesenchymal transition. miR-147 also induced cell mesenchymal-to-epithelial transition, inhibited cell invasion and motility, promoted cell G1 arrest and dramatically reversed the native drug resistance of the colon cancer cell line HCT116 to gefitinib(24, 25).

The expression of miR-147 was profoundly regulated in hepatocellular carcinoma (HCC). Sui and colleagues found that miR147 expression was significantly decreased in hepatocellular carcinoma tissue and HCC cell lines compared to the adjacent non-carcinoma tissues and normal liver cell lines. Further *in vitro* study confirmed that miR-147 significantly inhibited HCC proliferation and migration, increased 5-FU chemosensitivity through its downstream target gene HOXC6(26). Han and colleagues showed that miR-147 expression, together with other 5 miRNAs including miR-19a, miR-886–5p, miR-126,

miR-223 and miR-24, was upregulated in primary hepatocellular carcinoma (HCC) samples from patients who had developed HCC recurrence compared to those with non-recurrence following orthotopic liver transplantation(OLT). This six-miRNA signature was a significant independent predictor of overall survival and recurrence-free survival, had high sensitivity and specificity in predicting HCC recurrence, and may serve as biomarker for prognosis of HCC patients following OLT(27).

In non-small cell lung cancer (NSCLC), serum miR-147 expression level could also be a useful biomarker. miR-147 expression was decreased in NSCLC tissues comparing with their adjacent normal lung tissues. Serum miR-147 expression was down-regulated in NSCLC patients, especially in advanced NSCLC patients and the patients with lymph node metastasis. Low serum miR-147 expression level was an independent prognostic factor for poor prognosis of NSCLC(28, 29). miR-147 inhibited cell proliferation, migration and invasion in NSCLC through suppressing the expression of brain-derived neurotrophic factor (BDNF), one of its direct targets(29). However, miR-147 expression was up-regulated in small cell lung cancer tissues and was associated with chemoresistance(30).

Role of miR-147 was also investigated in breast cancer and bladder cancer. miR-147 was found to suppress the proliferation, invasion and migration of breast cancer cells through targeting the Akt/mTOR signaling pathway(31). miR-147 also suppresses breast cancer through co-targeting EGFR-driven cell-cycle network proteins and inhibits cell-cycle progression and proliferation in breast cancer(32). Chen and colleagues demonstrated that mir-147 mediated the role of hsa_circ_0068307 on bladder cancer through suppressing c-Myc expression, an important factor mediating cancer stem cell differentiation(33).

miR-147 and cardiovascular disease

miR-147 is well known for its role in the inflammation regulation. It also modulates cell proliferation, apoptosis and differentiation through different target genes and different signaling pathways. Recent studies further reveal the regulatory role of miR-147 in various cardiovascular diseases.

Hoekstra M and colleagues screened the profile of miRNAs in peripheral blood mononuclear cells (PBMCs) from patients with or without coronary artery disease (CAD). It was found that expression of miR-135 was 5-fold increased and miR-147 was 4-fold decreased in PBMCs from CAD patients as compared to controls, resulting in a 19-fold higher miR-135a/miR-147 ratio in CAD(34). Plasma expression of miR-147, together with several other miRNAs, was also found significantly decreased in children with dilated cardiomyopathy (DCM) compared to healthy controls(35). miR-147, together with other miRNAs, could be potential biomarkers for CAD and DCM. Recent study indicated that miR-147 could also be a candidate of therapeutic target for myocardial infarction treatment. In a rat myocardial infarction model, miR-147 expression was significantly decreased in the myocardium tissue of infarcted and border zones. Overexpression of miR-147 in rats with myocardial infarction can inhibit myocardial inflammation and apoptosis, and improve cardiac function *via* targeting HIPK2(36).

Mir-147 also appears to play a role in the coronary heart disease associated with the polymorphism rs3088442 G→A located in the 3' UTR of the SLC22A3 gene. Li and colleagues discovered that G→A substitution of SNP rs3088442 created a putative binding site for miR-147 in the SLC22A3 mRNA and recruited miR-147 to inhibit SLC22A3 expression, leading to alleviation of LPS-induced monocyte inflammatory response by interrupting NF-κB and MAPK signaling cascades in a histamine-dependent manner(37).

The development of abdominal aortic aneurysm is characterized by inflammatory infiltration and vascular remodeling. Recent work from Spinosa and colleagues has indicated that miR-147 also plays a role in abdominal aortic aneurysm. They used elastase-treatment to induce abdominal aortic aneurysm (AAA) in mice and administrated extracellular vesicles (EVs) that derived from mesenchymal stromal cell into the AAA mice. They found miR-147 was up-regulated in the murine aortic tissue of AAA mice. Administration of EVs derived from the cells transfected with miR-147 mimic, but not miR-147 inhibitor, significantly attenuated the aortic diameter, decreased elastic fiber disruption, and mitigated proinflammatory cytokines and inflammatory infiltration(38).

Long non-coding RNA (lncRNA) maternally expressed gene 3 (MEG3) has been identified as a regulatory molecule in angiogenesis. Xu and colleagues found that MEG3 induced cell apoptosis and suppressed cells viability, migration and tube formation in the human microvascular endothelial cell line (HMEC-1) by suppressing miR-147 expression. Further investigation demonstrated that miR-147 modulated the anti-atherogenic role of MEG3 through regulating ICAM-1 expression(39).

miR-147 and neurodegenerative disorder

Alzheimer's disease (AD) is one of the most common forms of dementia. Pathologically, AD is characterized with the intracellular accumulation of abnormal protein tau and extracellular deposition of Aβ peptides, derived by proteolytic processing of amyloid precursor protein (APP). Misregulation of APP has been confirmed to induce neurodegeneration and AD(40–43). Bioinformatics analysis has identified that there is a putative miR-147 binding site within the 3' UTR region of APP. miR-147 has been shown to efficiently decrease the endogenous expression of APP in Neuro2A cells and Hela cells. Strikingly, one of the APP variants, T171C mutation, has been shown to interfere the regulatory role of miR147 on APP expression by suppressing miR-147 binding due to its immediate adjacency to the miR-147 seed region(44).

Progressive supranuclear palsy is a sporadic neurodegenerative disorder. Tatura and colleagues screened 372 well-characterized microRNAs in the forebrains of progressive supranuclear palsy patients and controls and discovered that miR-147a expression was upregulated, accompanied by the downregulation of its target genes such as NF1, ACLY, ALG12 in these patients(45).

miR-147 also plays a role in the neural hypoxia injury. Han and colleagues found that expression of MEG3 was up-regulated in the hypoxia-injured neural PC12 cells, and aggravated the hypoxia injury. MEG3 suppressed the expression of miR-147, leading to

the upregulation of miR-147 target gene SOX2, and eventually the activation of NF-κB pathway and Wnt/β-catenin pathway(46).

miR-147 and other diseases

Given the role of miR-147 in the inflammatory regulation, it is not surprise to find that miR-147 also plays a role in inflammatory bowel disease (IBD). Crohn's disease (CD) is a major subtype of inflammatory bowel disease. Herb-partitioned moxibustion (HPM) has been proven to be effective in treating CD. miR-147 has been shown to be significantly downregulated in colons of rats with experimental CD and closely associated with the onset of the disease. HPM has been shown to extenuate the inflammatory responses and ameliorate colonic damages *via* upregulating miR-147 expression and subsequently decreasing the inflammation-related mRNAs, as well as the downstream inflammatory cytokines(47). Intriguingly, miR-147 expression has also been shown to be increased in the colonic mucosa and serum of a dog large intestinal IBD model(48).

Michalovicz and colleagues have performed genomic profiling and analysis in an effort to identify biomarkers or genes selectively expressed in astrocytes in astrogliosis. They employed the bacterial artificial chromosome-translating ribosome affinity purification (bacTRAP) technology in an aldehyde dehydrogenase 1 family member L1 (ALDH1L1) bacTRAP mouse model. A known dopaminergic neurotoxicant, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), was used to induce astrogliosis followed by the analysis of the mice striatal tissue. They identified TIMP1 and miR-147 as candidate biomarkers for astrogliosis because of their robust and specific increase after both MPTP and trimethyl tin exposures(49). Decrease of miR-147 expression was found in the dexamethasone-treated C2C12 cell, a mouse myoblast cell line, suggesting a role of miR-147 in dexamethasone-induced muscle atrophy(50). Tanshinone IIA, a well-known flavonoid, elicits an important therapeutic effect by inhibiting LPS-induced inflammatory response in RAW 264.7 cells. Decrease of miR-147 expression, as well as several other miRNAs such as miR-184 and miR-155, was found after Tanshinone IIA treatment(51). Wang and colleagues found that miR147a expression was significantly increased after the radiotherapy, accompanied by dramatic suppression of PI3K/AKT pathway. Using bioinformatics techniques for relationship analysis, they further discovered that miR-147a modulated PDPK1 transcription by binding to the 3′UTR region of PDPK1 mRNA and subsequently regulating AKT activity(52). In an *in vitro* cyclic mechanical stretch-induced apoptosis model, Du and colleagues found that miR-147 attenuated cyclic mechanical stretch-induced endoplasmic reticulum stress and cell apoptosis through its target gene BRMS1 in rat L6 myoblasts(53). Xu and colleagues reported that periodontitis promotes the diabetic development in obese rat by upregulating miR-147, promoting macrophage activation, and aggravating impaired glucose tolerance(54). Li and colleagues found that patients with accelerated phase and blast phase of chronic myeloid leukemia (CML) displayed decreased miR-147 level and increased methylation of miR-147 DNA promoter in comparison with healthy controls. Recent study further showed that miR-147 played important roles in the proliferation and apoptosis in leukemia cells (KCL-22 and K562) *in vitro*, and was the target of the long noncoding RNA MEG3(55).

Conclusion & Future Perspective

Since its first identification in 2002, miR-147 has been increasingly investigated. Changes of miR-147 expression have been reported in various diseases. Further mechanistic studies have demonstrated that miR-147 regulates various biological processes, including cell proliferation, apoptosis, migration, inflammatory responses, as well as virus replication, through binding to its different target mRNAs and suppressing the production of its target proteins. miRNAs are secreted into exosomes or microvessicles. These secreted miRNAs are very stable and can be taken up by cells in the surrounding tissue, or if the vesicles reached circulation, they can reach distant sites(56). miRNA can be easily isolated from cells, tissues and body fluids such as serum, plasma, tears or urine(57) and detected and compared between healthy and diseased individuals. Multiple studies have recommended miR-147, especially in combination with other miRNAs or known biomarkers, as a biomarker for various diseases. Given its increasingly important roles in the pathogenesis of human disease, it is presumable to consider miR-147 as a potential therapeutic target for the above mentioned diseases. Future investigations should be warranted for the mechanistic studies on miR-147 action details and its downstream target genes and signaling pathways.

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