REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

A Brief review of Circulating MicroRNAs and Essential Hypertension

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Abstract

Essential hypertension is a chronic medical condition affecting thousands of people worldwide. It is polygenic and multi-factorial disease resulting from the interaction between genetic and environmental factors. Essential hypertension is implicated in cerebrovascular, cardiovascular and renal diseases. MicroRNAs are considered endogenous, non-coding regulators of gene expression by targeting specific mRNAs for degradation and/ or translational repression. MicroRNAs participate in a variety of developmental processes as metabolism, cell proliferation, and apoptosis. Many studies have reported the possibility of using miRNAs as new biological markers for polygenic diseases as cancer, stem cell aging, coronary heart disease, and essential hypertension. The stability of these miRNAs as miRNA let-7e, miRNA 296-5p, miRNA 605, and miRNA 623 in biological fluids makes them amenable to detection and quantification. This review summarizes the mechanisms by which miRNAs can control normal cellular processes and gene expression and the association of some circulating miRNAs with the incidence of different diseases, particularly essential hypertension.

Keywords: Essential hypertension, microRNA Let-7e, miRNA 296-5p miRNA 605, miRNA 623.

1. Introduction

MicroRNAs (miRNAs) were first reported as a single stranded non-coding RNA molecule, lin-4, in the organism *Caenorhabditis elegans* (Lee et al., 1993). Later on, the regulation of a key gene by lin-4 was reported. Lin-4 was described as a temporal gene regulator, controlling the time of development stages in *C. elegans* (Lee and Ambros, 2001). A second miRNA, let-7, was described in the year 2000 (Reinhart et al., 2000). The prevalence of let-7 was evaluated across numerous species (Pasquinelli et al., 2000). Since then, hundreds of miRNAs have been identified in organisms ranging from viruses, plants, flies, fish, frogs, and mammals, including humans (Miska et al., 2007).Thus, miRNAs were recognized as important regulators of gene expression. More than

1000 microRNA genes were identified in the human genome (Kozomara and Griffiths-Jones, 2011). MiRNAs are the most prevalent class of small RNAs in animals (Farazi et al., 2008).

1.1.MiRNA biogenesis

MicroRNA production is endogenously regulated by their target genes, which are located throughout the genome. About 50% of miRNAs are expressed from intergenic, non-protein-coding regions, while others are encoded in intra-genic regions within the intronc regions (Lagos-Quintana et al., 2001). Some miRNA genes are clustered together in the genome and transcribed as poly-cistronic miRNA transcripts. Clustered miRNAs have a high degree of sequence similarity. Regulation of miRNA biosynthesis is a multistep process that starts in the nucleus of the cell, and continues in the cytoplasm until the mature miRNA can exert its function (Thum et al., 2007), (Figure 1).The sequence of this process is as follows:

1. MiRNAs are transcribed by RNA polymerase II as a primary miRNA (pri-miRNA) transcript that is capped by polyadenylation (Bartel, 2004).

2. The long transcript "hairpin structure", pri-miRNA, is recognized and cleaved by a multi-protein complex (microprocessor). The core component of this microprocessor is called DROSHA (an RNase III), and its associate DGCR8 (DiGeorge syndrome critical region gene 8, a double stranded RNA-binding domain protein), cleave pri-miRNA to a 60-70nucleotide stem-loop structure, called precursor miRNA (pre-miRNA) (Zeng and Cullen, 2003).

The Drosha- cleavage process is controlled by RNA binding proteins including the DEAD box RNA helicases p68 (DDX5) and DEAD box RNA helicases p72 (also known as DDX17), as well as heterogenous ribonucleoproteins (hnRNPs) (Gregory et al., 2004).

Without the DEAD box RNA helicases, Drosha cannot generate pri-miRNA (Fukuda et al, 2007).

3. Drosha cleavage product, pre- miRNAhas2 nt 3´ overhang that is recognized by Ran-GTP and exportin-5 (XPO5) minor export factor, which transport the pre- miRNA into the cytoplasm (Okada et al., 2009).

4. The exported pre-miRNA is processed in the cytoplasm to a duplex 22 nucleotides large. The pre-miRNA is cleaved again by a cytoplasmic RNase III called Dicer together with Trans -activator RNA (tar)-binding protein (TRBP) (Knight and Bass, 2001). Dicer has a single processing center with two dimerized RNase III domains. Each RNase domain independently cuts one RNA strand of the duplex and generates products with 2 nucleotide 3′ overhangs (Figure 1) (Filipowicz, 2005).

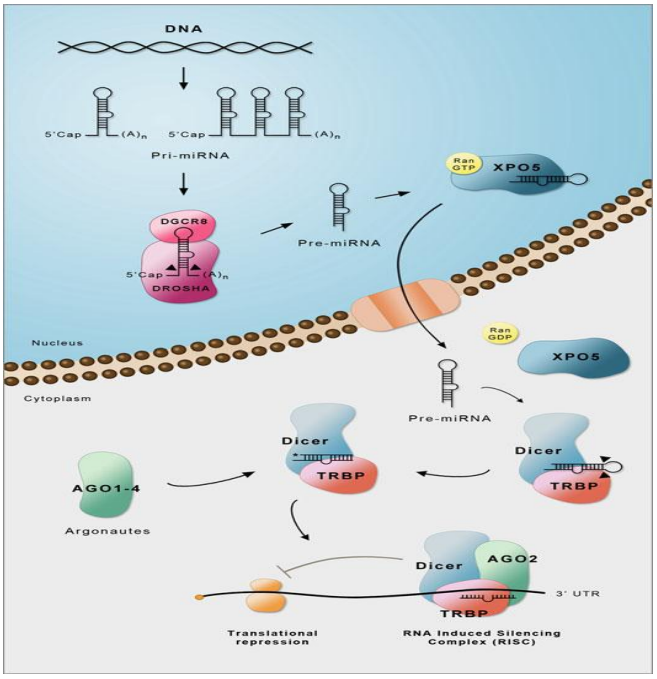

Figure 1.Biogenesis of miRNAs. Ago2, Argonaute; DGCR8, DiGeorge syndrome critical region gene 8;DROSHA, RNase III enzyme; RISC, RNA-induced silencing complex; pre-miRNA, precursor miRNA; pri-miRNAs, long primary transcripts; TRBP, TAR-binding protein; XPO5, exportin-5 (Thum et al., 2007).

5. The resulting new RNA duplex is loaded on Argonaute-2 protein (AGO2) generating the effector complex, RNA induced silencing complex (RISC). RISC is the cytoplasmic effector form of the miRNA pathway and contains a single-stranded miRNA which is ready to guide it to its target mRNAs. The RISC loading complex (RLC) is formed. It is a multi-protein complex composed of Dicer, TRBP, HIV-1 trans activating response (TAR) RNA binding protein and the core component AGO2. The mature miRNA remains bound to the AGO protein.

1.2.Mechanism of action of miRNAs

MiRNAs regulate gene expression by binding with complementary sequences of the 3' untranslated region (UTR) of targeted mRNAs, resulting in either translational suppression or transcript degradation (Buchan and Parker, 2007) (Figure 2). The mechanism of action depends on how much the miRNA forms a perfect Watson Crick pair with its target mRNA, which is achieved by two mechanisms. In the first mechanism (cleavage mechanism), miRNA is in a perfect or nearly perfect Watson-Crick pair with the target mRNA. The mature miRNA is loaded into RISC with TRBP and protein activator of protein kinase (PACT). Then, the AGO-2 endonuclease activity in RISC cleaves the passenger strand of the mature RNA, and miRNA single strand along with RISC complex targets the mRNA for degradation (Martinez et al., 2002) (Figure 3).

In the second mechanism, the sequences of miRNA and target mRNA are not completely complementary. Translational repression occurs by a bypass mechanism, which requires a helicase activity to unwind and discard the miRNA strand, rather than directly cleave the mRNA strand by AGO-2. Once the miRNA strand has been unwound or discarded, the RISC causes translational suppression. At least 60% of protein encoding genes are regulated by miRNAs (Bartel, 2009), and the same miRNA can regulate different mRNAs.

1.3 Functions of miRNAs

MiRNAs are involved in many biological processes, such as cell differentiation, cell proliferation, cell migration, apoptosis, metabolism, and cell defense (Zhang, 2009). They are also involved in development of malignancies and cardiovascular diseases (Ha, 2011). Expression of some miRNAs is tissue-specific (Lagos-Quintana et al., 2002); miR-1, miR-122, and miR-124 are expressed in the heart, liver, and brain, respectively.

2. Circulating miRNAs

Some miRNAs are extremely stable in extracellular fluids as blood plasma, serum,

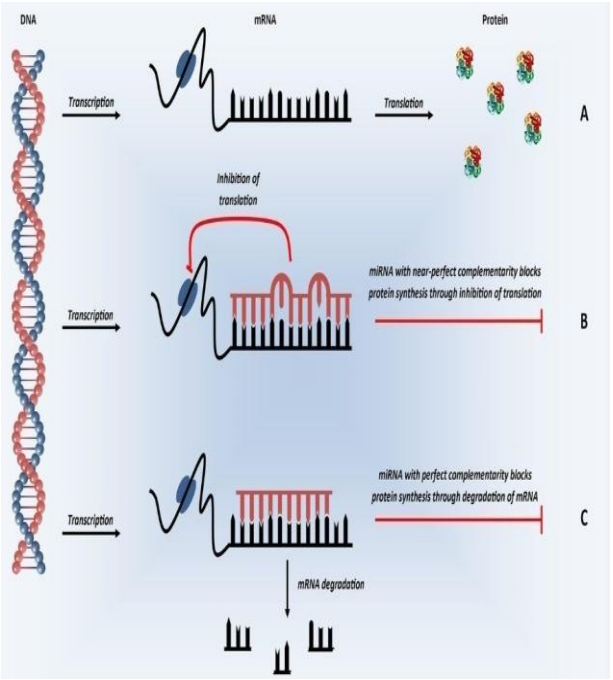

Figure 2. Schematic representation of microRNA mechanism of action (Romaine et al., 2015)

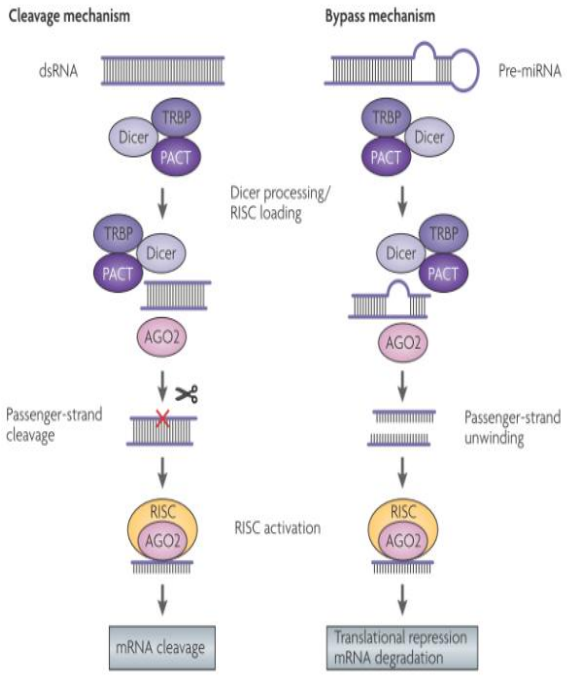

Figure 3. Mechanisms of how miRNAs mediate gene silencing: cleavage and translational suppression (Kim and Rossi, 2007).

urine, saliva, and semen (Weber et al., 2010). The stability of miRNAs in plasma or serum makes it easy to use them as potential biomarkers for detection, diagnosis, and prognosis of diseases. Circulating miRNAs are stable despite the action of ribonucleases. It has been suggested that miRNAs are included into microparticles to protect them from degradation. Microparticles can be exosomes, microvesciles or apoptotic bodies (El-Hefnawy et al., 2004). HDL is also a transporter for endogenous miRNAs (Vickers et al., 2011).

Active release of circulating miRNAs may support their actions as "hormones" in cell-to-cell communication. Plasma levels of miRNAs usually become dysregulated before physical symptoms of disease appear, making them acceptable biomarkers (Romaine et al., 2016).

The potential for using circulating miRNAs as non-invasive, plasma-based biomarkers for detection of disease has been researched and has opened up a field in the monitoring and screening of cardiovascular diseases including hypertension (Nemecz et al., 2016).

2.1. MiRNAs and diseases

Since miRNAs alter gene expression, studies have examined the association between miRNAs and initiation and progression of many diseases. The Human MicroRNAs Disease Database lists miRNAs implicated with diseases (Table 1).

2.1.1. MiRNAs and essential hypertension

MiRNAs are implicated directly and indirectly in the pathogenesis of essential hypertension (Nadar et al., 2006).

2.1.1.1. miRNAs that target vascular endothelium

The vascular endothelium contributes to the pathogenesis of hypertension by many mechanisms. In the hypertensive patient, high blood pressure leads to activation of endothelial cells, the release of inflammatory and pro-coagulant mediators, and the adherence of neutrophils and platelets. As a result, the endothelium becomes dysfunctional, leading to impaired vasodilatation and a pro-inflammatory and pro-thrombic phenotype of the vessel wall. (Landmesser and Drexler, 2007).

Endothelial dysfunction and defective angiogenesis are due to defective vascular endothelial growth factor (VEGF) signaling. MiRNA 126 is an effective factor for vascular integrity and angiogenesis. Furthermore, targeted deletion of miRNA 126 was associated with leaky vessels and hemorrhage (Wang et al., 2008), through controlling of endothelial response to VEGF. In another study, miRNA 21 was shown to inhibit angiogenesis by decreasing RhoB expression at endothelial cells (Sabatel et al., 2011).

Table 1. Association of miRNAs with common pathologies (Li and Kowdley, 2012).

Disease	MiRNA	References
Alzheimer's disease	miR9,miR 29, miR 146, miR 107	(Li and Kowdley, 2012) (Esteller, 2011)
Arrhythmia	miR 1, miR 133a	(Hedley et al., 2014)
Atherosclerosis	miR 10a, miR 143, miR 145, miR 126, miR 33	(van Rooij and Olson, 2012), (Esteller, 2011)
Cancer Breast cancer Lung cancer Liver cancer	miR 125, miR 145, miR 21, miR 210 miR 155, let-7a miR 29b	(Li and Kowdley, 2012)
Cardiac hypertrophy	miR 21, miR 199b	(van Rooij and Olson, 2012)
Metabolic disease	miR 33, miR 122	(Fernández-Hernando et al., 2013)
Pulmonary hypertension	miR 21, miR 145, miR 210	(Zhou et al., 2015)
Type 2 diabetes	miR 27a, miR 29a, miR 125a, miR 222	(Ferland-McCollough et al., 2010)

Many other miRNAs have been found either to be positive angiogenic factors (miR-27b, miR 130a, miR 210, miR 378, miR17–92 cluster, and miR let-7f), or to have negative angiogenic effect (miR 15, miR 16, miR 20a, miR 20b, miR 24, miR 221, miR 222) (Hartmann and Thum, 2011; Urbich et al., 2008).

2.1.1.2. miRNAs that target renal function

The kidneys play a critical role in maintenance of normal blood pressure through sodium homeostasis,blood volume, and rennin angiotensin aldosterone system (RAAS). MiRNAs play roles in both acute and chronic kidney diseases.The mechanism of action miRNAs at the kidneys were demonstrated by three methods:

a) Global depletion of miRNAs from specific cell types in kidneys by using conditional Dicer-knockout mouse models.

b) Analysis of differential miRNA expression in renal diseases to identify potential pathogenic miRNA species.

c) Study of miRNA regulation of specific genes that play pathogenic roles in renal disease (Bhatt et al., 2011).

Results from these studies showed that in certain Dicer knockout models of mice, pathological abnormalities of podocyte cells of the glomeruli was correlated with end stage renal disease and maintenance of blood pressure (Harvey et al., 2008). This mouse model clearly suggests that Dicer is a critical factor for the maintenance of podocyte homeostasis. It is suggested that the loss of miR-30 family miRNAs from podocytes may be responsible for the defect in the homoeostasis and function of podocytes in kidney (Agrawal et al., 2009).

2.1.1.3. miRNAs that target the RAAS system of kidney

The RAAS has a critical role in controlling BP through several enzymes, peptides, and receptors. For example, angiotensin II, a peptide hormone, has a vasoconstrictor effect and can release other hormones as aldosterone and vasopressin. A correlation between serum miRNA 155 and low risk of hypertension was demonstrated (Martin et al., 2006). The release of angiotensin II is controlled post-transcriptionally by miRNA 155. MiRNA 155binds to the angiotensin II coding gene, AT1, which inhibits its transcription (Martin et al., 2006). Another miRNA, miRNA 9 can decrease the hypertrophic effect of aldosterone in cardiac and vascular smooth muscle cells through suppressing myocardin expression (Wang et al., 2010).

A study of 850 miRNAs in renal tissue of hypertensive and healthy controls showed that reduced expression of miRNA 181a and miRNA 663 was associated with elevation of rennin mRNA expression (Marques et al., 2011). Studies also showed that 46 miRNAs had aberrant expression in hypertensive patients compared with healthy individuals. Among these, human cytomegalovirus-miR-UL112, miR-605, miR623, miR-let-7e, miR-516b, miR-600, kshv-miR-K12-6-3p, miR-602 and miR-1252 were up-regulated, andmiR-296-5p, miR-133b, miR-625, miR-1236, miR518b, miR-1227, miR-615-5p, miR-18b, miR-1249, miR-3243p, ebv-miR-BART17-3p, ebv-miR-BART19-5p, kshv-miRK12-10a, kshv-miR-K12-10b, miR-4865p, miR-30d, miR-664 and miR-634 21 were down regulated (Marques et al., 2015). Correlations were discovered between exercise and expression of certain miRNAs targeting the RAS genes in hypertensive patients. Other miRNAs as miR-130a are correlated to vascular remodeling which may be explained by the effect of RAAS system on the patho-physiology of vascular remodeling (Renna et al., 2013,Wu et al., 2011).

2.1.1.4. microRNAs that target vascular smooth muscle cells

Peripheral vascular resistance has a critical role in development of hypertension. Vascular smooth muscle cells (VSMCs) as a contractile factor can determine vascular tone and resistance. Proliferationof VSMCs in response to stress results in vascular remodeling, a correlating factor with essential hypertension (Feihl et al., 2008). Vasodilatation in response to essential hypertension was more frequent in mice with less VSMC synthesis. The synthesis of VSMCs was regulated with dicer.So, VSMC- specific deletion of dicer showed impairment of vascular system in mice models. Mice lacking miR-143 and miR-145were similar to that of the VSMC-specific Dicer knockout mice, showing an important role for VSMC differentiation and function (Albinsson and Sessa, 2011).

Another miRNA, microRNA 21, located in arterial smooth muscle cells, has been found to be a critical regulator of VSMC proliferation, which decreased with miRNA 21 inhibition (Ji et al., 2007).

2.2.miRNA let-7

Let-7 was first discovered and well studied in *Caenorhabditis elegans*, in which it regulates developmental timing (Reinhart et al., 2000), larval stage 4–to–adult transition (Grosshans et al., 2005), and stage-specific neuromuscular tissue development (Frasch M., 2008). In the mouse, let-7 is involved in neural lineage specificity of embryonic stem cells and brain development (Wulczyn et al., 2006). Let-7 is involved in many physiological processes as development of nervous system, muscle formation, cell adhesion and gene regulation (Cao et al., 2016).

Let-7 is also involved in many pathological diseases as inhibition of the growth of tumor cells in lung and hepatocellular carcinoma (Ardekani and Naeini, 2010,Barh et al., 2010), and neurodegenerative diseases as Parkinson's disease(Leggio et al., 2017).

2.2.1. Types of miRNA let-7 and diseases

There are 13 mature subtypes of miRNA let-7 family which have been identified in humans, including mir let-7a-1, let-7a-2, let-7a-3,mir let-7b, mir let-7c, mir let-7d, mir let-7e, mir let-f-1, let-7f-2, mir let-7g, mir let-7i, mir 98 and mir 202 (Fedorko et al., 2017).

.Exogenous let-7 over-expression was associated with antitumor efficacy in many human cancers (Guan et al., 2015). The let-7 miRNA family has been reported to regulate immune activation in various cell types. In human epithelial cells, let-7suppresses immune responses to pathogens by inhibition of Toll-like receptor 4 (TLR4), and down-regulation of let-7 restores immune activation (Chen et al., 2007). In mammalian macrophages exposed to pathogen invasion, let-7 controls the immune response via inhibition of the NFKB1 pathway or repression of cytokine expression (Kumar et al., 2015). Studies showed that the overexpression of miRNA let-7 family, including let- 7a/7b/7c/7e was correlated with hepatocellular carcinoma progression and poor prognosis (Shi et al., 2017). MicroRNA let-7a was studied with many diseases and was shown to suppresses breast cancer cell migration and invasion through down-regulation of C-C chemokine receptor type 7 (Kim et al., 2012). Subtypes of let-7a were studied separately with many types of tumors. MicroRNA Let-7a-1 was shown to be associated with colorectal cancer through inverse relationship between let-7a expression levels and the density of T cells in colorectal cancer tissue, which is positively associated with colorectal cancer-specific mortality (Dou et al., 2016).Lower expression levels of miRNA let-7a-1 and pituitary adenoma was studiedand revealed the role of let7a-1 as a tumor suppressor by targeting high mobility group AT-hook 2 (HMGA2)gene expression(Li et al., 2014).

Serum expression of let-7d and let-7e was different in patients with Crohn's disease. As a result, they are used as therapeutic biomarkers in patients with Crohn's disease(Fujioka et al., 2014).

Let-7i andlet-7f were significantly elevated in gastric cancer and serum let-7c was negatively correlated to pepsinogen C and its target gene, indicating that let-7 miRNA may be a potential biomarker for the diagnosis of gastric disease (Liu et al., 2015).

Let-7g induced increased expression of vascular endothelial growth factor-A (VEGF-A) and VEGF receptor-2, improving angiogenesis (Hsu et al, 2017). Other study suggested that miR-let-7g may serve as a potential therapeutic agent for treating atherosclerosis through inhibiting lectin-like oxLDL receptor (LOX-1) expression, which is expressed in VSMCs, vascular ECs and macrophages, and plays a critical role in the pathogenesis of atherosclerosis. Overexpression of LOX-1resulted in the significant promotion of proliferation and migration of human aortic smooth muscle cells (ASMCs), increasing the incidence of atherosclerosis (Liu et al., 2017).

Severe preeclampsia was correlated with up-regulation of miRNA 202-3p during the first trimester (Singh et al., 2017). MiR 202 may function as a tumor suppressor in endometrial adenocarcinoma (EAC) by targeting fork head box (FOXR2) oncogene, which may provide new insights into the molecular mechanism (Deng et al., 2017).

2.2.2. Biogenesis of let-7 and mechanism of action

The biogenesis of let-7 is similar to that of other miRNAs. The first step in miRNA biogenesis is transcription from the miRNA transcription unit by RNA polymerase II to produce a primary transcript called pri-miRNA. The pri-miRNA is processed by the microprocessor complex containing an RNAse III–like enzyme, Drosha, and its cofactor, a double-stranded RNA binding protein, Dgcr8, to produce an approximately 60–70 nt pre-miRNA (precursor miRNA).The pre-miRNA is then transported to cytoplasm by exportin 5 (XPO5), in a RAN-GTP (ras- related nuclear protein–guanosine triphosphate complex) – dependent way, where it is cleaved by Dicer (a cytoplasmic RNAse III), to generate an imperfect miRNA: miRNA* duplex of approximately 21–24 nt. One of the strands (the"guide strand") from the duplex is then incorporated into Argonaute (Ago)–containing ribonucleoprotein (RNP) complex; the other strand (the passenger strand) is degraded.

However, there are cases in which both strands of the duplex are detected in the cell. The miRNA–AgoRNP complex causes post-transcriptional regulation of genes, in which miRNA is used as a target to guide the complex to the specific mRNA. Many factors are implicated in regulation of let-7 synthesis (Figure 4).

1. Some factors have inhibitory effect as Lin28 gene and Lin28B gene (Reinhart et al., 2000).They act as post-transcriptional repressors of let-7 biogenesis. Many hypotheses suggested the mechanism either by binding to the loop portion of the pri-let-7 hairpin and the stem of pre-let-7 to inhibit the binding of Drosha or Dicer, or by targeting pre-let-7 through its degradation. When the DNA of the genes that are responsible for miRNAs synthesis are methylated, the expression of let-7 is affected (Lopez-Serra and Esteller, 2011).

2. Another inhibitory complex, is nuclear factor (NF) 90 andNF 45 which showed a higher affinity to pri-miRNA-let-7. They inhibit binding to Drosha- DGCR8 complex (Sakamoto et al., 2009).

3. Interleukin-6 (IL-6), nuclear factor kappa-light-chain-enhancer of activated B cells (NF_kB), insulin like growth factor II mRNA binding protein 1(IMP1), and oncogene c-Myc suppress miRNA let-7 synthesis either directly or indirectly through regulating Lin 28 expression as illustrated in (figure 4) (Barh et al., 2010; Psathas and Thomas-Tikhonenko, 2014; Wang et al., 2012a; Wei et al., 2016b)

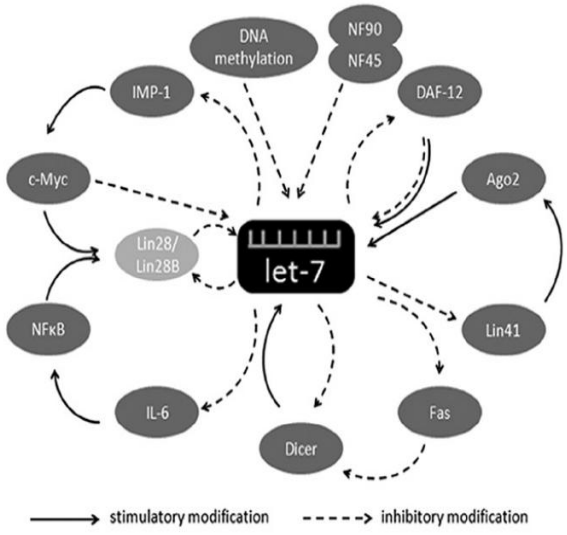

Figure 4. Factors that regulate miRNA let-7 expression. IL-6; Interleukin-6, Ago2; Argonate 2, Lin28 and Lin28B; post-transcriptional repressors genes, NF 90; nuclear factor90, NF45; nuclear factor 45, NF_kB; nuclear factor kappa-light-chain-enhancer of activated B cells, IMP1; insulin like growth factor II mRNA binding protein 1, c-Myc; oncogene, DAF-12; nuclear hormone receptor (Wang et al., 2012b).

4. Ago2, Dicer, and a nuclear hormone receptor (DAF-12), stimulatory factors which activate let-7 biogenesis, are able to directly regulate the transcription of let-7 positively or negatively without the activity of Lin 28 (Diederichs and Haber, 2007; Forman et al., 2008; Hammell et al., 2009) .

2.2.3. Implication of let-7 in cardiovascular disease and essential hypertension

MiRNA let-7 is bound in endothelial cells (ECs) and directly targets several angiogenesis-related factors, making let-7 a miR regulator of angiogenesis (Zhao and Popel, 2015). Studies have also suggested that let-7 may contribute to atherosclerotic disease by regulating tumor necrosis factor-α (TNF-α) (Katayama et al., 2015), glucose metabolism (Zhu et al., 2011), and inflammatory reactions (Liao et al., 2014).

miRNA let-7e was upregulated in Hashimoto's disease (Kagawa et al., 2016). It is used as plasma marker in metabolic dysfunction (Krause et al., 2015), and serum expression can be used in the prognosis of lung cancer (Zhu et al., 2014) and osteoarthritis **(**Beyer et al., 2015). Overexpression of microRNA let-7e correlates with disease progression and poor prognosis in hepatocellular carcinoma (Shi et al., 2017).

2.3. Other miRNAs that were recently studied with essential hypertension

2.3.1. miRNA 296

MiRNA 296 expression is both up- or down-regulated in different metastatic diseases. In parathyroid carcinomas and colon cancer miRNA 296 was down-regulated (Corbetta et al., 2010, Shivapurkar et al., 2013), but it was up-regulated in esophageal carcinomas and immortalized cancer cells (Hong et al., 2010, Yoon et al., 2011). MiRNA 296 functions as a tumor suppressive factor in lung carcinoma(Vaira et al., 2013), hepatocellular carcinoma(Vaira et al., 2012), and prostate cancer (Wei et al., 2011).

MiR 296 was suggested to regulate blood pressure through down-regulation of the Human with-no-lysine kinase-4 (hWNK4) protein at the post-transcriptional level. The hWNK4 protein is a member of the serine-threonine protein kinase family and it is an important factor involved in patho-physiological progress of hypertension through regulating ion channels, co-transporters, altering the balance of NaCl reabsorption and K^+ secretion in the distal part of nephron, and electrolyte homeostasis(Mao et al., 2010).Different studies have reported miRNA 296 to be either up- or down-regulated in hypertensive patients (Cengiz et al., 2015, Li et al., 2011).

2.3.2. miRNA 605

miRNA 605 was upregulated in hypertensive patients, and has been confirmed by microarray and quantitative real-time polymerase chain reaction (qPCR) (Ali et al., 2016). It is not clear how miRNA 605 affects blood pressure. It is hypothesized that there is an association between miRNA 605 and transcription of Syndecan 4 (SDC4) gene. SDC4 encodes the protein syndecan-4, a heparan sulfate proteoglycan whose over-production was associated with elevated BMI, lipid profile and elevated blood pressure (Rose et al., 2015). MiRNA 605 expression was reported to be up-regulated in blood of patients with stroke (Yuan et al., 2016).

A polymorphism of miRNA 605 gene was associated with increased risk of squamous cell carcinoma (Miao et al., 2016), Li-Fraumeni syndrome (Id Said and Malkin, 2015), prostate cancer (Huang et al., 2014), and gastrointestinal cancer (Zhang et al., 2012). MiRNA 605 was downregulated in melanoma cell lines and suppressed melanoma cell growth both in vitro and in vivo. Bioinformatics analysis suggested the mechanism by which the miRNA 605 works. Inositol polyphosphate 4-phosphatase type II (INPP4B) gene is a target of miR 605 and the inhibition of INPP4B is required for the suppressive role of miR605 on melanoma cell growth. Thus, miR605 functions as a tumor suppressor by negatively regulating INPP4B in melanoma (Chen et al., 2017).

2.3.3. miRNA 623

MiRNA 623 was upregulated in patients with cardiovascular diseases (Ali et al., 2016). MiRNA 623 and miRNA 605 were overexpressed in patients with essential hypertension, but serum expression did not correlate with elevated systolic and diastolic blood pressure. Rather, serum expression of both miRNAs correlated with dyslipidemia, indicating that they are not directly associated with essential hypertension but associated with the dyslipidemia that frequently accompanies the disease (Badawy Et al., 2018). MiRNA 623 was found to inhibit lung adenocarcinoma through decreasing expression of target gene Ku80 and metalloproteinases (MMPs), which promote tumor invasion, metastasis, and angiogenesis (Wei et al., 2016a).

3. Conclusion

The stability of miRNAs in biological fluids and resistance to degradation allow them to be easily detected and measured. There is a strong association between circulating miRNAs, as biological markers, and polygenic diseases as essential hypertension.

4. Conflict of interest

The authors report no declaration of conflict of interest.

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