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REVIEW ARTICLE

MicroRNAs in Retinoblastoma: Potential diagnostic and therapeutic biomarkers[†]

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Abstract

Retinoblastoma (Rb) is known as one of important childhood malignancies which due to inactivation of the *RB* gene (tumor suppressor gene). The early detection of Rb could provide better treatment for Rb patients. Imaging techniques (e.g. MRI, and CT) are known as one of effective diagnosis approaches for detection of patients with Rb. It has been showed that utilization of imaging techniques are associated with some limitations. Hence, identification new diagnosis approaches might provide a better treatment for Rb patients. Identification of new biomarkers could contribute to better understanding of pathogenesis events involved in Rb and provide new insights into design better treatment approaches for these patients. Among of various biomarkers, microRNAs (miRNAs) have been emerged as attractive tools for Rb detection. miRNAs are one classes of small non-coding RNAs which could anticipate in a variety of biological process via targeting sequence of cellular and molecular pathways. Deregulations of these molecules are associated with cancerous condition. Multiple lines evidence indicated that deregulation of various miRNAs involved in various stages of Rb. Here, we summarized a variety of tissue specific and circulating miRNAs involved in Rb pathogenesis which could be used as diagnostic, prognostic and therapeutic biomarkers in Rb patients. This article is protected by copyright. All rights reserved

Key words: Retinoblastoma; MicroRNA; Diagnosis; Therapy

Introduction

Retinoblastoma is known as a pediatric eye cancer which accounted as important health problems in children less than five years of age (Singh et al., 2016). It has been showed that inactivation of a tumor suppresser gene called RB1 could lead to initiation of retinoblastoma. A large number studies indicated that a various of cellular and molecular targets (e.g. RB1 gene, cancer stem cells, P53 family, epithelial cell adhesion molecule and Reactive oxide species) could contribute to initiation and progression of retinoblastoma (Jagadeesan et al., 2016; Singh et al., 2016). Despite many advances in recognition of cellular and molecular targets involved in Rb pathogenesis, a thorough understanding of a sequence of cellular and molecular pathways is currently lacking (de Carvalho et al., 2016). Hence, it seems that identification of new biomarkers and cellular/molecular targets could be helpful for better understanding of sequence of cellular and molecular pathways underlying in Rb. Moreover, the finding new biomarkers could help to choice better and effective therapeutic approach (de Carvalho et al., 2016).

Despite finding a variety of biomarkers which involved in Rb pathogenesis, there is still a lack of revelation of specific progression biomarkers and relation of expression biomarkers with Rb mechanism (Jagadeesan et al., 2016; Singh et al., 2016).

Among of various biomarkers, microRNAs (miRNAs) have been emerged as attractive tools for detection of Rb in various stages (de Carvalho et al., 2016; Mirakholi et al., 2013; Singh et al., 2016). MiRNAs are known as a class of small non-coding RNAs which act as cellular and molecular regulators (Hoseini et al., 2017; Mirzaei et al., 2017a; Mirzaei et al., 2016f; Moridikia et al., 2017; Salarinia et al., 2016). Multiple lines evidence indicated that these molecules via targeting a sequence of cellular and molecular pathways anticipated in pathogenesis events (Gholamin et al., 2017; Keshavarzi et al., 2017a; Keshavarzi et al.,

2017b; Mirzaei et al., 2016b). Deregulation of miRNAs could lead to initiation and progression of various diseases such as cardiovascular diseases, stroke, inflammatory diseases and cancer (Fathullahzadeh et al., 2016; Mirzaei et al., 2017b; Mirzaei et al., 2016e; Mohammadi et al., 2016; Rashidi et al., 2016; Saadatpour et al., 2016).

A large number studies indicated that miRNAs have critical roles in Rb pathogenesis. Up/down regulation of them could help to initiation and progression of Rb (Mirakholi et al., 2013; Reis et al., 2012). Hence, these molecules could be used as new candidates for detection of Rb in various stages.

It has been showed that a variety of tissue specific miRNAs (e.g. *miR-25*, *miR-373*, and *miR-20a*, *let-7b*, *let-7a*, *let-7c*, *miR-125b*, and *miR-181a*) and circulating miRNAs (e.g. miR-21, miR-320, let-7, miR-17, miR-18a, and miR-20a) could be applied as diagnostic, prognostic and therapeutic biomarkers for Rb (Mirakholi et al., 2013; Reis et al., 2012; Zhang et al., 2012).

Recent findings have showed that miRNAs could be stable in mammalian bio-fluids, which may originate from intracellular processes elsewhere in the body (Gholamin et al., 2016; Mirzaei et al., 2016g; Simonian et al., 2017). Numerous studies indicated that the circulating miRNAs have particular properties including fast, accessible and non-invasive than other biomarkers which could provide them as attractive diagnostic and therapeutic biomarkers for various types of cancer such as Rb (Liu et al., 2014a). Here, we summarized recent developments in utilization of circulating miRNAs as attractive candidates for treatment and diagnosis of Rb.

Biology functions and stability of circulating miRNAs

MiRNAs are small non-coding RNAs which the average length of them is 21-22 nucleotides. It has been showed that miRNA processed from a hairpin precursor (Kim, 2005; Krol et al., 2010; Mirzaei et al., 2016a). At first step, MiRNAs originate from *pri-microRNA* (pri-miRNAs). RNA polymerase II and some transcription factors could regulate this process. Ribonuclease III (Drosha) and its cofactors (PACT and TRBP) could cleavage pri-miRNAs in cytoplasm and provide a duplex miRNA with 21-22 nucleotides in length. After dissociated double strands of miRNA, one of strands could incorporate into the RISC (RNA-induced silencing complex) or RITS (RNA-induced transcriptional silencing). Single strand of miRNA present in the RISC or RITS are able to provide a target for various mRNAs and can inhibit their translation *via* cleavage and degrading of them (Kim, 2005)(Figure 1).

It has been showed that circulating miRNAs as diagnostic biomarkers for various types of cancer could be detected and accessible in various body fluids such as plasma, serum, and urine (Bail et al., 2010; Mitchell et al., 2008). A large number studies indicated that a variety of cellular damages and pathogenesis signals are able to change expression miRNAs in various types of cells. These alterations have significant roles in initiation and progression of various cancers such as Rb. The released miRNAs into body fluids employing variety of mechanisms such as microvesicles, and binding to some proteins to protect themselves of various hazards such as degraded by RNases (Bail et al., 2010; Mitchell et al., 2008). Hence, these properties led to the using of miRNAs as biomarkers in different cancers such as Rb.

MicroRNAs as diagnostic and prognostic biomarkers in Rb

The utilization of circulating miRNAs could be associated with a variety of advantages including non-invasive biomarker, accessible, fast detection which provide them as new

diagnostic and therapeutic platform (Kosaka et al., 2010; Waki et al., 2016). Multiple lines evidence indicated that miRNAs via targeting sequencing of various cellular and molecular targets are able to change behavior of cells in various conditions (Di Leva et al., 2014; Garzon et al., 2009; Hashemi Goradel et al., 2017; Lee and Dutta, 2009; Mirzaei, 2017; Rabieian et al., 2017). When the expressions of miRNAs have been deregulated, these events could lead to initiation and development of Rb (Xu et al., 2011). For example, let-7e is known as one of let-7 family members which deregulation of it are associated with initiation and progression of Rb. Down regulation of let-7e could lead to up regulation of various genes such as high-mobility group A1 (HMG A1) and high-mobility group A2 (HMG A2) which have critical roles in Rb progression (Mu et al., 2010b).

In a study, Zhao et al., assessed the expression of a variety of miRNAs in human retinoblastoma tissues by microarray technique, and also some of miRNAs were verified by in situ hybridization method and northern blot analysis (Zhao et al., 2009). Their results indicated that various tissue specific miRNAs including miR-129-1, miR-494, miR-198, miR-492, miR-513-2, let-7e, miR-513-1, miR-503, miR-518c*, miR-129-2, miR-498, miR-320, and miR-373* were up regulated in patients with Rb than healthy subjects. These findings suggested that a variety of miRNAs could be applied as new diagnostic biomarkers for patients with various stages of Rb (Zhao et al., 2009).

There is growing body of data showing the association of expression of a variety of circulating miRNAs (e.g. miR-21, miR-320, let-7, miR-17, and miR-20a) with initiation and progression of Rb (Table 1).

In a study, Liu et al., assessed some circulating of miRNAs as diagnostic biomarker in patients with Rb (Liu et al., 2014b). They applied 65 plasma samples from patients with Rb and 65 samples from healthy subjects to serve as controls. They showed that down regulation

of some plasma miRNAs including miR-320, let-7e and miR-21 are associated with progression of Rb. These findings suggested that circulating miRNAs could be applied as diagnostic biomarkers in patients with Rb (Liu et al., 2014b).

Beta and colleagues investigated expression of various serum miRNAs in Rb patients (Beta et al., 2013a). MiRNAs provided from 14 pooled serums from patients with advanced Rb and 14 normal subjects. Their results indicated that 21 serum miRNAs were up-regulated and 24 serum miRNAs were down-regulated in children with Rb than healthy group. They showed that deregulation of various serum miRNAs including miR-17, miR-18a, and miR-20a via affecting on a variety of cellular and molecular targets could induce cell proliferation and inhibit apoptosis in Rb cells (Beta et al., 2013a). Hence, it seems that finding of new circulating miRNAs and their cellular and molecular targets could provide a new diagnostic platform for early detection of Rb patients. Moreover, identification of new biomarkers could provide more insights into understanding of biology processes involved in Rb pathogenesis. Few studies assessed circulating miRNAs as diagnostic, prognostic and therapeutic biomarkers in Rb patients. Hence, we suggested that these molecules might be used as new diagnostic and therapeutic platform in Rb patients.

MicroRNAs as drugs or therapeutic targets in Rb

RB is found that as one of main intraocular tumor in children. There are various management approaches including laser therapy, chemotherapy, enucleation, or cryotherapy for Rb patients (Brichard et al., 2002; Eng et al., 1993). The identification of therapies which are able to target specific pathways involved in Rb pathogenesis could contribute to finding valuable alternative therapies for this disease. Multiple lines evidence indicated that deregulation of miRNAs could be implicated in various types of diseases such as Rb (Table 2) (Yang and Mei, 2015b). Hence, miRNA mimetics and suppressors could be used as attractive candidates for drug therapy in various diseases (Kota et al., 2009). Given that a

variety of miRNAs are up-regulated in Rb, a suppressor therapy applying antisense oligonucleotides could be considered as therapeutic approach for Rb patients (Wang et al., 2016). It has been showed that using of miRNAs as therapeutic options are associated with some advantages in therapy. For example, miRNAs are able to target multiple pathways and genes involve in disease pathogenesis (Van Rooij and Olson, 2007). On the contrary, the utilization of miRNAs could affect gene expression and lead to clinically significant side effects (Van Rooij and Olson, 2007). Various studies indicated that inhibition/induction of miRNAs expression might to be as an effective therapy on Rb cell lines and xenograft tumor models (Wang et al., 2016). Hence, the therapeutic properties of miRNAs have opened new horizon in treatment of Rb.

In a study, Montoya and colleagues assessed targeting of miR-31 and miR-200c as therapeutic biomarkers in Rb cells (Montoya et al., 2015b). It has been showed that miR-31 and miR-200c have critical roles in tumor proliferation. Their results indicated that these miRNAs down regulated in Rb cells. They confirmed that over expression of them could inhibit the expansion of a highly proliferative cell line (Y79). These findings suggested that these miRNAs might be applied as novel therapeutic biomarkers for treatment of patients with Rb (Montoya et al., 2015b).

MiR- 204 is other biomarker which has critical roles in pathogenesis events present in Rb (Wu et al., 2015b). It has been showed that miR-204 aces as a tumor suppressor in various cancer such as retinoblastoma. MiR-204 exerts its therapeutic effects via targeting cyclinD2 and MMP-9 could lead to inhibition of cell proliferation and invasive in Rb cells (Wu et al., 2015b). Wu et al., indicated that down regulation of miR-204could lead to tumor growth in Rb cells. Their results indicated that overexpression of miR-204 could inhibit tumor growth in Rb cells. These results suggested that miR-204 as a tumor suppressor could be used as a therapeutic biomarker in treatment of Rb (Wu et al., 2015b).

It has been showed that a variety of chemical drugs and natural compounds could exert their therapeutic affects via modulating and targeting various miRNAs involved in cancer pathogenesis (Mirzaei et al., 2016d; Rashidi et al., 2017; Salarinia et al., 2016). Among of various natural compounds, curcumin is known as an attractive therapeutic agent which show wide range therapeutic effects (Mirzaei et al., 2016c; Mirzaei et al., 2017c). It has been showed that miRNAs are one of important targets for curcumin. In a study, Sreenivasan et al., indicated that curcumin could exert its therapeutic effects via modulating of a variety of miRNAs in Rb (Sreenivasan et al., 2012b). Their results indicated that miR-22 is one of important target for curcumin. Down regulation of miR-22 are associated with progression of tumor cells in Rb. Tranfection of miR-22 could inhibit cell proliferation and metastasis. These results indicated that curcumin via up regulation of miR-22 could inhibit cell proliferation and migration in Rb cells (Sreenivasan et al., 2012b).

Conclusion

RB is one of common pediatric malignancy with poor prognosis. A large number studies indicated that early detection of Rb could provide better treatments for Rb patients. Hence, finding of ideal biomarkers for rapid and reliable diagnosis of Rb could help to improving of survival rate of Rb patients. Among of various biomarkers, miRNAs have been emerged as interesting tools for detection of various types of cancer such as Rb. Multiple lines evidence indicated that these molecules have critical roles in various cellular and molecular pathways involved in Rb pathogenesis. These studies confirmed that miRNAs might be a promising biomarker in the identification of patients with Rb. Few studies assessed circulating of miRNAs as diagnostic and prognostic biomarkers in Rb patients. Therefore, it seems that future investigations are required to introduce circulating miRNAs as diagnostic and prognostic biomarkers in clinical applications.

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Table 1. Diagnostic microRNAs (miRNAs) in Rb

MicroRNA	Expression in Rb	Material	Target gene (s)	Model	Sample (n)	Citation
miR-125b	Up-regulation		DRAM2	In vitro and		(Bai et al., 2016)
miR-101	Down-regulation	Tissue	EZH2	In vitro /human	87	(Lei et al., 2014)
let-7	Down-regulated	Tissue	*HGMA1*, *HGMA2*	human	44	(Mu et al., 2010a)
miR-17	Up-regulated	Serum		human	20	(Beta et al., 2013b)
miR-18a,	Up-regulated	Serum		Human	20	(Beta et al., 2013b)
miR-20a	Up-regulated	Serum		Human	20	(Beta et al., 2013b)
miR-19	Down - regulated	Serum		Human	20+20	(Beta et al., 2013b)
miR-92a	Down - regulated	Serum		Human	20+20	(Beta et al., 2013b)
miR-21	Up-regulated	Tissue	PTEN/PI3K/AKT	In vitro /human	30	(Gui et al., 2016)
miR-433	Down-regulated	Tissue	Notch1 and PAX6	Human	_	(Li et al., 2016b)

miR-365b-3p	Down-regulated	Tissue	PAX6	Invitro and human	6	(Wang et al., 2013)
miR-31	Down-regulated	Cell line	_	In vitro		(Montoya et al., 2015b)
miR-200a	Down-regulated	Tissue	_	In vitro		(Montoya et al., 2015b)
miR-129-3p	Down-regulated	Tissue		In vitro/ human	12	(Martin et al., 2013b)
miR-382	Down-regulated	Tissue		In vitro/ human	12	(Martin et al., 2013b)
miR-504	Down-regulated	Tissue		In vitro/ human	12	(Martin et al., 2013b)
miR-22	Down-regulated	Tissue		In vitro/ human	12	(Martin et al., 2013b)
miR-129-5p	Down-regulated	Tissue		In vitro/ human	12	(Martin et al., 2013b)
miR-494	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-513-1	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-513-2	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-518c*	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-129-1	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-129-2	Up regulation	Tissue		Human	9	(Zhao et

						al., 2009)
miR-198	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-492	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-498	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-503	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-373*	Up regulation	Tissue		Human	9	(Zhao et al., 2009)
miR-125b	Down-regulation	tissue	*CDK6, CDC25 A*, and *LIN28A*	human	3	(Yang and Mei, 2015a)
miR-25	Down regulation	tissue	*BCL2L1*	human	3	(Yang and Mei, 2015a)
miR-19b	Up regulation	Cell line		In vitro		(Shen et al., 2014)
miR-195	Up regulation	Cell line		In vitro		(Shen et al., 2014)
miR -222	Up regulation	Cell line		In vitro		(Shen et al., 2014)
miR-181c	Up regulation	Cell line		In vitro		(Beta et al., 2014a)
miR-130b		Cell line		In vitro		(Beta et al., 2014a)
miR-532-5p	Down-regulated	Tissue		In vitro/human	30	(Venkate san et al., 2015)
miR-486-	Down-	Tissue		In	30	(Venkate san et al.,

3p	regulated			vitor/human		2015)
miR-320	down regulation	plasma		human	65	(Liu et al., 2014a)
miR-21	down regulation	plasma		human	65	(Liu et al., 2014a)
let-7e	down regulation	plasma		human	65	(Liu et al., 2014a)
miR-376a	Up regulation	Cell line	caspase-3	In vitro		(Zhang et al., 2013)
miR-10b	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-29a	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-29b	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-29c	Up regulation	Cell line		In vitro		(Jo et al., 2011)
let-7c	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-34a,	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-34c-5p,	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-124,	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-135b,	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-142-5p,	Up regulation	Cell line		In vitro		(Jo et al., 2011)

let-7i	Up regulation	Cell line		In vitro		(Jo et al., 2011)
miR-24	Up regulation	Cell line	*p14 ARF*	In vitro		(To et al., 2012)
mir-34b/c	Down regulation	Tissue	P53	Human	130	(Carvalho et al., 2017)
miR-31	Down regulation	Tissue		In vitro/human	21	(Montoya et al., 2015a)
miR-200c	Down regulation	Tissue		In vitro/human	21	(Montoya et al., 2015a)
miR-181b	Up regulation	Cell line	HIF , VEGF	In vitro		(Xu et al., 2011)
miR-125a-3p	Up regulation	Cell line	HIF , VEGF	In vitro		(Xu et al., 2011)
miR-30c-2	Up regulation	Cell line	HIF , VEGF	In vitro		(Xu et al., 2011)
miR-491-3p	Down regulation	Cell line	HIF , VEGF	In vitro		(Xu et al., 2011)

Table 2. Therapeutic microRNAs (miRNAs) in Rb

MicroRNA	Expression in Rb	Material	Target gene (s)	Model	Sample (n)	Citation
miR-124	Down regulation	Tissue	STAT3	In vitro /human	40	(Qu et al., 2016)
miR-183	Down regulation	-	LRP6	In vitro	-	(Wang et al., 2014)
miR-34a	Down regulation	-	caspase-3/7	In vitro	-	(Dalgard et al., 2009)
miR -145	Down regulation	Tissue	ADAM19	In vitro /human	18	(Sun et al., 2015)
miR-613	Down-regulation	Tissue	E2F5	In vitro /human	45	(Zhang et al., 2017)
miR-26a	Down-regulated	Cell line	Beclin 1	In vitro		(Li et al., 2016a)
miR-125a-5p	Down-regulated	Cell line	TAZ-EGFR			(Zhang et al., 2016)
miR-204	Down-regulated	Cell line	CyclinD2, MMP-9	In vitro		(Wu et al., 2015a)
miR-22	Down regulation	Cell line		In vitro		(Sreenivasan et al., 2012a)
miR-449a	down regulation	Tissue		In vitro/human		(Martin et al., 2013a)
miR-449b	down regulation	Tissue		In vitro/human		(Martin et al., 2013a)

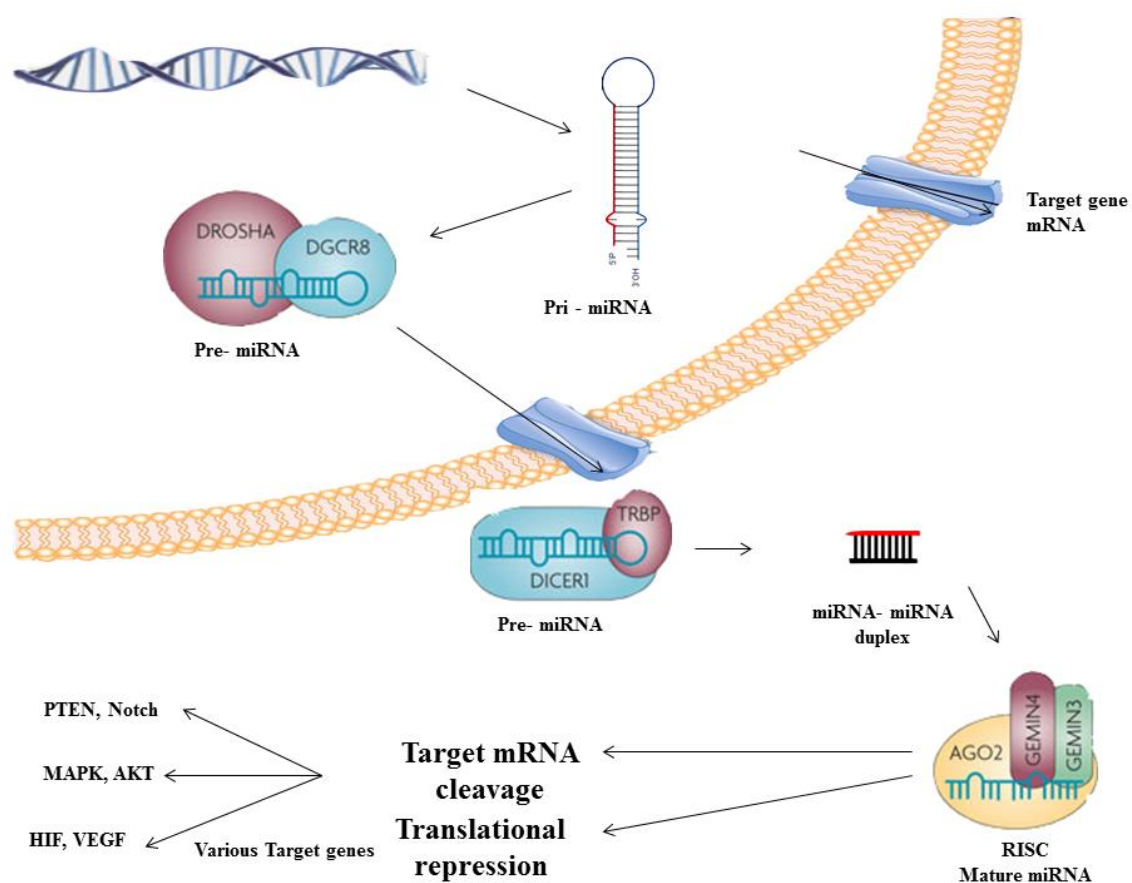| miR-181c	Up regulation	Tissue	Caspase 3	In vitro/human	30	(Beta et al., 2014b)
and miR-130b	Up regulation	Tissue	Caspase 3	In vitro/human	30	(Beta et al., 2014b)
miR-143	Down regulation	Tissue		In vitro/human	44	(Wang et al., 2016)
miR-497	Down regulation	Tissue		Human	23	(Li et al., 2017)

Figure 1. A scheme of miRNA biogenesis and its cellular targets