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Published

2014

Journal Title

Experimental and Molecular Pathology

Version

Accepted Manuscript (AM)

DOI

10.1016/j.yexmp.2014.08.002

Experimental and Molecular Pathology xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Experimental and Molecular Pathology

journal homepage: www.elsevier.com/locate/yexmp

Role of microRNA-34 family in cancer with particular reference to cancer angiogenesis

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ARTICLE INFO

Article history:
Received 31 July 2014
Accepted 1 August 2014
Available online xxxx

Keywords:
miRNA-34
Cancer
Angiogenesis

ABSTRACT

MicroRNA-34 is involved in pathogenesis in cancer by targeting different tumor-related genes. It could be a biomarker for predicting the prognosis of patients with cancer. In addition, miR-34 is involved in the tumor angiogenesis. Understanding the mechanism of the miR-34 in cancer and tumor angiogenesis will open horizons for development of anti-cancer and anti-angiogenesis drugs.

Contents

1. Introduction

Since the discovery of miRNA in *Caenorhabditis elegans* (Lau et al., 2001; Lee and Ambros, 2001), many researchers have focused their attention into elucidating the aspects of miRNA biology and function. Classed as the new generation of epigenetic gene regulators (Benetti et al., 2008; Cai et al., 2009; Szulwach et al., 2010), miRNAs are 20–25 nucleotides non-coding RNAs which is estimated that about 30% of gene expression is regulated using miRNA (Winter et al., 2009). Their main goal is repression of gene expression. After transcription by RNA polymerase II, the pri-miRNA is processed with Drosha (RNase III) and subsequently in the cytoplasm with Dicer to yield a double strand RNA. This form is then cleaved into a single strand RNA as a mature miRNA which is then incorporated into miRNA–protein (miRNP) complex. The miRNA in the miRNP complex identifies the seed sequence in the 3′ untranslated region of the target mRNA and then either suppresses the translation or degrades the mRNA. Both processes result in downregulated expression of protein (Bartel and Chen, 2004; Huang et al., 2011; Krol et al., 2010). Additionally, it has been shown that they are able to directly bind proteins (Hafner et al., 2010; van Kouwenhove et al., 2011). Therefore, on a hypothetical assumption and considering the account of mRNA genes, their varied expression patterns and consequently the vast potential of miRNA targets suggest that miRNAs are likely to be involved in an extended spectrum of cellular processes. More than 60% of human protein-coding genes are conserved targets of miRNA (Siomi and Siomi, 2010). The functional roles of miRNAs have been reported in many biological events including developmental timing (Ambros, 2011; Li et al., 2011), signal transduction (Inui et al., 2010) and tissue differentiation (Chen and Hu, 2012; Ge and Chen, 2011; Huang et al., 2011). Thus, miRNAs play variety of functions in

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http://dx.doi.org/10.1016/j.yexmp.2014.08.002
0014-4800/

the biology of human. Also, it has been shown that an alteration in miRNA expression is related to various diseases including cancer (Ebrahimi et al., 2014; Gopalan et al., 2014; Sayed and Abdellatif, 2011).

2. miR-34 family

The miR-34 microRNA precursor family was computationally discovered and later verified experimentally. The two distinct precursors are processed into three mature miRNAs: miR-34a, miR-b and miR-c. The mature miR-34a is a part of the p53 tumor suppressor network (Concepcion et al., 2012; Liu et al., 2012); therefore, it is hypothesized that miR-34 dysregulation is involved in the development of some cancers (Gopalan et al., 2014). This family is transcribed from two different sets of genes located on chromosomes 1 and 11. Higher expression of miR-34a was detected in brain and higher expression of miR-34b and miR-34c was noted in lungs (Lagos-Quintana et al., 2002). The presence of miR-34 products has also been confirmed in embryonic stem cells (Houbaviy et al., 2003). Their promoter region has p53 binding site therefore they are induced by p53 and thus involved in cell proliferation, survival, apoptosis (Yamakuchi et al., 2008), migration, invasion (Siemens et al., 2011) and angiogenesis (Chang et al., 2007; Yamakuchi and Lowenstein, 2009). Many controlling genes are regulated through the actions of this family. For example, ectopic expression of this family of miRNAs results in an increase in factors involved in cell cycle regulation and DNA damage response and suppression of cell cycle promoting genes (Wan et al., 2011). Each member of this family is able to induce similar gene expression and repression (Hermeking, 2010). Given their similar structure, such pattern was predictable e. On the other hand, it seems that each member has an extra affinity to a specific mRNA, which is the result of perfect complementary sequences. For instance, miR34b and miR34c have higher tendency to suppress c-myc.

miR-34a, miR-34b and miR-34c are responsible for cell-cycle arrest in the G1 phase. In addition, miR-34b/c inhibited proliferation and colony formation in soft agar. Interestingly, the introduction of miR-34a, miR-34b and miR-34c into primary human diploid fibroblasts induced cellular senescence. Microarray analyses after ectopic introduction of different members of the miR-34 family into various cell lines revealed hundreds of putative, downregulated miR-34 targets. Cyclin D1, cyclin E2, cyclin-dependent kinases 4 and 6, mitogen-activated protein kinase 1 (MEK1), R-Ras, platelet-derived growth factor receptor A (PDGFRA), and hepatocyte growth factor receptor are among the direct targets that have been experimentally validated (Li et al., 2009). As a member of p53 pathway, additionally mir34 regulates the genes involved in apoptosis (Bommer et al., 2007; Chang et al., 2007). Survivin and BCL2 (B-cell lymphoma 2) are anti-apoptotic proteins regulated by miR-34a. On the other hand, miR-34 targets the regulatory molecules of p53 which include SIRT1 (silent mating type information regulation 2 homolog1) and YY1 (yin yang 1). SIRT1 is a NAD + dependent class III histone deacetylase that protects cells against oxidative and genotoxic stress (Brooks and Gu, 2009). This downregulation creates a positive feedback loop for p53, enhancing its half-life and function. As p53 increases miR-34a transcription, increased amounts of p53 eventually lead to higher levels of miR-34a (Bommer et al., 2007; Yamakuchi et al., 2008).

3. Cancer and miR-34

Many miRNAs are deregulated in cancers via various mechanisms (Sevignani et al., 2007). Genomic abnormalities such as deletion (Sevignani et al., 2007), amplification (Hayashita et al., 2005; Rinaldi et al., 2007; Tagawa et al., 2007), and translocation (Dorsett et al., 2008) are common in tumorigenesis. miR-15a and miR-16-1 are examples which are clustered at chromosome 13q14, a frequently deleted region in B cell chronic lymphocytic leukemia and other cancers (Calin et al., 2002). Epigenetic factors are heritable transcriptional silencing which can also influence miRNA expression. CpG island hypermethylation and histone modification in promoter regions result in silencing of tumor-suppressor genes. Microarray analyses have indicated some miRNAs that are repressed by CpG hypermethylation in cancers relative to normal tissue (Lehmann et al., 2008). For instance, miR-9-1 in breast cancer and miR-34a in hematological malignancies are among the hypermethylated (Chim et al., 2010). Transcriptional and post-transcriptional regulations can also affect the expression of miRNAs. pri-miRNAs are induced by transcription factors, and many of which are oncogenes or tumor suppressors. Many miRNA–transcription factor relationships have been discovered in cancers such as in p53, c-Myc, and E2F (E2 transcription factor) (Tazawa et al., 2007).

mi-RNA processing and stability are also important factors that determine mi-RNA expression level. In addition, the expression levels of mi-RNA processing machinery, Dicer or Drosha, are altered in a number of cancers, likely due to the copy number gain (Blenkiron et al., 2007; Chiosea et al., 2007; Karube et al., 2005; Muralidhar et al., 2007).

Known to regulate cell cycle, apoptosis, and differentiation, miR-34 is one of the best-characterized tumor suppressor miRNAs to date. It is lost or expressed at reduced levels in many cancers. miR-34 functions downstream of p53 by regulating genes to induce cell cycle arrest, cellular senescence and apoptosis and re-introduction of miR-34 mimics growth inhibition in vitro and in vivo (Ji et al., 2008). Although p53 has direct activating effects, studies have shown that miR-34b is hypermethylated and therefore silenced in many types of cancer including colorectal carcinoma (Toyota et al., 2008), gastric carcinoma (Ji et al., 2008), mesothelioma (Kubo et al., 2011), breast carcinoma (Vogt et al., 2011), ovarian carcinoma (Corney et al., 2010; Segura et al., 2009), renal cell carcinoma, urothelial carcinoma (Catto et al., 2011), pancreatic carcinoma (Chang et al., 2007), prostatic carcinoma (Fujita et al., 2008), lung carcinoma (Bommer et al., 2007; Lodygin et al., 2008; Wiggins et al., 2010) and melanoma (Lodygin et al., 2008; Segura et al., 2009). This phenomenon is present despite the presence of wild type p53 (Christoffersen et al., 2010). In this regard, treatment with demethylating agents was able to activate its expression and inhibit malignant growth in vitro (Kong et al., 2012; Nalls et al., 2011; Roy et al., 2012). Thus, genetic and epigenetic mechanisms contribute to a loss of miR-34 expression.

The side effects and chemo-resistance tendencies of conventional chemotherapies are giving way to more selective non-toxic treatments, which target a defined a specific tumor related gene (Tsao et al., 2005; Welch and Moore, 2007). As modulators of gene expression and controllers of many cellular pathways, miRNAs play important role in the regulation of tumor suppression. Some of important miRNAs are let-7, miR-34 and miR-200 (Kasinski and Slack, 2011).

miRNA replacement treatment has resulted in anti-proliferative, pro-apoptotic, and death in cancer cell (Bader et al., 2010). miR-34 is a well-known tumor suppressor, and extensive aberrant expression Q7 profile has been observed in many cancers which reintroduction of miR-34a inhibits cancer cell growth and shows its important role in tumorigenesis. Additionally, studies have shown that an important ability of miR-34 is inhibition of cancer stem cells. CD44 or CD133 positive prostate and breast cancer cells express lower levels of miR-34a. Also, ectopic expression of miR-34 hampers sphere formation in soft agar and tumorigenicity in vivo (de Antonellis et al., 2011; Ji et al., 2009; Liu et al., 2011a; Yu et al., 2012).

This impact can be attributed to the inhibitory effects miR34 has on pluripotency genes *NANOG* (*Nanog homeobox*), *SOX2* (*SRY* (*sex determining region Y*)-*box 2*), and MYCN (v-myc myelocytomatosis viral related oncogene, neuroblastoma derived [avian]) (Choi et al., 2011; de Antonellis et al., 2011). Other pathways regulated by miR34 include Wnt signaling (Cha et al., 2012; Siemens et al., 2011), AKT (protein kinase B) pathway (Lal et al., 2011) and notch (Fujita et al., 2008) which regulate growth, epithelial–mesenchymal transition (EMT) and metastasis.

Given that more than 50% of all human cancers show defects in the p53 pathway, miR-34 replacement therapy is likely to become a

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powerful therapeutic approach. The ability of mir-34 to influence several pathways may be synergistically beneficial when combined with conventional therapies. As experiments have shown, mir-34a alleviates chemo-resistance in various cancer cell models (Fujita et al., 2008). This attenuation has been partly attributed to the modulatory role of miR-r-34 on HuR, Bcl-2, Sirt1 MAGE-A and p53 expressions (Kojima et al., 2010; Weeraratne et al., 2011). As cell models have shown the efficacy of miR-34 treatment, there are few animal studies which have shown that vector-based delivery of miR-34 has therapeutic potential (Hu et al., 2010; Kato et al., 2009; Kota et al., 2009; Kumar et al., 2008; Wiggins et al., 2010; Yan et al., 2011). However, the ultimate therapeutic benefits of miR-34 in vivo depend largely on the delivery system. As promising the animals are, development of a safe clinically relevant system needs further enhancement to achieve the standards of clinical trial drugs. In this regard, micro-RNA therapeutics initiated a screening process on various delivery systems with the aim of finding the most suitable system. The criteria included were (a) efficacy in mouse models of cancer, (b) miRNA bio-distribution, and (c) initial safety.

miRNAs have been the focus of many studies in cancer prognosis and diagnosis (Cho, 2010). Studies have shown that miRNAs are secreted as exosomes and can be used as early biomarkers in body fluids for disease diagnosis, prognosis, and response to treatment. As one of the tumorigenesis-related miRNAs, miR-34 has been studied extensively in cancers. miR-34a expression has been linked to metastases in prostate (Watahiki et al., 2011), breast (Javeri et al., 2013), and colorectal (Siemens et al., 2013) cancers suggesting that it could be a potential biomarker. Additionally, patient with non-small cell lung carcinoma that has undergone resecting surgery was noted to have a longer survival if the cancer shows up-regulated miR-34a expression (Mudduluru et al., 2011). In a study by Koufaris et al., it has been shown that hepatocellular carcinoma cells exposed to DNA damage or oxidative stress blocked abnormal cell proliferation when treated with miR-34a (Koufaris et al., 2012). This suggests that miR-34a can be utilized in the detection of hepatocellular carcinoma. Furthermore, it has been reported that decreased expression of miR-34a is linked with pathogenesis, adverse outcome (Koufaris et al., 2012) and poorer overall survival (Hu et al., 2013).

4. Angiogenesis and miR-34

Due to their high metabolic rate, cancer cells are dependent on extra amount of blood supply. Angiogenesis is one of the hallmarks of cancer. Angiogenesis is a normal physiological processes utilized in situations which higher levels of nutrients are needed, for example in wound healing and developing embryo (Breier, 2000). However, the growing tumor cells take advantage of this process. Several processes are involved in formation of new microvasculature. Detachment of pericytes, extra cellular matrix degradation and reformation by stromal cells and guided migration and proliferation of endothelial cells by molecular mediators, sequentially govern the formation of new blood vessels (Carmeliet, 2005; Flamme et al., 1997; Otrock et al., 2007).

There are many factors that regulate cancer angiogenesis. The most important is vascular endothelial growth factor (VEGF). VEGF was noted by regulating the pathogenesis and predicting the prognosis of human cancers (Ferrara et al., 2003; Harhaj et al., 2006; Salajegheh et al., 2011, 2013; Weekes et al., 2010; Yu et al., 2008a,b). It is the main target for treatment in human cancers. Other angiogenic factors include endothelins and their receptors (Irani et al., 2014a,b), angiopoietins and their respective Tie receptors (Loughna and Sato, 2001), fibroblast growth factor (Presta et al., 2005), and platelet-derived growth factor (Hellstrom et al., 1999).

Likewise, there are many studies showing the manifold impacts of mi-RNAs in the biology of endothelial cells. mi-RNAs have emerged as an important factor regulating cellular function and responses. The importance of mi-RNAs in endothelial cell function was demonstrated by the silencing of the Dicer enzyme, which resulted in the reduction of the mature mi-RNA profile. Increased activation of the eNOS pathway (Bonauer et al., 2009), reduced endothelial proliferation, migration and cord formation was the consequence of dicer knock down (Suárez et al.). The above results show that mi-RNAs are important in the physiological function of endothelial cells.

As a network, mi-RNAs regulate the process of angiogenesis in endothelial cells, balancing the pro- and anti-angiogenic responses. Twenty seven highly expressed mi-RNAs have been identified to play role in endothelial biology, 15 of which were predicted to regulate the expression of receptors for angiogenic factors. For example, the expression of VEGFR2, endothelial nitric oxide synthesis (eNOS) (Yang et al., 2005) and interleukin-8 (IL-8) (Bhaumik et al., 2009) is shown to be regulated via mi-RNAs. Other exemplary pro-angiogenic miRNAs include mi-R130a, mi-R210, mi-R424, let-7 family, miR-27b and the miR-17–92 cluster. Also, mir-221 and mir-222 are e anti-angiogenic miRNAs. The names and function of involved angio-miRs were summarized in Table 1.

A growing tumor, demands extra amount of oxygen and unlike physiological conditions, induces its own blood vessels via sprouting of existing capillaries or recruitment of circulating endothelial progenitor cells (Miles, 1999). Tumors are able to produce the above-mentioned angiogenic factors in copious amounts. It has been shown that a relatively high amount of VEGF and its receptor is expressed on tumor cells and the respective endothelial and stromal cells (Ferrara, 2002). To demonstrate the important role of VEGF, administration of anti-VEGF or anti-Flk-1 (VEGF receptor) antibodies in vivo was able to decrease tumor vessel density and inhibit tumor growth (Brekken et al., 2000). These evidences show that inhibition of VEGF activity in vivo results in reduced tumor angiogenesis and tumor growth.

On cellular level, tumor-induced vessels have abnormal structure. High amounts of VEGF along with Ang2 expression induce a rather "leaky vessel" structure with increased permeability, incomplete cellular junction and a lack of basement membrane (Manley et al., 2004). The vascular bed is sufficient to provide the tumor cells with adequate nutrient supply and the opportunity to enter the circulation and form distant metastases. In the tumor microenvironment, local oxygen concentrations regulate VEGF production. Hypoxia stimulates the binding of hypoxia-inducible factor (HIF) to the VEGF promoter, promoting VEGF gene transcription and mRNA stability (Arany et al., 2008). The pressure of hypoxic environment not only induces the production of VEGF, but also aids the selection of apoptosis resistant tumor cells. These cells are the P53 mutant-type cells and that explains the phenomenon of increased amount of cells harboring this phenotype in higher stages of cancer (Semenza, 2000, 2002).

IL-8 is another mediator which has shown angiogenic abilities. In the tumor microenvironment, IL-8 is produced from macrophages in a state of chronic inflammation (Chen et al., 2005; Koch et al., 1992). It has been shown that IL-8 is mitogenic and chemotactic for HUVECs and angiogenic in rat cornea (Waugh and Wilson, 2008). It also has the effect of increasing the expression and activity of matrix metalloproteinase 2 (MMP2) (Reis et al., 2012). Considering the important role of angiogenesis in the growth of tumor cells, inhibition of this process has been one of the major focuses in anti-cancer biology and therapeutic research (Ferrara and Kerbel, 2005; Shojaei, 2012; Sitohy et al., 2012; Welti et al., 2013). For example, bevacizumab, a FDA-approved monoclonal antibody against VEGF, has been successfully used in combination with chemotherapy agents in clinical trials (Aghajanian et al., 2014; Ferrara et al., 2004; Kopetz et al., 2010; Perren et al., 2011). Bevacizumab was able to inhibit endothelial sprouting and normalize the architecture of vessels, enhancing drug uptake of the tumor (Arjaans et al., 2013; Carmeliet and Jain, 2011; Ma et al., 2011). Since then, targeting the VEGF pathway was the focus of anti-angiogenesis developments. However, several groups described that these drugs may actually accelerate metastases formation. Therefore, other targets also need to be considered (Bagri et al., 2010).

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Table 1
List of miRNAs which have role in endothelial physiology and in tumor angiogenesis.

Name	Target	Function	References
miR-126	*SPRED1*, *PIK3R2*, *VCAM1*	Maintaining vascular integrity, endothelial cell proliferation, migration, tube formation and sprouting	Wang et al. (2008)
miR-221 and miR-222	*p27*, *c-kit* mRNA	Regulates cell cycle progression, decreased cell migration and downregulation of endothelial nitric oxide synthase expression	Nicoli et al. (2012)
miR-17–92 cluster	*HIF-1 alpha*, *E2F1*, *ITGA5*	Endothelial cell sprouting, tube formation, pro-angiogenesis phenotype and reduce p53	Doebele et al. (2010)
miR-130a	*GAX*, *HOXA5*	Proliferation, migration, and tube formation	Volpe et al. (2012), Zhang et al. (2011)
miR-21 and miR-31	*HIF-1alpha* expression, *PTEN* suppression	Inducing matrix metalloproteinase expression	Liu et al. (2011b)
miR-320	*VEGFR2*, *IGF-1*, *IGF-1R*	Anti-angiogenesis	Wang et al. (2014), Wu et al. (2014)
let-7 family and miR-27b	*Tsp-1*	Sprout formation	Bao et al. (2013)
miR-155	*Angiotensin II type I receptor*	Anti-angiogenesis	Kong et al. (2013)
miR-210	*Ephrin-A3* (*EFNA3*), *Neuronal pentraxin-1* (*NPTX1*)	Pro-angiogenesis, tubulogenesis and VEGF induced migration of endothelial cell growth	Alaiti et al. (2012)
miR-296	*Hepatocyte growth factor-regulated tyrosine kinase substrate*, *PDGFRβ*	Elevated in tumor endothelial cells, tubule length and branching of endothelial cells	(Savi et al. (2014); Vaira et al. (2012))
miR-378	*SUFU*, *FUS-1b*	Promotes tumorigenesis and angiogenesis in vivo	Chen et al. (2012)
miR-20a and miR-20b miR-15 and miR16	*VEGF*, *BCL2*	Induces apoptosis block cell cycle progression	Sun et al. (2013)
miR-34a	*SIRT1*, *Survivin*, *E2F3*, *CDK4*	Endothelial senescence	Yamakuchi et al. (2008)
miR-34b	*CREB*	Restoration of cell cycle abnormality reduce anchorage-independent growth	Mazar et al. (2011)
miR-217	*SIRT1*, *FOXO3A*	Endothelial senescence	Zhang et al. (2013)
miR-424	*CHK1*	Migration and proliferation of endothelial cells	Ghosh et al. (2010), Nakashima et al. (2010)
miR-200c	*ZEB1*	Senescence in response to proto-oncogene tyrosine-protein kinase (ROS) and increase p53 level	Rebustini et al. (2012)
miR-9	*E-cadherin*	Increased migration and angiogenesis	Zhuang et al. (2012)

mi-RNAs can control endothelial cell function as angioregulatory switches in tumor angiogenesis. Since a single mi-RNA has the ability to regulate a variety of endothelial functions by targeting multiple mRNAs, miRNA targeted therapy could greatly influence endothelial cell behavior. In this regard, miRNAs, especially those that are involved in endothelial cell biology, have attracted attention for targeted anti-angiogenesis therapy. Of note, in anti-cancer therapies, cellular senescence has an important role.

Numerous miRNAs are engaged in the regulation of cellular senescence of endothelial cells. A study evaluated the expression of miR-34a in primary endothelial cells and demonstrated that baseline expression increases during cell senescence (Ito et al., 2010). miR-34a regulates proliferation and differentiation of many cell types. Similarly, miR-34 controls the cycle in endothelial cells. It decreases SIRT1 levels and increases acetylation of p53 (Yamakuchi et al., 2008). Mammalian SIRT1 functions as a metabolic regulator by deacetylation of histones and large numbers of proteins including protein 53 (p53), Ku70 protein, nuclear factor κβ (NF-κβ), and peroxisome proliferator activated receptor γ (Brooks and Gu, 2009). It has been shown that miR-34a expression is downregulated in highly angiogenic endothelial cells (endothelial cells overexpressing Bcl-2) as compared to normal human endothelial cells (Zhao et al., 2010).

miR-34a expression was analyzed in head and neck squamous cell carcinoma cell line and 15 cancer r samples of oral cavity, oropharynx and larynx. Bhavna and the team demonstrated that miR-34a could regulate tumor angiogenesis through down-regulation of key proteins including E2F3, SIRT1, survivin and CDK4 whereby the function of endothelial cell was directly inhibited. E2F3a and E2F3b are important family of transcriptional factors that play pivotal role in cell proliferation and differentiation and cell cycle regulation. They also studied the correlation of VEGF expression to miR-34a as the main player in angiogenesis process and demonstrated that overexpression of miR-34a down-regulated the upstream proteins of VEGF expression such as E2F3, Myc and c-met in both of head and neck squamous cell carcinoma cell line and cancer tissue samples The expression of VEGF was significantly reduced in cell lines over-expressing miR-34a. In addition, the miR-34a was shown to have direct effects on the proliferation and migration of endothelial cells and tube formation was inhibited in vitro (Kumar et al., 2012).

5. Conclusion

Increased number of studies is vital to identify endothelial miRNAs and characterize their potential for anti-angiogenesis therapeutics in cancer. Investigations have shown that the altered expression of miRNAs in the endothelial cells is under VEGF-stimulation, hypoxia, or tumor signaling. However, utilization of miRNAs in therapy has the potential side effect of off target effects, which are likely due to the partial complementarity between a miRNA and target mRNA and depending on the cell type. Therefore, specific delivery strategies to the site of ongoing tumor angiogenesis are vital. Besides there can be different approaches: anti-angiogenesis miRNAs to sites of tumor which could directly 'switch off' the angiogenesis process or inhibit the activity of pro-angiogenesis miRNAs (antagomiRs).

Evaluation of the roles miRNAs play in endothelial biology and its relation in various ailments is a relatively new field of research, with high expectations for research and therapy applications. However, this field is in its first steps, and many pitfalls have to be overcome before successful miRNA targeted anti-angiogenesis therapy will reach the clinic. A better understanding of miRNA regulation in endothelial cell is essential. Moreover, a comprehensive mapped miRNA profile is necessary to identify the specific miRNAs involved in tumor angiogenesis. Hopefully, this new emerged research field will open prospect full horizons for the development of anti-angiogenesis drugs involving miRNAs.

6. Uncited references

Q8

Fleissner et al., 2010
Katoh, 2013

Please cite this article as: Maroof, H., et al., Role of microRNA-34 family in cancer with particular reference to cancer angiogenesis, Exp. Mol. Pathol. (2014), http://dx.doi.org/10.1016/j.yexmp.2014.08.002

Acknowledgments

The authors would like to thank the staff and students in Molecular Cancer Pathology team in Griffith Health for the help in manuscript. The work is supported by funding from Griffith University.

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Please cite this article as: Maroof, H., et al., Role of microRNA-34 family in cancer with particular reference to cancer angiogenesis, Exp. Mol. Pathol. (2014), http://dx.doi.org/10.1016/j.yexmp.2014.08.002

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Please cite this article as: Maroof, H., et al., Role of microRNA-34 family in cancer with particular reference to cancer angiogenesis, Exp. Mol. Pathol. (2014), http://dx.doi.org/10.1016/j.yexmp.2014.08.002

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Please cite this article as: Maroof, H., et al., Role of microRNA-34 family in cancer with particular reference to cancer angiogenesis, Exp. Mol. Pathol. (2014), http://dx.doi.org/10.1016/j.yexmp.2014.08.002