PROSPECTS
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The Pleiotropic Effects of miRNAs on Tumor Angiogenesis

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ABSTRACT

Angiogenesis, the process of new blood vessel formation and growth from already existing venules is critical in vascular development and homeostasis controlled by the balance of pro- and anti-angiogenic factors. Emerging evidence indicates the development, progression, and metastasis of various human cancers are strongly relied on angiogenesis. However, molecular mechanisms that underlie the complex regulation of angiogenic processes are still not fully elucidated. Recent studies revealed that microRNAs (miRNAs) were important regulators of tumor angiogenesis and the entire research in this area has entered into a so-called "miRNAs era." Thus, miRNAs might be important therapeutic targets or biomarkers for cancer. Due to the complexity of miRNA regulating mechanisms, how specific miRNAs intersect with and modulate tumor angiogenesis is still unclear. The conflicting results of the same miRNAs from different groups indicated that miRNAs might possess potent activity in a cell type or cell context specific manner. Here, we present a summary of latest advances in understanding the roles of angiogenic miRNAs as potential tools or targets in cancer therapy. J. Cell. Biochem. 116: 1807–1815, 2015.

KEY WORDS: miRNAs; ANGIOGENESIS; CANCER

Vessel generation is a vital process for the development and adult homeostasis. Generally, the development of the vascular system is classified into vaculogenesis and angiogenesis, which are two diverse physiological processes [Flamme et al., 1997; Adams and Alitalo, 2007; De and Black, 2009; Chang and Hla, 2011]. The key difference to the certain extent is the origin of new blood vessels. By the former pattern, the generation of new vessels is from mesenchymal cells, leading to the formation of primary vascular network [Carmeliet, 2003; Jain, 2003]. In contrast, the latter one implies the neovascularization is based on the pre-existing vasculature by sprouting and remodeling to a new capillary network [Adams and Alitalo, 2007]. The turnover of adult vasculature is rare except for several particular physiological and pathological processes such as ovarian cycle and wound healing [Denekamp, 1982; Klagsbrun and D'Amore, 1991; Folkman, 1995; Papetti and Herman, 2002; Liu and Deisseroth, 2006; Urbich et al., 2008; Yamakuchi et al., 2010]. Generally, the process of angiogenesis is under precise control, and aberrant angiogenesis is associated with tremendous diseases, including diabetic blindness, age-related macular degeneration, rheumatoid arthritis, psoriasis, thrombosis, atherosclerosis, and cancer [Dentelli et al., 2010; Yamakuchi et al., 2010].

Abbreviations: HUVEC, human umbilical vein endothelial cell; miRNAs or miRs, microRNAs; RNAi, interference; 3' untranslated region, 3' UTR; VEGF, vascular endothelial growth factor; HMECs, human microvascular endothelial cells; SCF, stem cell factor; TSP-1, thrombospondin-1; CTGF, connective tissue growth factor; RISC, RNA-induced silence complex.

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Due to tumor reliance on capillary network extension, angiogenesis has become an attractive therapeutic target [Dentelli et al., 2010]. And great progress has been made to develop anti-angiogenic drugs or treatments, including small molecules of tyrosine kinase inhibitors (TKIs), monoclonal antibodies, inhibitors of mTOR (mammalian target of rapamycin), such as Avastin, Erbitux, and Torisel, and last but not the least, genetic therapy. Generally, gene target strategies to degrate mRNAs were considered as a common approach to investigate the gene function or a promising cure against cancer. Now, this conception was challenged by the new findings of microRNAs (miRNAs) derived from intronic gene. Considering the increasingly significant role of miRNAs in development and occurrence of disease, these new evidence minimize the disruptive gene targeting strategies [Wang and Olson, 2009]. In fact, "many miRNAs are conserved in sequence between distantly related organisms, suggesting that these molecules participate in essential processes [Ling et al., 2011]." Karreth et al. [2011] revealed that competitive endogenous RNAs (ceRNAs) could block the effect of miRNAs on regulating mRNA transcripts which contain common microRNA recognition elements (MREs). The discovery of this mechanism has broadened our view of cell signalling regulation, and from now on, the functional role of non-coding miRNAs in cancer is becoming more attractive. Recently, the discovery of non-coding miRNAs that profoundly influence the biological process of angiogenesis is accumulating with the development of miRNAs research. This perspective briefly outlines the past and present strides in deciphering the regulatory role of miRNAs in angiogenesis, especially in cancer, and speculates on new frontiers in miRNAs research and prospects of miRNAs as therapeutic agents or diagnostic indicators in cancer.

miRNAs BIOGENESIS AND RELATIONSHIP WITH ANGIOGENESIS

MiRNAs are a class of short, non-coding RNAs that regulate gene expression via the RNA interference (RNAi) pathway and disruption of protein expression at the posttranscriptional level. They are known to inhibit or degrade mRNA transcripts through antisense binding to the mRNA 3′ untranslated regions (3′ UTRs) [Urbich et al., 2008; Wang and Olson, 2009; Dentelli et al., 2010]. However, other studies indicated that miRNAs might interfere with translation by binding to the 5′ UTR of their target mRNAs [Lytle et al., 2007; Ørom et al., 2008; Li et al., 2011]. And Lee et al. revealed a new class of microRNA target containing simultaneous 5′ UTR and 3′ UTR interaction sites [Lee et al., 2009]. Also, several groups proved that the binding sites might in the coding regions of target proteins [Duursma et al., 2008; Forman et al., 2008]. Those findings revealed further miRNA functions within this new target class, and the exact mechanism remains to be elucidated. Following transcription, primary miRNA (pri-miR) is modified into precursor miRNA (pre-miR) by a nuclear RNase III endonuclease Drosha, and the product is then transported to the cytoplasm where the ribonuclease enzyme Dicer cleaves the pre-miR into double-stranded RNA (miRNA: miRNA*). The mature miRNA derived from the miRNA dimer, could down-regulate, or accidentally degrade the target mRNAs according to the extent of the recognizing sequence complementarity, leading to trigger a different downstream process which is post-transcriptional gene silencing through RISC (RNA-induced silencing complex) or RNA interference (RNAi) pathway [Doench and Sharp, 2004; Zamore and Haley, 2005; He, 2007; Filipowicz et al., 2008; MacFarlane and Murphy, 2010; Melo and Kalluri, 2012]. Some reports demonstrated that both strands of miRNA duplex can enter the RISC, which indicated that either or both miRNAs might be functional [Heusschen et al., 2010]. In spite of this, only one strand of miRNA duplex could incorporate into the effector complex, RISC, but each strand might be chosen theoretically with similar frequency [Schwarz et al., 2003; Bartel, 2004] So far, the mechanism for choosing functional miRNA and relationship between the couple miRNAs hasn't been thoroughly explained.

First pieces of evidence that revealed the vital roles of miRNAs in angiogenesis were proved by a study on Dicer depletion in zebrafish [Giraldez et al., 2005; Yin et al., 2013]. Furthermore, it has been reported that Dicer knock down could cause severe dysregulation of angiogenesis-related genes in vitro and in vivo [Suárez et al., 2007; Kuehbacher et al., 2008; Roy and Sen, 2012]. Similarly, Shilo et al. found that angiogenesis was significantly down-regulated in Dicer$^{-/-}$ human microvascular endothelial cells (HMECs) despite elevated vascular endothelial growth factor (VEGF) expression [Shilo et al., 2008]. These findings, including the Drasha and Dicer, implied that miRNAs acted as important regulators in angiogenesis. Sooner after, accumulating data were consistent with this theory [Bernstein et al., 2003; Lee et al., 2007]. To date, numerous angiogenic miRNAs were identified and several of them were thoroughly investigated to interpret the mechanisms of specific miRNAs in angiogenesis (Table I, Fig. 1). And most of them have also been demonstrated by many groups to play a vital role in tumor angiogenesis [Yanaihara et al., 2006; Brenner et al., 2011; Ling et al., 2011].

miRNAs WITH PLEIOTROPIC EFFECTS ON ANGIOGENESIS

miR-126

Of all the tremendous miRNAs involved in angiogenesis, interestingly, miR-126 is only expressed in endothelial cells, and hematopoietic progenitor cells [Ye et al., 2014]. Hence, its role in neovasclularization and angiogenesis is self-evident. MiR-126 is located on an intron of *Eglf 7* which was proved to act as a key regulator of ECs migration and vasculogenesis. The new pieces of evidence indicated that miR-126 is actually the real effector causing vascular abnormality, not *Eglf 7* [Kuhnert et al., 2008]. It can be implied that miRNAs (intronic) should be considered in the gene target strategies in cancer therapy. In the studies of miR-126 targets, several groups showed similar results. Fish et al. firstly reported that miR-126 bind and silence the Sprouty-related protein 1(SPRED1) and phosphoinositol-3 kinase regulatory subunit 2 (PIK3R2) to repress VEGF pathway which subsequently cause the negative response of endothelial cells to VEGF and angiogenesis [Fish et al., 2008]. At the same time, "SPRED1 and VCAM1 were also identified in the involvement of miR-126 regulation using microarray analysis [Wang et al., 2008; Heusschen et al., 2010]." And these two targets

TABLE I. miRNA Detected in Endothelial Cells Involved in Angiogenesis and Their Targets. Partially Summarized by Chang and Hla [2011].

Name	Function	Target	Ref.
Let-7 family (Let-7a, -7b, -7c, -7d)	"Directly and indirectly regulate MYC and RAS expression. And Dicer and Drosha regulate the antiangiogenic effector TSP-1 via let-7 family members."	Myc, Ras	Johnson et al. [2005]; Barh [2008]; Grundmann et al. [2011]; Akao et al. [2006]; Kuehbacher et al. [2007]; Kumar et al. [2008]
miR-17∼92 cluster (miR-17-5p, -17-3p, -18, -19a, -19b, -20, -92a)	Inhibit the expression of TSP-1 and CTGF which acts as angiogenesis inhibitor. However, the function of individual component is distinct in different cell types and states.	TSP-1, CTGF	Bonauer et al. [2009]; Doebele et al. [2010]; Kuhnert and Kuo [2010]
miR-23∼34 cluster (miR-23a/b, -24, -27a/b, -29a, 30a/c, -31)	Inhibition of miR-23 and miR-27 function represses angiogenesis in vitro and postnatal retinal vascular development in vivo.	Sprouty2, Sema6A	Zhou et al., [2011]
miR-15b, miR-16	Control the expression of VEGF, and induce cell apoptosis	VEGF, Bcl-2	Hua et al. [2006]; Guo et al. [2009]
miR-100	"Modulates proliferation, tube formation, and sprouting activity of endothelial cells and migration of vascular smooth muscle cells and functions as an endogenous repressor."	mTOR	Akao et al. [2006]; Grundmann et al. [2011]; Sun et al. [2013]; Kumar et al. [2008]
miR-103a	Enhance angiogenesis by targeting antiangiogenic gene GAX and HOXA5.	GAX, HOXA5	Chen and Gorski [2008]
miR-106	Deregulate the G1/S checkpoint and promote rapid cell proliferation and induce angiogenesis.	p21, Bim	Boeri et al., [2011]
miR-125a/b	Inhibit tube formation of blood vessels	VE-cadherin	Muramatsu et al. [2012]
miR-126	"Regulates blood vessels structure integrity, angiogenesis and lymphangiogenesis."	PI3KR2, SPRED1, EGFL7	Fish et al. [2008]; Harris et al. [2008]; Wang et al. [2008] [Sasahira et al. [2012]; Chang and Hla [2011]
miR-128	Inhibit tumor growth and angiogenesis	P70S6K1	Shi et al. [2012]
miR-130a	Enhances EC migration and tube formation	GAX, HOXA5	Chen and Gorski [2008]
miR-132	"Inhibition of miR-132 suppresses angiogenesis and decrease tumor burden in an orthotopic xenograft mouse model." miR-132 involves in response to VEGF in an infectious ocular disease	p120RasGaP	Anand et al. [2010]; Mulik et al. [2012]
miR-199a	Inhibit cell invasion/migration	HIF-1α	Kang et al. [2012]
miR-210	"Enhances EC survival/migration/tube formation." miR-210 activates notch signaling pathway in angiogenesis induced by cerebral ischemia. miR-210 regulates cell growth, angiogenesis and apoptosis in different human tumor models.	Ephrin A3	Fasanaro et al. [2008]; Alaiti et al. [2012]; Hong et al. [2013]; Lou et al. [2012]
miR-221/222	Monitor angiogenesis in breast cancer microenvironment. Reduce SCF-induced EC survival, migration, tube formation.	c-Kit	Poliseno et al. [2006]; Chen et al. [2013]
miR-296	"Increases the levels of proangiogenic growth factor receptors such as VEGFR2 and PDGFR-β. Inhibit of miR-296 reduces angiogenesis in tumor xenograft."	HGS	Würdinger et al. [2008]
miR-320	Promote invasion and angiogenesis.	unknown	Khew-Goodall and Goodall [2012]

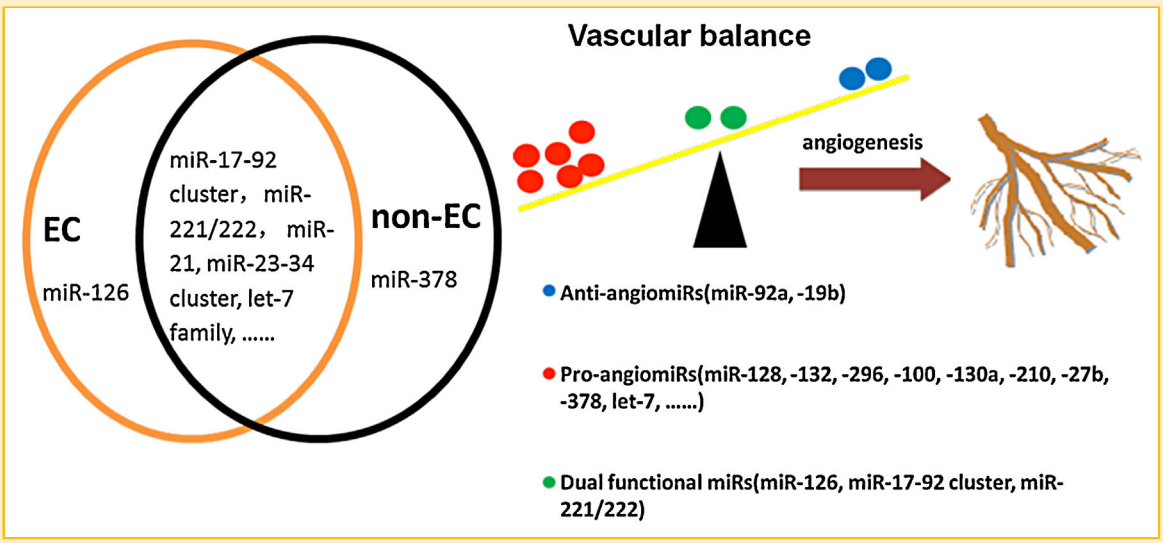

Fig. 1. The role of miRNAs in angiogenesis expressing in ECs and non-ECs. Tremendous miRNAs expressed not only in Ecs and also non-Ecs have been involved in the regulation of angiogenesis. These miRNAs have been classified into three groups, anti-angiogenic miRNAs(anti-angiomiRs), pro-angiogenic miRNAs(pro-angiomiRs) and dual functional miRNAs (dual funtional miRs), according to their specific activities in tumor angiogenesis.

were simultaneously determined by Kuhnert et al. [2008] and Harris et al. [2008] as well, respectively. Taken together, above data indicated that miR-126 was a pro-angiogenic factor in the VEGF induced angiogenesis. Both these features are known to occur in some angiogenesis diseases, and the literature on the regulation of miR-126 by angiogenesis stimuli is consistent with the above data. Nicoli et al. found that miR-126 was induced by mechano-sentitive zinc finger transcription factor klf2a5, 6, 7 to activate VEGF signaling in aortic arch remodeling [Nicoli et al., 2010]. And Zhang et al. reported that miR-126 was down-regulated in endothelial progenitor cells in coronary artery disease (CAD) patients [Zhang et al., 2011]. However, in the context of tumor, the literature came out with conflicting results. Recent evidence showed that miR-126 expression was decreased in ECs co-cultured with glioma cells [Würdinger et al., 2008]. It was recently reported that miR-126 was down-regulated in tumor tissue and correlate with microvessel density and survival outcomes in non-small-cell lung cancer [Jusufović et al., 2012]. Based on these results, it was suggested that miR-126 possessed anti-angiogenic activity in cancer [Quintavalle et al., 2011]. The controversy indicated that angiogenesis in tumor might be activated by alternative regulatory pathways and it also reflects a cell type or context specific function of miR-126. Latest published paper indicated that miR-126 could regulate angiopoietin-1 signaling and vessel maturation by targeting p85β [Sessa et al., 2012]. Based on these data, VEGF signaling might partially contribute to the effect of miR-126 in angiogenic regulation. And it is likely that other targets which have been proposed to be the key events resulting in loss of VEGF dependence are more vital in tumor angiogenesis, such as coverage by pericytes. Alternatively, the newly proposed modulating mechanism involving competitive endogenous RNAs (ceRNAs) in cancer should be considered [Karreth et al., 2011]. So far, there were no convincing results to explain the specific mechanism of miR-126 in tumor angiogenic regulation.

miR-221/222

The antiangiogenic role of miR221/222, another frequently detected mi-RNA family in ECS, was first confirmed by Poliseno et al. [2006]. They found that the mi-R221/222 family down-regulates stem cell factor (SCF) activity by binding to the 3′ UTR of its receptor, c-Kit. In their study, they hypothesized that miR-221/222-transfected cells would fail to undergo the same pro-angiogenic activities observed in control HUVECs. Experimental results proved their hypothesis to be correct. Whereas activation of c-Kit normally results in angiogenic processes, including tube formation, cell migration, and survival, Poliseno and colleagues showed that cells transfected with miR-221/222 displayed reduced tube formation and cell migration [Hulsmans et al., 2011]. Yet, interference of c-Kit activity at the protein level was not accompanied with a decrease in c-Kit mRNA levels, indicating that miR-221/222 modulates angiogenesis at the posttranscriptional level. Another interesting observation made by other groups is that a decrease in miR-221/222 led to a change in the miRNA profile of HUVECs, suggesting that miRNAs were affected by other miRNAs [Urbich et al., 2008]. Furthermore, Dentelli et al. have shown that miR-222 controls in vivo neoangiogenesis and vessel formation by interfering with the STAT5 pathway [Dentelli et al., 2010]. Recently, Zhang and the colleagues found that miR-221/222 was down-regulated in endothelial progenitor cells (EPCs) in CAD patients, which consisted that it act as an anti-angiogenic regulator. MiR-221 and miR-222 also inhibit expression of eNOS, an essential molecule in the regulation of vessel tone and angiogenesis [Suárez et al., 2007]. It seems like miR-221/222 could be an ideal agent in cancer therapy. However, new evidence suggested the pro-angiogenic effect of miR-221. Nicoli et al. [2012] demonstrated that miR-221 participates in tip cell proliferation and migration, as well as tip cell potential in forming mosaic blood vessels. The studies pointed out miR-221 acted as a different effector in endothelial tip and stalk cells which was highlighted in *Nature* [Le , 2012]. Additionally, a lot of groups proved that miR-222/221 possess opposing effect on tumor cells. Many studies demonstrated that miR-221/222 positively influence cellular proliferation in many types of cancers and overexpression of miR-221/222 helps to protect cancer cells against various kinds of apoptotic stimuli, including chemotherapeutics, radiotherapy, endocrine therapies, and anoikis [Howe et al., 2012; Melo and Kalluri, 2012]. Even in one study, decreased tumor growth was achieved through in vivo administration of cholesterol modified anti-miR-221 [Park et al., 2011]. Therefore, due to the fact that these miRNAs which have been classified as "anti-angiogenic miRNAs" before may exhibit opposite activities in tumorigenesis according to the current findings, the microRNA target strategies against cancer should be considered more carefully.

miR-17-92

Although miR-221 and miR-222 share the same seed region and thus have close functions in many contexts, they also have distinctive and opposing roles under a variety of pathophysiological circumstances [Dentelli et al., 2010]. The same is true for the miR-17-92 cluster, a family of miRNAs that are highly expressed in primary lymphoma, a wide range of tumor-derived cell lines and ECs. The cluster is coded by a polycistronic miRNA gene, chr13orf25 (chromosome 13, ORF 25), whose expression is strongly correlated with disease and amplified in follicular lymphoma, B-cell lymphoma and several lung, head, and neck carcinomas [Knuutila et al., 1998; Ota et al., 2004]. It consists of six mature miRNAs, including miR-17, miR-18a, miR-19a, miR-19b-1, miR-20a, and miR-92 [Mendell, 2008;]. "This unique gene structure of miR-17-92 may underlie the molecular basis for its pleiotropic functions in a cell type- and context-dependent manner [Olive et al., 2010]." Previous studies showed that overexpression of the entire miR-17-92 cluster leads to pro-angiogenic activity in tumors via inhibition of the antiangiogenic factors thrombospondin-1 (TSP-1) and connective tissue growth factor (CTGF) [Kuhnert and Kuo, 2010]. However, ensuing studies have revealed diverse functions of the specific component miRNAs of this cluster in angiogenesis. MiR-18a and miR-19a possess proangiogenic effects, whereas forced overexpression of miR-92 leads to deregulation of sprout formation, EC migration, and EC adhesion to fibronectin [Bonauer et al., 2009]. Bonauer et al. [2009] further confirmed the antiangiogenic function of miR-92a when they inhibited miR-92a in vivo with antagomiRNAs and found that angiogenic machinery and activity were restored in the cells. Additionally, our group found that up-regulated miR-19b could inhibit angiogenesis *in vitro* by down-regulating cyclin D1

expression which could block the cell cycle progression [Yin et al., 2012]. Similarly, Doebele et al. found that overexpression of miR-17, 18a, 19a, and -20a significantly inhibited in vitro and in vivo angiogenic activity of ECs, however, systemic inhibition of miR-17 and miR-20a did not affect tumor angiogenesis, which indicated that miR-17/20 may possess a context-dependent regulation of angiogenesis in vivo [Doebele et al., 2010]. Based on these results, it is imperative to reconsider the role of miRNAs in tumor angiogenesis which exhibited antiangiogenic activity in ECs. Inevitably, further studies are required to shed further light on the regulatory mechanisms of miRNAs involved in angiogenesis in tumor microenvironment.

miR-130A

Another miRNA that is frequently expressed in ECs is miR-130a. According to Yun Chen and David H. Gorski, miR-130a acts to increase angiogenesis in ECs. They showed that miR-130a down-regulated the expression of homeobox genes *GAX* and *HOXA5*, which are known to be antiangiogenic in ECs both in vitro and in vivo [Chen and Gorski, 2008]. And other groups paid attention to the functions of miR-130a in cancer. Boll et al. [2012] showed that "miR-130a, miR-203, and miR-205 corporately impacted the two major pathways in prostate carcinoma, including mitogen-activated protein kinase (MAPK), and androgen receptor (AR), and were deregulated in cancer tissue." This indicated that microRNAs could work together to act as tumor suppressors, which suggested a feasible mode of action in miRNAs regulation.

OTHER miRNAs EFFECT ON ANGIOGENESIS

HYPOXIA INDUCED miRNAs

Most all solid tumors embody hypoxic regions that induce angiogenesis to sustain tumor growth and metastasis [Hu et al., 2003; Huang et al., 2010; Yang et al., 2013]. Hypoxia inducible factors (HIFs), mainly HIF-1α and HIF-2α, act as pro-angiogenic factors and progress of solid human tumors [Hu et al., 2003; Holmquist-Mengelbier et al., 2006; Gordan and Simon, 2007; Ryan et al., 2000]. Recently, constantly emerging evidence outstand the significance of microRNAs (miRNAs) as a new class of genes regulated by HIFs induced by hypoxia, among which miR-210 is the most consistently and remarkably upregulated miRNA. Functional studies have demonstrated that miR-210 is a universal gene that involves in many aspects of hypoxia pathway in oncogenic pathway, which was well summarized [Hu et al., 2003; Huang et al., 2010; Yang et al., 2013]. The results from the HUVEC model have shown that miR-210 exhibited pro-angiogenic activity by targeting Ephrin-A3 [Fasanaro et al., 2008]. Later, Yang et al. found that tumor angiogenesis was repressed in the miR-210 knockdown nude mice model with human hepatoma xenograft when the protein expression of MNT, EFNA3, and AIFM3 which targeted by miR-210 were increased and HIF-1α protein was decreased [Yang et al., 2013]. These above findings supported a predominant effect for miR-210 on pro-angiogenesis in human cancers. Besides, Hua et al. screened 4 miRNAs out of 96 hypoxia related miRNAs, including miR-16, miR-15b, miR-20a, and miR-20b, which could downregulate angiogenesis by co-modulate VEGF and other angiogenic factors under hypoxic conditions [Hua et al., 2006]. Recently results demonstrate that miR-200b enables the angiogenesis in a response to hypoxia. Virtually in the hypoxic environment miR-200b down-regulation is required to the effect of Ets-1 which is a pro-angiogenic protein, leading to form new blood vessels [Chan et al., 2011]. Other miRNAs were also play a role in tumor angiogenesis, although the mechanisms were still unclear. Cha and et al. found that hypoxia-inducible factor-1α, which could induce VEGF expression under hypoxic conditions, is suppressed by miRNA-519c indirectly [Cha et al., 2010]. Yamakuchi et al. showed that miRNA-107 was also involved in inhibiting HIF-1, but only the other half of the dimer (HIF-1β) [Yamakuchi et al., 2010]. However, the role of miRNAs in tumor angiogenesis is still unclear and more evidence especially those on these miRNAs knockout mouse models are indispensable to shed new light on the angiogenic regulating mechanisms [Hu et al., 2003; Huang et al., 2010; Yang et al., 2013].

EXOSOMAL miRNAs EFFECT ON ANGIOGENESIS

Generally, signaling between endothelial cells, as well as signaling to other angiogenesis relative cells [Aicher et al., 2005; Pitchford et al., 2009], is triggered by intercellular contact, and exchange of excretive proteins [Boussat et al., 2000]. Additionally, exosomes, small vesicles (40–100 nm) secreted by a mass of cell types, have aroused interest for their pivotal role in cell-cell communication in extensive biological processes such as immune signaling, stress responses, tumor survival, and angiogenesis [Clayton et al., 2004; Janowska-Wieczorek et al., 2005; Lancaster and Febbraio, 2005; Liu et al., 2006; Valadi et al., 2007; Skog et al., 2008; Hood et al., 2009; Park et al., 2010; Eldh et al., 2010; Chaput and Théry, 2011]. The ability of exosomes carrying messenger RNAs (mRNAs) or miRNAs suggests their potential influence on the physiological signal of recipient cells [Fevrier and Raposo, 2004; Camussi et al., 2010]. Consideration of more and more important role of miRNAs in signaling regulation, exosomal miRNAs have gained a lot of attention and investigation of their mechanism by the analysis of exosomal miRNAs profile [Ekström et al., 2012]. It is demonstrated that endothelial cells possessed the ability to secrete exosomes and take exosomes from same or other disparate cell types [Zhan et al., 2009; Sheldon et al., 2010]. Several miRNAs have been proved to regulate endothelial function and angiogenesis by exosome pathway, such as miR-214 [van Balkom et al., 2013], miR-150 [Zhang et al., 2010], miR-143/145 [Hergenreider et al., 2012], and so on. Additionally, some other miRNAs such as miR-378 which was not expressed in ECs (reviewed in [Wang and Olson, 2009]), are also vital in angiogenesis. And miR-378 has been observed in cell secrete exosomes [Ekström et al., 2012], which indicated that miR-378 could modulate Ecs function by miRNAs communication. Thus, exosomes are intriguing to provide another possibility of signaling conduction to regulate endothelial cell function.

PROSPECTIVE

Today, researchers have already identified dozens of pro-angiogenic factors and anti-angiogenic factors, including miRNAs that are mentioned in this review. The prevailing paradigm suggests that antiangiogenic therapy is promising in cancer treatment. Meanwhile,

recent evidence indicates that restoring the intact structure and function of blood vessels (so-called "vascular normalization") might be benefit in cancer therapy [Jain, 2005]. Therefore, multi-targeted miRNAs become more attractive in cancer research.

Although miRNA research is at the forefront of oncological research, there are no approved, clinically-tested miRNA treatments that directly target angiogenesis as of yet. Due to the fact that miRNAs could act as either suppressors or activators in angiogenesis in a cell type- and context-dependent manner, it is hard to design ideal candidates for therapy. However, some of them were proved patents for the diagnosis and treatment of solid cancers, such as miR-125. Since miRNA research is considered a newer field, the mechanisms underlying miRNA and cancer angiogenesis is still being studied and will require more research before becoming approved and recognized cancer therapies.

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