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MicroRNAs: Opening a New Vein in Angiogenesis Research

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Activation of the angiogenic program in endothelial cells is vital for normal embryonic development and for physiological angiogenesis in the adult. In addition, angiogenesis is an important therapeutic target: Formation of new blood vessels is desirable for regenerative purposes, such as during tissue healing or transplantation, but can be pathological, as in diabetic retinopathy and cancer. The response of the vascular endothelium to angiogenic stimuli is modulated by noncoding RNAs called microRNAs. The endothelial cell–specific microRNA *microRNA-126* (*miR-126*) promotes angiogenesis in response to angiogenic growth factors, such as vascular endothelial growth factor or basic fibroblast growth factor, by repressing negative regulators of signal transduction pathways. Additional microRNAs have been implicated in the regulation of various aspects of angiogenesis. Thus, targeting the expression of microRNAs may be a novel therapeutic approach for diseases involving excess or insufficient vasculature.

The formation of blood vessels, whether in the developing embryo or in the adult, occurs by two distinct processes: vasculogenesis and angiogenesis. Vasculogenesis is the de novo generation of blood vessels by the differentiation of progenitor cells into the endothelial lineage. Initially thought to occur only during embryonic developmental stages, vasculogenesis is now considered an important contributor to postnatal vascular formation, as circulating endothelial progenitor cells and other bone marrow–derived multipotent cells are recruited to sites of tissue damage or tumorigenesis and differentiate to become incorporated into the growing vasculature (*1*). In contrast, angiogenesis is the process by which new blood vessels form through the growth of existing blood vessels, and involves the proliferation, sprouting, and migration of endothelial cells, followed by pruning and remodeling of the vascular network [reviewed in (*2*)].

Depending on the type of vascular bed, a single layer of endothelial cells is surrounded by pericytes or smooth muscle cells, both of which provide support to the vasculature. The endothelium is the main regulator of angiogenesis and is highly responsive to factors in the extracellular environment. Major promoters of angiogenesis include vascular endothelial growth factor (VEGF) and basic fibroblast growth factor (bFGF), which activate several downstream pathways, including the mitogen-activated protein kinase (MAPK) and phosphinositide 3-kinase (PI3K) pathways, to regulate cell motility, proliferation, and survival [(*3*), reviewed in (*4*, *5*)]. Several factors also inhibit angiogenic signaling, including the endothelial cell surface receptor Roundabout homolog 4 (Robo4) (*6*) and the Notch ligand Delta-like 4 (*7*), both of which antagonize VEGF signaling. MicroRNAs, which are a class of small noncoding RNAs that regulate vast numbers of transcripts at the posttranscriptional level [reviewed in (*8*–*10*)], are emerging as important modulators of angiogenesis (Fig. 1). Although microRNAs are primarily thought to negatively regulate gene expression by inhibiting mRNA stability or translation of target mRNAs, examples of microRNAs that can increase gene expression are emerging (*11*, *12*). Specific endothelial microRNAs have been implicated in controlling cellular responses to angiogenic stimuli (*13*–*18*), suggesting that microRNAs may be key modulators of angiogenic signal transduction pathways. Additionally, dynamic changes in microRNA expression in response to growth factor stimulation (*19*–*21*) or hypoxia (*22*) imply that microRNAs are an integral component of the angiogenic program. The regulatory pathways controlled by microRNAs, and the utility of therapeutic manipulation of microRNA expression to control vascular formation in human disease states, have yet to be fully elucidated.

The first evidence implicating microRNAs in the regulation of angiogenesis came from analysis of mice homozygous for a hypomorphic allele of *Dicer* (*23*), a ribonuclease III enzyme required for microRNA biogenesis (*24*). Although lacking the early developmental abnormalities of *Dicer*-null mice (*25*), these hypomorphs lacked angiogenesis and died between days 12.5 and 14.5 of gestation (*23*). In an independently derived, nonlethal *Dicer* hypomorph, females were sterile because angiogenesis failed in the corpus luteum (*26*), a structure required in early pregnancy. Although these studies implicated Dicer-generated microRNAs in regulating angiogenesis, the responsible cell type and specific microRNAs involved were unclear. Conditional ablation of *Dicer* from the endothelium resulted in a diminished angiogenic response in tumor models and in response to ischemia (*20*). Experiments with cultured endothelial cells also demonstrated a role for Dicer in several angiogenic processes, including proliferation, migration, capillary sprouting, and formation of endothelial cell networks resembling capillaries (*16*, *18*, *27*). Thus, microRNAs have a crucial role in regulating angiogenesis and appear to function in endothelial cells.

MicroRNA expression profiling in cultured endothelial cells has been performed to identify microRNAs that might contribute to angiogenic processes (*16*–*18*). Additionally, several microRNAs were highly enriched in endothelial cells derived from embryonic stem cells or isolated from mouse embryos, including *microRNA-126* (*miR-126*), which is an endothelial-specific microRNA (*13*). *miR-126* is a key positive regulator of angiogenic signaling in endothelial cells and of vascular integrity in vivo (*13*–*15*). Knockdown of *miR-126* during zebrafish embryogenesis or deletion of *miR-126* in mice resulted in defects in vascular development. For example, collapsed blood vessels and cranial hemorrhages occurred in zebrafish with reduced *miR-126* abundance (*13*), and mice deficient in *miR-126* exhibited delayed angiogenic sprouting, widespread hemorrhaging, and partial embryonic lethality (*14*, *15*). In addition, *miR-126* mutant mice that successfully completed embryogenesis displayed diminished angiogenesis and increased mortality after coronary ligation, a model for myocardial infarction (*14*). Endothelial cells deficient in *miR-126* failed to respond to angiogenic factors, including VEGF, epidermal growth factor (EGF), and bFGF (*13*–*15*). Two direct targets of *miR-126* are Sprouty-related EVH1 domain–containing protein 1 (Spred1) (*13*–*15*) and a regulatory

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subunit of PI3K, PIK3R2 (also known as p85β) (*13*, *15*). Because Spred1 and PIK3R2 are negative regulators of cellular signaling cascades, affecting the MAPK (*28*) and PI3K (*29*) signaling pathways, respectively, *miR-126* promotes VEGF and other growth factor signaling (Fig. 1). By targeting multiple signaling pathways, *miR-126* may fine-tune angiogenic responses.

Other microRNAs in addition to *miR-126* regulate the angiogenic response of cultured endothelial cells. For example, *miR-221* and *miR-222* inhibit stem cell factor (SCF)–dependent angiogenesis by decreasing the abundance of c-KIT, a ligand for the SCF receptor (*17*). In contrast, *miR-27b* and *Let-7f* are proangiogenic, because inhibition of these microRNAs reduces angiogenic sprouting (*18*). The abundance of other microRNAs dynamically changes in response to cellular stimulation, including VEGF treatment (*20*) and exposure to hypoxia (*21*). For example, hypoxia triggers the production of *miR-210*, which has proangiogenic activity because of its targeting of ephrin A3, a repressor of VEGF-dependent endothelial cell migration and formation of capillary-like structures (*22*). Exposure of cultured endothelial cells to serum leads to an increase in the abundance of *miR-130a*, which targets the genes encoding homeobox A5 (HOXA5) and growth arrest–specific homeobox (GAX) (*21*). Because the products of these homeobox genes inhibit angiogenesis, *miR-130a* has proangiogenic activity (*21*). In addition, the abundance of endothelial cell microRNAs can change in response to angiogenic factors produced by cancer cells. For example, *miR-296* becomes more abundant in endothelial cells cocultured with glioma cells or in response to VEGF stimulation, and promotes angiogenic signaling through the repression of hepatocyte growth factor–regulated tyrosine kinase substrate (HGS), which degrades VEGF receptor 2 and platelet-derived growth factor receptor β (*19*). In vivo inhibition of *miR-296* activity reduces vascularization of tumor xenografts (*19*). Thus, several microRNAs are dynamically regulated in endothelial cells and contribute to how endothelial cells respond to angiogenic stimuli.

Endothelial cells are exquisitely sensitive to signals present in their extracellular milieu, and a wealth of data now implicates endothelial microRNAs in controlling the cellular response to these signals. Not only are endothelial microRNAs important, it is likely that microRNAs in cells that interact with endothelial cells—including cells circulating in the blood, resident inflammatory cells, tumor cells, vascular smooth muscle cells, and pericytes—will affect signaling to endothelial cells by modulating the expression of secreted growth factors and other paracrine factors (Fig. 1). There is even evidence that cells may also secrete microRNA-containing microvesicles (*30*), which suggests that microRNAs may have non–cell-autonomous functions. Future work will determine the impact of microRNAs in endothelium and the surrounding cells in controlling endothelial signaling pathways, especially in disease states.

Of particular interest are diseases that involve pathological angiogenesis. As an example, microRNA expression is markedly altered in cancer cells [reviewed in (*31*)]. One mechanism by which these microRNAs may modulate tumorigenicity is by controlling the production of angiogenic factors, and therefore neovascularization. For instance, the cluster of microRNAs *miR-17* through *miR-92* (*miR-17-92*), which are transcribed as a polycistron that is stimulated by Myc, targets the secreted factors thrombospondin 1 (TSP1) and connective tissue growth factor, both of which inhibit angiogenesis (*32*). Another microRNA that promotes angiogenesis in tumor models is *miR-378*, which enhances cell survival and angiogenesis by targeting suppressor of fused homolog (SuFu) and tumor suppressor candidate 2 (TUSC2, also known as Fus-1), both of which are tumor suppressors (*33*). VEGF, which is secreted by tumor cells and is vital for neovascularization (*34*), is predicted to be targeted by multiple microRNAs, including *miR-15b*, *miR-16*, *miR-20a*, and *miR-20b* (*35*). Transfection of these microRNAs into cells can inhibit VEGF expression, but definitive proof of the regulation of VEGF by these microRNAs in a physiologically relevant setting remains to be demonstrated. Thus, microRNAs in cancer cells control tumor angiogenesis by affecting the cross-talk between cancer cells and vascular endothelium. This paradigm is likely also true of the interaction between "normal," noncancerous cell types and endothelium in other physiological and pathological processes.

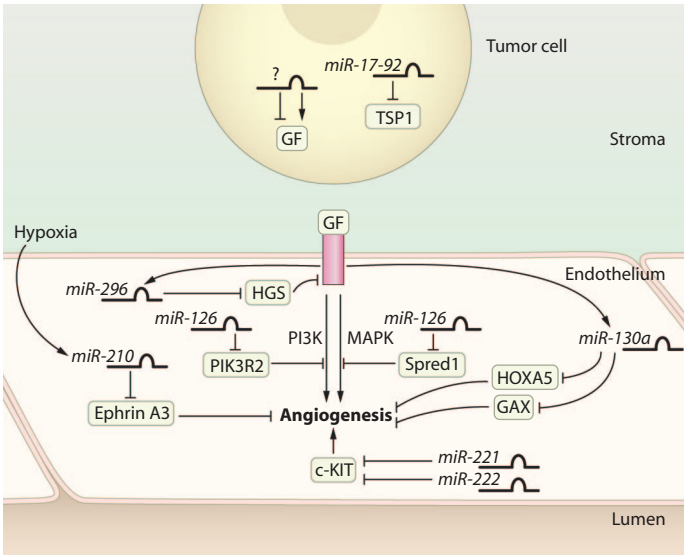

Fig. 1. Modulation of angiogenic signaling by microRNAs. Multiple microRNAs have been implicated in controlling the angiogenic response of endothelial cells to multiple growth factors, including vascular endothelial, basic fibroblast, and epidermal growth factors. Endothelial microRNAs that promote angiogenesis include *miR-126*, *miR-130a*, *miR-210*, and *miR-296*. Known targets and regulators for each microRNA are indicated. Two endothelial microRNAs that inhibit angiogenesis are *miR-221* and *miR-222*, which decrease the abundance of the stem cell factor ligand c-KIT. MicroRNAs present in cells that interact with the endothelium also regulate endothelial cell responses. For example, microRNAs in tumor cells promote angiogenesis by repressing thrombospondin-1 (TSP1), an antiangiogenic factor. MicroRNAs may also affect the amount of secreted growth factors, such as VEGF, released by tumor cells. GF, growth factors.

Considering the anticipated role of microRNAs in a multitude of human diseases [reviewed in (*36*)], in vivo inhibitors of microRNA function (*37*, *38*) and microRNA mimics are intriguing potential therapeutics. Because *miR-126* appears to be necessary for physiological angiogenesis (*13*–*15*), this microRNA may represent an exciting prospect for therapeutic application to enhance angiogenesis after myocardial infarction, stroke, or other ischemic events. Understanding how *miR-126* is regulated in disease states is an important next step. Of note, *miR-126* is encoded in an intron of *EGF-like domain 7* (*Egfl7*) (*39*), which encodes a secreted matrix component and endothelial chemoattractant (*40*) that is produced by angiogenic

endothelium of the tumor vasculature (*41*). If the abundance of *miR-126* is regulated in a similar manner to its host transcript, then *miR-126* may be relatively specific for angiogenic endothelium. Because *miR-126* positively regulates signaling downstream of several growth factor receptors, including VEGF, bFGF, and EGF (*13*, *14*), blocking *miR-126* function may potently inhibit angiogenesis in tumors and other pathological states, such as diabetic retinopathy and retinopathy of prematurity.

Although we have begun to appreciate the importance of microRNAs in the regulation of angiogenic signaling, much work remains to construct a usable lexicon of all the microRNAs involved and the target pathways affected. This area of investigation is likely to unearth a cornucopia of therapeutic targets for the treatment of various human pathologies, especially those involving the vasculature.

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