Vascularization and Cancer Biology

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Vascularization is another hallmark of cancer, whereby cancer cells promote the formation of blood vessels to deliver nutrients for fast-growing solid tumors. The most well-known process of vascularization is angiogenesis. In normal cells and tissues, the angiogenesis is a controlled process that is turned on or off depending on the needs of the cells; however, in cancerous cells and tumors, the angiogenesis process is continuous and there is a dysregulation of pro- and antiangiogenesis factors . This continuous activation of angiogenesis allows the cancer cells to form blood vessels to obtain sufficient nutrients for continuous growth and proliferation. There are other ways tumors can achieve vascularization, such as vascular co-option, intussusceptive microvascular growth and vasculogenic mimicry.

microRNA (miRNA) cancer biology angiogenesis

1. Vascularization Mechanisms in Cancer Cells

Vascularization, also known as angiogenesis, is the formation of new blood vessels surrounding a solid tumor into other ducts within the body. Vascularization generally starts when a solid tumor grows to a certain size, as this creates the need for extra nutrients and oxygen to be supplied to the tumor microenvironment for propagation of the primary tumor. This is triggered when there is low oxygen within the tumor microenvironment (Hypoxia). Hypoxia induces HIF1-α (hypoxia-inducible factor-1 alpha) expression, leading to the activation of downstream factors that are crucial for vascularization [1][2][3].

VEGF (vascular endothelial growth factor) is an HIF1-α induction-dependent factor and a potent inducer of tumor vascularization. It was found that anthracycline treatment in prostate cancer-xenografted mice, which blocks the HIF1-α DNA binding potential, attenuates vascular formation via downregulation of the VEGF activity. The results also showed that the reduction of VEGF leads to impaired growth of prostate cancer [4].

In addition, cellular protease was also found to be a contributor in tissue vascularization. An example is matrix metalloproteinase (MMP), a protease that is transcriptionally activated by HIF1-α [5][6]. It was found that fibroblasts surrounding the tumor could also affect angiogenesis; fibroblasts secrete factors crucial for MMP production in neighboring tumor cells [7]. Furthermore, downregulation of MMP attenuates angiogenesis, further supporting the suggestion that vascularization is MMP-dependent [8].

The changes in the genes mentioned earlier affect angiogenesis by modulating the tumor microenvironment, thereby affecting crucial proteins found most predominantly in tight junctions, as well as other cell-to-cell junctions,

such as adherens junctions and desmosomes. Additionally, exosomal secretion into the extracellular matrix (ECM) could also affect cell-to-cell junctions, which contribute to angiogenesis [9][10].

The regulation of vascularization via miRNA can be either direct or indirect. Direct regulation can be observed when the miRNA targets both activator and suppressor genes involved in tissue vascularization via 3′-UTR binding on their mRNAs. Similar miRNA–mRNA hybrids occur through indirect regulation; however, these miRNAs target specific factors (transcription cofactors) that influence genes involved directly in vascularization. Control can occur at different levels (exosomal, proteomic, genomic and transcript) of the central dogma of molecular biology, thereby leading to angiogenesis. The microRNA regulation associated with cancer angiogenesis is illustrated in **Figure 1**.

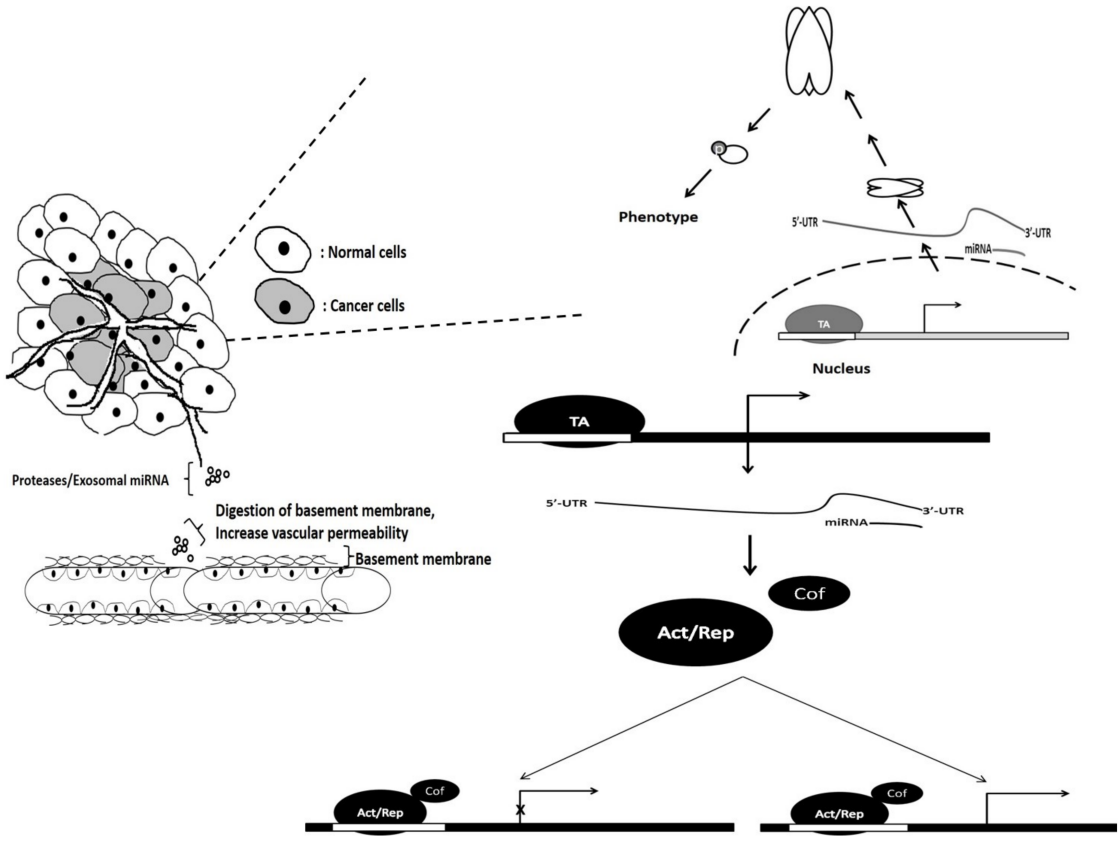

Figure 1. The microRNA-regulation-targeting genes involved in cancer angiogenesis, which occurs at the proteomic, genomic, exosomic and phenotypic levels. Act/Rep: Activator/repressor, Cof: Cofactor, miRNA: micro-RNA, UTR: untranslated region, TA: transcription activator, P: phosphate group.

2. The Role of miRNAs in the Vascularization of Cancer Cells

Cancer tissue vascularization requires specific signalling from various factors for its formation. These factors are regulated by miRNAs. Two high-risk miRNAs, namely miR-148a and miR-30, which regulate HIF1-α via binding directly to its inhibitor FIH1 (factors inhibiting HIF1-α) in the glioblastoma was reported by Wong et al. [11]. Inhibition of these miRNAs results in the downregulation of the HIF1-α protein, which corresponds to the reduction of VEGF

expression and attenuation of vascularization. This is an example of the effects of cofactor targeting via miRNA binding, which influences the activity of transcription factors that directly activate gene expression.

Another interesting miRNA control process occurs when the cancer itself secretes miRNA via exosomes, thereby affecting neighbouring cells. In this case, these would be endothelial cells, which allow for high vascular permeability. This was observed in colorectal cancer cells (CC), whereby exosomal secretion from the CCs containing the miR-25-3p significantly affected the vascular integrity [12]. Another study also found that hepatocellular carcinoma cells (HCCs) overexpressed miR-210, which was found in high abundance in HCC secretion (HSS). Further experimentation revealed exosome-rich miRNA, whereby treatment of HSS on HepG2 resulted in the induction of tubal formation by downregulating SMAD4 and STAT6. Furthermore, direct targeting of the miRNA processing via DROSHA downregulation attenuates angiogenesis [13]. Other examples of miRNAs involved in vascularization are shown in **Table 1**.

Table 1. The miRNA implicated in vascularization.

No	miRNA	Cancer	Target	Action	Reference
1	miR-124-3p	Glioblastoma	NRP-1, transcriptional	Overexpression leads to the attenuation of angiogenesis	[14]
2	miR-526b/miR-655	Breast cancer	PTEN tumor suppressor, transcriptional	Overexpression improved angiogenesis suggesting roles as oncomiR via PTEN-regulated HIF1-α pathway	[15]
3	miR-9	Nasopharyngeal Carcinoma	MDK, exosomal secretion	Suppression of miR-9 in patient suggest its role as oncomiR. Overexpression attenuated tubal formation HUVECs	[16]
4	miR-205	Ovarian Cancer	PTEN tumor suppressor, exosomal secretion	Treatment of HUVECs with miR-205 exosome leads to an increase in tubal formation	[17]
5	miR-6868-5p	Colorectal Cancer	FOXM1, transcriptional	Overexpression leads to the	[18]

No	miRNA	Cancer	Target	Action	Reference
				reduction in endothelial tubal formation	
6	miR-143-3p	Gallbladder Carcinoma	ITGA6, transcriptional	Suppression was observed in bad overall survival patients. Overexpression leads to increased tubal formation	[19]
7	miR-130b	Prostate cancer	TNF-α, transcriptional	Inhibition leads to attenuation of VEGFA, a downstream target of TNF-α suppressing angiogenesis	[20]
8	mR-23a	Nasopharyngeal Carcinoma	TSGA10, exosomal secretion	Exosomal overexpression enhanced angiogenesis	[21]
9	miR-21	Renal cell carcinoma	PCD4, proteomal	Inhibition of miR-21 attenuated MMP levels, besides inhibiting angiogenesis	[22]
10	miR-574-5p	Gastric Cancer Cells	PTPN3 proteomal	Binds to PTPN3, enhancing ERK/JNK activity and driving angiogenesis	[23]
11	miR-27a	Pancreatic Cancer	BTG2, Exosomal	miR-27a was highly expressed in cancer tissue. Exosomal mir-27a stimulates HMVEC tubal formation.	[24]
12	miR-155	Gastric Carcinoma	C-MYB/, Exosomal	Stimulates VEGF expression, leading to enhanced angiogenesis	[25]

No	miRNA	Cancer	Target	Action	Reference
				observed on HUVEC	
13	miR-183-5p	Colorectal Cancer	FOXO1, Exosomal	CRC-derived-exosome enhanced tubal formation of HMEC-1 cells	[26]
14	miR-619-5p	Non-Small Cell Lung Cancer	RCAN1.4, Exosomal	Mimic transfection and leads to the increase in HUVEC tube length and tube abundance	[27]
15	miR-3064-5p	Hepatocellular carcinoma	FOXA1, transcriptional	Overexpression improves overall survival of mice and reduces tumor size; angiogenic factor suppression observed	[28]
16	miR-141	Pancreatic cancer	TM5SF1 transcriptional	Angiogenic factors were induced following inhibition of miR-141	[29]
17	miR-195	Squamous cell lung cancer	VEGF transcriptional	miRNA-195 attenuates tubal formation	[30]
18	miR-136	Gall Bladder cancer	MAP2K4 transcriptional	Mimic treatment resulted in activation of angiopoiesis	[31]
19	miR-302	Chronic Myeloid leukemia	VEGFA, secretome	Low expression was associated with bad OS. Treatment of K562 media on HUVECS attenuate capillary formation	[32]

No	miRNA	Cancer	Target	Action	Reference
20	miR-148a miR-30	Glioblastoma	FIH1	Regulates HIF1-α via binding directly to its inhibitor FIH1 and attenuating vascularization	[11]
21	miR-29b	Breast cancer	AKT3	Overexpression resulted in the attenuation of vascularization by downregulating AKT3, which is crucial for VEGF activation	[33]
22	miR-140-5p	Breast cancer	VEGFA	Abrogates vascularization by binding and attenuating VEGFA	[34]
23	miR-1	Gastric cancer	VEGFA	Inhibition of miR-1 leads to accumulation of VEGFA	[35]
24	miR-30d	Prostate cancer	MYPT1	Downregulation resulted in the attenuation of angiogenesis, leading to reduction in endothelial capillary tube formation	[36]
25	miR-210	Hepatocellular carcinoma	SMAD4, STAT6	Promote angiogenesis by inhibiting SMAD4 and STAT6	[13]

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