Life Sciences 232 (2019) 116652

Contents lists available at ScienceDirect

Life Sciences

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

Review article

Epigenetics: The master control of endothelial cell fate in cancer

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ARTICLE INFO

Keywords:
Angiogenesis
Epigenetics
DNA methylation
Histone modification
microRNA

ABSTRACT

The development of new blood vessels from pre-existing vasculature is called angiogenesis. The growth of tumors depends on a network of supplying vessels that provide them with oxygen and nutrients. Pro-angiogenic factors that are secreted by tumors will trigger the sprouting of nearby existing blood vessels towards themselves and therefore researchers have developed targeted therapy towards these pro-angiogenic proteins to inhibit angiogenesis. However, certain pro-angiogenic proteins tend to bypass the inhibition. Thus, instead of targeting these expressed proteins, research towards angiogenesis inhibition had been focused on a deeper scale, epigenetic modifications. Epigenetic regulatory mechanisms are a heritable change in a sequence of stable but reversible gene function modification yet do not affect the DNA primary sequence directly. Methylation of DNA, modification of histone and silencing of micro-RNA (miRNA)-associated gene are currently considered to initiate and sustain epigenetic changes. Recent findings on the subject matter have provided an insight into the mechanism of epigenetic modifications, thus this review aims to present an update on the latest studies.

1. Introduction

Angiogenesis is one of the hallmarks of cancer. The vascular system provides oxygen and nutrients which are essential for cell function and survival, which forces virtually all tissue cells to reside within 100 μm of a capillary blood vessel [1]. Therefore, these requirements are met through the generation of tumor-associated neovasculature by the process of angiogenesis [2]. A plethora of anti-angiogenic agents have been discovered over the years with many of them demonstrating a successful therapeutic effect, but certain patients have shown resistance [3]. Inherent or adaptive resistance of the tumor is an issue that has been observed consistently in cancer therapy. Inherent resistance depends on the type of cancer but is found primarily in those where certain treatments are ineffective. On the other hand, adaptive resistance is when the tumors adapt to the anti-angiogenic therapy and continue to progress by hijacking other pathways [4–7]. Bevacizumab is a widely reported anti-angiogenic drug which causes tumors to be pro-metastatic post-treatment [4,8,9]. Therefore, researchers have chosen to focus on epigenetic modifications which provide a deeper understanding than only focusing on the proteins that regulate

Abbreviations: DNMT, DNA methyltransferase; HDAC, Histone deacetylase; HAT, Histone acetyltransferase; miRNA/miR, MicroRNA; SIRT, Sirtuin; bFGF, basic fibroblast growth factor; VEGF, Vascular endothelial growth factor; VEGFR, Vascular endothelial growth factor receptor; MeCP2, Methyl CpG binding protein 2; TGF, Transforming growth factor; MBD, Methyl-CpG–binding domain; HOPX, Homeodomain-only protein X; ADK, Adenosine kinase; JARID, Jumonji and AT-rich interaction domain (ARID) domain-containing protein; COX, Cyclooxygenase; NF-κB, Nuclear factor kappa-light-chain-enhancer of activated B cells; LSD1, Lysine-specific histone demethylase 1A; EGR-1, Early growth response protein 1; CDH1, E-cadherin; JMJD2C, Jumonji domain containing protein 2C; NuRD, Nucleosome Remodeling Deacetylase complex; ARHI, Aplysia ras homology member I; c-KIT, KIT proto-oncogene receptor tyrosine kinase; eNOS, Endothelial nitric oxide synthase; CRC, Colorectal cancer; HIF, Hypoxia inducible factors; TNF, Tumor necrosis factor; FGF, Fibroblast growth factor; IL, Interleukin; TIMP, Tissue inhibitor of metalloproteinases; Slit2, Slit homolog 2 protein; STAT3, Signal transducer and activator of transcription 3; PI3K, Phosphatidylinositol-3-kinase; MAP, Mitogen-activated protein kinase; CCL14, Chemokine(C-C motif) ligand 14; AKAP12, A-kinase anchor protein 12; PTPN22, Protein tyrosine phosphatase, non-receptor type 22; ERK, Extracellular signal–regulated kinases; PAI-1, Plasminogen activator inhibitor-1; SPRED1, Sprouty-related, EVH1 domain-containing protein 1; HMEC, Human microvascular endothelial cell; HUVEC, Human umbilical vein endothelial cells; VHL, von Hippel-Lindau; ODD domain, Oxygen dependent degradation domain

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https://doi.org/10.1016/j.lfs.2019.116652
Received 25 May 2019; Received in revised form 10 July 2019; Accepted 10 July 2019
Available online 11 July 2019
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angiogenesis. In doing so, they hope that it will provide answers to overcome the challenges faced in cancer therapy.

Neovascularization is fundamentally a four-step process, including tumor angiogenesis. The first step involves the enzymatic degradation of the vessel in basement membrane. Secondly, the angiogenic promoters activate the endothelial cells to migrate towards environmental cues. Third, the endothelial cells stabilize and proliferate. Fourth, the angiogenic process is affected by angiogenic factors continuously. There are plenty of angiogenic factors that have been secreted by tumor cells, such as platelet-derived endothelial growth factor, granulocyte colony-stimulating factor, VEGF, bFGF, hepatocyte growth factor, angiogenin, TGF-α, TGF-β, TNF-α, placental growth factor, interleukin-8, and epidermal growth factor that bind to specific angiogenic receptors [10]. There are three VEGF receptor family members including VEGFR1, VEGFR2, and VEGFR3 that have receptor protein tyrosine kinase activity and two non-enzymatic receptors (neuropilin-1 and -2) [11,12]. The VEGFs will stimulate the growth of blood vessels within the tumor and thus supplying the tumor with much-needed nutrients and oxygen for growth. However, there are other factors that also lead to angiogenesis which are classified as epigenetic changes.

Epigenetic is a wide range of mitotically or meiotically heritable changes that do not require primary DNA sequence modification [13]. Chemical modifications imposed on the DNA molecule and histone proteins by environmental signals affect the function of the gene and are collectively referred to as epigenetic phenomena. Modifications towards the pro- or anti-angiogenic genes could lead to tumor growth enhancement. The growth factors mentioned above have been linked to improving the angiogenic potential of the tumors through epigenetic modulation [13–15]. A novel study by Hellebrekers and colleagues, was the first to report that the epigenetic regulation of the genes in endothelial cells in the vicinity of tumor cells play a vital role in tumor angiogenesis [16]. This review focuses on the roles of DNA methylation, histone modifications and microRNA in the epigenetic regulation of angiogenesis (Fig. 1). DNA methylation subtypes include the locus-specific hypermethylation of CpG islands and global DNA hypomethylation whereas histone modifications occur through methylation, phosphorylation, acetylation, ubiquitylation, and sumoylation [2,17,18].

The details as to how epigenetic modifications lead to the sprouting of new blood vessels are explained in detail in the following subsections.

2. DNA methylation

DNA methylation involves adding a methyl group in a CpG dinucleotide to the cytosine base [17]. CpG islands are regions on the DNA strand where the cytosine nucleotide comes before the guanine nucleotide from the 5′ to 3′ direction. This region has a high frequency of CpG sites and a GC percentage greater than 50%. DNMT, which consists of DNMT1, DNMT3A, and DNMT3B was shown by the covalent addition of a methyl group, mainly in the context of a CpG dinucleotide, to methylate DNA at the 5-carbon position of cytosine. DNMT1 maintains the methylation profile of DNA while the latter two enzymes act *de novo* [13,19,20]. Hypermethylation of CpG-islands in certain genes' regulatory regions, global hypomethylation, and selective demethylation are now established to regulate transcription in conjunction with angiogenesis [18,21–23]. The tumor suppressor protein, p53 regulates thrombospondin-1 which is directly linked to angiogenesis. In most human tumors, the loss of p53 function can cause thrombospondin-1 levels to drop, thereby allowing new blood vessels to sprout towards tumors. The loss of p53 function was attributed to the mutation of one allele and inactivation of the promoter by CpG-methylation of another allele in various tumors [1,18]. Hypermethylation of the DNA usually occurs on the promoter regions principal to tumor suppressor genes

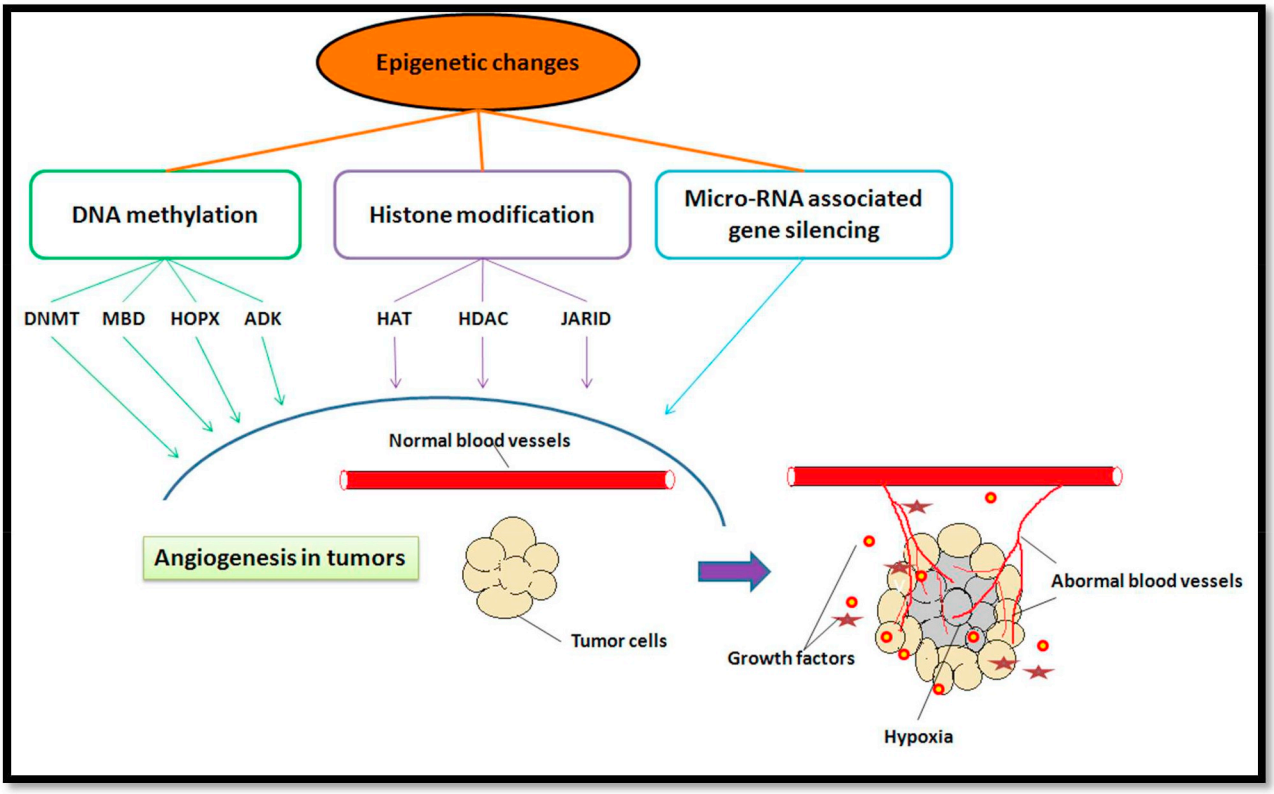

Fig. 1. Schematic diagram proposing the effect of epigenetic changes on tumor angiogenesis. Changes that occur through DNA methylation, histone modifications and micro-RNA associated gene silencing have been linked with the sprouting of new blood vessels towards tumors nearby. The epigenetic changes would contribute either positively or negatively towards the tumor microenvironment.

silencing, whereas activation of proto-oncogenes and genomic instability will be caused by the global DNA hypomethylation or demethylation. Demethylation can also reactivate transposable elements and lead to genetic mutations including allele translocations, insertions, exon deletions, and chromosomal loss [24–26].

Alterations in DNA methylome are commonly seen in animals and patients with vascular diseases, which are read by a conserved family of MBD proteins (i.e., MBD1, MBD2, MBD3, MBD4, and MeCP2) [24,27–31]. Removing of MBD2 has been demonstrated to enhance the actions of VEGFR2 and endothelial nitric oxide synthase that further promote angiogenesis [31]. It has been reported that MBD3 can regulate DNA activity positively or negatively by interacting with both methylated CpG and unmethylated CpG [32–35]. In an elegant study, Cui and colleagues showed the higher level of HIF2α mRNA was expressed because of the ectopic expression of MBD3 as a result of increasing angiogenic capacity in breast cancer [36]. The result from a DNA microarray study has demonstrated that methylation of HOPX-β resulted in the downregulation of HOPX mRNA and protein levels leading to angiogenesis and tumorigenesis in colorectal cancer [36].

Lyu and colleagues have reported that the expression of TIMP3 and CDH1 are inhibited by DNA hypermethylation, thereby reducing their anti-angiogenic activity to promote tumor angiogenesis (Fig. 2) [15]. In a recent study, Xu and colleagues have consummated that DNA hypomethylation of angiogenic genes promotes angiogenesis through the negative feedback transmethylation inhibition reaction in endothelial cells which inhibit intracellular adenosine [37]. Demethylation of the Fibromodulin have shown to regulate glial cell line-derived neurotrophic factor induced angiogenesis in endothelial cells [38].

3. Histone modifications

Histone modification involves post-translational modification to histone proteins. Histones package and order the DNA into specific structural units called nucleosomes. The histones, which are unique to eukaryotes, include histone(H) H1, H2A, H2B, H3 and H4 [39–44]. The individual modifications can be associated with gene activation or repression. Transcription is usually accompanied by acetylation and phosphorylation; sumoylation, deamination, whereas proline isomerization generally occurs in transcriptionally silent regions; both activation and repression of transcription are through methylation and

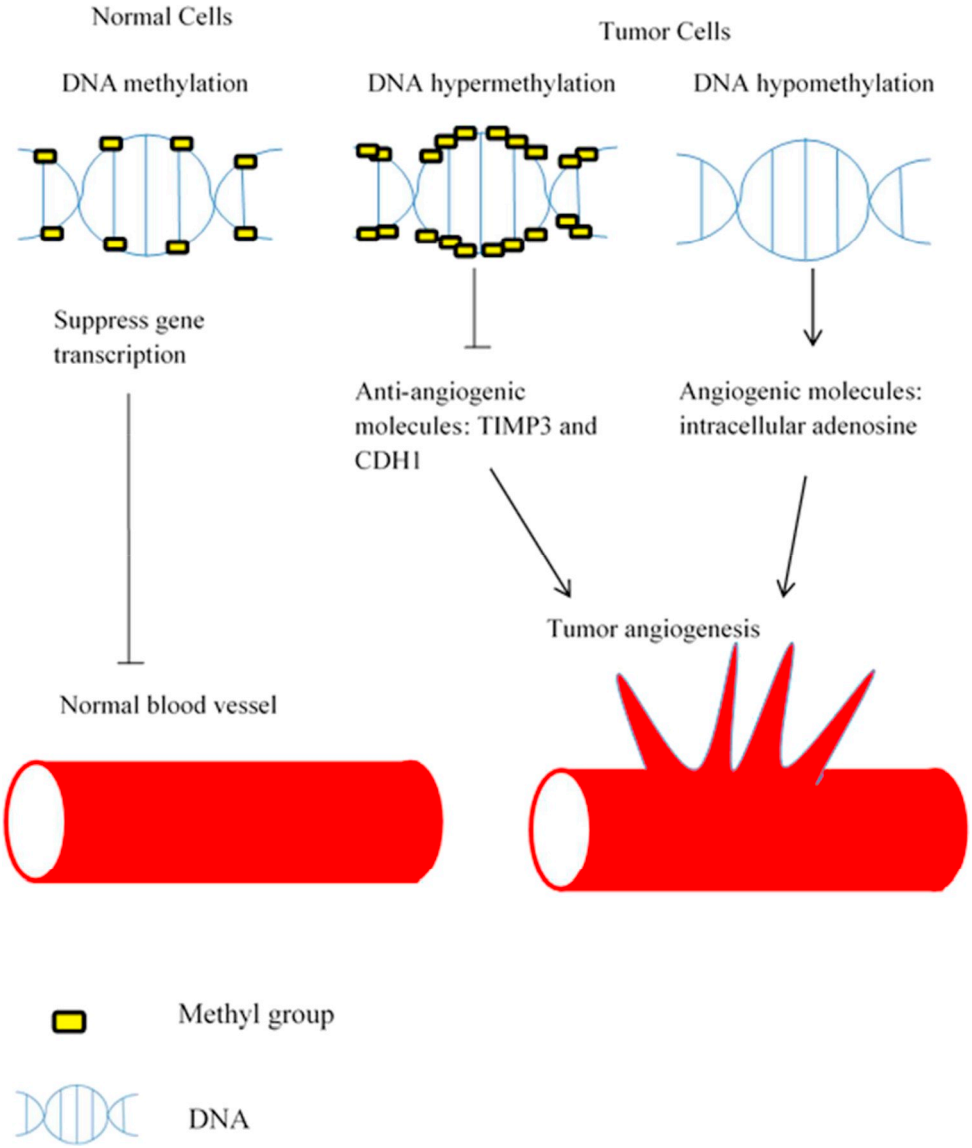

Fig. 2. Schematic diagram proposing the effect of hypermethylation and hypomethylation on tumor angiogenesis. DNA hypermethylation inhibits the expression of TIMP3 and CDH1 which decreases their anti-angiogenic activity leading to tumor angiogenesis. DNA hypomethylation on angiogenic genes on the other hand causes intracellular adenosine accumulation, therefore promoting angiogenesis.

Table 1
Effect of HDACs on tumor vasculature.

Class	Members	Cellular location	Effect on endothelial cells	References
I	HDAC1	Nucleus	HDAC1 was proven to downregulate p53 and VHL expression which increased HIF-1α protein expression to induce hypoxia. This in return promoted VEGF expression[54] which led to excessive migration and cell proliferation of endothelial cells in human prostate cancer, cervical cancer, and skin melanoma thus resulted in tumor growth [54,55].	[54,55]
	HDAC2	Nucleus	Hypoxia induced HDAC2 expression[54]. Expression of HDAC2 induced cell proliferation in colon, cervical and breast cancer which indefinitely resulted in tumor growth[56].	[54,56]
	HDAC3	Nucleus	HDAC3 was associated with ODD to stabilize HIF-1α protein expression which induced hypoxia [55] that led to excessive endothelial cells proliferation in cervical cancer [55] and colon cancer cell maturation ([57], p. 3) thus leading to tumor growth.	[55,57]
	HDAC8	Nucleus	HDAC8 increased interleukin-1 beta (IL-1b) expression ([58], p. 8) that led to the excessive increase in endothelial cells proliferation and clonogenic growth in neuroblastoma and lung cancer ([59], p. 8)	[58,59]
IIA	HDAC4	Nucleus/cytoplasm	Phosphorylation of HDAC4 in endothelial cells hypoxia models demonstrated increased migration and tube formation *in vitro* through HIF-VEGF signaling which led to enhanced angiogenesis *in vitro* and *in vivo* [60].	[60]
	HDAC5	Nucleus/cytoplasm	Silenced HDAC5 increased endothelial cell migration, sprouting and tube formation through upregulation of FGF2 and Slit2 factors to stimulate angiogenesis *in vivo* [61].	[61]
	HDAC7	Nucleus/cytoplasm	HDAC7 inactivated Stat3 protein expression which resulted in the reduced expression of AKAP12 protein leading to excessive endothelial cells proliferation in lung cancer and eventually promotion of tumor growth [62,63]. Enhanced endothelial cell migration, tube formation and sprouting from VEGF stimulation *in vitro* [64]	[62,63,64]
	HDAC9	Nucleus/cytoplasm	HDAC9 positively regulated endothelial cell tube formation and sprouting in *in vitro* and *in vivo* models [65]	[65]
IIB	HDAC6	Cytoplasm	HDAC6 have been proven to positively regulate angiogenesis and also increased endothelial cell migration, tube formation and sprouting [66,67].	[66,67]
	HDAC10	Nucleus/cytoplasm	Overexpression of HDAC10 increased endothelial cell tube formation and negatively regulated PTPN22 protein which promoted ERK1/2 pathway phosphorylation that resulted in angiogenesis in endothelial cells ([68], p. 10)	[68]
III	SIRT1	Nucleus/cytoplasm	SIRT1 downregulation inhibited endothelial cell proliferation and cell migration [69]. Silencing of SIRT1 downregulated the expression of VEGF which inhibited tumor angiogenesis *in vivo* [70].	[69,70]
	SIRT2	Cytoplasm	Suppressed SIRT2 inhibited the cell proliferation, migration and tube formation of endothelial cells *in vitro*. Knockdown of SIRT2 inhibited tumor angiogenesis *in vivo* by suppressing the STAT3/VEGFA pathway [71].	[71]
	SIRT3	Mitochondria	Deletion of SIRT3 downregulated the expression of proangiogenic factors VEGF and Angiopoietin-1 in endothelial cells which reduced tumor angiogenesis *in vivo* [72].	[72]
	SIRT4	Mitochondria	Silencing of SIRT4 enhanced apoptosis of inflammation-induced endothelial cells *in vitro* [73]. Reduced inflammatory response inhibited tumor angiogenesis [74] hence downregulation of SIRT4 may inhibit tumor angiogenesis by causing endothelial cell death.	[73,74]
	SIRT5	Mitochondria	Upregulation of SIRT5 was found to promote angiogenesis of endothelial progenitor cell [75] however not much is known regarding its effect on endothelial cells.	[75]
	SIRT6	Nucleus	Downregulation of SIRT6 inhibited tumor angiogenesis by promoting cell senescence in endothelial cell *in vivo* [76].	[76]
	SIRT7	Nucleolus/nucleus	Silencing of SIRT7 in human pulmonary artery endothelial cell (HPAEC) led to suppressed inflammatory responses *in vitro* [77]. The increased inflammatory response was found to foster tumor angiogenesis in liver cancer [78], hence silencing of SIRT7 may inhibit tumor angiogenesis by suppressing the inflammatory response.	[77,78]
IV	HDAC11	Nucleus/cytoplasm	HDAC11 remains poorly understood and studied with regards to its effects on endothelial cells.	

ubiquitination [41,45–48]. Histone acetylation and deacetylation are the processes by which as part of the gene regulation, lysine residues within the N-terminal tail protruding from the nucleosome histone core are acetylated and deacetylated.

Histone acetylation occurs *via* HAT which is essential for gene regulation. HDACs can also deacetylate residues of lysine. There are also two main types of HDACs: SIRT and classical HDAC. Classical HDAC is classed I, II, and IV, while the sirtuins are class III [13,49–51]. Table 1 shows the effect of HDACs on tumor vasculature. These enzymes contribute to the progression of cancer through increased proliferation, angiogenesis, cancer cell survival and resistance to cancer cell chemotherapy (Fig. 3). For example, H3K4, H3K26, and H3K79 methylation are associated with active marks, while repressive marks are associated with H3K9, H3K27 and H4K20 methylation [52,53]. Epigenetic changes in histone modification patterns can affect the integrity and structure of the genome and disrupt normal gene expression, which can also contribute to carcinogenesis [40,46].

SIRT1, a member of class III HDAC, plays a vital role in angiogenic signaling during blood vessel growth, it is highly expressed in vasculature where it controls the angiogenic activity of endothelial cells. When SIRT1 loses its function, branching morphogenesis of endothelial cells and sprouting angiogenesis will be blocked resulting in the downregulation of genes in blood vessel development and vascular remodeling [19,79]. Quercetin has been shown to inhibit COX-2-mediated angiogenesis in human endothelial cells in a dose-dependent manner and to effectively suppress the activity of p300 histone acetyltransferase (HAT), which leads to the attenuation of p300-mediated acetylation of NF-κB [40,80]. ARHI downregulation caused the DNMT and HDAC inhibitor to change the expression of angiogenesis-related factors. Recent discoveries have made HDACs in various cancer even more important [15]. Two pan-HDAC inhibitors, Vorinostat and Romidepsin, were recently approved by the FDA on the basis of impressive preclinical and clinical data. Both the drugs are currently under investigation for the treatment of cutaneous T cell lymphoma [81–83]. HDACi disrupts the pathways of cancer cells, such as cell differentiation and apoptosis, proliferation, angiogenesis; culminating in cell cytotoxicity by altering the expression of genes or function of proteins. Based on a recent study, a potent KAT3B/p300 inhibitor isolated from *Plumbago rosea* had been tested on several cancer models and has shown a decrease in growth of tumor cells, angiogenesis, and invasion of these models [84]. In esophageal and lung cancer, the overexpression of histone demethylase JMJD2C is thought to reduce histone H3 lysine 9 dimethylation (H3K9Me2) and histone 3 lysine 9 trimethylation (H3K9Me3) levels, which contributes to tumorigenesis [53,85]. Another JARID family histone demethylase, JARID1B was also co-purified with the NuRD complex in breast cancer cells, in which JARID1B and LSD1 coordinate to remove three histones H3 lysine 4 (H3K4) methylation forms on the promoter of CCL14 and antagonize the migration, angiogenesis, and metastasis caused by chemokine pathways [86,87].

4. MicroRNA(miRNA)

miRNAs can regulate gene expression at the level of transcriptional and post-transcription. They usually plays a role in the formation of heterochromatin, histone changes, methylation of DNA and gene silencing. In cancer, deregulation of important genes by involving miRNAs play vital roles in tumorigenesis and angiogenesis. miRNAs have been reported to have oncogenic or tumor suppressor roles

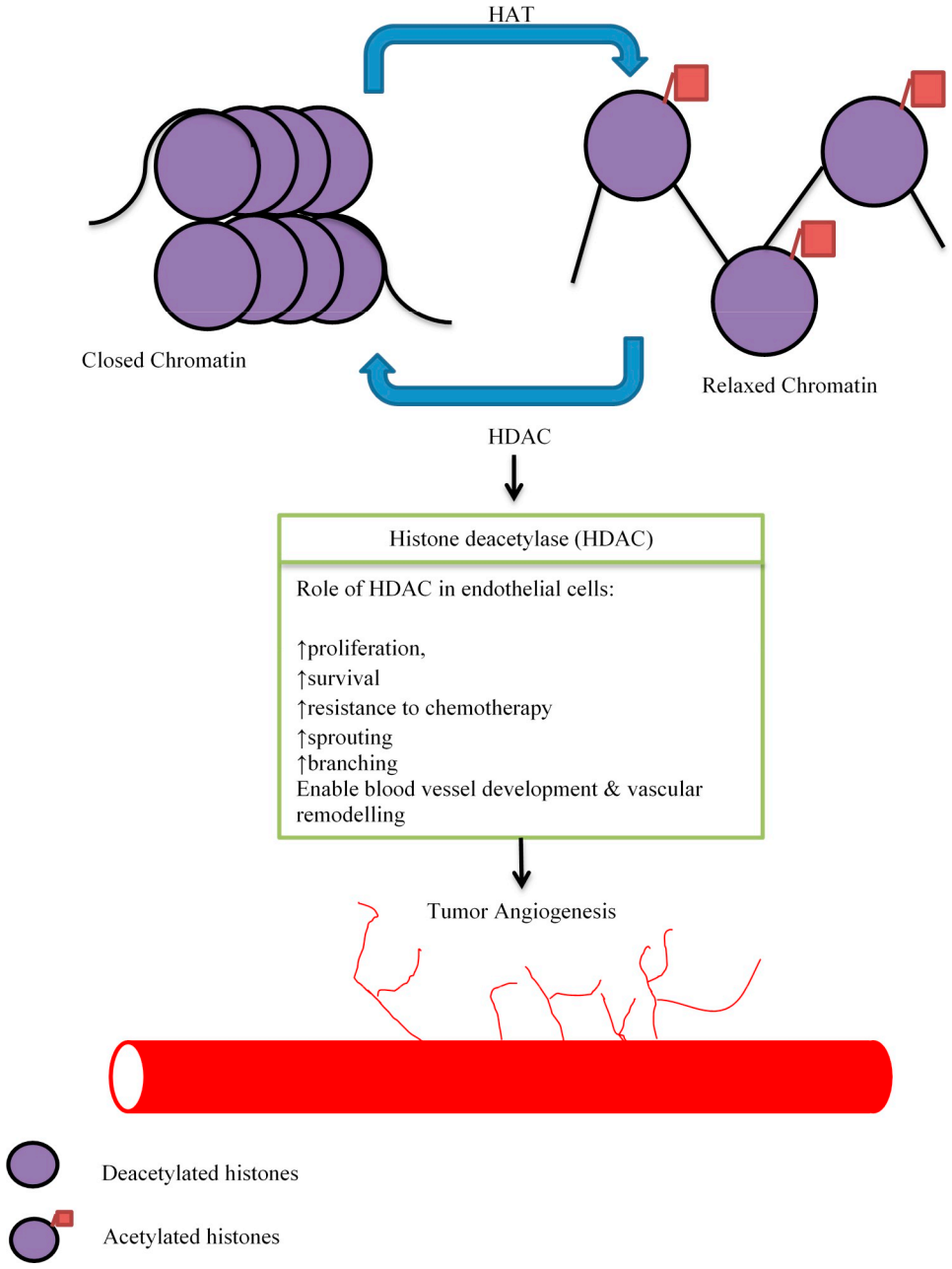

Fig. 3. Schematic diagram proposing the effect of deacetylated histones on tumor angiogenesis. HDACs play a major role increasing the proliferative ability and survival of endothelial cells, besides also enabling vessel development, increased sprouting, branching and vascular remodeling. HDACs also enables endothelial cells to have an increase resistance to chemotherapy.

[88–90]. miRNAs are important in the regulation of angiogenesis from the observations of that Dicer is necessary for embryonic angiogenesis and that deficiency of it will lead to seriously compromised embryos and yolk sacs and also reduced expression of some important positive angiogenesis regulators such as IL-8, angiopoietin receptor Tie-2, and VEGFR2 [19,89–92]. There are plenty of miRNAs acting as a promoter or suppressor of a tumor.

However, depending on the types of cancer, there are also miRNAs that would either be a promoter or a suppressor, for example, miR-22. The miR-22 is low in CRC, and it has been shown that the increased expression of miR-22 silences HIF-1α, leading to the repression of VEGF expression to block angiogenesis, and disruption of cancer progression. However, miR-22 has been shown to abolish the proliferation, migration, and invasion of cancer in clear renal cell carcinoma where its expression is often downregulated, but in prostate cancer the expression of miR-22 greatly stimulates cancer progression [93–95]. Some of the identified proangiogenic miRNAs are listed in Table 2. The miR-200 family downregulation leading to tumor invasiveness have been shown in several studies [51,96–99]. Tube formation and cell migration assays in matrigel have shown that miR-200b mimics in HMECs repressed angiogenic response, while miR-200b-depleted HMECs showed high angiogenesis [100,101]. Botla et al. have shown that methylation of miR-192 downregulates its expression. This decreased E-cadherin and increased PAI-1 expression in pancreatic ductal adenocarcinoma, resulting in metastasis from the increased proliferation and invasion of pancreatic tumor cells through the plasminogen system [102]. However, miR-192 has been identified as a versatile anti-angiogenic miRNA, since it can globally reduce the regulation of multiple pro-angiogenic pathways by regulating homeobox B9 and EGR1 which effectively inhibited growth and angiogenesis of tumor [16,103].

Table 2
Micro-RNAs involved in angiogenesis process.

	Micro-RNA	Mode of action	Type of cancer	Effect on tumor	References
1	miR-22, miR-192, miR-200 family (miR-200a, -200b, -200c, -429 and -141)	Pro/anti-angiogenic	Breast, cervical, ovarian, bladder, prostate, osteosarcoma, colorectal, liver, renal and lung cancer	Promoted tumor growth/ retarded tumor growth	[51,88,95,103]
2	miR1, miR17, miR18, miR-18a, miR-19a, miR-20a, miR-19b, miR-92a, miR181, let-7, miR-15, miR-16, miR-151, miR-155, miR-375, miR22, miR-17-92, miR-296, miR-18, miR-19, miR-210, miR-26b, miR27b, miR130a, miR-126, and miR-387	Pro-angiogenic	Gastric, colorectal, renal, leukemia, lymphoma, lung, testicular, ovarian, pancreatic and liver cancer	Promoted tumor growth	[14,19,88,89,101,102,103,104]
3	miR-221, miR-222, miR-15 and miR-16	Anti-angiogenic	Leukemia, glioma, breast and pancreatic cancer	Retarded tumor growth	[19,88,89,101,103]

A study carried out by Zhang et al. has revealed that the epigenetic silencing of miR-126, a known angiogenesis regulatory miRNA, led to the upregulation of VEGF expression and contributed to tumor invasion and angiogenesis in CRC [104]. In response to VEGF and bFGF, miR-126 has been shown to promote angiogenesis in endothelial cells by negative suppression regulators in signal transduction pathways [101,105–107]. In response to VEGF and bFGF, miR-126 implements its pro-angiogenic effects through promoting MAP kinase and PI3K in mouse knockout studies by targeting negative signaling pathways Spred-1 and PI3K regulatory subunit 2 [103,105,108]. On the contrary, there are other miRNAs that exhibit anti-angiogenic properties. The two prominent candidates are miR-221 and miR-222. A recent study on HUVEC cell lines that were transfected with miR-221 and -222, have demonstrated inhibition of tube formation and endothelial cell migration [19,109]. These miRNAs hinder endothelial cell proliferation, tube formation, and migration by targeting the expression of c-Kit and affecting eNOS indirectly [89,103,109,110]. Recent studies have presented that the miR-222 is involved in inflammation mediated by vascular growth factors, while miR-221 is needed for remodeling of vascular in liver tumorigenesis [101,111,112]. Furthermore, miR-15 and miR-16 also have shown to regulate the expression of VEGF by inhibiting angiogenesis in several cancers which causes the cessation of tumor growth [19,88,89].

A recent discovery of the long noncoding RNAs (LncRNAs) have shown to play an important role in angiogenesis. LncRNAs are non-protein coding RNAs with more than 200 nucleotides [113]. LncRNAs are predominantly found in cell nucleus. LncRNAs control diverse biological processes by regulating chromatin remodeling or protein translation. Recent studies have identified some highly expressed lncRNAs found in endothelial cells [114,115]. However, not much is known about the expression site and regulation of lncRNAs in angiogenesis. LncRNAs implicated in tumor angiogenesis include H19, HULC, MVIH and TUG1 as shown in Table 3 [113].

5. Conclusions and future perspectives

Angiogenesis provides a wide platform for finding biomarkers and therapeutic targets. Therefore, discovering a solution to halt the sprouting of new vasculature has been of great interest to researchers. Many studies have revealed that epigenetic changes are vital in promoting angiogenesis and tumor cell progression. These therapeutic targets and biomarkers have also been identified for future studies and improvement in the field of tumor therapy. However, there are still many challenges to address because of the intricate and intrinsic mechanisms of the epigenetic modifications that regulate tumor angiogenesis. Epigenetic modification has also been found to influence hematogenic metastatization in later phases of cancer through tumor endothelial cells [124]. Furthermore, the dogma postulating that excessive angiogenesis leads to tumor growth has mostly been challenged [125]. The blood vessel is responsible for the delivery of chemotherapy drugs to the tumor. However, tumors have blood vessels that are irregular and leak, causing unsuccessful delivery of the chemo drugs. Previous studies have reported that combination therapy of epigenetic drugs were used to enhance vascular repair, as well as eliciting a therapeutic effect against cancer cells [126–131]. This suggests that further developments in the research of epigenetic processes in endothelial cells in tumors will identify new methods for therapeutic intervention.

Acknowledgments

Ayappa V. Subramaniam is supported by the Universiti Sains Malaysia Graduate Assistant Scheme and the Universiti Sains Malaysia Research University Grant (RUI) (1001/CIPPM/812156). We thank Mataka Banda from Keele University, UK for helping with language proofreading.

Table 3
LncRNAs associated with angiogenesis.

LncRNAs	Effect on tumor angiogenesis	References
H19	H19 overexpression promotes endothelial cell tube formation *in vitro* resulting in increased brain cancer tumor growth *in vivo* [116].	[116]
	H19 silencing reduces endothelial cell proliferation, migration and tube formation (induced by brain cancer cells) *in vitro* [117].	[117]
	H19 overexpression promote endothelial tube formation (induced by stem-like cancer cells) *in vitro* [118].	[118]
HULC	HULC overexpression promote endothelial cell tube formation *in vitro* resulting in increased liver cancer growth *in vivo* [119].	[119]
MVIH	MVIH overexpression promote endothelial cell tube formation *in vitro* resulting in increased liver cancer growth *in vivo* [120].	[120]
TUG1	TUG1 knockdown reduces endothelial cell proliferation, migration, tube formation and spheroid sprouting *in vitro* resulting in reduced liver cancer growth *in vivo* [121,122].	[121,122]
lincRNA-p21	lincRNA-p21 silencing reduces endothelial cell tube formation (induced by lung cancer cells) *in vitro* [123].	[123]

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