# MOLECULAR MECHANISMS OF ANGIOGENESIS: BRAIN IS IN THE FOCUS

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**Abstract.** Deciphering the cellular and molecular mechanisms of the development and remodeling of blood vessels is one of the topical areas of modern (patho)physiology and cell biology. Initially, interest in these processes was mainly associated with the need to find the mechanisms of tissues and organ de-velopments, as well as the vascularization of tumors. In recent years, mechanisms of (neo)angiogenesis in physiological conditions and pathologies have attracted the increasing attention of researchers. In the context of the central nervous sys-tem physiology, this issue is quite new; however, there is accumulating experi-mental and clinical evidence that brain plasticity includes not only phenomenon of neurogenesis, synaptic transmission, dynamic changes in the number and ac-tivity of synapses, various intercellular interactions, secretion of a wide range of neurotransmitters, gliotransmitters, cytokines and growth factors, but also specif-ic changes in local microcirculation, establishment and regression of microvessels, and altered permeability of the blood-brain barrier in active brain regions. Until now, mechanisms underlying the development and involution of blood vessels in the brain tissue are very scattered; however, some signaling pathways have been identified, in particular, those associated with the response of cells to hypoxia. Obviously, identification of such mechanisms is important for a better under-standing of brain development and plasticity, searching for new marker mole-cules and target molecules used for the accurate diagnostics, effective treatment and reliable prognosis of brain pathologies associated with insuf-ficient or exces-sive tissue vascularization and aberrant vessel remodeling, as well as for adequate reproduction of cer-ebral vascular networks within the in vitro microphysiological systems.

**Keywords:** angiogenesis, brain plasticity, blood-brain barrier, neurodegeneration, hypoxia, endothelial cells, neu-rovascular unit.

**List of Abbreviations**

3D – 3-dimensional
Ang1, Ang2 – angiopoietin-1, 2
BBB – blood-brain barrier
BMP4 – bone morphogenetic protein 4
BNIP3 – bcl-2 interacting protein 3
CD – cluster of differentiation
CLDN-5 – claudin-5
CMA – cerebral microangiopathy
CNS – central nervous system
CSF – cerebrospinal fluid
DNMT DNA – methyltransferase
DOT1L – disruptor of telomeric silencing
FGF – fibroblast growth factor
GLUT – glucose transporter
HAT – histone acetyltransferase
HDAC – histone deacetylation
HIF – hypoxia-inducible transcription factor
JAM – junctional adhesion molecule
lncRNAs – long non-coding RNAs
MCT – monocarboxylate transporter
miRNA (miR) – microRNA
MnSOD – superoxide dismutase
MRI – magnetic resonance imaging
NAMPT – nicotinamide phosphoribosyl-transferase
ncRNAs – non-coding RNAs
NVU – neurovascular unit
PCR – polymerase chain reaction
PDGF – platelet-derived growth factor
PECAM-1 – platelet/endothelial cell adhe-sion molecule 1
Pgp – P-glycoprotein
piRNA – Piwi-interacting RNA
rRNA – ribosomal RNA
SCF – stem cell factor
SDF1 – stromal cell-derived factor-1
SIRT – sirtuins
SMC – smooth muscle cell
sncRNAs – small noncoding RNAs
snoRNA – small nucleolar RNA
snRNA – small nuclear RNA
SPION – superparamagnetic iron oxide na-noparticles

TLRs – toll-like receptors
tPA – tissue plasminogen activator
tRNA – transfer RNA
VEGF – vascular endothelial growth factor
VHL – von Hippel-Lindau
VWF – von Willebrand factor
ZO1 – zona occludens-1 protein

## Introduction

An interesting and still non-solved question in the physiology, neurology and neurobiology is the control of brain plasticity. Solving this question would be important for further progress in numerous interrelated fundamental and practi-cal problems: deciphering the mechanisms and control of neuroplasticity in nor-mal and pathological conditions, correction of neurological deficit in brain diseas-es, optimization of brain functioning at different stages of ontogenesis, develop-ment of modern models of the brain in vitro, including in the brain-on-a-chip format. It is well-known that brain plasticity implies not only changes in synaptic transmission, the landscape of interneuronal synaptic connections, and neurogen-esis processes, but also includes significant changes in local microcirculation and (neo)angiogenesis. These events are realized within the neurovascular unit (NVU) with the participation of endothelium, glia, pericytes, and neurons whose coordi-nated activity controls selective permeability of the blood-brain barrier (BBB) (Fig. 1).

Blood vessels are formed de novo from hematopoietic cells by means of vascu-logenesis (in the embryonic period of development). In the postnatal period, the mechanisms associated with the formation of new vessels (angiogenesis) are con-trolled by a wide range of molecules with pro- and anti-angiogenic activity in var-ious tissues. Both processes involve endothelial progenitor cells that are recruited from clonogenic niches and migrate to the angiogenesis zone followed by local differentiation into endothelial cells (Naito *et al*., 2020). Hypoxia and concomitant activation of hypoxia-inducible transcription factor (HIF)-1α are recognized as key inducers of angiogenesis in various tissues (Chertok *et al*., 2017). This leads to stimulation of angiogenesis due to the action of vascular endothelial growth factor VEGF (vascular endothelial growth factor), IGF-1 (insulin-like growth factor-1), PDGF (platelet-derived growth factor), FGF2 (fibroblast growth factor-2), angiogenin, and erythropoietin (Nefedova & Davydova, 2015; Elfayomy *et al*., 2015). Usually, angiogenesis is balanced by vascular regression, but if this balance is disturbed pathological processes associated with insufficient or excessive vascularization may occur (Chumak *et al*., 2020).

## General mechanisms of angiogenesis control

Angiogenesis is characterized by the expansion of the existing network of blood vessels, mainly due to the activity and migration of endothelial cells and pericytes. Neoangiogenesis can proceed by the mechanism of branching of vessels (sprouting) or splitting of the vascular wall with the formation of two new ves-sels (splitting), it is accompanied by the following processes: degradation of the basement membrane and extracellular matrix, migration and proliferation of en-dothelial cells which subsequently form new capillary tubes and basement mem-brane, and initiation of perfusion (Bishop, 2015). Angiogenesis involves the in-teraction of endothelial cells with myeloid cells and pericytes as well as with tis-sues-specific cells like astrocytes in the brain. Their invasion and migration take place in order to initiate the development of new blood vessels (Lugano *et al*., 2020). Activity of these cells is sufficient to establish the local microenvironment enriched with soluble regulatory molecules acting at their receptors expressed in endothelial cells and pericytes. Under physiological conditions, angiogenesis is activated primarily to provide blood supply to developing tissues, as well as to restore damaged tissues. The growth of new vessels is a complexly coordinated process that requires sequential activation of endothelial cell receptors by numer-ous ligands (Verclytte *et al*., 2015). Metabolic demands of tissues, exceeding the perfusion capacity of existing vessels trigger angiogenesis. The results of recent studies have confirmed this adaptive mechanism in hypoxia and hypoglycemia (Mel-

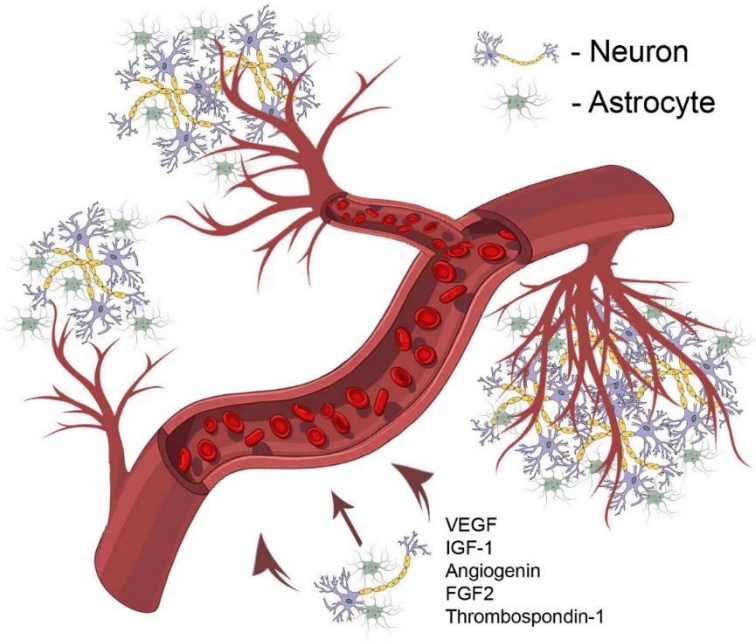


**Fig. 1.** Brain neurovascular unit and regulation of angiogenesis. Development of new microvessels is under the control of locally produced VEGF, IGF-1, Angiogenin, FGF2, Thrombospondin-1, etc.

incovici *et al*., 2018; Wierzbicki *et al*., 2019). It was initially demonstrated in tumor tissue that angiogenesis is associated with the implementation of the War-burg effect and an increase in the level of lactate in the extracellular space, expression of glycolytic enzymes, lactate and glucose transporters (MCTs, GLUTs) (Salmina *et al*., 2014). All these data support the role of tissue hypoxia in the in-duction of angiogenesis. In actively proliferative tissues, activation of glycolysis and angiogenesis is required for cells adaptation and survival (Acosta *et al*., 2018). However, similar events are also important for the induction of angiogen-esis in tissues with the prevalence on post-mitotic cells (for instance, in the brain).

Hypoxia-inducible transcription factor-1 (HIF-1) is recognized as a main trig-ger of the angiogenesis program. Activity of HIF-1 has been well-described in numerous reviews, so, we will briefly recapitulate the most important issues. Several HIF isoforms whose degradation in cells is inhibited by hypoxia ensure cell survival by regulating the expression of more than 200 genes and corre-sponding proteins involved in angiogenesis, erythropoiesis, apoptosis, energy metabolism, vasomotor control, and immunity (Wierzbicki *et al*., 2019; Elfayomy *et al*., 2015). Hypoxia stimulates apoptosis in both normal and neoplastic cells through changes in the expression level of the p53 transcription factor, genes of the bcl-2 family, HIF-1, and a number of other factors (Shemarova & Nesterov, 2019). For example, E2F8, a transcription factor containing two DNA-binding domains promotes angiogenesis by stimulating transcription of the gene encoding vascular endothelial growth factor in hypoxic cells (Kent & Leone, 2019). Hy-poxic tissue cells express a transcriptional protein dimer, HIF, consisting of two subunits (HIFa and HIFb). The HIFa subunit has several isoforms (HIF1a, HIF2a, HIF3a) that are able to respond to different levels of oxygen with various time-dependence (Wierzbicki *et al*., 2019). HIF1a is better studied and its expres-sion was found in the cells of many tissues and organs where it functions as a regulator of oxygen homeostasis. Being expressed constantly, regardless of hy-poxia, it is important for several physiological processes that are not directly linked to hypoxia (Elfayomy *et al*., 2015; Verclytte *et al*., 2015). HIF2a is found in embryonic vascular endothelial cells, in kidneys, lungs, and catecholamine-

syn-thesizing chromaffin cells. In tumor cells, HIF2a expression is associated with the grade of malignancy and Ki67 expression (Wierzbicki *et al*., 2019). HIF3a is the least studied, its activity is observed in the brain, kidneys and lungs. It is be-lieved that HIF3a acta as a negative regulator of the activity of genes induced by hypoxia (Nefedova & Davydova, 2015). Data on the interaction of HIF subunits are quite mosaic. The HIF1a subunit has a shorter half-life, therefore, its concen-tration under normoxic conditions is low (Teplyashina *et al*., 2021). It has been established that oxygen affects HIF1a in several ways. One of them is rapid deg-radation in the presence of a functional von Hippel-Lindau (VHL) protein known as a tumor suppressor (Liu *et al*., 2018; Salmina *et al*., 2014). Increased expres-sion of HIF1a was found in tumors with VHL mutations (Melincovici *et al*., 2018). Thus, overexpression of HIF1a has been confirmed in tumors of various localizations (Liu *et al*., 2018) and is associated with the expression of the gene of the mutant type of the p53 protein. It correlates with the degree of cell differentia-tion, angiogenesis, and is a negative prognostic sign in tumor progression (Wierzbicki *et al*., 2019). The molecular mechanism of HIF activity under conditions not associated with tumor progression, such as inflammation, includes the activation of TLRs (toll-like receptors) due to MAPK- and NF-kB-mediated sig-nal transduction. The HIF-1A transcription factor regulates several pro-apoptotic genes, including Bcl-2 interacting protein 3 (BNIP3) and stabilizing tumor sup-pressor p53 (Shao *et al*., 2018; Nefedova & Davydova, 2015).

Several peptide growth factors act as regulators of angiogenesis in tissues. Platelet growth factor PDGF-C has a proangiogenic potential, binds to its PDG-FRα receptor, and activates predominantly the PI3K-AKT signaling pathway (Zhang *et al*., 2018; Liu *et al*., 2018). Due to the presence of a highly conserved cysteine motif, PDGF-C belongs to the PDGF/VEGF family (Salmina *et al*., 2014). PDGF has an N-terminal CUB domain that blocks the binding of the C-terminal growth factor to its receptor. Plasmin and tissue plasminogen activator (tPA) activate PDGF-C (Verclytte *et al*., 2015) resulting in recruitment of endo-thelial cells, pericytes, and smooth muscle cells. Expression of the growth factor PDGF-C protects macrophages from apoptosis, which, in turn, are a source of angiogenic factors (Acosta *et al*., 2018). Dysregulation of the PDGF/PDGFR sys-tem, as well as constitutive activation of PDGFR or mutations that in-crease/decrease the activity of ligands and receptors, contribute to the formation of tumors (Chumak *et al*., 2020). Fibroblast growth factors FGF1 and FGF2 bind to specific cell receptors FGF-R1-4 and to heparan sulfate proteoglycans with ty-rosine kinase activity, initiate receptor dimerization and autophosphorylation by tyrosine kinase/PKC. These events promote angiogenesis, proliferation, migra-tion and differentiation of cells (Nefedova & Davydova, 2015; (Liu *et al*., 2018). It is noteworthy that pericytes surrounding endothelial cells and actively partici-pating in angiogenesis processes have a high level of expression of PDGFRs (Xiang *et al*., 2019). The role of vascular endothelial growth factors (VEGF-A, VEGF-B), angiopoietin-1, 2 (Ang1 and Ang2), leptin, adiponectin, thrombos-pondin-1, angiostatin, inhibitors of plasminogen activator-1 in positive or nega-tive regulation of angiogenesis is well known (Bishop, 2015; (Chumak *et al*., 2020). In particular, angiogenesis is induced by such factors as VEGF, stromal growth factor (SDF1), stem cell factor (SCF), and angiopoietin (Acosta *et al*., 2018). The initial stimulation of endothelial cell proliferation is mediated by the VEGF family of factors that are heparin-bound proteins. VEGF-A which binds at VEGFR1 and VEGFR2 (also known as KDR in humans, or Flk1 in rats), hepa-ran sulfate, and heparin are the most potent mitogenic and chemoattractant sig-nals for endothelial cells (Melincovici *et al*.,2018). Fibroblast growth factor FGF1 interacts with FGFR1 receptor, thereby stimulating angiogenesis (Elfayomy *et al*., 2015). Synthesis of FGF2 and its release from endothelial cells can be caused by inflammatory mediators such as L-1β, NO, prostaglandin E2. FGF1 can also inhibit p53 activity by phosphorylation of serine at the 15th position and promote its degradation

(Manousakidi *et al*., 2018). There are cross-roads between FGF2 and VEGF-A to stimulate angiogenesis: FGF2 increases vascular permeability through VEGF-A (Shao *et al*., 2018; Nefedova & Davydova, 2015). The presence of a cross functional relationships between FGF, PDGF, and VEGF that are rele-vant for the regulation of angiogenesis has been demonstrated (Chae *et al*., 2017).

Endothelial cells and pericytes are the main targets for all of the listed growth factors, cytokines and metabolites (Chen *et al*., 2019). In order for a mature ves-sel to form, only one endothelial cell must become a terminal cell - a tip-cell, un-like others that form stalk-cells. The growth of the vessel includes the selection of tip cells, their migration, proliferation of stalk cells, and, ultimately, stabilization of the vascular wall which is adjacent to perivascular cells of a non-endothelial nature (pericytes, astrocytes, etc.). Tip-cells are characterized by their position: they are located at the end of a growing vessel. These cells are mobile, invasive, highly polarized and have a large number of long processes that can increase in size and perceive guiding signals coming from the microenvironment which is important for their migration along the chemoattractant concentration gradient, thereby guiding the direction of the vessel growth (Margadant, 2020). Therefore, navigation is the main function of nonproliferating tip-cells (Fig. 2). Stalk-cells follow tip cells, and they actively proliferate, elongate processes, form gaps in the vessel for subsequent perfusion. During maturation, endothelial cells undergo some plastic changes. Competing for the leading positions, stalk-cells can be activated and become new tip-cells (Eelen *et al*., 2020). VEGF- and Notch-mediated signal transduction affects this conversion (Fernández-Chacón *et al*., 2021). For instance, VEGF-C activates VEGFR-3 in tip-cells to enhance Notch signaling which promotes tip to stalk conversion of endothelial cells at the fusion points of the vascular processes (Zhao *et al*., 2018). The interaction of VEGF with VEGFR2 increases Dll4 expression in tip-cells. Notch suppresses the tip cell phenotype by increasing and decreasing the expression of VEGFR1 and VEGFR2, respectively (Fig. 2) (Eelen *et al*., 2020). In general, tip-cell selection, outgrowth formation, stalk-cells proliferation, and vessel stabilization are the key steps in angiogenesis (Lugano *et al*., 2020).

Interactions between endothelial cells and the microenvironmental stimuli de-termines differentiation of endothelial cells toward tip-or stalk-cells (Ellis *et al*., 2009). There is a stable intermediate state between tip- and stalk-cell phenotypes when microenvironment could affect endothelial cells selection and maturation (Chen *et al*., 2019). After completing these changes, tip- and stalk-cells become to be quite different in the expression profiles and metabolism. In particular, high glycolytic activity is necessary for the functional activity of endothelial cells, and when cells acquire a tip-phenotype, glycolysis is intensified (Baratchi *et al*., 2017). The suppression of glycolysis contributes to the inhibition of angiogene-sis, and this suggests that the constant production of lactate by endothelial cells is comparable to the Warburg effect (Malinovskaya *et al*., 2016). Shear stress in endothelial cells stimulates glycolysis and oxidative phosphorylation in mito-chondria (Sun & Feinberg, 2015), although experimental data on this issue are controversial (Doddaballapur *et al*., 2015). In fact, high metabolic activity of en-dothelial cells itself forms a pro-angiogenic microenvironment in tissues. Even endothelial cells with obviously higher mitochondrial content (for instance, endo-thelial cells of cerebral microvessels) maintain energy supply due to extensive glycolysis (Salmina *et al*., 2015). In addition, cerebral endothelial cells are equipped with lactate transporters (MCTs, monocarboxylate transporters) and lactate receptors (GPR81) that make them susceptible to the effects of lactic acid produced by other perivascular cells (pericytes or astrocytes). We have demon-strated before that stimulation of GPR81 in brain microvessel endothelial cells stimulates mitochondrial biogenesis which supports (neo)angiogenesis (Khilazheva, *et al*., 2017).

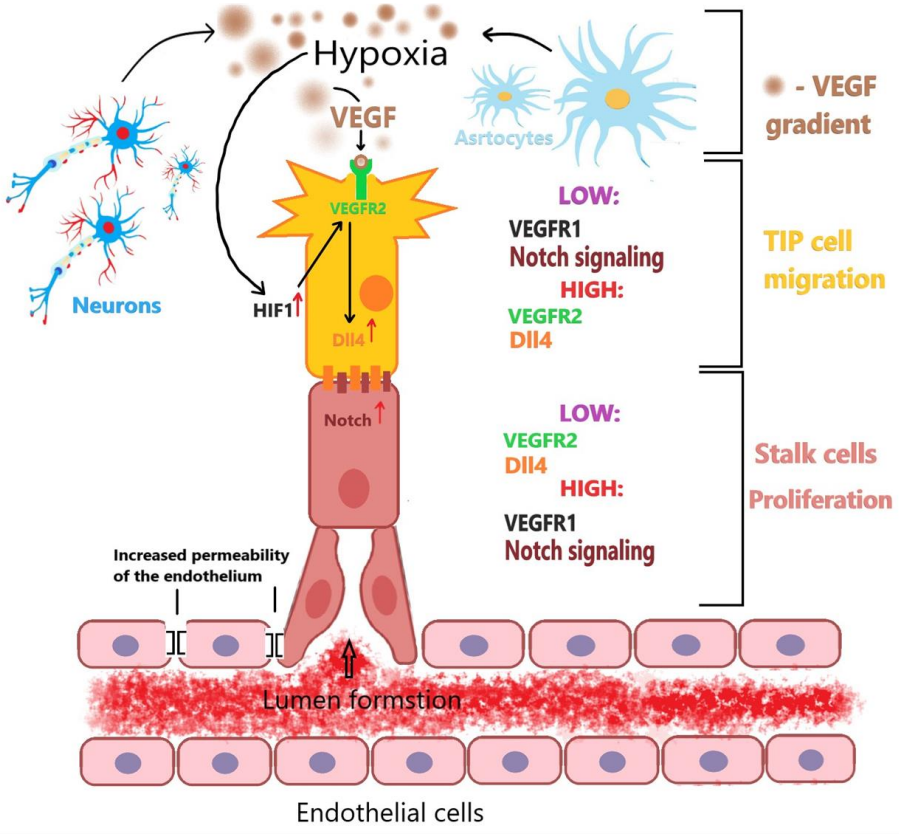


**Fig. 2.** The initial stage of angiogenesis in the brain. Selection and maturation of two types of endothelial cells. Gradient navigation and migration (provided by VEGF) is carried out by terminal non-proliferating tip cells. Proliferation and formation of the lumen of the vessel occurs due to the activity of proliferating stalk cells. VEGF- and Notch- signaling determines the specialization of these cells and maintains the selected phenotype

**Epigenetic mechanisms of angiogenesis regulation**

Long-term gene expression programs during angiogenesis are regulated by epi-genetic mechanisms such as DNA methylation and hydroxymethylation, histone modifications, and action of small non-coding RNAs. DNA methylation affects chromatin condensation and hence its accessibility to transcription factors and enzymes. This process is carried out by a group of enzymes called DNA methyl-transferases (DNMTs), which catalyze the transfer of a methyl group from S-adenosylmethionine to a cytosine residue present in CpG dinucleotides (Nara-yanan *et al*., 2018). One of the main epigenetic mechanisms by which gene ex-pression is regulated is a change in the methylation of cytosine nucleotides in the promoter region of a gene. Cytosine methylation changes the hydrophobic char-acteristics of DNA and inhibits binding of transcription activators or suppressors (Goyal D & Goyal R, 2019). Basically, the degree of promoter DNA methylation is inversely proportional to the intensity of transcription (Yang *et al*., 2014).

The regulatory role of DNA methylation in angiogenesis was clearly shown by Goyal (Goyal D & Goyal R, 2019). They hypothesized that formation of endo-thelial capillary tubes in 3D cultures is secondary to the changes in a gene pro-moter altered by methylation in human brain microvascular endothelial cells. As a result of genome-wide microarray and bioinformatic analysis, the authors iden-tified genes with a high level of expression during the formation of capillary tubes (VEGF, TP53, HGF,

ESR1, and CDKN1A). At the same time, hypermethylation of CpG sites suppresses FOSB, FZD7, HEY2, HSPA6, NR4A3, SELE, PTGS2, SMAD6, SMAD7 and SMAD9 that significantly inhibit angiogenic transfor-mation as well as endothelial cells migration.

The spatial organization of DNA affects the level of expression of angiogene-sis-inducing genes. Histone proteins form the scaffold on which DNA binds. Two units of each of the histones H2A, H2B, H3 and H4 combine to form the main histone octamer. Chemical modification of histone structure (acetylation, methylation, phosphorylation, ubiquitinylation, ADP-ribosylation, deamination and proline isomerization) changes the charge associated with the histone molecule and, consequently, its interaction with negatively charged DNA. Thus, these modifications alter the accessibility of transcription factors and cofactors to his-tone-associated DNA (He *et al*., 2018; Ihezie *et al*., 2021). In particular, acetyl groups are attached to lysine residues present in histone proteins. This process is catalyzed by the enzyme histone acetyltransferase (HATs/KATs) – aHAT (acety-lates nucleosomal histones and promotes their transcription) and bHAT (acety-lates newly synthesized histones before their inclusion into the nucleosomal com-plex). Within the nucleus, histone acetylation can be reversed by HDAC histone deacetylases, resulting in chromatin condensation and transcriptional repression. Eighteen HDACs of 4 classes have been identified in mammals: I) HDACs located in the nucleus (HDAC1,2,3,8); II) HDACs that run between the nucleus and the cytoplasm (HDAC4,5,6,7,9,10); III) NAD+-dependent proteins - sirtuins (SIRT); iv) HDAC11.

Several experimental data suggest that histone acetylation affects establish-ment of angiogenic program in endothelial cells. Using biochemical, pharmaco-logical and genetic approaches, Fath et al. have shown that acetylation of p300 (transcriptional coactivators) leads to inverse regulation of HIF-1α (Ellis et al., 2009). Indirect regulation of HIF-1α through HDAC6 inhibition causes its degra-dation (Qian *et al*., 2006; Ikeda & Kakeya, 2021). HDAC5 is involved in VEGF signaling and gene expression (Bahl & Seto, 2021), whereas HDAC7 controls vascular integrity since deficiency of this enzyme causes the death of animals in the embryonic period due to global vascular destruction (Velasco-Aviles, et al., 2022).

In last decades, there has been a growing interest in the family of evolutionarily conserved proteins known as sirtuins (SIRT) acting in numerous (patho)physiological processes (Carafa *et al*., 2016). SIRTs share a common NAD+-binding catalytic domain, sense the NAD+ levels in the cells, and act spe-cifically on different substrates depending on the biological processes in which they are involved. As an example, neuronal SIRT1 plays an important role in the protection against Alzheimer's disease, Parkinson's disease, and Huntington's disease (Jeong *et al*., 2013) by exerting a neuroprotective effect and participating in cell survival. The role of sirtuins in the regulation of NAD+ bioavailability in cells is also important; a functional relationship between nicotinamide phos-phoribosyltransferase (NAMPT) and SIRT1 has recently been shown. NAMPT is a therapeutic target against ischemic stroke by acting on vascular repair and neu-rogenesis. SIRT1-mediated deacetylation of NAMPT at K53 increases its activity (Yoon *et al*., 2015). SIRT2, the second member of the SIRT family, promotes neurodegeneration (Harting & Knoll, 2010), thus, pharmacological or genetic in-hibition of SIRT2 blocks α-synuclein-mediated neurotoxicity. There are three mi-tochondrial sirtuins (SIRT3, 4, and 5), and SIRT3 protects cochlear neurons from oxidative damage during caloric restriction and in response to superoxide dis-mutase (MnSOD) activation in microglia (Rangarajan *et al*., 2015). The role of SIRTs in the regulation of angiogenesis is under excessive assessment: SIRT1-mediated deacetylation of forkhead transcription factor Foxo1 suppresses its an-ti-angiogenic activity in endothelial cells (Potente *et al*., 2007), SIRT1 inhibition reduced the hypoxia-driven accumulation of HIF-1α in mesenchymal stem cells able to show the angiogenic phenotype (Chiara *et al*., 2014), SIRT3 controls gly-colytic metabolism of endothelial cells, thereby providing the mechanism of angi-ogenesis regulation (He *et al*.,

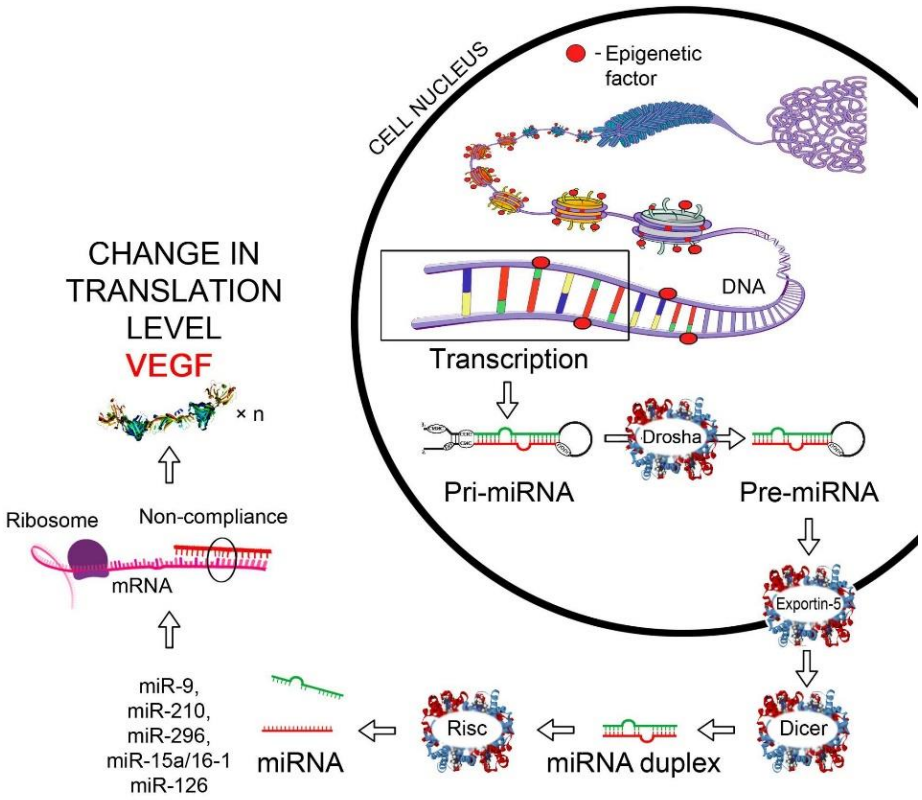


**Fig. 3.** Epigenetic regulation of VEGF expression in cells

2019), SIRT6 prevents vascular aging (D'Onofrio *et al*., 2015). However, contribution of SIRTs to the regulation of brain angiogen-esis remains unclear and requires further investigations.

Histone methylation in the nucleus is controlled by histone methyltransferases and histone demethylases. Methyl groups from S-adenosylmethionine are trans-ferred to a lysine or arginine residue present in histones H3 and H4 by histone methyltransferases. As a rule, H3 methylation at the 4th (K4) or 36th (K36) lysine residue activates transcription, while K9 and K27 repress gene methylation (Chen & Riggs, 2011). Another histone methyltransferase, called the disruptor of telomeric silencing (DOT1L), catalyzes the methylation of H3K79: DOT1L inter-acts with the transcription factor ETS-1 to stimulate VEGFR2 expression, thereby activating the ERK1/2 and AKT signaling pathways and promoting angiogen-esis (Duan *et al*., 2016).

Non-coding RNAs (ncRNAs) is a group of non-translated RNAs with regulato-ry functions. Depending on the length of the RNA, ncRNAs are divided into small (sncRNAs) and long (lncRNAs) subclasses. Small RNAs are typically of 18 to 35 nucleotides in size, while lncRNAs are over 200 nucleotides in length. Among sncRNAs, due to strong functional variations, there are transfer RNA (tRNA), ribosomal RNA (rRNA), small nuclear RNA (snRNA), small nucleolar RNA (snoRNA), Piwi-interacting RNA (piRNA) (Stamatovic *et al*., 2019). It was experimentally confirmed that the target effect of ncRNAs on mRNA in the form of complementary antisense oligonucleotides changes the expression level of tar-get genes controlling angiogenesis, namely VEGFA. Coupling of miR-9 mi-croRNA activity with neurogenesis and angiogenesis during brain development has been demonstrated (Madelaine *et al*., 2017; Coolen *et al*., 2013). There was a temporary increase in the cell pro-

*Table 1*

**Epigenetic regulation of angiogenesis**

| Epigenetic mechanism | Outcomes |
|---|---|
| DNA methylation | - change in chromatin condensation;<br>- inhibition of binding of activators or suppressors of transcription;<br>- inhibition of angiogenic transformation, as well as migration of endothelial cells; |
| Modification of histone structure | - change in histone charge and its interaction with negatively charged DNA;<br>- change in the availability of transcription factors and cofactors to DNA; |
| Histone methylation | - activation of transcription of early genes of signaling pathways, promoting angiogenesis;<br>- neuroprotective/neurodegenerative effect and involvement in cell survival, neuropathology and expression of brain-derived neurotrophic factor; |
| Action of non-coding RNAs | - change in the level of expression of target genes, including *VEGFA* (miR-9, miR-210, miR-296 and others). |

liferation associated with the reduction in the number of early-born neurons and increase in the number of late-differentiating neurons through inhibition of miR-9. miR-9 may directly target the transcription factors TLX and ONECUT to regulate VEGFA expression in perivascular cells, thereby affecting angiogenesis. Thus, miR-mediated regulation of translation in stem or progenitor cells could affect two mechanisms of brain plasticity – neuro-genesis and angiogenesis – within neurogenic niches.

A decrease in microRNA activity does not always lead to activation of the tar-get gene. The opposite effect was registered for microRNAs miR-210, miR-296, which promote the migration of vascular endothelial cells and the formation of tubular structures under hypoxic conditions in vitro (Zeng *et al*., 2014; Feng *et al*., 2015). However, in this case, the corresponding microRNA is also a key fac-tor in increasing the level of VEGF in the tissue.

In sum, a brief description of the epigenetic factors regulating VEGF-controlled angiogenesis is presented in Figure 3 and in the table (Table 1).

**Cerebral angiogenesis and brain plasticity**

Vasculogenesis and angiogenesis are the important parts of brain develop-mental program. From the moment of birth to the 5th day of a rodent postna-tal life, the density of blood vessels in the brain tissue increases (Uspenskaia *et al*., 2021) which is associated with the appearance of neuronal connections. However, excessive stimulation and repeated neuronal activation caused a de-crease in vascular density on the 15–25$^{th}$ days of postnatal life due to decrease in proliferation pf endothelial cells (Whiteus *et al*., 2014). Angiogenesis de-creases shortly after birth, since most cell migration pathways in the brain be-come largely inactive. An exception is the migration of neuroblasts/immature neurons from the subventricular zone of the lateral ventricles to the olfactory bulbs or brain tissue lesions which remains active in adulthood (Voskresen-skaia *et al*., 2018).

Similar mechanisms coordinate the establishment of vascular and neural networks. Signaling molecules such as Nogo proteins, netrins, ephrins, and others are involved in axonal guidance. They affect the growth of blood microvessels because they act as attractants or repellents. For instance, in the postnatal brain development, a membrane protein RTN4 (axon growth inhibi-tor) can act as a negative regulator of angiogenesis (Coelho-Santos *et al*., 2020). This protein is expressed close to vascular terminal endothelial cells and their processes. Genetic ablation or antibody-mediated neutralization of RTN4 in mice aged P4 or P8

leads to a significant increase in the number of terminal endothelial cells on the 10th day of postnatal life and the appearance of new capillary branches in microvessels. In the adult brain, the activity of angiogen-esis in the cerebral cortex and striatum is extremely low (Bogorad *et al*., 2019). However, other studies suggest that striatum, cortex and area CA1 of the hip-pocampus, subventricular zone of the lateral ventricles are the loci of the most extensive angiogenesis throughout the life (Nemirovich-Danchenko *et al*., 2019).

Recently, extensive experimental and clinical data have been accumulated confirming the involvement of the mechanisms of cerebral angiogenesis in the brain plasticity. Hippocampal vascularization supports the cognitive reserve, whereas suppression of hippocampal angiogenesis reduces the ability to learn (Kerr *et al*., 2010; Perosa *et al*., 2020). Regular physical activity, acting like a multi-stimulus (enriched) environment, promotes cerebral angiogenesis and an increase in cognitive reserve (Zimmerman *et al*., 2021). Recovery of lost func-tions after cerebral ischemia is accompanied by intensification of neoangiogen-esis and migration of cells with proangiogenic activity to the lesioned area (Hatakeyama *et al*., 2020). Maintaining the pool of neural stem cells and their recruitment to ensure neurogenesis is provided by changes in local microcircu-lation within the neurogenic niches of the brain, while functional hyperemia in the hippocampus is associated with an improvement in neurogenesis-dependent learning (Shen *et al*., 2019). Controlled permeability of the BBB in microvessels within neurogenic niches is an important regulatory signal for stem and progenitor cells development, microvascular scaffold and perivascu-lar astrocytes guide neuroblast migration from the niches to other brain regions (Hatakeyama *et al*., 2020). Secretory activity of endothelial cells of cerebral microvessels is important for ensuring the growth of neurites and synaptic activity (Wu *et al*., 2017). Memory consolidation is partially supported by the so-called early cortical angiogenesis which is necessary for neuronal and syn-aptic memory allocation, whereas subsequent regression of the newly formed vascular bed has been detected (Pulga, 2018).

**Angiogenesis in brain pathologies**

Many pathological conditions in the central nervous system are associated with aberrant angiogenesis. Brain aging and neurodegeneration are accompa-nied by serious changes in cerebral vessels (Wen *et al*., 2019; Gorin *et al*., 2020). Vascular alterations occur even in the preclinical phase of the Alz-heimer's disease before the development of cognitive impairment and detecta-ble accumulation of beta-amyloid or appearance of hyperphosphorylated tau protein in the cerebrospinal fluid (CSF). These events are accompanied by the loss of structural and functional integrity of the BBB (Iturria-Medina *et al*., 2016). In the progression of Alzheimer's disease, changes in the expression profile of cerebral endothelial cells and markers of neuroinflammation are de-tected (Bell *et al*., 2010; Salmina, et al., 2019). Interestingly, a decrease in the number of circulating endothelial progenitor cells in patients with Alzheimer's disease was previously considered as a manifestation of insufficient reparative processes in the brain tissue (Kong *et al*., 2011). However, cytostatic therapy aimed to suppress excessive cerebral angiogenesis restores the integrity of the BBB, prevents the progression of cerebral amyloid angiopathy and promotes the restoration of cognitive functions in animals with experimental Alzheimer's disease (Singh *et al*., 2021). Hypervascularization and the establishment of new microvessels with increased BBB permeability are the characteristics of Alzheimer's disease (Biron *et al*., 2011) as well as other types of chronic neu-rodegeneration. Unproductive angiogenesis due to altered DLL4/Notch-mediated mechanism of lateral inhibition and suppression of gamma-secretase activity in endothelial cells contribute to the development of neuroinflamma-tion in Alzheimer's disease (Alvarez-Vergara *et al*., 2021).

Systemic atherosclerosis affects the vascular wall of medium-sized and large arteries in the brain tissue. It associates with endothelial dysfunction and activation, monocyte/macrophage adhesion, activation and transendothelial mi-

gration, excessive oxidative stress, lipid deposition, aberrant extracellular matrix composition, smooth muscle cells migration and proliferation, plaque neovascularization. In the areas of atherosclerosis, local environment (relative anoxia, inflammation, oxidative stress) induces the expression of proangiogen-ic factors that promote the establishment of new vessels from the pre-existing vasa vasorum (Michel *et al*., 2007). Neovascularization provides supply of ox-ygen and nutrients, but further promotes the plaque progression. In addition, incomplete maturation of microvessel BBB leads to intraplaque hemorrhage and its rupture (Michel *et al*., 2014).

Small vessel disease (SVD) is a cluster of pathologies with heterogeneous etiology and pathogenesis, affecting such elements of the vascular system of the brain as small arteries, capillaries, arterioles and venules. The development of SVD is accompanied by decrease in the lumen in the affected vessels, as well as thickening of their walls which prevents perfusion (Litak *et al*., 2020). Neu-roimaging features are white matter hyperintensity, dilated perivascular spac-es, lacunae, subcortical infarcts, microbleeds, and brain atrophy. Some studies include in this group certain pathologies such as Binswanger's disease, leu-koareosis, cerebral microbleeds, and lacunar strokes (Issac *et al*., 2015). Defec-tive angiogenesis might be a part of SVD pathogenesis: development of endothelial dysfunction contributes to SVD progression (Quick *et al*., 2021), induc-tion of angiogenesis seen in animals with experimental models of SVD is a neuroprotective mechanism (Jiang *et al*., 2021), however, elevated levels of cir-culating endothelial progenitor cells and expression of VEGF-D have been found in humans with severe SVD (Kapoor *et al*., 2021), increased expression of bone morphogenetic protein 4 (BMP4) in cerebral pericytes results in exces-sive angiogenesis and astrogliogenesis in experimental SVD (Uemura *et al*., 2018).

In stroke, reduction in perfusion causes ischemic damage, and a decrease in blood flow promotes biphasic vascular remodeling, including angiogenesis. An increase in microvascular density due to angiogenesis correlates with better clinical outcomes and recovery after ischemic brain injury (Ribo *et al*., 2011; Kang *et al*., 2020). An increase in the permeability of the BBB in the ventricu-lar system of the brain in stroke contributes to the formation of new multiple neurogenic niches and the intensification of reparative neurogenesis (Lin *et al*., 2015). Excessive vascularization and the establishment of highly permeable BBB accompany the development of epilepsy (Ogaki *et al*., 2020). BBB breakdown and aberrant lactate-mediated signal transduction in brain microvessel endothelial cells take part in the pathogenesis of neuroinflammation (Boitsova *et al*., 2018). Autism is associated with persistent abnormal angio-genesis (Azmitia *et al*., 2016) and BBB breakdown (Fiorentino *et al*., 2016). Loss of BBB integrity is evident in depression (Dudek *et al*., 2020), and stimu-lation of hippocampal angiogenesis might be a part of antidepressant-mediated therapeutic effects in depression (Boldrini *et al*., 2012).

In sum, aberrant angiogenesis and/or microvessel remodeling are the key mechanisms in the pathogenesis of neurodegeneration, ischemic brain injury, neuroinflammation, and neurodevelopmental disorders.

**Methods used for assessing angiogenesis**

Magnetic resonance imaging (MRI) is widely used to study the remodeling of cerebral vessels. In their study, Kang et al., use superparamagnetic iron ox-ide nanoparticles (SPION) as the contrast agent for simultaneous monitoring of the macro- and microcirculatory system, and their changes in ischemia caused by the middle cerebral artery occlusion in rats (Kang *et al*., 2020). High-resolution ultra-short-term MR angiography with T1-contrast (UTE-MRA) visualized remodeling of the size of the pial arteries and veins. The authors showed that morphological changes in vessels, including but not limited to ve-nous blood vessels, are directly related to the corresponding status of brain tis-sue edema in rats with ischemic stroke.

A more general idea of the tissue structure in pathological changes in blood vessels after ischemic cerebral infarction is provided by an accurate histological quantitative assessment of

microvessel density in the tissue. Brem (Brem *et al*., 1972) was the first to propose a quantitative method for assessing the neovas-cularization of brain tumors. The method of quantitative assessment of angio-genesis in histological sections involves assessment of the area of vessels, their number, perimeter and length. The simplest, inexpensive and most common method of staining histological sections is the Pickworth staining with hema-toxylin and eosin (Leung *et al*., 2013) or application of some other protocols (Zadka *et al*., 2020; Garrido *et al*., 2021). Thomas Wälchli *et al*. proposed a method to show the correlation between the in vivo vascular conditions and angiogenic events in the 3D vascular network of the developing brain (Wälchli *et al*., 2015). The method is based on the use of markers such as Evans-Blue, isolectin or laminin, and registration of both the structure of the vascular wall and the appearance of the dye in the perivascular space. Using confocal laser scanning microscopy and stereological methods of analysis, the authors per-formed a detailed quantitative assessment of the 3D postnatal cerebral vascula-ture in the context of perfused and non-perfused vessels (volume fraction, length and number of vessels, number of branched points, and perfusion sta-tus) and obtained some markers of angiogenesis-related events (the density of endothelial tip-cells, the number of filopodia).

One of the methods for studying the microvasculature and angiogenesis is immunohistochemistry. The von Willebrand factor, CD31/PECAM-1, are the widely-used markers of mature endothelial cells, CD34 and CD133 are the markers of endothelial progenitor cells (Table 2). Nestin and PDGFR are the markers of pericytes, s100β and AQP4 as markers of perivascular astroglia (Pusztaszeri *et al*., 2006). Combination of these markers provide reliable in-formation on the microvessel density and remodeling in the brain tissue. In ad-dition, several markers of BBB structural and functional integrity like CLDN-5, ZO1, JAM, Pgp etc. are used. For instance, CD31 and CD34 are used to identify and assess the density of blood vessels in a tissue (Nefedova *et al*., 2016). Figueiredo et al applied and confirmed that labeling of blood vessels us-ing CD31 can be an important tool for assessing angiogenesis (Figueiredo *et al*., 2018). The von Willebrand factor (VWF), which at that time was called the FVIII-related antigen (Randi *et al*., 2018), is widely used to quantify blood ves-sels and angiogenesis, its expression in endothelial cells is enhanced by angio-genic factors, in particular, VEGF and FGF2 (Zanetta *et al*., 2000).

To study the molecular mechanisms of angiogenesis in vitro, 3D models are used when capillary-like structures are formed. This system is a unique model, as it makes it possible to evaluate the growth dynamics and migration rate of vascular cells, to identify the growth trajectory and the nature of the bifurca-tion of capillary-like structures (Semina *et al*., 2015). Uemura and Gil et al. (Uemura *et al*., 2010; Gil & Del Río, 2012) confirmed the advantages of this method, among others, in the culture of small fragments of the brain tissue ob-tained from mouse embryos. The method makes it possible to simultaneously distinguish newly formed blood vessels in the same sample, to conduct simul-taneous immunofluorescence in combination with an analysis of the state of perfusion of the vascular network, provides an accurate analysis of the 3D structure of vessels in the postnatal brain, and clearly identifies tip cells based on morphological criteria, as well as the possibility of combining with immu-nofluorescence using various other vascular markers. Other methods of molec-ular and systems biology (polymerase chain reaction (PCR), mass spectrome-try) can be used for a deeper study of the cellular and molecular mechanisms of angiogenesis (Lee *et al*., 2019).

The in vivo assessment of the permeability of BBB in pre-existing or newly formed microvessels can be performed with the following methods: 1) infrared spectroscopy with indocyanine green which has a fast clearance from the tis-sue; 2) high-resolution MRI with the assessment of the accumulation of a gado-linium-based contrast agents in the perivascular space; 3) positron emission tomography with radioligands, for instance, with 2-amino-3C-isobutyrate; 4) assessment of the accumulation of the dye (Evans Blue, sodium fluorescein, dextrans)

*Table 2*

**Some markers of endothelial progenitor and mature cells**

| Marker | Expression | References |
|---|---|---|
| CD31 | Adhesion molecule of endothelial cells and platelets. Expressed by endothelial cells, as well as by perivascular adventitious elements of vessels. | (Vockova *et al.*, 2021) |
| CD34 | Membrane protein, intercellular adhesion molecule, endothelial marker of lymph nodes. Mediates the binding of stem cells to the intercellular matrix | (Sonoda, 2021) |
| CD105 | Endoglin is a protein expressed by the proliferating endothelium. It is highly expressed on the surface of actively proliferating microvascular endothelial cells and is a marker for the quantitative assessment of neovascularization. | (Figueiredo *et al.*, 2018) |
| CD133 | Transmembrane glycoprotein, also known as prominin-1, is commonly expressed on undifferentiated cells, including endothelial progenitor cells, hematopoietic stem cells, fetal brainstem cells. | (Glumac & LeBeau, 2018) |
| CD135 | It is the human homologue of mouse prominin-1, a cell surface glycoprotein with five transmembrane domains. Expressed by hematopoietic, embryonic, renal stem and epithelial cells. | (Audiger & Lesage, 2020) |

in the brain tissue after parenteral administration (only in animals) (Ganau *et al*., 2020; Ahishali *et al*., 2020).

## Conclusion

Angiogenesis is an important and highly regulated process aimed to estab-lish new blood vessels in (patho)physiological conditions. In the brain, it is under the control of wide spectrum of pro- and antiangiogenic molecules whose expression is tightly coordinated in NVU/BBB cells. Aberrant angio-genesis contributes to the pathogenesis of various brain diseases (neurodegen-eration, neurodevelopmental disorders, brain ischemia, neuroinflammation), being the mechanism of altered brain plasticity. Further progress in decipher-ing the basis of cerebral angiogenesis will provide new approaches to enhanc-ing the cognitive reserve, correcting neurological deficits, creating the brain tis-sue modes in vitro, and designing new drug candidates. Application of in-formative protocols of cerebral microvessels visualization and functional anal-ysis would be helpful for the assessment of individual progression of brain pa-thology or efficacy of therapy.

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