

Vascular endothelial growth factor (VEGF) signaling in tumor progression

Robert Roskoski Jr. *

Blue Ridge Institute for Medical Research, 3754 Brevard Road, Suite 116A, Box 19, Horse Shoe, NC 28742, USA

Accepted 29 January 2007

Contents

1. Vasculogenesis and angiogenesis	180
1.1. Definitions	180
1.2. Physiological and non-physiological angiogenesis	181
1.3. Activators and inhibitors of angiogenesis	181
1.4. Sprouting and non-sprouting angiogenesis	181
1.5. Tumor vessel morphology	183
2. The vascular endothelial growth factor (VEGF) family	183
3. Properties and expression of the VEGF family	183
3.1. VEGF-A	183
3.2. VEGF-B	185
3.3. VEGF-C	185
3.4. VEGF-D	186
3.5. Placental growth factor (PlGF)	186
3.6. VEGF-E	186
4. VEGF receptors	186
4.1. VEGFR1 (Flt-1)	186
4.2. VEGFR2 (Flk-1/KDR)	187
4.3. VEGFR3 (Flt-4)	189
4.4. Neuropilin-1 and -2	190
4.4.1. Properties and expression	190
4.4.2. Tumor progression	191
4.5. Essential nature of the VEGF receptors	193
5. Proteolysis of VEGF isoforms and release from heparan sulfate proteoglycans	194
5.1. VEGF isoforms	194
5.2. Plasminogen activators, plasmin, and matrix metalloproteases	194
5.3. VEGF isoform proteolysis by plasmin	195
5.4. VEGF isoform proteolysis by urokinase type of plasminogen activator	195
5.5. VEGF isoform proteolysis by matrix metalloproteases	196
5.6. Differential stimulation of VEGF isoform action by heparin	196
6. Phenotypes of mice expressing specific VEGF isoforms	197
7. Regulation of VEGF gene expression by oxygen, growth factors, and oncogenes	197
7.1. Hypoxia-inducible transcription factor (HIF) family	197
7.2. HIF-1 α prolyl hydroxylation and proteasomal degradation	198

* Tel.: +1 828 891 5637; fax: +1 828 890 8130.

E-mail address: rrj@brimr.org.

7.3.	HIF-1 α asparaginyl hydroxylation and transcription	199
7.4.	Responses to hypoxia	199
7.5.	Growth factors and hormones	199
7.6.	Oncogenes	201
8.	VEGF and tumor progression	202
8.1.	Tumor growth and angiogenesis	202
8.2.	VEGF expression in tumors	202
9.	Inhibition of VEGF family signaling	202
9.1.	Anti-VEGF antibodies	202
9.2.	VEGF traps (genetically engineered VEGF-binding proteins)	203
9.3.	VEGF receptor protein-tyrosine kinase inhibitors	203
10.	Tumor metastasis, the pre-metastatic niche, and VEGFR1	203
11.	VEGF and vascular endothelial cell survival	204
12.	Epilogue	205
	Reviewer	206
	Acknowledgements	206
	References	206

Abstract

Vascular endothelial cells are ordinarily quiescent in adult humans and divide less than once per decade. When tumors reach a size of about 0.2–2.0 mm in diameter, they become hypoxic and limited in size in the absence of angiogenesis. There are about 30 endogenous pro-angiogenic factors and about 30 endogenous anti-angiogenic factors. In order to increase in size, tumors undergo an angiogenic switch where the action of pro-angiogenic factors predominates, resulting in angiogenesis and tumor progression. One mechanism for driving angiogenesis results from the increased production of vascular endothelial growth factor (VEGF) following up-regulation of the hypoxia-inducible transcription factor. The human VEGF family consists of VEGF (VEGF-A), VEGF-B, VEGF-C, VEGF-D, and placental growth factor (PlGF). The VEGF family of receptors consists of three protein-tyrosine kinases and two non-protein kinase receptors (neuropilin-1 and -2). Owing to the importance of angiogenesis in tumor progression, inhibition of VEGF signaling represents an attractive cancer treatment.

© 2007 Elsevier Ireland Ltd. All rights reserved.

Keywords: Angiogenesis; Hypoxia; Neuropilin; Proteolysis; Receptor protein-tyrosine kinase; Vasculogenesis

1. Vasculogenesis and angiogenesis

1.1. Definitions

The intricately branched circulatory network of vascular endothelial and supporting cells is essential for transporting oxygen, nutrients, and signaling molecules to and the removal of carbon dioxide and metabolic end products from cells, tissues, and organs [1]. Neovascularization, or new blood vessel formation, is divided into two components: vasculogenesis and angiogenesis. Embryonic or classical vasculogenesis is the process of new blood vessel formation from hemangioblasts that differentiate into blood cells and mature endothelial cells [2]. In the embryo and yolk sac, early blood vessels develop by aggregation of angioblasts into a primitive network of simple endothelial tubes [3]. As primitive vessels are remodeled into a functioning circulatory system, they undergo localized proliferation and regression, as well as branching and migration. In contrast, angiogenesis is the process of new blood vessel formation from pre-existing vascular networks by capillary sprouting. During this process, mature

endothelial cells divide and are incorporated into new capillaries. Vascular endothelial growth factor (VEGF) signaling is required for the full execution of vasculogenesis and angiogenesis.

Many observations associated with tissue ischemia and tumor formation are consistent with the concept that vasculogenesis also occurs during postnatal vessel development [4]. Asahara et al. were the first to describe the existence of endothelial progenitor cells in adult human blood that can differentiate into endothelial cells [5]. These progenitor cells normally reside in the bone marrow but may become mobilized into the circulation by cytokine or angiogenic growth factor signals [6]. During adult vasculogenesis, mobilized progenitor cells promote vessel formation by integrating into vessels and by supplying growth factors. Bone-marrow-derived endothelial progenitor cells may be recruited to sites of infarction, ischemia, or tissue trauma where they differentiate into mature endothelial cells and combine with other cells to form new vessels. These findings suggest that vasculogenesis and angiogenesis might constitute complementary mechanisms for postnatal neovascularization. Not all studies, however, support the concept of adult vasculogenesis [7], and

Download English Version:

<https://daneshyari.com/en/article/3330409>

Download Persian Version:

<https://daneshyari.com/article/3330409>

[Daneshyari.com](https://daneshyari.com)