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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

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* Tel.: +1 828 891 5637; fax: +1 828 890 8130.
E-mail address: rrj@brimr.org.

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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.

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