Microvascular Research 117 (2018) 1–9

Contents lists available at ScienceDirect

Microvascular Research

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

Important signals regulating coronary artery angiogenesis

Sara Shoeibi[a,*], Paul Mozdziak[b], Shabnam Mohammadi[c]

[a] Cellular and Molecular research Center, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran
[b] Graduate Physiology Program, North Carolina State University, Raleigh, NC
[c] Department of Basic Sciences, Faculty of Medicine, Gonabad University of Medical Sciences, Gonabad, Iran

ARTICLE INFO

Keywords:
Angiogenesis
Growth factor
Intraplaque

ABSTRACT

Angiogenesis is a complex process of budding, the formation of new blood vessels from pre-existing microvessels, via migration, proliferation and survival. Vascular angiogenesis factors include different classes of molecules that have a fundamental role in blood vessel formation. Numerous inducers of angiogenesis, such as the members of the vascular endothelial growth factor (VEGF) family, basic fibroblast growth factor (bFGF), angiopoietin (Ang), hepatocyte growth factor (HGF), and hypoxia inducible factor-1 (HIF-1), have an important role in angiogenesis. However, VEGF, platelet-derived growth factor (PDGF), and transforming growth factor β (TGF-β) expression appear to be important in intraplaque angiogenesis. Interaction and combined effects between growth factors is essential in endothelial cell migration, proliferation, differentiation, and endothelial cell-cell communication that ultimately lead to the microvessel formation. Since VEGF has a key role during angiogenesis; it may be considered as a good therapeutic target in the clinic. The essential function of several angiogenic factors involved in coronary angiogenesis and intraplaque angiogenesis in atherosclerosis are carefully considered along with the use of angiogenic factors in clinical practice.

1. Introduction

Angiogenesis is a highly regulated process leading to the development of new capillary sprouts from pre-existing microvascular networks. Angiogenesis increases the blood supply to tissues and results in developed microvessels and wound repair (Otrock et al., 2007) making it important for the treatment of cardiovascular disorders, cancer, diabetes, obesity, rheumatoid arthritis and psoriasis.

In vasculogenesis, new endothelial cells differentiate from endothelial precursor cells to form a primary vascular plexus, whereas angiogenesis is a complex process of budding, the formation of new blood vessels from pre-existing microvessels, migration, proliferation and survival (Griffioen and Molema, 2000). Numerous angiogenic molecules can initiate and regulate angiogenesis (Otrock et al., 2007). New vessels are similar to capillaries and they are 5–8 μm in diameter. Thus, the process of angiogenesis can be divided into two stages, growth of capillaries including the sprouting of capillaries from the pre-existing vessels, and blood vessel remodeling through which the enlargement of existing vessels (Bloor, 2005). Events that occur during angiogenesis include endothelial cell activation and vasodilatation of the parent blood vessel; digestion of the basement membrane and migration of endothelial cells from the parent vessel toward the site where angiogenesis is required by chemotactic derived from monocytes, platelets, mast cells, and neutrophils (Kutryk et al., 2001). The objective of this report is to provide an overview of the various factors that may affect in cardiac angiogenesis process and also studies the molecular mechanisms of angiogenesis in the heart.

1.1. Interaction of growth factors in adult angiogenesis

Mechanical forces such as shear stress, pressure and tension, alter the structure and function of endothelial cells. If coronary microvascular endothelial cells are under stress, they release paracrine and autocrine signals that enhance critical angiogenic events in endothelial cells leading to microvessel formation (Zheng et al., 2001). There are several stages in vessel formation: In the first phase, *endothelial cell activation and increased endothelial permeability* occurs in response to stress conditions. Under physiological or pathological condition e.g. hypoxia or ischemia, nitric oxide (NO) is released to increase endothelial permeability allowing plasma proteins to form a scaffold involving a fibrin-rich network. Cytokines released from various sources in response to the stressful situation induce the angiogenic cascade. Under the control of hypoxia inducible factor (HIF), vascular endothelial growth factor (VEGF) induces vasoconstriction and increases permeability via endothelial NO production. Plasma proteins can enter into the damaged tissue and facilitate the pathway that increases

* Corresponding author.
E-mail address: ShoeibiS901@gmail.com (S. Shoeibi).

https://doi.org/10.1016/j.mvr.2017.12.002
Received 21 October 2017; Received in revised form 7 December 2017; Accepted 8 December 2017
Available online 13 December 2017
0026-2862/

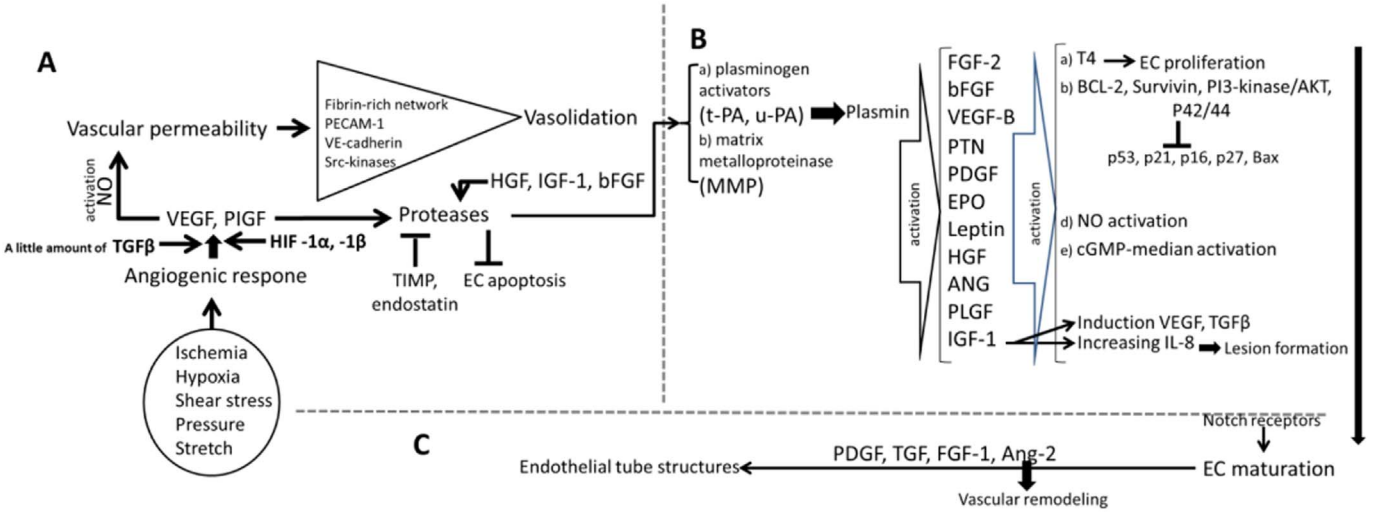

Fig. 1. Stage of angiogenesis. A, endothelial cell activation and permeability, VEGF is an important factor in the onset of angiogenesis that induces the permeability and dilation of the vessel; B, endothelial cell migration and proliferation; proteases such as plasminogen activators convert plasma protein plasminogen to plasmin which then induces the mobilization of angiogenesis factors from the extracellular matrix pool.; C, sprouting and maturation of endothelial cells. NO, nitric oxide; TIMP, tissue inhibitors of metalloproteinase; EC, endothelial cell; PECAM-1, Platelet endothelial cell adhesion molecule.

endothelial permeability, mediated by Src kinases, VE-cadherin, RAS/MAP kinase including protein kinase C, and tyrosine kinases (Carmeliet, 2000; Griffioen and Molema, 2000; Iruela-Arispe, 2005) (Fig. 1A). VEGF can induce proteases that have effects on cell invasion and tissue changes and also protect endothelial cells from apoptosis. Thus begins the second phase of angiogenesis, *endothelial cell migration and proliferation*, where endothelial cells migrate from their normal site, a process that is facilitated by the activity of Matrix Metalloproteinases (MMPs) with the release of growth factors, such as VEGF, fibroblast growth factor (FGF), and vascular insulin-like growth factor (IGF)-1 (Griffioen and Molema, 2000). Plasmin is an activating metalloproteinases, playing an important role in the mobilization of FGFs from endothelial cells (Carmeliet, 2000) (Fig. 1B). For example, FGF-2 is effective in modulating integrin levels that can cause integrin binding to endothelial proteins (Griffioen and Molema, 2000). Other protease secretory products such as urokinase-type plasminogen activator (u-PA) are also essential for myocardial angiogenesis (Carmeliet, 2000; Griffioen and Molema, 2000). In these interactions, transforming growth factor β (TGF-β) upregulates VEGF expression in cardiomyocytes lead to angiogenic stimulation (Zheng et al., 2001). TGF-β and VEGF initiate angiogenesis pathways dependent on αVβ5 integrin (Griffioen and Molema, 2000) (αVβ integrins, in particular αVβ3 play a critical role in angiogenesis).

Endothelial cell permeability is an important factor for the initiation of angiogenesis, since vascular leakage can lead to devastating effects on circulation. Angiopoietin (Ang) may act as an inhibitor to prevent excessive vascular leakage and protect vasculature without a bad effect on vascular morphology. However Ang-2 plays the most important role in angiogenesis in presence of VEGF (Carmeliet, 2000).

In general, the VEGF family of growth factors has specific function in the proliferation and migration of endothelial cells (Griffioen and Molema, 2000). For example, placental growth factor (PLGF) is a therapeutic target involved in angiogenic disorders and loss of PLGF does not affect physiological angiogenesis. Loss of VEGF-B effects on cardiac function after stenosis (Carmeliet, 2000; Luttun et al., 2002). NO and cGMP are important mediators in the activation of MAP kinase family.

The final step in the process of angiogenesis is *sprouting and maturation of endothelial cells* which is synonymous with cell differentiation and remodeling. Some endothelial cells which are called tip cells (growth buds) are selected for sprouting during angiogenesis. Key sprouting of endothelial cells includes phenotypic changes in the cells that provide invasive behavior, motor efficiency, activation of proteases, and finally locally digested basal membrane. Notch pathway receptors are necessary for sprouting of capillary networks. Therefore, blocking Notch signals greatly reduces sprouting, branching and fusion of endothelial tube. Mechanisms of Notch-induced differentiation of endothelial cells are directly related to VEGFA signaling (Adams and Alitalo, 2007). Interaction of endothelial cells with the extracellular matrix and mesenchymal cells is a prerequisite for maturation of the neovasculature. FGF-1 and TGF-β are molecules involved in the differentiation of endothelial cells during angiogenesis, allowing, for example, FGF-1 to cause vascular tube formation of endothelial cells. Ang-1 and its specific ligands (Tie1 and Tie2) are also implicated in endothelial differentiation, stability of blood vessels and capillary network formation (Griffioen and Molema, 2000) (Fig. 1C). It was also reported that Ang-1 in combination with VEGF, provides a synergistic effect in increasing the diameter and length of the vessels (Carmeliet, 2000). The role of Ang-2 at this stage is to sensitize endothelial cells to angiogenic factors (Griffioen and Molema, 2000).

Consequently, vascular angiogenesis factors can be directly or indirectly involved in the migration and deployment of endothelial cells and their differentiation resulting in the regulation of angiogenesis.

1.1.1. *Factors involved in regulating coronary angiogenesis*

In ischemic diseases (ischemic coronary artery disease, critical limb ischemia, and decubitus), angiogenesis is an effective treatment. Angiogenesis is induced by several mediators that are produced by a number of cells. Many of inducers of angiogenesis have been identified and they have an essential function in cardiovascular angiogenesis.

VEGF is a soluble pro-angiogenic factor (Griffioen and Molema, 2000; Morgan and Nigam, 2013), which has several isoforms that are the result in alternative processing of the gene (Griffioen and Molema, 2000). VEGF-A, is an efficient factor in vascular permeability in embryonic stage. As the inactivity of only one allele of this gene showed early embryonic lethality and leads to defects in endothelial cell development. Also interaction between VEGF-A and VEGFR2 is important in pathologic angiogenesis, as blocking this interaction leads to non-vessel formation (Olsson et al., 2006). Placental growth factor (PIGF) is an angiogenic factor that is expressed in endothelial cells, monocytes and trophoblasts. PIGF belongs to the family of VEGF (Siervo et al., 2010) and its expression is stimulated by cytokines via protein kinase C-dependent and MEK pathways (Osol et al., 2008). PIGF expression increases in angiogenesis, particularly in atherosclerotic plaques (Siervo