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Review

Angiogenic factors as potential drug target: Efficacy and limitations of anti-angiogenic therapy

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ABSTRACT

Formation of new blood vessels (angiogenesis) has been demonstrated to be a basic prerequisite for sustainable growth and proliferation of tumor. Several growth factors, cytokines, small peptides and enzymes support tumor growth either independently or in synergy. Decoding the crucial mechanisms of angiogenesis in physiological and pathological state has remained a subject of intense interest during the past three decades. Currently, the most widely preferred approach for arresting tumor angiogenesis is the blockade of vascular endothelial growth factor (VEGF) pathway; however, the clinical usage of this modality is still limited by several factors such as adverse effects, toxicity, acquired drug resistance, and non-availability of valid biomarkers. Nevertheless, angiogenesis, being a normal physiological process imposes limitations in maneuvering it as therapeutic target for tumor angiogenesis. The present review offers an updated relevant literature describing the role of well-characterized angiogenic factors, such as VEGF, basic fibroblast growth factor (bFGF), platelet derived growth factor (PDGF), placenta growth factor (PLGF), hepatocyte growth factor/scatter factor (HGF/SF) and angiopoetins (ANGs) in regulating tumor angiogenesis. We have also attempted to discuss tumor angiogenesis with a perspective of 'an attractive target with emerging challenges', along with the limitations and present status of anti-angiogenic therapy in the current state-of-the-art.

Contents

Abbreviations: VEGF, vascular endothelial growth factor; CRC, colorectal cancer; VEGFR, VEGF receptors; PLGF, placental growth factor; HGF, hepatocyte growth factor; Il, Interleukin; Del-1, developmentally-regulated endothelial cell locus 1 protein; FGF, fibroblast growth factors; CXCL1/Groα, growth-regulated alpha protein; CXCL6/GCP2, granulocyte chemotactic protein 2; bFGF, basic fibroblast growth factor; PDGF, platelet derived growth factor; HGF/SF, hepatocyte growth factor/scatter factor; ANG, angiopoetin; VPF, vascular permeability factor; kDa, kilo Dalton; Flt, Fms-like tyrosine kinase; Flk, fetal liver kinase; KDR, kinase insert domain receptor; HIF-1α, hypoxia inducible factors; NRP, neuropilin; SAF-1, serum amyloid A activating factor 1; HPSGs, heparan sulfate proteoglycans; FGFR, fibroblast growth factor receptors; PDGF-B, platelet-derived growth factor-Beta; miR, microRNA; FP1039, Five Prime Therapeutics; EC, endothelial cell; MMP, matrix metalloproteases; ET-1, endothelin-1; TGF, transforming growth factor; TNF, tumor necrosis factor; PO_2, partial pressure of oxygen; SMCs, smooth muscle cells; HUVEC, human umbilical vein endothelial cell; MAPK, Mitogen-activated protein kinase; PI3K, Phosphoinositide 3-kinase; PKC-zeta, Protein kinase C zeta; Sp1, specificity protein 1; U1snRNA, U1 small nuclear RNA; Tie-2, tunica intima endothelial kinase 2; GBM, glioblastoma multiforme; Erk, extracellular signal-regulated kinase; TKIs, tyrosine kinase inhibitors; mTOR, mammalian target of rapamycin; EGFR, epidermal growth factor receptor; Dll4, delta-like ligand 4; ECP, endothelial cell progenitor; G-CSF, granulocyte colony-stimulating factor; SDF, stromal derived factor; CECs, circulating endothelial cells; VCAMs, vascular cell adhesion proteins; NPDD, nanoparticle mediated drug delivery; hCG, human chorionic gonadotropin; ESDN, endothelial and smooth muscle cell-derived neuropilin-like protein

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1. Introduction

Since the publication of Judah Folkman's hypothesis that tumor growth is angiogenesis-dependent and a solid tumor must obtain an independent blood supply for its sustainable growth [107], the literature on angiogenesis research is accumulating in logarithmic fashion. Angiogenesis is a physiological process of development of new blood vascular network required for normal body functioning; however, clinically and pathologically it has been recognized as a basic prerequisite for progression, proliferation and metastatic spread of solid tumors. At the site of angiogenesis, new capillaries sprout from pre-existing vessels and there occurs remolding transition from avascular to vascular phases via neovascularization. Cascade of events activated by several pro-angiogenic factors happens during the process of tumor angiogenesis involving mainly dissolution of vascular basal membrane, increased vascular permeability and degradation of extracellular matrix resulting in endothelial cell migration, invasion, proliferation and tube formation [250]. Physiological angiogenesis is a complex process that is tightly controlled & regulated by numerous pro-angiogenic peptides as well as by an array of inhibitory factors; however, in pathological angiogenesis, there occurs an imbalance between pro- and anti-angiogenic factors [49]. Tumors can exist in dormant state for months or years without neovascularization by balancing pro- and anti-angiogenic factors. However, during tumor growth there is a change in angiogenic switch more in favor of pro-angiogenic phenotype. Subsets of the tumor with a pro-angiogenic phenotype secrete their own angiogenic factors and also retrieve angiogenic substances from the surrounding extracellular matrix, and induce host cells (monocytes/macrophages) to synthesize angiogenic molecules. Thus there occurs a shift in the microenvironment of the tumor in favor of the pro-angiogenic stimuli, either by down-regulation of endogenous angiogenic inhibitors or through up-regulation of pro-angiogenic cytokines. As a result of this shift, an angiogenic switch is activated causing a continuous neovessel formation emanating from the normally quiescent vasculature, which sustains tumor growth [6,130,131].

A plethora of research findings have accumulated in the literature, especially the pioneer angiogenesis research by Folkman [106–109, 261], and [98,100,104,274] has unraveled the fundamental and baseline secrets of angiogenic switch and played a leading role in establishing angiogenesis as a therapeutic target in the mainstream of anticancer research. This fundamental research was successfully transformed into therapeutic modality by Dr. Ferrara and his team at Genentech Ltd. (San Francisco, USA) which led to the development of Bevacizumab (Avastin), the first (VEGF) targeted anti-angiogenesis cancer therapy, approved by the FDA in 2004. In the current clinical practices, Avastin has been prescribed as a treatment of first-line therapy for colorectal cancer (CRC), neoadjuvant chemotherapy for breast cancer, metastatic breast cancer, non-small-cell lung cancer, metastatic renal cell carcinoma, and as second-line therapy in CRC and glioblastoma multiforme [23, 85,101]. Thus, development of a humanized anti-VEGF antibody for the treatment of cancer targeting angiogenesis stands out as landmark achievements in anti-cancer research.

Advances in the molecular biology, clinical biochemistry and pathophysiology of tumor growth led to a concrete understanding about the up- and down-regulation of angiogenic switch. Nevertheless, different strategies have been designed to stimulate or arrest the growth of new blood vessels and also identified potential ways to interfere with the process of tumor growth. The concept of treating solid tumors by targeting tumor angiogenesis is not new; rather it is more discussed in recent years owing to its significance as targeted anticancer therapy extending the life span of cancer patients. A plethora of literature has accumulated in recent years describing the significance of targeting tumor angiogensis for the design and development of novel antitumor agents that arrest tumor growth [47,49,115,116,163,197,222]. A review providing a comprehensive information on functional and structural peculiarities of the various angiogenic peptides, especially emphasizing more on structural opportunities available for manipulating functions of major angiogenic peptides has been recently published [114].

2. How many angiogenic factors support tumor growth?

A series of pro-angiogenic peptides especially the cytokines belonging to the vascular endothelial growth factor (VEGF) family such as VEGF A, B, C, D and VEGF receptors (VEGFR1, & 2), placental growth factor (PLGF), hepatocyte growth factor (HGF), axon guidance factors (semaphorin-4D, slit-2), interleukins (ILs-1, 6, 8 and stromal cell-derived factor 1), pro-angiogenic chemokines such as developmentally-regulated endothelial cell locus 1 protein (Del-1), β-estradiol, ephrins, fibroblast growth factors (FGF 1 & 2), follistatin, chemokines like Growth-regulated alpha protein (CXCL1/Groα), Granulocyte chemotactic protein 2 (CXCL6/GCP2) and angiopoietins have been reviewed in relation to their functional attributes with tumor angiogenesis [97,119,191, 216,249]. Fig. 1 summarizes the role of various angiogenic factors discussed in this study.

Effective novel targeted therapies with improved therapeutic index are warranted and angiogenesis is being considered as an attractive target. Designing strategies for targeting the pro-angiogenic peptides for the treatment of angiogenesis linked human ailments remains an exciting research area for further investigation. Extensive research on angiogenesis in recent years has discovered a series of new pro-angiogenic factors having direct or indirect influence in tumor angiogenesis. An updated list of more than 40 endogenous molecules that directly or indirectly influence angiogenesis, along with few others, being assessed and suspected for their angio-regulatory activities are summarized in Table 1.

With the advancement of technology and thereby more clear understanding about the pathophysiology of tumor development and the signaling pro-angiogenic factors, significant efforts have been made in converting these factors as therapeutic targets for designing novel antiangiogenic drugs [47,95,149,222]. An updated literature describing the role of best-characterized angiogenic factors such as VEGF, bFGF, PDGF, PLGF, HGF/SF and ANGs in regulating tumor angiogenesis is described below with special reference to the currently available drugs designed against these pro-angiogenic factors.

2.1. VEGF cytokine family

The pioneer work on vascular permeability factor (VPF) by [261], and the sequencing of VEGF by Ferrara and Henzel [100], revealed the identical nature of both factors that brought together important

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