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Review

Targeting tumor micro-environment for design and development of novel anti-angiogenic agents arresting tumor growth

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ABSTRACT

Angiogenesis: a process of generation of new blood vessels has been proved to be necessary for sustained tumor growth and cancer progression. Inhibiting angiogenesis pathway has long been remained a significant hope for the development of novel, effective and target orientated antitumor agents arresting the tumor proliferation and metastasis. The process of neoangiogenesis as a biological process is regulated by several pro- and anti-angiogenic factors, especially vascular endothelial growth factor, fibroblast growth factor, epidermal growth factor, hypoxia inducible factor 1 and transforming growth factor. Every endothelial cell destined for vessel formation is equipped with receptors for these angiogenic peptides. Moreover, numerous other angiogenic cytokines such as platelet derived growth factor (PGDF), placenta growth factor (PGF), nerve growth factor (NGF), stem-cell factor (SCF), and interleukins-2, 4, 6 etc. These molecular players performs critical role in regulating the angiogenic switch. Couple of decade's research in molecular aspects of tumor biology has unraveled numerous structural and functional mysteries of these angiogenic peptides. In present article, a detailed update on the functional and structural peculiarities of the various angiogenic peptides is described focusing on structural opportunities made available that has potential to be used to modulate function of these angiogenic peptides in developing therapeutic agents targeting neoplastic angiogenesis. The data may be useful in the mainstream of developing novel anticancer agents targeting tumor angiogenesis. We also discuss major therapeutic agents that are currently used in angiogenesis associated therapies as well as those are subject of active research or are in clinical trials.

Contents

Abbreviations: EC, endothelial cells; VEGF, vascular endothelial growth factor; VEGF Receptor, VEGFR; FGF, fibroblast growth factor; EGF, epidermal growth factor; epidermal growth factor receptor, EGFR; HIF-1, hypoxia inducible factor-1; TGF-α, transforming growth factor-alpha; TGF-β, transforming growth factor-beta; PGDF, platelet derived growth factor; PGDFR, platelet derived growth factor receptor; PGF, placenta growth factor; PGFR, placenta growth factor receptor; NGF, nerve growth factor; SCF, stem-cell factor; MCP, monocyte chemotactic protein; MIP, macrophage inflammatory protein; PDB, protein data bank; VHD, VEGF homology domain; NTS, 1,3,6-Naphthalenetrisulfonate; CML, chronic myelogenous leukemia; IGF, insulin-like growth factor; IGF-1R, insulin-like growth factor receptor type1; IGF-2R, insulin-like growth factor receptor type2; IGFBPs, IGF-binding proteins; IR, insulin receptors; Angp-1, Angiopoietin-1; Angp-2, angiopoietin-2; Tie2K, cytoplasmic kinase domain of Tie2; ATP, adenosine triphosphate; HGF, hepatocyte growth factor; SDF-1α, stromal cell-derived factor-1α; FIH, Factor-inhibiting hypoxia-inducible factor; PHDs, prolyl hydroxylases; TNF-α, Tumor necrosis factor-alpha; TNFR, TNF-receptor; p55, 55 kDa protein; p75, 75 kDa protein; DHLA, dihomo gamma-linolenic acid; ALA, alpha linolenic acid; IL-1, interleukin-1; IL1R, type I IL-1 receptor; IL-3, interleukin-3; IL-6, interleukin 6; IL-6r, interleukin 6 receptor; JAKs, janus kinases; CXCR1, CXC receptor1; CXCR2, CXC receptor2; Nrp1, Neuropilin1; Nrp 2, Neuropilin2; Ang, angiogenin; RNase-A, ribonuclease-A; CDRs, complementarity-determining regions; AM, andrenomedullin; PAMP, proadrenomedullin N-terminal 20 peptide; CGRP, calcitonin gene-related peptide; AMBP-1, AM binding protein-1; CLR, calcitonin receptor-like receptor; RAMP, receptor activity modifying protein; SDF-1alpha, stromal cell-derived factor-1α; CXCR4, CXC receptor4; GPCR, G protein coupled receptors.

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1. Introduction

Angiogenesis and lymphangiogenesis are the terms coined for processes describing development of new blood and lymphatic vessels from already existing ones. Tumor angiogenesis can be defined as process resulting in sustaining tumor expansion with aid of new blood vessel that sprout from an existing pool of blood vessels. Angiogenesis is a multistep complicated phenomenon that entails numerous steps. These events can be conceptually visualized as initial activation phase of endothelial cells (EC) that often results in release of proteases leading to degradation of the basement membrane of ECs present in vicinity of the existing vessel. Subsequent to this event, EC migrate to newly formed interstitial space followed by extensive cell proliferation phase forming new tubes for new vessels. Finally, blood flow initiates and new vasculature attains stability after maturation phase (Fig 1). Once the tumor cells acquire the ability to induce angiogenesis, tumor expansion is initiated (Hanahan and Folkman, 1996). Dysregulation of angiogenesis is thus hallmark of cancer. Plethora of research findings have accumulated in the literature, that have unraveled major 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. The vasculature provoked in consequence of tumor angiogenesis is decidedly deviant in the way it alter the tumor microenvironment and strongly control the manner in which cancers grow, evade the host's immune surveillance, and metastasize (Klauber-DeMore, 2012). There are two popular mechanisms that explains vessel formation in tumors, one of them include the *trans*-differentiation of cancer cells; more precisely termed as vasculogenic mimicry

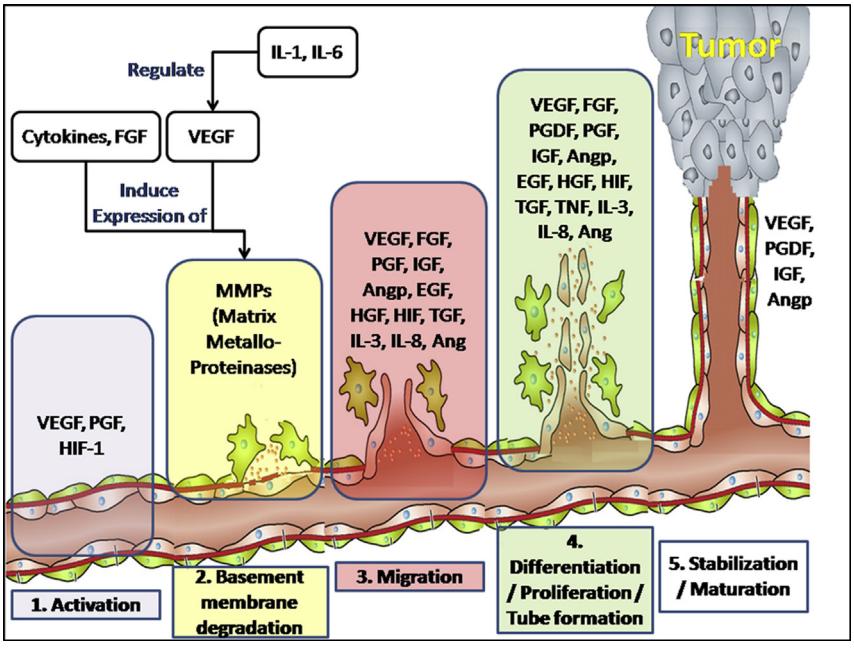

Fig. 1. Figure summarizing major events (step 1–5) that occur in process of angiogenesis along with the various factors that act in respective stage of angiogenesis.