REVIEWS

Antiangiogenic Drugs: Current Knowledge and New Approaches to Cancer Therapy

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ABSTRACT: Angiogenesis—process of new blood-vessel growth from existing vasculature—is an integral part of both normal developmental processes and numerous pathologies such as cancer, ischemic diseases and chronic inflammation. Angiogenesis plays a crucial role facilitating tumour growth and the metastatic process, and it is the result of a dynamic balance between proangiogenic and antiangiogenic factors. The potential to block tumour growth and metastases by angiogenesis inhibition represents an intriguing approach to the cancer treatment. Angiogenesis continues to be a topic of major scientific interest; and there are currently more antiangiogenic drugs in cancer clinical trials than those that fit into any other mechanistic category. Based on preclinical studies, researchers believe that targeting the blood vessels which support tumour growth could help treatment of a broad range of cancers. Angiogenic factors or their receptors, endothelial cell proliferation, matrix metalloproteinases or endothelial cell adhesion, are the main targets of an increasing number of clinical trials approved to test the tolerance and therapeutic efficacy of antiangiogenic agents. Unfortunately, contrary to initial expectations, it has been described that antiangiogenic treatment can cause different toxicities in cancer patients. The purpose of this article is to provide an overview of current attempts to inhibit tumour angiogenesis for cancer therapy. © 2008 Wiley-Liss, Inc. and the American Pharmacists Association J Pharm Sci 97:4129–4154, 2008

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INTRODUCTION

Angiogenesis describes the formation of new blood vessels from the preexisting microvasculature. Under physiological conditions, angiogenesis is a highly regulated phenomenon. Over the past years, the mechanisms underlying this process have been increasingly understood and have been demonstrated to be mediated by a tightly controlled and balanced synthesis of numerous proangiogenic and antiangiogenic factors.[1] Physiological angiogenesis normally takes place during embryonic development, that is during embryogenesis and early after birth, as well as in the adult in the context of wound healing and the female reproductive cycle. In physiologic conditions, cells are located within 100–200 μm from blood vessels, their source of oxygen. When a multicellular organism is growing, cells induce angiogenesis and vasculogenesis in order to recruit new blood supply.

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Unregulated angiogenesis is seen in pathological conditions, such as the chronic inflammatory disease psoriasis,[2–4] infantile haemangiomas,[5] peptic ulcers,[6] ocular neovascularisation,[7] atherosclerosis[2,8,9] or cancer.[10]

In cancer, neoplastic cell populations can only form a clinically observable tumour if the host produces a vascular network sufficient to sustain their growth. Then, in the context of cancer, angiogenesis is the creation of a network of blood vessels that supplies tumours with essential nutrients and oxygen and removes waste products. Tumour cells located more than 100 μm away from blood vessels become hypoxic and must acquire oxygen and nutrients by diffusion. If new blood vessels do not form, tumour cells will be typically confined within 1–1.5 mm diameter.[10] Early work in the field of angiogenesis was based on a simple model in which a tumour cell would release a soluble factor that would then bind to an endothelial cell and induce endothelial cell proliferation, leading to angiogenesis. Nowadays, this model has been refined, proposing that angiogenesis is actually the outcome of the balance between stimulatory and inhibitory factors. In the tumour conditions, the angiogenic balance will be skewed towards proangiogenic factors that are primarily expressed by the transformed and hypoxic tumour cells in order to guarantee adequate nutritional supply via formation of new blood vessels. The switch from an avascular tumour to an angiogenic phenotype has been termed as the "angiogenic switch" and represents a distinct step in the multistep pathogenesis of cancer. Furthermore, new blood vessels provide tumour cells with a gateway through which to enter to circulation and metastasise; establishment and growth of metastases are influenced by proangiogenic factors.[11] Moreover, the delicate balance of these stimulatory and inhibitory angiogenic factors can be regulated by oncogenes and tumour suppressor genes.[12]

The process of angiogenesis consists of a series of linked, sequential steps that ultimately lead to the establishment of a new vascular bed. Initially, host capillaries dilate and develop increased permeability. These "leaky" vessels allow fibrin to escape from the blood pool into the interstitium, creating an extracellular matrix (ECM) that facilitates cell growth. To generate capillary sprouts, endothelial cells proliferate, migrate, degrade the basement membrane, and form a structure, that is a new lumen organisation.[13] To stimulate angiogenesis, both tumour cells and host cells secrete a variety of factors. So far, more than a dozen proangiogenic molecules have been reported, including basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF; also known as vascular permeability factor [VPF]), interleukin-8 (IL-8), angiogenin, angiotropin, platelet-derived endothelial cell growth factor (PD-ECGF), platelet-derived growth factor (PDGF), transforming growth factor-alpha (TGF-alpha), TGF-beta, epidermal growth factor (EGF), and tumour necrosis factor-alpha (TNF-alpha; Tab. 1).[14–17] Many tissues and tumours, however, also generate factors that inhibit angiogenesis. The angiogenic phenotype of a tissue or a tumour is therefore determined by the net balance between positive and negative regulators of neovascularisation.[18]

Finally, although tumours have the ability to induce new blood-vessel growth by angiogenesis, the vascular system resulting form angiogenesis

Table 1. Endogenous Proangiogenic and Antiangiogenic Factors

Proangiogenic Factors	Antiangiogenic Factors
Vascular endothelial growth factor (VEGF)	Angiostatin
Basic fibroblast growth factor (bFGF)	Endostatin
Acidic fibroblast growth factor (aFGF)	Fragment of platelet factor 4 (PP4)
Hepatocyte growth factor (HGF)	Interferon α/β
Endothelial growth factor (EGF)	Angiopoietin-2
Placenta growth factor (PGF)	Thrombospondin-1
Platelet-derived endothelial cell growth factor (PD-ECGF)	Vascular endothelial growth factor inhibitor (VEGI)
Tumour necrosis factor alpha (TNF-α)	Fibronectin fragment
Transforming growth factor alpha (TGF-α)	Restin
Transforming growth factor beta (TGF-β)	Vasostatin
Angiotropin	Derivate of prolactin
Angiogenin	Osteopontin cleavage product
Interleukin-8 (IL-8)	Proliferin-related protein (PRP)