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Antibodies for angiogenesis inhibition, vascular targeting and endothelial cell transcytosis☆

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Abstract

The endothelium is increasingly recognized as a target for biomedical intervention, not only for its accessibility to molecular agents coming from the blood-stream, but also for the active role played by endothelial cell proliferation to support diseases such as cancer, blinding ocular disorders and chronic inflammatory conditions. The notion that solid tumors cannot grow beyond a size of few millimeters without inducing the proliferation of new blood vessels has stimulated the search for mediators of angiogenesis and for inhibitors of this process, culminating in the approval of a humanized monoclonal antibody to VEGF-A for oncology applications. In parallel, researchers have begun to consider imaging and therapeutic strategies based on the selective delivery of bioactive agents to the new blood vessels, mediated by monoclonal antibody derivatives. Recently, the field of vascular targeting research has been extended to the investigation of molecular agents that may mediate endothelial cell transcytosis, in the hope to overcome this body barrier for drug delivery. This article reviews some of the most significant advances in these areas, and outlines future challenges and opportunities.

Keywords: Antibodies; Cancer; Angiogenesis; Vascular targeting; Transcytosis

Contents

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1. Angiogenesis in physiology and pathology

To grow beyond a size of a few millimeters solid tumors need to ensure their supply with oxygen and nutrients by initiating the development of new blood vessels from preexisting ones. This process called angiogenesis is a characteristic feature of most cancers and of some chronic inflammatory disorders [1].

Angiogenesis is a physiological process in embryogenesis and development. In the adult the proliferation rate of endothelial cells is usually very low compared to other cell types [2]. Exceptions are found in wound healing as well as in the endometrium and the ovaries during the proliferative phase where physiological angiogenesis takes place. Similarly, an overexuberant pathological angiogenesis is observed in a variety of disorders such as diabetic retinopathy, rheumatoid arthritis, atherosclerosis, psoriasis as well as in solid tumors and metastasis.

In tumors, cells are initially oxygenated by simple diffusion of oxygen, but when tissues grow beyond the limit of oxygen diffusion, hypoxia triggers vessel growth by signaling through hypoxia inducible transcription factors (HIFs) [3]. These factors induce the production of proangiogenic compounds like vascular endothelial growth factor (VEGF), placental growth factor (PlGF), angiopoietin (Ang)-1 and various cytokines [1].

Already in the early 1970s it was postulated by the group of Folkman that the growth of new blood vessels is essential for tumor development [4]. As a consequence, inhibition of angiogenesis would represent an avenue for blocking tumor growth, possibly circumventing the multidrug resistance problem, since the endothelial cells, which line tumor blood vessels are genetically stable, unlike tumor cells [5]. This dogma has recently been questioned [6]. Furthermore inhibition of angiogenesis is considered a highly selective