Advanced Drug Delivery Reviews 63 (2011) 640–658

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

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

Role of tumor vascular architecture in drug delivery ☆

Ajit S. Narang *, Sailesh Varia

Bristol-Myers Squibb, Co., One Squibb Dr., PO Box 191, New Brunswick, NJ 08903-0191 USA

ARTICLE INFO

Article history:
Received 10 January 2011
Accepted 5 April 2011
Available online 14 April 2011

Keywords:
Angiogenesis
Vasculature
Drug therapy
Drug delivery
Targeting

ABSTRACT

Tumor targeted drug delivery has the potential to improve cancer care by reducing non-target toxicities and increasing the efficacy of a drug. Tumor targeted delivery of a drug from the systemic circulation, however, requires a thorough understanding of tumor pathophysiology. A growing or receding (under the impact of therapy) tumor represents a dynamic environment with changes in its angiogenic status, cell mass, and extracellular matrix composition. An appreciation of the salient characteristics of tumor vascular architecture and the unique biochemical markers that may be used for targeting drug therapy is important to overcome barriers to tumor drug therapy and to facilitate targeted drug delivery. This review discusses the unique aspects of tumor vascular architecture that need to be overcome or exploited for tumor targeted drug delivery.

Contents

Abbreviations: ABC, ATP-binding cassette; ADCC, antibody-dependent cellular toxicity; APC, antigen presenting cell; bFGF, basic fibroblast growth factor; FGF-2, fibroblast growth factor-2; CRC, Cancer Research Campaign; DMXAA, 5,6-dimethylxanthenone-4-acetic acid; ECM, extra-cellular matrix; EORTC, European Organization for Research and Treatment of Cancer; EPR, enhanced permeation and retention; EGFR, epidermal growth factor receptor; FITC, fluorescein isothiocyanate; GAG, glycosaminoglycan; IFP, interstitial fluid pressure; IgG, immunoglobulin G; IV, intravenous; MDR, multi-drug resistance; MMP, matrix metalloproteinase; MRP, multidrug resistance related proteins; NCI, National Cancer Institute; NF-κB, nuclear factor-κB; PA, plasminogen activators; PEG, polyethylene glycol; PG, proteoglycan; PGP, P-glycoprotein; SCID, severe combined immunodeficient; SEM, scanning electron microscopy; TNF, tumor necrosis factor; TRAIL, TNF-related apoptosis inducing ligands; VCAM, vascular cell adhesion molecule; VEGF, vascular endothelial growth factor.

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on " Target Cell Movement in Tumor and Cardiovascular Diseases".

* Corresponding author. Tel.: +1 732 227 7351; fax: +1 732 227 3986.
E-mail addresses: ajit.narang@bms.com (A.S. Narang), sailesh.varia@bms.com (S. Varia).

0169-409X/$ – see front matter © 2011 Elsevier B.V. All rights reserved.
doi:10.1016/j.addr.2011.04.002

1. Introduction

Cancer is a leading cause of compromised quality of life, and death. The significant diversity and complexity of the molecular events in cancer have led to this being a key research area of several institutions in academia and industry, and non-profit organizations such as the National Cancer Institute (NCI) in the United States, the European Organization for Research and Treatment of Cancer (EORTC), and the British Cancer Research Campaign (CRC) [1]. Drug therapy of cancer traditionally focused on the identification of cytotoxic compounds. These drugs tend to have high dose-limiting toxicities with a narrow therapeutic window. They are often dosed close to their maximum tolerated levels [1]. Targeted drug delivery to tumor site could increase the efficacy and reduce toxicities of anticancer agents. Targeting a drug in the systemic circulation to the tumor site requires an appreciation of the pathophysiology of cancer.

Tumor results from uncontrolled proliferation of cells. This growing cell mass inherently requires metabolic substrates for nourishment and removal of metabolic end products. During the early stages of development of a spontaneous tumor, blood supply to the tumor tissue predominantly comes from the vasculature supplying the surrounding healthy tissue. As the tumor exceeds a critical mass, it must induce the development of its own blood supply to support its growth. The growth of vasculature in tumor tissue, however, is chaotic. Therefore, tumor vasculature differs from normal tissue vasculature in several aspects. The therapeutic significance of tumor vascular architecture and angiogenesis stems from the identification of biochemical events that may be modulated for cancer treatment and for targeted drug delivery to tumor sites. For example, intervessel distances and abnormal reactivity of tumor microcirculation can form the basis of therapeutic approaches, such as the use of radio-sensitizers and hyperthermia, that are based on hypoxia or proliferation gradients [2]. Although several general reviews [3–15] on tumor physiology and drug delivery are available, the role of tumor vascular architecture was last reviewed over 10 years ago [16] in a very specific area. This paper will focus on the development and salient characteristics of tumor vascular architecture, and the ways in which it facilitates and provides obstacles to tumor targeted drug delivery. In addition, the role of tumor vasculature on drug therapy and drug delivery in cancer will be discussed.

2. Tumor vasculature

Tumors are characterized by uncontrolled cellular proliferation. The increase in cell mass is usually associated with the formation of extracellular matrix (ECM). ECM is the connective tissue that provides structural support. The ECM could be differentiated into two parts—basement membrane, which anchors the cells, and the bulk of the ECM, termed the interstitial matrix. The ECM is formed of an interlocking meshwork of polysaccharides and fibrous proteins, which form a gel and provide support to the cellular mass [14]. The unbranched polysaccharides consisting of repeating disaccharide units are known as glycosaminoglycans (GAGs). The GAGs are highly viscous, negatively charged polymers. These are exemplified by hyaluronic acid, chondroitin sulfate, heparin, heparan sulfate, and keratan sulfate. Most of the GAGs are covalently linked to core proteins, forming proteoglycans (PGs), also known as mucopolysaccharides. Tumor growth requires ECM remodeling. To this end, the tumor cells frequently recruit fibroblasts, endothelial cells, smooth muscle cells, and immune cells into the ECM matrix [17]. Small tumors, less than 2 mm in diameter, are perfused by the vasculature of the surrounding host tissues [18]. Further tumor growth in restricted space results in increased metabolic tissue need and greater distancing of cells from the existing vasculature. Therefore, successful tumors establish vascular networks that grow by protrusion and outgrowth of pre-existing blood vessels—a process known as *angiogenesis*.

2.1. Angiogenesis

Neovascularization is the formation of vasculature in an avascular tissue. This process may involve angiogenesis, secondary growth of blood vessels involving the extension of pre-existing blood vessels [19], and/or recruitment of circulating endothelial progenitor cells [20]. Vascularization of tumor by angiogenesis is essential to tumor progression [21] and is mediated by diffusible growth factors such as the vascular endothelial growth factor (VEGF) [22] and the basic fibroblast growth factor (bFGF) [23].

Angiogenesis is a net result of the imbalance of interplay between diffusible pro- and anti-angiogenic molecules that are released by cancer cells and other cells, such as the endothelial cells, stromal cells,