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Nanotechnology and tumor microcirculation☆

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ABSTRACT

Though much progress has been made in the development of anti-tumor chemotherapeutic agents, refractoriness is still a major clinical difficulty because little is known about the non-autonomous mechanisms involved. Abnormal capillary structures in tumors, for example, are well documented, but a thorough characterization of microcirculation, including functional consequences with particular regard to drug delivery and intratumor accumulation, is still required for many kinds of tumor. In this review, we highlight how use of synthesized nanoparticles, themselves a product of emerging nanotechnology, are beginning to open up new perspectives in understanding the functional and therapeutic consequences of capillary structure within tumors. Furthermore, nanoparticles promise exciting new clinical applications. We also stress the urgent necessity of developing clinically relevant tumor models, both in vivo and in vitro.

Contents

1. Introduction

A major difficulty for patients with inoperable tumors and those treating them is disease resistance to chemotherapy. The reasons for this refractoriness have been studied in various ways including tumor cell-autonomous mechanisms, chemosensitivity and/or chemoresistance [1], higher metastatic tendency [2,3], and intratumor heterogeneity including stemness [4,5]. Another promising approach has been to analyze what surrounds tumor cells, or the tumor microenvironment [6,7]. This microenvironment has several major components including fibrotic tissue, various immune cells and, most important of all to this paper, tumor capillaries. This review will focus on the delivery of nano-sized drugs (which we will refer to as "nanoparticles") and the structure of tumor capillaries, or microcirculation within a tumor.

Microcirculation is the key peripheral system involved in delivering and distributing oxygen, nutrition, and drugs to the whole body. As with normal organs, diseased loci have microcirculation. Judah Folkman [8] was the first person to recognize this in 1971, and thereafter capillaries in tumors have been studied extensively [6,7,9]. Tumors induce the formation of capillaries, in a process now known as angiogenesis, via secretion of growth factors such as vascular endothelial growth factor (VEGF) [10], in connection with tumor hypoxia [11,12]. Capillaries formed in tumor angiogenesis are both leaky and disorganized (Fig. 1) [13]. VEGF signaling is thought to be one of the principal causes of leakiness and capillary disorganization [14]. And VEGF was first identified as

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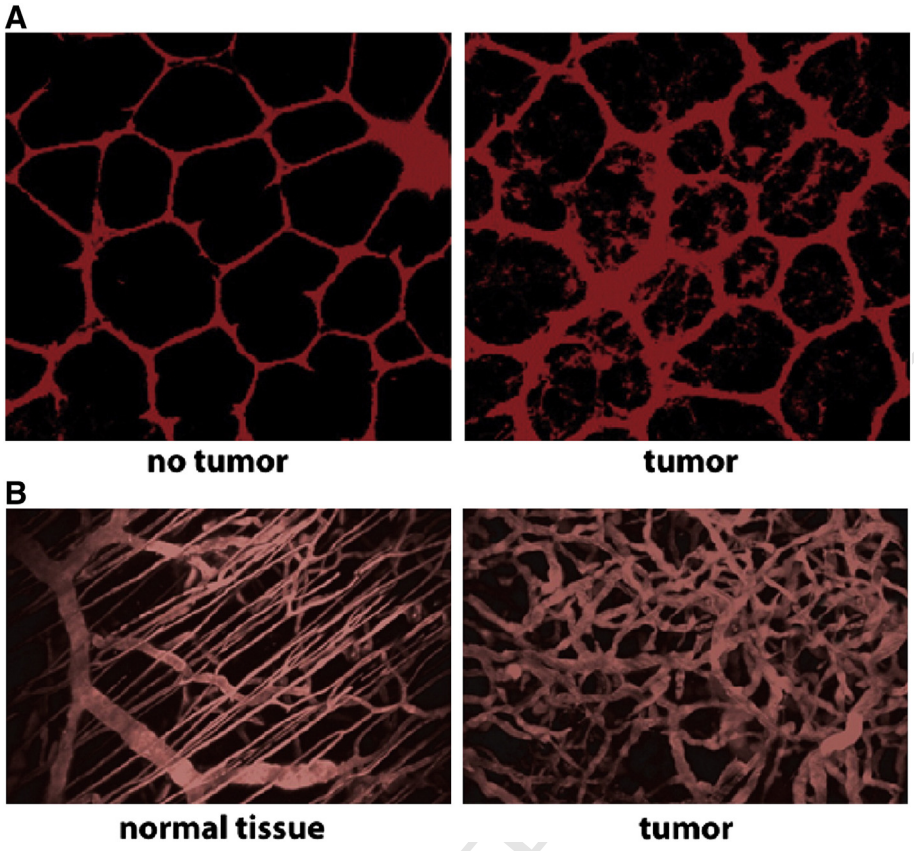

Fig. 1. Tumor capillary. (A) Distribution of injected dextran illustrates the leakiness of tumor capillaries compared to normal capillaries. (B) Intravital imaging of capillaries in normal tissue and tumors. Capillaries in tumors are disorganized compared to those in normal tissue.
From [38], Figs. 13.15 and 13.34.

a "vascular permeability factor (VPF)" [15]. Therefore inhibition of VEGF signaling has become a target for inhibition of tumor growth. Bevacizumab, for example, is licensed to treat various cancers via inhibition of VEGF-A [16]. Although Bevacizumab was designed to act on its own, clinical studies have shown its adjuvant capacity to enhance the effects of other chemotherapeutic agents [17]. This works as part of the vascular normalization theory [18] in which antiangiogenic agents temporarily "normalize" both structure and function of tumor vasculature and make more efficient the delivery of oxygen and therapeutic drugs. We know little, however, about this temporary normalization process and nanoparticle delivery.

Use of synthesized nanoparticles in biomedicine can offer exciting new perspectives, just as past technological innovations have done [19]. First, the discovery of microcirculation, invisible to the naked eye, by Marcello Malpighi in 1661 [20] was made possible by utilizing the new microscope invented by Galileo Galilei and others around 1600. Furthermore, the cellular wall surrounding microcirculation was also discovered using new technology. Application of chemical dyes invented during the 19th century made it possible for Theodor Schwann to discover the cells surrounding the capillary lumen in 1839 [21]. However, the first modern anatomical studies of the human body, its organs and systems began in the Renaissance with Andreas Vesalius and publication of *De Humani Corporis Fabrica* (1543) [22]. And it was William Harvey (1578–1657) who experimentally proved in 1628 the circulation of blood in men and animals: *Exercitatio de motu cordis et sanguinis in animalibus* [23].

In this review and in others in this series, we will explore how new technologies, especially nanotechnology, can open up new viewpoints in biomedicine.

2. Nanoparticles and tumor microcirculation

2.1. Structure of tumor microcirculation and distribution of nanoparticles in tumor tissue

Nanoparticles already in clinical use are known to be effective for a number of tumor types — at least in animal studies. However, most nanoparticles are clinically approved for only a few types of tumors. For example, Doxil, or PEGylated liposome incorporating Doxorubicin, shows potential in animal models of colon cancer [24] but have been approved by the FDA only for Kaposi's sarcoma, recurrent ovarian cancer and for multiple myeloma (MM), although only in combination with Bortezomib for MM [25]. It is not yet licensed for colon cancer. Since there may be a discrepancy between preclinical and clinical results it is important to have reliable preclinical models to predict the effects of use in humans. A common model of colon cancer uses CT26 murine colon cancer cells. And preclinical tests of Doxil have been done using the same cell line [24].

As a model nanoparticle, large molecular weight dextran is commonly used since estimated hydrodynamic diameter of 2,000,000 (2M) Da dextran is 50 nm [26]. However, dextran of 70,000 (70k) Da, with an estimated hydrodynamic diameter of 15 nm, is more commonly used in experiments perhaps because it has the same molecular weight as the albumin molecule [26]. Dextran of various molecular weights is already used clinically as a plasma volume expander. We previously examined the extravasation of 2M Da dextran in the CT26 murine colon model and found that a certain amount of the molecule extravasated [27]. This observation confirmed the results of preclinical tests with nanoparticles such as Doxil [24]. The observation was also

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