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Human pathological basis of blood vessels and stromal tissue for nanotechnology ☆

Hiroshi Nishihara *

Department of Translational Pathology, Hokkaido University, Graduate School of Medicine, N15W7, Kita-ku, Sapporo 060-8638, Japan

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ABSTRACT

The recent development of nanotechnology has already produced clinically applicable "nanodrugs," which are largely dependent on a novel concept for the drug delivery system. Thus the elucidation of local pharmacokinetics of nanodrugs is indispensable for the further development of nanomedicine; however, the detailed pathophysiology associated with nano-sized materials especially in pathologic lesions has not been well-described. In this review article, the microscopic appearance of vascular pericytes in addition to endothelial cells is discussed in the normal state and also in several pathological conditions which could be the major targets for nanomedicine. Moreover, the role of stromal tissue including myofibroblasts is also focused on, as well as inflammatory cells. Finally, the significance of disease-specific tissue structure in the establishment of personalized nanomedicine is discussed.

Contents

1. Introduction

The promising efficacy of nanomedicine is highly prescribed by the permeability and retention of nanodrugs within the target lesion, which is described as the enhanced permeability and retention (EPR) effect especially in solid tumor [1,2]. Most of the nanodrugs are delivered via blood flow, i.e. through blood vessels; therefore, the role of vasculatures in normal tissue as well as in pathologic lesions has been well-characterized including morphological abnormalities such as fenestration or defect of endothelial cells in solid tumor [3–5]. In addition, the involvement of vascular pericytes in the permeation of

Abbreviations: EPR, enhanced permeability and retention; CAFs, cancer associated fibroblasts; TAMs, tumor-associated macrophages; PDGFRβ, platelet-derived growth factor receptor beta; αSMA, alpha smooth muscle actin; TGFβ, transforming growth factor beta; 5-FU, 5-fluorouracil; VEGF, vascular endothelial growth factor; HGF, hepatocyte growth factor; TNF-α, tumor necrosis factor alpha; iNOS, inducible nitric oxide synthase; MHC, major histocompatibility complex; LDL, low-density lipoprotein.

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* Tel.: +81 11 706 5053; fax: +81 11 706 5902.
E-mail address: hnishihara@med.hokudai.ac.jp.

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nanoparticles was recently reported [6]. However, detailed pathological observation of vascular elements in view of nanodrug-associated pathophysiology is still lacking, especially in human tissue.

In recent cancer research, the significance of a non-vascular microenvironment which consists of non-cancer cells such as cancer associated fibroblasts (CAFs) or tumor-associated macrophages (TAMs) has been recognized as a major factor for cancer promotion [7]. These stromal components could be possible players to modulate pharmacokinetics not only for small molecules but also for nanodrugs, because the stromal cells are usually located between the blood vessels and the pharmacological targets such as cancer cells. However, the pathophysiological approach for non-vascular stromal cells in nanomedicine has been insufficiently discussed.

This review summarizes and discusses the microscopic appearance of histological components, especially the blood vessels and stromal cells, in normal and major pathological conditions. Such aspects will give us idea regarding how to establish the tissue-type specific personalized nanomedicine.

2. Histopathology of blood vessels

Intravenously injected nanodrugs will be delivered via blood flow into the pathological lesion through arterioles (20 to 100 μm in diameter), and released from capillaries (7 to 8 μm), not from arteries or veins except in hemorrhagic conditions; thus, the principal vasculature for nanomedicine must be such smaller vessels, and the major players here are vascular endothelial cells and pericytes. The basic structure of arterioles and capillaries is shown in Fig. 1. Arterioles consist of endothelial cells, vascular smooth muscle cells and adventitia as well as larger muscular arteries, while capillaries lined by endothelial cells are supported on the outside by pericytes embedded in a thin basement membrane [8,9].

2.1. Endothelial cells

The entire vascular system is lined internally by a single layer of spindle-shaped endothelial cells. In human tissue, these cells can be identified immunohistochemically with antibodies against CD31, CD34 and factor VIII-related antigen (Fig. 2A, C) [9]. Their structural integrity is fundamental to maintain vessel wall homeostasis and permeability. Endothelial cells form junctional complexes by tight, adherens or gap junctions[10]. Claudin family proteins within tight junctions create the barrier and regulate electrical resistance between cells (Fig. 2B, D) [11,12]. Adherens junctions regulate permeability to soluble molecules and have a role in contact inhibition. Gap junctions consisting of connexin family proteins form channels between adjacent cells [13]. In association with nanodrug delivery, endothelial cells (1) serve as a semipermeable membrane, controlling the transfer of small and large molecules through the walls of arterioles and capillaries; (2) modulate vascular tone and blood flow which directly affect the accumulation of nanodrugs; (3) regulate inflammatory response controlling leukocyte interactions with vessel walls; and (4) modify lipoproteins such as oxidized LDL causing endothelial dysfunction in the artery wall [9].

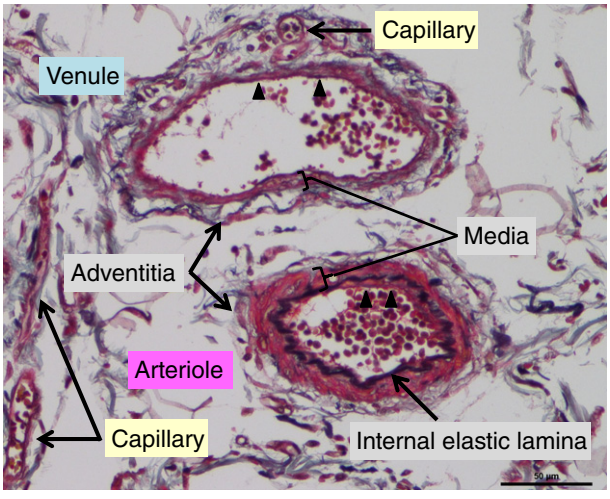

Fig. 1. Basic structure of blood vessels. Elastica–Masson staining of human duodenum is shown. The arteriole and venule consist of intima (arrow head), media and adventitia. Intimal elastic lamina can be identified in arteriole, while it is often ambiguous in venule. Arteriole consists of thick vascular smooth muscle layer (media), while media in venule are thin and often discontinuous. The capillary is composed of thin layer of mural cell. It is hard to identify endothelial cells by Elastica–Masson stain or Hematoxylin and Eosin stain in capillaries or even larger vessels. Scale bar is 50 μm.

2.2. Pericytes

Historically, pericytes were discovered and originally describe more than 100 years ago by scientists who were interested in the nature of capillary contractility [10]. The basic definition of mature pericytes as a mural cell embedded within the vascular basement membrane was made by electron microscopic observation in capillaries [10], although the term pericyte is frequently adopted to denote any microvascular periendothelial mesenchymal cells including vascular smooth muscle cells [11]. Currently, no pericyte-specific molecular markers have yet been identified, while several molecules expressed in murine pericytes, such as NG2, PDGFRβ and RGS-5, have been reported [11]. In general human pathology, the term pericyte is scarcely described, while the vascular smooth muscle cells have been well characterized [9], and established immunohistochemical markers for pericytes are limited. As shown in Fig. 2, αSMA, which is most reliable immunohistochemical marker for vascular smooth muscle cell (Fig. 2E), is also expressed in pericyte in capillary, while discontinuous or defective staining pattern is often observed (Fig. 2G). Anti-PDGFRβ antibody is another attractive candidate to identify pericytes in capillary, although myofibroblast adjacent to pericyte is also positive for PDGFRβ (Fig. 2H). In addition, mural cells in precapillary arteriole are positive for both PDGFRβ and αSMA (Fig. 2), thus it is hard to distinguish pericytes from vascular smooth muscle cells by immunohistochemistry. In human specimen, desmin is negative in vascular mural cells except in large muscular artery (Fig. 2F).

2.3. Pathologic condition of blood vessels

In diagnostic pathology, the alteration of vasculature in number and morphology is often recognized as a disease-specific phenomenon. In this section, the representative appearance of vascular alteration in cancerous tissue and inflammatory tissue including infectious diseases, which are major target diseases for nanomedicine, is presented.

2.3.1. Cancer

The EPR effect is now the central dogma for anticancer drug design using nanotechnology [1], which is based on the unique anatomical–pathophysiological nature of tumor blood vessels that facilitates transport of macromolecules into tumor tissues. Molecules larger than 40 kDa such as nanodrugs are selectively leaked out from tumor vessels, but not from normal vasculatures [14–18]; therefore, it is essential to comprehend the vascularity and the structure of tumor blood vessels in target cancerous lesion for nanomedicine. In practical surgical pathology, however, the morphological appearance and the number of vasculatures vary according to the organ or histological subtypes of tumor. In fact, even within the same histological subtype of "adenocarcinoma," the majority of ovarian cancer and colon cancer belong to the category of hypervascular tumor, while the scirrhous type of gastric cancer and pancreas cancer is usually categorized into hypovascular tumor. More importantly, the structure of tumor vasculature appears to be different according to each tissue. The αSMA-positive mural cells were discontinuously observed in tumor vessels of ovarian and colonic

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