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Tumor microvasculature and microenvironment: Targets for anti-angiogenesis and normalization

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Abstract

A solid tumor forms an organ-like entity comprised of neoplastic cells and non-transformed host stromal cells embedded in an extracellular matrix. Similar to normal tissues, blood vessels nourish cells residing in tumors. However, unlike normal blood vessels, tumor vasculature has abnormal organization, structure, and function. Tumor vessels are leaky and blood flow is heterogeneous and often compromised. Vascular hyperpermeability and the lack of functional lymphatic vessels inside tumors cause elevation of interstitial fluid pressure in solid tumors. Each of these abnormalities forms a physiological barrier to the delivery of therapeutic agents to tumors. Furthermore, elevated tumor interstitial fluid pressure increases fluid flow from the tumor margin into the peri-tumor area and may facilitate peri-tumor lymphatic hyperplasia and metastasis. Abnormal microcirculation in tumors also leads to a hostile microenvironment characterized by hypoxia and acidosis, which hinder the effectiveness of anti-tumor treatments such as radiation therapy and chemotherapy. In addition, host–tumor interactions regulate expression of pro- and anti-angiogenic factors and hence contribute to their imbalance and resulting pathophysiological characteristics of the tumor. Restoration of pro- and anti-angiogenic balance in tumors may "normalize" tumor vasculature and thus improve its function. Indeed, anti-angiogenic treatments directly targeting angiogenic signaling pathways as well as indirectly modulating angiogenesis show normalization of tumor vasculature and microenvironment at least transiently in both preclinical and clinical settings. Combination of cytotoxic therapy and anti-angiogenic treatment during the vascular normalization exhibits synergistic effect.

Keywords: Angiogenesis; Lymphangiogenesis; Tumor; Stromal cells; Vascular endothelial growth factor; Microenvironment; Hypoxia; Acidosis; Interstitial fluid pressure; Metastasis

Contents

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Since solid tumors require angiogenesis for their growth and metastasis, anti-angiogenic therapy has been extensively studied in both preclinical and clinical settings (Folkman, 2000). While these anti-angiogenic drugs have been approved for cancer treatment, it appears that clinical application of anti-angiogenic therapy is more complex than originally thought (Jain et al., 2006). The mechanisms of action of anti-angiogenic therapy are yet to be sorted out. Therefore, it is important to understand the biology of the tumor vasculature —the target of anti-angiogenic therapy. Tumor vasculature is not a simple supply line of nutrients to tumors. It governs pathophysiology of solid tumors and thus, tumor growth, invasion, metastasis, and response to various therapies. In this review, we will discuss the structure and function of tumor vasculature, the resulting abnormal microenvironment, causes and consequences of these abnormalities, regulation of angiogenic factor expression by host–tumor interactions, and potential normalization of these abnormalities by anti-angiogenic therapy.

Pathophysiological characteristics of solid tumors

Abnormal blood vessel architecture and function in tumors

The normal microvessels consist of arterioles, capillaries, and venules, and form a well-organized, regulated, and functional architecture (Fig. 1A) (Jain, 2003). In contrast, tumor vessels are dilated, saccular, tortuous, and heterogeneous in their spatial distribution (Fig. 1A) (Jain, 1988). Normal vasculature is characterized by dichotomous branching, but tumor vasculature is unorganized and has trifurcations and branches with uneven diameters. Vessel wall structure is also abnormal in tumors (Chang et al., 2000; di Tomaso et al., 2005; McDonald and Choyke, 2003). Large inter-endothelial junctions, increased numbers of fenestrations, vesicles, and vesico-vacuolar channels, and a lack of normal basement membrane are often found in tumor vessels (Dvorak et al., 2002; Winkler et al., 2004). Perivascular cells have abnormal morphology and heterogeneous association with tumor vessels. The molecular mechanisms causing these abnormal vascular architectures are not well understood, but the imbalance of pro- and anti-angiogenic factors is considered to be a key contributor (Jain, 2005). Solid (mechanical) stress generated by proliferating tumor cells also compresses vessels in tumors (Padera et al., 2004; Roose et al., 2003). The combination of both molecular and mechanical factors may render the tumor vasculature abnormal.

Extravasation of molecules from the bloodstream occurs by diffusion, convection, and, to some extent, by transcytosis in an exchange vessel. Diffusion is considered to be the major form of transvascular transport in tumors (Jain, 1987). The diffusive permeability of a molecule depends on its size, shape, charge, and flexibility as well as the transvascular transport pathway. In agreement with the above-mentioned ultrastructural alterations in the tumor vessel wall, vascular permeability in solid tumors is generally higher than that in various normal tissues (Fig. 1B).

Arterio-venous pressure difference and flow resistance govern blood flow in a vascular network. Flow resistance is a function of geometric (vascular architecture) and viscous (blood viscosity, rheology) resistances. Abnormalities in both vasculature and viscosity increase the resistance to blood flow in tumors (Jain, 1988). Focal leaks, which often exist in some of the tumor vessels, may also compromise the downstream blood flow. As a result, overall perfusion rates (blood flow rate per unit volume) in tumors are lower than in many normal tissues and the average RBC velocity in tumor vessels can be an order of magnitude lower than in normal vessels (Fig. 1C). Unlike normal vessels, RBC velocity is independent of the diameter of tumor vessels. Furthermore, tumor blood flow is unevenly distributed, fluctuates with time, and can even reverse its direction in some vessels—therefore regions with poor perfusion, or none at all, are commonly seen. The heterogeneity of tumor blood flow causes abnormal microenvironment in tumors and hinders the delivery and efficacy of therapeutic agents to tumors.

Interstitial hypertension and abnormal lymphatics in tumors

Both animal and human tumors exhibit interstitial hypertension while the interstitial fluid pressure (IFP) in normal tissues is around zero mm Hg (Fukumura and Jain, in press; Jain et al., 2007). The abnormal structure and function of blood and lymphatic vessels in tumors cause the IFP elevation. Tumor vessels lack perm selectivity due to the high vascular permeability. As a result, the hydrostatic and oncotic (colloid osmotic) pressures become almost equal between the intravascular and extravascular spaces (Boucher and Jain, 1992; Tong et al., 2004). In fact, tumor IFP equivalently increases or decreases in ~10 s after the modification of microvascular pressure (Netti et al., 1995). Reduced transmural pressure gradients decrease convection across tumor vessel walls. Furthermore, IFP is uniformly high throughout a tumor and drops precipitously in the tumor margin (Boucher et al., 1990). Fluid convection or bulk flow is negligible inside tumors due to the lack of interstitial pressure gradients. Thus, the uniformly elevated IFP compromises the delivery of therapeutic agents both across the blood vessel wall and interstitum in tumors. Furthermore, transmural coupling between IFP and microvascular pressure due to the high permeability of tumor vessels can abolish pressure difference between up and down stream of tumor blood vessels