Functional characterization of the microcirculation in tumors

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Summary

This review describes some aspects of tumor vessels and the influence of vasoactive agents on tumor blood flow, particularly the characteristic microcirculation of tumors with regard to its selective increase in blood flow. Elevation of blood pressure by infusion of angiotensin II produced a severalfold increase in tumor blood flow. The increase was selective and specific to the tumor vessels as long as the mean arterial blood pressure was kept under 150 mm Hg. Pressure elevation by angiotensin II also selectively increased tumor oxygen tension and influx of lymph flow from the primary transplanted lesion to the lymph node metastatic lesion. Newly devised techniques for analyzing microhemodynamics of tumor vessels showed that the velocity of tumor blood flow, the vascular area in tumor tissue, and the hydrostatic pressure difference between the tumor vessel and extravascular tissue were markedly enhanced. Thus, the extravasation of material into tumor tissues can be increased by the enhancement of blood flow. This demonstration allowed the development of a new approach to cancer chemotherapy, in which the delivery to tumor tissue of systemically administered anticancer drugs can be selectively enhanced.

Introduction

For solid tumors to proliferate beyond a certain size, tumor blood vessels are indispensable (1–3). Many studies on vessel formation and morphology have been reported, and will not be reviewed here. If the circulatory functions in tumor vessels however, could be analyzed and understood, they could be utilized very effectively for diagnosis of and therapy for cancer. It would be especially important to elucidate the functional characteristics of tumor blood vessels that are entirely different from those of the microcirculation prevalent in normal tissues. In this review, we describe some aspects of tumor vessels and their functional characteristics in the microcirculation of tumors, particularly with regard to selective enhancement of tumor blood flow (4–13). We also briefly outline a new approach (8, 14–16) to cancer chemotherapy, i.e., induced hypertension chemotherapy with angiotensin II. This approach is based on the finding that delivery to tumor tissue of systemically administered anticancer drugs can be selectively enhanced without any increase in drug delivery to normal tissues.

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Some aspects of tumor vessels

In experiments on transplanted tumors, Ide et al (17) and Algire et al (18) observed new vascular formation from the host to the tumor, and this observation prompted many active studies on tumor angiogenesis. The new vessels were presumed to have been formed by extracellular humoral substances made of cancer cells (19). Folkman and his co-workers (20-22) confirmed that extracts of tumor cells can also promote neovascularization, and they named the diffusable agent inducing this phenomenon 'tumor angiogenesis factor'. Recently, however, other factors, such as prostaglandins, have been shown to induce a strong angiogenic response (23).

Tumor vessels arise from preexisting microcirculatory systems by endothelial sprouting (24-29). Gradual changes also occur in preexisting arterioles and venules in the zone where tumor cells proliferate. In the course of this development, the density and shape of tumor vessels change remarkably. The existing arterioles and venules deform and expand into vessels that supply the growing tumors. For a detailed review of the process of tumor vascularization, the reader is referred to a paper by Yamaura and Sato (24).

Unlike the vessels of inflammatory granulation tissues, tumor vessels are characterized by a steady progression to necrosis without any intervening stable maturation phase. The permeability of tumor vessels also changes during the various stages of neovascularization, and the tumor tissue in which the various stages of blood vessels coexist is not uniform in either its functional or morphological aspects (5, 24, 30-33). This inhomogeneity must be taken into account when analytical studies of tumor blood flow, drug concentration, permeability of vessels, and PO₂ are performed.

The basic unit of blood vessels and tumor parenchyma has been termed by Thomlinson and Gray (34) as the ‘tumor cord’, i.e., tumors have cylindrical proliferation cores with radii of 150 μm around vessels. This concept is based upon the fact that the diffusion radius of oxygen from tumor vessels is about 150 μm. However, the tumor cords are only observed around the vessels in the terminal stage; they are not seen in highly proliferative parts of the tumor, which have high vessel density.

Morphological features of tumor blood vessels are fully described by Warren (35). Tumor vessels have been found to be immature, lacking adrenergic nerves and smooth muscles in the vessel walls (36). In subcutaneously transplanted rat ascites hepatoma AH109A, we observed that the structure of tumor vessels, as a rule, consisted of a layer of endothelial cells, many layers of basement membranes, and pericytes. We rarely observed contractile elements and neural junctions, and those we did observe were considered to be the remains of normal vessels.

Functional characteristics of tumor vessels that selectively increase tumor blood flow

The literature contains many reports on the influence of vasoactive drugs on tumor blood flow. The variable responses of tumor vessels to vasoactive drugs have been documented (37-52). Many studies report that the response of tumor vessels to vasoconstrictors does not differ from that of normal tissues. Mattson and Peterson (51) stated in a review on the influence of vasoactive drugs on tumor blood flow that ‘reports could be found of both increased, normal, or decreased sensitivity to vasoactive drugs in the tumor microvascular bed’ and that ‘great caution is needed in comparing the results of different studies using different techniques for blood flow recording in different tumors’. They came to the conclusion that ‘the tumor vascular bed is normally in a state close to maximal dilatation, in which it is rather resistant to further pharmacological dilatation, but on the other hand sensitive to vasoconstricting drugs’ (51).

However, tumor vessels may be considered passive vascular beds that are not directly responsive to vasoactive agents, but rather are influenced secondarily by the response of the host vessel (8). A few reports have shown improved tumor blood flow following the systemic administration of vasoactive agents such as acetyl-β-methylcholine (38) and verapamil (50), but little is known about possible ways to selectively and markedly increase blood flow in malignant tissue.