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MINIREVIEW

Tumor Sinuses – Vascular Channels

Facts and fictions

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The existence of tumor cell-lined sinuses (vascular channels) in various experimental and human cancer is known for almost a half a century described by a Hungarian pathologist, Béla Kellner. Meanwhile, even the existence as well as the pathomechanism and the possible functional significance of these sinuses are heavily challenged in the recent literature. Ultrastructural studies however provide evidence for the presence of tumor cell-lined sinuses in human melanoma and breast cancer. The generation of such sinuses can be suggested in two ways: by *de novo* formation, when tumor cells recapitulate an embryonic geno- and phenotype by reexpressing endothelial genes or by a secondary mechanism, where the incorporated microvessels degenerate due to the predominant expression of anti-angiogenic factors. Literature data are available for the potential diagnostic and clinical significance of the tumor sinuses (vascular channels) stimulating further studies on this issue. (Pathology Oncology Research Vol 6, No 2, 83–86, 2000)

Keywords: tumor sinus, vascular channel, melanoma, breast cancer, pathomechanism

Introduction

Tumor-induced neoangiogenesis is the hallmark of malignant tumors without which solid tissue cannot grow beyond 1–2 mm^3 and which also promotes dissemination.[1,2] The genetic background of the "angiogenic switch" during tumor progression is not fully understood, but recent discoveries of the main angiogenic factors, VEGF, bFGF, PDGF, suggest that the switch is able to turn on the expression of the genes of these factors in tumors. Later studies identified several anti-angiogenic factors as well,[3] suggesting that the "angiogenic switch" might also control the expression of these factors. Neoangiogenesis therefore means the predominance of pro-angiogenic over anti-angiogenic machineries in tumors.

Recently, a new form of tumor vascularization was suggested based on the findings that tumor cells themselves are able to form channels in vitro and the existence of such tumor sinuses was suggested in vivo in human melanomas.[4,5] Furthermore, the genetic background of such channel formation was also discovered: tumor cells can ectopically express endothelial-specific genes such as TIE1, uPA, HGF/c-met, by recapitulating an embryonic geno- and phenotype.[4-6]

This idea was sharply criticized in the literature questioning convincing ultrastructural evidence of such sinuses in tumors[7] as well as their significance and function.[8] This summary intends to briefly review the field, providing some unquoted references and a small piece of new data on the topic.

Facts

The discovery of the existence of tumor cell-lined sinuses (vascular channels) in human tumors has its history in the literature. The first report suggesting the existence of such red blood cell-containing tumoral sinuses is dated back to 1941, when a Hungarian pathologist, Béla Kellner, described them based on light microscopic studies of various cancer types (primarily sarcomas).[9] Since then in almost each decade papers re-discover the presence of

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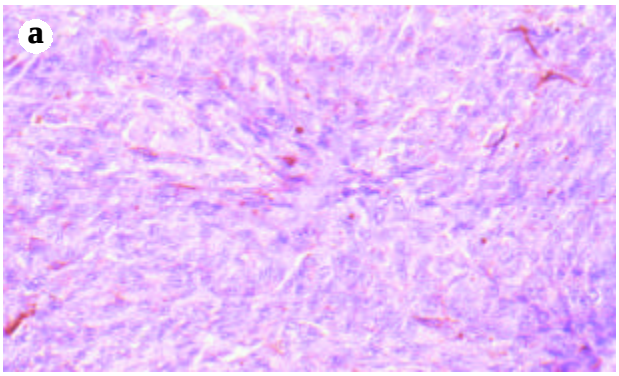
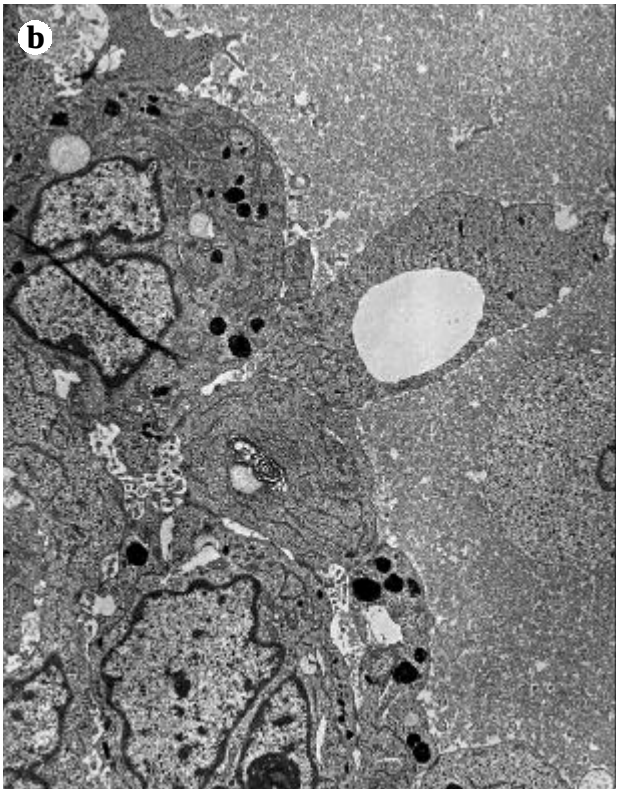
such sinuses in experimental as well as human cancer.[10-13] The recent critique, that there is no convincing electron microscopic proof for the existence of such sinuses is challenged by a paper from 1979.[11] We have analyzed several human uveal melanomas by electron microscopy and were able to identify without difficulty melanoma cell-lined intratumoral sinuses (*Figure 1*). Furthermore, in primary and metastatic breast cancer tissue, such sinuses can be readily found both by light and electron microscopy (*Figure 2*). Accordingly, the existence of tumor sinuses in human cancer is unquestionable.





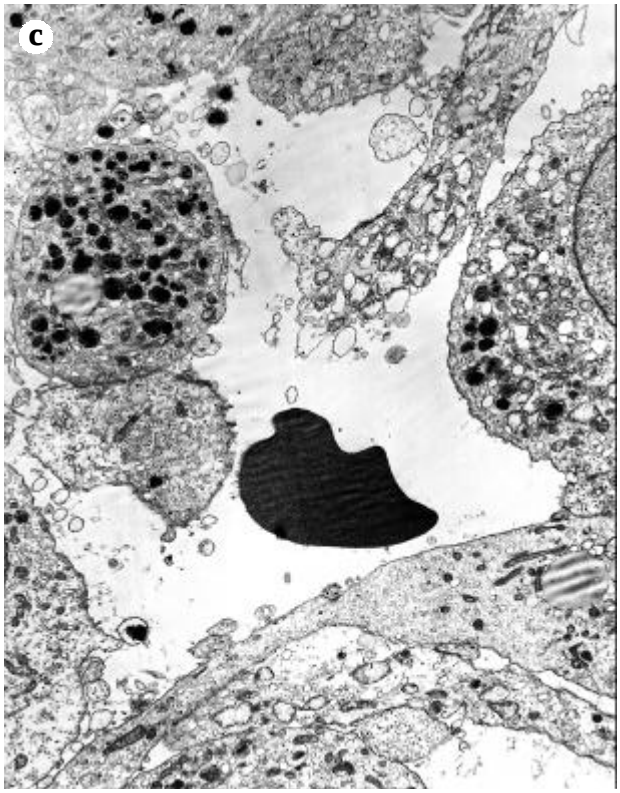


Figure 1. Tumor sinuses (vascular channels) in human uveal melanoma samples. a) Tumor sinus in uveal melanoma. Light microscopy, H&E staining. b) Transmission electron microscopy of the inner wall of a tumor sinus in the same tumor as on ure 1a. Note the melanosome-containing tumor cells (arrow) lining the channel. Bar: 1 μm. c) Transmission electron microscopy of a tumor sinus in a hypoxic area of an uveal melanoma. Note the presence of red blood cell in the lumen. Bar: 1 μm

Fictions

In the meantime, the mechanism of the formation of tumor sinuses is a challenging issue. Maniotis et al.[4] and Folberg et al.[5] suggested de novo formation of these structures due to the re-expression of "endothelial genes" in tumor cells, called embryonic swith. This mechanism suggests that tumor cells can form channels, which are connected accidentally to the existing intratumoral microvessels in an undiscovered manner. However, there are other theoretical pathways, which may lead to the formation of such sinuses. It is an alternative mechanism for the blood supply of malignant tumors when the growing tumor tissue incorporates the preexisting host vessels, called "cooption".[2,14-18] It was demonstrated that such tumors produce pro- and anti-angiogenic factors, the balance of which fundamentally influencing both the angiogenetic process as well as the remodeling of the coopted vasculature. It was observed that the predominance of anti-angiogenic factors (such as Ang-2) in the center of the tumors results in degeneration and apoptotic death of endothelial cells of the incorporated vessels[16,18] which can lead to the formation of sinuses lined by tumor cells and still containing red blood cells. These channels theoretically might maintain their

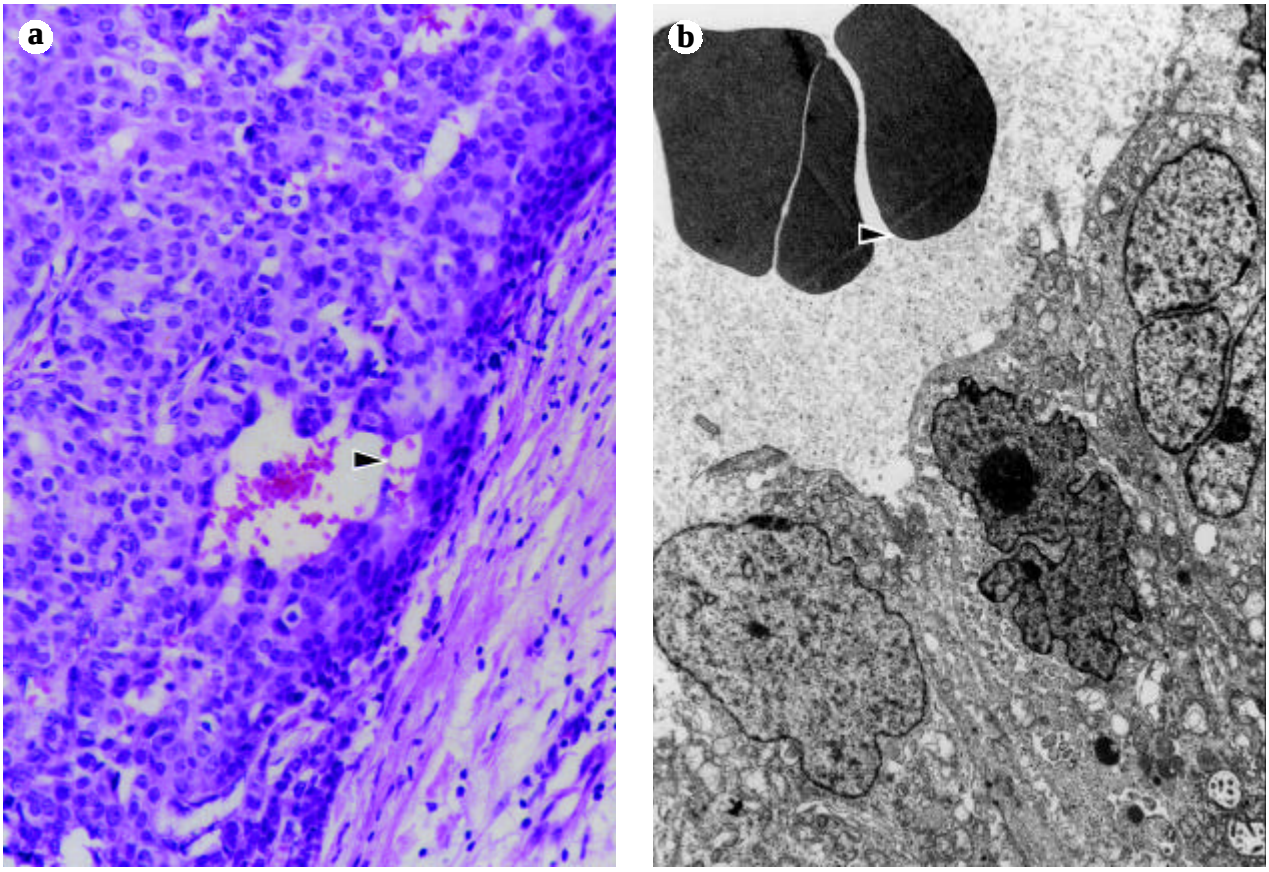


Figure 2. Tumor sinuses in human breast cancer. a) Light microscopy of a primary breast cancer containing tumor sinuses (arrow). b) Electron microscopy of metastatic breast cancer containing tumor sinus (arrow).

connections to the "surviving" intratumoral microvessels by the preexisting subendothelial matrix network.

The recent debate over the existence of vascular channels in tumors questioned also their function and significance.[7,8] Studies on the tumor sinuses suggested that they contain red blood cells and platelets but did not provide direct evidence for the morphologic connection to the intratumoral vessels. If such a connection exists, tumor cells lining such sinuses can get an easy access to the microcirculation (the primary event of the hematogenous spread) without the struggle of the complex process of intravasation. On the other hand, such connections might also promote survival of the poorly vascularized areas in a given tumor.

The identification of tumor sinuses can have significance in another area of cancer biology. In case of uveal melanomas, unique patterns of intratumoral sinuses provide additional data to assess the progression potential of this tumor type. Clinical data on this issue are already available from the literature.[19,20,4] It is another aspect of the tumor sinuses and the discovery of the occurrence of the endothelial phenotype of malignant tumor cells, that these could form potential targets for the newly discovered anti-angiogenic therapies.[21]

The repeated discovery of the existence of tumor sinuses in human cancer in the past decades indicates that such structures exist, however, these studies failed to go beyond the phenomenon to solve their function(s). Recent finding of the ectopic expression of endothelial genes in tumor cells added new turn to this old story, but did not lead us closer to the functional significance. Further systematic studies on tumor sinuses as well as on the geno- and phenotype of tumor cells are necessary to solve the mystery of such channels and to reveal their clinical and/or pathological significance.

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