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Dissertations-Kurzfassung

Characterization of tumor endothelium in a murine model of hepatocellular carcinoma and in hepatic melanoma metastasis

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Hepatocellular carcinoma (HCC) is one of few tumors that benefits from treatment with anti-angiogenic therapy. Nonetheless the mechanisms and characteristics of angiogenesis in HCC are not well known. The liver has a unique vascular bed that is characterized by a very high vascular density; it is mostly composed of specialized sinusoidal endothelial cells (LSECs). LSECs are fenestrated endothelial cells that lack a basal membrane. Functionally, LSEC serve the clearance of noxious blood factors from the circulation and regulate portal blood pressure. In HCC, it is an open question whether tumor vascularisation is due to vessel cooption or de novo angiogenesis. While LSEC features would rather be expected to be maintained in vessel cooption, tumor angiogenesis might be accompanied by endothelial transdifferentiation. In hepatic metastasis, the most common malignant tumor of the liver, tumor vascularisation is also not well characterized and it is unclear whether the process is similar compared to vascularization in HCC.

Here, tumor endothelium (TEC) of murine primary hepatocellular carcinoma (HCC AST-model) and of hepatic melanoma metastasis (B16) was analyzed by comparison with healthy LSECs in situ. Known LSEC marker genes (Stabilin-1, Stabilin-2, CD32b, Lyve-1) as well as a general EC marker gene (CD31) and a novel Type-I Transmembrane-Protein (Leda-1) were investigated by immunofluorescence and immunohistochemistry.

LSEC marker genes Stabilin-2, CD32b and Lyve-1 were almost absent in TEC in murine HCC in comparison to normal LSEC. Stabilin-1 was still present, but strongly reduced in TEC. In contrast, Leda-1 and CD31 were found to be expressed on LSEC as well as TEC. In hepatic melanoma metastasis, the majority of TEC strongly expressed CD31, but they were negative for Lyve-1, Stabilin-1 and Stabilin-2. However, some Stabilin-2 or Lyve-1 positive vessels were found in the tumor vasculature of hepatic melanoma metastasis in contrast to HCC.

Thus, TEC of hepatocellular carcinoma display a markedly different expression pattern in comparison to LSEC indicating loss of LSEC features and gain of normal blood vascular marker proteins, a process called capillarization of LSEC. Because of the marked transdifferentiation of LSEC during this process, HCC vascularisation may be rather due to neoangiogenesis than vessel cooption. If this phenotypic transdifferentiation could be confirmed in other models of HCC and in the human system, Stabilin-1, Stabilin-2, CD32b and Lyve-1 might be used as early and sensitive markers of capillarization and tumor vascularization in HCC. The heterogeneity of TEC in hepatic melanoma metastasis implies that metastatic tumours might be able to use both mechanisms of tumor vascularization in the liver, i.e. co-option of exisiting vessels as well as neoangiogenesis likely mediated by complex interactions of the tumor-associated- and liver-microenvironment with endothelial cells and other associated cells.