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ORIGINAL ARTICLE

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Immunohistochemical patterns of human liver sinusoids under different conditions of pathologic perfusion

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Abstract This study reports the effects of altered hepatic perfusion on the sinusoidal bed and the phenotypic characteristics of sinusoidal endothelial cells (SECs). Sinusoids were studied by the application of endothelial cell markers (CD31, CD34, CD105, and ATZ 11) in lesions with localized increased perfusion (liver cell adenoma, focal nodular hyperplasia, and macroregenerative nodule), in chronic congestion, in decreased portovenous inflow (portal vein thrombosis), and in decreased arteriohepatic perfusion (obliterative arteriopathy in chronic allograft rejection). SECs react in a sensitive and uniform way to all investigated conditions of different pathologic liver perfusion: expression of CD31, CD34, and ATZ 11 by SEC is found in inflow areas, CD105-positive SECs are found at the end of the sinusoidal blood stream. This blood flow-orientated phenotypic shift of SECs was accompanied by a perisinusoidal accumulation of activated hepatic stellate cells and collagen IV. These findings are helpful in liver biopsies and provide new insights into the angioarchitecture of benign nodular lesions.

Keywords Liver sinusoids · Pathologic liver perfusion · Endoglin · Sinusoidal endothelial cell

Introduction

The liver receives 25% of cardiac output, and the hepatic parenchyma is the most richly perfused of any of the organs. Portal blood accounts for about two-thirds of total flow, and the rest is supplied by the hepatic artery [3, 14]. The microvascular unit of the liver is the hepatic acinus. All entrances to the acinus occur in the periportal region, while all exits occur at the periphery. This unique one-way flow arrangement results in a strong gradient for oxygen and other nutrients [23].

Sinusoids of the human liver are highly specialized vessels, forming an interconnecting network in the acinar zone 1. Downstream from the periportal area, the sinusoids become organized as parallel vessels that terminate in terminal hepatic venules. The endothelial lining is discontinuous and devoid of basement membrane, allowing easy and quick contact between blood plasma and hepatocytes [29].

The effects of altered hepatic perfusion on the sinusoidal bed and the phenotypic characteristics of sinusoidal endothelial cells (SECs) were the scope of this study. The effects of predominant arterial inflow can be studied in focal nodular hyperplasia (FNH), a localized hyperplasia which is supplied by anomalous arteries [8, 9, 28]. Furthermore, predominant arteriohepatic perfusion is observed in hepatocellular adenomas (HA) and in macroregenerative nodules (MN). The latter usually develop in advanced Budd-Chiari syndrome, they are non-neoplastic lesions and share histoarchitectural similarities with FNH [25, 31]. The outflow obstruction due to hepatic vein thrombosis and the liver involvement in congestive cardiac failure leads to chronic congestion, parenchymal atrophy, and fibrosis, respectively, cirrhosis. The consequence of diminished portovenous inflow can be studied in cases of thrombotic occlusion of large portal veins in non-cirrhotic livers. Chronic ischemic damage as a result of reduced arterial inflow appears in human liver allografts after vascular rejection with obliterative arteriopathy.

Sinusoids were studied by a broad spectrum of endothelial cell markers. In addition, deposition of collagen IV (major basement membrane protein) and the expression of α-smooth muscle actin (α-SMA) by hepatic stellate cells (HSC) were investigated. Immunoreactivity for α-SMA is generally accepted as an indicator of the activated status of HSC [22, 24].

In our opinion, Rappaport's acinus is fitting best to the functional view of hepatic microanatomy based on microcirculation. Therefore, this concept to subdivide

Dedicated to Prof. Dr. U. Pfeifer on the occasion of his 65th birthday.

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Table 1 Data of patients, kind of specimen and underlying disorder. *FNH* focal nodular hyperplasia; *HA* hepatocellular adenoma; *MN* macroregenerative nodule

Specimen	FNH (*n*=10) Resected liver specimens	HA (*n*=6) Resected liver specimens	MN (*n*=10) Four explanted (cirrhotic) organs	Chronic congestion (*n*=13) Four explanted (cirrhotic) livers, 1 liver obtained at autopsy, one small surgical specimen, and seven needle biopsies	Portal vein thrombosis (*n*=6) Small surgical specimens	Obliterative arteriopathy (*n*=5) Explanted grafts failed due to chronic rejection
Age range (years)	28–54	23–54	14–36	14–75	7–59	43–62
Mean age (years)	(30.2)	(37.8)	(25.5)	(40.25)	(34.8)	(52.6)
Gender (male/female)	0/10	0/6	3/1	9/4	0/6	3/2
Underlying disorder	Arterial malformation?	Oral contraceptive steroids?	Hepatic vein thrombosis due to polycythaemia vera	Hepatic vein thrombosis (polycythemia vera 4×; heparin-induced thrombocytopenia II 1×) and cardiac failure	Umbilical vein thrombosis (1×) and undefined (5×) in non-cirrhotic livers	Chronic rejection

liver parenchyma by blood flow direction was applied on all different types of pathologic perfusion. Simplifying this model, we distinguish between inflow and outflow areas.

Materials and methods

Liver tissue obtained by means of needle biopsy (*n*=7), by surgical resection (*n*=23), at explantation (*n*=9), and at autopsy (*n*=1) was investigated (Table 1). Small specimens resected before implantation of human liver allografts served as control cases (*n*=10). All specimens were fixed in 4% buffered formaldehyde and embedded in paraffin. For routine staining, hematoxylin and eosin (HE), Sirius-red, periodic acid–Schiff (PAS), and iron stain were used. For immunohistochemistry, monoclonal mouse antibodies (CD31, CD34, CD105, Ki-67, α-SMA, collagen IV, Hep Par 1: Dako, Germany; ATZ 11: Wieslab, Sweden) were applied. Detection was done with the standard avidin-biotin-peroxidase (ABC) method.

The staining results were graded semiquantitatively: (–) no reactivity of SECs (CD31, CD105, and ATZ), respectively few CD34-positive SECs/very weak respectively no reactivity for collagen IV and α-SMA; (+) expression of CD31, CD34, CD105, and ATZ 11 in a sinusoidal segment not longer than one-fourth of the distance between portal tract (respectively inflow area) and draining vein/weak reactivity for collagen IV and α-SMA; (++) expression of CD31, CD34, CD105, and ATZ 11 in a sinusoidal segment not longer than one-half of the distance between portal tract (respectively inflow area) and draining vein/moderate reactivity for collagen IV and α-SMA; (+++) expression of CD31, CD34, CD105, and ATZ 11 in a sinusoidal segment longer than one-half of the distance between portal tract (respectively inflow area) and draining vein/strong reactivity for collagen IV and α-SMA.

Results

In the acinus of normal liver tissue, expression of the CD34 antigen was restricted to few SECs located in the direct vicinity of portal tracts. In addition, CD34 was expressed by portal vessels and draining veins (Fig. 1A). Antibodies against the basement membrane component collagen IV sometimes demonstrated a scanty staining result beneath the endothelial cell lining, with a slight predominance in perivenular areas.

Few small α-SMA-positive HSC were detected almost only in the acinar zone 3. The antibody against CD31 and the antibody ATZ 11 did not stain SECs; immunoreactivity was only observed in portal vascular structures and the endothelial lining of draining veins. CD105 immunoreactivity was restricted to the endothelium of veins and, in very few SECs in the direct vicinity of these veins, portal blood vessels were negative. Under condition of pathologic perfusion, liver sinusoids showed a different expression of the antibodies mentioned above. A summary of the immunohistochemical findings is given in Table 2, Table 3, Table 4, and Table 5.

The highest absolute difference in numbers of CD34 positive SECs was found between normal liver tissue and lesions with increased arteriohepatic perfusion (FNH, MN, and HA). The endothelial lining of these nodular lesions showed a characteristic pattern (Fig. 2A, C). Increased immunoreactivity for CD34 was found in inflow areas that were originating from portal tract-like respectively radiating septal structures in FNH and MN. CD31 immunoreactivity of SECs showed the same distribution pattern, but the number of reacting cells was less than for CD34. This observation was also found in all other groups of altered perfusion (obliterative arteriopathy, chronic congestion, and portal vein thrombosis) which were investigated in this study. The antibody ATZ 11 detected only few SECs restricted to inflow areas of these three types of nodular lesions. SECs of all other conditions of pathologic perfusion showed negative

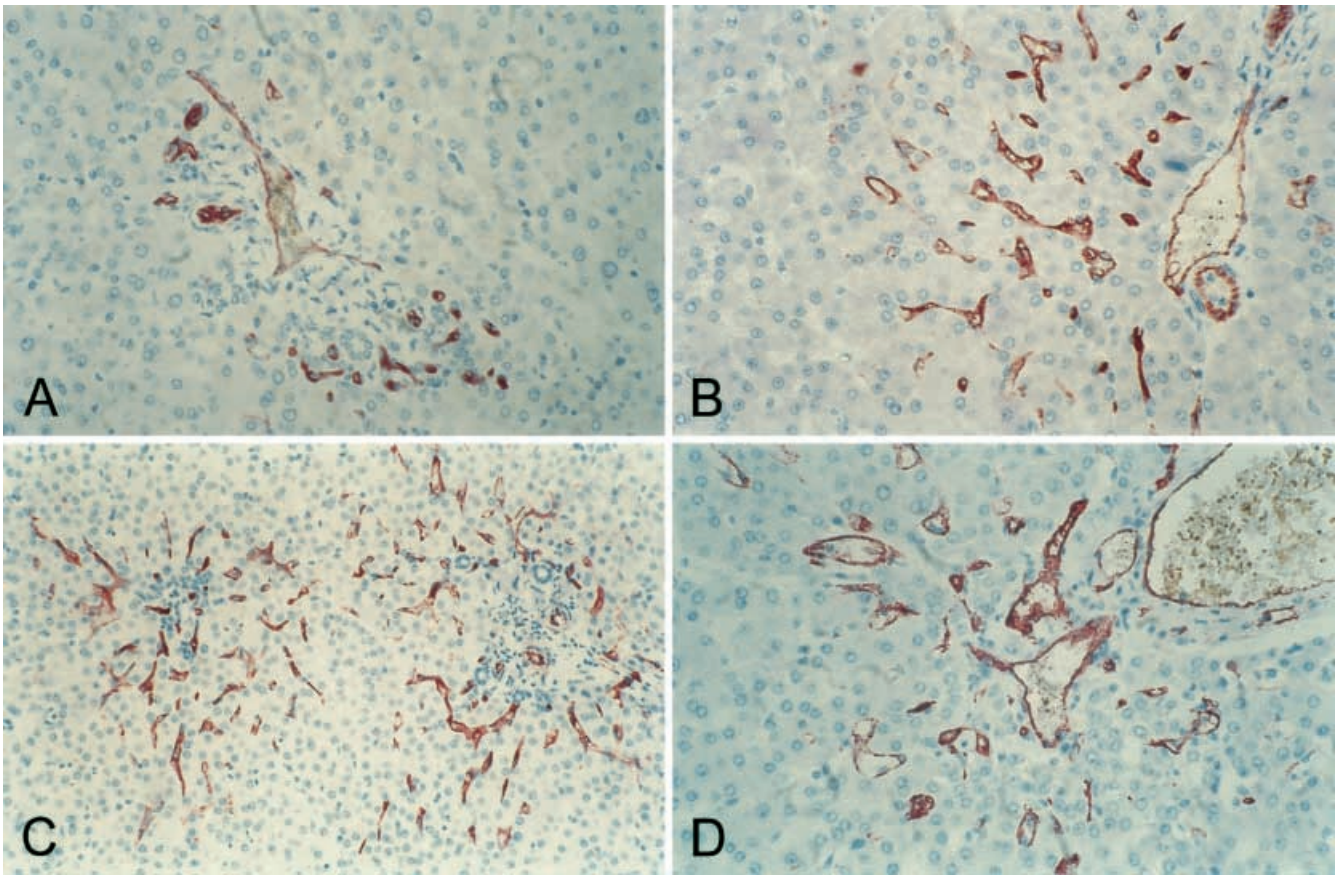

Fig. 1 CD34 expression of periportal sinusoidal endothelial cells. **A** In normal liver tissue, CD34 expression is restricted to portal vascular structures (×200). Different conditions of pathologic liver perfusion are characterized by increased immunoreactivity of periportal inflow areas as demonstrated here in chronic congestion (**B**; ×200), in portal vein thrombosis (**C**; ×130), and in chronic liver allograft rejection with obliterative arteriopathy (**D**; ×200)

staining results with this antibody. In contrast to the distribution of CD31, CD34, and ATZ 11, expression of CD105 was found predominantly on SECs in the surrounding of draining veins and in regions of congestion/sinus dilatation. In some HA, the reactivity for CD34 visualized a "lobular-like" vascular architecture of the solid tumor tissue (Fig. 2C). This finding was surprising, because, in routinely HE-stained tissue, a typical liver cell adenoma consists solely of uniform hepatocytes arranged in plates and lacks an apparent lobular structure of parenchyma. Other HA contained large, irregularly distributed areas of liver parenchyma with a CD34-positive vascular bed. Nevertheless, all HA had CD34-negative, CD105-positive sinusoids which were constantly orientated to draining veins (Fig. 2D). In FNH and MN, α-SMA-positive cells and collagen IV depositions were demonstrated perisinusoidal in the vicinity of portal tract-like respectively radiating septal structures. In contrast, HA showed a different pattern: α-SMA and collagen IV immunoreactivity was found predominantly in perivenular areas at the end of the sinusoidal blood stream.

Interestingly, (1) decreased arterial inflow, (2) decreased portovenous inflow, and (3) chronic congestion showed a similar immunohistochemical staining pattern of the sinusoids. Constantly, CD31 and CD34 were expressed by SECs in inflow areas (Fig. 1B–D). CD105-positive SECs and perisinusoidal accumulation of α-SMA-positive cells and collagen IV were again restricted to outflow areas. Nevertheless, there were differ-

Table 2 Immunoreactivity of liver sinusoids under the condition of increased arteriohepatic perfusion (*FNH* focal nodular hyperplasia; *HA* hepatocellular adenoma; *MN* macroregenerative nodule

Site of antigen	Antibody/epitope	Inflow area	Outflow area
Sinusoidal endothelial cells	CD31	+/++	–
	CD34	+++	–
	CD105	–	++ (FNH, HA) + (MN)
	ATZ 11	+ (FNH, MN) –/+ (HA)	–
Space of Disse	Collagen IV	++ (FNH, MN) + (HA)	++ (HA) – (FNH, MN)
Hepatic stellate cells	α-SMA	++ (FNH, MN) + (HA)	++ (HA) – (FNH, MN)

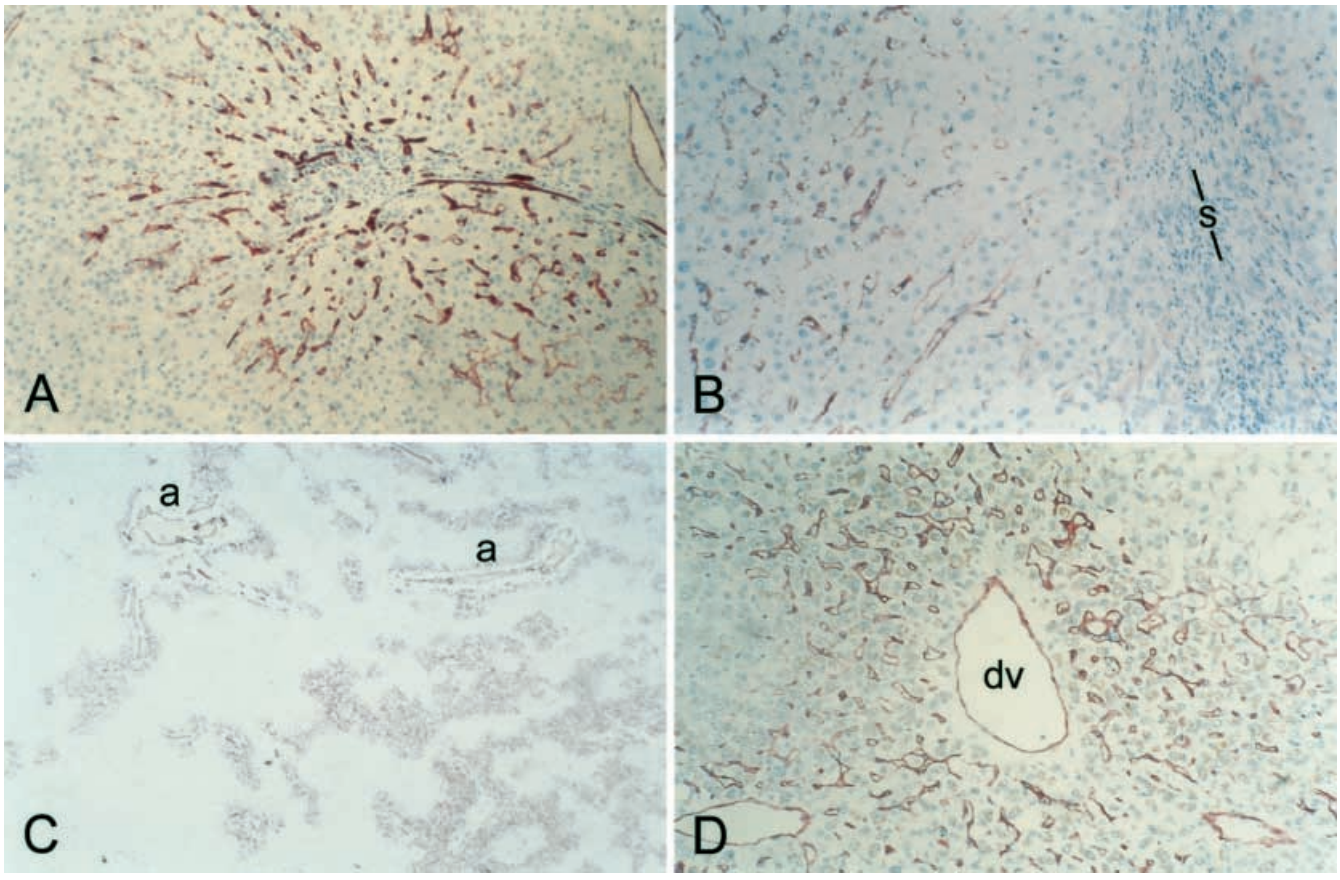

Fig. 2 Immunophenotypical changes of sinusoidal endothelial cells (SECs) in non-malignant nodular hepatic lesions with predominant arterial inflow. Increased immunoreactivity of SECs for CD34 is found in sinusoids radiating from portal tract-like structures of focal nodular hyperplasia (inflow area; **A**; ×80). In hepatocellular adenomas (**C**; ×20), CD34 expression is restricted to tumor areas surrounding small arterial vessels (*a*). This visualizes a "lobular" vascular architecture in some liver cell adenomas (**C**; *right* part of the figure) in contrast to normal liver tissue (**C**; *left* part). CD105-positive sinusoidal segments are found in the periphery of pseudolobules in focal nodular hyperplasia (B; ×80; *s* portal tract-like structure) and in the vicinity of draining veins (*dv*) in adenomas (**D**; ×80)

Table 3 Immunoreactivity of liver sinusoids under the condition of outflow obstruction

Site of antigen	Antibody/ epitope	Inflow area	Outflow area
Sinusoidal endothelial cells	CD31	+	–
	CD34	++	–
	CD105	–	+ to +++
	ATZ 11	–	–
Space of Disse	Collagen IV	–	+ to ++
Hepatic stellate cells	α-SMA	–	+ to ++

Table 4 Immunoreactivity of liver sinusoids under the condition of decreased portovenous inflow due to portal vein thrombosis

Site of antigen	Antibody/ epitope	Inflow area	Outflow area
Sinusoidal endothelial cells	CD31	+/–	–
	CD34	+	–
	CD105	–	+/–
	ATZ 11	–	–
Space of Disse	Collagen IV	–	+
Hepatic stellate cells	α-SMA	–	+

Table 5 Immunoreactivity of liver sinusoids under the condition of decreased arteriohepatic perfusion due to obliterative arteriopathy

Site of antigen	Antibody/ epitope	Inflow area	Outflow area
Sinusoidal endothelial cells	CD31	+	–
	CD34	++	–
	CD105	–	+/++
	ATZ 11	–	–
Space of Disse	Collagen IV	–	+/++
Hepatic stellate cells	α-SMA	–	++

ences within and between these three groups regarding the staining pattern. Severe chronic congestion in Budd-Chiari syndrome was associated with intense expression of CD105 by SECs in perivenular atrophic areas (Fig. 3A). Concerning CD31 and CD34, a marked expression of these antigens was observed in SECs near portal tracts. Slight/moderate chronic congestion due to cardiac failure was characterized by a similar pattern, but

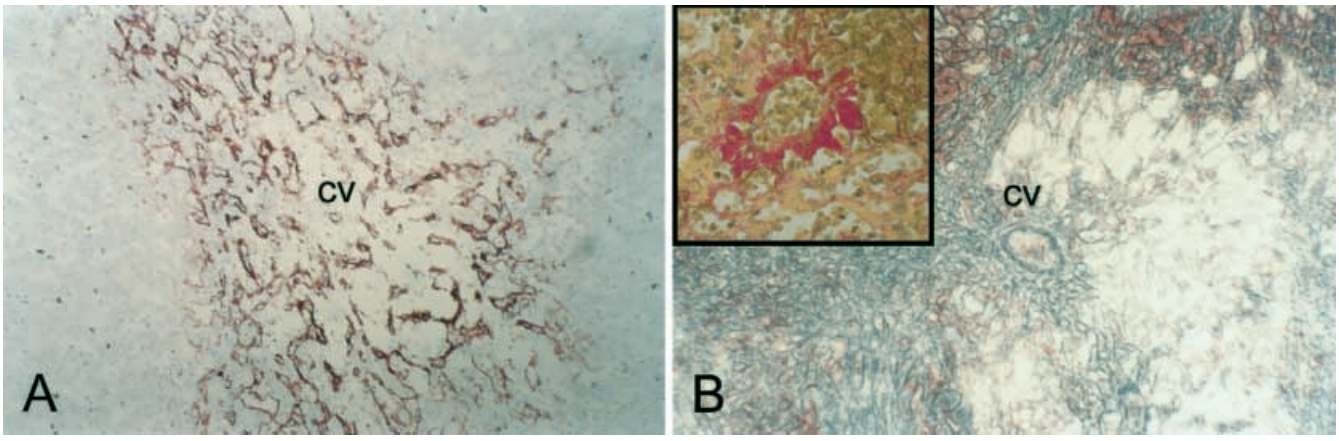

Fig. 3 Strong CD105 expression of sinusoidal endothelial cells in a centrilobular area of Budd-Chiari syndrome with parenchymal extinction (**A**; ×80). Similar findings can develop in chronic liver allograft rejection with persistent centrilobular cell loss (**B**; Hep Par 1 combined with reticulin stain; ×80). Note the fibrous thickening of hepatic venules (*cv*) in chronic rejection (*inset*; **B**; Sirius-red stain; ×260)

the extent of this atypical marker expression was not that high.

In the investigated organs with obliterative arteriopathy, quality and extent of immunohistochemical staining reactions were alike to slight/moderate chronic congestion. Both types of pathologic perfusion were characterized by CD105-positive liver sinusoids in the surroundings of draining veins. Under the condition of obliterative arteriopathy, CD105 expression was associated with a perivenular "drop out" of hepatocytes. In chronic congestion, the liver trabecules close to dilated CD105-expressing sinusoids were atrophic.

Reduced portovenous inflow was characterized only by a mild increase in CD31- and CD34-positive periportal SECs compared with normal liver tissue. CD105 expression by SECs was detectable only in one case of long-standing portal vein thrombosis. The overall picture shows that – under condition of pathologic perfusion – the expression of these endothelial cell markers is orientated along the sinusoidal blood flow direction.

In normal liver tissue and under all investigated conditions of pathologic perfusions, only very few Ki-67-positive SECs were found along the sinusoids. In contrast to the endothelial antigens, there was no obvious predominance in inflow or outflow areas, respectively. In addition, there was no visible difference between the investigated groups. Because of the small number of Ki-67-positve SECs, a further semiquantitative analysis was not performed.

Discussion

Most studies on liver mesenchyma were focused mainly on stellate cells, fibrogenesis, and matrix degradation. In contrast, SECs have received little attention in the literature. We could demonstrate that all different conditions of pathologic liver perfusion investigated here are characterized by an abnormal marker expression of SECs.

One main feature was the blood flow-orientated expression of endothelial antigens. Under all investigated conditions of pathologic perfusion, expression of CD31 and CD34 was found in a similar pattern predominantly in inflow areas. CD34-expressing (periportal) sinusoidal segments were longer than CD31-expressing segments. The antibody ATZ 11 stained only few SECs in inflow areas of the nodular lesions. Immunoreactivity of SECs for ATZ 11 was not observed in either normal liver or under the other conditions of altered perfusion (obliterative arteriopathy, chronic congestion, and portal vein thrombosis). Obviously, the ATZ 11 reactivity is restricted to endothelial cells of mature blood vessels. In contrast to CD34, CD31, and ATZ 11, CD105 immunoreactivity was constantly restricted to outflow areas. This blood flow-orientated phenotypic shift of SECs was accompanied by a perisinusoidal accumulation of HSC and a basement membrane formation.

Under the condition of localized and nearly exclusive arteriohepatic hyperperfusion in different nodular lesions (FNH, HA, and MN), arterial blood flow must be considered as a causal factor inducing a stepwise centrifugal transformation of SECs. It remains to be elucidated whether an increase in local blood pressure or high oxygenation are possible stimulating factors for this phenotypic shift.

Complete/incomplete blockage of portal blood flow is followed by increased arteriohepatic inflow. In the case of prehepatic portal block (occluding thrombus) and intrahepatic portal hypertension (severe chronic congestion, Budd-Chiari syndrome), the atypical CD31/CD34 expression in inflow areas possibly reflects this compensatory changed inflow condition. Regarding obliterative arteriopathy, the etiopathogenetic factors of this phenomenon in inflow areas are unclear. It remains speculative whether a complex disturbance of microcirculation in the denervated graft is responsible for this phenotypic shift of SECs.

Interestingly, there are remarkable similarities between chronic congestion and chronic liver allograft rejection, not only in the immunohistochemical but also in the histopathologic feature: centrilobular parenchymal

cell loss (Fig. 3A, B). In association with chronic rejection of liver allografts, late or persistent centrilobular cell loss is a lesion of unknown etiology [15, 18, 21] and was found in three of the five failed grafts in our study. In these grafts, we have observed a marked acellular fibrous thickening of hepatic venules [26]. These venous lesions (Fig. 3B, inset) may lead to sinusoidal outflow blockage and subsequent chronic congestion with "drop out" of hepatic cell plates. This observation poses the question of whether some of the histopathological (cell loss) and immunohistochemical findings in the liver allografts were caused (in part?) by chronic congestion.

As explained above, one of the most striking phenotypic characteristics was the expression of CD31 and CD34. The exact role of these molecules in the liver sinusoids is unclear. CD31 (PECAM-1) is a member of the immunoglobulin superfamily and has been shown to be the main intercellular adhesion molecule of microvascular endothelia in which it localizes at intercellular contacts [1, 12, 17, 20]. The CD34 molecule is found at intercellular contacts on normal microvascular endothelial cells and is likely to be an adhesion protein also [5, 7]. It is known that the fragile system of SECs is susceptible to various kinds of injury, resulting, e.g., in sinusoidal dilatation and peliosis hepatis [30]. Therefore, the expression of these two adhesion molecules by SECs might represent an attempt to stabilize and to prevent disruption of the sinusoidal endothelial lining which could be caused by pathologic perfusion.

Up to now, little is known regarding the intrahepatic expression of endoglin (CD105). Endoglin, a transforming growth factor-β_1 (TGF-β_1)-binding protein, is abundant on human endothelial cells [4]. Within the liver, increased immunoreactivity was demonstrated in necroinflammatory areas in chronic hepatitis [2, 10]. According to these authors, TGF-β_1 mediates the neoangiogenesis observed in inflammatory liver diseases. This interpretation may well be true but is not able to explain the endoglin expression by SECs of preexisting sinusoids without obviously increased proliferative activity. Therefore, enhanced expression of endoglin by SECs is not only a sign of angioproliferation.

TGF-β_1 is an effective mediator for stimulation of matrix protein synthesis in chronic liver disease [6, 11, 16, 19]. SECs themselves are able to synthesize basement membrane proteins and extracellular matrix proteins [19]. Furthermore, some data suggest that SECs are also involved in the complex process of matrix remodeling by secretion of metalloproteinases [27] and their tissue inhibitors, respectively [13]. In our study, the strongest expression was observed in severe chronic congestion and Budd-Chiari syndrome (Fig. 3A). Therefore, one can speculate that upregulation of CD105 expression is a response of preexisting sinusoids to parenchymal atrophy/cell loss and that the upregulation of the TGF-β_1 receptor leads to a TGF-β-mediated basement membrane formation by the SECs.

This hypothesis is incapable of explaining the CD105 immunoreactivity in FNH and MN, since these nodular lesions are devoid of atrophy and parenchymal extinction. Furthermore, in FNH and MN, basement membrane formation was found in CD34-positive inflow areas and not in the CD105-positive outflow segments of sinusoids. The only common feature in all investigated conditions of pathologic perfusion was the constant restriction of endoglin expression to outflow areas. Therefore, one can conclude that the inducing factors are more or less dependent on the blood flow.

To summarize, this study demonstrates that human SECs react in a sensitive and surprisingly uniform way to different kinds of pathologic liver perfusion. Although the initiating factors remain unclear, the characteristic immunohistochemical patterns are indicators of altered perfusion. They are helpful findings in liver biopsies and, especially, CD34 has to be considered as a very sensitive marker. Furthermore, this panel of endothelial cell markers allows for a better understanding of the characteristic angioarchitecture of different benign nodular lesions (FNH, HA, and MN). In particular, areas of arteriohepatic inflow can be distinguished from outflow regions. This is in contrast to the immunohistochemically monotonous vascular bed of malignant liver tumors.

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