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Is Liver Disease Caused by Increased Pressure? Interstitial Pressure as a Causative Mechanism in Carcinogenesis and in the Differential Blood Supply in Liver Tumors from the Hepatic Artery

Laurent Schwartz[1] **and Douglas Coldwell**[2*]

[1]*Ecole Polytechnique, Paris, France*

[2]*University of Louisville, Louisville, KY, USA*

[*]**Corresponding author:** Douglas Coldwell, MD, Ph. D., University of Louisville, 530 South Jackson St. Louisville, KY 40202, USA, Tel: 502-852-5875; Email: dmcold01@louisville.edu

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Abstract

Background: Inflammation has been noted to occur due to increased interstitial pressure. This same interstitial pressure in the liver is likely the cause of tumors receiving their blood supply primarily from the hepatic artery.

Aim: The aim of the present study was to explore whether the same interstitial pressure in the liver is likely the cause of liver tumors receiving their blood supply primarily from the hepatic artery.

Methods: Interstitial pressures were measured in normal and tumor parenchyma during the performance of liver biopsies.

Results: The interstitial pressures in the tumors were significantly higher than the interstitial pressure in normal tissues and these pressures were high enough that only arterial blood flow could supply them.

Conclusion: The interstitial pressure is the cause of the blood supply difference between normal and tumor parenchyma. This increased interstitial pressure may represent a carcinogenic agent.

Keywords: Inflammation; Interstitial pressure; Hepatocellular carcinoma

Introduction

Inflammation of the liver can be caused by hepatitis C or B, alcoholic liver disease, antitrypsin deficiency, hemochromatosis, and tyrosinemia or direct trauma. Previous study and studies of others recently demonstrated that inflammation results from increased interstitial pressure [1-3]. There is increased osmotic pressure in the inflammatory fluid due to the presence of a large quantity of protein. This increased extracellular osmolarity results in the secretion of pro-inflammatory cytokines such as Tumor Necrosis Factor (TNF).

Liver cancer is frequently associated with such pre-existing inflammation and fibrosis. Between 60% and 90% of hepatocellular carcinoma occurs in patients with hepatic macronodular cirrhosis [4,5]. Chronic liver diseases of any type are risk factors for liver cancer. Evidence for a cause-effect link between cirrhosis and hepatocellular carcinoma is lacking. The relation may often be one of chance alone, since not all cirrhotics develop cancer.

The normal hepatic parenchyma is supplied by the portal vein; tumors are supplied by the hepatic artery. This is the basis for embolotherapy and intra-arterial chemotherapy. Prior research has demonstrated that metastatic tumors to the liver are supplied by portal venous branches until the lesion is approximately 2 mm in diameter. Only then, the tumor will receive its supply from the hepatic artery. The physiological reasons for this shift occurs are unclear.

Nonetheless, diseases that cause cirrhosis also increase the risk of hepatocellular carcinoma [5]. Furthermore, the more disorganized the liver becomes, the higher the risk of hepatocellular carcinoma [5,6].

The seminal work of D'Arcy Thompson demonstrated that physical forces play a key role in plant and animal morphogenesis [7]. The goal of this study is to explore the role of physical forces in the development of hepatic cirrhosis and its possible complication; liver cancer. We also focused on one of the characteristics of liver cancer; its peculiar blood supply.

Materials and Methods

During hepatic biopsy, interstitial pressure of the normal hepatic parenchyma was measured while a 17 or 19 gauge guiding needle was being advanced to the tumor under CT guidance. The pressure was then obtained when the needle entered the periphery of the tumor. If frank blood appeared in the guiding needle, the needle was repositioned so that blood did not appear. Additionally, blood pressure at the time of pressure measurement was obtained and the mean arterial pressure was calculated. A single arm t-test was used to determine significance with $p<0.05$.

Results

All tumors biopsied were greater than 2 cm in diameter. Interstitial pressure measurements were obtained in 42 patients (24 men, 18 women) with a mean age of 55 years. Diagnoses included metastatic

colorectal cancer (17 patients), breast cancer (9 patients), neuroendocrine cancer (8 patients), primary hepatocellular carcinoma (5 patients) and cholangiocarcinoma (3 patients). The mean interstitial pressure found in the normal parenchyma in metastatic disease was 4 mm Hg with the interstitial pressure in the tumor found to be 15 mm Hg in metastatic colorectal cancer, 18 mm Hg in metastatic breast cancer, and 22 mm Hg in metastatic neuroendocrine cancer (Table 1).

Site Measured	Pressure (mmHg)	Statistical Significance between site and normal	Statistical Significance between site and cirrhosis
Normal Parenchyma	4	N/A	p<0.01
Cirrhosis	13	p<0.01	N/A
Primary Hepatic Tumor	25-26	p<0.01	p<0.01
Metastatic Hepatic Tumor	15-22	p<0.01	Not significant

Table 1: Measured Interstitial Pressures

In the primary tumors, the normal parenchyma pressure was 13 mm Hg and the interstitial pressure in HCC were 26 mm Hg and in cholangiocarcinoma patients was 25 mm Hg. The mean arterial pressure in the patients was 137 mm Hg. All metastatic tumoral interstitial pressure was found to be significantly higher than the normal hepatic pressure and, similarly, the interstitial pressure of the hepatic primary tumors was higher than the uninvolved portion of the liver (Table 2).

Site	Pressure (mm Hg)	Statistical Difference between tumor and vascular pressures
Tumor	15-26	N/A
Portal Vein	4	p<0.01
Mean Arterial	137	p<0.01

Table 2: Interstitial Pressures compared to vascular pressures

Discussion

Our data demonstrated that the hepatic parenchyma (4 mm Hg) is under increased pressure in liver cirrhosis (13 mm Hg) and in primary or metastatic cancer (between 15 and 25 mm Hg). The pressure was higher in primary cancer than in metastatic lesions to the liver probably because of preexisting hepatic cirrhosis. The increased interstitial pressure may be responsible for the most common features of cirrhosis and/or cancer such as hepatocyte necrosis, extensive fibrosis, connective tissue deposition, vascular distortion, infiltration by immune cells and nodular regeneration of the remaining tissue parenchyma [5]. Increased pressure is known to induce collagen deposition and modulate cell proliferation either by cell death or by cell multiplication [8]. Exposure of immune cells to increased osmotic pressure doubled their half-life [3].

During carcinogenesis, architectural changes (the epithelium increases in depth) and cytological modifications (increased mitoses and cellular polymorphisms) coexist. Normal hepatocytes are organized along a structural axis which allows cell adhesion to the mesenchyme on one side, and act as functional epithelium in the lumen of the bile ducts [9]. This functional polarity is maintained by the cytoskeleton, by vesicular trafficking that proceeds along the microtubules, by organelles such as the centrosomes and, in general, by the interpretation of cues coming from the surrounding tissue [10]. One side of the epithelial cell lies on the basement membrane, one side faces the lumen, and there are cells on the other surrounding sides. This normal epithelial cell can only divide in one plane and it cannot jump toward the lumen and create a new cell layer. During carcinogenesis, there is progressive fibrosis of the tissue, accompanied by a progressive increased number of cell layers. Epithelial cells have been able to change planes and jump on top of each other. This is possible because of an alteration in the gap junctions in carcinogenesis [9,10]. These altered gap junctions explain that the cancer cells can change plane thus explaining the radiating, stellar shape of cancer [9,10].

Numerous carcinogens target these gap junctions as well as physical forces. Recent investigations demonstrated how various types of mechanical load, like strain, pressure, shear stress, or cyclic stretch affect cell biology and gap junction intercellular communication [11]. These forces modulate the expression and function of certain connexins such as Cx43 and the demonstration that the alterations of the physical environment may promote cancer lie in decades-old literature on physical carcinogenesis. It has been documented that some foreign bodies induce cancer [12-16]. The carcinogenicity of foreign bodies is linked to their shape. Cellulose membrane filters of specific shapes, texture or size generate sarcomas with intense inflammation and proliferative fibrosis preceding tumor formation. The combination of shape and size (about the width of a human cell) may also be critical [15,16]. The carcinogenicity of a chemically inert molecule is also linked to particle shape and size.

It is probable that increased pressure in the liver parenchyma explains multiple features of both cirrhosis and liver cancer such as progressive hardening, increased depth of the liver capsule, portal hypertension and its complications like ascites or oesophageal varices.

Metastatic disease to the liver is one of the most common presentations of tumor spread. This is particularly true for colorectal carcinoma and midgut/hindgut originating neuroendocrine tumors. The hepatic parenchyma is normal with the superposition of the tumor on to that milieu. On the other hand, the hepatic primary tumors usually occur in the presence of cirrhosis which was present in each of these patients in this series.

In patients with normal liver, the portal pressure should be less than 6 mmHg and in cirrhotic patients, greater than 10 mm Hg. The metastatic lesions were found to have interstitial pressures greater than the normal portal pressure and less than the mean arterial pressure indicating that the blood flow to the tumors must arise from the hepatic artery and not the portal vein. Similarly, even though the

cirrhotic patients had pressures greater than 10 mm Hg, the pressures found in the tumors were high enough to require an arterial source.

The interstitial pressures are also noted to rise with the increased vascularity of the tumor. Neuroendocrine tumors have far greater amount of neovascularity of the tumor than breast cancer which was higher than colon cancer. The interstitial pressures in tumors that form such neovascularity are sensitive to bevacizumab which, according to the prior research performed on this drug, decreases the neovascularity by blocking the vascular endothelial growth factor. The first sign of bevacizumab's effectiveness has been reported in its initial trials was the decrease in the interstitial pressures found in the tumor.

Conclusion

The role of physical forces in the pathogenesis and the development of liver diseases have been overlooked. It is probable that change in physical constraints play a major role in liver pathogenesis such as inflammation, fibrosis and carcinogenesis.

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