CHAPTER 6

THE ROLE OF THE RENIN-ANGIOTENSIN SYSTEM IN HEPATIC FIBROSIS

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1. INTRODUCTION

The liver is the second largest organ of the body and has a multitude of functions including carbohydrate and fatty acid metabolism, lipid transport, protein synthesis, storage of fat-soluble vitamins as well as detoxification and modification of compounds absorbed from the small intestine. It has a dual blood supply, with approximately 75% coming from the portal vein and 25% from the hepatic artery. The primary functional unit of the liver, the hepatic lobule, consists of a hexagonal zone of hepatic parenchyma surrounding a central hepatic vein with a number of portal tracts at the periphery which contain a terminal portal vein, bile ductule and hepatic arteriole. In the normal liver, blood flows from portal venous branches through specialised vascular channels called hepatic sinusoids, into the centrilobular hepatic vein. Hepatic sinusoids lack a distinct basement membrane and their endothelial cells have fenestrations which permit bidirectional free passage of solutes between the sinusoid and a sub-sinusoidal space known as the space of Disse. Hepatocytes, account for 70% of liver mass. These cells, which have microvilli on their basolateral surface to facilitate the interchange of nutrients with the sinusoid, are responsible for most of the metabolic and synthetic functions of the liver.

Chronic liver diseases disturb the normal structure and function of the liver by initiating hepatic fibrosis, a process that can eventually lead to progressive destruction of the normal hepatic architecture, loss of functioning hepatocytes and the development of liver cirrhosis. Angiotensin II, the main effector peptide of the renin-angiotensin system (RAS), is known to play an important role in chronic tissue injury and fibrosis in cardiovascular disease, chronic renal disease and diabetes. Its...
role in liver disease is less well established, however, recent studies indicate that, as in other organs, there is a renin-angiotensin-system within the liver and that locally generated angiotensin II plays an important role in the pathogenesis of liver injury and hepatic fibrosis. There is also evidence that in the fibrotic liver angiotensin II contributes to portal hypertension by stimulating contraction of perisinusoidal myofibroblasts and increasing sinusoidal resistance to portal flow. In addition to these local effects in the liver, the systemic RAS is activated in patients with advanced liver disease in response to mesenteric and systemic vasodilatation and has an important homeostatic role in maintaining adequate perfusion pressure to the kidney and other vital organs. It also contributes to renal sodium and water retention by releasing aldosterone and by stimulating secretion of antidiuretic hormone (ADH) from the posterior pituitary. These multiple roles of the RAS in liver disease have lead to major interest in the potential role of RAS antagonists in the prevention of liver fibrosis and the treatment of chronic liver disease and its complications.

2. PATHOGENESIS AND SIGNIFICANCE OF HEPATIC FIBROSIS

There are a large number of chronic liver diseases which cause hepatic fibrosis, including chronic viral hepatitis, alcoholic liver disease, non-alcoholic fatty liver disease, iron overload, diseases of the biliary tract and immune and metabolic liver diseases. Cirrhosis, the end stage of hepatic fibrosis, is characterised by the presence of extensive fibrotic septa separating and surrounding parenchymal nodules of regenerating hepatocytes. This disturbance of the normal hepatic architecture, in conjunction with vasoconstriction within the liver, impedes portal blood flow causing portal hypertension; this is the cause of many of the serious complications of cirrhosis including variceal bleeding, hepatic encephalopathy and ascites. Hepatitis B infection is the most common cause of cirrhosis worldwide. It is also the single most important cause of hepatocellular carcinoma, a disease responsible for nearly one third of the world’s cancer-related deaths (Lodato et al 2006).

Currently the only proven treatment for hepatic fibrosis is to remove the responsible injurious agent. Recent studies have shown that if this can be achieved, for example by eliminating viral replication in patients with chronic hepatitis B or C, hepatic fibrosis and even early stage cirrhosis can resolve. In patients with end-stage cirrhosis and liver failure, therapy is limited to symptom control and the prevention of life threatening complications such as variceal bleeding whilst cure can only be achieved with liver transplantation. Unfortunately despite major advances in antiviral therapy in recent years, many patients with chronic hepatitis do not respond to therapy. There are also a number of chronic liver diseases for which we currently do not have effective treatment. There is therefore an ongoing need to develop anti-fibrotic therapies that can be used to prevent fibrosis progression and the development of cirrhosis.

In the healthy liver, extracellular matrix (ECM) consists of collagens (predominantly type IV), glycoproteins, proteoglycans and glycosaminoglycans which provide a structural and functional framework for cellular migration, adhesion,