Mechanisms of hepatic fibrogenesis

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GENERAL ASPECTS OF FIBROSIS AND CIRRHOSIS

Cirrhosis represents the end-stage consequence of fibrosis of the hepatic parenchyma resulting in nodule formation and altered hepatic function. Mounting evidence has now established that even advanced fibrosis and cirrhosis are reversible. Examples include alcohol abstinence, lamivudine treatment for chronic hepatitis B, treatment of hepatitis C with interferon/ribavirin, surgical decompression of biliary obstruction, immunosuppressive therapy for autoimmune hepatitis, and phlebotomy for hemochromatosis. Fibrosis and cirrhosis represent the consequences of a sustained wound-healing response to chronic liver injury from a variety of causes. Cirrhosis affects hundreds of millions of patients worldwide. In the USA, it is the most common non-neoplastic cause of death among hepatobiliary and digestive diseases, accounting for approximately 30,000 deaths per year. In addition 10,000 deaths occur due to liver cancer, the majority of which arise in cirrhotic livers, with mortality rate steadily rising.

The molecular composition of the scar tissue in cirrhosis is similar regardless of etiology, and consists of the extracellular matrix constituents, collagen types I and III (i.e. “fibrillar” collagens), sulfated proteoglycans, and glycoprotein. These scar constituents accumulate from a net increase in their deposition in liver, and not simply collapse of existing stroma.

HEPATIC FIBROSIS IS THE LIVER’S WOUND-HEALING RESPONSE TO INJURY

There has been steady progress in defining the cells responsible for accumulation of scar, or extracellular matrix (ECM), the signals that drive ECM production, and the enzymes that can degrade scar. Even after acute injury the fibrogenic pathways are already being harnessed, but in order for these to eventuate in scar, the injury must be sustained.
Stellate cells also make a major contribution to the regulation of intrahepatic blood flow. The microvascular unit of the liver, the sinusoid, is remarkably similar to peripheral capillary beds. Sinusoids are lined by endothelial cells, and on their basal surface are stellate cells within the space of Disse. Hepatic stellate cells resemble tissue pericytes, a cell population that has smooth muscle features and is thought to regulate blood flow by modulating pericapillary resistance. During stellate cell activation they increase their expression of the contractile protein alpha smooth muscle actin. Incubation of isolated human stellate cells with vasoconstrictors such as angiotensin-II and thrombin, leads to phenotypic changes including cellular rounding, which are associated with increased intracellular calcium. Furthermore, studies using in-vivo microscopy to co-localize sinusoidal constriction with associated autofluorescence, provide more direct evidence that stellate cells are contractile and can regulate intrahepatic blood flow. The increased intrahepatic vascular resistance characteristic of cirrhosis is thought to arise from an imbalance between vasodilator/vasoconstrictor forces that regulate hepatic vascular tone, as reviewed in related chapters in this book. In summary, the contractile phenotype and perisinusoidal orientation of stellate cells make them ideally positioned to regulate sinusoidal blood flow.

REGULATION OF HEPATIC FIBROSIS - THE ROLE OF THE HEPATIC STELLATE CELL

Hepatic stellate cells represent one-third of the non-parenchymal (i.e. non-hepatocyte) population, or about 15% of the total number of resident cells in liver. In normal liver they are the principal cell for storing vitamin A, primarily as retinyl esters within perinuclear cytoplasmic droplets. “Stellate cells” actually represent a heterogeneous group of cells which are functionally and anatomically similar, but may differ in the types of cellular filaments they express and their potential for activation into more fibrogenic “myofibroblasts”.

Because stellate cells are wrapped around the sinusoid they are able to interact readily through long cytoplasmic processes with all neighboring cell types, including Kupffer cells, hepatocytes, sinusoidal endothelial cells, and immune cells. This orientation facilitates paracrine (i.e. cell-to-cell) interactions that are essential for both normal liver function and the fibrotic response to injury.

The hepatic stellate cell (previously called lipocyte, Ito, fat-storing, or perisinusoidal cell) is the primary source of the extracellular matrix in normal and fibrotic liver. Hepatic stellate cells are resident perisinusoidal cells in the subendothelial space between hepatocytes and sinusoidal endothelial cells. They are the primary site for storing retinoids and therefore can be recognized by their vitamin A autofluorescence in normal unfixed liver and following their isolation. In addition, their perisinusoidal orientation and expression of the cytoskeletal proteins desmin, glial acidic fibrillary protein and smooth muscle actin (in injured liver) facilitate their identification in situ.