THE CELLULAR AND MOLECULAR BASIS OF PORTAL HYPERTENSION

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One of the most feared complications of cirrhosis is portal hypertension. Portal hypertension results from either increased resistance to blood flow or increased splanchnic flow or both. Although most forms of cirrhosis encompass aspects of each, in most cases of portal hypertension, increased intrahepatic resistance to flow is a key element. The level of increased intrahepatic resistance varies with specific forms of liver disease and may occur at presinusoidal, sinusoidal or postsinusoidal levels. Within the sinusoid, it has been proposed that an important potential contributing factor is the hepatic stellate cell (also known as an Ito cell or fat-storing cell), a perisinusoidal cell with prominent contractile features; in this scenario perisinusoidal stellate cell constriction regulates sinusoidal blood flow and intrahepatic resistance to flow. Although other factors contributing to altered blood flow patterns in cirrhosis include regenerative nodules, intrahepatic shunts and hepatocyte swelling, in the context of data highlighting stellate cell contractility, it has been proposed that both fixed (i.e. matrix, regenerative nodules) and modulable elements (i.e. stellate cells) contribute to the increased intrahepatic resistance typical of portal hypertension. Further, regulable elements represent an important potential target of therapeutic intervention.

Because of the dynamic nature of stellate cell contractility, we have focused on agents that induce stellate cell contraction as well as those which cause relaxation. In this regard, the family of endothelins has emerged as the most potent stimulators of stellate cell contractility, while nitric oxide (NO) has been shown to be the most important relaxing agent. Importantly, we have also demonstrated that stellate cell contractility is greatest in the cirrhotic liver, at a time when smooth muscle proteins such as smooth muscle actin are upregulated. Further, the potent vasoconstrictor, endothelin-1, is overproduced in the cirrhotic liver, apparently due to dysregulation of the converting enzyme (endothelin converting enzyme-1) that controls conversion of precursor endothelin-1 to the mature peptide.

In contrast to the endothelin paradigm, endothelium-derived NO produced by the endothelial isoform of NO synthase (ecNOS) is reduced after liver injury. This occurs despite the fact that the level of ecNOS is unaltered after injury. This finding has important implications for the molecular regulation of ecNOS in sinusoidal endothelial cells after injury. Further, these data suggest that decreased production of NO by sinusoidal endothelial cells, particularly in the presence of overproduced vasoconstrictor compounds such as endothelin, is likely to contribute to increased intrahepatic resistance to blood flow. Thus, the dynamic nature of vascular homeostasis implies that interplay of vasoconstrictive (i.e., endothelin-1) and vasorelaxing (i.e., NO) compounds within the hepatic microcirculatory unit regulates intrahepatic vascular resistance. These data are compelling pathophysiologically and moreover provides critical information when considering therapeutic intervention in portal hypertension.