LIVER CIRRHOSIS: NEW RESEARCHS

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Liver fibrosis and its end stage, cirrhosis, represent enormous worldwide healthcare problems. In the United Kingdom, more than two thirds of the 4000 people who died of cirrhosis in 1999 were under 65, and the incidence of cirrhosis related death is increasing.1 Worldwide, the common causes of liver fibrosis and cirrhosis include hepatitis B and hepatitis C and alcohol. Other causes include immune mediated damage, genetic abnormalities, and non-alcoholic steatohepatitis, which is associated with diabetes and the metabolic syndrome.2 Changing patterns of alcohol consumption in the West and the increasing rates of obesity and diabetes mean that advances in preventing and treating viral hepatitis may be offset by an increasing burden of fibrosis and cirrhosis related to alcohol and non-alcoholic steatohepatitis.

Current treatments for cirrhosis are limited to removing the underlying injurious stimulus (where possible); eradicating viruses using interferon, ribavirin, and lamivudine in viral hepatitis; and liver transplantation. Transplantation is a highly successful treatment for end stage cirrhosis, with a 75% five year survival rate. But limited availability of organs, growing lists of patients needing a transplant, issues of compatibility, and comorbid factors mean that not everyone is eligible for transplantation. As a result, effective antifibrotic treatments are needed urgently.

Liver fibrosis and cirrhosis represent a continuous disease spectrum characterised by an increase in total liver collagen and other matrix proteins which disrupt the architecture of the liver and impair liver function.4,5 Fibrosis results from sustained wound healing in the liver in response to chronic or iterative injury. The wound healing response is an integral part of the overall process of inflammation and repair: it is dynamic and has the potential to resolve without scarring. High quality experimental evidence supports the hypothesis that the final common pathway of fibrosis is mediated by the hepatic stellate cells.4–7 Hepatic stellate cells in normal liver store retinoids and reside in the spaces of Disse. In injured areas of the liver, hepatic stellate cells undergo a remarkable transformation: they resemble myofibroblasts and express contractile proteins. In this “activated” phenotype, hepatic stellate cells proliferate and are known to be the major source of the fibrillar collagens that characterise fibrosis and cirrhosis. The mechanisms mediating activation of hepatic stellate cells are a major subject of research.

In injured areas, soluble factors (cytokines) are released by the incoming inflammatory cells, the damaged and regenerating hepatocytes, and other liver cells that target the hepatic stellate cells, activating them so they become the central mediators of wound healing. Because of the key role of inflammation, removing the causative agent and treating the patient with

immunosuppressive drugs are effective interventions for some diseases (box). Greater understanding of the specific cytokine and chemokine messengers that mediate the inflammatory process in liver disease is informing the design of future treatments. This is exemplified by the identification of interleukin-10 as a downregulator of the inflammatory response and tumour necrosis factor α as a pro-inflammatory mediator. Studies using interleukin- knockout mice have identified this cytokine as a major anti-inflammatory effector in fibrotic liver injury. A pilot study suggested that interleukin-10 may be valuable clinically in the context of hepatitis C virus infection, but definitive evidence of efficacy has yet to be produced in a large scale clinical trial. Antagonising tumour necrosis factor α would also be expected to downregulate hepatic inflammation. Reagents to neutralise tumour necrosis factor α are available for clinical use, and this approach is likely to be investigated further in the clinic.

Another approach to chronic liver fibrosis is to block the signals which promote transition of hepatic stellate cells from a quiescent to an activated phenotype and promote collagen secretion. Foremost among the soluble mediators promoting the fibrogenic response from hepatic stellate cells is transforming growth factor β-1 (box). This cytokine also has a role in the development of fibrosis in other organs, including the lung and kidney.The activated hepatic stellate cells respond to it by increasing production of collagen and decreasing its breakdown (see below). Models in other internal organs suggest that modifying the secretion or activity of transforming growth factor β-1 can attenuate fibrosis, which indicates that this is a possible antifibrotic target in the liver. Recent studies of experimental liver fibrosis have shown the potential of this approach.

At present, the clinical assessment of antifibrotic interventions relies on serial liver biopsies. Liver biopsy remains associated with a (small) morbidity and mortality, and even though effective fibrosis scoring systems have been introduced, liver biopsy is prone to sampling error. It may not be an appropriate way of monitoring in a dynamic situation such as a clinical trial of an antifibrotic agent. A further likely development is the identification of a panel of serum fibrosis markers which can be used to predict the stage of fibrosis and monitor disease progression or resolution without recourse to repeated liver biopsies. In future, patients with cirrhosis are likely to be treated simultaneously with a targeted anti-inflammatory agent, an agent to lower portal pressure, and an antifibrotic or fibrolytic agent, and the effectiveness of the treatment may well be monitored by using a panel of serum markers. The development of effective targeted treatments and the tools to monitor their effectiveness non-invasively will change the way we view and treat cirrhosis.

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