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## Addressing liver fibrosis with lipid-based drug carriers targeted to hepatic stellate cells

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**Addressing liver fibrosis with  
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to hepatic stellate cells**

Joanna E. Adrian

referred to as liver cirrhosis, or reverse under certain conditions and then the normal function of the liver may be restored.

The progression of fibrosis can reverse or slow down in response to removal of the primary cause of damage. However, for complete cure of advanced liver fibrosis, medical intervention is required. A number of different antifibrotic strategies are tested in laboratories and in clinical trails, but so far no effective treatment other than liver transplantation has been established. In the USA and Europe, liver cirrhosis is the most common non-neoplastic cause of death among hepatobiliary and digestive diseases (17). The urge to improve current strategies for the treatment of liver fibrosis is growing. Liver transplantation is a complex and costly operation that also is hampered by a lack of donor livers. The number of patients waiting for liver transplantation is approximately four times higher than the number of available donor livers. In addition, epidemiological prognoses indicate that, in the coming years the prevalence of liver fibrosis will significantly increase due to increasingly occurring cases of hepatitis C infections (increased number of infected patients and aging of already infected) (18). The growing group of patients with NASH is also significantly contributing to the rising number of patients with liver cirrhosis. The underlying pathology of NASH is not fully understood, but it is strongly linked with food intake and composition, physical activity (referred as “lifestyle”) as well as central obesity, insulin resistance and genetic factors (19).

The clinical manifestation of liver cirrhosis is determined by the nature and severity of the primary cause of the disease and the stage of fibrosis in the liver tissue and varies from the absence of symptoms to complete liver failure. Liver fibrosis is often a long term disease; up to 40 % of patients is asymptomatic and may have no manifestation for more than a decade (20). This aspect of liver fibrosis urges us also to develop appropriate diagnostic tools, especially reliable early markers of the fibrotic process.

### **Mechanism of liver fibrosis**

Hepatic stellate cells are considered to play a central role in liver fibrosis although development of this disease is a complex process, involving several other types of liver cells. Two main phases can be distinguished in the progression of the disease: inflammation and fibrogenesis. In the initial steps of liver fibrosis, various hepatotoxic factors induce the production of mediators which cause an inflammatory reaction in hepatic cells. For example, acetaldehyde, the oxidative metabolite of alcohol, and the bacterial toxin, LPS released from the gut stimulate Kupffer cells to secrete reactive oxygen species (ROS), TGF- $\beta$ , TNF- $\alpha$  and IL-6 in livers of alcohol abused patients. Decreased excretion of bile (cholestasis) results in accumulation of bile acids in the liver, which promotes biliary epithelial cells to secrete TNF- $\alpha$ , ET-1 and PDGF. Hepatitis C infection primarily causes damage to hepatocytes and subsequent production of ROS, TGF- $\beta$ , TNF- $\alpha$ , EGF and IGF by these cells. In this stage of fibrosis development, cytokines released by the injured hepatic cells provide an additional stimulus to Kupffer cells, which further enhances the inflammation phase. Liver endothelial cells, activated by Kupffer cell derived TNF- $\alpha$ , express adhesion molecules, including ICAM-1, enabling leukocyte infiltration in the areas of injured liver tissue. In addition, activated LEC produce cytokines and growth factors like PDGF, VEGF, IL-1, TGF- $\beta$ , ET-1 and molecules such as NO and ROS (21). Microarray analysis of endothelial cell gene expression in normal and cirrhotic rat livers revealed up-regulation of endothelial genes involved in inflammation, ECM production

**Front cover:** schematic representation of hepatic sinusoid structure in a healthy (top) and injured (bottom) liver (detailed description in chapter 1, figure 2).

**Back cover:** schematic representation of liposome structure. Properties of liposomes can be modulated by coupling different ligands to their surface. Drug molecules can be incorporated into the lipid bilayer or encapsulated in the inner part of the vesicle.

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After all, science is essentially international, and it is only through lack of the historical sense that national qualities have been attributed to it.

Maria Curie-Sklodowska