Gene Therapy for Liver Fibrosis

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INTRODUCTION

Liver fibrosis is diagnosed as a histological change in the liver characterized by the severe destruction of normal liver tissues, followed by replacement with fibrotic tissue primarily produced from Hepatic Stellate Cells (HSCs) [1-3]. Fibrosis leads to liver cirrhosis, which is the final outcome of chronic liver diseases and is a leading cause of morbidity and mortality worldwide. The etiology varies, including viral hepatitis (hepatitis B virus, hepatitis C virus, etc.), alcoholic liver injury, nonalcoholic steatohepatitis, parasite infection, and autoimmune diseases [primary biliary cirrhosis and autoimmune hepatitis] [1]. Disease severity depends on hepatic reserve functions and portal hypertension that causes various symptoms. The symptoms include jaundice, ascites, bacterial infection/translocation, spontaneous bacterial peritonitis, hepatorenal syndrome, hepatopulmonary syndrome, gastrointestinal varices, and hepatic encephalopathy [1]. Hepatocarcinogenesis is another complication of liver fibrosis. Annually, hepatocellular carcinomas (HCC) are found in 3–5% of liver cirrhosis patients. Therapeutic options for the etiology, such as interferon, molecular medicines (NS3/4A protease inhibitor, NSSB polymerase inhibitor, NDA inhibitor, and nuclear analogues), corticosteroids, ursodeoxycholic acid, abstinence support for alcohol abuse, nutritional support, have improved liver injuries and contributed to a reduction in the HCC occurrence rate. Therapies for HCC have also been developed, including local resections, transarterial chemoembolization, ablation, chemotherapy using Sorafenib, and bone marrow transplantation [21]. With regard to gene therapy, MMP-expressing gene delivery has been studied using various gene transfer methods. Among those studies, delivery of MMP-1 [4], MMP-8 [5], and MMP-13 [14-16], which are interstitial collagenases, have been reported till date. MMP-13 has recently been investigated as a key factor for recovering from liver fibrosis, and its gene transfer has been tested to examine gene therapeutic effects [2,3,10]. Various methods of gene transfer, including chemicals [14], viral vectors [15], and nonviral physical methods [16] have been tested in vivo. Kim et al. reported the newly designed hyaluronic acid-shielded polyethyleneimine complex efficiently delivered MMP-13-expressing plasmids to a mouse liver cirrhosis model and showed a decrease of collagen deposition in the liver [14]. Endo et al. reported the therapeutic effect of recombinant adenovirus-mediated human MMP-13 gene transfer to a rat liver cirrhosis model [15]. Abe et al. have recently reported that hydrodynamic gene delivery of MMP-13-expressing plasmids showed efficient inhibition of collagen deposition and liver injury in a bile duct ligation liver fibrosis model in rats [16]. These results suggest that gene therapy with MMP can be an effective therapeutic option in the near future, and the promising results will encourage hepatologists to conduct translational research in order to develop treatment for liver fibrosis for improving the prognosis and condition of liver cirrhosis patients. With the recent advances in various gene delivery methods [22-24], further studies to develop an optimum...
gene transfer procedure and long-term studies to show the safety and effectiveness will contribute to the application of these methods in clinical trials.

ACKNOWLEDGMENT

The authors would like to thank Enago for their English language review. This work was supported in part by Grant-in-Aid for Scientific Research from the Japanese Society for the Promotion of Sciences (22890064, 23790595, and 26860354), a Takara Bio Research Grant from JSGT, and an Adaptable and Seamless Technology Transfer Program through target-driven R&D, JST (AS251Z01854P) to Kenya Kamimura.

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