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Review Article

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, gastroesophageal varices, and hepatic encephalopathy [1]. Hepatocarcinognesis 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, NS5B polymerase inhibitor, NS5A 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 Sorafeniband contribute to improving patient prognosis. While these therapies have been significantly advantageous for patients, there have been no standard therapies till date, other than liver transplantation, to reduce the fibrotic tissue in cases of liver cirrhosis. Currently, efforts have been made to establish cell and gene therapies for liver fibrosis patients in order to reduce fibrotic tissue and recover liver function [4-9]. Persistent hepatitis and other liver injuries activate HSCs in the space of Disse and cause the release of several cytokines, enzymes, and Extracellular Matrix (ECM). HSCs play a pivotal role in resolving fibrosis through various enzymes such as Matrix Metalloproteinases (MMPs) and also contribute to the progression of liver fibrosis [2,3,10]. Therefore, the situation can be summarized as an imbalance between production and dissolution of ECM after liver injury [1,3,10].

The current focus of basic research to define a therapeutic target for liver fibrosis include: 1) suppressing the inflammation by therapy for the original etiology as mentioned above [1]; 2) controlling the activation and proliferation of HSCs [11-13]; and 3) enhancement of ECM degradation [2,4,5,14-16]. To control HSC activation, various signaling pathways have been tested including the angiotensin-II type 1 receptor pathway leading to activation of the RhoA/Rho-kinase pathway, PI3K pathways, Janus kinase pathways [11], insulin-like growth factor binding protein-related protein 1 with SMAD3-dependent mechanisms [12]. Recent studies on miRNA showed that miR-214-5p and miR-21 activate HSCs and promote the progression of liver fibrosis [13]. On the other hand, some miRNAs inhibit hepatic fibrosis. miR-16 [17] and miR-146a [18] inhibit the proliferation of HSCs, miR-29b suppresses type I collagen [19], and miR-335 inhibits HSC migration [20]. These studies have revealed possible therapeutic targets for liver fibrosis. Control of ECM includes the expression of MMPs [2,4,5,14-16], antagonists for MMP inhibitor (tissue inhibitors of metalloproteinase; TIMPs), 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 polyethylenimine 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 inclinical trials.

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