Liver-directed Gene Therapy

Kenya Kamimura1*, Hiroyuki Abe1, Takeshi Suda1, Yutaka Aoyagi3 and Dexi Liu2

1Division of Gastroenterology and Hepatology, Graduate School of Medical and Dental Sciences, Niigata University, Japan
2Department of Pharmaceutical and Biomedical Sciences, University of Georgia, College of Pharmacy, USA

Liver is a vital organ in the body responsible for detoxification, protein synthesis and metabolism. Pathologically, the liver is involved in many metabolic and monogenic diseases [1]. The intrinsic anatomic properties of liver make it a preferred target for gene therapy of liver originated or monogenic diseases. Although none of the currently available methods of gene delivery is optimal for liver gene therapy, the concerted effort from researchers has provided a wide range of choices for gene transfer to the liver [2-4]. The objective of this mini-review is to provide a brief summary for various methods developed thus far that are applicable to liver gene therapy (Table 1). Major advantages and disadvantages of each method are also provided for practical consideration.

Virus-based gene-delivery system

Virus-based gene delivery system represents a group of artificially made, replication deficient viruses [5]. The most commonly used ones are adenov-assiated viral vectors [6], lentiviral vectors [7], and ademoviral vectors [8]. Viral vectors under the development include foamy viral vectors [9], herpes simplex viral vectors [10], and oncoretroviral vectors [11]. Viral vector-mediated gene delivery to liver can be achieved via the hepatic artery [12,13], portal vein [14,15], or bile duct [14] or by direct injection to the liver [14]. Recent progress in a pilot phase-II trial revealed that the hepatic arterial injection of recombinant adenovirus p53 is safe and effective in unresectable hepatocellular carcinoma [15]. Adeno-associated virus 8 prefers hepatocytes [17] and has been used for liver-targeted gene therapy intended for treatment of the citrullinemia [18], hemophilia [19], alpha 1-antitrypsin deficiency [20] and viral hepatitis [21] diseases. Viral vectors are highly effective in gene delivery and have been used in approximately 67% clinical trials [22]. Viral vector based carcinogenesis and immunogenicity represent currently the major hurdle for viral vector-mediated gene therapy.

Nonviral gene-delivery system

Compared to viral vectors that employ their natural ability to transfer gene into cells, nonviral gene delivery systems use a physical force or cellular function of endocytosis to facilitate gene transfer to target cells. They are divided into two categories including nonviral vector-mediated gene delivery and physical methods.
parameters in order to ensure clinical success in gene therapy for various liver diseases.

**PERSPECTIVES**

Despite the progress made in developing various methods for effective gene delivery, gene therapy for treatment of liver diseases remains in its infancy. This is primarily due to the fact that many of the liver diseases progress into a fibrotic stage with significant change of liver parenchyma, vasculature, and sinusoids. Consequently, efficient gene delivery by various highly effective methods established using health liver in animals cannot be achieved, resulting in insufficient production of gene product and failure to achieve a successful cure. Evidently, future studies need to take into the consideration of disease status when optimizing a method of gene delivery. There is no doubt, however, gene therapy will become one of the most effective treatments for liver diseases that are not curable with currently available modalities.

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**REFERENCES**


