An Update on Reversal of Liver Fibrosis

Essay

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List of Abbreviations

BDEC : Bile Duct Epithelial Cells

bFGF : Basic Fibroblast Growth Factor

CCl4 : Carbon Tetrachloride

CLD : Chronic Liver Disease

CTGF : Connective Tissue Growth Factor

ECM : Extracellular Matrix

EMT : Epithelial– Mesenchymal Transition

FXR : Farnesoid-X-Receptor

HBV : Hepatitis B Virus

HCC : Hepatocellular carcinoma

HCV : Hepatitis C Virus

HGF : Hepatic Growth Factor

HIV : Human Immunodeficiency Virus

ICAM : Intercellular Adhesion Molecule

LAP : Latency-Associated Protein

LPS : LipopolySaccharide

MCP-1 : Monocyte chemoattractant protein-1

MMP : Matrix Metalloprotieniases

NGF : Nerve Growth Factor

PAMPs : Pathogen-Associated Molecular Pattern

PDGF : Platlet Derived Growth Factor

PPARs : Peroxisome Proliferators Activated Receptors

PRRs : Pattern Recognition Receptor

PXR : Pregnane-X-Receptor

SAP : Serum Amyloid P

siRNA : small interfering RNA

TCRs : T-Cell antigen Receptors

TGF β : Transforming Growth Factor β

TIMPs : Tissue Inhibitors of Metalloproteinases

TLR : Toll-Like Receptor

TRAIL : TNF-Related Apoptosis-Inducing Ligand

uPA-R : Uroplasminogen Activator Receptor

VEGF : Vascular Endothelial Growth Factor

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Ayman Samwel Zaky

I would like to dedicate this essay to the soul of my ***Father****, to my* ***Mother*** *and to my* ***Wife*** *to them I will never find adequate words to express my gratitude.*

Also to all my family

Introduction

Cirrhosis is the final stage of chronic liver damage of various etiologies. It used to be considered an irreversible lesion, but enormous advances in our understanding of hepatic cellular and molecular biology in the past 2 decades have challenged this view. There is now substantial evidence that cirrhosis can be a reversible process. This concept is supported by an increasing number of clinical reports showing the disappearance of cirrhotic lesions from liver biopsies taken from patients cured of their liver disease. The reversal of cirrhosis usually occurs in patients with short-lived liver disease, after the successful treatment of the underlying liver damage ***(Bortolloti and Guido, 2007).***

Following chronic liver injury of any etiology, there is progressive fibrosis. To date, removing the causative agent is the only effective therapy to stop or even reverse liver fibrosis. Therefore, the development of effective antifibrotic therapies represents a challenge for modern hepatology. In the past decade, dramatic advances have been made in the understanding of the cellular and molecular mechanisms underlying liver fibrogenesis ***(Bataller and Brenner, 2001).***

Thus, not only is there good support for treating the underlying cause of liver injury and disease, but there also is

hope that fibrosis that results from liver disease that is not amenable to treatment can be treated with agents that are targeted specifically at fibrosis . Abundant evidence suggests that activation of stellate cells is a key feature in hepatic fibrosis. Additional data suggest that activated stellate cells play an important role in portal hypertension ***(Rocky, 2006).***

Detailed analysis of the cellular and molecular mechanisms that mediate liver fibrosis has provided a framework for therapeutic approaches to prevent, slow down or even reverse fibrosis and cirrhosis. A pivotal event in the development of liver fibrosis is the activation of quiescent hepatic stellate cells (HSCs) to scar-forming myofibroblast (MFB)-like cells. Consequently, HSCs and the factors that regulate HSC activation, proliferation and function represent important anti-fibrotic targets.

Drugs currently licensed in the US and Europe for other indications target HSC-related components of the fibrotic cascade. Their deployment in the near future looks likely.

Ultimately, treatment strategies for liver fibrosis may vary on an individual basis according to etiology, risk of fibrosis progression and the prevailing pathogenic milieu, meaning that a multi-agent approach could be required. The field continues to develop rapidly and starts to identify exciting

potential targets in proof of concept preclinical studies. Despite this, no anti-fibrotics are currently licensed for use in humans.

With epidemiological predictions for the future prevalence of viral, obesity- and alcohol-related cirrhosis painting an increasingly gloomy picture, and a shortfall in donors for liver transplantation, the clinical urgency for new therapies is high ***(Fallowfield, 2011).***

Aim of the Work

In this essay we aimed to discuss the latest available data on prevention of hepatic cirrhosis including all data on hepatic stellate cell and passing to early diagnosis of hepatic fibrosis and newly emerging treatments.

Chapter (1)
Overview of Liver Fibrosis

1.1 An Overview

Hepatic fibrosis, or scarring of the liver, is emerging as a treatable complication of Chronic liver disease, following significant progress in understanding its underlying mechanisms. Efforts have focused on the hepatic stellate cell, as these cells can undergo 'activation' into proliferative and fibrogenic myofibroblast-like cells during liver injury. Stimuli driving stellate cell activation include hepatocellular necrosis due to oxidant stress, apoptosis, and soluble growth factors. Specific lymphocyte subsets can also stimulate fibrogenesis ***(Friedman, 2004)***.

A cascade of signaling and transcriptional events in stellate cells underlies the fibrogenic response to liver injury, with each step in the cascade being a potential target for antifibrotic therapy. Disease-specific fibrogenic mechanisms have also been uncovered: in hepatitis C, this may include direct stimulation of stellate cell activation by viral infection; in nonalcoholic steatohepatitis, elevated levels of leptin and increased leptin signaling by stellate cells increase fibrogenesis. Determinants of fibrosis progression include both environmental and genetic factors, with ongoing efforts to define specific polymorphisms correlating with fibrosis progression rates. Human studies now indicate that fibrosis and

even cirrhosis could be reversible, especially if the underlying disease is eradicated ***(Papastergiou et al., 2012).***

A key challenge is to establish noninvasive means of assessing fibrosis stage and progression using either serum tests and/or imaging. In addition, endpoints of antifibrotic clinical trials need to be established so that reliable evidence of benefit can be identified. Detection and quantification of hepatic fibrosis represents a longstanding challenge in Hepatology. Currently, accurate assessment of liver fibrosis has become increasingly important in order to make therapeutic decisions, determine prognosis and to follow-up disease progression ***(Papastergiou et al., 2012).***

Chronic liver injury, irrespective of cause, is generally associated with the accumulation of matrix proteins, a process referred to as fibrosis. In parallel with this, there is a continued stimulus for regeneration, leading to further distortion of the hepatic architecture and vascular structures (portal veins, hepatic veins) ***(Wallace et al., 2008).***

This results in a transformation to a nodular architecture, so-called cirrhosis. The composition of extracellular matrix molecules in the fibrotic liver is similar to those of other fibrosing parenchyma, including lung and kidney, and is also similar among different etiologies of liver disease Typically fibrosis requires years or decades to become clinically apparent, but notable exceptions in which cirrhosis develops over months may include pediatric liver disease (e.g. biliary atresia), drug-induced liver disease, and viral hepatitis associated with

immunosuppression after liver transplantation ***(Wallace et al., 2008).***

Rapid progress in understanding the mechanisms of hepatic fibrosis exemplifies how basic research has begun to yield meaningful prospects for translation into new diagnostics and treatments for patients with liver disease. These advances include the isolation and characterization of fibrogenic cell types in liver, the clarification of general and disease-specific pathogenic mechanisms, and the broader appreciation of the natural history and reversibility of hepatic fibrosis ***(Friedman, 2004).***