Liver Fibrogenesis - How to Stop Progression?

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Hepatic Fibrosis is the Liver’s Wound Healing Response to Many Chronic Injuries

- Inherited Metabolic Disorders
- Schistosomiasis
- Hepatitis Viruses
- NASH
- Cholestatic Disorders
- Immune Disorders
- Alcohol
- Drugs
Natural History of Chronic Liver Disease

- Normal liver
- Chronic hepatitis with fibrosis (10-50 yrs)
- Cirrhosis
- Hepatocellular Carcinoma
- Liver Transplant
Fibrosis in Liver Disease

Sinusoidal Fibrosis is the earliest site of ECM deposition in liver injury.
Hepatic Stellate cell Activation - A Central Event in Liver Fibrosis

Normal Liver

Activated HSC with Fibrosis

Friedman SL and Arthur, Science and Medicine, 2002
QuickTime™ and a YUV420 codec decompressor are needed to see this picture.
Pathways of Stellate cell Activation

**Initiation**

- INJURY
- Oxidative Stress, cFn

**Perpetuation**

- Proliferation
- Contractility
- Fibrogenesis
- Matrix Degradation
- HSC Chemotaxis
- Retinoid Loss

- ↑ MMP-2
- ↑ Matrix Degradation

**RESOLUTION**

- APOPTOSIS?

**REVERSION?**

Cirrhosis is Reversible!

Evidence in:
- HBV
- HDV
- HCV
- Secondary biliary cirrhosis
- AIH
- PBC
- Wilson’s disease
- Thalassemia after bone marrow xplant
- Animal models
Reversal of Fibrosis after HBV Rx. -

Alpha Smooth Muscle Actin Staining

Improvement in Fibrosis from Long-term Adefovir Therapy

Hadziyannis, et al, Gastro 2006
Reversibility of Cirrhosis Following Treatment of Hepatitis C

Poynard et al, Gastroenterology 2002; 122:1303-1313
Diagnosis of Hepatic Fibrosis - Current Status

- Non-invasive tests (e.g., *Fibrospect, Fibrotest, ELF markers*) are increasingly specific for early or late stages
  - Offer an ‘integrated’ readout of fibrosis.
  - Not yet validated for individual management over time
- Breath tests to measure metabolic reserve are under study and could complement imaging methods
- *Fibroscan* is emerging as an excellent test to diagnose cirrhotic stages in patient with chronic liver disease
- Newer methodologies (modified CT, PET scanning) are being developed
Fibrosis Assessment with Fibroscan®

- Measurements are performed on the right lobe of the liver in intercostal position.
- The patient is lying supine with the right arm placed behind his head.
- Examination time is about 5 minutes.
- Interobserver reproducibility: CVS < 10 %.

Courtesy of M. Ziol
Transient Elastography (Fibroscan) for Assessment of Hepatic Fibrosis

- Correlates with “stiffness”
- ROC= 0.88 for sign fibrosis > F2
- ROC= 0.99 for cirrhosis (F4)

Potential Role of Antifibrotic Therapy

Chronic hepatitis with fibrosis

Normal liver

Cirrhosis

Antifibrotic Therapy

Hepatocellular Carcinoma

Liver Transplant
Emerging Therapies for Hepatic Fibrosis

1. Reduce primary disease

2. Downregulate early stellate cell activation

3. Inhibit properties of activated stellate cells: e.g., proliferation, contractility, fibrogenesis

4. Stimulate stellate cell apoptosis

5. Degrade “scar” matrix
Reduce Primary Disease:
- Antivirals
- Metabolic therapy

HCV, NASH

Resolution

Friedman SL, J Biol Chem, 2000
Block HSC activation:
• Alpha / gamma interferon
  • PPARγ ligands

Resolution
- Caspase inhibitors
- HGF mimetics
- Antioxidants
- FXR ligands

“Hepatoprotectants”

Reduce Injury

Resolution
- PDGF-R antagonists (MoAb, Gleevec)
- RTK antagonists
- Na+ exchange inhibitors
- TGFβ1 & TGFβ1 receptor antagonists
- Collagen inhibitors (halofuginone, ProOHase inhib)
- Hepatocyte growth factor agonists
- AT-Receptor antagonists, ACE Inhibitors
  - Adioponectin
  - Adenosine agonists

Resolution

Fibrogenesis
RESOLUTION

APOPTOSIS?

INJURY

REVERSION?

- Apoptotic ligands, e.g., TRAIL
- TIMP antagonists
- Cannabinoids
- Immunomodulators (e.g., Copaxone)
How to stop progression of fibrosis - Summary

- Reversibility of fibrosis following treatment of underlying disease is now well established.
- Current and developing anti-fibrotic therapies attack pathways of fibrogenesis, promote stellate cell apoptosis, and/or accelerate degradation of scar matrix.
- We still need to learn more about:
  - Determinants and predictors of reversibility - e.g., when is cirrhosis truly irreversible?
  - Mechanisms underlying matrix degradation and regeneration.