Regression of liver fibrosis and innovative anti-fibrotic therapies - *from bench to bedside*

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Reversibility of secondary biliary fibrosis after drainage of the common bile duct

Secondary biliary fibrosis due to compression of common bile duct

30 months after decompression of common bile duct

Progression and regression of liver fibrosis in animal models

Hydroxyproline (% of control)

Control  6 weeks  8 weeks  12 weeks  4 weeks  12 weeks  24 weeks  52 weeks

Issa et al. Gastroenterology 2004
Specific interventions to reduce liver fibrosis

- Autoimmune hepatitis
- Hepatitis B
- Hepatitis C
- Alcoholic liver fibrosis
- Hemochromatosis
- NASH in obese subjects
Regression of fibrosis in patients with chronic hepatitis C and sustained virological response

Controlled studies have shown that sustained virological response (SVR) is associated with a significant decrease in fibrosis stage compared to non-sustained virological response (NSVR) and controls. The charts illustrate the change in fibrosis stage over a period of 3 years or more in paired liver biopsies.

- Paired liver biopsies < 3 yrs
- Paired liver biopsies ≥ 3 yrs

Non-specific interventions for regression of liver fibrosis

- Hepatocytes
- Immune cells
- Endothelial cells
- Stellate cells / Myofibroblasts
- Kupffer cells

Cytokines, Chemokines, Growth factors, TIMPs, MMPs
Interaction between immune mediators and TIMPs

CX3CR1

HSC stimulation with fractalkine

TIMP1 mRNA expression/β-actin

Control  CX3CL1

Wasmuth et al. J Hep 2007, in press
Non-specific interventions for regression of liver fibrosis

Hepatocytes

Kupffer cells

Immune cells

Endothelial cells

Stellate cells / Myofibroblasts

IL-10
IL-10 suppresses liver fibrosis in vivo

Safadi et al. Gastroenterology 2004
Reduced liver fibrosis in CCL5 knockout mice

**CCl4**

- CCL5 WT
- CCL5 KO

**MCD**

- CCL5 WT
- CCL5 KO

Hyroxypoline (µg/g liver)

- $P = 0.02$
- $P = 0.03$

Rueland et al. AASLD 2007
Phenotypic changes in the immune system in CCL5 knockout mice

Rueland et al. AASLD 2007
High IL-10 is associated with reduced SMA expression

CCL5 WT  CCL5 KO

Rueland et al. AASLD 2007
IL-10 administration ameliorates liver fibrosis in patients with hepatitis C

4 or 8 µg/kg IL-10/daily for 12 months

Nelson DR et al. Hepatology 2003
Non-specific interventions for regression of liver fibrosis
IFN-γ has antifibrotic properties in animal models

Shi et al. PNAS 1997
Results of a clinical trial of IFN-\(\gamma\)1b for fibrosis regression in chronic hepatitis C

![Bar chart showing change in Ishak Score for IFN-\(\gamma\)1b at 200 \(\mu\)g (n = 157), IFN-\(\gamma\)1b at 100 \(\mu\)g (n = 169), and Placebo (n = 162).]

- IFN-\(\gamma\)1b 200 \(\mu\)g: 12% Point reduction, 12% No Change, 16% Worsening
- IFN-\(\gamma\)1b 100 \(\mu\)g: 12% Point reduction, 12% No Change, 16% Worsening
- Placebo: 12% Point reduction, 12% No Change, 16% Worsening

Patients with a strong induction of CXCL11 (ITAC) benefit from IFN-γ administration

Pockros et al. Hepatology 2007
Interferon-inducible chemokines are ligands of the receptor CXCR3

Immune cells

CXCL9 (MIG)
CXCL10 (IP-10)
CXCL11 (ITAC)

Stellate cells / Myofibroblasts

CXCR3
Deletion of CXCR3 leads to increased fibrosis *in vivo*

Sirius Red, 100 x

**CXCR3 WT**

**CXCR3**

**Histological fibrosis score**

**CXCL9 concentration**

\[ P = 0.003 \]

\[ P = 0.0017 \]

Deletion of CXCR3 leads to increased fibrosis *in vivo*
Non-specific intervention strategies for resolution of liver fibrosis - summary

Therapeutic Intervention

- Adiponectin ↑
- Insulin resistance ↓
- Activated myofibroblast
- Apoptotic stellate cell
- Resolution of extracellular matrix

Th1- cell
Th2- cell

T-helper cell

IL-12 ↑

IFN-γ

Wasmuth & Trautwein. Hepatology 2007

Non-specific intervention strategies for resolution of liver fibrosis - summary