Mechanisms of hepatic fibrogenesis in chronic liver disease

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**OVERVIEW**

- **ACUTE INJURY**
- **INFLAMMATION**
- **FIBROGENESIS**
- **CIRRHOSIS**
- **CONSEQUENCES**

**Healthy** → **Inflammation** → **Fibrogenesis** → **Cirrhosis** → **Consequences**

- **Myofibroblasts**
- **Hepatic Stellate Cells (HSCs)**

**Activation**

- Other cells implicated

**Morphological and functional features**
Causes of fibrogenesis

• Numerous liver functions → various causes

**Primary causes**
- Viral hepatites: rapid progression
- Alcoholic liver disease: most frequent in Western countries
- Non-alcoholic liver disease

**Secondary causes**
- Extrahepatic infections
- Disseminated cancer

• Family association, genetic predisposition
Injury becomes chronic

ACUTE INJURY

HEALTHY
INFLAMMATION
FIBROGENESIS
CIRRHOSIS
CONSEQUENCES

MYOFIBROBLASTS

HEPATIC STELLATE CELLS (HSCs)

Morphological and functional features

ACTIVATION

Other cells implicated
ORIGIN OF THE MYOFIBROBLAST

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2888531/
Healthy → Inflammation → Fibrogenesis → Cirrhosis → Consequences

ACUTE INJURY

Injury becomes chronic

Healthy

Inflammation

Fibrogenesis

Cirrhosis

Consequences

Myofibroblasts

Morphological and functional features

Hepatic Stellate Cells (HSCs)

Activation

Other cells implicated
HEPATIC STELLATE CELLS (HSCs)

Morphological features

Drawing of the organisation in the liver. Cambridge.org
LIVER, NORMAL
The space of Disse contains small amounts of **type IV collagen** which is highlighted as blue by trichrome staining.

LIVER, FIBROGENESIS
The space of Disse contains large amounts of **type I collagen**

Functional features

- Liver fibrosis
- Liver development and regeneration
- Immunoregulation
- Angiogenesis

→ Retinoid metabolism

pathpedia.org
Injury becomes chronic

ACUTE INJURY

HEALTHY  INFLAMMATION  FIBROGENESIS  CIRRHOSIS  CONSEQUENCES

MYOFIBROBLASTS

HEPATIC STELLATE CELLS (HSCs)

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Injury becomes chronic
OTHER CELLS IMPLICATED

Neighboring cells of HSCs

Normal endothelial cells → Endothelial cells without functions → Hepatocytes

HSCs
Quiescent phenotype → Activated phenotype

"profibrogenic macrophages" → "restorative macrophages"

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Matrix Metalloproteinase (MMP)

HSCs
TGFβ + PDGF ECM component

Increase of fibrogenesis

ECM: Extracellular matrix
Other immune cells

- **Th1**
  - **IFNγ**
  - ANTIFIBROGENIC

- **NK cells**
  - **Apoptosis of HSCs**

- **Th2**
  - **IL-3**
  - PROFIBROGENIC

- **Th17**
  - **IL-17**

- Role not well-defined for B cells and Treg cells
Molecular mechanism

- Hepatic homeostasis is disturbed → FIBROGENESIS

Diagram:

- Apoptosis of the parenchymal cells
  - Activation
  - Stellate cells
  - Macrophages
  - Hepatocytes
  - Reactive Oxygen Species
  - Decrease of NADP oxidase

- Leukocyte infiltration
- Lack of inflammatory cells

Final result: FIBROGENESIS
Acute injury becomes chronic, leading to inflammation, fibrogenesis, cirrhosis, and other consequences. Myofibroblasts and hepatic stellate cells (HSCs) are activated with morphological and functional features. Other cells are also implicated.
HEPATIC STELLATE CELL’S ACTIVATION

• It’s responsible of liver fibrosis
• We can observe it in chronic hepatic injury

• It occurs in two majors phases :
  1. Initiation
  2. Perpetuation
Initiation

INJURY
Oxidative Stress, cFn

Perpetuation

Proliferation
PDGF
ET-1
TGF-β1
PDGF, MCP-1
MCP-1
PDGF, Serum

Contractility

Fibrogenesis

? MMP-2

? Matrix Degradation

HSC Chemotaxis

Retinoid Loss

RESOLUTION

REVERSION?

APOPTOSIS?
First phase: Initiation

- Results mostly from paracrine stimulation from neighboring cells
- Also due to exposure to lipid peroxides and products of damaged hepatocytes
• Kupffer cells and endothelial cells stimulate Hepatic stellate cells, by producing TGF-β
• Hepatocyte apoptosis following injury also promotes stellate cell initiation

• Cytochrome CYP2E1
Second phase: Perpetuation

- Changement in cell behavior
- The net effect of these changes is to increase accumulation of extracellular matrix
- There are two main profibrogenetics consequences of this changement
  - Increasing number of extracellular matrix producing cells
  - Increasing matrix production per cell
Increasing cell number

- Hepatic stellate cell mitosis, due to mitogens factors (PDGF)

- Cells that migrate towards cytokine chemoattractants (PDGF, MCP-1, and CXCR3)
Increasing matrix production

- The most potent stimulus for matrix production by stellate cells is TGF-β (paracrine and autocrine source)
- Fully activated hepatic stellate cells shut down expression of MMP
- Activated stellate cells produce functional TIMPs (collagenase inhibitor)
- Protein α-Smooth Muscle Actin is increased
Healthy → Inflammation → Fibrogenesis → Cirrhosis → Consequences

Injury becomes chronic

Acute injury

Myofibroblasts

Morphological and functional features

Hepatic stellate cells (HSCs)

Activation

Other cells implicated
CONSEQUENCES

- **Portal hypertension**
  → Decrease of compliance in the liver leads to higher venous pressure

- **Hepatocarcinoma**
  → Chronic disease: constant cycle of damage and repair

- **Angiogenesis**
  → HSC’s produce angiogenic growth factors

- **Two mechanisms of angiogenesis**
  → After injury: overexpression of growth factors
  → During tissue hypoxia
Regression

- Regression of liver fibrosis can occur when underlying disease is treated
- Increase collagenolytic activity

http://www.jci.org/articles/view/24282/figure/4
Regression (2)

- TIMP-1 is expressed during liver disease
- TIMP-1 naturally inhibits MMP’s
- MMP-1 is responsible for degradation of type 1 collagen
- When disease is treated: TIMP-1↓ which results in MMP↑
Prospective therapies

- Current treatment → Target the underlying disease
- Some treatments targeting specific receptors in early phase
- CB1 and 2 receptors in fibrogenic cascade
- PPAR agonist shows reduced inflammation
CONCLUSION

- Healing mechanism → disease
- HSCs → myofibroblasts → overproduction of ECM
  - Influencing cells
    - Macrophages
    - Endothelial cells
    - Other immune cells
- Main long run cause: overconsumption of alcohol
- Main long run consequence: portal hypertension
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S.L.I.F.

Thank you!

(SORRY. LIVER. IT'S. FRIDAY.)