Mecanismos de fibrosis inducida por alcohol

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I have no conflict of interests related to this presentation
Cirrhosis: a condition with multiple etiologies

- Alcohol
- Viral hepatitis B, C, D (e)
- NASH
- DILI
- Genetic
  - Hemochromatosis
  - Wilson, α-1AT
- Autoimmune hepatitis
- «Cardiac»
  - C. Per, BCS, TVD
- «Biliary»
  - PBC, PSC, B. Atresia
  - Cystic fibrosis
Let’s review how alcohol can lead to fibrosis & cirrhosis
Cirrhosis is the 12th leading cause of death in the world.

Alcohol is responsible for half of those cirrhosis-related deaths.

Around 3.3 million deaths in 2012 were directly related to alcohol.

Rehm J & Shiedl KD., Alcohol research : current reviews. 2013
Probably there is no ‘safe’ level of drinking
Chief Medical Officers: There is no ‘safe’ level of drinking

Department of Health

Changes to low risk weekly drinking guidelines for men.

Was 21 units/week

Now 14 units/week

One standard drink = 12-14g of alcohol

300ml  100ml  50ml

Cirrhosis is proportional to amount of alcohol intake

Felix Stickel, Jochen Hampe
Published 2012 in Gut
What is the mechanism for fibrosis?

Singal AK, et al. Am J Gastroenterol 2018
Bataller R & Gao B. Sem Liv Dis 2015
Fibrosis... Liver Gut

A TALE OF TWO CITIES
CHARLES DICKENS
In the liver, the problem starts with ethanol metabolism.

It looks simple, but...
Acetaldehyde induces inflammation and hepatocyte death

**INFLAMMATION & APOPTOSIS**
- Redox state changes in NAD/NADH ratio
- Acetaldehyde formation (adducts)
- Mitochondrial damage
- Cytokine formation (TNFα)
- Kupffer cell activation
- Hypoxia
- Reactive oxygen species (ROS)
- Lipid peroxidation
- Oxidative stress
The Gut-Liver Axis

Alcohol affects the gut...

- Bacterial overgrowth
- Increased gut permeability
- Bacterial translocation
- Endotoxins (PAMPs - LPS)

Szabo G. Gastroenterology. 2015
Arroyo V. & Schnabl B. Nat Rev Dis Primers 2016
Alcoholic liver disease is transmittable in mice

Llopis M, Cassard AM, Perlemuter G Gut 2016
Fecal microbiota transplantation in steroid-ineligible patients with alcoholic hepatitis

Actuarial probability of survival

- Survived 87.5%
- Survived 33.3%

$P = .018$

<table>
<thead>
<tr>
<th>Group</th>
<th>At risk</th>
<th>Events</th>
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<td>FMT N = 8</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>HC N = 18</td>
<td>18</td>
<td>9</td>
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Time (months)

Activation of Kupffer cells is a central event in ALD
KCs are potent immune cells

Resident liver macrophages located in sinusoids (liver’s first line of defense)...

Karl Wilhelm von Kupffer (1876)
Activated Kupffer cells can “choose” an M1 or M2 phenotype...

Adapted from Thu NLA & Horuzsko A. Enzymology & Metabolism, 2015
Activated Kupffer cells can induce activation of stellate cells

Hepatocytes

Ethanol, Viruses, Toxins, Steatosis

Injury

Oxidative stress

Kupffer cell Activation

ROS, TGFβ, Cytokines

TGFβ, PDGF

Activated Kupffer cell

Quiescent Stellate cell

Activation

Activated Stellate cell

PDGF, CTGF, TGFβ

COL1A1, COL1A2

Increased ECM production

TIMP1

MMP1/13

Matrix Remodeling

Fibrosis

Activated stellate cells turn into myofibroblasts and start fibrosis.
Myofibroblasts = fibrosis & much more...

Fibrosis alters liver architecture...

Normal Liver

Fibrotic Liver

Friedman PNAS 1985
Friedman JBC 2000
Iredale JCI 2007
The process may be reversible if alcohol intake ceases...

Friedman SL. PNAS 2012
Mistery? only ~35% of heavy drinkers develop AH ± cirrhosis
There are many possible factors to explain this fact...

- Pattern of consumption
- Beverage type
- Age/Gender
- Obesity/Smoking
- Race/Ethnicity
- Genetics PNPLA3 p.I148M
- Nutritional factors
- Alcohol-Drug interactions
- Other diseases: HFE/AAT1
Summary

• Alcohol is responsible for 50% of deaths from cirrhosis

• Alcohol metabolism damages the liver and the gut

• Gut-Liver Axis induce activation of Kupffer & stellate cells

• Risk modifiers and antifibrotics are under investigation...