Role of lipogenesis and ER stress in hepatic steatosis

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NAFLD : Non alcoholic fatty liver disease

NAFLD

Steatosis

NASH

Cirrhosis

Triglycerides

Triglycerides + Inflammation

20% in the general population

90% in the obese population
Role of lipogenesis in the development of steatosis

Major contribution

1/3 of the triglycerides stored

(Donnelly, JCI, 2005)

Lipogenesis

Lipogenesis is controlled by insulin through SREBP-1c

Glucose

Insulin

Glucose-6P

Glycolysis

SREBP-1c

Esterification

Lipogenesis

Triglycerides

Fatty acids

Citrate

Fatty acid synthase (FAS)

Acetyl-CoA carboxylase (ACC)
SREBP-1c is induced by insulin

SREBP-1c activates the lipogenic program and induces hepatic steatosis when overexpressed
In obese animals with a fatty liver ...

High gluconeogenesis
Insulin resistance
High lipogenesis

SREBP-1c is overexpressed in the liver of obese rodents

Can SREBP-1c be induced by another mechanism than insulin?
ER stress:
An imbalance between ER protein load and ER folding capacity

Excessive protein synthesis
Accumulation of unfolded proteins

ER STRESS

ER protein load
ER capacity of maturation

The Unfolded Protein Response

Inhibition of translation
Activation of transcription of ER proteins
Protein degradation (ERAD)
Apoptosis
The Unfolded Protein Response

**UPR activation**

Inhibition of translation

Activation of transcription

chaperones, foldases
SREBP-1c proteolytic cleavage is induced by ER stress in hepatocytes

If an ER stress is responsible for SREBP-1c proteolytic cleavage in the liver of obese animals, then inhibition of ER stress should reverse the high lipogenesis and steatosis observed in these animals?

Overexpression of the chaperone Bip/GRP78
Bip overexpression reduces ER stress and inhibits SREBP-1c proteolytic cleavage \textit{in vitro}

SREBP-1c proteolytic cleavage is reduced in ob/ob mice when ER stress is inhibited

Kammoun et al. JCI, 2009
ER stress inhibition decreases lipogenic enzymes gene expression

ER stress inhibition improves hepatic steatosis
**ER stress inhibition restores insulin sensibility in ob/ob mice**

![Graph showing glucose infusion rate, glucose utilisation, and glucose production](image)

**Effect of ER stress inhibition on insulin signalling in the liver of ob/ob mice**

![Diagram showing insulin signalling pathways](image)

**ER stress inhibition restores IRS2-mediated insulin signalling in the liver**
SREBP-1c interacts with an ER stress activated protein: TRB3

**Interaction domain SREBP-1c/TRB3**

**Colonies**

- nSREBP-1c +
- D50 +
- D155 +
- D189 +

**Input GST pull down**

- GST
- GST (1µg)
- GST (1µg) + TRB3 V5 lysate
- Control Lysate

**Diagram**

- PERK
- elf2αP
- ATF4
- CHOP
- TRB3

Inhibition of translation

**Domaine homologue aux Ser/Thr kinases**

- NH₂
- IV
- V
- VI
- VII
- VIII
- IX
- X
- XI
- COOH
TRB3 expression is induced by insulin and ER stress in primary hepatocytes

TRB3 activation by insulin and ER stress is dependent on SREBP-1c
Inhibition of TRB3 expression by ShRNA in hepatocytes

Ad ShTRB3 leads to SREBP-1c mature form disappearance in cultured hepatocytes
Ad ShTRB3 leads to SREBP-1c disappearance in liver of ob/ob mice.

Ad Sh control
Ad Sh TRB3

Plasma triglycerides
Liver triglycerides
Plasma glucose

Plasma cholesterol
Liver cholesterol
Plasma insulin
The ShTRB3 mice have increased hepatic insulin sensitivity

Conclusion