



13TH PARIS HEPATOLOGY CONFERENCE (PHC) 2020
JANUARY 13, 2020-JANUARY 14, 2020

PATHOPHYSIOLOGY OF NAFLD AND NASH

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www.ucl.ac.uk/medicine/liver-and-digestive-health

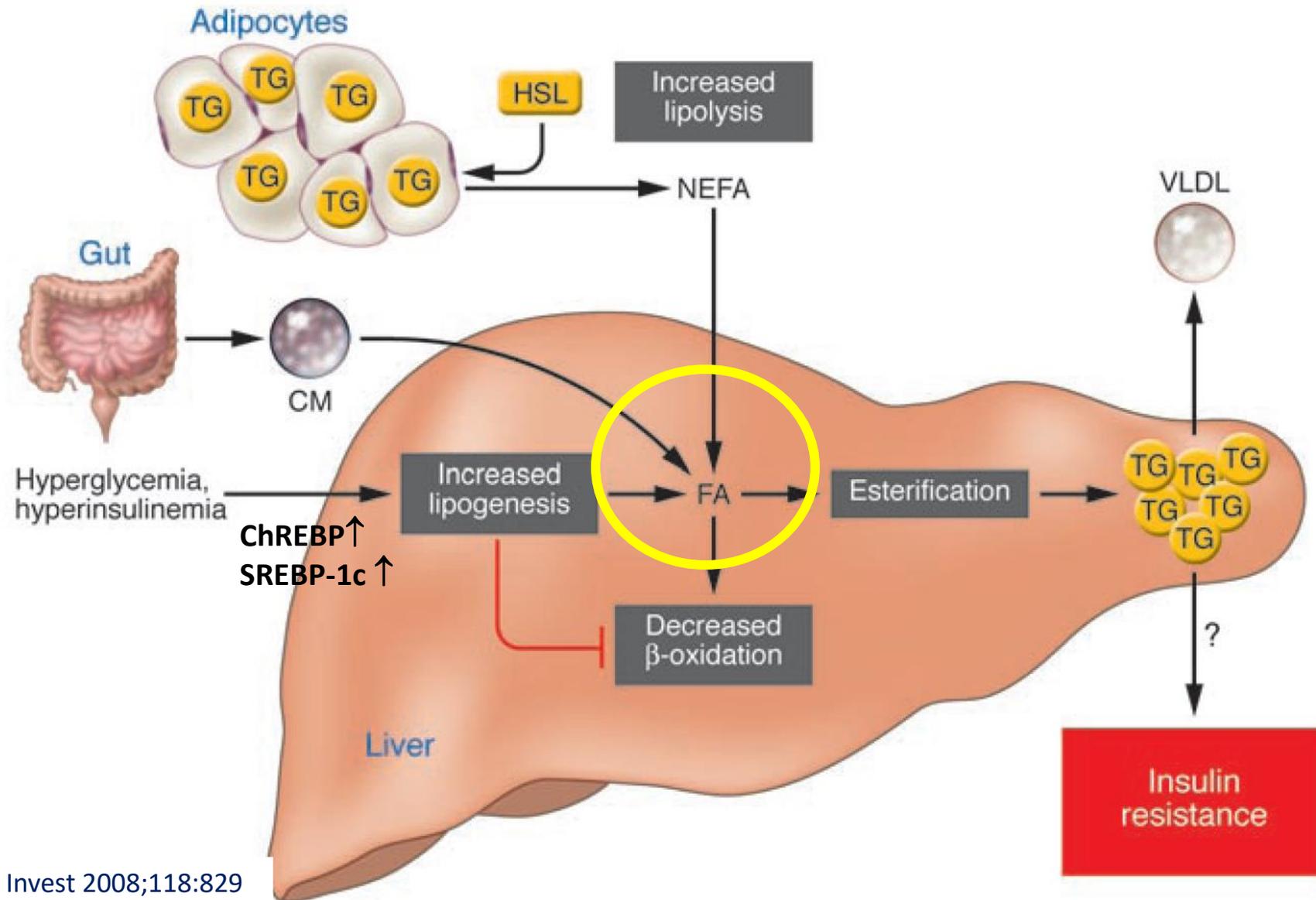
Disclosures (2020)

1. Inventor and patent holder ELF test (Siemens)
2. Speakers bureau: Echosens (Paris, France)
3. SAB/Consultancy: Promethera (Belgium); NeuroVive (Sweden); Chemomab (Israel); Median Technology (France/USA); Boheringer-Ingelheim (Germany); Takeda (USA)
4. Co-Founder and Director, Engitix Ltd (UCL Spin-out) (UK)*
5. Co-Founder and Director, 3P-Sense Ltd (UCL Spin-out) (UK)**
7. Chair EASL Consortium for Regenerative Hepatology (2019-2022)

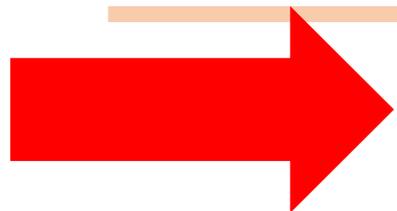
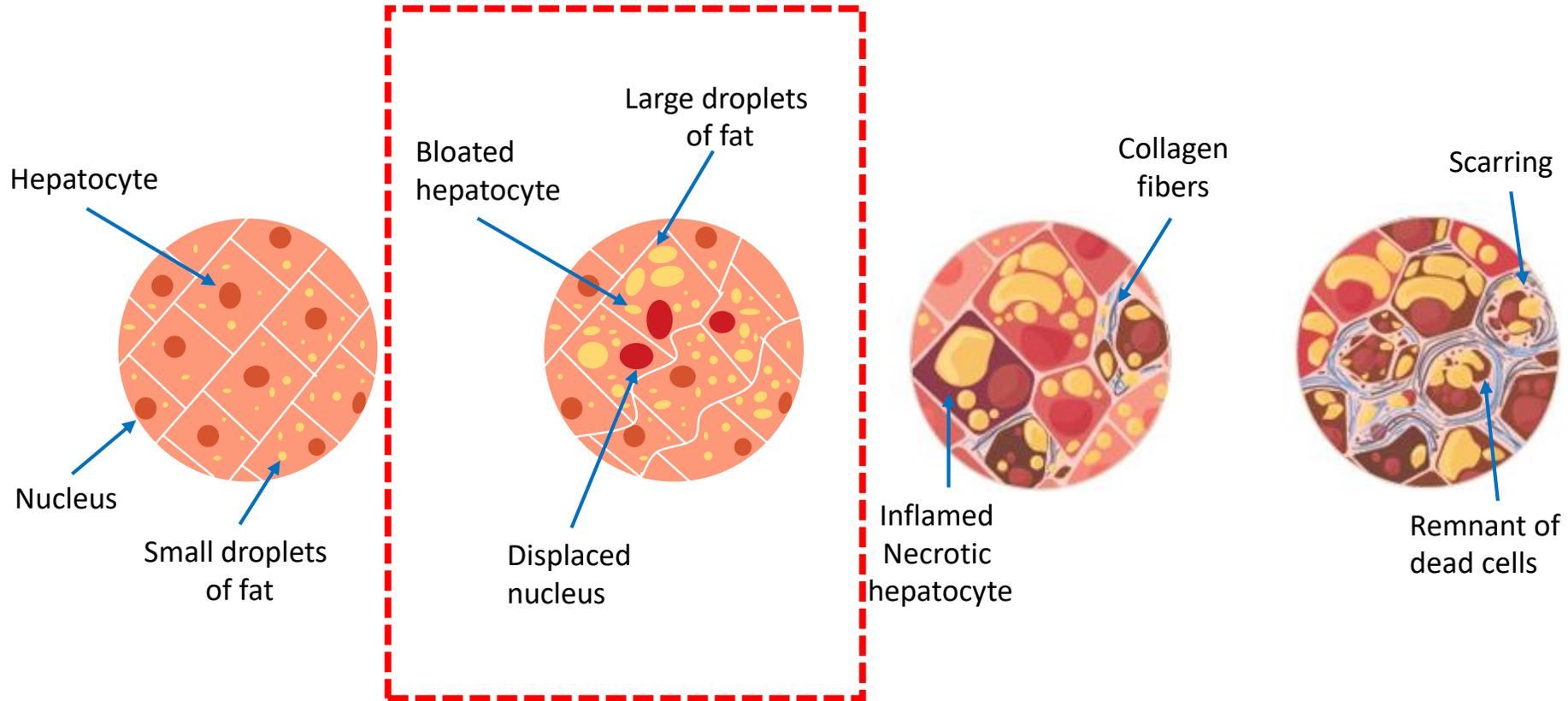
* Regenerative medicine and tissue engineering

** Nanotechnology diagnostics

Metabolic Defects Leading to Steatosis



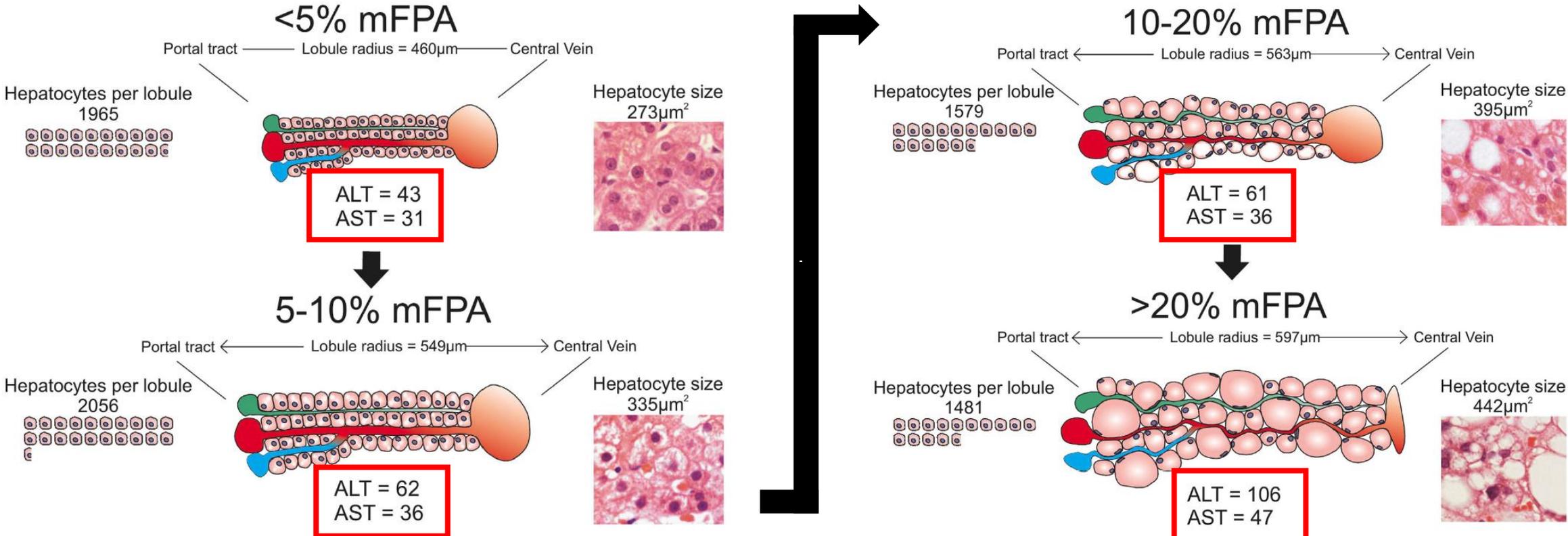
NAFLD: Natural History



ADAPTATION

PATHOLOGY

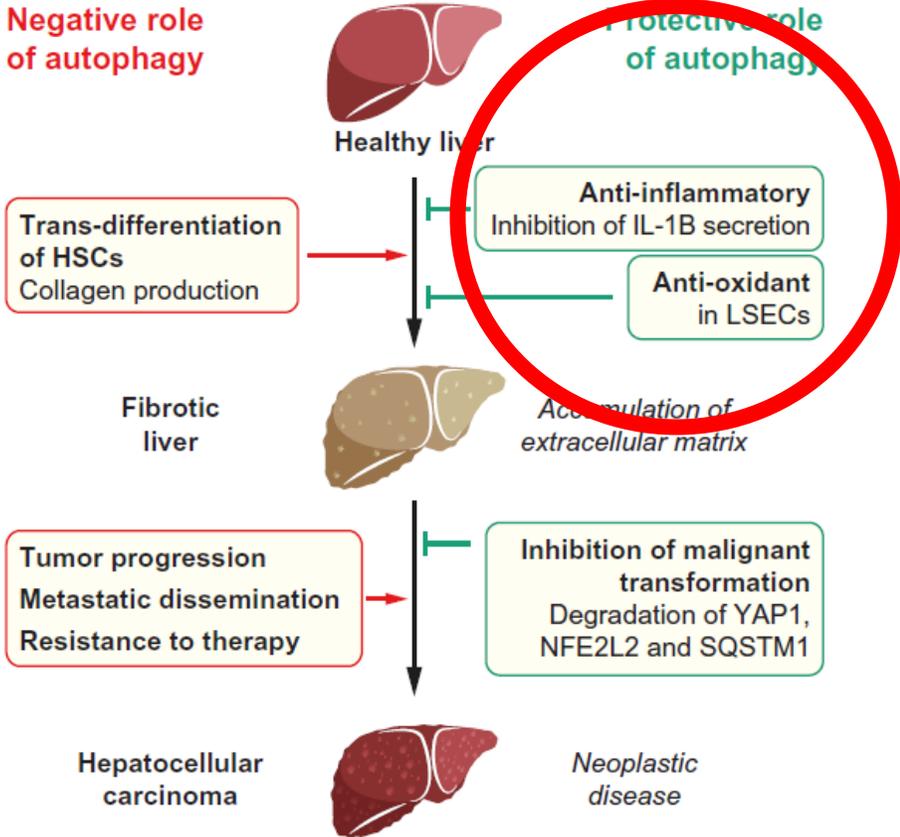
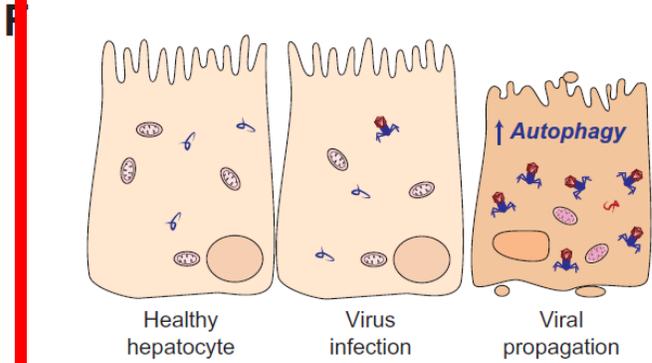
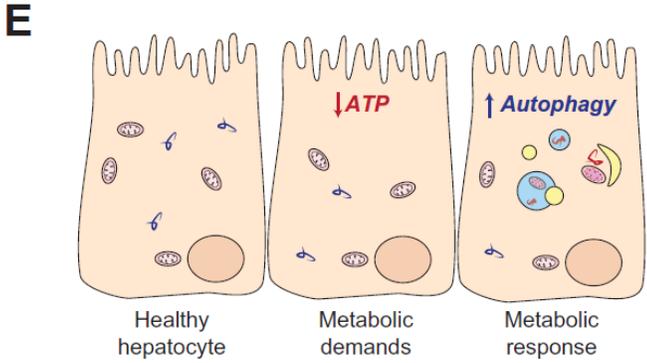
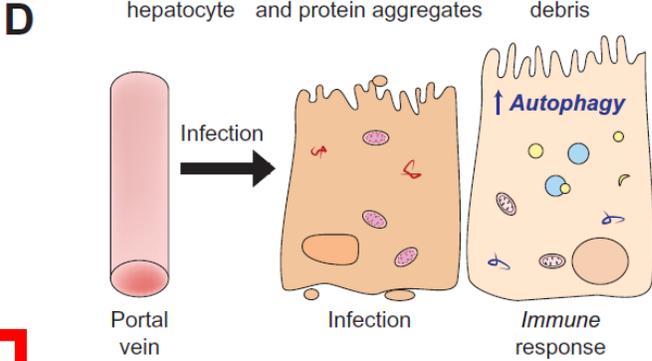
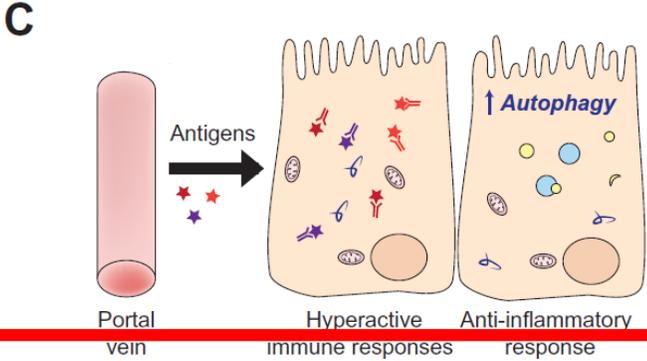
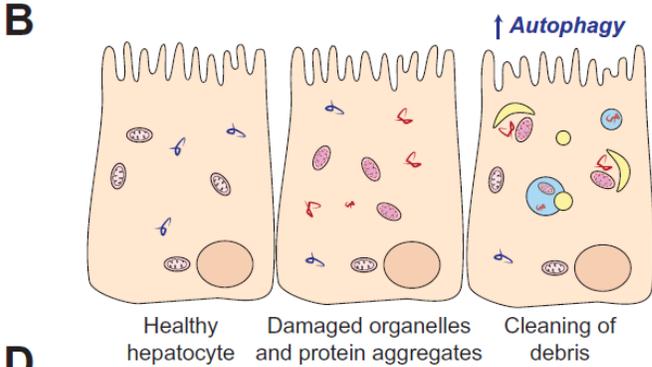
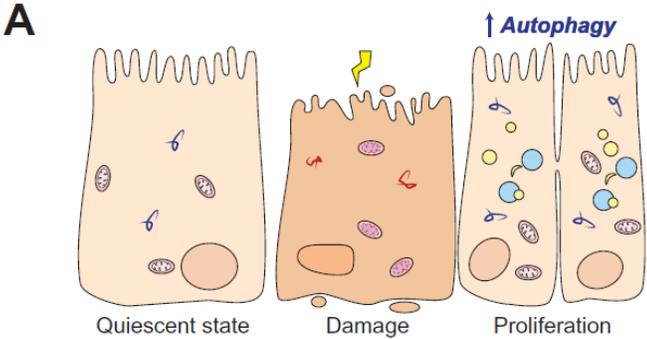
Adaptation of the Liver Lobule with Increasing Fat Accumulation



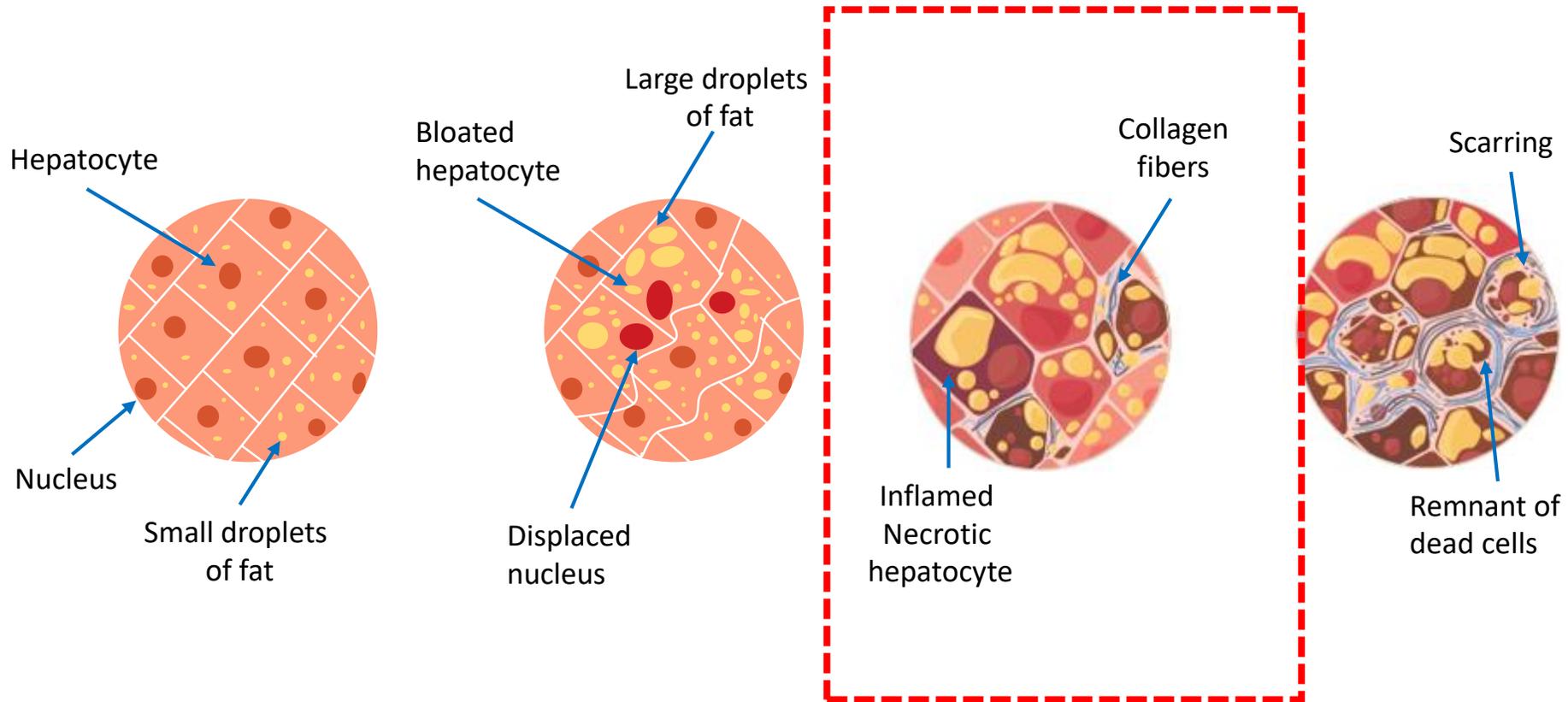
Micro-environmental predisposing condition to oxidative stress?
 Role of Autophagy?

Autophagy in hepatic adaptation to stress

Younis Hazari^{1,2,3}, José Manuel Bravo-San Pedro⁴, Claudio Hetz^{1,2,3,5,*}, Lorenzo Galluzzi^{6,7,8,9,†}, Guido Kroemer^{4,9,10,11,12,13,*}



NAFLD: Natural History



ADAPTATION



PATHOLOGY

Type of Fibrosis

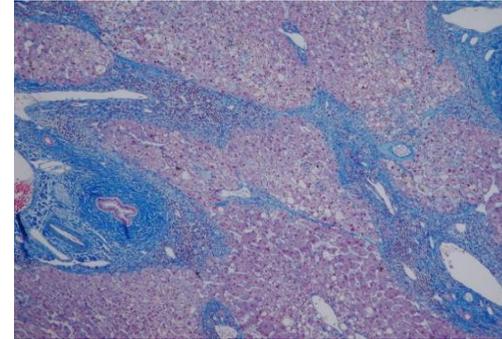
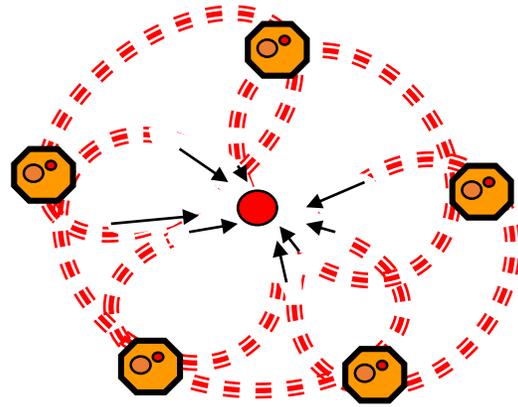
Pattern

Histology

Prevalent Mechanisms

Post-necrotic:

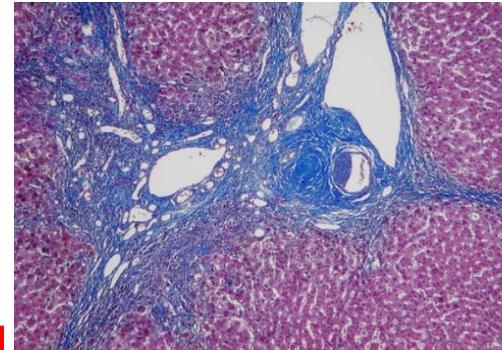
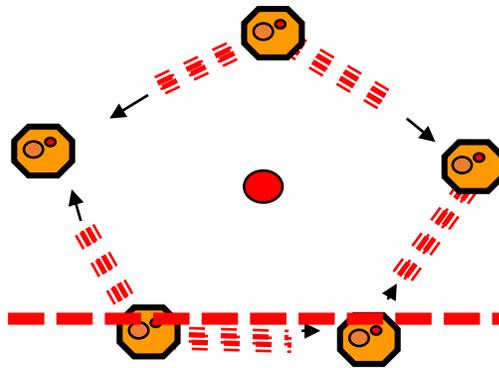
Viral Hepatitis,
Autoimmune
Hepatitis



Chronic Wound
Healing

Biliary:

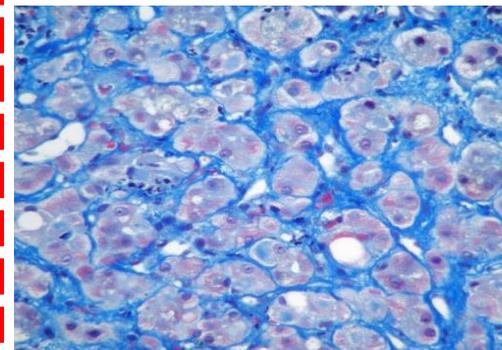
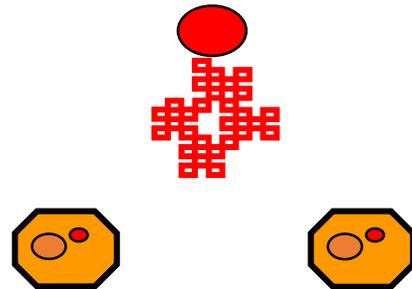
Primary Biliary
Cirrhosis
Primary Sclerosing
Cholangitis
Secondary Biliary
Cirrhosis



Epithelial-
Mesenchymal
Disruption,
Reactive
Cholangiocytes,
Bile salt toxicity.
Deranged gut-
liver immunity?

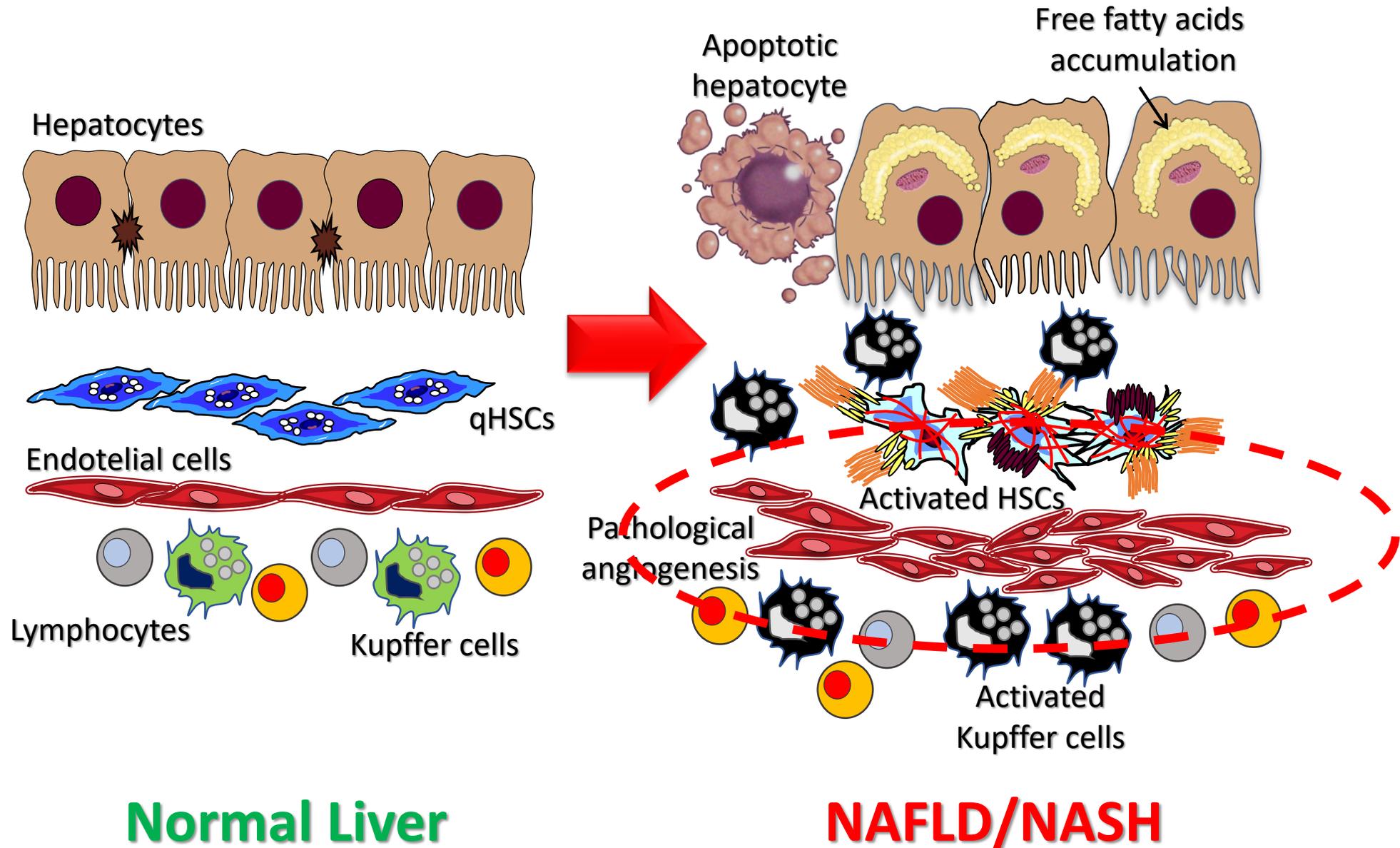
Pericellular:

Alcoholic
Steatohepatitis
Non Alcoholic
Steatohepatitis
(Haemochromatosis/
Wilson Disease)

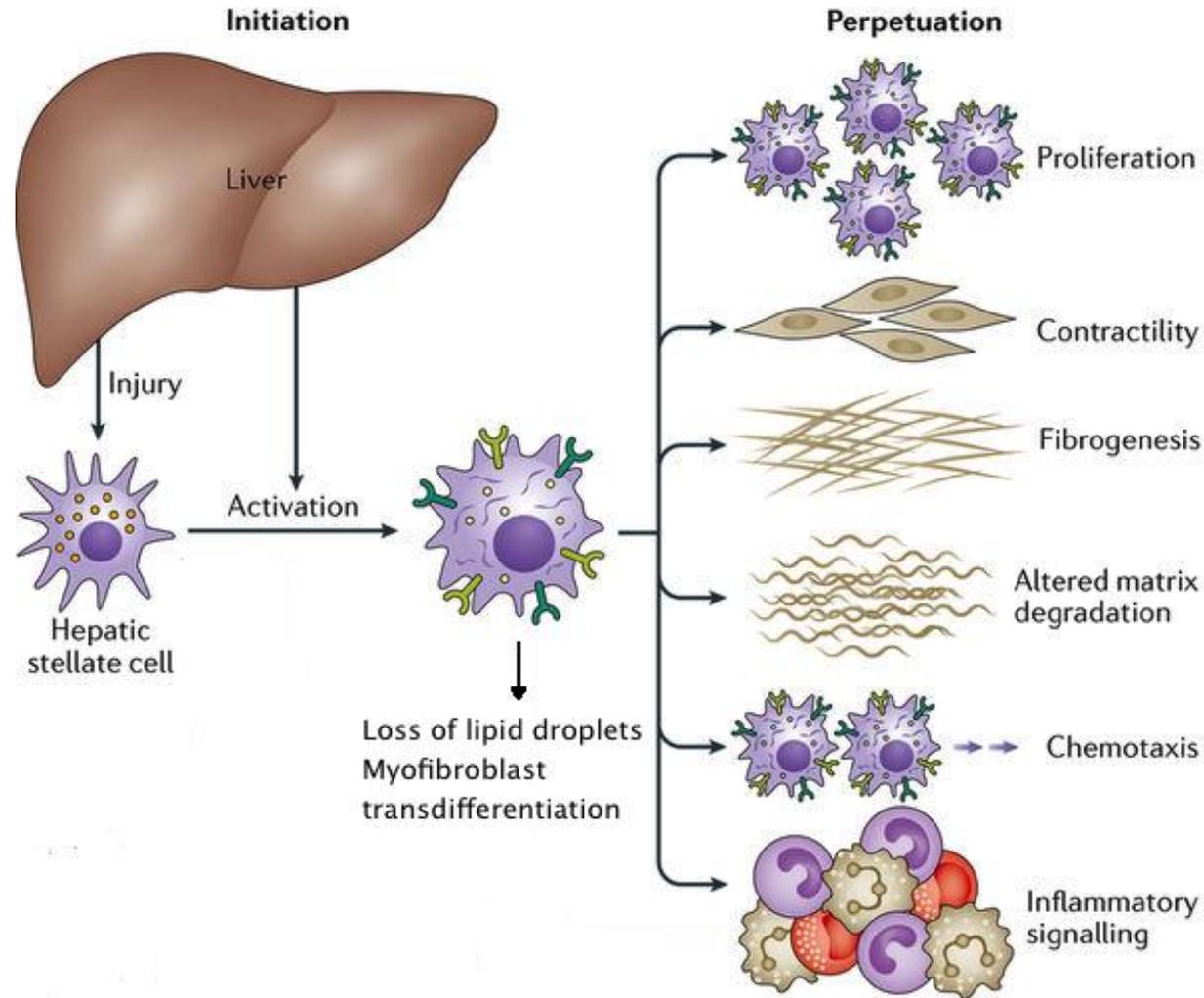


Oxydative
Stress,
Reactive
Aldehydes,
Lipotoxicity

Pathogenesis of NASH



Pathways of Stellate Cell Activation in Liver Injury

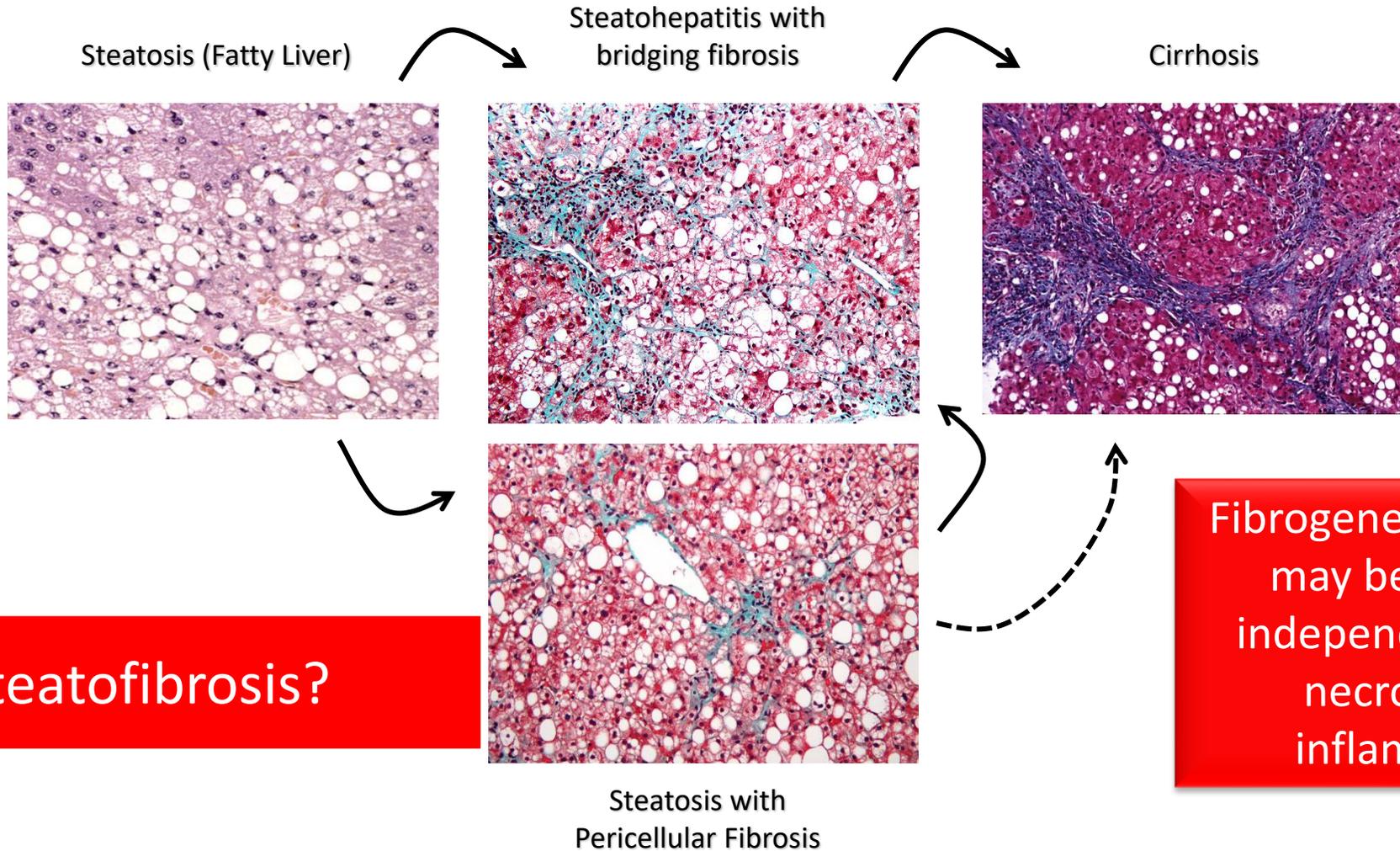


Increased tissue tension and stiffness

Changes in ECM quantity and relative composition

ECM as a bio-reservoir of pro-inflammatory and pro-angiogenic factors

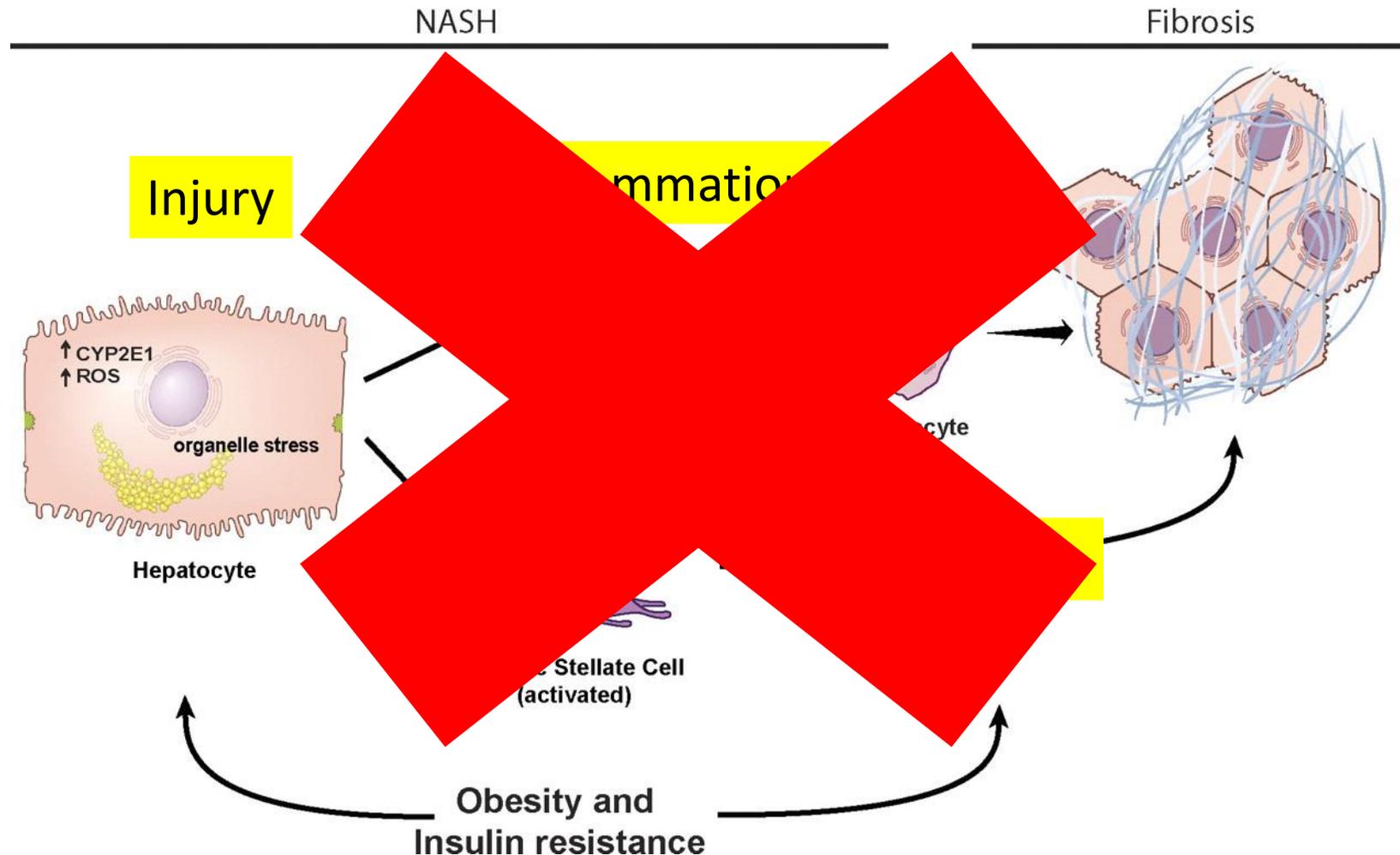
Fibrotic Evolution of NASH



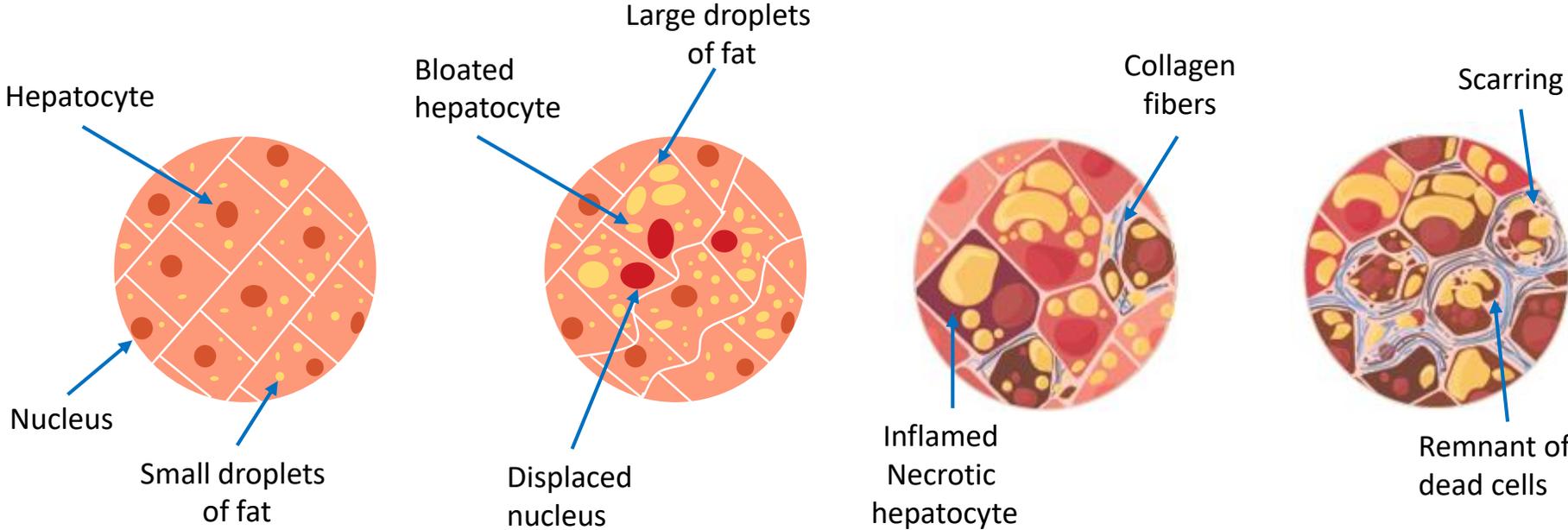
Steatofibrosis?

Fibrogenesis in NAFLD may be partially independent of cell necrosis and inflammation

Fibrosis in NASH: A Chronic Wound Healing Response?



NASH Fibrosis: Stage-dependent Mechanisms



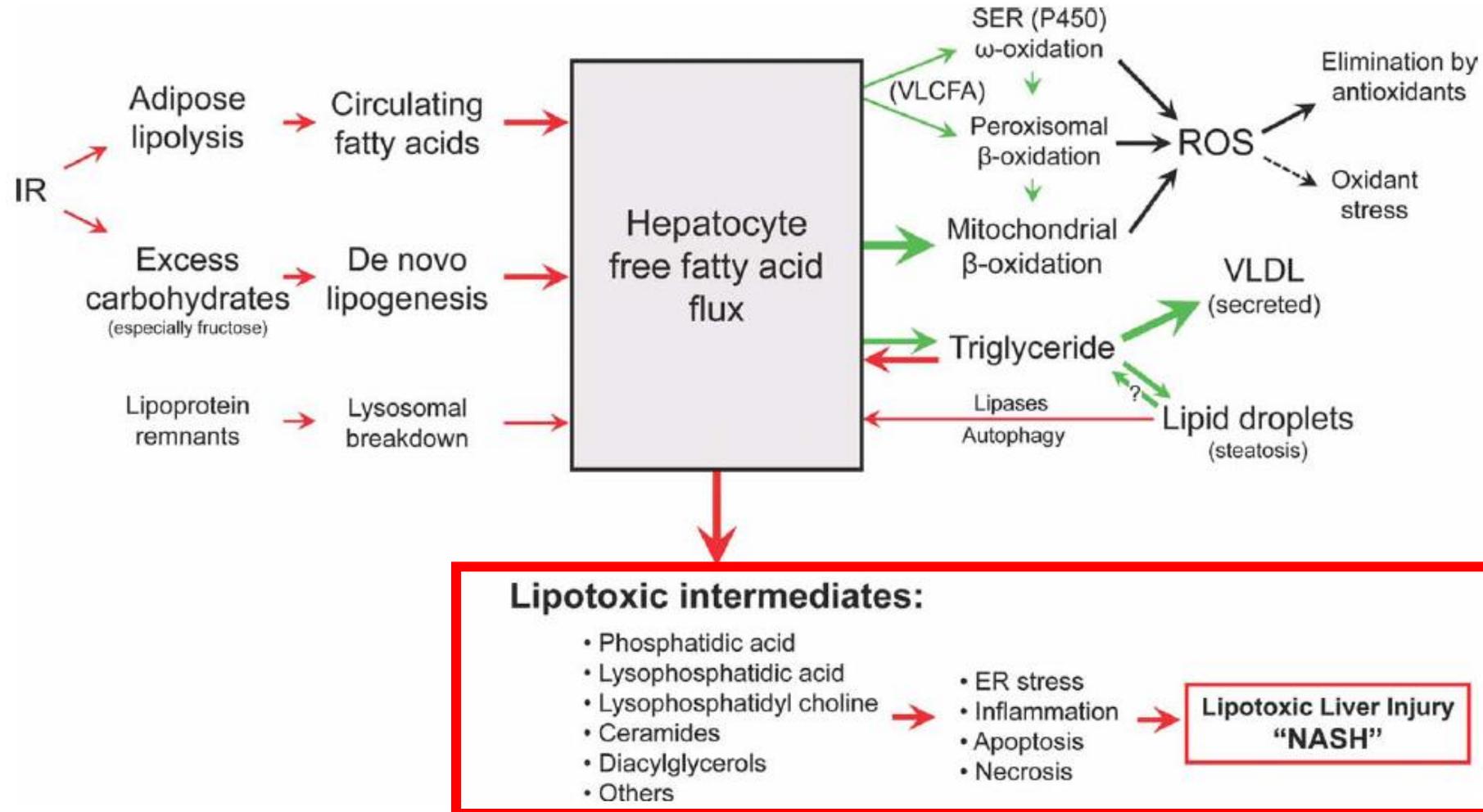
No evident necrosis

- Defective Autophagy
- LIPOTOXICITY
- Oxidative Stress
- Genetic factors

Evident necrosis

- Chronic Wound Healing
- Increase intestinal permeability
- Complex inflammatory networks
- Genetic factors

Pathways of Lipotoxic Liver Injury



Effectors and Targets of Lipotoxicity

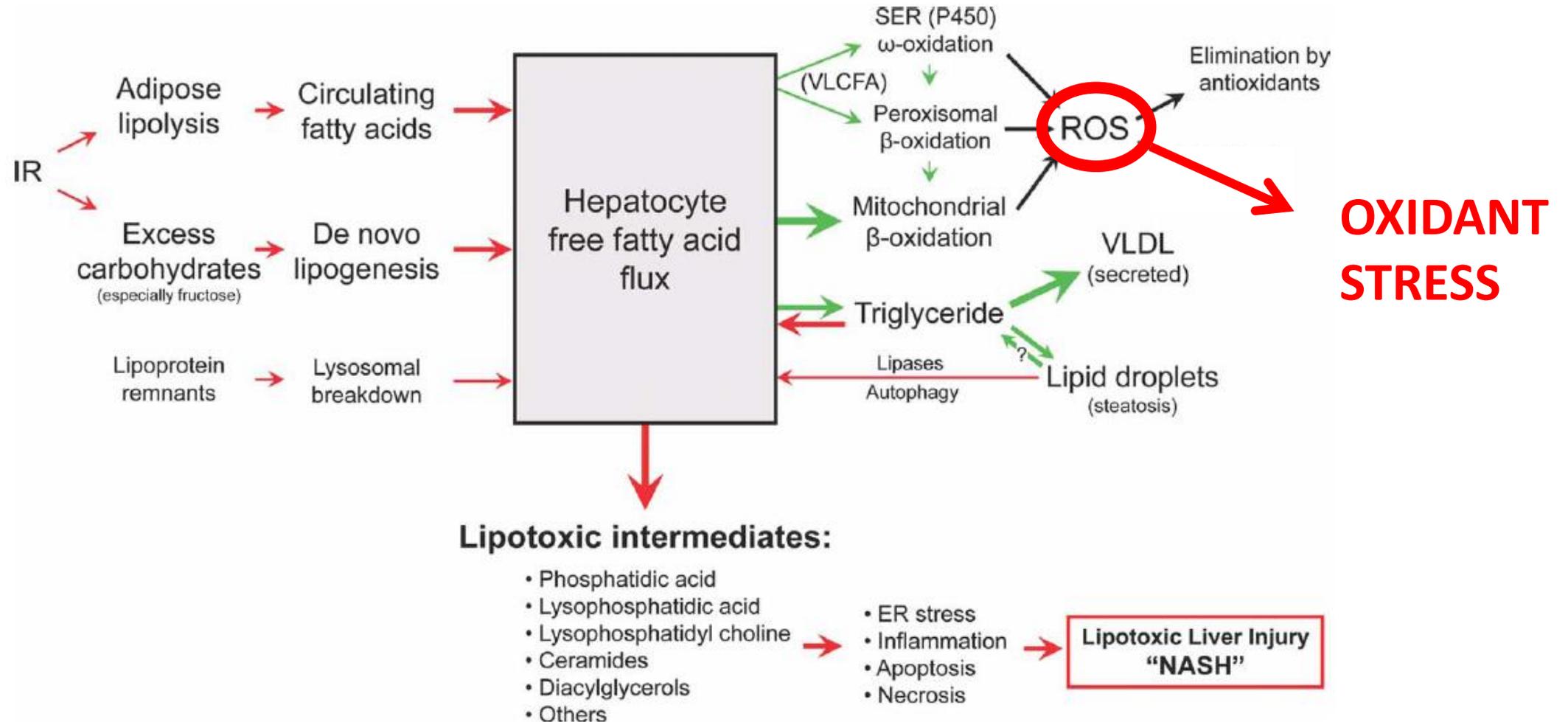
EFFECTORS

Free fatty acids
Free cholesterol
Ceramides
Sphingosines
Phospholipids
Leukotrienes

TARGETS

Mitochondria
Lipid droplets
Autophagy
Cholangiocytes

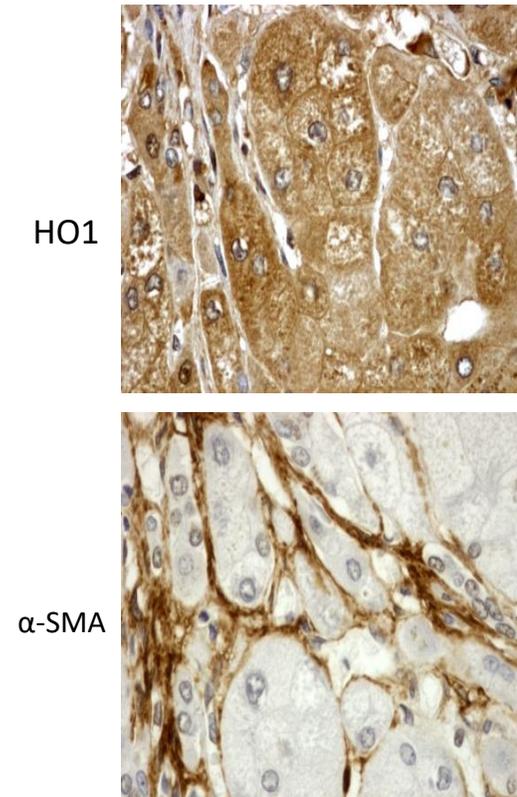
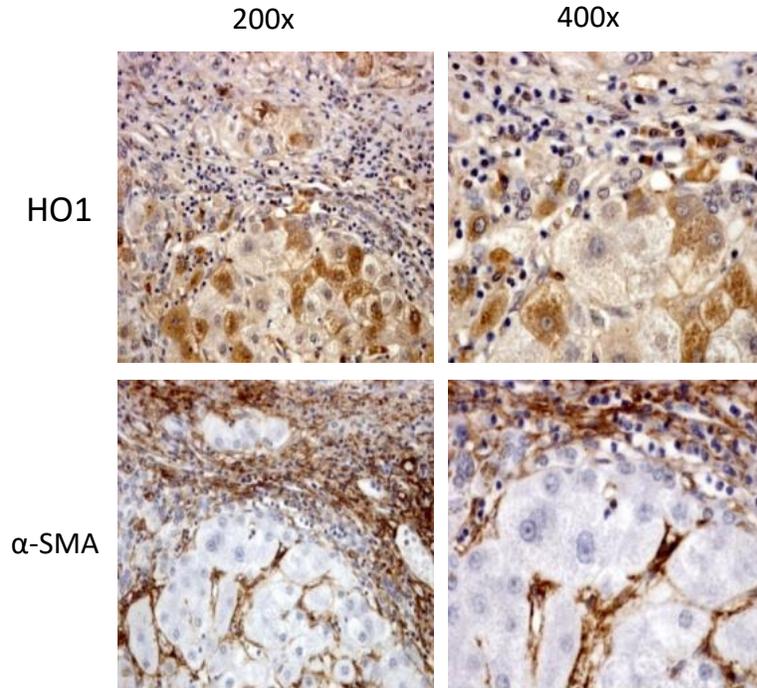
Pathways of Lipotoxic Liver Injury



Oxidative Stress a Common Denominator in Chronic Liver Diseases

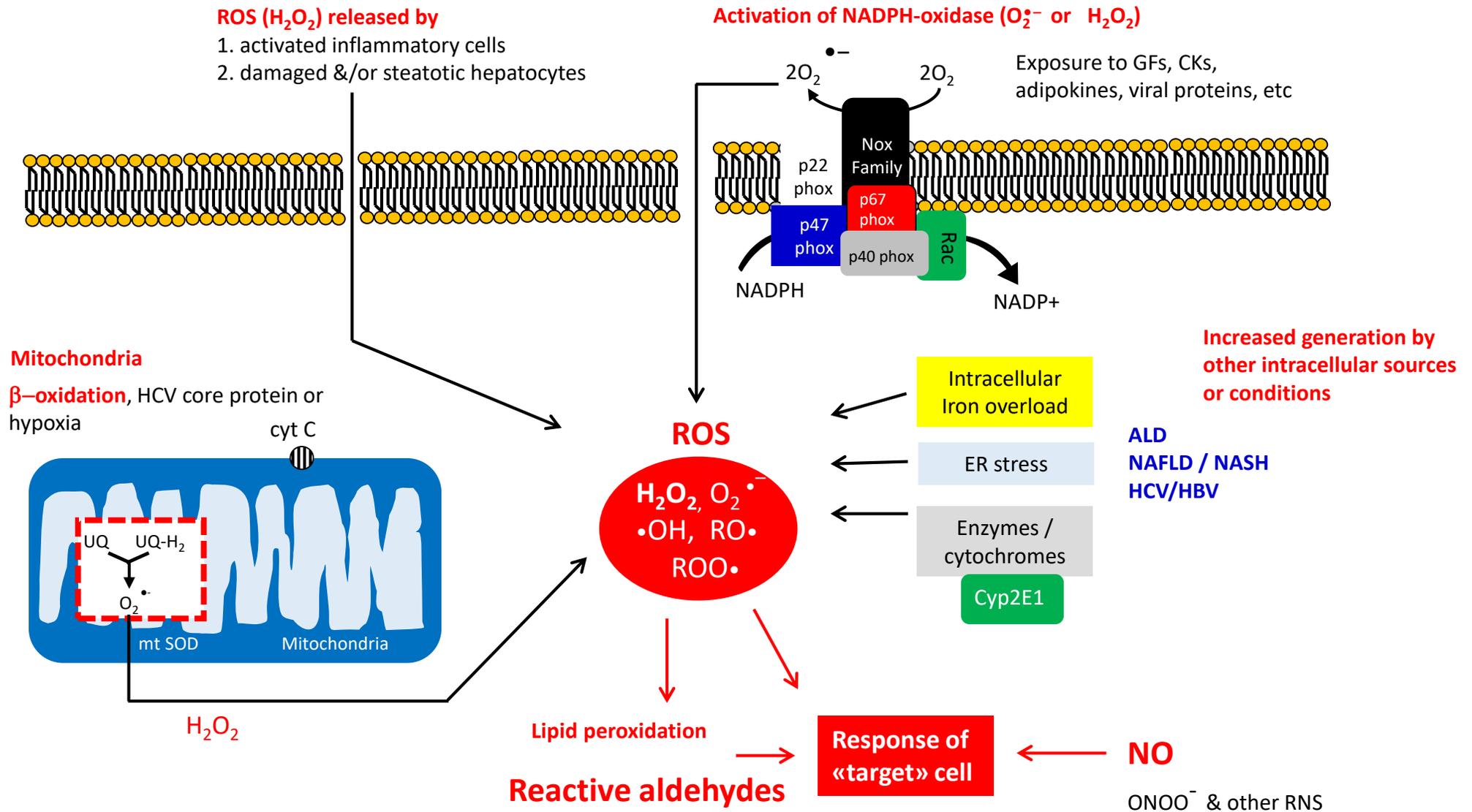
Increased intracellular ROS levels

potentially any liver cell but mainly hepatocytes and activated HSC

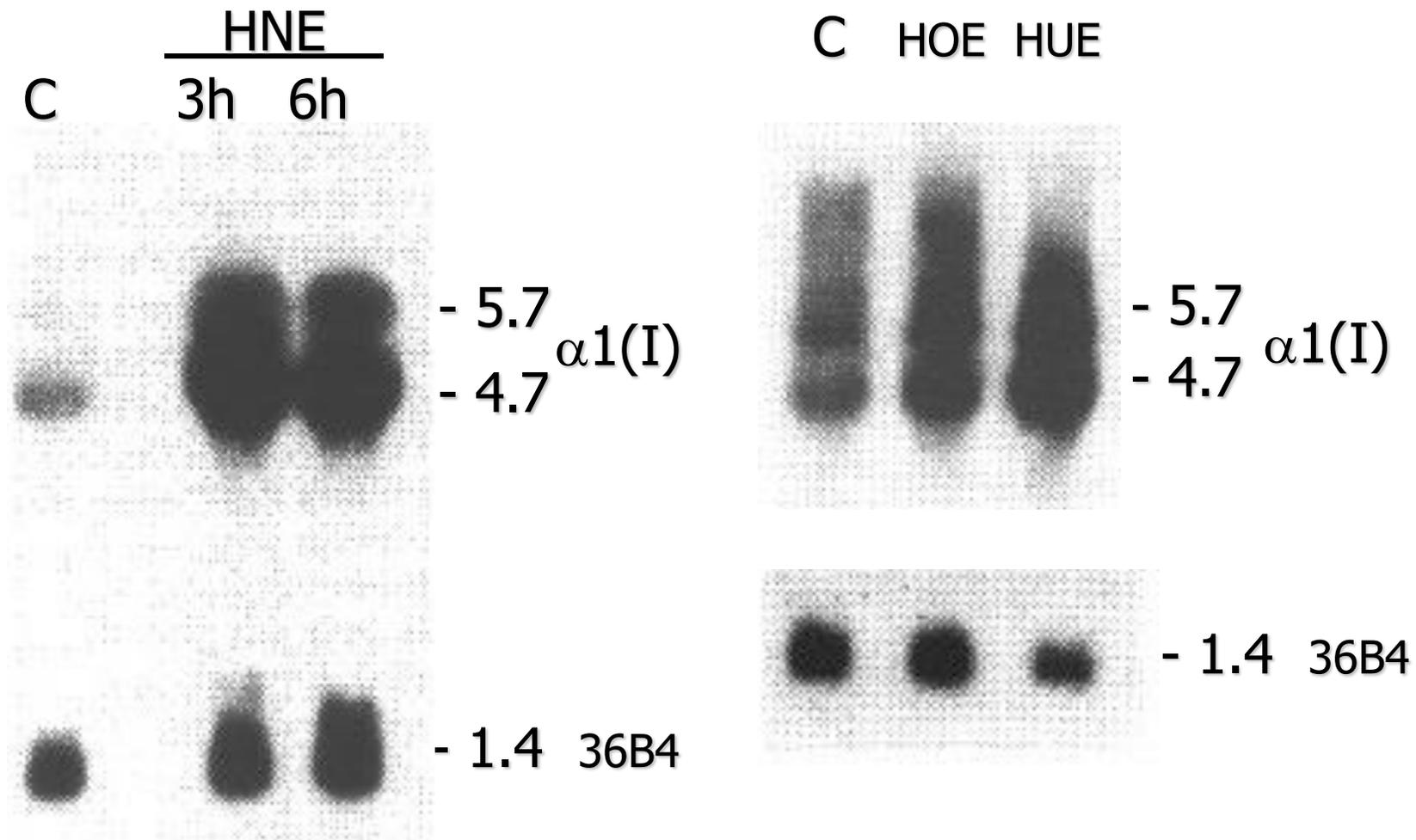


HO1: heme-oxygenase 1, a redox sensitive gene up-regulated in cells undergoing or exposed to oxidative stress

Sources of Intracellular ROS and Related Intermediates in Chronic Liver Injury



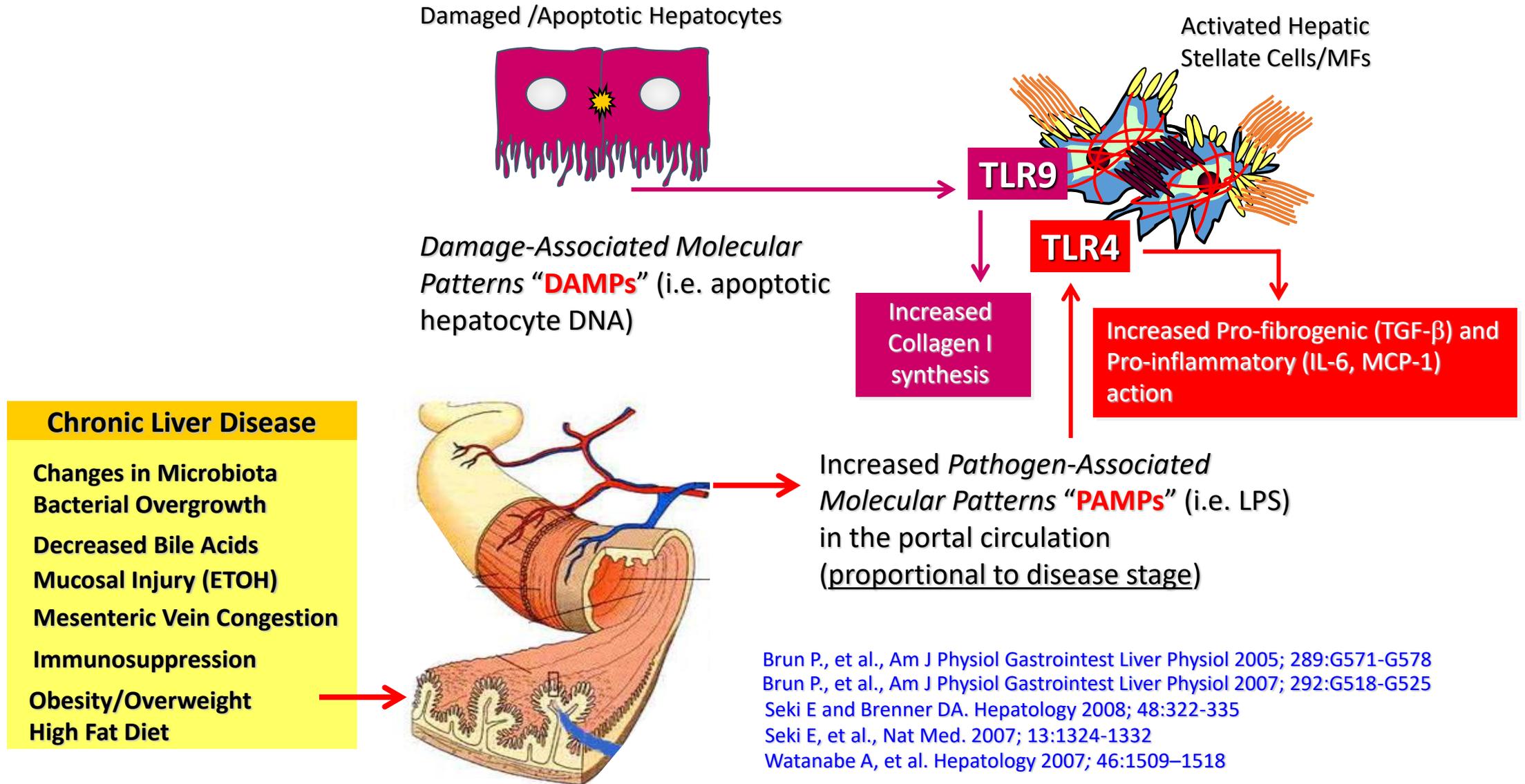
Reactive Aldehydes induce a direct pro-fibrogenic effect in human HSC



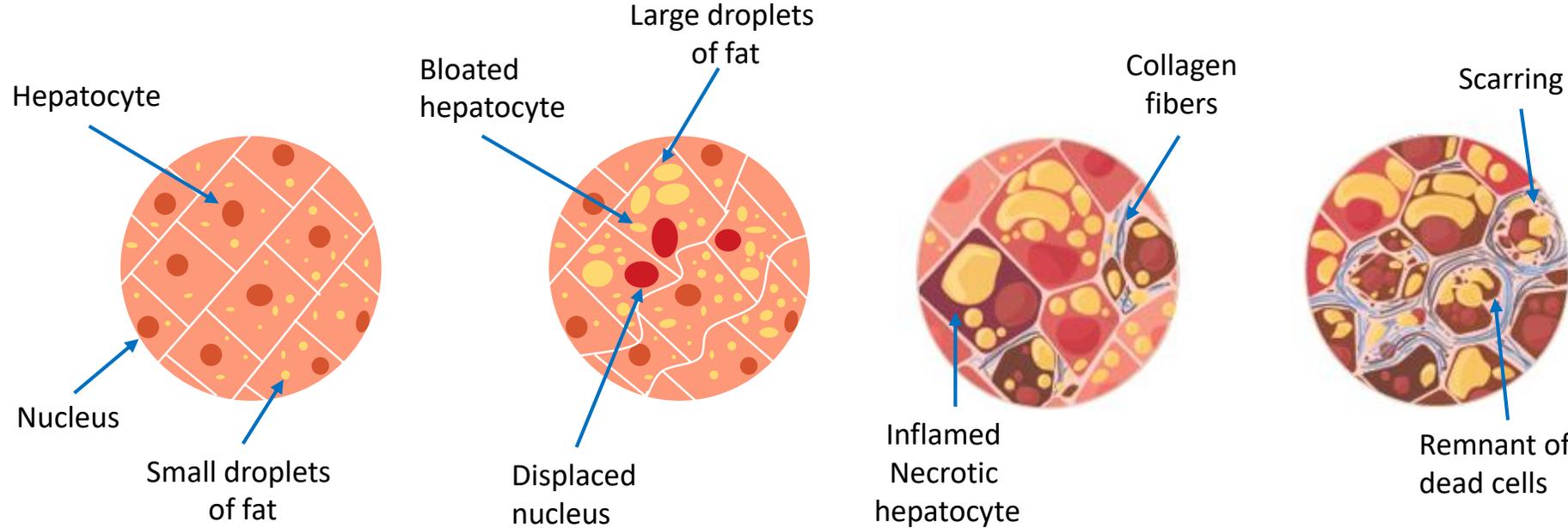
Parola M. et al., Biochem Biophys Res Comm 1996; 222:261-264

Parola M. et al., J Clin Invest 1998; 102:1942-1950

Intestinal Permeability and the Activation of Gut-Liver Innate Immunity



NASH Fibrosis: Stage-dependent Mechanisms



<p>No evident necrosis</p>	<p>Evident necrosis</p>
<p>Defective Autophagy LIPOTOXICITY Oxidative Stress Genetic factors</p>	<p>Chronic Wound Healing Increase intestinal permeability Complex inflammatory networks Genetic factors</p>

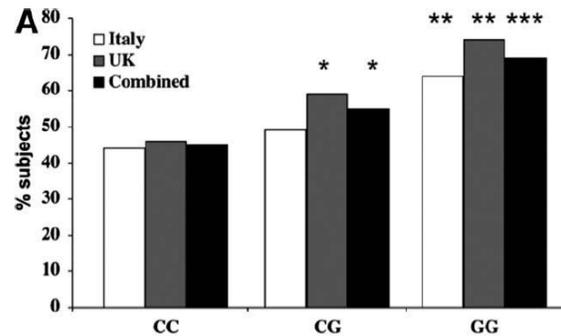
PNPLA3 and NAFLD

Severity of liver disease

HCC

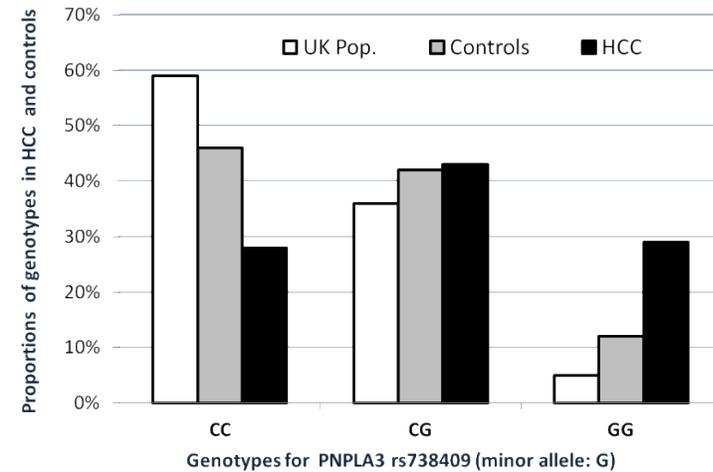
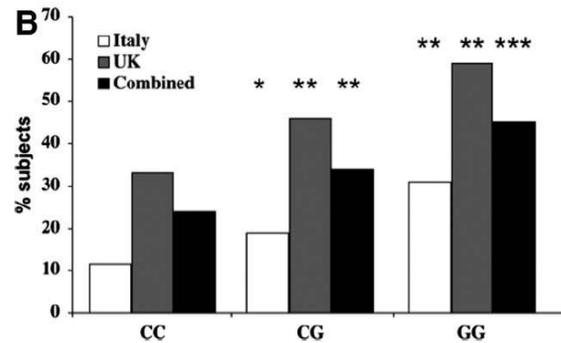
Presence of NASH

OR 1.5 (1.12-2.04)



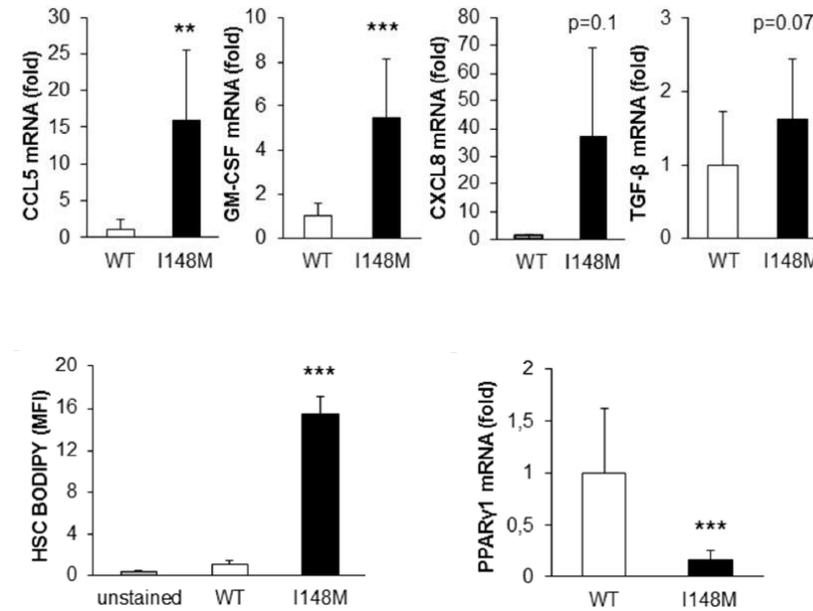
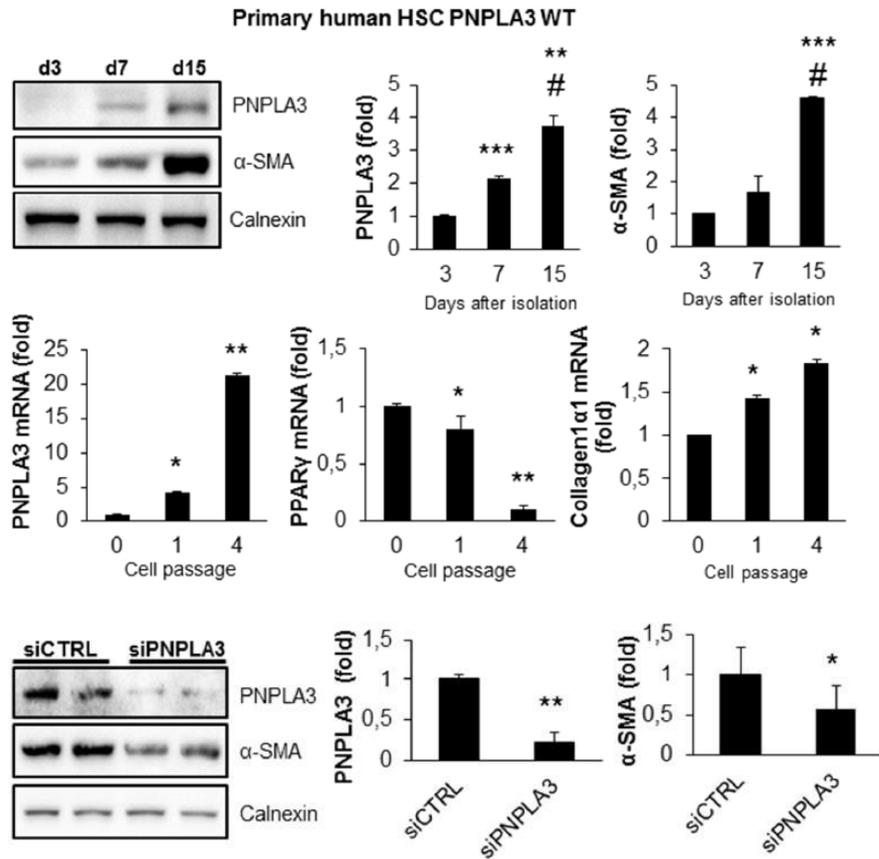
Fibrosis >F1

OR 1.5 (1.09-2.12)



Variables	OR (95% CI)	P-value
PNPLA3 rs738409	2.26 (1.23-4.14)	0.0082
Age	1.24 (1.17-1.32)	<0.0001
Gender (Male)	11.11 (4.17-33.33)	<0.0001
BMI	0.94 (0.87-1.02)	0.148
Diabetes	2.33 (0.93-5.81)	0.070
Cirrhosis	9.37 (3.82-23.00)	<0.0001

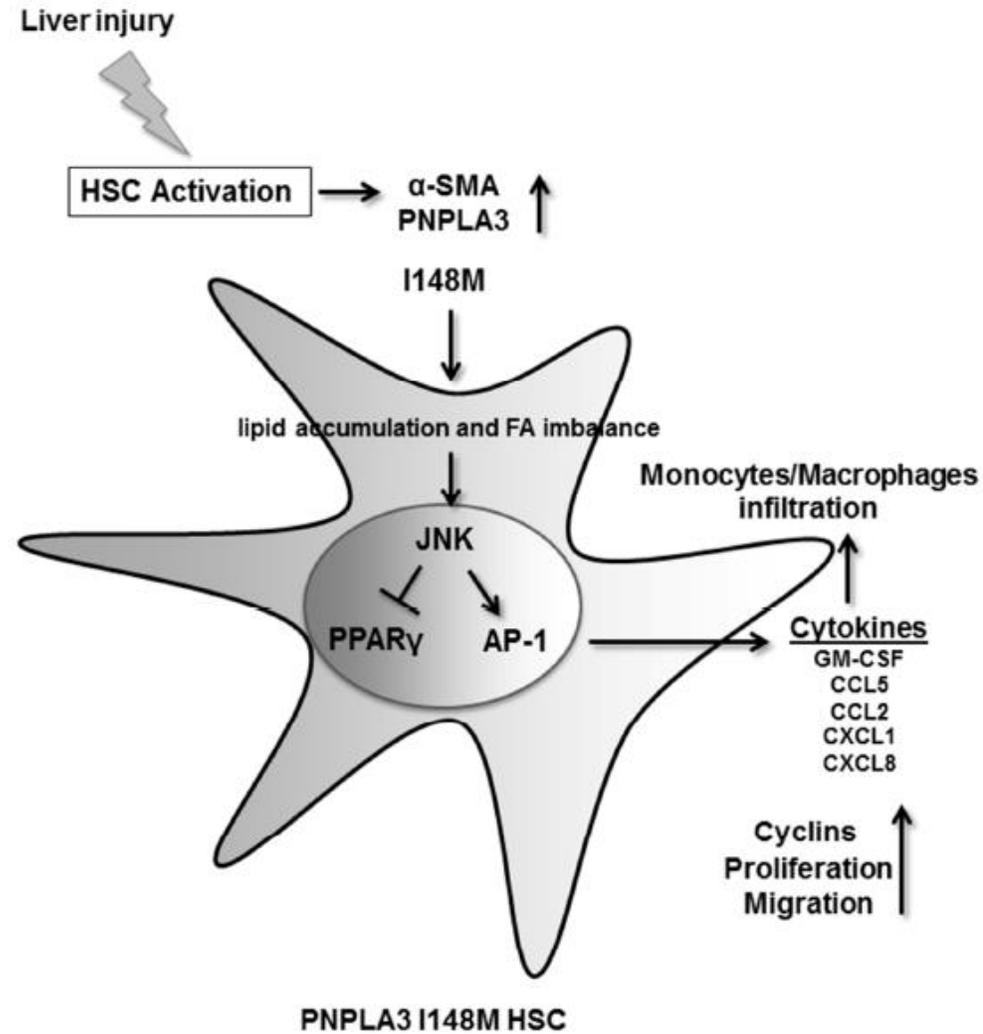
PNPLA3 is required for HSC activation and its genetic variant I148M potentiates the pro-fibrogenic phenotype of human HSC



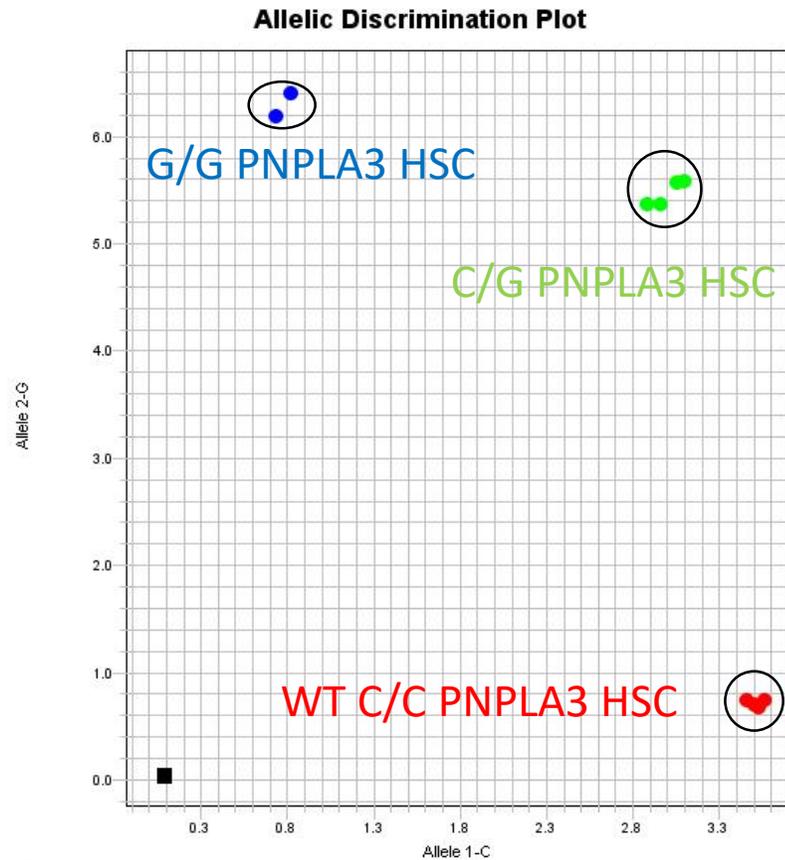
PNPLA3 I148M confers a pro-inflammatory and pro-fibrotic profile

**PNPLA3 expression increases with HSC activation
Silencing PNPLA3 reduces HSC activation**

Mutated PNPLA3 confers a pro-fibrogenic phenotype to human HSC



Human HSC: Primary Genotyping for PNPLA3 I148M PNPLA3 SNP variant



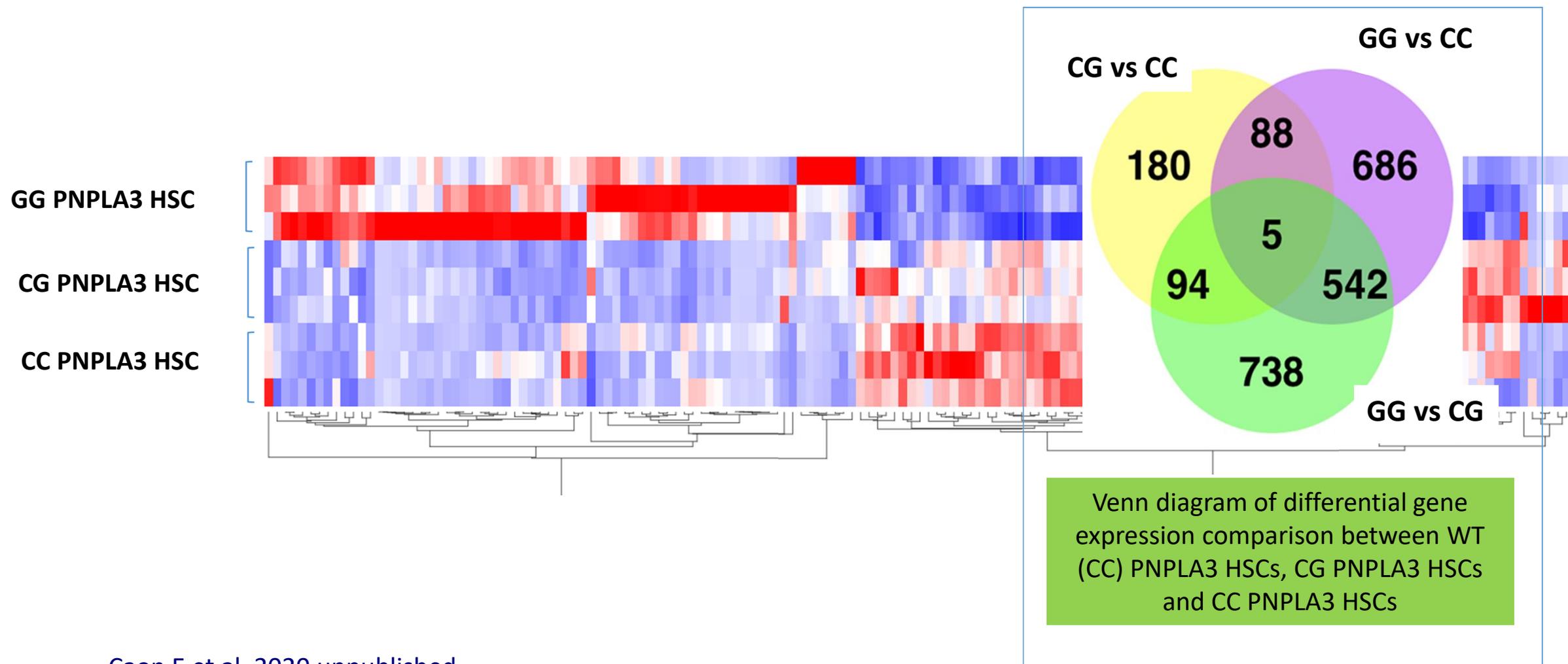
Legend

- Allele 1-C / Allele 1-C
- Allele 2-G / Allele 2-G
- Allele 1-C / Allele 2-G
- ✕ Undetermined

Primary hHSC were isolated (n = 23 donors), cultured in 2D followed by genotyping for PNPLA3(I148M) and RNAseq data analysed with **Ingenuity pathway analysis (IPA)**.

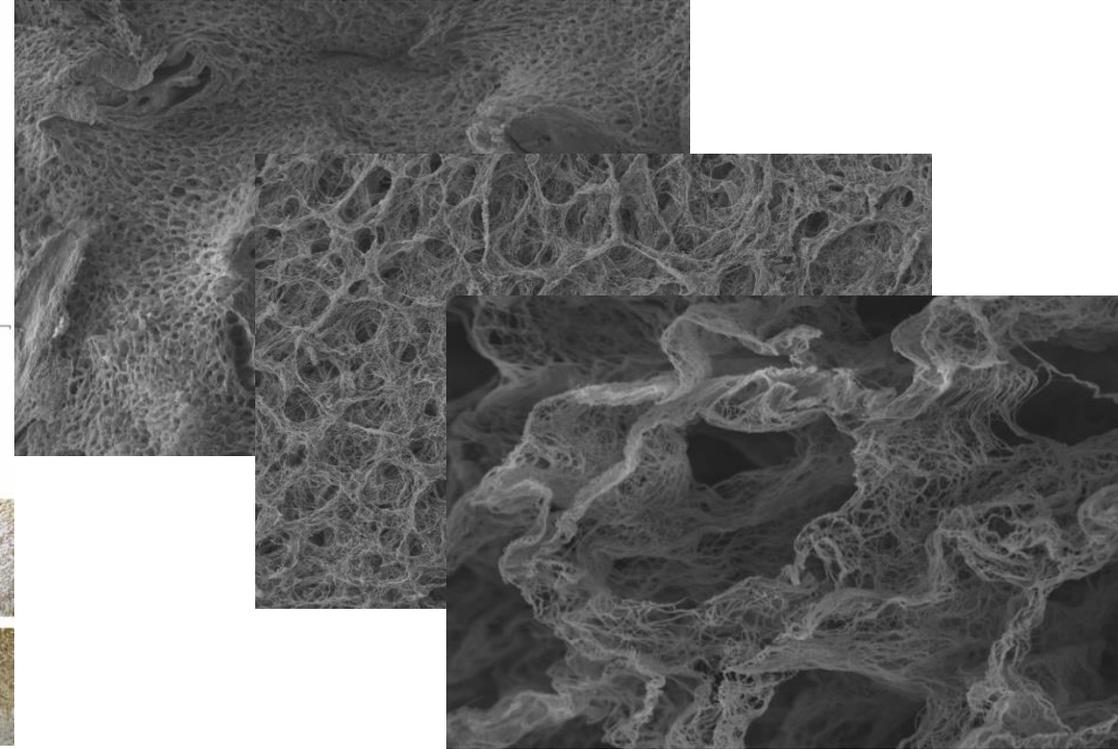
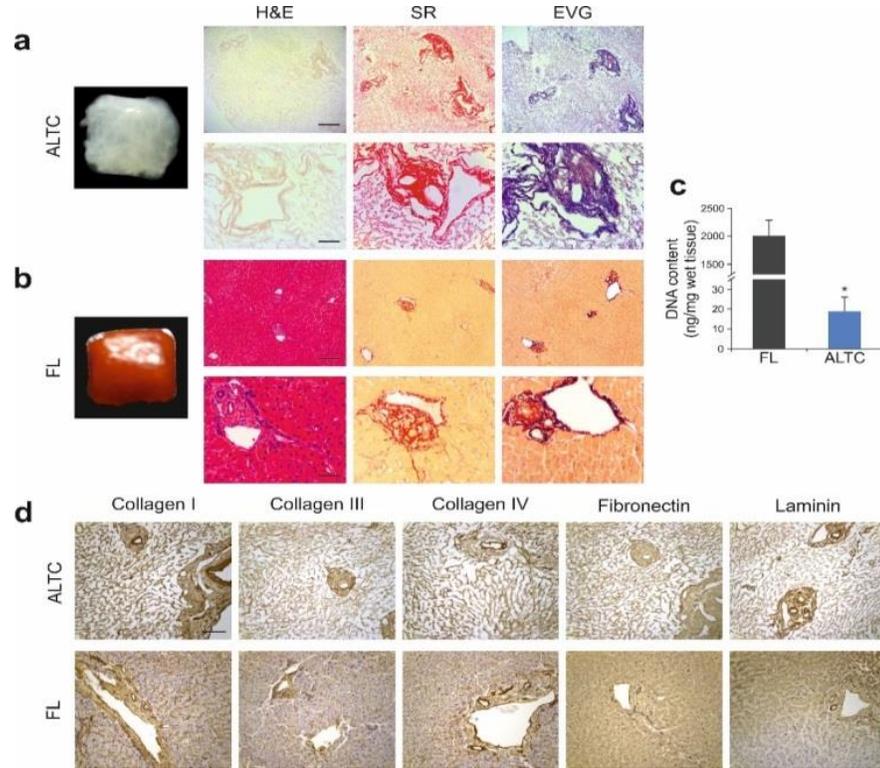
- **WT PNPLA3 HSC**: homozygous for Allele C (C/C)
- **C/G PNPLA3 HSC**: heterozygous for Allele C and G (C/G)
- **G/G PNPLA3 HSC**: homozygous for Allele G (G/G)

PNPLA3 (148M) SNP promotes the activation of human HSC through a dysregulated oxidative stress response

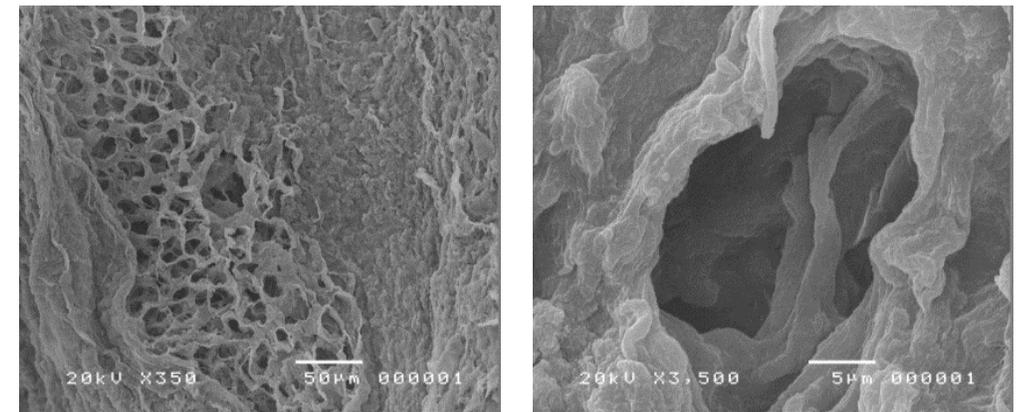
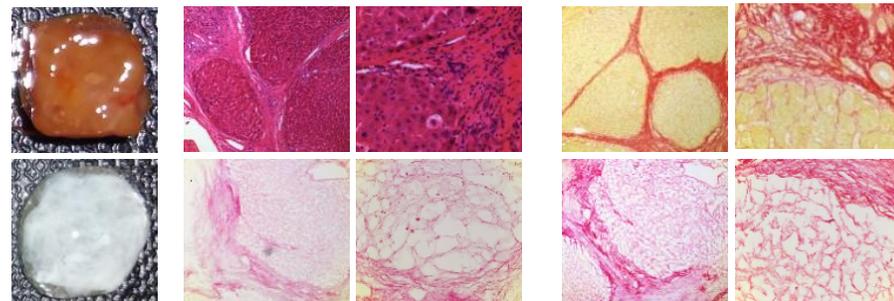


3D Human Healthy and Fibrotic Liver ECM

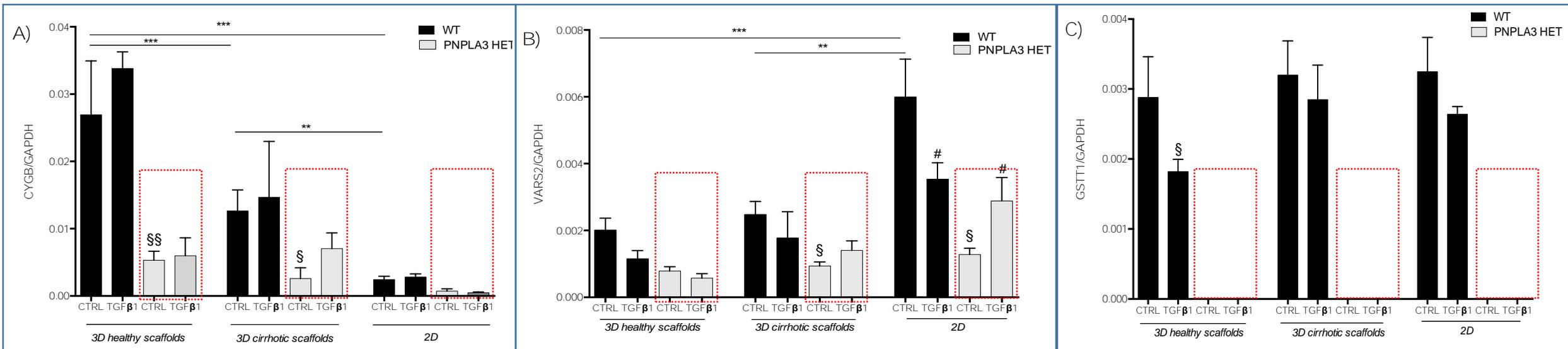
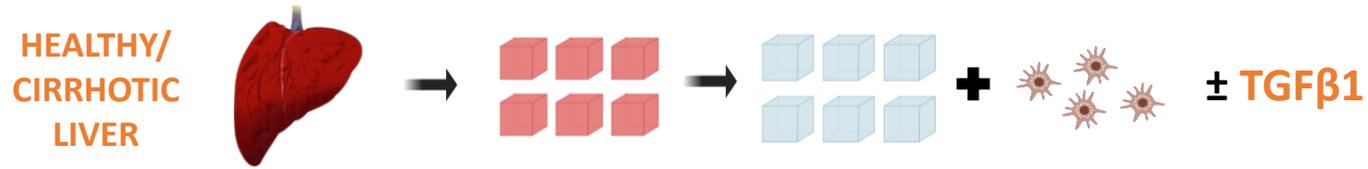
Donor healthy human liver



Explanted cirrhotic liver



PNPLA3 (148M) SNP promotes the activation of human HSC through a dysregulated oxidative stress response

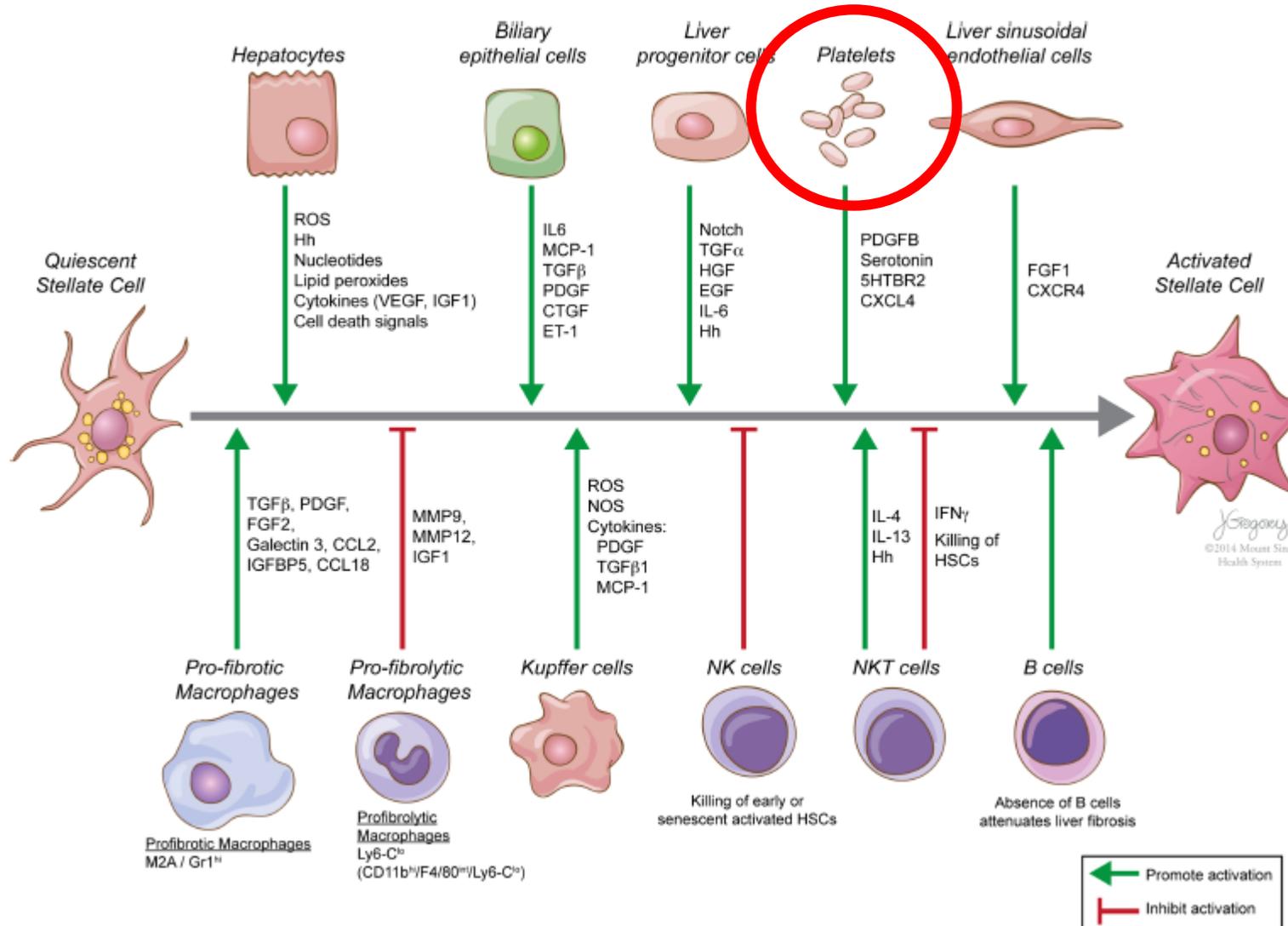


Cytoglobin B: HSC quiescence marker

VARS2: a mitochondrial enzyme involved in fatty acid metabolism

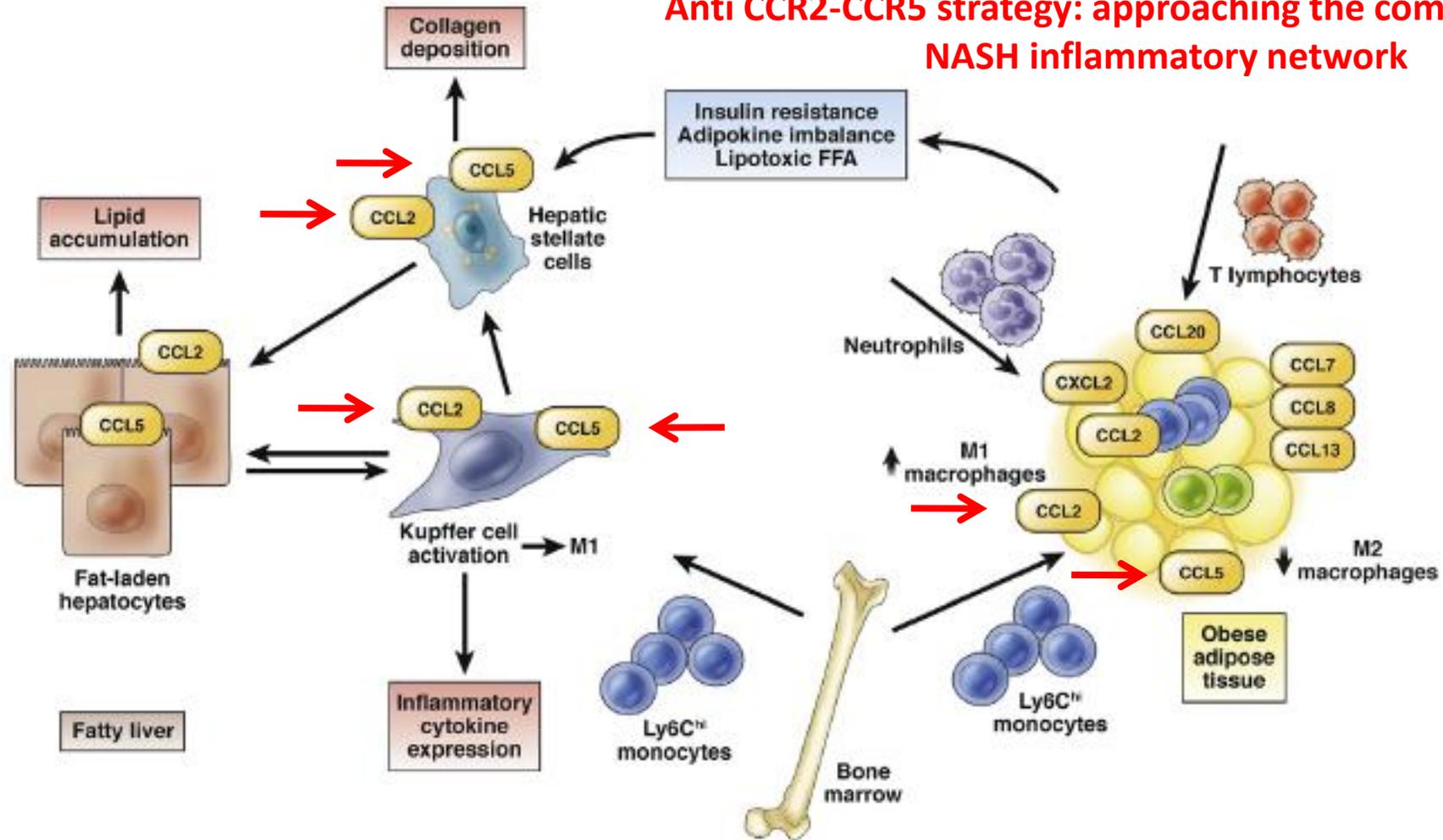
GSTT1, a Glutathione-S-Transferase

Cellular Cross-Talk in Liver Fibrogenesis

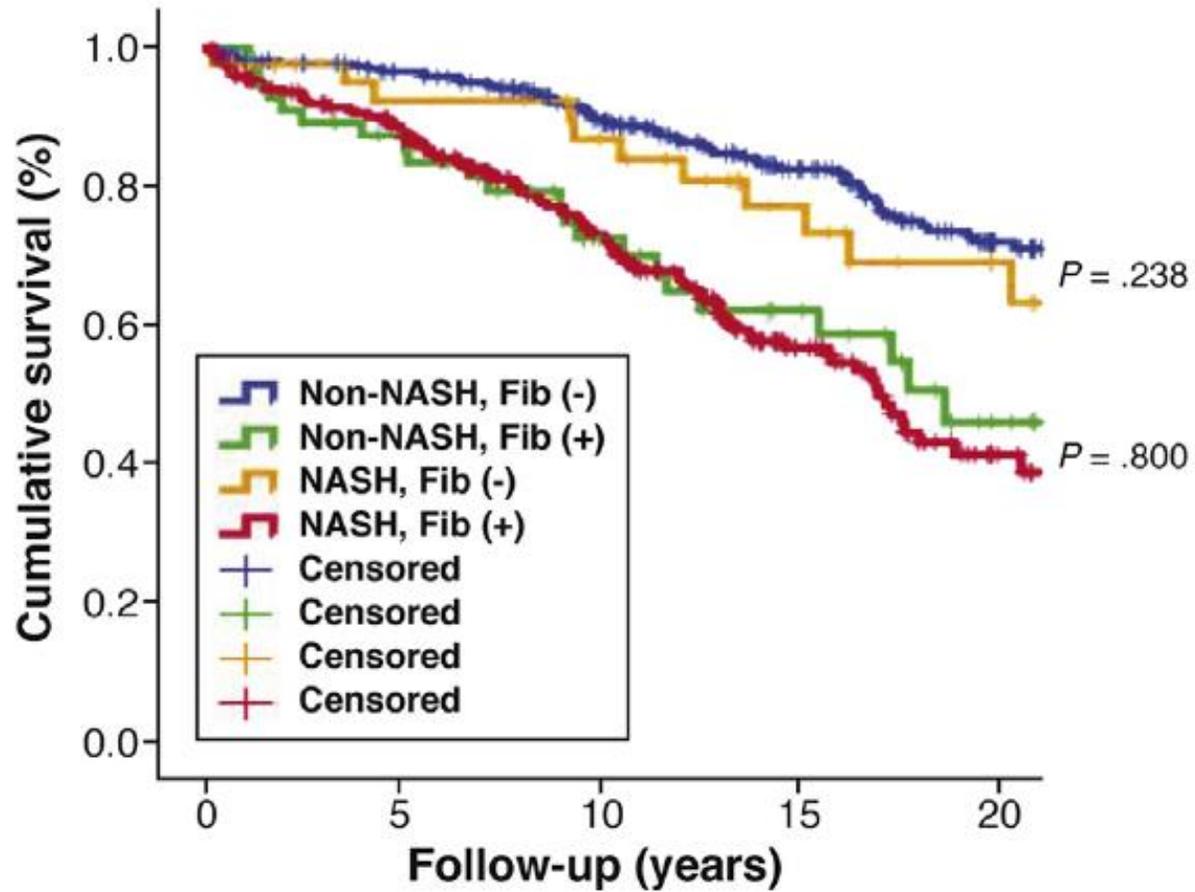


Chemokines and NASH Progression

Anti CCR2-CCR5 strategy: approaching the complexity of the NASH inflammatory network



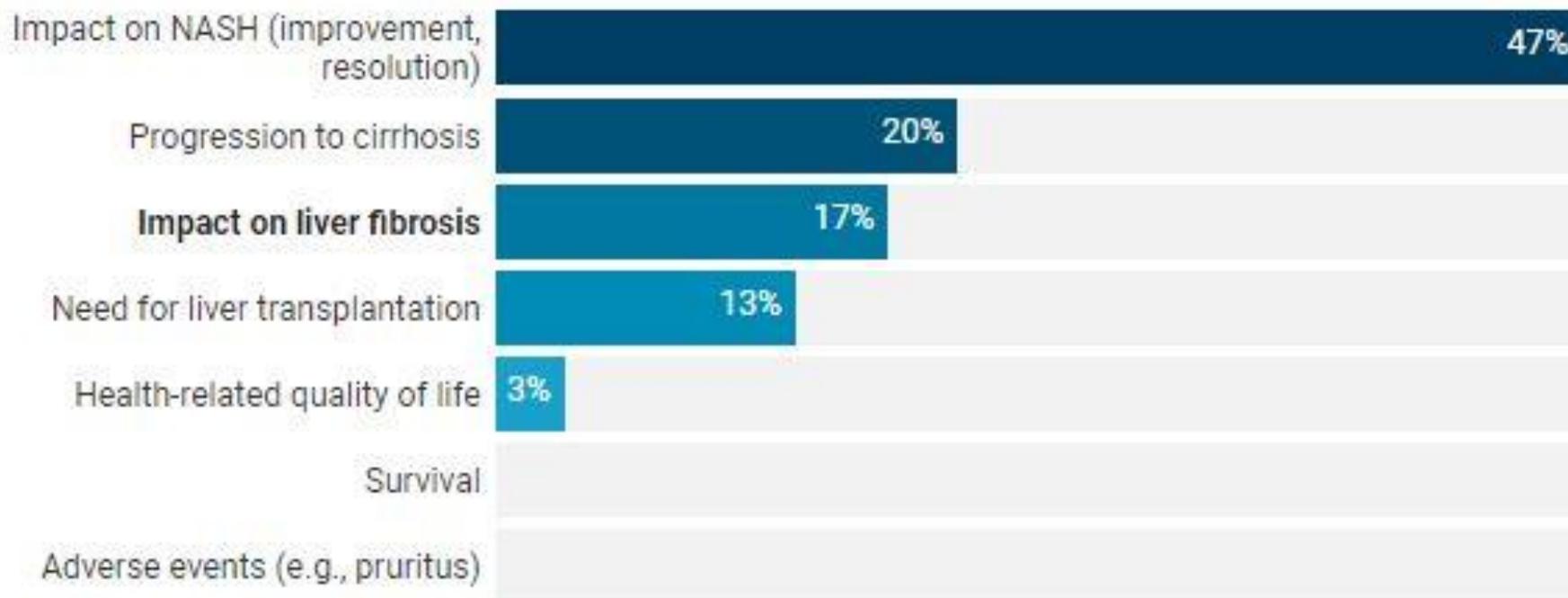
Fibrosis and NAFLD Outcome



279	241	197	137	72	Non-NASH, Fib (-)
56	46	30	19	7	Non-NASH, Fib (+)
43	35	31	20	12	NASH, Fib (-)
241	197	124	58	18	NASH, Fib (+)

Fibrosis in NASH: Still a Confused End-point!!!!

Despite liver fibrosis being the only end point currently a strong predictor of negative outcomes in NASH patients – it's not the most important factor to payers...



Which of the following clinical measures would you consider most important when assessing the cost-effectiveness of a novel drug for the treatment of NASH. Percentage of MCO PD/MDs (n=30). Survey data collected December 2017.

NASH pipeline crowds at mid-stage, but has few advanced candidates

PHASE I (14 drugs)

- butanoic acid
- CER209
- evogliptin
- DUR928
- MK-4074
- OPRX-106
- PF06865571
- PF06882961
- PXS-5382A
- RG-125
- RYI-018
- seladelpar
- SGM-1019
- TVB-2640

PHASE II (29 drugs)

- medications
- ARX618
 - BI 1467335
 - DS102
 - EDP-305
 - emricasan
 - gemcabene
 - GR-MD-02
 - GRI-0621
 - GS-0976
 - GS-9674
 - IMM-124E
 - IONIS-DGAT2Rx
 - IVA-337
 - lipaglyn
 - LJN452
 - LMB763
 - MGL-3196
 - MN-001
 - MSDC-0602K
 - NC101
 - NGM282
 - NS-0200
 - ozempic
 - PF-05221304
 - PF-06835919
 - remogliflozin etabonate
 - SHP626
 - TVB-2640
 - VK2809

PHASE III (5 drugs)

- cenicriviroc
- elafibranor
- Ocaliva (obeticholic acid)
- Selonsertib
- aramchol

UCL ILDH

Giuseppe MAZZA

Krista ROMBOUITS

Walid Al-Akkad

Luca Frenguelli

Lisa Longato

Kessarin Thanapirom

Maria Giovanna Vilia

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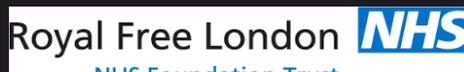
Paolo De Coppi

Panagiotis Maghsoudlou

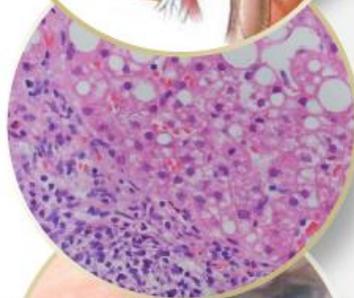
Luca Urbani



University College London
Hospitals Biomedical
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- *Hot topics in hepatology*
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