2021 14th Paris Hepatology Conference
PHC 2021
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The Digital Paris Hepatology Conference

PATHOPHYSIOLOGY OF NAFLD AND NASH

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NHS Foundation Trust

NIHR | University College London Hospitals Biomedical Research Centre

Disclosures (2021)

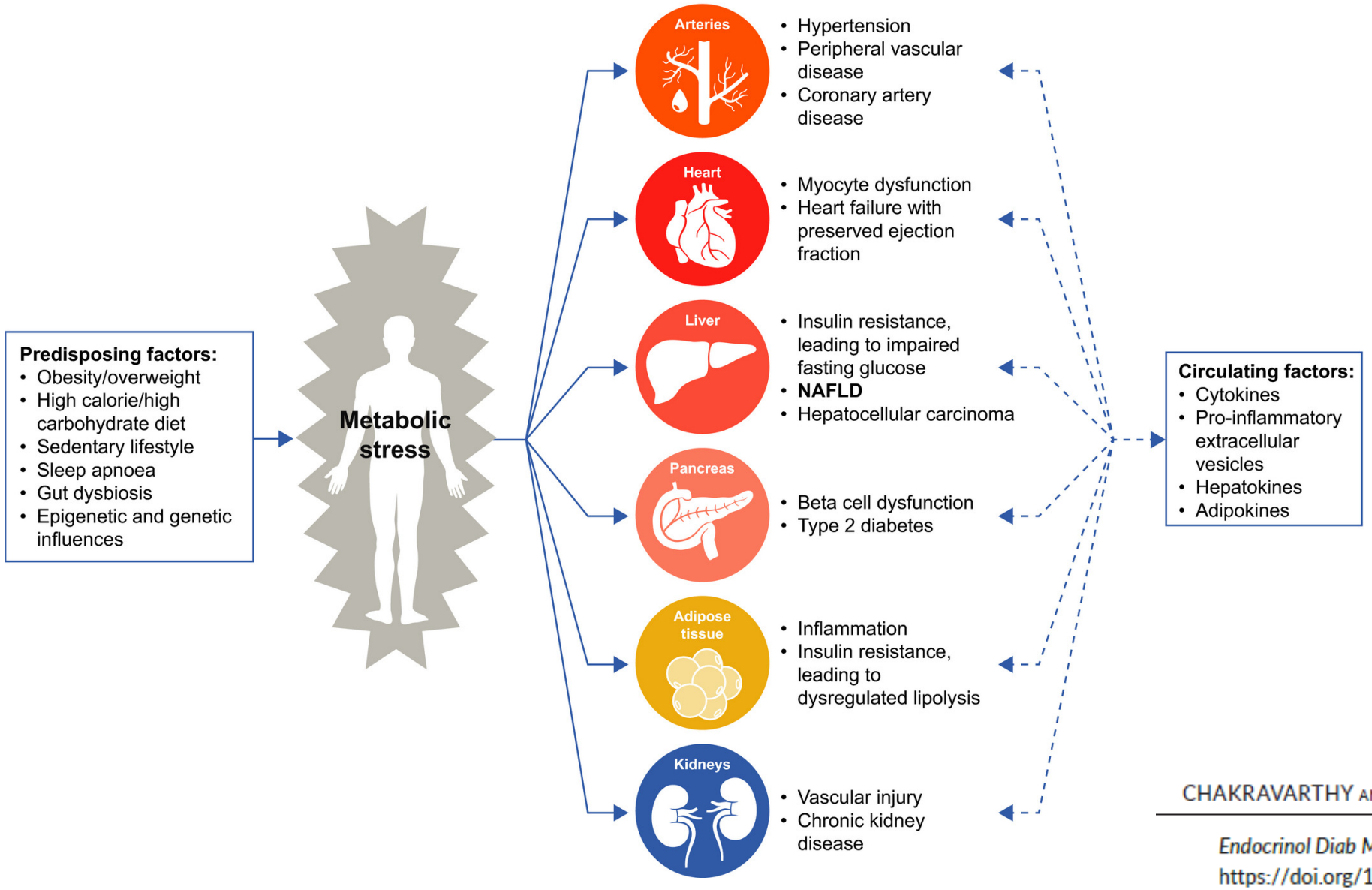
1. Inventor and patent holder ELF test (Siemens)
2. Speakers bureau: Echosens (Paris, France)
3. SAB/Consultancy: Promethera (Belgium); Chemomab (Israel); Takeda (USA); LimmaTech Biologics (Switzerland)
4. Co-Founder and Director, Engitix Therapeutics Ltd (UCL Spin-out) (UK)*
5. Co-Founder and Director, 3P-Sense Ltd (UCL Spin-out) (UK)**
6. CMO, Hepatotargets Ltd (Cambridge University Spin-out) (UK)***
7. Chair EASL Consortium for Regenerative Hepatology (2019-2022)

* ECM-based Drug discovery

** Nanotechnology diagnostics

*** Liver Cell therapy

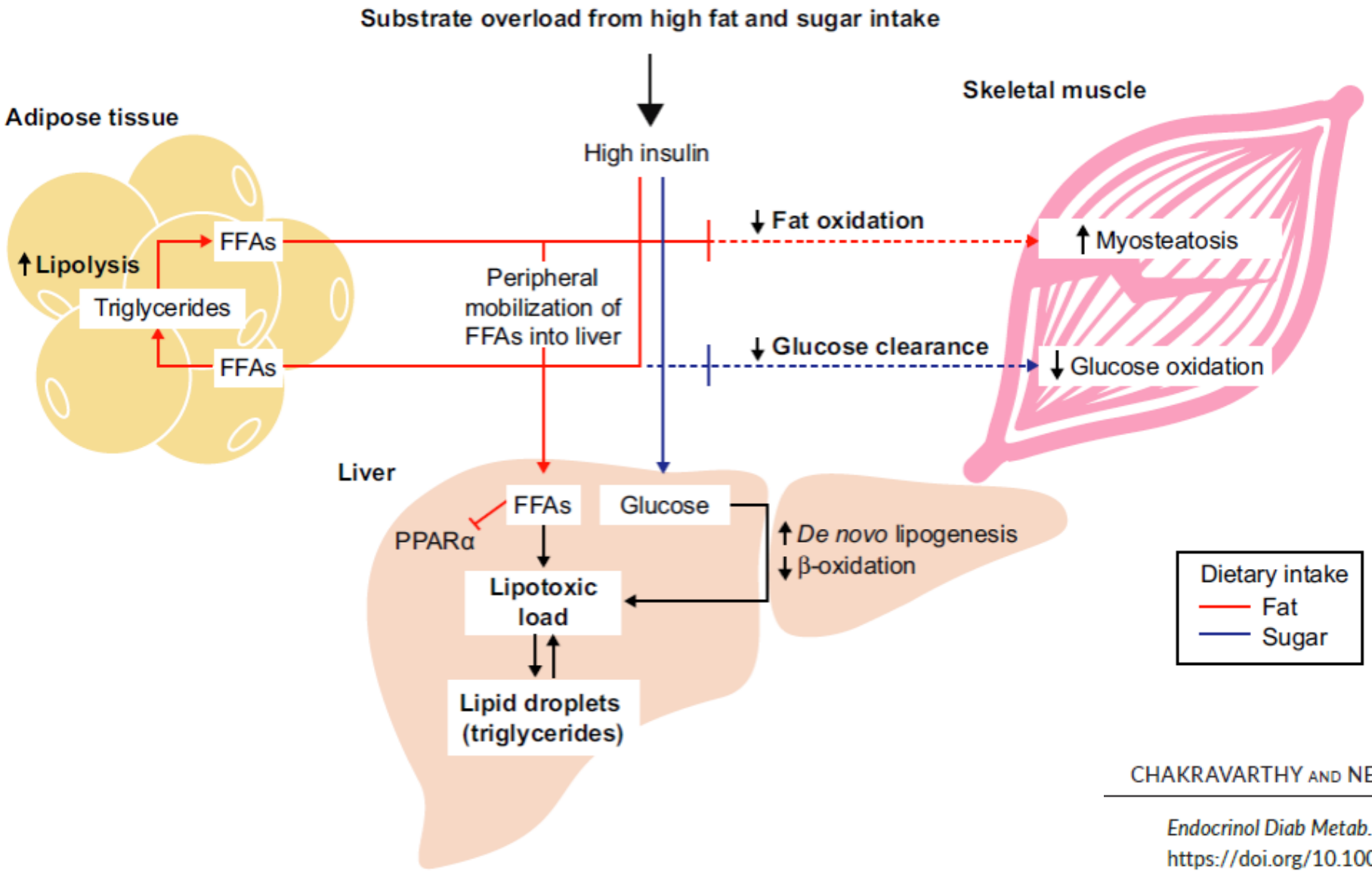
Metabolic “Stress” and the Metabolic Syndrome



CHAKRAVARTHY AND NEUSCHWANDER-TETRI

Endocrinol Diab Metab. 2020;3:e00112.
https://doi.org/10.1002/edm2.112

Metabolic Inflexibility Leads to Dysregulated Glucose and Lipid Metabolism



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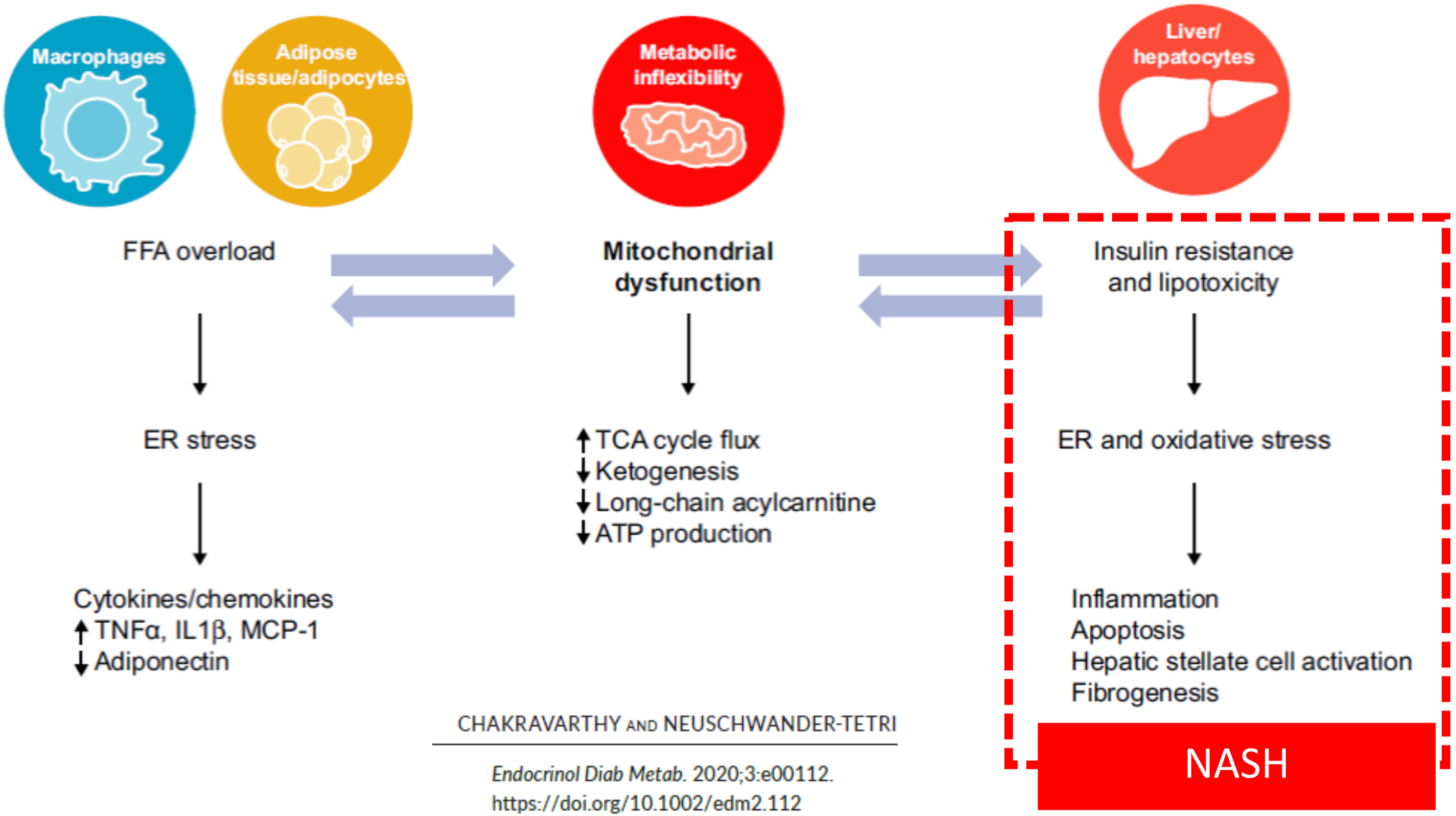
NASH Occurs in a Context of Multi-tissue Involvement



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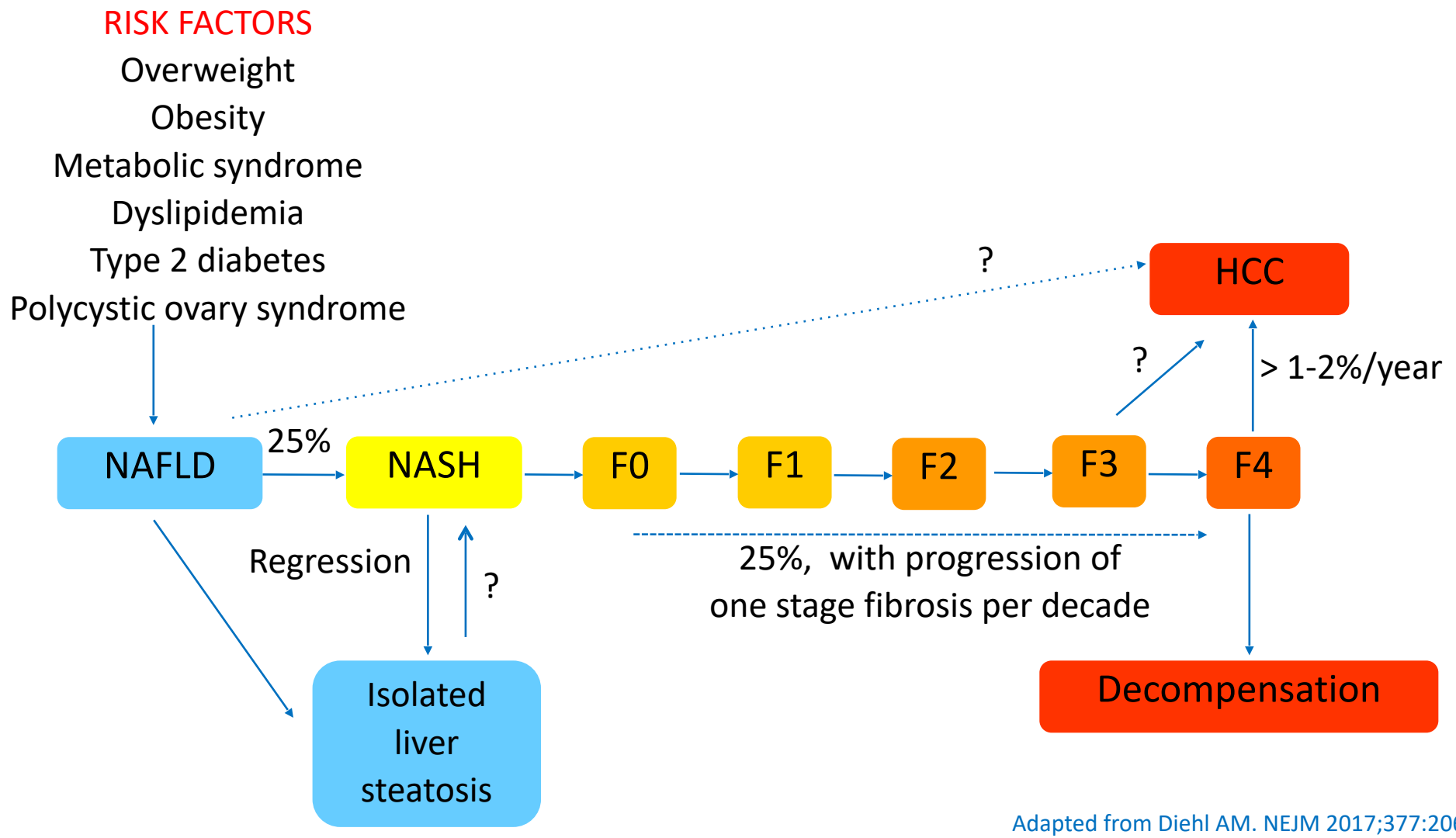
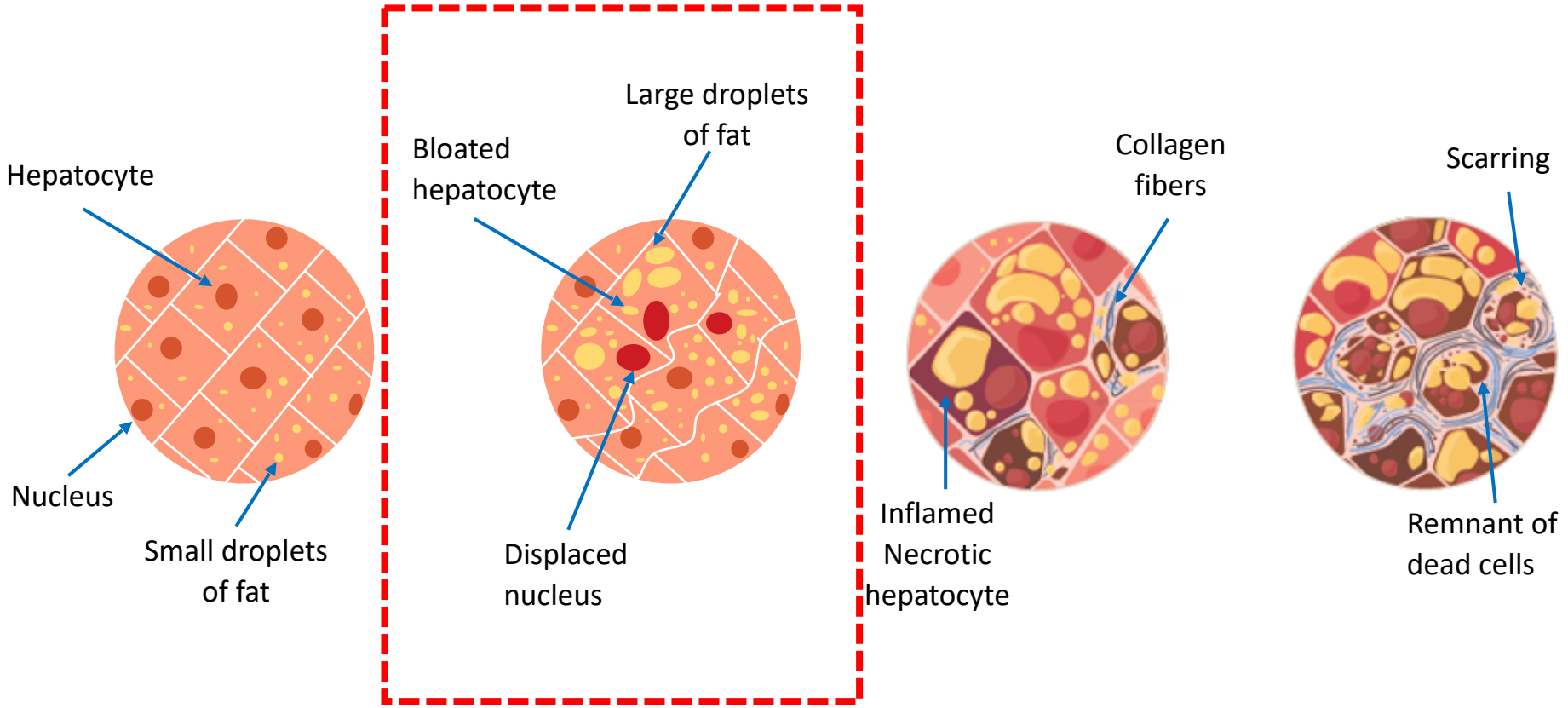
NAFLD: Natural History



Adapted from Diehl AM. NEJM 2017;377:2063-72

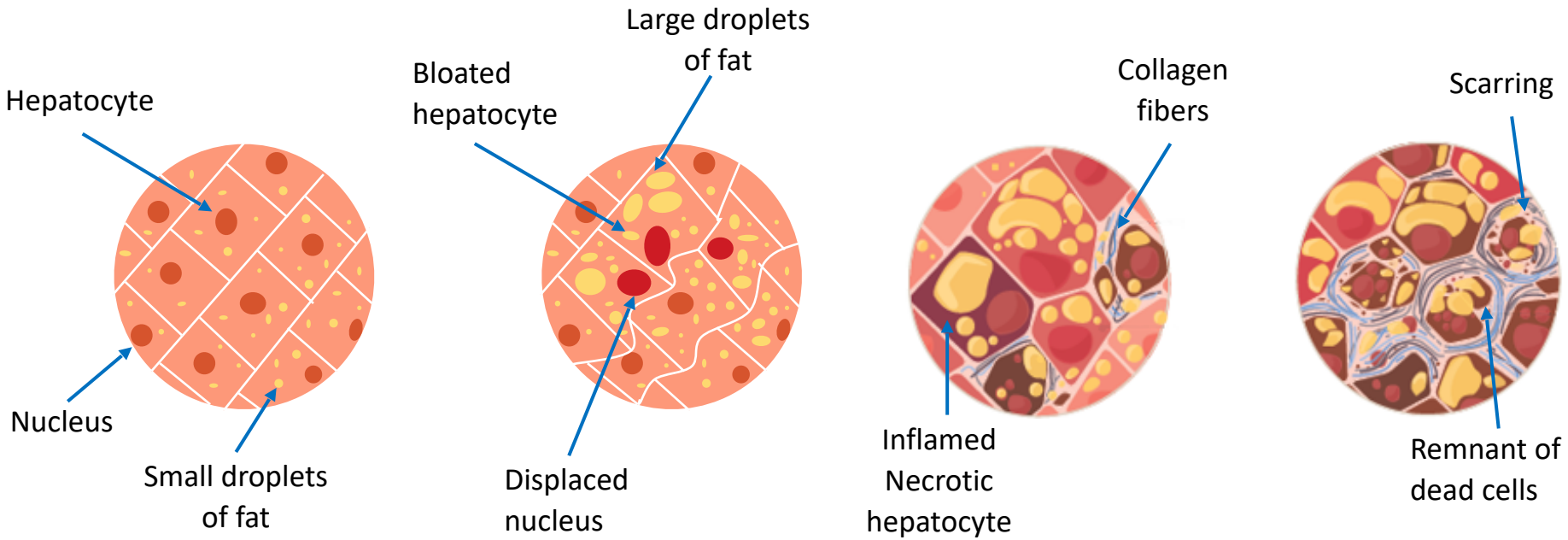
NAFLD: Natural History



ADAPTATION

PATHOLOGY

NASH Fibrosis: Stage-dependent Mechanisms



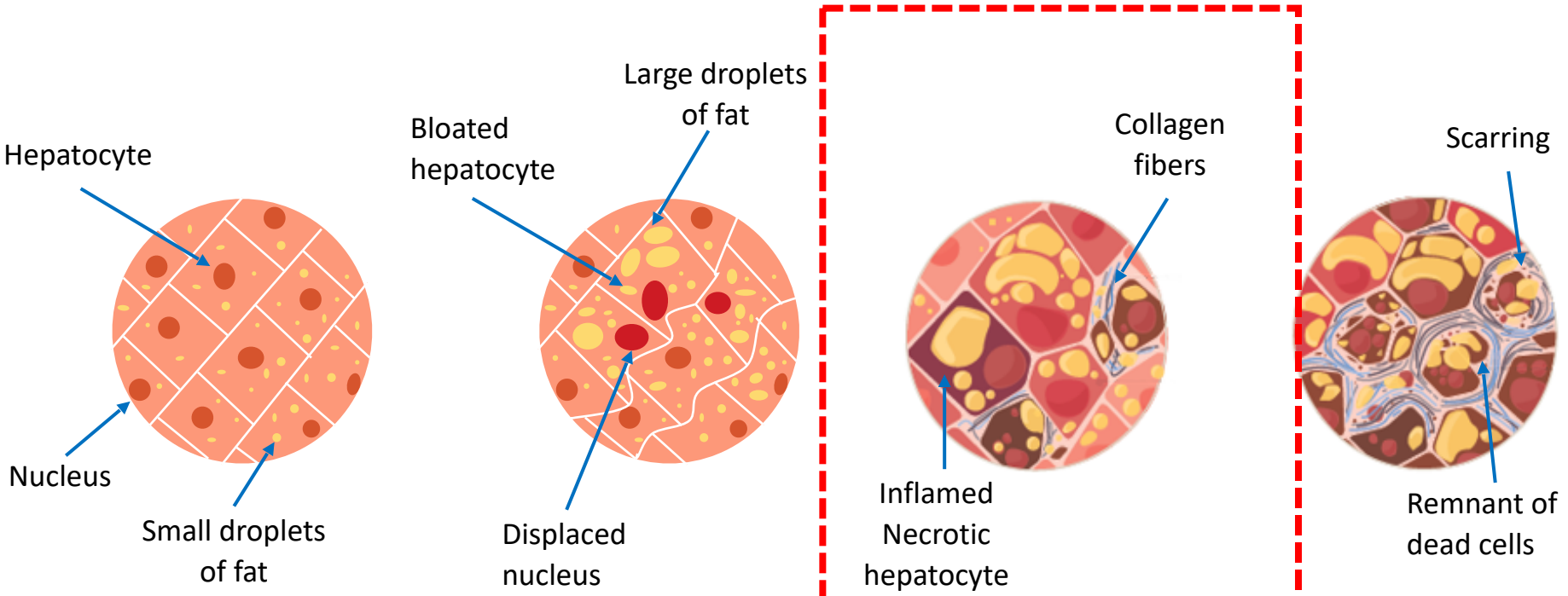
No evident necrosis

Defective Autophagy
LIPOTOXICITY
Oxidative Stress
Genetic factors

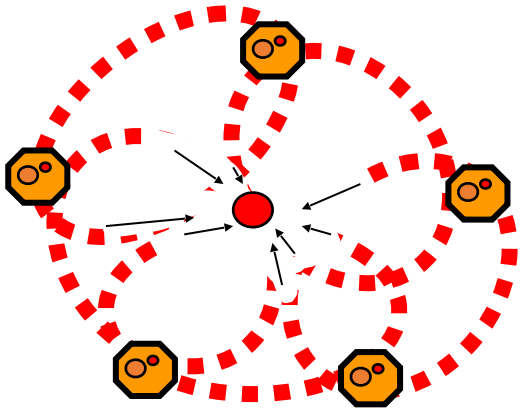
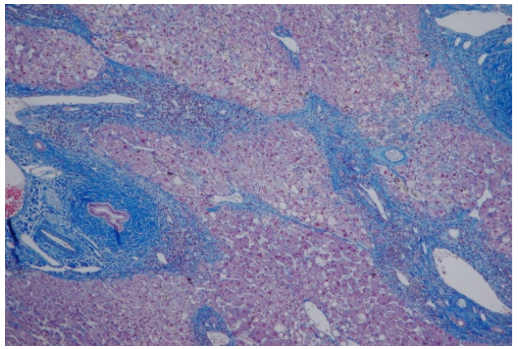
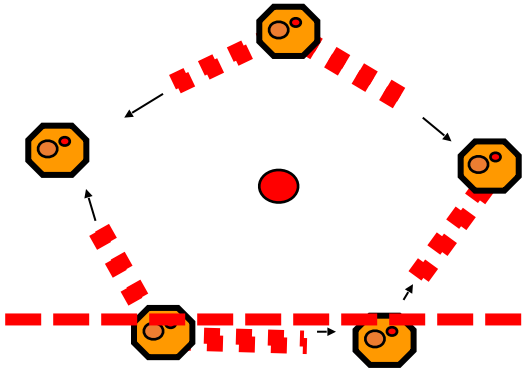
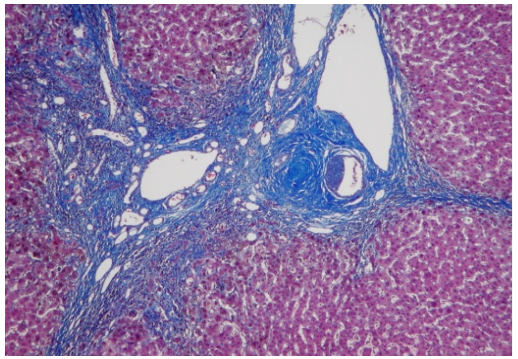
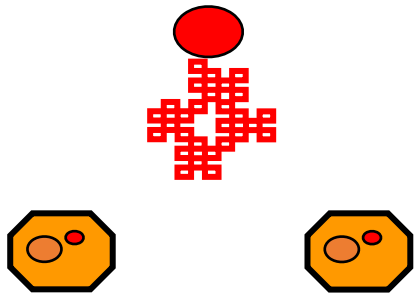
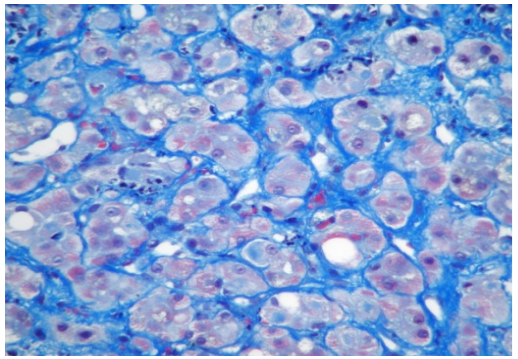
Evident necrosis

Chronic Wound Healing
Increase intestinal permeability
Complex inflammatory networks
Genetic factors

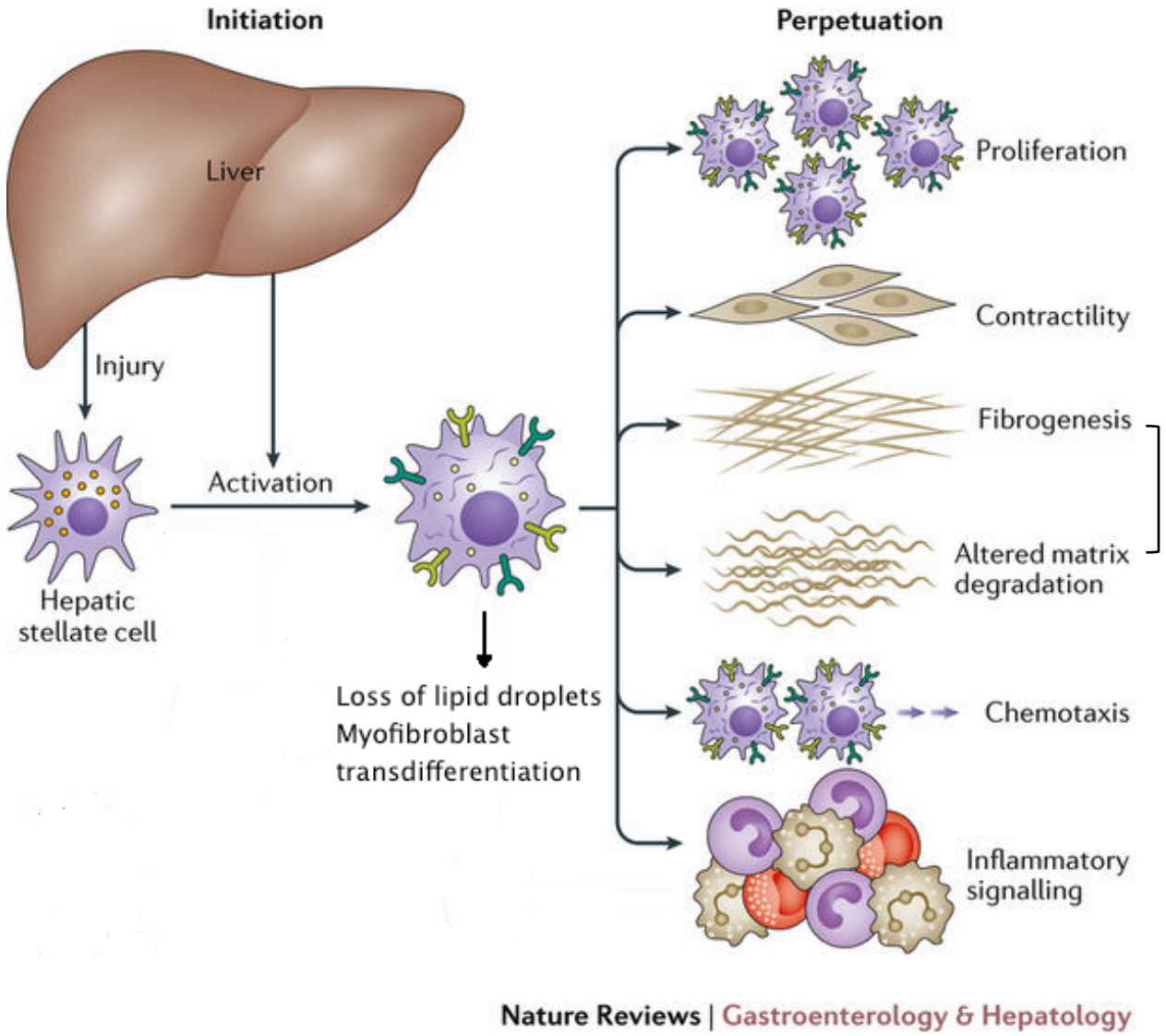
NAFLD: Natural History



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

Pathways of Stellate Cell Activation in Liver Injury

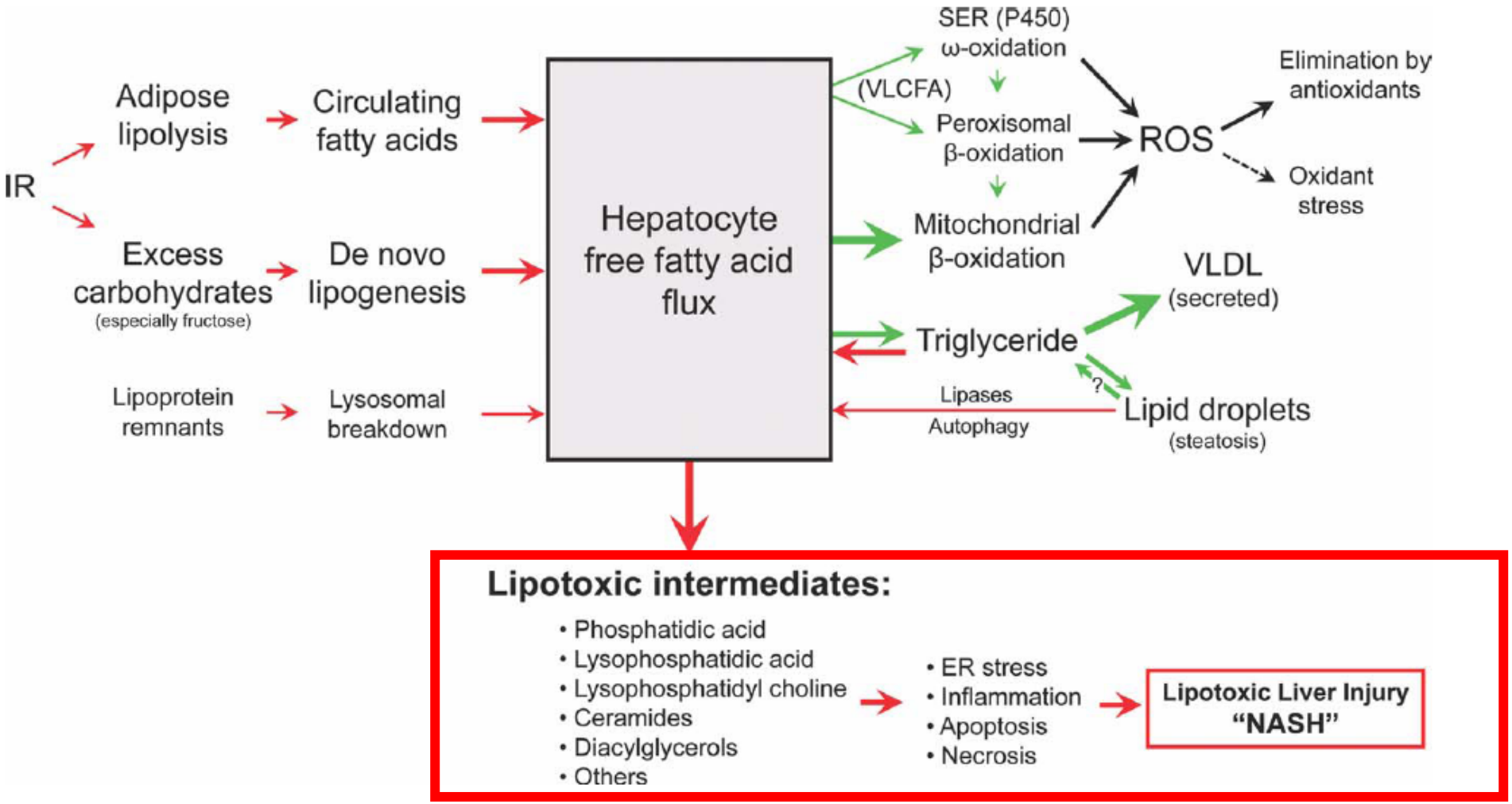


Increased tissue tension and stiffness

Changes in ECM quantity and relative composition

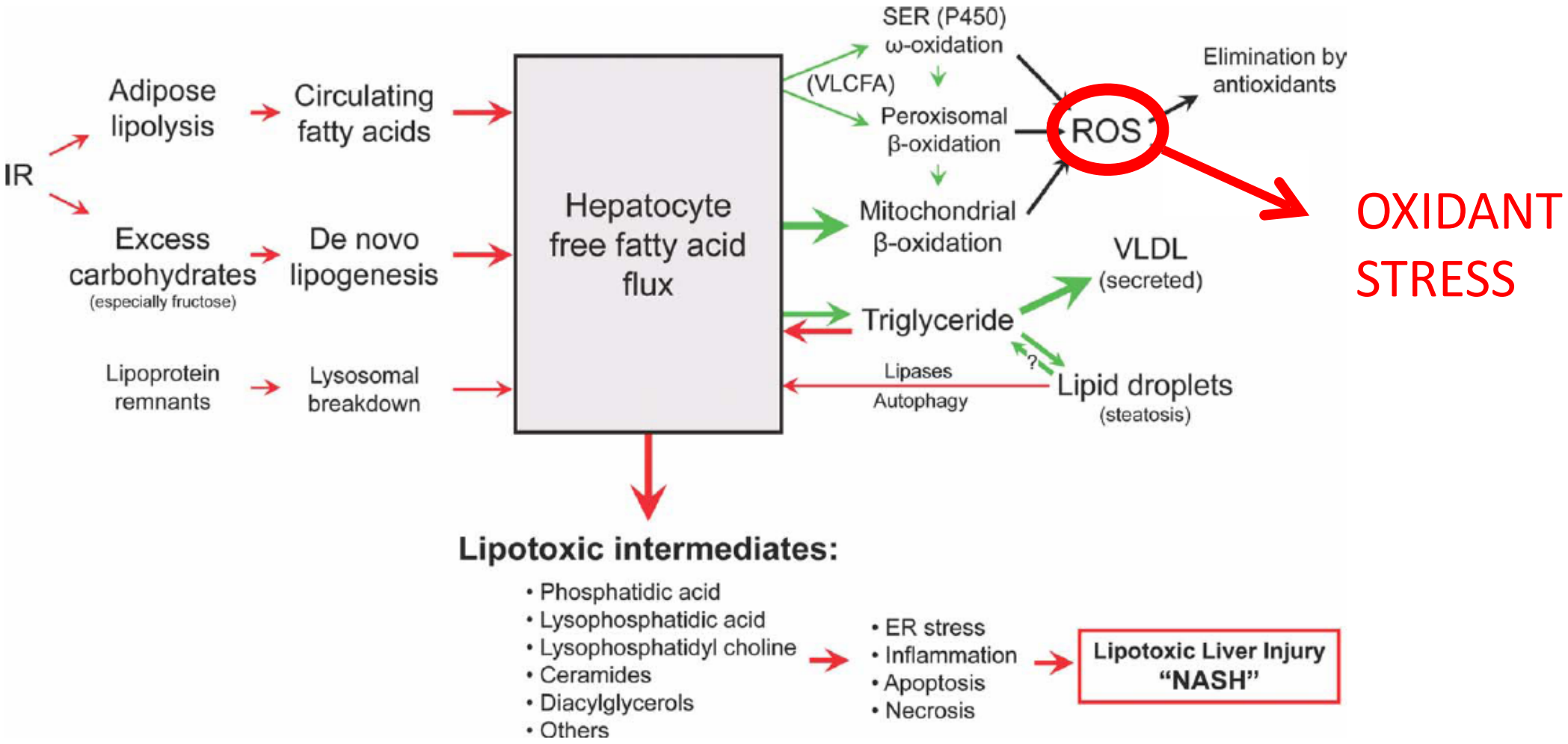
ECM as a bio-reservoir of pro-inflammatory and pro-angiogenic factors

Pathways of Lipotoxic Liver Injury



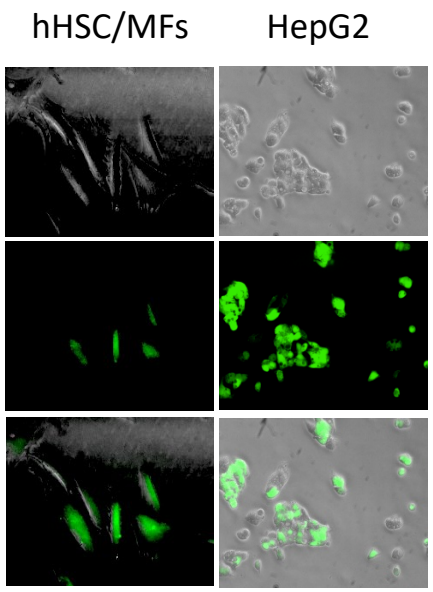
Neuschwander-Tetri Hepatology 2010;52:774C

Pathways of Lipotoxic Liver Injury

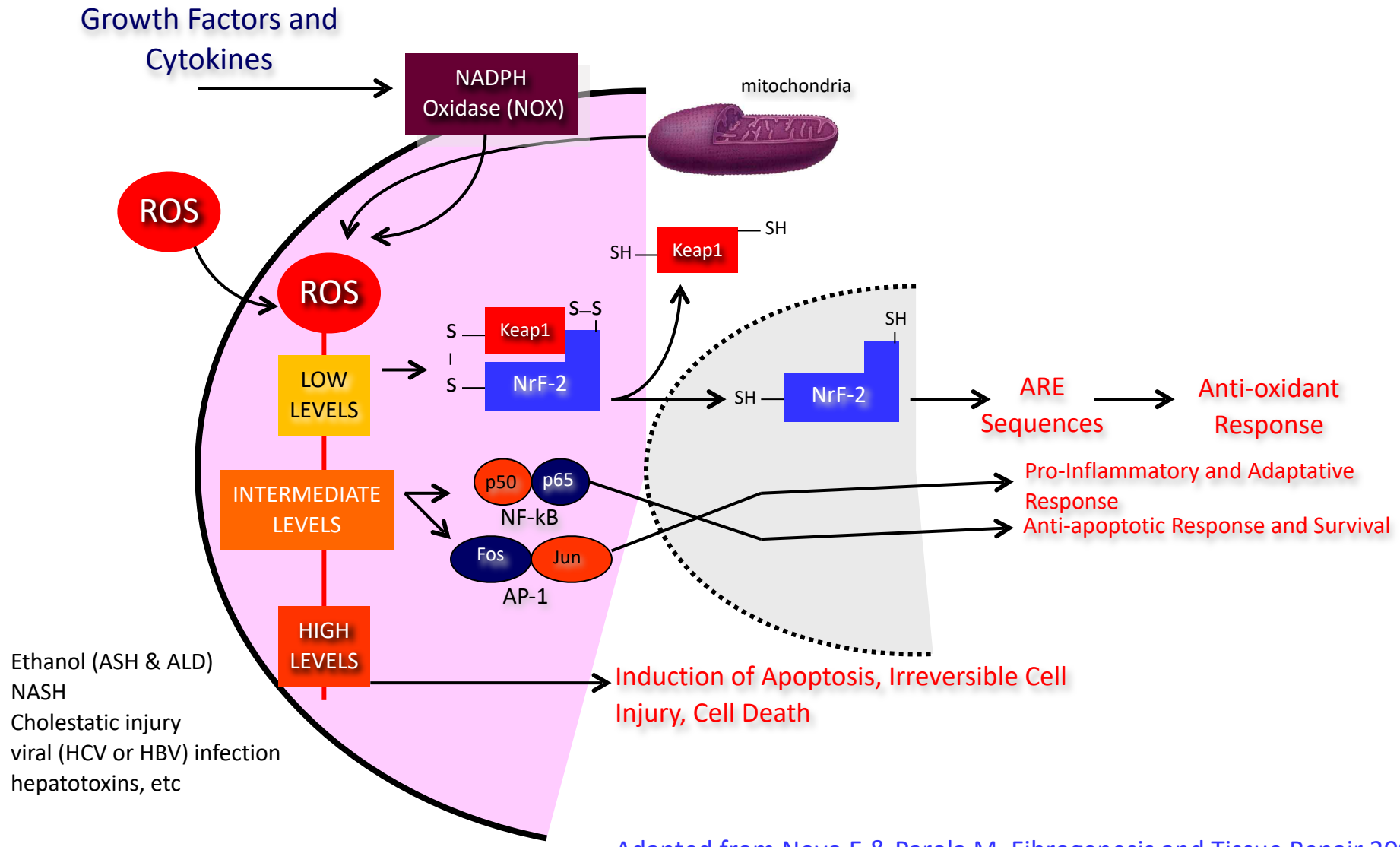


Neuschwander-Tetri Hepatology 2010;52:774C

Cellular Responses Following Increased Intracellular ROS

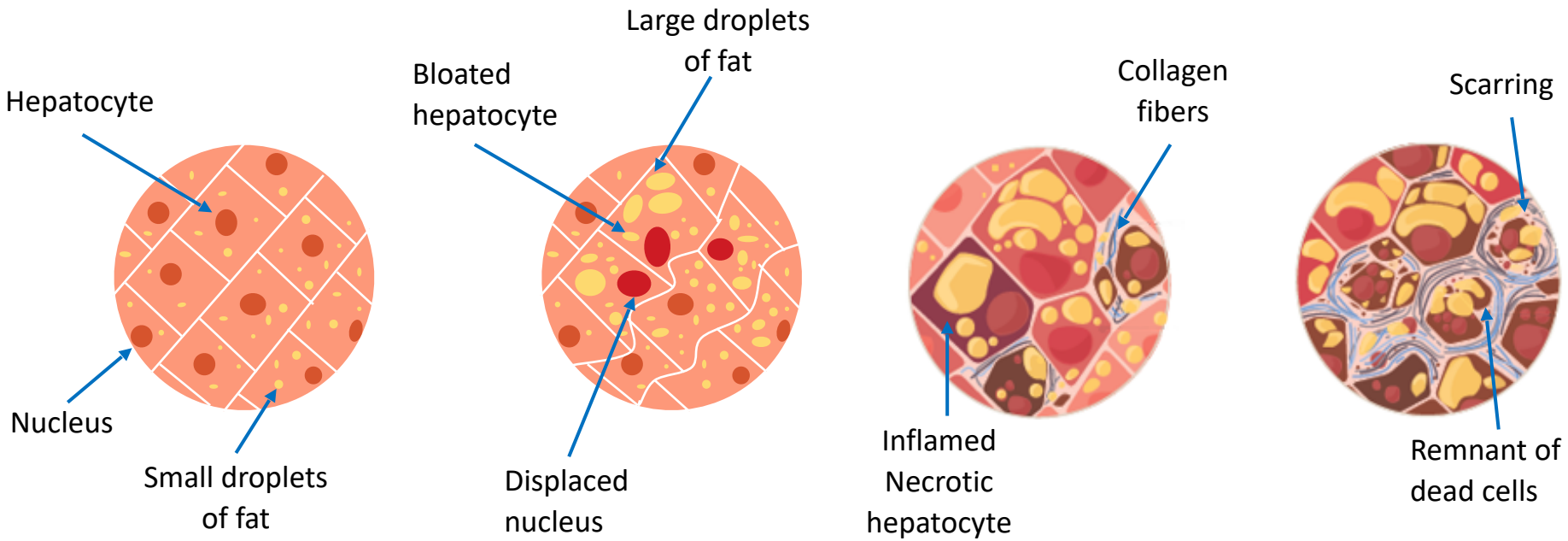


DCFH-DA technique



Adapted from Novo E & Parola M, Fibrogenesis and Tissue Repair 2008

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

PNPLA3 and NAFLD

Severity of liver disease

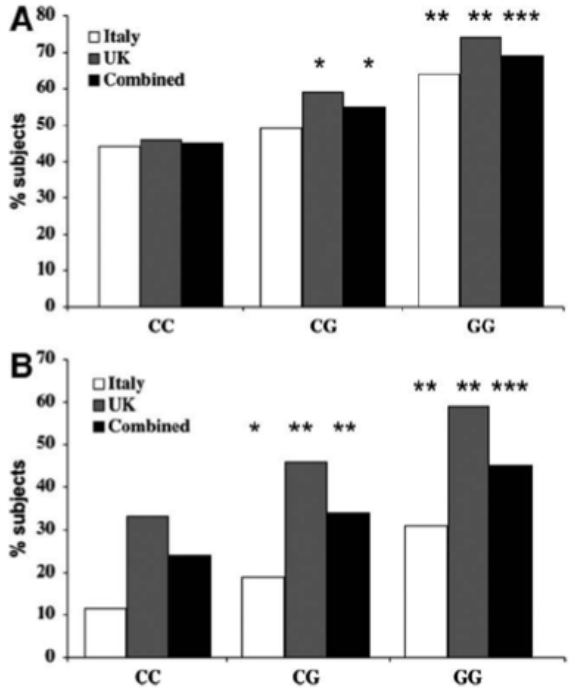
HCC

Presence of NASH

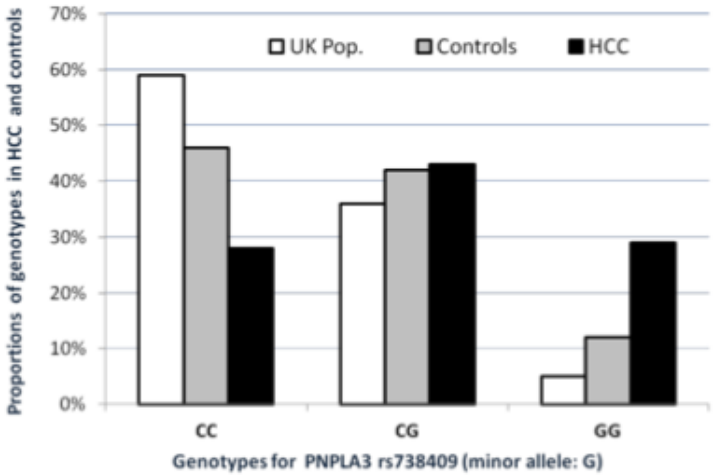
OR 1.5 (1.12-2.04)

Fibrosis >F1

OR 1.5 (1.09-2.12)



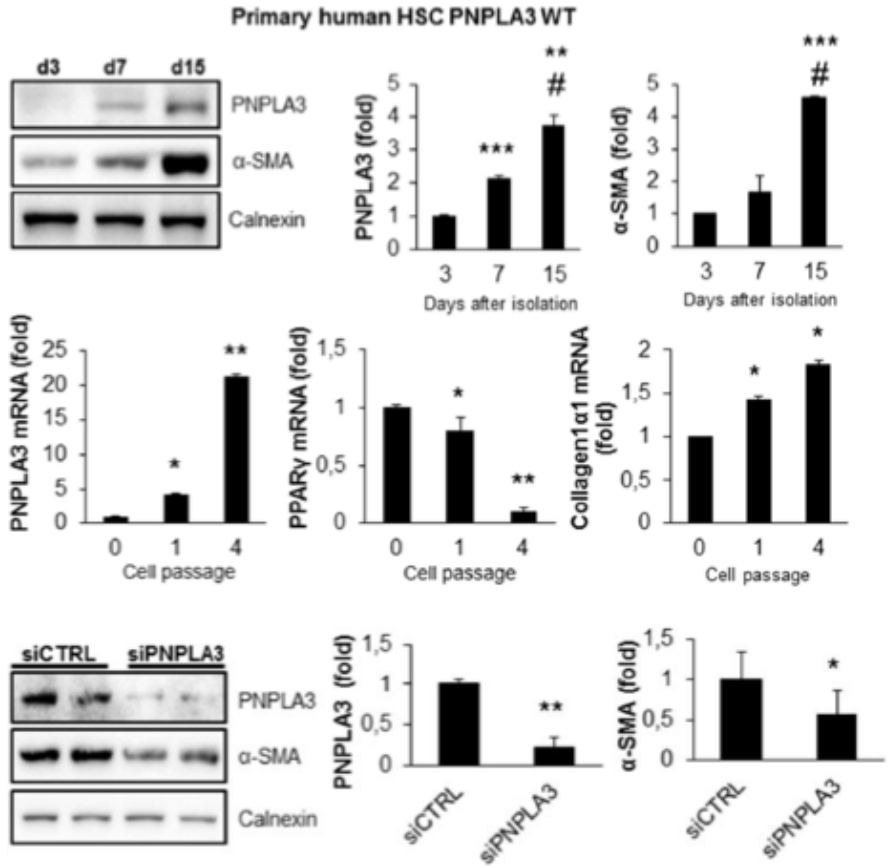
Valenti et al. Hepatology 2010



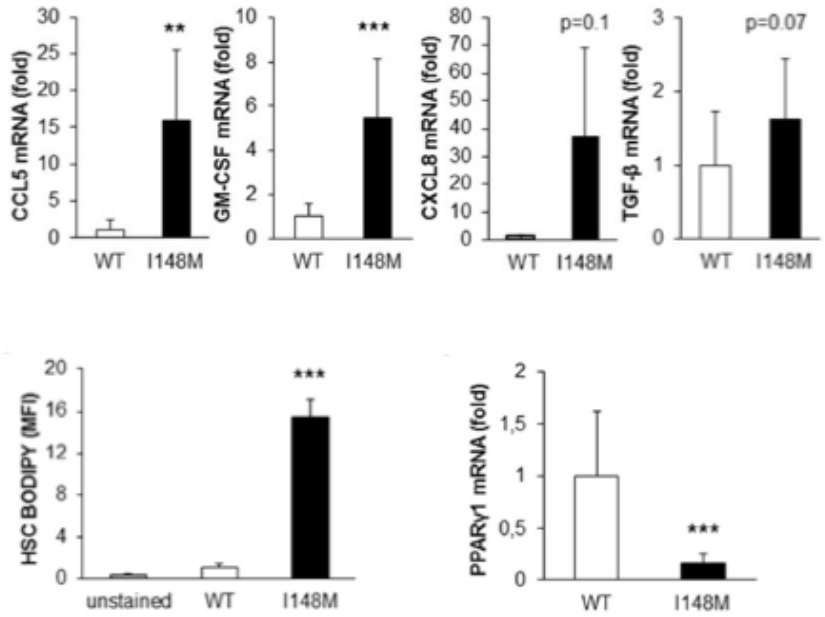
Variables	OR (95% CI)	P-value
PNPLA3 rs738409	2.26 (1.23-4.14)	**0.0082**
Age	1.24 (1.17-1.32)	**<0.0001**
Gender (Male)	11.11 (4.17-33.33)	**<0.0001**
BMI	0.94 (0.87-1.02)	0.148
Diabetes	2.33 (0.93-5.81)	0.070
Cirrhosis	9.37 (3.82-23.00)	**<0.0001**

Liu et al. J Hep 2014

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



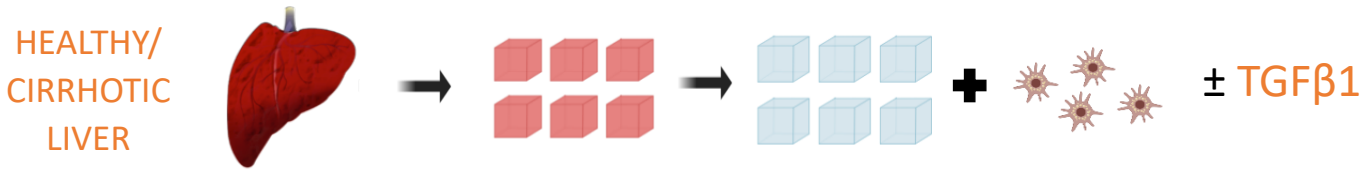
PNPLA3 expression increases with HSC activation
Silencing PNPLA3 reduces HSC activation

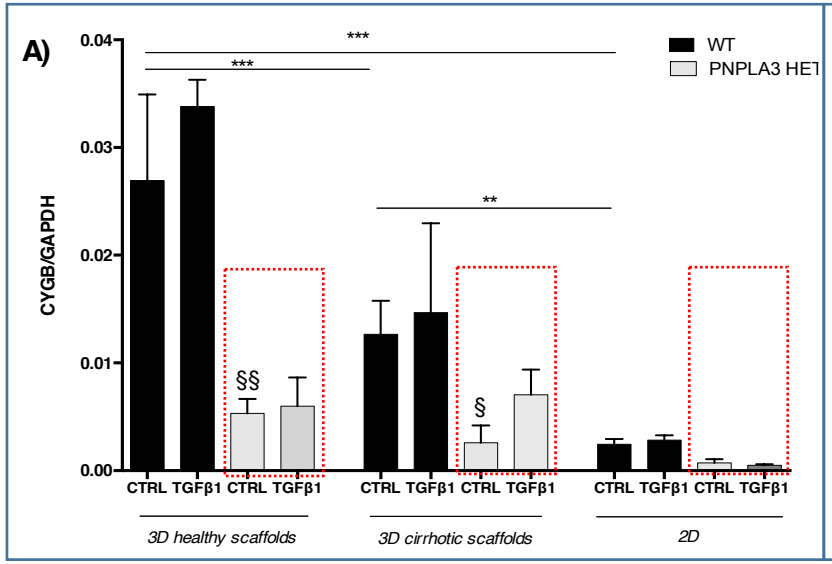


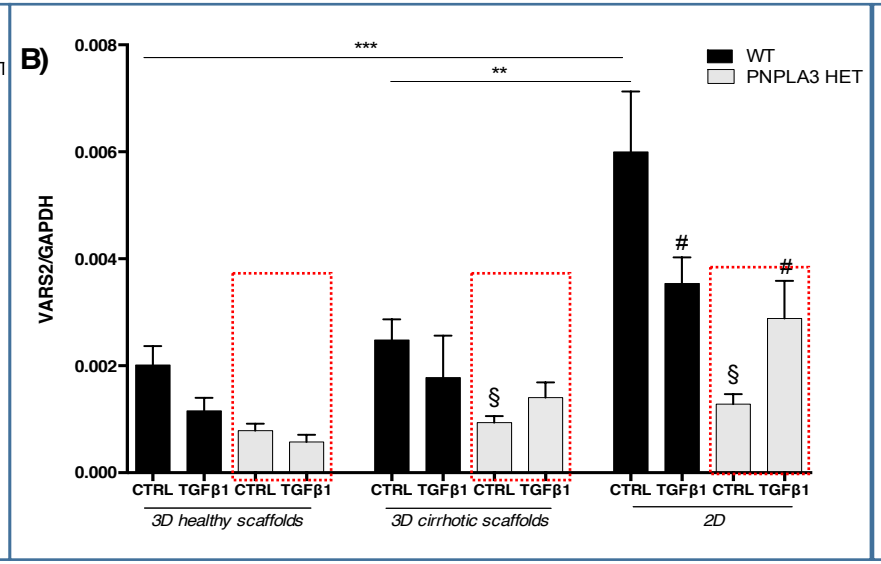
PNPLA3 I148M confers a pro-inflammatory and pro-fibrotic profile

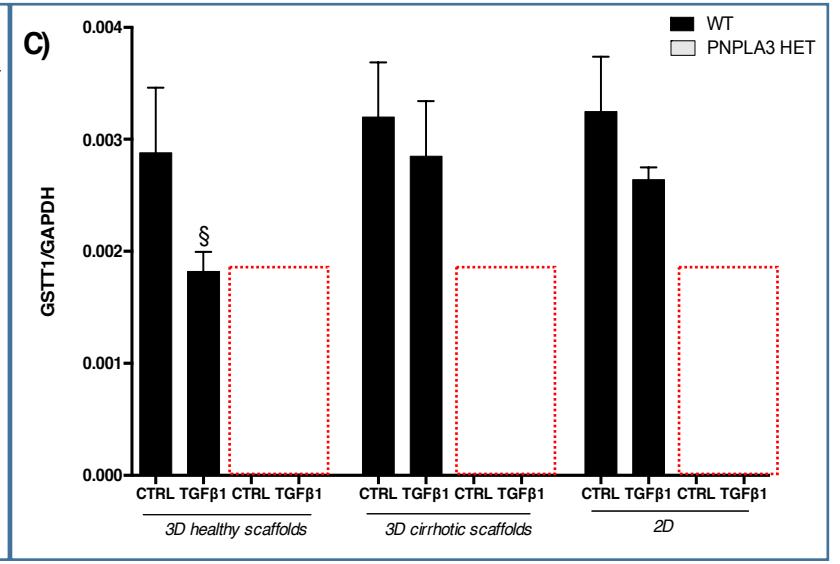
Bruschi F. et al. Hepatology 2017

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









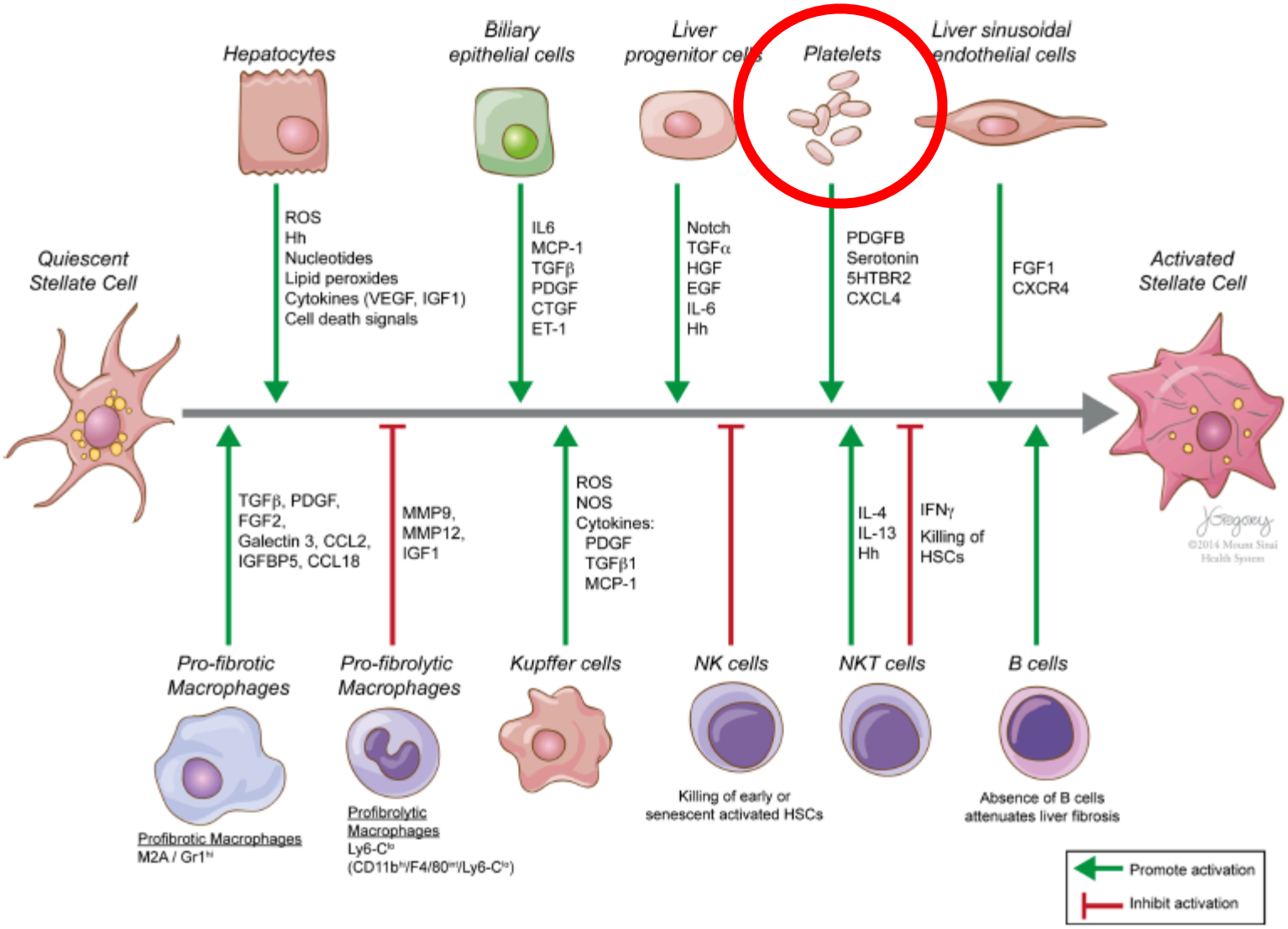
Cytoglobin B: HSC quiescence marker

VARS2: a mitochondrial enzyme involved in fatty acid metabolism

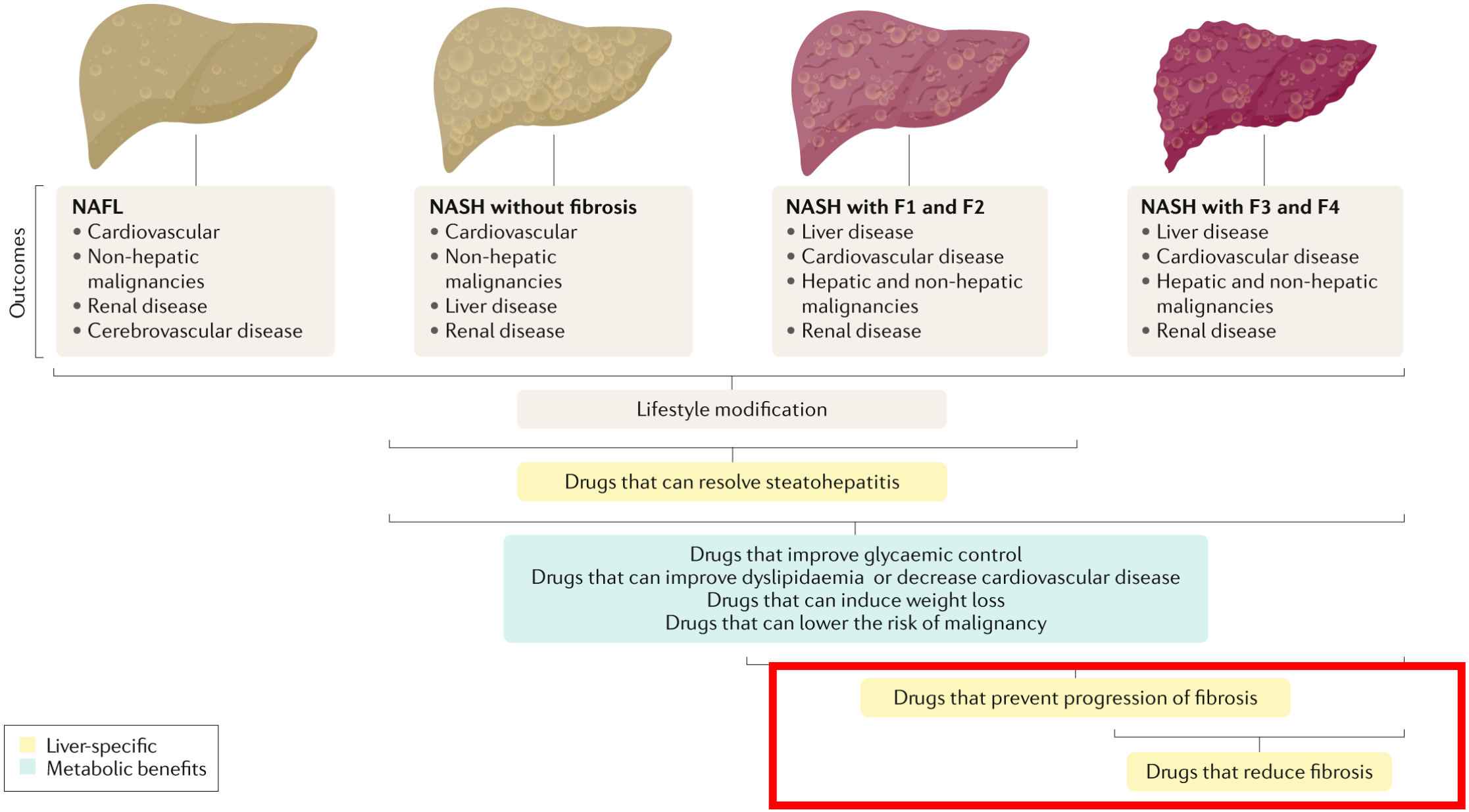
GSTT1, a Glutathione-S-Transferase

Caon E et al. 2020 unpublished

Cellular Cross-Talk in Liver Fibrogenesis

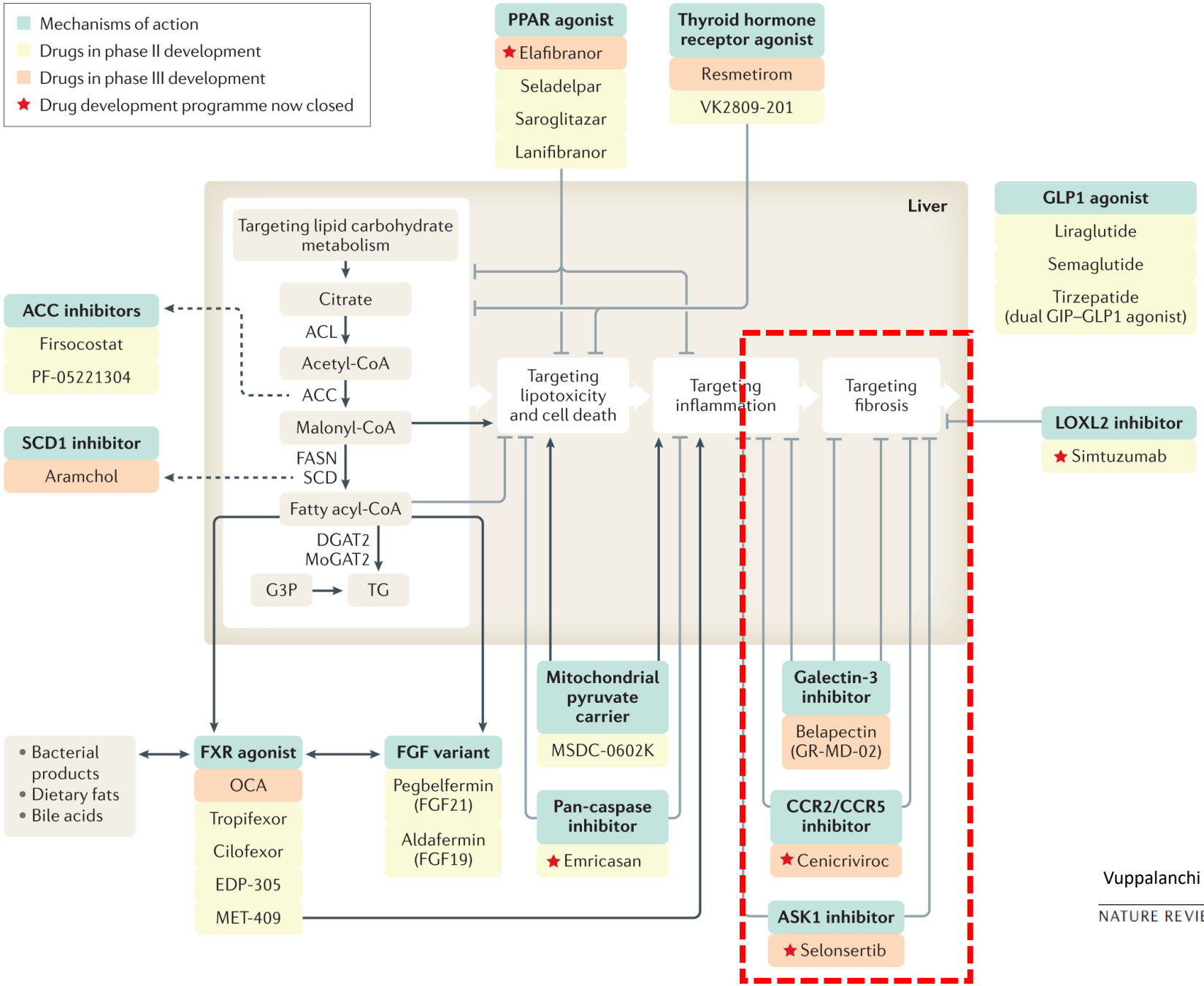


Lee et al., Gut 2015



Vuppalanchi R at al., 2021

2021



Vuppalanchi R at al., 2021

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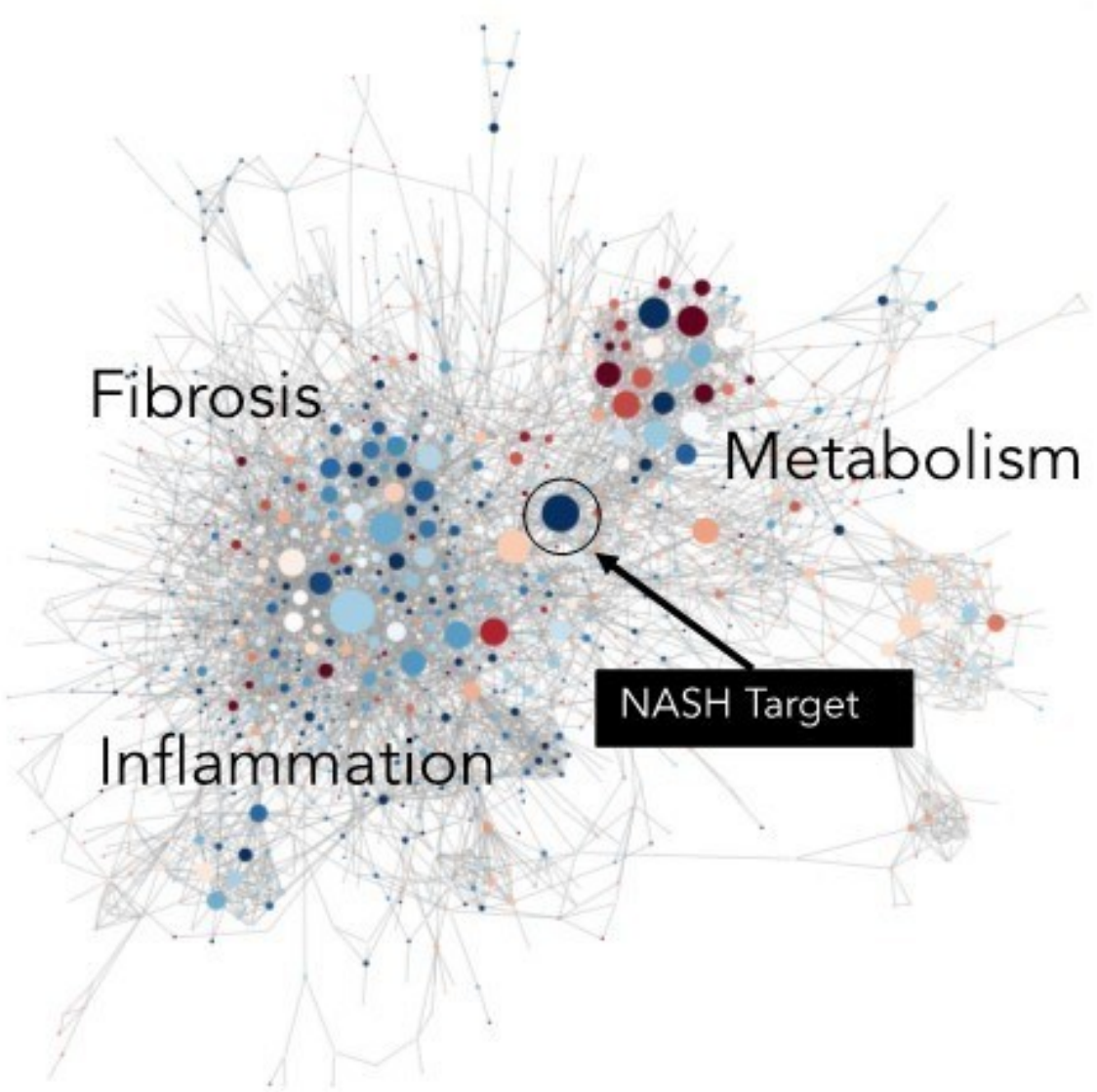

HemoShear has identified and validated a target that impacts several NASH disease pathways to reduce fibrosis, restore metabolic signaling and inhibit inflammatory signaling in the REVEAL-TxTM NASH model.

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