

**International Congress on  
Coagulopathy in Liver Disease**

**Hemostasis and Thrombosis in  
Liver Disease:  
from Bench to Bedside**

Castellana Grotte (BA)- 8-10 April 2026



# Endothelial dysfunction in chronic liver disease

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# COIs

## Research grant, consulting or travel grant (last 3 years)

Gilead Sciences

Inventiva

BrudyLab

GAT Therapeutics

Surrozen

Quinton International

Novo Nordisk

Cell Pharma

Oncomatryx

## Stock ownership

Barcelona Liver Bioservices

# Agenda

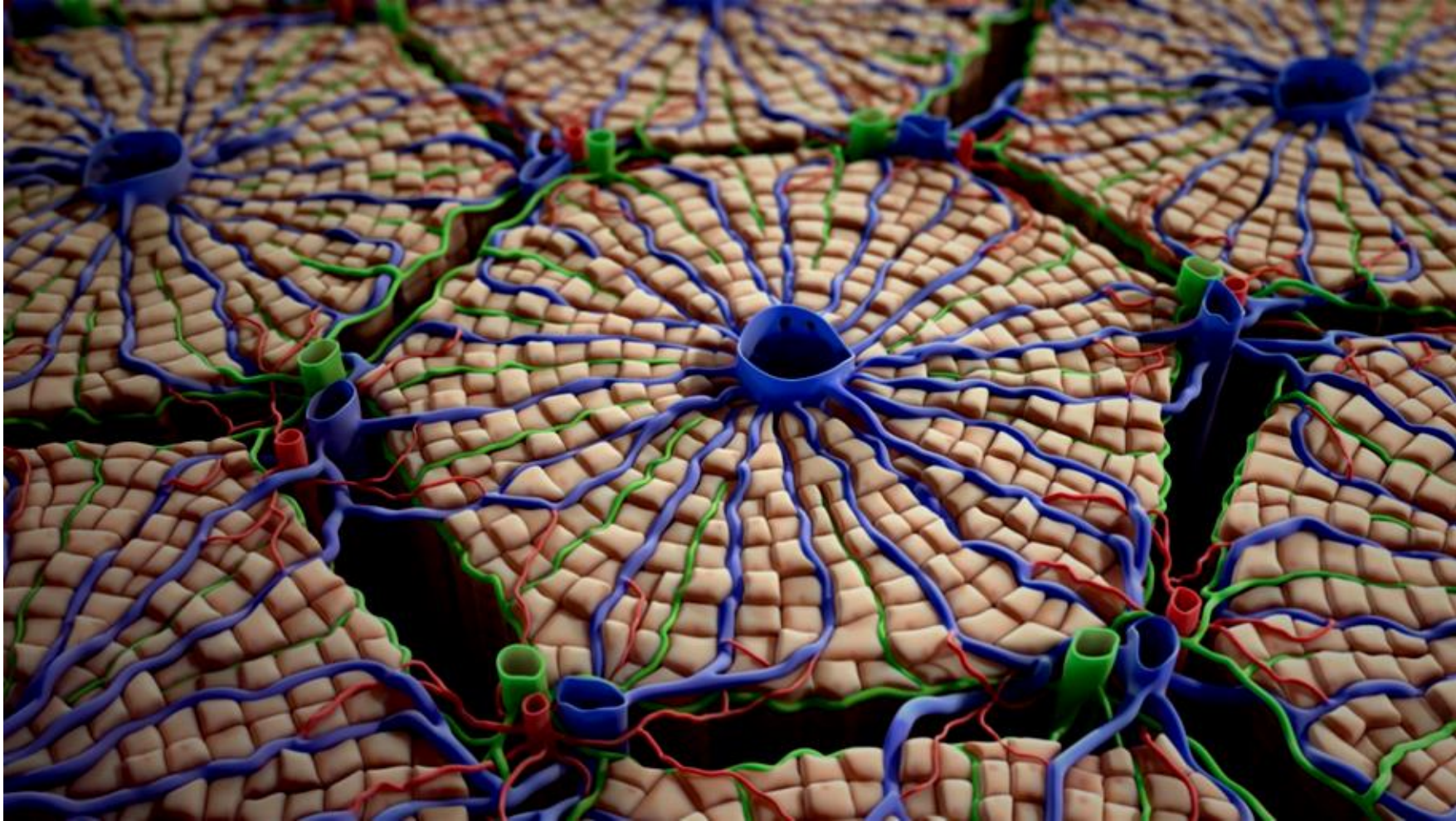
Introduction on LSECs

LSEC dysfunction as key mechanism of CLD progression & PH development

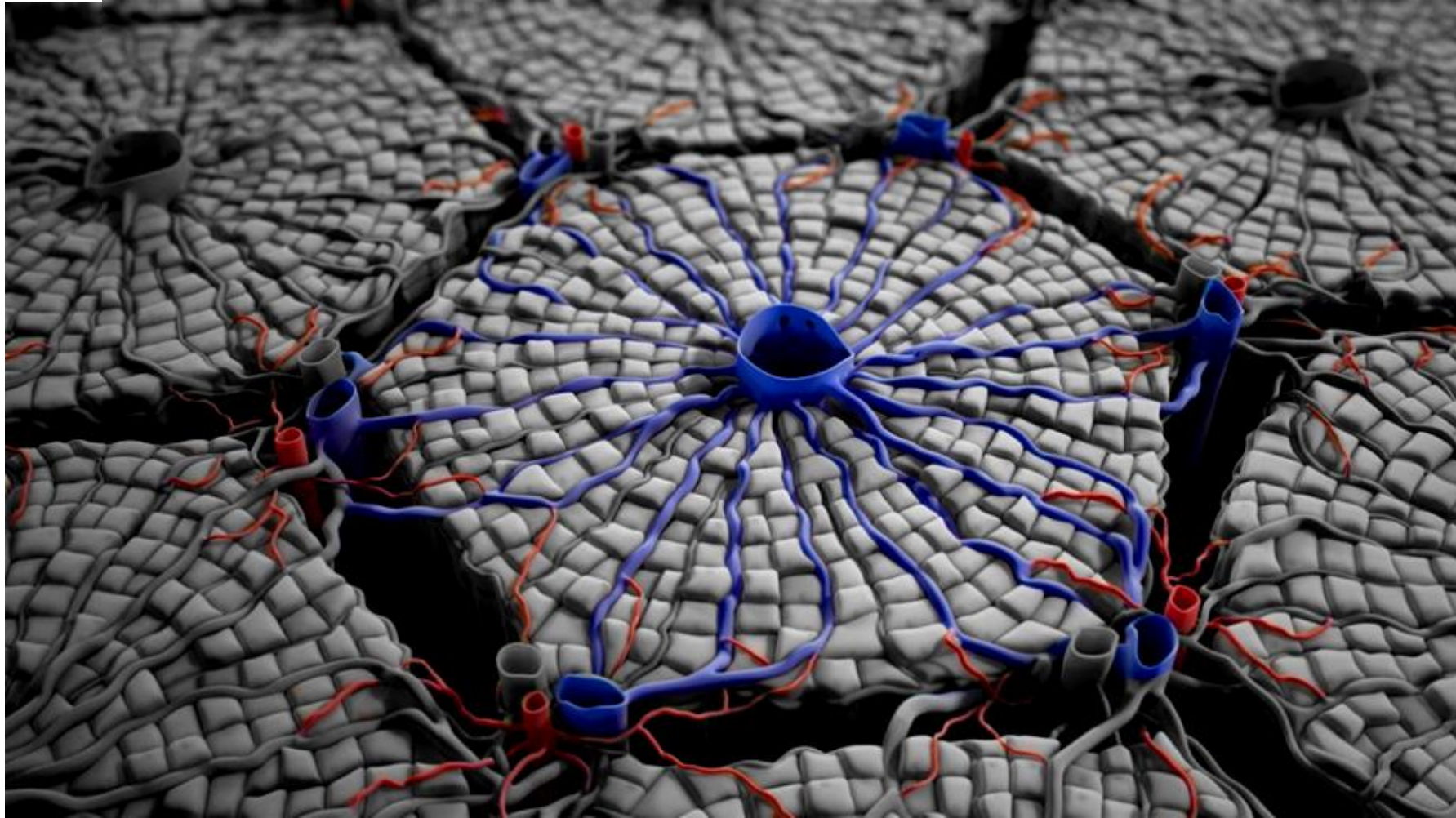
Mechanisms underlying LSEC dysfunction in CLD

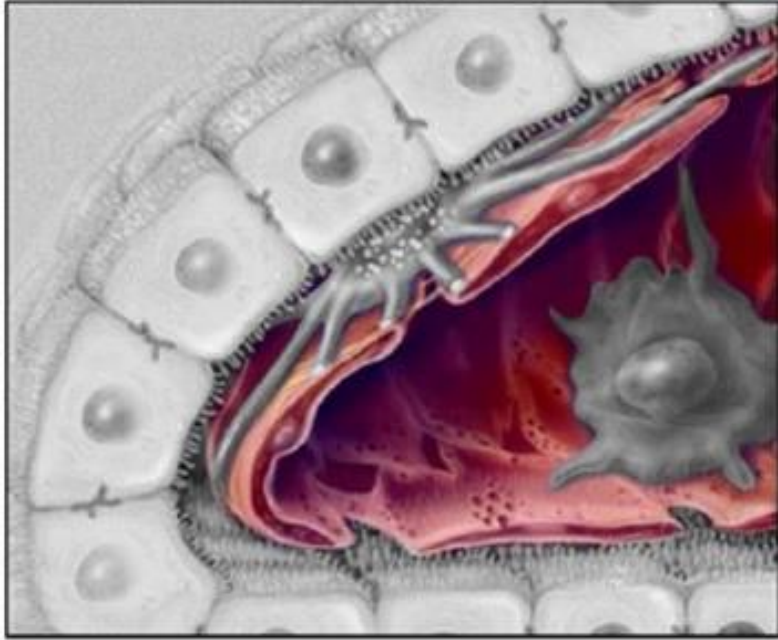
Therapeutic strategies targeting LSECs in CLD

# The liver sinusoid



# The liver sinusoid





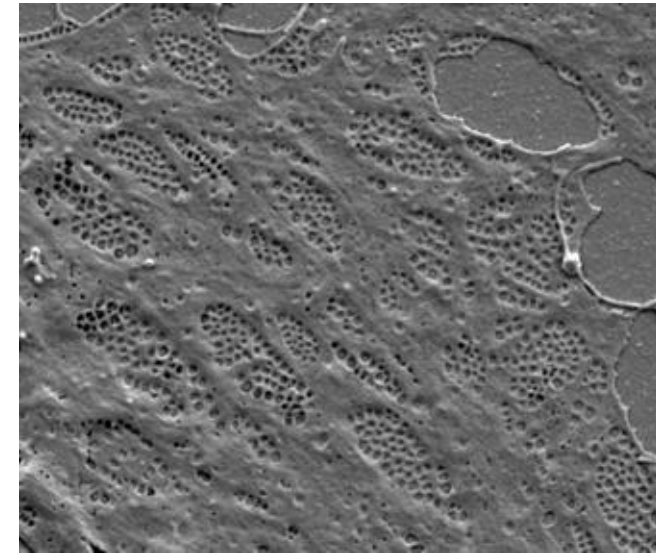
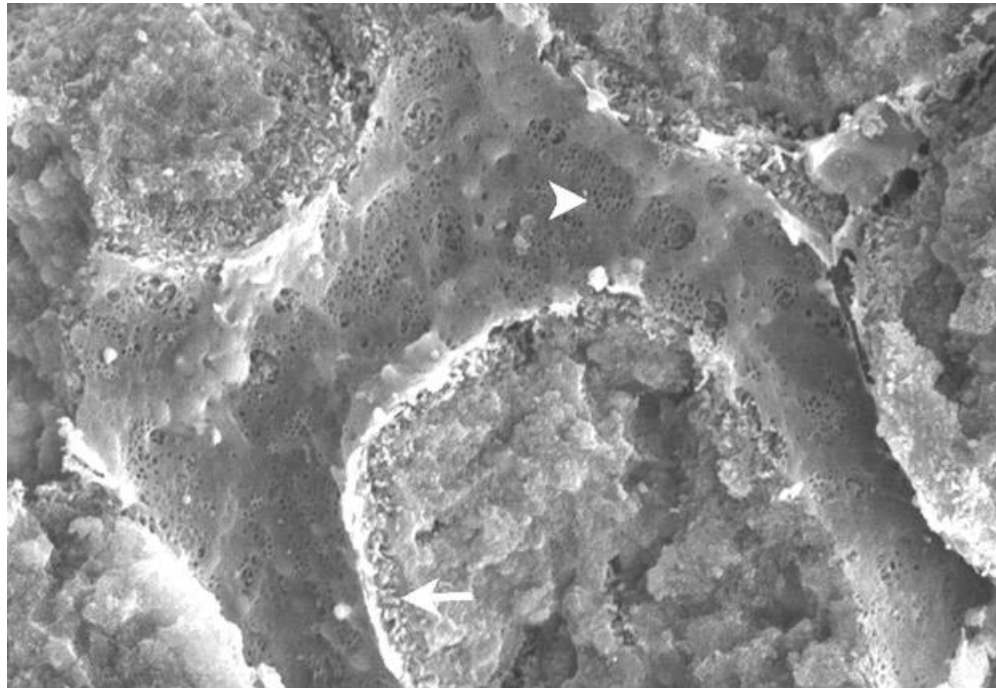
## Liver Sinusoidal Endothelial Cells (LSEC)

- Discontinuous (fenestrae, lack of basal membrane).
- Haemostasis, inflammation, toxicants clearance and regulation of vascular tone.

## Liver sinusoidal endothelial cells

Characterized by Prof. Wisse in 1970, LSEC have a unique phenotype defined by the lack of basal membrane and the existence of fenestrae grouped in sieve plates.

In front of a chronic injury, LSEC become “capillarized” loosing fenestrae and developing basal membrane, thus interfering with blood/hepatocyte communication.

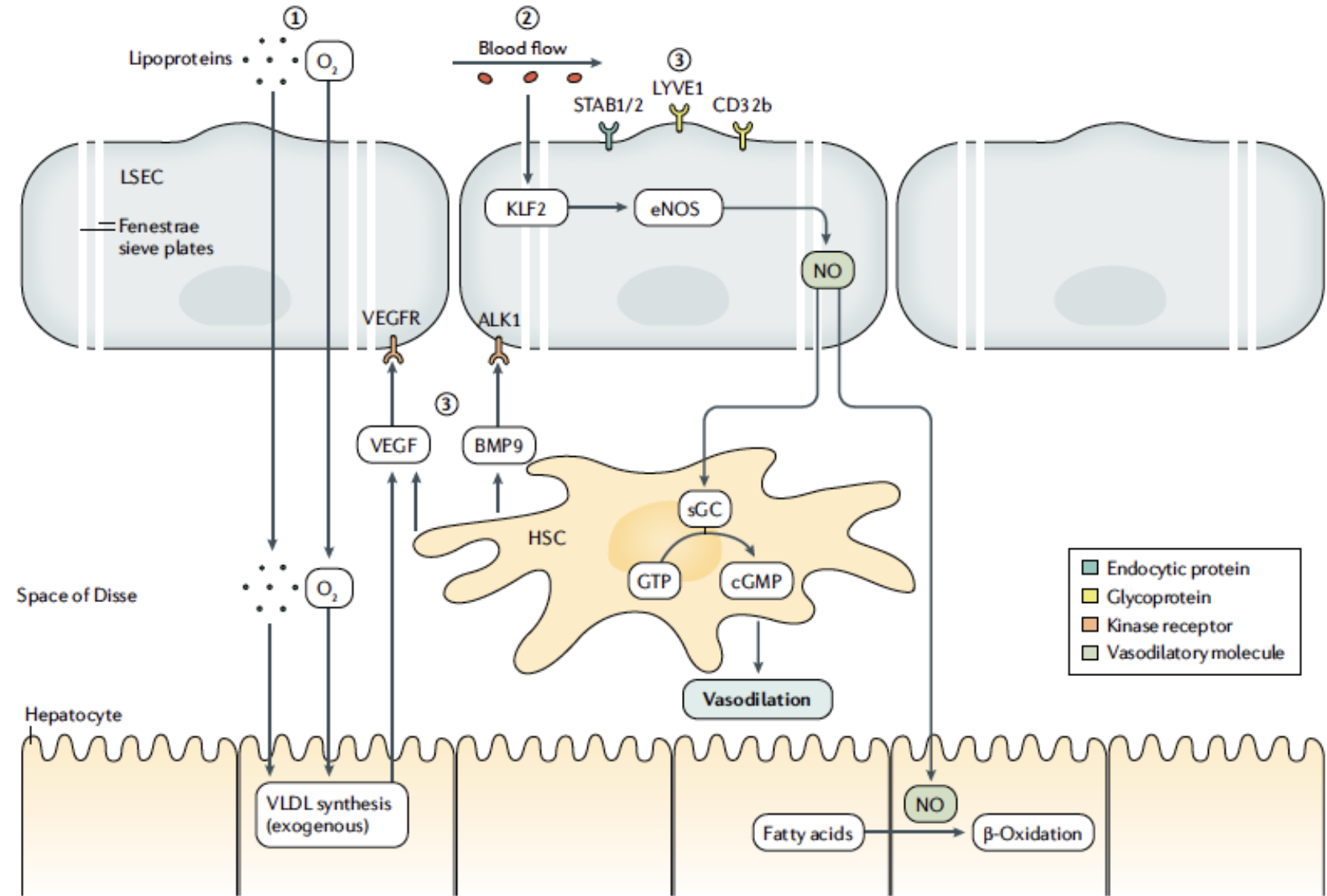


# Liver sinusoidal endothelial cells in health

Gracia-Sancho et al, Nature R Gastro Hepatol 2021

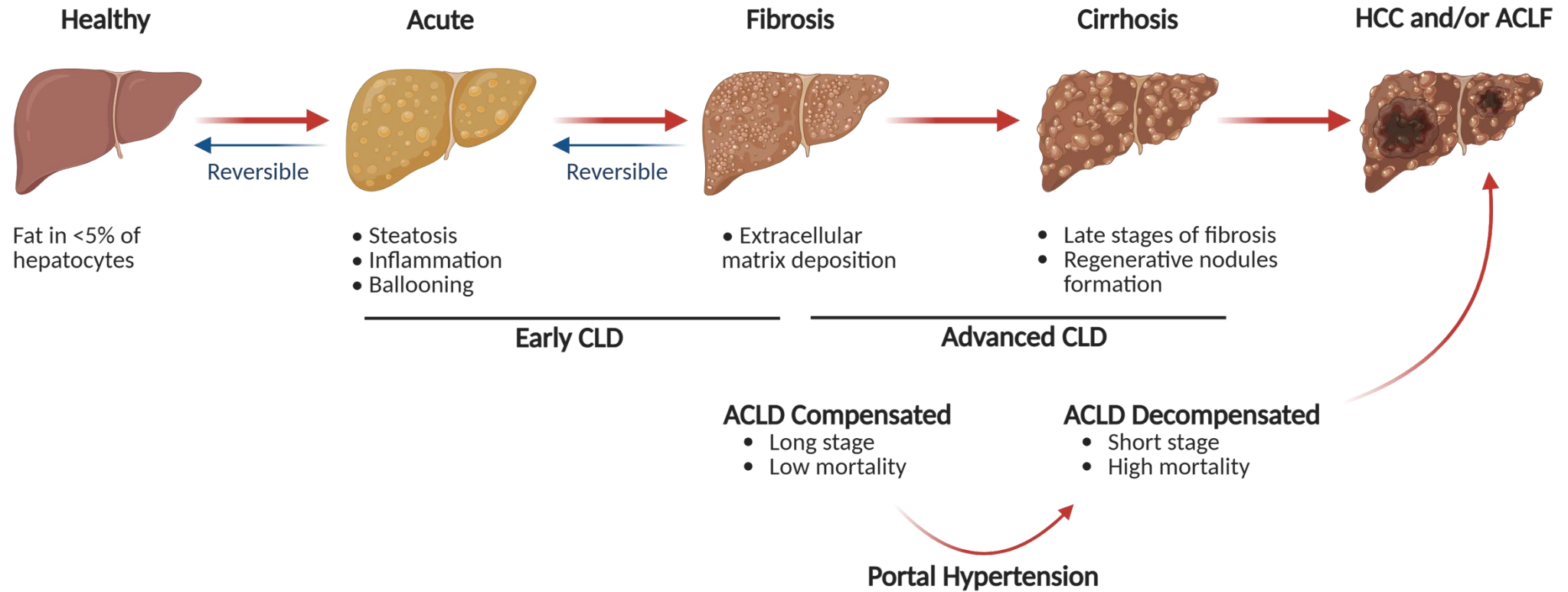
## Key features and functions:

- 1- Blood – parenchyma communication
- 2- Vascular tone control
- 3- Endocytic capacity
- 4- Inflammation control
- 5- Coagulation control

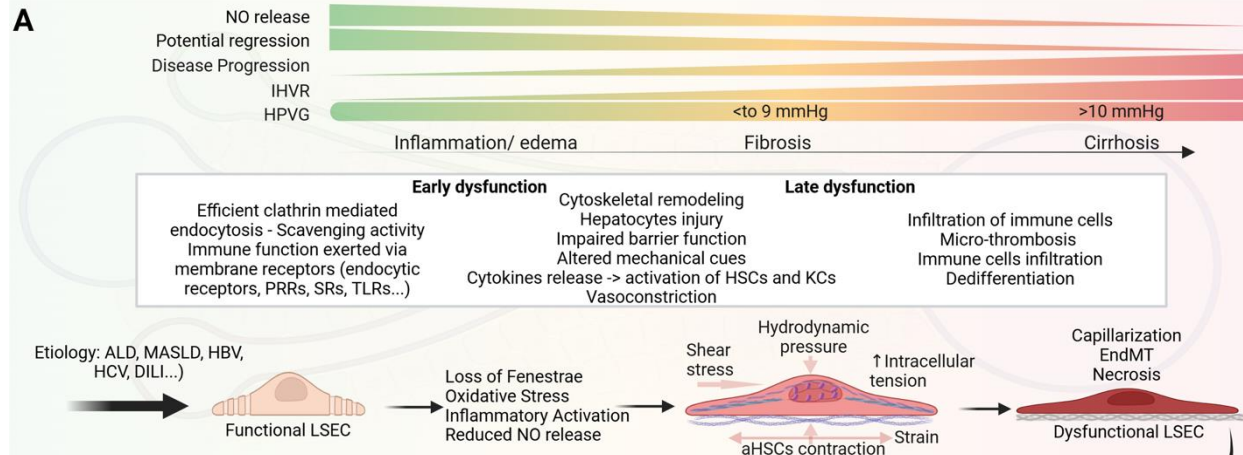


# CLD progression & PH development

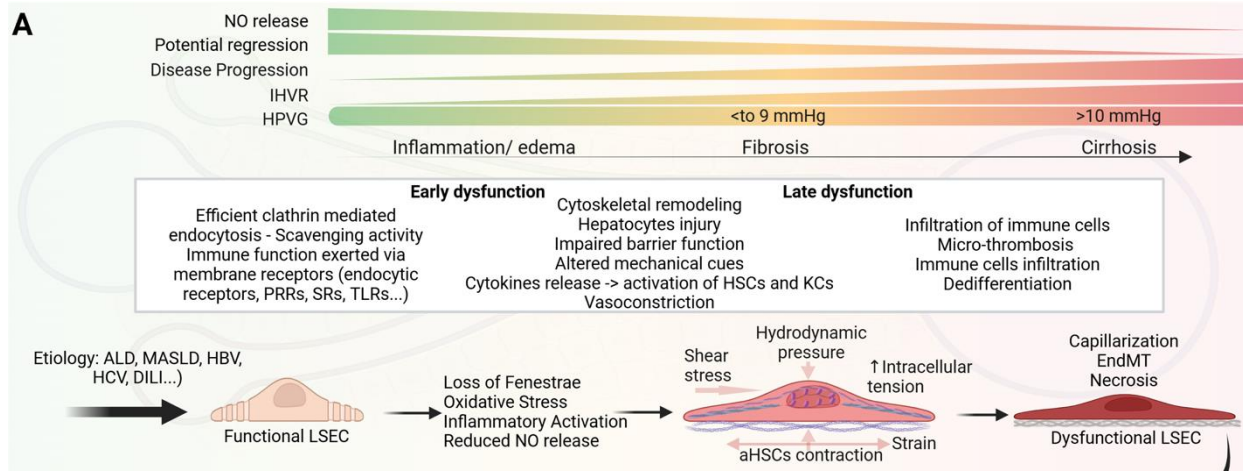
Gracia-Sancho et al, Nature R Gastro Hepatol 2019  
Guixé-Muntet ... Gracia-Sancho J. Lancet G&H 2024  
Priego-Parra ... Gracia-Sancho J. Trends Endocr Metab 2024



# LSECs orchestrate CLD progression and PH development

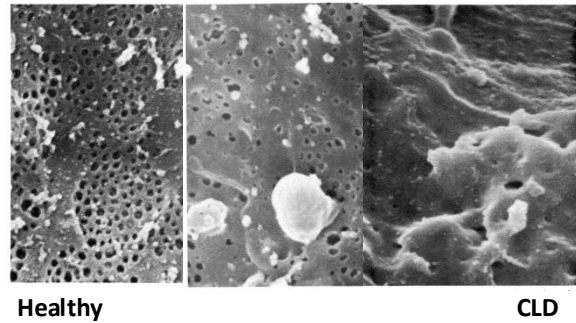


# Specific features of LSEC dedifferentiation in CLD – pre-omics research

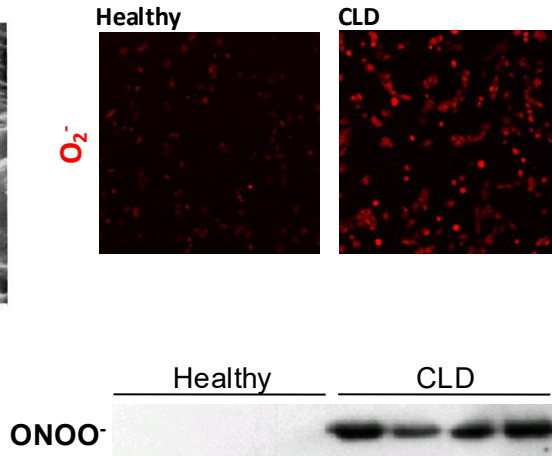


Horn et al. Hepatology 1987  
Rockey and Chung, Gastroenterology 1998  
Gracia-Sancho ... García-Pagán. J of Hepatology 2007  
Gracia-Sancho ... García-Pagán. Hepatology 2008  
Connolly et al. J Immunol 2010  
Furuta et al. JCI 2021  
Felli ... Gracia-Sancho, J of Hepatology 2026

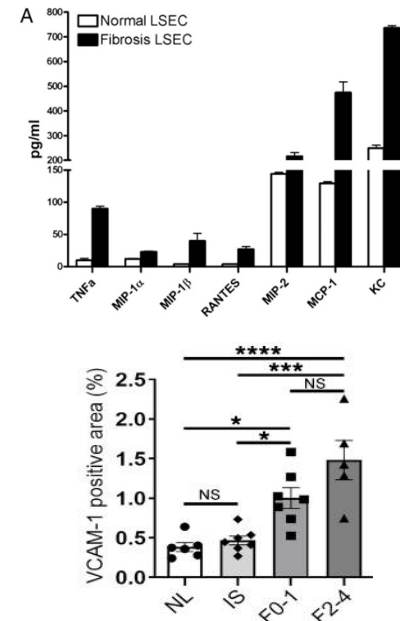
## Capillarization



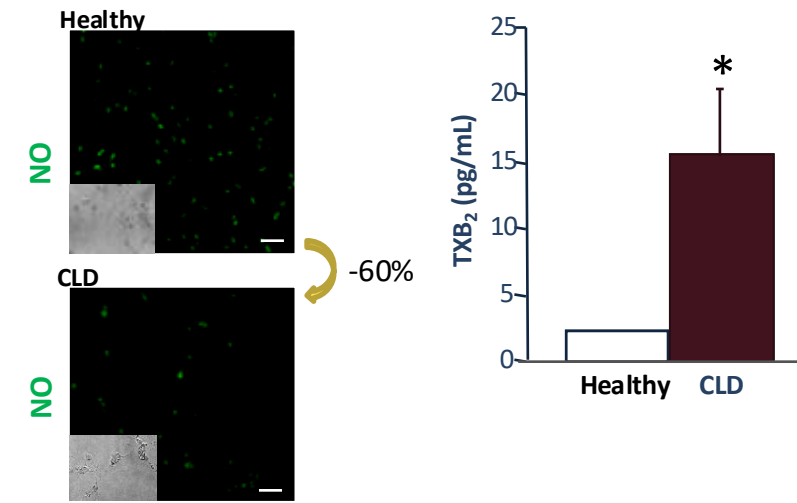
## Oxidative stress



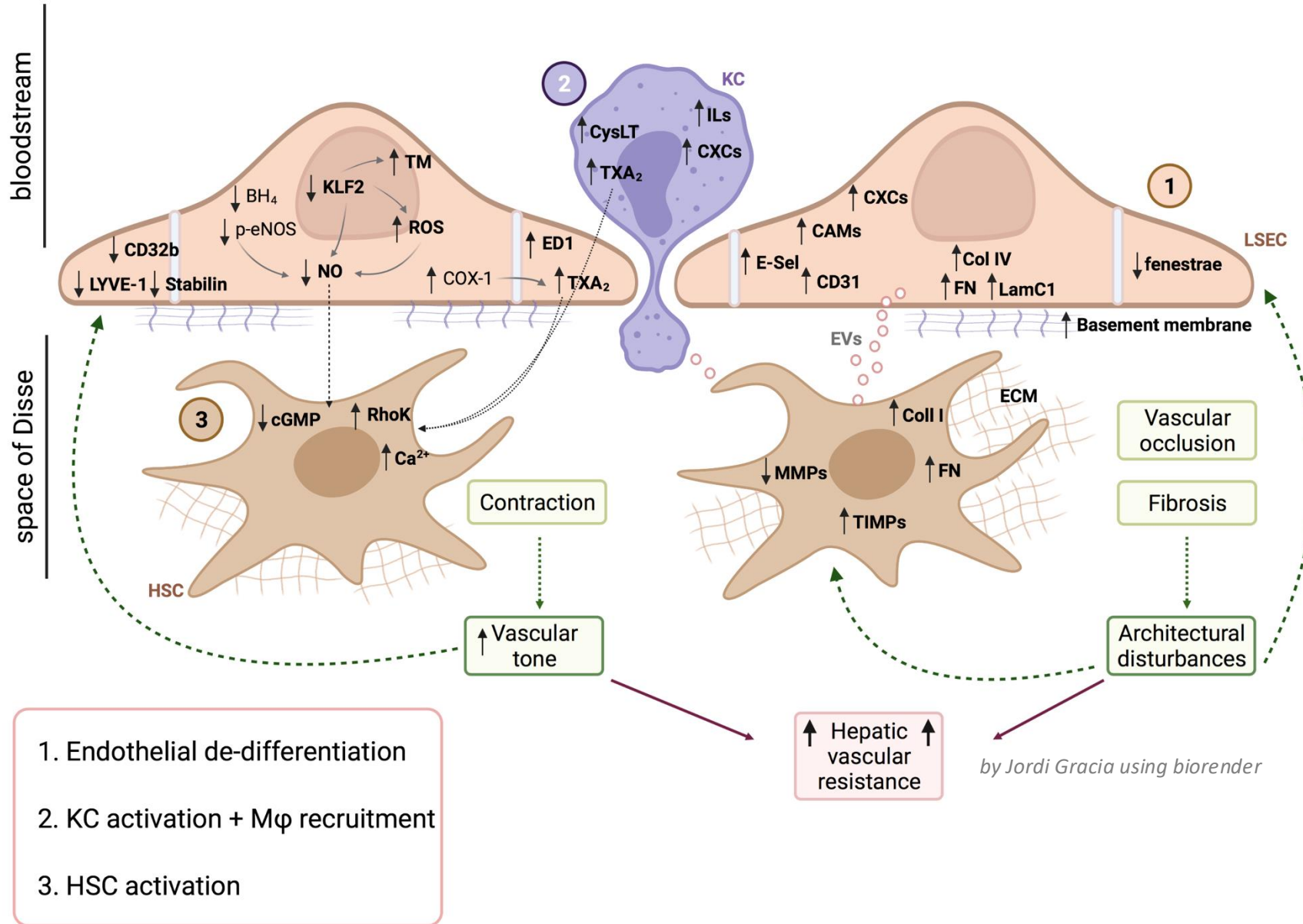
## Inflammation



## Vasoconstriction

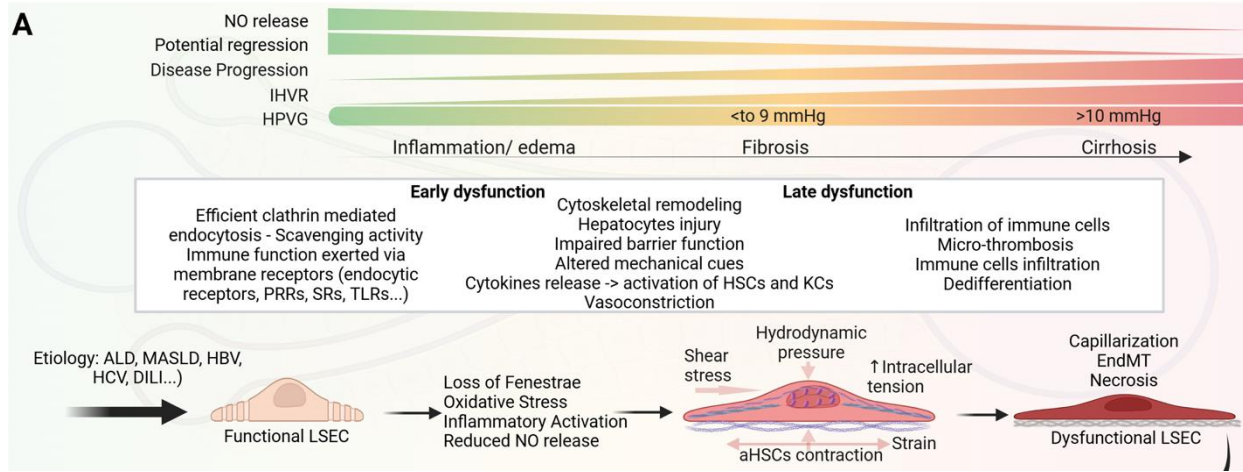


# LSECs orchestrate CLD progression and PH development

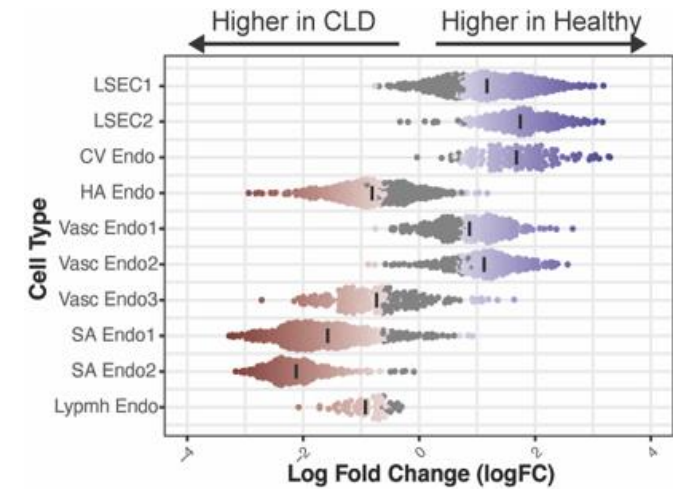


# Specific features of LSEC dedifferentiation in CLD – omics age

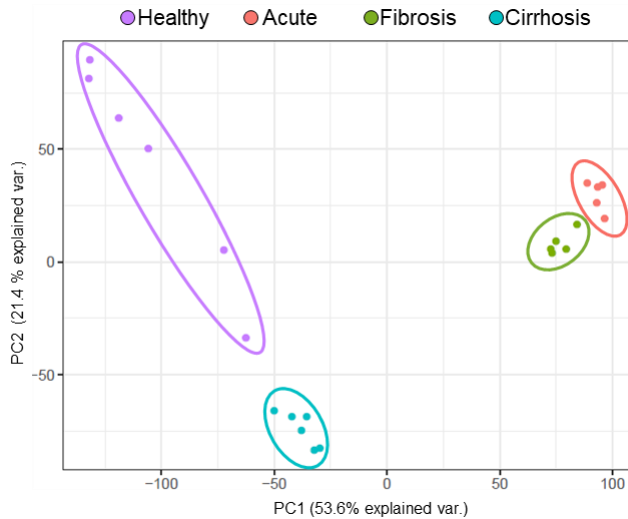
Papachristoforou, Kong et al. Bioarxiv 2025  
 Manicardi, Fdez-Iglesias ... Gracia-Sancho, Cancers 2021  
 Inverso et al. Dev Cell 2021  
 Felli ... Gracia-Sancho, J of Hepatology 2026  
 Guixé-Muntet, Fdez-Iglesias ... Gracia-Sancho. BMC Medicine 2026



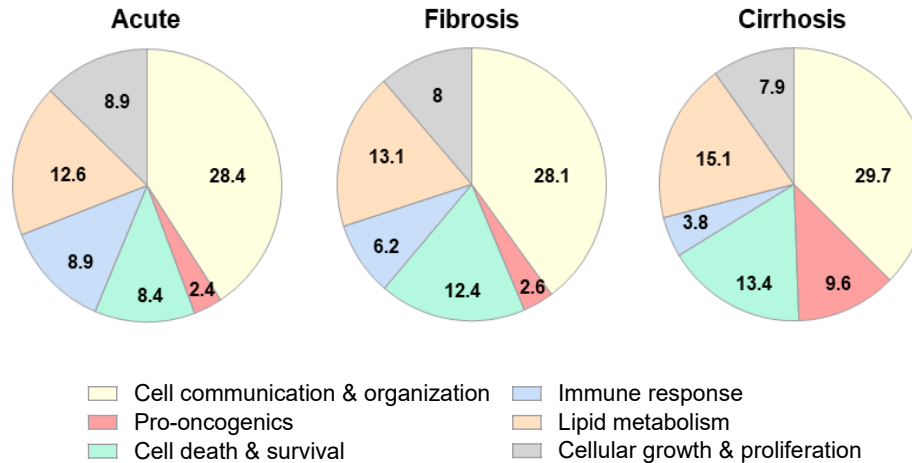
## sc RNAseq hLSECs



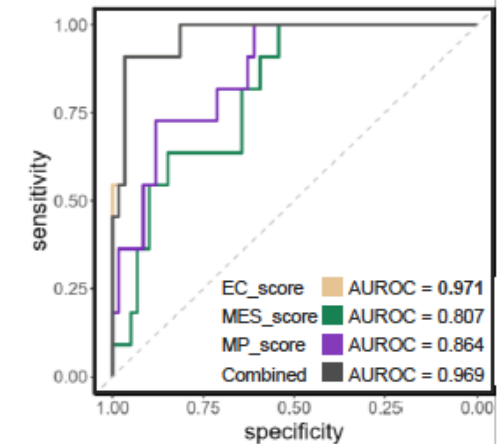
## RNAseq rLSECs



## Molecular processes (%)

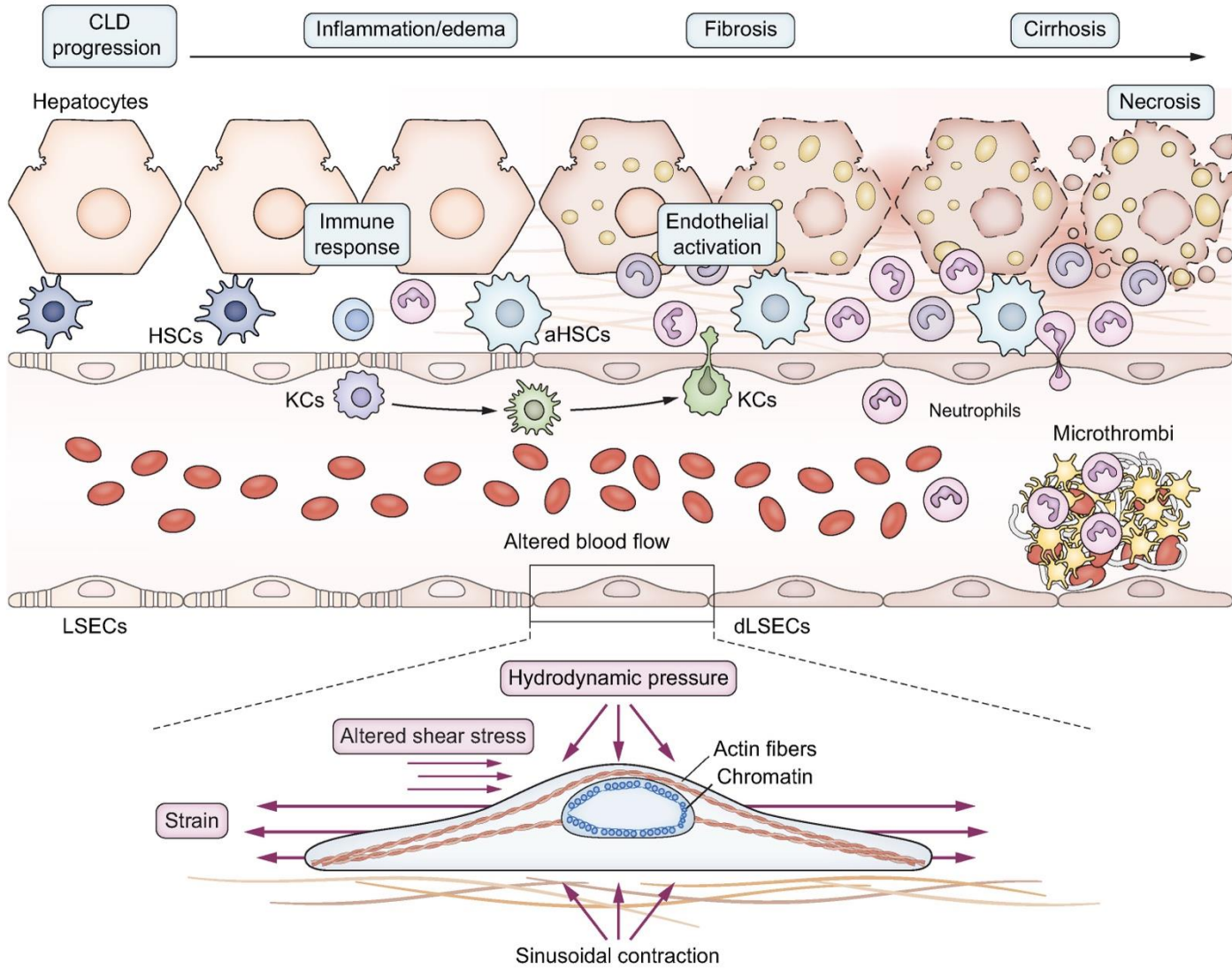


## LSEC specific biomarkers in CLD

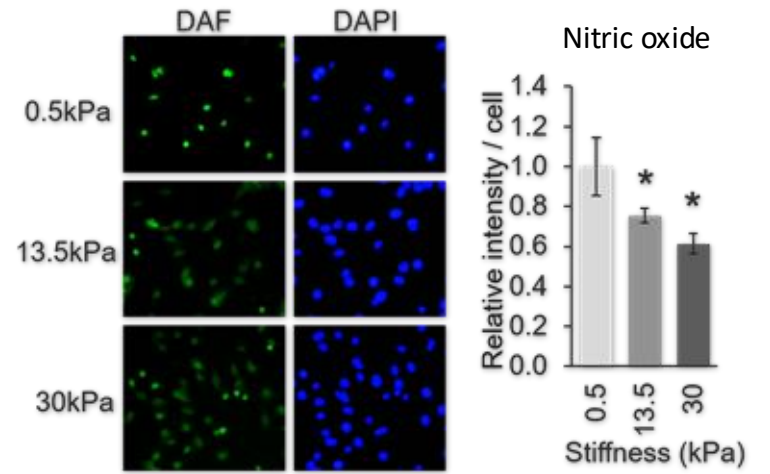


# Biomechanical deregulation of LSECs in CLD

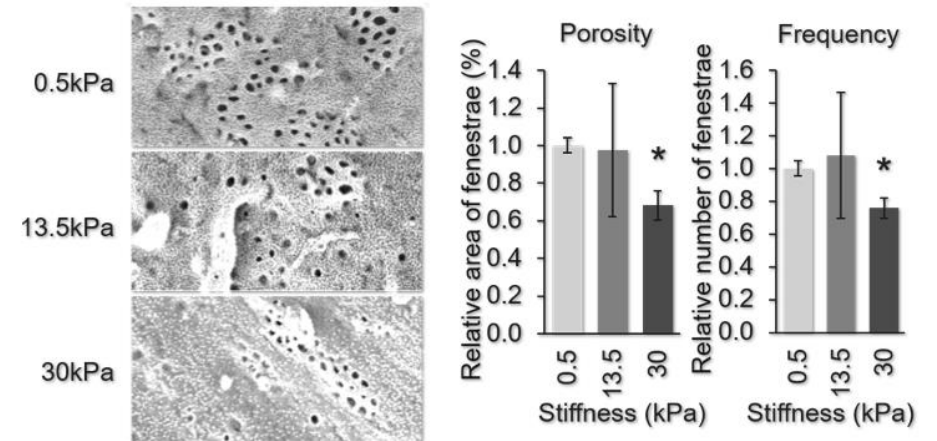
Guixé-Muntet, Ortega-Ribera ... Gracia-Sancho, JHEP Reports 2021  
Felli ... Gracia-Sancho, JHEP Reports 2023



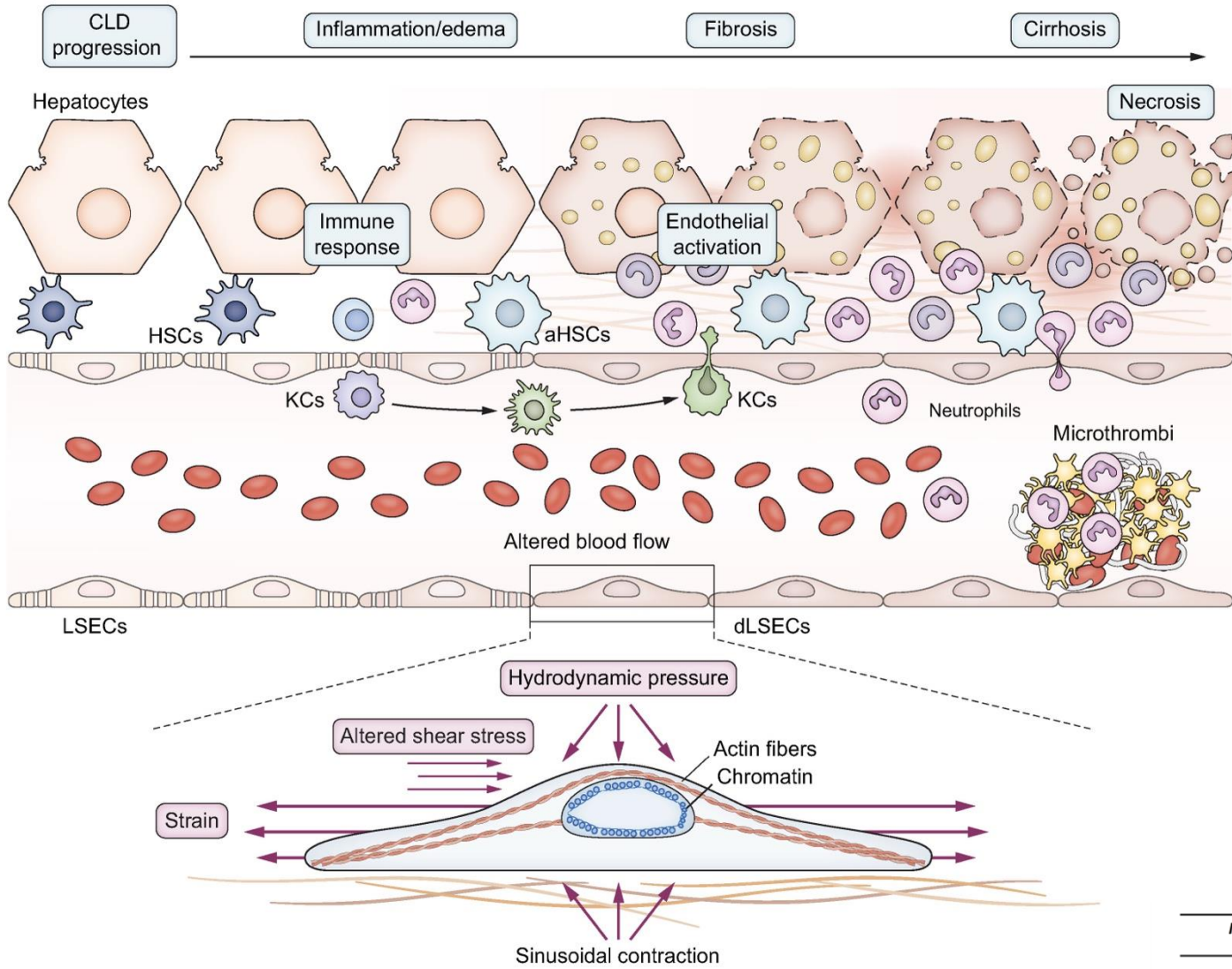
## Matrix stiffness



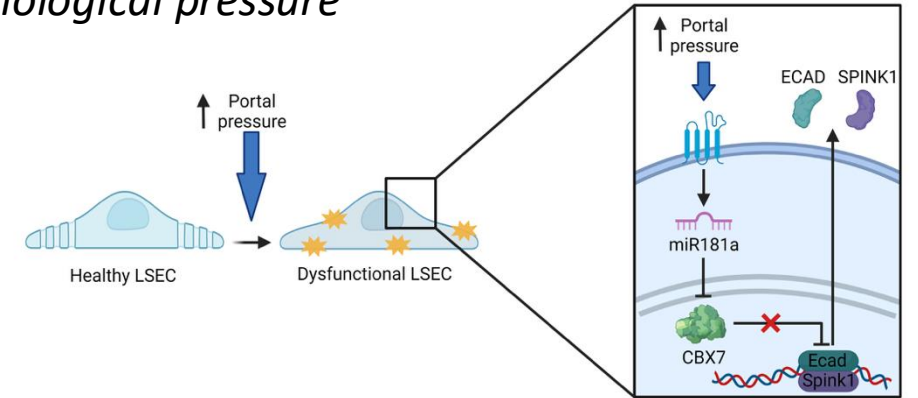
## Fenestrae



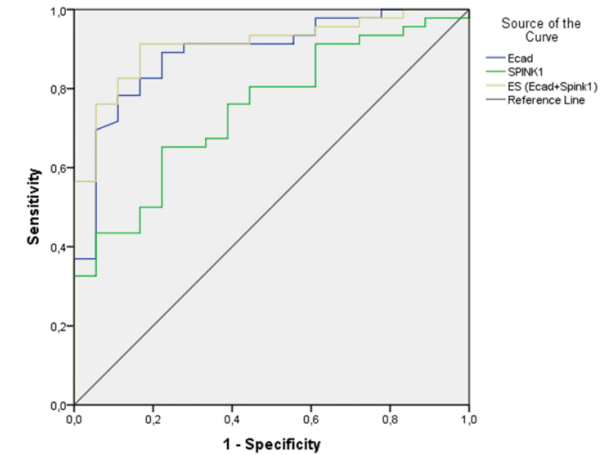
# Biomechanical deregulation of LSECs in CLD



## Pathological pressure

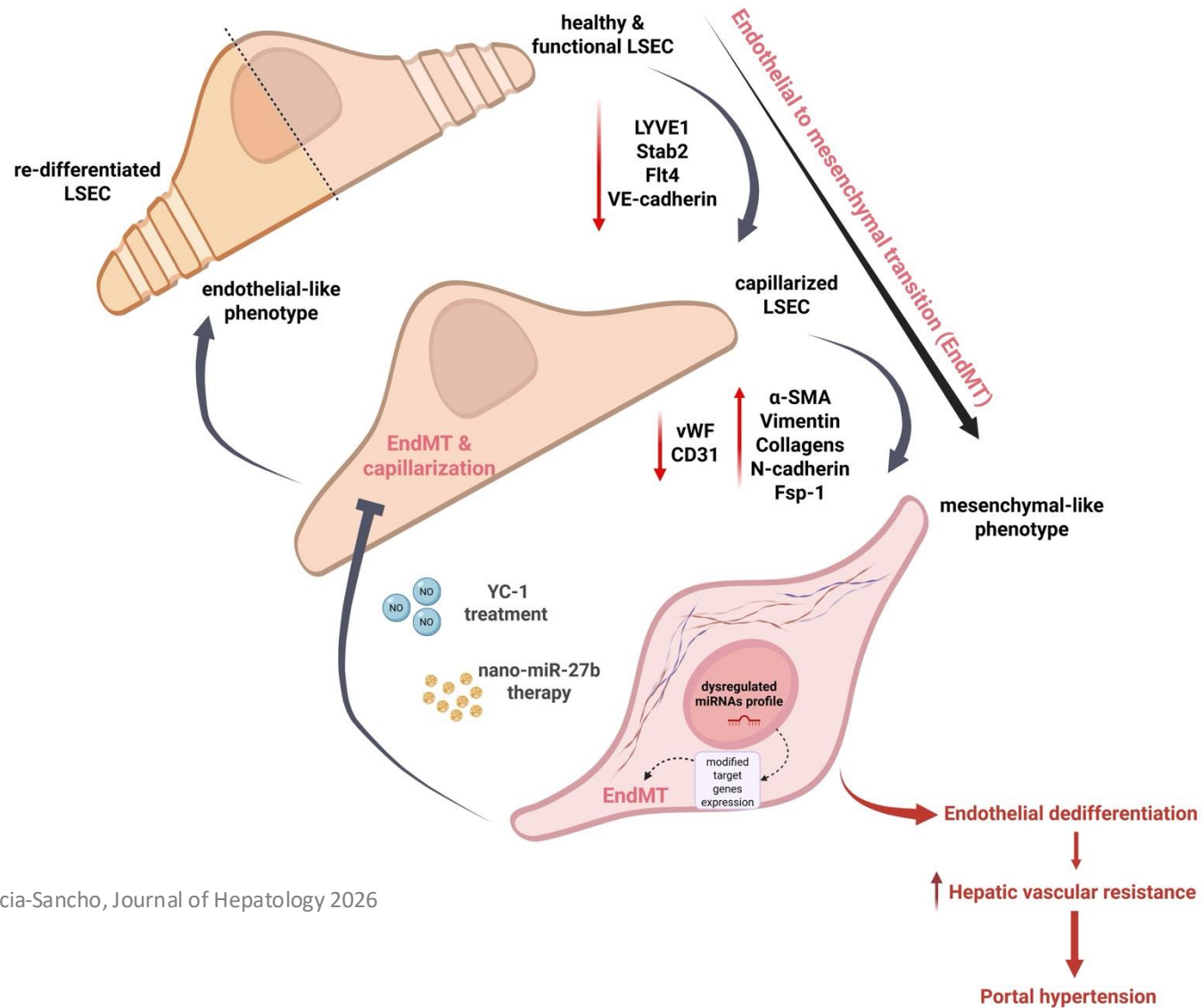


Ortega-Ribera ... Gracia-Sancho, JHEP Reports 2023

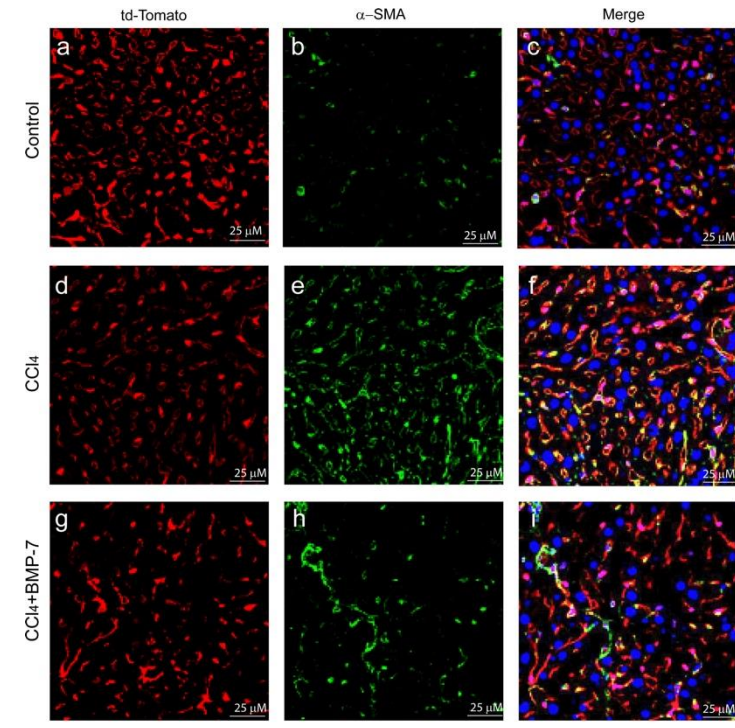
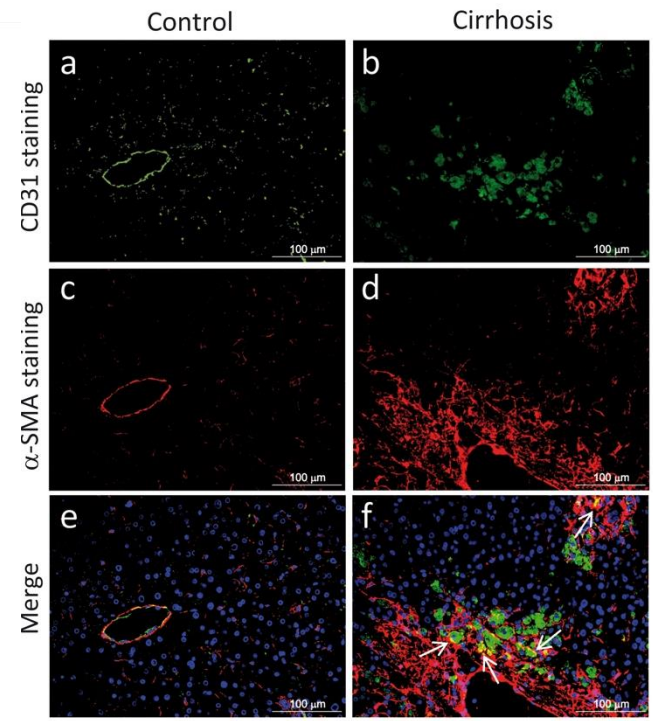
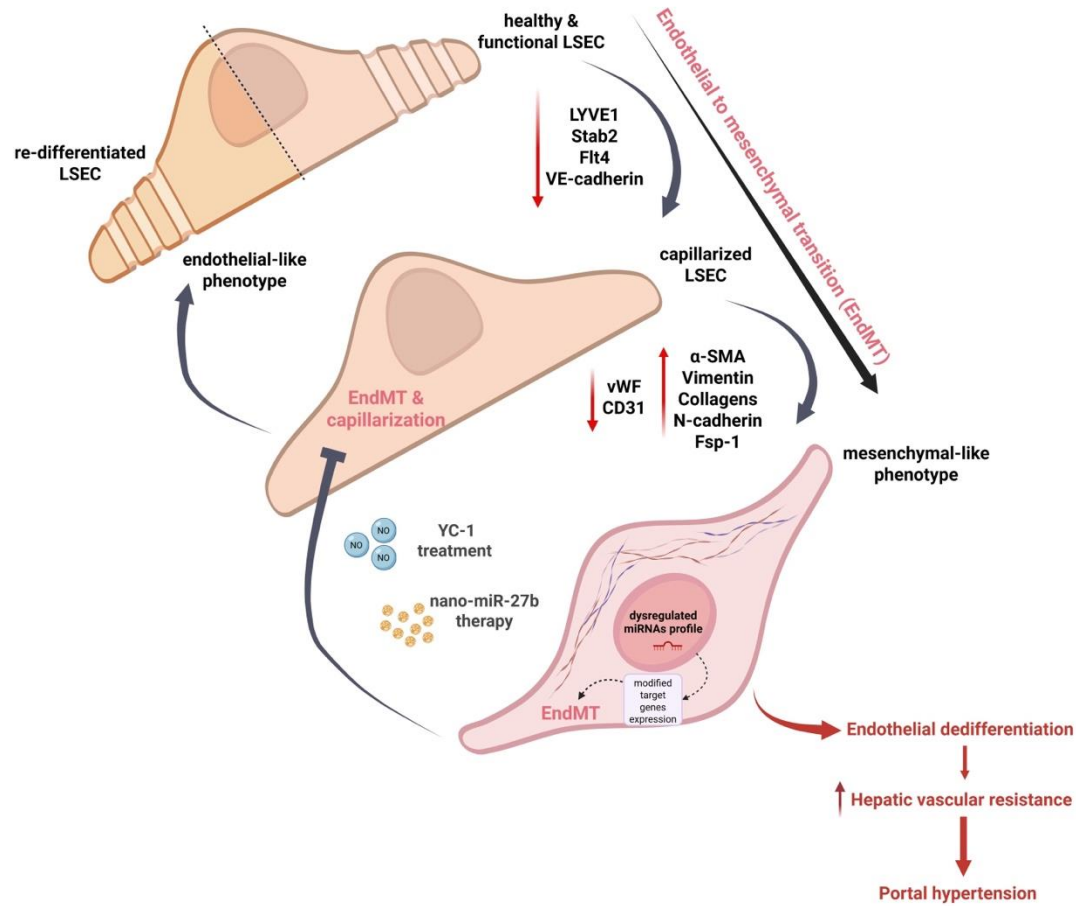


Marker	n (</> 5mmHg)	AUROC (95% CI)	Cut-off	Sens (%)	Spec (%)	PPV (%)	NPV (%)
ECAD	18/46	0.889 (0.802 to 0.977)	57.673	89.1	77.8	91.12	73.64
SPINK1	18/45	0.747 (0.622 to 0.871)	16.040	80.0	55.6	81.83	52.65
ECAD + SPINK1	18/46	0.911 (0.838 to 0.983)	0.579	91.3	83.3	93.32	78.93

# Novel mechanisms of LSECs dedifferentiation – 1. EndMT

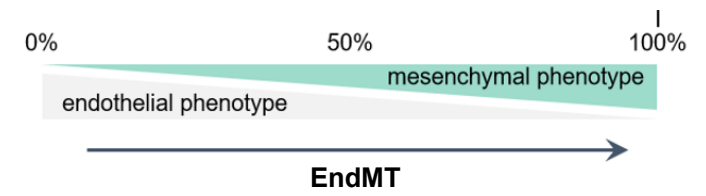
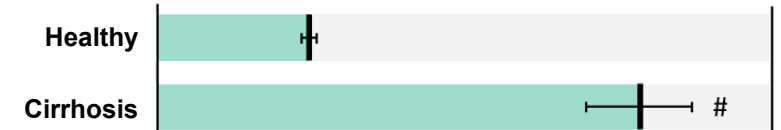
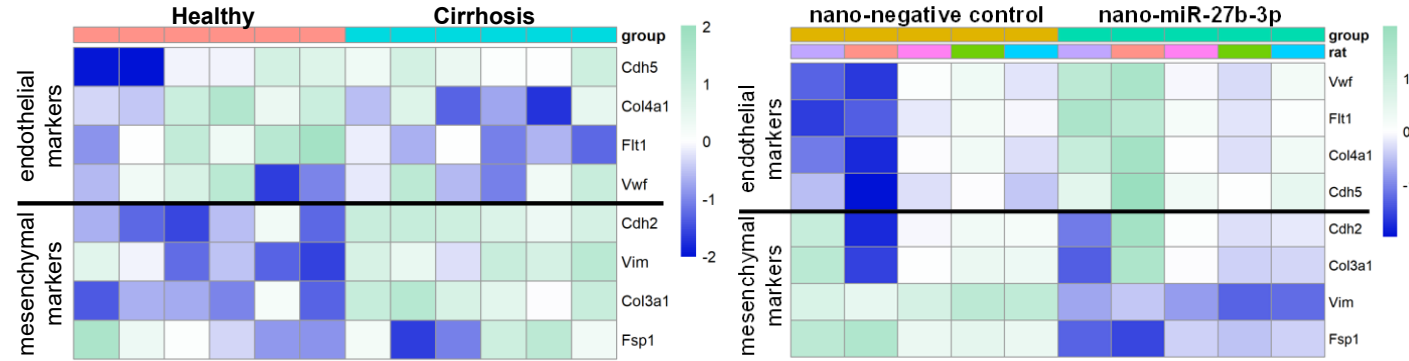
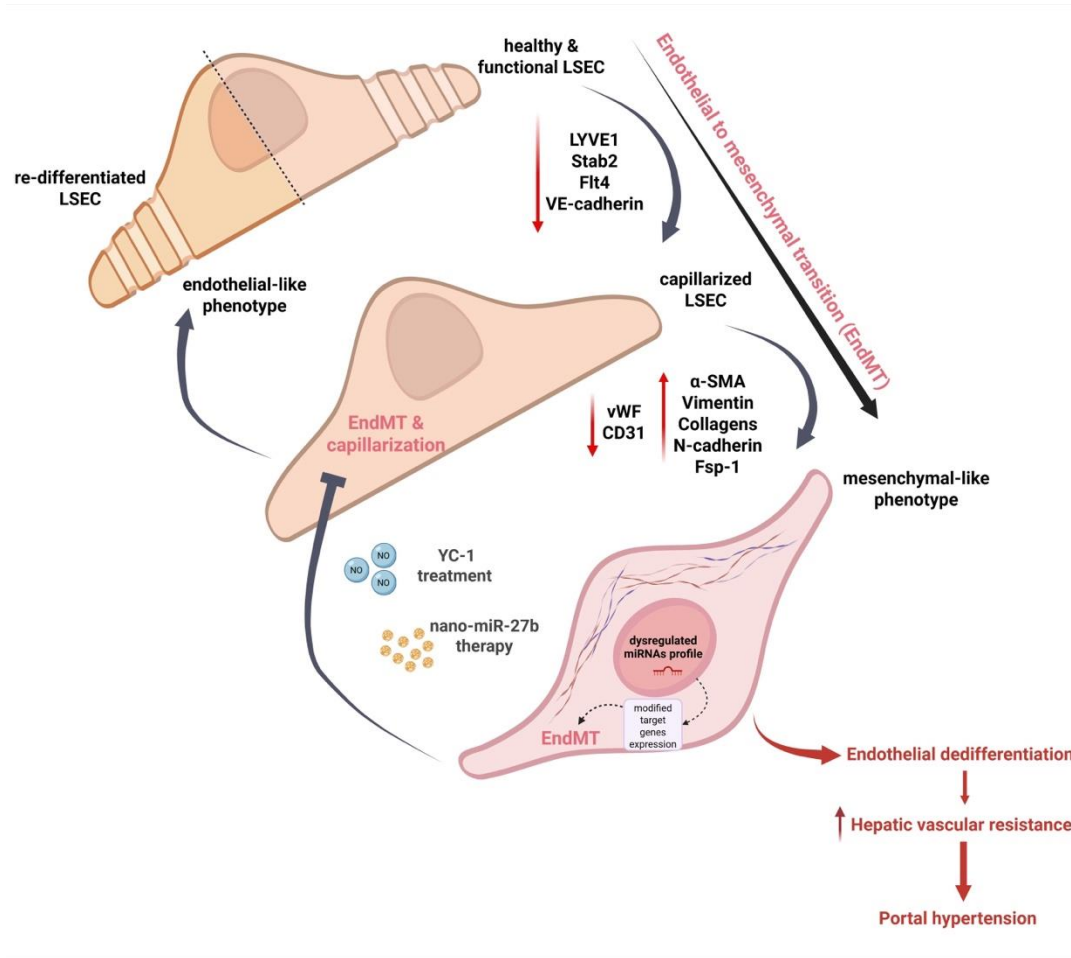


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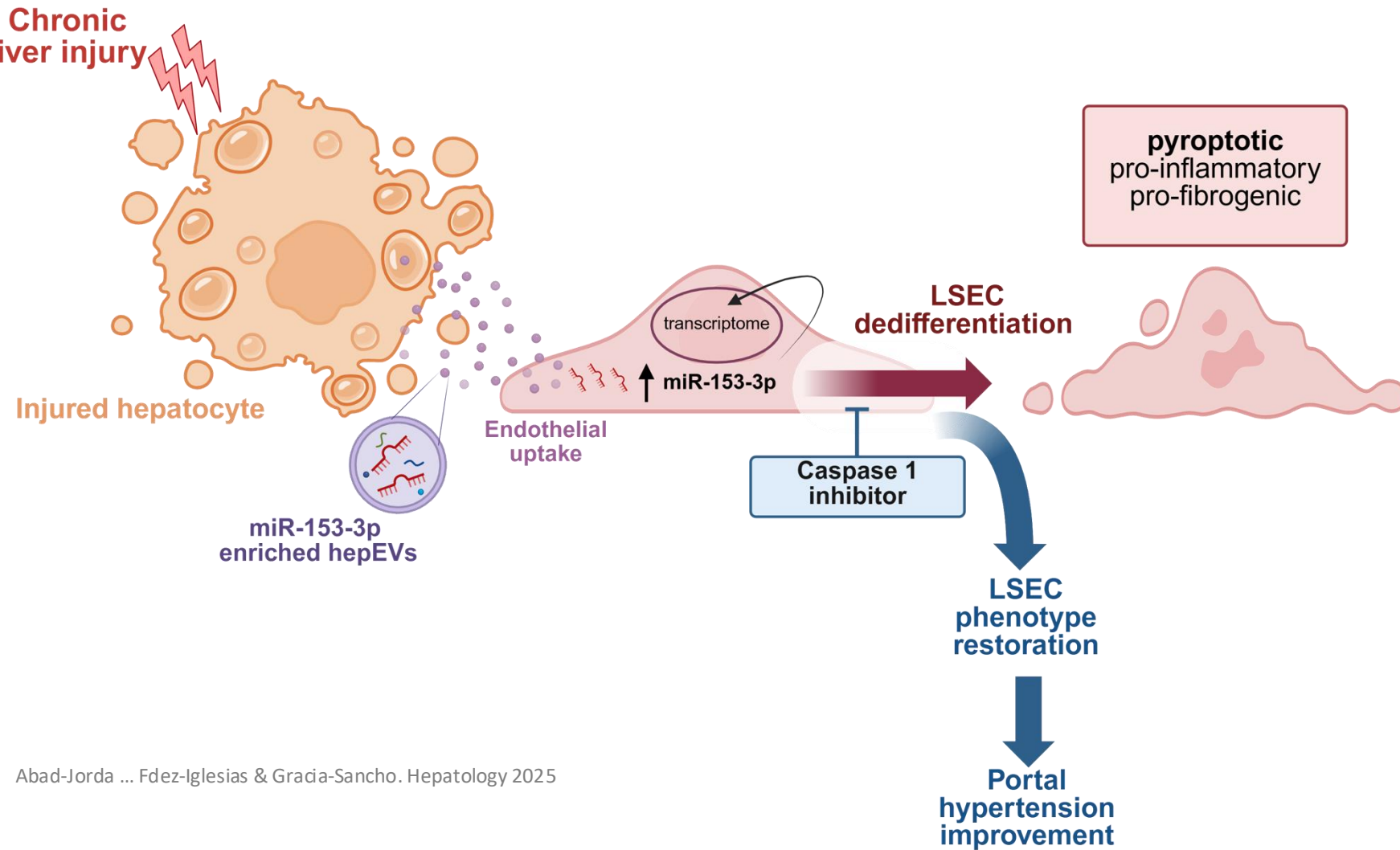


Ribera et al. Am J Phys GLP 2017

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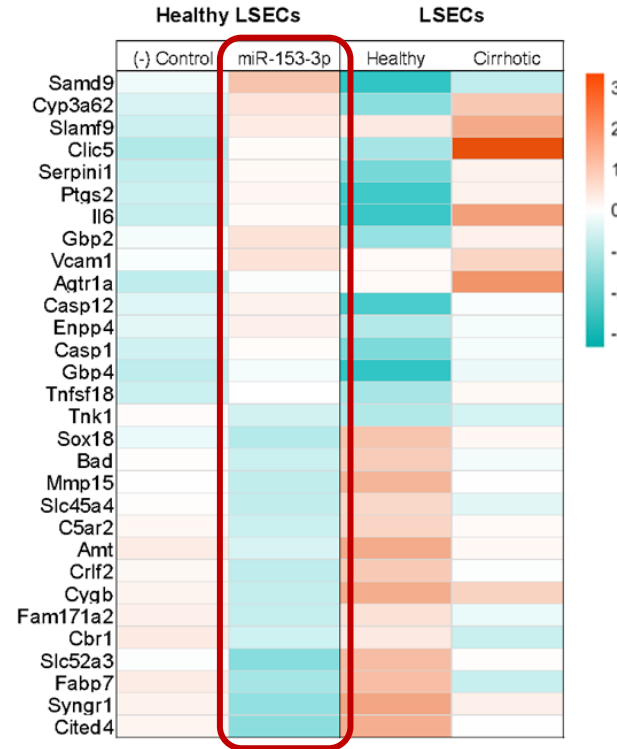
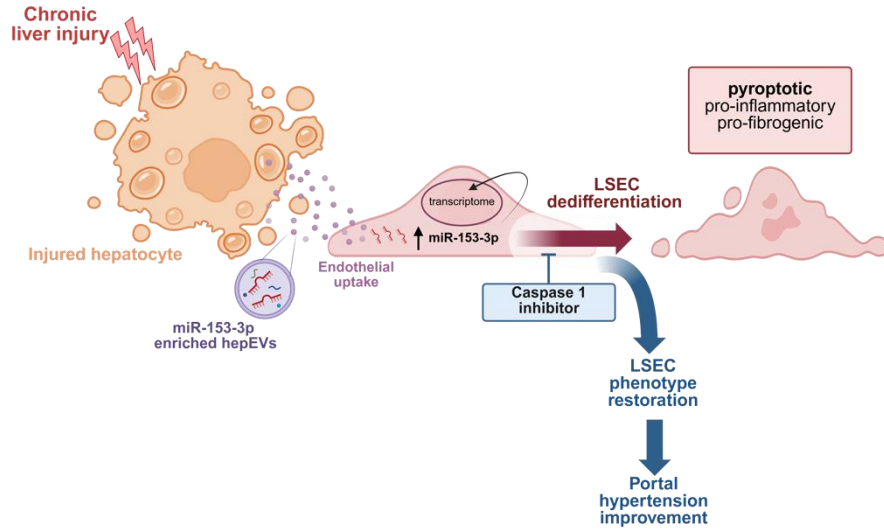


# Novel mechanisms of LSECs dedifferentiation – 2. Hep miRNAs

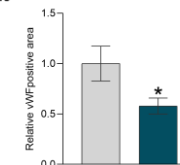
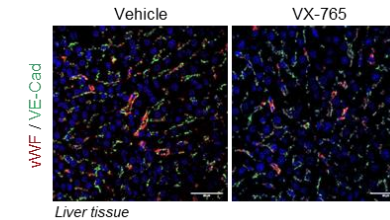
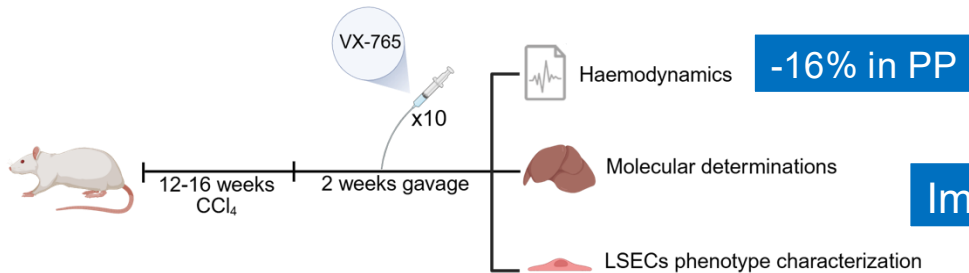
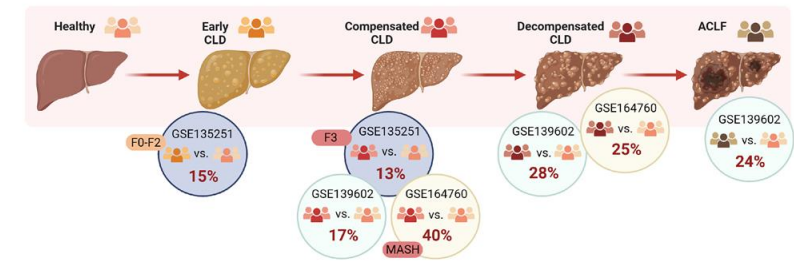
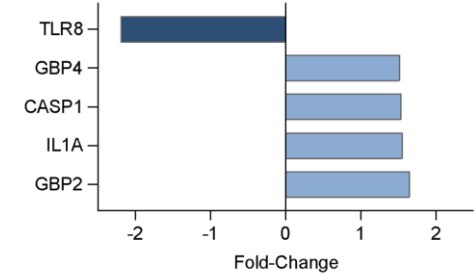


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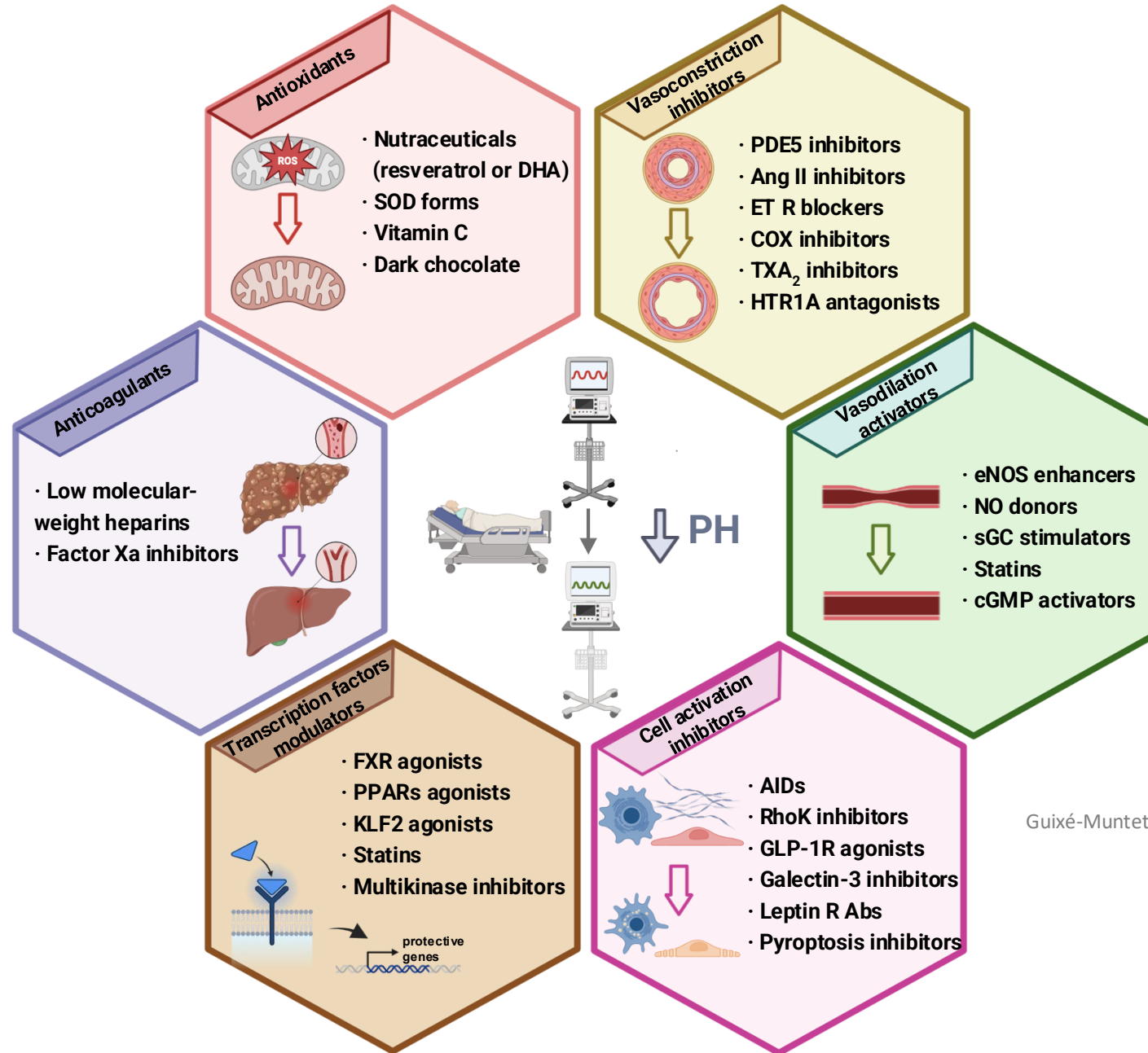
Abad-Jorda ... Fdez-Iglesias & Gracia-Sancho. Hepatology 2025



Pyroptosis

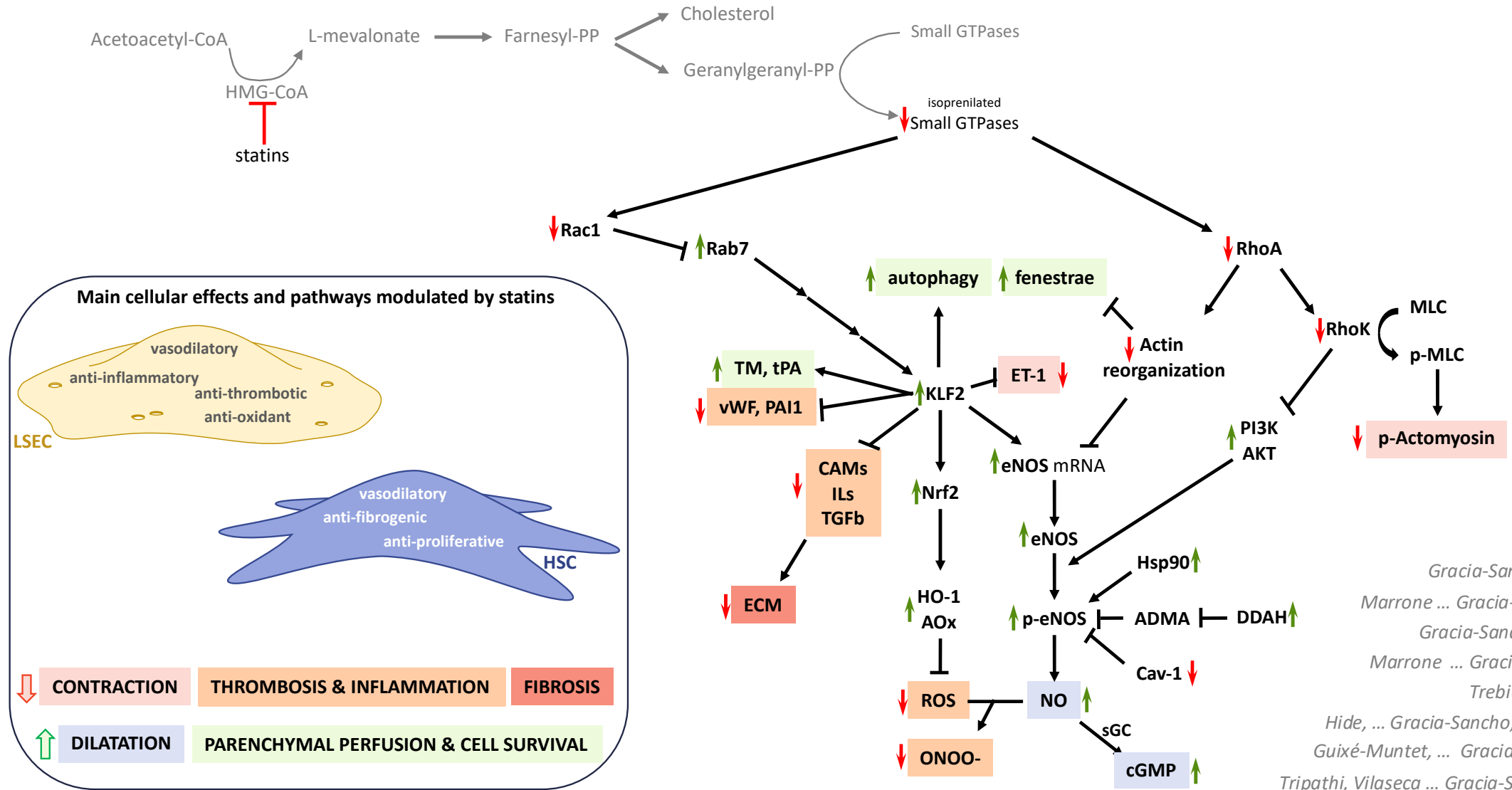


# LSECs in CLD – Therapeutic mosaic



Guixé-Muntet ... Gracia-Sancho J, Lancet G&H 2024

# LSECs in CLD – Therapeutics: Statins



Gracia-Sancho et al, Gut 2011  
 Marrone ... Gracia-Sancho, JHep 2013  
 Gracia-Sancho et al, JHep 2013  
 Marrone ... Gracia-Sancho, Gut 2015  
 Trebicka et al, JHep 2012  
 Hide, ... Gracia-Sancho, Scientific Rep 2016  
 Guixé-Muntet, ... Gracia-Sancho, JHep 2017  
 Tripathi, Vilaseca ... Gracia-Sancho, Gastro 2018  
 Maeso, ... Gracia-Sancho, Aging Disease 2019  
 Bosch, Gracia-Sancho & Abraldes, Gut 2020  
 Hide, ... Gracia-Sancho, J Gerontol 2021

# LSEC dysfunction in CLD – Take home messages

- **LSEC dysfunction is an early and central event** in chronic liver disease, driving microvascular dysfunction and fibrogenesis.
- Loss of nitric oxide and increased vasoconstrictors make **LSECs key contributors to intrahepatic vascular resistance and portal hypertension.**
- **Fibrotic/cirrhotic liver mechanobiology** further impacts on LSECs dedifferentiation.
- **Restoring LSEC phenotype and signalling** offers a promising therapeutic approach to reverse fibrosis and reduce portal pressure.

Join us at The Liver Sinusoid Meeting 2026!

Registration open until May 15th

