



Biology of endothelial cells in NASH

Pierre-Emmanuel RAUTOU

Inserm U1149, Centre de recherche sur l'inflammation, Paris

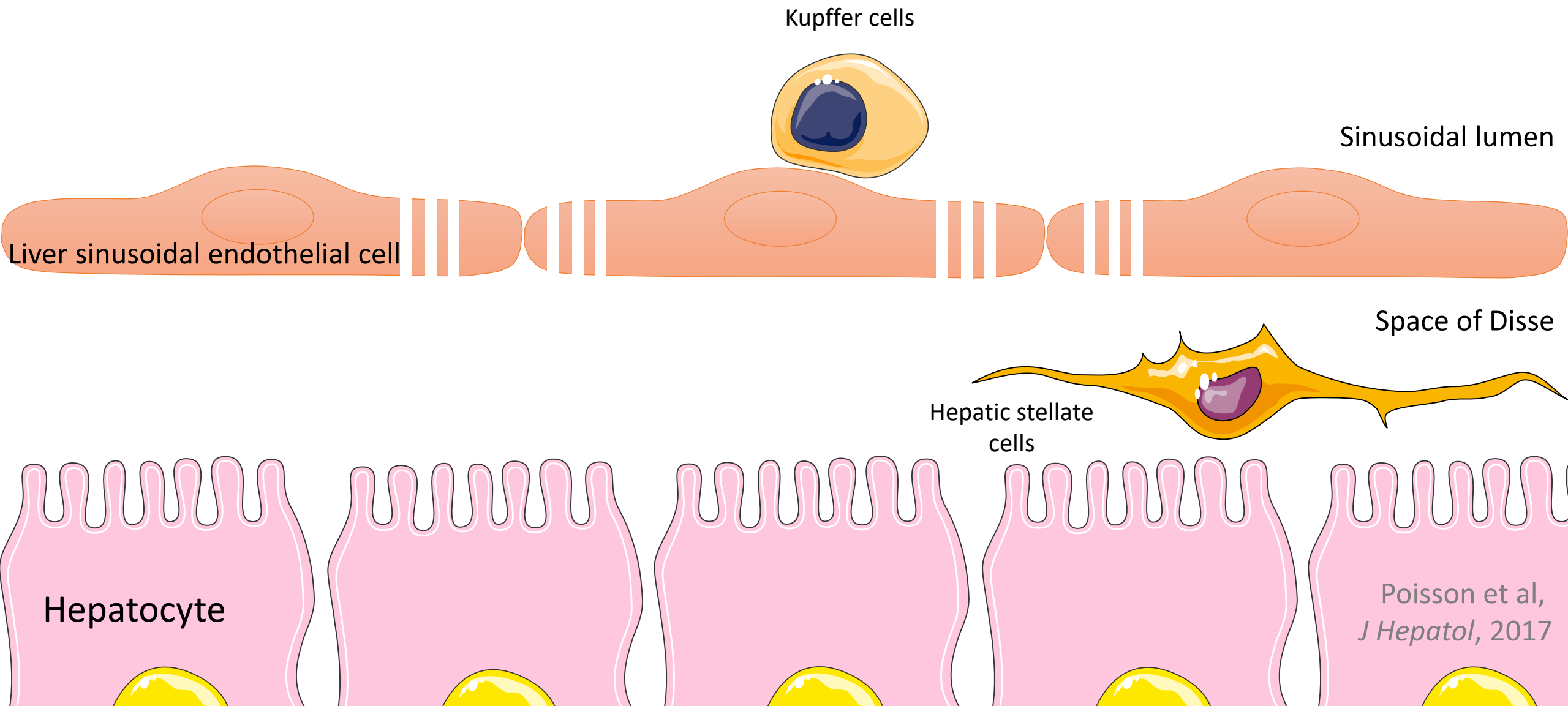
Service d'hépatologie, Hôpital Beaujon, Clichy, France

pierre-emmanuel.rautou@inserm.fr

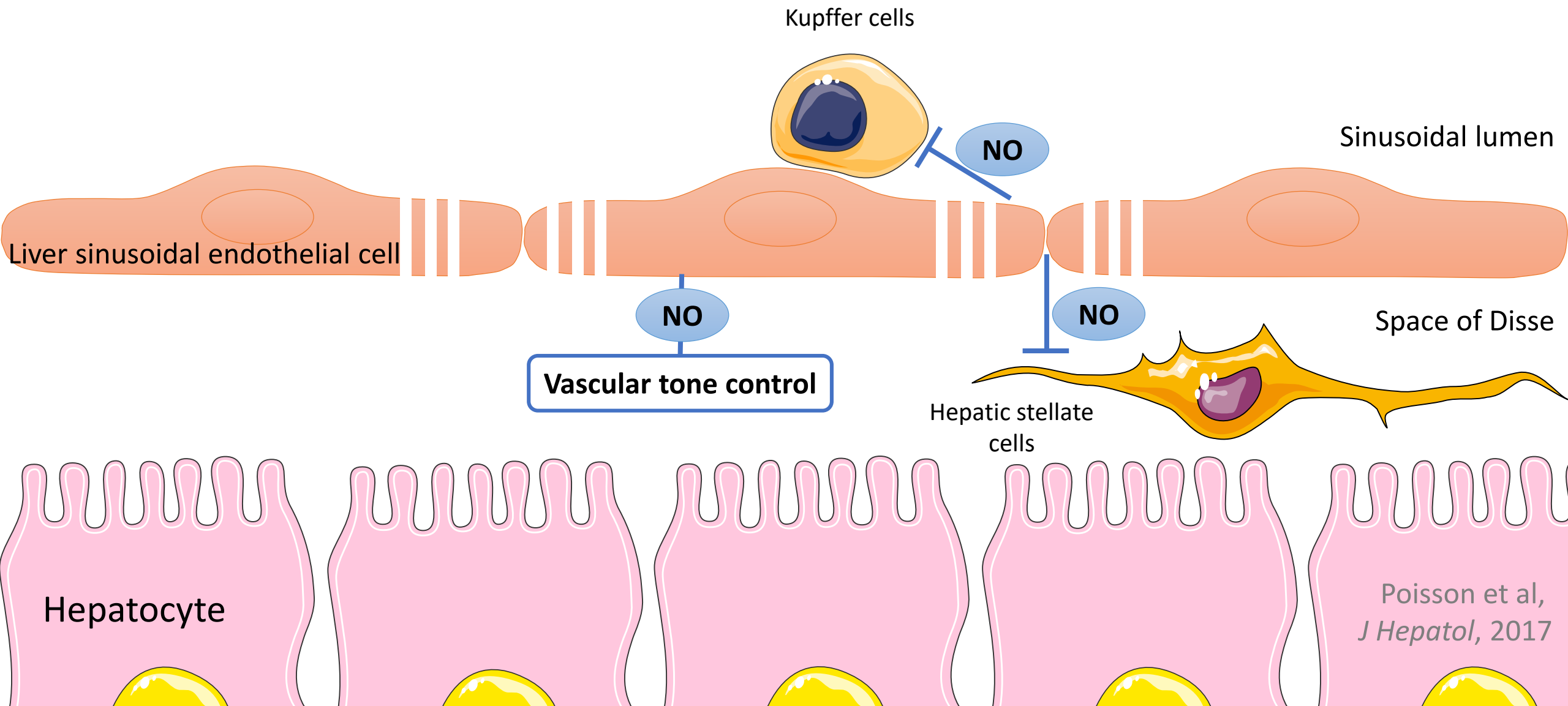
Liver endothelial cells in NASH

- What changes occur in endothelial cells in NAFLD?
- What causes those changes?
- What is the consequence of these changes?

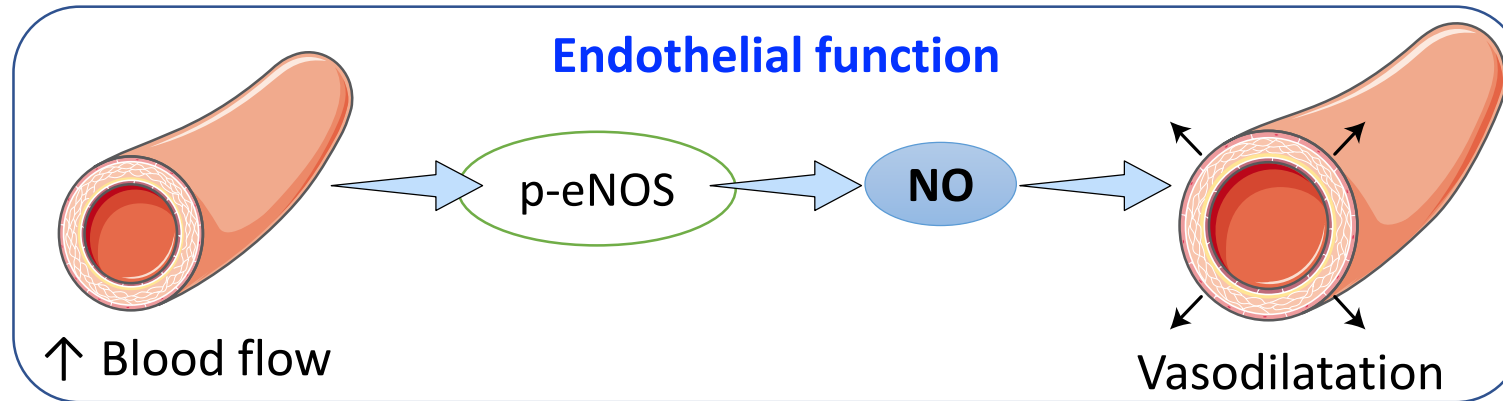
Liver sinusoidal endothelial cells (LSECs)



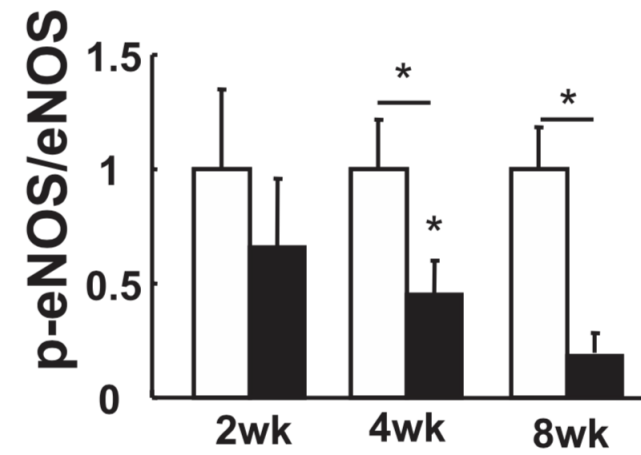
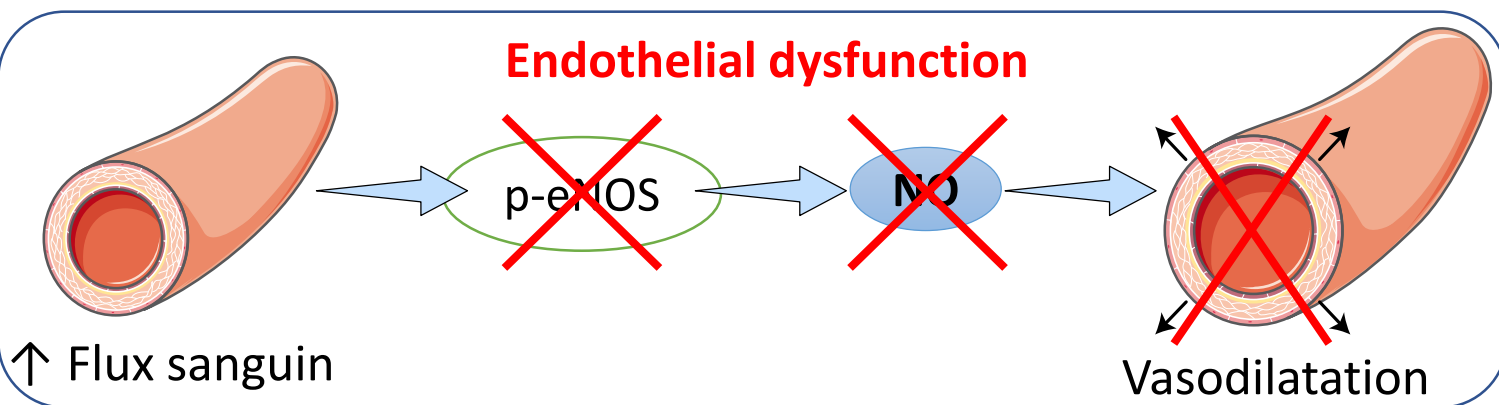
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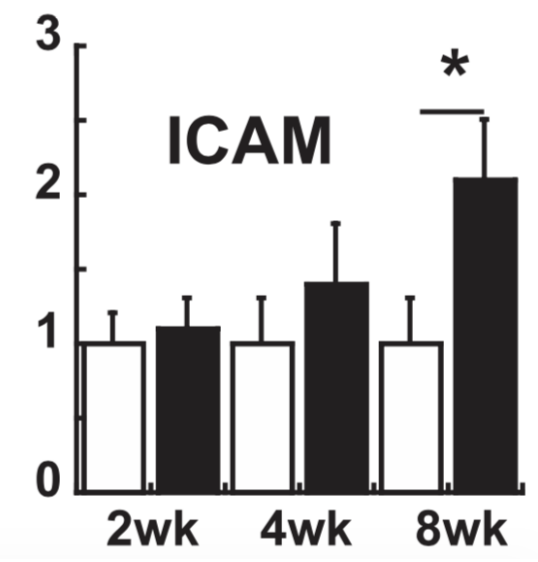
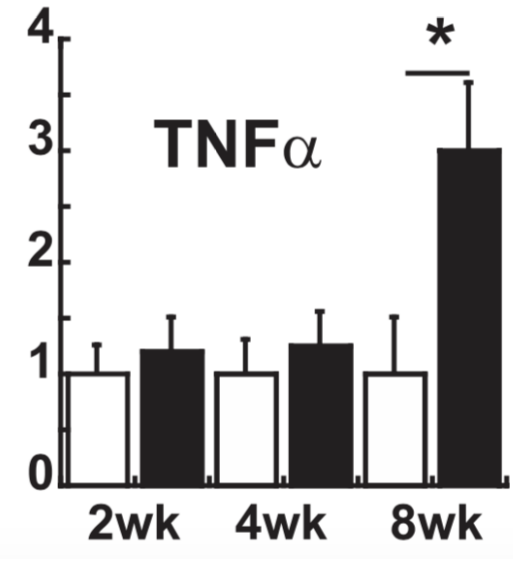
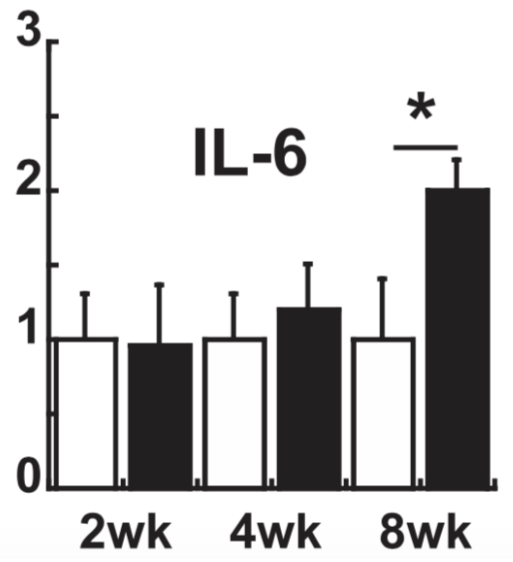
Endothelial function



Endothelial dysfunction precedes liver inflammation



□ Chow diet
 ■ High fat diet



Liver sinusoidal endothelial cells (LSECs)

Endothelial *fenestrae*

Kupffer cells

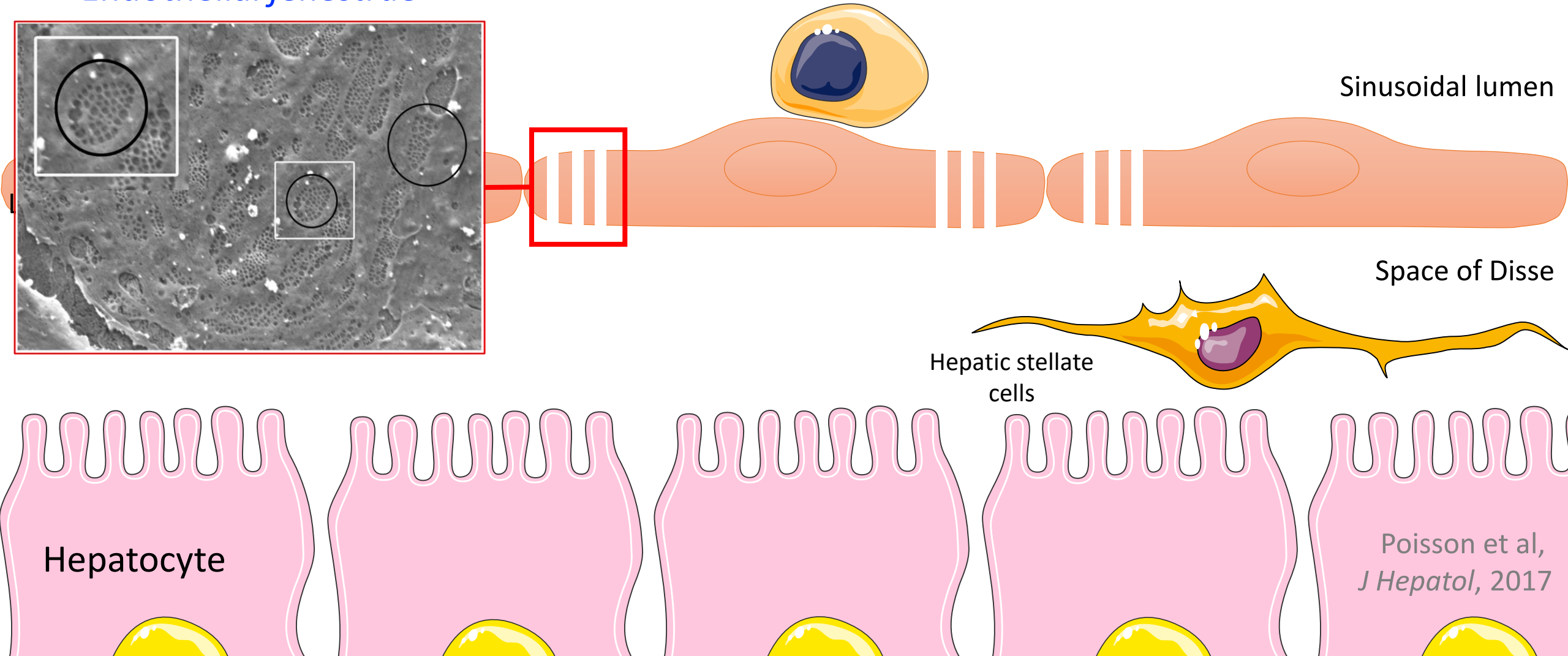
Sinusoidal lumen

Space of Disse

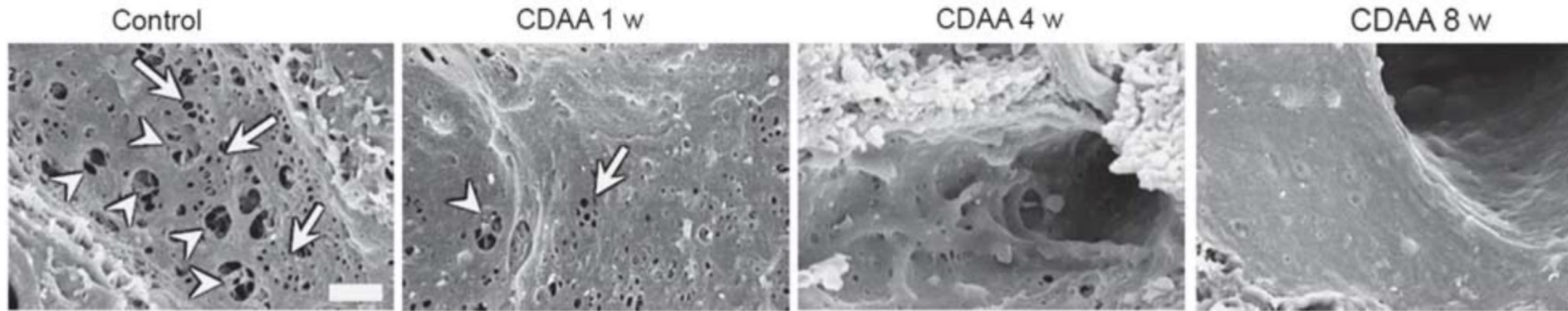
Hepatic stellate cells

Hepatocyte

Poisson et al,
J Hepatol, 2017

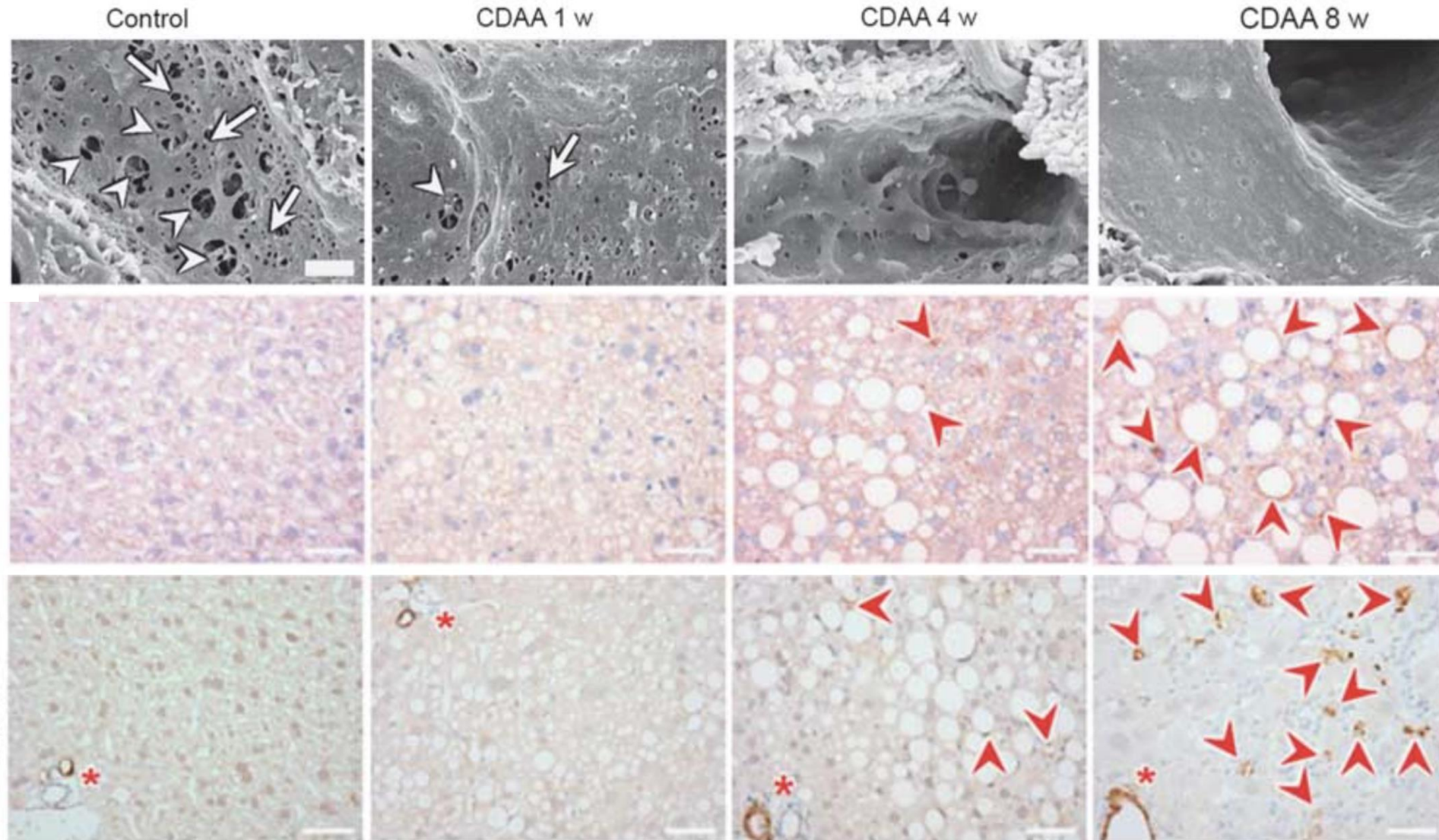


Endothelial cell capillarization in NASH

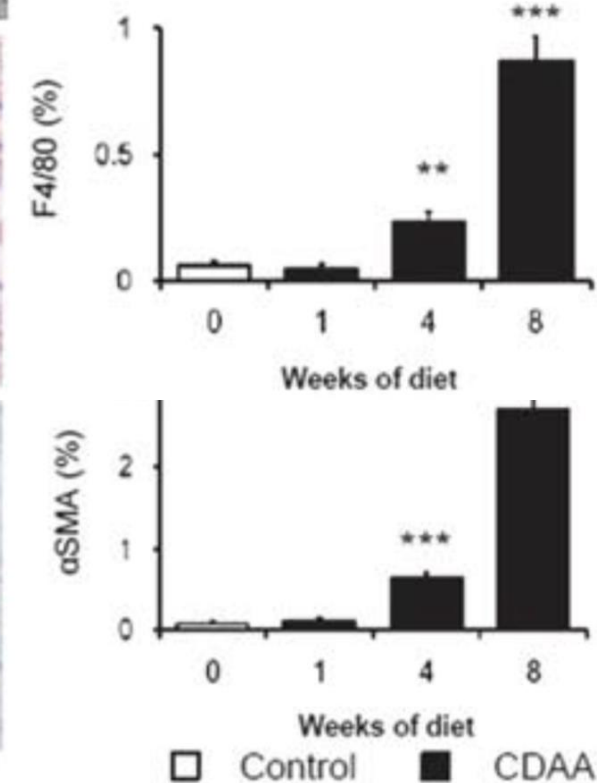


Miyao,
PloS One, 2015

Capillarization precedes NASH

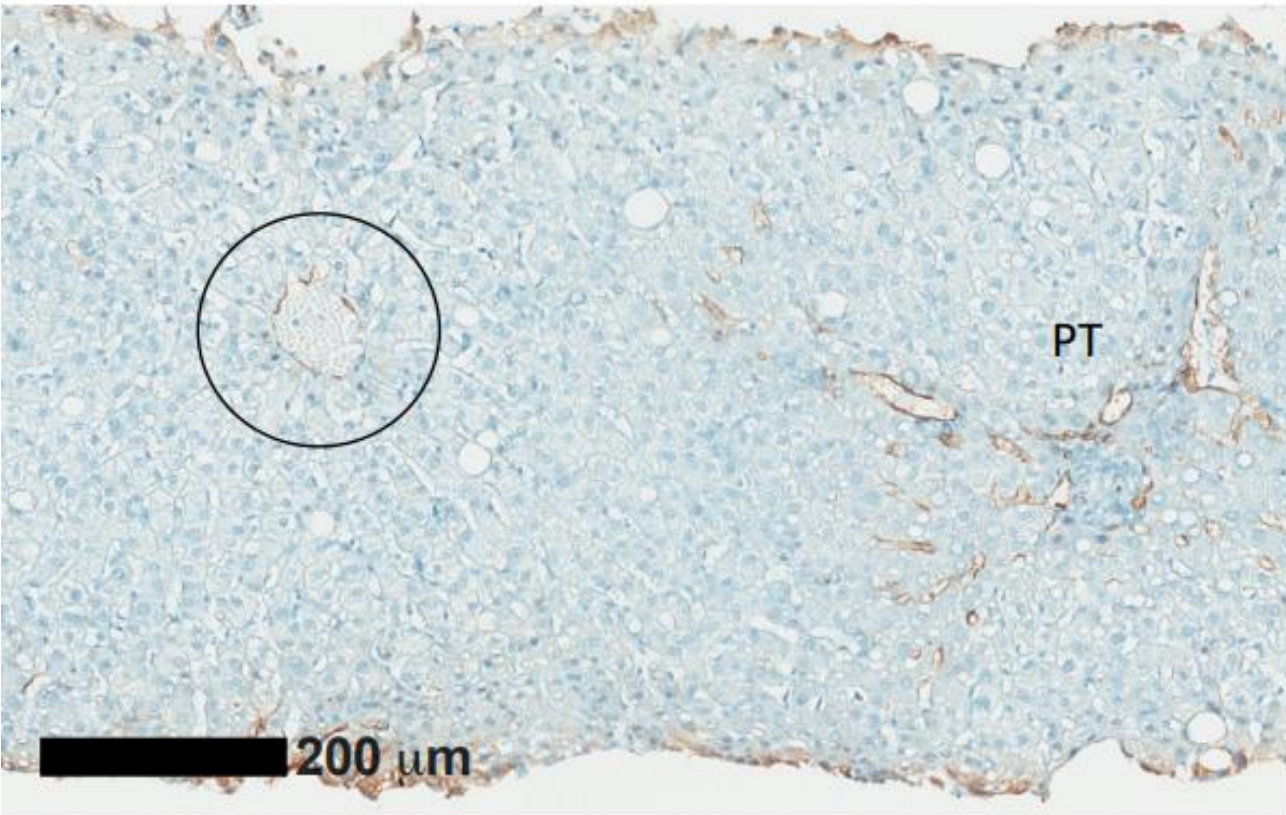


Miyao,
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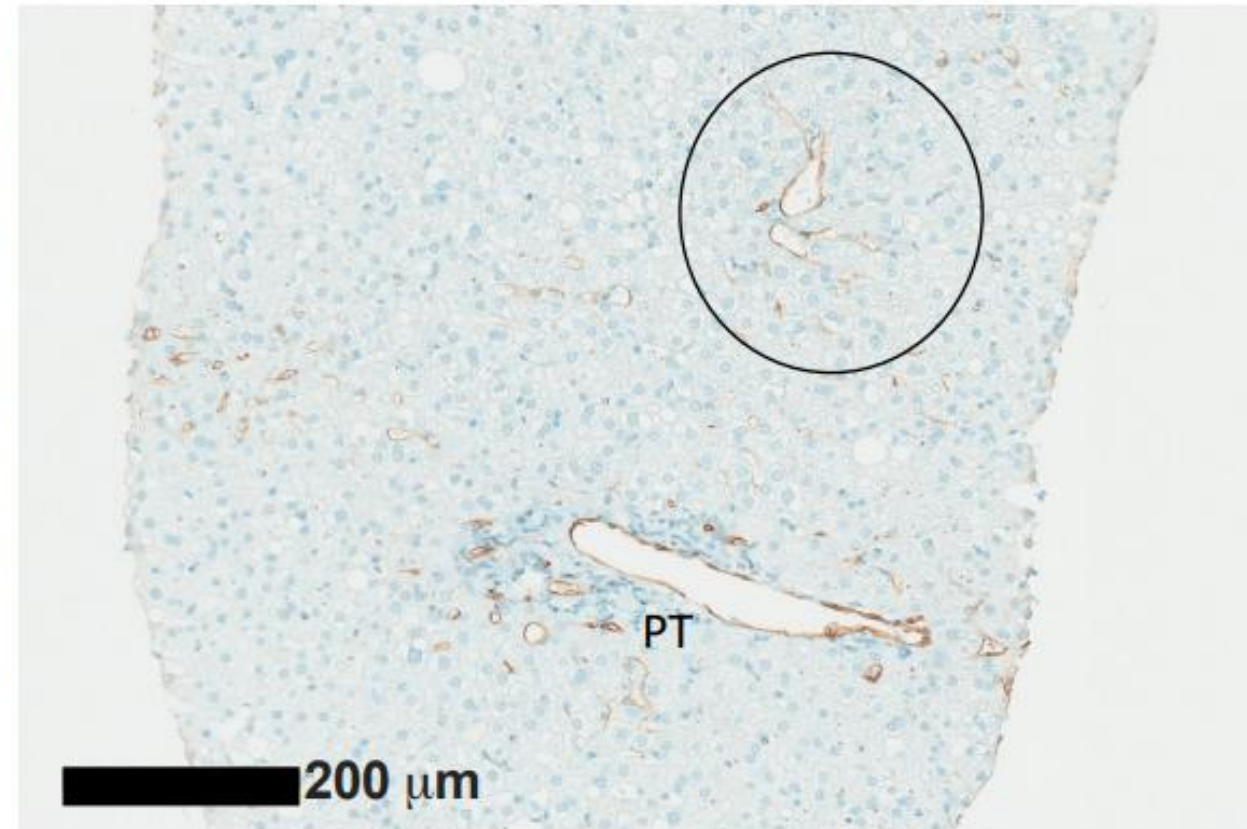
Capillarization precedes NASH: CD34 staining in patients

No NAFL



Lobular score: 0/3, Periportal score 1/3

NAFL



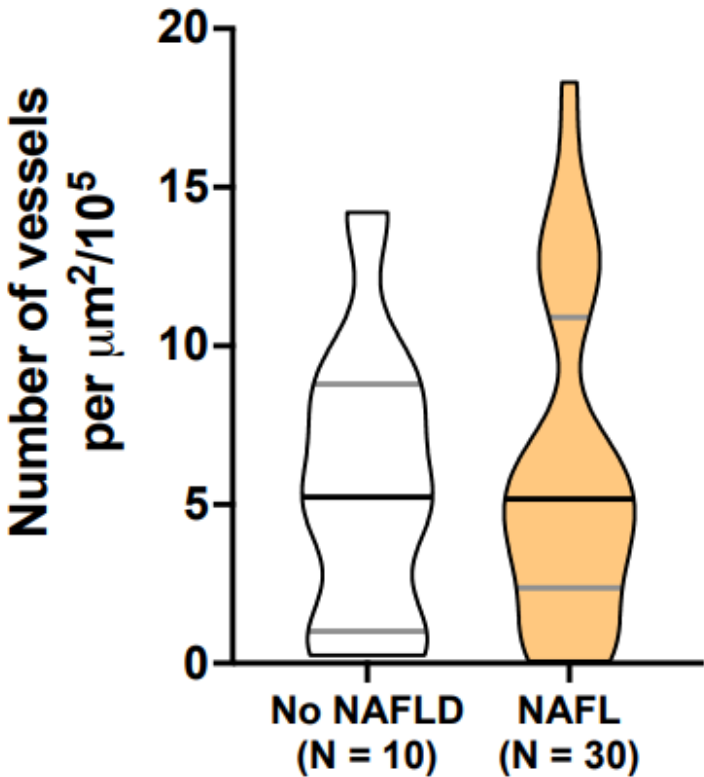
Lobular score: 1/3, Periportal score 1/3

38 patients considered for inclusion in the NATIVE trial
CD34 staining

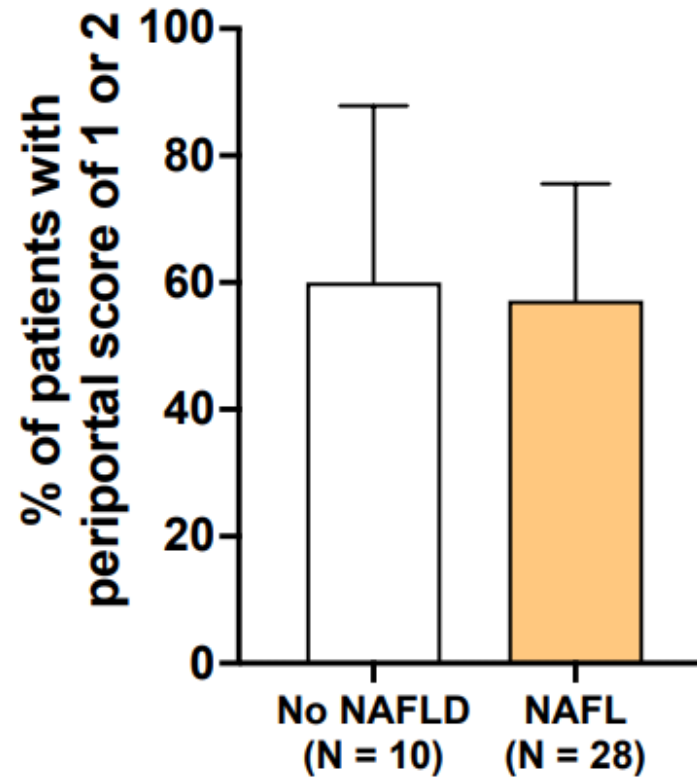
Rautou et al, AASLD 2021
Francque, NEJM 2021

Capillarization precedes NASH: CD34 staining in patients

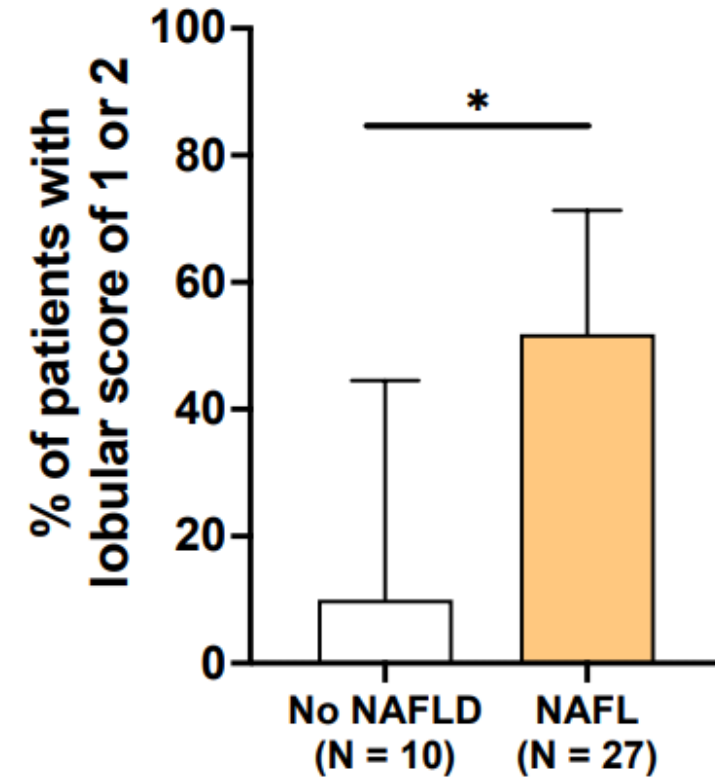
Morphometry



Periportal score



Lobular score

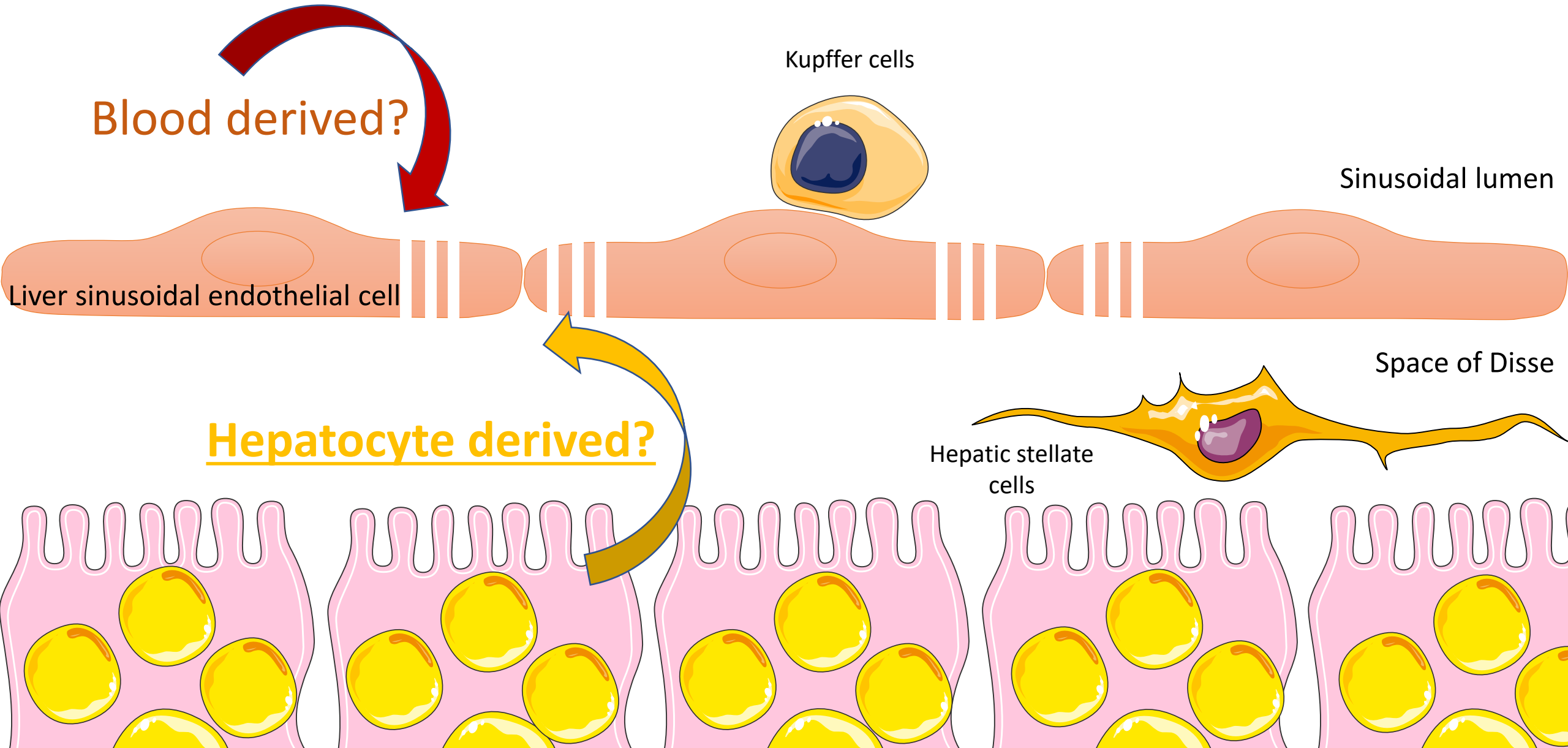


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Liver endothelial cells in NASH

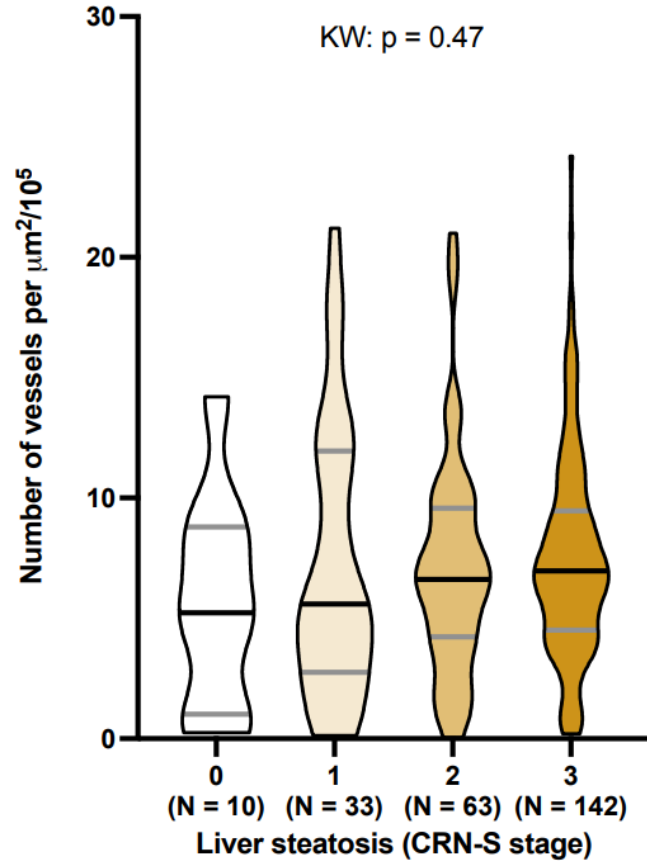
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Liver sinusoidal endothelial cells (LSECs)

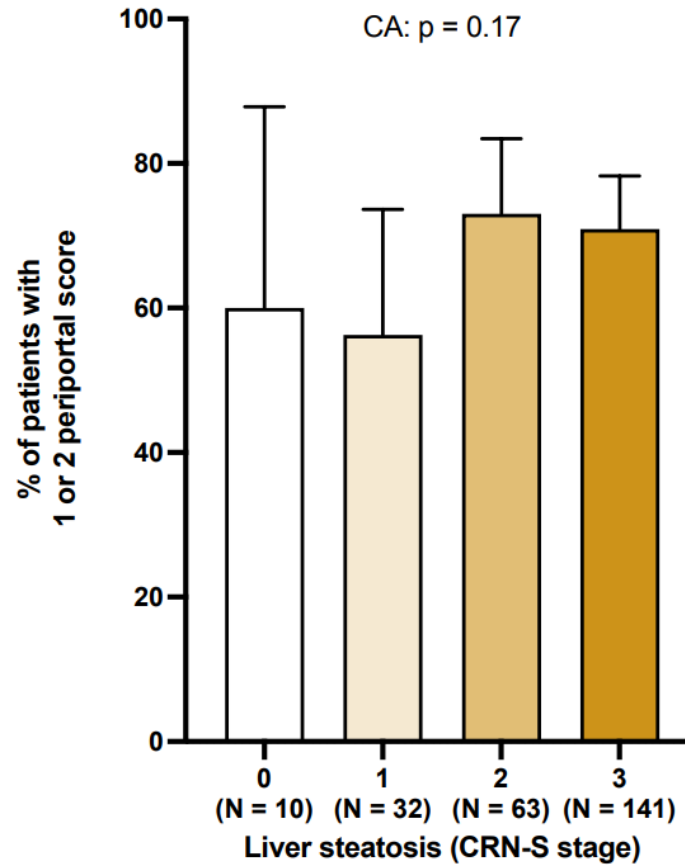


Capillarisation and steatosis: no link in patients

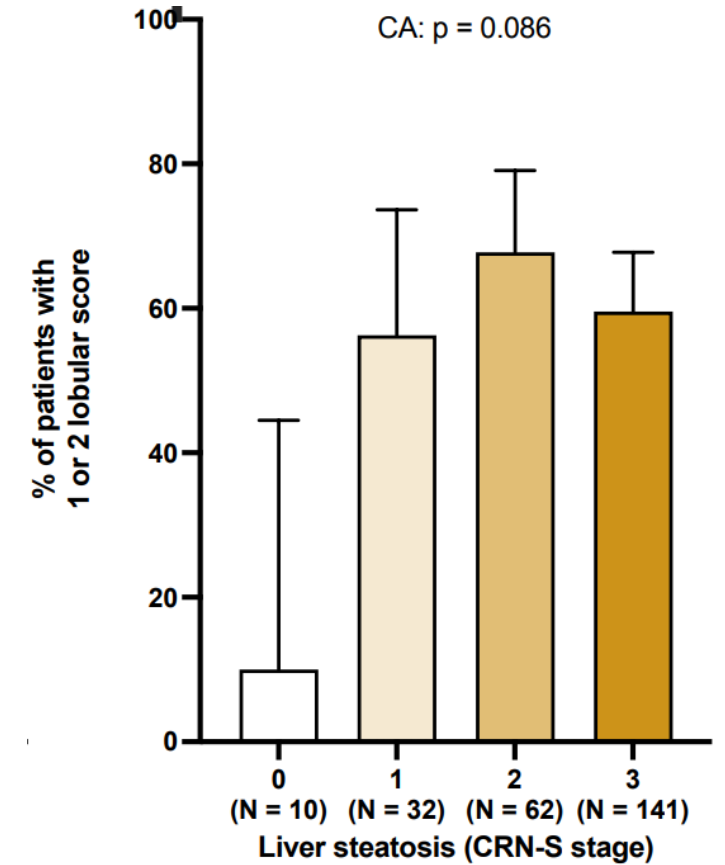
Morphometry



Periportal score



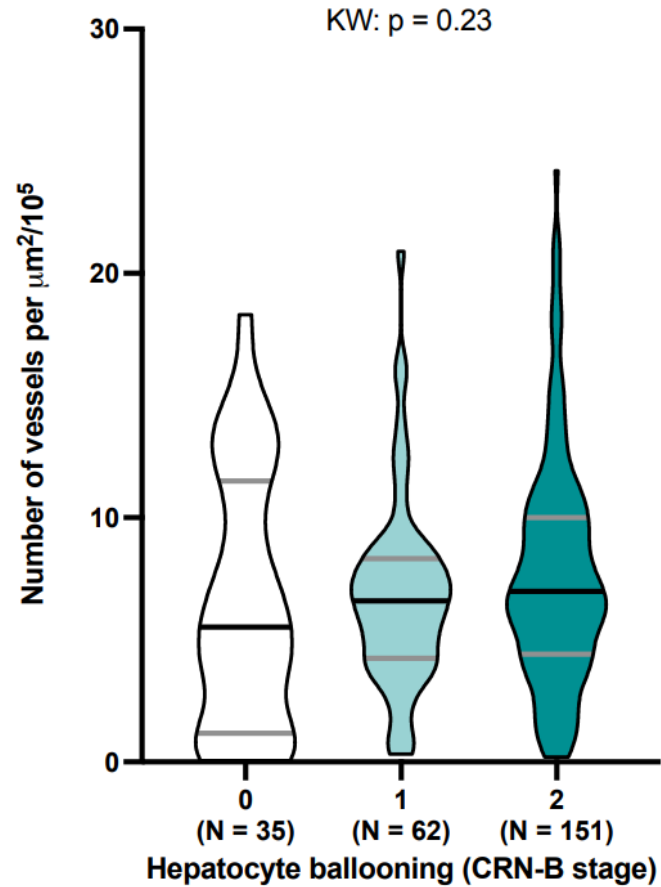
Lobular score



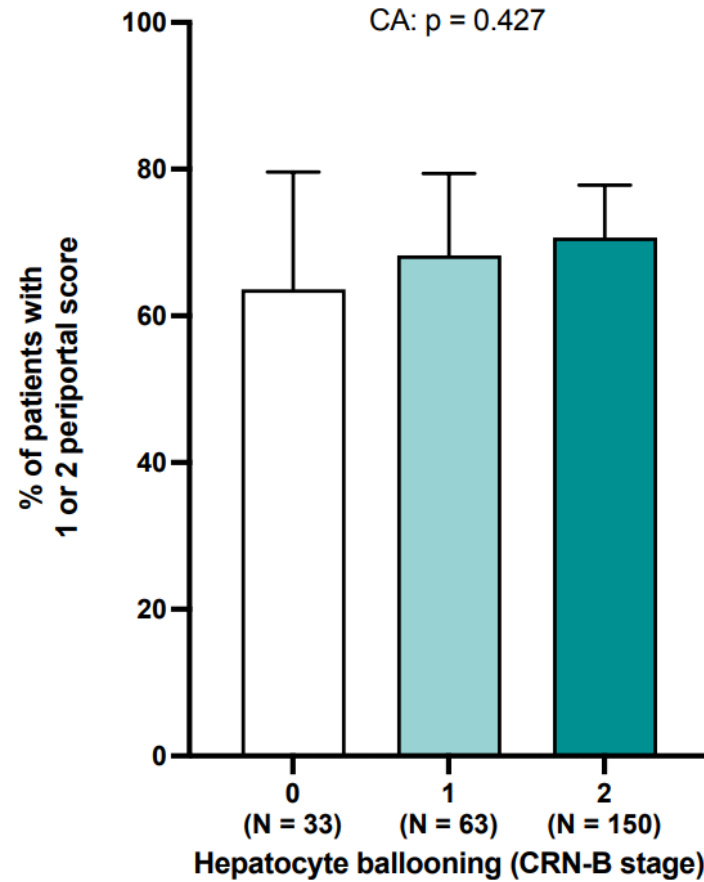
248 patients considered for inclusion in the NATIVE trial
CD34 staining

Capillarisation and ballooning: no link in patients

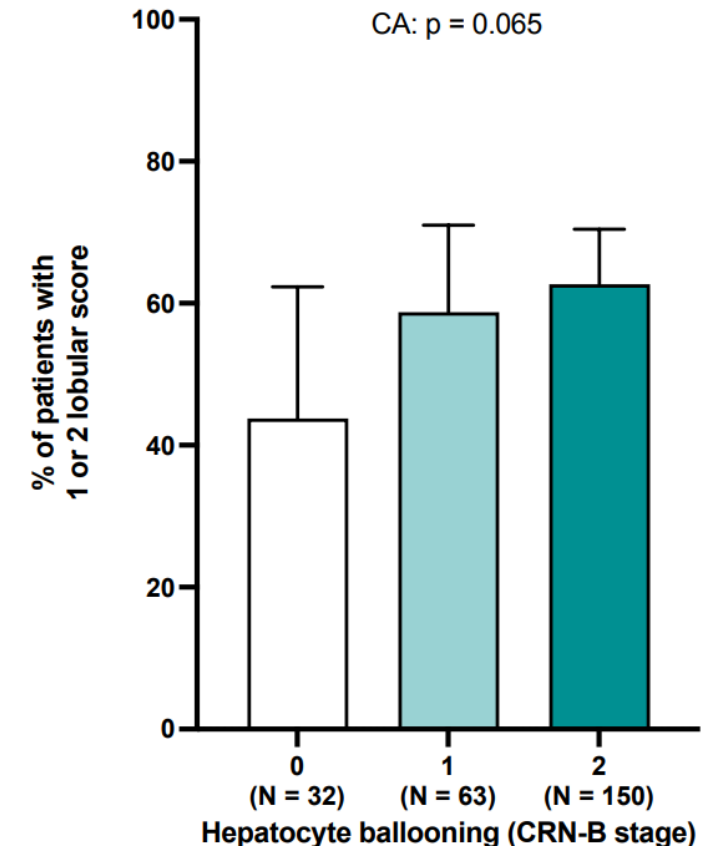
Morphometry



Periportal score

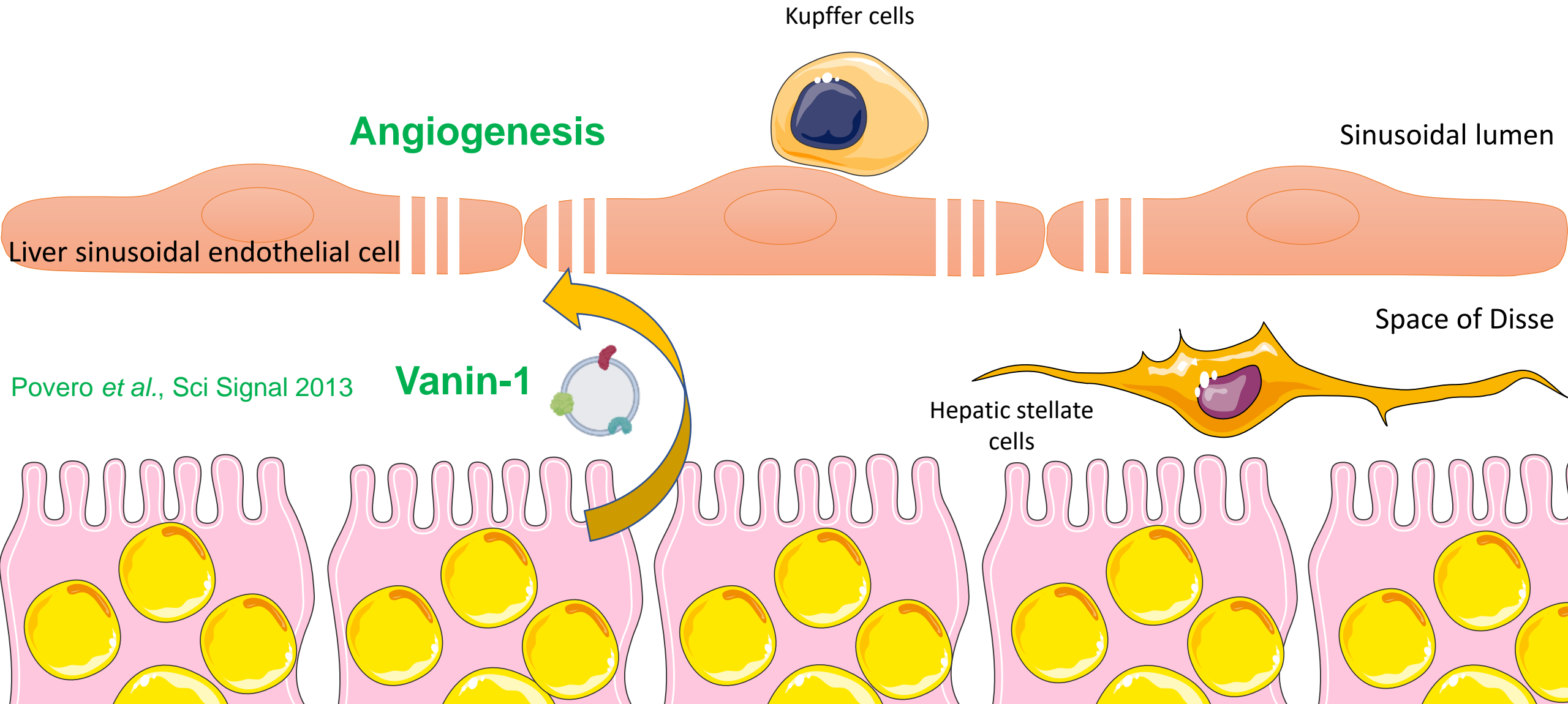


Lobular score



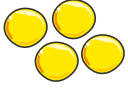
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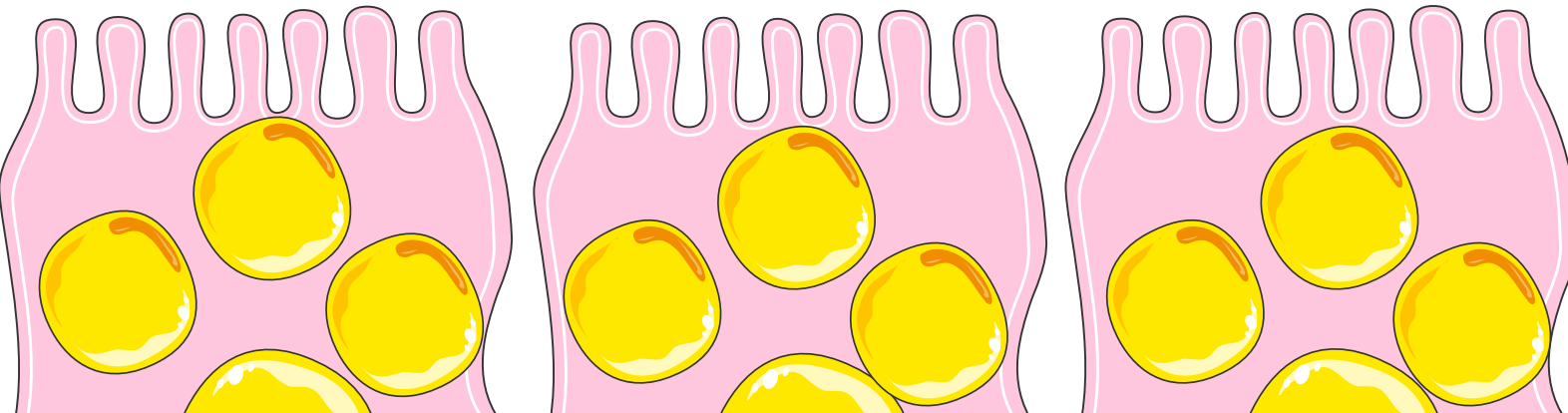
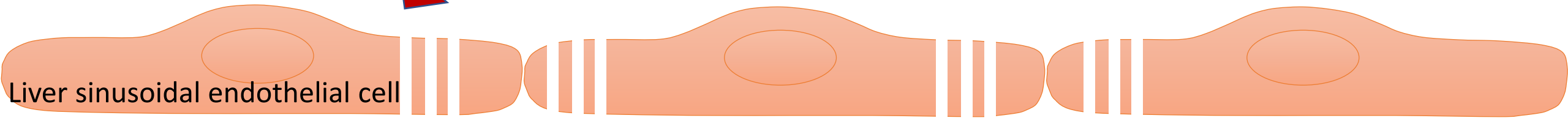
Liver sinusoidal endothelial cells (LSECs)



Liver sinusoidal endothelial cells (LSECs)

Blood derived?

- Ox-LDL or fatty acids 
- Inflammatory mediators
- Mechanical forces



Schild et al, *Biochim Biophys Acta*, 2008

Tatteya et al, *Diabetes*, 2011

Herrnberger et al, *PloS One*, 2014

Zhang et al, *J Mol Endocrinol*, 2014

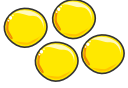
Matsumoto et al, *Free Radic Biol Med*, 2018

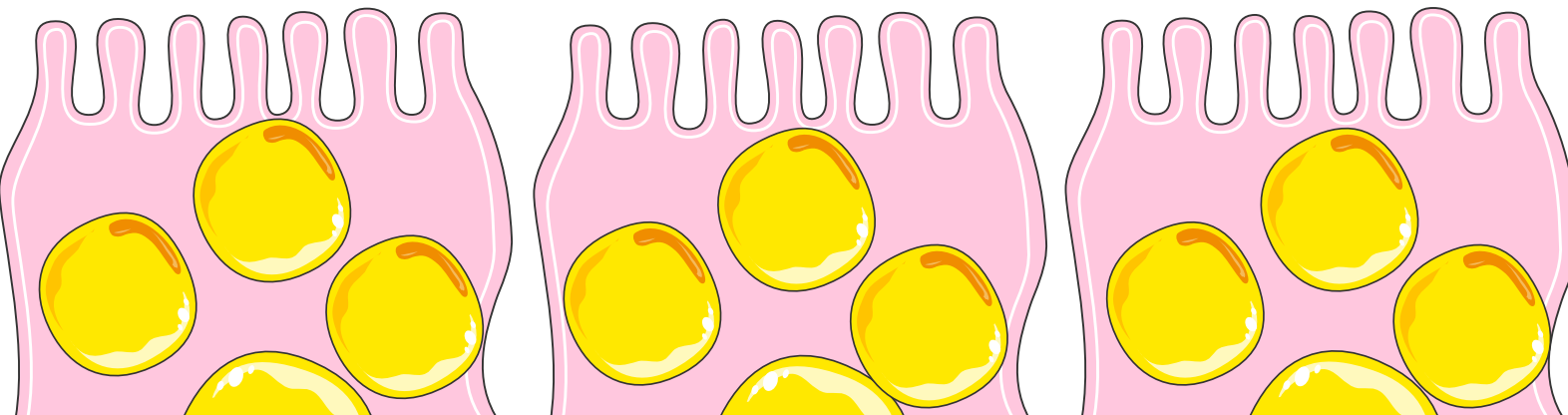
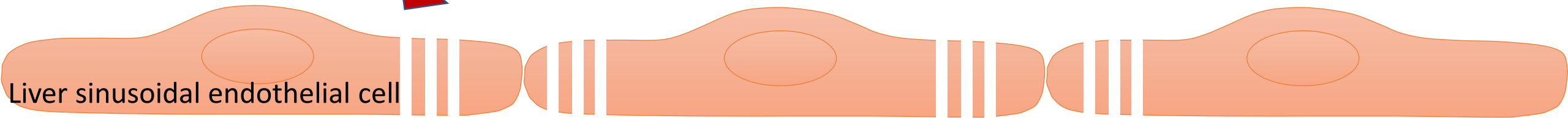
Furuta et al, *JCI* 2021

Hammoutène & Rautou, *J Hepatol* 2019

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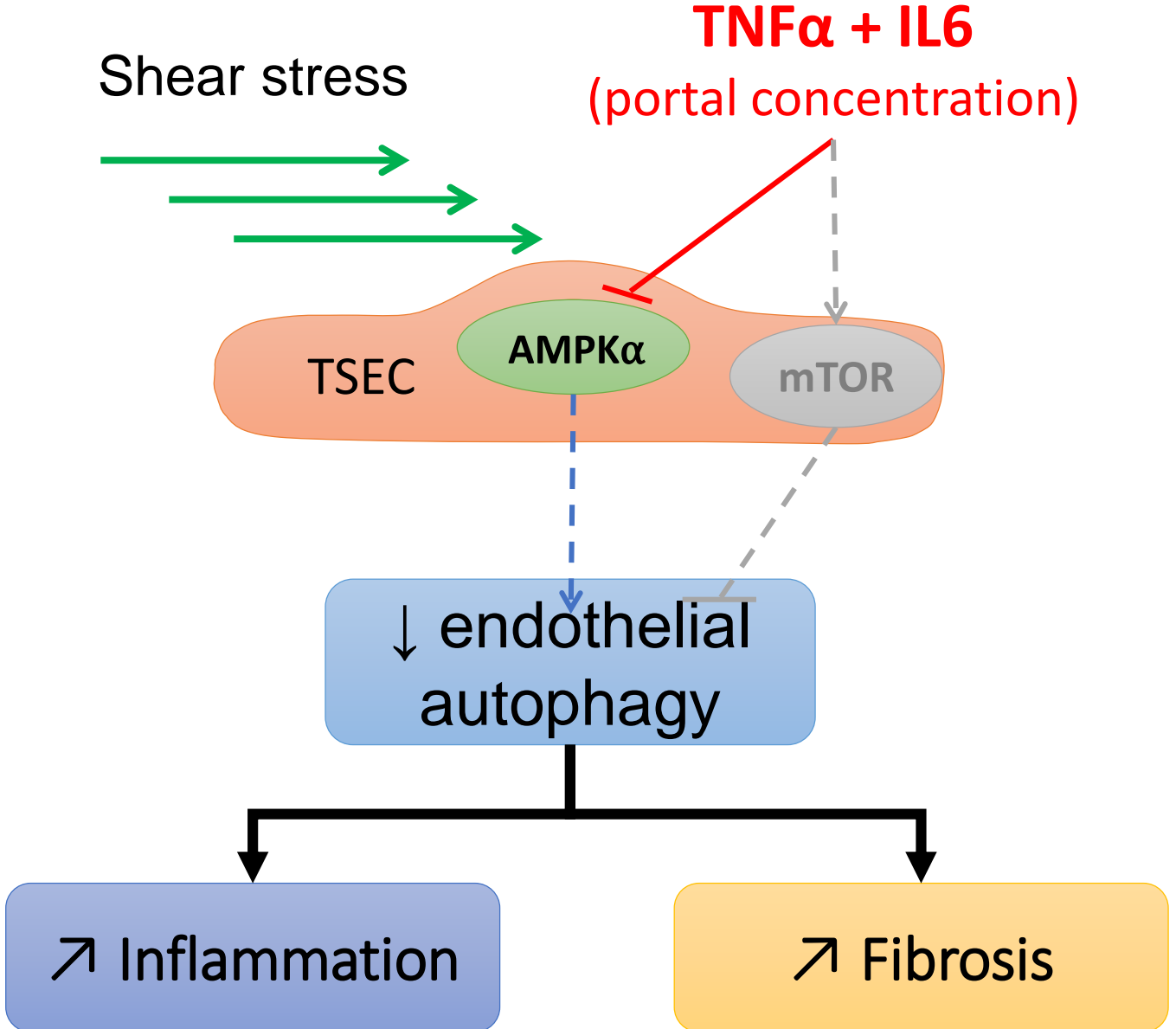
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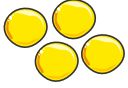
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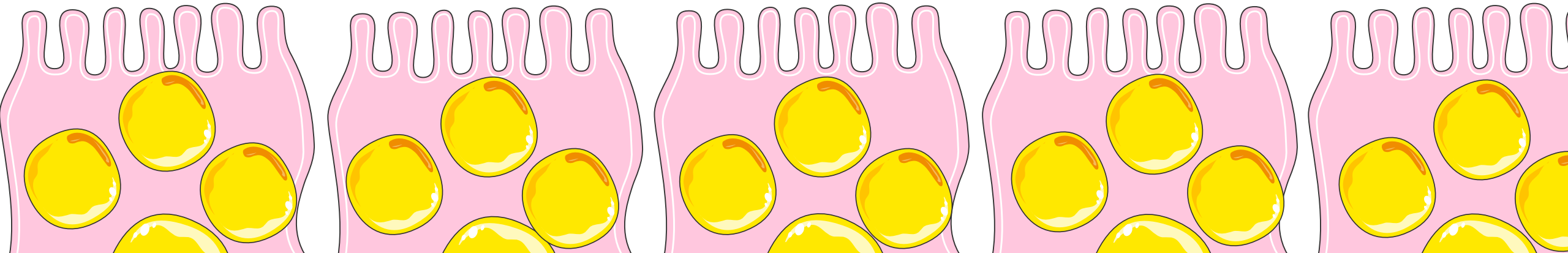
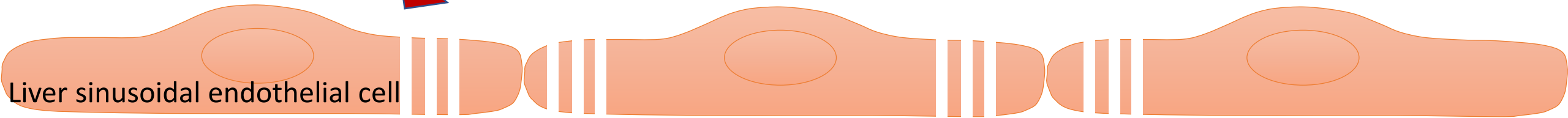
Low dose TNF α and IL6 induce a defect in endothelial autophagy



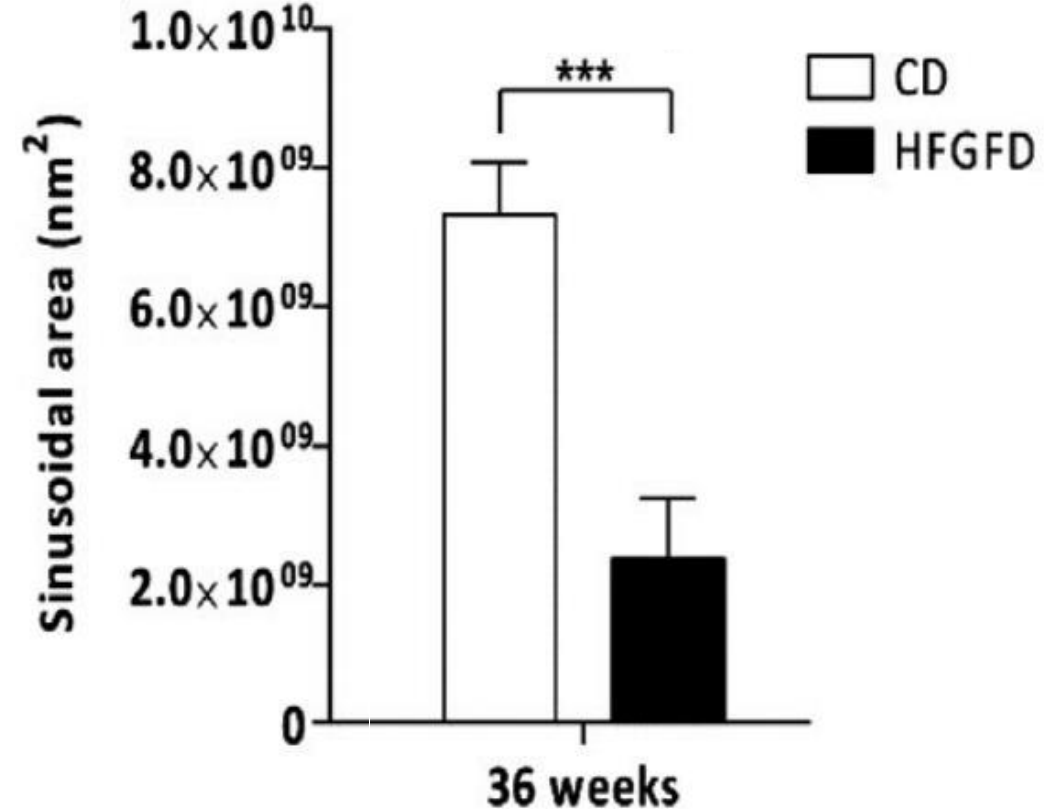
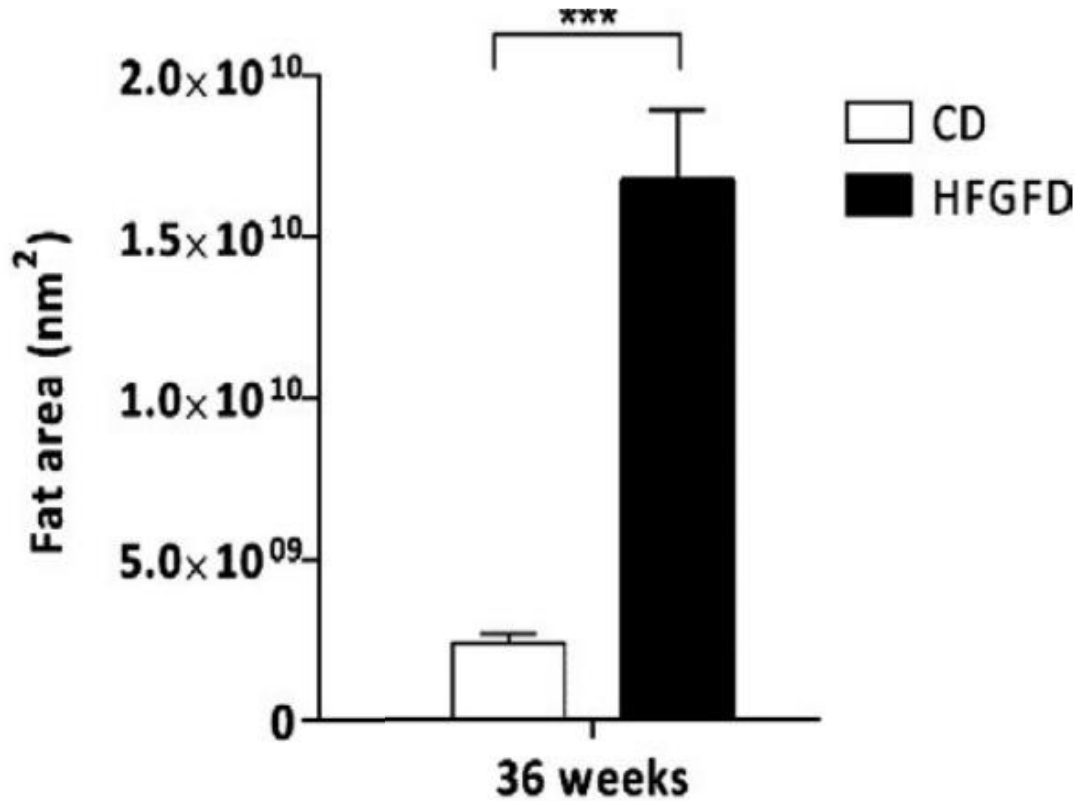
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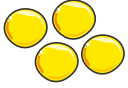


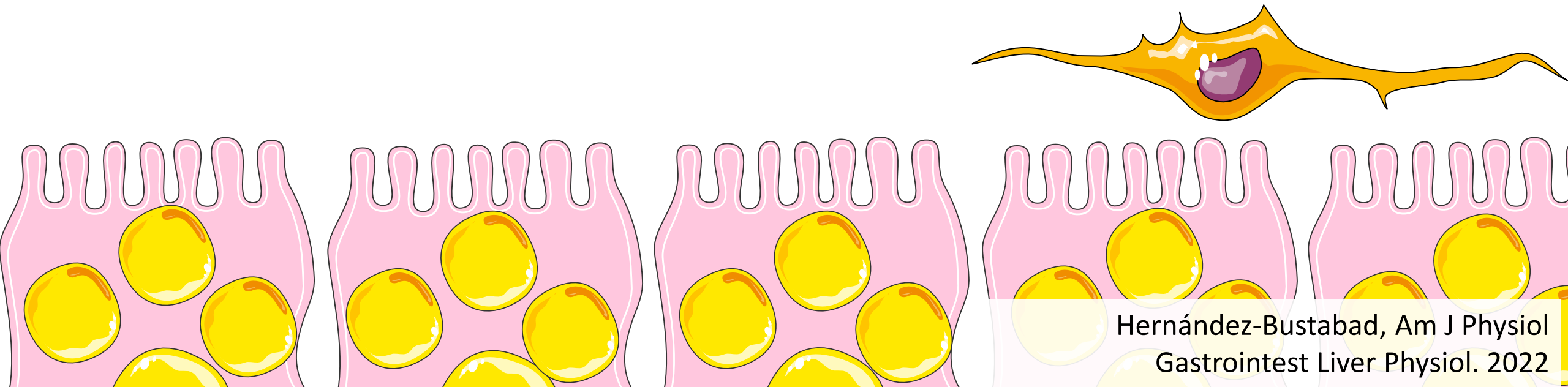
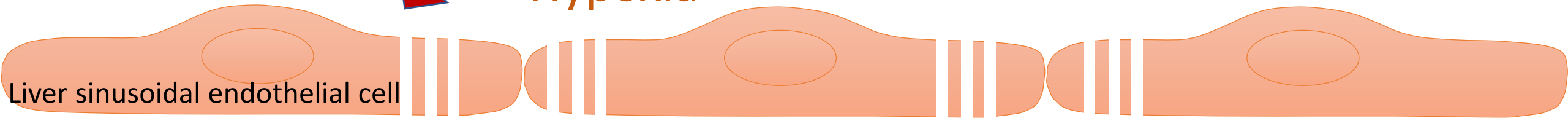
Mechanical forces: Shear stress related to decrease sinusoidal diameter



Liver sinusoidal endothelial cells (LSECs)

Blood derived?

- Ox-LDL or fatty acids 
- Inflammatory mediators
- Mechanical forces
- Hypoxia

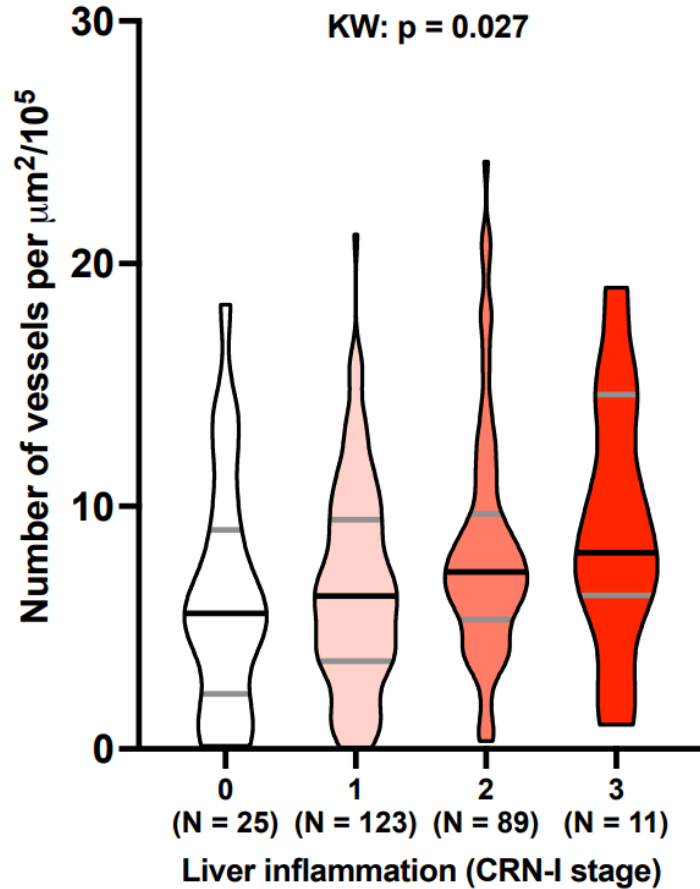


Liver endothelial cells in NASH

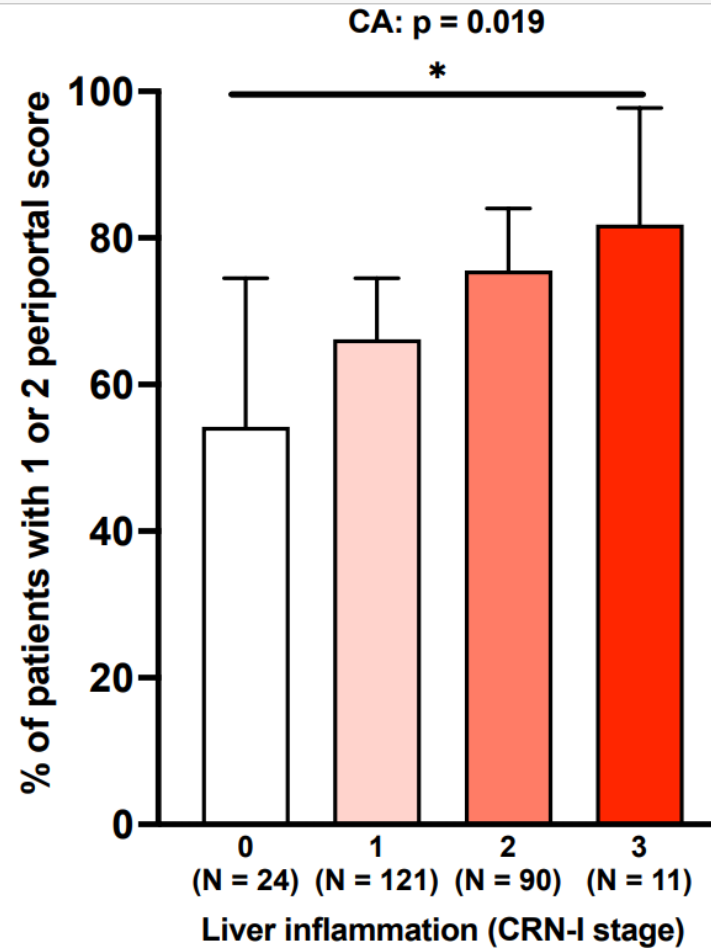
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LSEC capillarization and liver inflammation in patients with NALFD

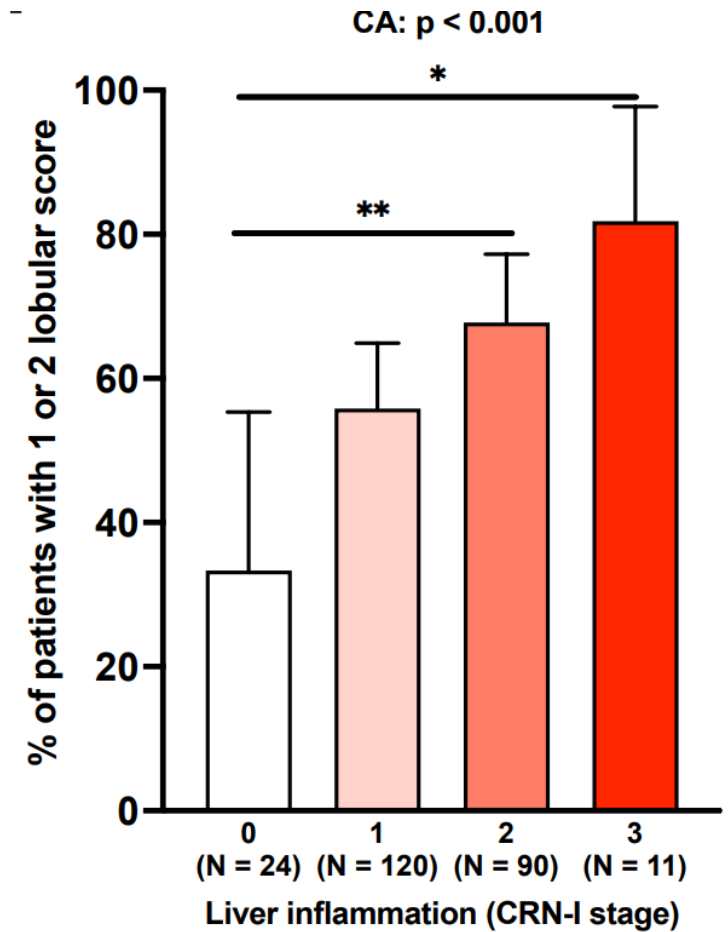
Morphometry



Periportal score



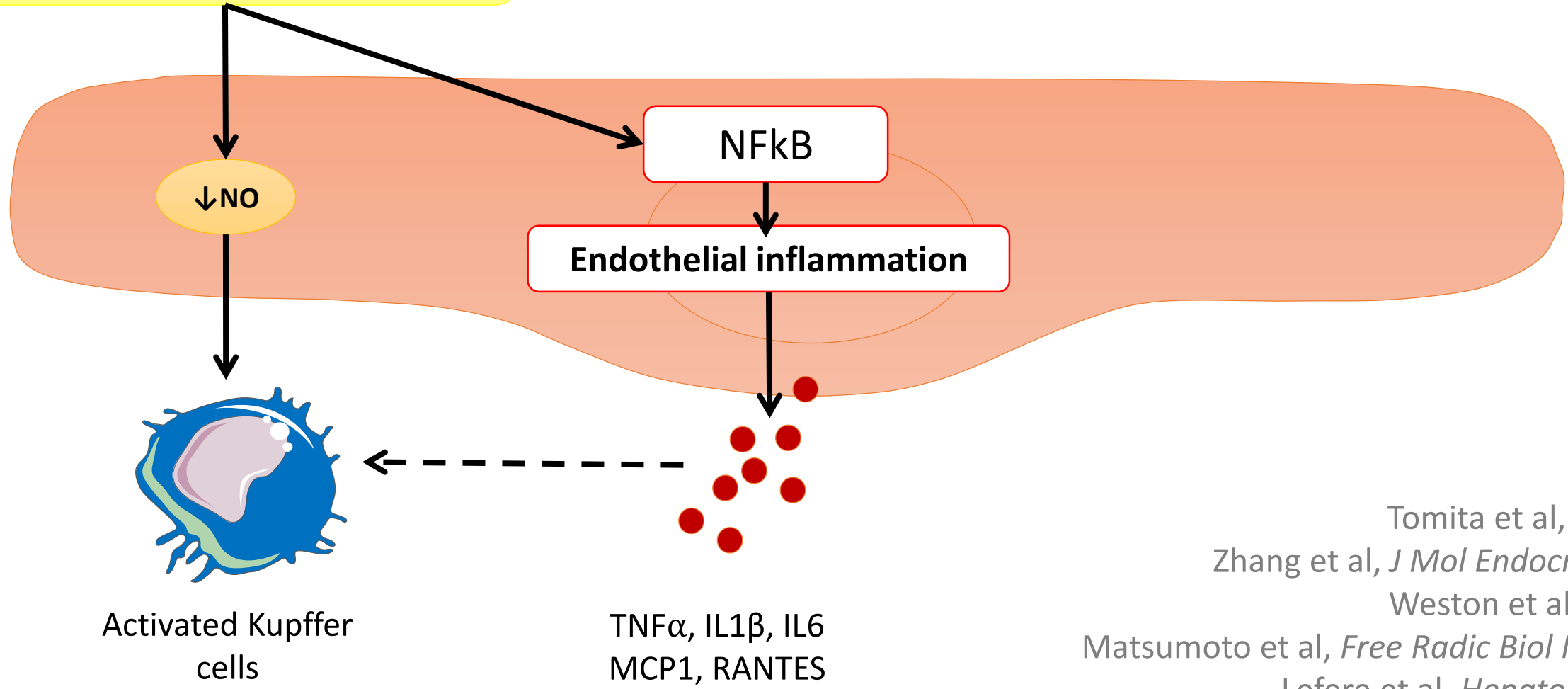
Lobular score



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CD34 staining

Role of liver endothelium on liver inflammation

Lipotoxicity / ROS
Inflammation / Adipokines
Gut microbiota



Activated Kupffer cells

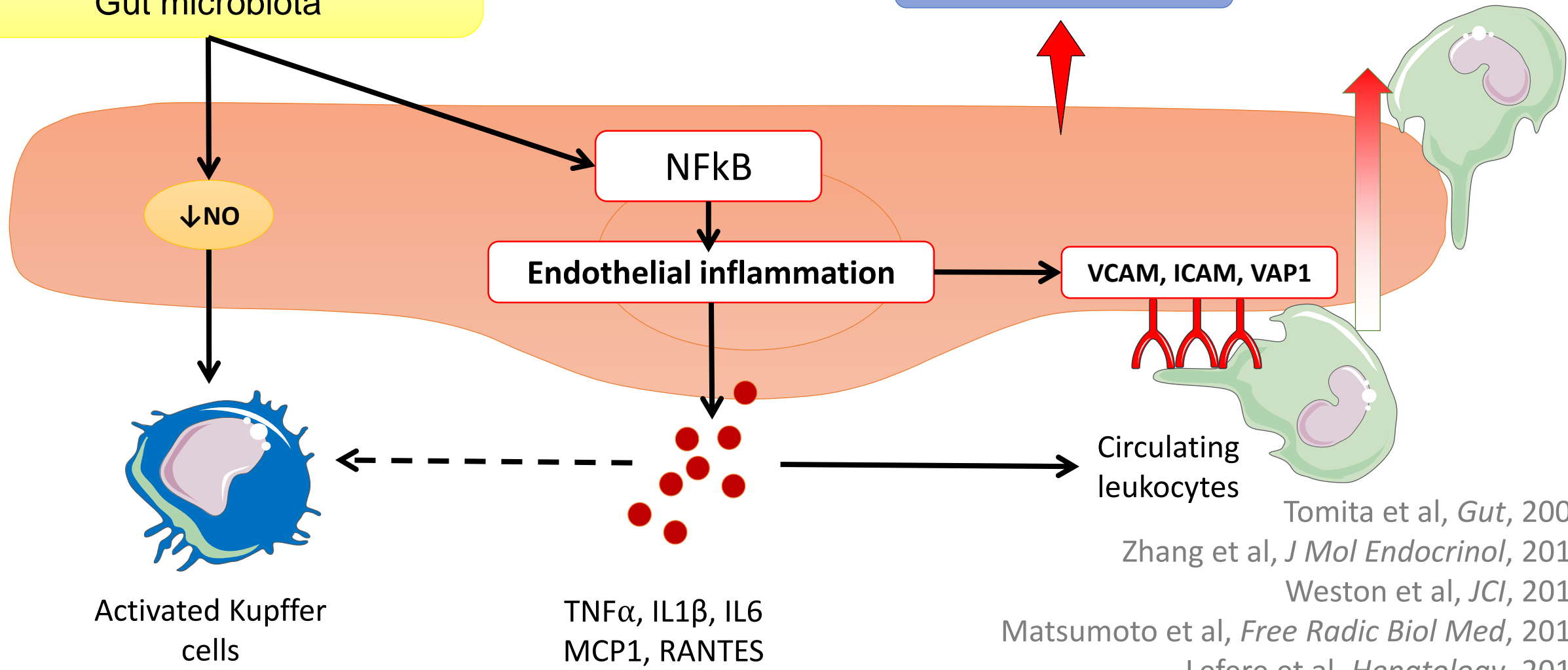
$\text{TNF}\alpha$, $\text{IL1}\beta$, IL6
MCP1, RANTES

Tomita et al, *Gut*, 2006
Zhang et al, *J Mol Endocrinol*, 2014
Weston et al, *JCI*, 2015
Matsumoto et al, *Free Radic Biol Med*, 2018
Lefere et al, *Hepatology*, 2018

Role of liver endothelium on liver inflammation

Lipotoxicity / ROS
Inflammation / Adipokines
Gut microbiota

↑ Inflammation



Activated Kupffer cells

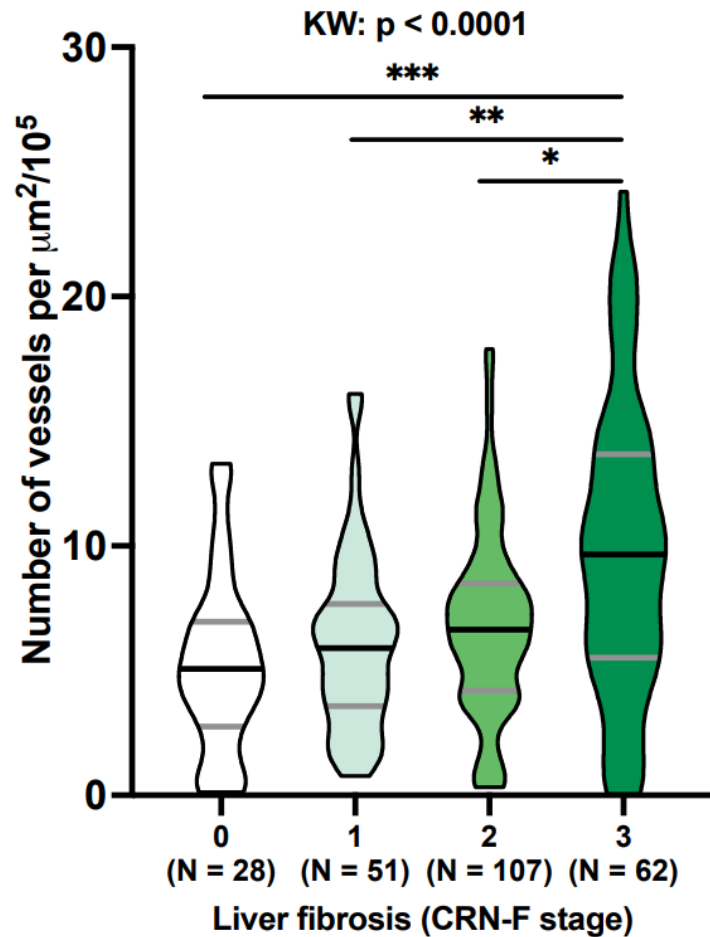
TNFα, IL1β, IL6
MCP1, RANTES

Circulating leukocytes

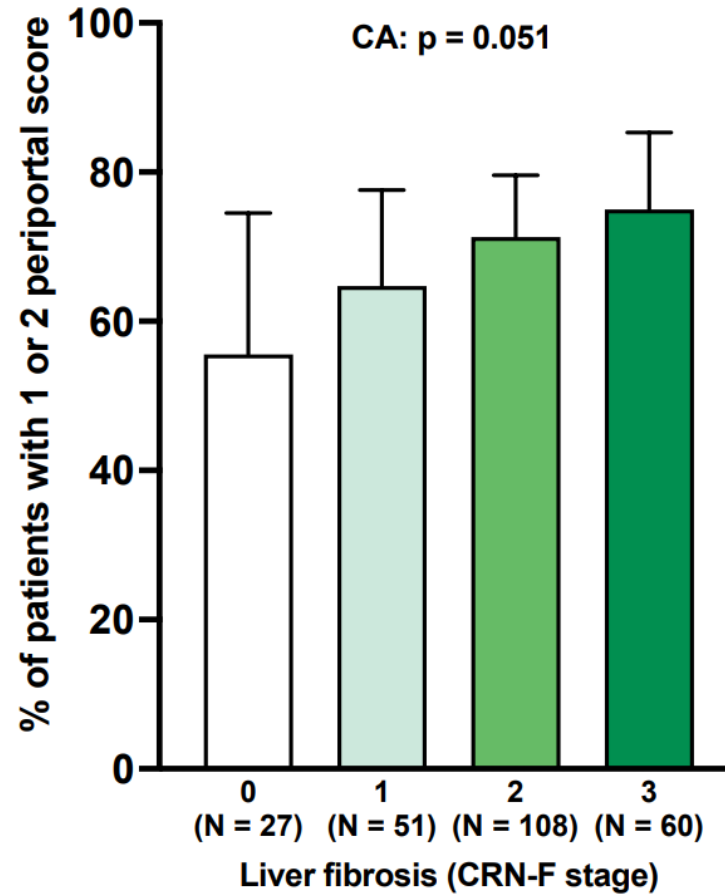
Tomita et al, *Gut*, 2006
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Matsumoto et al, *Free Radic Biol Med*, 2018
Lefere et al, *Hepatology*, 2018

LSEC capillarisation and liver fibrosis in patients with NALFD

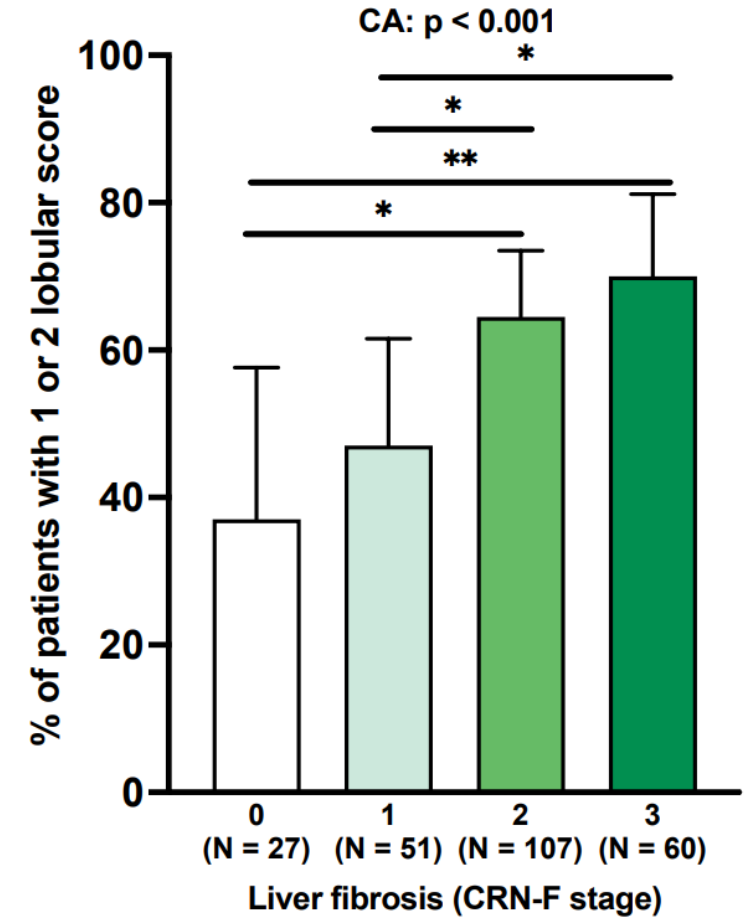
Morphometry



Periportal score



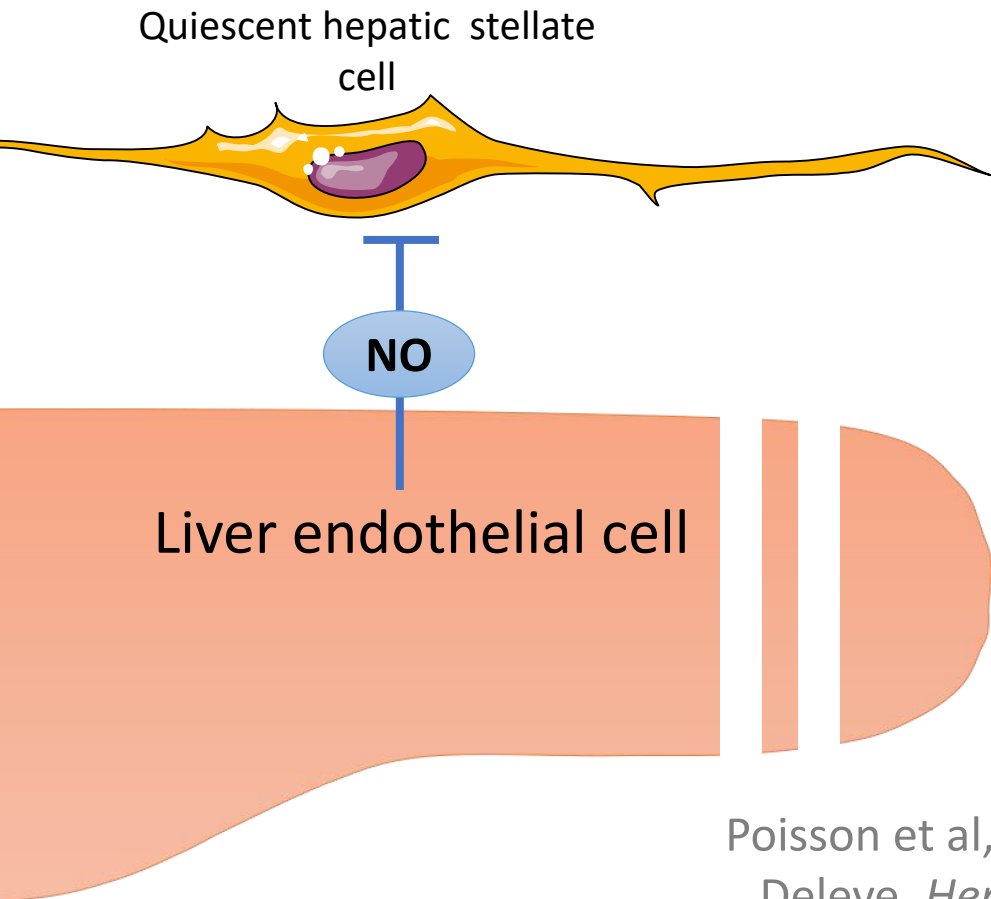
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Role of liver endothelium on liver fibrosis

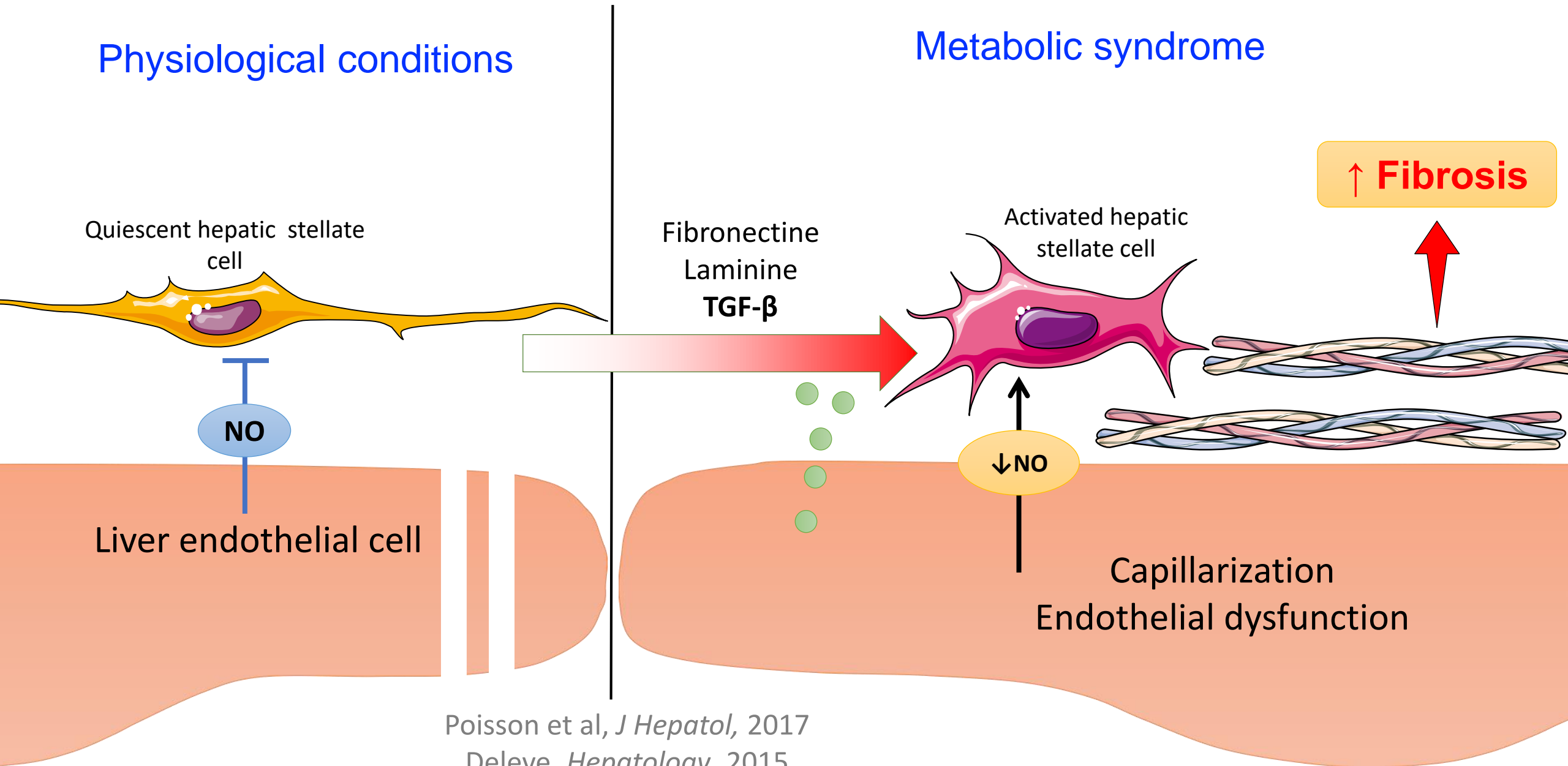
Physiological conditions



Poisson et al, *J Hepatol*, 2017

Deleve, *Hepatology*, 2015

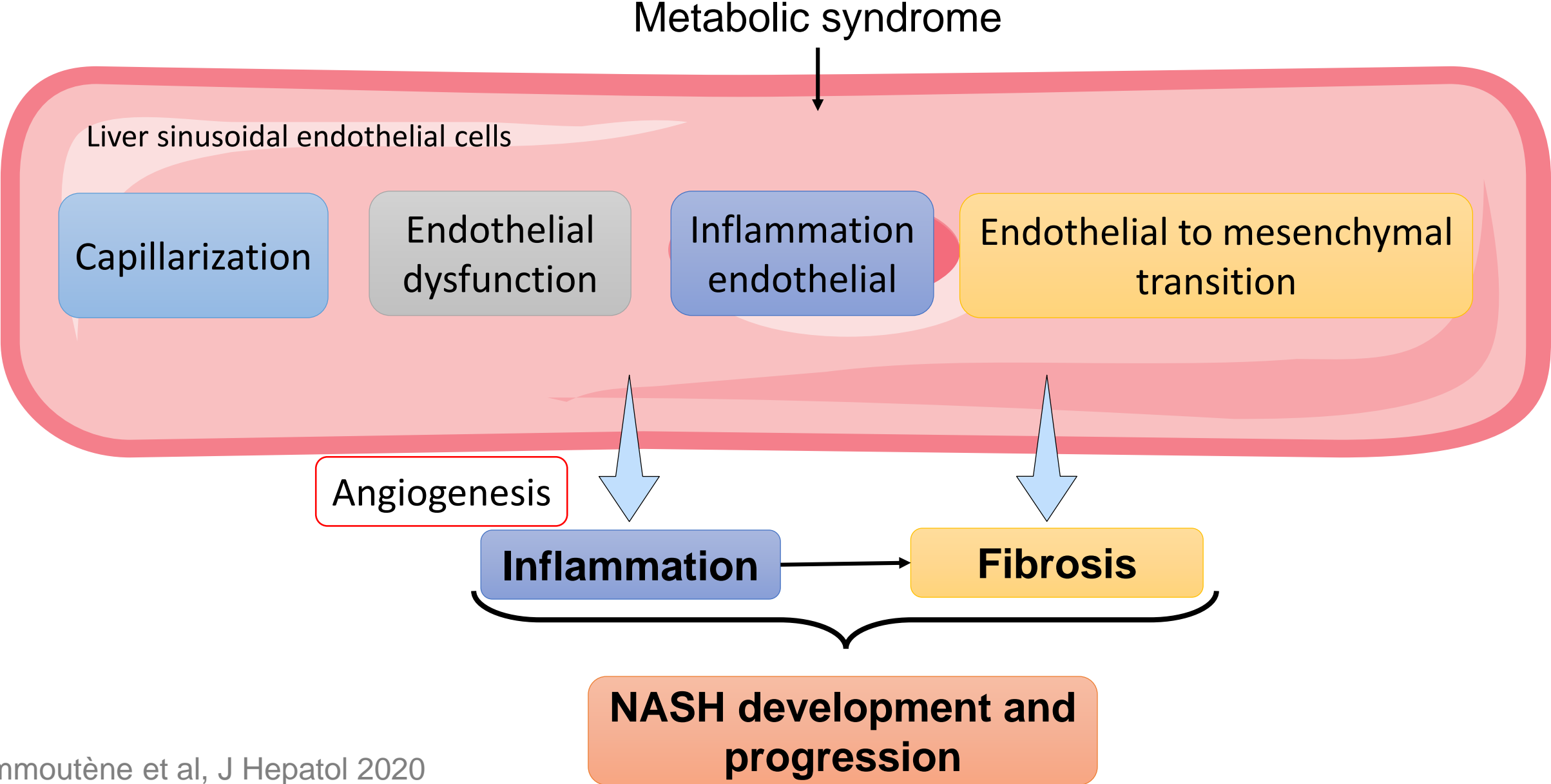
Role of liver endothelium on liver fibrosis



Poisson et al, *J Hepatol*, 2017

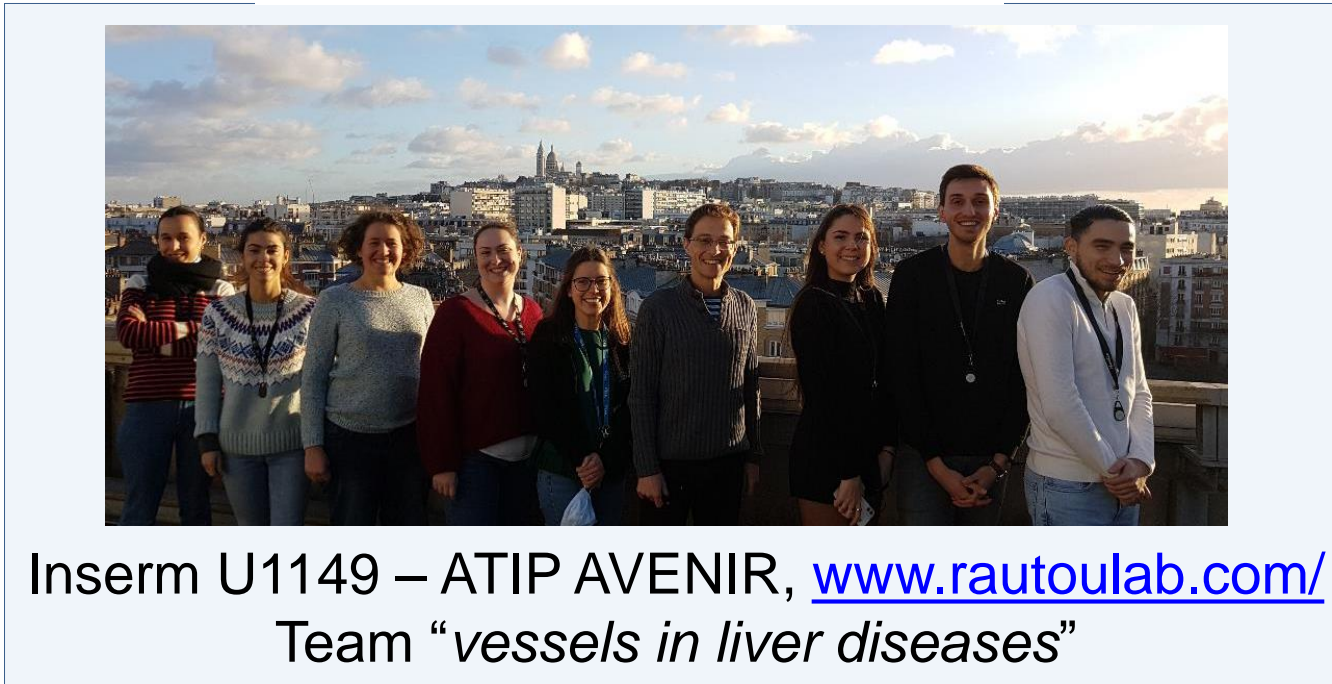
Deleve, *Hepatology*, 2015

Conclusion: role of liver endothelial cells in NASH





Hepatology unit, Beaujon Hospital
Reference center for vascular liver diseases



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