MÁSTER EN HEPATOLOGÍA

ORGANIZA:

¿Qué debe saber el clínico de la fisiopatología del trasplante hepático?

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Inselspital, Bern

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Agenda

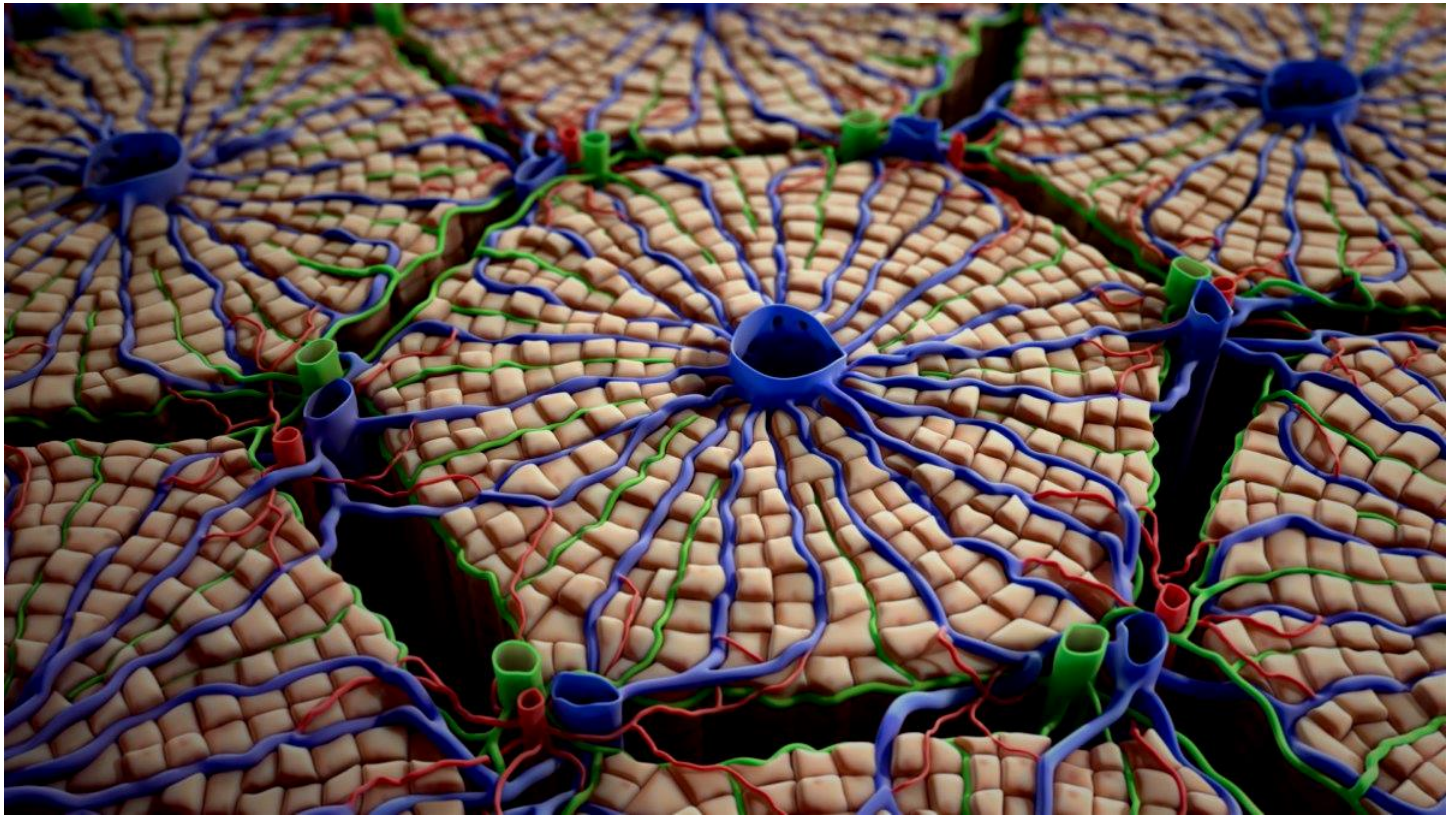
- The liver & its microcirculation

- Ischemia/Reperfusion Injury (IRI) during liver transplantation

- Therapeutics to improve hepatic IRI

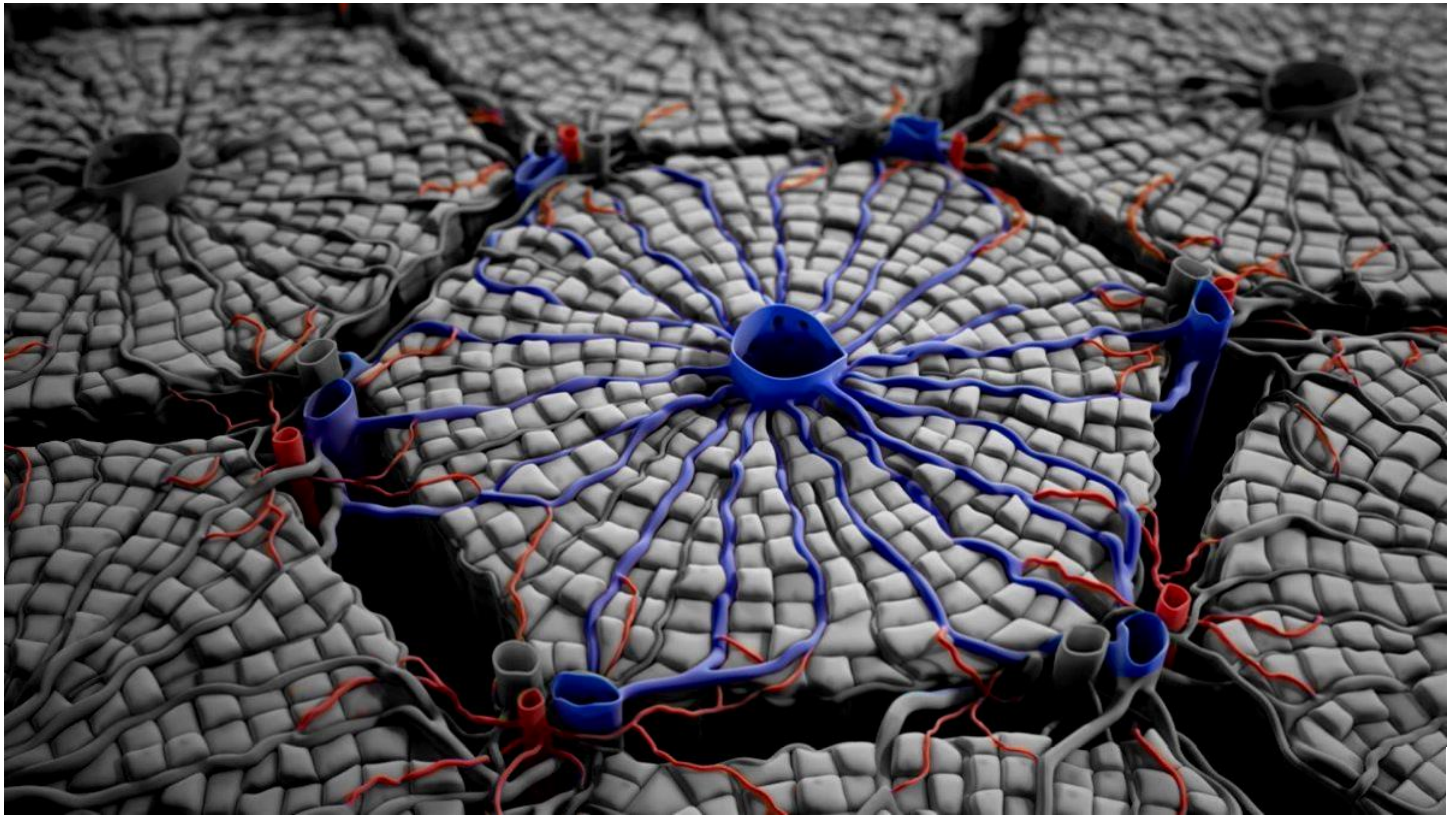
- An overview on liver regeneration

The Liver & its Microcirculation

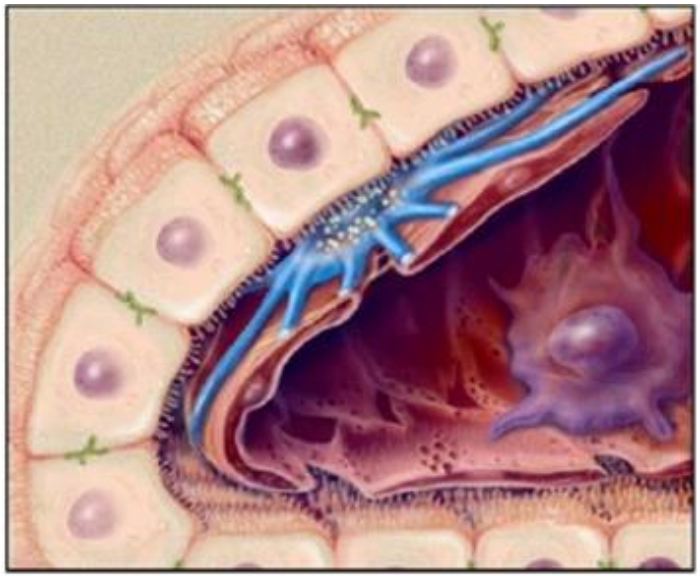


Aird WC. *Circ Res*. 2007

The Liver & its Microcirculation



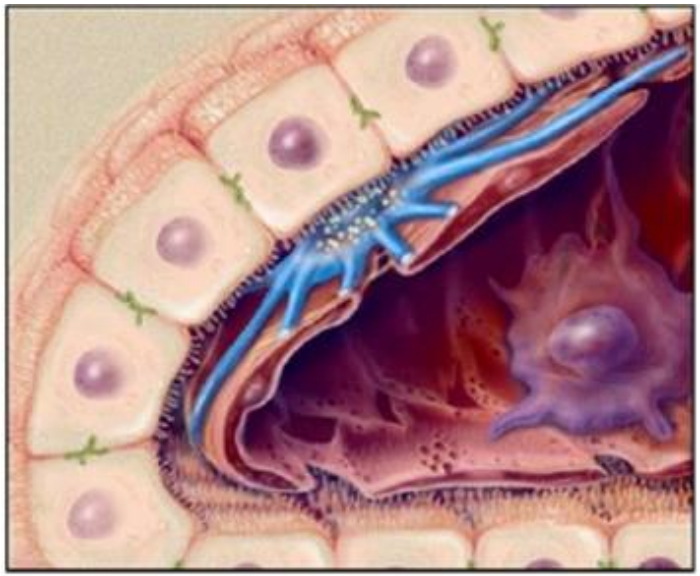
Liver cells



Friedman SL. *Nat Clin Pract Gastroenterol Hepatol* 2004

Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida & Friedman, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

Liver cells - Hepatocytes

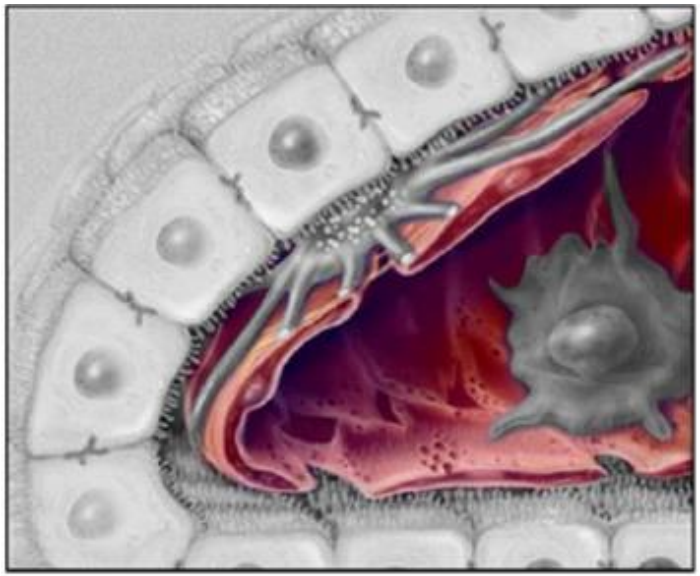


Hepatocytes

- Main cell type of the liver.
- Synthesis of proteins, metabolism of molecules, detoxification.

Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida & Friedman, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

The liver sinusoid - LSEC

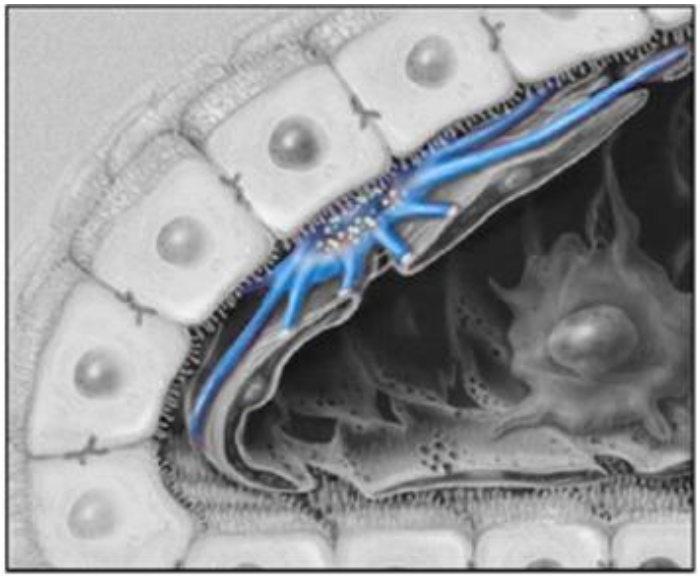


Liver Sinusoidal Endothelial Cells (LSEC)

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

Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida & Friedman, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

The liver sinusoid - HSC



Liver Sinusoidal Endothelial Cells (LSEC)

- Discontinuous (fenestrae, lack of basal membrane).
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Hepatic Stellate Cells (HSC)

- Contractile properties.
- Vitamin A storage

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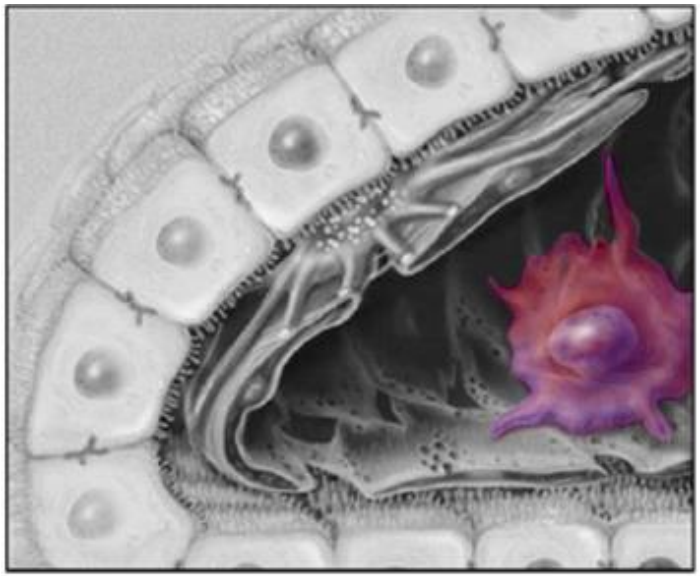
Tsuchida & Friedman, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

The liver sinusoid - KC



Liver Sinusoidal Endothelial Cells (LSEC)
- Discontinuous (fenestrae, lack of basal membrane).
- Haemostasis, inflammation, toxicants clearance and regulation of vascular tone.

Hepatic Stellate Cells (HSC)
- Contractile properties.
- Vitamin A storage

Kupffer Cells (KC)
- Resident macrophages: defense, inflammation, tissue remodelling.

Gracia-Sancho J et al, *Nature Reviews Gastro & Hepatol* 2021
Tsuchida & Friedman, *Nature Reviews Gastro & Hepatol* 2017
Tacke F. *Journal of Hepatology* 2017

Ischemia & Reperfusion Injury

Ischemia

Biomechanical injury

↓ Shear stress
↓ KLF2
↓ eNOS, TM, Nrf2

Hypoxia injury

↓ O_2
↓ ATP
↑ Lactate

Reperfusion

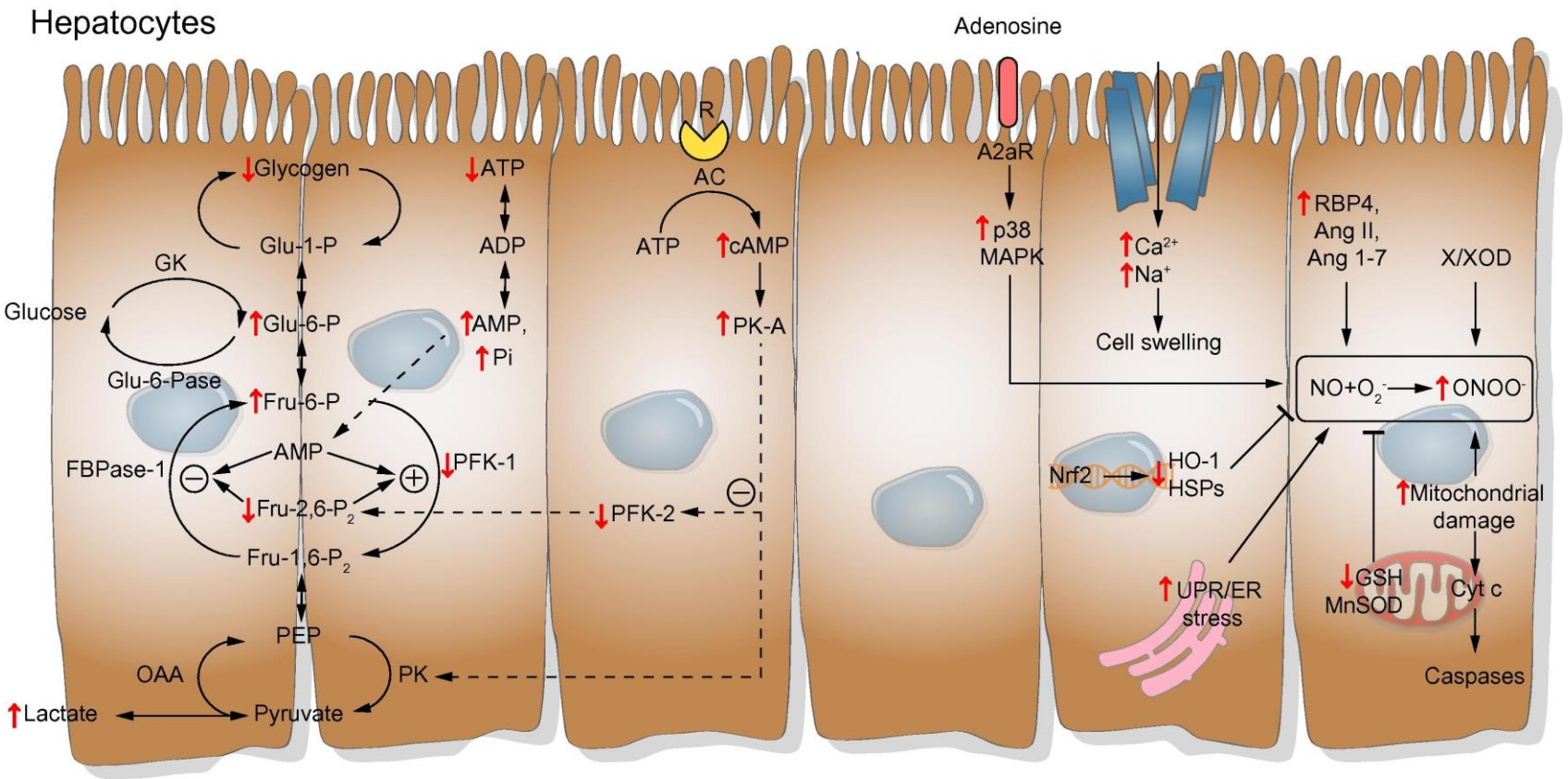
ROS injury

↑ O_2
↑ ROS
↑ Cell death

Immune Response → therapeutics
M Rodríguez-Perálvarez

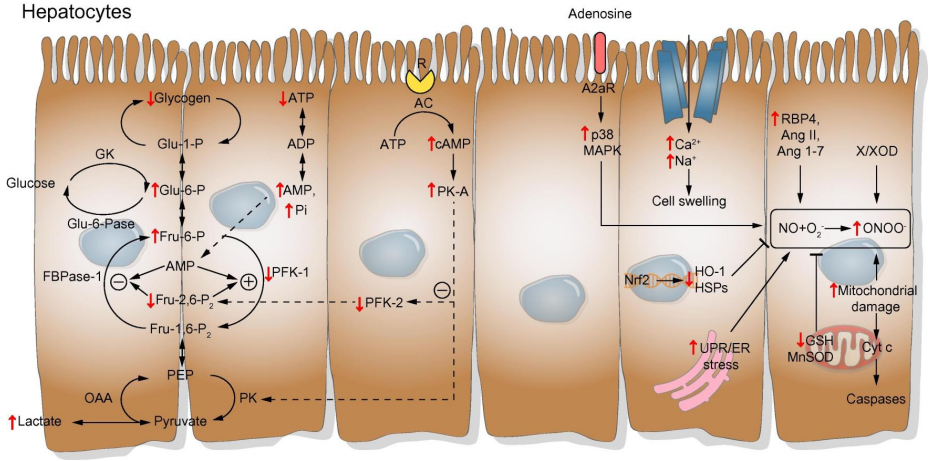
Peralta & Gracia-Sancho, Journal of Hepatology 2013

Ischemia & Reperfusion Injury – Effects in the parenchyma



Peralta & Gracia-Sancho, Journal of Hepatology 2013

Ischemia & Reperfusion Injury – Effects in the parenchyma

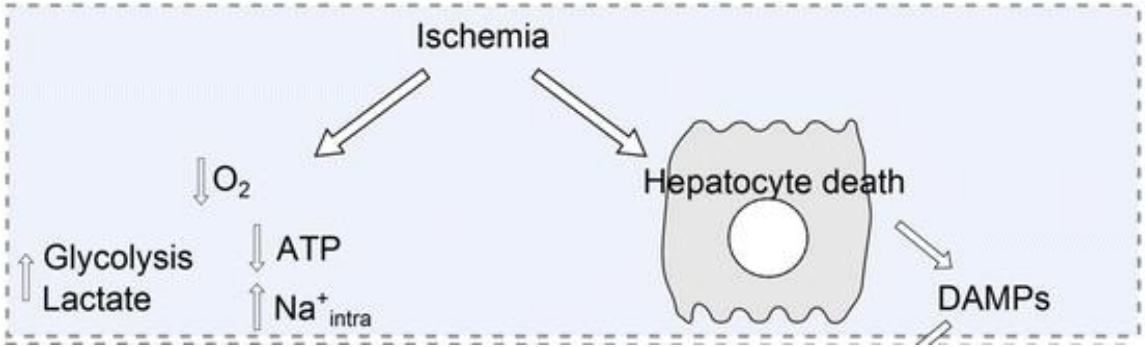


Major consequences:

- Acute inflammatory response
- Burst in oxidative stress
- Liver cell dysfunction & death

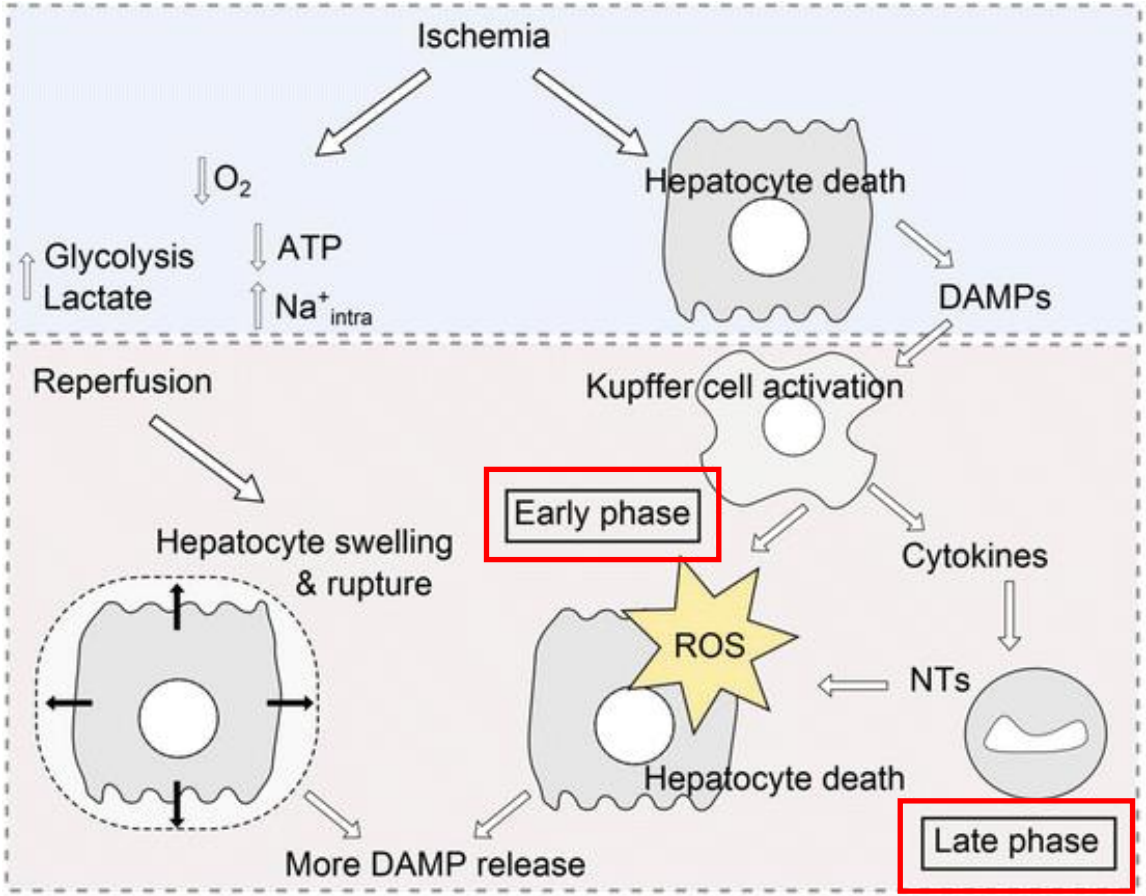
Peralta & Gracia-Sancho, Journal of Hepatology 2013
Peralta, Romero & Gracia-Sancho, Liver Transplantation 2019

Ischemia & Reperfusion Injury – Effects in the parenchyma



McGill & Jaeschke, Biomarkers in Liver Disease 2016

Ischemia & Reperfusion Injury – Effects in the parenchyma



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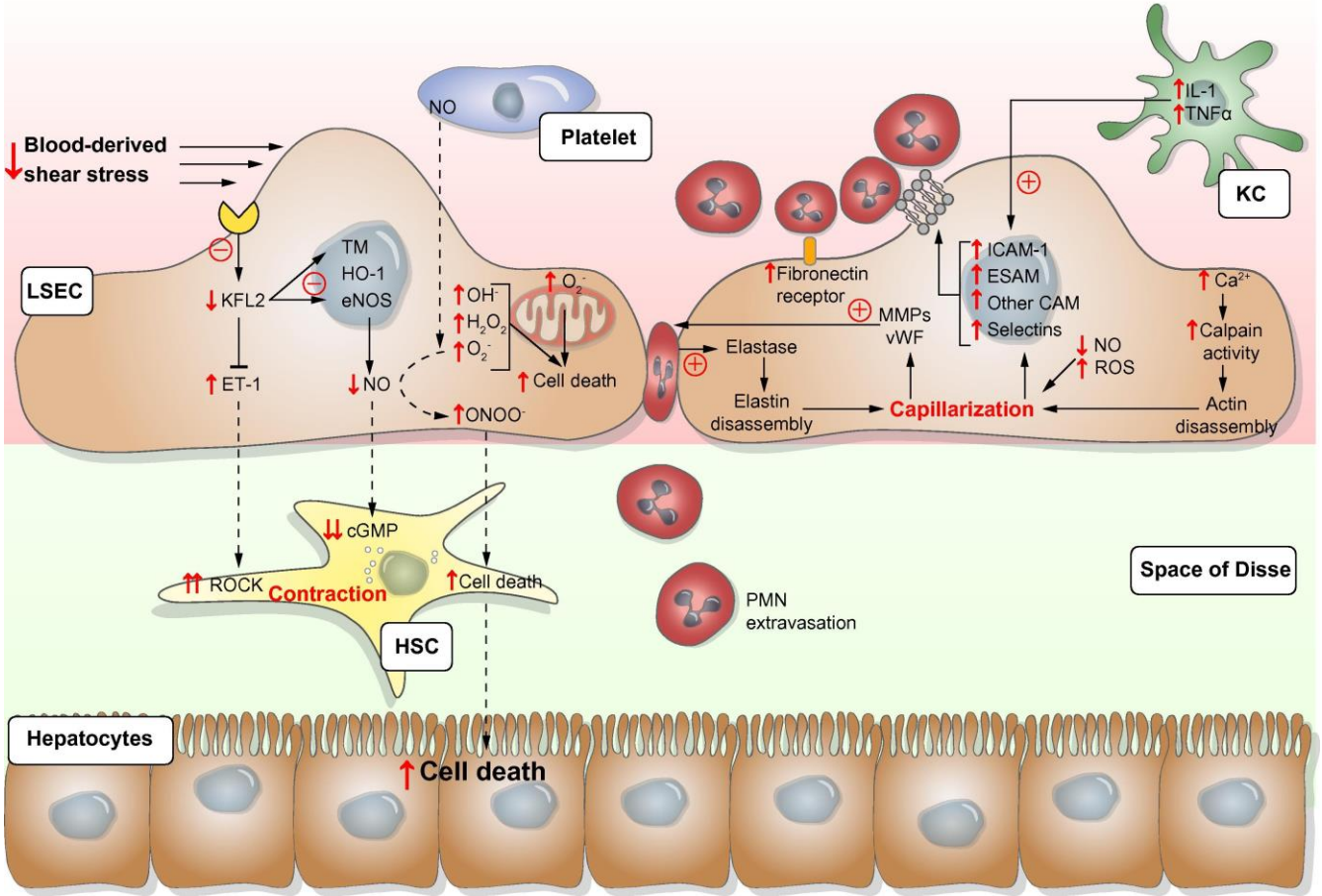
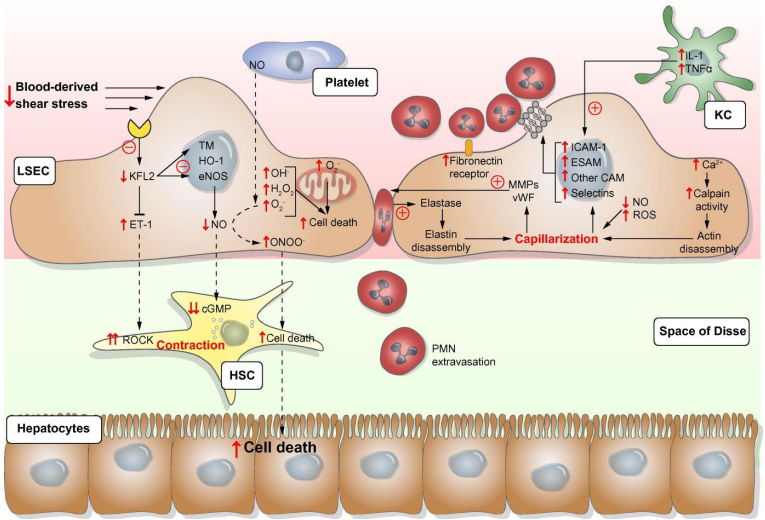
Ischemia & Reperfusion Injury – Effects in the sinusoid



Peralta & Gracia-Sancho, Journal of Hepatology 2013

Ischemia & Reperfusion Injury – Effects in the sinusoid

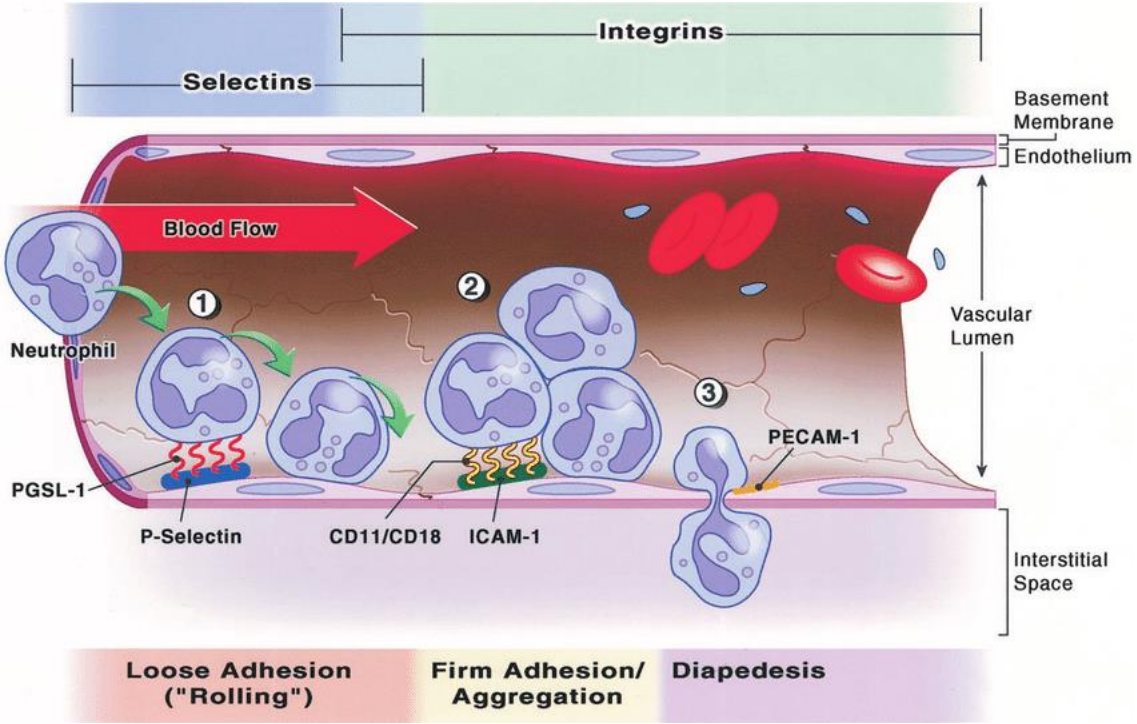


Major consequences:

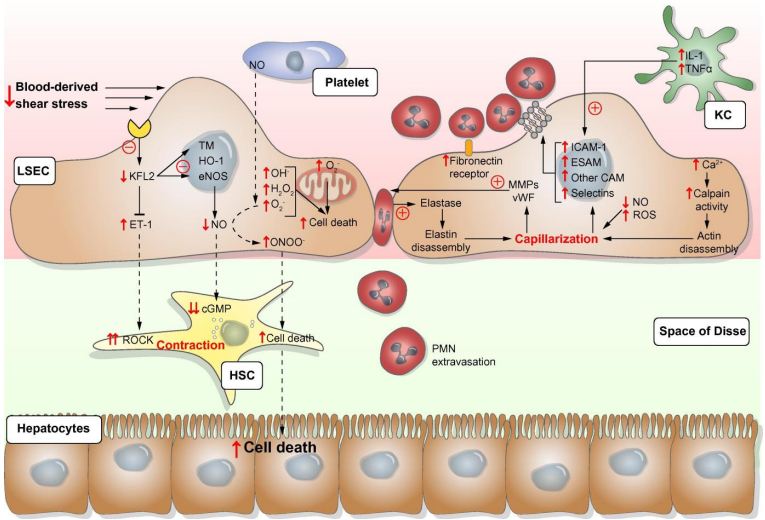
- Acute endothelial dysfunction + inflammatory cells recruitment
- Increase in hepatic vascular resistance
- Reduced parenchymal perfusion
- Portal Hypertension
- Splanchnic congestion

Peralta & Gracia-Sancho, Journal of Hepatology 2013
Peralta & Gracia-Sancho, Clinical Science 2015

Ischemia & Reperfusion Injury – Effects in the sinusoid – Inflammatory cells recruitment



Ischemia & Reperfusion Injury – Effects in the sinusoid



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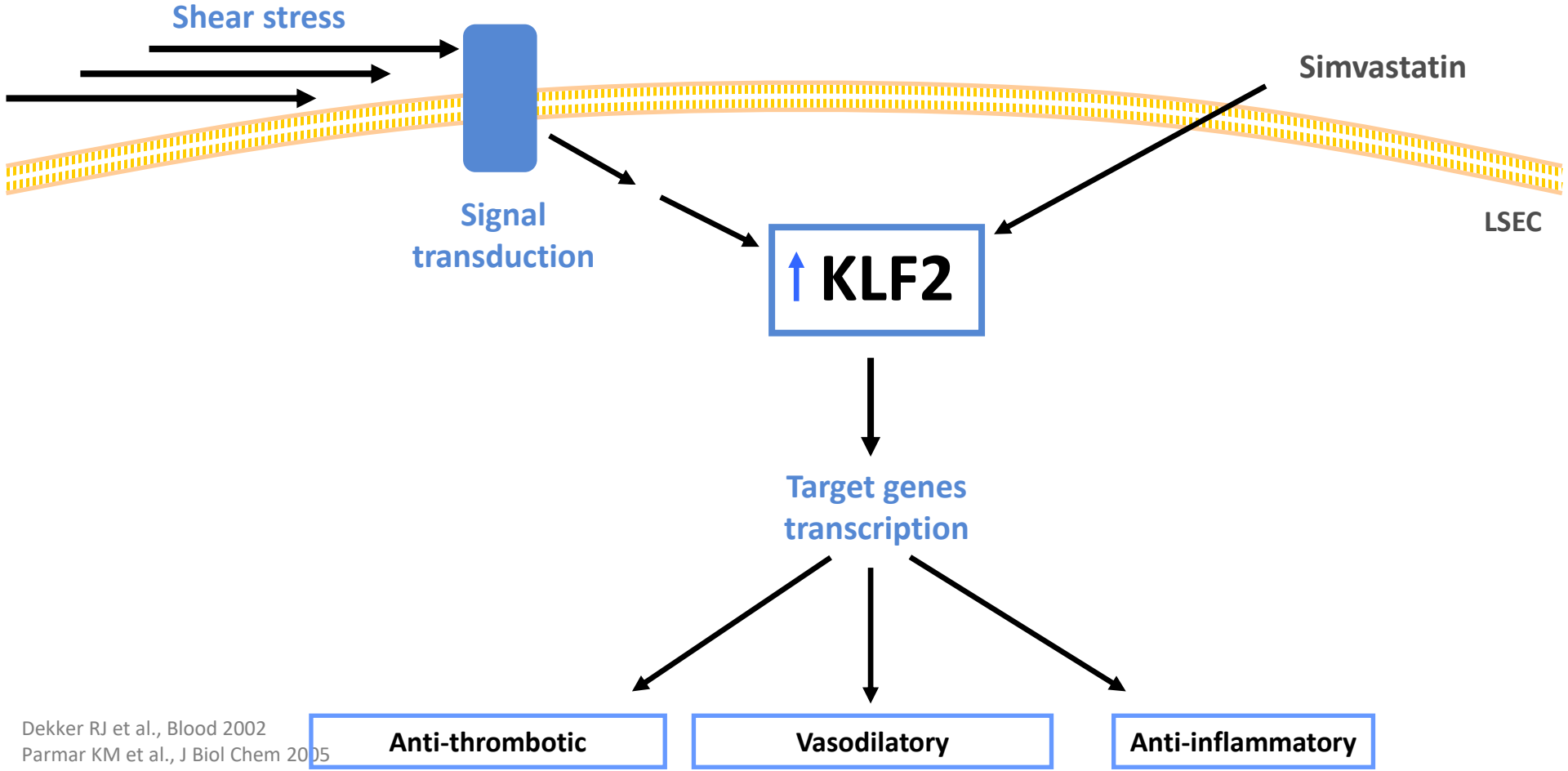

Dekker RJ et al., Blood 2002
Parmar KM et al., J Biol Chem 2005
Gracia-Sancho J et al., Gut 2011

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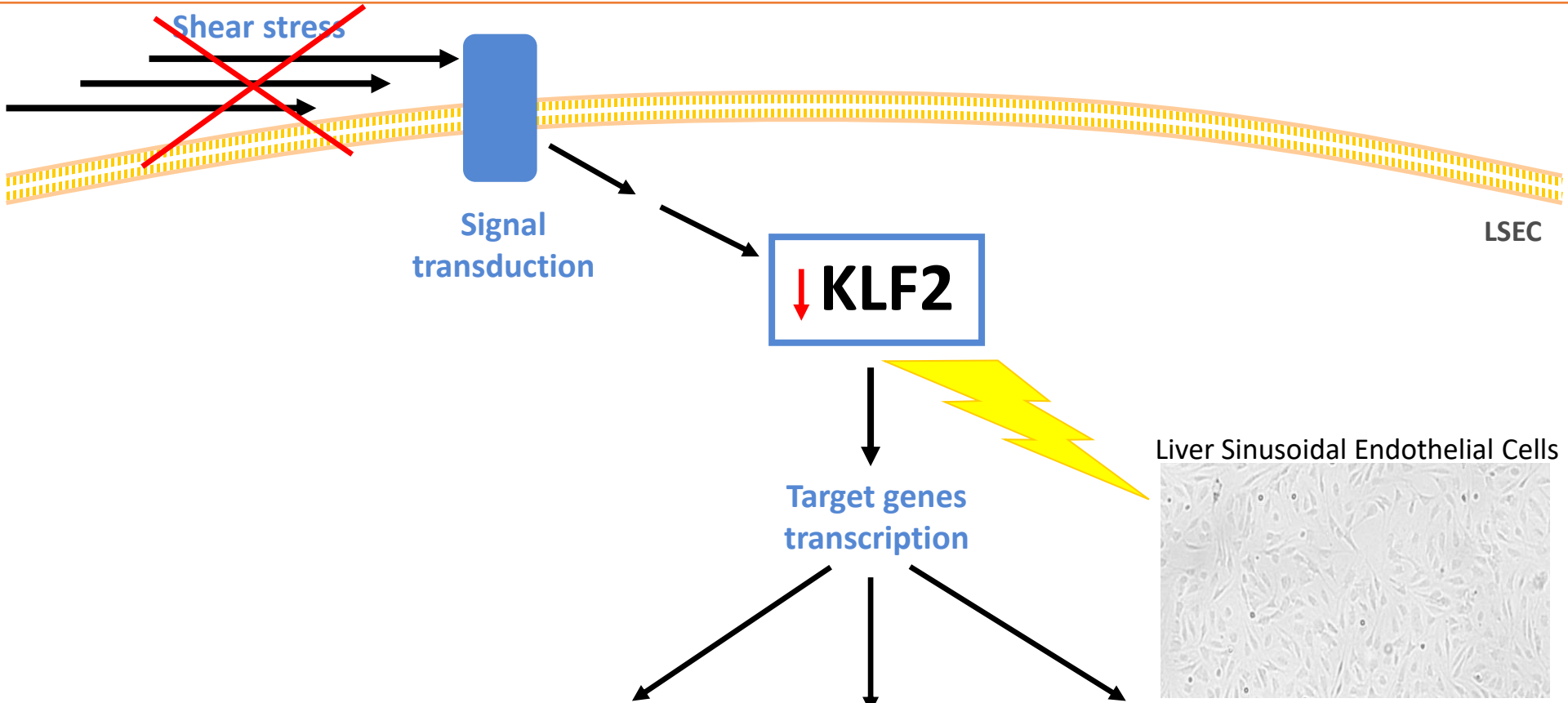

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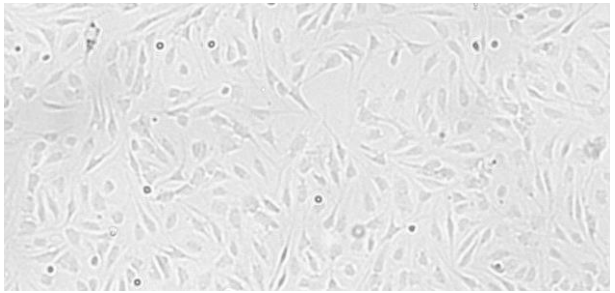
Ischemia & Reperfusion Injury – Effects in the sinusoid – Pharmacological strategy

Simvastatin → **KLF2** ⊣

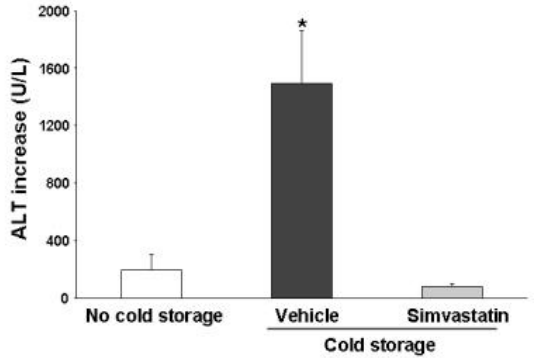
Liver Sinusoidal Endothelial Cells

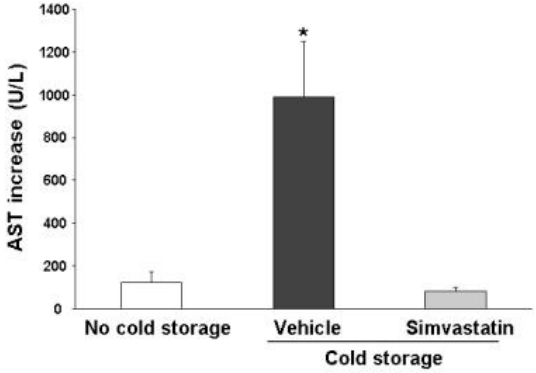


Gracia-Sancho et al, Journal of Hepatology 2013
Russo & Gracia-Sancho, et al, Hepatology 2012
Hide … Gracia-Sancho, 2014, 2016 & 2018

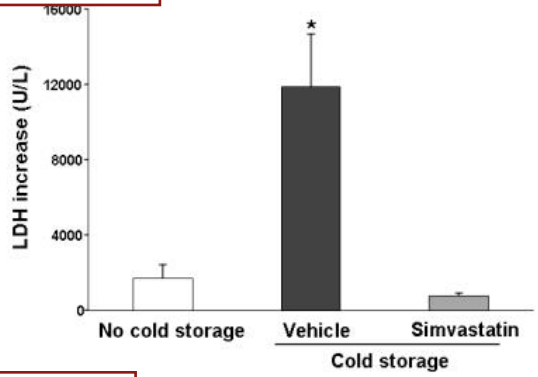
Ischemia & Reperfusion Injury – Effects in the sinusoid – Pharmacological strategy

ALT/AST

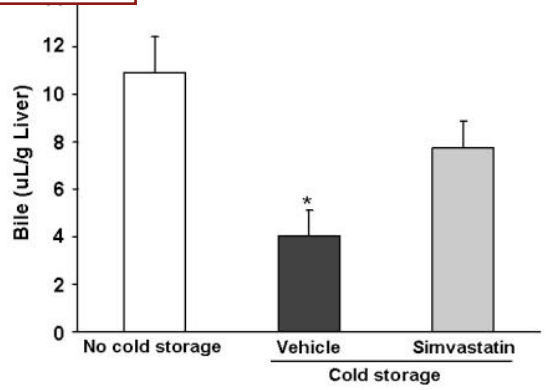




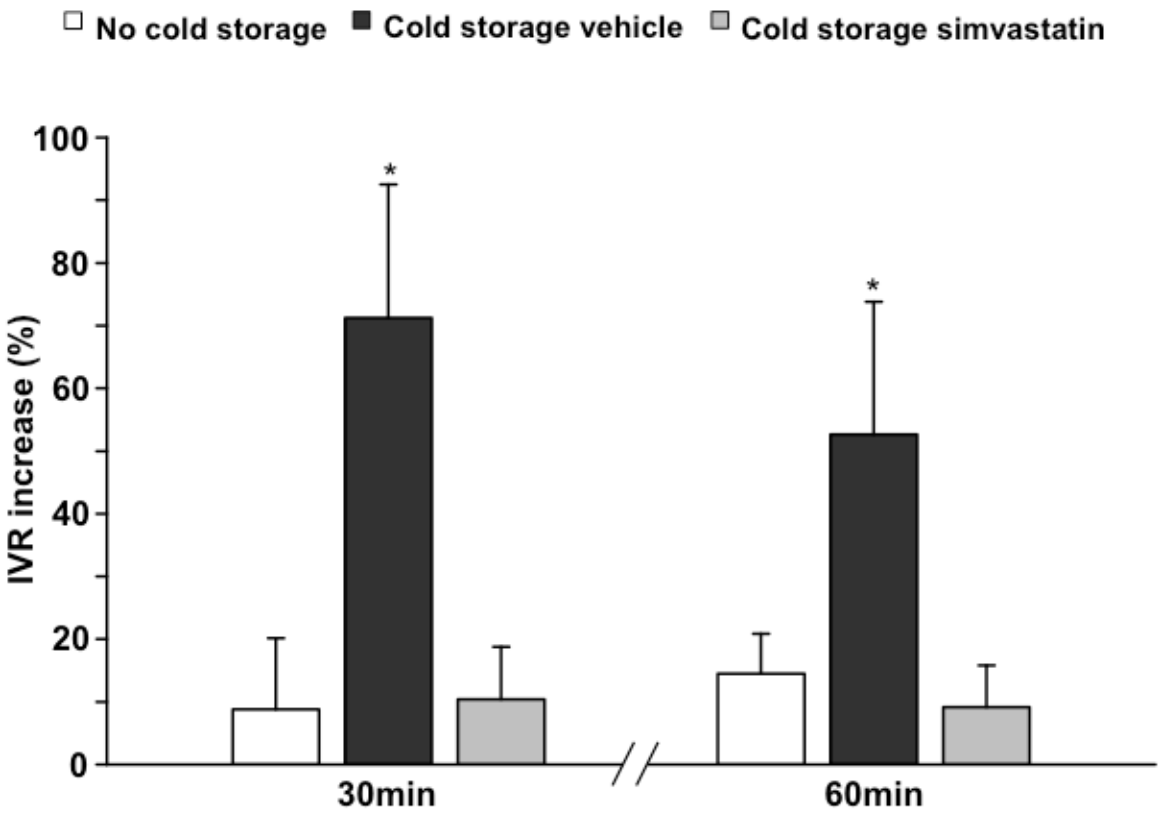
LDH



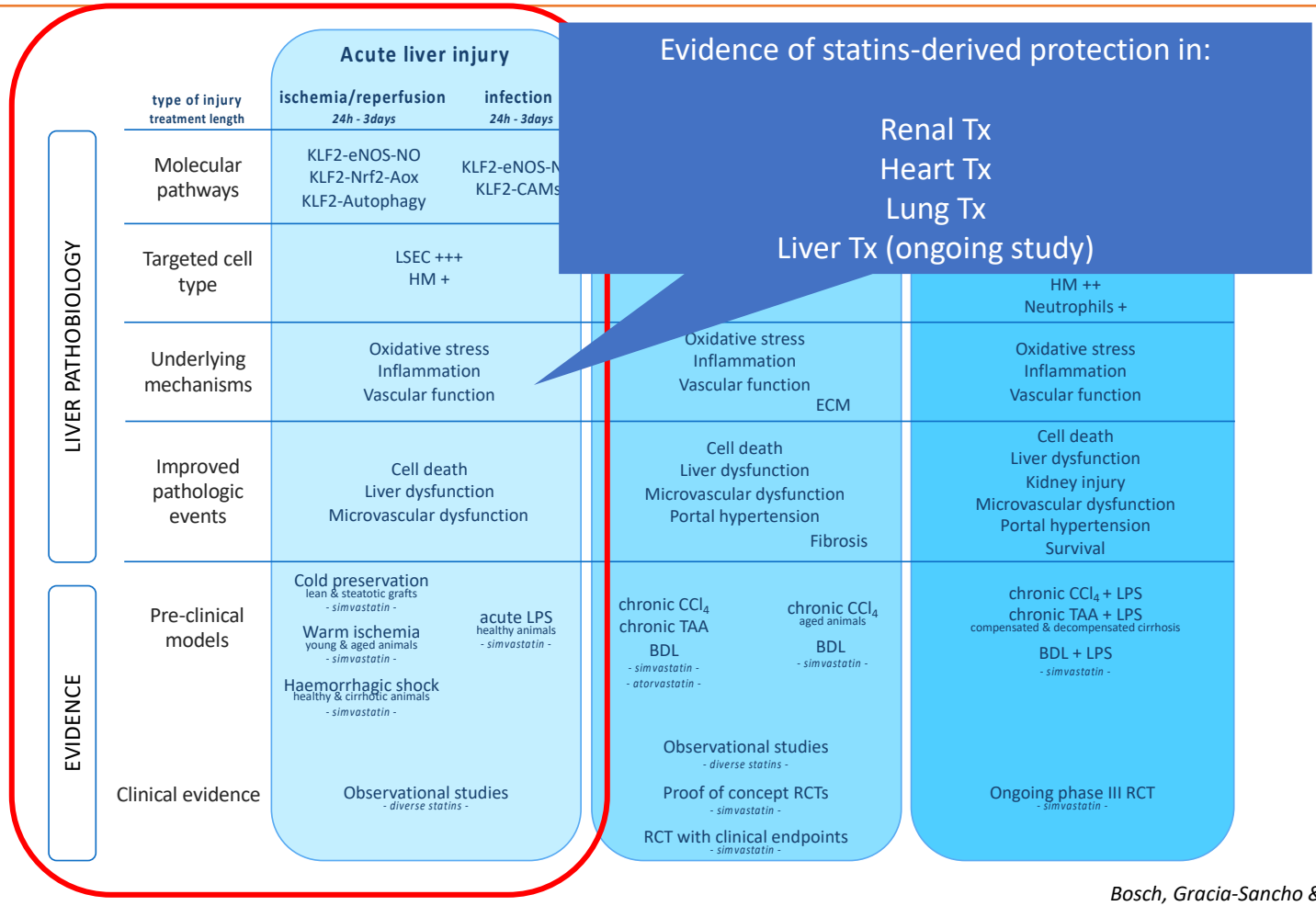
Bile



Ischemia & Reperfusion Injury – Effects in the sinusoid – Pharmacological strategy



Ischemia & Reperfusion Injury – Effects in the sinusoid – Pharmacological strategy



Bosch, Gracia-Sancho & Abraldes, Gut 2020

Ischemia & Reperfusion Injury

Ischemia

Biomechanical injury

Hypoxia injury

Shear stress → KLF2 → eNOS, TM, Nrf2

O_2 → ATP → Lactate

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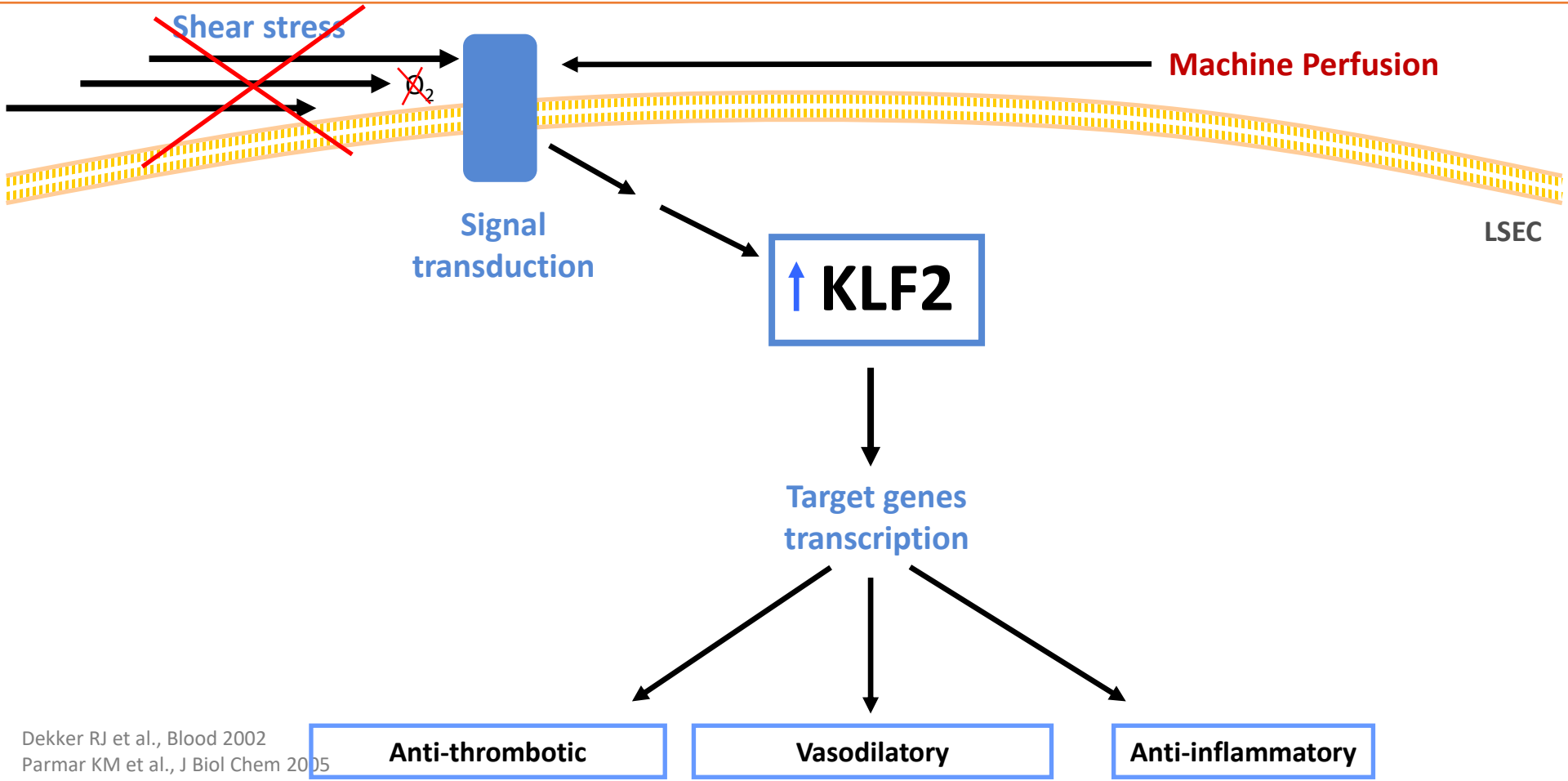
O_2 → ROS → Cell death

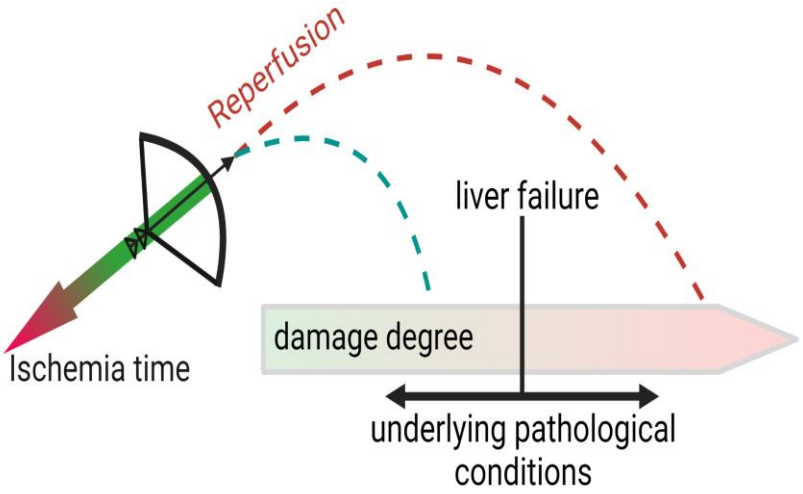
Peralta & Gracia-Sancho, Journal of Hepatology 2013

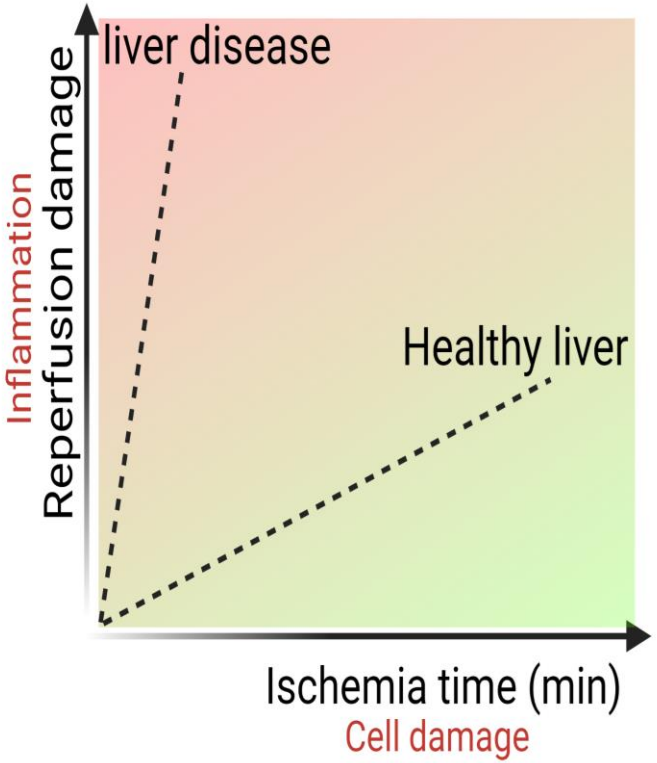
Ischemia & Reperfusion Injury – Effects in the sinusoid



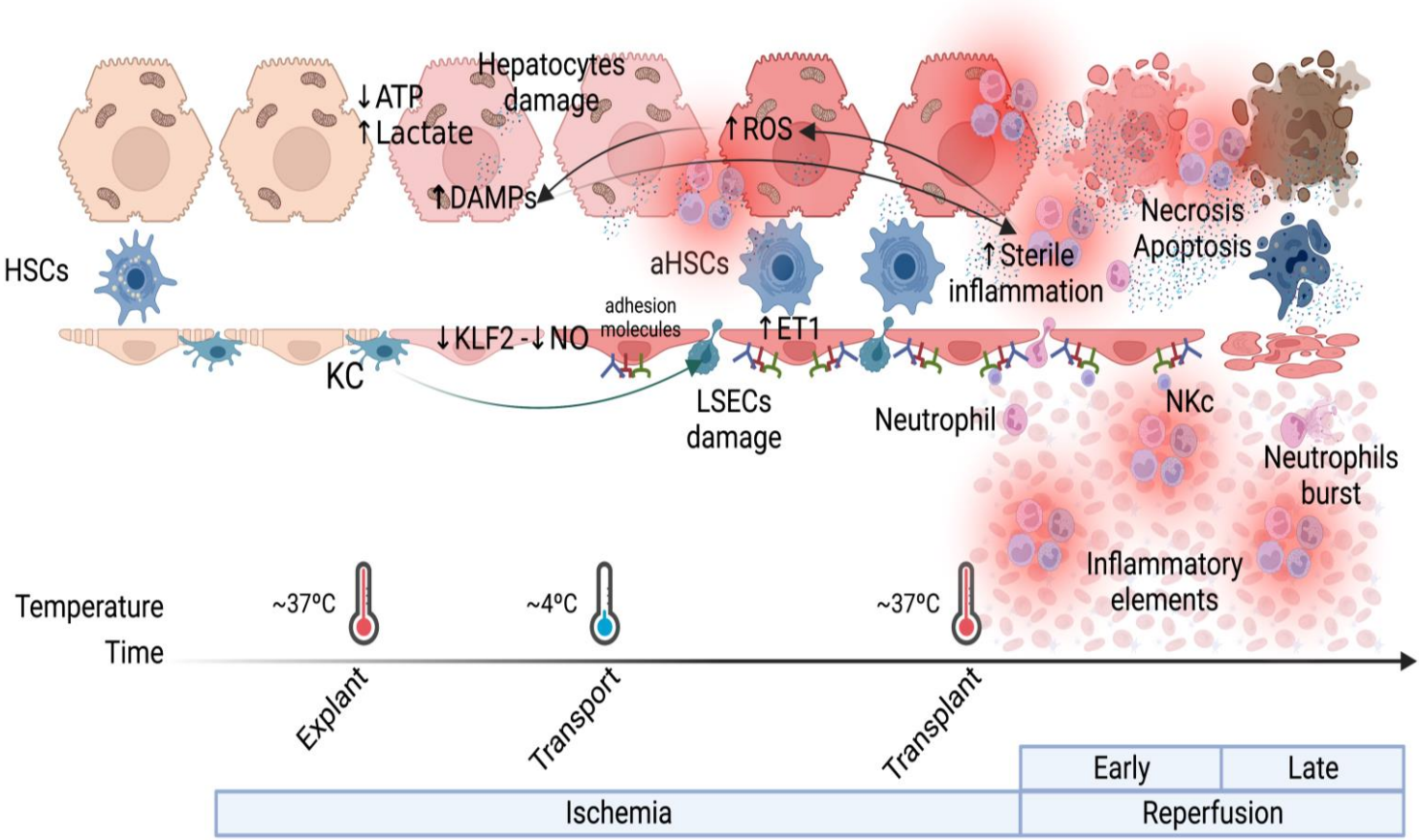
Dekker RJ et al., Blood 2002
Parmar KM et al., J Biol Chem 2005
Gracia-Sancho J et al., Gut 2011

Take home messages (I)

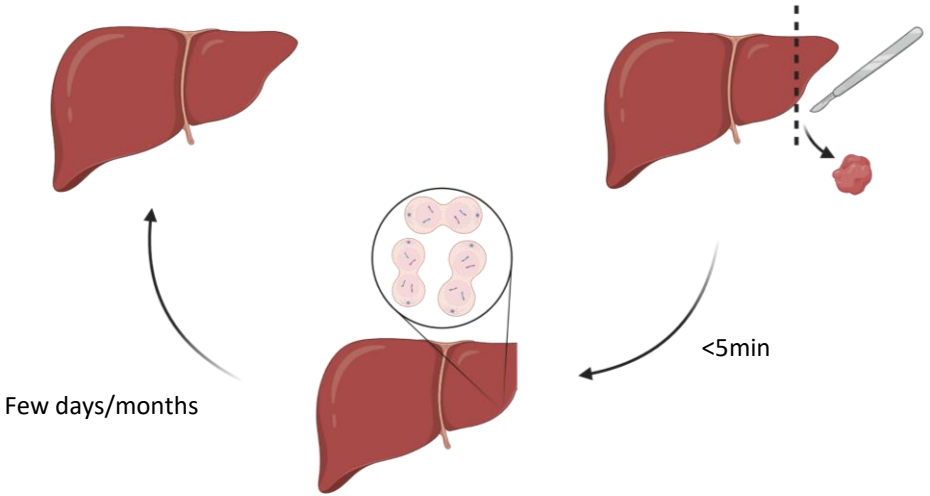




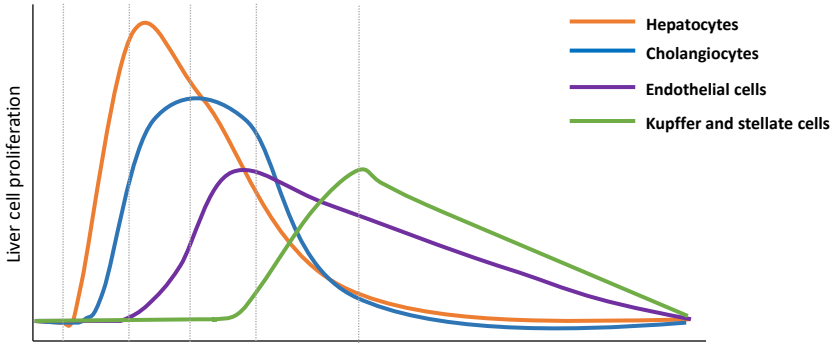
Take home messages (II)

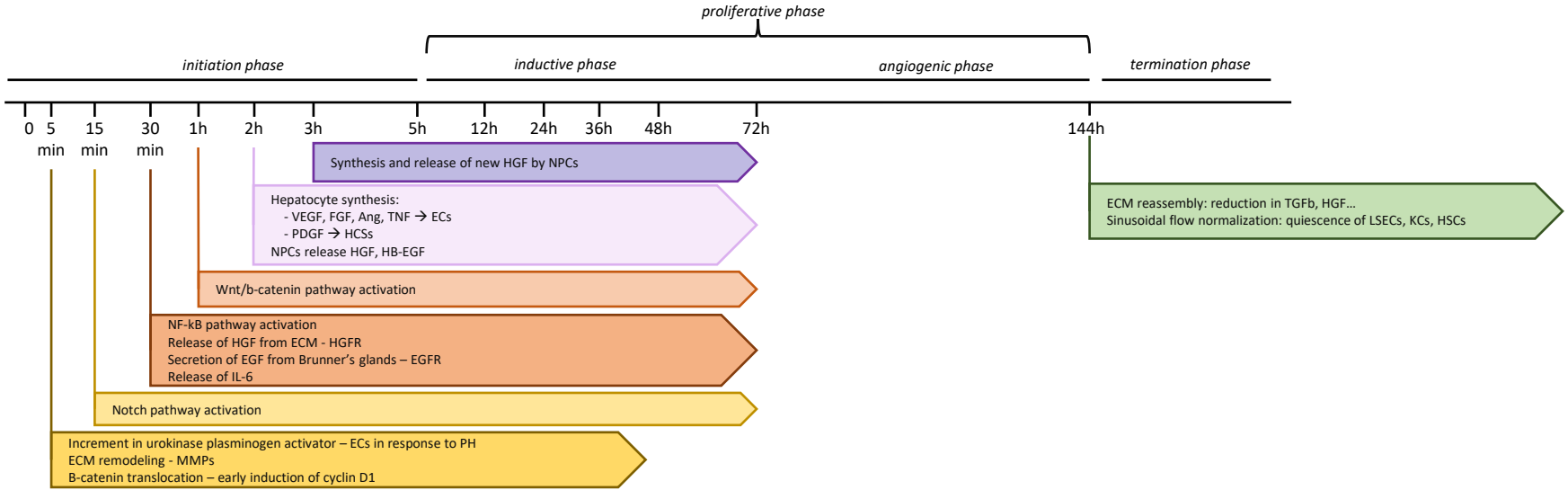


Liver regeneration

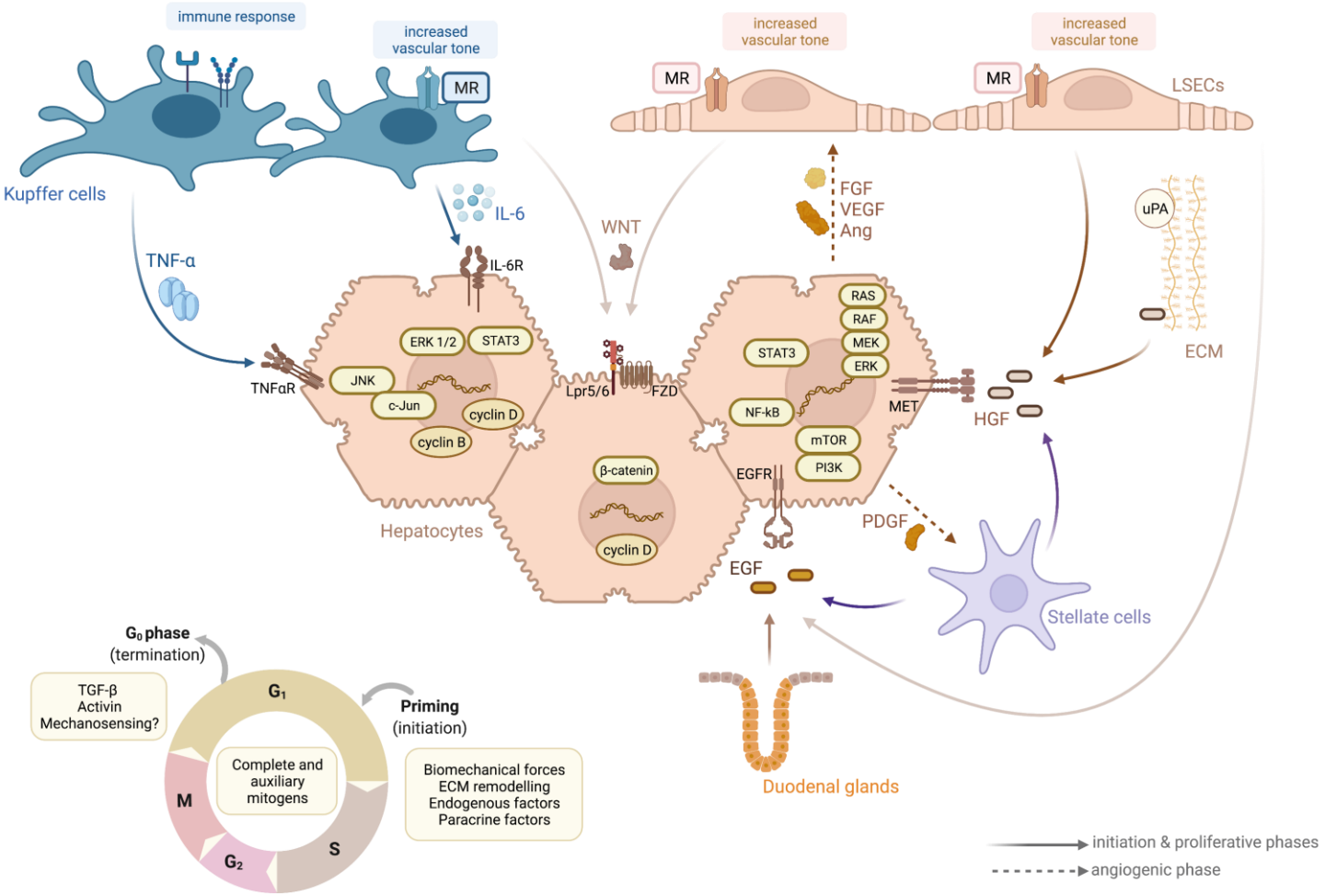


Liver regeneration phases





Liver regeneration – molecular pathways



Liver regeneration – take home messages

- The liver is the unique visceral organ able to regenerate (hepatocytes increase in size and number)

- Extremely well defined process, involving all liver cells and ECM

- After few days – months of PHx the liver recovers its original size (but not anatomical structure)

- Liver regeneration also takes place in response to liver injury

- Different factors may influence regenerative capacity (insults, immunosupression, steatosis, age…)

- Hepatic progenitor cells also participate in liver regenerative capacity (still not well understood)