



MÁSTER EN HEPATOLOGÍA

UAM
Universidad Autónoma
de Madrid

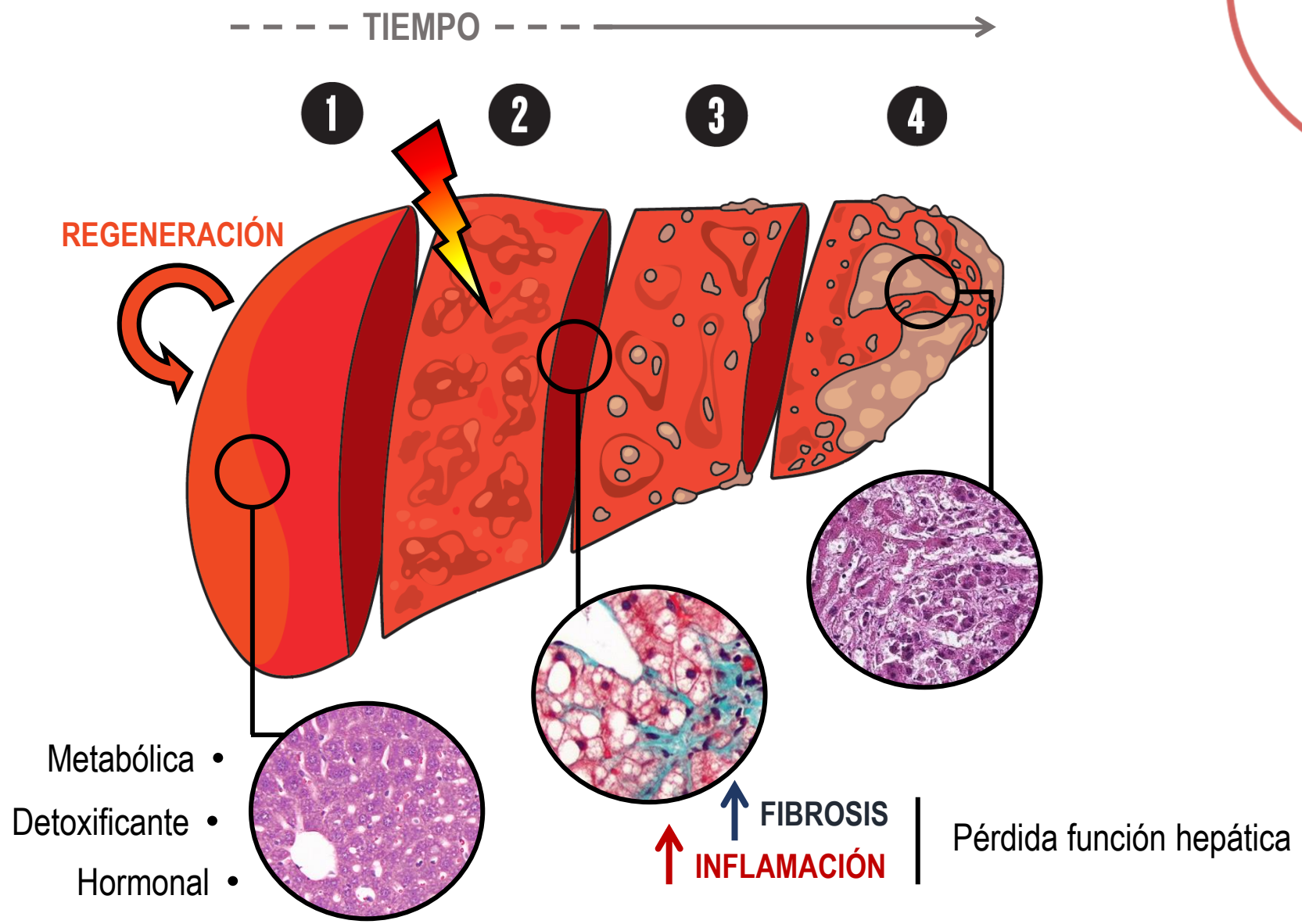
 Universidad
de Alcalá

**“Daño de la barrera intestinal en la cirrosis:
contribución a la inflamación sistémica y progresión”**

Rubén Francés

Universidad Miguel Hernández, IIS ISABIAL, Hospital General Alicante, CIBERehd

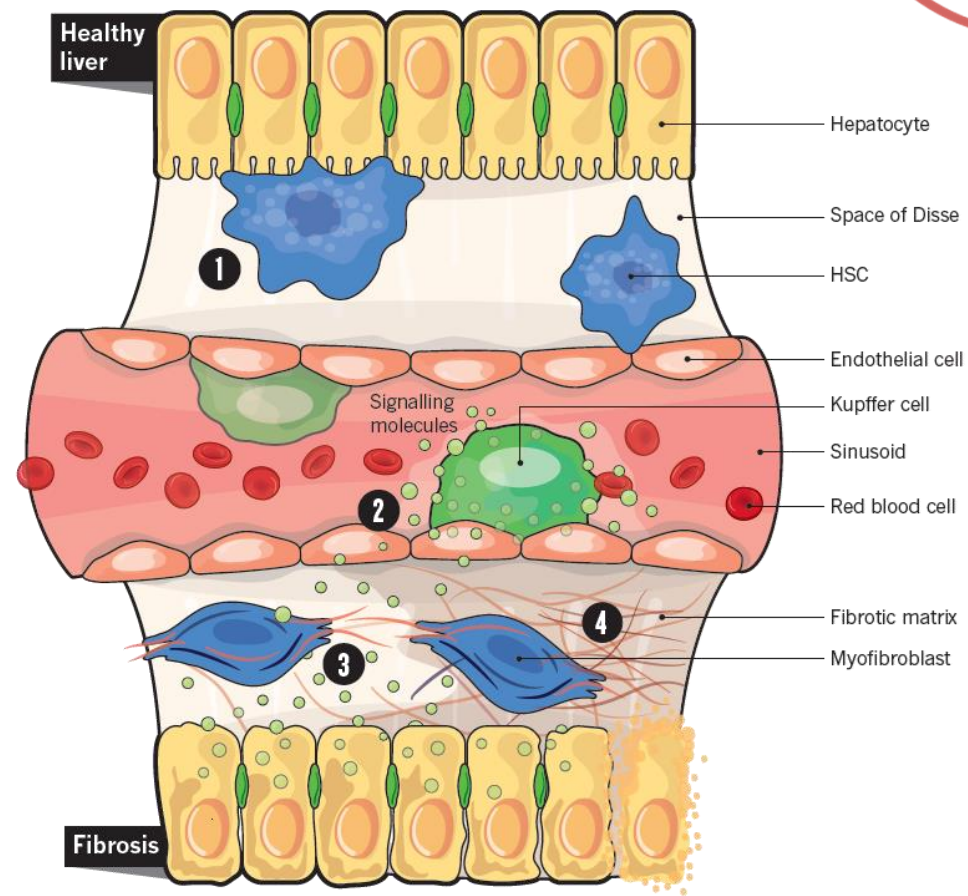
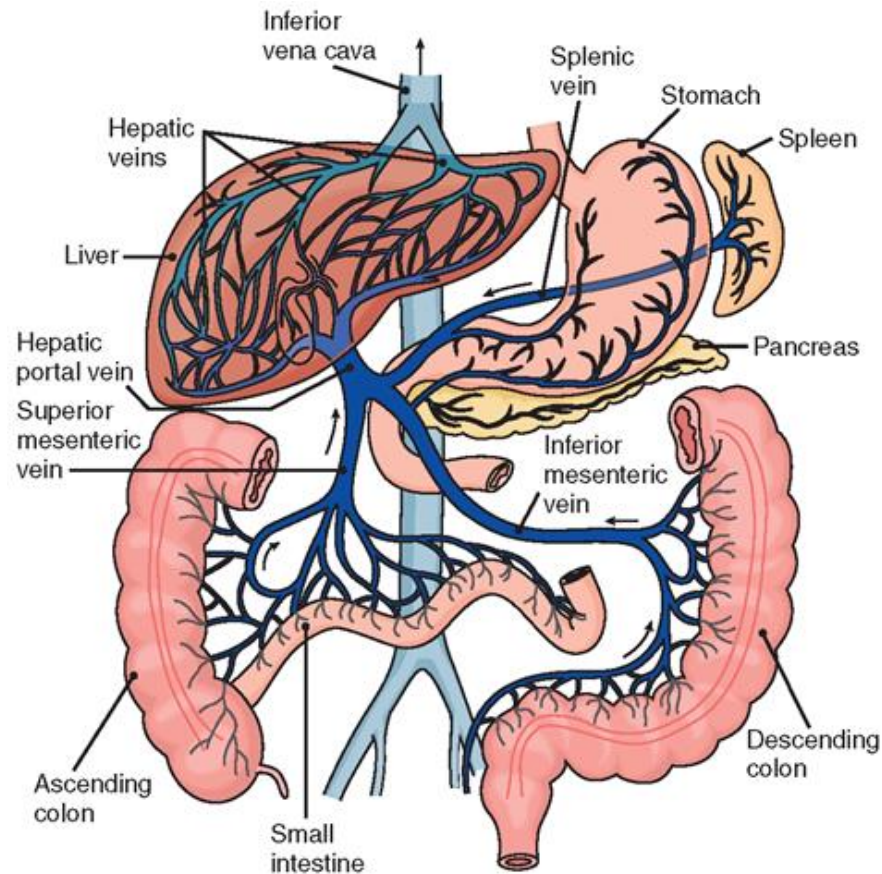
[@get_ruben](https://twitter.com/get_ruben)



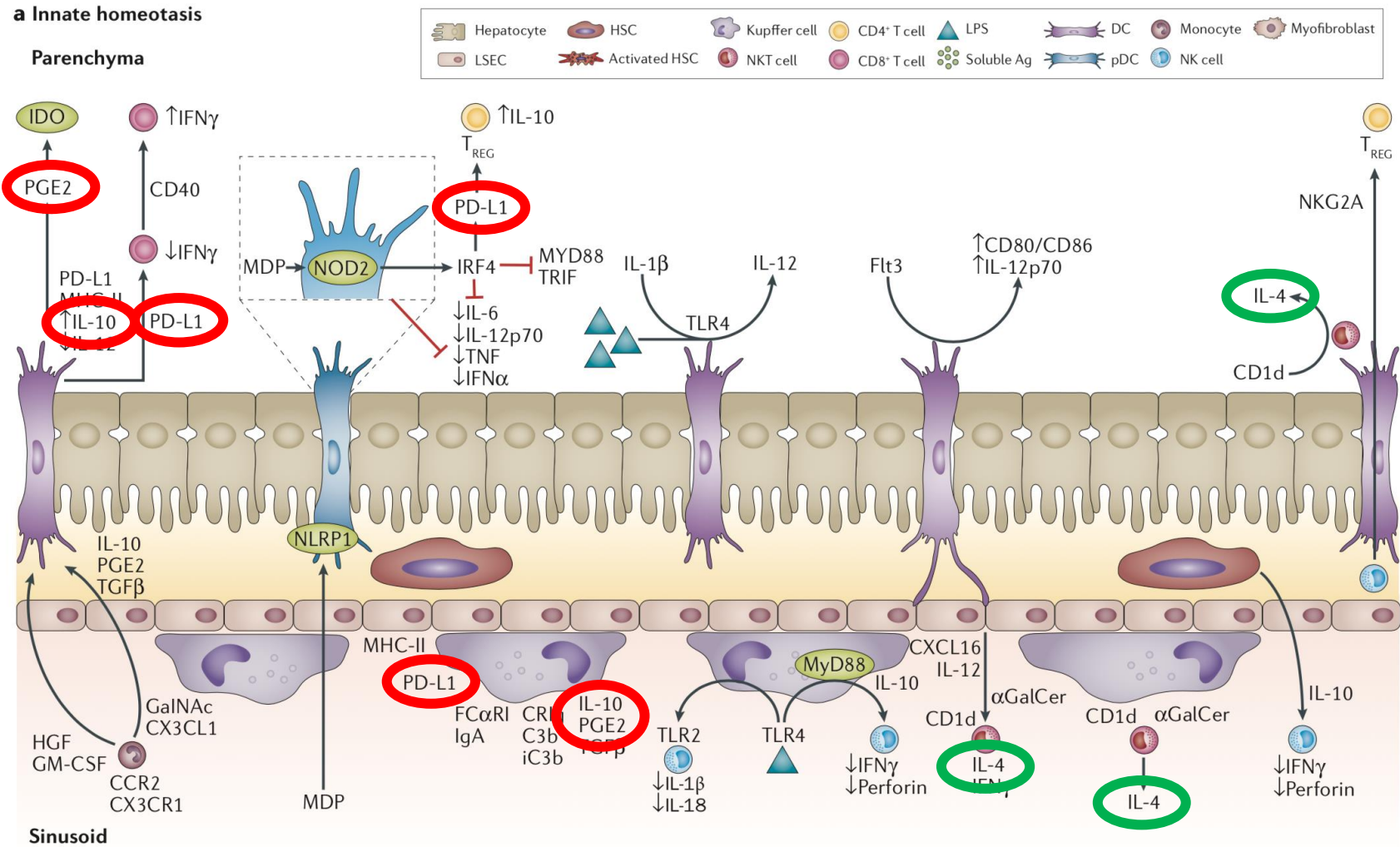
Índice

1. Función del hígado en el scouting de la sangre portal
2. Eje hígado – intestino
3. Composición de la barrera intestinal
4. Disbiosis intestinal en la cirrosis
5. Sistema Inmunitario y respuesta inflamatoria
6. Recuperación de la integridad de la barrera intestinal

1. Función de scouting de la sangre portal



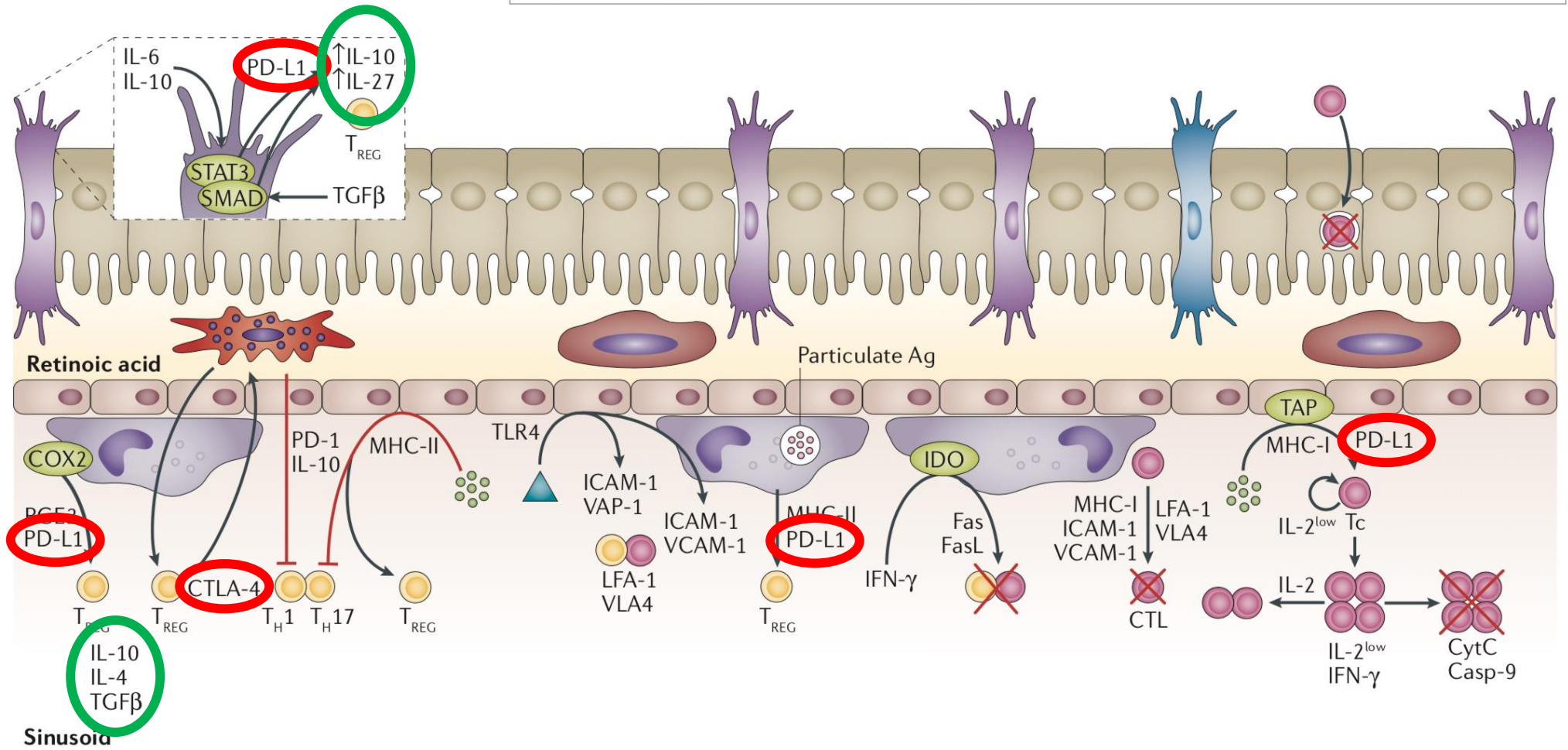
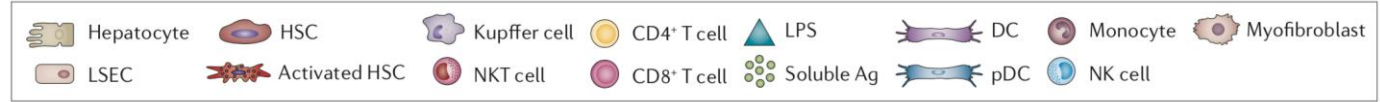
Equilibrio → Tolerancia



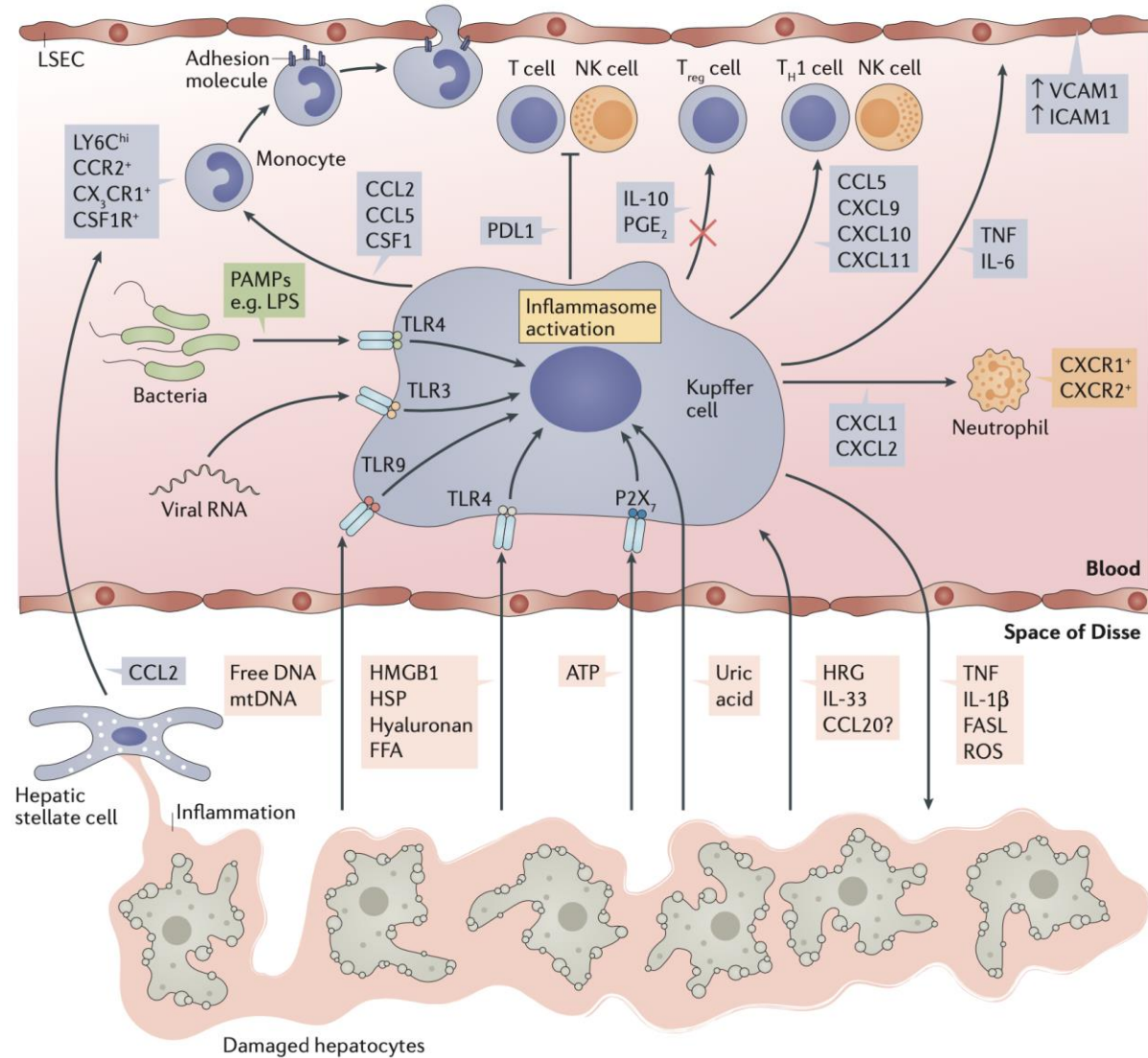
Equilibrio → Tolerancia

b Adaptive homeostasis

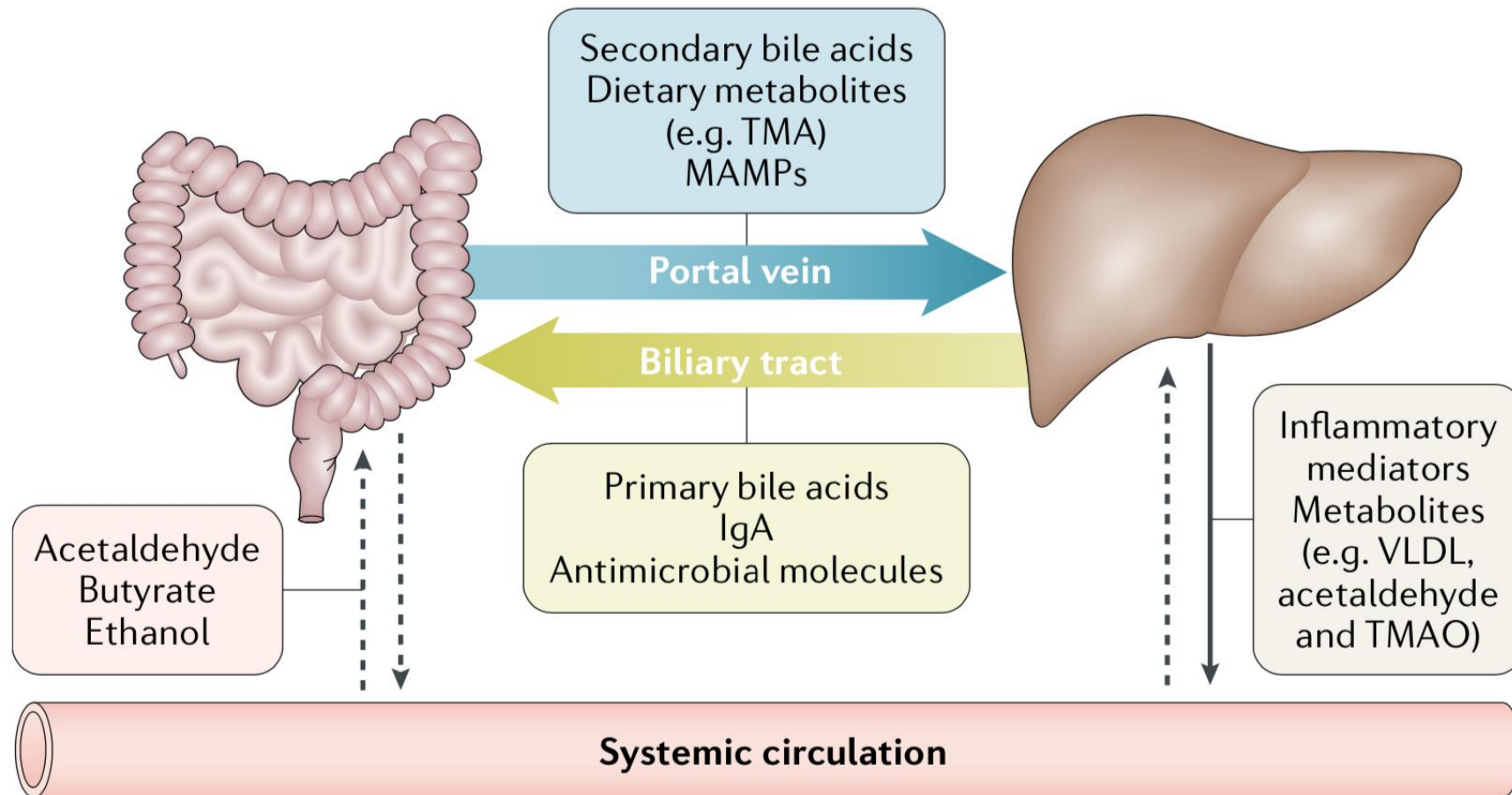
Parenchyma



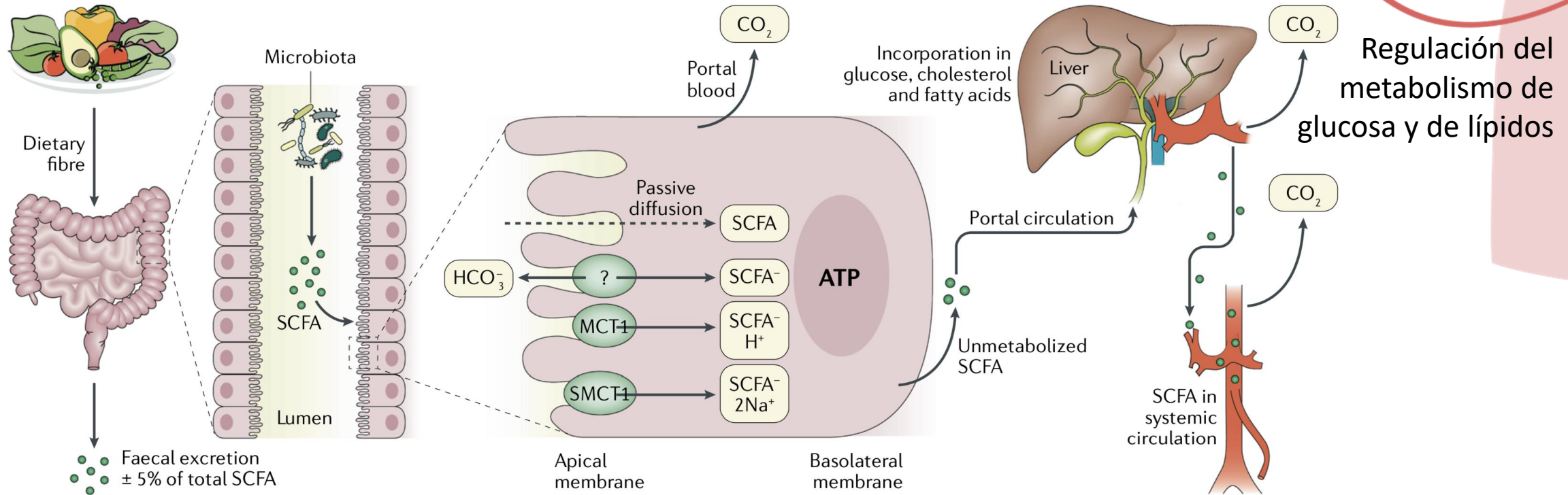
Desequilibrio → Inflamación



2. Eje hígado - intestino



Ácidos grasos de cadena corta

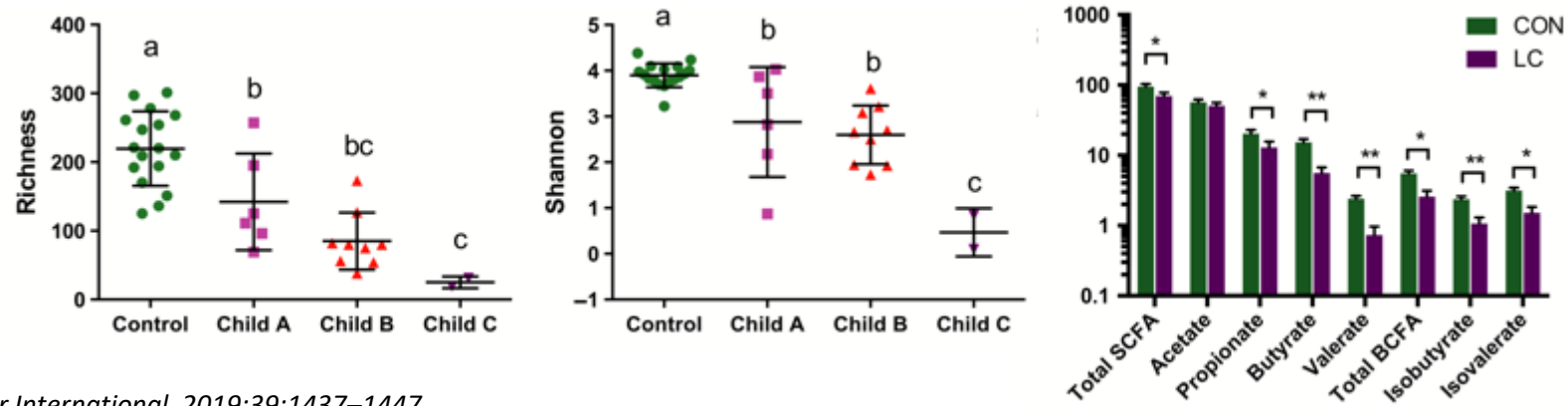


Nat Rev Gastroenterol Hepatol. 2019; 16: 461-478

Regulación de la presión sanguínea
Regulación de la respuesta inflamatoria

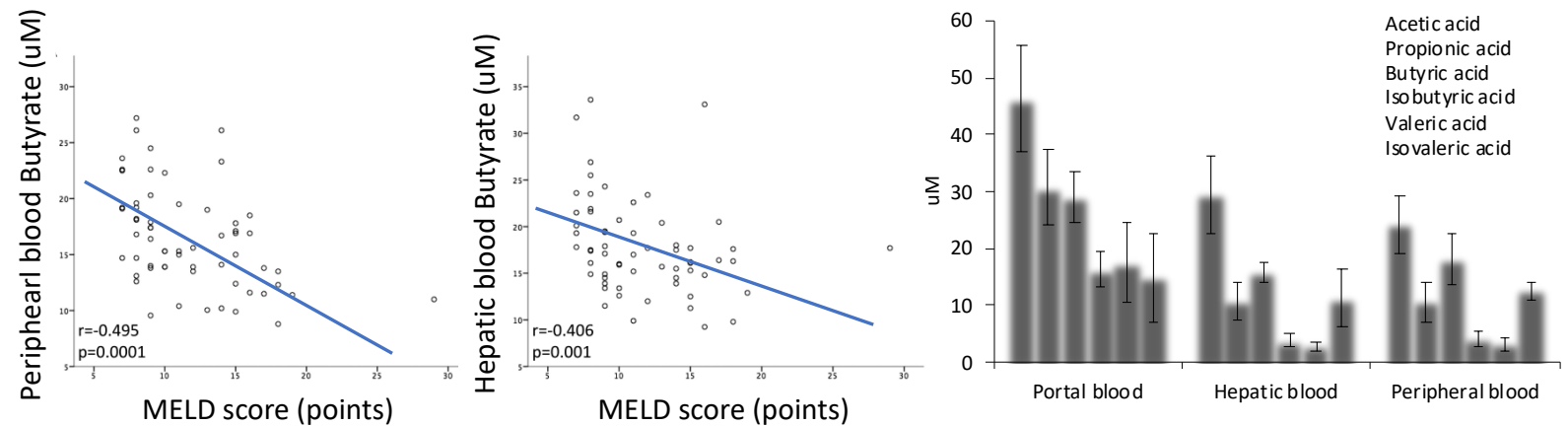
Ácidos grasos de cadena corta

Reduced capacity of fecal microbiota to produce SCFAs in cirrhosis



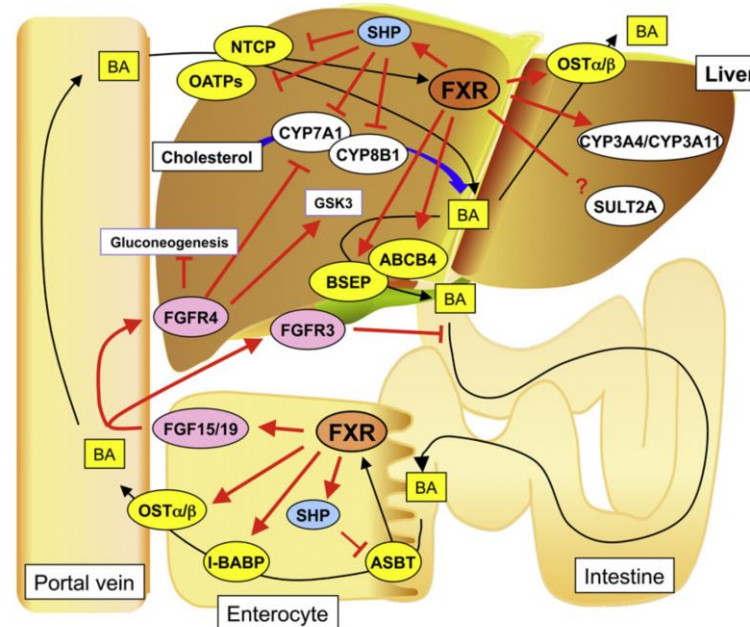
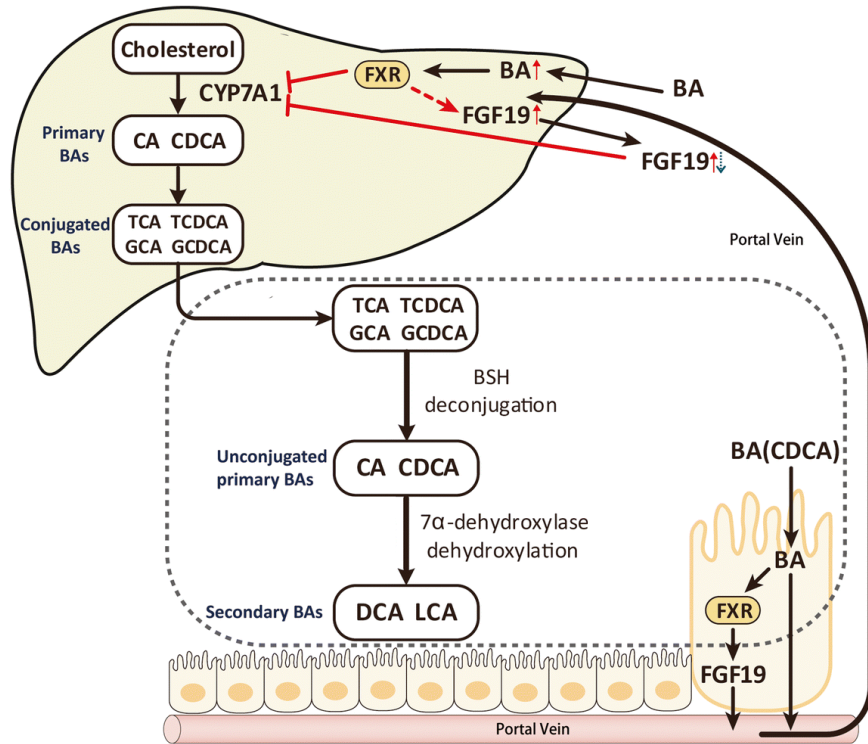
Liver International. 2019;39:1437–1447

Reduced SCFAs in cirrhotic patients is associated with more advanced liver disease



FASEB J. 2019; 33: 11595–11605

Ácidos biliares



moco
péptidos antimicrobianos
Integridad barrera

Cirrosis

Hígado: ↓ flujo de ácidos biliares
Intestino: ↓ ácidos biliares primarios
↑ ácidos biliares secundarios
↓ señalización por FXR

Clinical Reviews in Allergy & Immunology 58 (2020) 25–38

Molecular and Cellular Endocrinology 368 (2013) 17–29

Ácidos biliares y FXR en cirrosis

Median values in $\mu\text{g}/100 \text{ mg dry stool}$	Controls (n = 14)	Early cirrhosis (n = 23)	Advanced cirrhosis (n = 24)
Total bile acids	206.5	156.1	39.0*
Primary			
CA (% in whom detected)	36.0 (14)	64.6 (22)	16.0 (71)**†
CDCA (% in whom detected)	3.1 (51)	10.1 (57)	12.4 (83)**†
Secondary			
LCA (% in whom detected)	83.2 (100)	63.8 (87)	12.7 (46)**†
DCA (% in whom detected)	110.7 (100)	35.8 (83)	8.3 (50)**†
Secondary/primary ratios			
LCA/CDCA	39.7	7.6	2.2*
DCA/CA	6.3	3.2	0.9*
LCA + DCA/CDCA + CA	79.8	9.6	0.004*

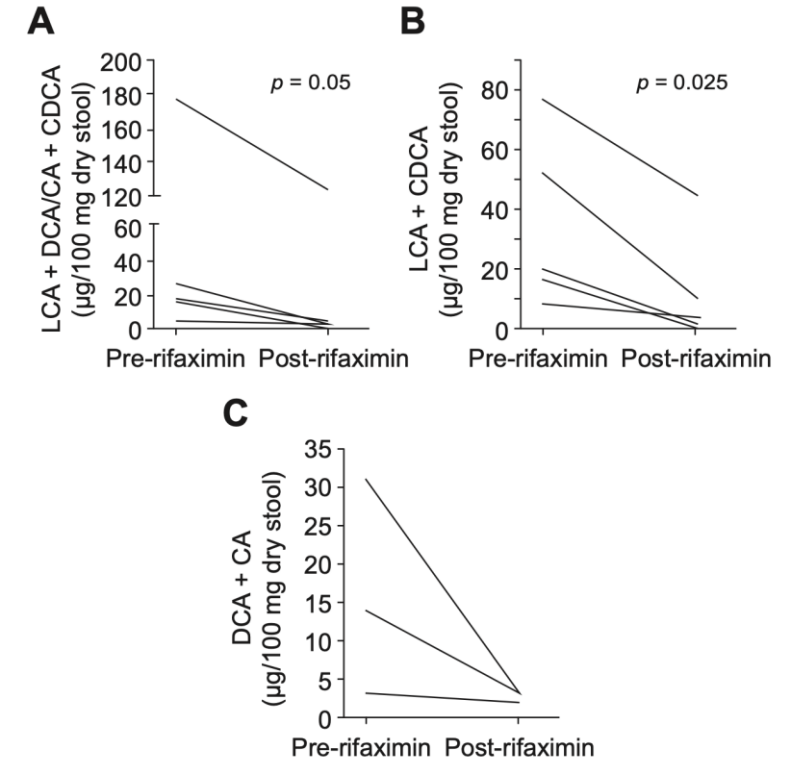
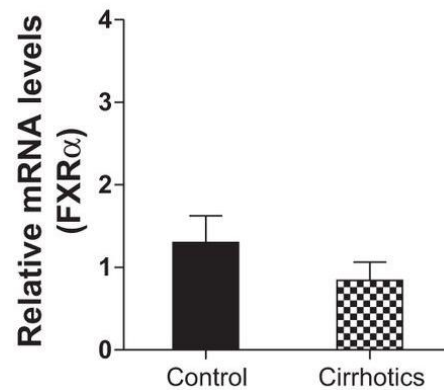
* $p < 0.05$ between groups on Kruskal–Wallis tests on median concentrations.

† $p < 0.05$ between groups on percent in whom the respective bile acids were detected.

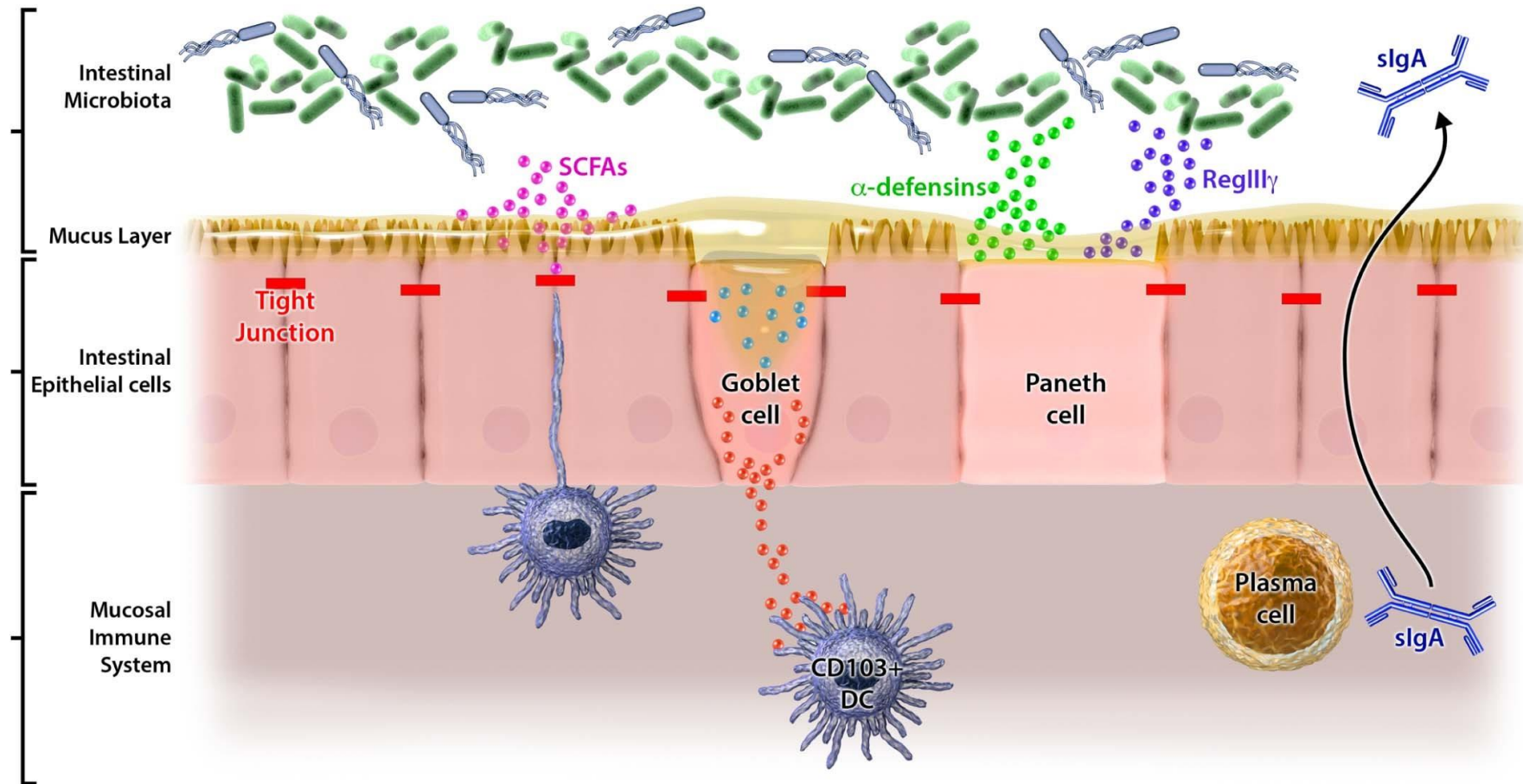
CA, cholic acid; CDCA, chenodeoxycholic acid; LCA, lithocholic acid; DCA, deoxycholic acid.

Journal of Hepatology 2013; 58: 949–955

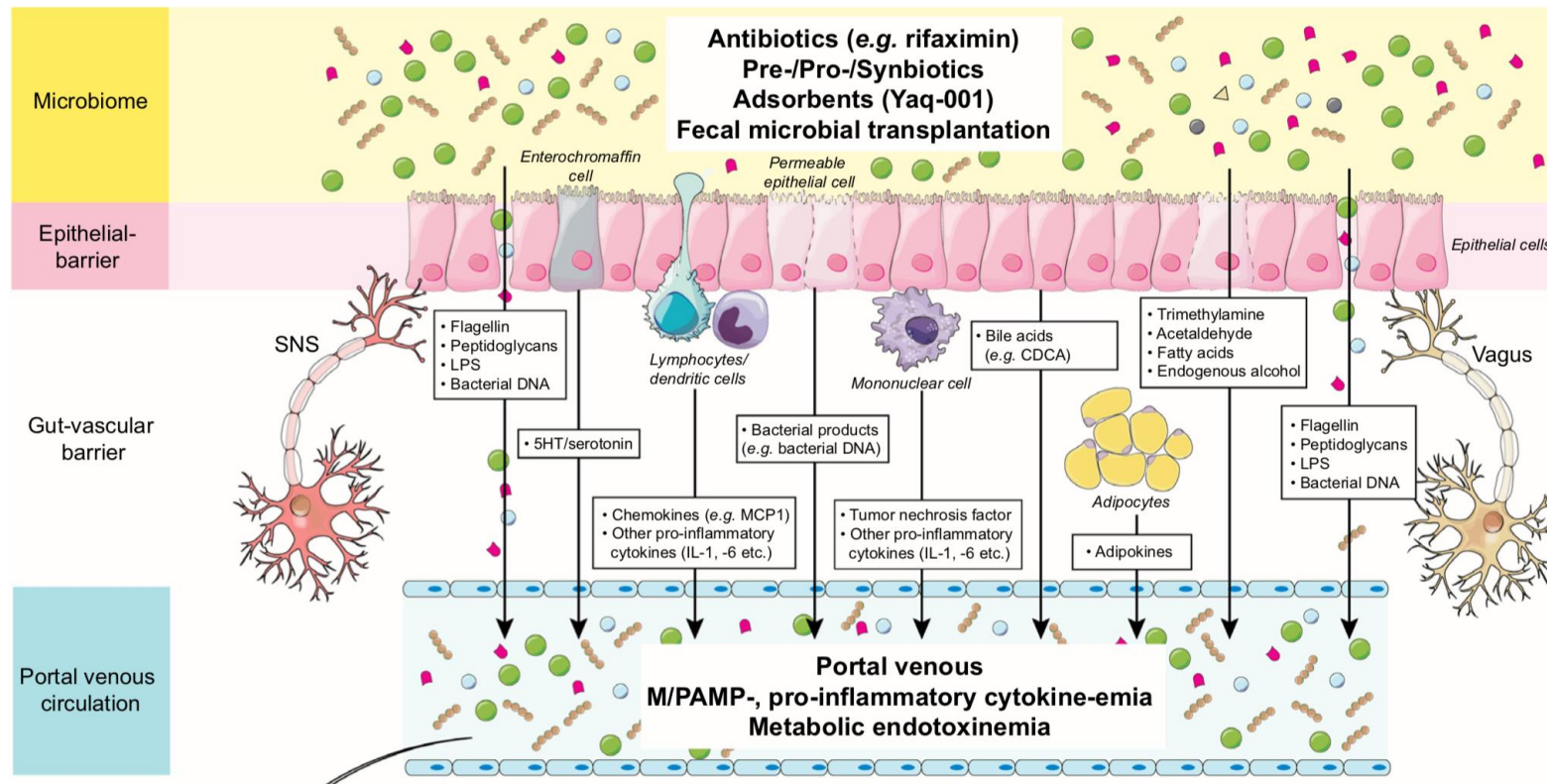
Hepatology 2003; 37:551-557



3. Composición de la barrera intestinal



Composición de la barrera intestinal



J Hepatol. 2017 Nov;67(5):1084-1103

- Cirrhosis impairs the muco-epithelial barrier promoting pathological BT via the portal-venous circulation.

- This barrier appears to be FXR-modulated, as FXR-agonists reduce portal-venous BT.

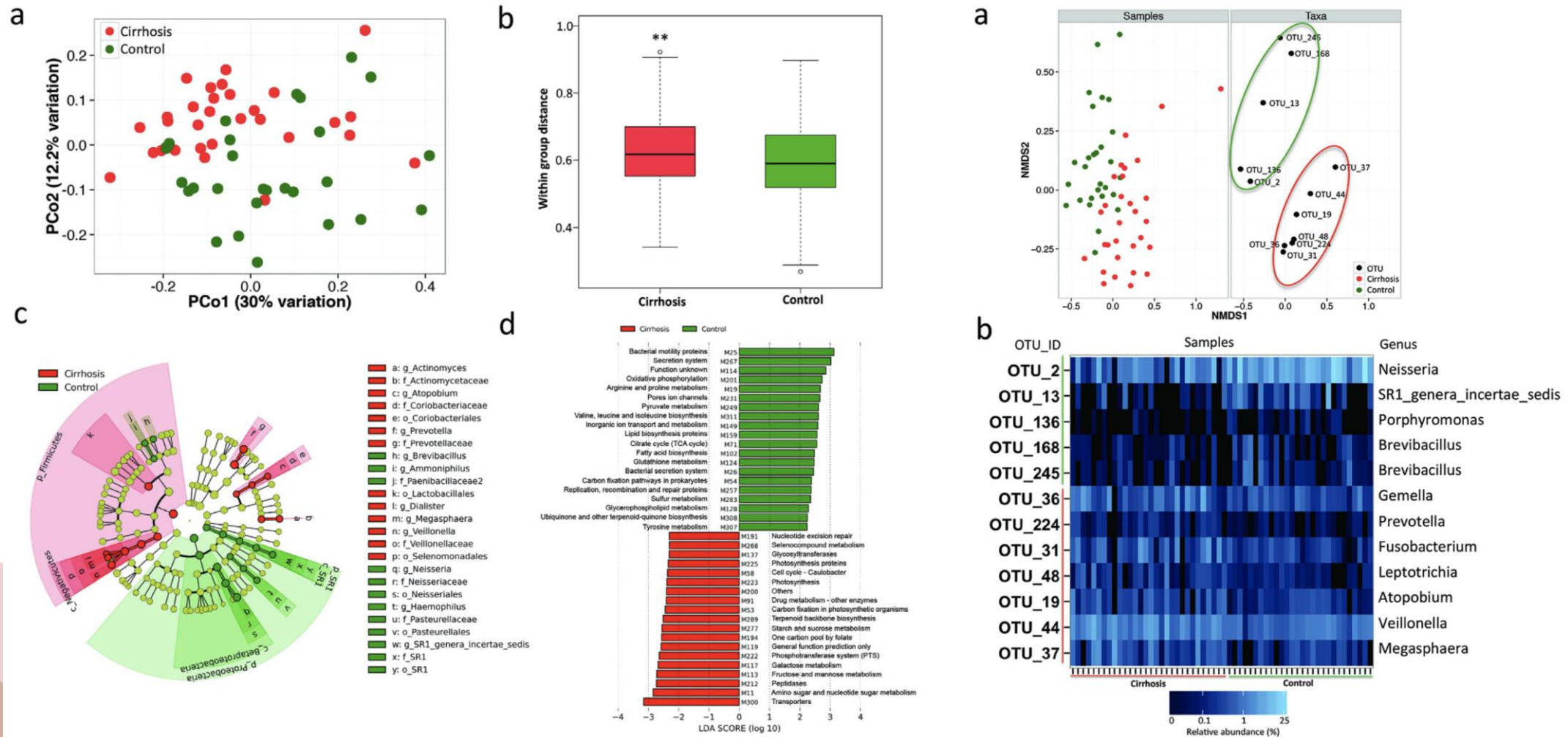
J Hepatol. 2019 Jul 8. pii: S0168-8278(19)30389-7

- During diet-induced dysbiosis the GVB is disrupted.

- OCA can control GVB disruption in preventive and therapeutic ways.

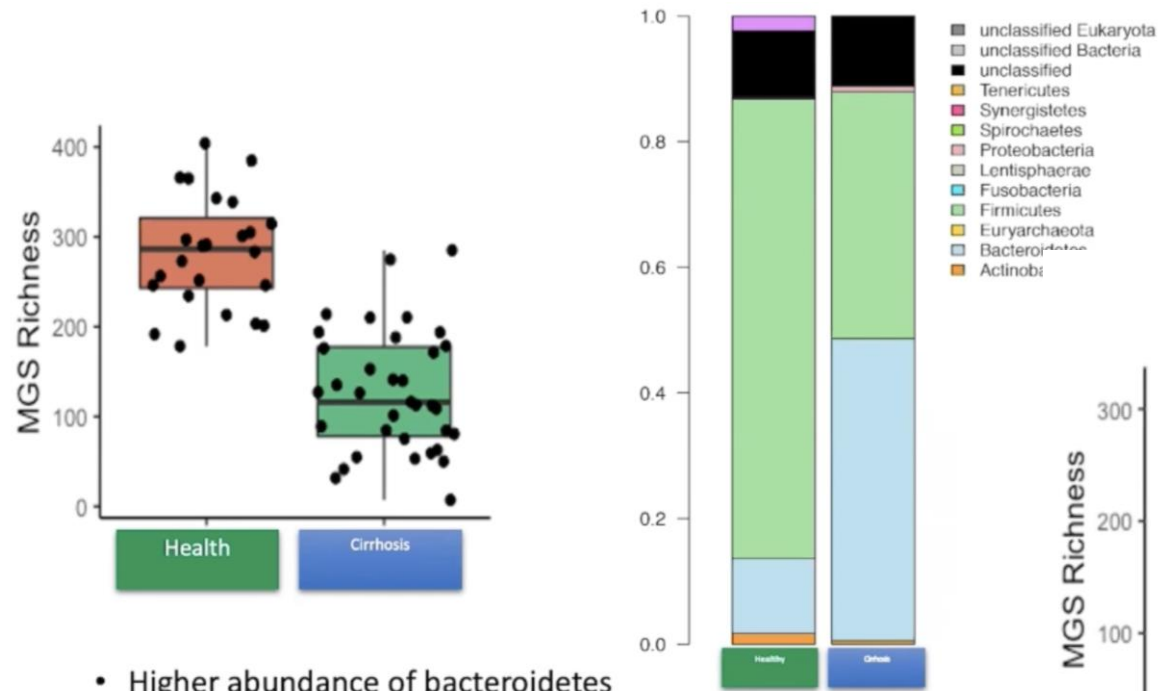
J Hepatol. 2019 Aug 13. pii: S0168-8278(19)30471-4

4. Disbiosis intestinal durante la cirrosis



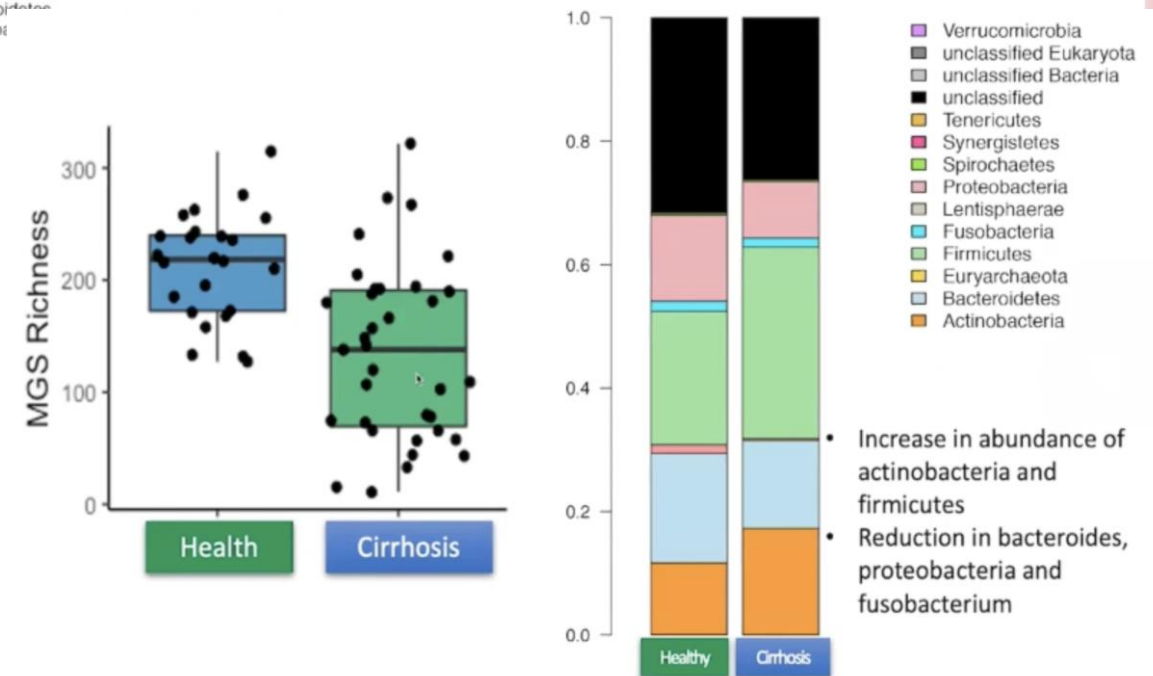
Disbiosis intestinal durante la cirrosis

Reduced gut microbial diversity



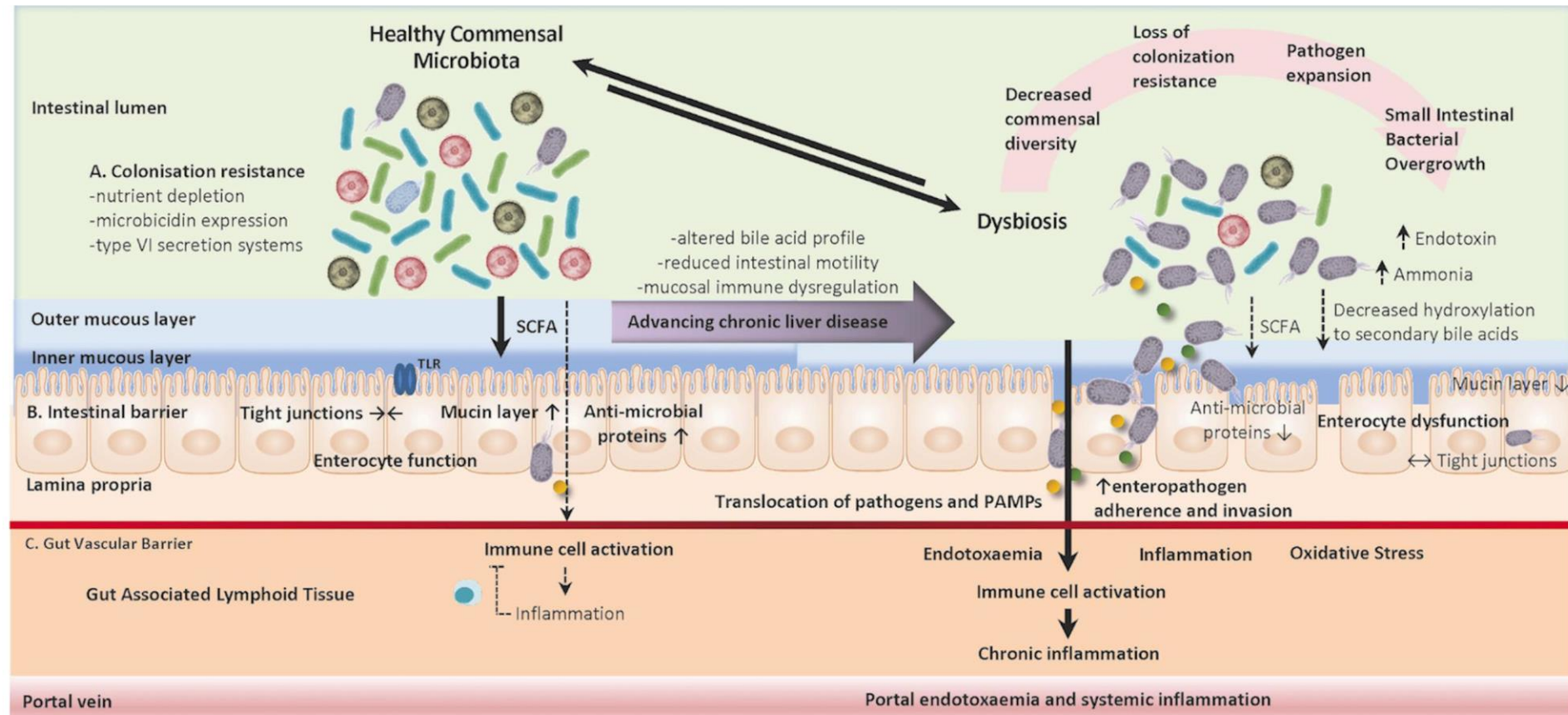
- Higher abundance of bacteroidetes
- Reduction in actinobacteria and firmicutes in cirrhosis

Reduced saliva microbial diversity

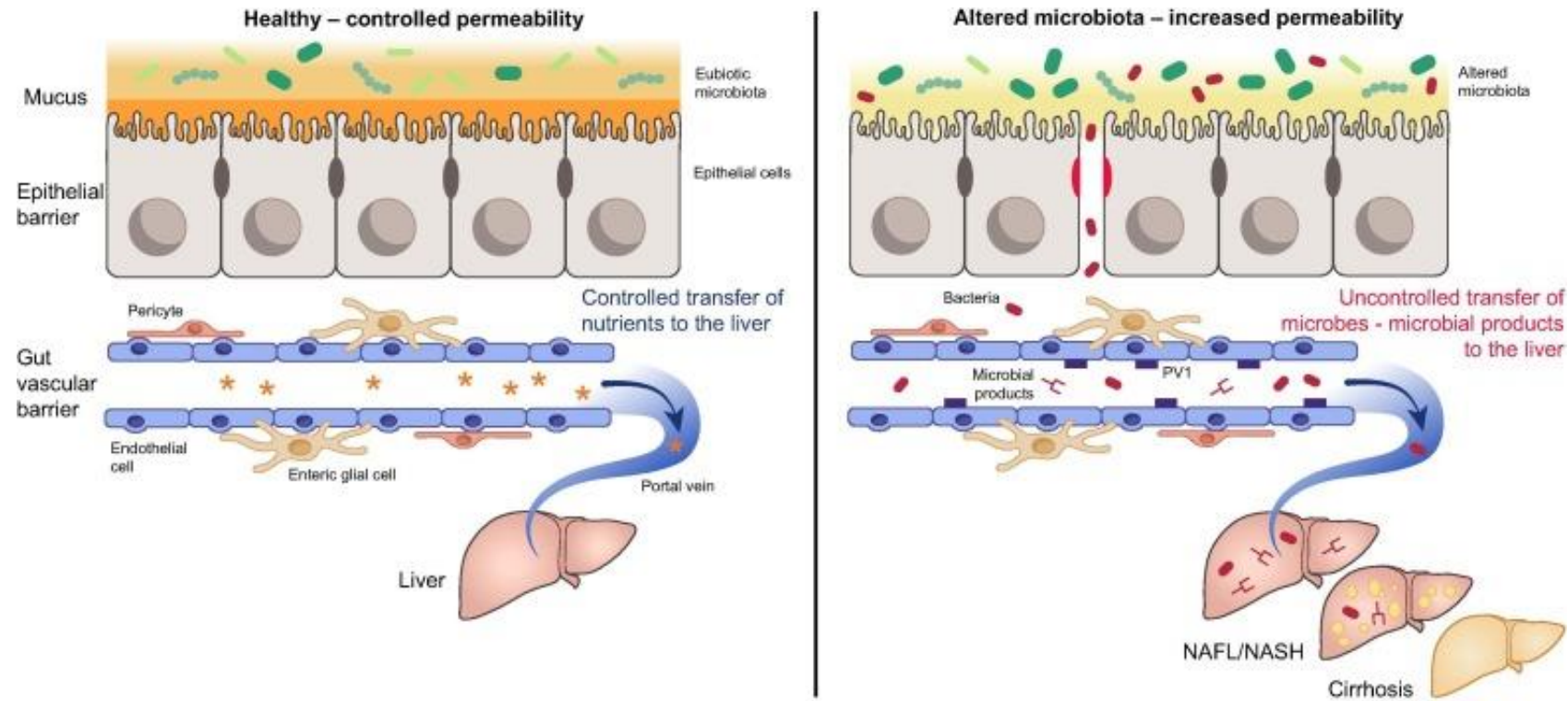


- Increase in abundance of actinobacteria and firmicutes
- Reduction in bacteroidetes, proteobacteria and fusobacterium

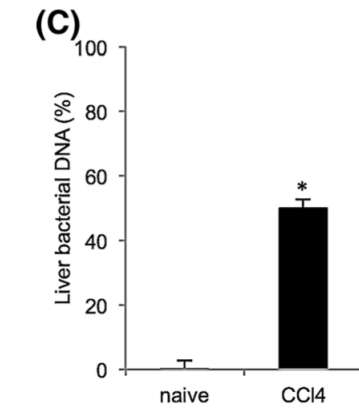
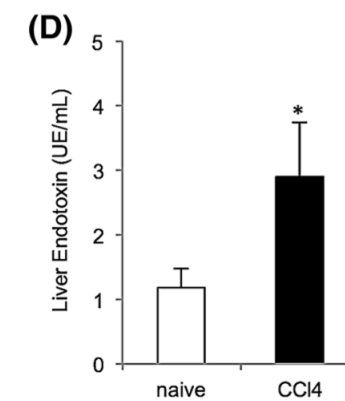
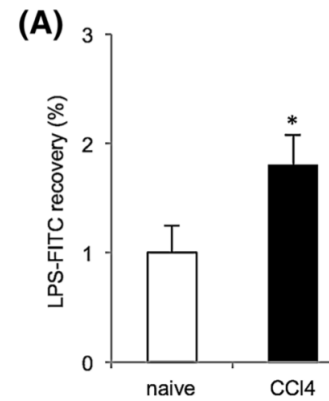
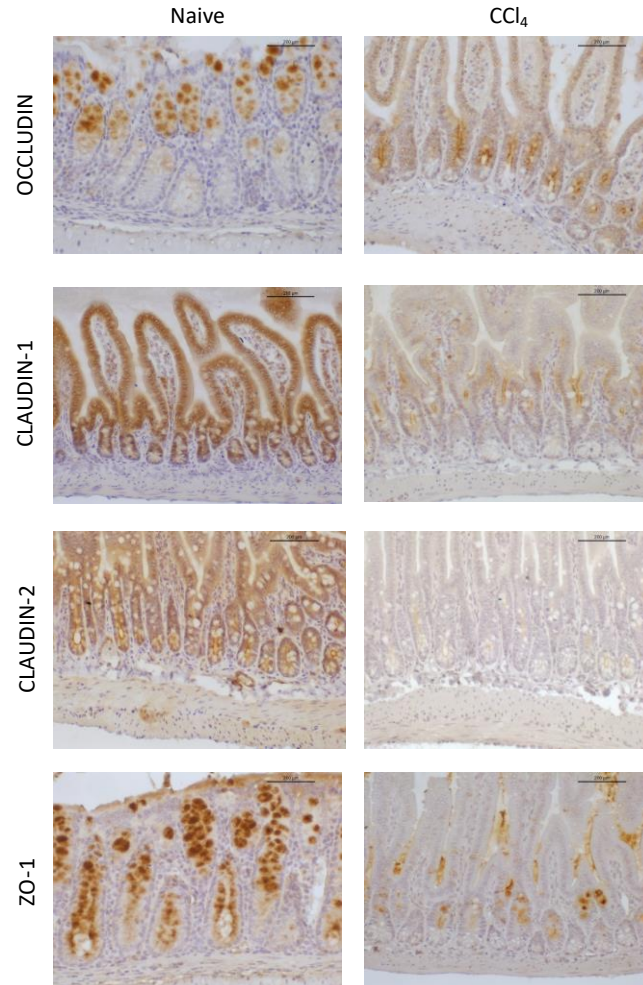
Disbiosis intestinal durante la cirrosis



Disbiosis intestinal en la cirrosis



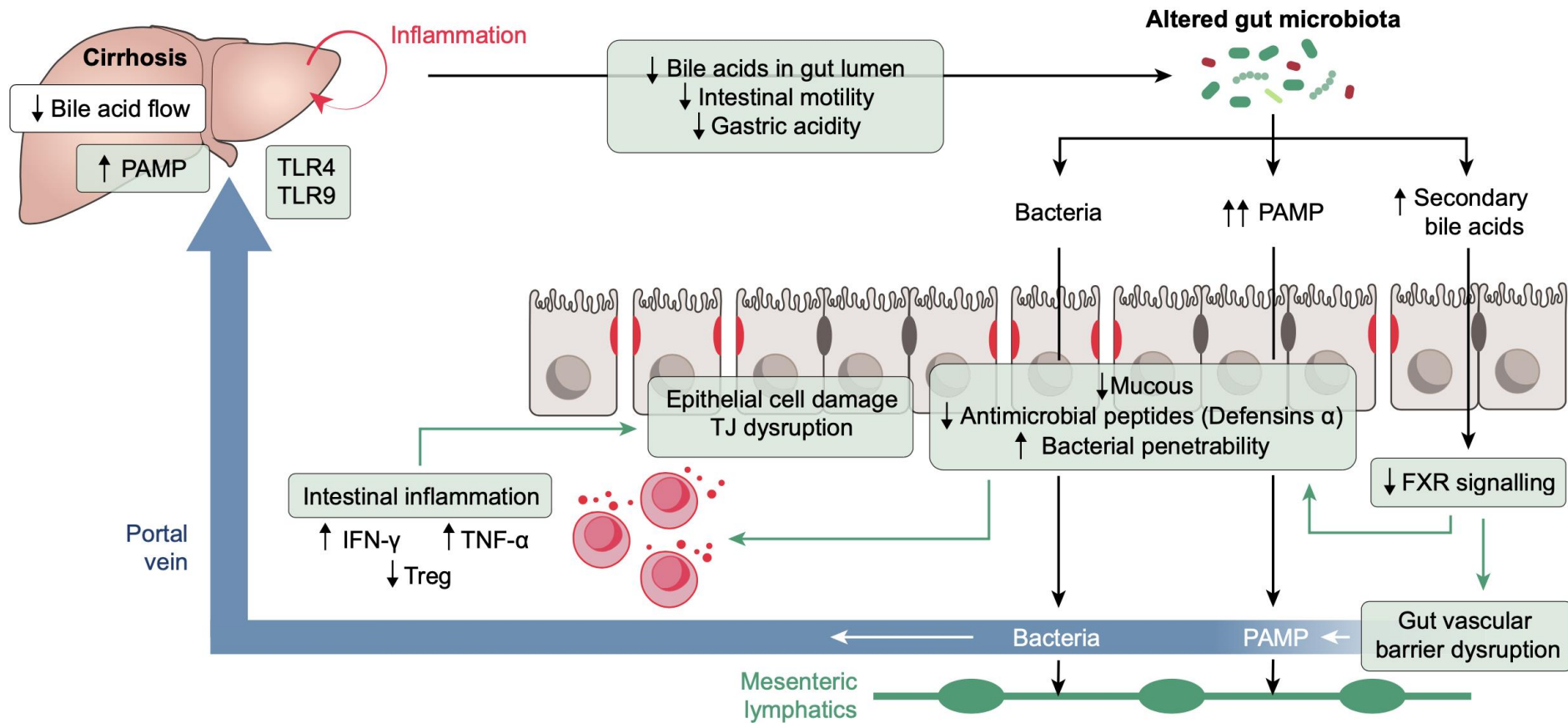
Integridad de la barrera intestinal



Eur J Nutr. 2016;55:197-206

J Hepatol. 2019 Dec;71(6):1126-1140

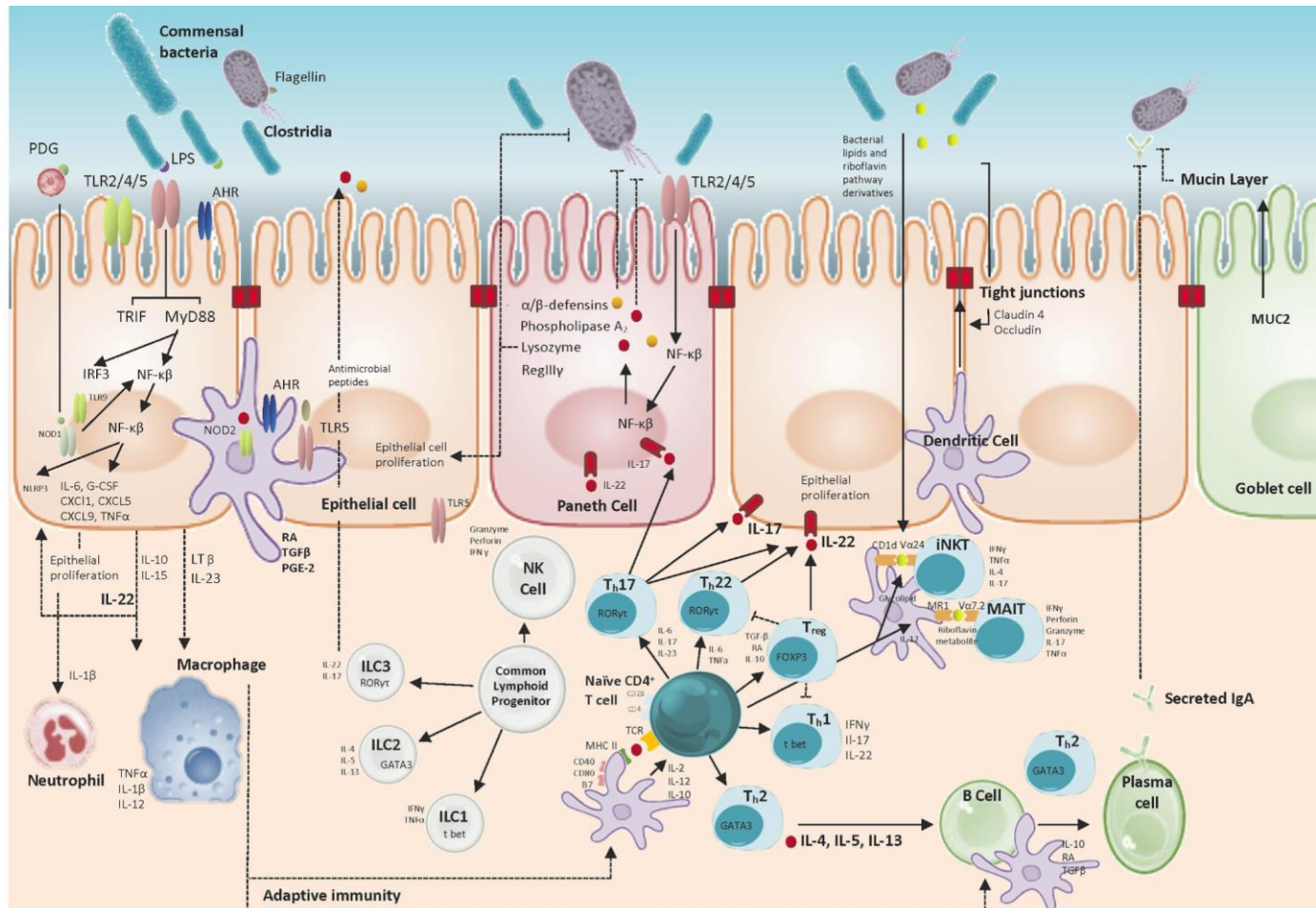
Integridad de la barrera en la cirrosis



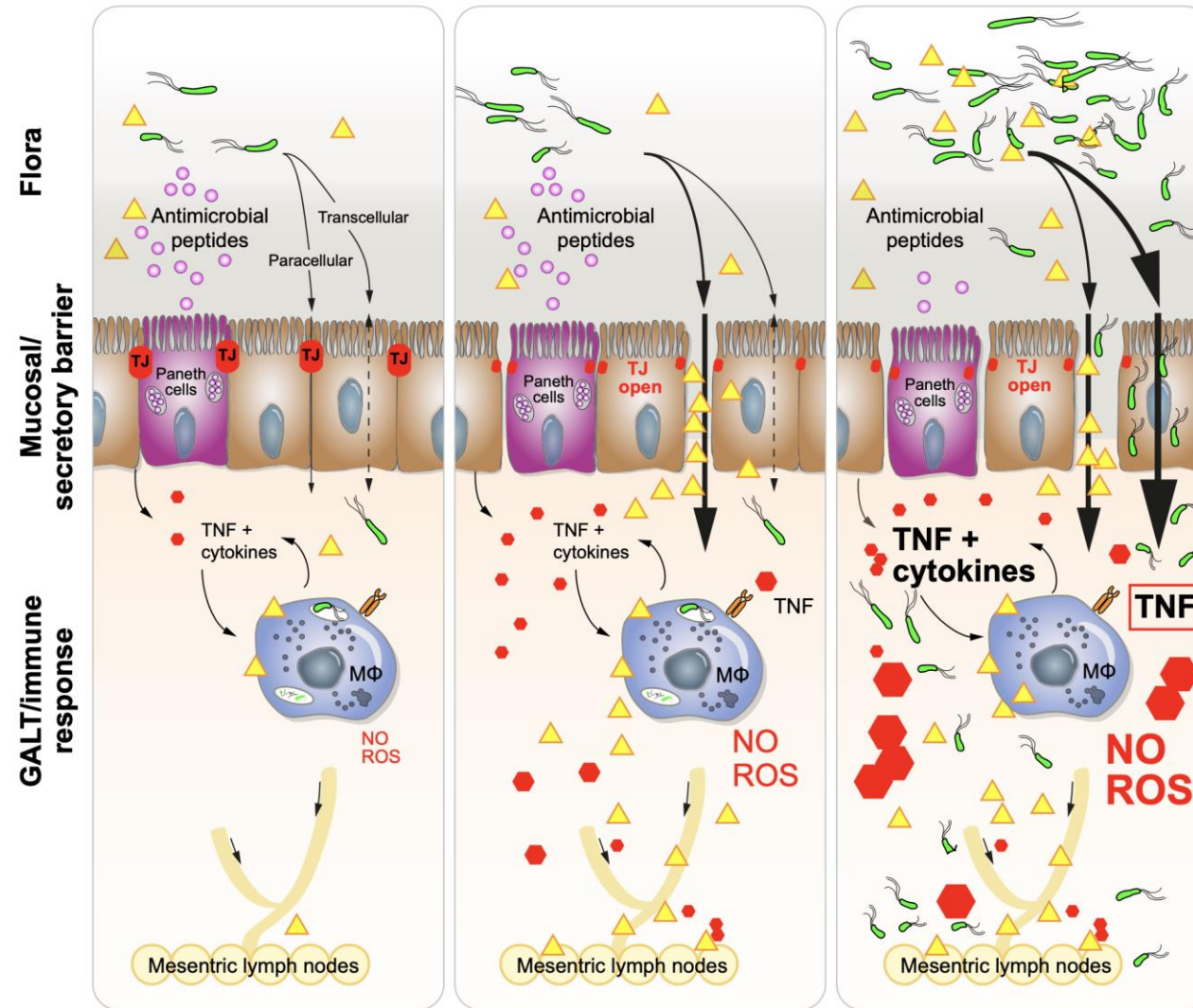
Disfunción de la barrera en ALD y NAFLD

Component	Alcohol-related liver disease	Non-alcoholic fatty liver disease	Cirrhosis
Gut microbiome	Proteobacteria↑: Enterobacteriaceae↑* Bacteroidetes↓: Bacteroidaceae ↓ Firmicutes↓: Streptococaceae↑, Lactobacillaceae↓, Lachnospiraceae↓, Veillococcaceae↑ Candida↑	Proteobacteria↑: Enterobacteriaceae↑ Bacteroidetes↑: Prevotellaceae↑, Rikenellaceae ↑ Firmicutes↓: Lactobacillaceae↑, Lachnospiraceae↓, Ruminococcaceae↓	Proteobacteria↑: Enterobacteriaceae↑ Bacteroidetes↓: Bacteroidaceae ↓ Firmicutes↓: Streptococaceae↑, Clostridiaceae↑, Lachnospiraceae↓, Veillococcaceae ↑, Ruminococcaceae↓ Fusobacteria↑: Fusobacteriaceae↑
Intestinal bacterial overgrowth	Present	Present**	Present
Intestinal permeability	Increased	Increased***	Increased (ascites)
Intestinal inflammation	Intestinal TNF-α ↑	Intestinal TNF-α↑, IFN-γ↑, Treg cells↓	Intestinal TNF-α↑, IFN-γ↑, Treg cells↓
Intestinal antimicrobial proteins	Intestinal Reg3 lectins↓	-	Intestinal alpha-defensins
Bile acids pool	Hepatic synthesis and faecal bile acids↑ Faecal secondary bile acids ↑ Intestinal FXR signalling↓	Faecal secondary bile acids ↑ Intestinal FXR signalling↓	Hepatic synthesis and faecal bile acids↓ Faecal secondary bile acids ↑ Intestinal FXR signalling↓
Intestinal bacterial metabolites	Intestinal LCFA ↓ Blood ethanol and acetaldehyde↑	Intestinal trimethylamine↑ Intestinal SCFA↓ Intestinal BCCA and AAA↑ Blood ethanol↑ Blood choline↓	
Translocation of bacteria and bacterial products (PAMP)	Blood PAMP↑	Blood PAMP↑	Blood PAMP↑ Viable bacteria in blood/lymph nodes

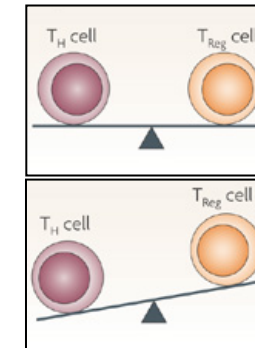
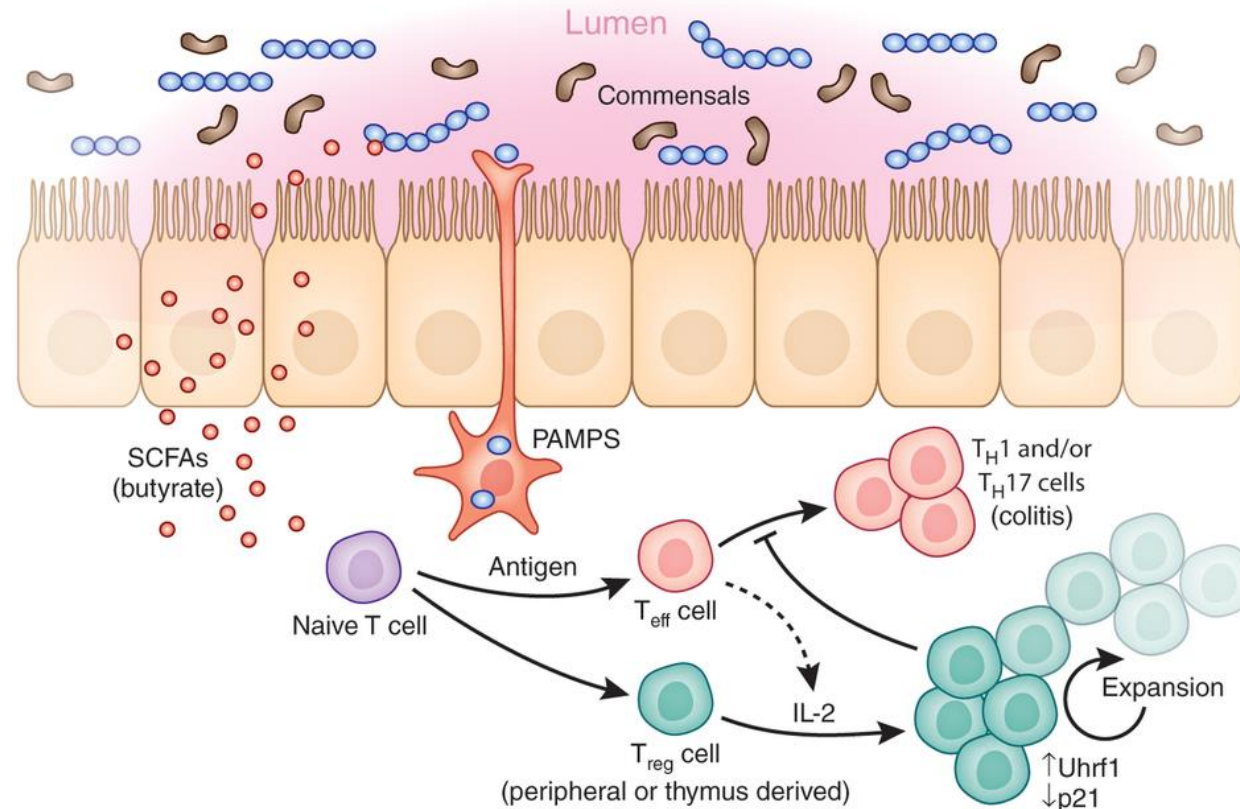
5. Sistema Inmune y respuesta inflamatoria



Sistema Inmune y respuesta inflamatoria



Sistema Inmune y respuesta inflamatoria

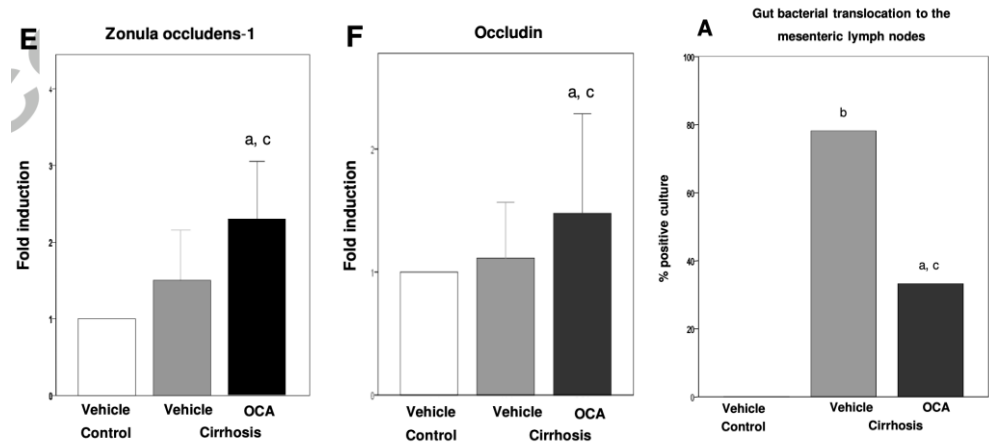


Eubiosis

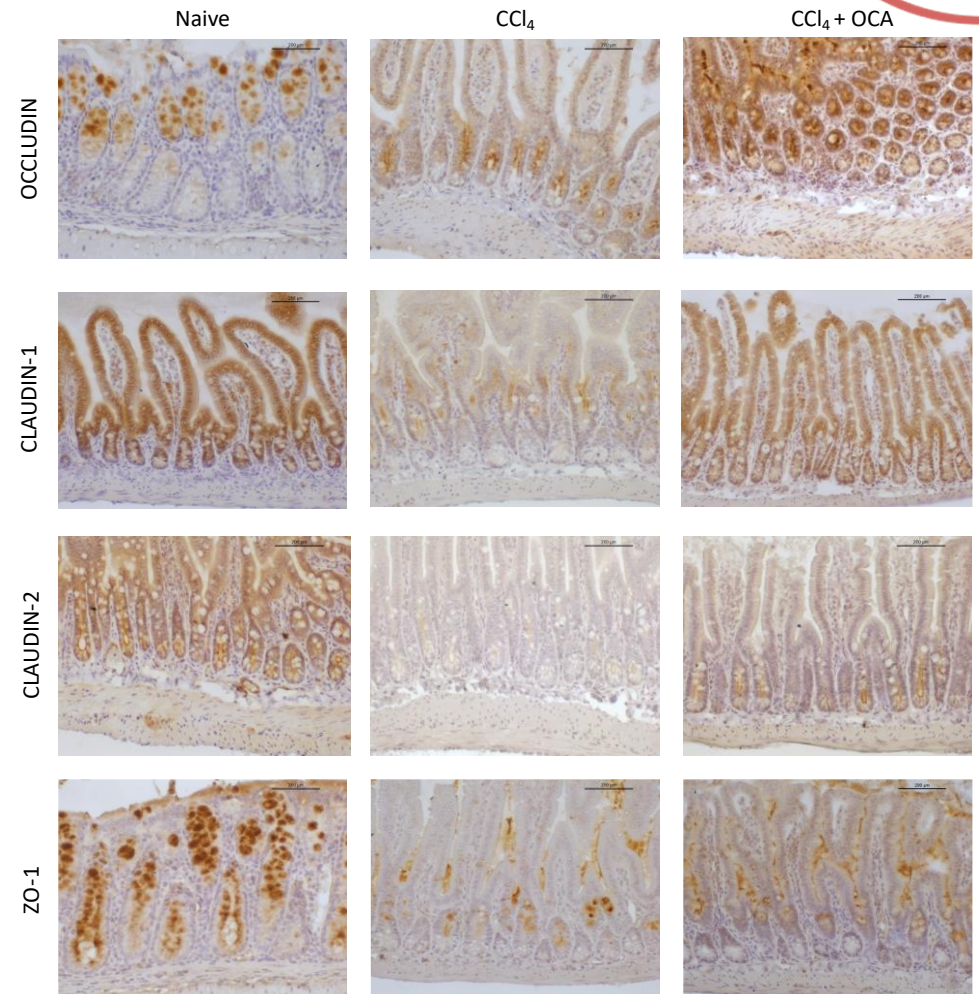
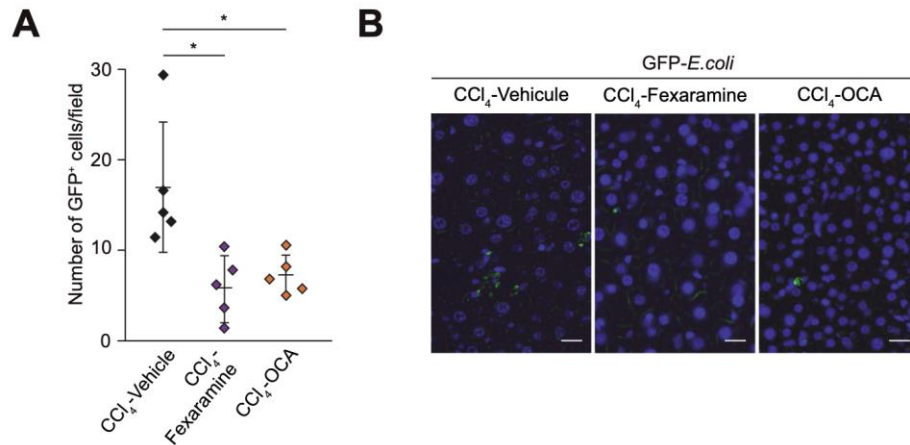
Dysbiosis

6. Recuperación de la integridad de la barrera

Recuperación de FXR



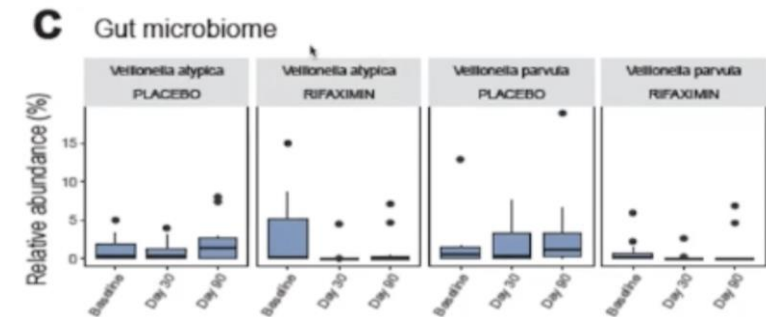
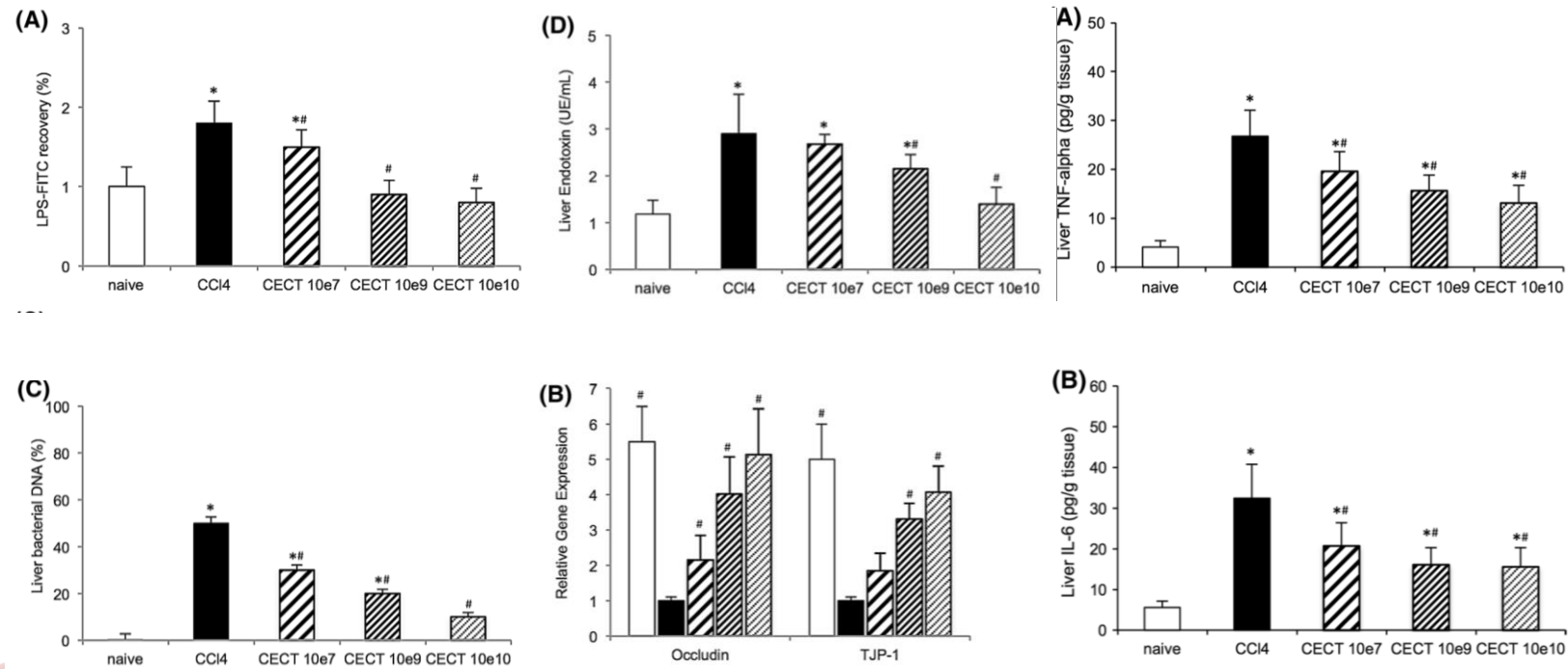
J Hepatol. 2016 May;64(5):1049-1057



J Hepatol. 2019 Dec;71(6):1126-1140

Recuperación de la integridad de la barrera

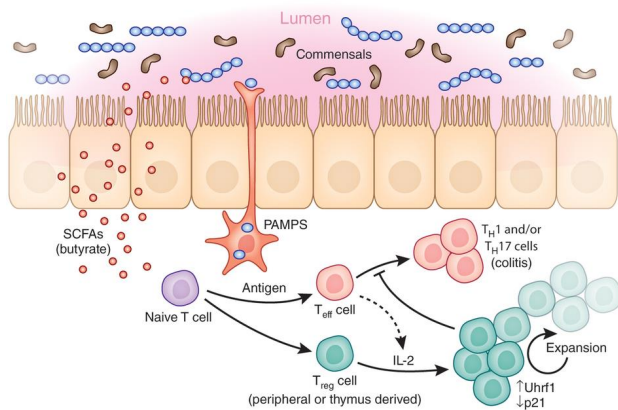
Recuperación de eubiosis



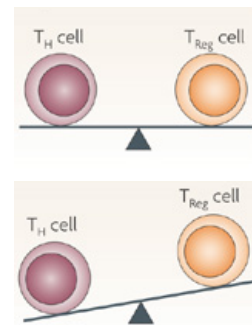
RFX suppresses the growth of bacteria with mucin-degrading capacities

Recuperación de la integridad de la barrera

Recuperación de Tregs

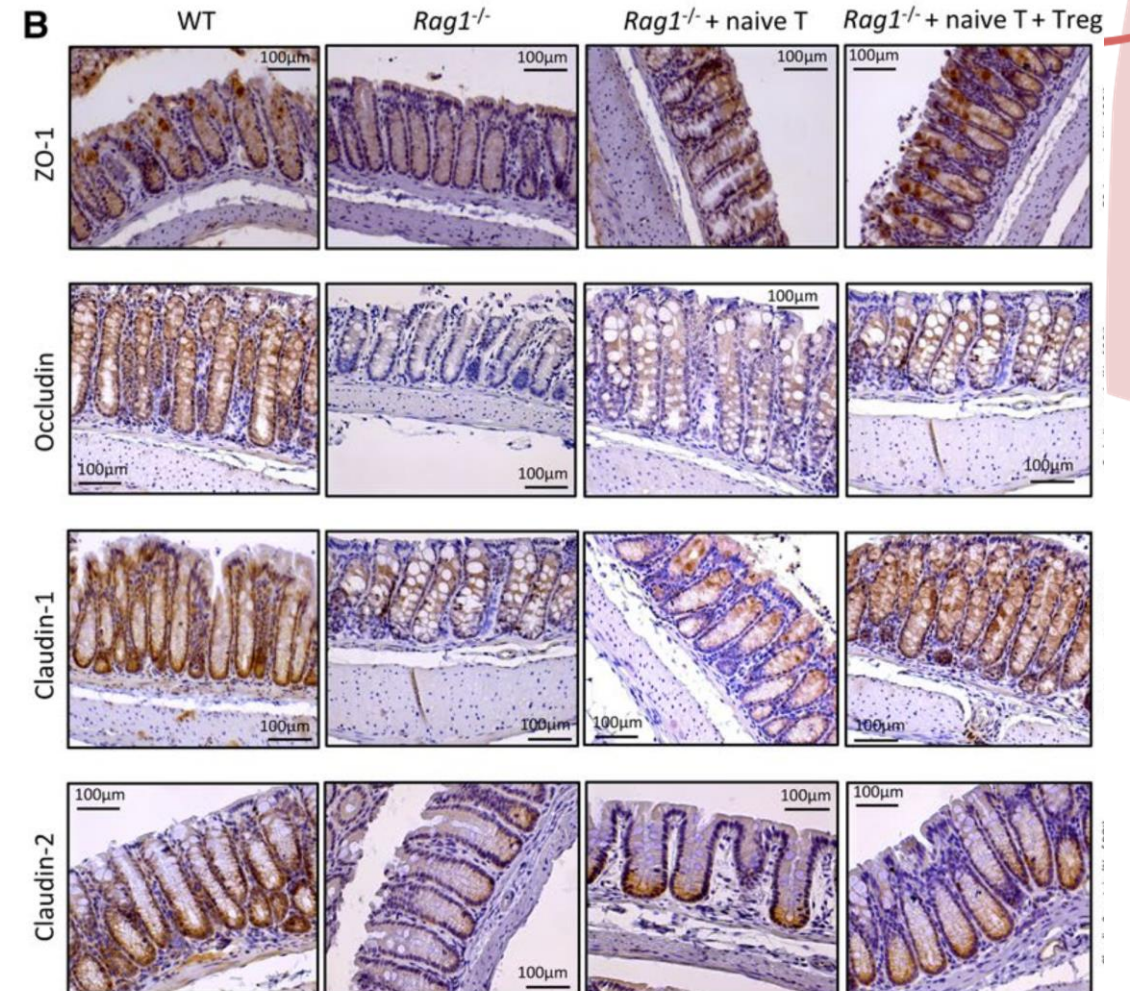


Nat Rev Immunol 9, 313–323 (2009)



Eubiosis

Dysbiosis



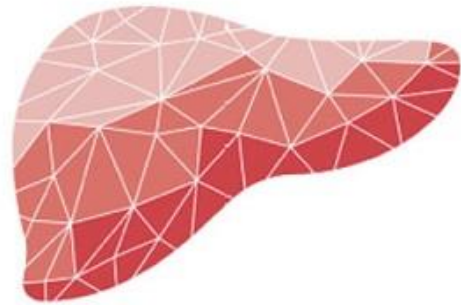
Conclusiones

Hígado e intestino intercambian sustancias constantemente de forma bidireccional. En la cirrosis esta comunicación se encuentra alterada.

El descenso en el flujo de ácidos biliares contribuye a un descenso en la señalización a través de FXR (TJs, moco, AMPs): **pérdida de integridad** de la barrera.

La **disbiosis intestinal** produce un descenso de SCFAs y señales tolerogénicas: aumento de la traslocación espontánea de productos microbianos.

La actividad inmunitaria se polariza hacia un fenotipo inflamatorio que **aumenta la distorsión** de la barrera, la TB y la liberación **sistémica** de mediadores inflamatorios.



MÁSTER EN HEPATOLOGÍA



Universidad
de Alcalá