

MÁSTER EN HEPATOLOGÍA

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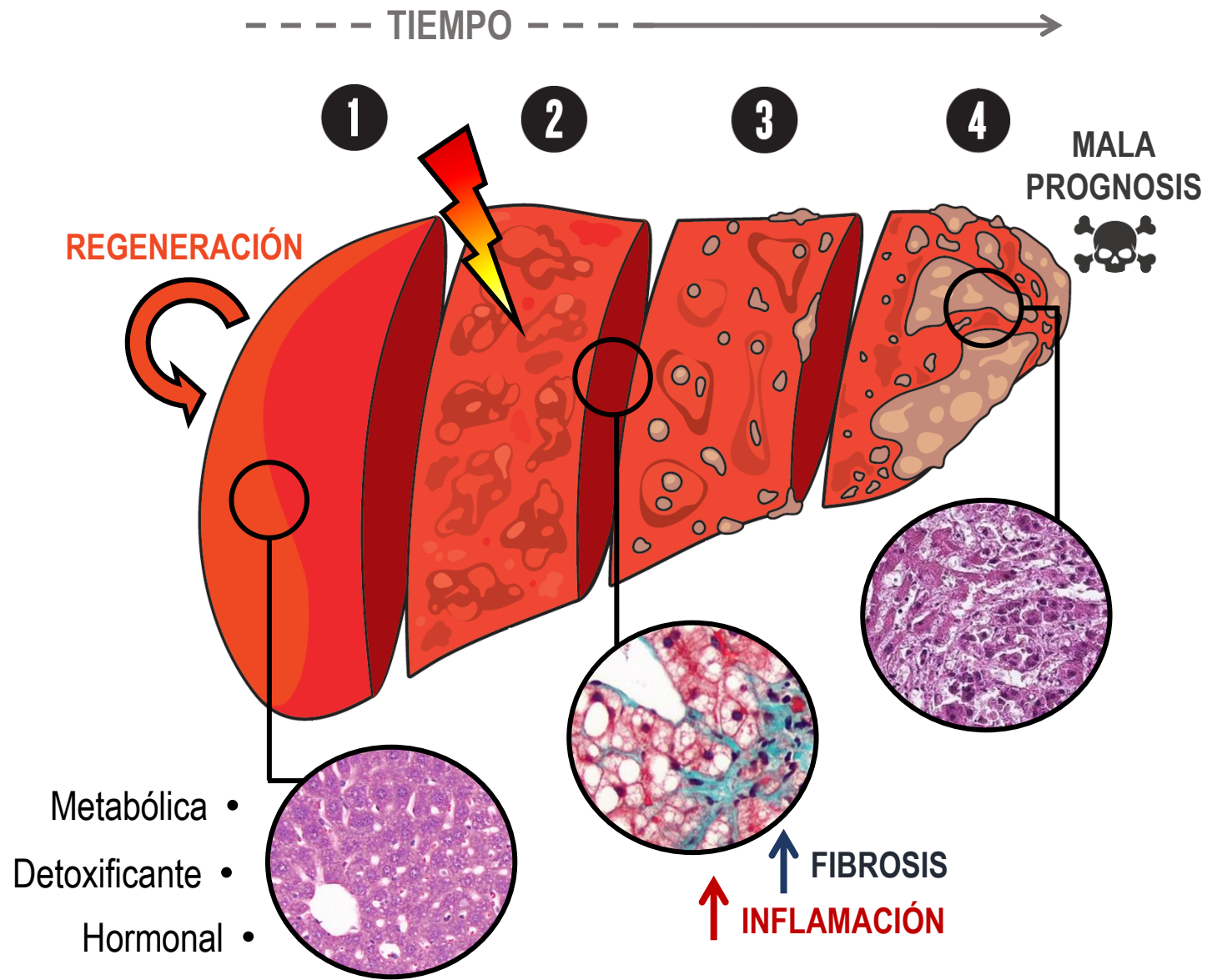
Asignatura: Cirrosis III

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

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

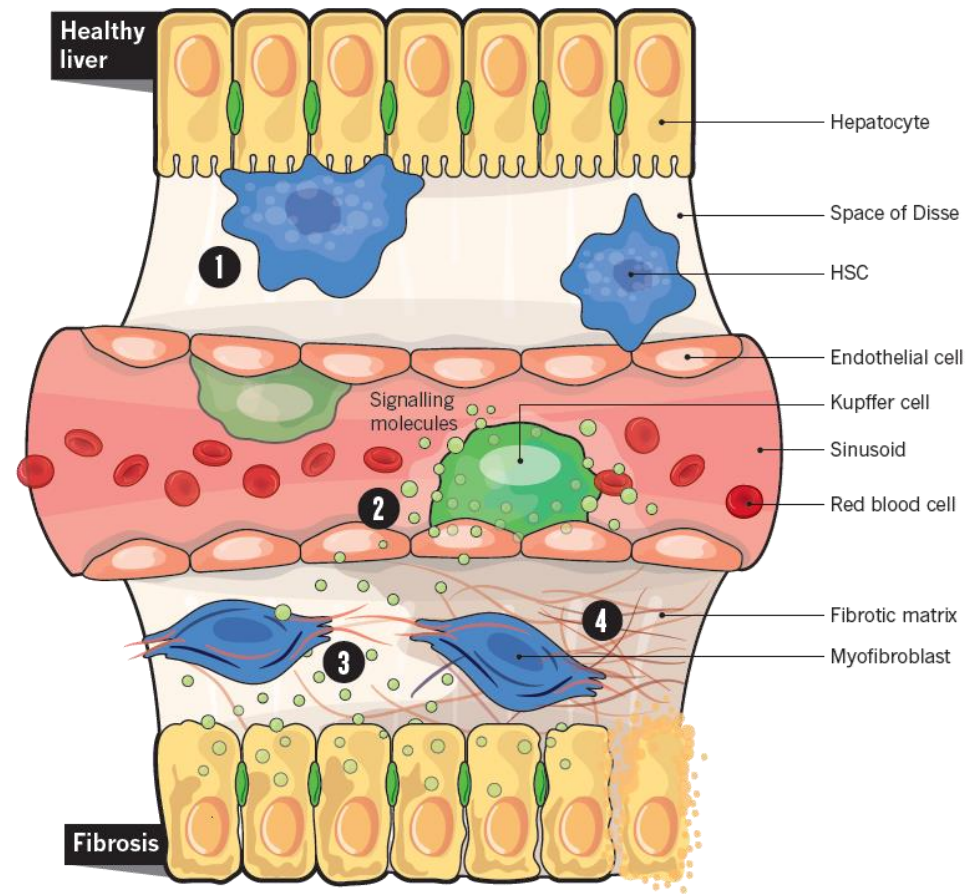
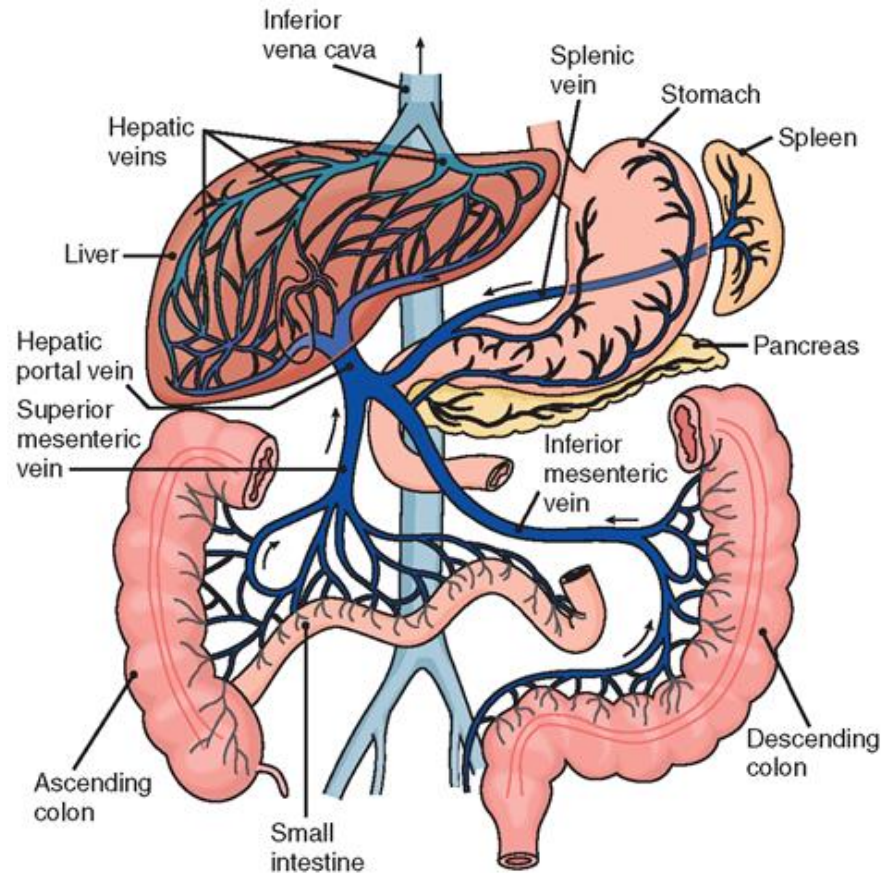
[@get_ruben](https://twitter.com/get_ruben)



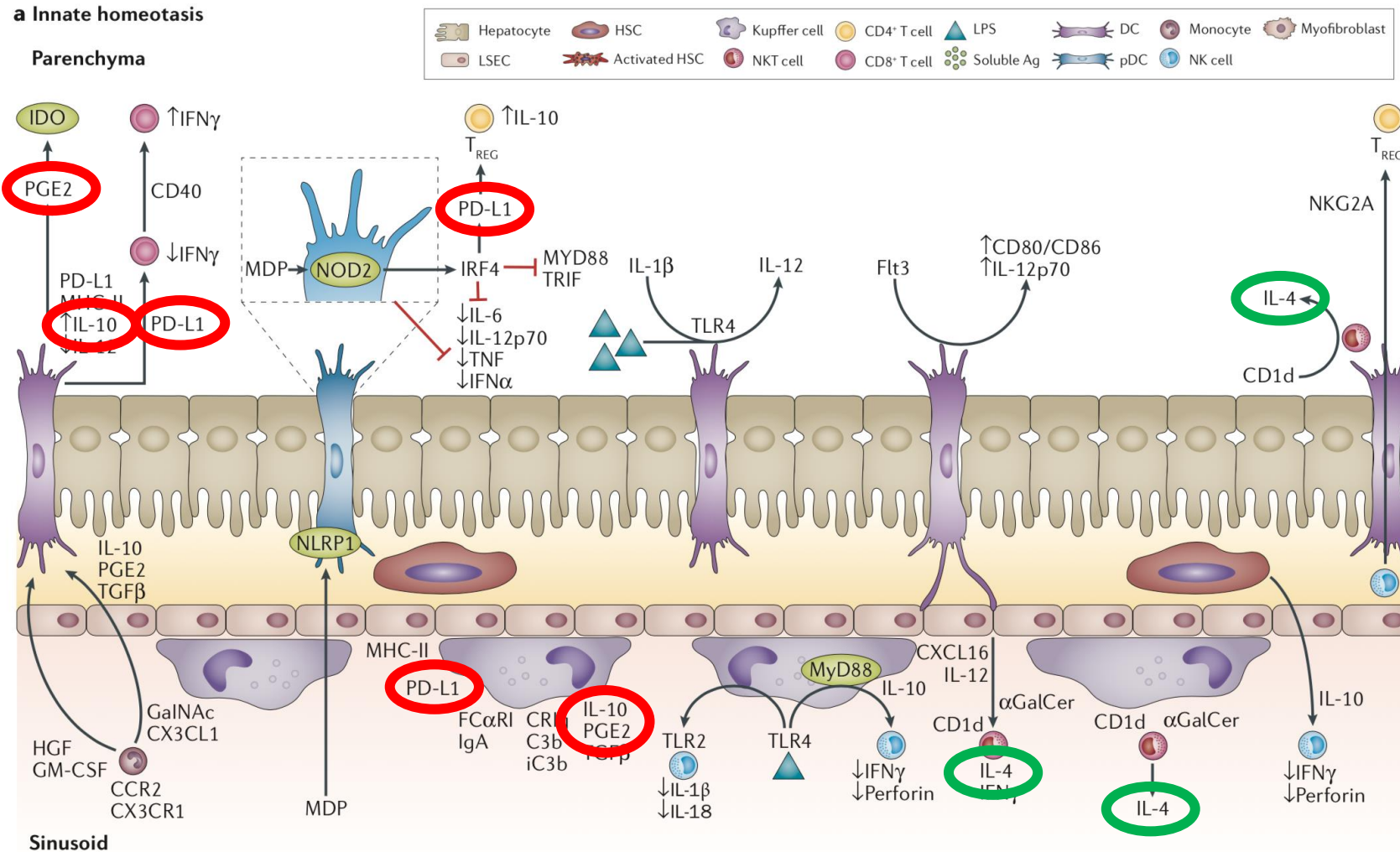
Índice

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

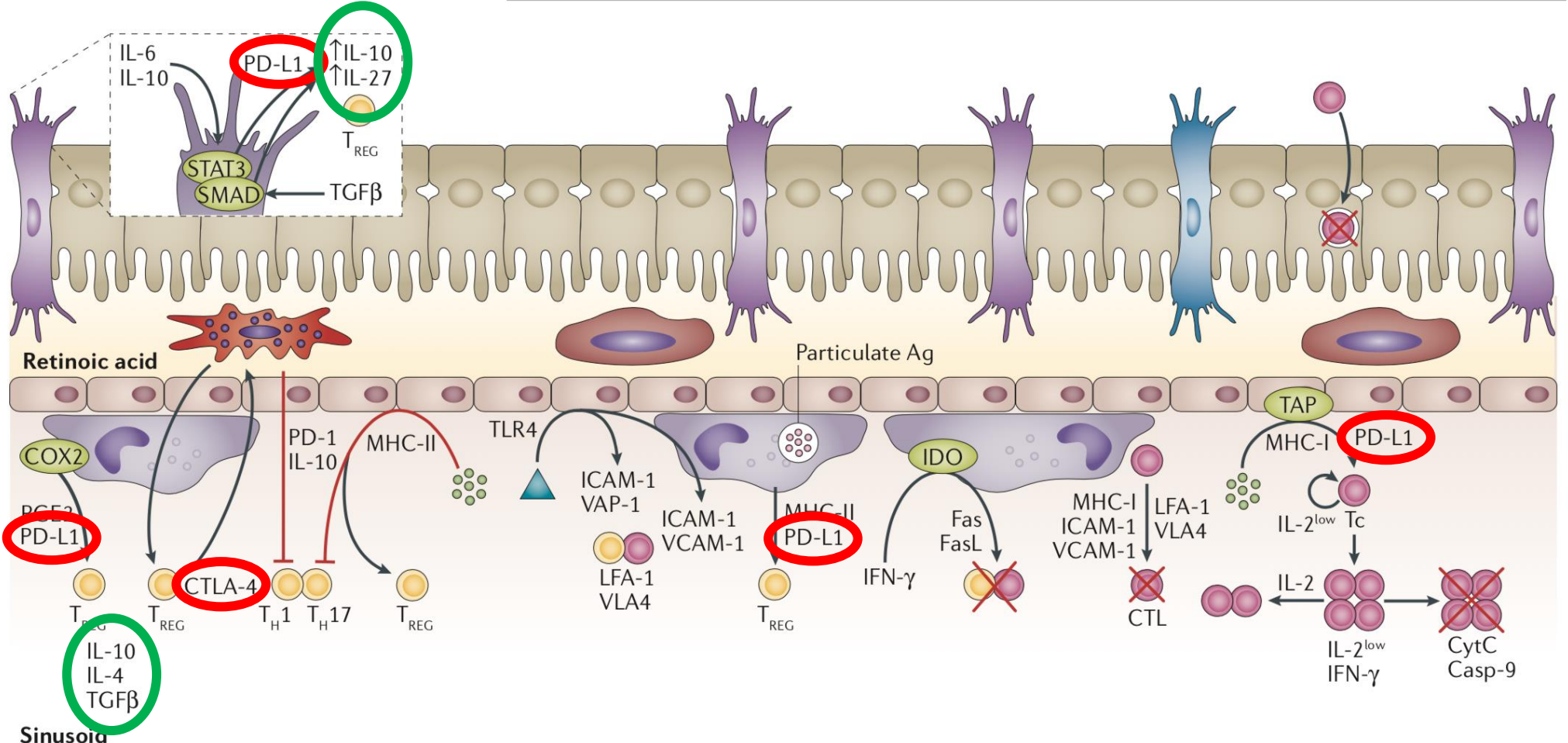


Equilibrio → Tolerancia

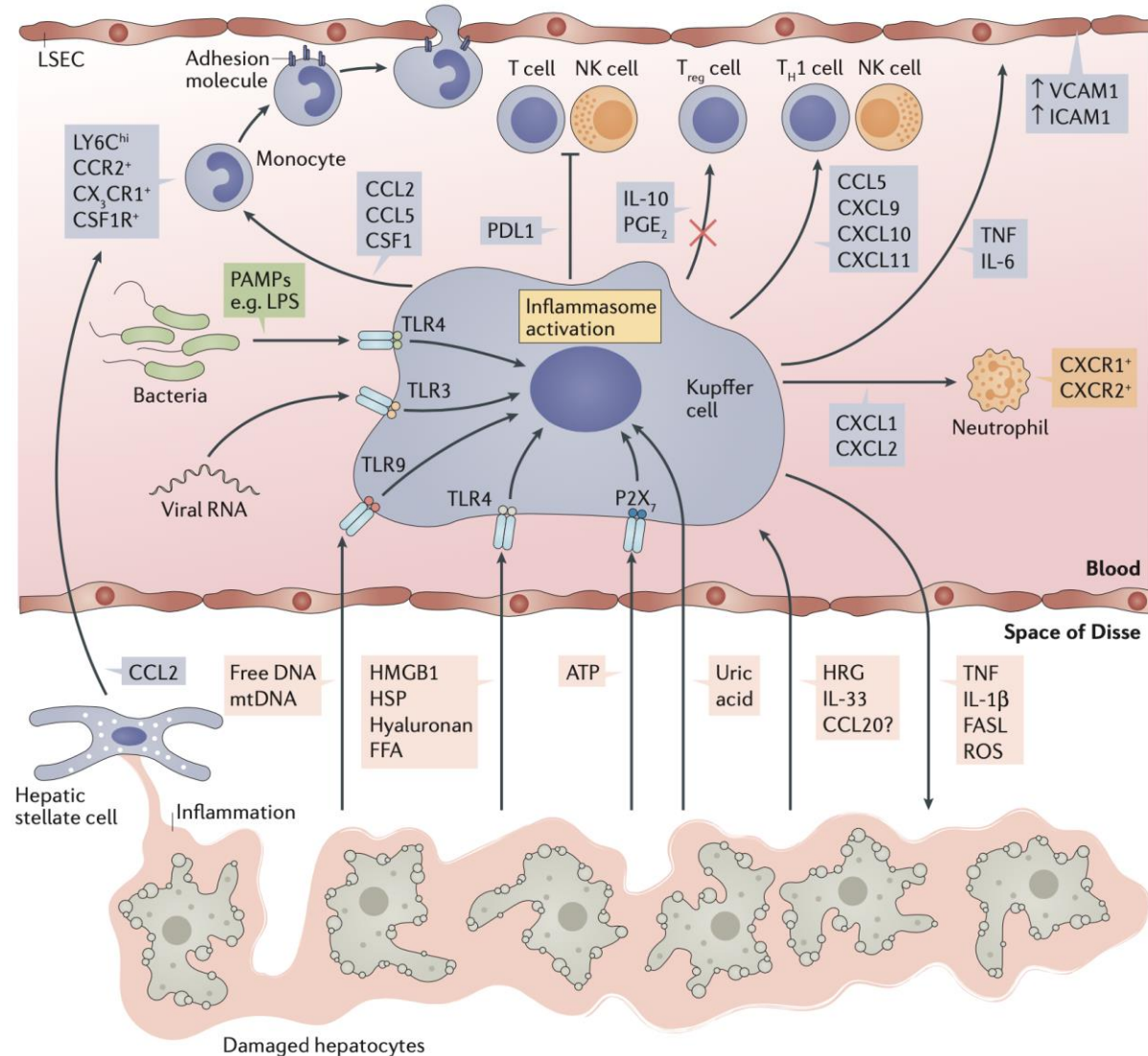
b Adaptive homeostasis

Parenchyma

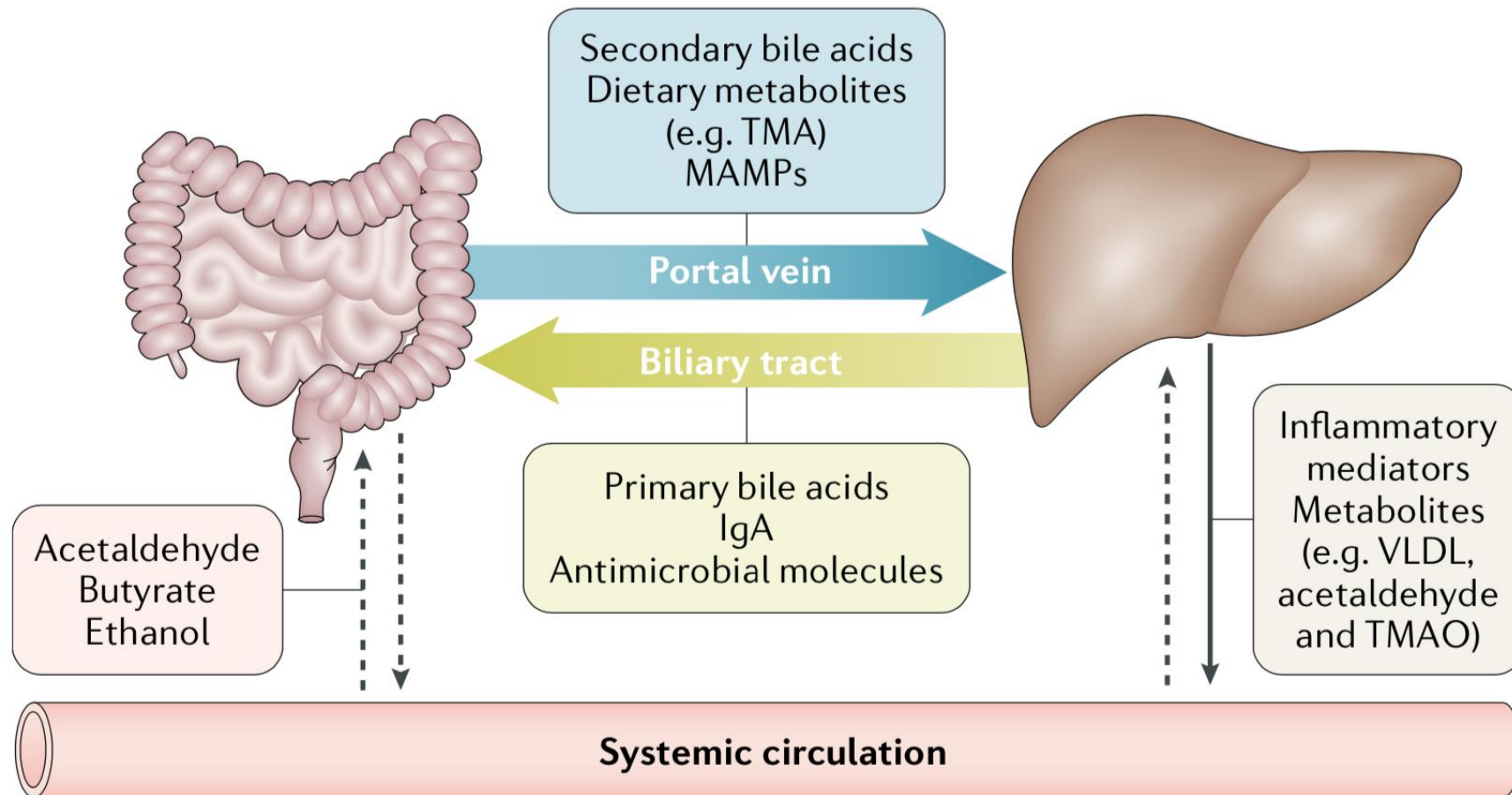
Hepatocyte	HSC	Kupffer cell	CD4+ T cell	LPS	DC	Monocyte	Myofibroblast
LSEC	Activated HSC	NKT cell	CD8+ T cell	Soluble Ag	pDC	NK cell	



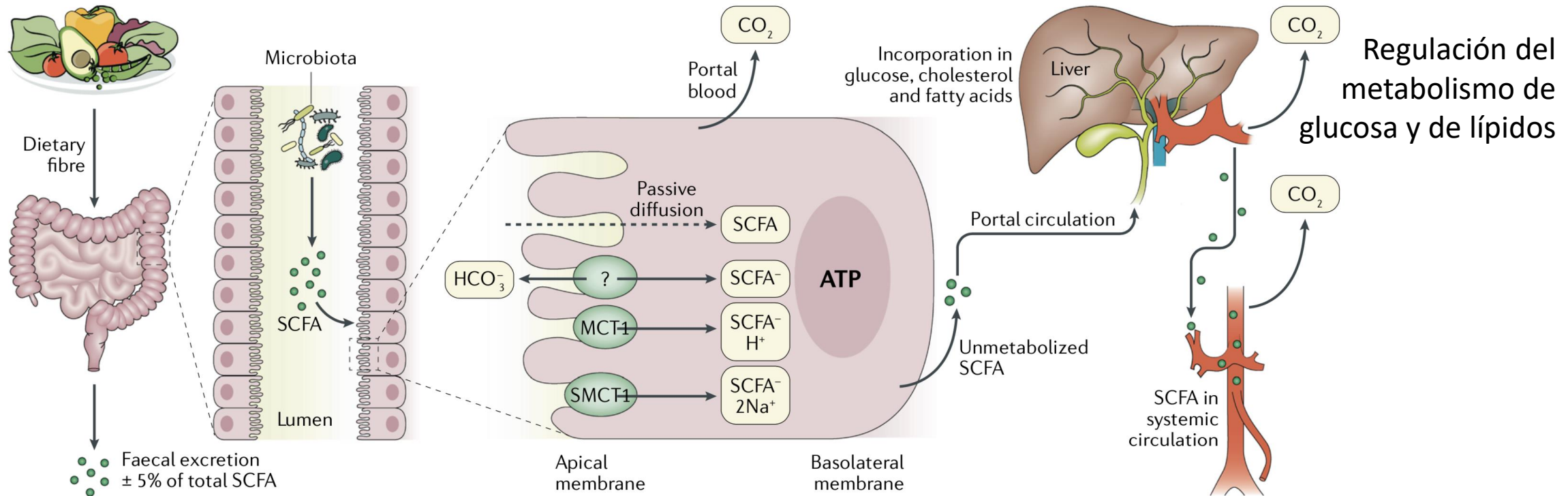
Desequilibrio → Inflamación



2. Eje hígado - intestino



Ácidos grasos de cadena corta

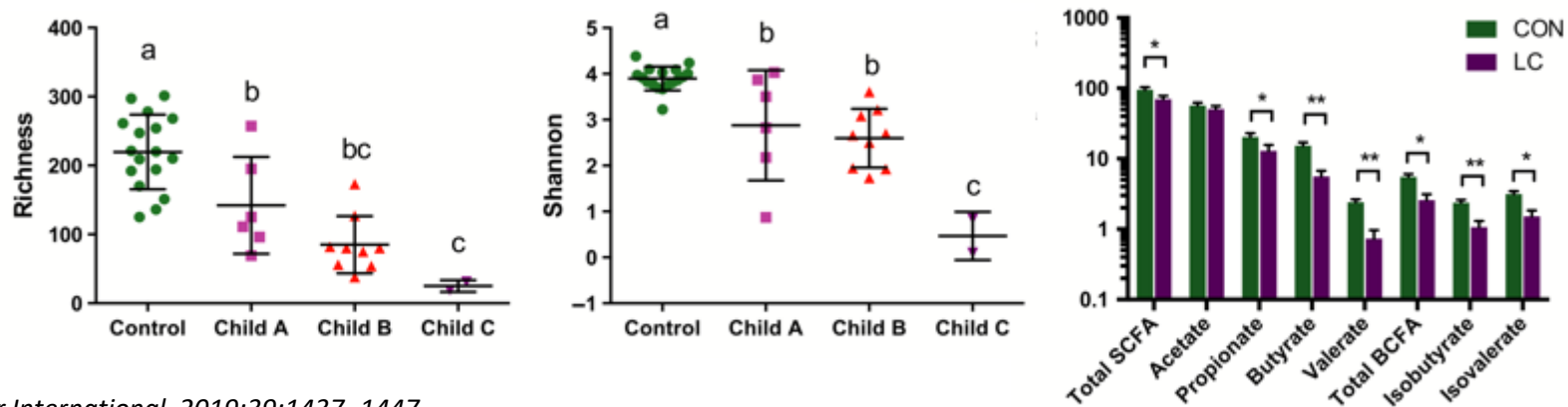


Nat Rev Gastroenterol Hepatol. 2019; 16: 461-478

Regulación de la presión sanguínea
Regulación de la respuesta inflamatoria

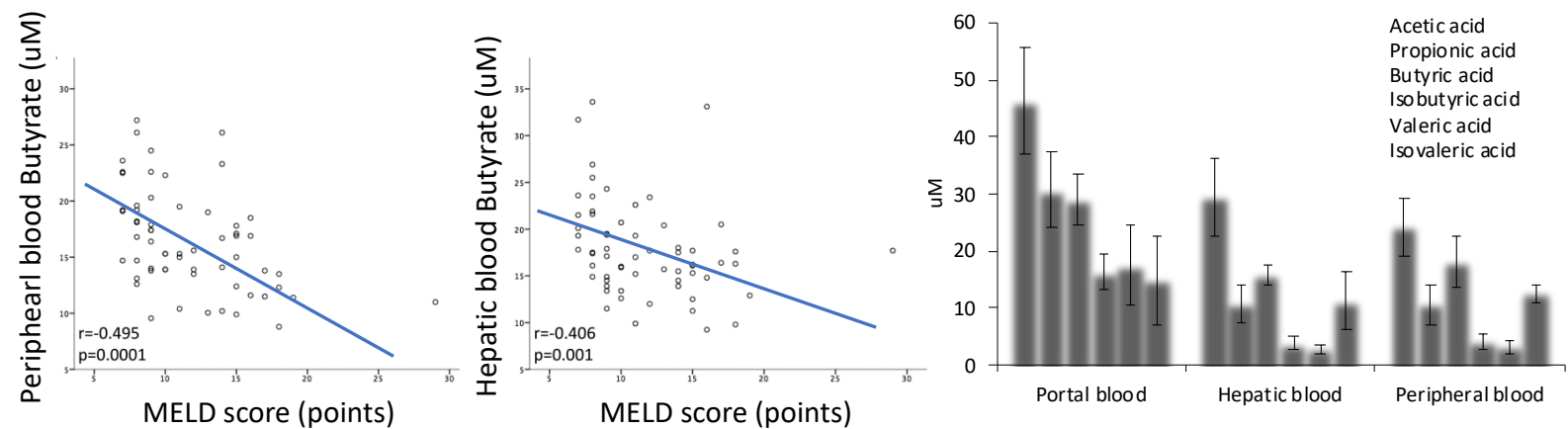
Ácidos grasos de cadena corta

Reduced capacity of fecal microbiota to produce SCFAs in cirrhosis



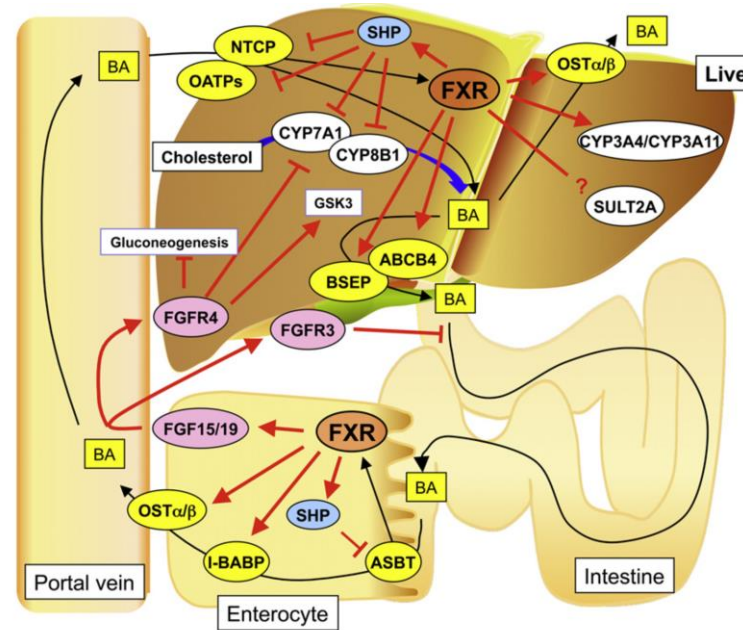
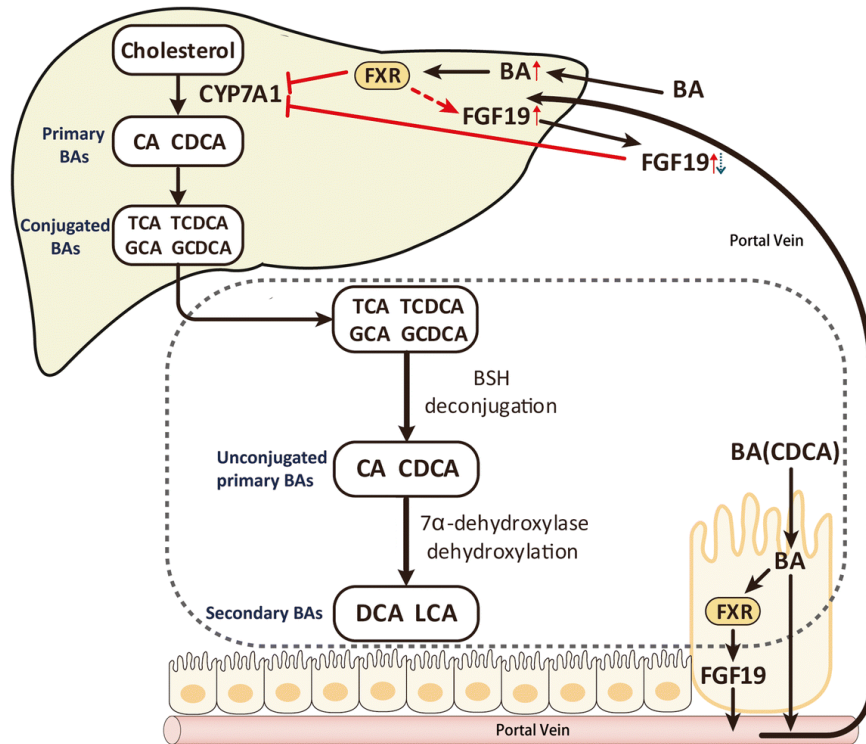
Liver International. 2019;39:1437–1447

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



FASEB J. 2019; 33: 11595–11605

Ácidos biliares



Cirrosis

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

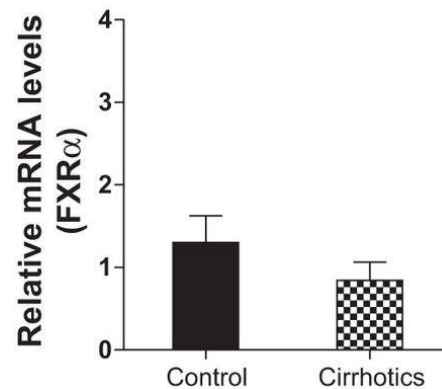
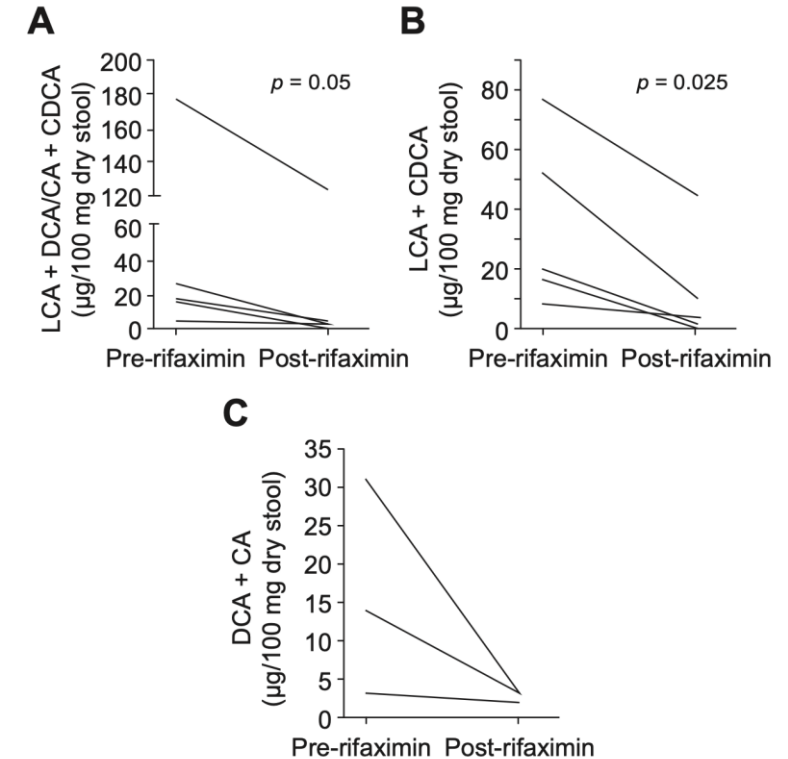
Ácidos biliares y FXR en cirrosis

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.

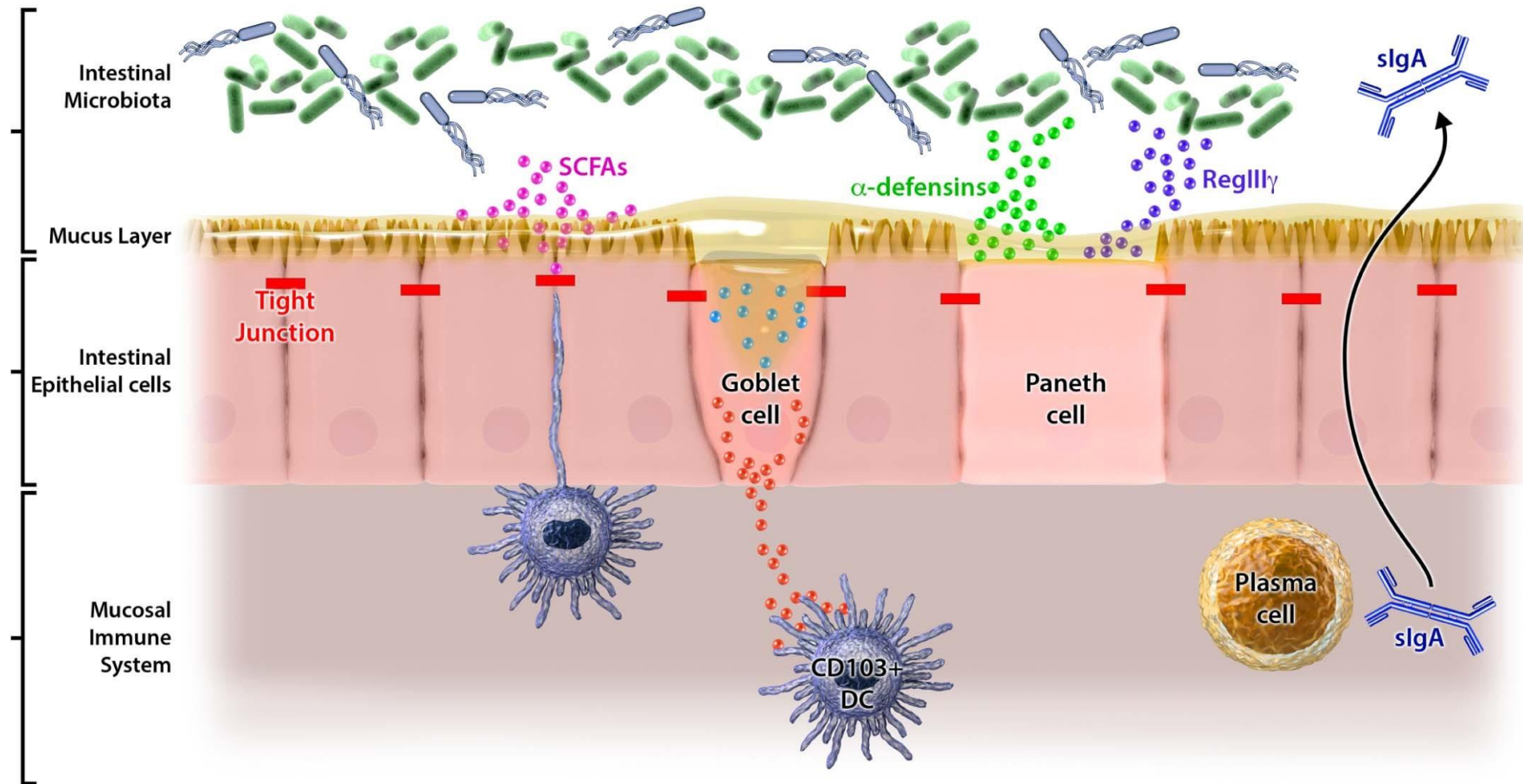
CA, cholic acid; CDCA, chenodeoxycholic acid; LCA, lithocholic acid; DCA, deoxycholic acid.



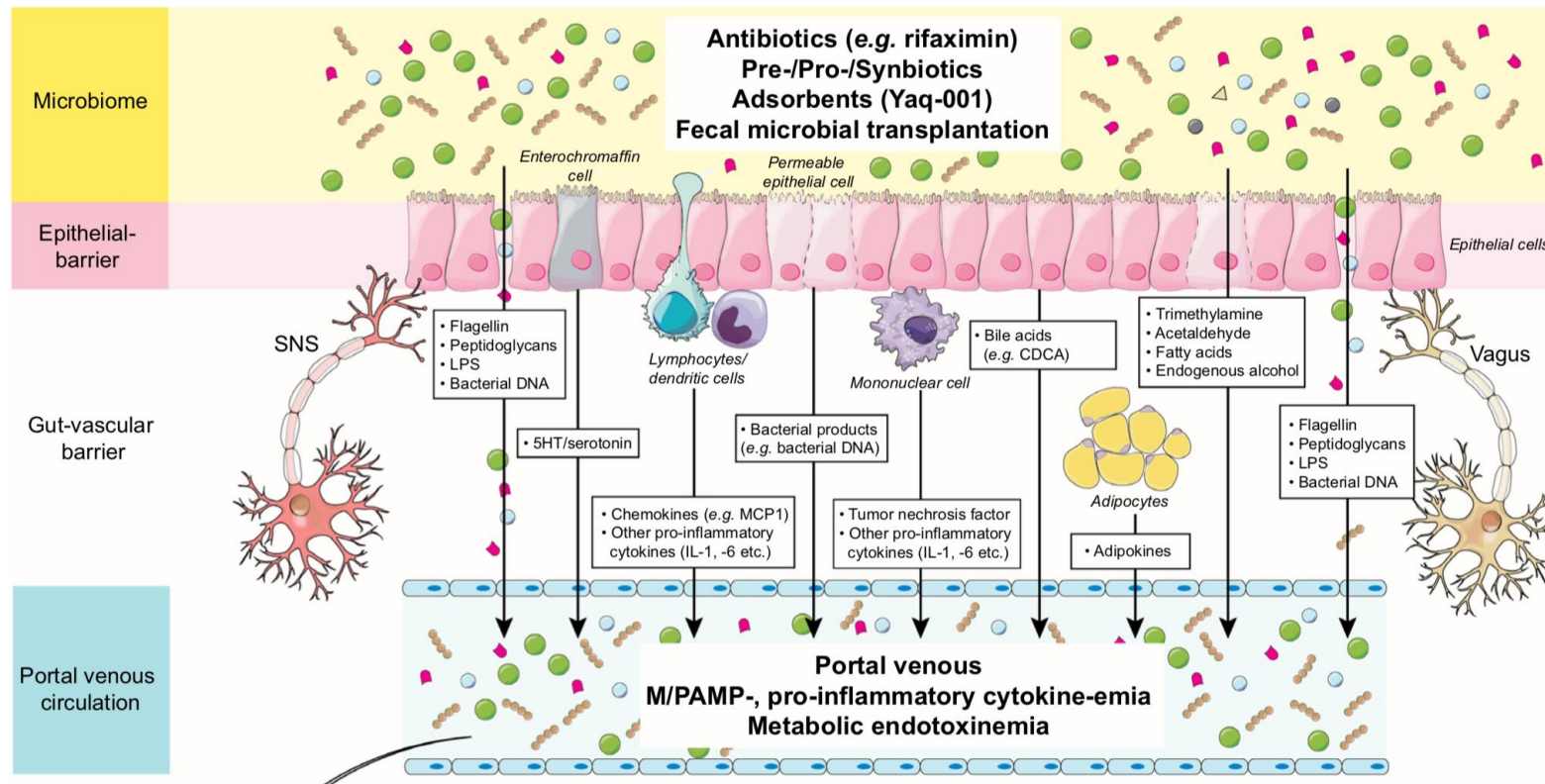
Journal of Hepatology 2013; 58: 949–955

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.

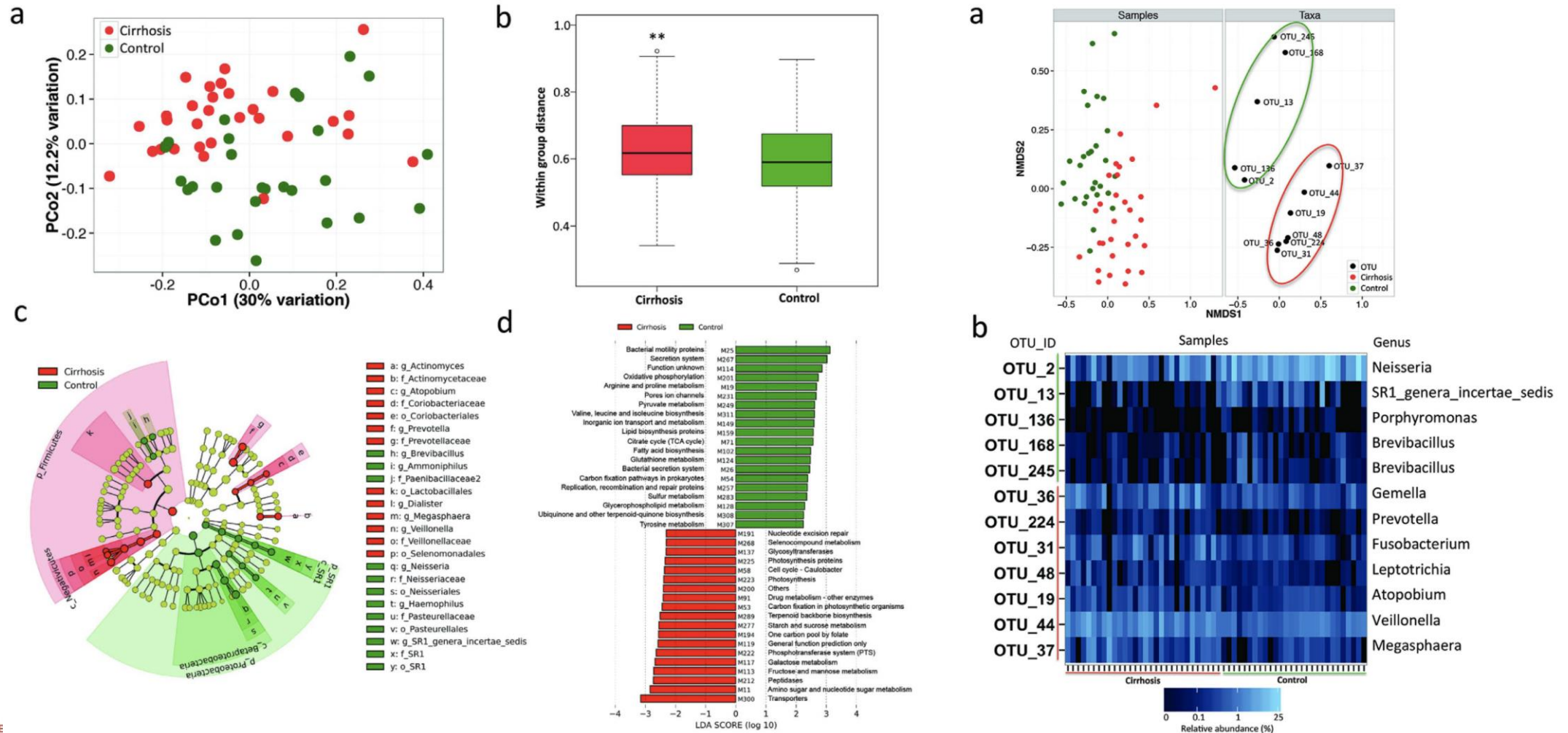
J Hepatol. 2019 Jul 8. pii: S0168-8278(19)30389-7

- During diet-induced dysbiosis the GVB is disrupted.

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

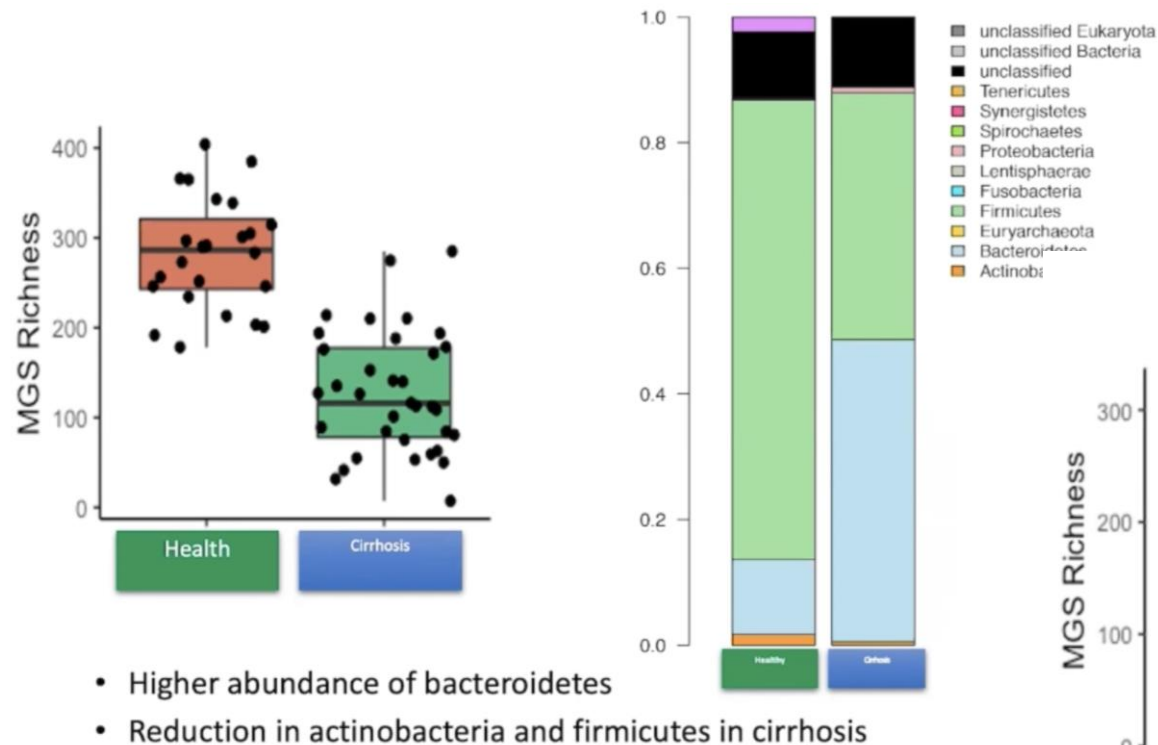
J Hepatol. 2019 Aug 13. pii: S0168-8278(19)30471-4

4. Disbiosis intestinal durante la cirrosis

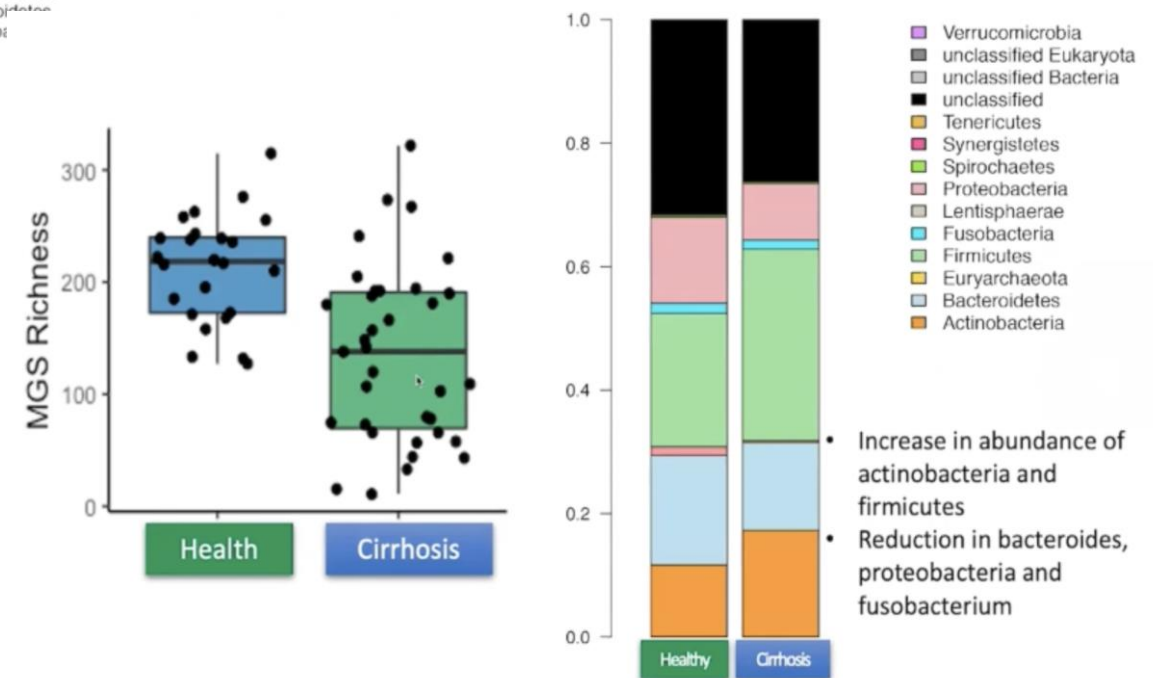


Disbiosis intestinal durante la cirrosis

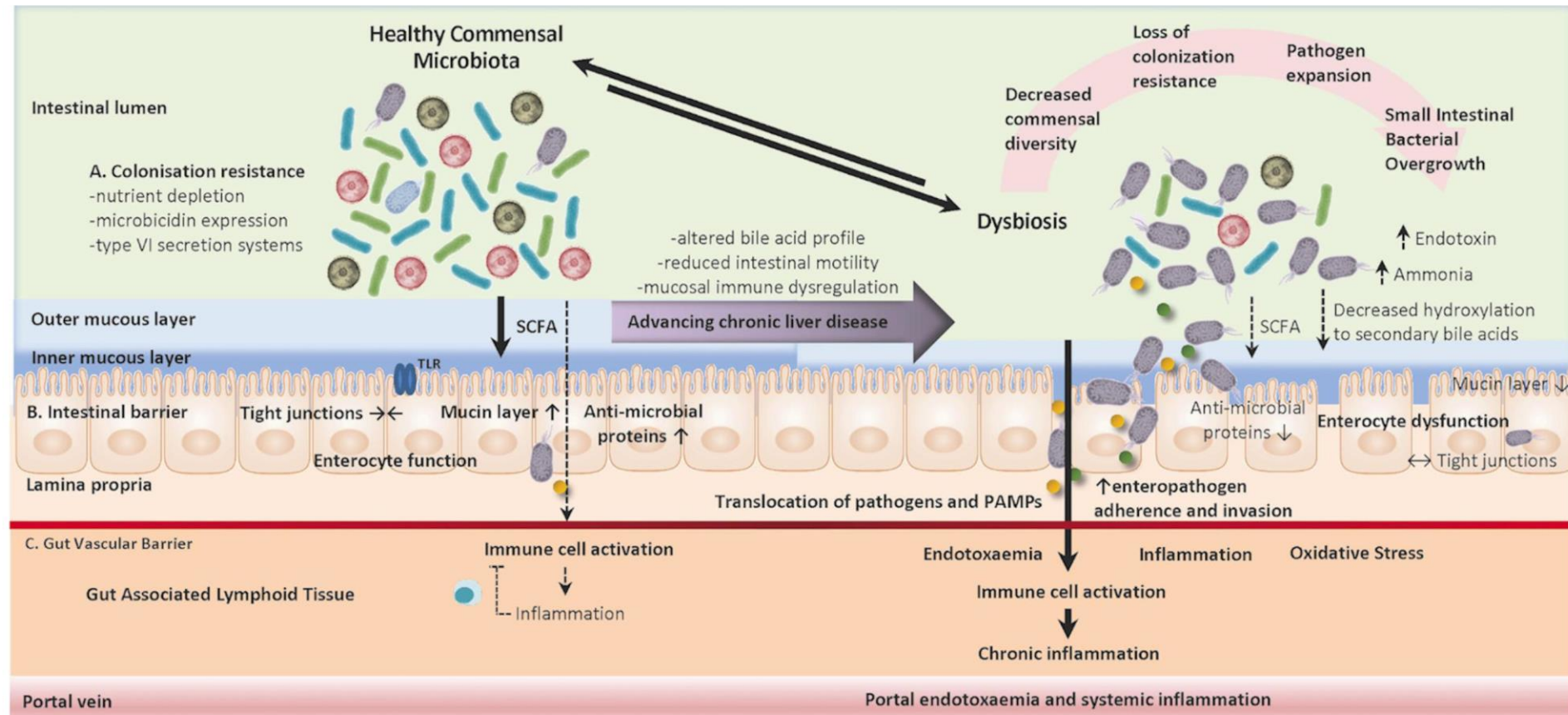
Reduced gut microbial diversity



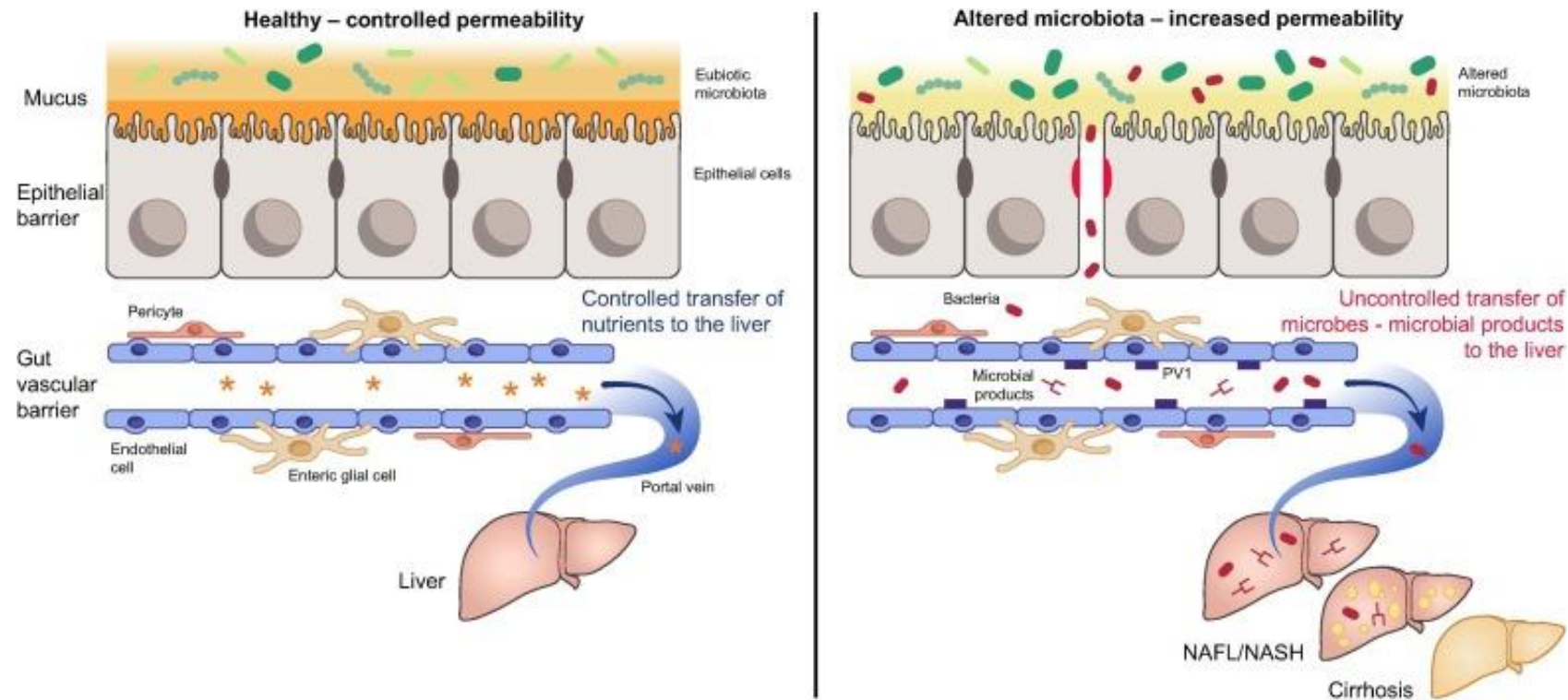
Reduced saliva microbial diversity



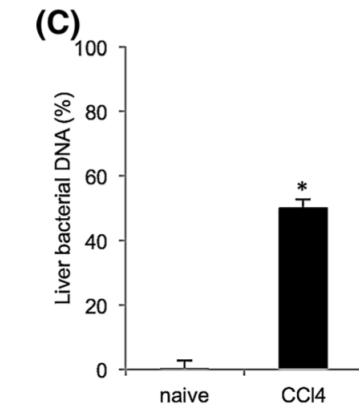
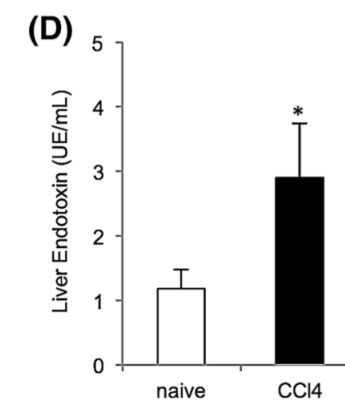
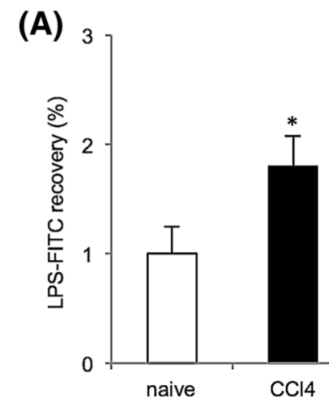
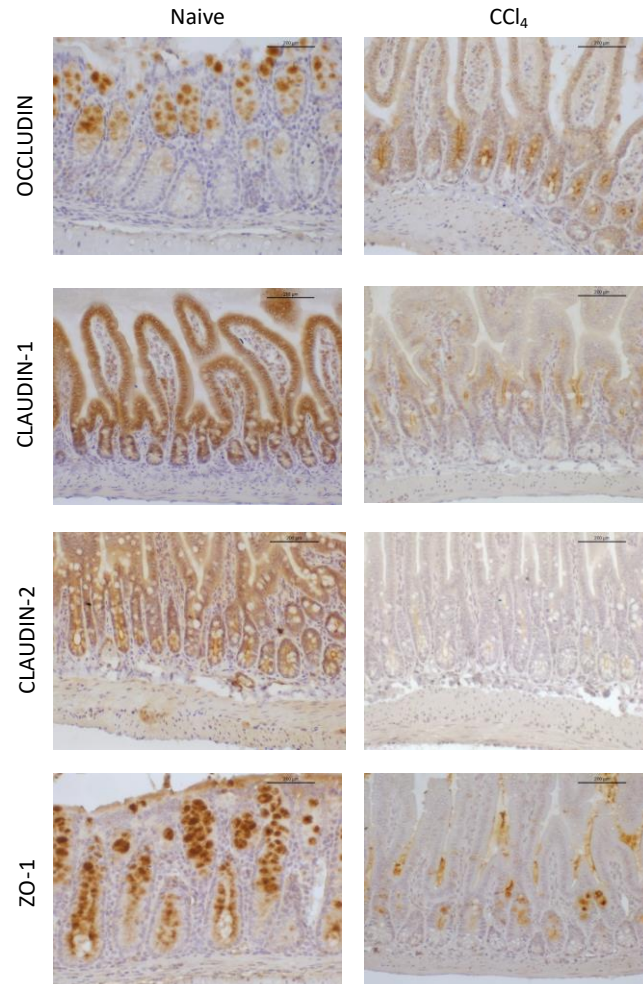
Disbiosis intestinal durante la cirrosis



Disbiosis intestinal en la cirrosis



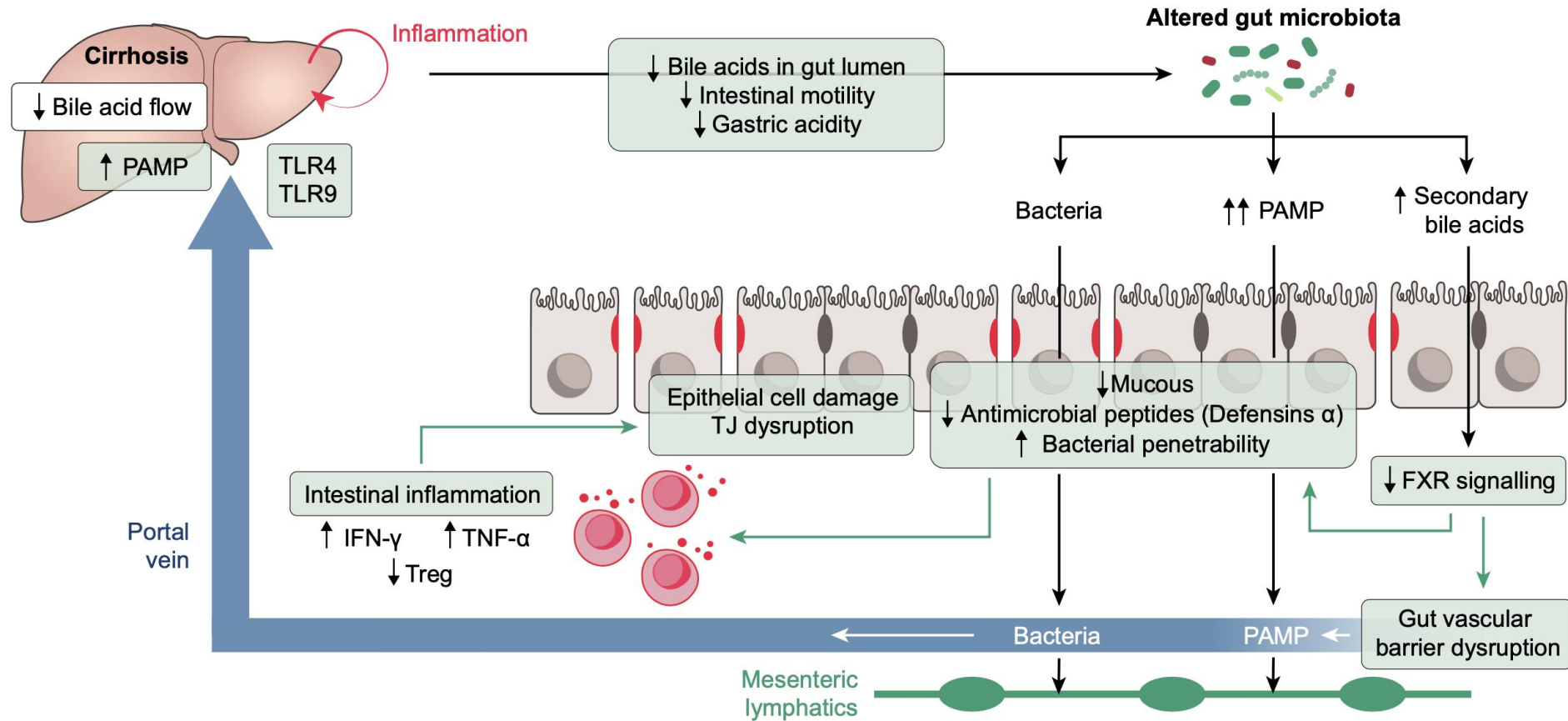
Integridad de la barrera intestinal



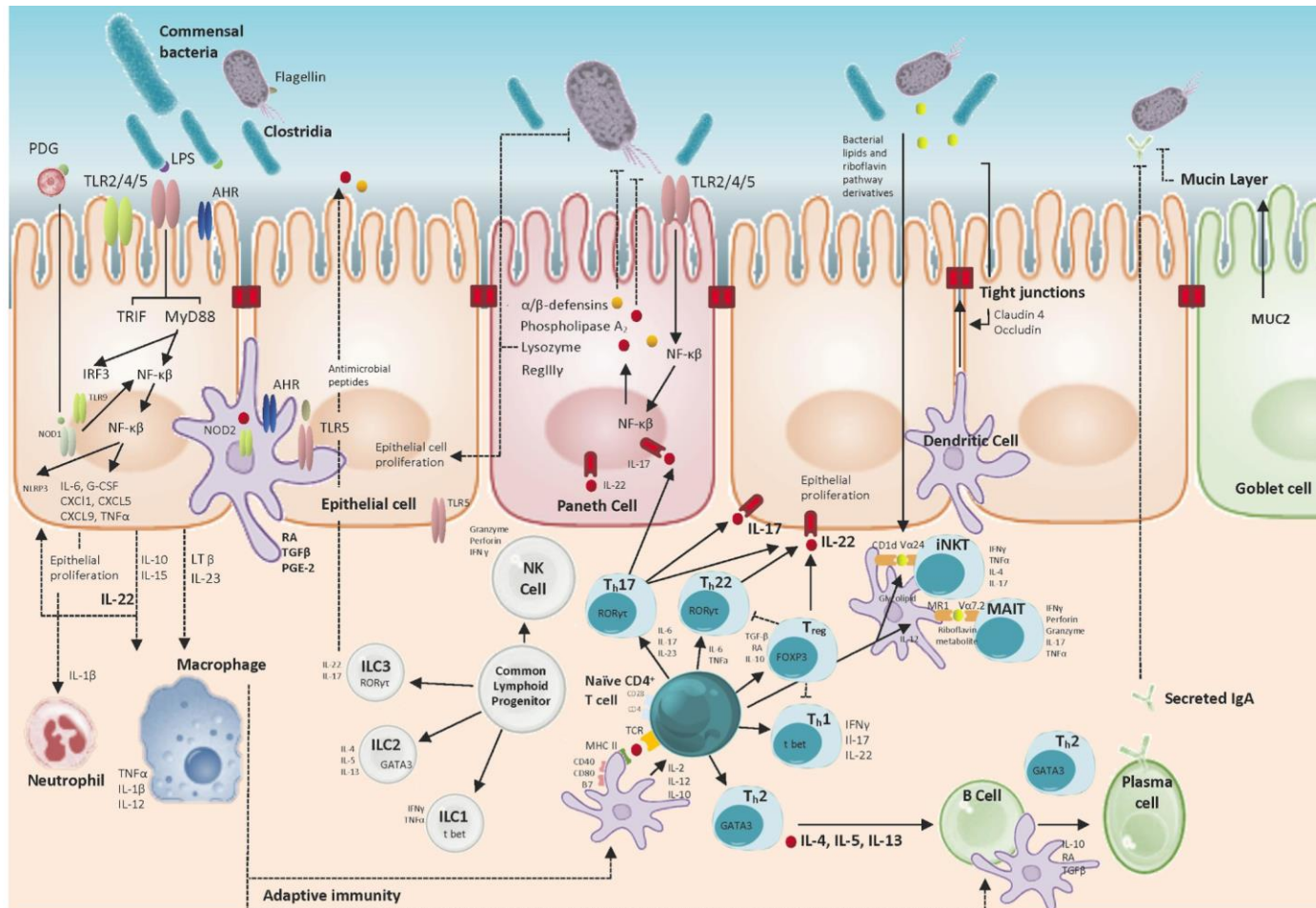
Eur J Nutr. 2016;55:197-206

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

Integridad de la barrera en la cirrosis

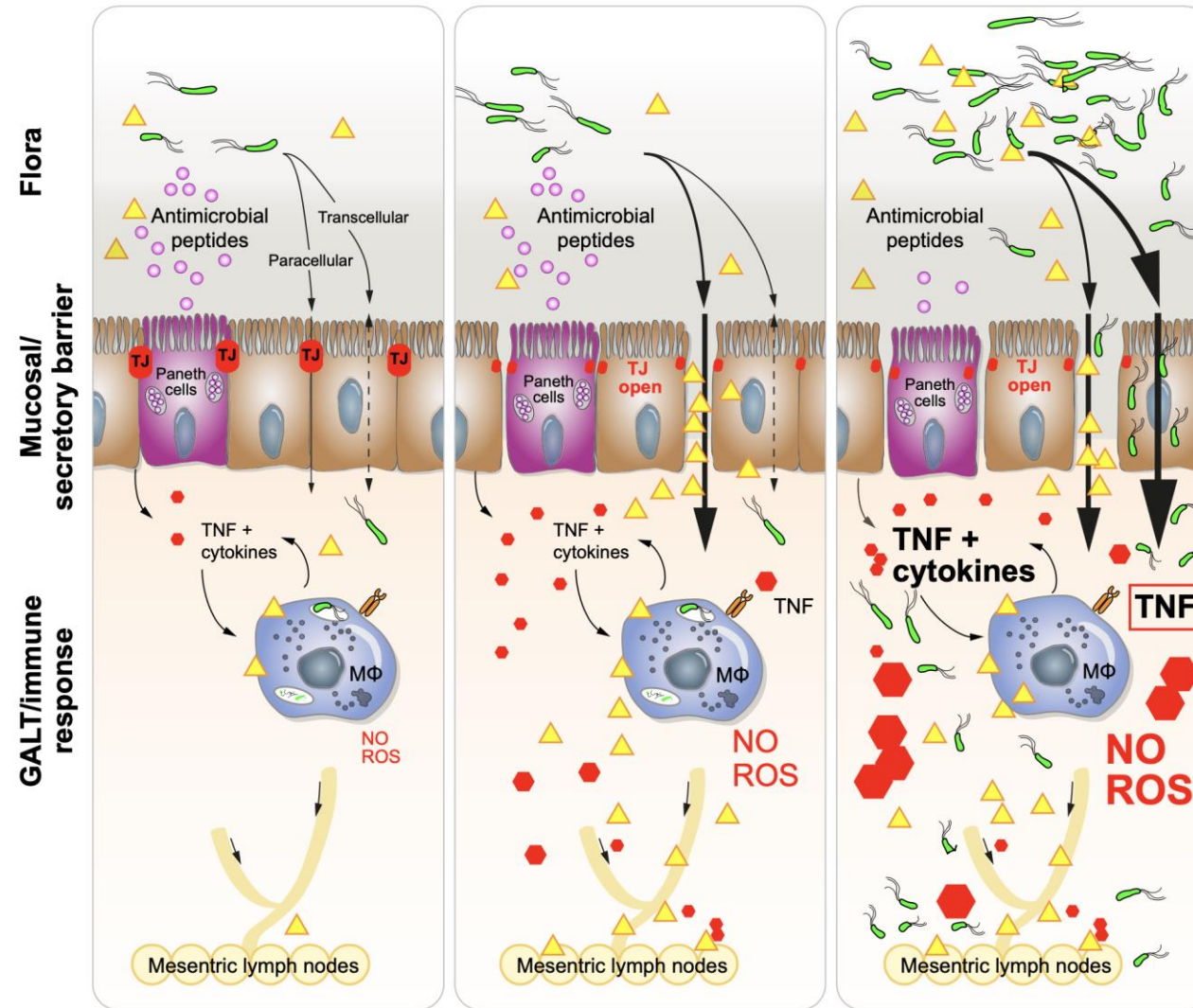


5. Sistema Inmune y respuesta inflamatoria

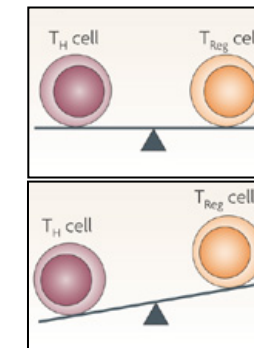
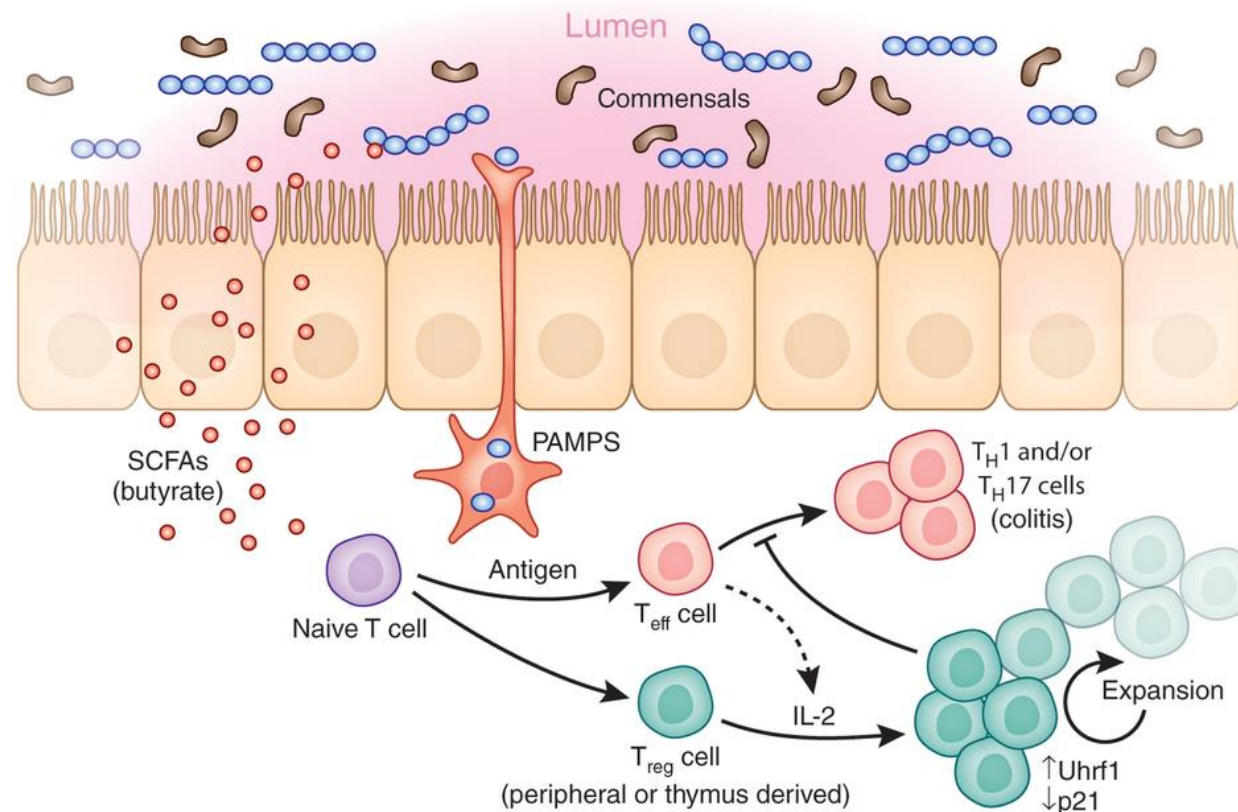


Gut 2020 Oct 15;gutjnl-2020-320786.

Sistema Inmune y respuesta inflamatoria



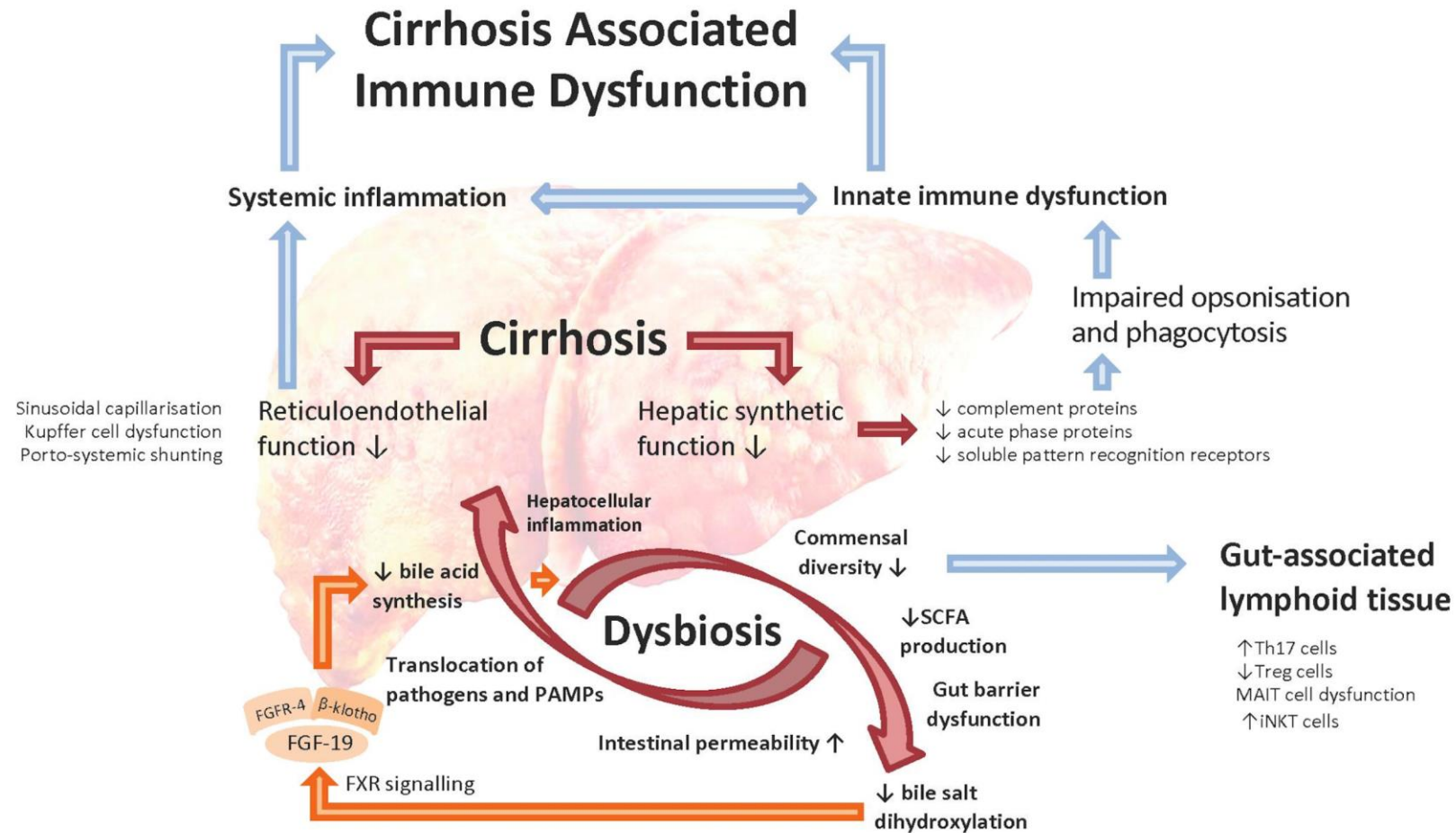
Sistema Inmune y respuesta inflamatoria



Eubiosis

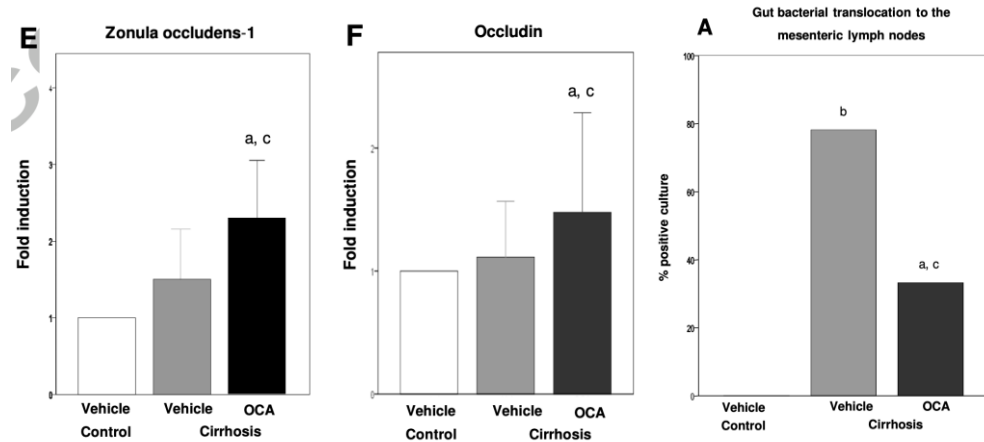
Dysbiosis

Sistema Inmune y respuesta inflamatoria

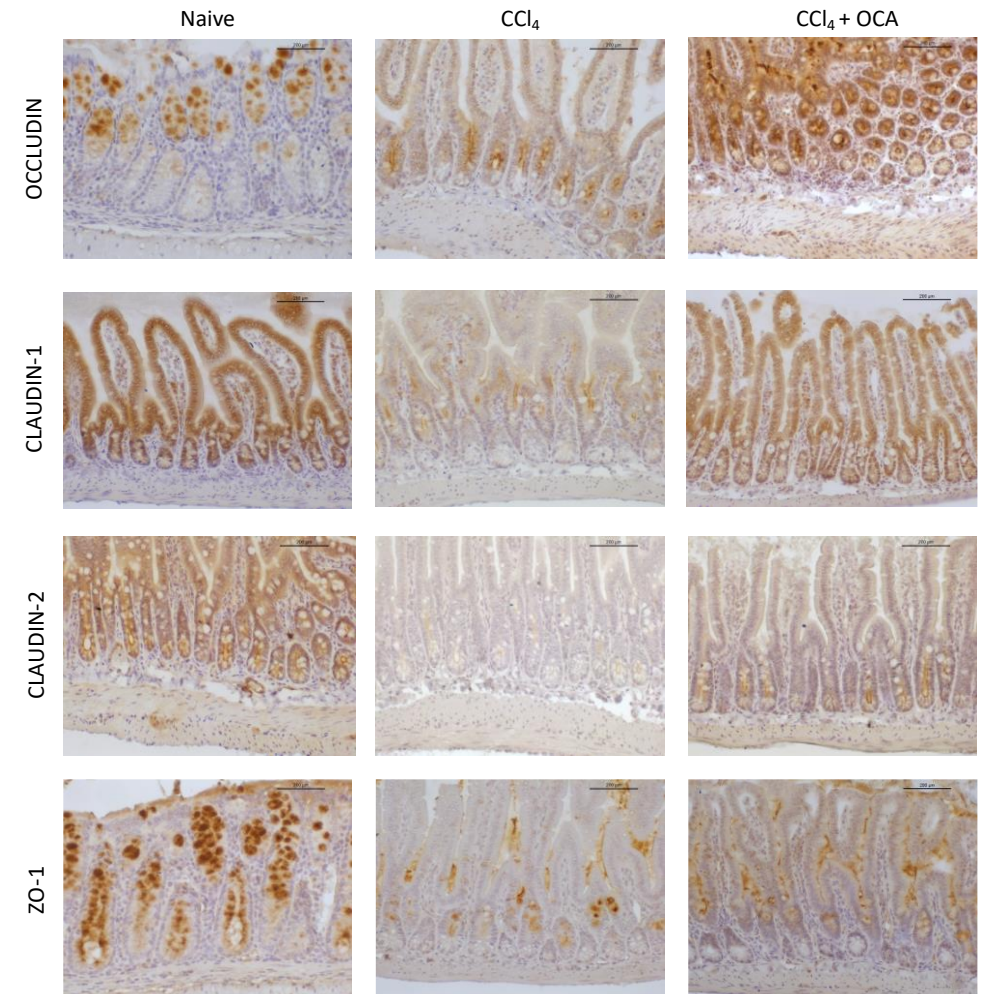
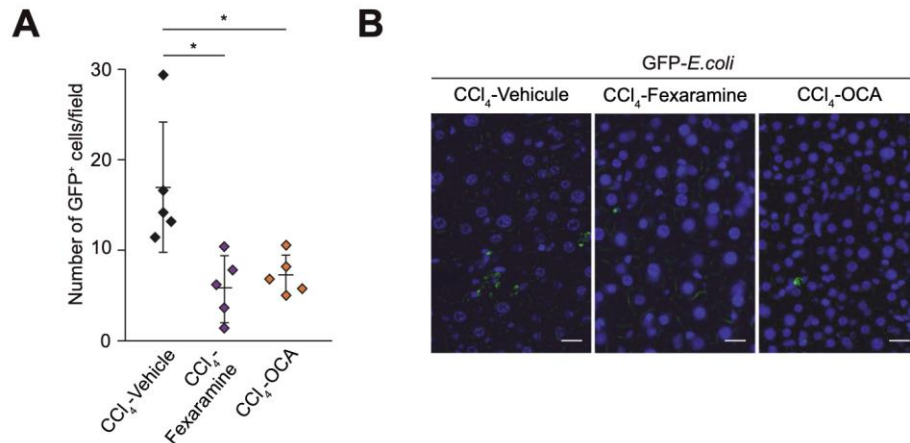


6. Recuperación de la integridad de la barrera

Recuperación de FXR



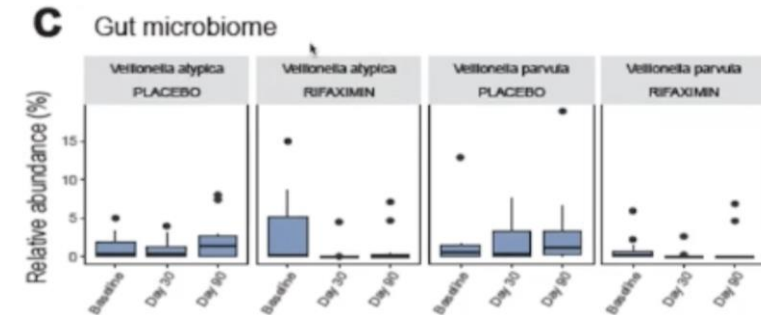
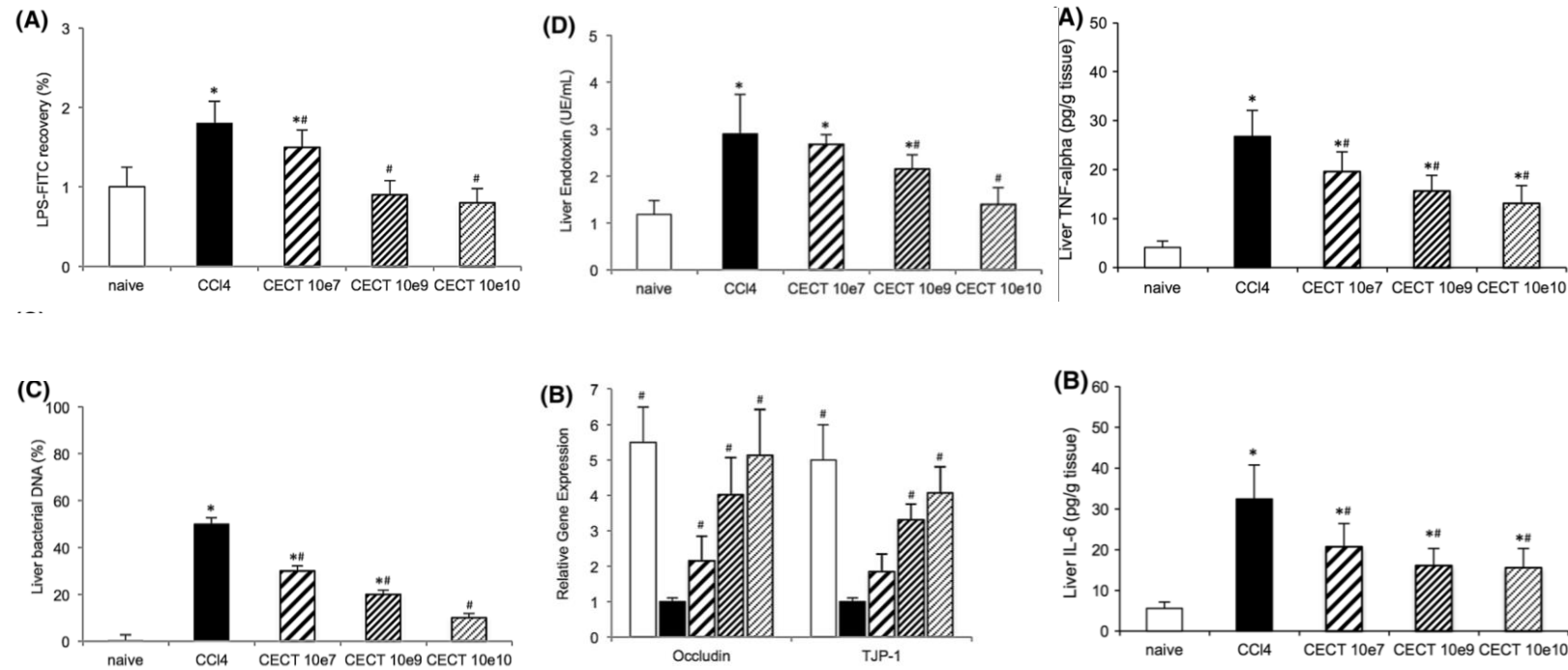
J Hepatol. 2016 May;64(5):1049-1057



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

Recuperación de la integridad de la barrera

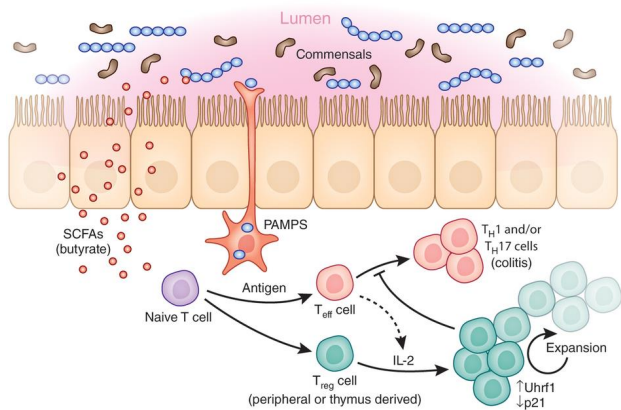
Recuperación de eubiosis



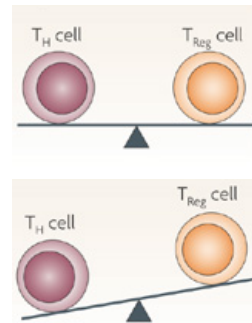
RFX suppresses the growth of bacteria with mucin-degrading capacities

Recuperación de la integridad de la barrera

Recuperación de Tregs

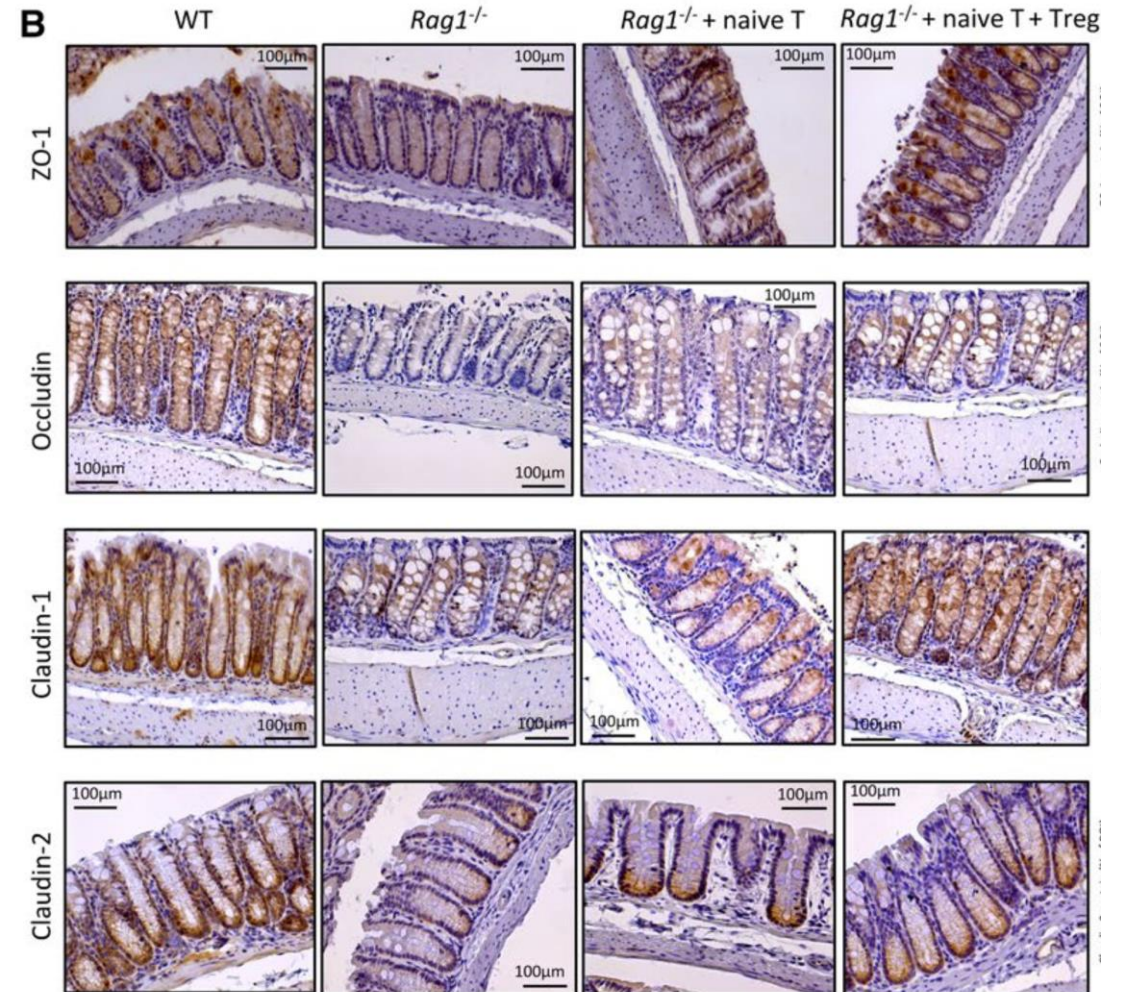


Nat Rev Immunol 9, 313–323 (2009)



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.



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