MÁSTER EN HEPATOLOGÍA

UAM Universidad Autónoma de Madrid

Universidad de Alcalá

Disfunción del sistema inmune asociada a la cirrosis

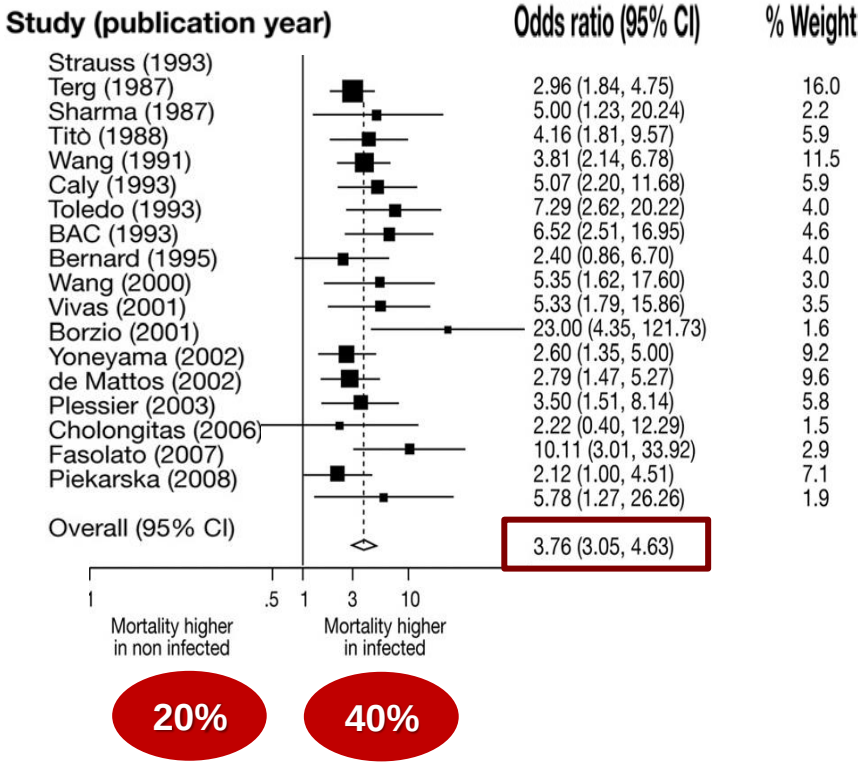
Agustín Albillos

Hospital Universitario Ramón y Cajal, IRYCIS,

Universidad de Alcalá, CIBERehd, Madrid

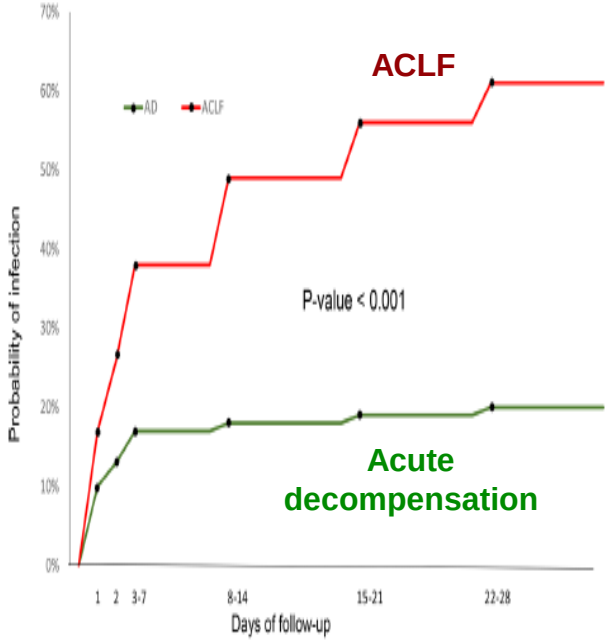
Clinical evidences of immunodeficiency in cirrhosis

Bacterial infection in cirrhosis



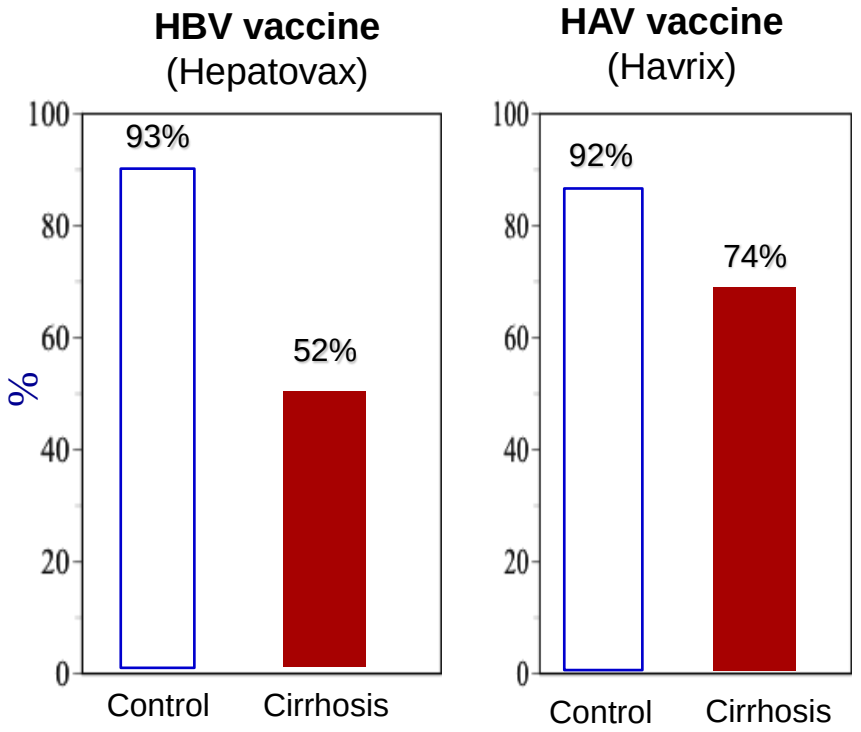
V Arvanity et al. Gastroenterology 2010
J Bajaj et al. Hepatology 2012

Bacterial infection in ACLF



J Fernández et al. Gut 2018

Response to vaccines in cirrhosis



DH Van Thiel et al. Dig Dis Sci 1992

EB Keeffe et al. Hepatology 1999

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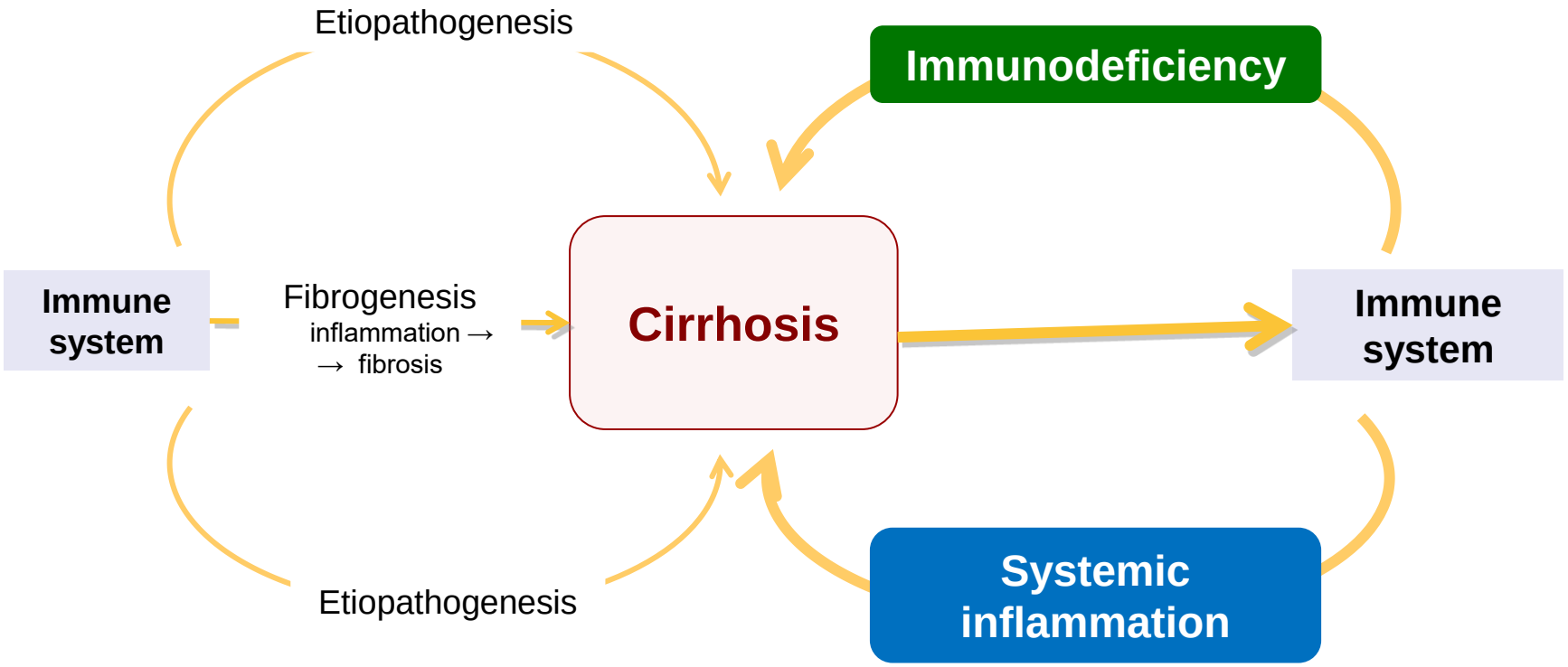
Cirrhosis-associated immune dysfunction (CAID): the impairment of the immune system in cirrhosis



Cirrhosis-associated immune dysfunction (CAID)

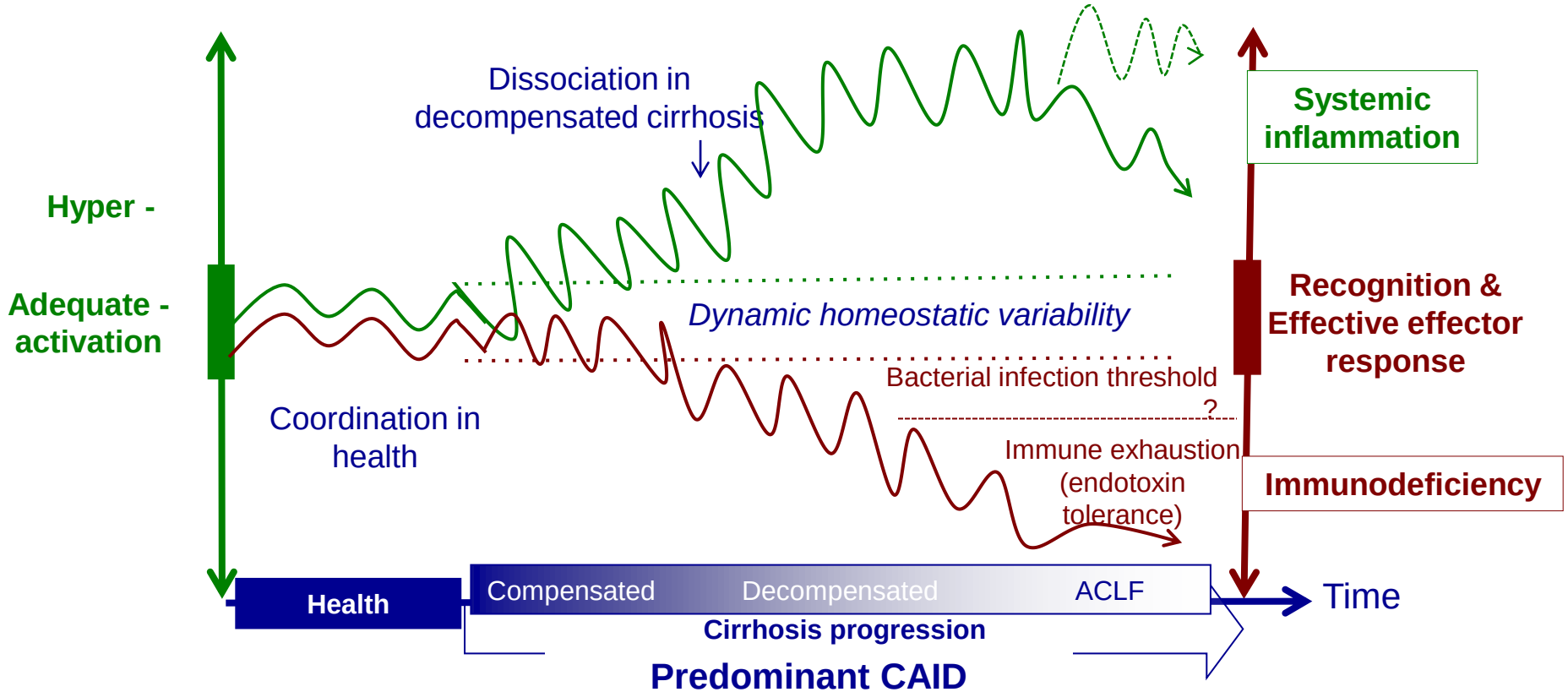
Agenda

Concept and phenotypes

Systemic inflammation

Immunodeficiency

Cirrhosis-associated immune dysfunction: Phenotypes



Predominant CAID phenotypes

Immune characteristic	Pro-inflammatory	Immunodeficient
Pro-inflammatory cytokines (e.g. TNFa, IL-6, IL-1b)	↑↑	↑
Anti-inflammatory cytokines (e.g. IL-10, TGFb)	↑	↑↑
Phagocytosis (e.g. dendritic cells)	↑	↓
HLA-DR/co-stimulatory molecules expression on monocytes/macrophages	↑	↓
Expression of negative regulators (e.g. IRAK-M)	↓	↑

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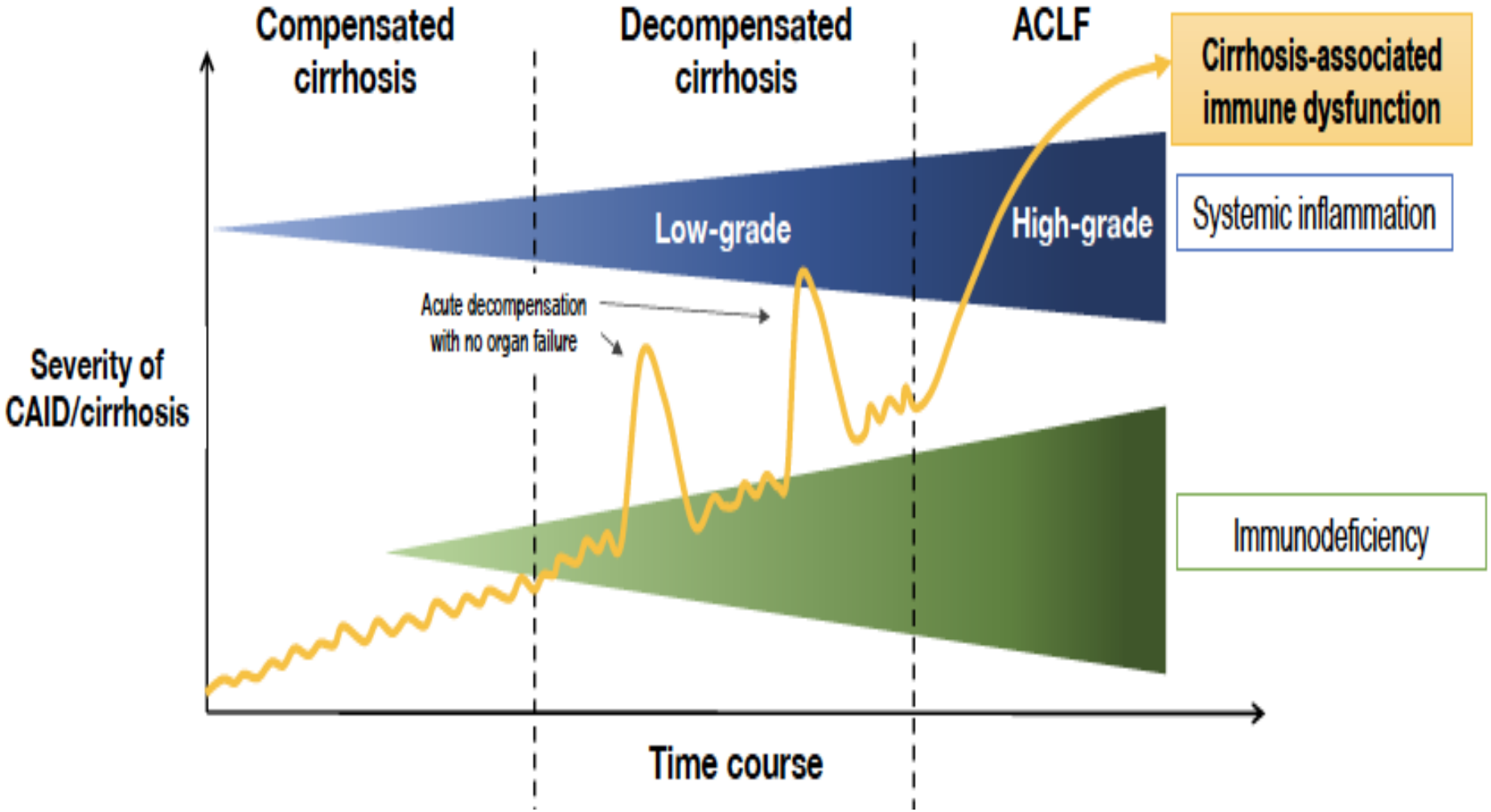
A Albillos et al. JHEP 2014

Cirrhosis-associated immune dysfunction (CAID): dynamics and phenotypes



A Albillos, R Martin et al. NRGH 2021

Cirrhosis-associated immune dysfunction (CAID)

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Concept and phenotypes

Systemic inflammation

Immunodeficiency

Evidences of systemic inflammation in cirrhosis

		Compensated and decompensated cirrhosis*	ACLF
Soluble molecules (serum)	**Acute phase proteins**	↑CRP, ↑LBP	↑↑↑ CRP
	Pro-inflammatory cytokines	↑TNF, IL-1b, IL-6, IL-17, MCP-1, MIP-1b	↑↑↑ Pro-/Anti-inflammatory cytokines
	Endothelial activation	↑ICAM-1, VCAM, VEGF ↑Nitrates/nitrites	↑↑ VEGF
Immune cells	**Neutrophil activation**	↑Respiratory burst ↑CD11b	
	Monocyte activation	↑HLA-DR expression ↑CD80/CD86 expression ↑TNF production	↑↑ CD163 in serum
	T-lymph activation	Th1 polarization ↑IFNγ production	
	B-lymph activation	↑HLA-DR expression	

* Intensity of the abnormalities correlates with the severity of cirrhosis

The intensity of systemic inflammation parallels cirrhosis progression

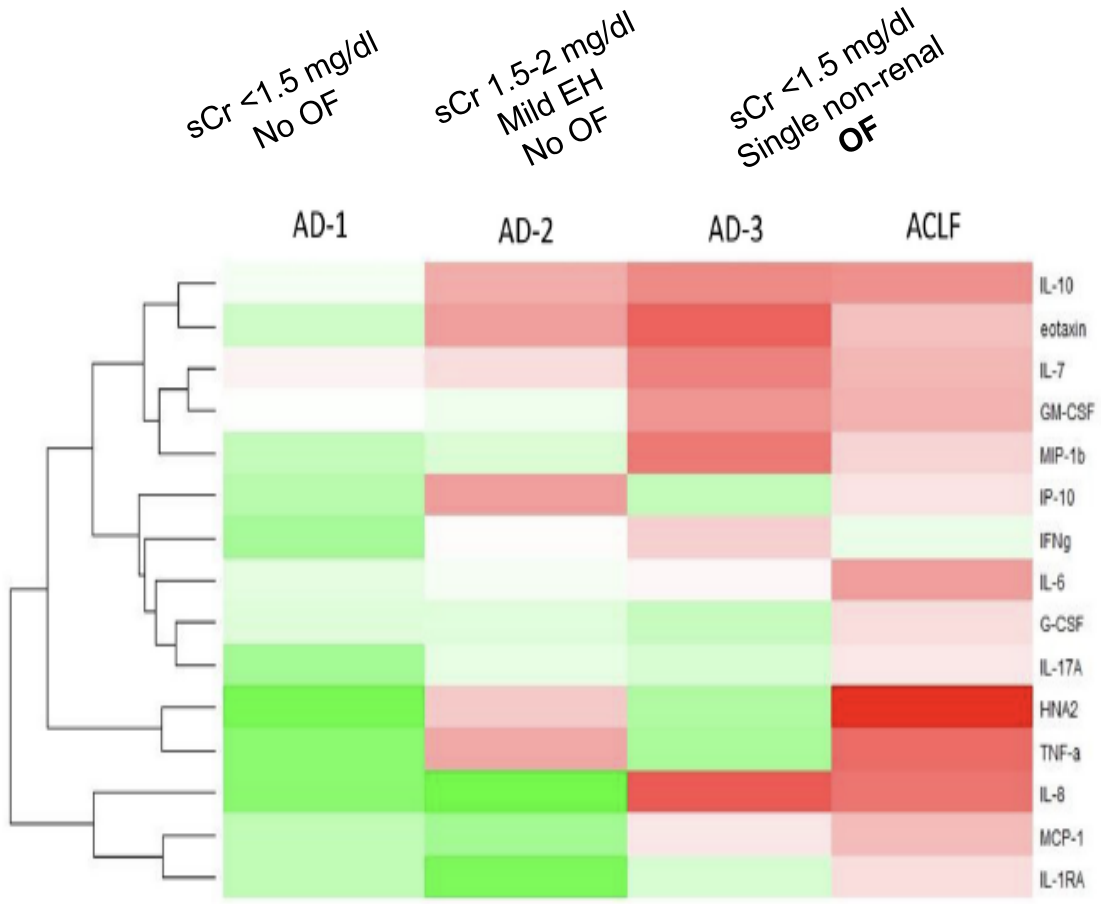
Pro-inflammatory cytokines in serum of patients with compensated and decompensated cirrhosis

	Healthy controls (n=30)	Cirrhotic patients w/o ascites (n=31)	Cirrhotic patients with ascites (n=71)	
			Normal LBP (n=41)	High LBP (n=30)
Endotoxin (EU/ml)	0.29 ± 0.04	0.34 ± 0.03	0.37 ± 0.03	0.68 ± 0.06*
sCD14 (ng/ml)	1384 ± 138	1498 ± 132	1552 ± 98	2676 ± 104*
TNF-α (pg/ml)	1.74 ± 0.4	3.81± 0.3*	5.34 ± 0.4*	**8.5 ± 0.5***
IL-6 (pg/ml)	3.1 ± 0.5	11.2 ± 0.9*	16.3 ± 1.5*	**31.6 ± 1.6***
sTNF-RI (pg/ml)	818 ± 56	1158 ± 68	1510 ± 88*	**2442 ± 354***

* P<0.01 vs. controls

A Albillos et al. Hepatology 2003

Heat-map of systemic inflamation biomarkers in patients with cirrhosis and acute decompensation



J Trebicka et al. Front Immunol 2019

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Mechanisms of inflammasome activation in compensated and decompensated cirrhosis

DIGESTIVO RAMON Y CAJAL MADRID

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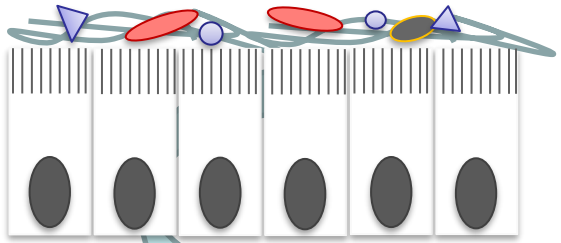
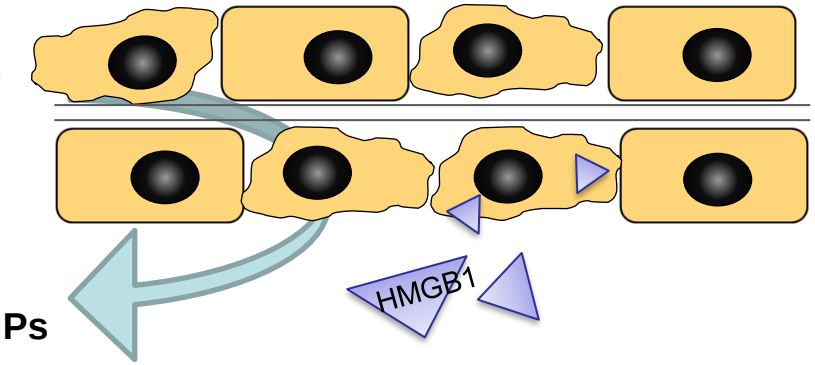
1 **Intestinal barrier dysfunction**
Intestinal dysbiosis



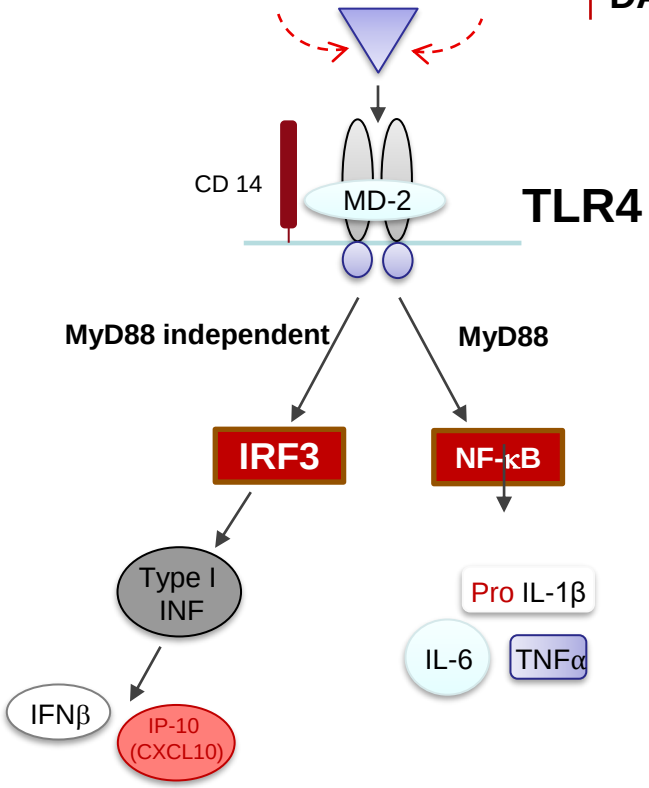
LPS

↑↑ **PAMPs**

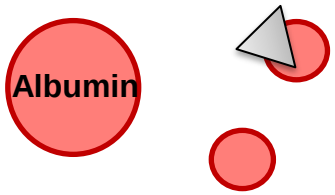
2 Chronically injured hepatocytes (alcohol, virus, steatosis,…)



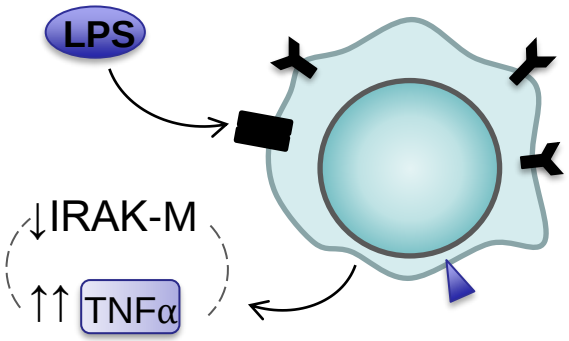
↑ **DAMPs**



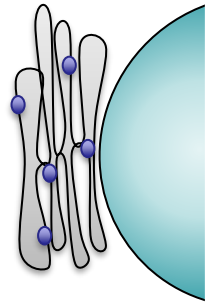
3 Decreased and dysfunctional albumin



4 **Loss of tolerance**



Increased TNFα upon LPS stimulation



Altered unfolded protein response

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Enteric bacterial products drive low-grade systemic inflammation in decompensated cirrhosis: Role of activated monocytes

DIGESTIVO RAMON Y CAJAL MADRID

Universidad de Alcalá

Pro-inflammatory cytokines in serum of patients with compensated and decompensated cirrhosis

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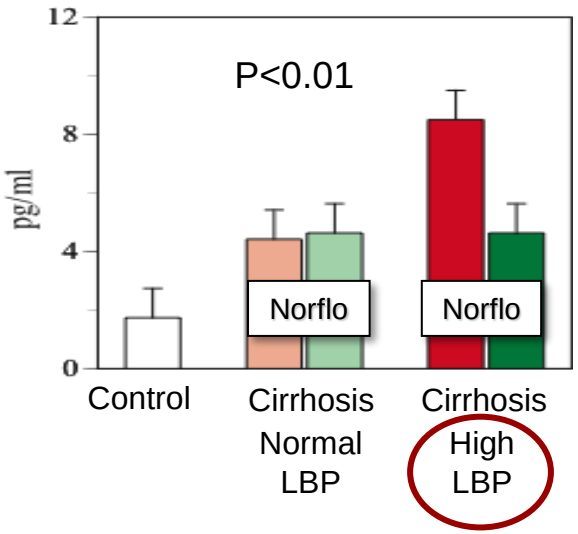
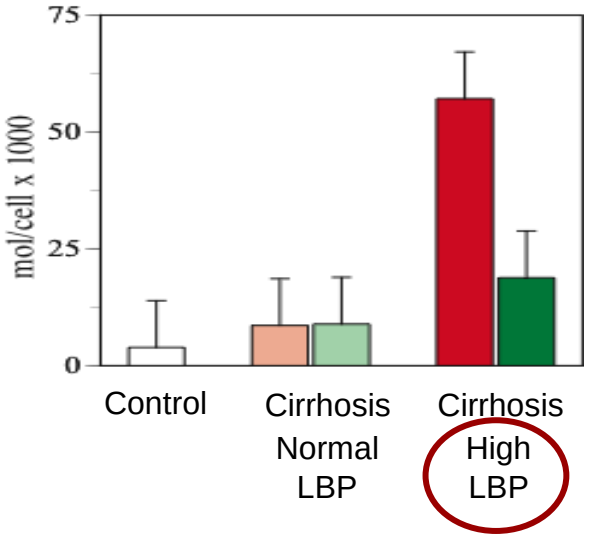
Cirrhosis with ascites

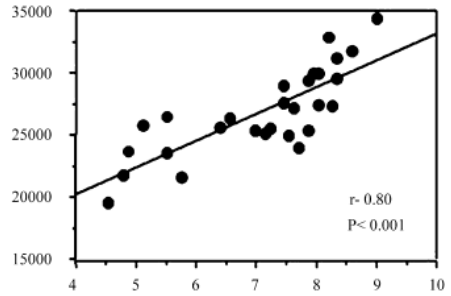
TNFα in serum



Circulating monocytes $CD14^+TNF\alpha^+$



Circulating monocytes $CD14^+TNF\alpha^+$



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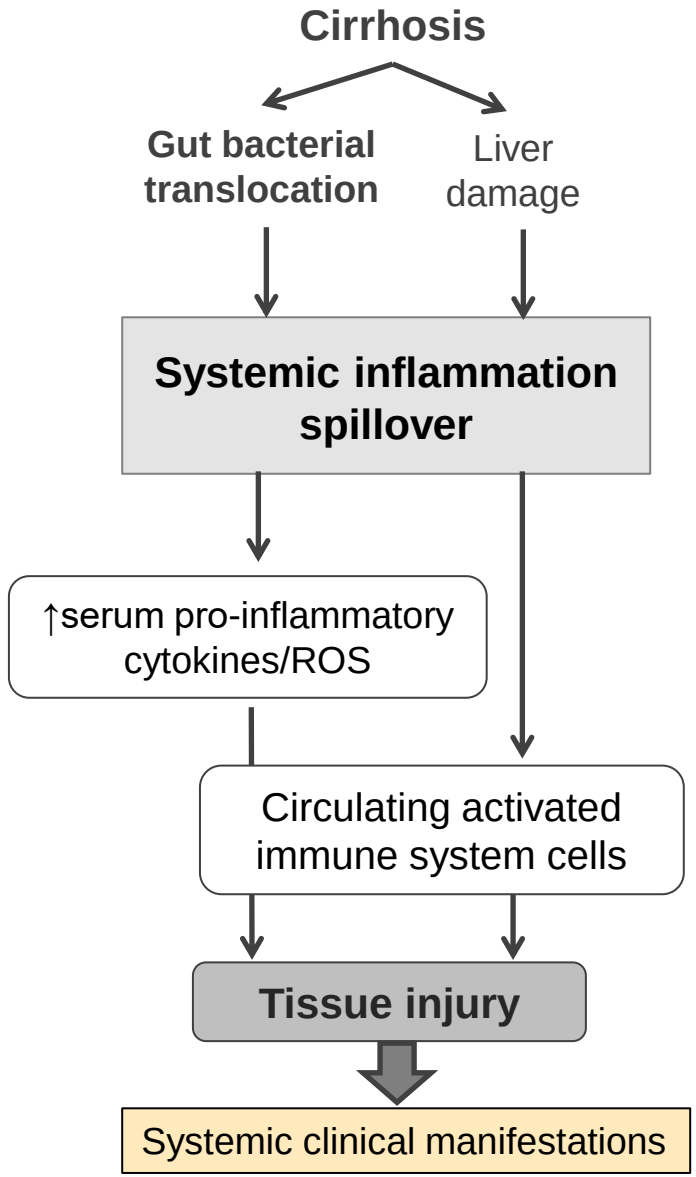
A Albillos et al. Hepatology 2003

A Albillos et al. JHEP 2004

Pathogenesis and consequences of low-grade systemic inflammation

Pathogenesis

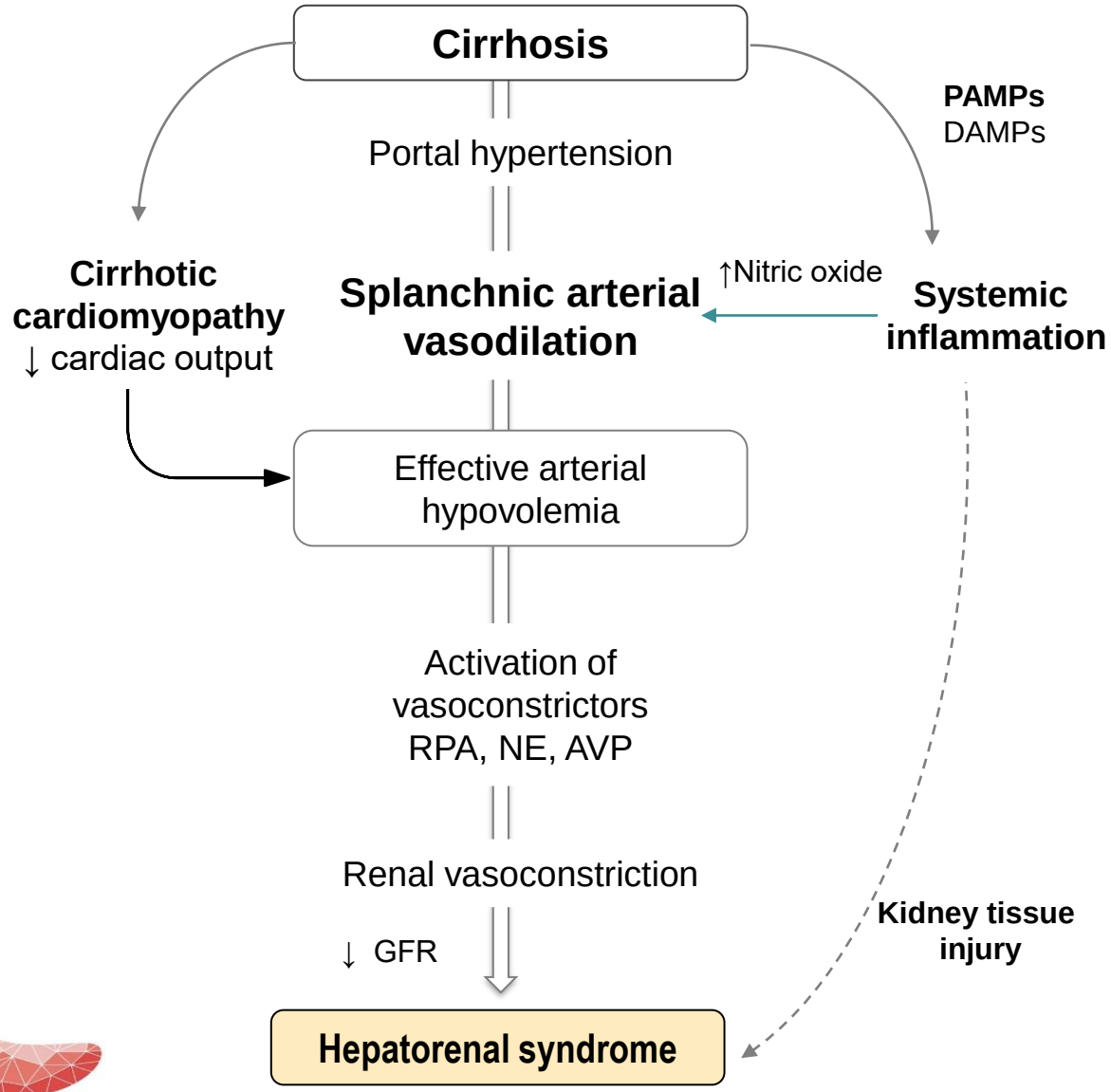


Consequences

Vessels	**Endothelial dysfunction**
Kidney	**Acute kidney injury**
Muscle	Sarcopenia/Frailty
Muscle/ adipose tissue	Insulin resistance
Bone	Osteopenia
Liver	CRP & acute-phase proteins Anemia
Central nervous system	Fatigue, depression

A Albillos et al. NRGH 2021

Portal hypertension, circulatory dysfunction and systemic inflammation as drivers of cirrhosis progression

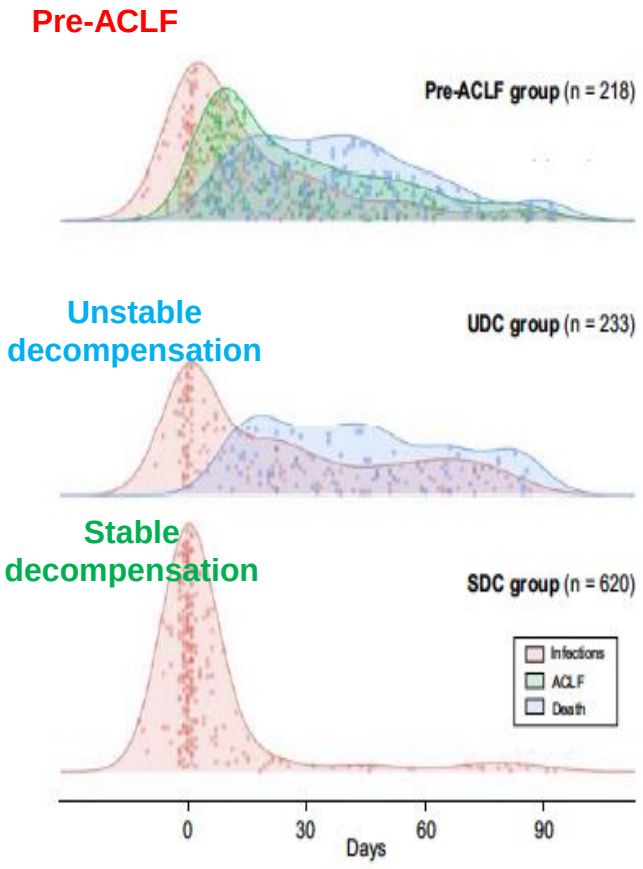


Acute decompensation in cirrhosis: three clinical courses

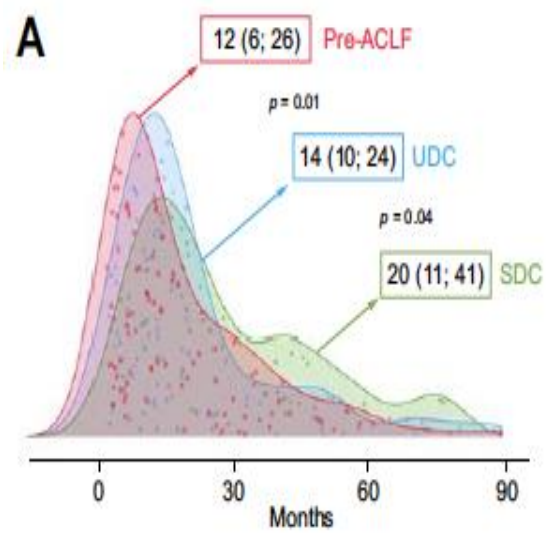
PREDICT study

1071 patients with cirrhosis with acute decompensation (w/o organ failure)
Follow-up 3 months and 1 year after the event

Density curves of events

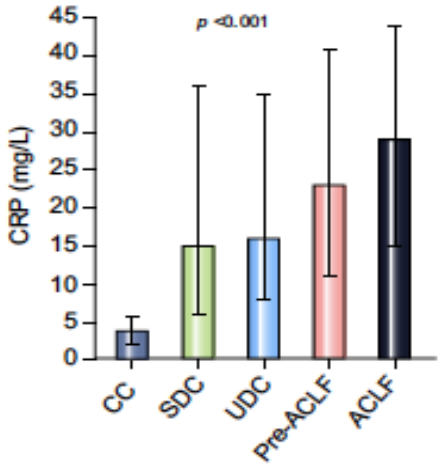


Density curves of LTx/death

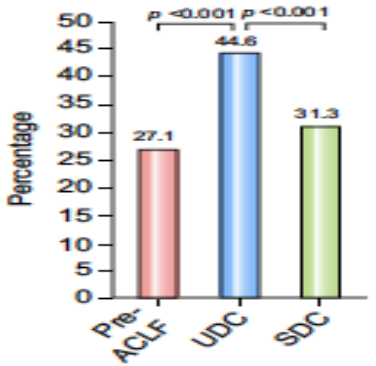


J Trebicka et al. JHEP 2020

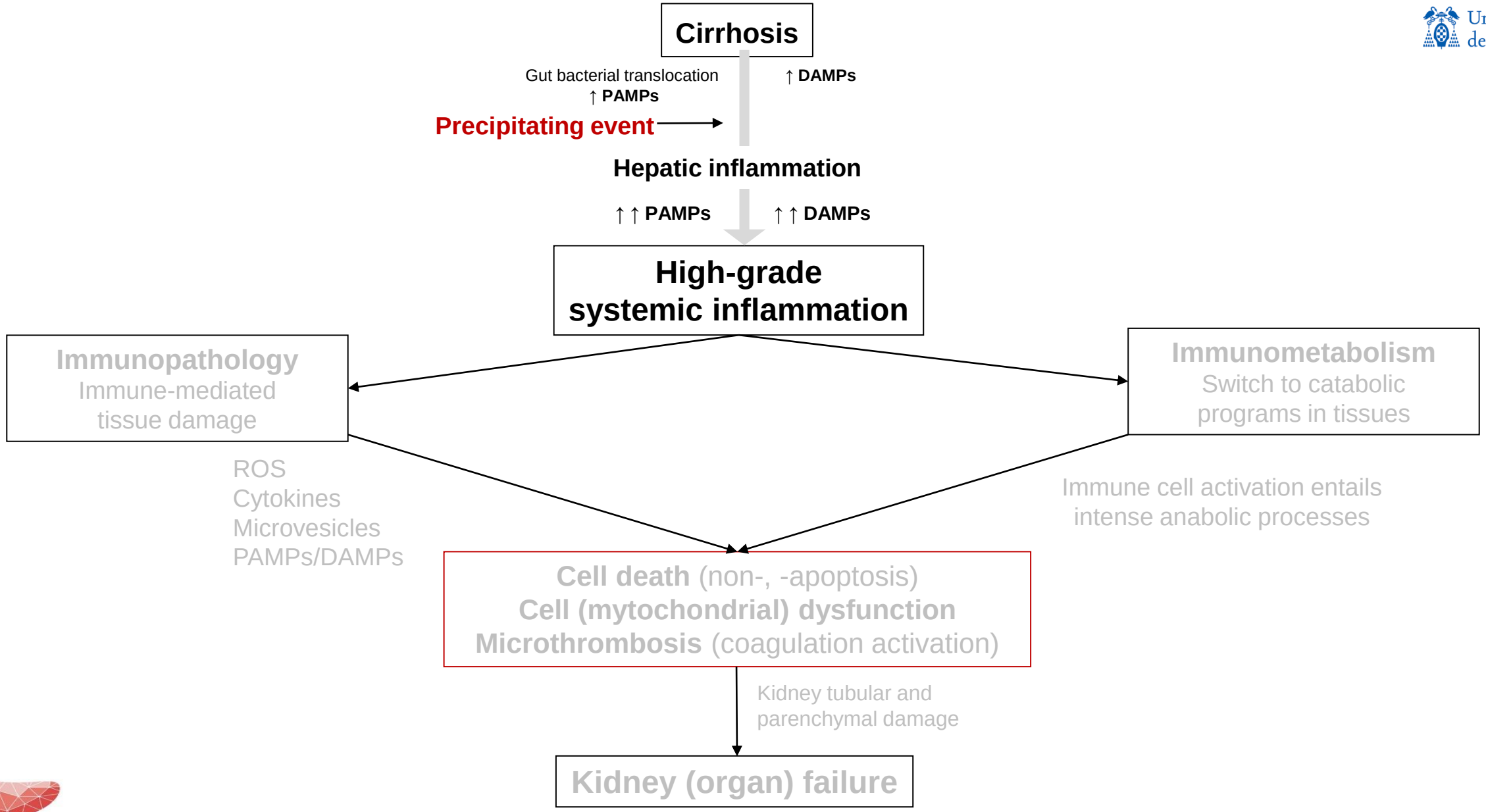
C-reactive protein



Surrogate of severe portal hypertension

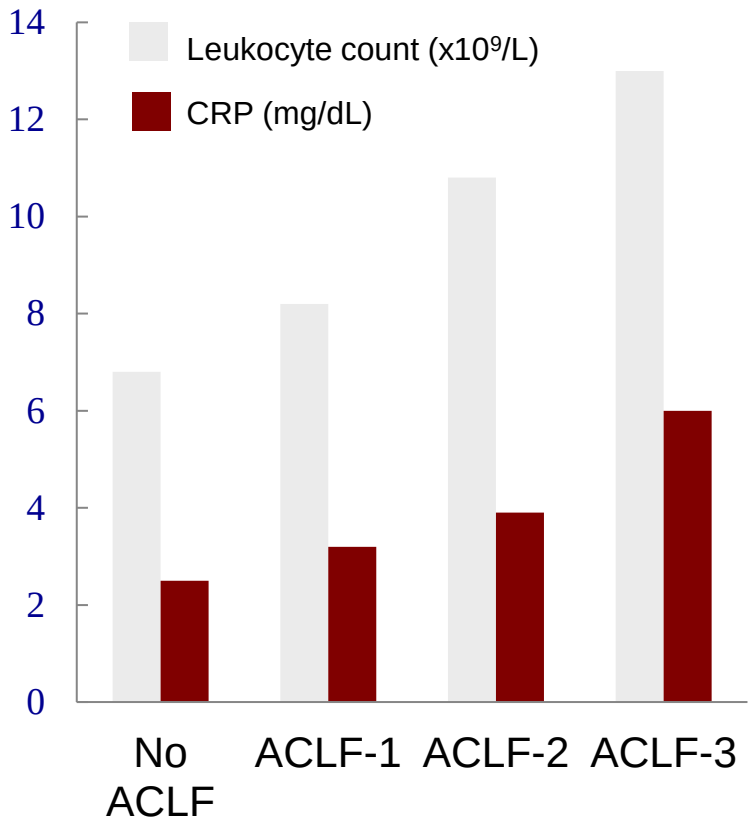


Pathogenesis of non-HRS-AKI in ACLF



High-grade systemic inflammation in ACLF: relationship with the number of organ failures (ACLF grade)

Relationship between ACLF and inflammatory markers



Relationship between ACLF and inflammatory markers

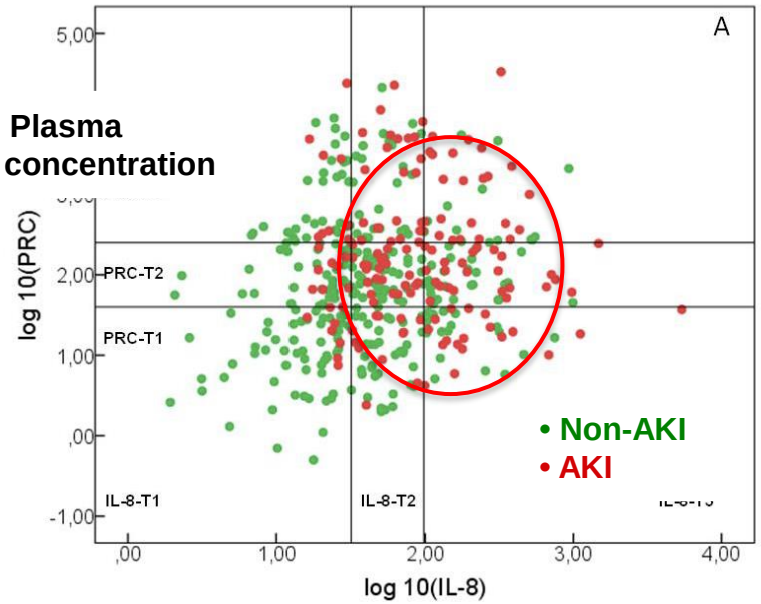
	ACLF-I N = 126	ACLF-II N = 86	ACLF-III N = 25	P Value*
Markers of SCD				
Plasma renin concentration (microIU/mL)	169 (40-383)	114 (28-352)	87 (33-258)	0.771
PCC (pmol/L)	34 (16.62)	27 (13-45)	47 (11.134)	0.224
Proinflammatory cytokines				
TNFα (pg/mL)	30 (21-43)	26 (15-36)	32 (17-43)	0.029
IL-6 (pg/mL)	34 (18-96)	43 (13-106)	111 (32-355)	0.018
IL-8 (pg/mL)	62 (37-112)	97 (48-192)	144 (80-292)	<0.001
MCP-1 (pg/mL)	412 (299-633)	376 (277-646)	660 (322-1,773)	0.089
IP-10 (pg/mL)	1,218 (717-2,258)	1,162 (617-1,946)	1,689 (899-2,728)	0.267
MIP-1β (pg/mL)	27 (18-43)	28 (19-55)	46 (20-61)	0.112
G-CSF (pg/mL)	32 (15-70)	29 (14-81)	39 (15-209)	0.673
GM-CSF (pg/mL)	6.8 (3.7-15.0)	7.5 (2.7-20.1)	11.3 (5.1-29.6)	
Anti-inflammatory cytokines				
IL-10 (pg/mL)	4.3 (1.1-17.9)	15.3 (5.5-41.5)	12.4 (6.6-40.8)	<0.001
IL-1ra (pg/mL)	17 (10-45)	26 (8-63)	49 (24-135)	0.019

R Moreau et al. Gastroenterology 2013

J Claria et al. Hepatology 2017

Renal dysfunction is associated with markers of systemic inflammation in ACLF

Relationship between plasma renin concentration and IL-8 in AKI of ACLF

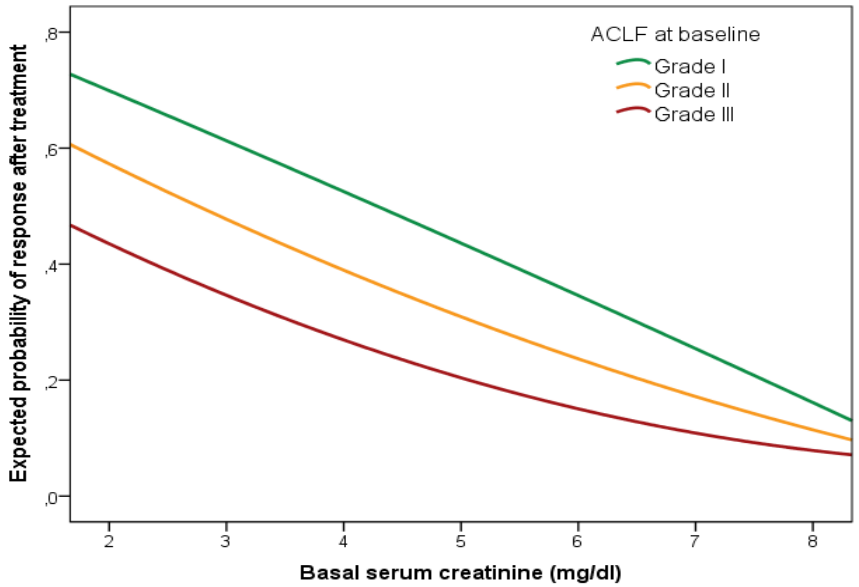


Interleukin-8

Normal plasma renin concentration in 15% of AKI in ACLF

J Claria et al. Hepatology 2017

Relationship between ACLF grade and response to terlipressin in HRS



S Piano et al. CGH 2019

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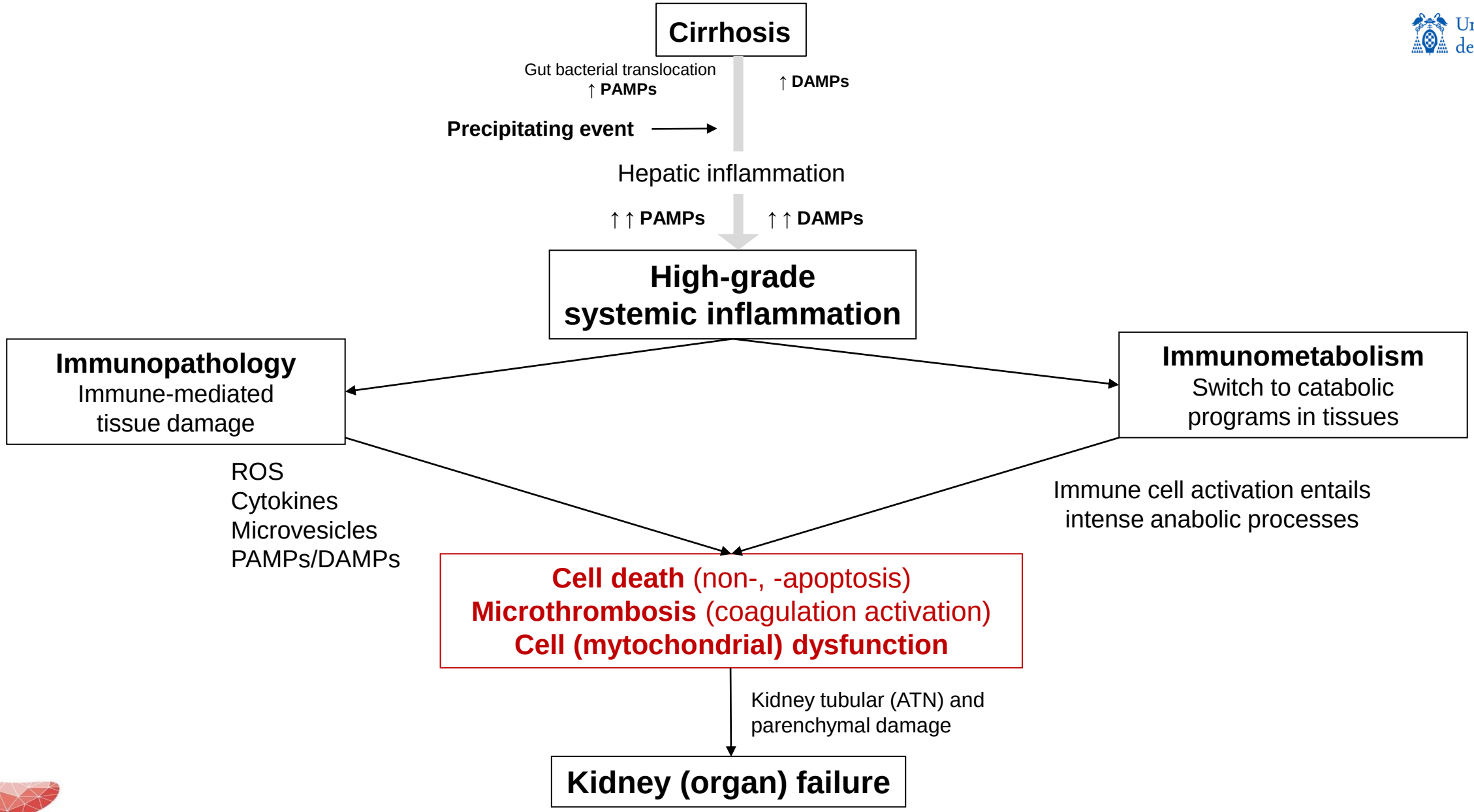
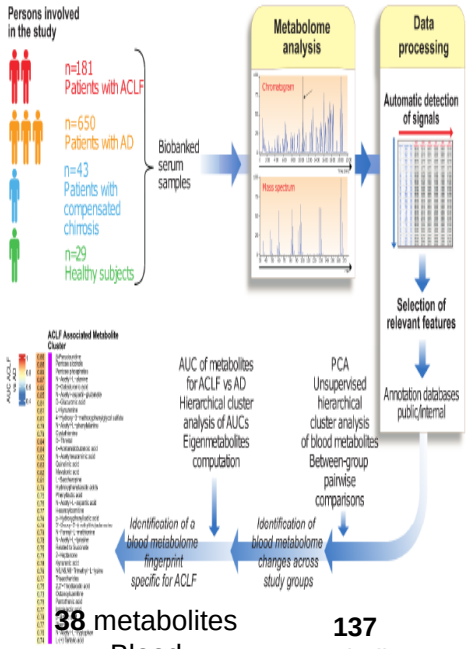


A distinctive blood metabolite fingerprint in ACLF uncovers inflammation-associated mitochondrial dysfunction

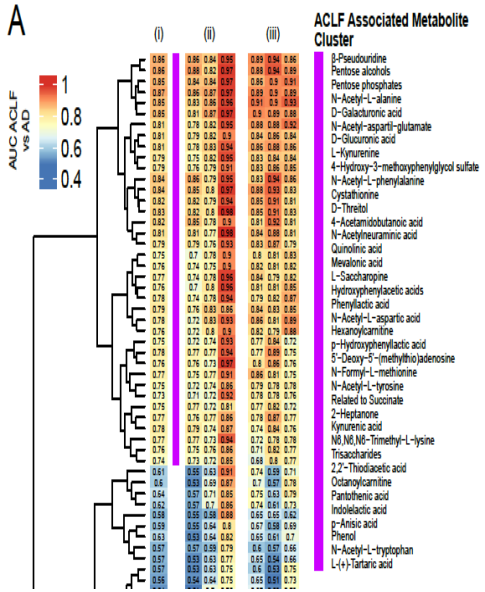
ACLF metabolome fingerprint



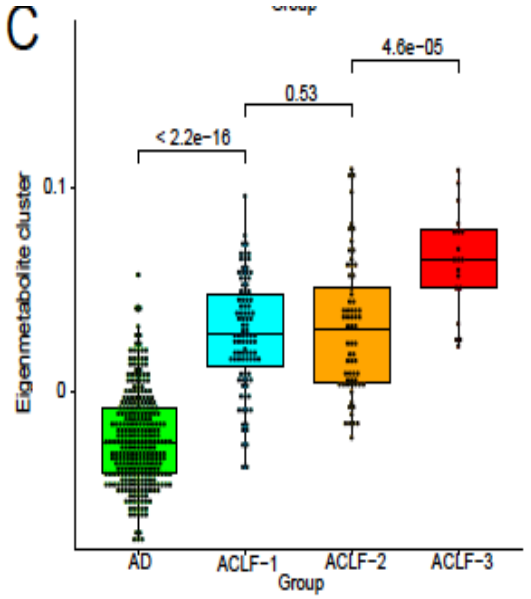
38 metabolites
Blood fingerprint

137 metabolites

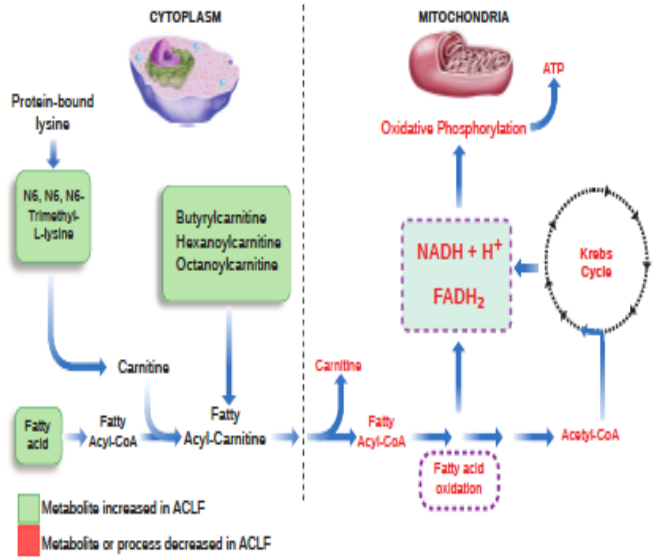
Intensity of metabolome fingerprint



- **Fingerprint** similar across ACLF phenotypes



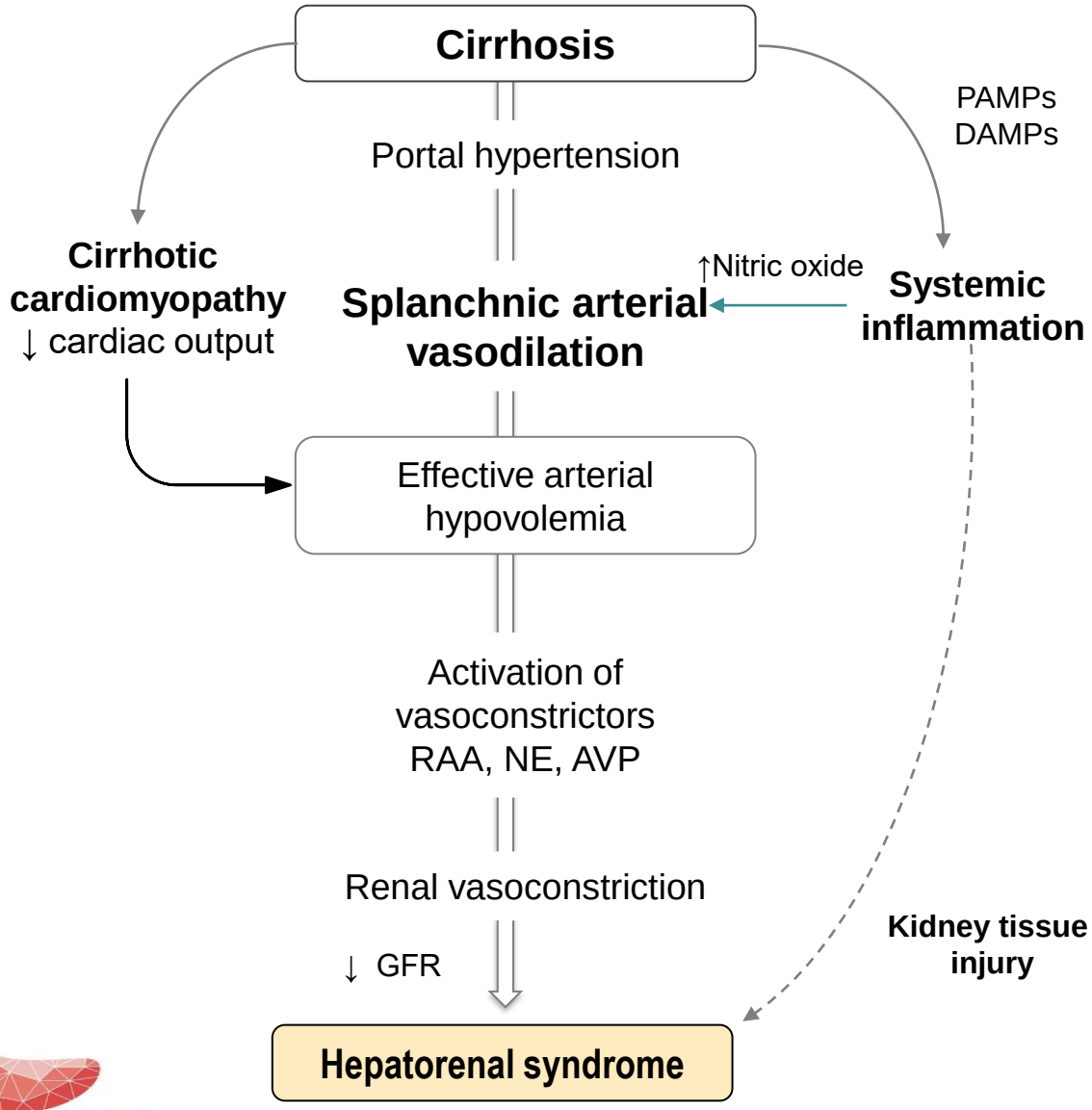
- Intensity correlated with systemic inflammation biomarkers

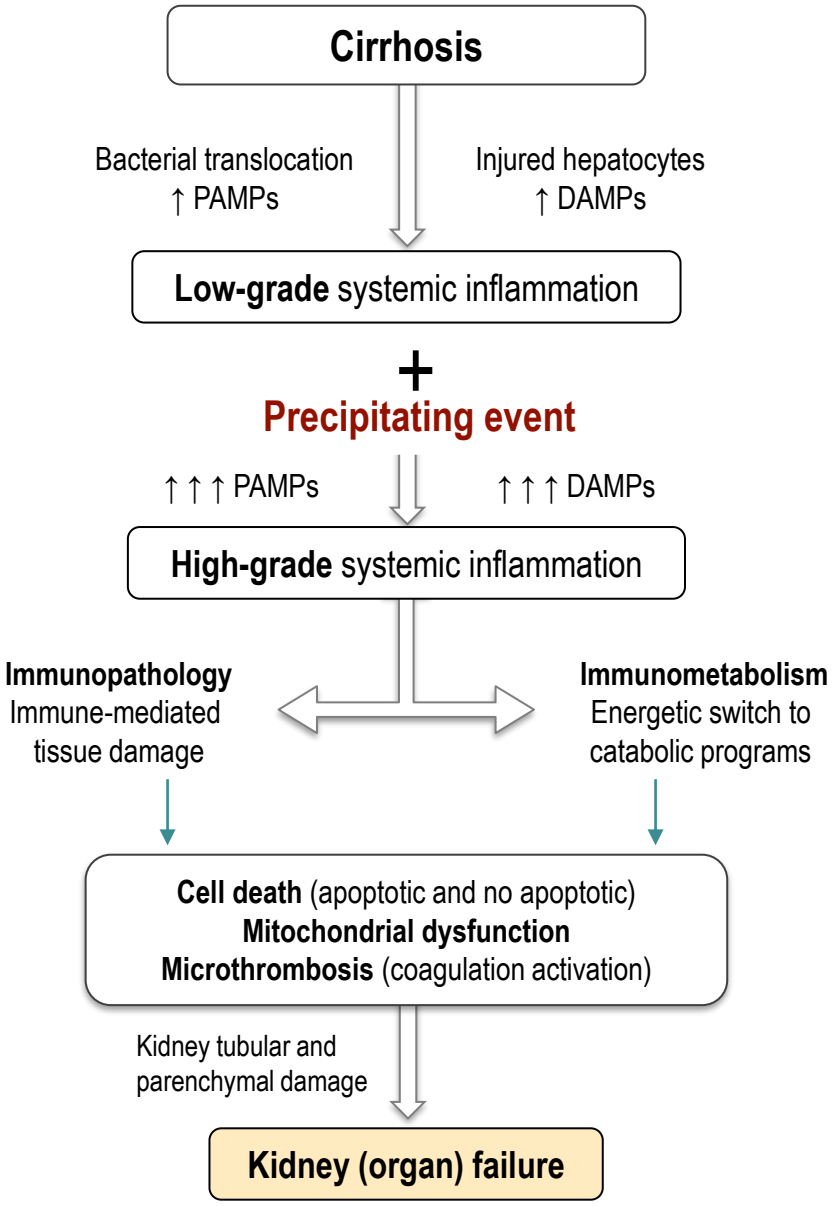


↓ mitochondrial oxidative phosphorilation (OXPHOS): ↓ATP, ↓FA-ox
↑ aerobic glycolysis: ↓ ATP, ↑lactate
↑ lypolisys and proteolysis

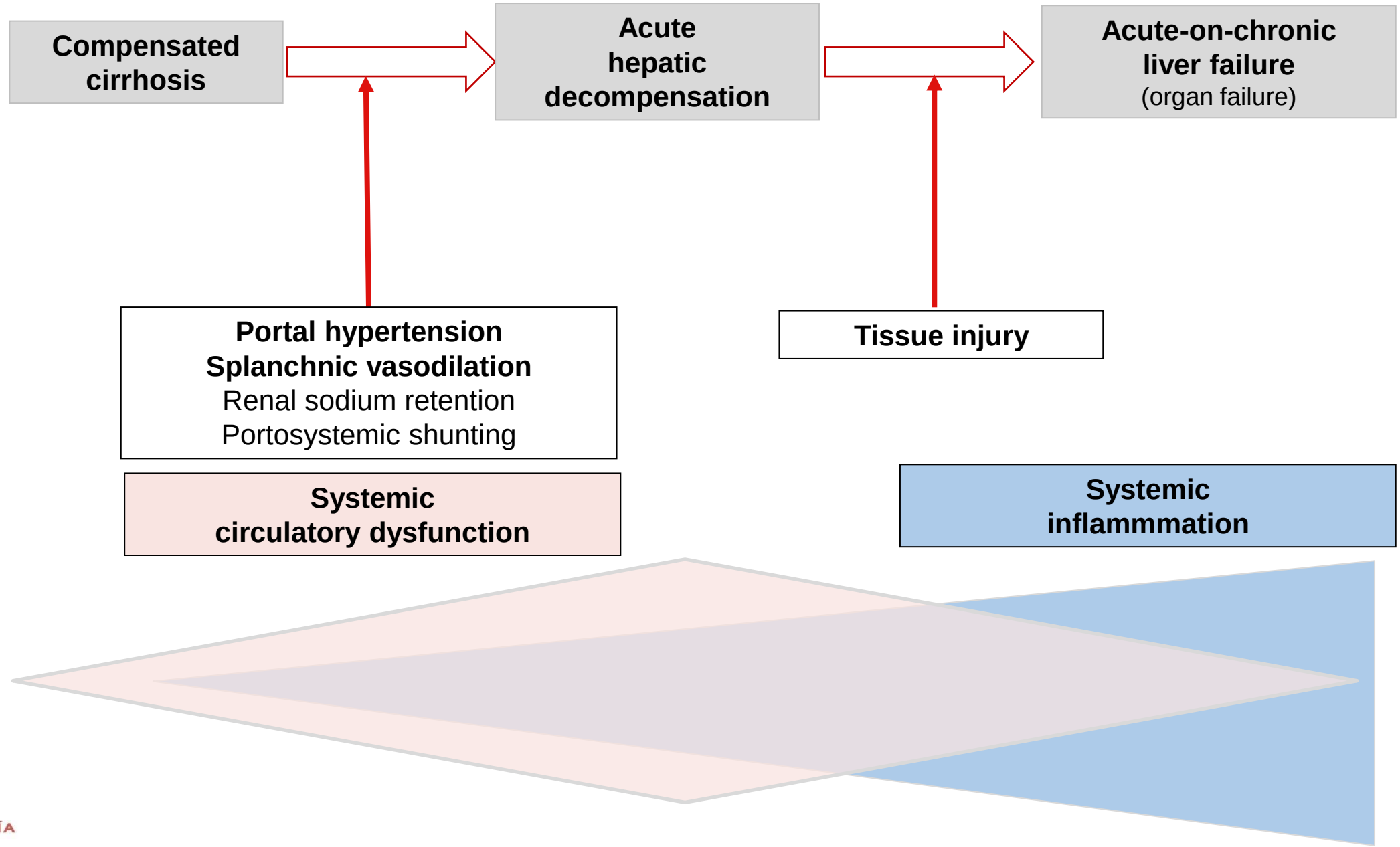
R Moreau et al. JHEP 2020

Portal hypertension, circulatory dysfunction and systemic inflammation as drivers of cirrhosis progression





Drivers of cirrhosis progression



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Immunodeficiency

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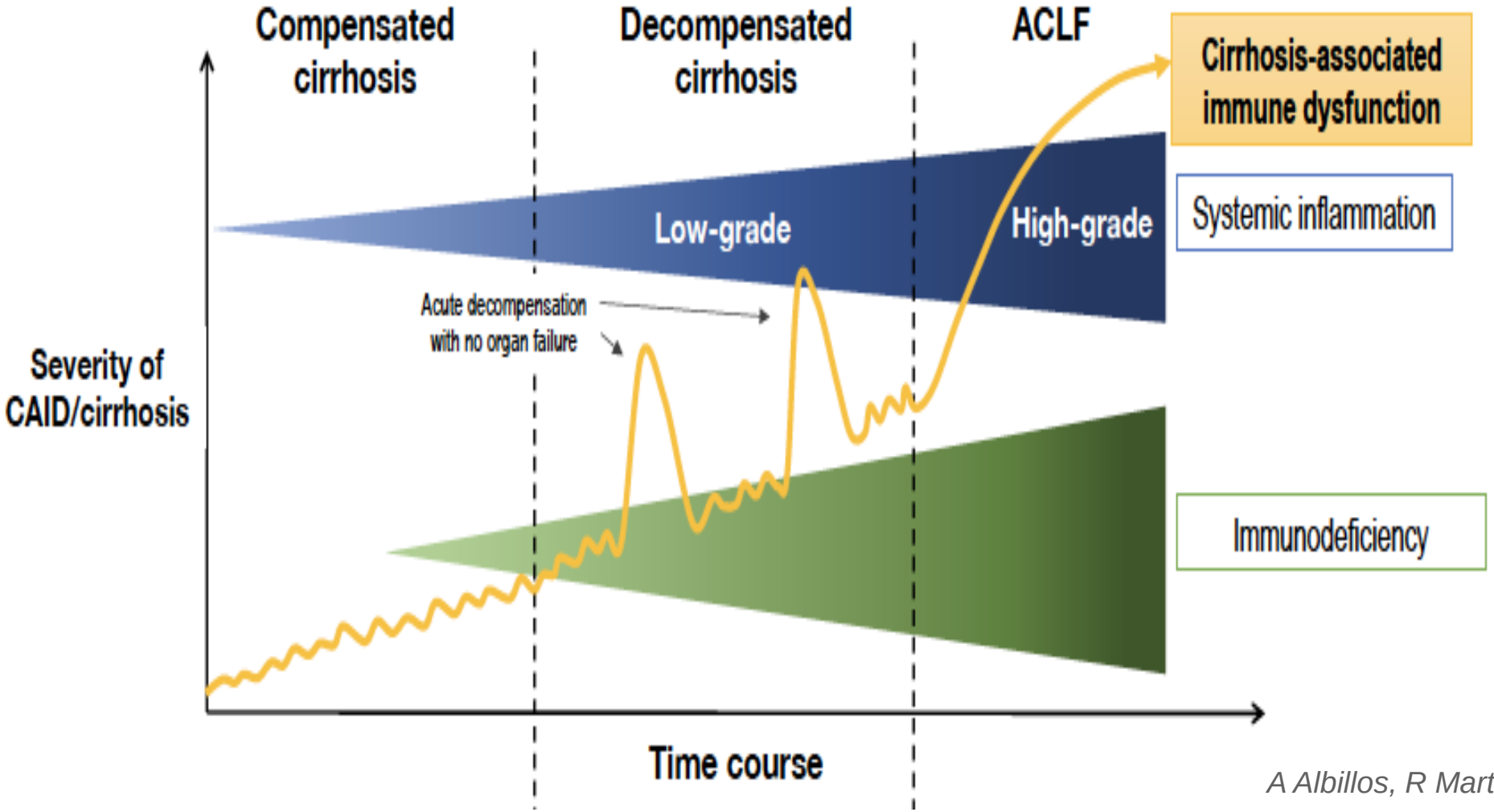
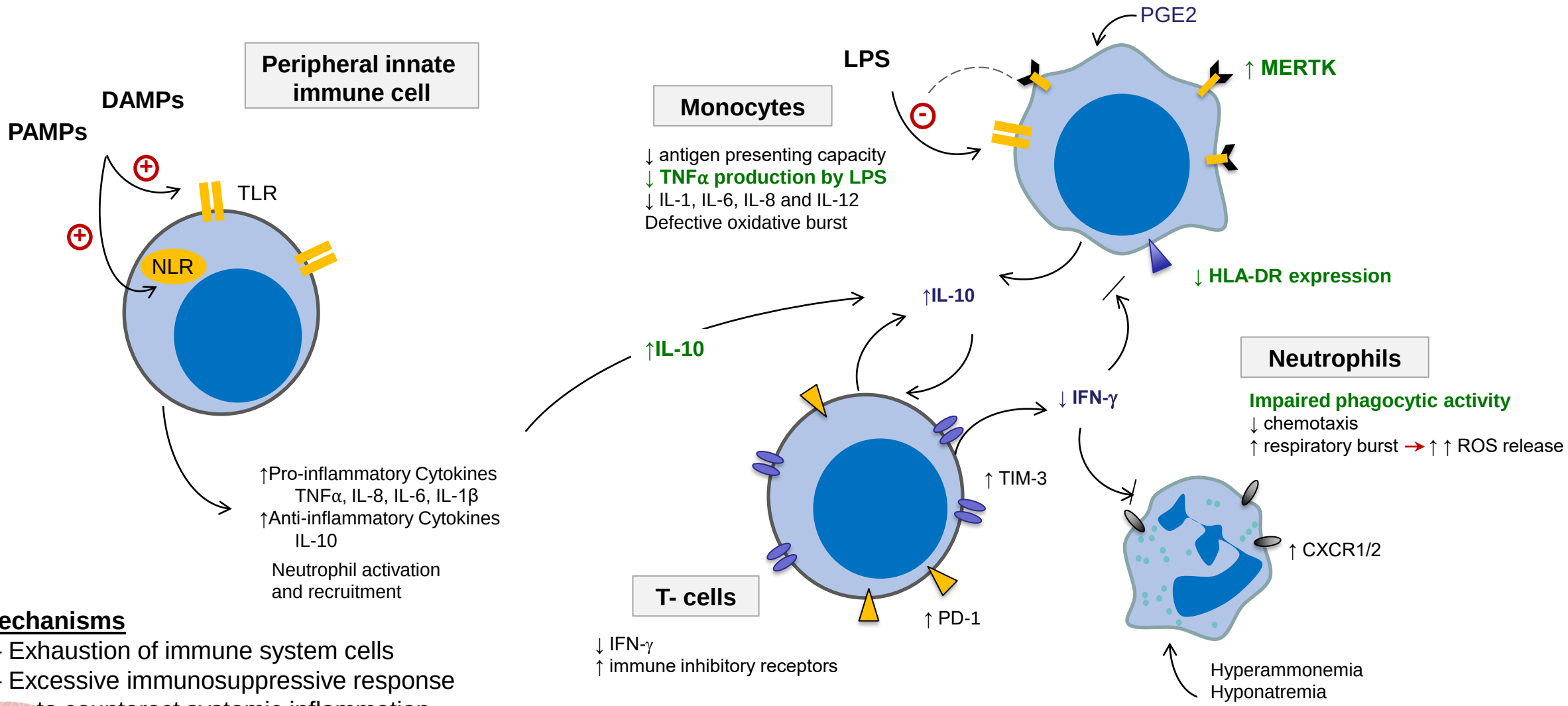


A Albillos, R Martin et al. NRGH 2021

Dysfunctional immune response in ACLF

High-grade systemic inflammation

Immune cell paralysis



Mechanisms

— Exhaustion of immune system cells

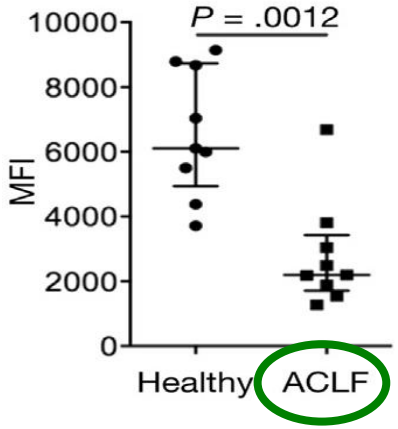
— Excessive immunosuppressive response to counteract systemic inflammation

— Reprogramming of immune system cells by energetic imbalance and metabolic abnormalities of cirrhosis

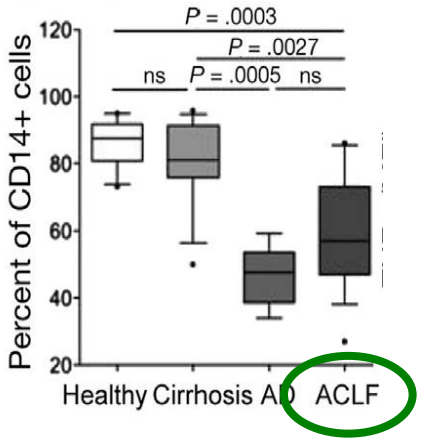
R Martin et al. Front Immunol 2020

“Immunoparesis” of monocytes from patients with ACLF: relationship with increased monocytes expressing the tyrosine kinase receptor, MERTK

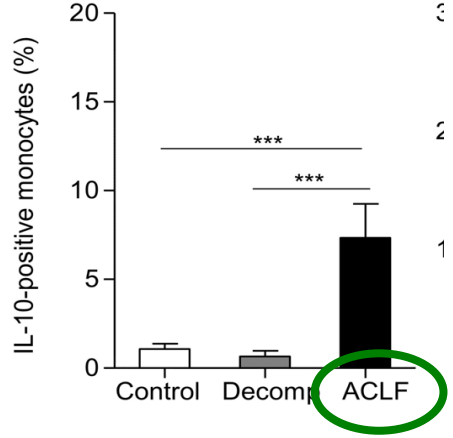
HLA-DR



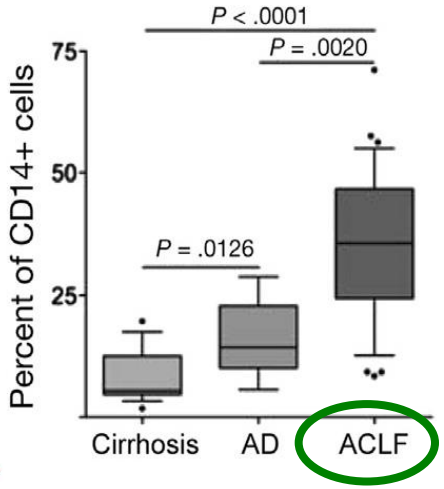
TNFα production with LPS stimulation



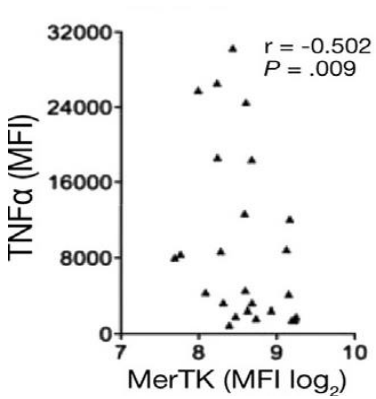
IL-10 positive monocytes



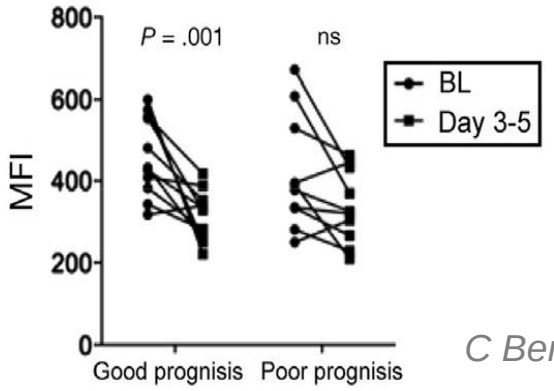
MERTK+



LPS induced TNFα negatively correlates with MERTK+



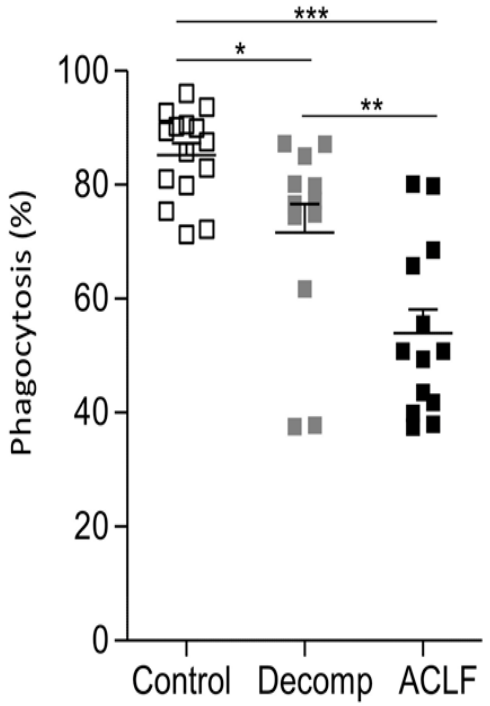
MERTK+ correlates with prognosis



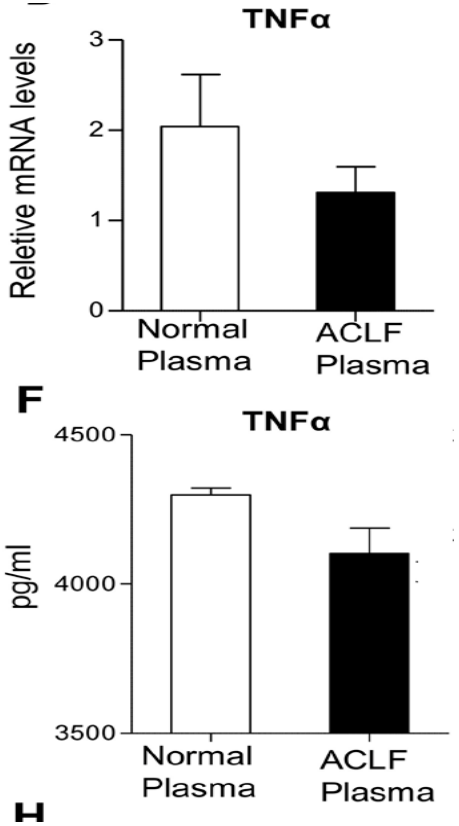
HE Wasmuth et al. JHEP 2005
A O’Brien et al. Nat Med 2014
C Bernsmeier et al. Gastroenterology 2015
H Korf et al. Gut 2020

Pharmacological regulation of metabolic programs partially restores dysfunction of monocytes in ACLF

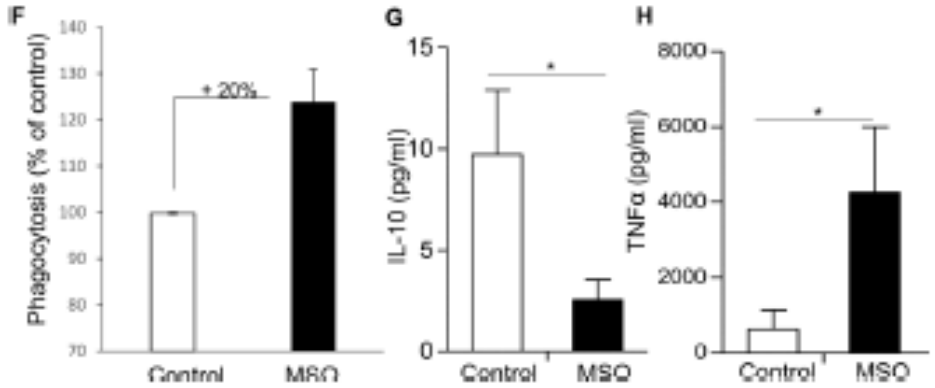
Reduced phagocytosis after E coli challenge

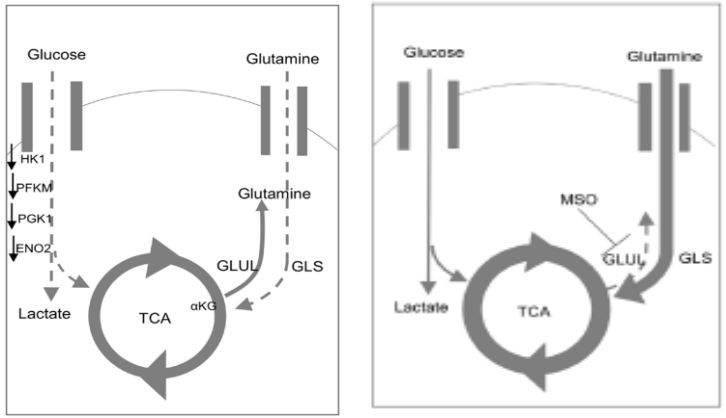


Reduced TNFα in CD14+CD16- monocytes from healthy donors



Blocking glutamine synthetase restores phagocytosis, ↓ IL-10 and ↑TNFα production …





… and fuels TCA cycle in monocytes

H Korf et al. Gut 2019

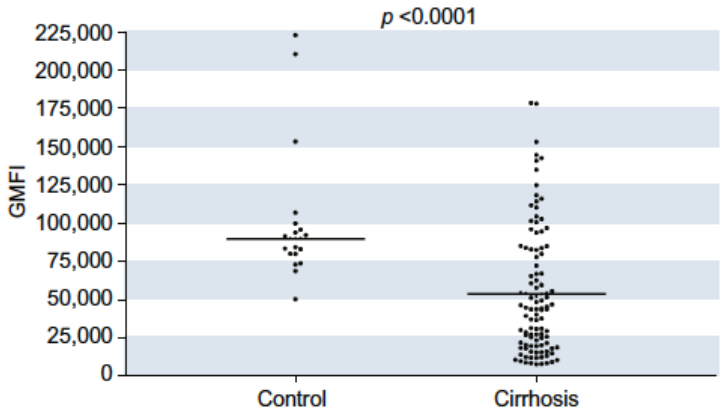
MÁSTER EN HEPATOLOGÍA

Plasma from patients with cirrhosis induces phagocytic dysfunction in normal neutrophils

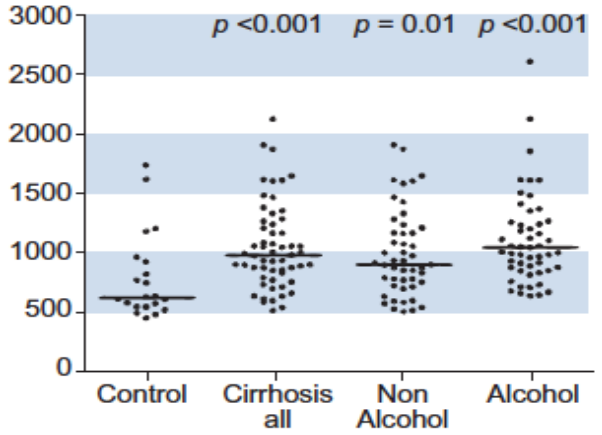
DIGESTIVO RAMON Y CAJAL MADRID

Universidad de Alcalá

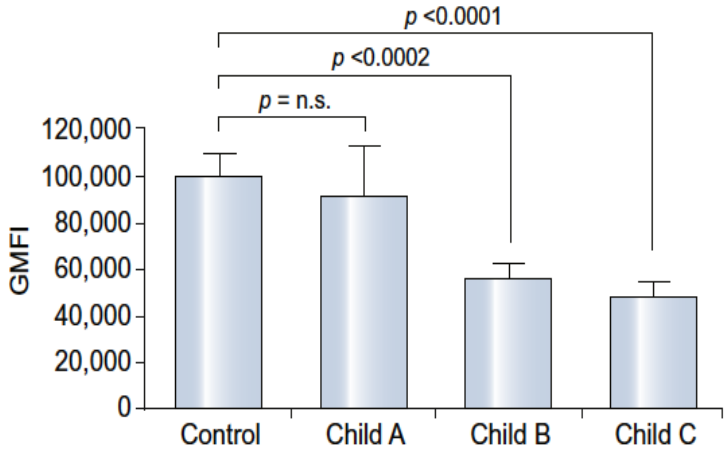
Phagocytic capacity of normal neutrophils after incubation with control or patient plasma



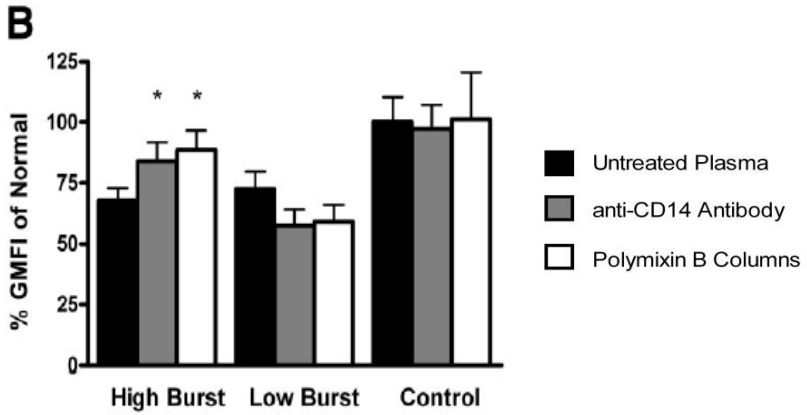
Expression of TLR4 by incubation of neutrophils with plasma



Neutrophil phagocytic capacity according to the severity of liver disease



Reversal of impaired phagocytosis after incubation of neutrophils with endotoxin removed plasma



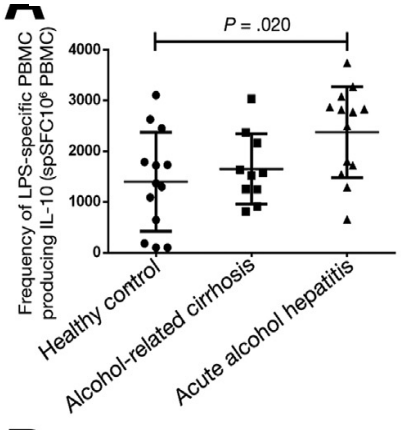
R Mookerjee et al. Hepatology 2007
G Tritto et al. JHEP 2011

MÁSTER EN HEPATOLOGÍA

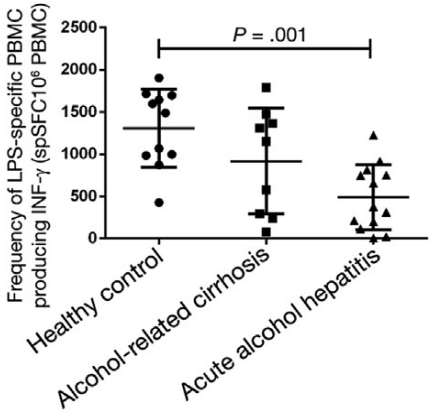
Blockade of PD1 and TIM3 restores adaptative and innate immunity in acute alcoholic hepatitis

20 patients with AAH
16 patients with advanced alcoholic cirrhosis
12 healthy controls

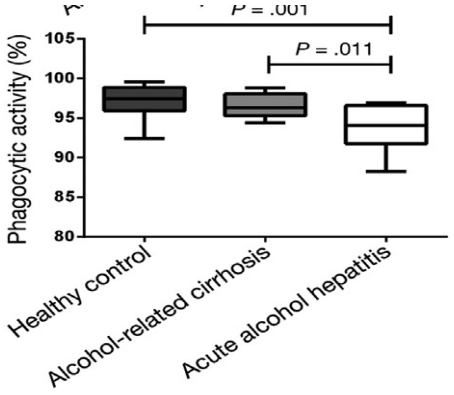
Increased LPS PBMC producing IL-10



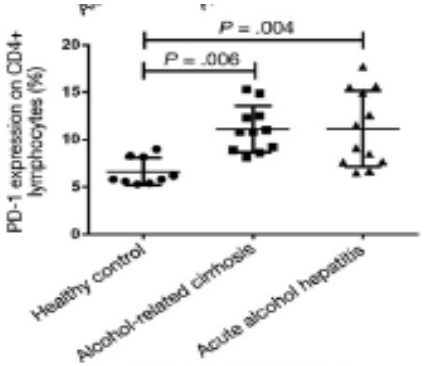
Decreased LPS PBMC producing INF-γ



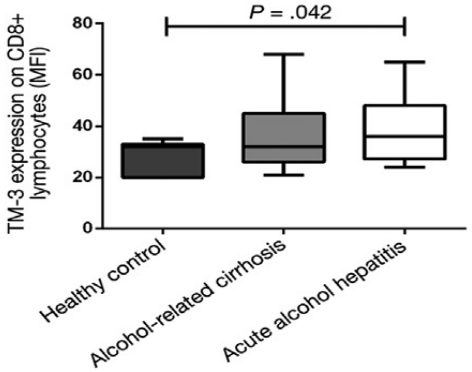
Reduced neutrophil phagocytosis



Higher PD1 expression on T cells



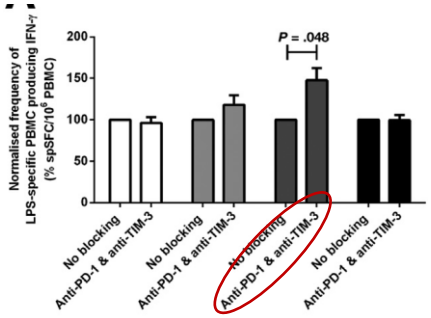
Higher TIM-3 (and PDL1) expression on T cells



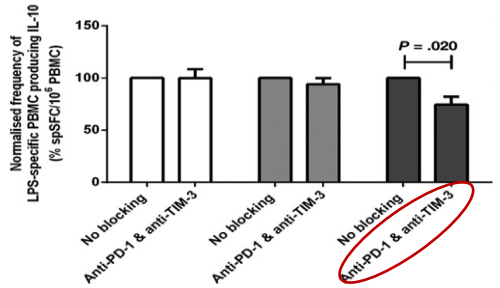
- Increased LPS in plasma caused over expression of PD1 and TIM3 via TLR4 binding to CD14+ monocytes

Antibodies against PD1 and TIM3 …

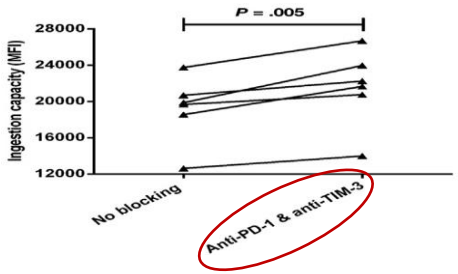
… restored production of INF-γ by T-cells



… reduced IL-10 producing T-cells

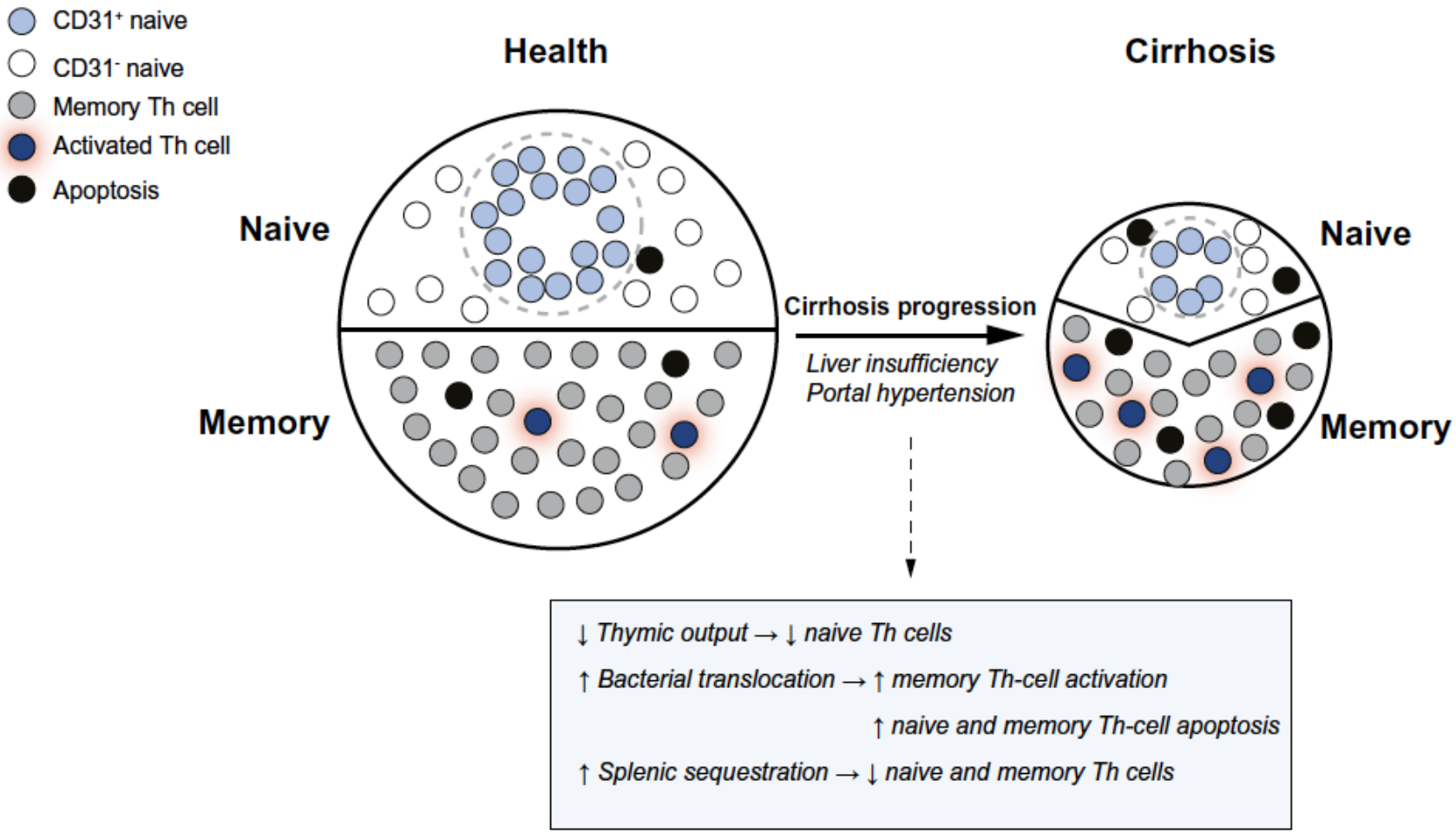


… increased neutrophil antimicrobial activity



LJL Markwick et al. Gastroenterology 2015

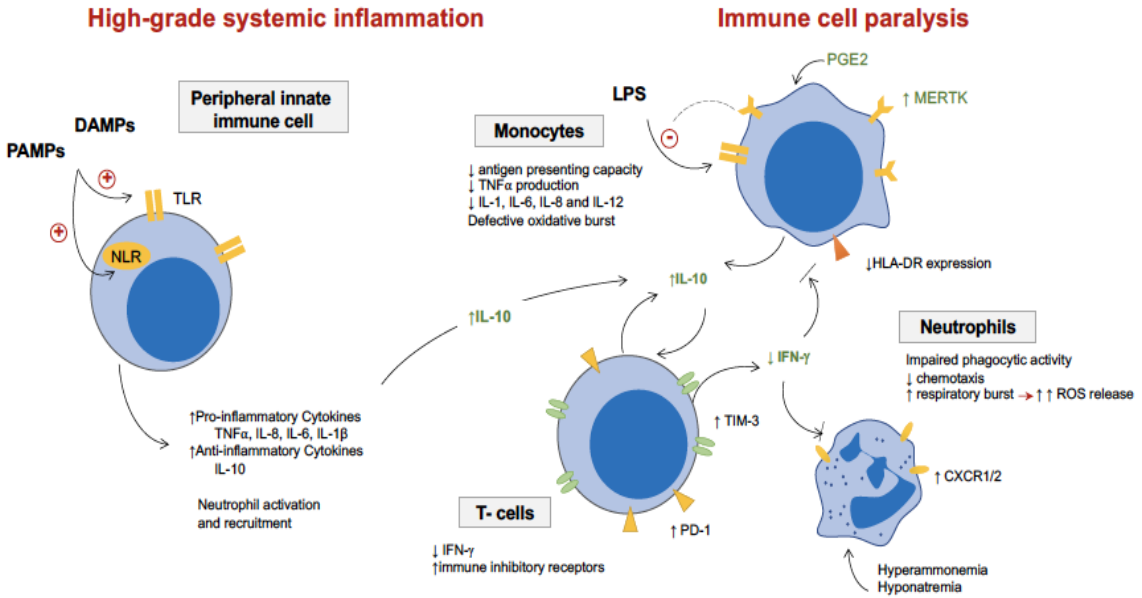
Abnormalities of the peripheral blood T helper-cell compartment in cirrhosis



M Lario et al JHEP 2013

Modulation of cirrhosis-associated immune dysfunction

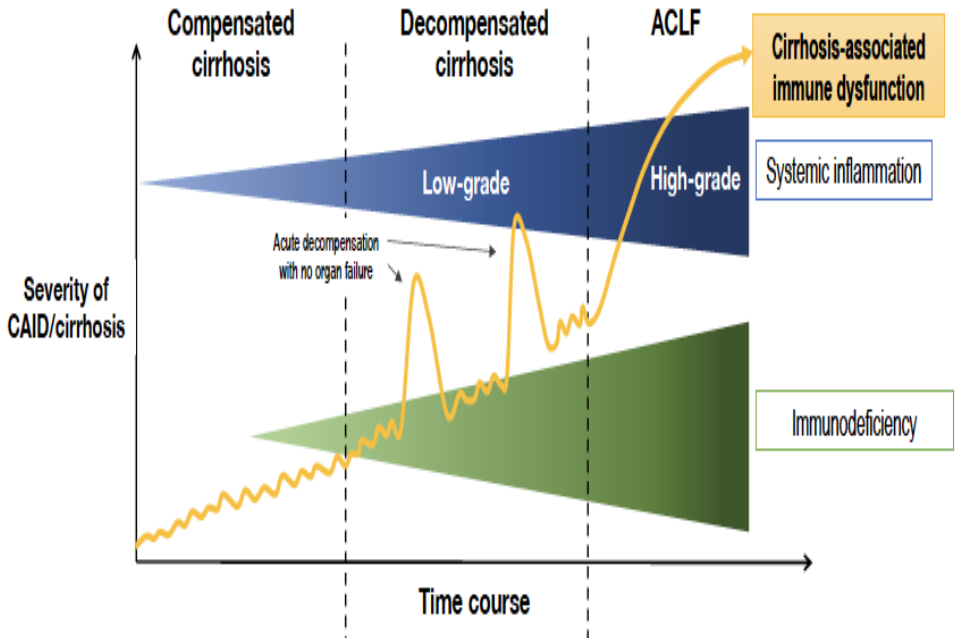
Reversibility of the functional impairment of immune system cells in ACLF



Target	Gut bacterial translocation	Circulating humoral factors	Inmuno-metabolism	Immune cell signalling
Mechanism	↓Endotoxin, ↓ priming	Endotoxin, PGE2, DAMPS	Cellular bioenergetics Ammonia	Neut: AKT-p38 MAPK Monoc: ↑MERKT
• Therapy	• Poorly abs antibiotics • FMT *Trials* • CARBALIVE • Probiotics/Rifaximin	• Albumin *Trials* • DIALIVE • TAK242	• Various for ammonia *Experimental* • GLS inhibition • GLUL inhibition	*Experimental* • TLR7/8 agoni, CL097 • MERKT inh UNC569 • PD1 and TIM-3 inh

A Albillos, R Martin et al. NRGH 2021

Cirrhosis-associated immune dysfunction (CAID)



- **Low-grade SI** (systemic inflammation) **phenotype:**
  - increased expression of surface activation antigens in circulating immune cells
  - increased production of pro-inflammatory cytokines
  - subtle compromise of the effector immune response

- **Progression to the decompensated state:**
  - mechanisms of CAID more pronounced → persistent bacterial challenge →
  - → impairment of the effector immune response
  - incidental events → worsening of the systemic circulatory dysfunction

- **High-grade SI phenotype:**
  - High-grade SI → multi-organ failure
  - *plus* compensatory anti-inflammatory response and exhaustion of effector immune cells → **severe immunodeficiency**