

Mechanisms of action of albumin in cirrhosis

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Outline

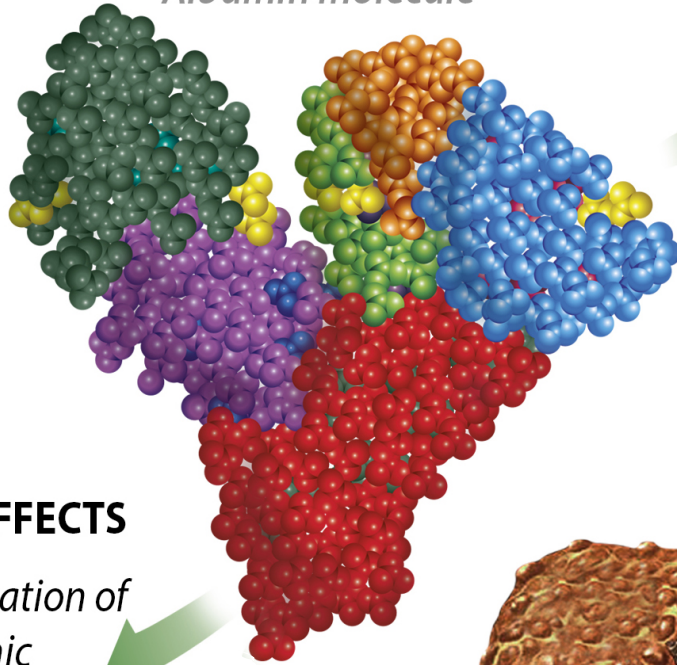
- Anti-inflammatory effects of albumin
 - Effects on cytokines
 - Effects on immune cell transcriptomics
 - Effects on immune cell defense functions
- Mechanisms of action of the albumin molecule
 - Intracellular albumin trafficking
 - Interaction with endosomal TLRs
- Tissue protective effects of albumin
 - Effects on cytokine-induced immunopathology
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Human serum albumin (HSA). Therapeutic use in patients with acutely decompensated (AD) cirrhosis.

Albumin molecule



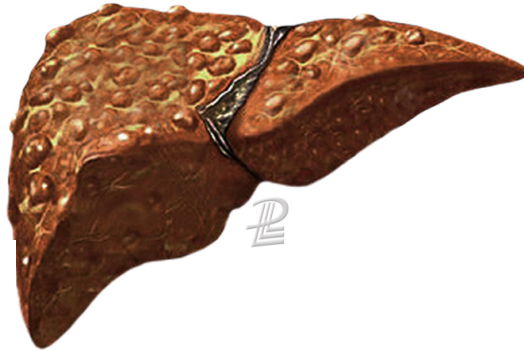
TRADITIONAL INDICATIONS

- Plasma volume expander
- Prevention paracentesis-induced circulatory dysfunction
- Prevention and treatment hepatorenal syndrome

NEW EFFECTS

- Attenuation of systemic inflammation

Gastroenterology 2019;157:149–162



Sort et al. *N Engl J Med*. 1999
Arroyo et al. *J Hepatol*. 2014
Caraceni et al. *Lancet*. 2018
Bernardi et al. *Gut* 2021

CLINICAL—LIVER

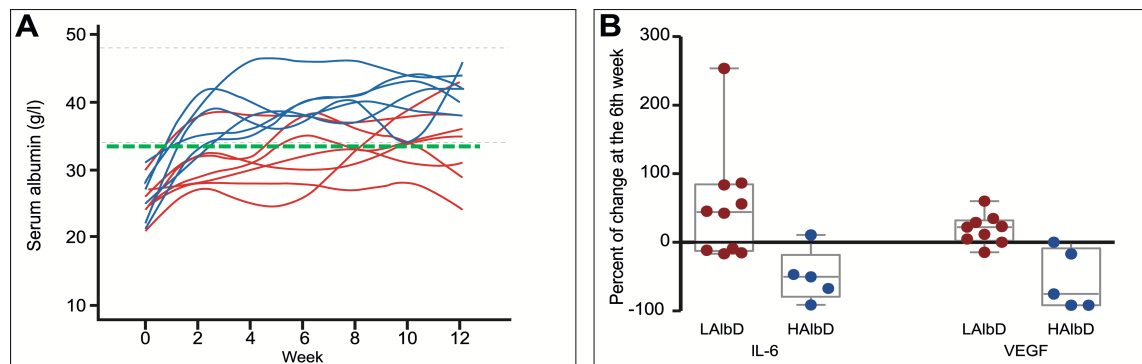
Effects of Albumin Treatment on Systemic and Portal Hemodynamics and Systemic Inflammation in Patients With Decompensated Cirrhosis

Javier Fernández,^{1,2,*} Joan Clària,^{1,2,*} Alex Amorós,¹ Ferrán Aguilar,¹ Miriam Castro,² Mireia Casulleras,² Juan Acevedo,³ Marta Duran-Güell,² Laura Nuñez,⁴ Montserrat Costa,⁴ Mireia Torres,⁴ Raquel Hornillo,⁴ Luis Ruiz-del-Arbol,⁵ Cándido Villanueva,⁵ Verónica Prado,² Mireya Arteaga,⁶ Jonel Trebicka,^{1,7} Paolo Angeli,^{1,8} Manuela Merli,⁹ Carlo Alessandria,¹⁰ Niels Kristian Aagaard,¹¹ German Soriano,¹² François Durand,¹³ Alexander Gerbes,¹⁴ Thierry Gustot,¹⁵ Tania M. Welzel,¹⁶ Francesco Salerno,¹⁷ Rafael Bañares,¹⁸ Victor Vargas,¹⁹ Agustín Albillos,⁹ Anibal Silva,² Manuel Morales-Ruiz,² Juan Carlos García-Pagán,² Marco Pavesi,¹ Rajiv Jalan,²⁰ Mauro Bernardi,²¹ Richard Moreau,^{1,13,22} Antonio Páez,¹ and Vicente Arroyo¹

HSA attenuates systemic inflammation in patients with AD cirrhosis

Pilot-Preciosa: proof of concept, open-label, multicenter, nonrandomized, prospective, phase 4 study in patients with AD cirrhosis.

Long-term (12 weeks) low (1 g/kg every 2 weeks) and high (1.5 g/kg every week) HSA dosages.



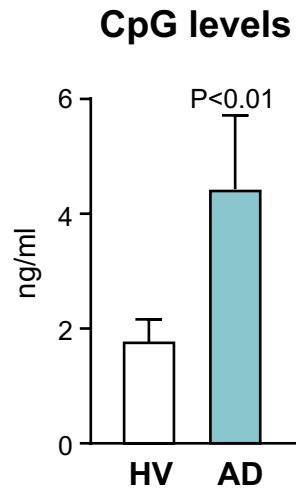
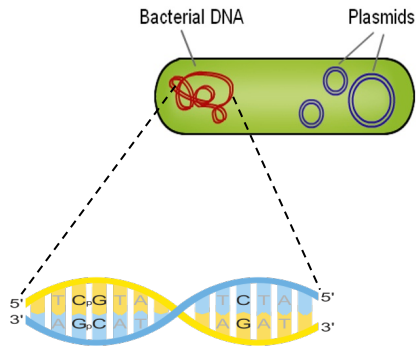
INFECIR-2: phase 4, randomized, controlled, open-label, multicenter trial in patients with AD cirrhosis and bacterial infections.

Short-term (1 week) HSA treatment, 1.5 g/kg on day 1 and 1 g/kg at day 3.

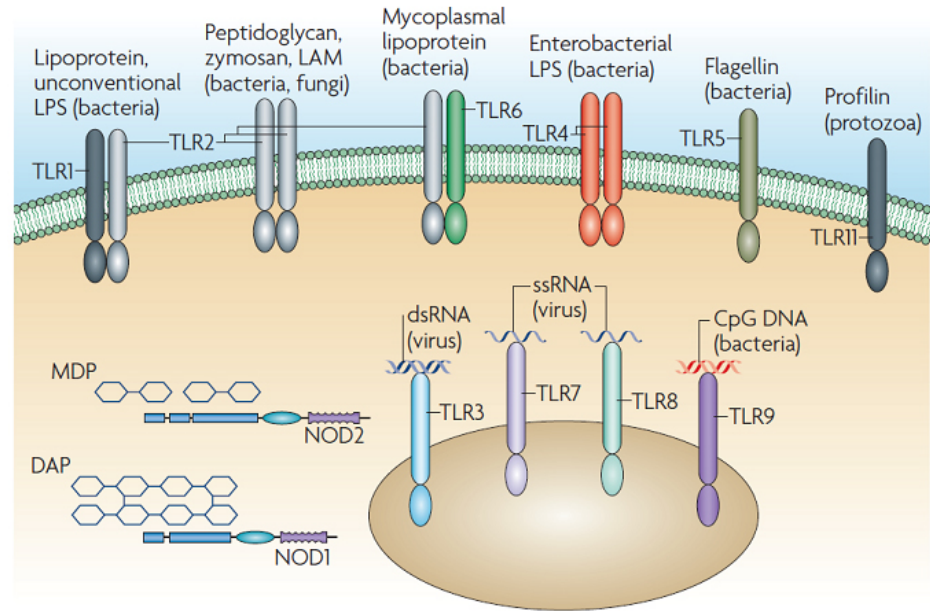
Fernández J, Clària J, et al. *Gastroenterology* 2019

Standard Medical Therapy (n=40)				Standard Medical Therapy Plus Albumin (N=38)			
	Baseline	Absolute change	P Value	Baseline	Absolute change	P Value	
TNFα	37.9 (23.3 to 50.0)	-2.8 (-12.6 to 3.2)	0.05	31.1 (21.2 to 45.3)	-3.4 (-14.7 to 3.1)	0.01	
G-CSF	74.4 (19.2 to 185.5)	-3.4 (-55.3 to 11.5)	0.33	73.5 (33.6 to 115.0)	-41.5 (-65.1 to 8.4)	0.01	
IL-1ra	29.6 (8.3 to 71.5)	-0.6 (-28.0 to 9.0)	0.37	29.9 (8.3 to 76.5)	-0.5 (-34 to 2.1)	0.05	
IL-6	37.7 (18.3 to 94.7)	-7.0 (-19.9 to 20.7)	0.53	36.9 (23.9 to 158.9)	-7.7 (-33.1 to 0.3)	0.003	
IL-10	10.7 (6.3 to 20.9)	-0.2 (-6.7 to 4.4)	0.74	11.0 (6.7 to 15.1)	-1.5 (-7.6 to 2.8)	0.03	
IL-12p40	25.2 (3.6 to 57.8)	-1.2 (-14.0 to 7.4)	0.51	5.6 (1.5 to 34.3)	3.4 (-0.6 to 11.2)	0.05	

Bacterial DNA is rich in unmethylated CpG motifs

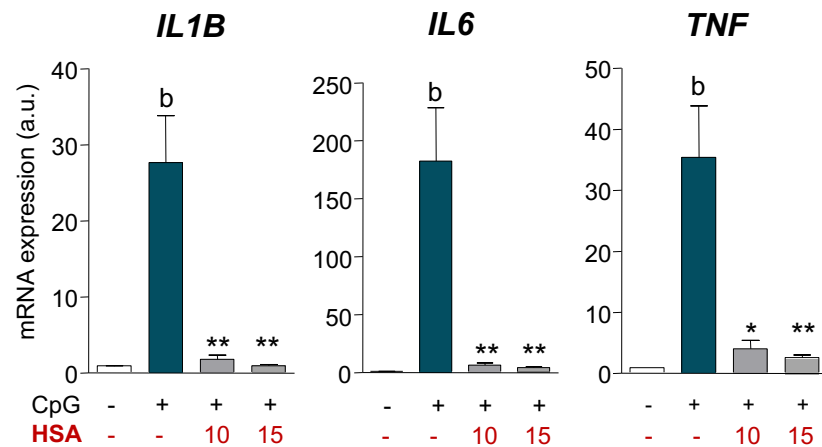
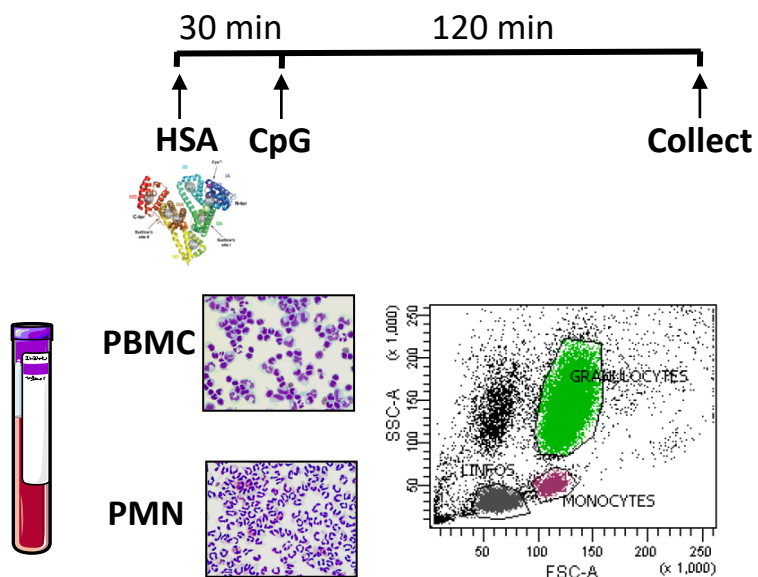


Recognition of pathogen-associated molecular patterns (PAMPs) by Toll-like receptors (TLRs)



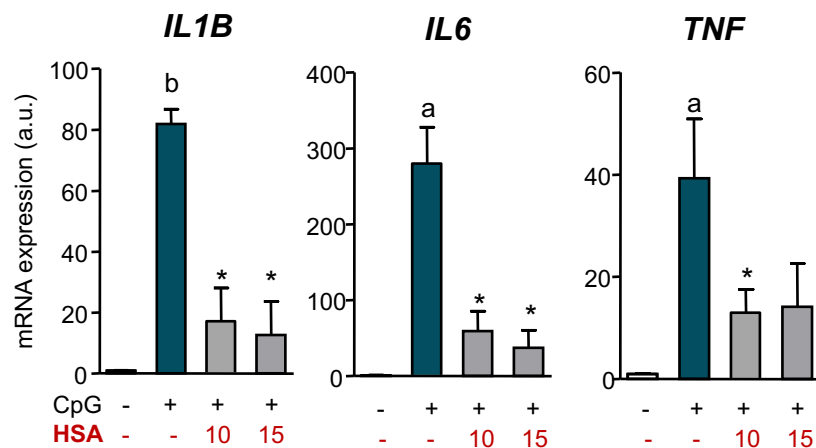
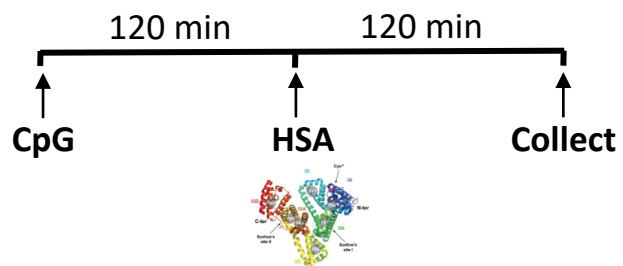
HSA blocks CpG-DNA induced cytokine release

Preventive

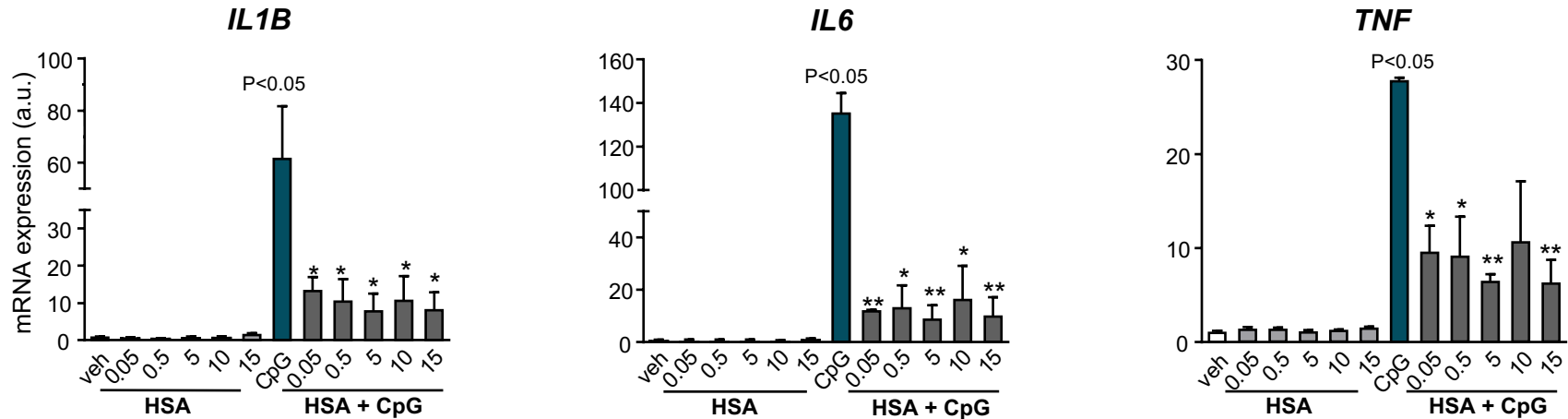


Independent on HSA scavenging properties

Therapeutic

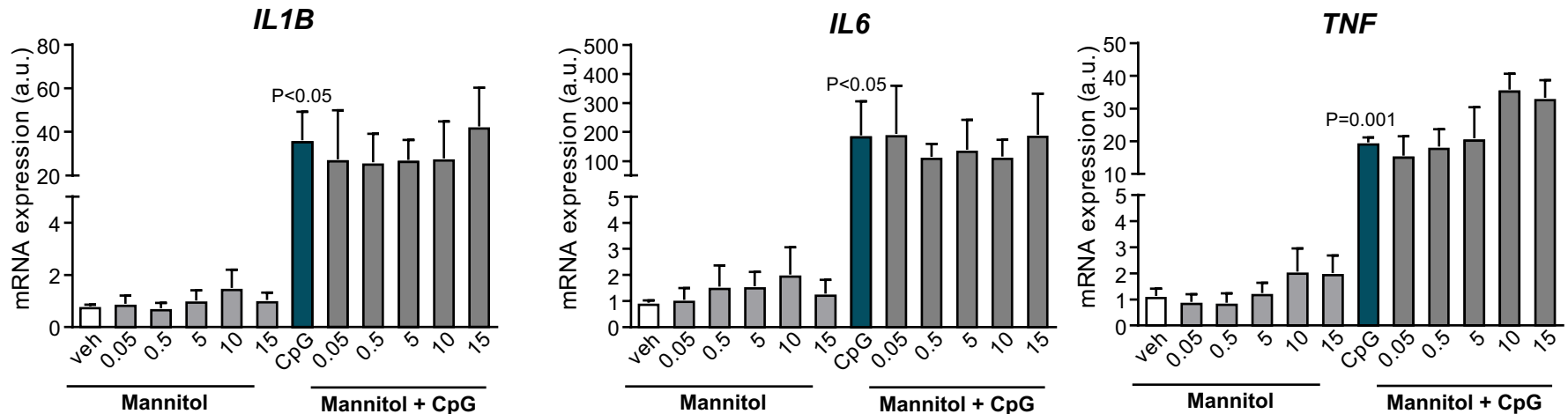


The anti-inflammatory effects of HSA are independent of its oncotic properties



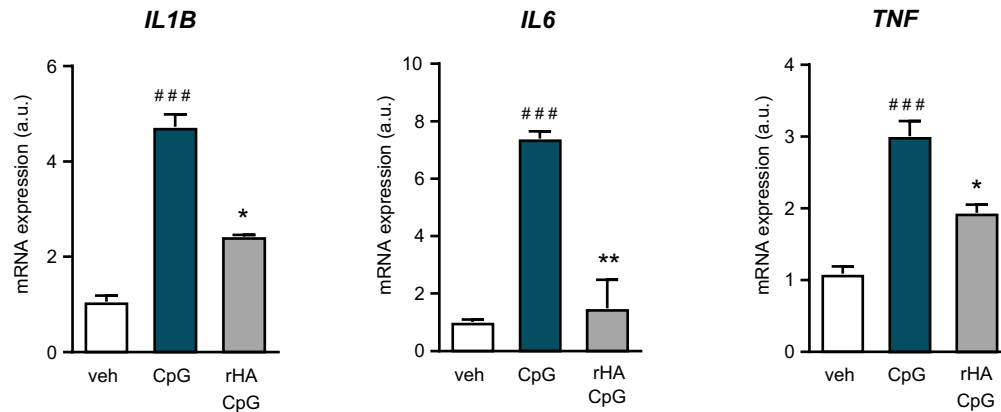
*, P<0.005 and **, P<0.001 vs CpG alone

Independent on HSA oncotic properties

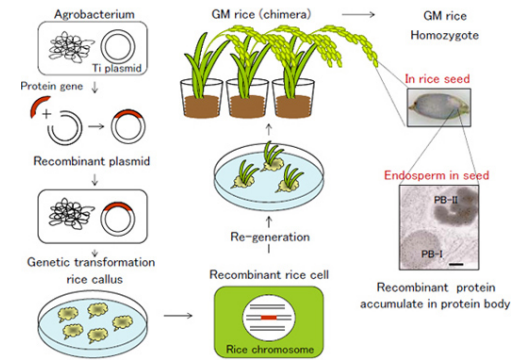


The anti-inflammatory properties of HSA are intrinsic to the albumin molecule

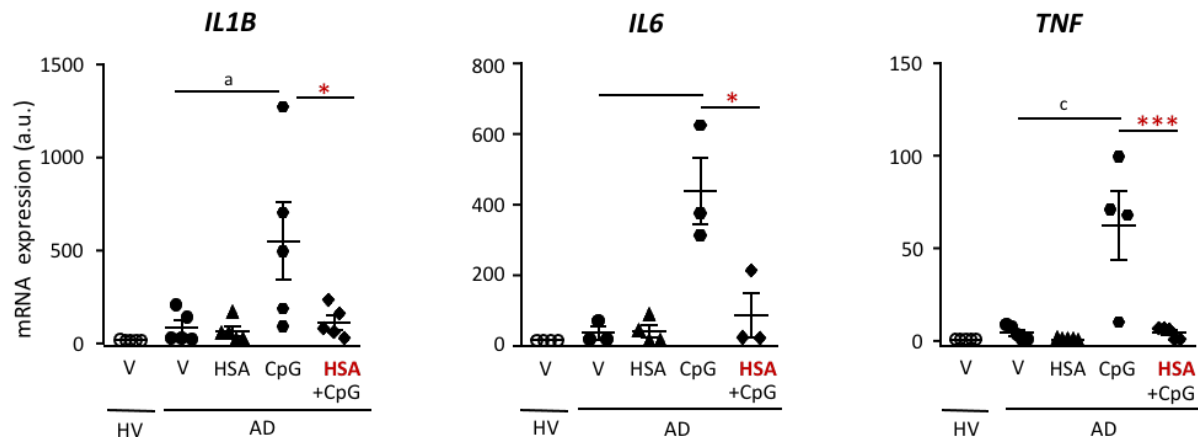
Independent on serum factors bound to the albumin molecule



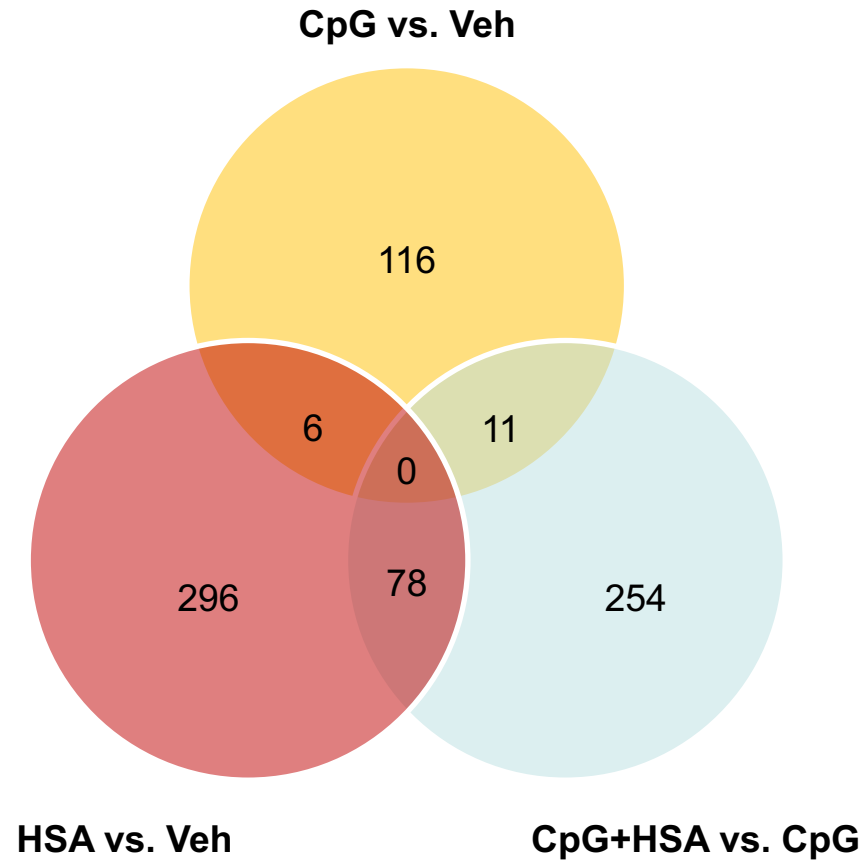
Recombinant albumin expressed in *Oriza sativa*.



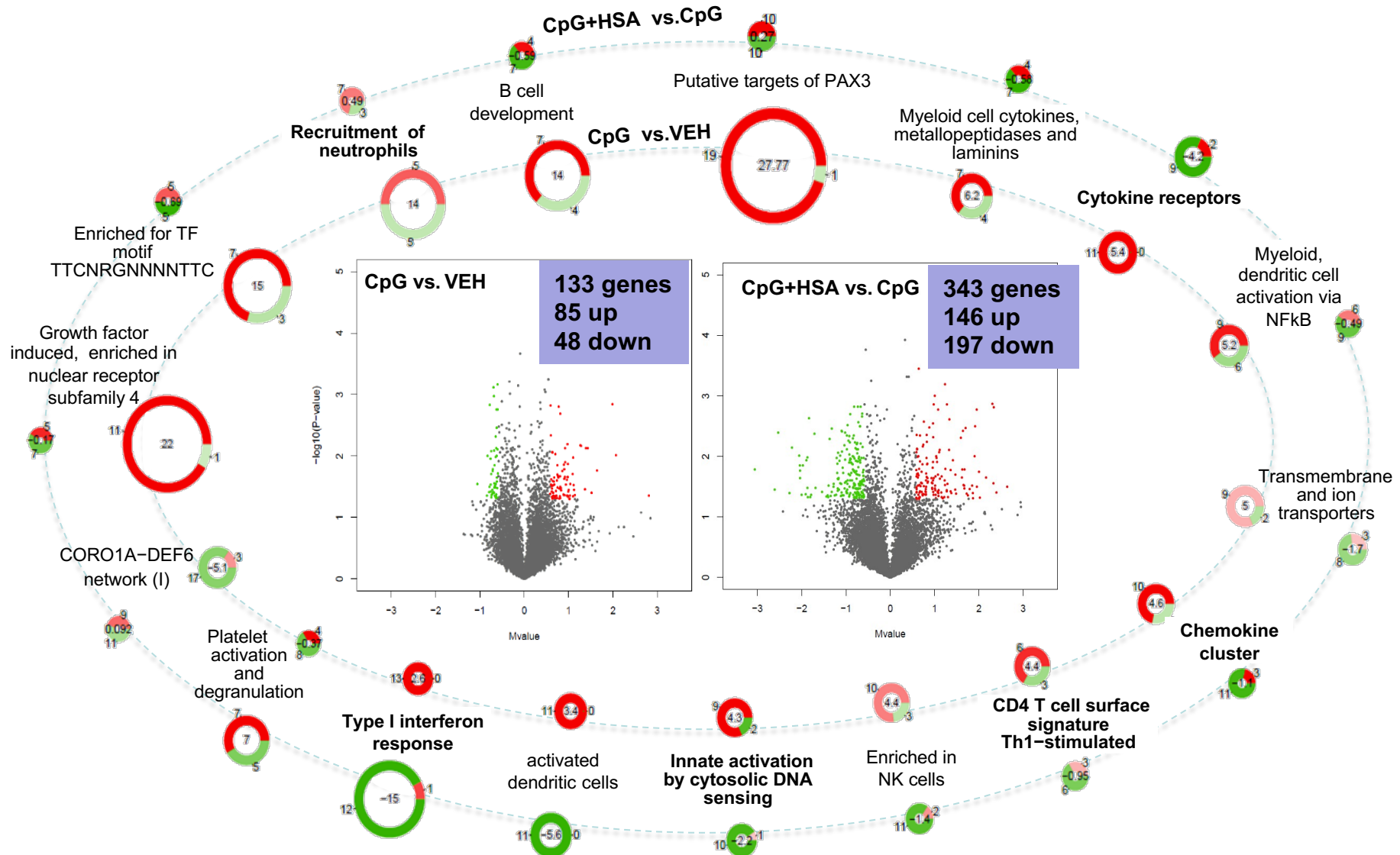
Confirmed in PBMCs from patients with AD cirrhosis



HSA induces widespread changes in the transcriptome profile of immune cells



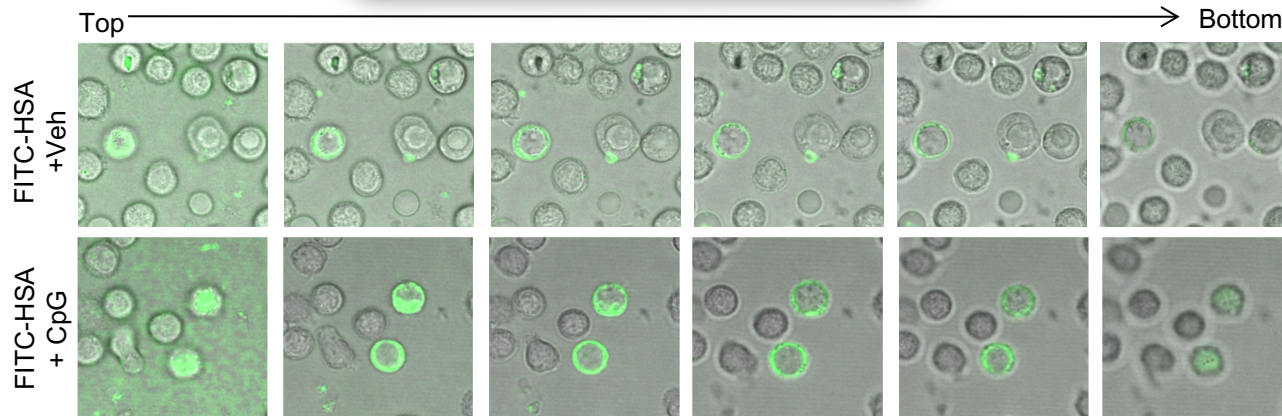
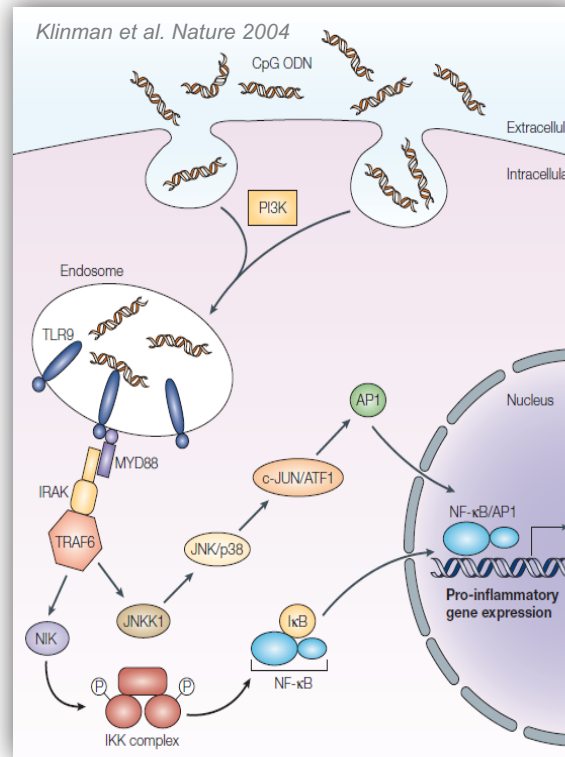
HSA induces remarkable changes in the immune cell transcriptome



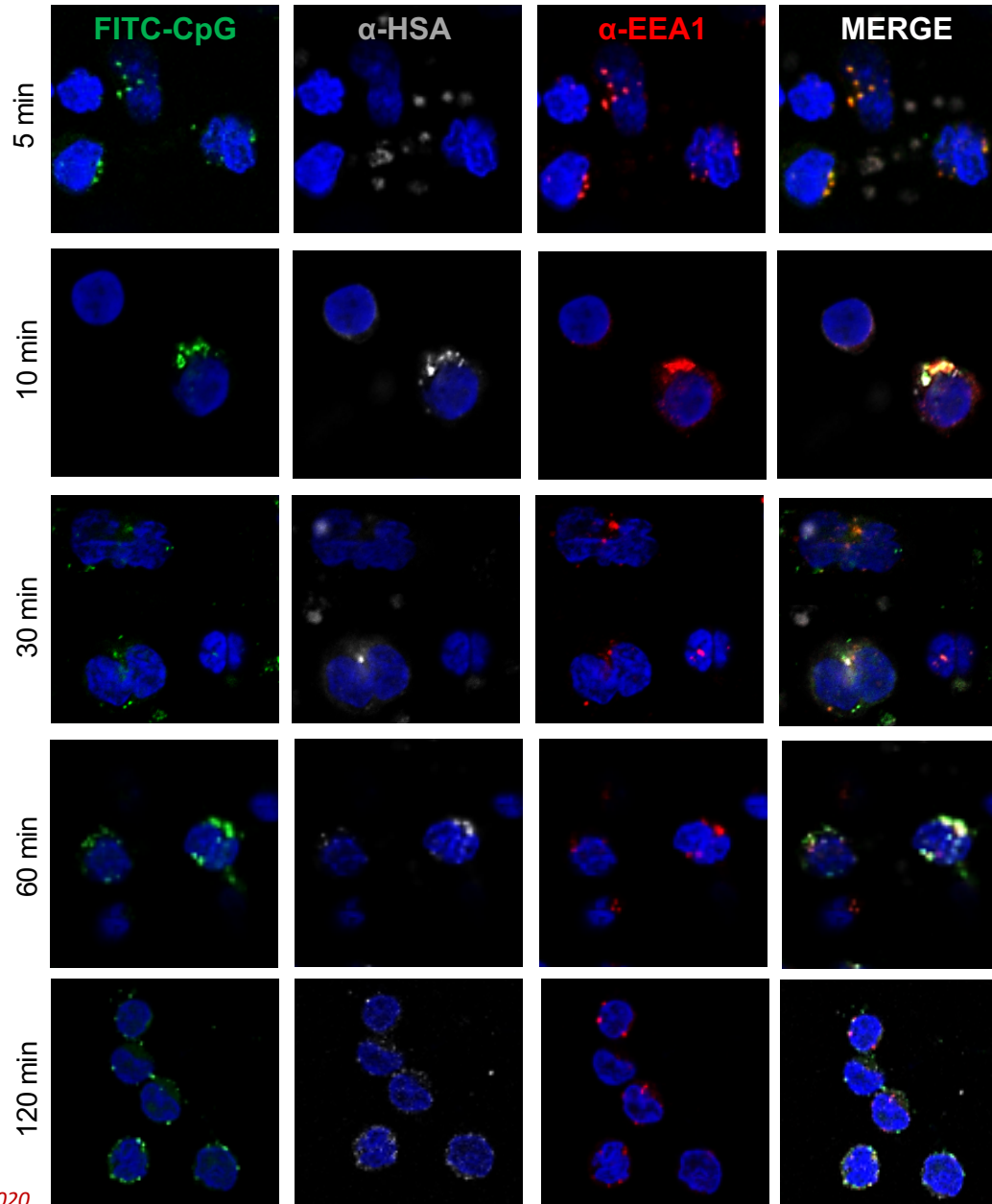
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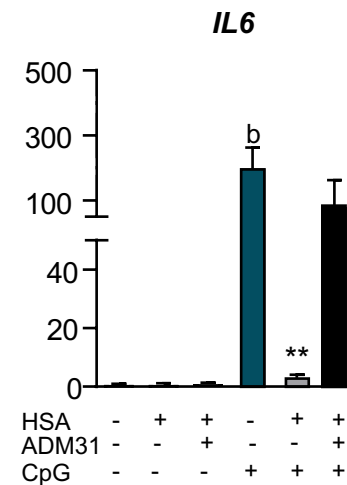
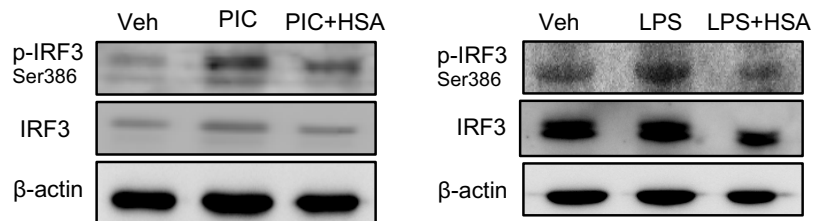
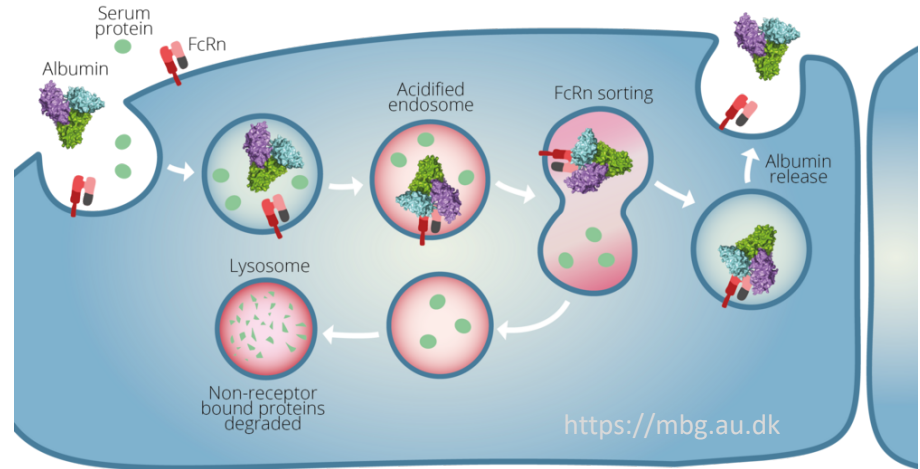
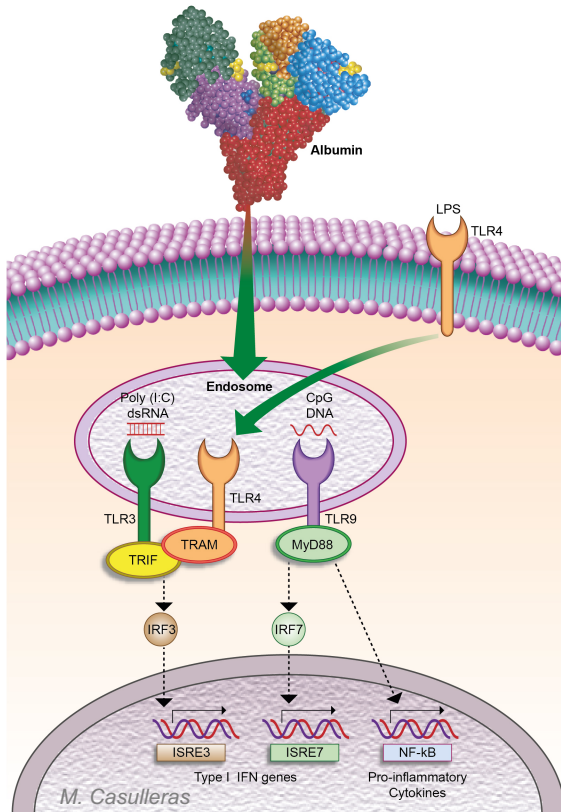
HSA acts intracellularly blocking endosomal TLR9 signaling



HSA colocalizes with CpG-DNA in the endosomes

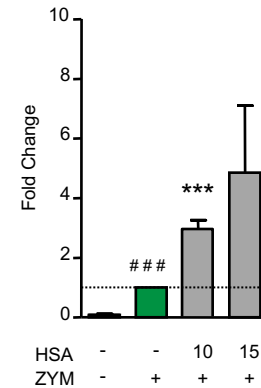
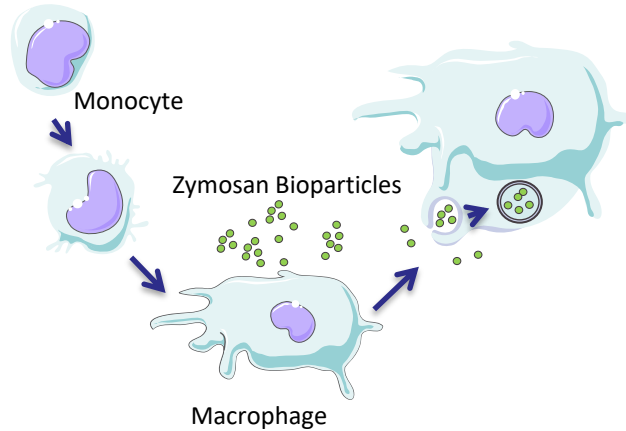


The HSA blocking action is generalized to all endosomal TLRs and is mediated by FcRn

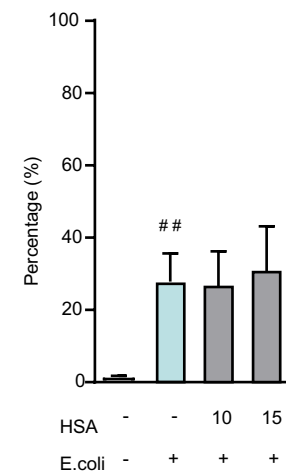
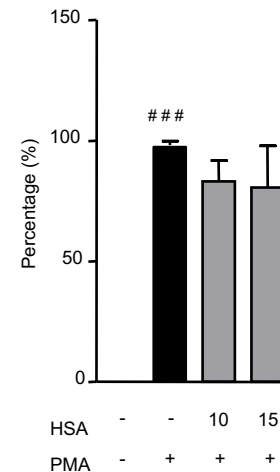
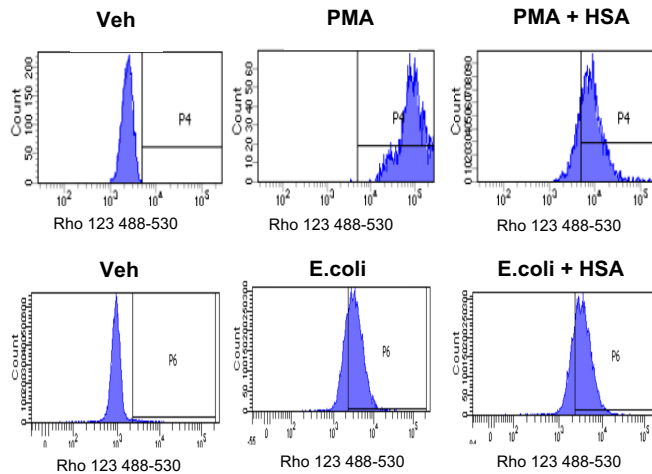


HSA does not impair immune defense mechanisms

Phagocytosis



Oxidative burst



Translation of *in vitro* findings to *in vivo*

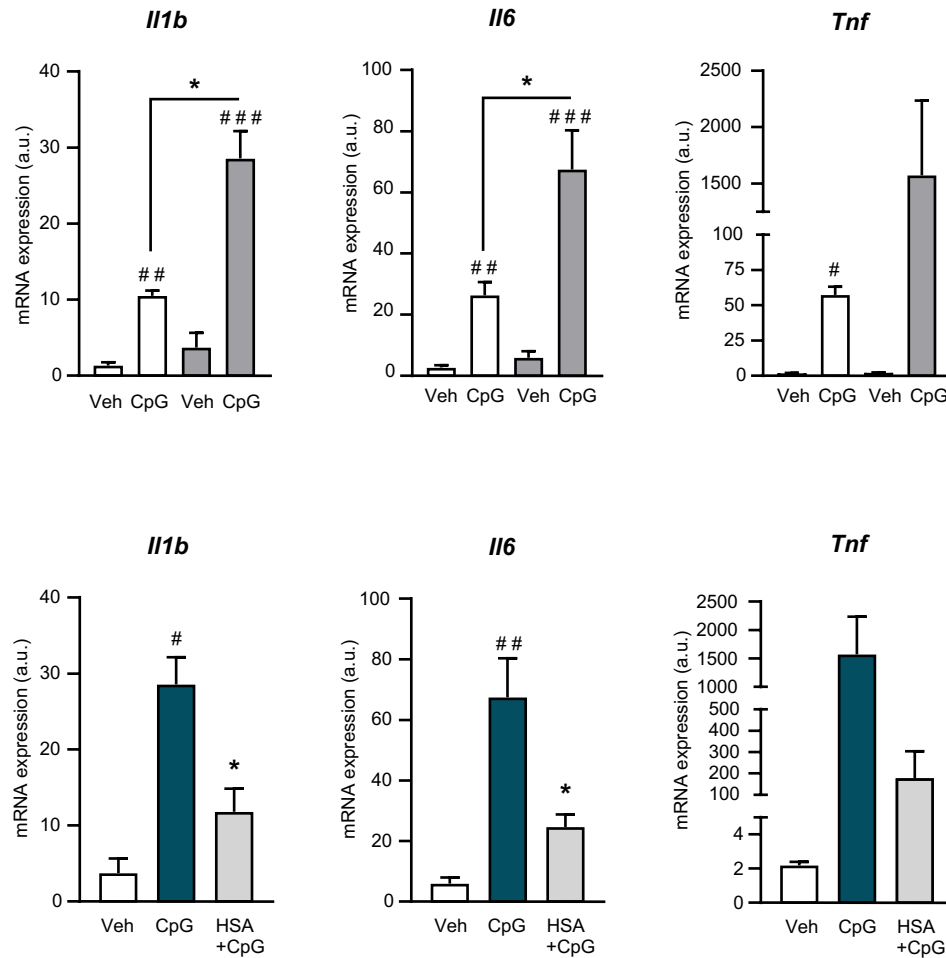


Wild-type mice



Alb^{-/-} hFcRn^{+/+} mice

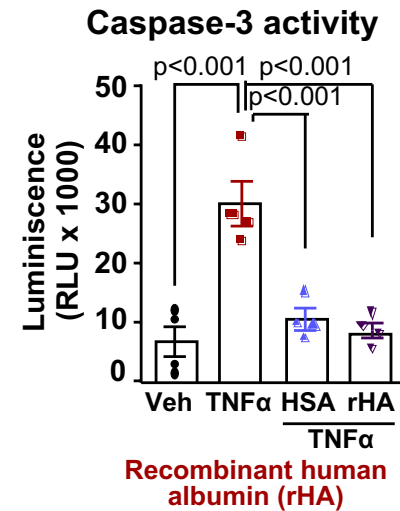
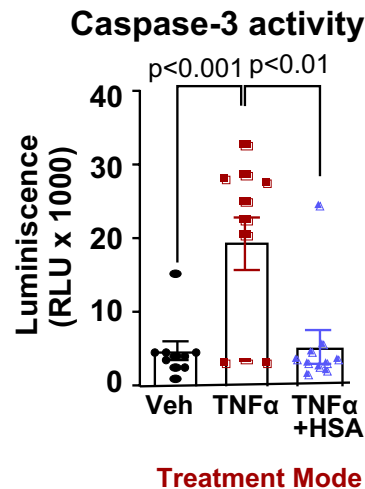
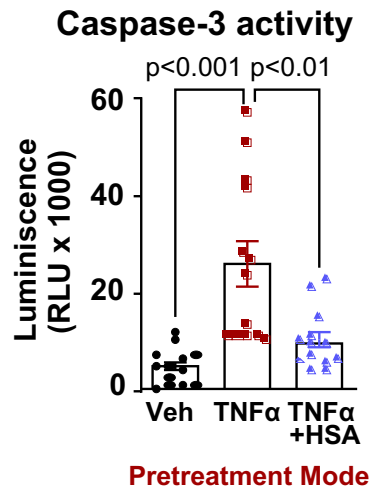
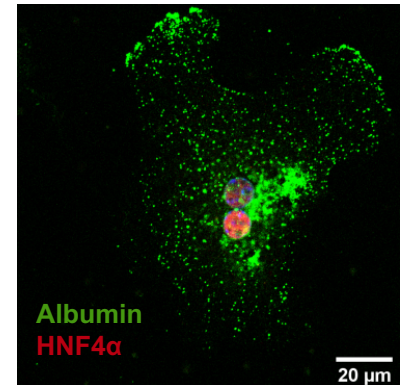
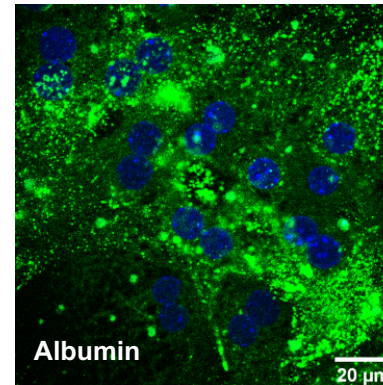
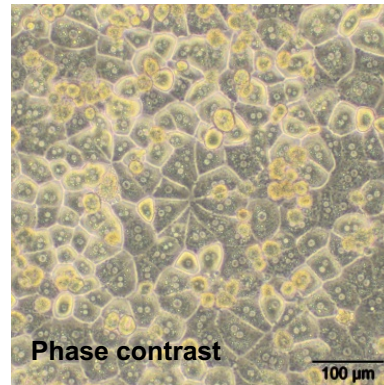
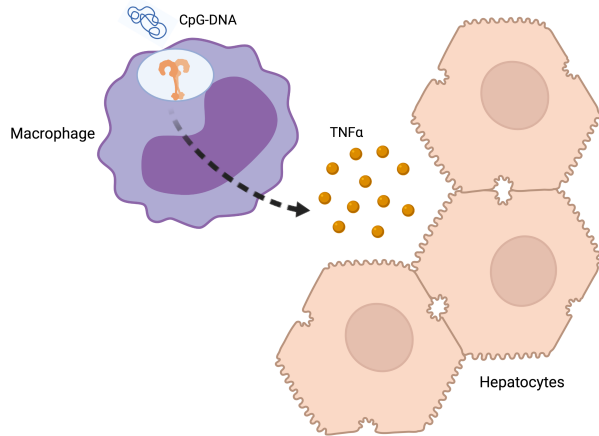
Analbuminemic mice expressing the human FcRn receptor



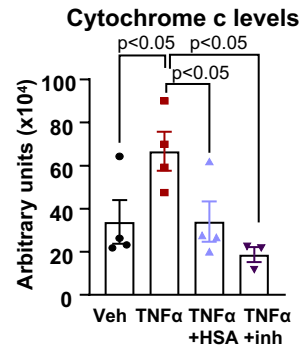
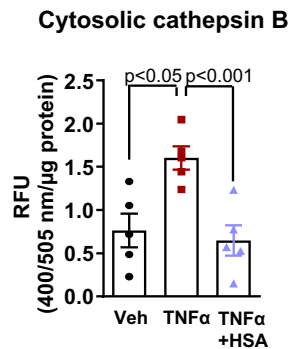
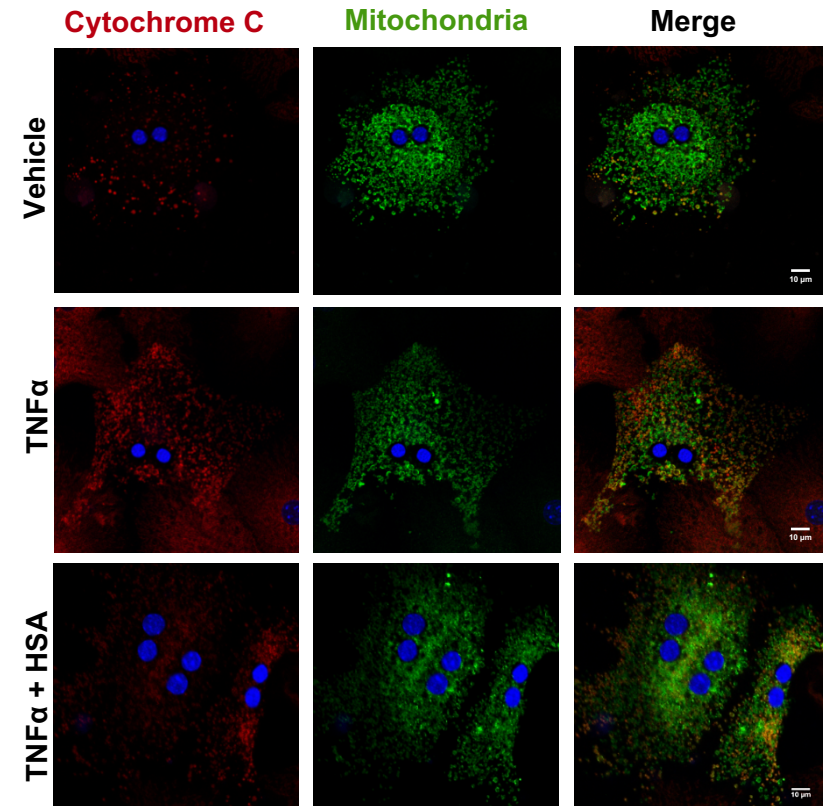
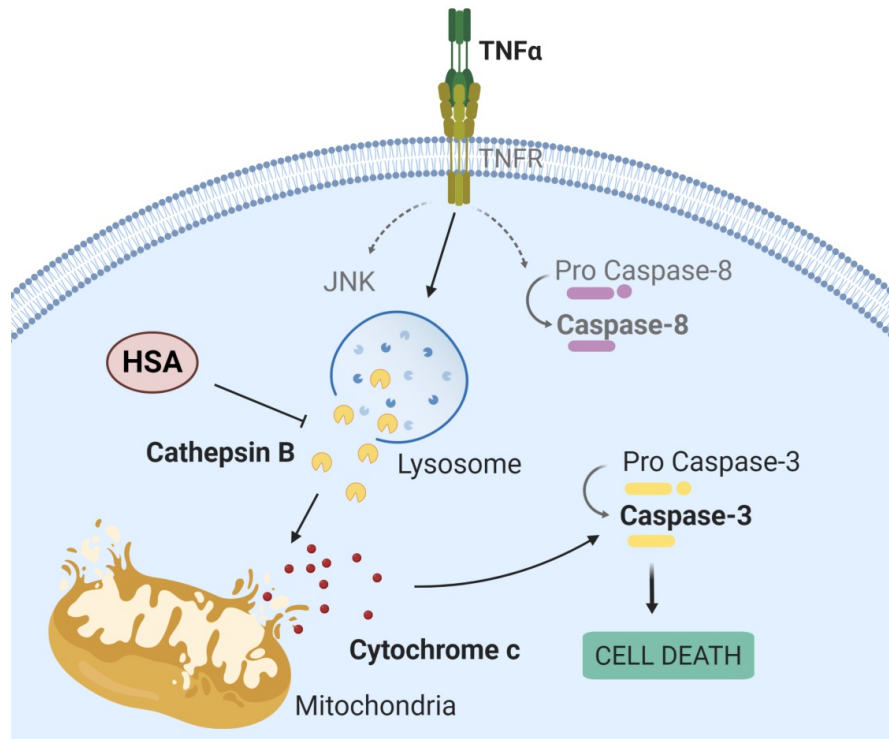
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HSA reduces TNF α -induced hepatocyte death



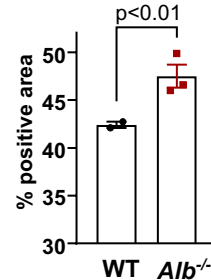
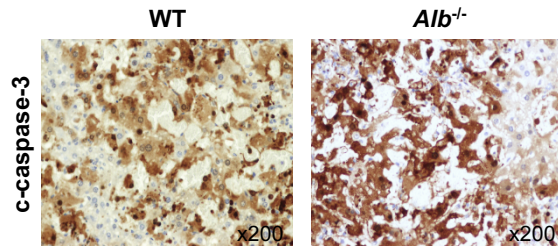
Mechanisms of action of HSA against TNF α -induced injury



Duran-Güell et al. FASEB J 2021

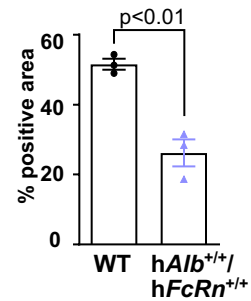
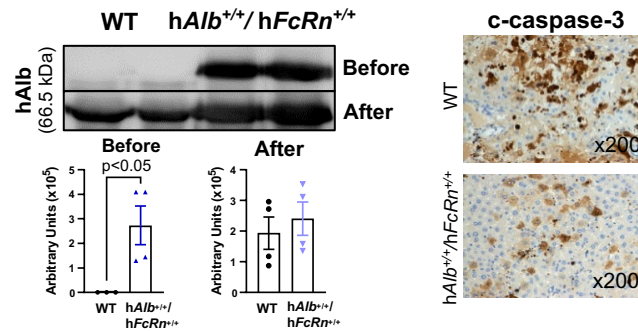
Effects of HSA on a TNF α -dependent model of liver injury.

Alb^{-/-} mice

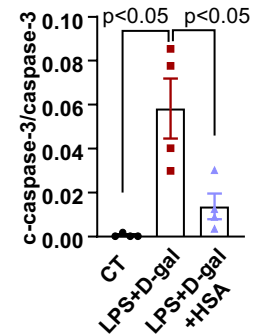
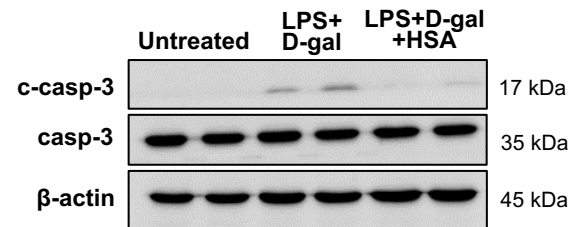
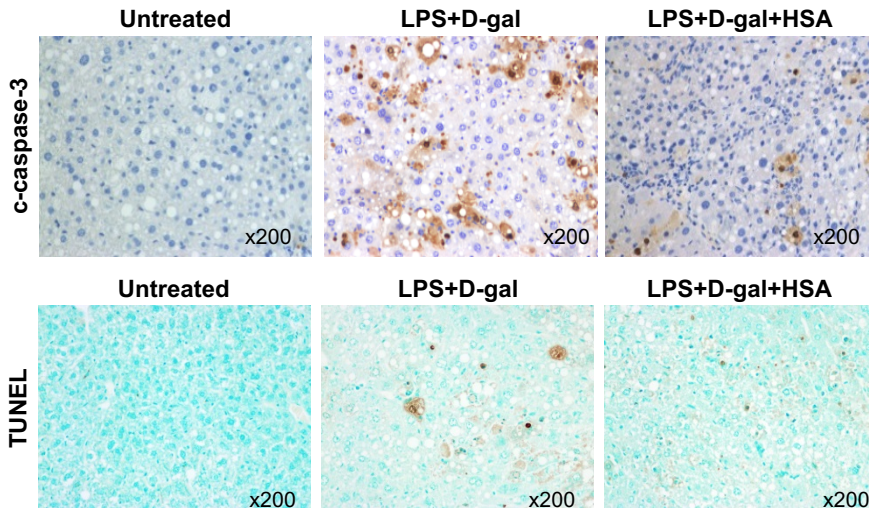


hAlb^{+/+}, hFcRn^{+/+} mice

Humanized models:
enhanced predictability
toward human physiology



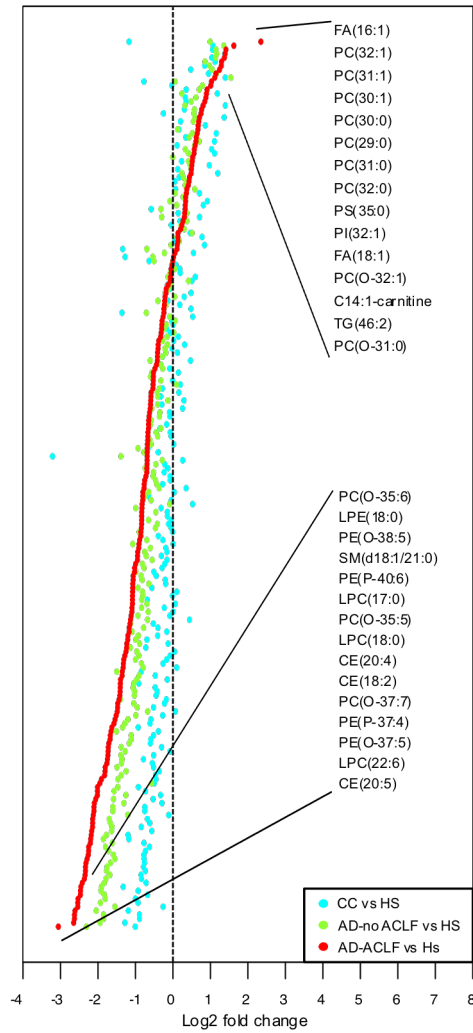
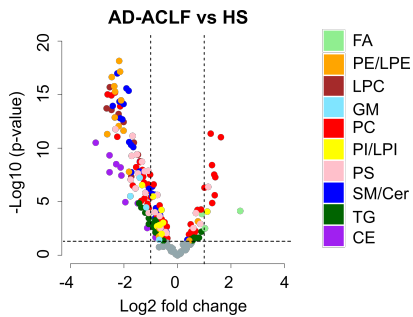
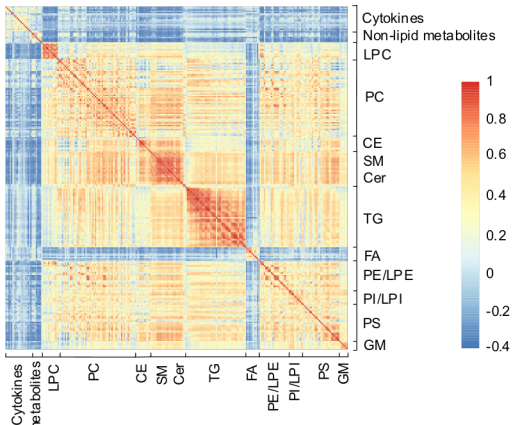
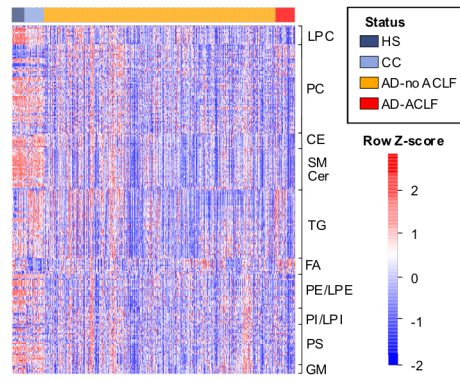
hAlb^{+/+}, hFcRn^{+/+} mice induced to cirrhosis



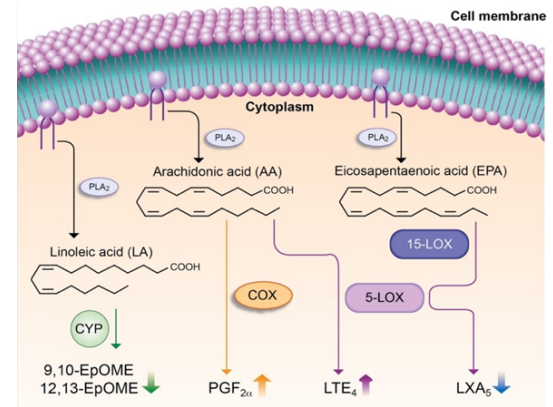
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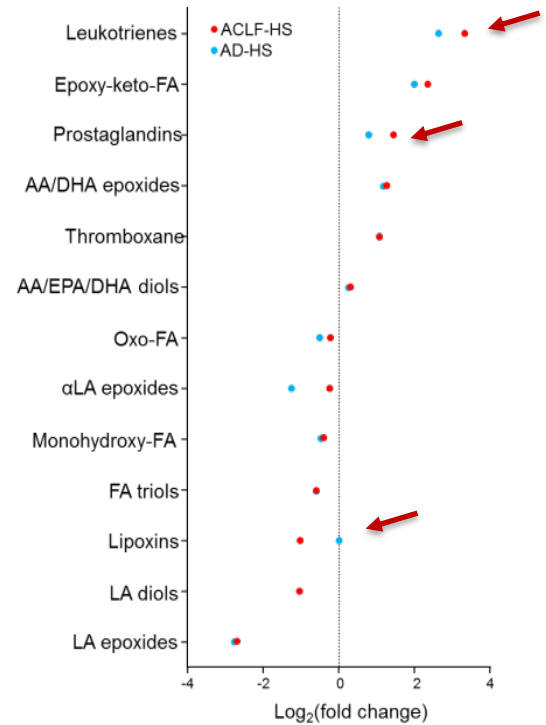
The plasma lipidome of patients with advanced liver cirrhosis



Clària et al. J Hepatol (in press)



López-Vicario et al. J Hepatol 2020



Summary and conclusion

- ✓ HSA blocks the production of pro-inflammatory cytokines by immune cells stimulated with bacterial CpG-DNA.
- ✓ HSA effects are independent of its scavenging and oncotic properties.
- ✓ HSA is internalized by leukocytes and interacts with the binding of PAMPs to endosomal TLRs (i.e. CpG-DNA binding to TLR9).
- ✓ HSA also has the ability to reduce cytokine-induced tissue injury.
- ✓ HSA not only induces anti-inflammatory actions without impairing immune defense systems but also exerts pro-resolution activities.

These data provide evidence of non-oncotic actions of the albumin molecule, which contribute to the understanding of the clinical benefits of HSA infusions in patients with AD cirrhosis.