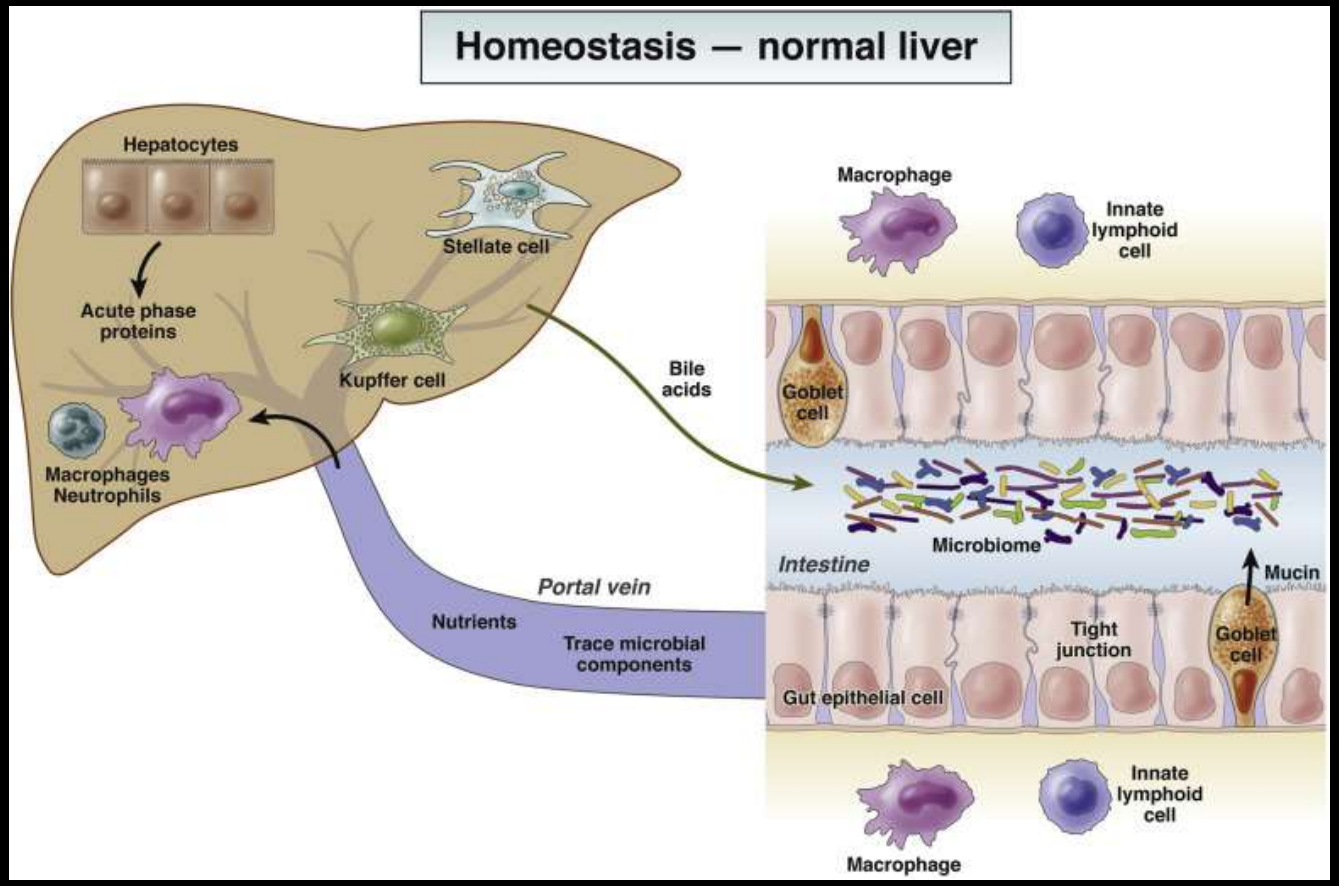
GUT-LIVER CROSSTALK in GASTROINTESTINAL MALIGNANCIES- IS THERE a ROLE FOR SPECIFIC BACTERIAL SPECIES

MICHAEL KARIN
UCSD School of Medicine
Depts of Pharmacology and Pathology

When it comes to Gastrointestinal Cancers are Bacteria in the Driver's Seat?

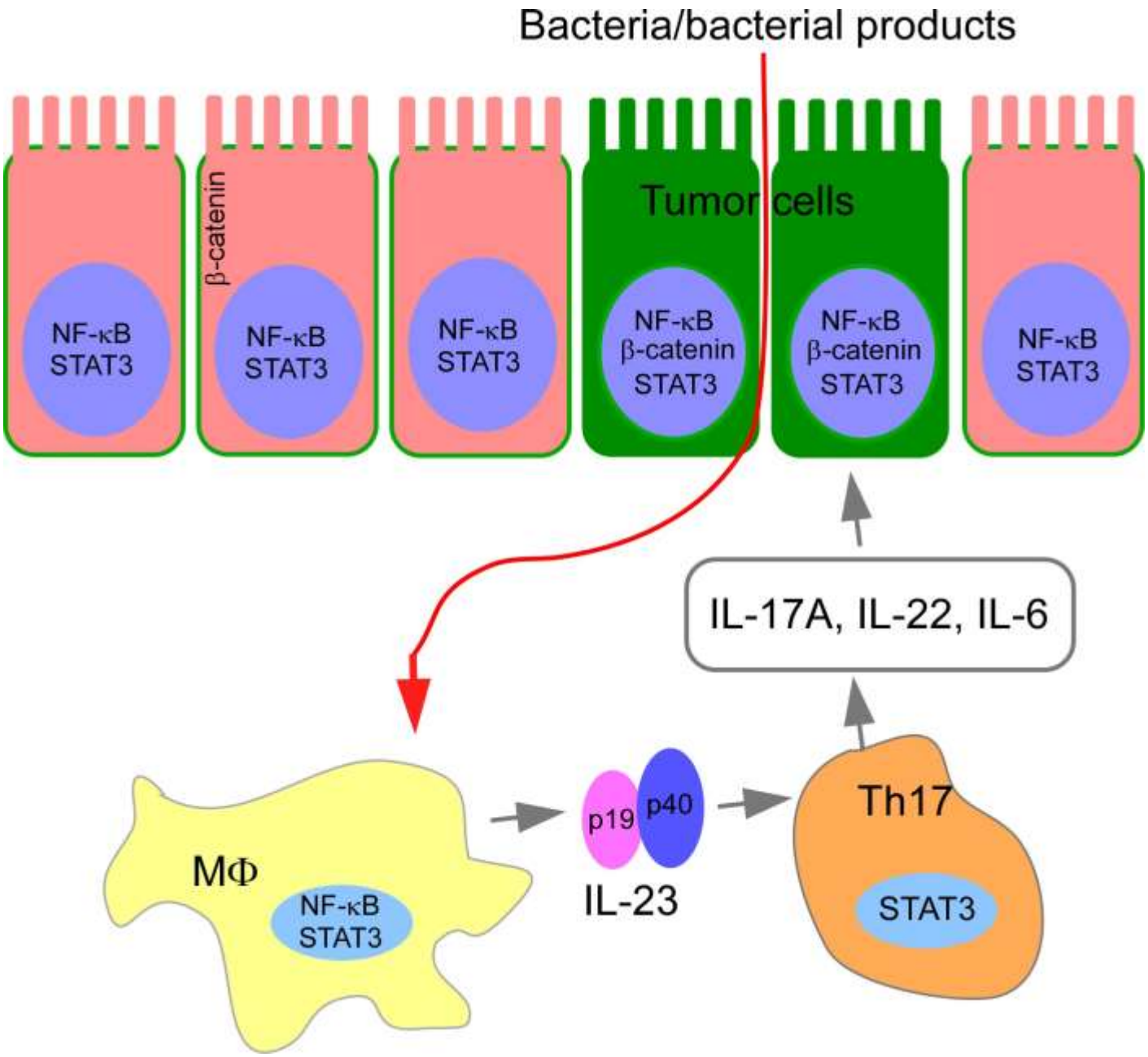
Only one bacterium, *Helicobacter pylori,* has been recognized by the WHO as a carcinogen.

The intestine and the liver are connected via the portal circulation

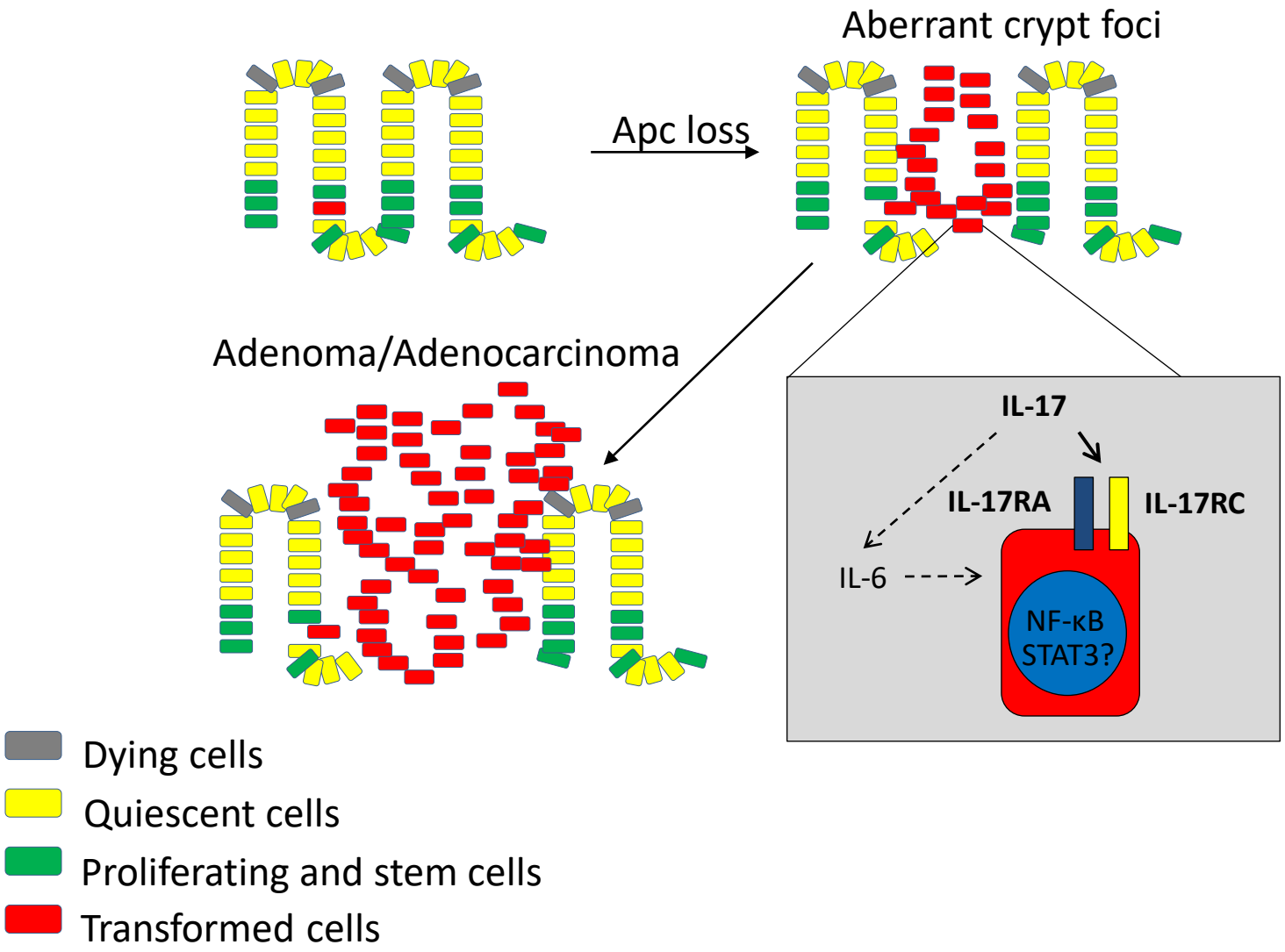


Therefore, what happens in the intestine, including barrier disruption, epithelial erosion, etc., has a profound impact on the liver.

Figure: Gyongyi Szabo, **Gastroenterology** Volume 148, Issue 1, January 2015, Pages 30-36


Bacteria/bacterial products
Tumor cells
β-catenin
NF-κB
STAT3
NF-κB
β-catenin
STAT3
IL-17A, IL-22, IL-6
MΦ
p19
p40
IL-23
Th17
STAT3

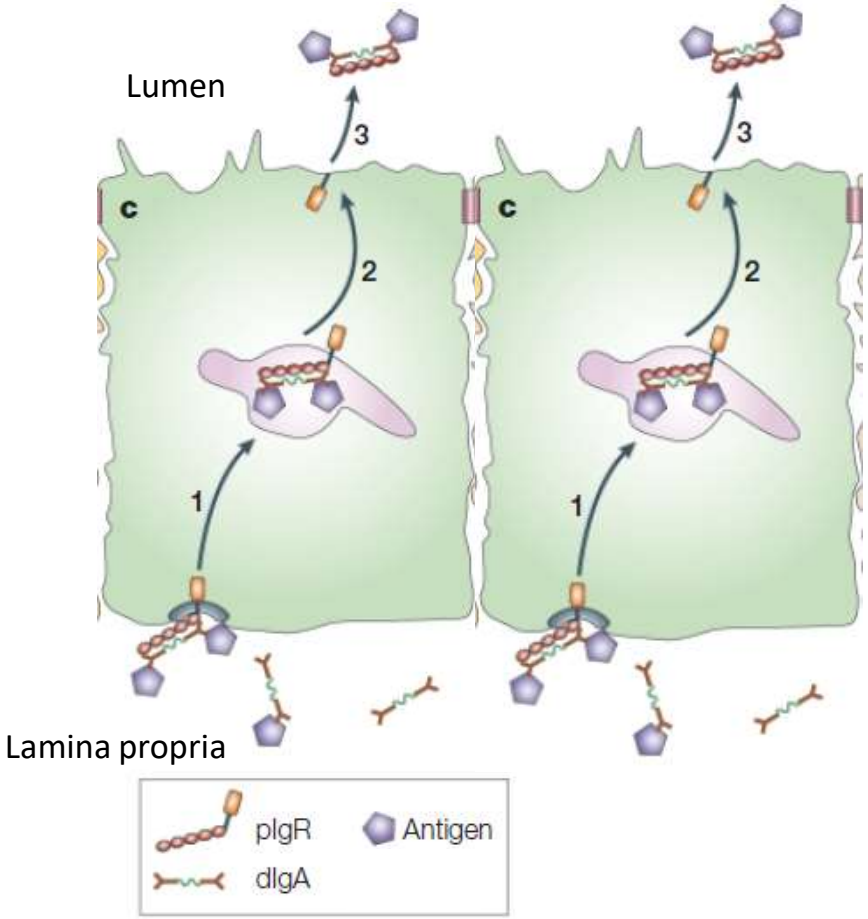
IL-17RA signals in transformed enterocytes to promote early colorectal tumorigenesis

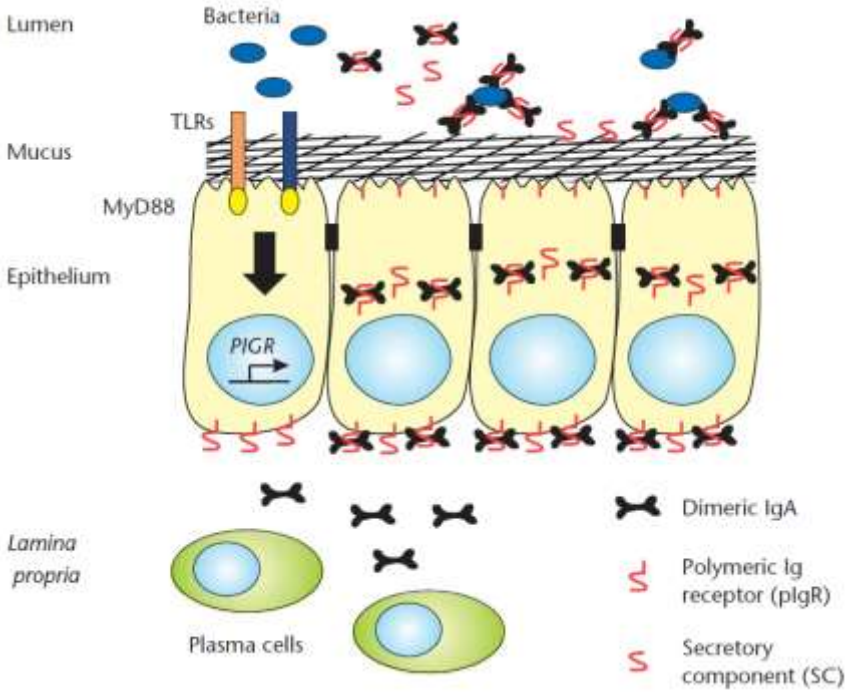


Colorectal cancer has been attributed to dysbiosis and microbial translocation

1. What is the origin of dysbiosis and microbial translocation?
2. Do dysbiosis or translocation preceed tumor development?

The IgA-PIgR System: A Critical Regulator of Intestinal Immune Homeostasis and a Component of the Barrier

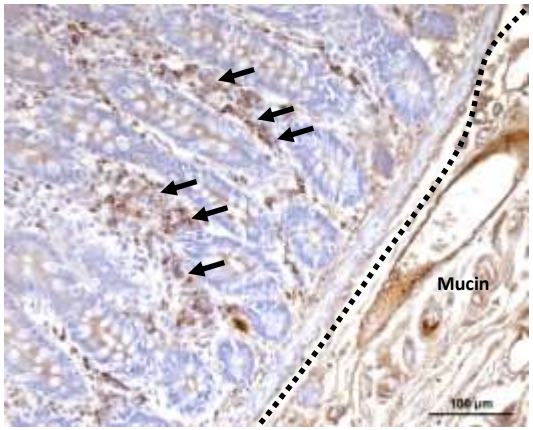


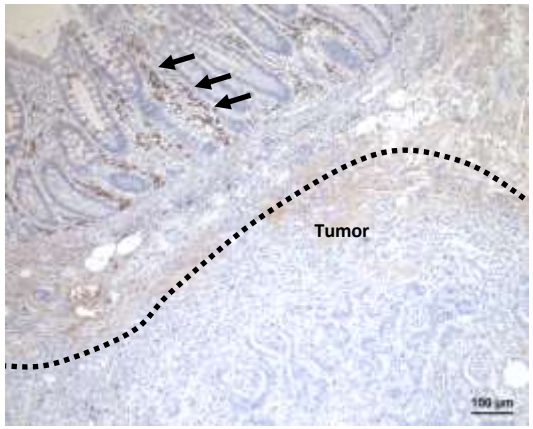


Rojas *et al*, Nature Rev Mol Cell Biol, 2002
Kaetzel *et al*, eLS, 2013

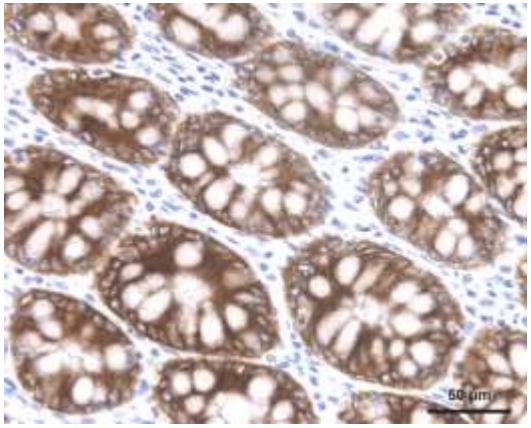
Loss of IgA and PIgR in human colorectal cancer

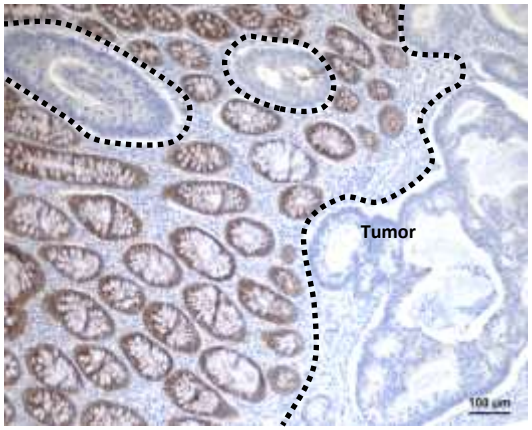
IgA+ cells





PIgR+ cells

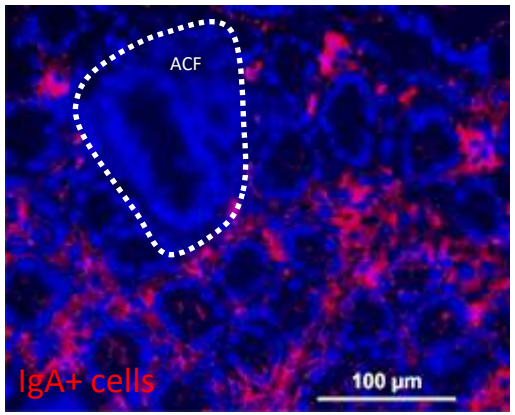


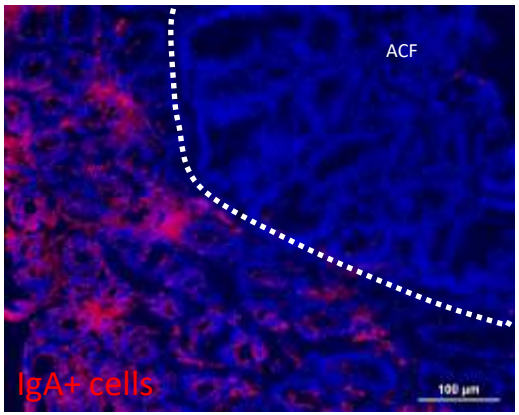


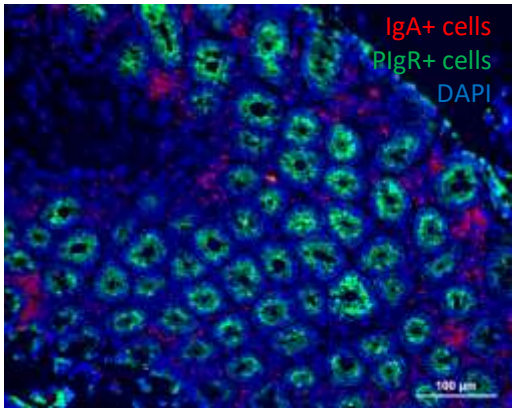
TMA data		Death		Logistic regression	
		no	yes	O.R. (95%C.I.)	P
		(n=36)	(n=126)		
IgA-PIgR	No	29	116	1.00 ref.	
	Yes	7	10	0.36 (0.12-1.02)	0.06

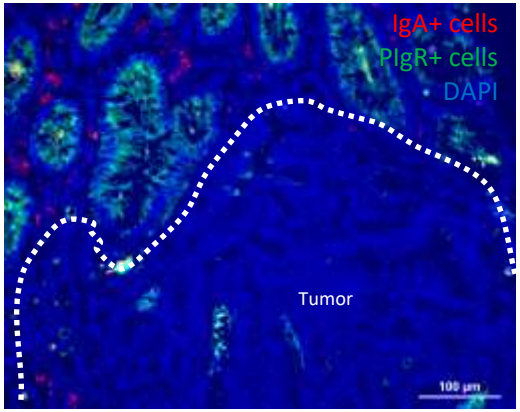
Loss of IgA, PIgR and CCL28 (plasma cell chemoattractant) In murine colonic cancer

$Apc^{F/F}$-$Cdx2^{Cre-ERT2}$: **1 week** **4 weeks**

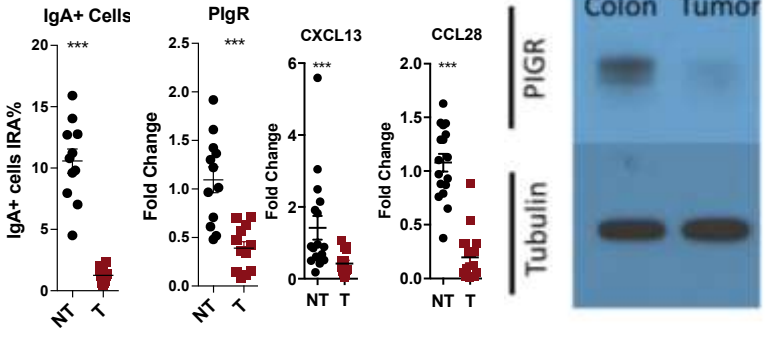


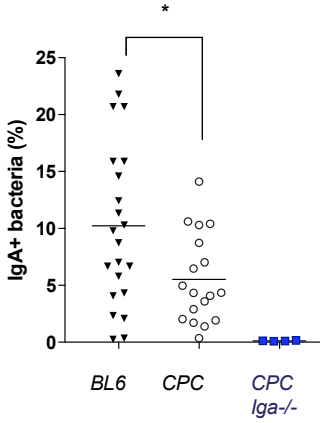


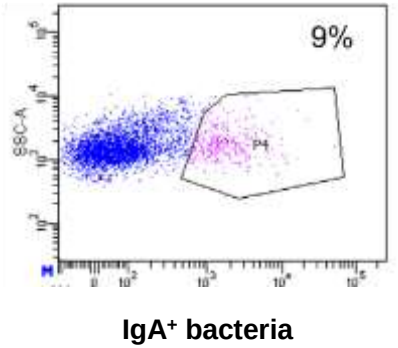




CPC-APC

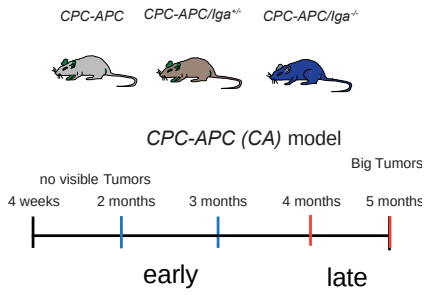




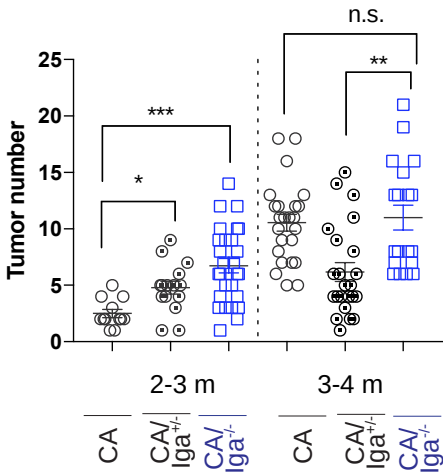


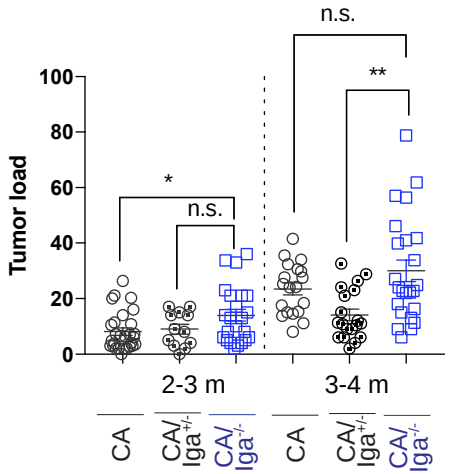
IgA⁺ bacteria

Loss of IgA enhances colorectal carcinogenesis in CPC-APC and AOM-treated mice

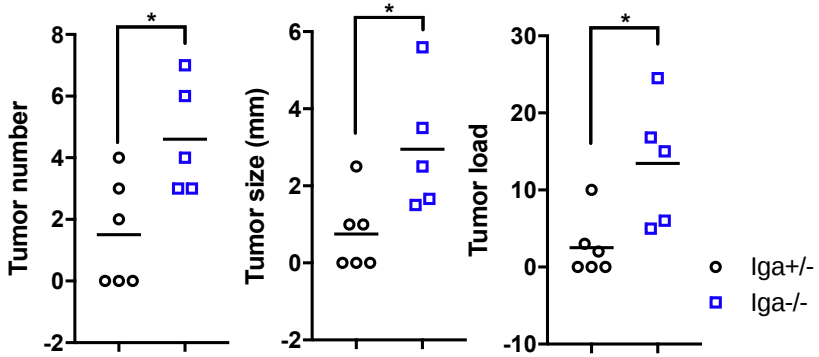


CPC-APC mice

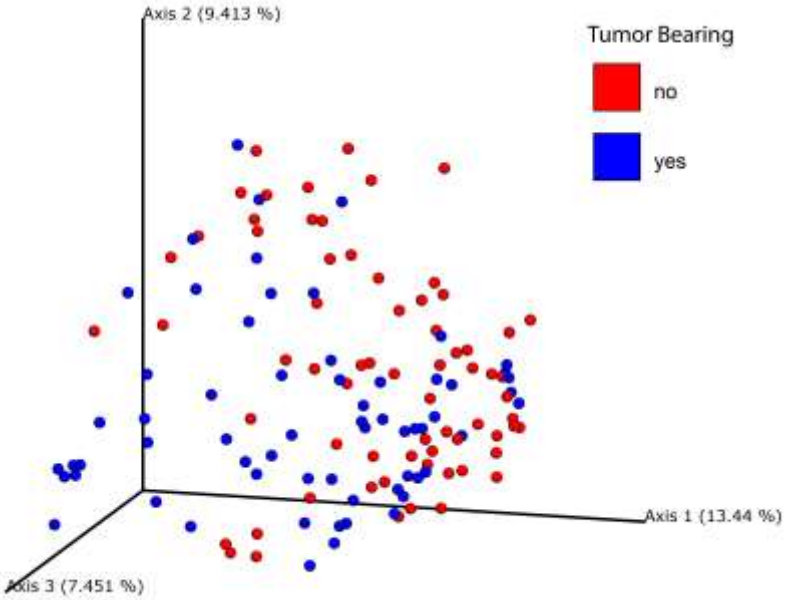


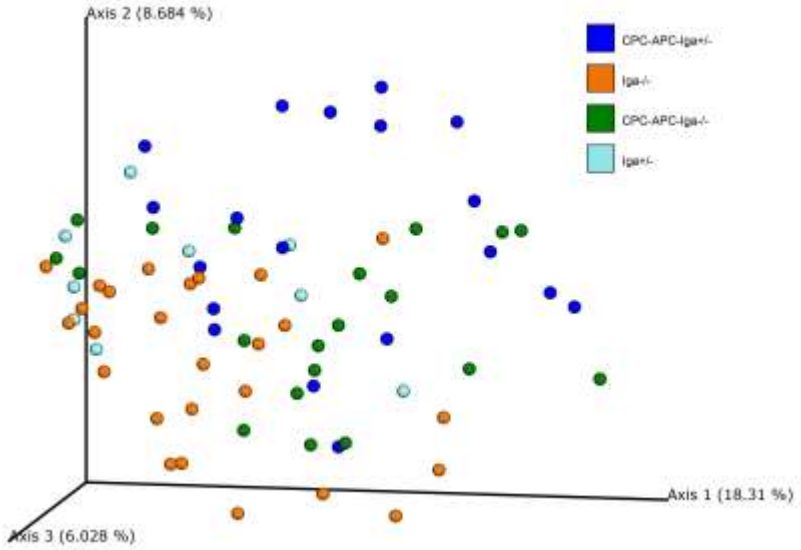


AOM treatment

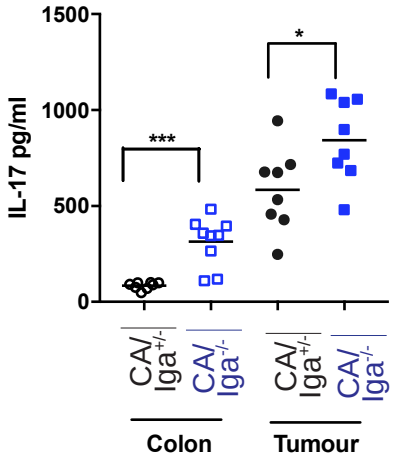


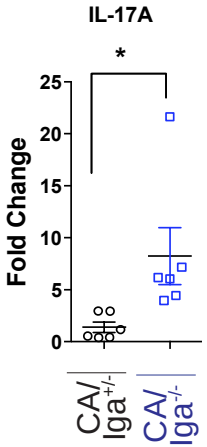
Colorectal adenomas and IgA deficiency induce dysbiosis

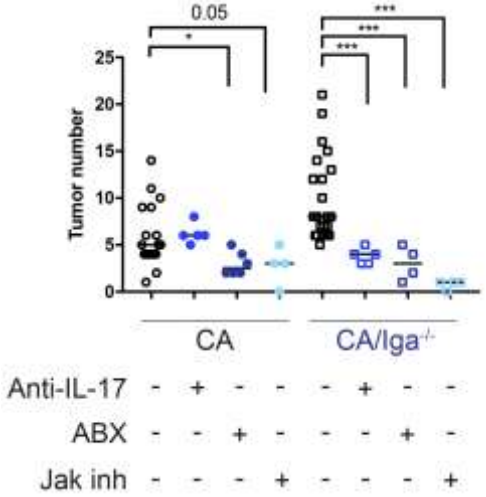


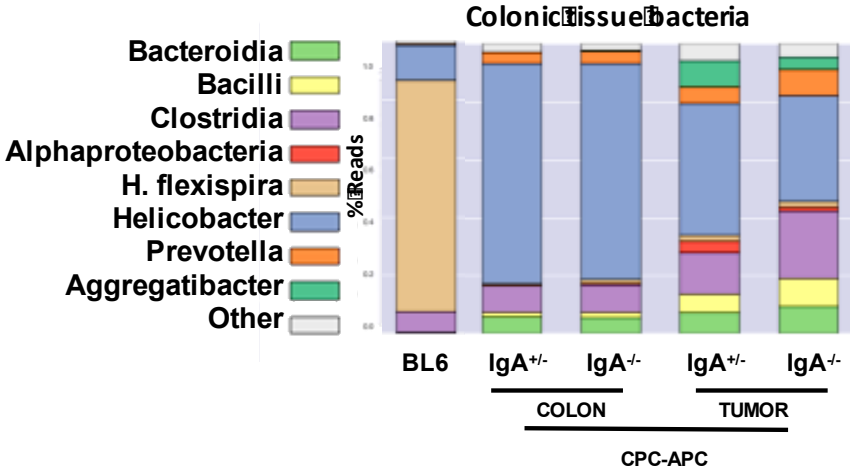


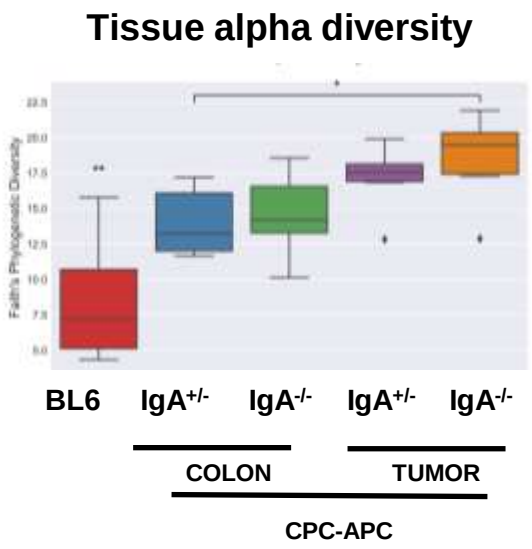
Enhanced carcinogenesis in IgA deficient mice depends on bacteria and IL-17



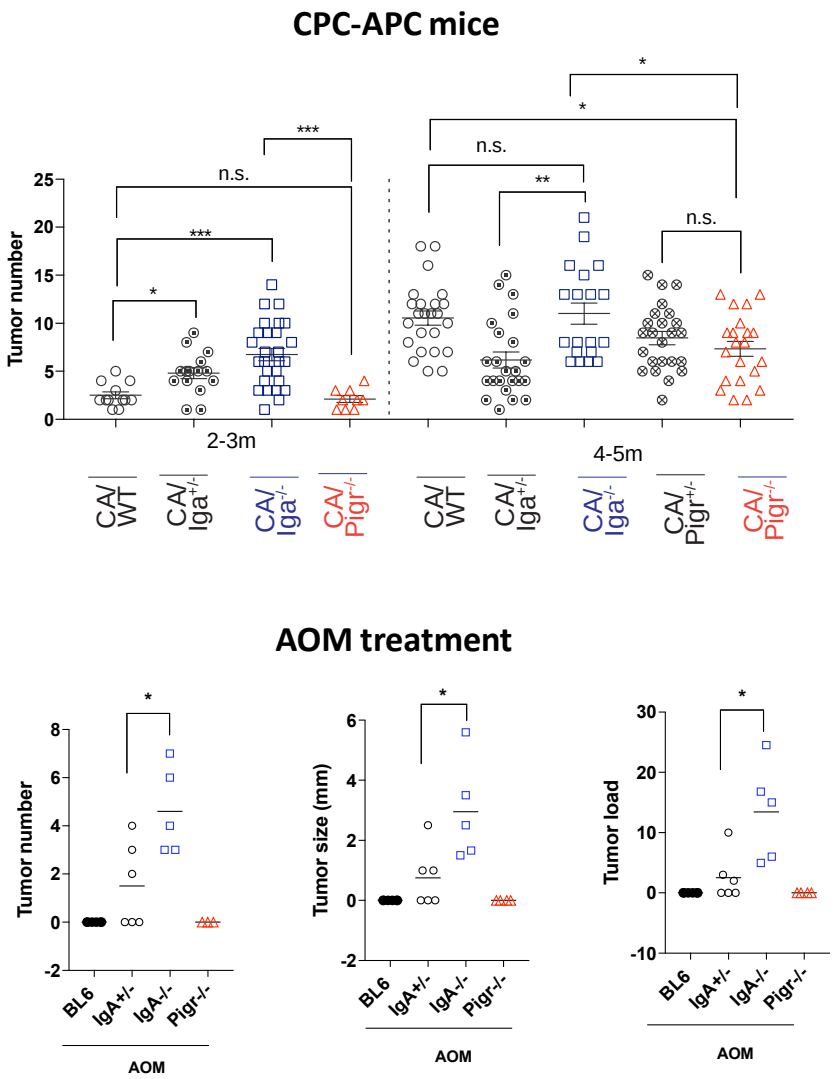




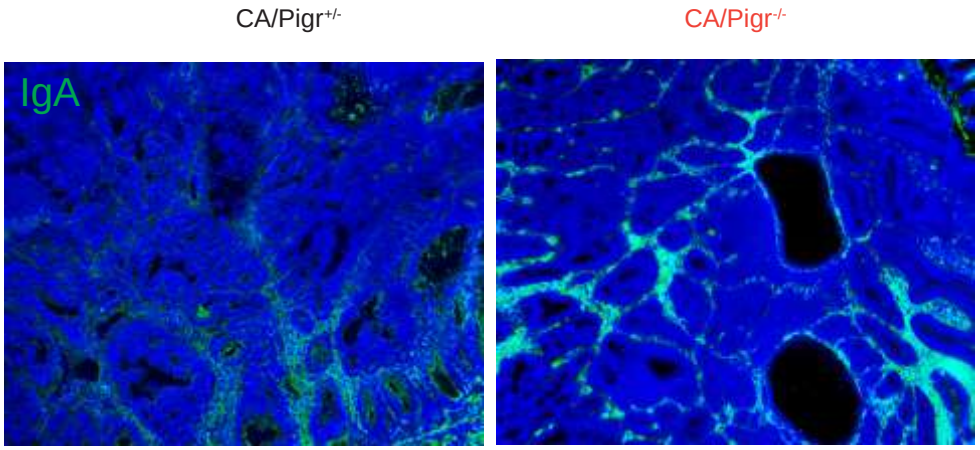


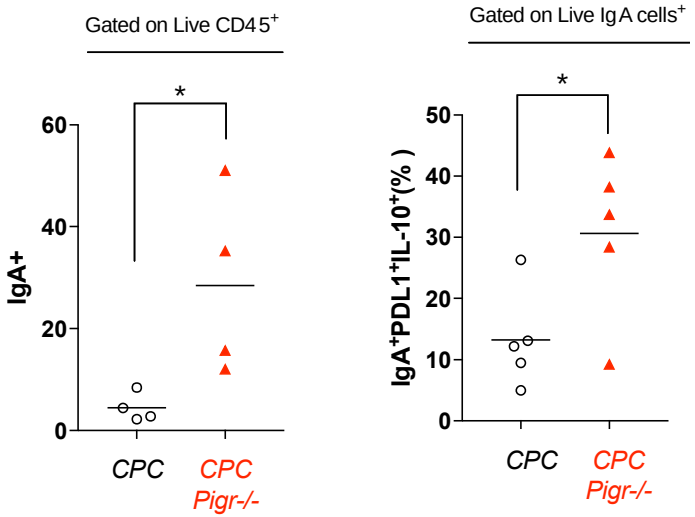


By Contrast to IgA Ablation PIgR Ablation Fails to Enhance Colorectal Tumorigenesis



By Remaining in the Lamina Propria of PIgR ko Mice IgA Continues to Protect From Invading Colitogenic Bacteria

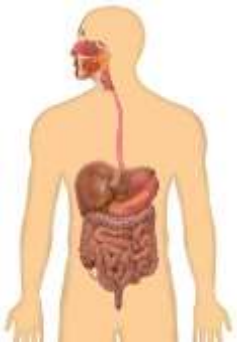


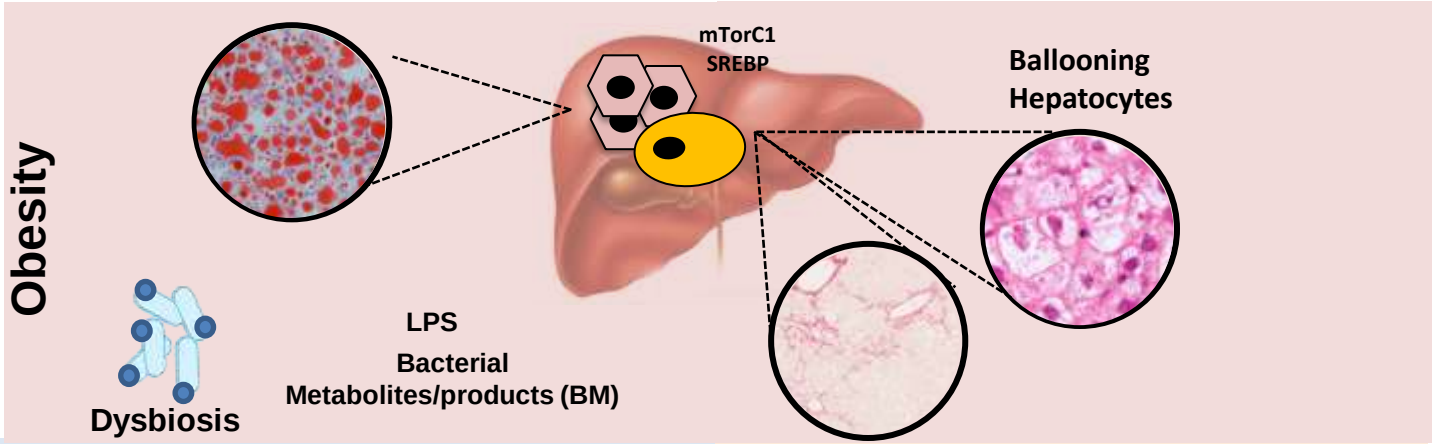


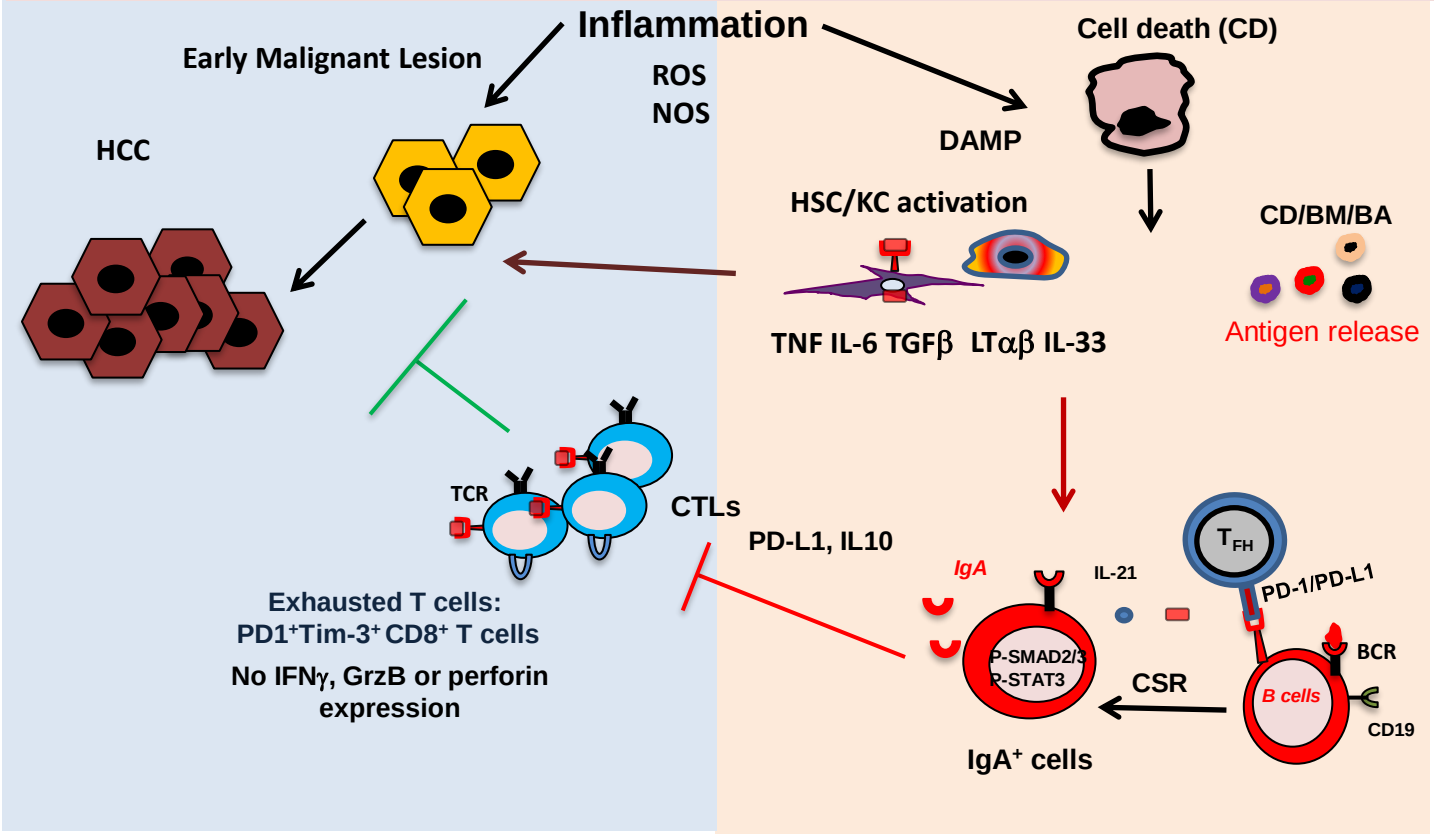
Conclusion:Colonic tumor development results in loss of barrier integrity and local IgA production

It is the loss of IgA rather than PIgR that leads to dysbiosis and increased proliferation of colitogenic bacteria

Inflammation-induced IgA$^+$ cells dismantle anti-liver cancer immunity

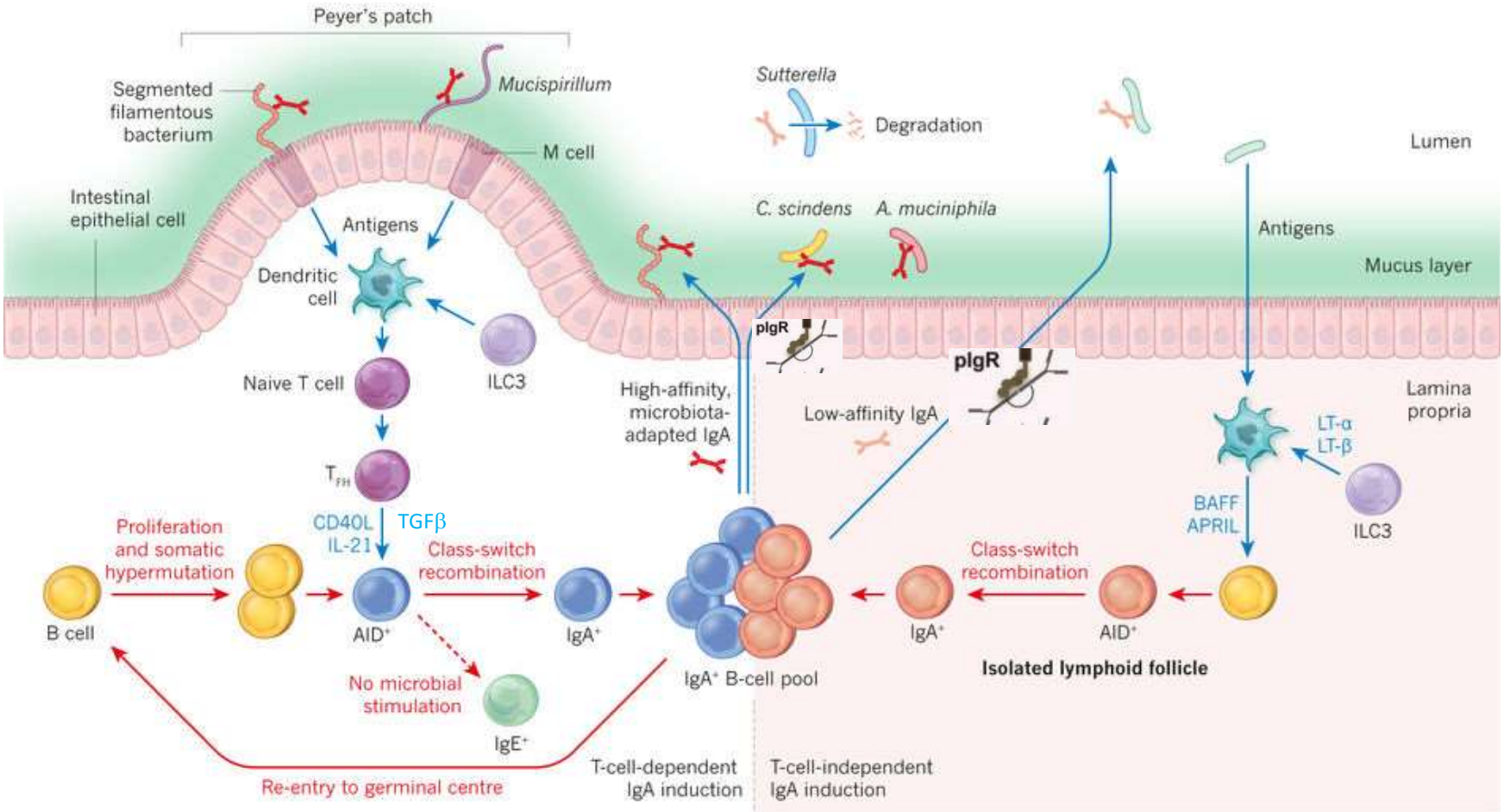






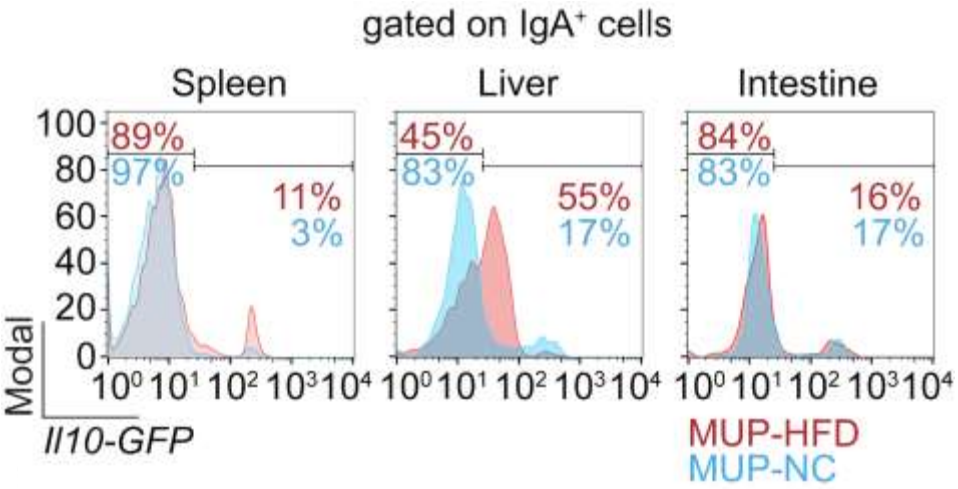
Shalapour et al., *Nature, Nov, 2017*

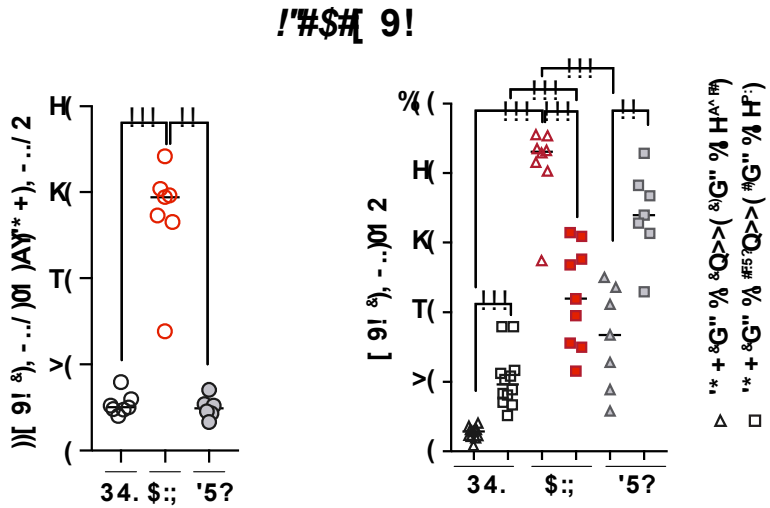
T cell -dependent and -independent class switch recombination (CSR) to IgA



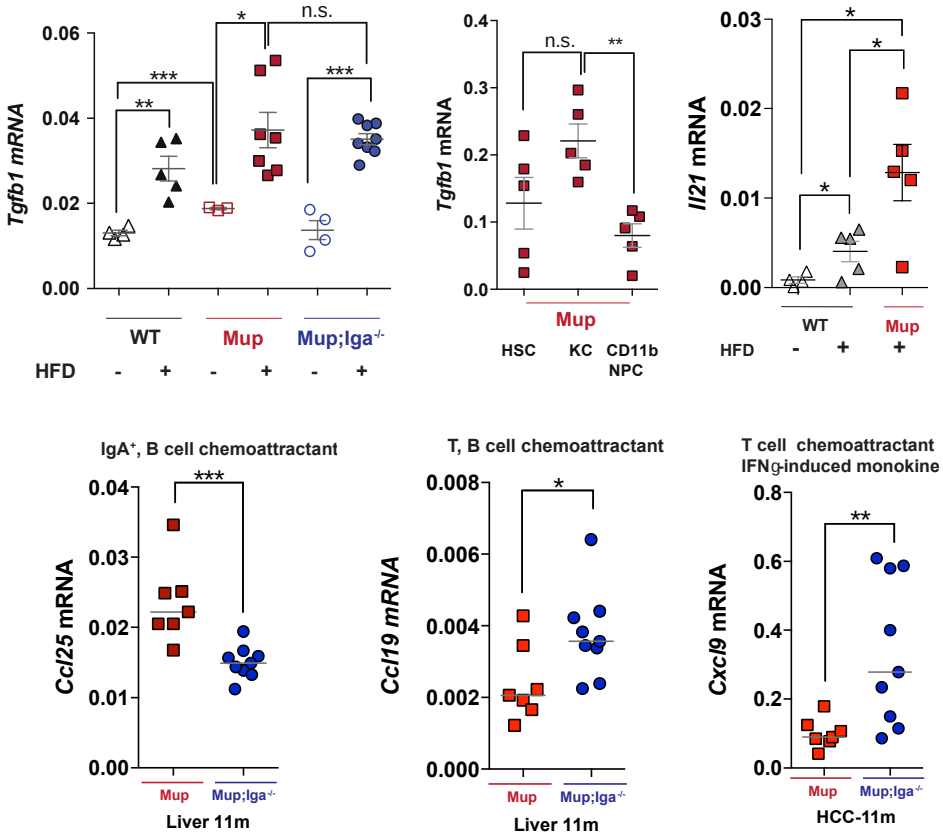
The microbiota in adaptive immune homeostasis and disease. Litman et al. *Nature* 535, 75–84 (07 July 2016)

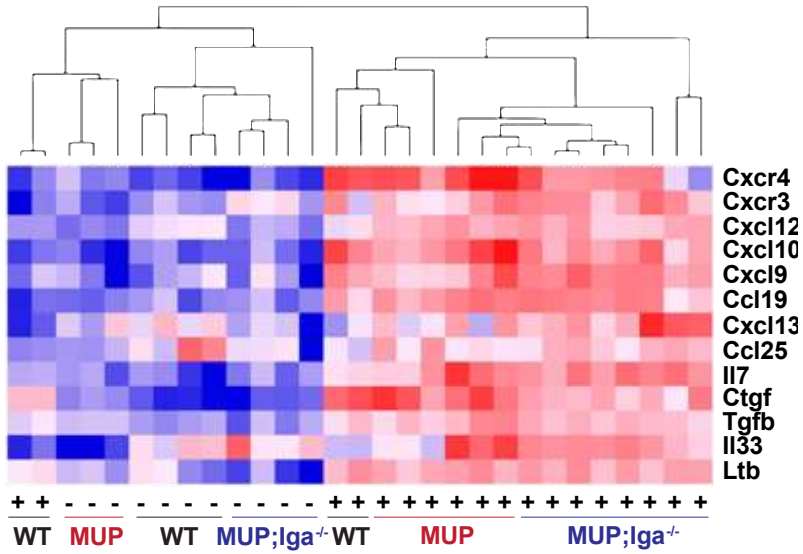
NASH enhances liver but not intestinal IgA plasmocyte development



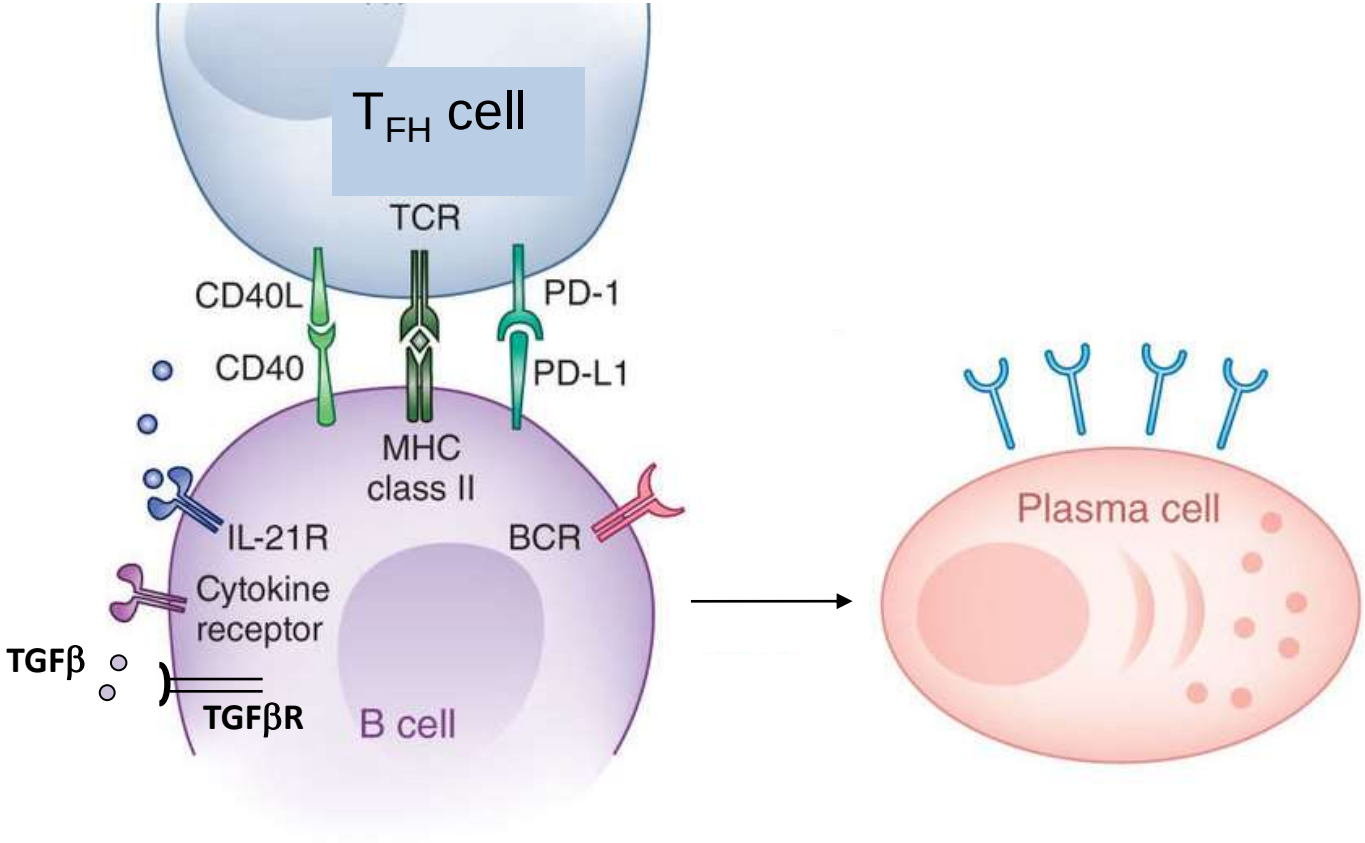


Tgfb1 and *IL-21* ,as well as numerous B and T cell chemokines are induced during liver fibrosis



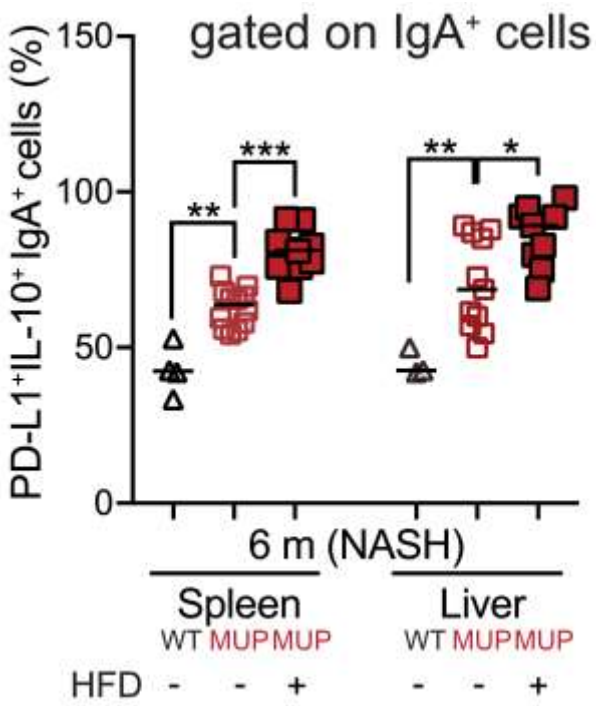


PD-1 signaling between germinal center B cells and T_{FH} cells is needed for plasma cell development.



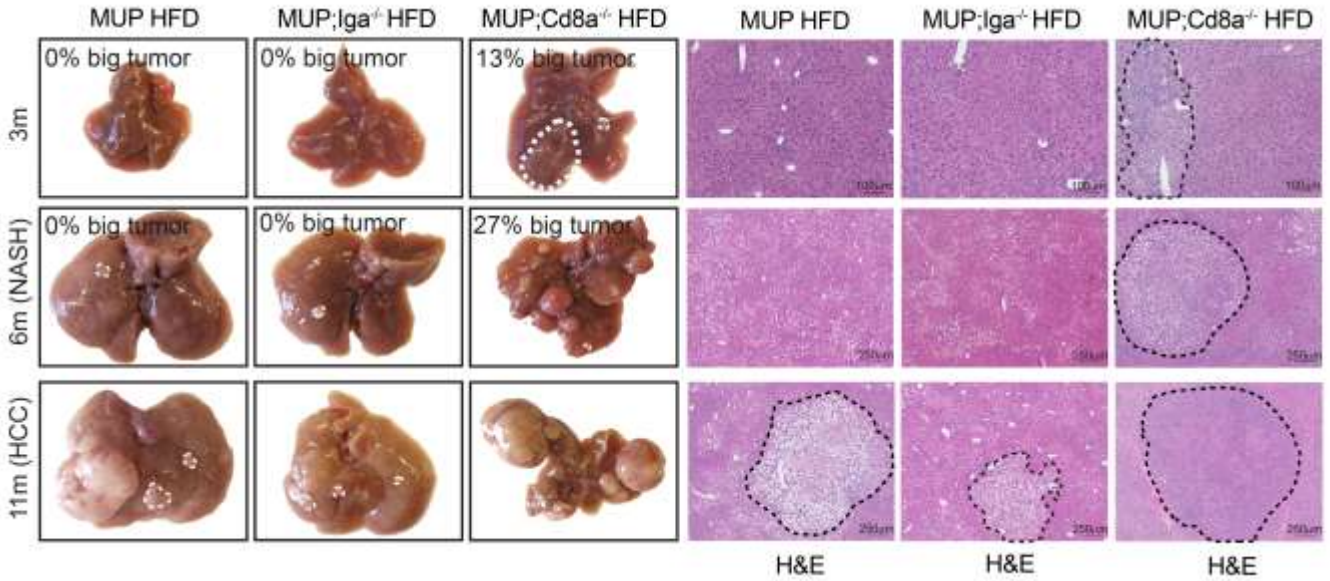
Adapted from: Pillai et al. Nature Medicine 2013

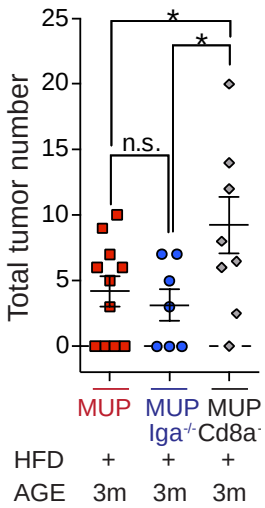
HFD increases the number of PD-L1^{+}IL-10^{+}IgA^{+} cells in spleen and liver

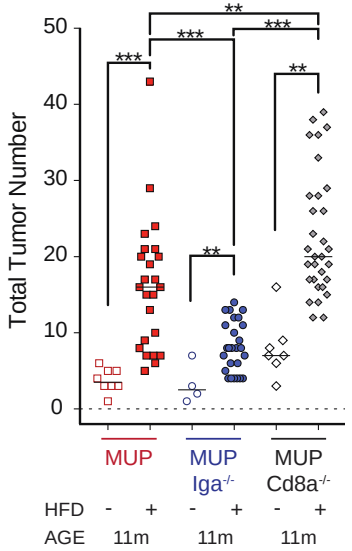


Shalapour et al. *Nature* 2017

While CD8$^+$ T cells suppress, IgA$^+$ plasmocytes promote HCC

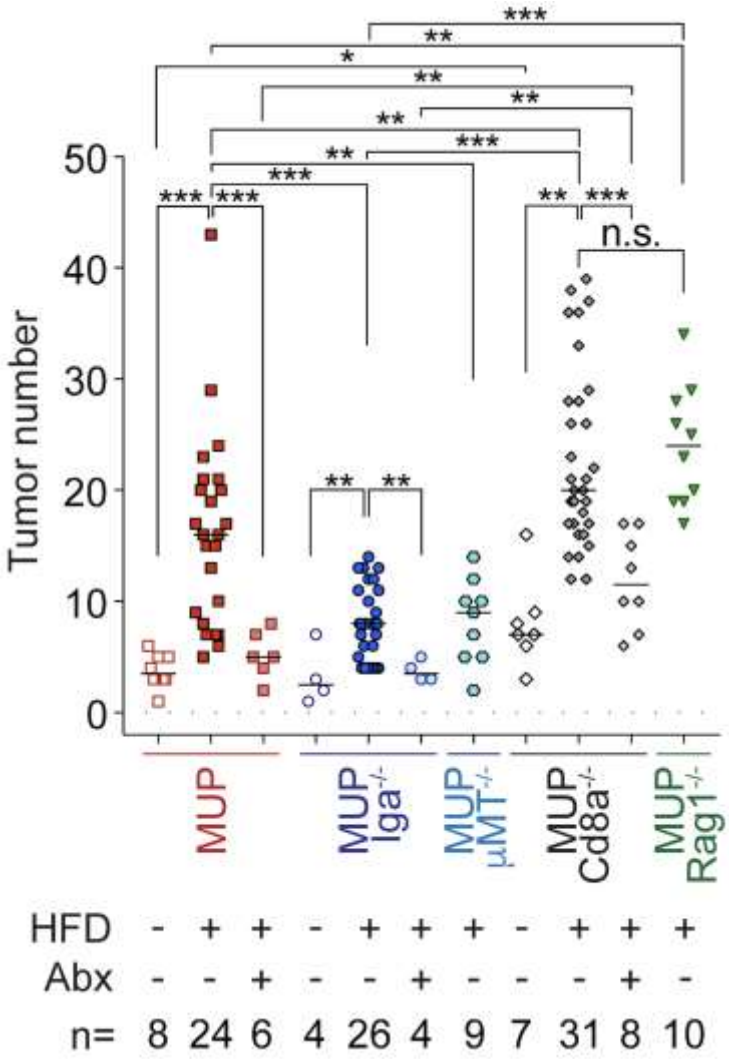




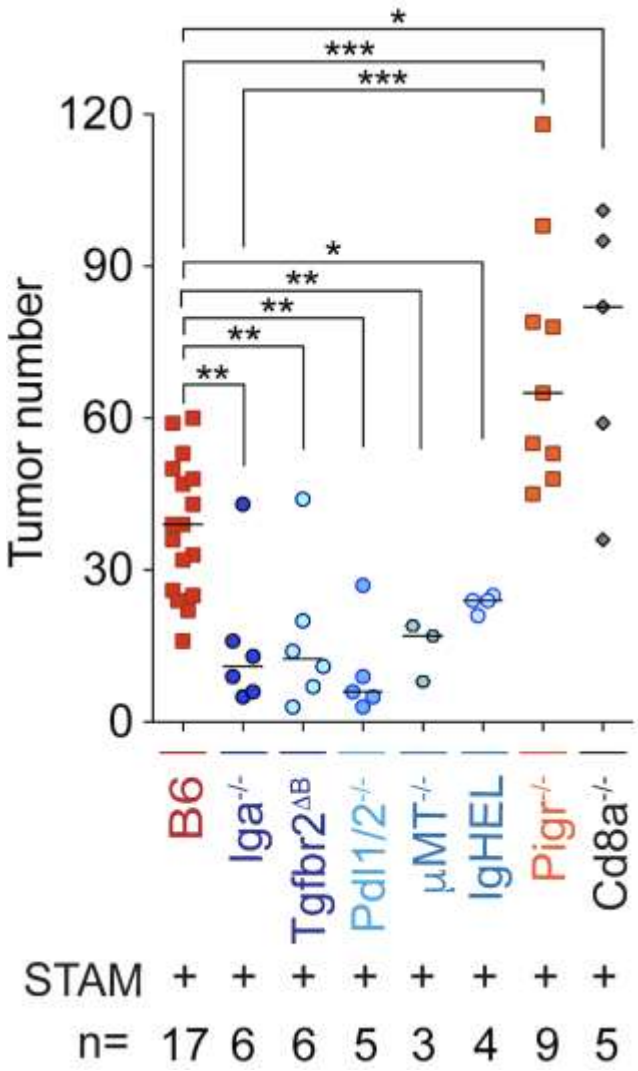


Shalapour et al. *Nature* 2017

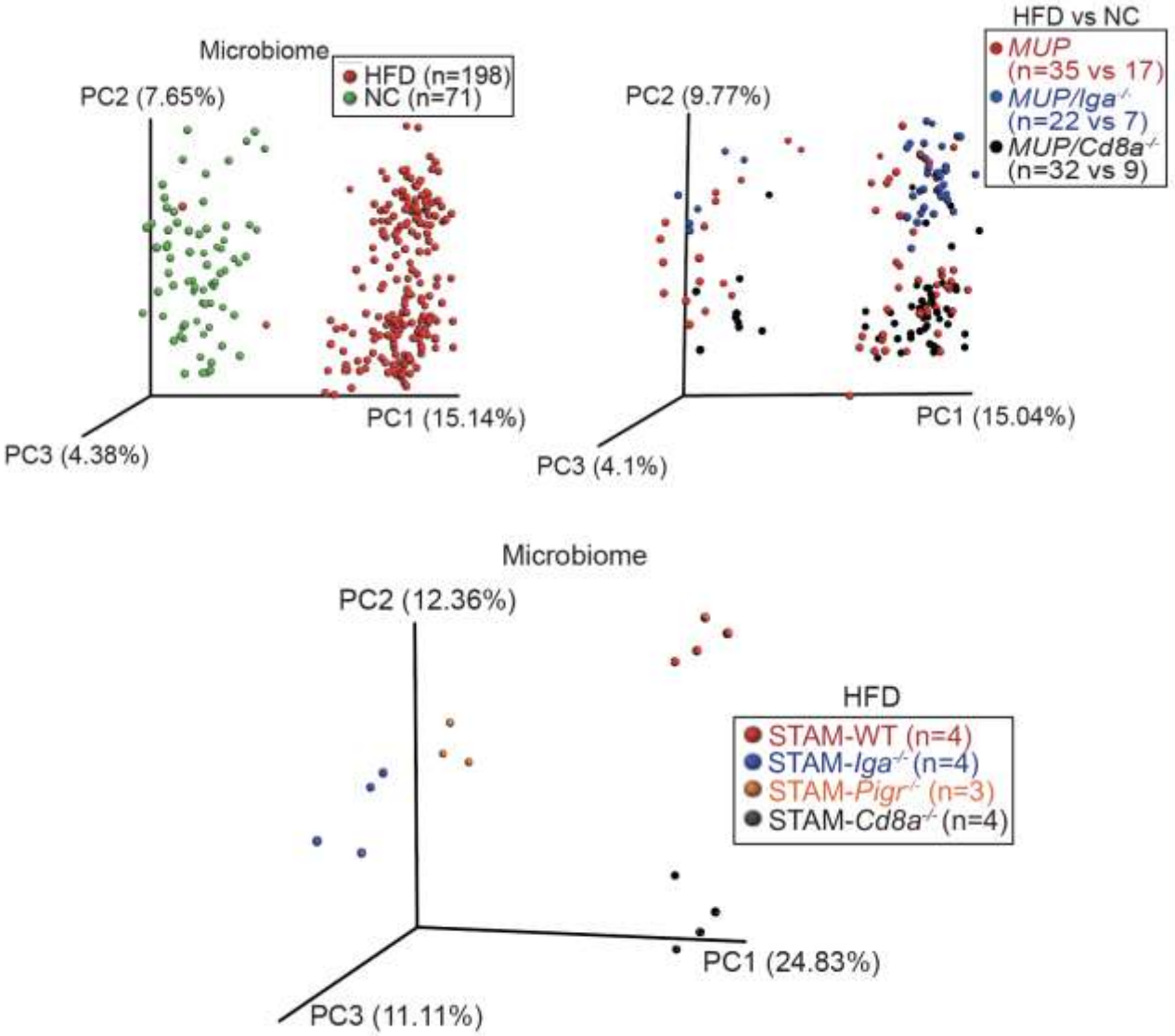
The gut microbiota promotes HCC development by enhancing liver inflammation and IgA immunosuppressive plasma cell generation



By Contrast to its Effect on Colorectal Cancer PIgR Deficiency Enhances HCC Development



Despite their Opposing Effects on NASH- Driven Liver Tumorigenesis both IgA and PIgR Deficiencies Result in Similar Dysbiosis



ACKNOWLEDGEMENTS

UCSD

Liver

Shabnam Shalapour

Xue-Jia Lin

Ingmar Bastian

Weihua Li

Sylvia Choi

Andres Perkins

Brian Dang

NIH-P01

UCSD

Colon

Giuseppe Di Caro

Shabnam Shalapour

Lei Liu

UCSD Collaborators:

Rob Knight lab:

Alison Vrbanac

Jose Navas

Pieter Dorrestien Lab:

Alexander Aksenov

Rohit Loomba- UCSD

Christopher Benner- UCSD

Ruth Yu and Michael Downes-Salk

Seed grant-UCSD-Microbiome

Southern California Research Center for ALPD and Cirrhosis grant

Fructose is a risk factor for metabolic diseases and cancer

Overconsumption of fructose is now considered a major contributor to NAFDL/NASH in adults and children due to the ability of this carbohydrate to stimulate hepatic *de novo* lipogenesis.

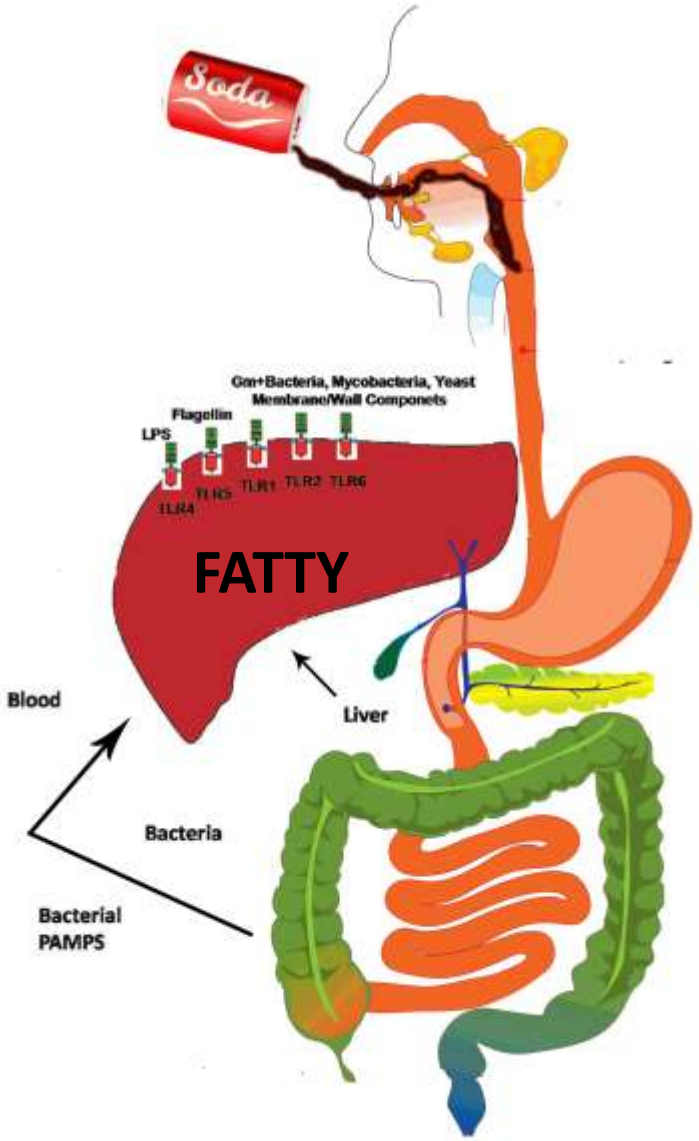
Fructose promotes obesity, insulin resistance and type 2 diabetes.

Moreover fructose consumption has been associated with increased risk of colon, pancreatic and liver cancer.

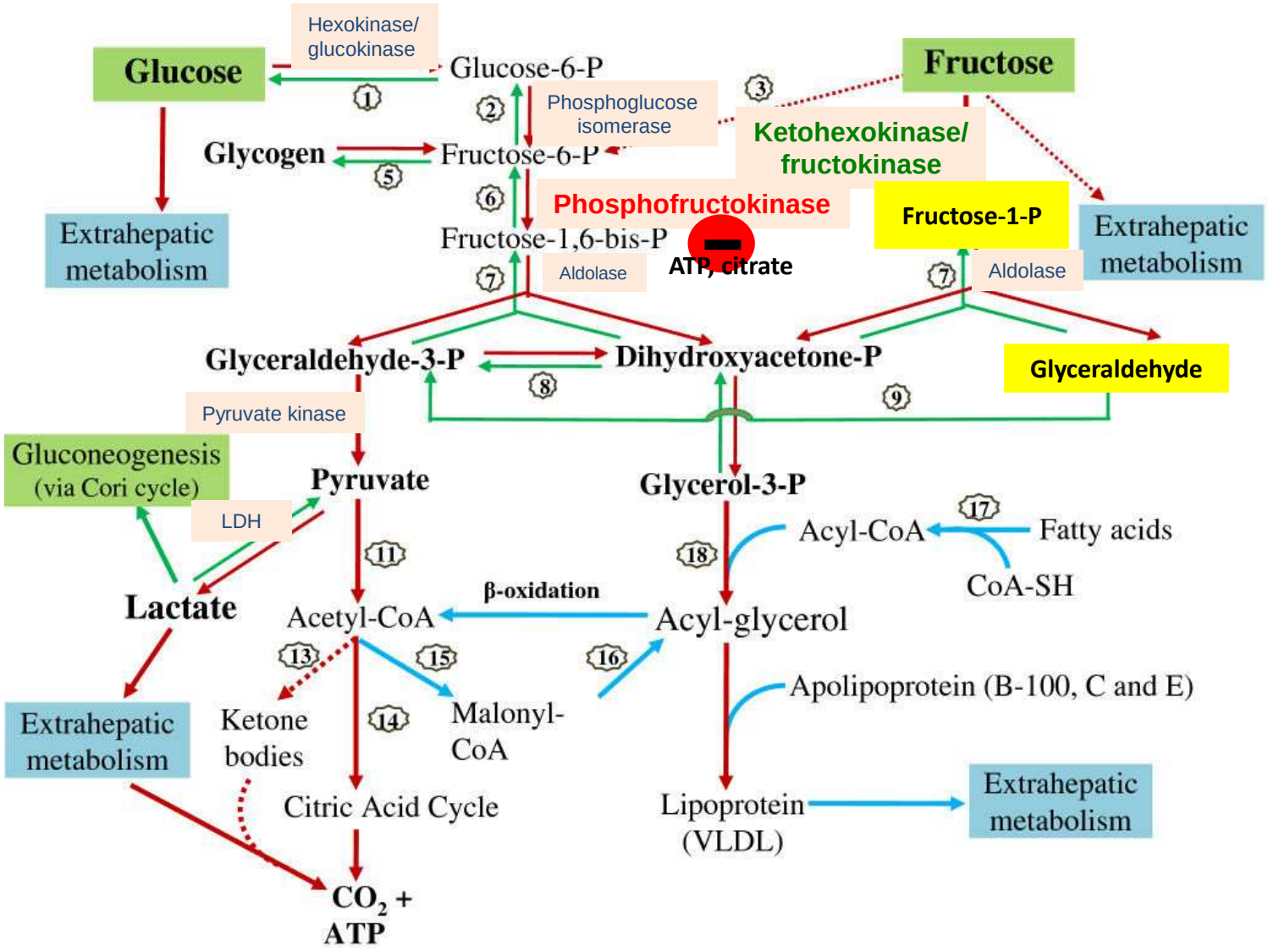
Sources of fructose in the Western diet include cane sugar (sucrose) and high fructose corn syrup (HFCS), a corn-based sweetener that has been on the market since about 1970.

HFCS accounts for more than 40 percent of the caloric sweeteners added to foods and beverages, and it is the sole sweetener used in American soft drinks.

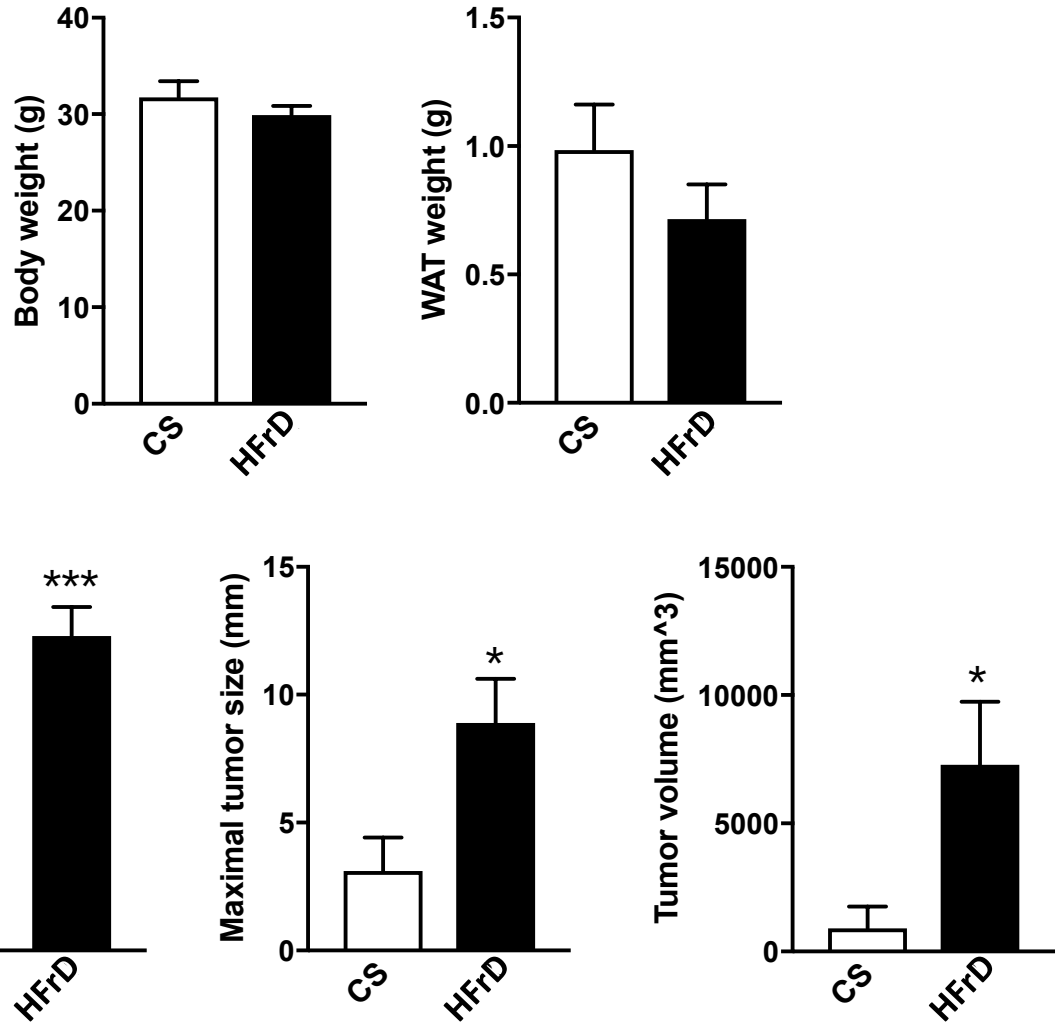
High fructose corn syrup induces hepatic steatosis presumably by preferential uptake of fructose by the liver.



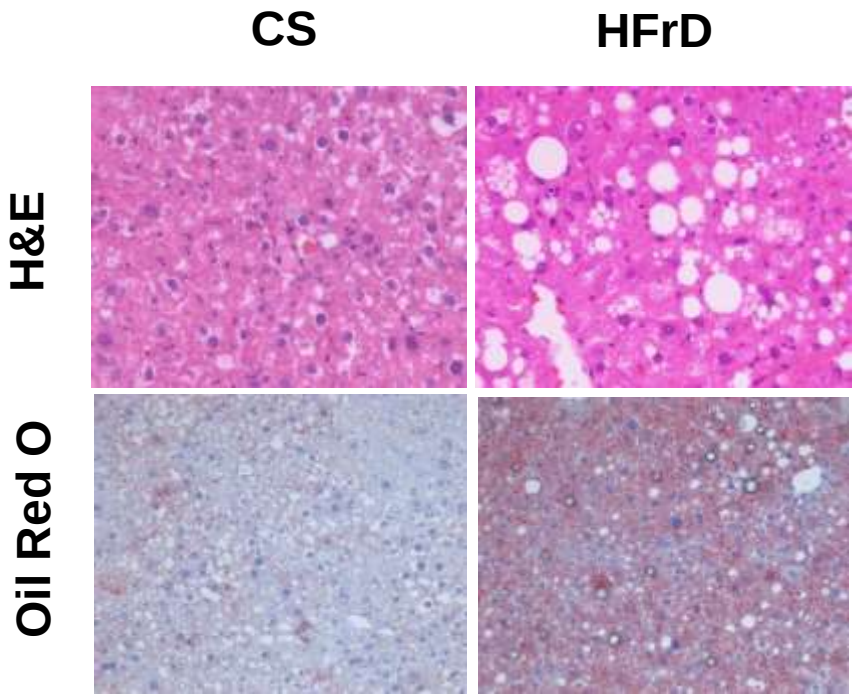
Unlike glucose, fructose was suggested to be metabolized almost completely by the liver in an insulin-independent manner bypassing key negative feedback controls.

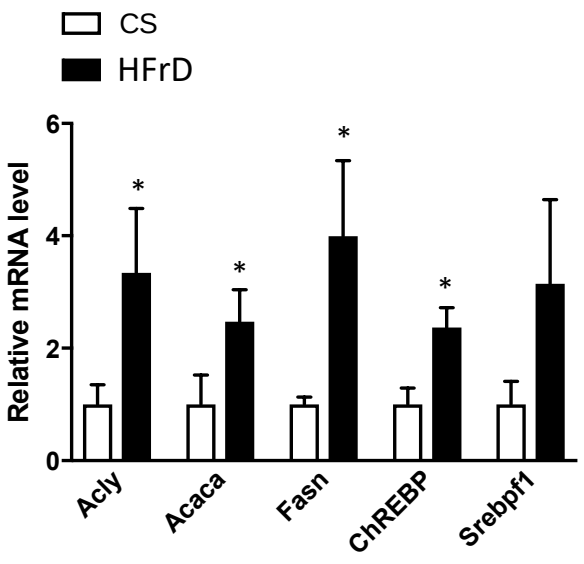


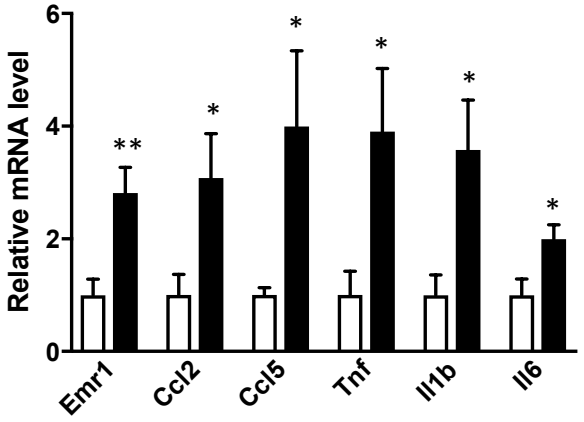
MUP-uPA mice fed HFrD diet show increased tumor formation at 12 months of age compared to CS diet-fed littermates.



Fructose causes hepatic steatosis in MUP-uPA mice (6m) and induces genes that mediate de novo lipogenesis and inflammation.







Leaky gut and liver cancer

The gut microbiota is composed of 100 trillion bacteria of diverse taxonomy (2000 distinct species).

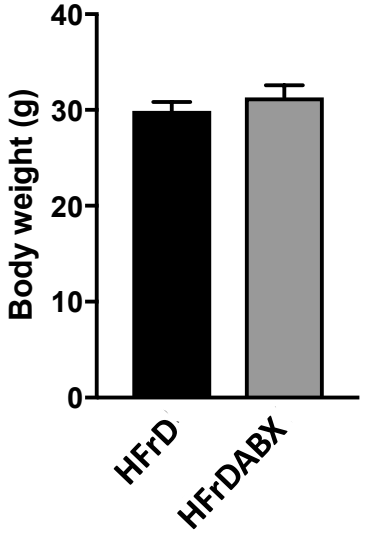
Disruption of microbial homeostasis is associated with obesity, malnutrition, inflammatory bowel diseases (IBD), neurologic disorders and liver diseases such as NASH, ASH and HCC.

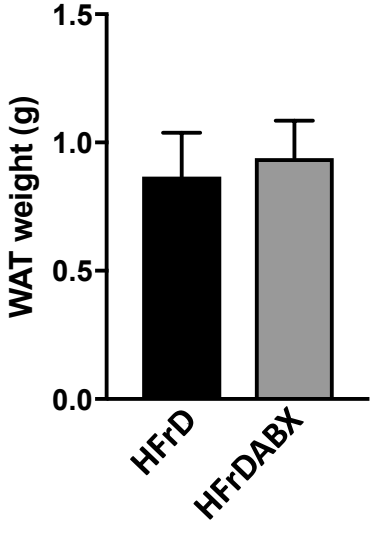
Intestinal dysbiosis causes colonic inflammation, which is mediated by chemokine (C-C motif) ligand 5 (CCL5).

Intestinal inflammation results in an increase in intestinal permeability, which leads to translocation of microbial products to the liver.

Binding of these microbial products to Toll-like receptors (TLRs) in the liver is associated with exacerbated hepatic steatosis driving NASH or ASH progression.

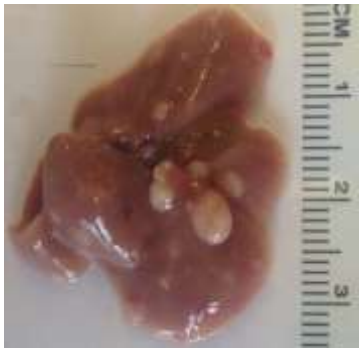
Antibiotic treatment abrogated HFrD-induced hepatocarcinogenesis in MUP-uPA mice.

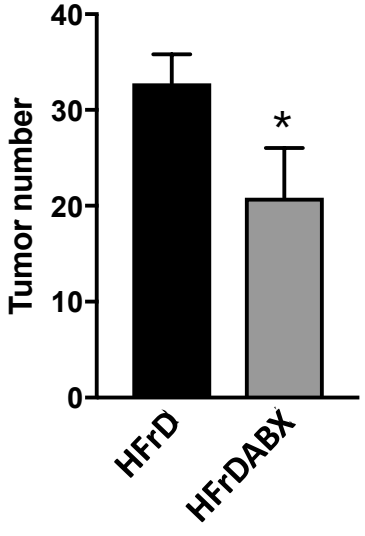


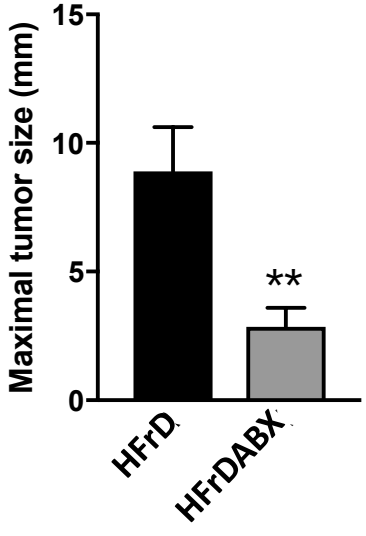


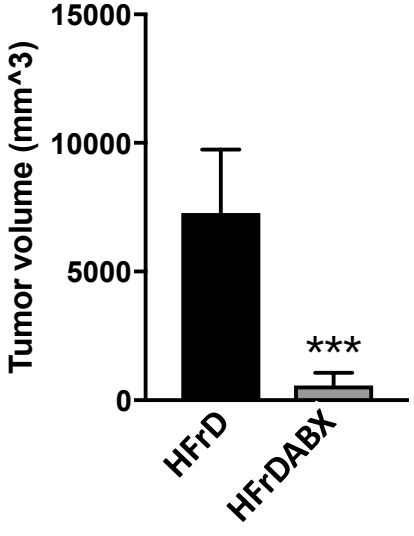
HFrD

HFrDABX

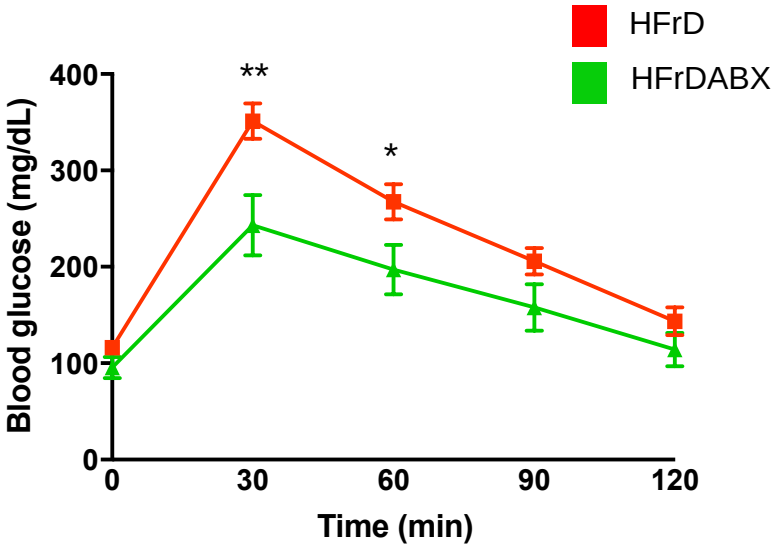


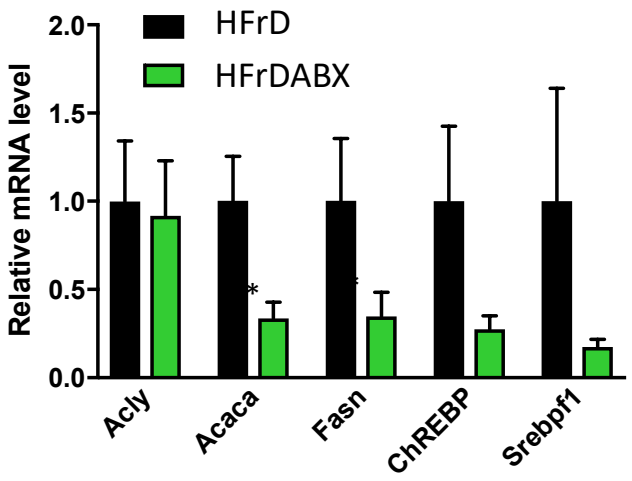




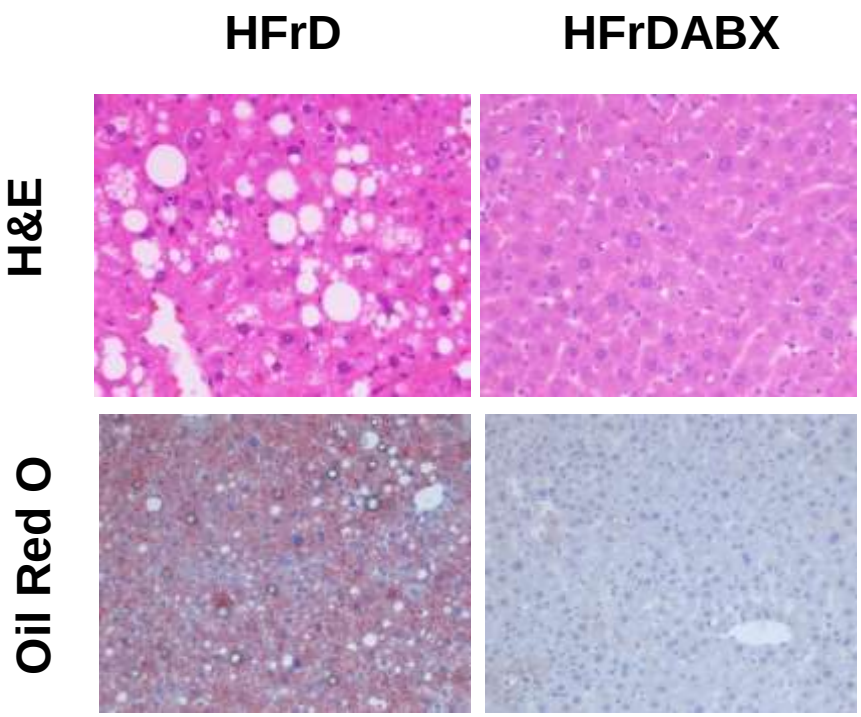


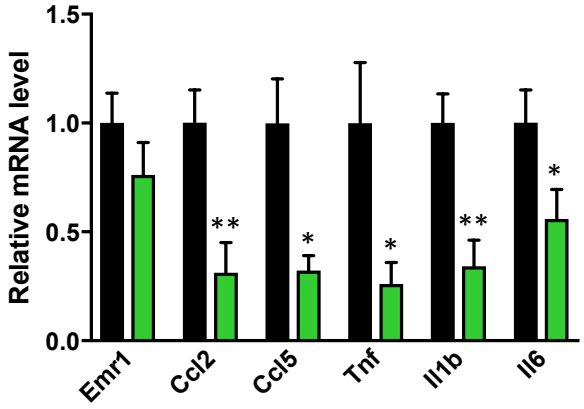
Antibiotic treatment ameliorated glucose intolerance and abrogated induction of *de novo* lipogenesis genes in 6 month-old HFrD-fed MUP-uPA mice.



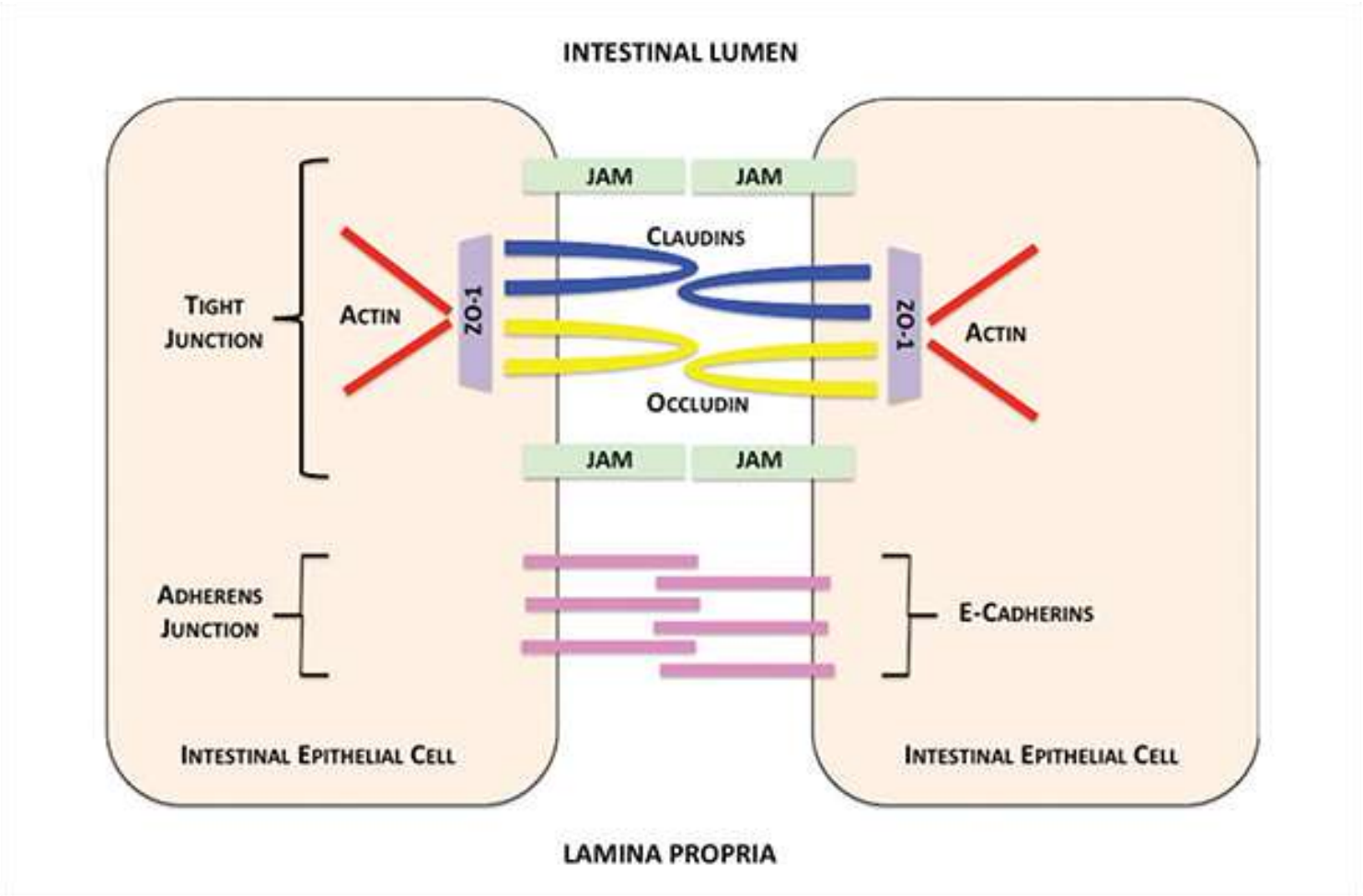


Antibiotics prevent hepatic steatosis and inflammatory gene induction in HFrD-fed MUP-uPA mice.



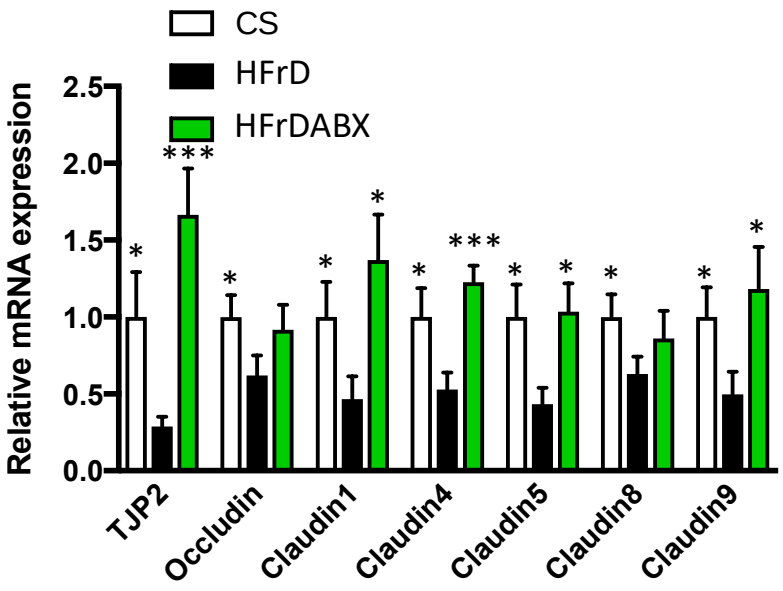


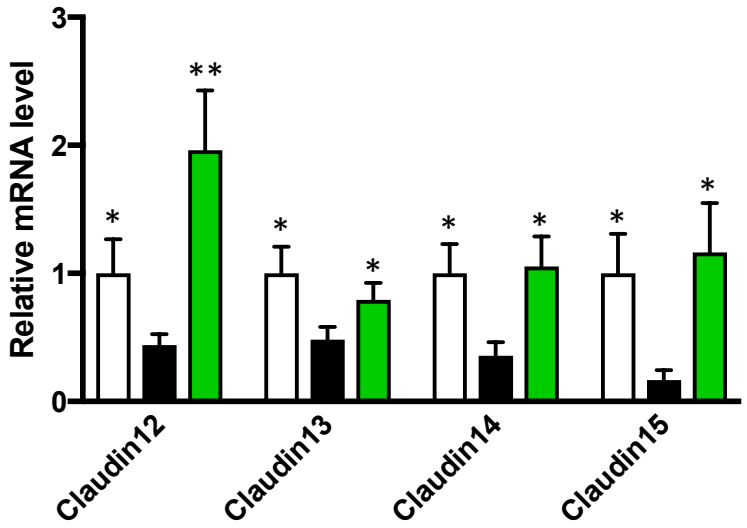
The epithelial tight junction (TJ) is a multi-protein complex that forms a selective permeable seal between adjacent epithelial cells. Disruption of the intestinal TJ barrier, followed by permeation of luminal molecules, induces a perturbation of the mucosal immune system and inflammation.



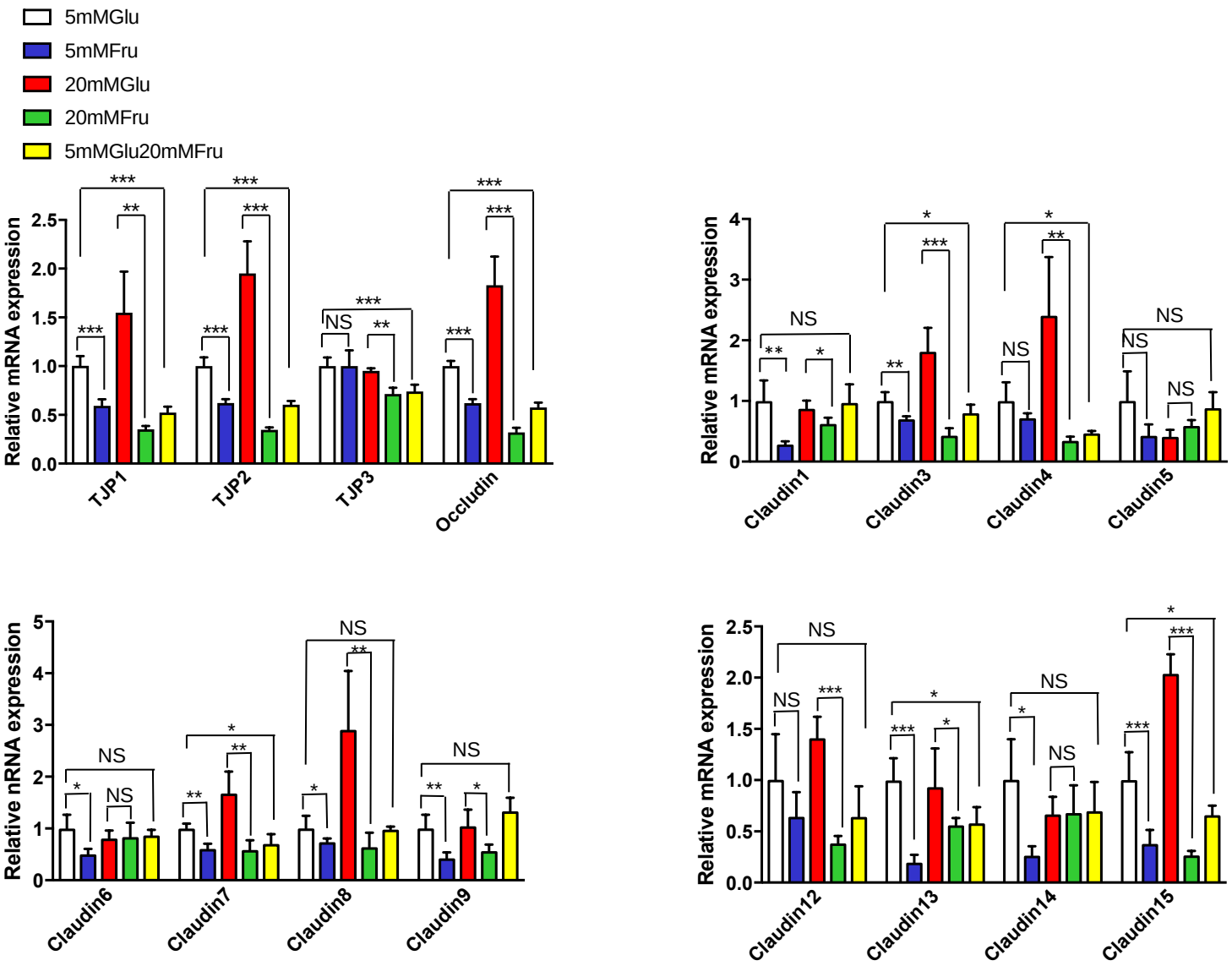
HFrD-induced suppression of intestinal tight junction-related genes is restored by antibiotic-treatment.

Colon

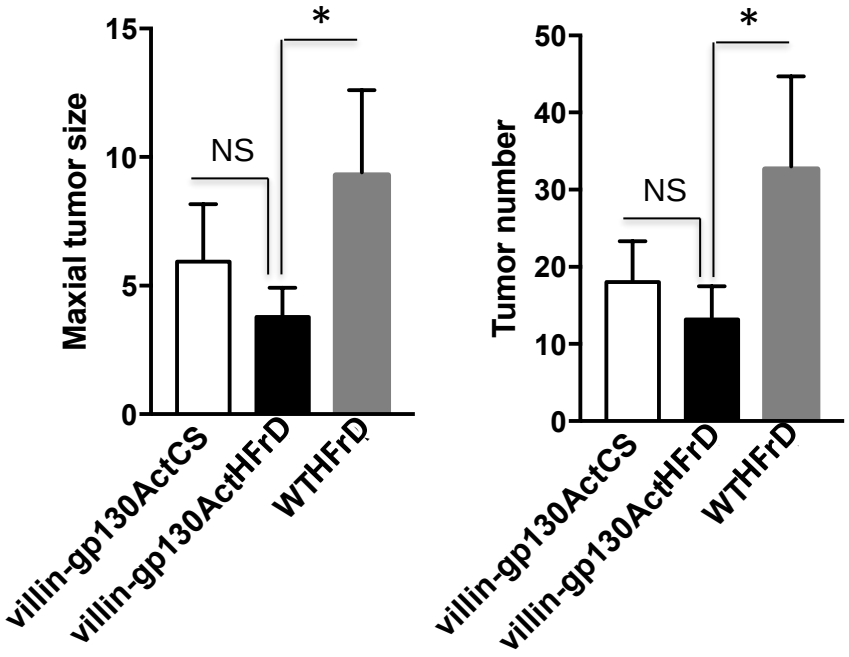




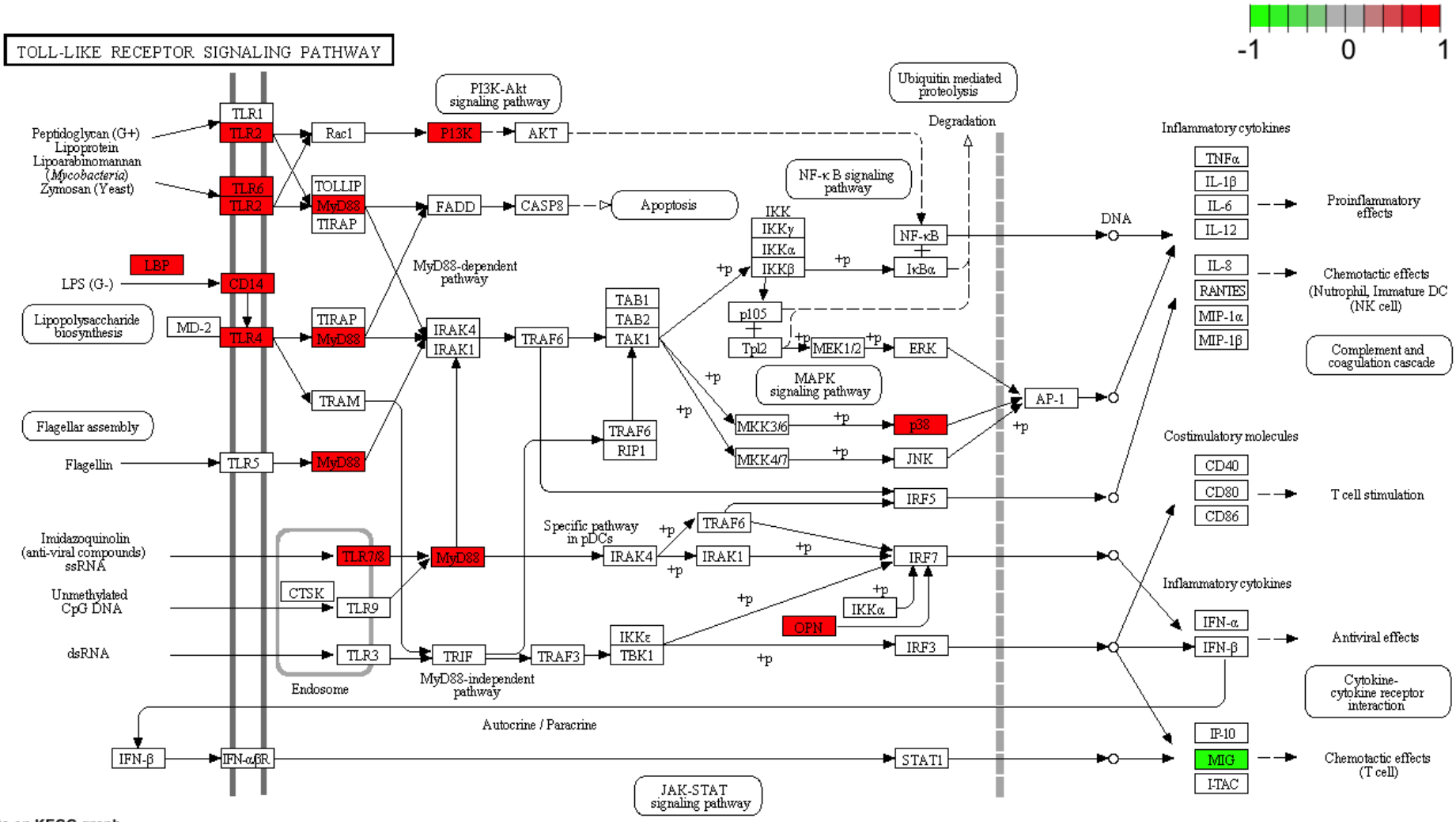
Fructose is inhibits expression of several intestinal tight junction-related genes in colonic organoids

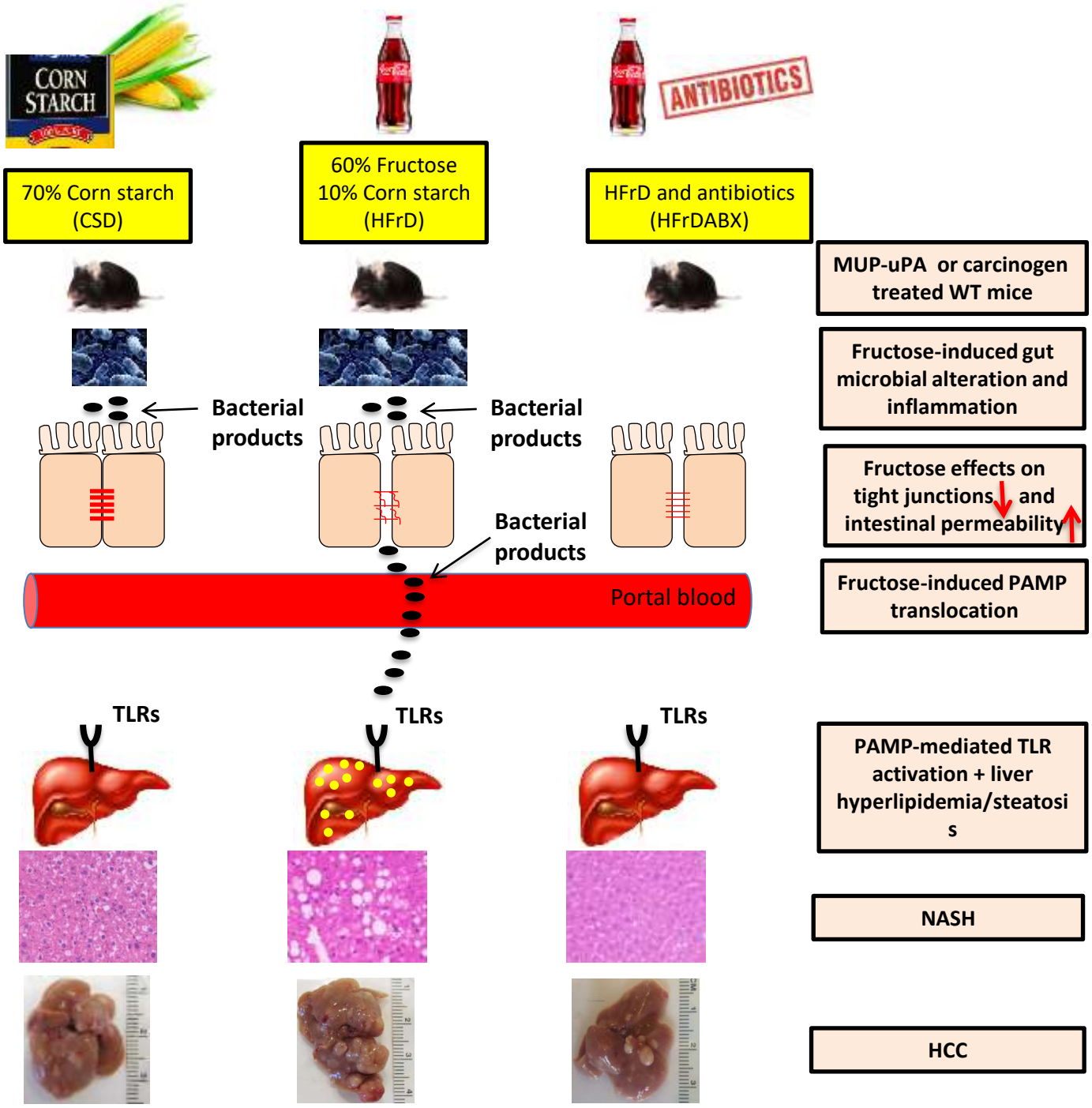


Villin-gp130Act mice that rapidly regenerate intestinal barrier are protected against HFrD-induced HCC development



TLR signaling is upregulated in DEN-treated mice fed HFrD.




CORN STARCH
ANTIBIOTICS
70% Corn starch (CSD)
60% Fructose 10% Corn starch (HFrD)
HFrD and antibiotics (HFrDABX)
MUP-uPA or carcinogen treated WT mice
Fructose-induced gut microbial alteration and inflammation
Bacterial products
Bacterial products
Bacterial products
Fructose effects on tight junctions and intestinal permeability
Fructose-induced PAMP translocation
Portal blood
TLRs
TLRs
TLRs
PAMP-mediated TLR activation + liver hyperlipidemia/steatosis
NASH
HCC

Acknowledgments

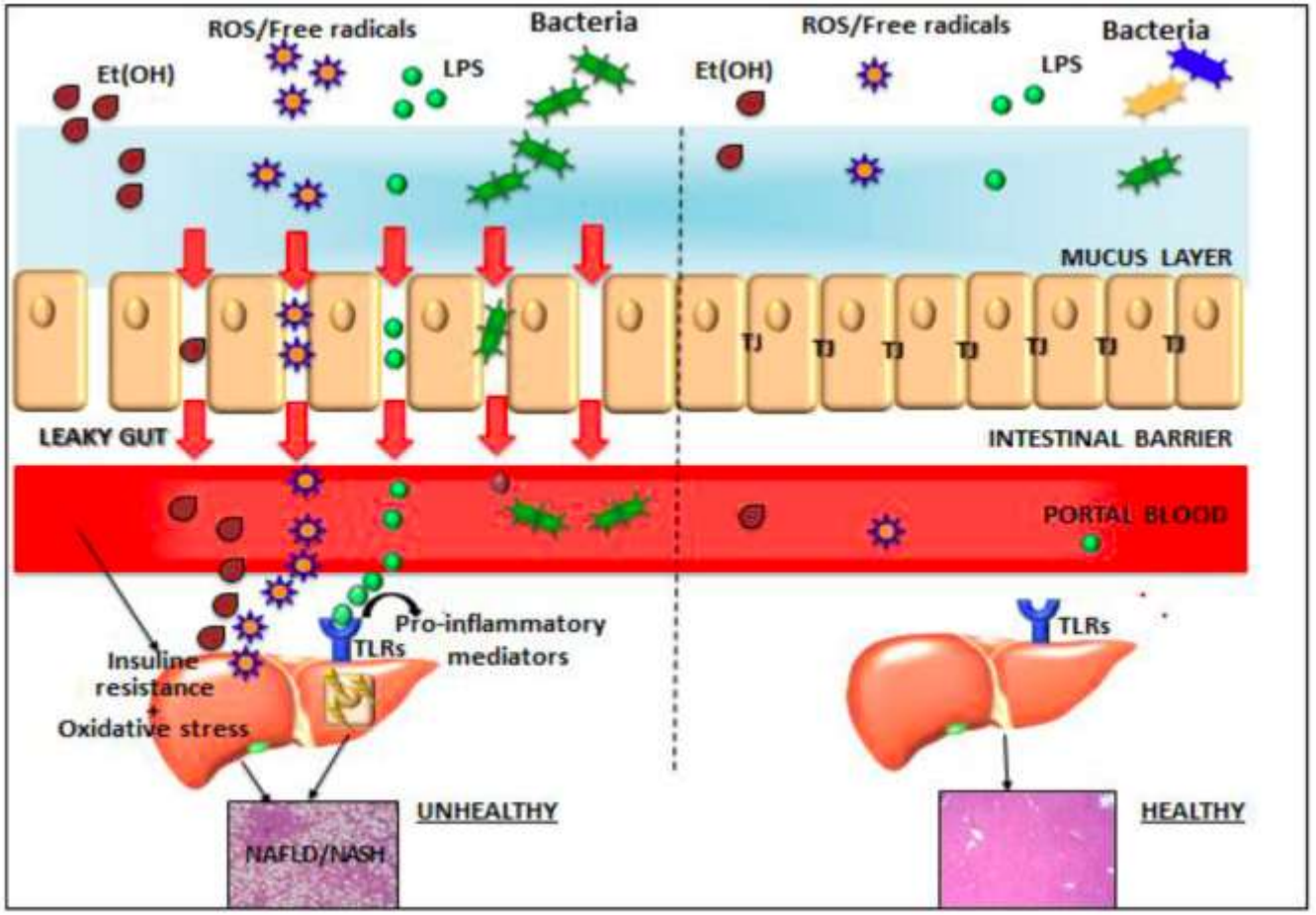
University of California, San Diego

Jelena Todoric
Giuseppe Di Caro
Koji Taniguchi

Garvan Institute of Medical Research

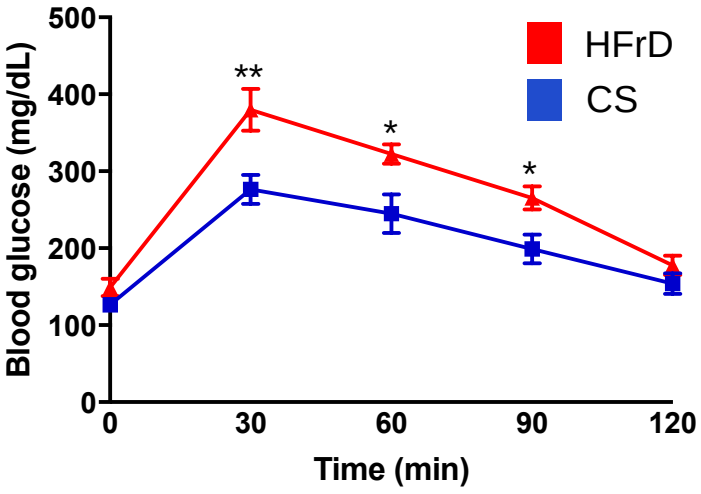
Mark Febbraio
Saskia Reibe-Pal
Darren Henstridge

Conclusion: Barrier disruption comes first and the increased influx of microbes or microbial products leads to the inflammation that stimulates NASH and HCC development



Fructose is more diabetogenic than corn starch in both models.

DEN-treated B6 mice



MUP-uPA mice