Paris NASH Meeting

International Think Tank

How Will New Therapies Affect HCC Development?

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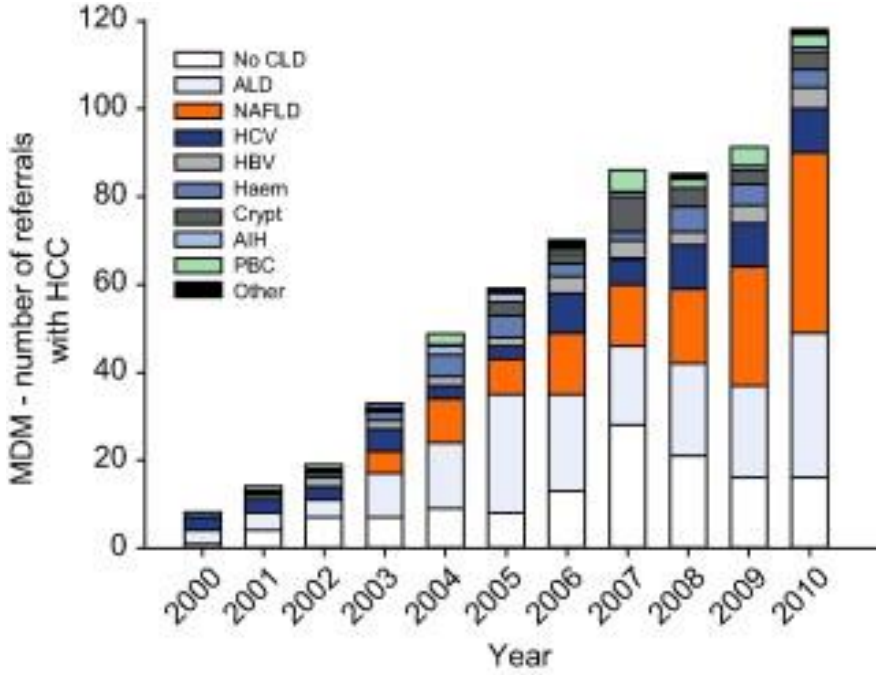
Mount Sinai

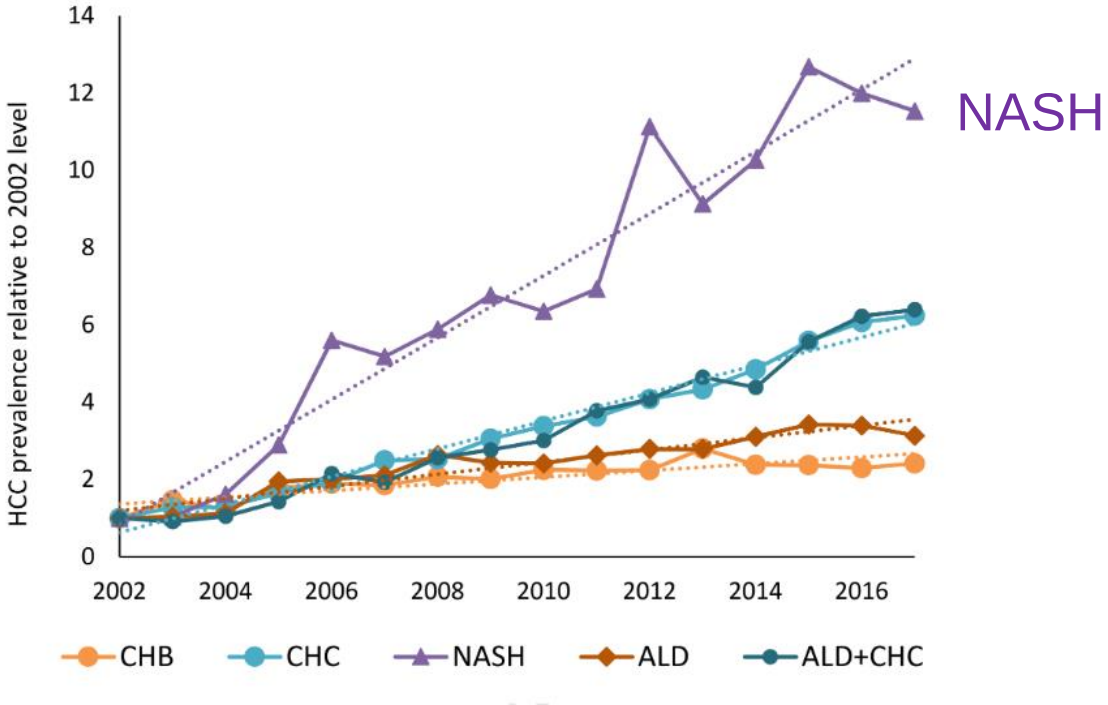
Rising Contribution of NAFLD to HCC in Newcastle, UK



- NAFLD accounted for 34.8% of HCC
- 30% did not have cirrhosis
- If PNPLA3 polymorphism present, OR=12.9

Dyson et al, *Journal of Hepatology*, Volume 60, 110 – 117, 2014

NASH is the Fastest Growing Cause of HCC Among Liver Diseases



Younossi et al, J Clin Gastro Hep, 2018, in press.

Mechanisms of Increased Cancer Risk Associated with Obesity

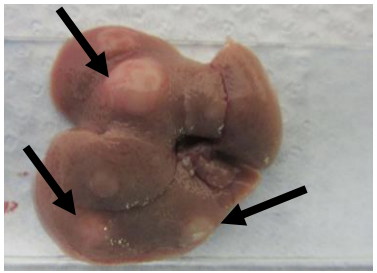
Obesity confers increased risk of all cancers, but esp. HCC

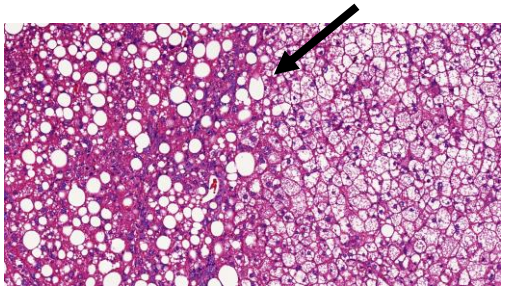
- A chronic inflammatory state, with more oxidant stress, DNA damage and mutations
- Increased estrogen production by fat
- Higher circulating IGF and insulin
- Increased adipokines, especially leptin, which is a mitogen
- Altered gut microbiome

Genomic Features of HCC in NASH

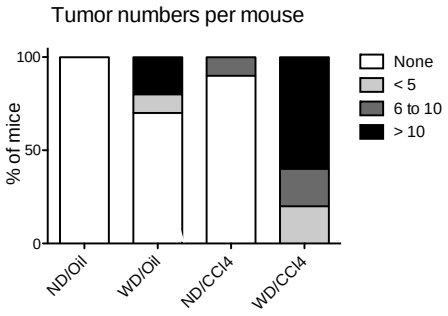
- Very few studies; too early to draw conclusions
- Pathways regulated by HNF4 reported in one study (Frades, PLoS one, 2015)
- Prognostic signatures reported (Frades, PLoS one, 2015)
- May have unique epigenetic features (Deconti, Mol Canc Res, 2017; Dechass, Mol Carcinogenesis, 2018)

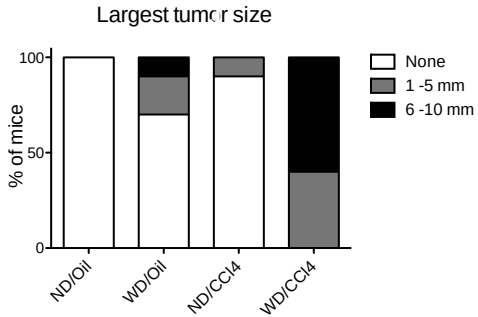
HCC Development in Western Diet/CCl_4 NASH Model





High fat, high cholesterol, high fructose diet with weekly CCl_4 IP

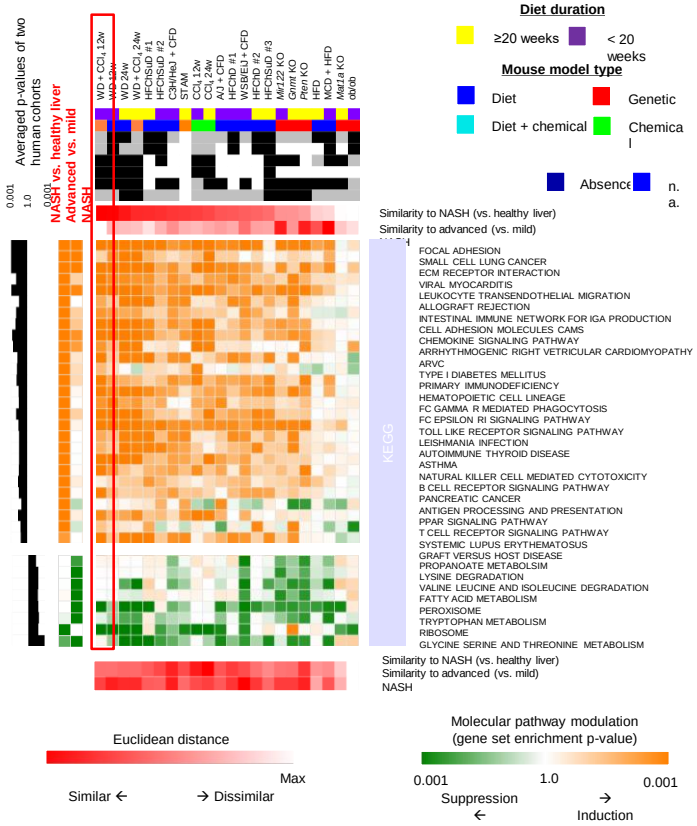




Tsuchida et al, J Hepatol in press

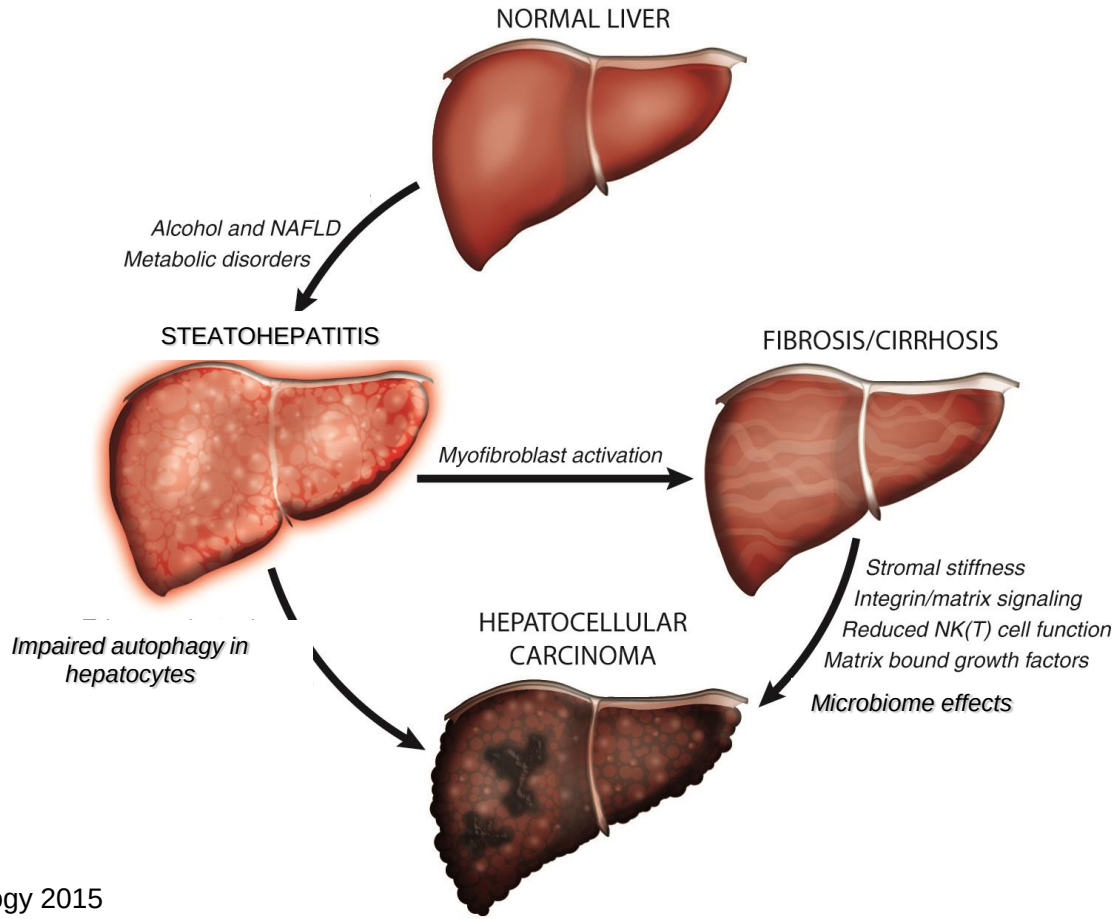
Using Big Data Approaches to Identify Disease-relevant Pathways

Comparison of Animal Models and Human NAFLD



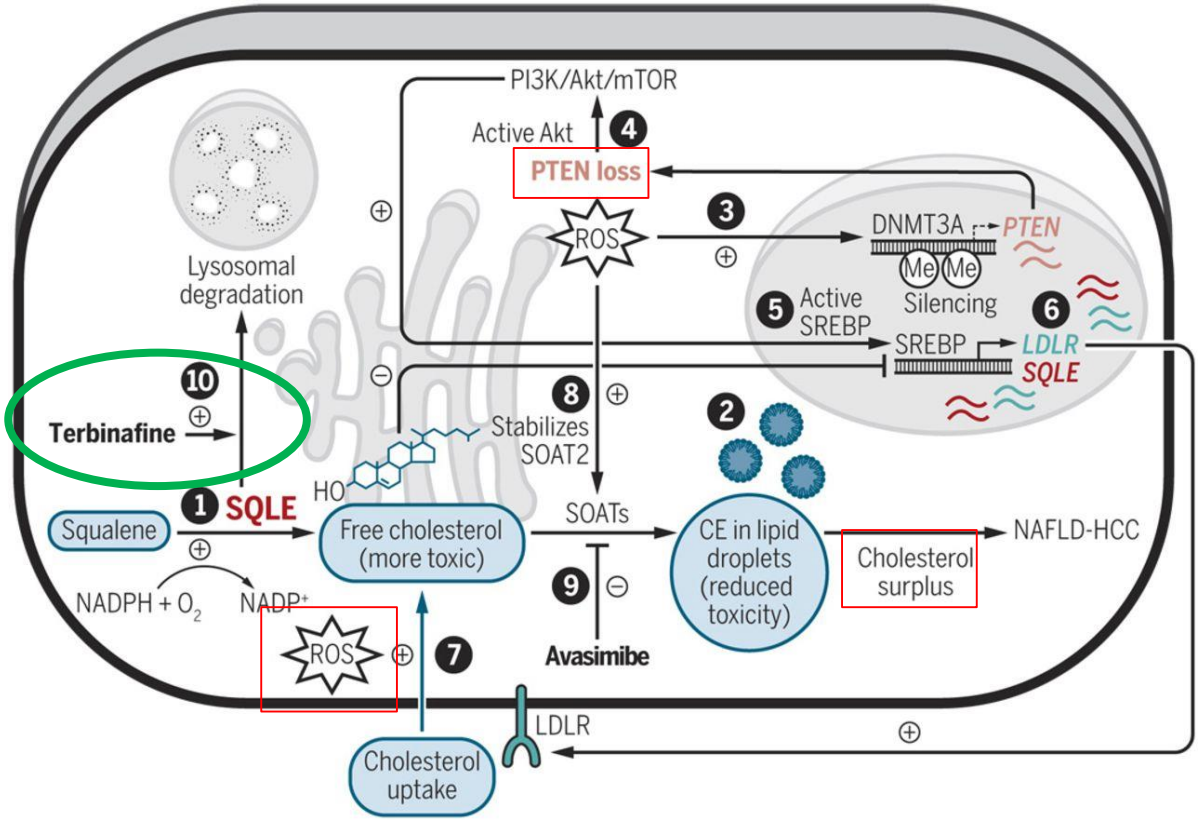
Tsuchida et al, J Hepatol in press

Links from NASH to HCC



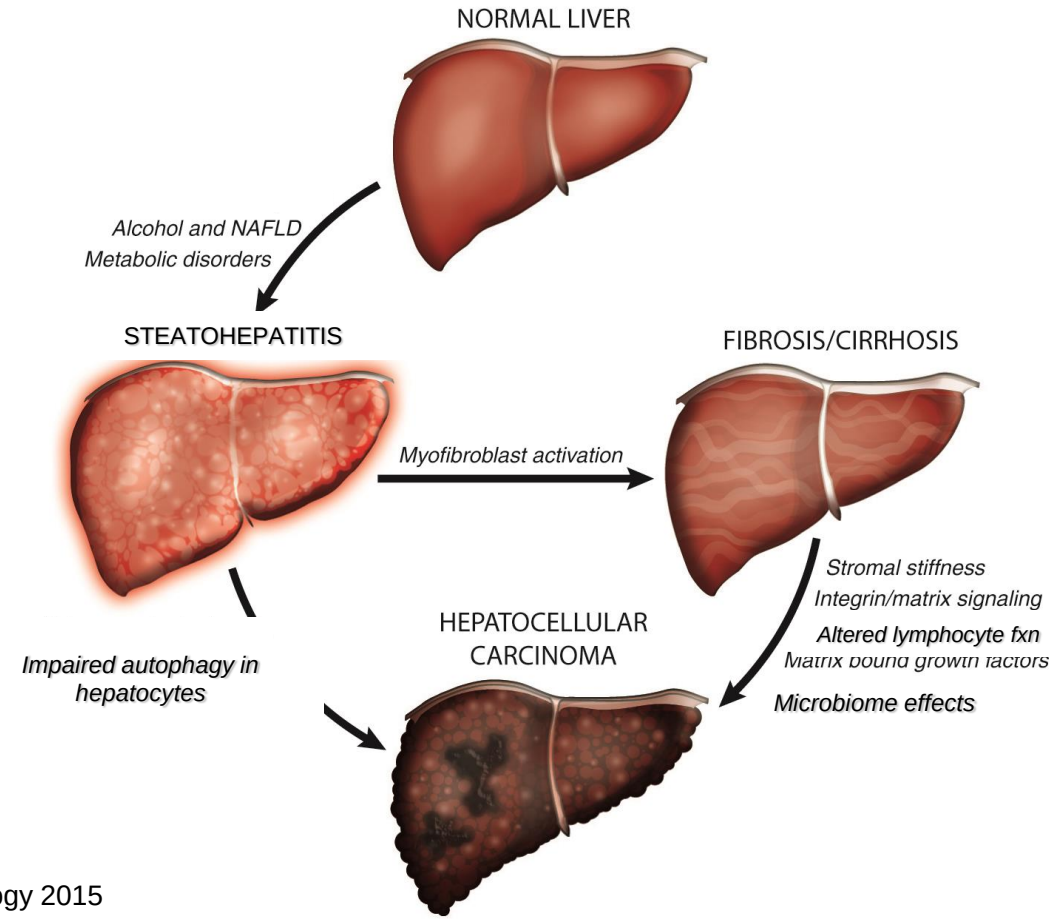
Zhang & Friedman. Hepatology 2015

Squalene Epoxide Drives NAFLD-HCC



Ngee Kiat Chua et al., Sci Transl Med 2018;10:eaat3741

Links from NASH to HCC



Zhang & Friedman. Hepatology 2015

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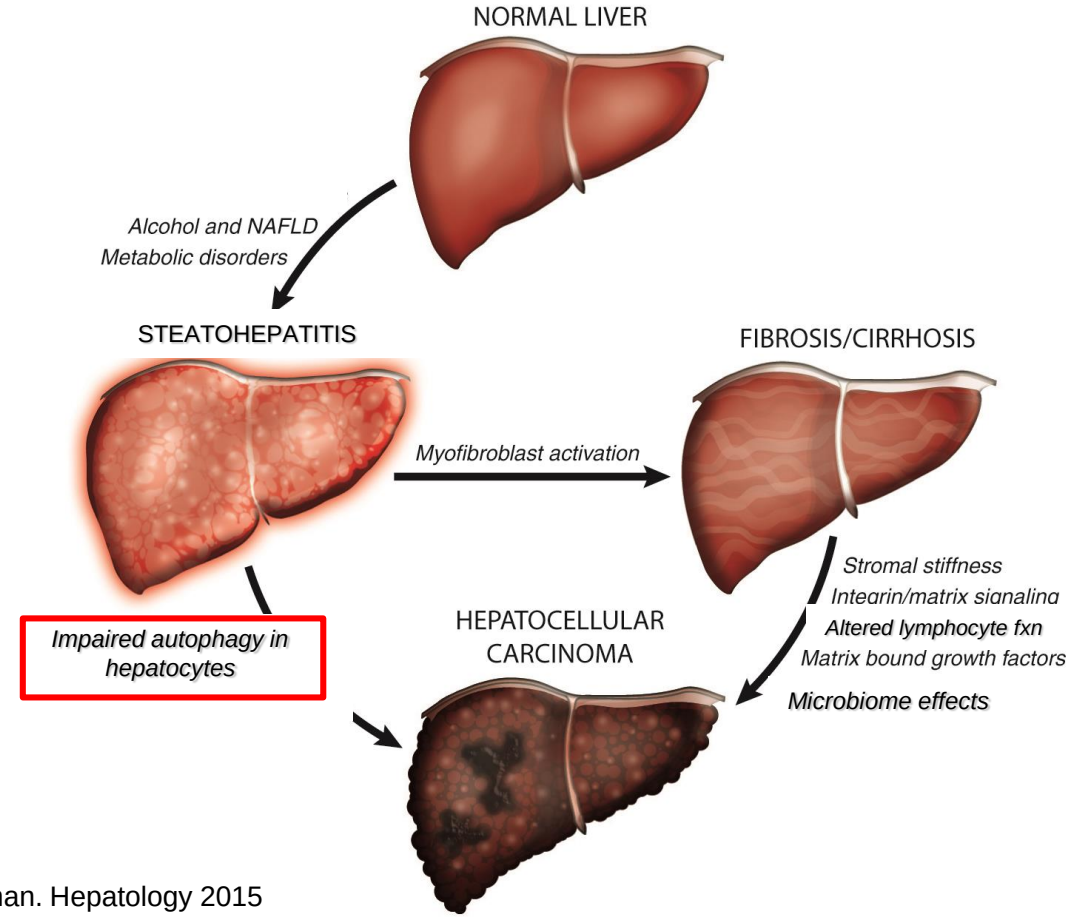
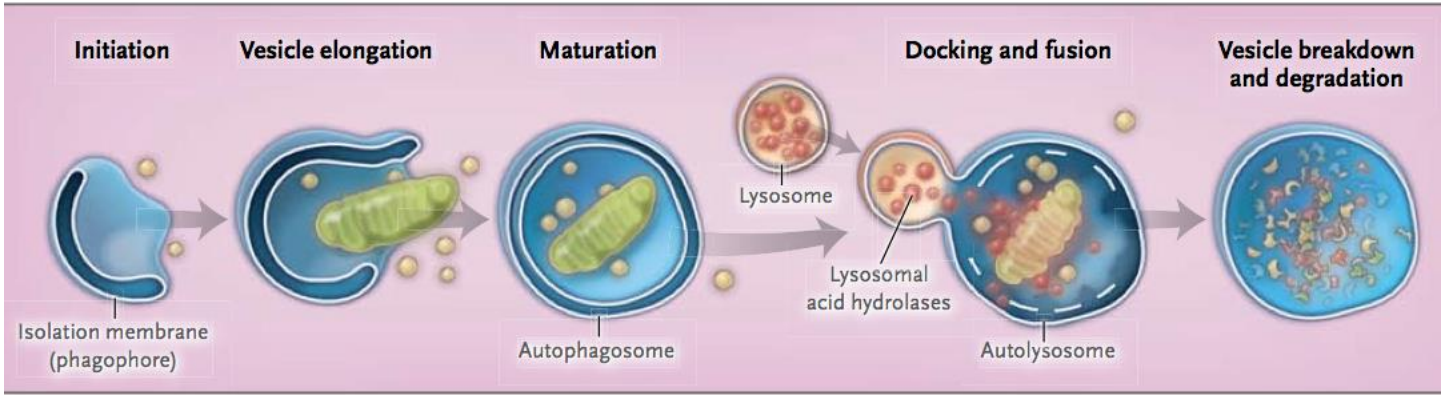


Zhang & Friedman. Hepatology 2015

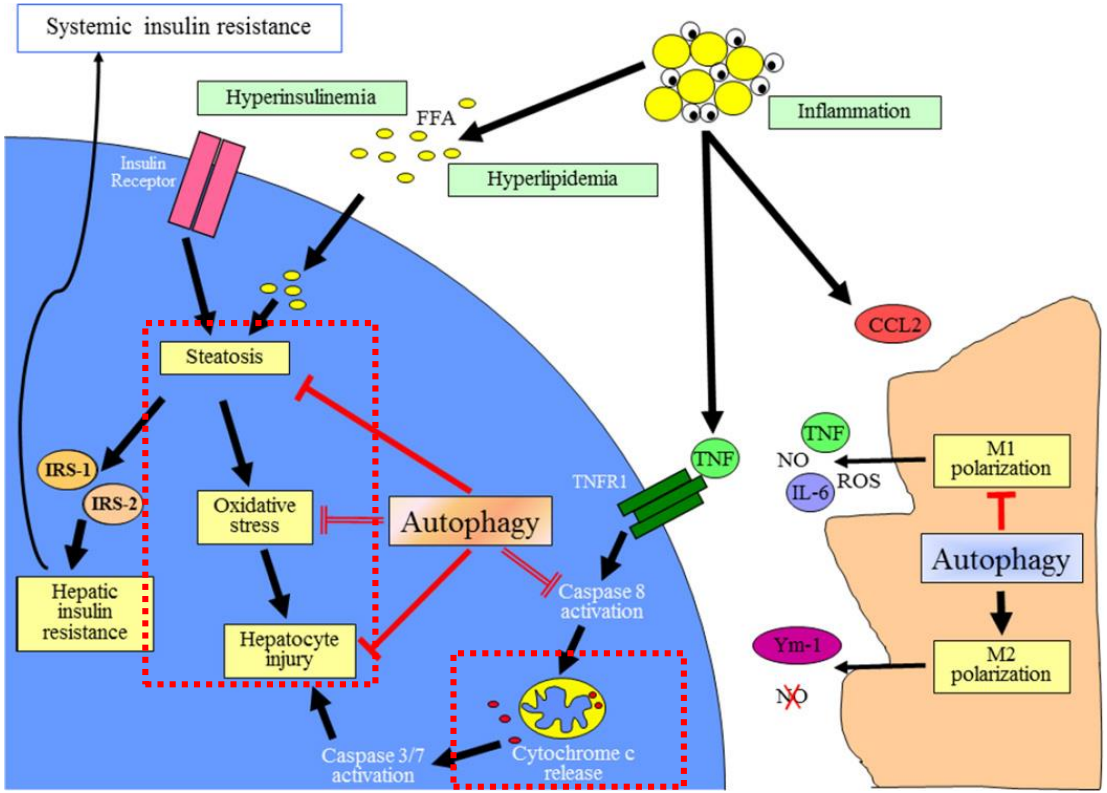
Autophagy

A highly conserved cellular pathway to preserve energy homeostasis through degradation of intracellular substrates



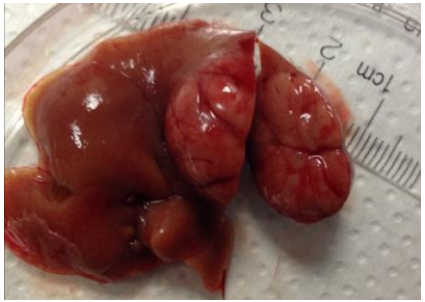
Choi et al, 2013 NEJM

Autophagy is Defective in NAFLD



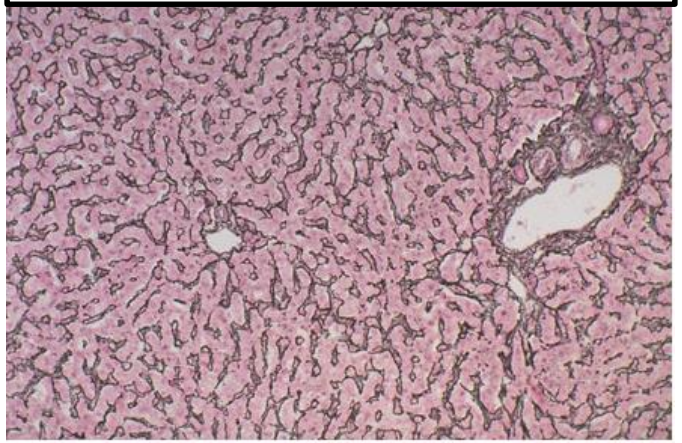
Czaja, Dig Dis Sci, 2016

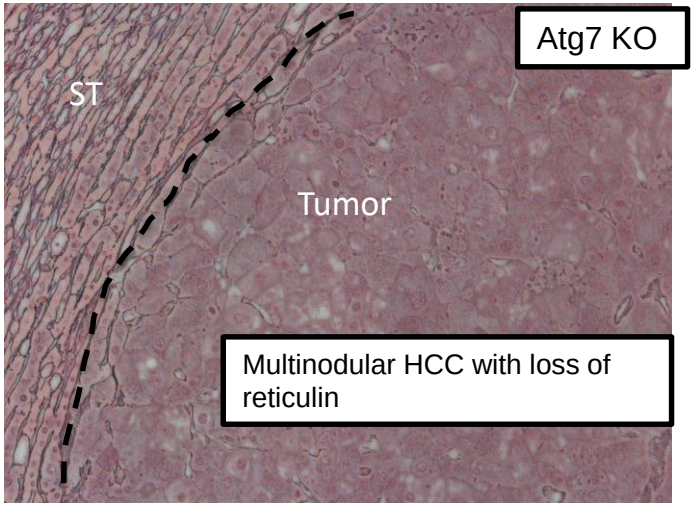
Autophagy-defective mice develop HCC



Mice with hepatocyte-specific deletion of Atg7, a key autophagy effector

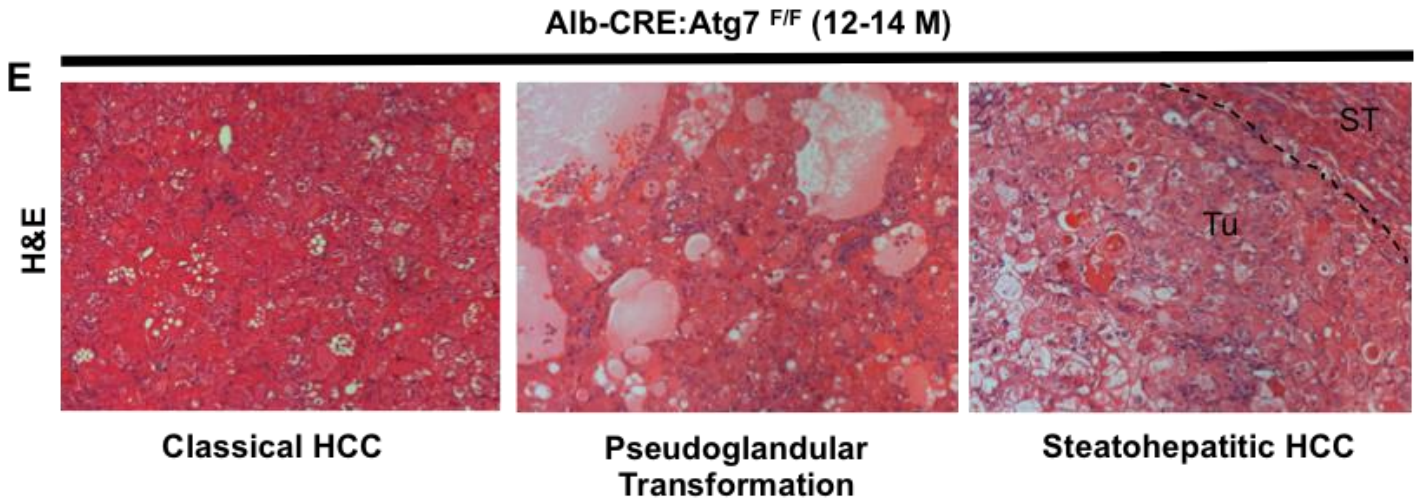
Reticulin staining in normal liver





Youngmin Lee

Atg7 KO mice Display Varying HCC subtypes



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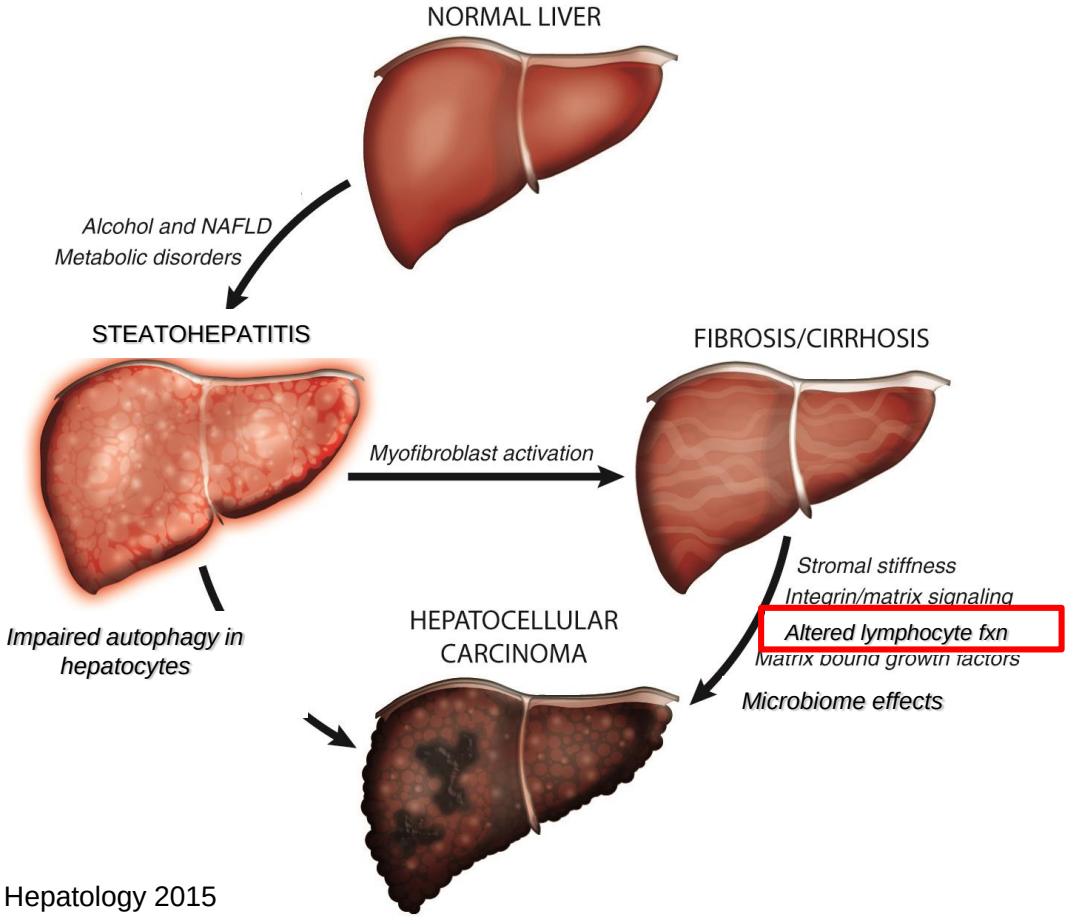
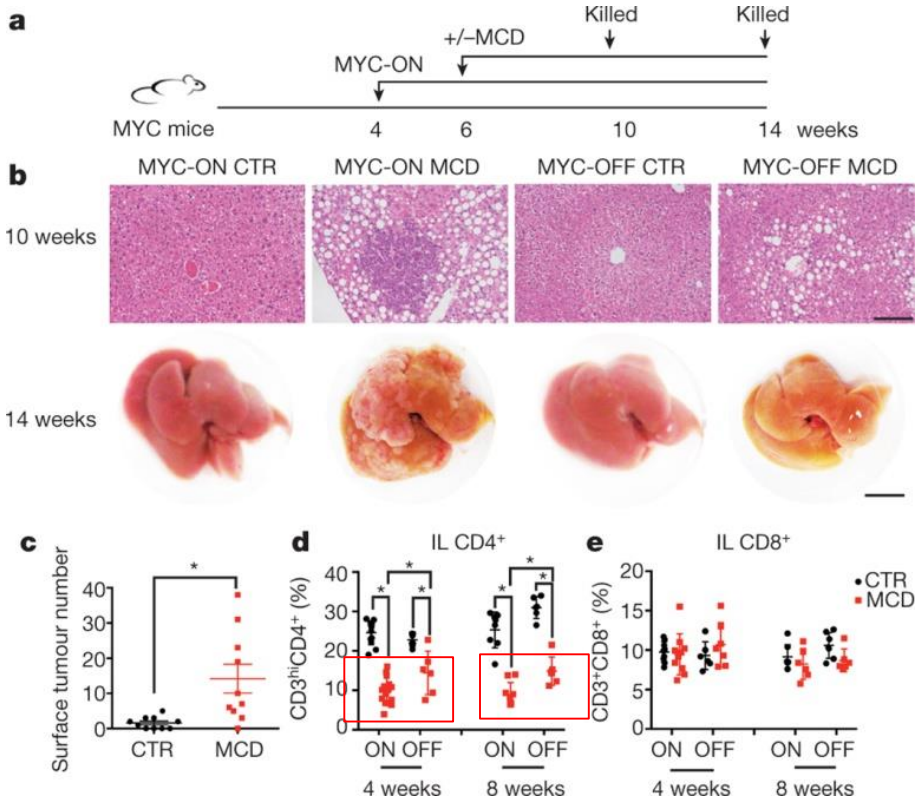
Links from NASH to HCC



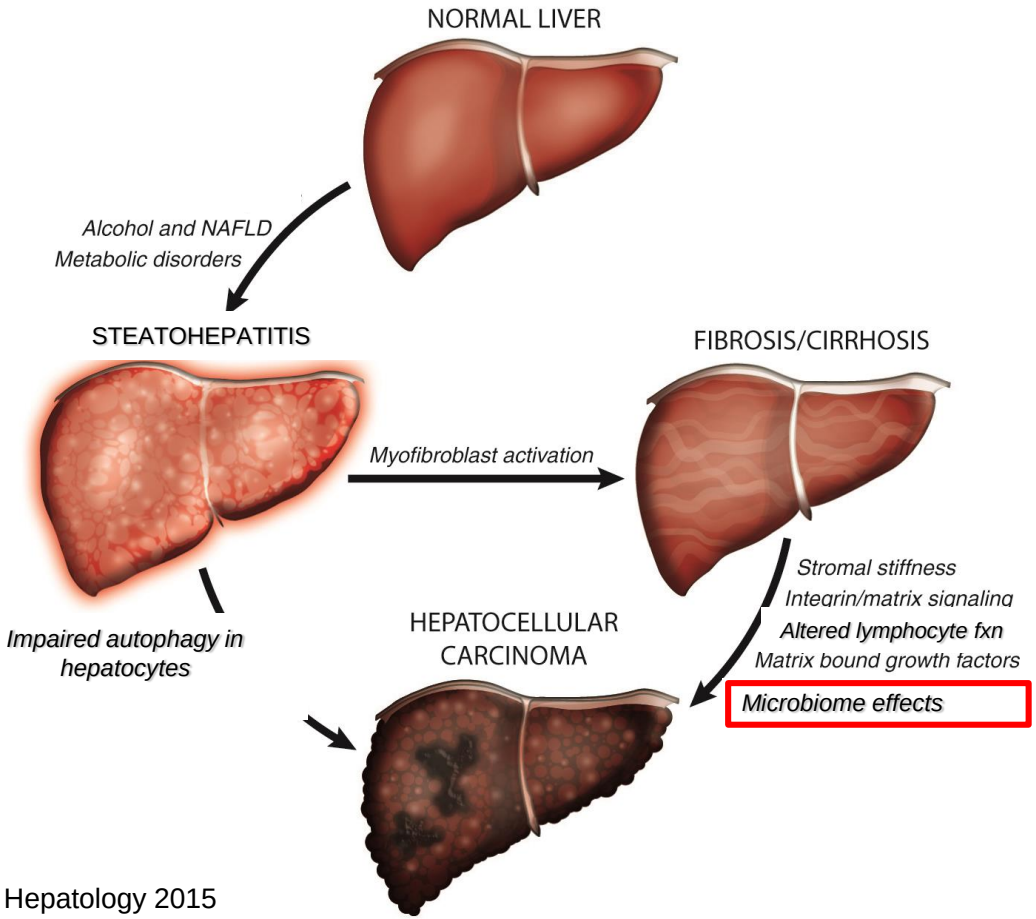
Zhang & Friedman. Hepatology 2015

NAFLD Induces a Selective Loss of Intrahepatic CD4$^+$ T lymphocytes and Promotes HCC



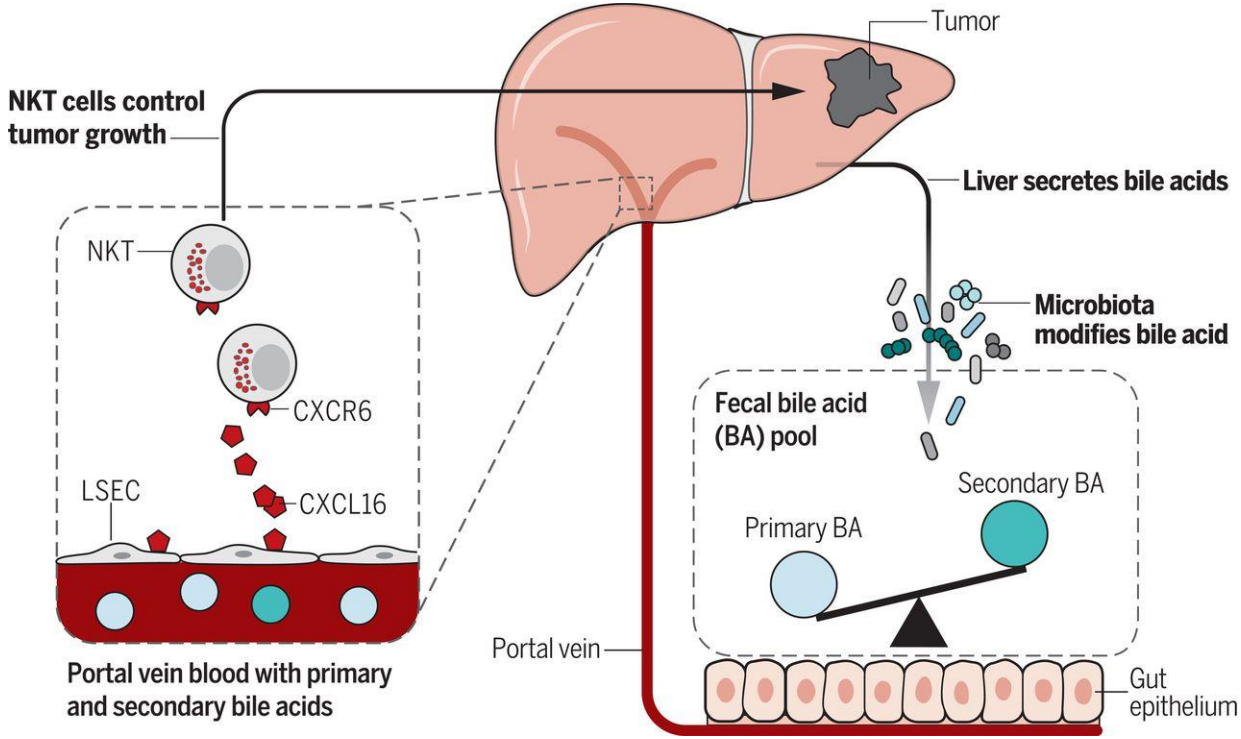
C Ma *et al. Nature* 1–5 (2016) doi:10.1038/nature16969

Links from NASH to HCC



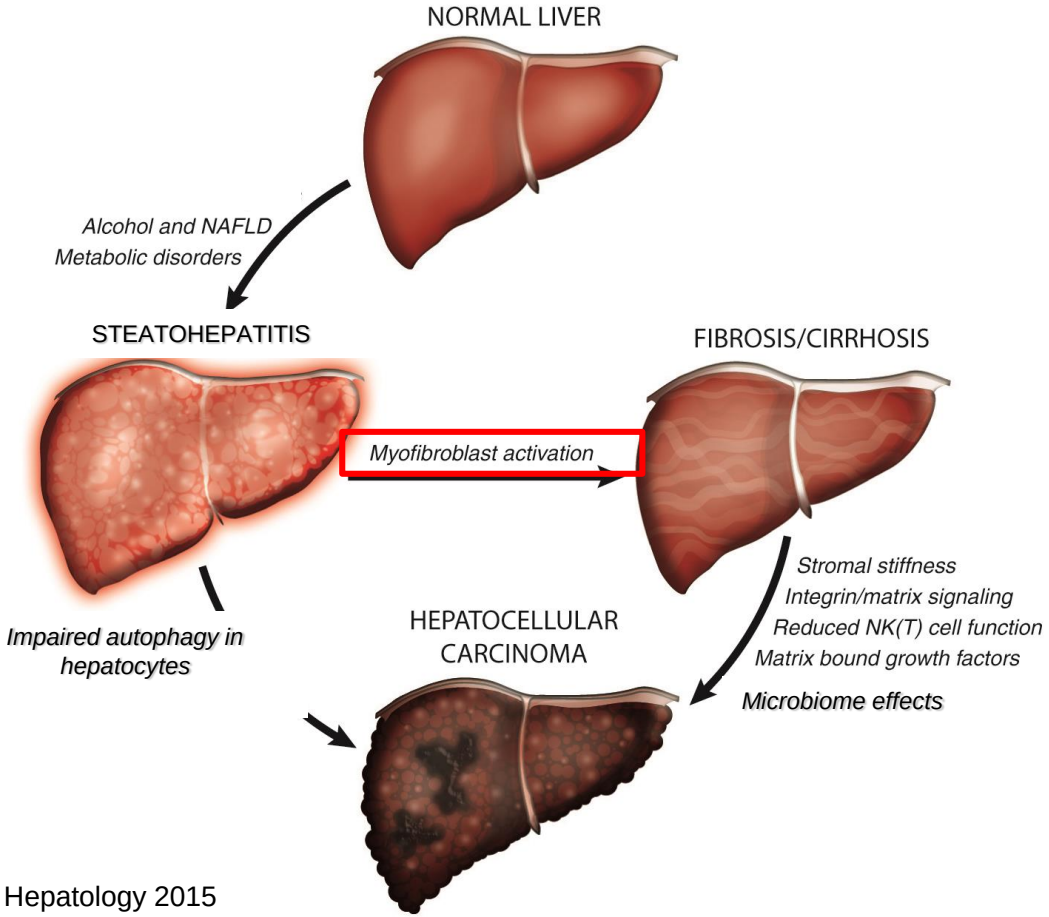
Zhang & Friedman. Hepatology 2015

Gut Microbiome Modulates Liver Cancer through Bile acid–regulated NKT cells



Chi Ma et al. Science 2018;360:eaan5931

Links from NASH to HCC

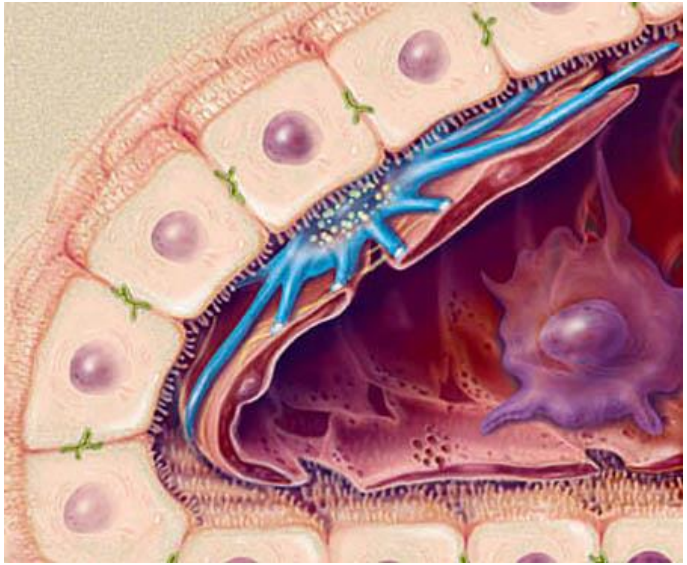


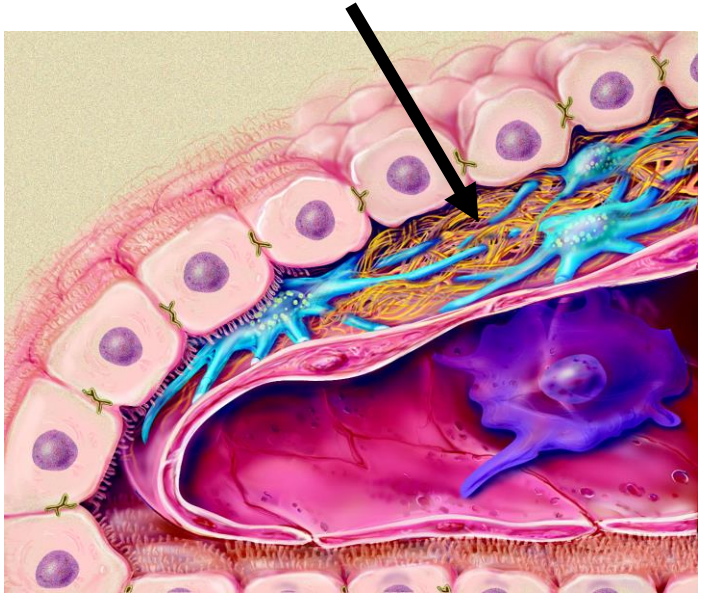
Zhang & Friedman. Hepatology 2015

Hepatic Stellate cell Activation - *A Central Event in Liver Fibrosis*

Normal Liver

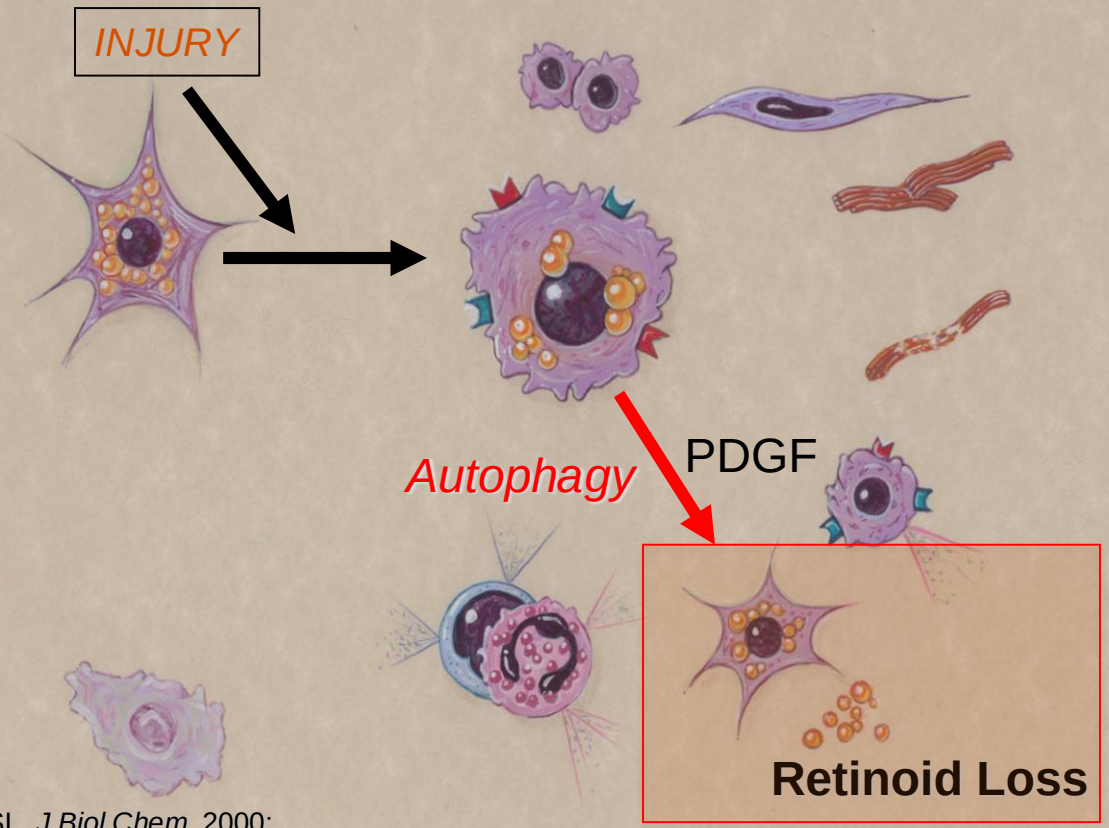
Activated HSC with Fibrosis





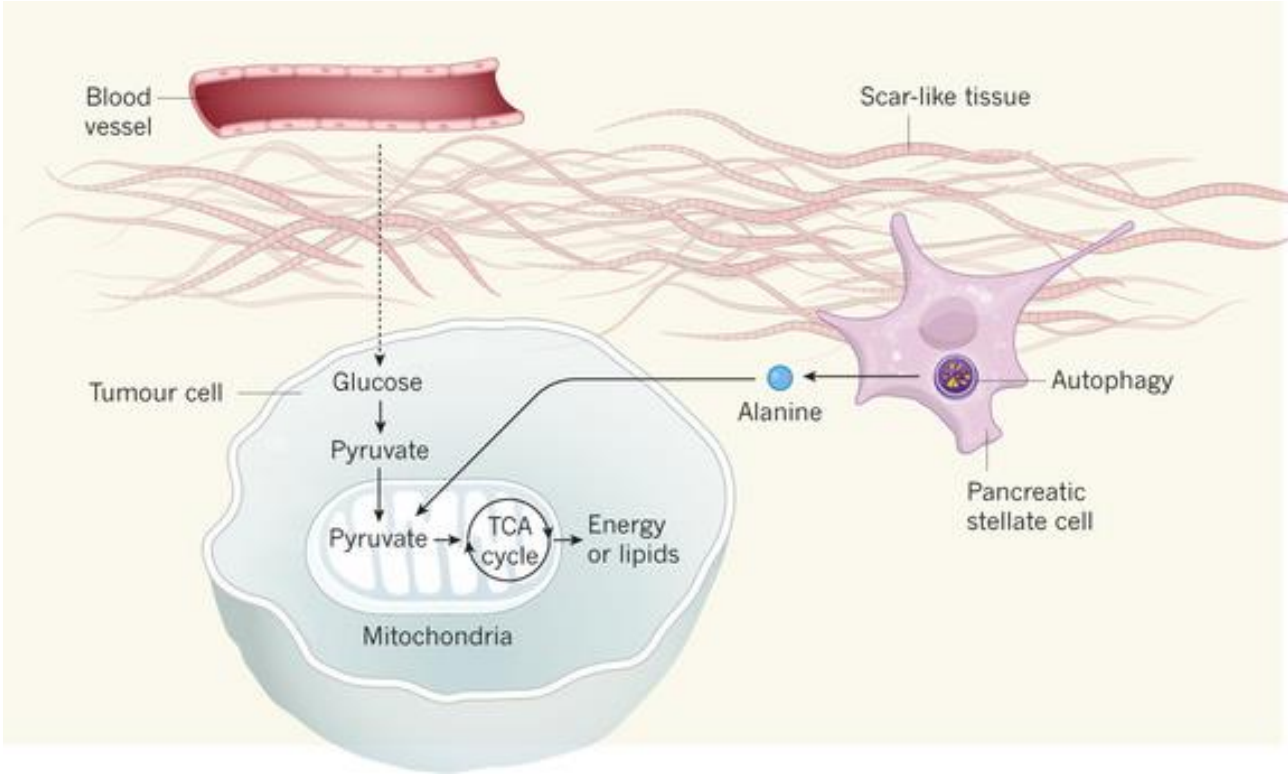
Friedman SL and Arthur, *Science and Medicine*, 2002

Activation of HSCs is Associated with Loss of Retinyl Ester Droplets



Friedman SL, *J Biol Chem*, 2000;
Hernandez-Gea, Gastroenterology 2015

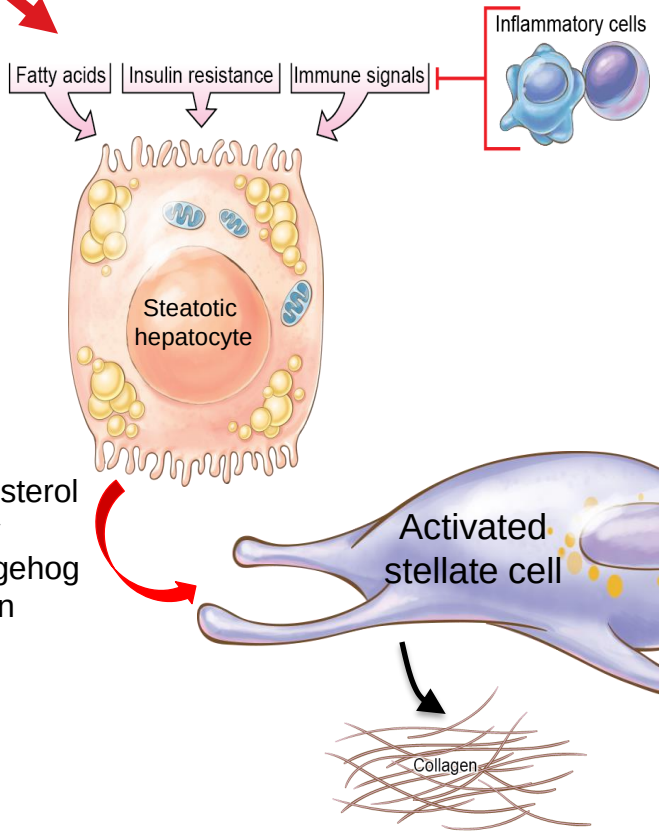
Pancreatic Stellate Cells feed a Tumor through Autophagy-Regulated Alanine Secretion



Kamphorst and Gottlieb based on Sousa et al, Nature 536, 479–483, 2016

Hepatic Drivers of Fibrosis in NASH

- Adipokine dysregulation
- Cannabinoids
- Insulin / IGF1
- ER Stress

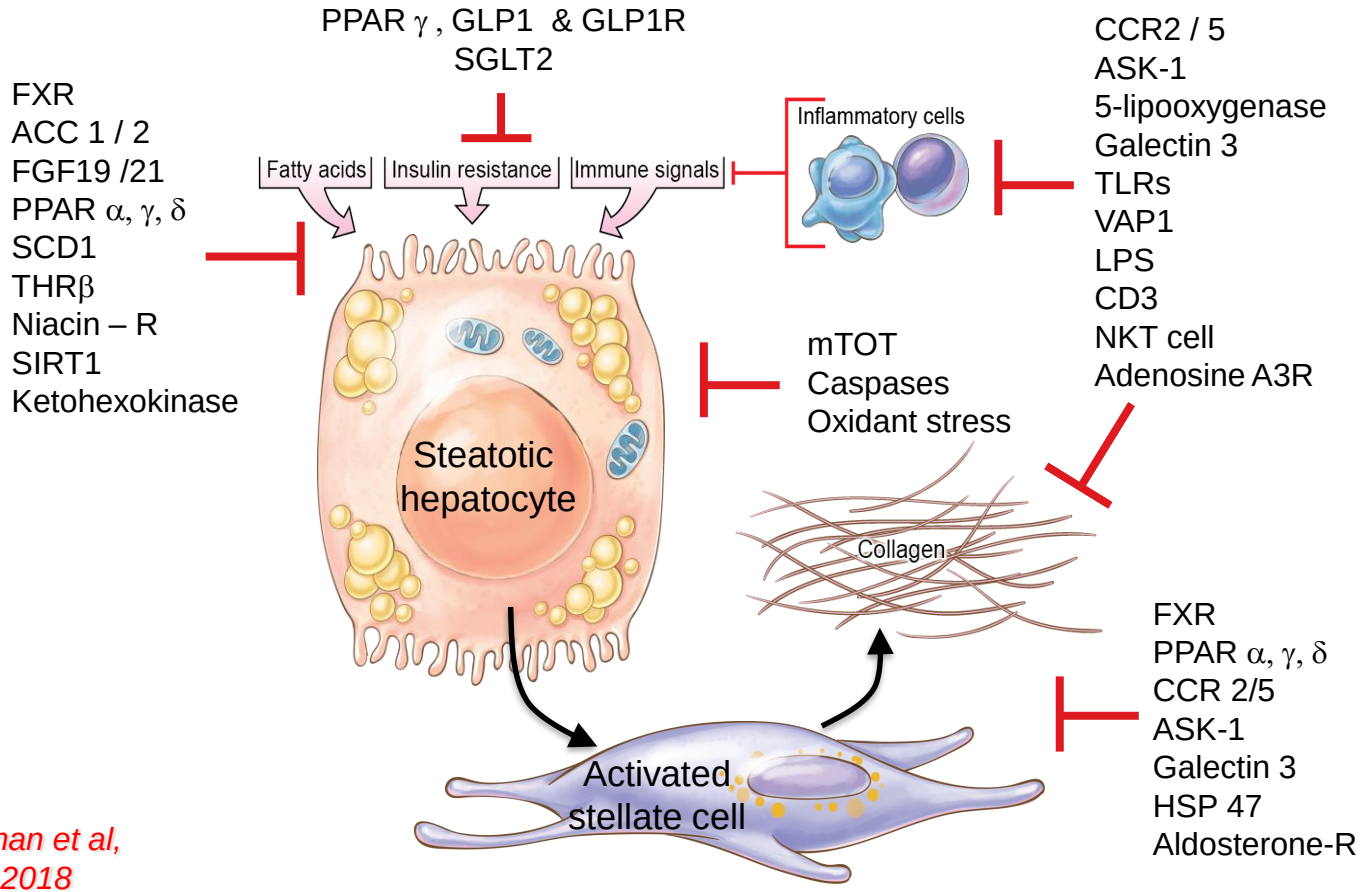


- Chemokines
- Innate immune signaling
- Inflammasome activation

- Free Cholesterol
- Lipotoxicity
- Indian hedgehog
- Osteopontin

- Epigenetic changes
- Yap / Hippo
- Cannabinoids
- ER stress

Liver-Related NASH Targets in Phase 2 and 3 Trials



Based on Friedman et al, Nature Med, 2018

Summary - How Will New Therapies Affect HCC Development?

1. Many potential mechanisms link inflammation to fibrosis and cancer in liver; some but not all are NASH-specific

2. Obesity directly increases the risk of all cancers. Persistent obesity will likely confer sustained risk.

3. The relative effects of NASH therapies on HCC will depend on the specific target (e.g., autophagy, immunity, microbiome), but no ‘hierarchy’ of importance in HCC development has been established yet.

4. Because there are risk factors related to obesity and fat, reversal of fibrosis alone is unlikely to be sufficient to eliminate HCC risk.