



**PARIS
MASH
MEETING**

11th edition

**September 11 & 12, 2025
Institut Pasteur, Paris**



Is Tumor-associated Fibrosis Harmful or Beneficial in MASH-HCC?

Scott L. Friedman, M.D.

Fishberg Professor of Medicine

Director, Institute for Liver Research

Chief Emeritus, Division of Liver Diseases

Dean for Research Collaborations and Partnerships



**Mount
Sinai**

Disclosures – Scott Friedman MD

Consulting: *Aditum Bio, Abbvie, AGED Diagnostics, Boehringer Ingelheim, Boston Pharmaceuticals, Curie Bio, Engine Biosciences, Esperion, Forth Therapeutics, Gordian Biotechnology, Hepta Bio, In vitro, Junevity, Kriya, Mediar Therapeutics, Merck Pharma, Moderna, Ochre Bio, Pfizer Pharmaceuticals, Resolution Therapeutics, Sagimet*

Stock options: *AGED Corporation, CAN FITE, Cargene, ChemomAb, Galmed, Gordian Biotechnology, Hepgene, Hepta, In vitro, Junevity, Mediar, North Sea, Ochre Bio, Sagimet, Scholar Rock, Sunbird Bio, Surrozen.*

Research Activities with Commercial Entities:

Novo Nordisk, Abalone Bio (SBIR Grant)

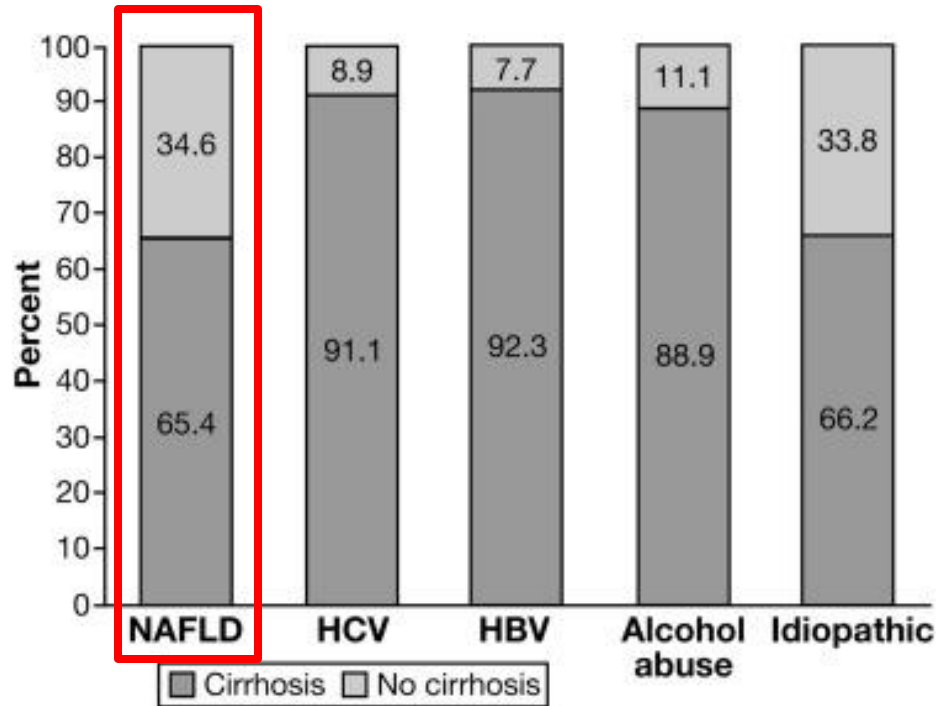
Overview

1. Clinical context – HCC in Metabolic dysfunction-associated steatotic liver disease (MASLD).
2. Stellate cell biology, heterogeneity, and pathways of HCC prevention and promotion.
3. Therapeutic implications and horizons.

Overview

1. Clinical context – HCC in Metabolic dysfunction-associated steatotic liver disease (MASLD).
2. Stellate cell biology, heterogeneity, and pathways of HCC prevention and promotion.
3. Therapeutic implications and horizons.

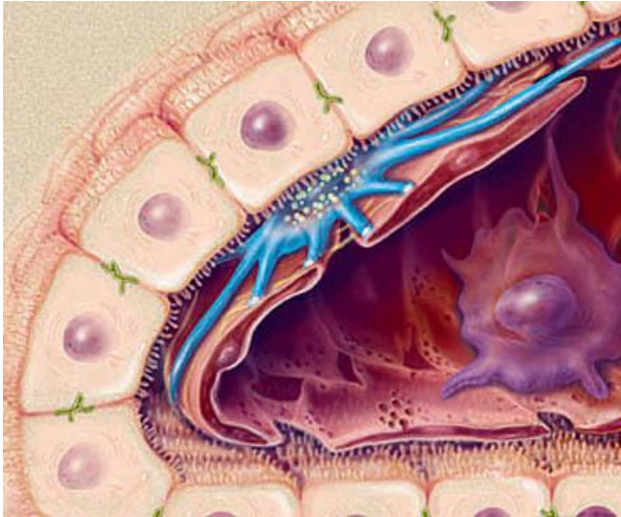
> 1/3 of HCCs in MASLD Occur in Non-Cirrhotics in a VA Population



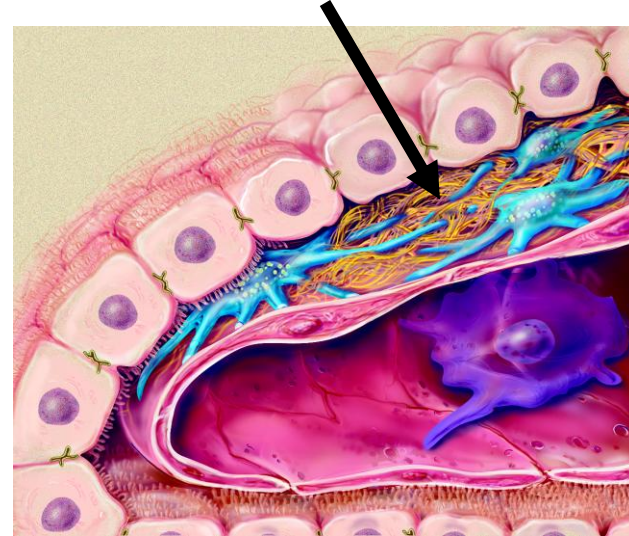
Overview

1. Clinical context – HCC in Metabolic dysfunction-associated steatotic liver disease (MASLD).
2. Stellate cell biology, heterogeneity, and pathways of HCC prevention and promotion.
3. Therapeutic implications and horizons.

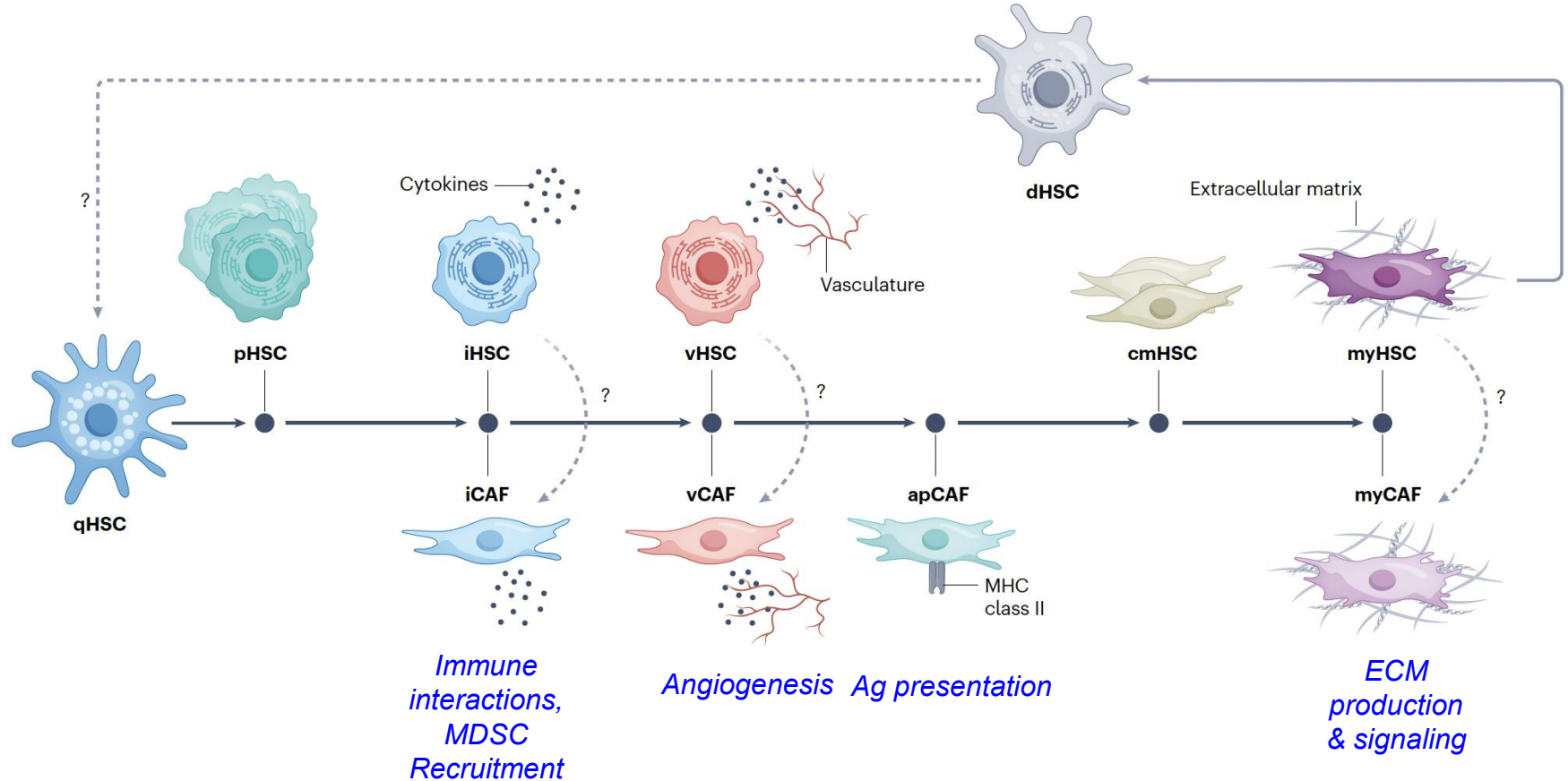
Hepatic Stellate cell Activation - *A Central Event in NASH Fibrosis*



*Activated HSC
with Fibrosis*



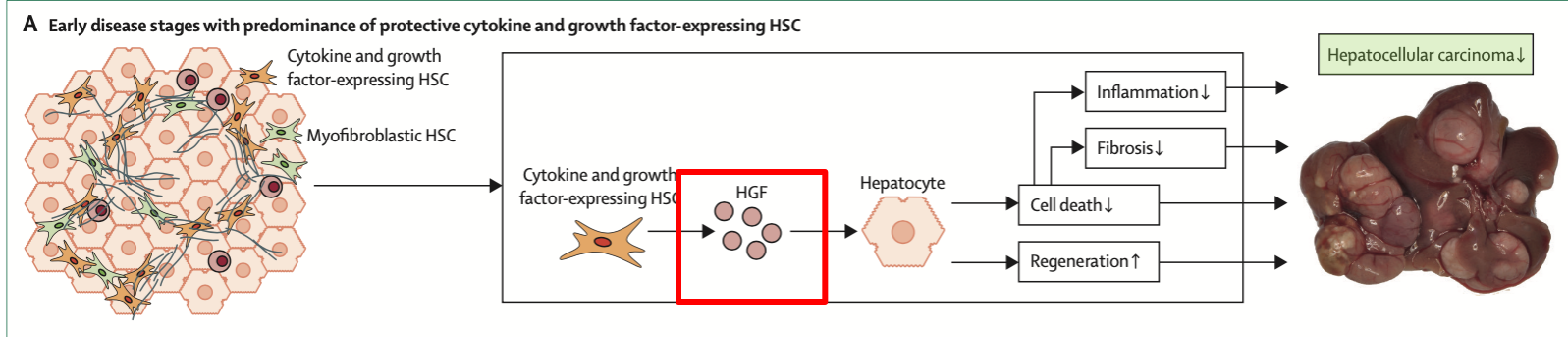
HSC / CAF Plasticity Confers Multiple Functions that Promote HCC



The Yin Yang of CAFs in MASH-HCC

Yin and yang represent two primal, opposing, yet complementary forces in the universe according to ancient Chinese philosophy

HCC
Preventive



Does Fibrosis Restrict Tumor Growth?



Clinical Imaging

Volume 76, August 2021, Pages 77-82



Body Imaging

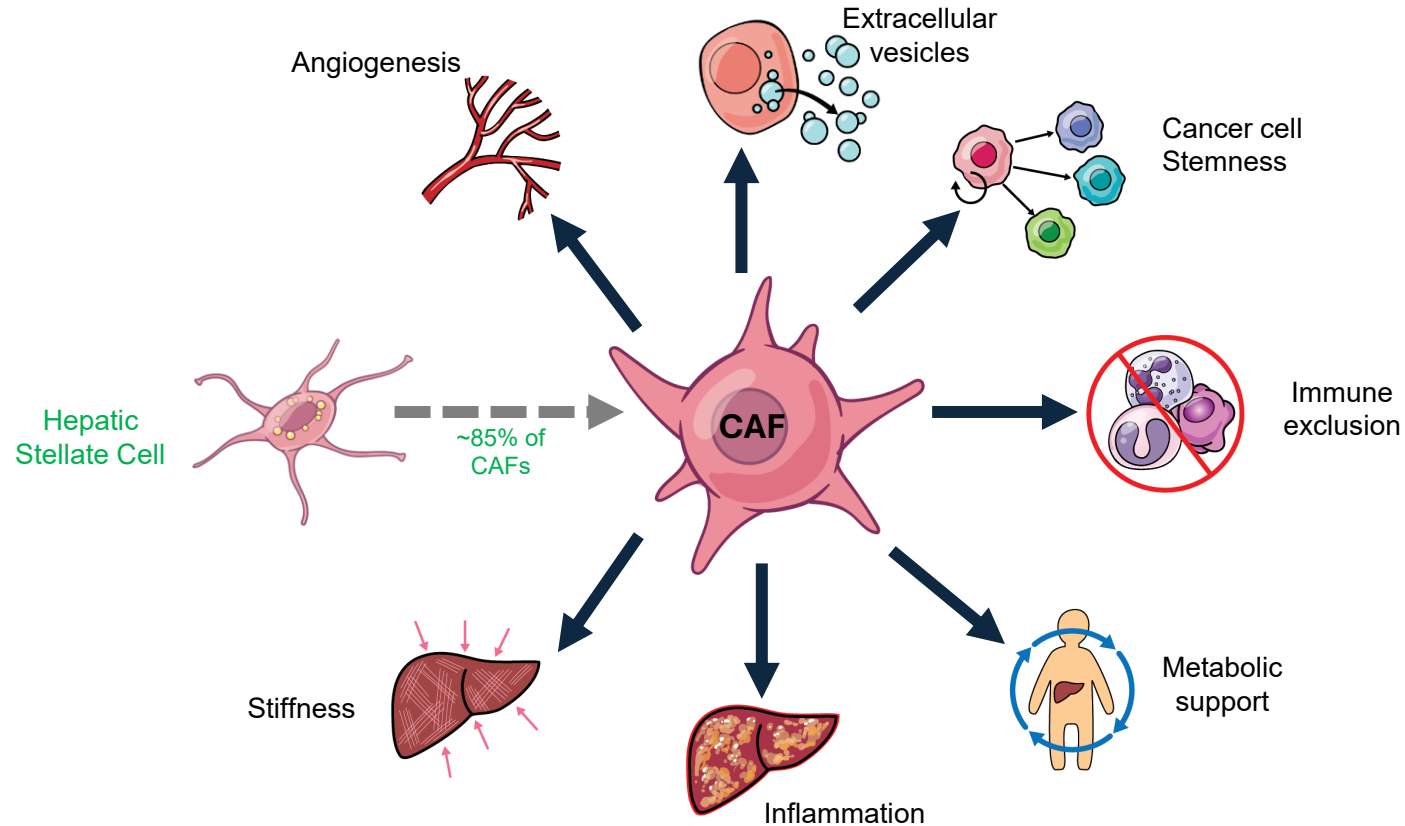
The importance of a nonsmooth tumor margin and incomplete tumor capsule in predicting HCC microvascular invasion on

*Data are sparse and
not convincing*

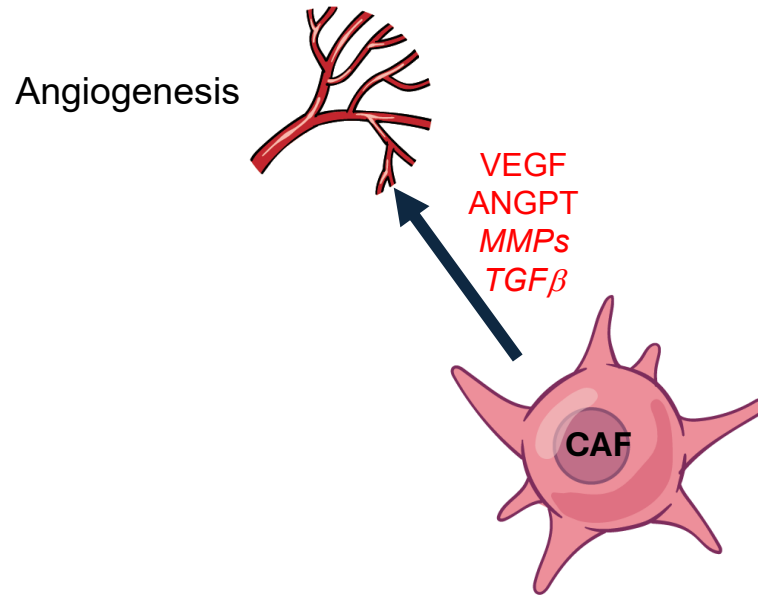
Journal of Surgical Oncology 2012;105:85–90

**Encapsulation is a Significant Prognostic Factor for Better Outcome
in Large Hepatocellular Carcinoma**

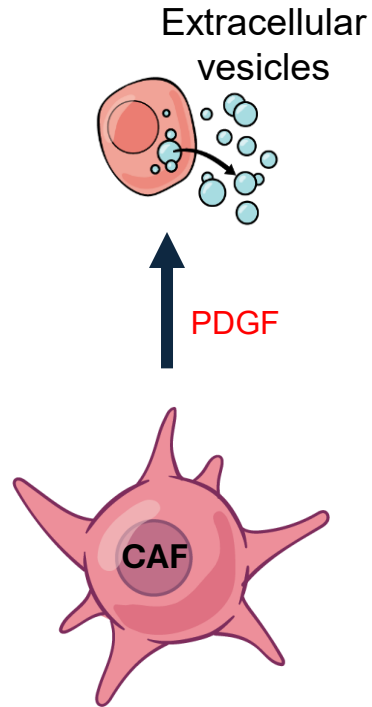
Roles of HSCs/CAFs in Hepatocellular Carcinoma



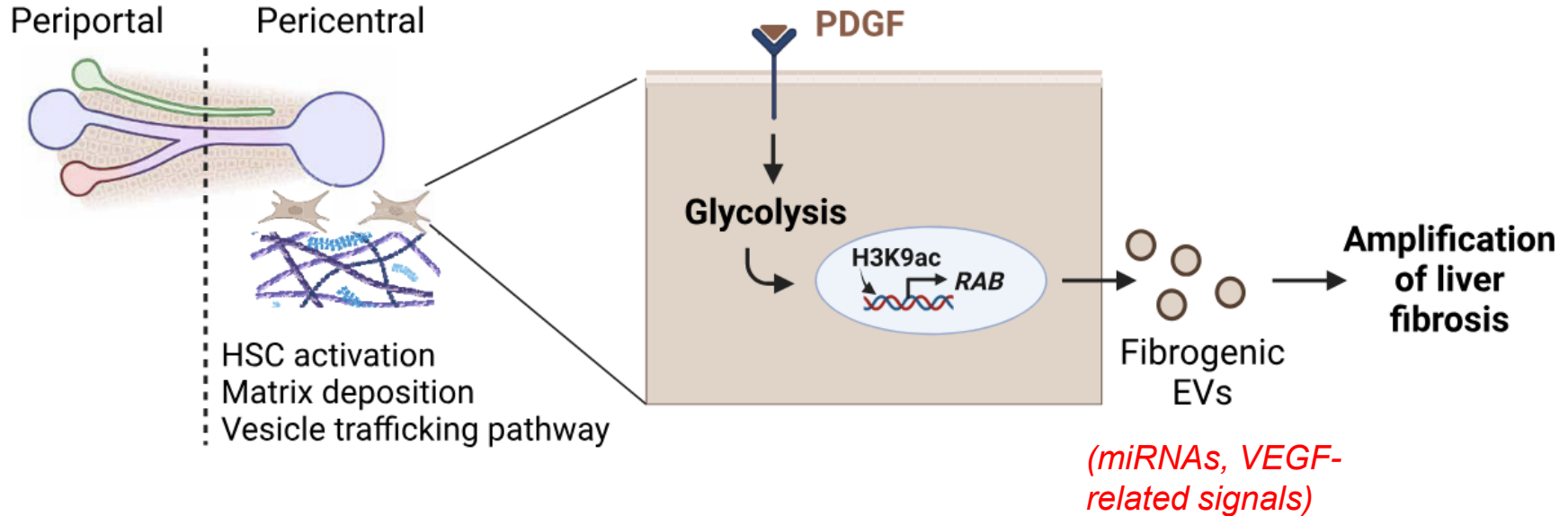
Role of HSCs/CAFs in Hepatocellular Carcinoma



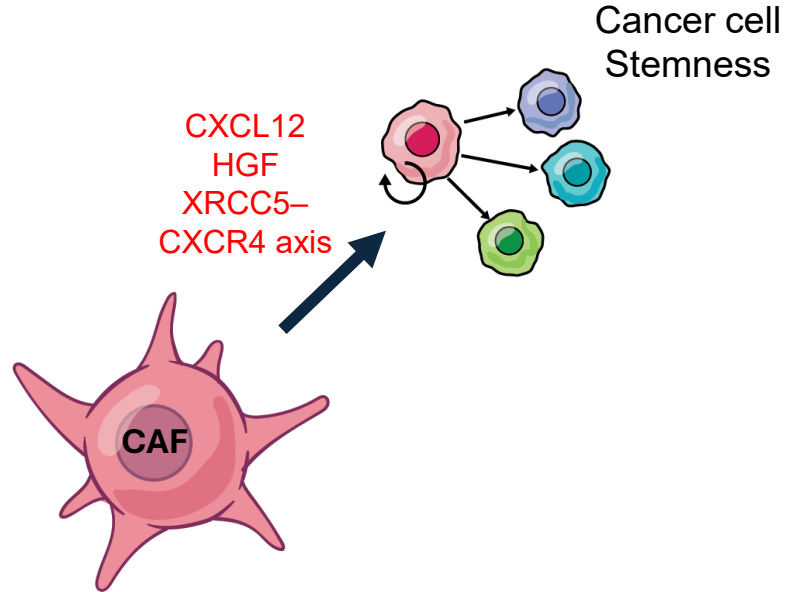
Role of HSCs/CAFs in Hepatocellular Carcinoma



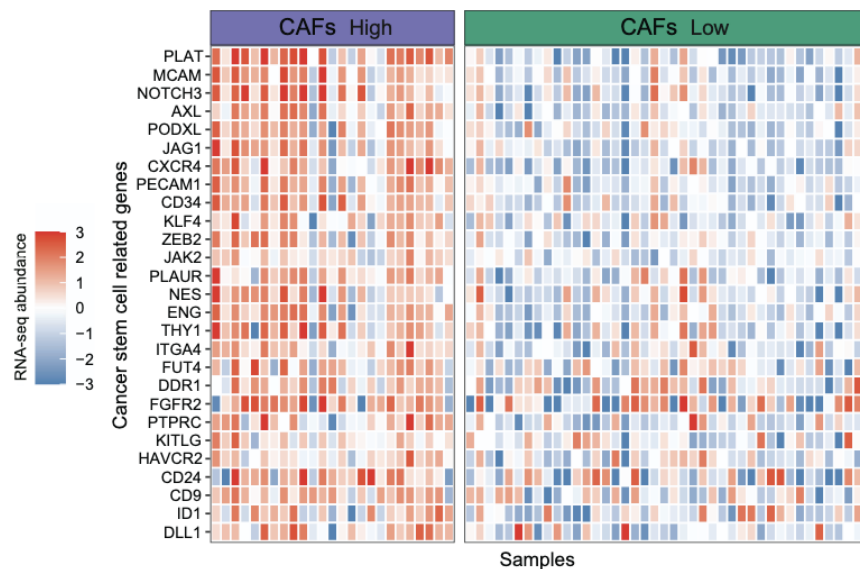
CAF-Derived Extracellular Vesicles Amplify Fibrosis and Angiogenesis



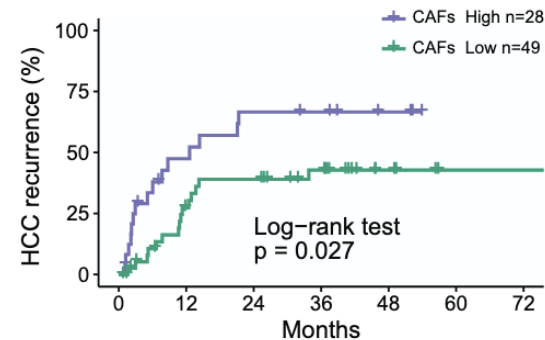
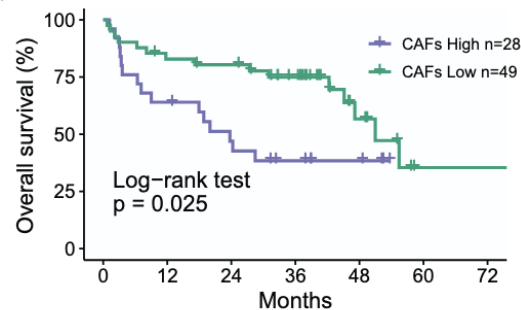
Role of HSCs/CAFs in Hepatocellular Carcinoma



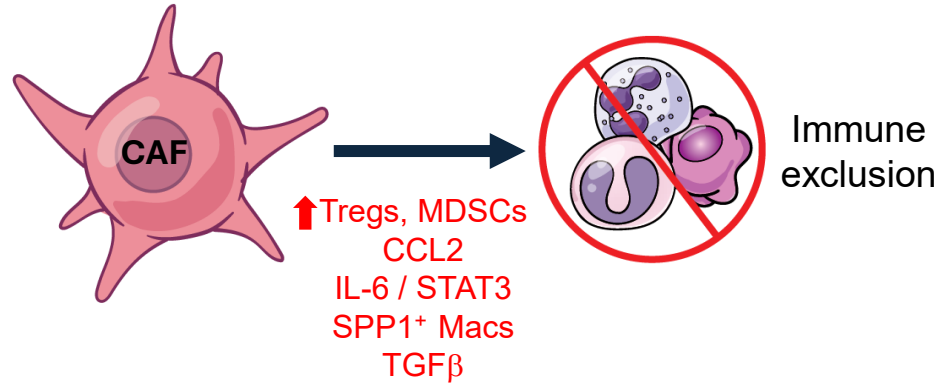
CAF Infiltration is Linked to Cancer Stemness and Poor Survival in HCC



DEGs in the cancer stem cells pathway in patients with high or low CAF scores



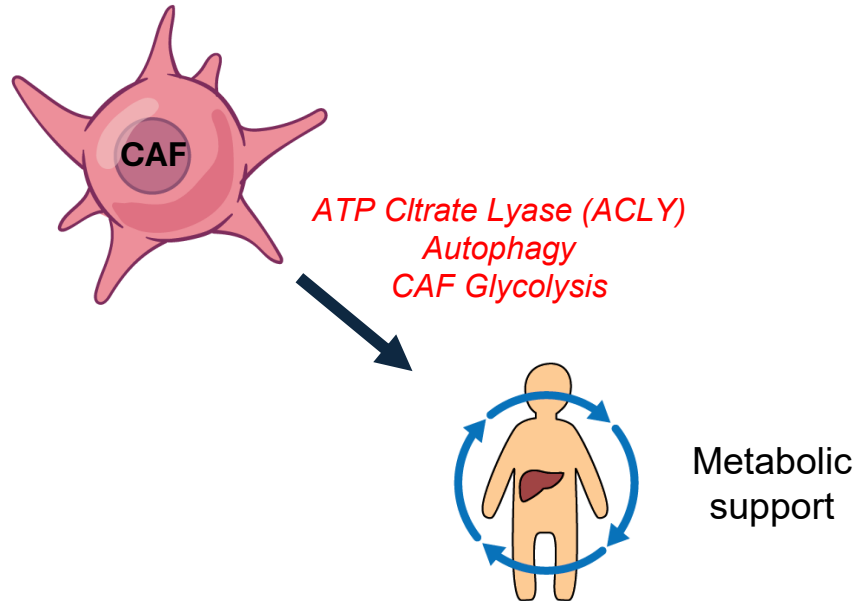
Role of HSCs/CAFs in Hepatocellular Carcinoma



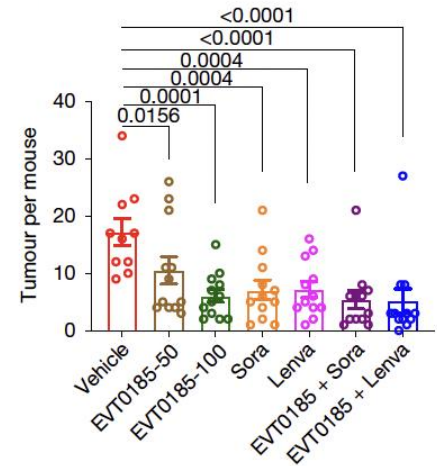
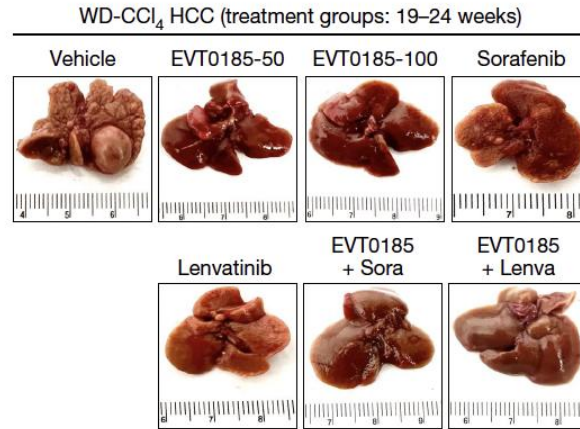
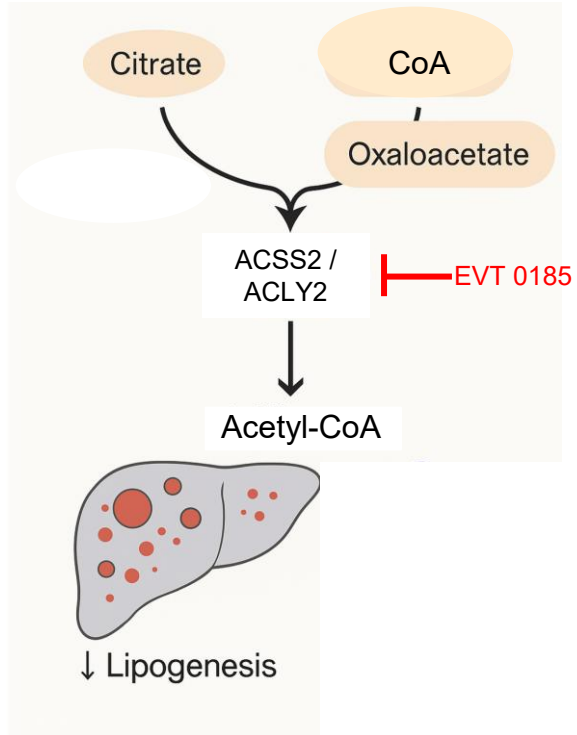
Immunosuppressive Effects of CAFs on HCC

	Immune cells	CAFs-secreted factors	Mechanisms	Phenotype
HCC-CAFs	TAMs	CXCL12;	CXCL12/CXCR4–PAI-1;	M2 polarization of TAMs;
		GAS6	Endosialin-CD68	<u>macrophage recruitment and polarization</u>
	TANs	SDF1a;	IL6/STAT3-PDL1;	Chemotaxis of TAN;
		CLCF1	CLCF1 – CXCL6/TGF- β	TAN infiltration and polarization
	NK cells	PGE2, IDO	-	<u>Inducing deactivation of NK cells</u>
	DCs	SDF-1 α	IL-6/STAT3-IDO	Induction into rDC / promotion of <u>Tregs expansion</u>
	MDSCs	SDF1a;	IL-6/STAT3;	<u>Inducing monocytes to differentiate into MDSCs / Impairing T cells function</u>
		M-CSF, MCP-1;	-;	
		COX-2; PGE2	ERK/COX2/PGE2	

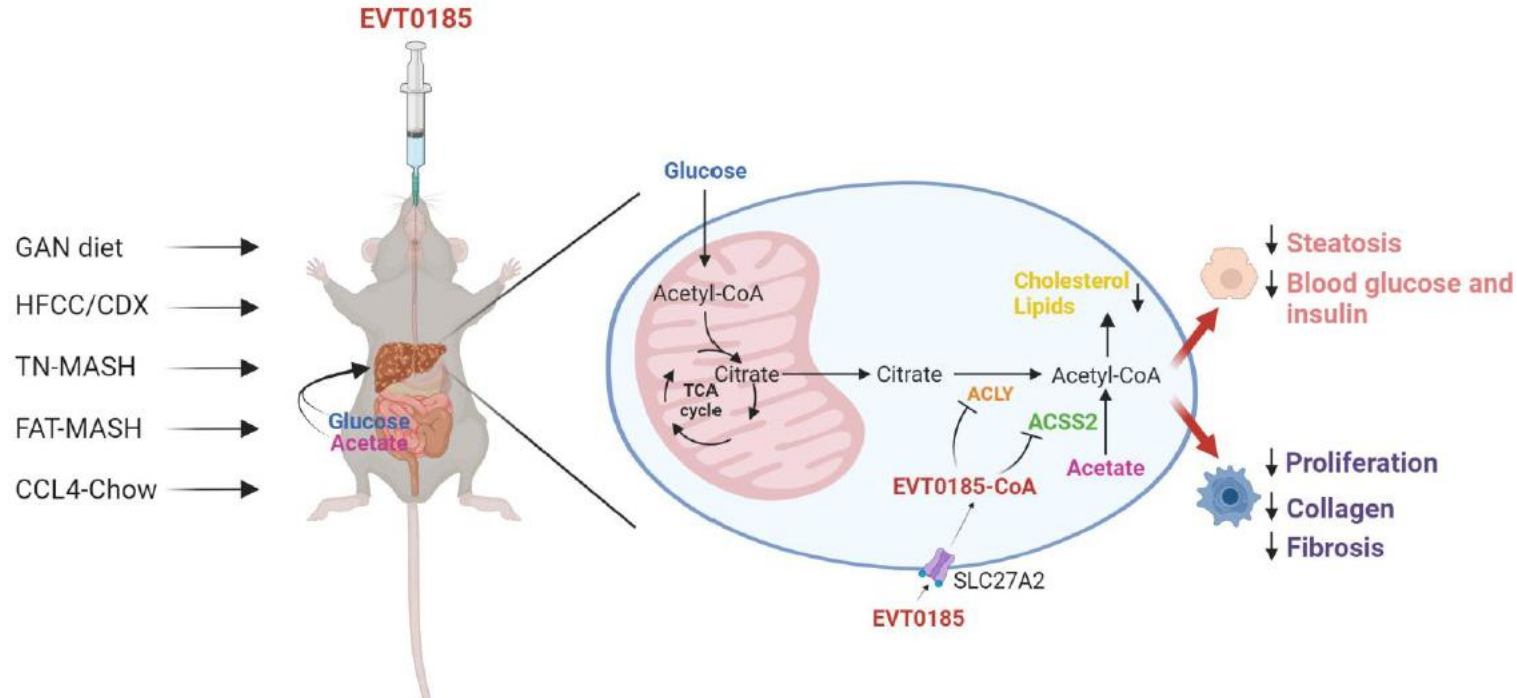
Role of HSCs/CAFs in Hepatocellular Carcinoma



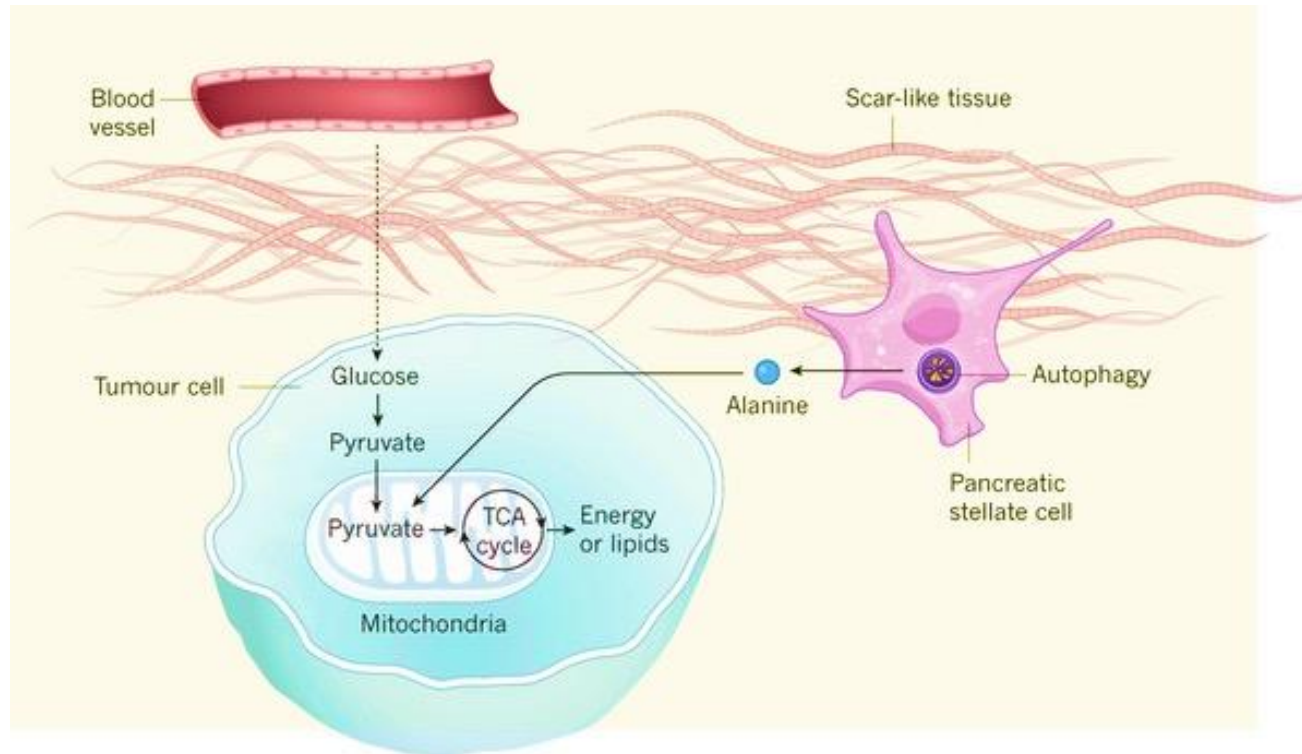
Effects of an ACLY/ ACSS2 Inhibitor (EVT0185) in MASH - HCC



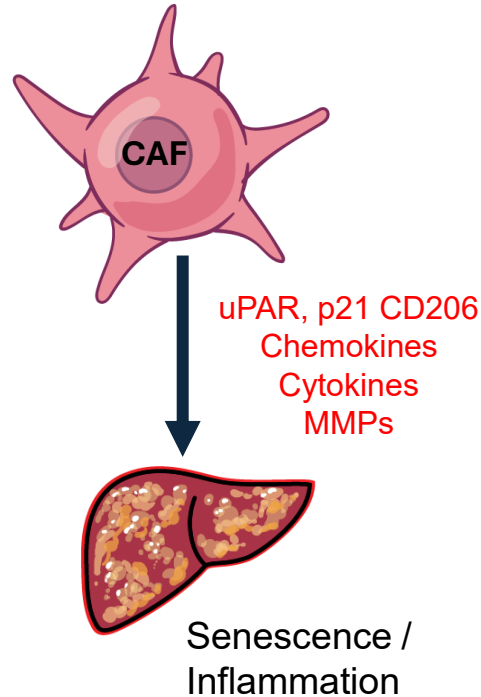
Dual Targeting of Metabolism and Fibrosis by an ACLY / ACSS2 Inhibitor (EVT0185)



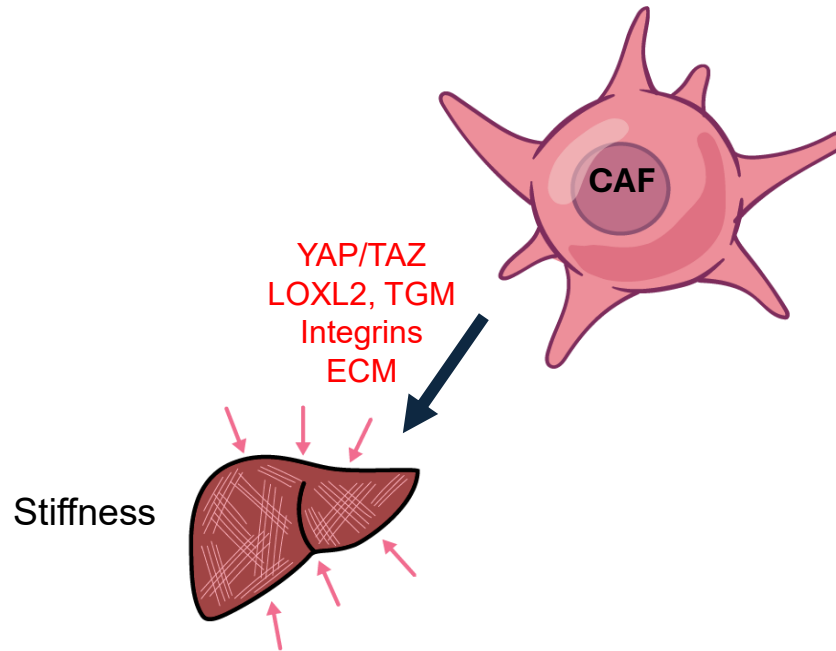
Pancreatic Stellate Cells feed a Tumor through Autophagy-Regulated Alanine Secretion



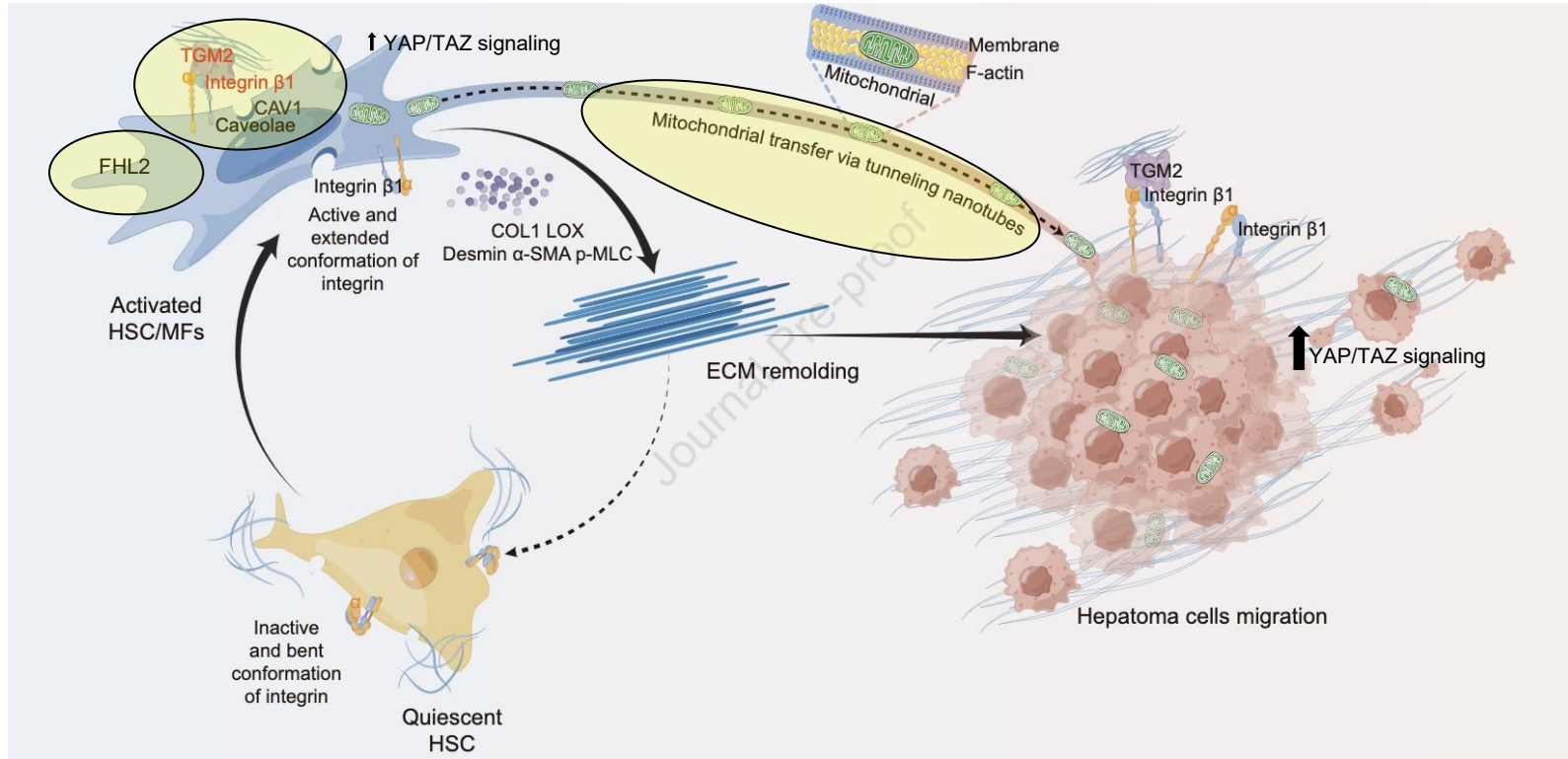
Role of HSCs/CAFs in Hepatocellular Carcinoma



Role of HSCs/CAFs in Hepatocellular Carcinoma



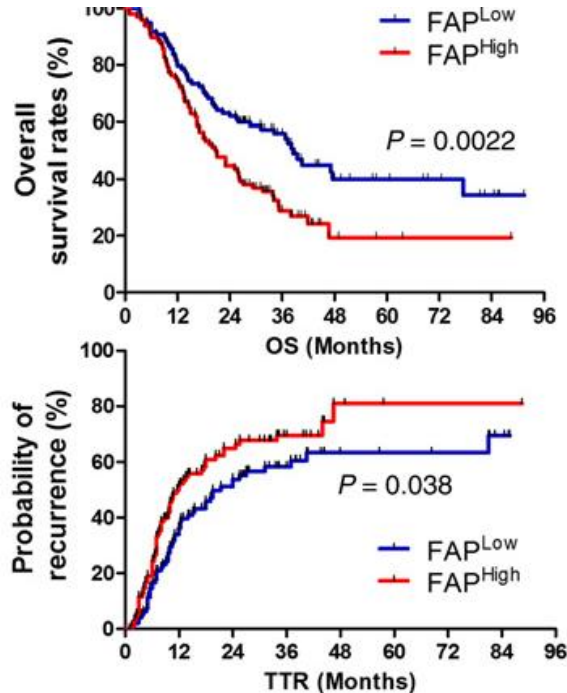
Stiffness-activated HSCs Boost HCC Migration



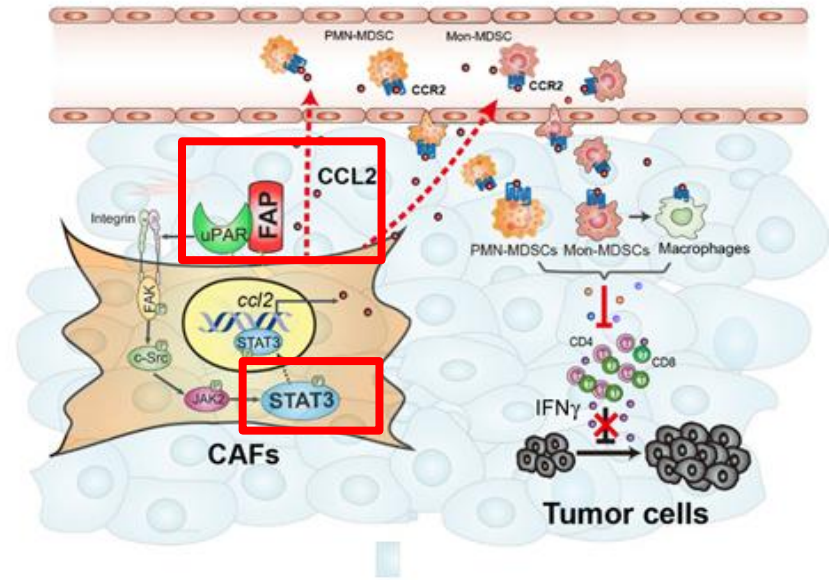
Overview

1. Clinical context – HCC in Metabolic dysfunction-associated steatotic liver disease (MASLD).
2. Stellate cell biology, heterogeneity, and pathways of HCC prevention and promotion.
3. Therapeutic implications and horizons.

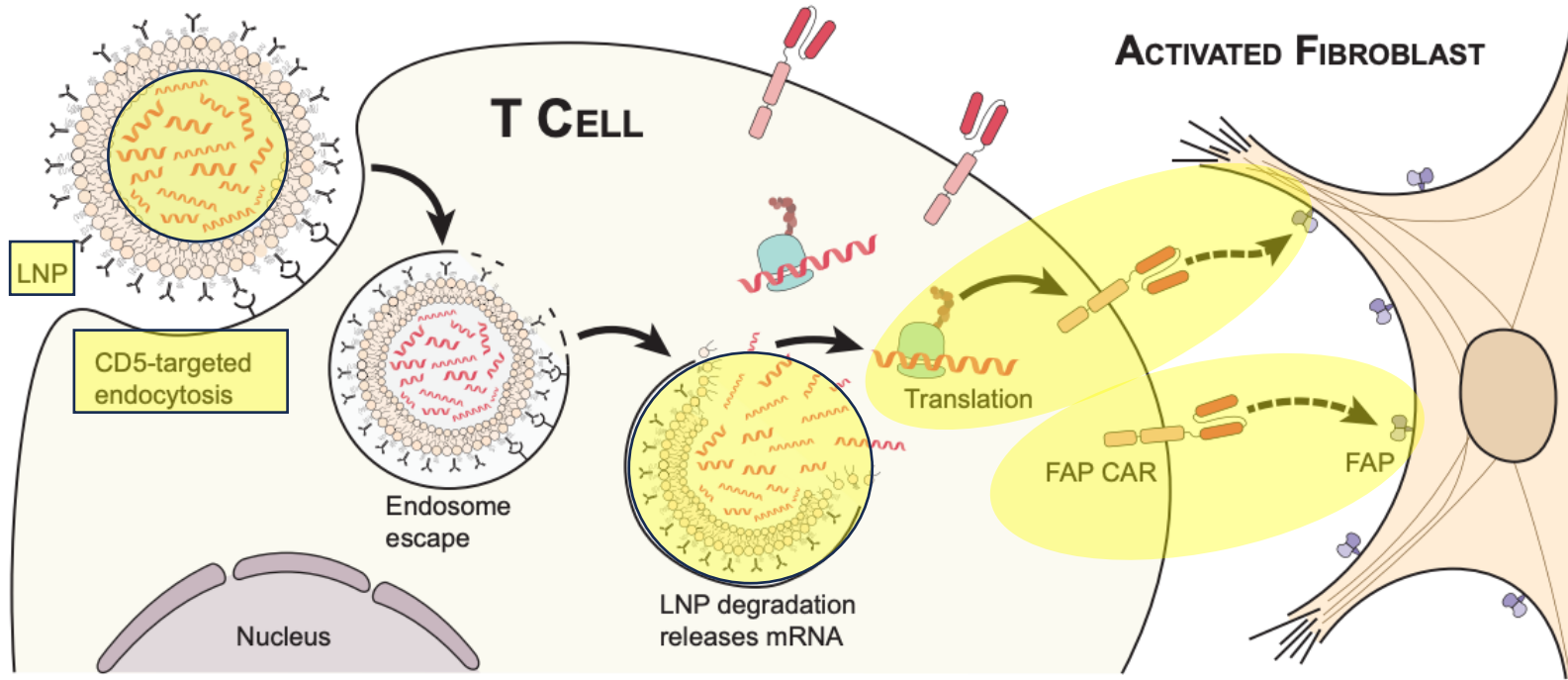
FAP+ CAFs Promote Tumor Growth and Immunosuppression



FAP expression by CAFs correlates with outcomes in HCC

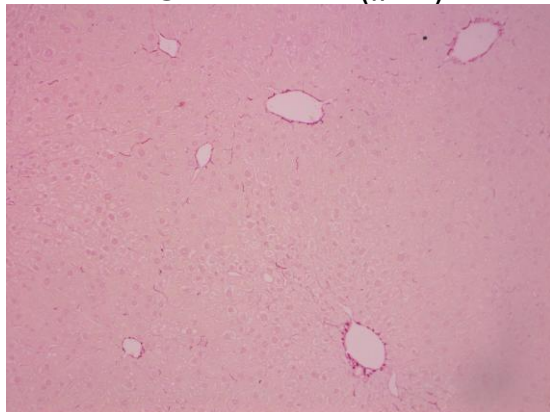


In Vivo CAR T cells Targeting FAP on Cardiac Fibroblasts

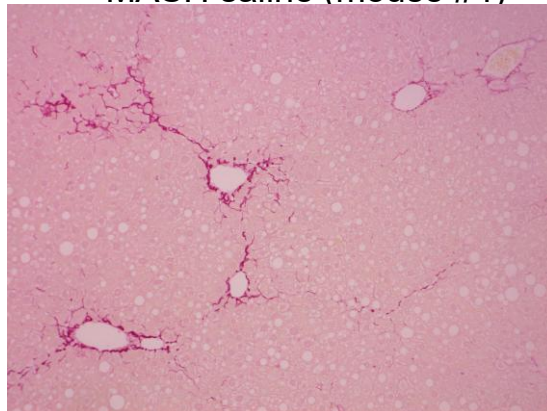


FAP-directed in vivo CAR T cells Reduce Fibrosis in FAT MASH mice

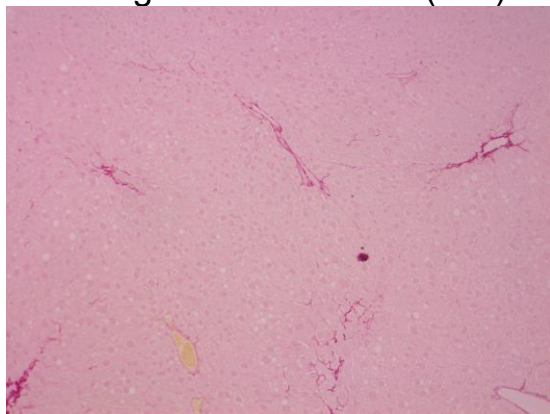
Chow saline (#42)



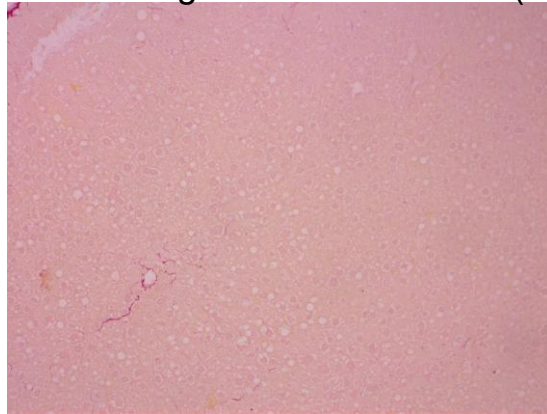
MASH saline (mouse #4)



IgG FAPCAR LNP (#11)

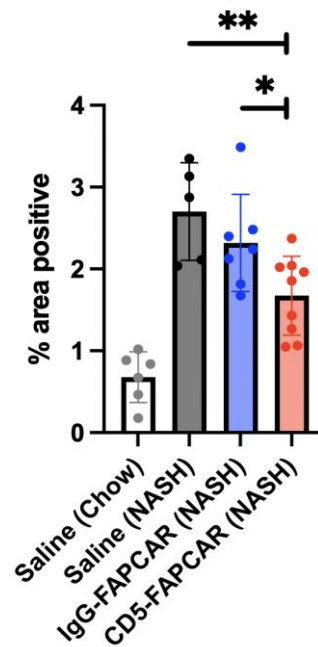


CD5-targeted FAPCAR LNP (#25)



10x

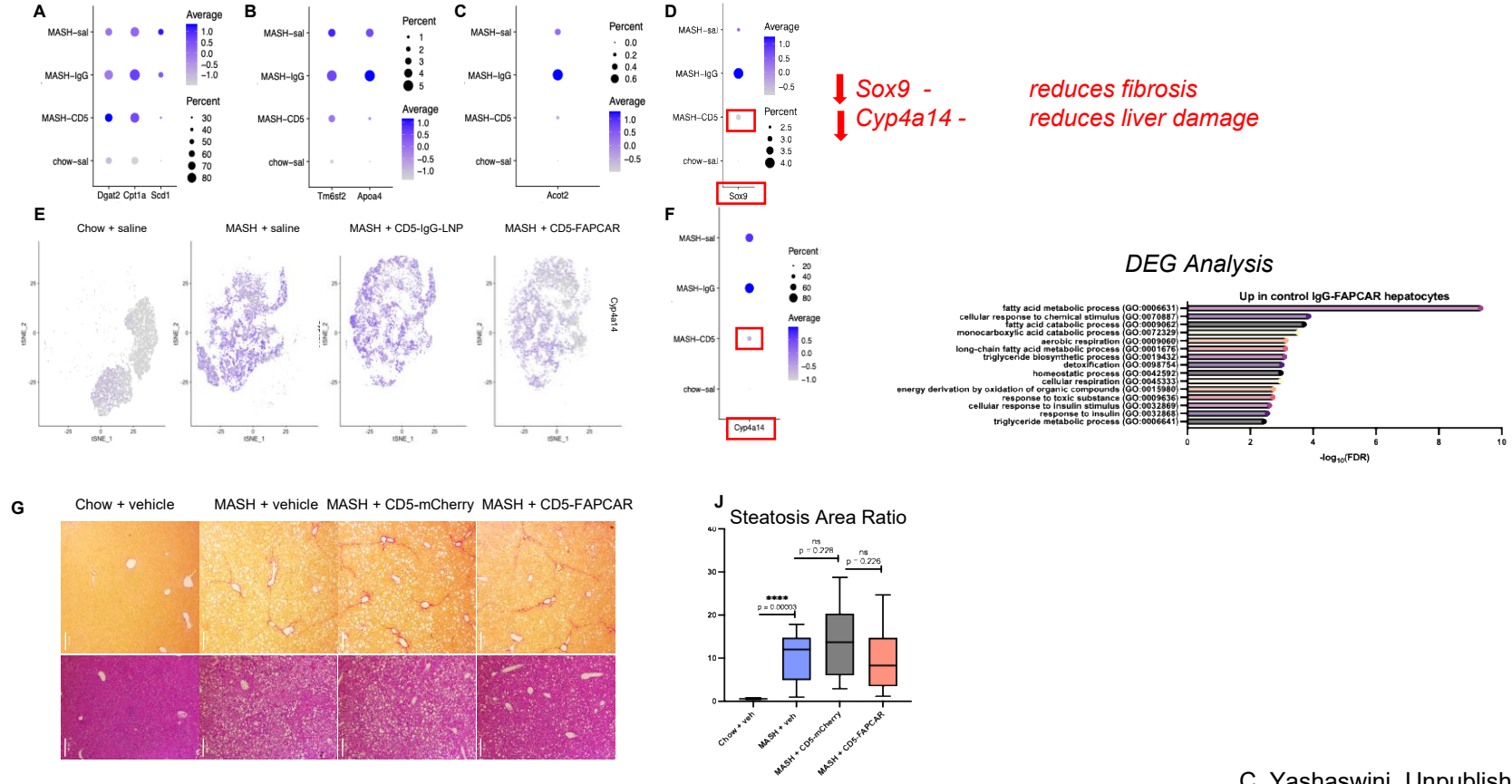
Sirius Red 28d post-injection



Unpublished

FAP⁺ HSC Targeting by in vivo anti-FAP CAR T cells

Reprograms Hepatocytes and Favors Steatosis Reduction



Tumor Associated Fibrosis – Help or Harm?

Summary

1. Major advances in defining HSC / CAF heterogeneity have uncovered their pleiotropic role in HCC.
2. The bulk of evidence implicates CAFs and fibrosis in promoting HCC.
3. There are multiple pathways by which CAFs promote HCC.
4. Depletion of stellate cells is appealing for Rx of fibrosis and possibly HCC, but must account for their support of regeneration and liver homeostasis.