



PARIS MASH MEETING

11th edition

Organized by
Arun Sanyal & Lawrence Serfaty

September 11 & 12, 2025
Institut Pasteur, Paris





**PARIS
MASH
MEETING**

11th edition

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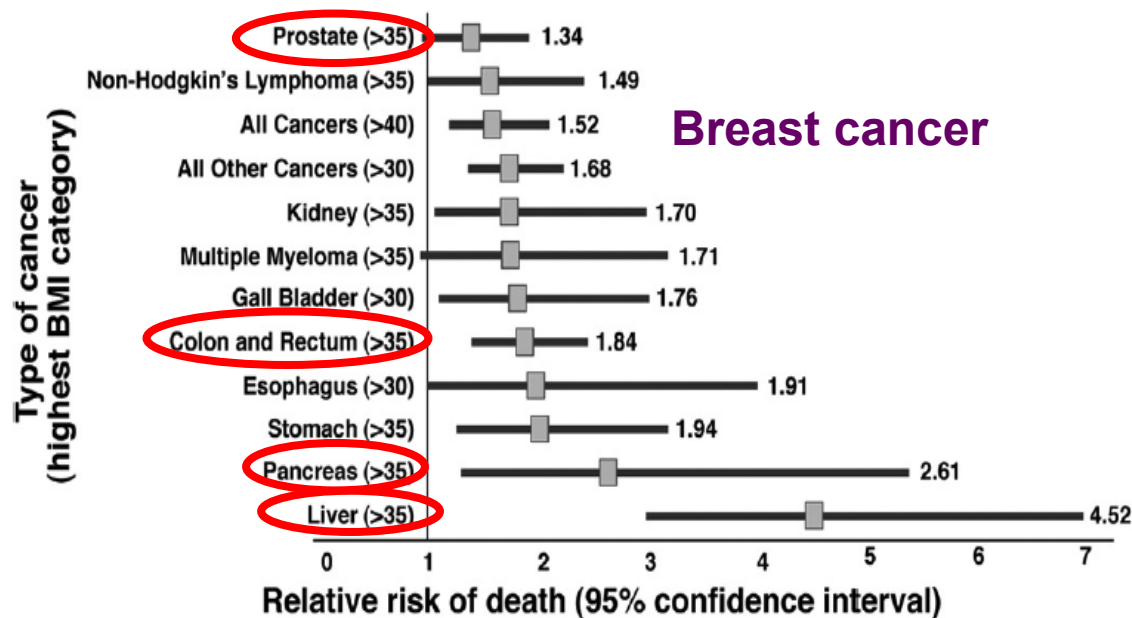


MASH as a driver of colorectal cancer and cancer metastasis



**Ekihiro Seki, M.D., Ph.D.
Professor of Medicine, Director, Basic Liver Research
Cedars-Sinai Medical Center, Los Angeles, CA, USA**

Obesity Increases Risk of Liver and extrahepatic Cancers



Calle EE, & et al, N Engl J Med 2003

NIH NATIONAL CANCER INSTITUTE
Division of Cancer Prevention

In 2023, 153,020 people will be diagnosed with colorectal cancer in the U.S. and 52,550 will die of the disease.



In a recent study, higher BMI was associated with increased colorectal cancer risk.

7/5/2023

Steatotic Liver Disease Increases Risk of Extrahepatic Cancer

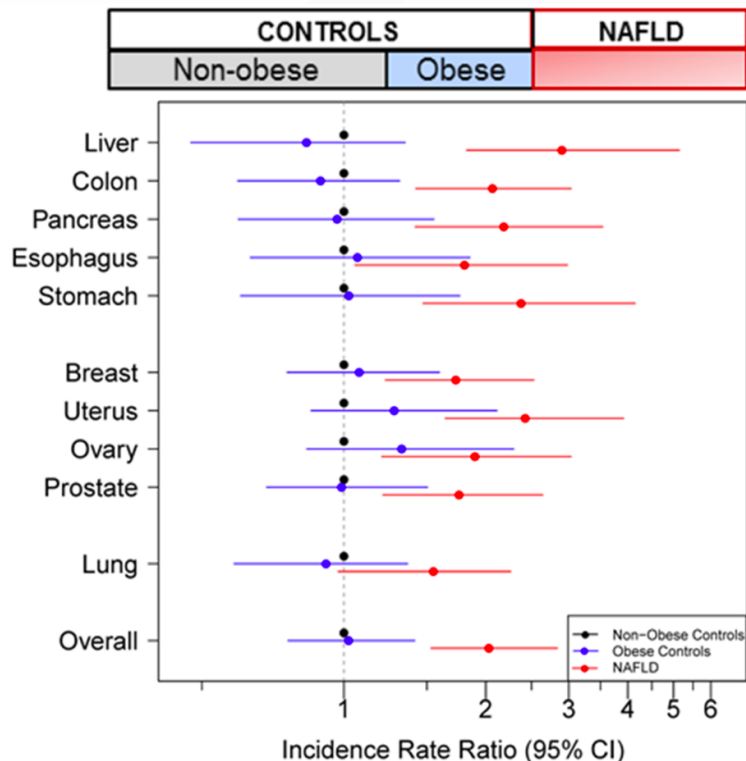
Mayo clinic study

14,441
matched controls

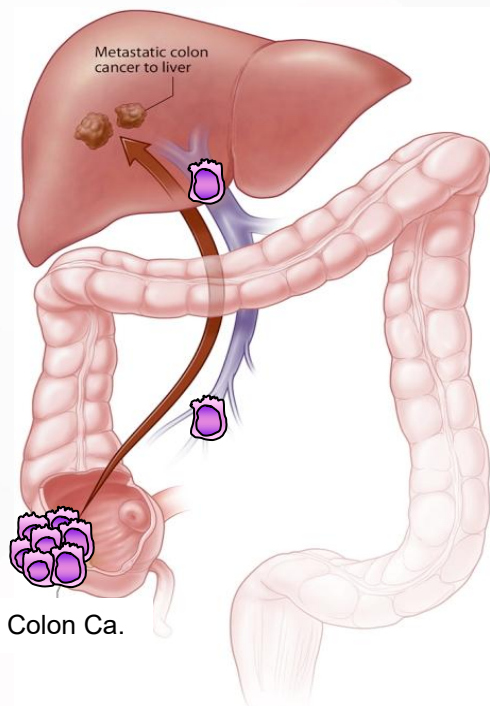
Follow up to
21 years

4,722
with NAFLD

Allen et al, *J Hep* 2019 71: 1229-1236,
Kim et al, *J Hep* 2017 17: 32294-8



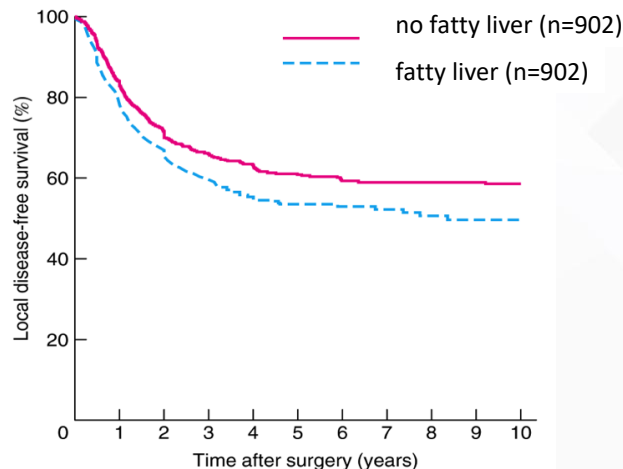
Fatty Liver Increases the Risk of Liver Metastasis



- All cancers can metastasize to the liver – Colorectal Ca., Pancreatic Ca., Gastric Ca., Breast Ca., Melanoma, Lung Ca.

- Up to 50% of Colorectal ca. patients develop liver metastasis. 5-year survival rate ~13%.

- Steatosis increased the recurrence of CRC liver metastasis after liver resection (N=1,804). Hamady, Br J Surgery 2013



Effect of Non-alcoholic Fatty Liver Disease on the Risk of Synchronous Liver Metastasis: Analysis of 451 Consecutive Patients of Newly Diagnosed Colorectal Cancer

TABLE 1 | Clinicopathological parameters of primary colorectal cancer in the NAFLD group and control group.

Factor	NAFLD group (n = 60)	Control group (n = 391)	$\chi^2/t/Z$ Value	P
SynCRLM (yes/no)	11/49	29/362	7.669	0.006
Stage of disease (TNM)			7.939	0.047
Stage I	7 (11.67)	62 (15.86)		
Stage II	19 (31.67)	141 (36.06)		
Stage III	23 (38.33)	159 (40.66)		
Stage IV	11 (18.33)	29 (7.42)		

The prevalence of MASLD 13.30% in this study
The median prevalence of MASLD in China ~ 15.3%

ORIGINAL RESEARCH
published: 28 February 2020
doi: 10.3389/fonc.2020.00251

Yan Lv and Hai-jun Zhang*

Department of Oncology, The Affiliated Zhongda Hospital of Southeast University, Medical School of Southeast University, Nanjing, China

TABLE 2 | Univariate and multivariate logistic regression analysis of the significant predictors for synchronous colorectal liver metastasis.

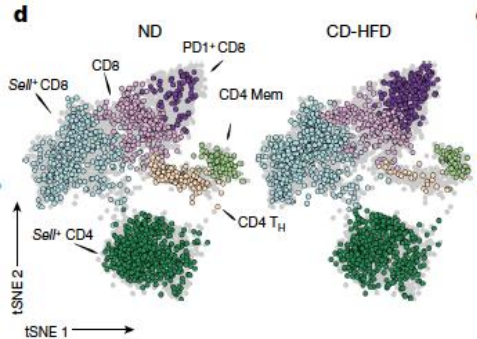
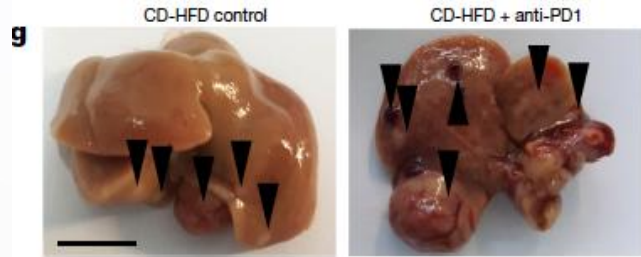
Variables	Univariate analysis		Multivariate analysis	
	OR (95% CI)	P value	OR (95% CI)	P value
NAFLD	2.802 (1.317 ~ 5.965)	0.008	3.930 (1.616 ~ 9.560)	0.003
CEA	1.009 (1.004 ~ 1.013)	<0.001	1.005 (1.002 ~ 1.008)	0.003
CA19-9	1.016 (1.010 ~ 1.023)	<0.001	1.013 (1.006 ~ 1.020)	<0.001

TABLE 3 | Comparison of synCRLM between different levels of FIB-4, APRI, NFS, and BRAD score.

Group	With synCRLM	Without synCRLM	χ^2 value	P
FIB-4			5.455	0.020
High-level FIB-4	2 (6.67%)	28 (93.33%)		
Low-level FIB-4	28 (93.33%)	21 (70.00%)		

MASH-HCC are resistant to anti-PD1 therapy due to increased exhausted CD8 T cells

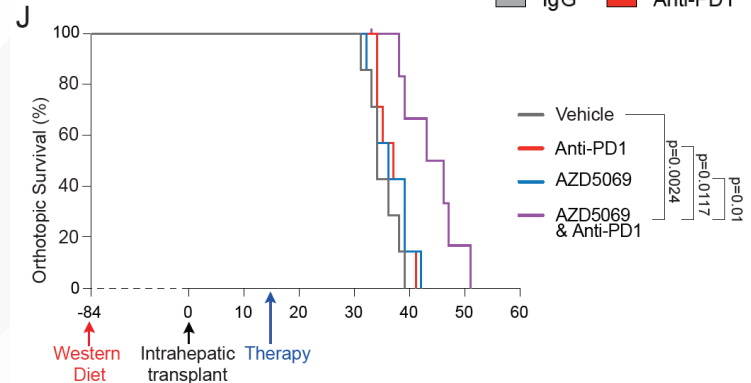
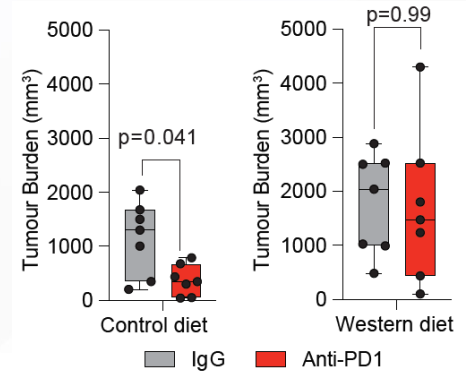
NASH limits anti-tumour surveillance in immunotherapy-treated HCC



Pfister & Heikenwalder.
Nature 2021

CXCR2 inhibition enables NASH-HCC immunotherapy

Leslie & Mann. *Gut* 2022



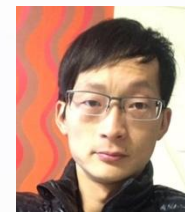
Metastatic Niche in Steatotic Liver Disease

1. How Steatotic Liver affects Primary and Metastatic Tumor Growth?
2. How Primary and Metastatic Tumors affect TME, Steatosis and Fibrosis?
3. How Steatosis and tumors affect the Immune Microenvironment?

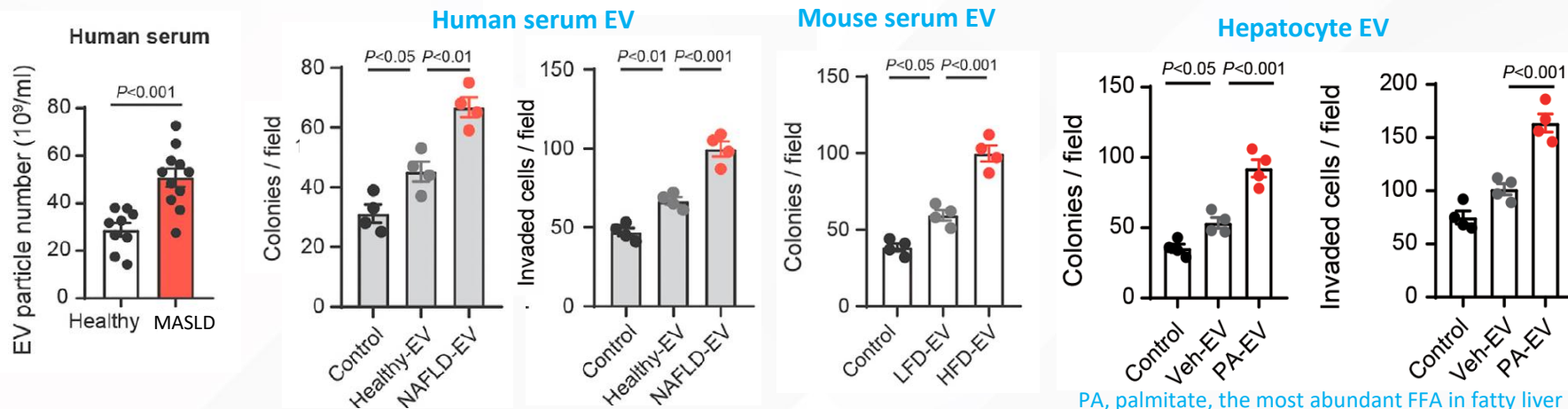
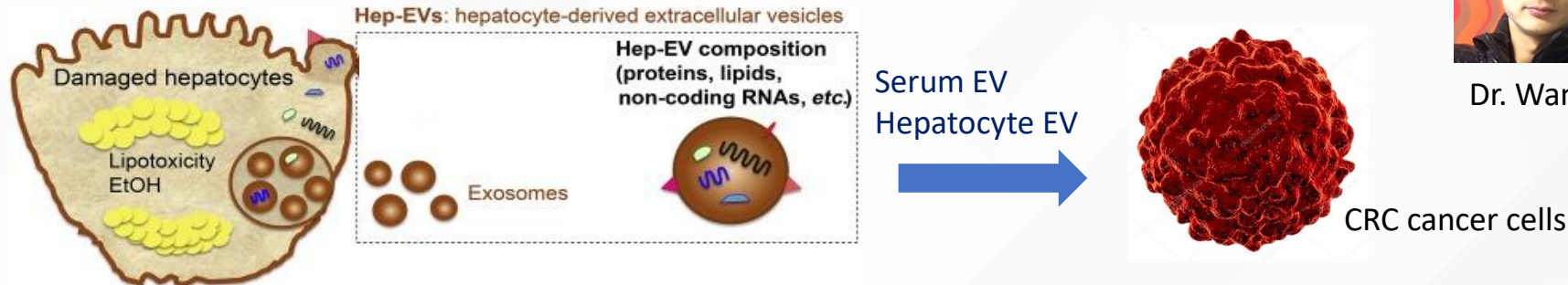
Liver Metastasis in Steatotic Liver Disease

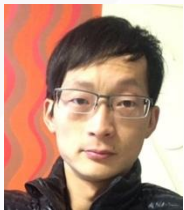
1. How Steatotic Liver affects Primary and Metastatic Tumor Growth?
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Steatotic liver modulates Extracellular Vesicle production, which enhances liver metastasis growth



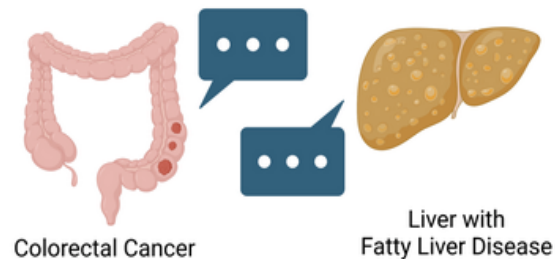
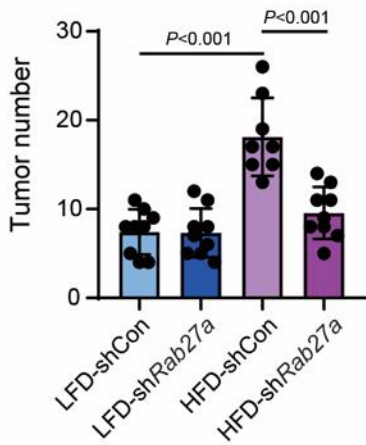
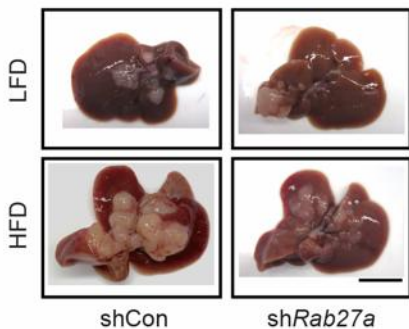
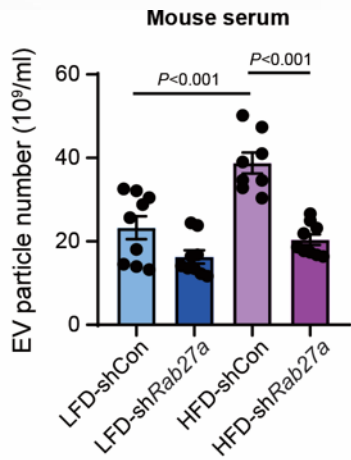
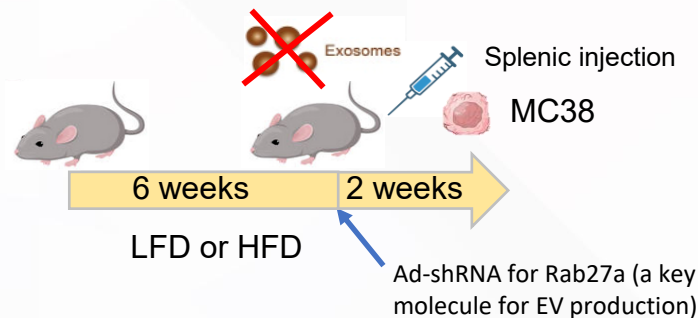
Dr. Wang





Dr. Wang

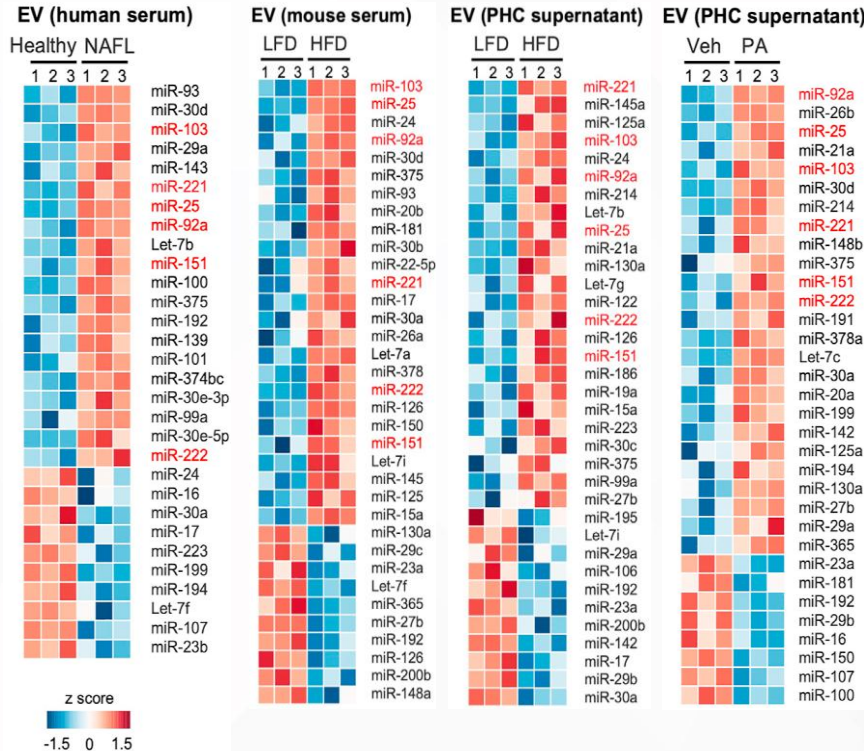
Steatotic liver modulates Extracellular Vesicle production and Metastatic Tumor Microenvironment



Fatty livers send "message bubbles" to colorectal cancer as it spreads, encouraging the cancer to grow in the liver and preventing the immune system from attacking cancer in the liver.
Credit: Created with BioRender.com

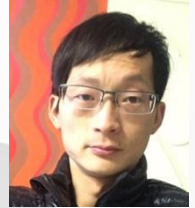
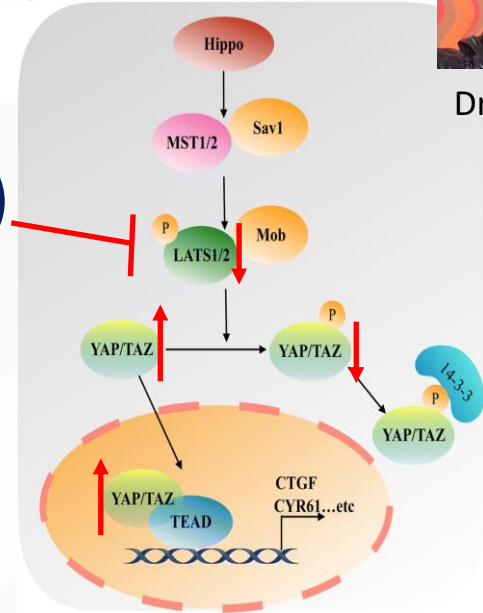
Jaber, NCI 2023 July

YAP regulating miRNAs in EVs from fatty liver hepatocytes



Hep-EV composition
(proteins, lipids,
non-coding RNAs, etc.)

miR-25
miR-92
miR-103
miR-151
miR-221
miR-222



Dr. Wang

Metastatic Niche in Steatotic Liver Disease

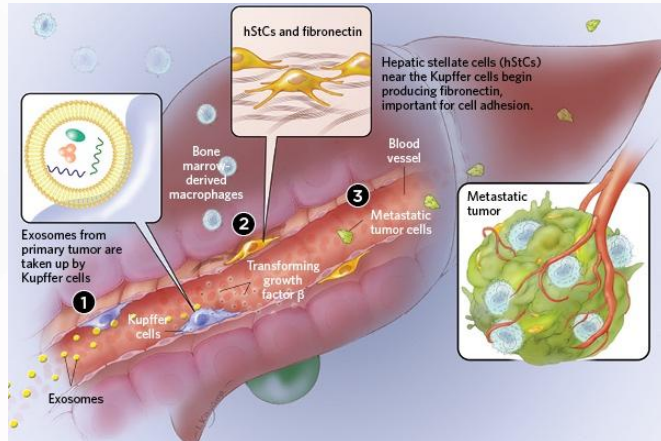
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Cancer-derived EVs and metastasis

nature
cell biology 2015

Pancreatic cancer exosomes initiate pre-metastatic niche formation in the liver

Bruno Costa-Silva¹, Nicole M. Aiello², Allyson J. Ocean³, Swarnima Singh¹, Haiying Zhang¹, Basant Kumar Thakur^{1,4}, Annette Becker¹, Ayuko Hoshino¹, Milica Tešić Mark⁵, Henrik Molina⁶, Jenny Xiang⁶, Tuo Zhang⁶, Till-Martin Theilen¹, Guillermo García-Santos¹, Caitlin Williams¹, Yonathan Ararso¹, Yujie Huang¹, Gonçalo Rodrigues^{1,7}, Tang-Long Shen⁸, Knut Jørgen Labori⁹, Inger Marie Bowitz Lothe^{10,11}, Elin H. Kure¹¹, Jonathan Hernandez¹², Alexandre Doussot¹², Saya H. Ebbesen¹, Paul M. Grandgenett¹³, Michael A. Hollingsworth¹³, Maneesh Jain¹⁴, Kavita Mallya¹⁴, Surinder K. Batra¹⁴, William R. Jarnagin¹², Robert E. Schwartz¹⁵, Irina Matei¹, Héctor Peinado^{1,16}, Ben Z. Stanger^{3,19}, Jacqueline Bromberg^{17,19} and David Lyden^{1,18,19}



Article

Tumour extracellular vesicles and particles induce liver metabolic dysfunction

<https://doi.org/10.1038/s41586-023-06114-4>

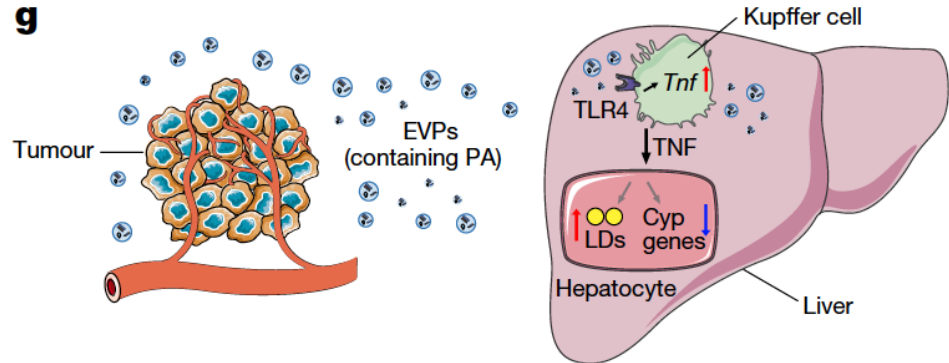
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Check for updates

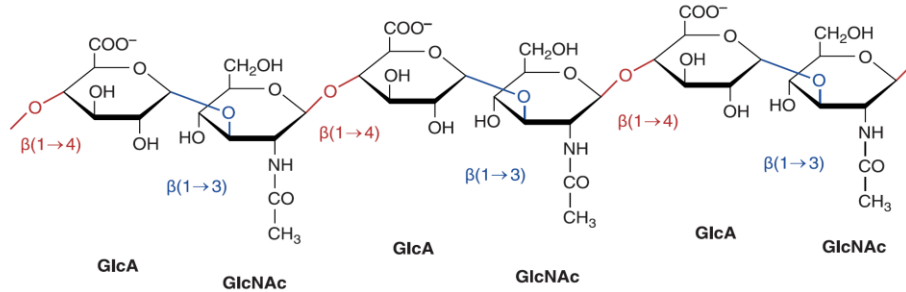
Gang Wang^{1,26}, Jianlong Li^{1,2,26}, Linda Bojmar^{1,3}, Haiyan Chen^{1,4,5}, Zhong Li⁶, Gabriel C. Tobias¹, Mengying Hu¹, Edwin A. Homan¹, Serena Lucotti¹, Fengbo Zhao^{1,9}, Valentina Posada⁸, Peter R. Oxley¹⁰, Michele Cioffi¹, Han Sang Kim^{1,11}, Huajuan Wang¹, Pernille Lauritzen¹, Nancy Boudreau¹, Zhanjun Shi², Christine E. Burd¹, Jonathan H. Zippin¹², James C. Lo⁷, Geoffrey S. Pitt¹, Jonathan Hernandez^{13,14}, Constantinos P. Zambirinis^{13,15}, Michael A. Hollingsworth¹⁶, Paul M. Grandgenett¹⁶, Maneesh Jain¹⁶, Surinder K. Batra¹⁶, Dominick J. DiMaio¹⁷, Jean L. Grem¹⁸, Kelsey A. Klute¹⁸, Tanya M. Trippett¹⁹, Mikala Egeblad²⁰, Doru Paul²¹, Jacqueline Bromberg²², David Kelsen²², Vinagolu K. Rajasekhar²⁴, John H. Healey²⁴, Irina R. Matei¹, William R. Jarnagin¹⁹, Robert E. Schwartz²⁵, Haiying Zhang^{1,23} & David Lyden^{1,23}



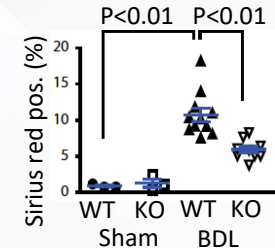
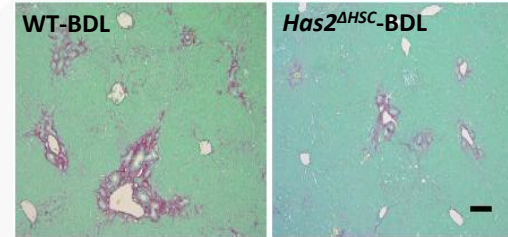
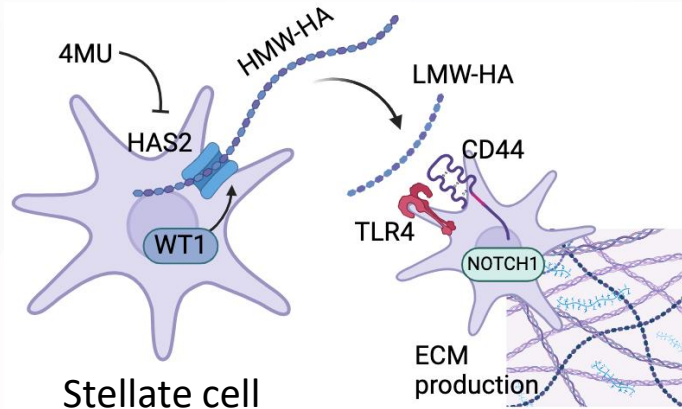
Hyaluronan (hyaluronic acids, HA)



Dr. Yang



- A major **Extracellular matrix**
- Composed of repeating polymeric disaccharides D-glucuronic acid and N-acetyl-D-glucosamine linked by glucuronic bond
- Endogenously produced during tissue injury, tissue repair, and wound healing

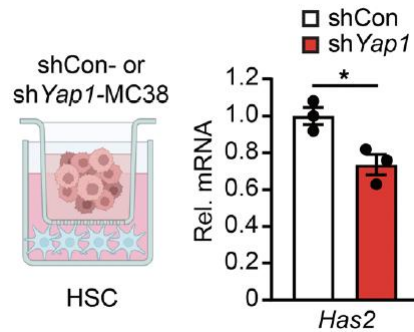
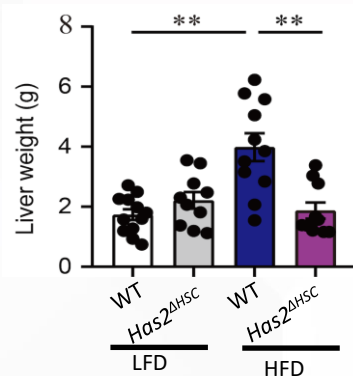
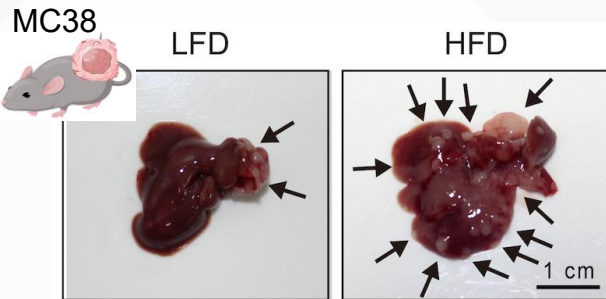


Yang et al. *Science Trans Med.* (2019)

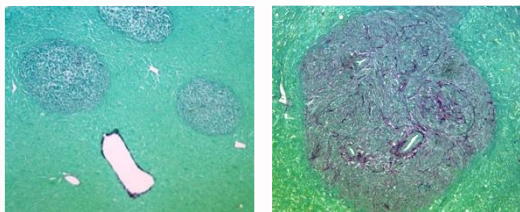
Hepatic steatosis creates fibrotic TME and hyaluronic acid (HA) deposition in CRC Liver Metastasis



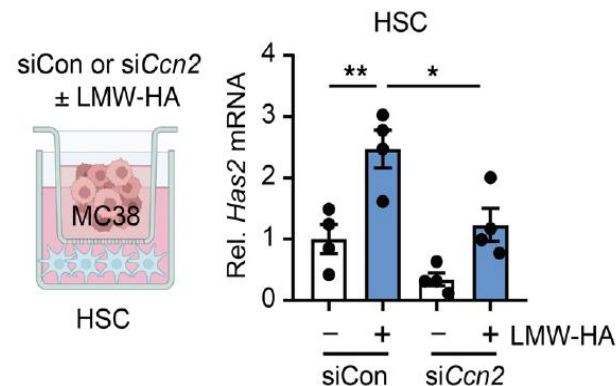
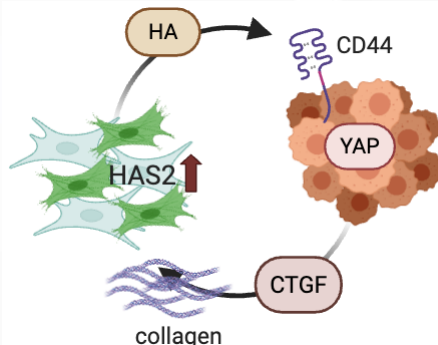
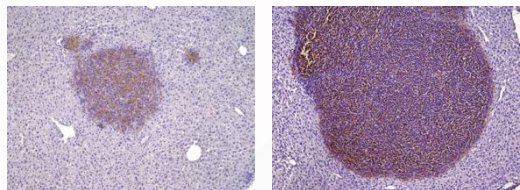
Dr. Yang



Sirius Red



HA



Metastatic Niche in Steatotic Liver Disease

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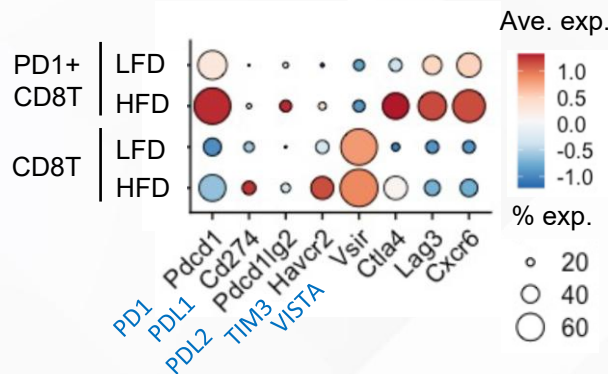
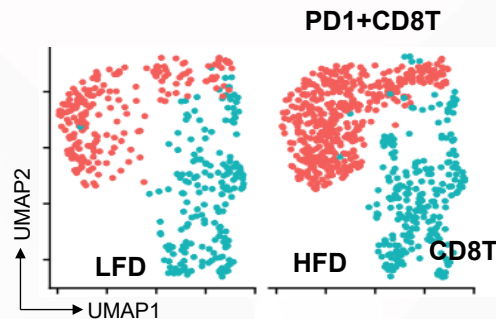
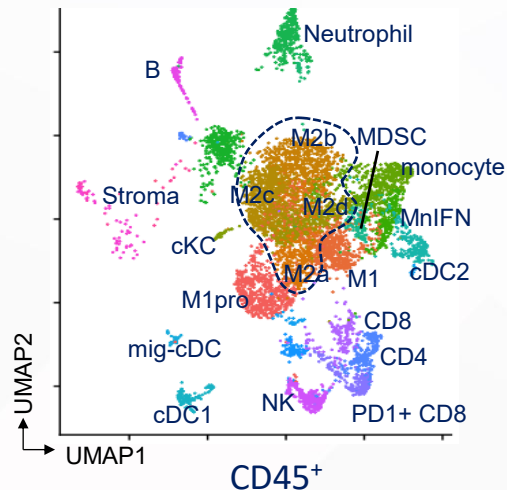
Single Cell RNA-seq for mouse liver metastasis with steatotic liver



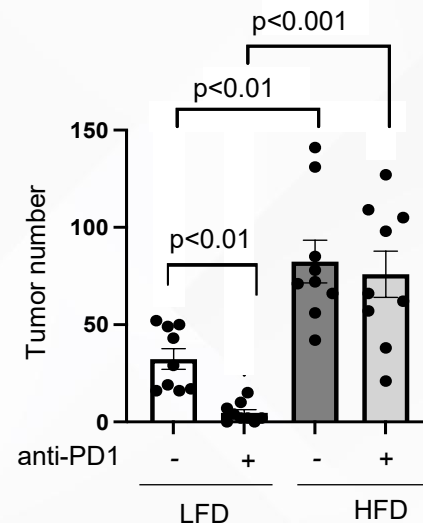
Dr. Kim



scRNA-seq only
for tumors

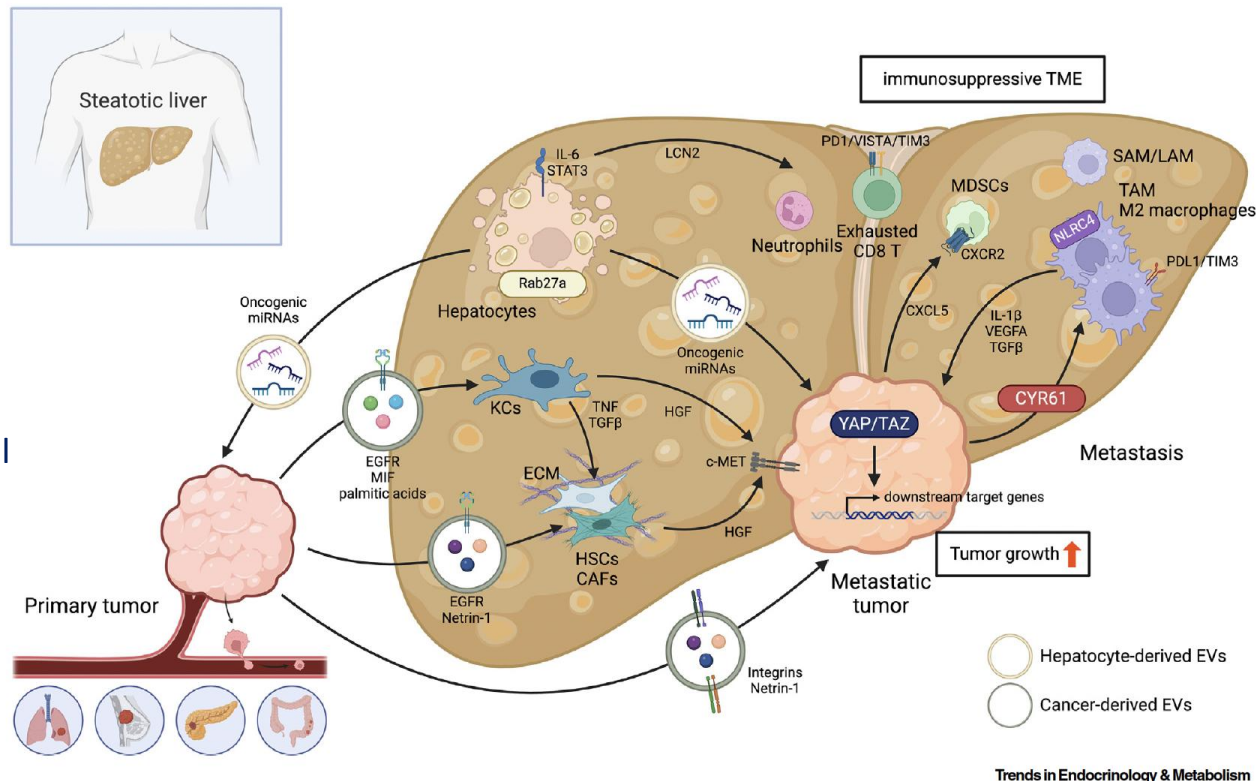


anti-PD1 treatment

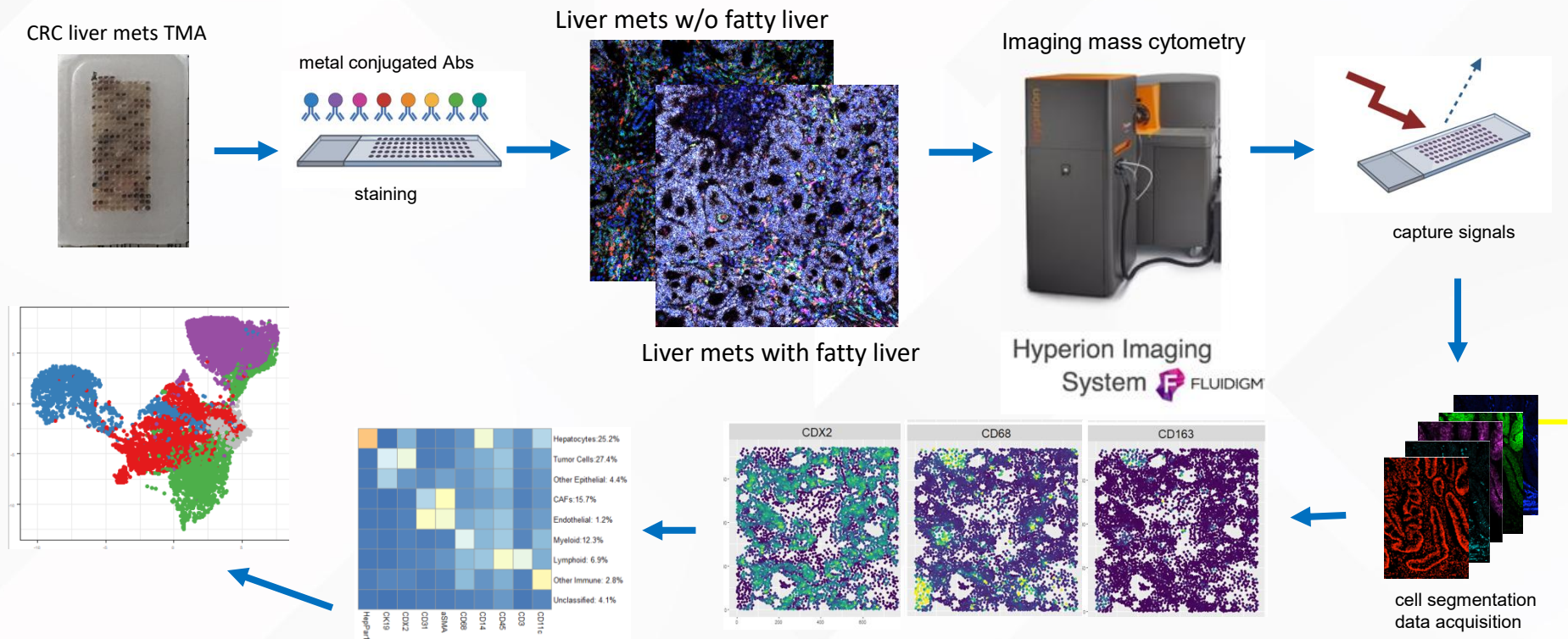


Immune Cell Regulation of Liver Metastasis with Steatosis

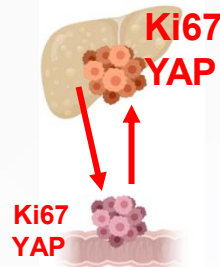
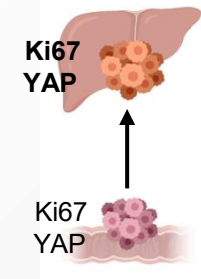
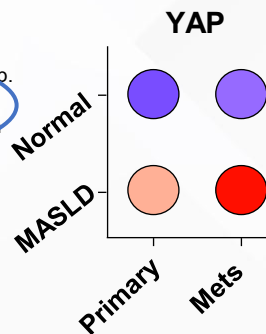
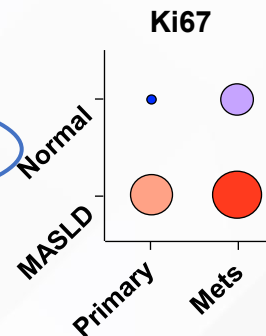
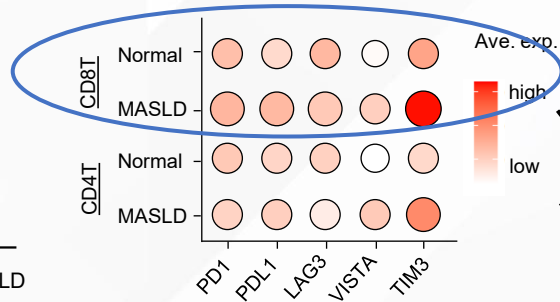
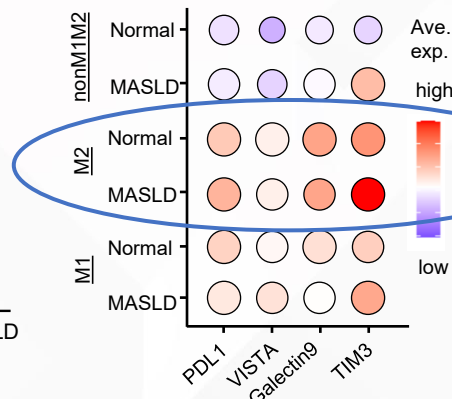
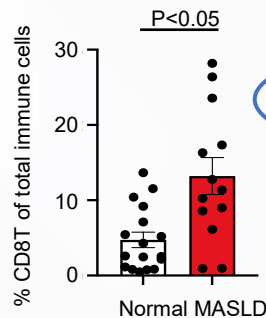
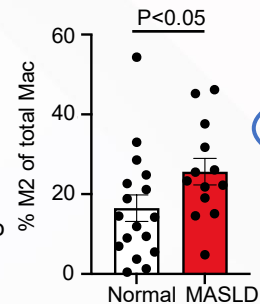
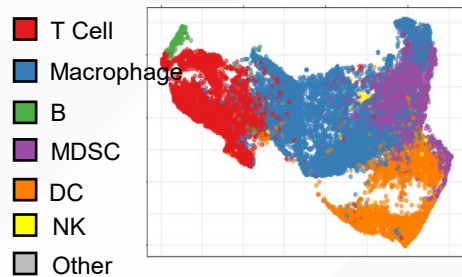
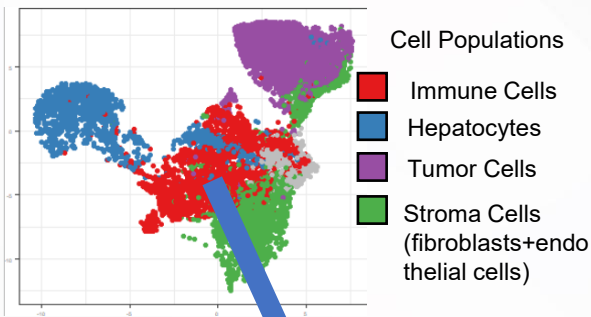
Kim and Seki
Trends Endocrinol
Metab 2024



IMC for human liver mets TMA specimens



Imaging Mass Cytometry Analysis for human CRC liver mets

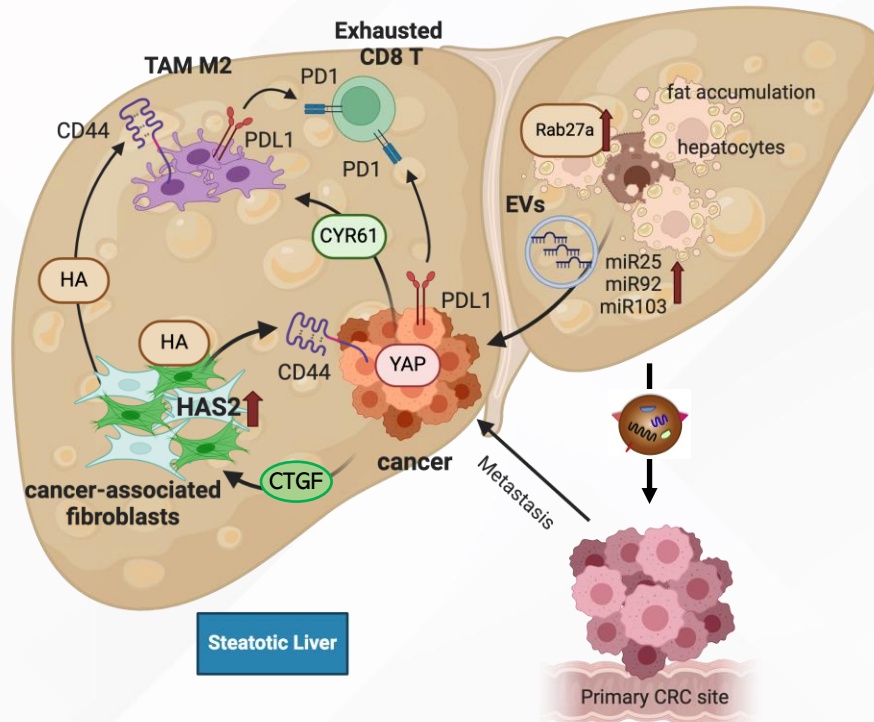
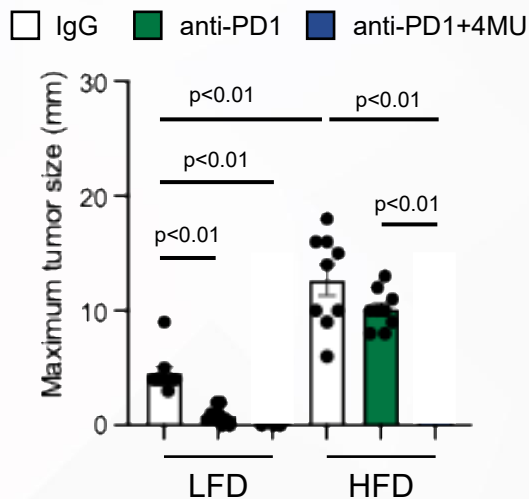


Steatotic Liver creates fibrotic and immunosuppressive TME through EV production in CRC Liver Metastasis



Dr. Jieun Kim

Anti PD-1 therapy



SUMMARY

- Hepatic steatosis is a risk factor for CRC as well as CRC liver metastasis.
- MASLD-derived EVs promote metastasis to the liver via their oncogenic cargo miRNAs.
- MASLD modulates TME to enhance ECM production, which further promotes tumor growth.
- Cancer YAP activation is crucial for creating immunosuppressive TME in MASLD.
- MASLD limits anti-PD1 treatment for CRC liver metastasis.
- Liver metastasis patients with MASLD may require different clinical management than patients without MASLD.

Acknowledgement



Current lab member

So Yeon Kim PhD

Jieun Kim PhD

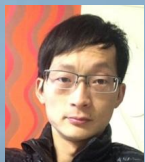
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Sadam Bhat, PhD

Mustafa Karabici PhD

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Takashi Tsuchiya



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Michitaka Matsuda MD, PhD



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