



PARIS MASH MEETING

10th edition

**Organized by
Arun Sanyal & Lawrence Serfaty**



**September 5 & 6 2024
Institut Pasteur, Paris**



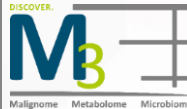
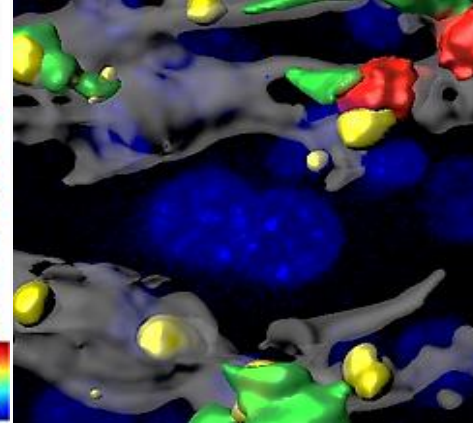
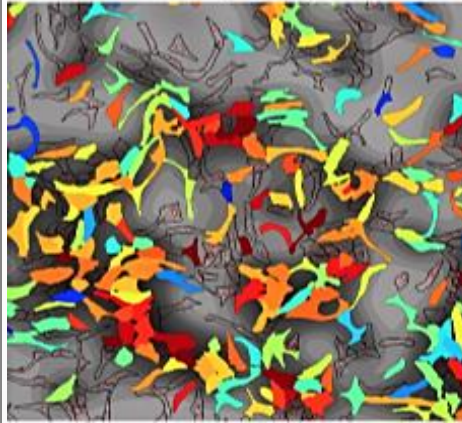
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MASH
MEETING

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Hepatocyte-immune cell crosstalk and their role in MASH/ MASH HCC progression



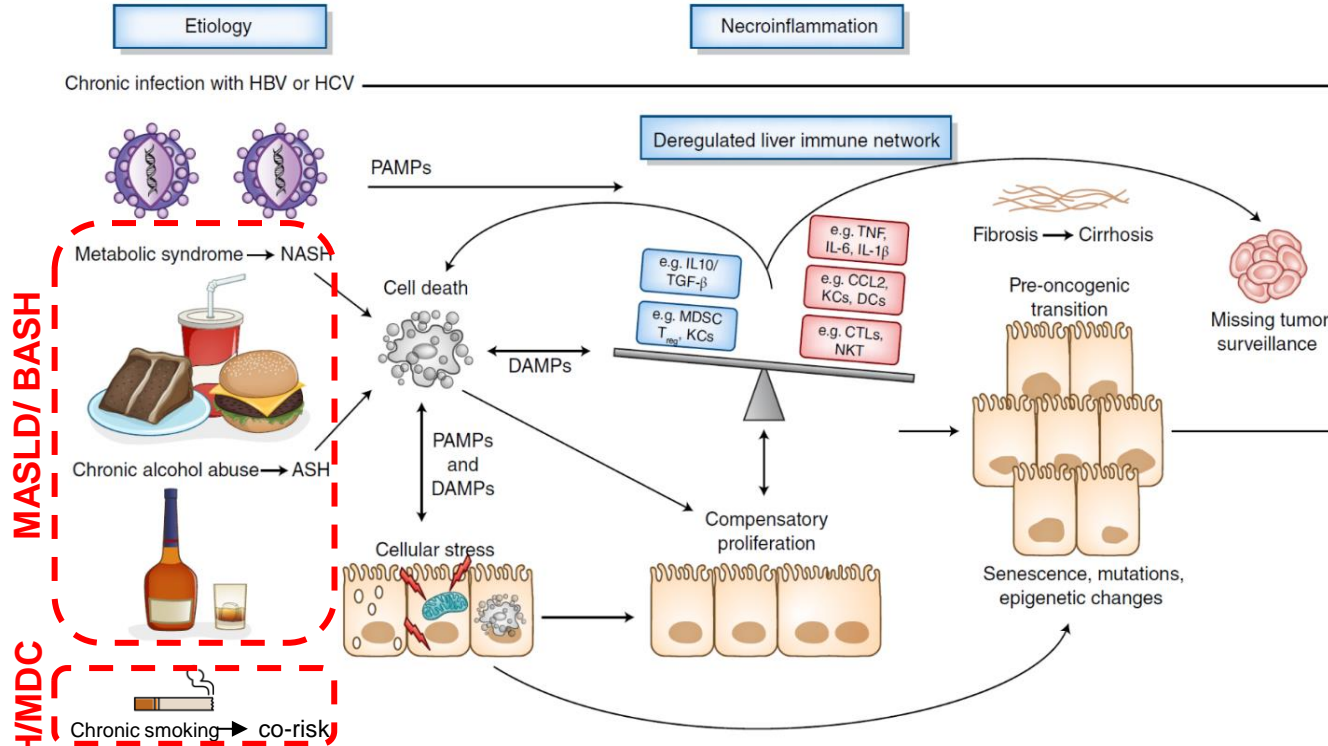
Mathias Heikenwälder

The M3 Research Center, Medical faculty, Eberhard-Karls University Tübingen,
University Clinic Tübingen (UKT)

Division Chronic Inflammation and Cancer, German Cancer Research Center (DKFZ)

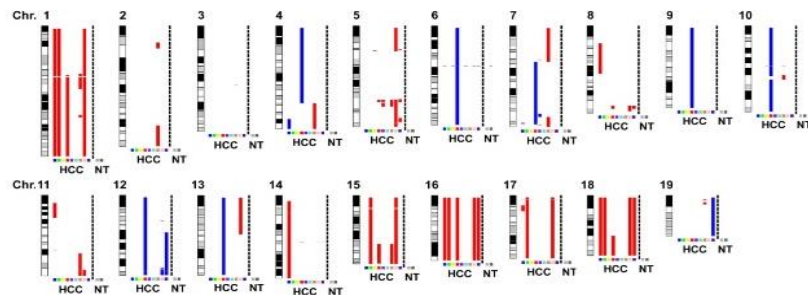
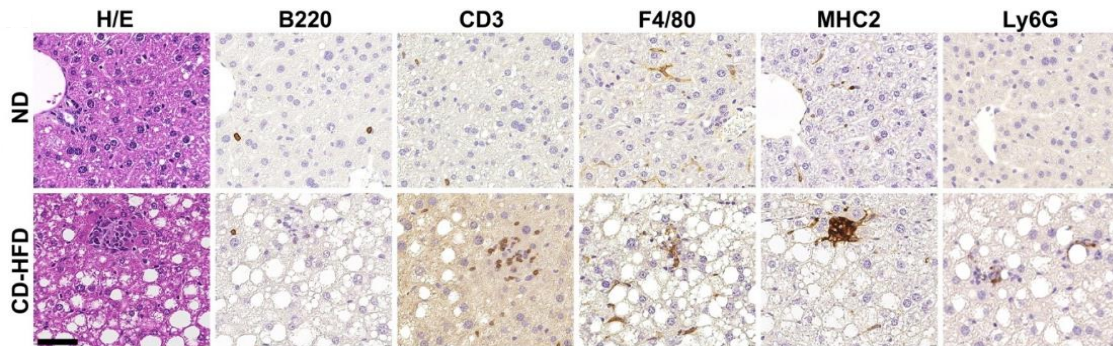
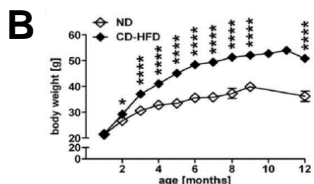


Chronic hepatitis induces liver cancer

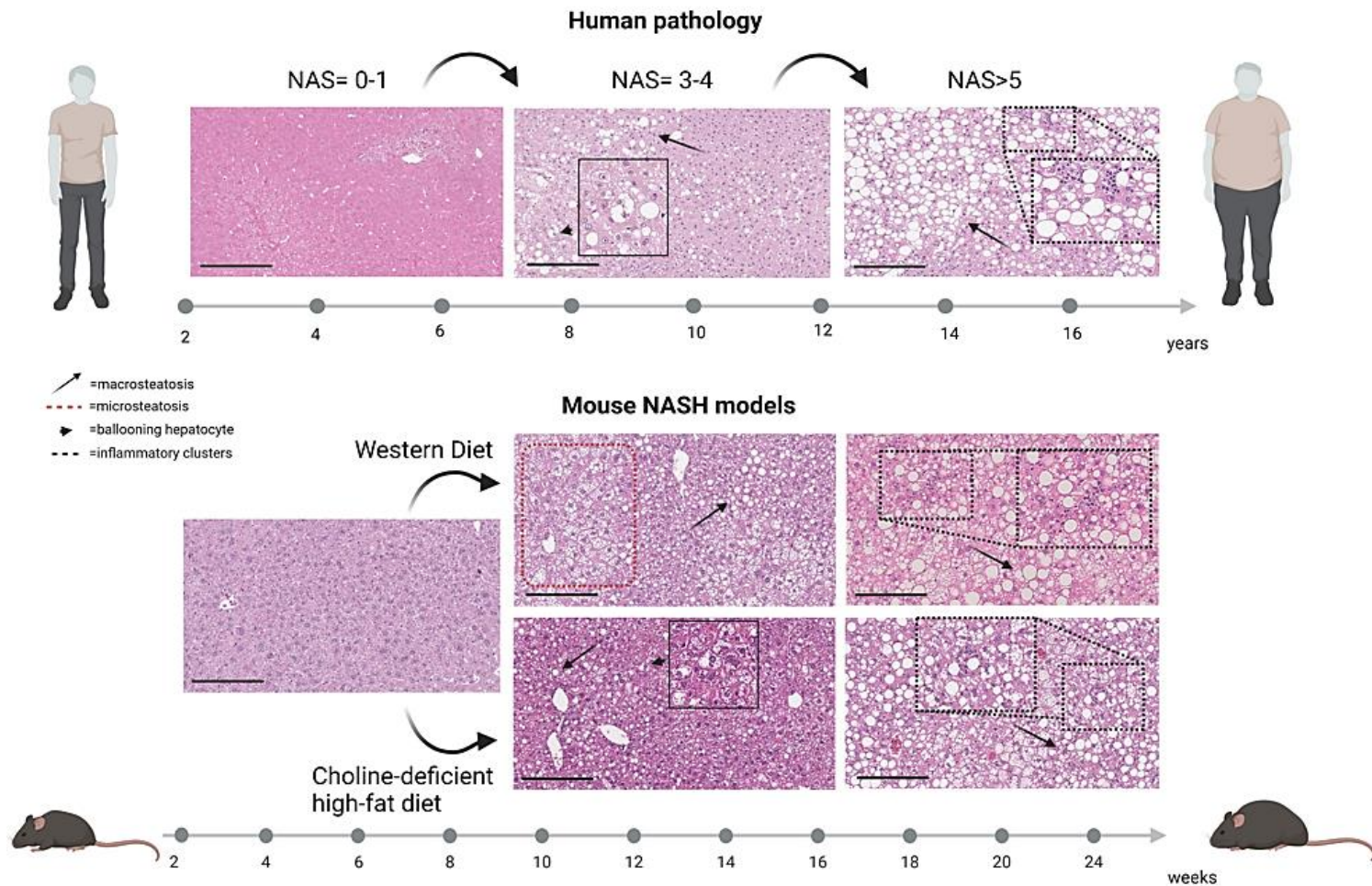


Liver cancer is caused by chronic necro-inflammation

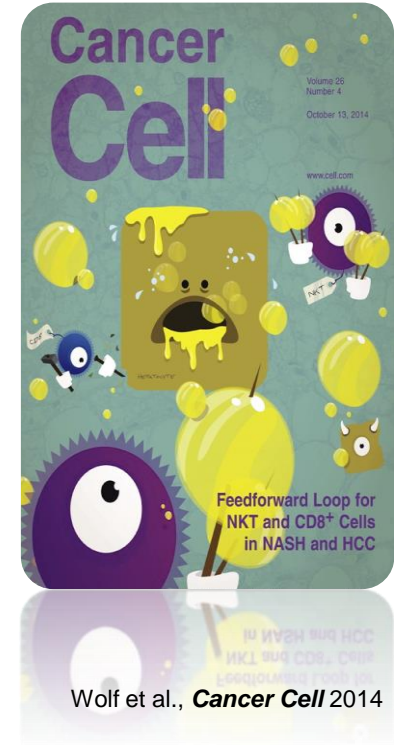
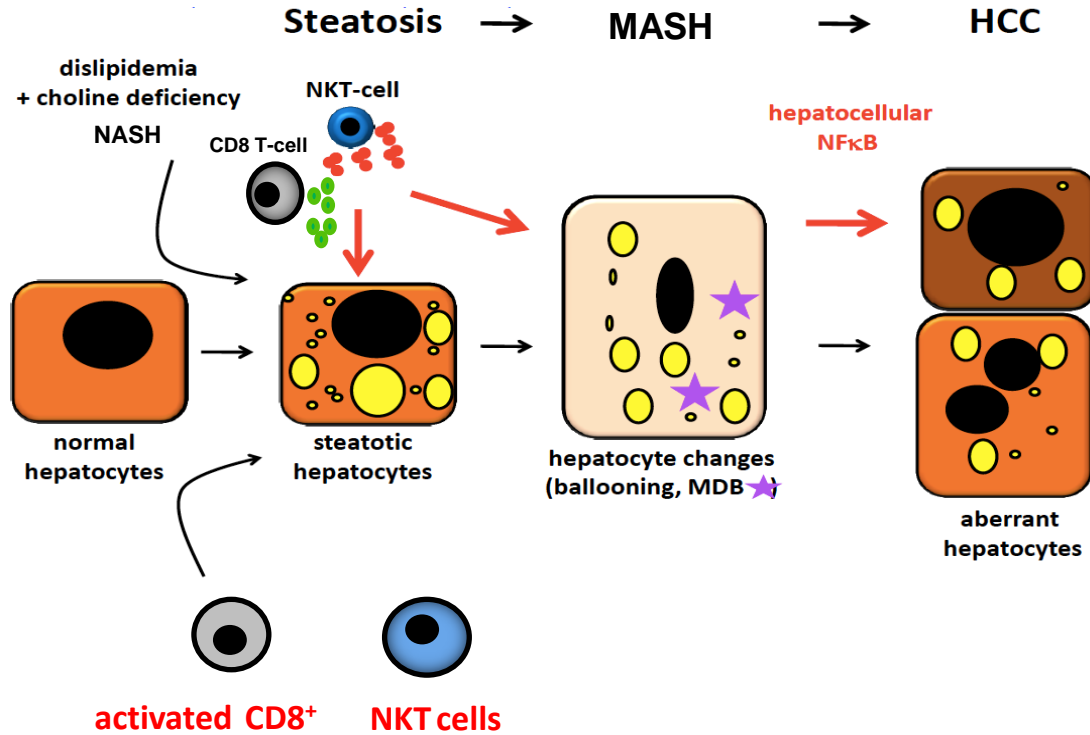
Smoking and Western diet



Gallage et al., Cell Metabolism 2024



Contribution of lymphocytes to steatosis-induced HCC



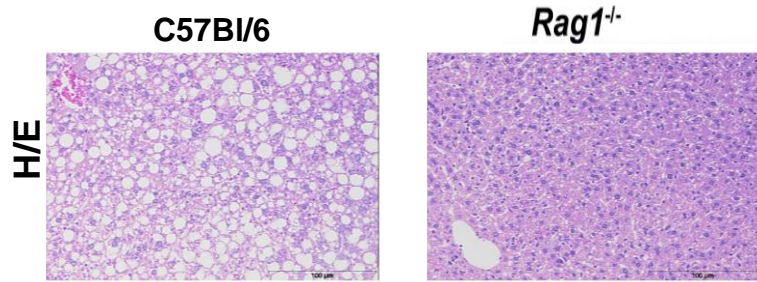
Similar inflammatory/ metabolic/ HCC signatures in patients



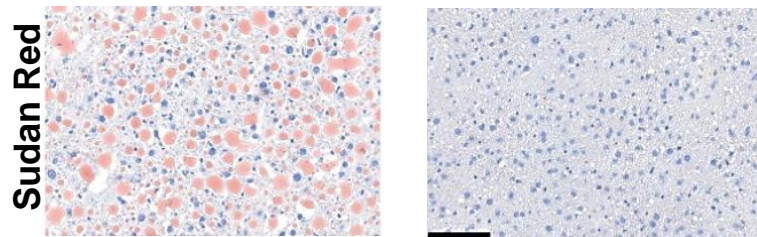
Universitätsklinikum
Tübingen

Adaptive immune cells dictate hepatic steatosis

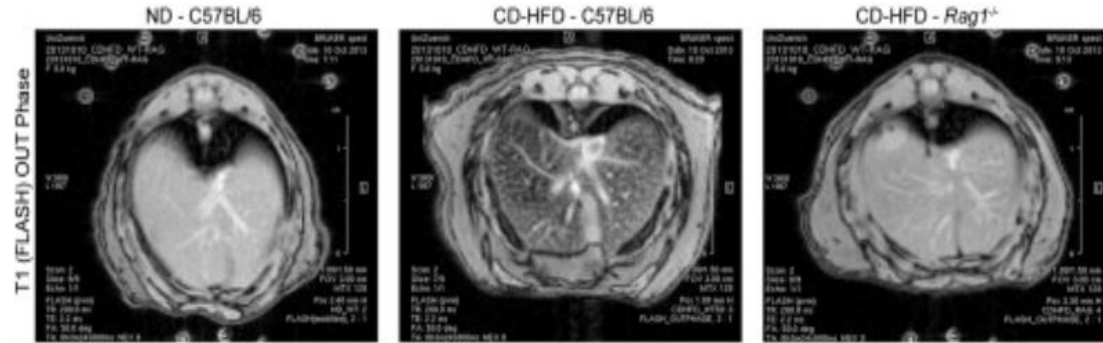
A



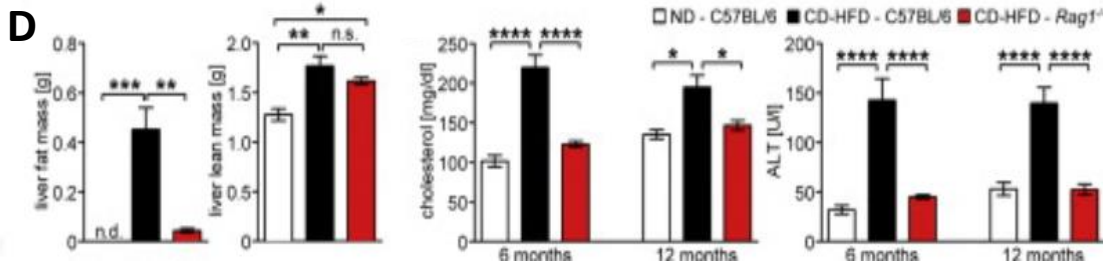
B



C

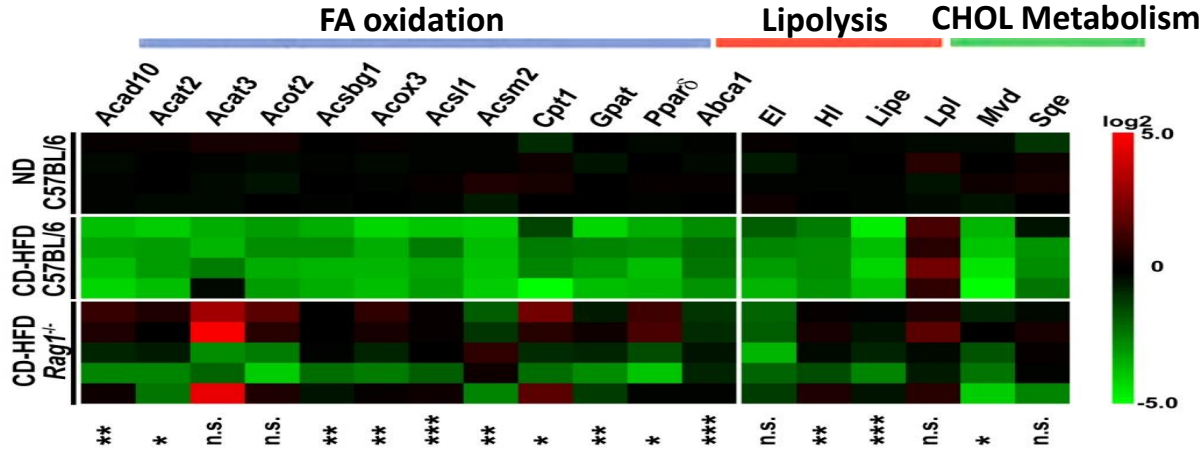


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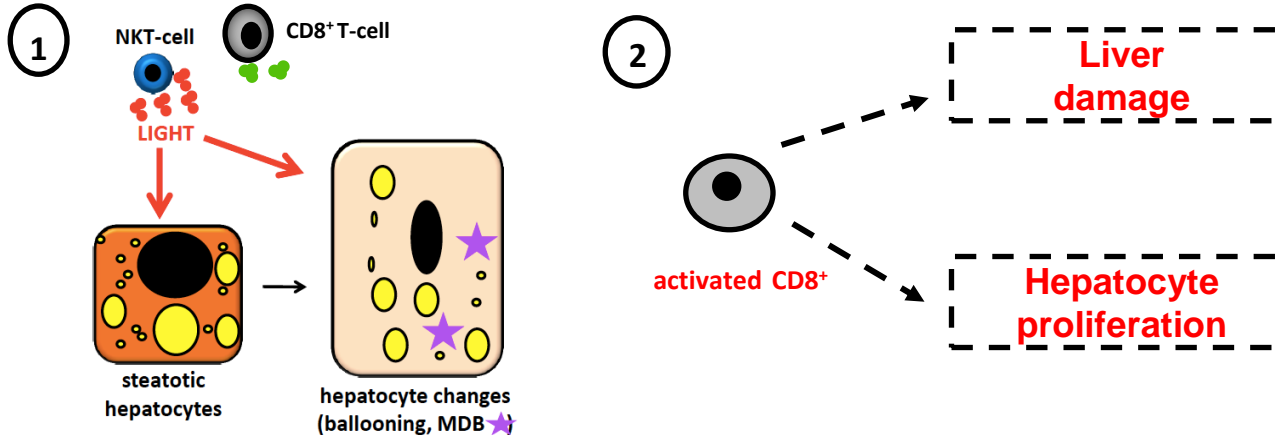


Metabolic re-programming/ hepatocyte damage, proliferation

A



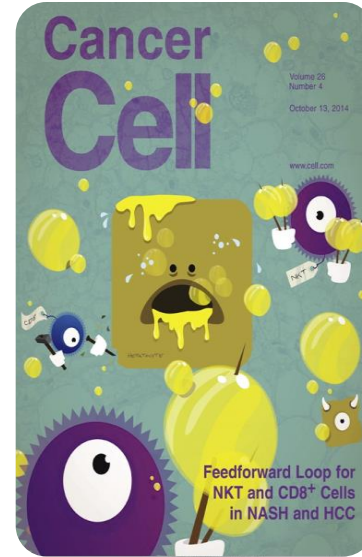
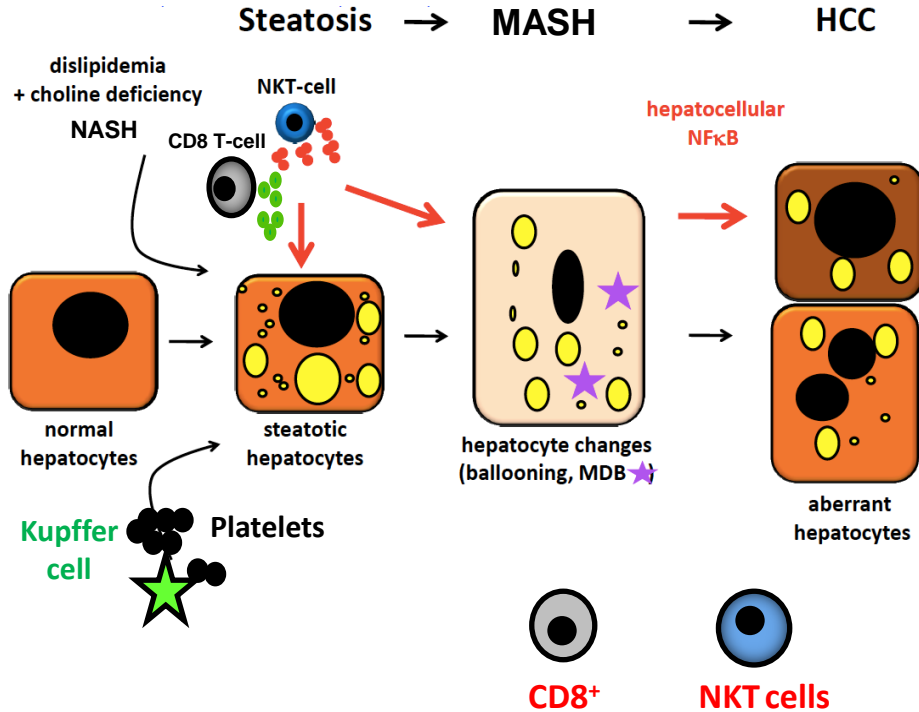
B



Metabolic re-programming



Anti-platelet-therapy (APT) in MASH and HCC



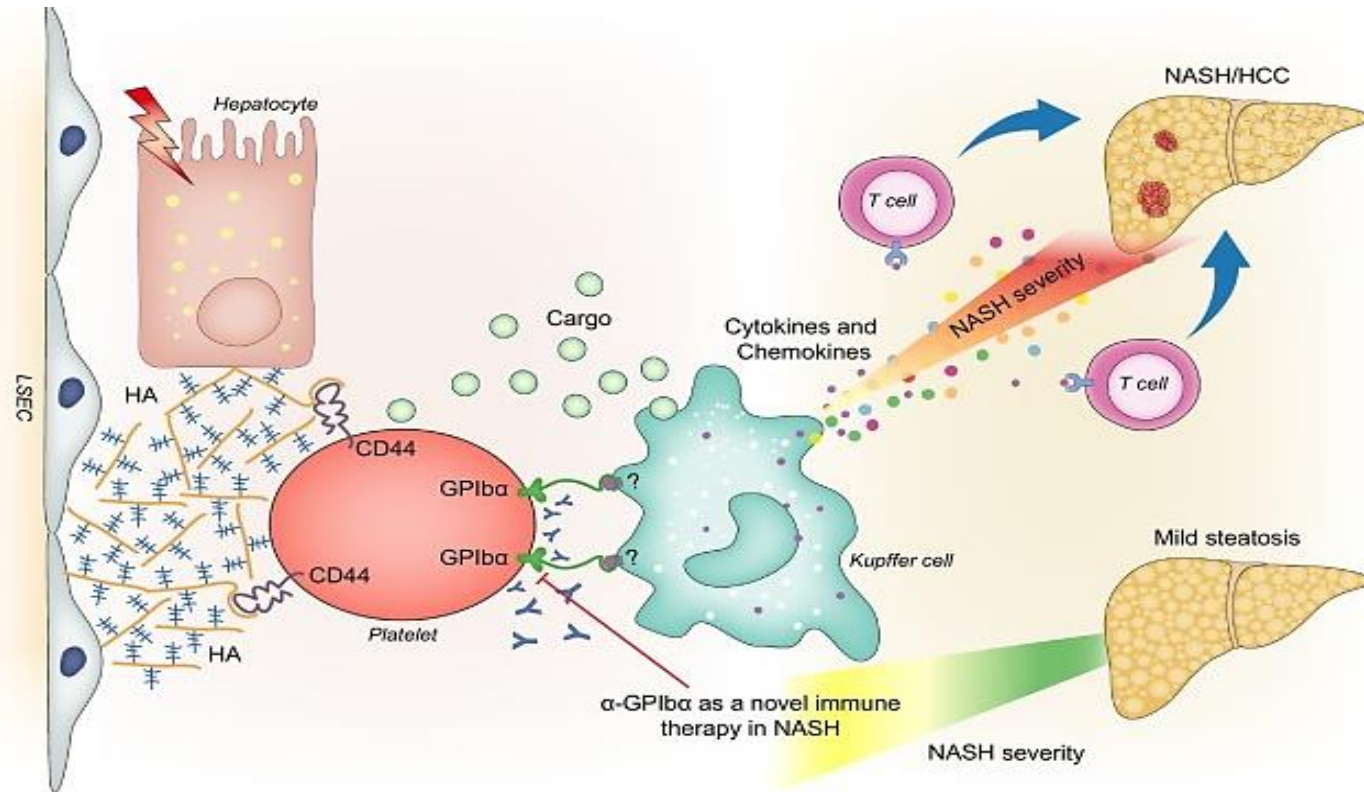
Wolf et al., *Cancer Cell* 2014
 Ma et al., *Nature*, 2016
 Boege et al., *Cancer Cell* 2017
 Dudek et al., *Nature* 2021



Mahleir et al., *Nature Medicine* 2019

Therapeutic efficacy of APT in NAFLD/MASH patients

Platelet GPIb α is a mediator of MASH and subsequent liver cancer



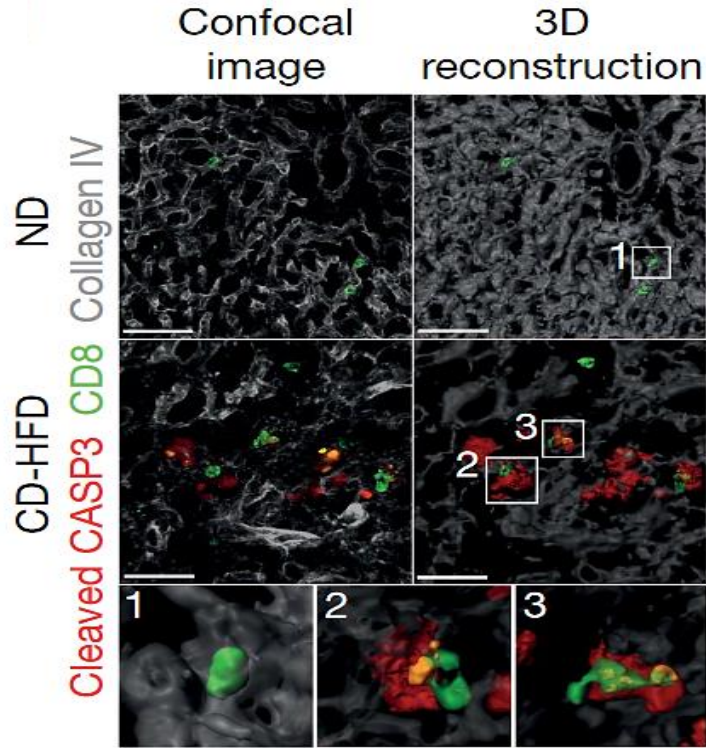
Human anti-GPIb α antibody selected for GMP-production



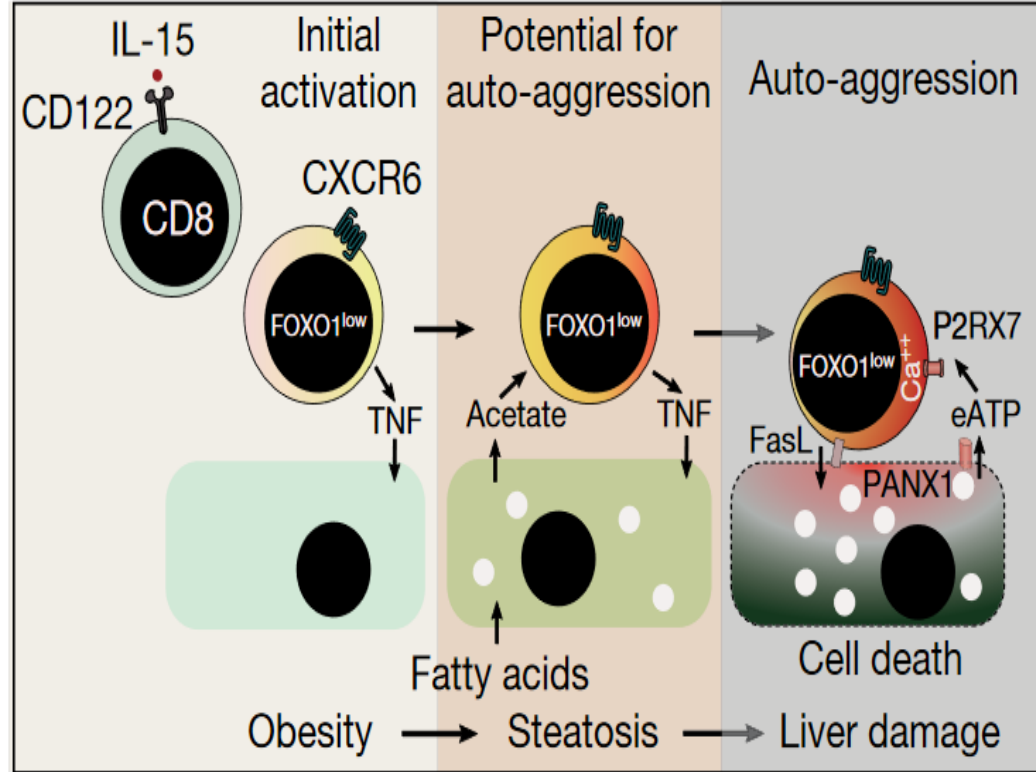
Universitätsklinikum
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Autoaggressive, metabolically activated CD8⁺CXCR6⁺PD1^{hi}T cells in MASH

A



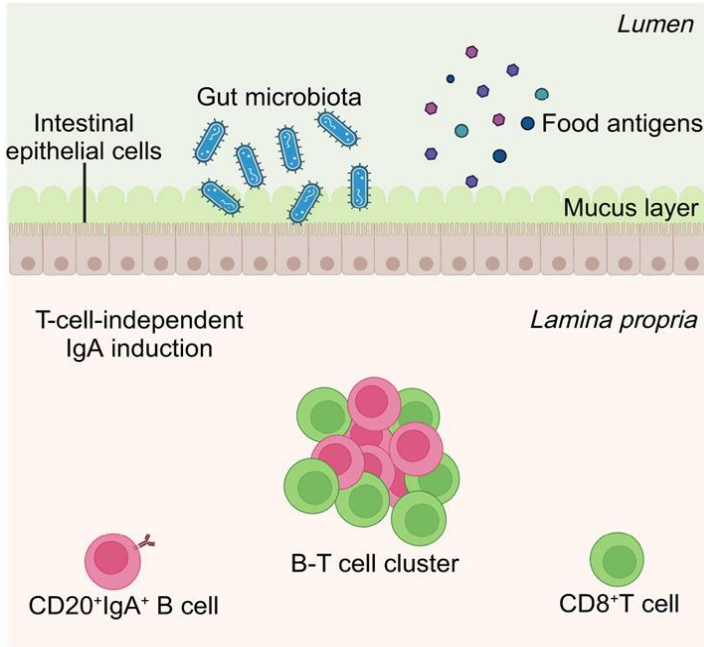
B



Role of other immune cells in metabolically priming T cells?

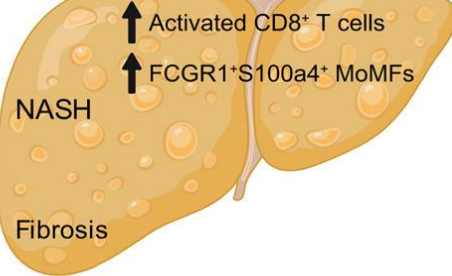
Location of priming ?

Small intestine



Activated CD8⁺ T cells
Portal vein

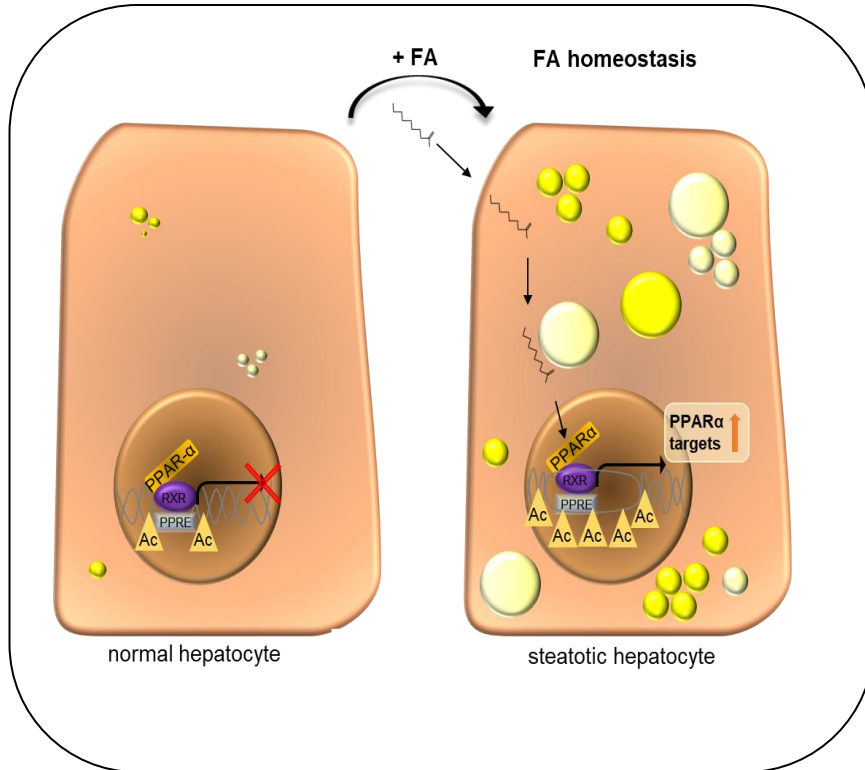
Liver



(IgA⁺) B cells
Systemic circulation

Secondary lymphoid organs

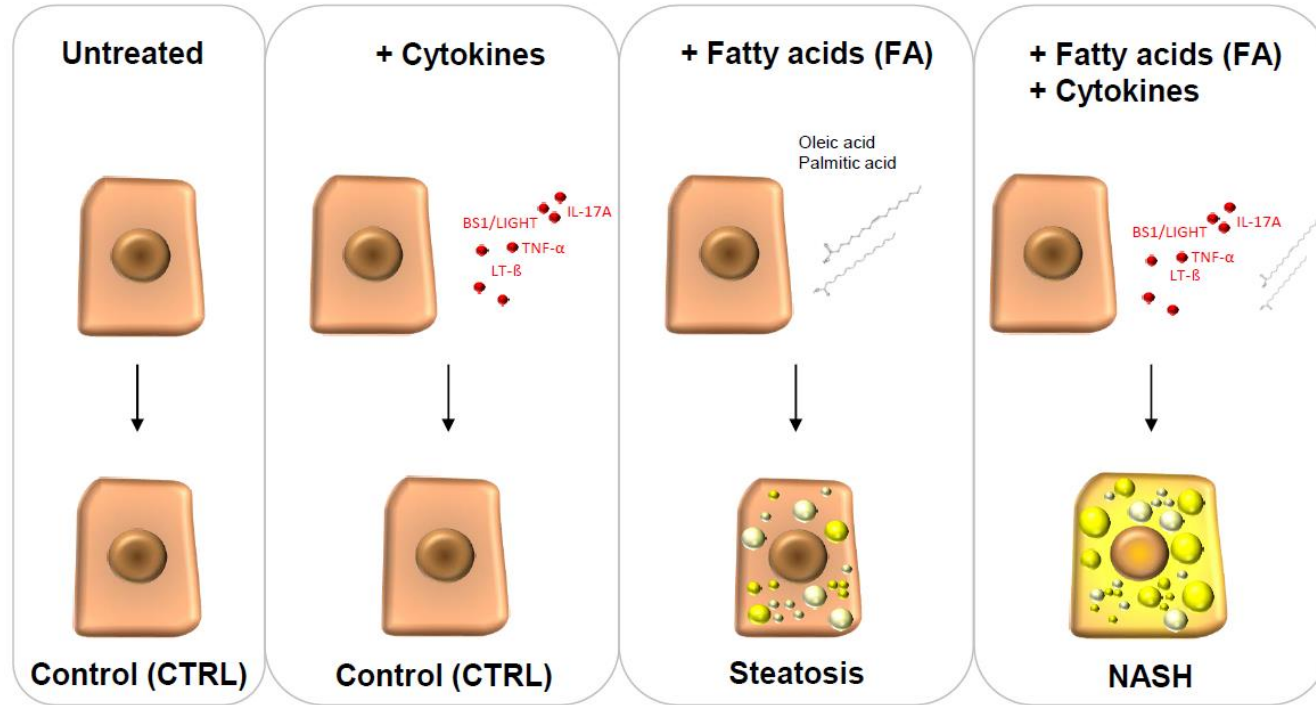
Metabolic and epigenetic state in steatosis



+ Fatty acids (FA) induce:

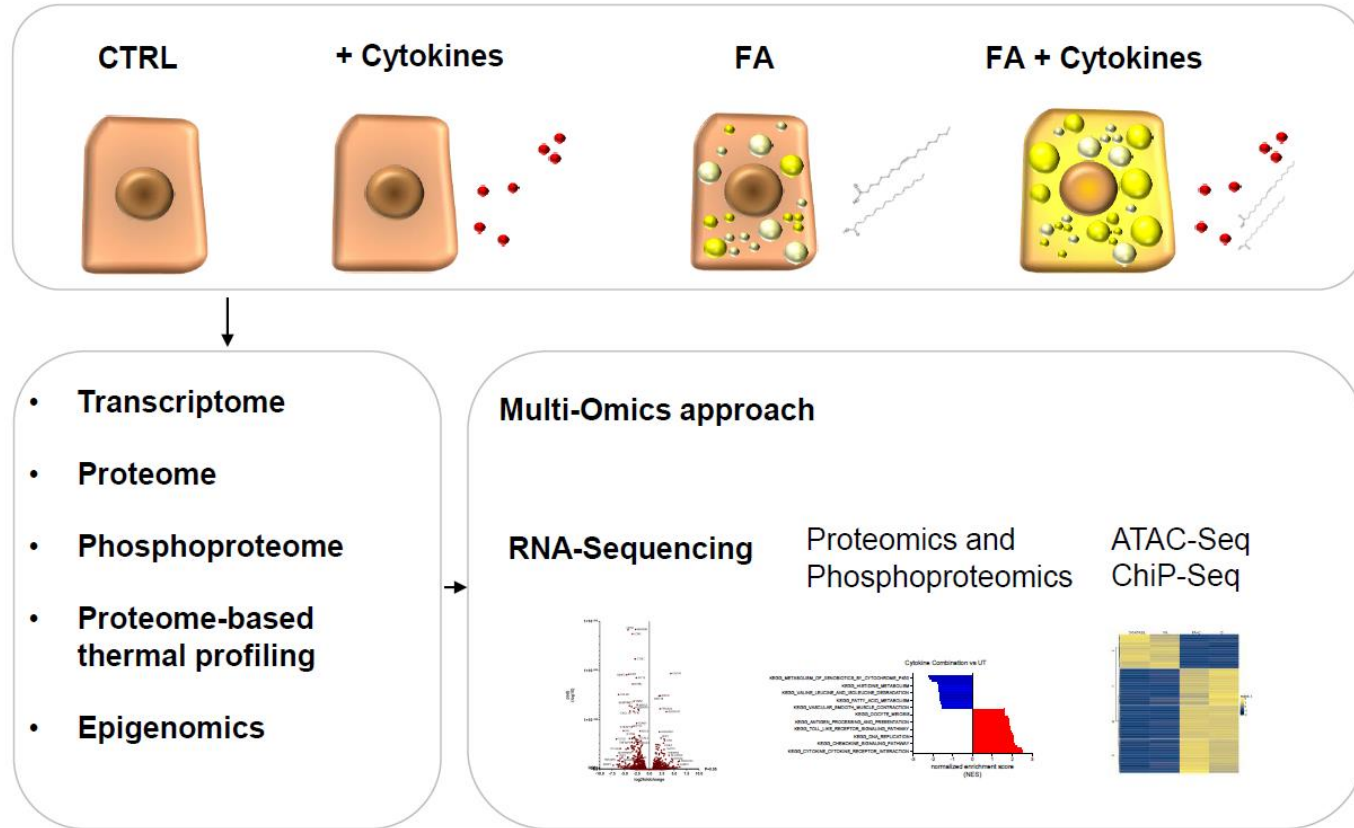
- **Histone hyperacetylation (H3K27ac),**
- FA- uptake, storage, and oxidation, regulated by **PPARα activation**

Inflammation triggered metabolic re-programming



MASH in vitro model to mimic different stages during disease progression

Inflammation triggered metabolic re-programming

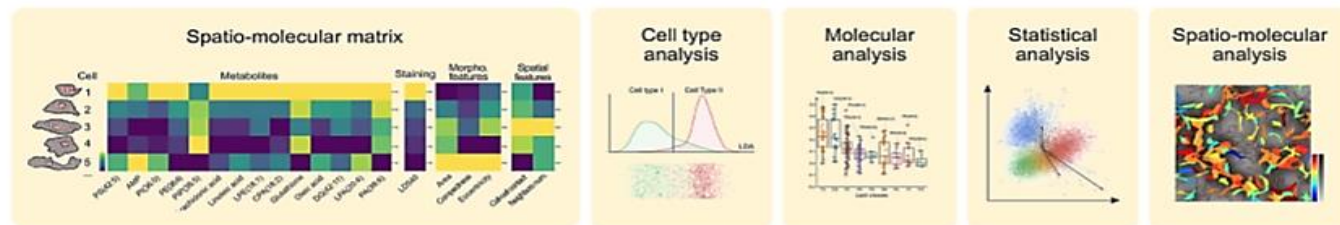
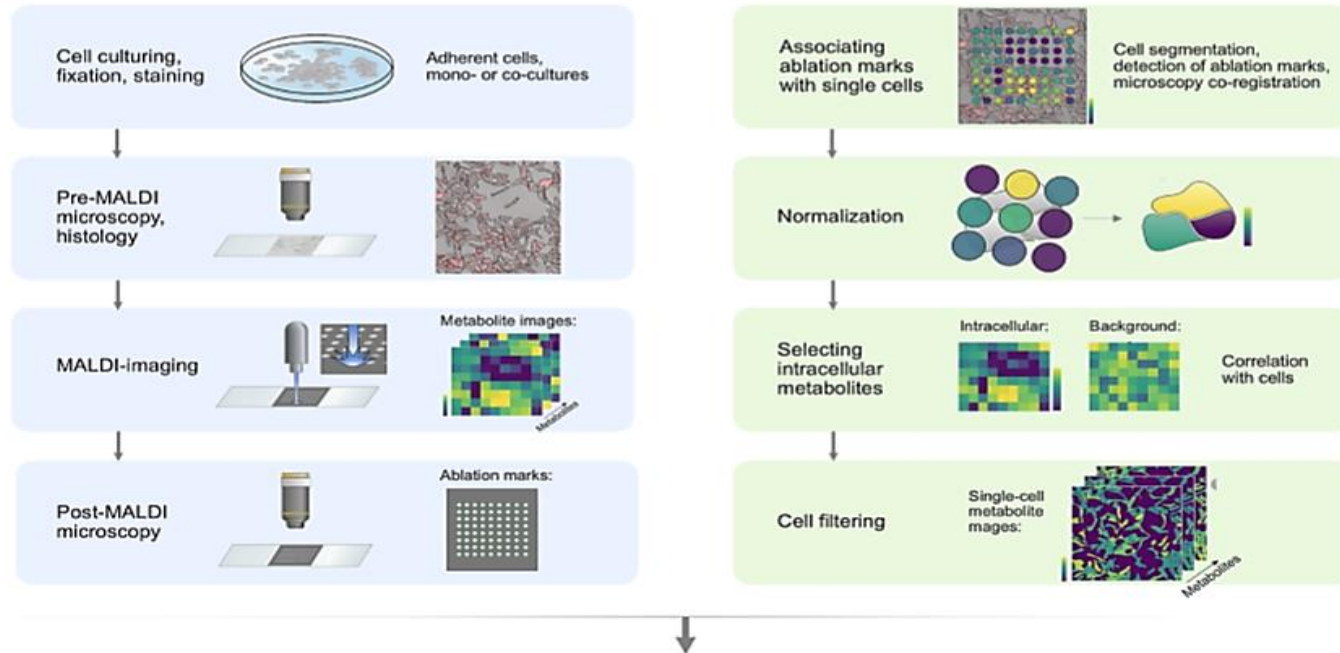


SpaceM: **Spatial** single-cell metabolomics

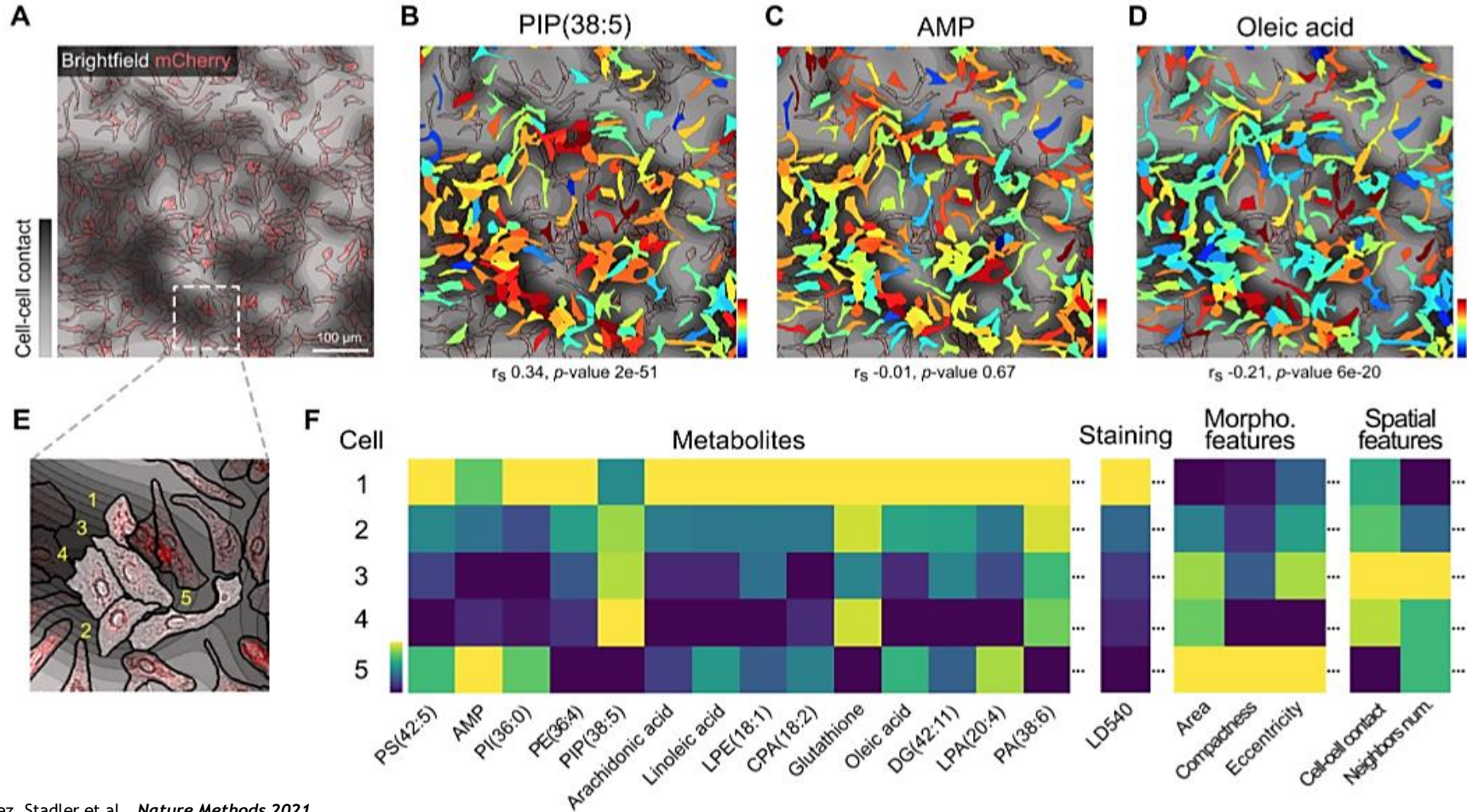
Experimental analysis



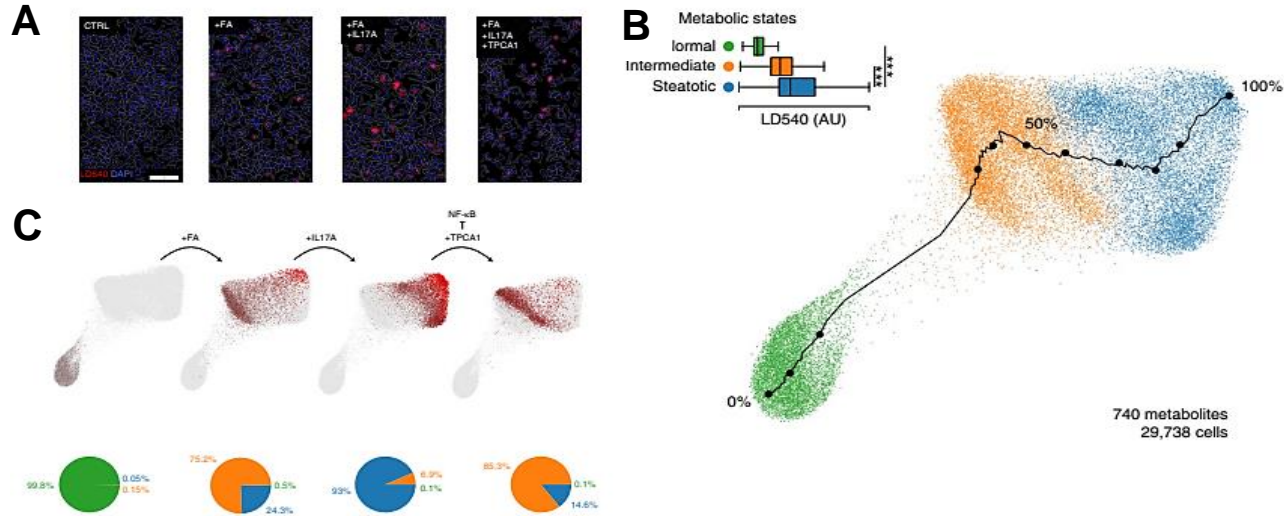
Data integration



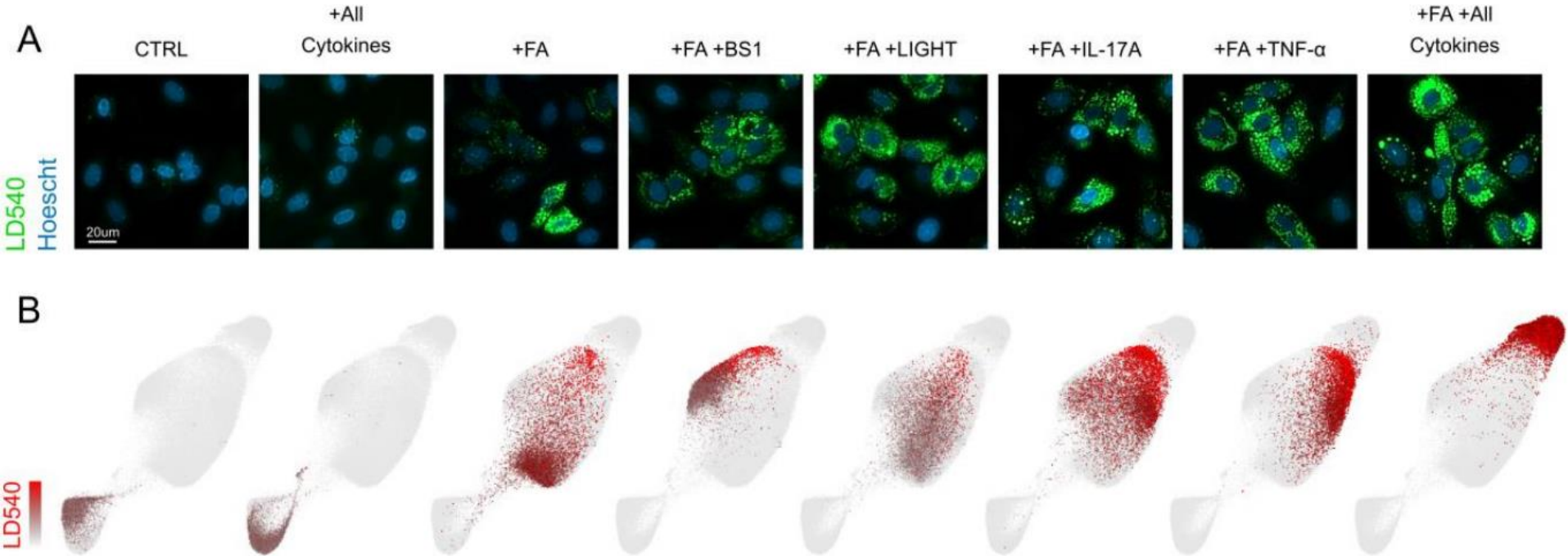
SpaceM: **Spatial** single-cell metabolomics



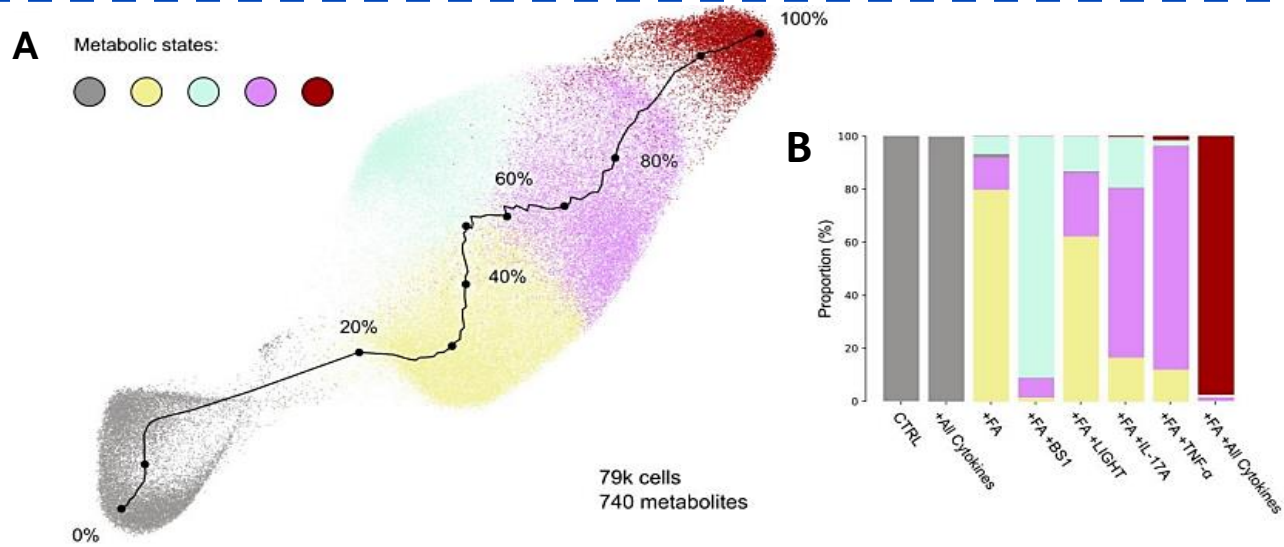
SpaceM: **Spatial** single-cell metabolomics



SpaceM: **Spatial** single-cell metabolomics



SpaceM: **S**patial single-cell metabolomics



SpaceM: **Spatial** single-cell metabolomics

SpaceM resolves individual cells in co-cultures

- **Single-cell resolution** for most of detected molecules

Lipids, fatty acids, metabolites

- Co-cultured cells metabolically intermix with their neighbours

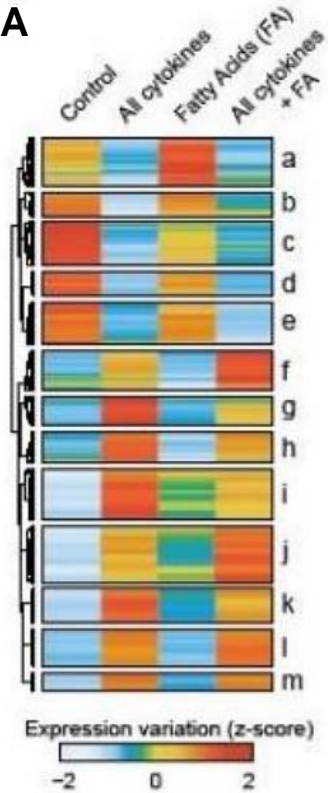
Intimate vicinity of immune cells to hepatocytes is needed to efficiently induce metabolic reprogramming

- **Spatial analyses in frozen tissue ongoing**

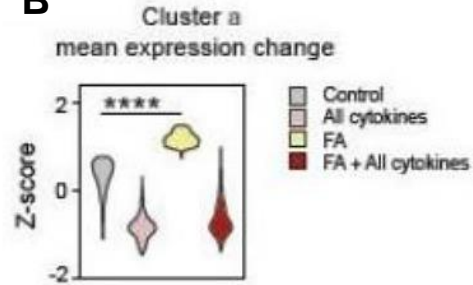


Epigenetic regulation of metabolism

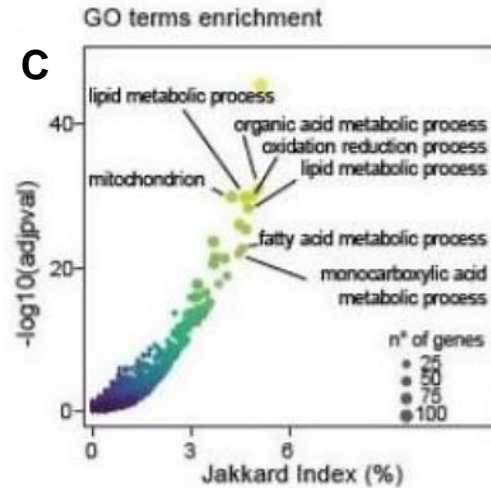
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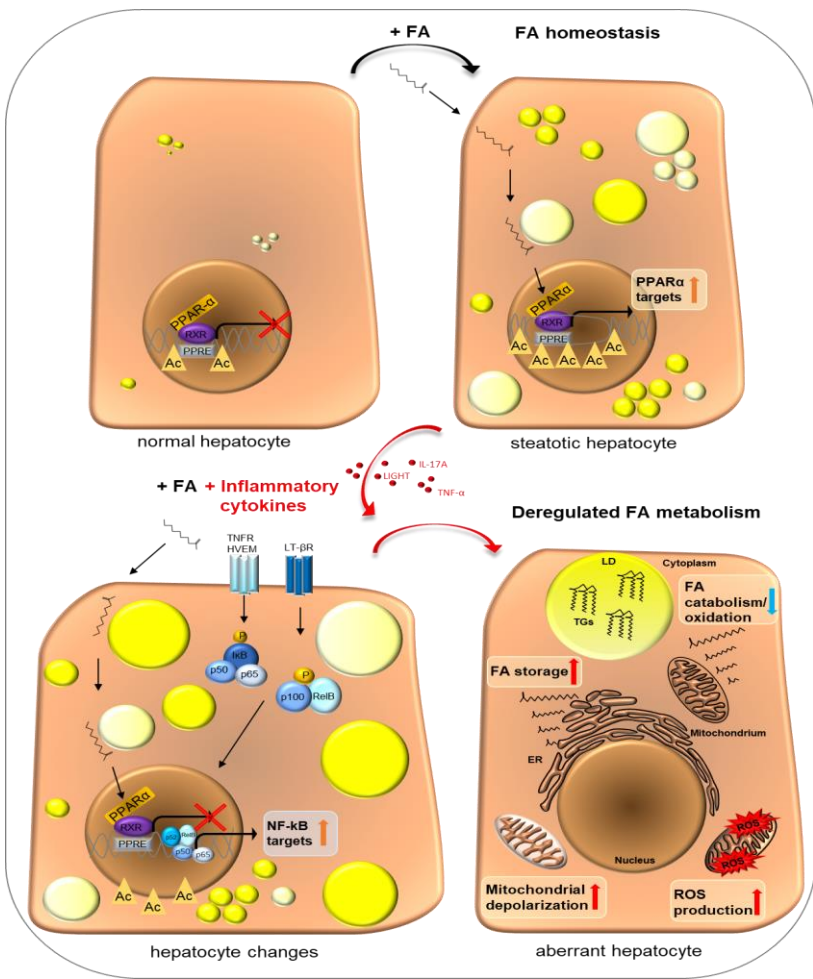


B



C





+ Fatty acids (FA) induce:

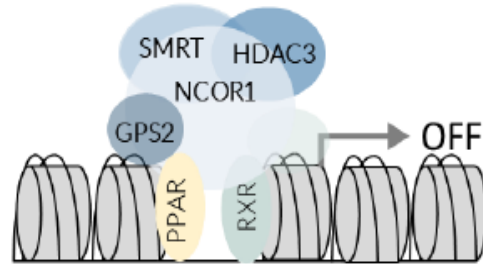
- **Histone hyperacetylation (H3K27ac),**
- **FA- uptake, storage, and oxidation, regulated by PPARα activation**

+ FA plus inflammatory cytokines

- **induce deacetylation and repress the expression of PPARα target genes - metabolic catastrophe**
- **exacerbate FA storage via NF-κB signalling**
- **ROS production▲, mitochondrial dysfunction▲, facultative apoptosis, DNA instability**

Epigenetic regulation of metabolism

Co-repressor complex

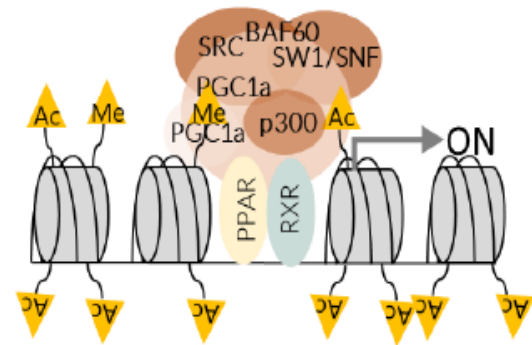


Genomic regulatory regions
(promoters or enhancers)

metabolites
hormones
chemicals



Co-activator complex



Histone modifications
(acetylation (Ac) or methylation (Me))








Intermittent fasting (IF) has emerged as a popular and effective intervention against metabolic diseases

Intermittent fasting:

Period of voluntary **abstinence** from intake of **foods and calorie dense liquids** irrespective of the total calories in non-fasted period.



IF 5:2 regimen

Monday	Tuesday	Wednesday	Thursday	Friday	Saturday	Sunday
						

A **5:2** intermittent fasting regimen **ameliorates MASH, fibrosis and subsequent liver cancer.**

IF 5:2 regimen



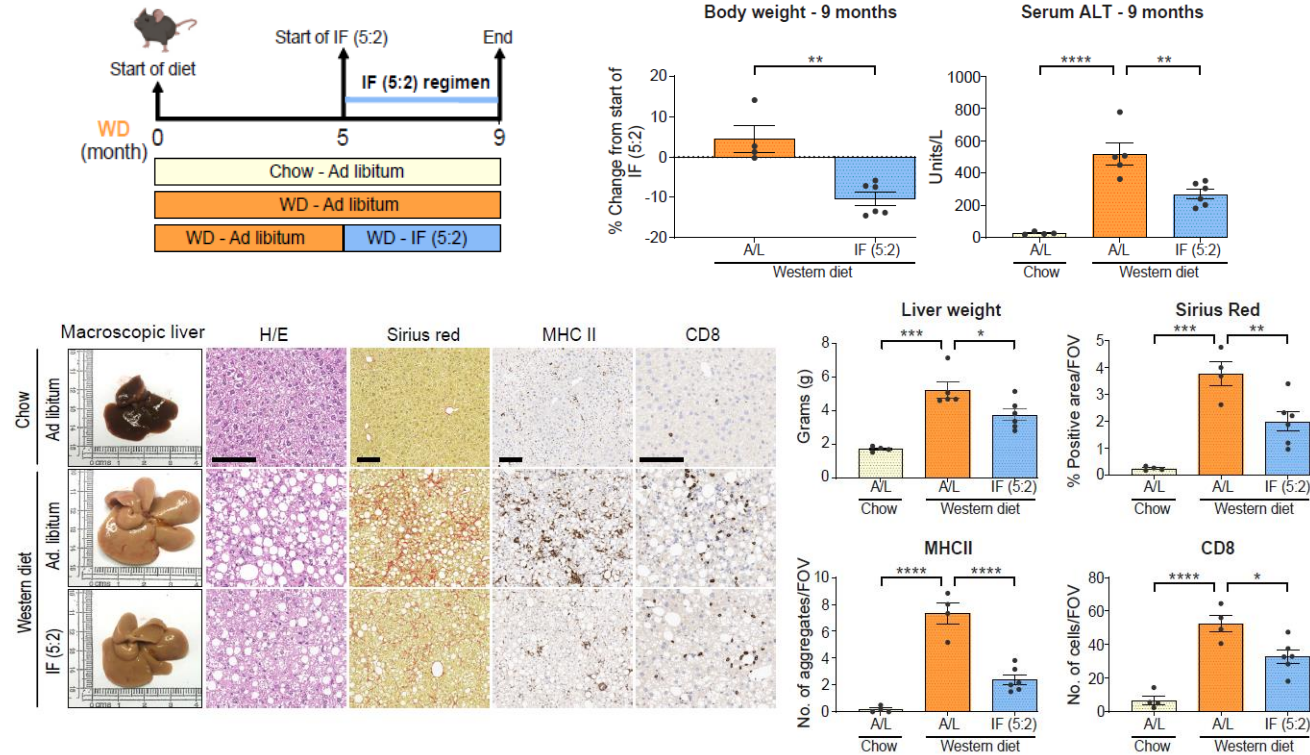
MASH and Liver Cancer



Gallage et al., *Cell Metabolism*, 2024

5:2 IF regimen **ameliorates** established MASH

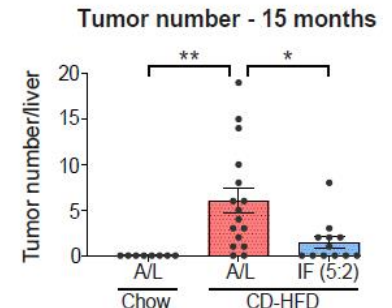
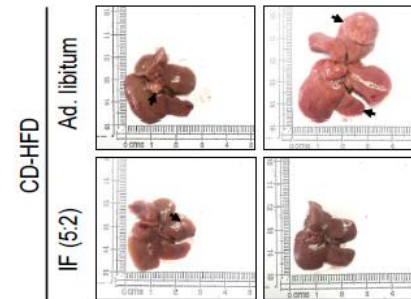
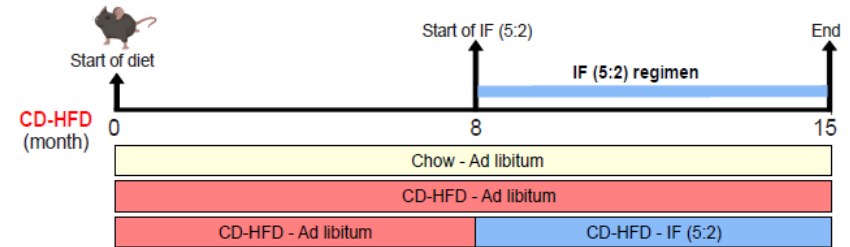
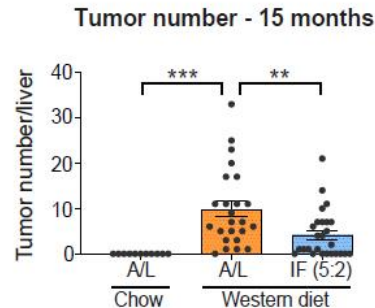
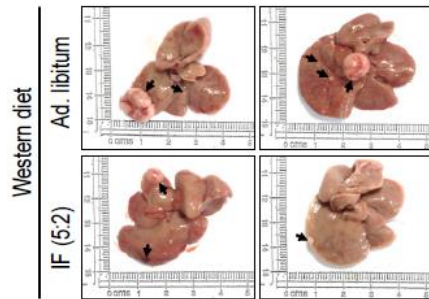
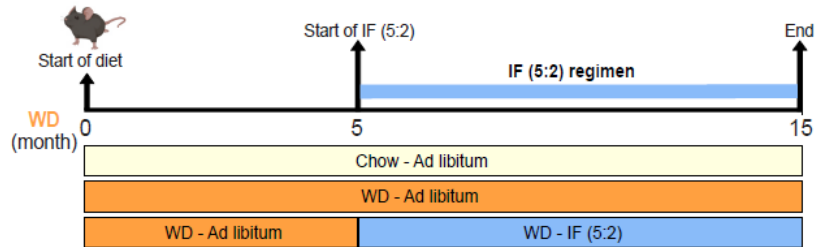
Can **IF** in a **therapeutic** approach **ameliorate** established **MASH**? i.e., possibility to translate to clinics.



IF 5:2 regimen **ameliorates established MASH in a **therapeutic** manner.**

5:2 IF regimen **blunts** subsequent HCC development

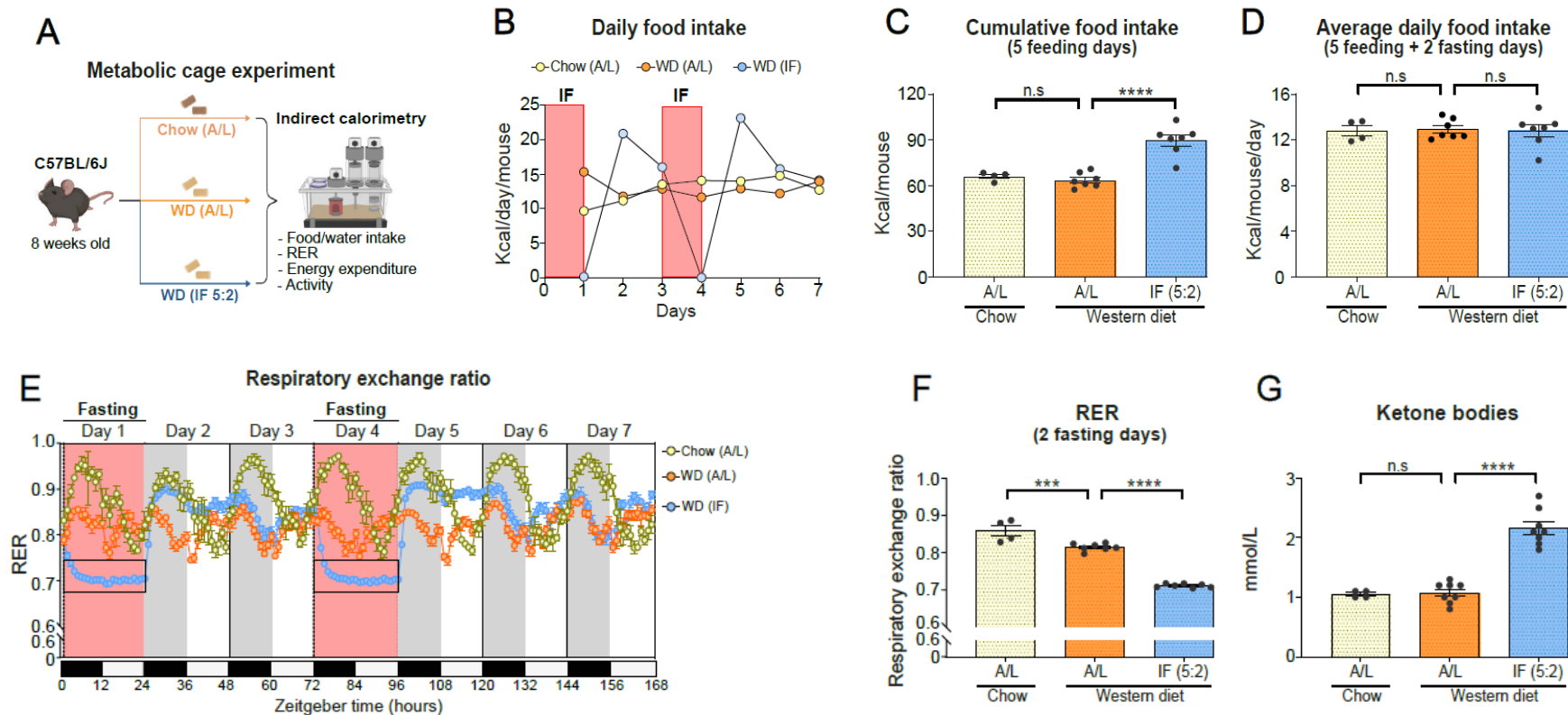
Can IF in a therapeutic approach blunt MASH to HCC transition?



IF 5:2 regimen **blunts** MASH-HCC transition in two distinct models of MASH.

Fasting-mediated benefits are independent of total calorie intake

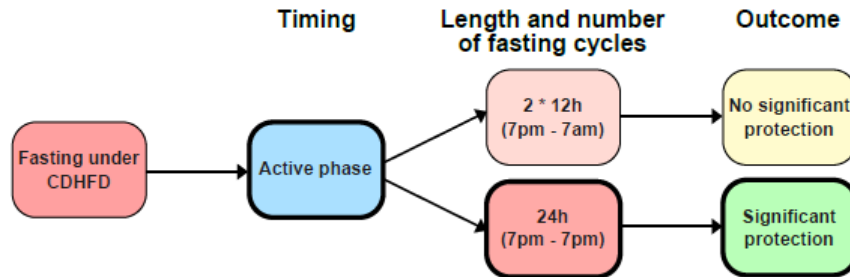
Does IF affect total calorie intake and systemic metabolism?



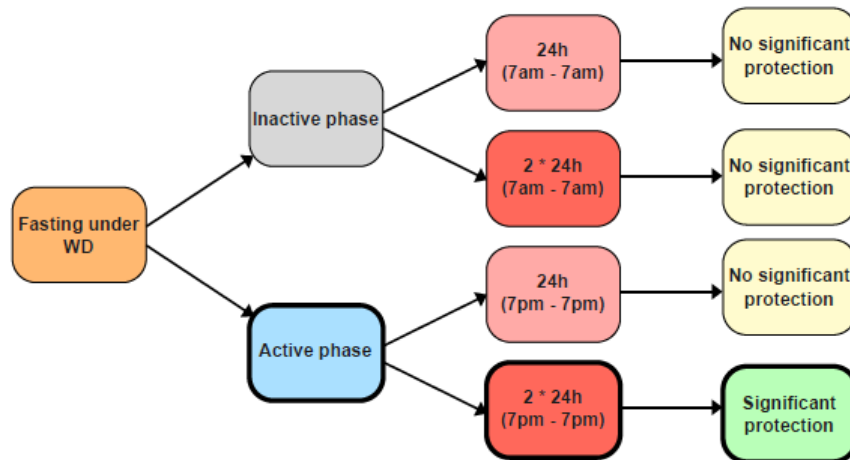
The timing, duration and number of fasting cycles influence the outcome

What constitutes an **effective** fasting regimen?

Mild MASH diet



Aggressive MASH diet

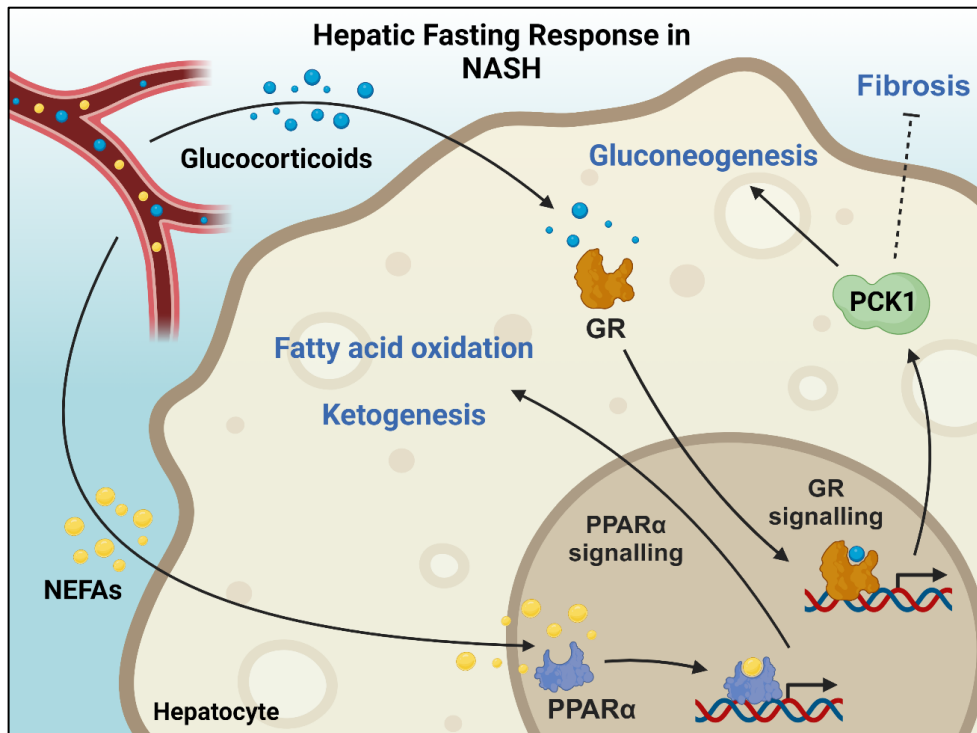


Four critical parameters:

1. **Timing** of fasting.
2. **Length** of fasting cycles.
3. **Number** of fasting cycles.
4. **Diet** composition.

Hepatic fasting response is orchestrated by a concerted effort of PPAR α and PCK1

Multiomic approach (transcriptomics, proteomics, metabolomics) and **GoF/LoF mechanistic experiments *in vivo*** to prove **causality**.



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- **Cynthia Lebeau**



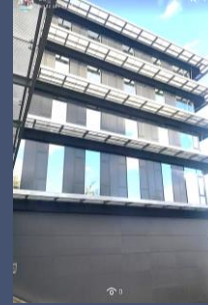
Deutsche Krebshilfe
HILFEN. FORSCHEN. INFORMIEREN.



European Research Council

The M3 Research Institute

Malignome & Metabolome & Microbiome



- Interested PIs, Postdocs, Ph.D. students are welcome!
- Germ free facility, Single cell technologies, Translational research
- Machine Learning Hub (40 Bio-informaticians)



**Universitätsklinikum
Tübingen**



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