



# miRNA and intrahepatic cell-cell cross talk in MASH progression

Pierre-Emmanuel RAUTOU

Inserm U1149, Centre de recherche sur l'inflammation, Paris

Service d'hépatologie, Hôpital Beaujon, Clichy, France

[pierre-emmanuel.rautou@inserm.fr](mailto:pierre-emmanuel.rautou@inserm.fr)



# Intrahepatic miRNAs in MASLD

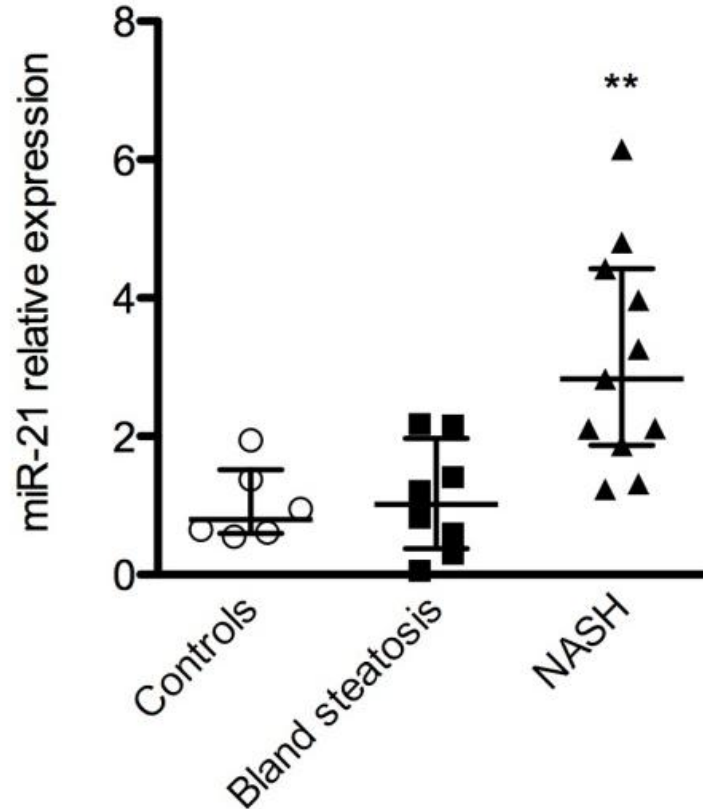
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- Liver miRNAs deregulated in MASLD
- Extracellular miRs
- miRNAs and therapeutic approaches

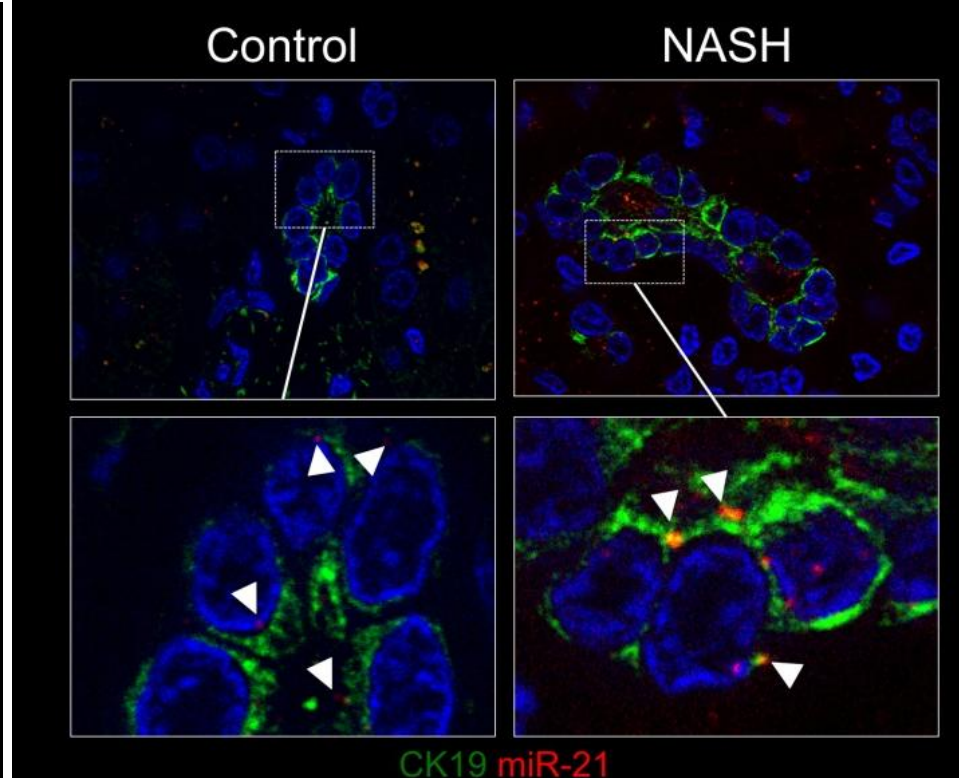
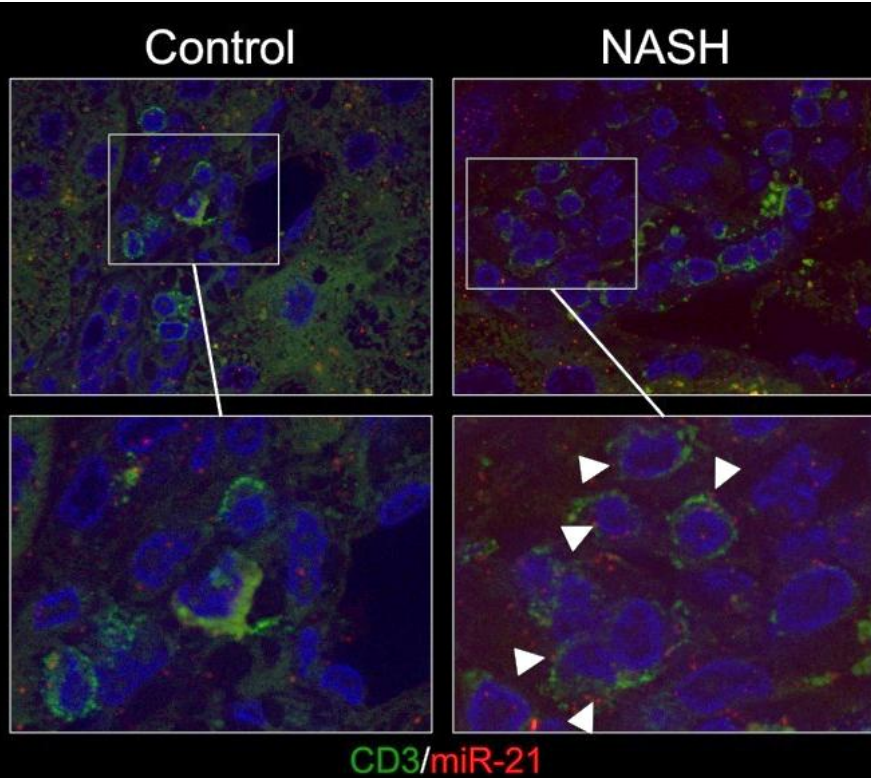
# Deregulated miRNAs in the liver in MASLD

miRNA	Expression	Reference (PMID)
miR-122	↓	19030170
miR-34a	↑	19030170, 30142428
miR-33	↑	27669236
miR-21	↑	19030170, 26338827
miR-192	↑	24973316, 30142428
miR-375	↓	19030170, 30142428, 26874844
miR-146b	↑	19030170, 28119530
miR-221/222	↑	19030170, 22267590
miR-132	↑	28381526
miR-181b	↑	19030170
miR-422	↓	28119530
miR-139	↓	28119530

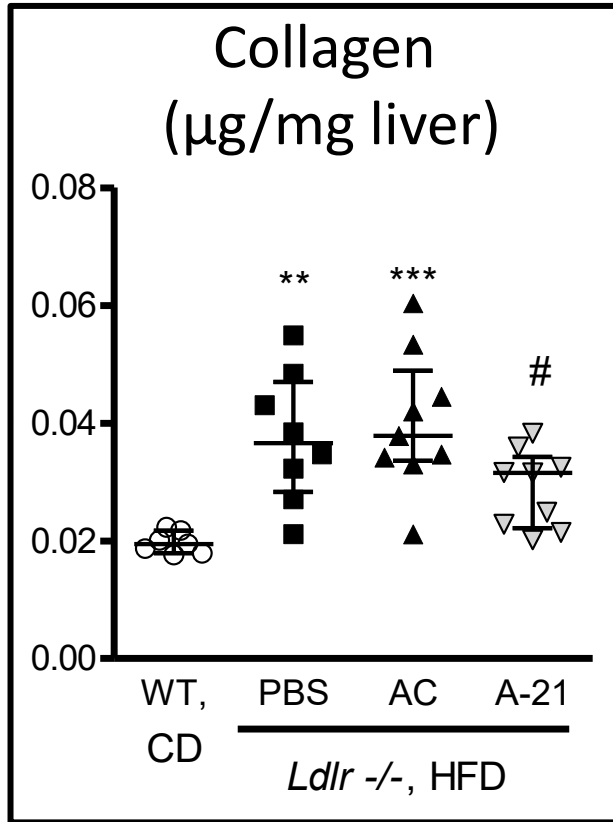
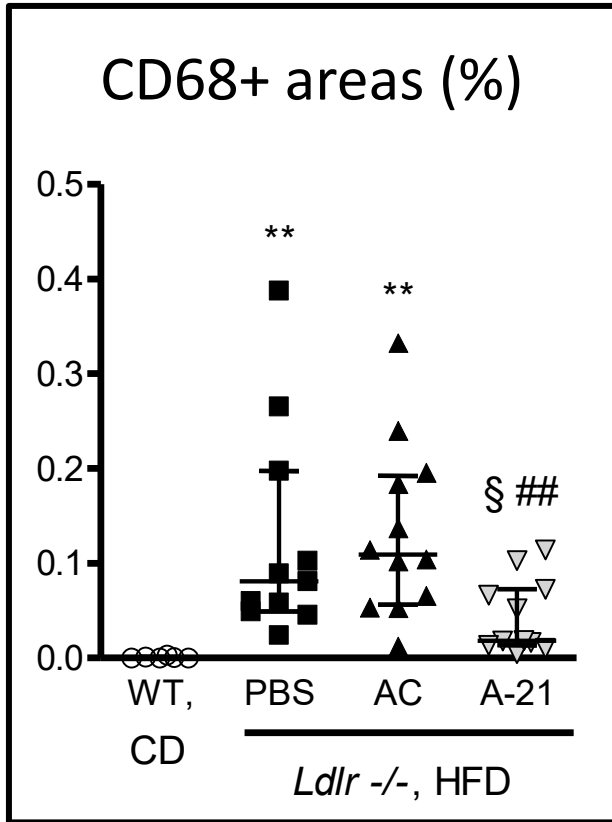
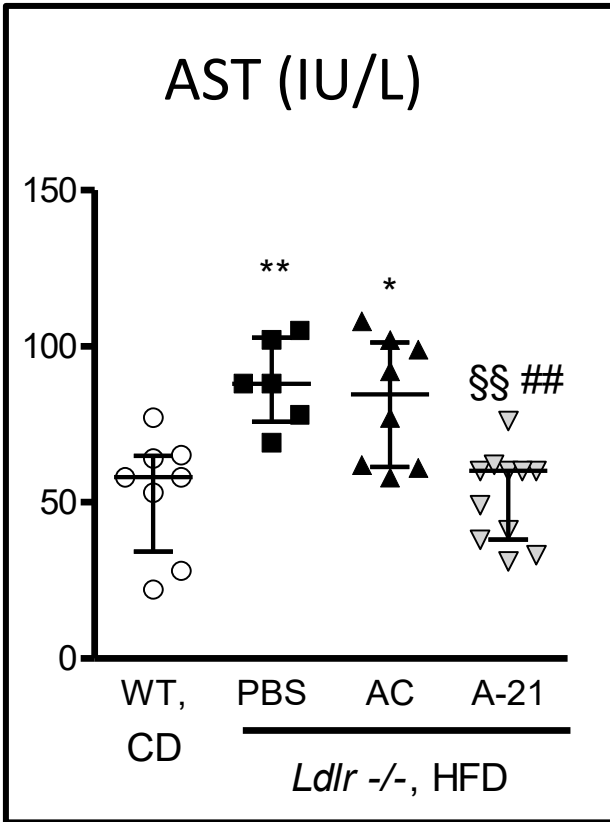
# miR-21 is Overexpressed in the Liver of Patients With MASH Primarily in Inflammatory Cells



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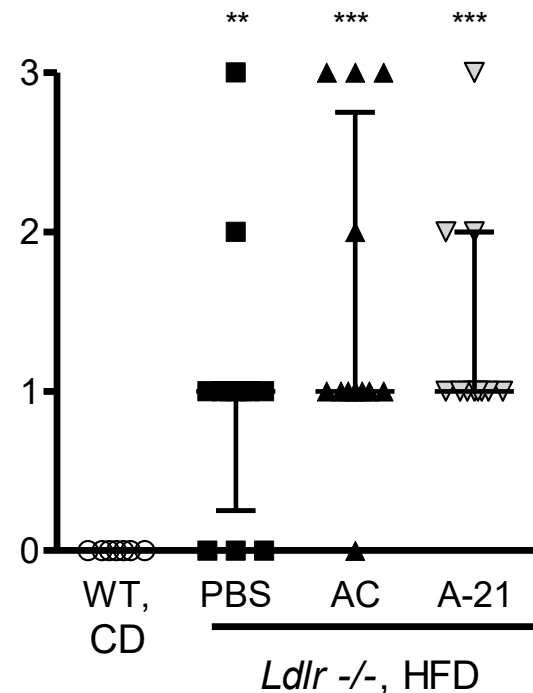
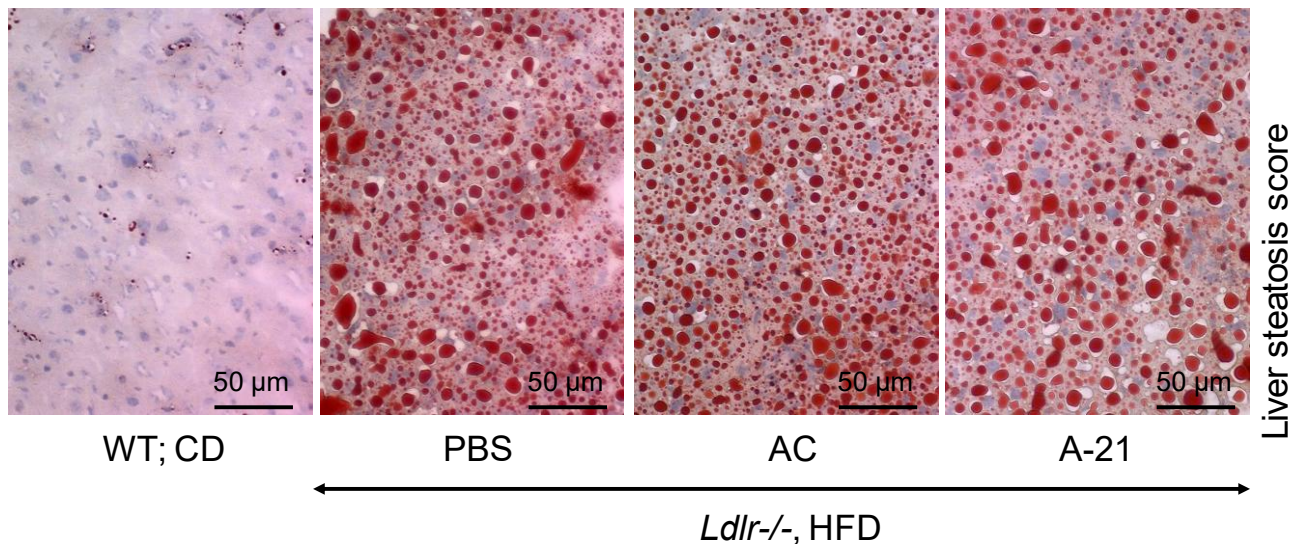


# *Ldlr*<sup>-/-</sup> mice under HFD treated with antagomir-21



**Antagomir-21 reduces liver injury, inflammation and fibrosis**

# Ldlr<sup>-/-</sup> mice under HFD treated with antagomir-21



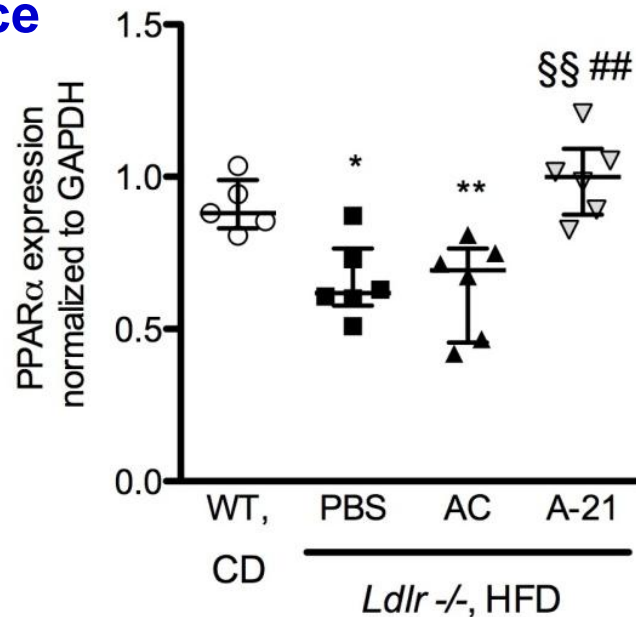
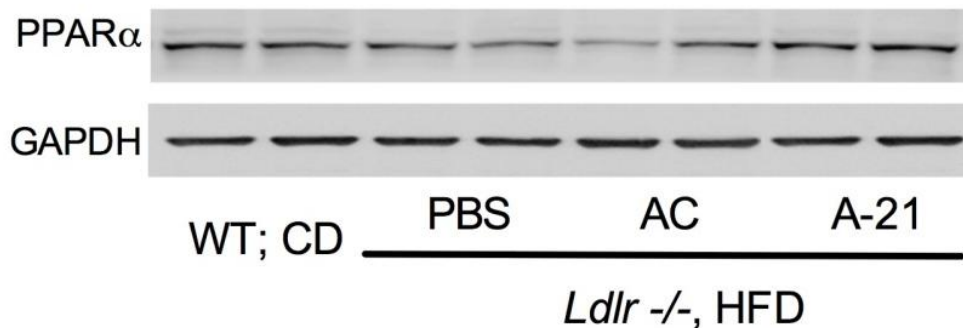
**... but not Liver Steatosis**

**Similar results in *miR-21*<sup>-/-</sup> mice fed MCD**



# PPAR $\alpha$ is responsible for miR-21 effects in MASH

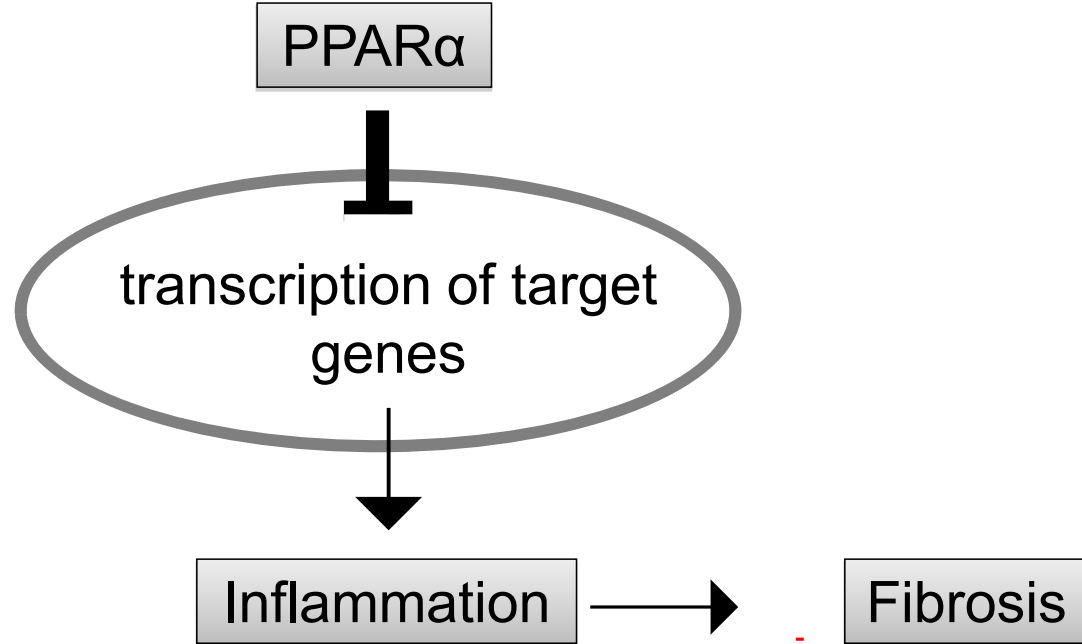
## PPAR $\alpha$ expression in AntagomiR-21 treated mice



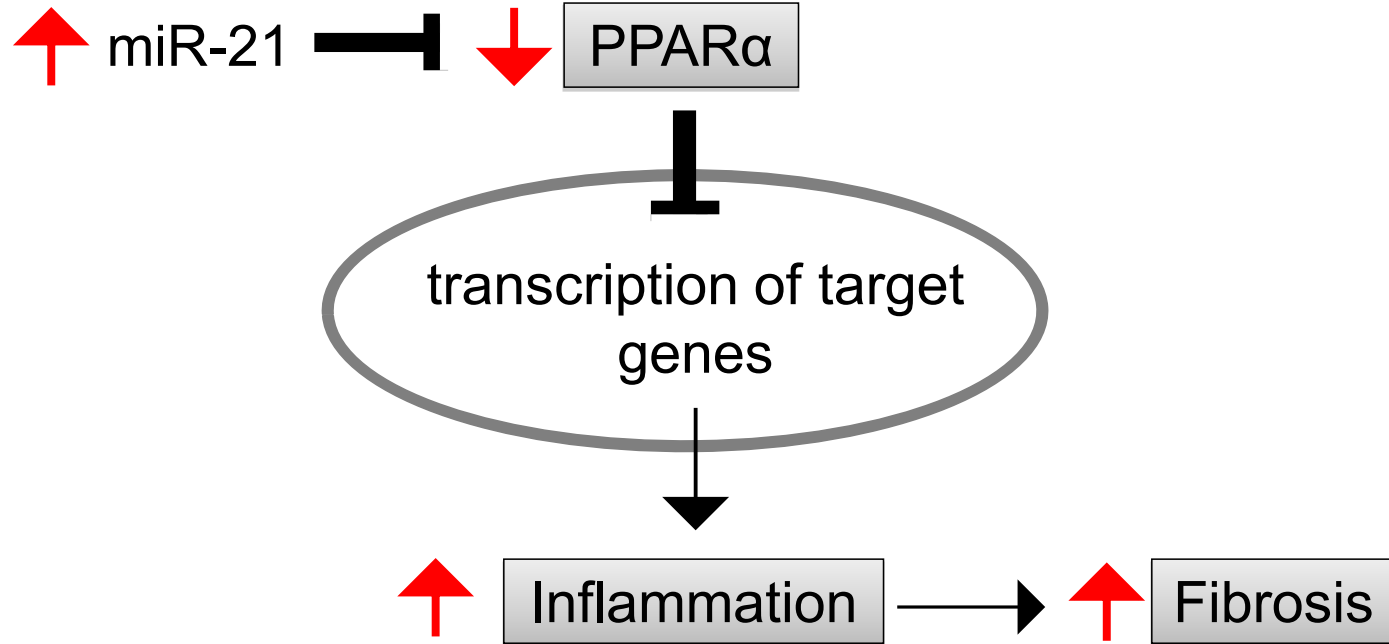
Similar results in *miR-21*<sup>-/-</sup> mice fed MCD



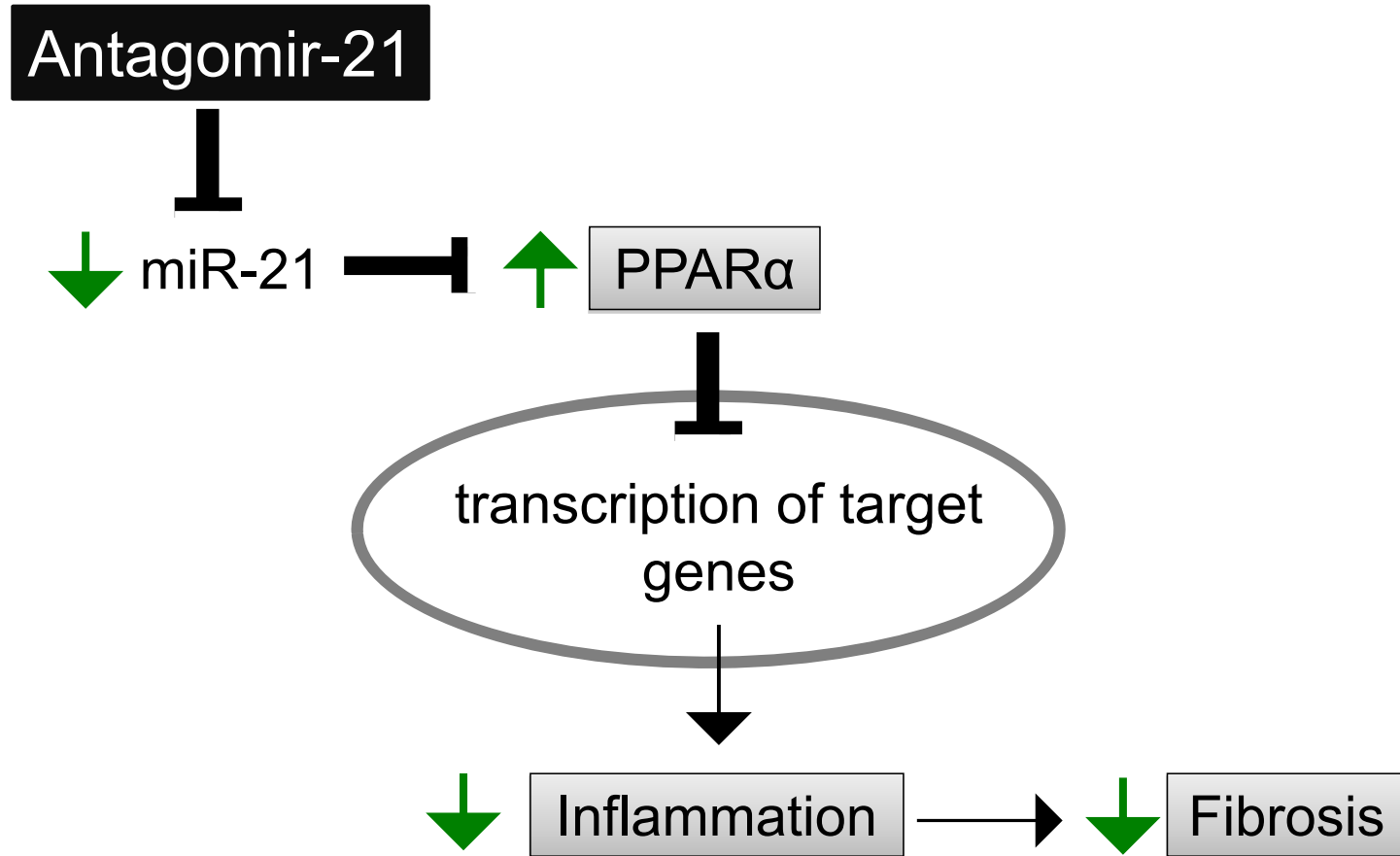
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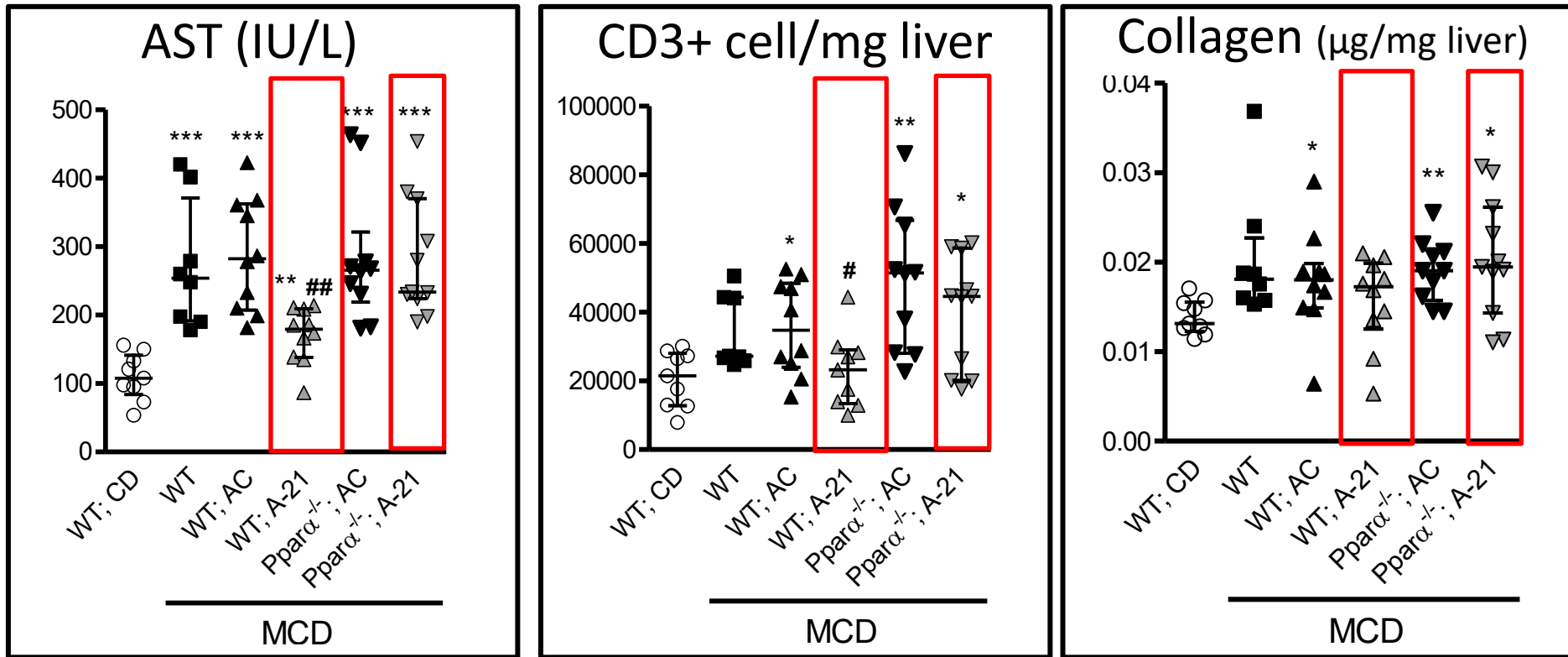
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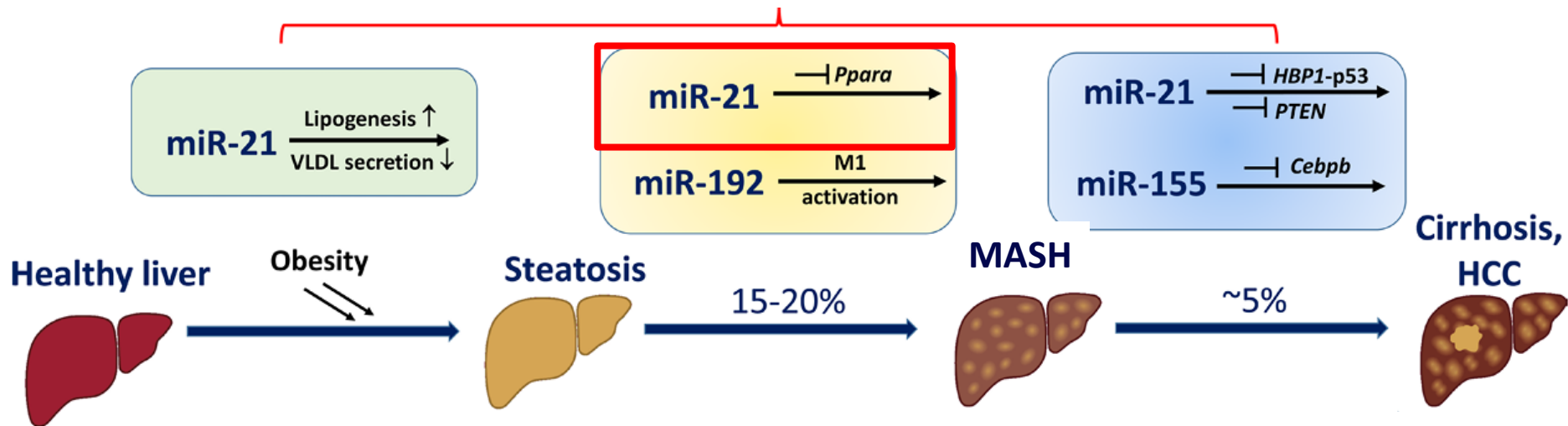
# PPAR $\alpha$ is responsible for miR-21 effects in MASH



**Antagomir-21 Does not reduce Liver Injury, Liver Inflammation and Liver Fibrosis**

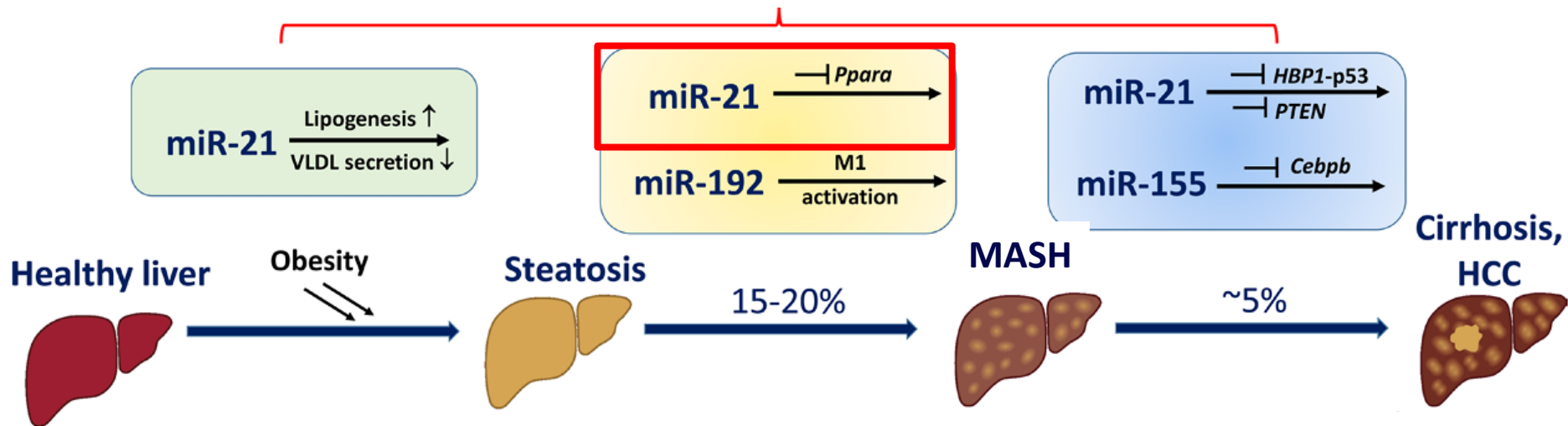
# Roles of microRNAs in the progression of MASLD

miRNA promote MASLD progression



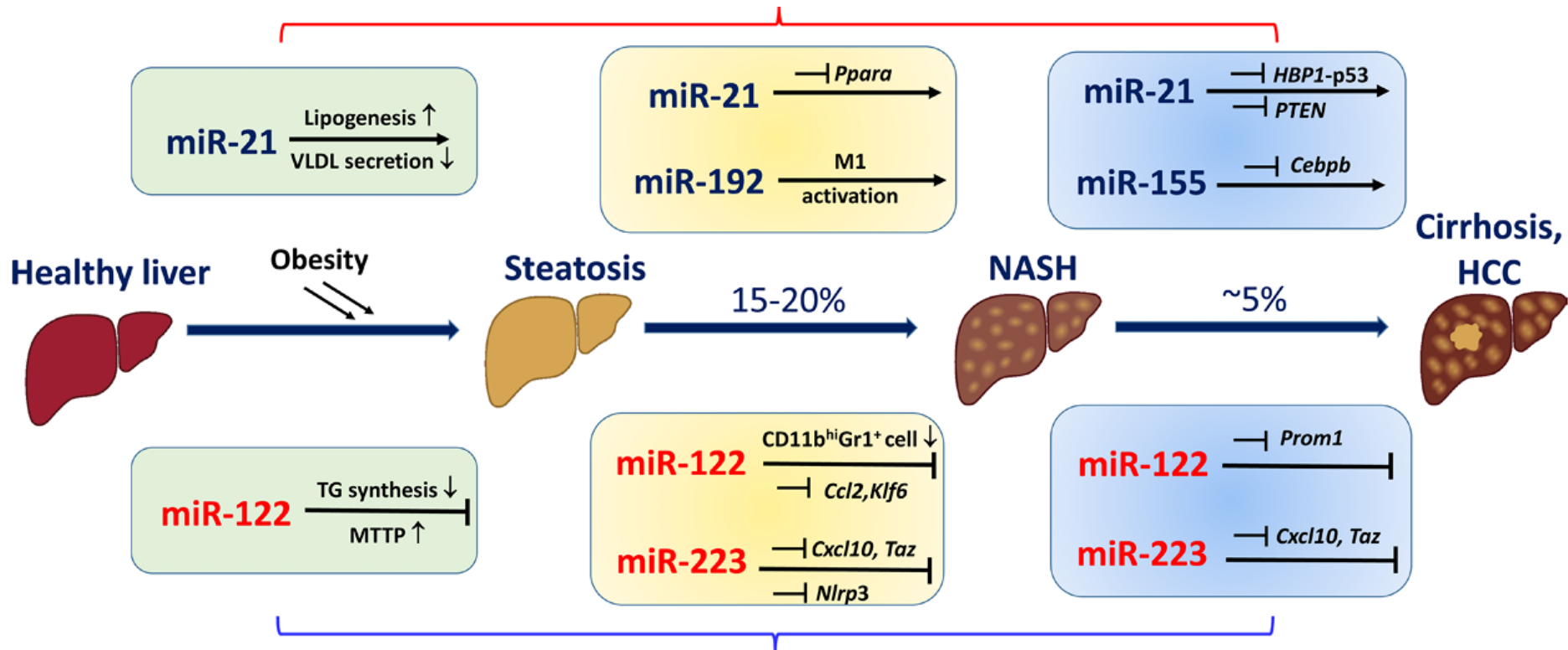
# Roles of microRNAs in the progression of MASLD

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# Roles of microRNAs in the progression of MASLD

miRNA promote MASLD progression



miRNA inhibit MASLD progression

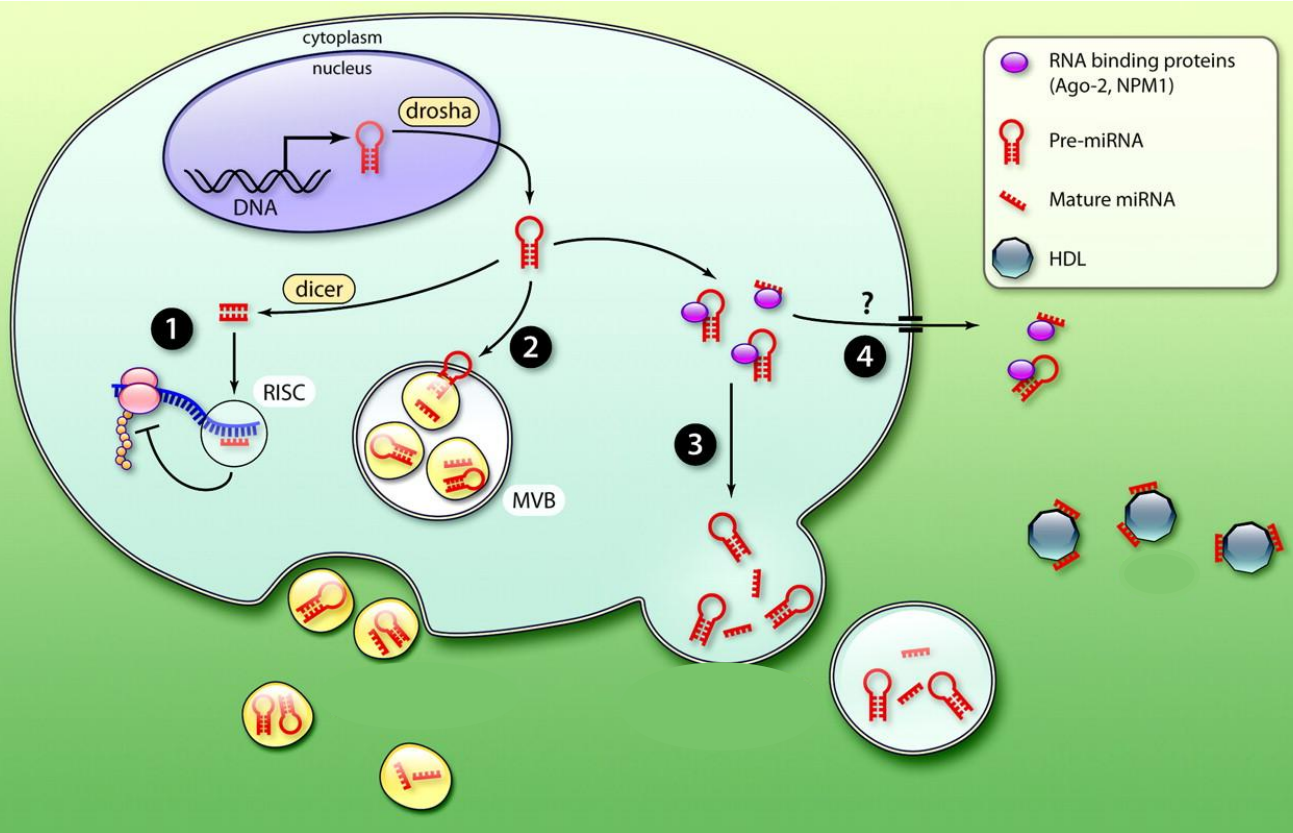


# Intrahepatic miRNAs in MASLD

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# Extracellular miRNAs

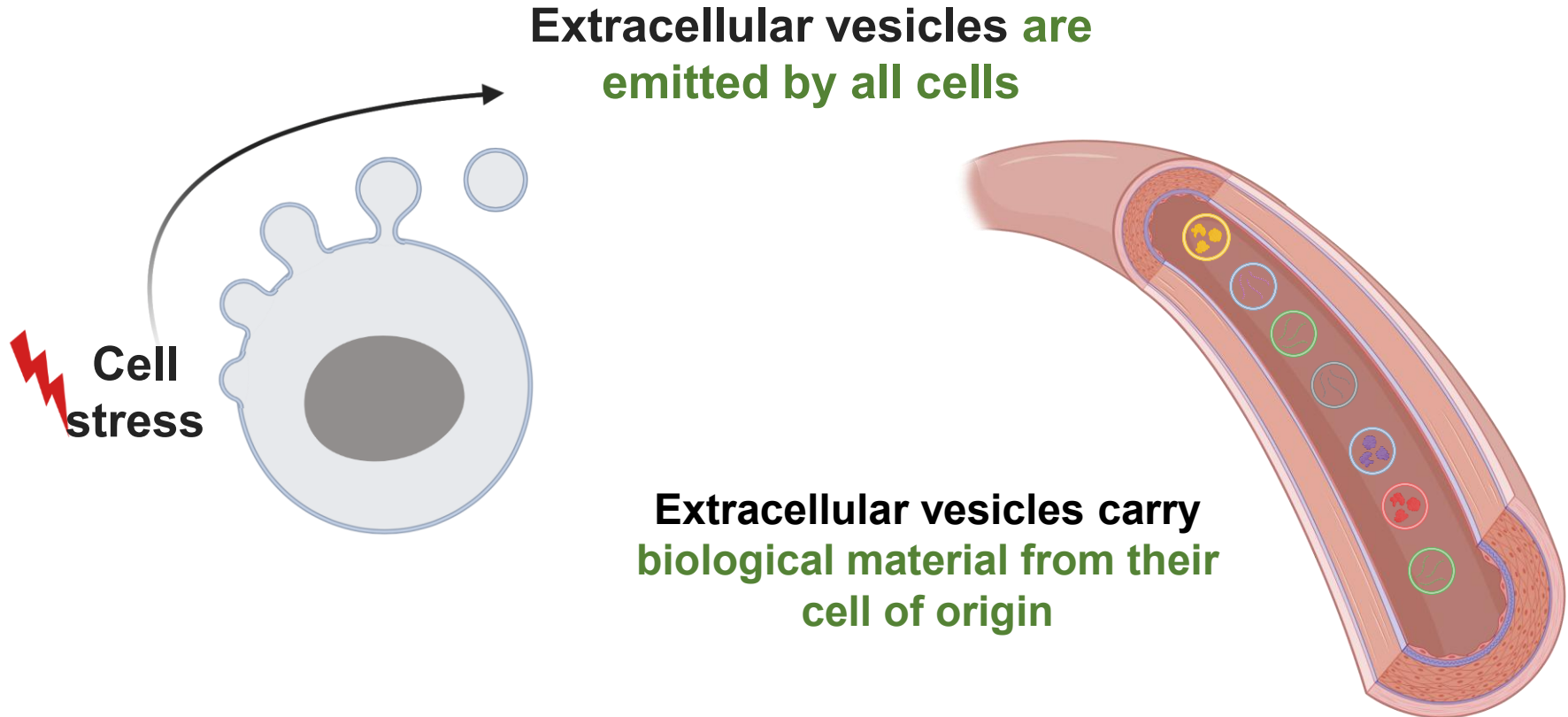


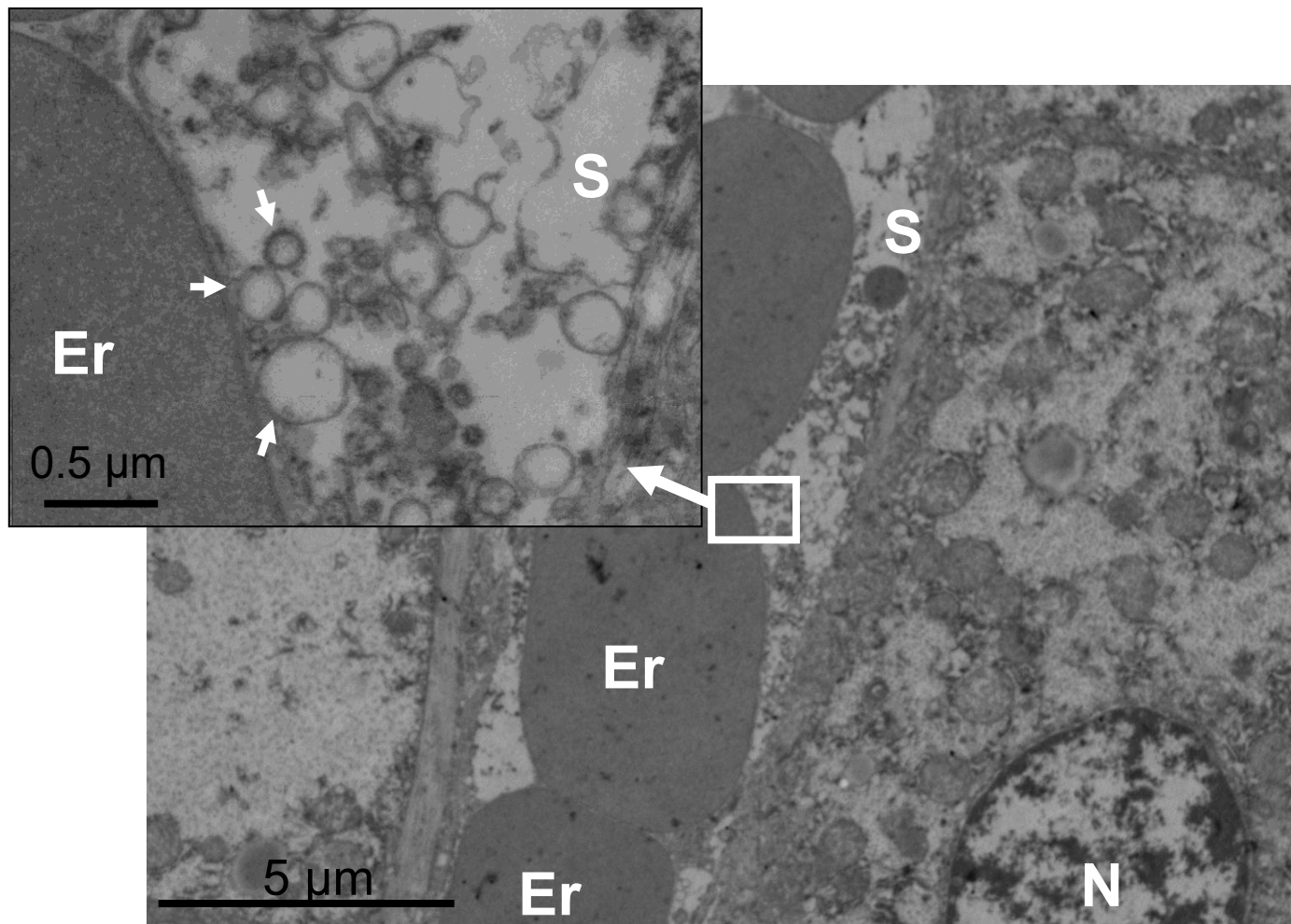
RNA binding  
proteins

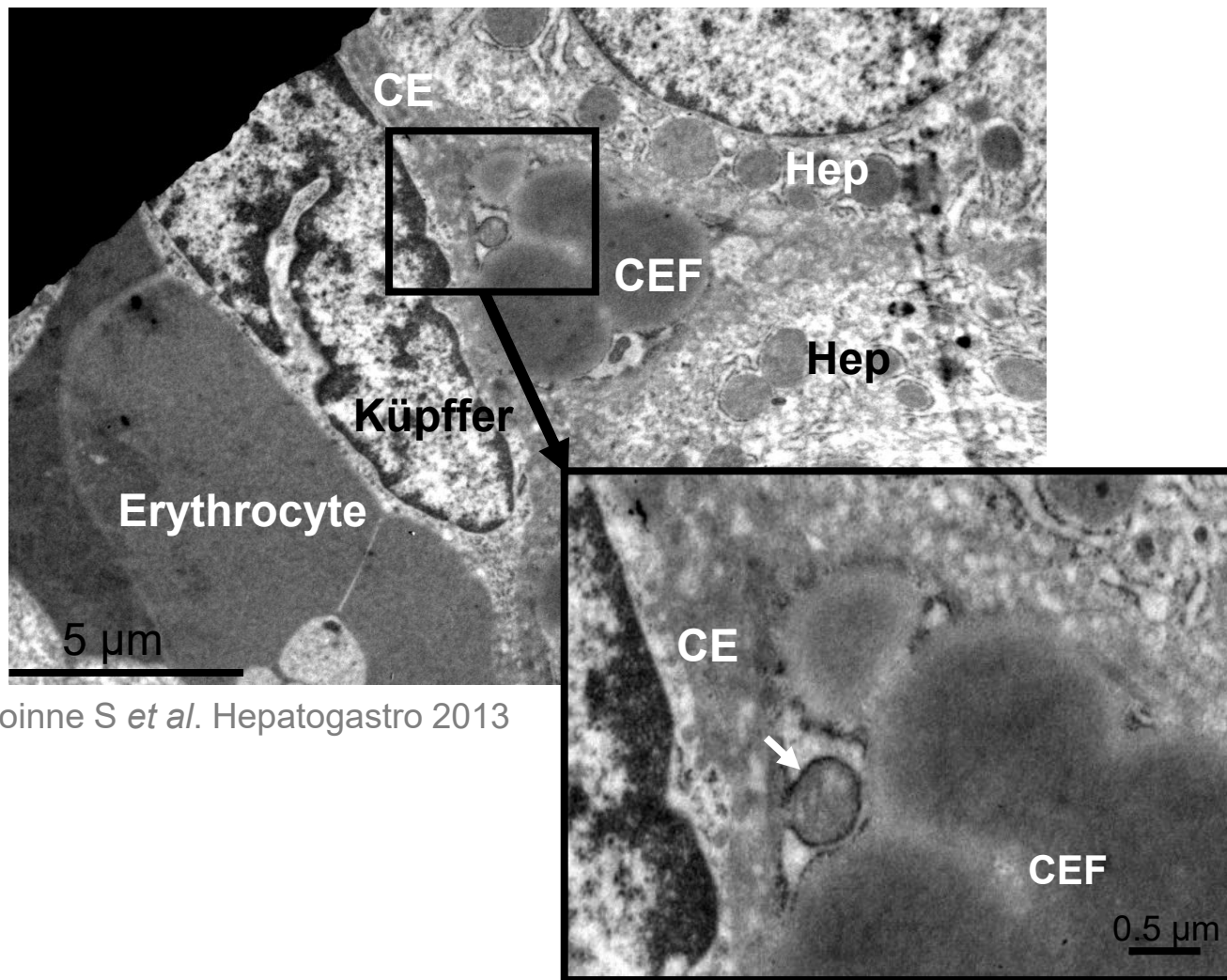
HDL

Extracellular  
vesicles

# Extracellular vesicles

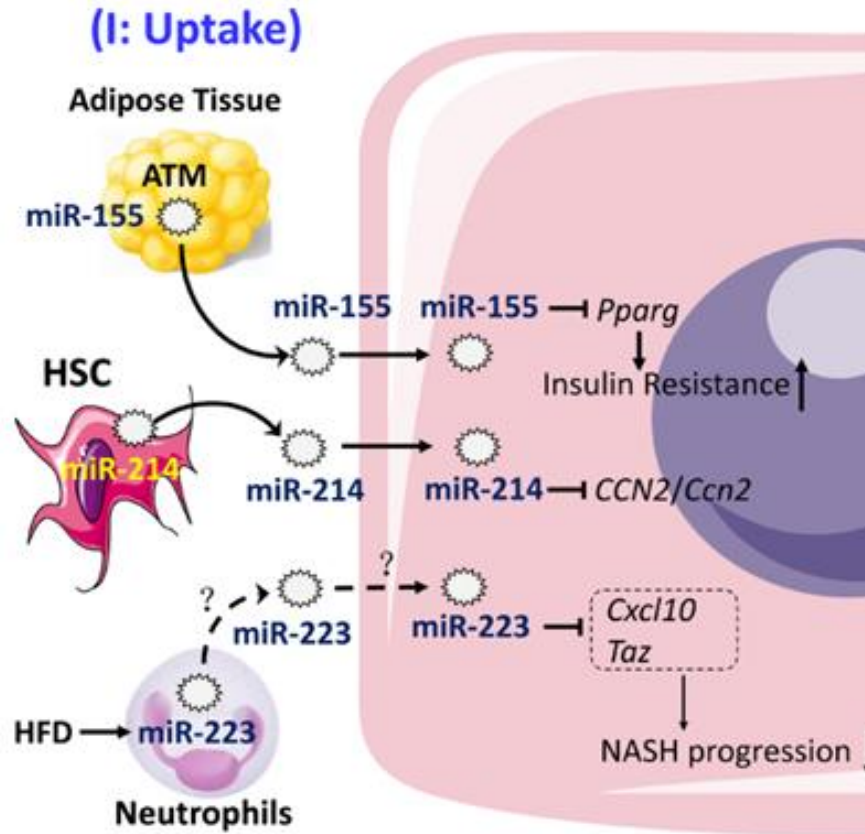




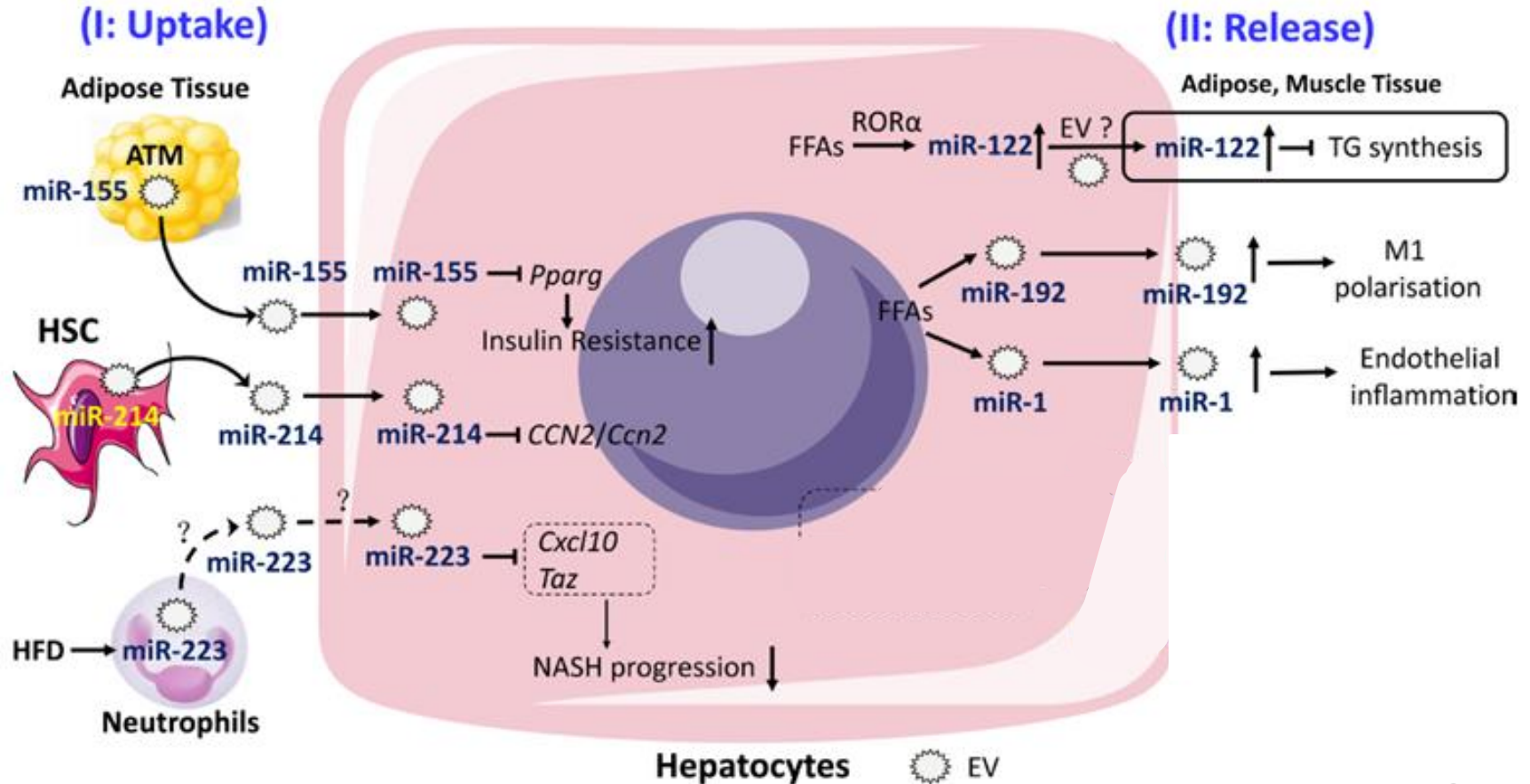


Lemoine S *et al.* Hepatogastro 2013

# Hepatocytes take up and release EV microRNAs



# Hepatocytes take up and release EV microRNAs



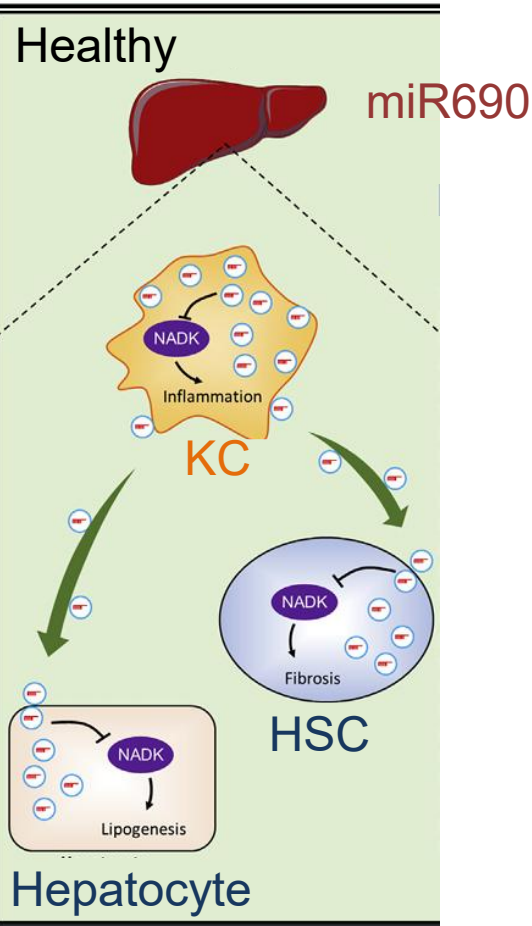


# Intrahepatic miRNAs in MASLD

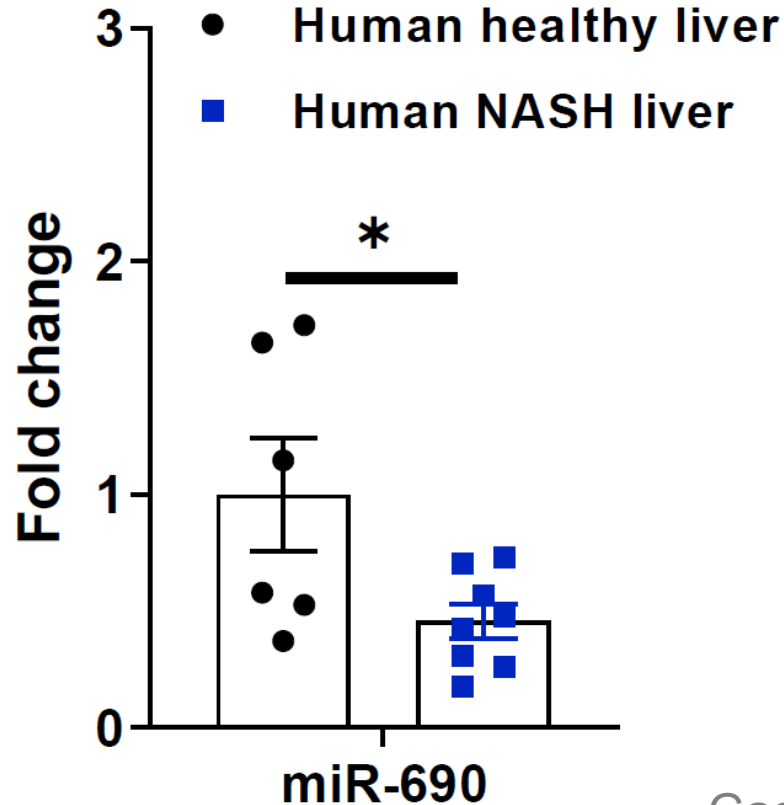
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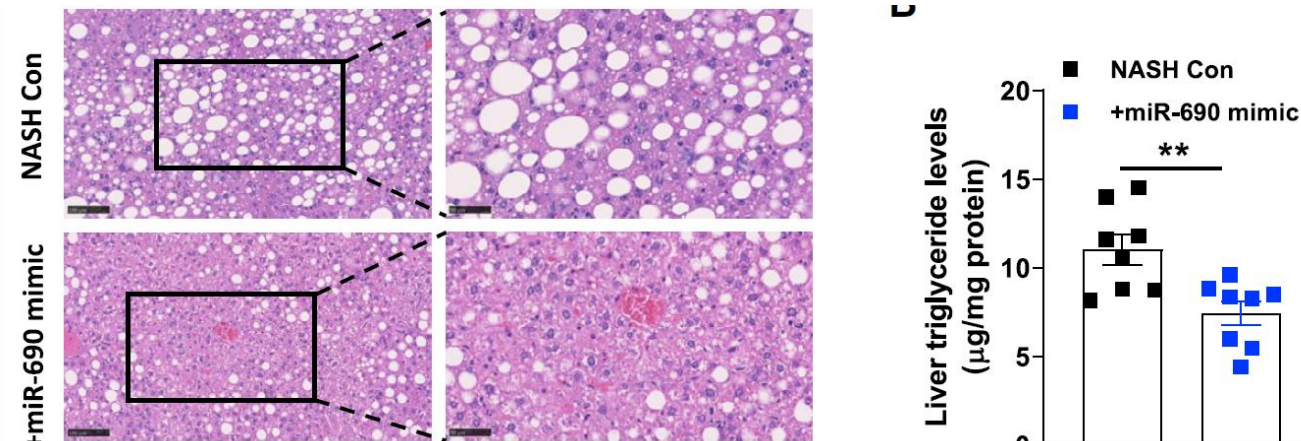
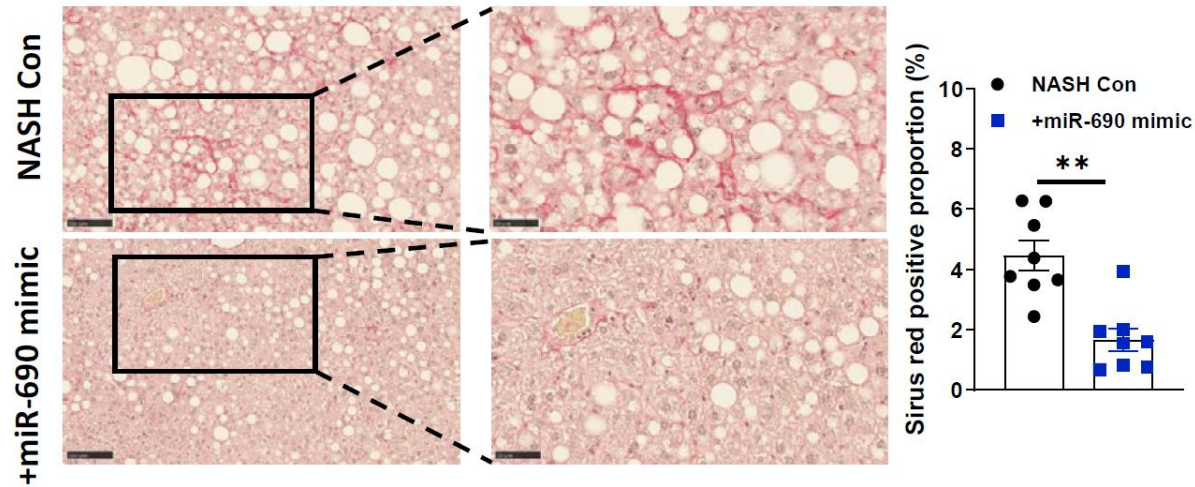
# MicroRNAs: towards new therapeutic options



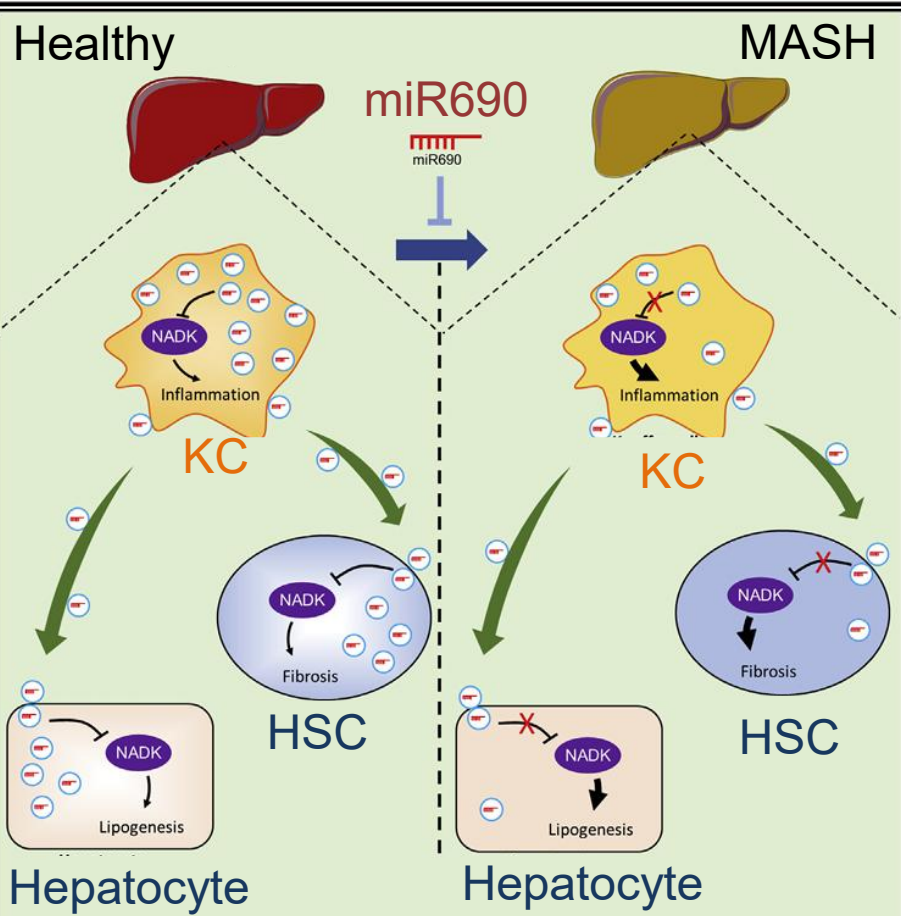
# MicroRNAs: towards new therapeutic options



# MicroRNAs: towards new therapeutic options



# MicroRNAs: towards new therapeutic options



**MiR-690 ttt in MASH:**

- Inhibits NAD kinase
- ↓ fibrosis and steatosis
- restore specific Kupffer cell functions

# Conclusion: Intrahepatic miRNAs in MASLD

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- miRNA regulate physiological and pathological liver functions
- miRNAs = intercellular communication between hepatocytes and other types of cells via extracellular vesicles
- miRNA may base therapy for liver diseases





**Inserm**  
Institut national  
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Université  
Paris Cité



Hepatology unit, Beaujon Hospital  
Reference center for vascular liver diseases



Inserm U1149 [www.rautoulab.com/](http://www.rautoulab.com/)  
Team "vessels in liver diseases"



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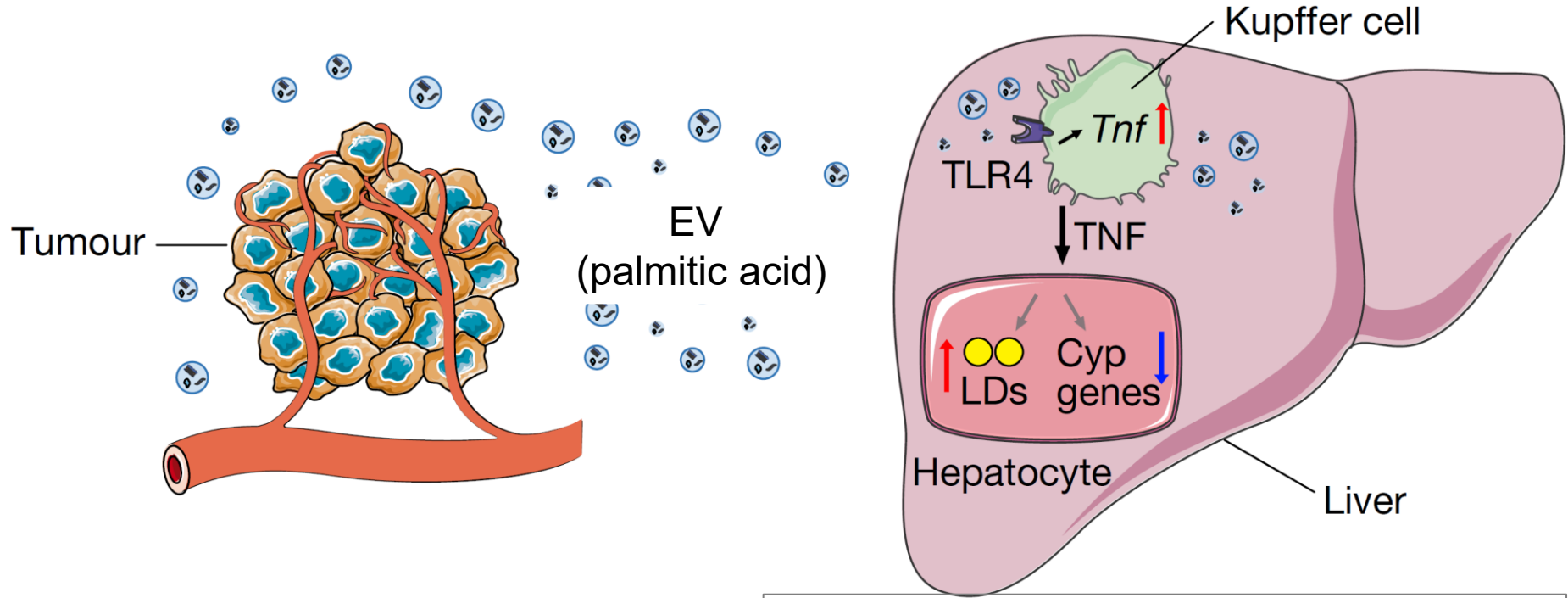
Les Programmes Hospitaliers  
de Recherche Clinique  
(PHRC)



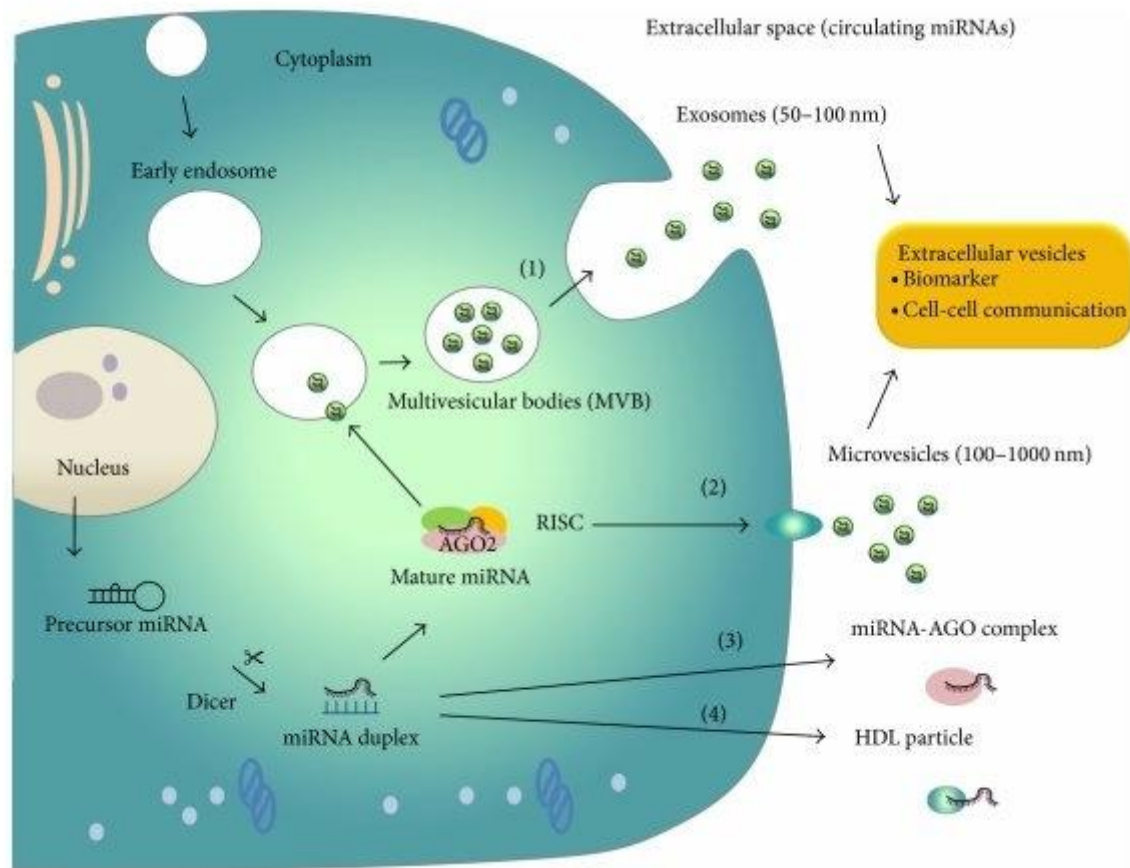


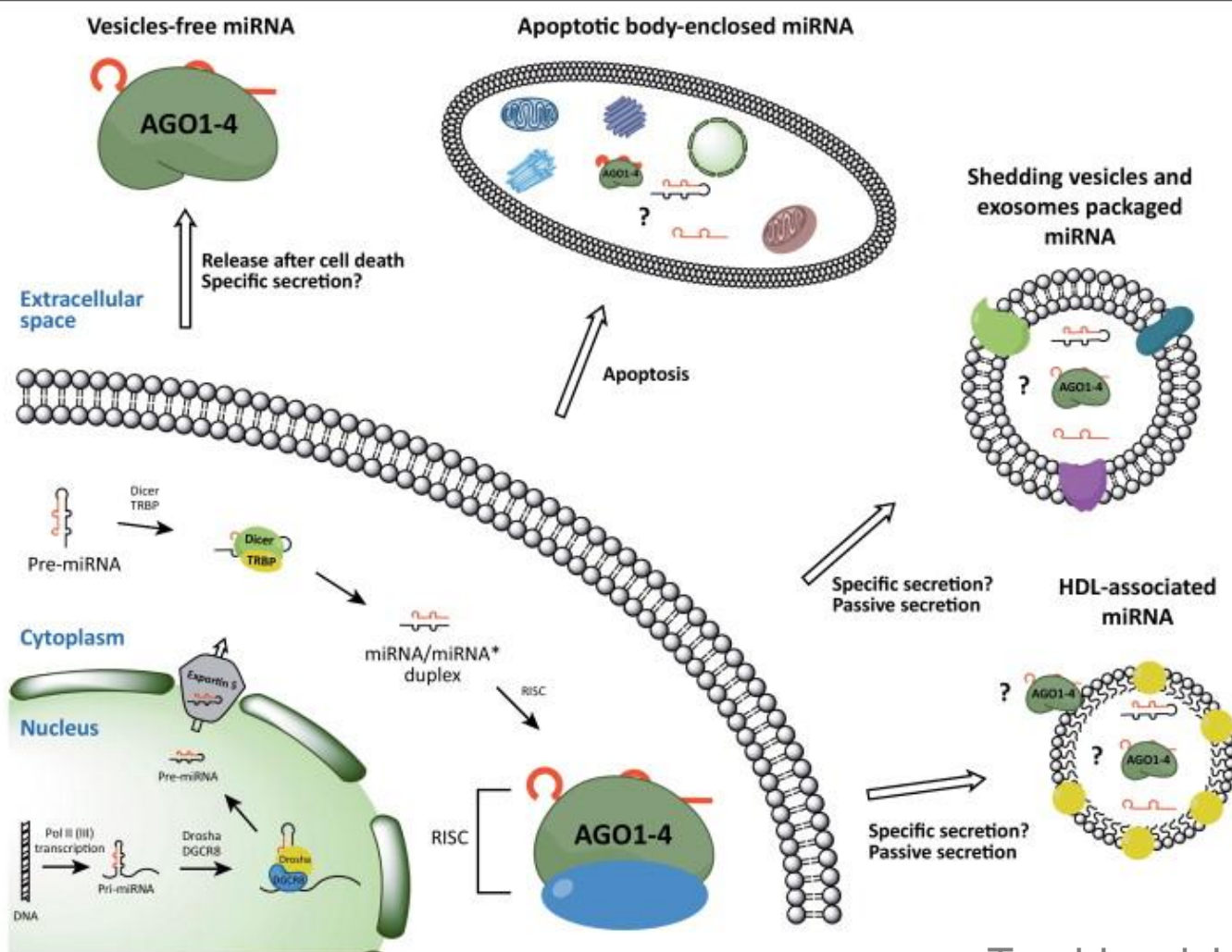
- **Total circulating miRNAs** are found in several forms:
  - Inside **extracellular vesicles** (exosomes, microvesicles, apoptotic bodies).
  - Bound to **protein complexes** (e.g., Argonaute2, HDL, NPM1).
  - In lipoprotein particles.
- **Proportion in EVs:**
  - Early studies (e.g., Arroyo et al., 2011, *PNAS*) showed that the **majority (>90%) of circulating miRNAs** are encapsulated in EVs.
  - Later studies confirmed this: only about **1–10% of extracellular miRNAs** are encapsulated in EVs.
  - However, while quantitatively fewer, **EV-associated miRNAs may be functionally more important**.
- **Important caveat:** Different isolation methods (ultracentrifugation, size-exclusion chromatography) can yield different proportions of miRNAs in EVs.

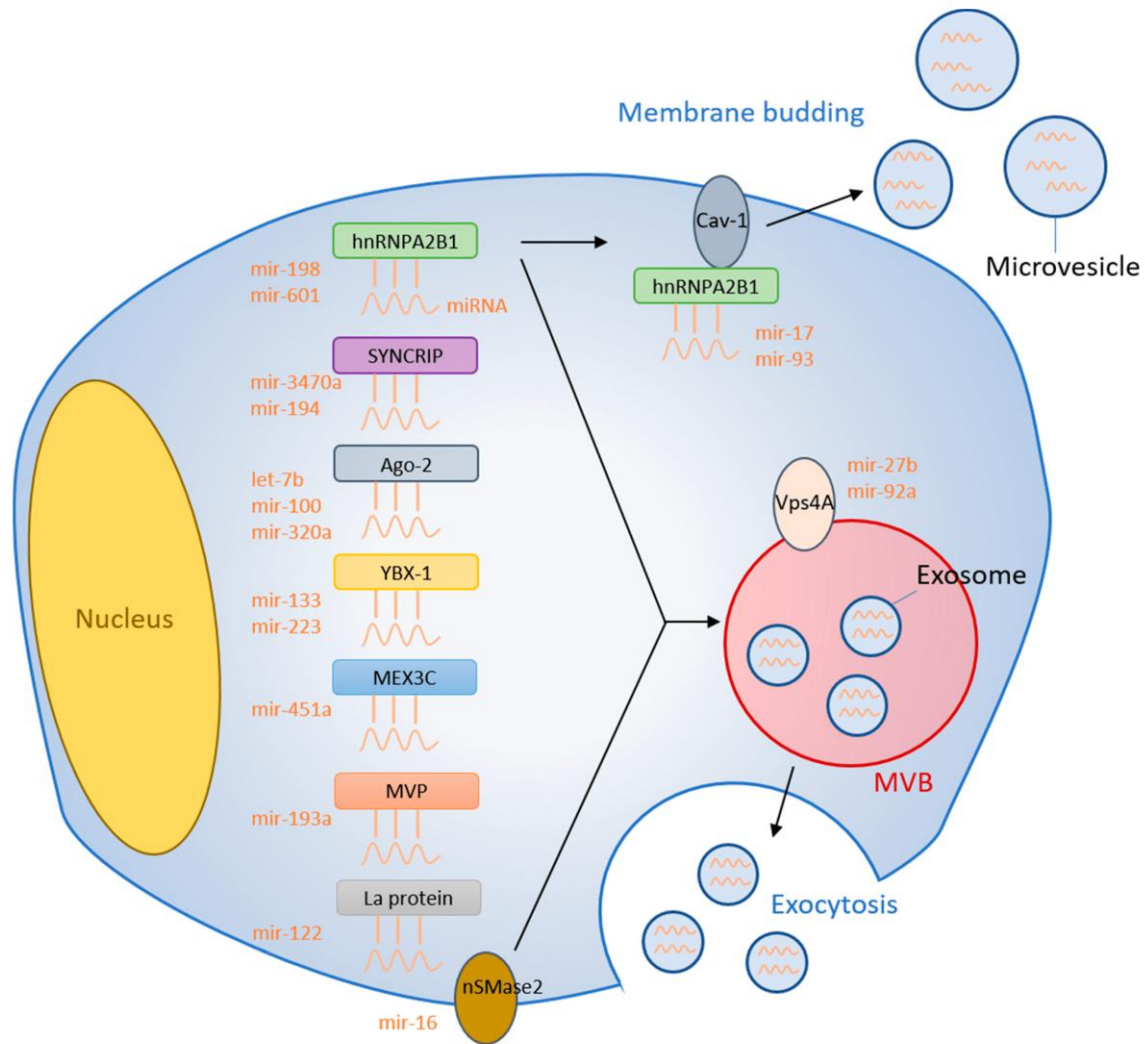
# Tumor EVs induce liver metabolic dysfunction

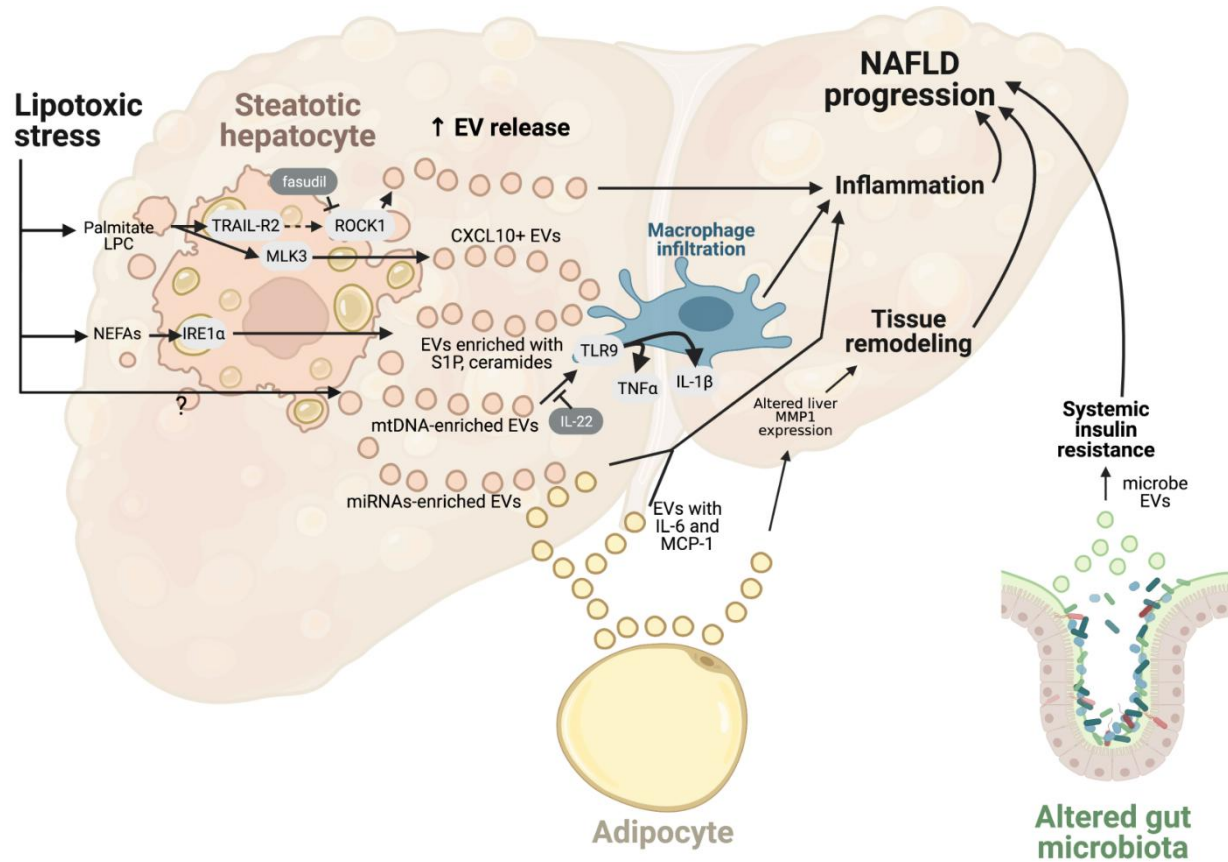


- Steatosis
- Side effects of chemotherapy



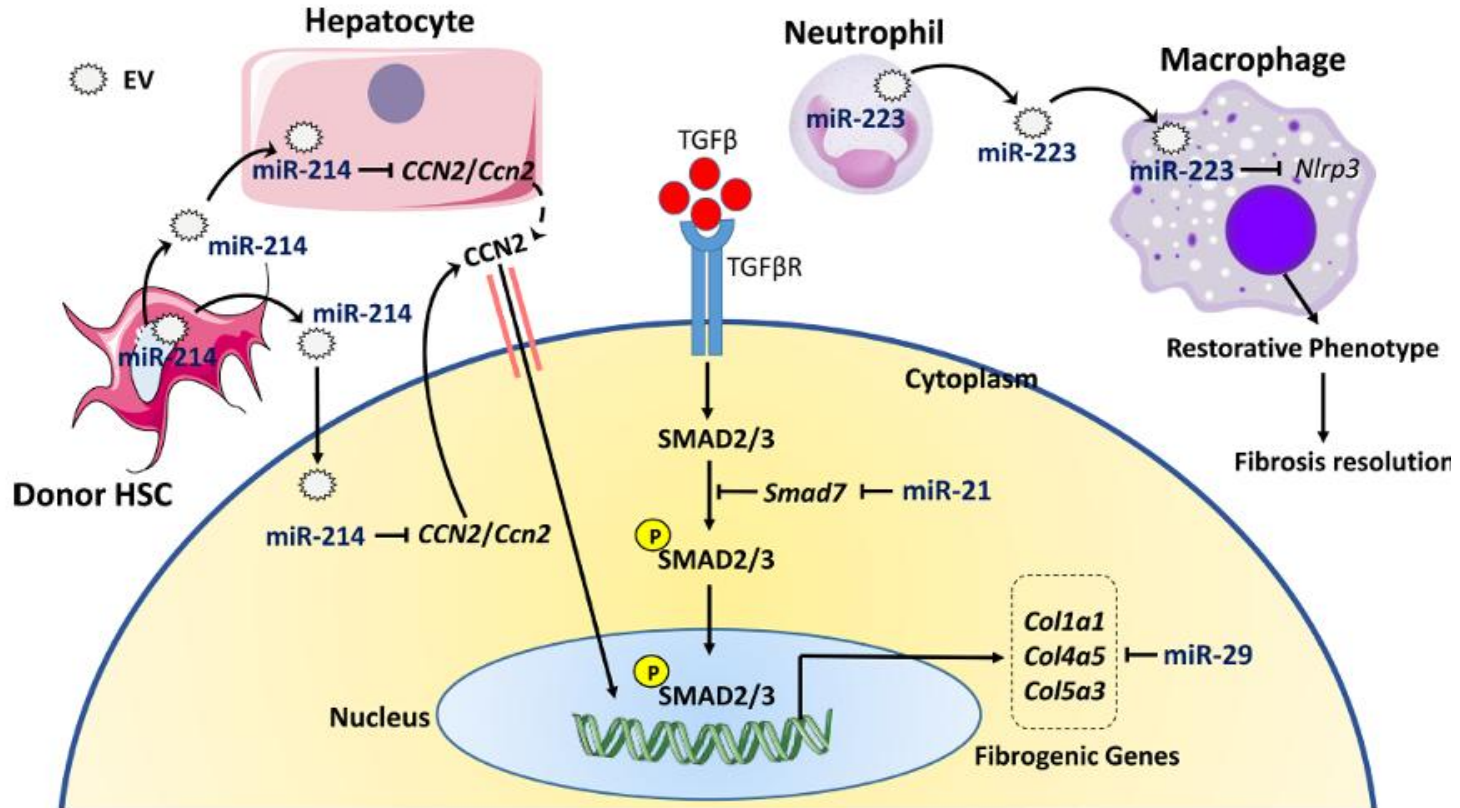






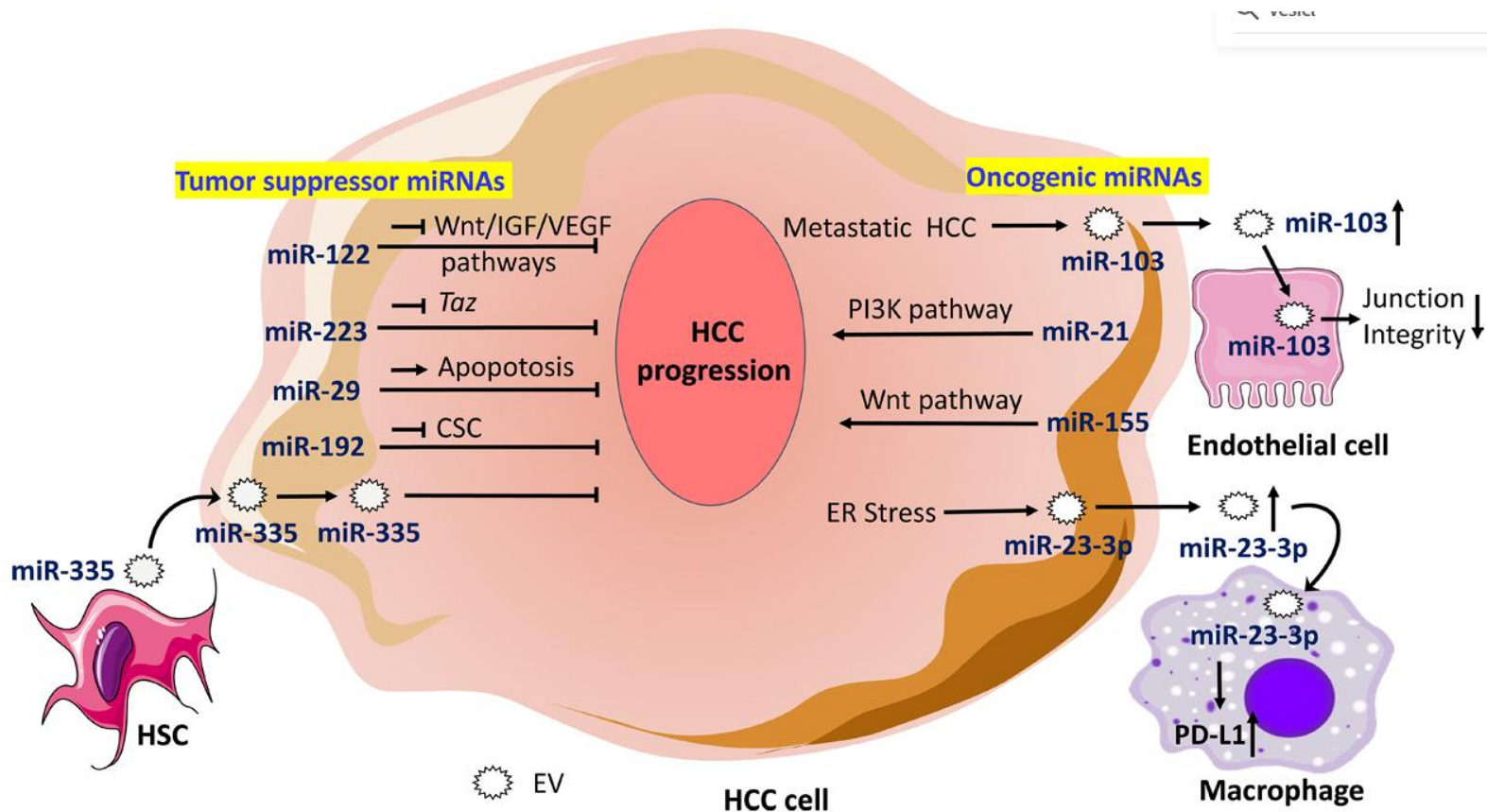


# Roles of microRNAs in progression of liver fibrosis





# Functions of microRNAs in HCC cells



# COST ACTION:

## European vascular liver diseases network (EURO-VALDI-NET)

**Start Date:** 30/10/2024

**End Date:** 29/10/2028



Pierre-Emmanuel Rautou (Chair)

Virginia Hernandez-Gea (Vice-Chair)

Laure Elkrief (Grant holder scientific representative)

Sarwa Darwish-Murad (Grant Awarding Coordinator)

Filipe Andrade (Science Communication Coordinator)

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