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Lipotoxicity as a Trigger for Liver Damage

Harmeet Malhi, M.B.B.S.

NASH-TAG 2018 Conference, The Chateaux Deer Valley
January 5, 2018

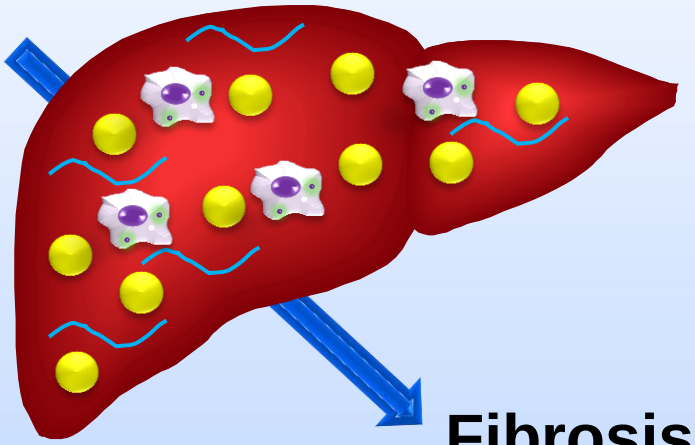
Lipotoxicity in NASH Pathogenesis

Hepatocyte Lipotoxicity

- Organelle Stress
  - ER Stress
- Sub-lethal Injury
- Lethal Injury

Innate Immune Activation

- Recruited Myeloid Cells



Fibrosis

- Hepatic Stellate Cells

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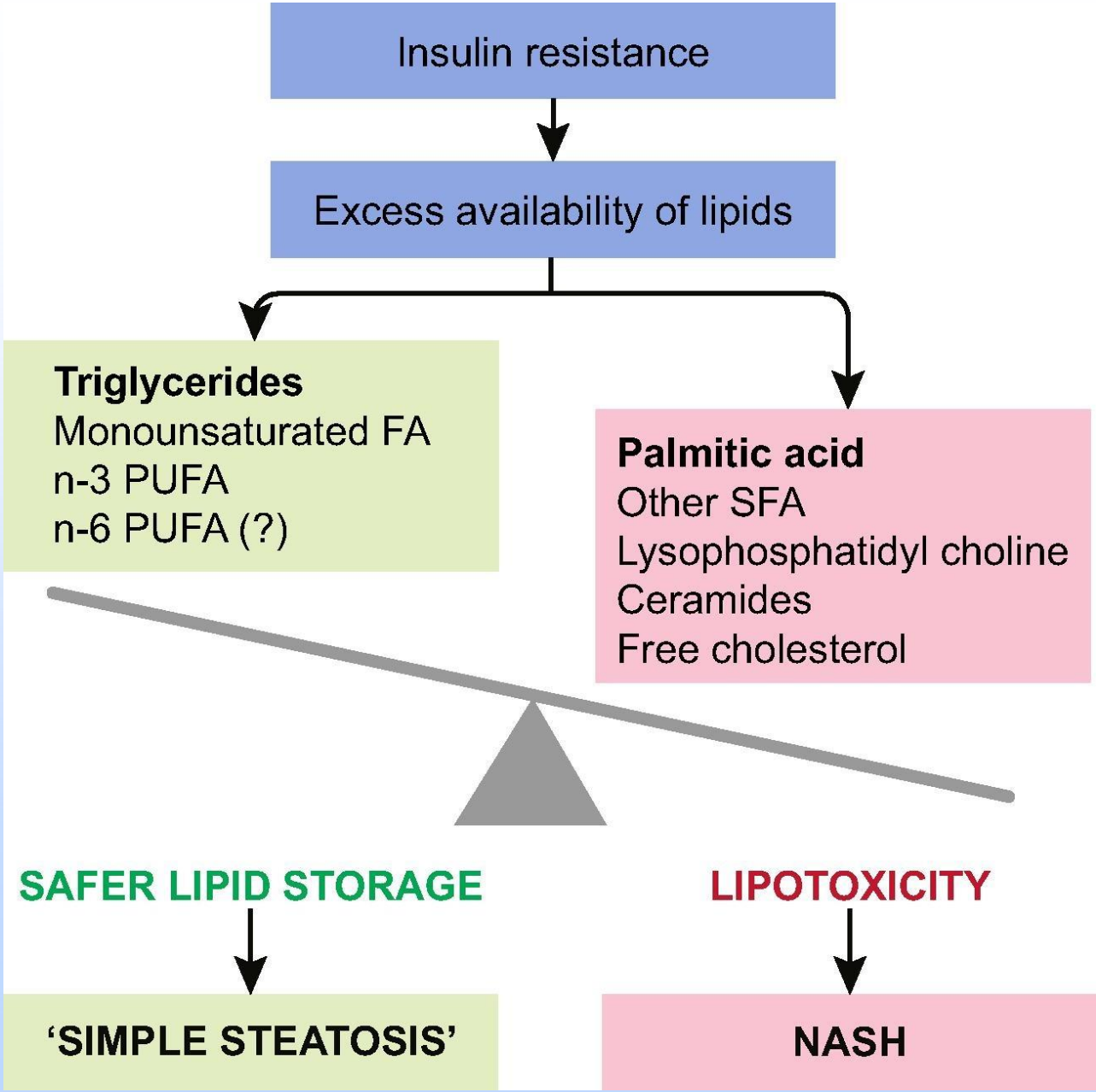
Lipids Implicated in Toxicity in NASH



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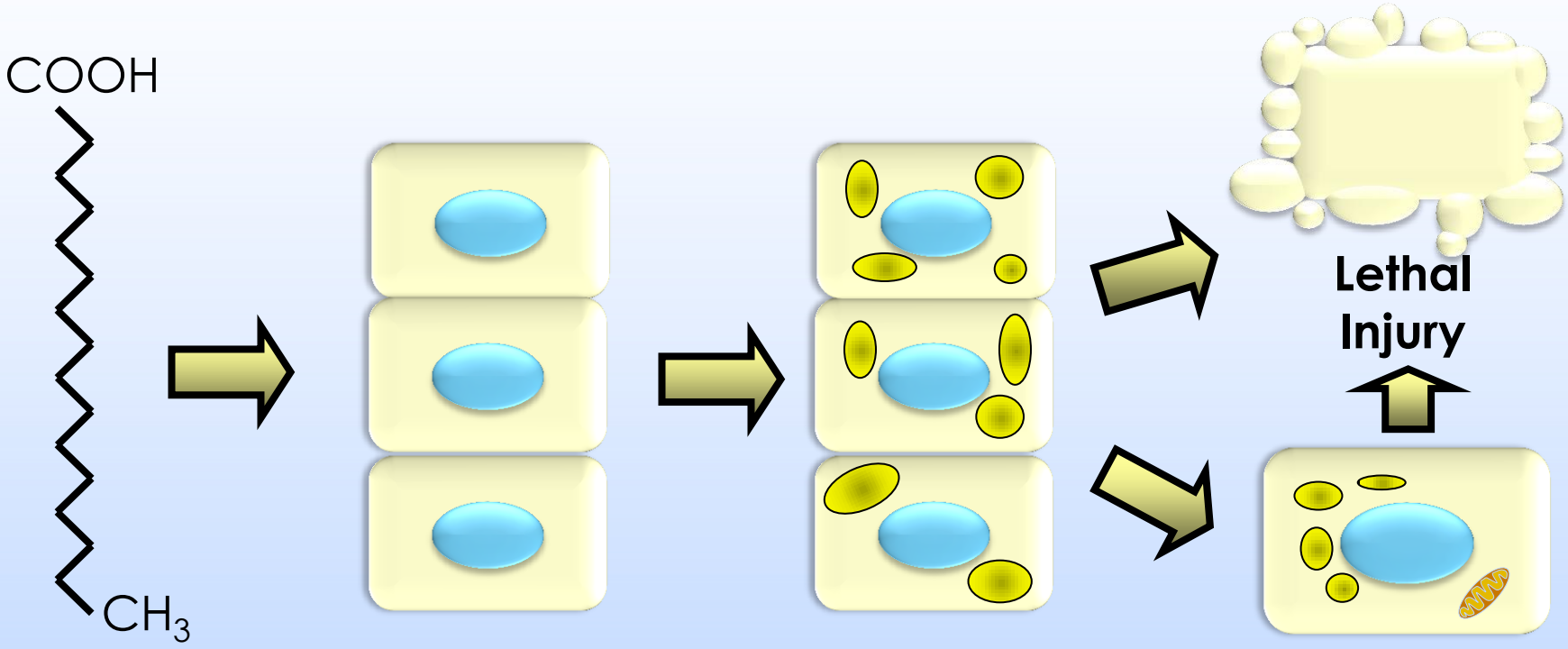
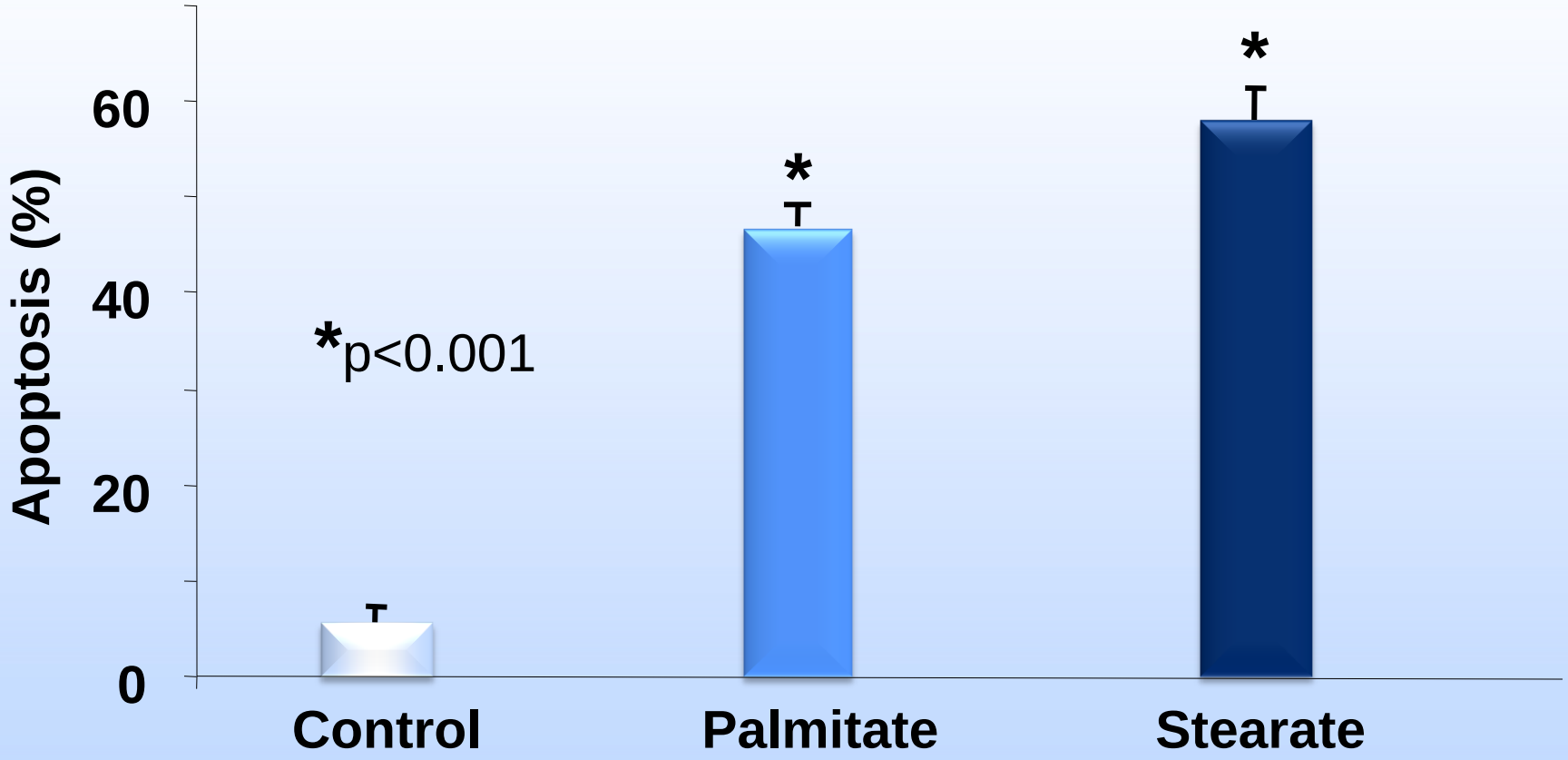
Marra and Svegliati-Baroni. https://doi.org/10.1016/j.jhep.2017.11.014

Saturated Free Fatty Acids Induce Hepatocyte Stress



Saturated FFAs Induce Hepatocyte Lipoapoptosis



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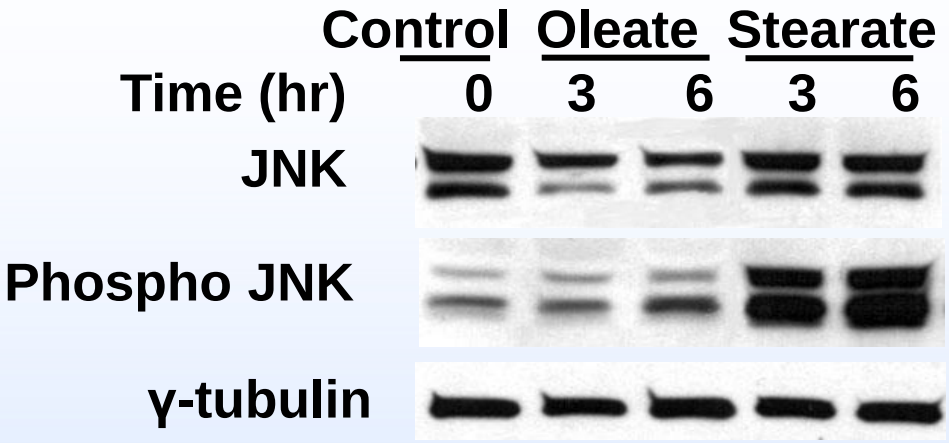
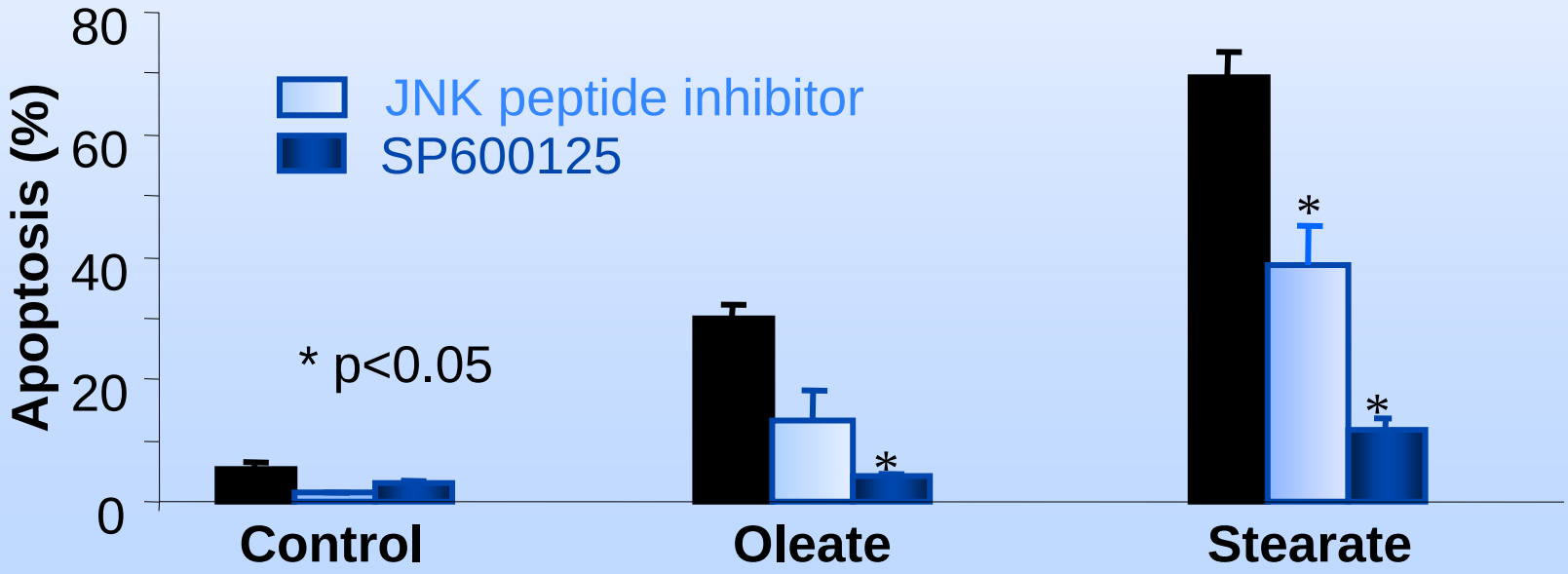
Malhi et al. J Biol Chem. 2006;281:12093

Hepatocyte Lipoapoptosis is JNK-dependent





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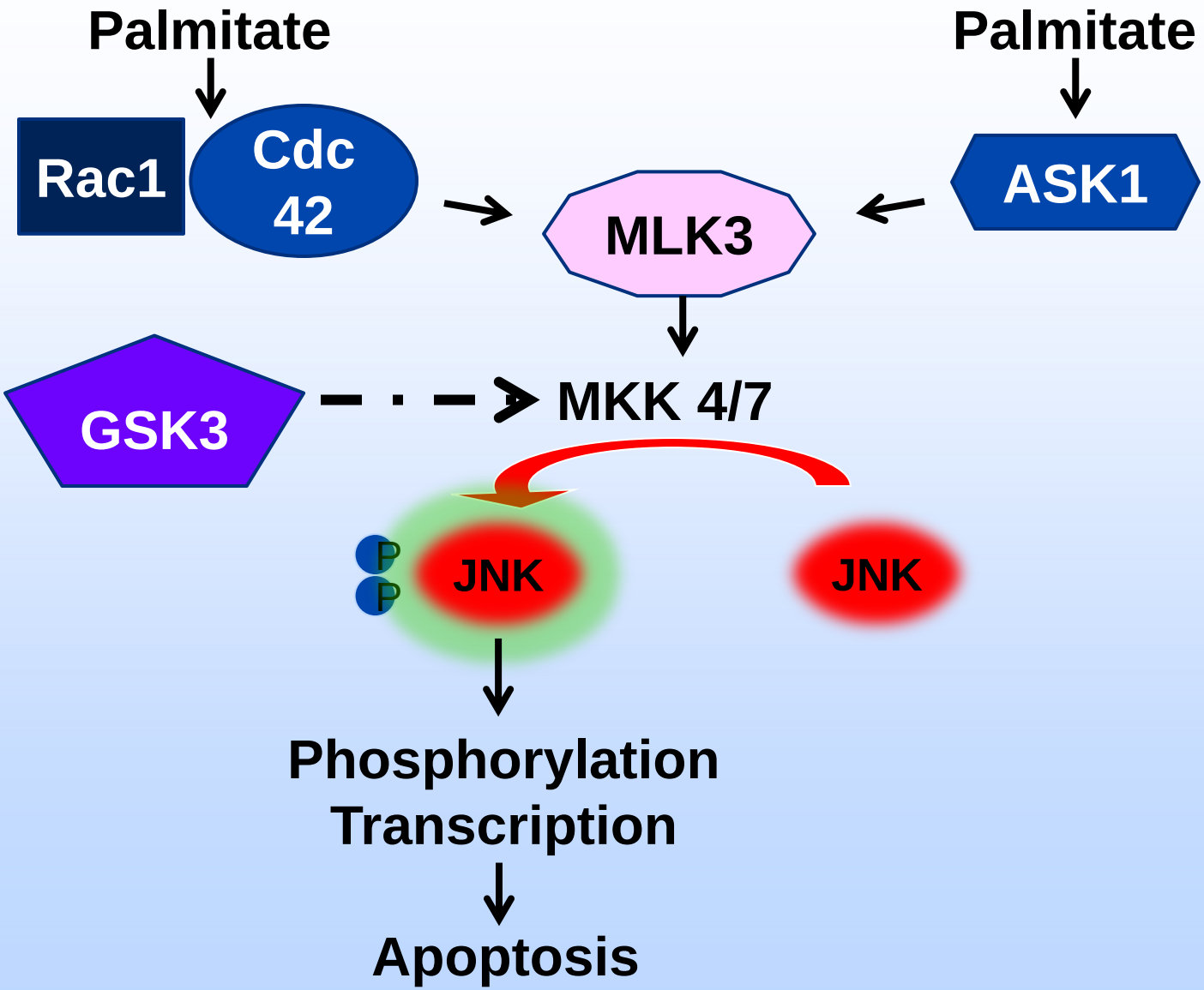
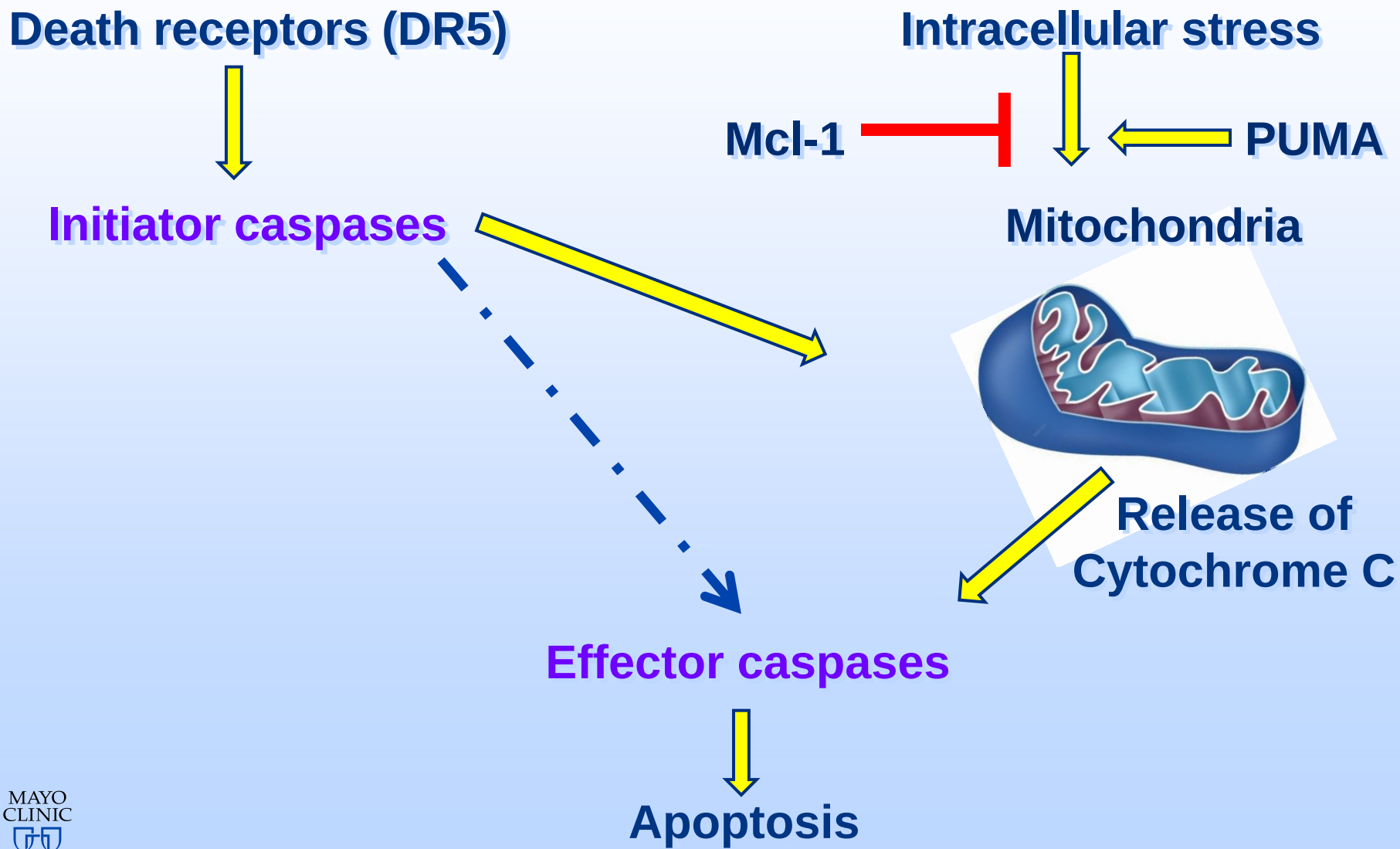
Malhi et al. J Biol Chem. 2006;281:12093

FFA-induced JNK Activation



Ibrahim et al. J Hepatol. 2011;54:765. Sharma et al. J Hepatol. 2012;56:192.

JNK Activates both the Extrinsic and Intrinsic Pathways of Apoptosis



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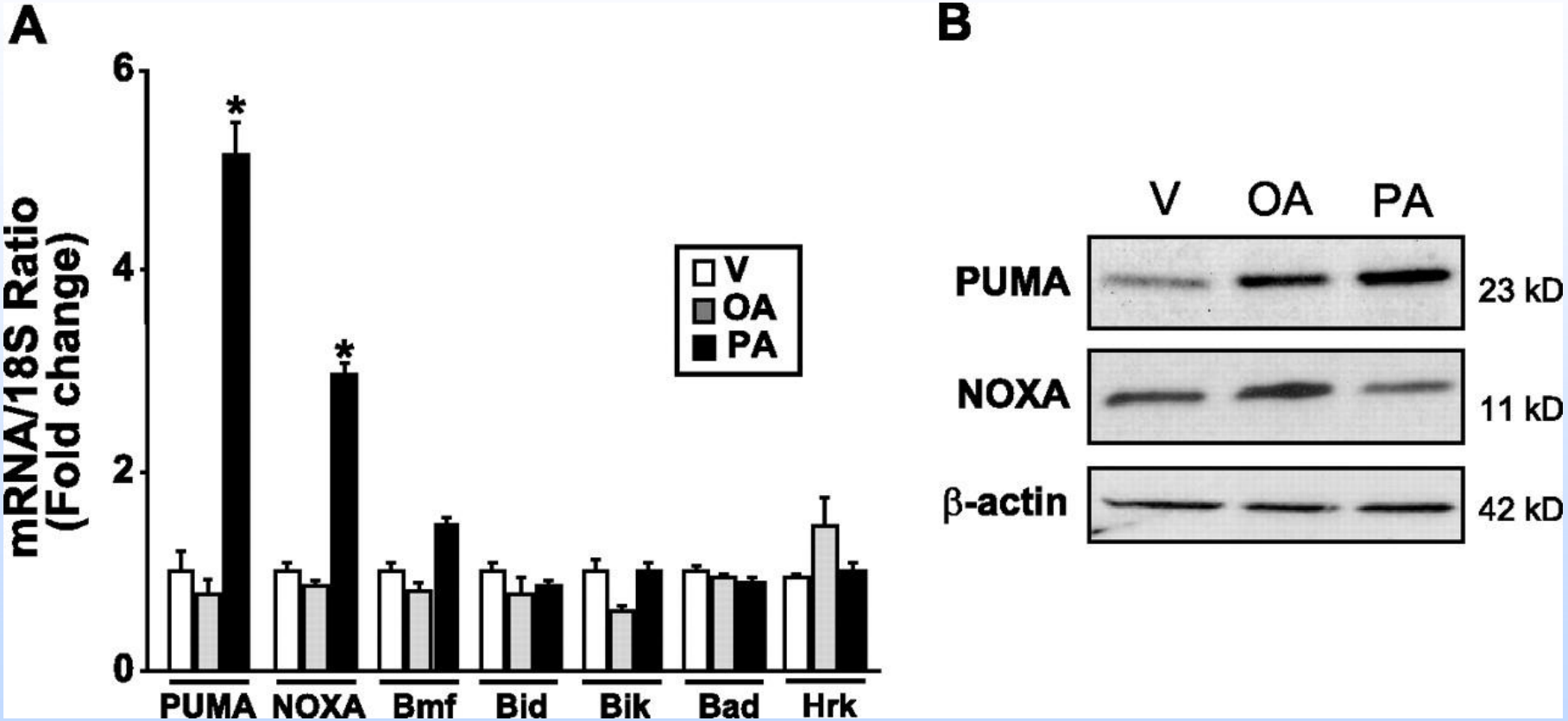
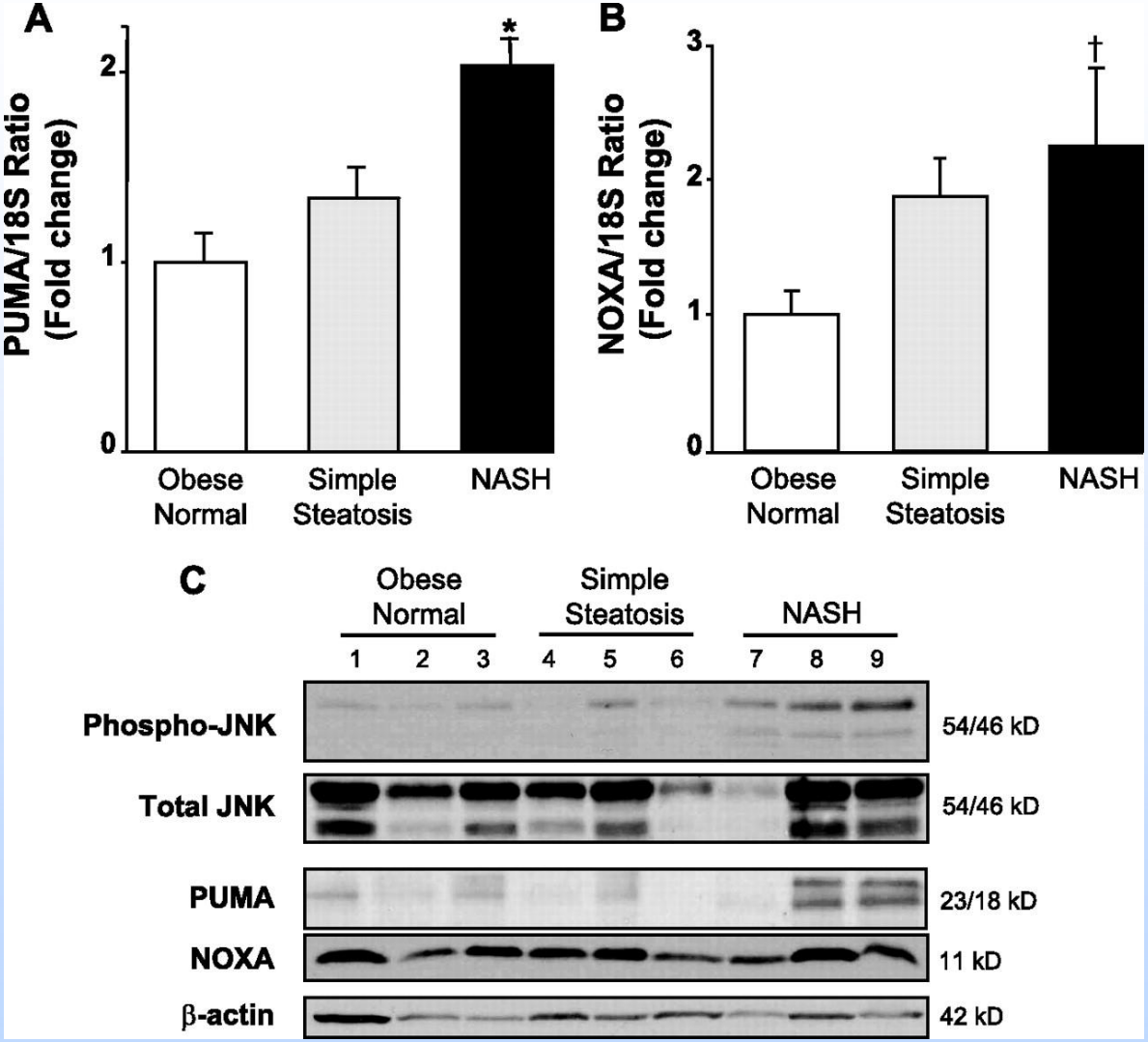
PUMA Expression is Increased by PA



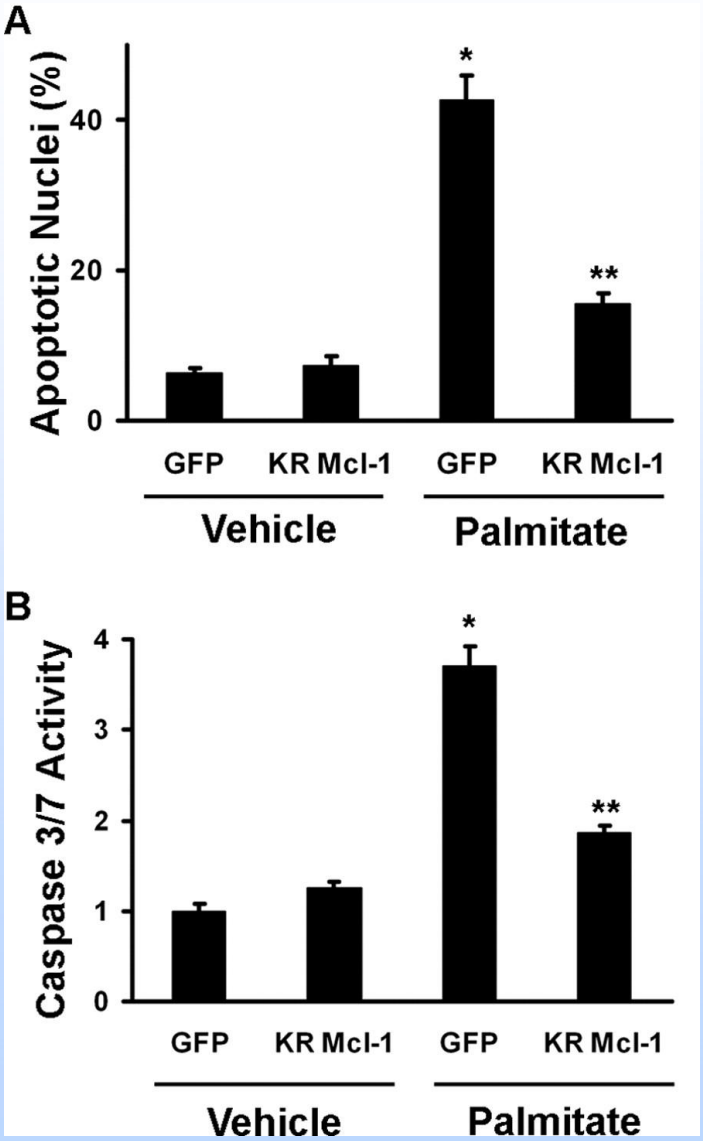
Cazanave et al. J. Biol. Chem. 2009;284:26591

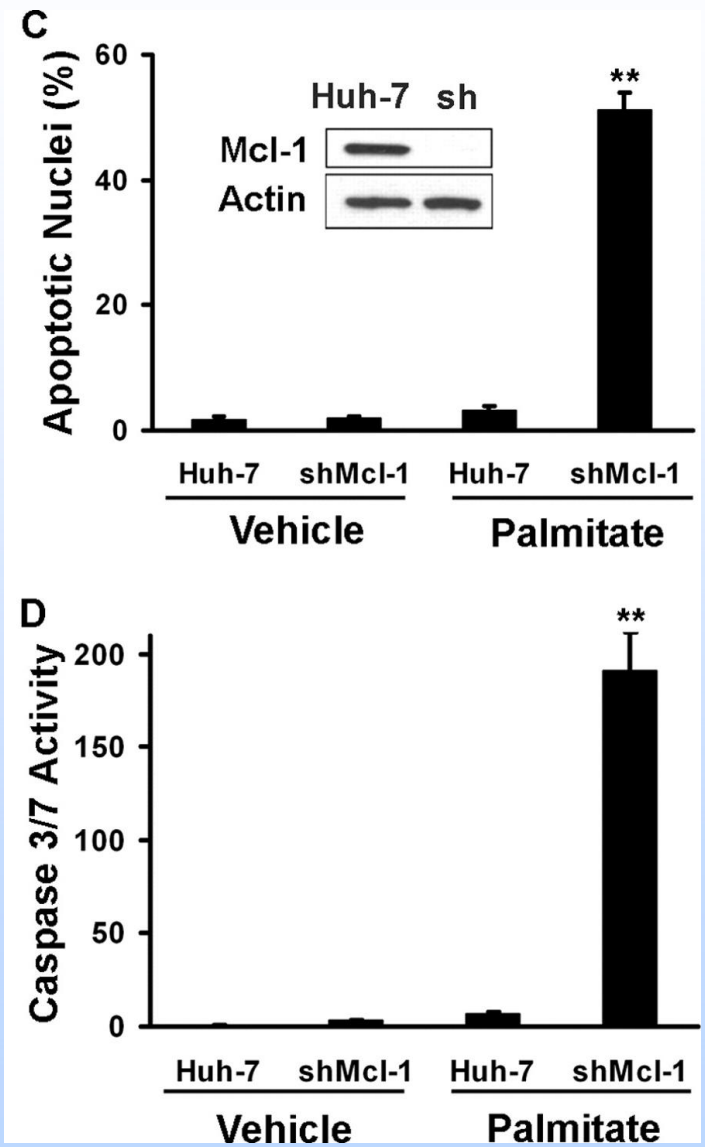
Hepatic PUMA Expression is Increased in Human NASH



Cazanave et al. J. Biol. Chem. 2009;284:26591

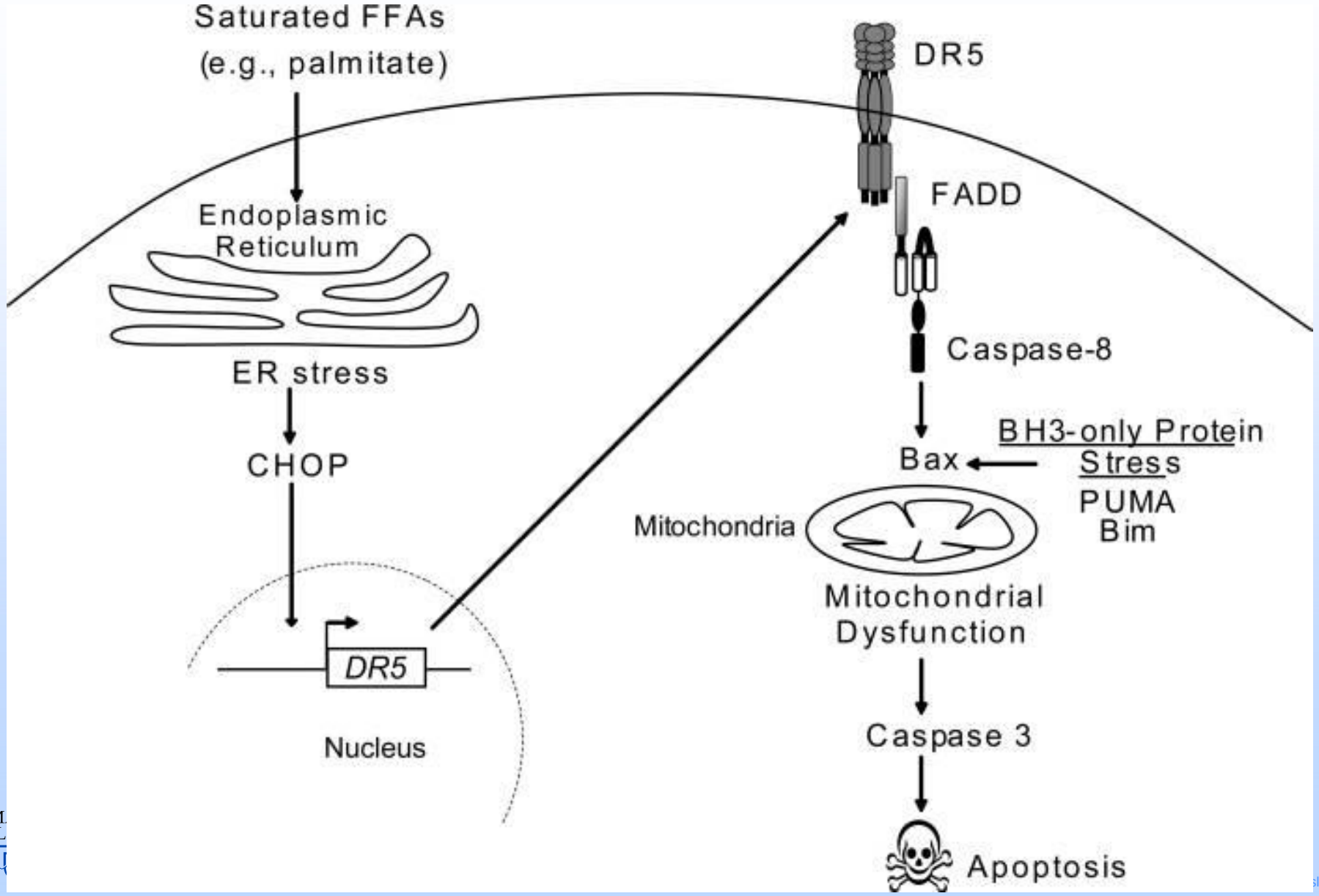
PA-leads to a Reduction in Mcl-1 levels and Mcl-1 Modulates PA-induced Lipoapoptosis



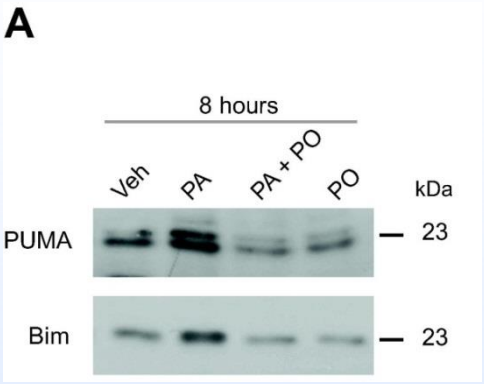


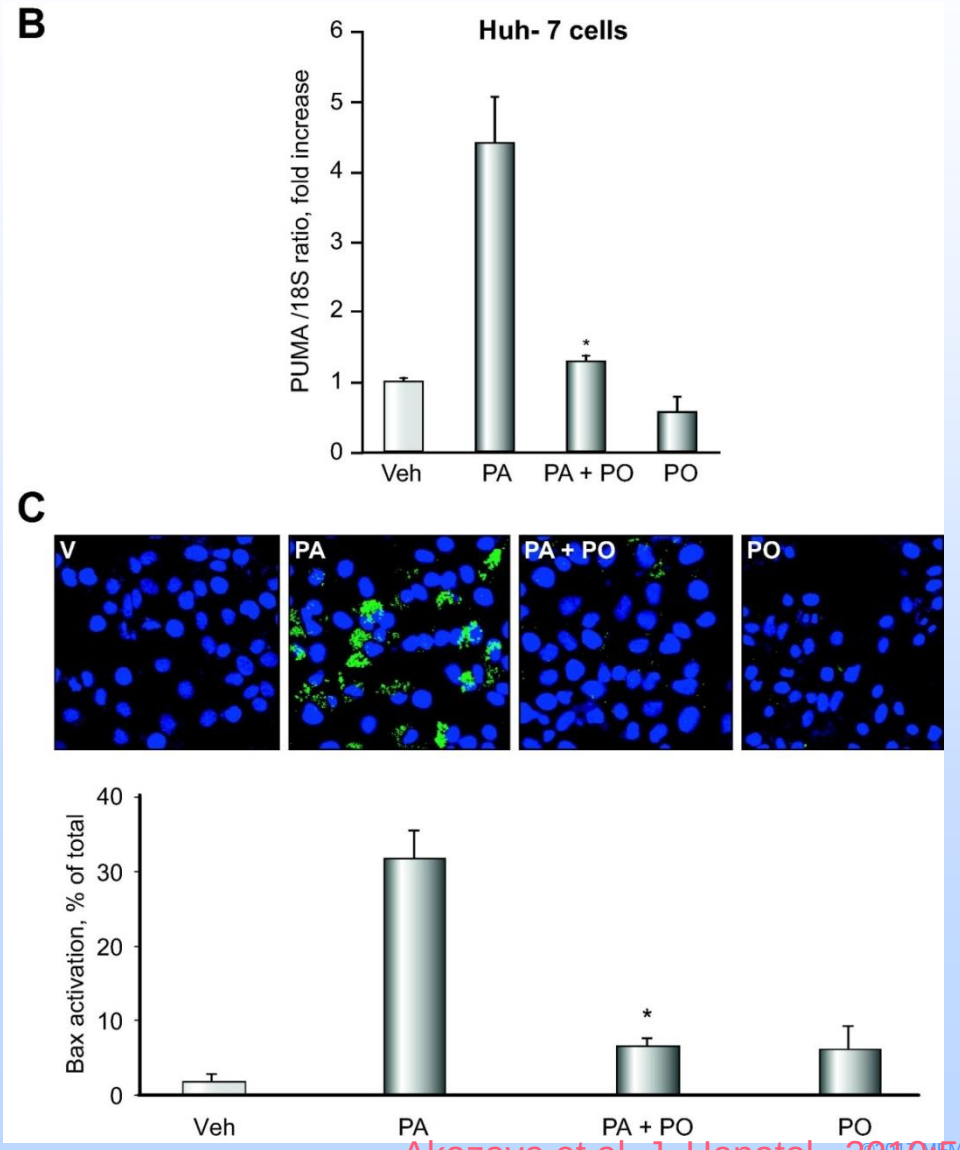
Masuoka et al. J. Biol. Chem. 2009;284:30039

PA Activates TRAIL receptor (DR5)-mediated Apoptosis



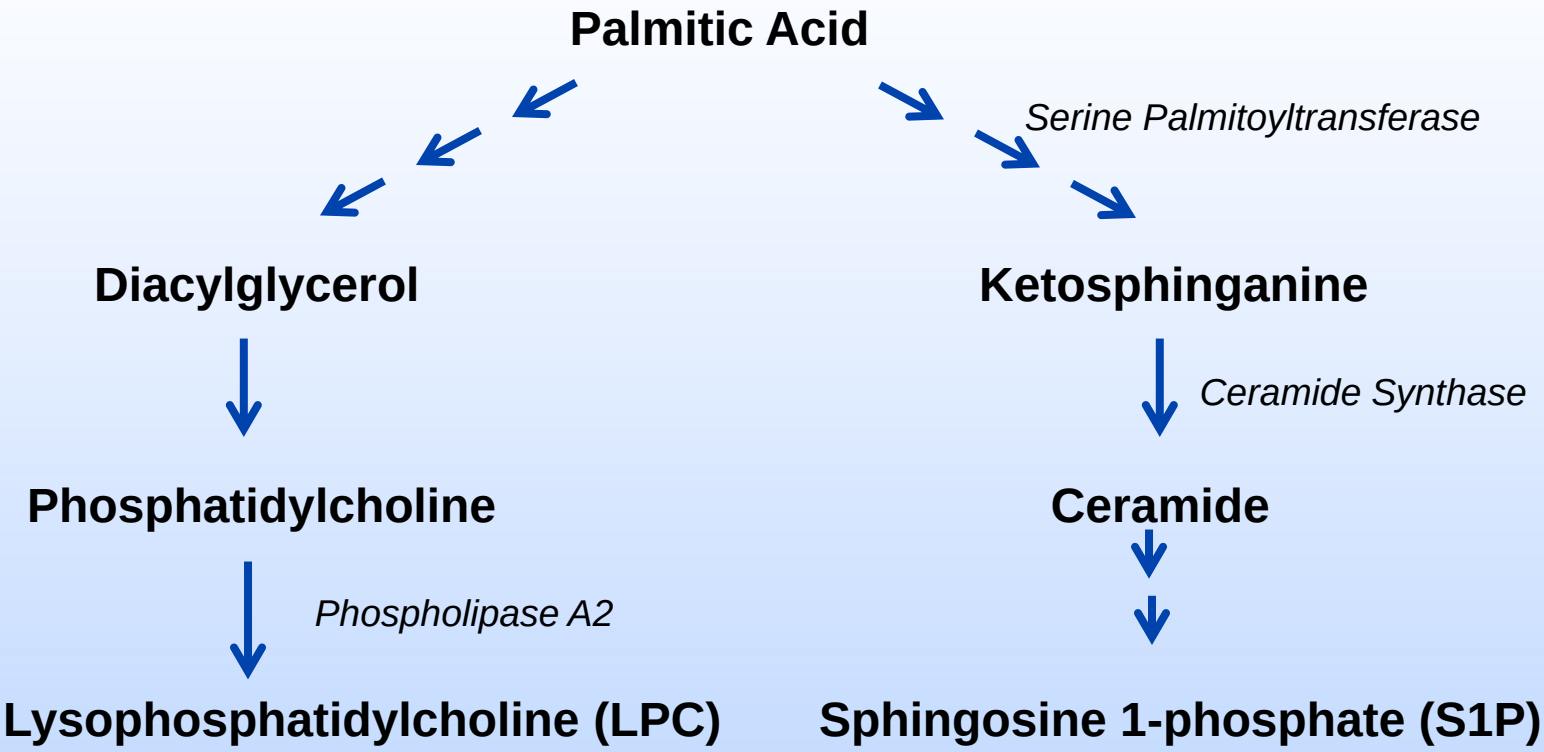
Palmitoleate Inhibits PA-induced Lipoapoptosis





Akazava et al. J. Hepatol. 2010;52:586

Toxicity of PA Derivatives



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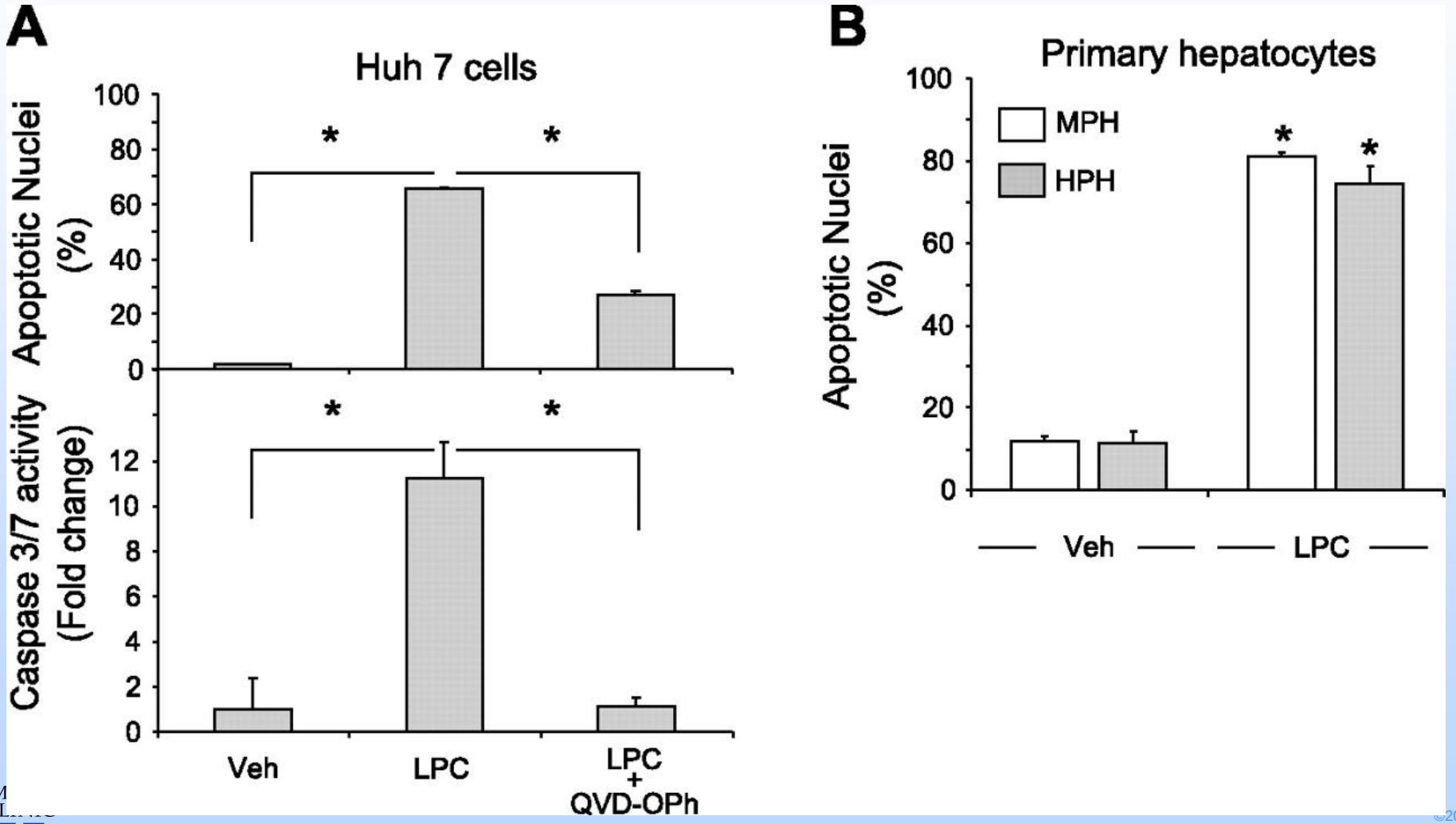
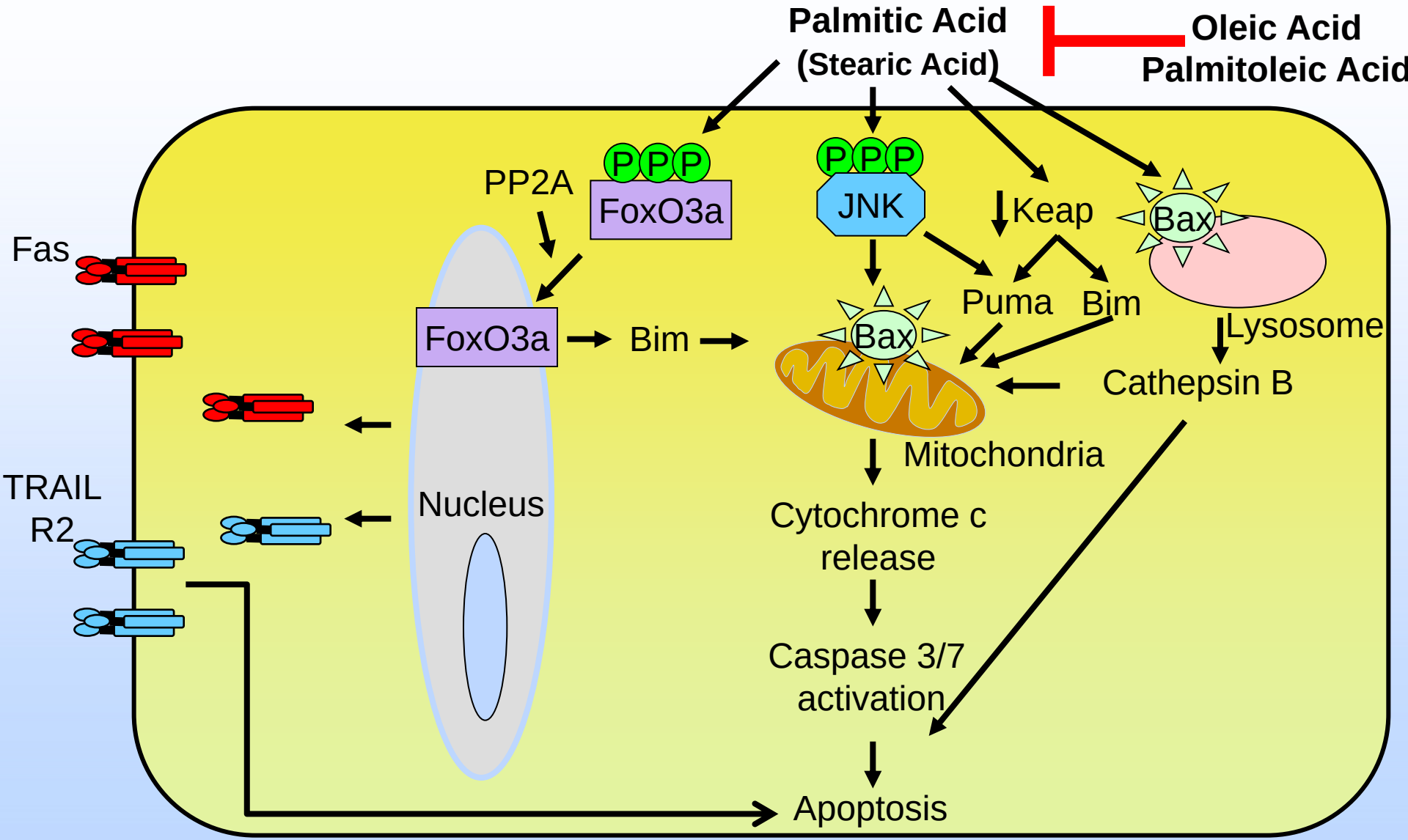
Lysophosphatidylcholine (LPC) Induces Caspase-dependent Apoptosis



Kakisaka et al. Am J Physiol Gastrointest Liver Physiol 2012;302:G77

Palmitate-induced Hepatocyte Apoptosis



Steatotic Hepatocyte

Malhi and Gores. 2008. Seminars in Liver Disease

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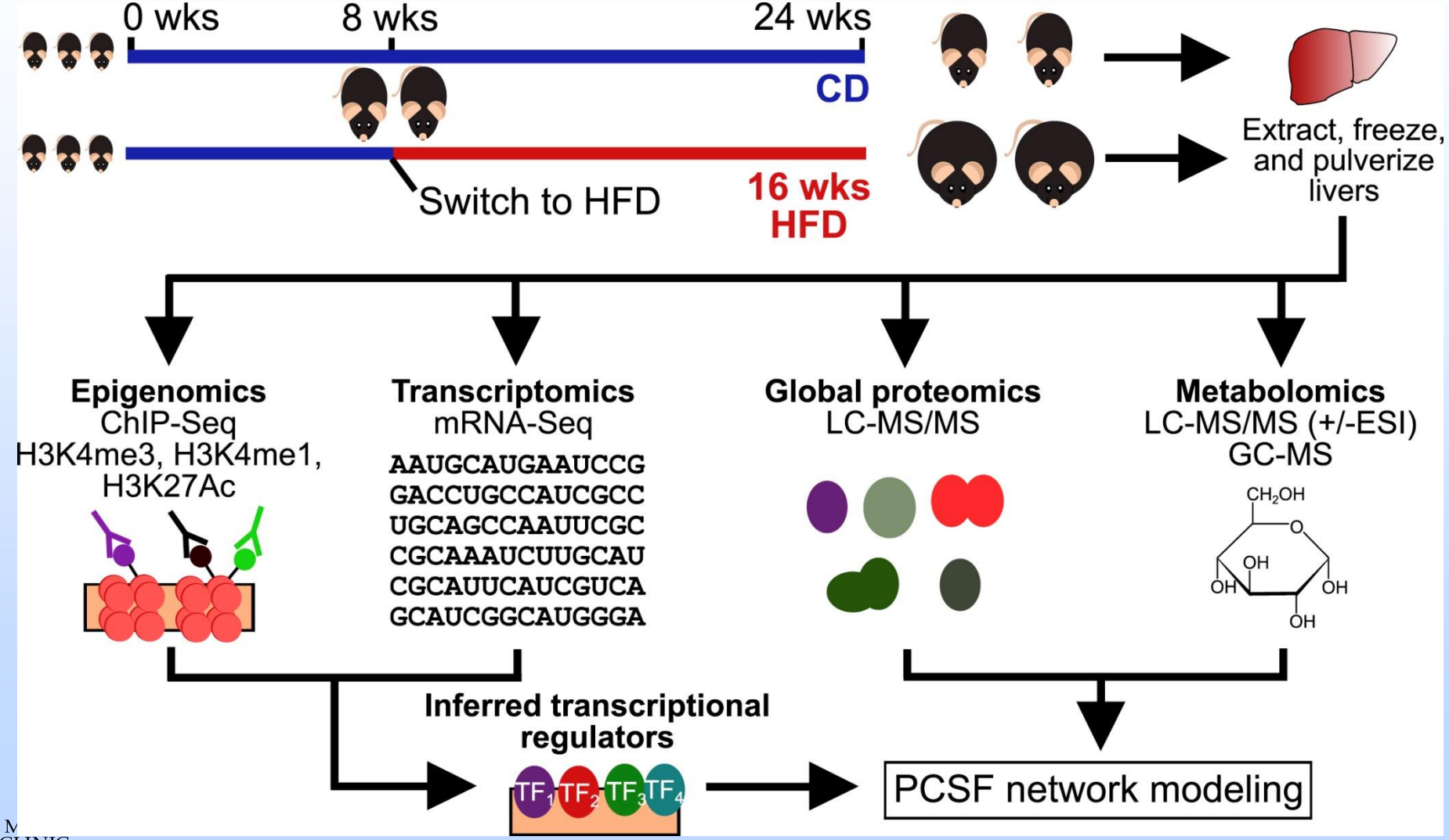
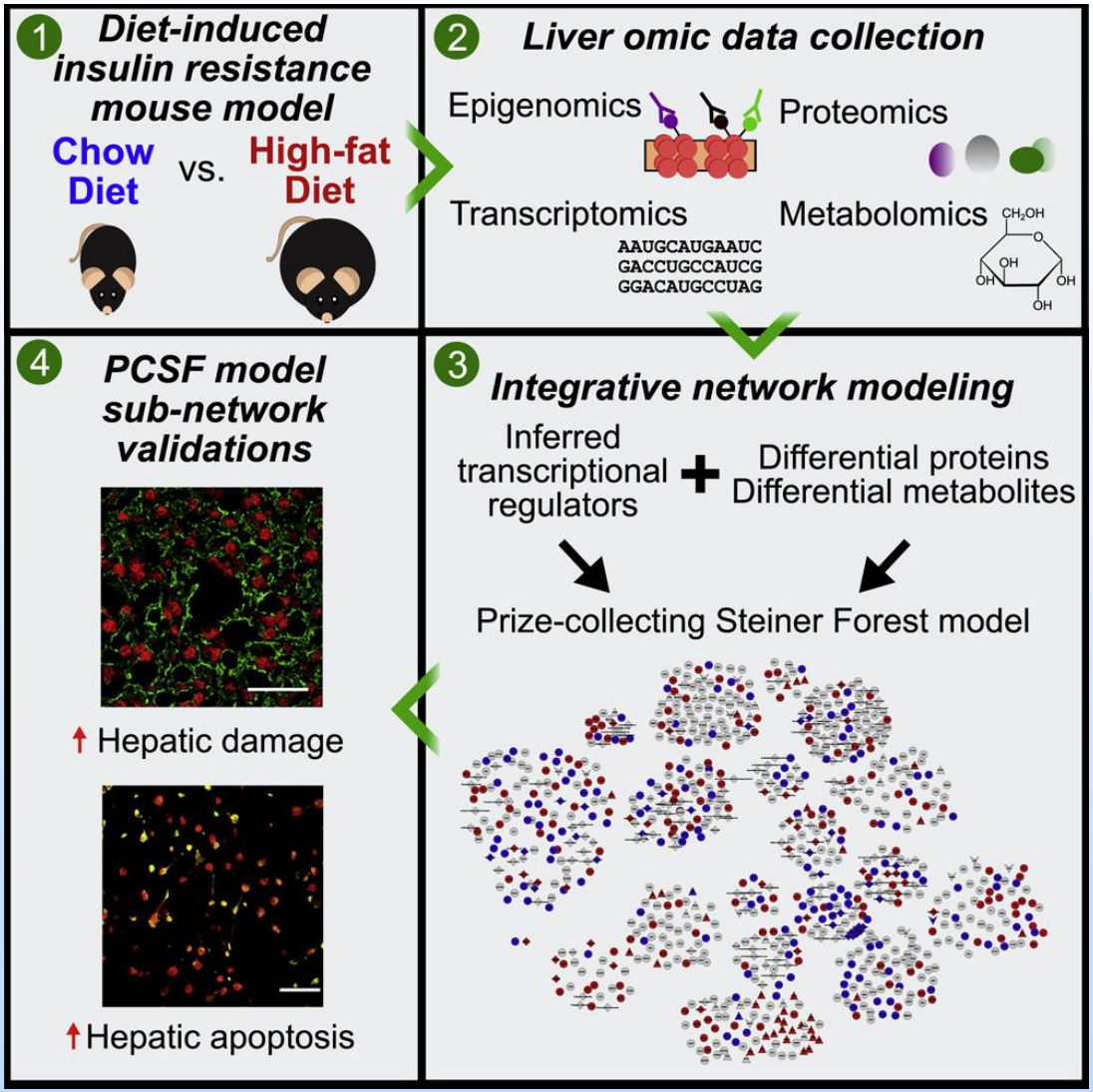
Hepatic Dysfunction Caused by Consumption of a High Fat Diet



Cell Reports 2017 21, 3317-3328DOI: (10.1016/j.celrep.2017.11.059)

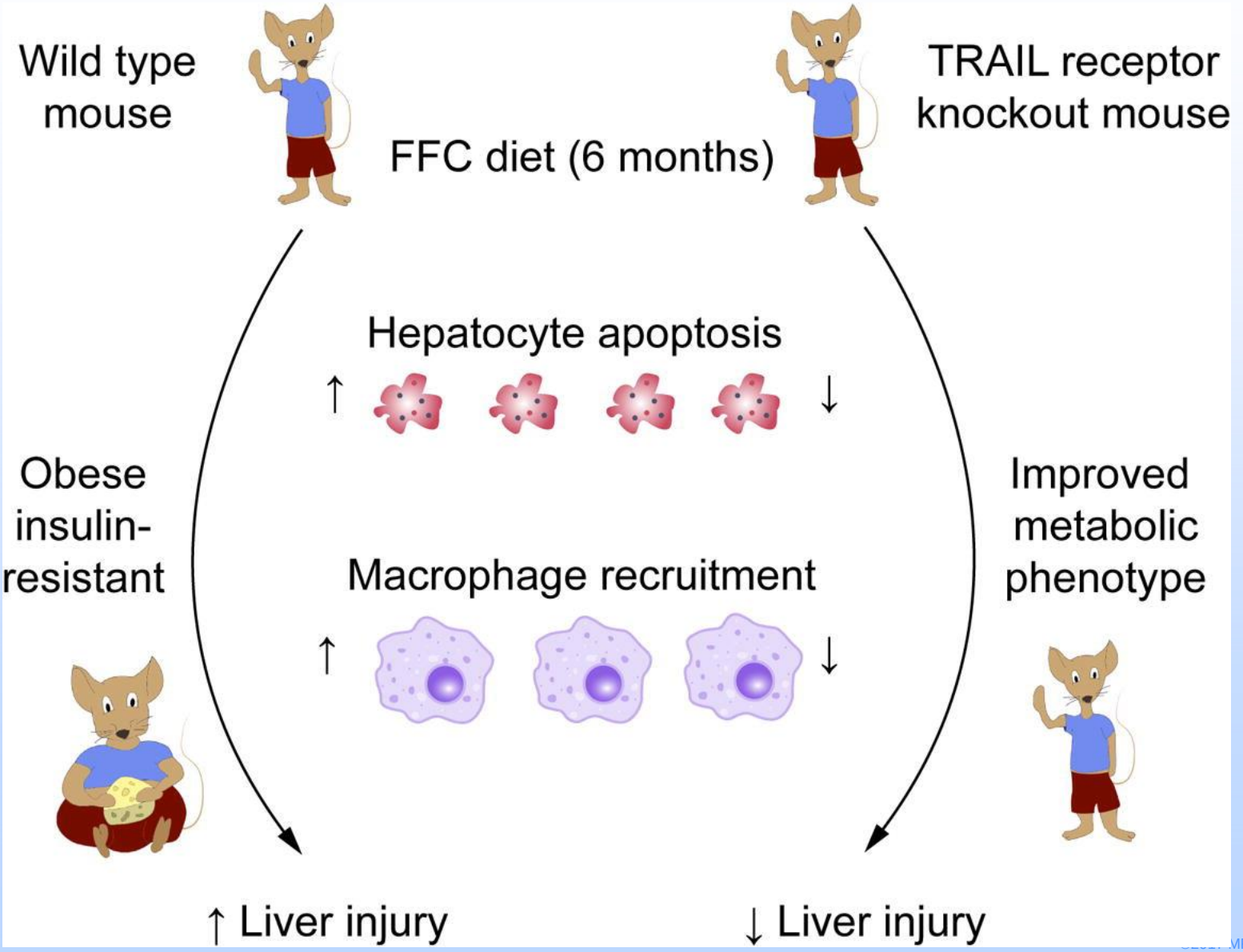
Hepatocellular Injury and Hepatocyte Apoptosis Mediate HFD-Induced Liver Phenotype



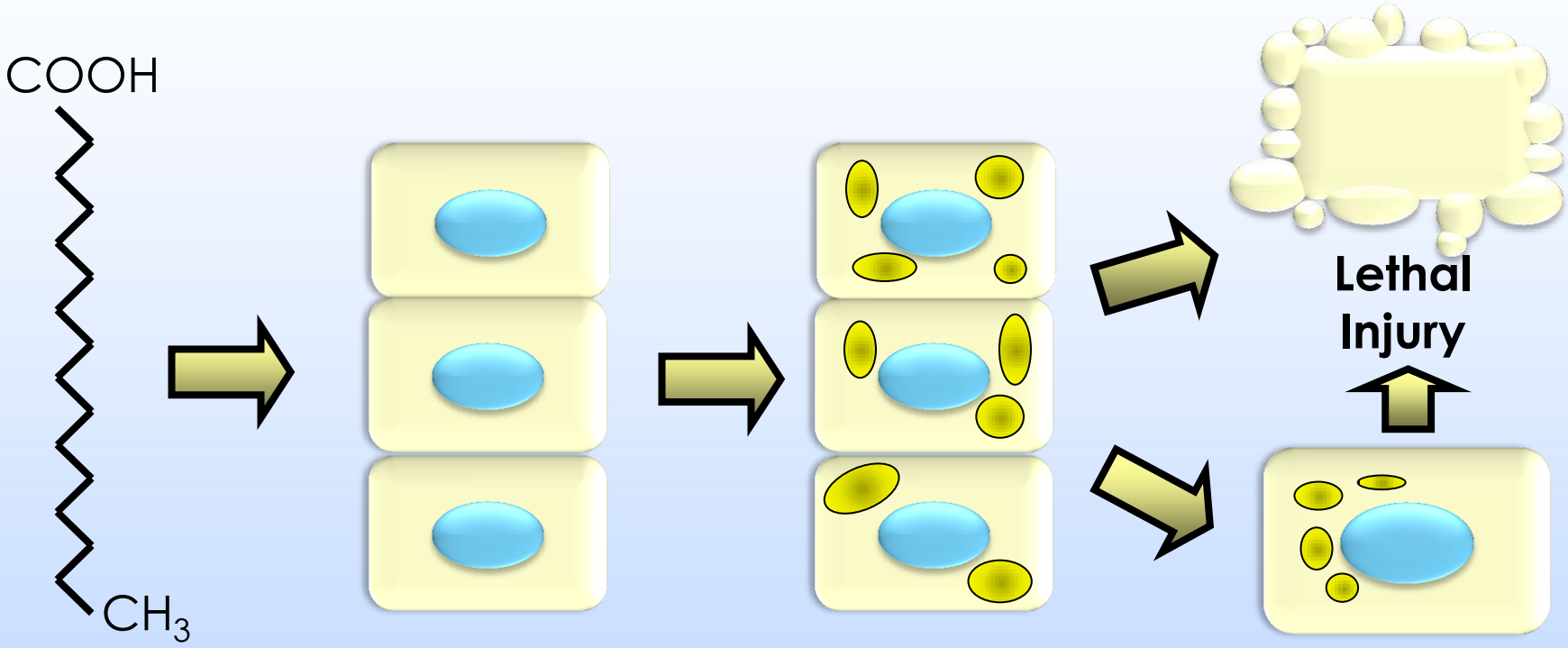
Importantly, it also revealed poorly characterized aspects of the condition, including hepatocellular injury, cell-cell interactions, extracellular matrix (ECM) organization, and apoptosis.

Cell Reports 2017 21, 3317-3328DOI: (10.1016/j.celrep.2017.11.059)

DR5 (TRAIL receptor) Deletion Suppresses the Inflammation of Nutrient Excess

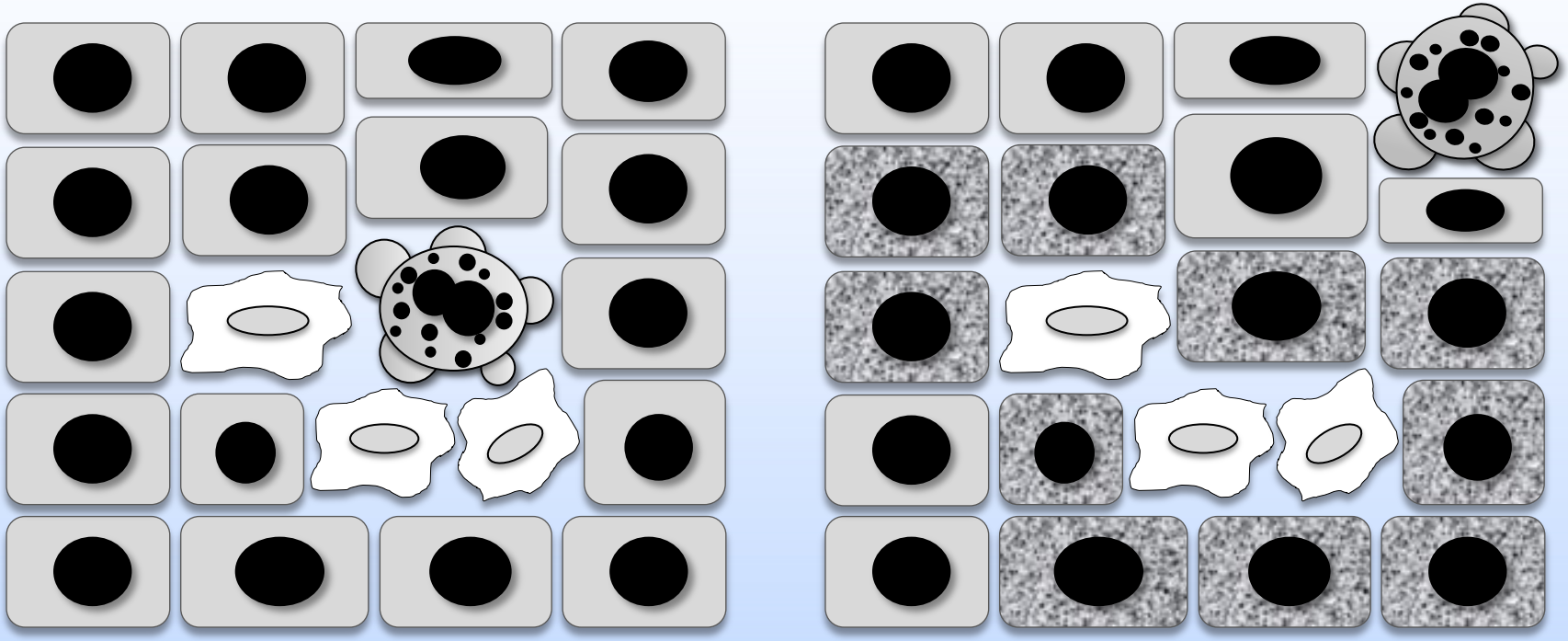


Saturated Free Fatty Acids Induce Hepatocyte Stress



A. Cell death as an initiator of inflammation:
cell death-induced inflammation

B. Cell death as a biomarker for stressed cells:
stress-induced inflammation



Hepatocyte | Stressed Hepatocyte | Apoptotic Hepatocyte | Inflammatory Cell

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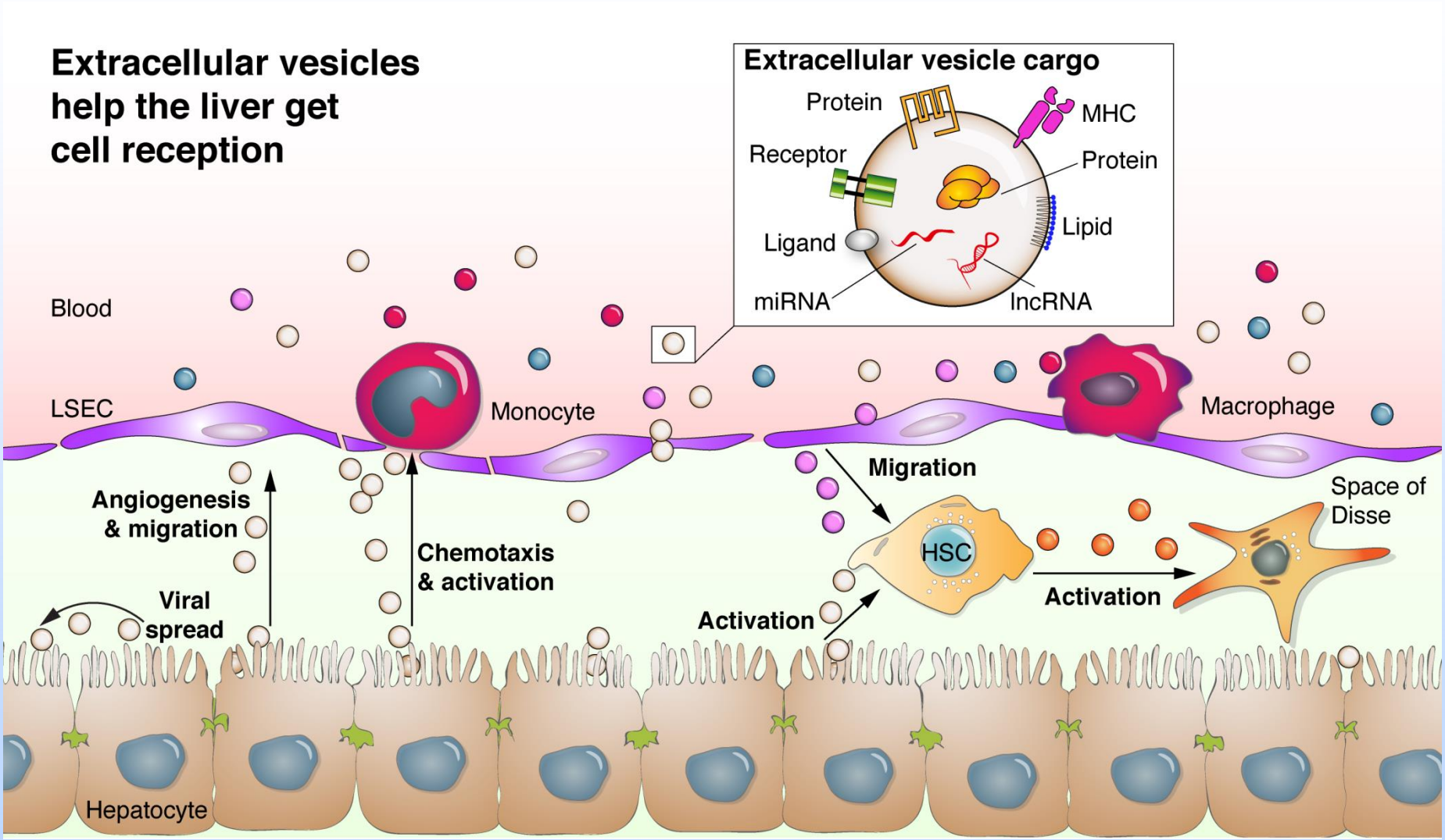
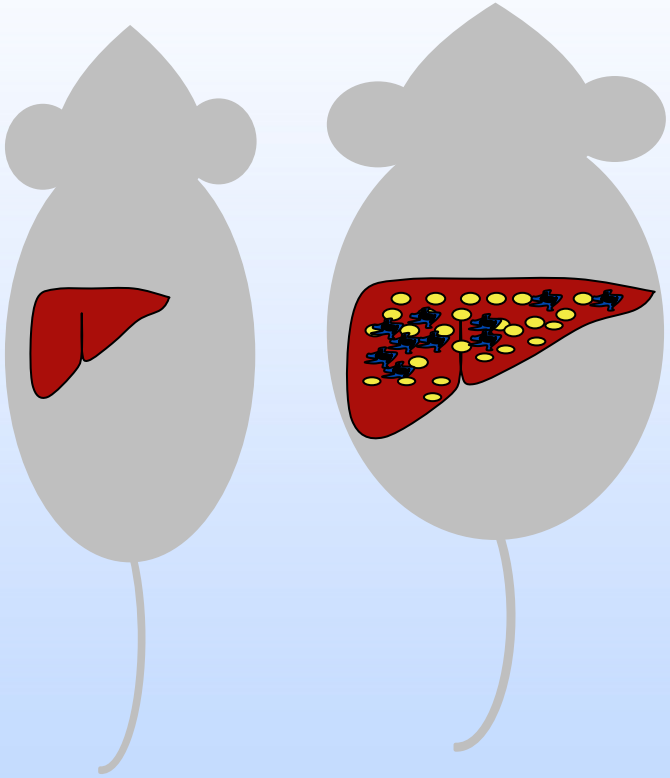
Extracellular Vesicles in Liver Diseases



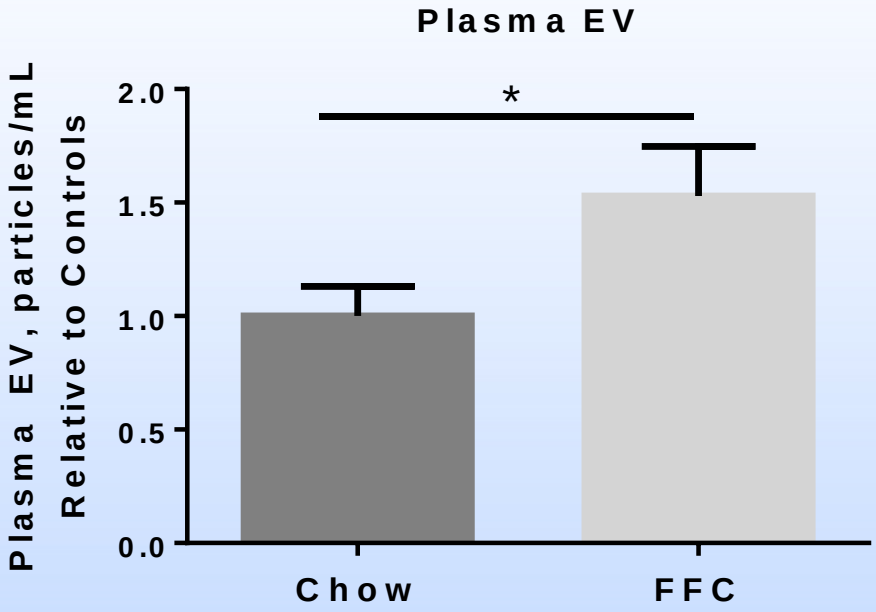
Cover of *Hepatology*. December 2016.

Circulating EVs are Increased in a Dietary Murine Model of NASH



Chow Fed
24 weeks

FFC Diet Fed
24 weeks



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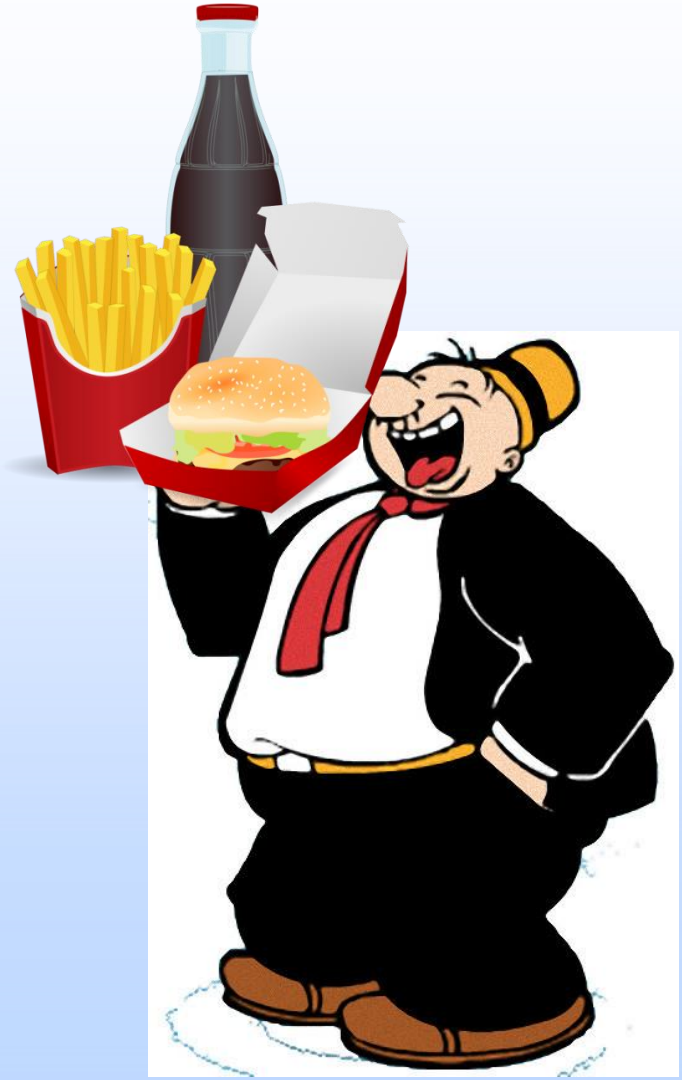
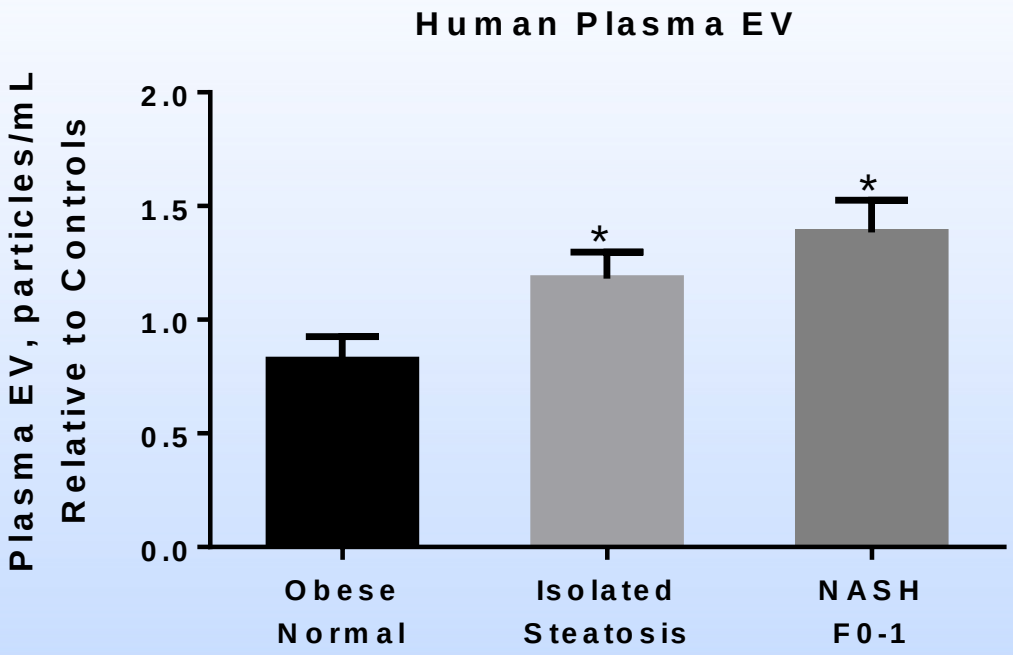
Circulating EVs are Increased in Human NASH





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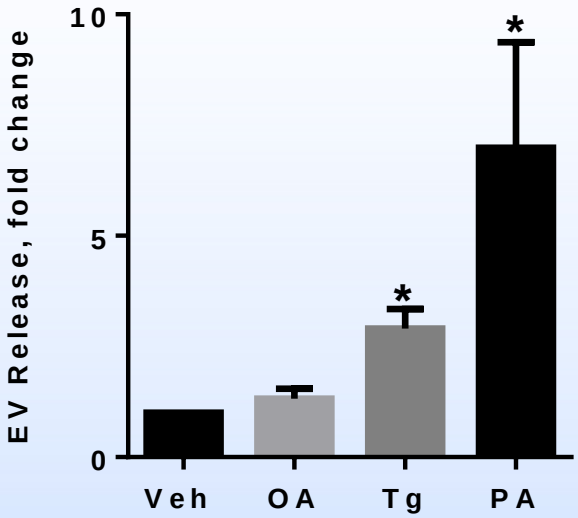
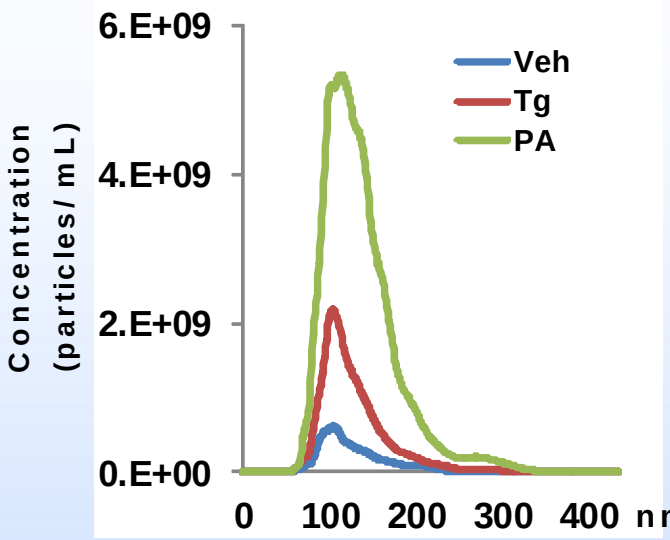
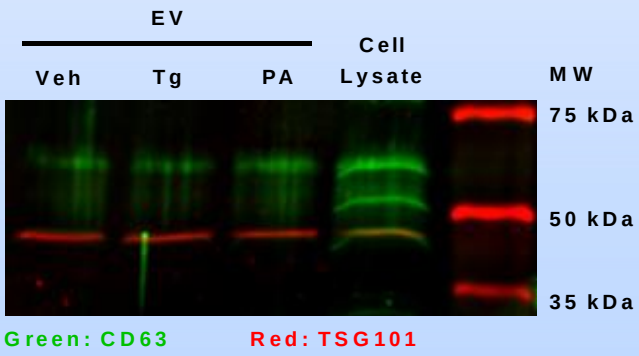
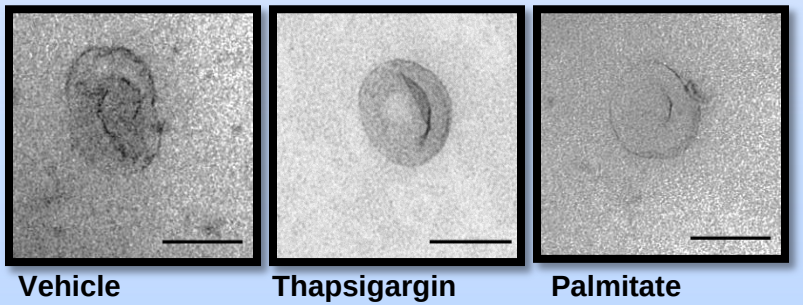
PA-treated Hepatocytes Release EV









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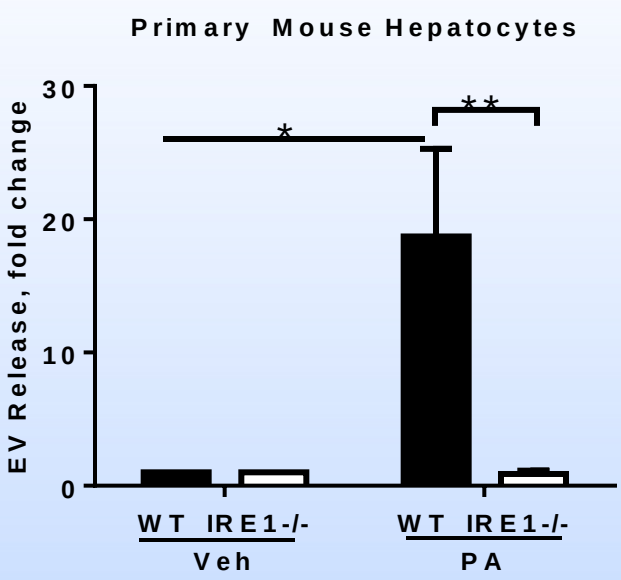
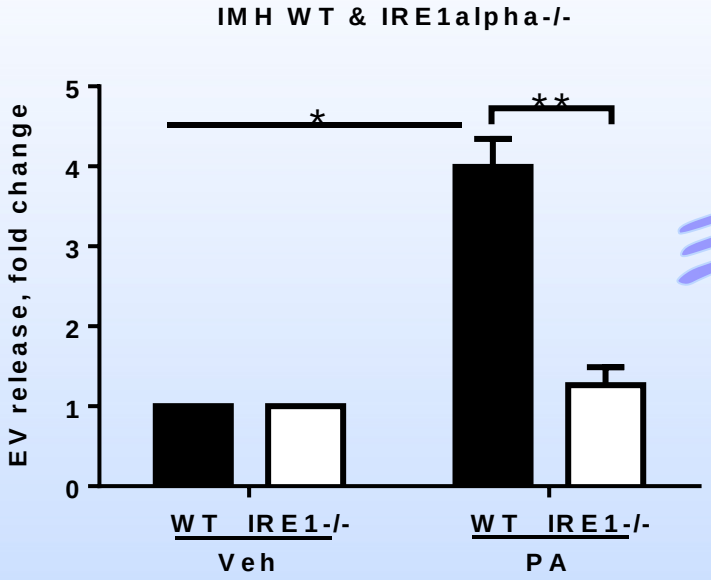
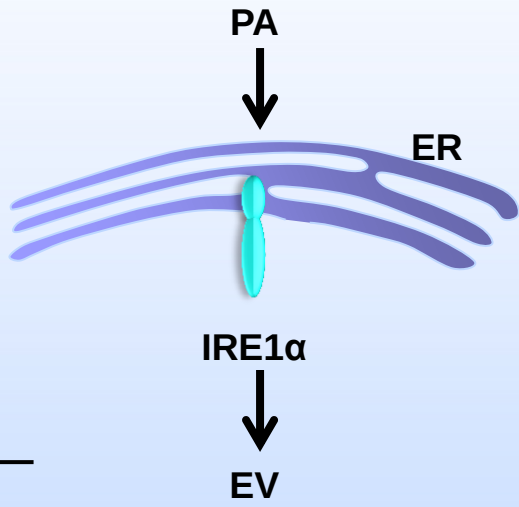
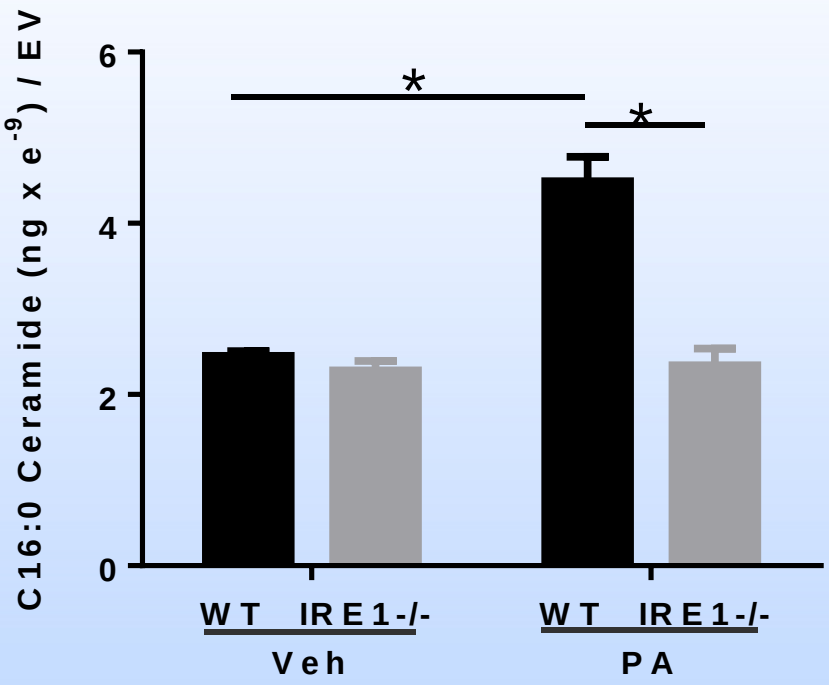
PA-Induced EV Release is IRE1α-dependent

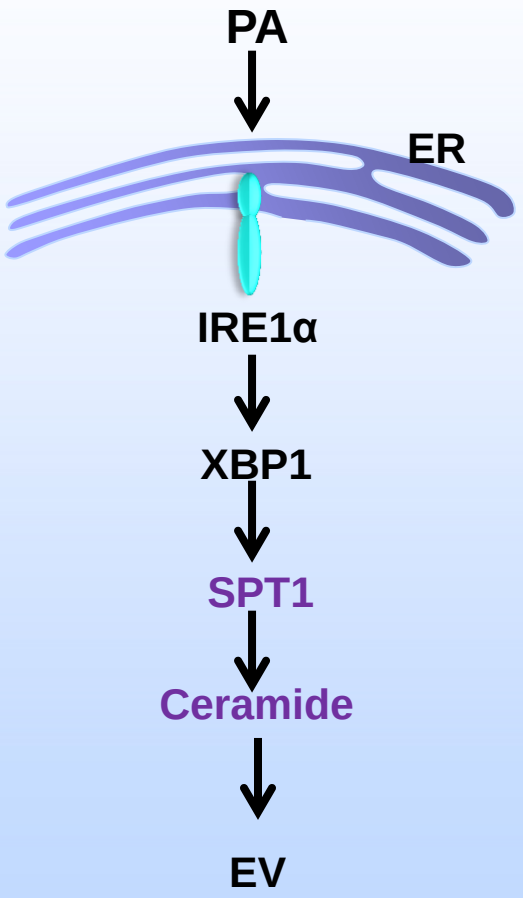




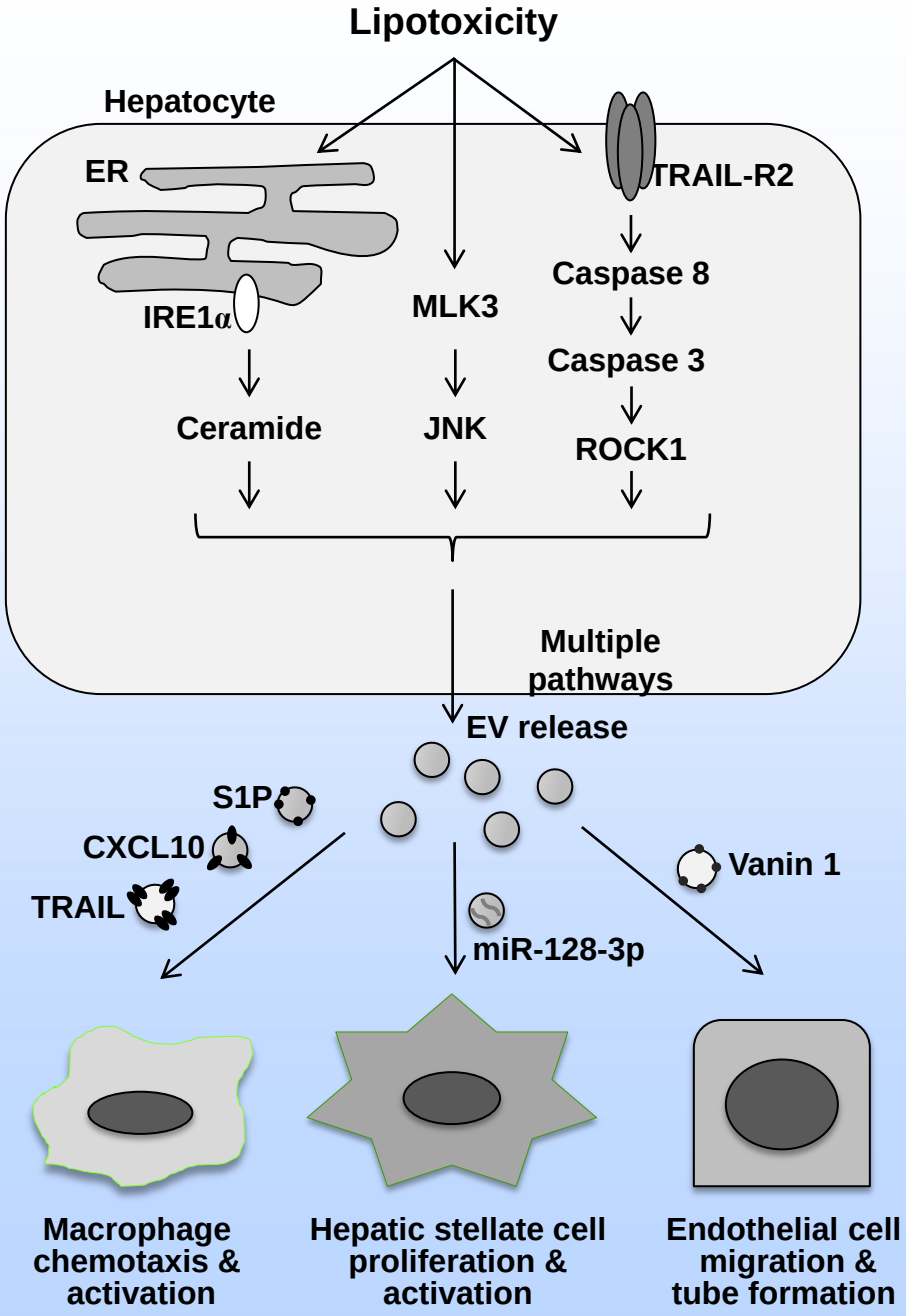


Ceramides are Enriched in PA-stimulated EVs

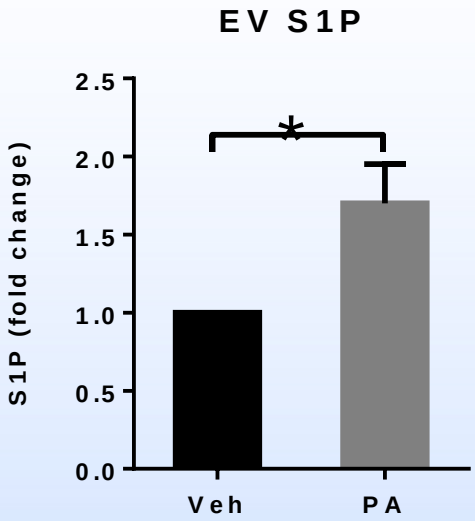


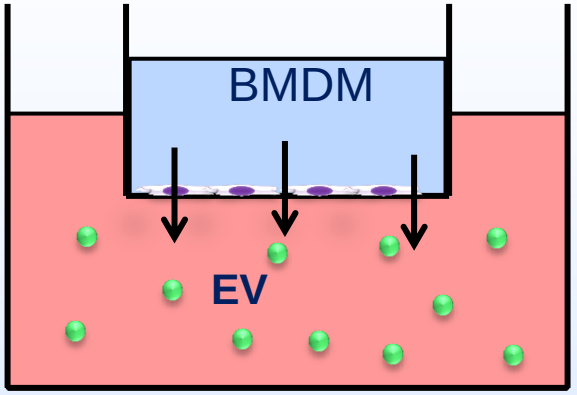


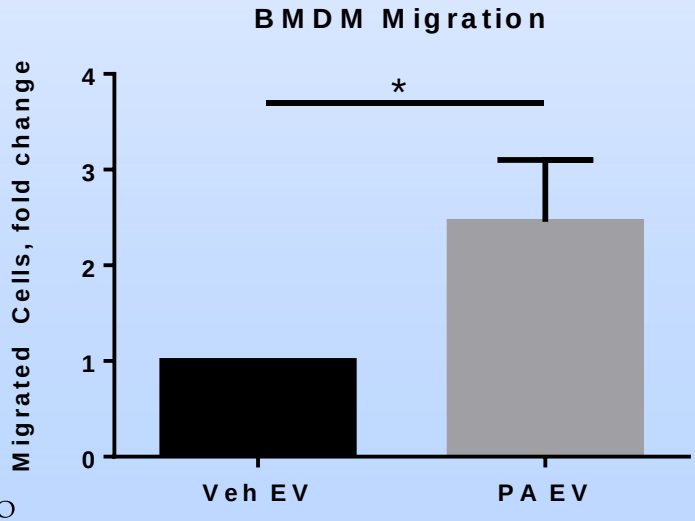
EV Release and Cargo During Lipotoxicity

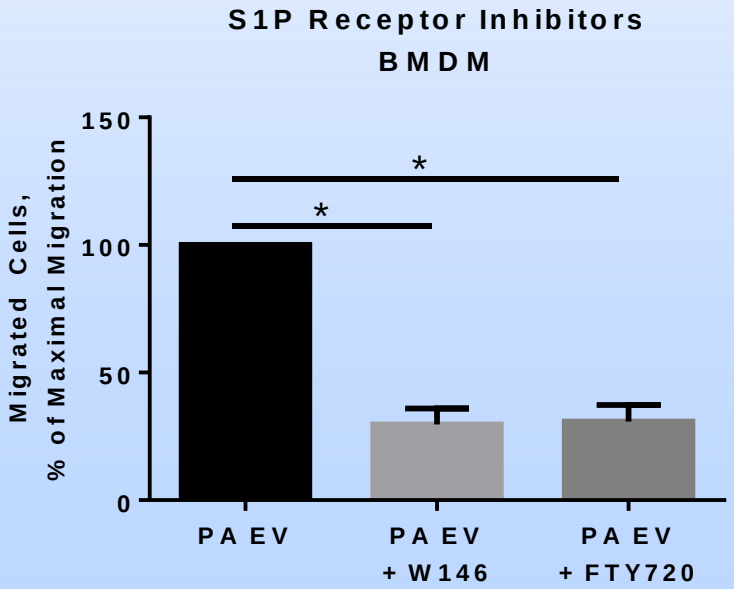


PA-induced EVs are Chemo-attractive to Macrophages via S1P Signaling









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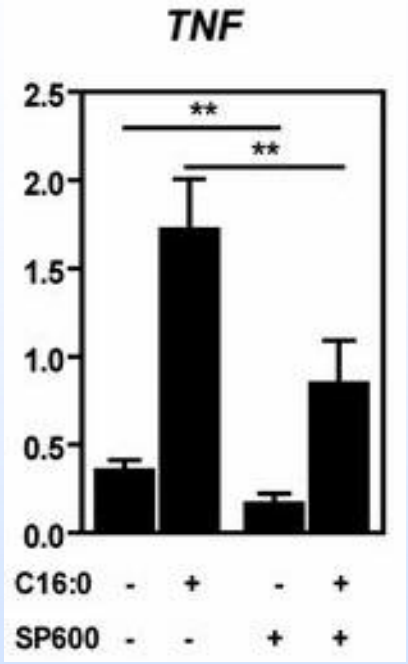
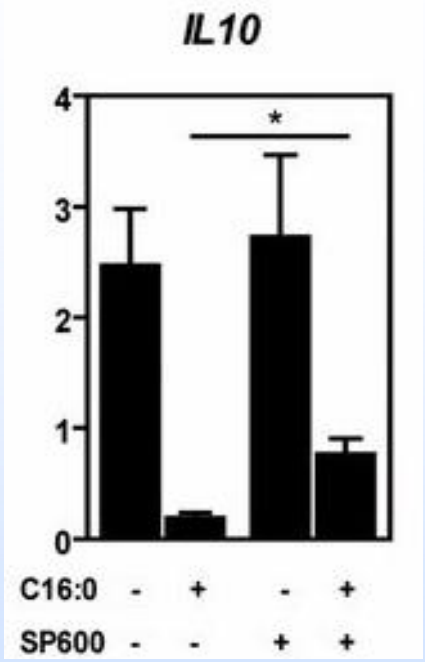
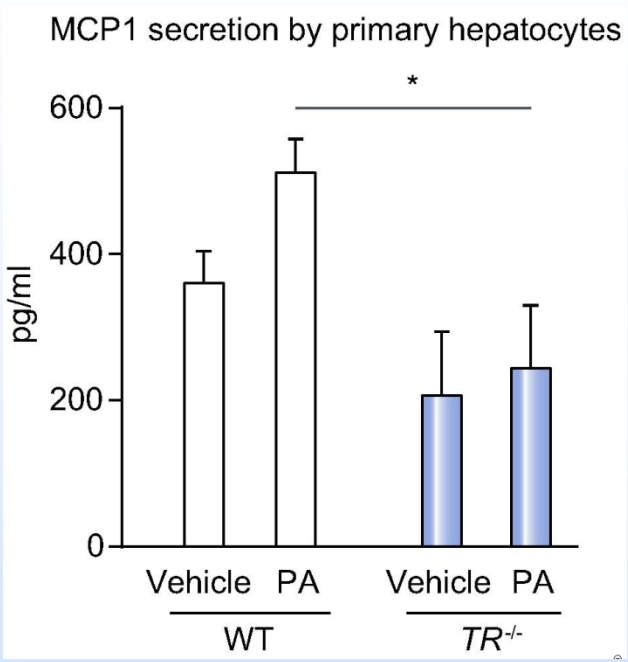
Palmitate Activates Inflammatory Signaling







Macrophages

Hepatocytes

Wen et al. *Nature Immunology* **12**, 408–415 (2011)
Marta Riera-Borrull et al. J Immunol 2017;199:3858-3869
Idrissova et al. J Hepatology 20

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Other Cell Types Targeted by Toxic Lipids

- Palmitate is toxic to isolated hepatic stellate cells
- Palmitate is toxic to isolated cholangiocytes
- … ? in vivo relevance

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What are the Modifiers of Lipotoxicity?

- Small subset of subjects with lipid overload that develop lipotoxicity

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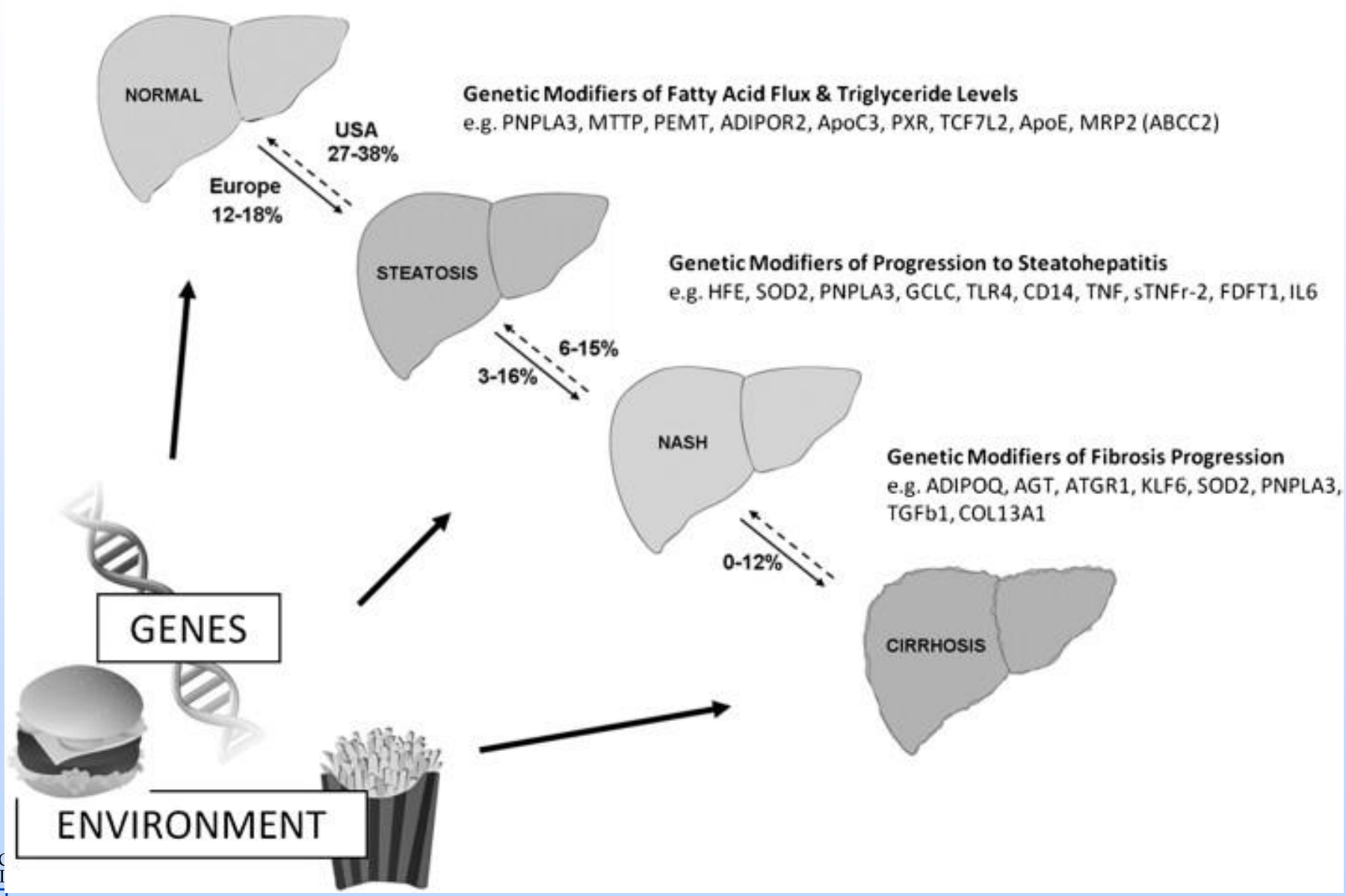
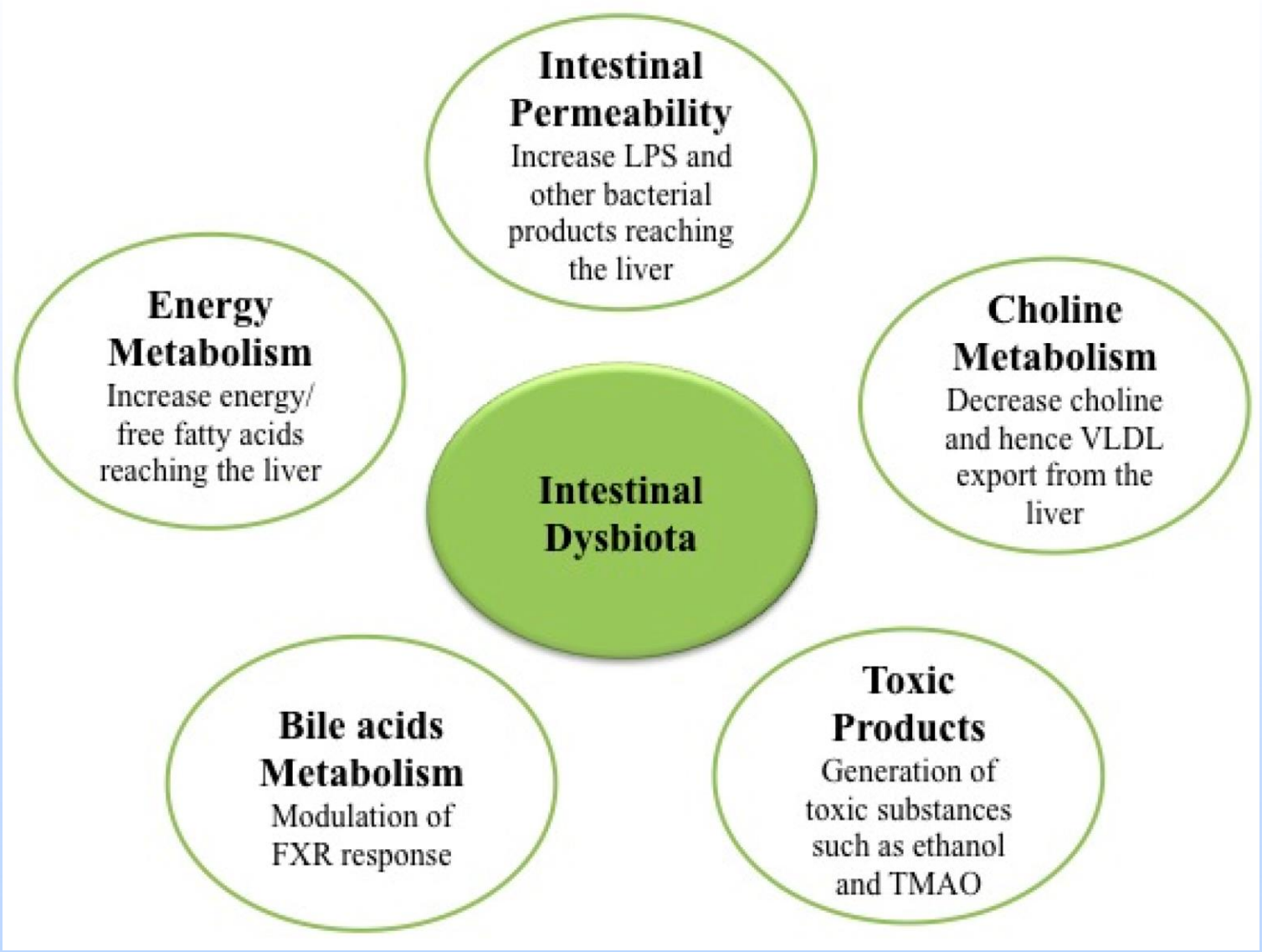
Genetic Modifiers of Lipotoxicity



Anstee. *BBA* 1812(2011), 1557

Microbiome and Lipotoxicity



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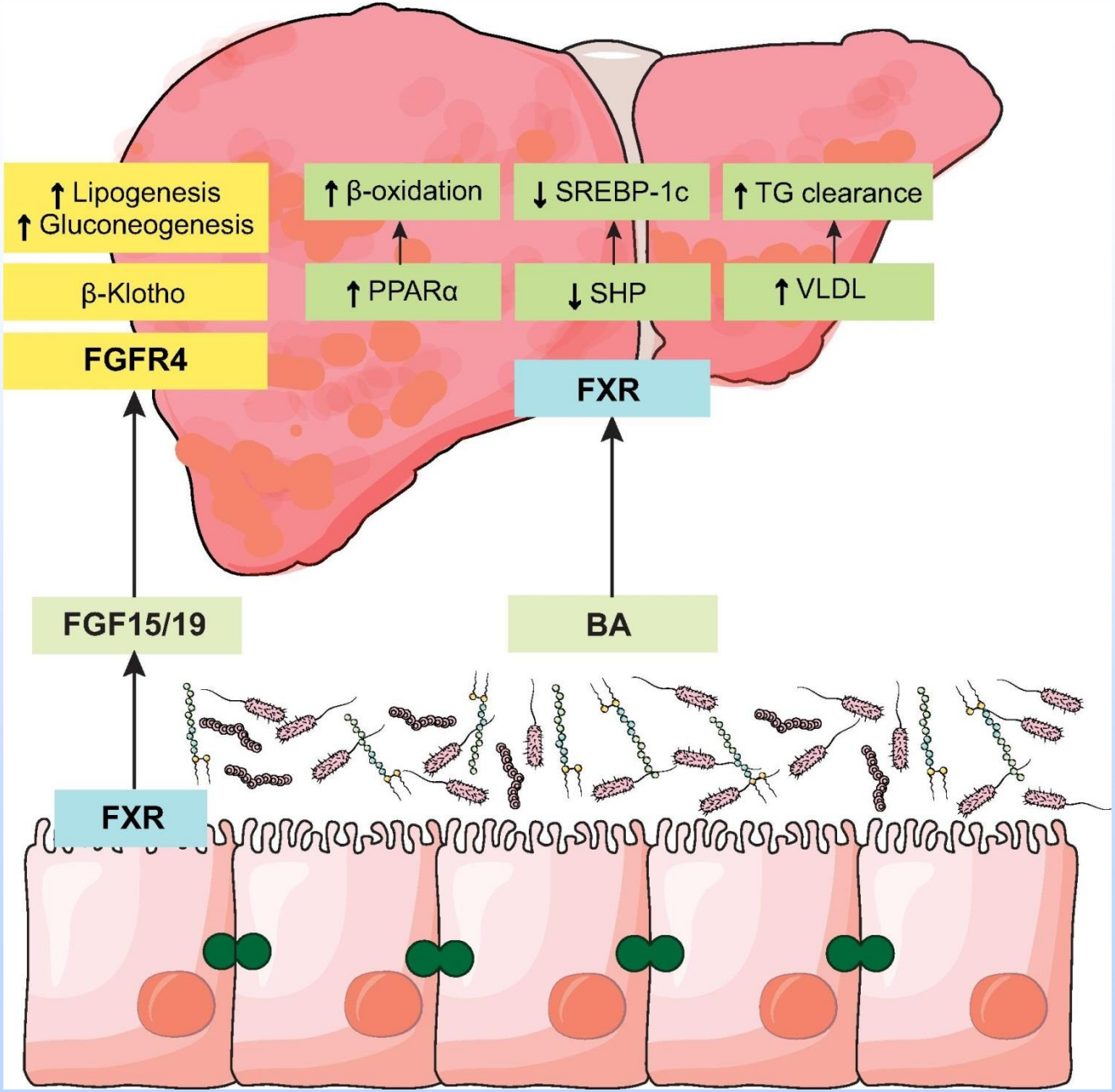
Int. J. Mol. Sci. **2016**, *17*(4), 481

Gut-Liver Axis



Individual Differences in Lipid Species

- Short-lived reactive lipid species
- Other signaling lipids, such as resolvins

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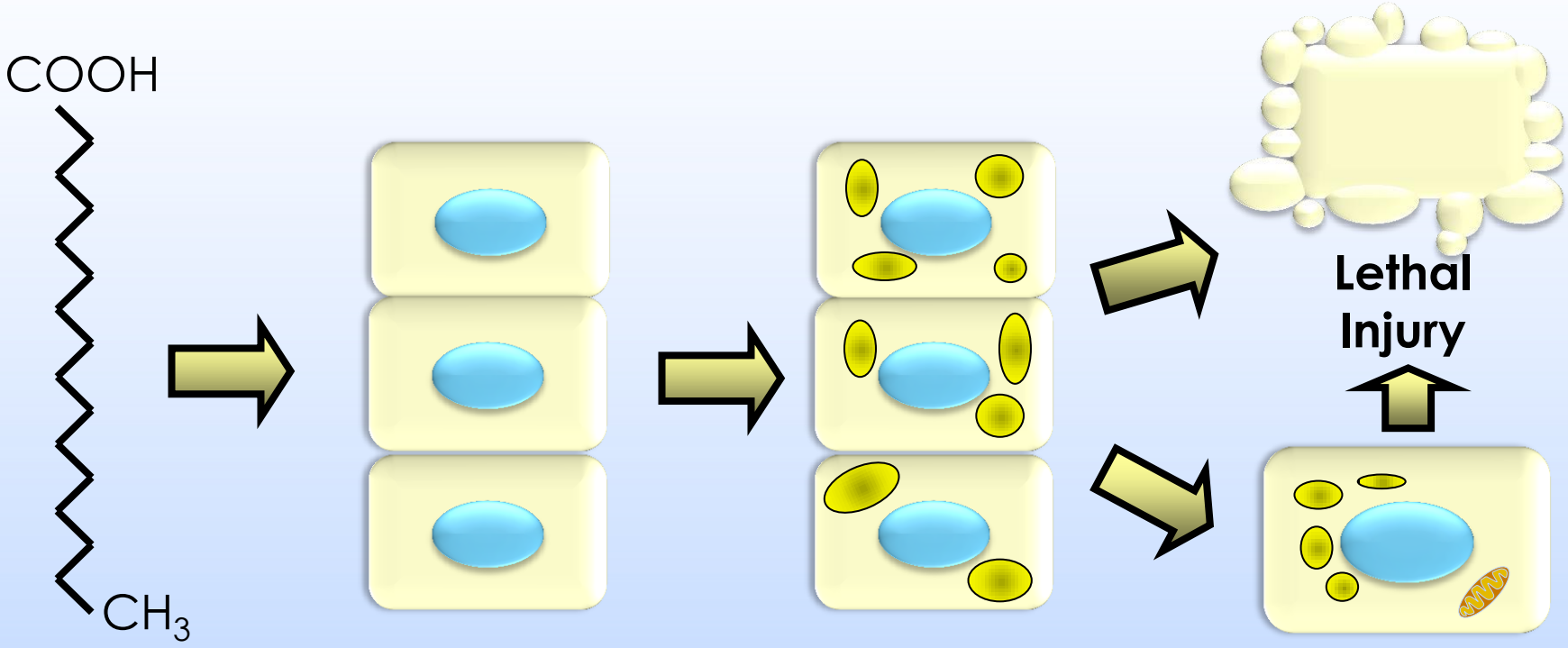
Rius et al. FASEB J. 2014 Feb;28(2):836-48

FFA-induced Sublethal and Lethal Hepatocyte Injury Mediate NASH Pathogenesis



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Thank You

malhi.harmeet@mayo.edu