

NASH Pathogenesis

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Disclosures

- Consultant/Advisor:
 - Allergan, Alnylam, Arrowhead, Axcella, Boehringer Ingelheim, BMS, Durect, Enanta, Ferring, Fortress, Gelesis, Genfit, Gilead, HepGene, High Tide, HistoIndex, Intercept, Lipocine, Madrigal, Medimmune, Merck, Mundipharma, NGM, pH-Pharma, Siemens
- Institutional research grants:
 - Allergan, BMS, Cirus, Cymabay, Enanta, Genfit, Gilead, Intercept, Madrigal, NGM

It's obvious: Full parking garages cause car accidents

- Observations:
 - Most car accidents on city streets occur during the daytime
 - City parking garages are often quite full of cars during the daytime
- Conclusion:
 - Full parking garages cause car accidents



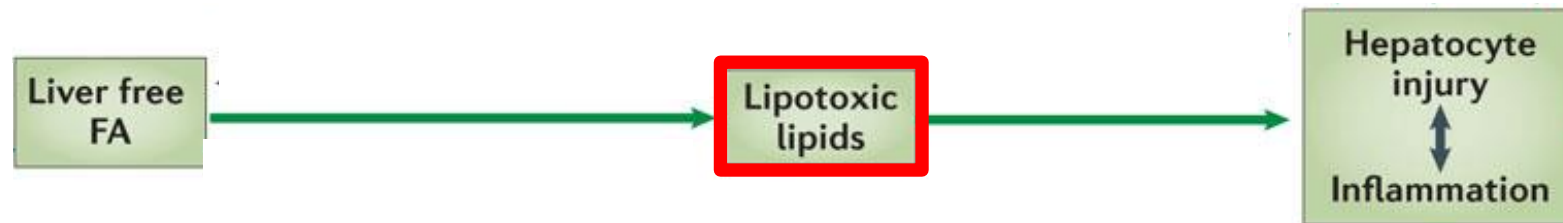
Pathogenesis of NASH

- Pathogenesis not fully understood, complex, multifactorial:
 - Genetics
 - Epigenetics (maternal effects, gut microbiome)
 - Environment: what we do and what we eat
- NASH likely has different underlying causes in different patients
 - Personalized medicine requires understanding the contributing factors in individual patients
 - We are not there yet

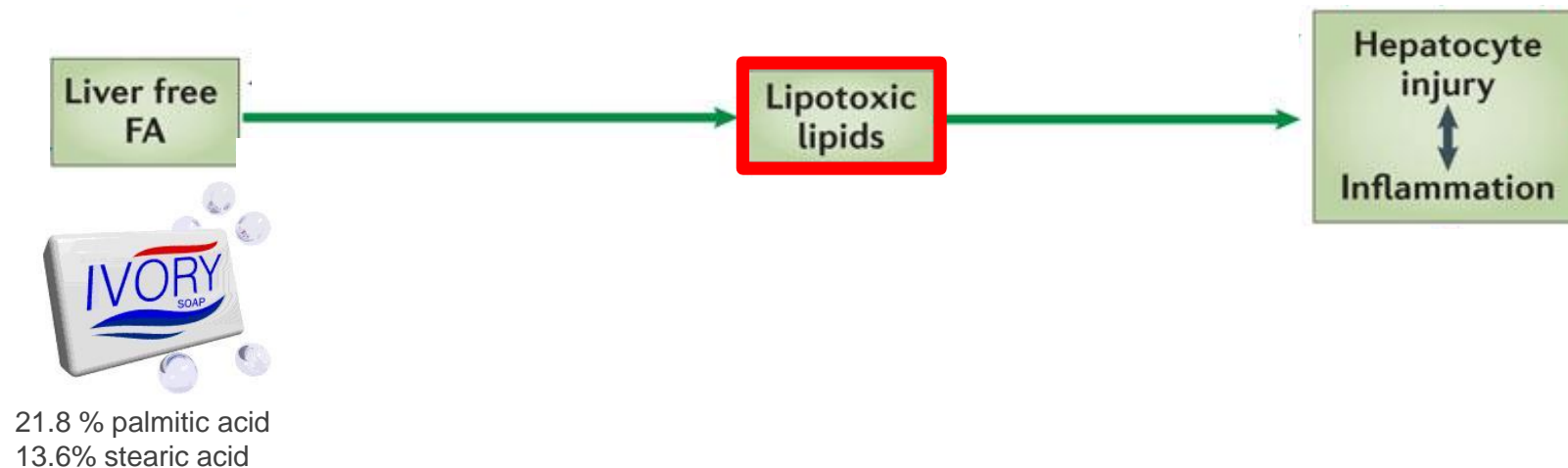
Pathogenesis of NASH

- “Substrate overload lipotoxic liver injury”
 - Free fatty acids promote the generation of toxic lipids to cause NASH
 - Neuschwander-Tetri. Hepatology 2010;52:774–788.
 - Cusi. Gastroenterology 2012;142:711–725.
 - Fuchs. J Hepatol 2012;56:291–293.
 - Mota. Metabolism 2016;65:1049–1061.
 - Hardy. Annu Rev Pathol 2016;11:451–496.
 - Machado. Gastroenterology 2016;150:1769–1777.
 - Hirsova. J Lipid Res 2016;57:1758–1770.
 - Marra. J Hepatol 2018;68:280–295.
 - Musso. Gastroenterology 2018;155:282–302.
- It’s not all about triglyceride (fat droplets) in the liver
 - Triglyceride (think Crisco) is inert
 - Storage of fatty acids at triglyceride may be a protective response
 - Contrary view: Romeo. Cell Metab 2020;31: 35-45.

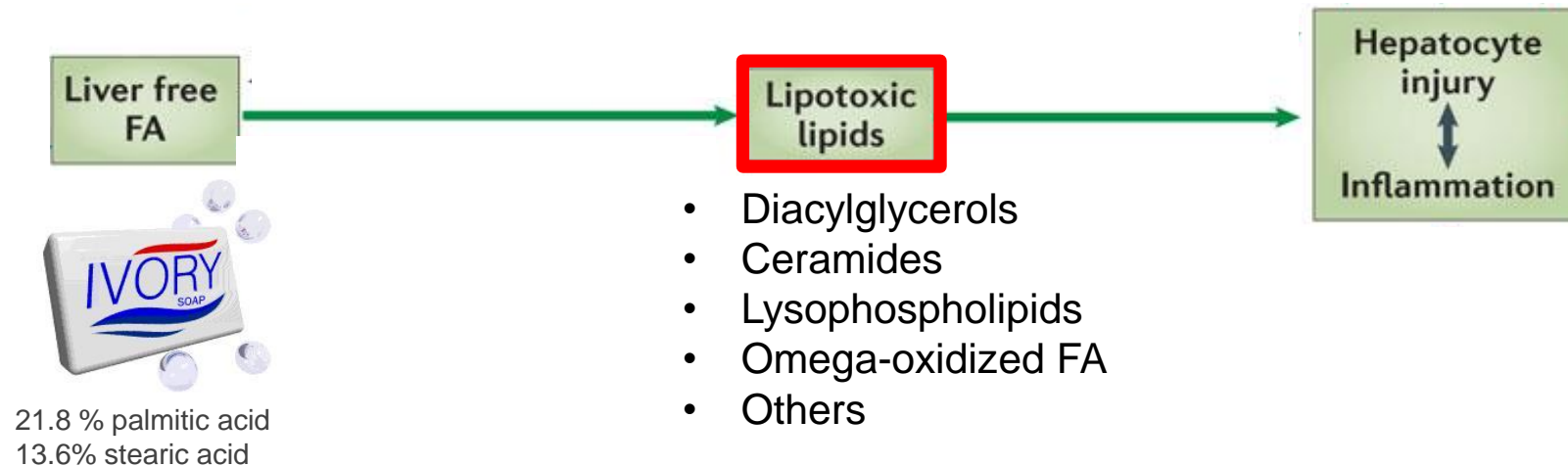
Pathogenesis of NASH (lipotoxic liver injury)



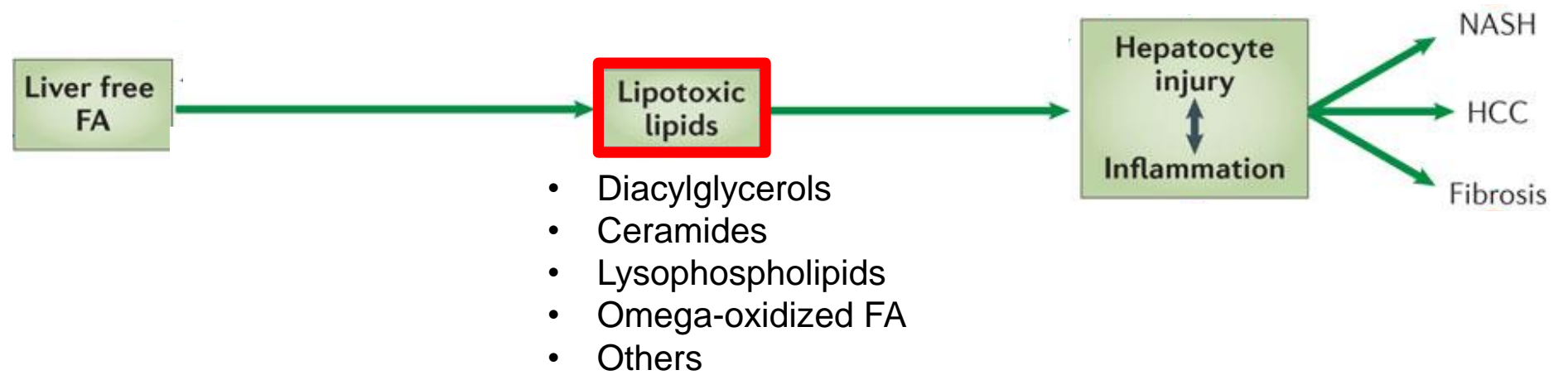
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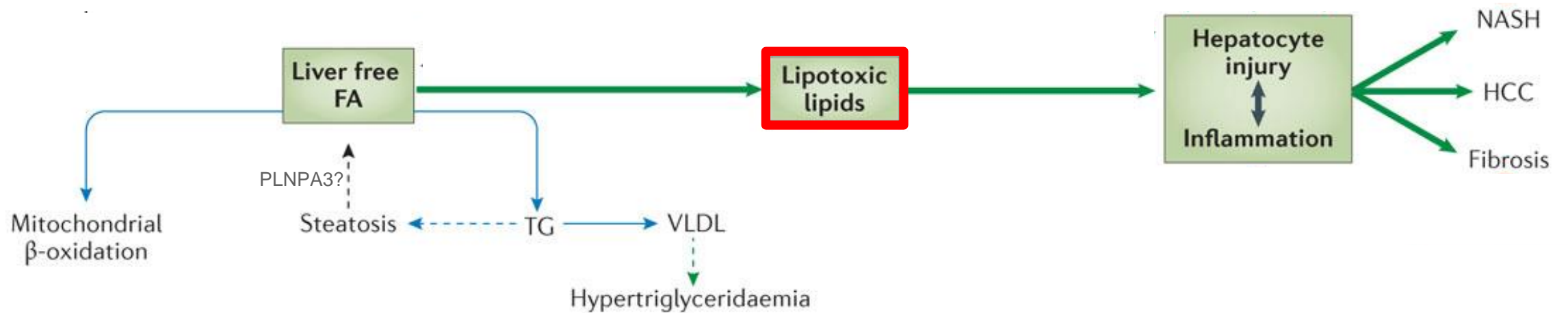
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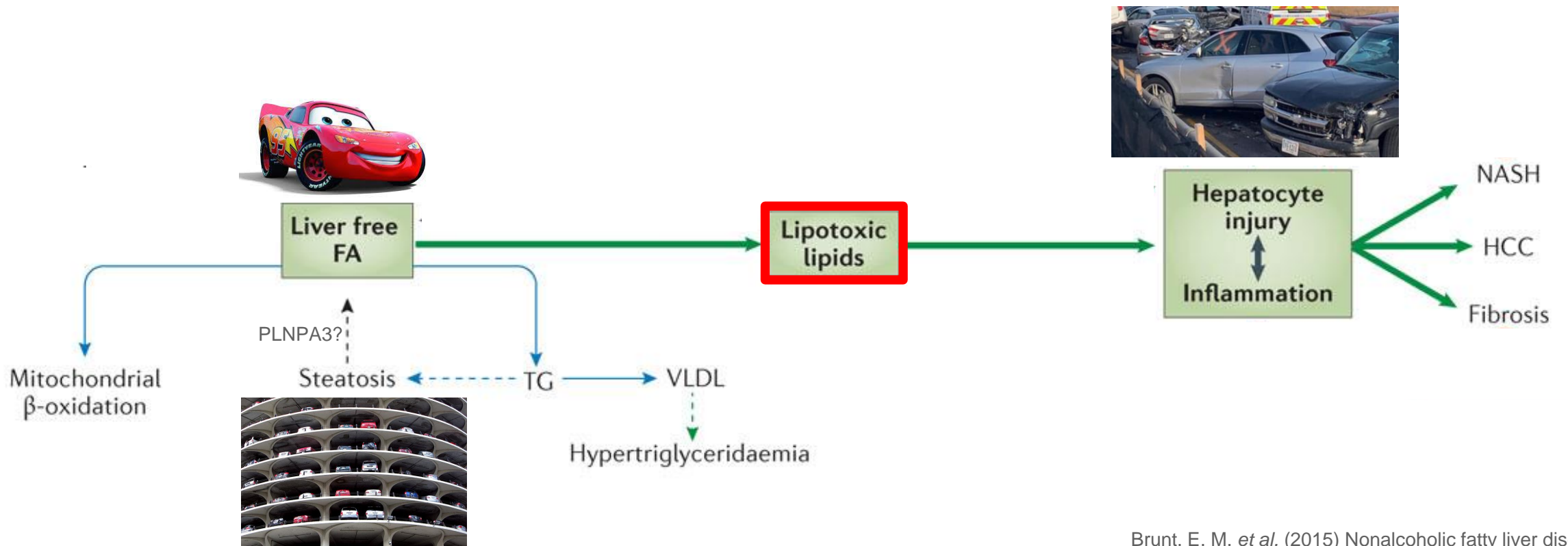
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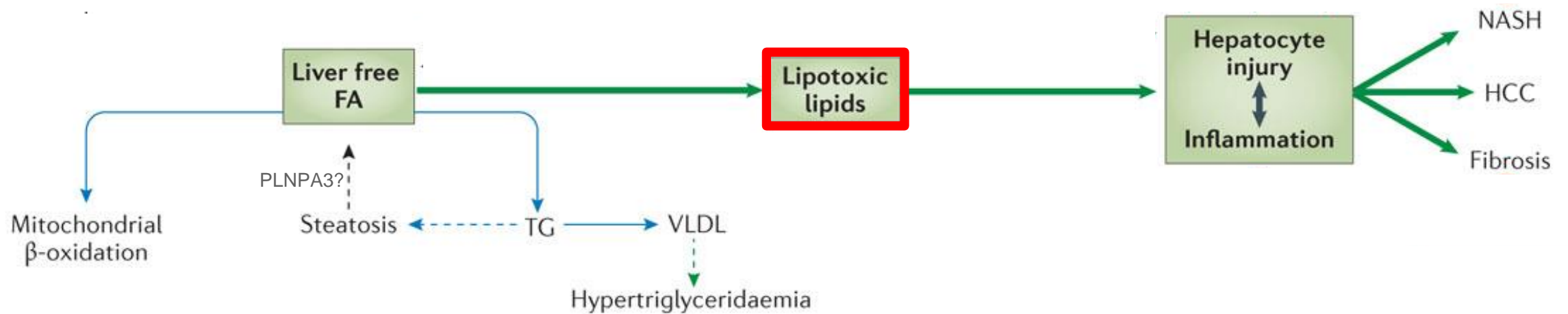
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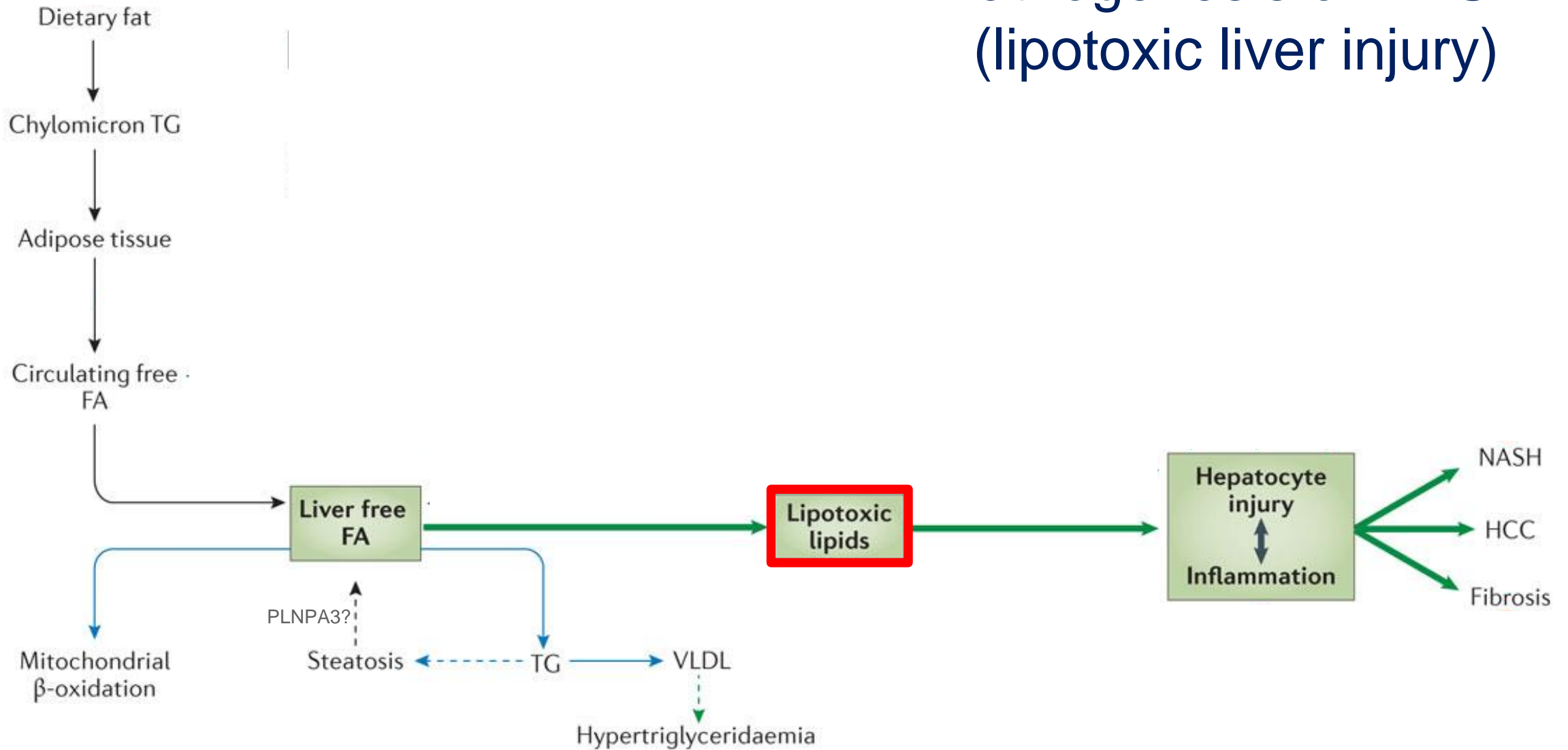
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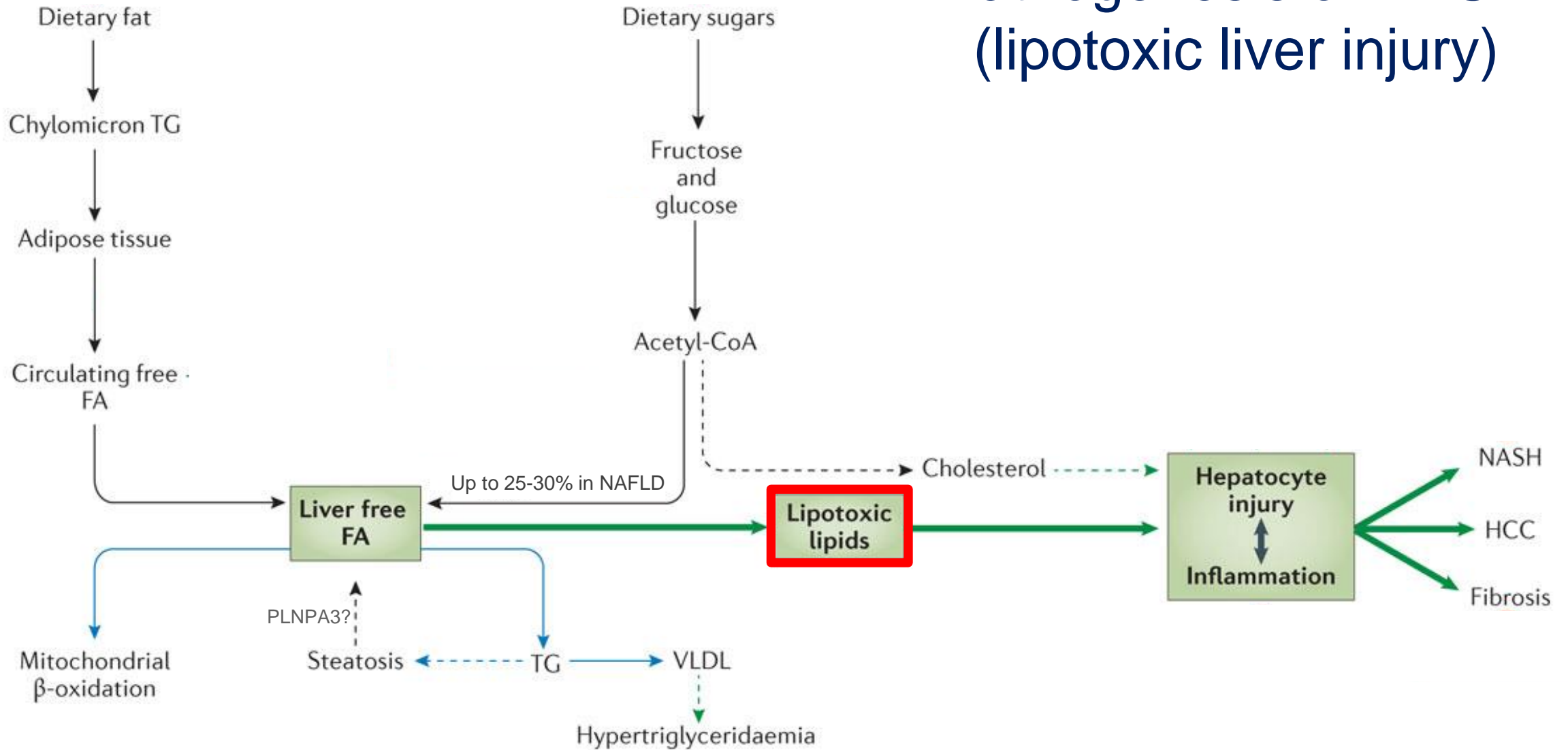
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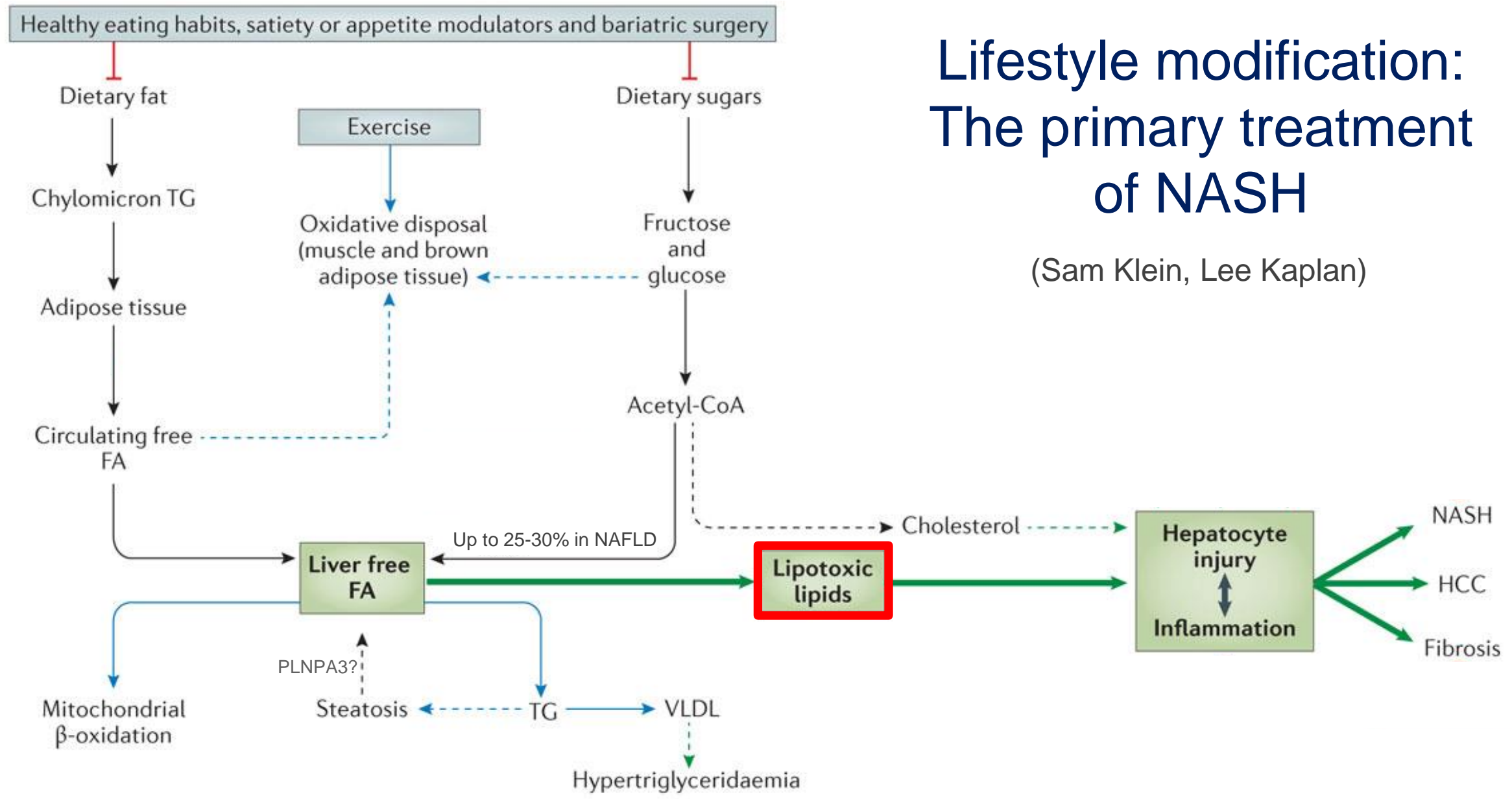


Pathogenesis of NASH (lipotoxic liver injury)



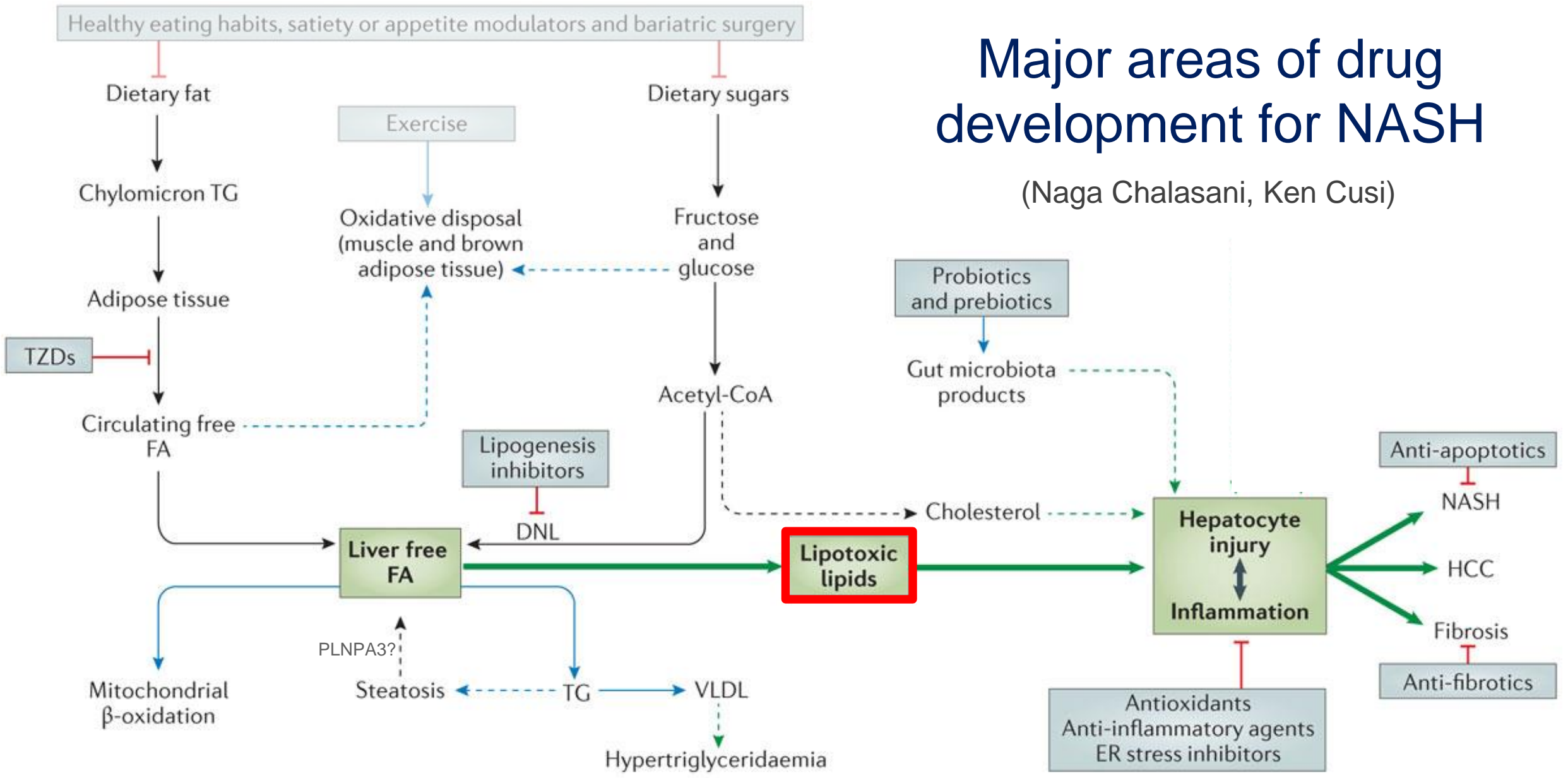
Lifestyle modification: The primary treatment of NASH

(Sam Klein, Lee Kaplan)



Major areas of drug development for NASH

(Naga Chalasani, Ken Cusi)



Neuschwander-Tetri, B. A. *Hepatology* (2010) 52: 774-788

Brunt, E. M. et al. (2015) *Nat. Rev. Dis. Primers* doi:10.1038/nrdp.2015.80