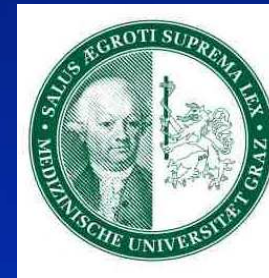




NAFLD: Advances in Pathogenesis

Michael Trauner
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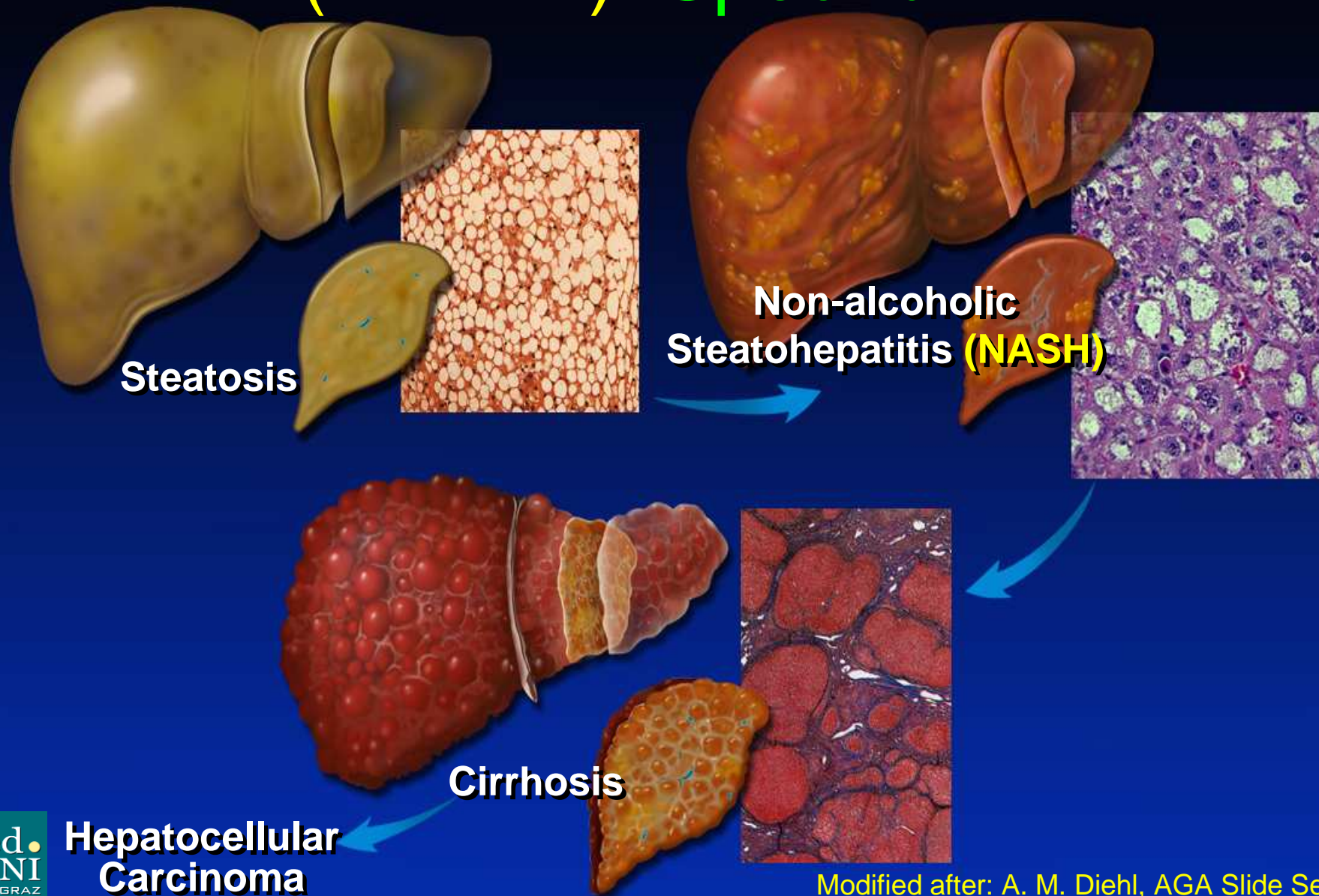


Advances Pathogenesis of NAFLD

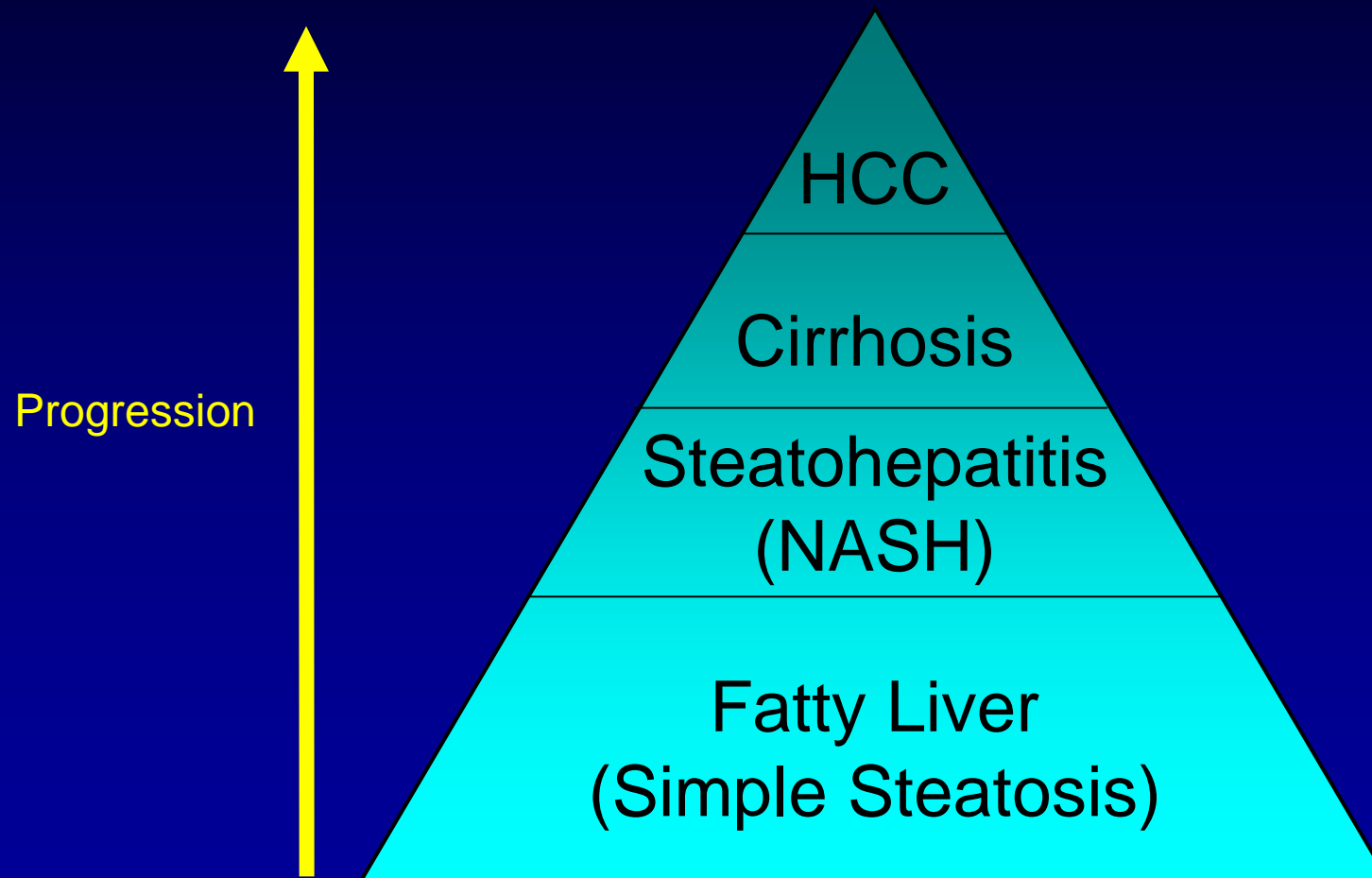
Key Concepts

- Lipocentric view – lipotoxicity (FA)
- Cytokines & oxid. stress ~ final pathway
- Novel genetic markers (KLF6, PNPLA3)
- Diet (fructose, trans fats)
- Moderate C₂ (<10g/d) protective (IR)
- Role of obstructive sleep apnea (hypox)
- Bacterial overgrowth, permeability (diet)

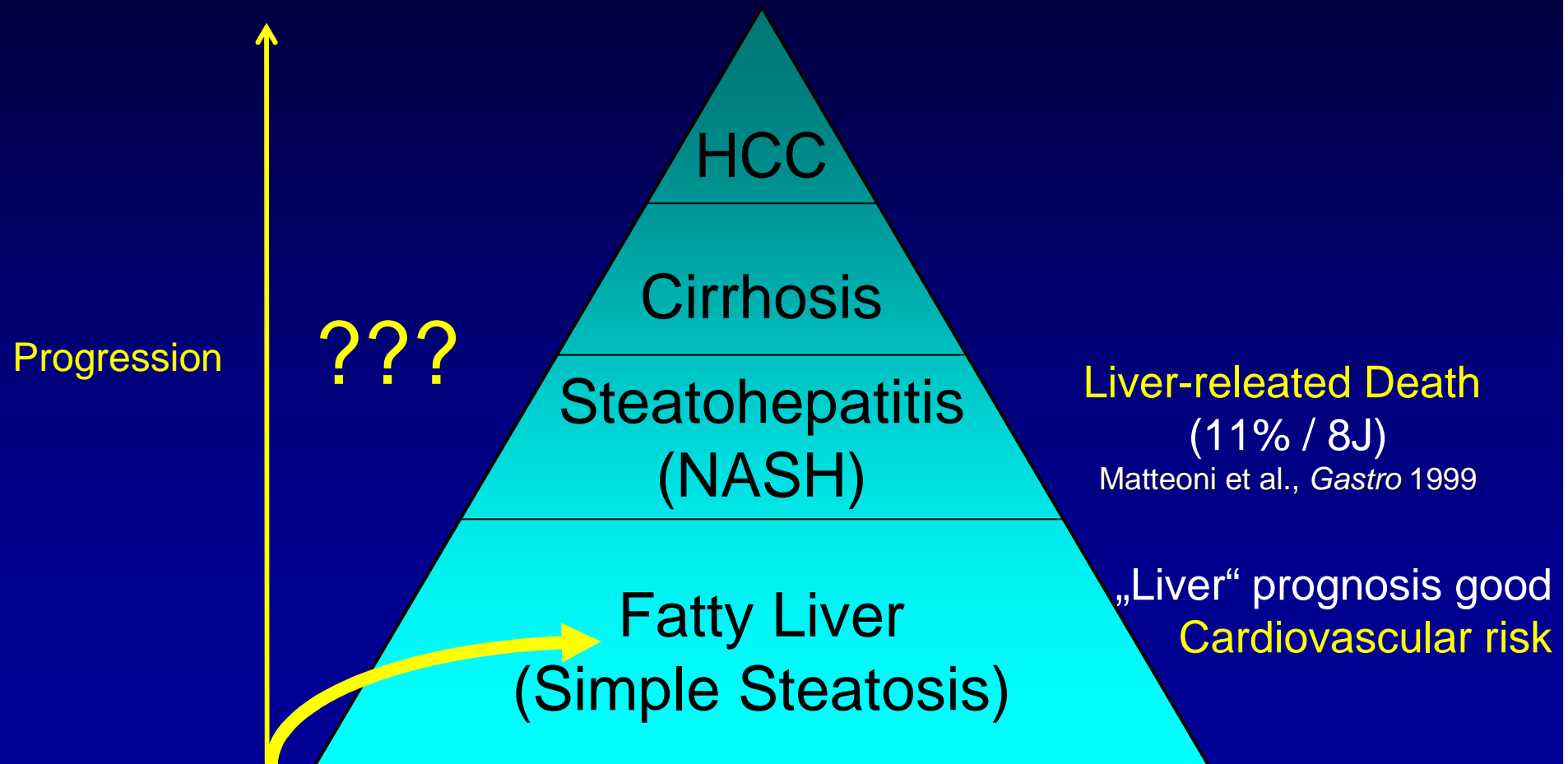
Non-alcoholic Fatty Liver Disease (NAFLD): Spectrum



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Adams et al., *Gastro* 2005; 129: 113

Ruttmann et al., *Circulation* 2005; 112: 2130

Ioannou et al., *Hepatology* 2006; 43: 1145

NAFLD & Metabolic Syndrome



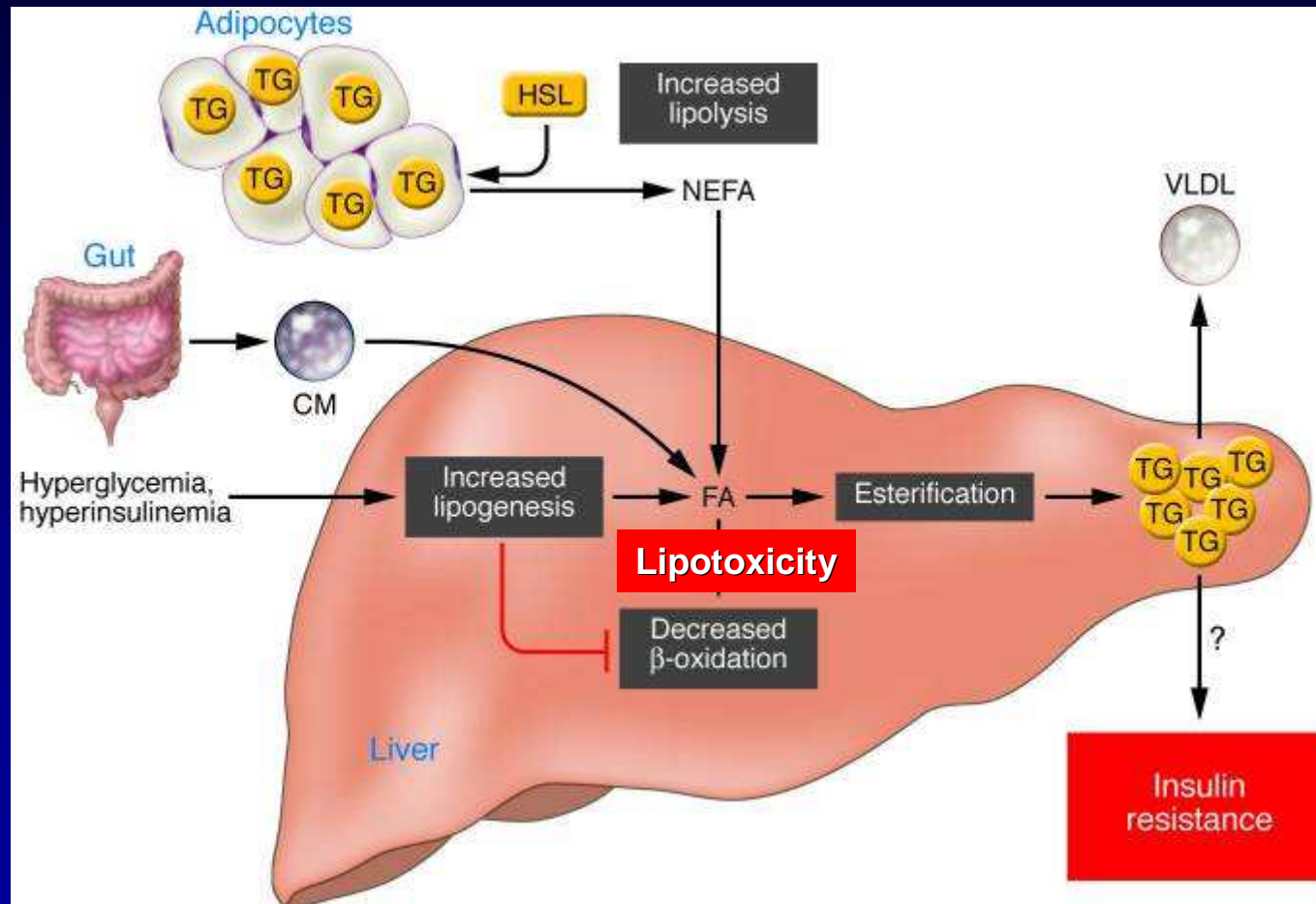
- **Primary NAFLD**
 - Insulin resistance

Central obesity
T2D, Glc >100
HDL-Chol <50
TG >150

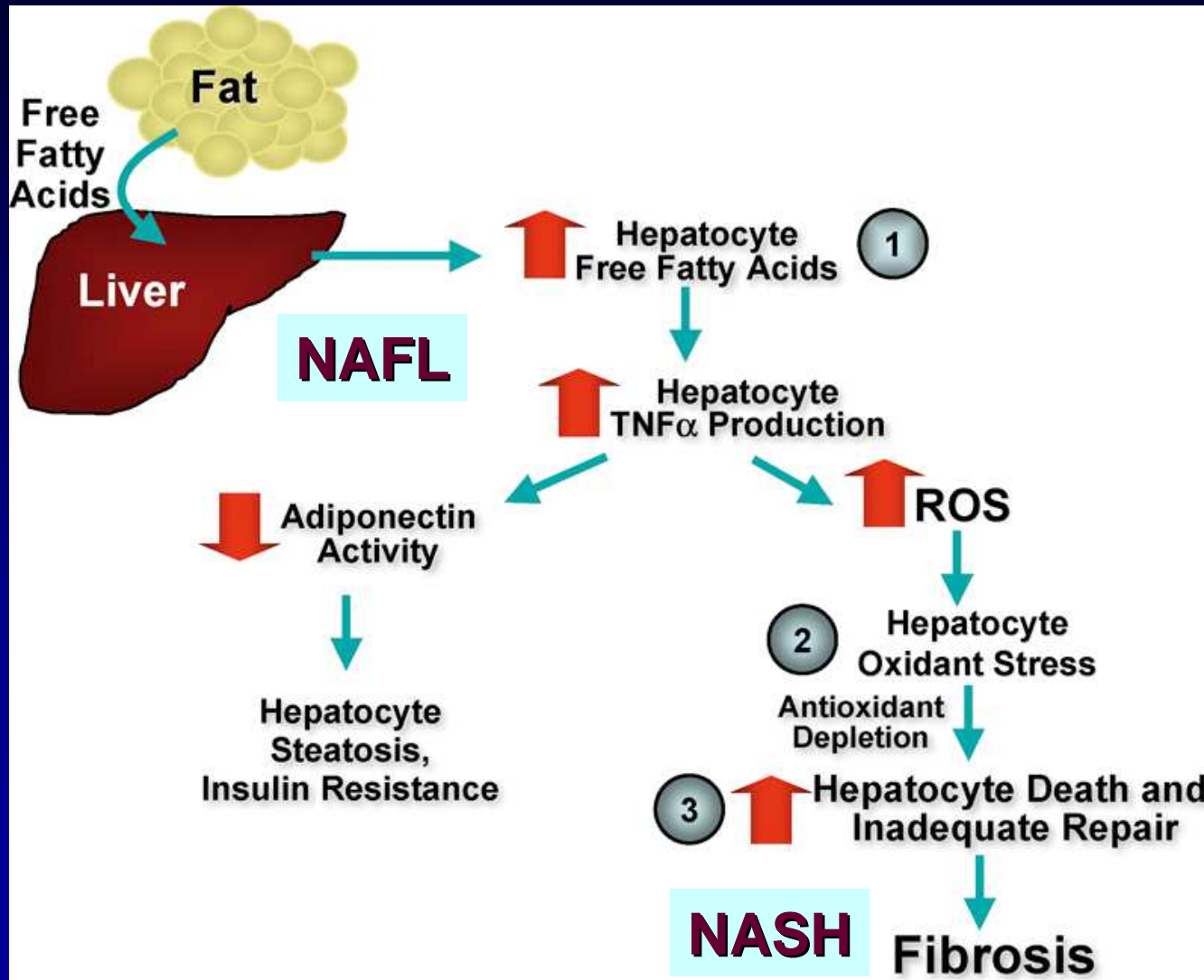
- **Other causes (2° NAFLD)**
 - Drugs (e.g., tamoxifen)
 - Total-parenteral nutrition
 - Intestinal bacterial overgrowth

Chitturi et al., *Hepatology* 2002; 35: 373
Marchesini et al., *Hepatology* 2003; 37: 917
Bugianesi et al., *Hepatology* 2005; 42: 987

Metabolic Defects Leading to the Development of Primary NAFLD

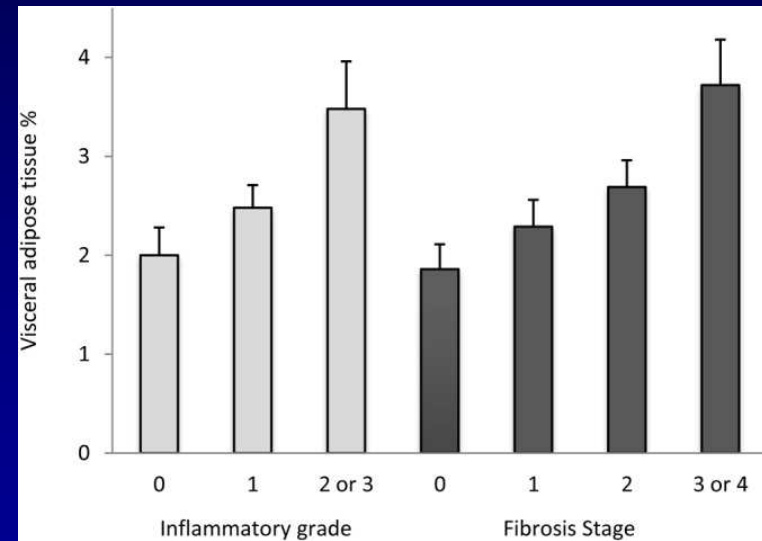
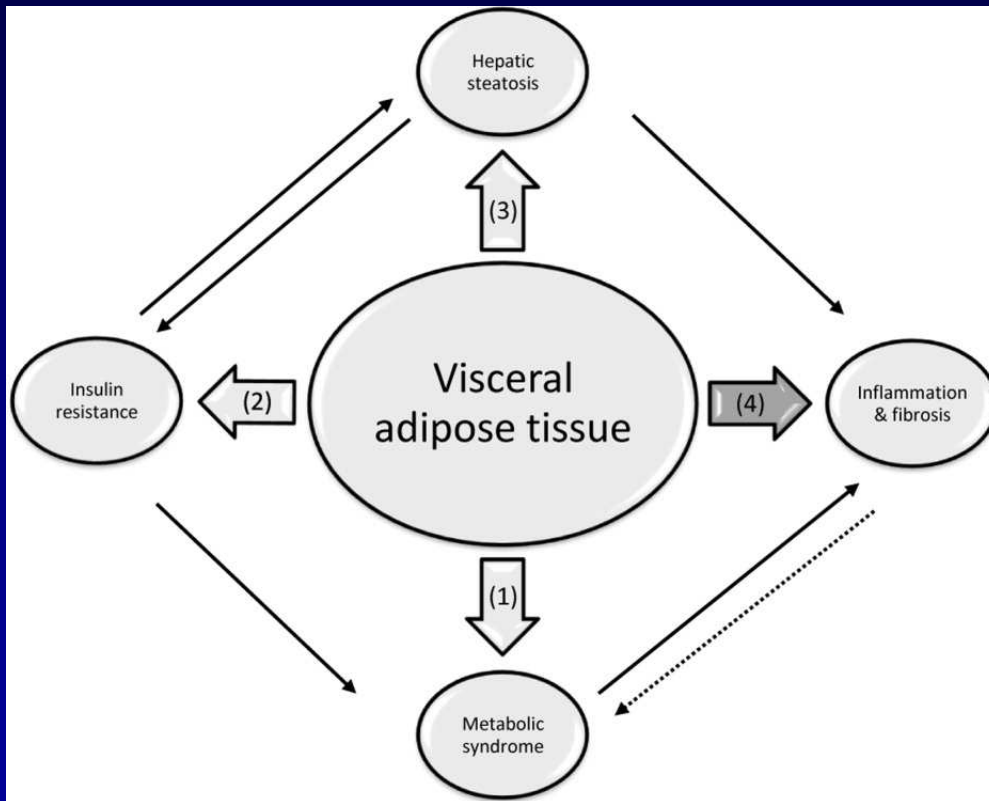


FA as Initiators of Hepatic Inflammation Oxidative Stress, & Fibrogenesis

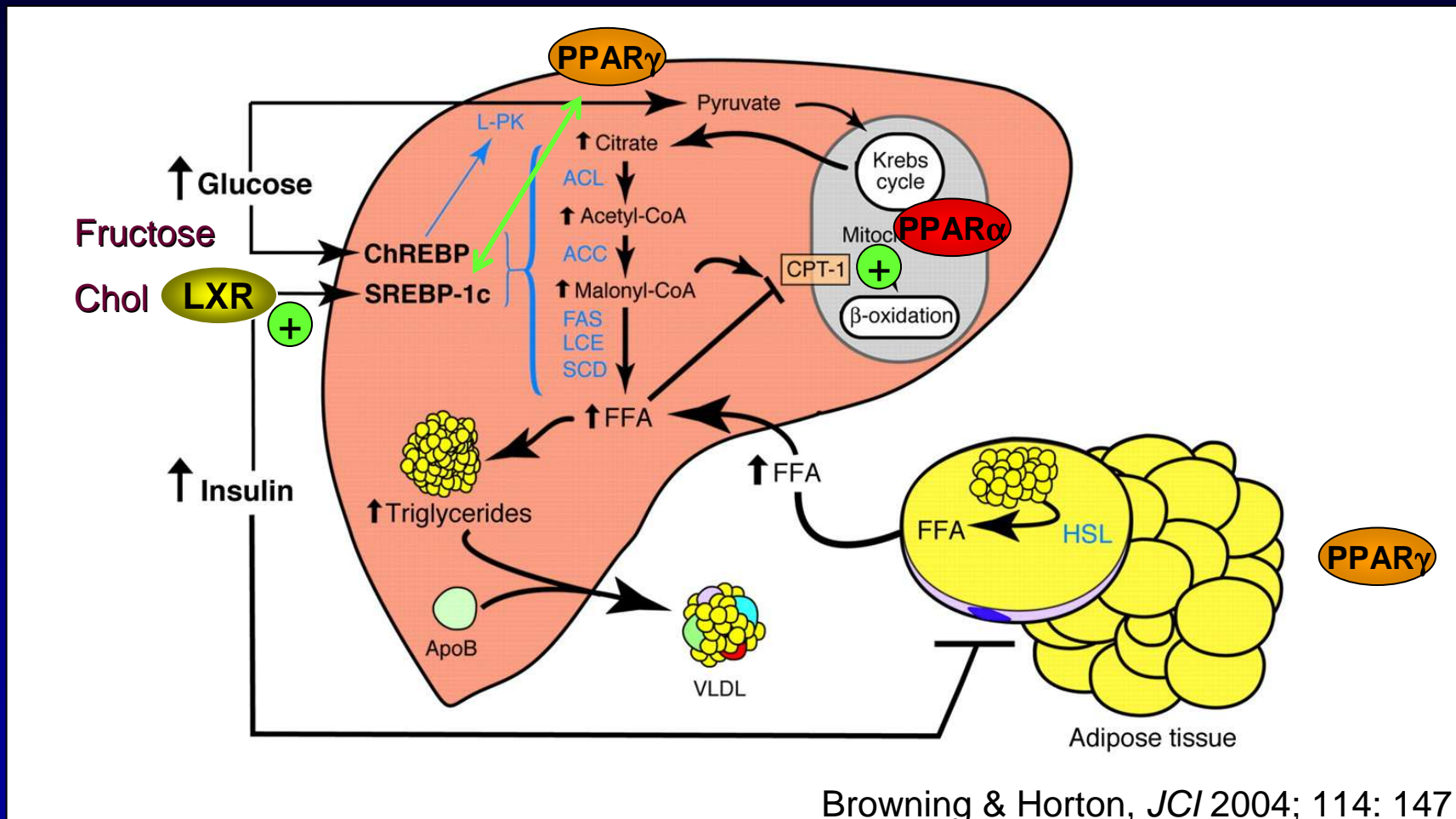


Visceral Fat: A Key Mediator of Steatohepatitis in Metabolic Liver Disease

David van der Poorten,¹ Kerry-Lee Milner,² Jason Hui,³ Alexander Hodge,¹ Michael I. Trenell,⁴ James G. Kench,⁵ Roslyn London,¹ Tony Peduto,⁶ Donald J. Chisholm,² and Jacob George¹

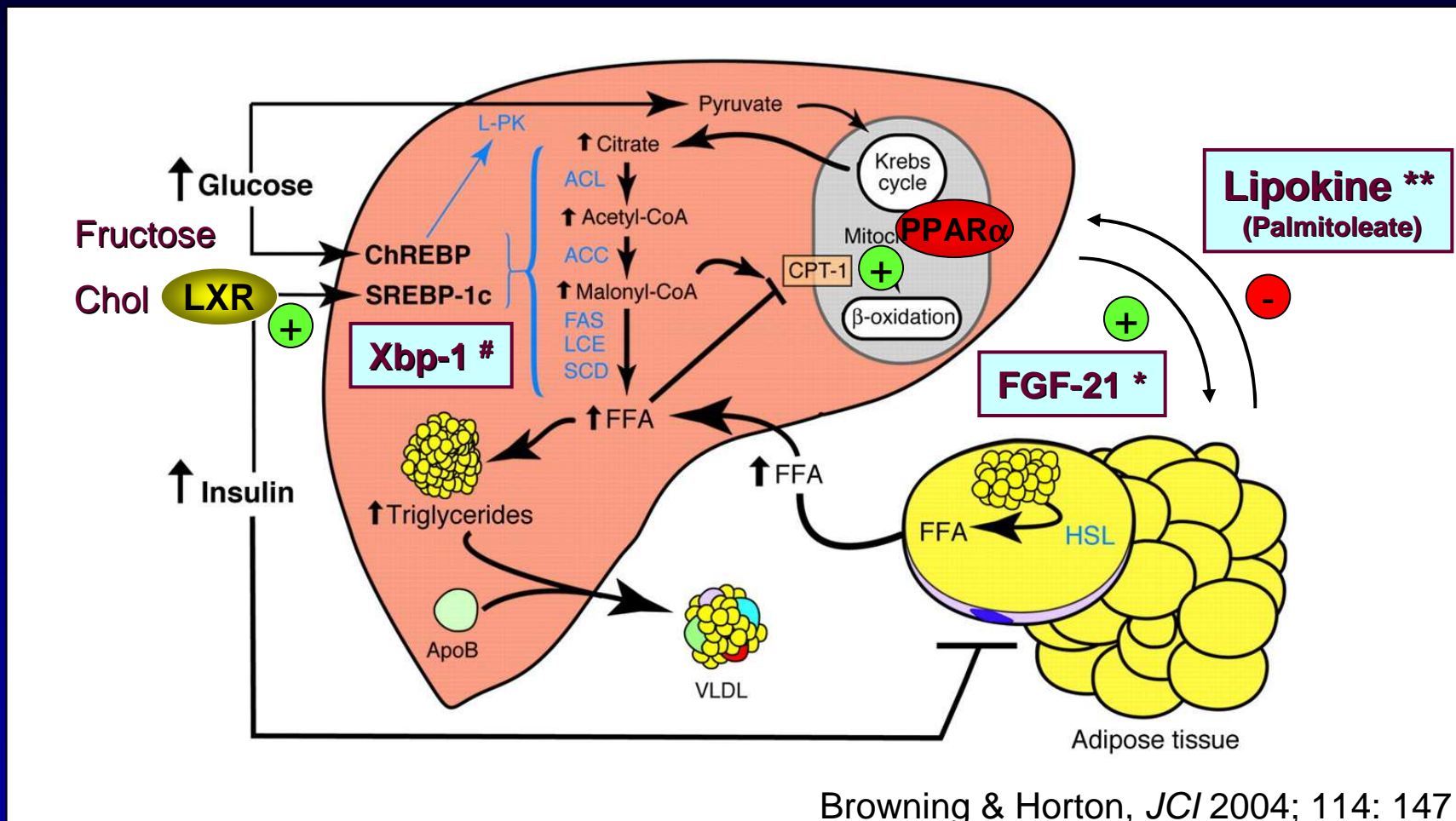


Molecular Regulation of Hepatic FA and TG Metabolism in NAFLD



Browning & Horton, *JCI* 2004; 114: 147
 Reddy & Rao, *AJP* 2006; 290: G852

New Players in Regulation of Hepatic FA and TG Metabolism in Mice



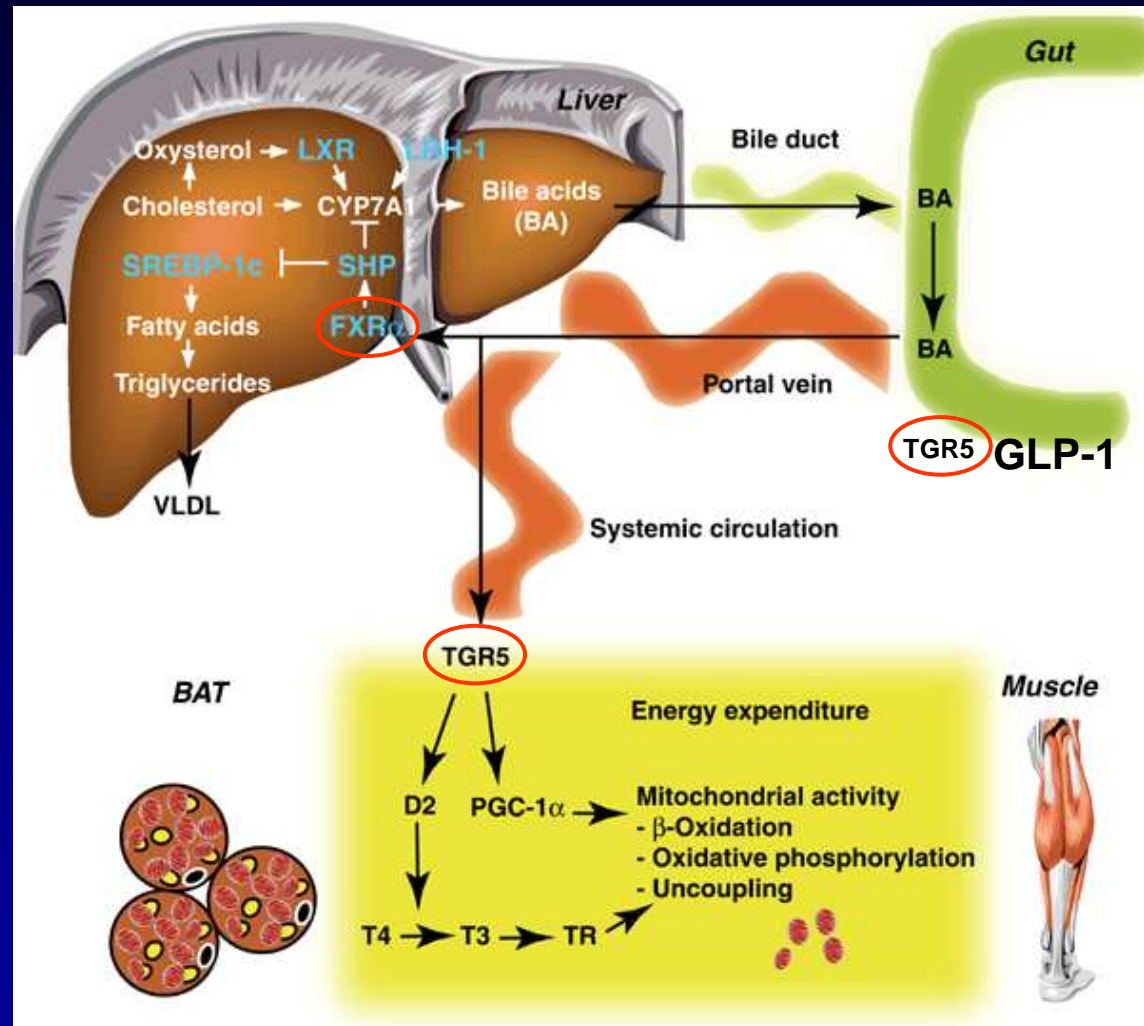
Browning & Horton, *JCI* 2004; 114: 147

*Inagaki et al. *Cell Metabolism* 2007; 4: 405

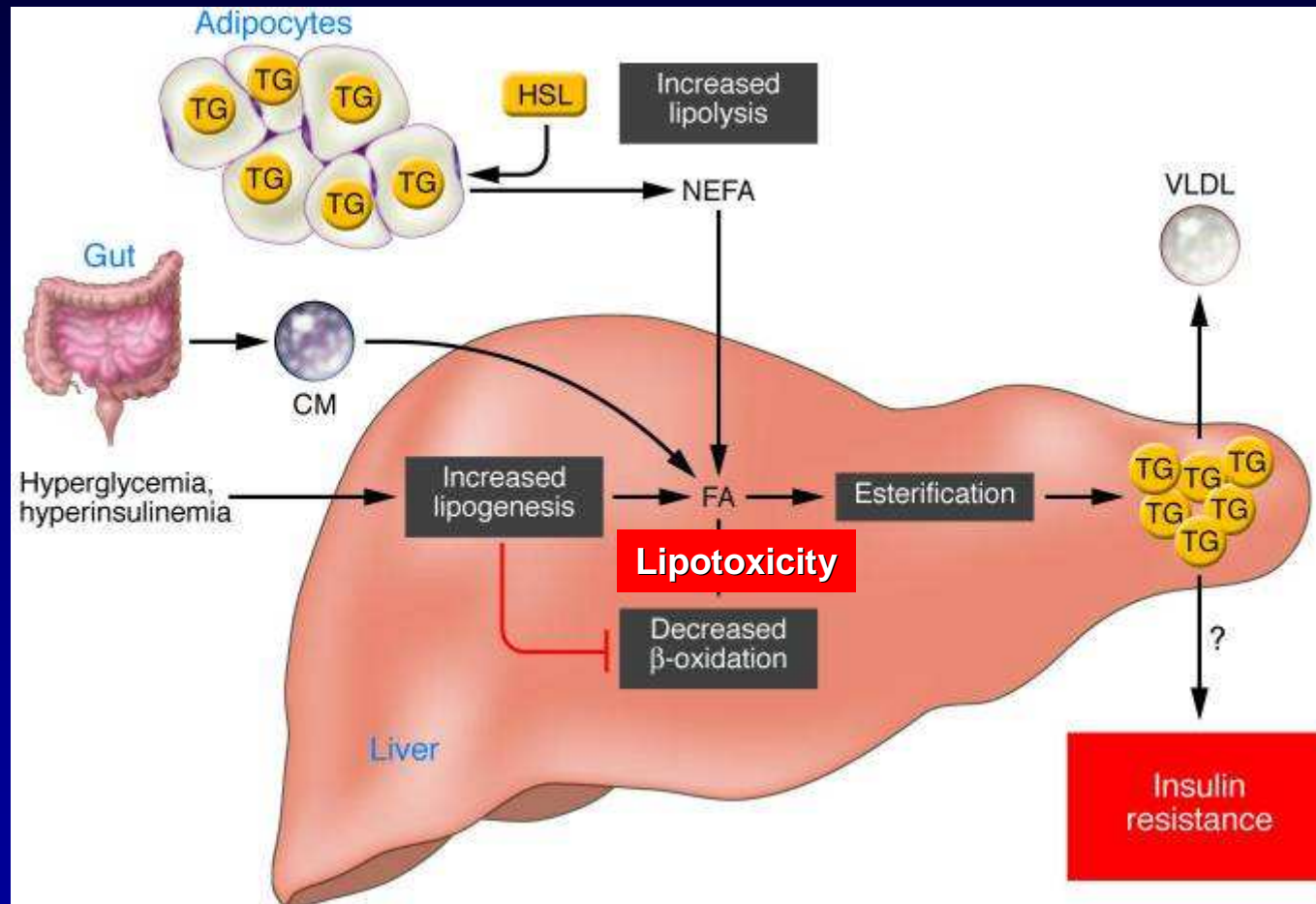
**Cao et al., *Cell* 2008;134: 933

#Lee et al., *Science* 2008; 320: 1492

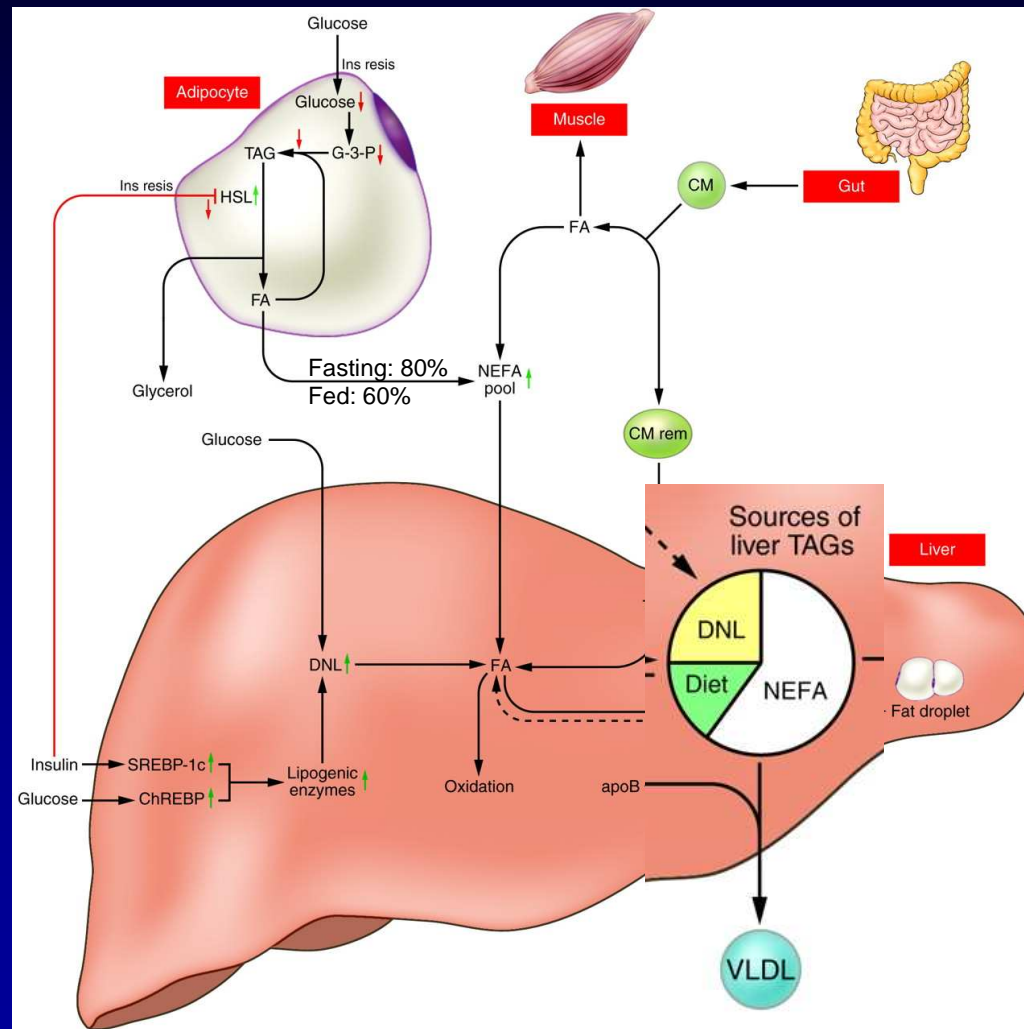
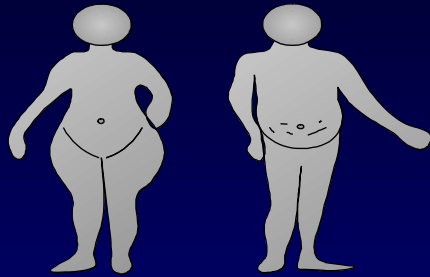
Bile Acids (BA) as Modulators of Hepatic FA and TG Metabolism in NAFLD



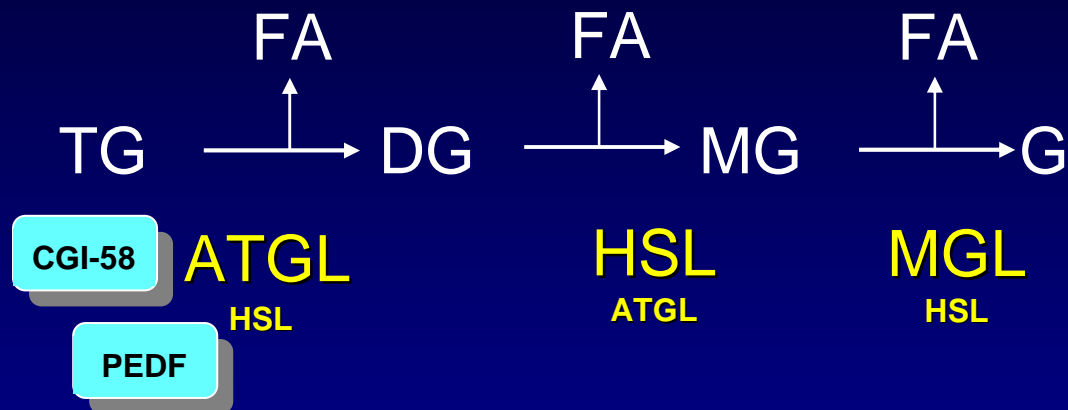
Metabolic Defects Leading to the Development of NAFLD



White Adipose Tissue as Major Source of FA and Liver Fat in NAFLD



TG Lipolysis is a Multistep Process Requiring Several Tissue Lipases



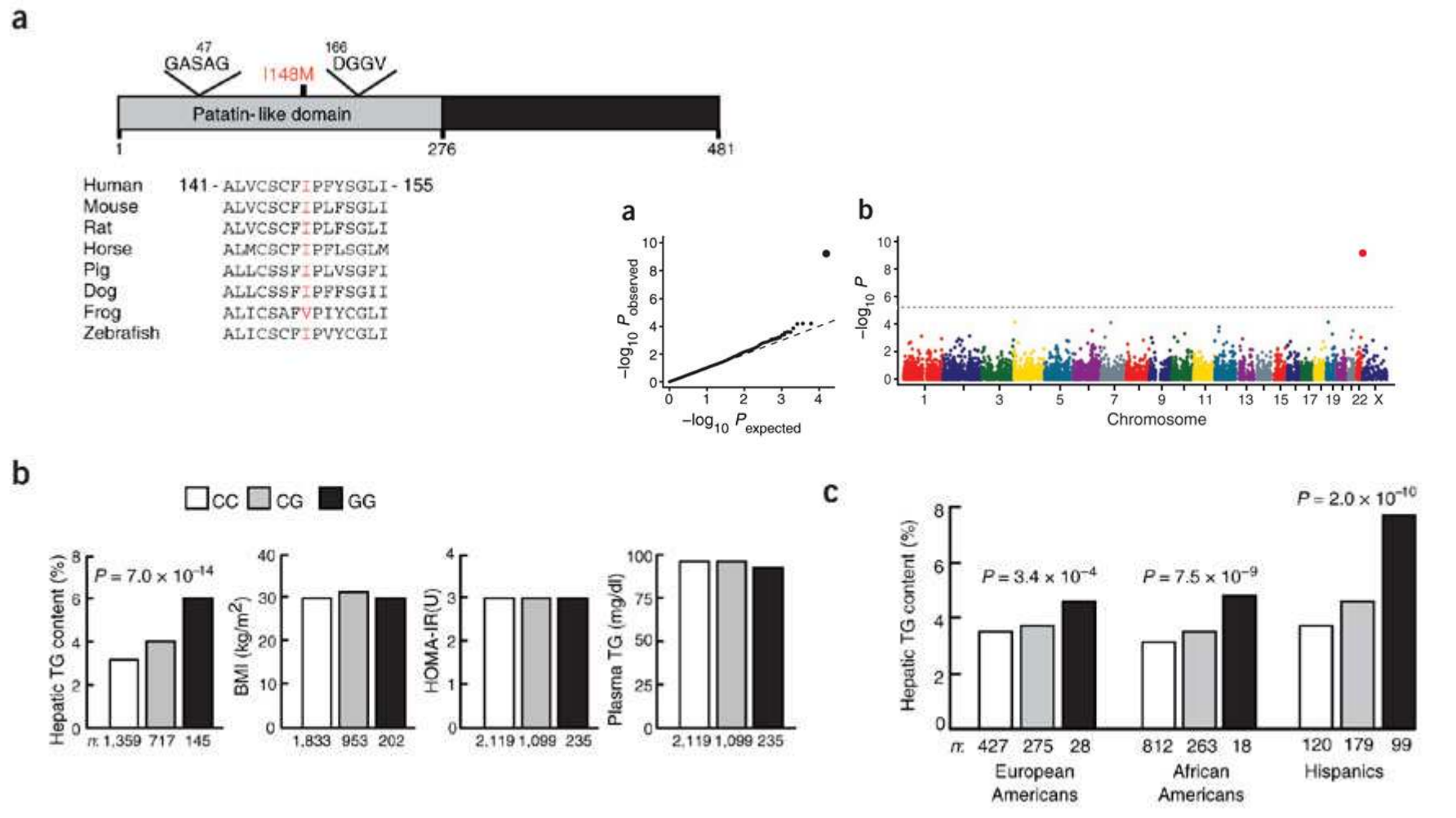
Fat Mobilization in Adipose Tissue Is Promoted by Adipose Triglyceride Lipase

Robert Zimmermann,^{1*} Juliane G. Strauss,^{1*}
 Guenter Haemmerle,¹ Gabriele Schoiswohl,¹
 Ruth Birner-Gruenberger,³ Monika Riederer,¹
 Achim Lass,¹ Georg Neuberger,² Frank Eisenhaber,²
 Albin Hermetter,³ Rudolf Zechner^{1†}

Defective Lipolysis and Altered Energy Metabolism in Mice Lacking Adipose Triglyceride Lipase

Guenter Haemmerle,¹ Achim Lass,¹ Robert Zimmermann,¹ Gregor Gorkiewicz,² Carola Meyer,⁵
 Jan Rozman,⁵ Gerhard Heldmaier,⁵ Robert Maier,³ Christian Theussl,⁶ Sandra Eder,¹
 Dagmar Kratky,⁴ Erwin F. Wagner,⁶ Martin Klingenspor,⁵ Gerald Hoefler,² Rudolf Zechner^{1*}

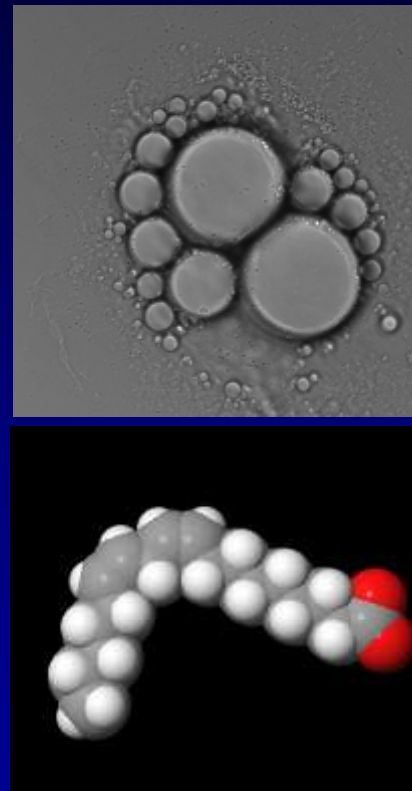
Genetic Variation in *PNPLA3* (Patatin-like Lipase) Confers Susceptibility to NAFLD



Lipotoxicity of FA Resulting from Dysbalance in Lipogenesis & Lipolysis

Lipolysis

Energy substrate
Precursor of lipid metabolites
Protein acylation
Ligands for nuclear receptors



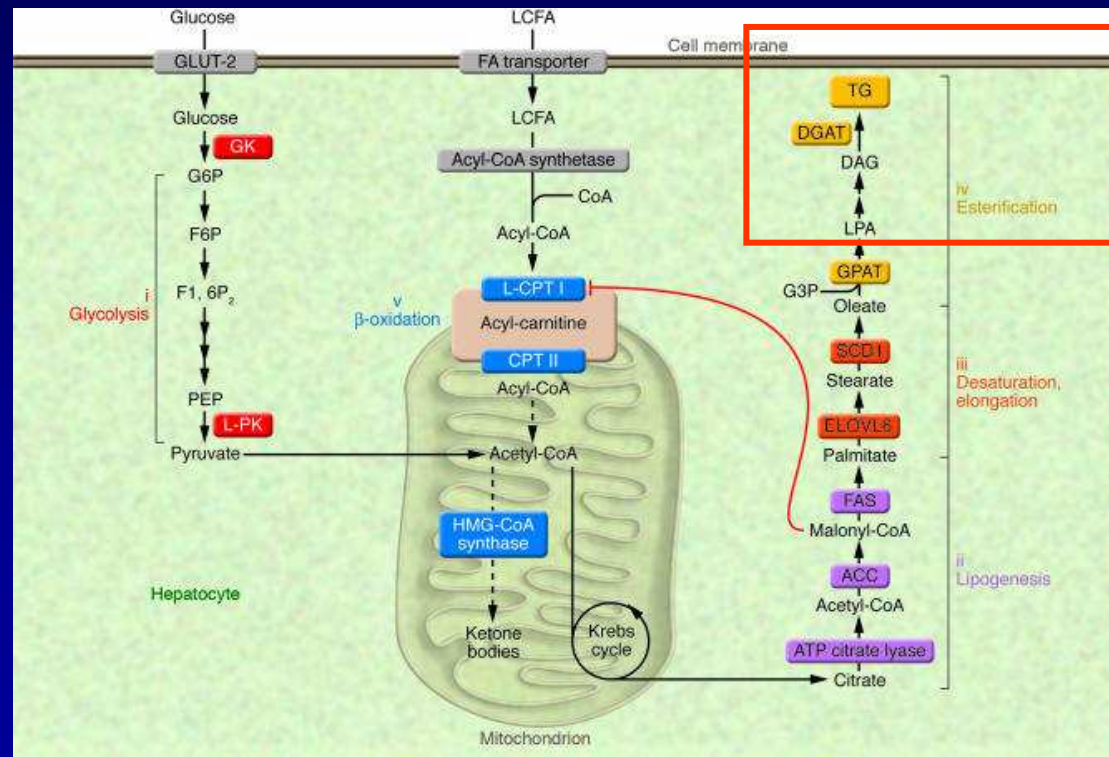
Lipogenesis

Detergents
Acidic
Lipotoxic
Apoptosis

Inhibiting Triglyceride Synthesis Improves Hepatic Steatosis but Exacerbates Liver Damage and Fibrosis in Obese Mice with Nonalcoholic Steatohepatitis

Kanji Yamaguchi,¹ Liu Yang,¹ Shannon McCall,² Jiawen Huang,¹ Xing Xian Yu,³ Sanjay K. Pandey,³ Sanjay Bhanot,³ Brett P. Monia,³ Yin-Xiong Li,¹ and Anna Mae Diehl¹

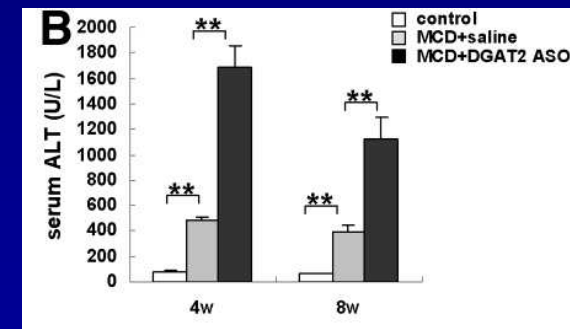
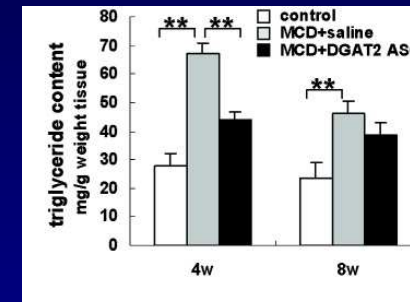
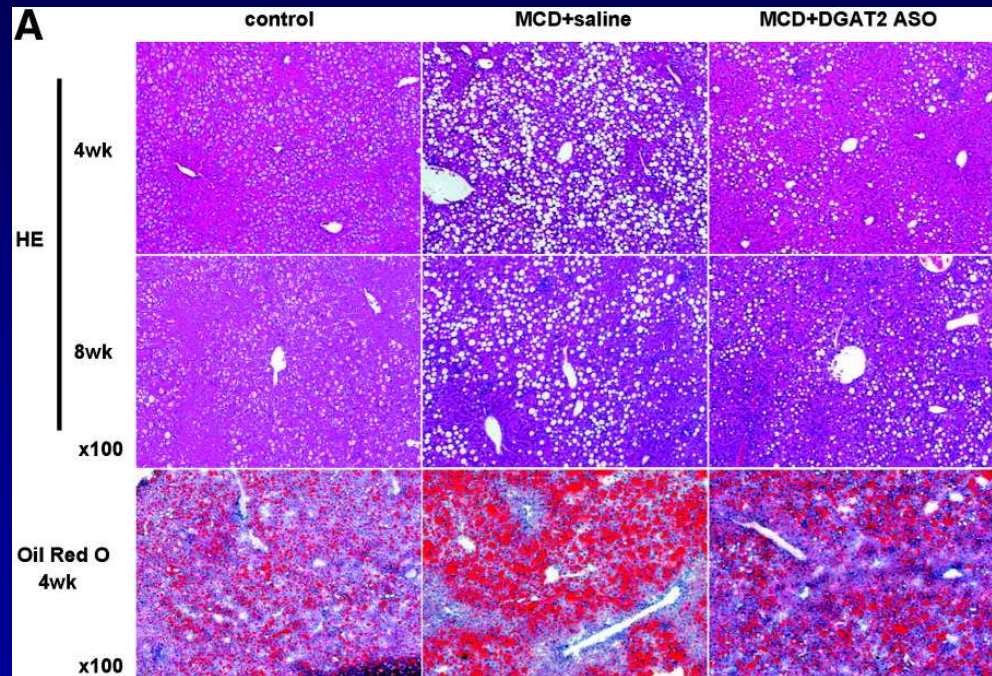
Yamaguchi et al., *Hepatology* 2007 & 2008



Diacylglycerol
Acyltransferases
(DGAT)

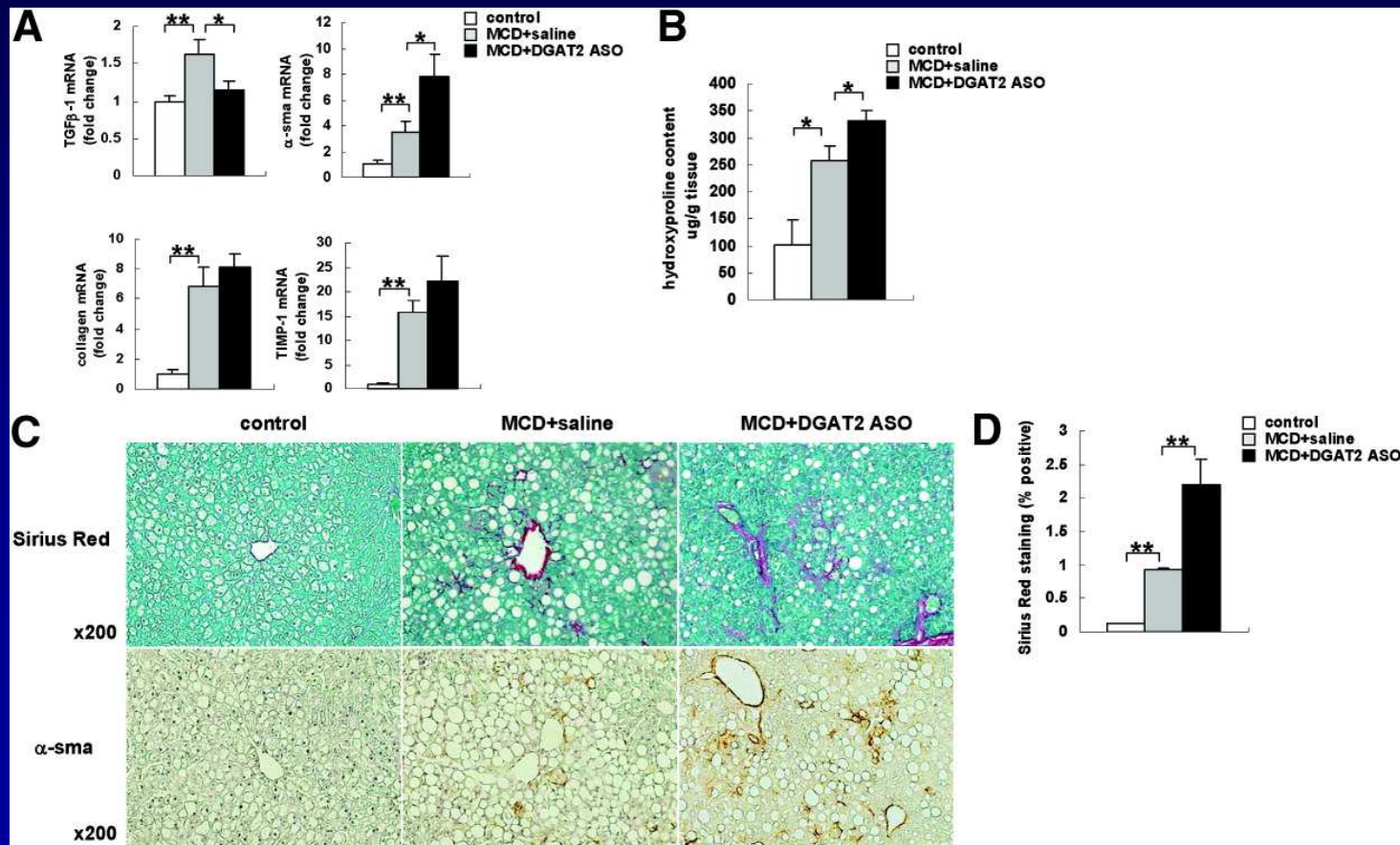
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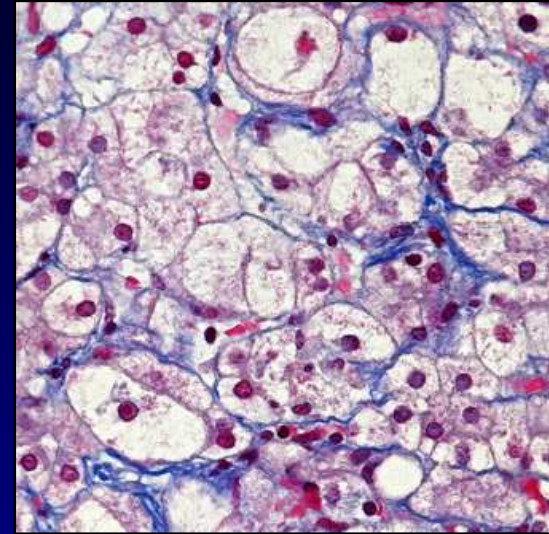
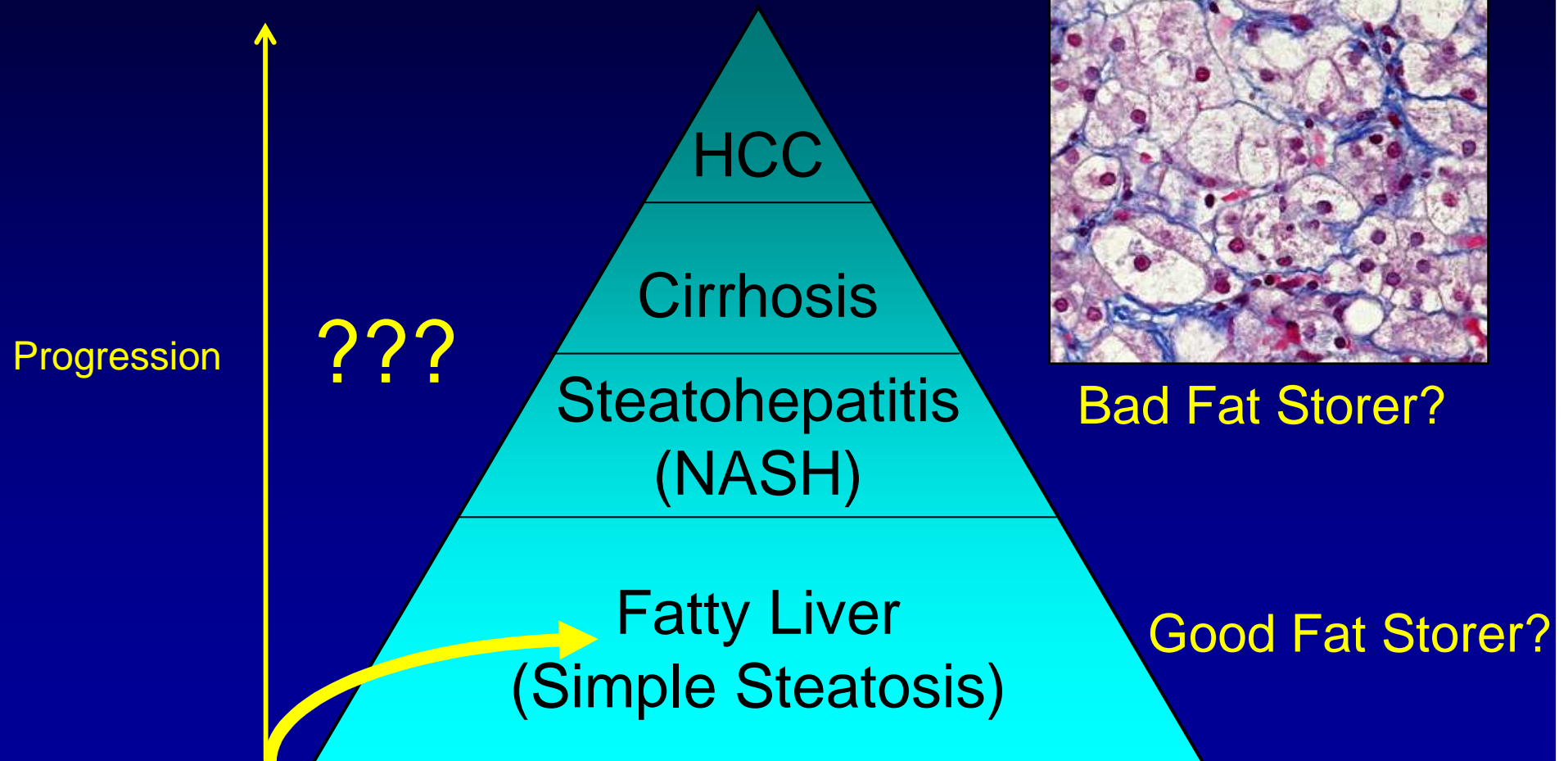


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Thank you for your attention!