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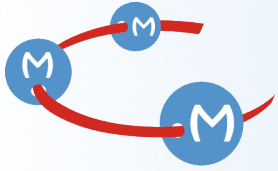
Modulation de l'autophagie par les nutriments

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Co-Head with Albert Tran of the
Team 8 "hepatic complications of obesity"
INSERM U1065, C3M, Nice, France**



Déclaration d'intérêts en rapport avec la présentation

- **Activités de conseil, fonctions de gouvernance, rédaction de rapports**
Non
- **Essais cliniques, autres travaux, communications de promotion**
Non
- **Intérêts financiers (actions, obligations)**
Non
- **Liens avec des personnes ayant des intérêts financiers ou impliquées dans la gouvernance**
Non
- **Réception de dons sur une association dont je suis responsable**
Non
- **Détention d'un brevet, rédaction d'un ouvrage utilisé par l'industrie**
Non



Autophagy

-Autophagy, or cellular self-digestion, is a catabolic process which targets cell constituents (damaged organelles, unfolded proteins, intracellular pathogens) to lysosomes for degradation.

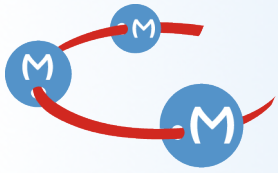
Autophagy turnover maintains cellular energy homeostasis

Cellular pathway is crucial for development, differentiation, survival and homeostasis.

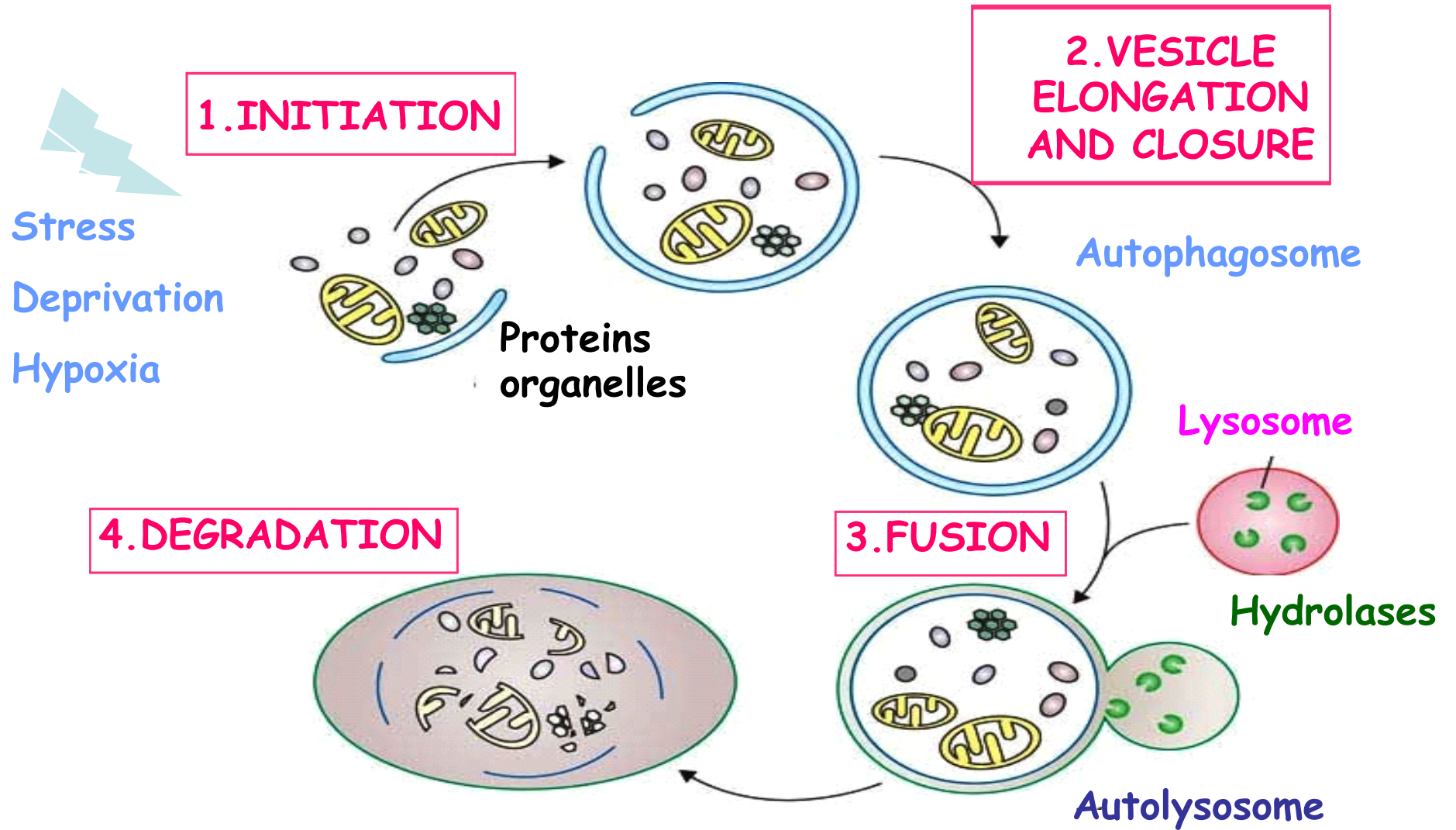
Important links between the regulation of autophagy and obesity (food intake, adipose tissue development, β cell function, insulin sensitivity and hepatic steatosis).

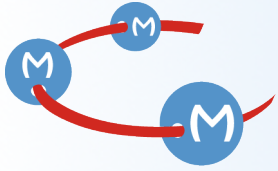
Three types of autophagy:

- macroautophagy
- chaperone-mediated autophagy
- microautophagy



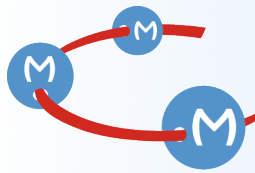
Autophagy





Autophagy

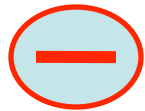
- Dynamic process (Autophagic flux)
- Responses dependent on the activation level (positive or deleterious response)
- Difference between acute and chronic stimulus
- Organs and Cells "specific":
 - Liver ↔ Adipose tissue
 - Hepatocyte ↔ Stellate cells
- Dependent on vesicle trafficking
Cytoskelton and Membrane composition



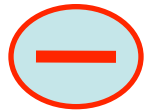
Basic molecular machinery of autophagy



**Fatty Acids
(Palmitate)**



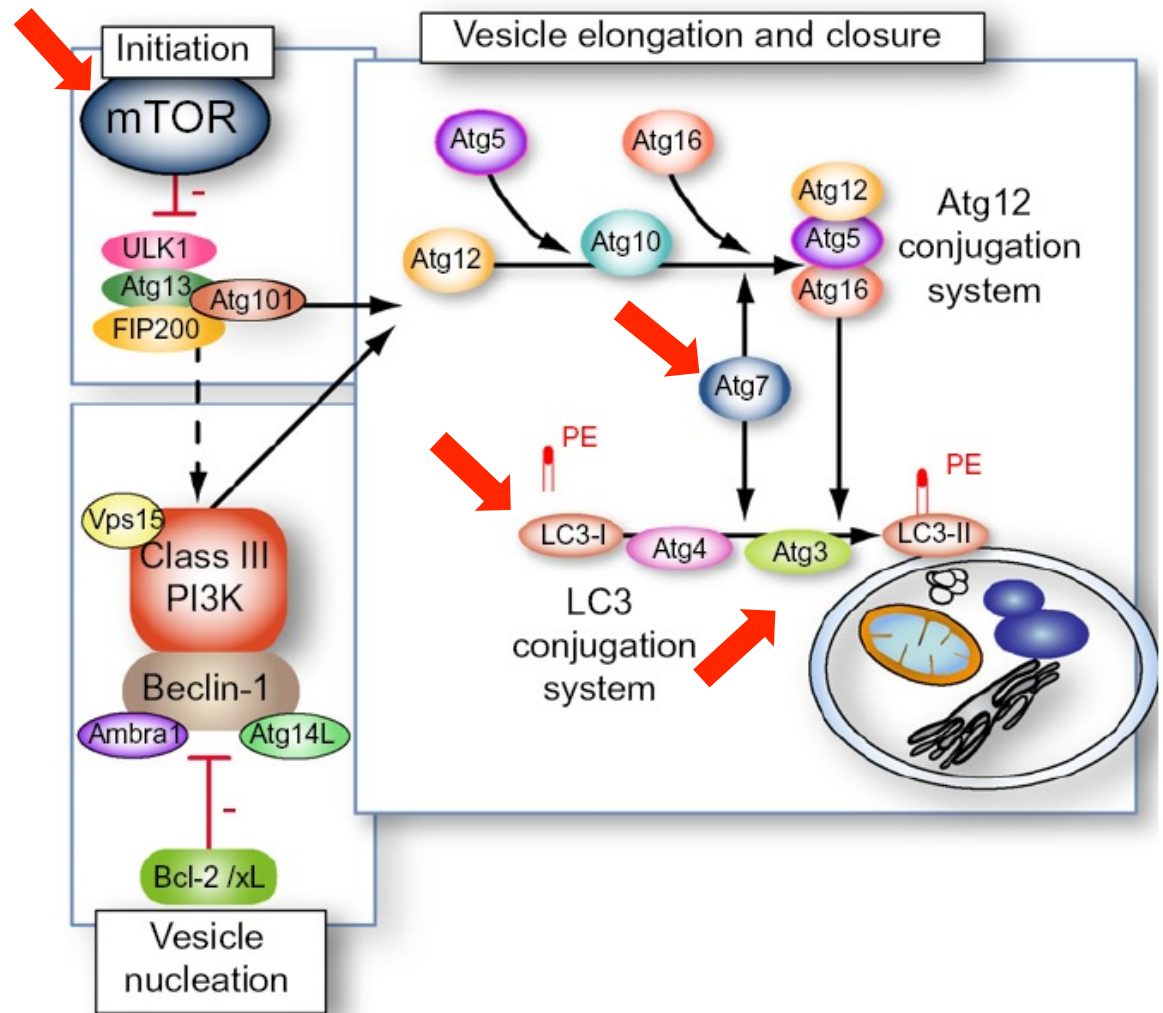
**Amino acids
(L-leucine)**



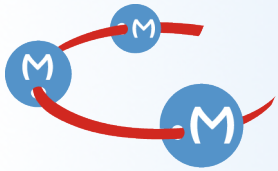
**Lipides
(membranes structure)
Alcohol
(oxidants and reactive
metabolites)**



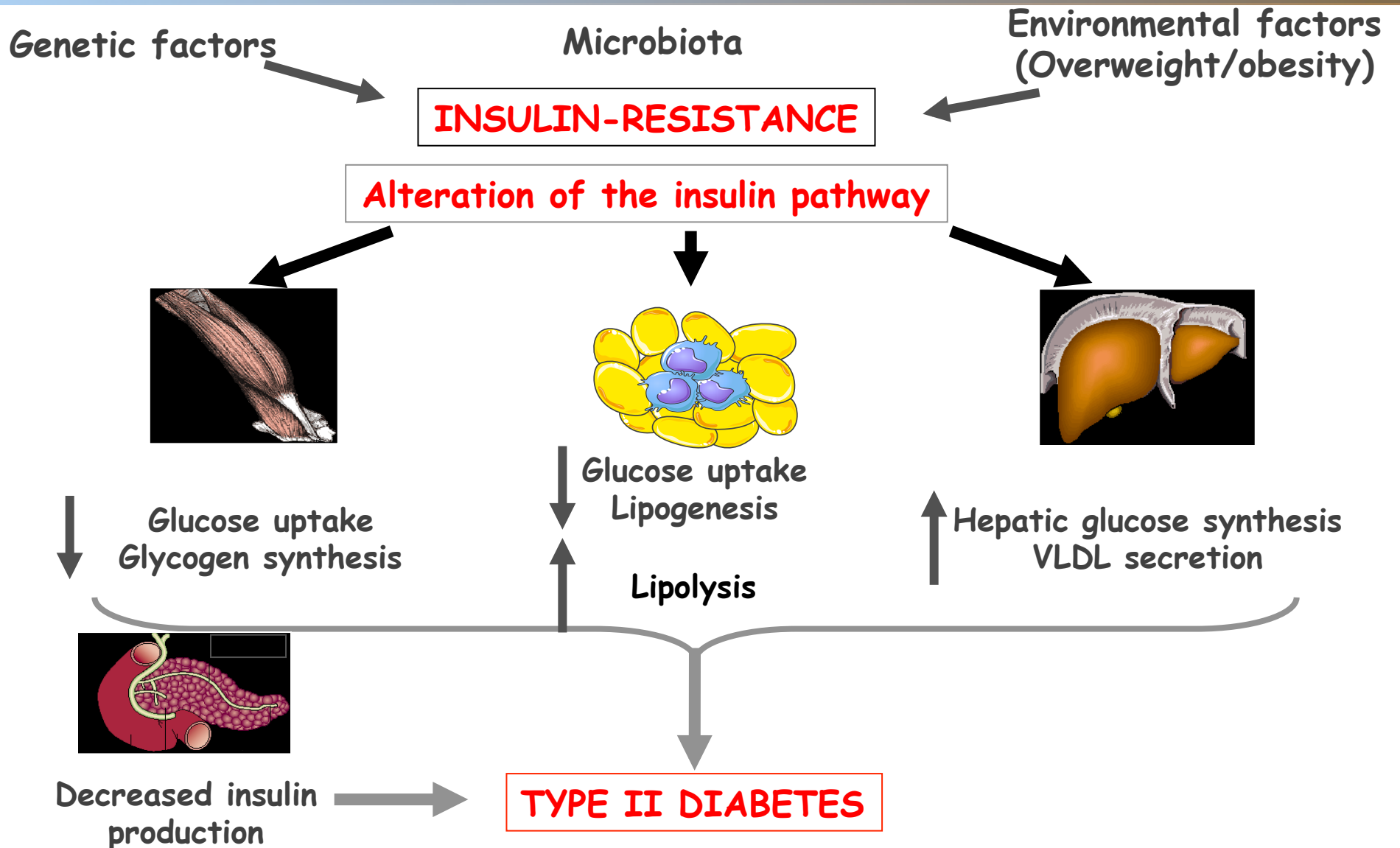
Coffee: caffeine

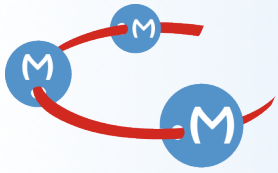


(Rautou *et al*, *J Hepatol*. 2010;53(6):1123-34)

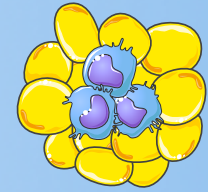


Etiology of Type 2 Diabetes



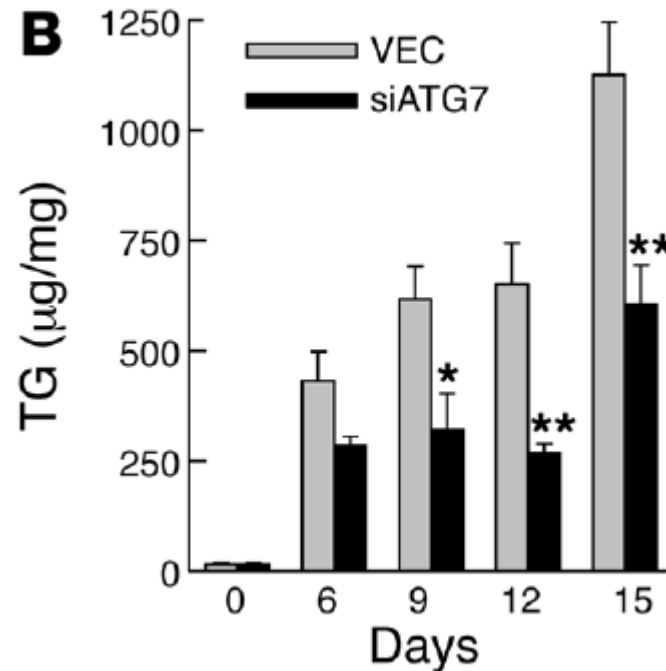
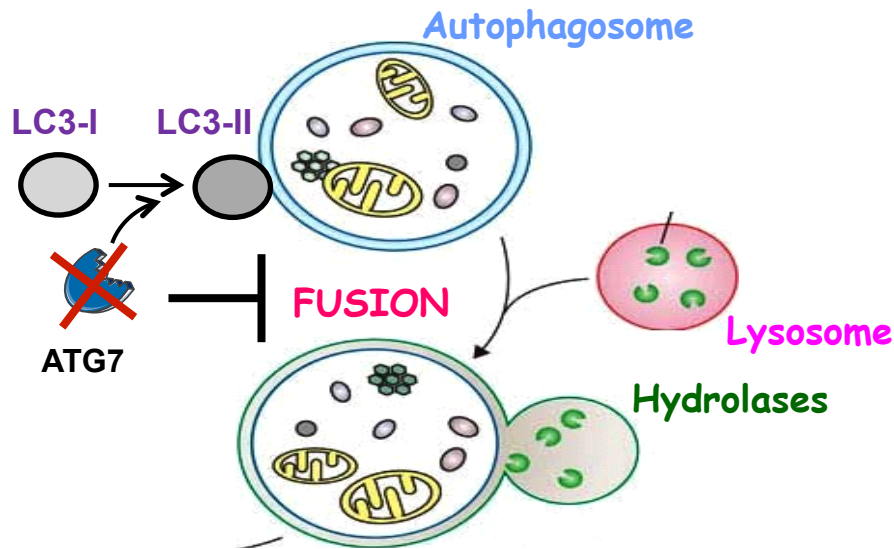


Autophagy regulates Adipose tissue development

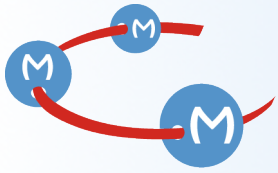


Autophagic flux
in 3T3-L1
(siATG7)

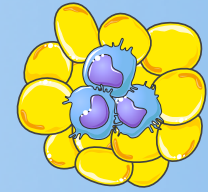
Adipocyte differentiation



(Singh *et al*, *JCI*, 2009: 119(11):3329-39)

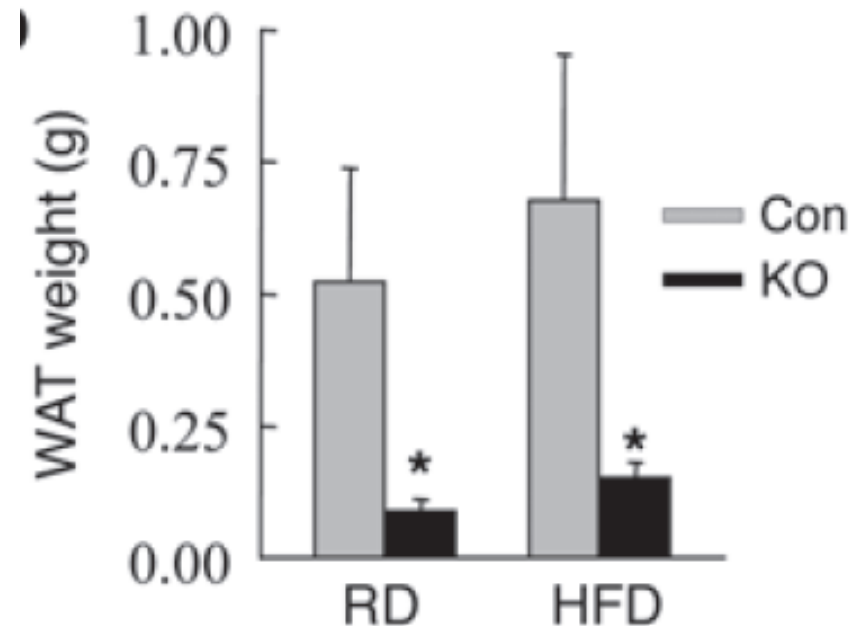
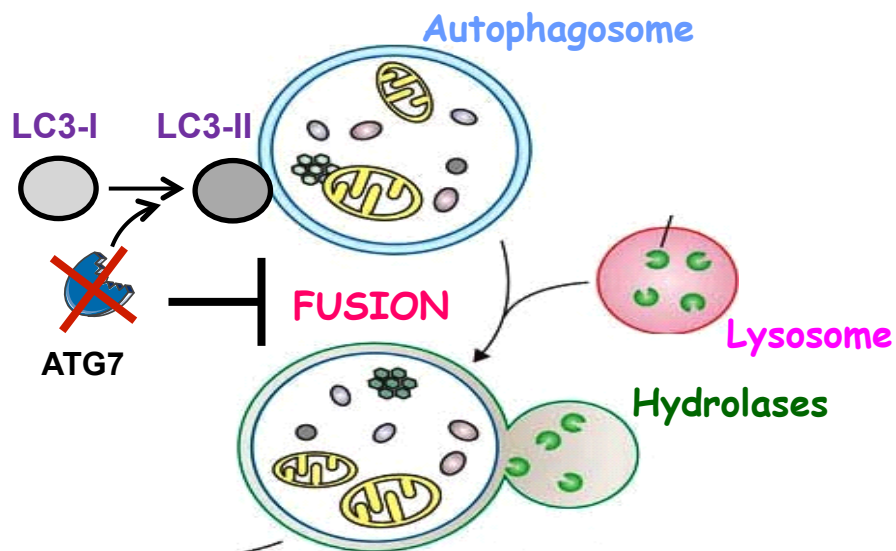


Autophagy regulates Adipose tissue development

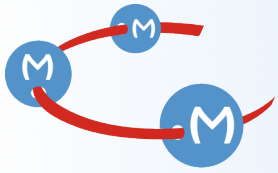


↓ Autophagic flux in adipose tissue (aP2-ATG7 KO)

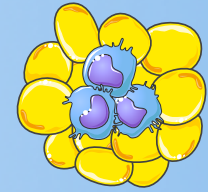
↓ Adipose tissue development



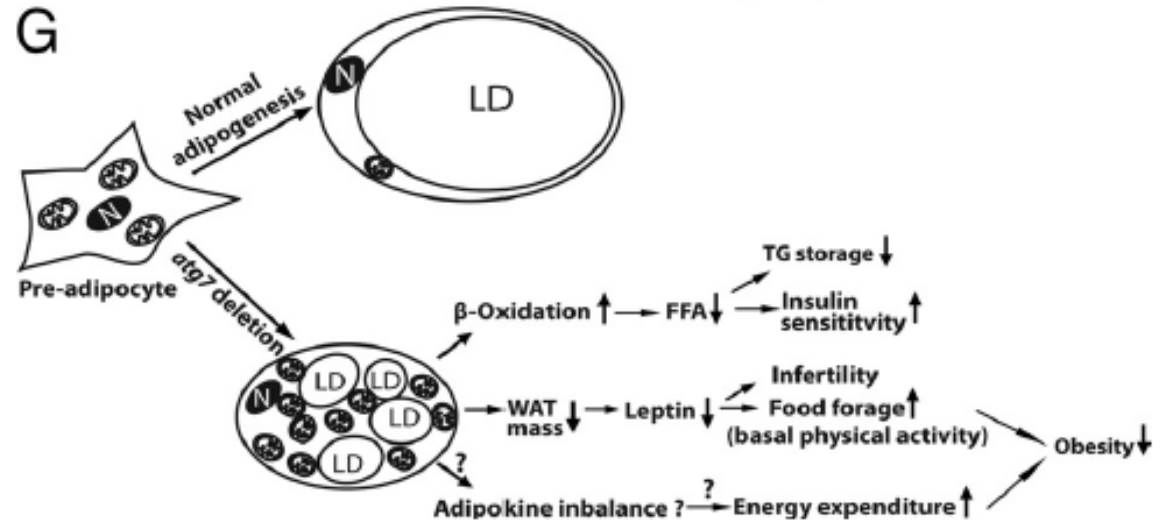
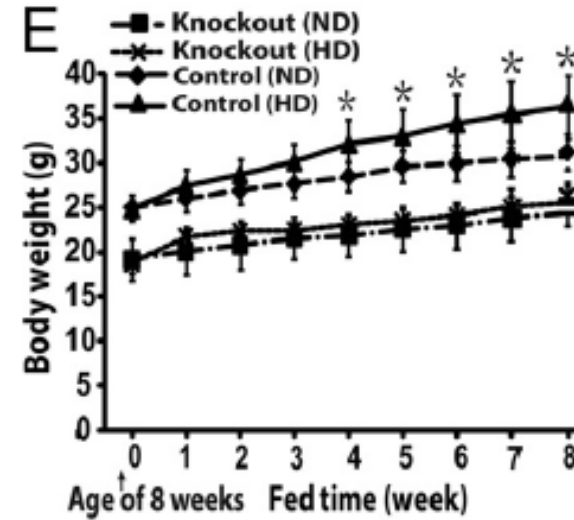
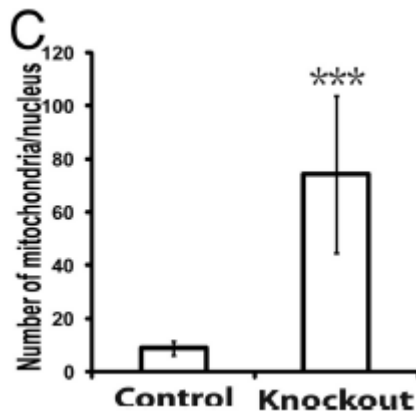
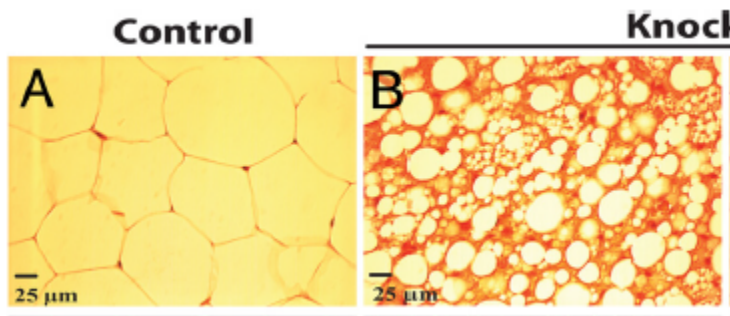
(Singh *et al*, *JCI*, 2009: 119(11):3329-39)



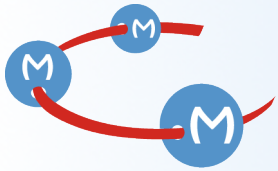
Autophagy regulates The "brownisation" of AT tissue



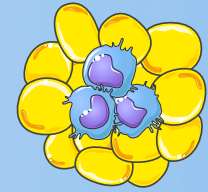
Autophagic flux
in adipose tissue
(aP2-ATG7 KO)



(Zhang *et al*, *PNAS*. 2009;106(47):19860-5)

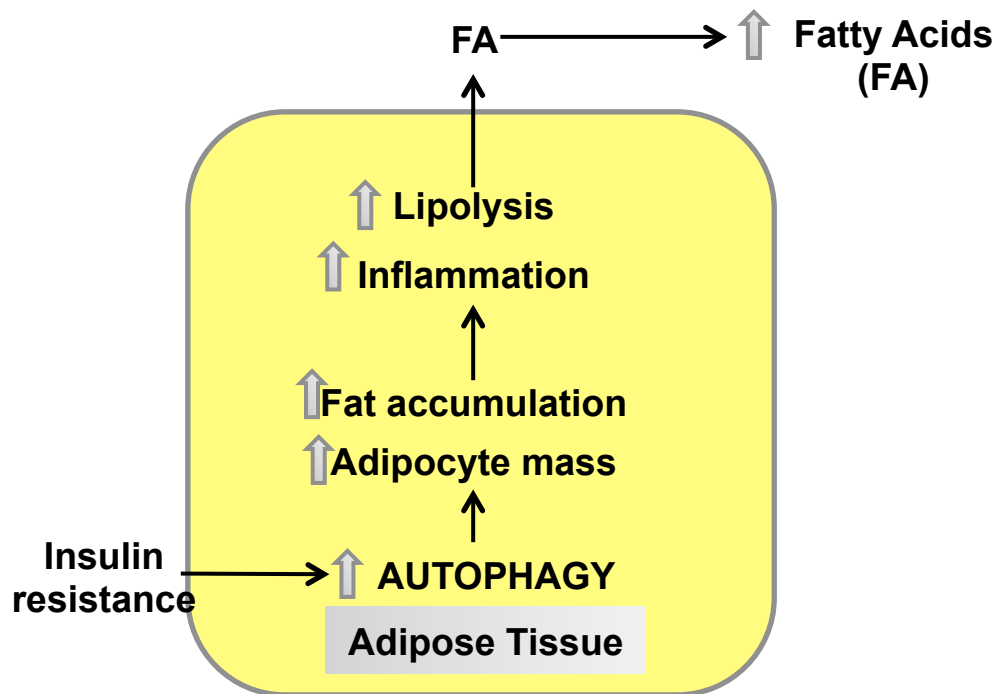


Autophagy and Adipose tissue

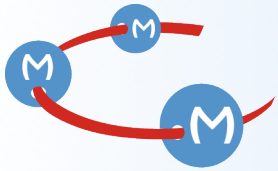


Increased autophagy in AT has been associated with obesity and type-2 diabetes in mice and humans.

(Kovsan *et al.* *J Clin Endocrinol Metab* 2011; 96: E268-E277)
(Goldman *et al.* *Autophagy* 2010; 6: 179-181)



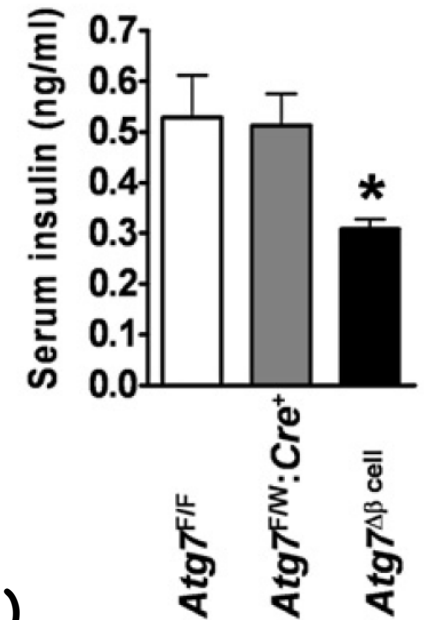
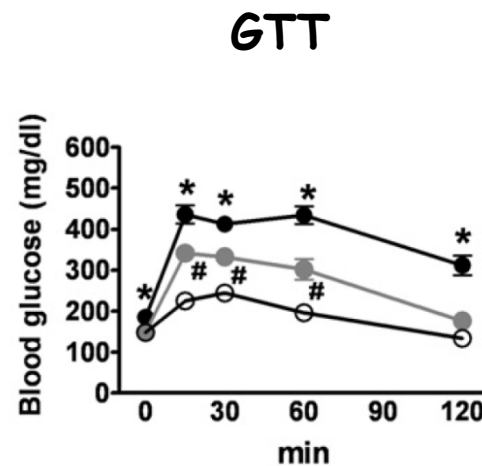
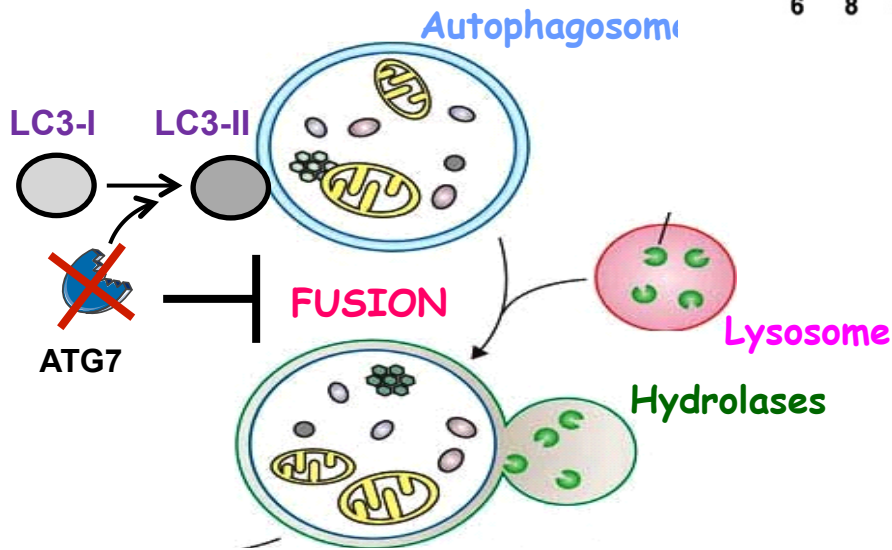
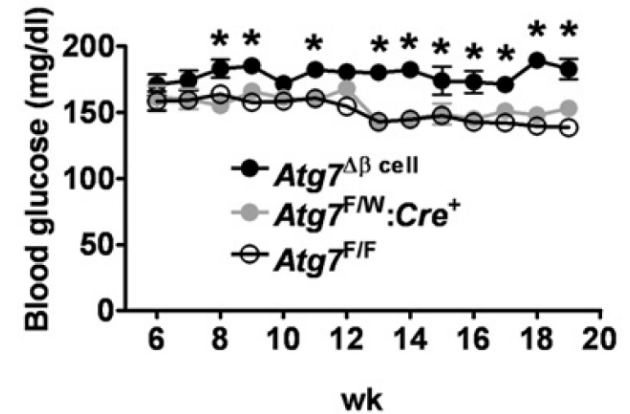
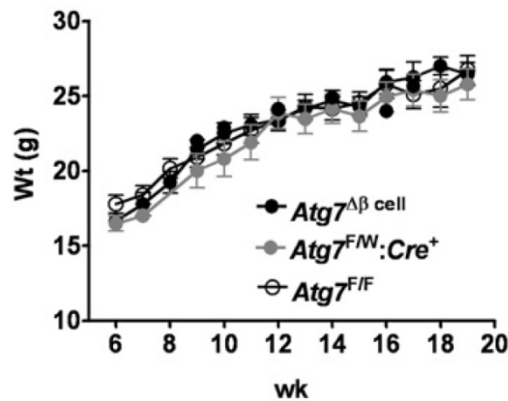
(Lavallard *et al.* *Pharmacol Res.* 2012;66(6):513-25)



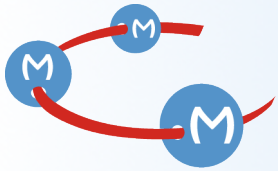
Basal Autophagy in β Cells



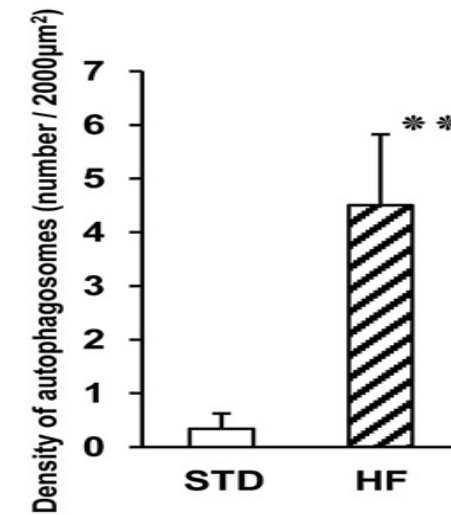
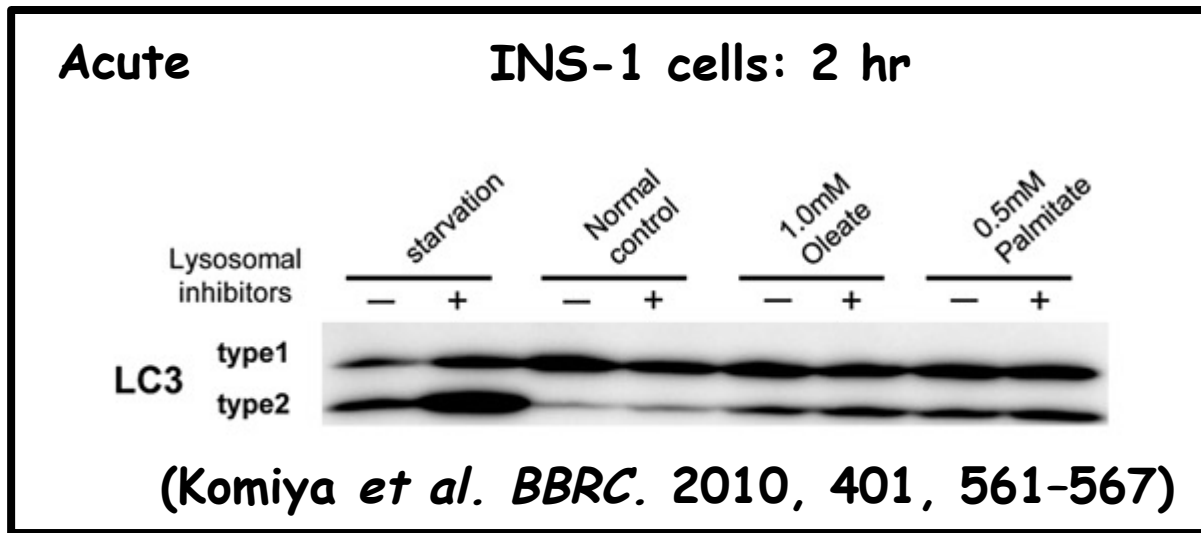
Autophagic flux
in adipose tissue
($\Delta\beta$ -ATG7 KO)



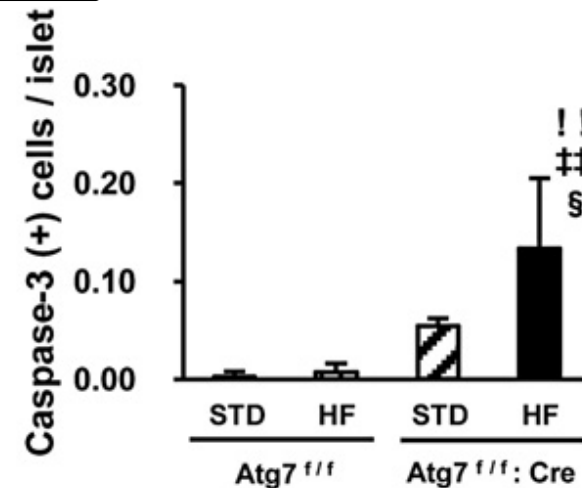
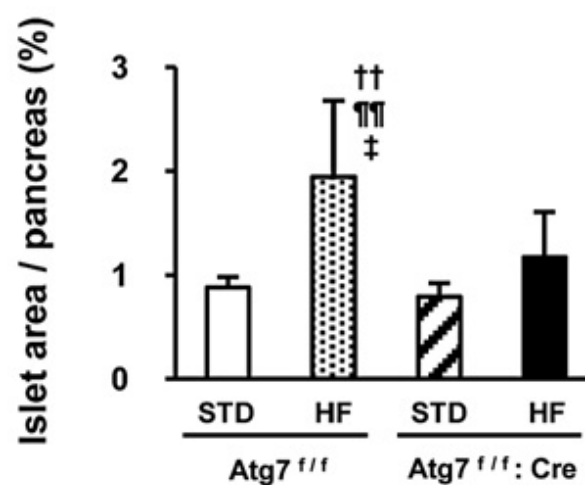
(Jung *et al. Cell Metab.* 2008;8(4):318-24)



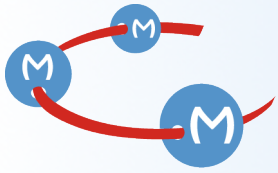
Compensatory effect in HFD



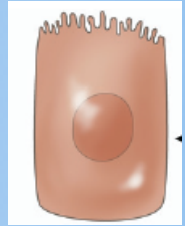
↓
Autophagic flux
in adipose tissue
($\Delta\beta$ -ATG7 KO)



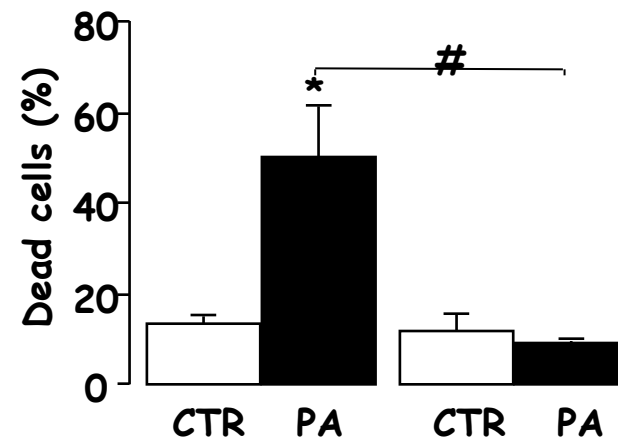
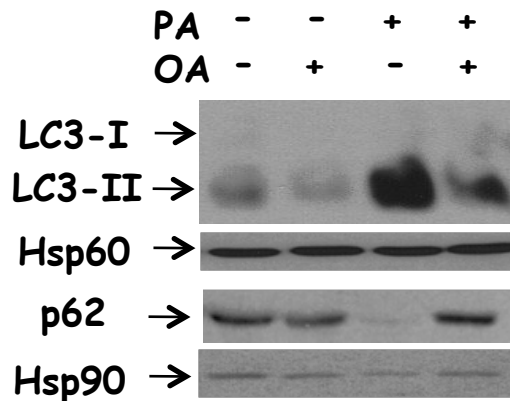
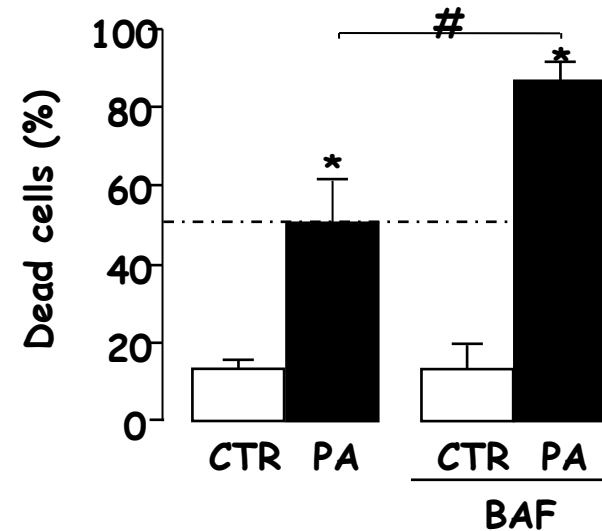
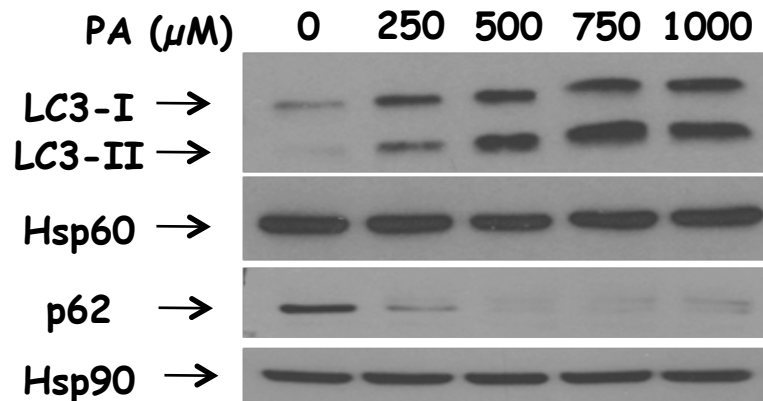
(Ebato *et al.* *Cell Metab.* 2008;8(4):325-32)



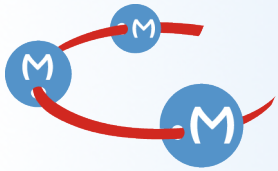
Autophagy is activated for cell survival after lipo-apoptosis in HepG2 cells



Acute



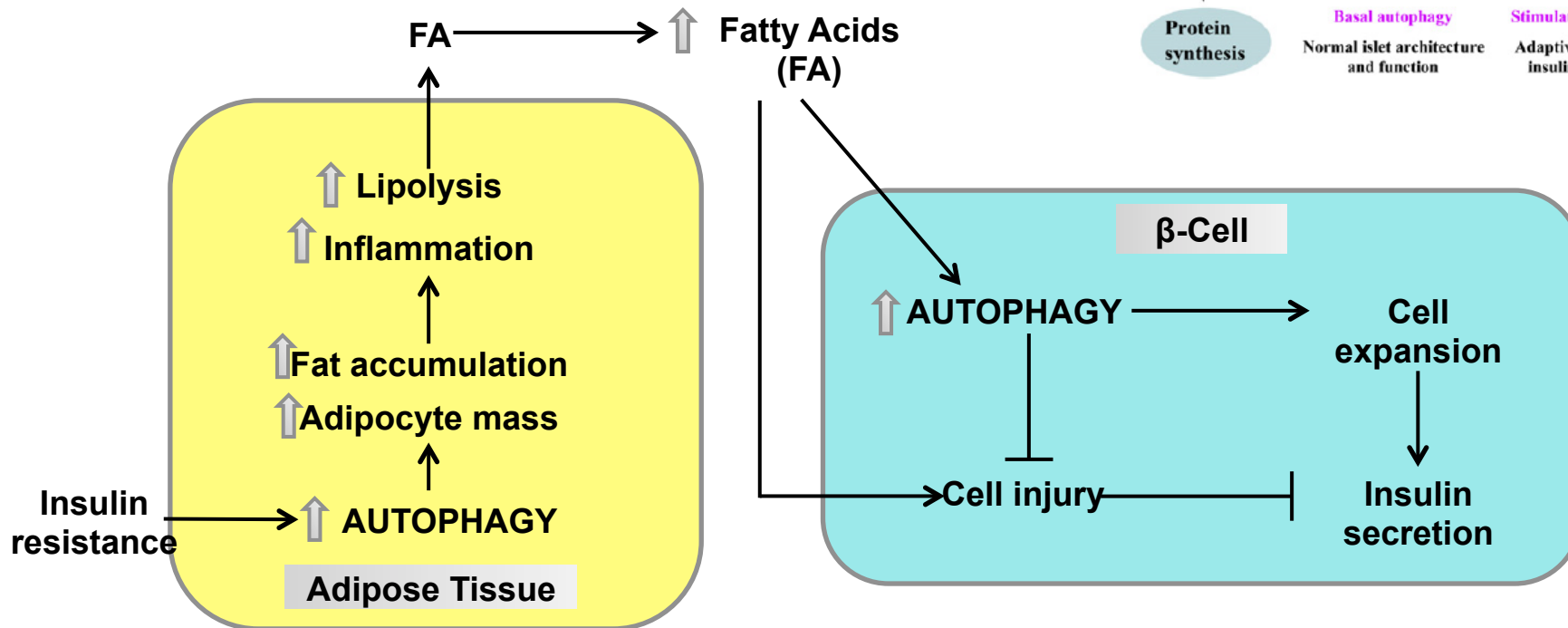
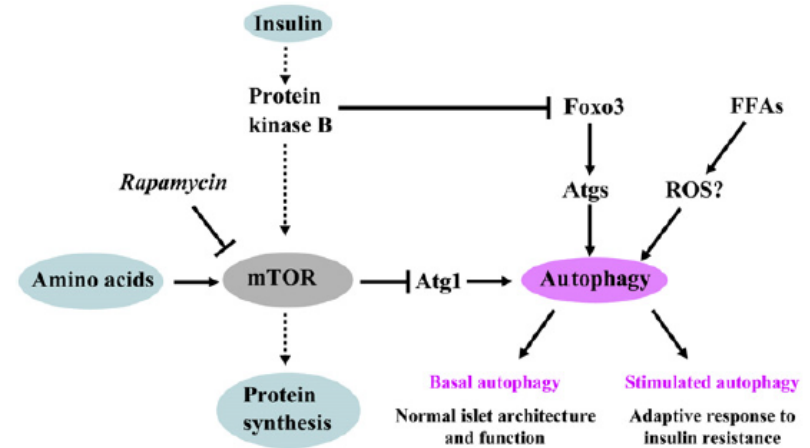
(Lavallard *et al*, 2013 in preparation)



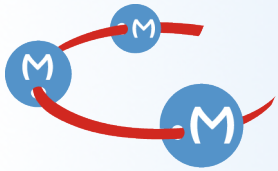
Autophagy and β Cells



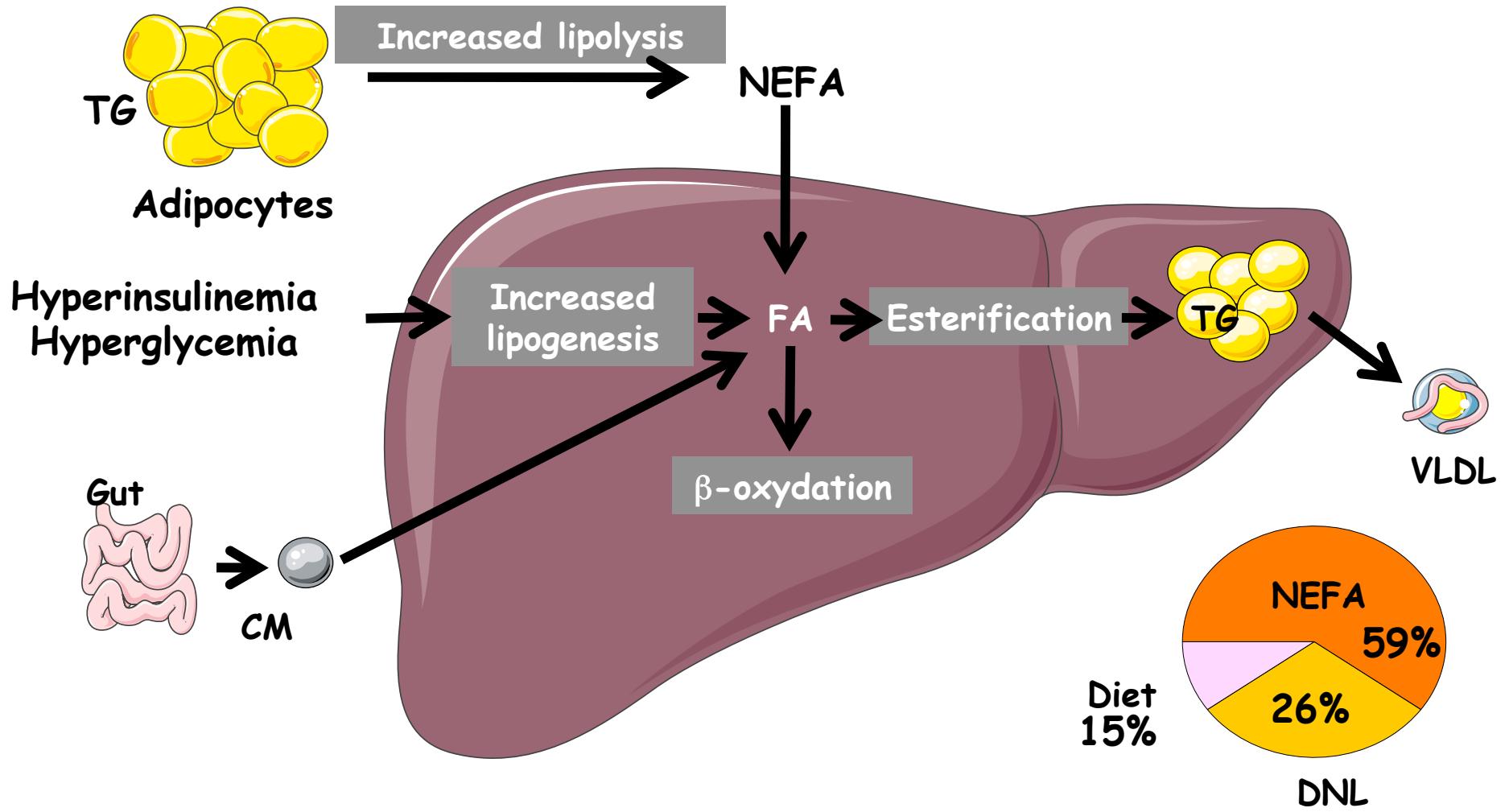
(Meijer AJ, Codogno P.,
Cell Metab. 2008 Oct;8(4):275-6)



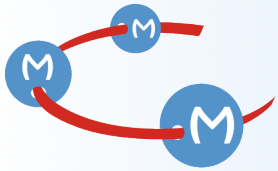
(Lavallard *et al*, *Pharmacol Res.* 2012;66(6):513-25)



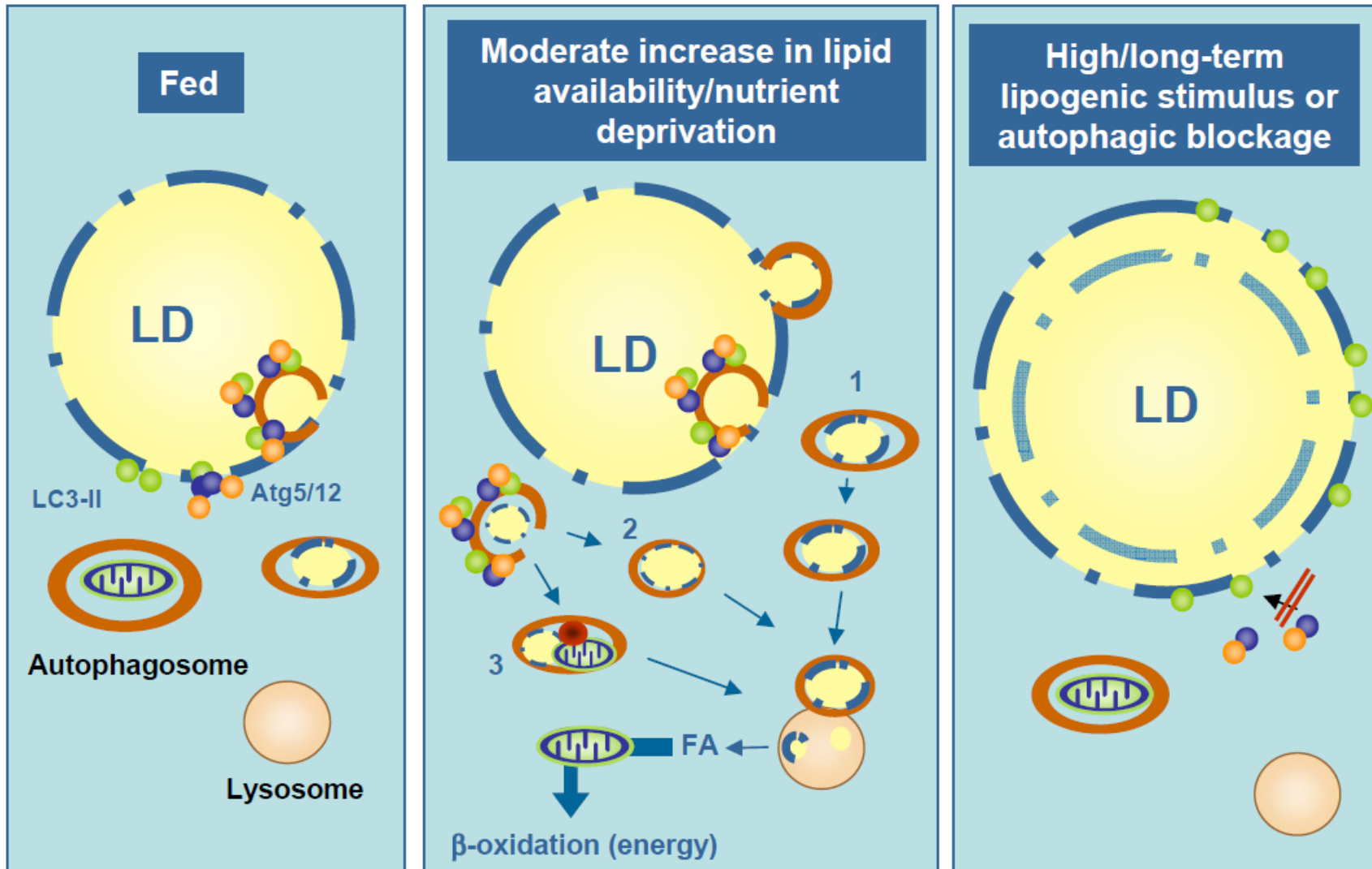
Development of hepatic steatosis

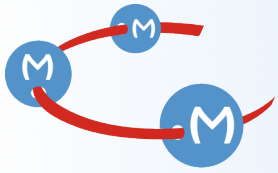


(Donnelly *et al.* *J Clin Invest.* 2005;115(5):1343-51)

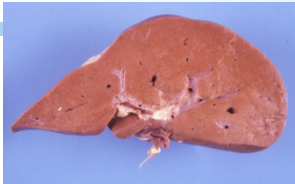


Hepatic Lipophagy





Hepatic autophagy and steatosis



Normal liver



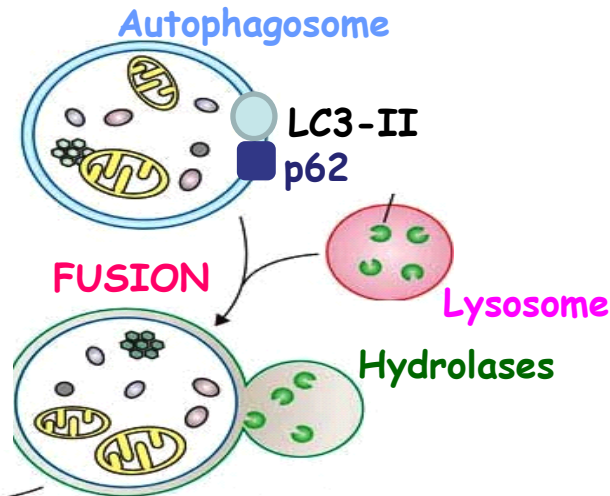
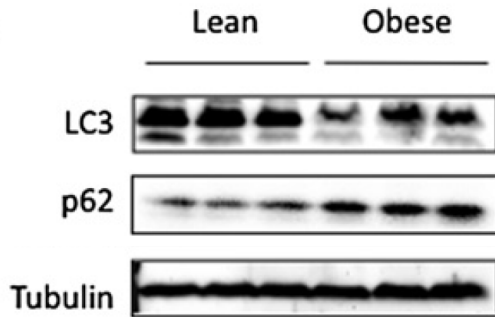
Steatosis



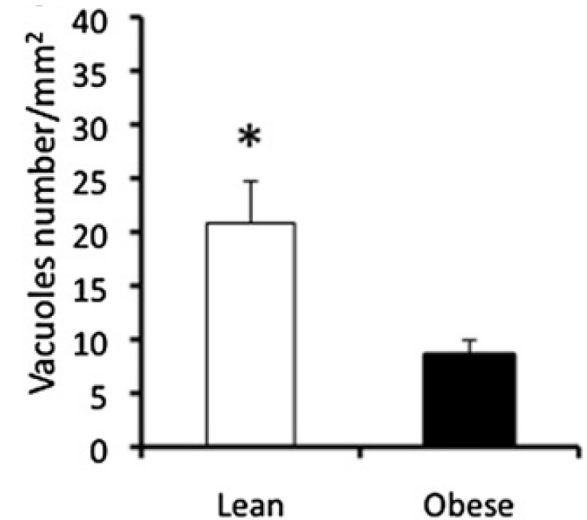
Triglyceride accumulation
Insulin resistance



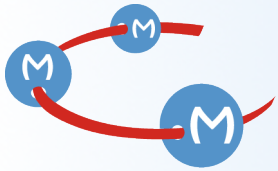
Hepatic autophagic markers



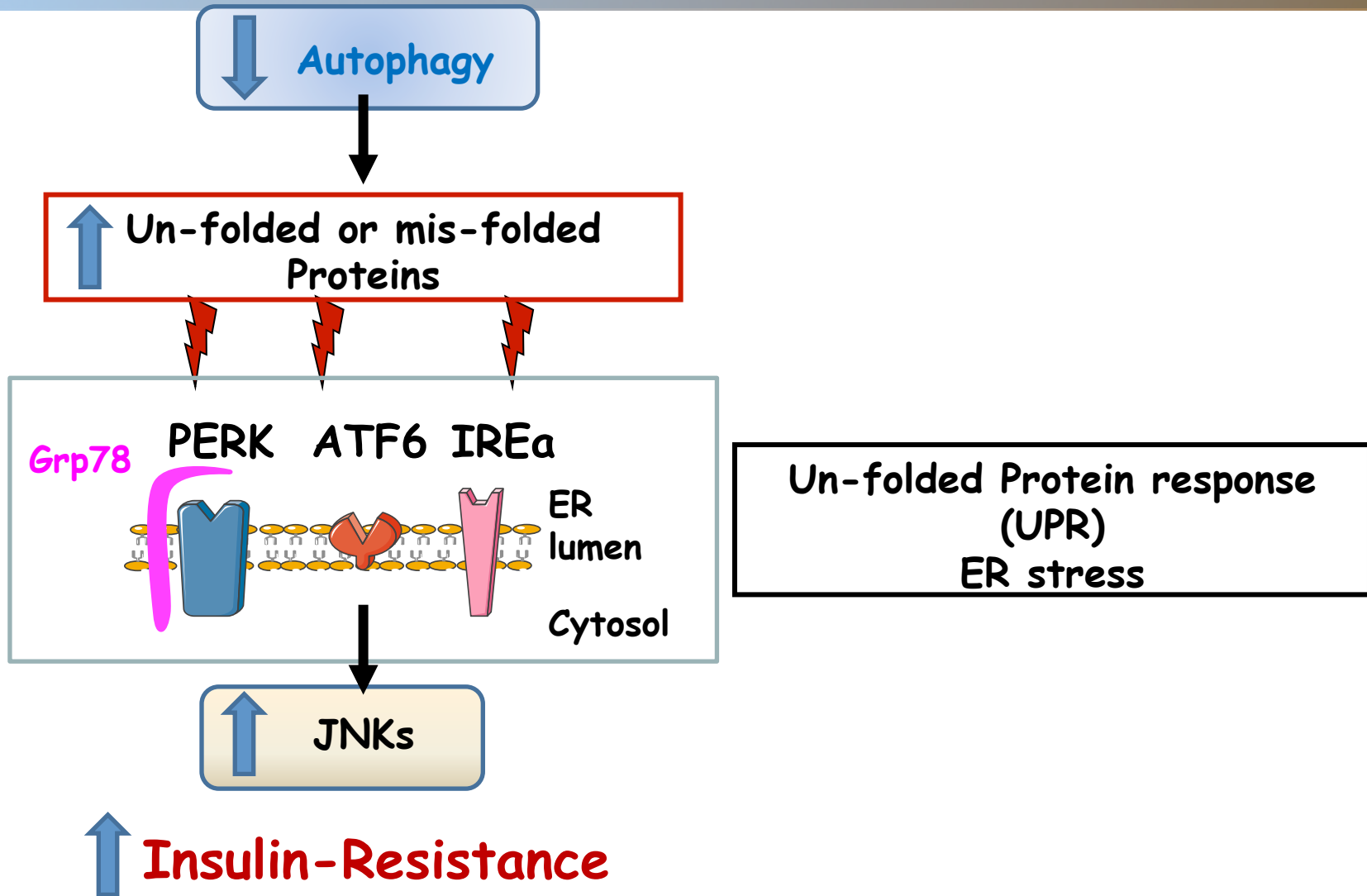
autophagolysosome-like vacuoles (EM)



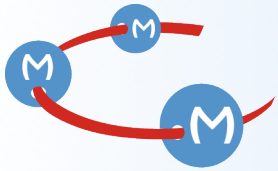
(Singh *et al*, *Nature*. 2009;458(7242):1131-5)



Hepatic Autophagy and ER stress



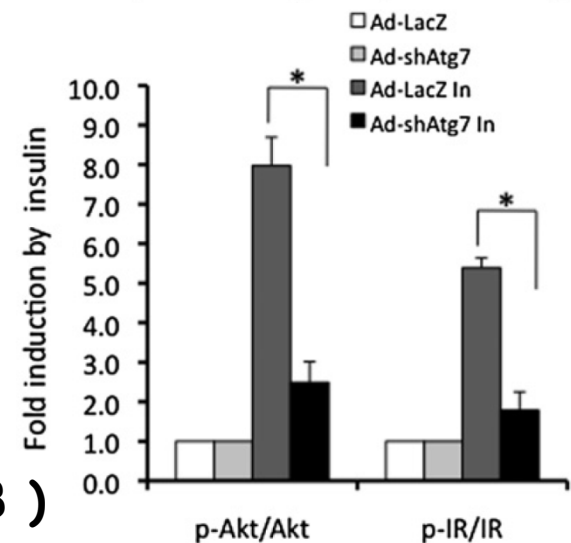
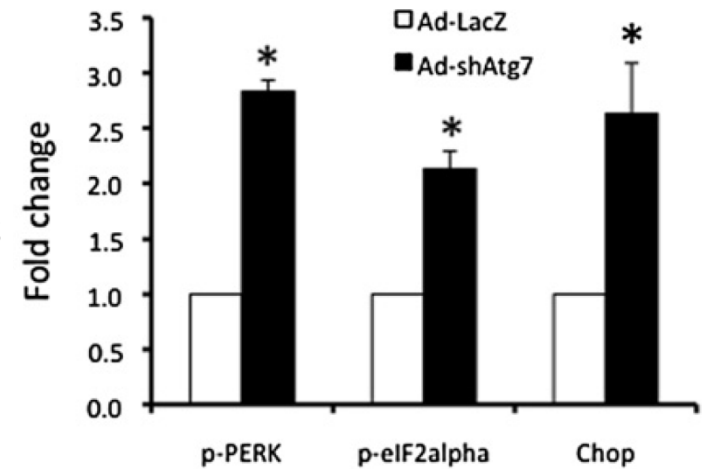
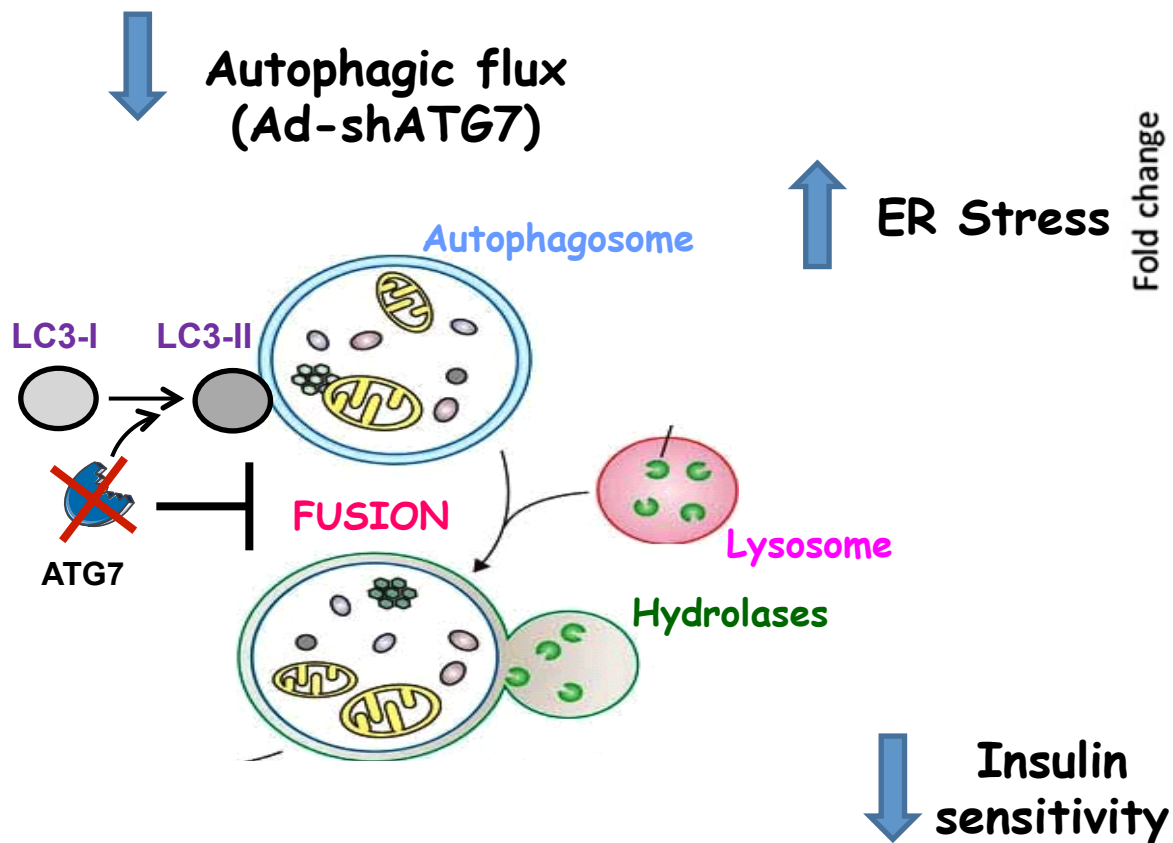
(Yang *et al*, *Cell Metab.* 2010 Jun 9;11(6):467-78)



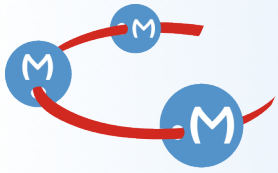
Hepatic Autophagy and ER stress



Defective autophagy results in elevated ER stress and insulin resistance in lean mice



(Yang *et al*, *Cell Metab.* 2010 Jun 9;11(6):467-78)



Hepatic Autophagy and ER stress



Restoration of Autophagy and Improvement of Insulin Action by Reconstitution of Atg7 in Obese Mice (*ob/ob*)



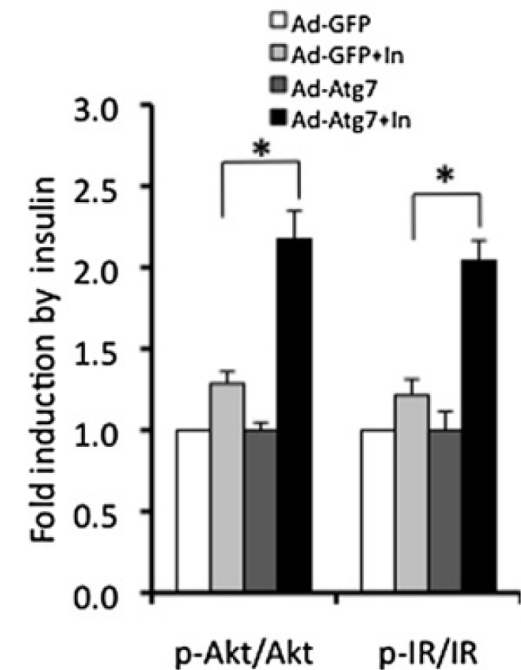
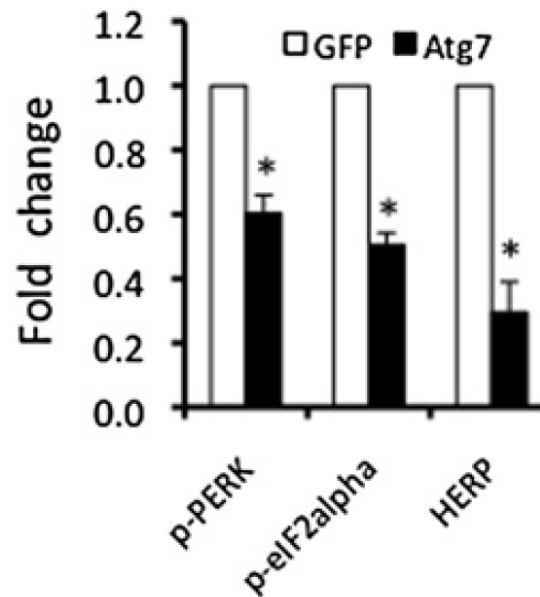
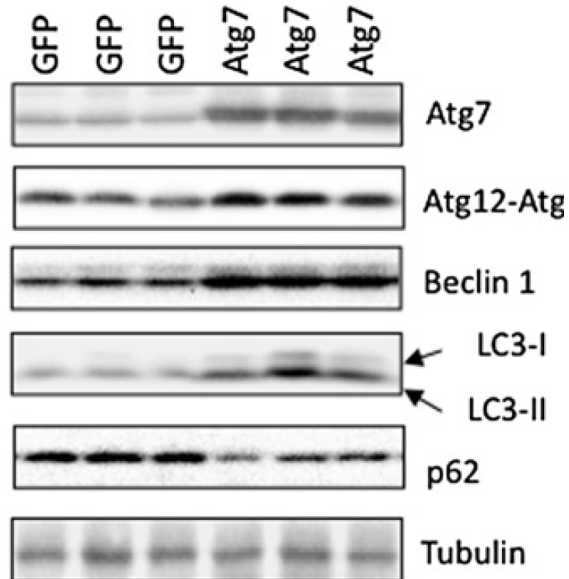
Autophagic flux



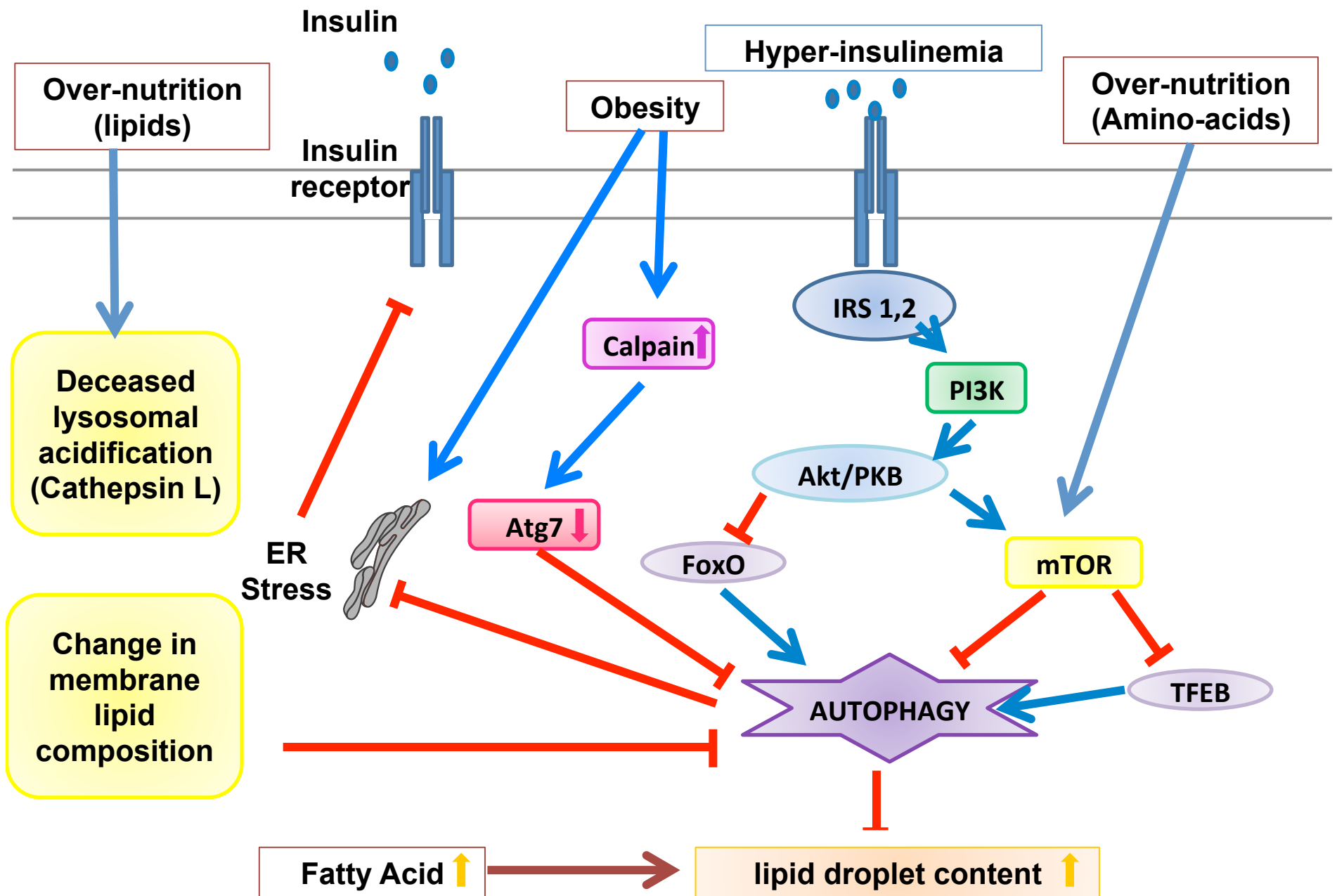
ER Stress



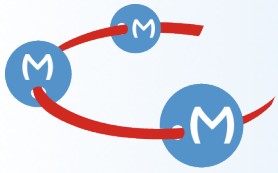
Insulin sensitivity



(Yang *et al*, *Cell Metab*. 2010 Jun 9;11(6):467-78)



(Lavallard *et al*, *Pharmacol Res.* 2012;66(6):513-25)

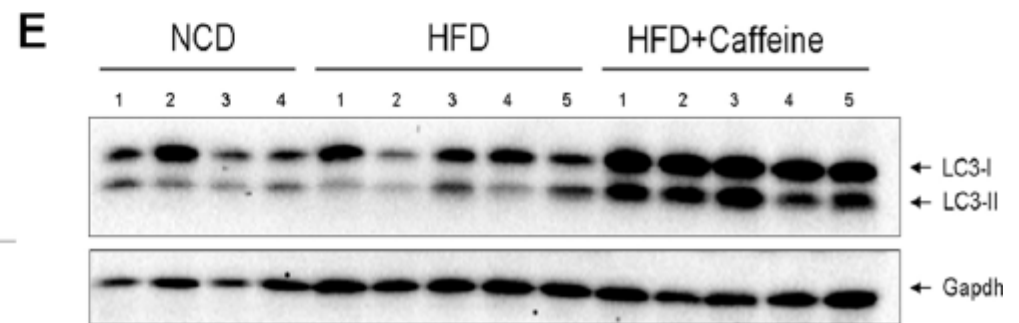
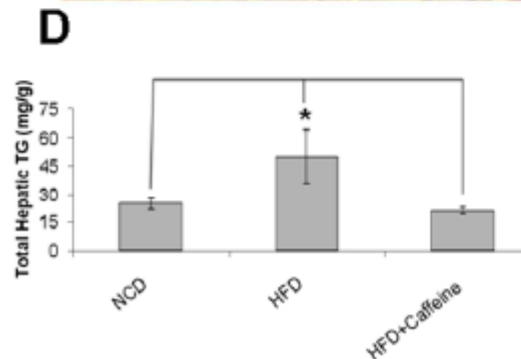
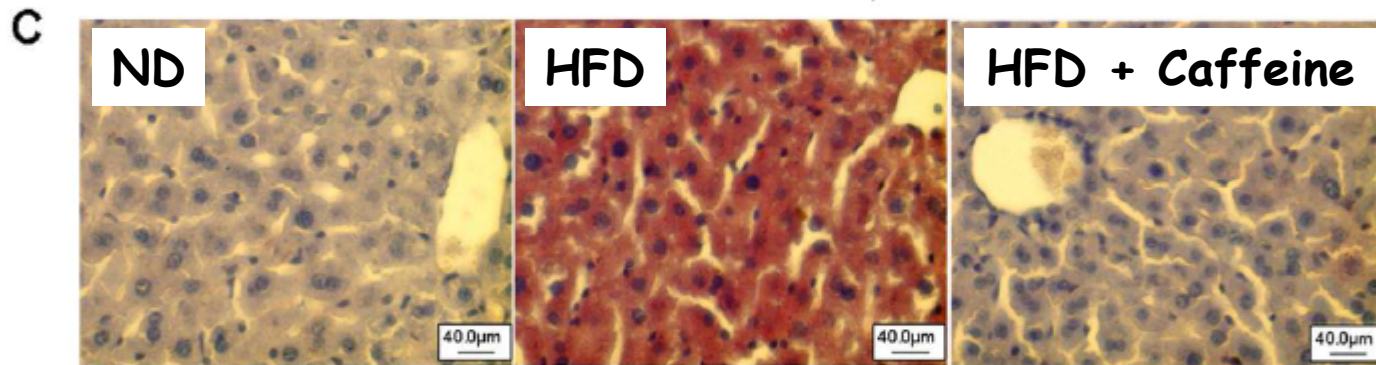
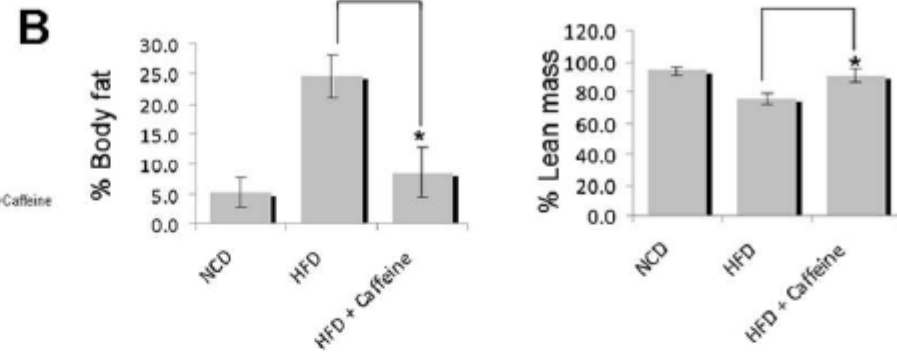
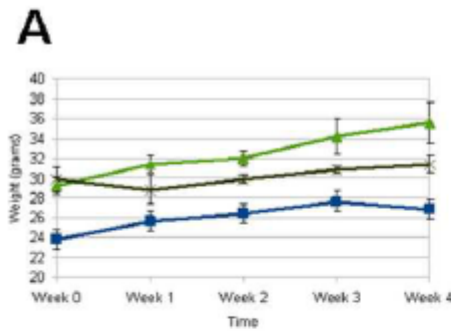


Coffee and Hepatic steatosis



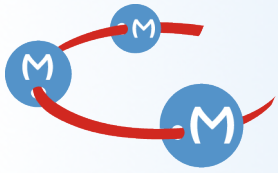
MRI

4 weeks HFD
+ 4 weeks HFD
± 0.05% w/vol
caffeine in
drinking water

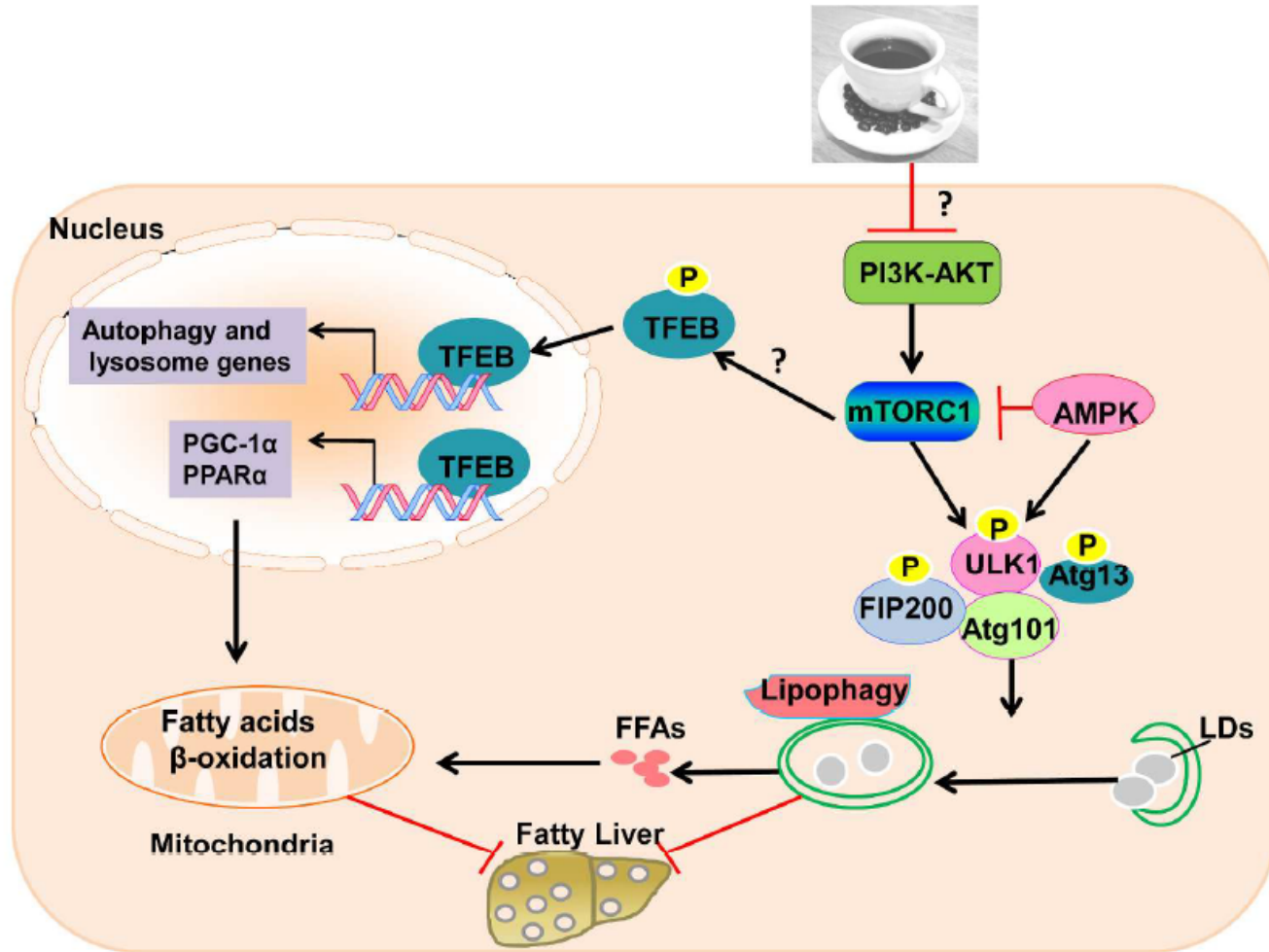


TG content

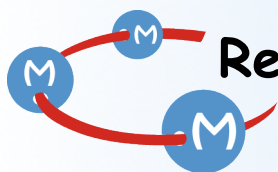
(Sinha *et al.* *Hepatology*. 2013, in press)



Drinking coffee burns hepatic fat by inducing lipophagy coupled with mitochondrial β -oxidation.



(Ding WX. *Hepatology*. 2013, in press)



Regular coffee drinking is protective against fibrosis in morbidly obese women with NAFLD



Table 3. Characteristics of the patients according to the stage of fibrosis.

Variable	Fibrosis <F2 (n = 127)	Fibrosis ≥F2 (n = 68)	p value
Gender (F/M)	102/25	59/9	n.s.
Age (yr)	39.3 ± 12.4	39.6 ± 12.2	n.s.
BMI (kg/m ²)	42.3 ± 5.0	42.2 ± 4.0	n.s.
Waist circumference (cm)	119.7 ± 12.1	120.2 ± 13.5	n.s.
ALT (IU/L)	29.7 ± 19.2	37 ± 24.4	0.03
AST (IU/L)	26.0 ± 7.7	31.3 ± 14.4	0.001
HDL-cholesterol (mmol/L)	1.3 ± 0.4	1.3 ± 0.4	n.s.
LDL-cholesterol (mmol/L)	3.2 ± 1.0	3.2 ± 0.8	n.s.
Triglyceride (mmol/L)	1.45 ± 0.8	1.54 ± 0.8	n.s.
Blood glucose (mmol/L)	5.0 ± 1.1	5.3 ± 1.5	n.s.
C-peptide (pmol/L)	868.7 ± 367.8	907.9 ± 392.5	n.s.
HOMA1-IR	5.3 ± 4.1	7.3 ± 8.5	0.04
Glycosylated hemoglobin (%)	5.8 ± 0.7	5.8 ± 0.8	n.s.
Type 2 diabetes n (%)	21 (16.5)	15 (22.1)	n.s.
Metabolic syndrome n (%)	53 (41.7)	40 (58.8)	0.02
Total caffeine (g/wk)	2.55 ± 2.52	1.98 ± 2.04	n.s.
Number of espresso/wk	10.0 ± 16.5	11.4 ± 19.3	n.s.
Quantity of espresso consumed (ml/wk)	578.3 ± 986.5	682.1 ± 1157.8	n.s.
Caffeine from espresso (g/wk)	0.96 ± 1.64	1.14 ± 1.93	n.s.
Quantity of regular coffee consumed (ml/wk)	1441.7 ± 2889.9	575.4 ± 1254.5	0.02
Caffeine from regular coffee (g/wk)	1.00 ± 2.02	0.40 ± 0.88	0.02
Caffeine from tea and chocolate (g/wk)	0.29 ± 0.41	0.25 ± 0.32	n.s.
Total caffeine soda (g/wk)	0.29 ± 0.45	0.18 ± 0.26	n.s.
Tobacco use (packages per yr)	4.9 ± 11.1	6.0 ± 14.0	n.s.
Cannabis (joints per yr)	0.2 ± 1.8	0.09 ± 0.7	n.s.
NAFLD activity score (NAS)			
≥3 n (%)	45 (35.4)	36 (52.9)	0.02
≥4 n (%)	20 (15.7)	24 (35.3)	0.002
≥5 n (%)	7 (5.5)	13 (19.1)	0.003
NASH n (%)	17 (13.4)	21 (30.9)	0.003

F, female; M, male; BMI, body mass index; ALT, alanine amino-transferase; AST, aspartate amino-transferase; HDL, high density lipoprotein; LDL, low density lipoprotein; HOMA1-IR, homeostasis model assessment of insulin resistance; IDF, International Diabetes Federation; NAS, NAFLD activity score; NASH, non-alcoholic steatohepatitis; n.s., not significant.

Stage of fibrosis was assessed using the NASH Clinical Research Network Scoring System Definition and Scores in Study Set.

195 severely/morbid obese womens

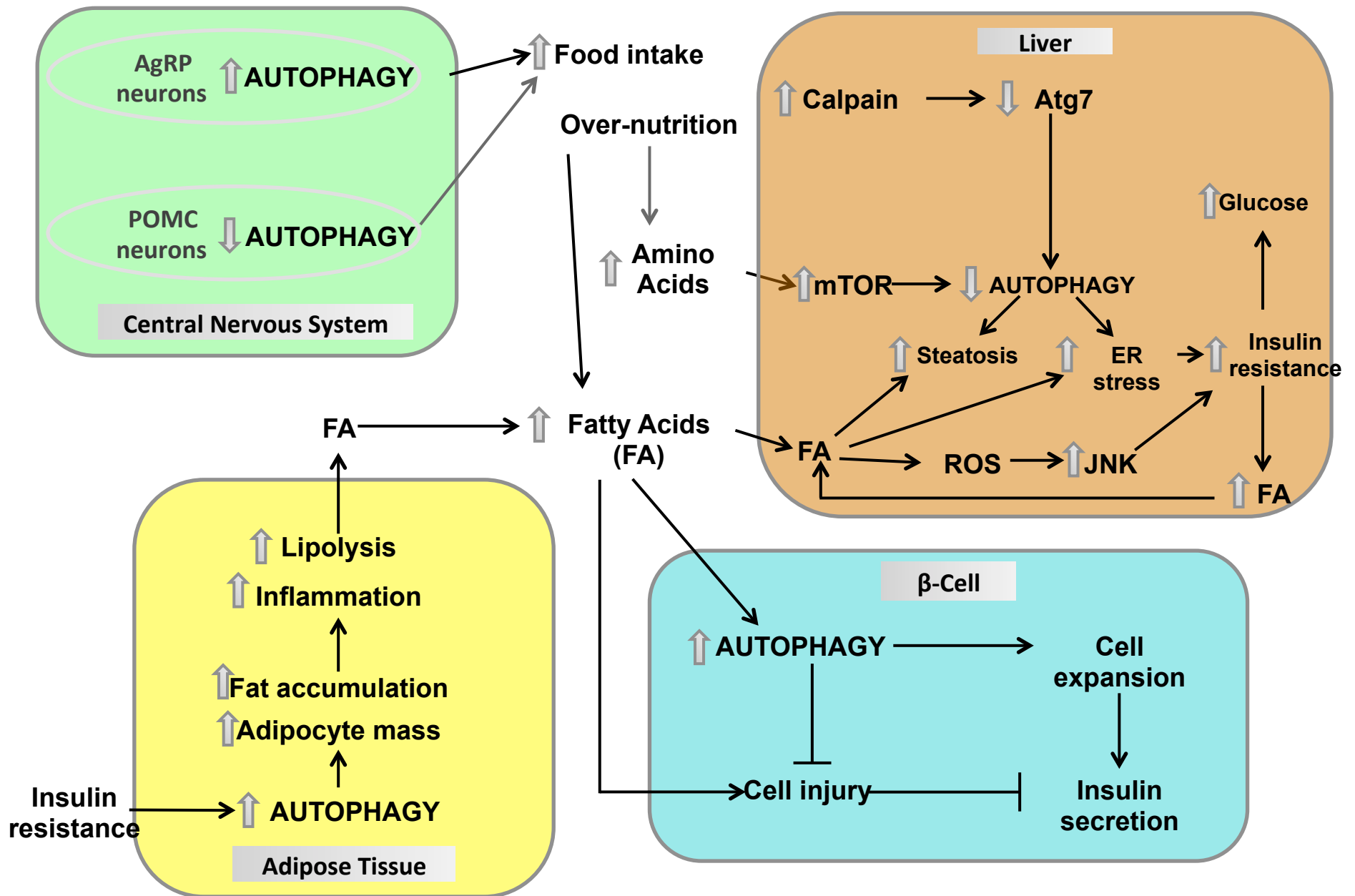
Table 4. Multivariate analysis assessing factors associated with significant fibrosis (≥F2) in morbidly obese patients.

	OR	95% CI	p value
AST	1.039	1.004-1.076	0.029
Caffeine from regular coffee*	0.752	0.578-0.980	0.034
HOMA-IR	0.993	0.955-1.032	0.706
NASH	2.413	1.007-5.782	0.048
IDF metabolic syndrome	1.253	0.622-2.527	0.528

*Caffeine from regular coffee intake (g/week) reflects consumption of regular coffee.

Stage of fibrosis was assessed using the NASH Clinical Research Network Scoring System Definition and Scores in Study Set.

(Anty et al., J Hepatol. 2012;57(5):1090-6)



(Lavallard *et al*, *Pharmacol Res.* 2012;66(6):513-25)

Inserm

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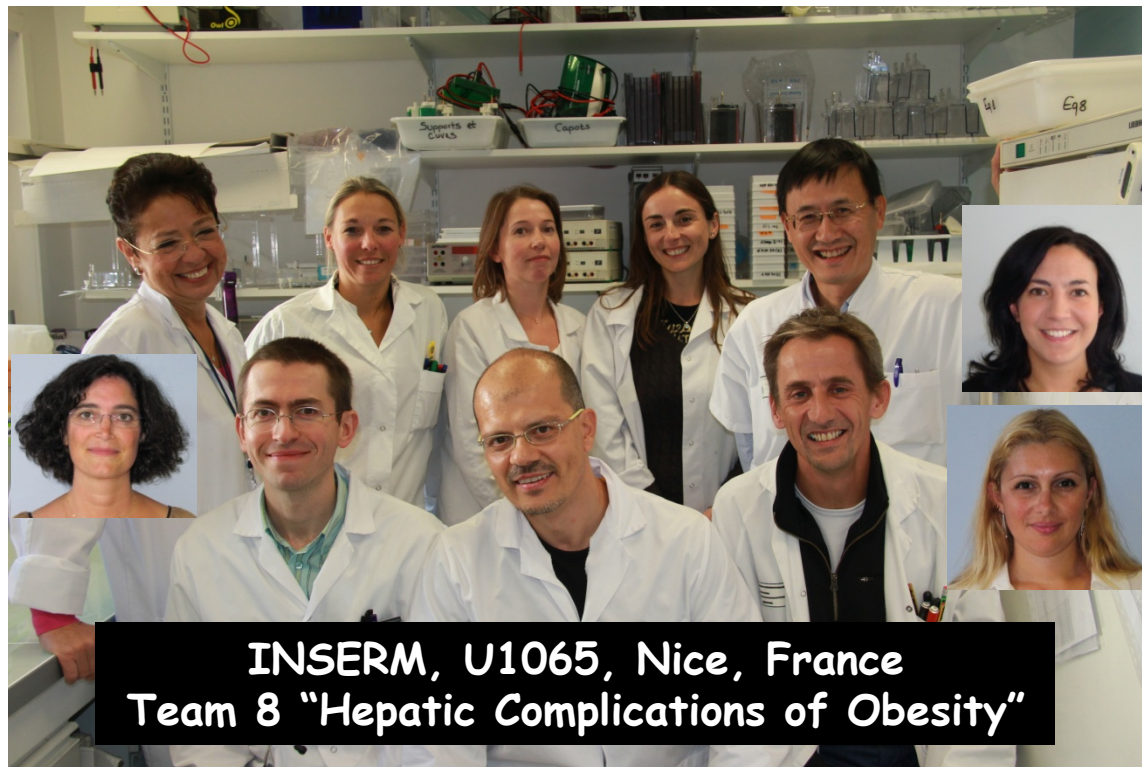
Thank you for your attention

Thanks to...

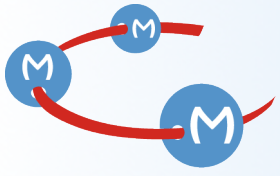
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Gual Philippe, DR2, Ph D

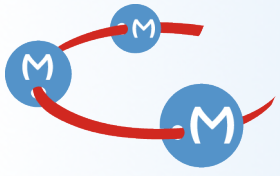
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Antonio Iannelli, MD, Ph D
Rodolphe Anty, MD, Ph D
MC Saint-Paul, MD
Dominique Crenesse; MD, Ph D

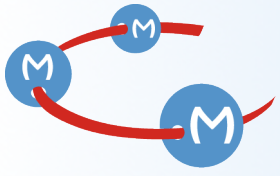
Béatrice Bailly-Maître, CR1, Ph D
Elvire Gouze, CR1, Ph D
Déborah Rousseau, Engineer
Stéphanie Bonnafous, Engineer
A-S Schneck, Ph D Student
Stéphanie Patouraux, Ph D Student
Stéphanie Cassagnaud, Ph D Student

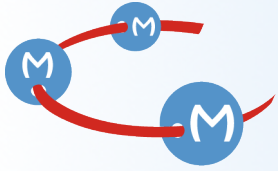


**INSERM, U1065, Nice, France
Team 8 "Hepatic Complications of Obesity"**







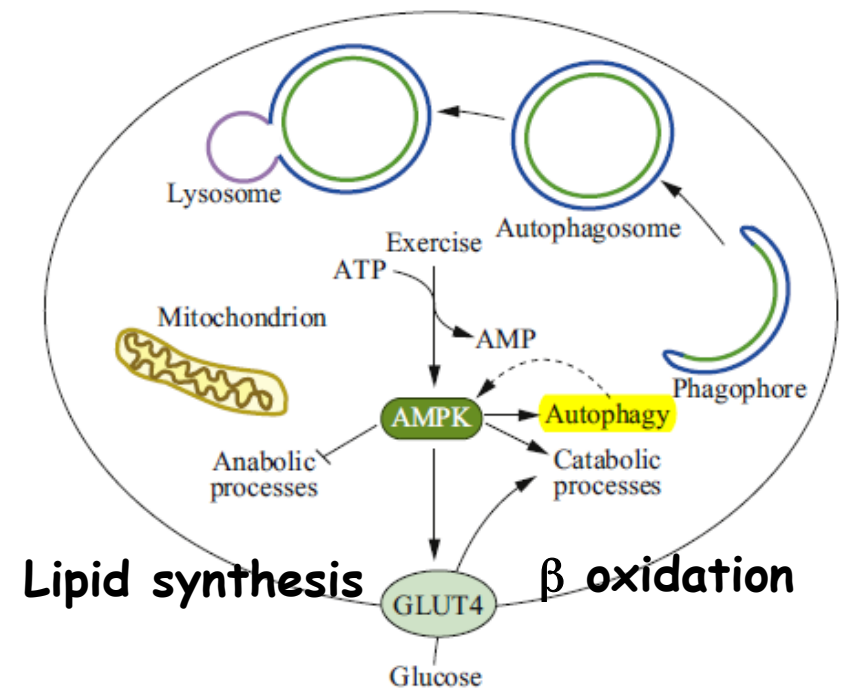


Muscle and autophagy

Exercise

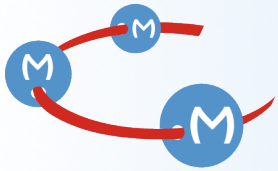
(BCL2 mutant constitutively associated with Beclin)

Mutant mice fed a HFD but not exercised are largely indistinguishable from Wt mice regarding these metabolic parameters, suggesting that basal autophagy does not contribute substantially to resting lipid or glucose homeostasis.



(He et al. *Nature* 2012.481, 511-515)

(Klionsky et al. *Cell Metabolism*, 2012, 15, 273-4)

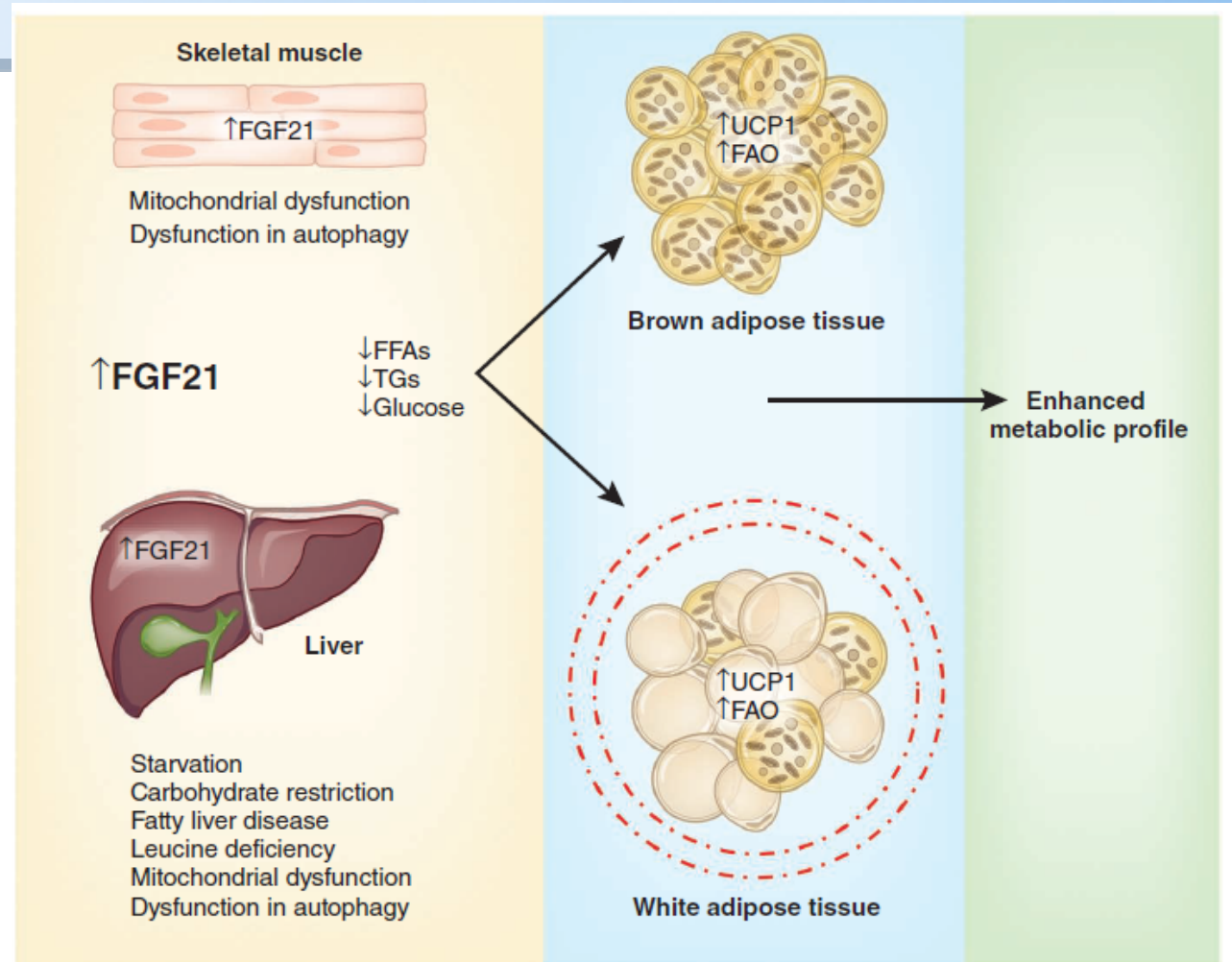


Muscle and autophagy

↓
Autophagic flux
in muscle
(Δ Muscle-ATG7
KO)

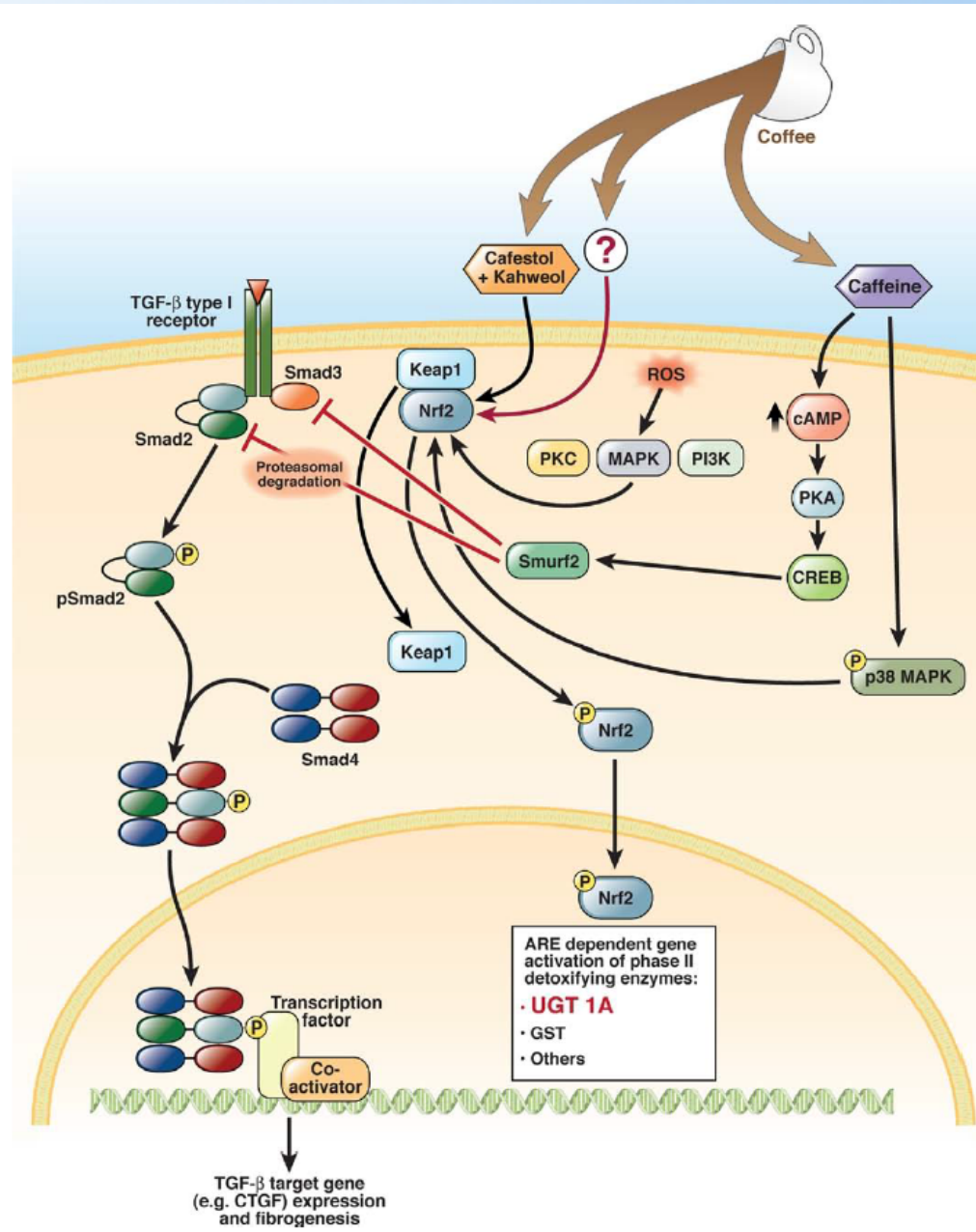
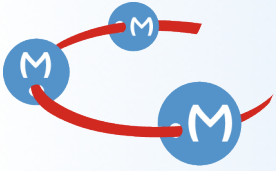
-decreased fat mass

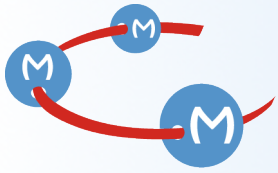
-protected from diet
-induced obesity
and insulin resistance;



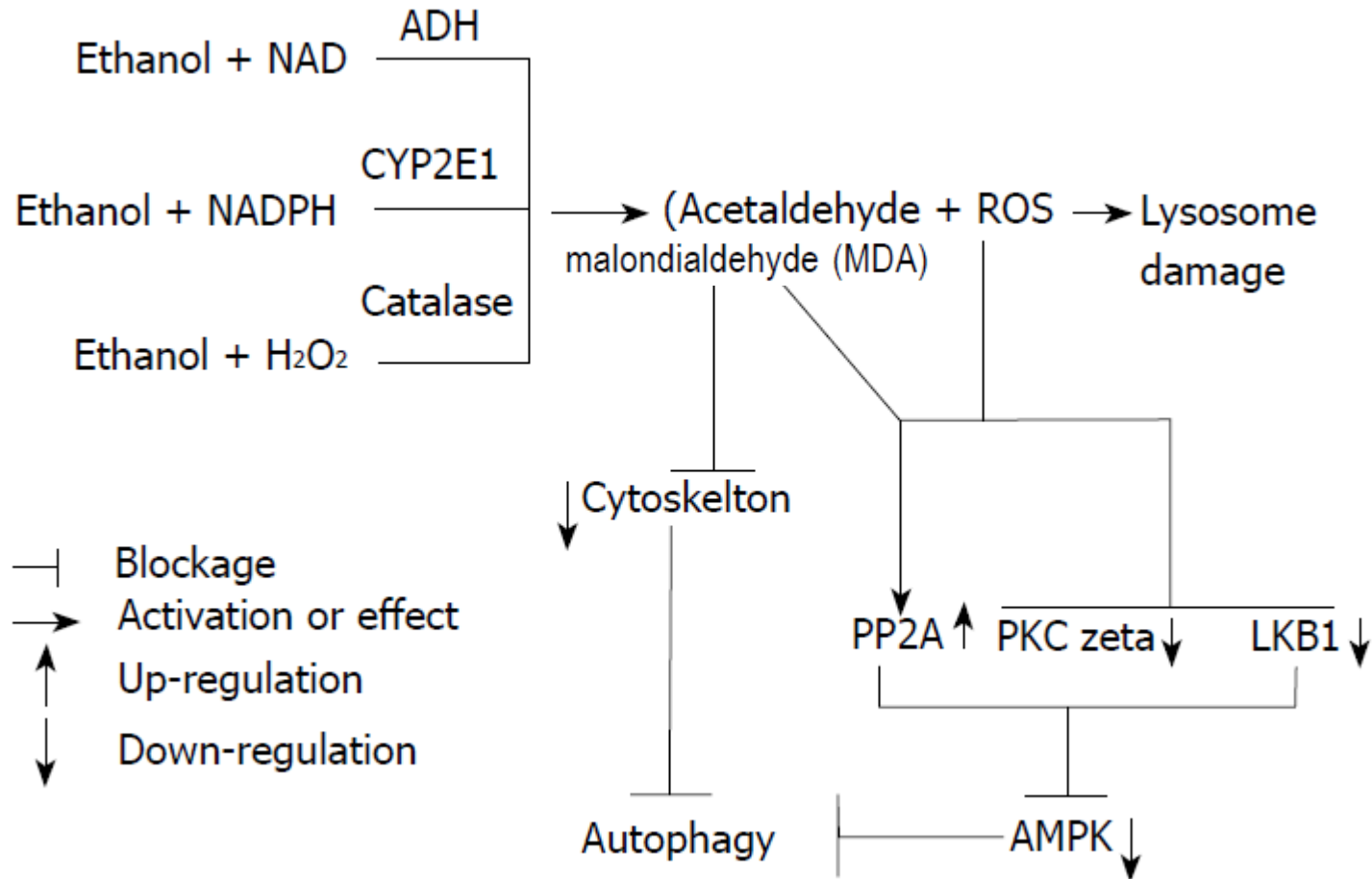
(Kim *et al.* *Nat Med.* 2013;19(1):83-92.)

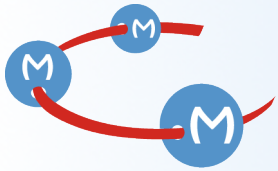
(Fisher FM *et al.* *Nat Med.* 2013 Jan;19(1):17-8)



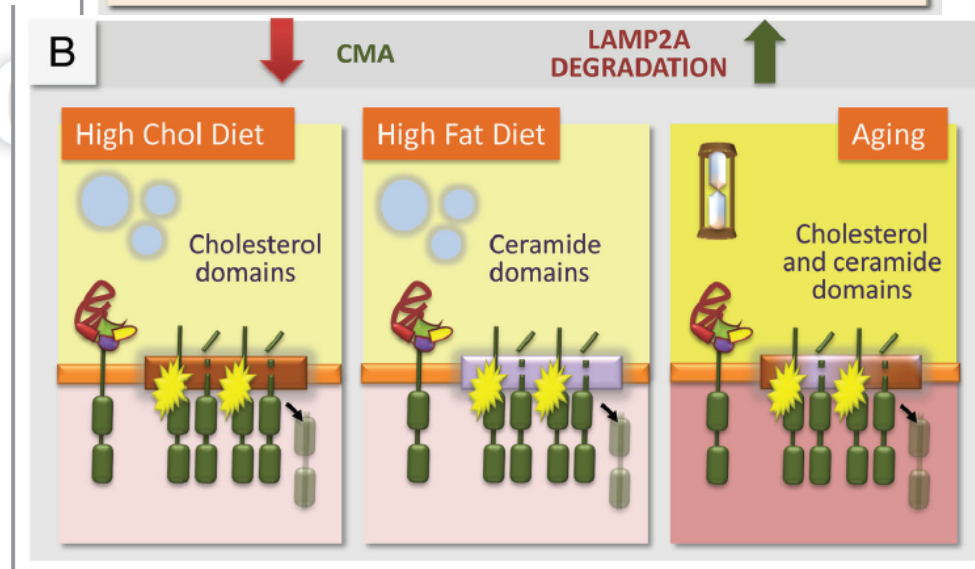
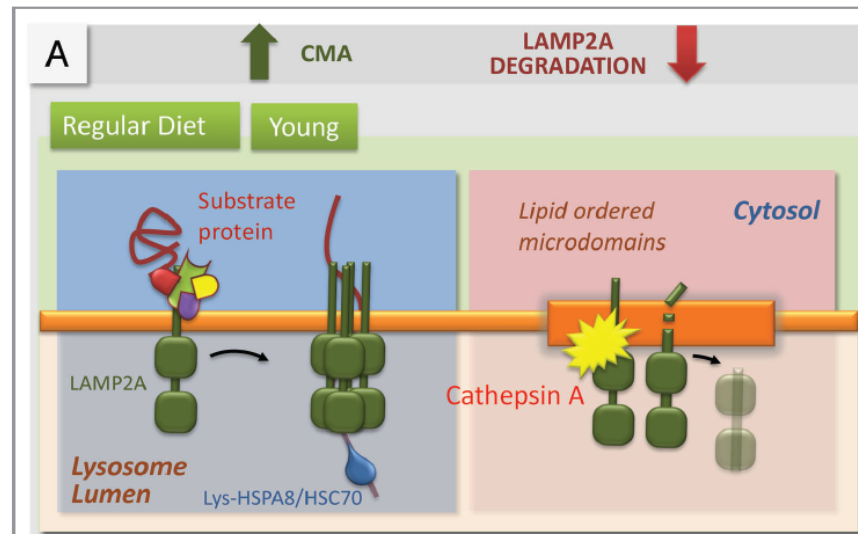


Ethanol and autophagy

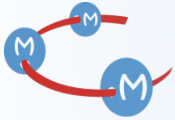




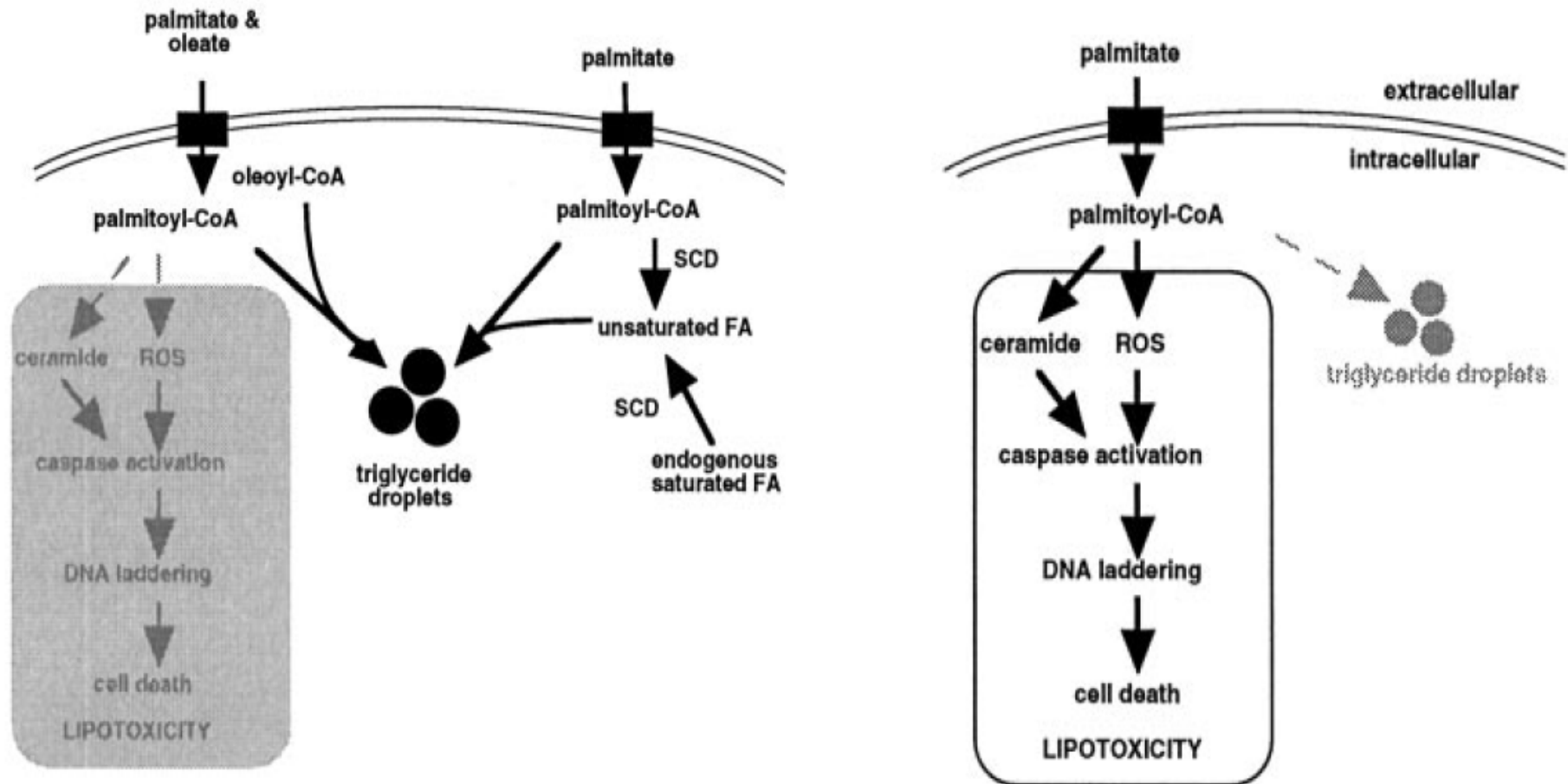
Chaperone Mediated Autophagy



(Rodriguez-Navarro JA, Cuervo AM. Autophagy. 2012;8(7):1152-4)



Lipotoxicity



FFA < TG

FFA > TG

(Listenberger *et al.*, *PNAS*, 2003, 100,6 ,3077-3082)

