Concept course „Cell Biology“: 551-0326-00L

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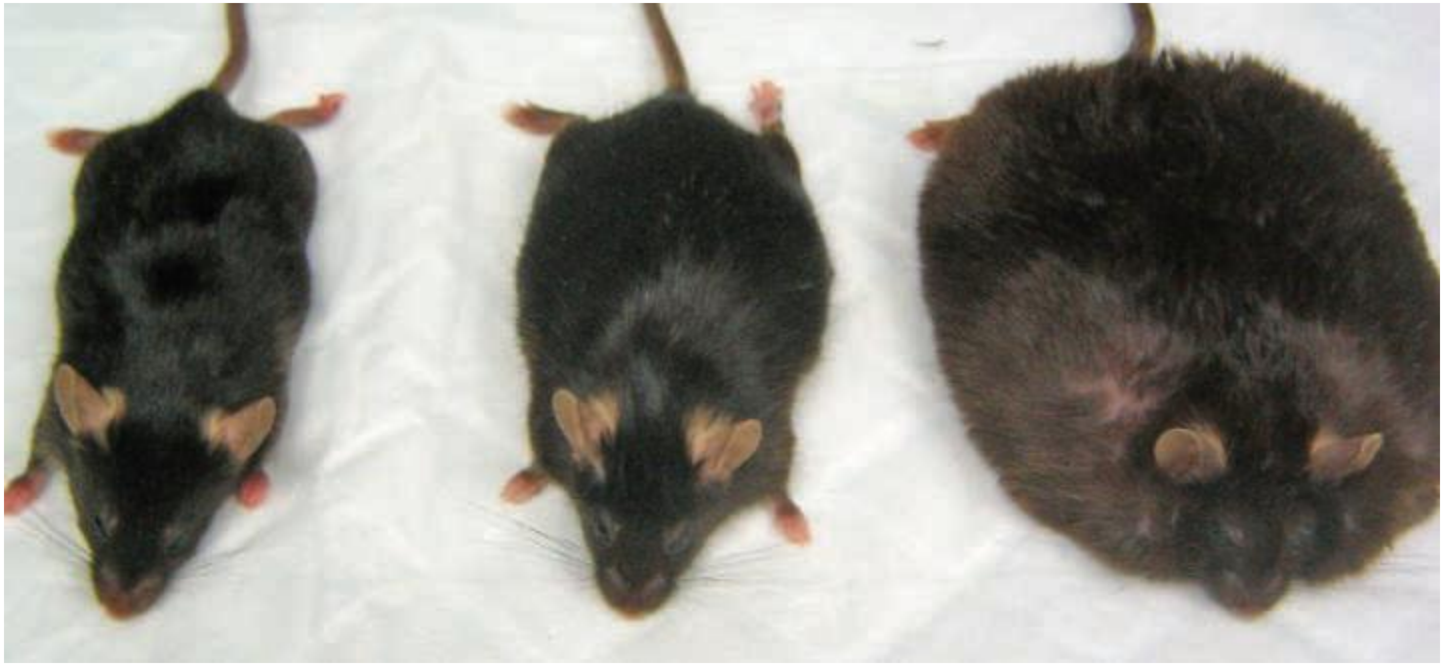
Dr. Werner Kovacs

ETH Zürich, Institute of Molecular Health Sciences, HPL H16

werner.kovacs@biol.ethz.ch



Wild-type Perilipin knockout ob/ob

Obesity

- Obesity: Having a very high amount of body fat in relation to lean body mass, or Body Mass Index (BMI) of 30 or higher.

- Body Mass Index (BMI): a measure of an adult’s weight in relation to his or her weight, specifically the adult’s weight in kilograms divided by the square of his or her height in meters. BMI is used to assess the extent of general obesity.

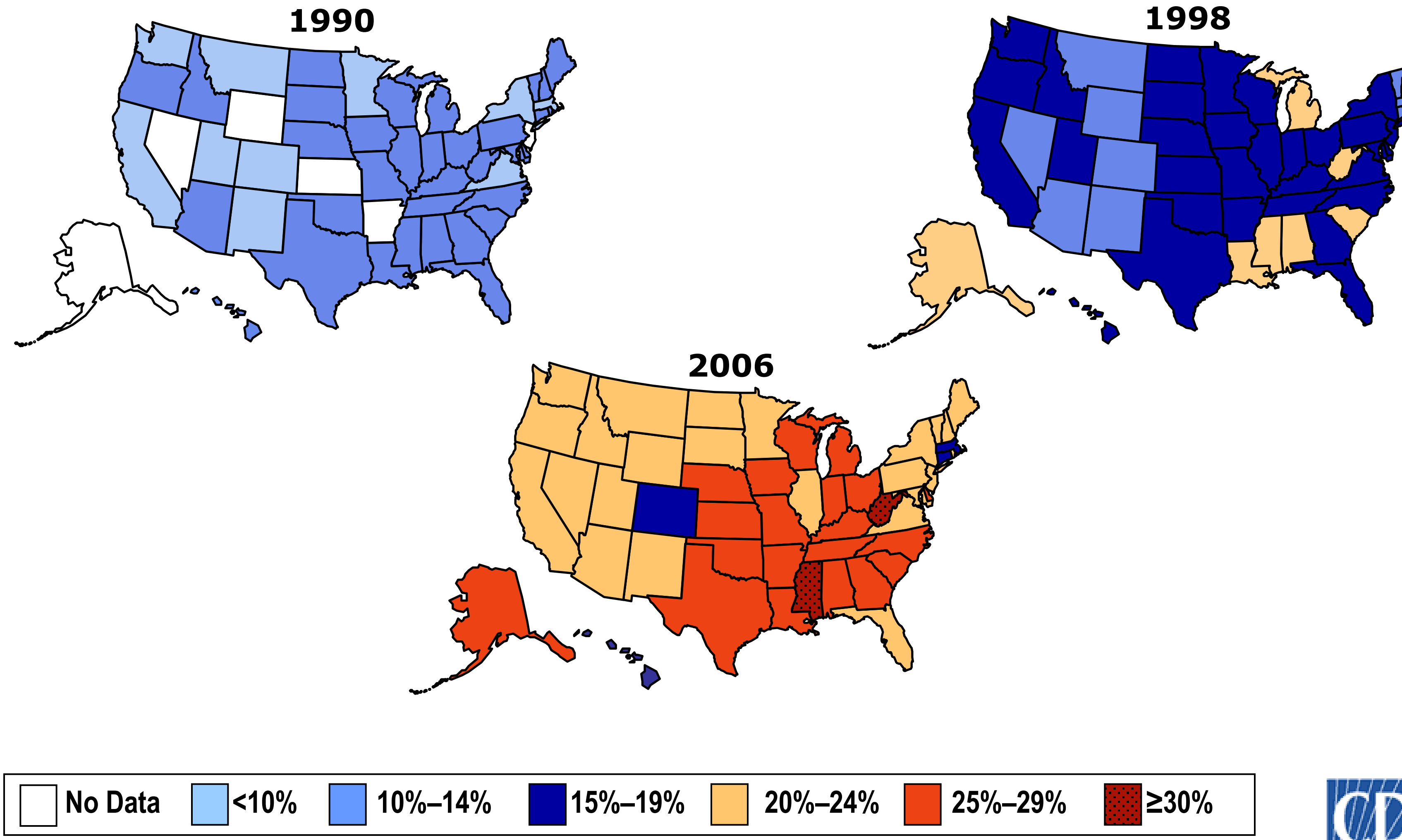
- Waist-to-hip-ratio (WHR): parameter for central obesity (apple-shaped or pear-shaped obesity)

- Obesity is a complex trait, driven by the interaction between genetic and environmental factors.

Obesity Trends* Among U.S. Adults

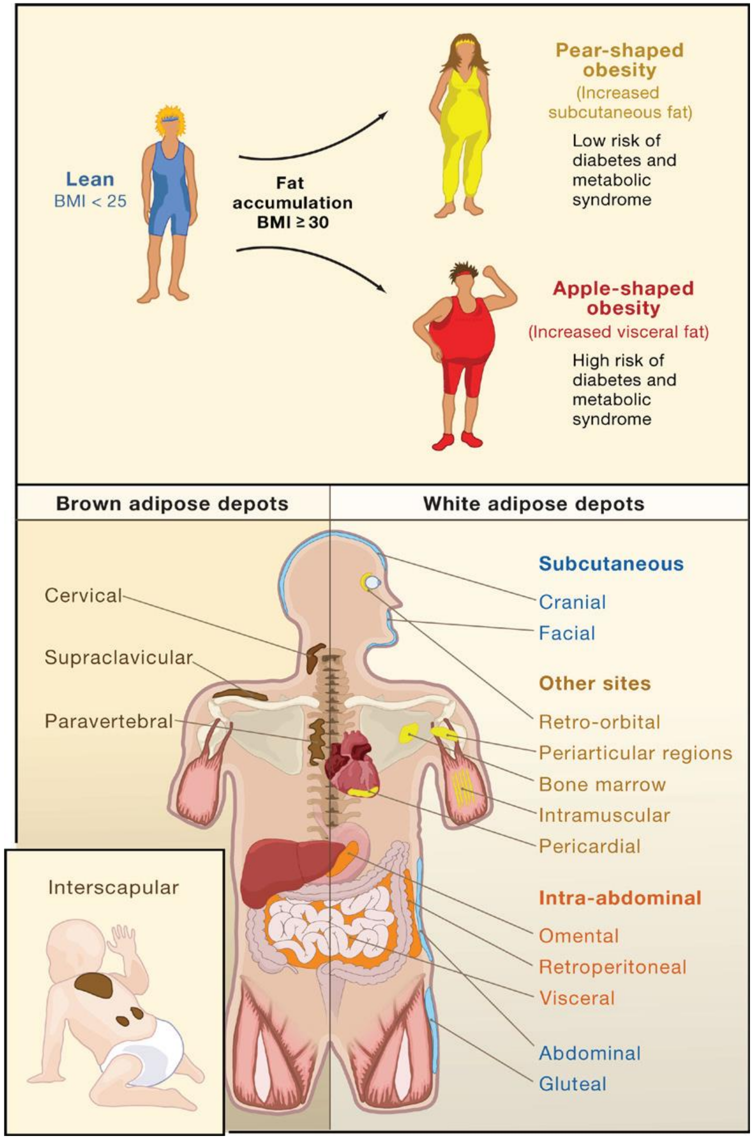
BRFSS, 1990, 1998, 2006

(*BMI ≥30, or about 30 lbs. overweight for 5’4” person)



Fat distribution influences risks associated with obesity in humans

normal BMI
normal WHR

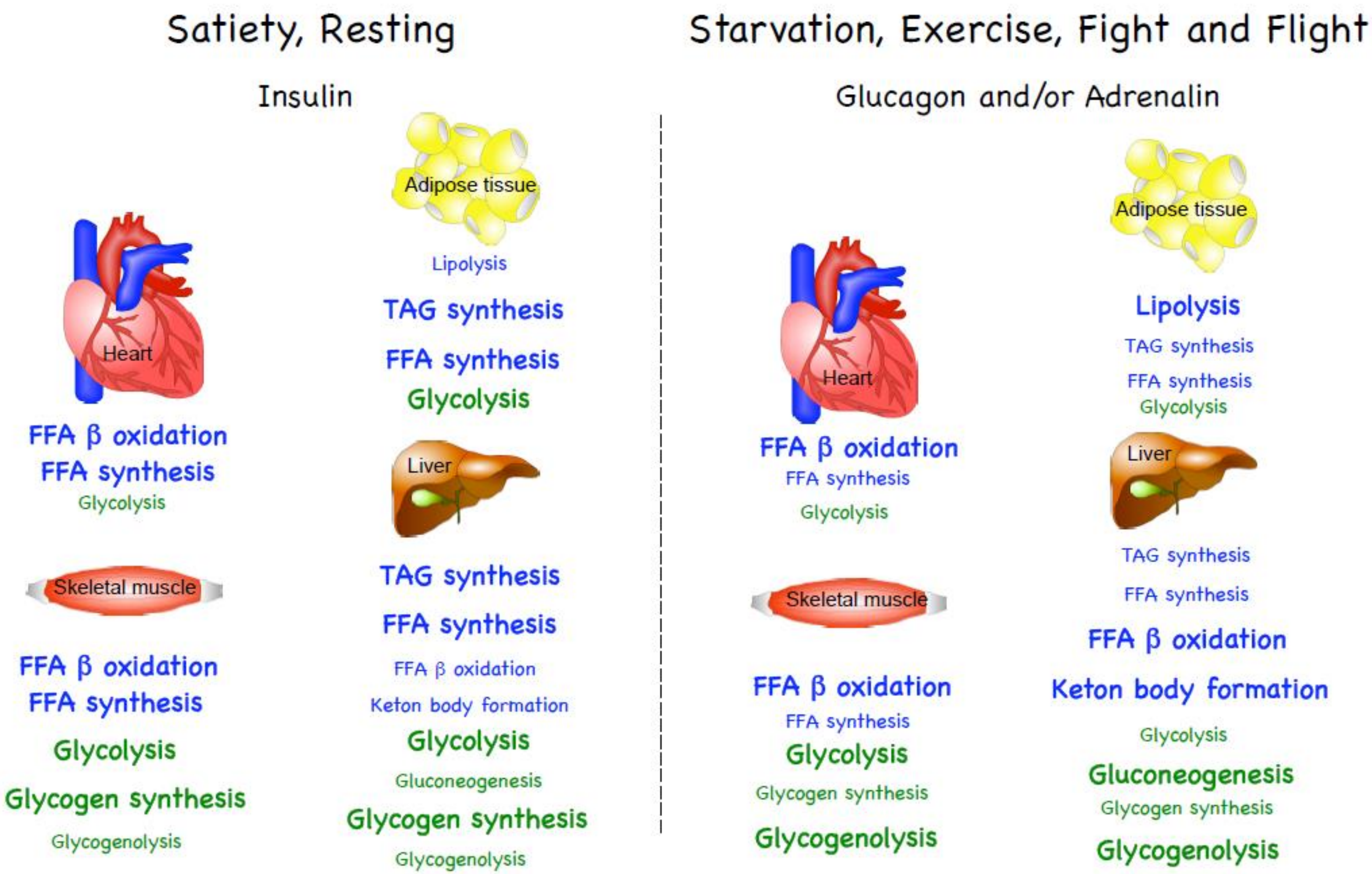


high BMI
low WHR

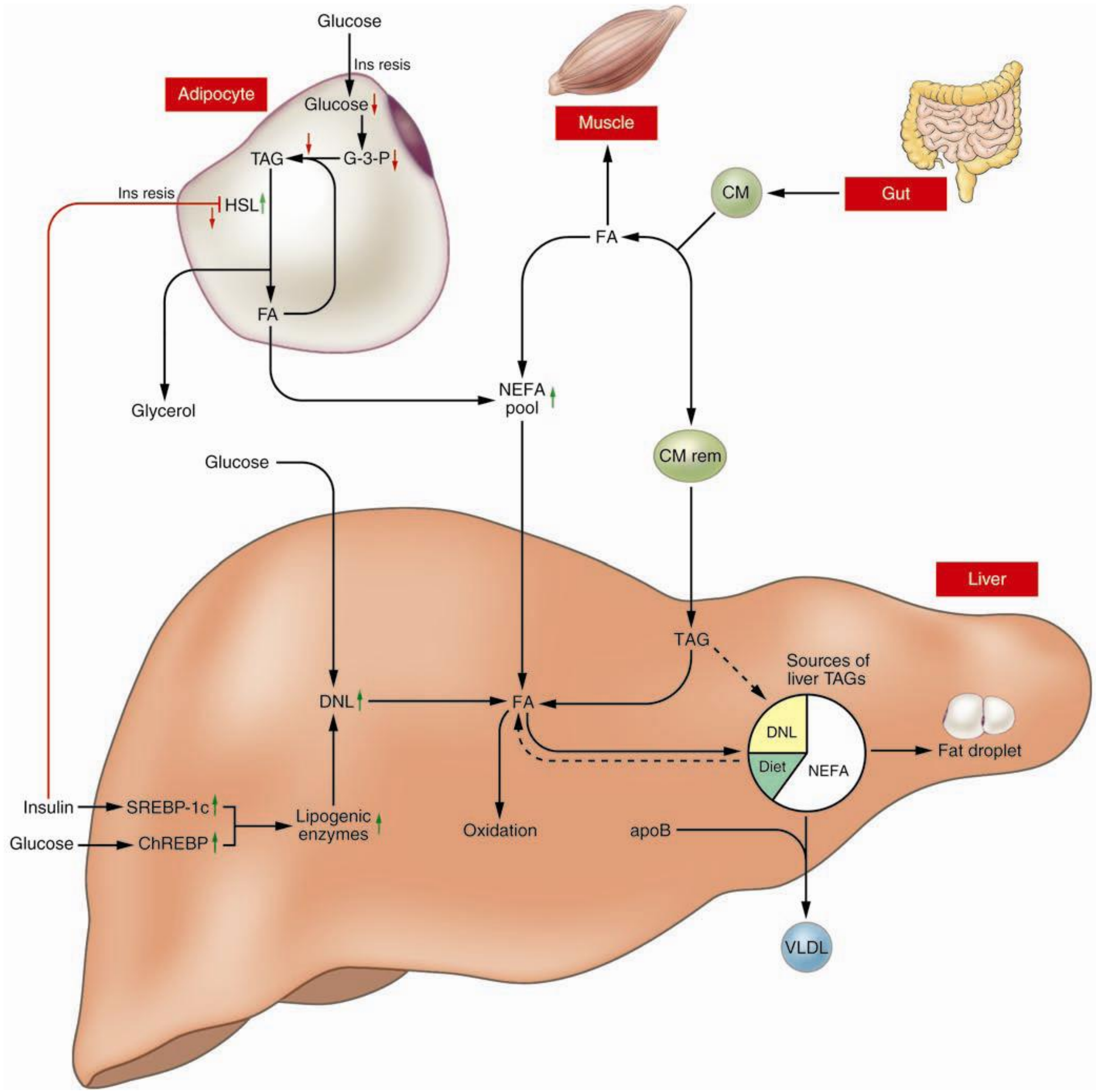
high BMI
high WHR

Gesta et al., Cell (2007)

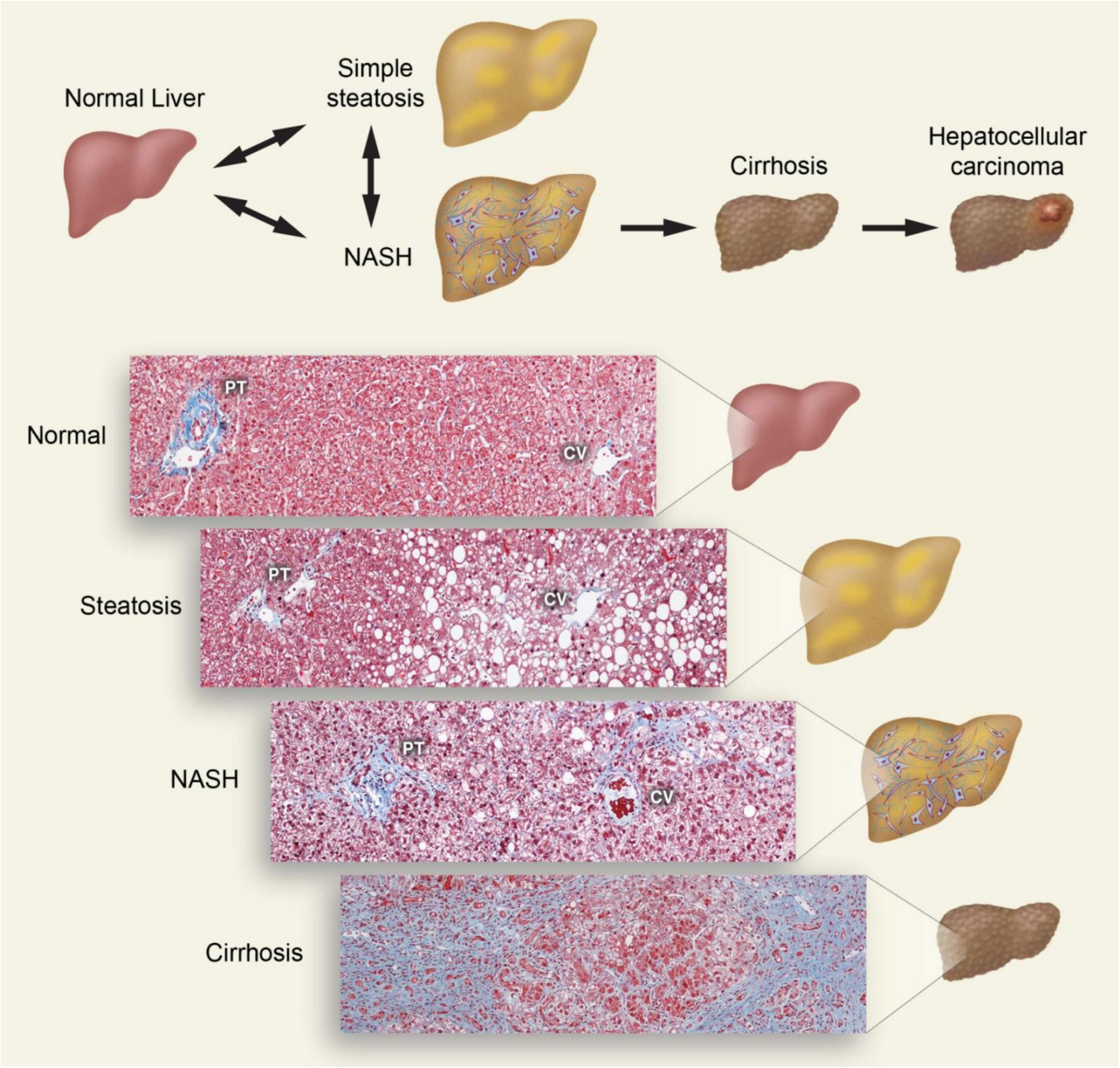
Lipid and glucose homeostasis under different physiologic conditions



Model of lipid flux through the liver

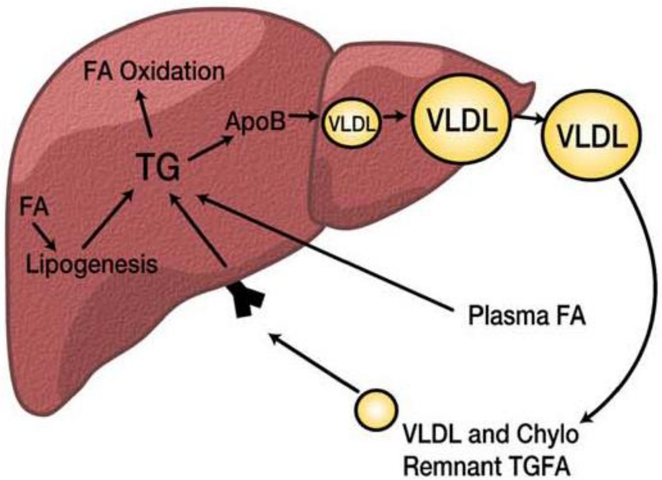


The disease spectrum of nonalcoholic fatty liver disease

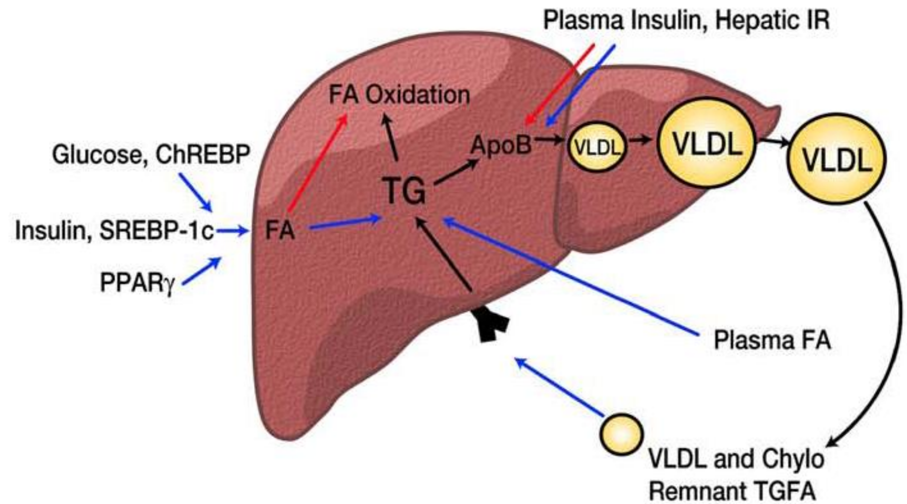


Hepatic lipid metabolism in steatosis and steatohepatitis

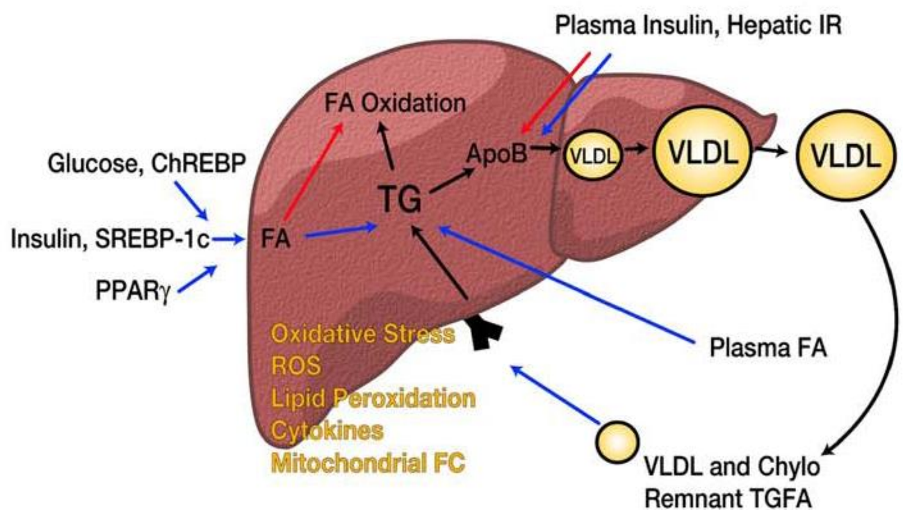
A **Forces regulating hepatic lipid homeostasis**



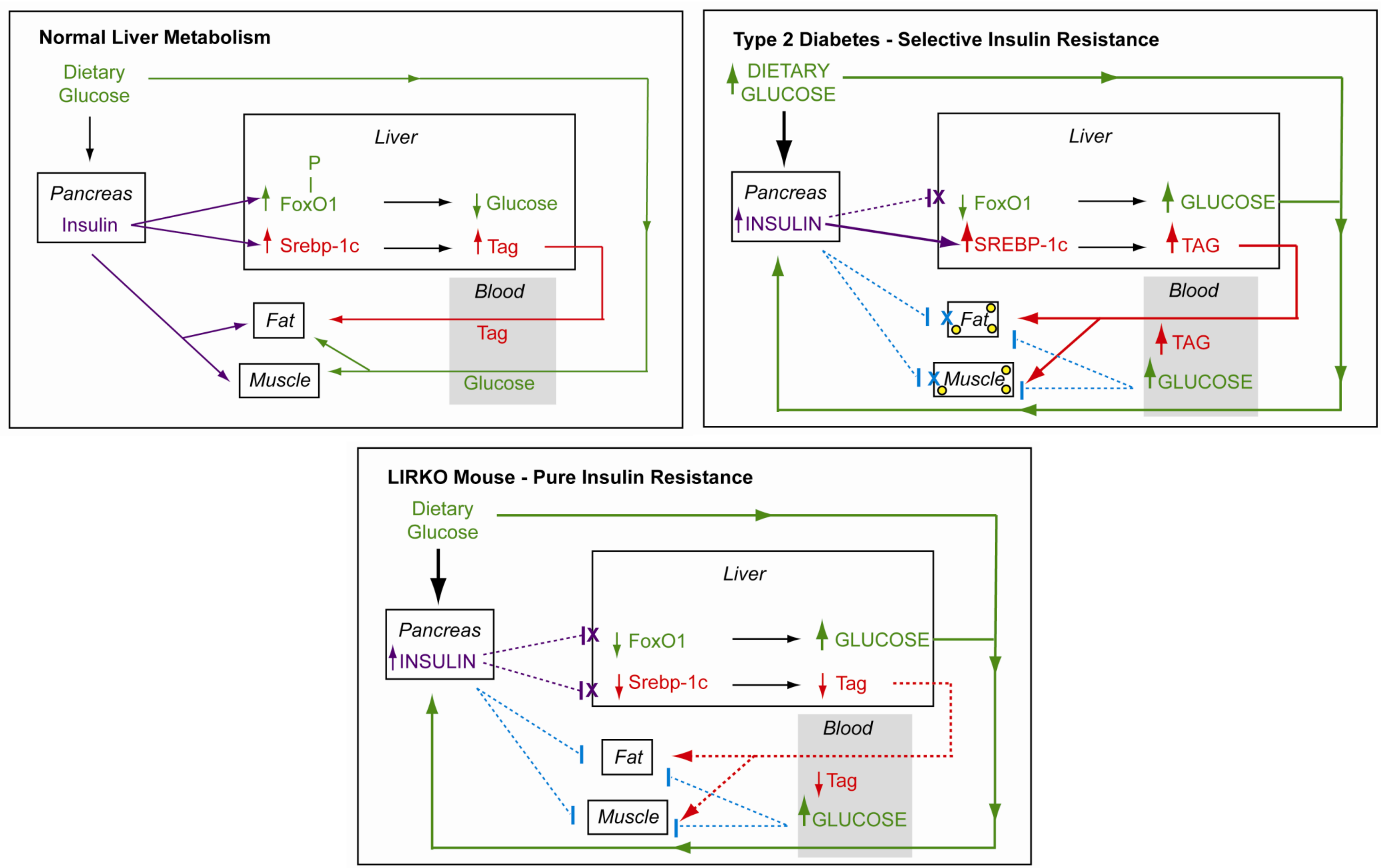
B **Dysregulation of hepatic lipid homeostasis leading to steatosis**



C **Dysregulation of hepatic lipid homeostasis leading to steatohepatitis**

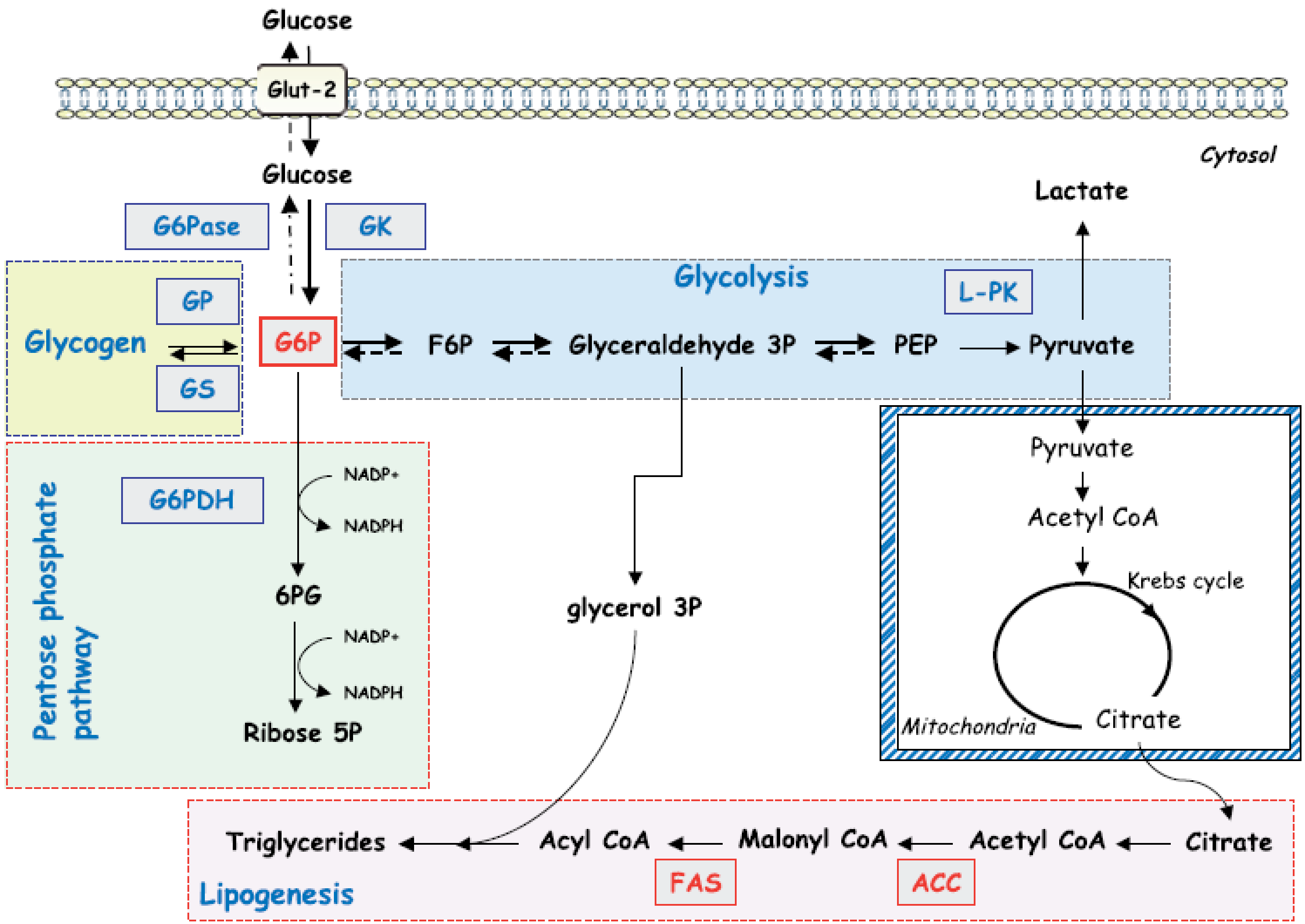


Selective insulin resistance in the liver produces a more severe metabolic defect than total insulin resistance



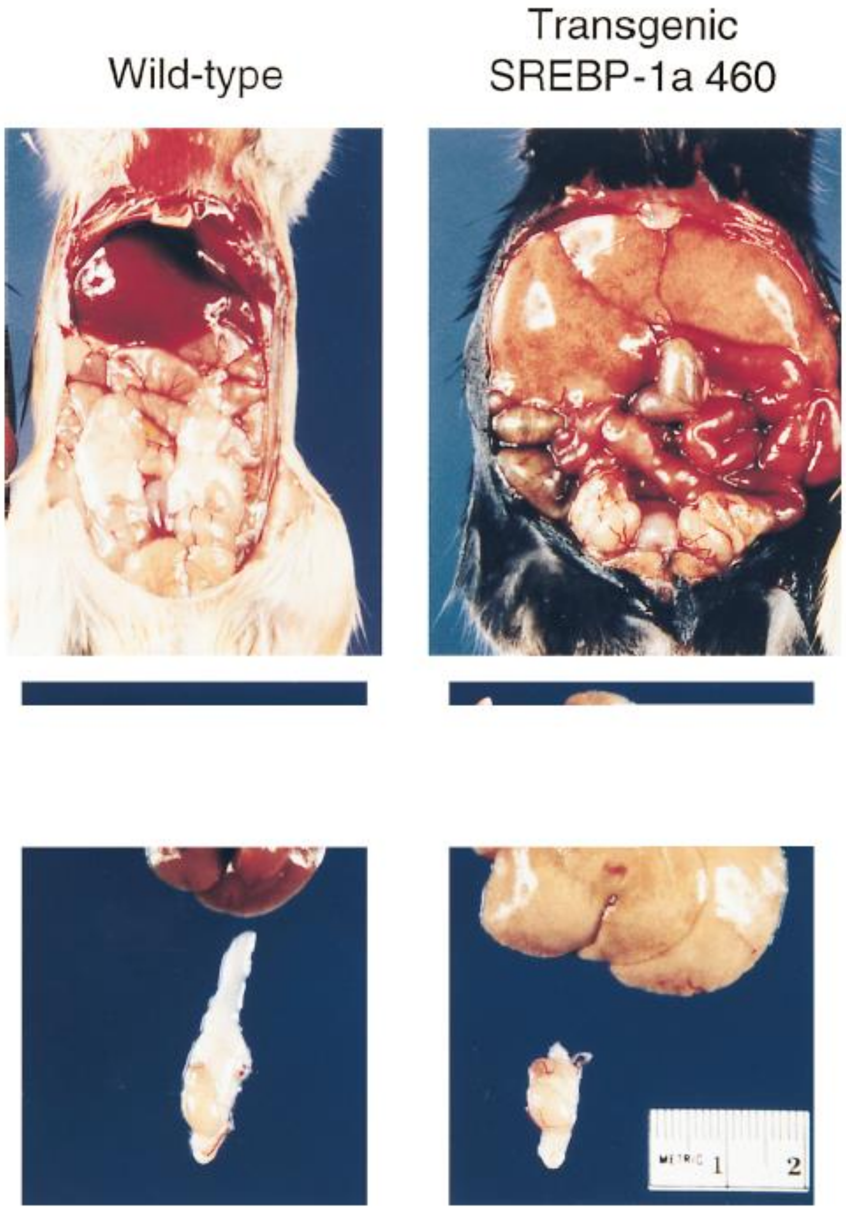
Brown and Goldstein, Cell Metab. (2008)

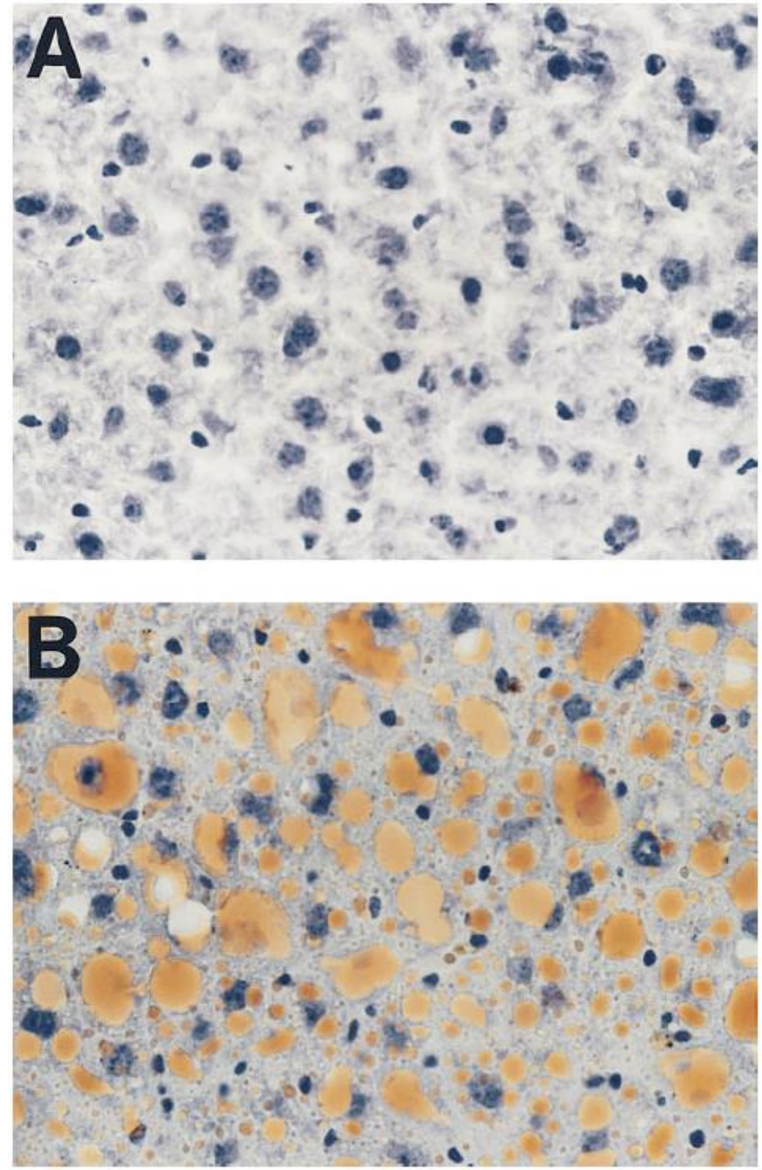
Metabolic pathways leading to the synthesis of triglycerides in the liver



Postic et al., Annu. Rev. Nutr. (2007)

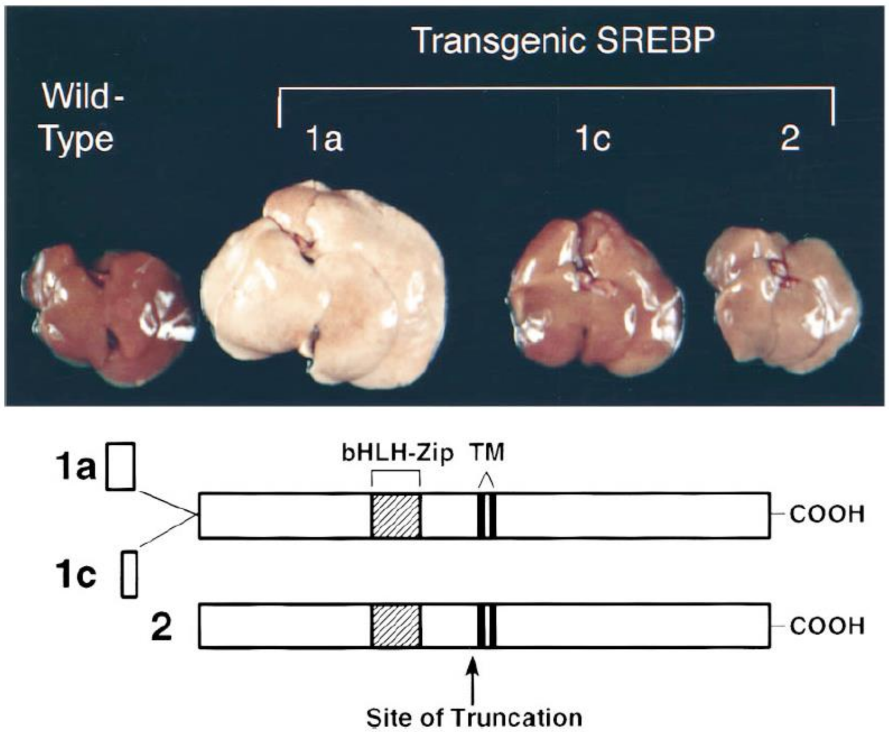
Transgenic mice expressing truncated SREBP-1a



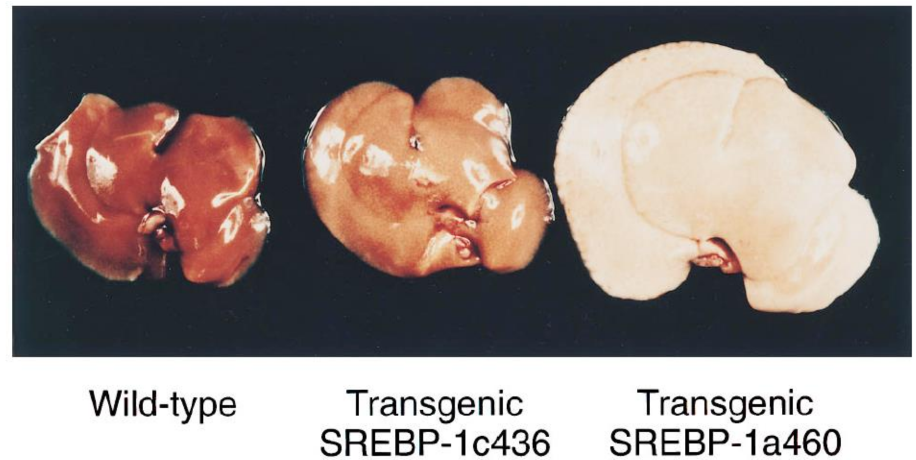


Shimano et al., J. Clin. Invest. (1996)

Livers from wild-type and transgenic mice expressing truncated dominant-positive SREBP-1a, -1c, and -2

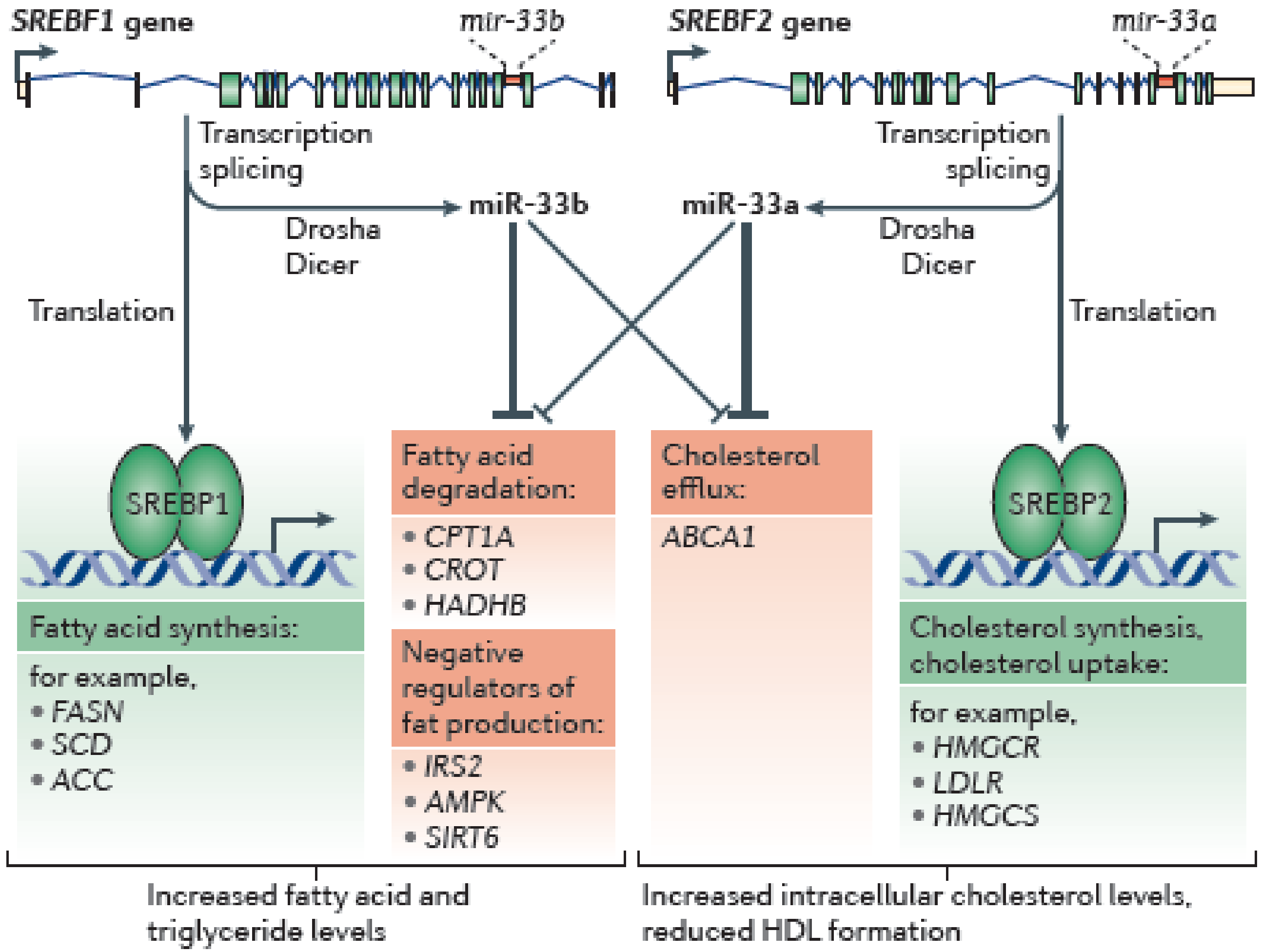


Horton et al., J. Clin. Invest. (1998)

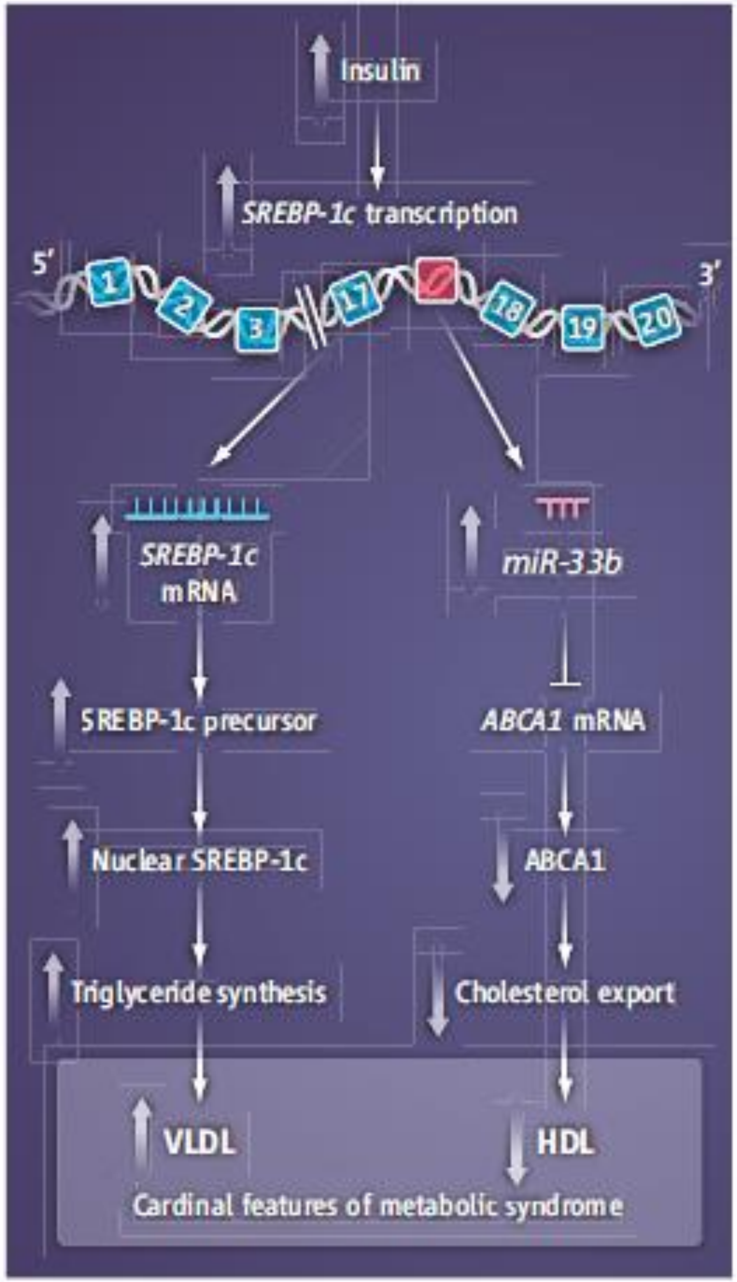


Shimano et al., J. Clin. Invest. (1997)

Model of the SREBP and miR-33 circuit

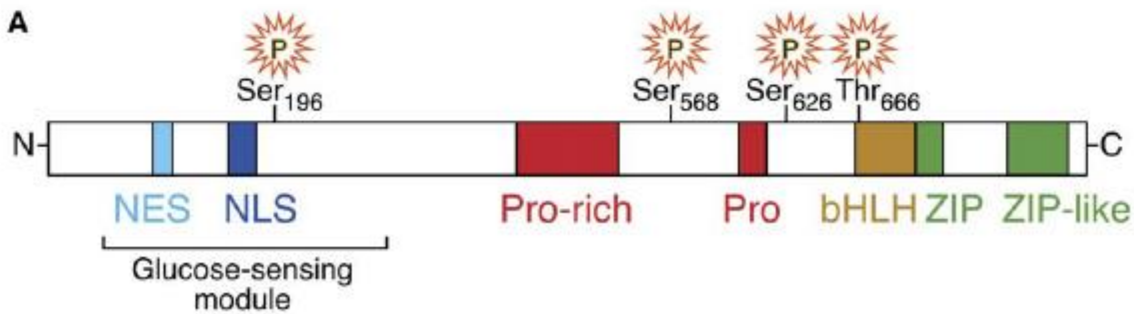


Rottiers and Näär, Nat. Rev. Mol. Cell Biol. (2012)

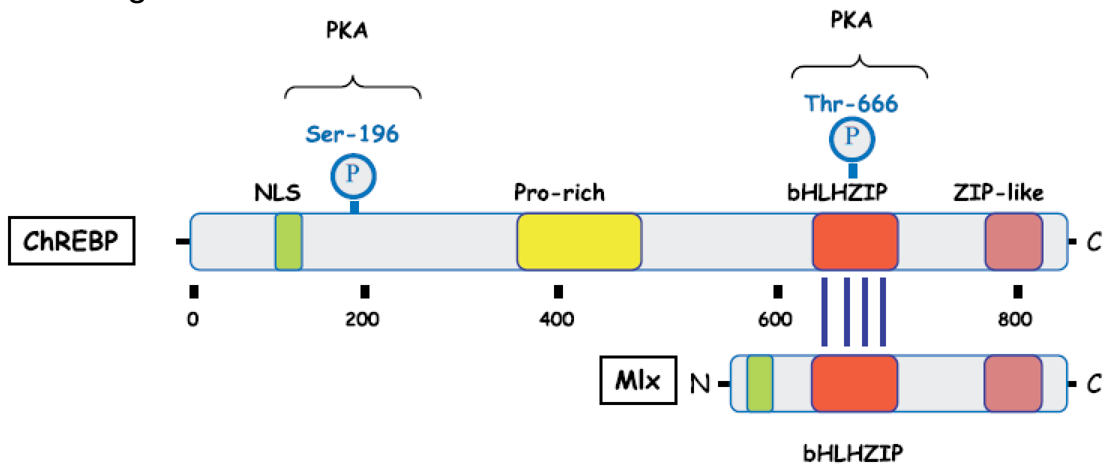


Brown et al., Science (2010)

ChREBP and Mlx protein structures

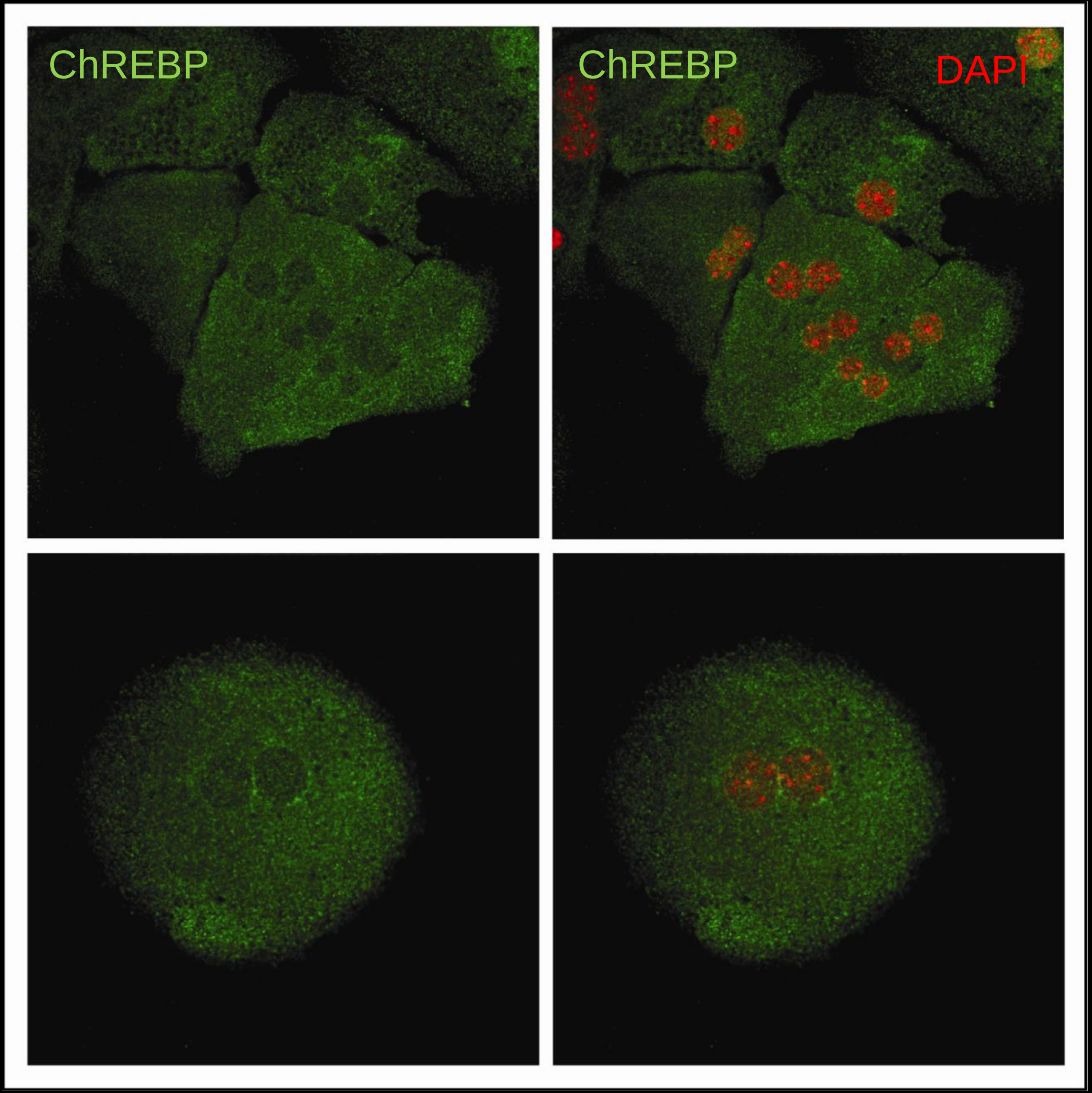


NES: nuclear export signal
NLS: nuclear localization signal

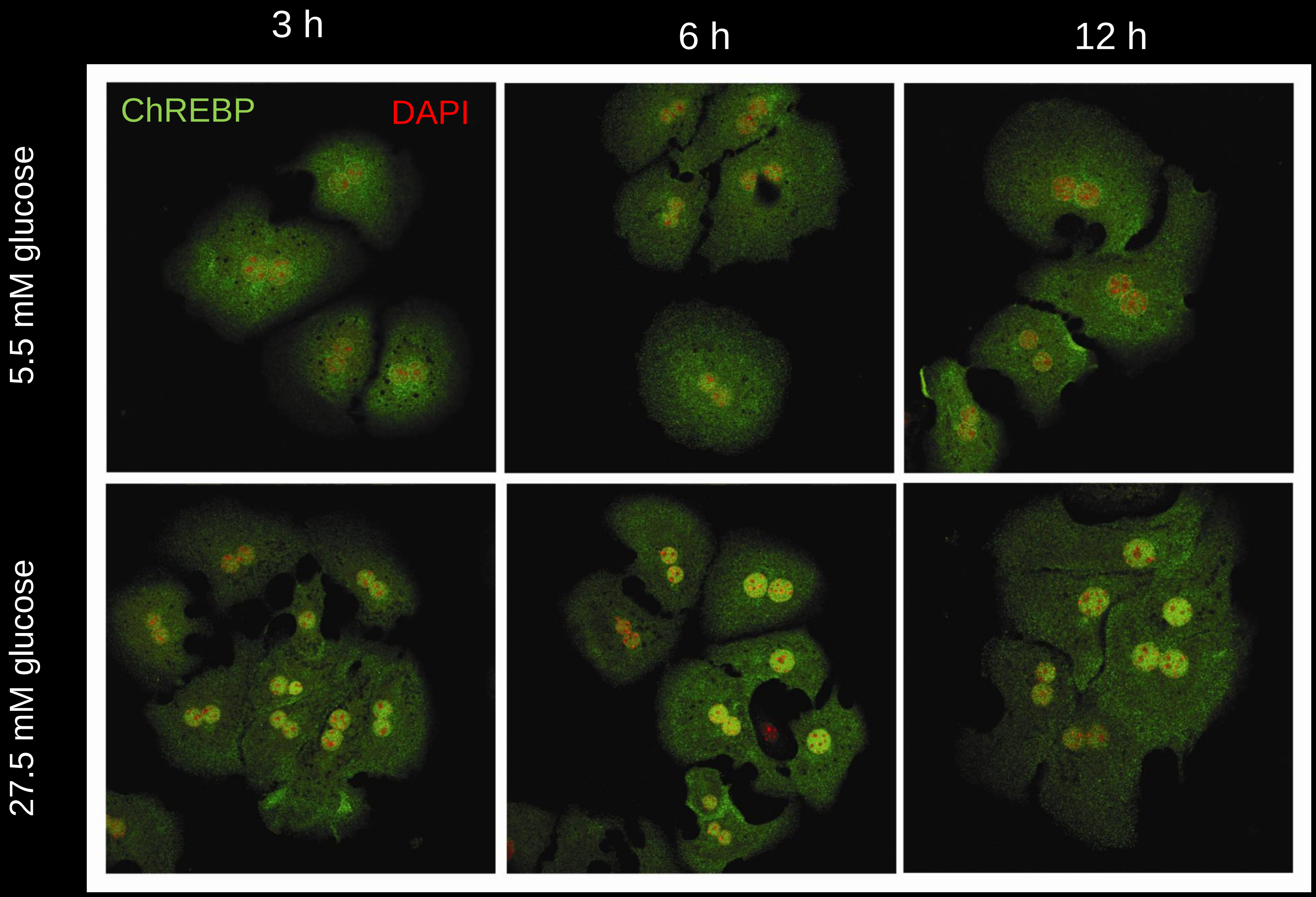


Uyeda and Repa, Cell Metab. (2006)
Postic et al., Annu. Rev. Nutr. (2007)

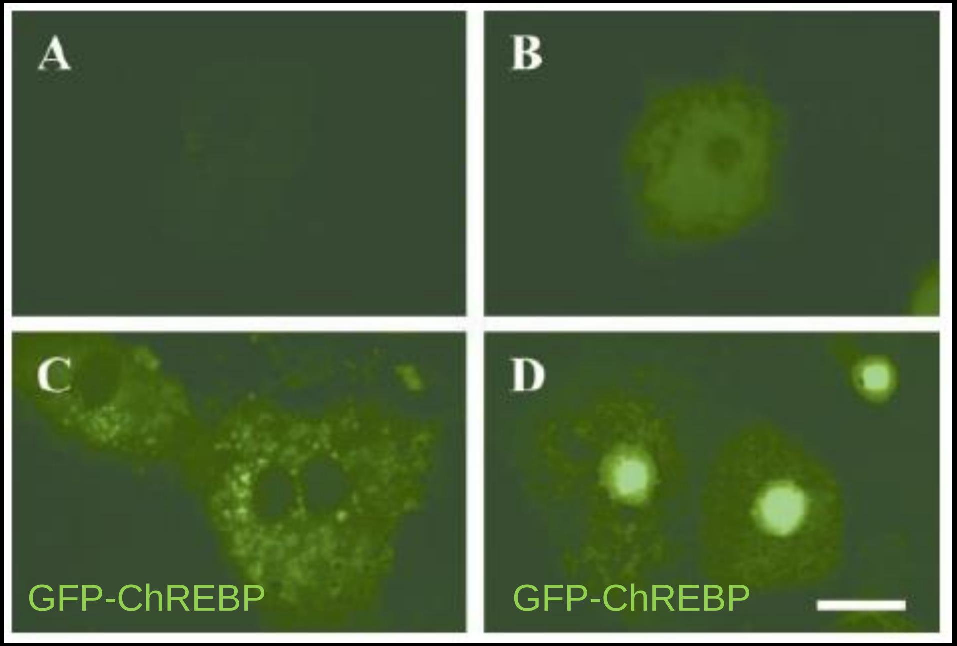
ChREBP localization in glucose-starved mouse hepatocytes



ChREBP localization under low and high glucose concentrations

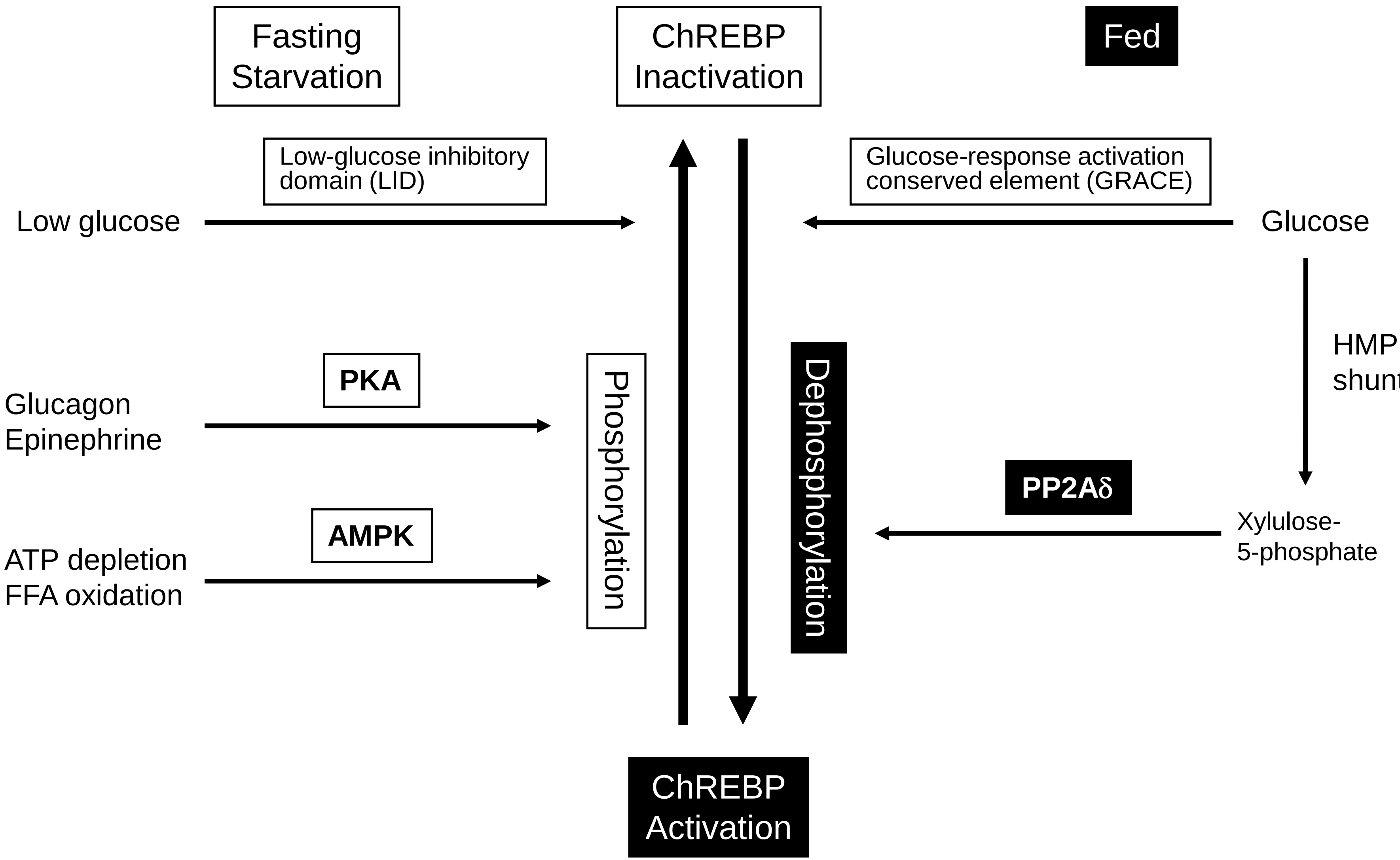


Subcellular localization of GFP-ChREBP under low or high glucose

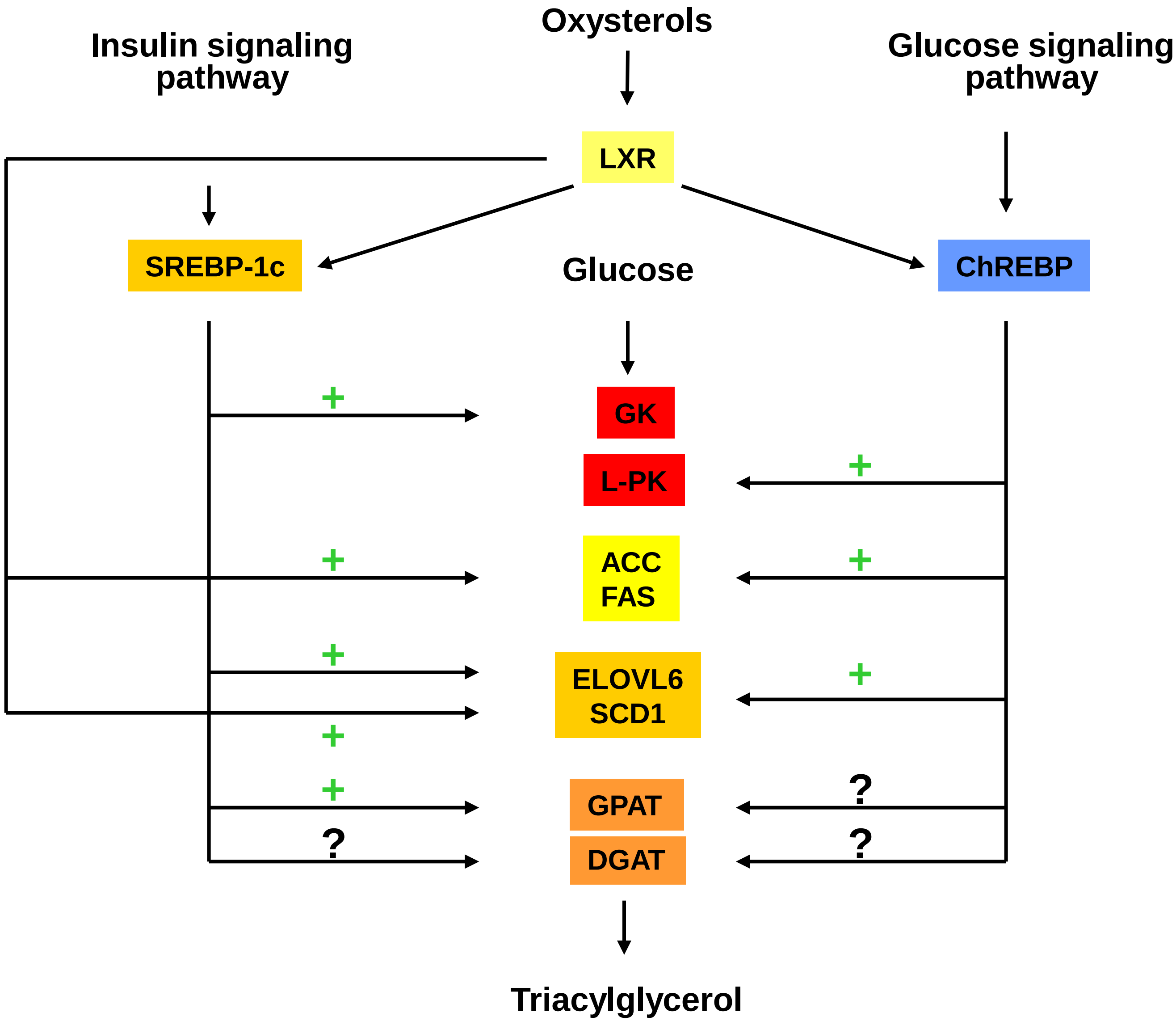


Kawaguchi et al., PNAS (2001)

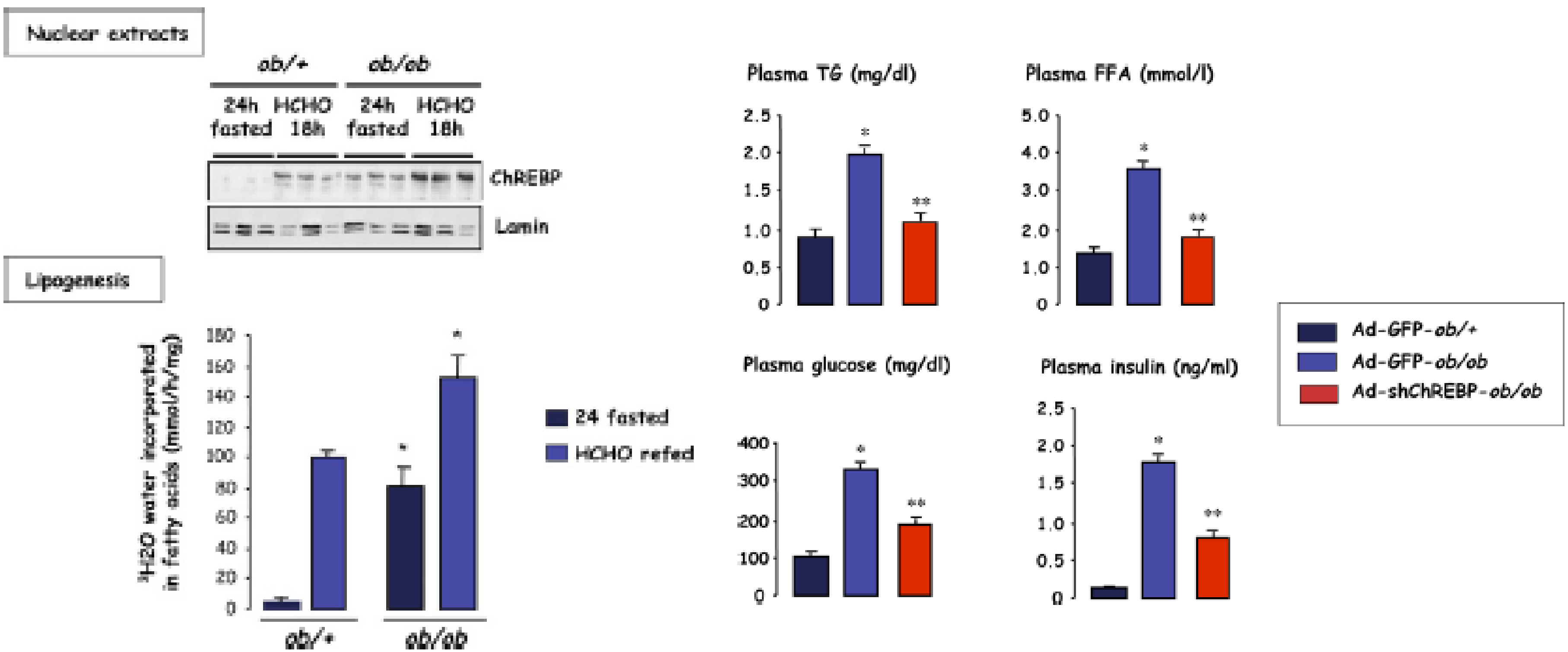
Nutrient/hormone-mediated changes in protein phosphorylation determine ChREBP transactivity



Transcriptional regulation of hepatic lipogenesis by insulin and glucose via ChREBP, SREBP-1c, and LXR



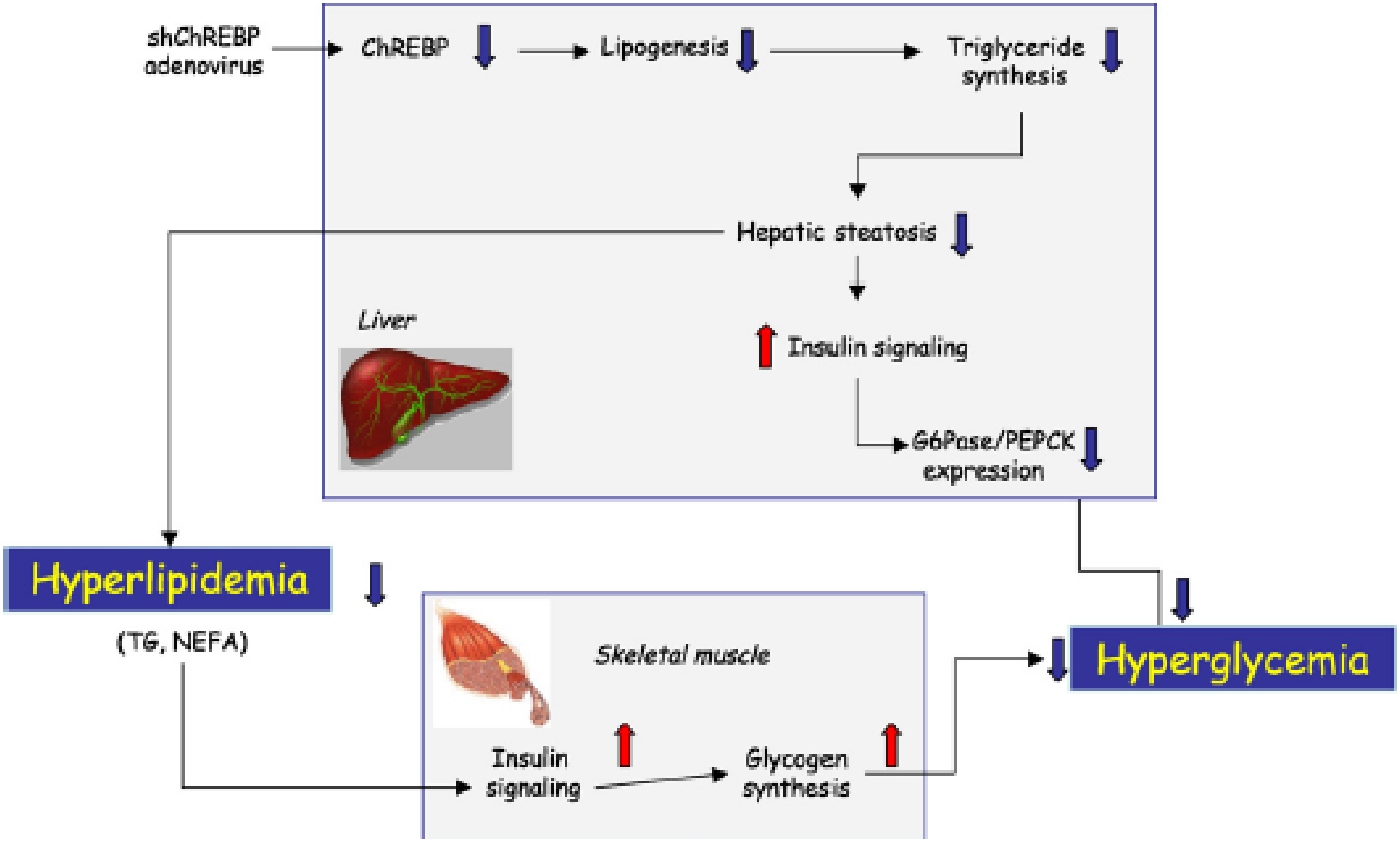
ChREBP knockdown in liver



HCHO: high-carbohydrate diet

Denechaud et al., FEBS Lett. (2008)

Summary of ChREBP knockdown in liver



Denechaud et al., FEBS Lett. (2008)

LIPID METABOLISM IN CANCER

A limited set of phenotypes exists in virtually all aggressive cancers:

- Metabolic reprogramming in tumors occurs as a consequence of mutations in cancer genes and alterations in cellular signaling.

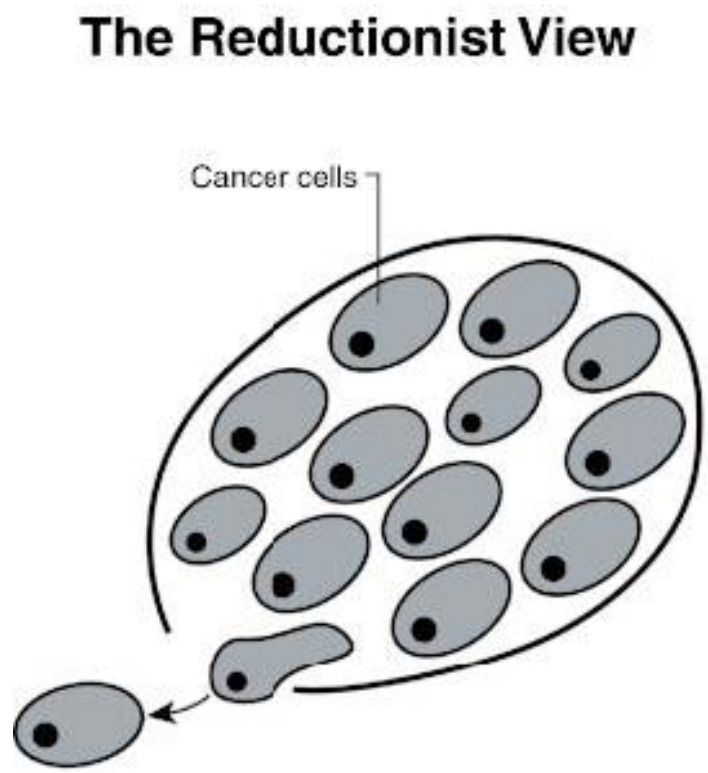
- Aerobic glycolysis (Warburg effect): Cancer cells consume high amounts of glucose and produce lactic acid; provides cancer cells growth advantages in the tumor microenvironment.

- Increased glutamine metabolism; glutamine-derived α-ketoglutarate contributes to the production of citrate.

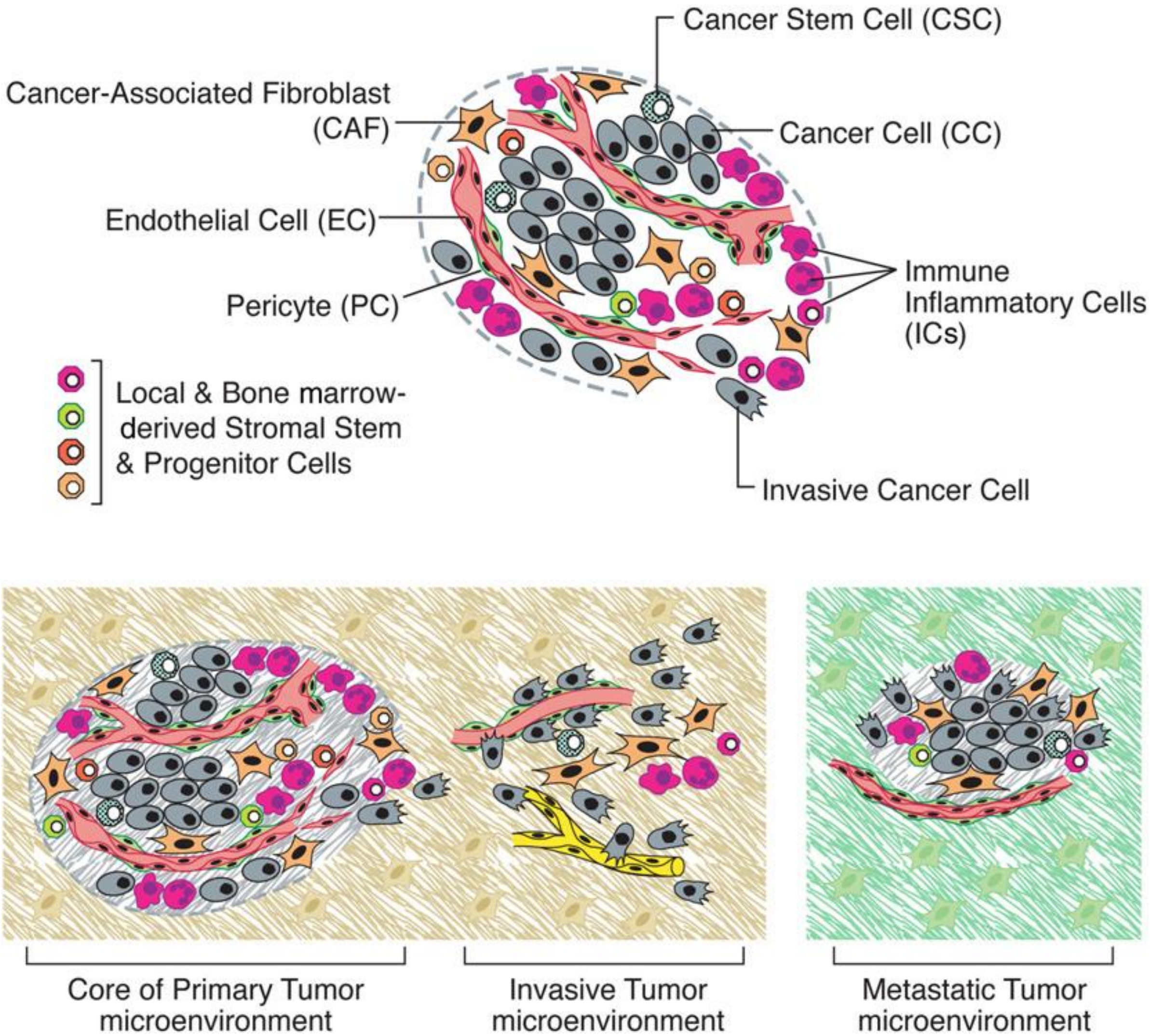
- High rate of energy-consuming processes driving increased protein synthesis (e.g., mTOR pathway) and more active DNA synthesis.

- **Increased *de novo* fatty acid synthesis, which is functionally related to the glycolytic pathway (glycolysis provides energy and precursors for FA synthesis).**

Tumors as complex tissues

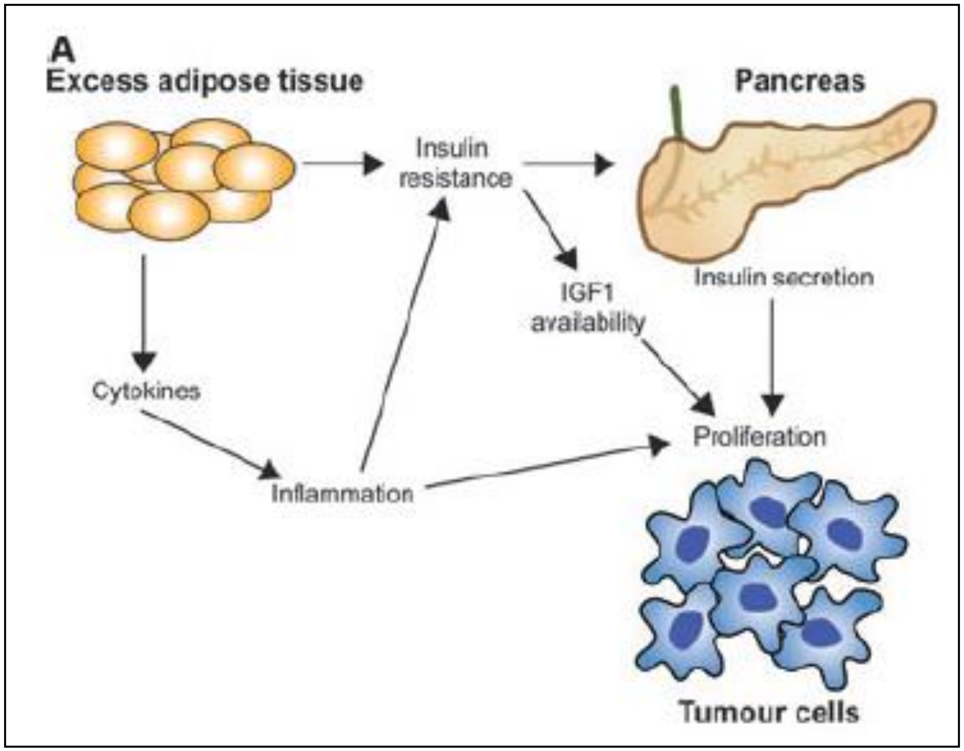


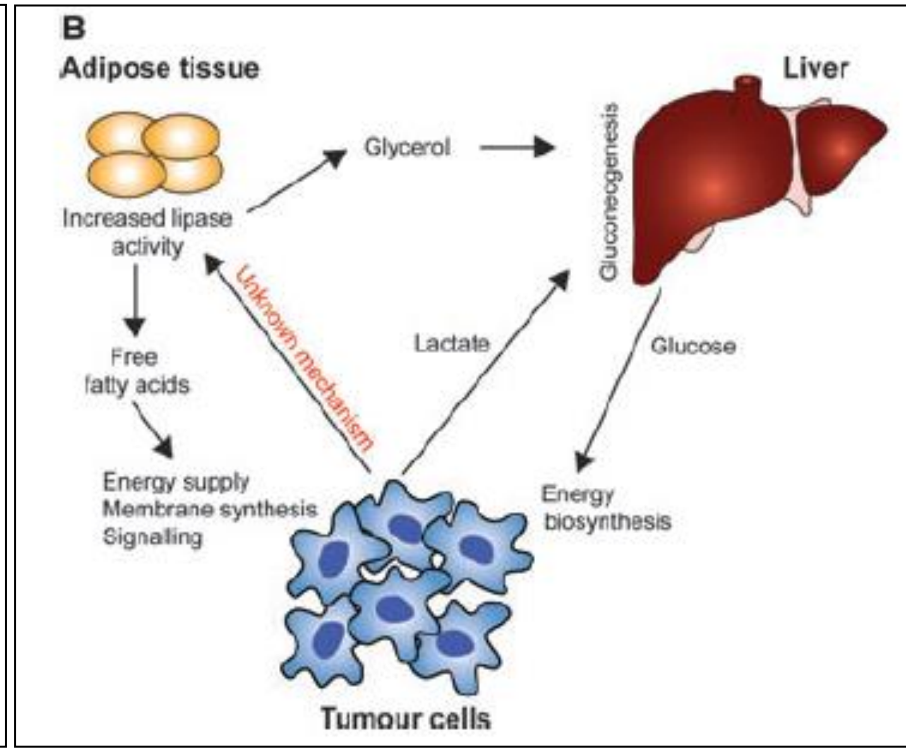
The tumor microenvironment



Hanahan and Weinberg, Cell (2011)

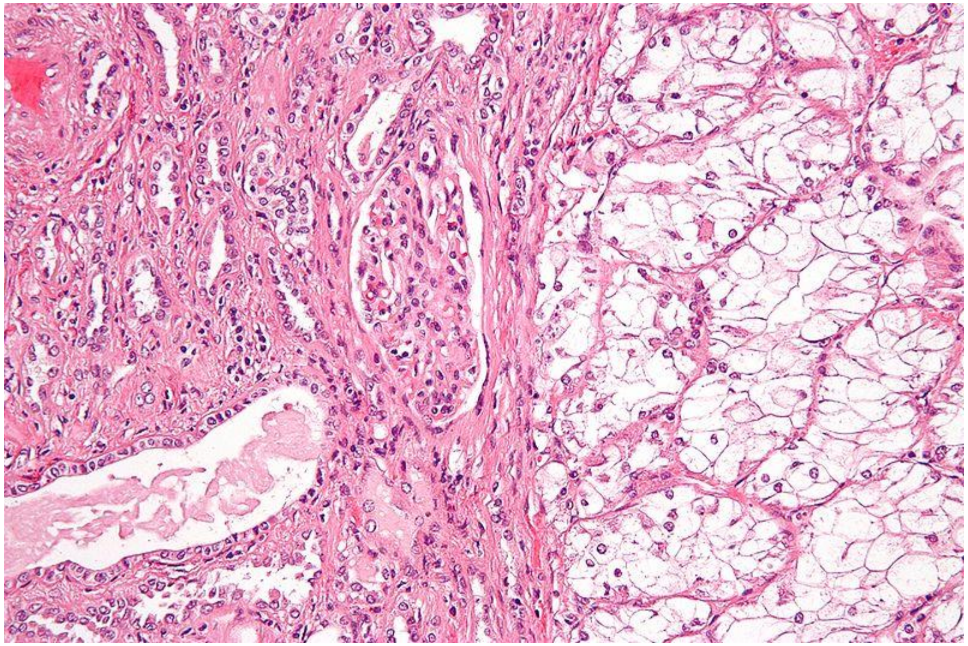
Whole-body lipid metabolism and cancer



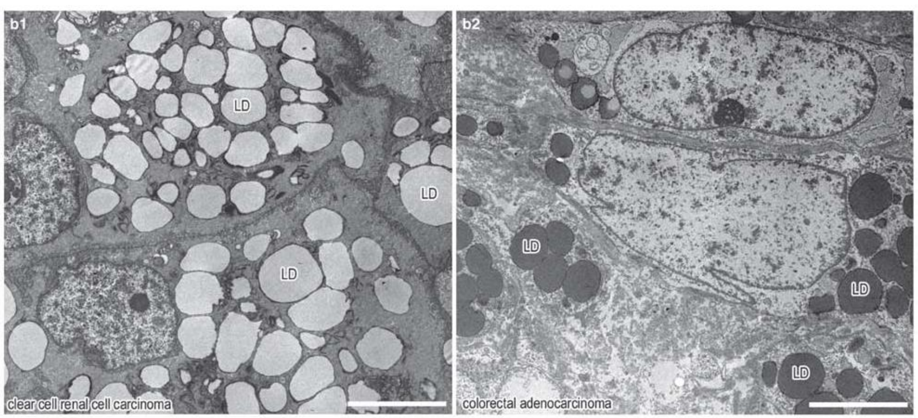


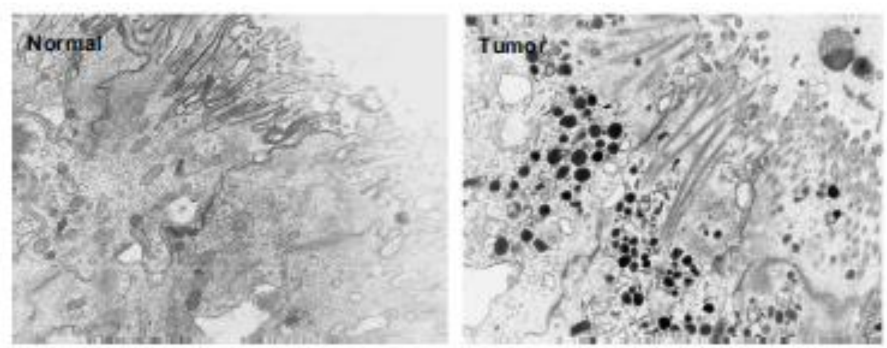
Santos and Schulze, FEBS J. (2012)

The lipogenic phenotype in cancer pathogenesis



Clear cell renal cell carcinoma (ccRCC)

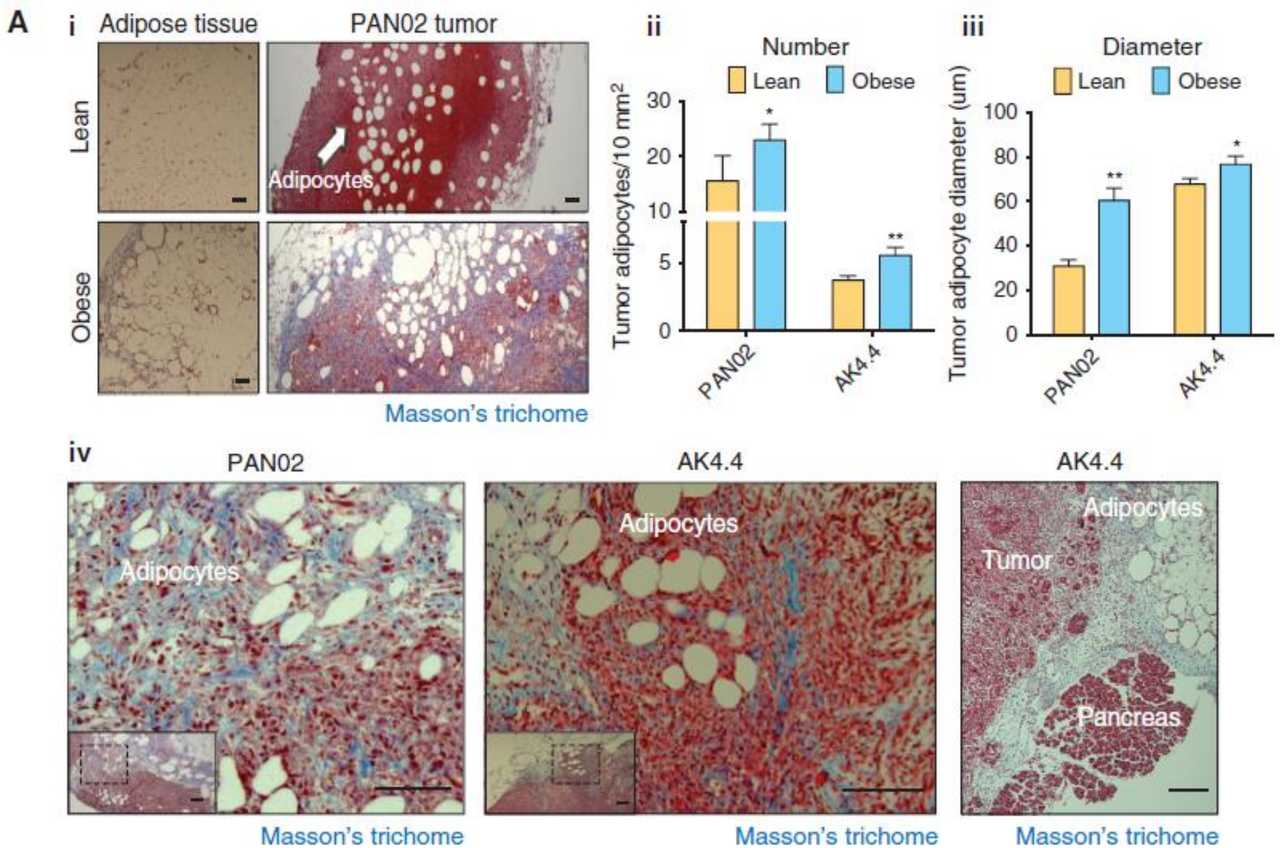




Colon cancer

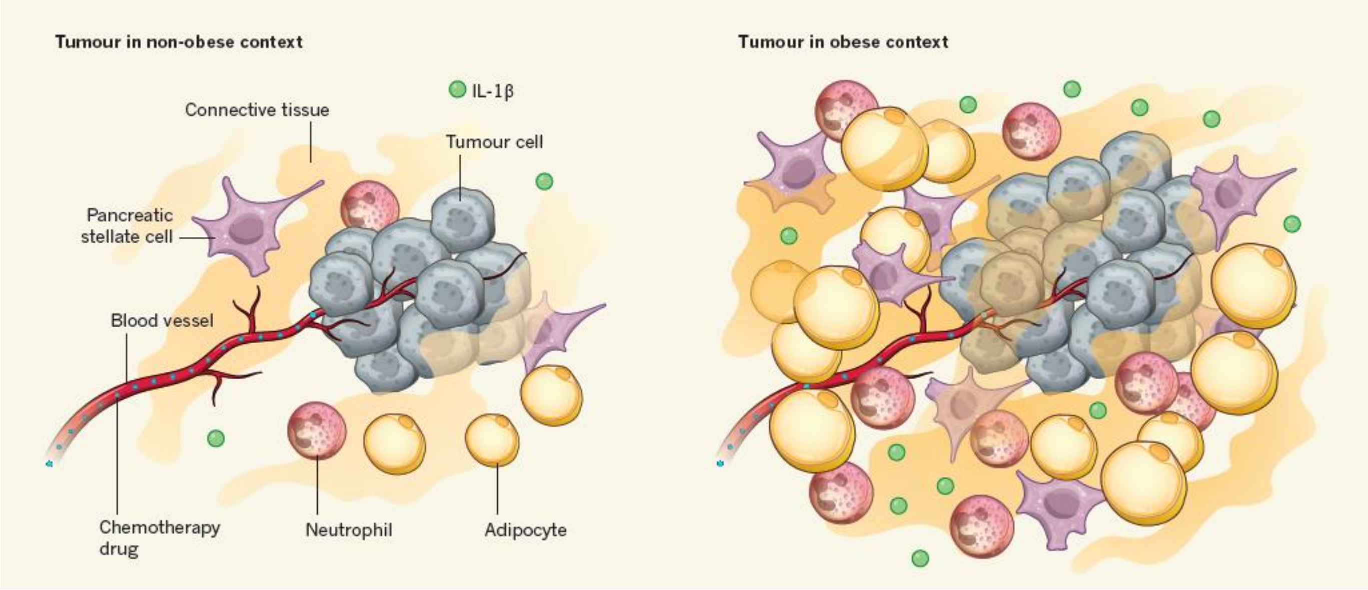
Fat cells remodel the microenvironment around pancreatic tumors

- PDAC: pancreatic ductal adenocarcinoma
- Obesity is a major risk factor for PDAC
- PDAC is fourth most-common cause of cancer-associated death



Incio et al., Cancer Discov. (2016)

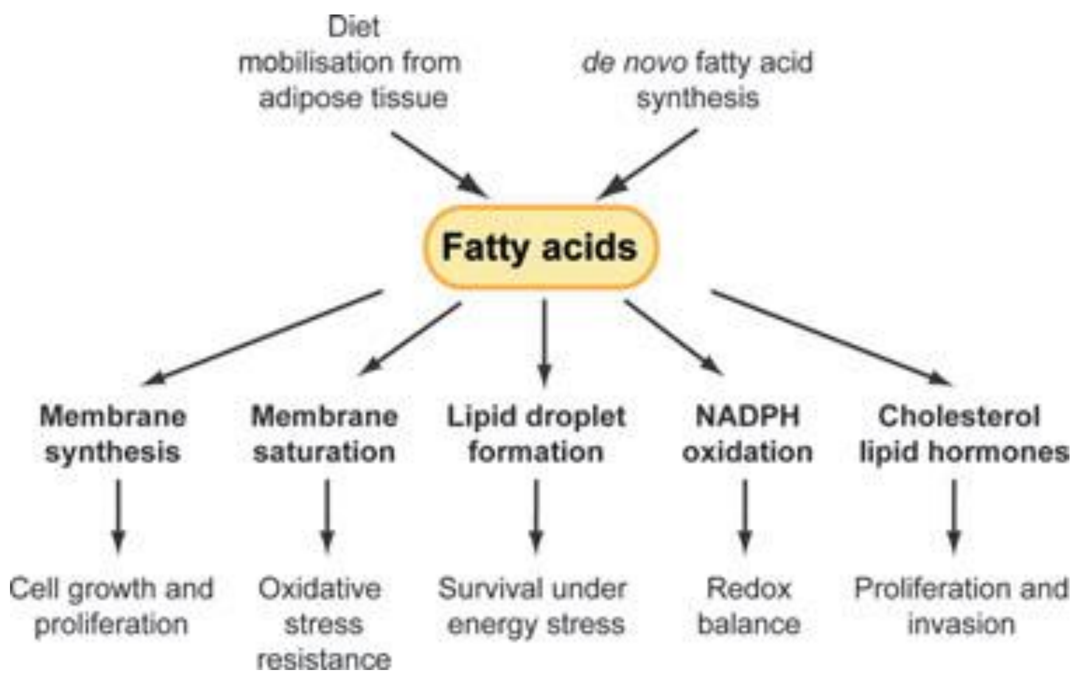
Fat cells remodel the microenvironment around pancreatic tumors



- Adipocytes, immune cells and pancreatic stellate cells signal through IL-1β and the AT1 angiotensin receptor to drive migration of neutrophils to the tumor microenvironment
- This increases the inflammatory and fibrotic response in the tumor microenvironment
- Denser cellular microenvironment puts extra mechanical tension on the tissue and may restrict blood-vessel perfusion
- Associated with poor response to chemotherapy and poor prognosis
- Depletion of neutrophils or blocking activity of IL-1β reduce cancer progression

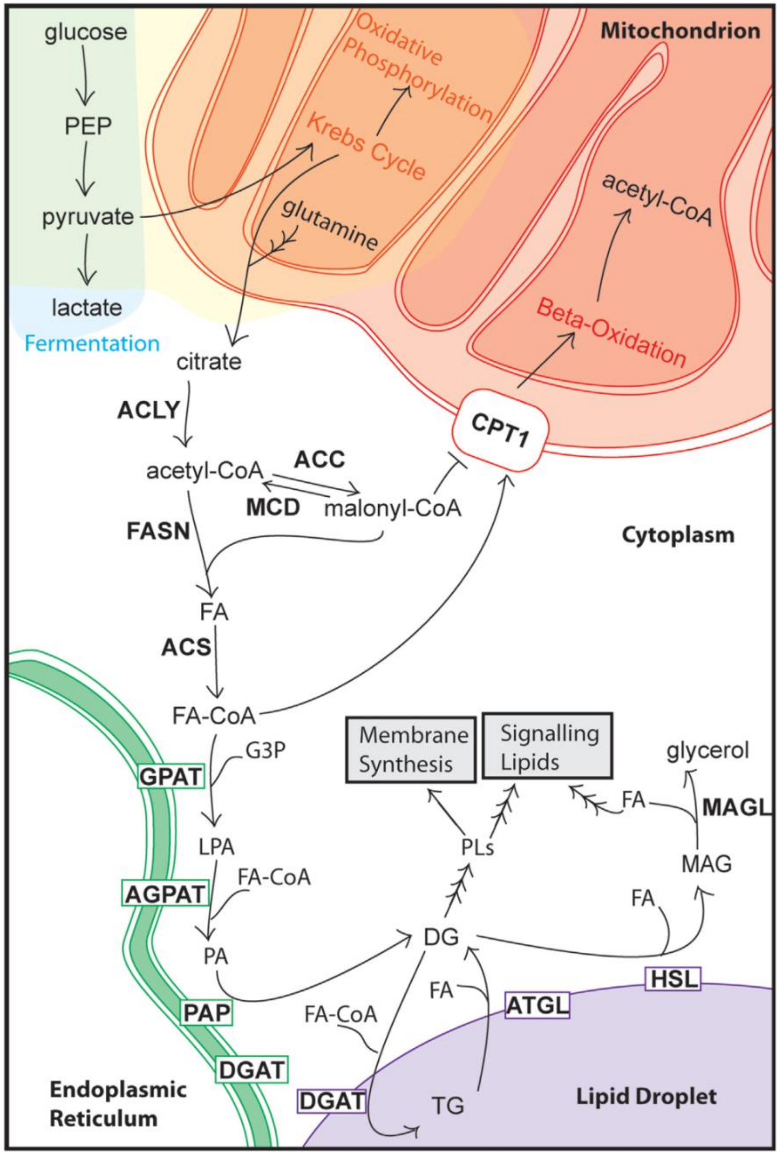
Arkan, Nature 2016

Lipids can promote different aspects of cancer development



Santos and Schulze, FEBS J. (2012)

Cellular fatty acid metabolism



FA, fatty acid
LPA, lysophosphatidic acid
PA, phosphatidic acid
MAG, monoacylglycerol
DG, diacylglycerol
TG, triacylglycerol

ACLY: ATP citrate lyase
ACC: acetyl-CoA carboxylase
FASN: fatty acid synthase
ACS: fatty acid-CoA ligase
MCD: malonyl-CoA decarboxylase
CIC, citrate carrier

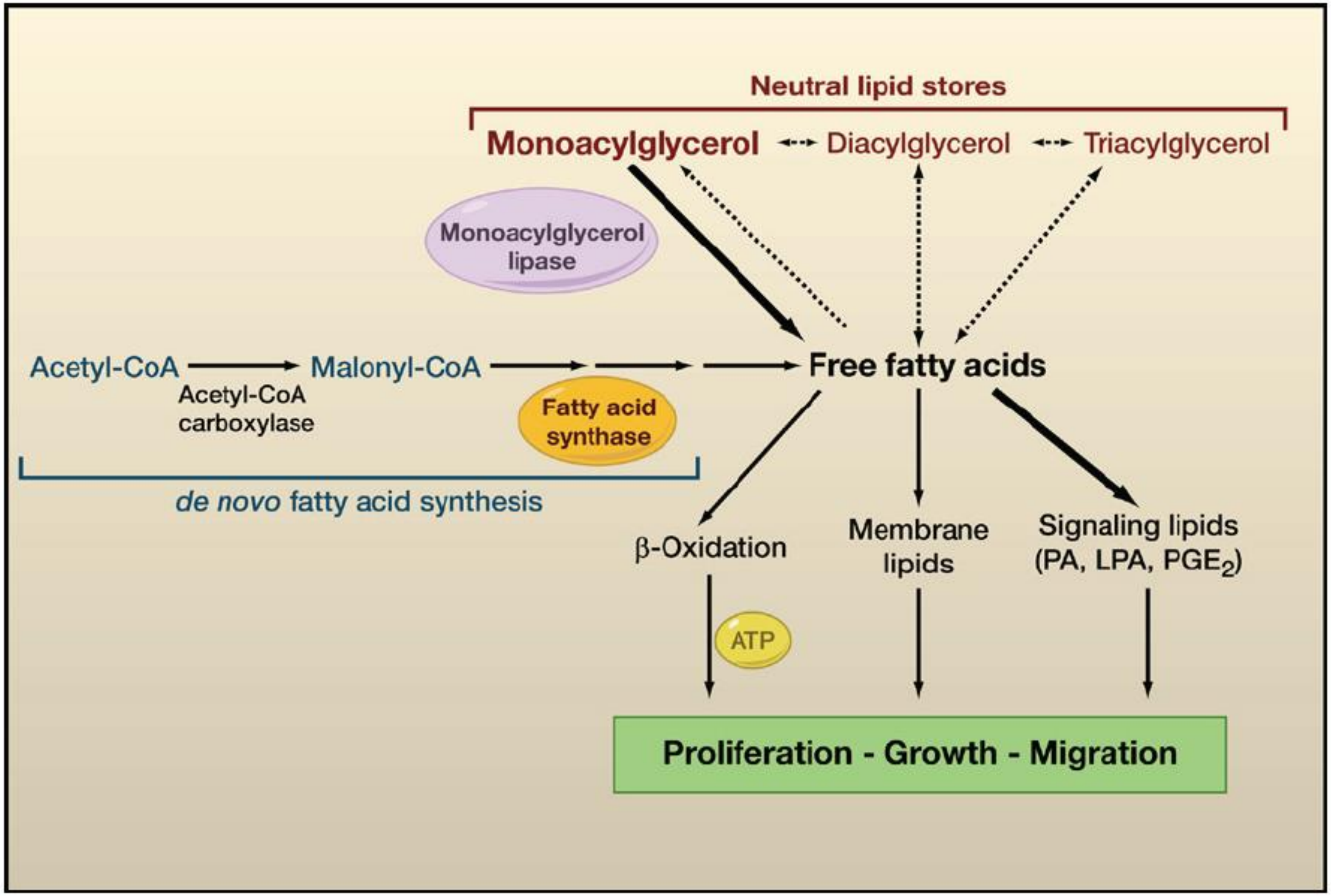
CPT1: carnitine palmitoyl transferase

GPAT: glycerol-3-phosphate acyltransferase
AGPAT: acylglycerolphosphate acyltransferase
PAP: phosphatidic acid phosphohydrolase
DGAT: diacylglycerol acyltransferase

ATGL: adipose triglyceride lipase
HSL: hormone sensitive lipase
MAGL: monoacylglycerol lipase

Currie et al., Cell Metab. (2013)

Free fatty acids and tumorigenesis



Yecies and Manning, Cell (2010)

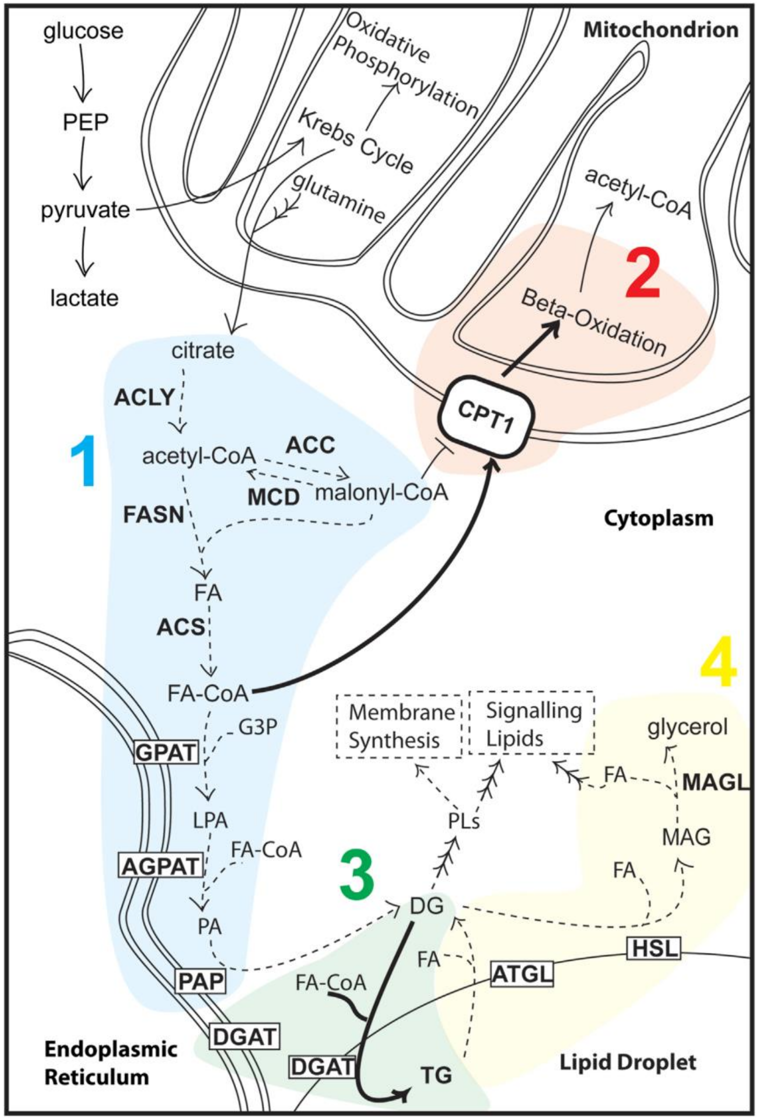
Model showing how limiting fatty acids in the cell might limit cancer cell proliferation

ACLY: ATP citrate lyase
ACC: acetyl-CoA carboxylase
FASN: fatty acid synthase
ACS: fatty acid-CoA ligase
MCD: malonyl-CoA decarboxylase
CIC, citrate carrier

CPT1: carnitine palmitoyl transferase

GPAT: glycerol-3-phosphate acyltransferase
AGPAT: acylglycerolphosphate acyltransferase
PAP: phosphatidic acid phosphohydrolase
DGAT: diacylglycerol acyltransferase

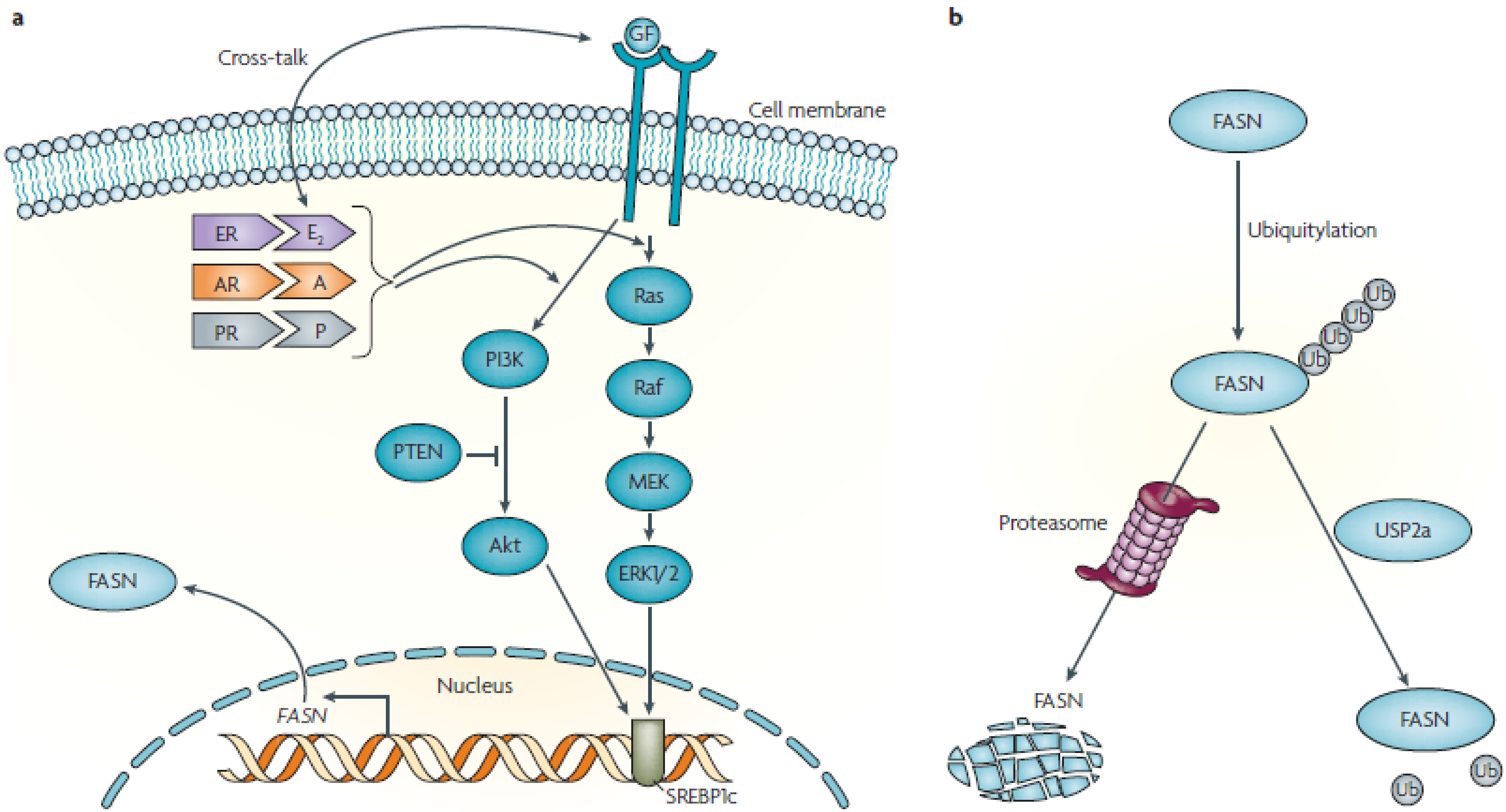
ATGL: adipose triglyceride lipase
HSL: hormone sensitive lipase
MAGL: monoacylglycerol lipase



Currie et al., Cell Metab. (2013)

ETH zürich

Two main pathways regulate the expression of tumor-associated FASN



ER, oestrogen receptor
E2, oestradiol
AR, androgen receptor
A, androgens
PR, progesterone receptor
P, progestins

USP2a, ubiquitin-specific protease 2a

Menendez and Lupu, Nat. Rev. Cancer (2007)

De novo fatty acid synthesis

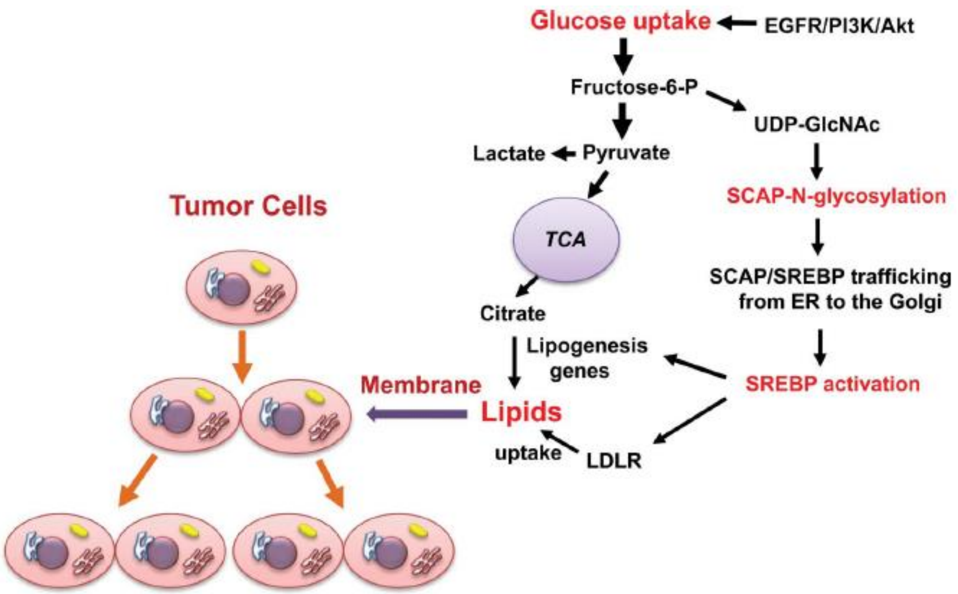
- Two sources: exogenously-derived (dietary) FAs and endogenously-synthesized FAs
- Biosynthesis is catalysed by the multifunctional, homodimeric fatty acid synthase (FASN)
- Predominant product of FASN is palmitate (C16:0)
- In well-nourished individuals the role of FASN is of minor importance owing to sufficient levels of dietary fat.
- Most normal cells and tissues, even those with high cellular turnover, seem to preferentially use circulating lipids for the synthesis of new structural lipids.
- In normal conditions FASN converts excess carbohydrate into FAs that are then esterified to storage TAGs.
- De novo FA synthesis is very active during embryogenesis and in fetal lungs (production of lung surfactant).

De novo fatty acid synthesis

- A wide variety of tumors and their precursor lesions undergo exacerbated de novo biogenesis of FAs irrespective of the levels of circulating lipids.
- Neoplastic lipogenesis is reflected by significantly increased activity and coordinate expression of several lipogenic enzymes in tumor cells [e.g., FASN, ATP citrate lyase (ACLY), acetyl-CoA carboxylase (ACACA)].
- Upregulation of FASN represents a nearly-universal phenotypic alteration in most human malignancies.
- FAs synthesized in cancer cells are esterified predominantly to phospholipids and incorporated into membrane lipids by proliferating cells.
- Many of the genes that encode the enzymes of the FA biosynthetic pathway, including ACLY, ACACA, FASN, reside on human chromosome 17q. This is a common site for gene rearrangement and is the location of many oncogene amplifications. However, only one study evaluating the correlation of the expression levels of lipogenic enzymes with gene copy number alterations has detected a significant increase in FASN copy number in prostate cancer.
- Increased FA synthesis in tumor cells seems to involve the modulation of multiple lipogenic enzymes at various levels (e.g., increased transcription, enhanced protein stabilization).

SCAP links glucose to lipid metabolism in cancer cells

A



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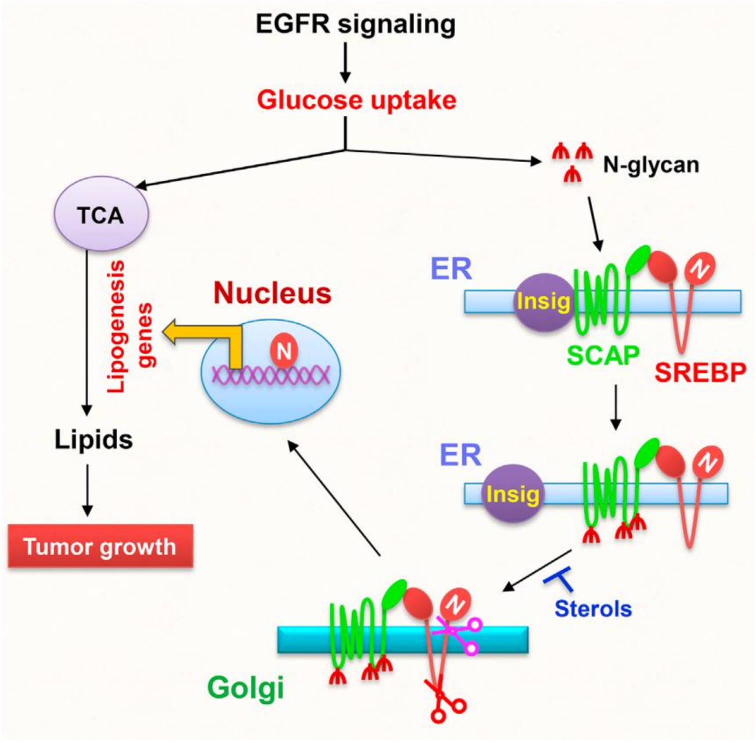
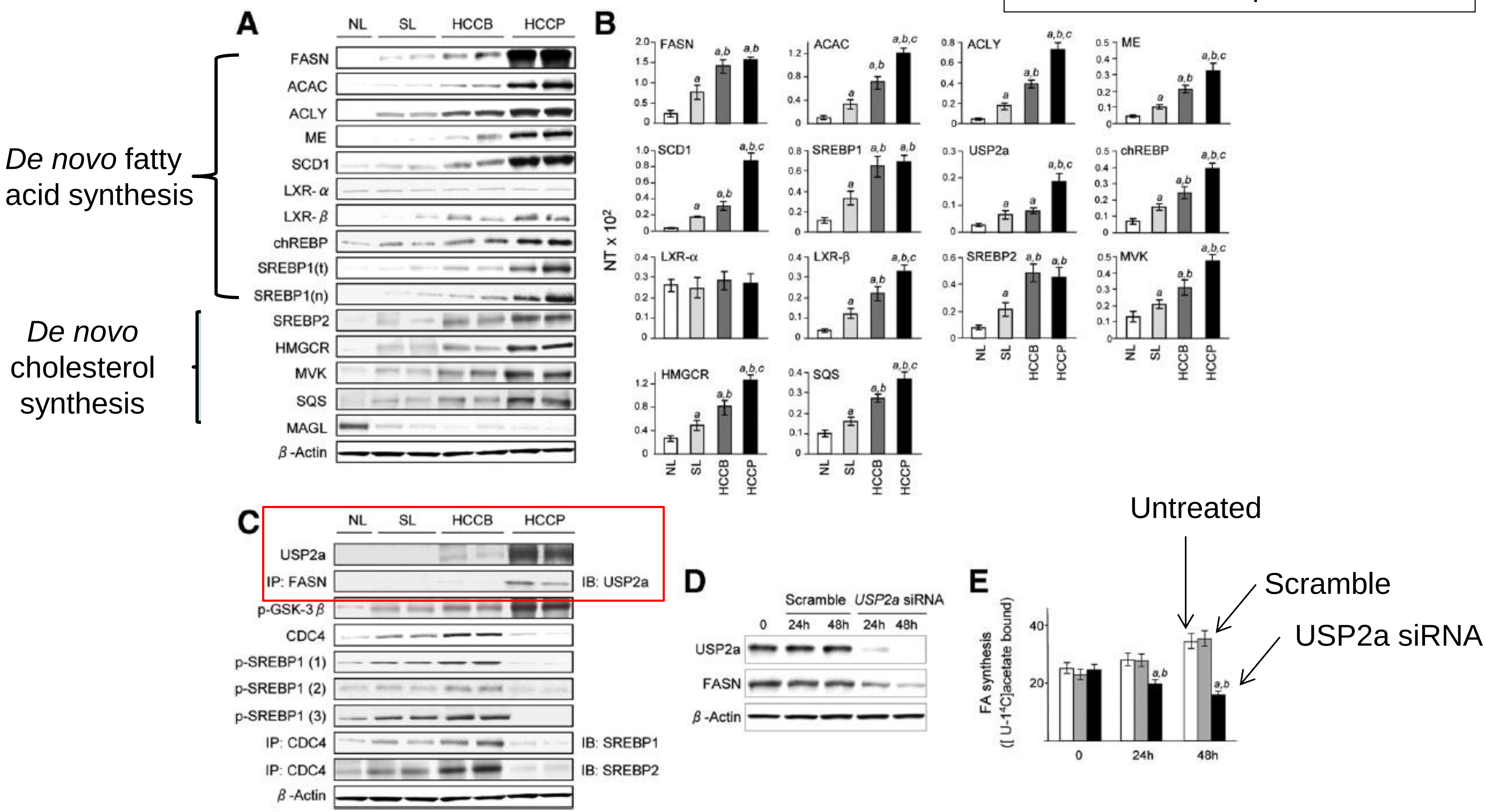


Guo, Mol. Cell. Oncol. (2016)

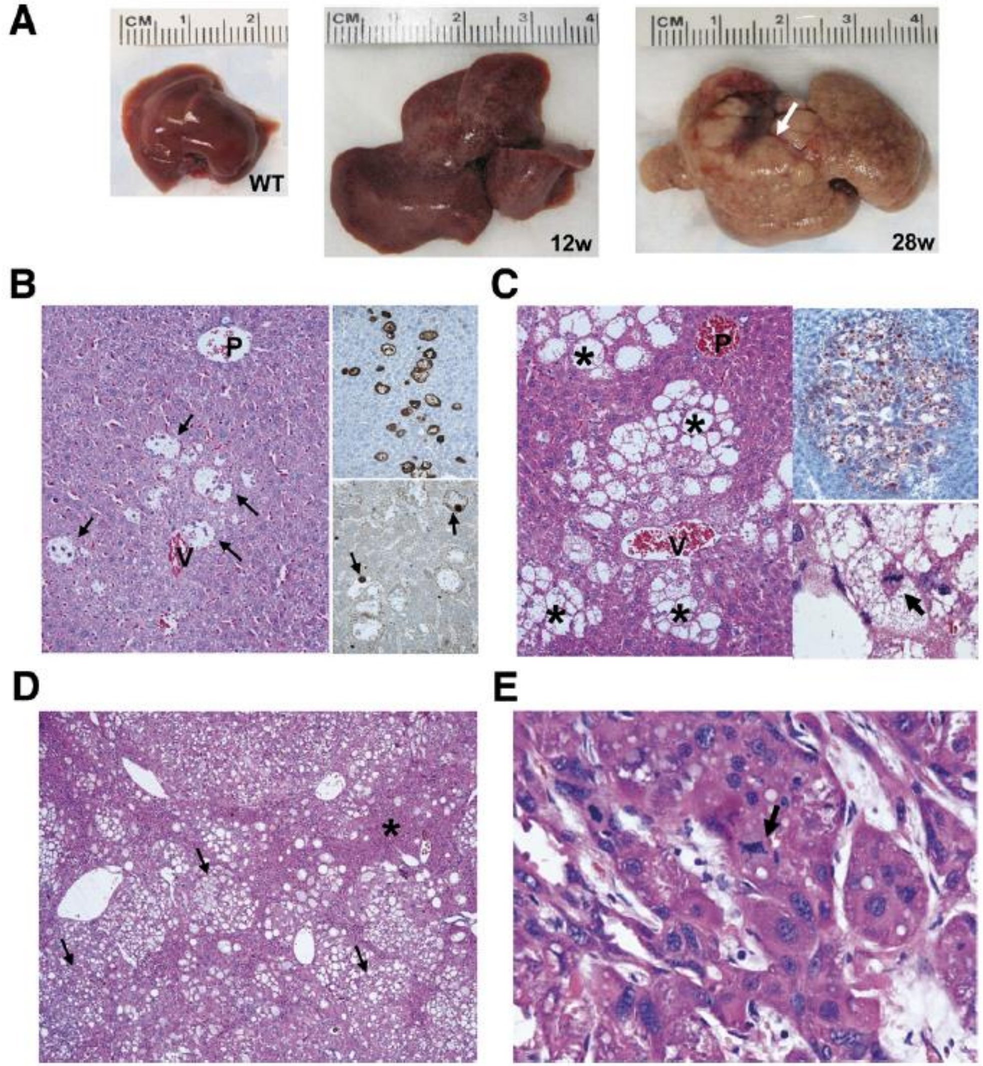
Increased lipogenesis promotes development of human hepatocellular carcinoma (HCC)

NL, normal liver
SL, surrounding liver
HCCB, HCC with better outcome
HCCP, HCC with poor outcome



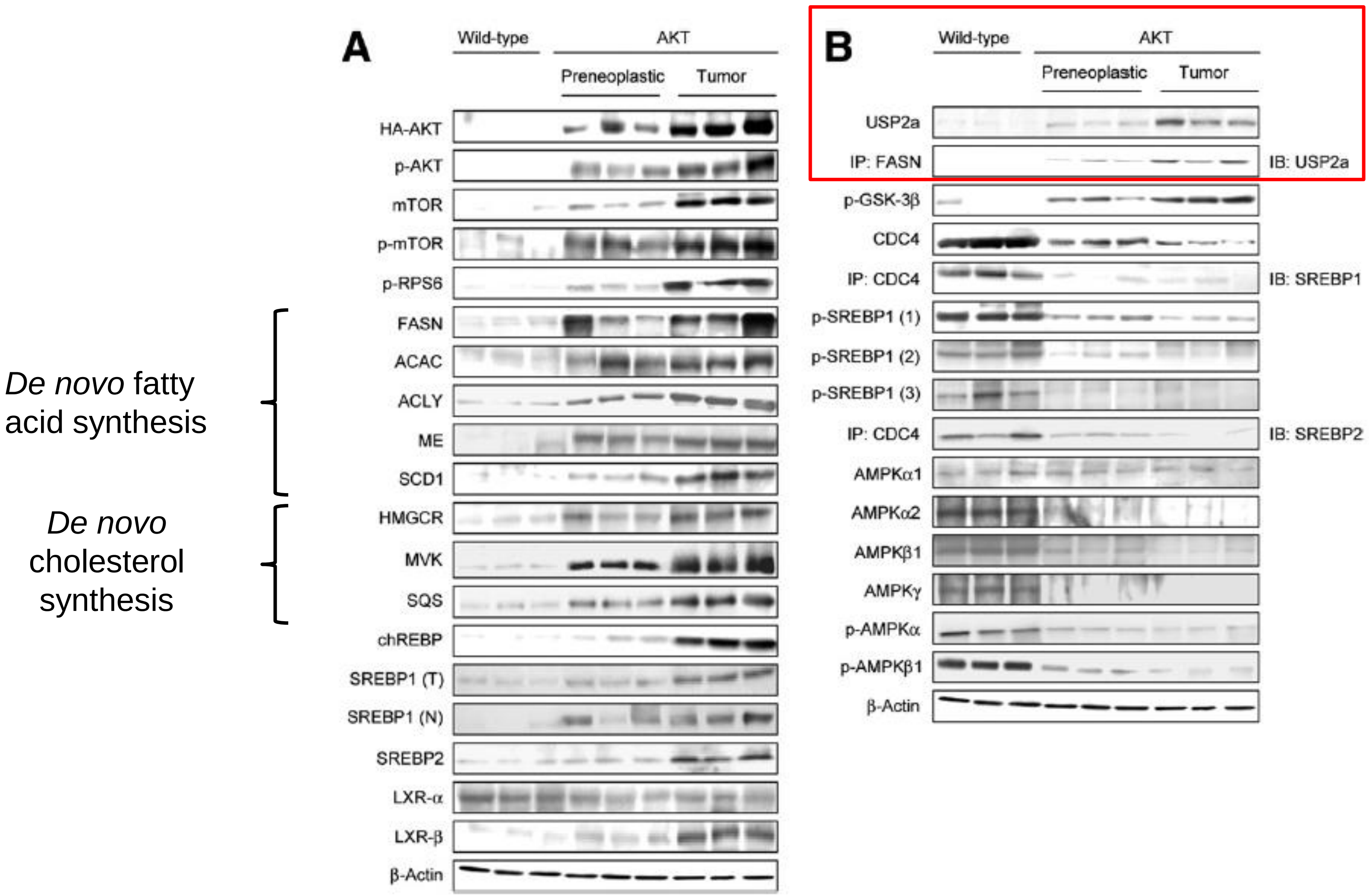
Calvisi et al., Gastroenterology (2011)

Stepwise development of hepatocarcinogenesis in AKT-overexpressing mice



Calvisi et al., Gastroenterology (2011)

Stepwise development of hepatocarcinogenesis in AKT-overexpressing mice



Calvisi et al., Gastroenterology (2011)

www.sciencemag.org SCIENCE VOL 333 8 JULY 2011

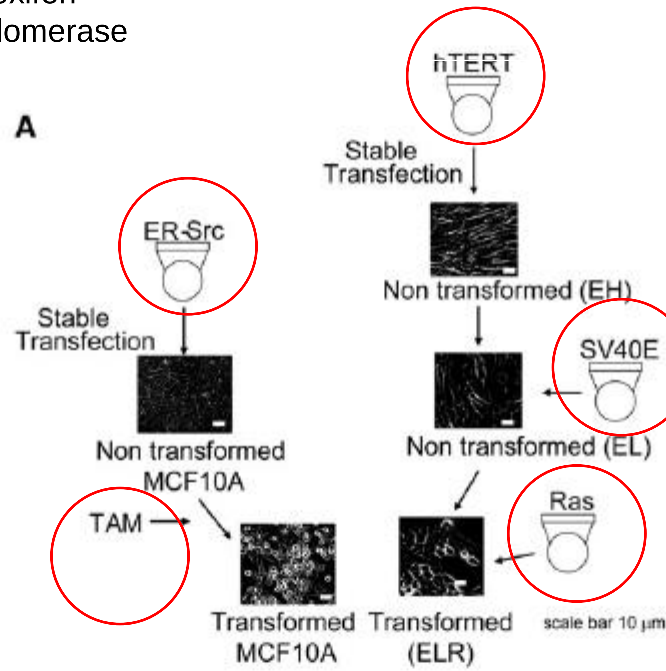
Adipose Triglyceride Lipase Contributes to Cancer-Associated Cachexia

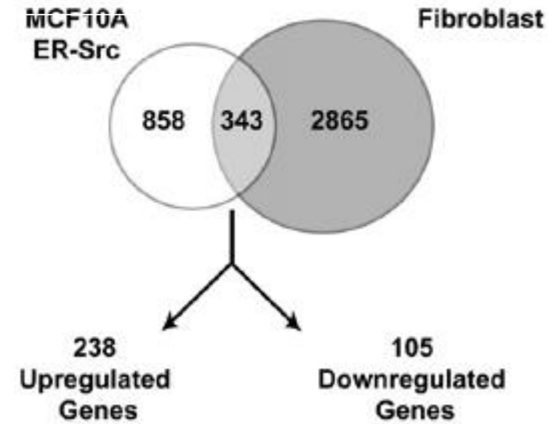
Suman K. Das,[1] Sandra Eder,[2] Silvia Schauer,[1] Clemens Diwoky,[3] Hannes Temmel,[1] Barbara Guertl,[1] Gregor Gorkiewicz,[1] Kuppusamy P. Tamilarasan,[1] Pooja Kumari,[1,4] Michael Trauner,[4] Robert Zimmermann,[2] Paul Vesely,[1] Guenter Haemmerle,[2] Rudolf Zechner,[2]* Gerald Hoefler[1]*

Cachexia is a multifactorial wasting syndrome most common in patients with cancer that is characterized by the uncontrolled loss of adipose and muscle mass. We show that the inhibition of lipolysis through genetic ablation of adipose triglyceride lipase (*Atgl*) or hormone-sensitive lipase (*Hsl*) ameliorates certain features of cancer-associated cachexia (CAC). In wild-type C57BL/6 mice, the injection of Lewis lung carcinoma or B16 melanoma cells causes tumor growth, loss of white adipose tissue (WAT), and a marked reduction of gastrocnemius muscle. In contrast, *Atgl*-deficient mice with tumors resisted increased WAT lipolysis, myocyte apoptosis, and proteasomal muscle degradation and maintained normal adipose and gastrocnemius muscle mass. *Hsl*-deficient mice with tumors were also protected although to a lesser degree. Thus, functional lipolysis is essential in the pathogenesis of CAC. Pharmacological inhibition of metabolic lipases may help prevent cachexia.

A transcriptional signature and common gene networks link cancer with lipid metabolism

MCF10A, normal mammary epithelial cells
ER-Src, Src kinase oncoprotein fused to ligand-binding domain of estrogen receptor
TAM, tamoxifen
hTERT, telomerase

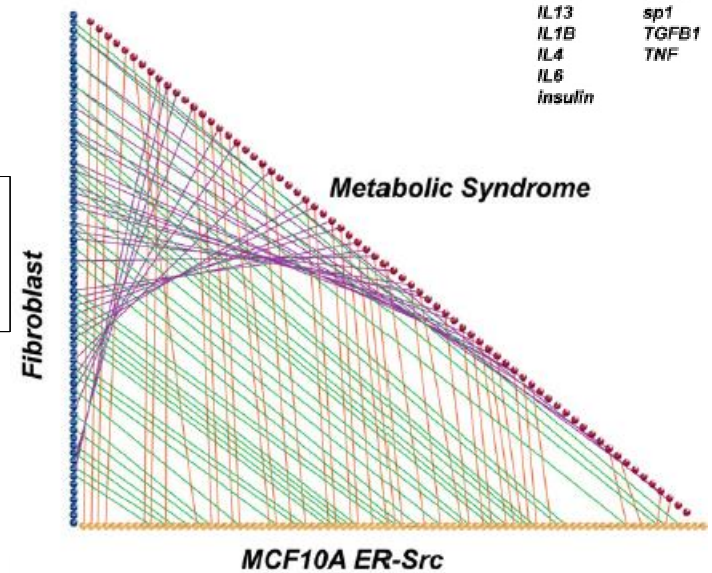


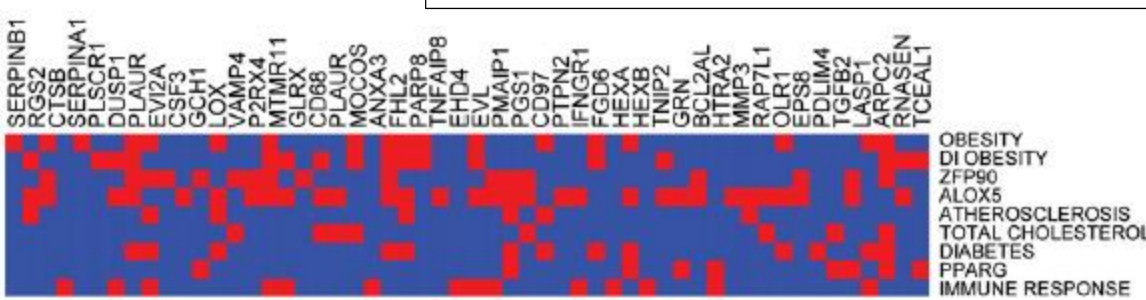


Common Nodes

AP1, CDKN1A, CEBPA, EGF, ERBB2, HIF1A, IFNB1, IFNG, IL13, IL1B, IL4, IL6, insulin, LDL, MAPK, myc, NFkB, NR3C1, p53, PDGF, PI3K, sp1, TGFB1, TNF

hTERT, telomerase
SV40E, small T antigen of Simian virus 40
Ras, Ras oncogene





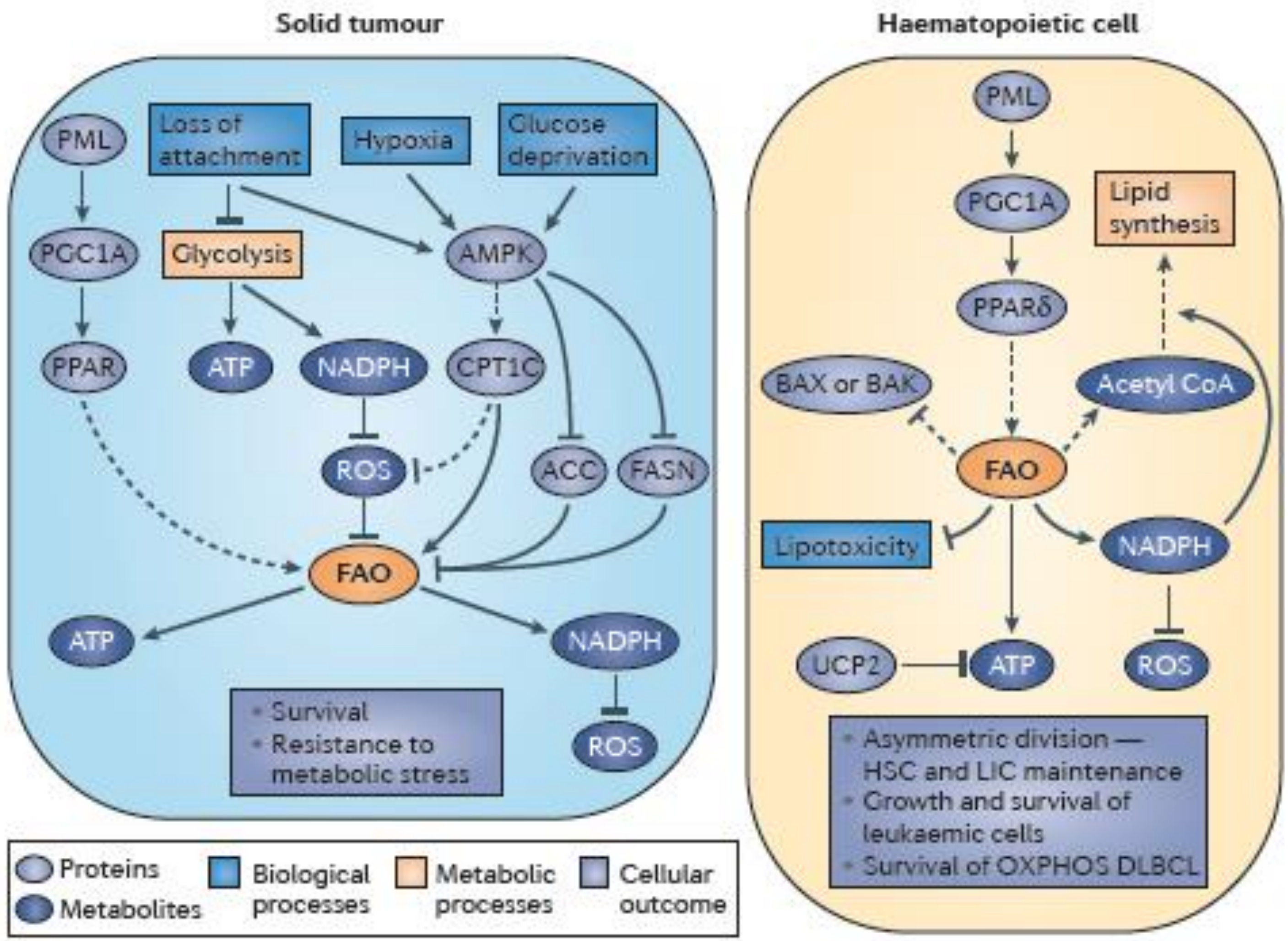
Hirsch et al., Cancer Cell (2010)

A transcriptional signature and common gene networks link cancer with lipid metabolism

- Transcriptional profiling of two isogenic models of transformation identified a gene signature linking cancer with inflammatory and metabolic diseases
- Many drugs used for treatment of diabetes and cardiovascular diseases inhibit transformation and tumor growth.
- Lipid metabolism genes are important for transformation and are upregulated in cancer tissues.
- As in atherosclerosis, oxidized LDL and its receptor OLR1 activate the inflammatory pathway through NF-κB, leading to transformation.
- OLR1 is important for maintaining the transformed state in diverse cancer cell lines and for tumor growth, suggesting a molecular connection between cancer and atherosclerosis.

Hirsch et al., Cancer Cell (2010)

Contribution of fatty acid oxidation to cancer cell function



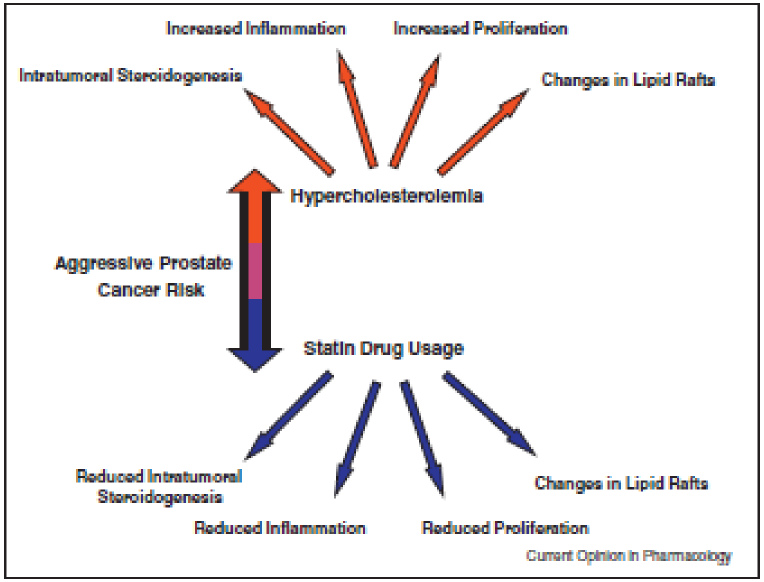
Carracedo et al., Nat. Rev. Cancer (2013)

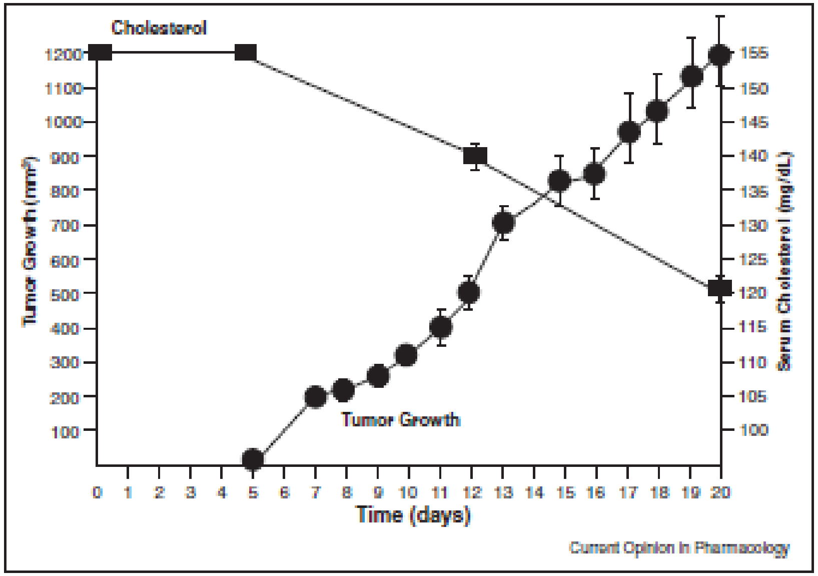
Cholesterol/isoprenoid biosynthesis and cancer

- Cancer cells have a deficient feedback control of HMGCR or increased HMGCR expression, suggesting that dysregulation of the mevalonate pathway might drive malignant transformation
- Statins might exert anticarcinogenic activity, however, the mechanisms do not necessarily involve cholesterol lowering
- Mevalonate is a precursor of several products regulating the cell cycle, including dolichol, geranylgeranyldiphosphate (GGPP) and farnesyldiphosphate (FPP).
- Dolichol has a stimulatory effect on DNA synthesis.
- GGPP and FPP cause isoprenylation of the intracellular G proteins Ras and Rho, which in turn regulate the signal transduction of several membrane receptors crucial for the transcription of genes involved in cell proliferation, differentiation, and apoptosis.

Cholesterol and prostate cancer

- Prostate cancer has a genetic component, though it is not well defined.
- Environmental factors play a large role in prostate cancer risk (e.g., Western diet)
- Epidemiological studies suggest that men with hypercholesterolemia are at increased risk for prostate cancer or late stage, aggressive disease.
- Cholesterol-sensitive mechanisms in prostate cancer progression: cell proliferation, inflammation, steroidogenesis.

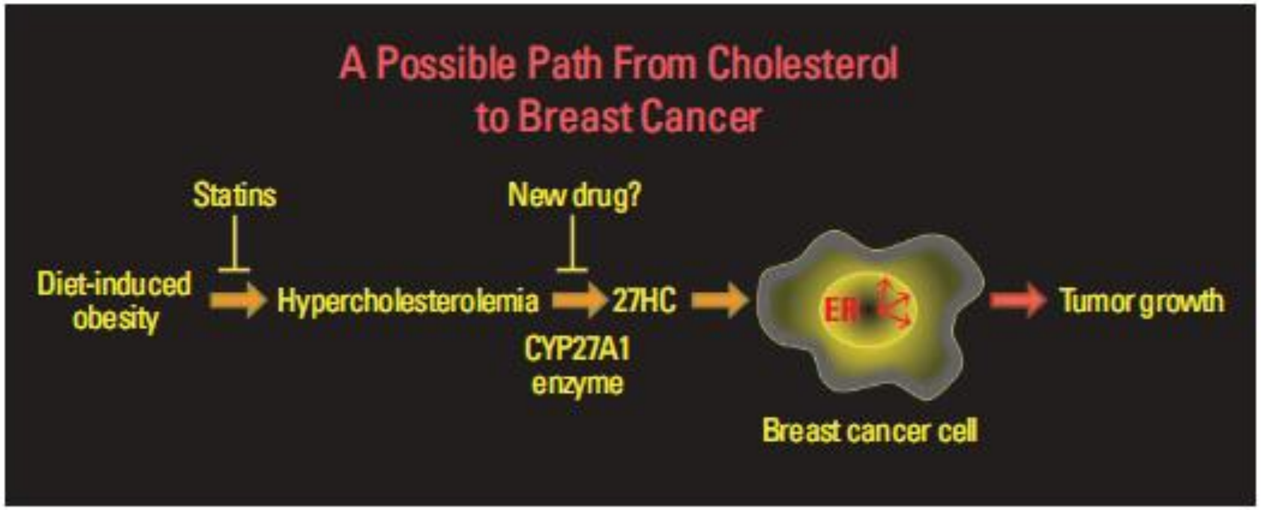




Pelton et al., Curr. Opin. Pharmacol. (2012)

Cholesterol and breast cancer development

- Hypercholesterolemia and metabolic syndrome are risk factors for breast cancer.
- The cholesterol metabolite **27-hydroxycholesterol (27-HC)** mimics estrogen in certain tissues. Estrogen-driven breast tumors may rely on 27-HC to grow when estrogen isn't available.
- Aggressive breast tumors have higher levels of CYP27A1, which converts cholesterol into 27-HC. Breast cancer patients with low tumor levels of CYP7B1, an enzyme that breaks down 27-HC, didn't live as long as women with the highest levels.
- 27-HC may play a role in other hormone-driven cancers (e.g. Endometrial cancer).



ER = estrogen receptor

Kaiser, Science (2013)