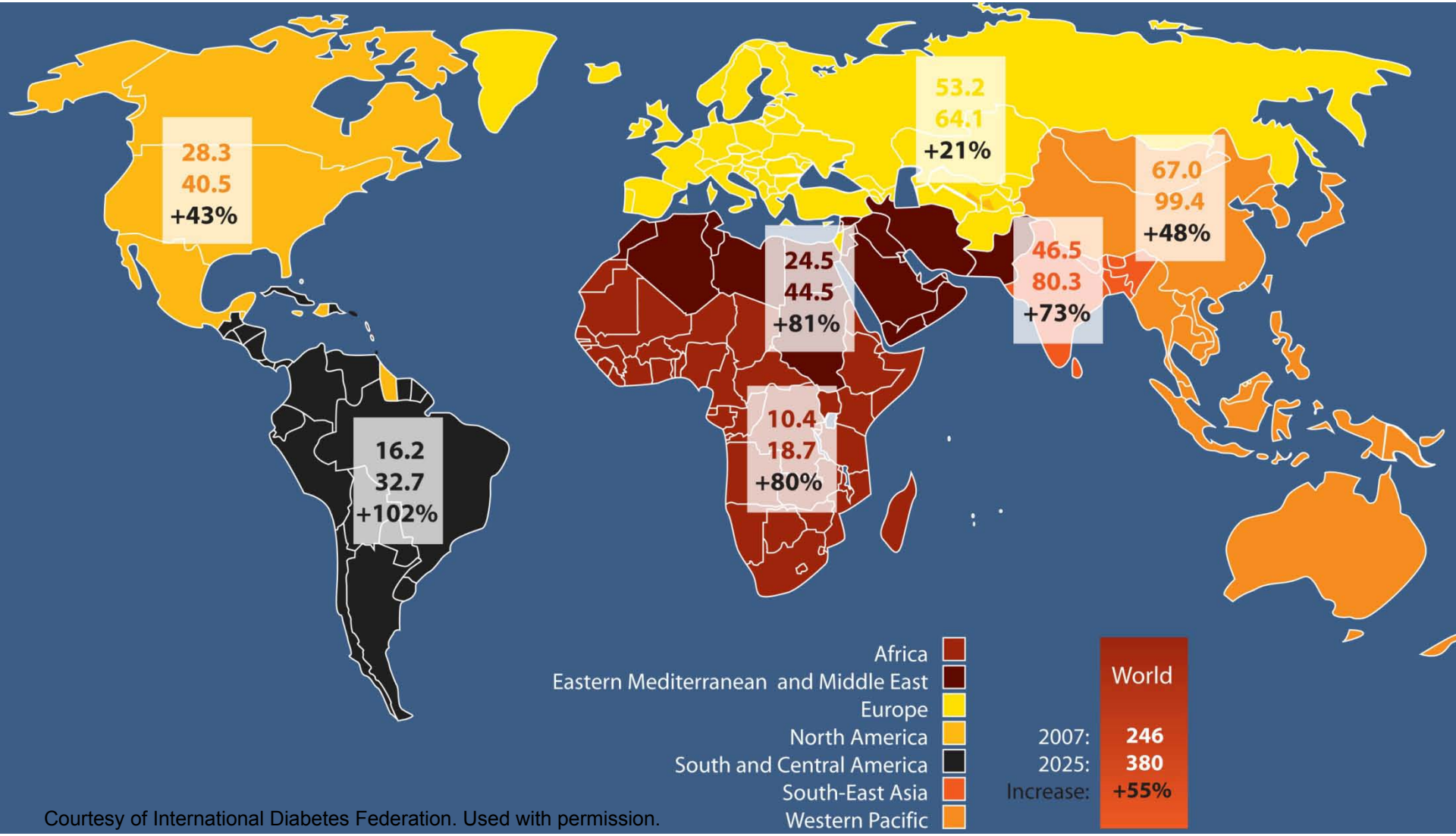
Inflammation, Obesity, and Diabetes

20.380 S'10

How big of a problem is Diabetes worldwide?



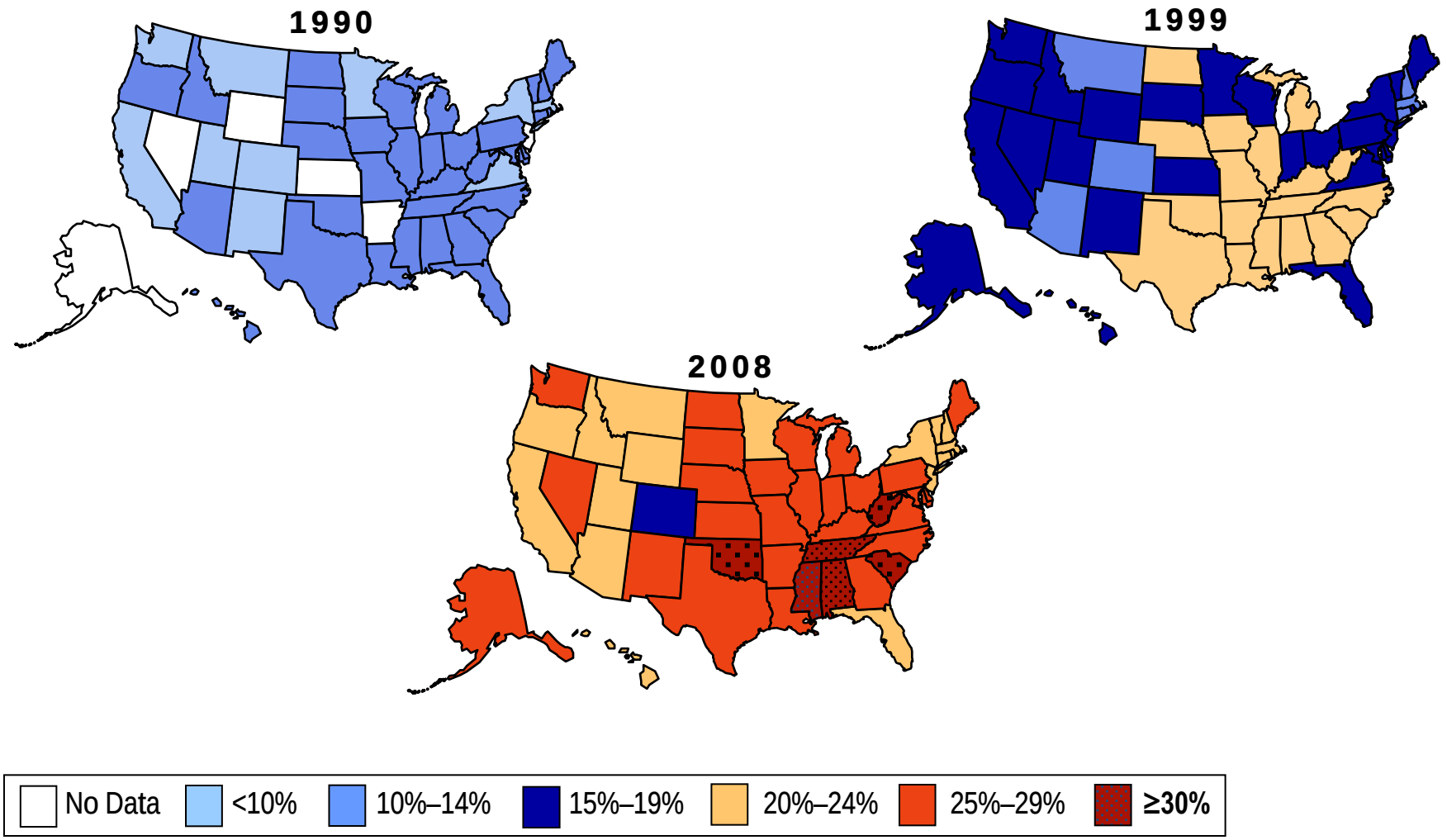
Courtesy of International Diabetes Federation. Used with permission.

Projected totals, in millions

Obesity Trends* Among U.S. Adults

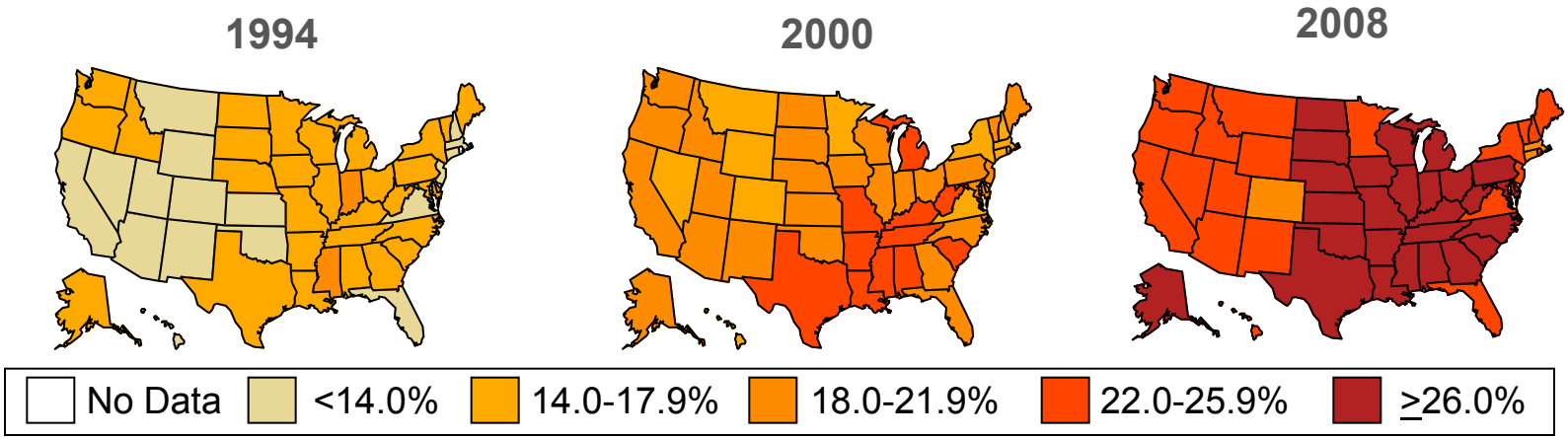
BRFSS, 1990, 1999, 2008

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

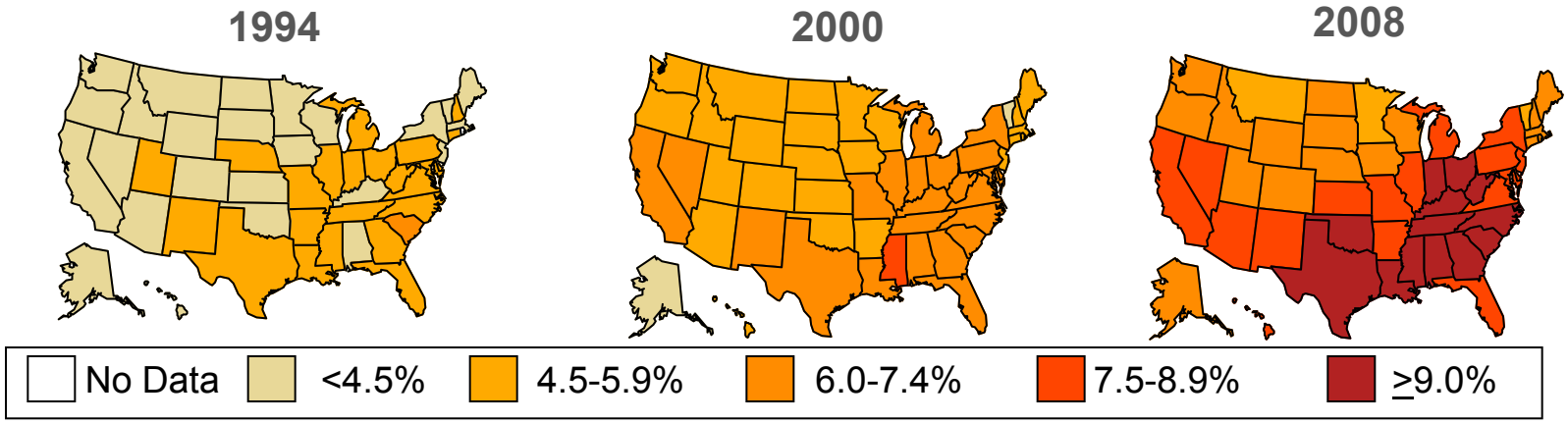


Age-adjusted Percentage of U.S. Adults Who Were Obese or Who Had Diagnosed Diabetes

Obesity (BMI ≥30 kg/m^2)



Diabetes



CDC's Division of Diabetes Translation. National Diabetes Surveillance System available at http://www.cdc.gov/diabetes/statistics

Normal Physiology and Insulin Effects

Insulin Action

Glucose

Pancreas

Insulin

Liver

Glycogen storage

Gluconeogenesis

Muscle

Glucose Uptake

Adipocytes

Glucose Uptake

Fruits and vegetables photo courtesy of val'sphotos on Flickr. Pancreas and liver images from US HHS. Muscle and adipocyte images by MIT OpenCourseWare.

Insulin Resistance – Positive Feedback

Insulin Resistance

Glucose

Pancreas

Insulin

Liver

Gluconeogenesis

Increased Glucose

Muscle

Glucose Uptake

Increased Glucose

Adipocytes

Glucose Uptake

Increased Glucose

Burger and fries photo courtesy of stu_spivack on Flickr.
Pancreas and liver images from US HHS. Muscle and adipocyte images by MIT OpenCourseWare.

Time Course of Diabetes Development

Focus for therapuetics

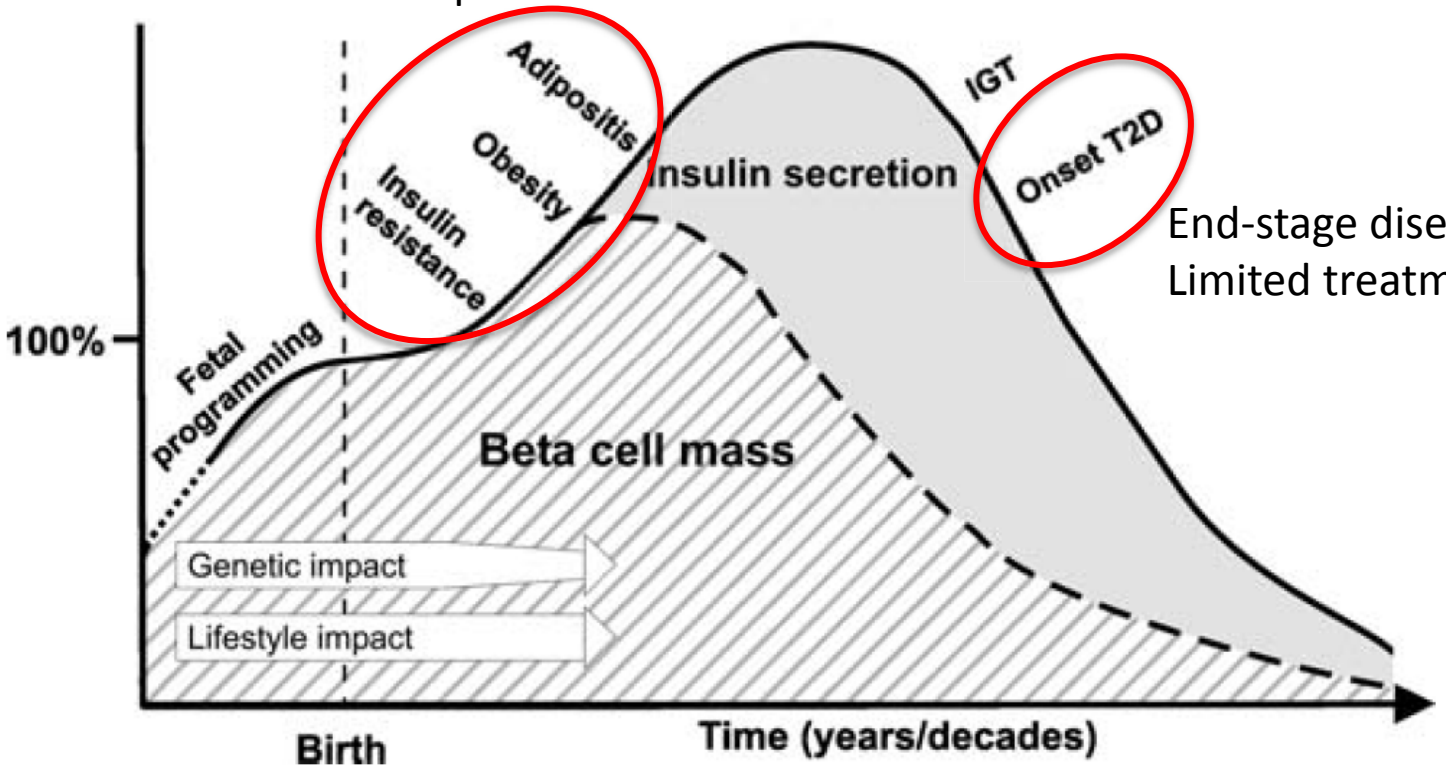


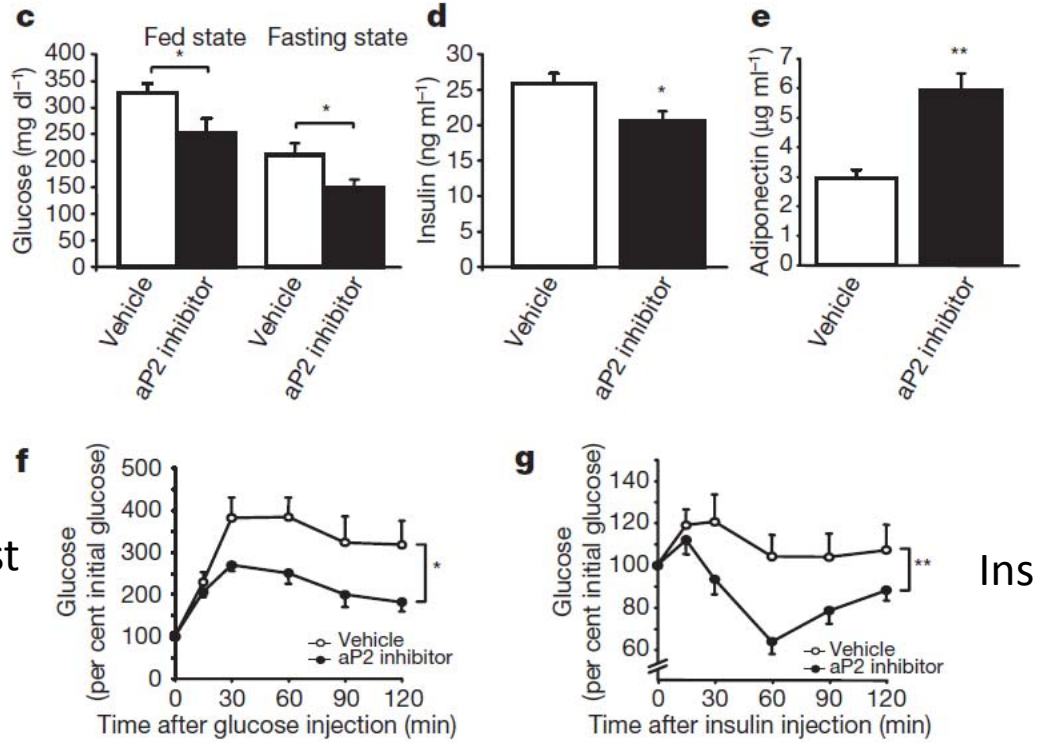
FIGURE 1. Natural course of type 2 diabetes, a generalized and simplified scheme. Programming of metabolic regulation and gene expression occurs *in utero*. Insulin resistance with or without obesity develops in childhood, adolescence, or early adulthood and is compensated by increased beta cell mass and insulin secretion. Probably in response to obesity/fat cell stress macrophages invade fat tissue and give rise to local inflammation ("adipositis"). The failure of islets to compensate for increased insulin demand is primarily caused by beta cell death. This leads to IGT and eventually to overt T2DM. Evidence of systemic low grade inflammation and of oxidative stress/mitochondrial dysfunction is noted from early on.

Kempf et al. Ann. N.Y. Acad. Sci. 1084: 30–48 (2006). © 2006 New York Academy of Sciences.
doi: 10.1196/annals.1372.012

Phenotyping Insulin Resistance

	WT	*ob/ob*
Glucose (mg/dl)	92.4 ± 11.6[A]	313.8 ± 76.6
Insulin (ng/ml)	1.83 ± 0.51[B]	7.85 ± 1.02
Triglycerides (mg/dl)	147.2 ± 27.34[B]	300.37 ± 114.2
FFA (mmol/l)	2.05 ± 0.93	3.13 ± 0.13

Kim et al., J. Clinical Investigation 2007, 117, 2621-2637

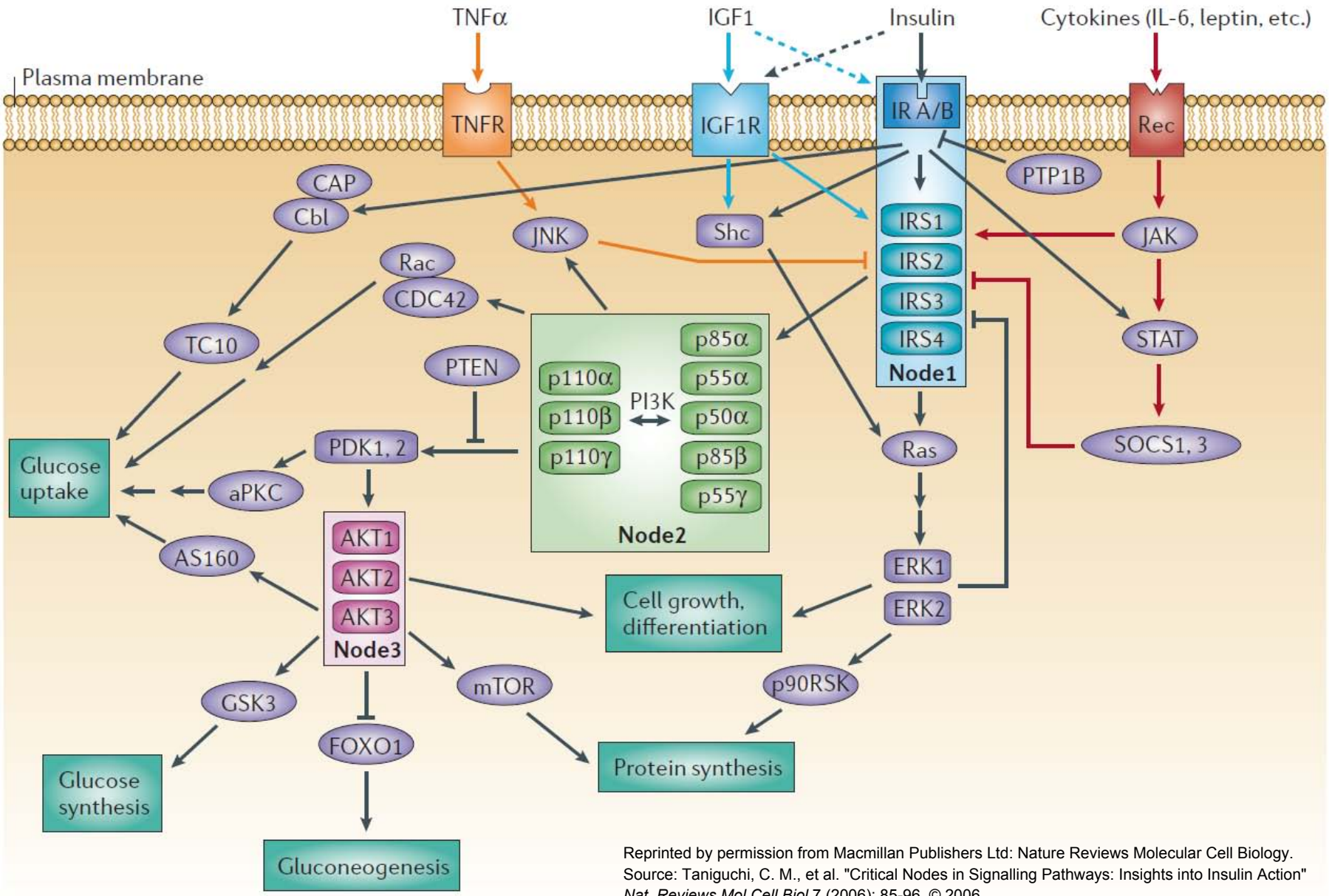


Glucose Tolerance Test

Insulin Tolerance Test

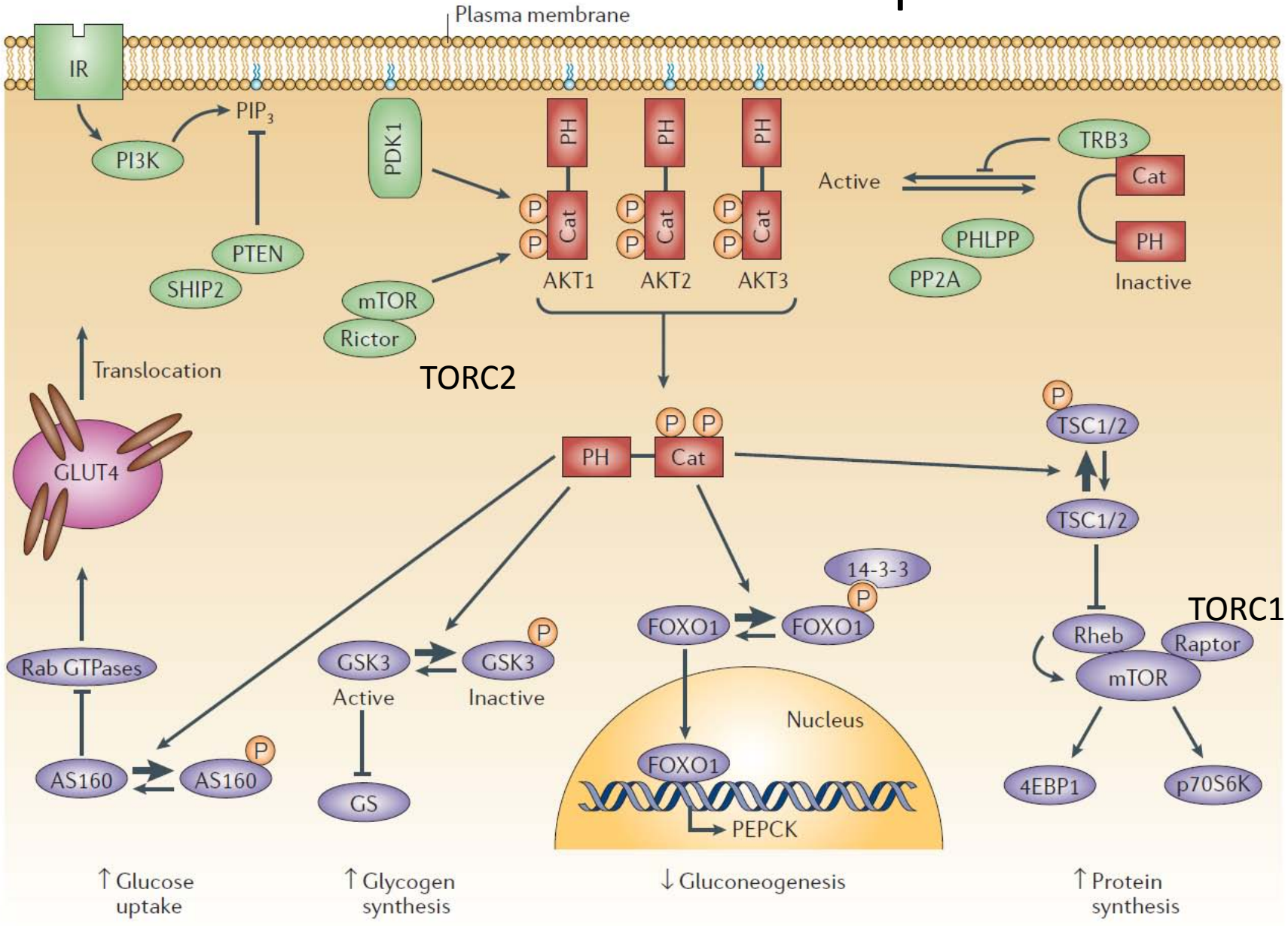
Furuhashi et al., Nature 2007, 447, 959-965

Insulin Signaling Network Overview



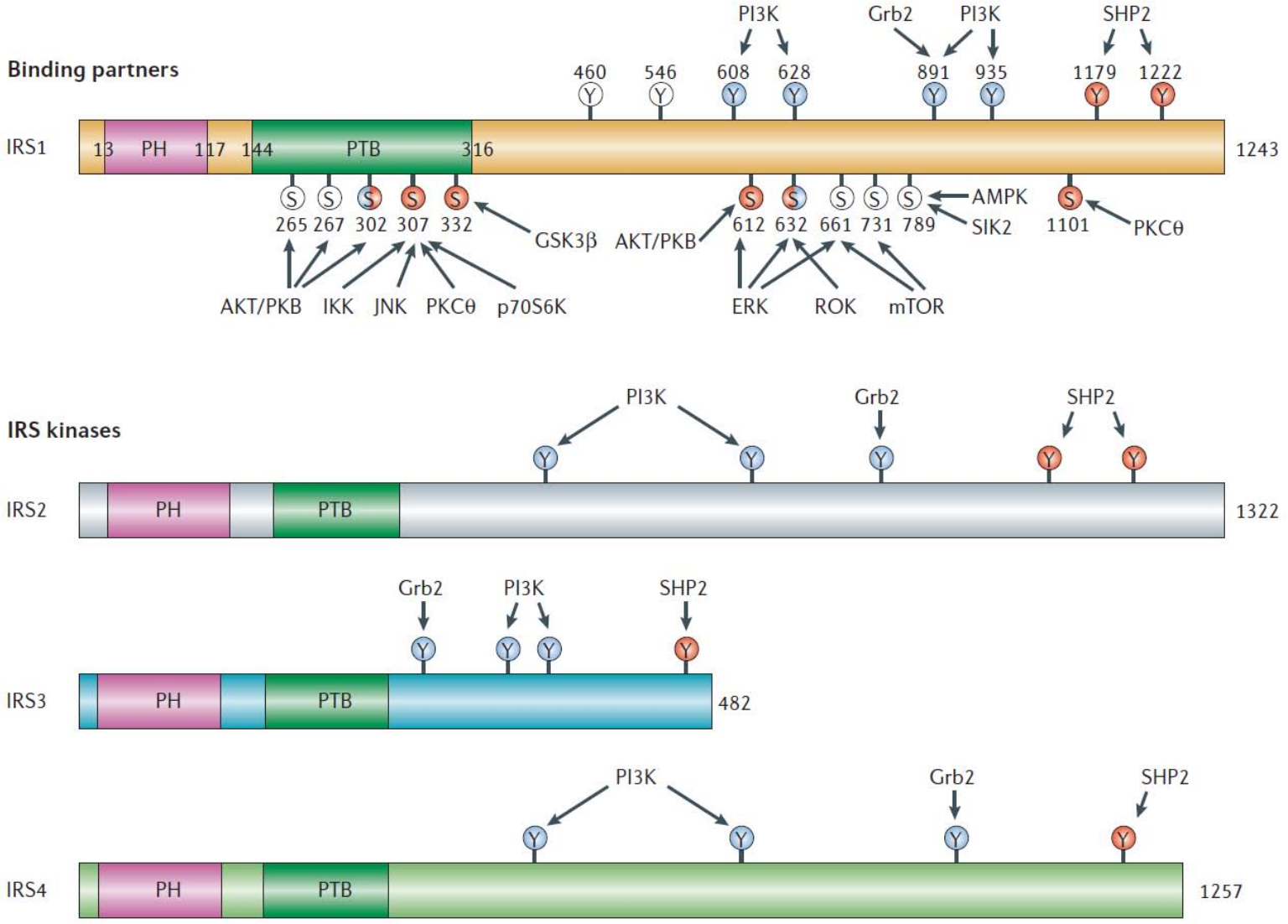
Taniguchi et al, Nat. Reviews Mol. Cell Biol, 2006

IR – PI3K – Akt – Insulin Response



Taniguchi et al, Nat. Reviews Mol. Cell Biol, 2006

Complex signaling on Insulin receptor substrates



Taniguchi et al, Nat. Reviews Mol. Cell Biol, 2006

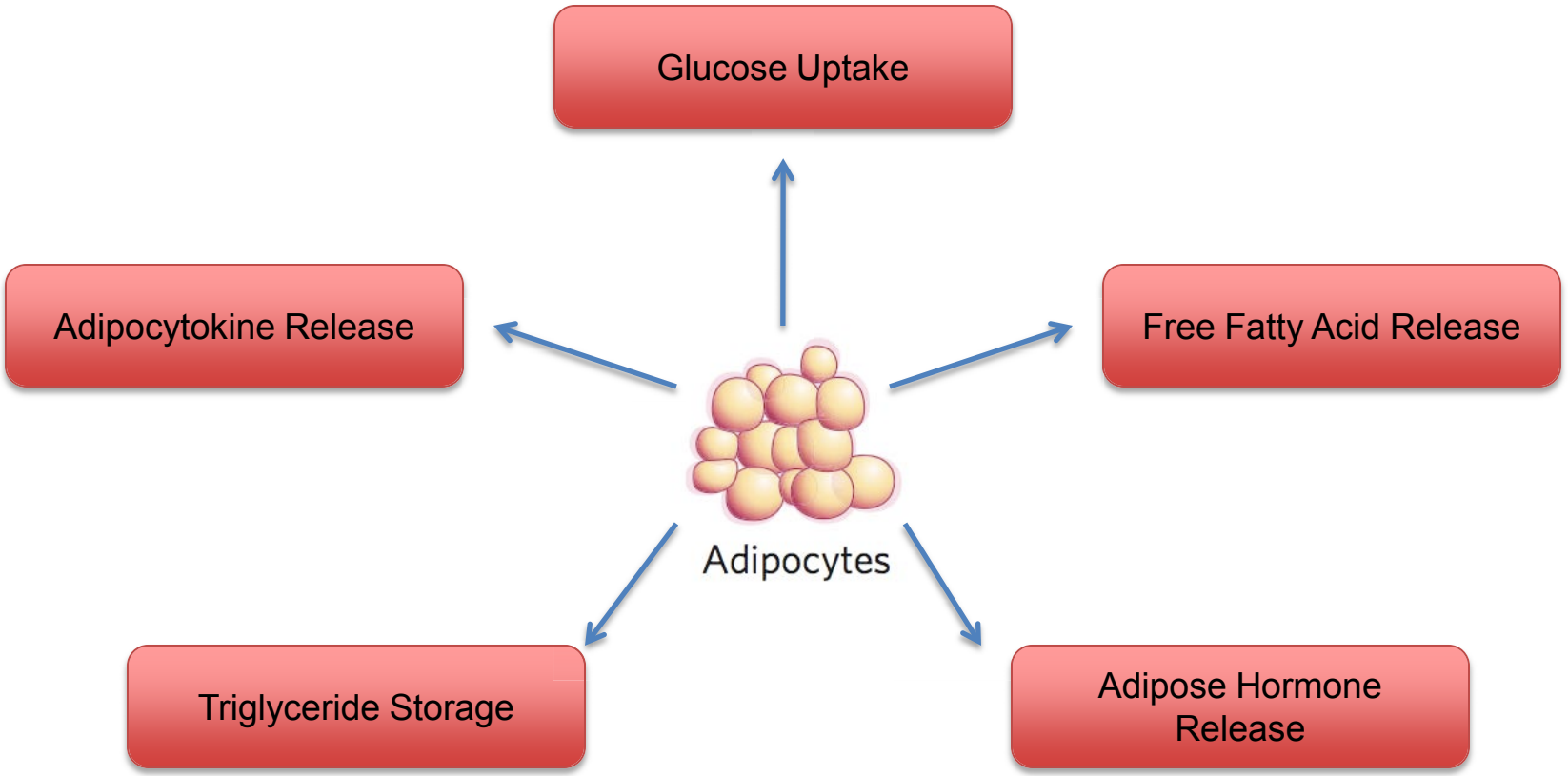
IRS proteins play key roles in regulating insulin function

Image removed due to copyright restrictions. See Figure 4 in Taniguchi, C. M., et al. "Critical Nodes in Signalling Pathways: Insights Into Insulin Action." *Nat Rev Mol Cell Biol* 7 (2006): 85-96.

Taniguchi et al, Nat. Reviews Mol. Cell Biol, 2006

Adipocytes – key regulators of insulin action

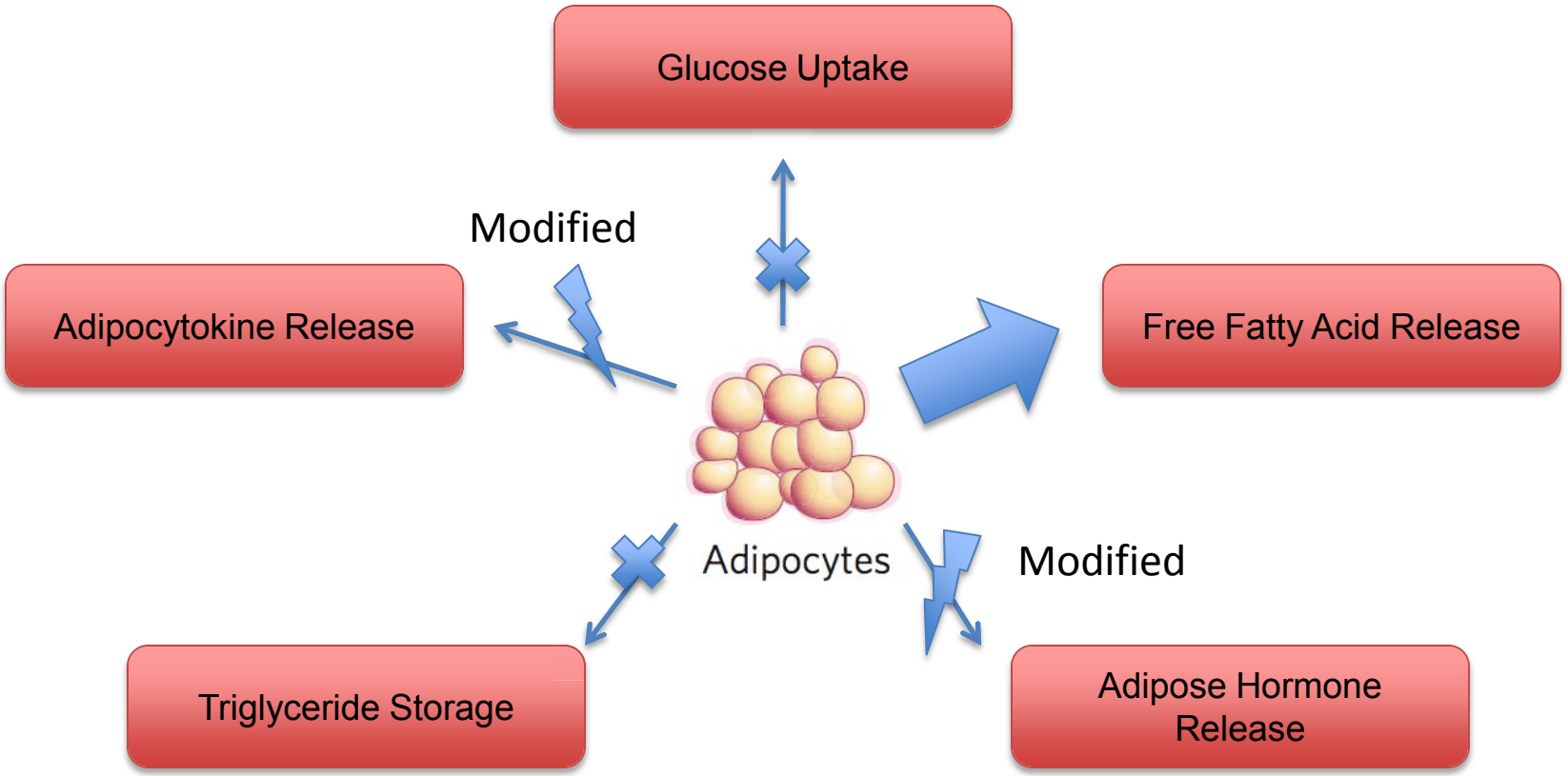
Adipocyte Functions



Slide courtesy of Bryan Owens and Emily Miraldi. Used with permission.

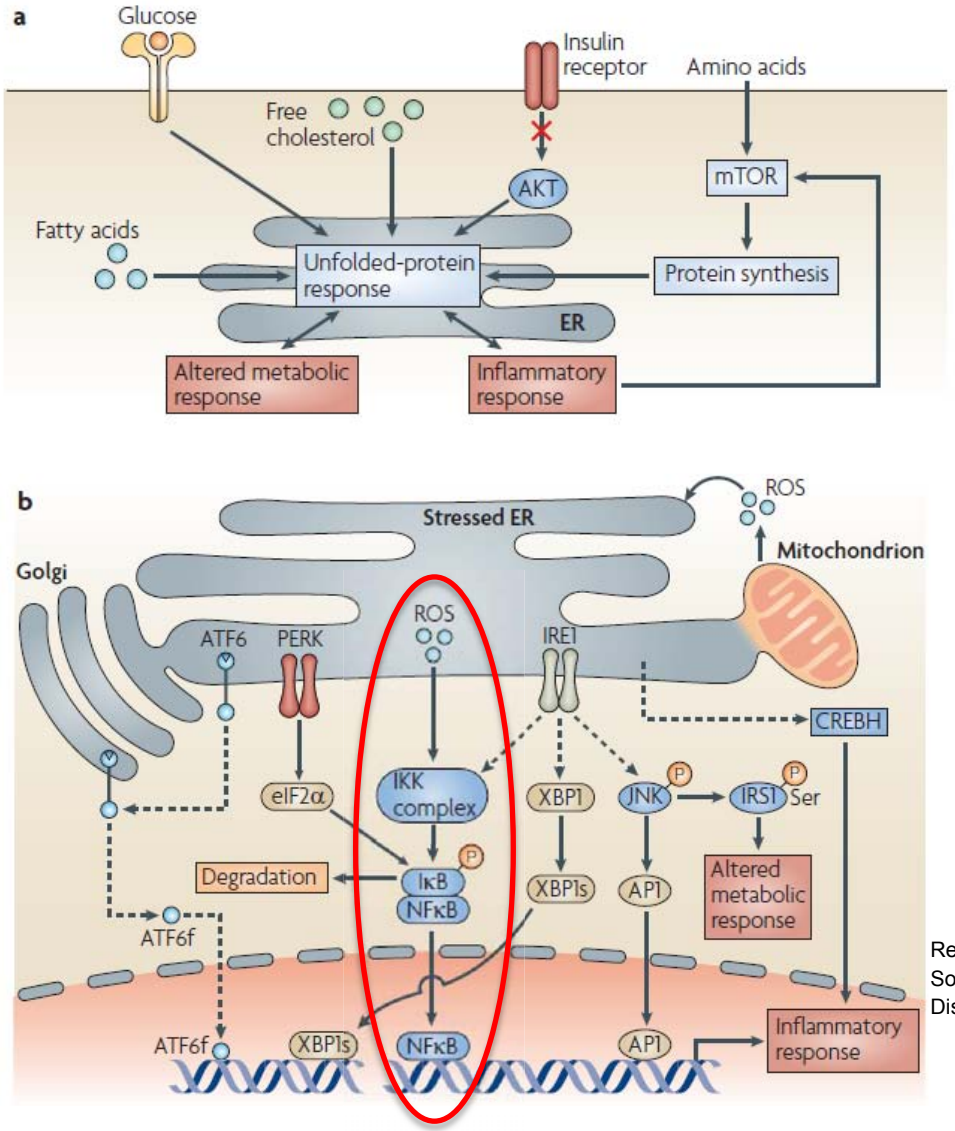
Adipocytes in insulin resistance

Adipocyte Functions



Slide courtesy of Bryan Owens and Emily Miraldi. Used with permission.

The beginning (?) – ER stress, the unfolded protein response, and inflammation

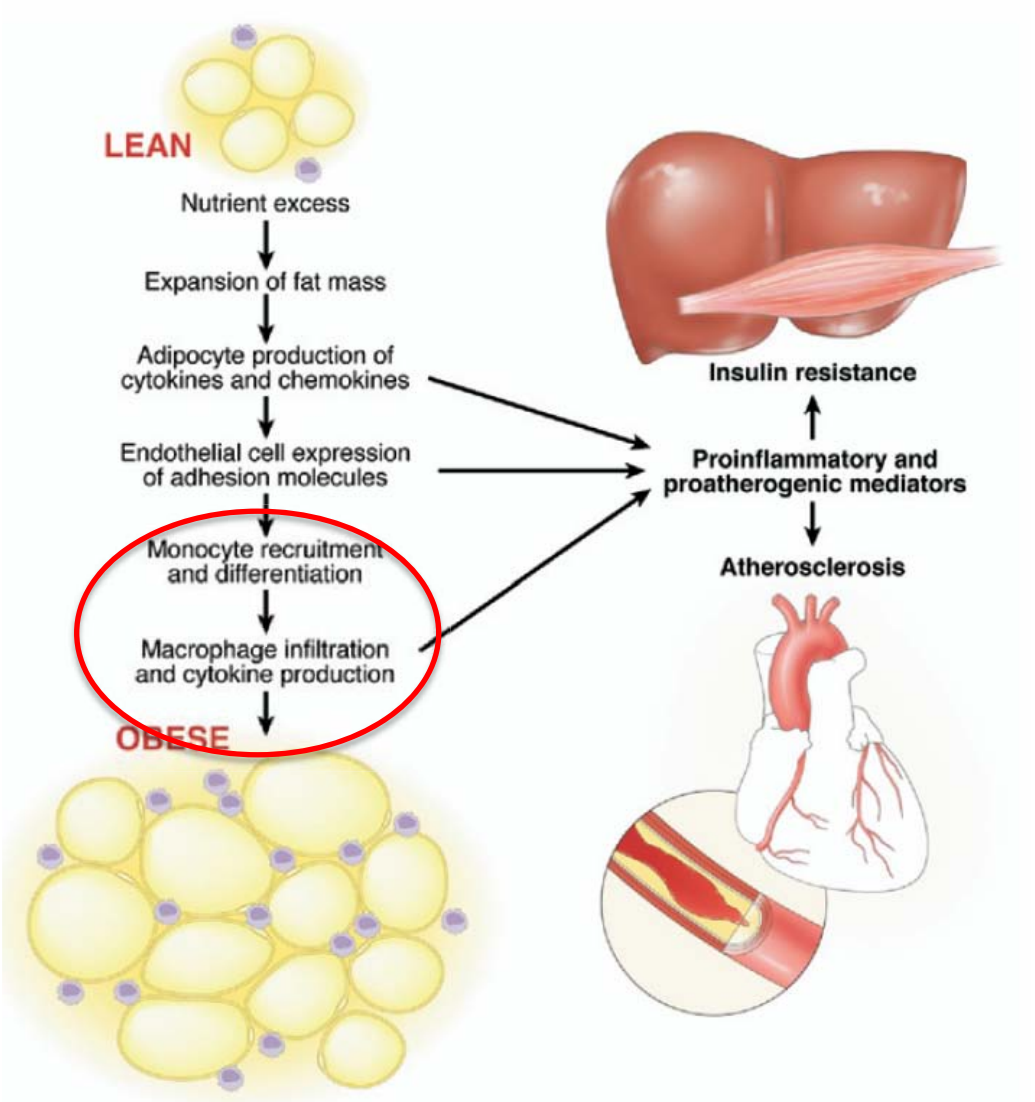


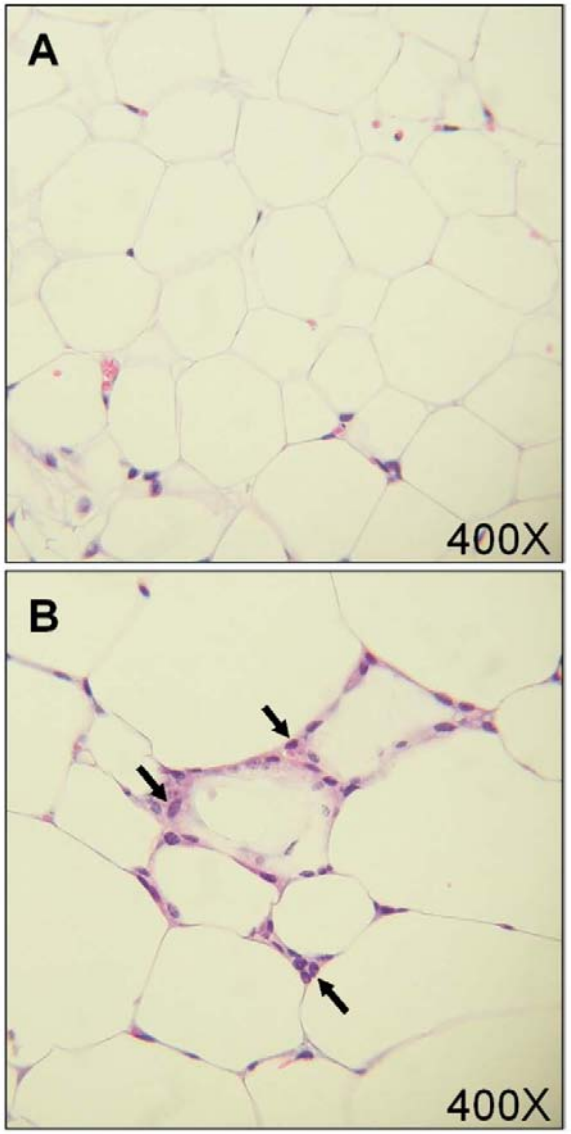
NFκB target genes:

IL-1β
TNF-α
IL-6
MCP-1 (monocyte chemotractant protein 1) (CCL2)
Interferon β
+many, many others including pro- and anti-inflammatory genes

Hotamisligil and Erbay, Nat. Reviews Immunology, 2008

Overnutrition leads to increased adipocyte size and macrophage recruitment



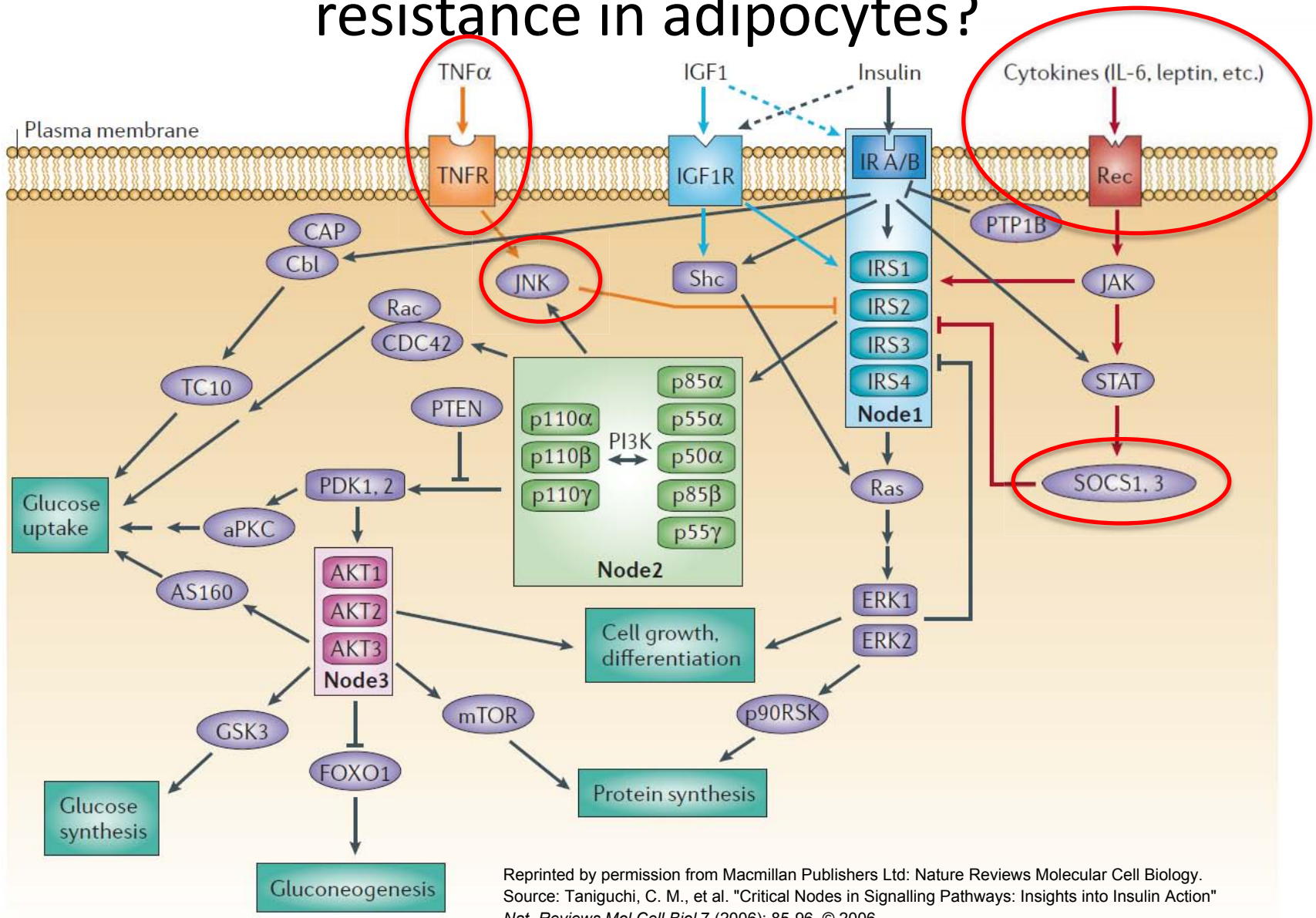


Shoelson, Gastroenterology (2007) 132, 2169-2180

More granularity – increased adiposity and inflammation

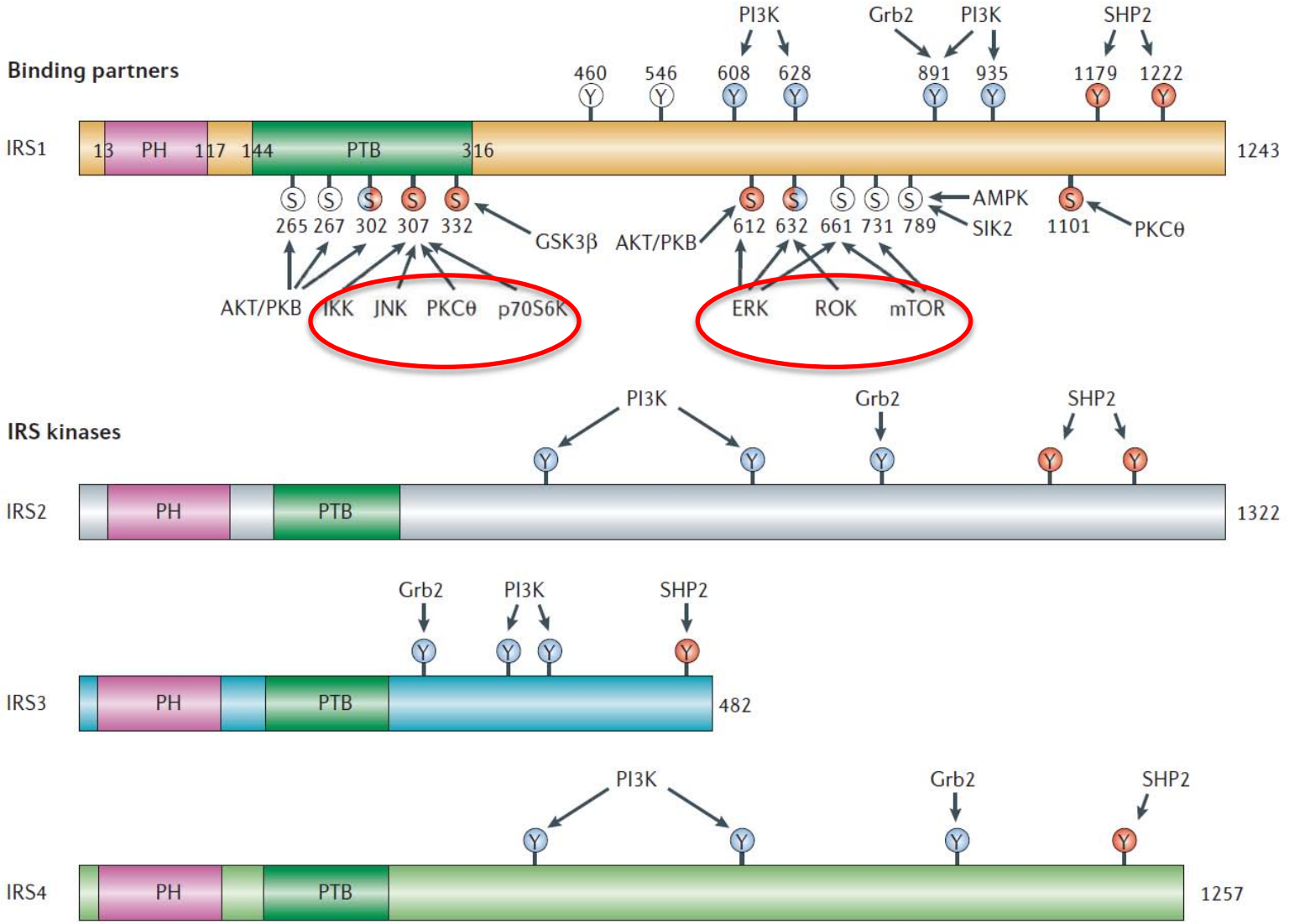
Schenk et al, J. Clinical Investigation, 2008, 118, 2992-3002

How does macrophage recruitment affect insulin resistance in adipocytes?



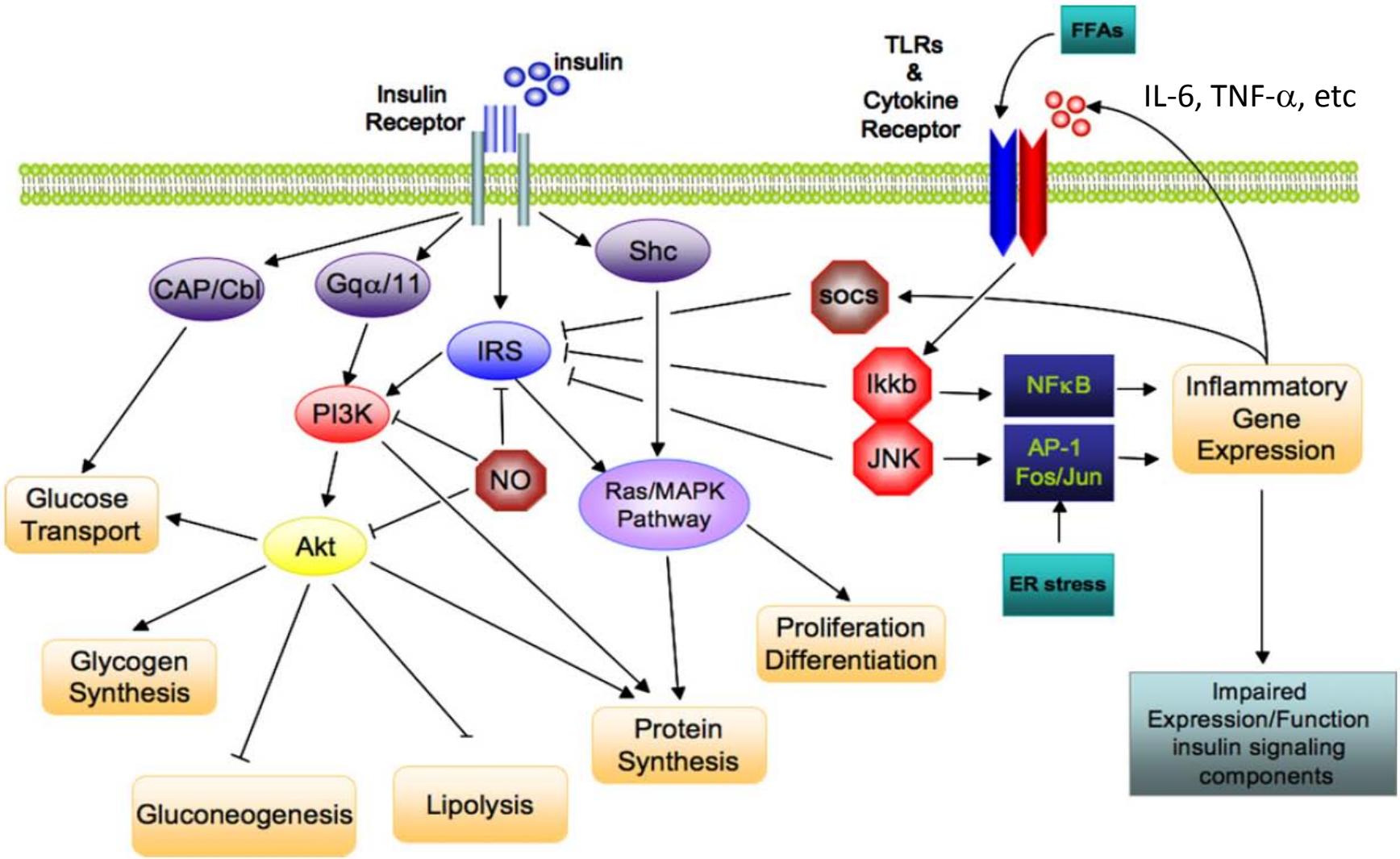
Taniguchi et al, Nat. Reviews Mol. Cell Biol, 2006

Complex signaling on Insulin receptor substrates



Taniguchi et al, Nat. Reviews Mol. Cell Biol, 2006

Free fatty acids, TNF, and NO drive insulin resistance



De Luca and Olefsky, FEBS letters, 2008

Where do free fatty acids come from?

Multiple sources, including diet and adipocytes

β-oxidation in muscle mitochondria (exercise)

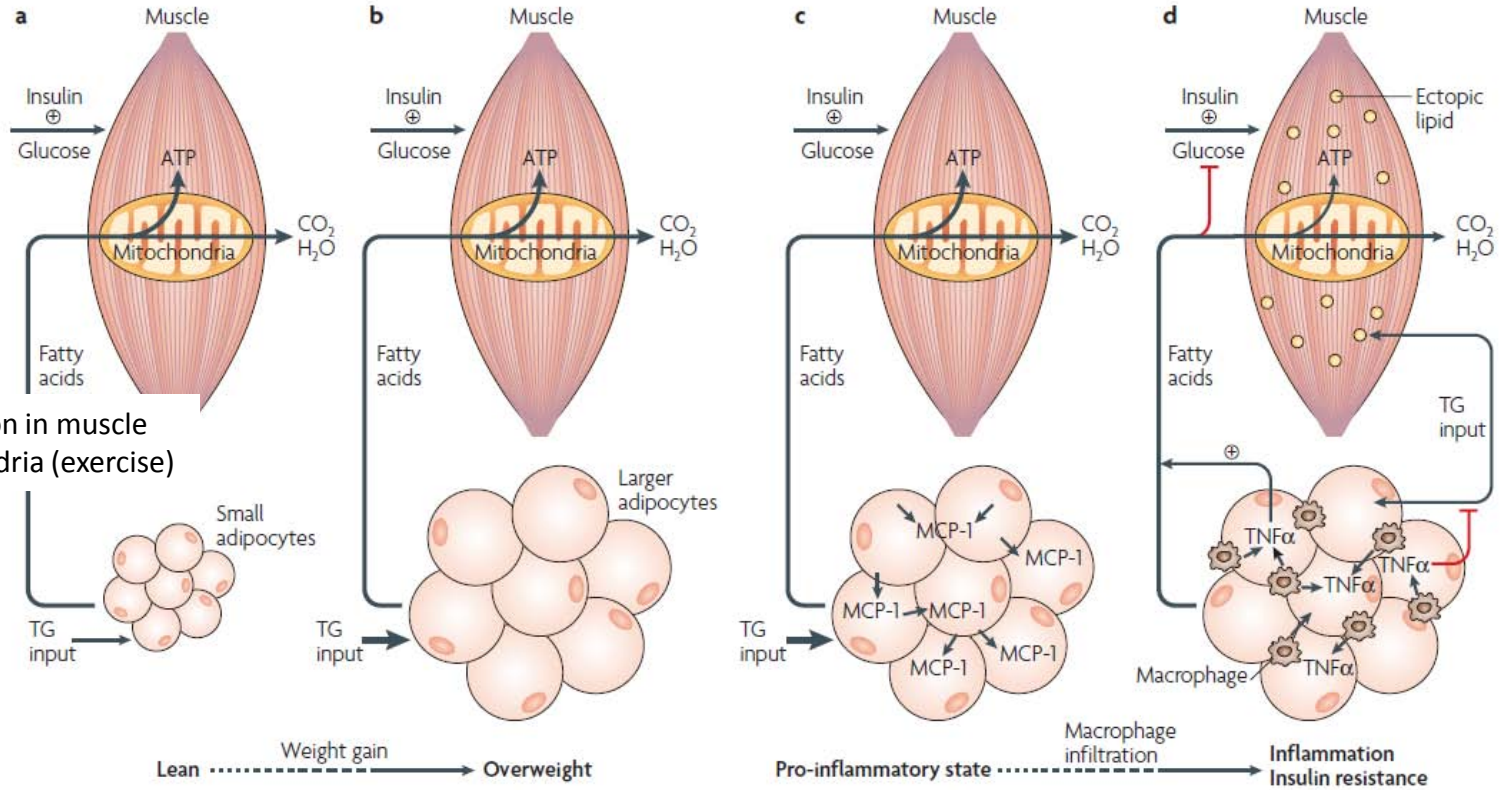
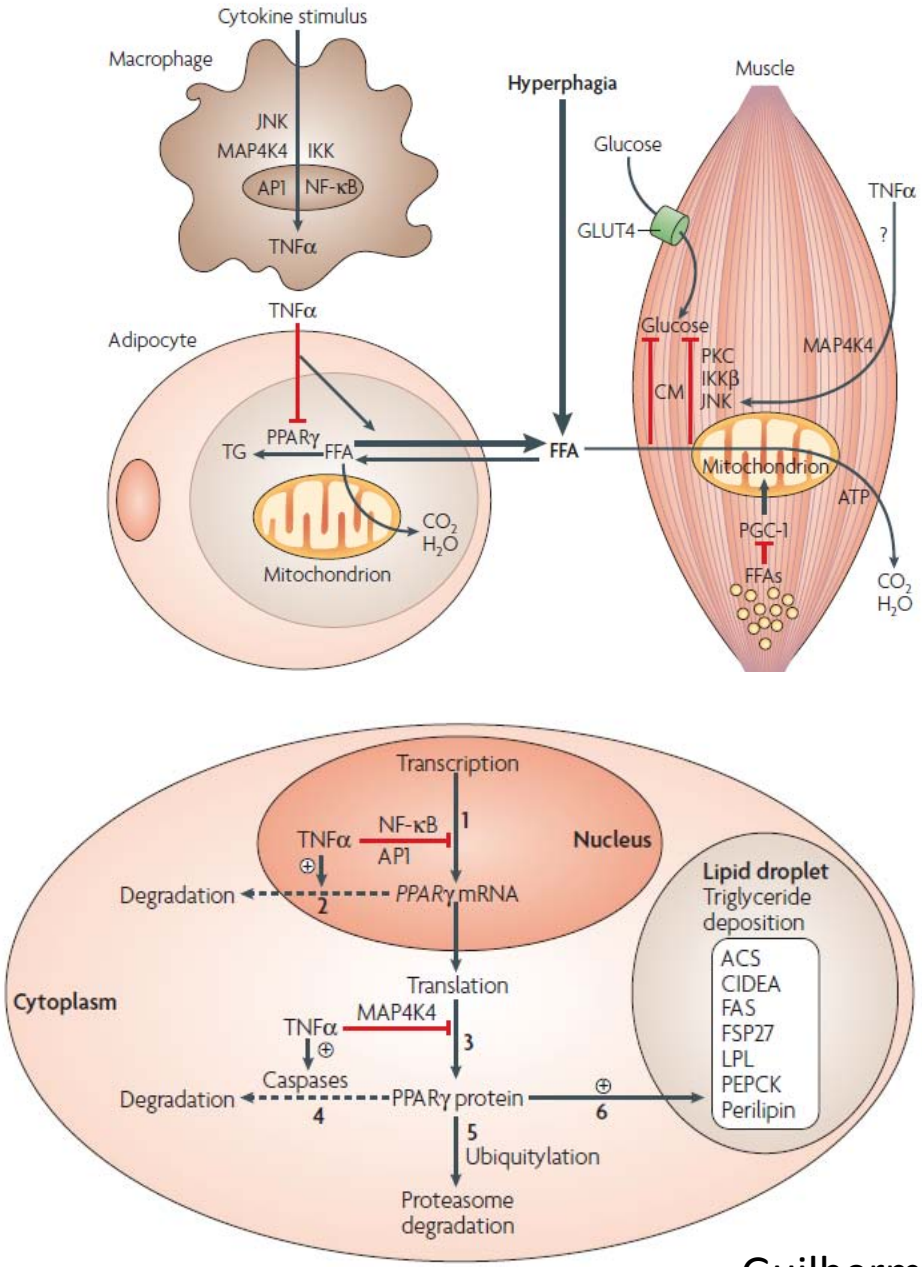


Figure 1 | **Chronic inflammation in adipose tissue triggers insulin resistance in skeletal muscle. a** | In the lean state, small adipocytes efficiently store fatty acids as triglyceride (TG input, arrow), which can be mobilized and used to generate ATP through the mitochondrial β-oxidation pathway in muscle during periods of caloric need. Insulin-stimulated glucose uptake under these conditions is normal. **b** | Excess caloric intake leads to metabolic overload, increased TG input and adipocyte enlargement. Nonetheless, in non-diabetic overweight individuals, TG storage by adipose cells and β-oxidation in muscle can often be maintained to prevent insulin resistance. **c** | On further overloading with TG, hypertrophy of adipocytes and increased secretion of macrophage chemoattractants occurs, including the secretion of monocyte chemoattractant protein-1 (MCP-1; arrows), which recruits additional macrophages. **d** | Macrophage recruitment in turn results in a pro-inflammatory state in obese adipose tissue. Infiltrating macrophages secrete large amounts of tumour-necrosis factor-α (TNFα), which results in a chronic inflammatory state with impaired TG deposition and increased lipolysis (arrow and plus signal). The excess of circulating TG and free fatty acids results in the accumulation of activated lipids in the muscle (yellow dots), disrupting functions such as mitochondrial oxidative phosphorylation and insulin-stimulated glucose transport, thus triggering insulin resistance.

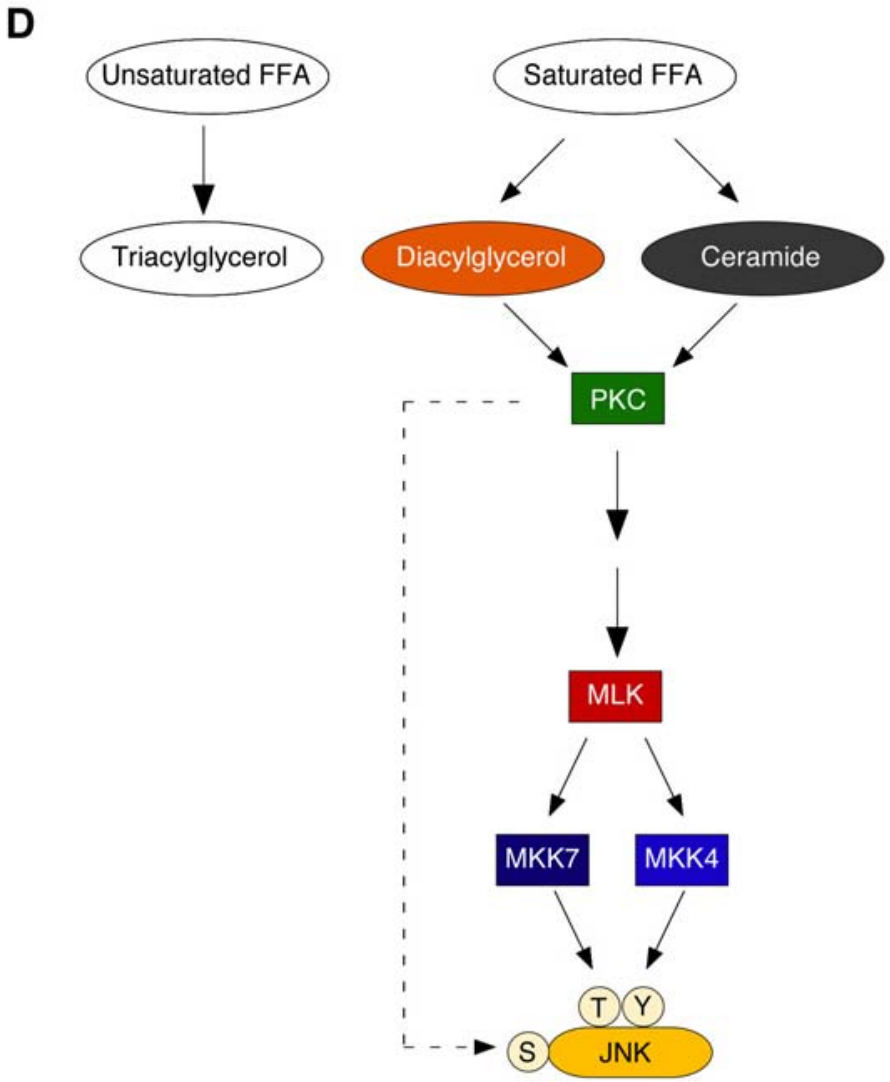
Guilherme et al, Nat Rev Mol Cell Biol. 2008

More granularity of FFA release from adipocytes



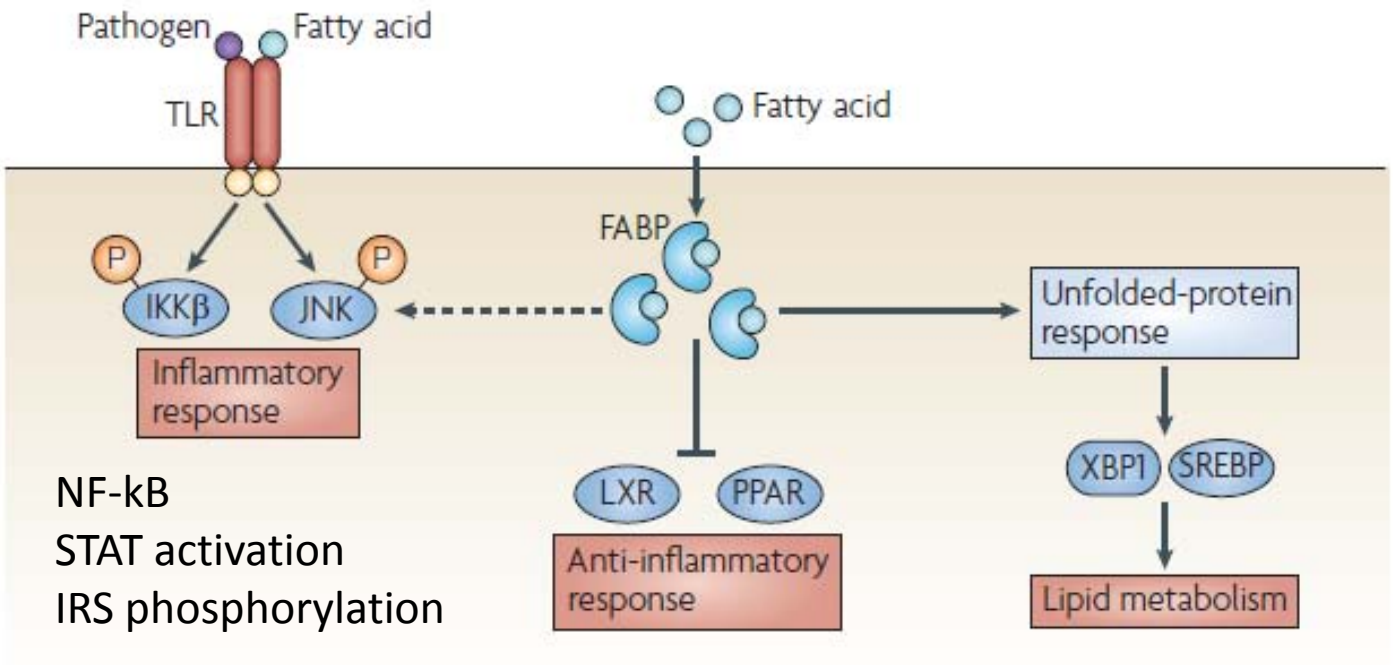
Guilherme et al, Nat Rev Mol Cell Biol. 2008

Saturated free fatty acids lead to JNK activation and to IRS phosphorylation on Thr-307



Jaeschke and Davis, Molecular Cell, 2007

Free fatty acids also bind to TLR's and FABPs, driving insulin resistance through multiple mechanisms

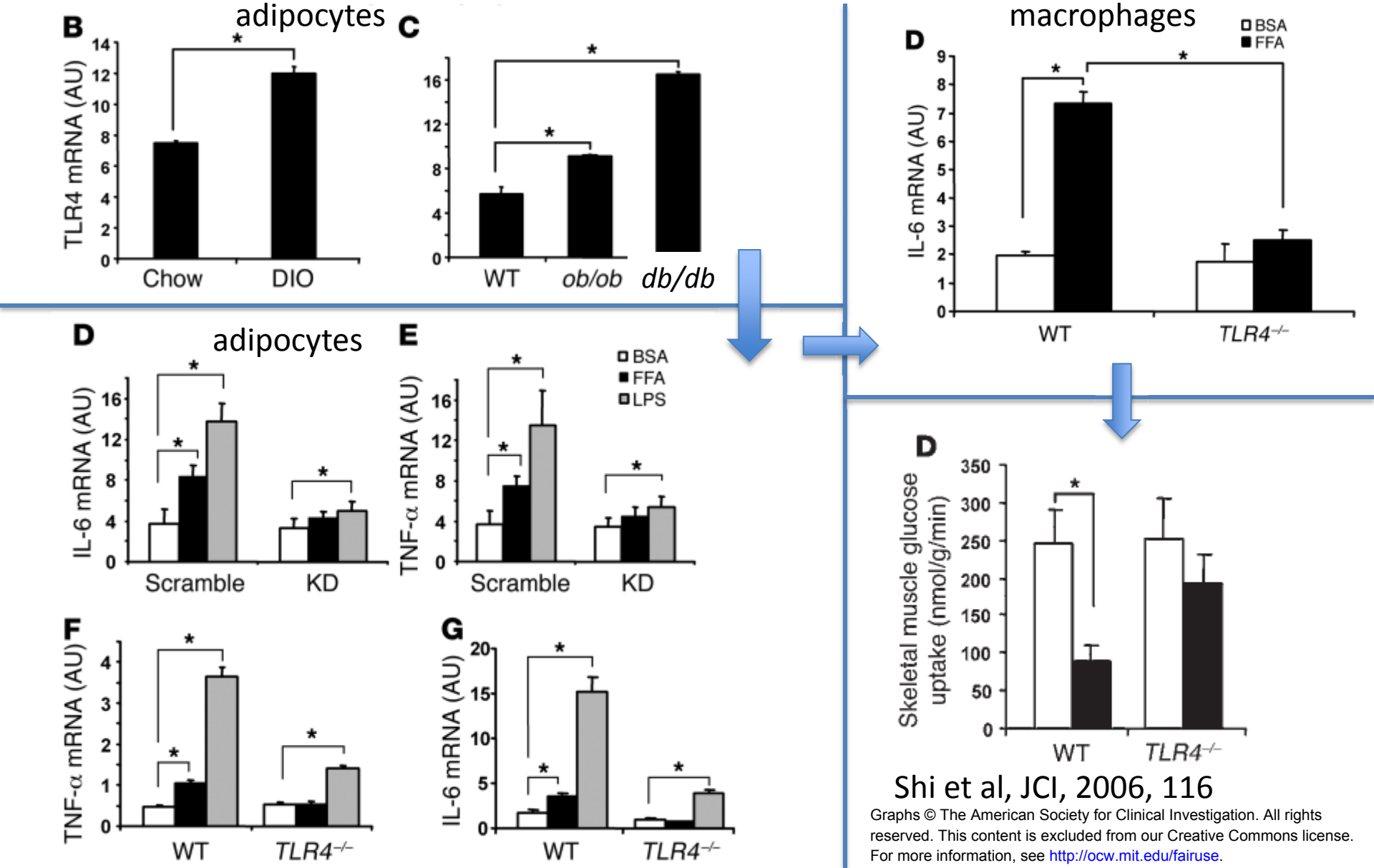


NF-kB
STAT activation
IRS phosphorylation

IL-10
Adiponectin

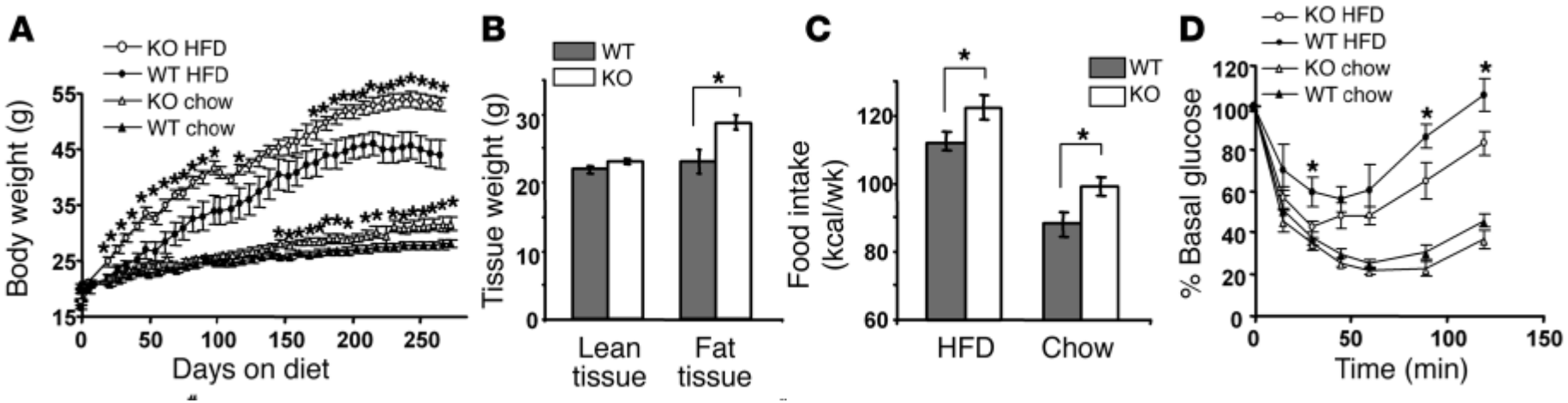
Hotamisligil and Erbay, Nat. Reviews Immunology, 2008

If TLR's play a critical role in this process, why not target them in insulin resistance?

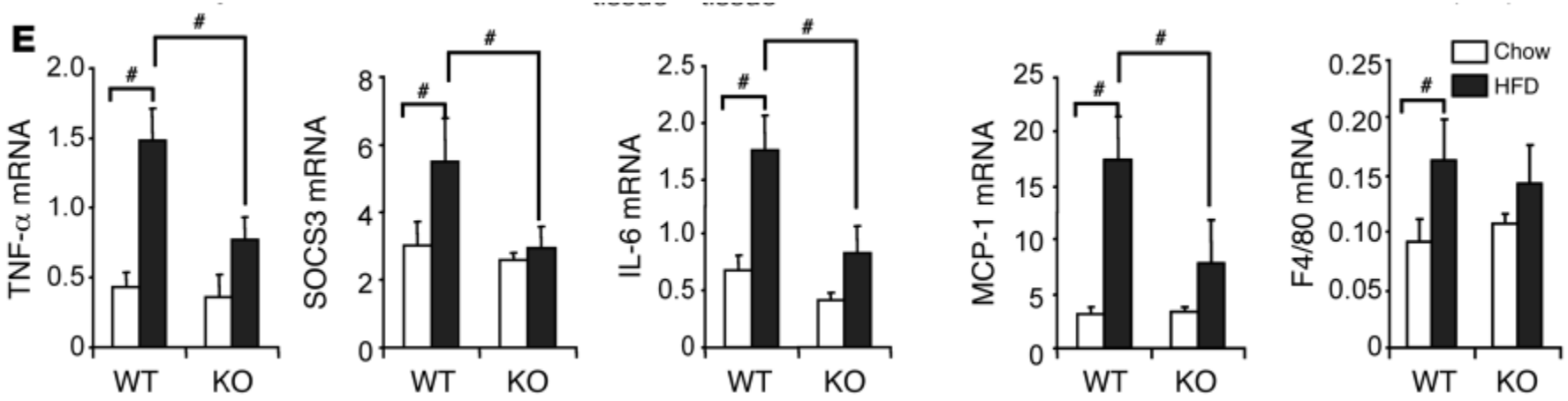


Shi et al, JCI, 2006, 116

TLR4$^{-/-}$ looks promising for IR?



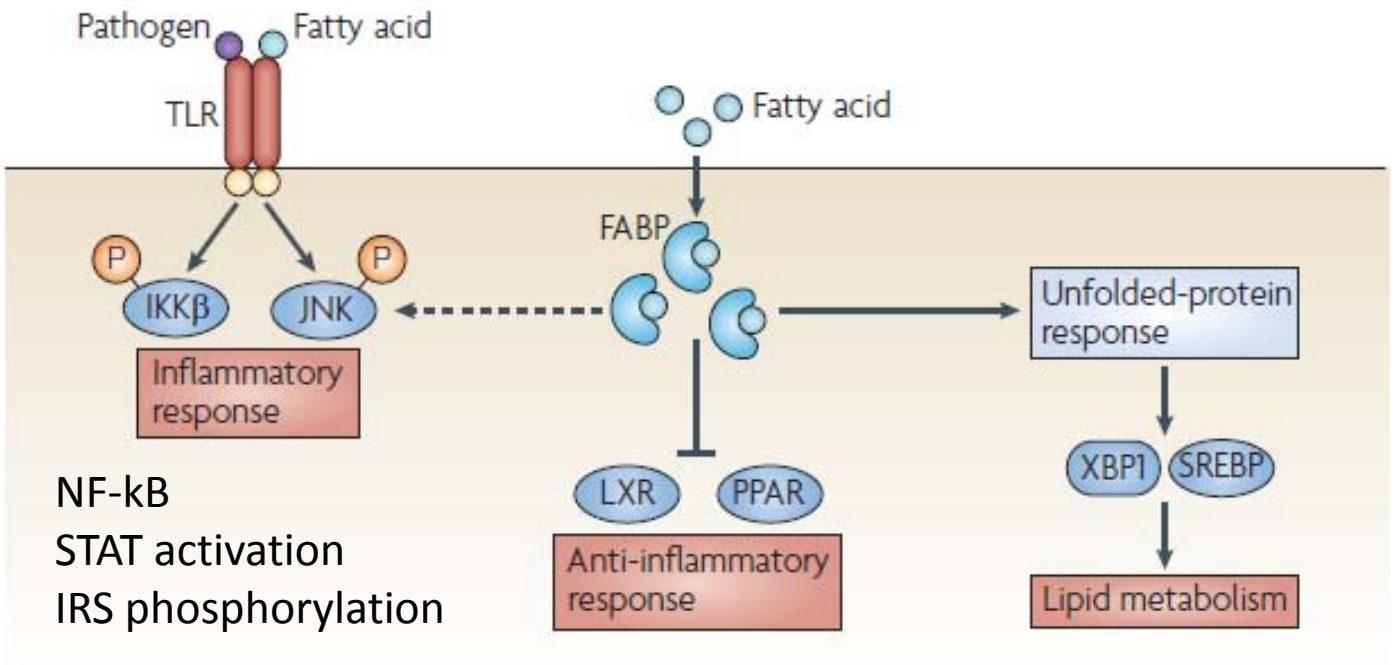
Increased weight gain, but….



Overall improved insulin sensitivity in fat, even with weight gain

Shi et al, JCI, 2006, 116

Free fatty acids also bind to TLR's and FABPs, driving insulin resistance through multiple mechanisms

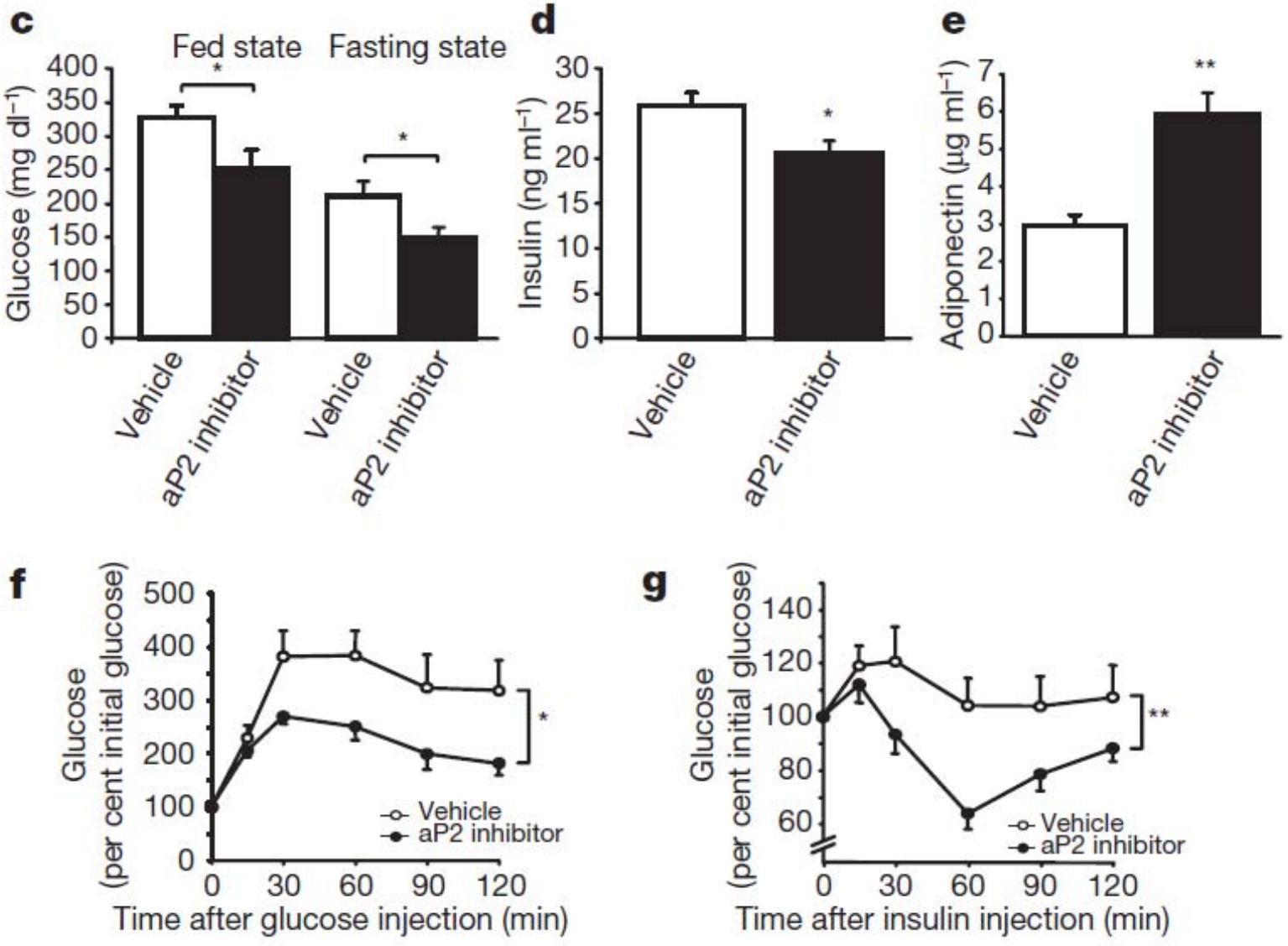


NF-kB
STAT activation
IRS phosphorylation

IL-10
Adiponectin

Hotamisligil and Erbay, Nat. Reviews Immunology, 2008

Another interesting target: FABPs



Furuhashi et al., Nature 2007, 447, 959-965

Multiple other knock-out mice with IR phenotypes

Table 1. Knockout Mice With Potentially Relevant Metabolic Phenotypes

Gene	Phenotype
IL-6	Mature onset obesity and insulin resistance[65]
TNF-α	Improved insulin sensitivity and insulin signalling[78]
PAI-1	Improved insulin sensitivity[103]
IL-18	Hyperphagia, obesity, and insulin resistance[125]
IL-1α	Lower fasting glucose and insulin with improved insulin sensitivity[81]
Resistin	Improved glucose tolerance on HFD[126]
MCP-1	Decreased monocyte recruitment to adipose tissue, decreased adiposity, hepatic steatosis, and insulin resistance[10,39]
ICAM-1	Exacerbation of obesity and increased susceptibility to diet-induced insulin resistance[127]
iNOS	Protection against HFD-induced insulin resistance[128]
IKKβ	Improved insulin sensitivity[17,49]
JNK1	Improvement of insulin resistance in diet-induced and genetic obesity[52]
SOCS1	Decreased blood glucose levels and sustained insulin receptor phosphorylation[129]

ICAM, intracellular adhesion molecule; iNOS, inducible nitric oxide synthase; SOCS, suppressors of cytokine signaling.

Shoelson, Gastroenterology (2007) 132, 2169-2180

Adipocytokines in lean and obese states

Figures removed due to copyright restrictions.
See Figures 1 and 2 from Tilg and Moschen,
Clinical Science 114 (2008): 275-288.

Tilg and Moschen, Clinical Science (2008) 114, 275-288

Adiponectin – anti-inflammatory adipocytokine

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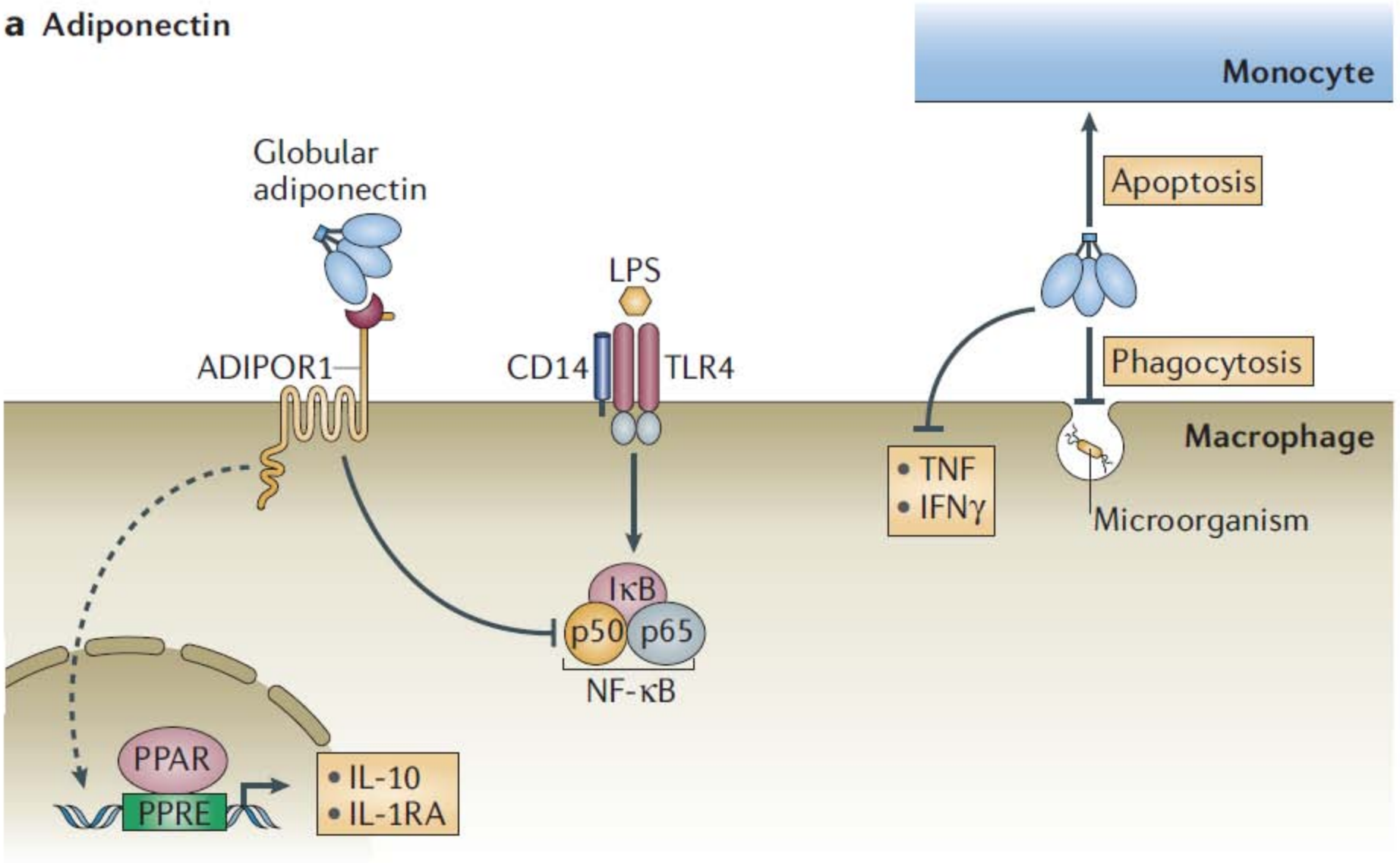
See Figures 1 and 2 from Tilg and Moschen,
Clinical Science 114 (2008): 275-288.

Tilg and Moschen, Clinical Science (2008) 114, 275-288

Adiponectin – anti-inflammatory adipocytokine



Tilg and Moschen, Nat. Rev. Immunol. 2006, 6, 772-783

Adiponectin as a primary systemic therapy?

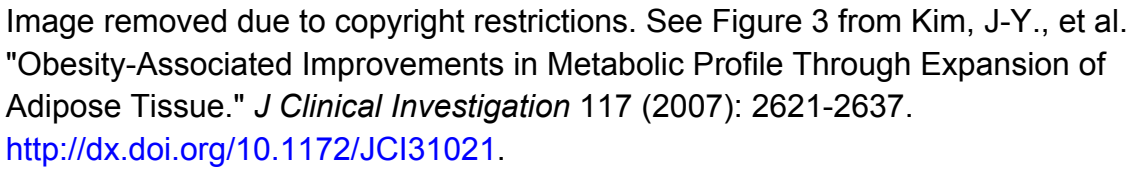
The adiponectin $^{ob/ob}$ mouse

Taubes 17 JULY 2009 VOL 325 SCIENCE www.sciencemag.org

Adiponectin overexpression effects

Kim et al., J. Clinical Investigation 2007, 117, 2621-2637

Adverse(?) adiponectin overexpression effects



Kim et al., J. Clinical Investigation 2007, 117, 2621-2637

Positive adiponectin overexpression effects

Image removed due to copyright restrictions. See Figure 3 (G & I) and 4 (E) from Kim, J-Y., et al., "Obesity-Associated Improvements in Metabolic Profile Through Expansion of Adipose Tissue." *J Clinical Investigation* 117 (2007): 2621-2637.

Kim et al., J. Clinical Investigation 2007, 117, 2621-2637

Adipocytokines in lean and obese states

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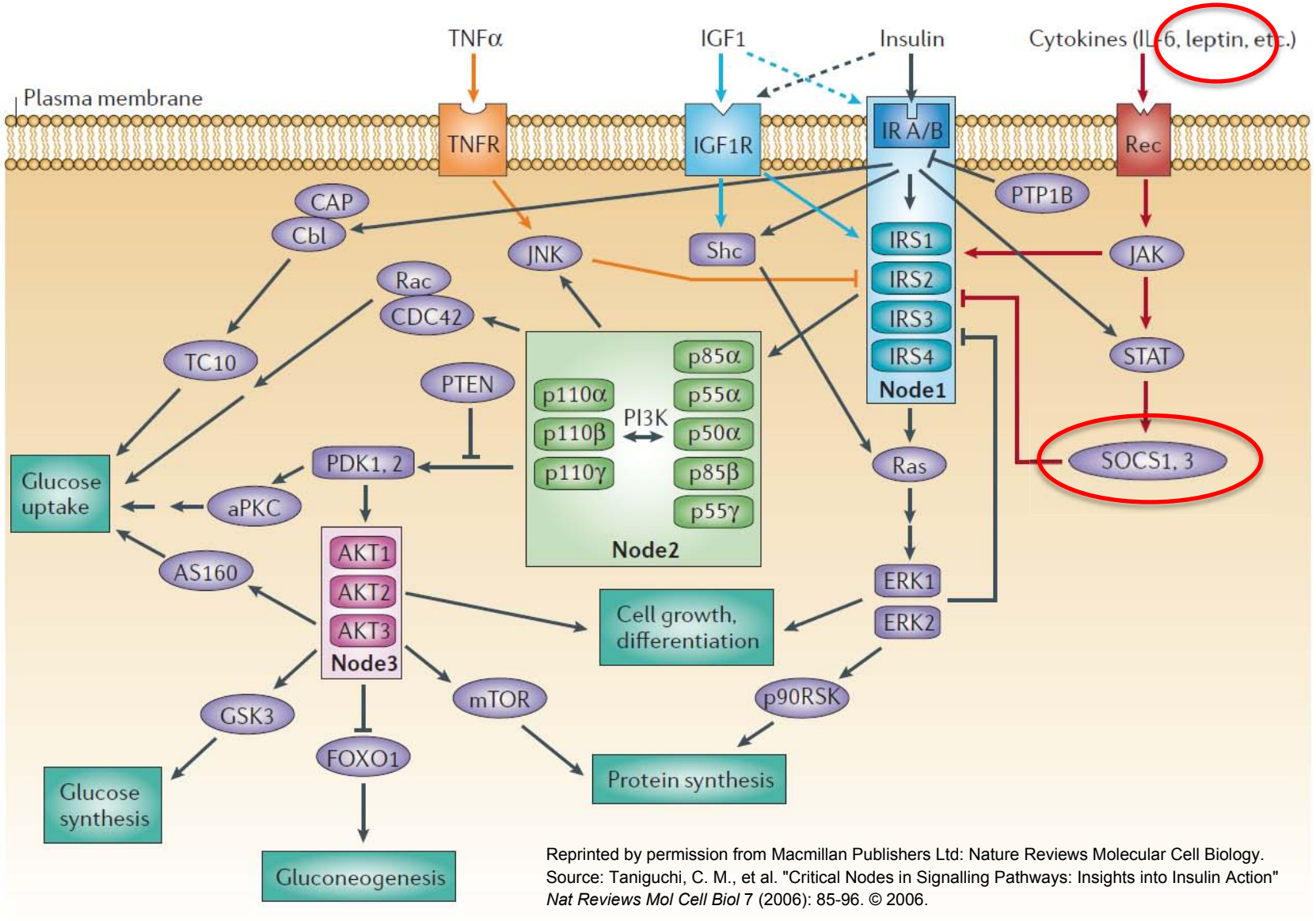
See Figures 1 and 2 from Tilg and Moschen,
Clinical Science 114 (2008): 275-288.

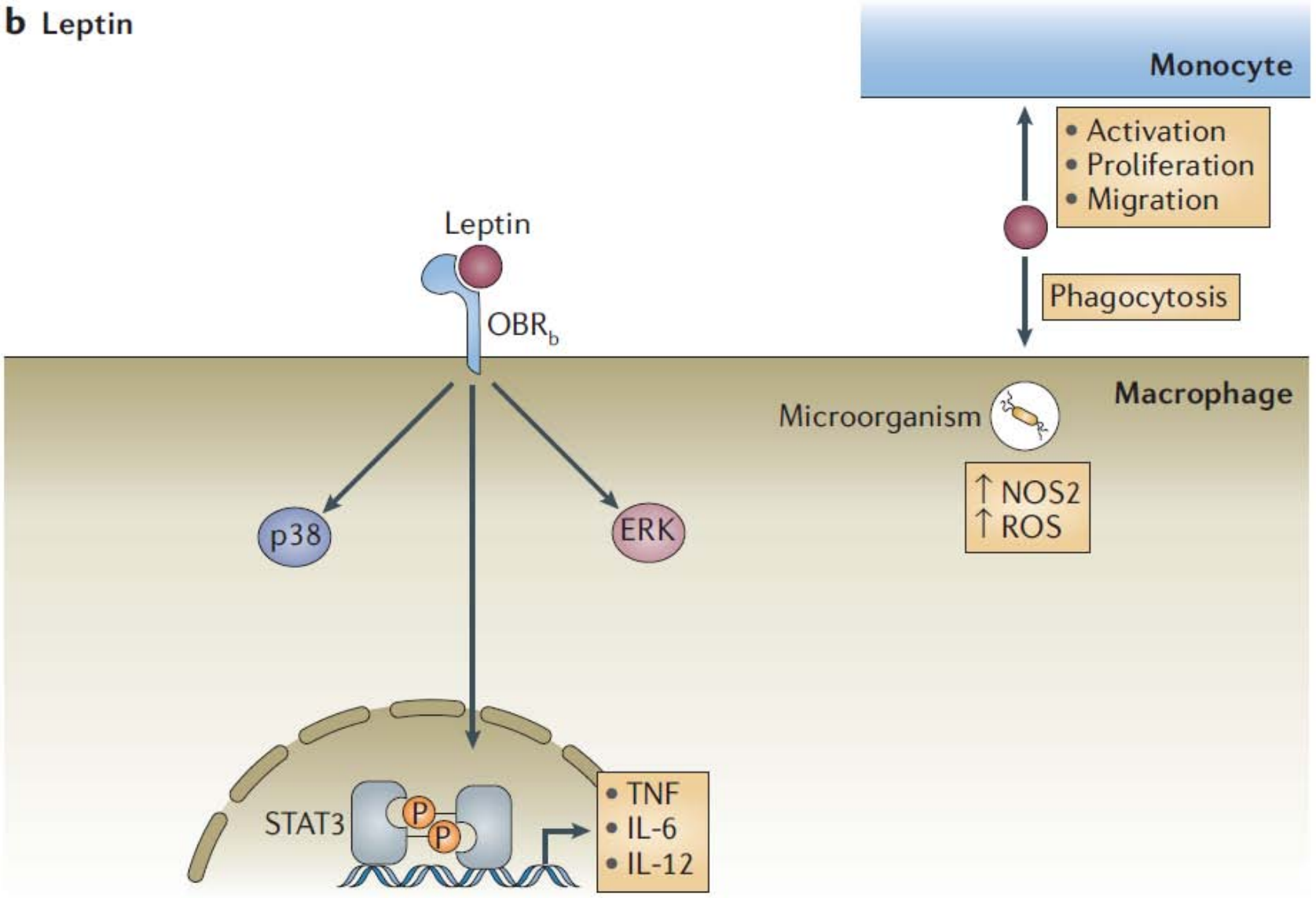
Tilg and Moschen, Clinical Science (2008) 114, 275-288

Insulin activation leads to leptin release – a slow negative feedback loop to shut down the Insulin signal



Taniguchi et al, Nat. Reviews Mol. Cell Biol, 2006

Leptin – pro-inflammatory adipocytokine



Tilg and Moschen, Nat. Rev. Immunol. 2006, 6, 772-783

If inflammation is bad and adiponectin is good, then leptin must be bad?

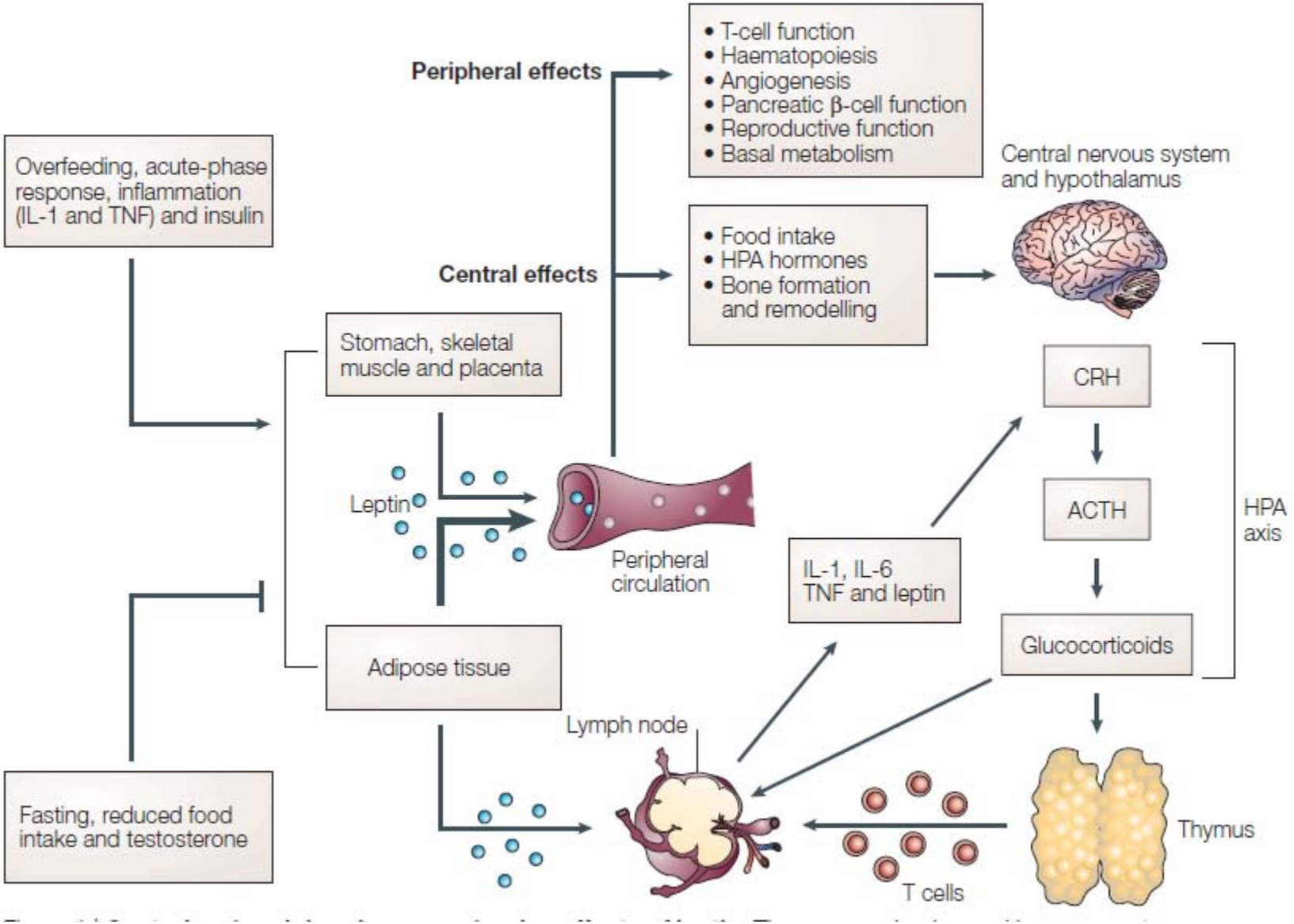
The ob/ob mouse and the db/db mouse:

Mouse models of obesity and diabetes in which leptin or leptin receptor is knocked out or dysfunctional.

Why are these mice obese and diabetic? Appetite – leptin signaling in the hypothalamus leads to transcriptional regulation of neuropeptides which can either promote feeding and weight gain ('orexigenic' peptides) or those that suppress feeding and weight ('anorexigenic' peptides).

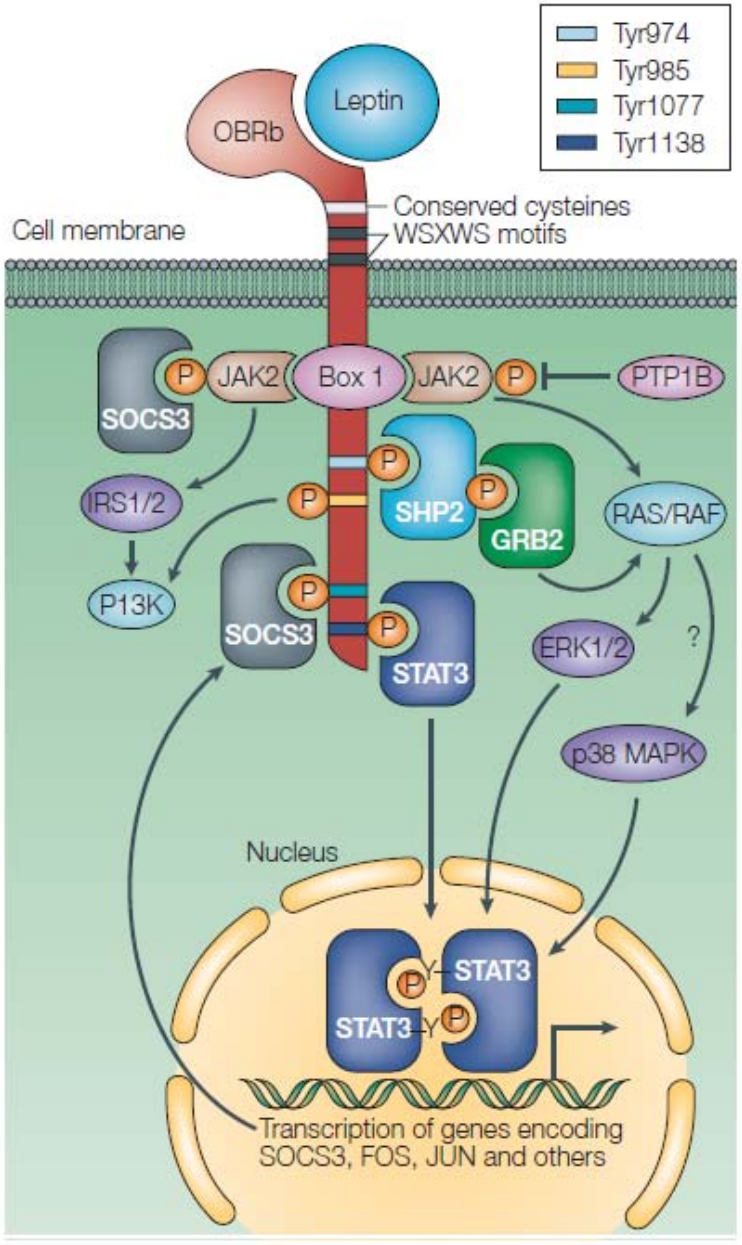
Leptin suppresses neuropeptide Y (NPY) and agouti-related peptide (AgRP), while increasing α-melanocyte stimulating hormone (MSH) and cocaine- and amphetamine regulated transcript (CART).

Leptin plays a very complex systemic role



La Cava and Matarese, Nat. Rev. Immunol. 2004

Simple leptin signaling



Leptin resistance:
SOCS3
STAT activation
PTP1b

Druggable target?

La Cava and Matarese, Nat. Rev. Immunol. 2004

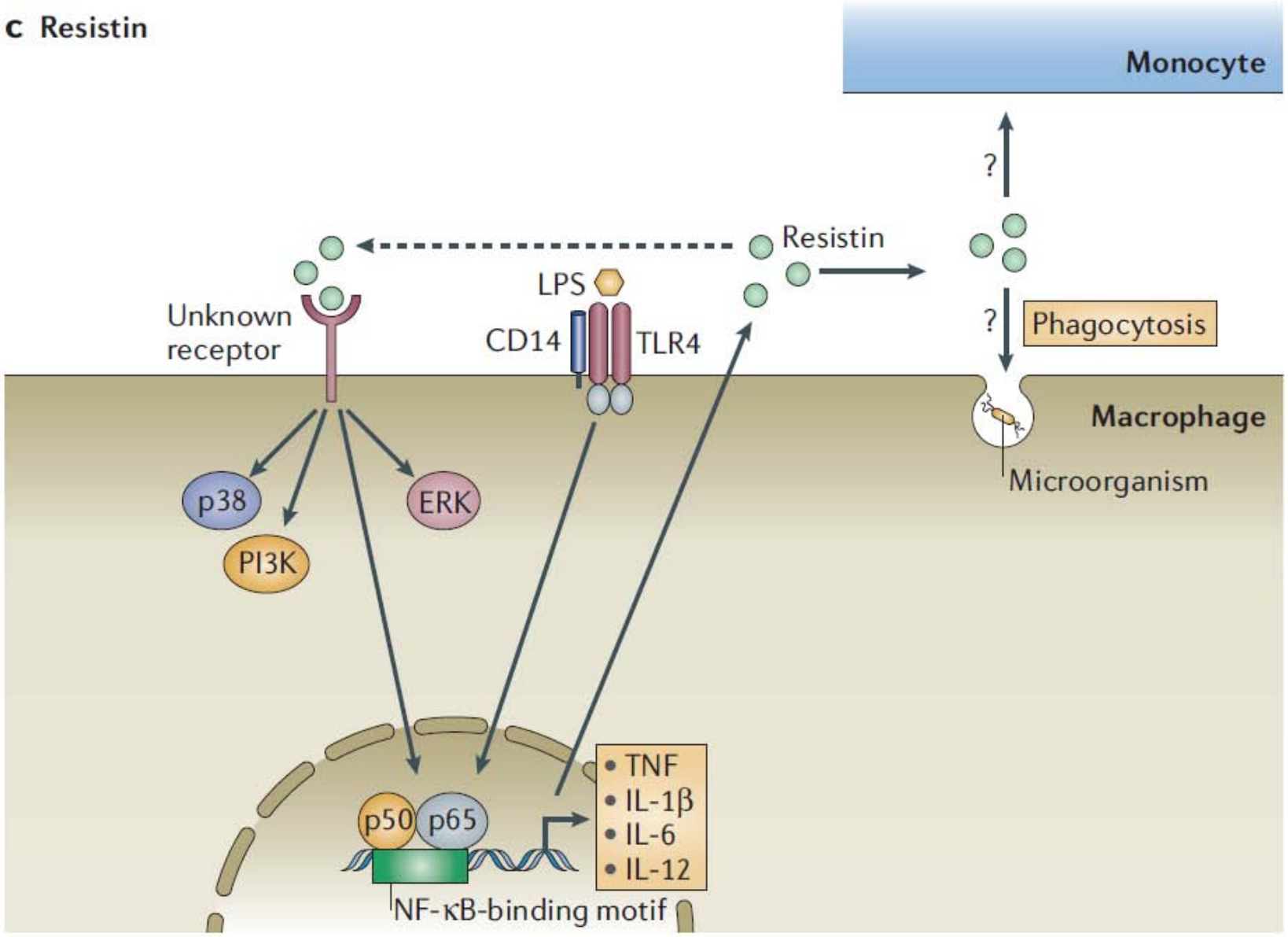
Leptin affects immune response, loss of leptin reduces autoimmune diseases

Table 1 | **Susceptibility of leptin-deficient *ob/ob* mice to experimentally induced inflammatory/autoimmune diseases**

Disease model	Susceptibility of *ob/ob* mice	Cytokines and inflammatory factors involved	Antibodies present	Effects of leptin administration	Refs
EAE	Reduced/resistant	Increased IL-4; absent IFN-γ after myelin-specific stimulation of T cells	Increased myelin-specific IgG1; reduced IgG2a	Restores IFN-γ secretion and disease susceptibility is comparable to wild-type mice; promotes myelin-specific antibody switch from IgG1 to IgG2a	52,53
AIA	Reduced/resistant	Increased IL-10; reduced IFN-γ after mBSA stimulation of T cells; reduced synovial IL-1β and TNF	Decreased serum antibody specific for mBSA	N.D.	51
EIC	Reduced/resistant	Reduced IFN-γ, TNF, IL-1β, IL-6, IL-10 and IL-18; reduced chemokines CCL3 and CXCL2; reduced MPO activity; reduced COX2 expression	N.D.	Restores normal secretion of IFN-γ, TNF, IL-1β, IL-6, IL-10 and IL-18; restores disease susceptibility to a level comparable to wild-type mice	56
EIH	Reduced/resistant	Reduced serum TNF and IL-18	N.D.	Restores TNF and IL-18 secretion; restores disease susceptibility to a level comparable to wild-type mice	37,50
EINN	Reduced/resistant	Undetectable *in vitro* proliferative and cytokine T-cell responses against sheep IgG; reduced glomerular IgG deposition	Reduced or no difference in sheep-IgG-specific serum antibodies	N.D.	59

La Cava and Matarese, Nat. Rev. Immunol. 2004

Resistin, another pro-inflammatory adipocytokine(?)



Tilg and Moschen, Nat. Rev. Immunol. 2006, 6, 772-783

Effects of adopicytokines – a reference table

Table 1 | **Effects of adipocytokines on the immune system and linked diseases**

Adipocytokine	Inflammatory effect	Effects on immunity		Associated diseases
		Innate	Adaptive	
Adiponectin	Anti-inflammatory	↓ Endothelial adhesion molecules[40] ↓ NF-κB[40,41,43] ↓ TNF[35] ↓ IL-6(REF. 42) ↓ IFNγ[42] ↑ IL-10 (REF. 42) ↑ IL-1RA[42] ↓ Phagocytosis[42]	↓ B-cell lymphopoiesis[117] ↓ T-cell responses[42]	• Insulin resistance and type 2 diabetes mellitus[33,35] • Atherosclerosis[57,58,60] • Experimentally induced liver disease: non-alcoholic and alcoholic fatty liver disease[49]; CCl_4 liver fibrosis (REF. 50); LPS-treated KK-A^y mice (REF. 51); and experimentally induced hepatitis (ConA)[52] • Cardiac injury[55,56] • Cancer[102,103] • Inflammatory bowel disease[112] • Rheumatoid arthritis[115]
	Pro-inflammatory	↑ CXCL8 in presence of LPS[44]	ND	
Leptin	Pro-inflammatory	↑ TNF[68,71] ↑ IL-6 (REF. 68) ↑ IL-12 (REF. 68) ↑ Neutrophil activation (CD11b)[70] ↑ ROS[70] ↑ Chemotaxis[70] ↑ NK-cell function[72]	↑ Lymphopoiesis[73] ↑ Thymocyte survival[73] ↑ T-cell proliferation[64] ↑ T_H1 response (IL-2 and IFNγ)[64] ↓ T_H2 response (IL-4)[64]	• Insulin resistance[9] • Experimentally induced hepatitis (ConA)[75,76] • EAE and antigen-induced arthritis[4,77] • Experimentally induced colitis: $CD4^+CD45RB^{hi}$ T-cell transfer[78]; and IL-10-deficient mice[113] • Asthma[110] • Cancer[104]
Resistin	Pro-inflammatory	↑ TNF[86,87] ↑ IL-1β[86] ↑ IL-6 (REF. 86) ↑ IL-12 (REF. 86) ↑ NF-κB[87] ↑ Endothelial adhesion molecules (VCAM1 and ICAM1)[88]	ND	• Insulin resistance (mice)[5] • Type 2 diabetes mellitus (mice)[80] • Rheumatoid arthritis[86] • Atherosclerosis[92] • Non-alcoholic fatty liver disease[118] • Chronic kidney disease[94]
Visfatin	ND	↑ IL-6 (REF. 119) ↑ IL-8 (REF. 119) ↓ Apoptosis of neutrophils[98]	ND	• Insulin resistance and type 2 diabetes mellitus[95] • Acute lung injury[97] • Sepsis[98]

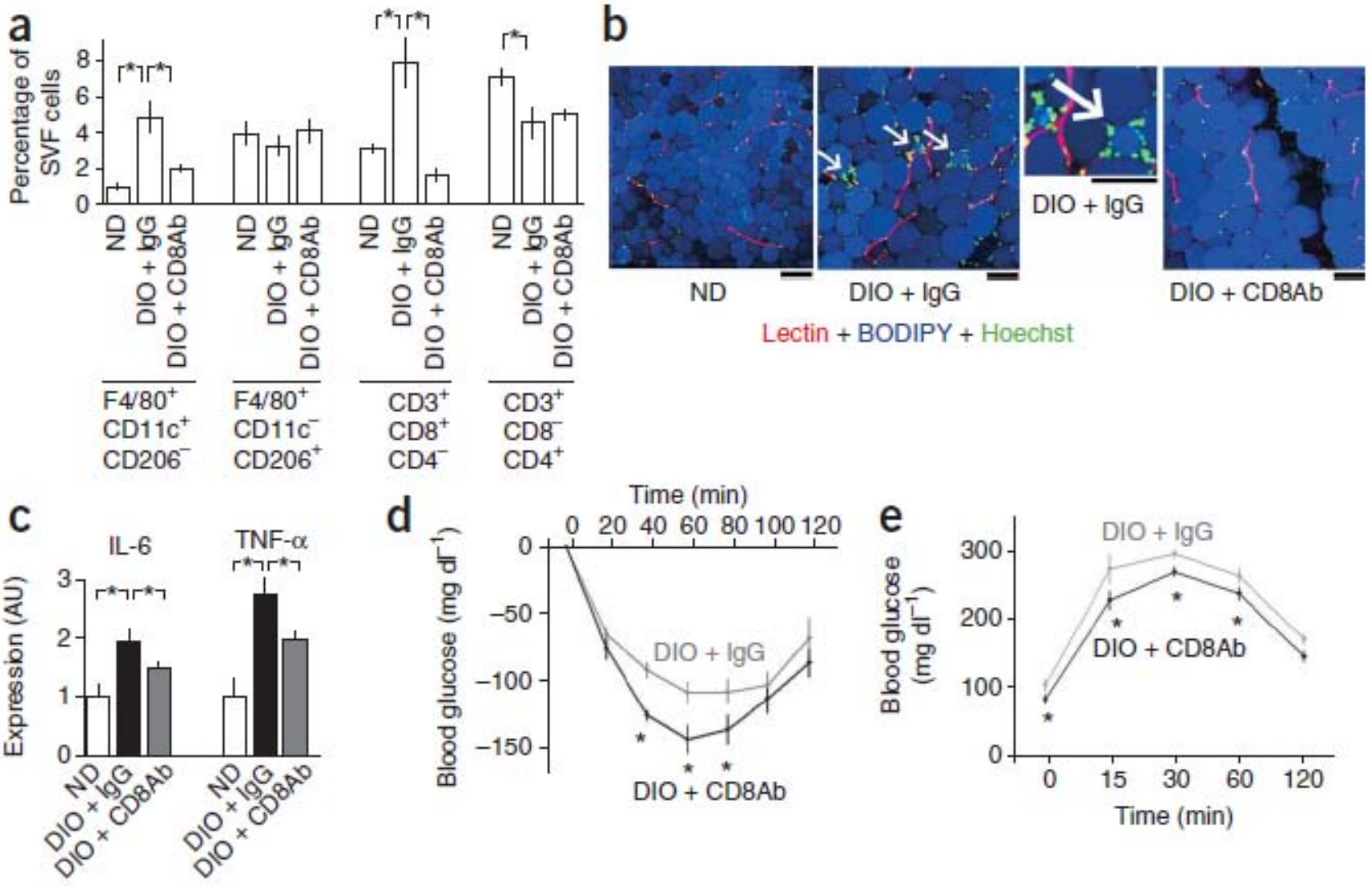
CCl_4, carbon tetrachloride; ConA, concanavalin A; CXCL, CXC-chemokine ligand; EAE, experimental autoimmune encephalomyelitis; ICAM, intercellular adhesion molecule; IFNγ, interferon-γ; IL, interleukin; IL-1RA, IL-1 receptor antagonist; LPS, lipopolysaccharide; ND, not determined; NF-κB, nuclear factor-κB; NK, natural killer; ROS, reactive oxygen species; T_H, T helper; TNF, tumour-necrosis factor; VCAM, vascular cell-adhesion molecule.

Tilg and Moschen, Nat. Rev. Immunol. 2006, 6, 772-783

Two views of the key drivers of insulin resistance

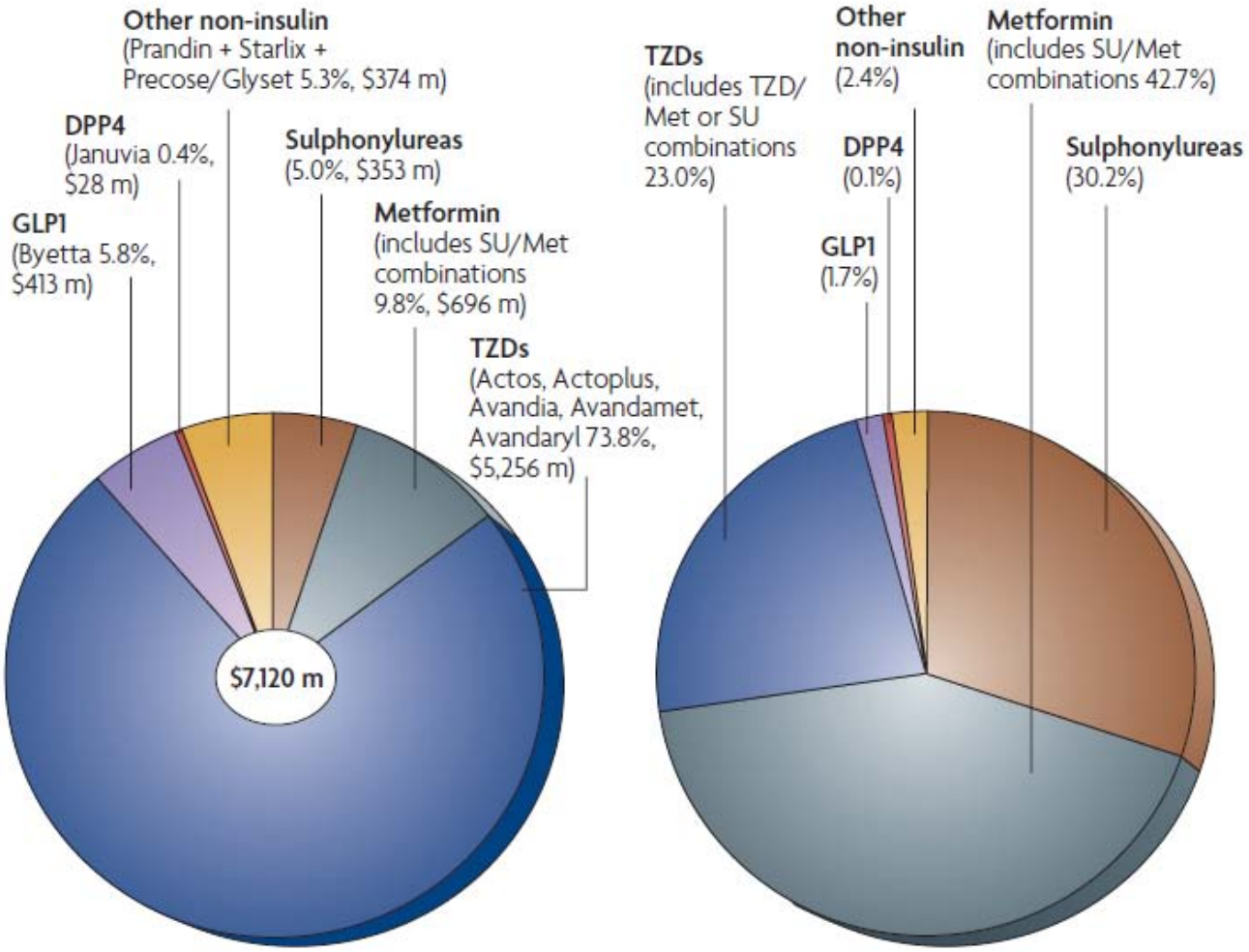
Image removed due to copyright restrictions. See schematic of two explanations for the mechanism of insulin resistance, from Taubes, G. "Insulin Resistance: Prosperity's Plague." *Science* 325, no. 5938 (July 17, 2009): 256-260. http://dx.doi.org/10.1126/science.325_256

What about the adaptive Immune Response?



Nishimura et al, Nature Medicine, 2009

Current Treatment Options



GLP1 = glucagon like peptide 1
DPP4 = dipeptidyl peptidase 4

Ashiya and Smith, Nat. Rev. Drug Disc. 2007

Thiazolidinediones (TZD's) for insulin resistance/diabetes

Troglitazone, Rosiglitazone, Pioglidazone

Mechanism:

- PPAR-g agonists activate/repress transcription of PPARg target genes
- Adiponectin increases, along with beneficial effects (anti-inflammatory)
- Leptin decreases (increased appetite)
- increased triglyceride storage
- Decreased synthesis of TNF-a, other pro-inflammatory signals (including MCP-1)

Benfits:

- Increased insulin sensitivity – decreased basal glucose and insulin levels

Downside

Weight gain – increased adiposity, increased TG storage with increased adiponectin
Coming off of TZD's typically not an option
Not a cure – more effective to stabilize disease

Metformin and AICAR for insulin resistance/diabetes

Metformin and AICAR activate AMPK, potentially through LKB1

Salicylates as a novel therapeutic option

Targets: Cyclooxygenase 1,2; IKKB - NFkB

Image removed due to copyright restrictions. See Figure 1 in Yuan, M., et al. "Reversal of Obesity- and Diet-Induced Insulin Resistance with Salicylates or Targeted Disruption of *Ikkß*." *Science* 293, no. 5535 (August 31, 2001): 1673-1677.

Yuan et al, SCIENCE, 2001

Salicylates as a novel therapeutic option

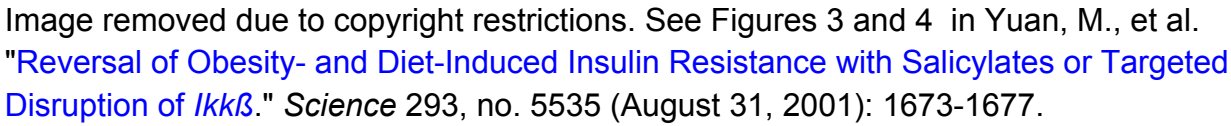
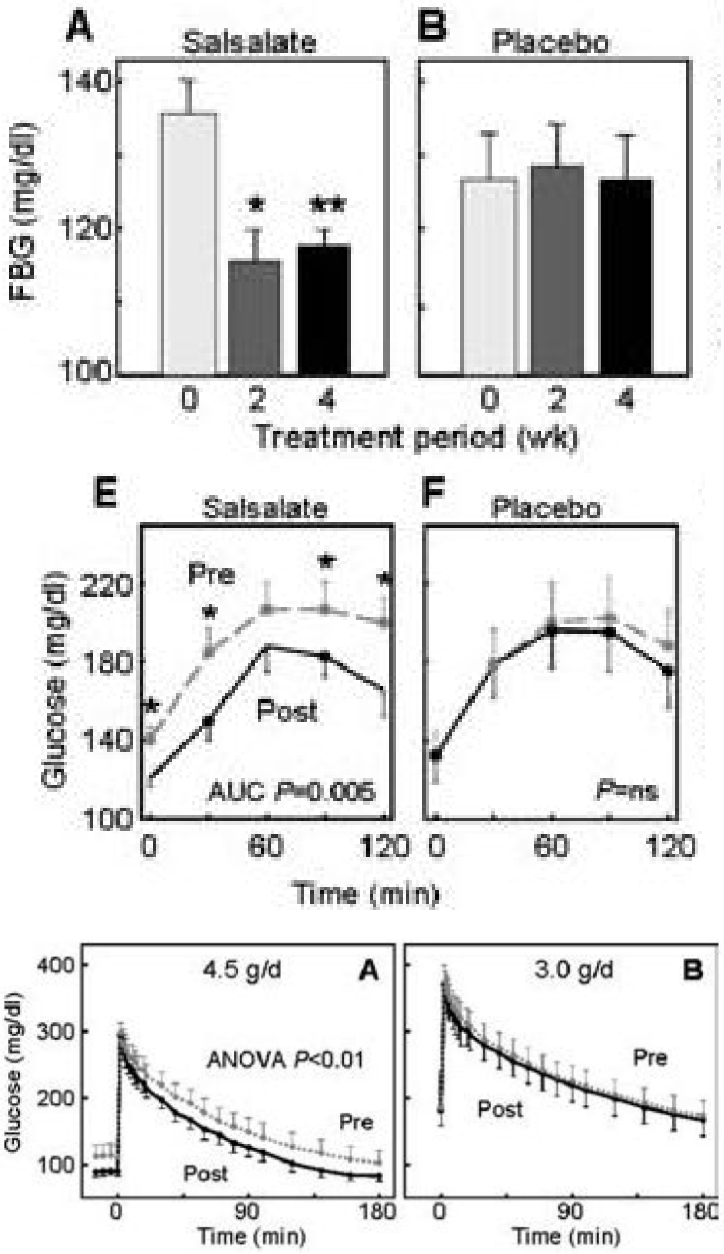
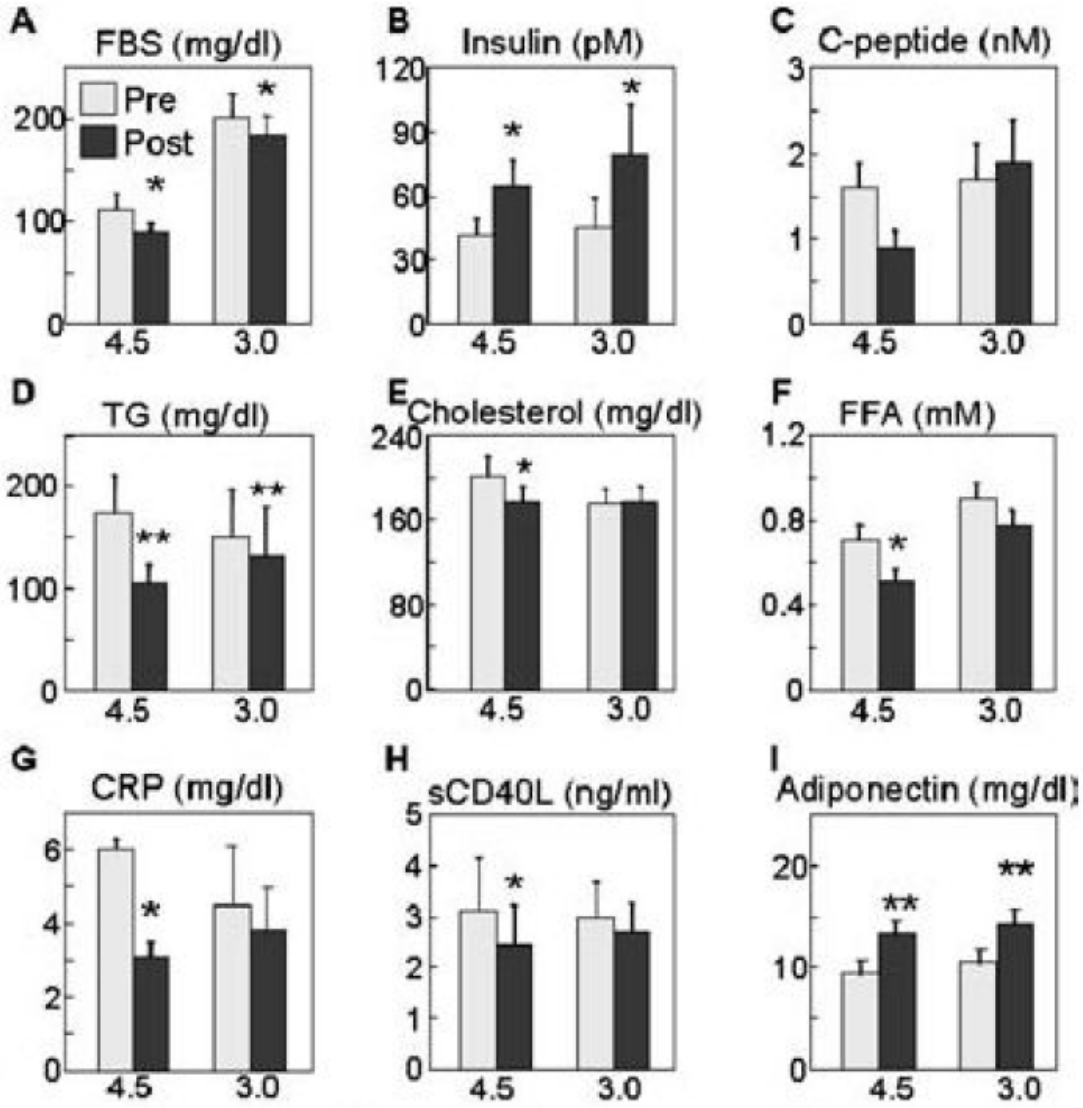


Image removed due to copyright restrictions. See Figures 3 and 4 in Yuan, M., et al. "Reversal of Obesity- and Diet-Induced Insulin Resistance with Salicylates or Targeted Disruption of *Ikkß*." *Science* 293, no. 5535 (August 31, 2001): 1673-1677.

Yuan et al, SCIENCE, 2001

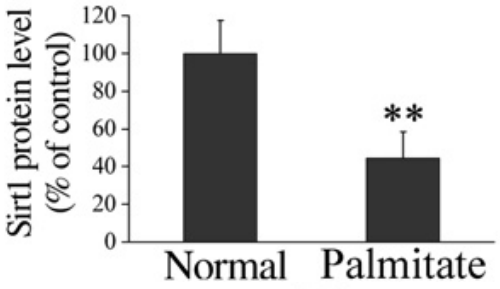
Salsalate as a therapeutic – clinical trial results

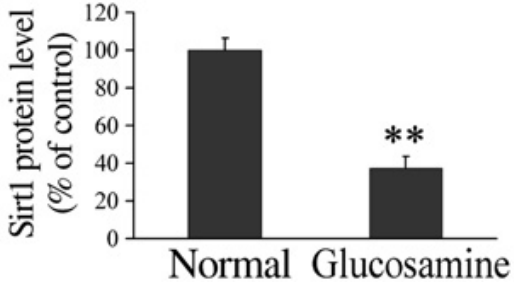


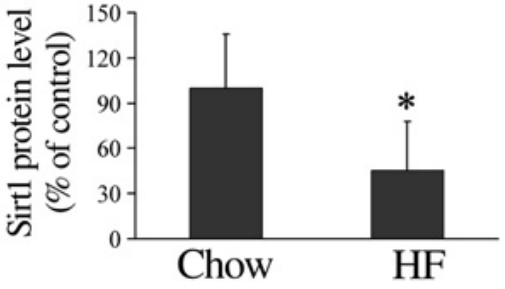


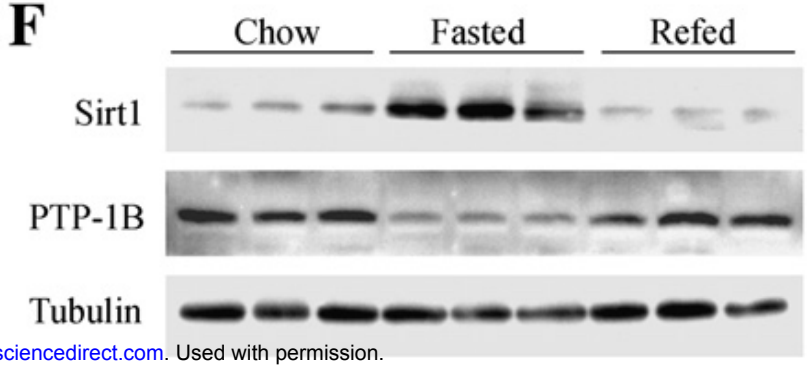
Goldfine et al, Clin. Transl. Sci, 2008

Resveratrol and Sirtuins as modulators of insulin signaling?

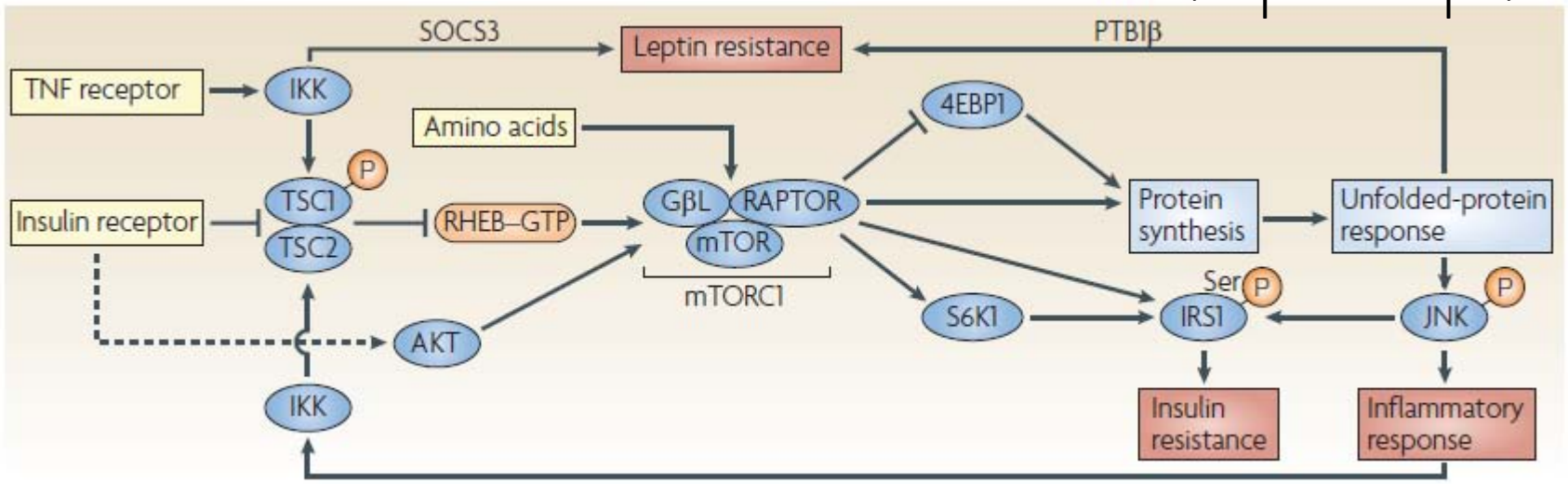






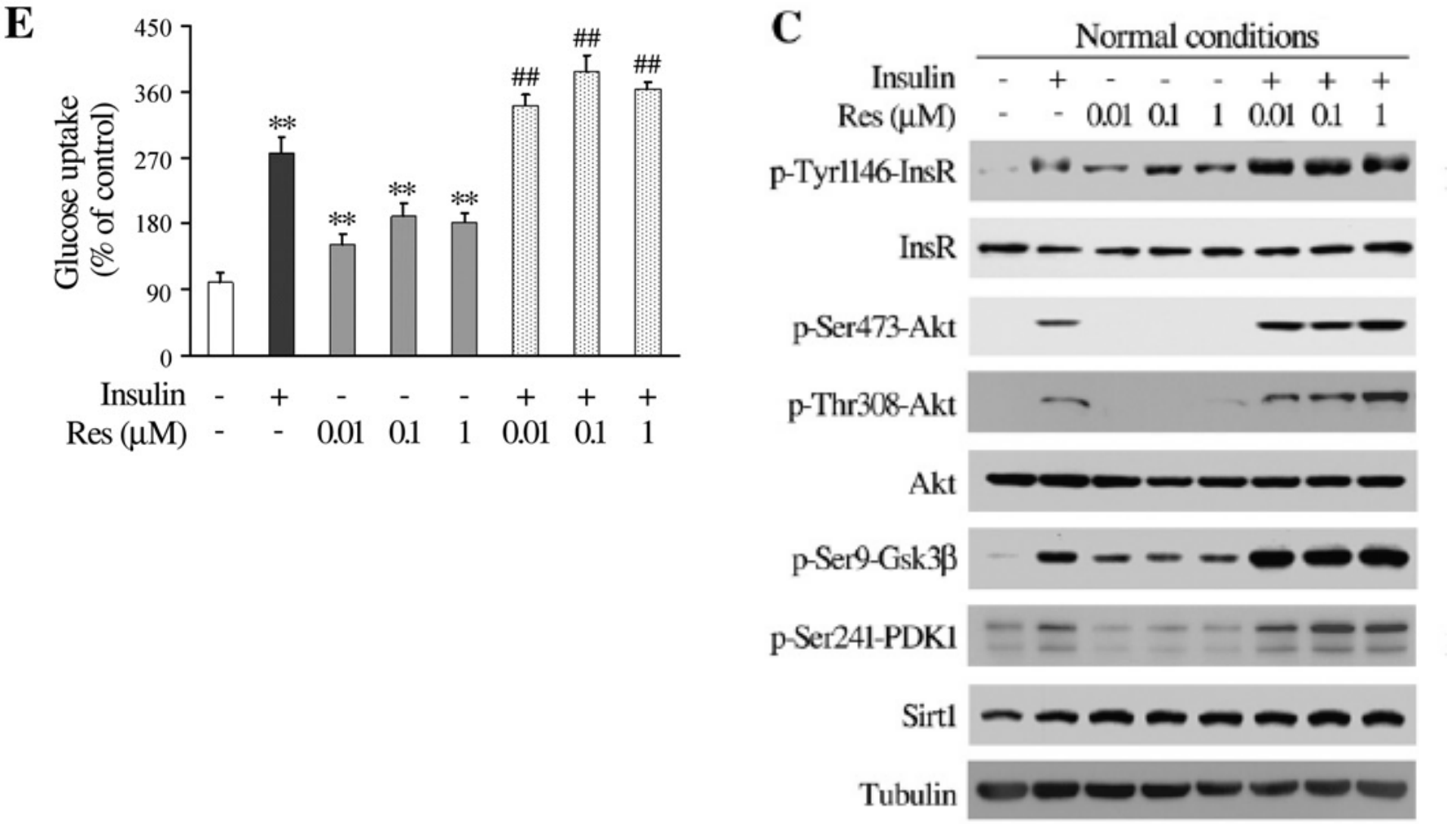


Sun et al, Cell Metabolism, 2007



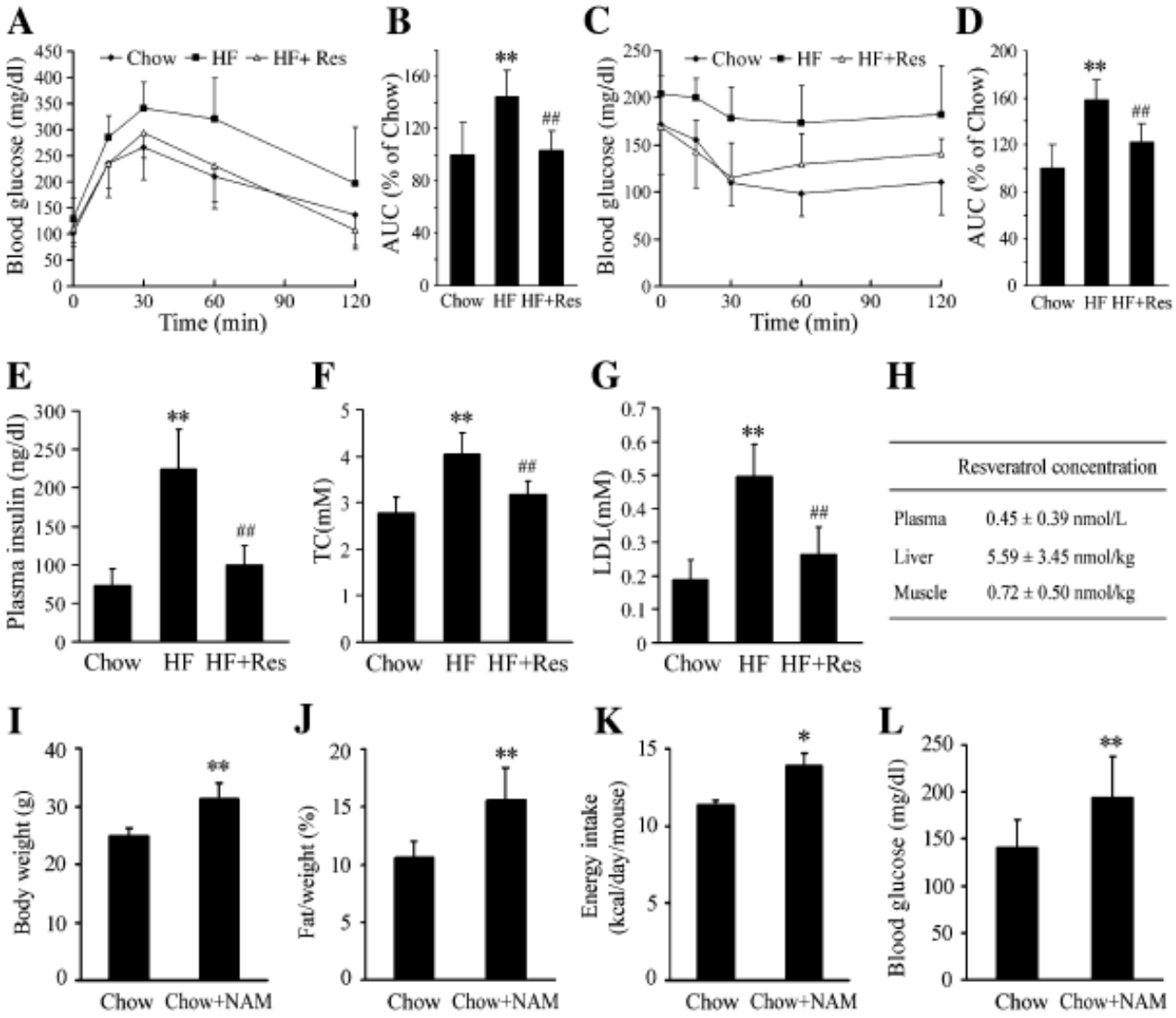
Hotamisligil and Erbay, Nat. Reviews Immunology, 2008

The multiple positive effects of red wine Resveratrol, a SIRT1 agonist



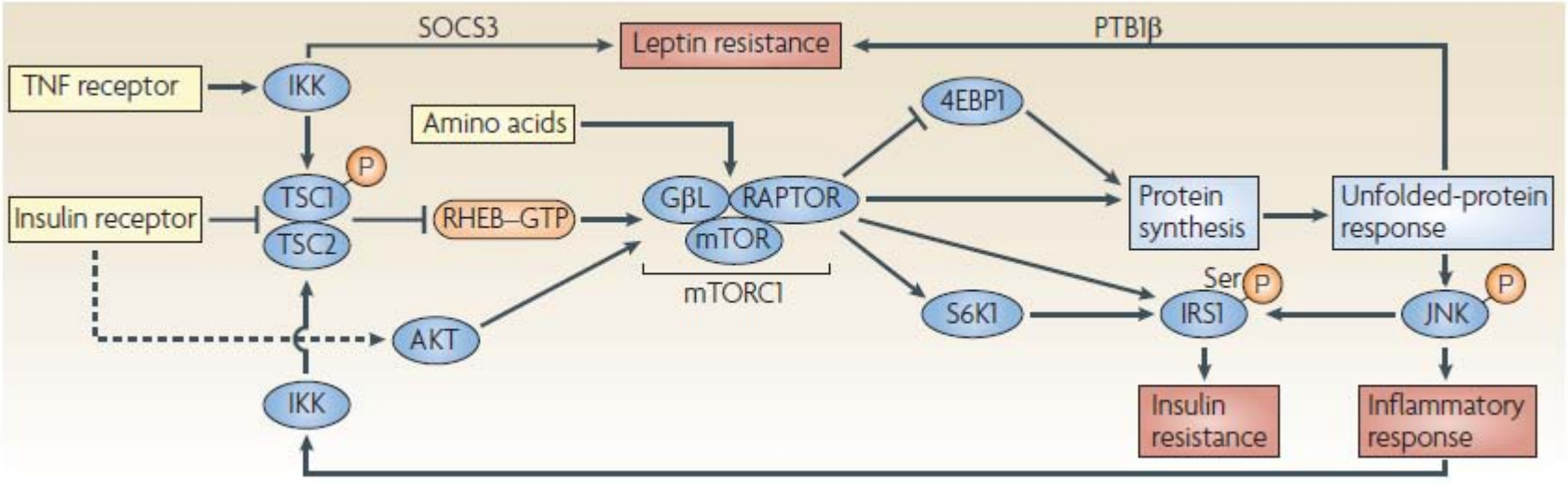
Sun et al, Cell Metabolism, 2007

The multiple positive effects of red wine Resveratrol, a SIRT1 agonist



Sun et al, Cell Metabolism, 2007

Targeting mTORC1 as an insulin sensitizer?



Hotamisligil and Erbay, Nat. Reviews Immunology, 2008

Rapamycin hits mTORC2 (Akt activation complex)

mTORC1 is one of the key nutrient sensors

Diet and exercise as the most effective therapeutic?

Exercise Effects

- Increased mitochondrial activity, increased B-oxidation of fatty acids
- Decreased ATP, increased AMP
- Increased AMPK activity
- Decreased blood glucose
- Decreased basal insulin levels
- Increased leptin and insulin sensitivity

Diet Effects

- Decreased food intake → decreased mTOR activation, decreased ER stress
- Less saturated fat → decreased JNK activation
- Smaller, leaner adipocytes → less macrophage recruitment, less inflammation
- Improved insulin and leptin response → decreased appetite

One very powerful strategy – targeting appetite through leptin or GLP-1 (or other gut hormones)

At the end, it all comes back to caloric intake

Insulin Resistance

Glucose

Insulin

Pancreas

Liver

Gluconeogenesis

Increased Glucose

Muscle

Glucose Uptake

Increased Glucose

Adipocytes

Glucose Uptake

Increased Glucose

Burger and fries photo courtesy of stu_spivack on Flickr.
Pancreas and liver images from US HHS. Muscle and adipocyte images by MIT OpenCourseWare.

20.380J / 5.22J Biological Engineering Design

Spring 2010