Inflamación, resistencia insulínica y DM-obesidad

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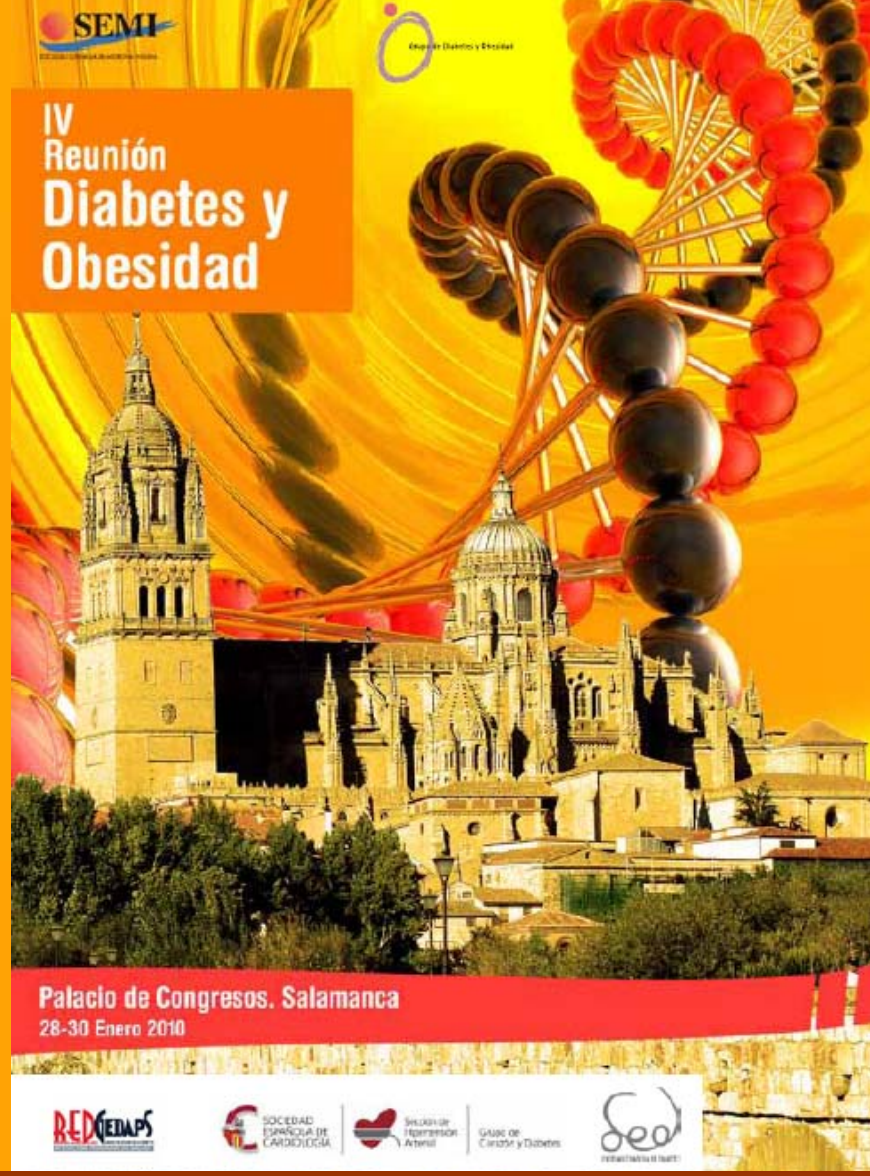


ciberobn
Centro de Investigación Biomédica En Red
Fisiopatología de la Obesidad y Nutrición

MESA REDONDA: Nuevas hipótesis patogénicas de la DM tipo 2 y de la obesidad

Salamanca, 29 Enero 2010

ESQUEMA GENERAL

Evidencia epidemiológica y genética

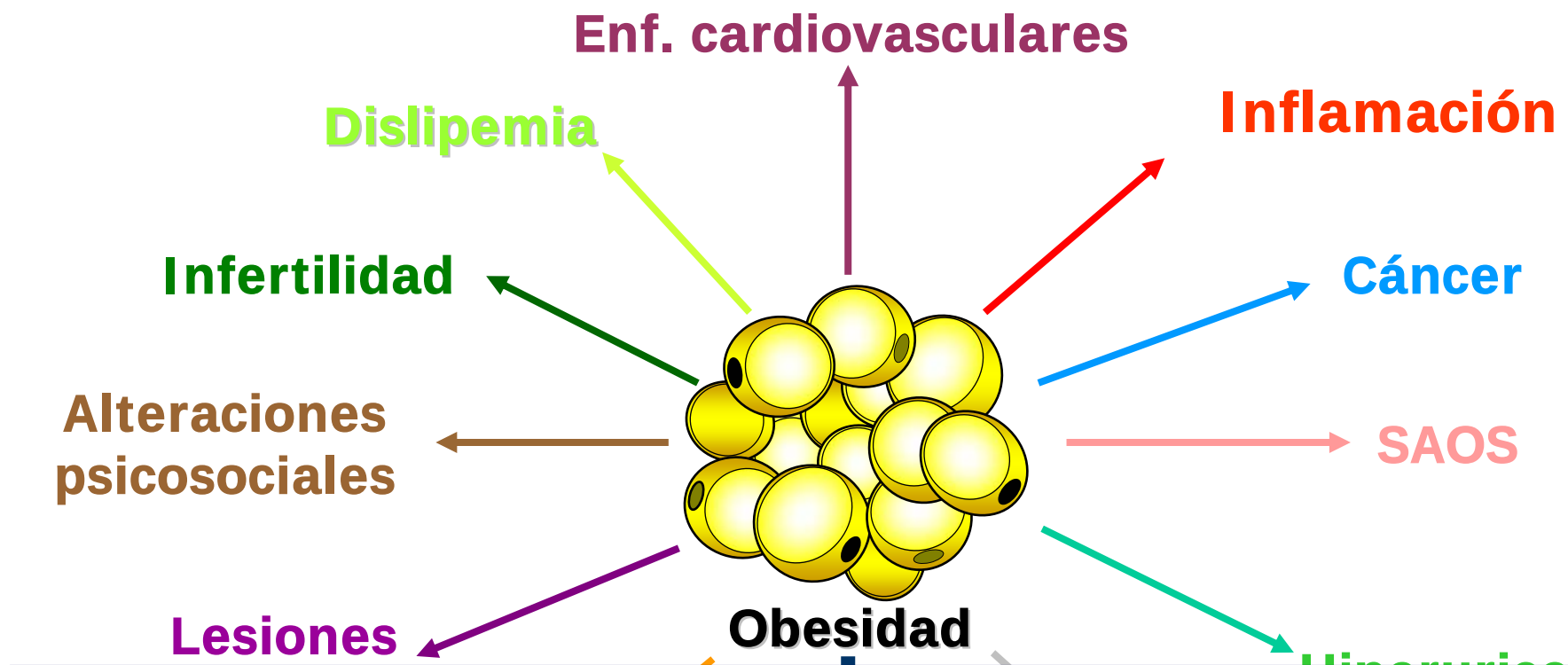
Características generales del tejido adiposo

Adipoquinas, insulino-resistencia e inflamación

Vías relacionadas con el metabolismo lipídico

Genes de respuesta a hipoxia

Nuevos hallazgos - implicaciones



Variable	Total (N = 195 005)	Body Mass Index: Normal (n = 84 469)	Overweight (n = 70 231)	Obese, Class 2 (n = 35 767)	Obese, Class 3 (n = 4538)
Diabetes					
Yes, % (SE)	7.9 (0.11)	4.1 (0.12)	7.3 (0.18)	14.9 (0.70)	25.6 (1.16)
Age adjusted		1.00	1.59 (1.47-1.72)	3.66 (3.38-3.96)	8.51 (7.41-9.78)
Fully adjusted		1.00	1.59 (1.46-1.73)	3.44 (3.17-3.74)	7.37 (6.39-8.50)

Insulino-resistencia
Diabetes tipo 2

Mokdad et al, *JAMA* 2003

Genetic variants associated with T2DM at or near genome-wide levels of statistical significance

Marker	Chromosome	Locus	Type of mutation	Function of gene	Risk allele	Odds ratio
rs10923931[36]	1	*NOTCH2*	Intronic	Transmembrane receptor involved in the formation of the pancreas	T	1.13
rs7578597[36]	2	*THADA*	Missense: Thr1187Ala	Expressed in thyroid adenomas; binds to PPARγ	T	1.15
rs4607103[36]	3	*ADAMTS9*	38 kb upstream	Secreted metalloproteinase expressed in muscles and pancreas	C	1.09
rs4402960[83]	3	*IGF2BP2*	Intronic	Growth factor binding protein involved in pancreatic development	T	1.14
rs1801282[84]	3	*PPARG*	Missense: Pro12Ala	Transcription factor involved in adipocyte development	C	1.19
rs10010131[83]	4	*WFS1*	Intron–exon junction	Transmembrane protein of the endoplasmic reticulum	G	1.15
rs7754840[83]	6	*CDKAL1*	Intronic	Islet glucose toxicity sensor; inhibits CDK5 activation	C	1.12
rs864745[36]	7	*JAZF1*	Intronic	Transcriptional repressor associated with prostate cancer	T	1.10
rs13266634[83]	8	*SLC30A8*	Missense: Arg325Trp	Zinc transporter involved in insulin storage and secretion	C	1.12
rs10811661[83]	9	*CDKN2A/B*	125 kb upstream	Cyclin-dependent kinase inhibitor and tumor suppressor involved in islet development	T	1.20
rs12779790[36]	10	*CDC123-CAMK1D*	Intergenic region	Cell-cycle regulator and protein kinase	G	1.11
rs7903146[13]	10	*TCF7L2*	Intronic	Transcription factor that regulates genes that encode proglucagon and insulin	T	1.37
rs1111875[83]	10	*HHEX*	7.7 kb downstream	Transcription factor involved in pancreatic development	C	1.13
rs5219[9]	11	*KCNJ11*	Missense: Glu23Lys	Potassium channel that regulates insulin secretion	T	1.14
rs2237892[38]	11	*KCNQ1*	Intronic	Pore-forming α subunit of potassium channel	C	1.42
rs1387153[44]	11	*MTNR1B*	28.3 kb upstream	High-affinity, G-protein-coupled receptor for melatonin	T	1.15
rs7961581[36]	12	*TSPAN8-LGR5*	Intronic	Cell-surface glycoprotein implicated in gastrointestinal tumors	C	1.09
rs8050136[83]	16	*FTO*	Intronic	Function unknown; affects BMI in general population	A	1.17
rs757210[83]	17	*HNF1B*	Intronic	Transcription factor involved in pancreatic development	A	1.12

[a]$P < 5 \times 10^{-8}$. Abbreviation: T2DM, type 2 diabetes mellitus.

Stolerman & Florez (2009)
Genomics of type 2 diabetes mellitus: implications for the clinician

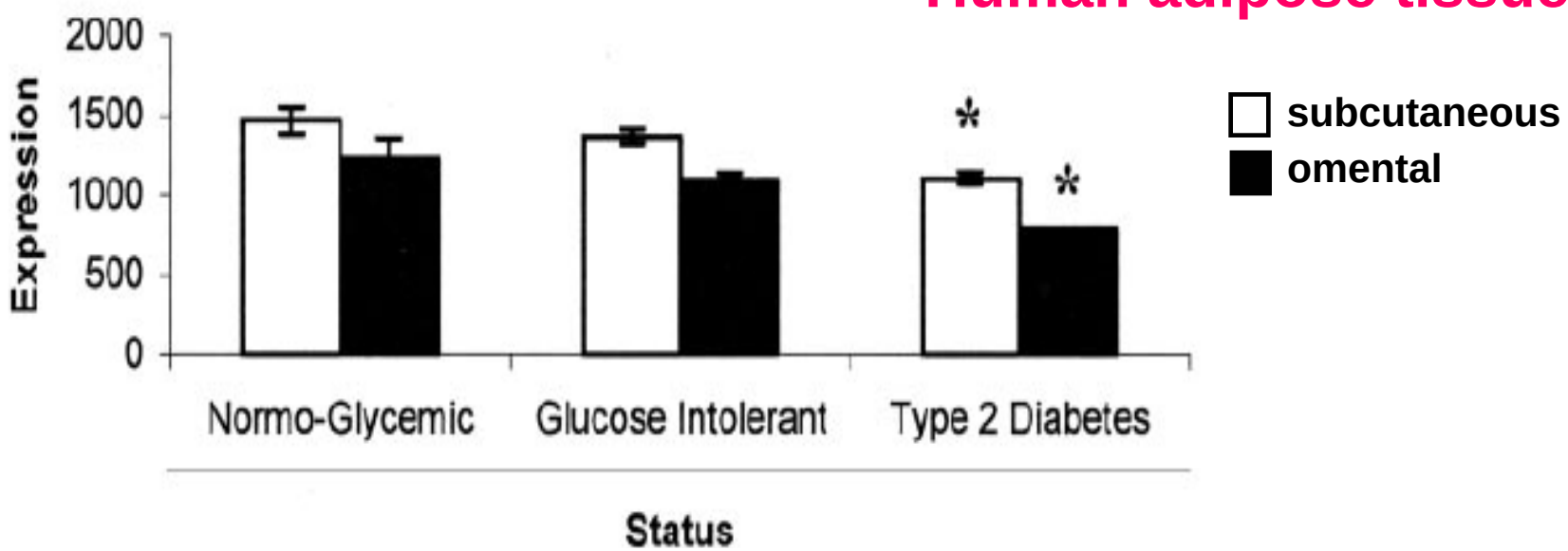
nature REVIEWS ENDOCRINOLOGY

Transcription Factor *TCF7L2* Genetic Study in the French Population

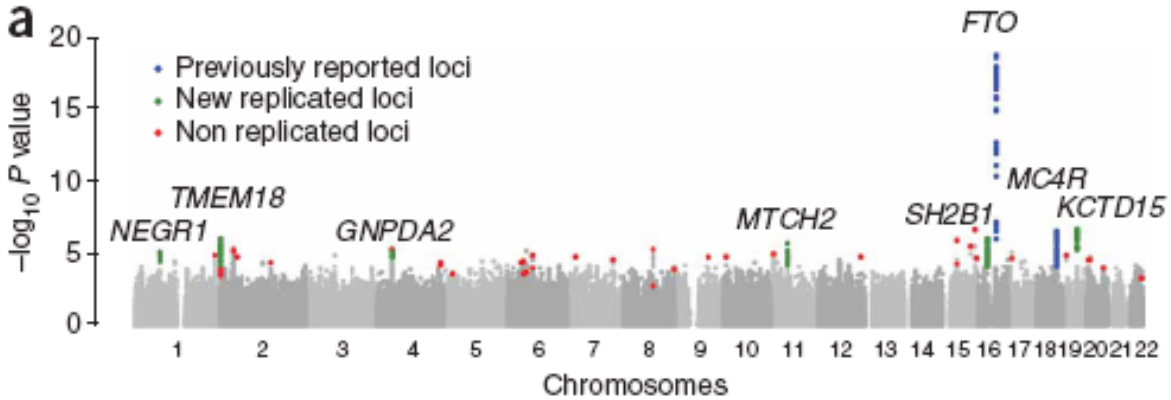
Expression in Human β-Cells and Adipose Tissue and Strong Association With Type 2 Diabetes

Stéphane Cauchi,[1] David Meyre,[1] Christian Dina,[1] Hélène Choquet,[1] Chantal Samson,[1] Sophie Gallina,[1] Beverley Balkau,[2] Guillaume Charpentier,[3] François Pattou,[4] Volodymyr Stetsyuk,[5] Raphaël Scharfmann,[5] Bart Staels,[6,7,8] Gema Frühbeck,[9] and Philippe Froguel[1,10]

Human adipose tissue



Six new loci associated with body mass index highlight a neuronal influence on body weight regulation



nature genetics

Jan 2009

The FTO obesity gene

Genotyping and gene expression analysis in morbidly obese patients

- Mayor expresión RNAm de *FTO* en tejido adiposo subcutáneo pacientes obesos mórbidos frente a controles
- Correlaciones de expresión de *FTO* subcutánea:
  - * NEGATVA con triglicéridos séricos
  - * POSITIVA con expresión de:
    - leptina
    - perilipina
    - visfatina
- Expresión de *FTO* y perilipina con depósito de grasa visceral

Zabena et al. Obes Surg 2009 (Jan)

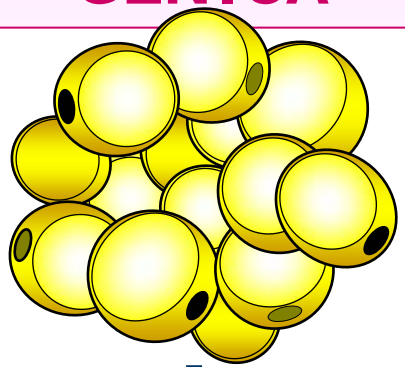
nature genetics

New genetic loci implicated in fasting glucose homeostasis and their impact on type 2 diabetes risk

Levels of circulating glucose are tightly regulated. To identify new loci influencing glycemic traits, we performed meta-analyses of 21 genome-wide association studies informative for fasting glucose, fasting insulin and indices of beta-cell function (HOMA-B) and insulin resistance (HOMA-IR) in up to 46,186 nondiabetic participants. Follow-up of 25 loci in up to 76,558 additional subjects identified 16 loci associated with fasting glucose and HOMA-B and two loci associated with fasting insulin and HOMA-IR. These include nine loci newly associated with fasting glucose (in or near *ADCY5*, *MADD*, *ADRA2A*, *CRY2*, *FADS1*, *GLIS3*, *SLC2A2*, *PROX1* and *C2CD4B*) and one influencing fasting insulin and HOMA-IR (near *IGF1*). We also demonstrated association of *ADCY5*, *PROX1*, *GCK*, *GCKR* and *DGKB-TMEM195* with type 2 diabetes. Within these loci, likely biological candidate genes influence signal transduction, cell proliferation, development, glucose-sensing and circadian regulation. Our results demonstrate that genetic studies of glycemic traits can identify type 2 diabetes risk loci, as well as loci containing gene variants that are associated with a modest elevation in glucose levels but are not associated with overt diabetes.

Expresión génica en tejido adiposo

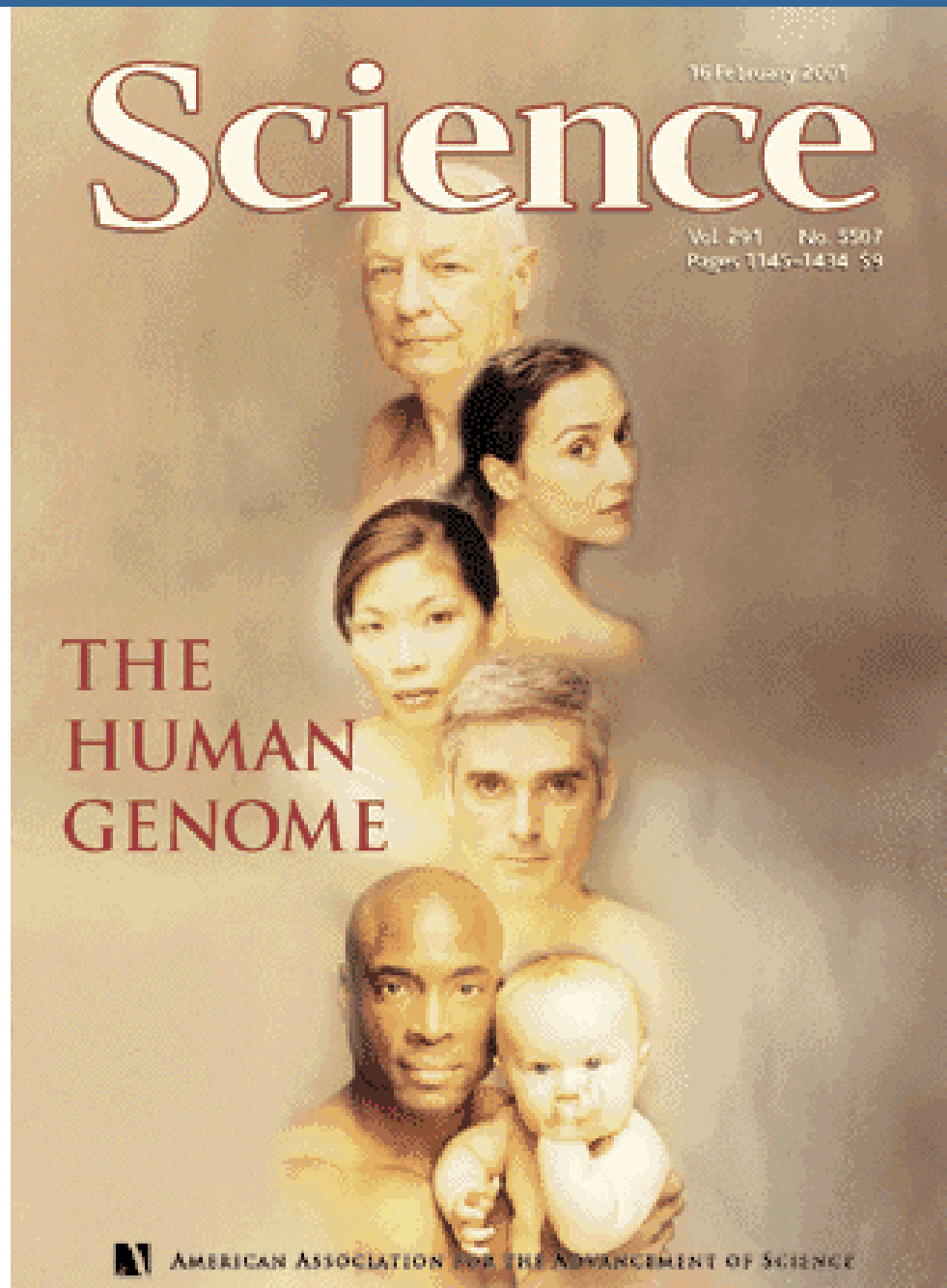
PERFIL DE EXPRESIÓN GÉNICA



Mecanismos de regulación

Rutas bioquímicas

Insulino-resistencia
Diabetes tipo 2

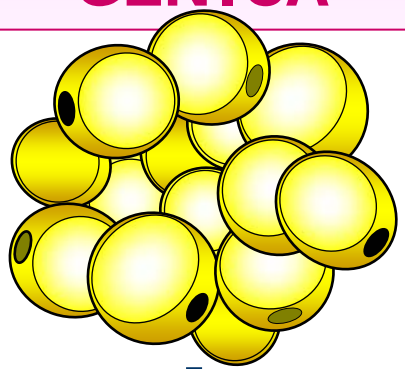


Expresión génica en tejido adiposo

Análisis a gran escala

- Depósitos grasos
- Tipos celulares
- Grado de diferenciación
- Animales *wt* vs *KO*
- Efectos de tratamientos, cirugía, ejercicio físico

PERFIL DE EXPRESIÓN GÉNICA



Mecanismos de regulación

Rutas bioquímicas

Señalización de la insulina

Vías ore- y anorexigénicas

Lipolisis

Adipogénesis

Transporte y almacén ácidos grasos

Inflamación

Metabolismo de la glucosa

Proliferación y diferenciación

Angiogénesis

Insulino-resistencia
Diabetes tipo 2

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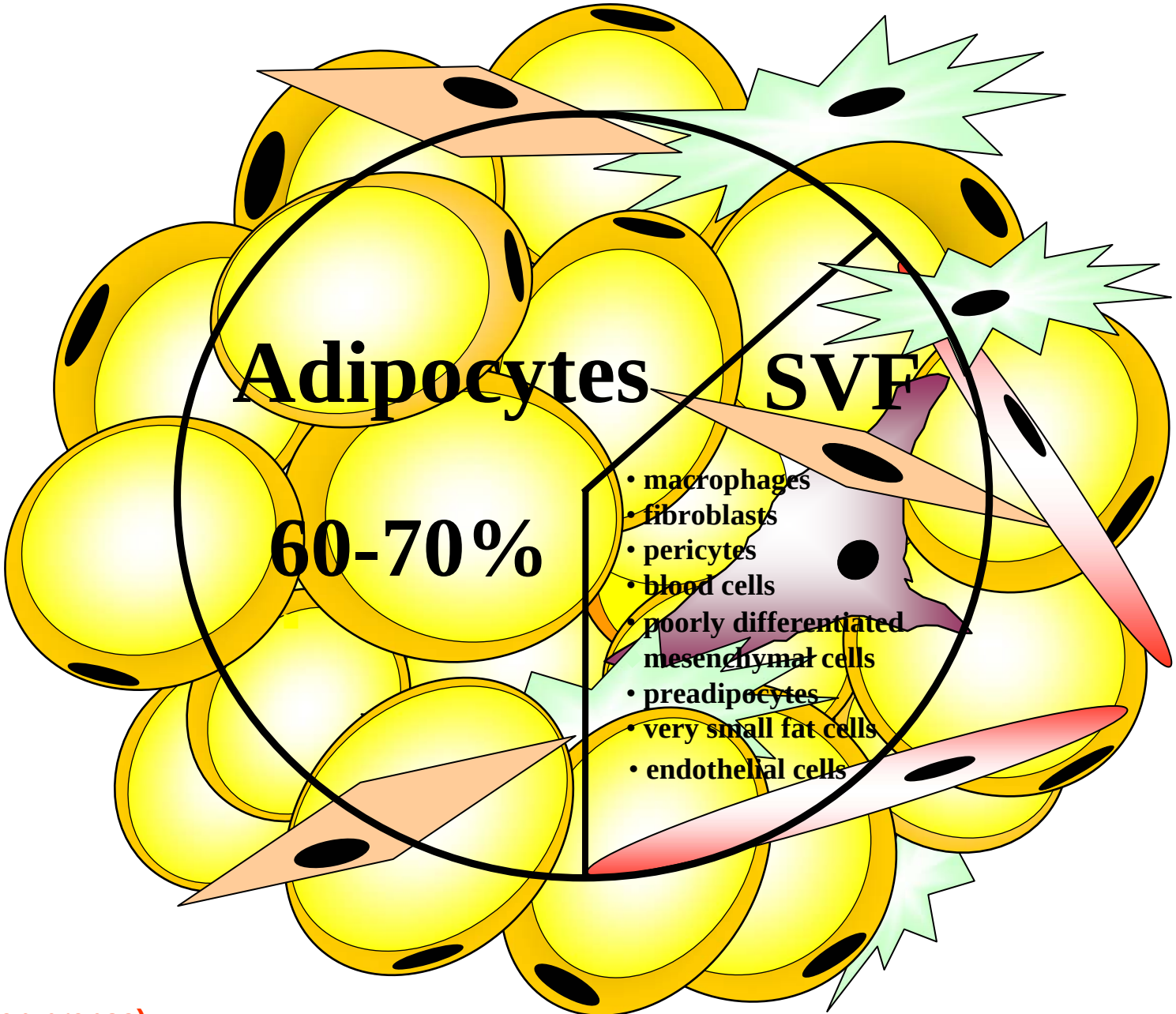
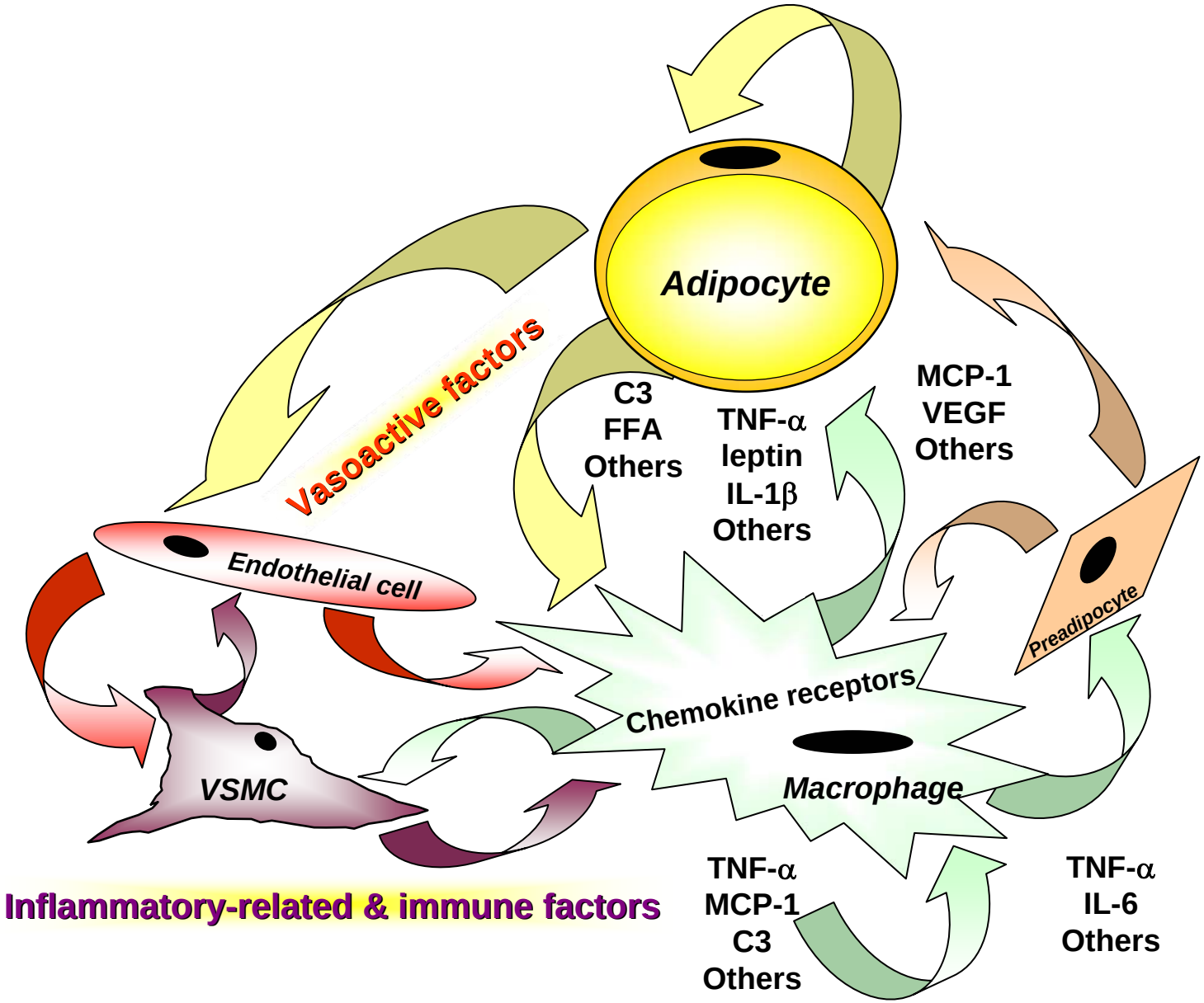
MULTICELULARIDAD DEL TEJIDO ADIPOSO

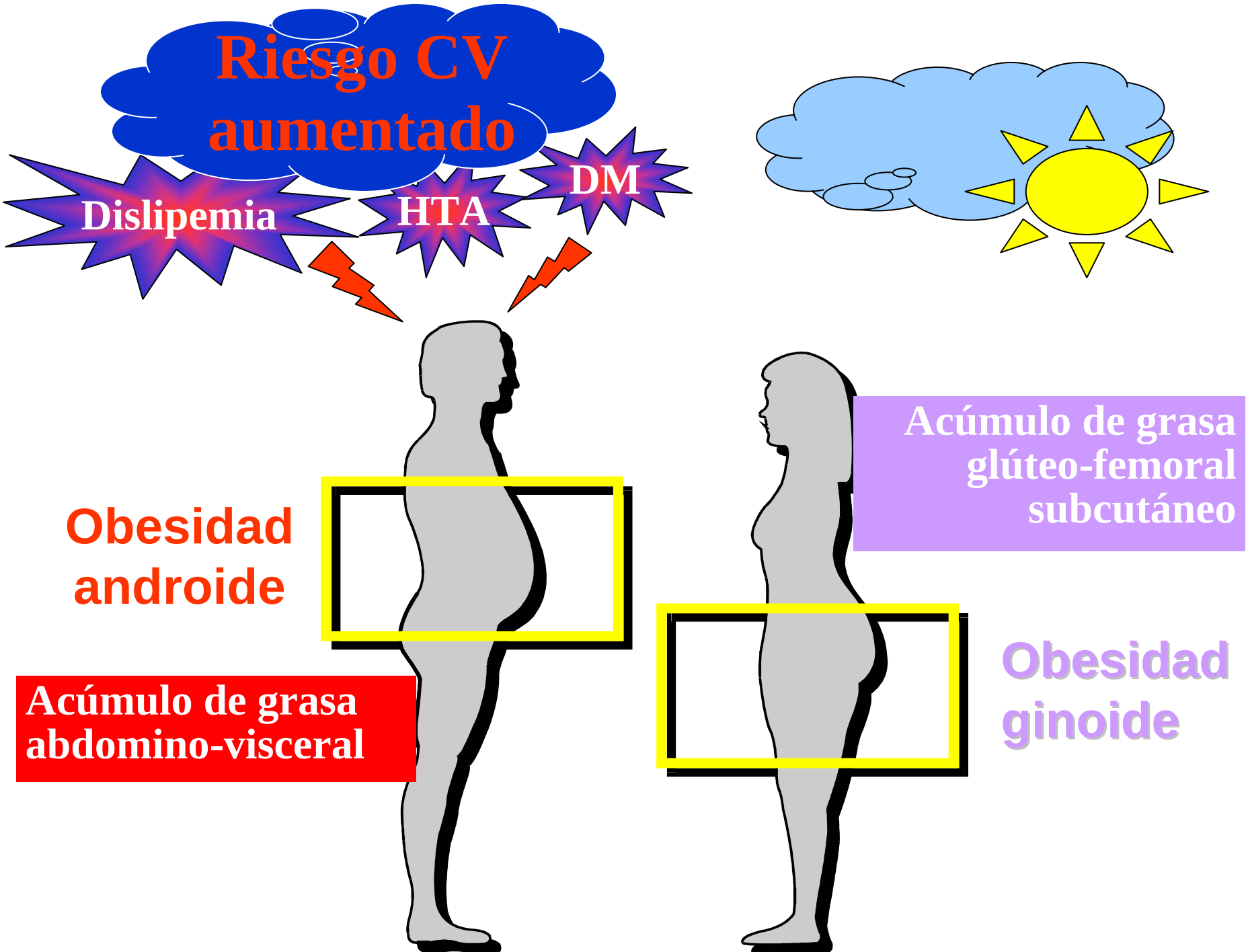


Frühbeck (en prensa)

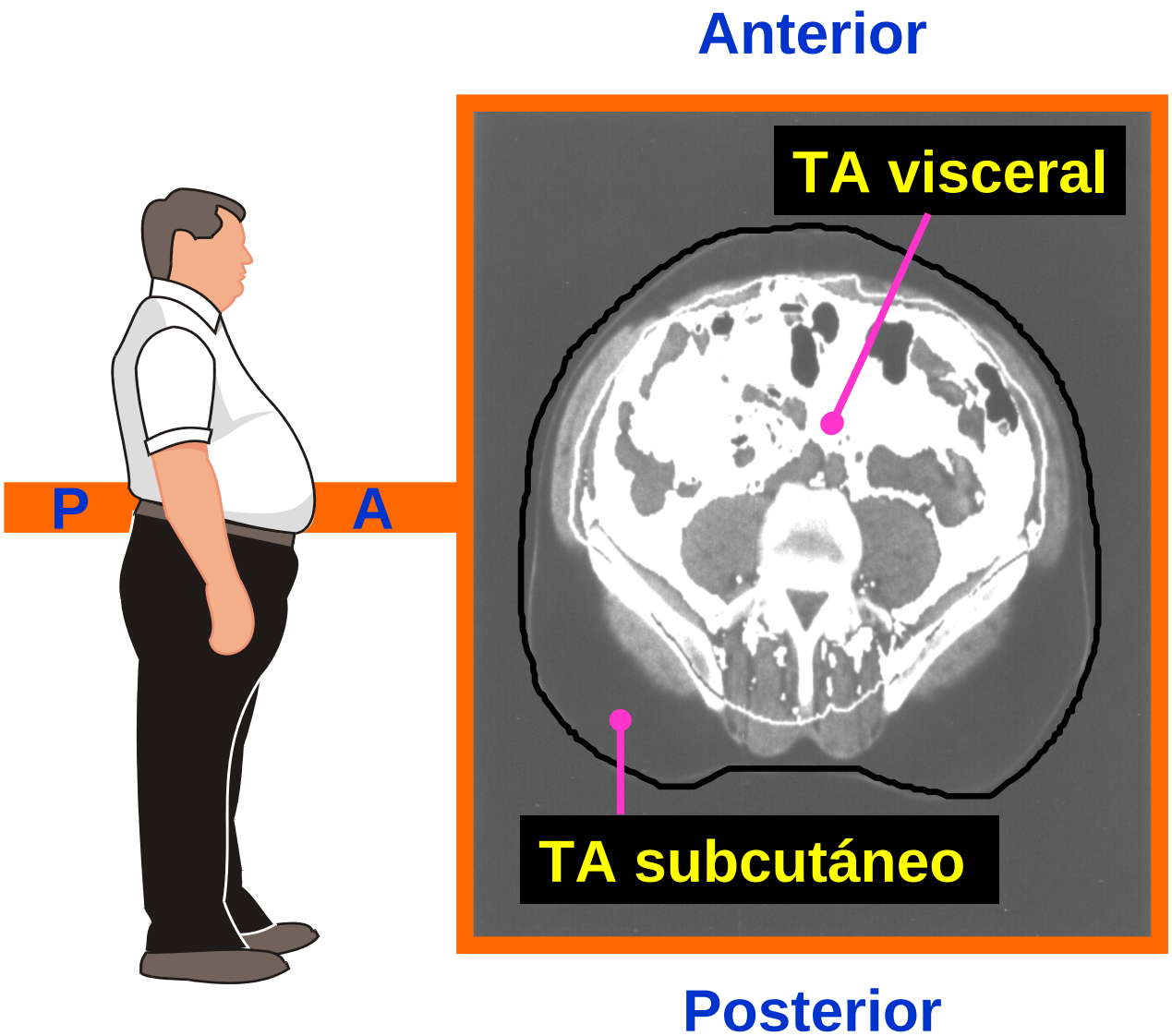
“CROSS-TALK” AUTOCRINO / PARACRINO



Frühbeck (en prensa)


Riesgo CV aumentado
Dislipemia
HTA
DM
Obesidad androide
Acúmulo de grasa abdomino-visceral
Acúmulo de grasa glúteo-femoral subcutáneo
Obesidad ginoide

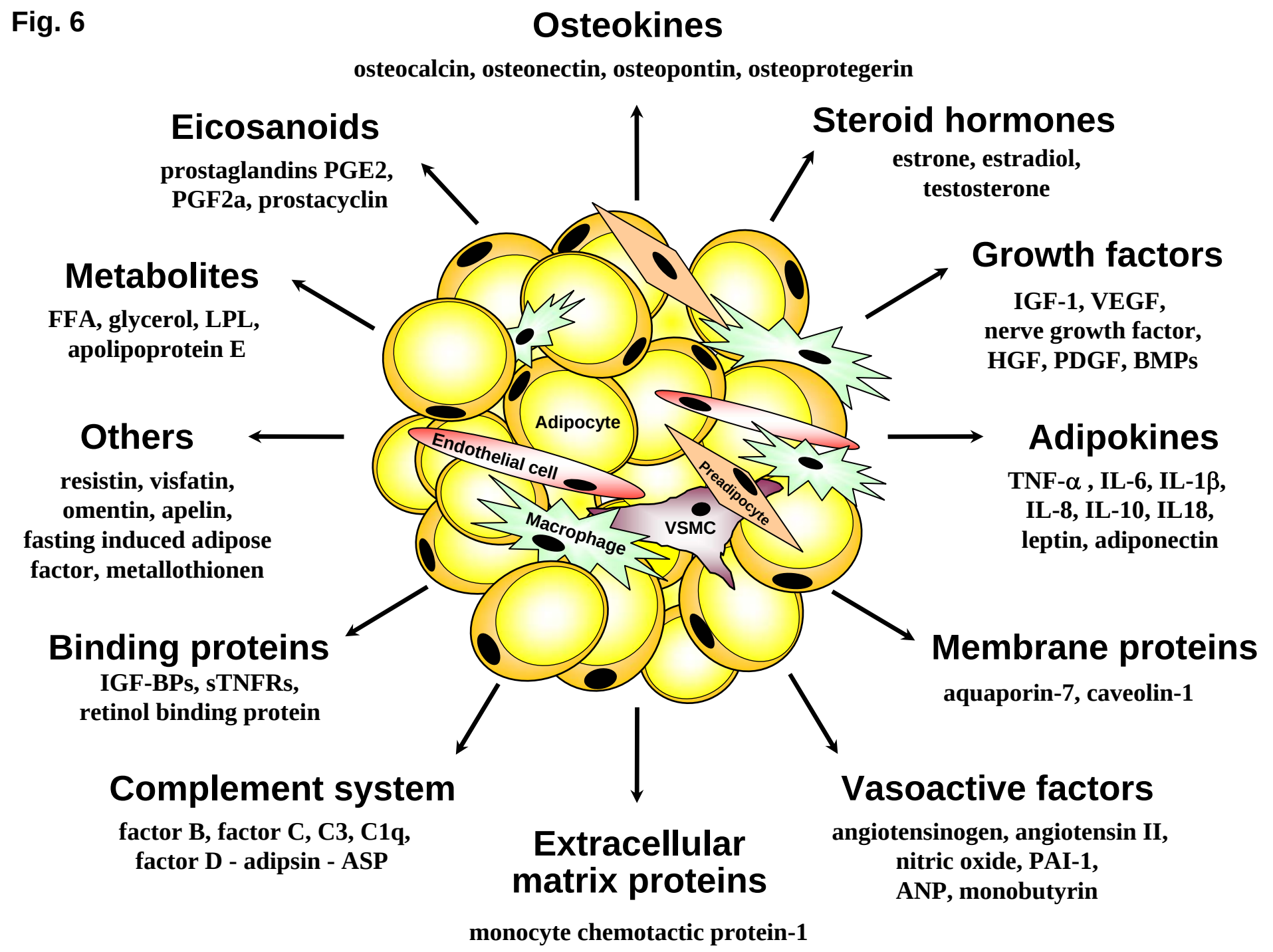
Tejido adiposo visceral



Características diferenciales

- tamaño y nº de adipocitos
- inerv. + vasc.
- drenaje portal
- activ. metab.
- perfil secretor

Fig. 6


Osteokines
osteocalcin, osteonectin, osteopontin, osteoprotegerin
Eicosanoids
prostaglandins PGE2, PGF2a, prostacyclin
Steroid hormones
estrone, estradiol, testosterone
Metabolites
FFA, glycerol, LPL, apolipoprotein E
Growth factors
IGF-1, VEGF, nerve growth factor, HGF, PDGF, BMPs
Others
resistin, visfatin, omentin, apelin, fasting induced adipose factor, metallothionen
Adipokines
TNF-α , IL-6, IL-1β, IL-8, IL-10, IL18, leptin, adiponectin
Adipocyte
Endothelial cell
Preadipocyte
Macrophage
VSMC
Binding proteins
IGF-BPs, sTNFRs, retinol binding protein
Membrane proteins
aquaporin-7, caveolin-1
Complement system
factor B, factor C, C3, C1q, factor D - adipsin - ASP
Extracellular matrix proteins
monocyte chemotactic protein-1
Vasoactive factors
angiotensinogen, angiotensin II, nitric oxide, PAI-1, ANP, monobutyrin

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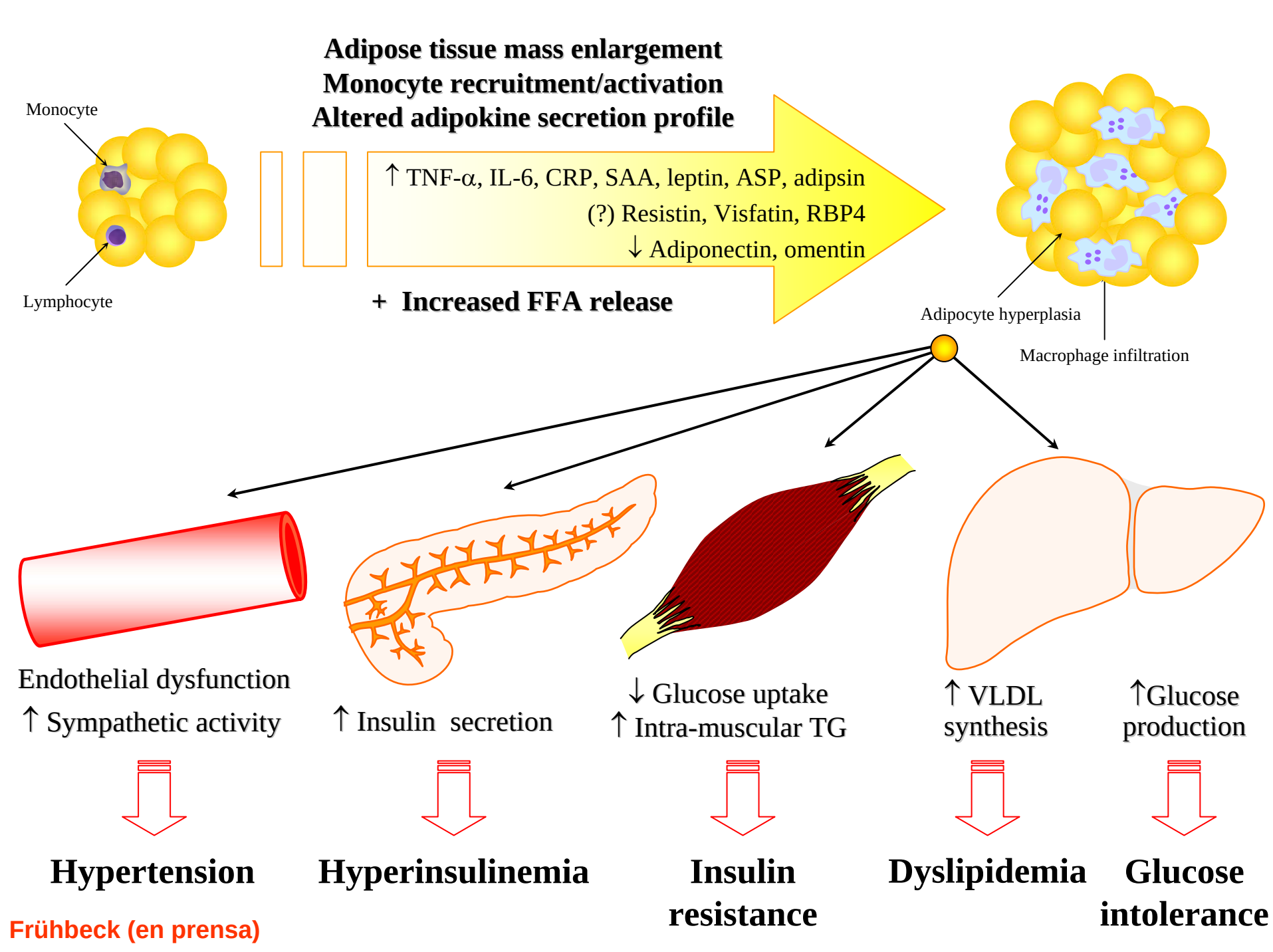


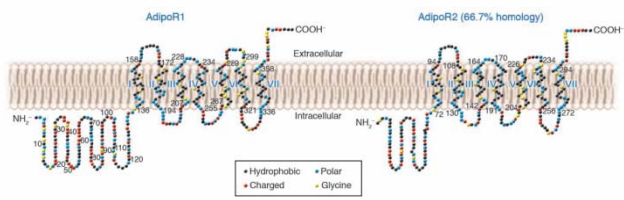
Frühbeck (en prensa)

Adiponectina

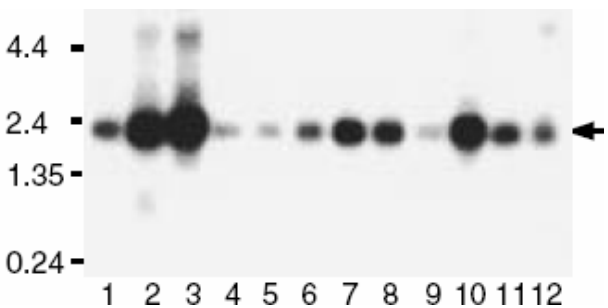
- ACRP30, AdipoQ, GBP28 o apM1
- 244 aa
- Expresada en adipocitos
- 0,01% proteínas plasmáticas
- Protectora frente T2DM y ECV

- Receptores AdipoR1 y AdipoR2

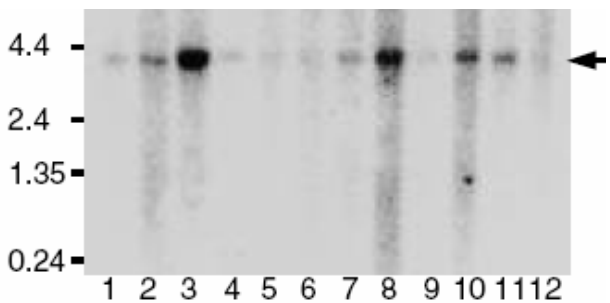
Yamauchi et al. *Nature* 2003



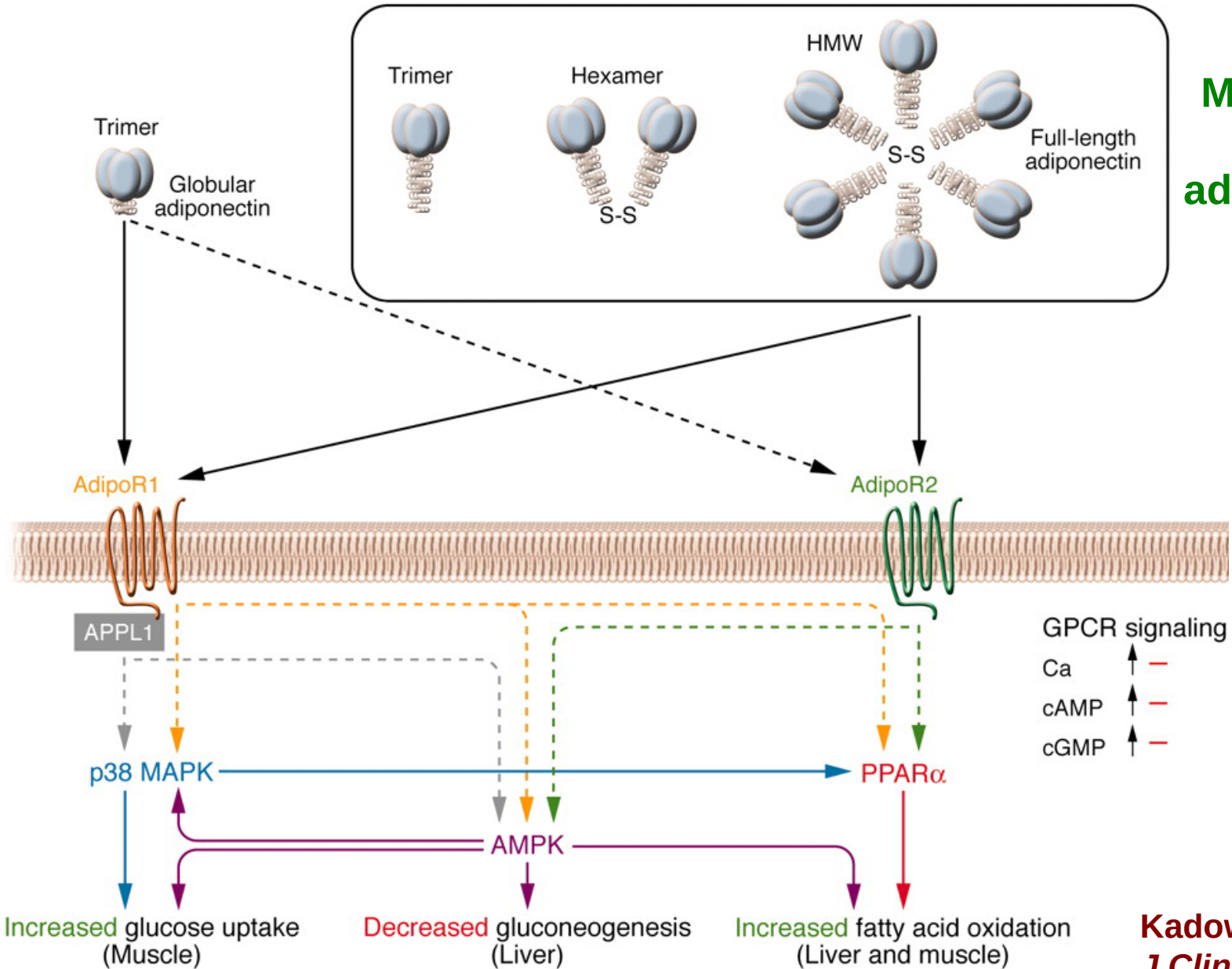
AdipoR1



AdipoR2



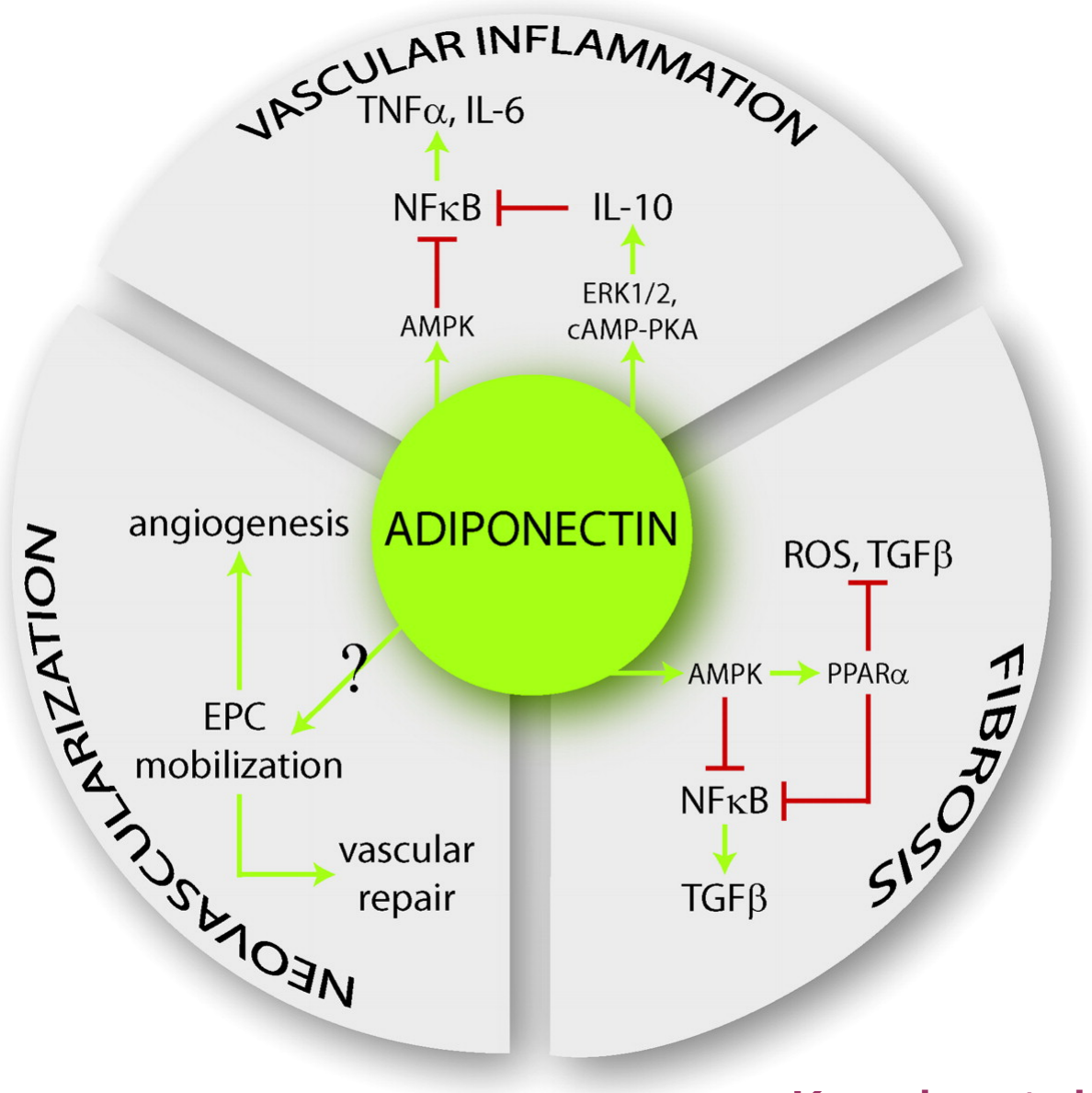
1. Cerebro
2. Corazón
3. Músculo
4. Colon
5. Timo
6. Bazo
7. Riñón
8. Hígado
9. Intestino delgado
10. Placenta
11. Pulmón
12. PBL



Multímeros de adiponectina

Kadowaki et al.
***J Clin Invest* 2006**

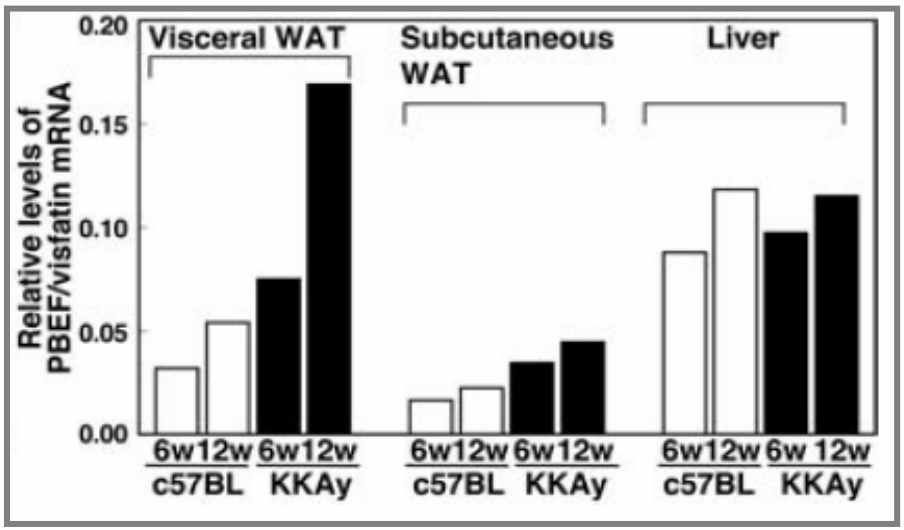
Adiponectina e inflamación



Krenning et al. *Circ Res* 2009

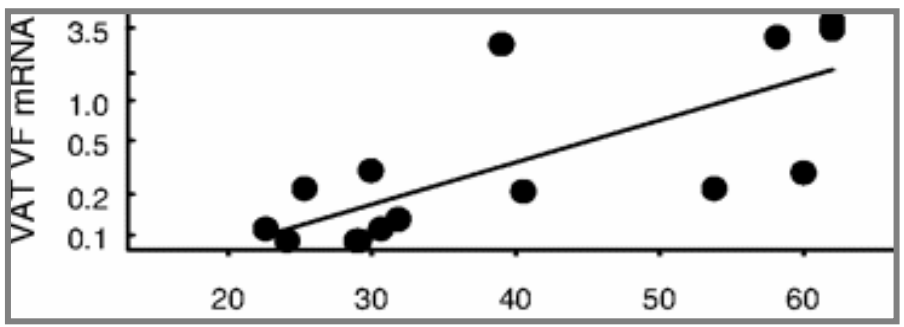
Expresión génica de nuevas adipoquinas inflamatorias

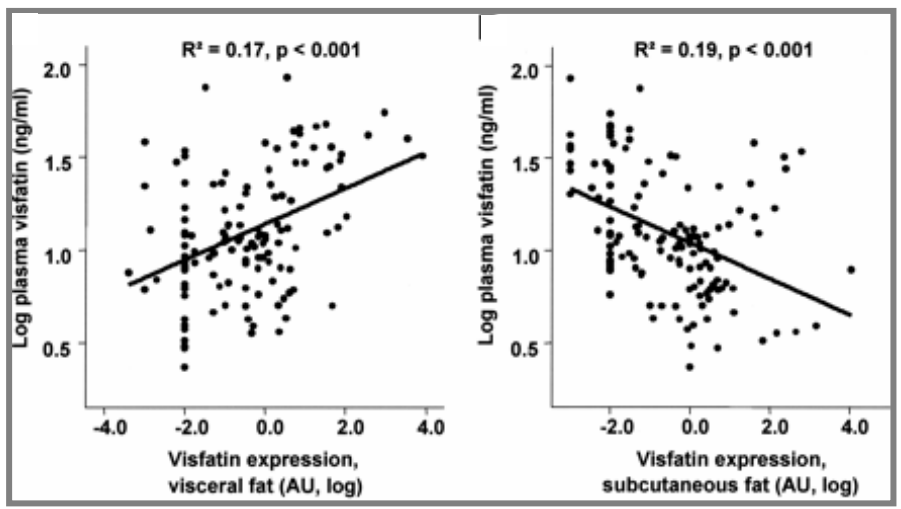
Visfatina



↑ Expresión de visfatina

- Ratones obesos y resistentes a insulina
- Pacientes obesos con diabetes tipo 2
- Correlación con IMC

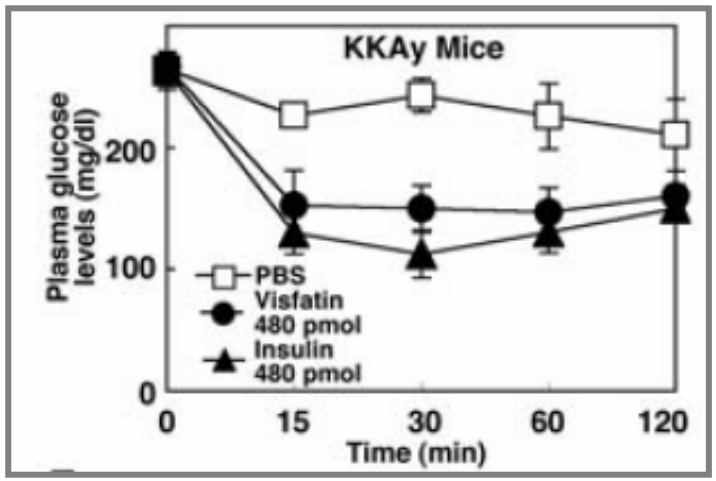


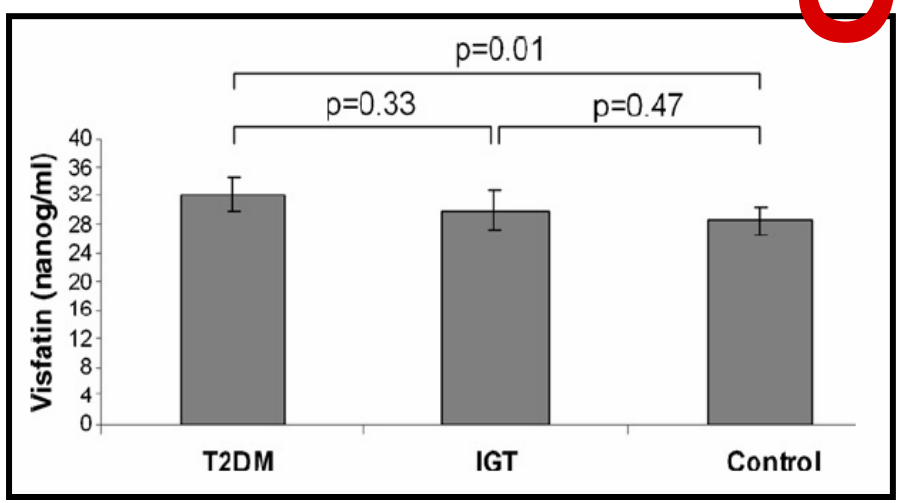


Expresión en visceral > Expresión en subcutáneo

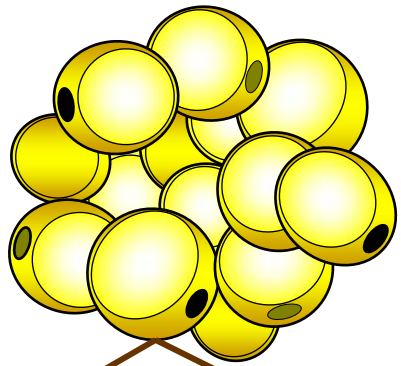
Fukuhara et al. *Science* 2005; Bernt et al. *Diabetes* 2005; Hammarstedt et al. *J Clin Endocrinol Metab*, 2006

Expresión génica de nuevas adipoquinas inflamatorias





Visfatina



Tejido adiposo visceral

Visfatina

¿ ?

Insulina

Receptor de insulina

P

P

MAPK

IRS1-IRS2

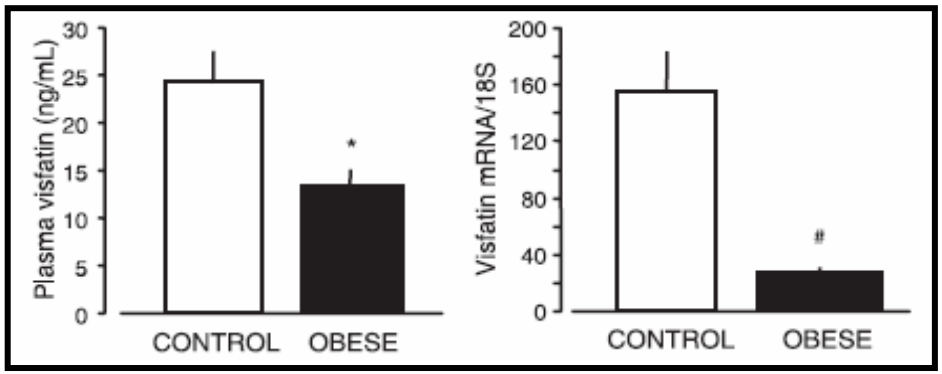
PI3K

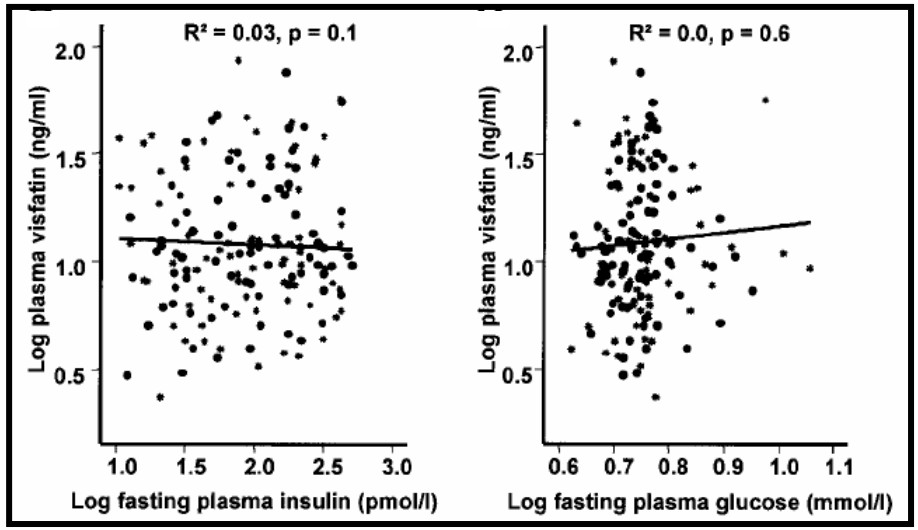
Akt

Murphy et al. *Nature Medicine* 2006; Dogru et al. *Diabetes Res Clin Prac* 2007; Filippatos et al. *J Endocrinol Invest* 2007; Haider et al. JPGN 2006; Filippatos et al. *Clin Endocrinol* 2008

Expresión génica de nuevas adipoquinas inflamatorias

Visfatina





Independent variable **HOMA**	B	SE	*P* value
BMI (kg/m^2)	−0.0109	0.0353	ns
Visfatin (ng/ml)	−0.0003	0.0114	ns
Waist circumference (cm)	0.0583	0.0171	0.001

Visfatin: A Protein Secreted by Visceral Fat That Mimics the Effects of Insulin

Atsunori Fukuhara,[1,2*] Morihiro Matsuda,[1*] Masako Nishizawa,[3*] Katsumori Segawa,[1] Masaki Tanaka,[1] Kae Kishimoto,[3] Yasushi Matsuki,[3] Mirei Murakami,[4]

RETRACTION. Fukuhara *Science* 2007

Berndt et al. *Diabetes* 2005; Pagano et al. *J Clin Endocrinol Metab* 2006; Ingelson et al. *Diabetes Care* 2007

Expresión génica de nuevas adipoquinas inflamatorias

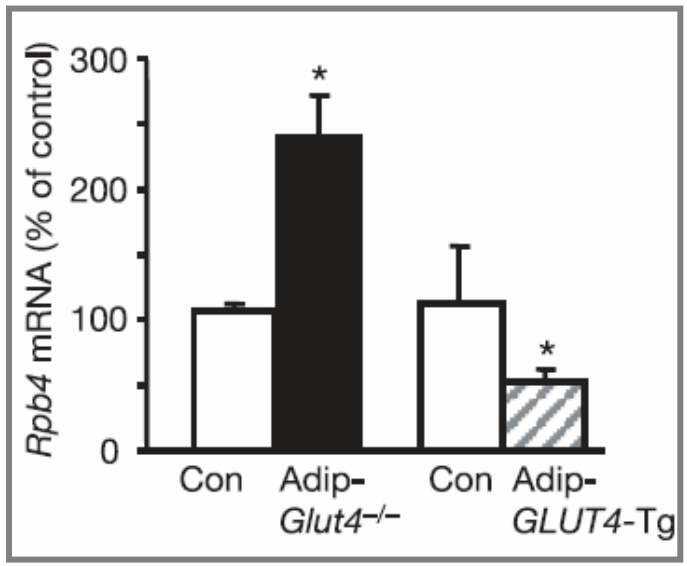
GLUT4

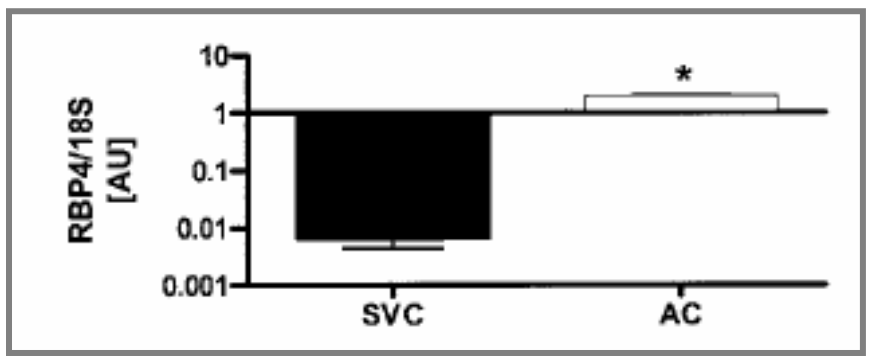
RBP4

KO GLUT4

Flujo normal de glucosa

↓↓ Flujo de glucosa

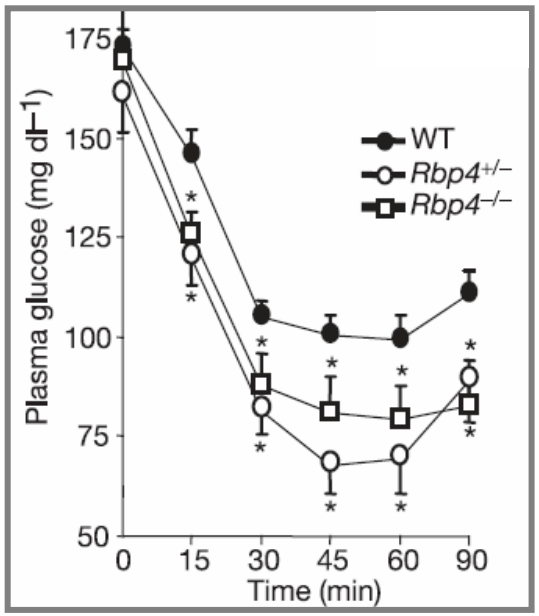


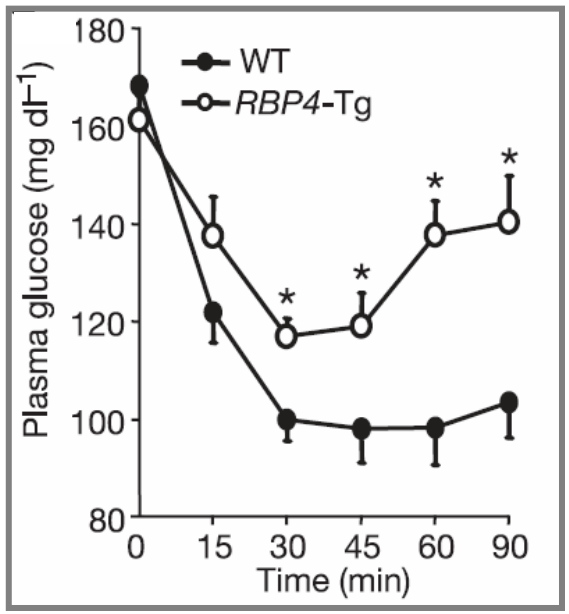


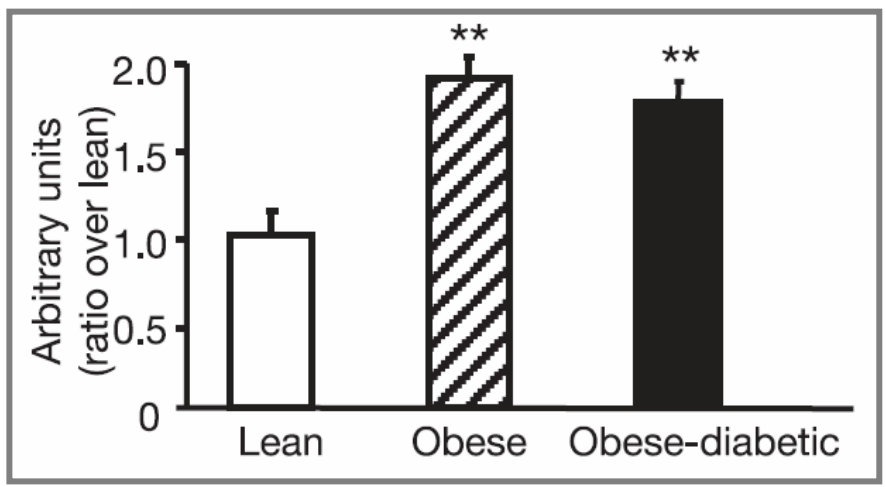
Yang et al. *Nature* 2005; Tamori et al. *Nature Medicine* 2006; Janke et al. *Diabetes* 2006

Expresión génica de nuevas adipoquinas inflamatorias

RBP4



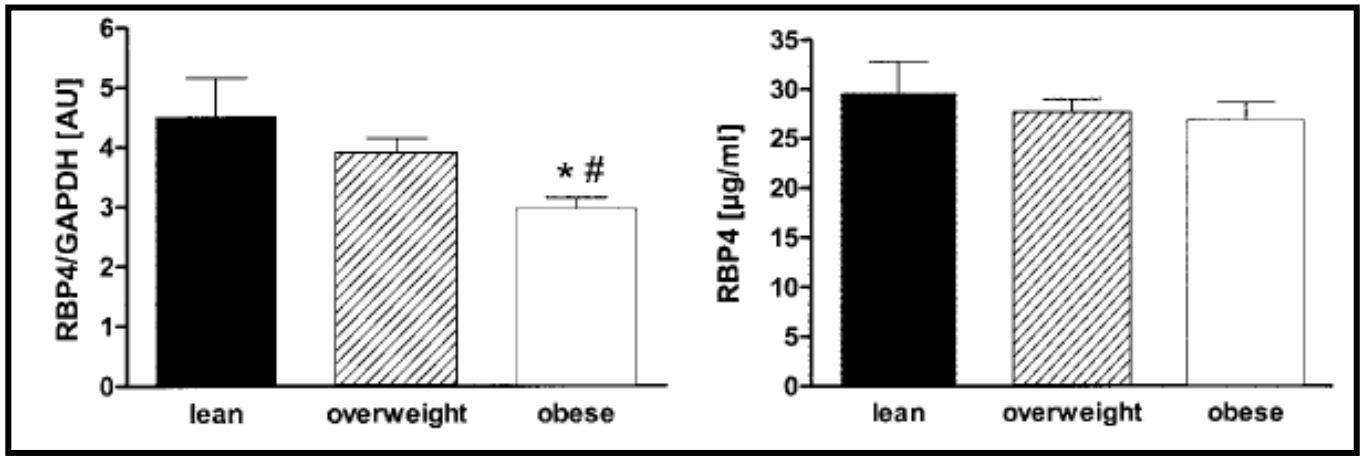


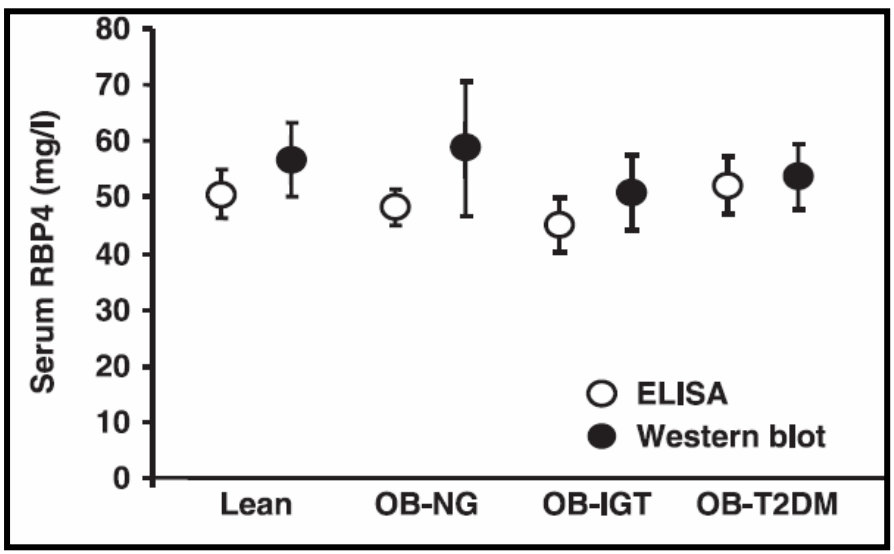


Yang et al. *Nature* 2005

Expresión génica de nuevas adipoquinas inflamatorias

RBP4





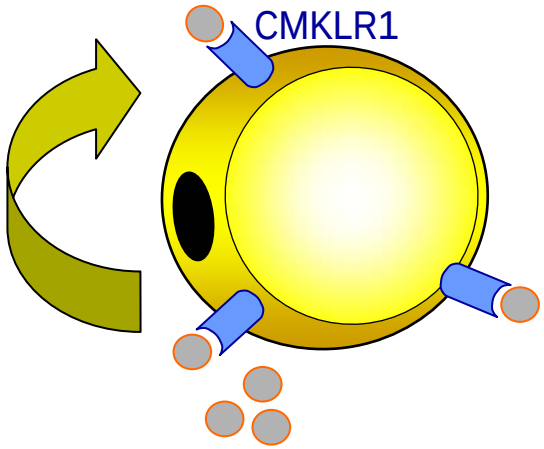
- **Edad de los pacientes**
- **Medicación de los pacientes**
- **Duración y progresión de la enfermedad**
- **Microalbuminuria asociada a la DMT2**

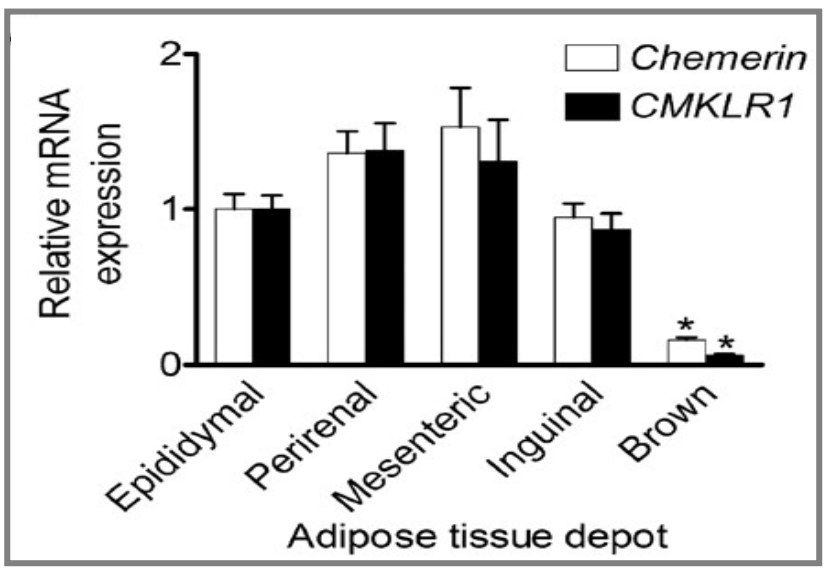
INFLAMACIÓN: CORRELACIÓN CON CD68, MCP-1, PCR, ADPN (-)

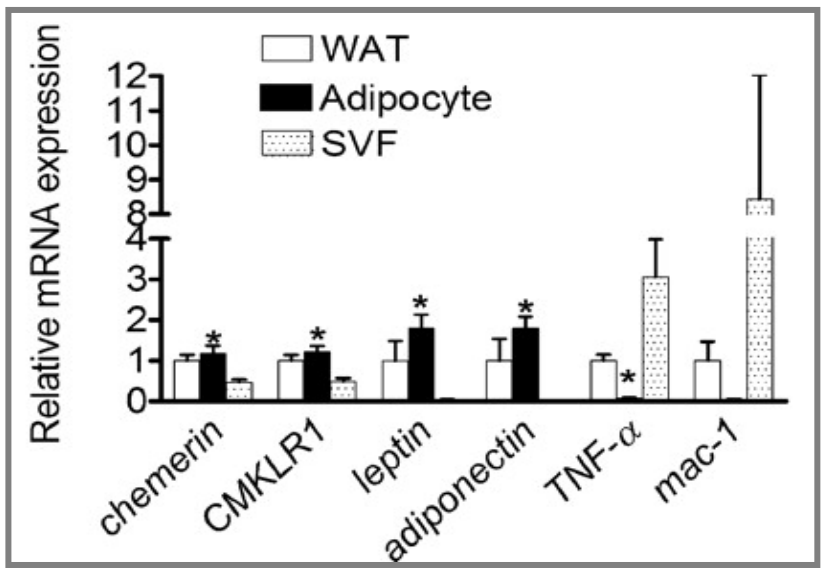
Janke et al. *Diabetes* 2006; Broch et al. *Diabetes Care* 2007; Gómez-Ambrosi et al. *Clin Endocrinol* 2008

Expresión génica de nuevas adipoquinas inflamatorias

Chemerina



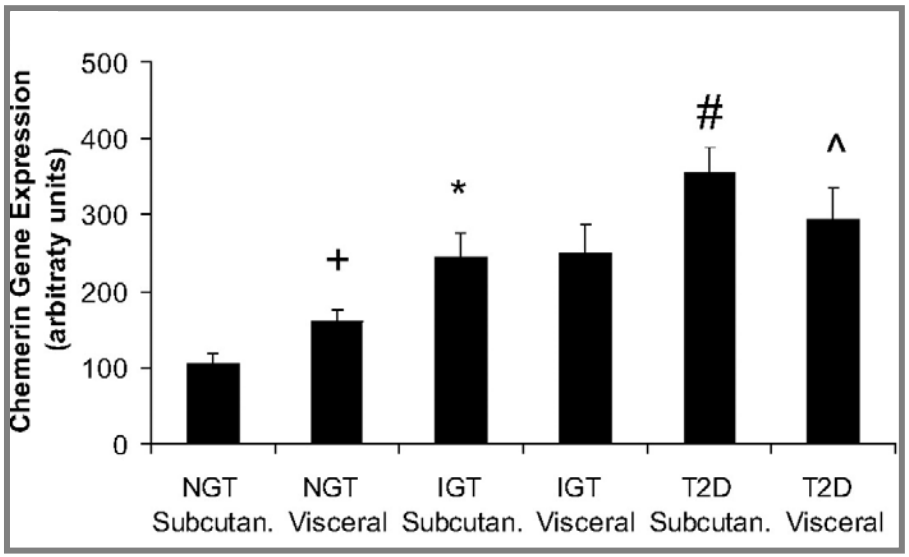


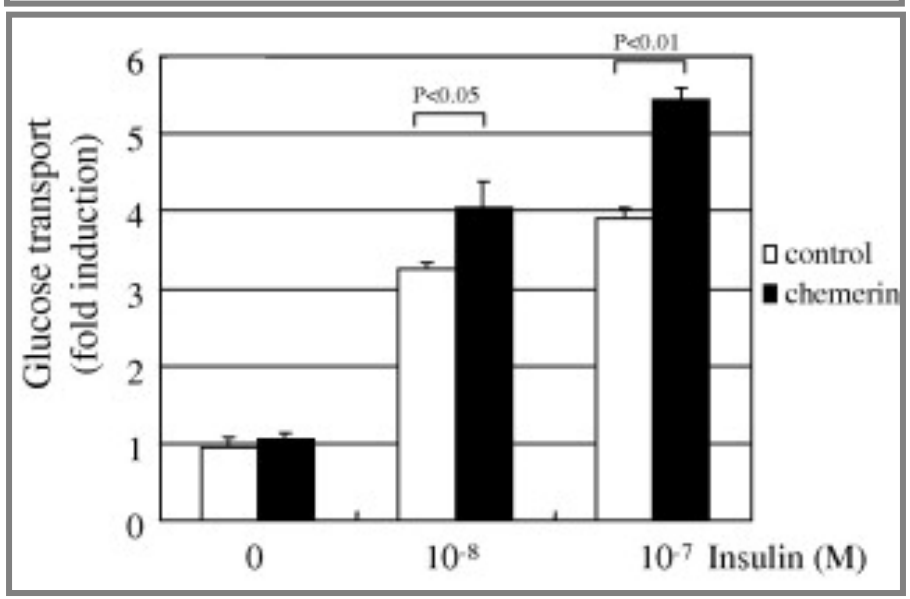


Bozaoglu et al. *Endocrinology* 2007; Goralski et al. *J Biol Chem* 2007

Expresión génica de nuevas adipoquinas inflamatorias

Chemerina





CORRELACIÓN:
Porcentaje de grasa corporal
Glucosa basal y a las 2 h
Insulina en ayuno y a las 2h
HOMA
Colesterol
Presión diastólica
HDL (-)

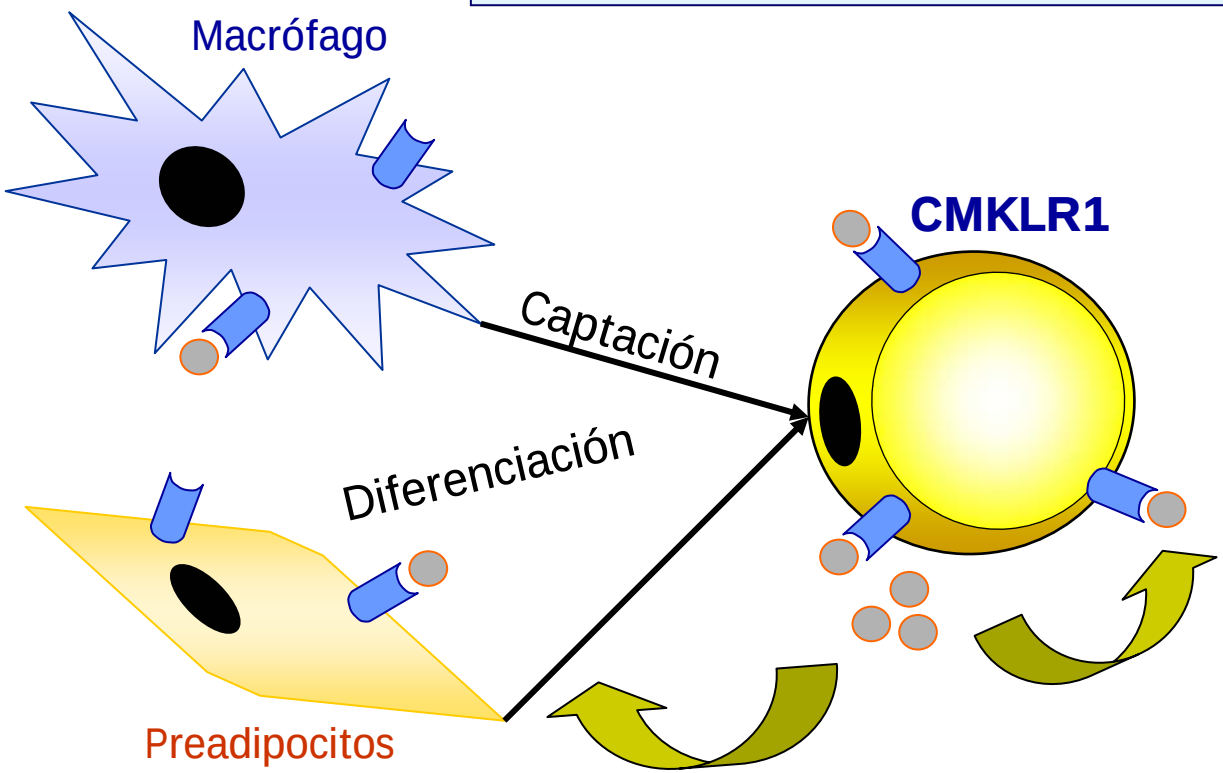
Bozaoglu et al. *Endocrinology* 2007; Takahashi et al. *FEBBS Lett* 2008

Expresión génica de nuevas adipoquinas inflamatorias

Chemerina

Activación: catepsina G

Modulador de las funciones de los adipocitos



Actividad autocrina

Efectos en la expresión de genes de adipocitos implicados en metabolismo lipídico y glucídico

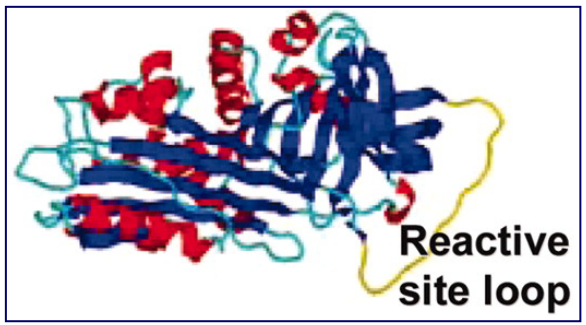
Actividad paracrina

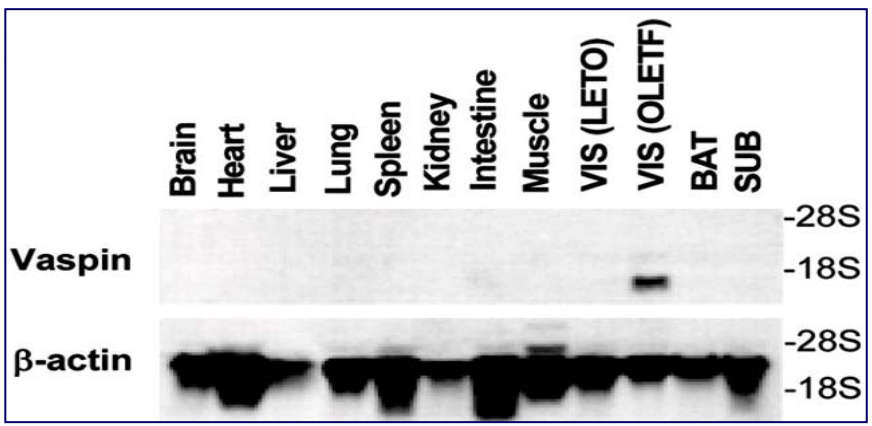
Goralski et al. *J Biol Chem* 2007

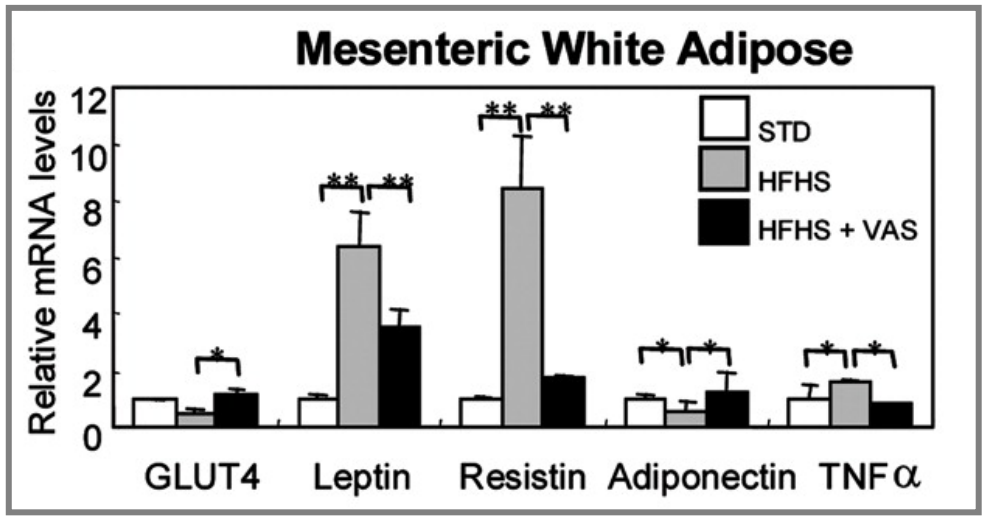
Expresión génica de nuevas adipoquinas inflamatorias

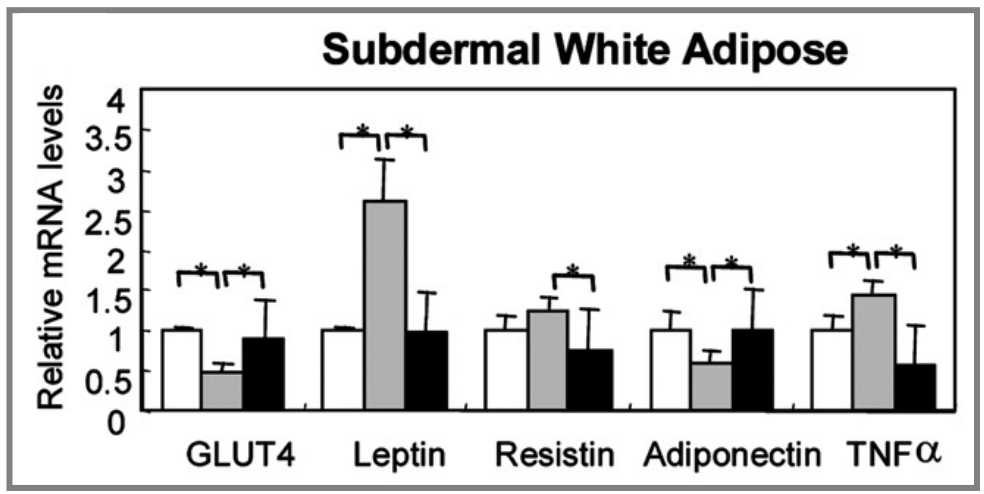
Vaspina

Inhibidor de serín-proteasas





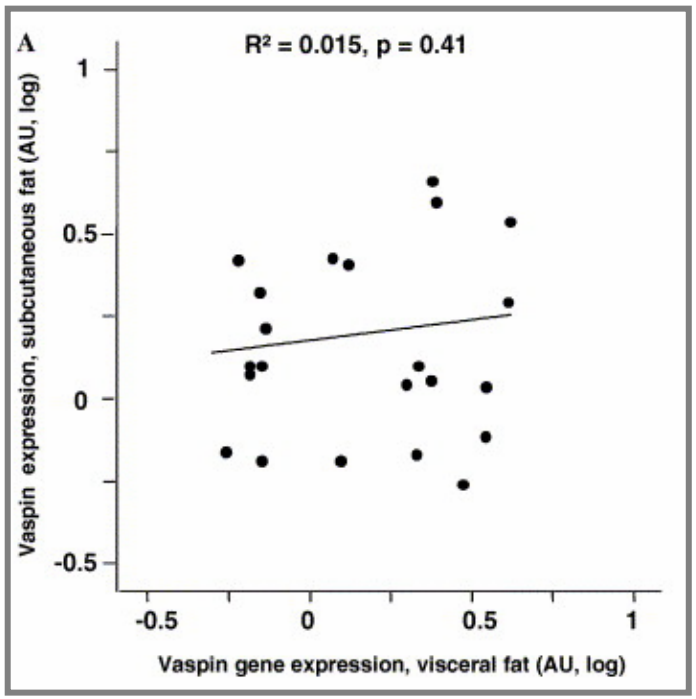


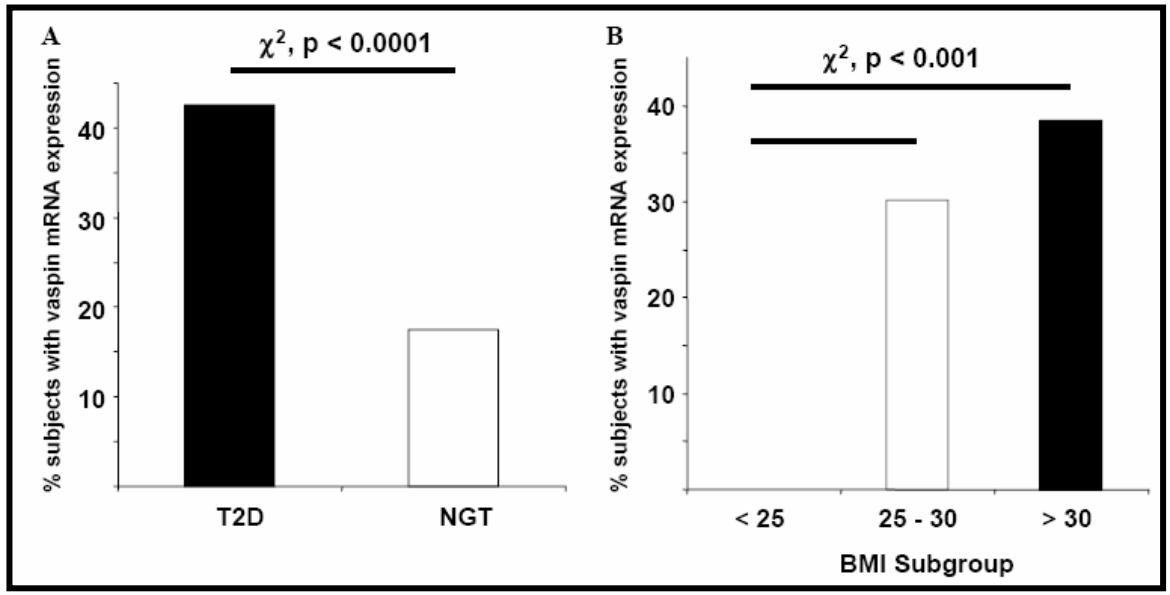


Hida et al. *PNAS* 2005

Expresión génica de nuevas adipoquinas inflamatorias

Vaspina





Visceral mRNA Vaspina

Porcentaje de grasa (+)

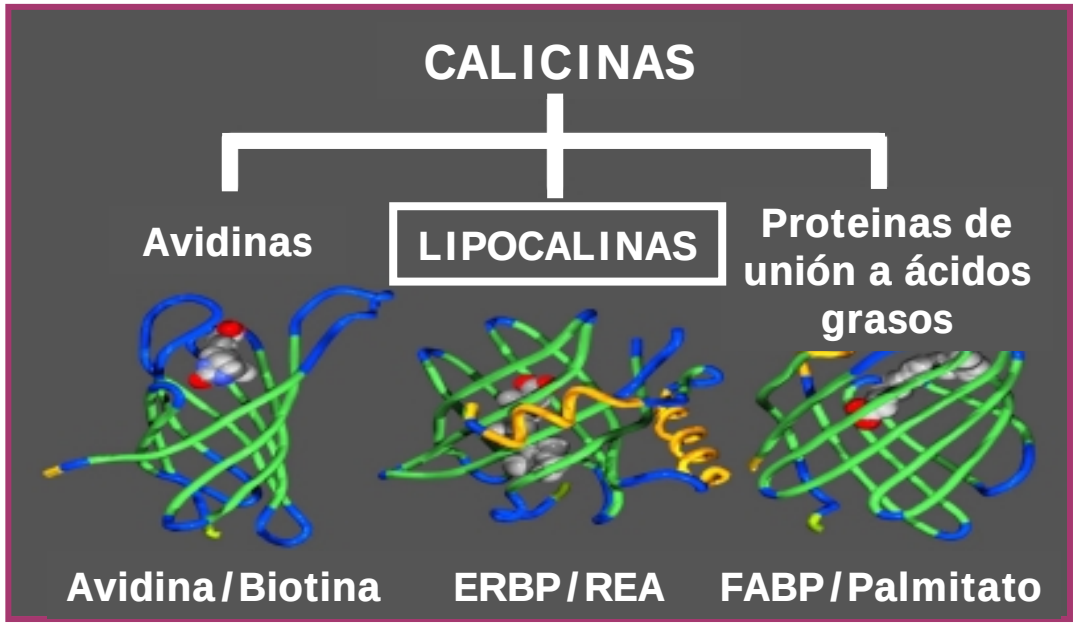
Subcutáneo mRNA Vaspina

Índice cintura-cadera (-)

Aumento de expresión en obesidad y DMT2

Kloting et al. *BBRC* 2006

Lipocalinas



***Lipos*: grasa — *Calyx*: copa**

Estructura muy conservada

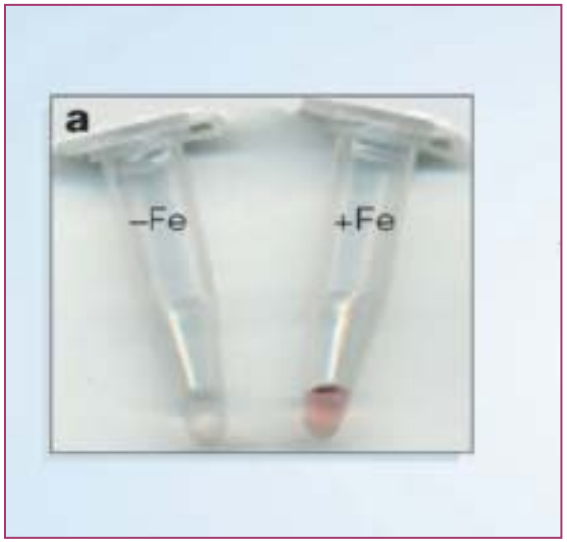
Unión a ligandos hidrófobos y receptores específicos

Diversidad funcional: transporte del retinol, síntesis de prostaglandinas, regulación de procesos celulares, coloración, modulación del sistema inmune

Proteínas de transporte extracelular

Lipocalina 2

NGAL (neutrophil gelatinase-associated lipocalin), 24p3, Uterocalin, Siderocalin



Nature, 2004

Lipocalin 2 mediates an innate immune response to bacterial infection by sequestrating iron

Trude H. Flo[1,2*], Kelly D. Smith[1,3*], Shintaro Sato[4], David J. Rodriguez[1], Margaret A. Holmes[5], Roland K. Strong[5], Shizuo Akira[4] & Alan Aderem[1]

Cell, 2005

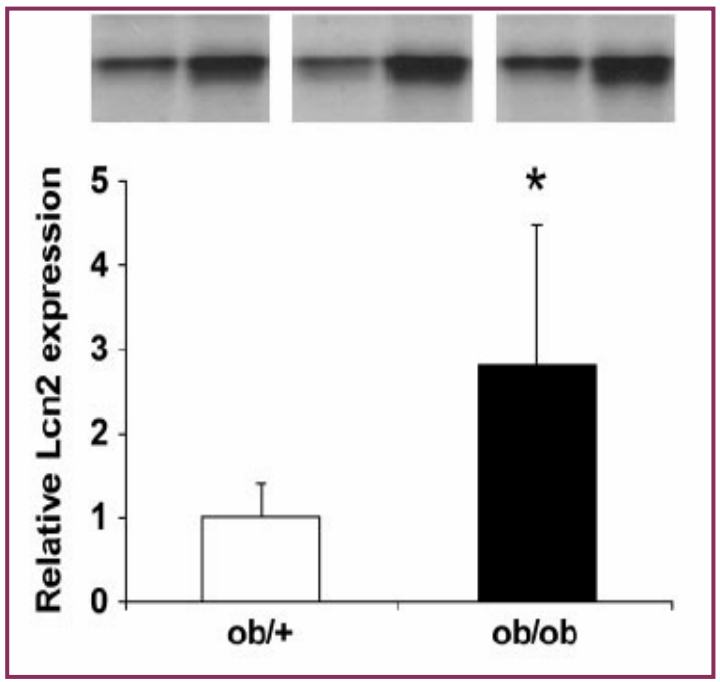
A Cell-Surface Receptor for Lipocalin 24p3 Selectively Mediates Apoptosis and Iron Uptake

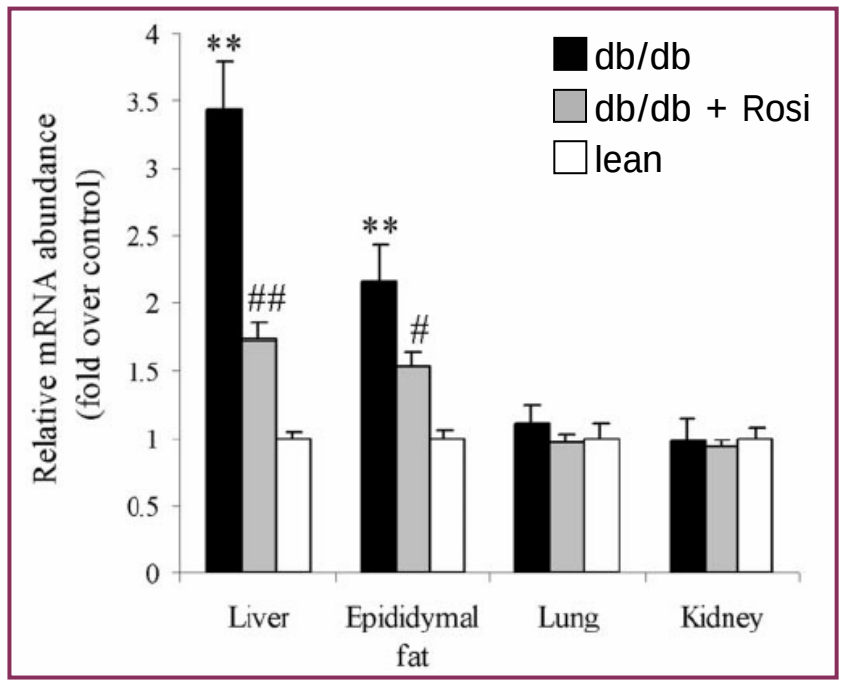
Laxminarayana R. Devireddy,[1,2] Claude Gazin,[1,2] Xiaochun Zhu,[1] and Michael R. Green[1,*]

- **Glicoproteína de 25 kDa**
- **Identificada por primera vez en neutrófilos y células renales**
- **Descrita en otros tejidos (adiposo, hígado, pulmón)**
- **Transporte de ácidos grasos y HIERRO**
- **Inducción de apoptosis y respuesta inmune innata**
- **Estímulos inflamatorios activan su expresión**

Barasch. *Nature*, 2004; Flo. Nature, 2004; Lim. *Int J Cancer*, 2007; Fernández. *Clin Cancer Res*, 2005; Yan. *J Biol Chem*, 2001

Lipocalina 2 y obesidad

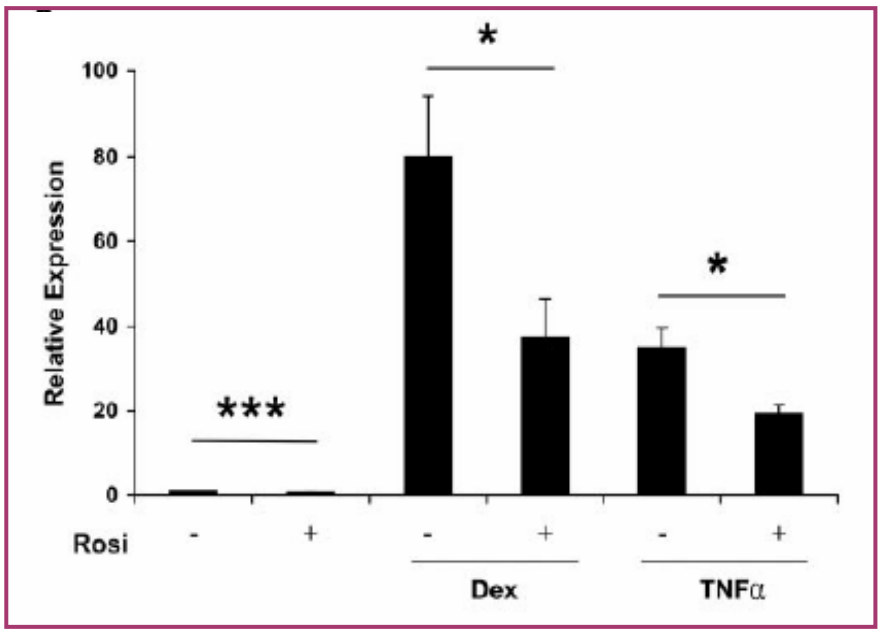


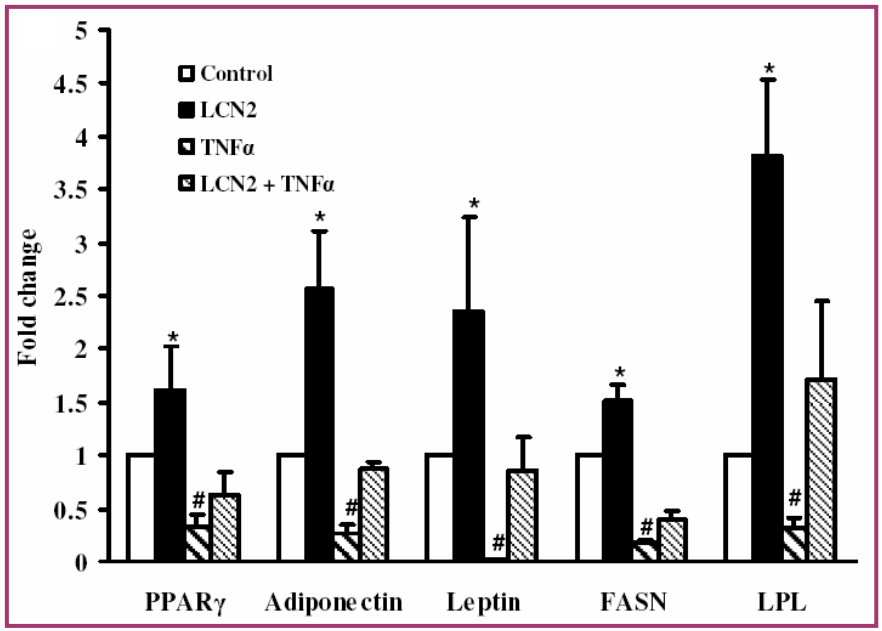


- Expresión en hígado y tejido adiposo aumentada en ratones *db/db* y *ob/ob* y se reduce tras tratamiento con rosiglitazona

Wang et al. *Clin Chem* 2007

Lipocalina 2 y obesidad





Inducción por factores que inducen insulino-resistencia:

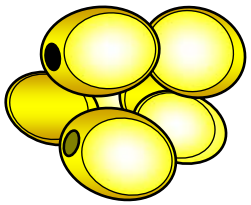
Dexametasona y TNF-α

Contrarresta efectos de TNF-α

INSULINA: Aumenta la expresión de LCN2

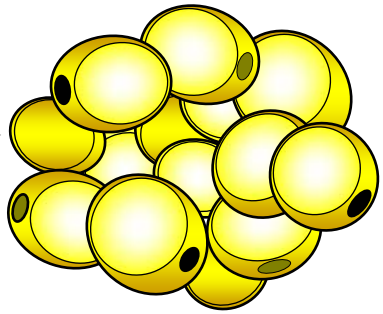
Yan et al. *Diabetes* 2007; Zhang et al. *Mol Endocrinol* 2008; Tan et al. *Diabetes Care* 2008

Lipocalina 2 y MMP-9



adipogéneis, angiogénesis

remodelado matriz extracelular



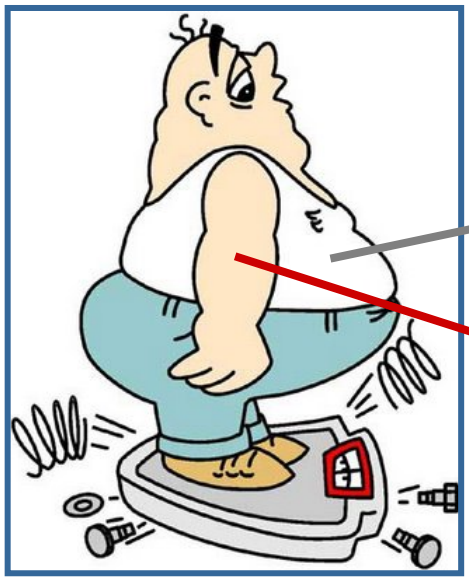
MMP-2 **MMP-9**

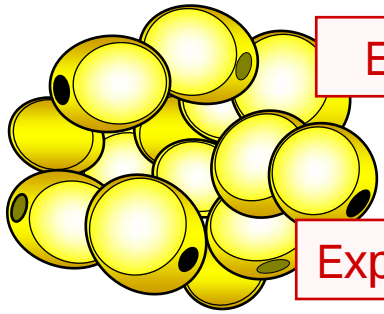
- Enzimas clave en la remodelación de la ECM
- Regulación de la diferenciación de los adipocitos
- Secreción modulada durante la diferenciación de los adipocitos
- Implicadas en la respuesta inflamatoria
- Expresión inducida por TNF-α

LCN2 se une covalentemente a MMP-9 inhibiendo su degradación y manteniendo su actividad enzimática

Bouloumié A et al. Diabetes 2001; Yan L et al. J Biol Chem 2001; Christiaens et al. Thromb Haemost 2008

¿POSIBLE INFLUENCIA EN OBESIDAD HUMANA?





Expresión génica LCN2

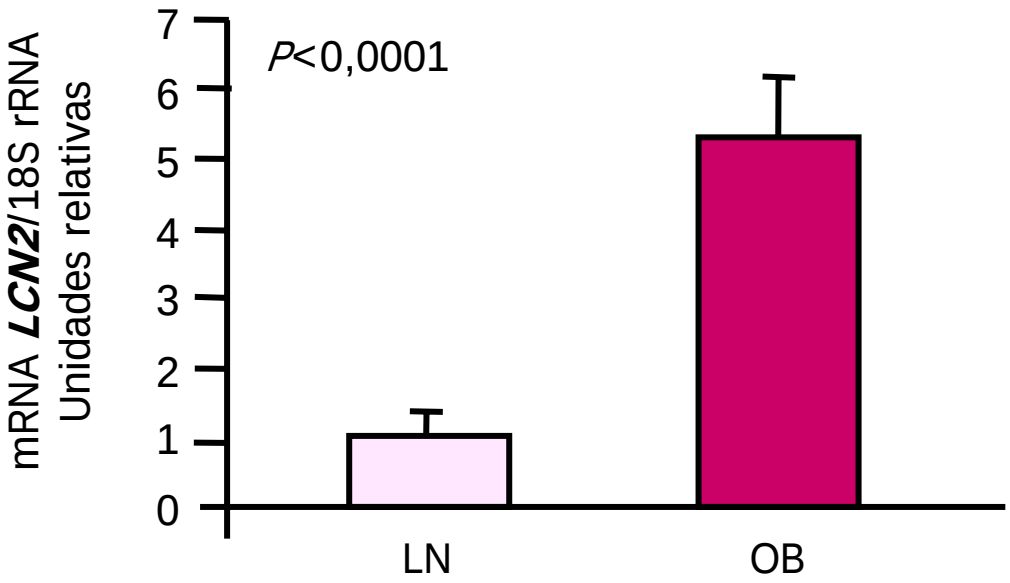
Expresión proteica LCN2

Concentraciones circulantes LCN2

Relación LCN2-INFLAMACIÓN

Importancia complejo LCN2/MMP-9 en obesidad

LCN2. Niveles de expresión génica



LN: n=8; OB: n=39

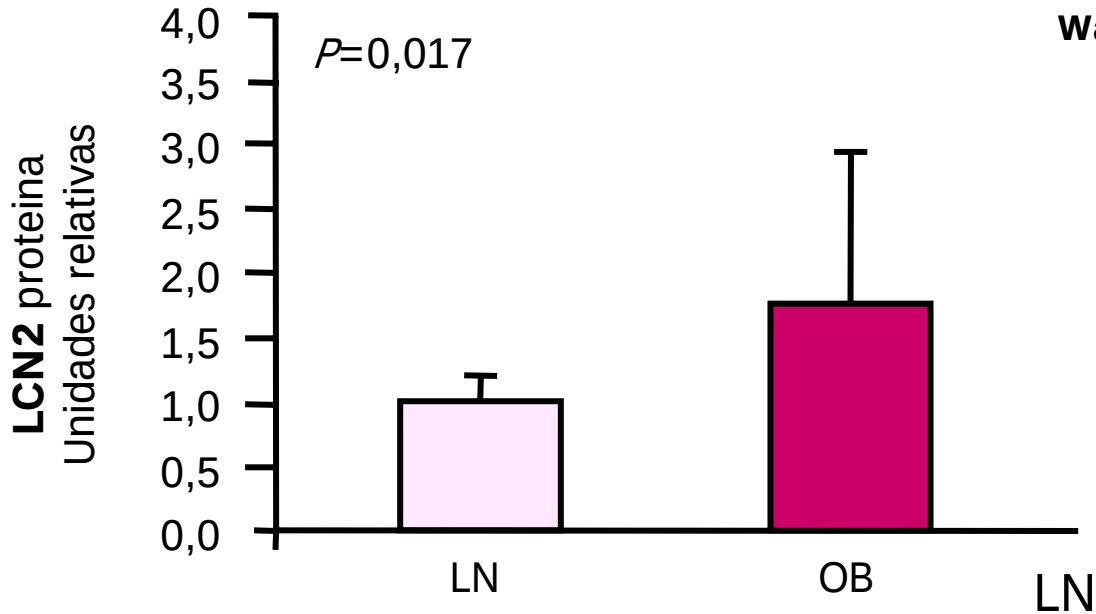
Niveles de expresión génica elevados en tejido adiposo visceral en pacientes obesos

LCN2-IMC
CORRELACIÓN r=0,40; *P*=0,012

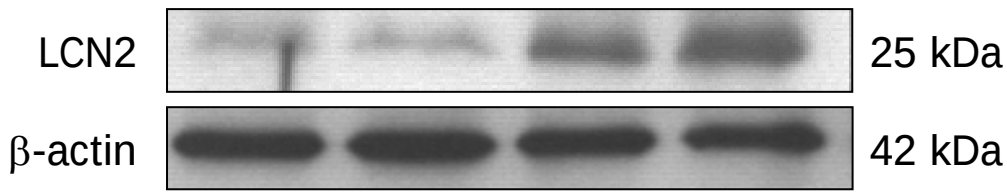
Catalan et al. *J Mol Med* 2009

LCN2. Niveles de expresión proteica

Yan et al. *Diabetes* 2007
Wang et al. *Clin Chem* 2007



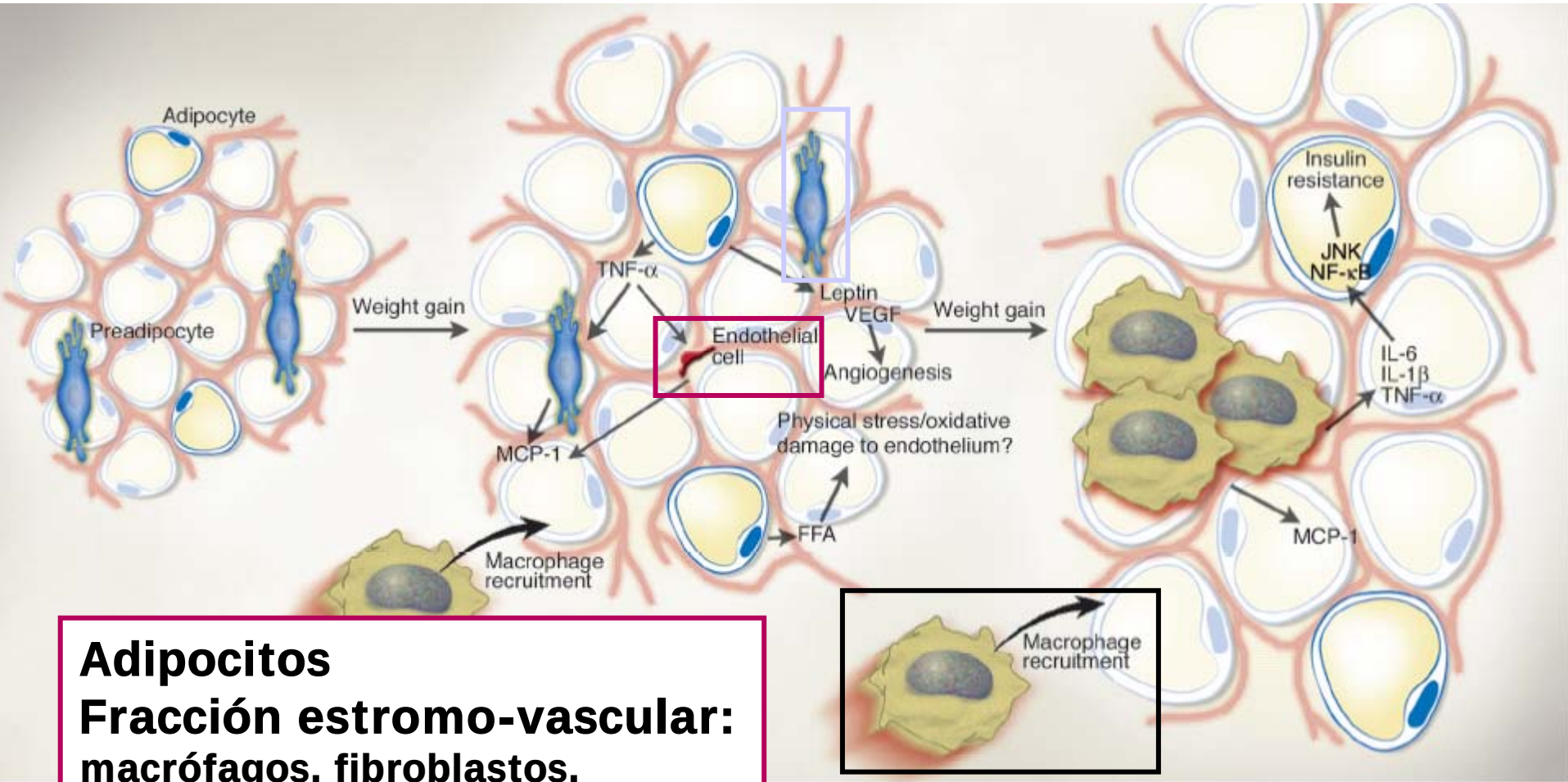
LN: n=5; OB: n=20



Niveles de expresión proteica siguen la misma tendencia
CORRELACIÓN r=0,50; *P*=0,010

Catalan et al. *J Mol Med* 2009

Multicelularidad del tejido adiposo



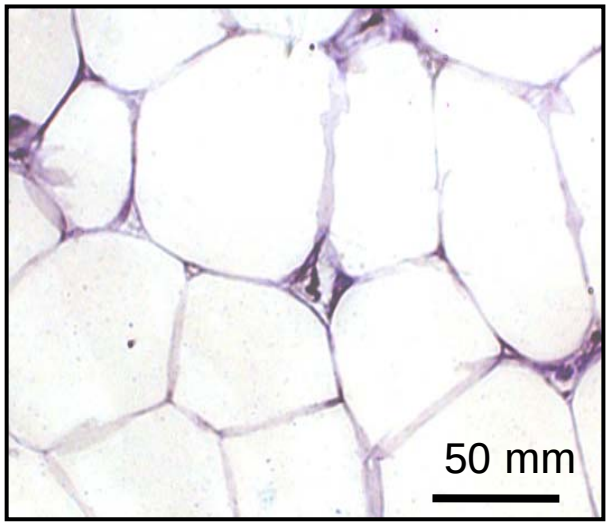
Adipocitos

Fracción estromo-vascular:
macrófagos, fibroblastos, pericitos, preadipocitos, células endoteliales y mesenquimales

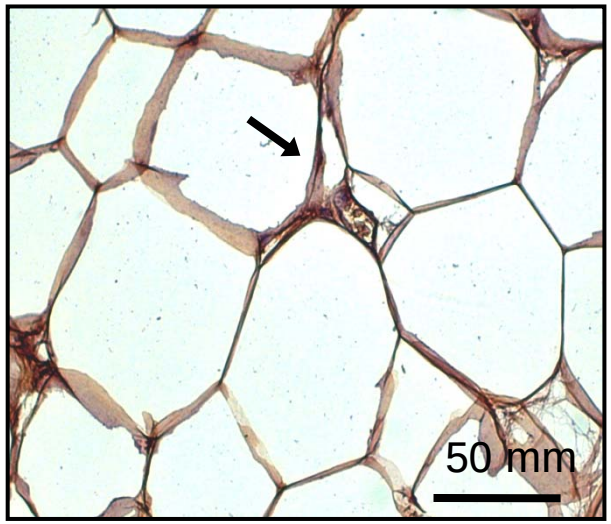
“Cross-talk” autocrino-paracrino

Wellen and Hotamisligil. J Clin Invest, 2003

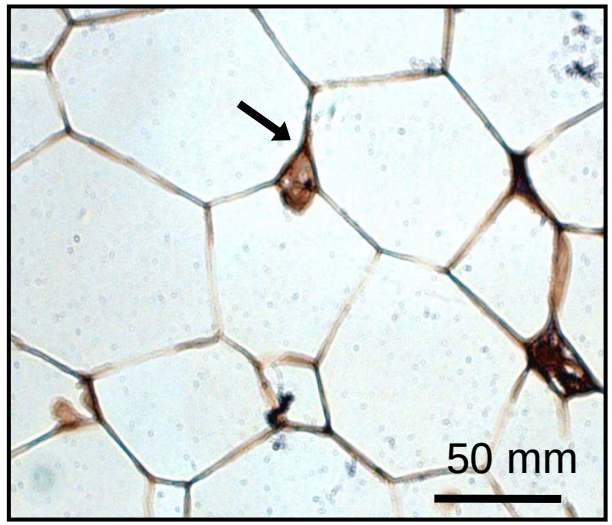
LCN2. Análisis inmunohistoquímico



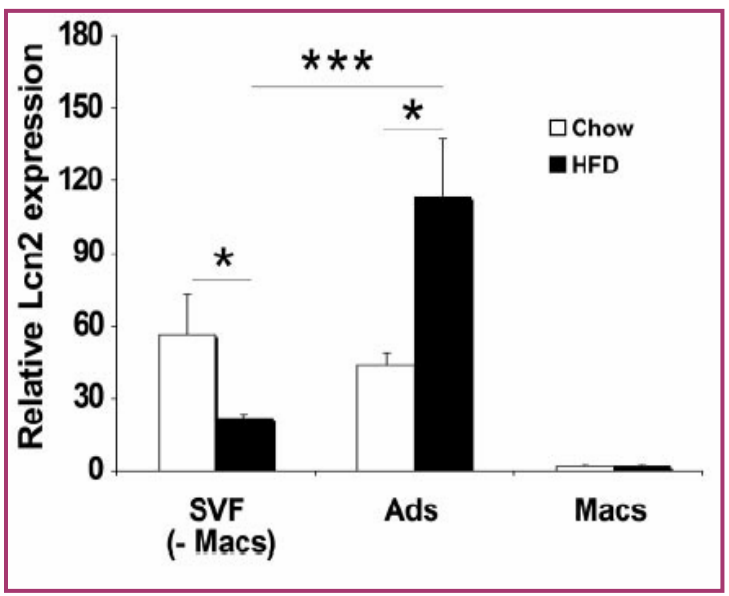
Control negativo



LCN2



CD68



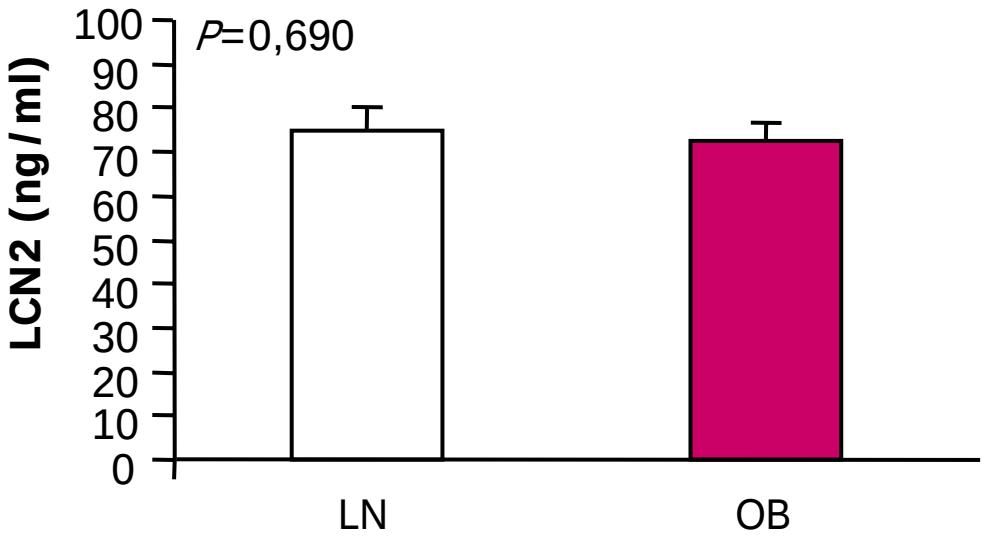
Yan et al. *Diabetes* 2007
Zhang et al. *Mol Endocrinol* 2008
Fain et al. *Metabolism* 2008

Expresión en adipocitos y en SVF

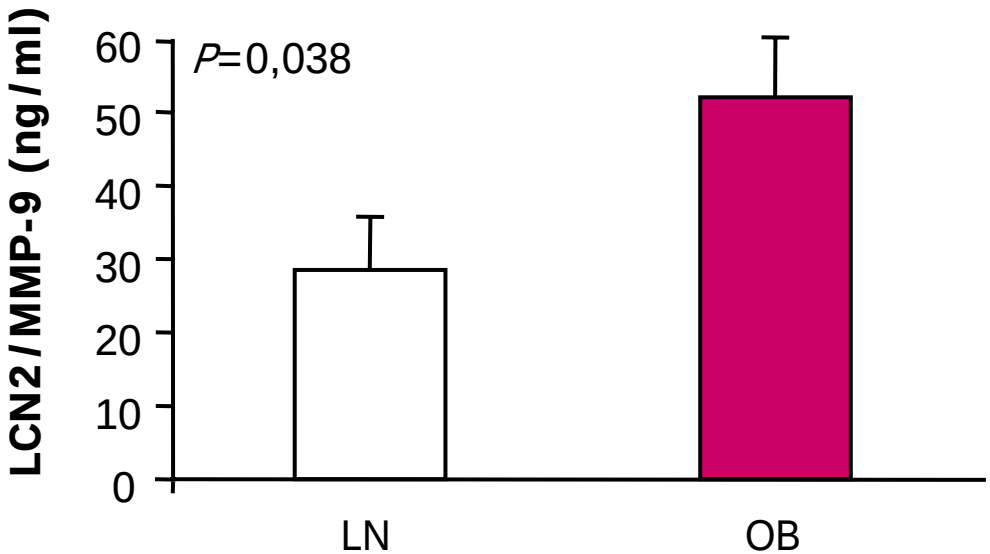
Aumento de expresión en adipocitos tras HFD

Catalan et al. *J Mol Med* 2009

LCN2. Niveles circulantes



LN: n=13; OB: n=27



CORRELACIONES

mRNA LCN2: r=-0,19; *P*=0,430

Proteína LCN2: r=-0,09; *P*=0,861

Choi et al. *Clin Endocrinol* 2009

Stejskal et al. *Horm Metab Res* 2008

¿RBP-4? Yang Q et al. Nature 2005; Gómez-Ambrosi J et al.I Clin Endocrinol 2008

¿Complejo LCN2/MMP-9?

CORRELACIONES

IMC: r=0,49; *P*=0,003

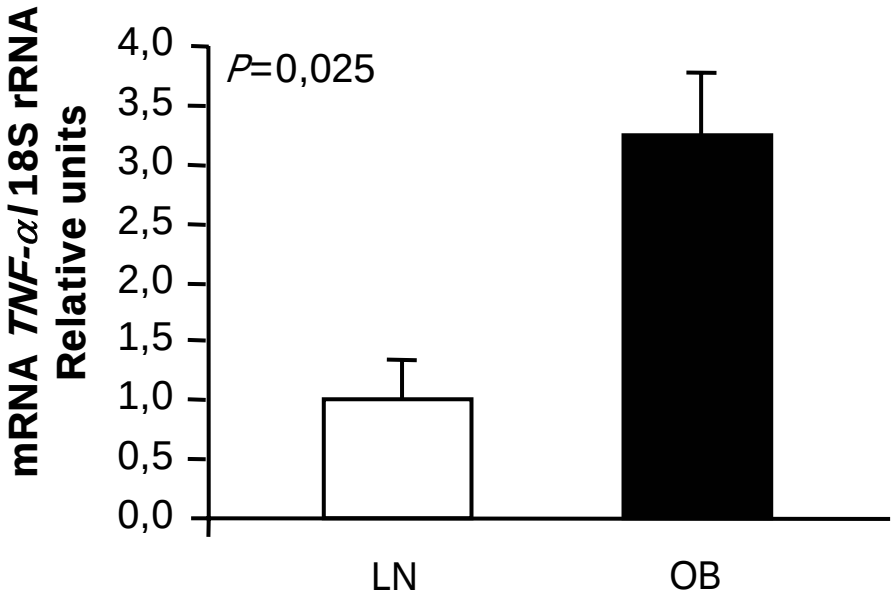
Leptina: r=0,50; *P*=0,025

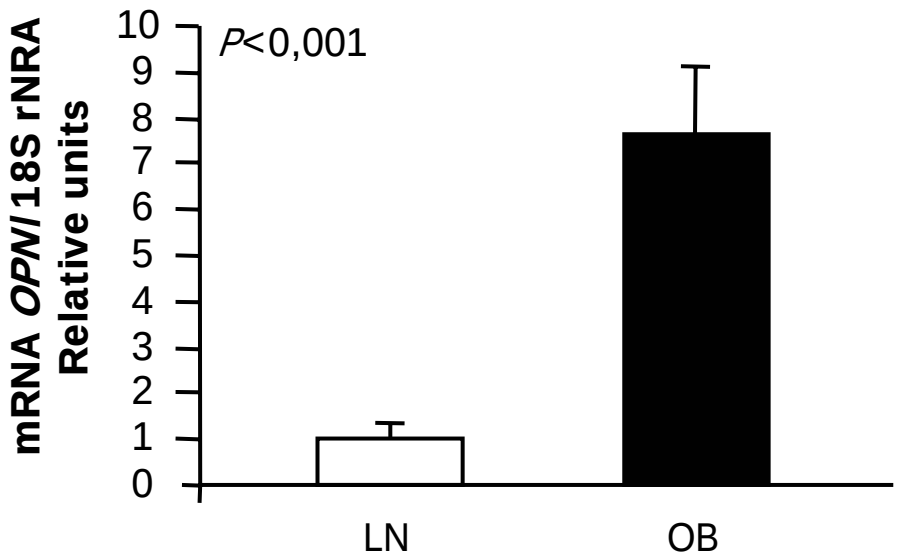
PCR: r=0,74; *P*<0,001

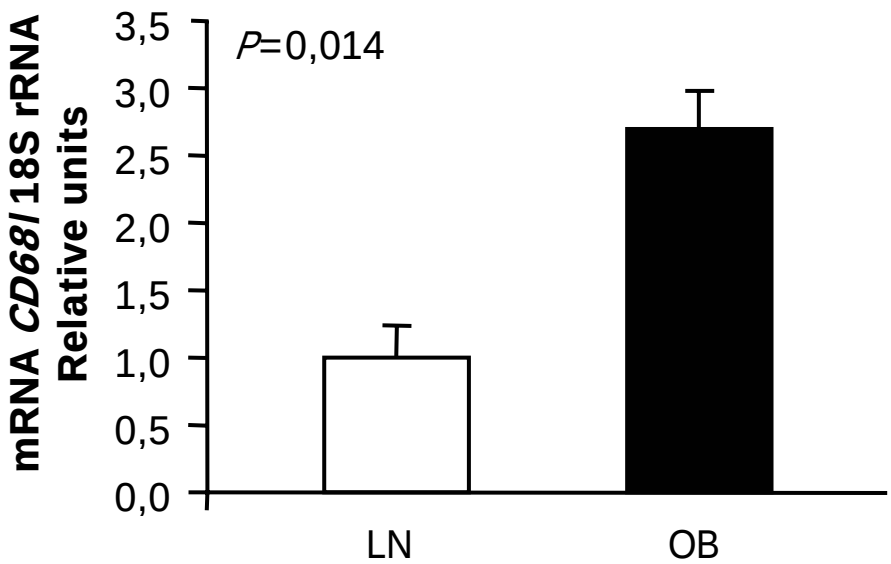
Fibrinógeno: r=0,61; *P*<0,001

Catalan et al. *J Mol Med* 2009

Marcadores de inflamación







LN: n=8; OB: n=39

Catalan et al. *J Mol Med* 2009

ESQUEMA GENERAL

Evidencia epidemiológica y genética

Características generales del tejido adiposo

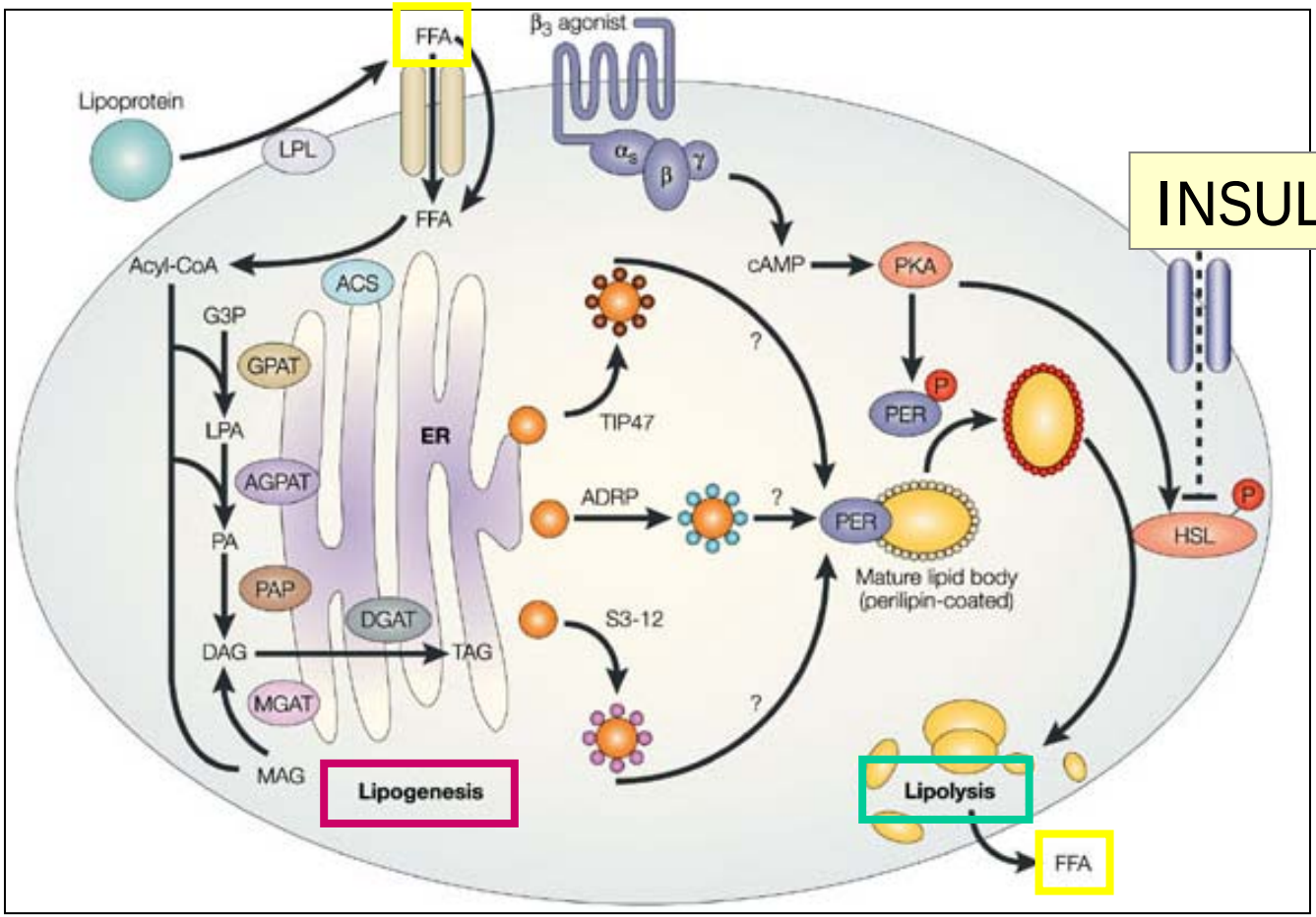
Adipoquinas, insulino-resistencia e inflamación

Vías relacionadas con el metabolismo lipídico

Genes de respuesta a hipoxia

Nuevos hallazgos - implicaciones

Genes del metabolismo lipídico



INSULINA

PPARγ

SREBP-1

FAS

SCD1

LIPOGÉNESIS ⟷ **LIPOLISIS**

HSL/ATGL

Estado nutricional

Factores endocrinos: insulina o catecolaminas

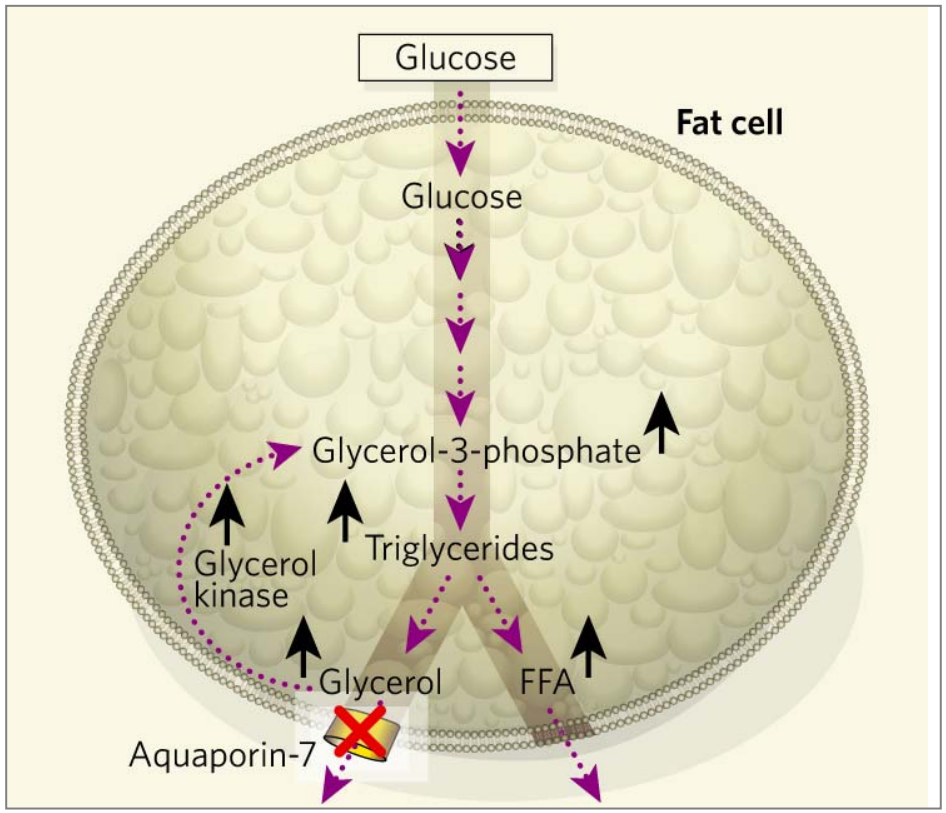
Proteínas transportadoras

CD36 FATP FABP

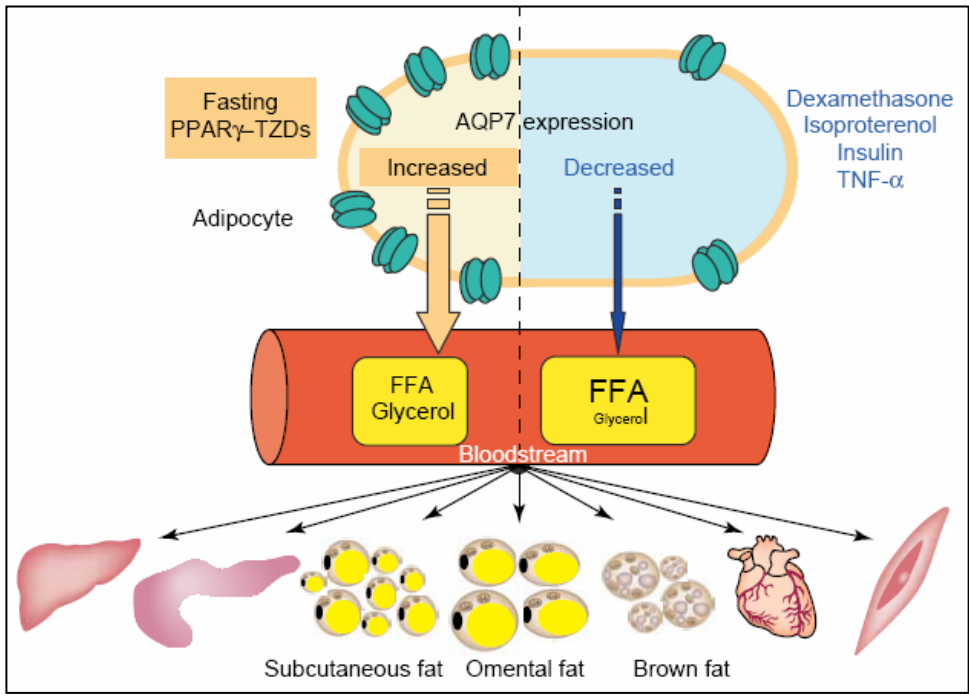
Shi et al. ***Nat Rev Drug Discov*** **2004**

Proteínas integrales de membrana

AQP7



Frühbeck *Nature* 2005

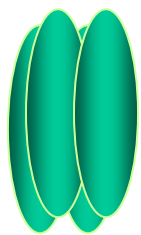


Frühbeck et al. *Trends Pharmacol Sci* 2006

Expresión en visceral>
Expresión en subcutáneo

Sjöholm et al. *J Clin endocrinol Metab* 2005

WAT

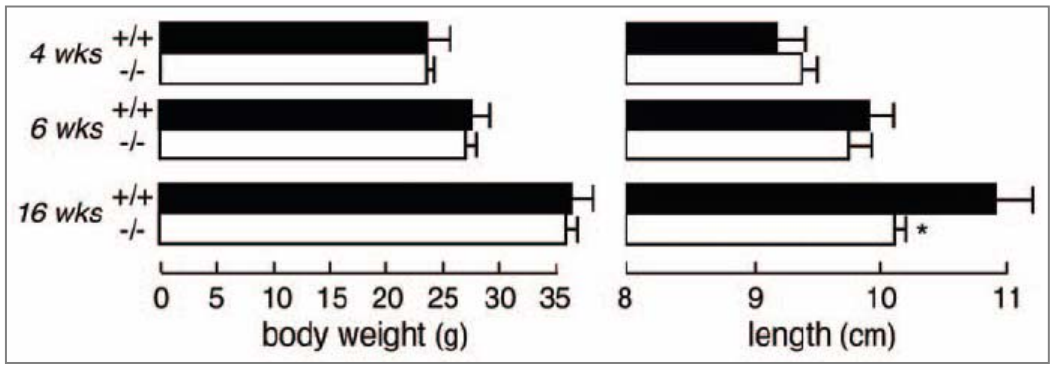


AQP-7

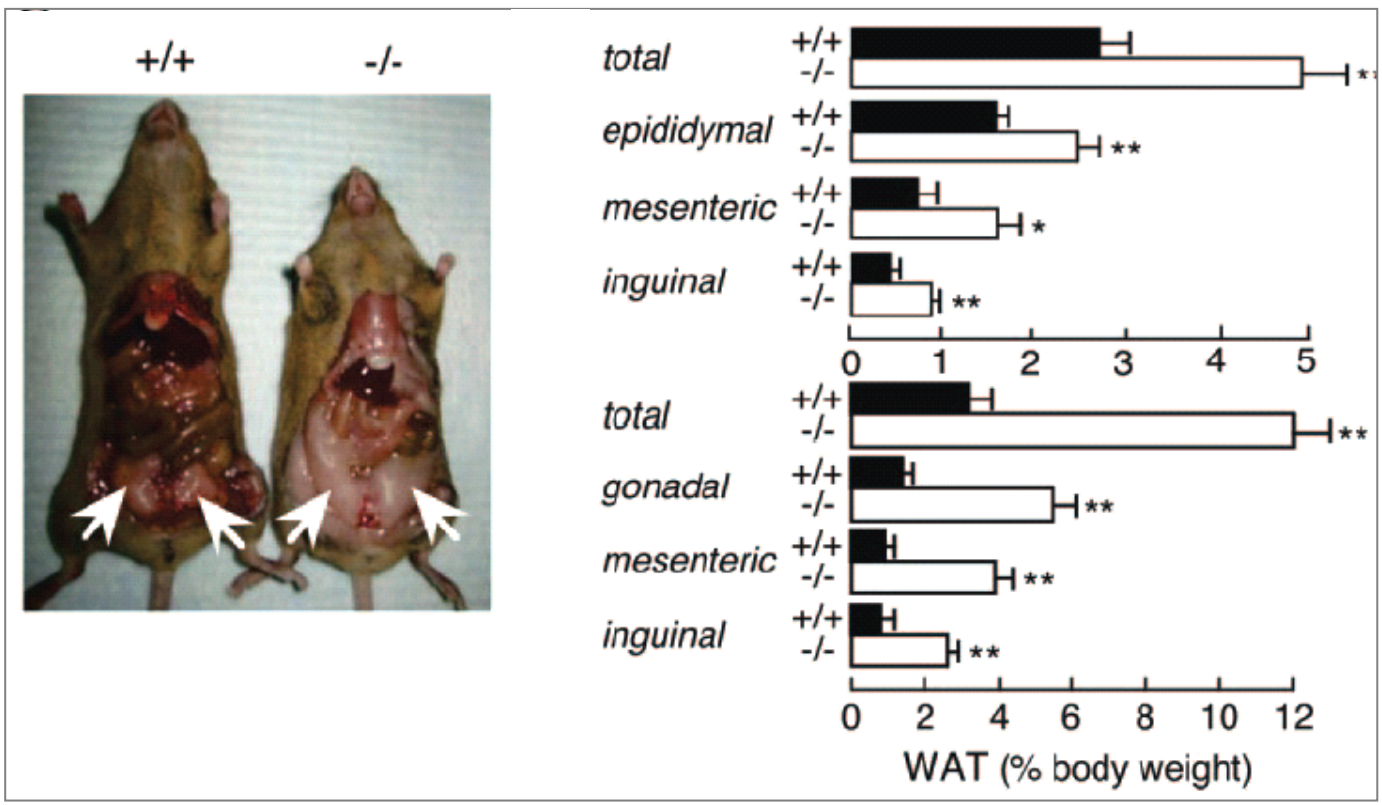
Kuriyama et al. *BBRC* 1997

Proteínas integrales de membrana

AQP7



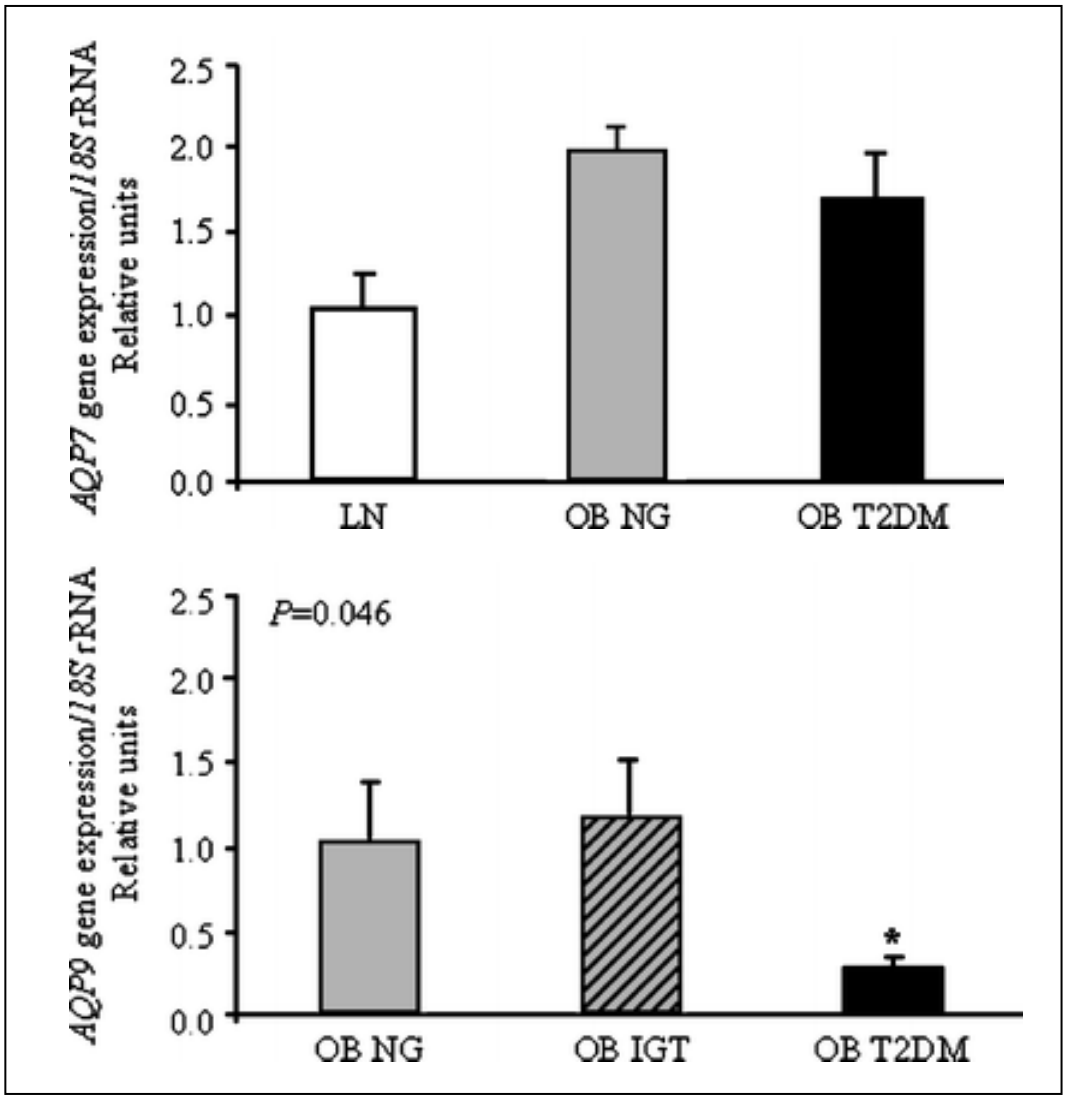
Aqp7 -/-
Menor nivel plasmático de glicerol
Acumulación en los adipocitos



Hara-Chikuma et al. *JBC* 2005

Proteínas integrales de membrana

AQP7



No dif. de expresión de AQP7 en grasa visceral obesos tanto normoglucémicos como T2DM

Dism. expresión hepática AQP9

Dism. expresión de AQP7 en grasa subcut obesos mórbidos

No efecto adicional de T2DM

Correlaciones:

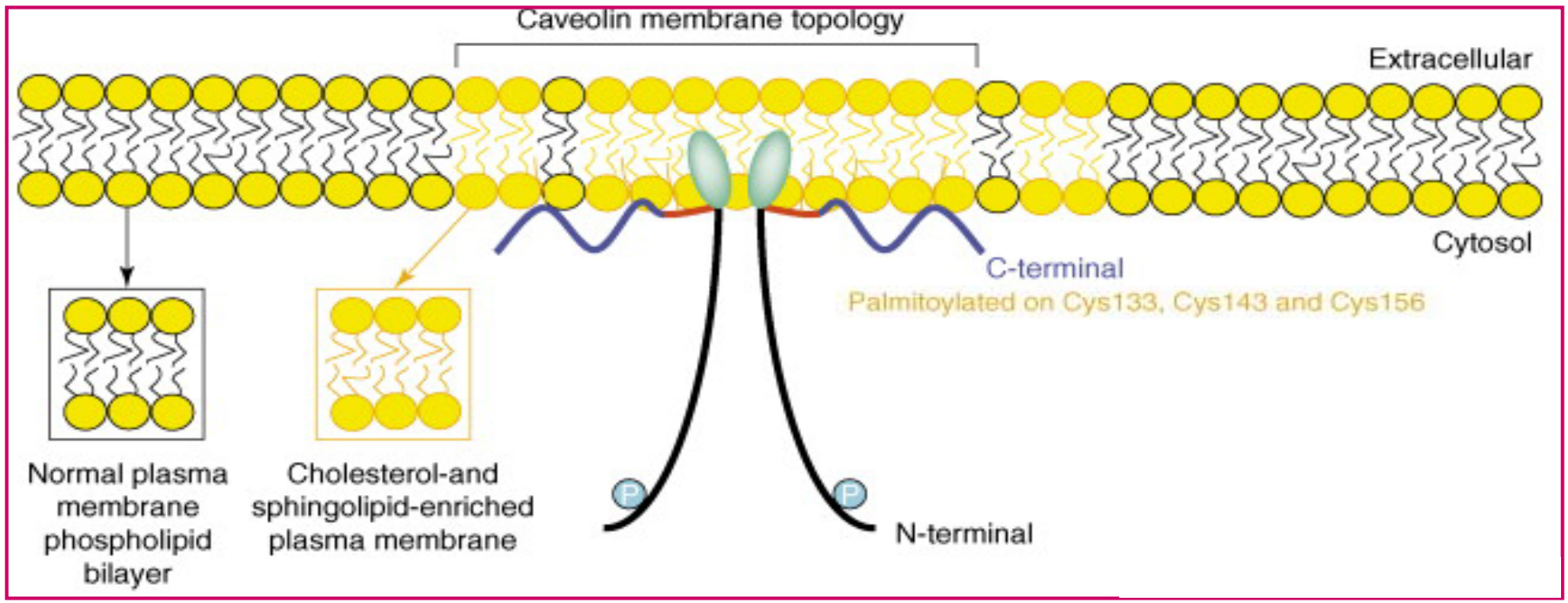
- **MCP-1 y TNFα (-)**
- **PPARγ mRNA (+)**

Catalán et al. *Obes Surg* 2008

Ceperuelo et al. *J Clin Endocrinol Metab* 2007

Proteínas integrales de membrana

Caveolina 1



Endocytosis

Transcytosis

Lipid metabolism (cholesterol transporter/regulator)

Signalling

Frühbeck et al. *Trends Endocrinol Metab* 2007

- **Cav-1 and -2**

(most cells except cardiac & skeletal muscle)

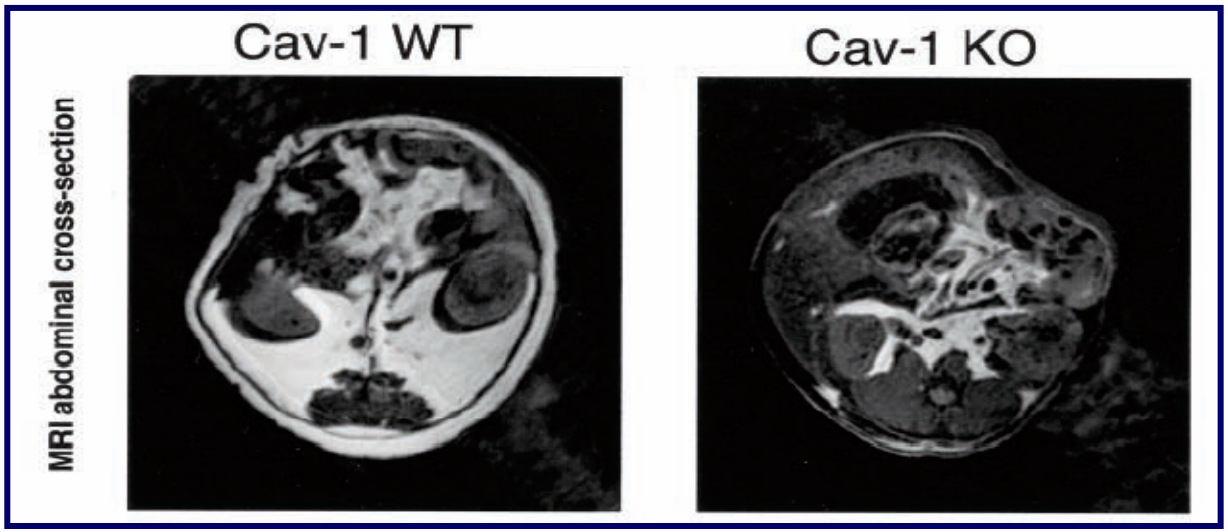
- **Cav-3**

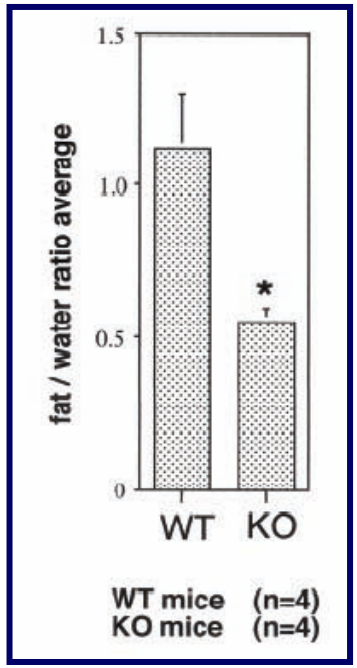
(myoblast lineage: cardiac, skeletal, and smooth muscle cells)

Fra et al, 1995; Monier et al, 1995; Song et al, 1997; Thiele et al, 2000

Integral membrane proteins

Caveolin 1





*** Defects in lipids homeostasis**

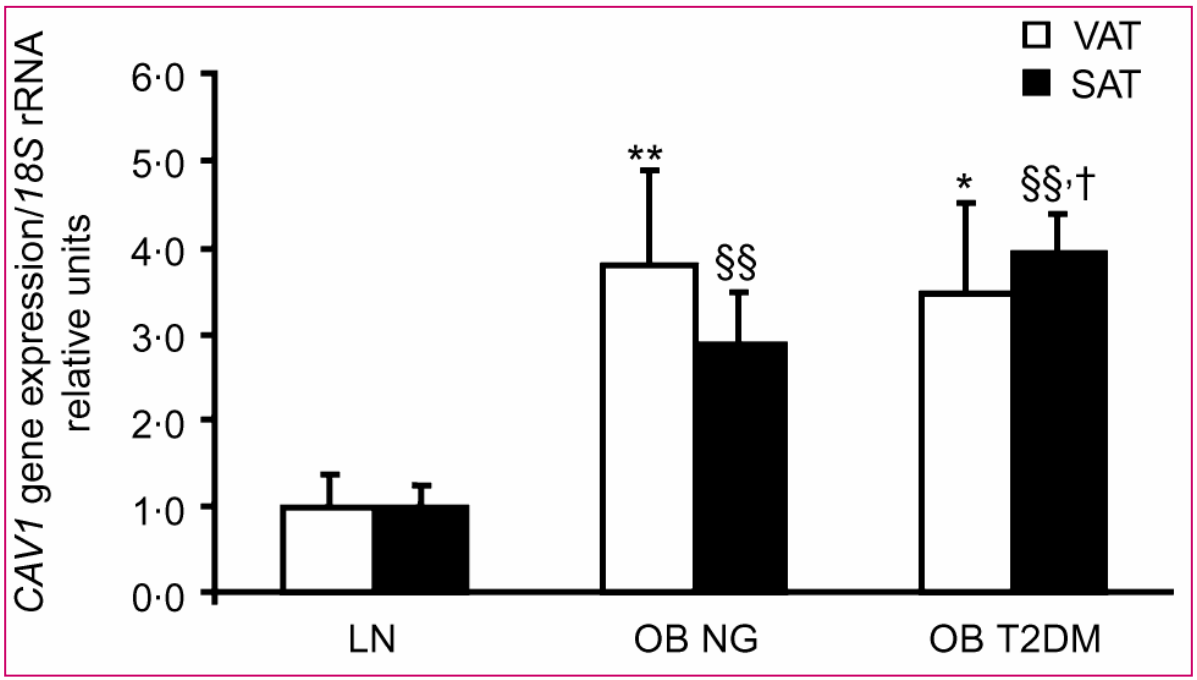
- Lean and resistant to diet-induced obesity
- Increased fat accumulation with age
- Decreased leptin and adiponectin concentracions
- Hipertriglyceridemia
- Reduced lipid clearance ability

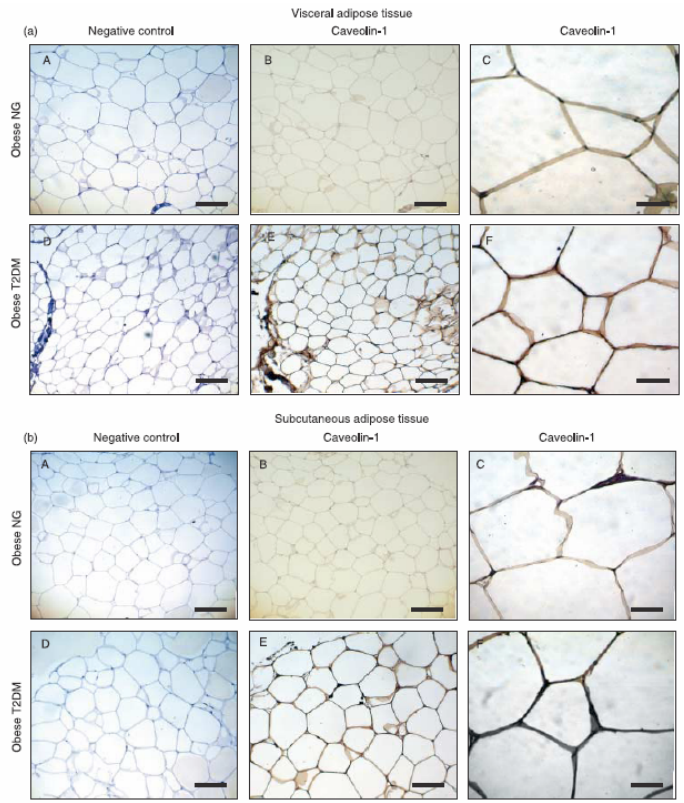
*** Insulin resistance**

Razani et al. *J Biol Chem*, 2002; Cohen et al. Am *J Physiol Cell Physiol*, 2003

Proteínas integrales de membrana

Caveolina 1





CORRELATIONS

BMI and percentage body fat

mRNA MCP1, sialic acid and fibrinogen

Catalán et al. *Clin Endocrinol* 2007

Genetic analysis of *CAV1* gene in hypertension and metabolic syndrome

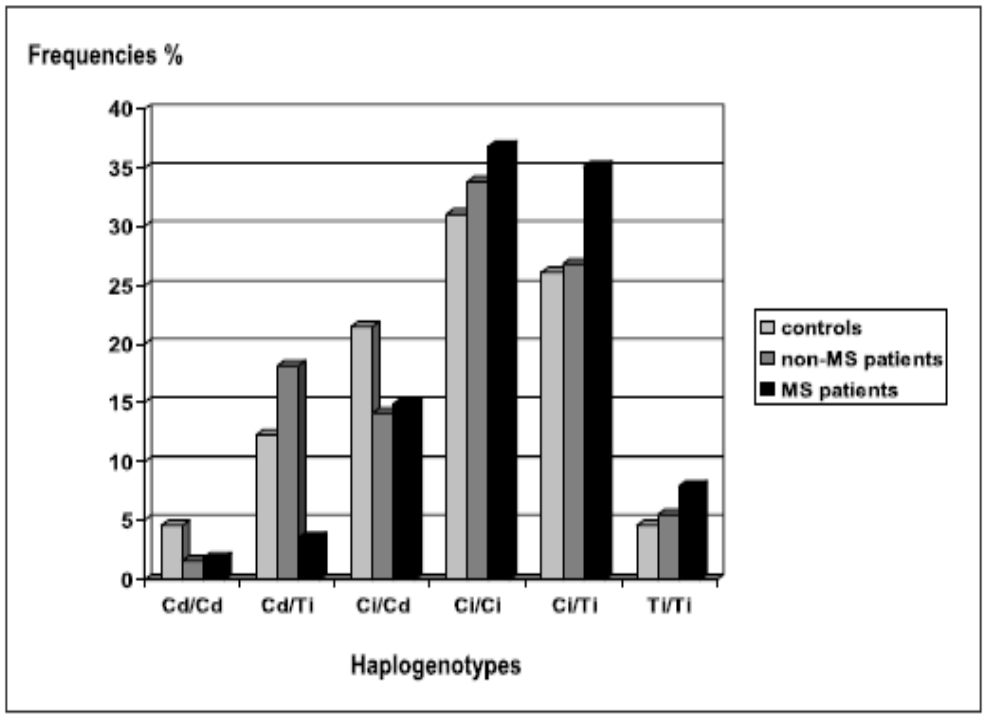


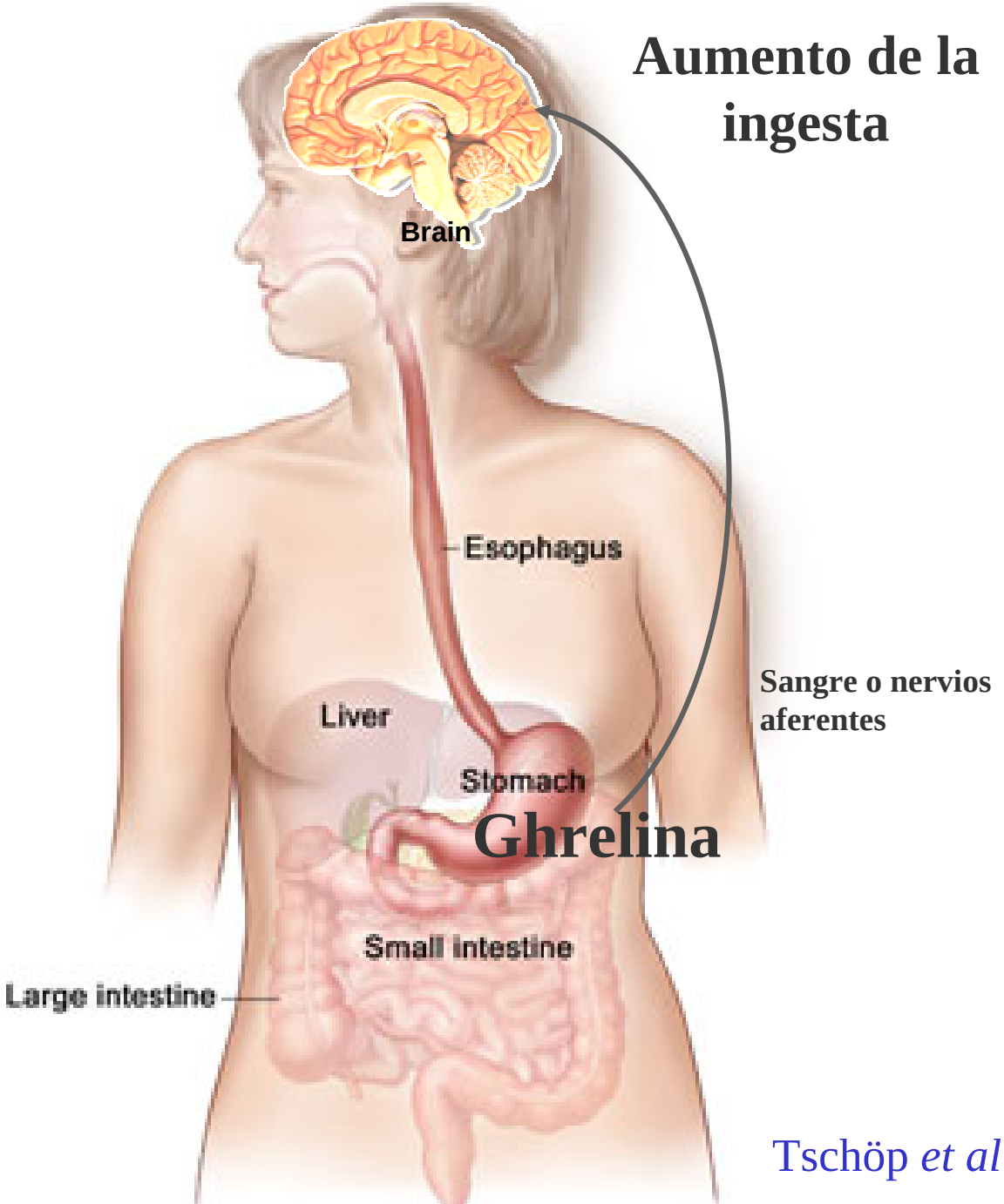
Figure 3: Distributions of *CAV 1* haplogenotypes.

Table 3: Comparison of haplotypic frequencies (%) between controls, MS hypertensive patients and non-MS hypertensive patients. The haplotypic frequencies and p values were calculated using the Thesias software. All p values were age corrected. *Haplotype used as reference.

Haplotype	Frequencies (%)			Statistical		
	Control group	Non-MS patients	MS patients	Control vs. non-MS	Control vs. MS	MS vs. non-MS
Ci*	54.79	54.79	61.18	R	R	R
Cd	21.46	17.71	10.96	NS	OR=0.45 p=0.0012	OR=0.54 p=0.027
Ti	23.74	27.95	27.19	NS	NS	NS

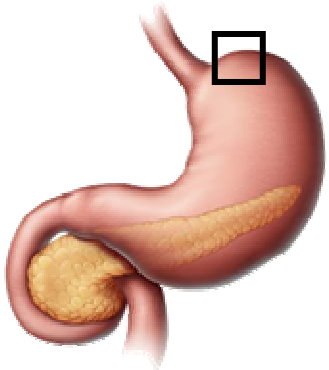
Grilo et al. *Thromb Haemost* 2006

Ghrelina

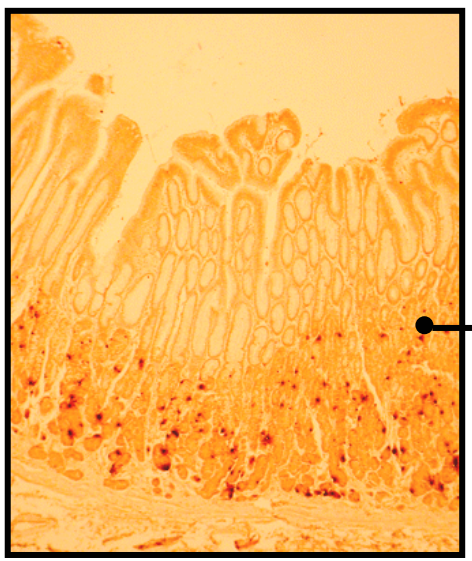


Tschöp *et al*. Nature 2000

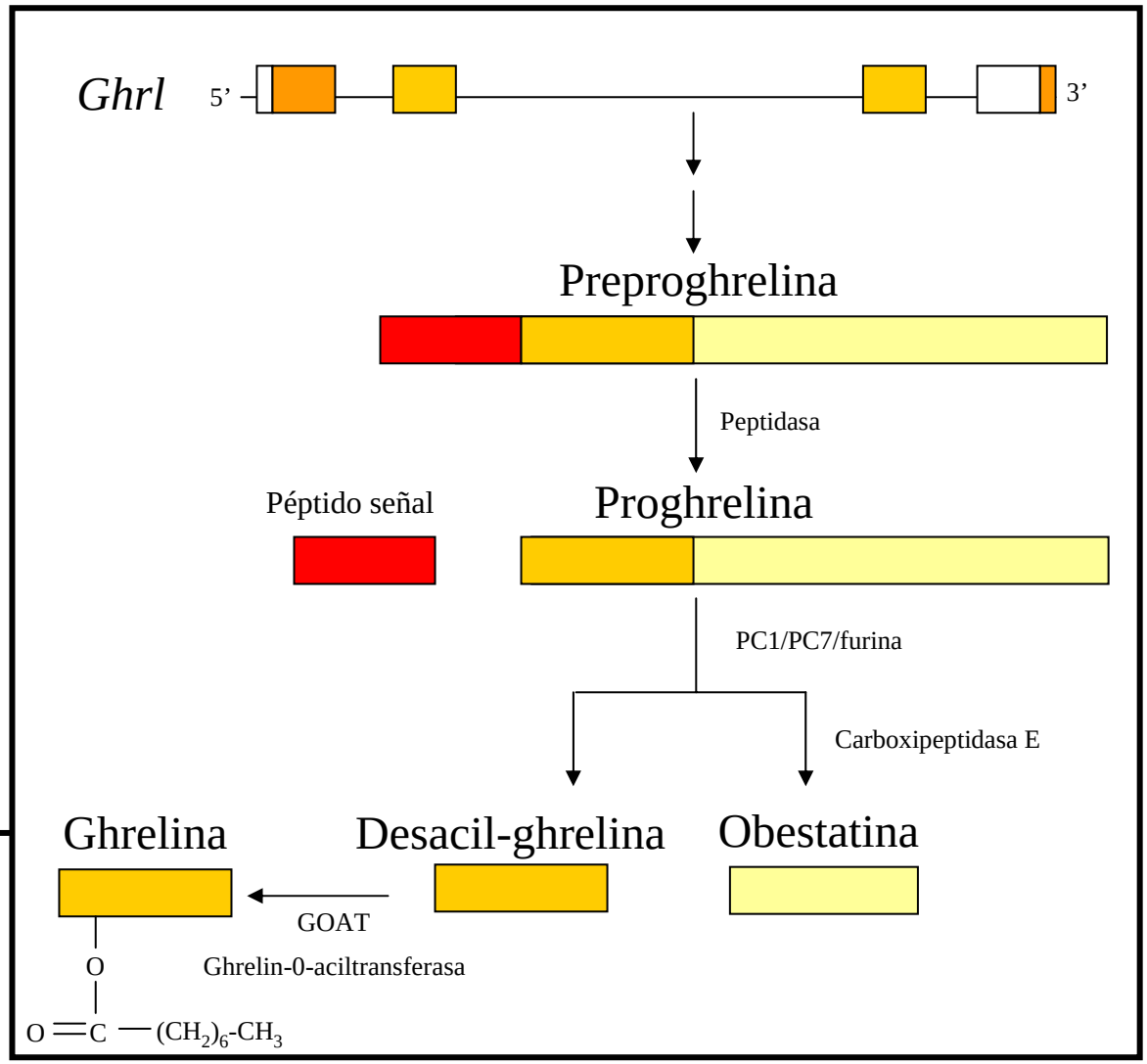
Ghrelina



Estómago



Glándulas oxínticas de la mucosa del fundus

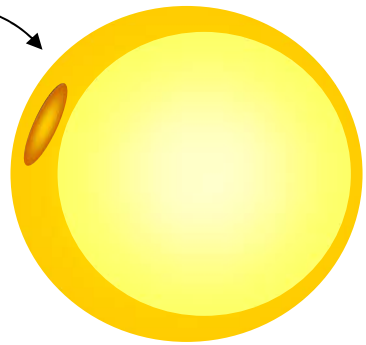


Hosoda *et al*. Biochem Biophys Res Comm 2000; Jefferey *et al*. Endocrinology 2005; Yang *et al*. Cell 2008

Estudio del efecto de la ghrelina y desacil-ghrelina sobre adipogénesis y lipogénesis

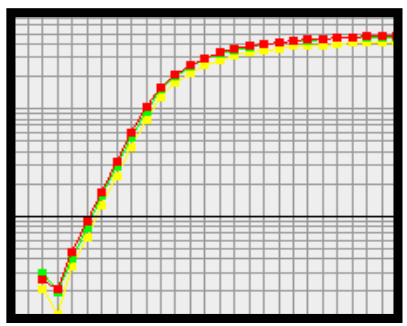
Ghrelina

(0,1-1000 pmol/L)



Adipocito

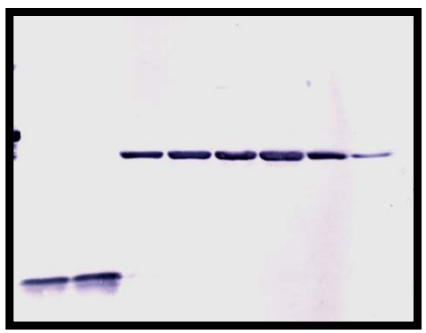
RT-PCR



PPARg

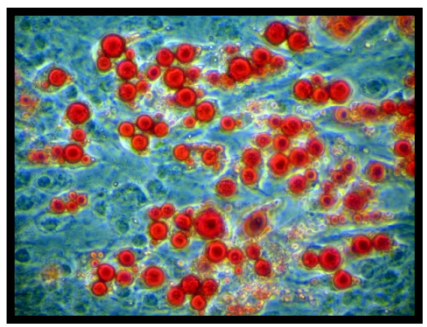
SREBF1

Western-blot



Adipophilina, perilipina, AQP7, FABP, ACC, FAS, LPL

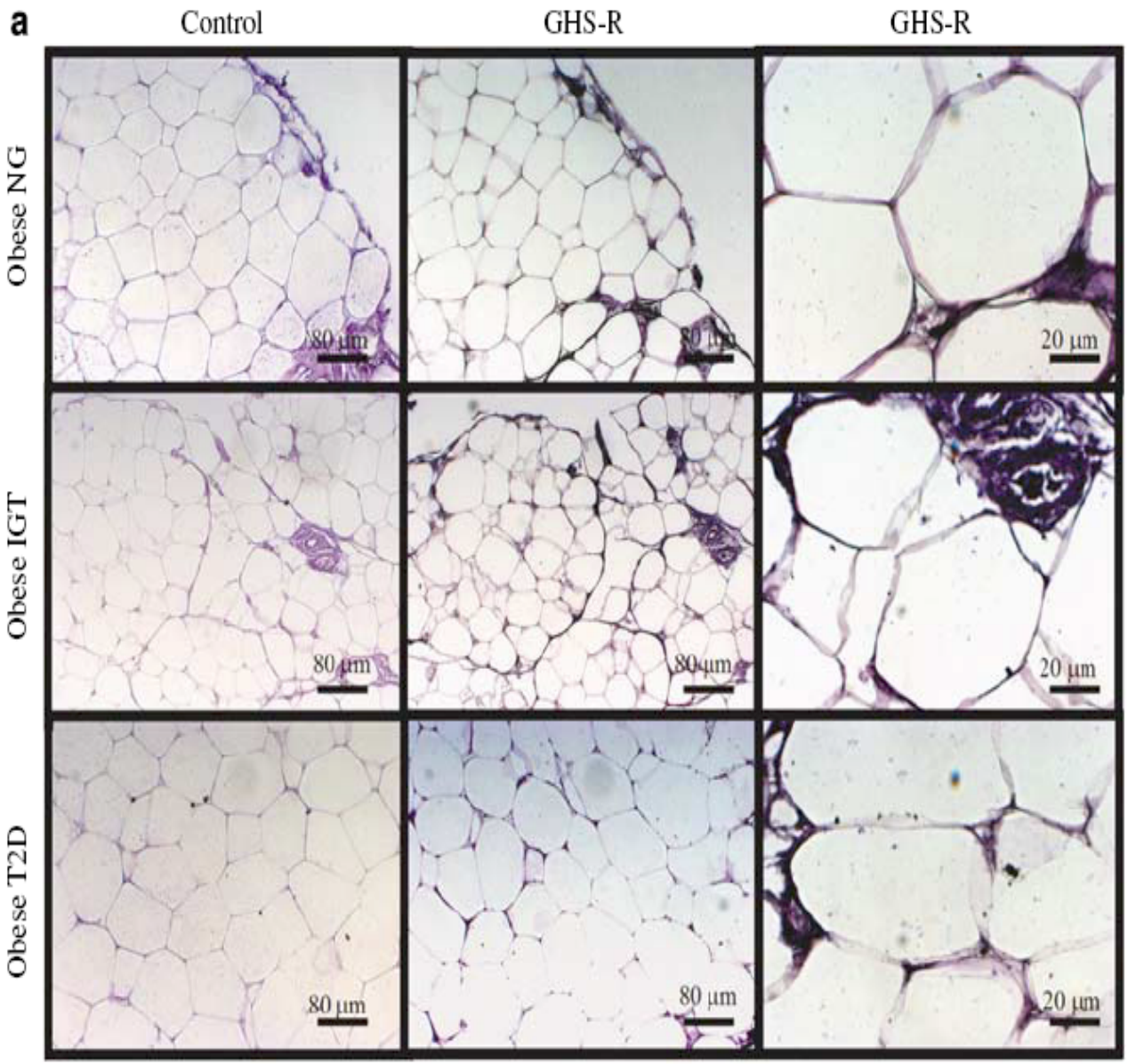
TG intracelulares



Métodos enzimáticos

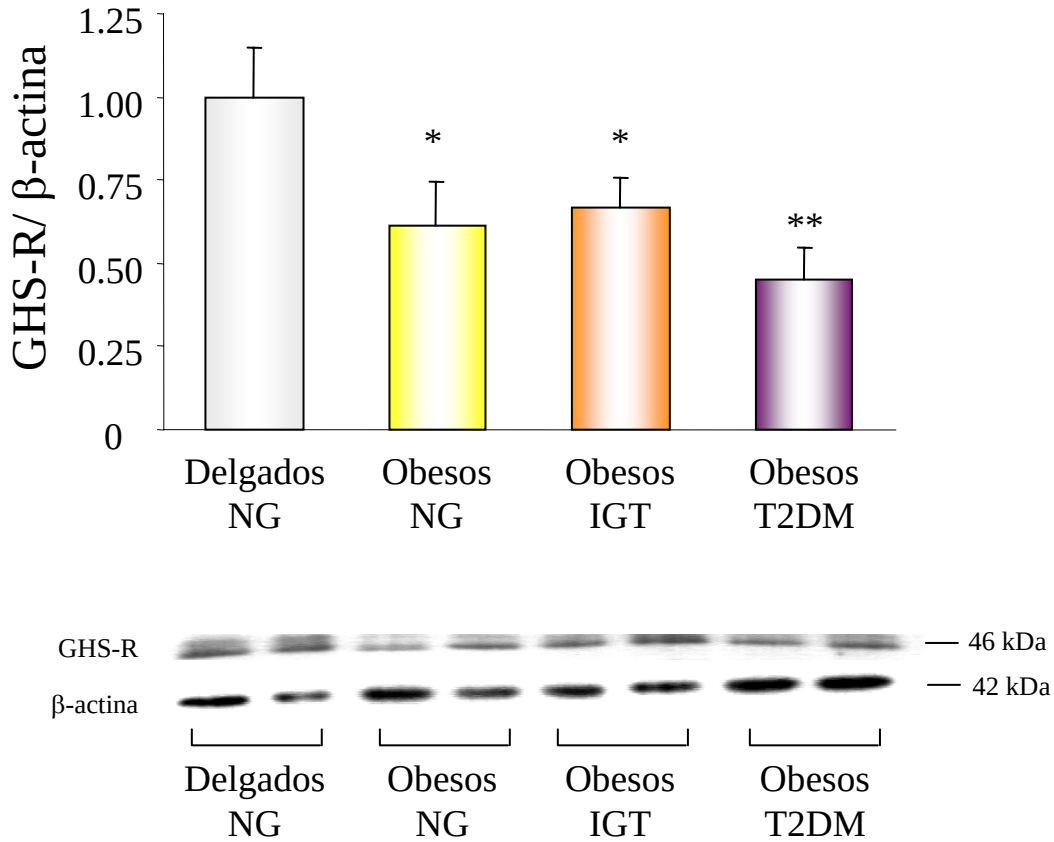
Oil Red O

Expresión de GHS-R en grasa omental



Rodríguez et al, IJO 2009

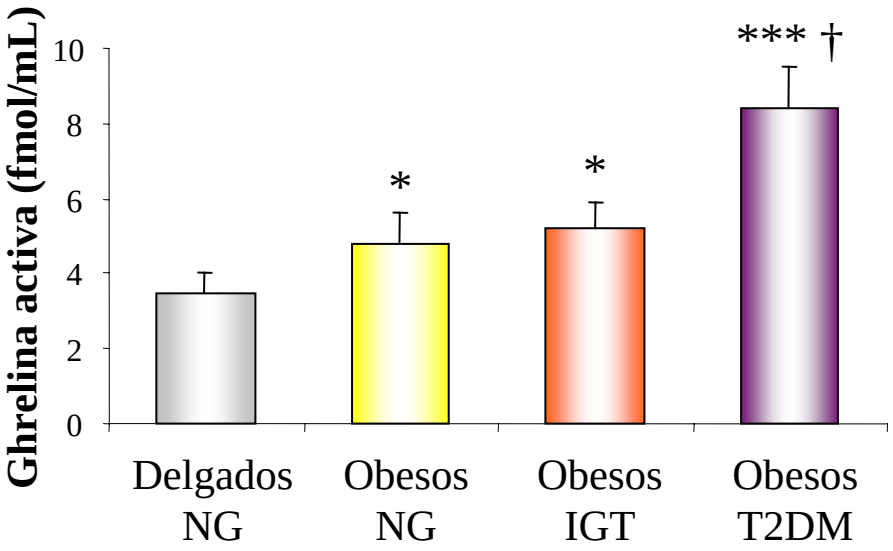
Expresión de GHS-R en grasa omental



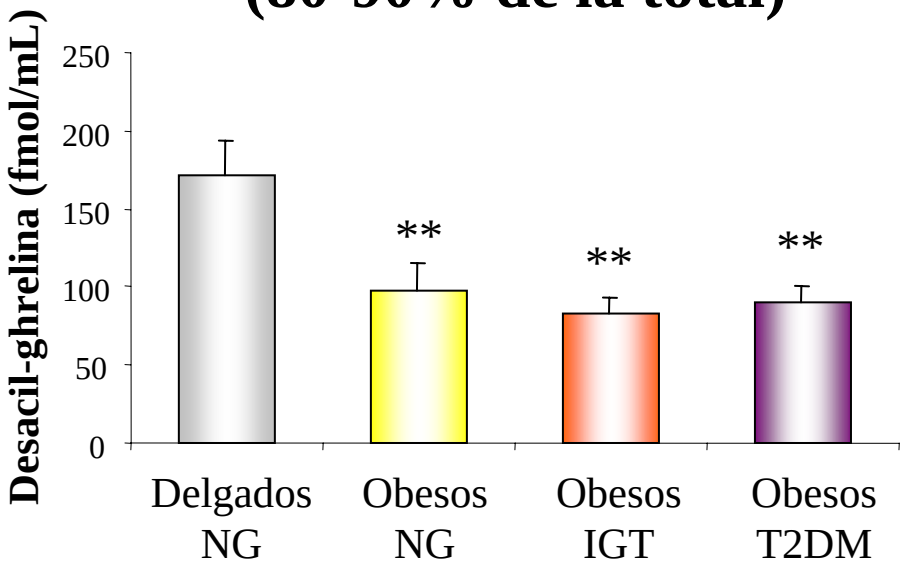
Rodríguez et al, IJO 2009

Niveles circulantes de ghrelina y desacil-ghrelina

Ghrelina acilada



Desacil-ghrelina plasmática (80-90% de la total)

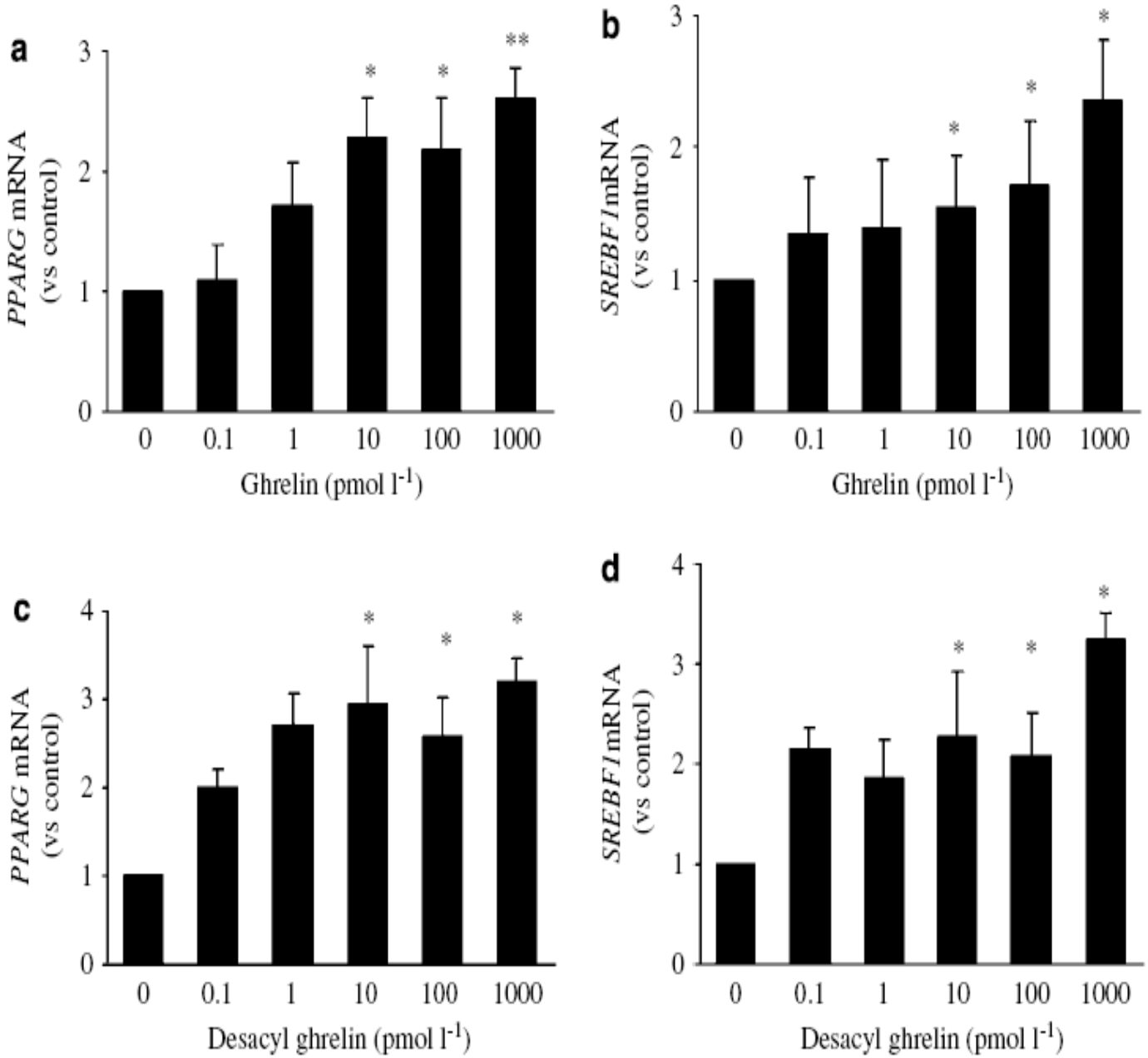


NG, normoglucémico; IGT, intolerante a la glucosa; T2DM, diabético de tipo 2

*P<0,05 and ***P<0,001 vs delgados; † P<0,05 vs obesos NG

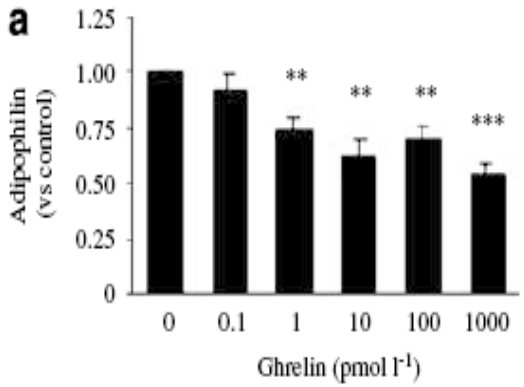
Rodríguez et al, IJO 2009

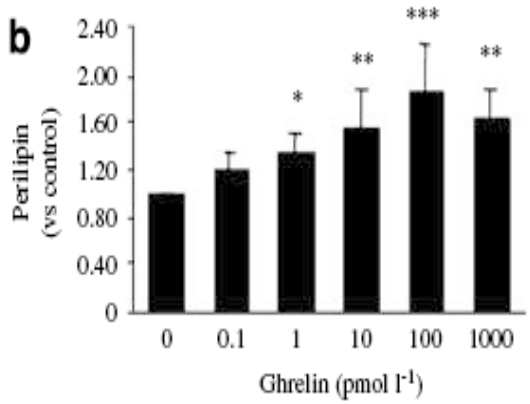
Estimulación de la adipogénesis



Efecto ghrelina

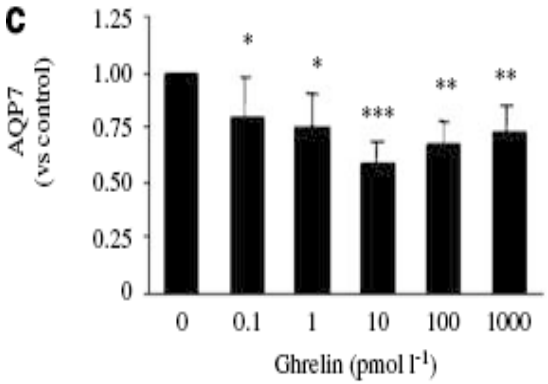
Adipofilina

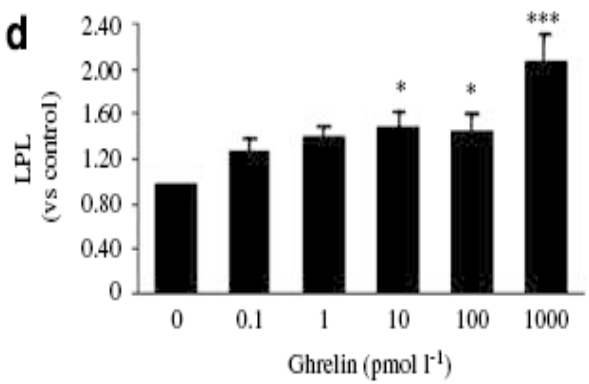




Perilipina

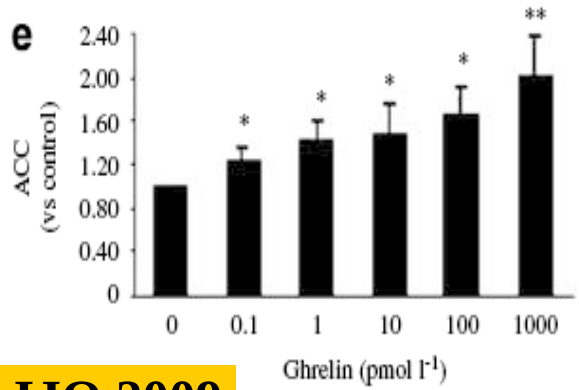
AQP7

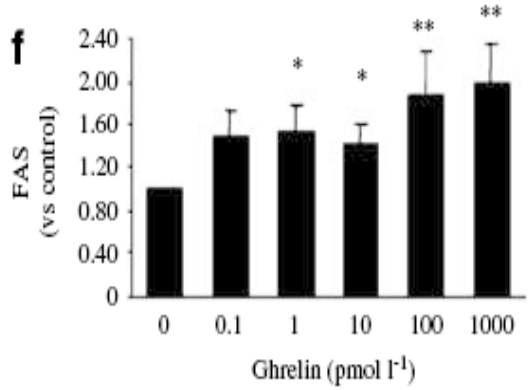




LPL

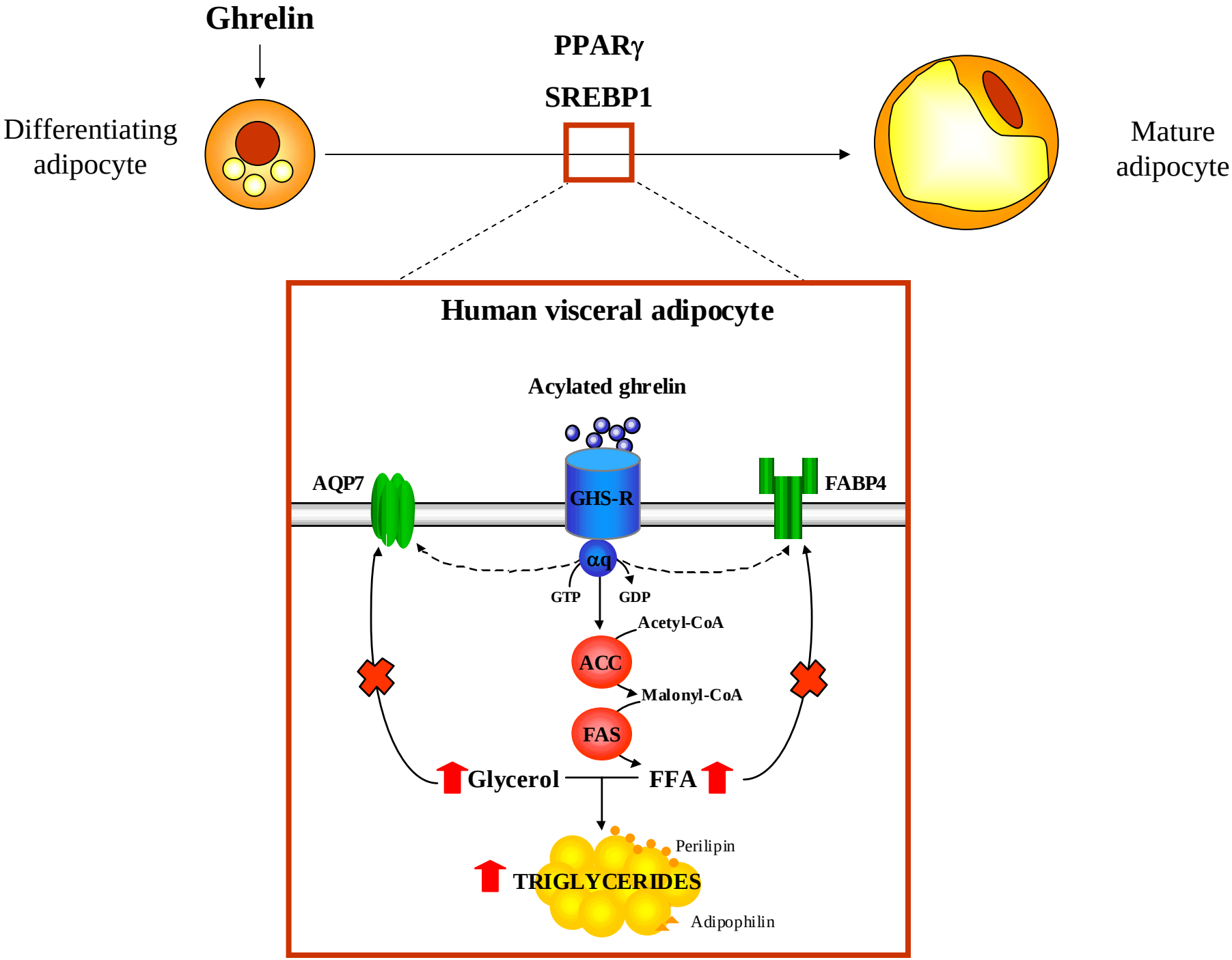
ACC



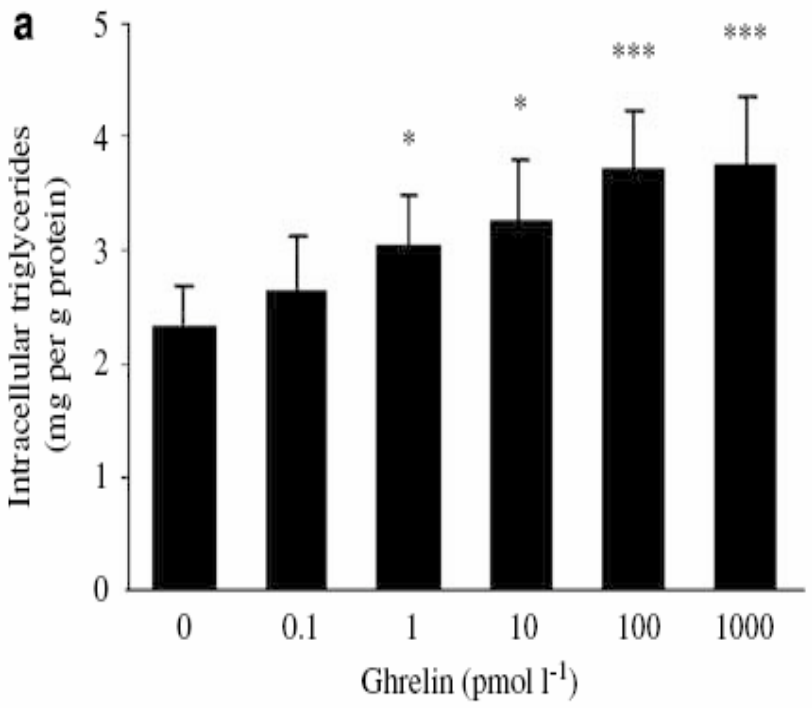


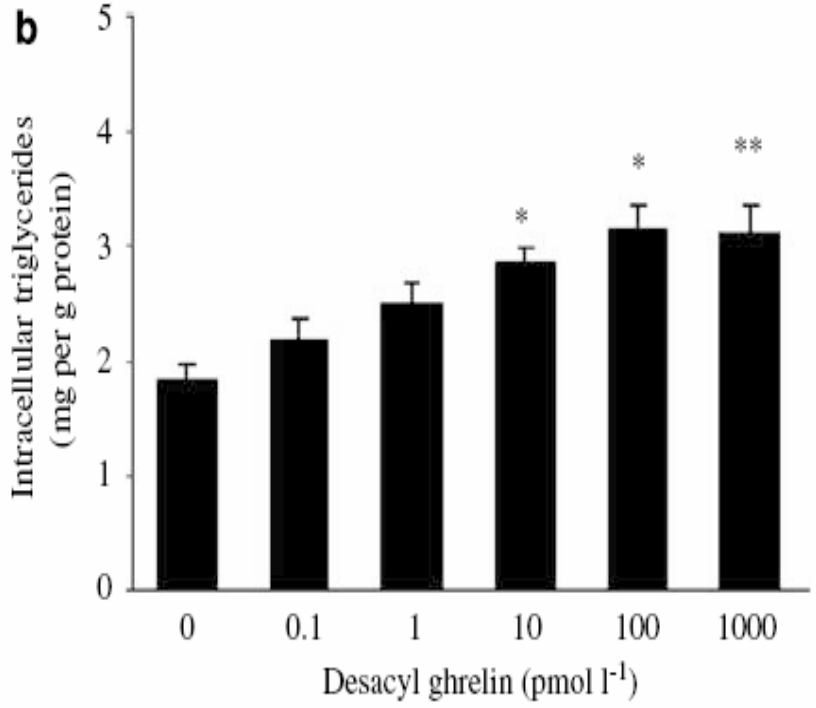
FAS

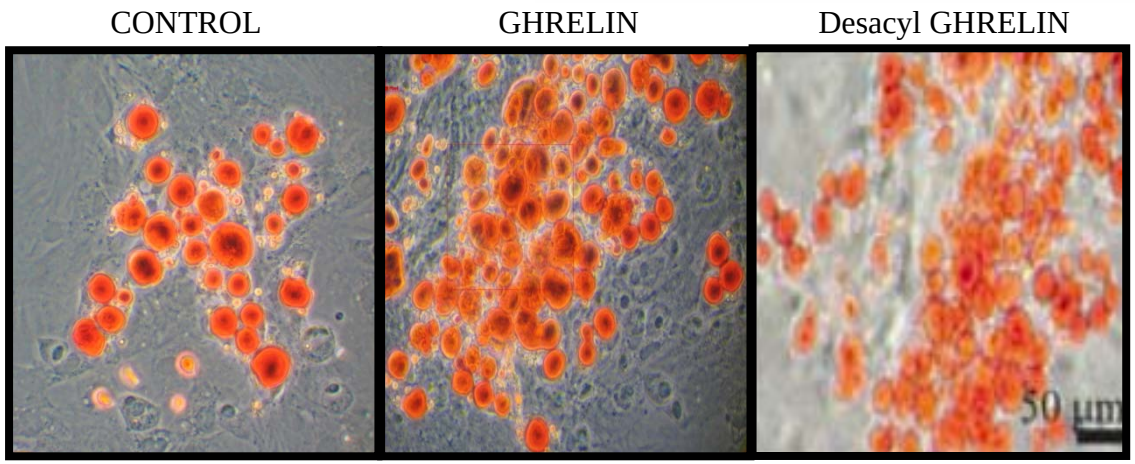
Rodríguez et al, IJO 2009


Ghrelin
PPARγ
SREBP1
Differentiating adipocyte
Mature adipocyte
Human visceral adipocyte
Acylated ghrelin
AQP7
GHS-R
FABP4
αq
GTP
GDP
Acetyl-CoA
ACC
Malonyl-CoA
FAS
Glycerol
FFA
Perilipin
TRIGLYCERIDES
Adipophilin

Acumulación intracelular de lípidos







Rodríguez et al, IJO 2009

ESQUEMA GENERAL

Evidencia epidemiológica y genética

Características generales del tejido adiposo

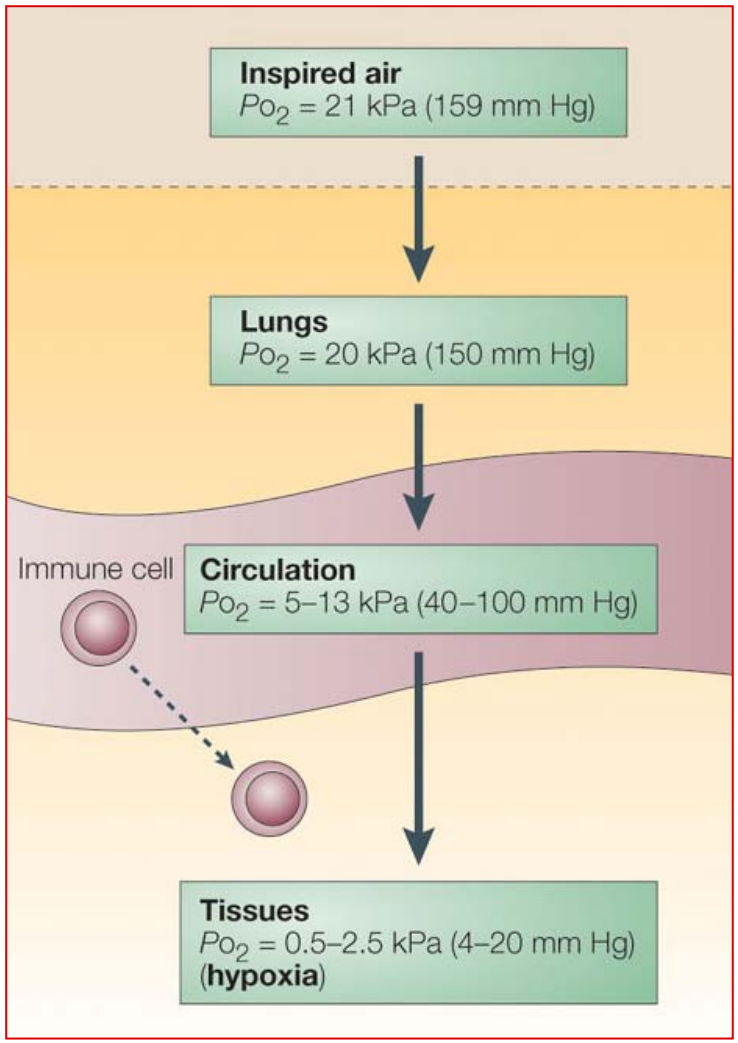
Adipoquinas, insulino-resistencia e inflamación

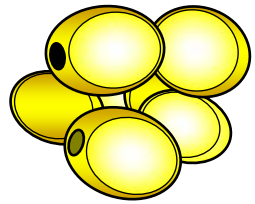
Vías relacionadas con el metabolismo lipídico

Genes de respuesta a hipoxia

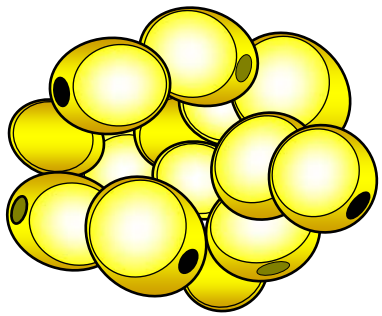
Nuevos hallazgos - implicaciones

Genes de respuesta a hipoxia





HIPOXIA



Hipertrofia
Hiperplasia

↑ HIF1

Adaptación metabólica

ALDA, ENO1, GAPDH, GLUT1, GLUT3, GPI, HK1, HK2, LDHA, PFKBF3, PFKL, PGK1, PGM, TPI

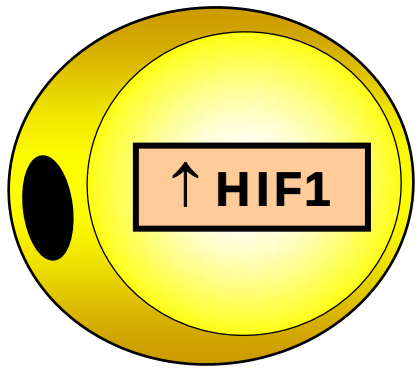
Angiogénesis

Apoptosis

Genes de respuesta a hipoxia

↑ Angpt14
Apelina
IL-1β, IL-6
Leptina
MMP2, MMP9
MT-3
PAI-1, VEGF
Visfatina
GLUT1, GLUT3, GLUT5
PDK

HIPOXIA

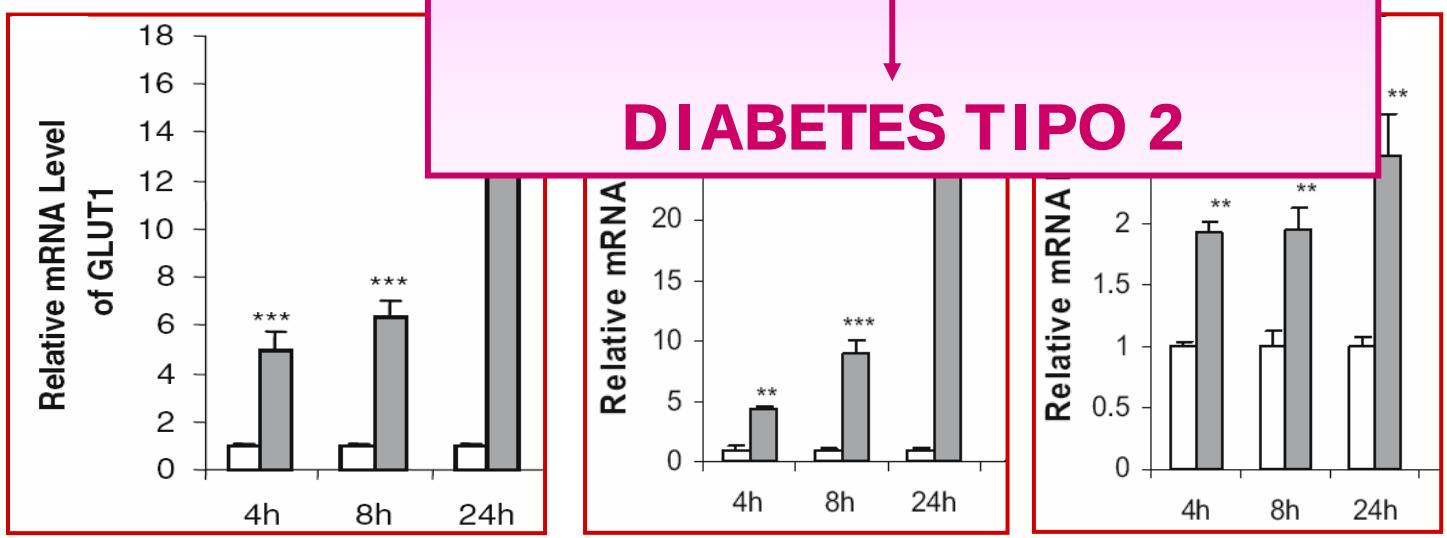


↓ Adiponectina
Haptoglobina
PPARγ

INFLAMACIÓN

↓

DIABETES TIPO 2



Segawa et al. *BBRC* 2006; Wang et al. *Pflugers Arch* 2007; Trayhurn et al. *Br J Nutr* 2008

ESQUEMA GENERAL

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Características generales del tejido adiposo

Adipoquinas, insulino-resistencia e inflamación

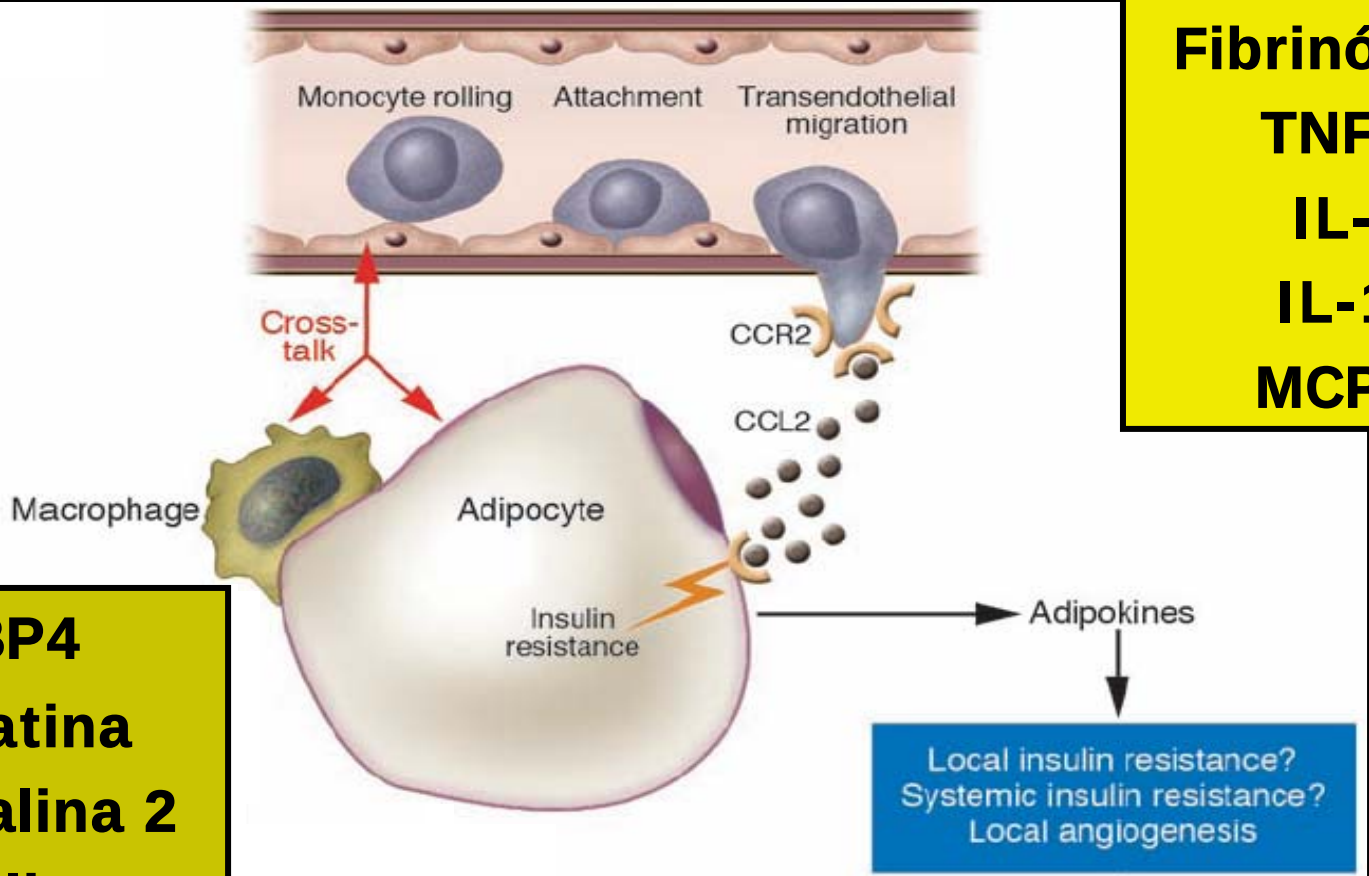
Vías relacionadas con el metabolismo lipídico

Genes de respuesta a hipoxia

Nuevos hallazgos - implicaciones

Expresión génica de nuevas adipoquinas inflamatorias

PCR
Fibrinógeno
TNF-α
IL-6
IL-1β
MCP-1



RBP4
Visfatina
Lipocalina 2
Apelina
Chemerina
Vaspina

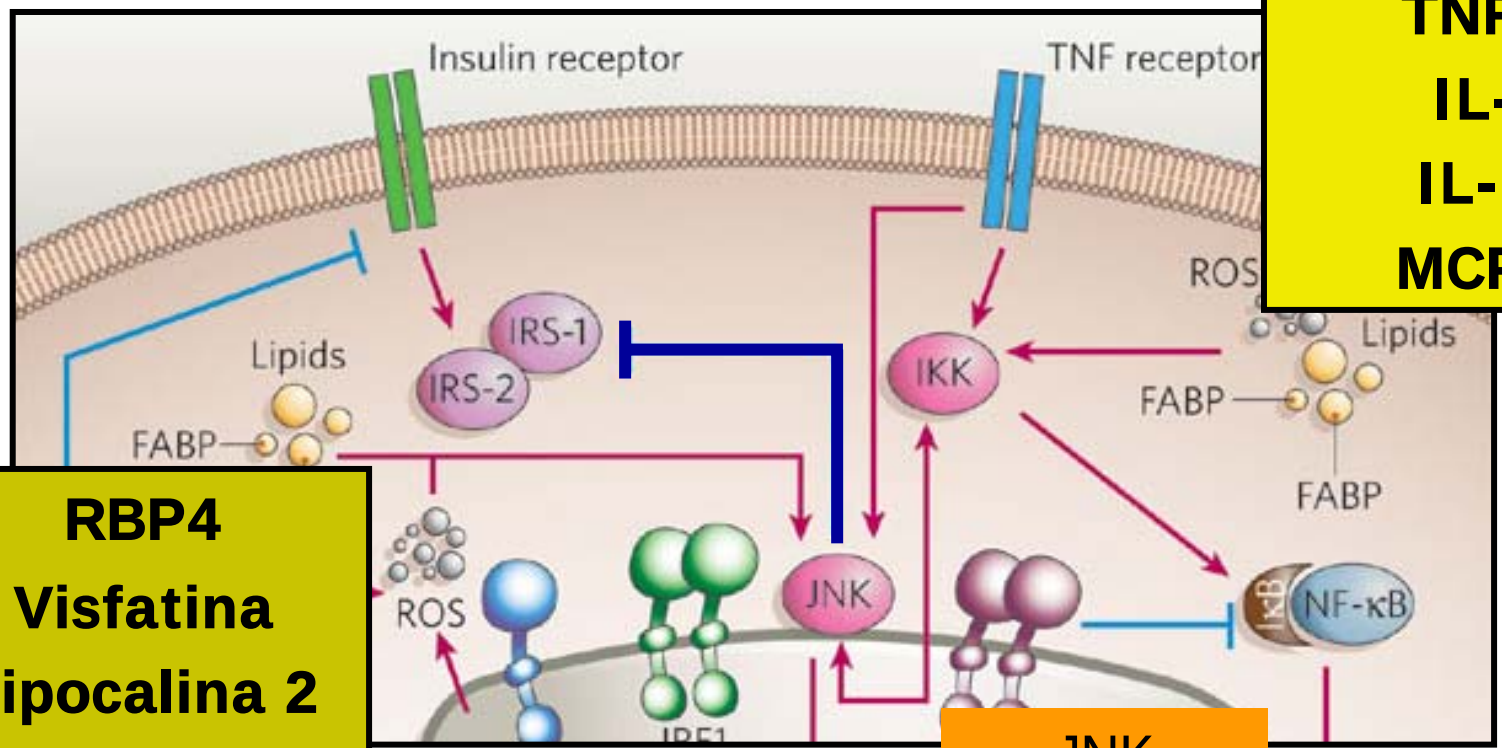
Inflamación-Diabetes tipo 2

¿Asociación independiente de la obesidad?

Schmidt et al. *Lancet* 1999; Dandona et al. *Trends Inmunol* 2004; Neels and Olefsky. *J Clin Invest* 2006

Expresión génica de nuevas adipoquinas inflamatorias

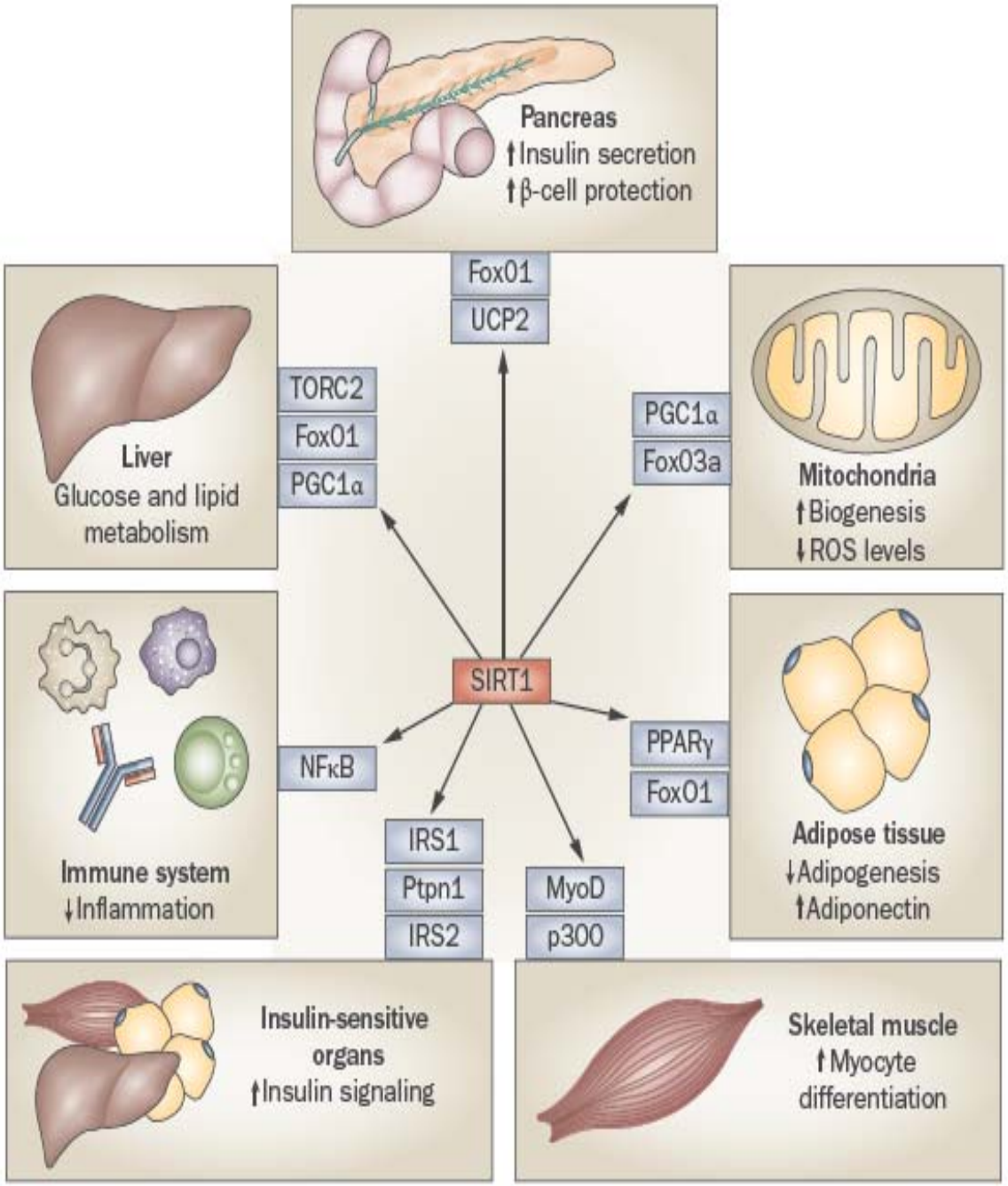
CRP
Fibrinógeno
TNF-α
IL-6
IL-1β
MCP-1



RBP4
Visfatina
Lipocalina 2
Apelina
Chemerina
Vaspina

JNK
NF-κB
PKC

Schmidt et al. *Lancet* 1999; Dandona et al. *Trends Inmunol* 2004; Neels and Olefsky. *J Clin Invest* 2006



SIRT1 activation

↓

glucose ↓

insulin ↓

glucose tolerance ↑

insulin sensitivity ↑ ?

mitochondrial function ↑

hepatic steatosis ↓

⊥

type 2 diabetes

Liang et al, *Nat Rev Endocrinol* 2009

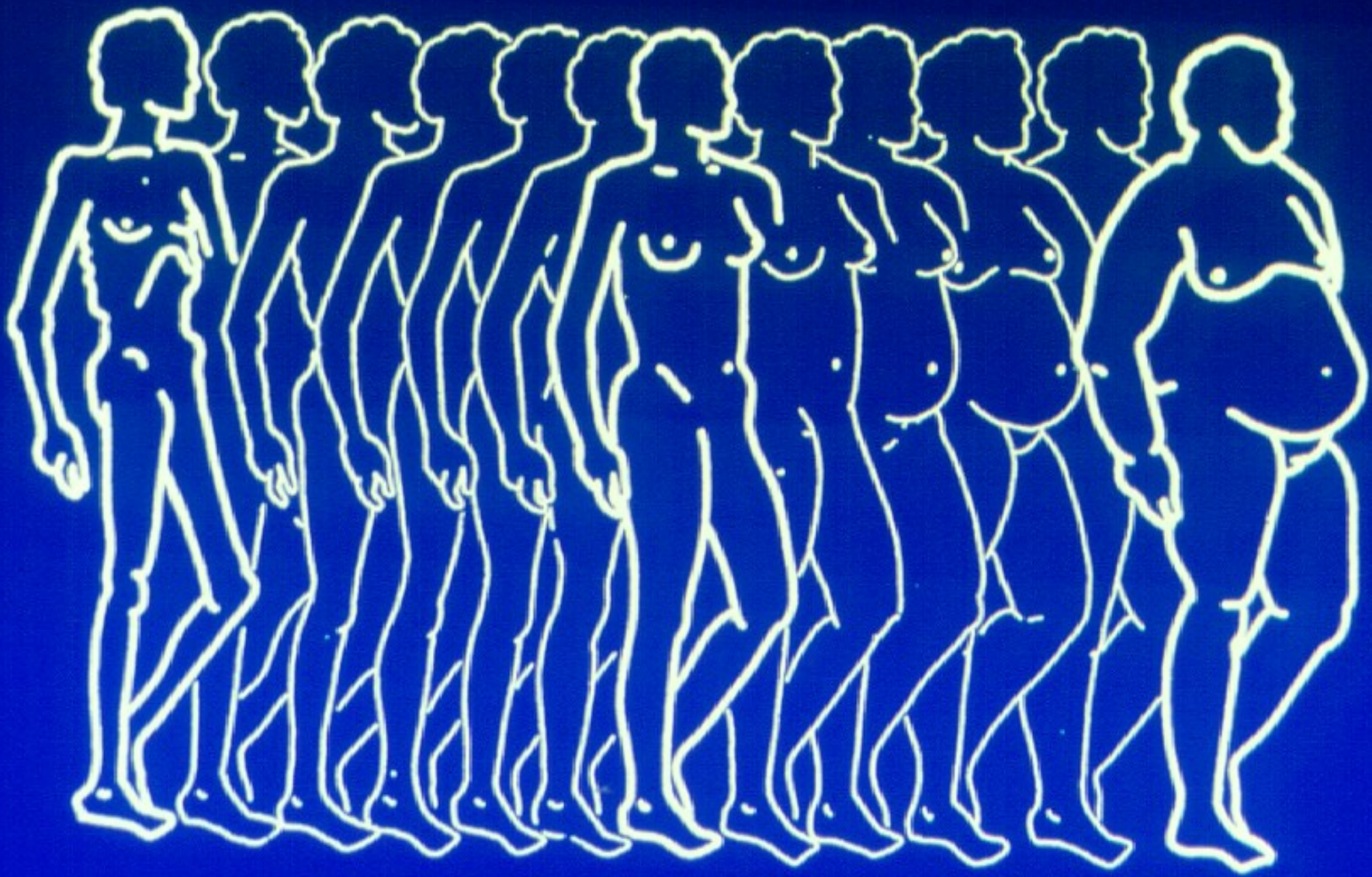
An Increase in the Circulating Concentration of Monocyte Chemoattractant Protein-1 Elicits Systemic Insulin Resistance Irrespective of Adipose Tissue Inflammation in Mice

Chronic inflammation in adipose tissue is thought to be important for the development of insulin resistance in obesity. Furthermore, the level of monocyte chemoattractant protein-1 (MCP-1) is increased not only in adipose tissue but also in the circulation in association with obesity. However, it has remained unclear to what extent the increased circulating level of MCP-1 contributes to insulin resistance. We have now examined the relevance of circulating MCP-1 to the development of insulin resistance in mice. The plasma concentration of MCP-1 was increased chronically or acutely in mice to the level observed in obese animals by chronic subcutaneous infusion of recombinant MCP-1 with an osmotic pump or by acute intravenous infusion of MCP-1 with an infusion pump, respectively. Whole-body metabolic parameters as well as inflammatory changes in adipose tissue were examined. A chronic increase in the circulating level of MCP-1 induced insulin resistance, macrophage infiltration into adipose tissue, and an increase in hepatic triacylglycerol content. An acute increase in the circulating MCP-1 concentration also induced insulin resistance but not macrophage infiltration into adipose tissue. In addition, inhibition of signaling by MCP-1 and its receptor CCR2 by administration of a novel CCR2 antagonist ameliorated insulin resistance in mice fed a high-fat diet without affecting macrophage infiltration into adipose tissue. These data indicate that an increase in the concentration of MCP-1 in the circulation is sufficient to induce systemic insulin resistance irrespective of adipose tissue inflammation. (*Endocrinology* 151:

Tateya et al. **Endocrinology. First published ahead of print January 7, 2010**

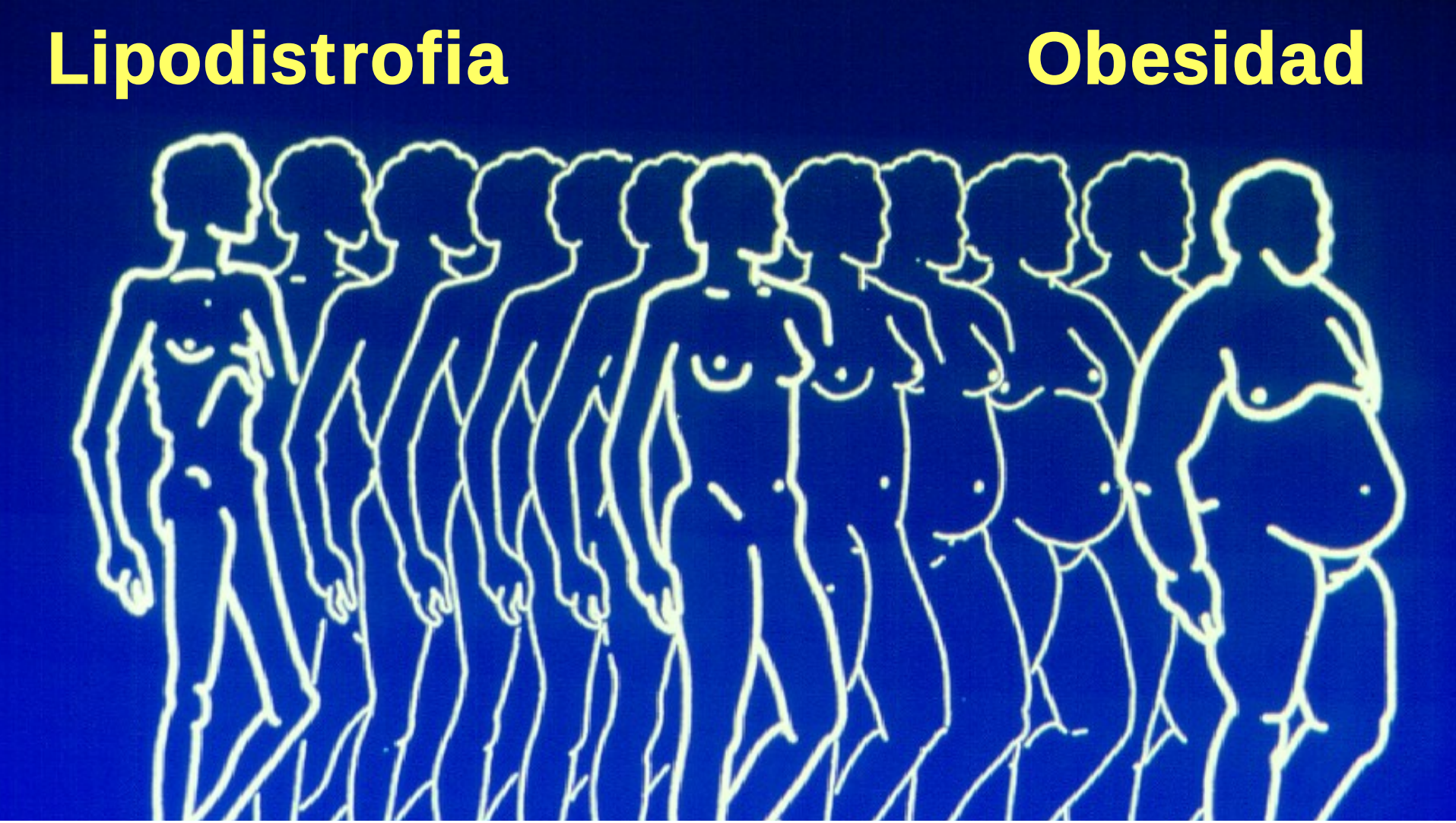
Lipodistrofia

Obesidad



Lipodistrofia

Obesidad



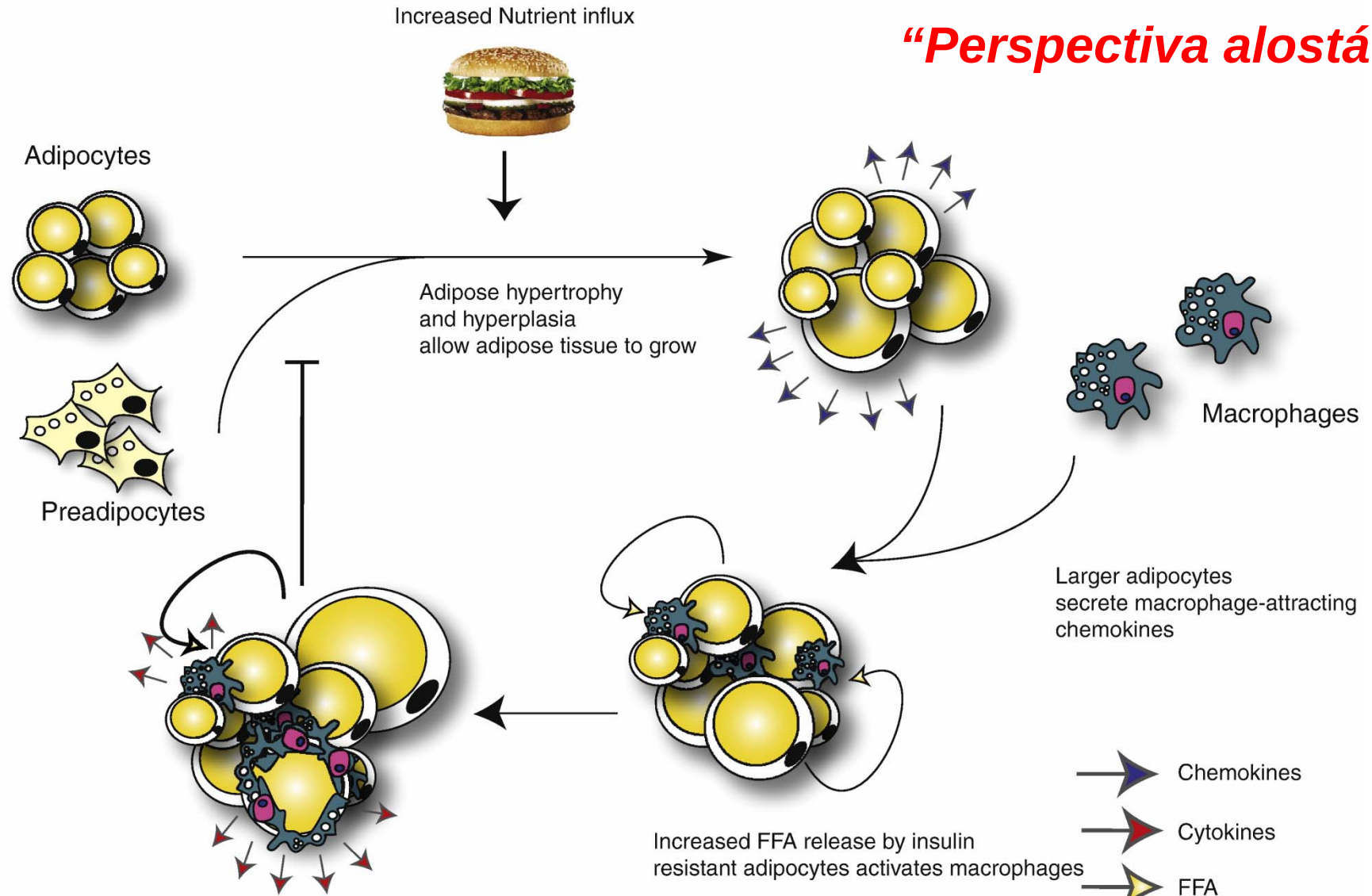
Inflammation and adipose tissue macrophages in lipodystrophic mice

240–245 | PNAS | January 5, 2010

Laura Herrero[1], Hagit Shapiro, Ali Nayer, Jongsoon Lee, and Steven E. Shoelson[2]

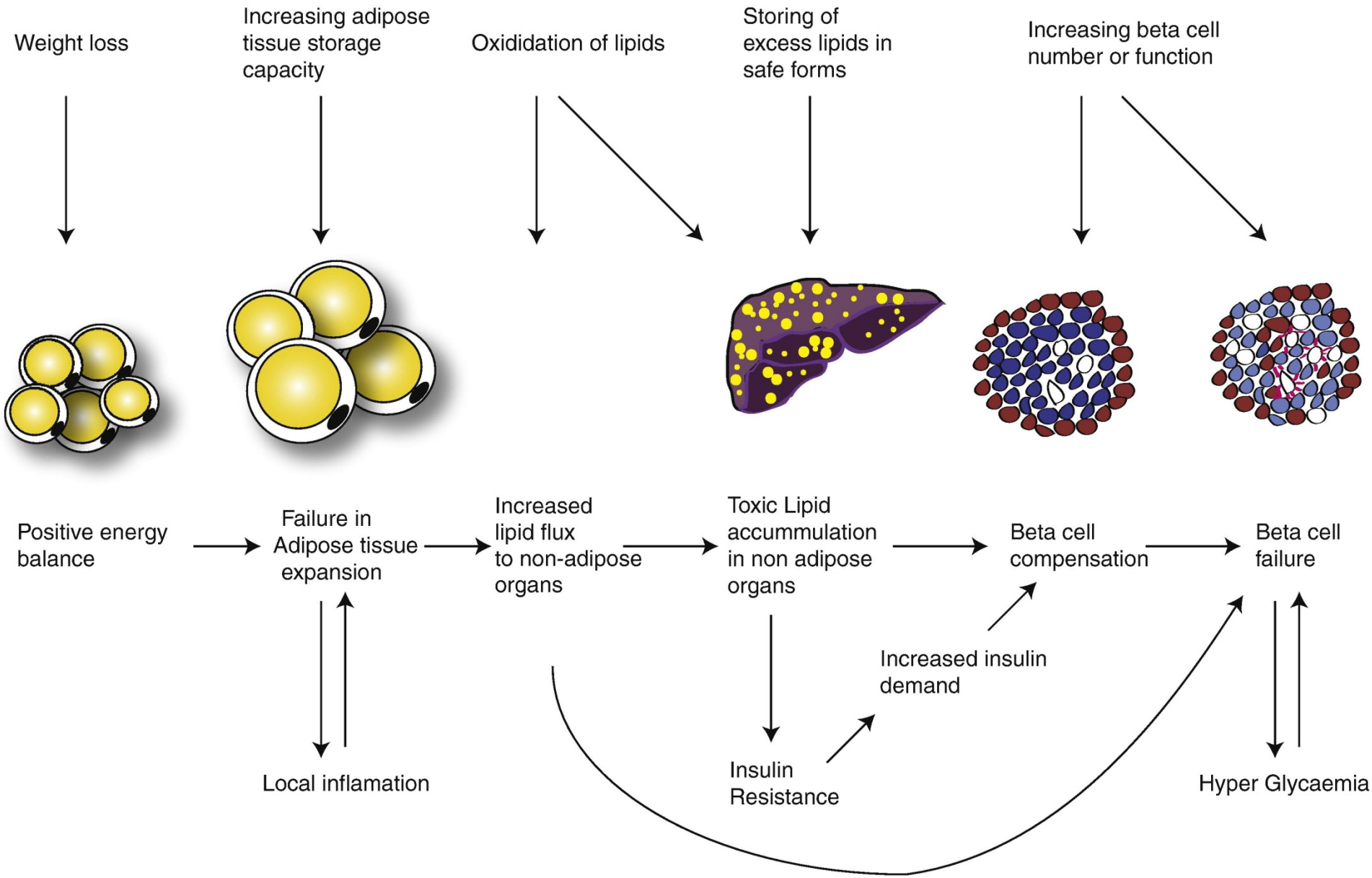
Expansibilidad del tejido adiposo, lipotoxicidad y sínd. metab.

"Perspectiva alostática"



Virtue & Vidal-Puig, Biochim Biophys Acta 2010 (in press)

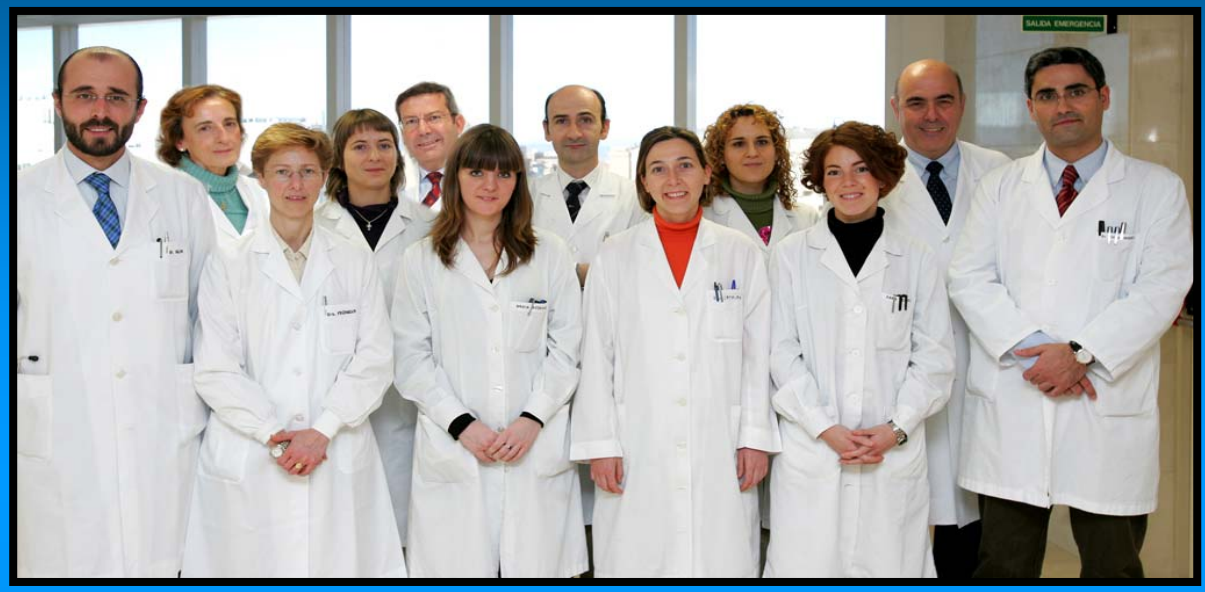
Expansibilidad del tejido adiposo, lipotoxicidad y sínd. metab.



Virtue & Vidal-Puig, Biochim Biophys Acta 2010 (in press)

Clínica Universidad de Navarra

Equipo Multidisciplinar de Diagnóstico y Tratamiento de la Obesidad



Lab. Investigación Metabólica

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Beatriz Ramírez
Sara Becerril
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Centro de Investigación Biomédica En Red
Fisiopatología de la Obesidad y Nutrición

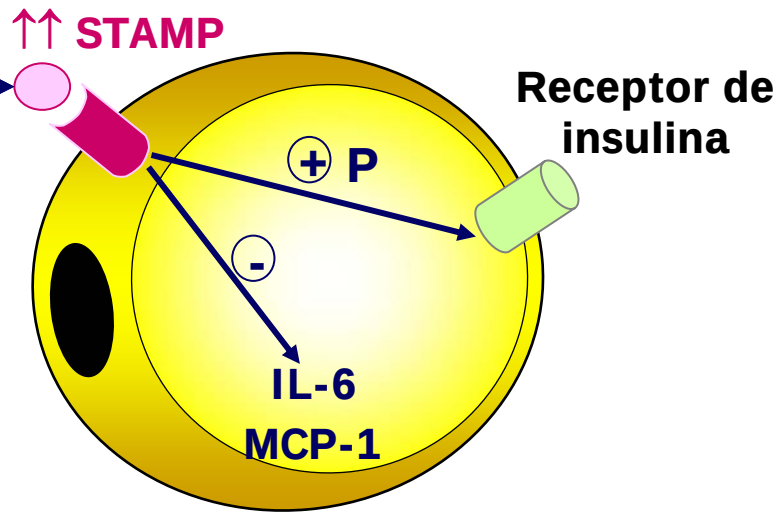
Expresión génica de nuevas adipoquinas inflamatorias

STAMP

STAMP$^{-/-}$: Resistentes a la insulina

Ácidos grasos libres

Citoquinas inflamatorias



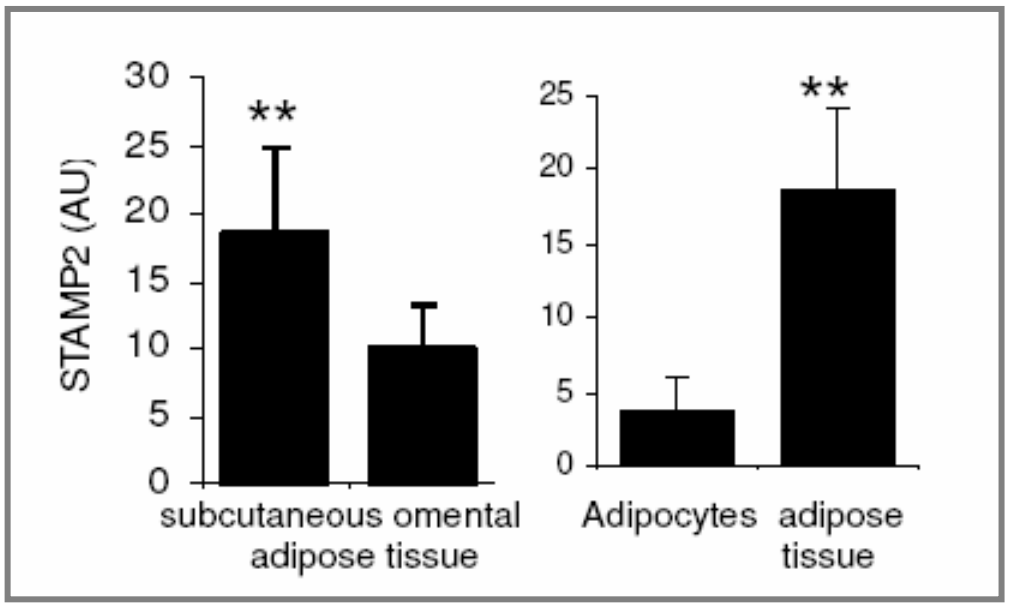
Aumento en captación de glucosa

Disminución de la inflamación

Waki et al. *Cell* 2007; Wellen et al. *Cell* 2007

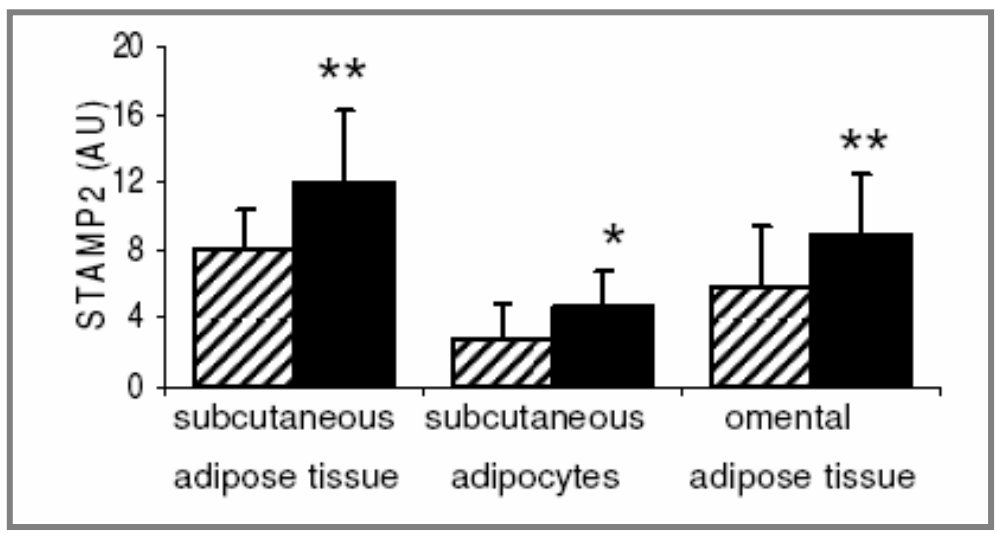
Expresión génica de nuevas adipoquinas inflamatorias

STAMP



Expresión en subcutáneo> Expresión en visceral

¿Expresión por SVF?

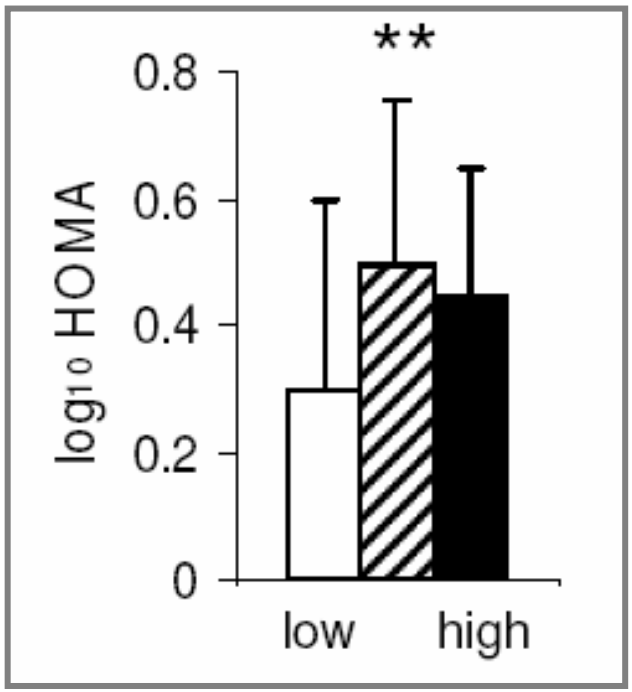


Expresión en obesos> Expresión en delgados

Arner et al. *J Clin Endocrinol Metab* 2008

Expresión génica de nuevas adipoquinas inflamatorias

STAMP



Aumento de la expresión de STAMP al aumentar la insulino-resistencia

TNF-α activa STAMP en cultivos

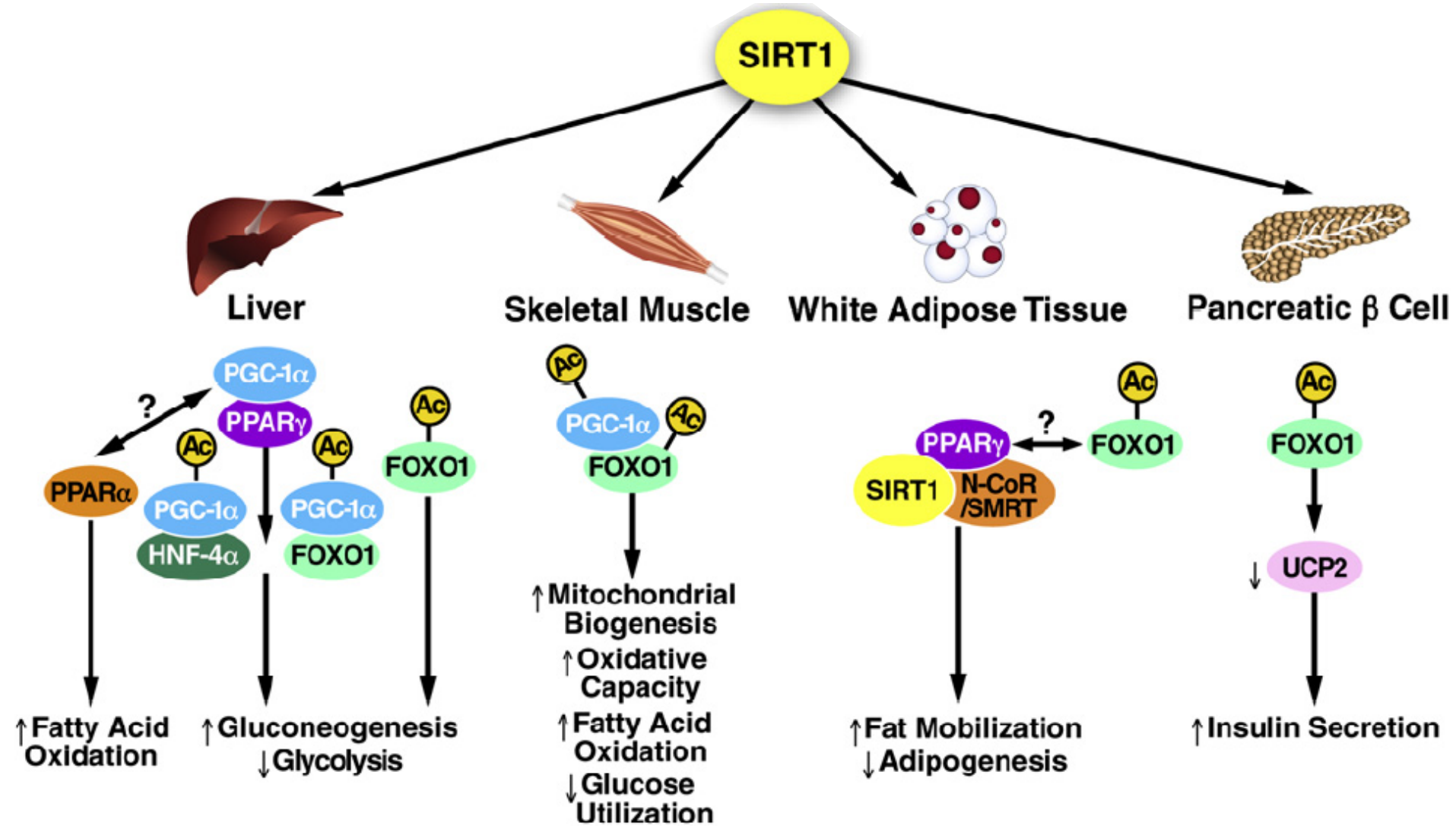
	STAMP2	
	Correlation coefficient	P-value
CD68	0.35	0.0005
TNFA	-0.036	0.73
IL6	-0.014	0.90

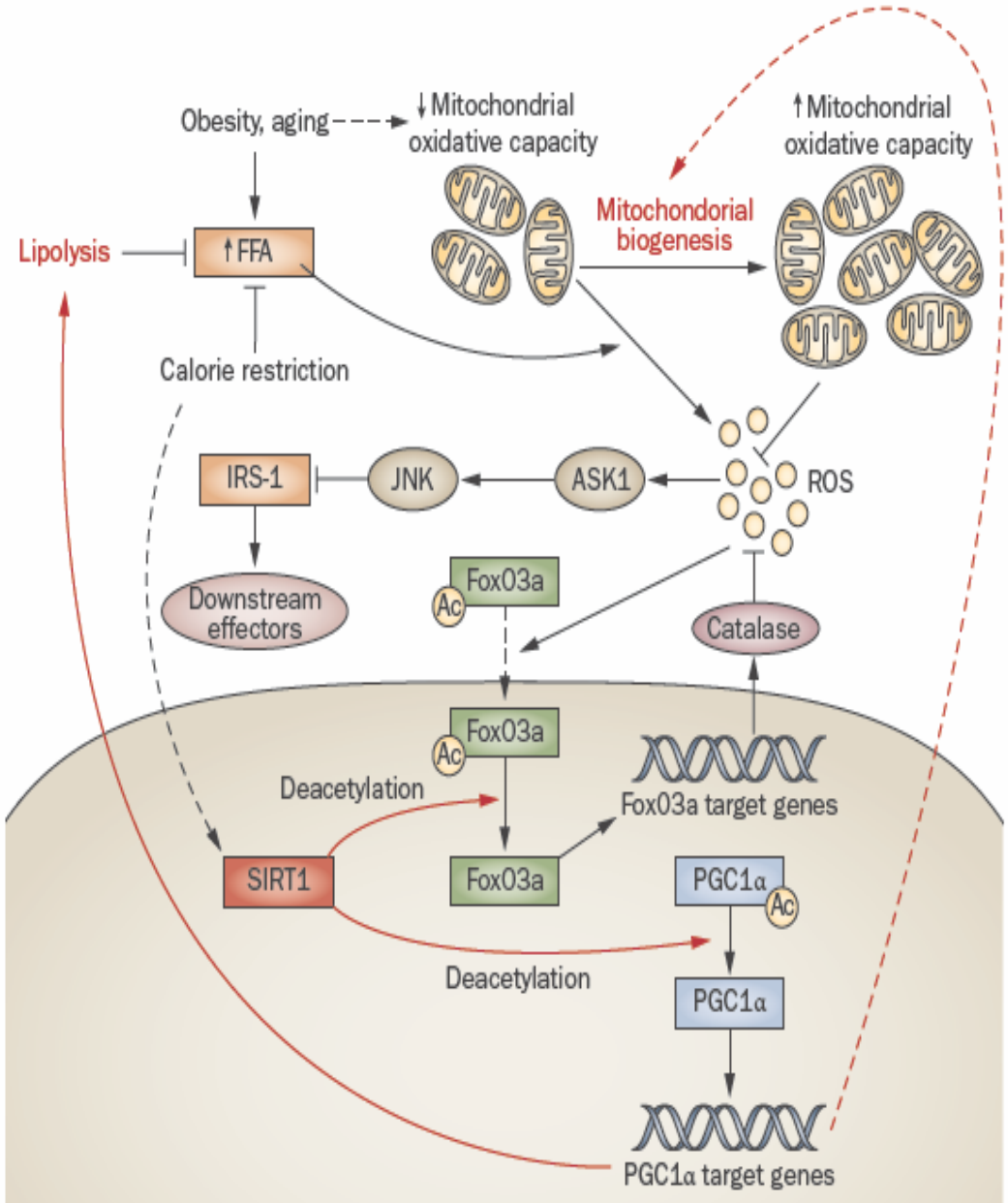
Vías alternativas de activación

Aumento en obesidad
Relación con insulino-resistencia

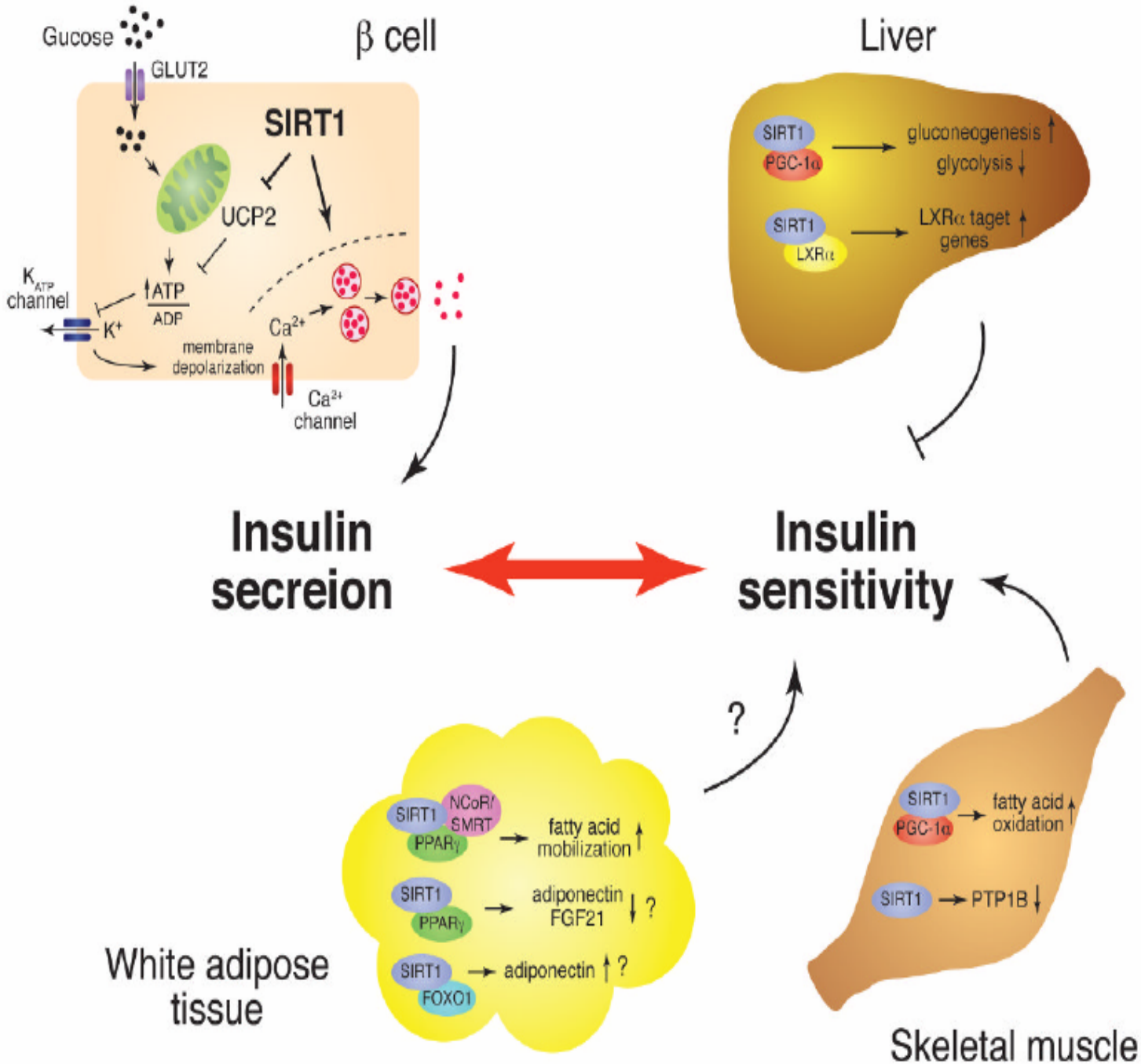
Arner et al. *J Clin Endocrinol Metab* 2008

Pleotropism of Sirtuin1

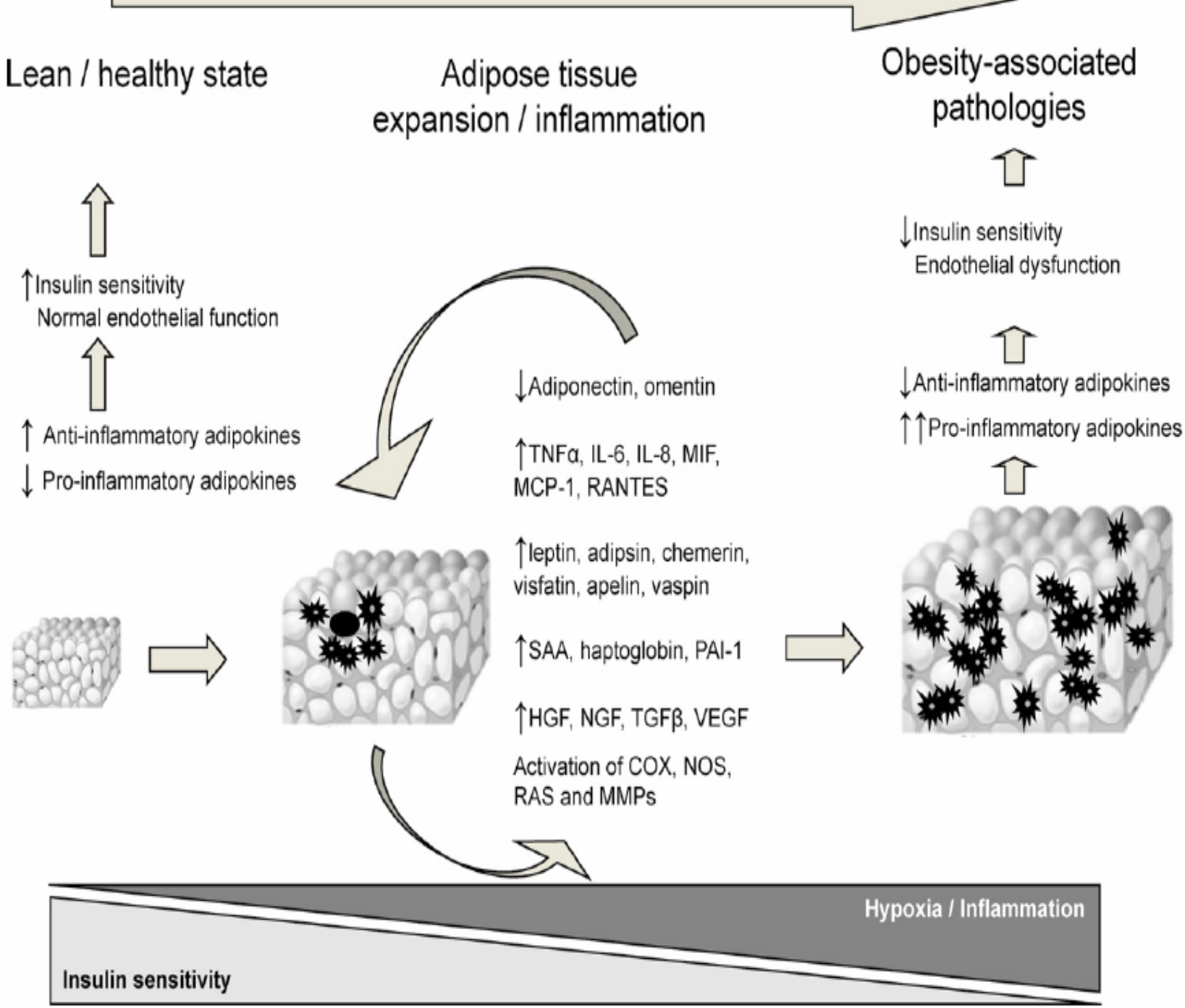


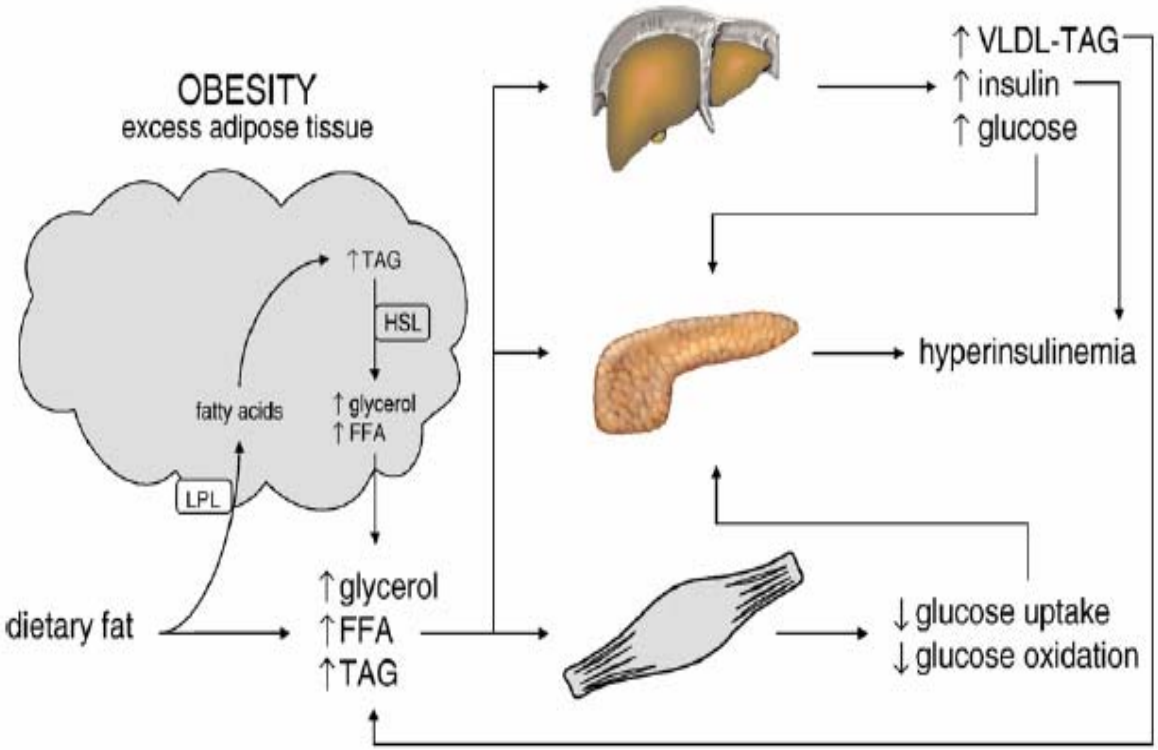


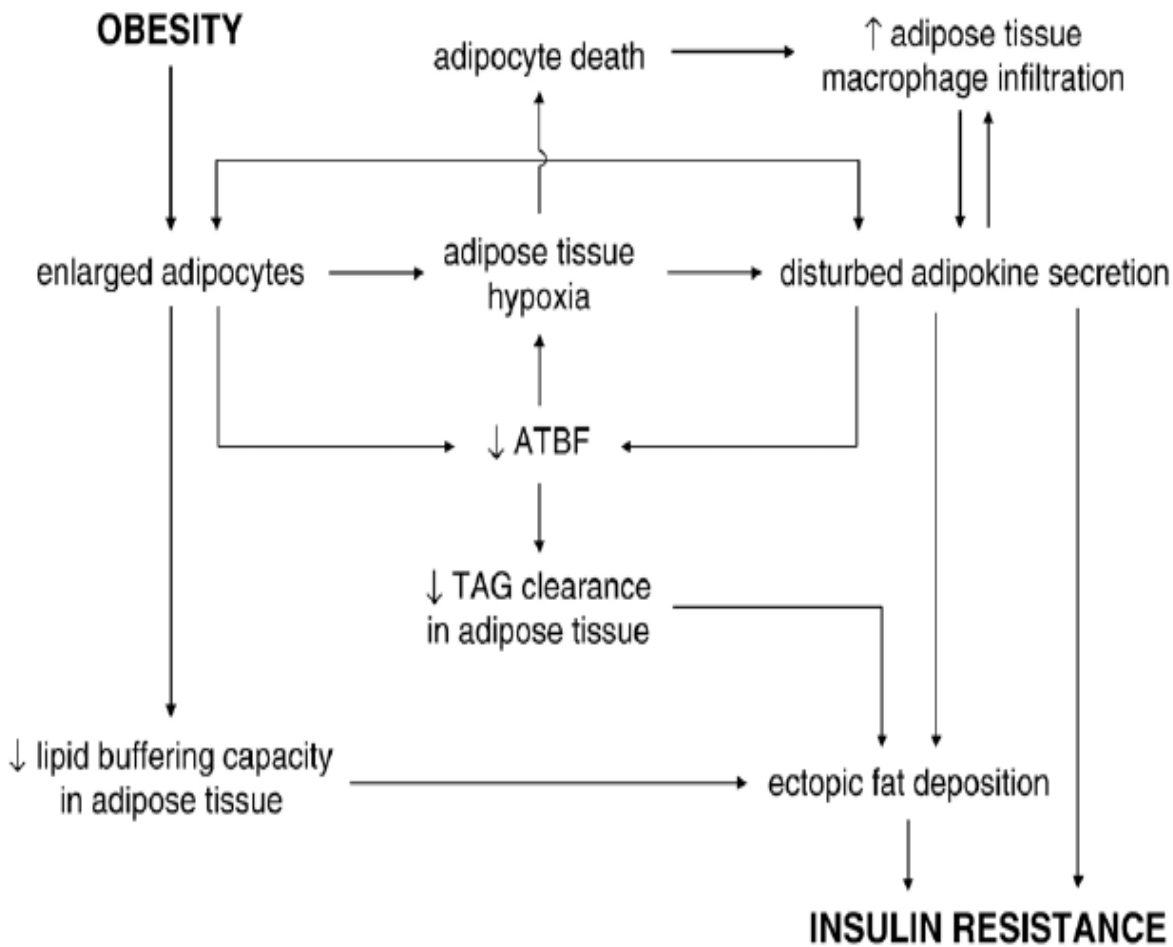
Liang et al, *Nat Rev Endocrinol* 2009



Imai & Kiess, *Front Biosci* 2009


Lean / healthy state
Adipose tissue expansion / inflammation
Obesity-associated pathologies
↑Insulin sensitivity
Normal endothelial function
↑ Anti-inflammatory adipokines
↓ Pro-inflammatory adipokines
↓Adiponectin, omentin
↑TNFα, IL-6, IL-8, MIF, MCP-1, RANTES
↑leptin, adipsin, chemerin, visfatin, apelin, vaspin
↑SAA, haptoglobin, PAI-1
↑HGF, NGF, TGFβ, VEGF
Activation of COX, NOS, RAS and MMPs
↓Insulin sensitivity
Endothelial dysfunction
↓Anti-inflammatory adipokines
↑↑Pro-inflammatory adipokines
Hypoxia / Inflammation
Insulin sensitivity


OBESITY
excess adipose tissue
↑TAG
HSL
fatty acids
↑ glycerol
↑ FFA
LPL
dietary fat
↑glycerol
↑FFA
↑TAG
↑ VLDL-TAG
↑ insulin
↑ glucose
hyperinsulinemia
↓glucose uptake
↓glucose oxidation


OBESITY
adipocyte death
↑ adipose tissue
macrophage infiltration
enlarged adipocytes
adipose tissue
hypoxia
disturbed adipokine secretion
↓ ATBF
↓ TAG clearance
in adipose tissue
↓ lipid buffering capacity
in adipose tissue
ectopic fat deposition
INSULIN RESISTANCE

Inflammation and adipose tissue macrophages in lipodystrophic mice

240–245 | PNAS | January 5, 2010

Laura Herrero[1], Hagit Shapiro, Ali Nayer, Jongsoon Lee, and Steven E. Shoelson[2]

adipose tissue macrophages (ATMs) in lipodystrophy and obesity are very different in terms of activation state, gene expression patterns, and response to lipopolysaccharide. Although ATMs are even more abundant in lipodystrophy than in obesity, they have distinct phenotypes and likely roles in tissue remodeling, but do not appear to be involved in the pathogenesis of insulin resistance.