# The role of the c-Jun N-terminal kinase (JNK) in insulin resistance

Carme Caelles

Department of Biochemistry and Molecular Biology
School of Pharmacy, University of Barcelona
&
Institute of Biomedicine from the University of Barcelona

ccaelles@ub.edu

Universitat de Barcelona

I=B+UB

# Inflammation is at the origin and/or the progression of many diseases

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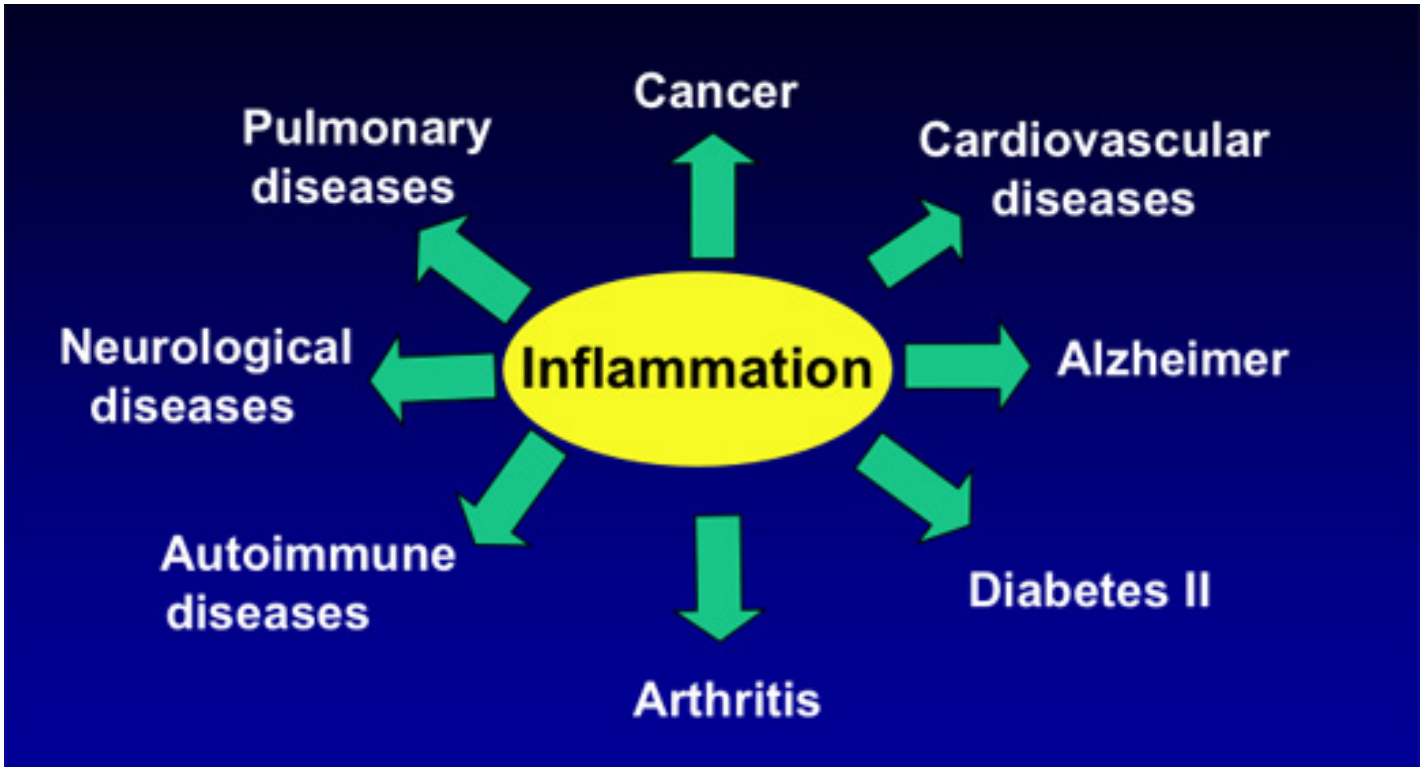
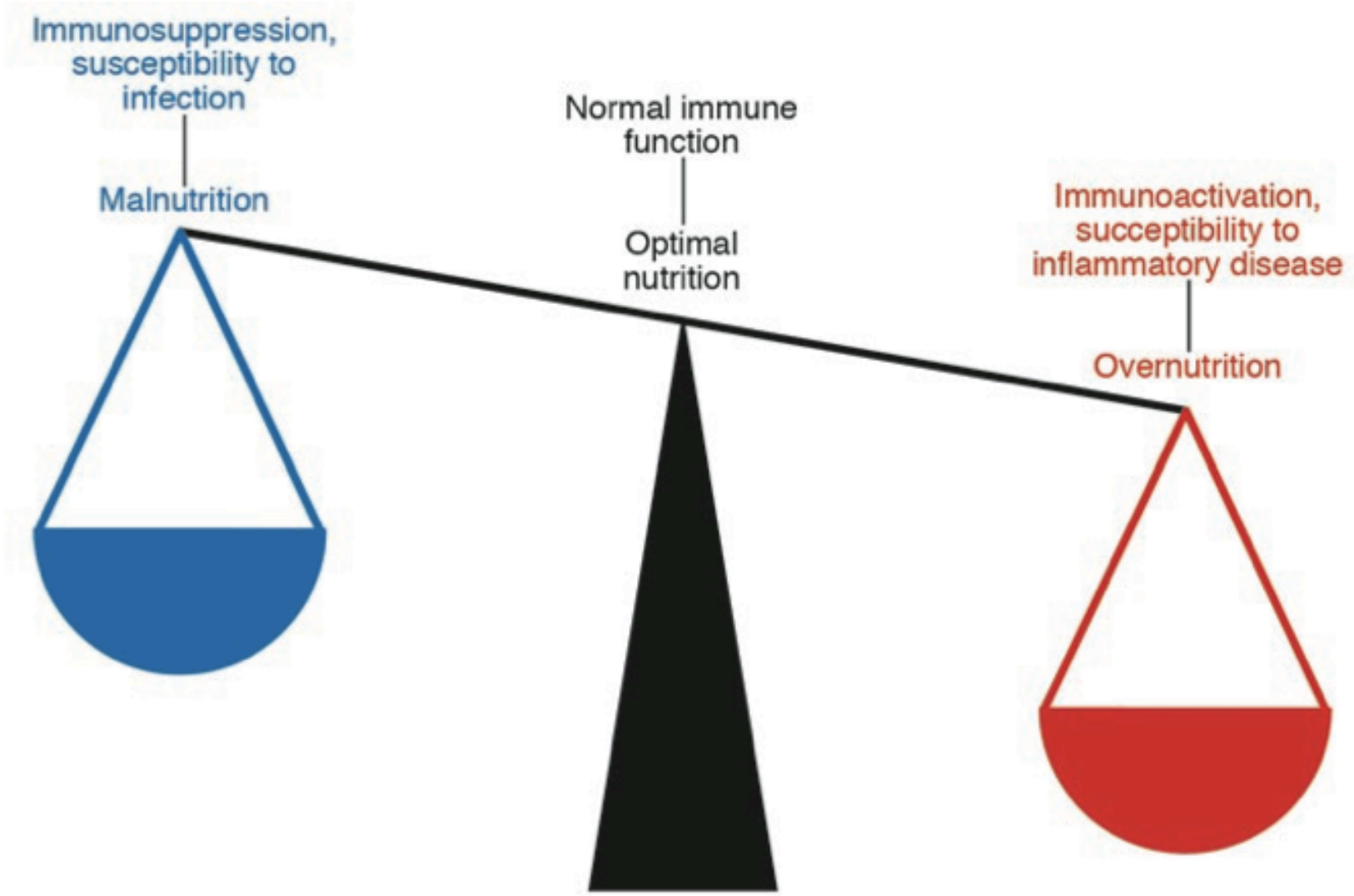
Pro-inflammatory cytokines
Stress


Inflammation

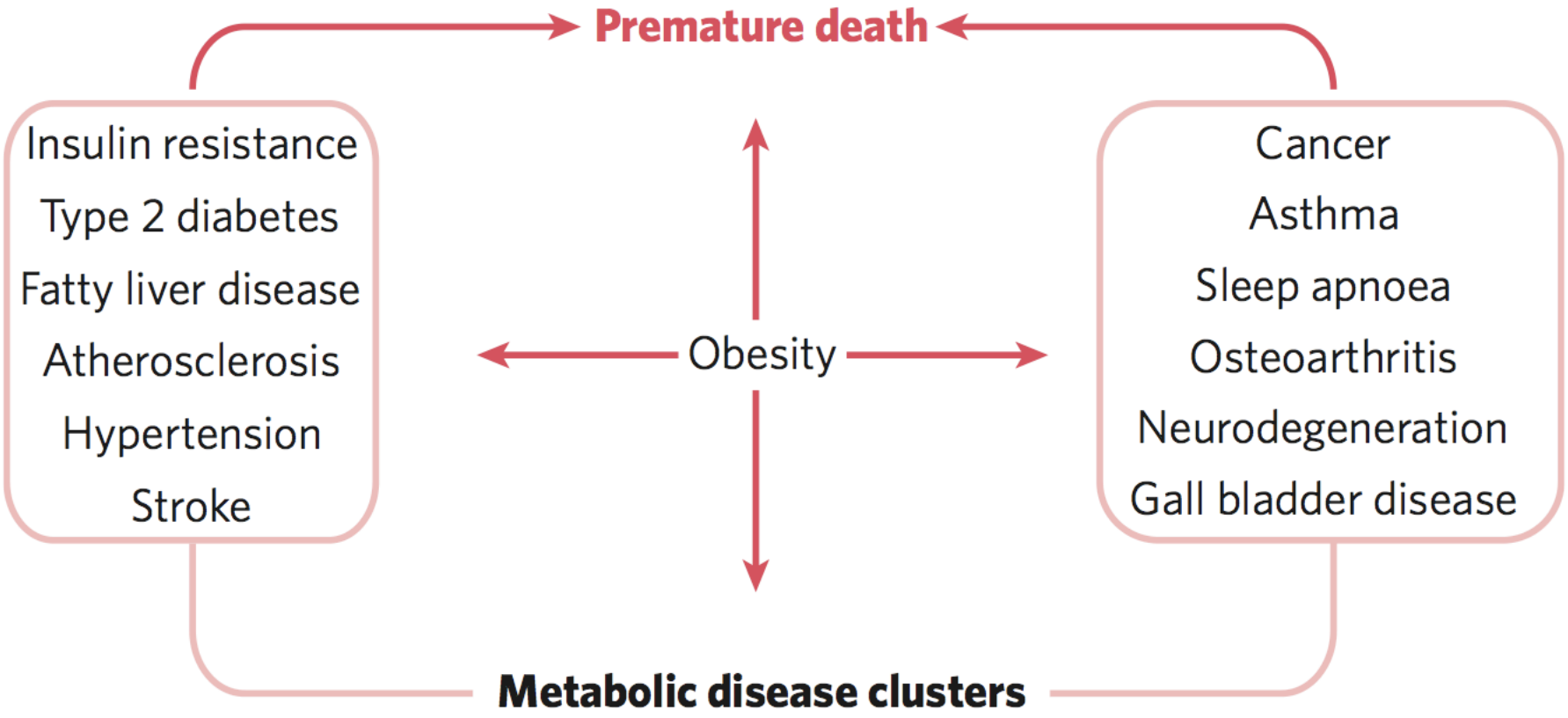


# Metabolism and immunity are closely linked



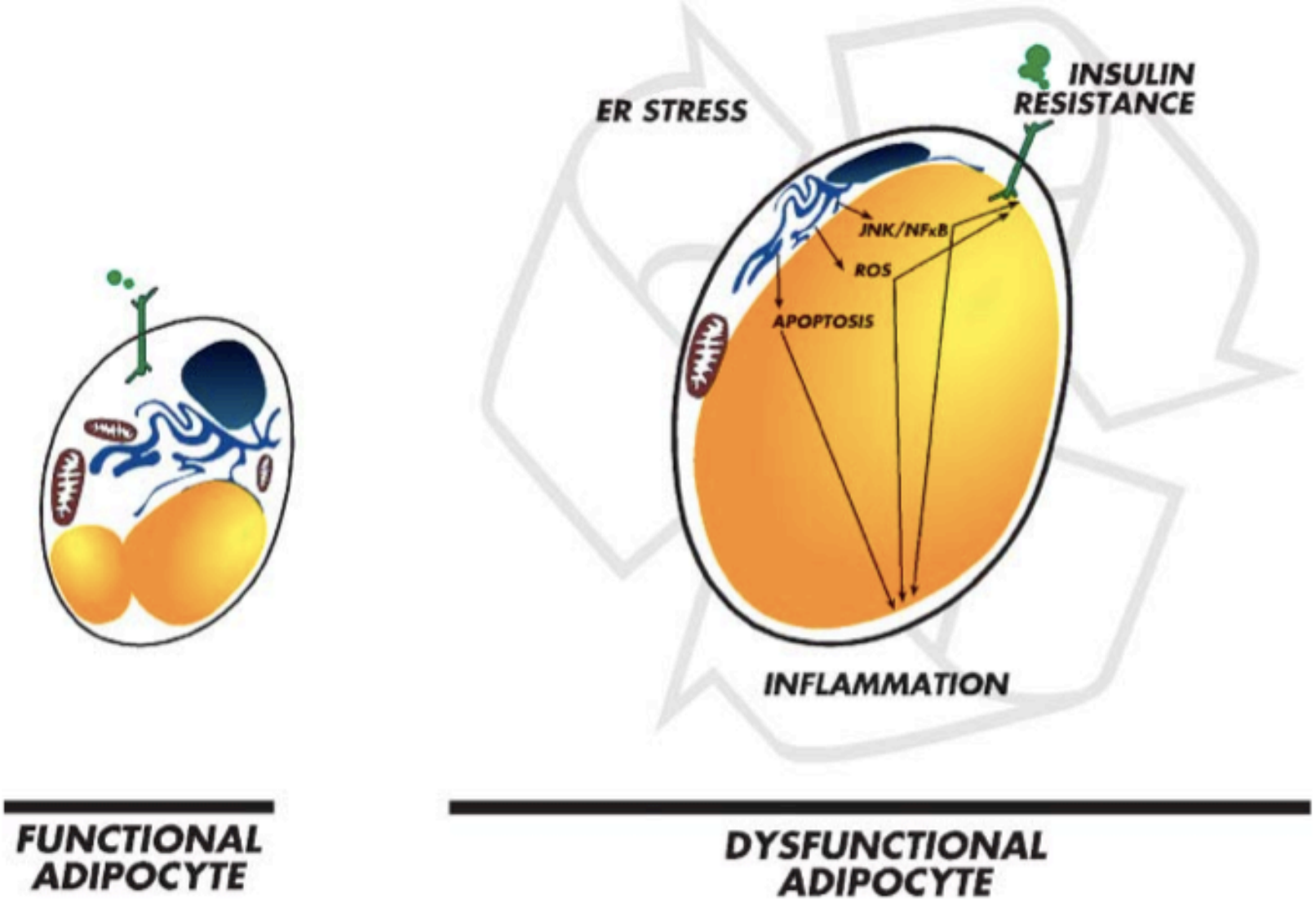

Wellen & Hotamisligil (2007) JCI 115:1111-9

# Obesity is a major risk factor for a vast array of diseases



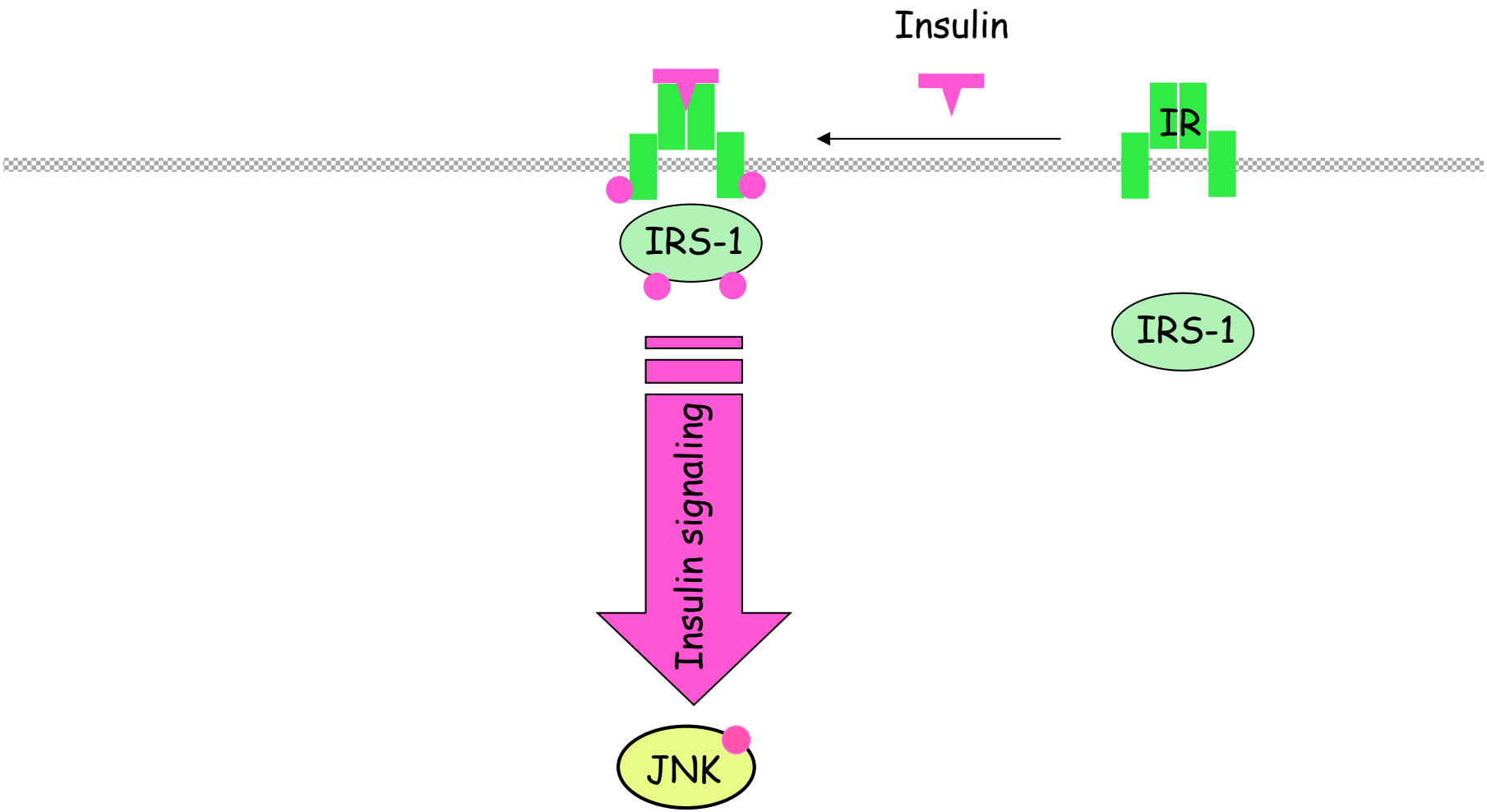

Hotamisligil (2006) Nature 444:860-7

# Many alterations are found in the hypertrophic adipocyte

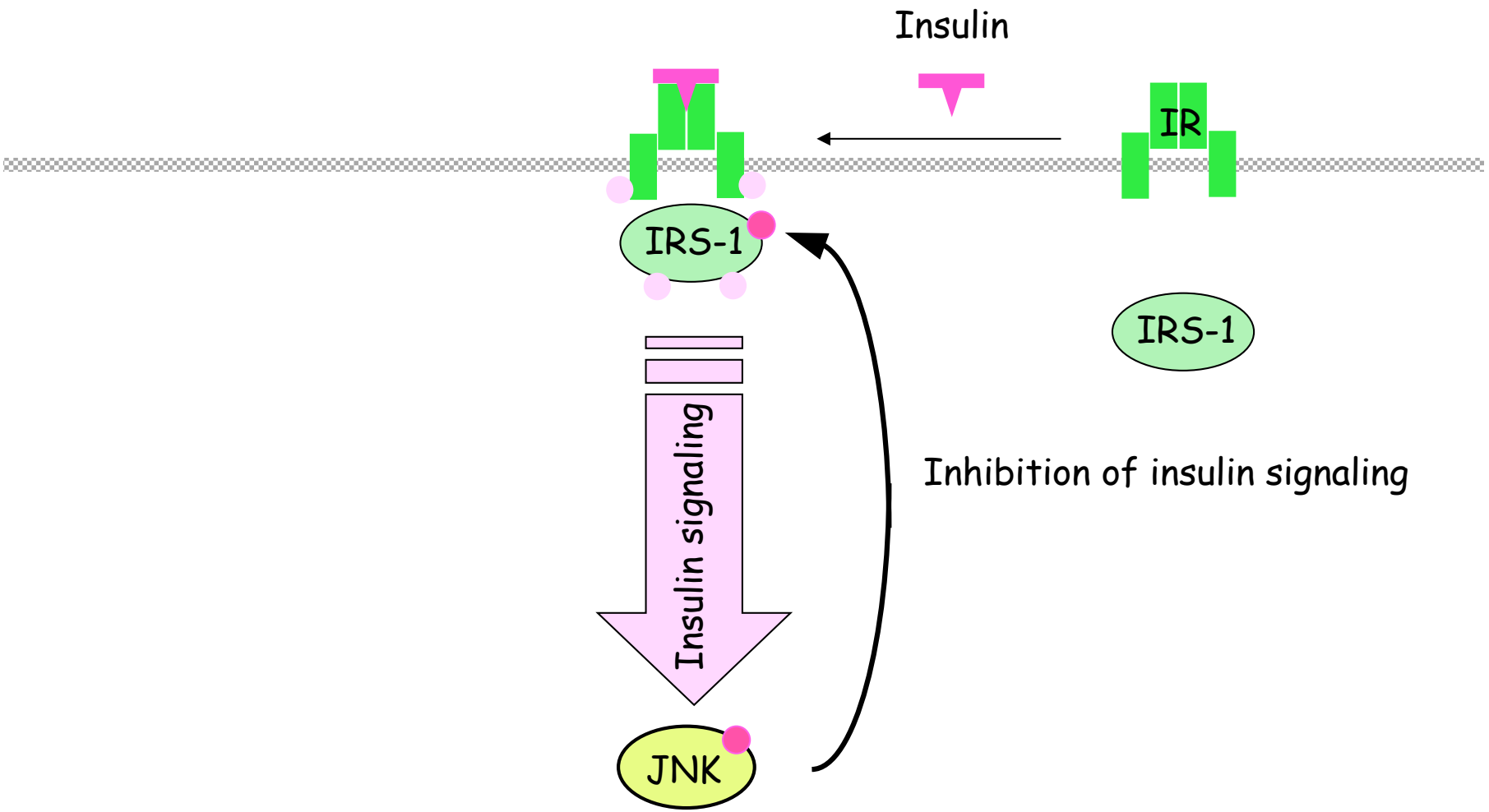



Gregor & Hotamisligil (2007) J. Lipid. Res.

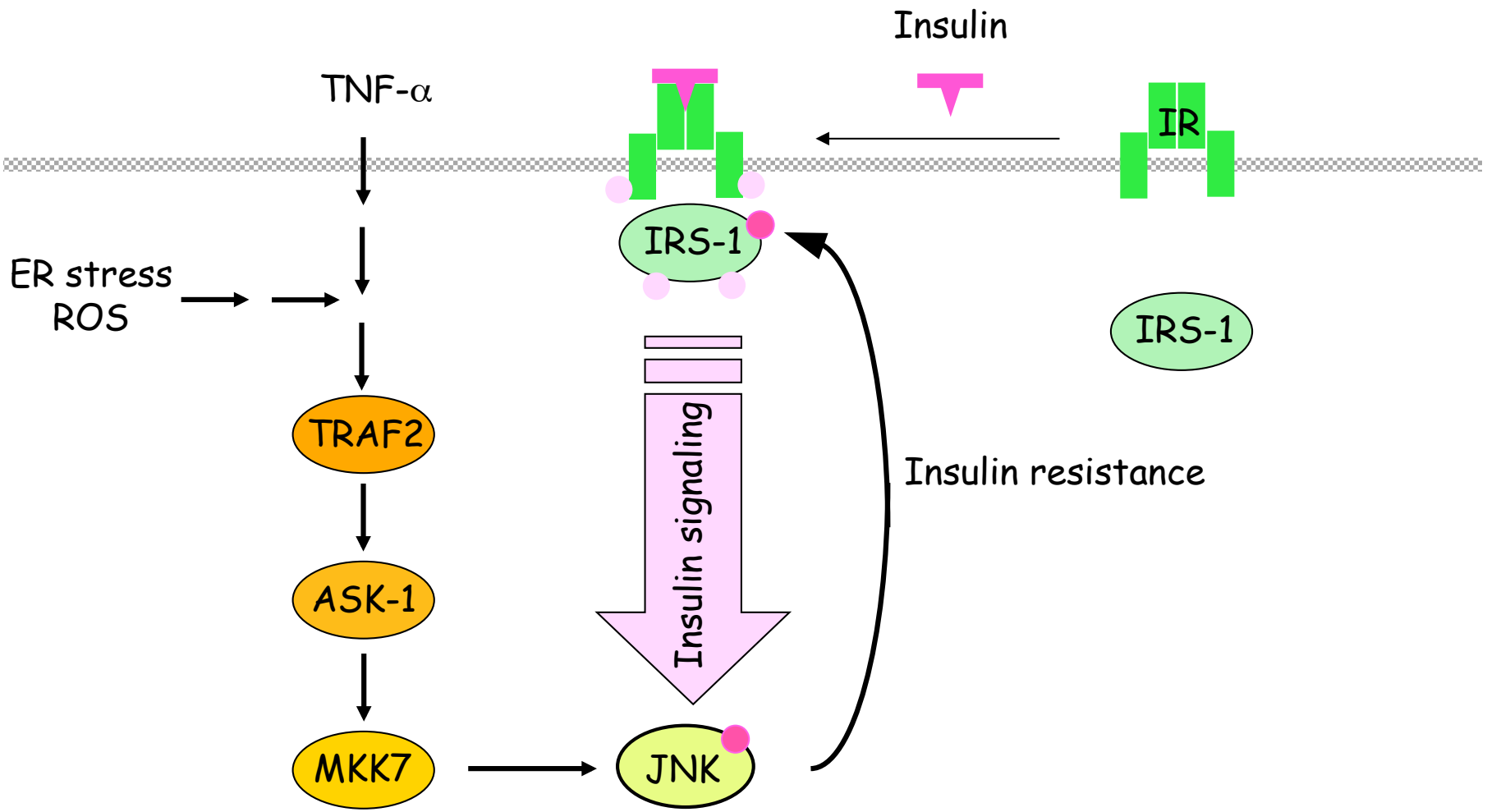
# JNK is activated by insulin signaling



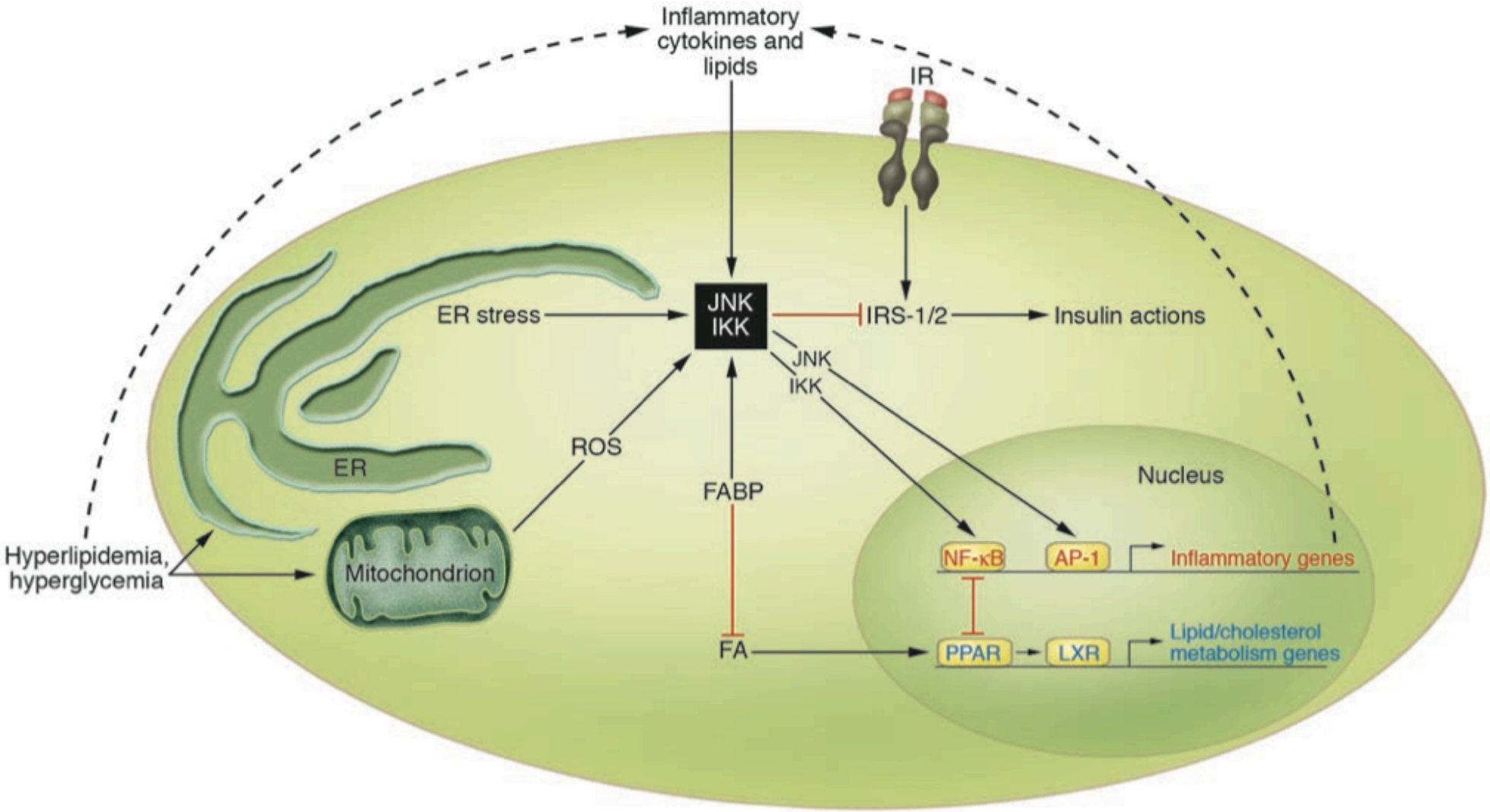
# JNK activation down-regulates insulin signaling



# Exacerbated JNK activation induces insulin resistance



# Inflammatory pathway activation in adipocytes and macrophages



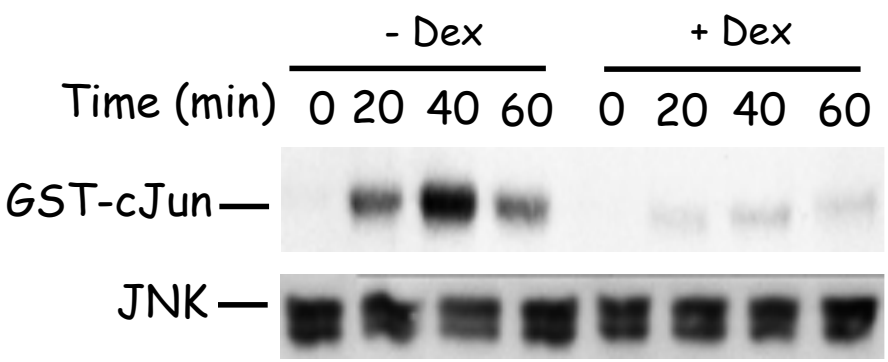

Wellen & Hotamisligil (2007) J. Clin. Invest.

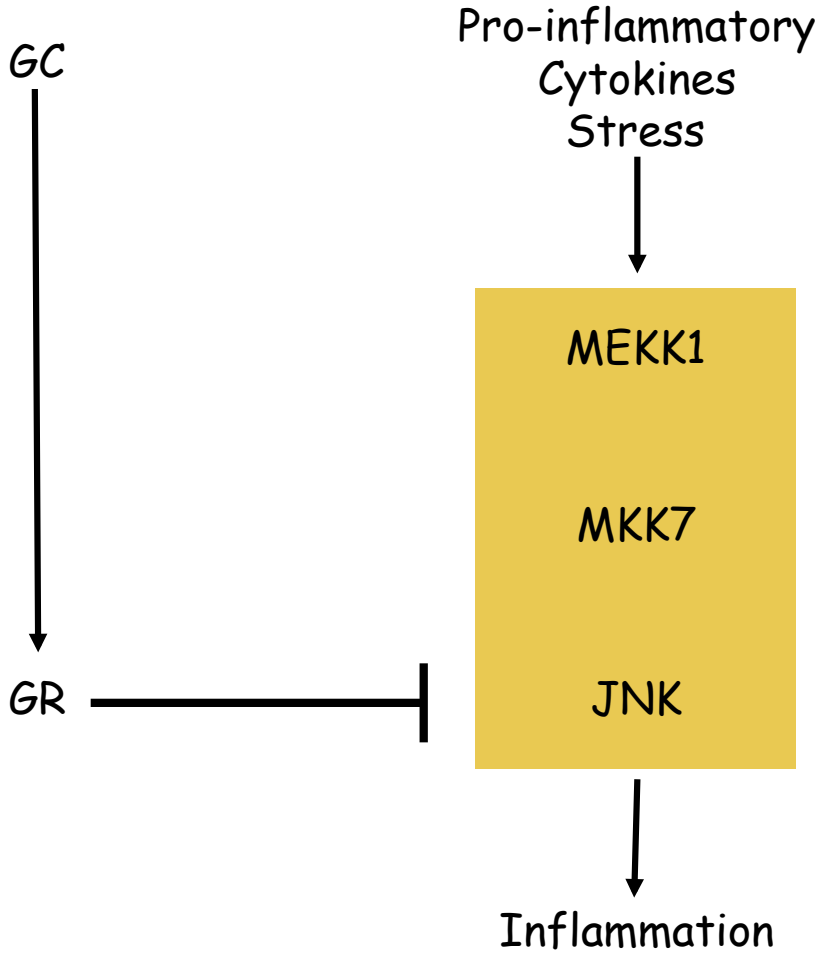
# The role of the JNK pathway in insulin resistance

* The involvement of JNK in the antidiabetic action of TZD/PPARγ

* *In vivo* effects of JNK activation in pancreatic β-cells

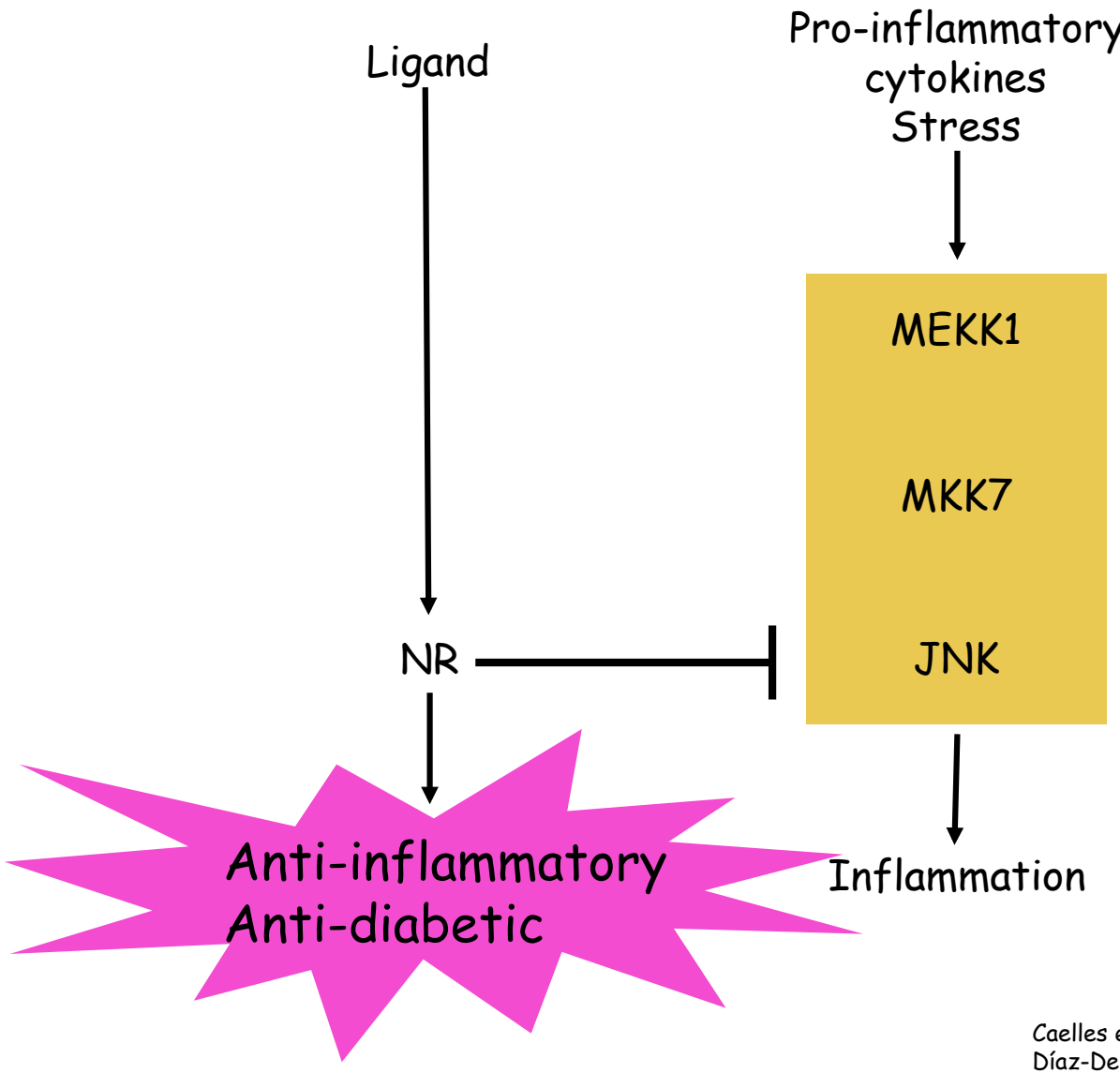
# GC/GR-JNK pathway negative crosstalk




Caelles, C. et al. (1997) Genes & Dev.

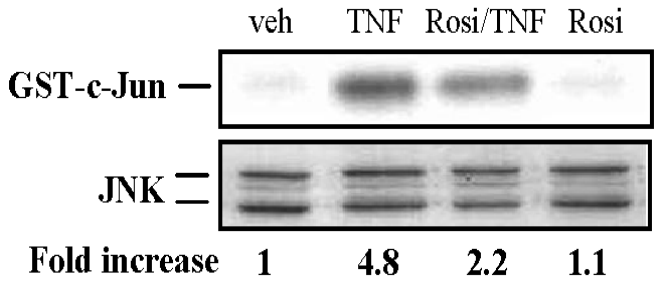
# Actions of the nuclear receptor-JNK pathway crosstalk

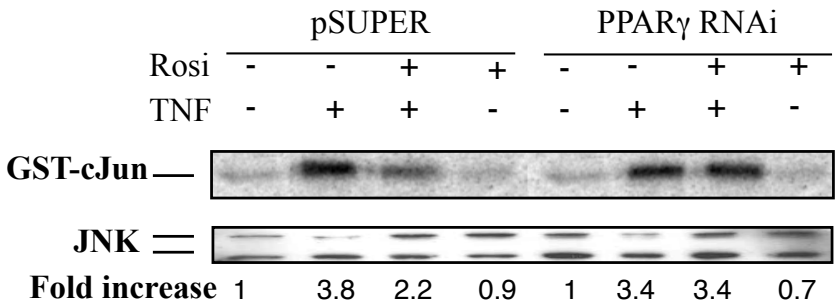



Caelles et al. (1997) Genes & Dev. 11, 3351-64
Díaz-Delfín et al. (2007) Diabetes 56, 1865-71

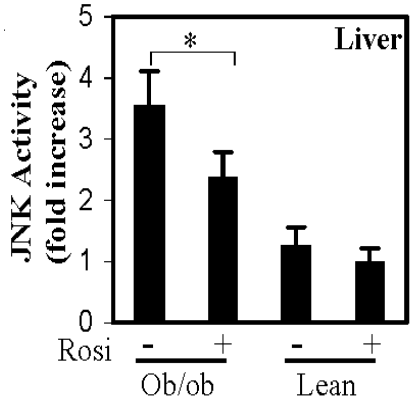
# TZDs inhibit JNK activation in a PPARγ–dependent manner

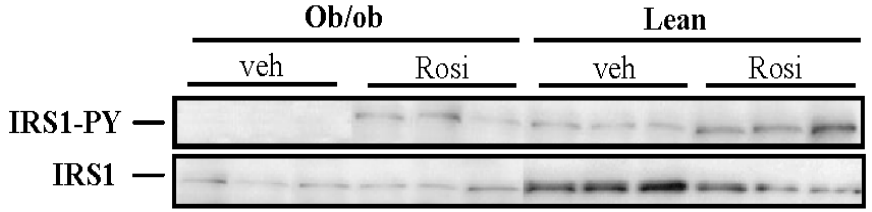
A. 3T3L1 adipocytes



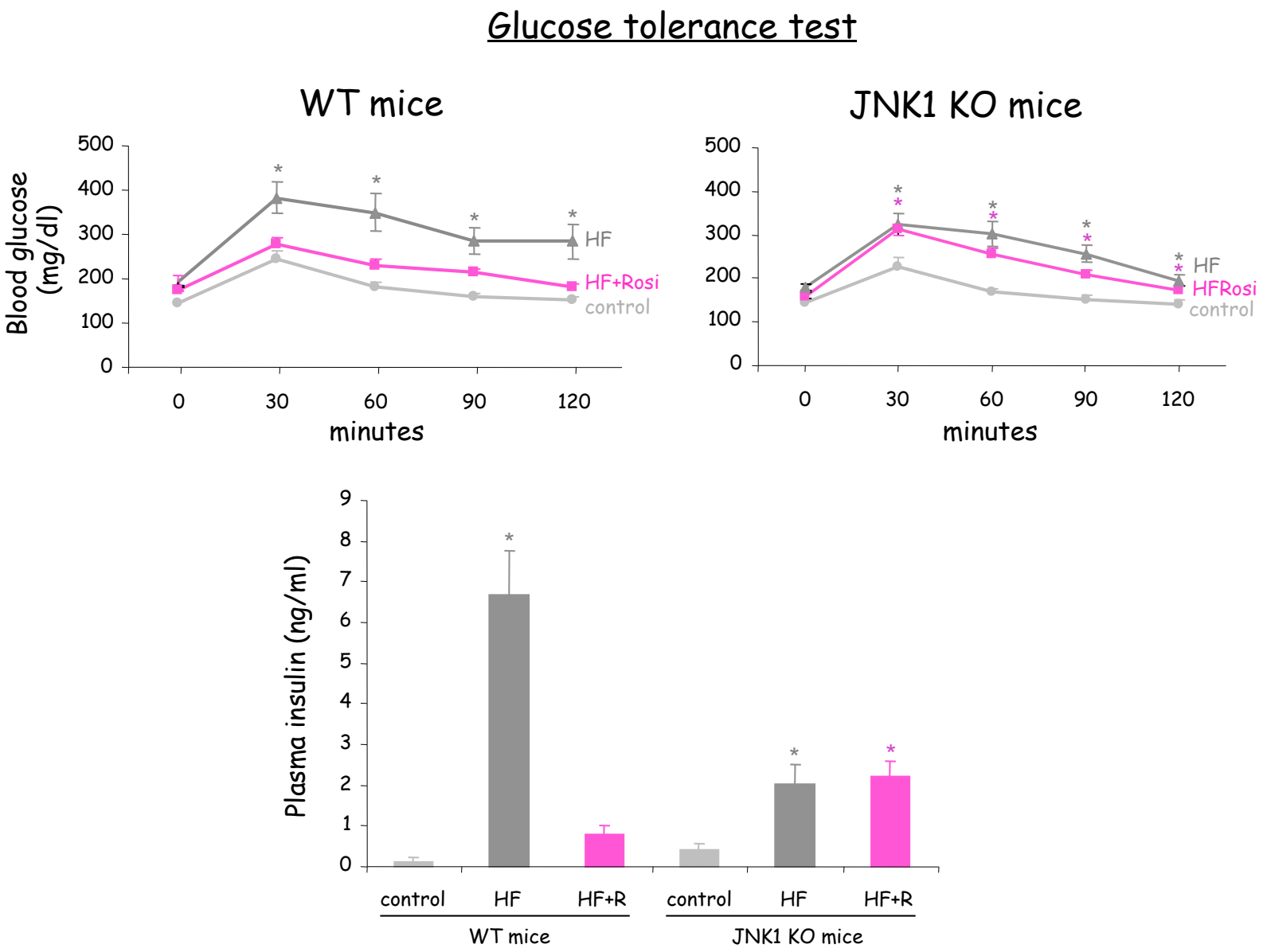

B. In vivo



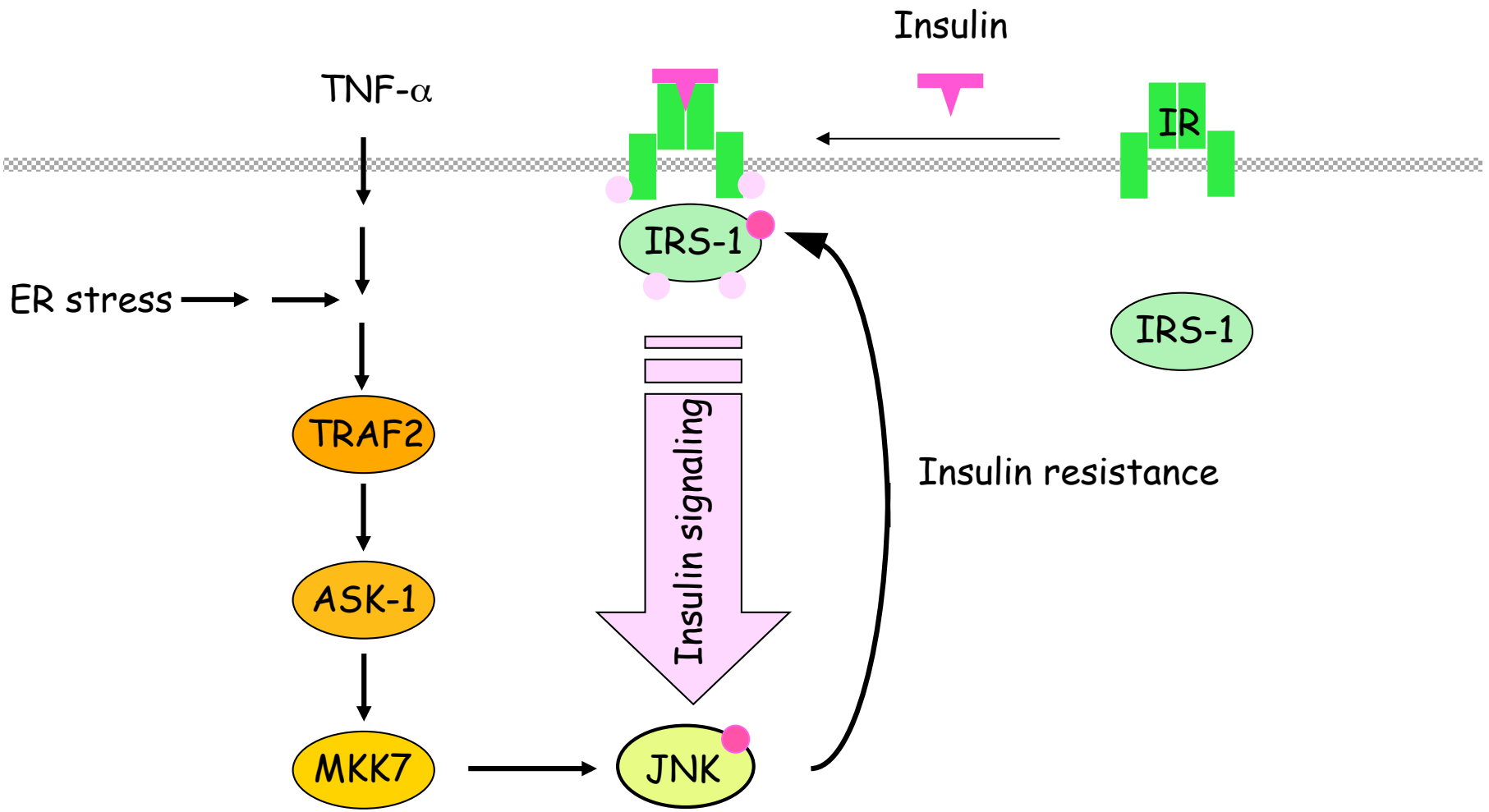

Díaz-Delfín et al. (2007) Diabetes

# JNK1 inhibition mediates TZD insulin-sensitizing action

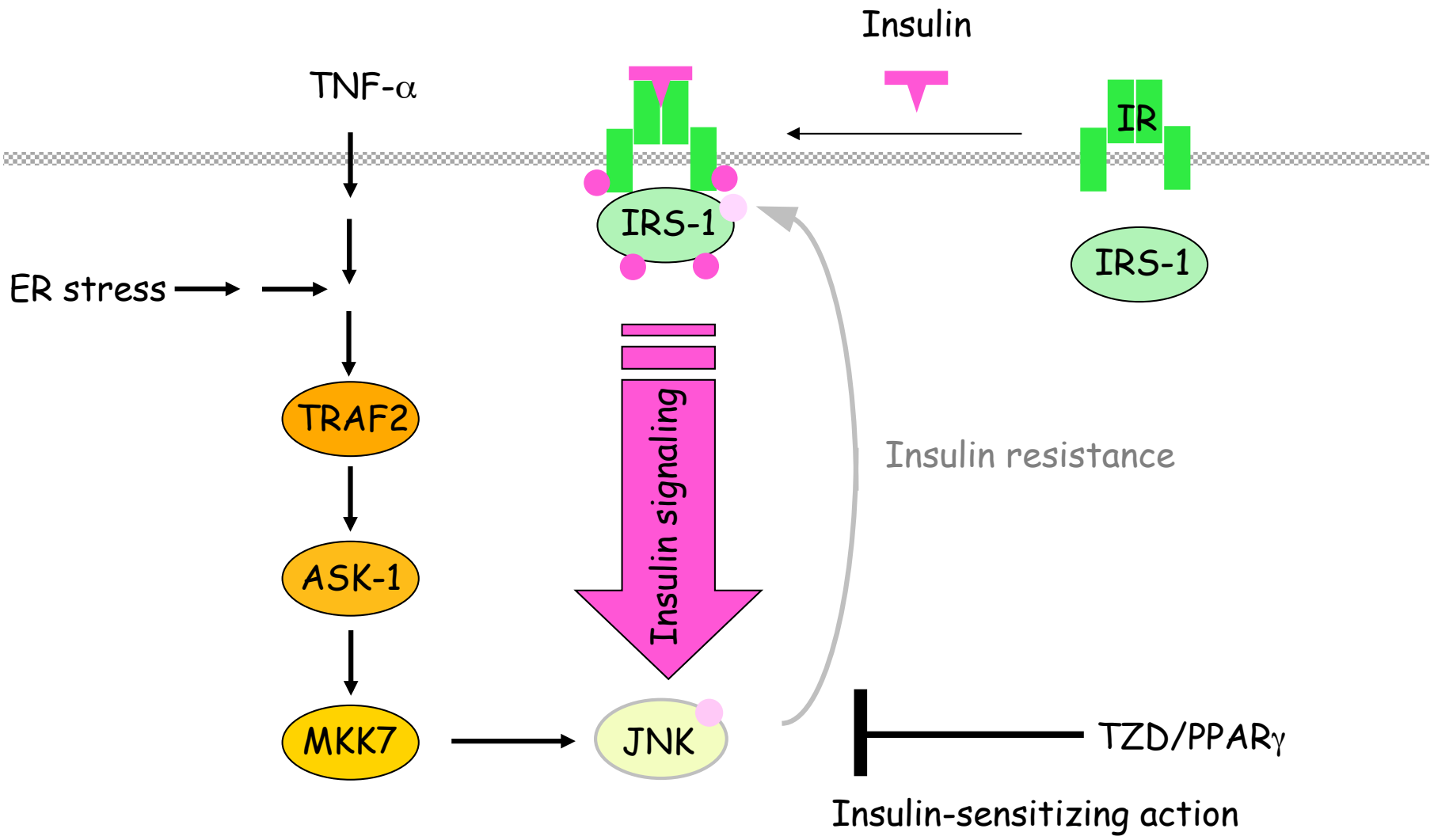



Díaz-Delfín et al. (2007) Diabetes

# Exacerbated JNK activity induces insulin resistance



# JNK pathway inhibition mediates TZD/PPARγ insulin-sensitizing action

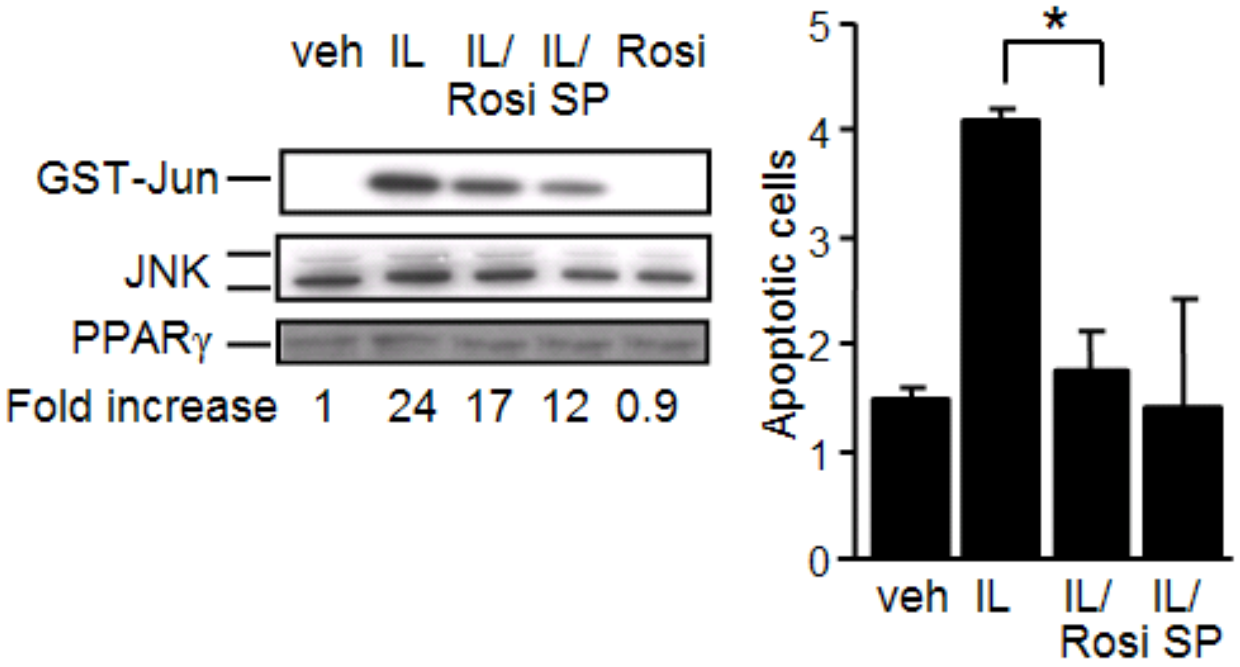


# The role of the JNK pathway in insulin resistance

* The involvement of JNK in the antidiabetic action of TZD/PPARγ

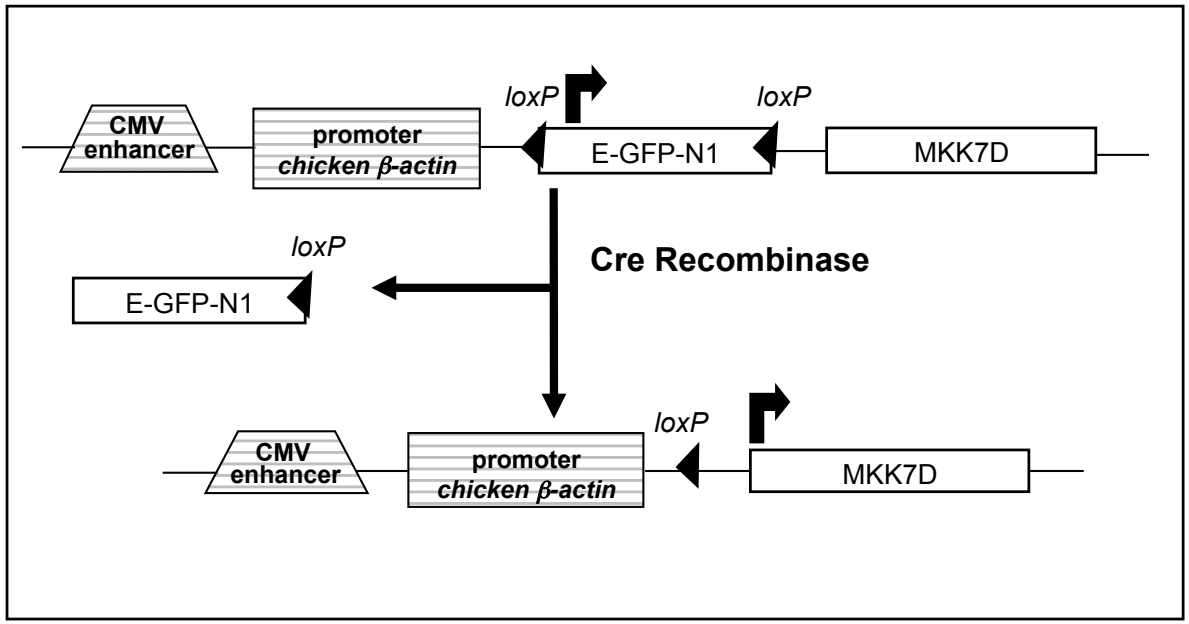
* *In vivo* effects of JNK activation in pancreatic β-cells

# JNK inhibition by TZDs in insulin-secreting cell lines protects from IL-1β-induced apoptosis



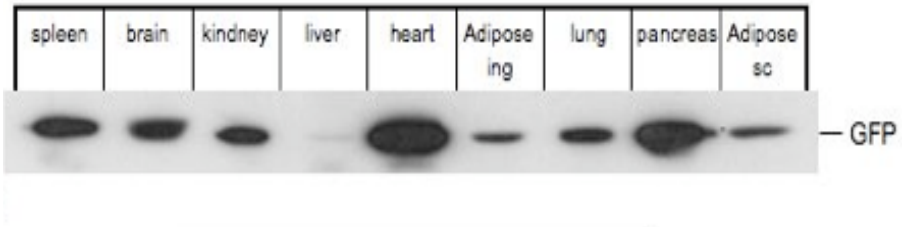

Díaz-Delfín et al. (2007) Diabetes

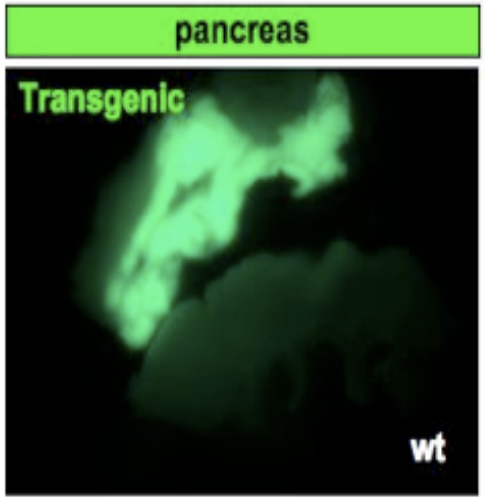
# Cre-conditional transgene encoding a constitutively-activated mutant of the JNK MAP2K MKK7



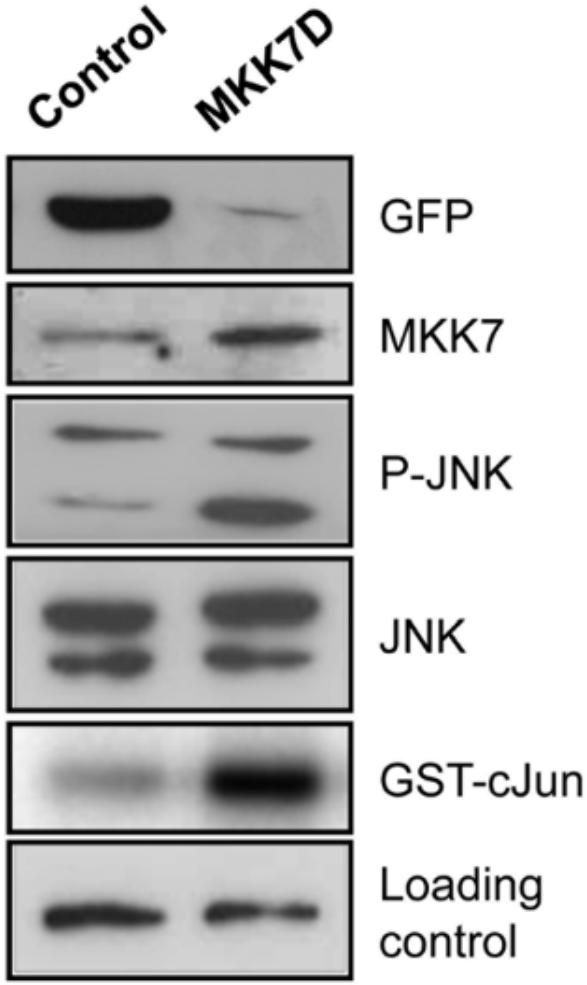

Lanuza et al. (2013) Diabetes

# Generation of a transgenic mouse for conditional activation of JNK *in vivo*




X *C57Bl/6-Tg(Ins2-Cre)25Mgn*

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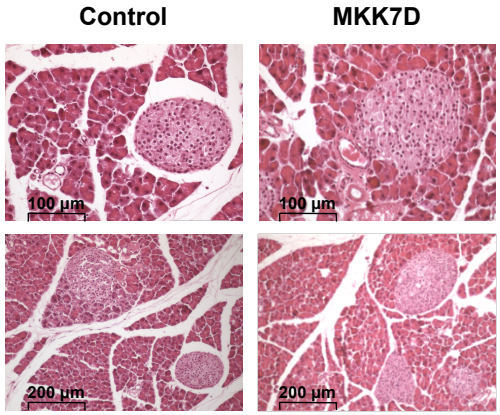
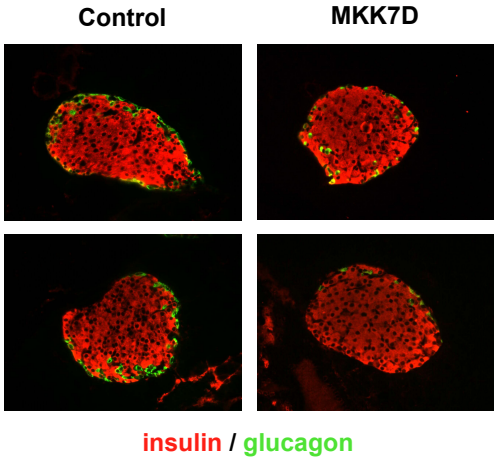
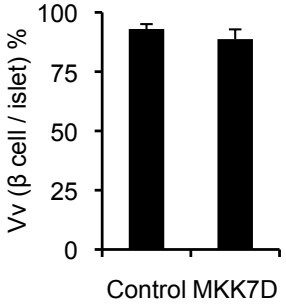
# JNK activation in pancreatic β cells alter neither the overall islet structure nor their insulin content and does not induce β-cell death

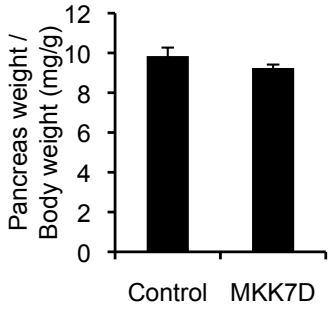



Normal islet shape and size

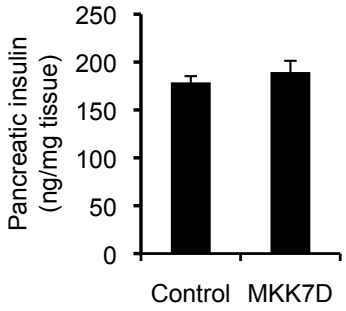


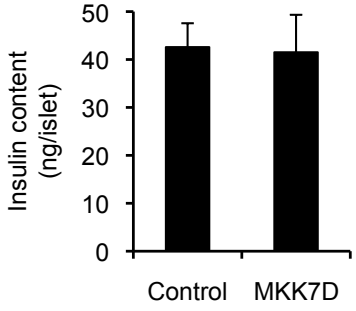

Normal α/β cell proportion and distribution



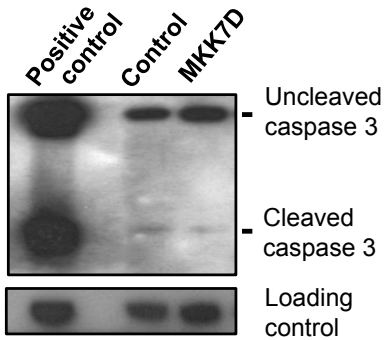



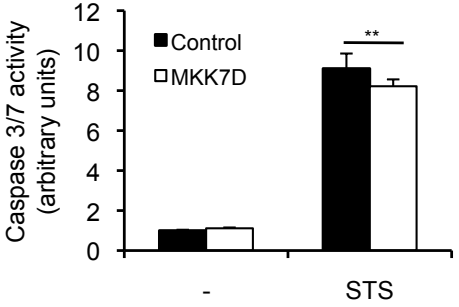

Normal size of the pancreas




Normal pancreatic and islet insulin content




No caspase 3 activation

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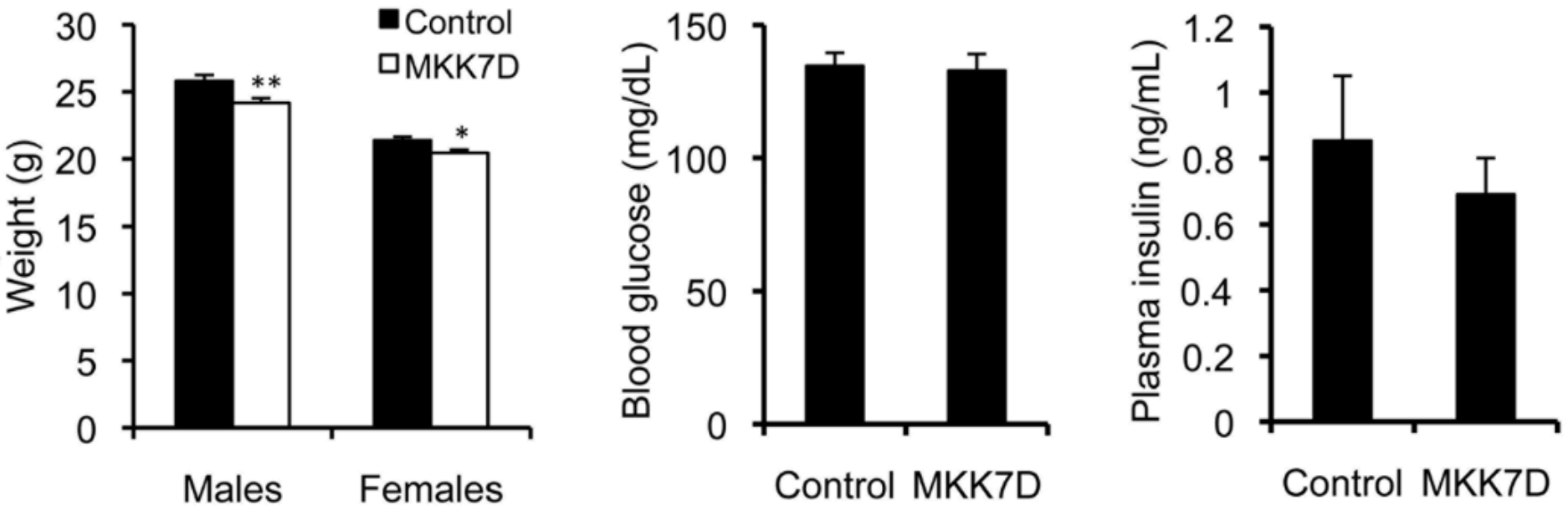
# JNK activation in pancreatic β-cells does not affect basal glycemia or insulinemia

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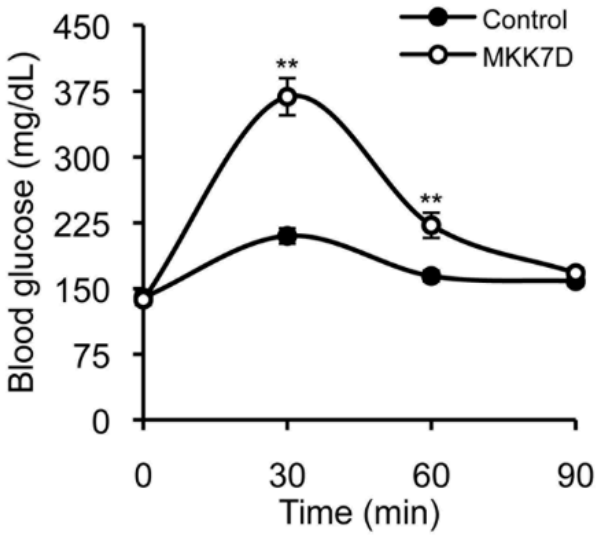
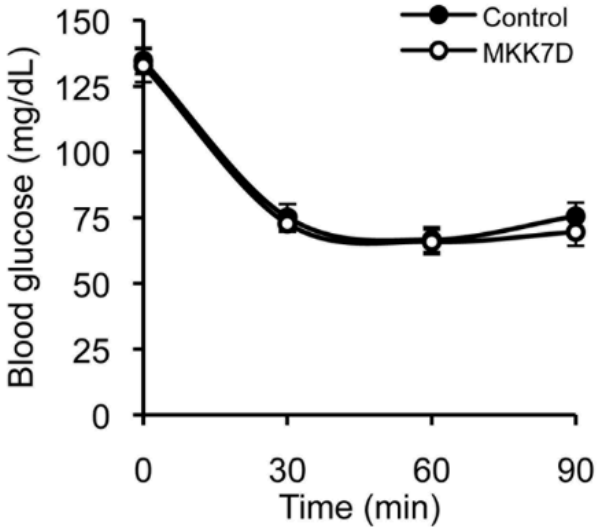
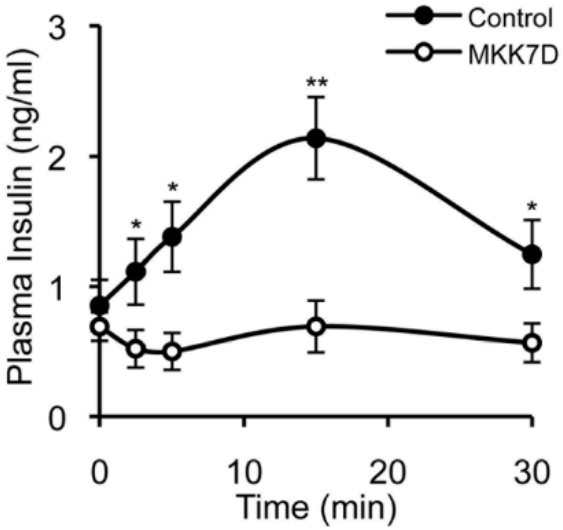
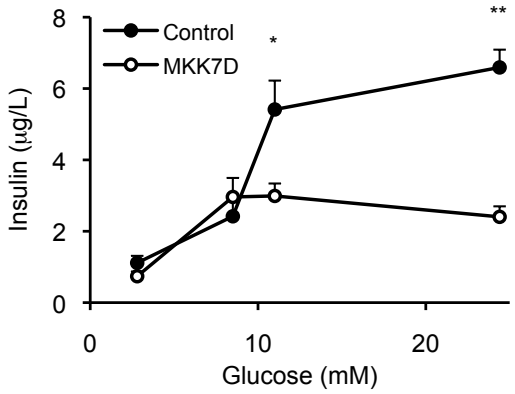
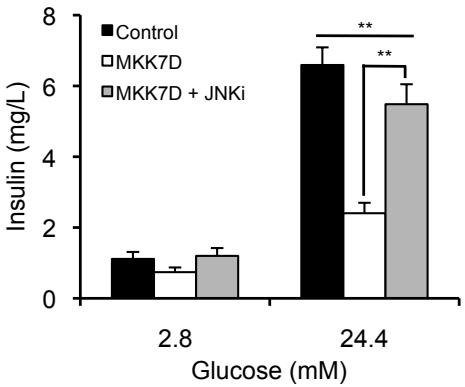
# JNK activation in pancreatic β cells leads to glucose intolerance due to impairment of glucose-induced insulin secretion

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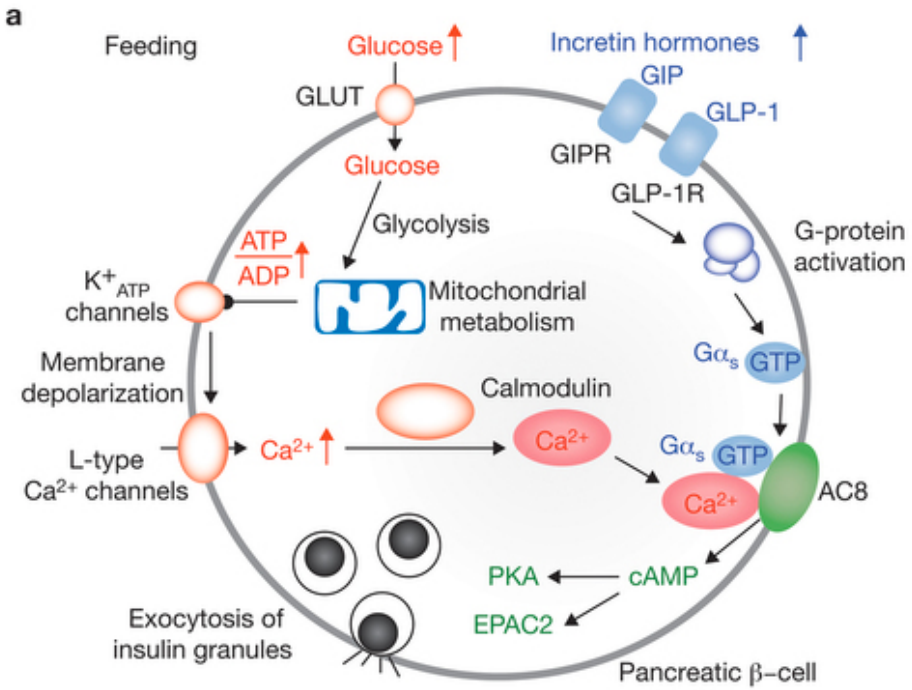
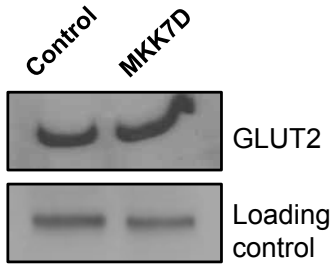
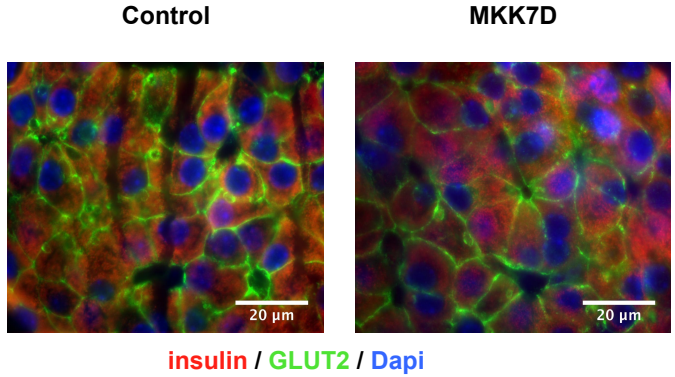
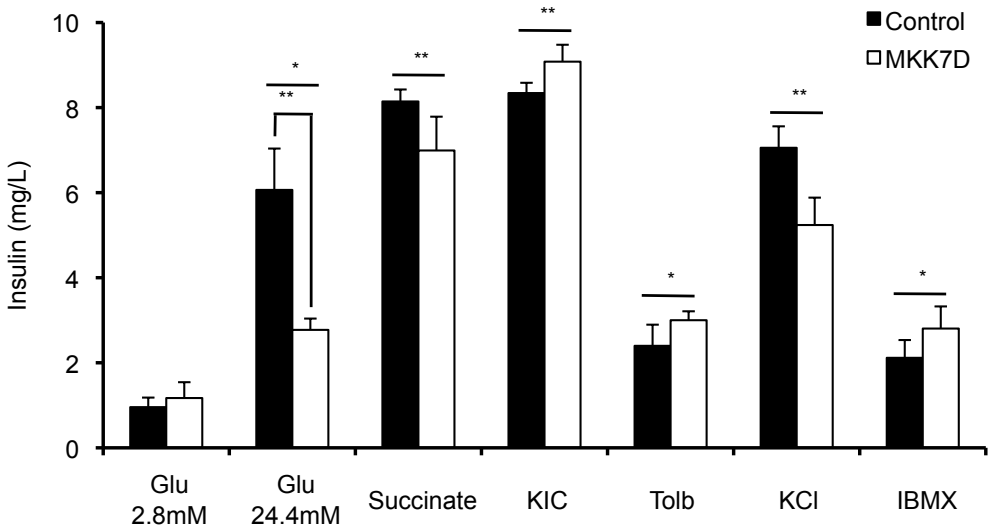
# JNK activation in pancreatic β cells does not interfere with the first phase of glucose-induced insulin secretion

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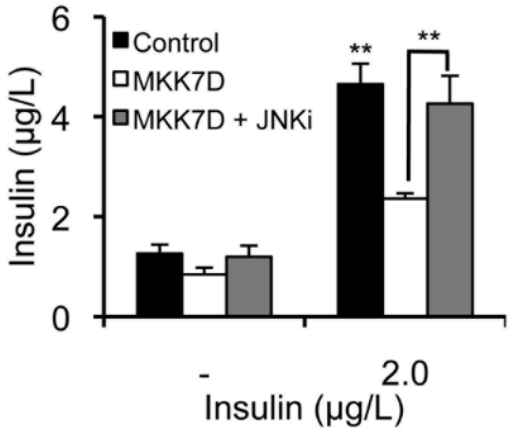
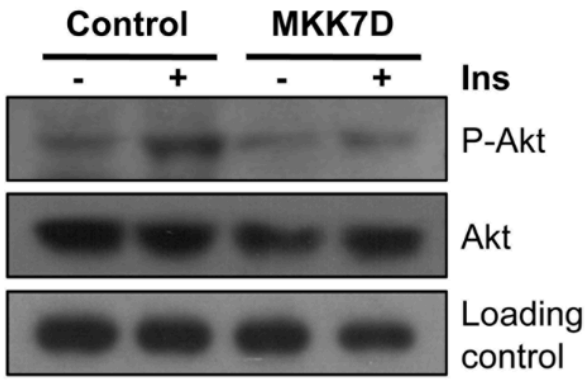
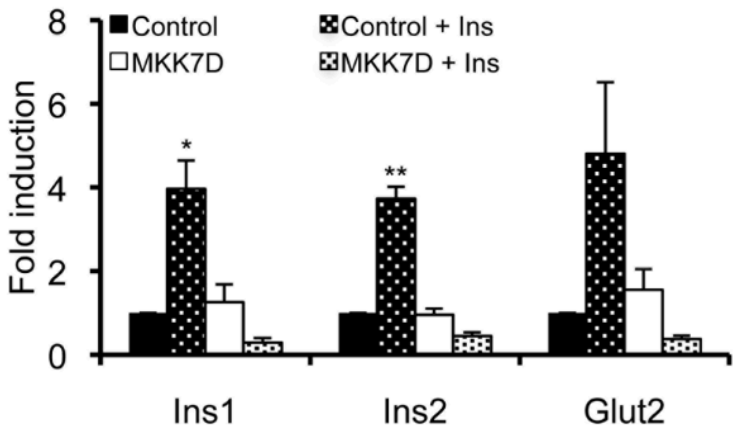
# JNK activation in pancreatic β cells interferes with the second phase/insulin-dependent glucose-induced insulin secretion

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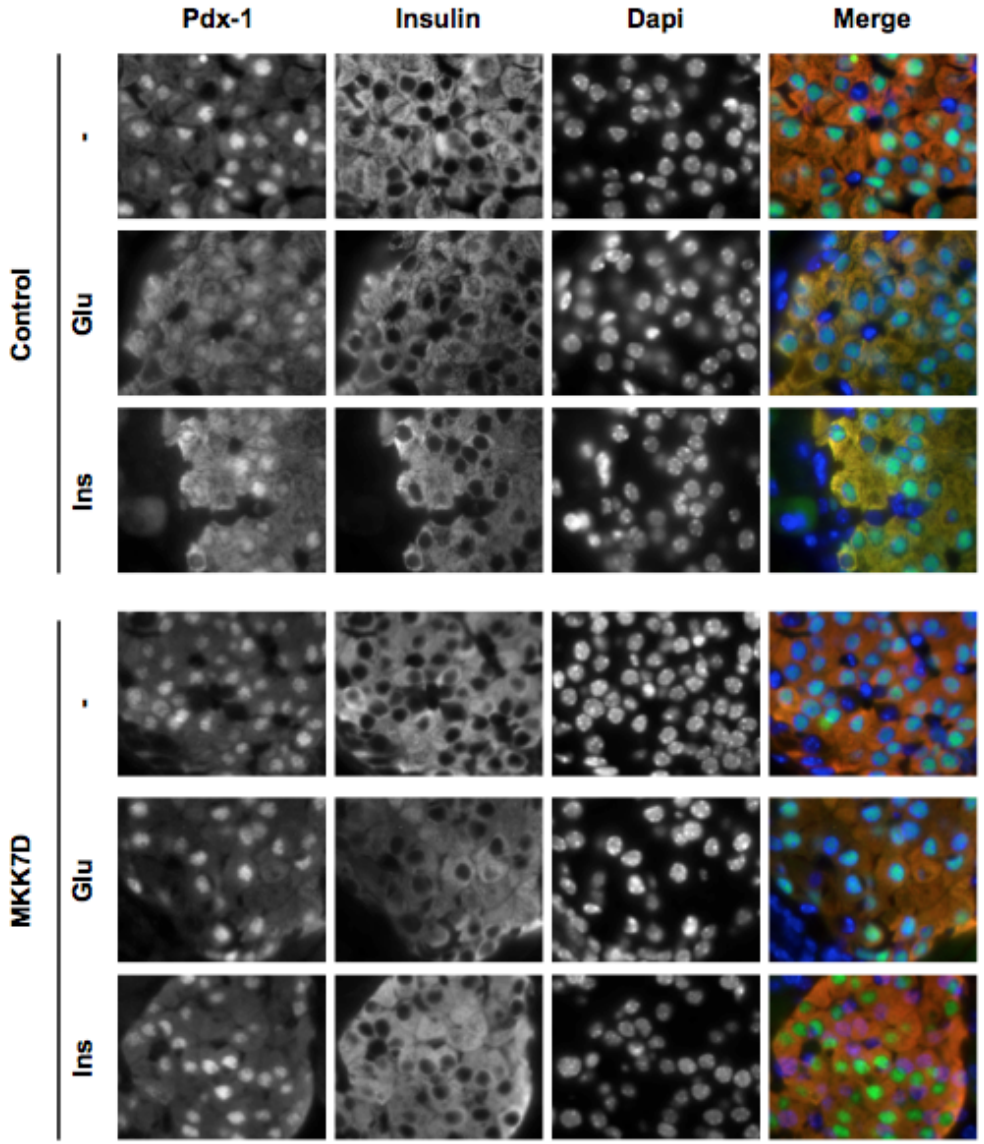
# JNK activation blocks insulin signaling in pancreatic β cells *in vivo*

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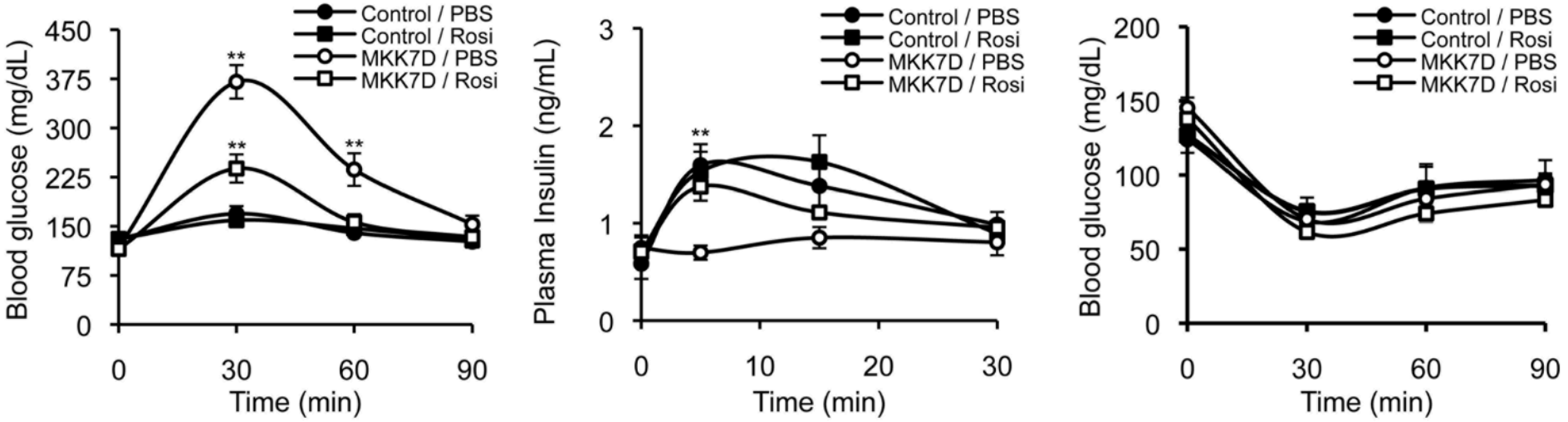
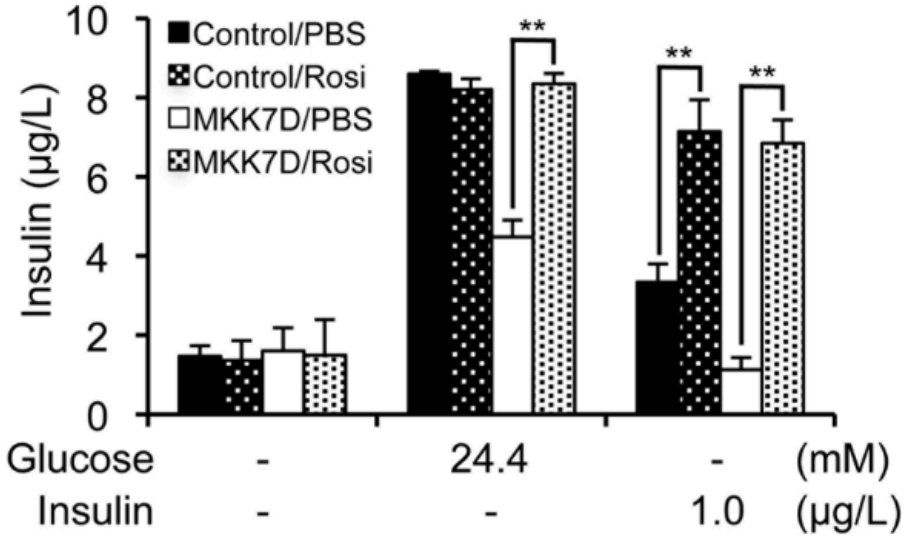
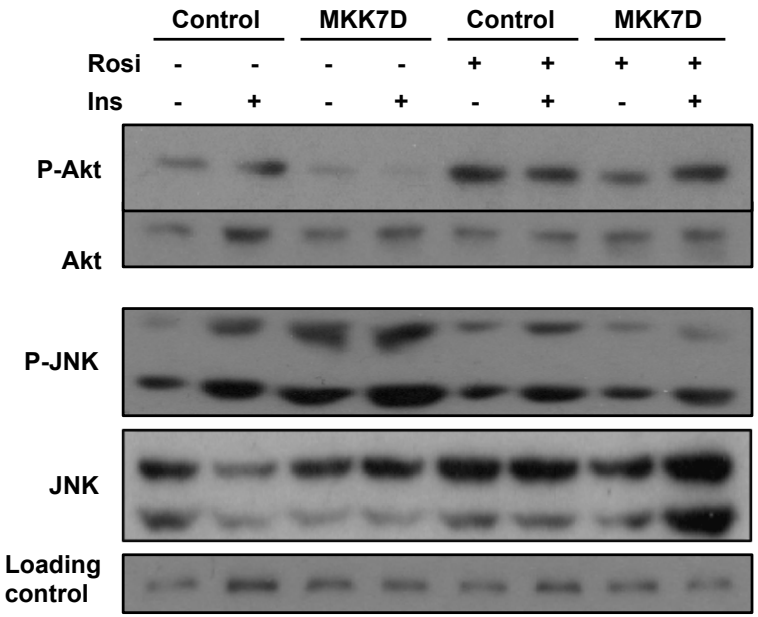
# Rosiglitazone treatment alleviates insulin resistance induced by JNK activation in pancreatic β cells

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UNIVERSITAT DE BARCELONA

Mònica Morales
Julieta Díaz-Delfín

M. Isabel Arévalo
Jordi Lanuza
Giuseppe Pulice

Albert Barberà
Ramón Gomis
(IDIBAPS)

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