INFLAMACIÓ I ALTERACIONS METABÒLIQUES EN LA CARDIOMIOPATIA DIABÈTICA

Universitat de Barcelona

ciberdem

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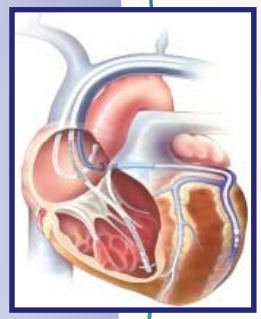
Donat el caràcter i la finalitat exclusivament docent i eminentment il·lustrativa de les explicacions a classe d'aquesta presentació, l'autor s'acull a l'article 32 de la Llei de Propietat Intel·lectual vigent respecte de l'ús parcial d'obres alienes com ara imatges, gràfics o altre material contingudes en les diferents diapositives

Given the exclusively educational purpose and the highly illustrative nature of the explanations given in class during this presentation, the author invokes the Article 32 of the Law on Intellectual Property of the current legislation with respect to the partial use of foreign material, such as pictures, graphics or other material contained in the different slides

Background

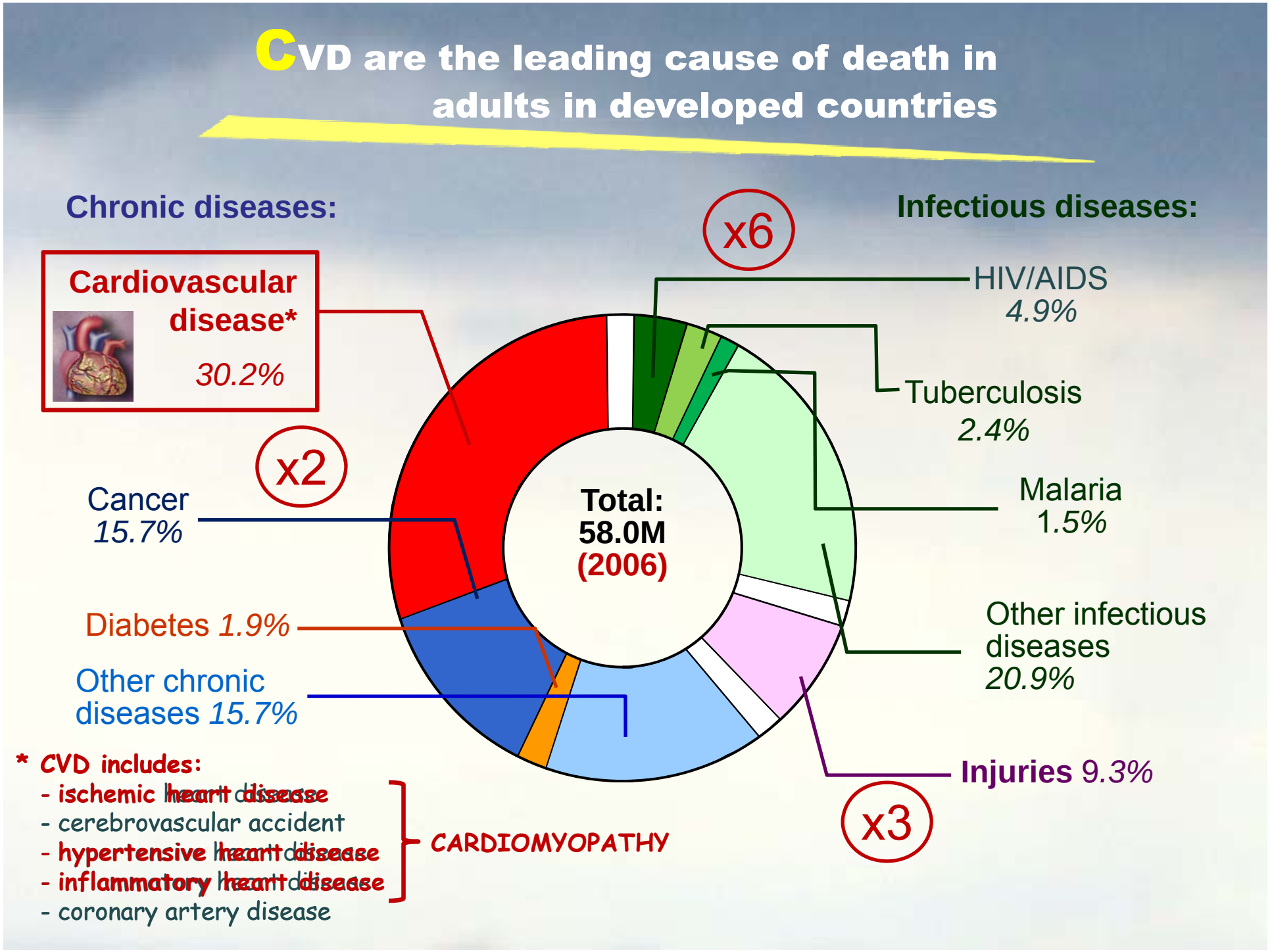
Some facts and trivia about the human heart



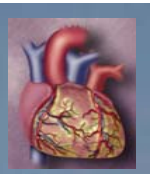
- ✓ Weights 200-425 g
- ✓ Beats ~80 times/min (144,000 times/day), to carry out the mighty job of pumping 7,500 L/day of blood:
  - ➢ through the 96,500 km of vessels (7.5X Ø of the earth!)
  - ➢ to almost all of the body's 50-100 billion cells (only the corneas do not receive blood supply)
- ✓ Consumes more ATP than any other organ: the heart produces and immediately hydrolyzes ~5 - 30 kg of ATP every day
- ✓ Every day, the heart creates enough energy to drive a truck 32 km → In a 70y lifetime this is equivalent to driving to the moon and back (the average distance is 384,403 km)

Ferrari et al. Eur Heart J Supplements (2008) 10(Supplement F): F7-F10; http://facts.randomhistory.com/human-heart-facts.html

CVD are the leading cause of death in adults in developed countries



Cardiomyopathy



What is cardiomyopathy?

- Group of diseases that primarily affect the heart muscle and are associated with cardiac dysfunction
- Incidence: 3-10 cases per 100,000 people
- Prognosis:
  - death from **Heart Failure** { 1 year: 25% ; 5-year: 40-80% }
  - complete recovery is rare

HF: a life-threatening condition in which the heart is not able to pump enough blood to the rest of the body.

Classification

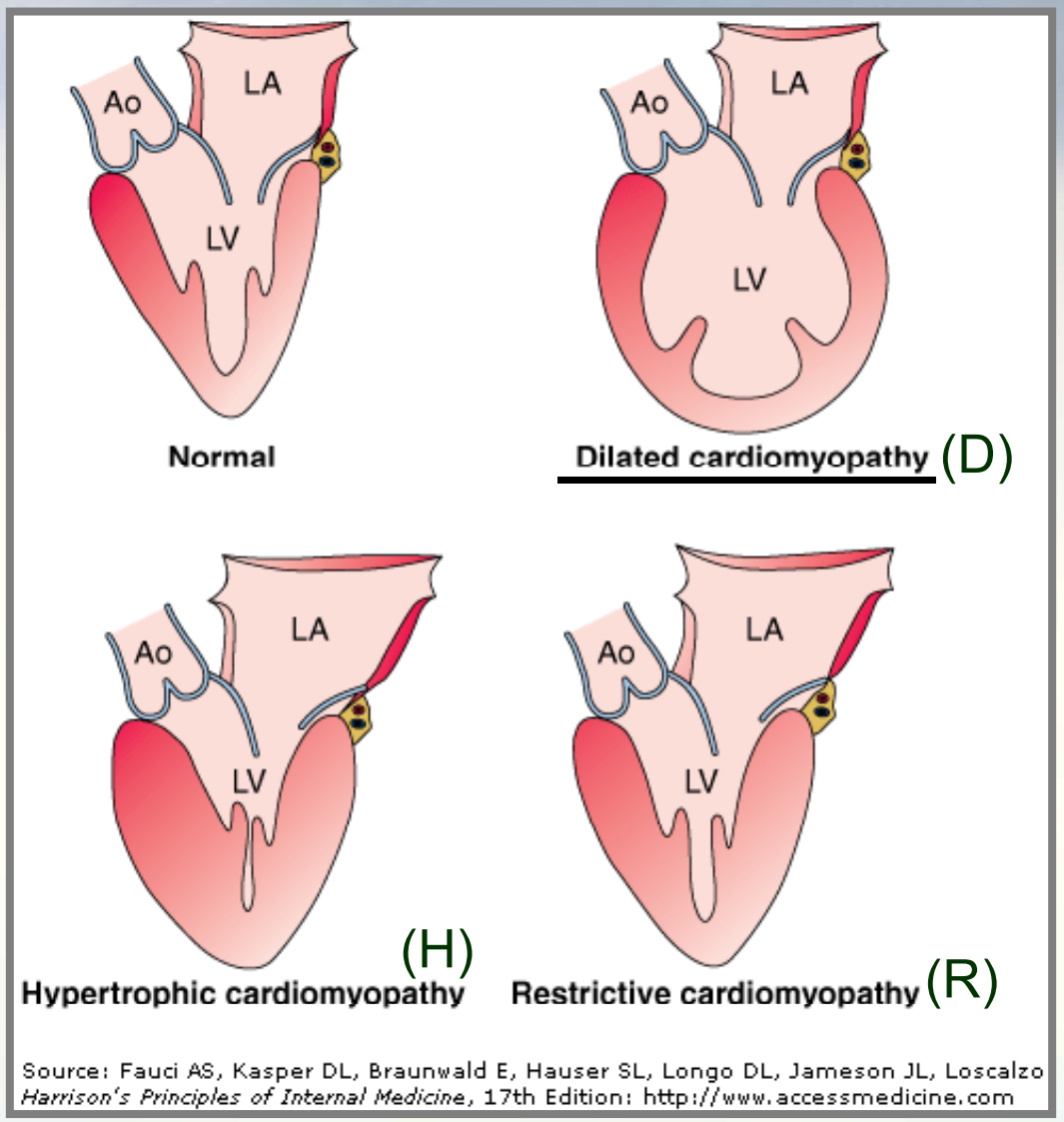
Etiologic

- **Primary type**: Idiopathic (D,R,H) / Genetic (D,R,H)
- **Secondary type**: known cause or associated with a systemic disease
  - Inflammatory: Infectious (D) / Non-infectious (D; SLE, RA, Peripartum)
  - Hypertensive
  - Granulomas and malignancies (R,D)
  - Toxic agents (D): Alcohol, Radiation, Drugs (Cocaine)
  - **Metabolic (D,R)**

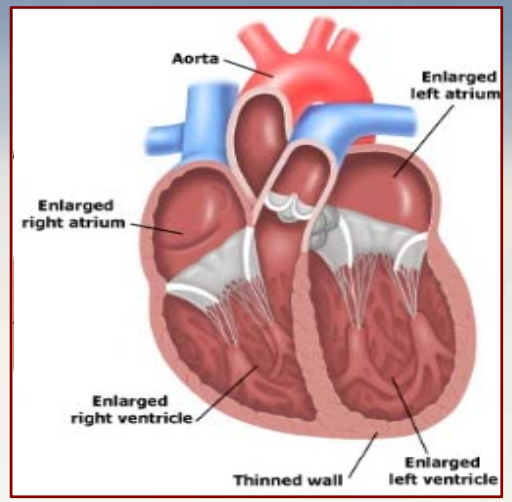
Morphologic (WHO)

- Dilated/congestive (D), Restrictive (R), Hypertrophic (H)

Diabetic cardiomyopathy:
Morphology & clinical features



Source: Fauci AS, Kasper DL, Braunwald E, Hauser SL, Longo DL, Jameson JL, Loscalzo *Harrison's Principles of Internal Medicine*, 17th Edition: http://www.accessmedicine.com



Diabetic cardiomyopathy

- LV muscle dilation (stretch & thin) → chamber enlargement (spreads to RV and atria) (D)
- Abnormal contraction: decreased (D) systolic function and diastolic dysfunction (H,R)
- Inadequate blood pumping → HF

Diabetic cardiomyopathy: DM1 & DM2

DM2: metabolic disorder of multiple etiology characterized by chronic hyperglycemia that results from defects in insulin secretion and/or action (**insulin resistance**)

Epidemiology of DCM

- Originally described in 4 diabetic patients with HF but no evidence of CAD/HTA

Display Settings: Abstract

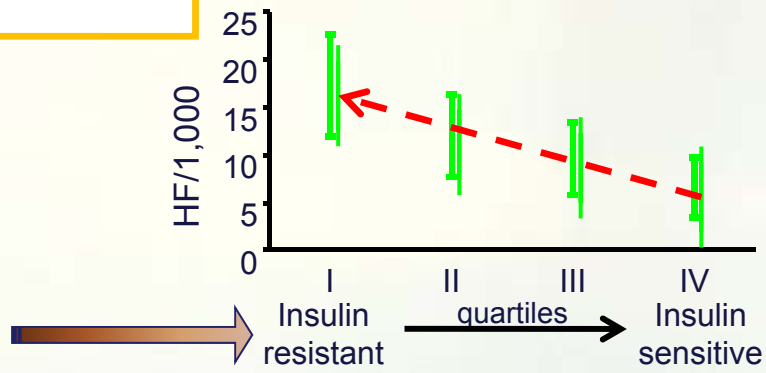
PubMed.gov
US National Library of Medicine
National Institutes of Health

Am J Cardiol. 1972 Nov 8;30(6):595-602.

New type of cardiomyopathy associated with diabetic glomerulosclerosis.

Rubler S, Dlugash J, Yuceoglu YZ, Kumral T, Branwood AW, Grishman A.

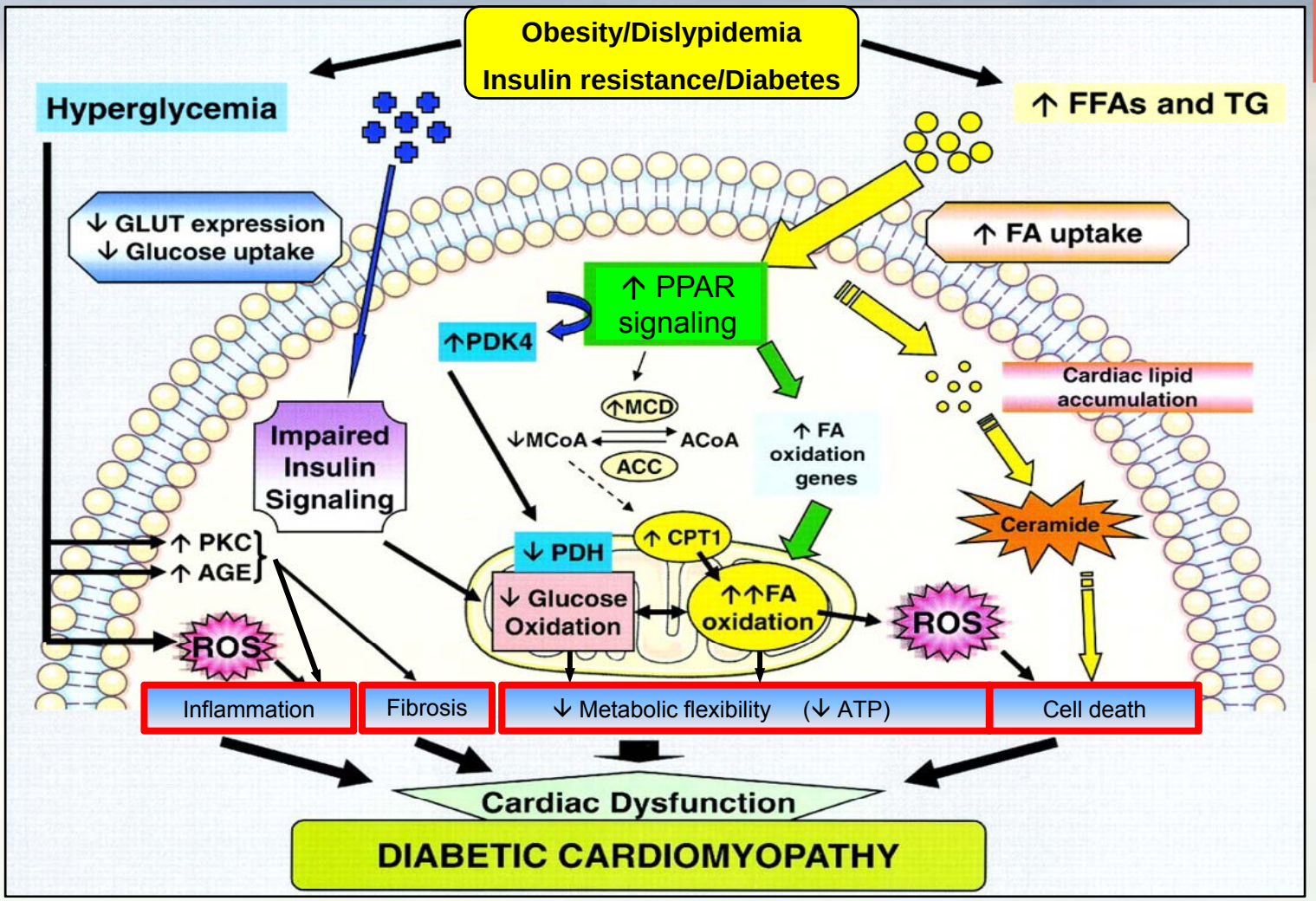
- HF prevalence in general population 1-4%
  → **in diabetic population 15%!**
- Inverse relationship between HF incidence and insulin sensitivity



Ingelsson et al. *JAMA* (2005) 294:334-41

Diabetic cardiomyopathy

Pathophysiological mechanisms



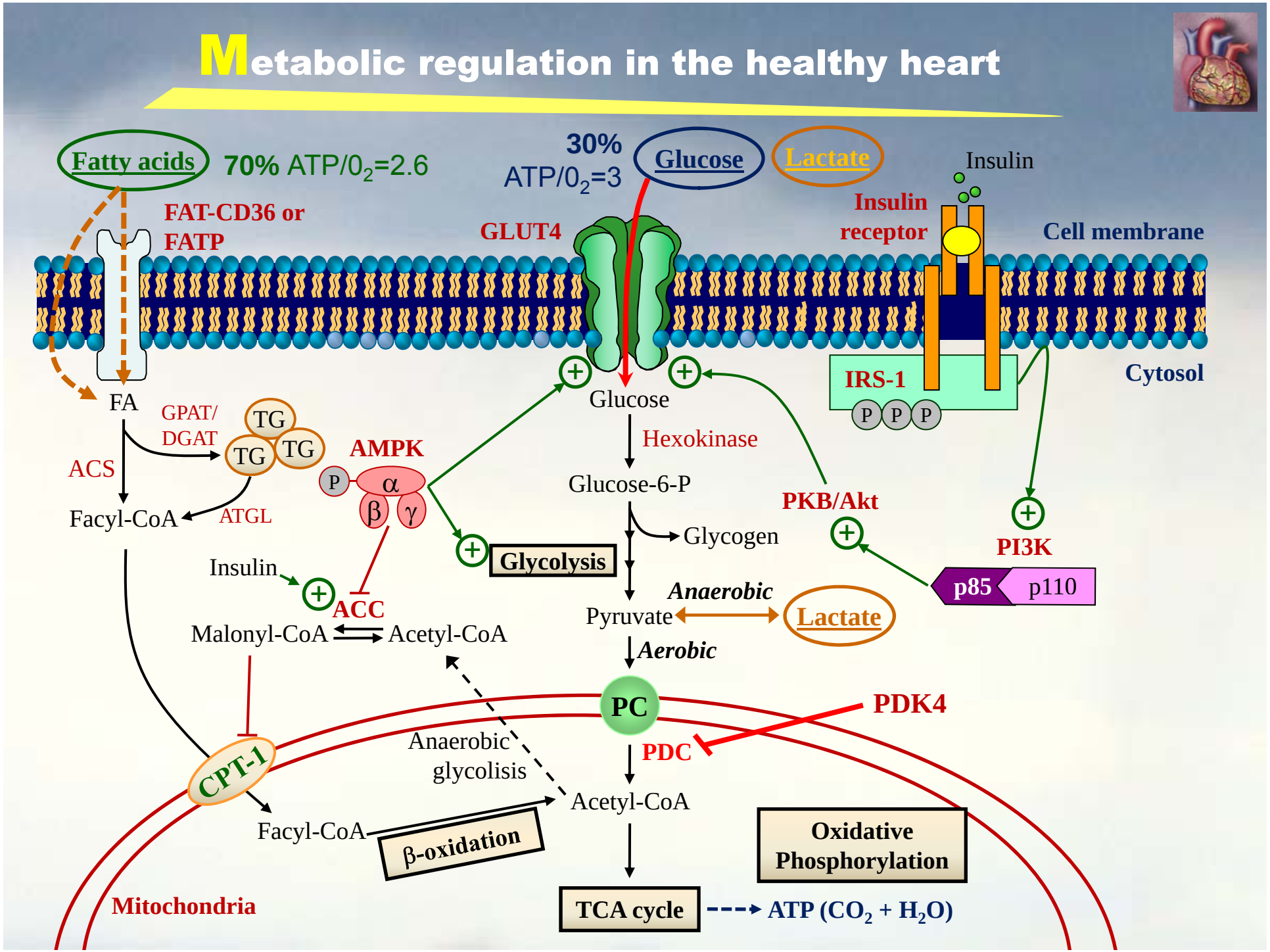
Circulation (2007) 115:3213-3223

Peroxisome Proliferator-Activated Receptors (PPARs)

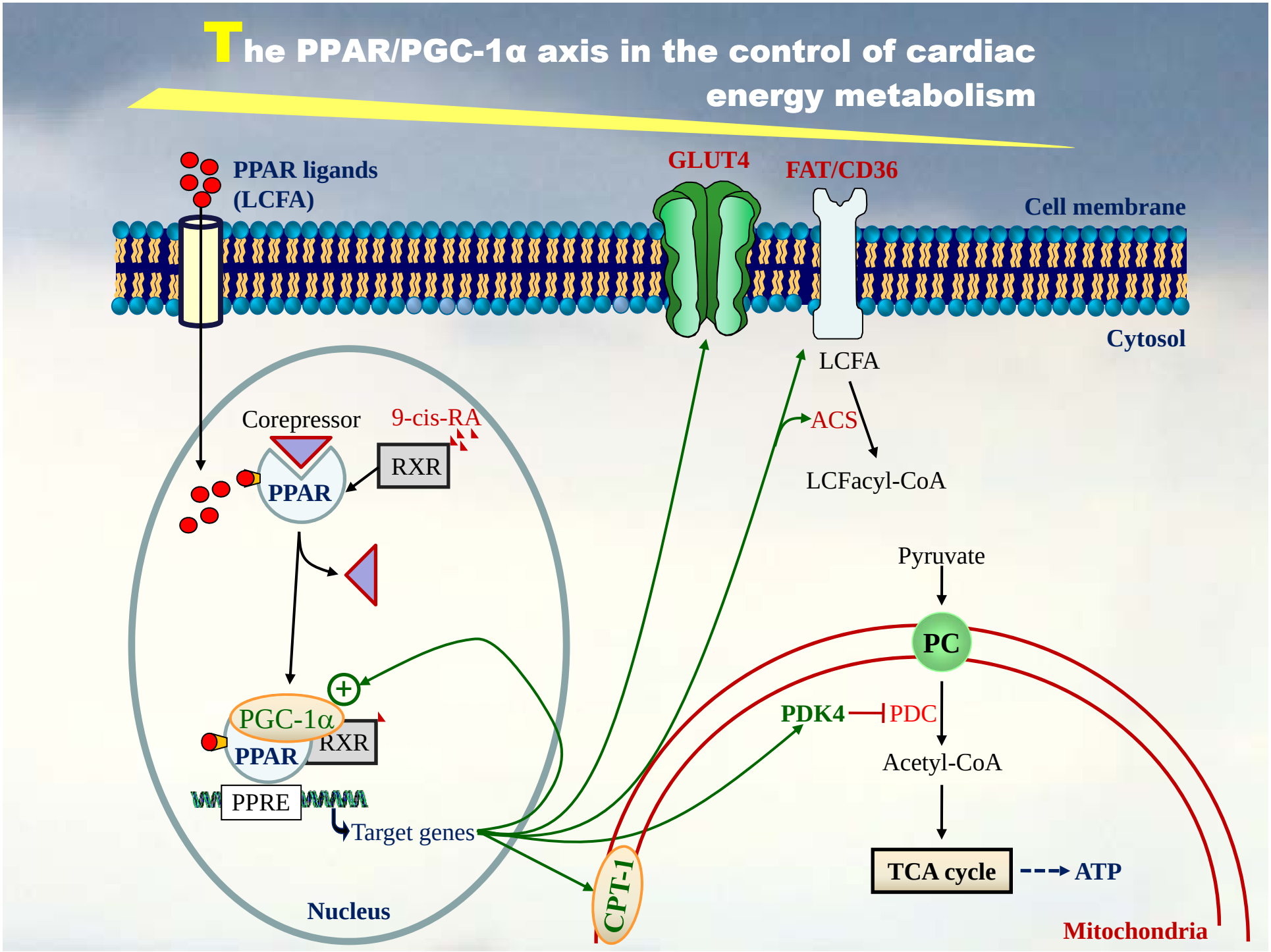
- Transcription factors that belong to the superfamily of nuclear hormone receptors
- 3 subtypes: PPARα (NR1C1), PPARβ/δ (NR1C2) and PPARγ (NR1C3)

PPARα	***PPARγ***	***PPARβ/δ***
FA β-oxidation and uptake	Glucose metabolism Adipogenesis (diff.) → FA uptake	FA β-oxidation and uptake
Anti-inflammatory	Anti-inflammatory	Anti-inflammatory
Liver, kidney, **heart**, skeletal muscle	Adipose tissue, macrophages	Ubiquitous (**heart**, **skeletal muscle**, skin, adipose tissue, brain)

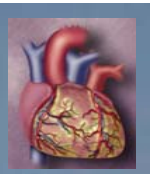
- As such are capable of limiting myocardial inflammation and hypertrophy via inhibition of NF-κB


Metabolic regulation in the healthy heart
Fatty acids
70% ATP/0_2=2.6
30%
ATP/0_2=3
Glucose
Lactate
Insulin
FAT-CD36 or
FATP
GLUT4
Insulin
receptor
Cell membrane
Cytosol
IRS-1
P P P
FA
GPAT/
DGAT
TG
TG
TG
ACS
Facyl-CoA
ATGL
AMPK
P
α
β
γ
Glucose
Hexokinase
Glucose-6-P
PKB/Akt
PI3K
p85
p110
Glycogen
Glycolysis
Insulin
ACC
Malonyl-CoA
Acetyl-CoA
Anaerobic
Pyruvate
Lactate
Aerobic
PC
PDK4
PDC
CPT-1
Anaerobic
glycolisis
Acetyl-CoA
Facyl-CoA
β-oxidation
Oxidative
Phosphorylation
Mitochondria
TCA cycle
ATP (CO_2 + H_2O)

The PPAR/PGC-1α axis in the control of cardiac energy metabolism



Diabetic cardiomyopathy

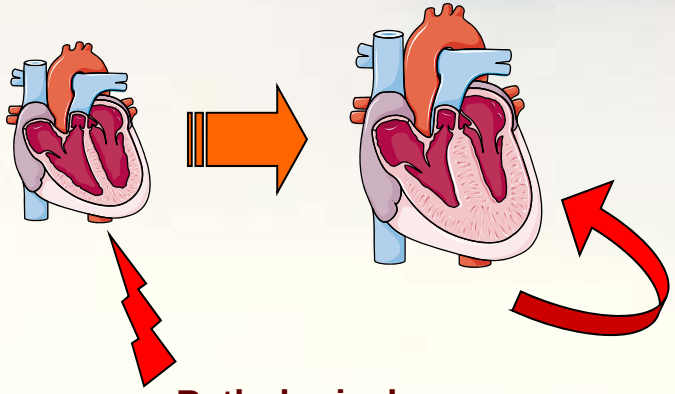


Loss of metabolic flexibility and inflammation in the heart

Healthy heart
FA β-oxidation
(glucose and lactate)

Cardiomyopathy
LOSS OF METABOLIC FLEXIBILITY

Diabetic / obese dysregulation



PGC-1α
PPAR
RXR
Nucleus
PPRE
Target genes

IL-6, MCP-1, TNF-α
(NF-κB)

Pathological stimulus

DCM
(CH, HF, MI)

Stimuli related to NF-κB during diabetes in the heart

Hyperglycemia, AGEs,
ROS
Hyperlipidemia
Chemokines & cytokines

Objectives

Main objective

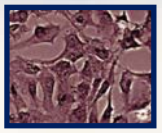
- Donat que un nombre creixent d'evidències suggereix l'existència d'un vincle entre les malalties metabòliques (RI, DM2, obesitat) I els processos inflamatoris crònics de baixa intensitat, **el principal objectiu d'aquest treball ha consistit en establir noves relacions moleculars entre el metabolisme i la inflamació durant la cardiomiopatia diabètica**

Specific objectives

1. És capaç l'activació de PPARβ/δ de bloquejar la inflamació induïda per lípids en el cor?
2. Existeix algun vincle entre la via PPARβ/δ-PGC-1α/PDK4 i NF-κB en la cardiomiopatia diabètica?
   - 2.1. Quins són els mecanismes moleculars implicats?
   - 2.2. Hi ha altres factors de transcripció involucrats?

Materials & Methods

Non-differentiated human cardiac AC16 cells



Palmitate (0.25 mM 18h)
TNF-α (1-100 ng/mL, 24h)
GW501516 (10 μM, 24h)

+Additional treatments

3 to 5-month-old CD1 ♂ mice

±HFD (59% kcal from fat)
GW501516 (3 mg/kg, 2 months)

3 to 5-month-old PPARβ/δ KO

±HFD (45% kcal from fat, 91.5% SFA) for 2 months

2 to 3-month-old TNF 1.6 ♂ mice

RNA

Protein (NE/CP, TP)

Culture media/Plasma

Molecular and biochemical analyses

Objectives

Main objective

- Donat que un nombre creixent d'evidències suggereix l'existència d'un vincle entre les malalties metabòliques (RI, DM2, obesitat) I els processos inflamatoris crònics de baixa intensitat, **el principal objectiu d'aquest treball ha consistit en establir noves relacions moleculars entre el metabolisme i la inflamació durant la cardiomiopatia diabètica**

Specific objectives

1. **És capaç** l'activació de **PPARβ/δ de bloquejar la inflamació** induïda per **lípids** en el **cor**?
2. Existeix algun vincle entre la via PPARβ/δ-PGC-1α/PDK4 i NF-κB en la cardiomiopatia diabètica?
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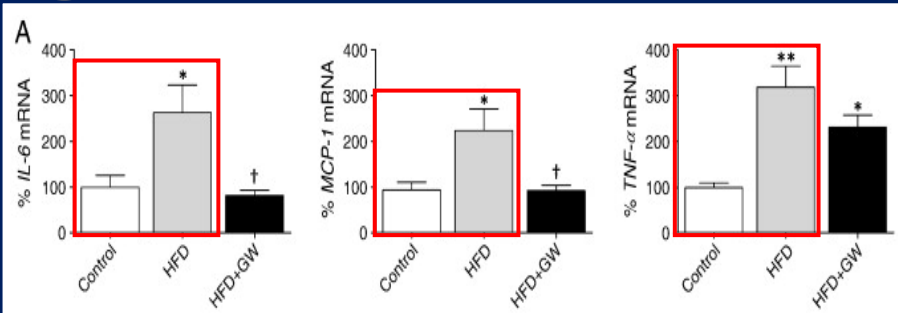
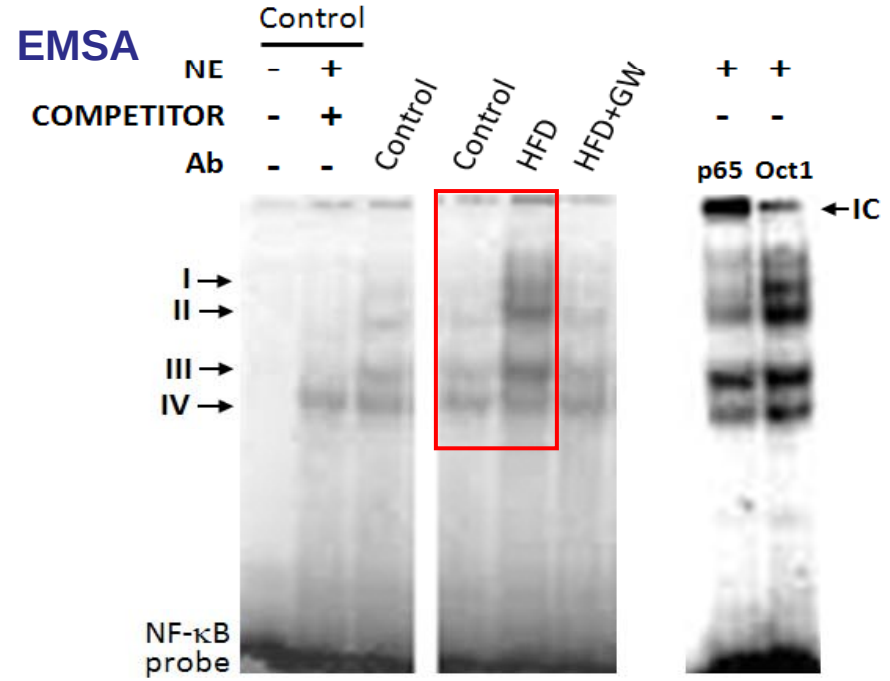
PPARβ/δ activation blocks lipid-induced inflammation in the heart (1)

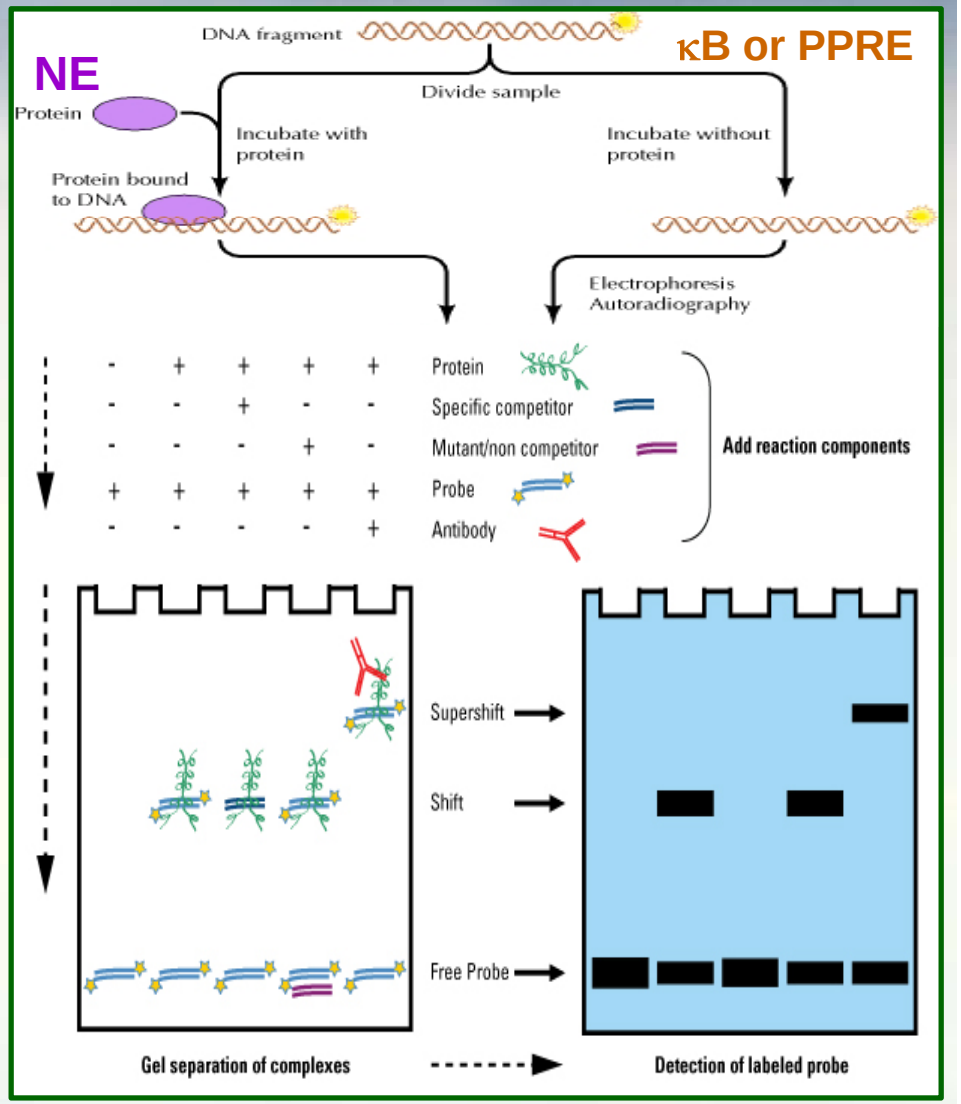
HFD-induced obesity stimulates inflammation in the heart





BBA (2011) 1811:59–67

CD1 mice +HFD



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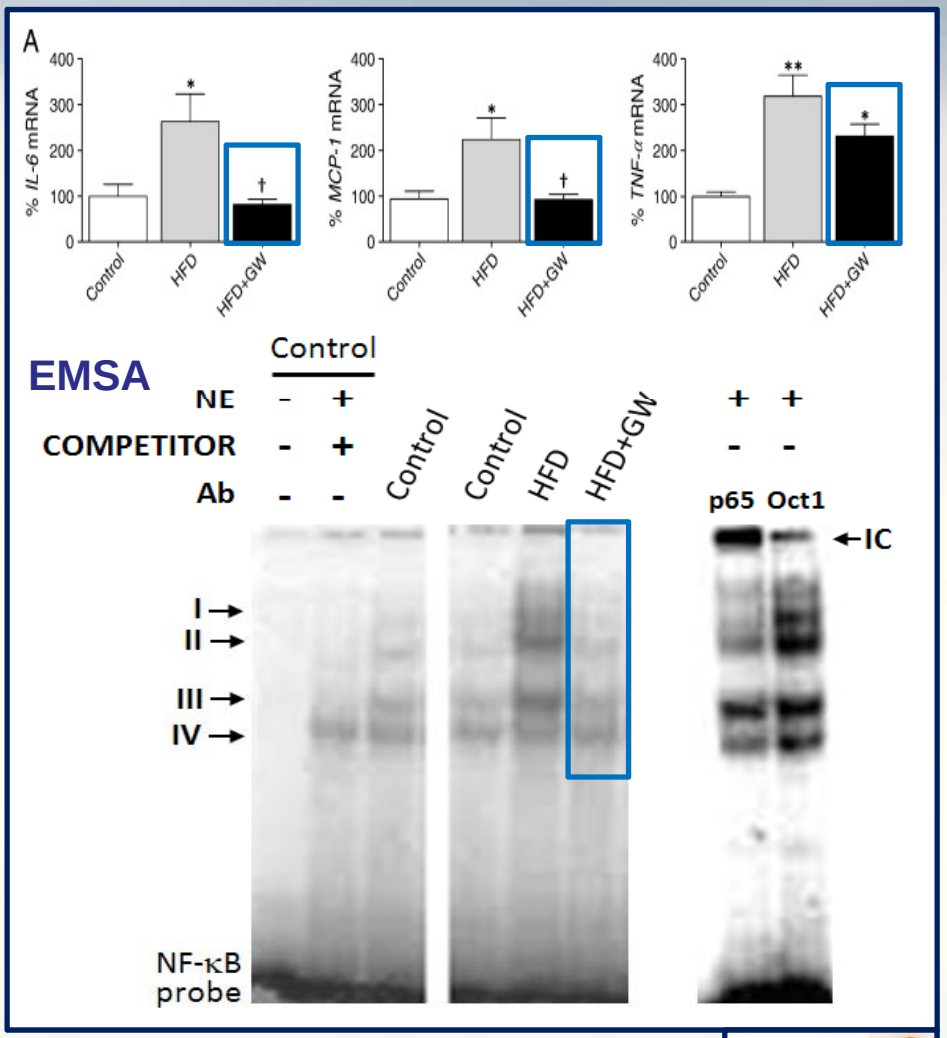
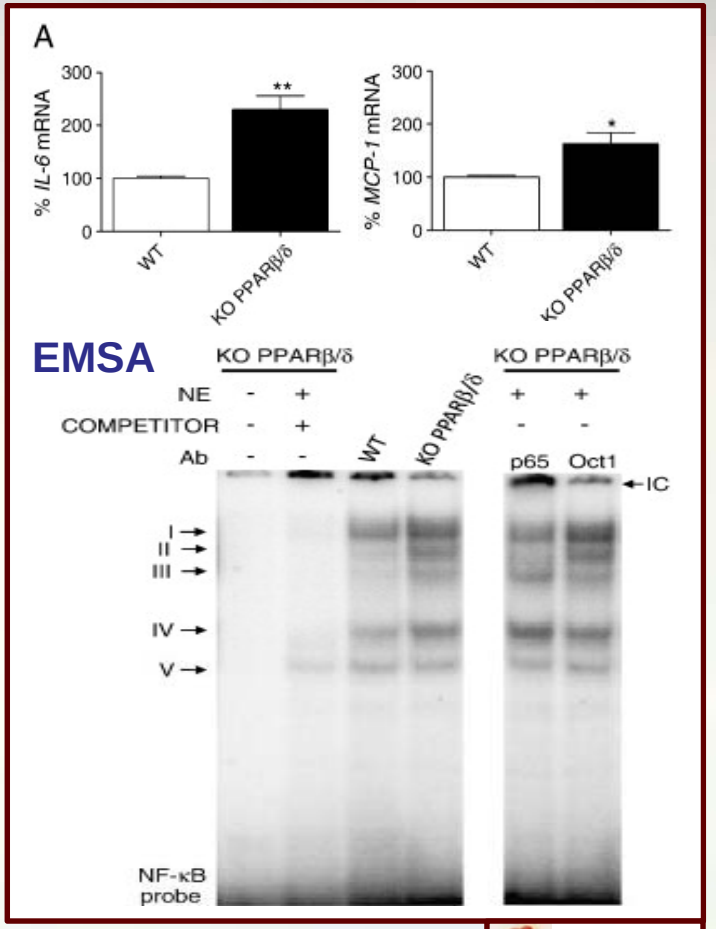


BBA (2011) 1811:59–67

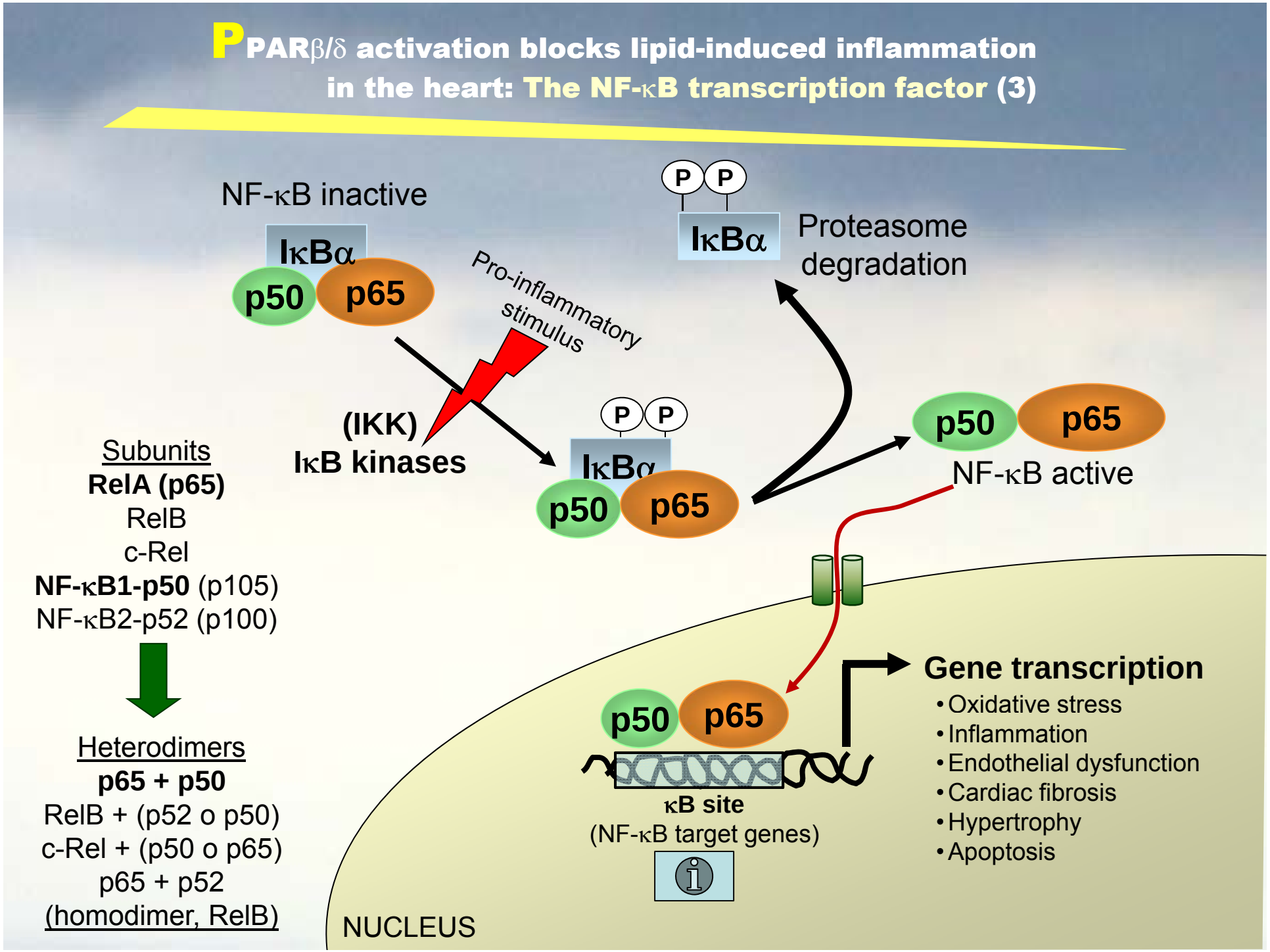
CD1 mice +HFD

….and PPARβ/δ inhibits it



PPARβ/δ KO mice

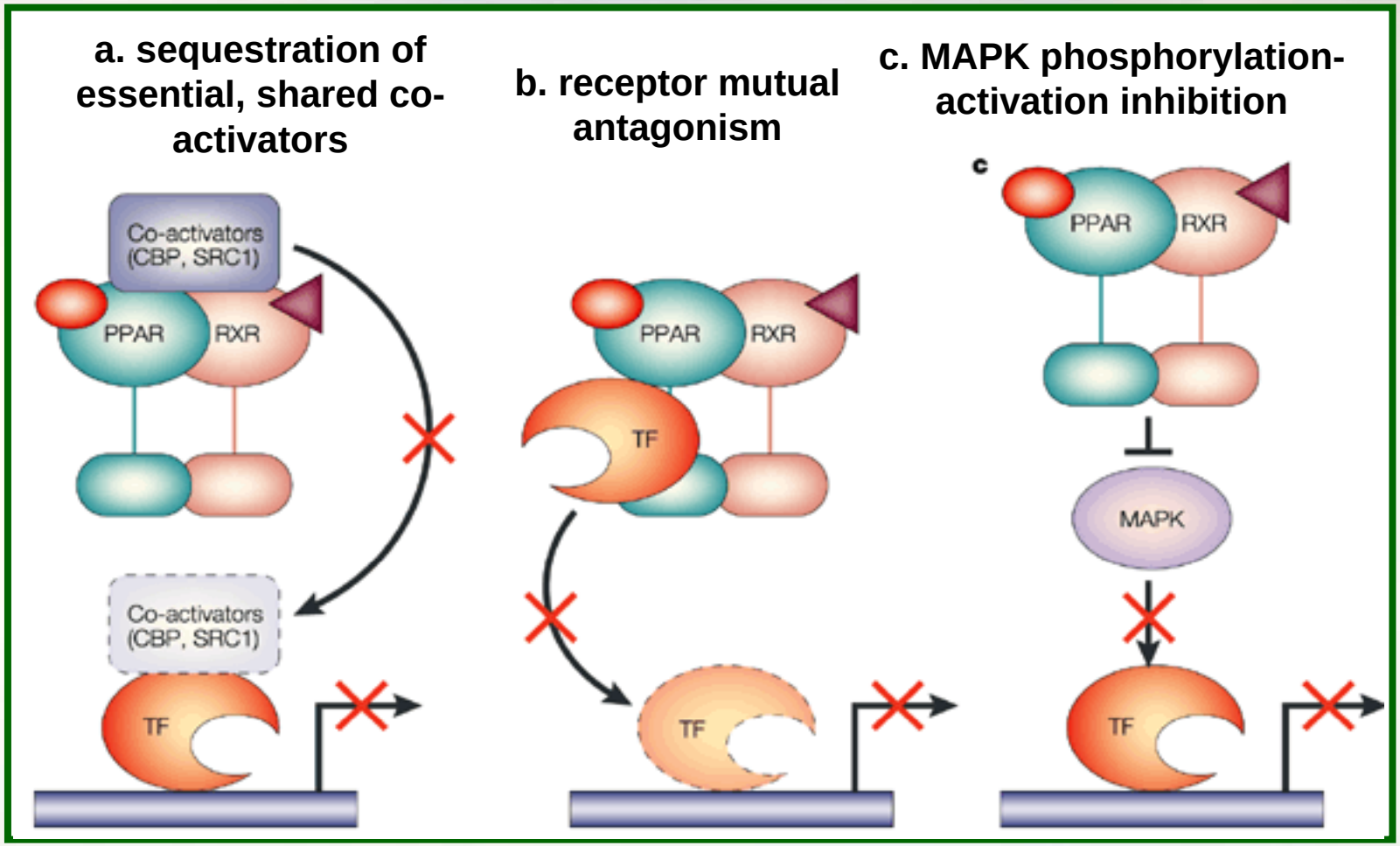
PPARβ/δ activation blocks lipid-induced inflammation in the heart: The NF-κB transcription factor (3)



PPARβ/δ activation blocks lipid-induced inflammation in the heart: Anti-inflammatory mechanisms of PPARs (4)

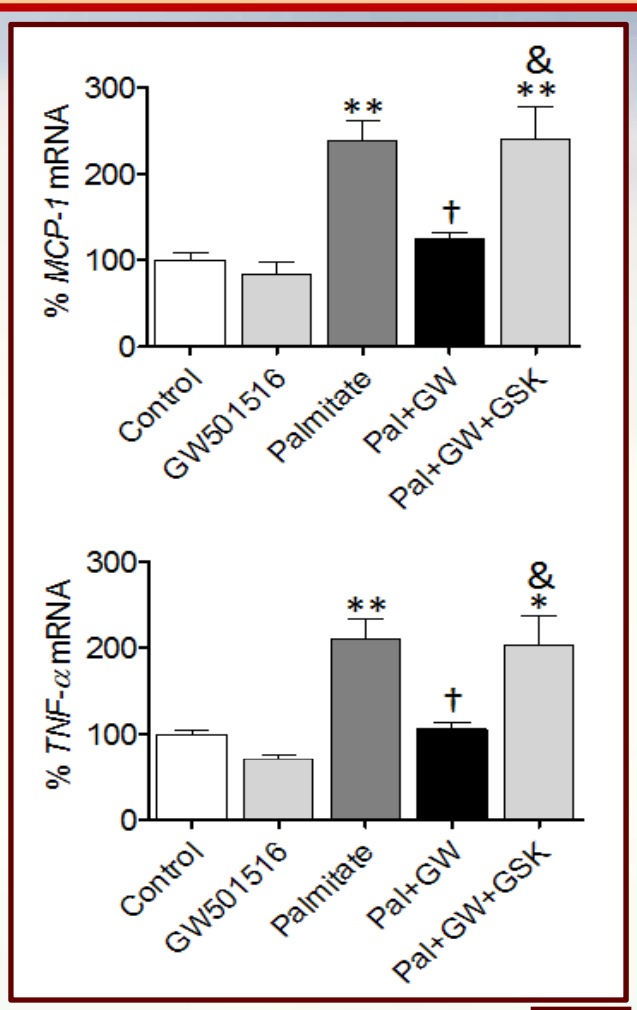
Trans-repression

Ligand and **RXR dependent / PPRE independent**



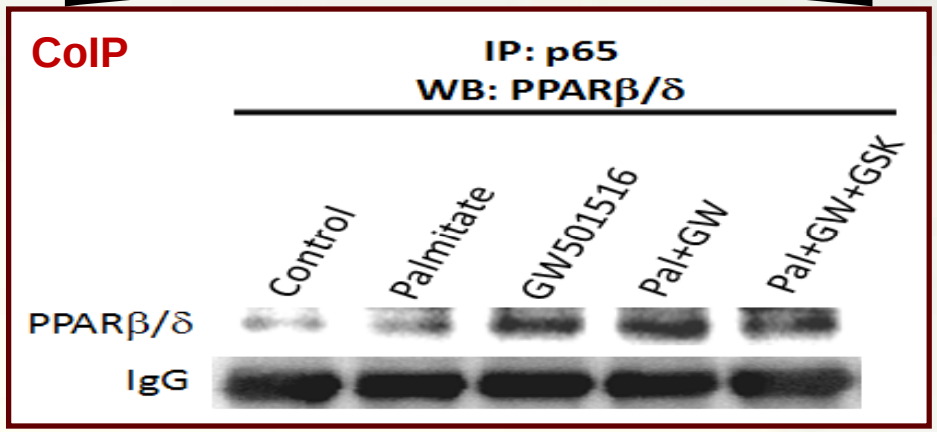
PPARβ/δ activation blocks lipid-induced inflammation in the heart (5)

Palmitate induces inflammation in human cardiac cells



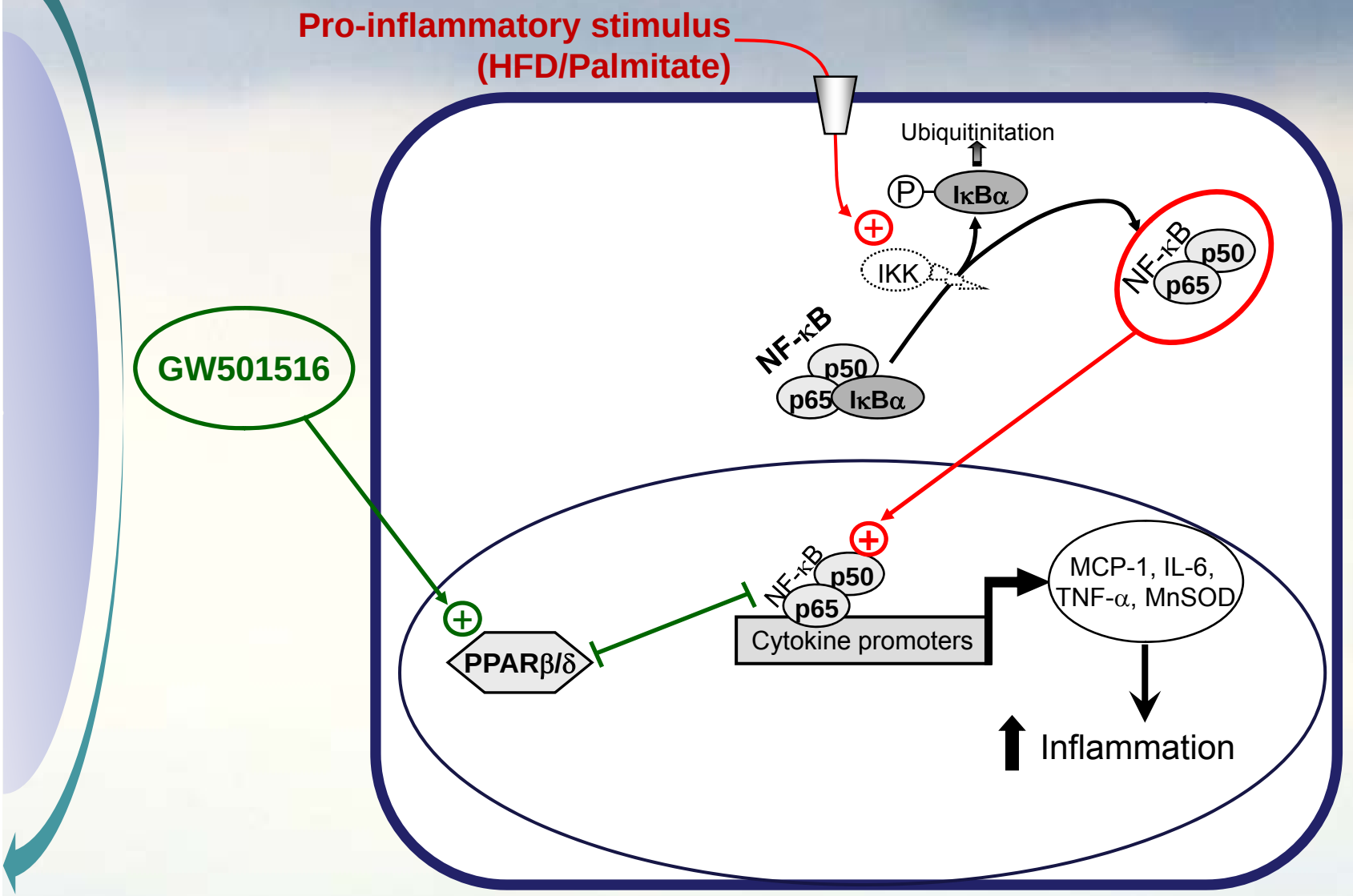
Human cardiac AC16 cells

The anti-inflammatory effects of GW: mutual receptor antagonism



BBA (2011) 1811:59–67

PPARβ/δ activation blocks lipid-induced inflammation in the heart: SUMMARY (6)



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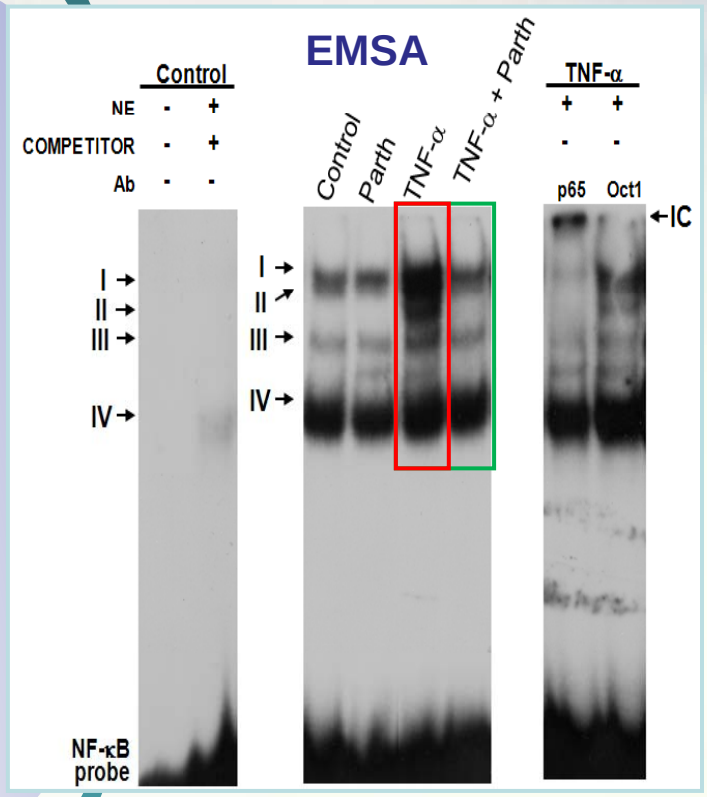
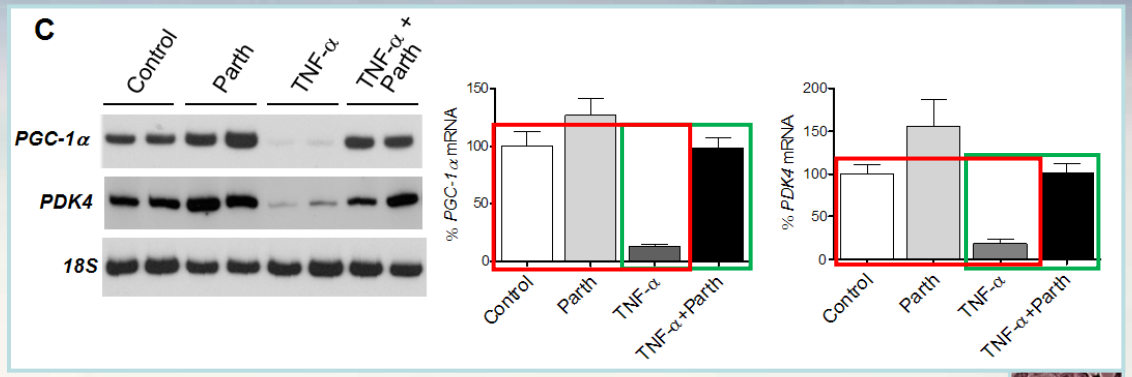
The interplay between PGC-1α, metabolism and NF-κB: NF-κB inhibits PGC-1α and PDK4 expression (1)

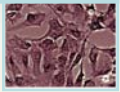
TNF-α induces NF-κB transcriptional activity

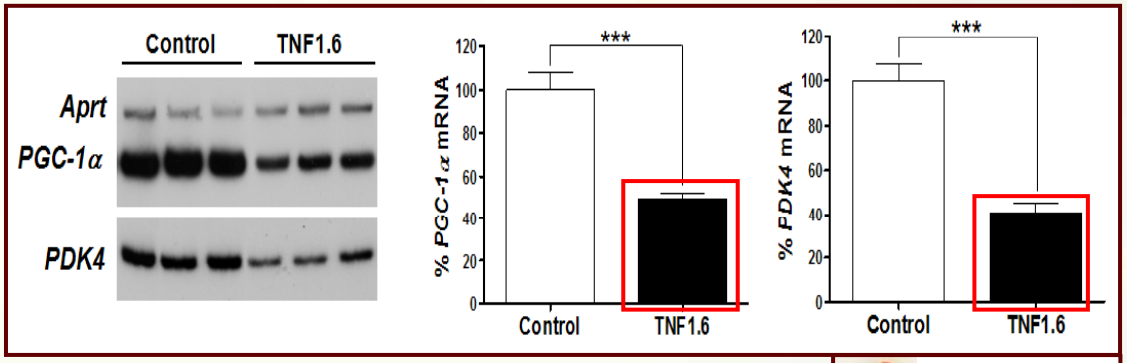


….and inhibits *PGC-1α* and *PDK4* expression



Human cardiac cells



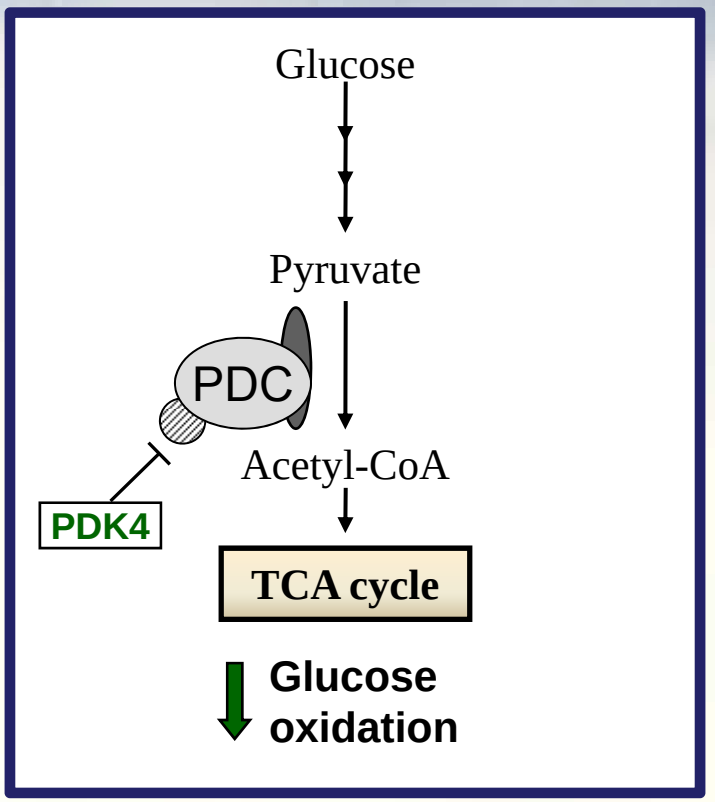


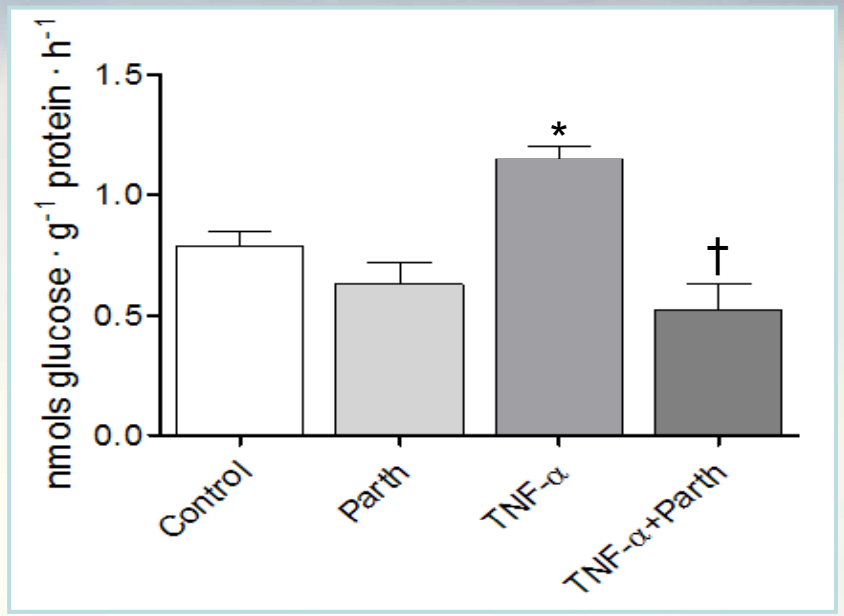
TNF1.6 mice

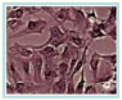
Cardiovasc Res (2009) 81, 703-712

The interplay between PGC-1α, metabolism and NF-κB: NF-κB inhibits PGC-1α and PDK4 expression (2)

….thereby enhancing glucose oxidation and reducing FA β-oxidation







Human cardiac cells

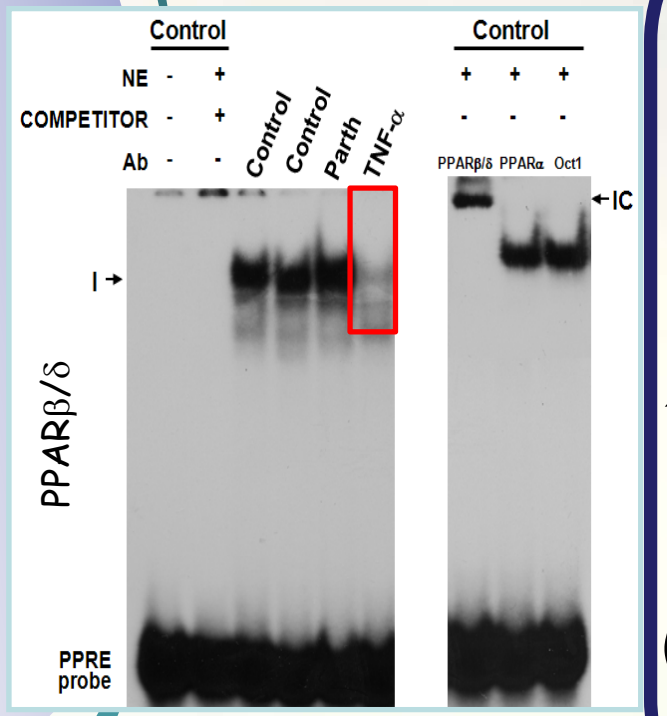
Cardiovasc Res (2009) 81, 703-712

The interplay between PGC-1α, metabolism and NF-κB:
Mechanism: Is there a role for PPARs? (3)

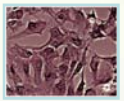
NF-κB inhibits PPARβ/δ

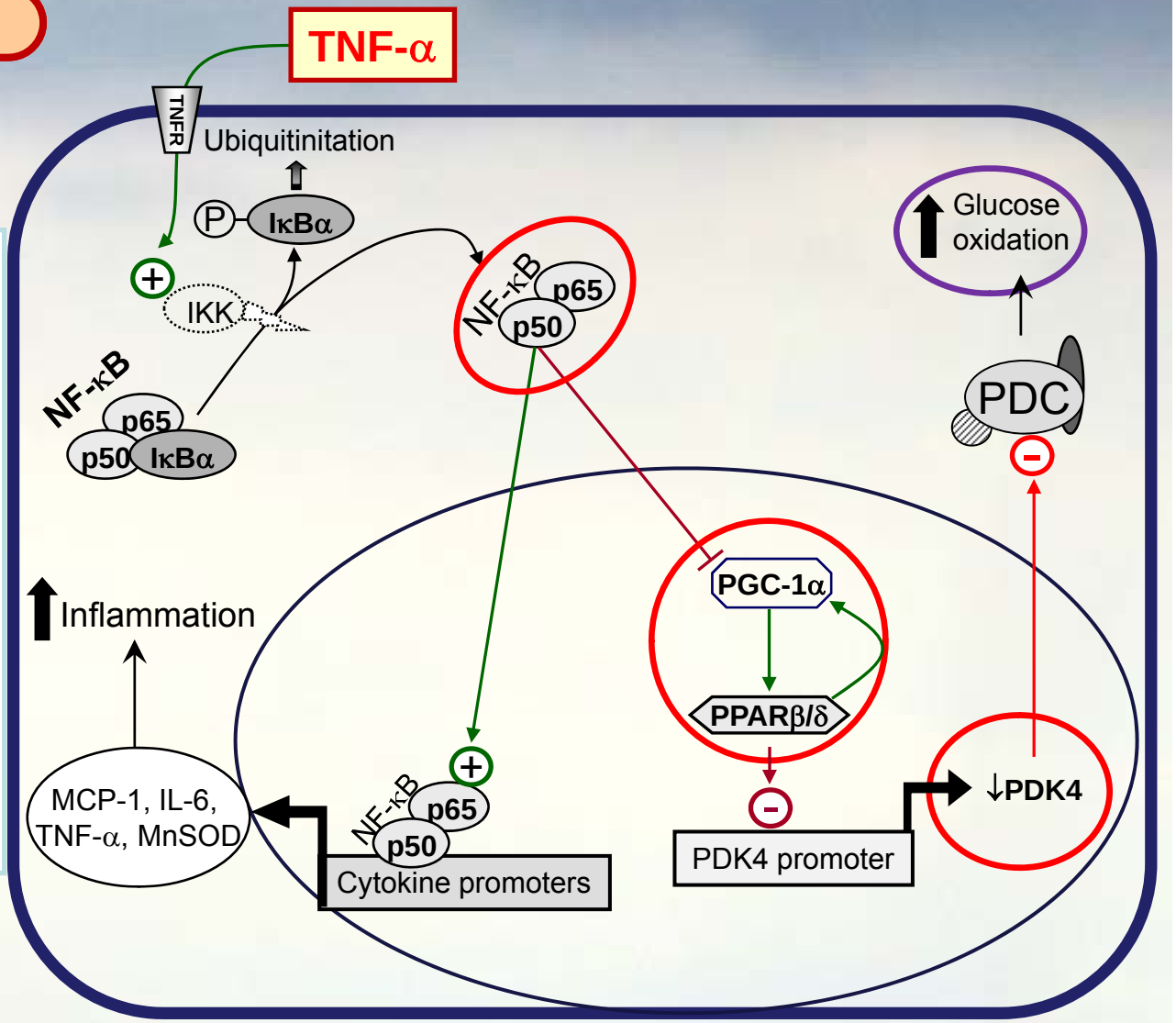
TNF-α

EMSA



Human cardiac cells





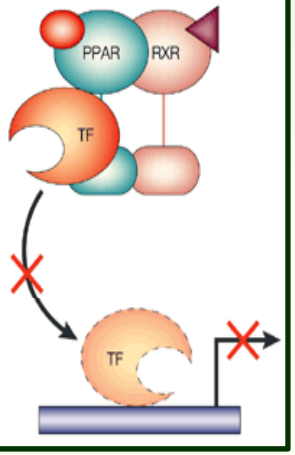
Cardiovasc Res (2009) 81, 703-712

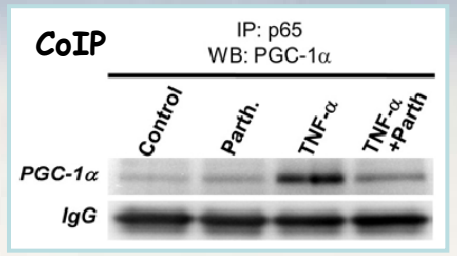
The interplay between PGC-1α, metabolism and NF-κB: Mechanism: Is there a role for PPARs? (4)

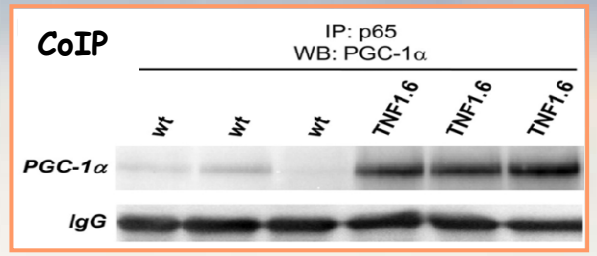
Trans-repression?

physical interaction between p65 and PGC-1α!

2. receptor mutual antagonism

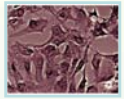






TNF1.6 mice

Human cardiac cells

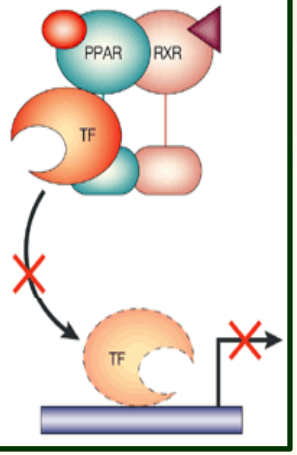


Cardiovasc Res (2010) 87:449-458

The interplay between PGC-1α, metabolism and NF-κB: Mechanism: Is there a role for PPARs? (4)

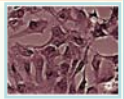
Trans-repression?

2. receptor mutual antagonism

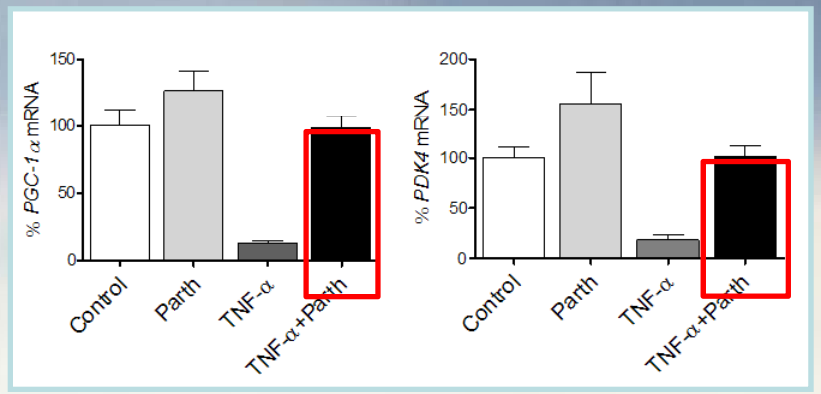


TNF1.6 mice

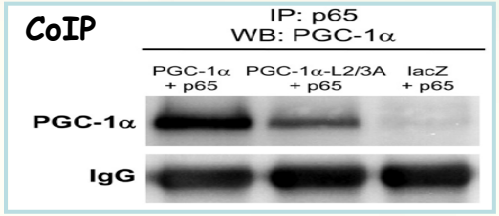
Human cardiac cells

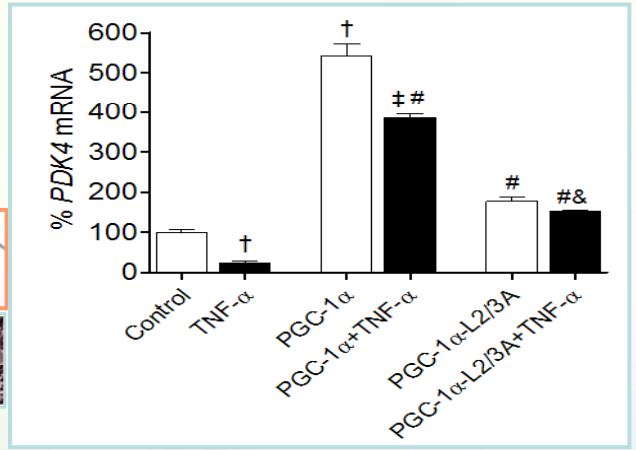


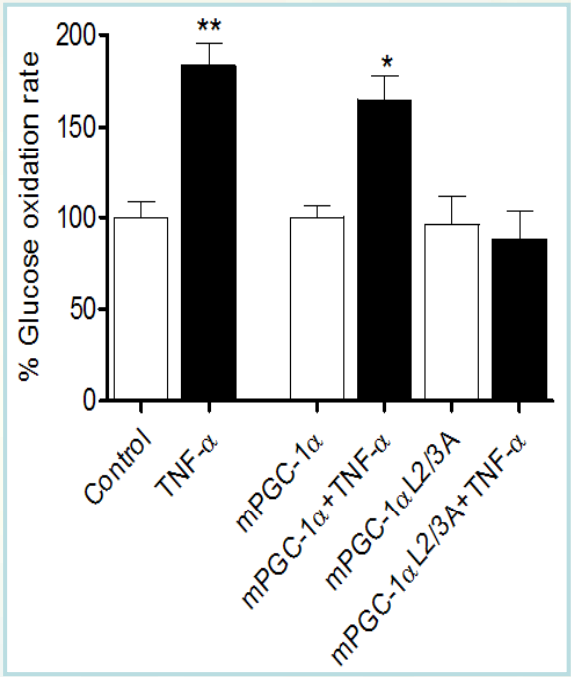
Cardiovasc Res (2010) 87:449-458



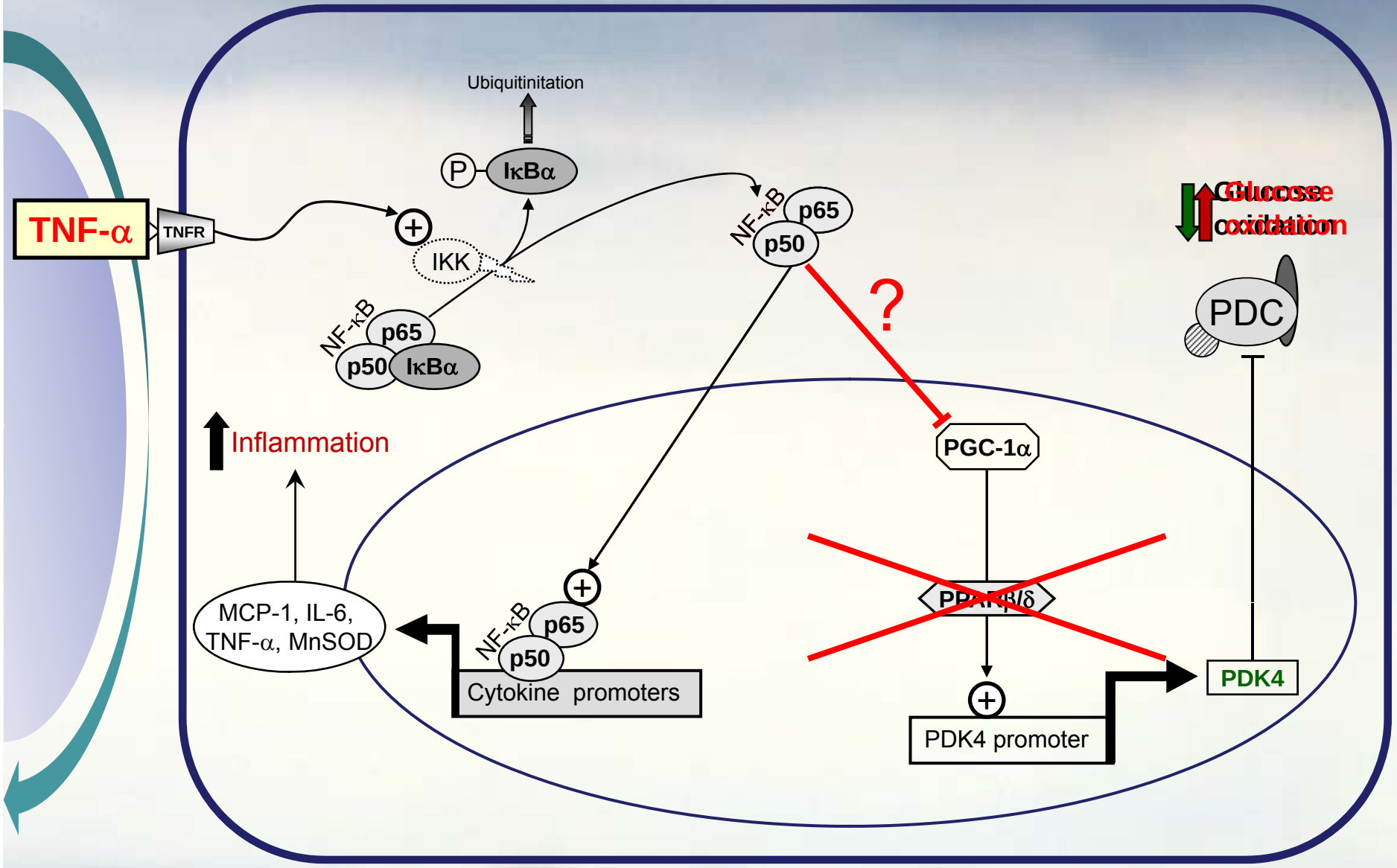
LXXLL domains of PGC-1α are involved in its association with p65







The interplay between PGC-1α, metabolism and NF-κB: SUMMARY (5)



Objectives

Main objective

- Donat que un nombre creixent d'evidències suggereix l'existència d'un vincle entre les malalties metabòliques (RI, DM2, obesitat) I els processos inflamatoris crònics de baixa intensitat, **el principal objectiu d'aquest treball ha consistit en establir noves relacions moleculars entre el metabolisme i la inflamació durant la cardiomiopatia diabètica**

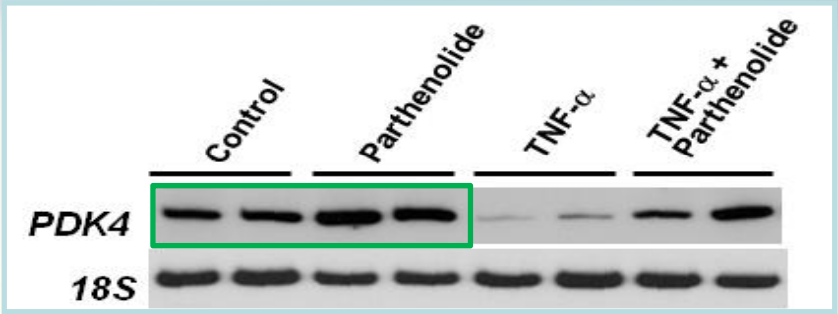
Specific objectives

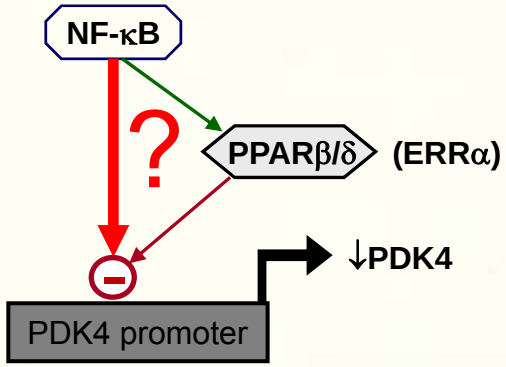
1. És capaç l'activació de PPARβ/δ de bloquejar la inflamació induïda per lípids en el cor?
2. Existeix algun vincle entre la via PPARβ/δ-PGC-1α/PDK4 i NF-κB en la cardiomiopatia diabètica?
   - 2.1. Quins són els mecanismes moleculars implicats?
   - 2.2. Hi ha **altres factors de transcripció involucrats**?

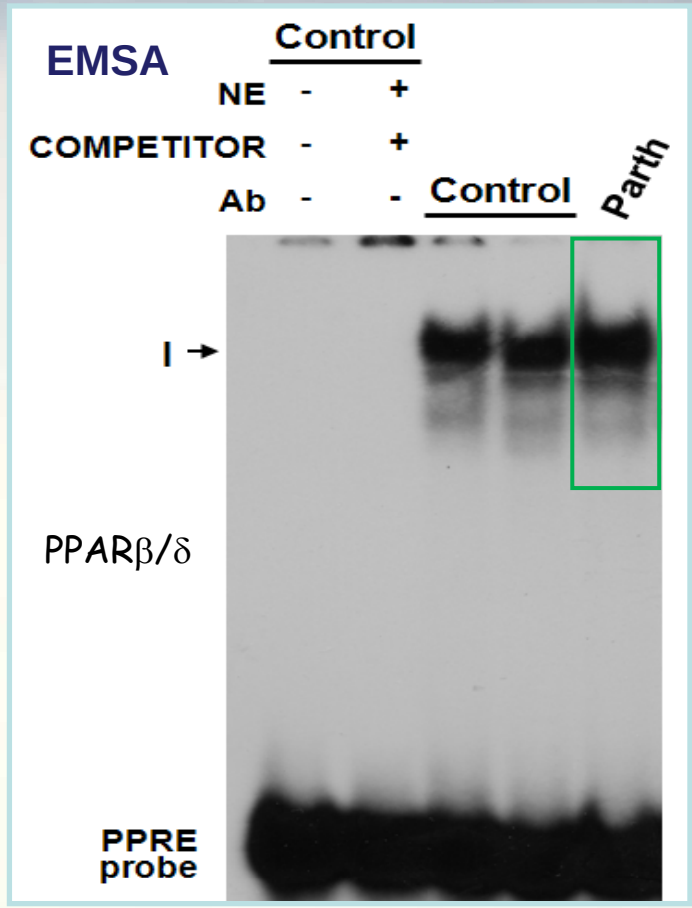
PPAR-independent mechanisms linking PDK4 and inflammation in the heart: Why another mechanism? (1)

Why another mechanism?

Human cardiac cells





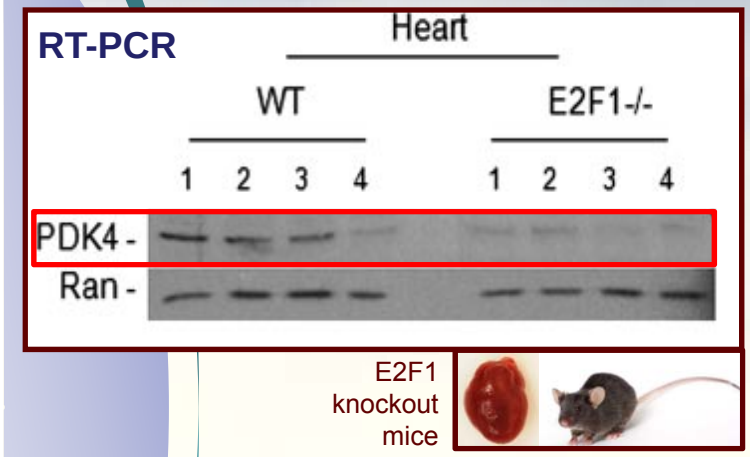


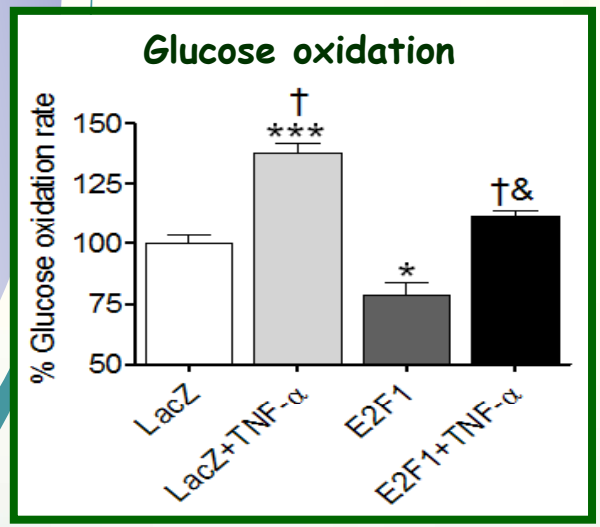
Cardiovasc Res (2009) 81:703-712

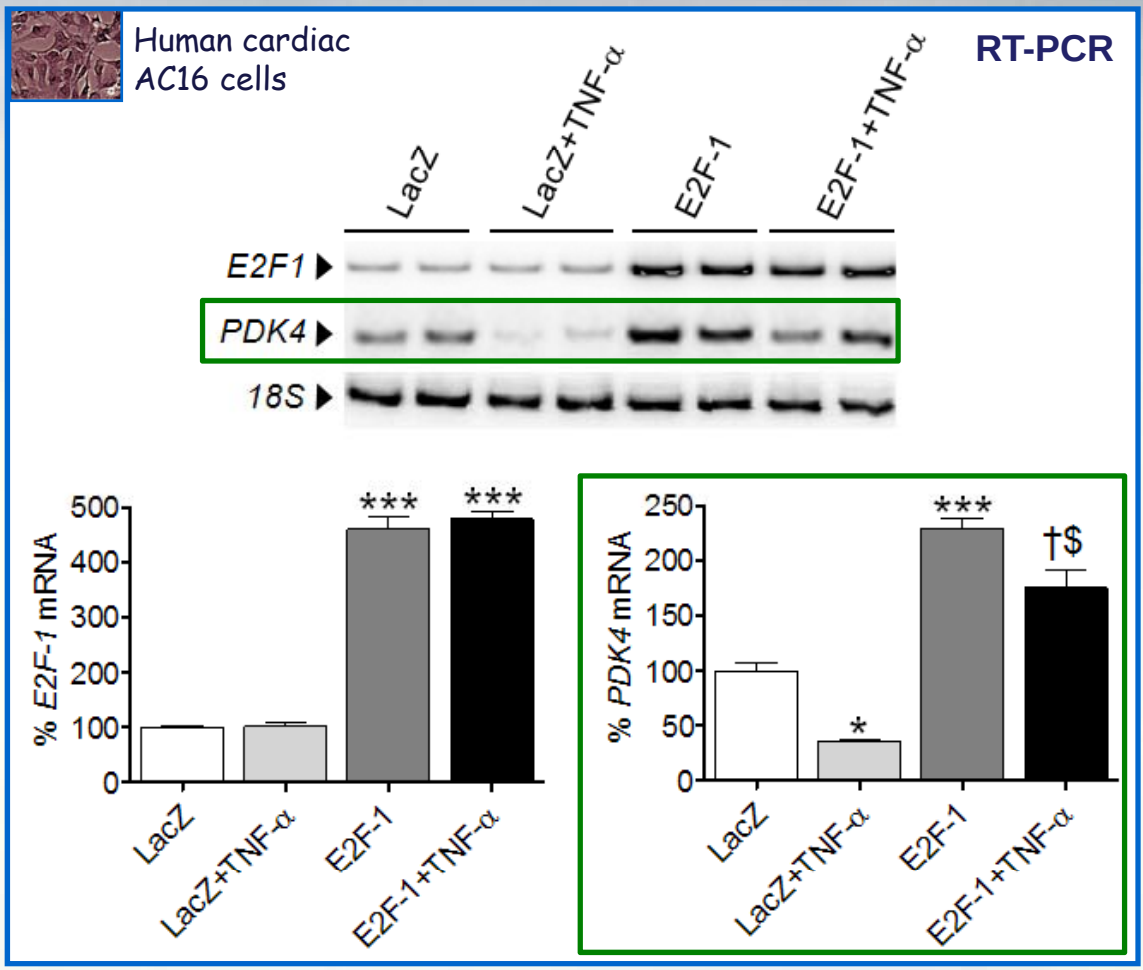
PPAR-independent mechanisms linking PDK4 and inflammation in the heart: E2F1 (2)

E2F1 regulates *PDK4* expression

…and this influences glucose oxidation





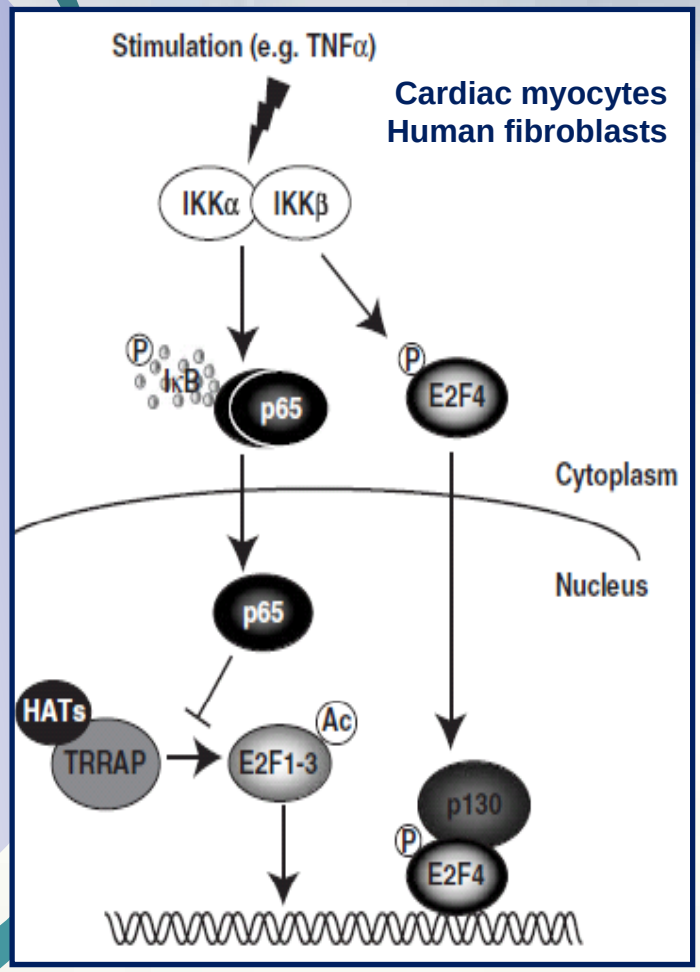


JBC (2008) 283: 27410–27417

PLoS One (2011) 6(5):e1972

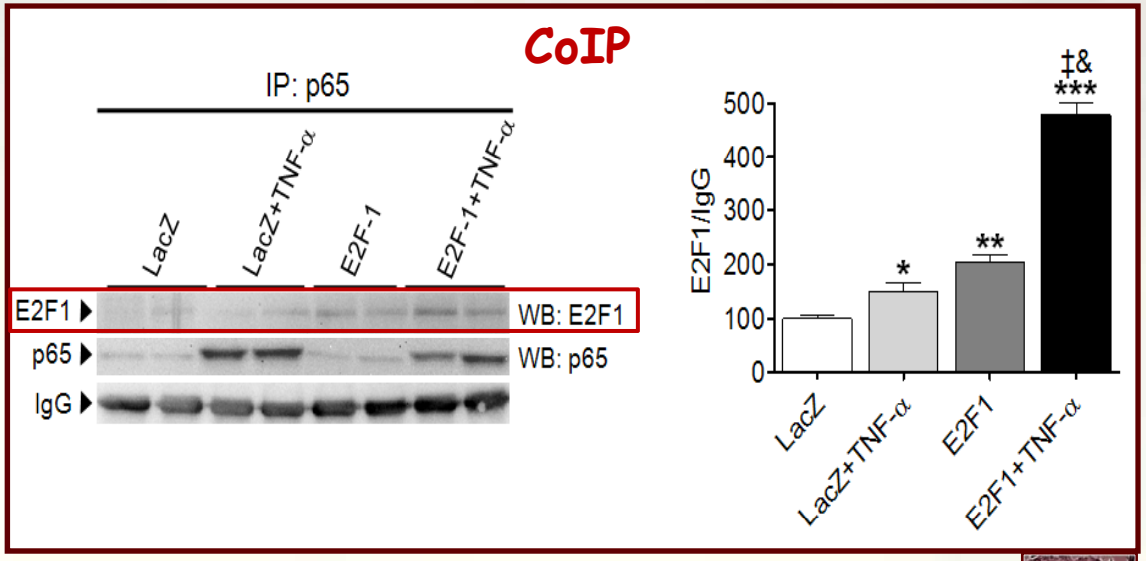
PPAR-independent mechanisms linking PDK4 and inflammation in the heart: E2F1 (3)

E2F1 regulates the G1/S phase transition of the cell cycle… that interacts with p65



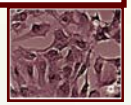
FEBS J (2006) 273(8):1669-80; Proc Natl Acad Sci USA (2008) 105(52):20734-9; Oncogene (2008) 27:5696–5705

TNF-α enhances E2F1/p65 physical interaction



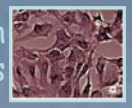
PLoS One (2011) 6(5):e1972

Human cardiac cells

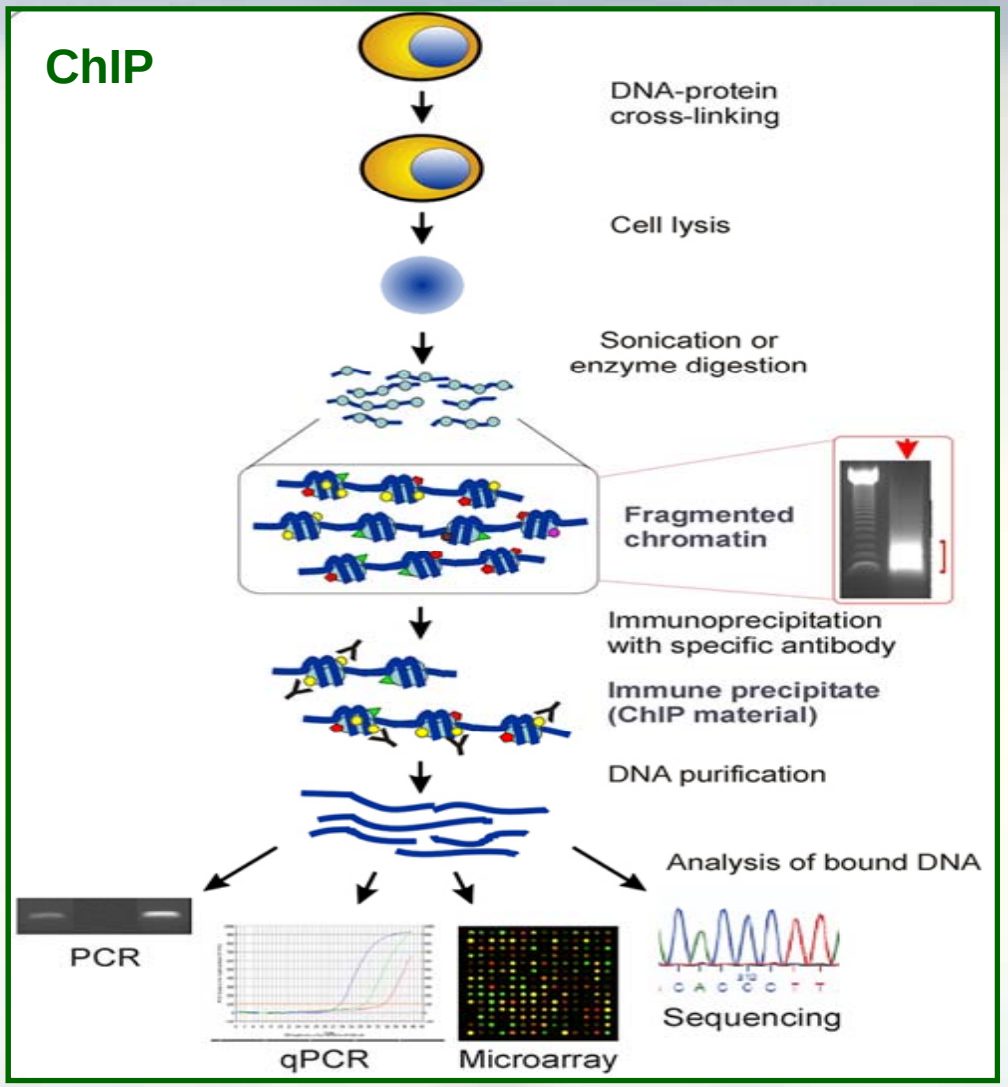


PPAR-independent mechanisms linking PGC-1α/PDK4 and inflammation in the heart: E2F1 (4)

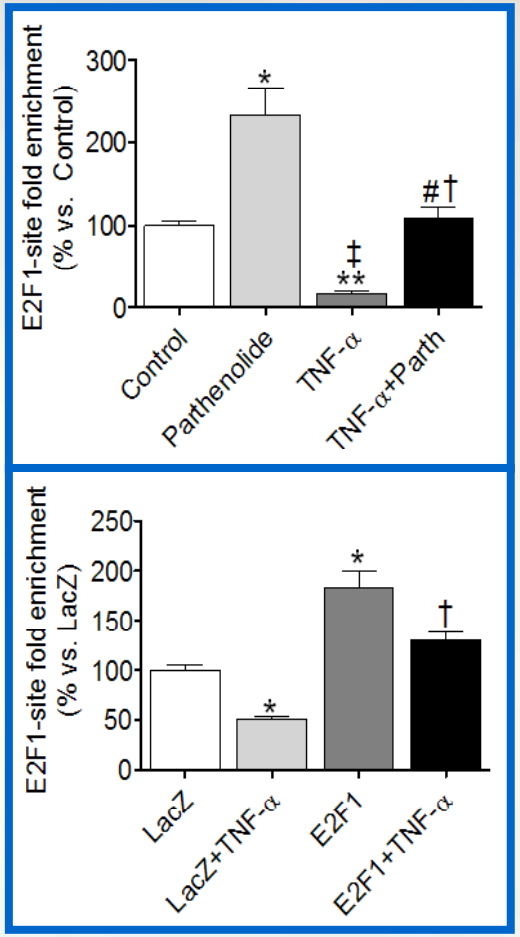
Human cardiac cells



p65/E2F1 physical interaction prevents the recruitment of E2F1 to the PDK4 promoter

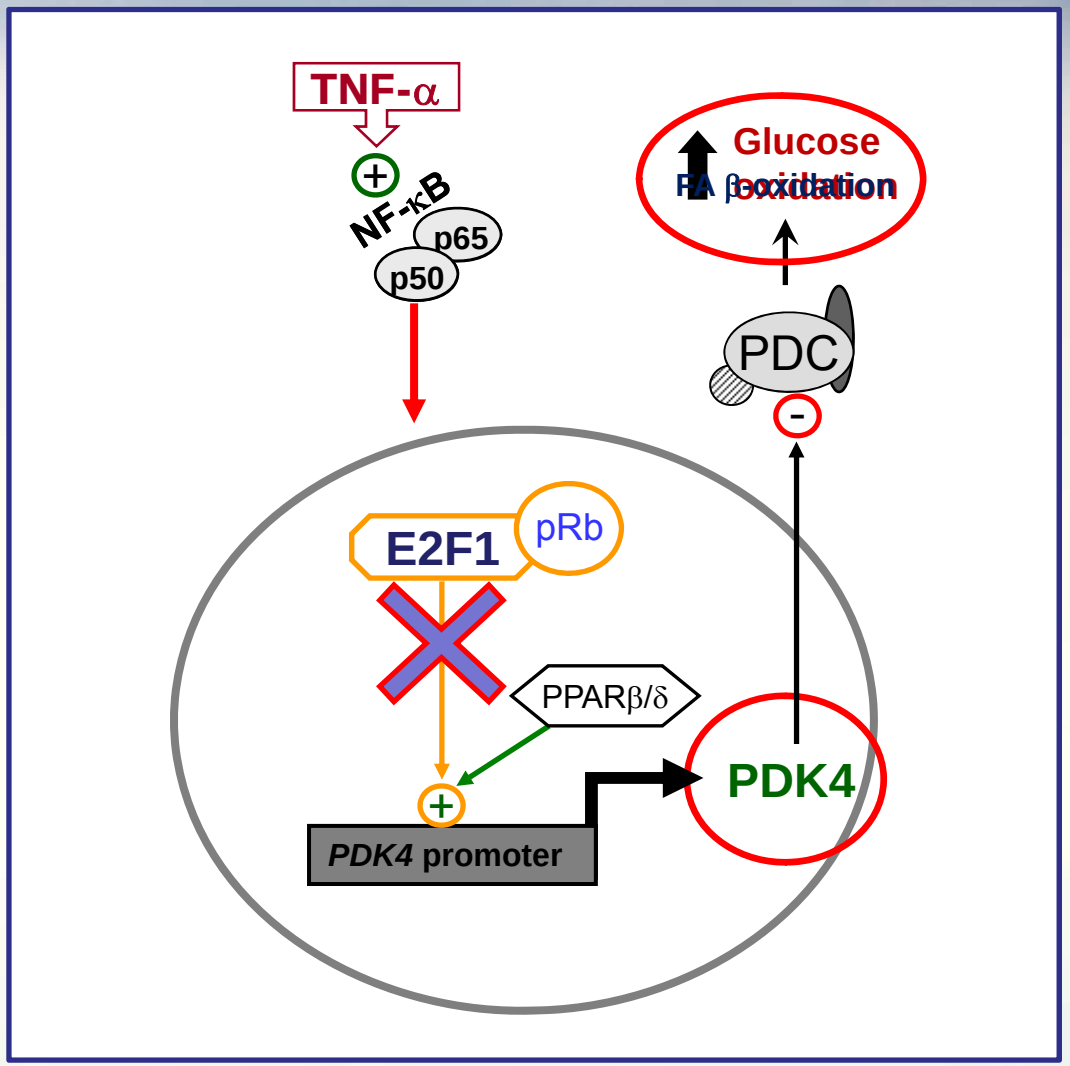


ChIP PDK4



PLoS One (2011) 6(5):e1972

PPAR-independent mechanisms linking PGC-1α/PDK4 and inflammation in the heart: SUMMARY (5)



Take home messages

- Els AGL són el substrat energètic preferit al cor adult (glucosa, lactat).
- La utilització d'AGL/glucosa està controlat en gran part per l'eix PPAR/PGC-1α → *PDK4*.
- Durant la diabetis, la desregulació d'aquest l'eix provoca que el miocardi subsisteixi gairebé exclusivament de la β-oxidació mitocondrial d'AG → lipotoxicitat, ↑ ROS i activació NF-κB → Cardiomiopatia diabètica.
- L'activació de PPARβ/δ és capaç de limitar els processos inflamatoris en el cor per mitjà de diversos mecanismes (trans-repressió per antagonisme mutu de receptors, inhibició d'AMPK)
- NF-κB funciona com un interruptor molecular que regula l'activitat de PGC-1α/PDK4 (taxa d'oxidació de glucosa i AG). Nosaltres hem demostrat dos nous mecanismes de regulació:
  1. la inhibició de PGC-1α per interacció física amb NF-κB (p65);
  2. la inhibició d'E2F1/PDK4 per part de NF-κB (p65).