Cell Metabolism
Article

Glycogen Synthase Kinase-3α Promotes Fatty Acid Uptake and Lipotoxic Cardiomyopathy

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GROUP B

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Students

Ioannis Lempesis, Ioanna Papatheodorou, Dimitra Palioura, Dimitrios Giannis

Introduction

Obesity, Insulin resistance, Diabetes

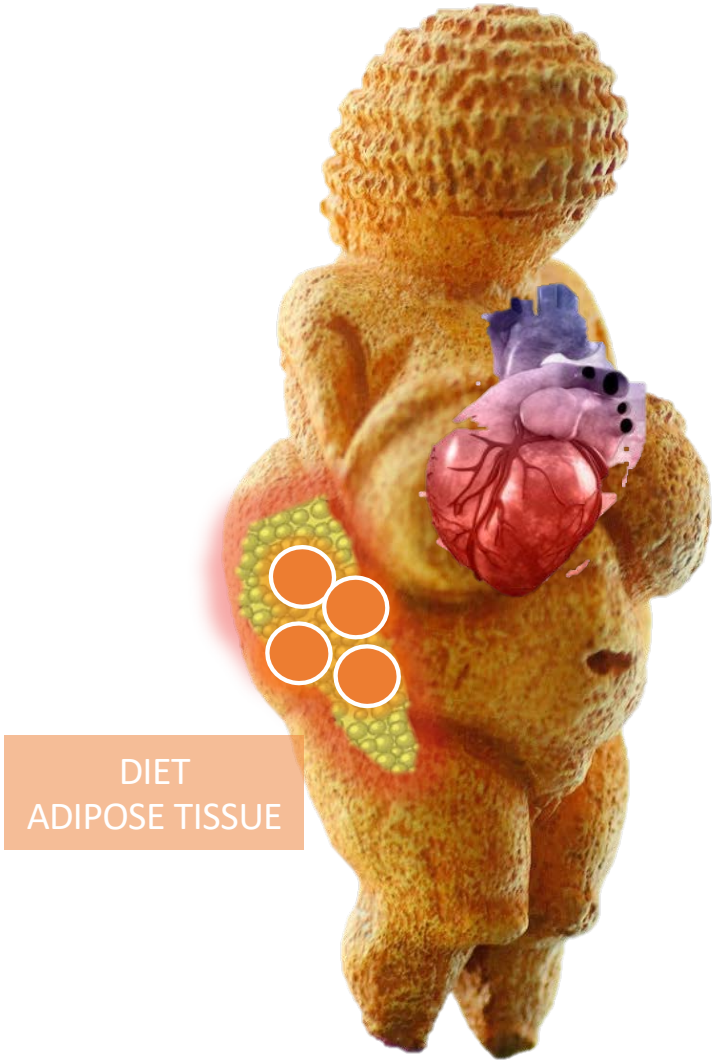
Characterized by:

- ectopic lipid accumulation

(non-adipose tissue)

↓

- imbalance in Fatty Acids (FA) metabolism



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Introduction

Lipitoxicity & Cardiomyopathy

Uptake / Synthesis of FA – ***Consumption***

(FA oxidation - FAO)

↓

intracellular accumulation of lipid intermediates

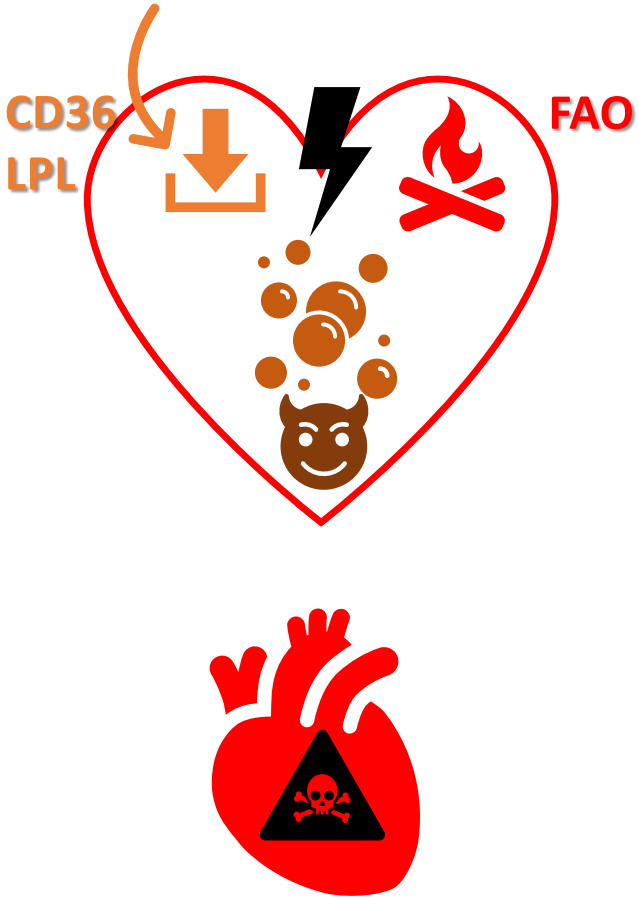
↓

cellular dysfunction & death

↓

Lipotoxic cardiomyopathy

How the balance of FA metabolism is disrupted in obesity ???



Adapted from Goldberg et al. (2012) Cell Metabolism

Introduction

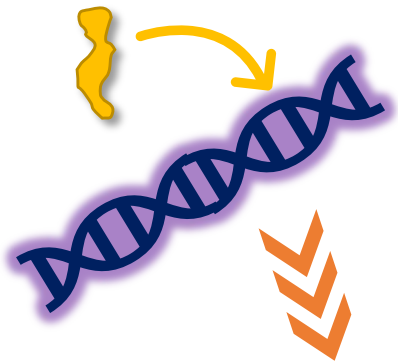
Lipid metabolism – PPARα

PPARα

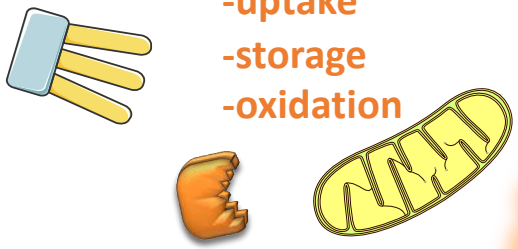
Peroxisome proliferator-activated receptor α

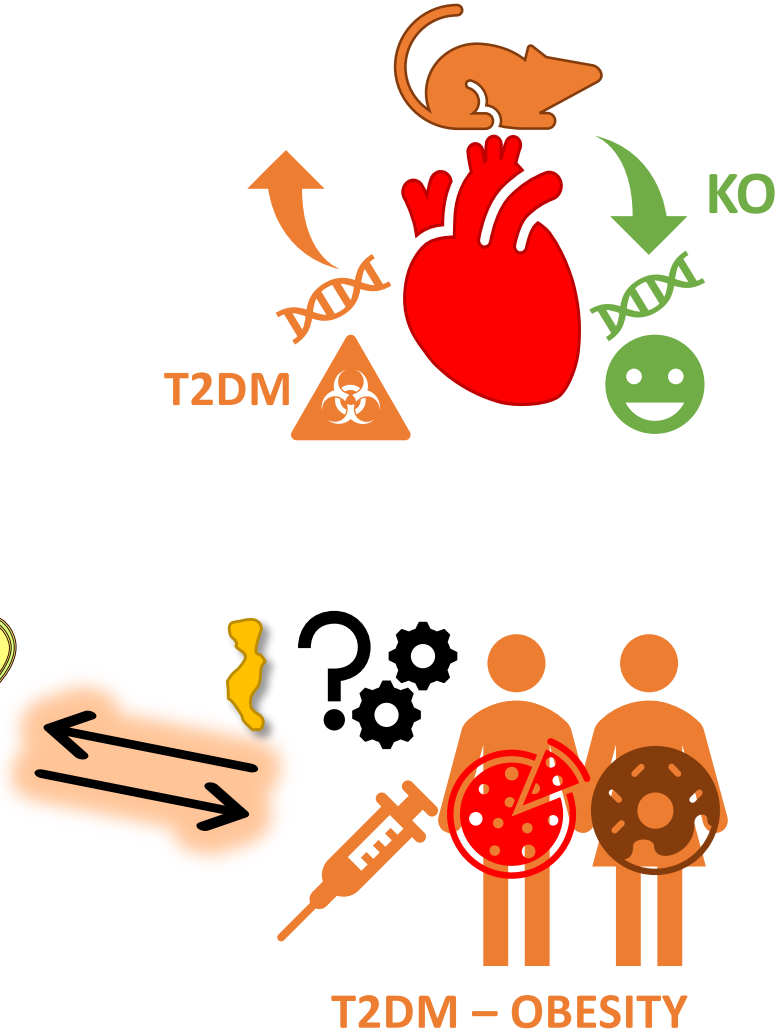
Nuclear receptor transcription factor

ligand-binding domains ***(LBDs)***



FA metabolism
-uptake
-storage
-oxidation





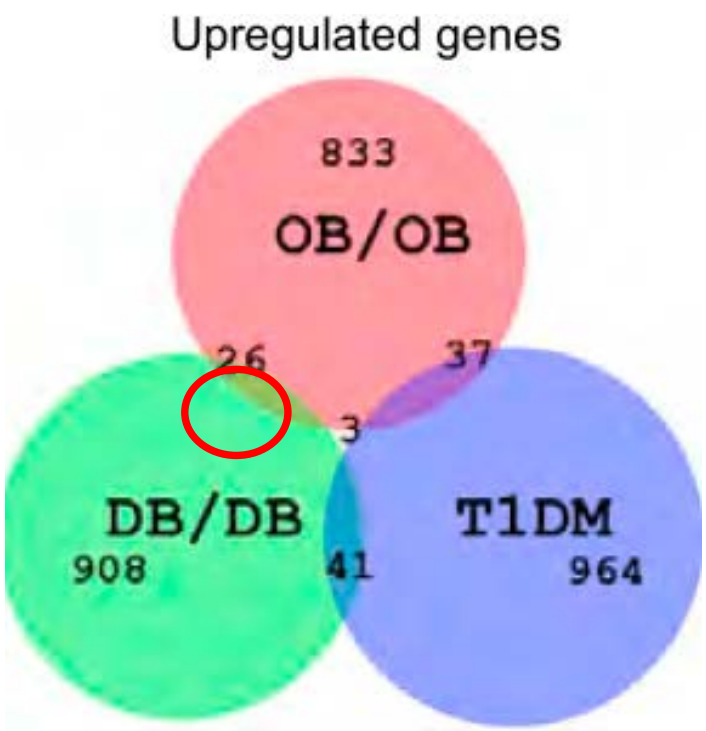
Rationale and Study Goals

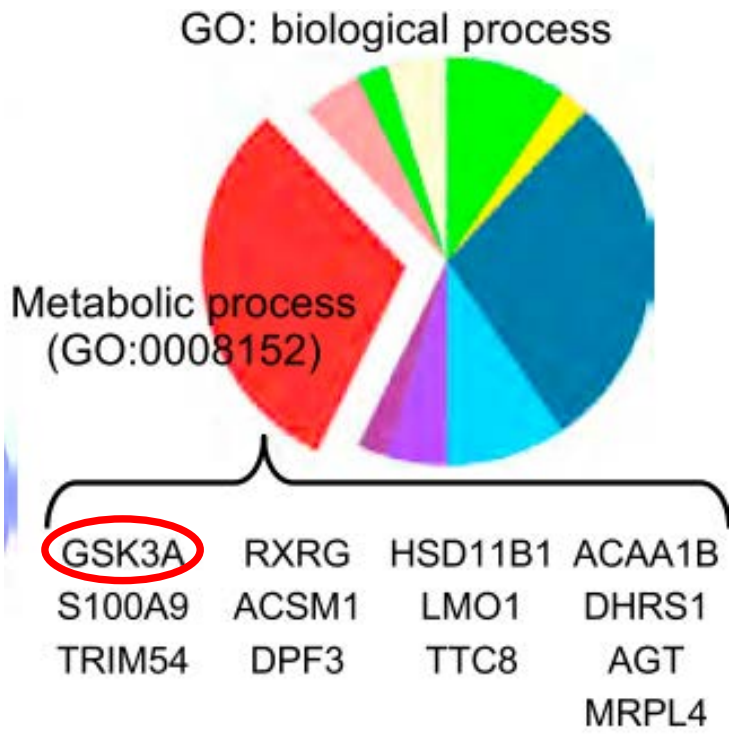
- ✓ Define molecular mechanism of PPARα regulation
- ✓ In mouse models of obesity and diabetes
- ✓ Iduced by high-fat diet (HFD) consumption & genetic alteration

Results

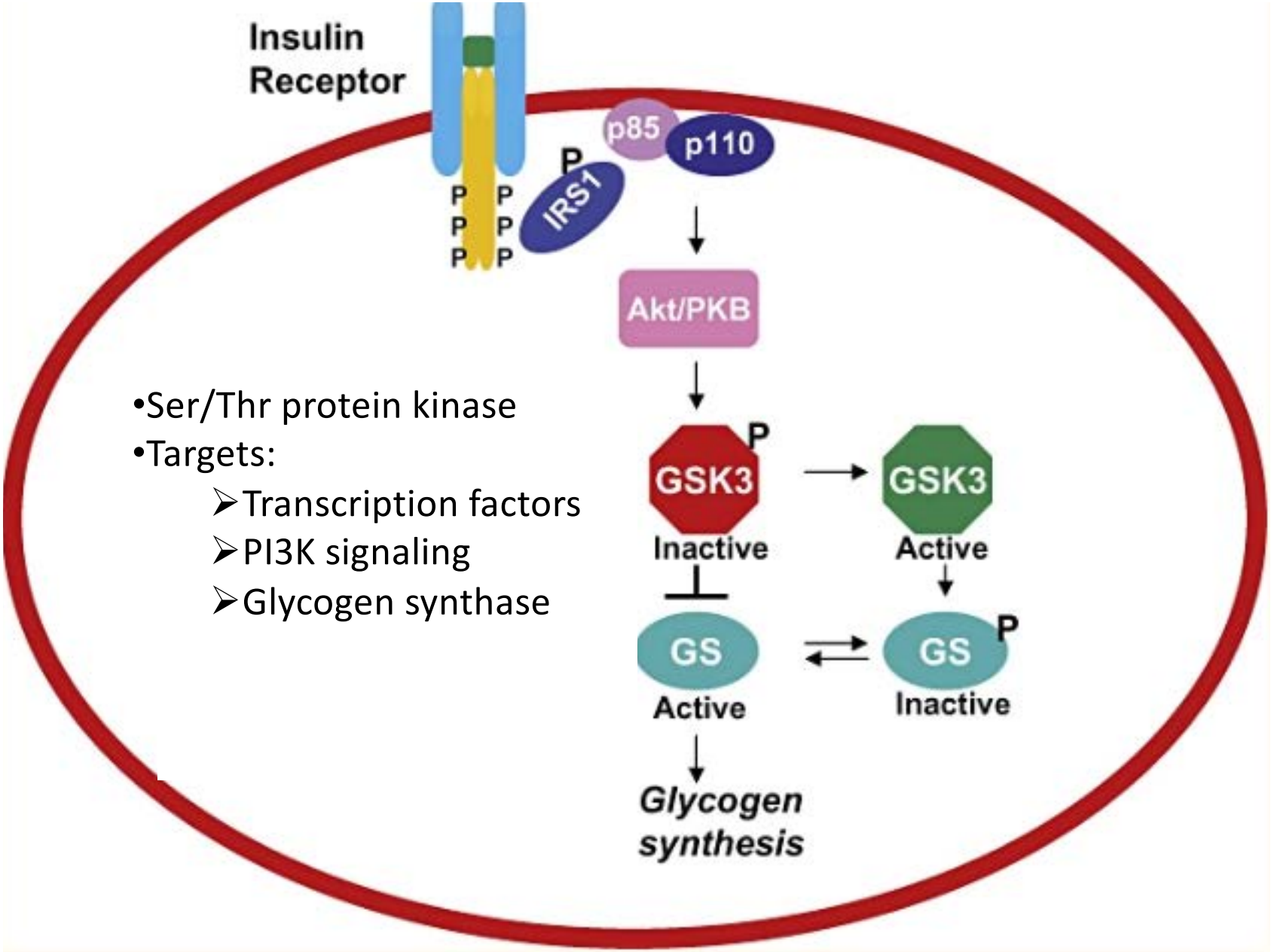
HFD – Induced Cardiomyopathy Ontology Analysis

- Publicly available gene expression datasets (GEO:GESE16790, GEO:GSE36875)
- STZ induced DM heart data excluded (GSE5606)
- 26 genes ↑ in both ob/ob and db/db
- GO biological processes analysis





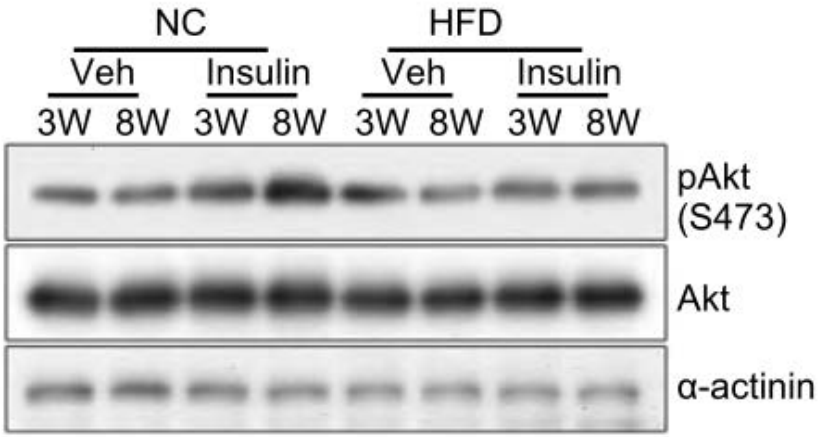
GSK-3α and insulin interaction

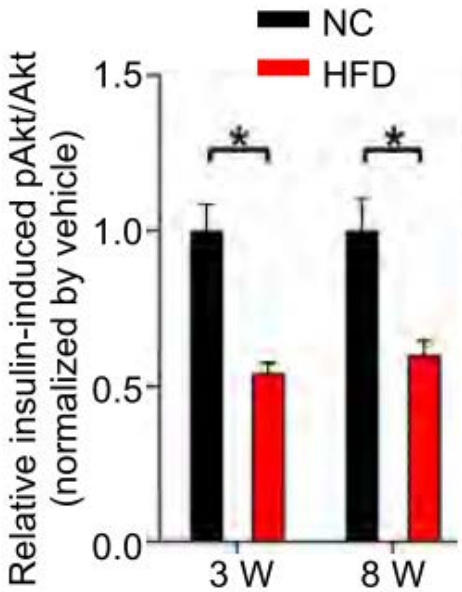


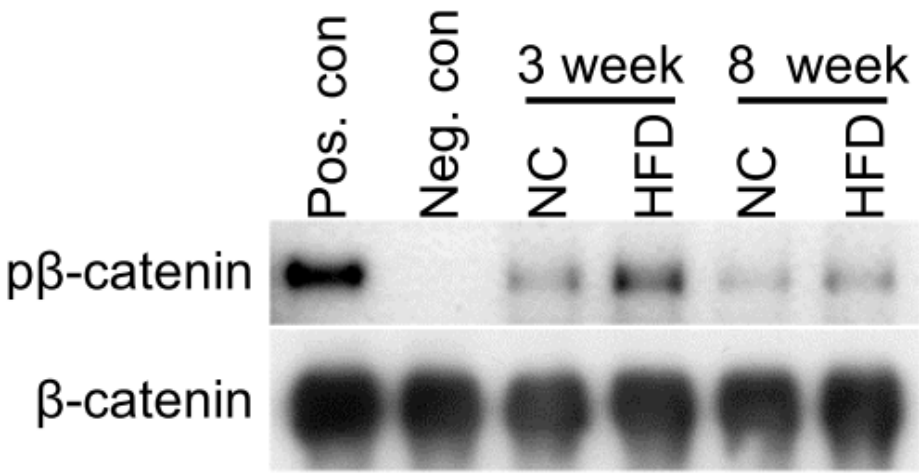
- Ser/Thr protein kinase
- Targets:
  - Transcription factors
  - PI3K signaling
  - Glycogen synthase

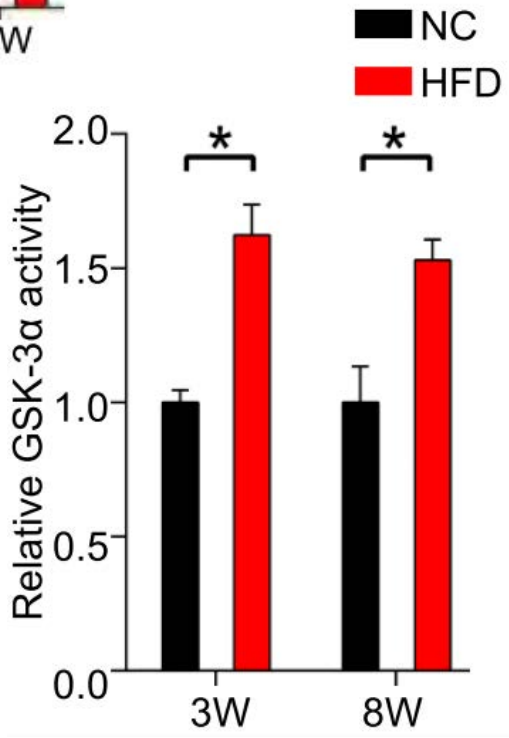
Results

GSK-3α Upregulation in Diet –Induced Obesity Mouse Model



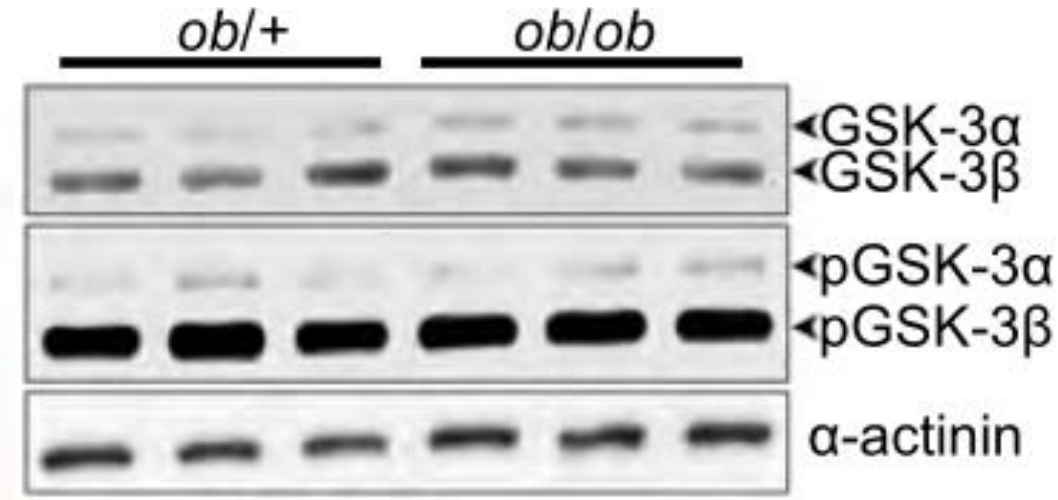


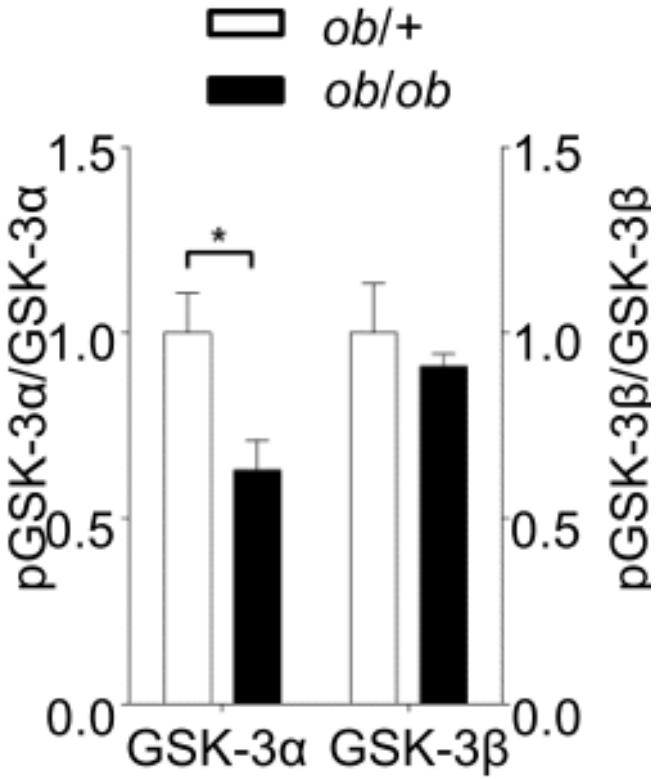




Results

GSK-3α activation in genetically obese (ob/ob) mouse heart



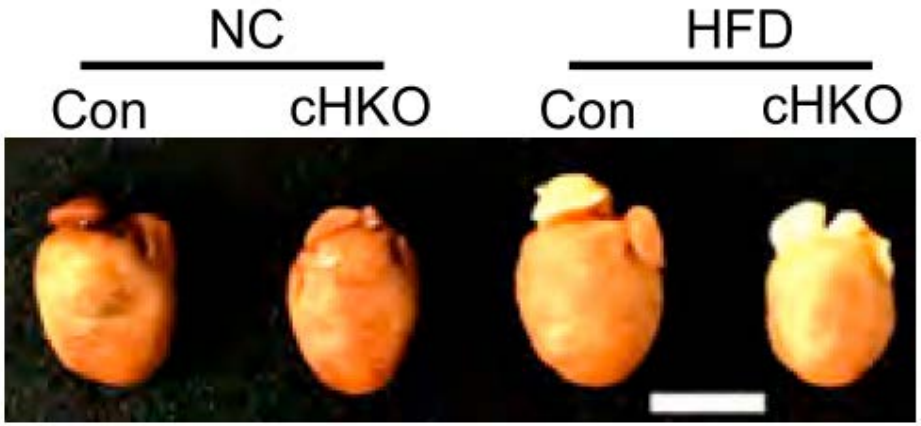


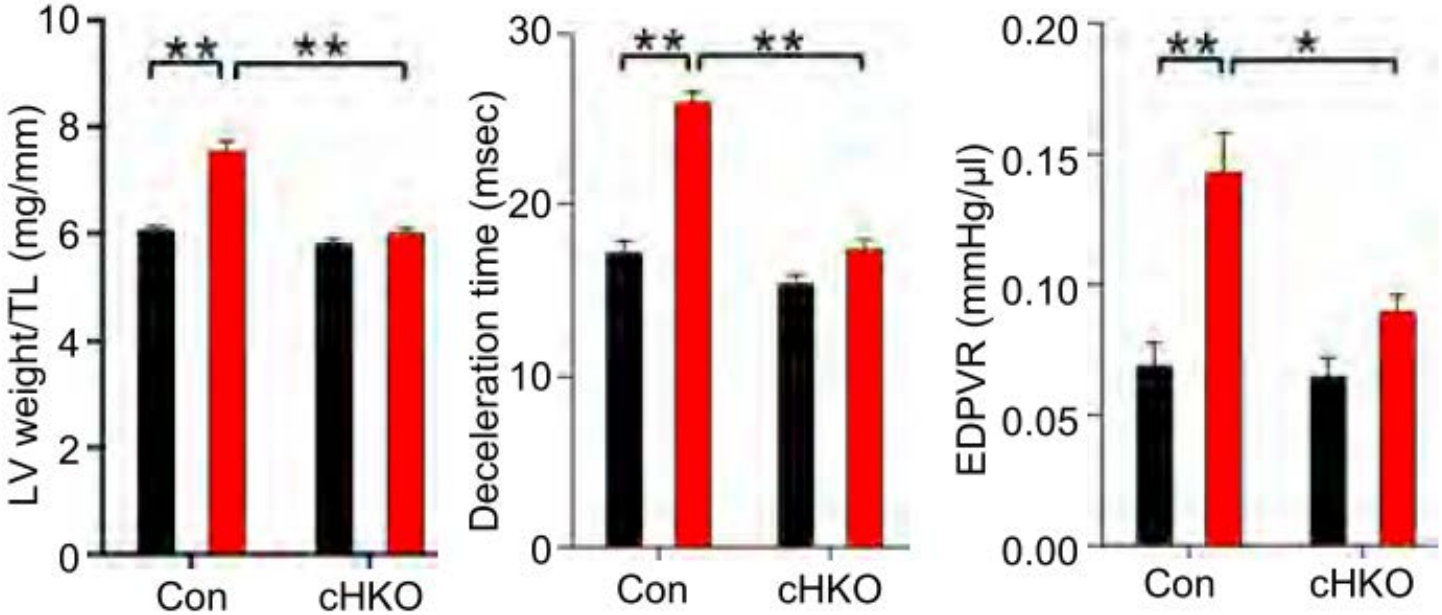
Results

Cardiac-specific GSK-3α haploinsufficiency ameliorates HFD- induced cardiomyopathy

- **LV weight ↓**
- **Diastolic dysfunction ↓**
- **EDPVR slope ↓**

No difference in:
- LV systolic function
- Weight gain
- Insulin resistance



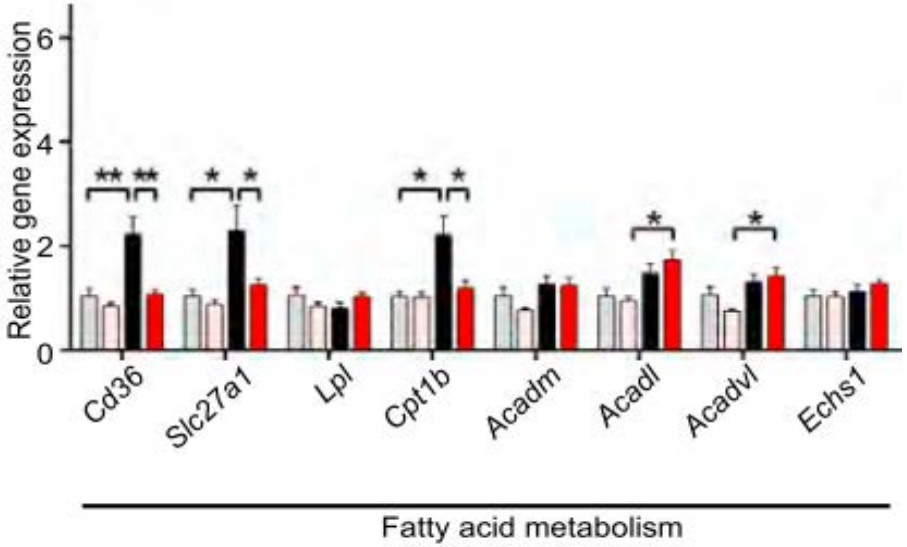


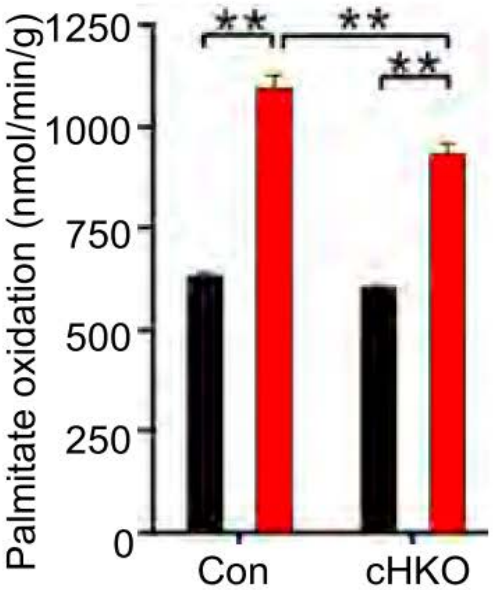
Cardiac specific GSK3a heterozygous mice fed with HFD (cHKO vs het floxed)

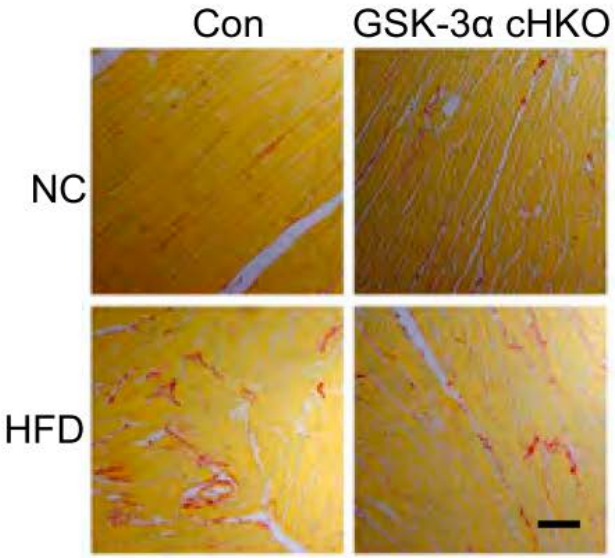
Results

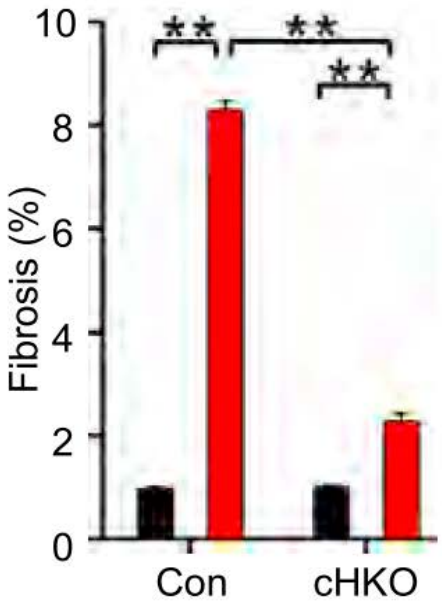
Cardiac-specific GSK-3α haploinsufficiency ameliorates HFD- induced cardiomyopathy

- Intramyocardial lipid accumulation ↓
- Cardiac fibrosis ↓
- FA metabolism involved genes↓







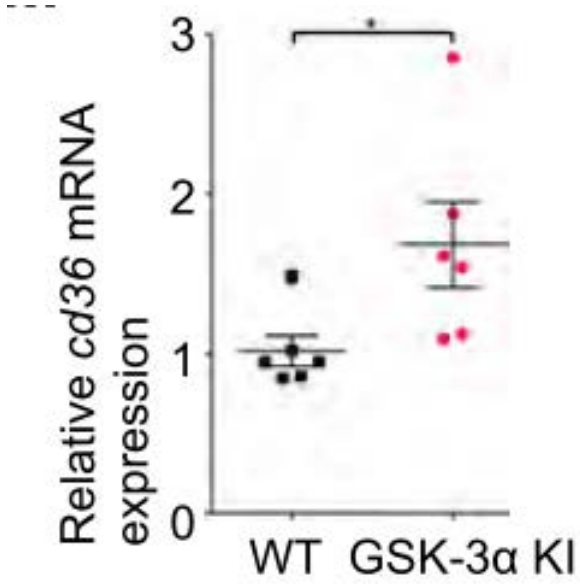


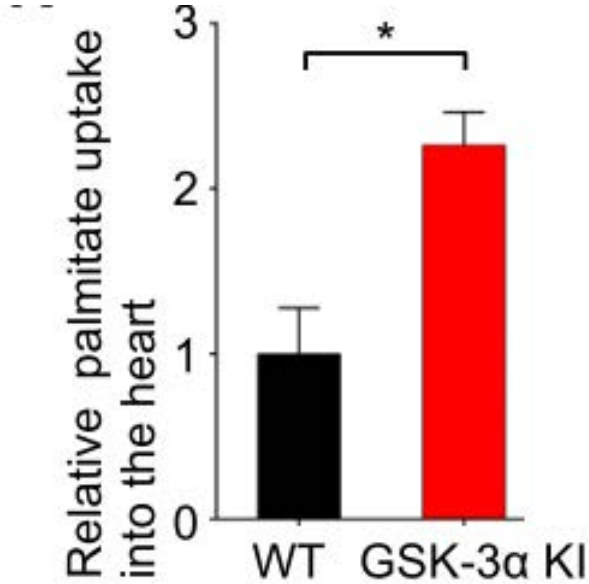
Cardiac specific GSK3a heterozygous mice fed with HFD (cHKO vs het floxed)

Results

PPAR-mediated GSK-3α lipid metabolism regulation

- S21A homozygous KI mice constitutively active GSK-3α
- GSEA →PPAR signaling most significantly enriched
- CD36 mRNA expression↑(PPAR target)
- Intramyocardial lipid accumulation↑
- FAO↑





Results

GSK-3α – PPARα physical interaction

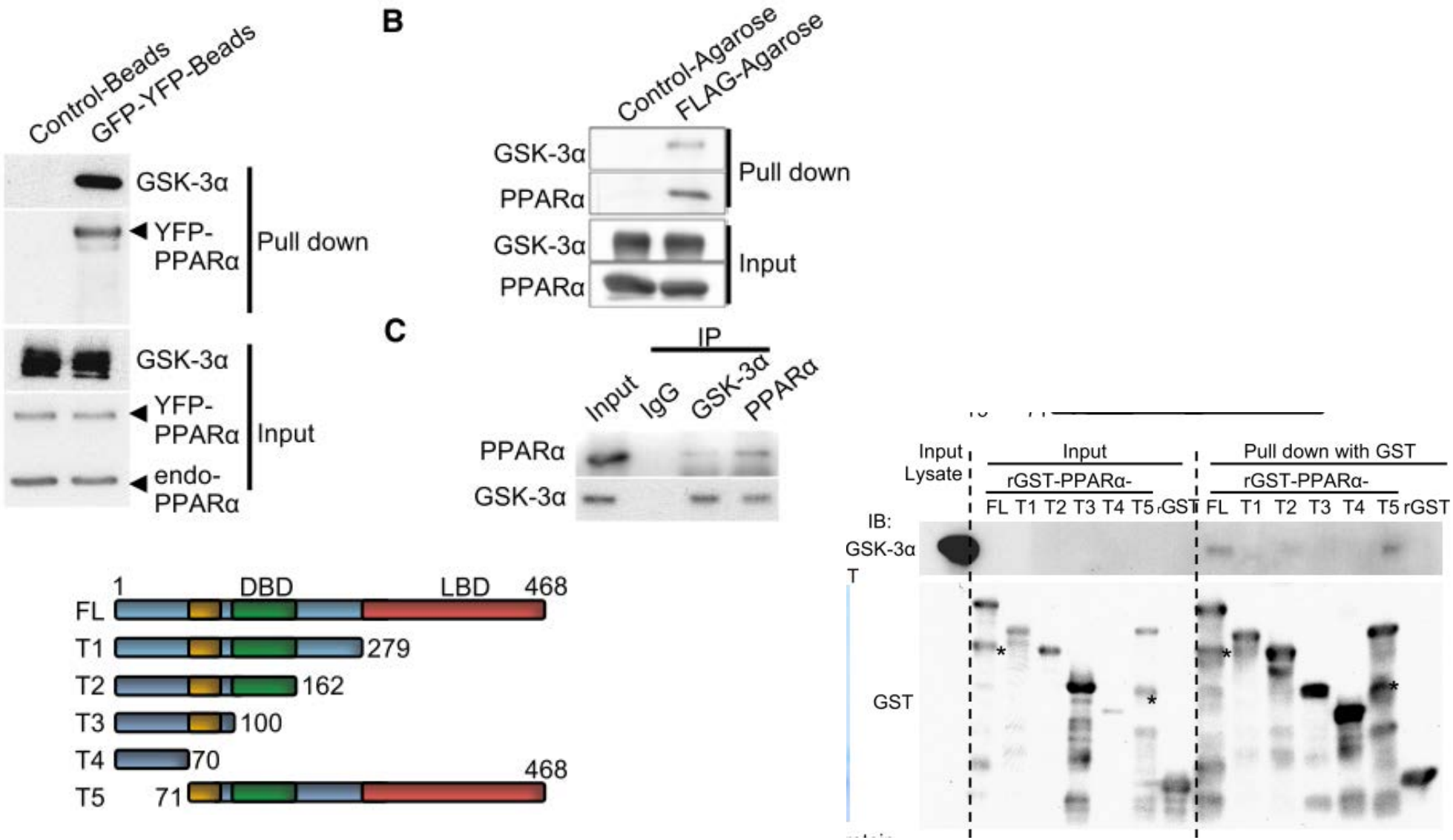
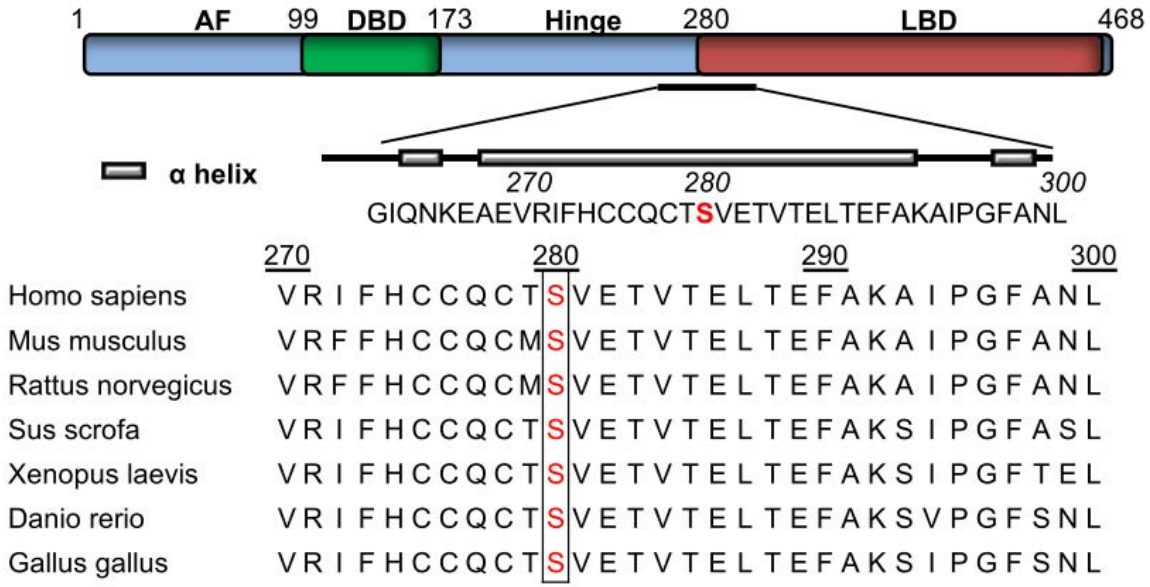


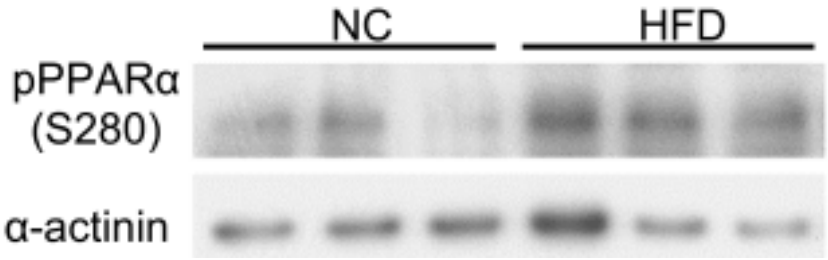
Figure 2. GSK-3α Physically Interacts with and Phosphorylates PPARα at Ser280 in Cardiomyocytes (CMs) and in the Heart

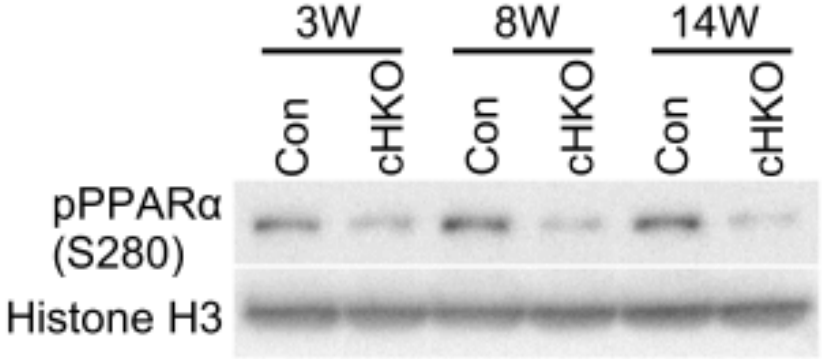
(A and B) IP assays to test the interaction between endogenous GSK-3α and exogenously expressed PPARα. YFP-tagged PPARα or FLAG-tagged PPARα was overexpressed in CMs using adenovirus (A) or in transgenic mouse hearts under the control of the αMHC promoter (B), respectively.

Results

GSK-3α phosphorylates PPARα at Ser280

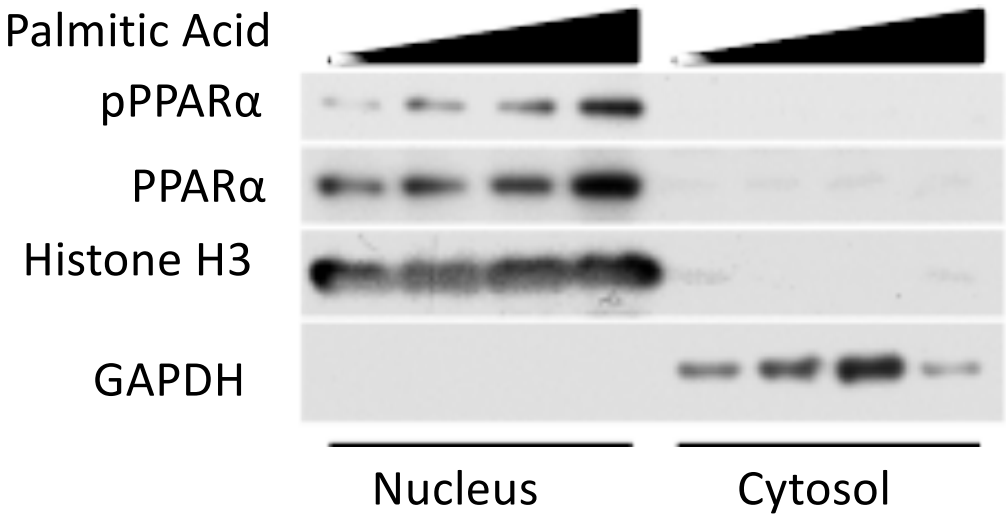






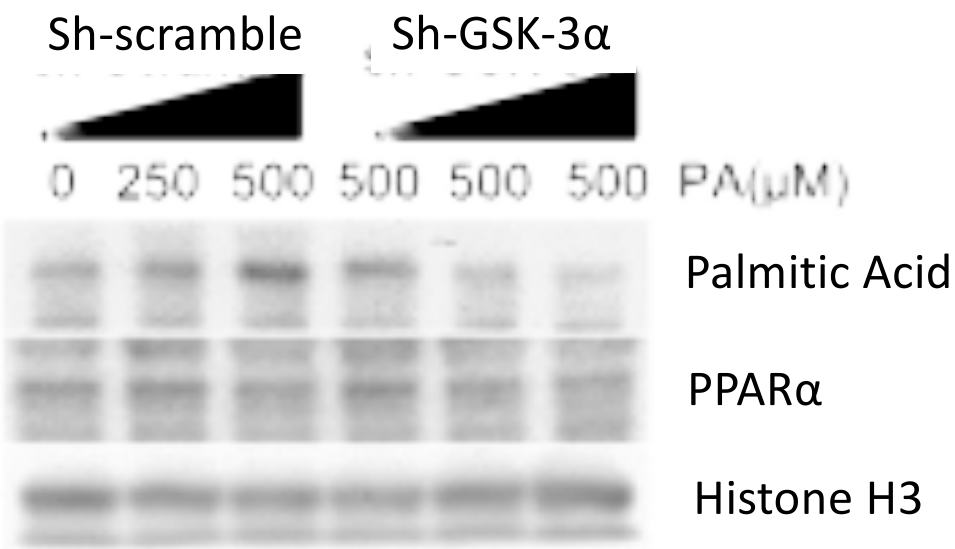
Results

GSK-3α mediated phosphorylation of PPARα enhances its transcriptional activity



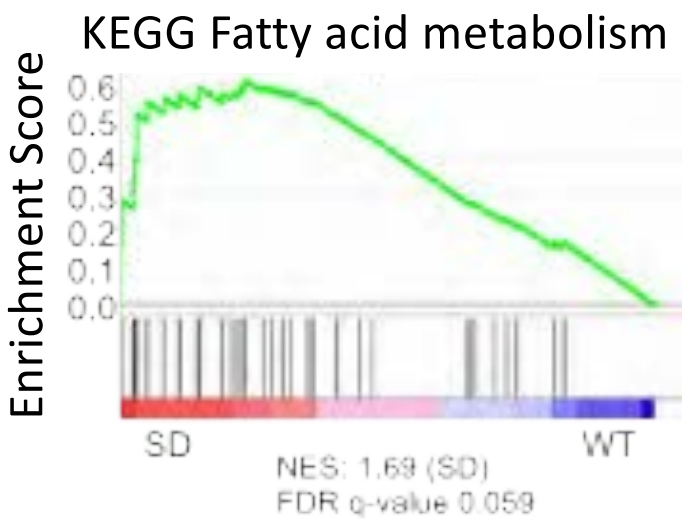
Palmitic Acid induces PPARα Ser280 phosphorylation

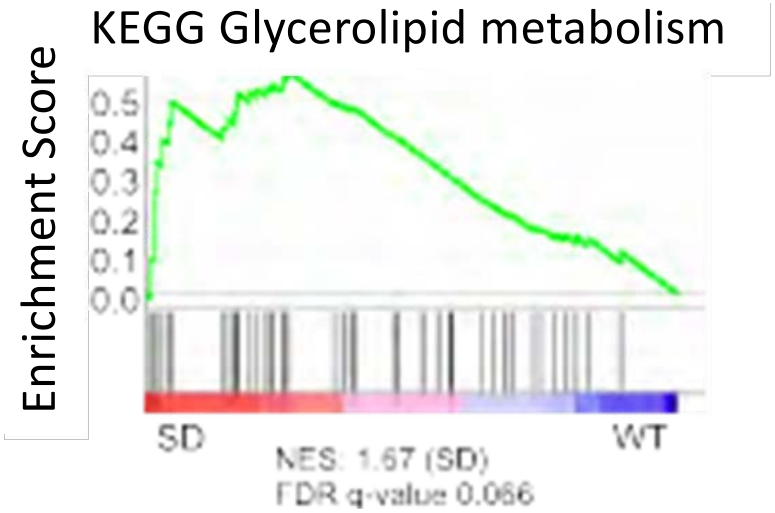
Abolishment of the result upon GSK-3a knockdown



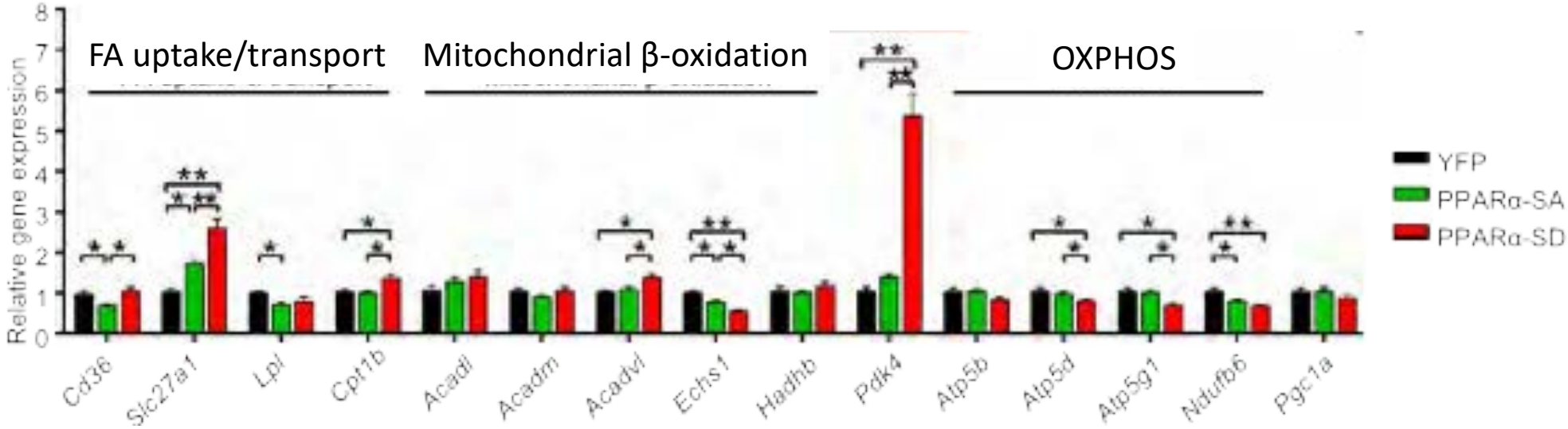
Results

GSK-3α mediated phosphorylation of PPARα induces a metabolic shift





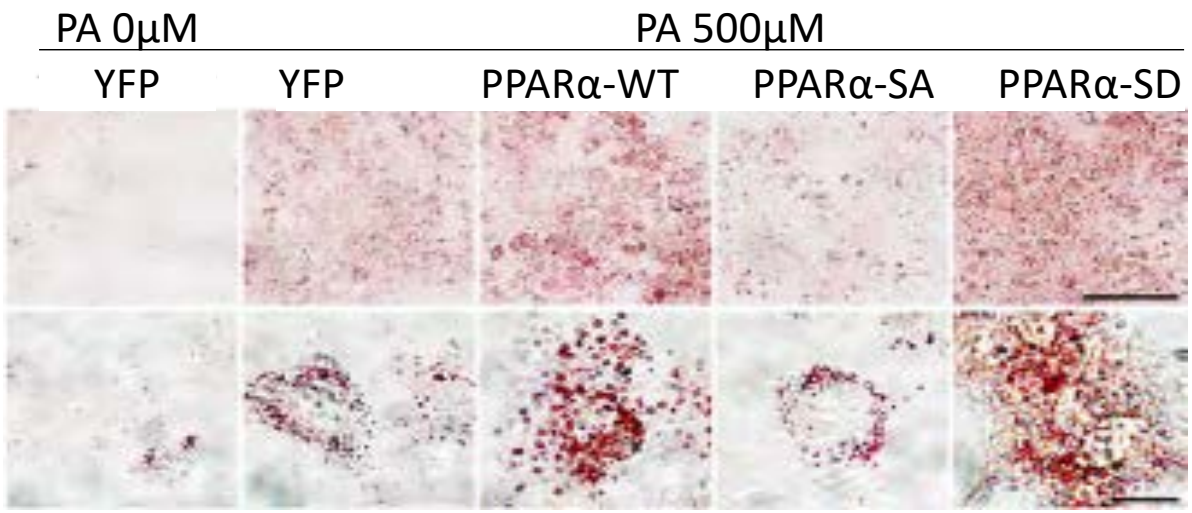
pPPARα upregulates genes involved in FA uptake and storage and not FAO

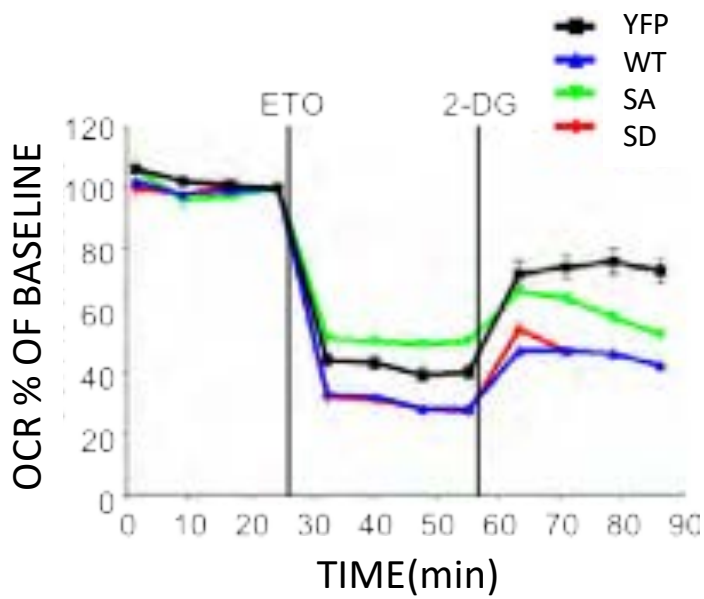


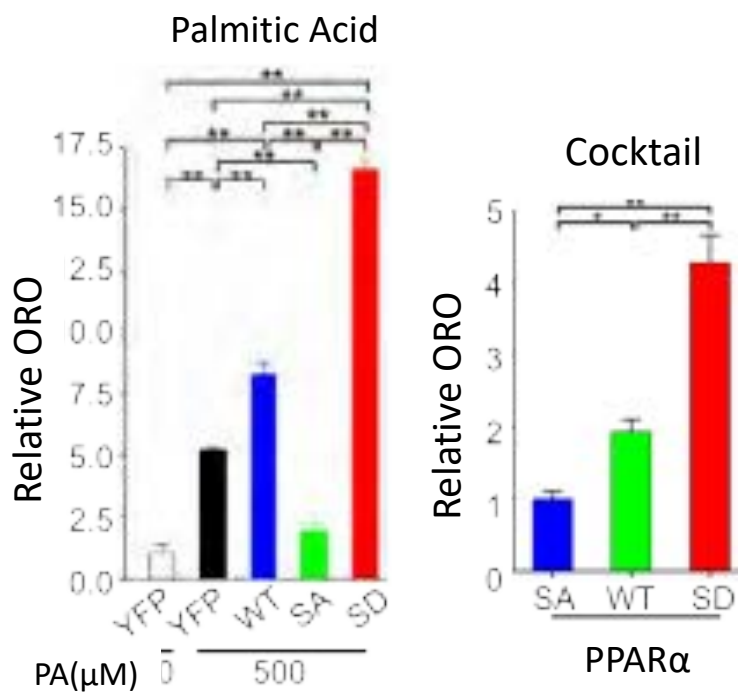
Results

GSK-3α mediated phosphorylation of PPARα promotes lipid accumulation

PPARα Ser280 phosphorylation induced **metabolic shift** may promote **lipid accumulation**

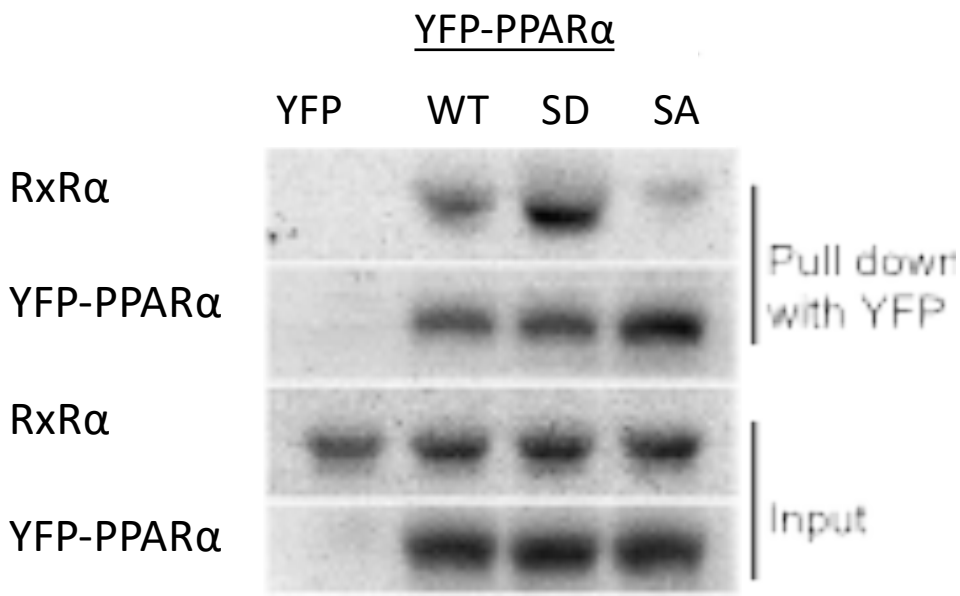


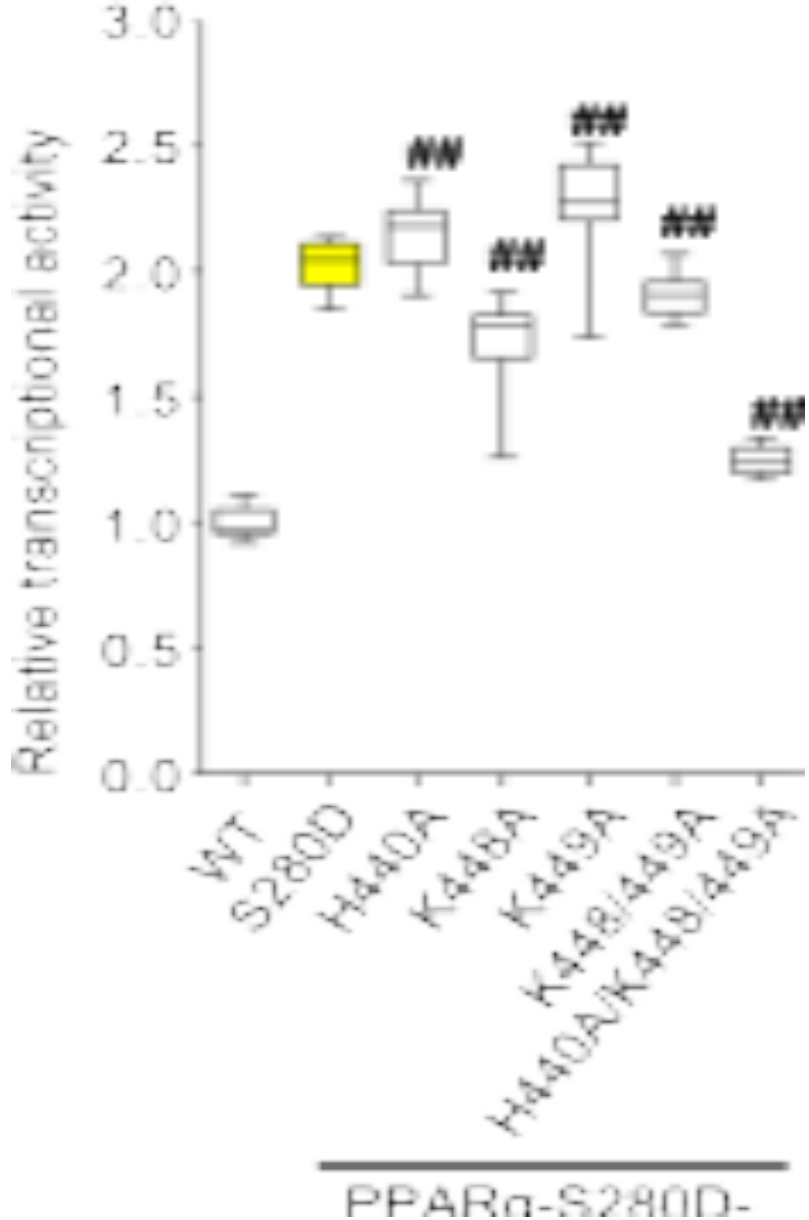




Results

Phosphorylation of PPARα at Ser280 increases interaction with RxR





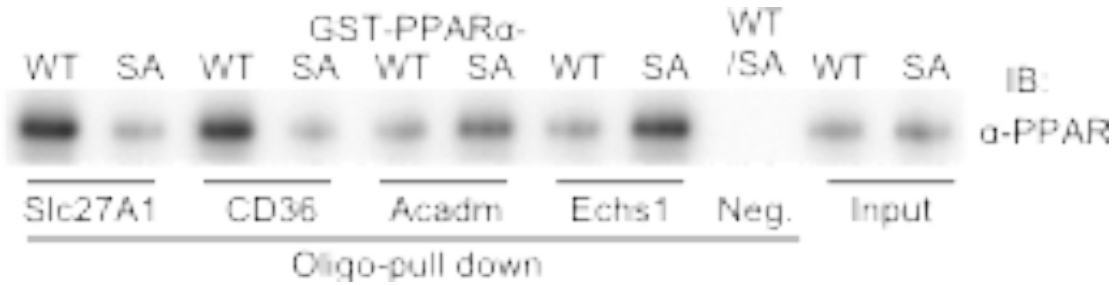
mutations ⟶ PPARα-SD and RxRα binding

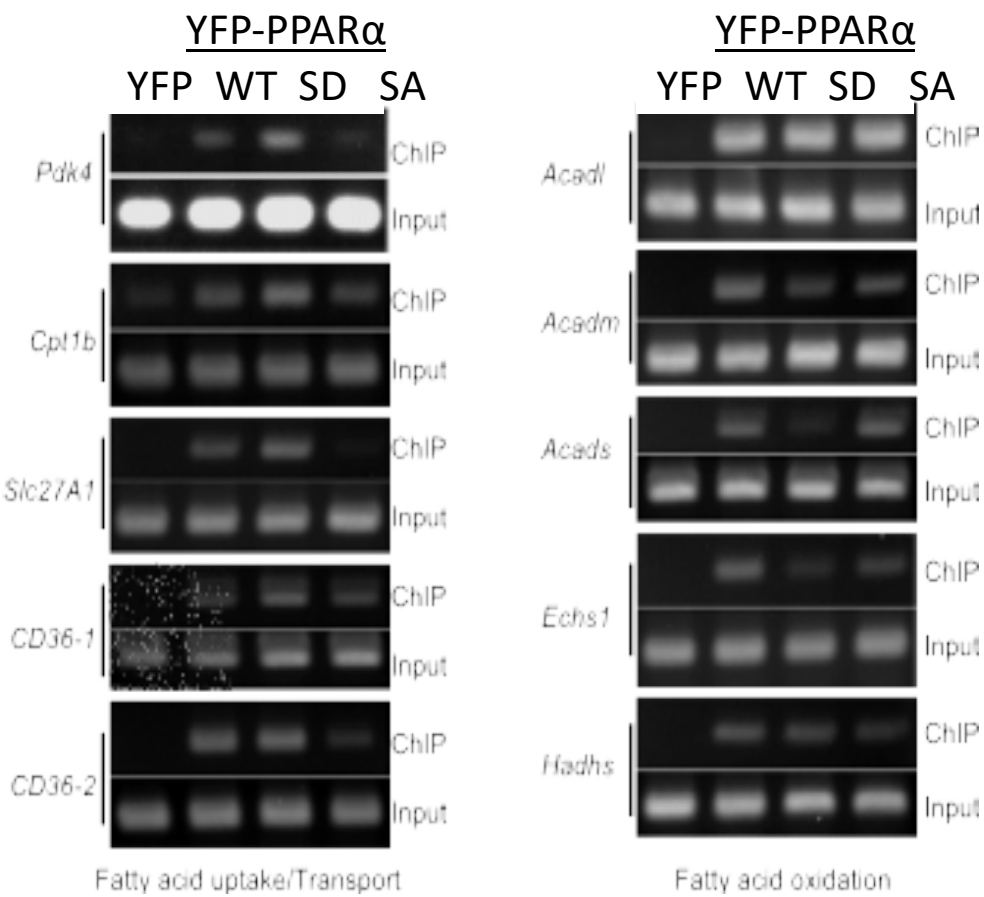
↓

FA uptake and storage gene promoters activation

Results

Phosphorylation of PPARα at Ser280 increases specific DNA binding





Specific motifs in the PPREs**: phosphoPPARα preferential transcription**

vs

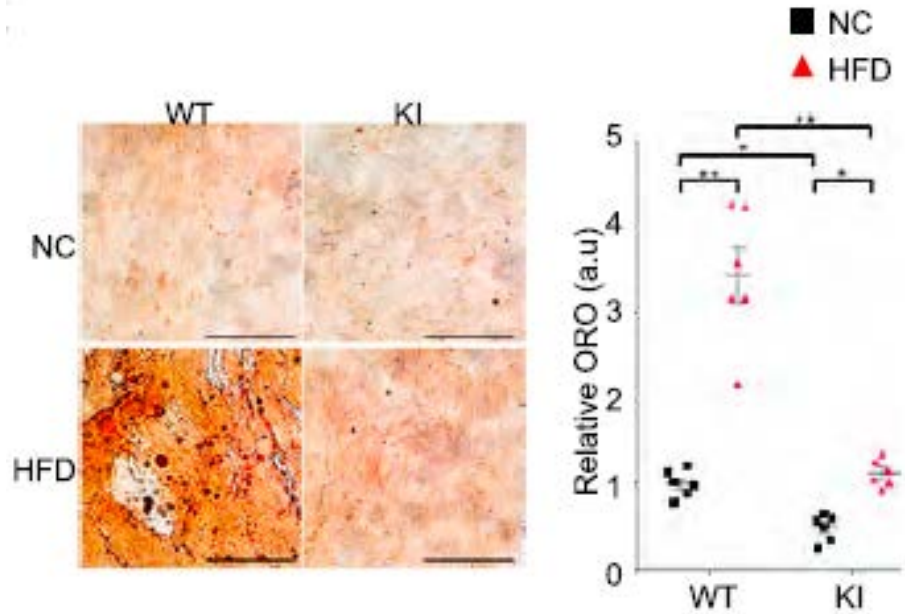
Non phosphorylated PPARα prefers motifs found in **FAO gene promoters**

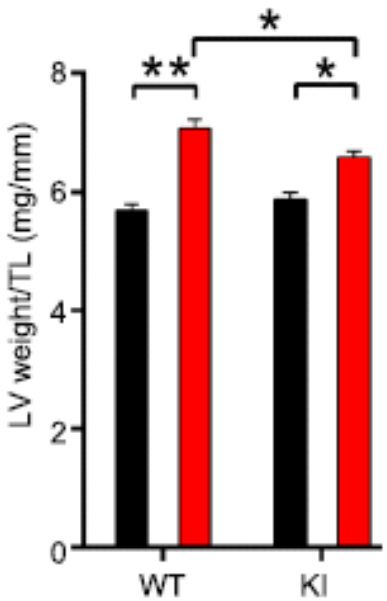
Results

Phosphorylation of PPARα in lipid derangement

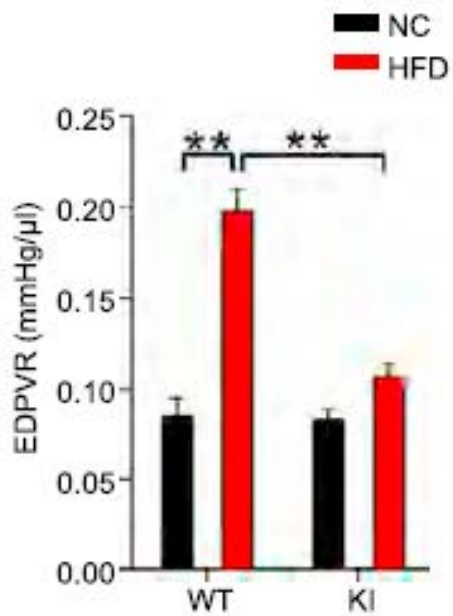
HFD-fed PPARα-S280A het KI mice

Attenuation of lipid accumulation in the absence of PPARα





✓ **Cardiac hypertrophy**



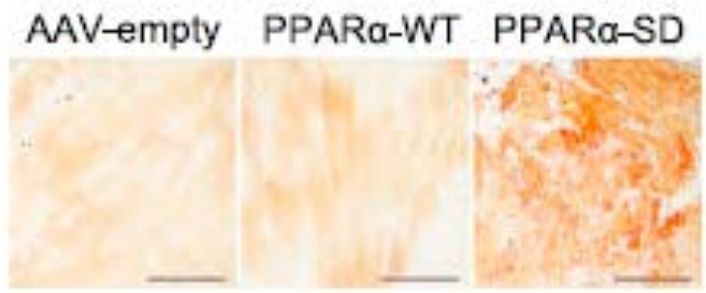
✓ **Cardiac diastolic dysfunction**

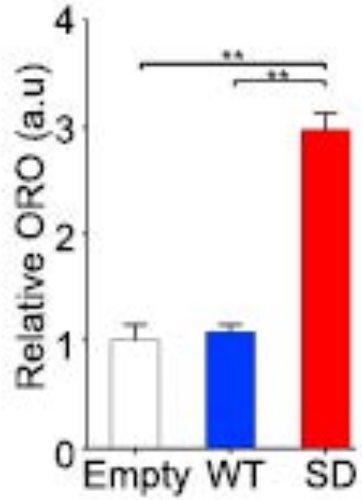
Results

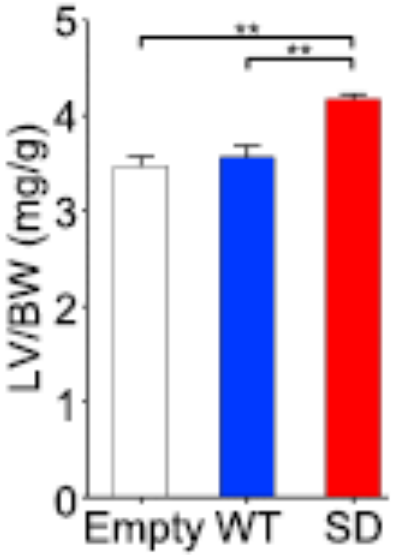
Phosphorylation of PPARα in lipid derangement

NC PPARα-S280D –expressing mice

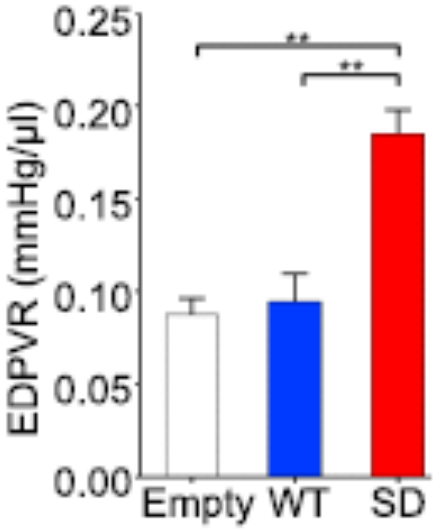
Induction of lipid accumulation







Cardiac hypertrophy



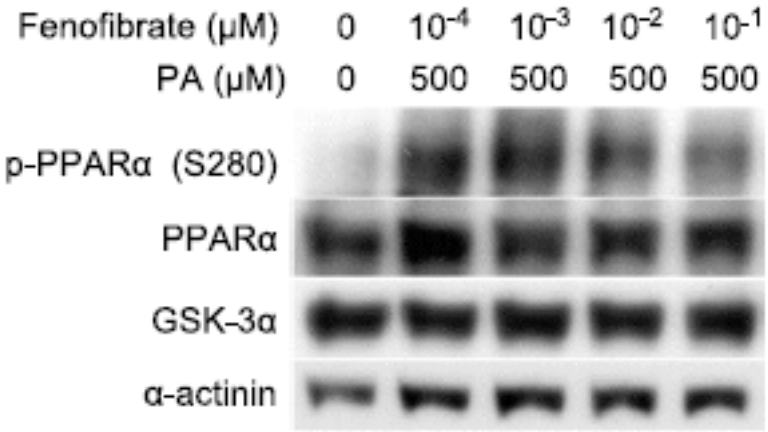
Cardiac diastolic dysfunction

Results

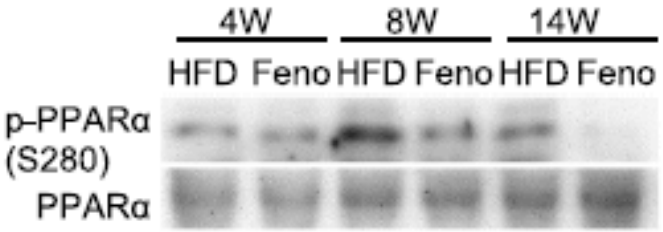
Inhibition of GSK-3a-mediated phosphorylation of PPARα by PPARα ligands

Fenofibrate → inhibition of PPARα-Ser280 phosphorylation

PA-treated cardiomyocytes

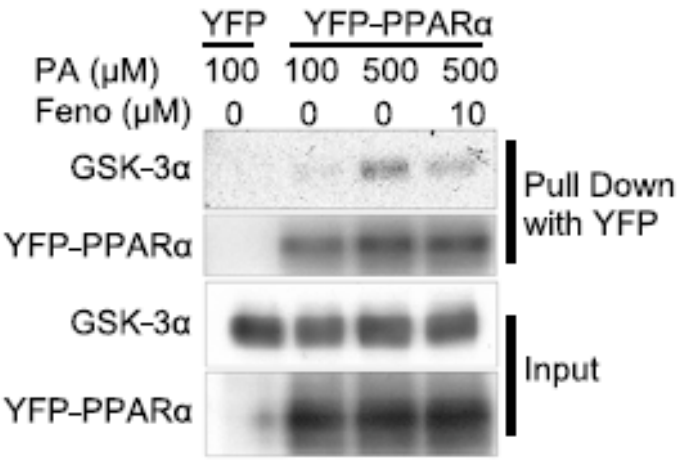


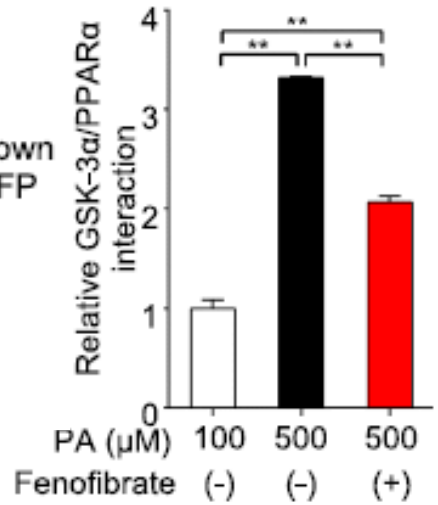
HFD mice hearts



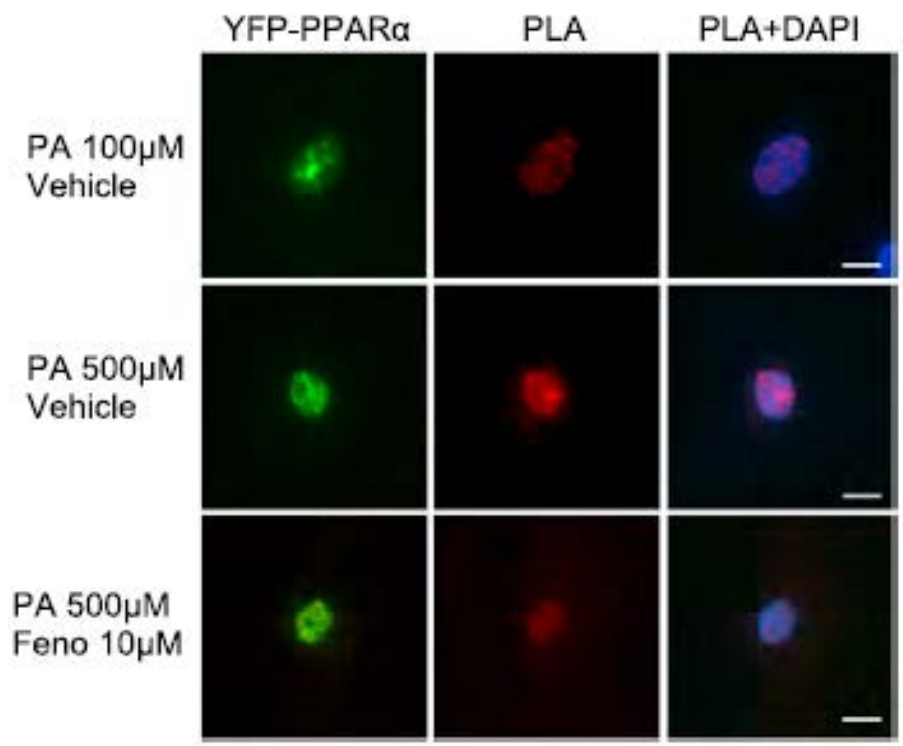
Results

Inhibition of GSK-3a-mediated phosphorylation of PPARα by PPARα ligands



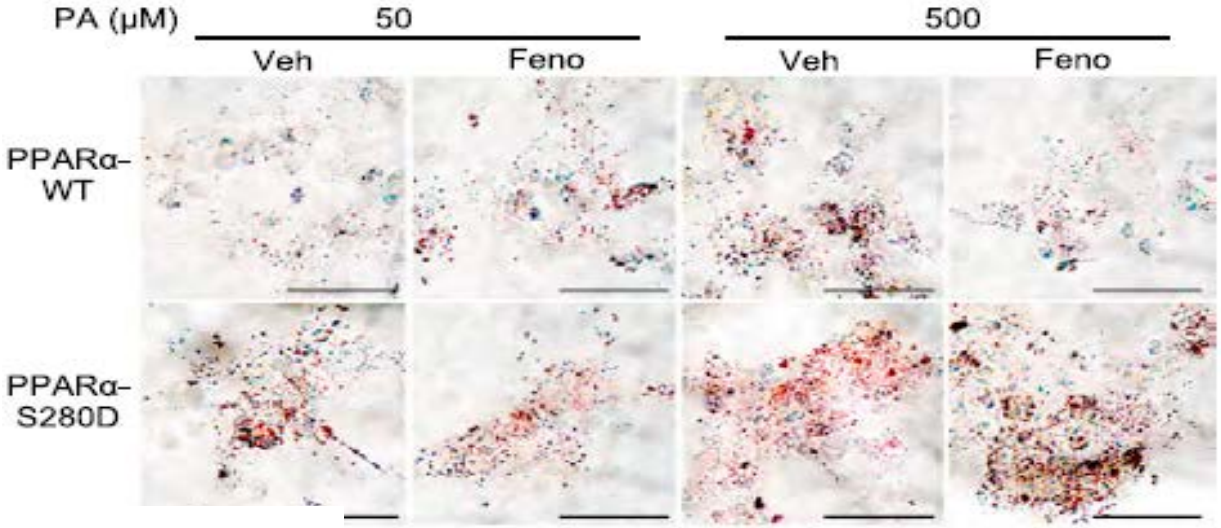


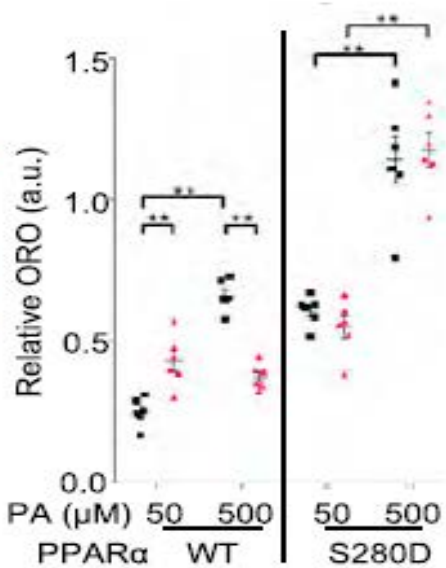
Fenofibrate-induced inhibition of GSK-3α & PPARα interaction

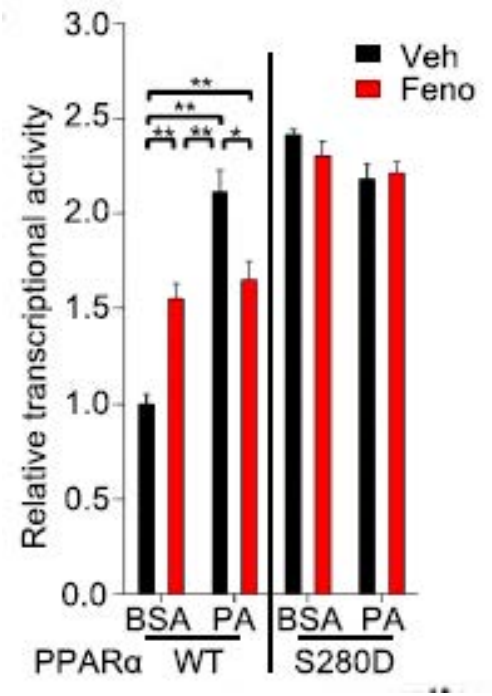


Results

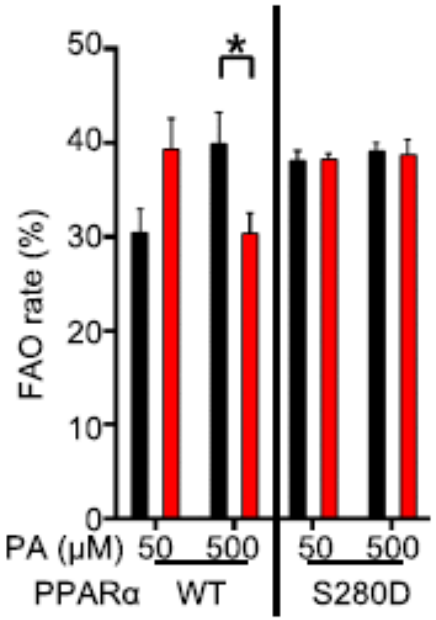
Inhibition of GSK-3a-mediated phosphorylation of PPARα by PPARα ligands





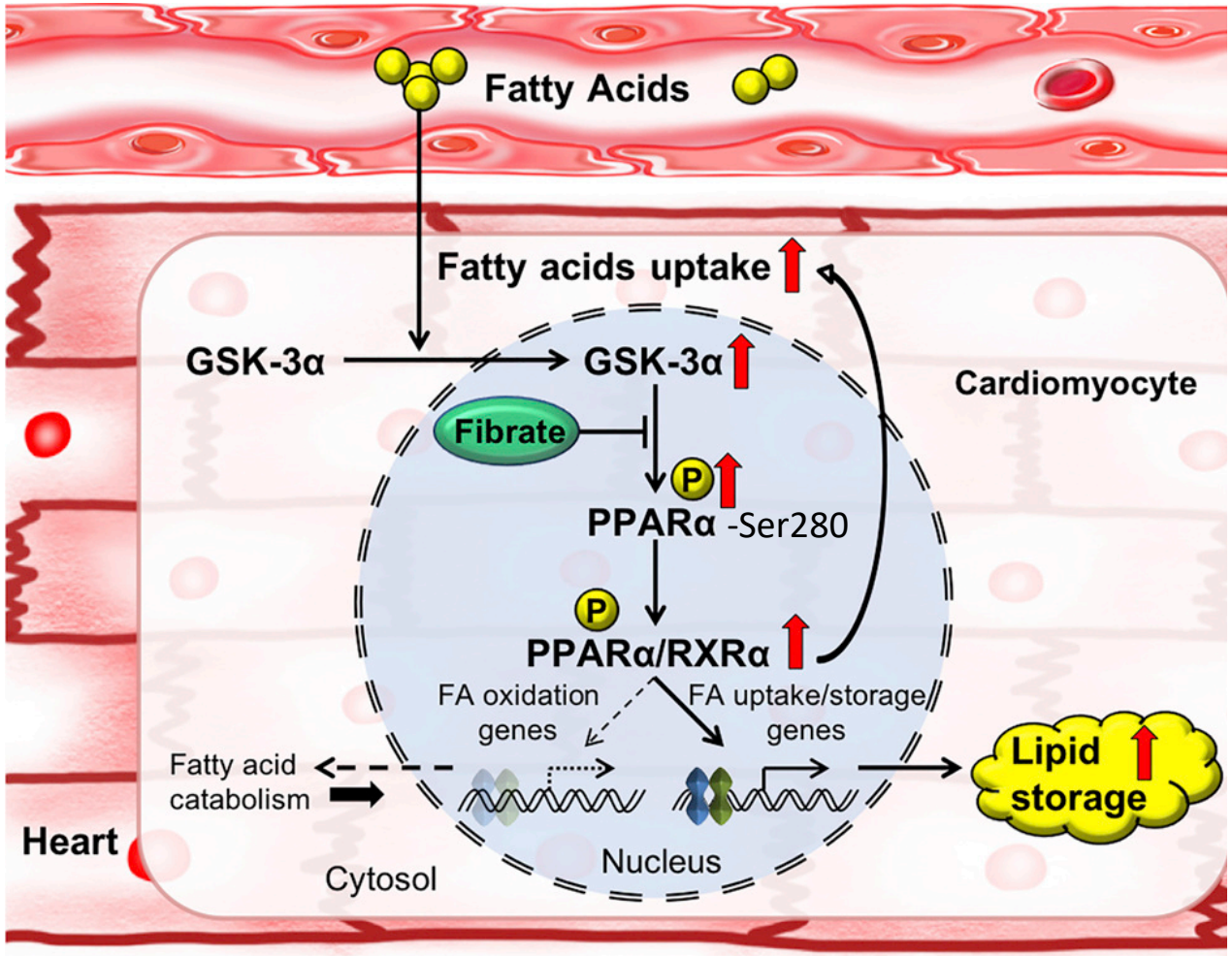


Fenofibrate
↓
~~Suppression of PPARα activity~~



Fenofibrate
↓
~~Suppression of FAO~~

SUMMARY



Lipid catabolism << Lipid anabolism

Sustained stimuli (obesity or diabetes)

Lipid storage disease (Lipotoxic cardiomyopathy)

THANK YOU FOR YOUR ATTENTION!

World

Hellenic

Biomedical

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WHBA, Inc.