

**CONGRESSO SID AMD Regione Lazio
IL PAZIENTE DIABETICO AL CENTRO: RICERCA, ASSISTENZA
E INNOVAZIONE
Roma, 8-9 maggio 2015**

Galectina-3, adipogenesi ed omeostasi glucidica

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Dipartimento di Medicina Clinica e Molecolare, Università "La Sapienza", Roma.

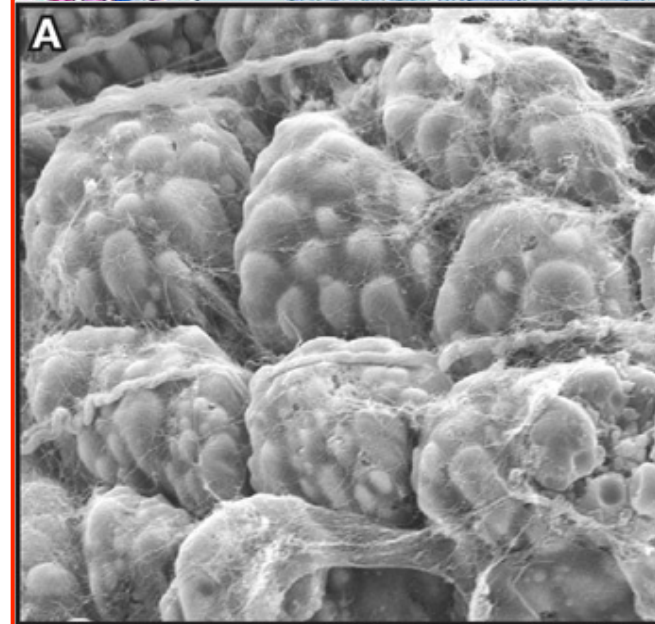
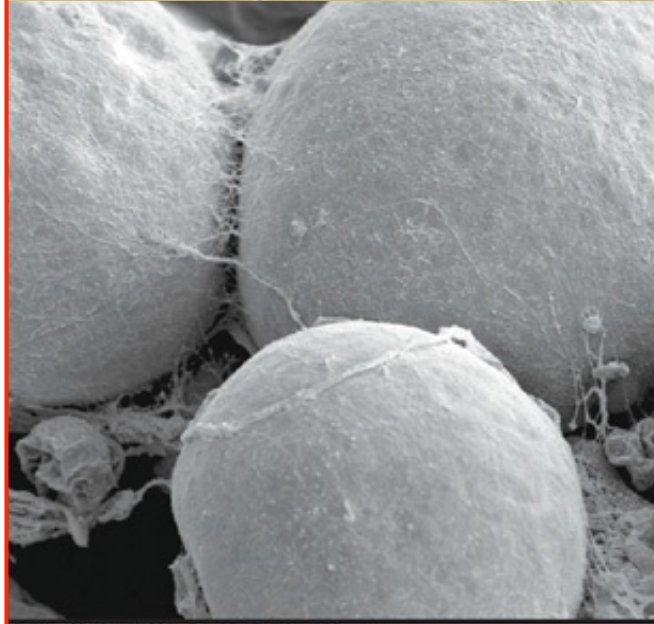
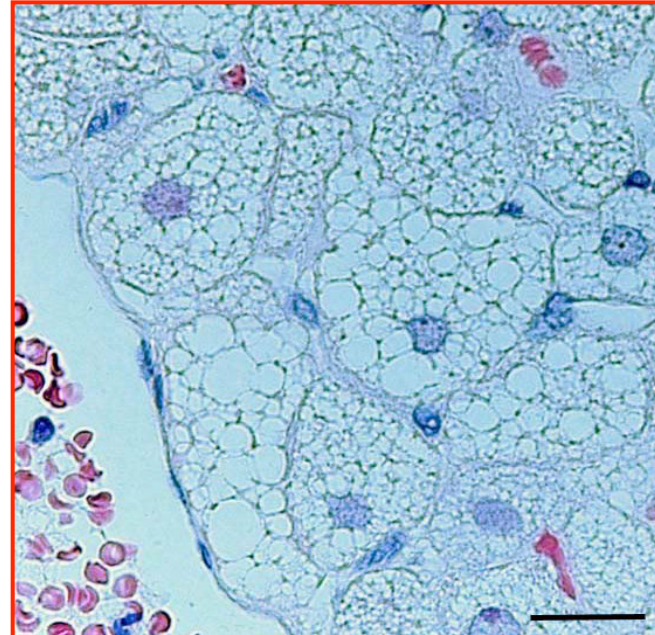
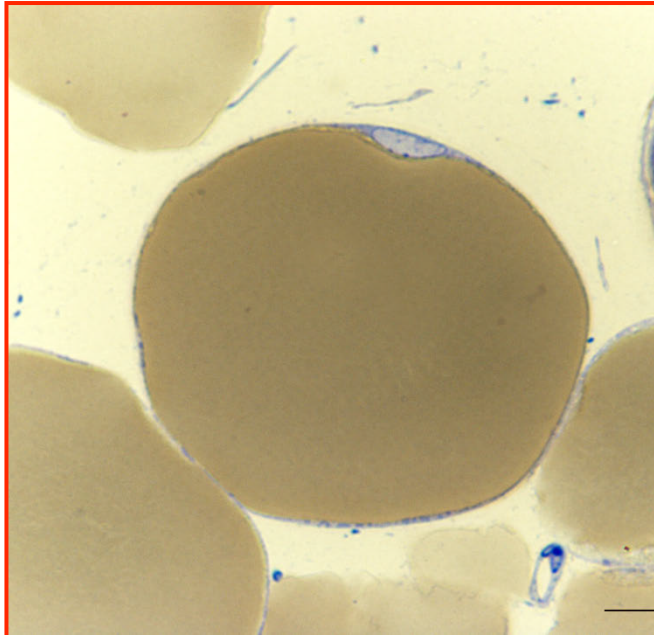
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La dr. ssa Claudia Blasetti Fantauzzi dichiara di NON aver ricevuto negli ultimi due anni compensi o finanziamenti da Aziende Farmaceutiche e/o Diagnostiche

Adipocytes

White

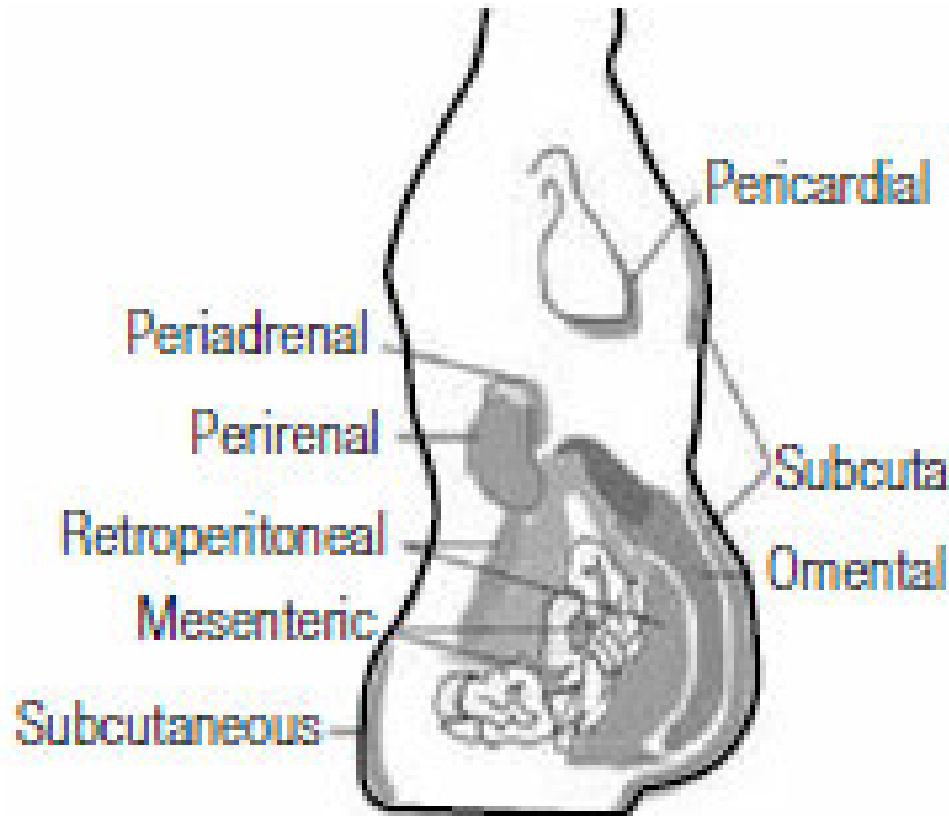
Brown



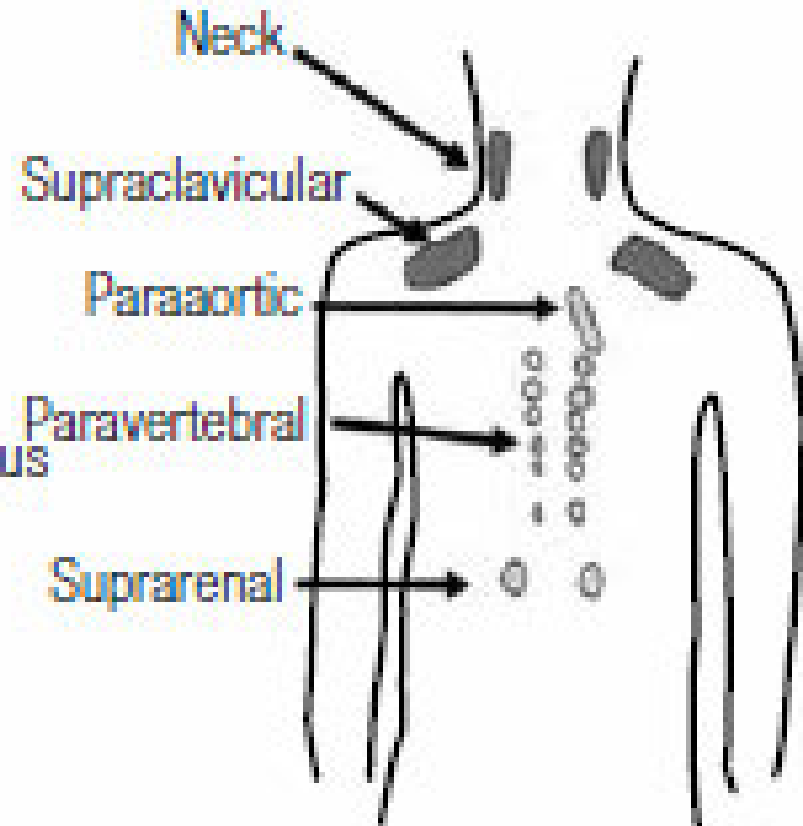
The Adipose Organ

Saverio Cinti

The white (WAT) and brown (BAT) adipose tissue



White Adipose Tissue

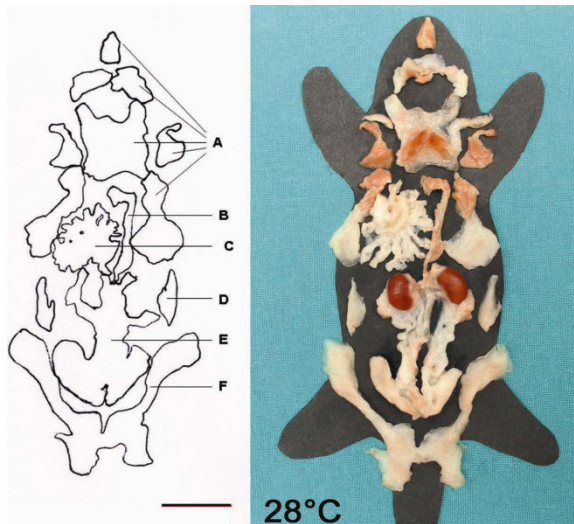


Brown Adipose Tissue

Obesity, insulin resistance and comorbidities - Mechanisms of association

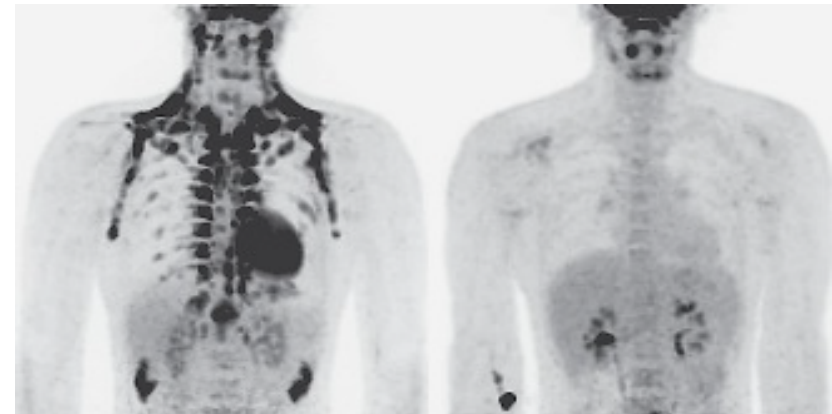
Obesidade, resistência à insulina e comorbidades - Mecanismos de associação

Reversible De Novo Differentiation-Transdifferentiation



Cold Exposure

Thermoneutral Conditions



Cold Exposure

The Adipose Organ

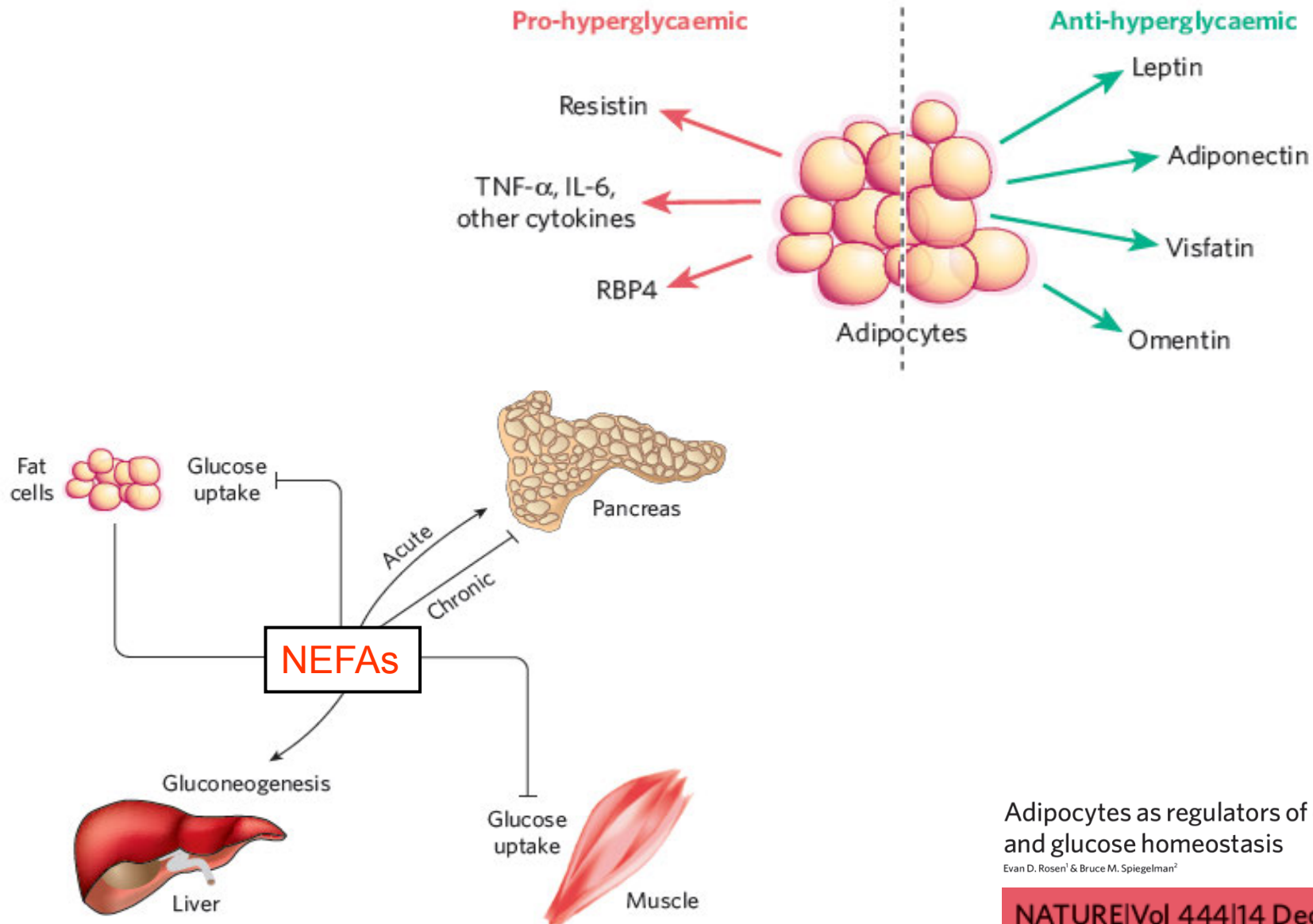
Saverio Cinti

Cold-Activated Brown Adipose Tissue
in Healthy Men

Wouter D. van Marken Lichtenbelt, Ph.D., Joost W. Vanhommerig, M.S.,
Nanda M. Smulders, M.D., Jamie M.A.F.L. Drossaerts, B.S.,
Gerrit J. Kemerink, Ph.D., Nicole D. Bouvy, M.D., Ph.D.,
Patrick Schrauwen, Ph.D., and G.J. Jaap Teule, M.D., Ph.D.

N Engl J Med 2009;360:1500-8.

Adipocytes as regulators of glucose homeostasis: the Adipose Organ

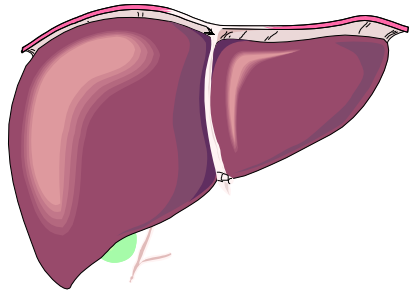


Adipocytes as regulators of energy balance and glucose homeostasis

Evan D. Rosen¹ & Bruce M. Spiegelman²

NATURE|Vol 444|14 December 2006

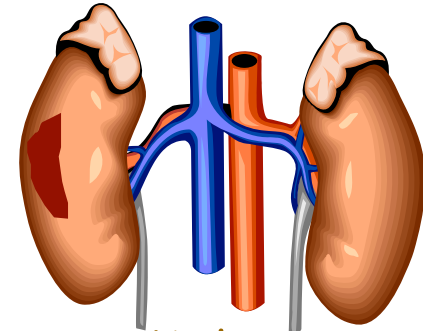
Galectin-3 is expressed in various tissues



liver

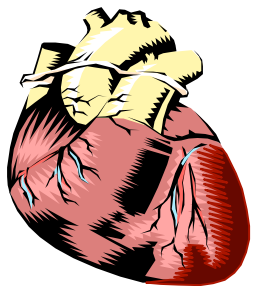


muscle

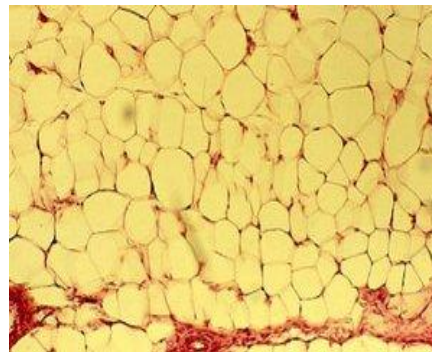


Kidney

Galectin-3



heart &
vessels

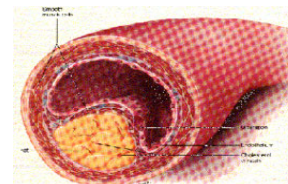
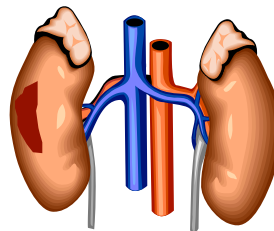
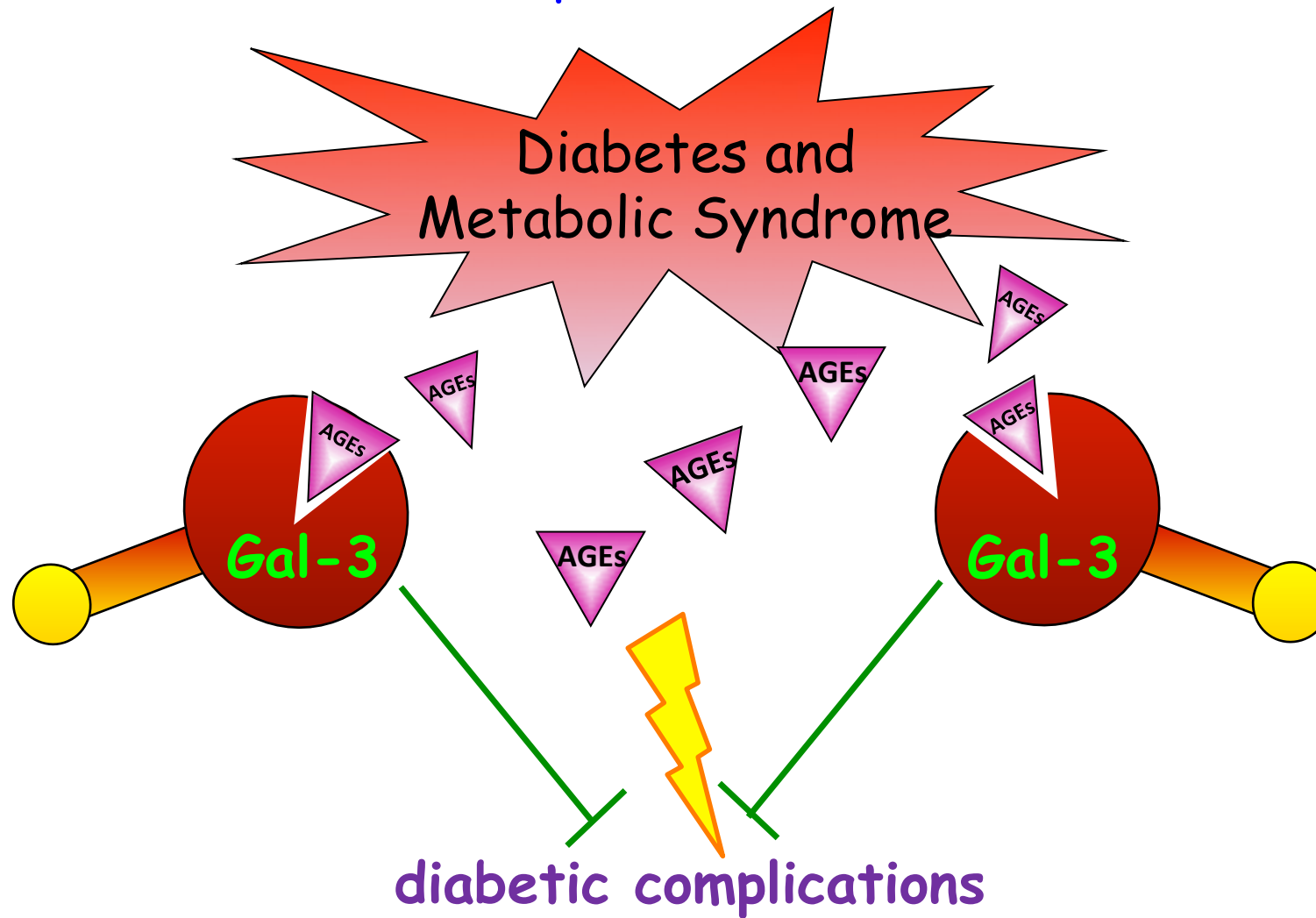


adipose
tissue



bone

Galectin-3 as an AGE-receptor

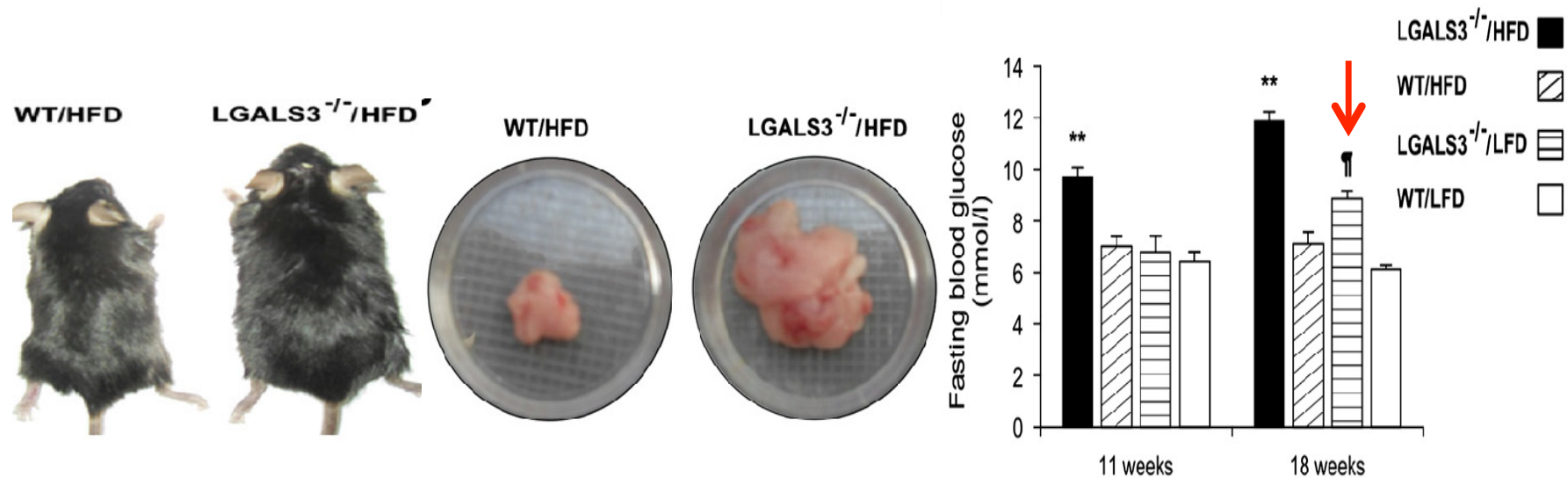


Role of Gal-3 in HFD-induced obesity and glucose intolerance

Galectin-3 Deficiency Accelerates High-Fat Diet-Induced Obesity and Amplifies Inflammation in Adipose Tissue and Pancreatic Islets

Pejnovic NN et al.

Diabetes, 2013



Increased Adiposity, Dysregulated Glucose Metabolism and Systemic Inflammation in Galectin-3 KO Mice

Pang Jet al.

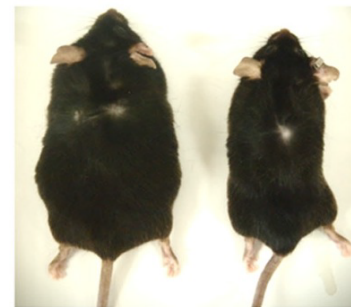
PLOS ONE, 2013

Role of Gal-3 in HFD-induced obesity and glucose intolerance

Galectin-3 Activates PPAR γ and Supports White Adipose Tissue Formation and High-Fat Diet-Induced Obesity

Baek J.H. et al.

Endocrinology, 2015



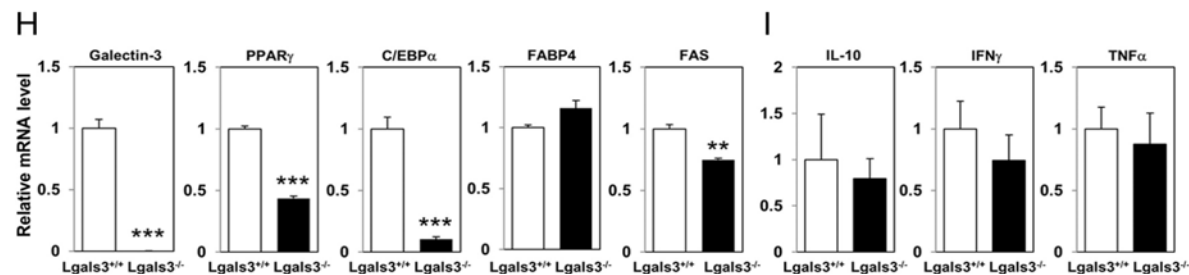
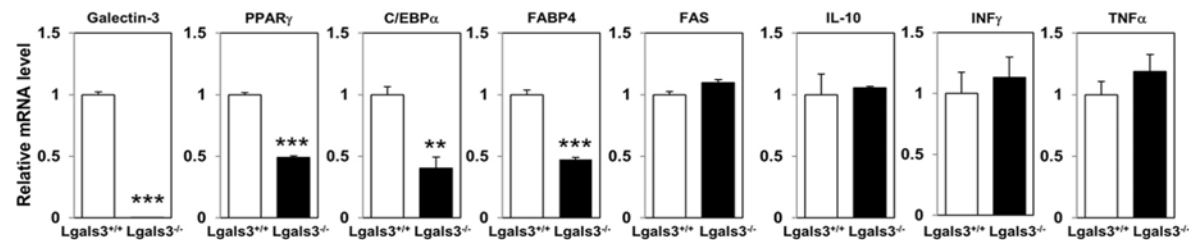
Lgals3^{+/+}

Lgals3^{-/-}



Lgals3^{+/+}

Lgals3^{-/-}

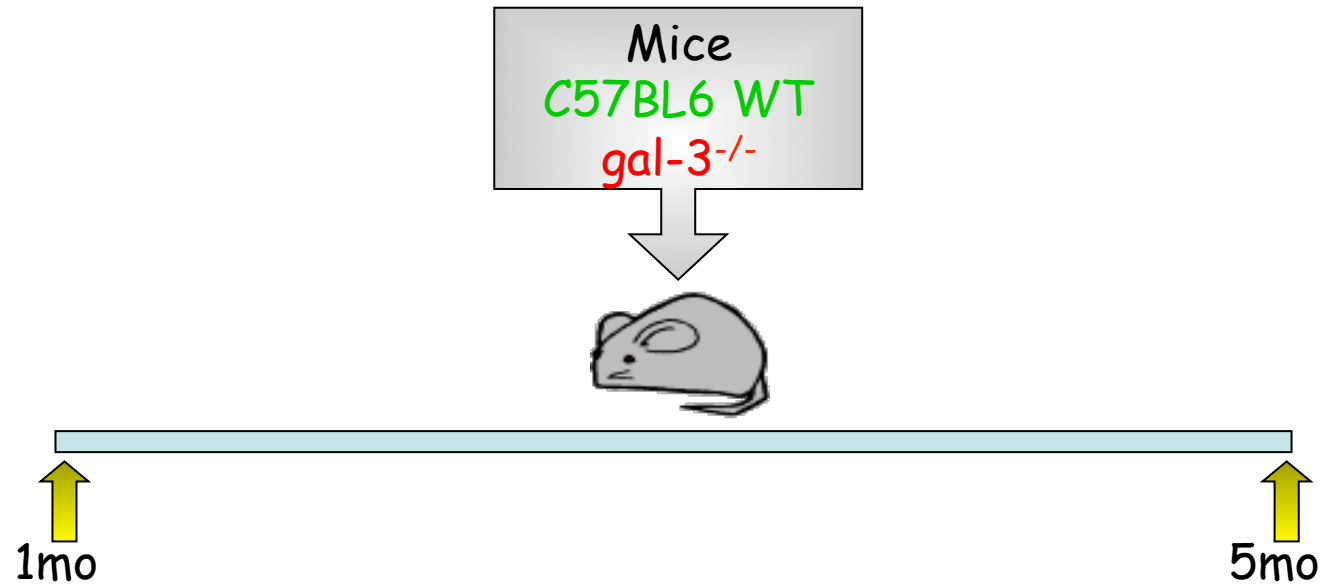


Aim

To investigate the role of Gal-3 in the relationship between glucose metabolism and adipose tissue we analyzed the effect of Gal-3 ablation on:

- 1) glucose homeostasis
- 2) adipose tissue phenotype

Experimental design: metabolic phenotype

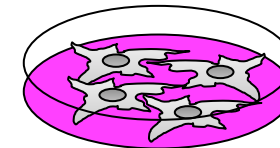
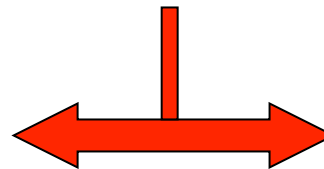
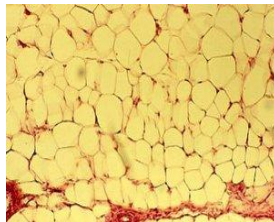


Body weight and fasting glucose once a month

IPGTT, Insulinemia and HOMA-IR at 1 and 5 months of age

Experimental design: adipose tissue phenotype

Mice
C57BL6 WT
gal-3^{-/-}



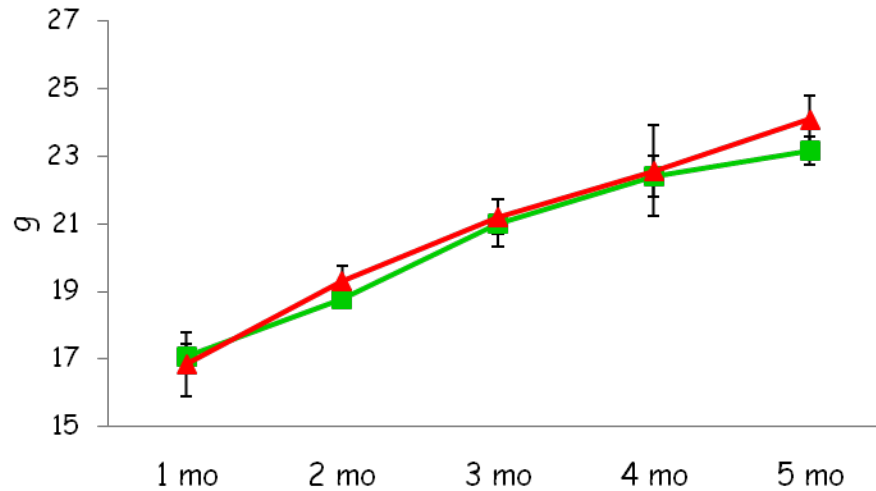
WAT and BAT histology

mRNA expression of markers of lipid metabolism, differentiation and inflammation (Real Time PCR) in VAT

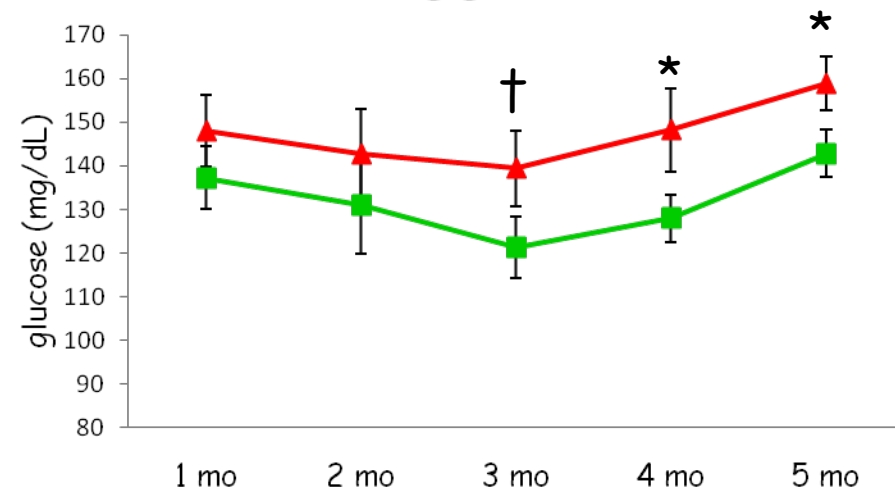
Adipose-derived Stem Cells (ASC) isolation and adipogenic differentiation

Results: metabolic phenotype

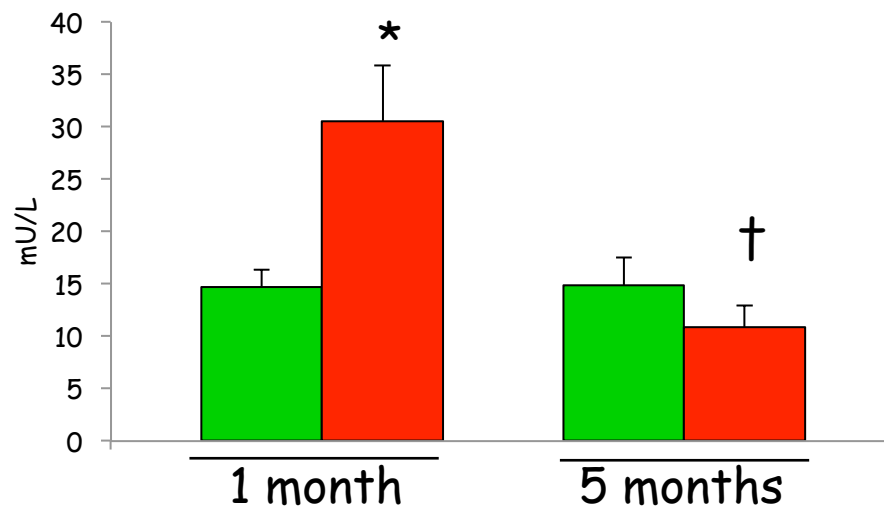
Body weight



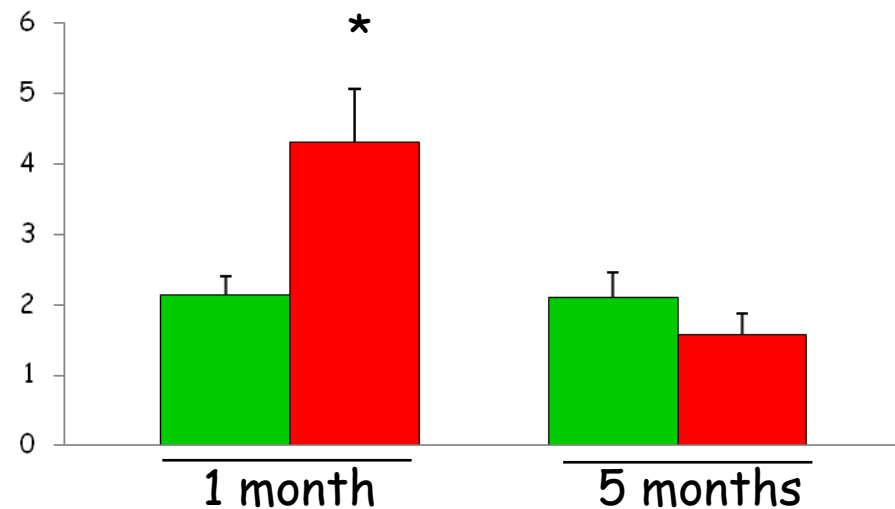
Fasting glucose



Insulinemia



HOMA-IR

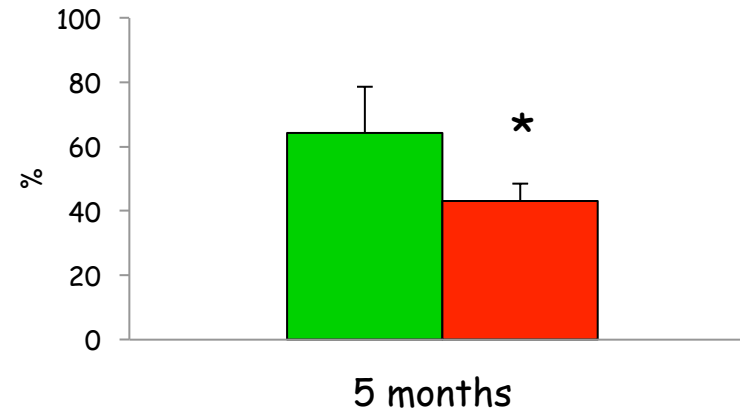


■ WT ■ Gal-3^{-/-}

* $P < 0.01$ or † $P < 0.05$ vs. WT; ‡ $P < 0.0001$ vs. 1 month

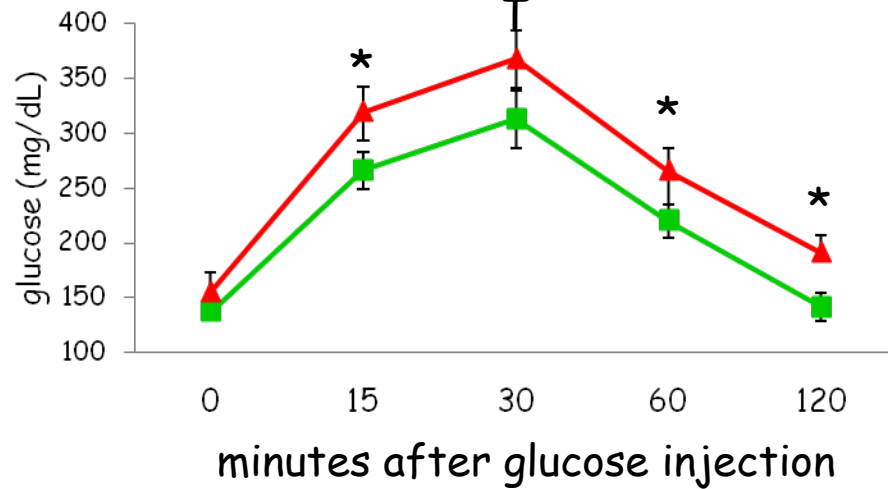
Results: metabolic phenotype

HOMA-% β

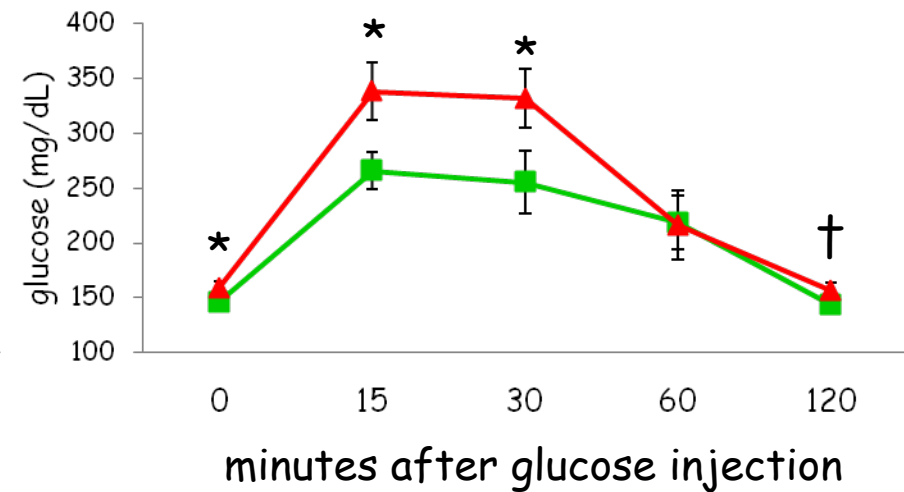


* $P < 0,05$ vs. WT

IPGTT 1 month



IPGTT 5 months

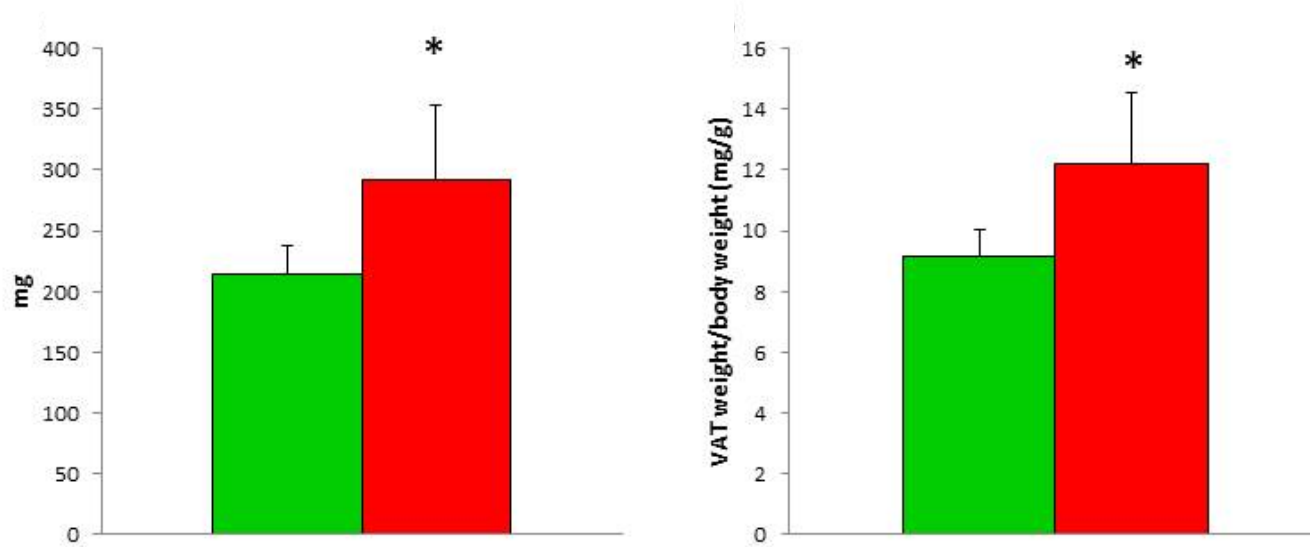


■ WT ■ Gal-3^{-/-}

* $P < 0.01$ or † $P < 0,05$ vs. WT

Results: adipose tissue phenotype

Visceral adipose tissue (VAT) weight

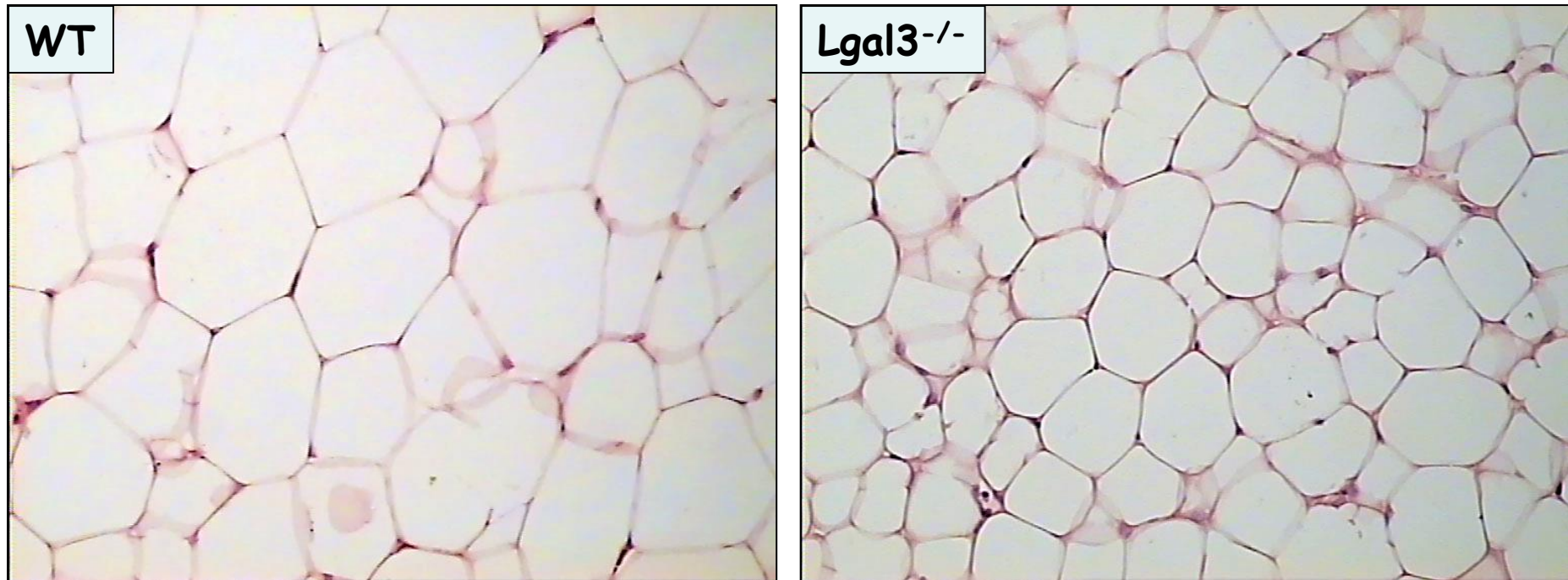


■ WT ■ Lgals3^{-/-}

* P<0.01 vs. WT

Results: adipose tissue phenotype

E/E, Original magnification, 250X

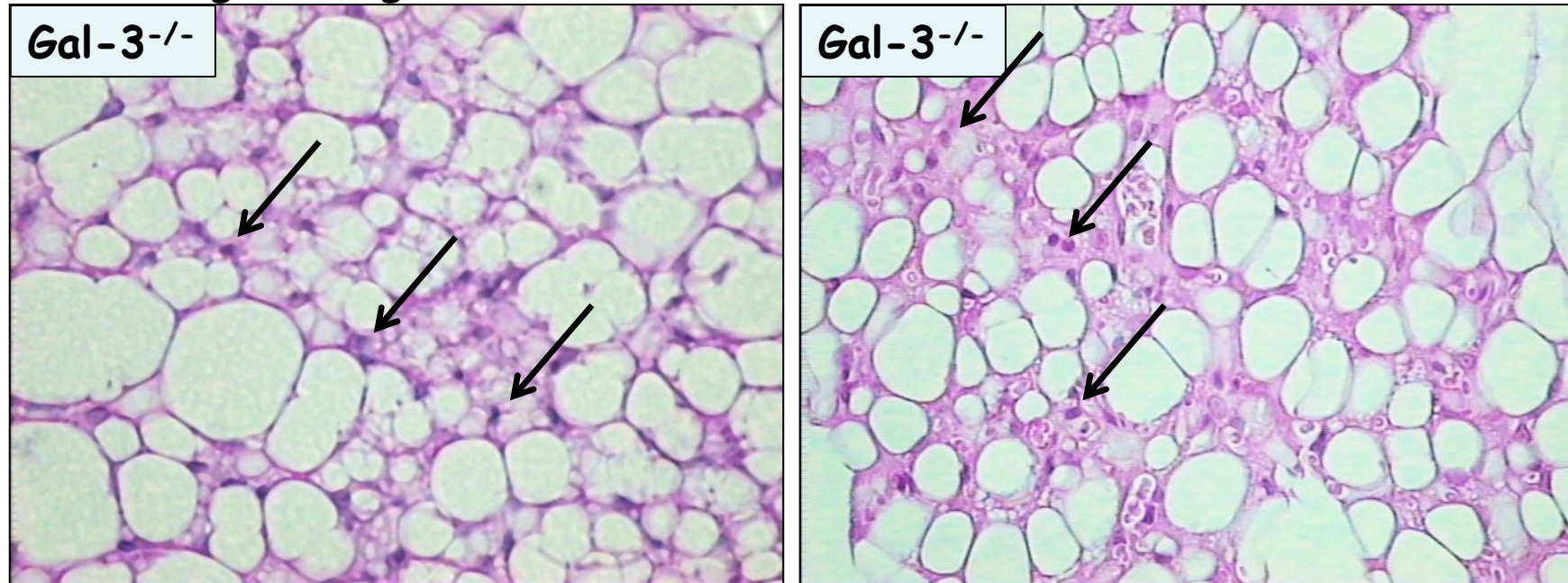


Visceral Adipose Tissue (VAT) Histology

VAT adipocytes accumulate less lipids in Lgal3^{-/-} mice

Results: adipose tissue phenotype

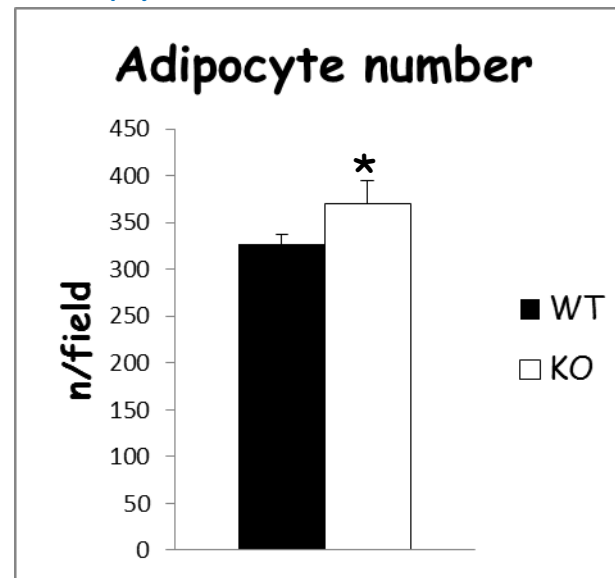
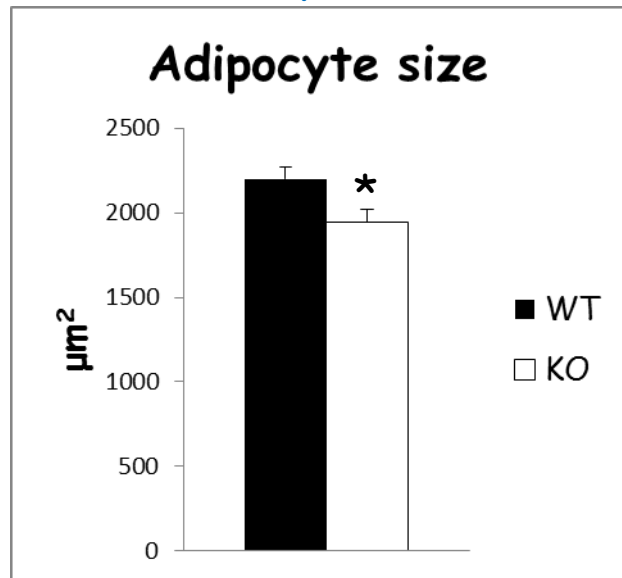
E/E, Original magnification, 400X



Visceral Adipose Tissue (VAT) Histology

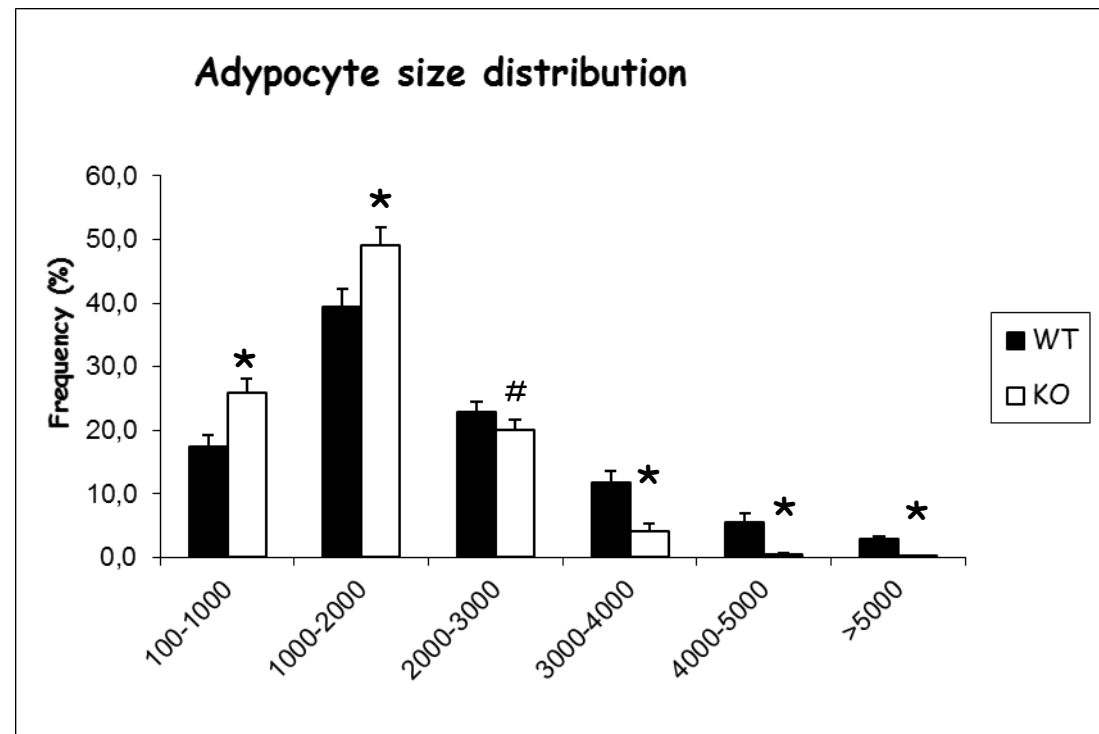
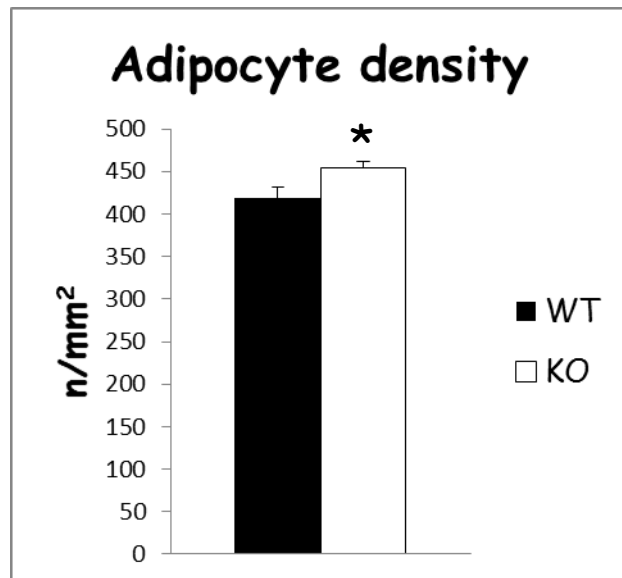
Lipolysis (left panel) and inflammation (arrows)
in VAT from *Gal-3^{-/-}* mice

Results: adipose tissue phenotype

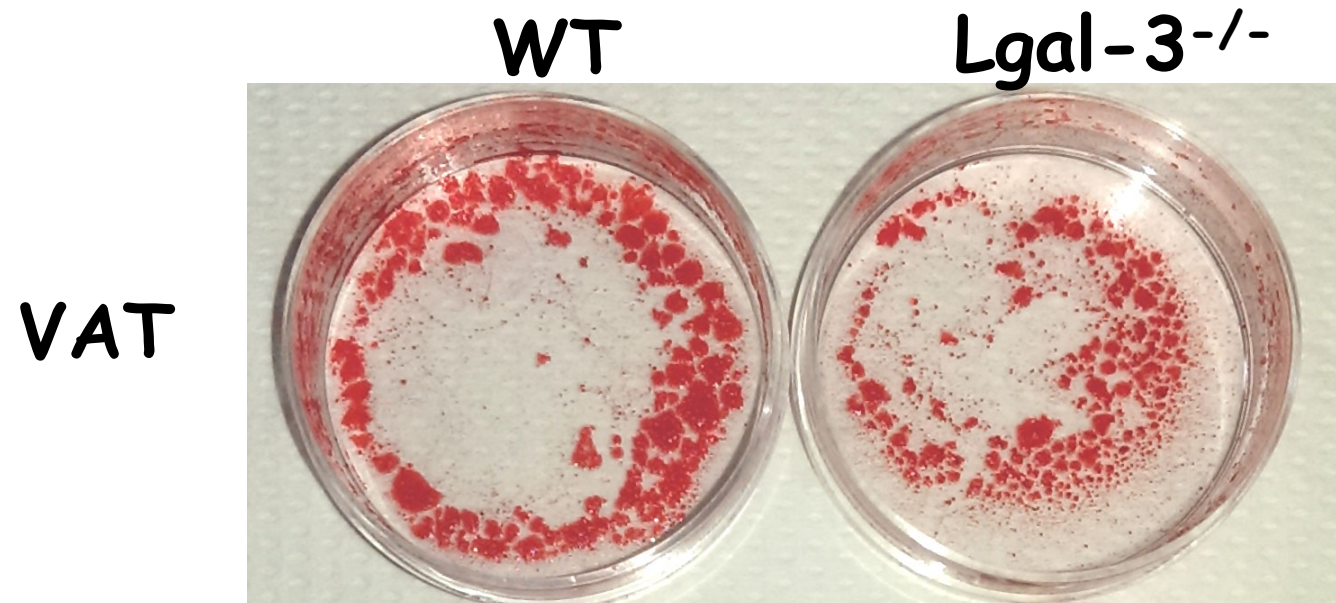


* $P < 0.01$ vs. WT

$P < 0.05$ vs. WT



Results: adipose tissue phenotype

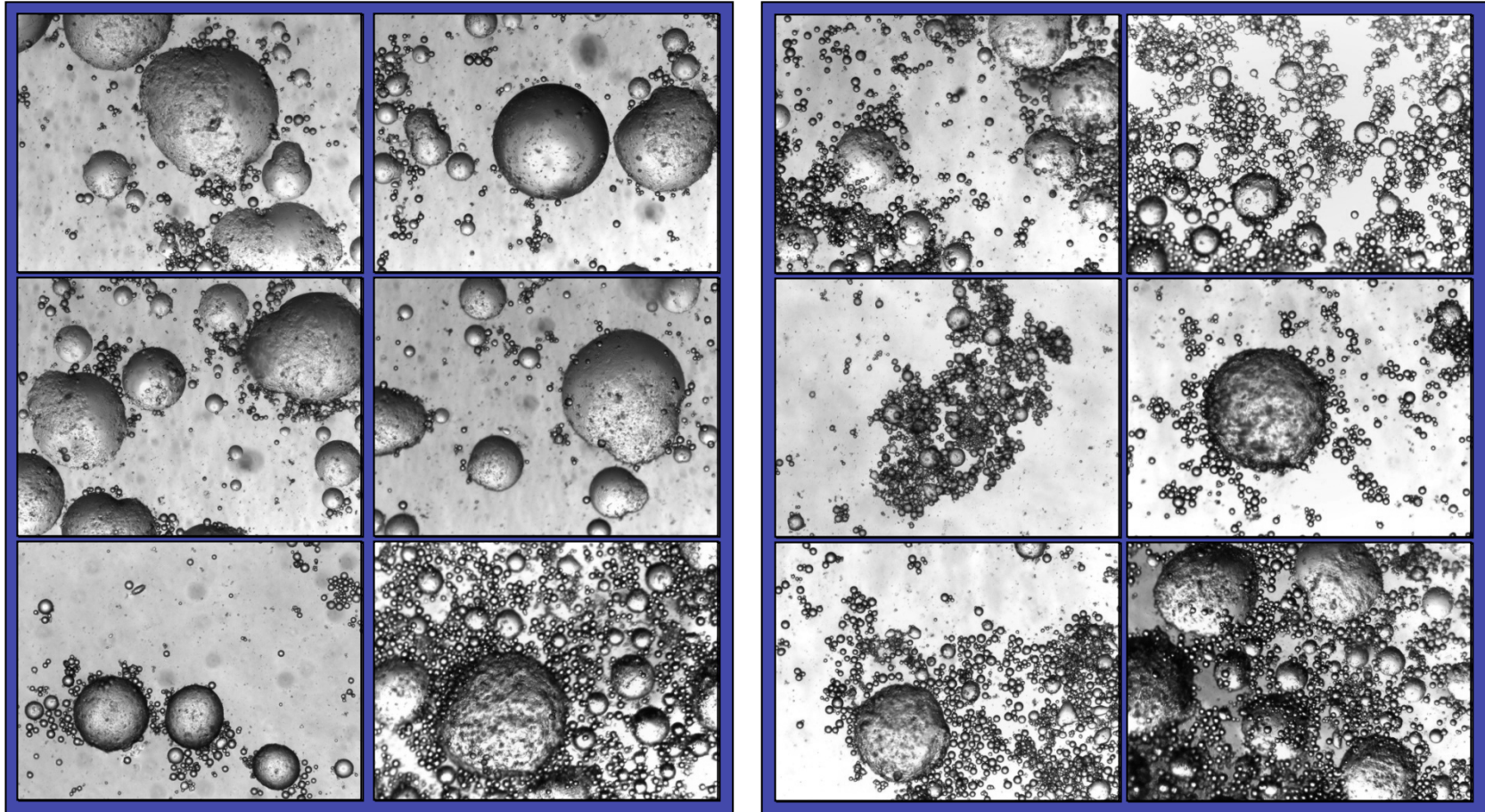


Adipocytes isolated from VAT pads. Oil Red O staining

Results: adipose tissue phenotype

WT

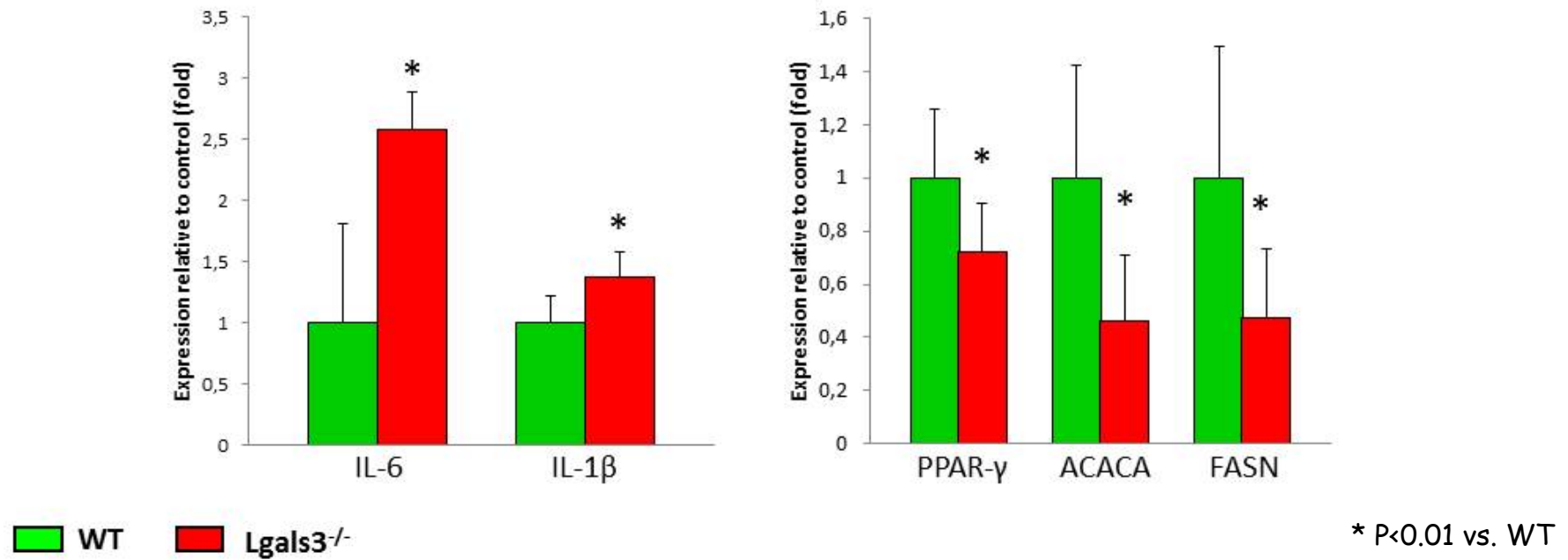
Lgal-3^{-/-}



Light Microscopy, 5X

Adipocytes isolated from VAT pads

qRT-PCR analysis of inflammatory and adipogenic markers expression in VAT

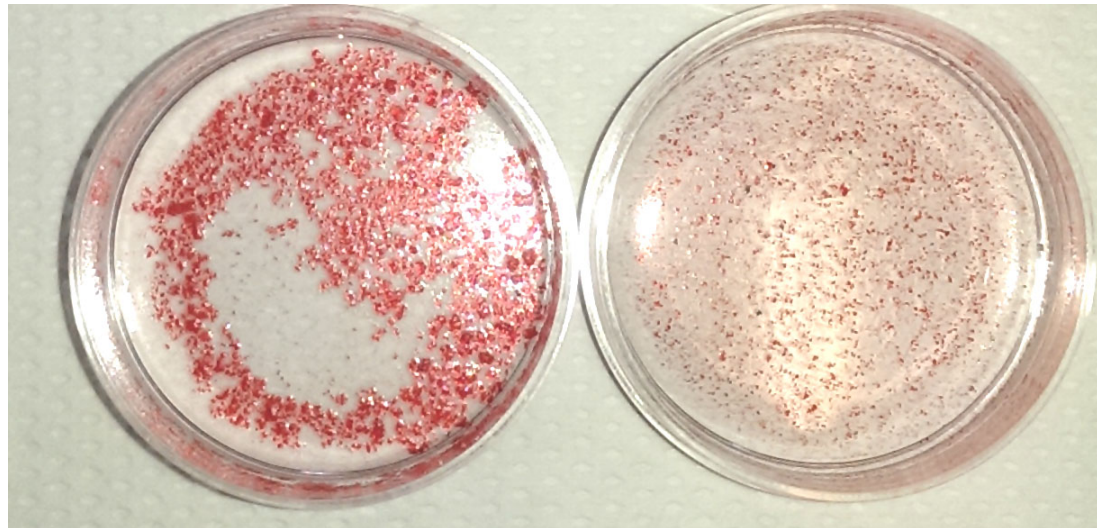


Results: Posterior Subcutaneous Adipose Tissue (SAT)

WT

Lgal-3^{-/-}

SAT



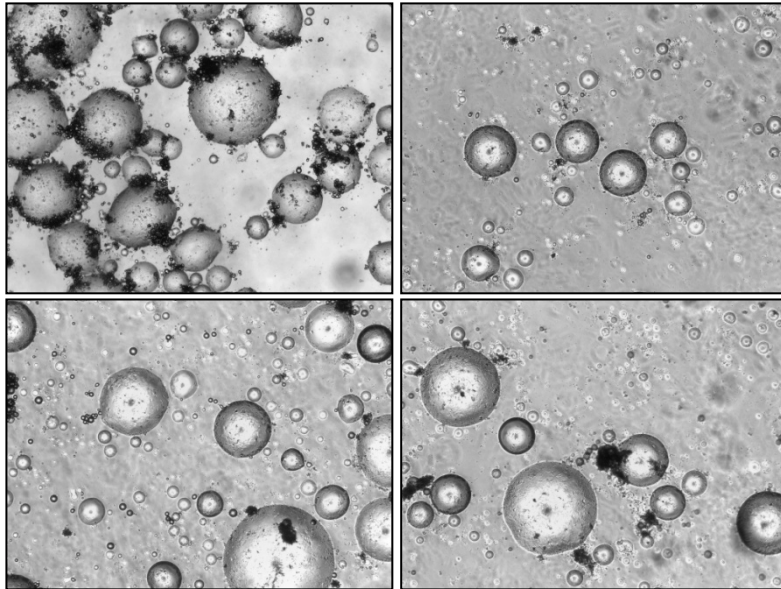
Oil Red O staining

Adipocytes isolated from SAT pads.

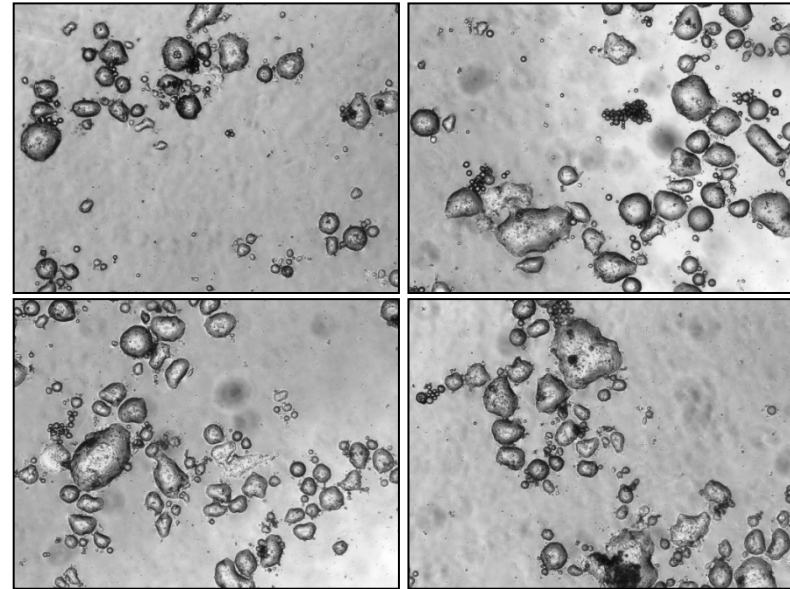
Also SAT adipocytes accumulate less lipids in Lgal3^{-/-} mice

Results: Posterior Subcutaneous Adipose Tissue (SAT)

WT



Lgal-3^{-/-}



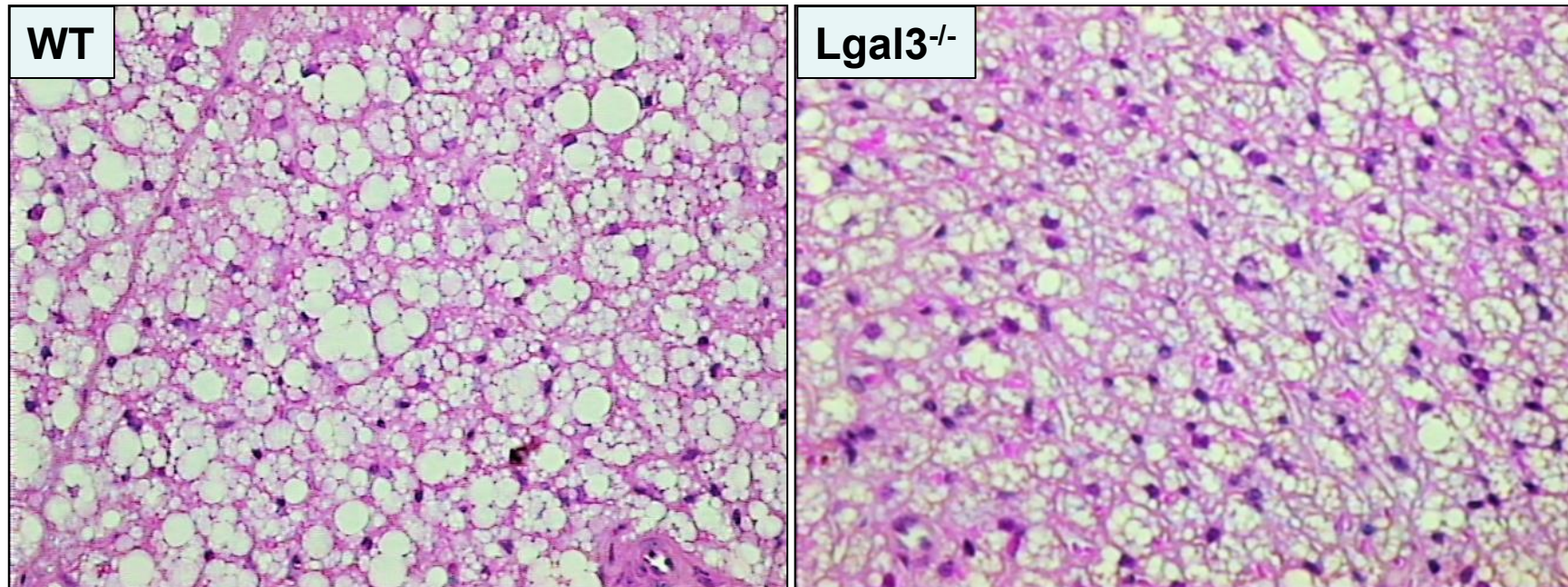
Light Microscopy, 5X

Adipocytes isolated from SAT pads.

Also SAT adipocytes accumulate less lipids in Lgal3^{-/-} mice

Results: Interscapular Brown Adipose Tissue (BAT) Hystology

E/E, Original magnification, 400X.



Interscapular Brown Adipose Tissue (BAT)

Also brown adipocytes accumulate less lipids in $Lgal3^{-/-}$ mice

Results: Interscapular BAT lipotrophy in *Lgal3*^{-/-} mice

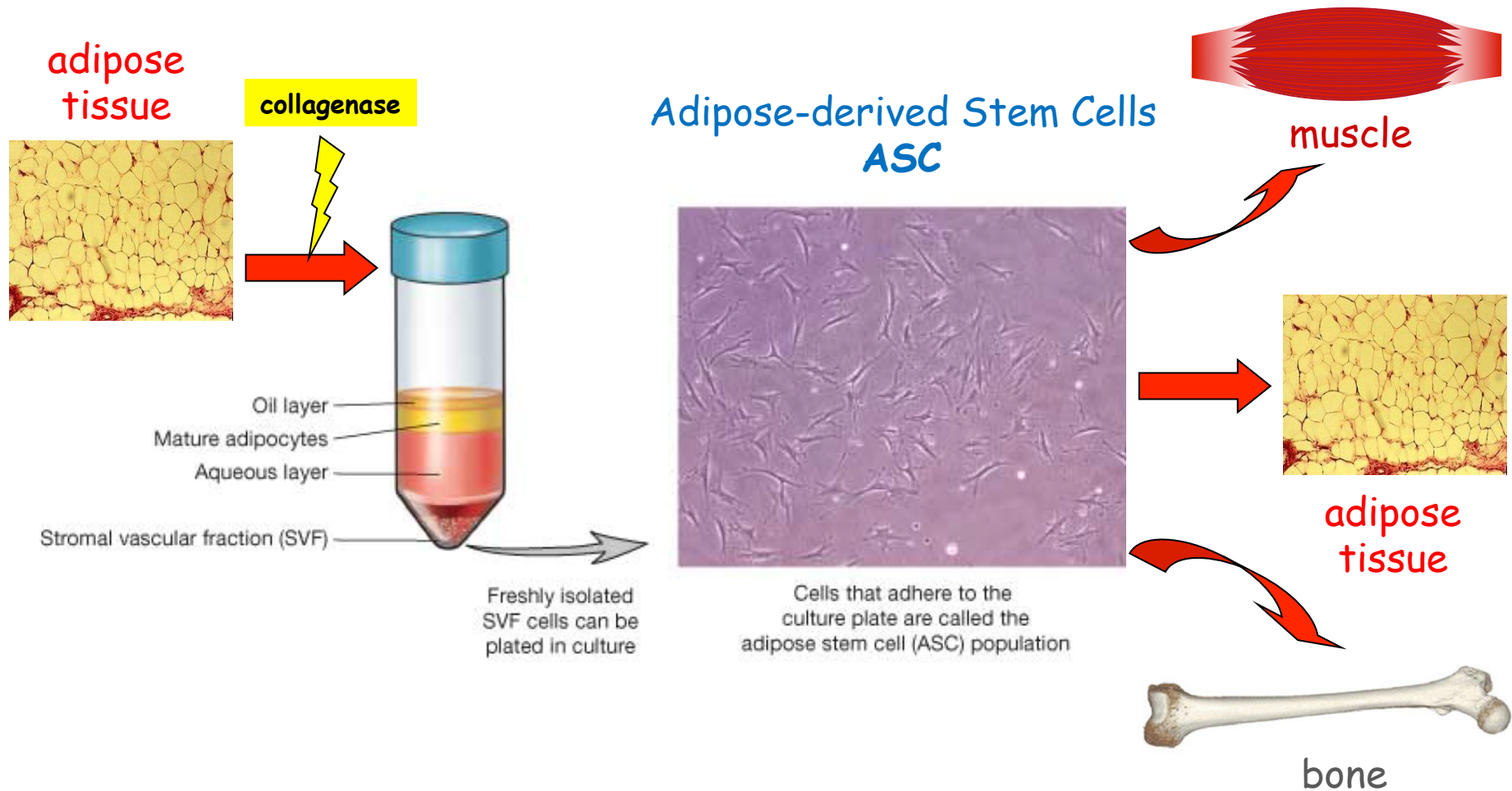
WT



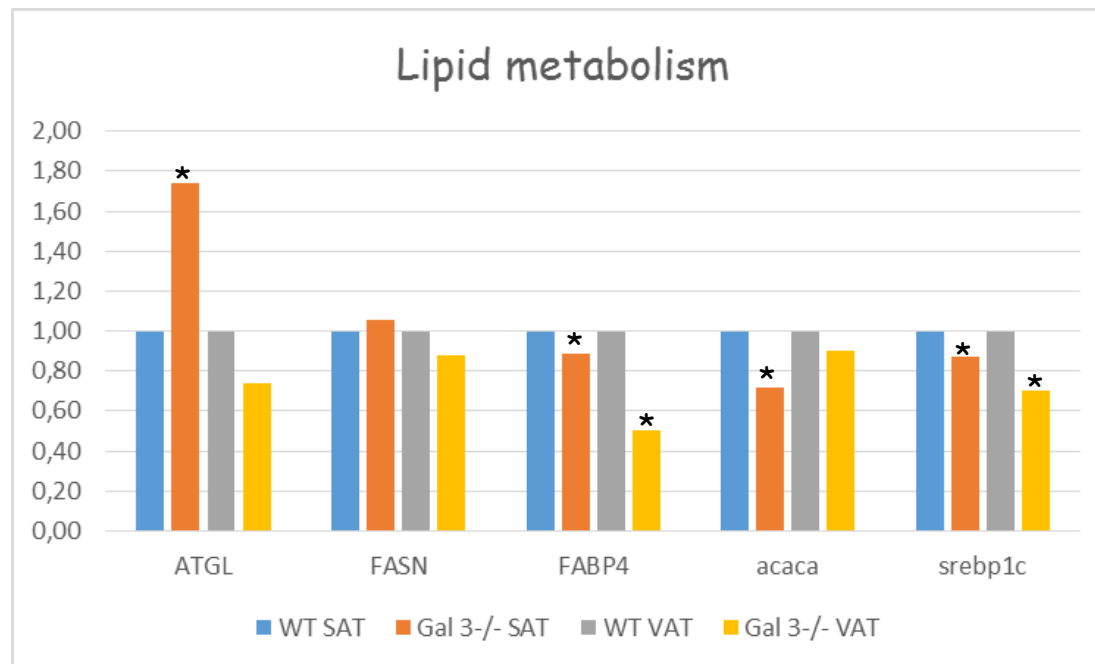
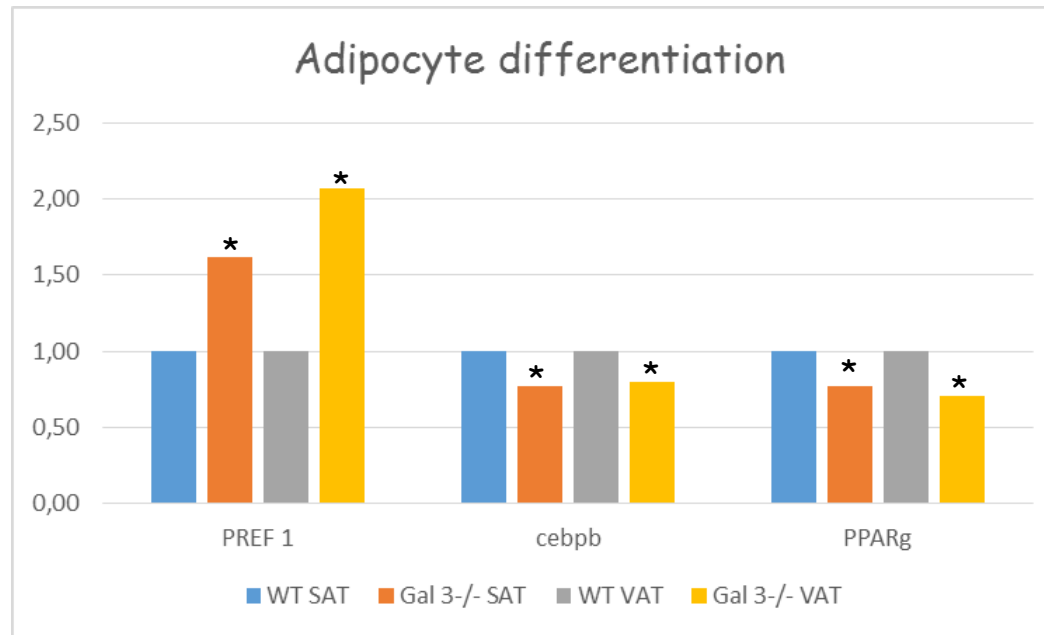
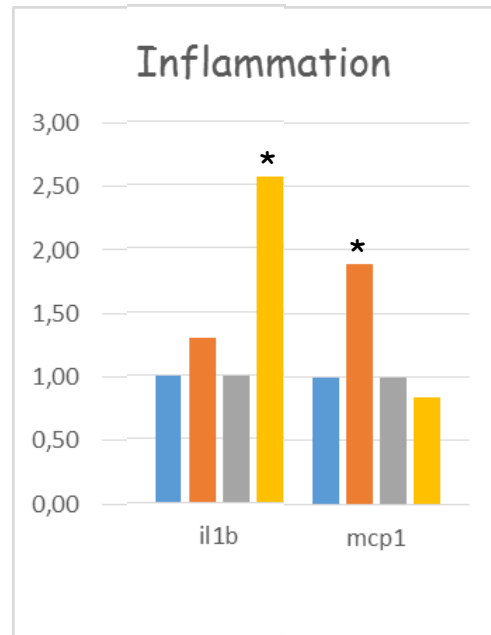
***Lgal3*^{-/-}**



Method: Isolation and Differentiation of Adipose-derived Stem Cells (ASC)

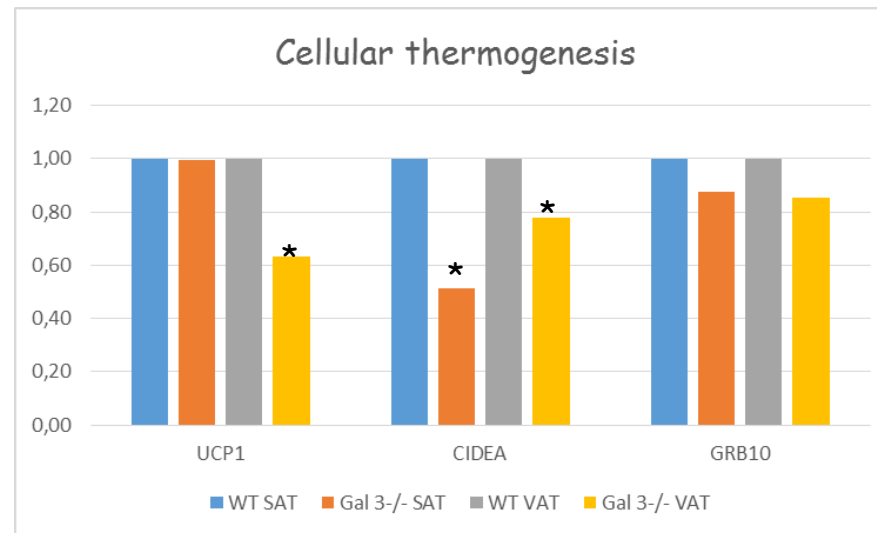
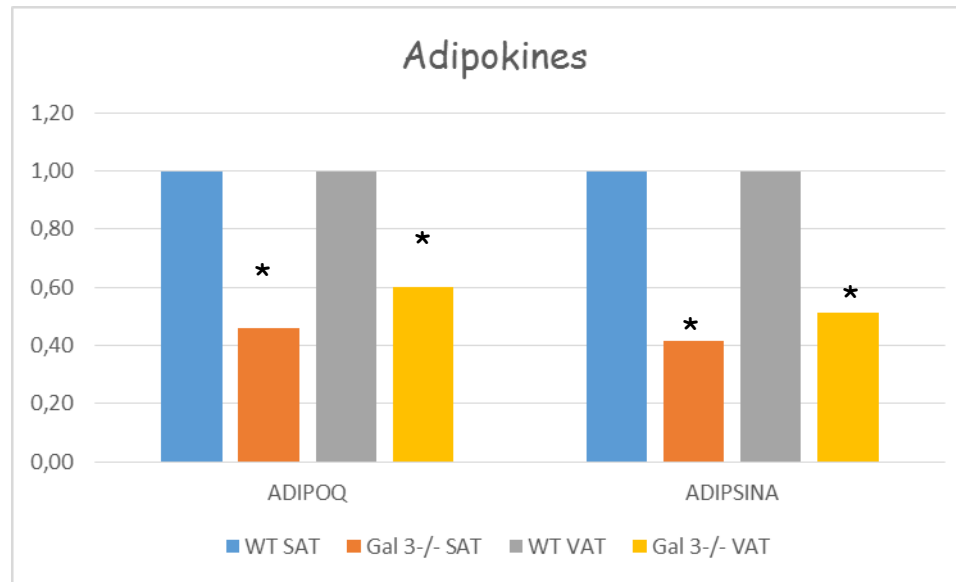


Results: mRNA expression in ASC isolated from SAT and VAT



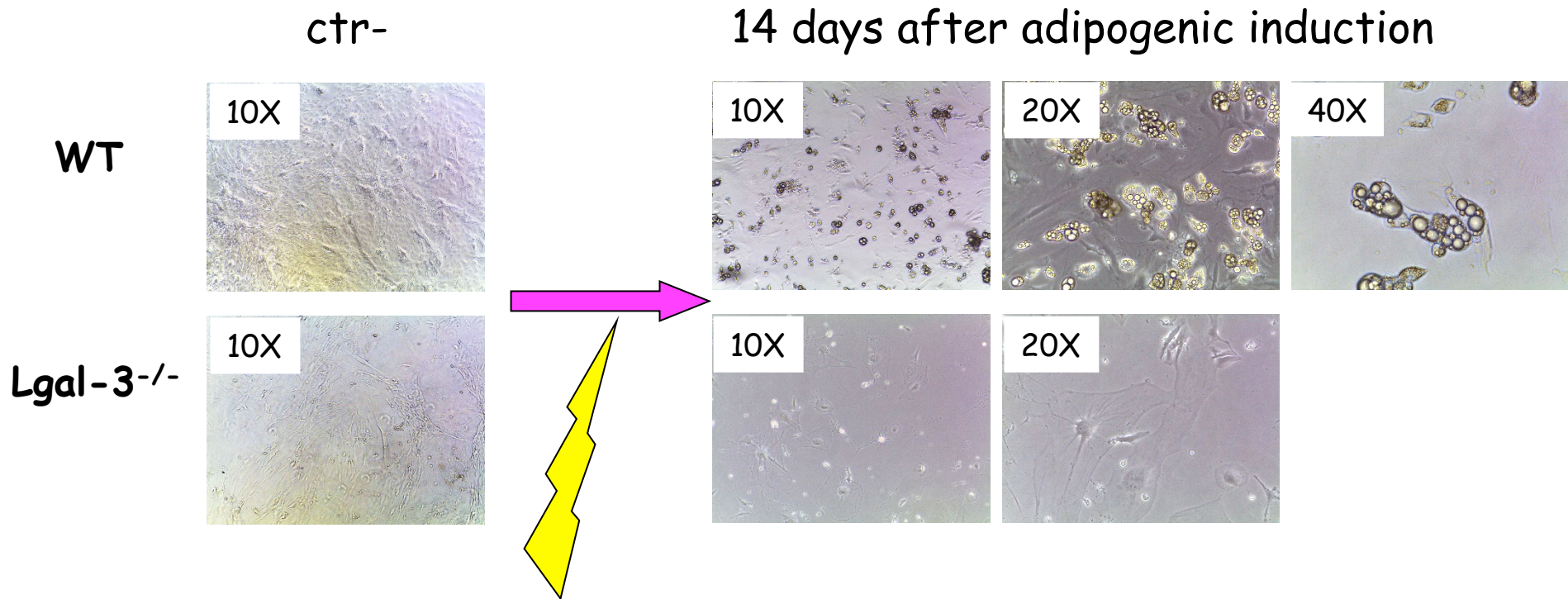
* P<0.05 vs. WT

Results: mRNA expression in ASC isolated from SAT and VAT



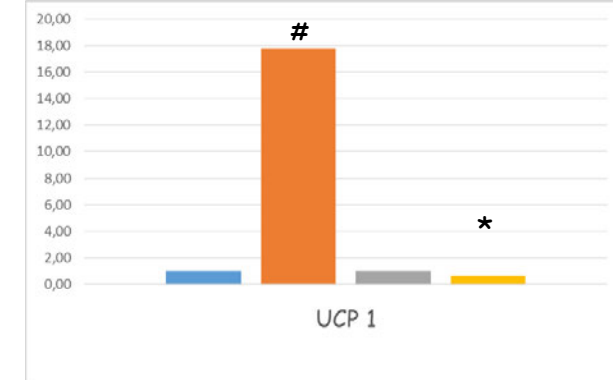
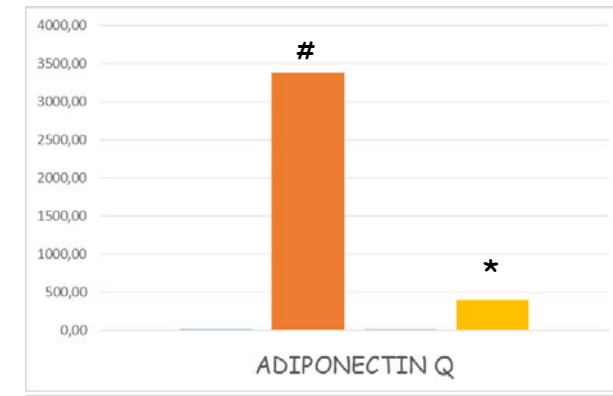
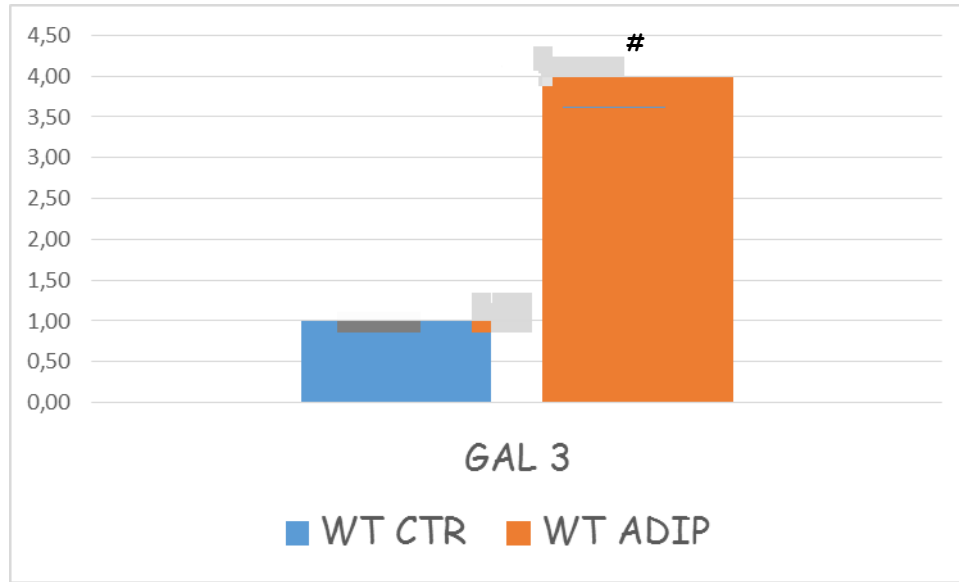
* P<0.05 vs. WT

Results: Adipogenic Differentiation of Adipose-derived Stem Cells

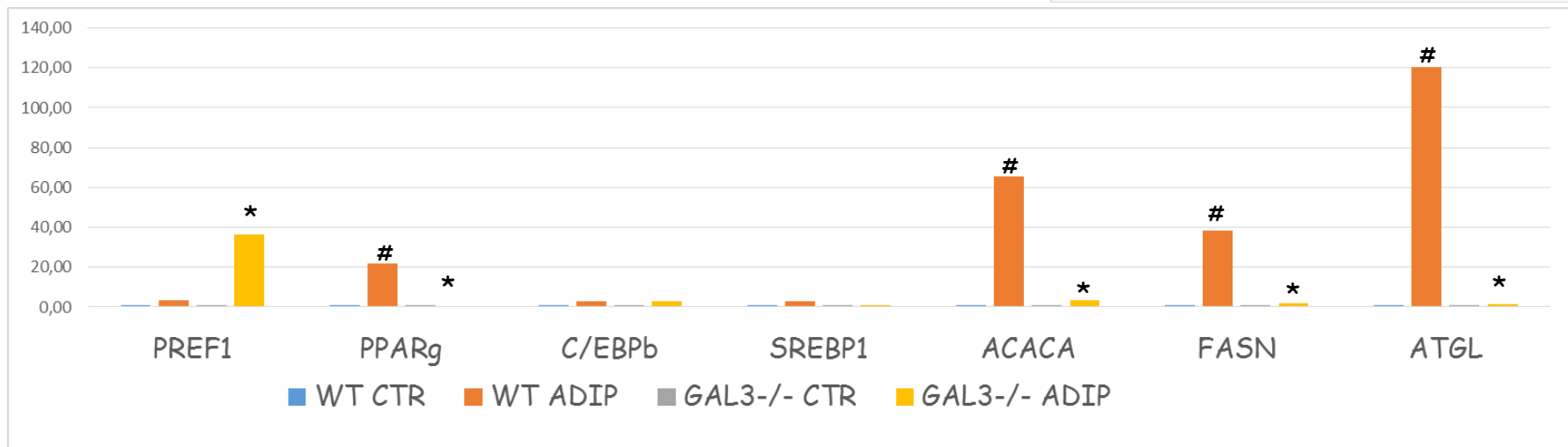


Adipogenic differentiation medium
Complete DMEM/F12 medium with added:
50 μ M indomethacine
0.5 μ M hydrocortisone
0.5 mM isobutylmethylxanthine
5 μ g/ml insulin

Results: Adipogenic Differentiation of Adipose-derived Stem Cells



* P<0.05 vs. WT; # P<0.05 WT adip vs. WT ctr-



Summary and conclusions

Galectin-3 ablation is associated with:

➤ impaired glucose homeostasis characterized by:

- a. hyperglycemia;
- b. early increase in insulin secretion with insulin resistance, followed by impaired β -cell function.

➤ alteration of the adipose tissue phenotype characterized by:

- a. impairment of the molecular mechanisms underlying adipocyte differentiation;
- b. marked inflammatory phenotype.

Taken together, these molecular, biochemical, and histological data reveal that *Gal-3* is involved in both adipogenic differentiation and glucose homeostasis.

Further studies are needed to assess the interaction between adipose tissue and glucose metabolism in *Gal-3*^{-/-} mice.

Thank you