Inflammasome-mediated caspase-1 activity

Gatekeeper of inflammation in the adipose tissue

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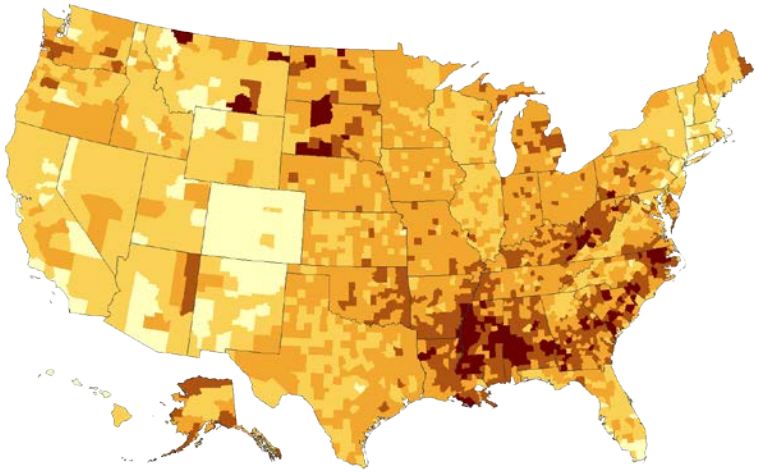
For quality of life

Obesity promotes the development of insulin resistance and type 2 diabetes

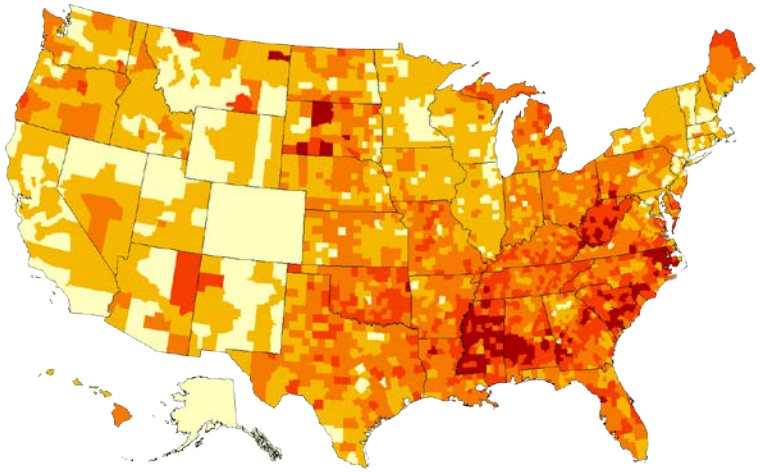
County-level Estimates of Obesity among Adults aged ≥ 20 years

2004



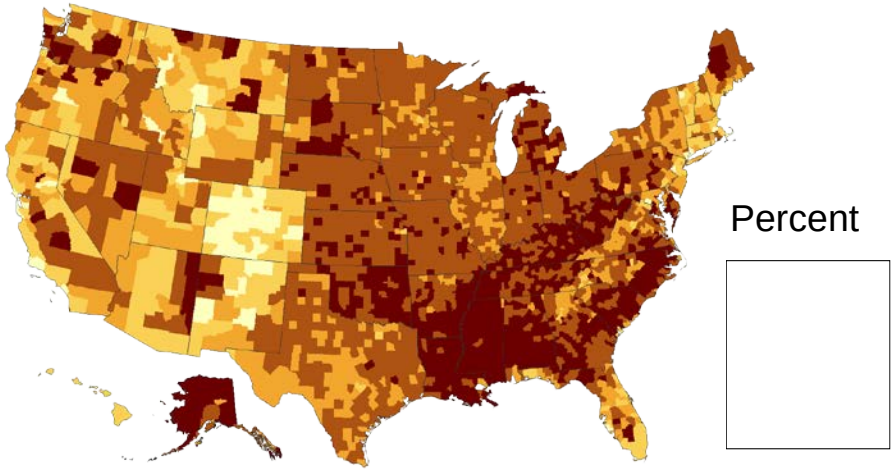
County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years

2004



County-level Estimates of Obesity among Adults aged ≥ 20 years

2008



County-level Estimates of Diagnosed Diabetes among Adults aged ≥ 20 years

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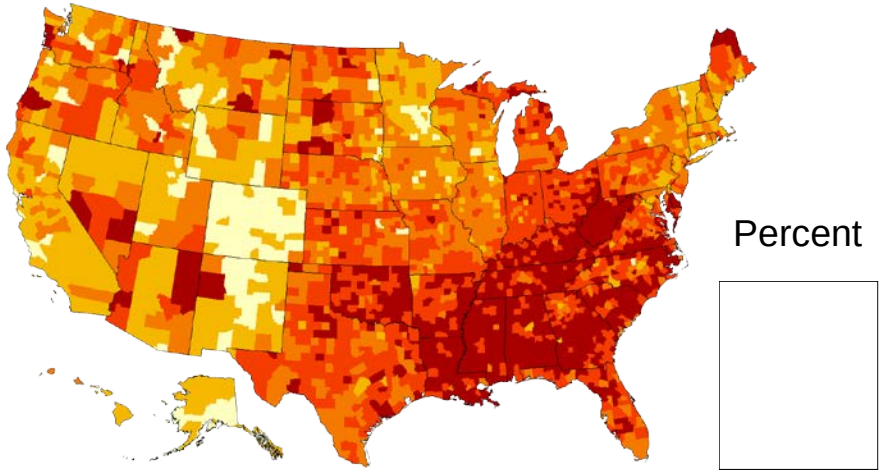
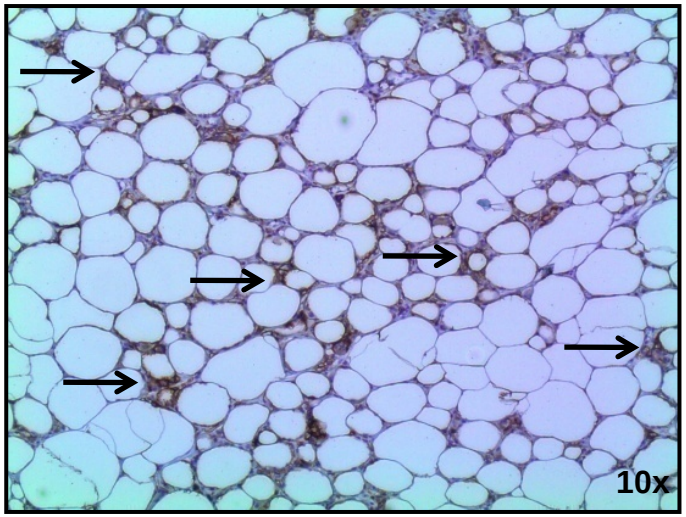


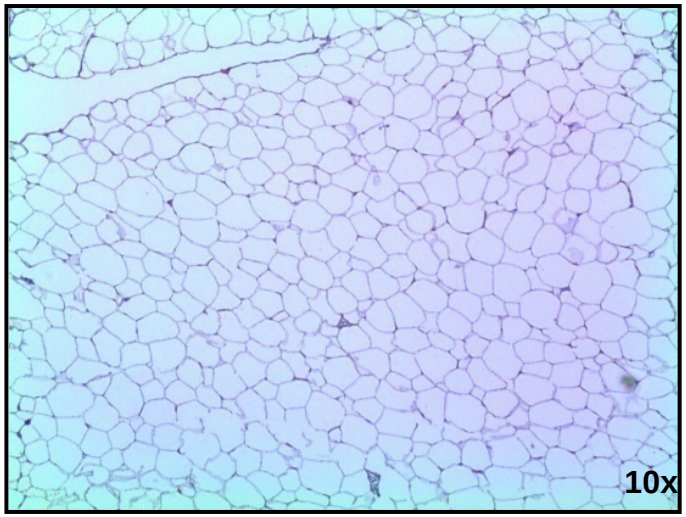
Adipose tissue inflammation

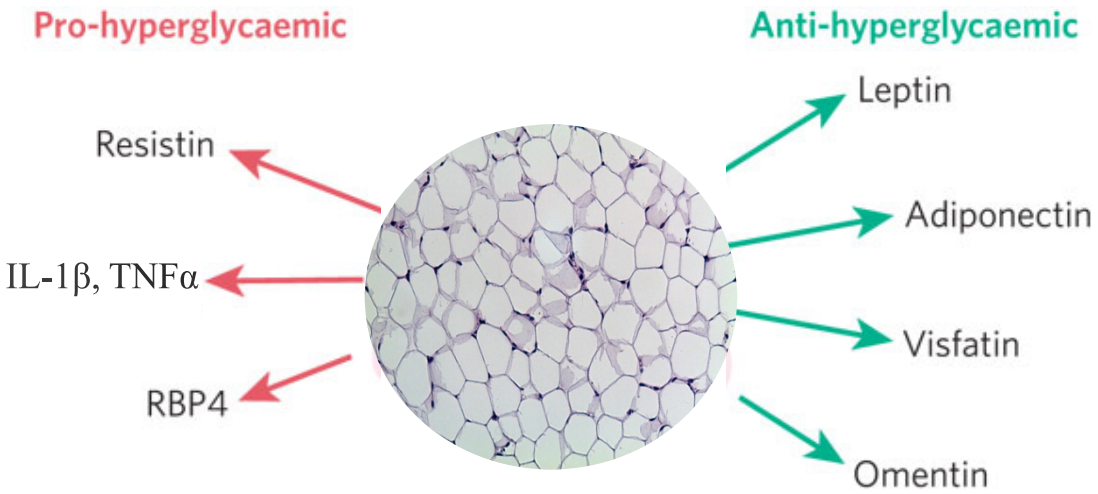
Macrophage influx into the adipose tissue

High Fat Diet



Low Fat Diet





Evan D. Rosen and Bruce M. Spiegelman,2006, Nature

The pro-inflammatory cytokine IL-1β and Type 2 Diabetes
Current knowledge

- IL-1β inhibits insulin signaling
- IL-1β negatively affects pancreatic β-cell function
- Elevated levels of interleukin-1β (IL-1β) are predictive of Type 2 Diabetes
- Inhibition of the IL-1 signalling cascade by treatment with IL-1 receptor antagonist is beneficial in patients with Type 2 Diabetes and leads to reduced markers of systemic inflammation

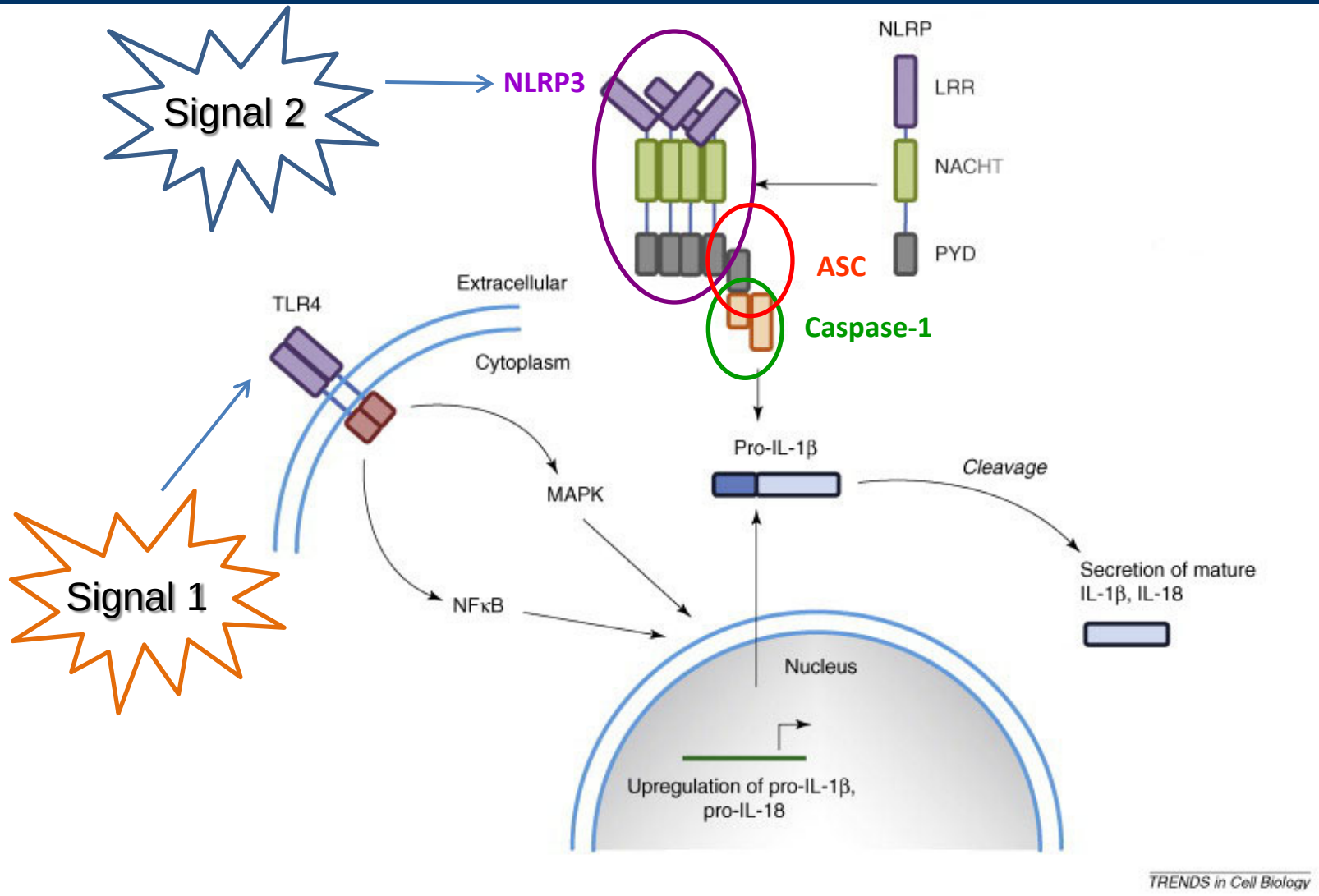
The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

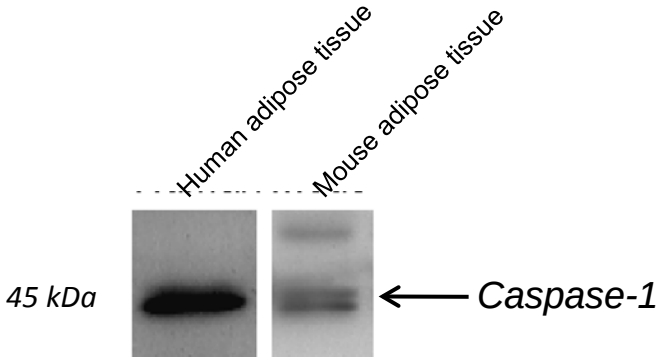
Interleukin-1–Receptor Antagonist in Type 2 Diabetes Mellitus

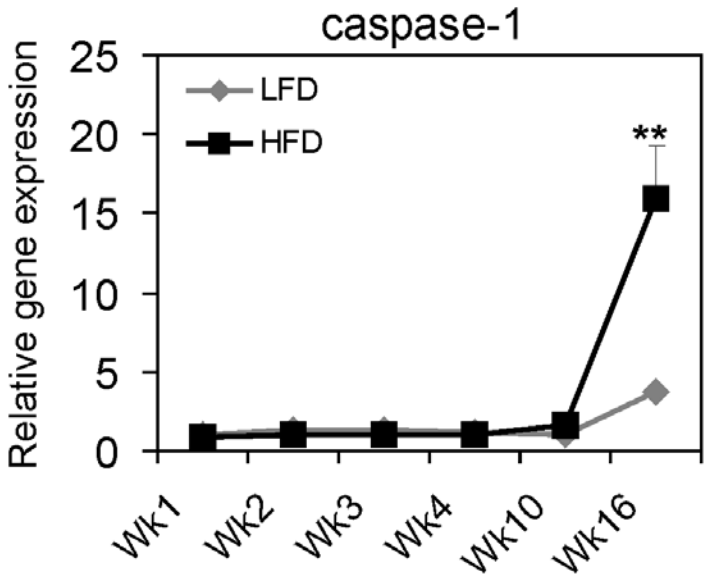
Claus M. Larsen, M.D., Mirjam Faulenbach, M.D., Allan Vaag, M.D., Ph.D., Aage Vølund, M.Sc., Jan A. Ehses, Ph.D., Burkhardt Seifert, Ph.D., Thomas Mandrup-Poulsen, M.D., Ph.D., and Marc Y. Donath, M.D.

The NLRP3-inflammasome controls IL-1β release

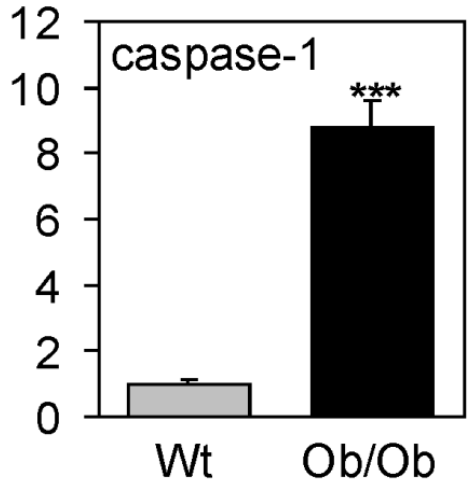


Is caspase-1 present in adipose tissue and regulated during obesity ?





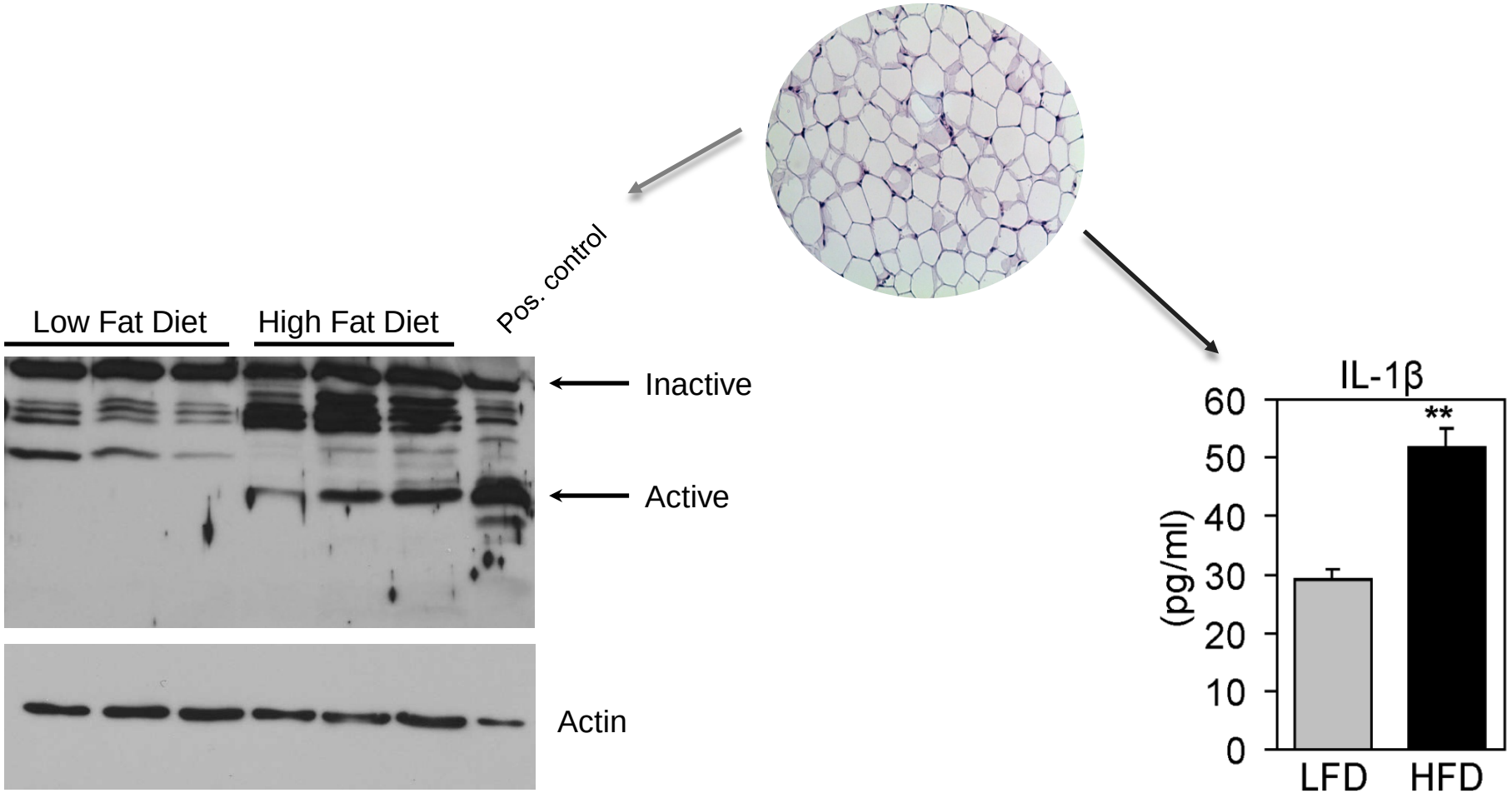
Diet-induced obesity



Genetically-induced obesity

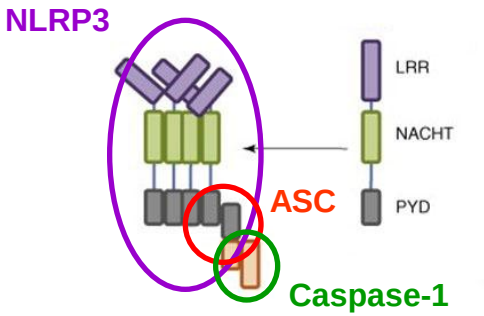
Note: no increase in caspase-1 gene expression levels in liver or muscle

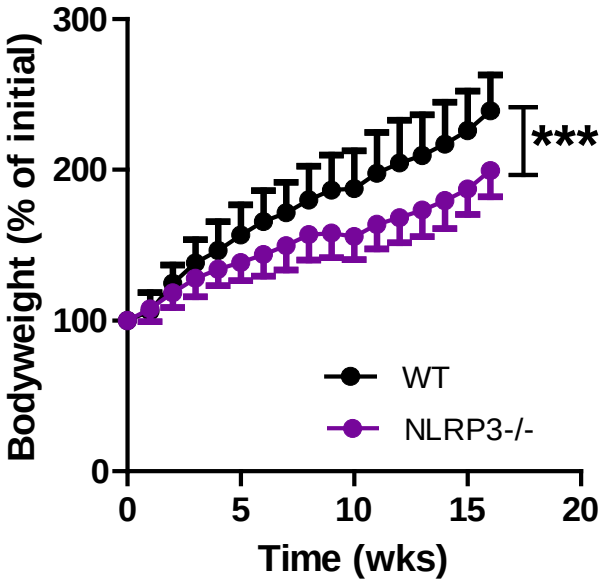
Caspase-1 activation in adipose tissue is accompanied by increased levels of IL-1β

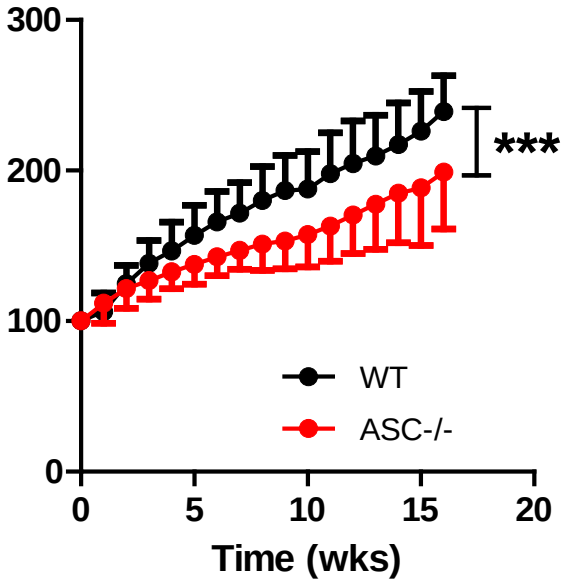


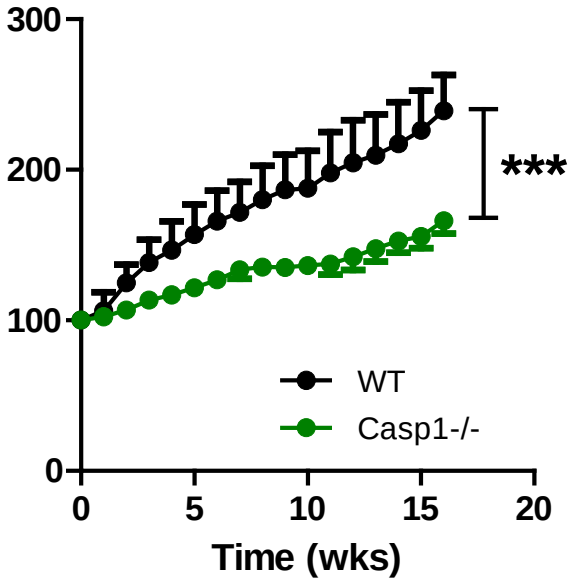
Does inflammasome-mediated caspase-1 activity contribute to the development of obesity-induced adipose tissue inflammation and insulin resistance?

High fat diet-induced obesity in NLRP3-/-, ASC-/-, Casp-1-/- animals

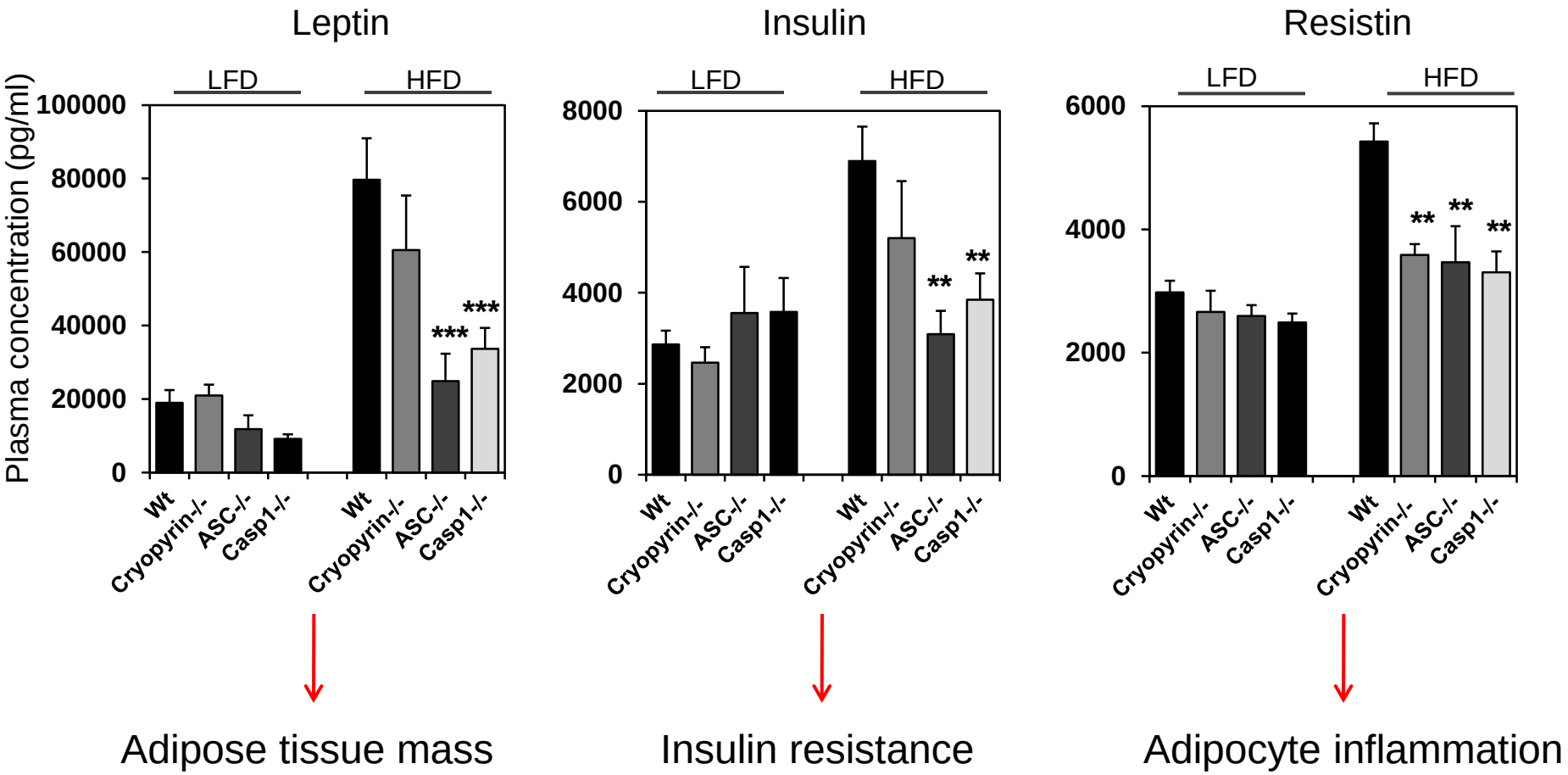






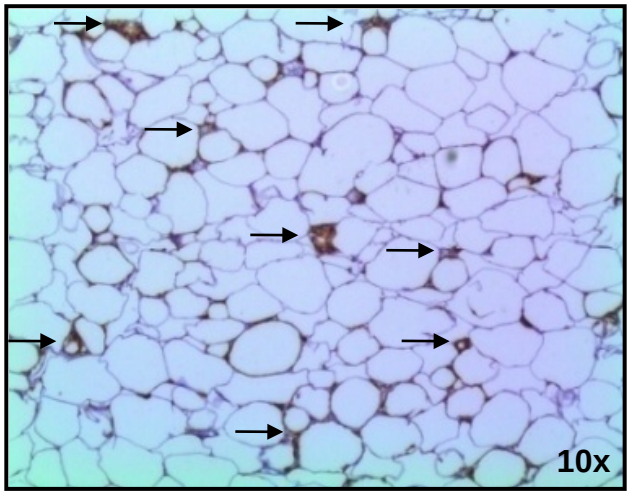


Plasma levels of adipokines and insulin

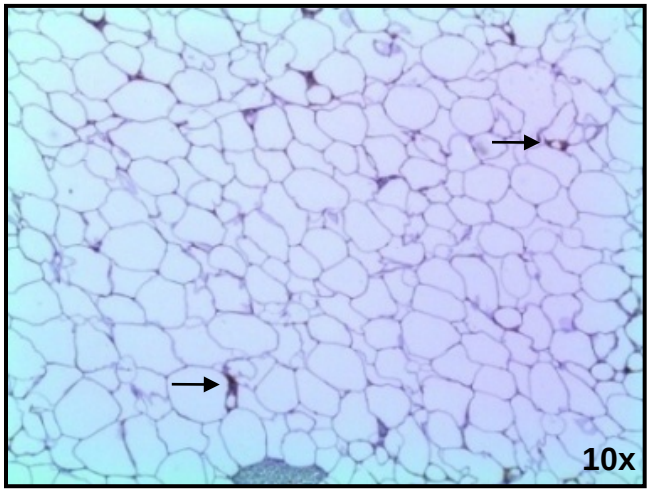


Adipose tissue inflammation in HFD-fed wild-type and caspase-1-/- animals

Wildtype-HFD



casp-1-/-HFD



Protection against the influx of macrophages paralleled by reduced levels of the chemoattractant MCP-1

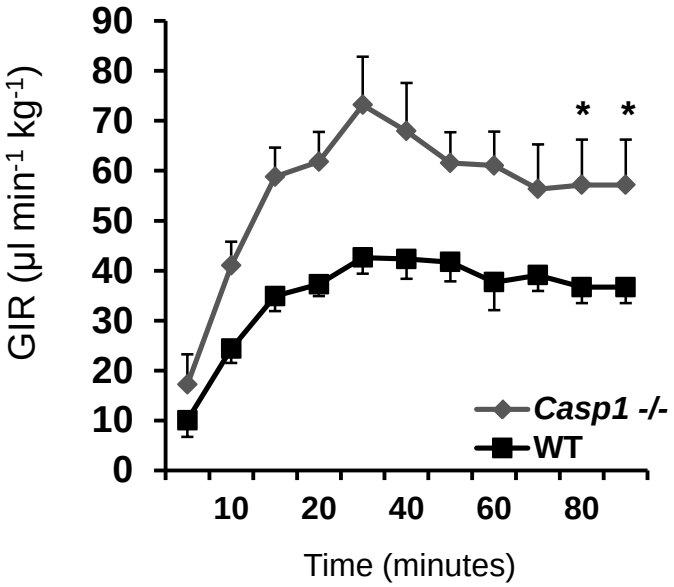
Does the absence of caspase-1 improves systemic insulin sensitivity?

Hyperinsulinemic euglycemic clamp study in HFD-fed Wild-type and caspase-1-/- animals

Approach: Infusion of high levels of insulin together with infusion of glucose to keep plasma glucose at a normal level during the clamp procedure

Readout: glucose infusion rate (GIR) → Low infusion rate: insulin resistant

→ High infusion rate: insulin sensitive



Inhibition of caspase-1 in obese and insulin resistant animals ?

Daily treatment with caspase-1 inhibitor
Pralnacasan

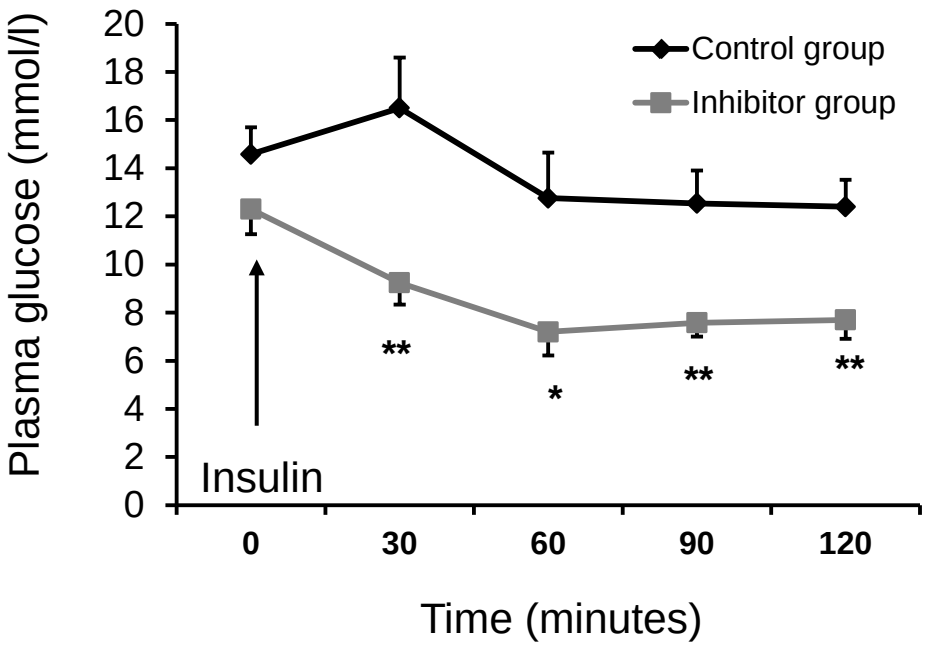
Two weeks

- ITT test
- Bodyweight development

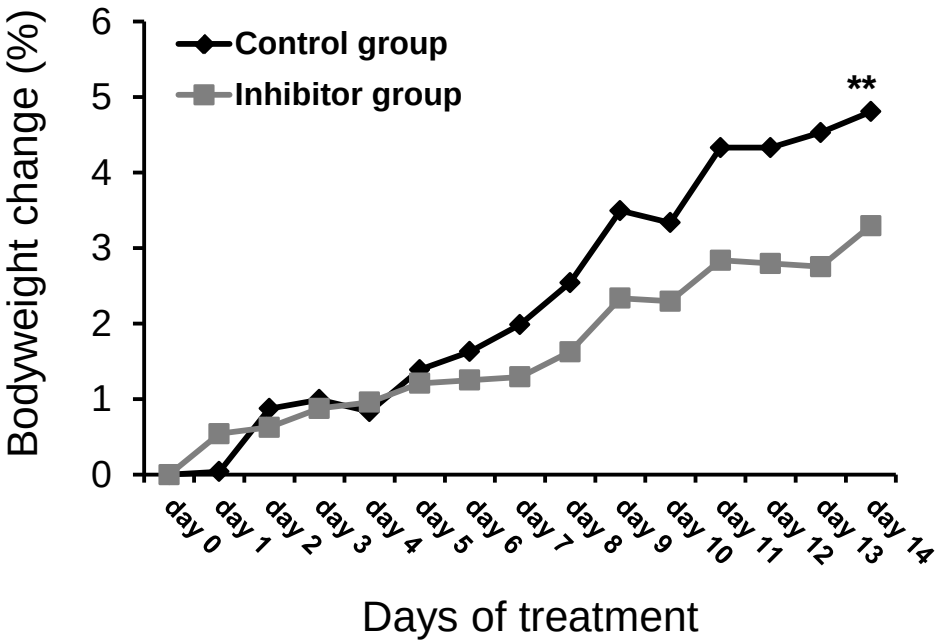
Ob/ob mouse

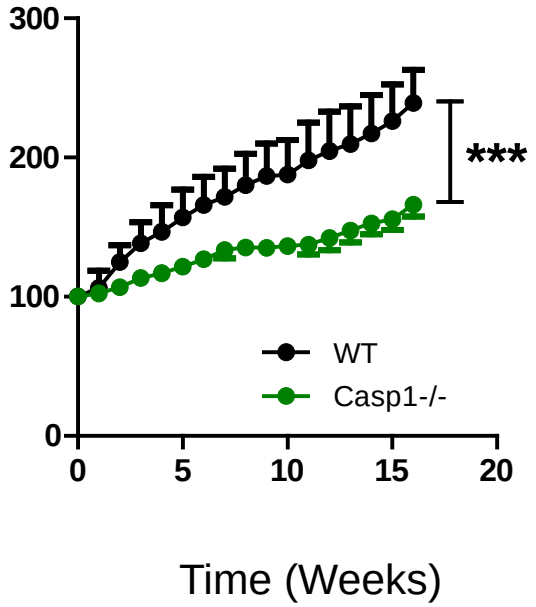
- Obese
- Insulin resistant
- High levels of caspase-1 in adipose tissue

Insulin sensitivity is robustly improved in Ob/Ob animals after 2 weeks of caspase-1 inhibition



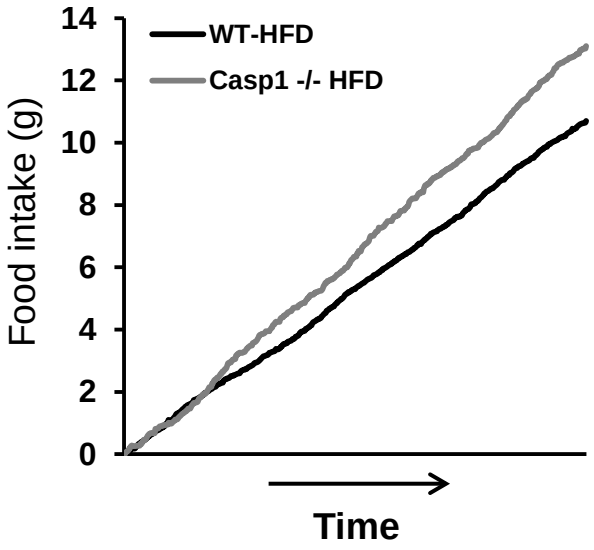
Caspase-1 inhibition limits bodyweight gain

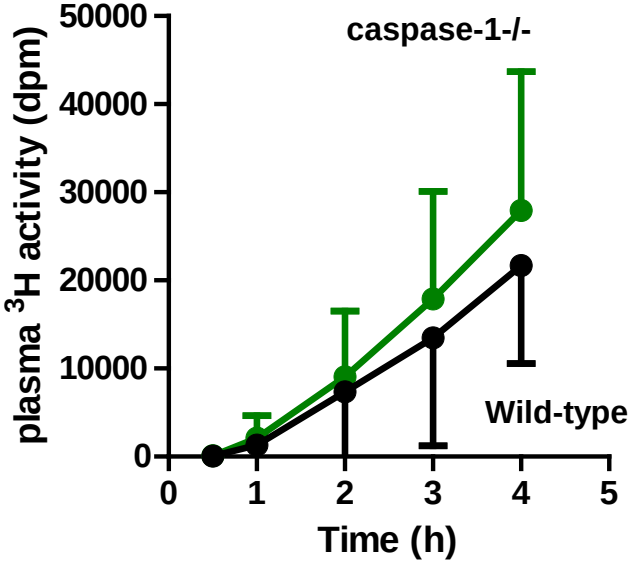


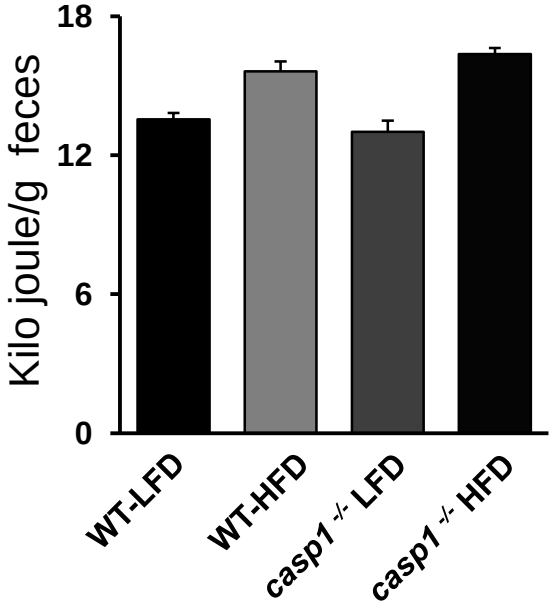


Inhibition or absence of caspase-1 prevents weight gain > mechanism?

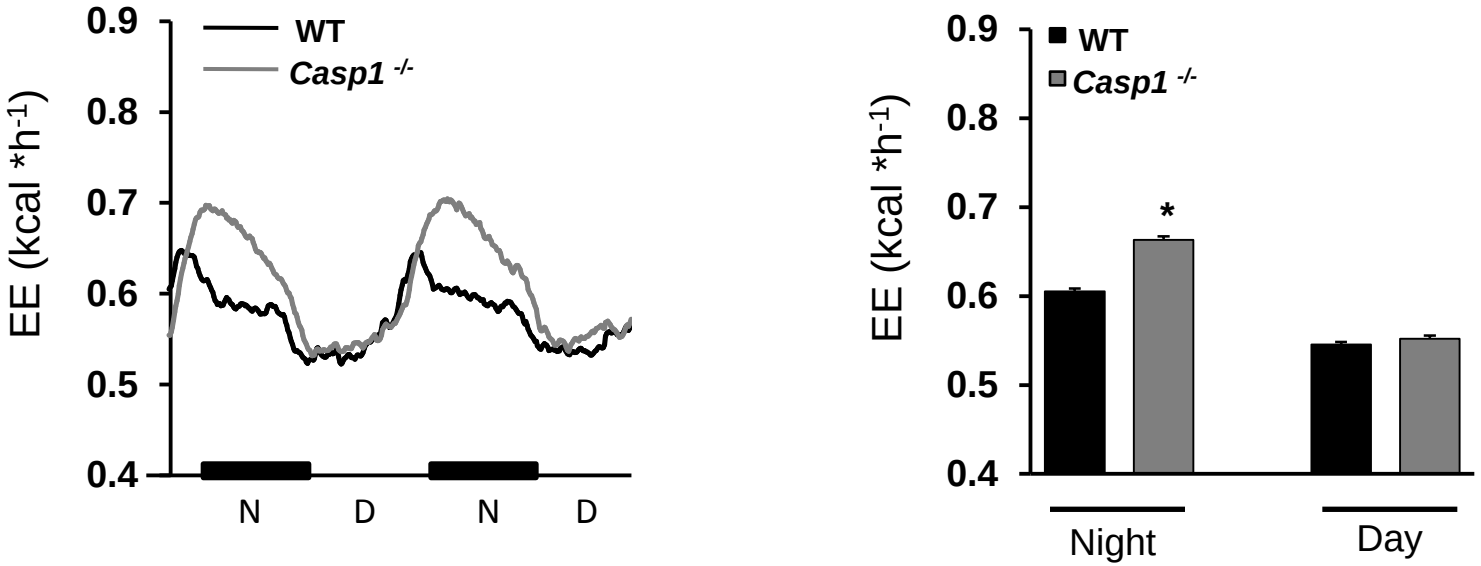
Food intake and intestinal absorption







Energy expenditure is enhanced in the absence of caspase-1



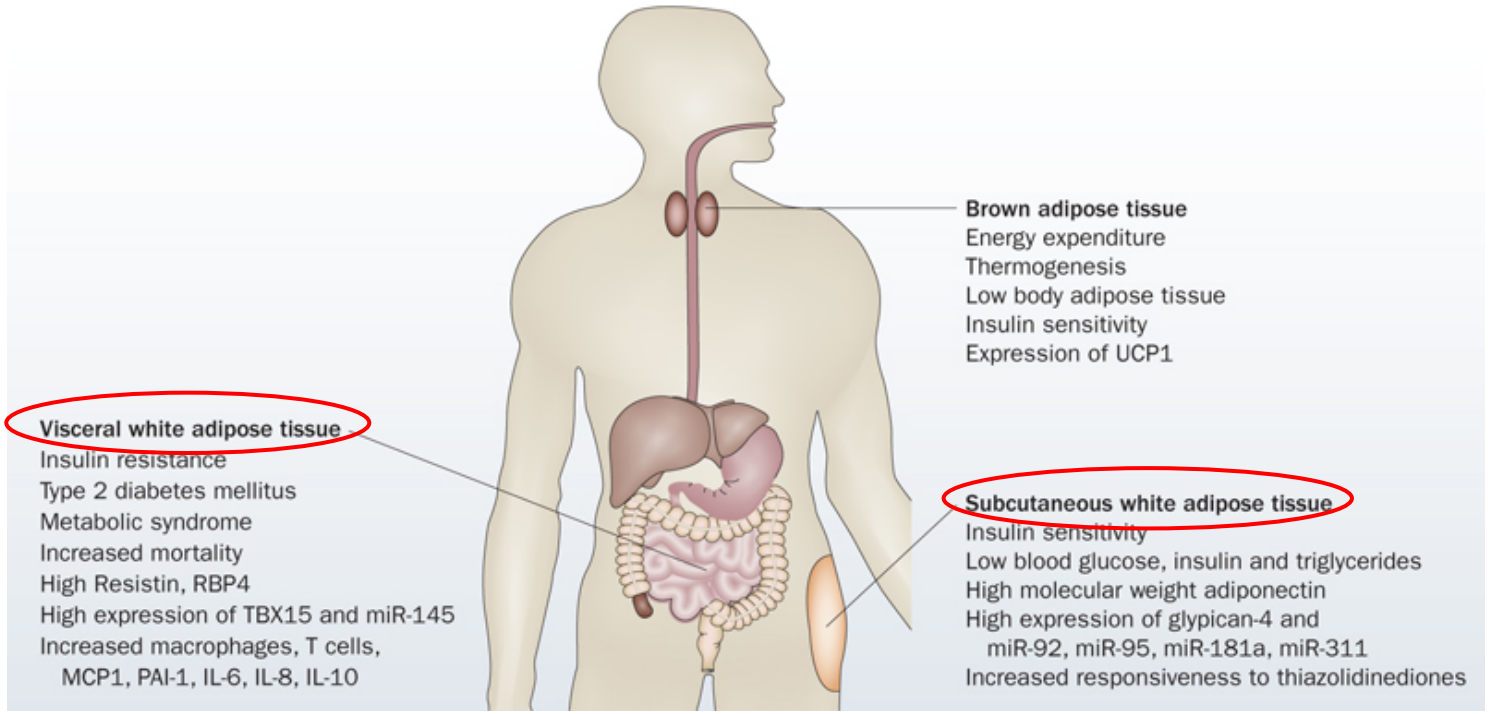
Note: overall activity levels were similar in both genotypes

Inhibition/absence of caspase-1

- No change in food intake or intestinal absorption
- Enhanced energy expenditure

Therapeutic target in the treatment of obesity and insulin resistance?

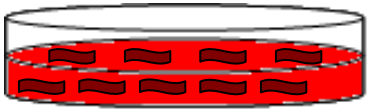
The inflammasome and caspase-1 in human adipose tissue



Tran, T. T. & Kahn, C. R. (2010) Transplantation of adipose tissue and stem cells: role in metabolism and disease *Nat. Rev. Endocrinol.*

The location is important: Increased visceral adipose tissue is associated with adverse health risks including insulin resistance, type 2 diabetes mellitus, dyslipidemia, hypertension, atherosclerosis and hepatic steatosis.

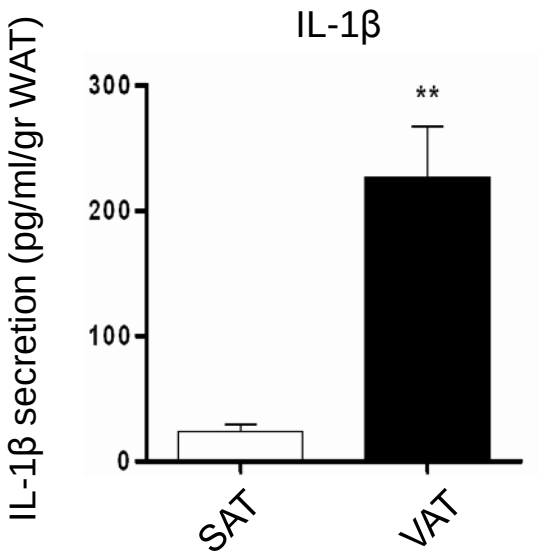
IL-1β secretion by human VAT vs. SAT ?

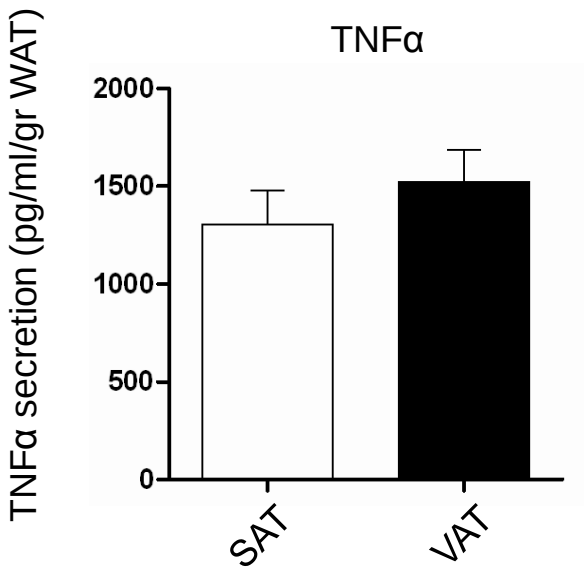


Ex-vivo: adipose tissue explant culture (24 hrs)

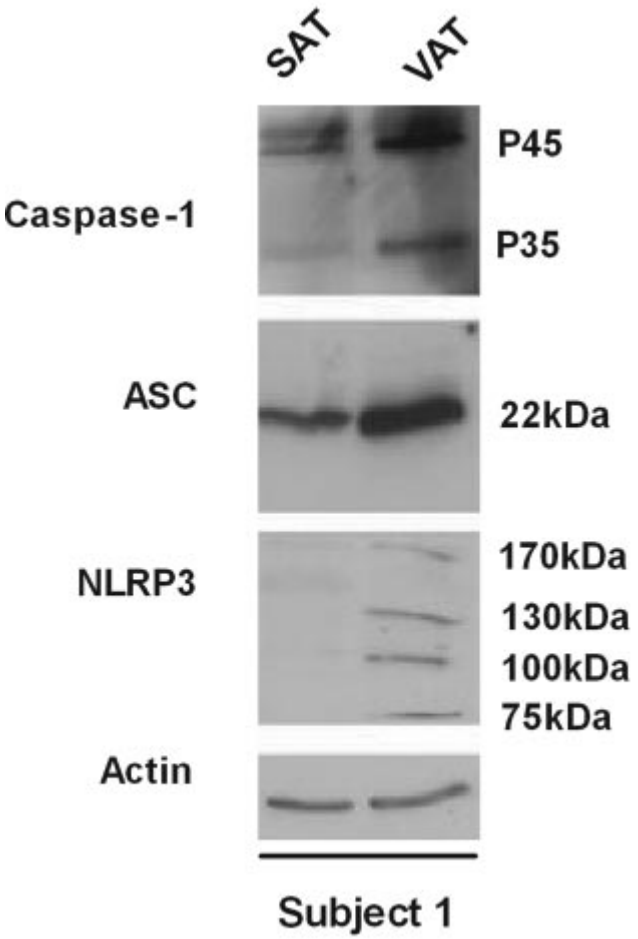
From five mildly obese subjects

(BMI: 25-28 kg/m²; aged 40-60 yrs)

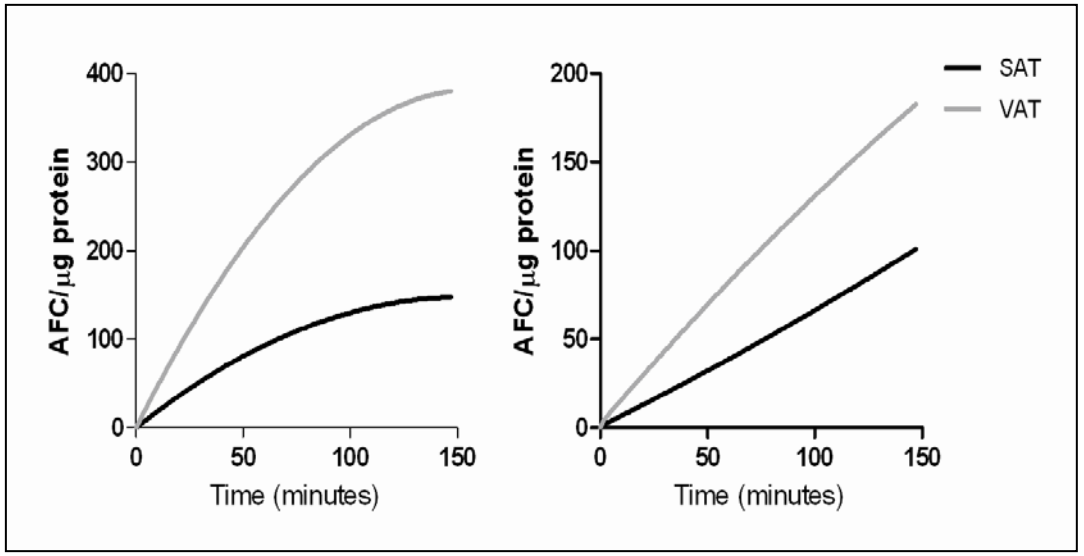




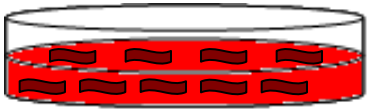
Caspase-1 activity is enhanced in human VAT compared to SAT



caspase-1 activity assay



Inhibition of caspase-1 specifically inhibits IL-1β production by VAT

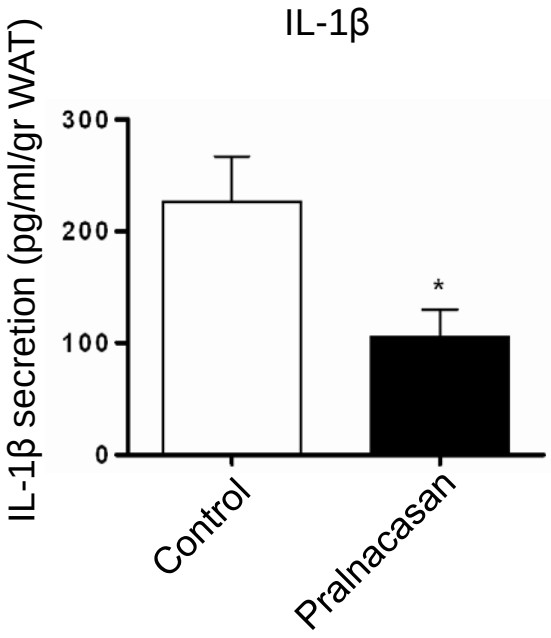


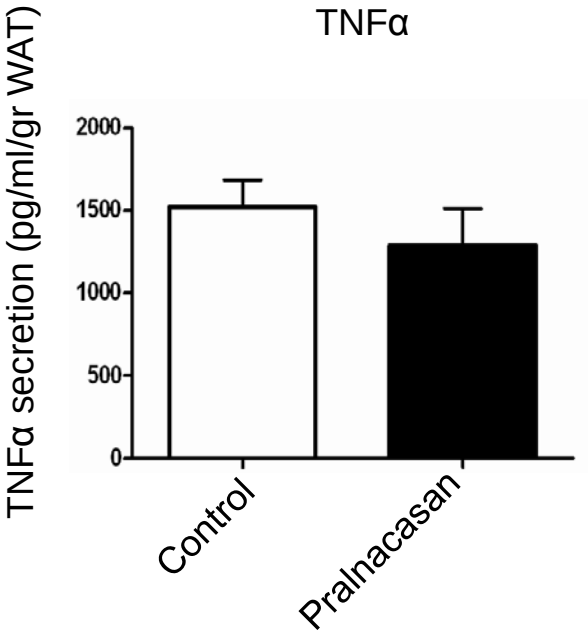
Ex-vivo: AT explant culture (24 hrs)

+ or – caspase-1 inhibitor Pralnacasan

From five mildly obese subjects

(BMI: 25-28 kg/m^2; aged 40-60 yrs)





Summary

- Caspase-1 is activated in adipose tissue of obese and insulin resistant animals leading to increased levels of IL-1β in adipose tissue

- Absence of caspase-1 protects against the development of diet-induced obesity and insulin resistance

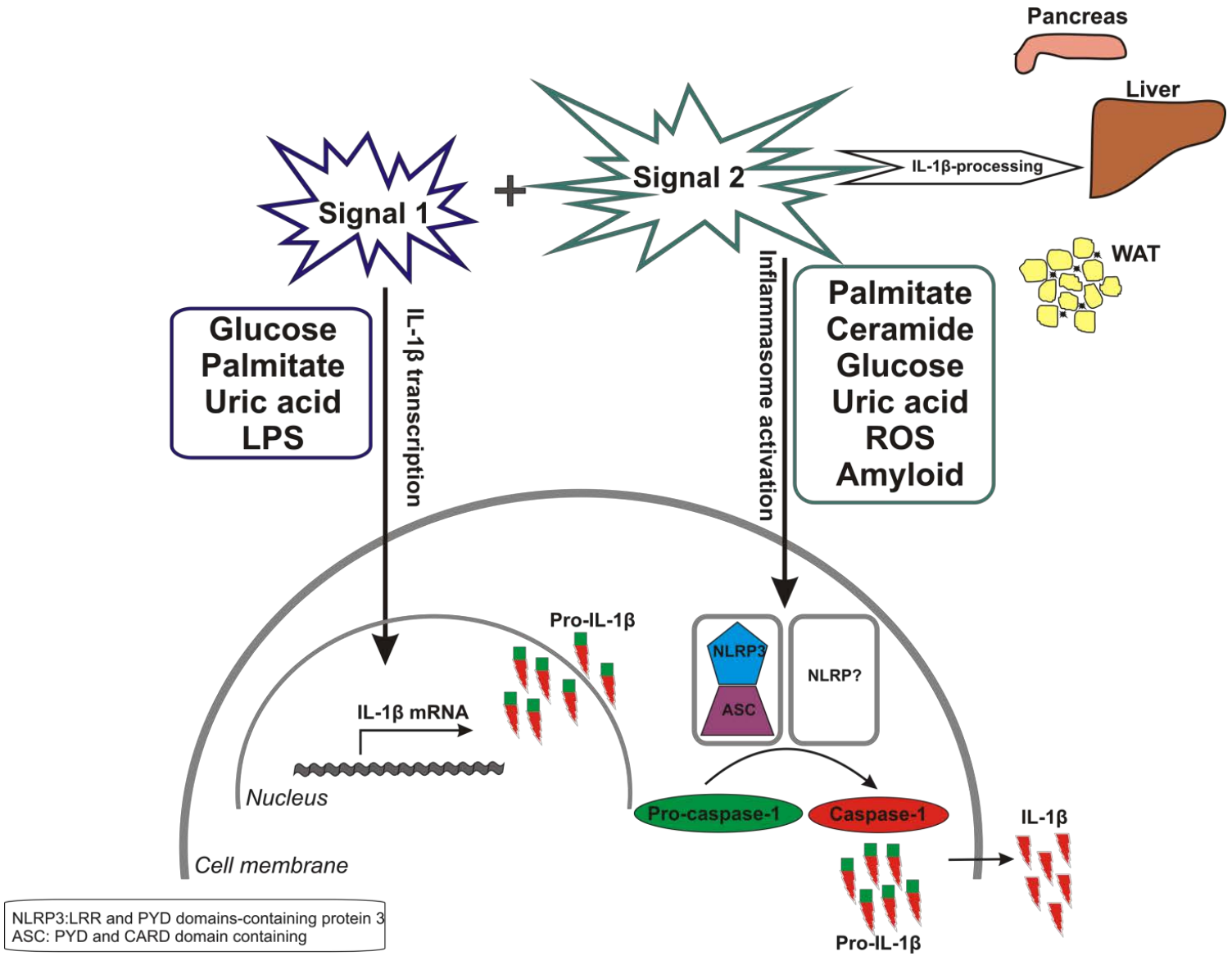
- Inhibition of caspase-1 in obese animals improves insulin sensitivity and limits weight gain

- Caspase-1-/- animals display enhanced levels of energy expenditure

- Visceral adipose tissue of mildly obese individuals is characterized by enhanced caspase-1 activity levels and higher production of IL-1β as compared to subcutaneous adipose tissue

Future perspective

Identification of potential triggers of inflammasome activation



Conclusion

Inflammasome-mediated caspase-1-activity represents an attractive therapeutic target in the treatment of obesity-induced insulin resistance

Acknowledgements

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-Tim Koenen
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