Obesity-induced inflammation as a driver of metabolic disease

Focus on white adipose tissue

Rinke Stienstra

10th of June 2021

Radboudumc

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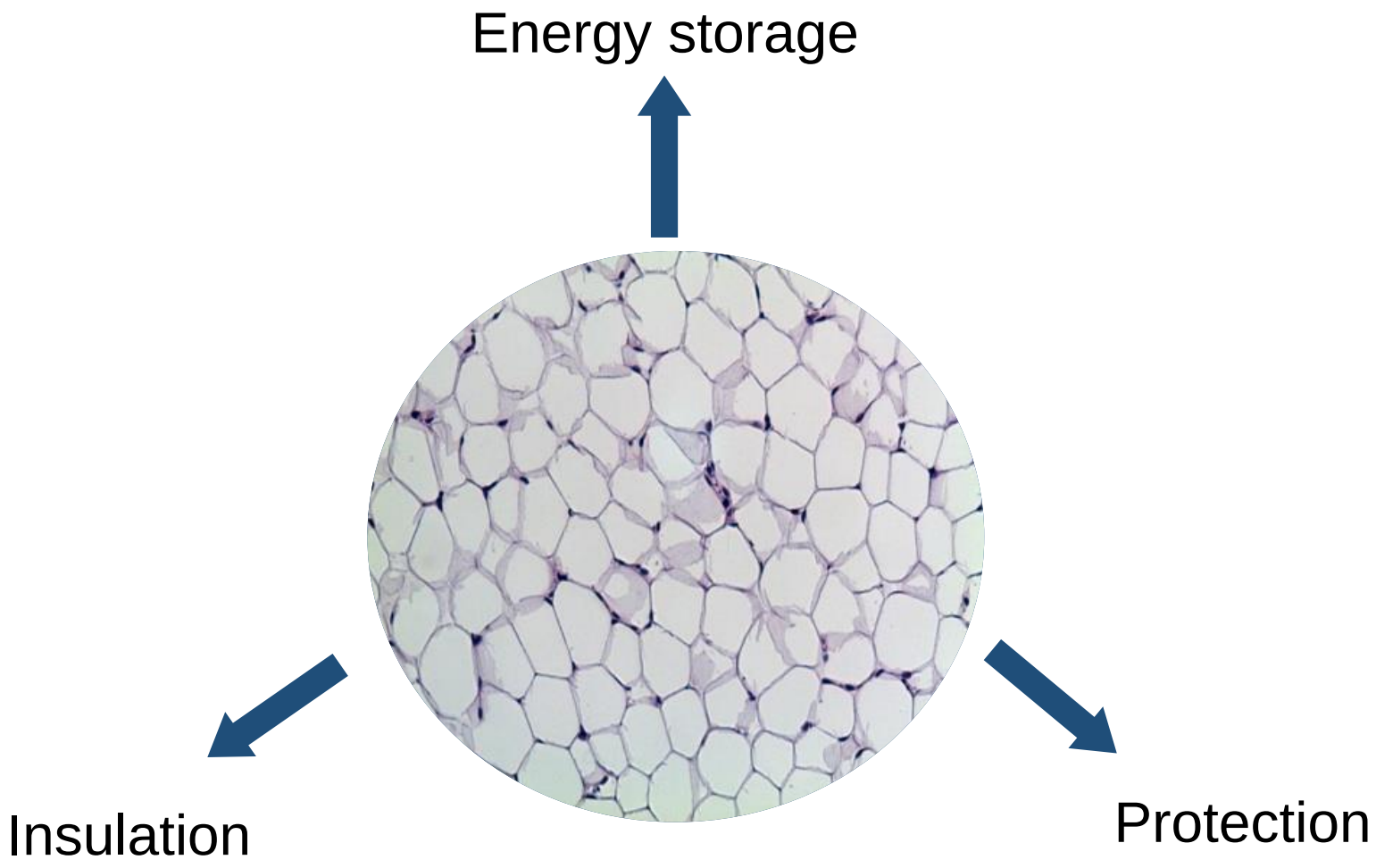
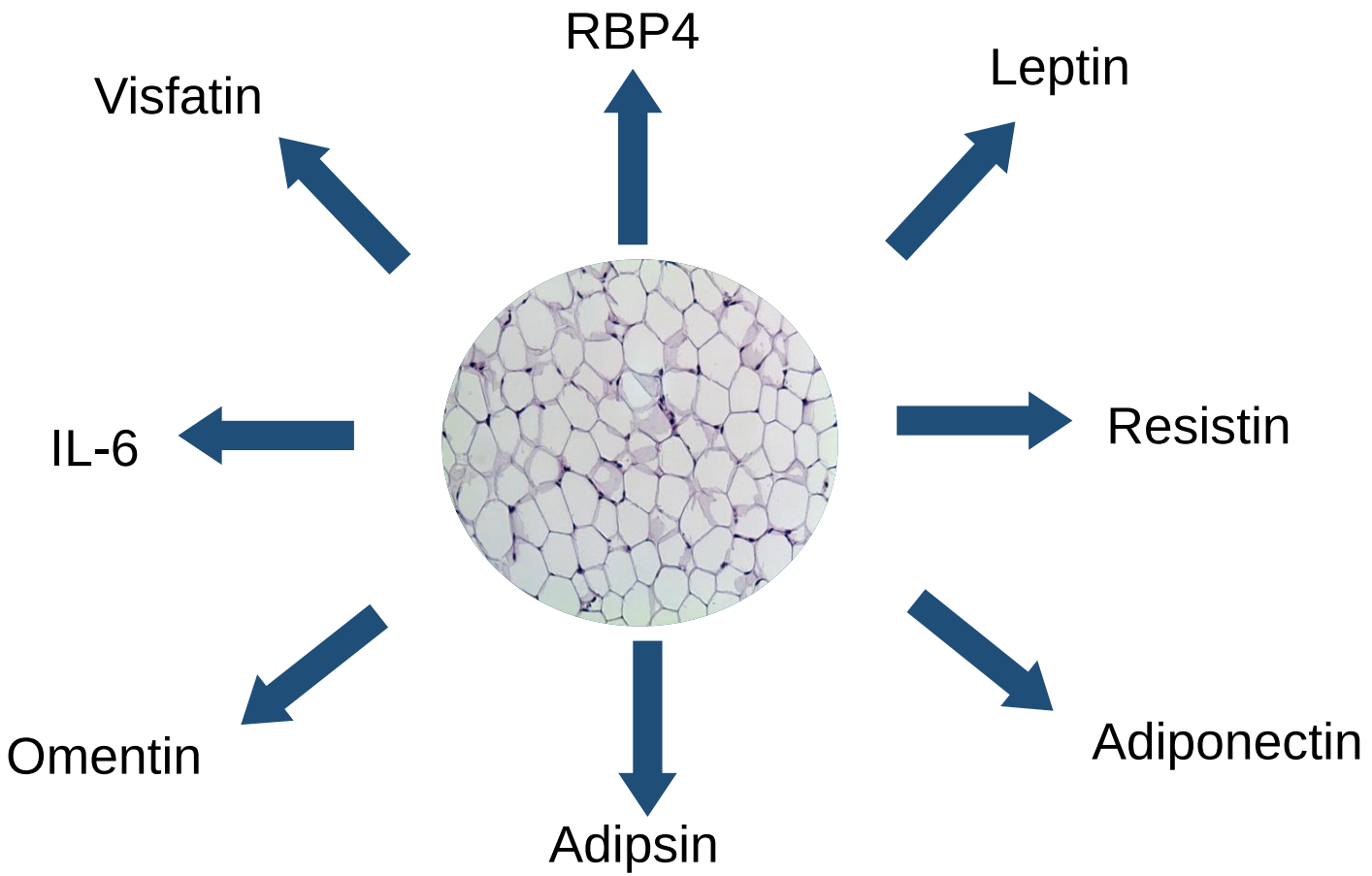
For quality of life

Obesity, the adipose tissue and type 2 diabetes



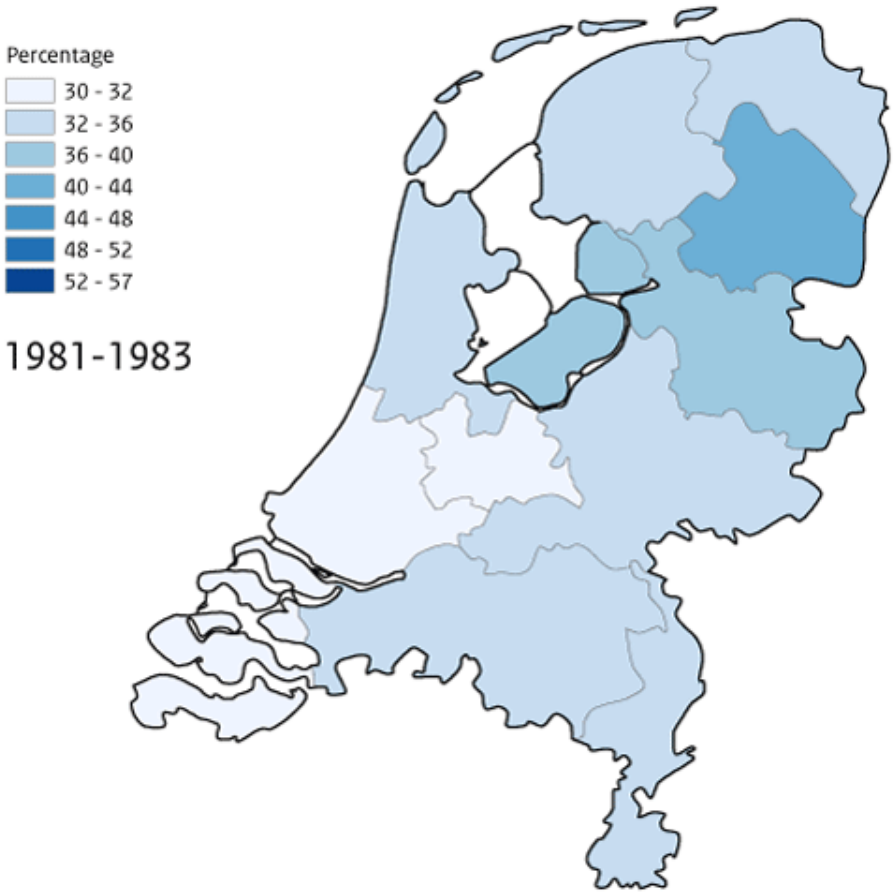
Adipose tissue as an endocrine organ

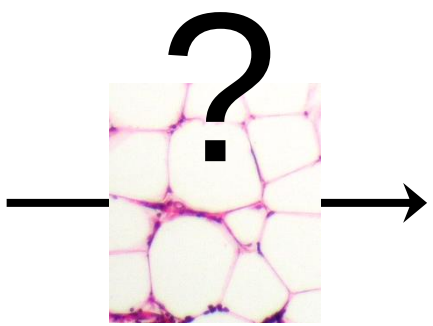
secretion of a wide variety of 'adipokines'



Autocrine, paracrine, and endocrine functions related to energy homeostasis, insulin sensitivity and various other processes

What functional changes occur in the adipose tissue?



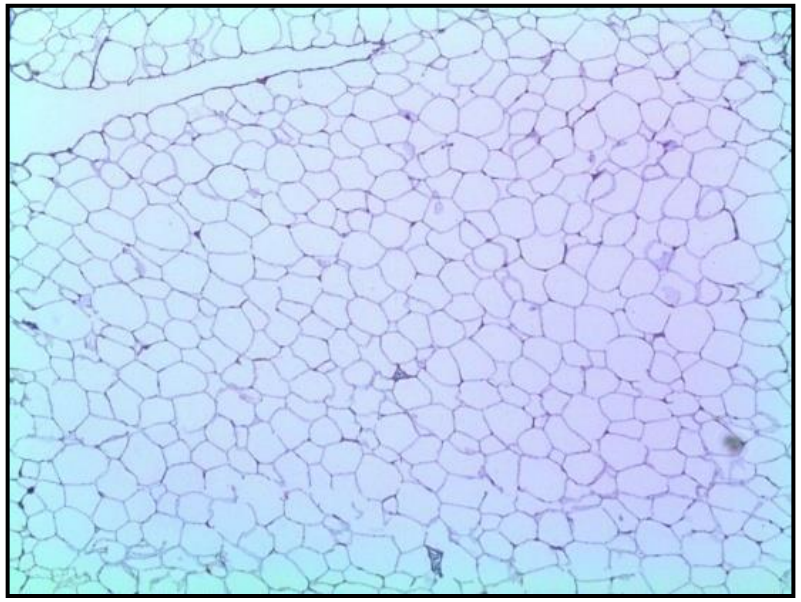


- <u>Type 2 diabetes</u>
- Atherosclerosis
- More infections
- Many others

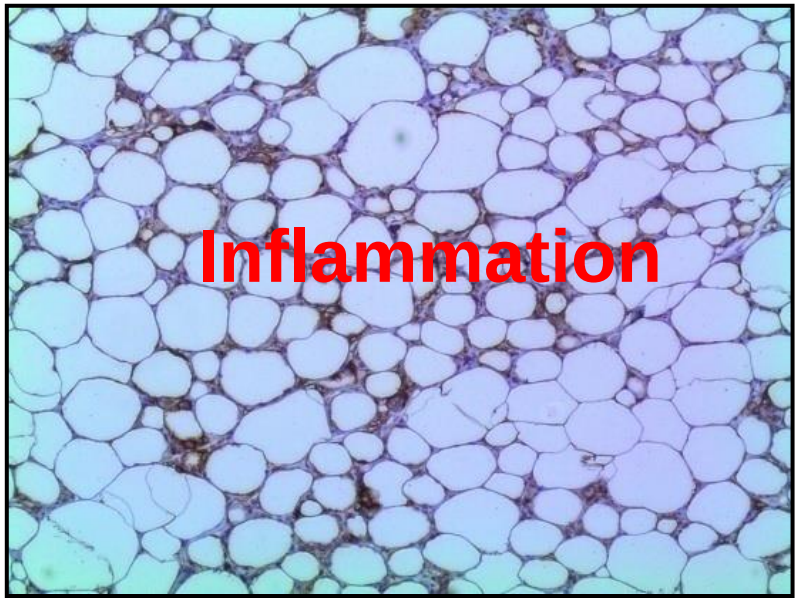
BMI >25 kg/m^2

Adipose tissue inflammation

Lean



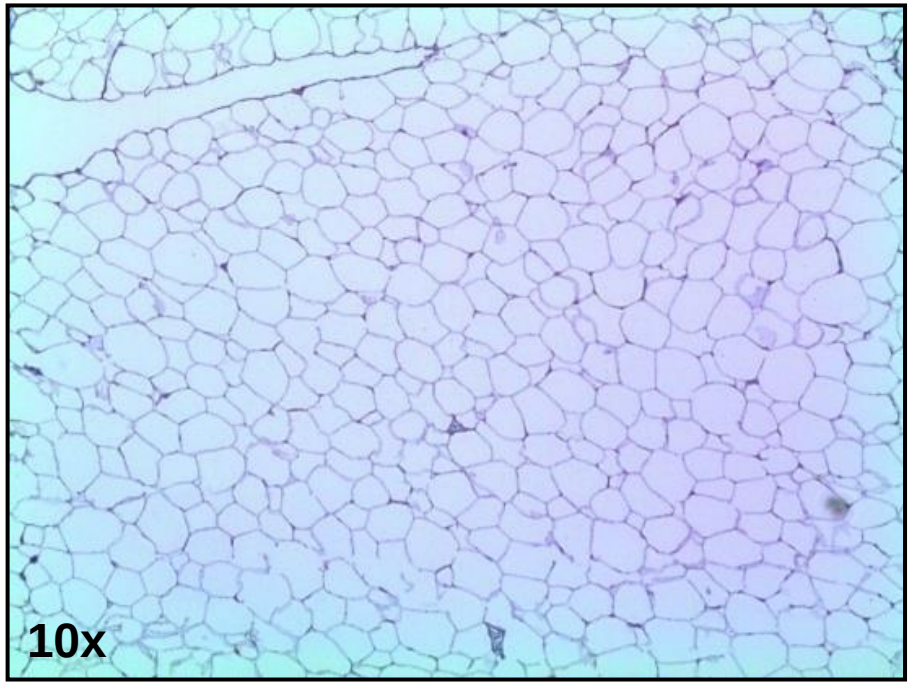
Obese



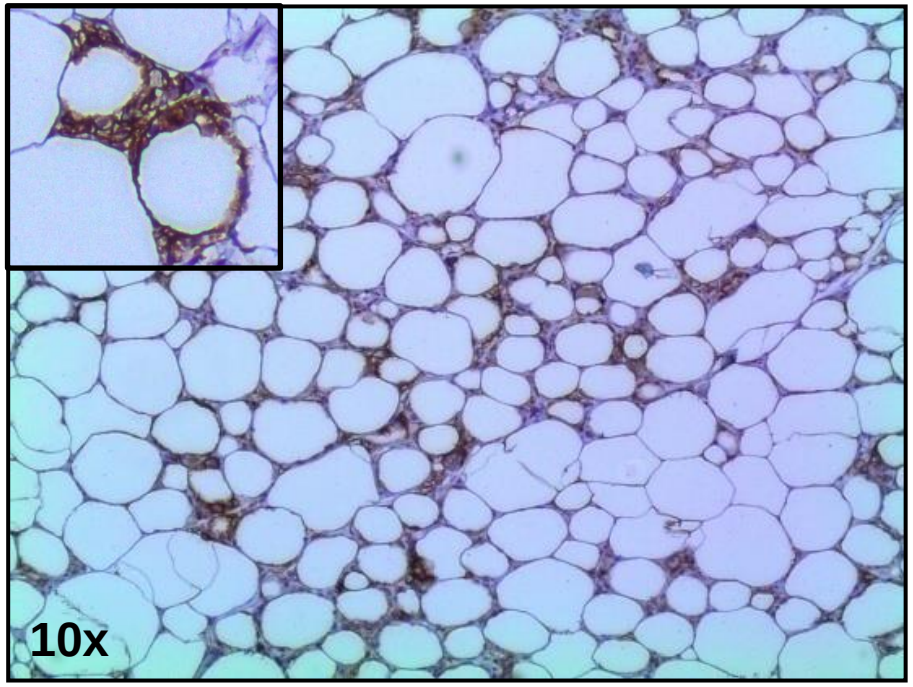
Impacts on the endocrine function of the adipose tissue

Adipose tissue macrophages promote a chronic low-grade inflammation during obesity

Lean



Obese



- ✓ **Adipocyte hypertrophy**
- ✓ **Macrophage influx**
- ✓ **Crown like structures**

Anti-inflammatory > Pro-inflammatory macrophages

Inflammation interferes with insulin sensitivity > resistance > diabetes

Topics

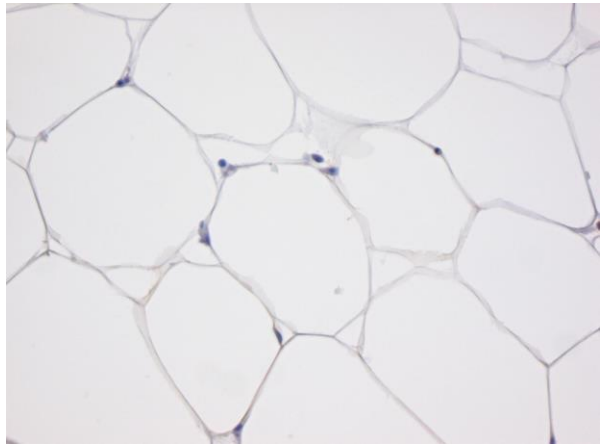
1. What is the importance of macrophage-mediated inflammation in human adipose tissue?

2. What are the mechanisms underlying the pro-inflammatory activation of adipose tissue ?

3. What can we do with this knowledge?

Importance of macrophages in human adipose tissue

Adipose tissue biopsies were collected in > 140 individuals (lean/obese/diabetes) and were characterized



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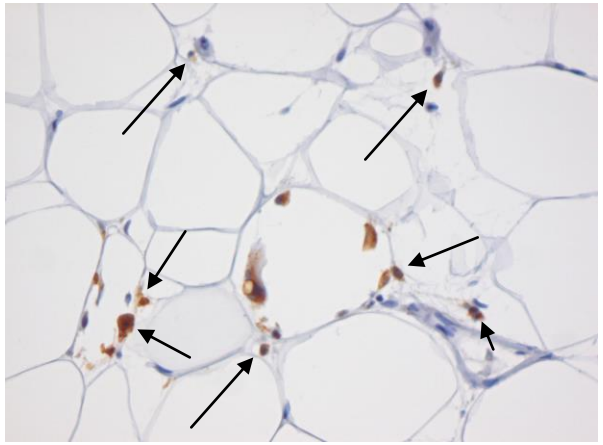

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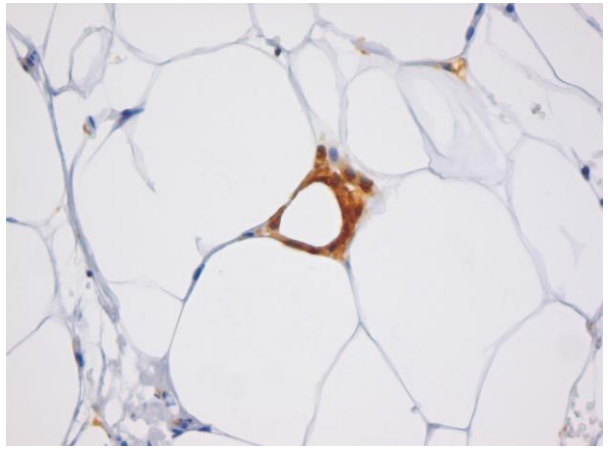
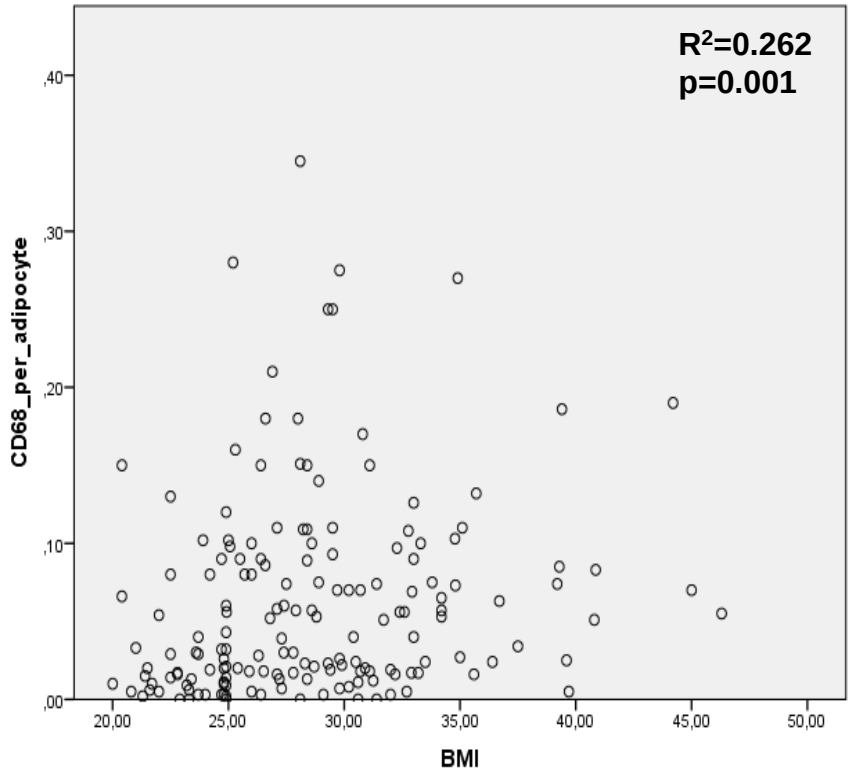


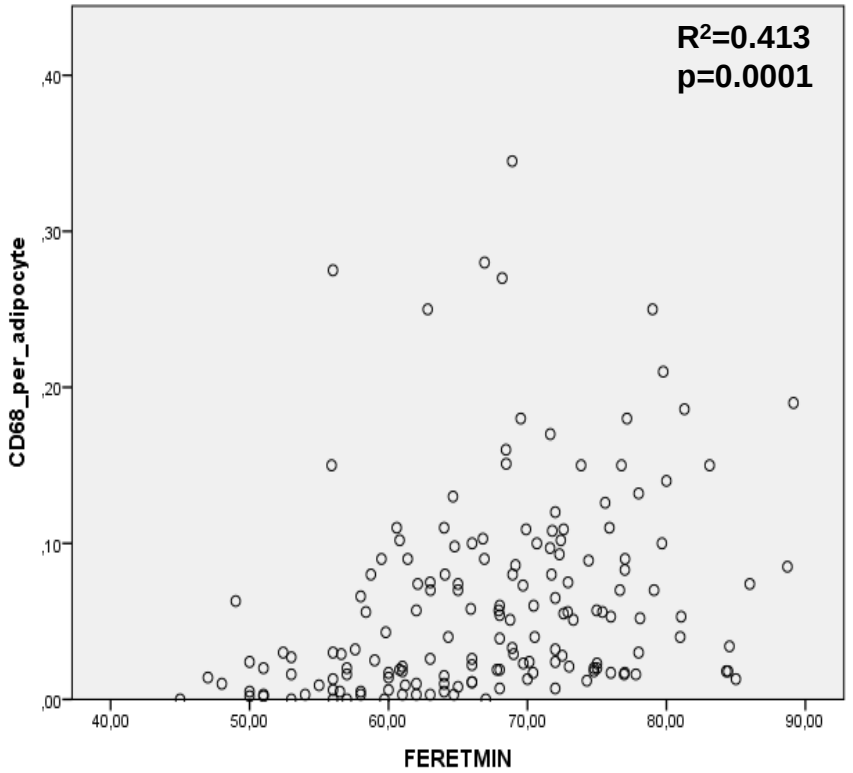
III

Variation between individuals

CD68 staining to visualize macrophages

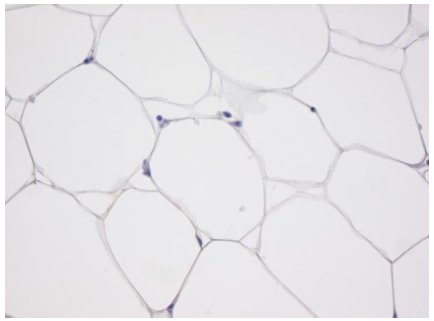
Adipose tissue characteristics





Positive association of the number of macrophages with BMI and adipocyte size

Adipose tissue inflammation in humans



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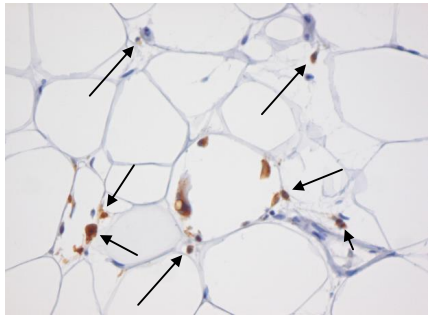

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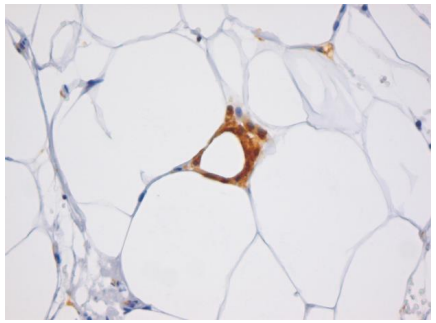


III

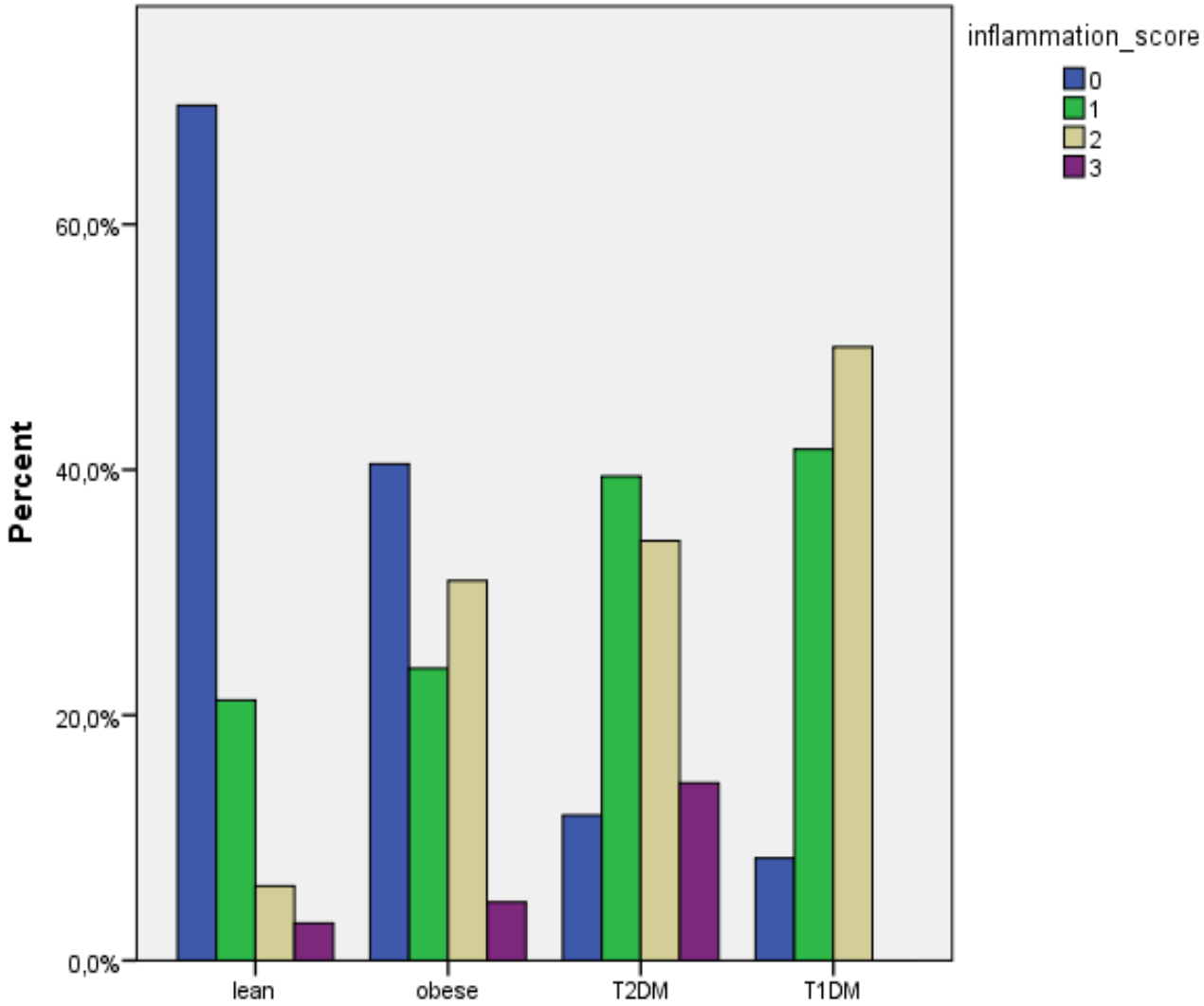
- Adipocyte size
- Macrophage influx
- Presence of crown like structures

Inflammatory score
+ 1 adipocyte size
+ 1 number of macrophages
+ 1 if CLS is present

Score of 0= no inflammation
Score of 3= severe inflammation

Inflammatory score of the adipose tissue

Inflammatory score
+ 1 adipocyte size
+ 1 number of macrophages
+ 1 if CLS is present

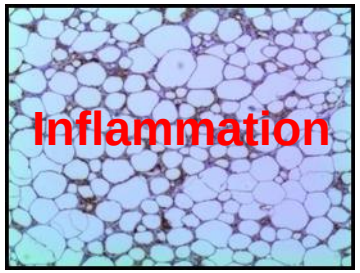


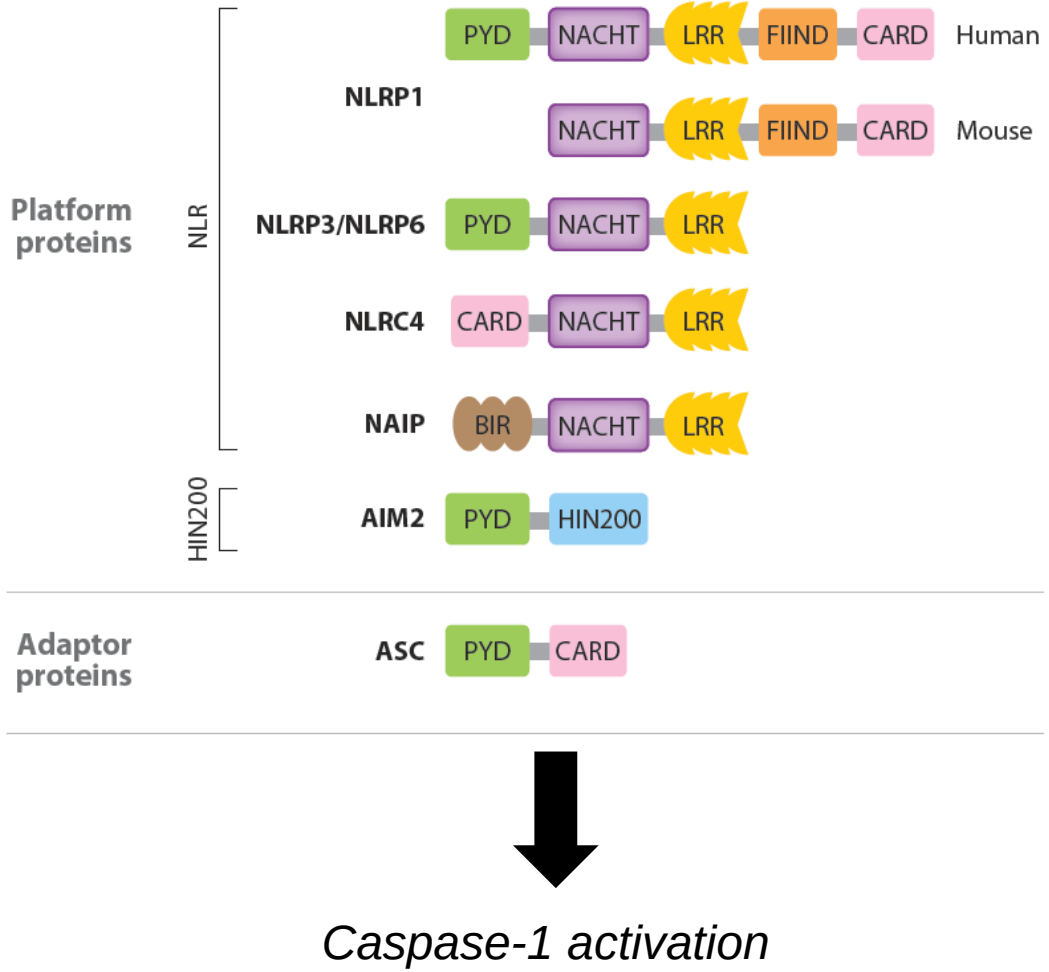
What are the mechanisms underlying the pro-inflammatory activation of adipose tissue ?

The Inflammasome

Innate immunity > The Inflammasome

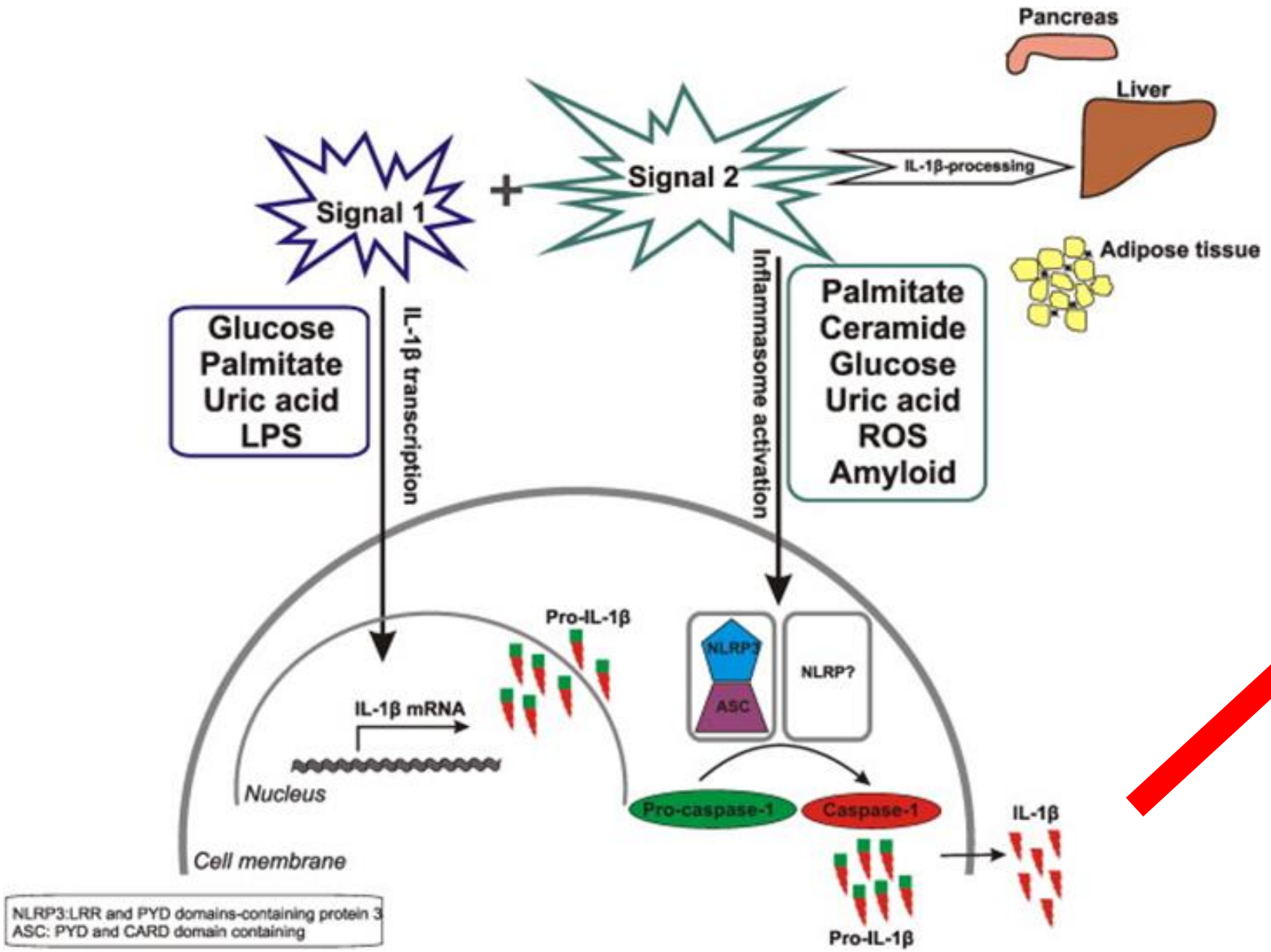
Pathogen Recognition through Pathogen Recognition Receptors > The cornerstone of Innate Immunity





Annu. Rev. Cell Dev. Biol. 2012. 28:7.1–7.25

The Inflammasome > caspase-1 > Interleukin 1β release

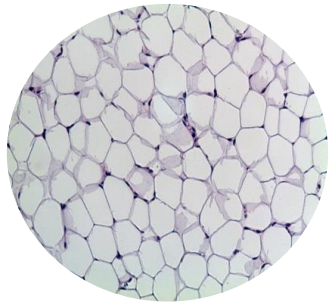


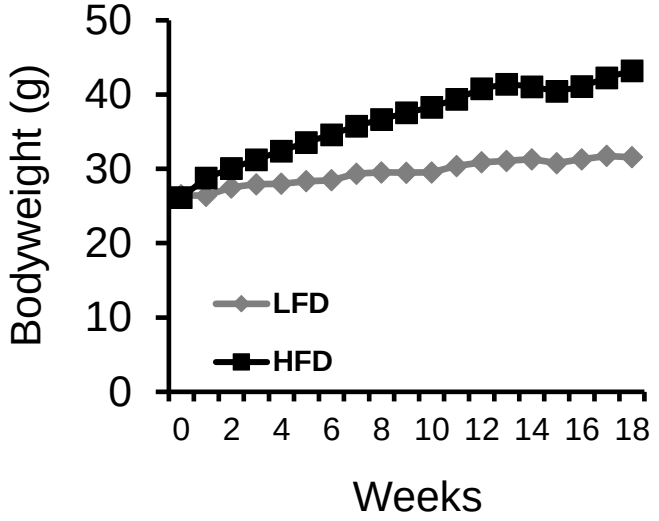
IL-1β promotes insulin resistance

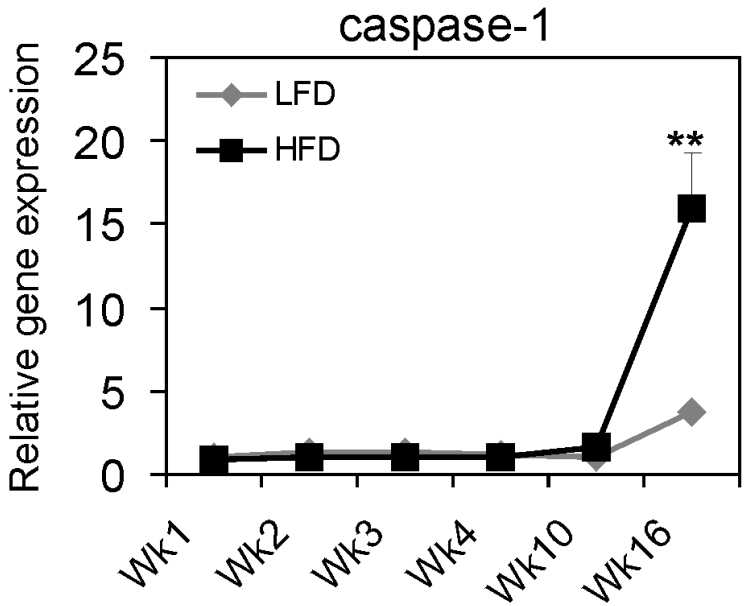
Caspase-1 is activated in adipose tissue during the development of obesity

Low fat diet (10 energy% from fat)

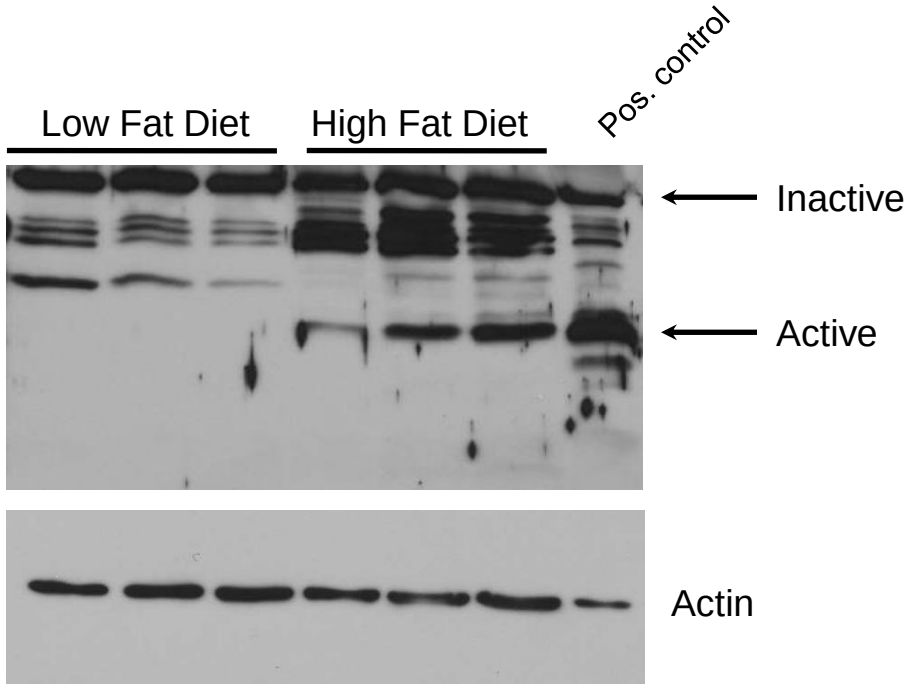
High fat diet (45 energy% from fat)

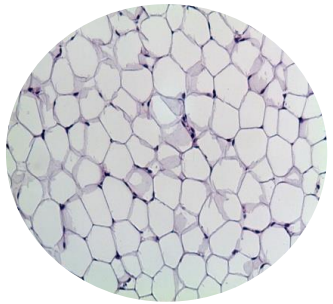


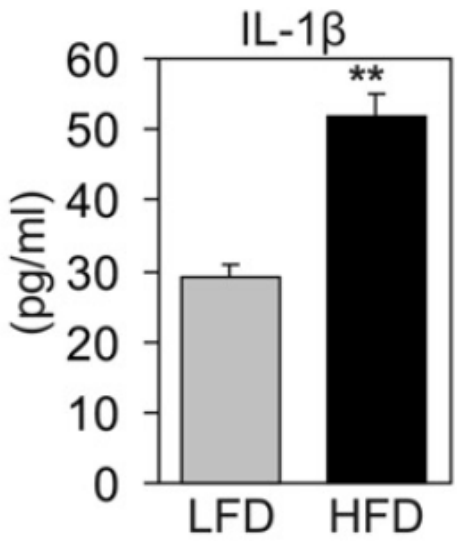




Caspase-1 activation in adipose tissue enhances cytokine production

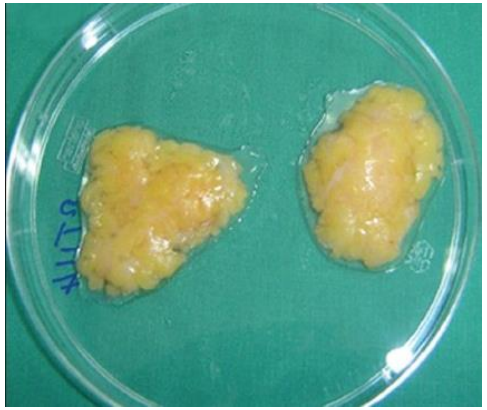


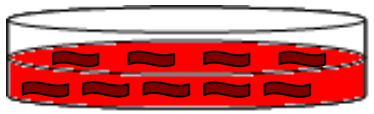




Insulin resistance

Is the inflammasome present in human adipose tissue?

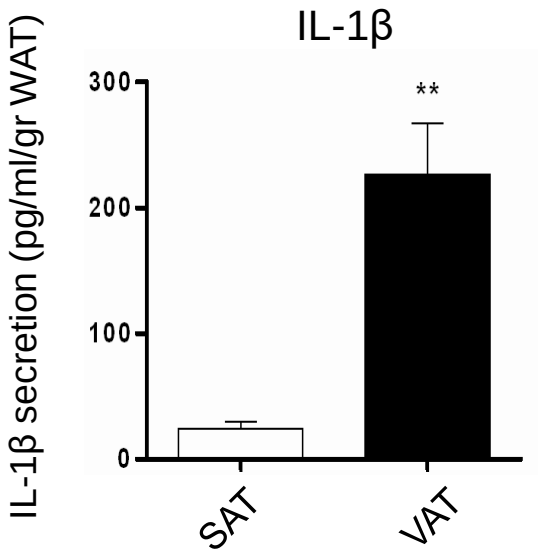




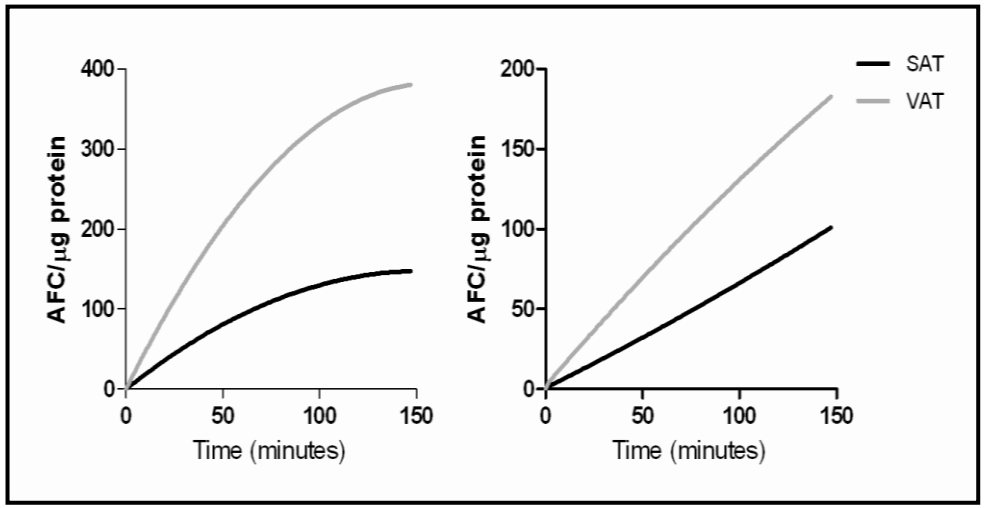
Ex-vivo: adipose tissue explant culture

From five mildly obese subjects

(BMI: 25-28 kg/m²; aged 40-60 yrs)

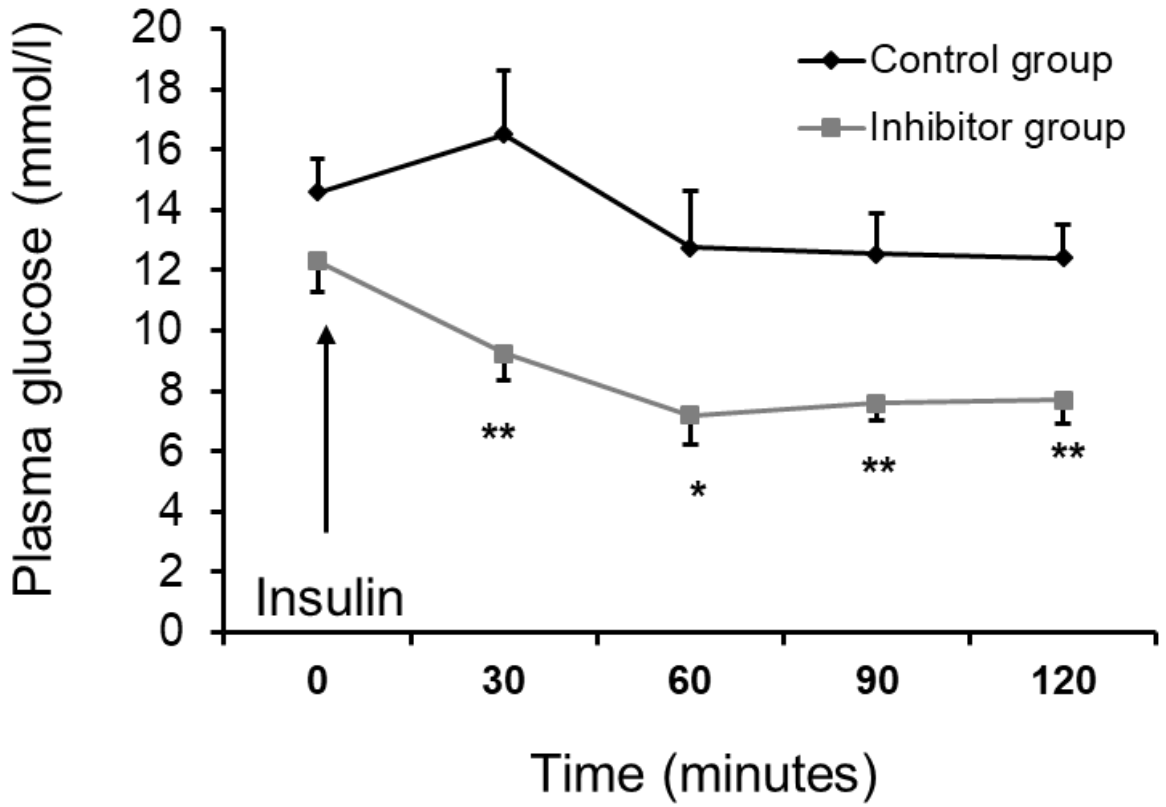


Caspase-1 activity assay



What can we do with this knowledge?

Insulin sensitivity is robustly improved in obese animals after caspase-1 inhibition



Anti-inflammatory approaches in humans

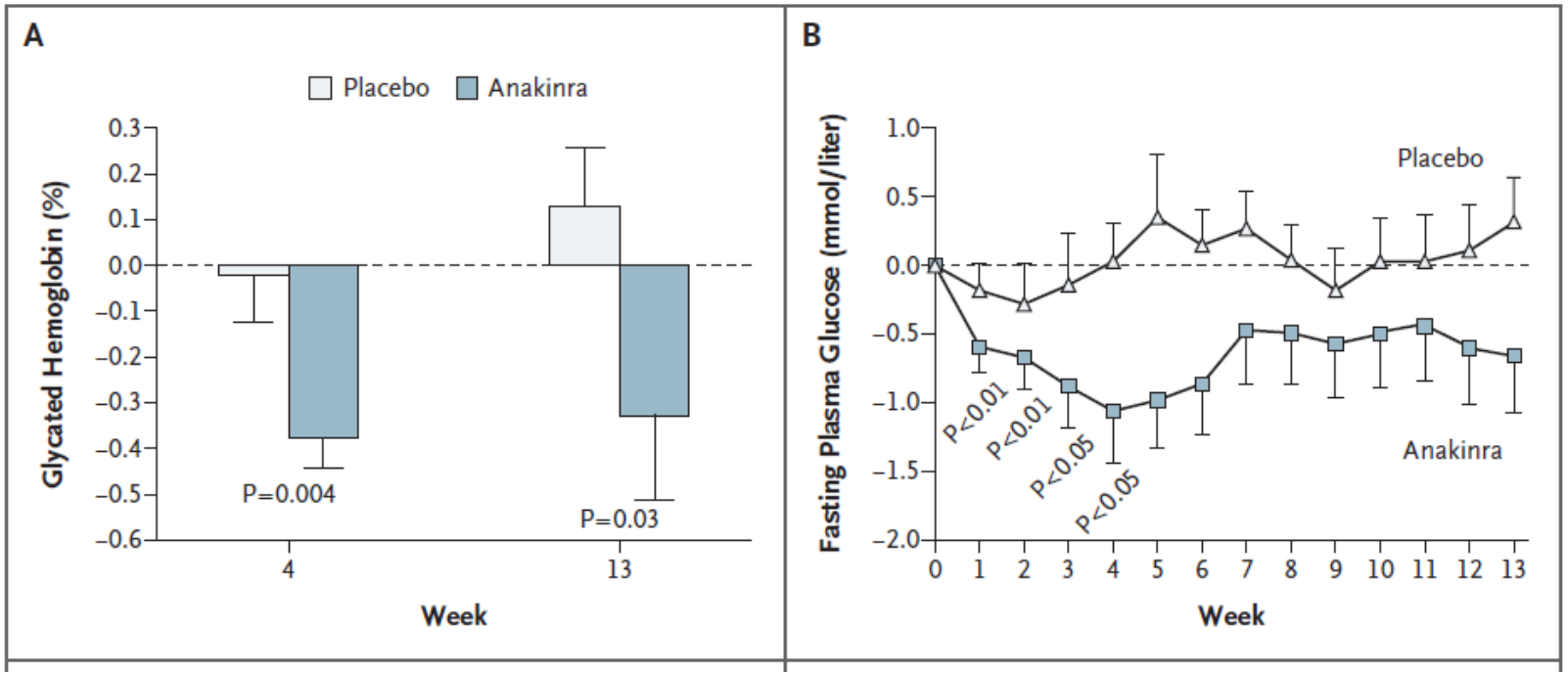
Proof of principle using IL-1 blockage

The NEW ENGLAND JOURNAL of MEDICINE

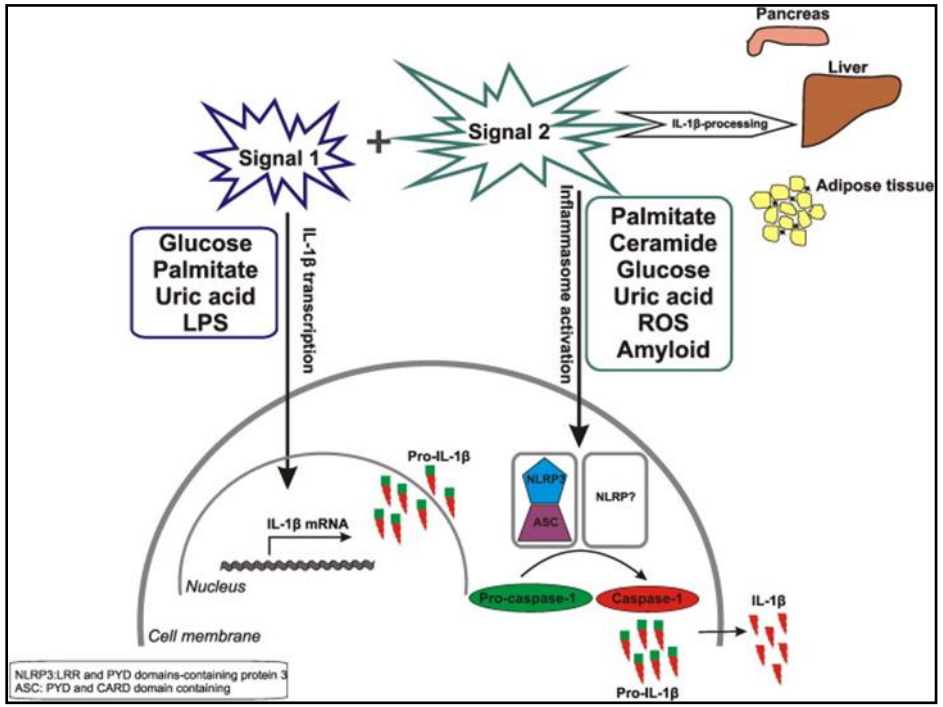
ORIGINAL ARTICLE

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.



Inflammasome inhibition using nutritional approaches

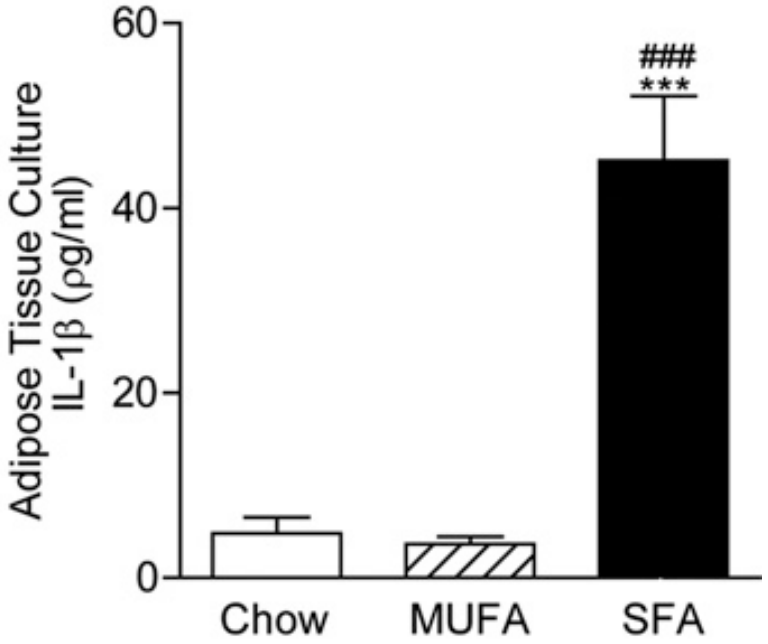


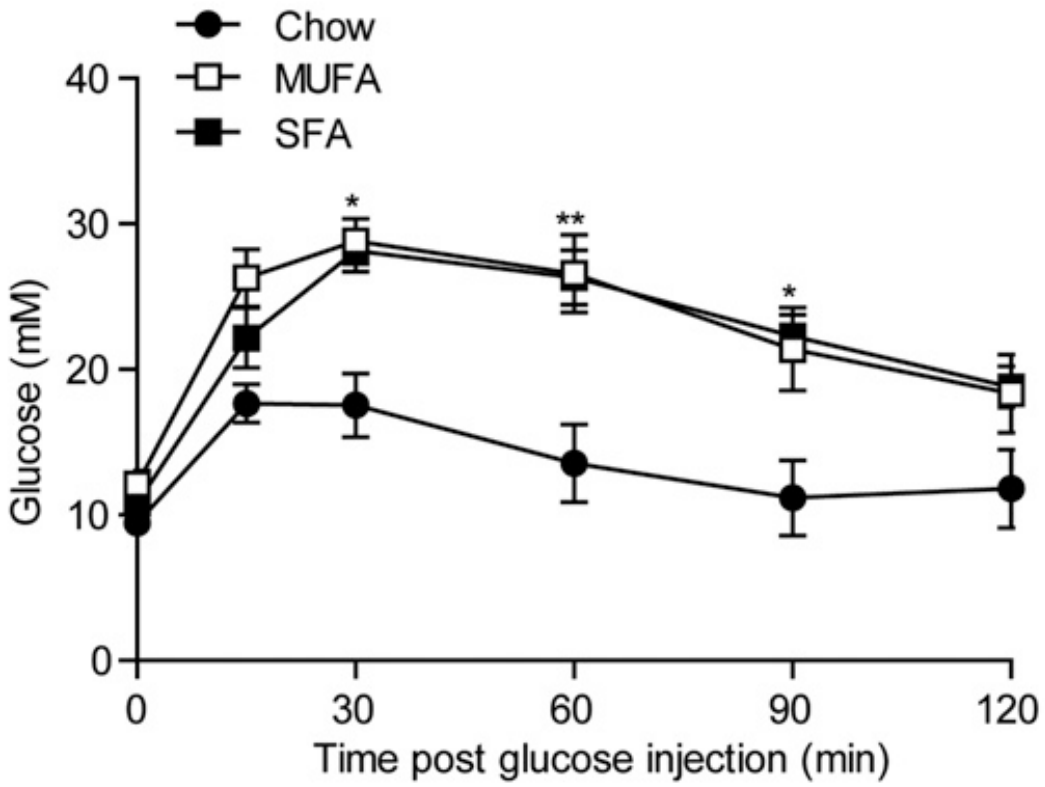
- ✓ Lower concentrations of nutrients that serve as potent activators of the inflammasome
- ✓ Inflammasome is activated by saturated fatty acids

Replacing saturated fatty acids with monounsaturated fatty acids

Monounsaturated Fatty Acid–Enriched High-Fat Diets Impede Adipose NLRP3 Inflammasome–Mediated IL-1β Secretion and Insulin Resistance Despite Obesity

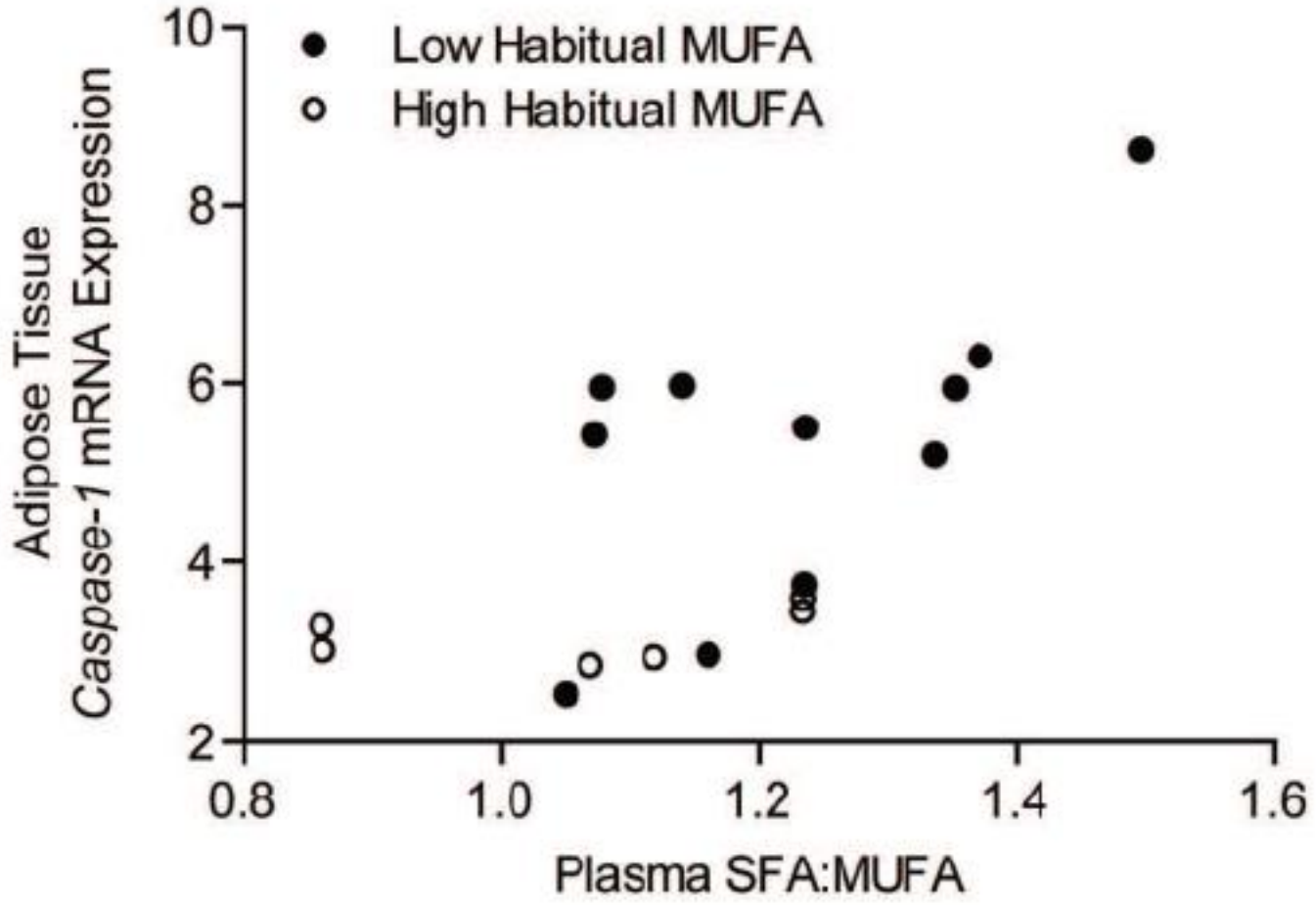
Diabetes 2015;64:2116–2128 | DOI: 10.2337/db14-1098





Higher plasma levels of MUFA are associated with a lower level of caspase-1 activation

Diabetes 2015;64:2116–2128 | DOI: 10.2337/db14-1098

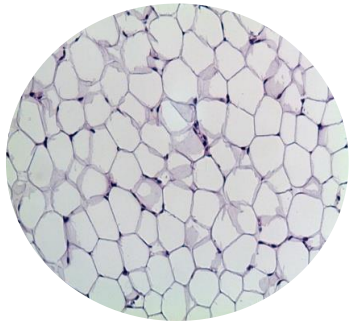


Correlation between caspase-1 and plasma SFA:MUFA ratio

Conclusions

- ❑ Adipose tissue inflammation drives metabolic complications during obesity
- ❑ Macrophages are key cells in obesity-induced inflammation, however adaptive immune cells also contribute.....
- ❑ Mechanistically, the inflammasome is a key driver of adipose tissue inflammation
- ❑ Blocking inflammation appears to mitigate obesity-associated metabolic complications

To consider.....



- ✓ Do all obese individuals develop a chronic inflammatory state of the adipose tissue?
- ✓ Healthy versus unhealthy obese phenotypes?
- ✓ Reversibility of the chronic inflammatory state of the adipose tissue?
- ✓ How do frequent fluctuations in bodyweight impact on adipose tissue inflammation?

Acknowledgements

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Diabetes Fonds

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Research Foundation

NWO

EFSD European Foundation for the Study of Diabetes