

Obesity-induced inflammation as a driver of metabolic disease

Focus on white adipose tissue

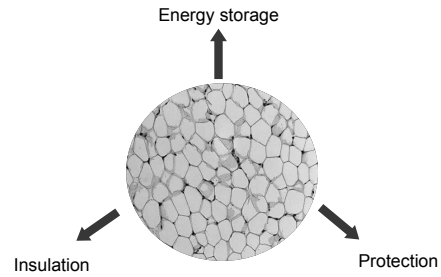
Rinke Stienstra

10th of June 2021

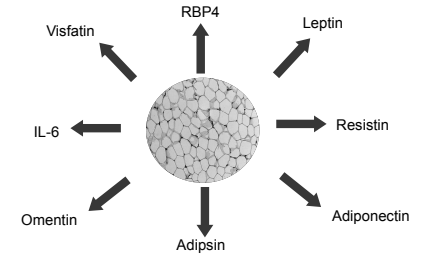
Radboudumc



Obesity, the adipose tissue and type 2 diabetes

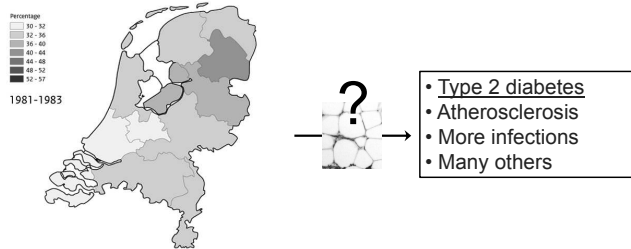


Adipose tissue as an endocrine organ secretion of a wide variety of 'adipokines'

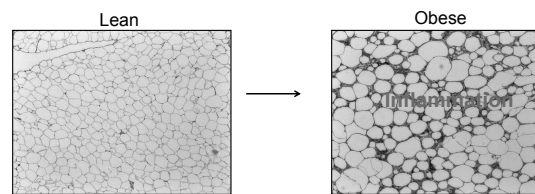


Autocrine, paracrine, and endocrine functions related to energy homeostasis, insulin sensitivity and various other processes

What functional changes occur in the adipose tissue?

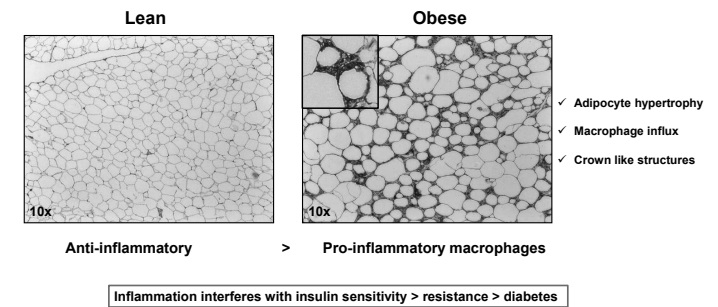


Adipose tissue inflammation



Impacts on the endocrine function of the adipose tissue

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

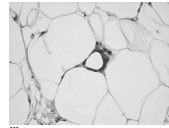
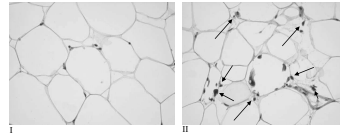


Topics

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

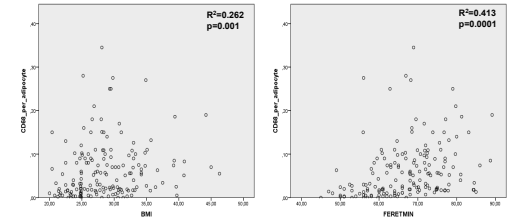
Adipose tissue biopsies were collected in > 140 individuals (lean/obese/diabetes) and were characterized



Variation between individuals

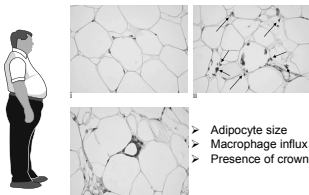
CD68 staining to visualize macrophages

Adipose tissue characteristics



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

Adipose tissue inflammation in humans



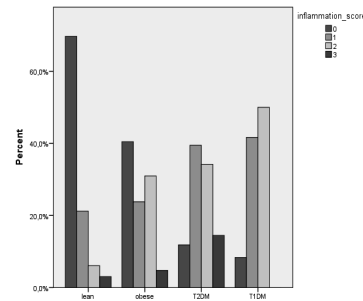
- Adipocyte size
- Macrophage influx
- Presence of crown like structures

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

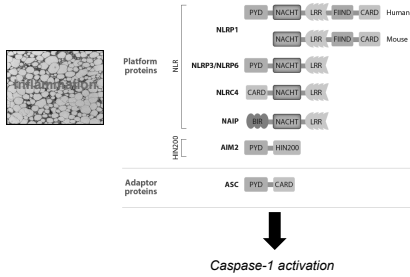
- + 1 adipocyte size
- + 1 number of macrophages
- + 1 if CLS is present

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

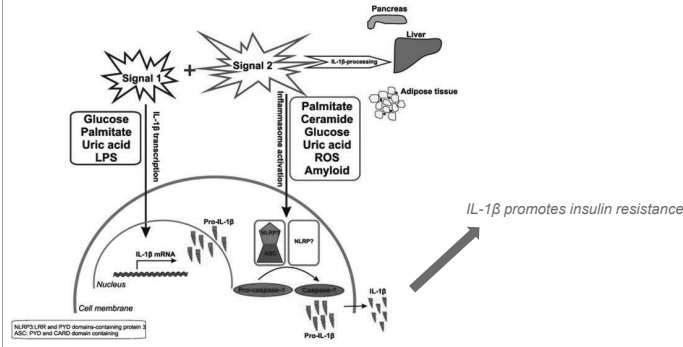
The Inflammasome

Innate immunity > The Inflammasome

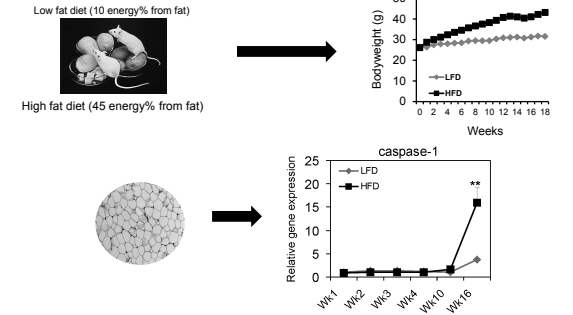
Pathogen Recognition through Pathogen Recognition Receptors > The cornerstone of Innate Immunity



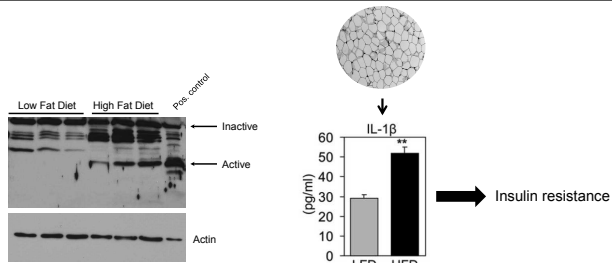
The Inflammasome > caspase-1 > Interleukin 1β release



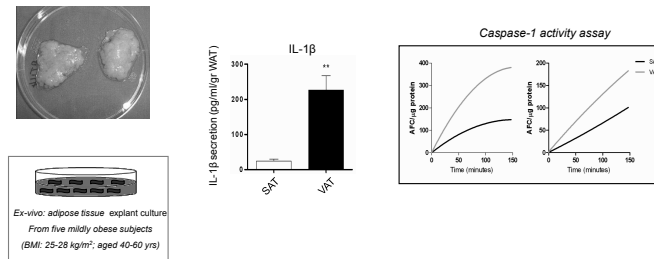
Caspase-1 is activated in adipose tissue during the development of obesity



Caspase-1 activation in adipose tissue enhances cytokine production

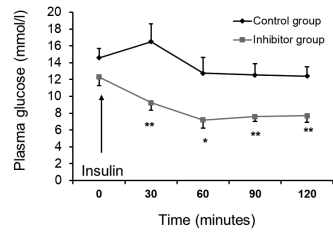


Is the inflammasome present in human adipose tissue?



What can we do with this knowledge?

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



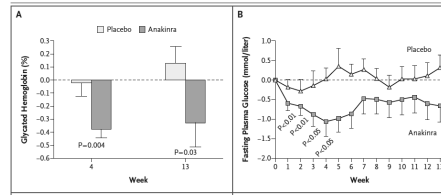
Anti-inflammatory approaches in humans

Proof of principle using IL-1 blockade

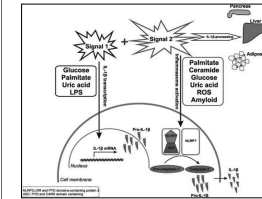
THE NEW ENGLAND JOURNAL OF MEDICINE ORIGINAL ARTICLE

Interleukin-1-Receptor Antagonist in Type 2 Diabetes Mellitus

Claus M. Larsen, M.D., Mirjam Fadenbach, M.D., Allan Vaag, M.D., Ph.D., Aage Vølund, M.Sc., Jan A. Egholm, Ph.D., Burkhard Selten, Ph.D., Thomas Mandrup-Rousten, M.D., Ph.D., and Marc Y. Donath, M.D.



Inflammasome inhibition using nutritional approaches

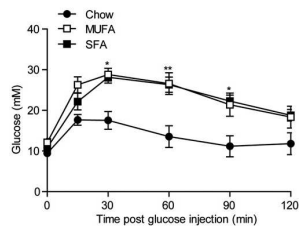
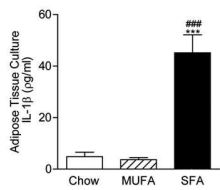


- ✓ Lower concentrations of nutrients that serve as potent activators of the inflammasome
- ✓ Inflammasome is activated by saturated fatty acids

Replacing saturated fatty acids with monounsaturated fatty acids

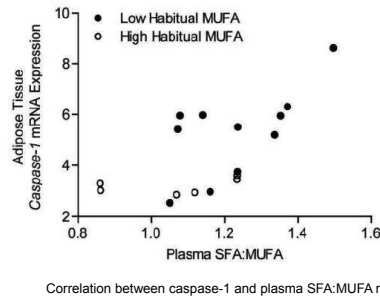
Monounsaturated Fatty Acid-Enriched High-Fat Diets Impede Adipose NLRP3 Inflammasome-Mediated IL-1β Secretion and Insulin Resistance Despite Obesity

Obesity 2015;64:2116-2128 | DOI: 10.2337/ob151086



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

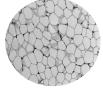
Obesity 2015;64:2116-2128 | DOI: 10.2337/ob151086



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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-Sander Kersten

Diabetes
Fonds

Dutch Diabetes
Research Foundation



EFSD
European Foundation for the Study of Diabetes