

# Mechanisms driving adipose tissue mass growth

-the role of fat cell size and local inflammation



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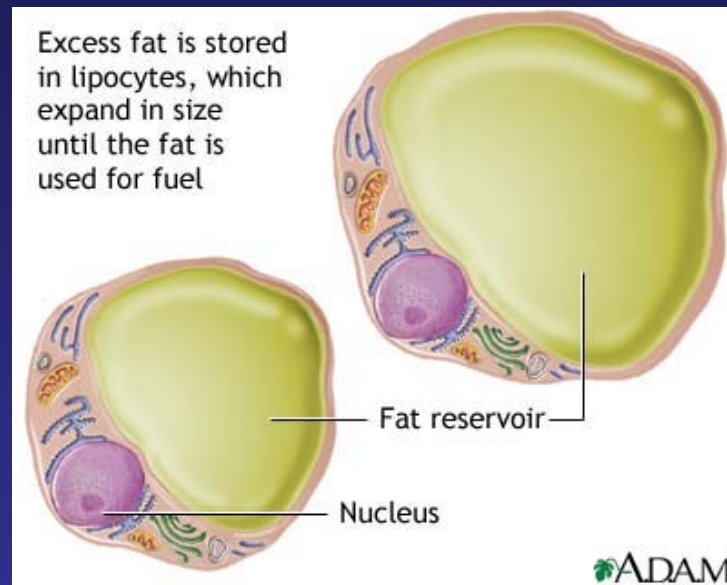
Karolinska University Hospital, Huddinge

Stockholm

Sweden

# Obesity development-the old view

Once generated in childhood, fat cells are retained and alter in size according to weight changes Based on studies of fat cell size and number on prisoners before and after dietary induced weight change



# Obesity development-the new view

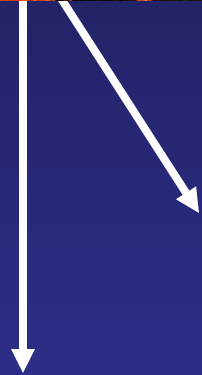
The growth of fat tissue is dependent on a constant renewal (adipogenesis) involving both cell growth (hypertrophy) and proliferation (hyperplasia)

*Why?.....*

# Strategy to establish cellular age by measuring the nuclear bomb test derived $^{14}\text{C}$ in DNA

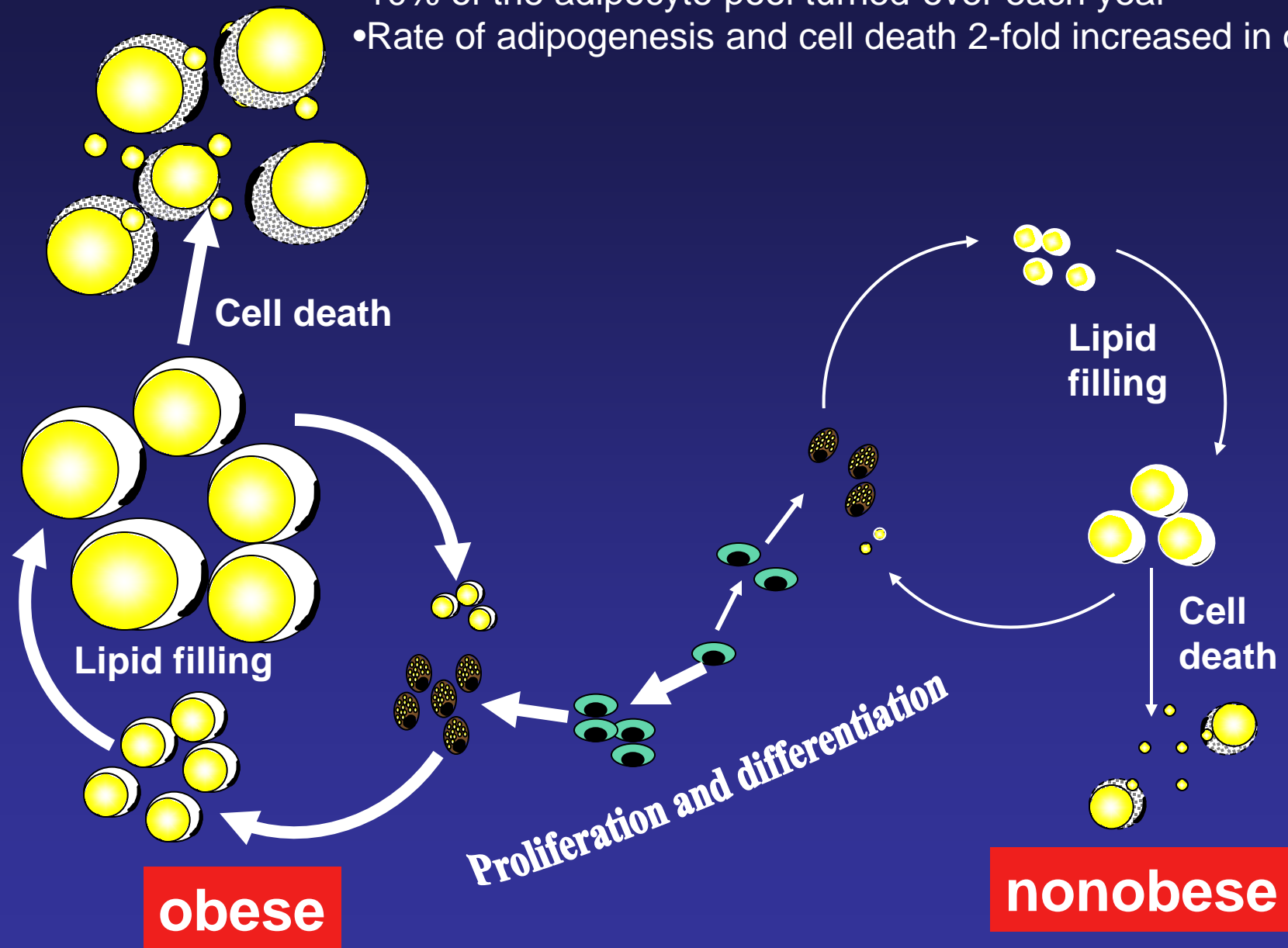


Cellular age ←  $^{14}\text{C}$  reading ←

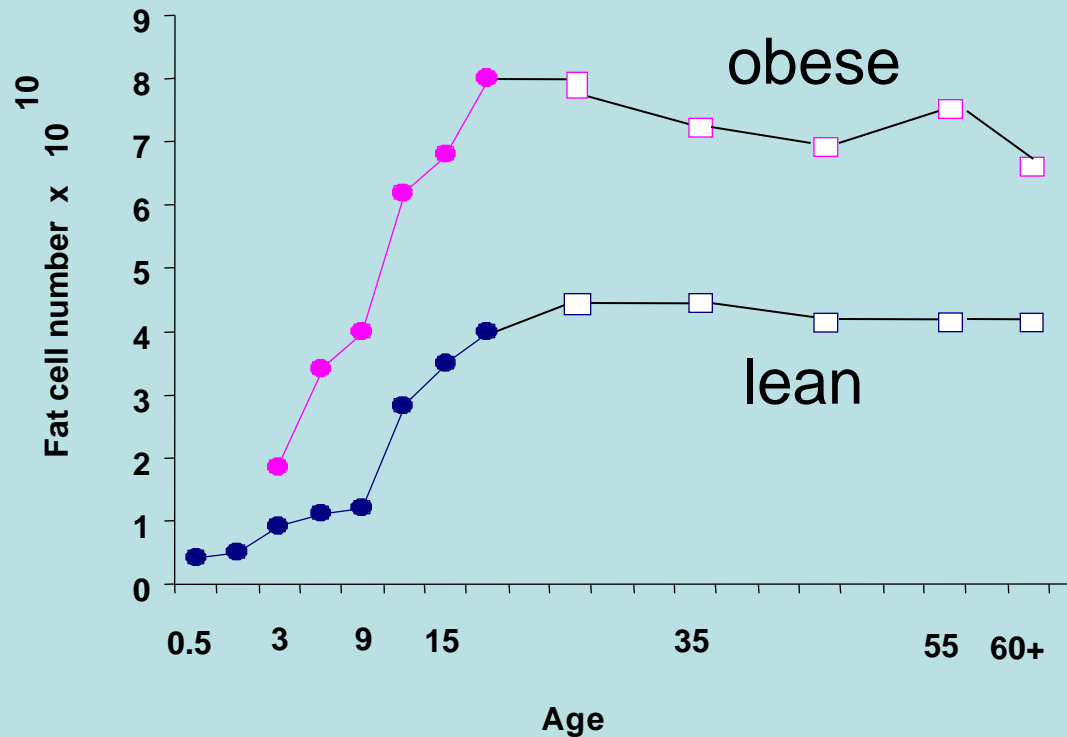


## Adipocyte turnover in adult humans

- 10% of the adipocyte pool turned-over each year
- Rate of adipogenesis and cell death 2-fold increased in obesity



# Constant fat cell number during ageing among adults



Children data from  
Knittle et al *JCI*  
63:239,1979

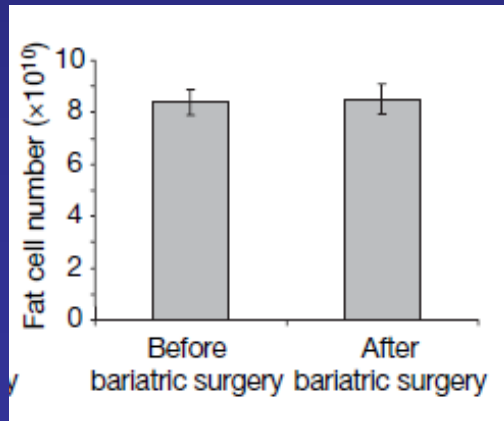
# Adipocyte turnover in adult humans

## Fat cell number is constant!

- **Constant fat cell number throughout adult life**

Spalding et al *Nature* 2008;453:783-7

- **What about weight loss?**



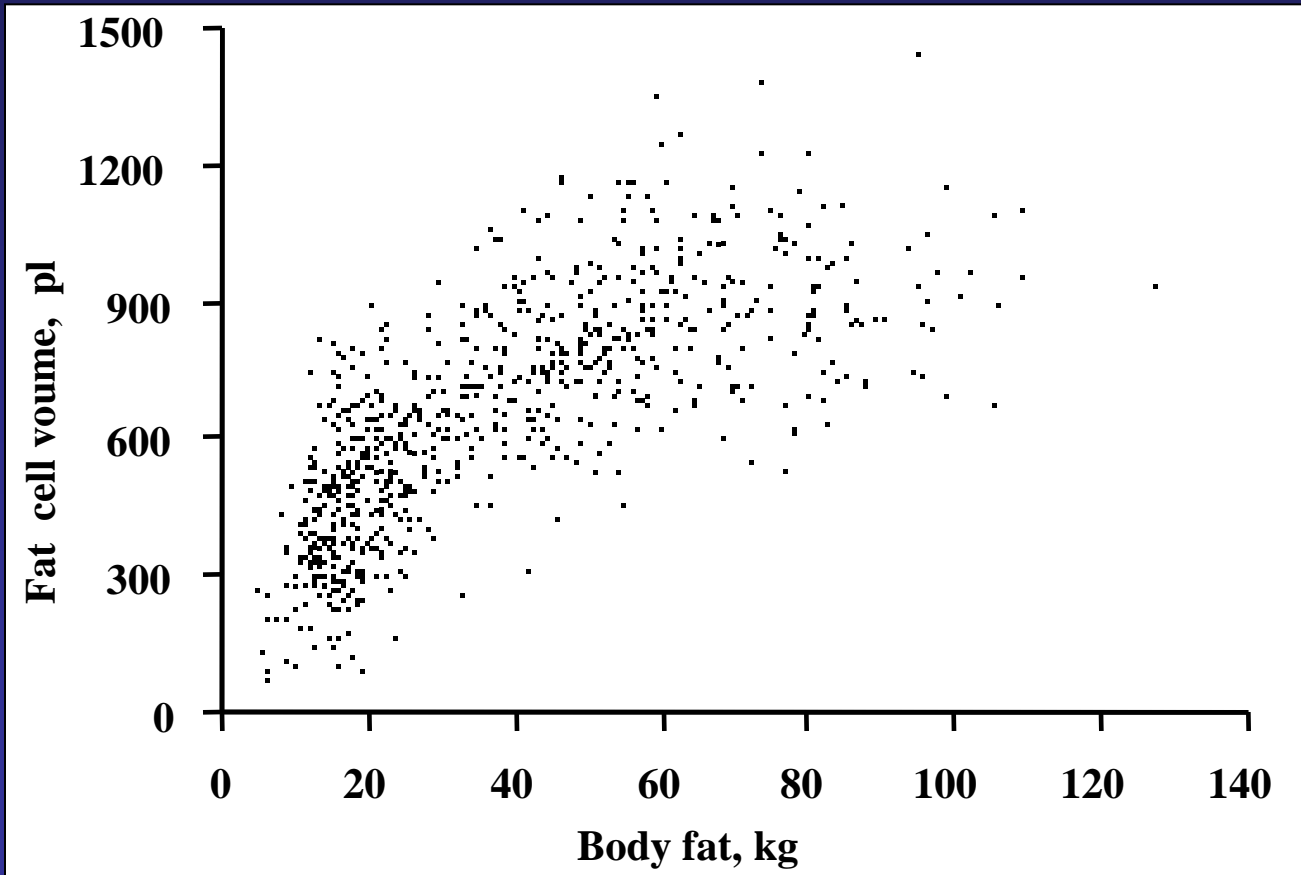
**Cancer cachexia Rydén et al *Cancer* 2008 113:1695-704**

**Bariatric surgery Spalding et al *Nature* 2008;453:783-7**

# Relationship between fat cell size and body fat

Large fat cells associate with

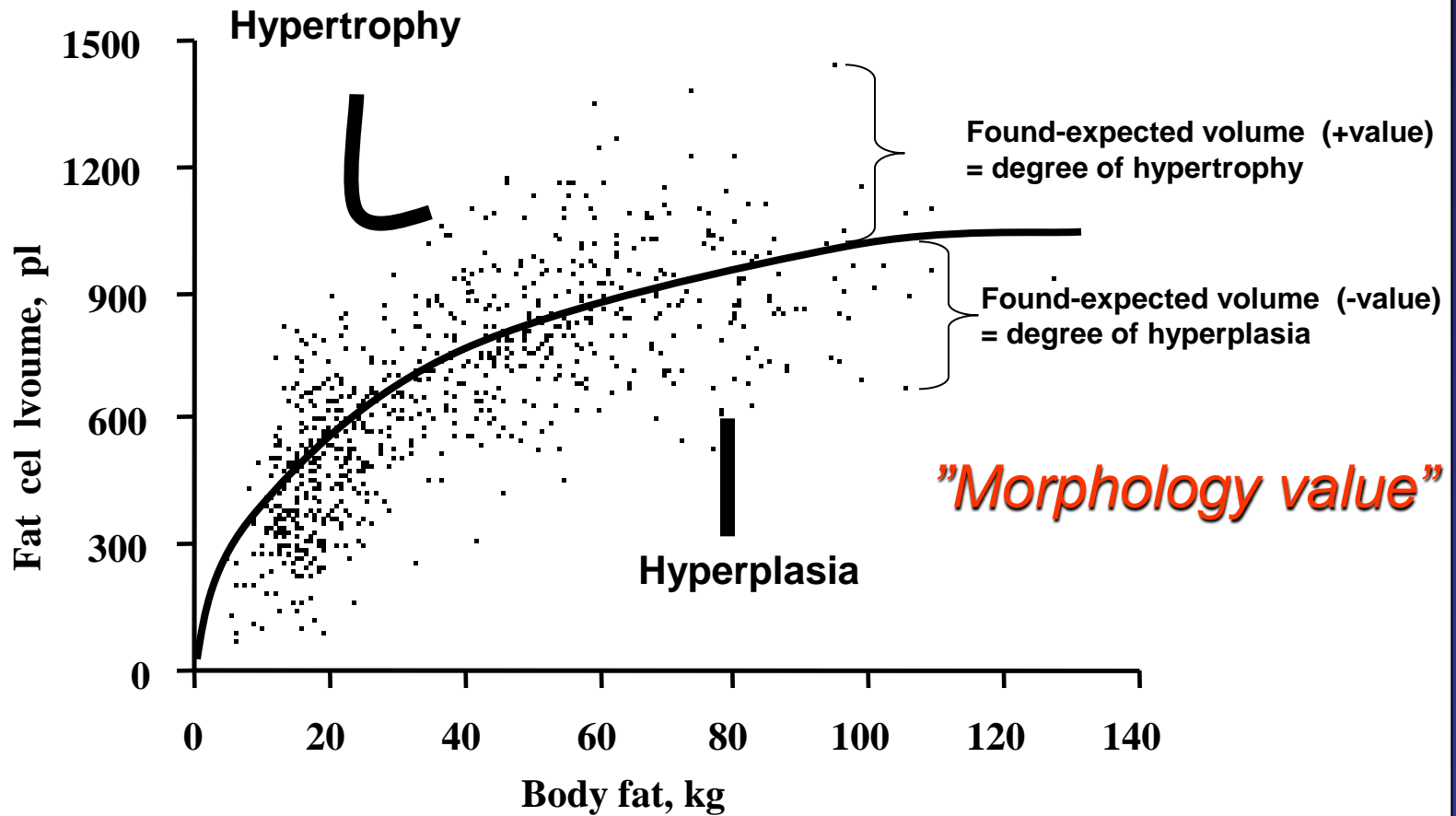
- Insulin resistance
- Increased risk of developing type 2 diabetes



HOW CAN WE  
SEPARATE THE  
EFFECT OF  
CELL SIZE  
FROM THE EFFECT OF  
BODY  
FAT?

# How can we estimate the impact of fat cell size?

Algorithm to obtain body fat independent classification



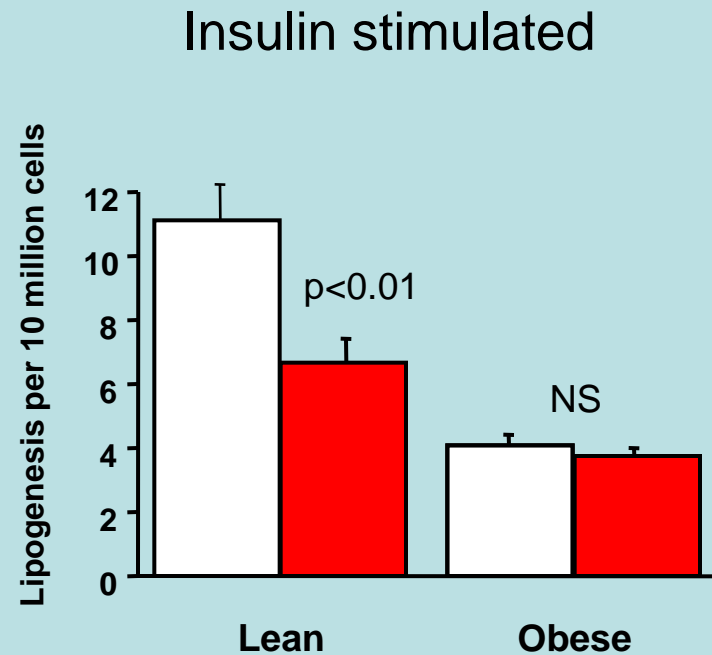
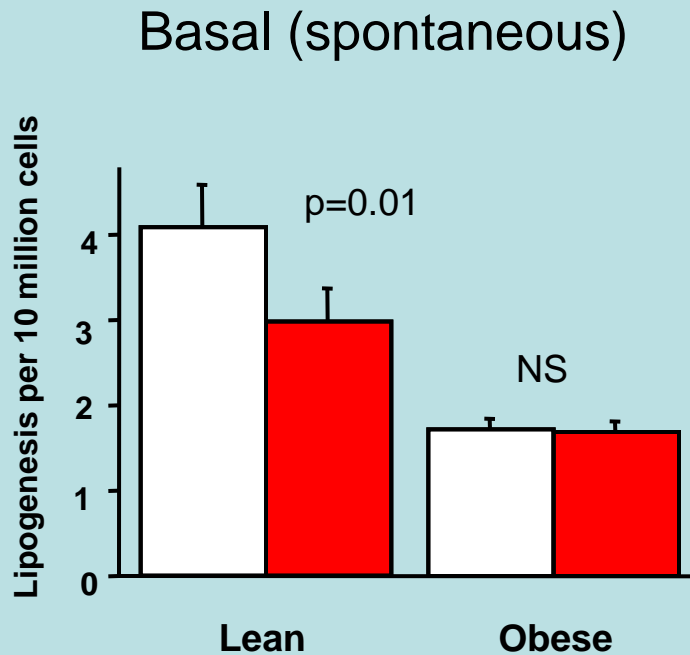


# Relationship between the morphology value and insulin sensitivity in 230 lean and 400 obese



# Adipose cellularity in 90 lean and 310 obese

## Adipocyte lipogenesis

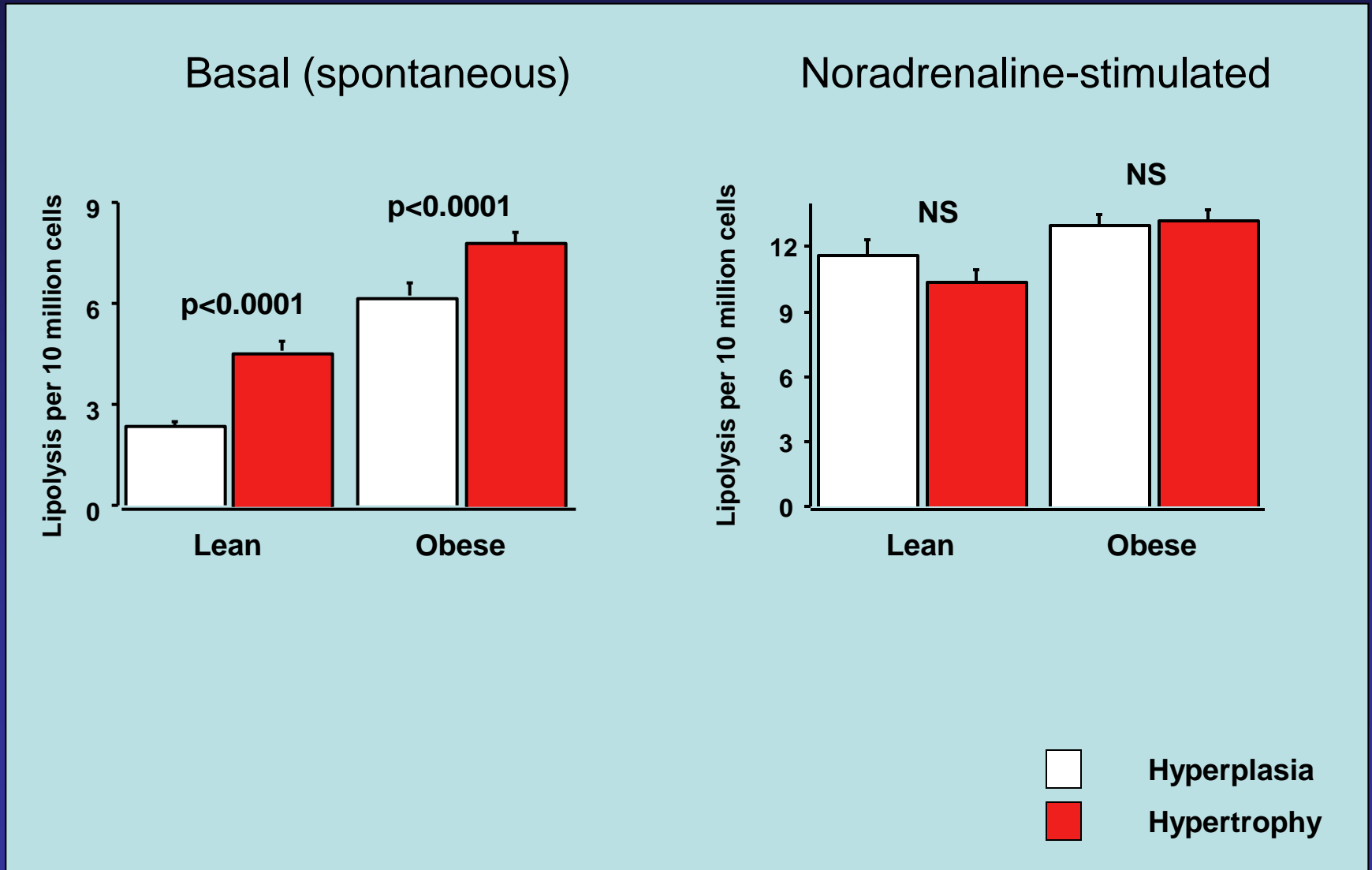


Hyperplasia

Hypertrophy

# Adipose cellularity in 220 lean and 300 obese women

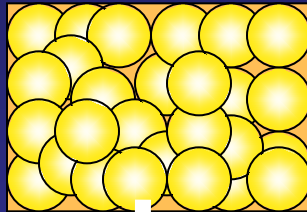
## Adipocyte lipolysis



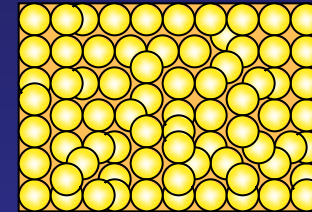
# Fat cell size and number matters

Irrespective of whether you are lean or obese, your adipose tissue can be in two different ways

HYPERTROPHY



HYPERPLASIA



- **Risk to develop type 2 diabetes**

C Weyer et al *Diabetologia* 43: 1498-1506, 2000

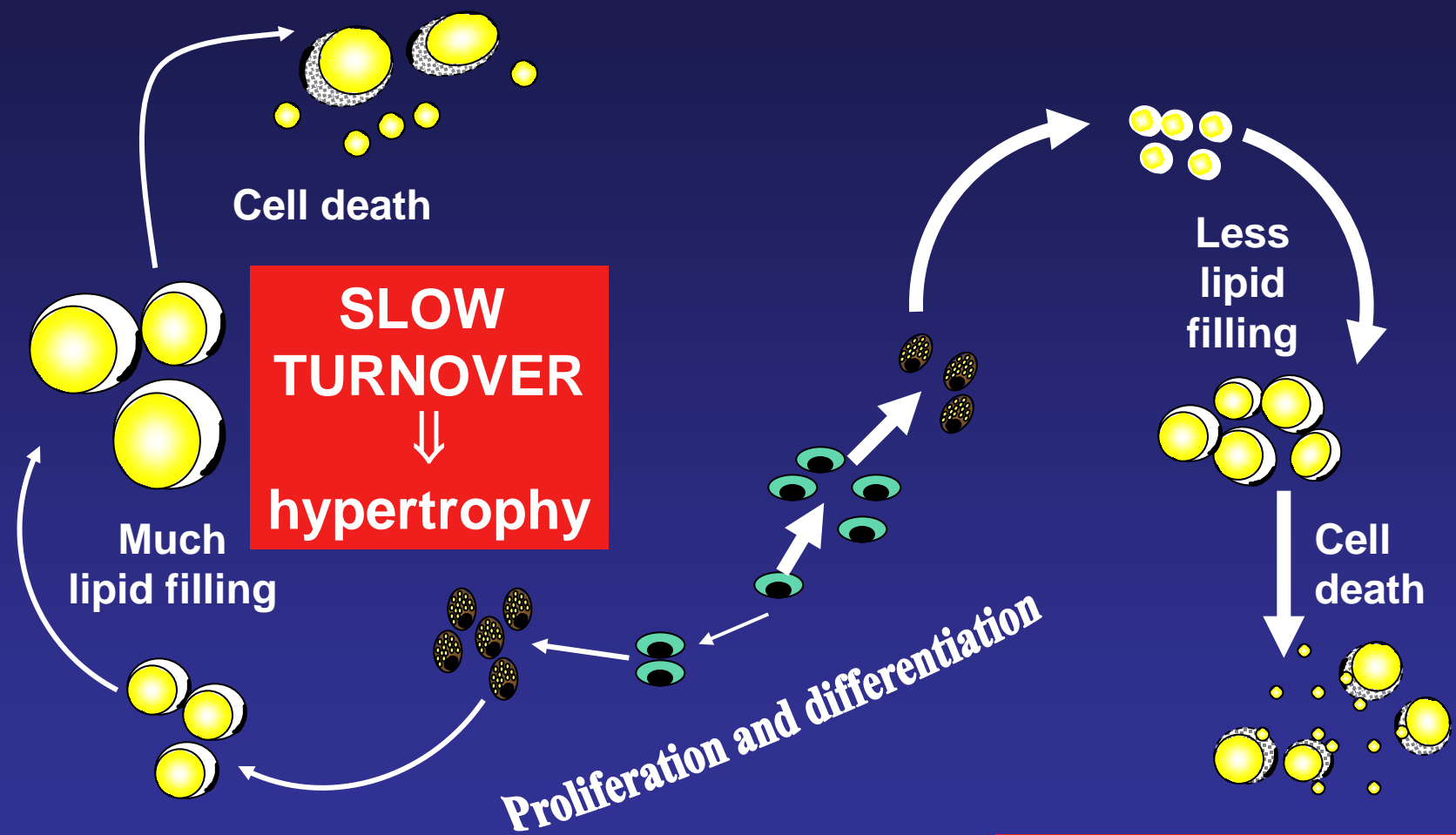
M Lönn et al *FASEB J.* 24:326-31. 2010

**Protective**

- **Strong heredity for type 2 diabetes**

P Arner et al *PLoS One* 6:e18284, 2011

# Mechanisms causing different forms of morphology



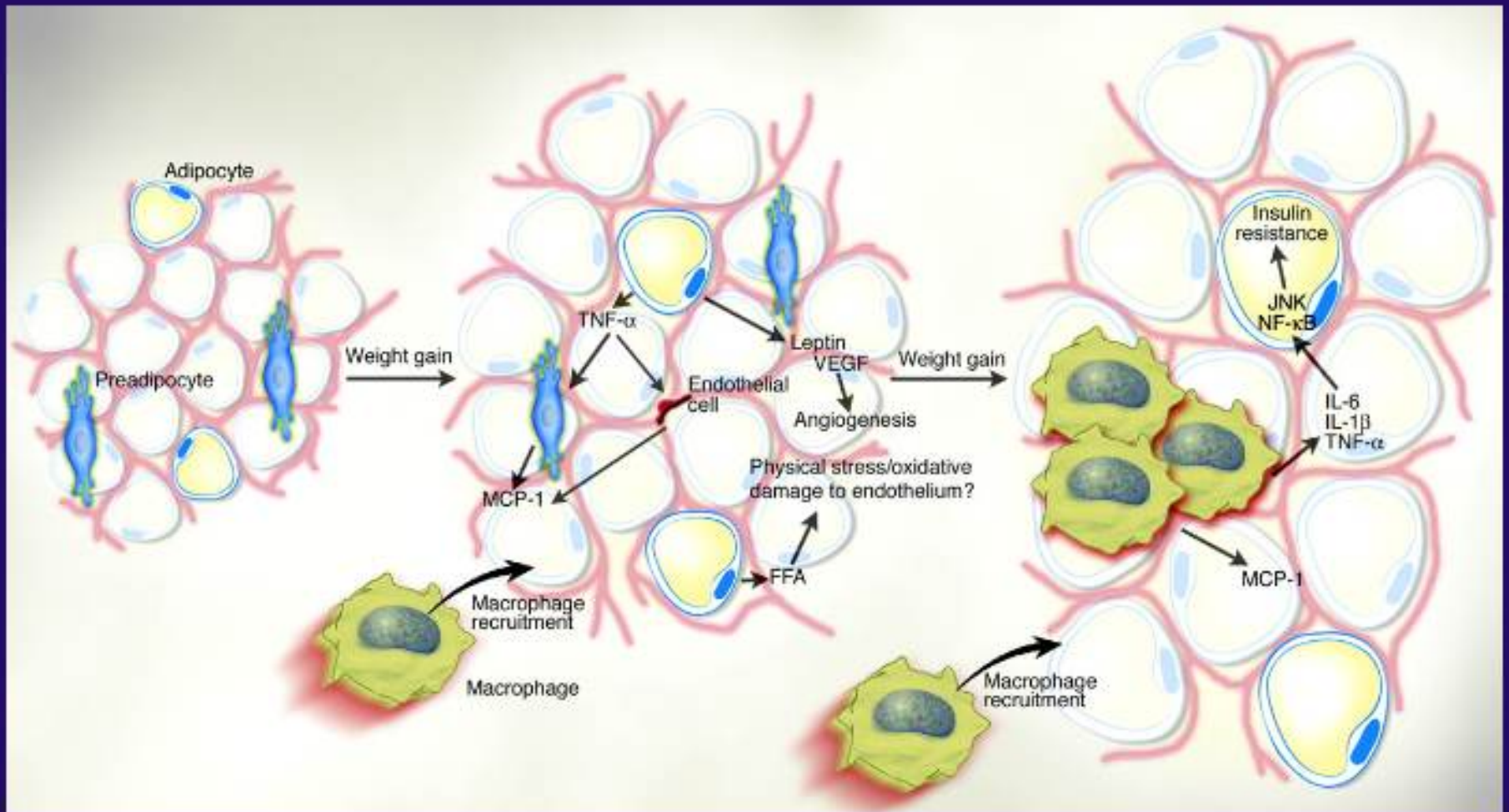
**RAPID TURNOVER**  
↓  
**hyperplasia**

# WHAT KEEPS HUMAN ADIPOCYTE TURNOVER GOING?



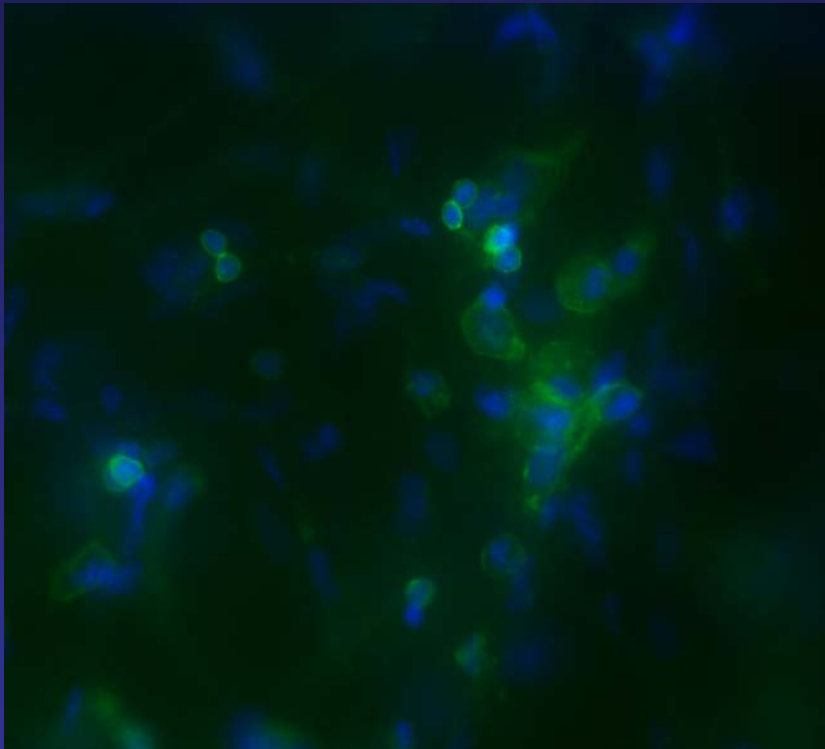
# Inflammation makes the fat go bad

## The old view



# The inflamed adipose tissue among obese

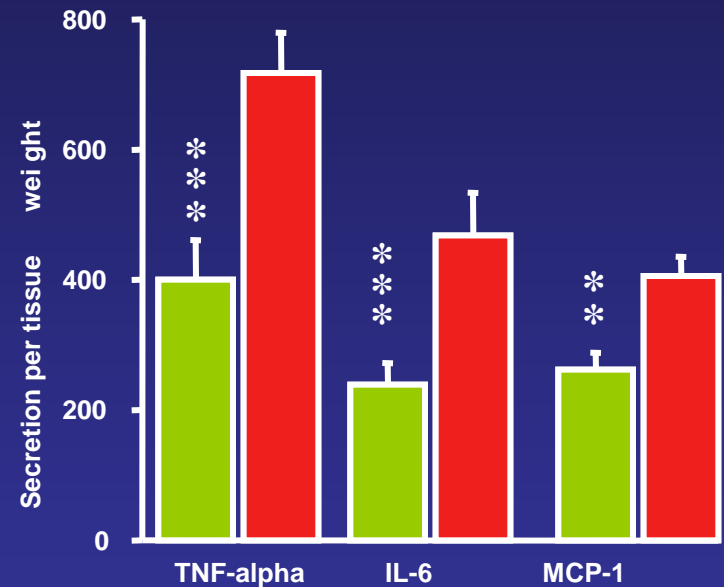
Leucocyte infiltration in obese adipose tissue



**GREEN** = the leukocyte antigen CD45

**BLUE** = nuclear staining with DAPI

Secretion of inflammatory proteins from human sc adipose tissue



NONOBESE

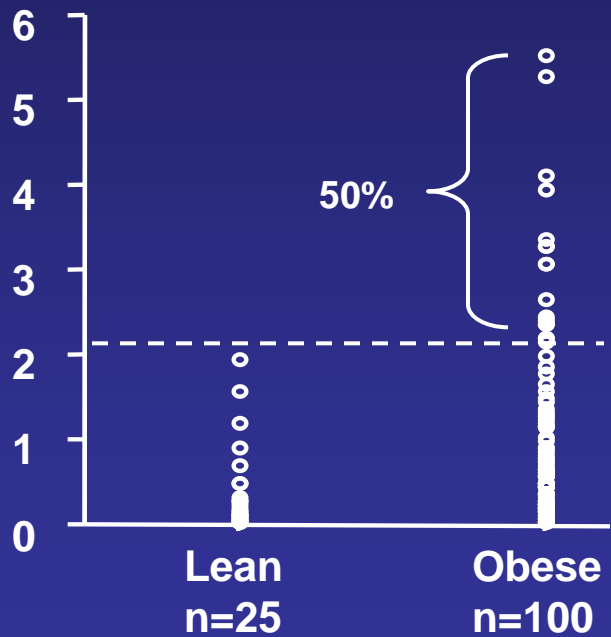


OBESE



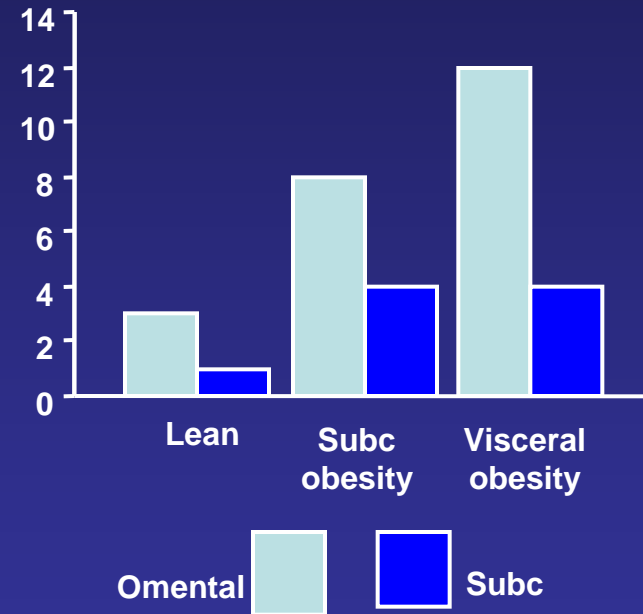
# Macrophage infiltration and $TNF\alpha$ secretion in adipose tissue obese and nonobese subjects

## $TNF\alpha$ secretion from sc adipose tissue



Rydén M et al, unpublished

## Macrophages in human adipose tissue. Percentage of all tissue cells



Adopted from Harman-Boehm et al, *JCEM*, 92:2240-47, 2006

# Effects of TNF $\alpha$ on adipocytes

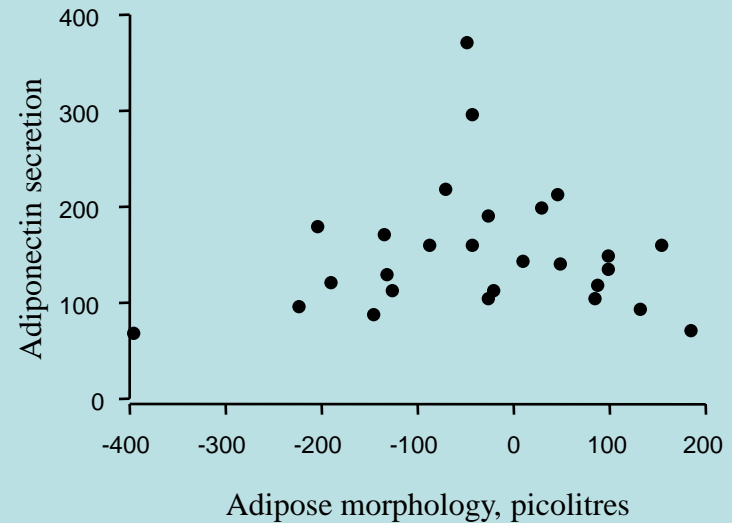
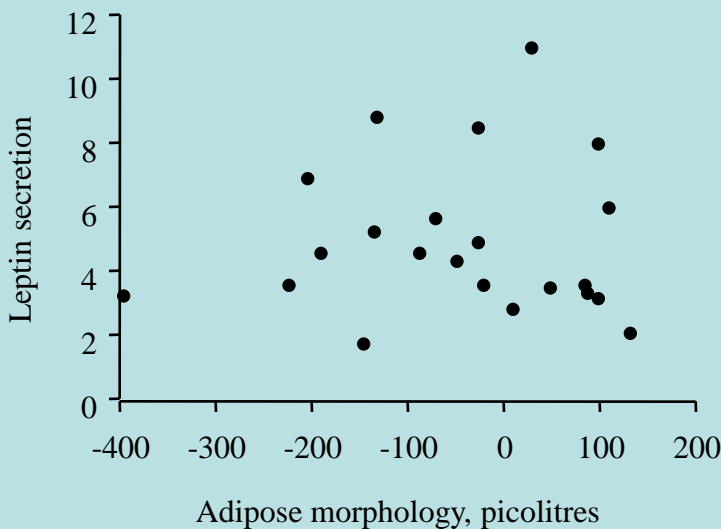
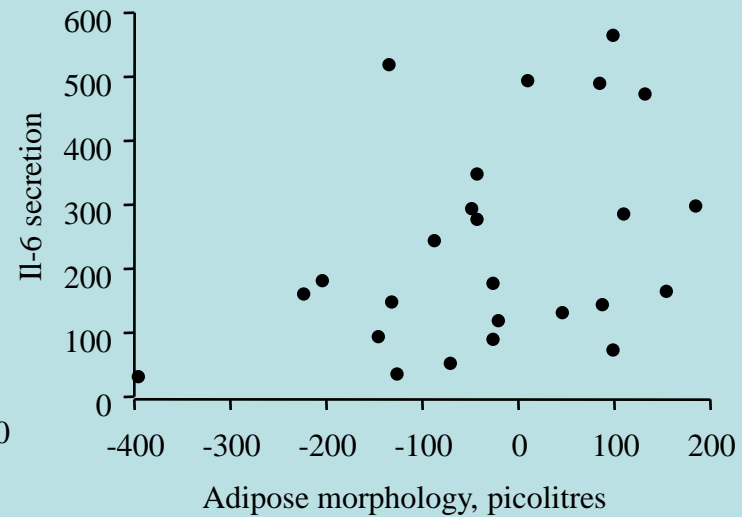
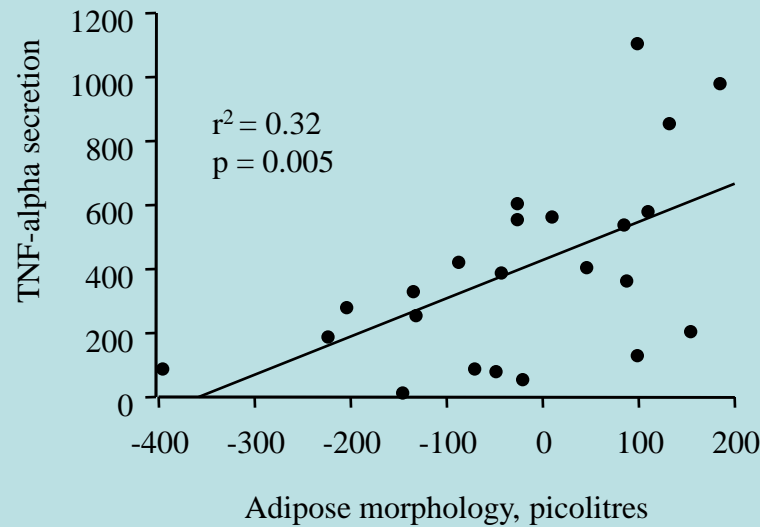
- Increases lipolysis
- Decreases lipogenesis
- Attenuates preadipocyte proliferation and adipocyte differentiation
- Increases adipocyte cell death



Are adipose  
inflammatory factors  
just bad  
or have we  
misunderstood them?

# Adipokine secretion in relation to adipose cellularity in lean healthy women (BMI < 25 kg/m<sup>2</sup>)

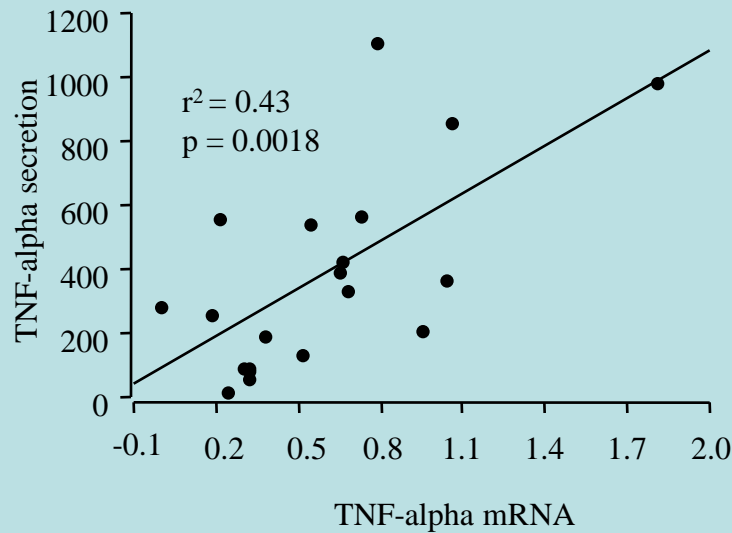
E Arner et al *N Engl J Med*, 362:1151-3, 2010



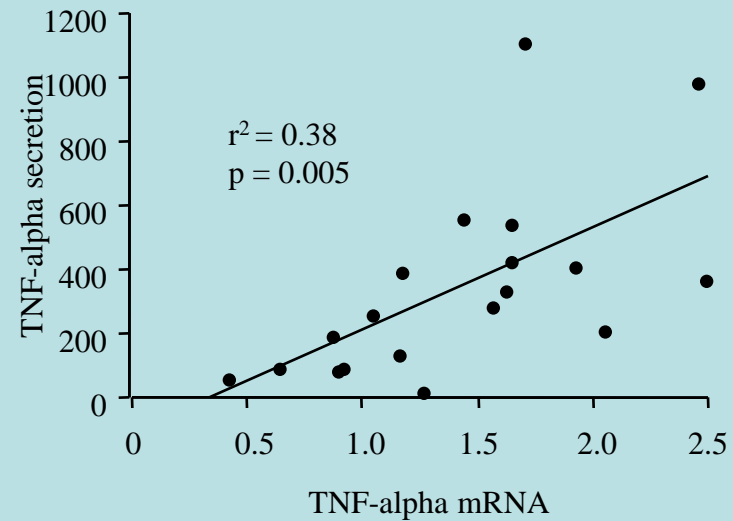
# TNF-alpha secretion and gene expression in adipose tissue of lean healthy women (BMI < 25 kg/m<sup>2</sup>)

E Arner et al *N Engl J Med*, 362:1151-3, 2010

## Tissue



## Adipocytes



# Could TNF $\alpha$ play a physiological role?

- Inhibit adipocyte growth?
- Limit fat cell proliferation and increase fat cell death?
- A response which becomes maladaptive in an environment with constant caloric over-supply?

Geoffrey  
RUSH

Judy  
DAVIS



The Pride of a Nation. The Heart of a Champion.

A FILM BY RUSSELL MULCAHY

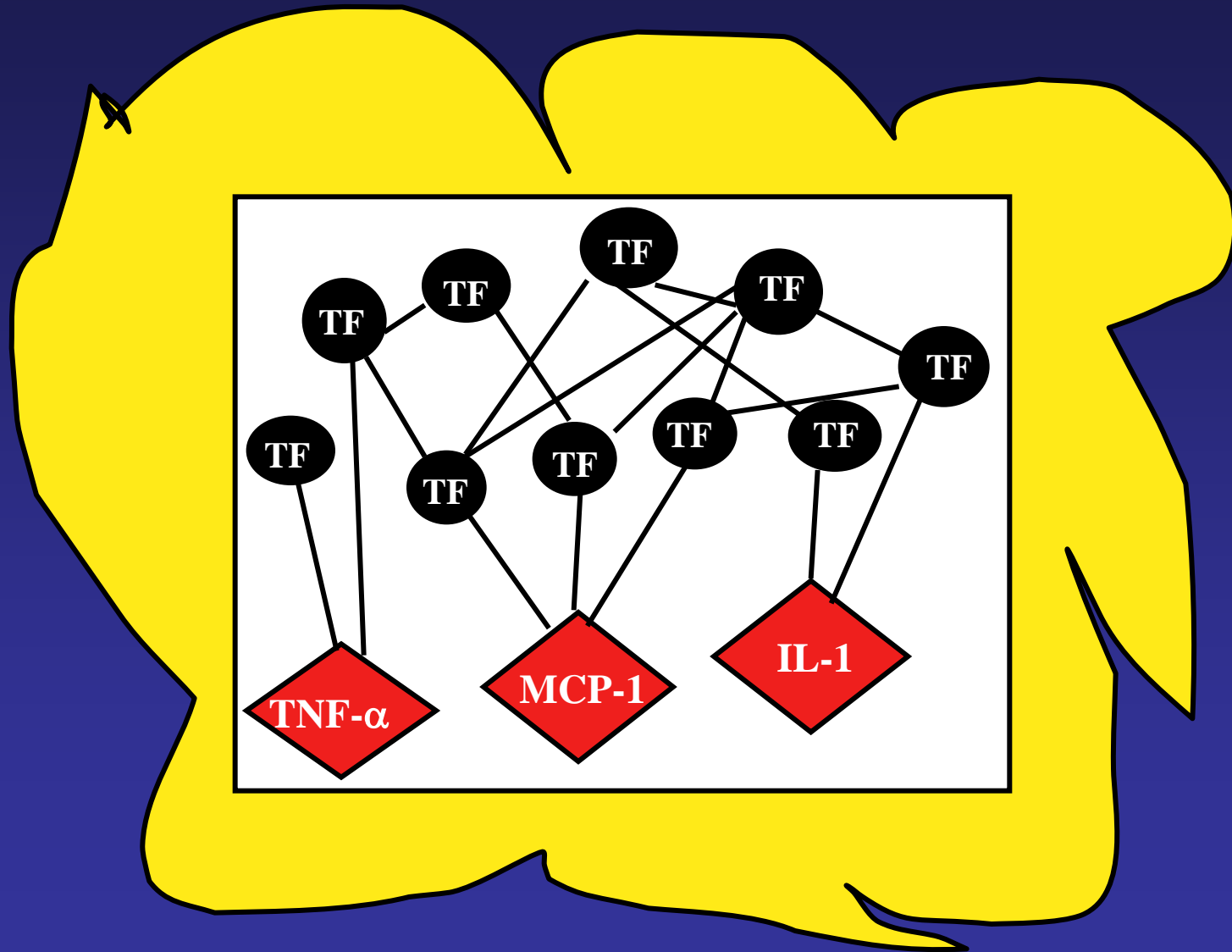
# swimming upstream

CRUSADER ENTERTAINMENT PRESENTS A FILM BY RUSSELL MULCAHY GEOFFREY RUSH JUDY DAVIS "SWIMMING UPSTREAM" JESSE SPENCER  
TIM DRAXL COSTUME DESIGNER ANN ROBINSON EXECUTIVE PRODUCERS JOHNNY KLIMEK AND REINHOLD HEIL PRODUCED BY ANGUS STRATHIE PRODUCED BY ROGER FORD COSTUME DESIGNER MARCUS D'ARCY  
DIRECTOR OF PHOTOGRAPHY MARTIN McGRATH ACS EXECUTIVE PRODUCERS NICK MORTON EXECUTIVE PRODUCERS CAROL HUGHES PRODUCED BY ANDREW MASON WILLIAM J. IMMERMAN ANTHONY FINGLETON  
PRODUCED BY HOWARD BALDWIN, KAREN BALDWIN, PAUL POWLIAN WRITTEN BY ANTHONY FINGLETON AND DIANE FINGLETON

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Upstream regulator(s)  
of human  
adipose  
inflammation?

# A network of transcription factors is linked to inflammatory proteins in human fat cells

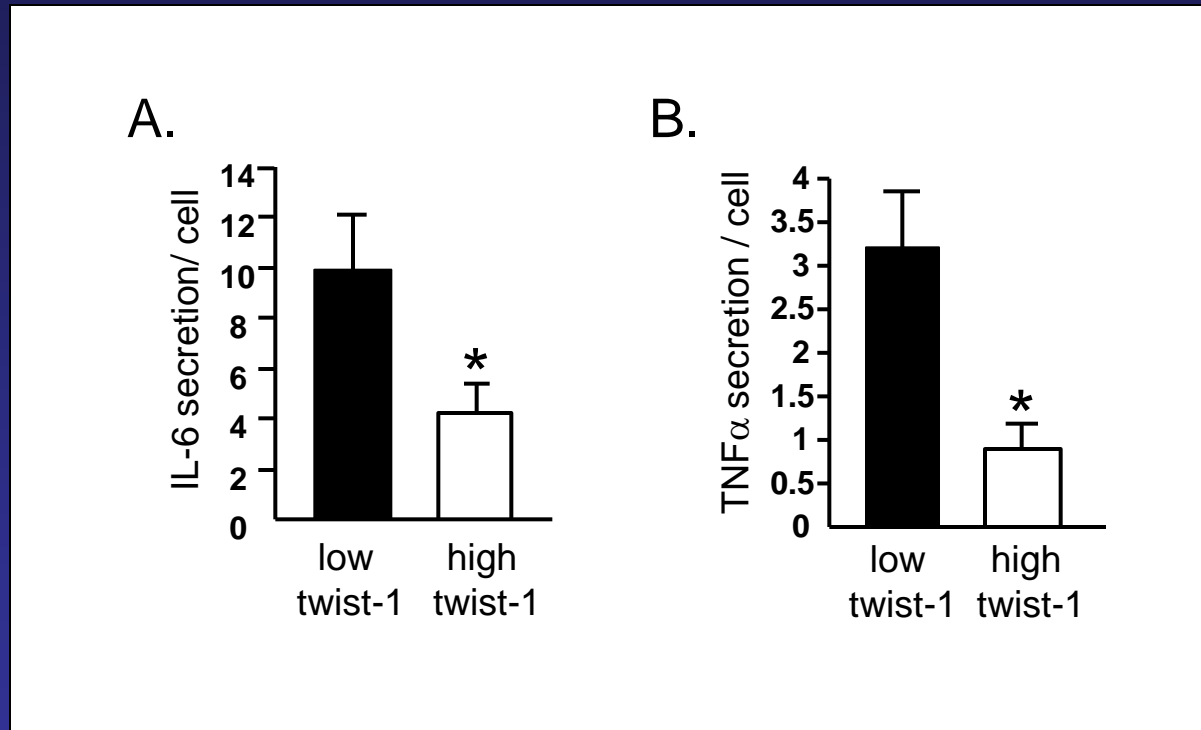




# Twist-1

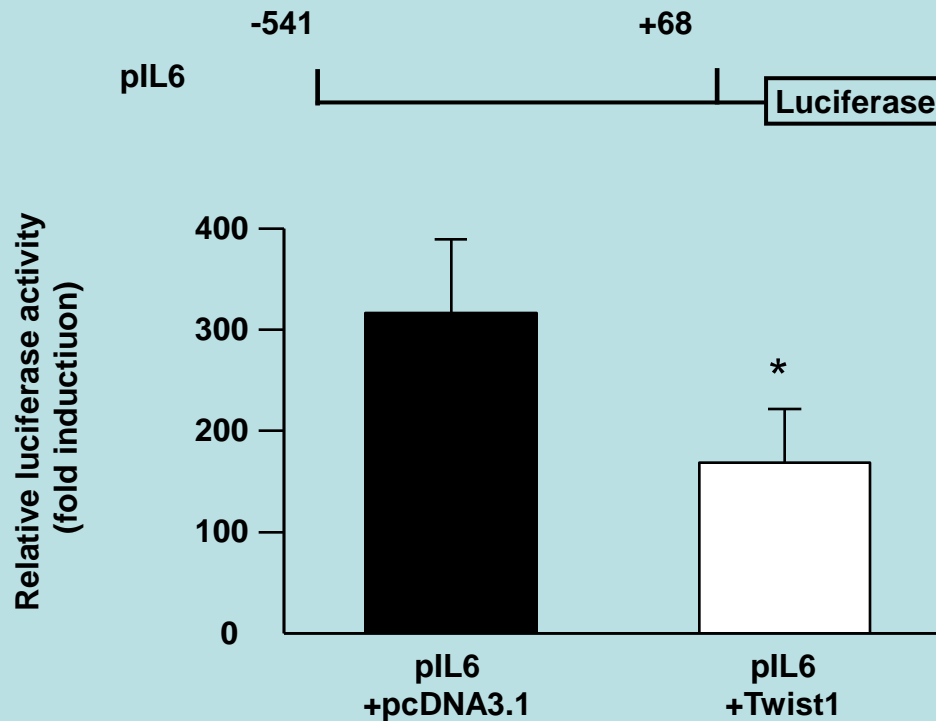
- In a gene expression profile on sc adipose tissue from lean and obese twist1 expression was significantly lower in obese subjects (Dahlman I unpublished data)
- Basic helix-loop-helix transcription factor
- Identified in *Drosophila melanogaster*
- Binds to E-boxes with the CANNTG motif
- Implicated in bone formation and tumor metastasis
- Mutations associated with Saethre-Chotzen syndrome
- Twist-1 and -2, 66% identity at aa-level
- *Twist2*<sup>-/-</sup> and *twist1*<sup>+/-</sup> *twist2*<sup>+/-</sup> mice have increased levels of TNF $\alpha$ , IL-6 and IL-1 $\beta$  (Šošić D *et al.* Cell 2003)
- Twist1 negatively regulates transcriptional activity of PGC-1 $\alpha$  in murine BAT (Pan D *et al.* Cell 2009)

# Relationship between Twist-1 gene expression and secretion of inflammatory proteins in human subcutaneous adipose tissue

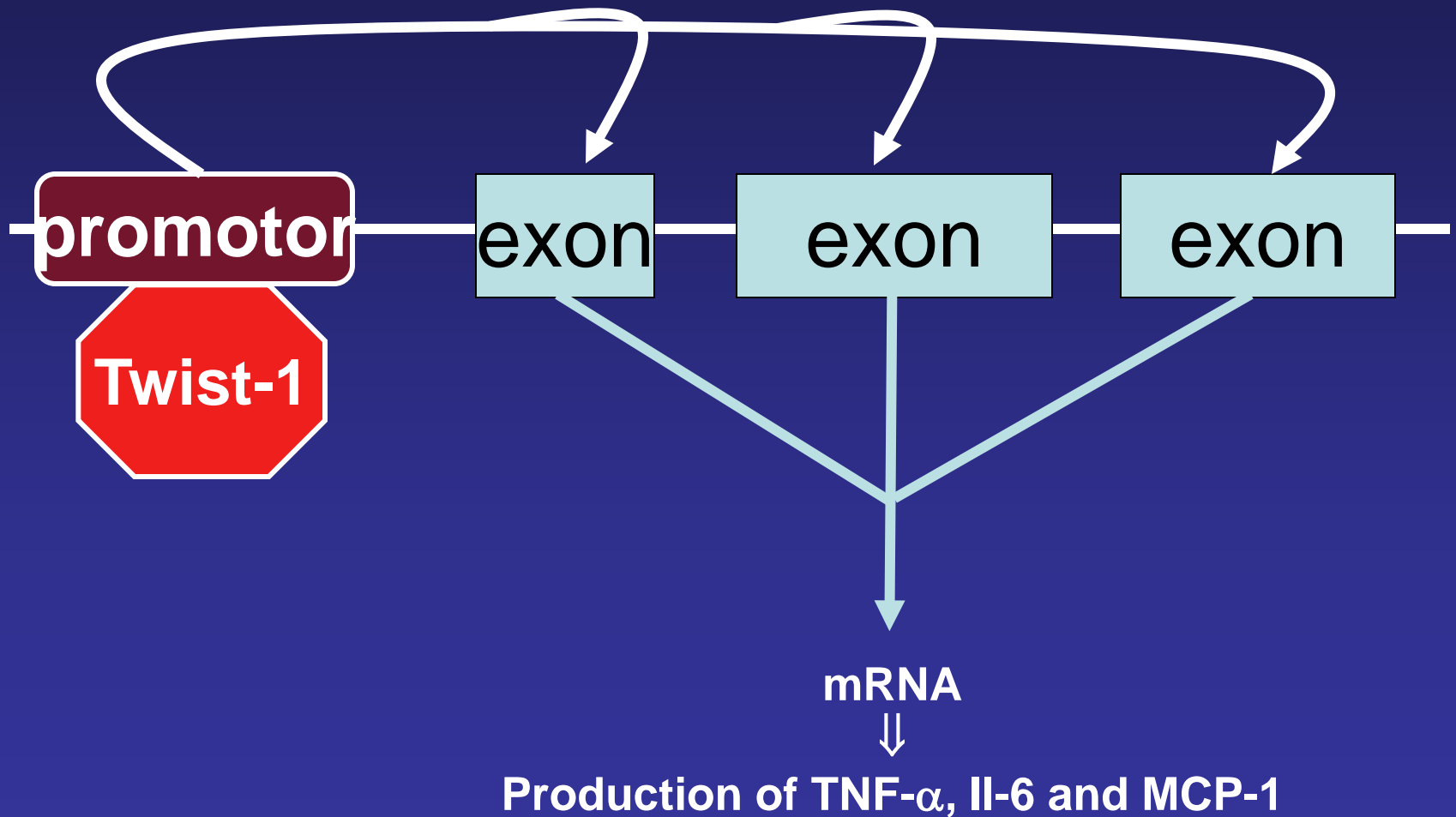


# Twist1 regulates cytokine expression

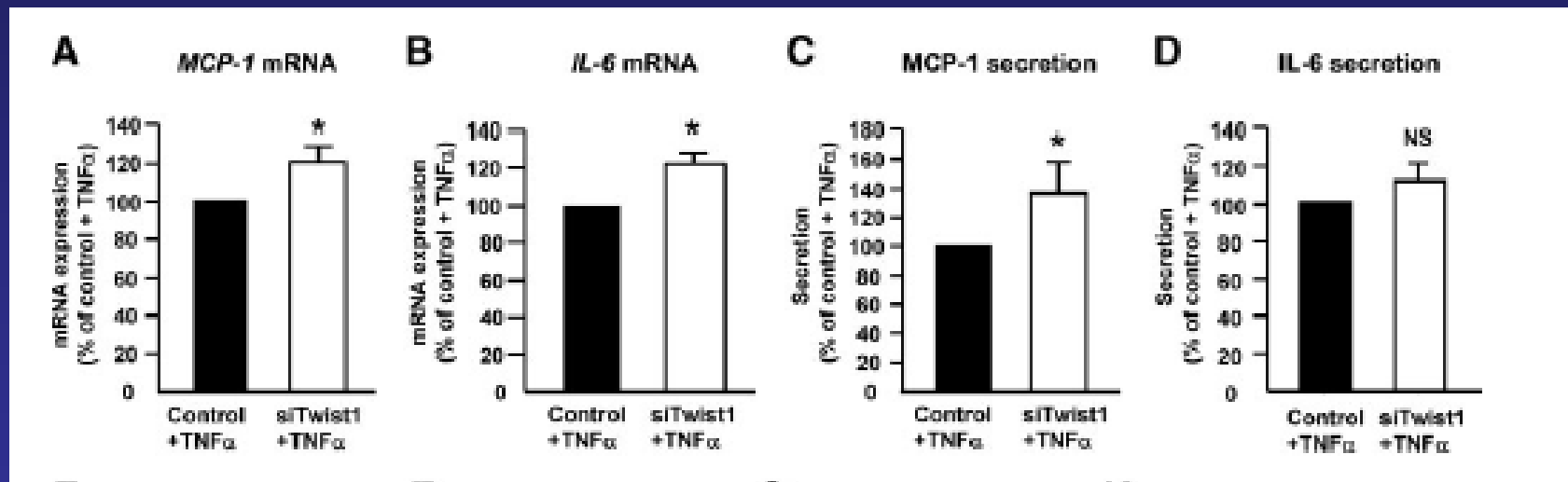
3T3-L1 cells were transfected with Twist1 cDNA and a gene reporter construct for IL-6 (pIL) or empty pcDNA3.1



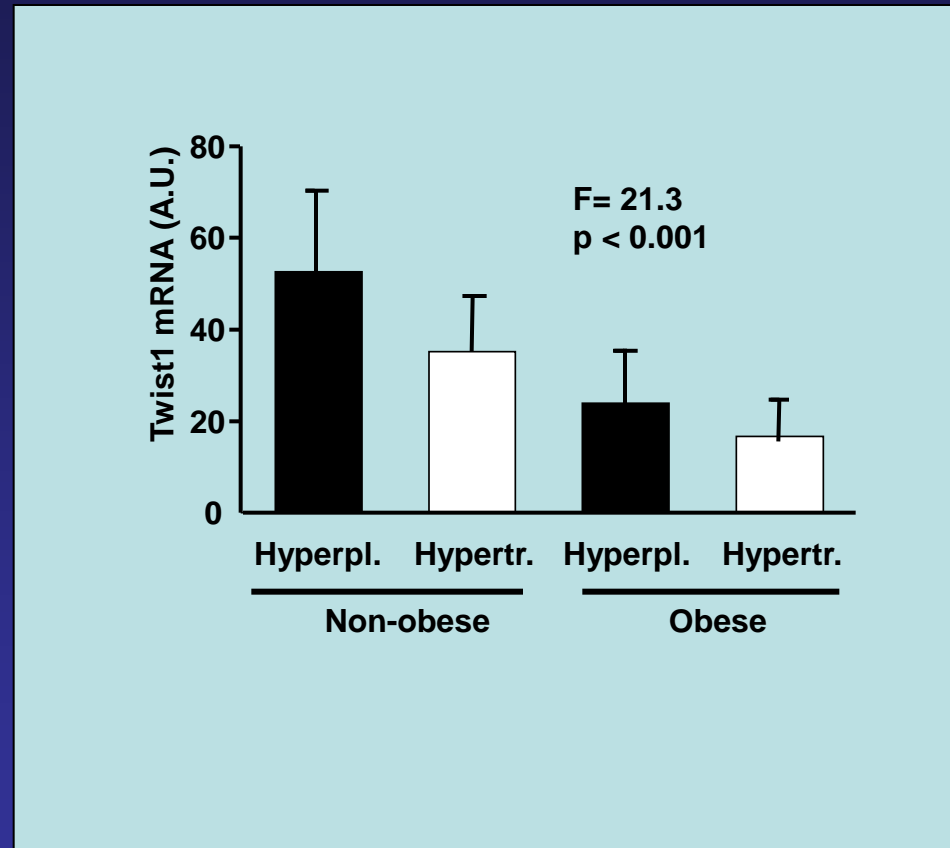
# Interaction between Twist-1 and inflammation in human adipose tissue



# Reduced Twist1 potentiates the pro-inflammatory effect of TNF $\alpha$

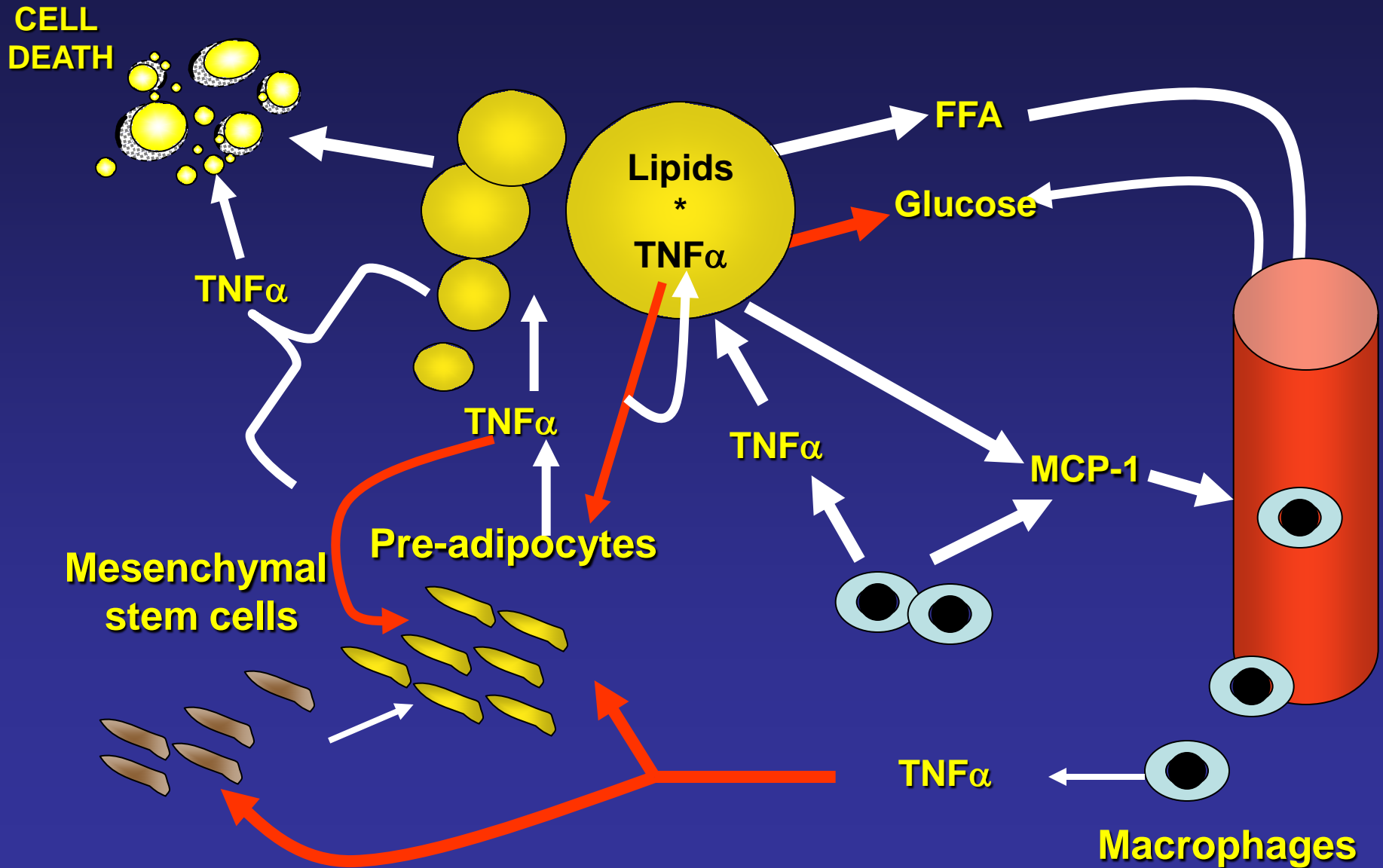


# Relationship between Twist-1 gene expression and the morphology of human subcutaneous adipose tissue



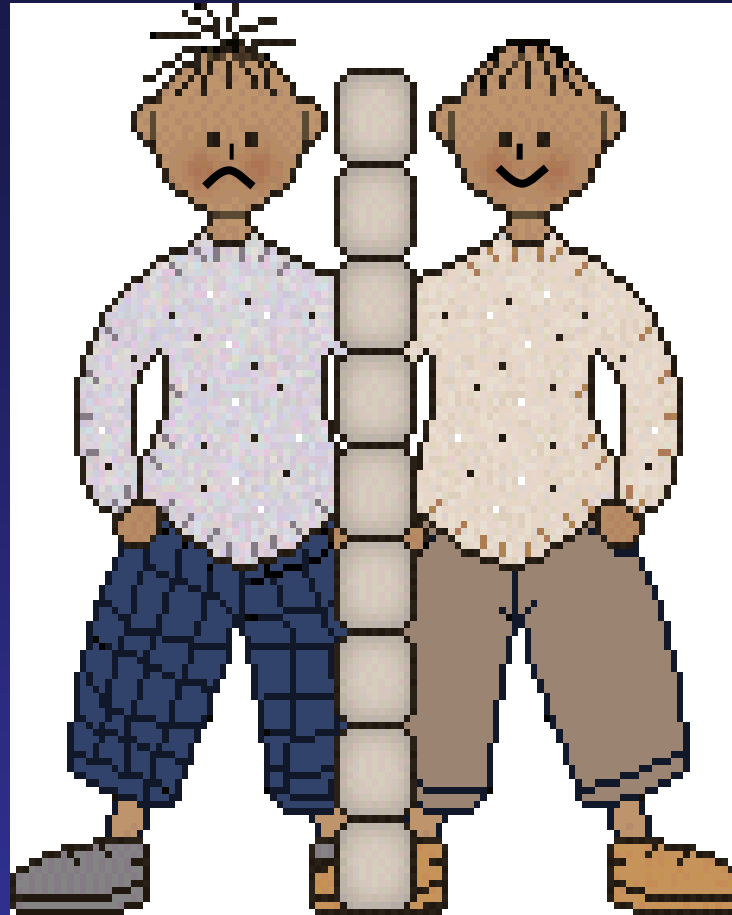
# Role of adipose inflammation in man

## DIFFERENTIATION AND LIPID FILLING OF FAT CELLS



# Adipose cellularity is clinically important for nonobese

hypertrophy



hyperplasia

Alterations  
in transcription  
factor regulation



Decreased  
insulin sensitivity



Type 2  
diabetes risk

Protected



# SUMMARY

## The link between inflammation and adipogenesis

- There is a high turnover of fat cells in adult life although the total number of fat cells is constant
- Hypertrophic fat (few but large cells) is linked to development of insulin resistance irrespective of BMI
- Lean apparently healthy subjects with adipose hypertrophy have decreased insulin sensitivity
- Adipocyte turnover is an important determinant of adipose hypertrophy/hyperplasia, turnover (and thereby adipogenesis) and is high in hyperplasia
- Local inflammation may impact on morphology (hypertrophy/hyperplasia) of adipose tissue, hypertrophy is associated with inflammation
- Adipose inflammation is governed by a network of transcription factors
- Characterization of factors regulating turnover/morphology currently under way

# ADIPOCYTE TURNOVER WORKING FORCE

## LIPID LABORATORY

- Peter Arner
- Gaby Åström
- Eva Sjölin
- Kerstin Wåhlen
- Clara Bambace
- Amanda Petterson
- Ingrid Dahlman
- Britt-Marie Leijonhufvud
- Katarina Hertel
- Hans Wahrenberg
- Elisabeth Dungner
- Jurga Laurencikiene
- Johan Hoffstedt
- Patrik Löfgren
- Daniel Andersson
- Agne Kulyte
- Silvia Lorente
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- Samuel Bernard
- Bruce Bucholz
- Olaf Bergman
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- Mats Eriksson
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- Moustapha Hassan
- Jonas Frisén
- Erik Näslund
- Per Heden
- Claes Carnheim
- Ian Cassady
- David Hume
- Shalender Bhasin
- Karin Dahlman-Wright
- Mireille Cormont
- Jean-Francois Tanti
- Erik van Nimwegen
- Keith Frayn



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NUGENOB, Cost Action BM0602, ADAPT



*Thank you for your attention!*