

Connessioni molecolari tra Obesità e invecchiamento

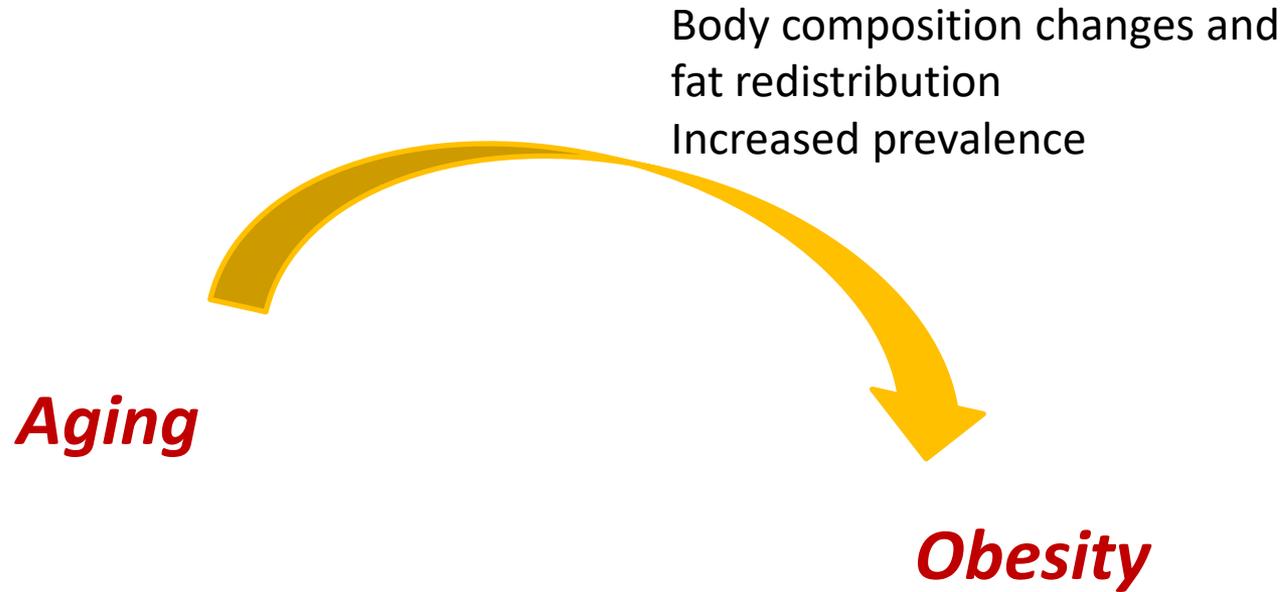


Elena Zoico, MD, PhD

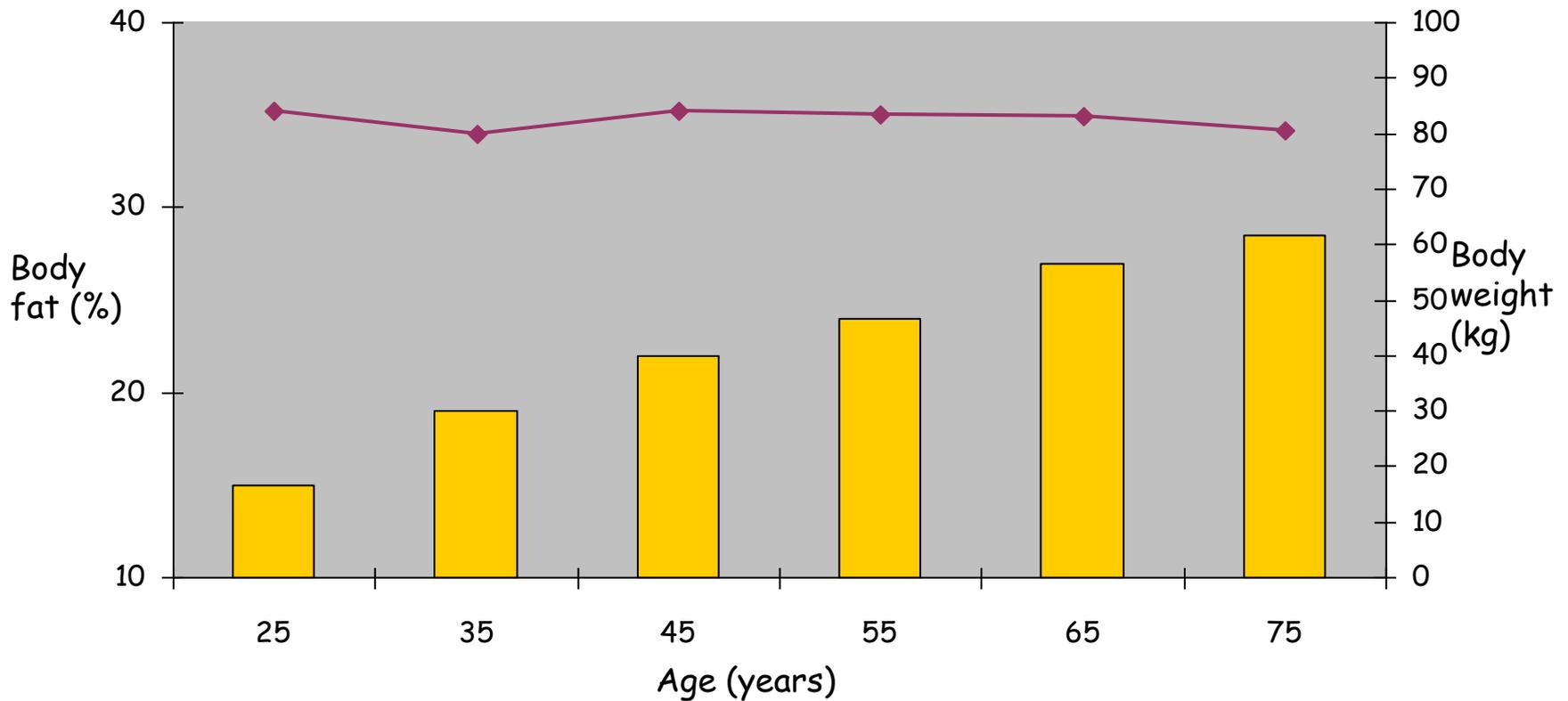
*Università di Verona
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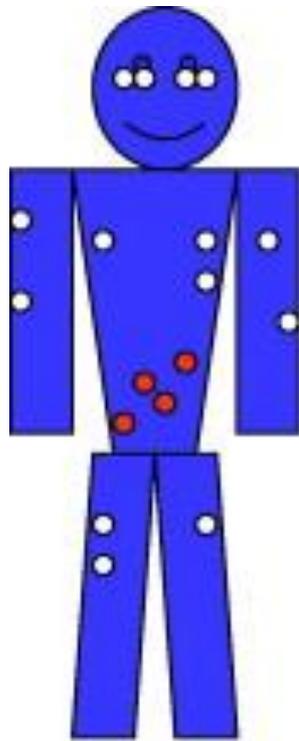
Rationale for the existence of a connection between Aging and Obesity



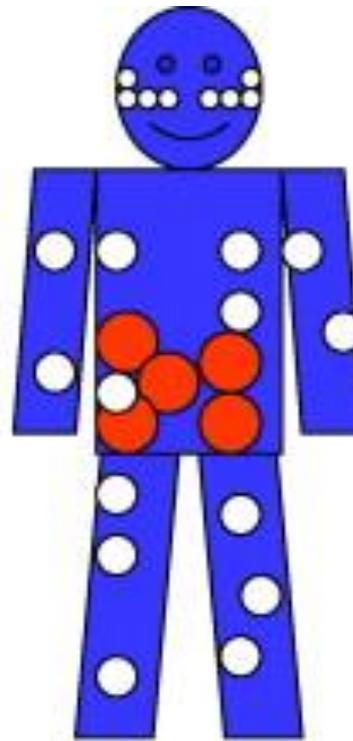
Age related increase in body fat for normal males at constant body mass index (BMI)



Age-associated changes in fat distribution



20 year old
(young)



50 year old
(middle age)

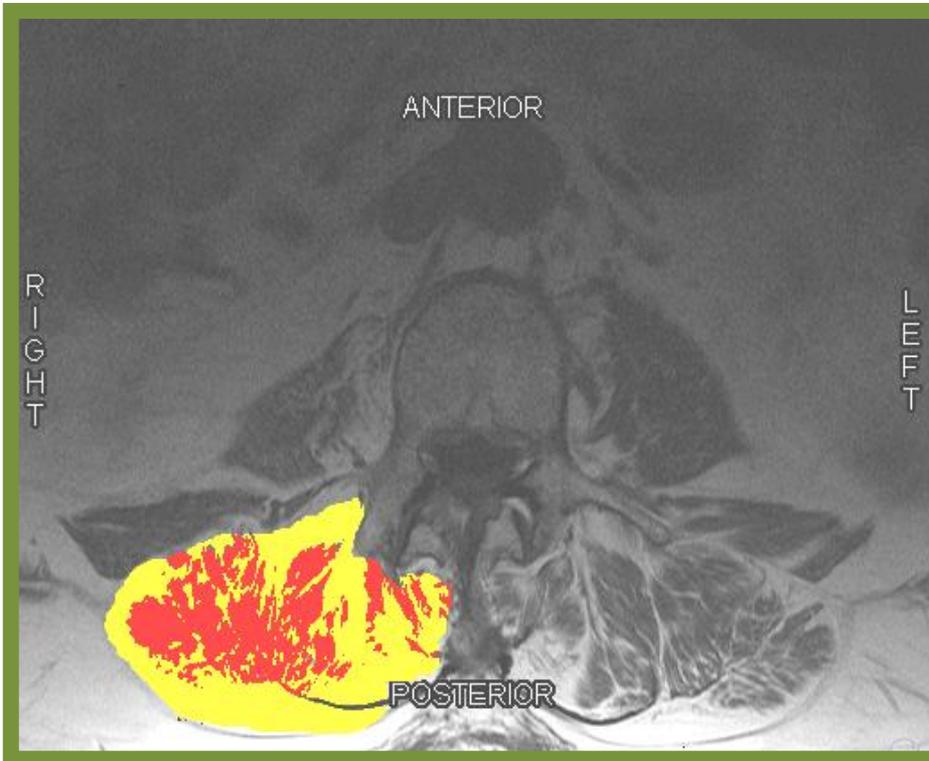


>70 year old
(old age)

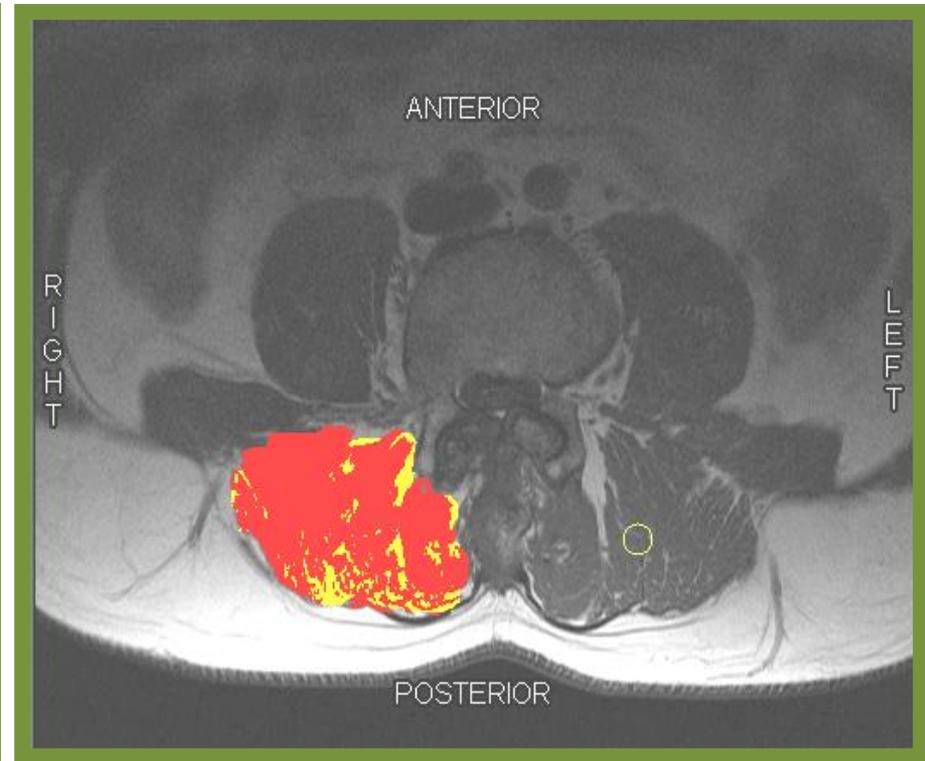
- subcutaneous fat
- visceral fat
- fat in non-adipose tissue.

Age-related changes in total and regional fat distribution

Thigh intermuscular fat in **elderly** subjects
with different BMI values

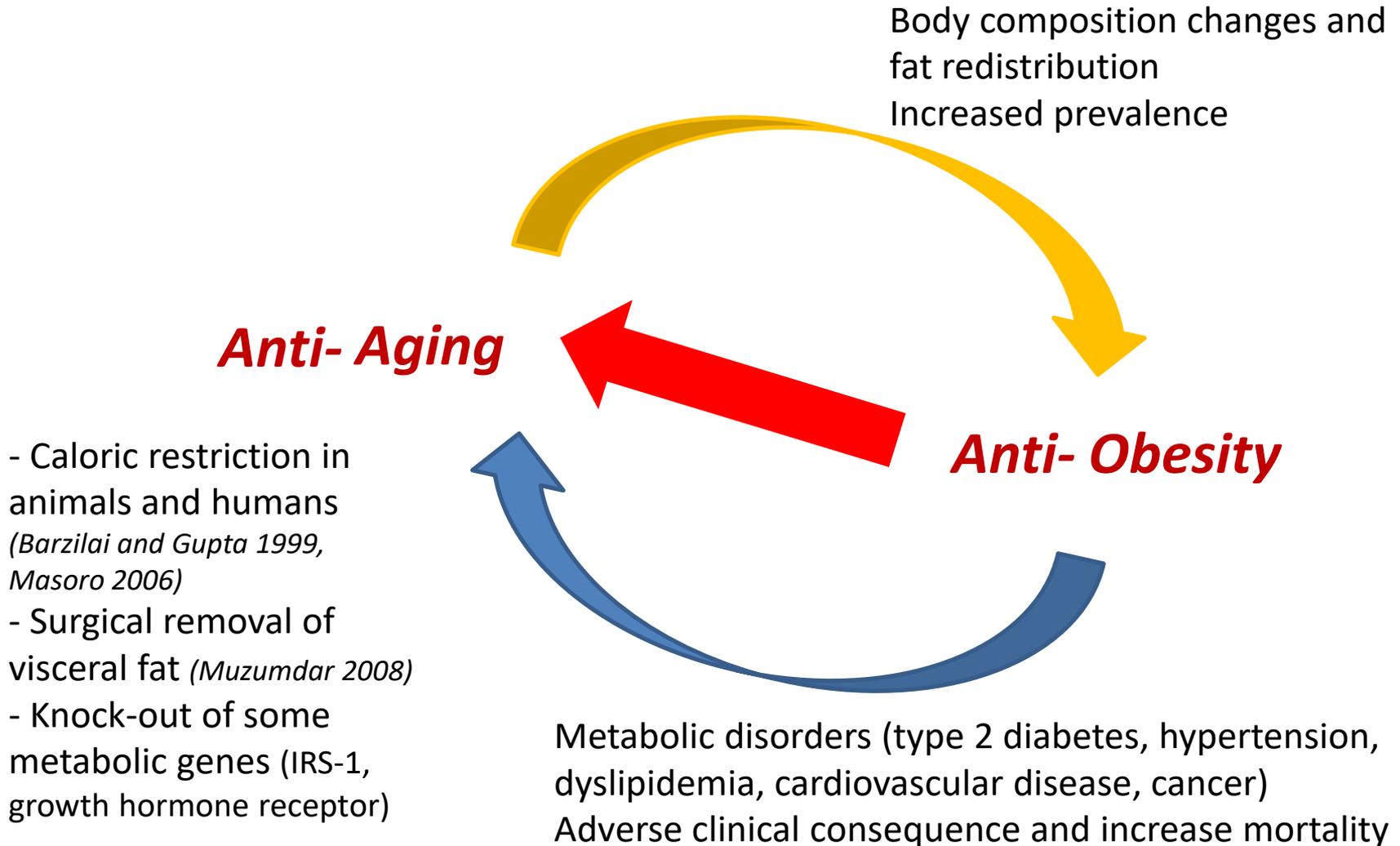


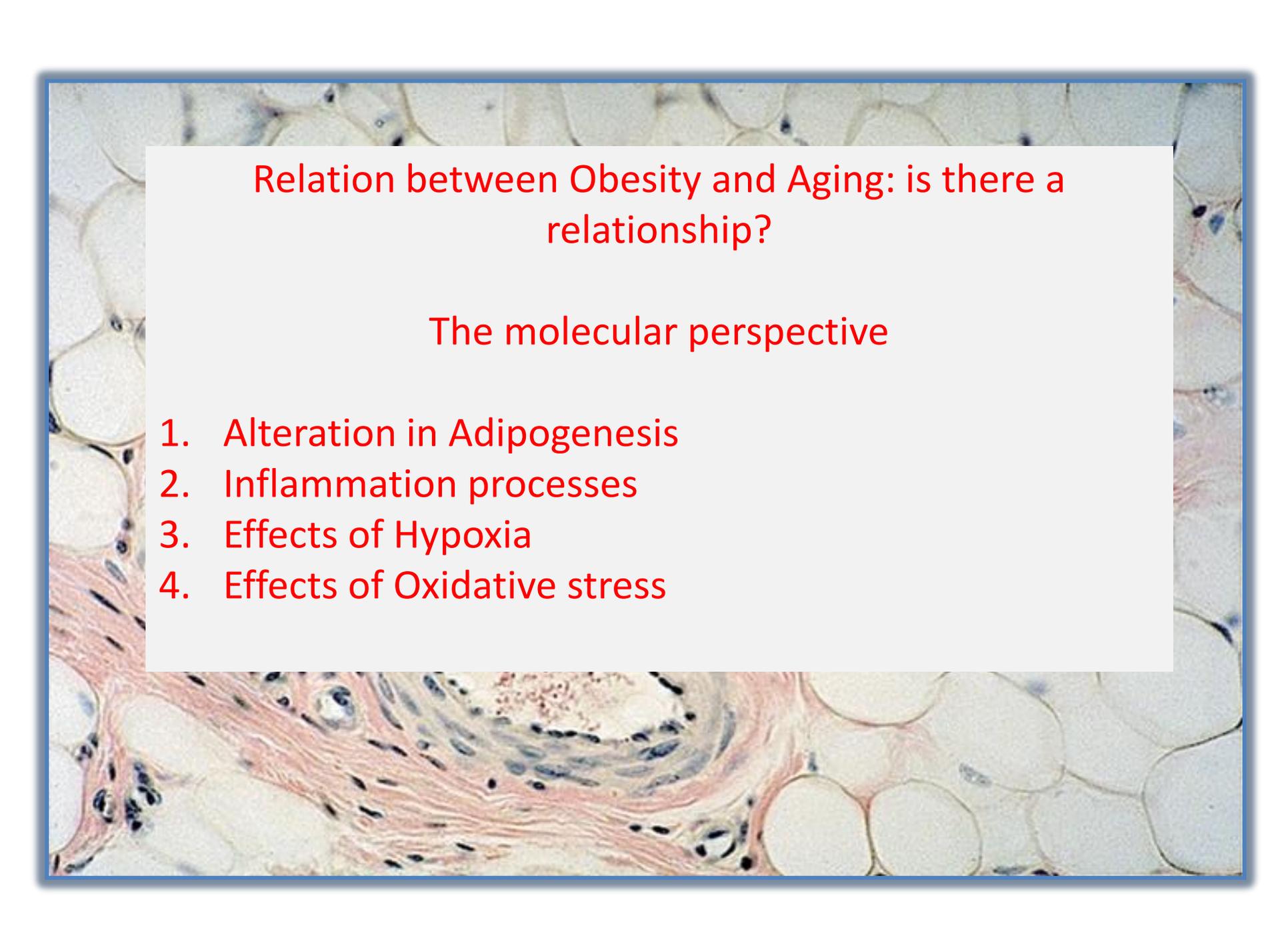
Age 79 years
BMI 35.2 Kg/m²



Age 80 years,
BMI 26 Kg/m²

Rationale for the existence of a connection between Aging and Obesity



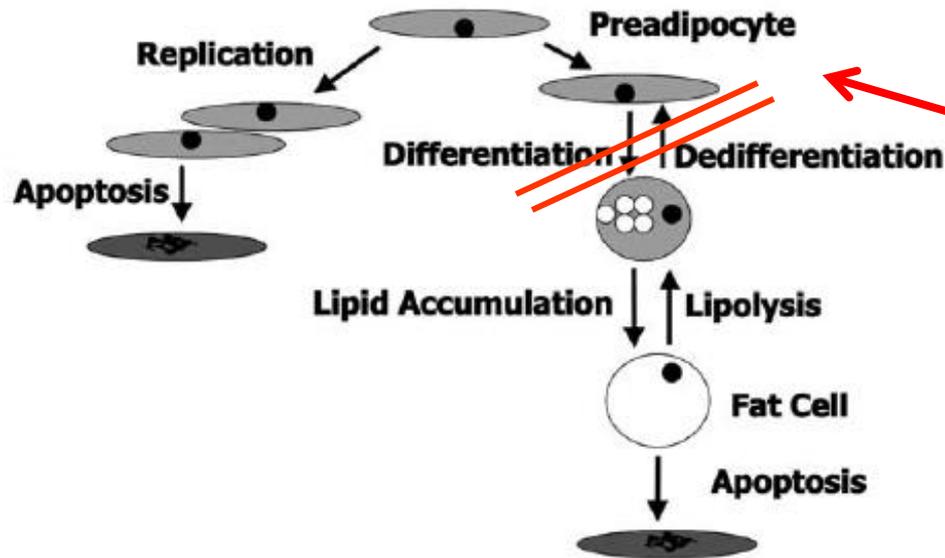
A microscopic image of adipose tissue, showing large, clear, circular cells (adipocytes) with thin, pink-stained cell walls. The cells are arranged in a somewhat regular pattern, with some darker-stained nuclei visible. The overall appearance is that of a healthy, well-organized adipose tissue.

Relation between Obesity and Aging: is there a relationship?

The molecular perspective

1. Alteration in Adipogenesis
2. Inflammation processes
3. Effects of Hypoxia
4. Effects of Oxidative stress

Aging processes
(telomeres or higher ROS)



↓ C/EBP α e ↓ PPAR γ
(transcription factors decline)

↑ cytokines production

“The capacity of preadipocytes to become fully functional adipocytes declines with aging.....”

“... since preadipocytes normally defend against lipotoxicity by becoming fat cell that sequester fatty acids...increased risk of insulin resistance”

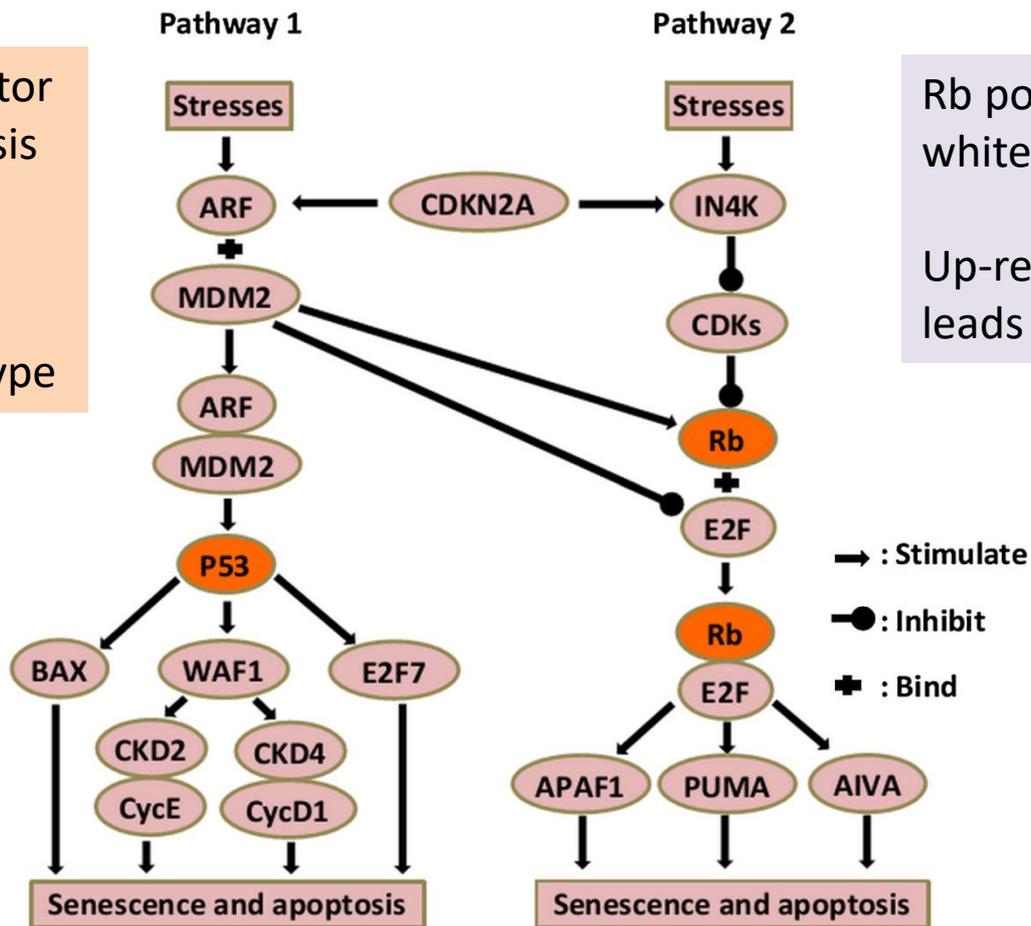
Kirkland et al, 2002

Kirkland et al, 2007

Adipose p53 and retinoblastoma protein are two main players in cellular pathways of aging (cellular senescence and apoptosis)

p53 negative regulator of white adipogenesis

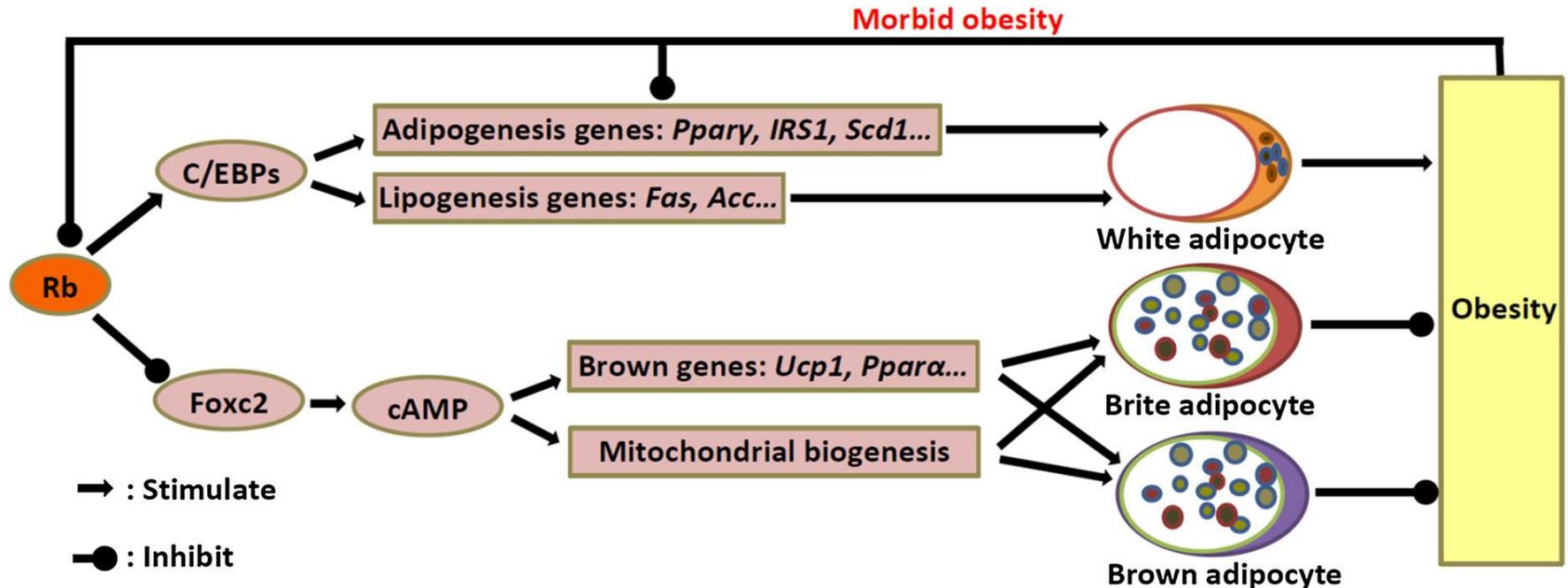
p53 inhibition or deletion leads to an obesogenic phenotype



Rb positive regulator of white adipogenesis

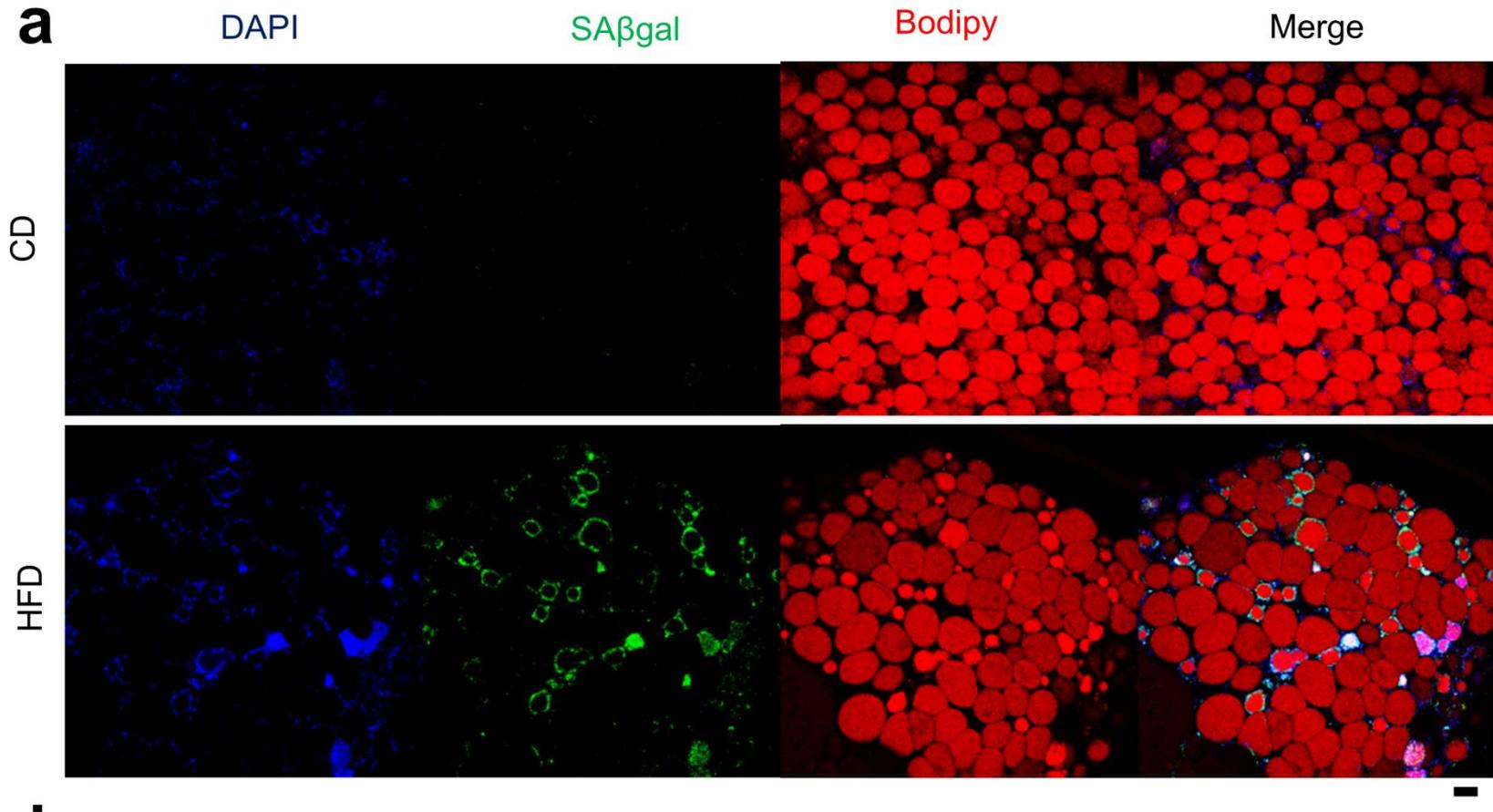
Up-regulation of Rb leads to obesity

Retinoblastoma protein, adipogenesis and Obesity

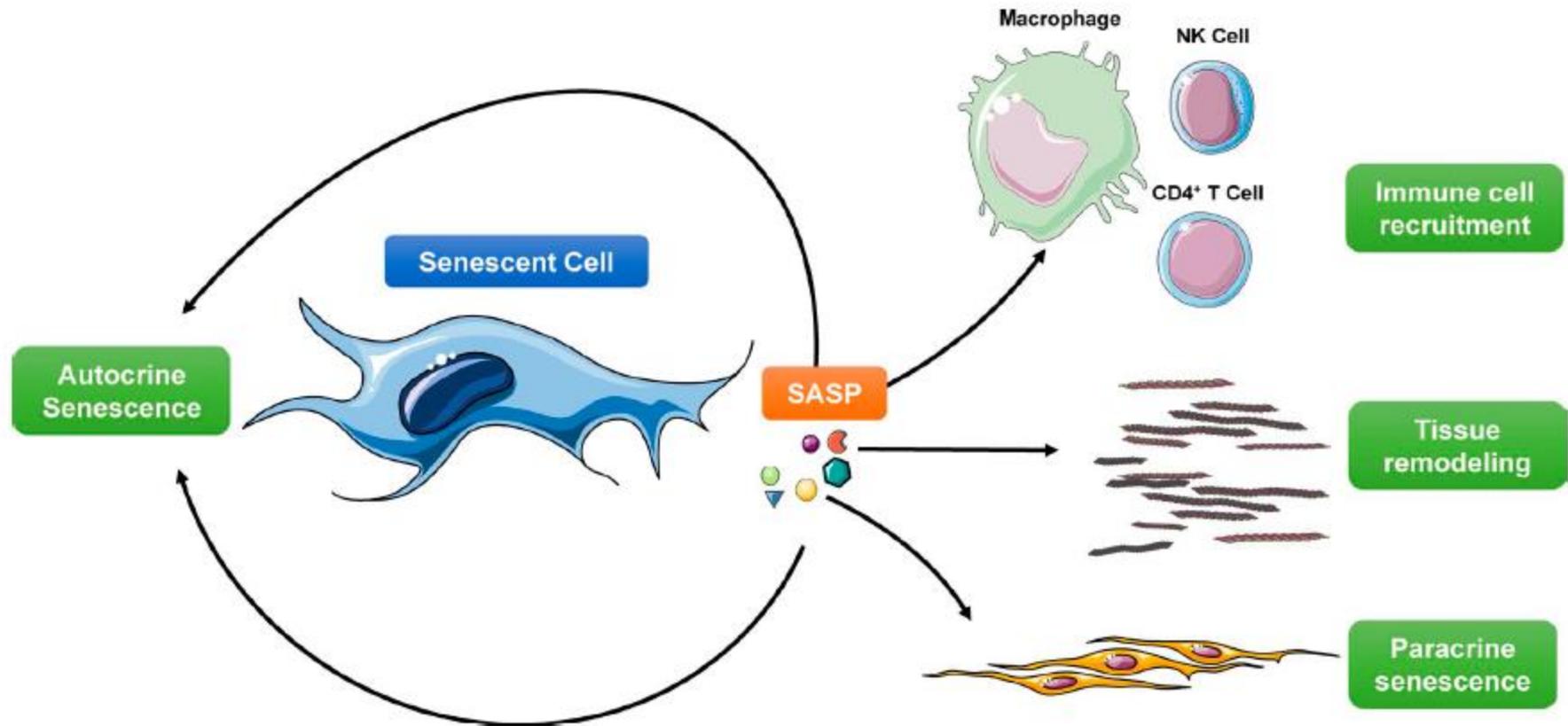


Accumulating evidence that p53 and Rb could be molecular linkages between aging and obesity

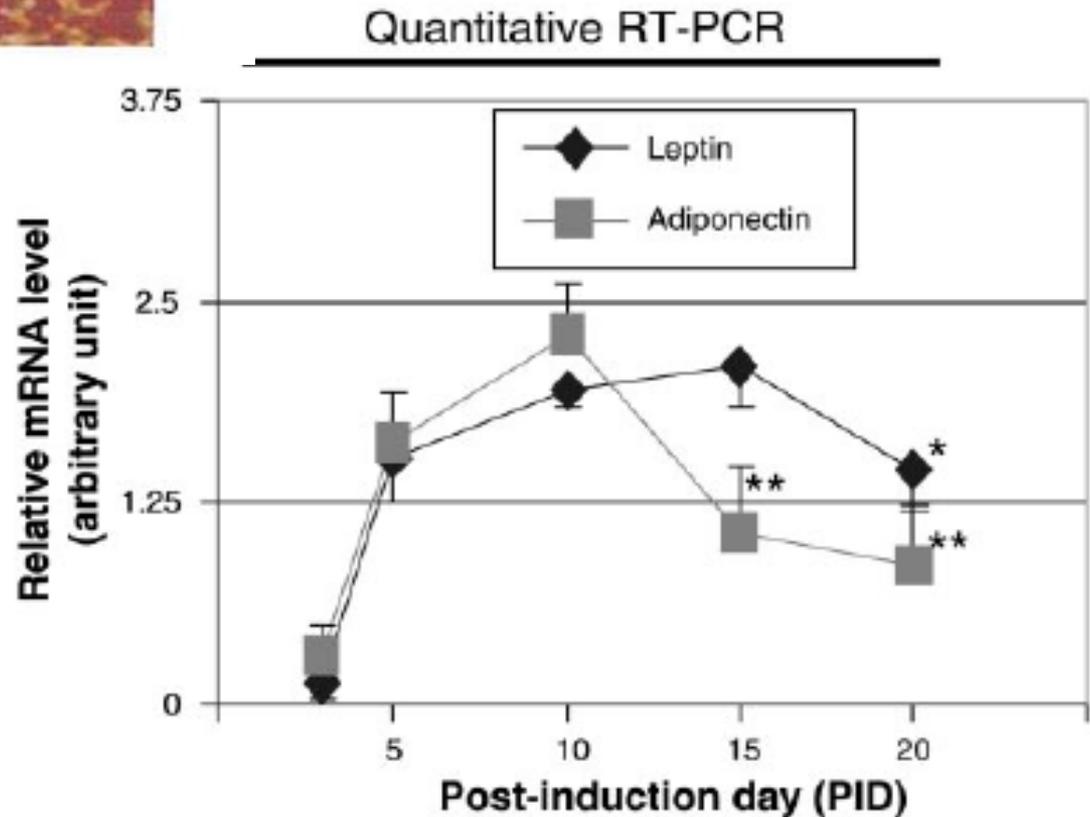
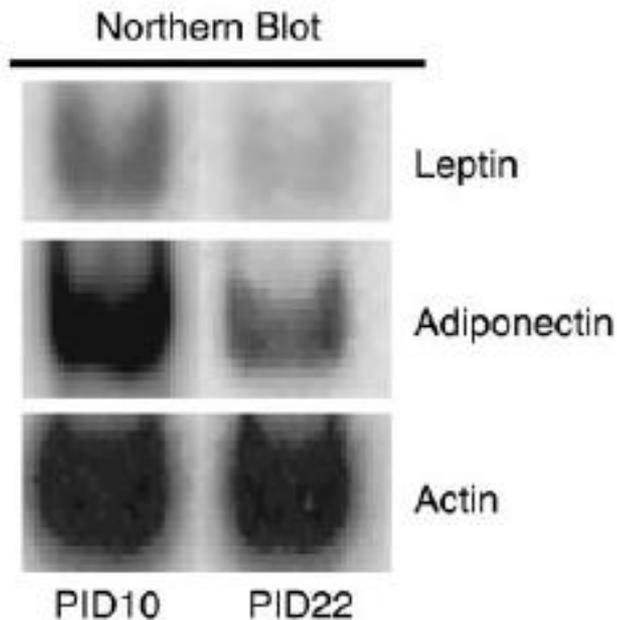
Visceral fat accumulation with aging is associated to an increase in senescence-like adipocytes



Senescence-like adipocytes present a proinflammatory secretome (SASP) contributing to inflammaging and decreasing adipogenesis



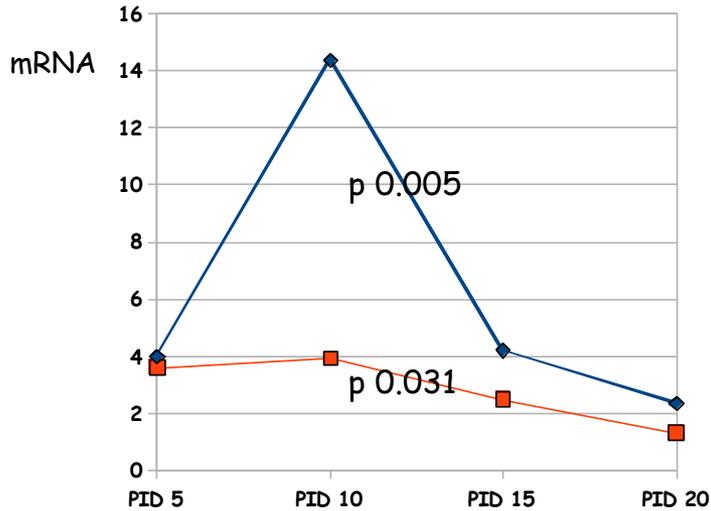
Adipocyte aging is associated with a reduction in gene expression of the secretory proteins adiponectin and leptin



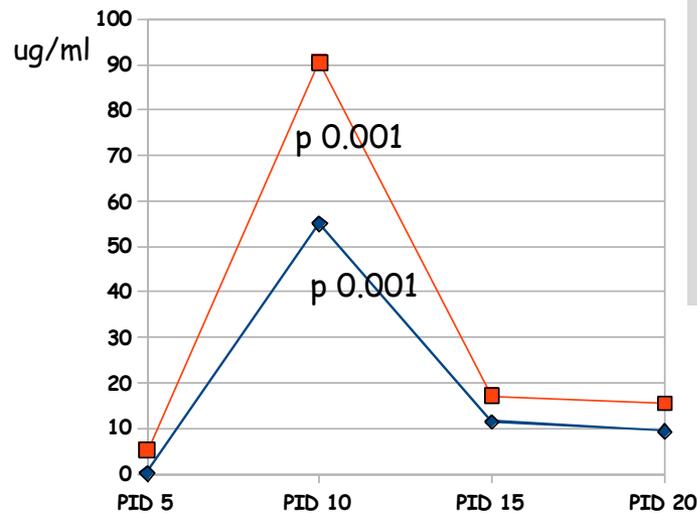
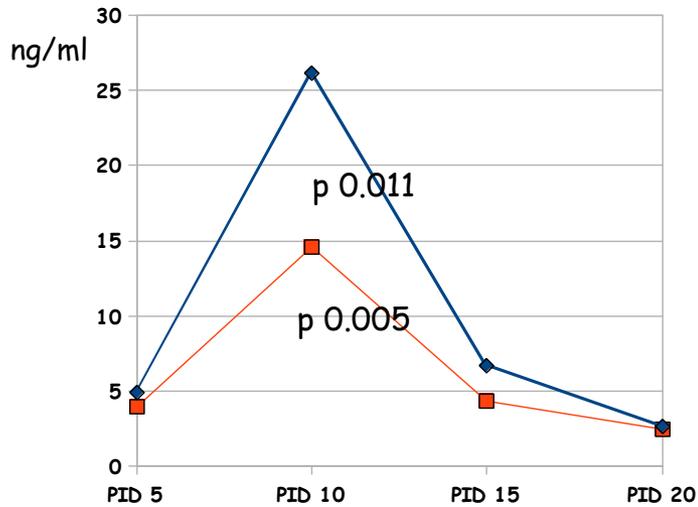
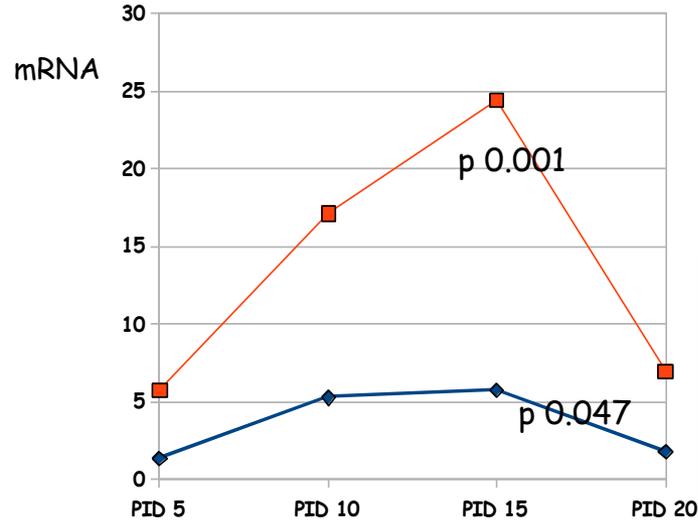


Adipocyte aging, Adiponectin and IL-6 gene expression and protein secretion in culture medium of 3T3-L1 adipocytes

Adiponectin

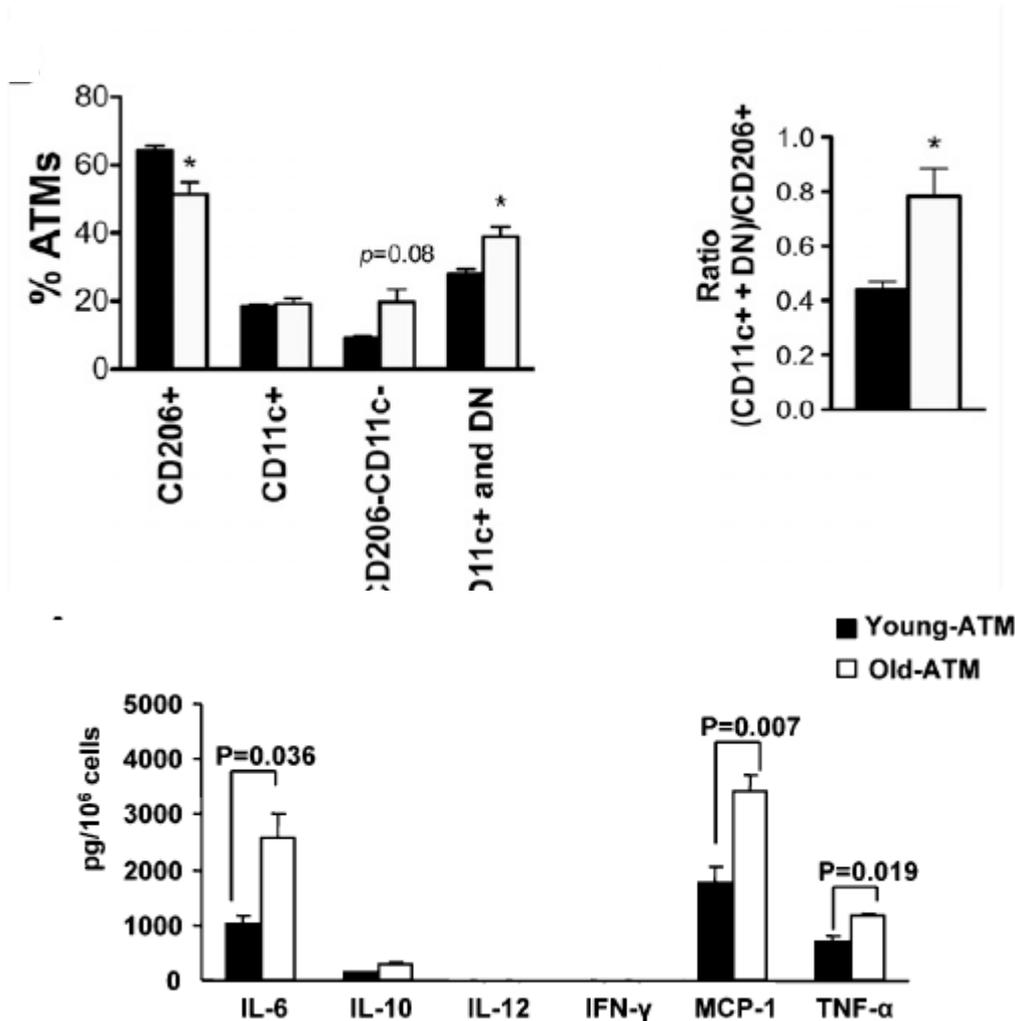


IL-6



Aging mimics the effects of LPS stimulation on adipocytes supporting the existence of an intrinsic inflammation with aging

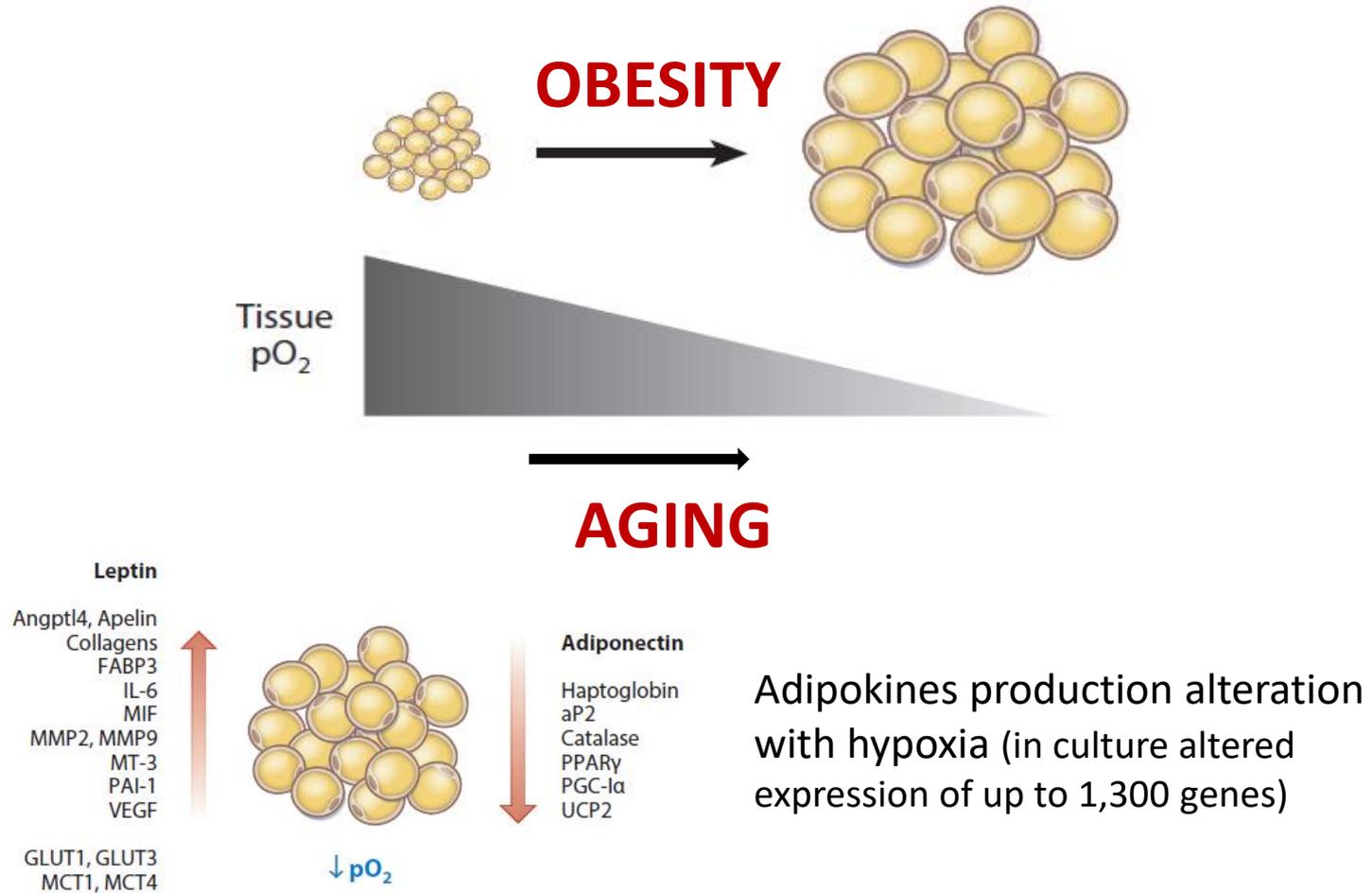
Aging is associated with a dysfunctional AT with an altered adipokines secretory profile and with qualitative changes in ATMs subpopulations



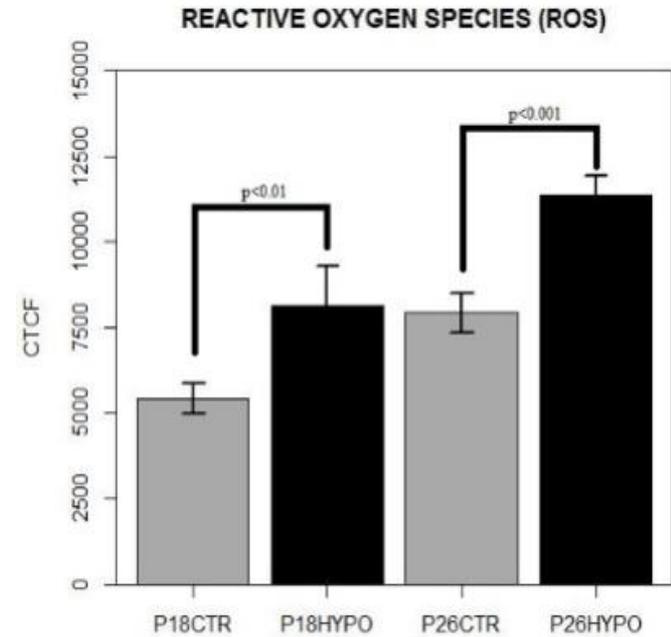
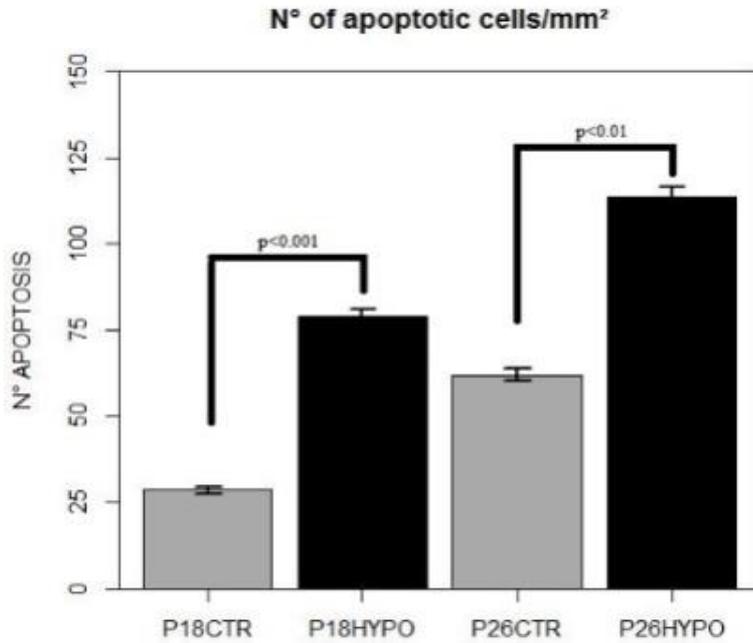
Qualitative changes in ATMs with aging generate a decrease in resident M2 ATMs.

The profile of ATMs in old fat shifts toward a proinflammatory environment

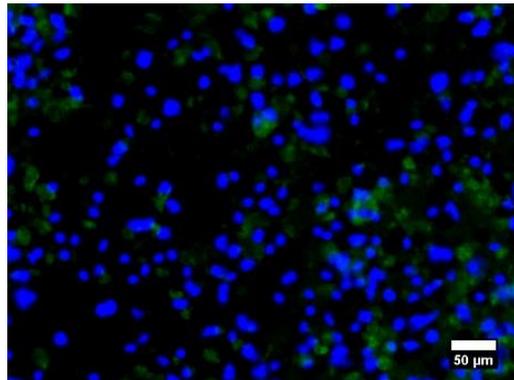
White tissue expansion in Obesity and Age-related adipose tissue disfunctions reduce the oxygen tension in adipose tissue



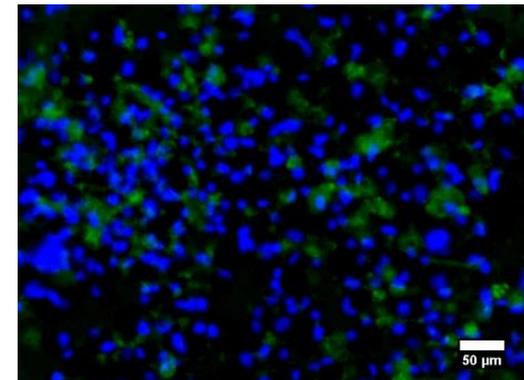
Effects of exposure of 3T3-L1 adipocytes in different stages of senescence to hypoxia (severe hypoxia 1% O₂ for 24 h)



ROS
(PID 18)



ROS
(PID 26)



Effects of hypoxia on the key functions of white adipocytes: new targets in the treatment of obesity and age-related disorders?

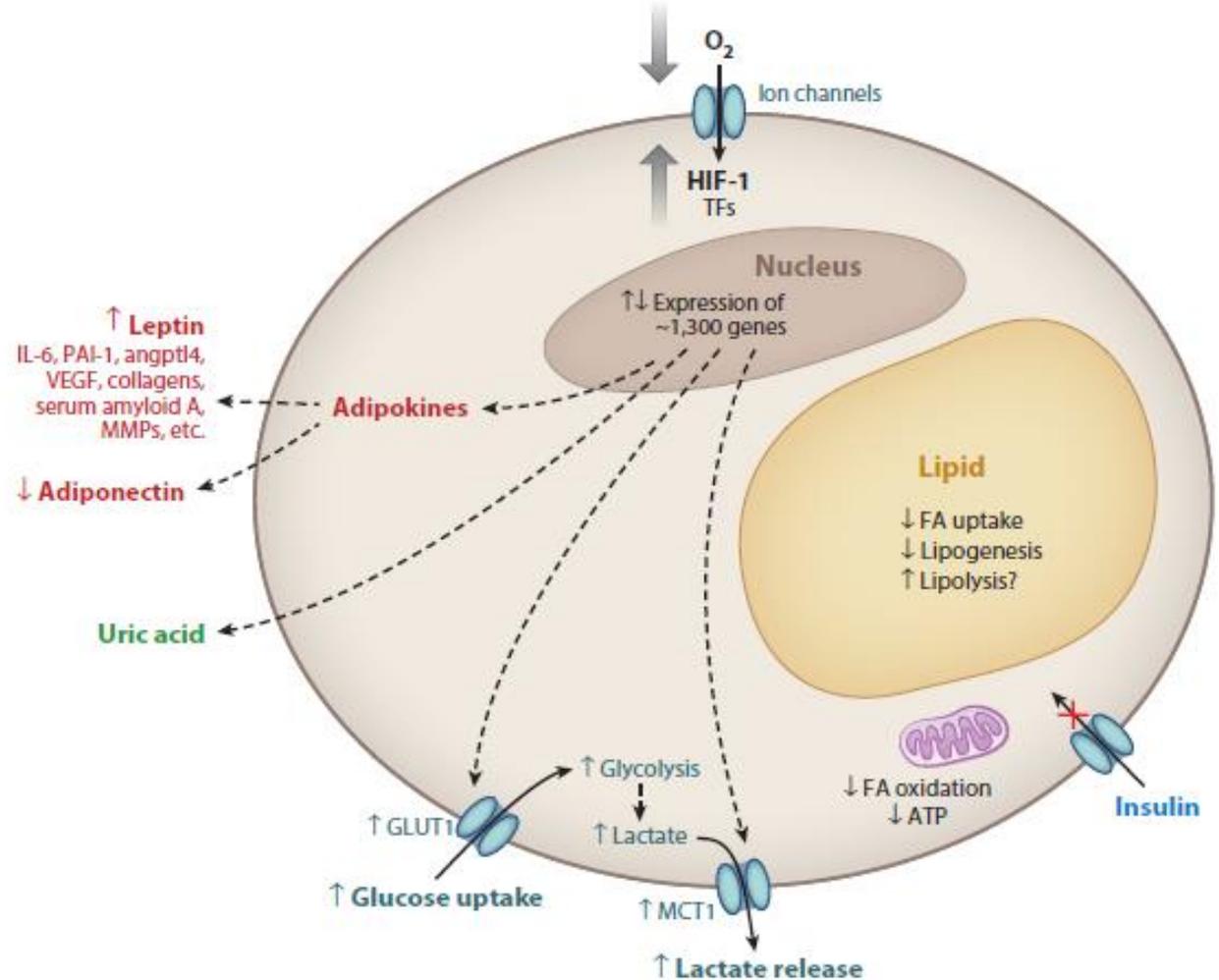
Alteration in adipokines secretion

Inhibition of genes expression linked to oxidative metabolism

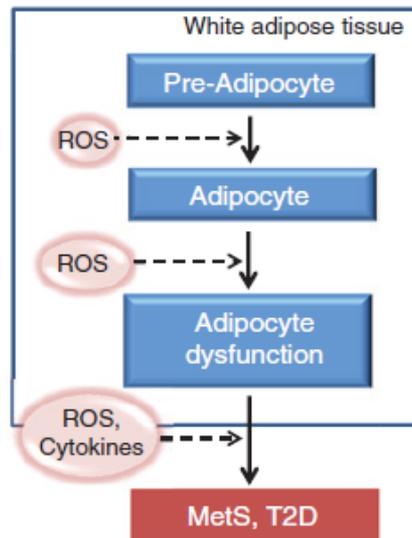
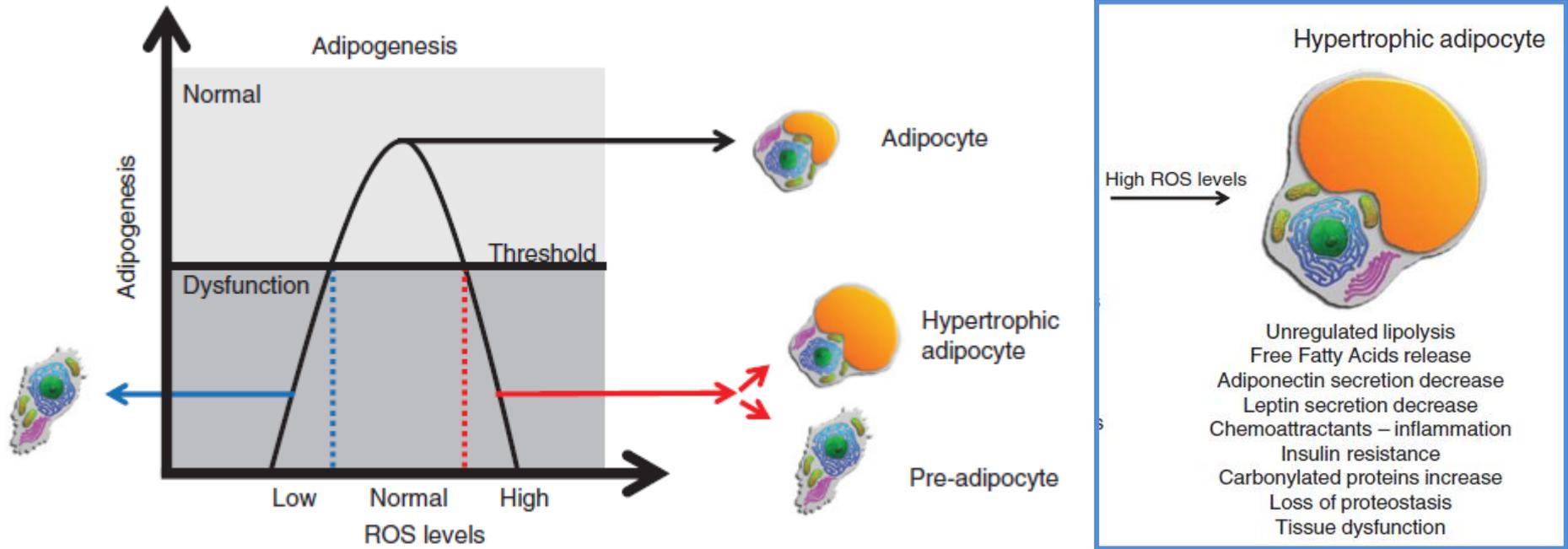
Stimulation of the expression of glycolytic genes

Stimulation of glucose uptake and lactate release

Decrease in insulin sensitivity



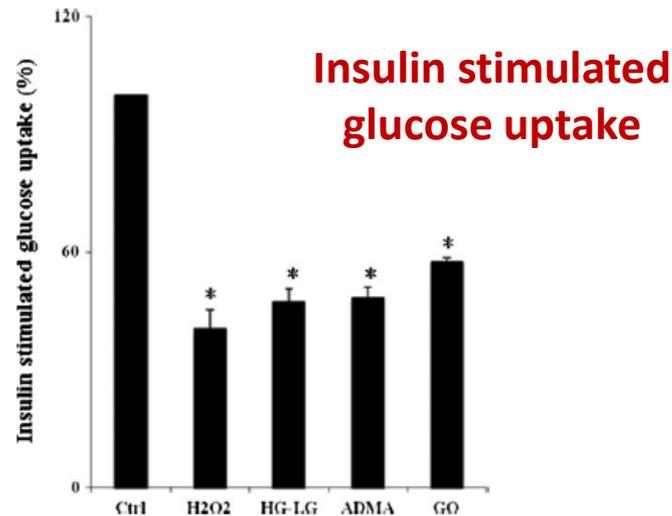
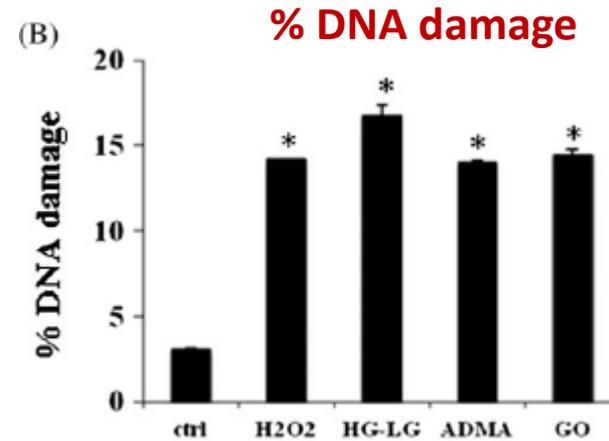
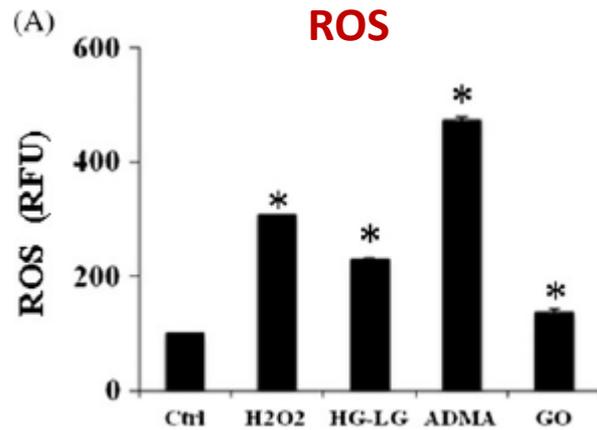
Oxidative stress effects on adipose tissue biology in aging and diseases



ROS trigger adipocyte dysfunction acting at different levels with effects depending on type, dose and target

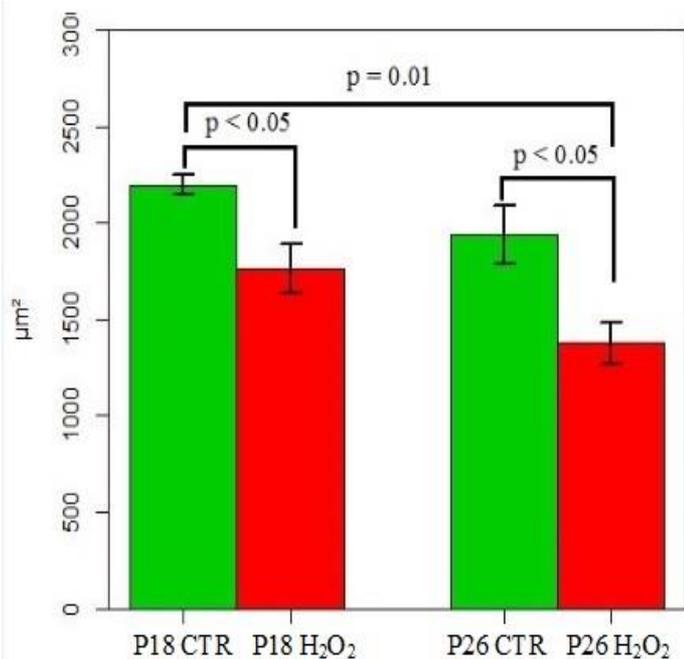
Mod. From Castro JP, Biol Chem 2016

Induction of oxidative stress and senescence in 3T3-L1: effects on ROS generation, DNA damage, telomere length and glucose uptake

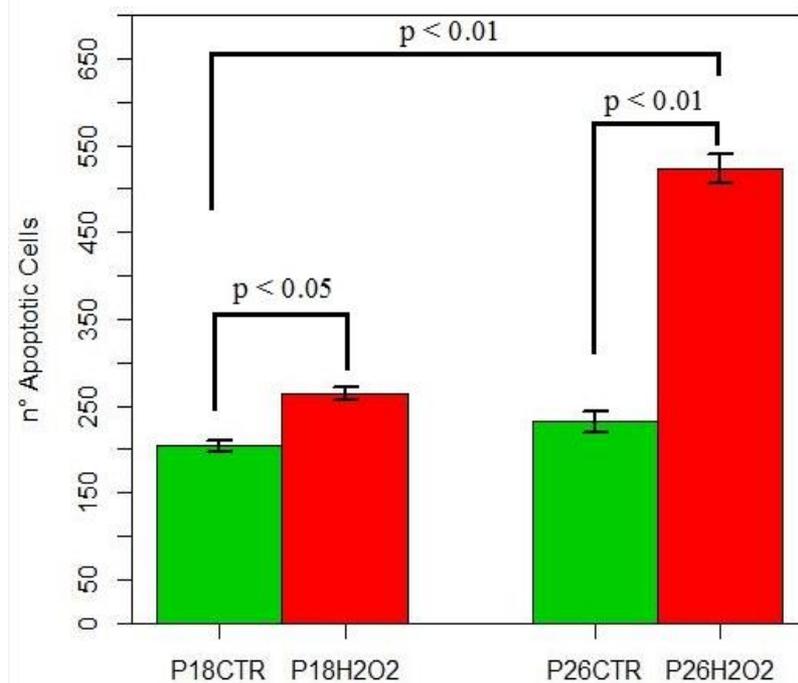


Effects of exposure of 3T3-L1 adipocytes in different stages of senescence to H₂O₂ as inducer of oxidative stress

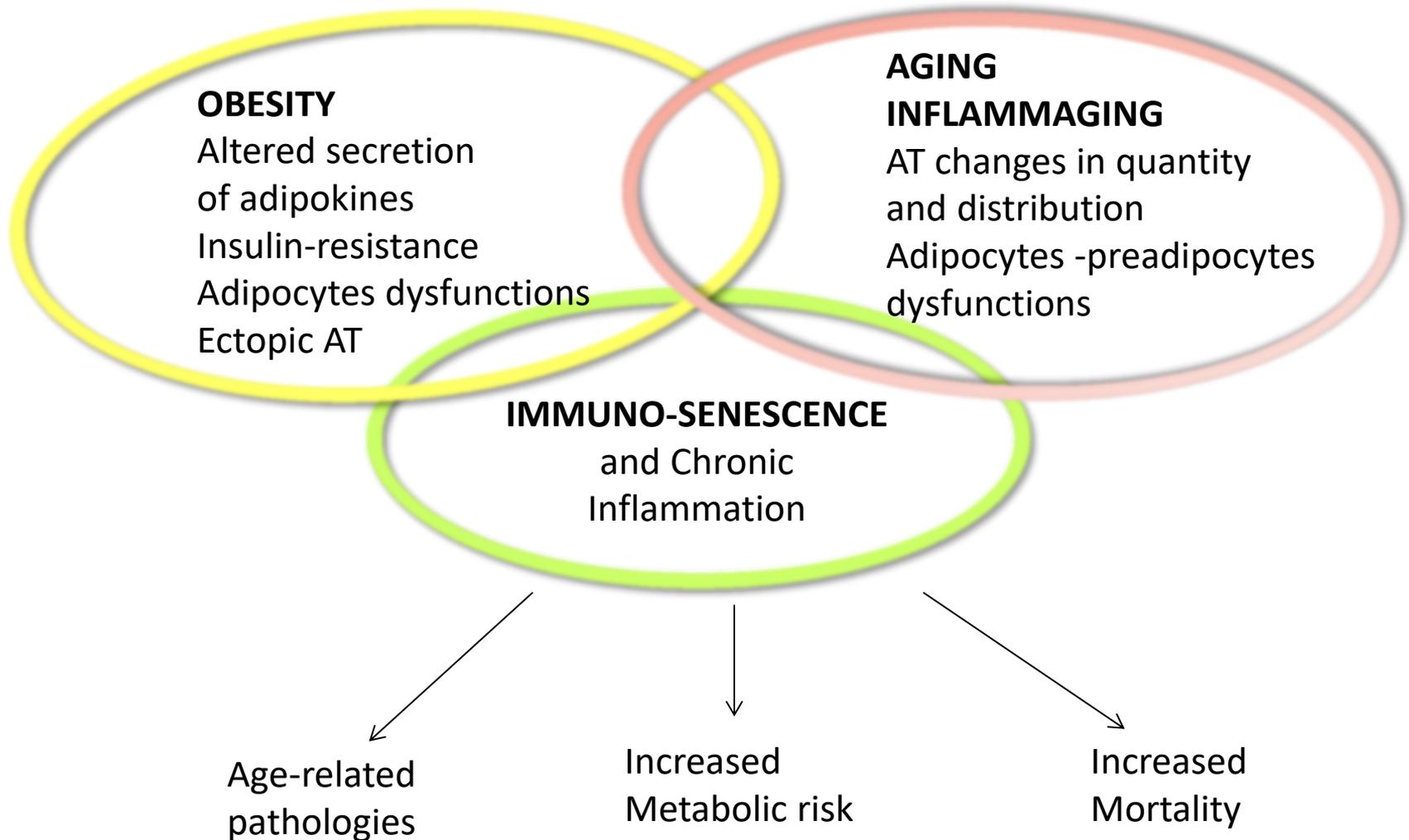
Area of adipocytes



Apoptotic cell (n)



Common etiopathogenesis features of Obesity and Aging and the need for biomolecular targets to improve many age-related diseases



INSULIN-R

GRAZIE PER L'ATTENZIONE

