

The biology of adipose tissue and animals' efficiency: renewed interests on oxido-reduction pathways

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Questions to be addressed

❖ Is body fat an important trait to consider ?

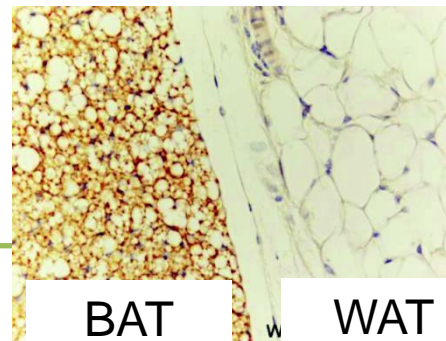
⇒ Adipose tissue (AT) metabolism between phylogenetically-divergent species (pig/chicken) ?

❖ Is AT metabolism triggering part of feed efficiency in meat animals ?

⇒ Interests for oxidative/anti-oxidant pathways ?

❖ Could we modulate AT metabolism through oxidative challenges or specific ingredients with anti-oxidant properties ?

Two types of very different fat tissues



Brown adipose tissue (BAT)

- ❑ Abundant in newborns and hibernating animals
- ❑ Hallmark of BAT: *UCP1*, a mitochondrial uncoupling protein involved in energy dissipation as heat and thermogenesis
- ❑ Found in all mammals, except pigs (*Berg et al., 2006; Hou et al., 2017*). Likely absent in chicken (*Emre et al., 2007*)

White adipose tissue (WAT)

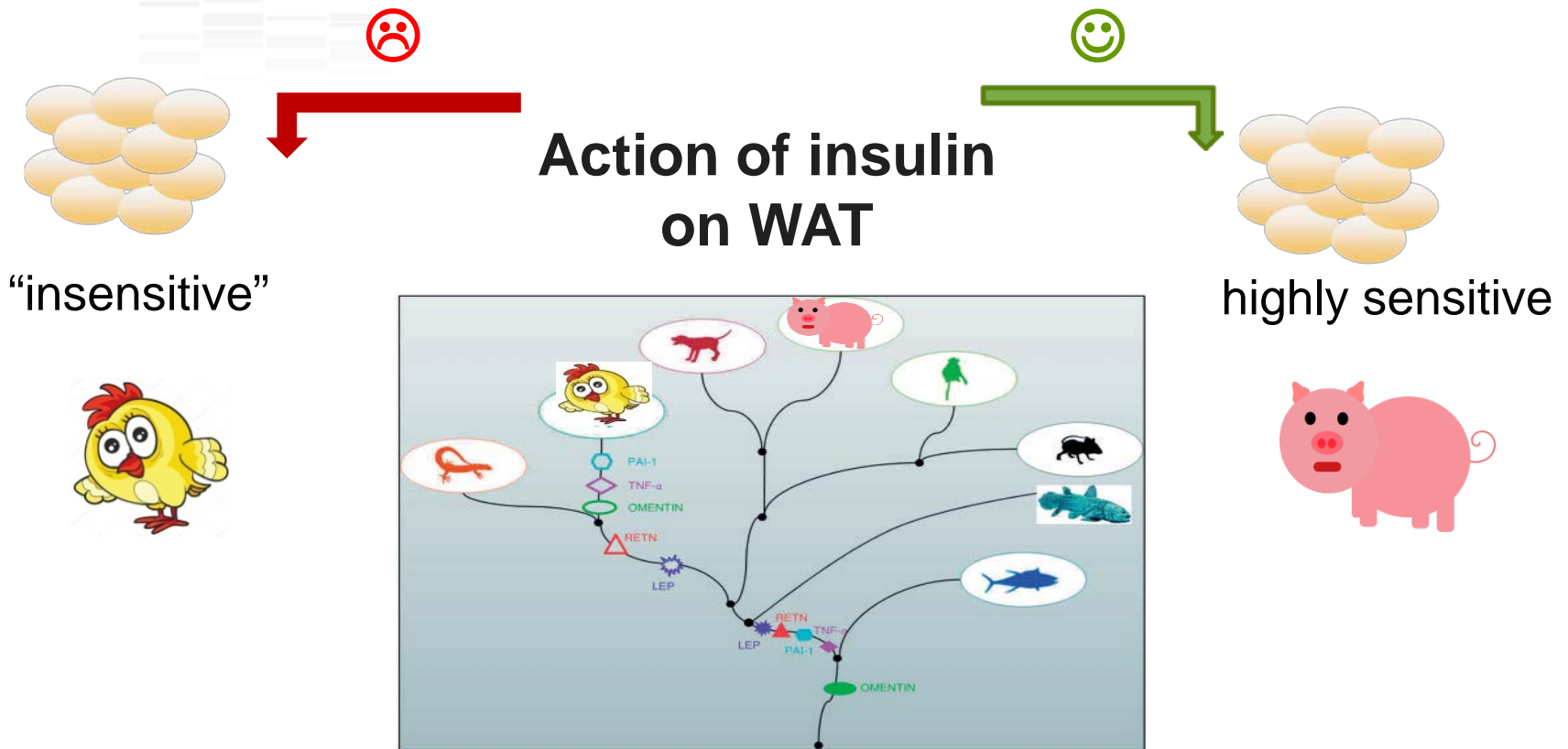
- ❑ Abundant in all animals, notably growing & adults
- ❑ Involved in energy storage and many other functions

Q1: Importance of white adipose tissue (WAT)

- ❖ Information regarding WAT is economically important as those producing animals and selling meat products put **efforts to obtain leaner animals**
- ❖ **A variable part of body mass**
 - ~10-25% in pigs from 10 to 138 kg BW
 - ~3-27% in chicken from 0.4 to 3.3 kg BW

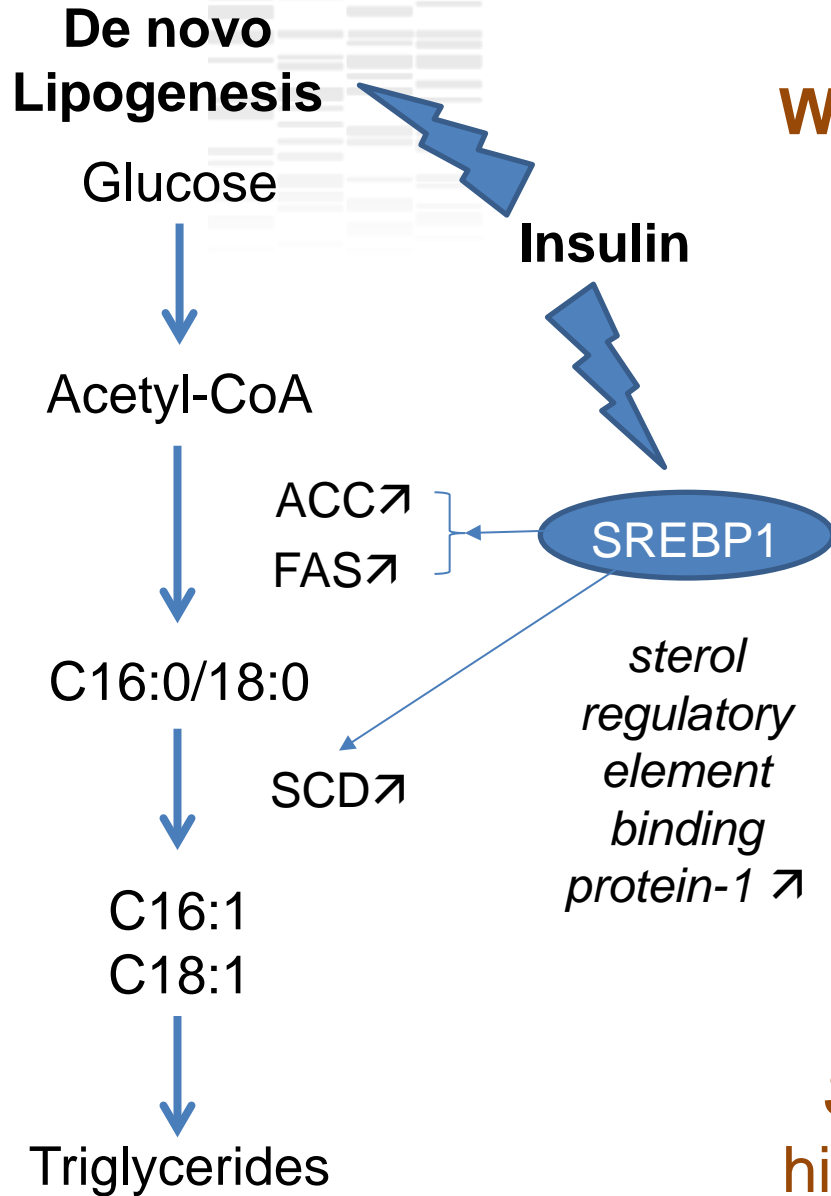
(Mitchell et al., 1996, 1997, 2001; Latshaw & Bishop, 2001)
- ❖ **Physiologically, WAT has a considerable capacity to expand**, due to internal factors (age, sex, breed, etc.) and environmental effects (feeding, etc.)
 - ⇒ **imbalance in lipid deposition/lipolysis**

Species-specific mechanisms drive lipid synthesis

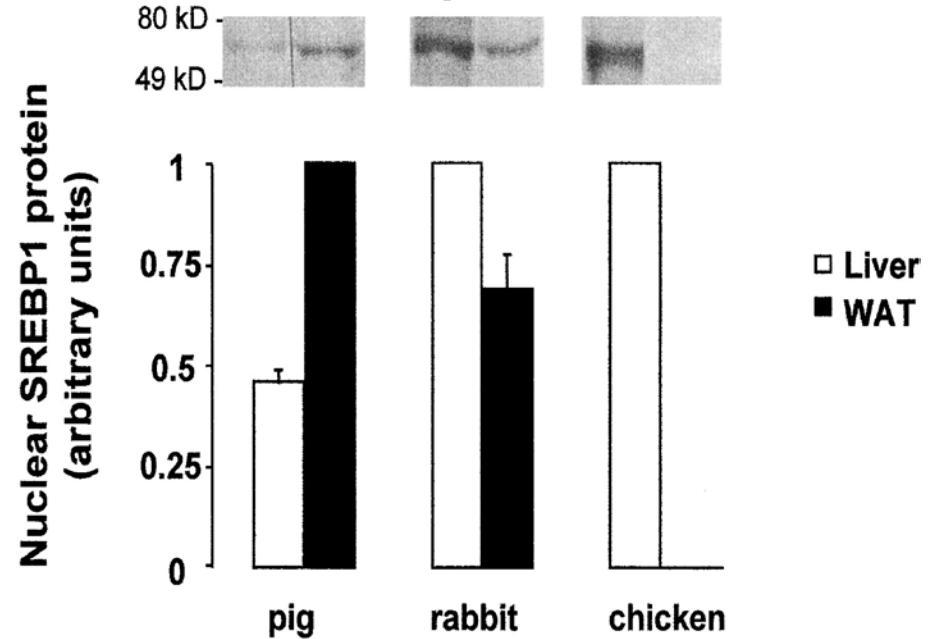


Adipokines inhibiting insulin sensitivity : resistin, TNF α , PAI-1/SERPINE1 and those enhancing insulin sensitivity : omentin, were lost in the chicken genome (Dakovic et al., 2014)

De novo lipogenesis (DNL): WAT in pigs ≠ liver in chicken



Nuclear content of SREBP1 protein



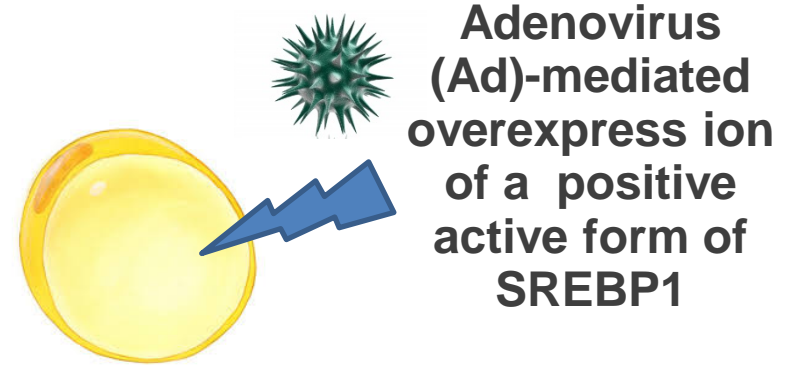
Gondret et al., 2001

SREBP1 is associated with the hierarchy of organs in lipogenesis

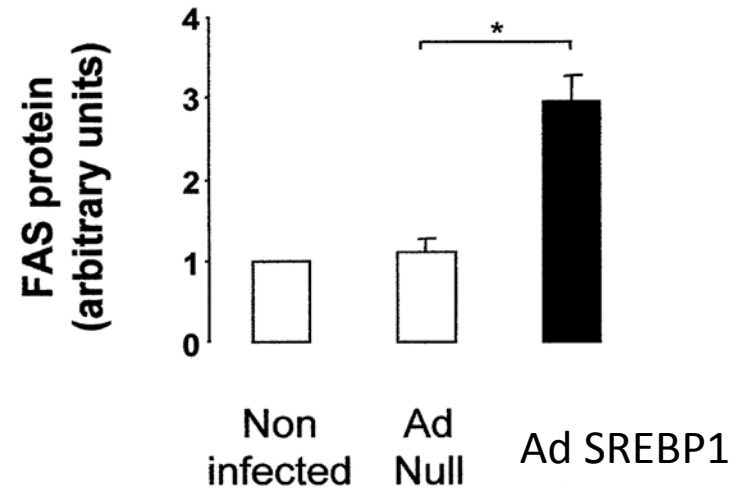
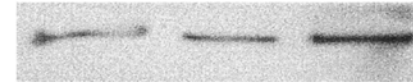
Genome array studies confirmed that *SREBP1* was “not expressed” in chicken adipose tissue

Wang et al., 2017

***SREBP1*: a key transcriptional determinant of the site of lipogenesis across species**

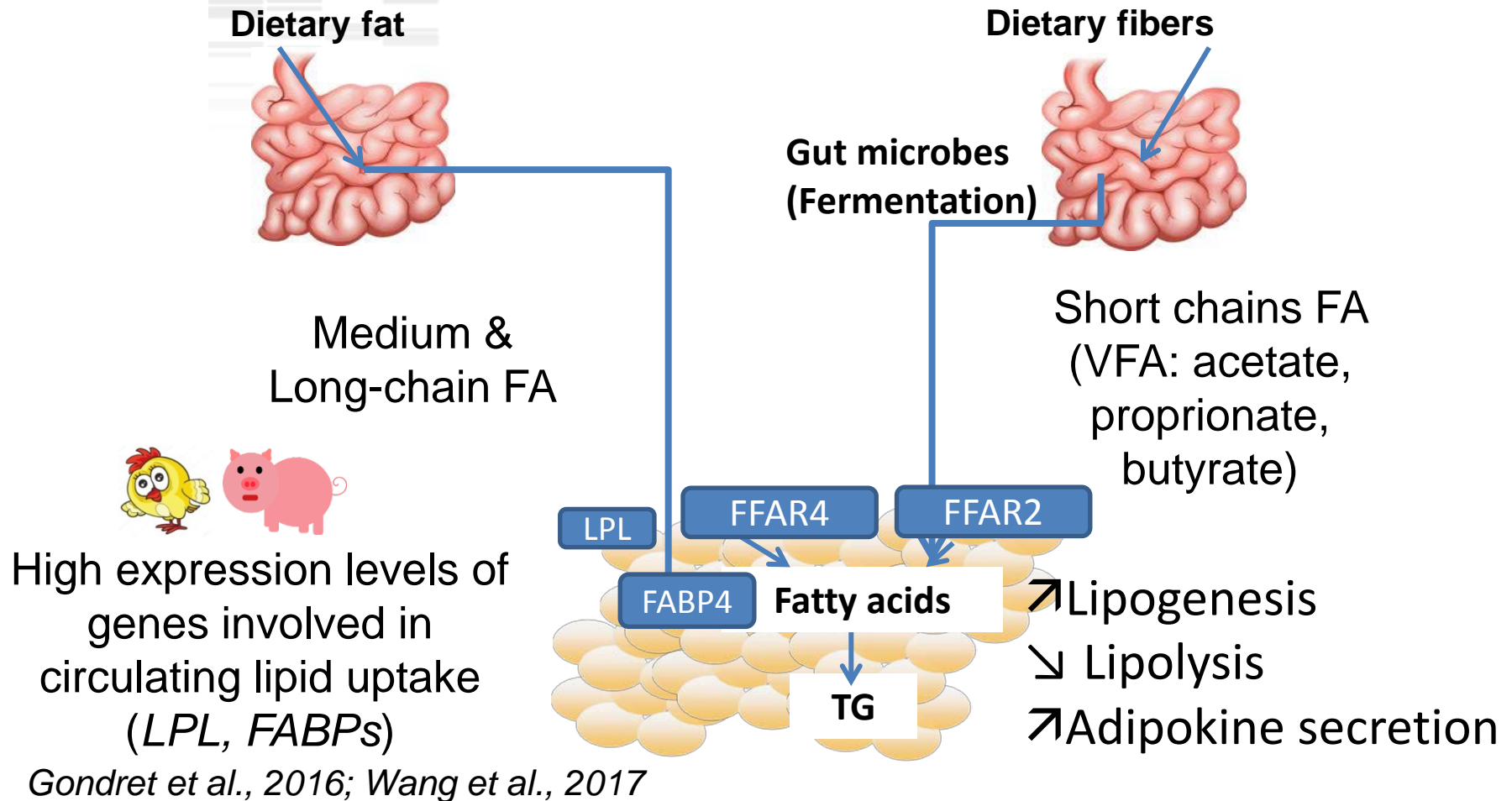


200 KD



Gondret et al., 2001

Species-specific mechanisms drive lipid deposition

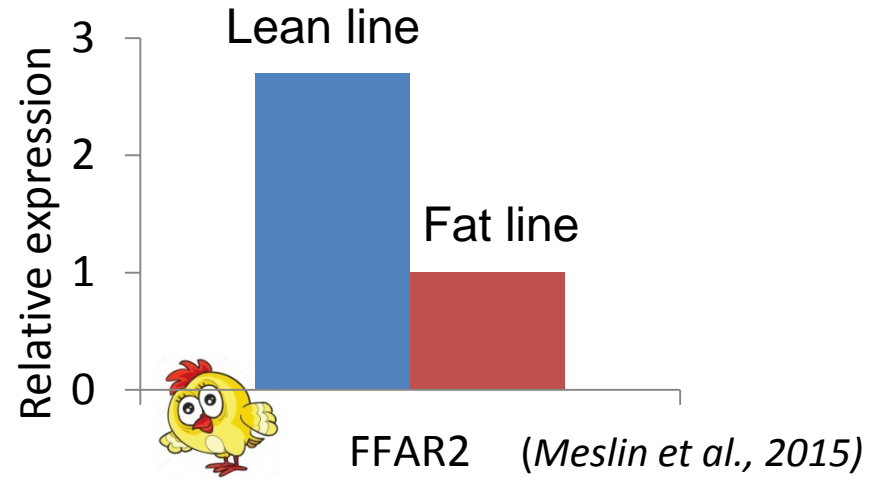


Free fatty acid receptors:

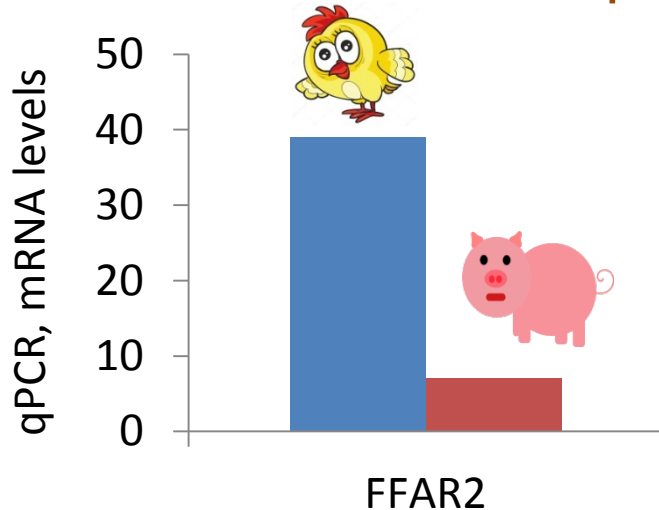
FFAR4 is activated by medium and long-chain FA
FFAR2 is selectively activated by short-chain FA

□ FFAR2: a metabolic sensing receptor regulating AT mass

- ✓ Mice overexpressing AT-specific FFAR2 are lean
- ✗ FFAR2 k/o mice are obese



□ Differences in FFAR2 expression between species in WAT



- FFAR2 was detected with **23 paralogs in the chicken genome** (\neq 1 paralog in pig)

(Meslin et al., 2015)

Relevance for specific ability to use nutrients derived from fiber-rich diets ?



Q1 Is body fat an important trait to consider ?

Body fat content is an important trait in meat animals

Various pathways act on body fat

Clear differences between species in:

- their hierarchy in organs acting in fat regulation
- expressions of the main metabolic actors

Q2: May adipose tissue trigger part of feed efficiency ?

❖ **Fat deposition requires 16 % more energy per unit of gain** than protein deposition

de novo lipogenesis (DNL) : the most “energetically costly” road to drive extra calories

❖ **High feed efficient animals have reduced fat depots**
(e.g., high feed efficient chickens: ∨ abdominal fat)

❖ **Fatty animals are generally less efficient**
(e.g., castrated & females pigs: ↗ fat, ∨ feed efficiency than male pigs)

But this is not
always true !

Refeeding after restriction in pigs:

↗ feed efficiency *(Heyer et al., 2007)*

↗ rate of lipid deposition

❖ Relationships between adipose tissue traits and residual feed intake (RFI \approx net feed efficiency)

RFI = observed feed intake - predicted feed intake
(based on maintenance and growth performance)

Low RFI animals = high feed efficient animals

❑ Moderate but **positive genetics association** between RFI and body fat content in pigs (*Gilbert et al., 2007*) and chicken (*Zhuo et al., 2015*)

❑ **Low RFI pigs (= high efficient) had less carcass fat**
(*Young & Dekkers, 2012; Gilbert et al. 2017*)

❑ **Results may depend on :**

- age of animals
- traits related to body fat content included or not in the selection index

=> Adipose tissue was less affected than muscle by selection for RFI in pigs (*Gondret et al. 2017*)



□ Gene expression analyses in WAT

RNA-seq in WAT of chicken ranked for RFI

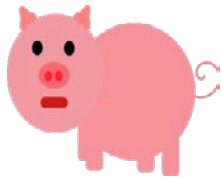
(Zhuo et al., 2015)



in the high efficient group (low RFI animals):
↗ Lipid hydrolysis

Porcine oligo microarrays in WAT in pigs divergently selected for RFI

(Louveau et al., 2016; Gondret et al. 2017)

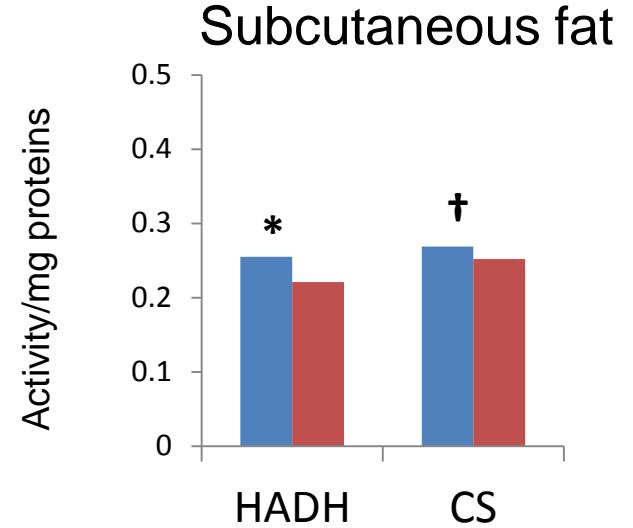
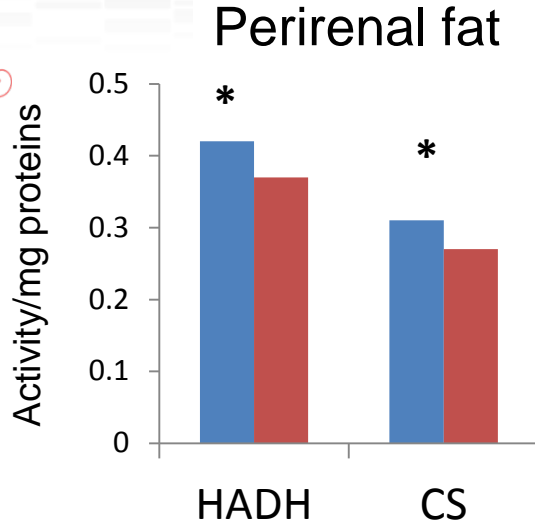


in the high efficient group (low RFI animals):
↗ Lipid hydrolysis
↗ **Fatty acid oxidation**
↗ **Oxido-reduction process & electron chain transport**
↗ **Mitochondrial** organization
↗ or ↘ genes involved in the response to **oxidative stress**

- Up-regulated genes in high feed efficient (low RFI) pigs : *HADH (fatty acid oxidation)*, *CS*, *IDH1* (Krebs cycle), subunits of NADH dehydrogenases, etc.

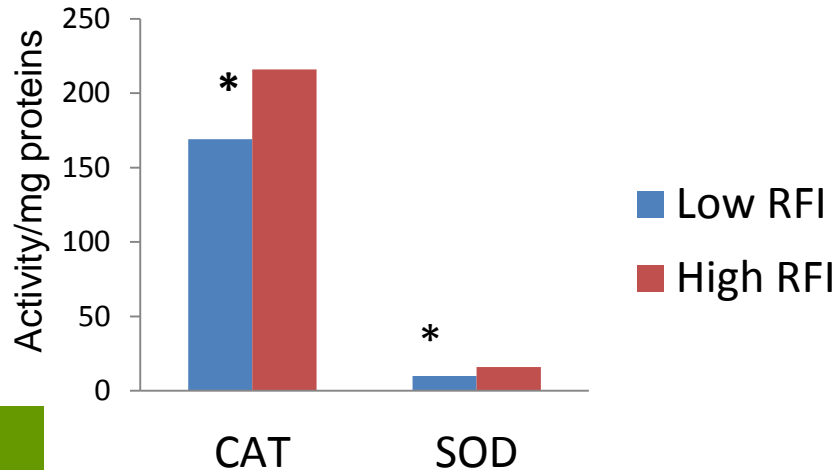


Enzyme activities

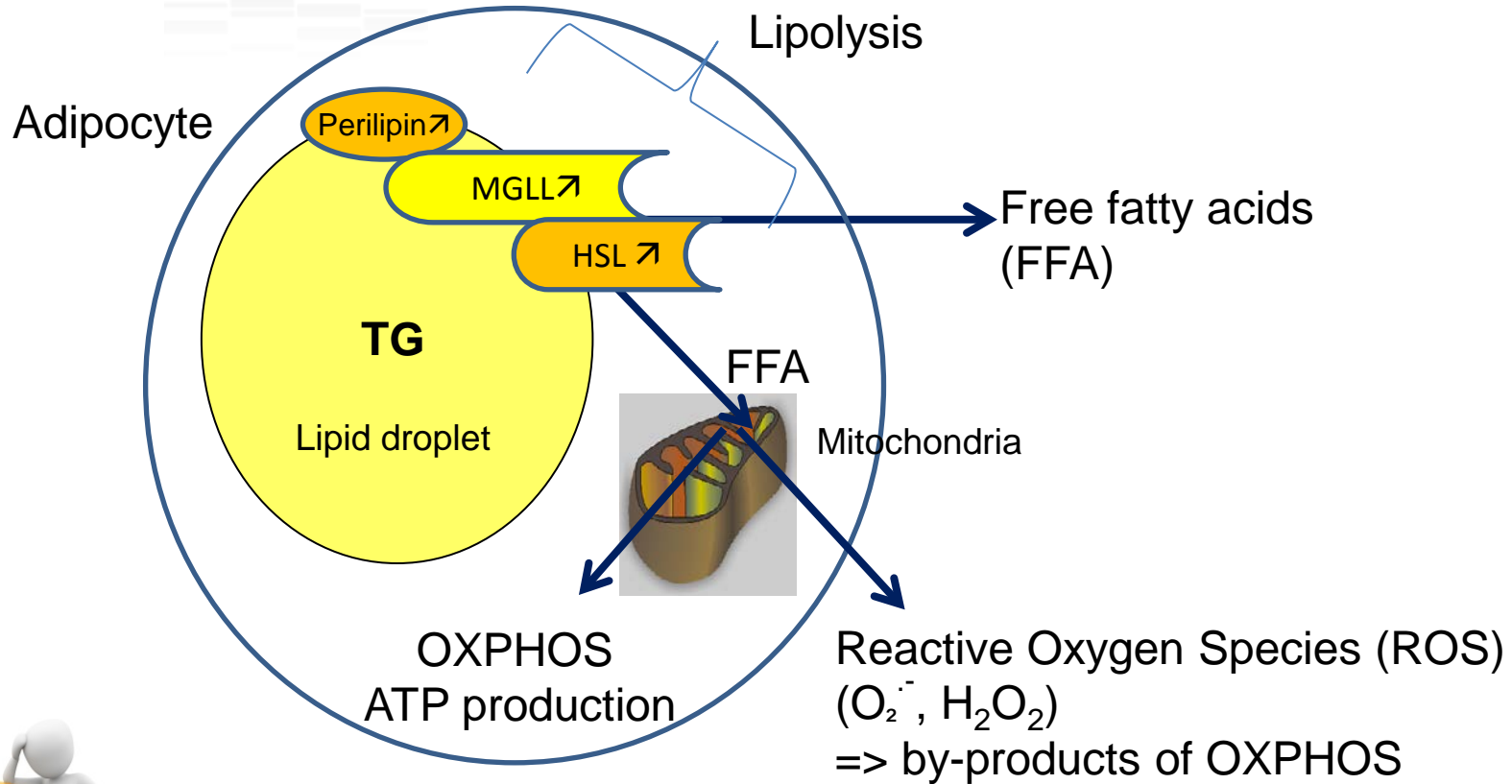


- Antioxidant capacities

Enzyme activities



❖ Catabolic nutrient processes in adipocytes



Mitochondria in WAT \Rightarrow generating ATP to support lipid metabolism, adipokines production and adipocyte differentiation



In lean vs fat lines:

↗ FA β -oxidation: *HADH*, *PHYH* & *HSD17B4/6*

(*Resnyk et al., 2013; 2015*)

Human and rats:

Negative relationships between oxidative capacity of mitochondria (OXPHOS) in WAT and obesity

(review: *Flachs et al., 2013*)

Induction of FA oxidation and uncoupling O₂ consumption from ATP synthesis:

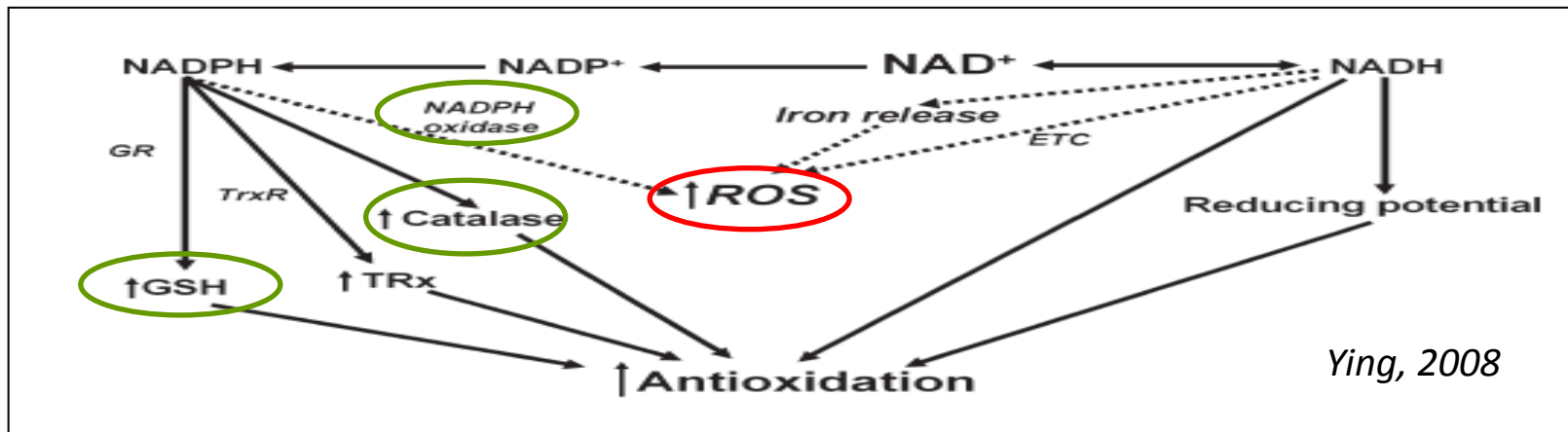
↗ the use of fatty acids within the adipocyte

↘ their release into the bloodstream

↘ **incidence on body fat content**

□ Increased numbers of metabolic intermediates in Krebs cycle:

- ↗ NADH generation
- ↗ H gradient across mitochondrial membranes
- ↗ ROS generation from the electron transport chain
- ↗ anti-oxidant pathways



- ↗ **Modulation of oxidative stress**
- ↗ **Changes in nutrient efficiency**



Q2 Is AT metabolism triggering part of feed efficiency in meat animals ?

Negative relationships between body fat and feed efficiency at the animal level

Mitochondrial pathways in WAT may participate to net feed efficiency

- ↳ Looking further at FA oxidation, respiratory pathway and ROS production in WAT
- ↳ Modulating antioxidant pathways, also in WAT, might be important to improve animal performance

Q3: Modulations of WAT metabolism by oxidant/antioxidant challenges



clean

Degradation of hygiene housing conditions



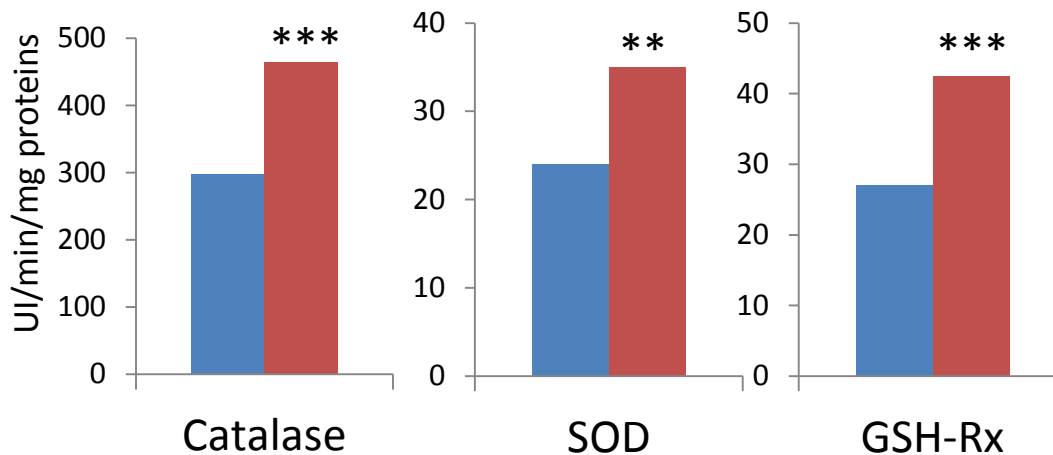
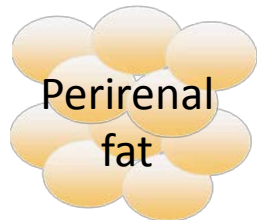
dirty

6 wks during growth

⇒ ↘ feed efficiency, = % fat content

⇒ induction of oxidative stress (↗ plasma H₂O₂)

clean
dirty



↗ Catalase, SOD, and GSH-Rx activities in WAT

(Sierzant *et al.* 2016)

Effects of AA with antioxidant properties

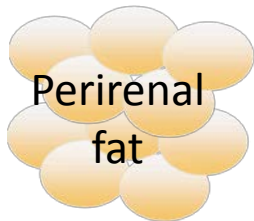
Methionine ⇒ Cysteine ⇒ Glutathione

Glutathione is the main cellular non-enzymatic antioxidant



Met deficient diet fed during 10 days
in post-weaning period (from 42 days-old)

- ⇒ ∨ feed efficiency, ↗ fat content
- ⇒ induction of systemic oxidative stress



↗ Oxidized glutathione (GSSG) content
↗ Catalase, SOD and GSH-Rx activities
in WAT

Castellano et al, 2015

Natural ingredients with antioxidant properties

Scutellaria baicalensis -> baicalin (flavonoid-type polyphenol)

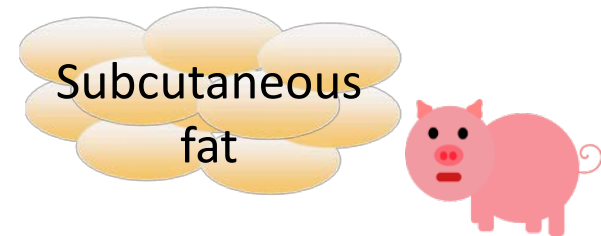
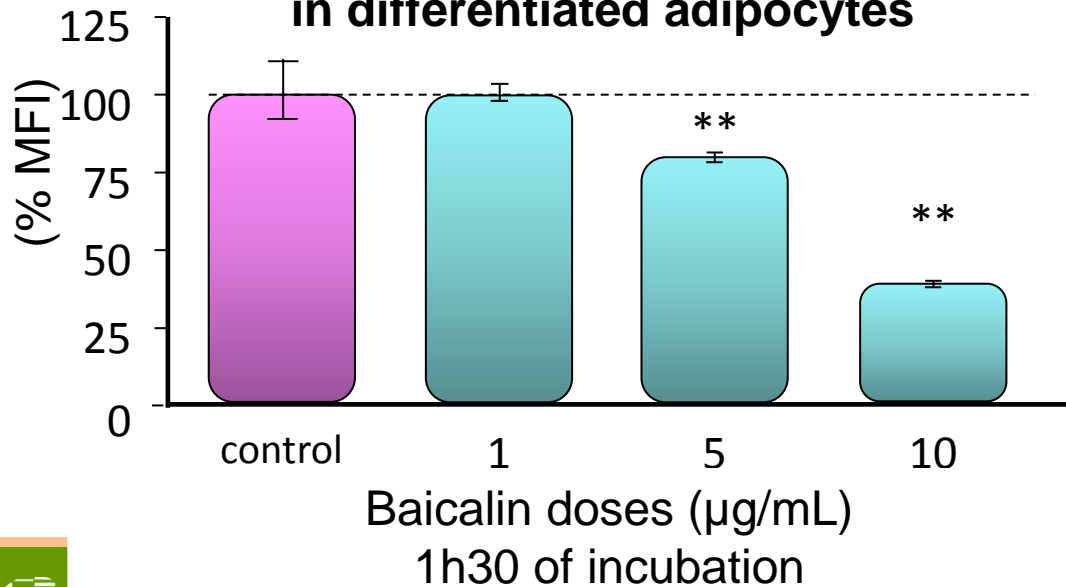


Used in traditional Chinese medicine

Liver-protective effects

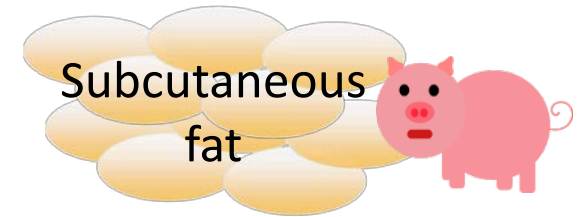
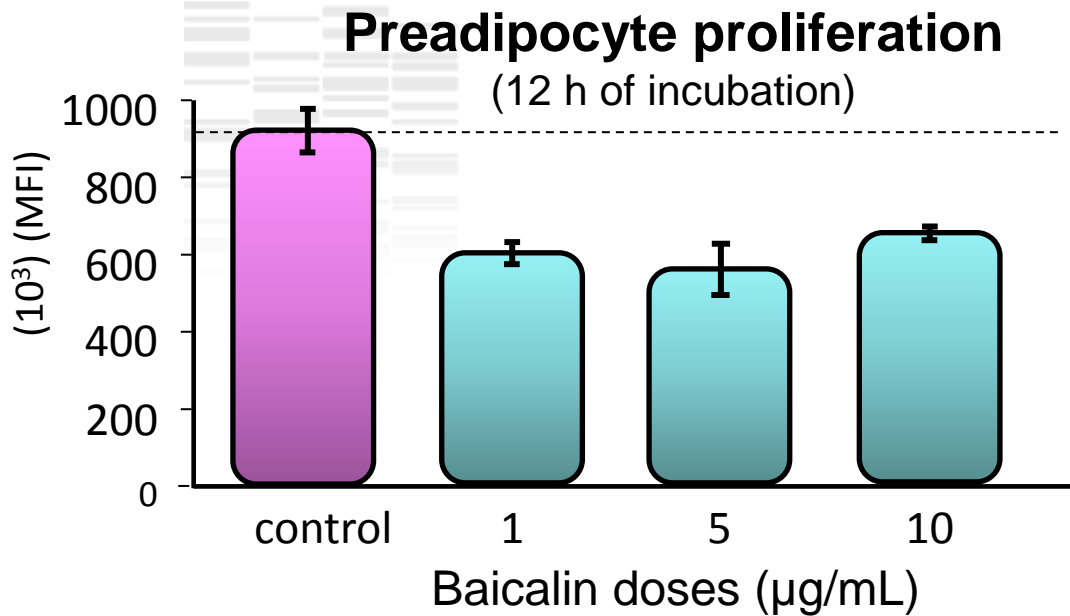
Anti-inflammatory & anti-tumoral effects

ROS production in differentiated adipocytes



Anti-oxidative effects
on pig adipocytes

Perruchot et al, unpublished



Anti-proliferative effects on pig adipocytes

Perruchot et al., unpublished

Plants extracts rich in polyphenols (berries, grapes, nuts, etc.)

Polyphenol-rich extracts : able to protect murine preadipocytes against H₂O₂, to decrease ROS production and increase superoxide dismutase (SOD) expression levels

Polyphenols may induce lipolysis, FA oxidation & benefit body composition

Resveratrol-rich grape extracts: ↗ FA oxidation, ↘ fat deposition in pigs

Review in farm animals: Gessner et al., 2016



Conclusions

The role of adipose tissue (AT) is far beyond the simple role of fat storage and participates to physiological (energy) homeostasis

AT metabolism differs between species (pigs, chicken)

AT metabolism and feed efficiency are, at least in part, related

Both lipolysis and mitochondrial oxido-reduction pathways are modulated in response to changes in feed efficiency

Oxidative/antioxidant challenges can modulate AT antioxidant pathways



A renewed interest for nutrient oxidation and redox metabolism within adipocytes is needed, with possible benefits for fat content and feed efficiency