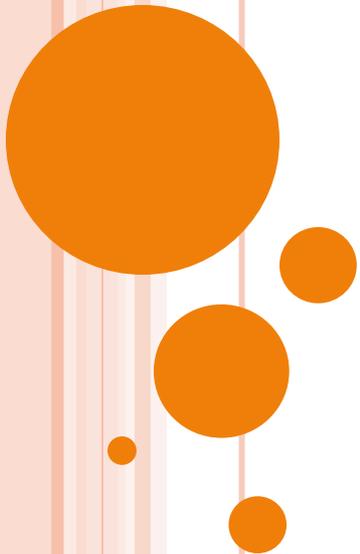


# MÉTABOLISME, DIABÈTE ET VIEILLISSEMENT

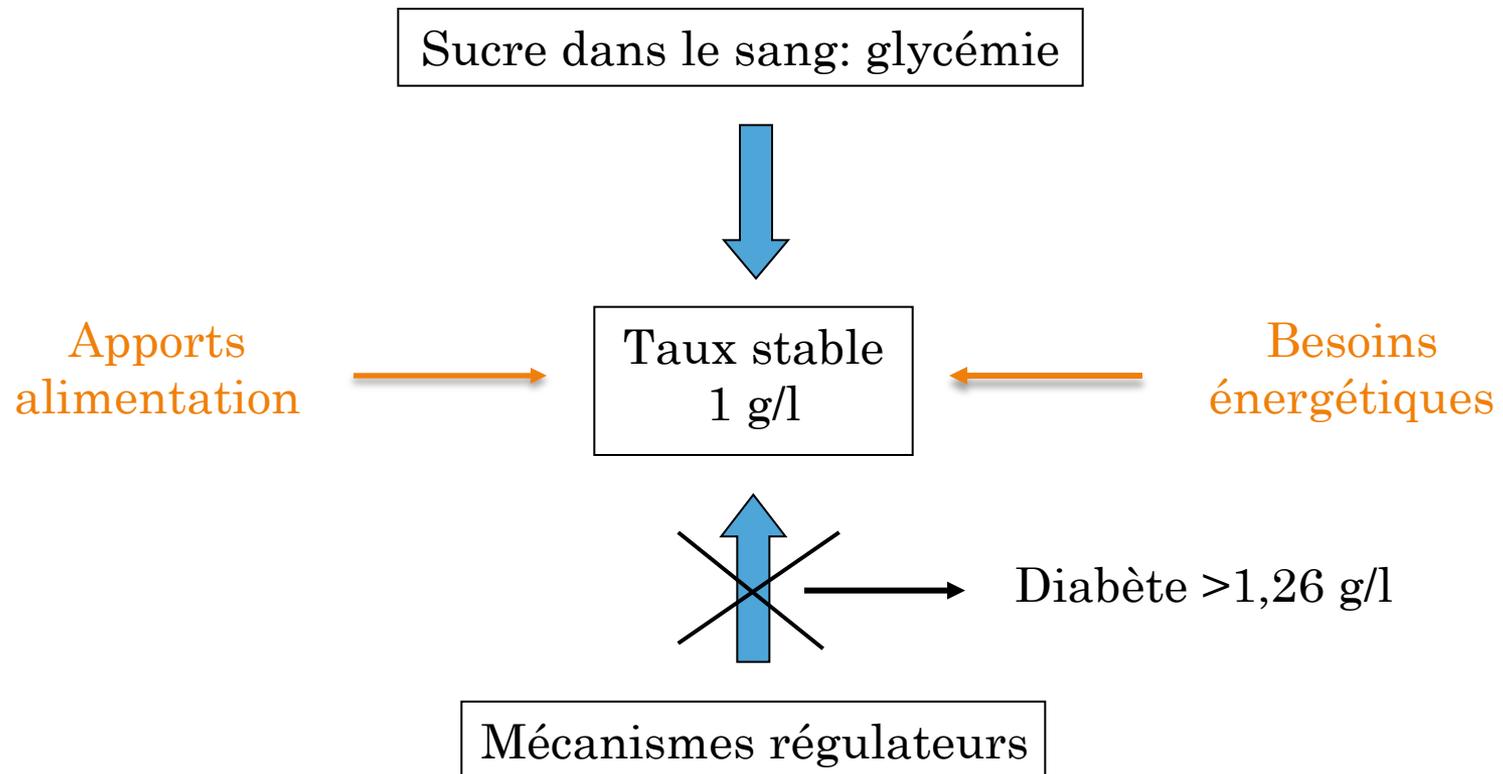
**Pr Anne Lajoix**  
**Directeur BC2M**

**[anne-dominique.lajoix@umontpellier.fr](mailto:anne-dominique.lajoix@umontpellier.fr)**



# LE DIABÈTE

Maladie métabolique caractérisée par un excès chronique de sucre dans le sang



# LE DIABÈTE

463 millions sujets atteints dans le monde (2019)

→ Diabète de type 1 (10%)

- début: sujet jeune
- cause: dérèglement du système immunitaire  
destruction des cellules pancréatiques produisant l'insuline

→ Diabète de type 2 (90%)

- début: âge mur
- cause: dysfonctionnement du pancréas: défaut de sécrétion d'insuline  
résistance des tissus cibles à l'insuline

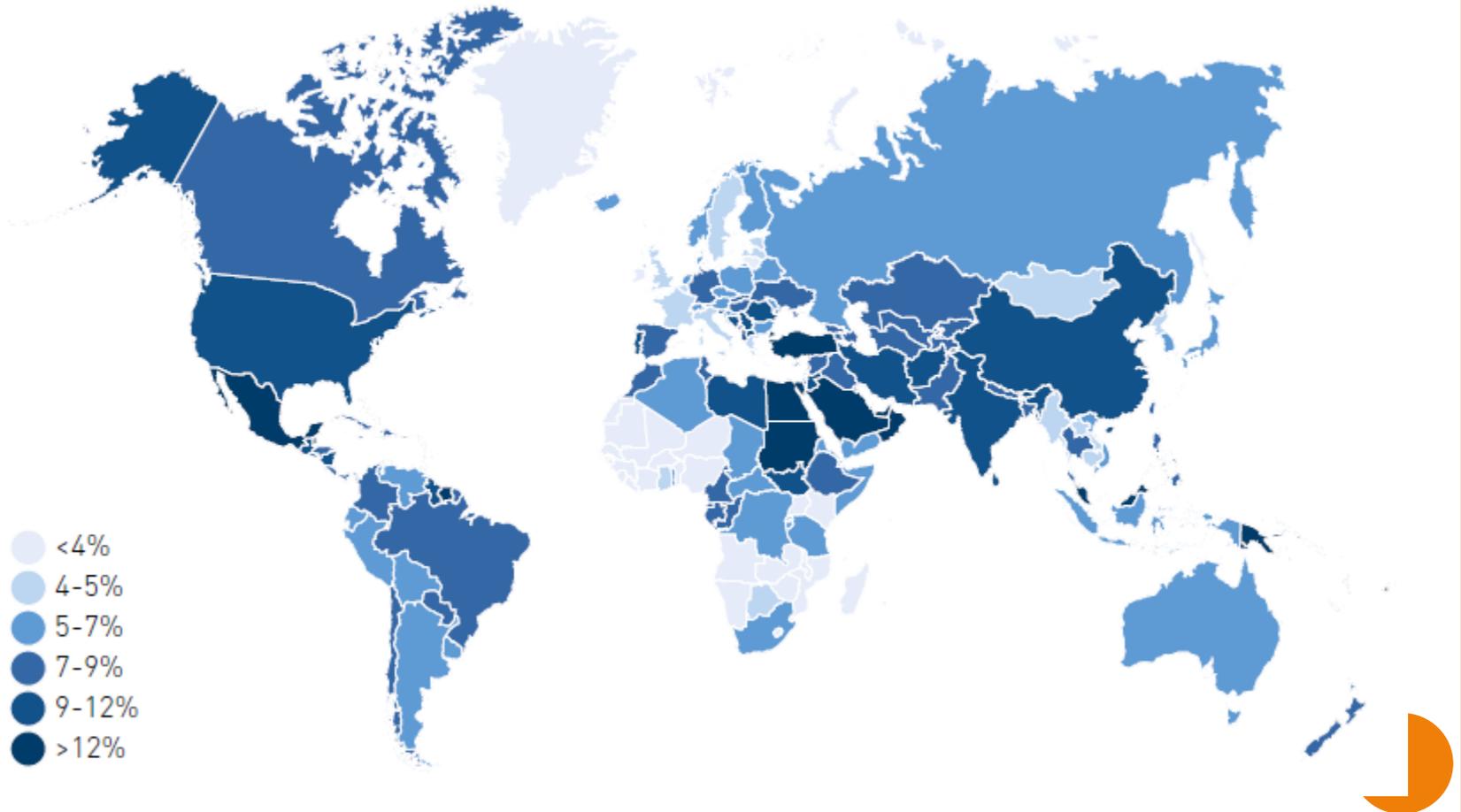


Une maladie liée au vieillissement de la population



# LE DIABÈTE DE TYPE 2

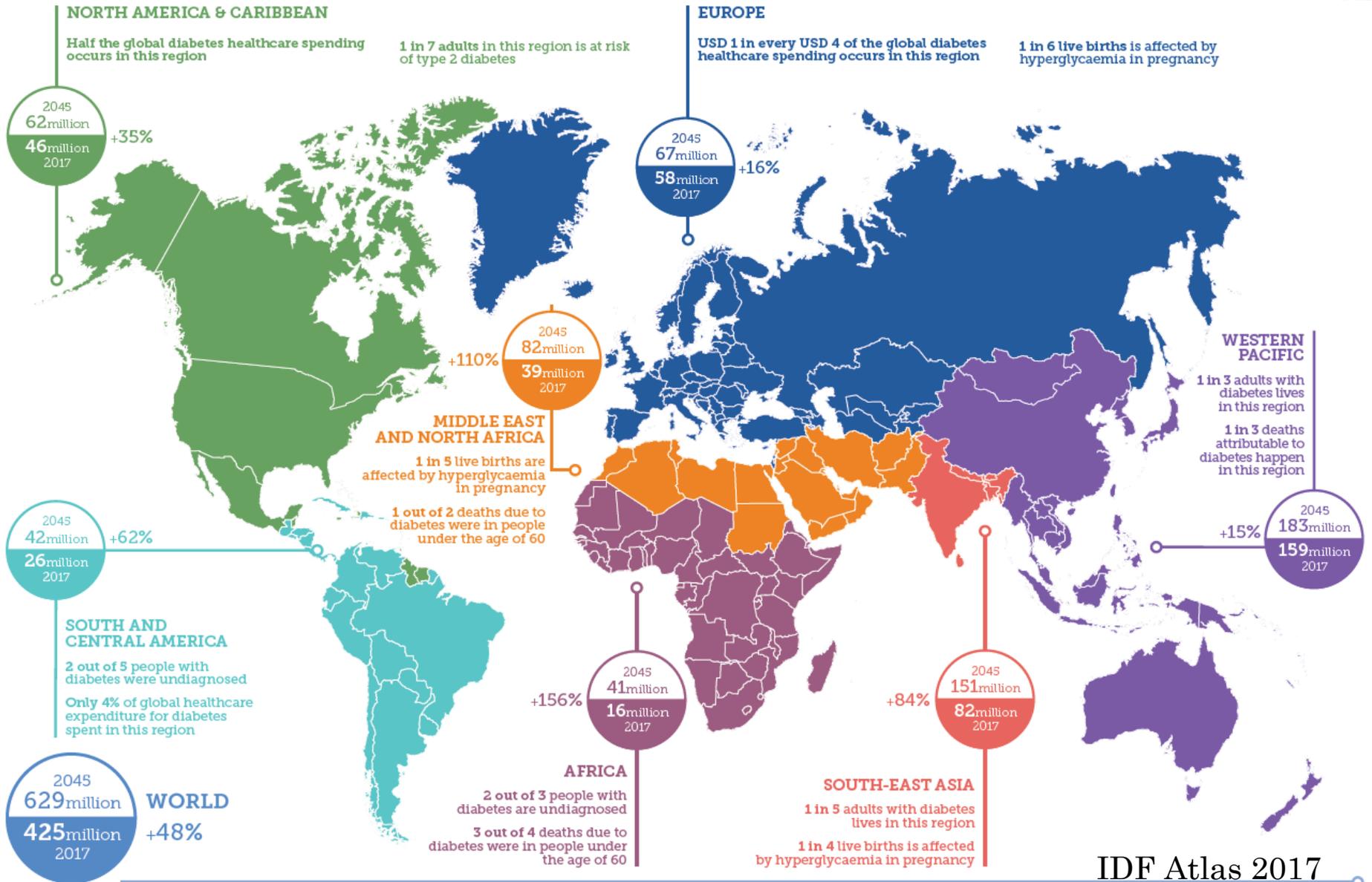
→ Maladie de plus en plus fréquente:



**Epidémie de diabète**

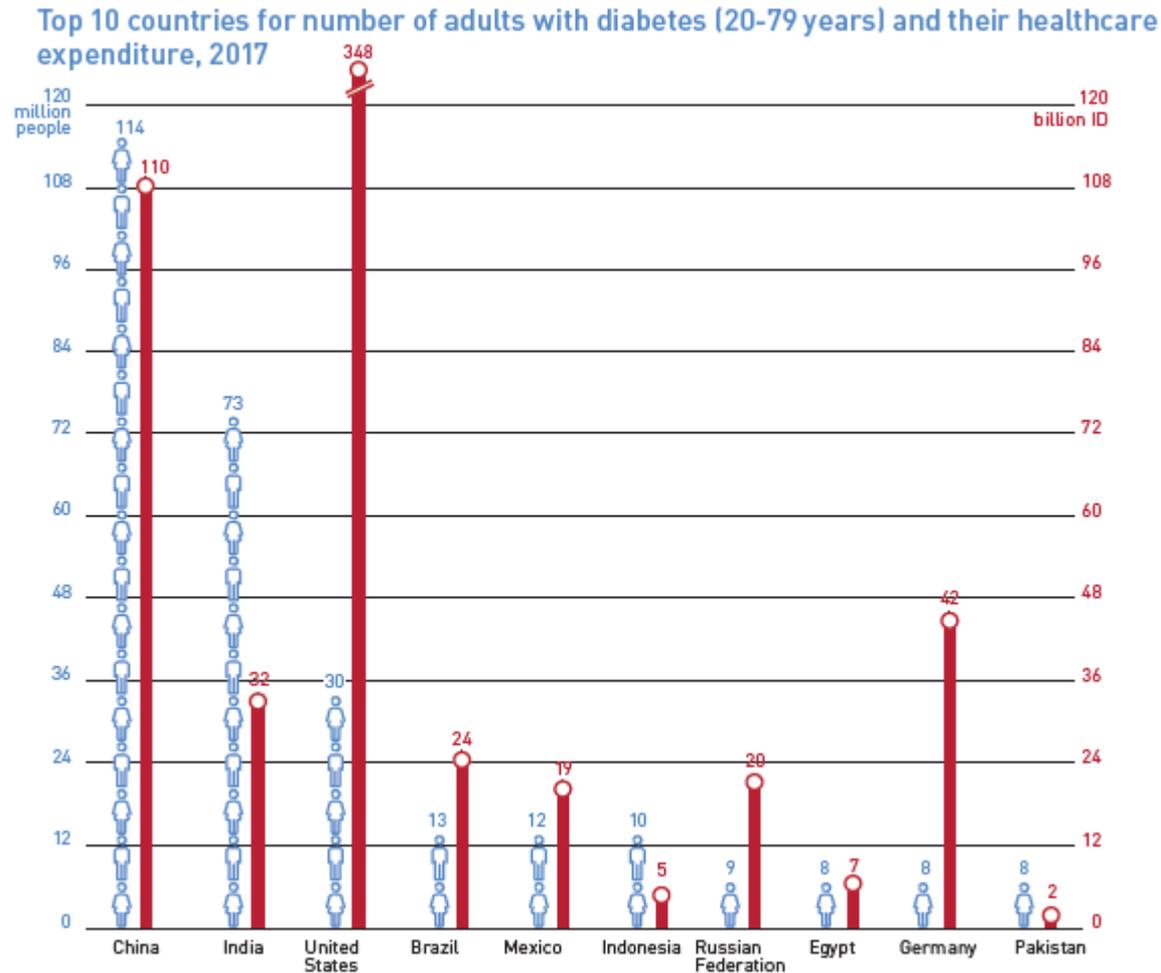
IDF Atlas 2017

# LE DIABÈTE DE TYPE 2



# LE DIABÈTE DE TYPE 2

→ Répartition dans le monde

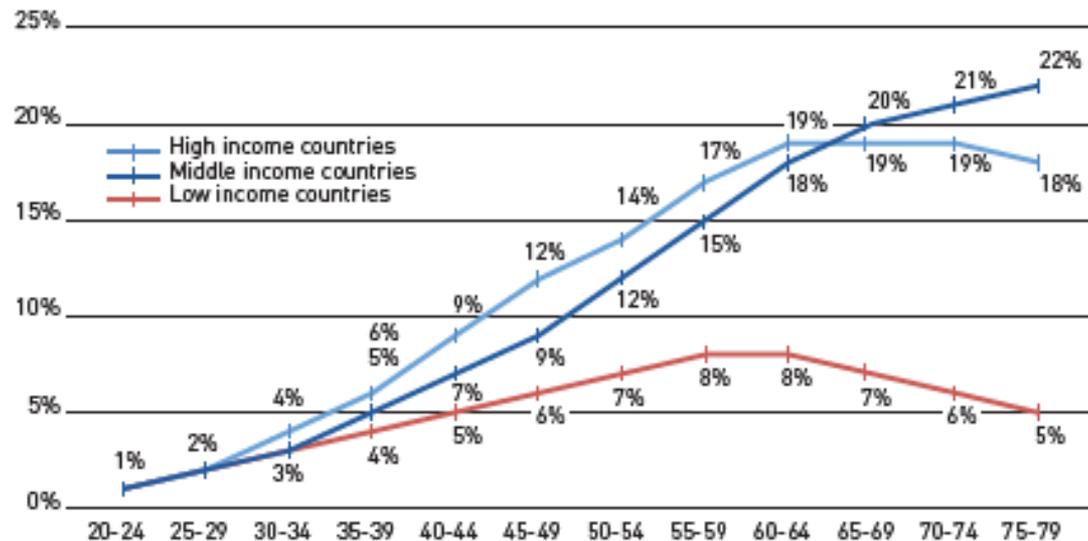


# LE DIABÈTE DE TYPE 2

→ Touche majoritairement les pays industrialisés

Mais 4 diabétiques sur 5 vivent dans des pays émergents

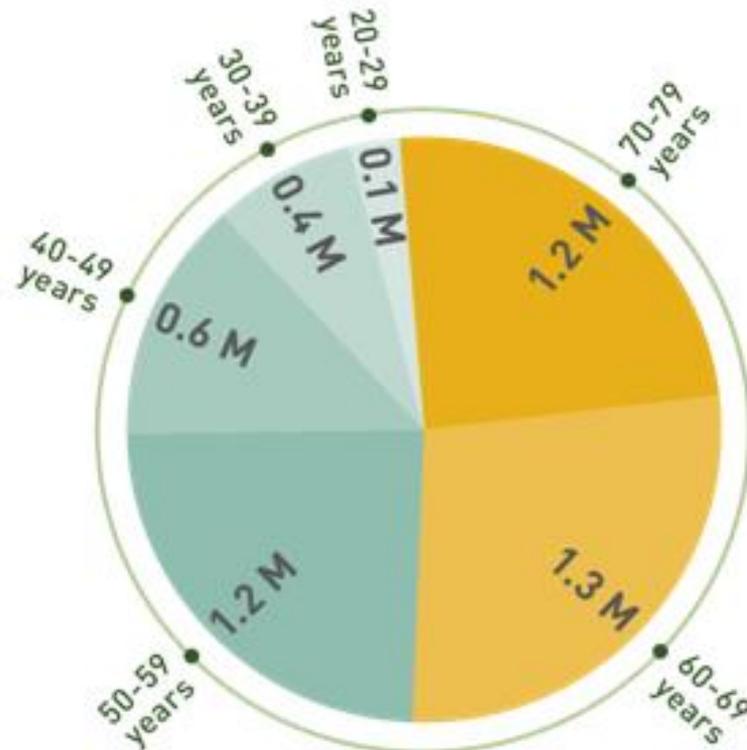
Prevalence (%) estimates of diabetes (20-79 years)  
by income group and age



# LE DIABÈTE DE TYPE 2

→ Affecte les personnes d'âge mur

DEATHS ATTRIBUTABLE TO DIABETES BY AGE (20-79 YEARS)



# LES COMPLICATIONS DU DIABÈTE

Rétinopathie:

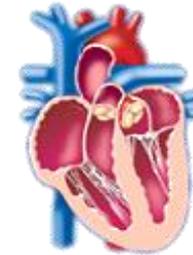
Cécité  
1<sup>ère</sup> cause



Attaques:  
2 fois plus



Maladies  
cardio-vasculaires:  
2-4 fois mortalité

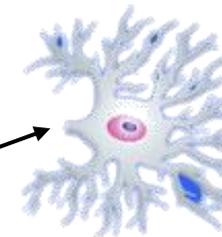


Néphropathie:

Insuffisance rénale  
1<sup>ère</sup> cause



Neuropathie:  
Amputation  
1<sup>ère</sup> cause



Espérance de vie réduite

6<sup>ème</sup> cause de décès



# HOMÉOSTASIE GLUCIDIQUE

Glucides complexes  
(amidon, glycogène)



Alimentation

Glucides simples



Excrétion  
urinaire

Organes  
producteurs

Production  
glucose

Glucose  
plasmatique

Utilisation  
glucose

Organes  
utilisateurs

Journée {  
Foie: 80%  
Reins: 15%  
Intestins: 5%

Jeun {  
Foie: 35%  
Reins: 45%  
Intestins: 20%

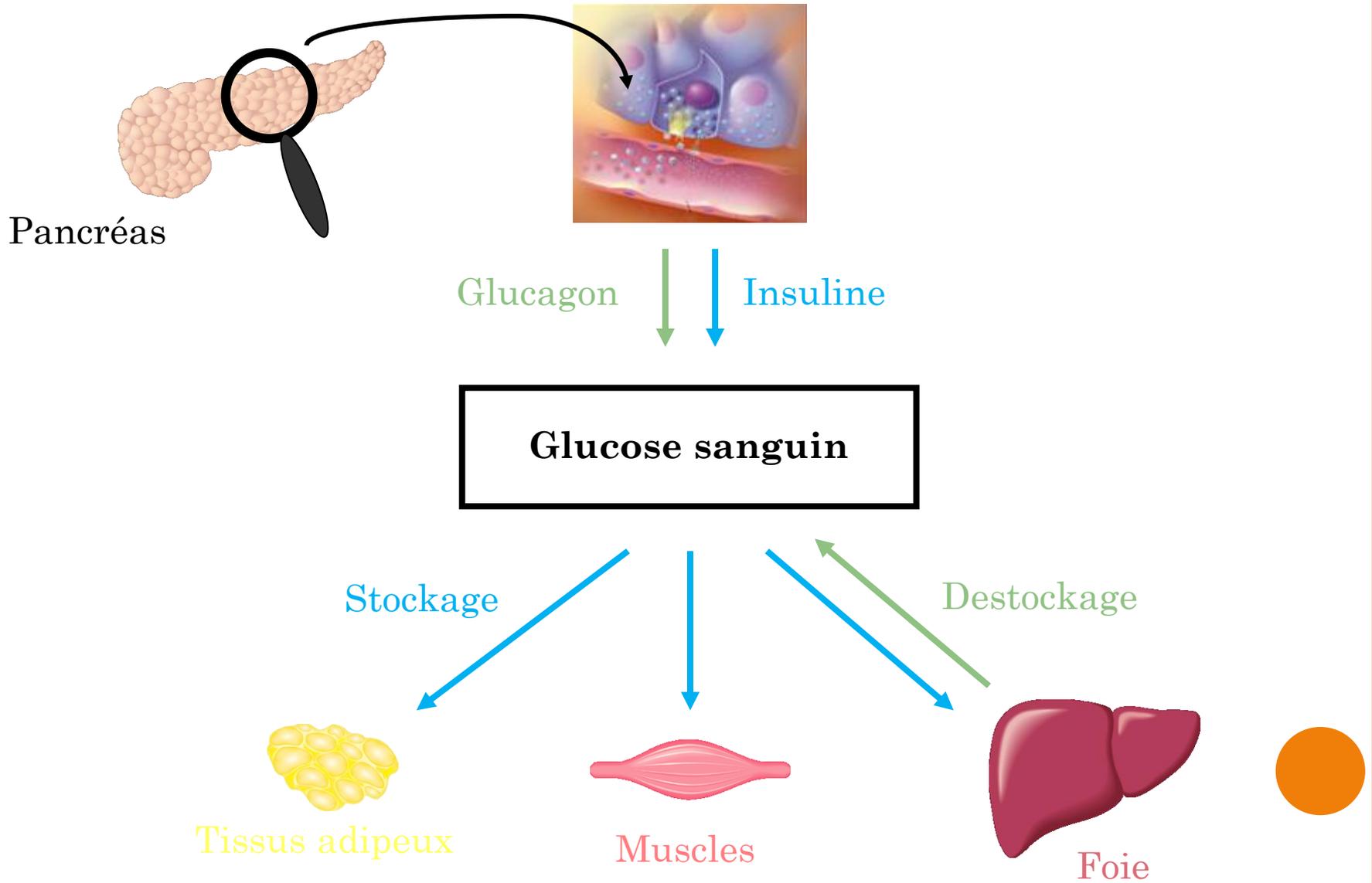
Limites physiologiques: 0,8-1,2 g/l

Besoins  
énergétiques

Exercice

Cerveau: 50%  
Muscles: 15%  
Intestins: 15%  
Tissu adipeux: 5%  
Autres: 15%

# HOMÉOSTASIE GLUCIDIQUE



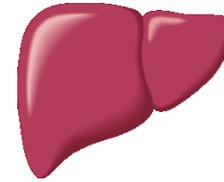
# PHYSIOPATHOLOGIE DU DIABÈTE DE TYPE 2



Tissus adipeux



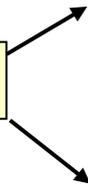
Muscles



Foie



Facteurs d'environnement

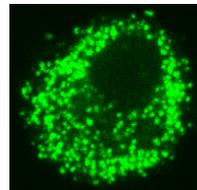


Hyperglycémie



Facteurs génétiques

Déficit de sécrétion d'insuline



Cellule  $\beta$



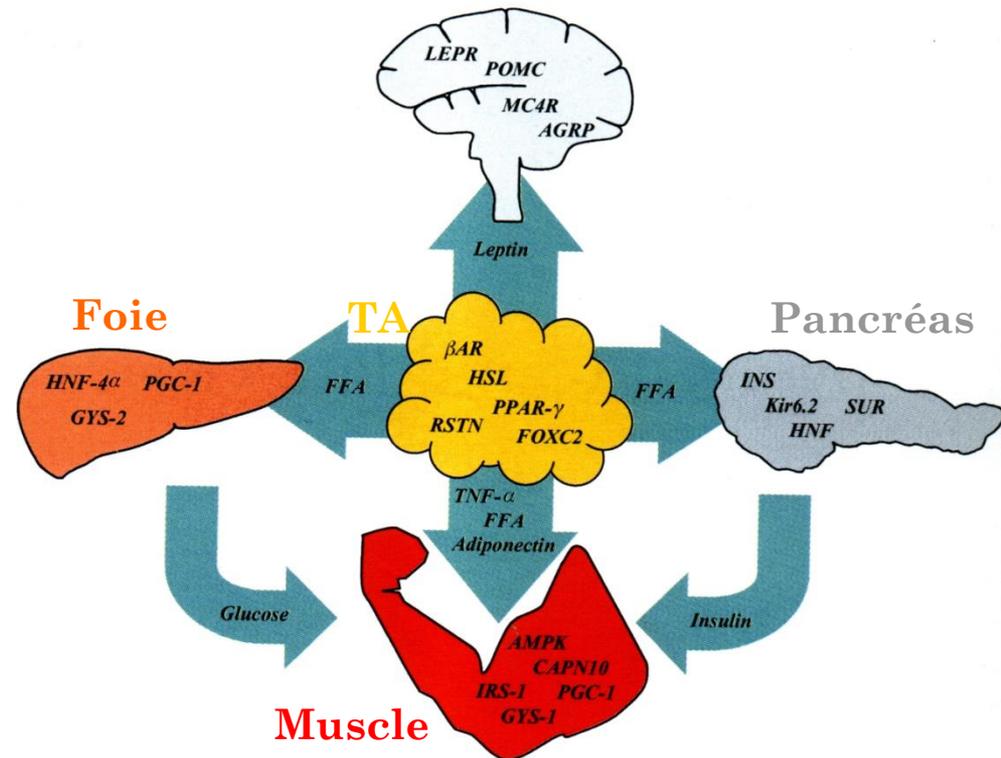
# PHYSIOPATHOLOGIE DU DIABÈTE DE TYPE 2

→ Predisposition génétique

---

Population générale	6 %
Jumeau monozygote	100%
Jumeau dizygote	30 %
Groupe ethnique	50 %
- Indiens Pima	
- Iles du Pacific sud	

---



« Maladie polygénique »

# PHYSIOPATHOLOGIE DU DIABÈTE DE TYPE 2

## → Facteurs environnementaux

- **Surpoids ( $25 < \text{IMC} < 30$ ):** 2012: 32,3 % (Etude ObEpi)
- **Obésité ( $\text{IMC} > 30$ ):** 2012: 15 % (+3,4% en 3 ans)  
43 % diabétiques sont obèses
- **Activité physique:** sédentarité
- **Alimentation:** apports caloriques trop élevés  
trop riches en graisses saturées et en sucres  
pas assez de fibres

## → Autres facteurs

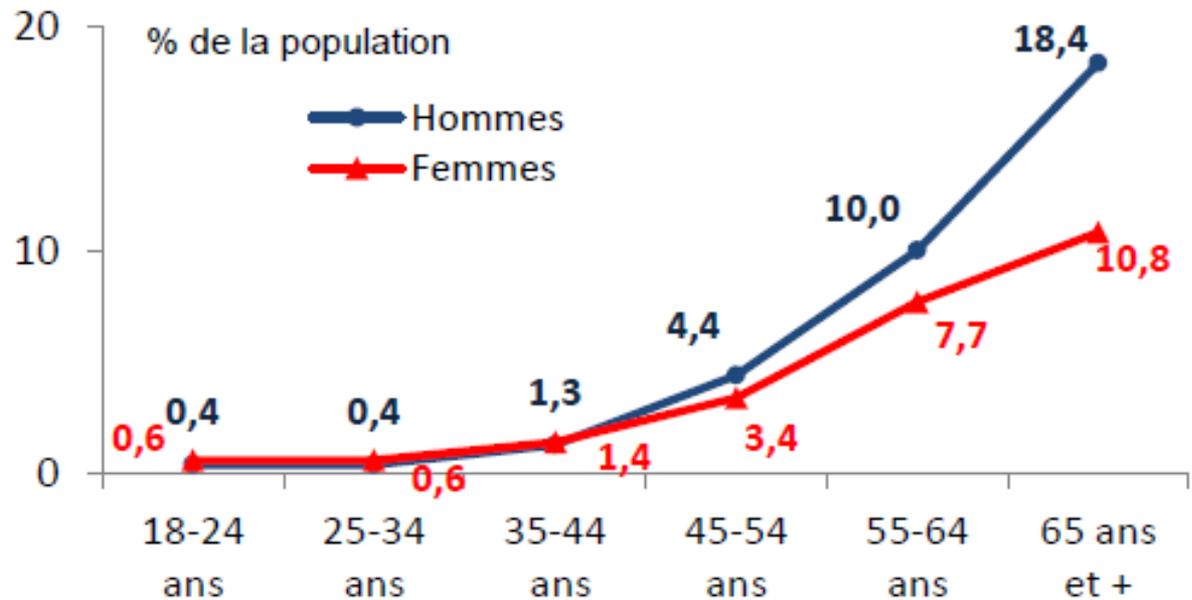
- **Faible poids de naissance**
- **Vieillesse de la population**



# DIABÈTE ET VIEILLISSEMENT

→ Prévalence du DT2 augmente avec l'âge: USA: 20 à 65 ans: 11,3%  
après 65 ans: 26,9%  
France: 5,5% en 2012

Prévalence du diabète  
en fonction de l'âge  
(Etude ObEpi 2012)

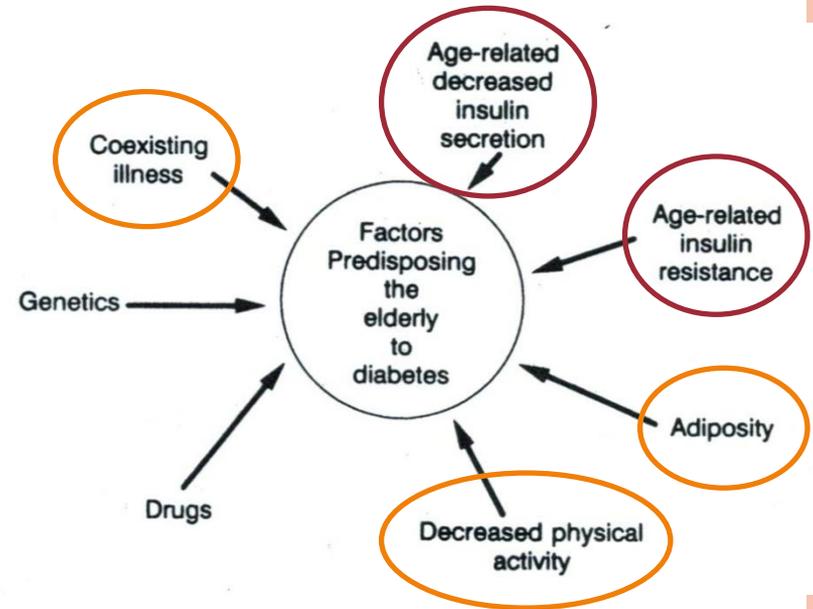
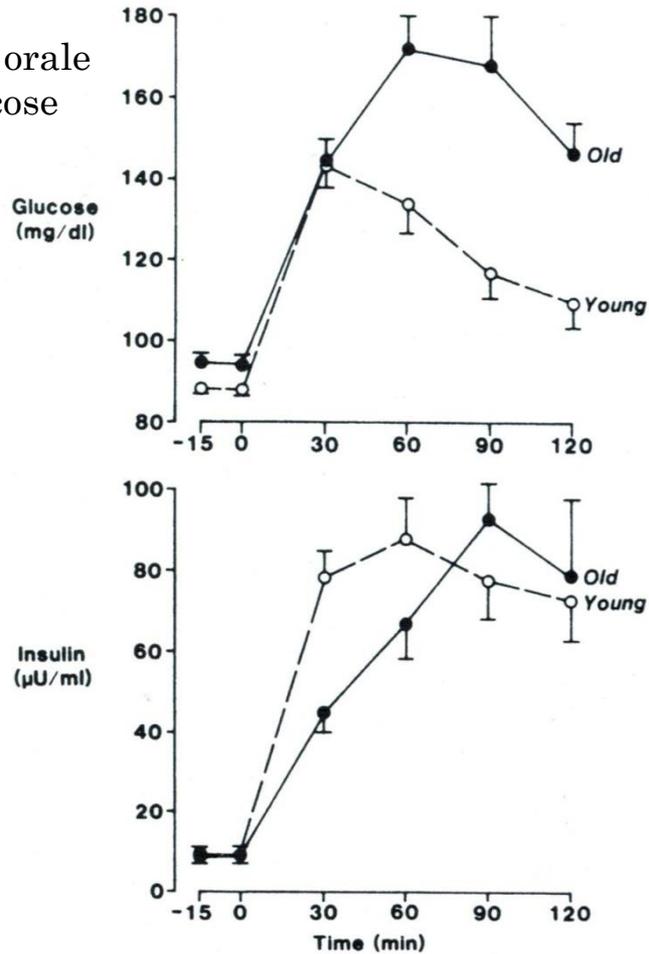


→ Incidence de nouveaux cas /an augmente avec l'âge:  
0,5-1% : au-delà de 65 ans  
< 0,2%: 25-44 ans

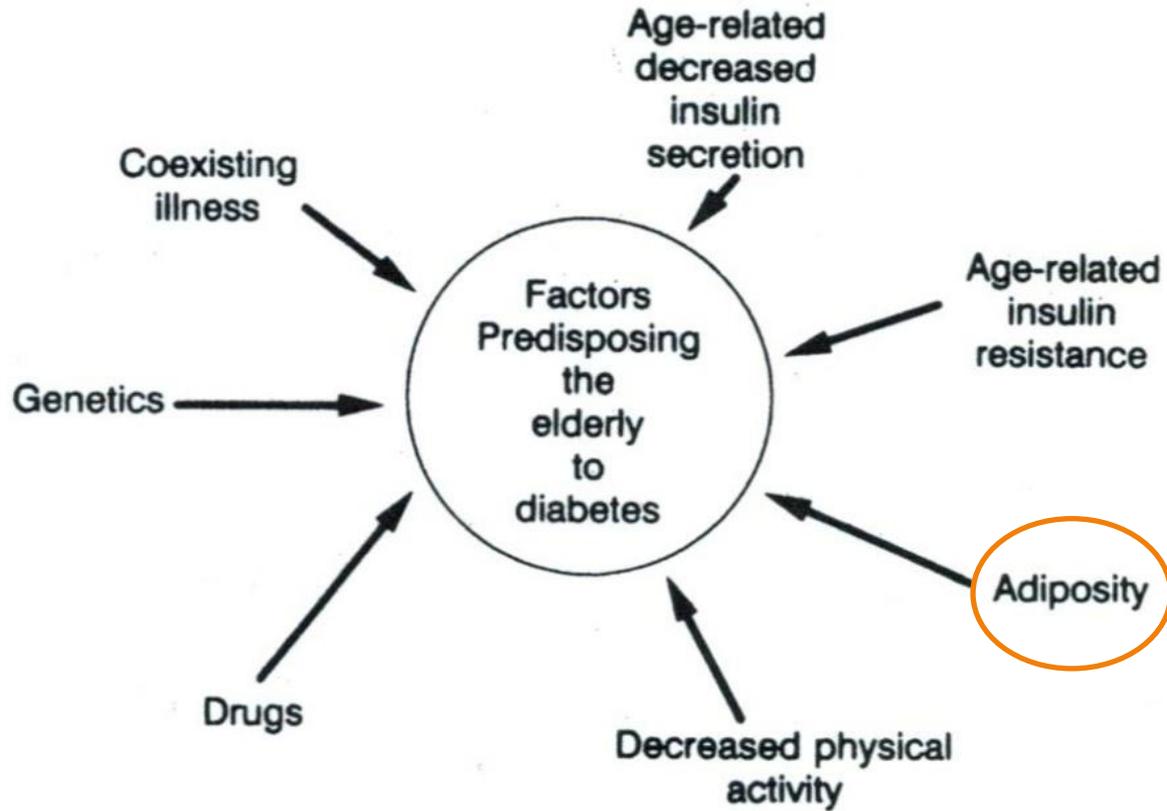


# DIABÈTE ET VIEILLISSEMENT

OGTT: ingestion orale  
de 100g de glucose



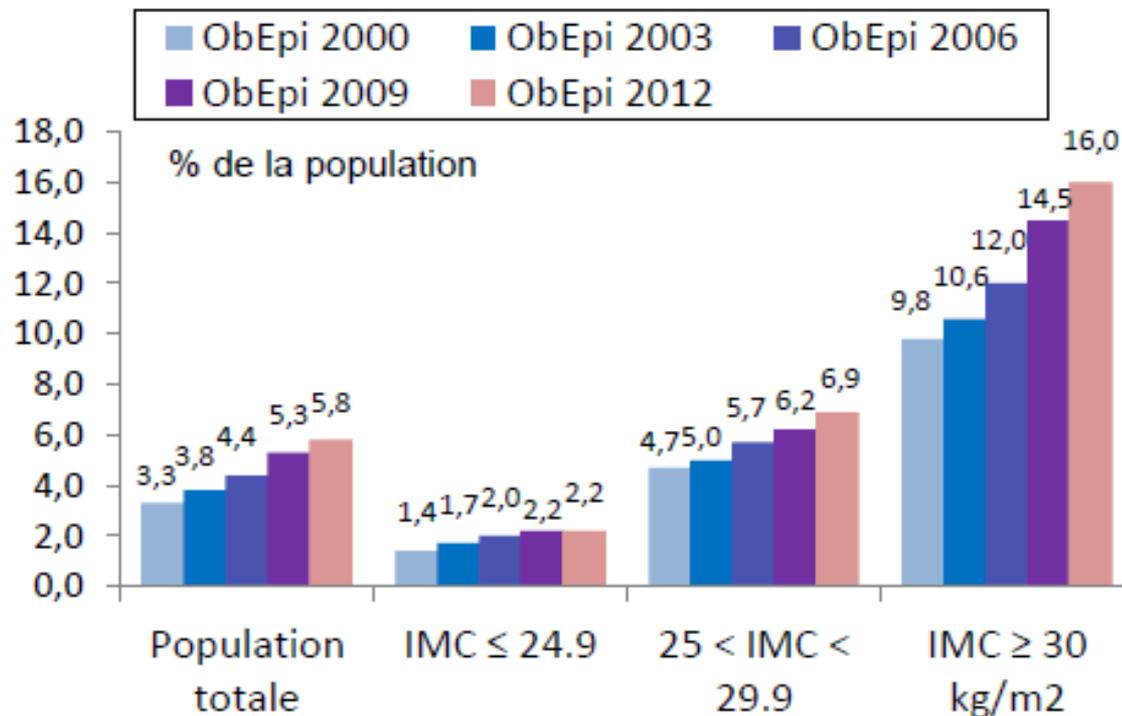
# ADIPOSITÉ



# ADIPOSITÉ

→ Surpoids et obésité

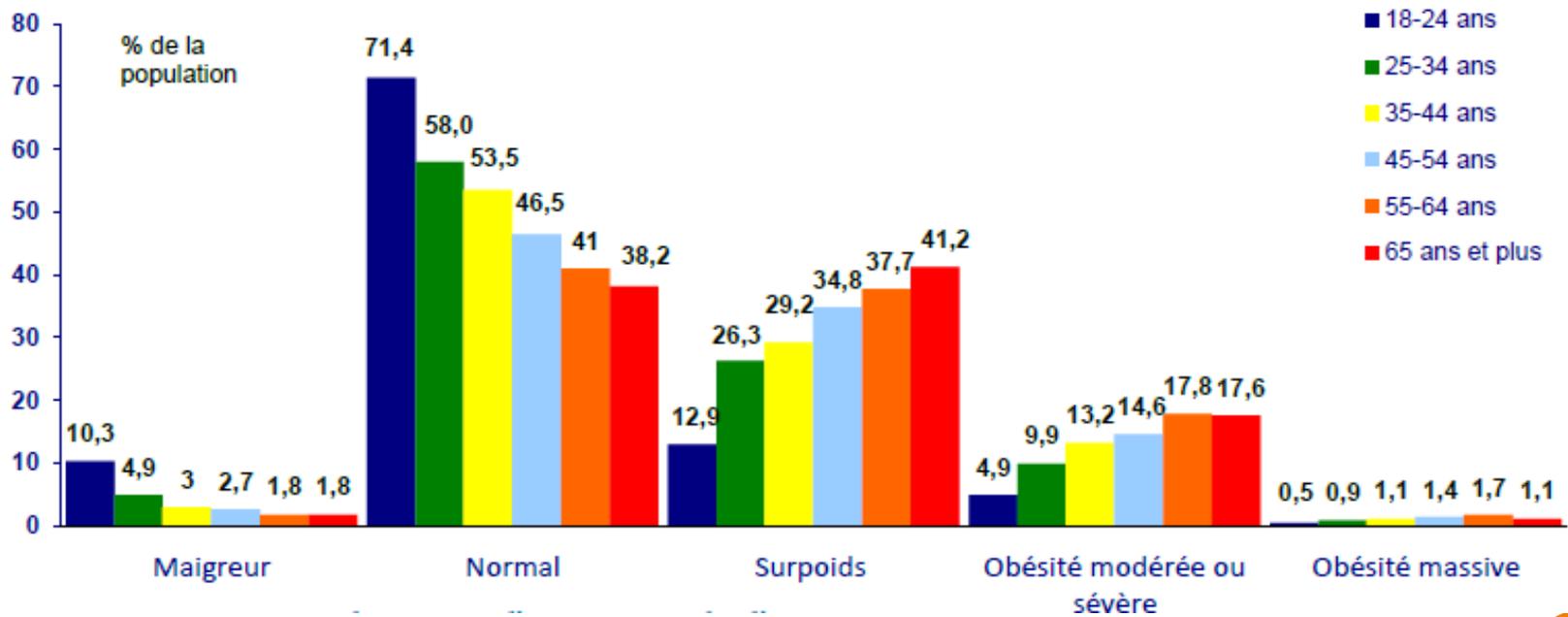
Prévalence du diabète  
en fonction de l'IMC  
(ObEpi 2012)



# ADIPOSITÉ

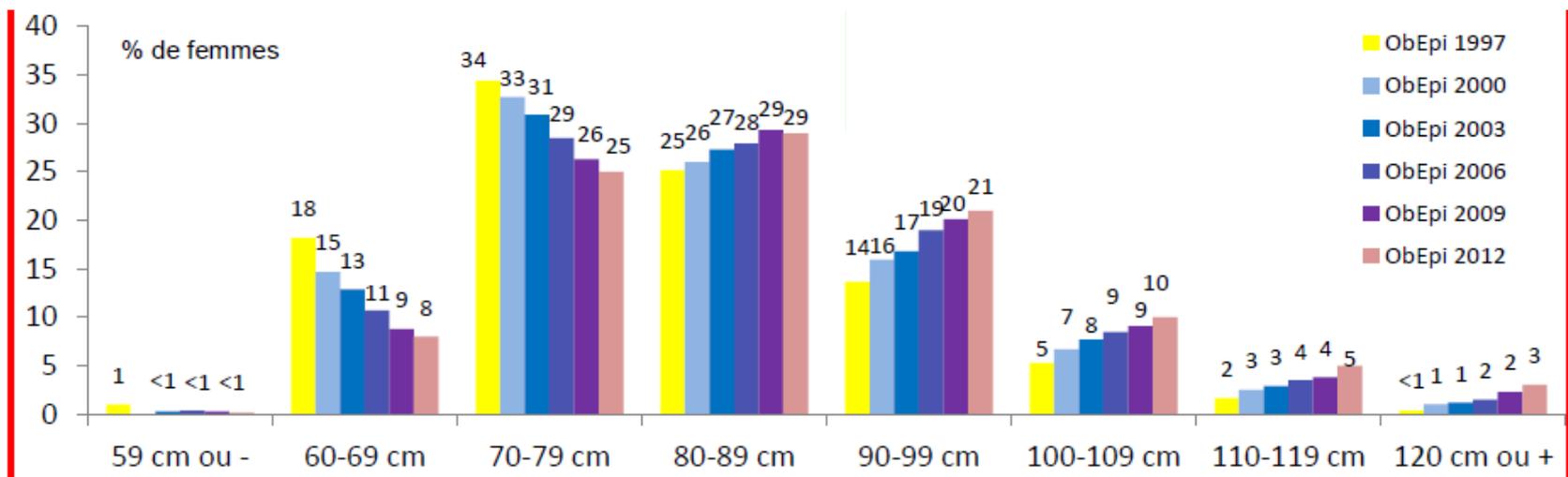
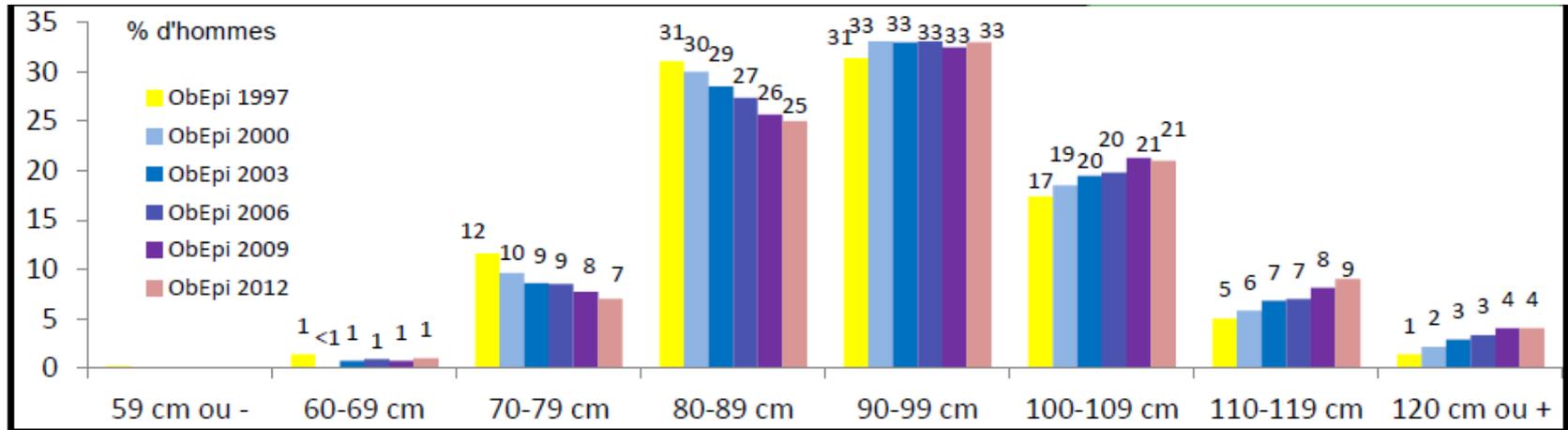
→ Surpoids et obésité

## L'IMC MOYEN SELON L'ÂGE



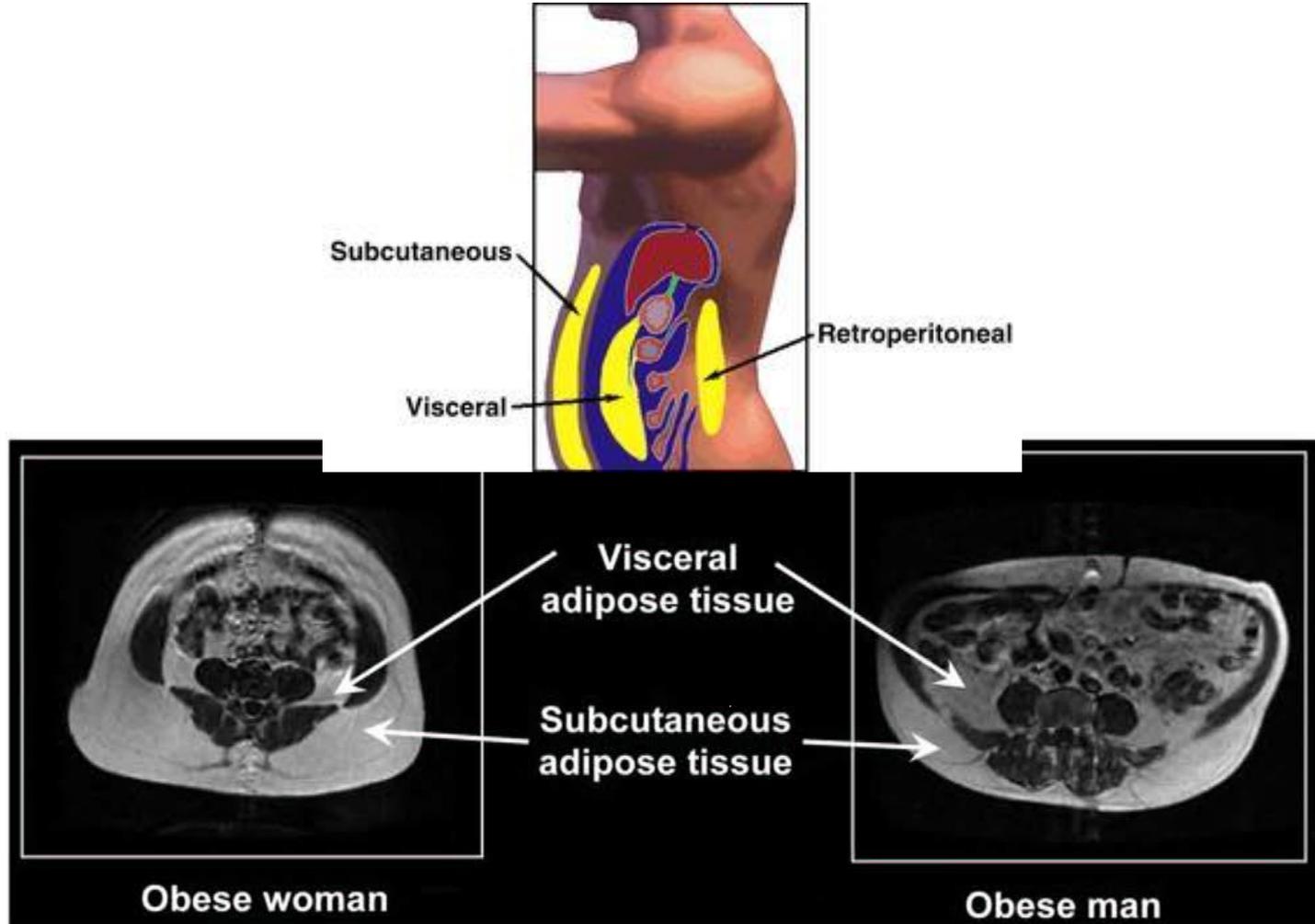
# ADIPOSITÉ

→ Evaluation: tour de taille



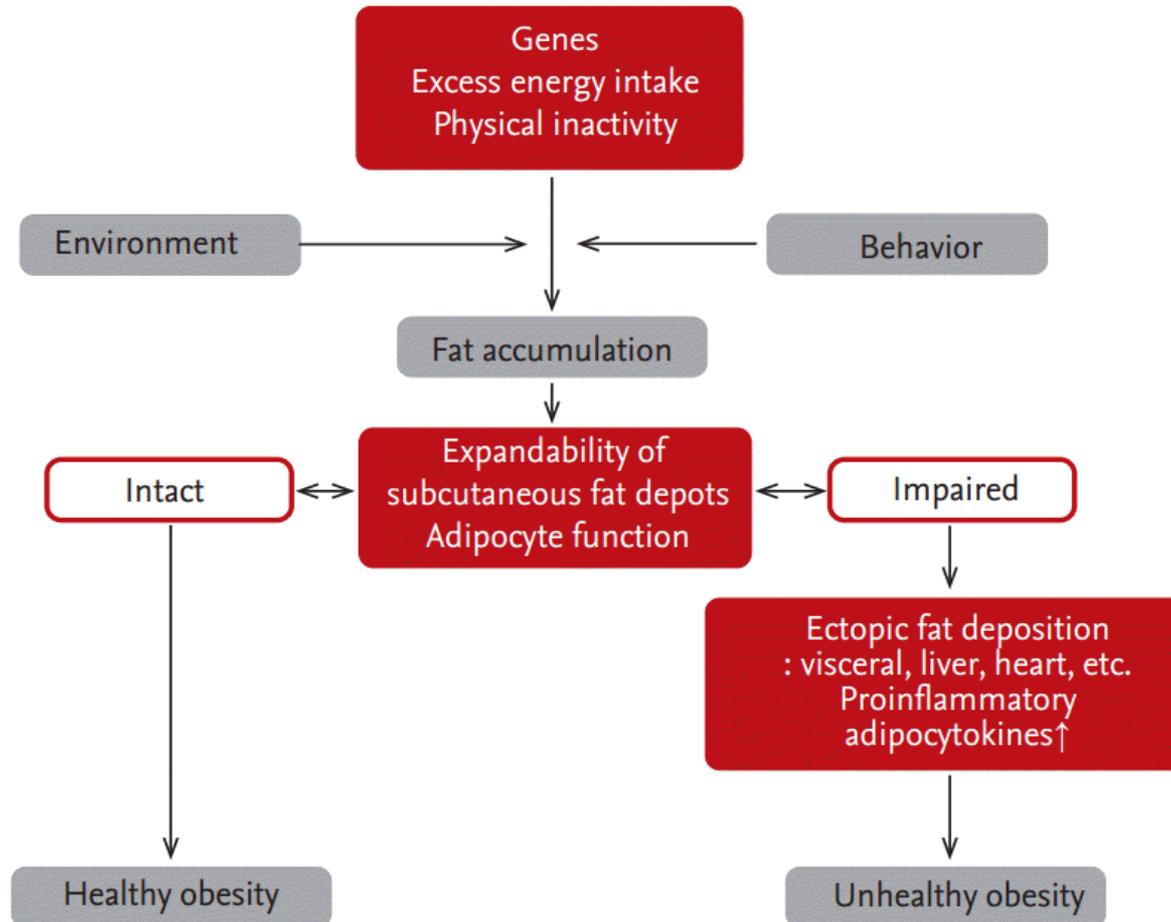
# ADIPOSITÉ

→ Tissus adipeux sous-cutané vs viscéral



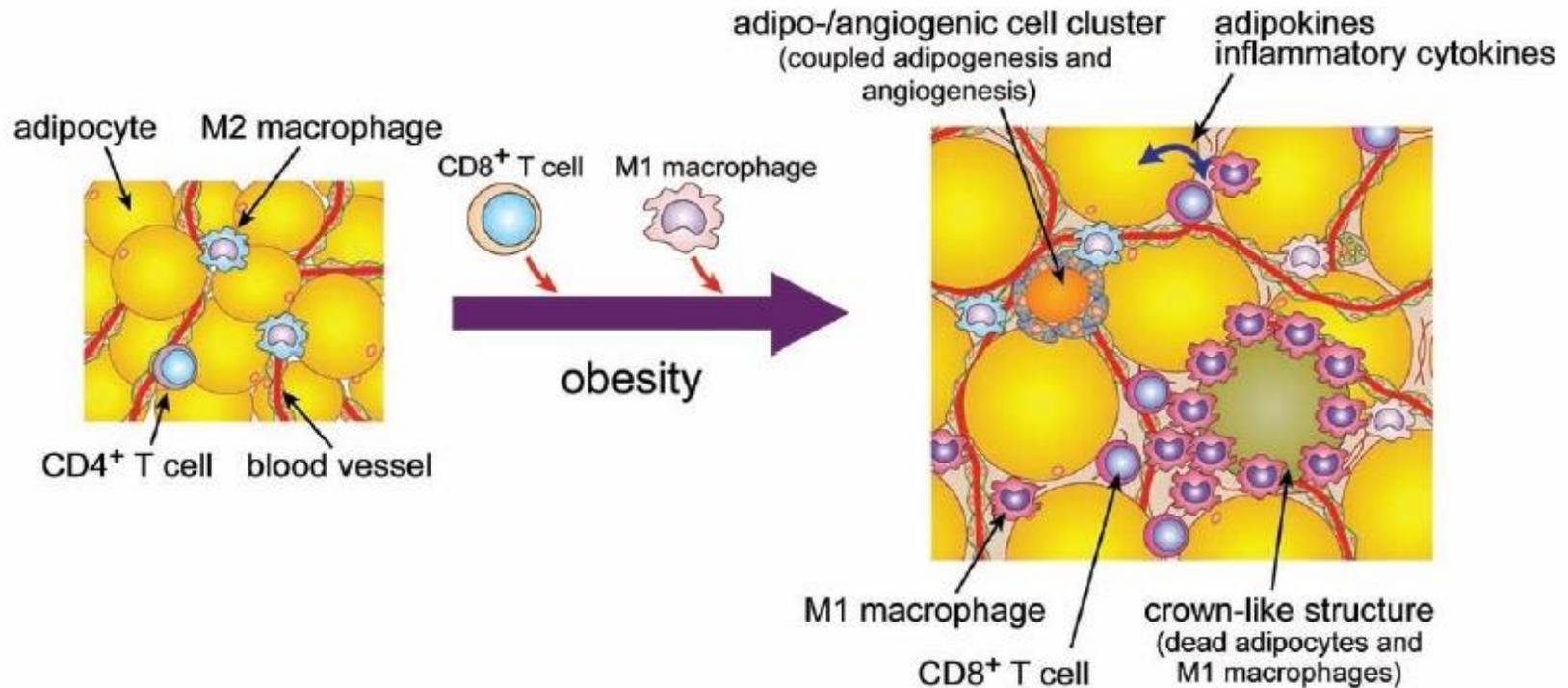
# ADIPOSITÉ

→ Tissus adipeux sous-cutané vs viscéral



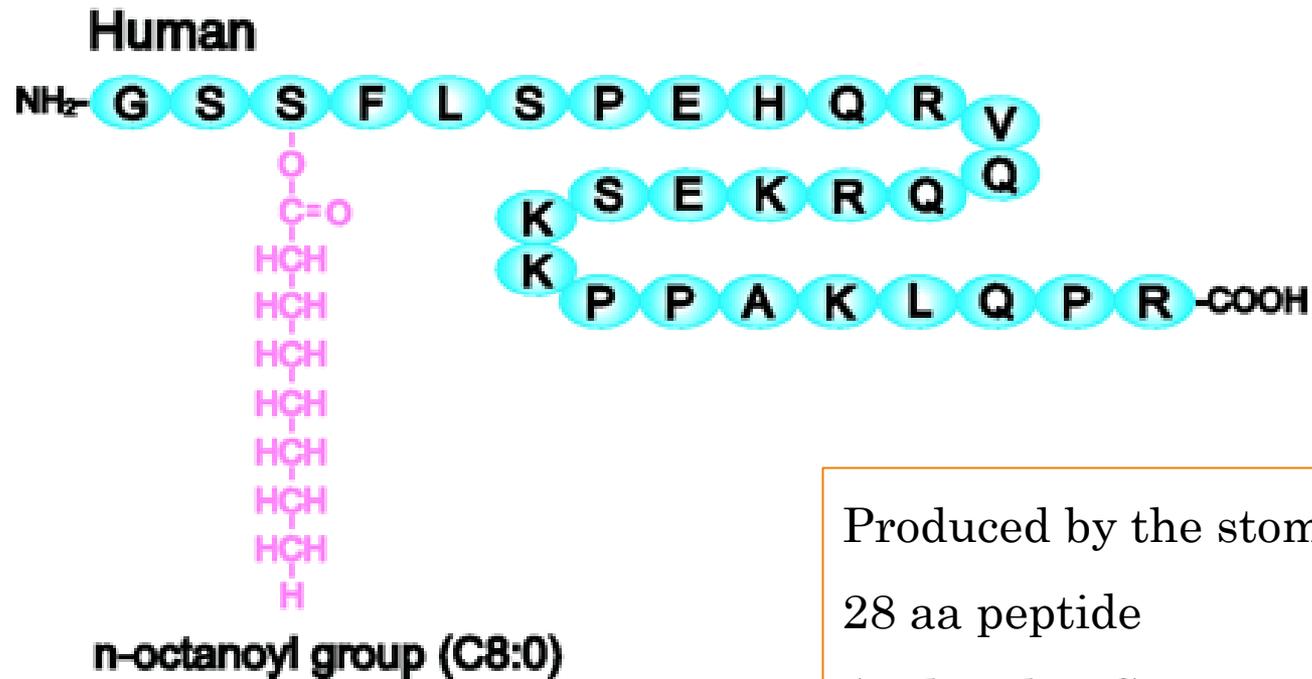
# ADIPOSITÉ

→ Inflammation chronique du TAV



# ADIPOSITÉ

→ Récepteur de la ghréline

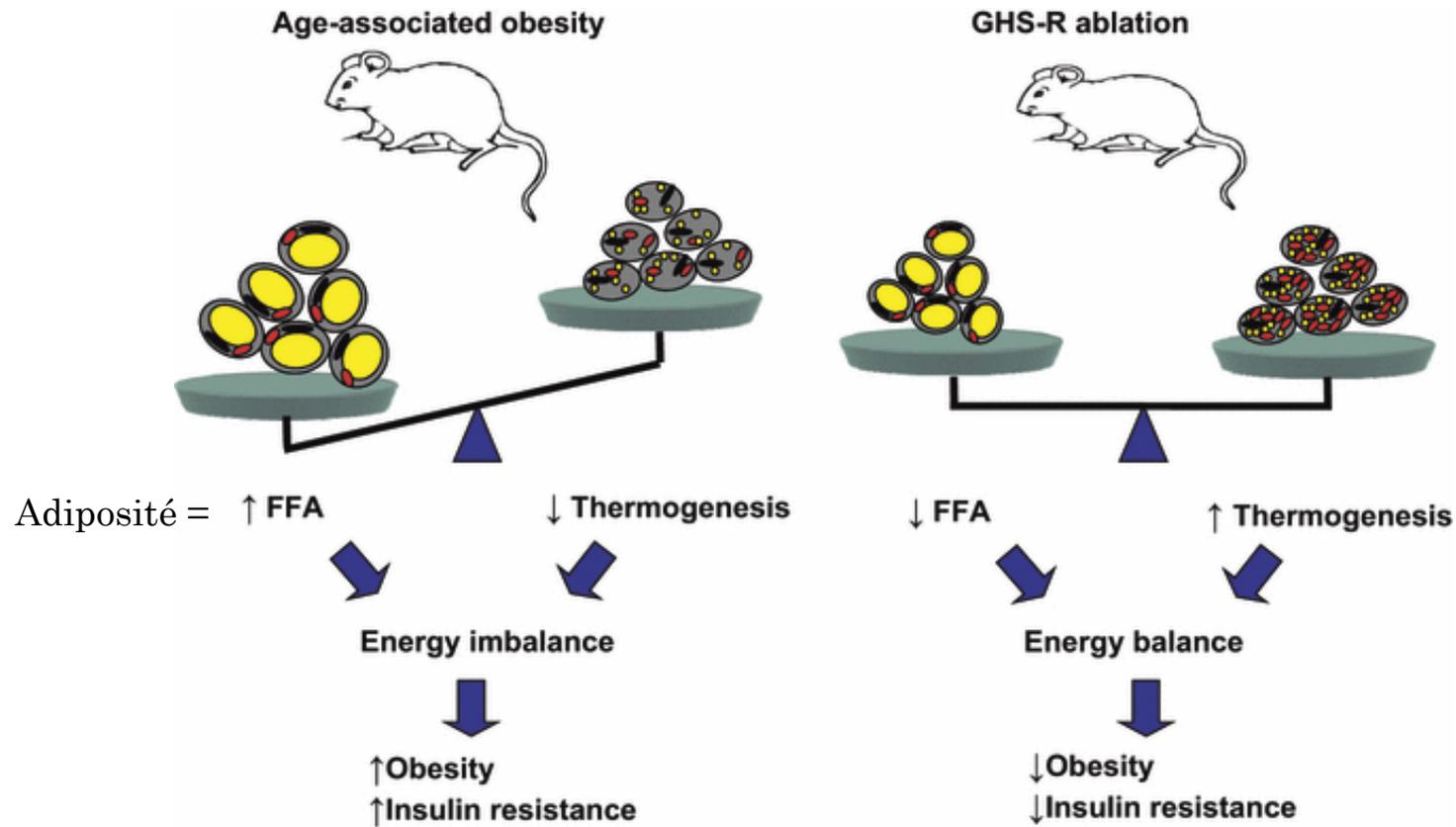


Produced by the stomach  
28 aa peptide  
Acylated at Ser 3

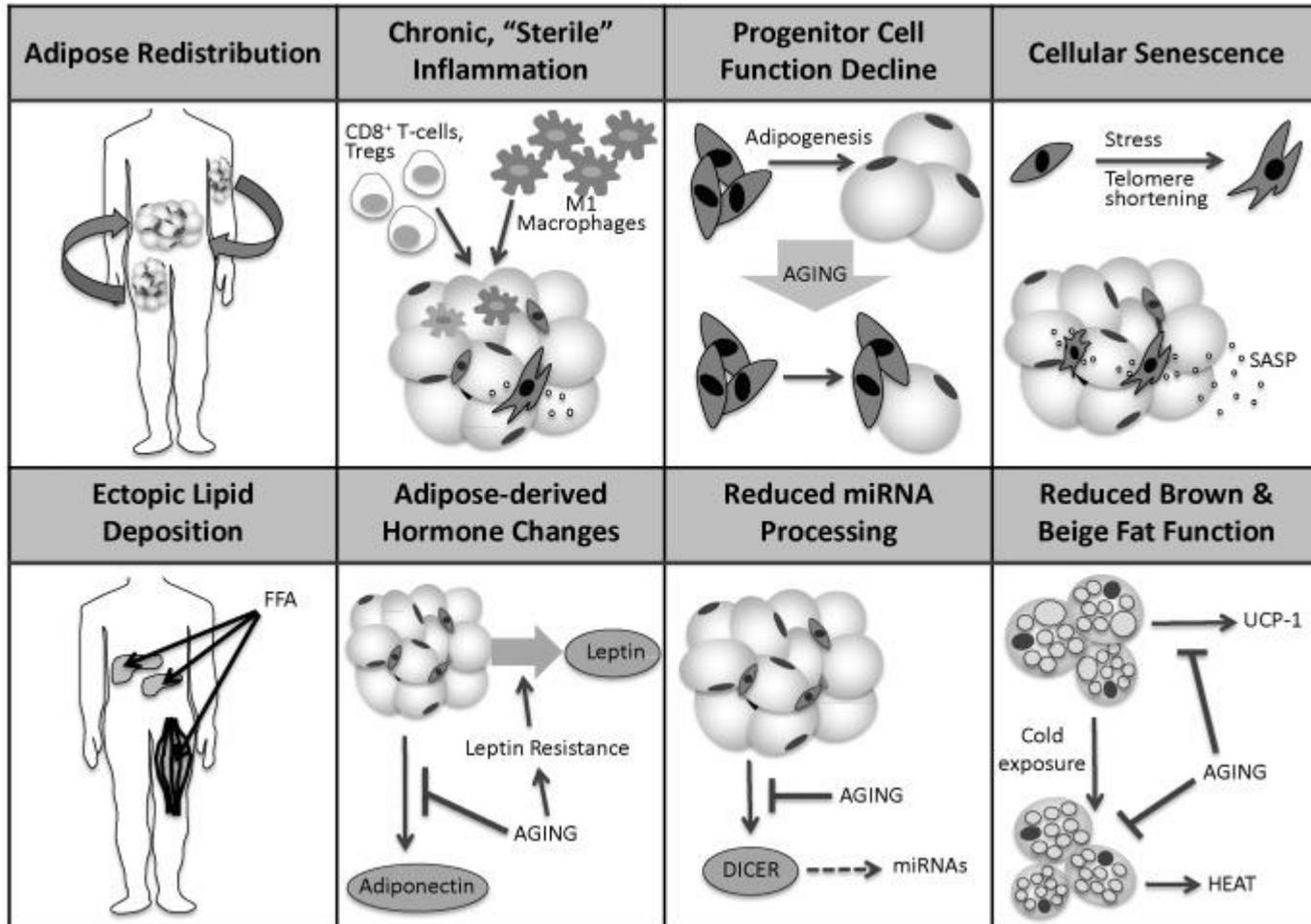


# ADIPOSITÉ

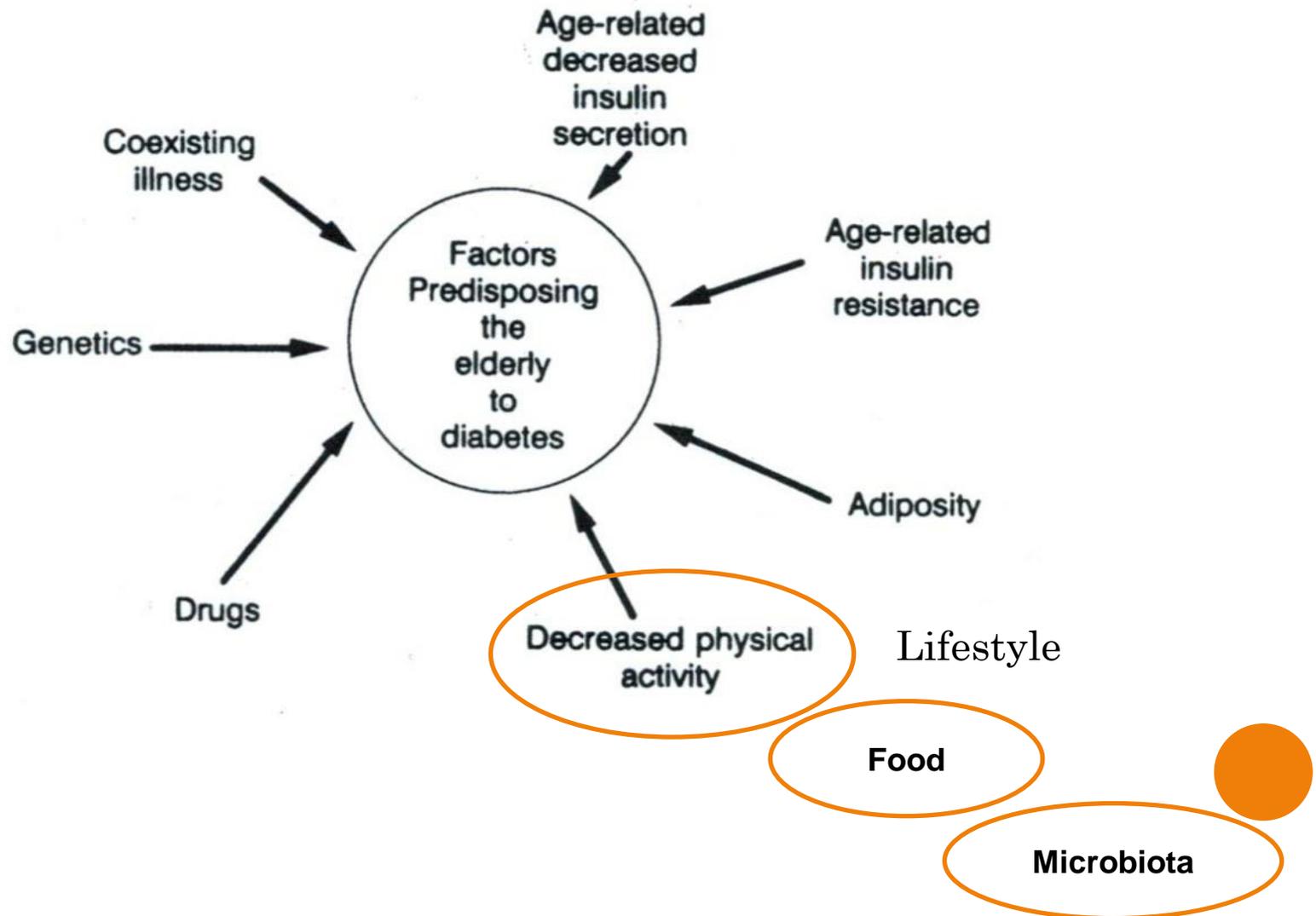
→ Récepteur de la ghréline: souris KO pour GHS-R



# ADIPOSITÉ



# ACTIVITÉ PHYSIQUE

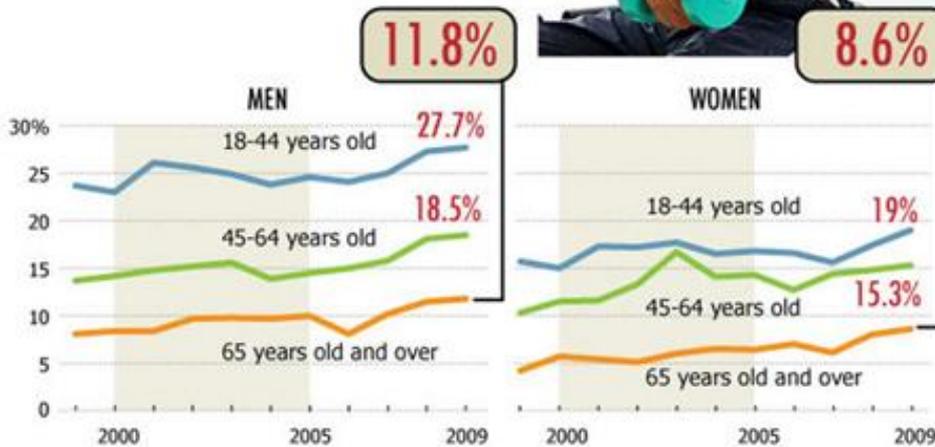


# ACTIVITÉ PHYSIQUE

## → Exercice

Researchers report that people over the age of 60 need to lift weights more often than younger adults to maintain muscle mass and muscle size. And maintaining muscle mass, the researchers conclude, is essential to healthy aging.

Percentage of people who participate in aerobic and muscle-strengthening activities:



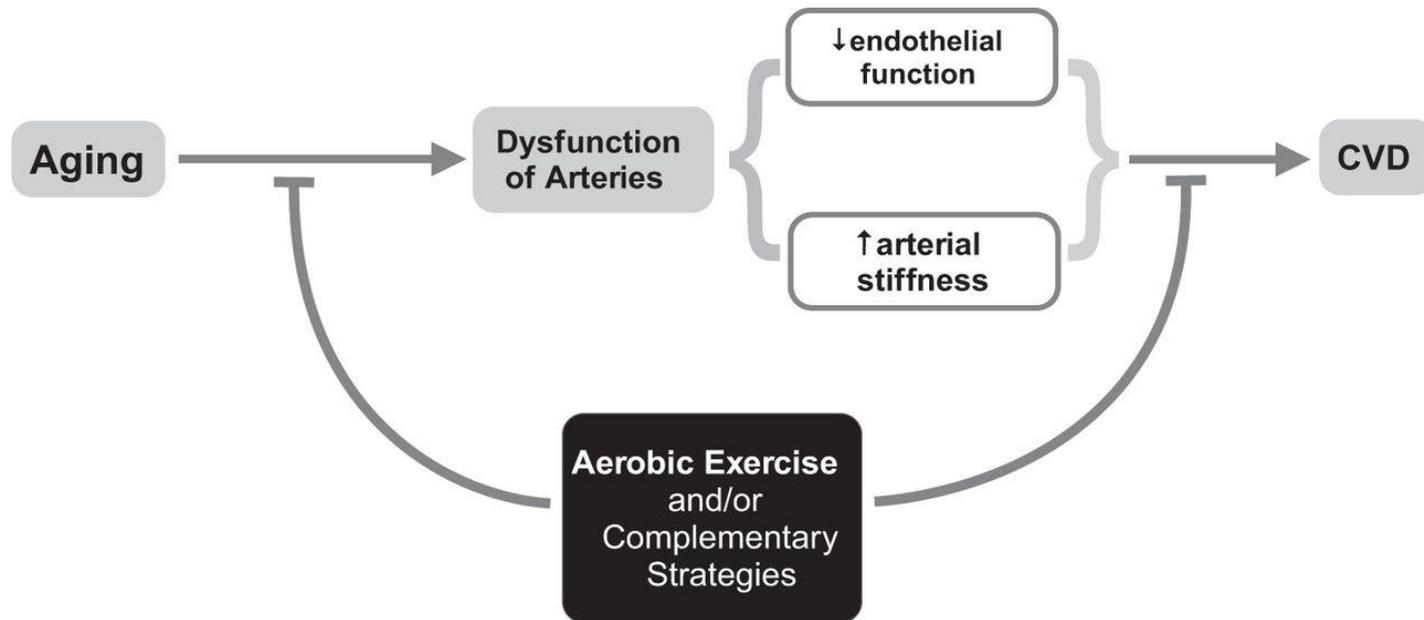
Exercise vs. aging		
	Effect of aging	Effect of exercise
<b>Metabolism</b>		
Metabolic rate	Decrease	Increase
Body fat	Increase	Decrease
Blood sugar	Increase	Decrease
Insulin levels	Increase	Decrease
LDL ("bad") cholesterol	Increase	Decrease
HDL ("good") cholesterol	Decrease	Increase

30 minutes d'exercice modéré  
quotidien



# ACTIVITÉ PHYSIQUE

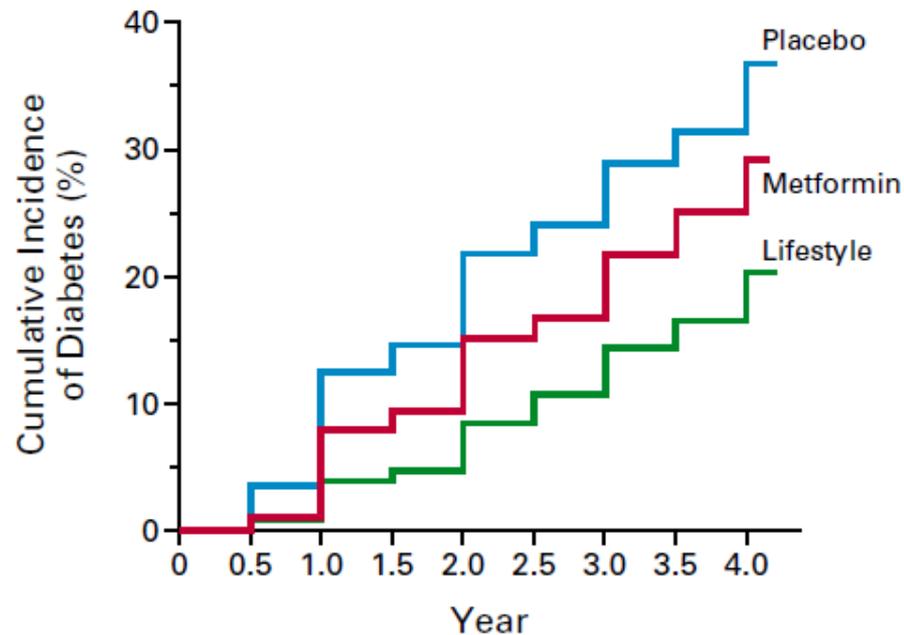
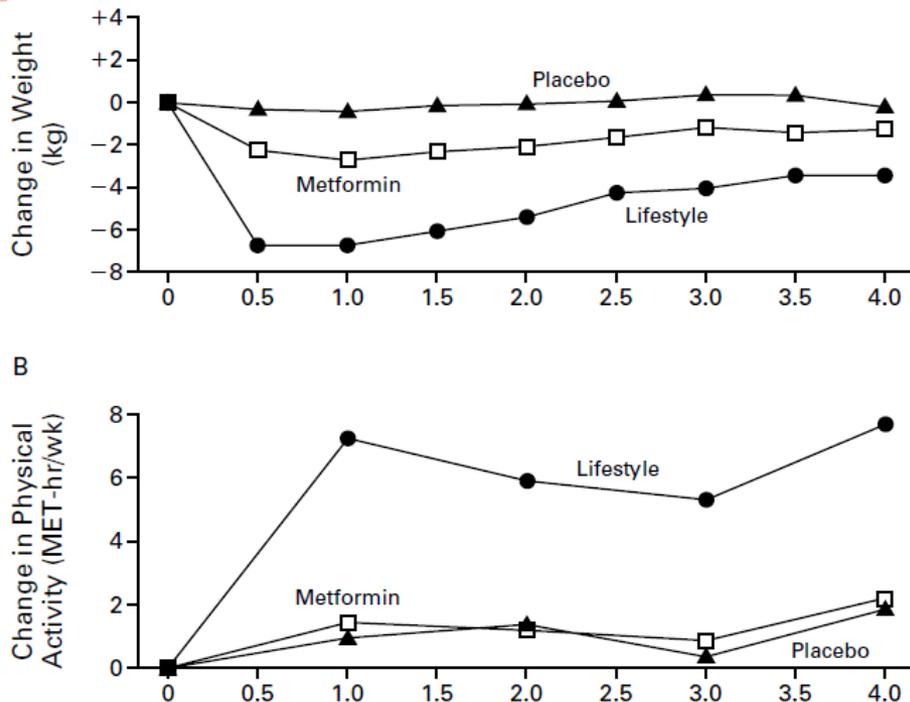
→ Exercice et complications vasculaires



# ALIMENTATION

→ Restriction calorique: Etude DPP (Diabetes Prevention Program)

Lifestyle intervention: exercice + régime alimentaire



# ALIMENTATION

## → Magnésium

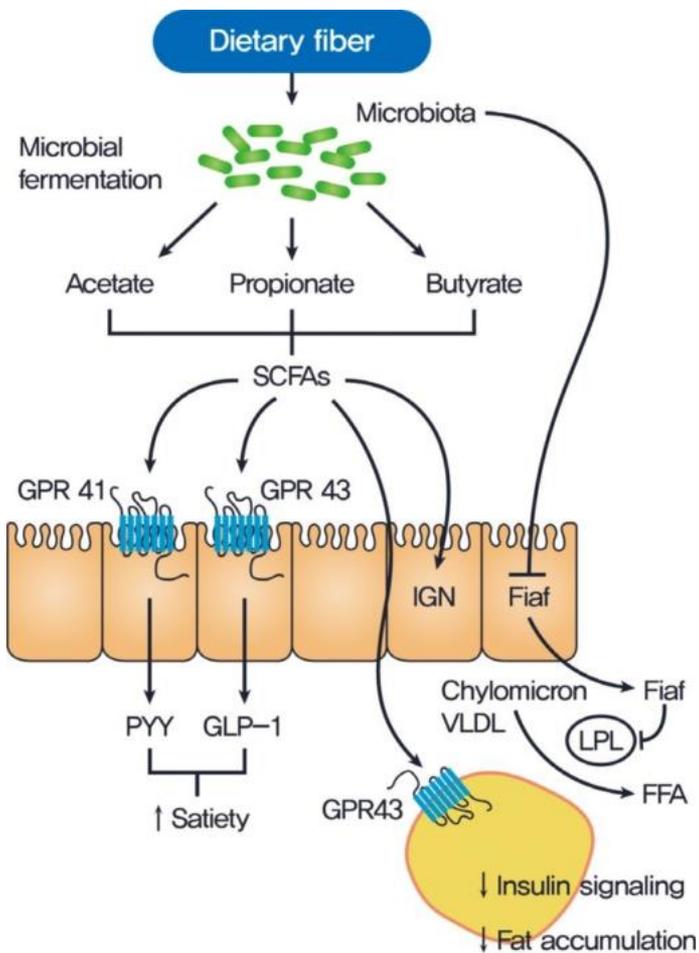
Sujets âgés: 72,3 ans

47% hommes, 53% femmes

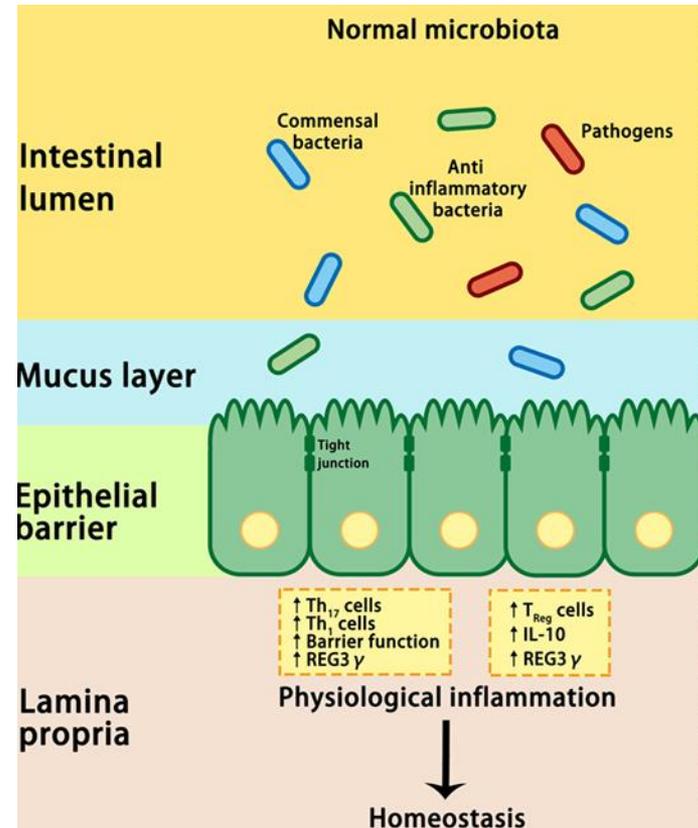
Variables	Quartile of Mg intake				P for trend
	Q1 (n = 52)	Q2 (n = 53 )	Q3 (n = 52 )	Q4 (n = 53 )	
Quartile range of Mg intake (mg/kg)	< 2.3	2.3 - 3.2	3.3 - 4.4	≥4.5	
Mean Mg intake (mg/kg) <sup>2</sup>	1.8 ± 0.4	2.8 ± 0.3	3.7 ± 0.3	5.8 ± 1.4	<0.001
Waist circumference (cm) ≥80 for men or ≥90 for women	1.00	0.41 (0.11-1.54)	0.57 (0.14-2.27)	0.09 (0.02-0.37)	0.001
Metabolic syndrome	1.00	2.10 (0.73-6.06)	1.68 (0.60-4.70)	0.49 (0.17-1.43)	0.153
Body fat percentage (%) ≥25 for men or ≥30 for women (obese) *	1.00	0.80 (0.32-2.05)	0.55 (0.21-1.44)	0.21 (0.07-0.61)	0.004
Body mass index (kg/m <sup>2</sup> ) ≥27 (obese) *	1.00	0.63 (0.26-1.53)	0.21 (0.07-0.61)	0.09 (0.02-0.35)	<0.001

# MICROBIOTE

→ Role métabolique et immunitaire

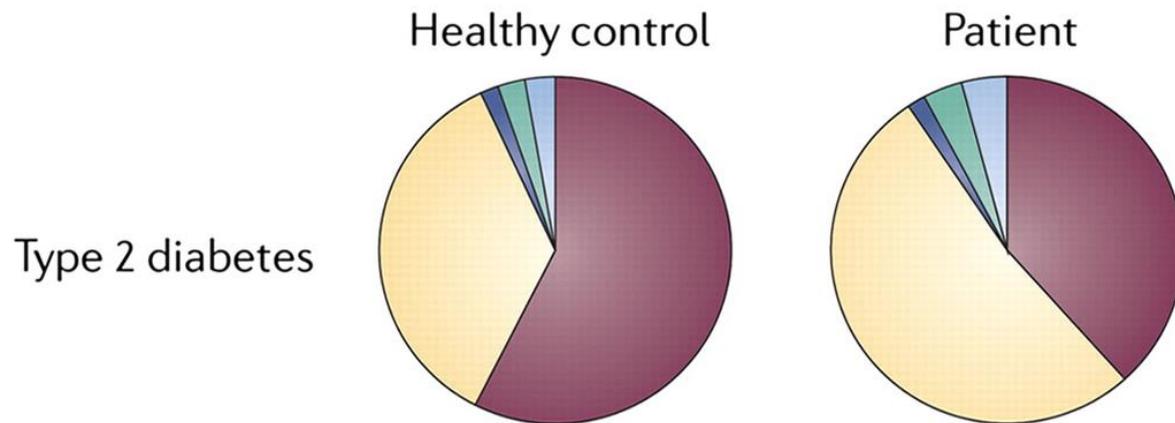


SCFA= short chain fatty acid

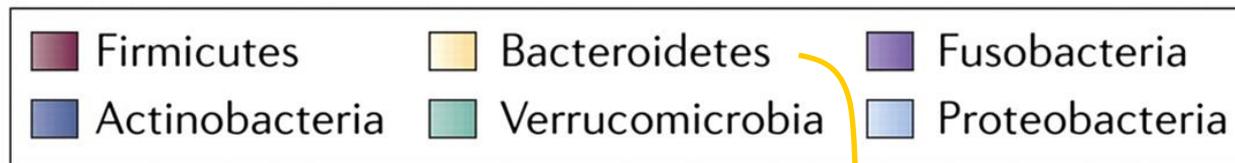


# MICROBIOTE

→ Dysbiose du diabétique



Même profil chez le sujet agé > 65 ans



Synthèse des SCFAs  
Activité  
Anti-inflammatoire

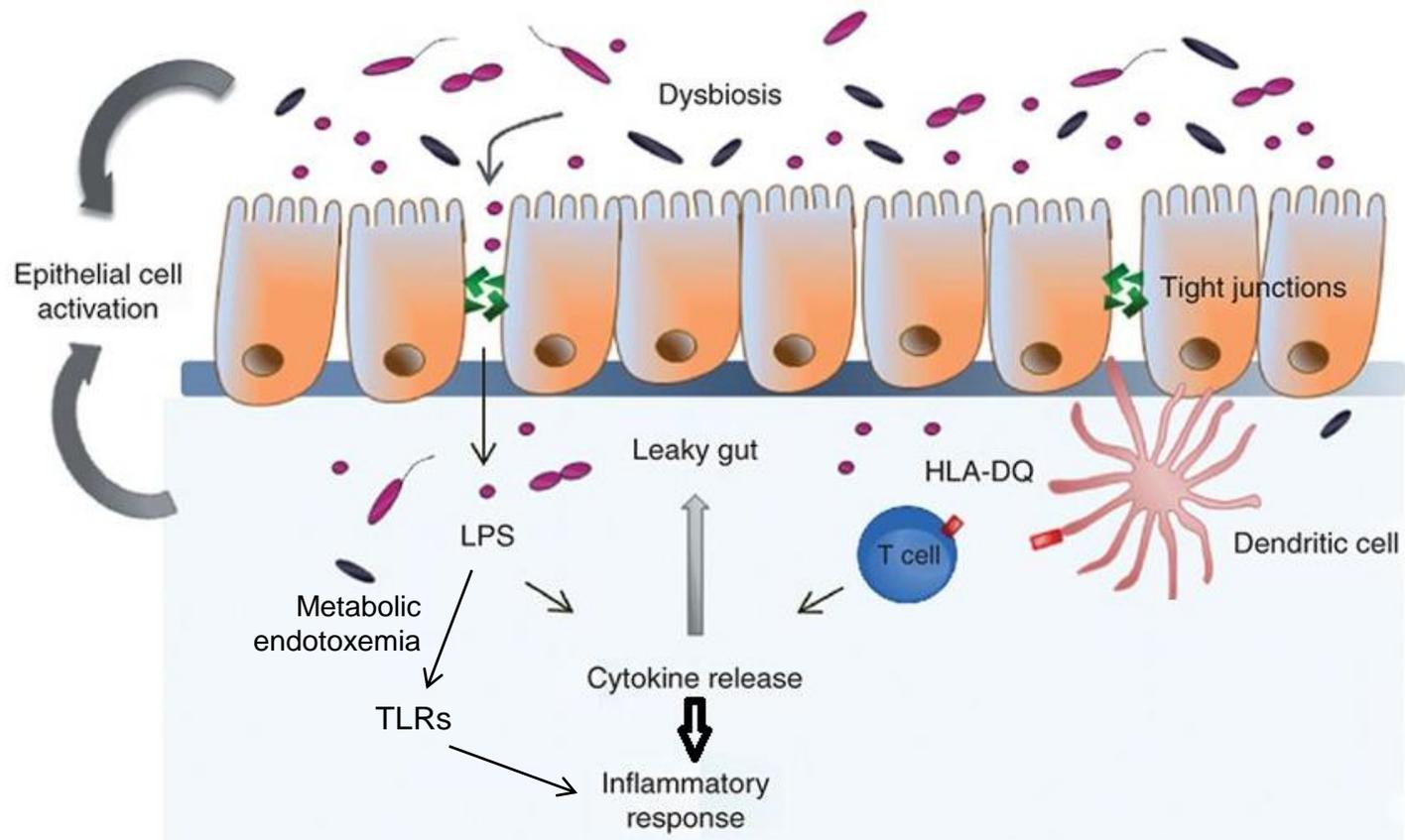
Activité  
proinflammatoire

SCFA= short chain fatty acid

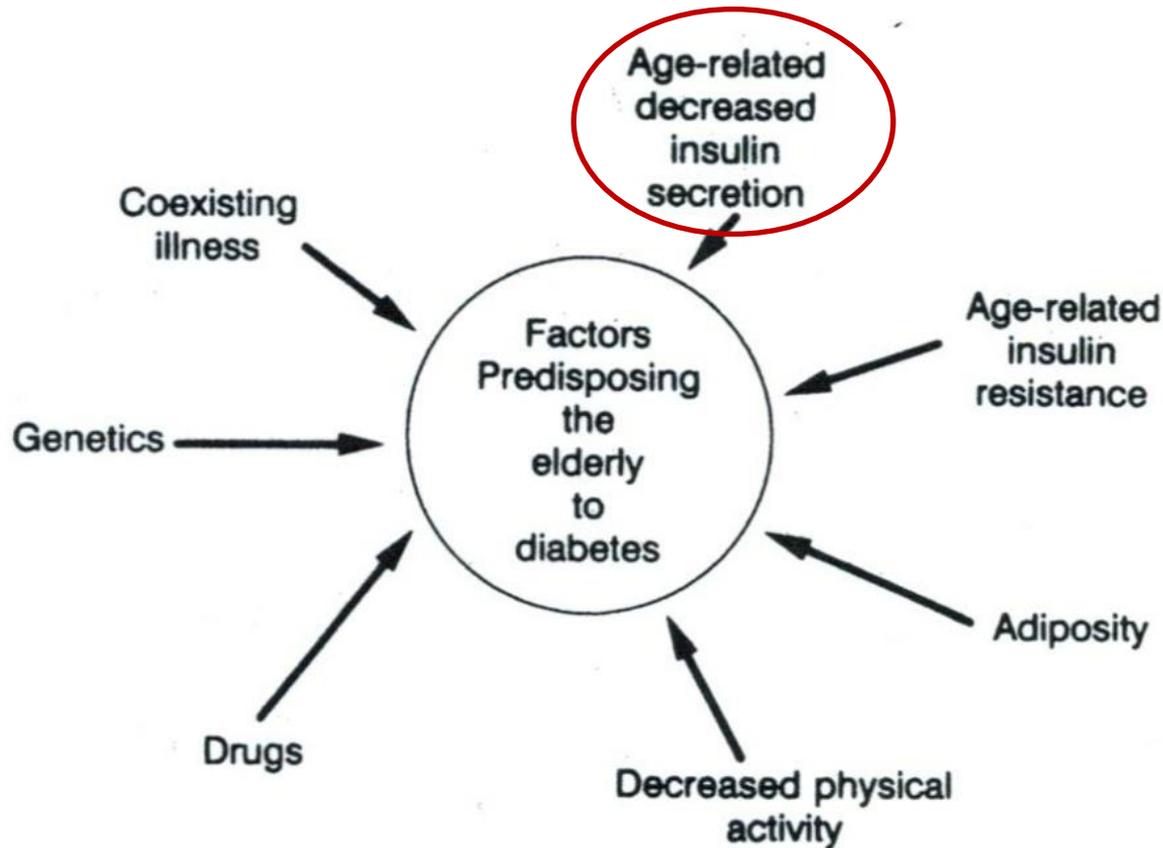


# MICROBIOTE

→ Dysbiose du diabétique

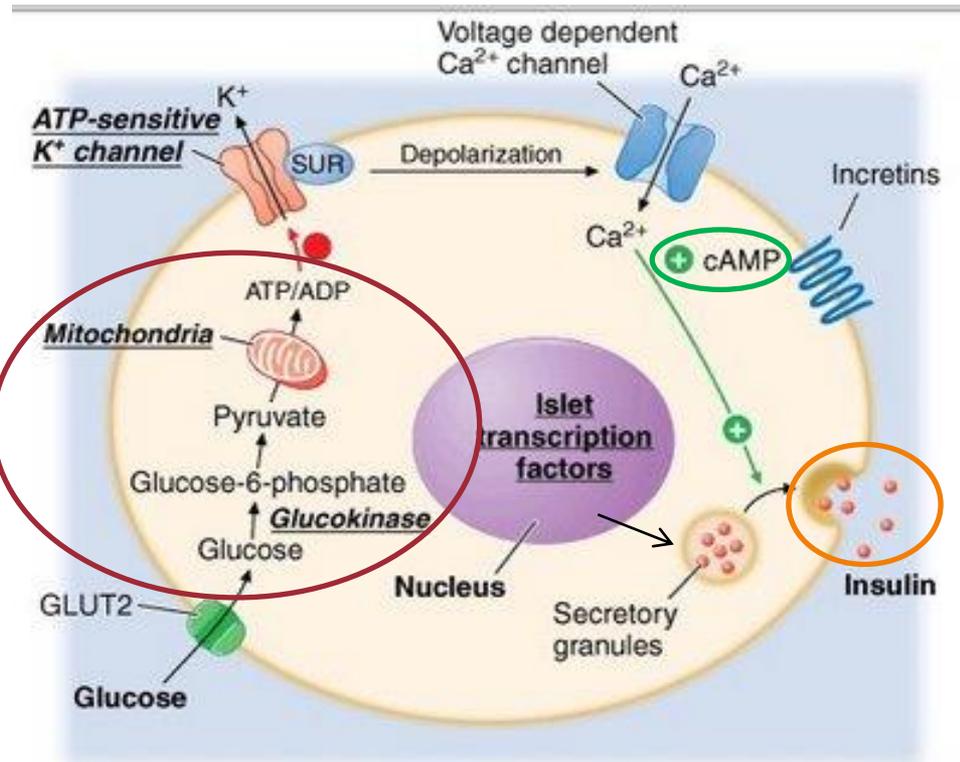


# ALTÉRATIONS DE LA SÉCRÉTION D'INSULINE



# ALTÉRATIONS DE LA SÉCRÉTION D'INSULINE

## Dysfonction des cellules $\beta$



Oxydation  
du glucose

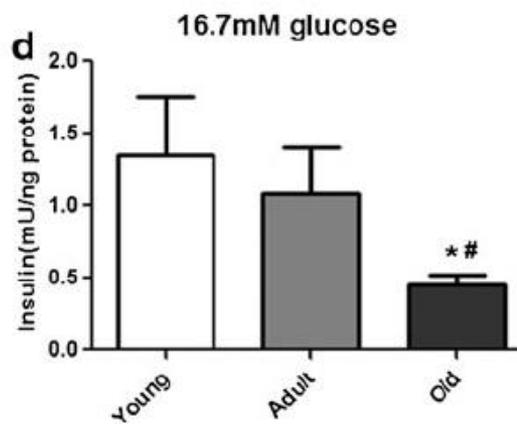
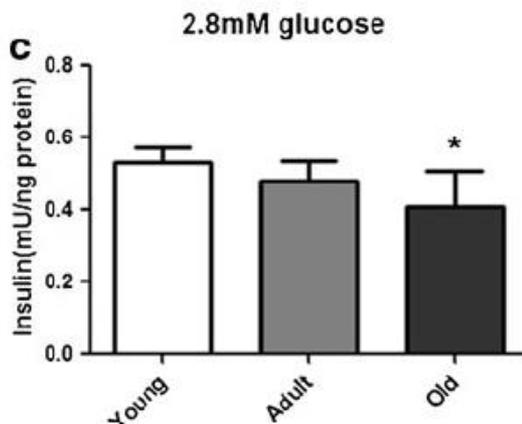
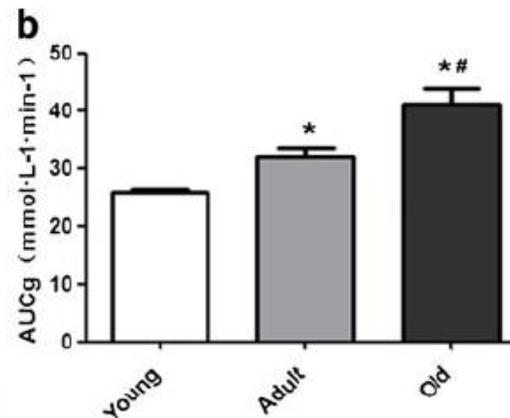
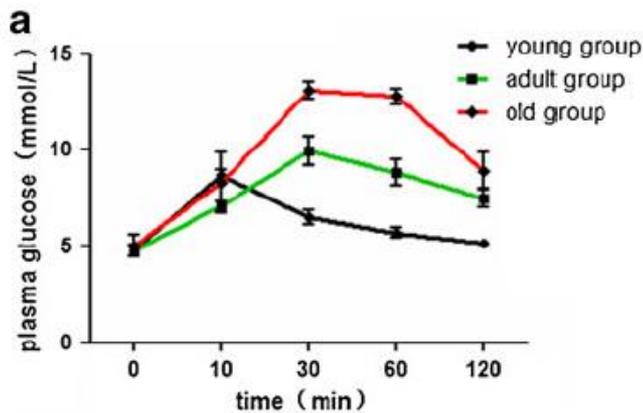
Fusion des granules  
Transcription gène de l'insuline  
Production proinsuline



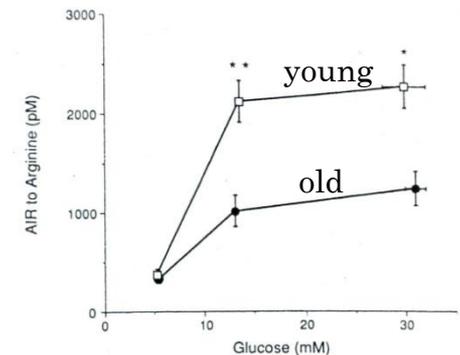
# ALTÉRATIONS DE LA SÉCRÉTION D'INSULINE

## Dysfonction des cellules $\beta$

Rats âgés de 4, 14 et 24 mois: OGTT

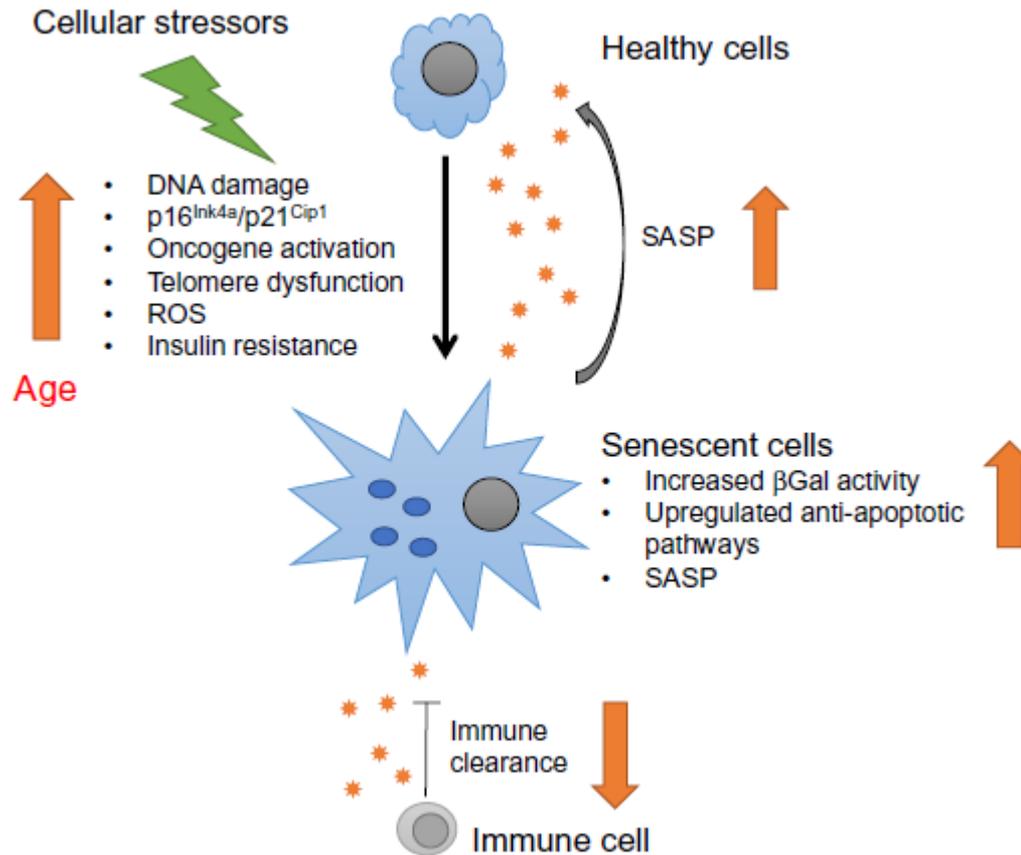


Autre sécrétagogue:  
arginine



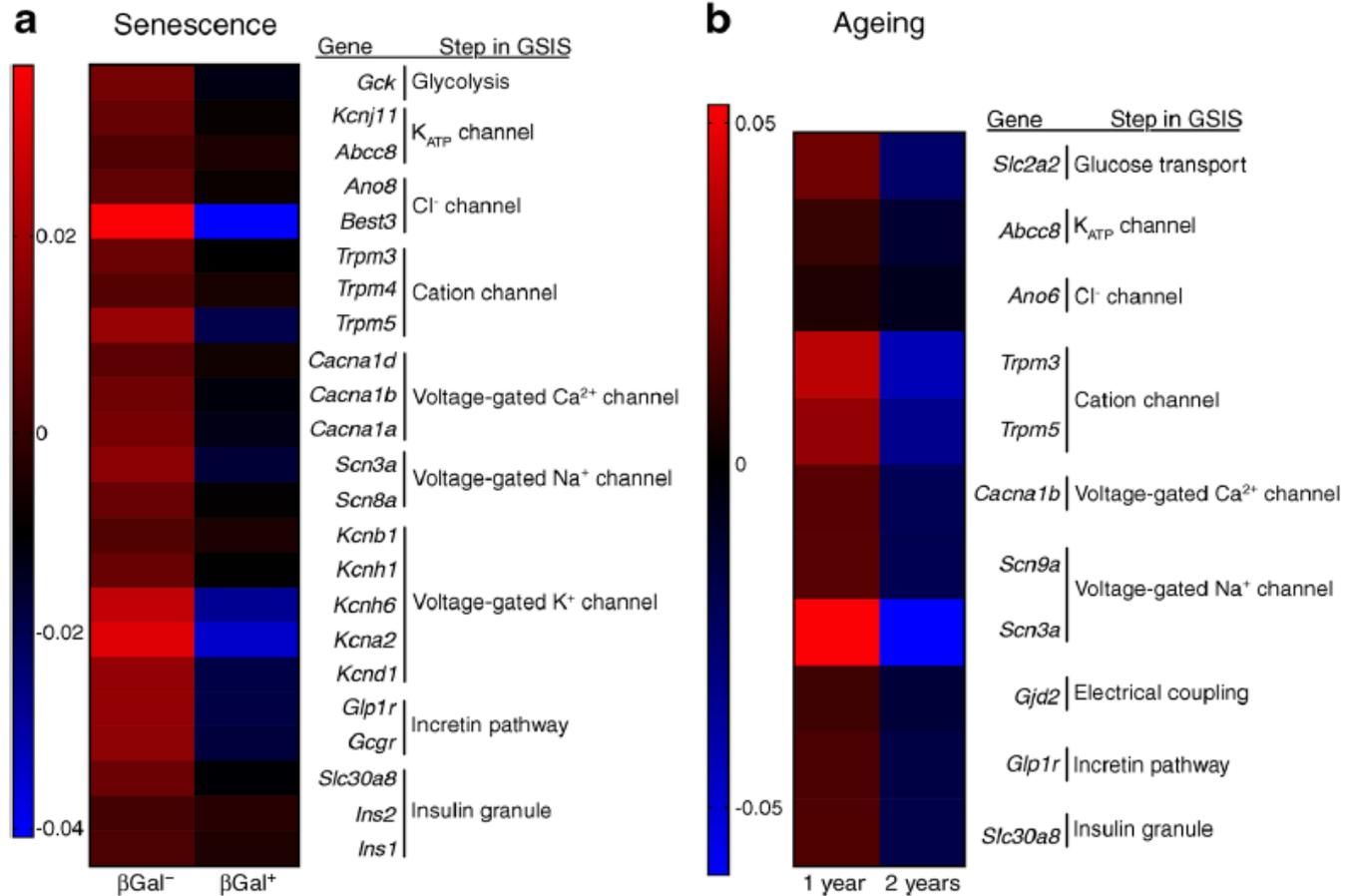
# MÉCANISMES MIS EN JEU

## ➤ Sénescence



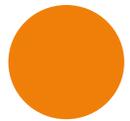
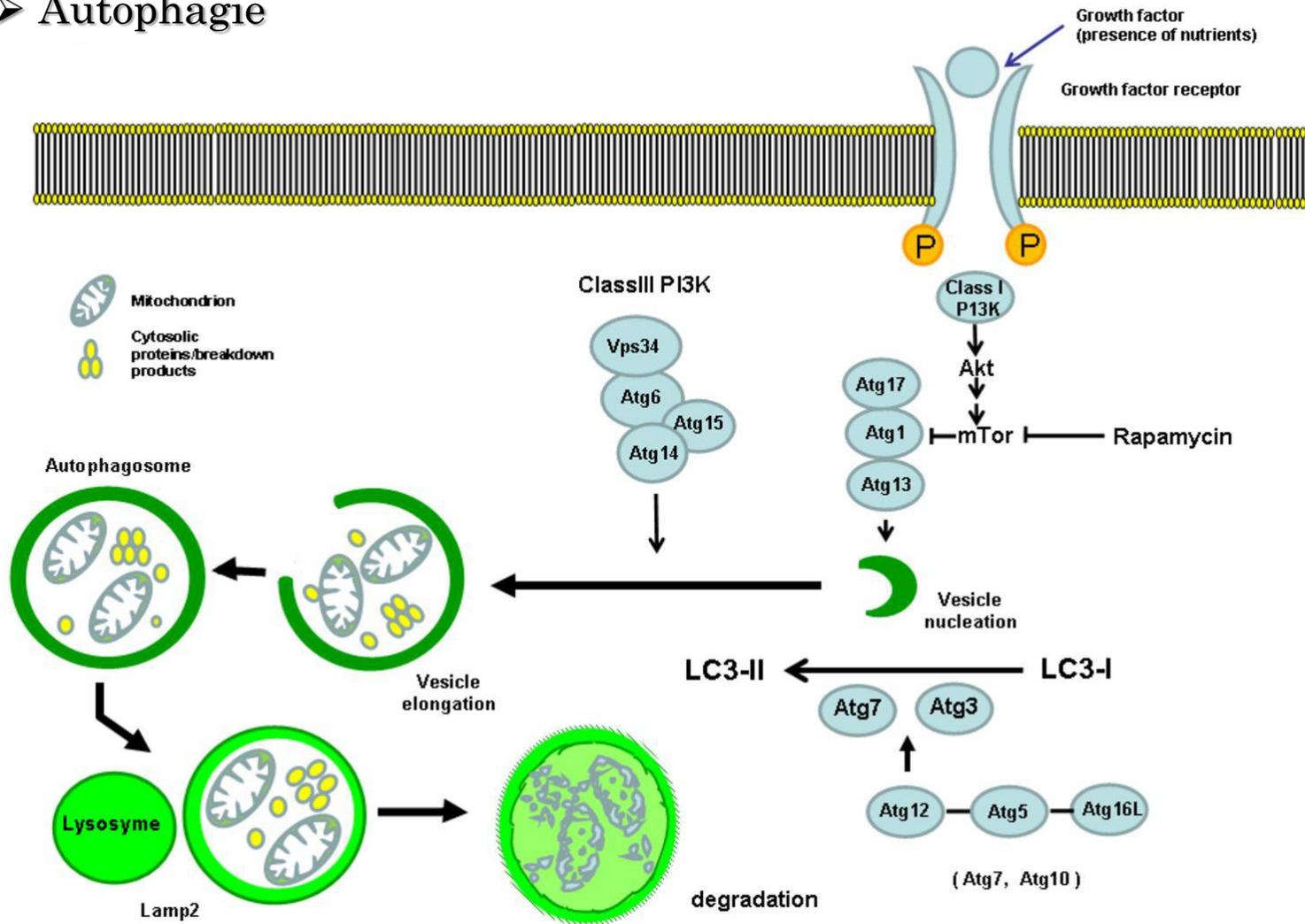
# MÉCANISMES MIS EN JEU

## ➤ Sénescence



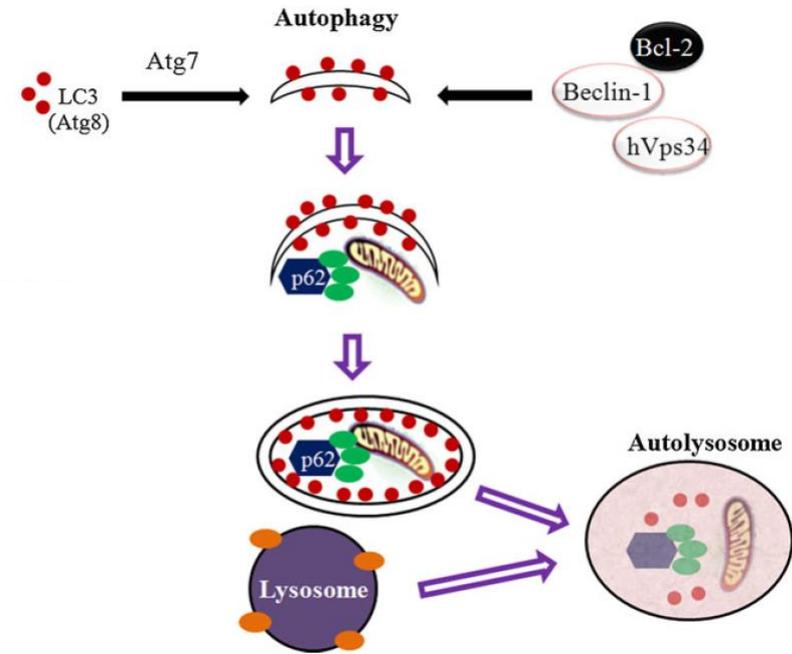
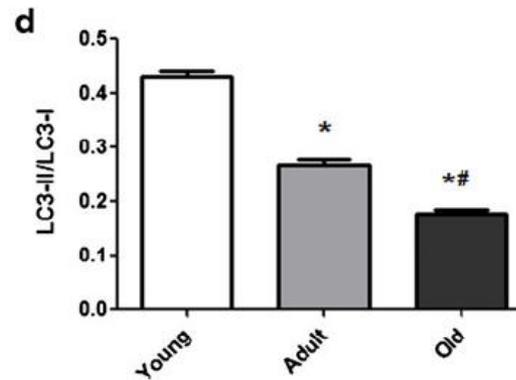
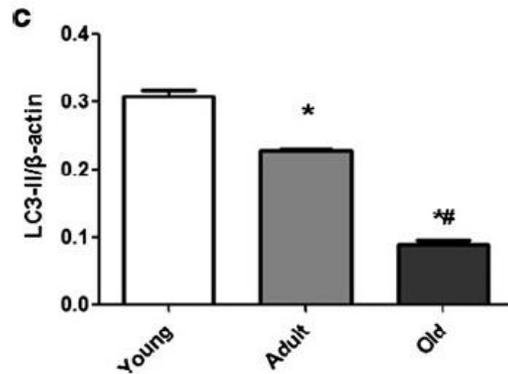
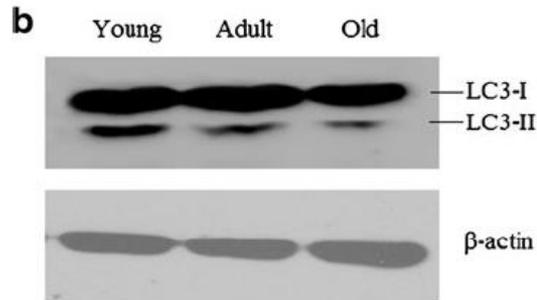
# MÉCANISMES MIS EN JEU

## ➤ Autophagie



# MÉCANISMES MIS EN JEU

## ➤ Autophagie

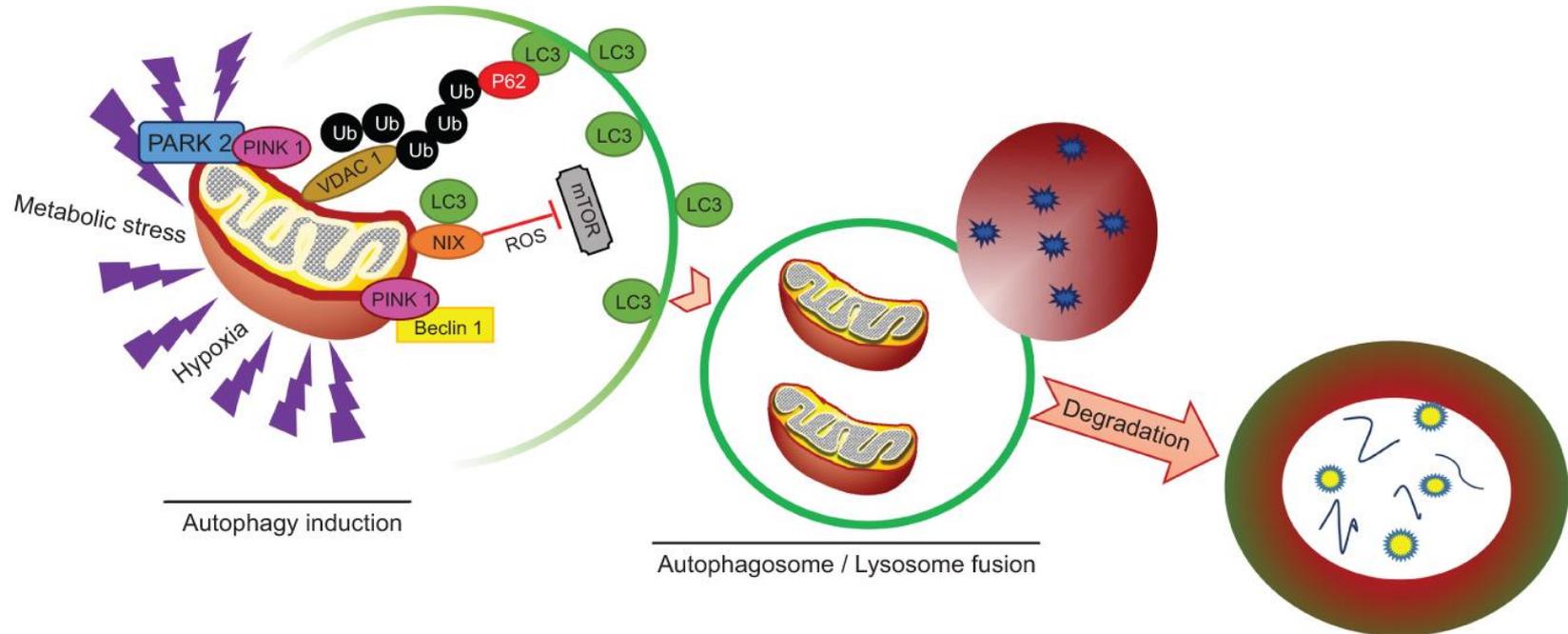


➔ Accumulation de protéines mal repliées



# MÉCANISMES MIS EN JEU

## ➤ Mitophagie



Altération du potentiel membranaire mitochondrial

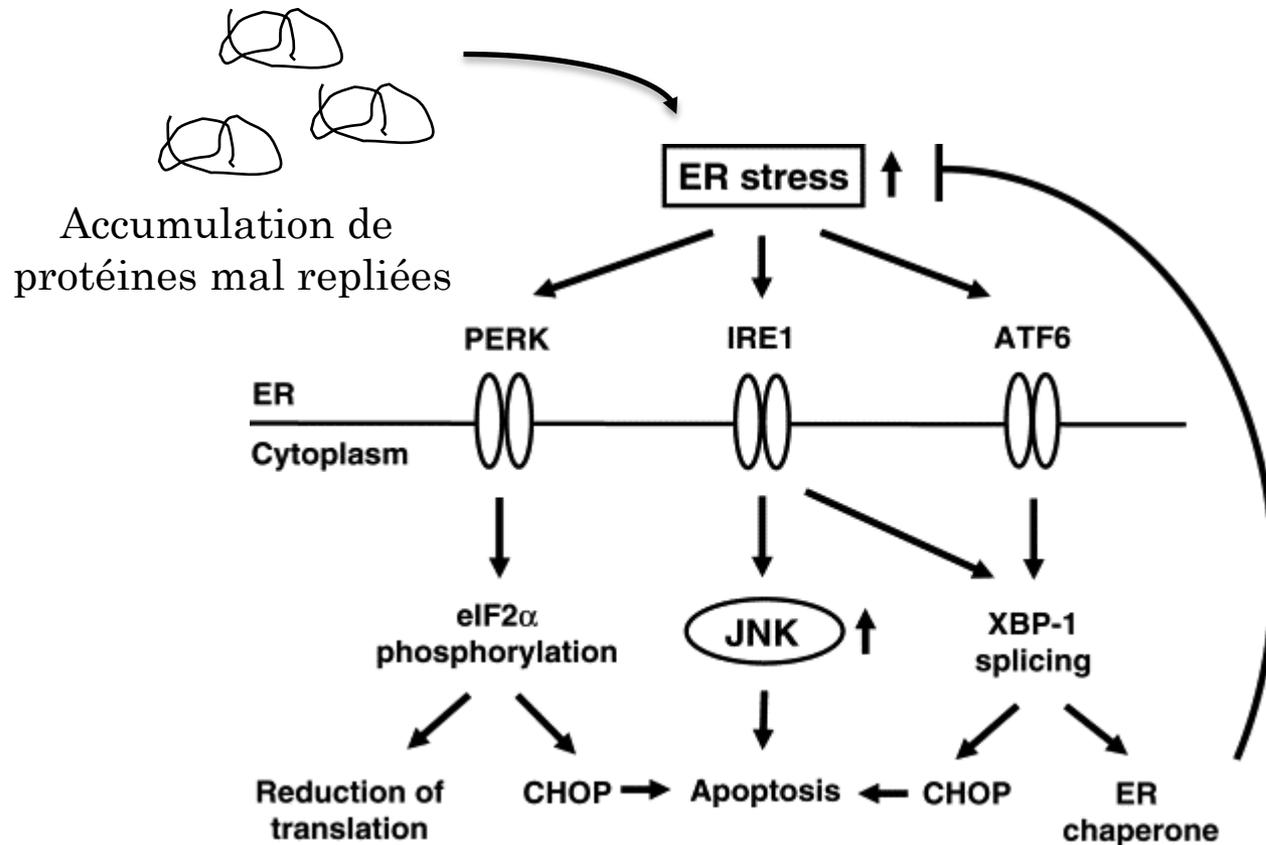
→ Pas dégradation mitochondries altérées

Diminution du nombre de mitochondries



# MÉCANISMES MIS EN JEU

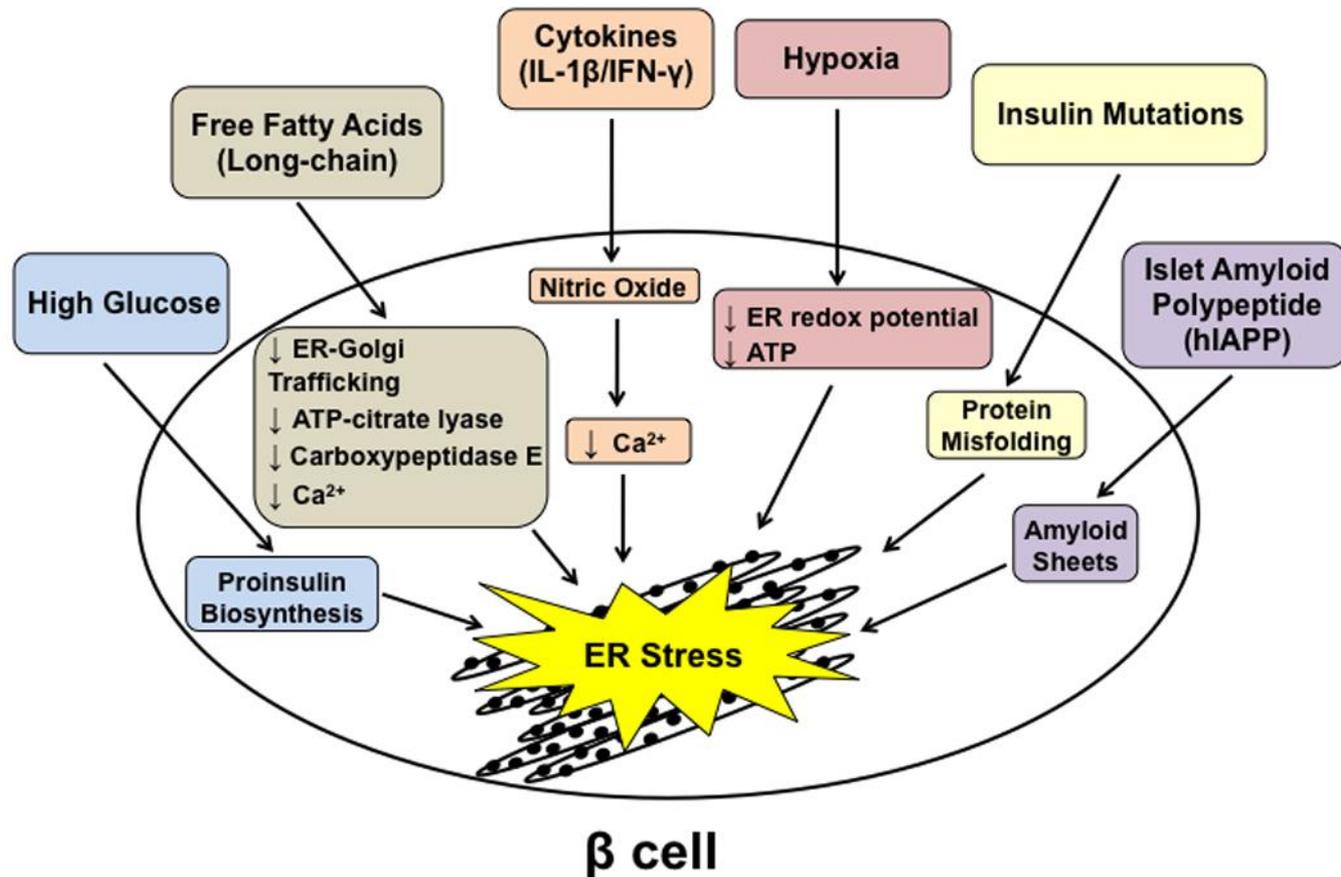
## ➤ Stress du réticulum endoplasmique



→ Age: baisse expression des chaperonnes du RE et des enzymes de repliement

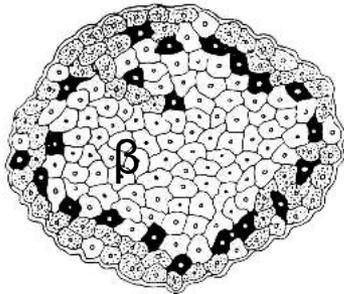
# MÉCANISMES MIS EN JEU

## ➤ Stress du réticulum endoplasmique

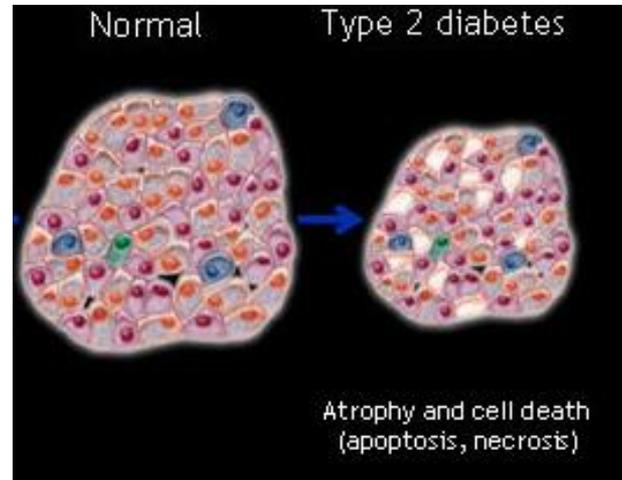


# ALTÉRATIONS DE LA SÉCRÉTION D'INSULINE

Perte de masse des cellules  $\beta$

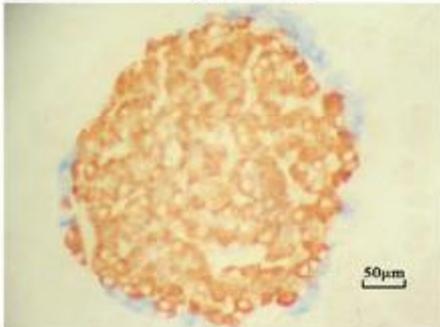


Ilot de Langerhans

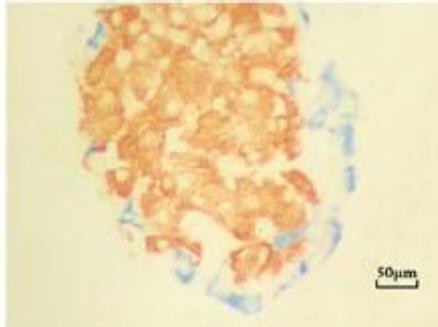


a

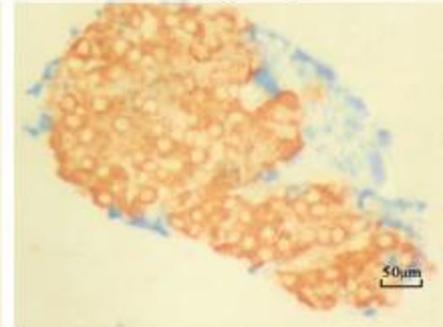
Young group



Adult group

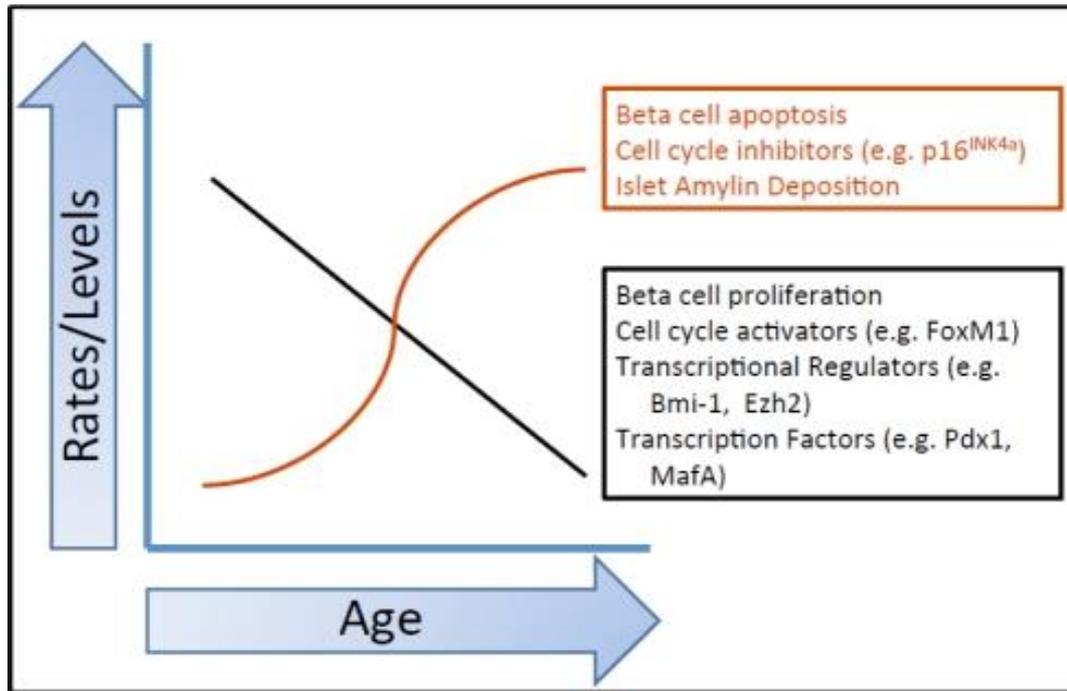


Old group



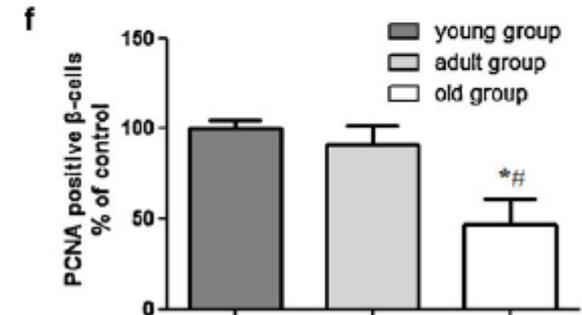
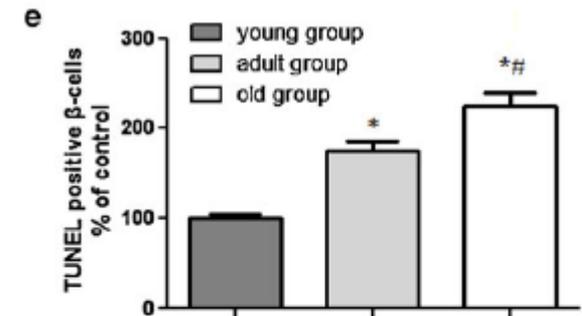
# MÉCANISMES MIS EN JEU

## ➤ Prolifération/apoptose



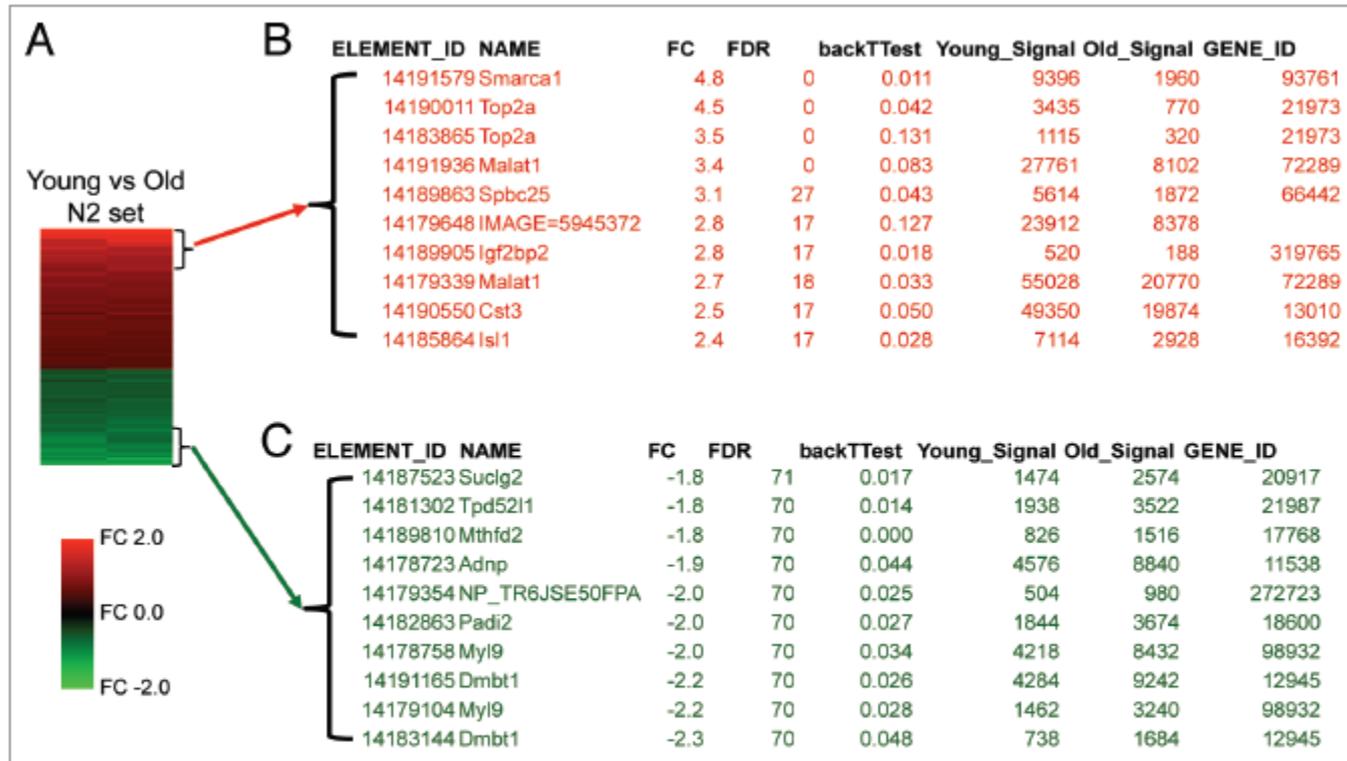
Gunasekaran U. et al., Aging, 2011

Rats âgés de 4, 14 et 24 mois



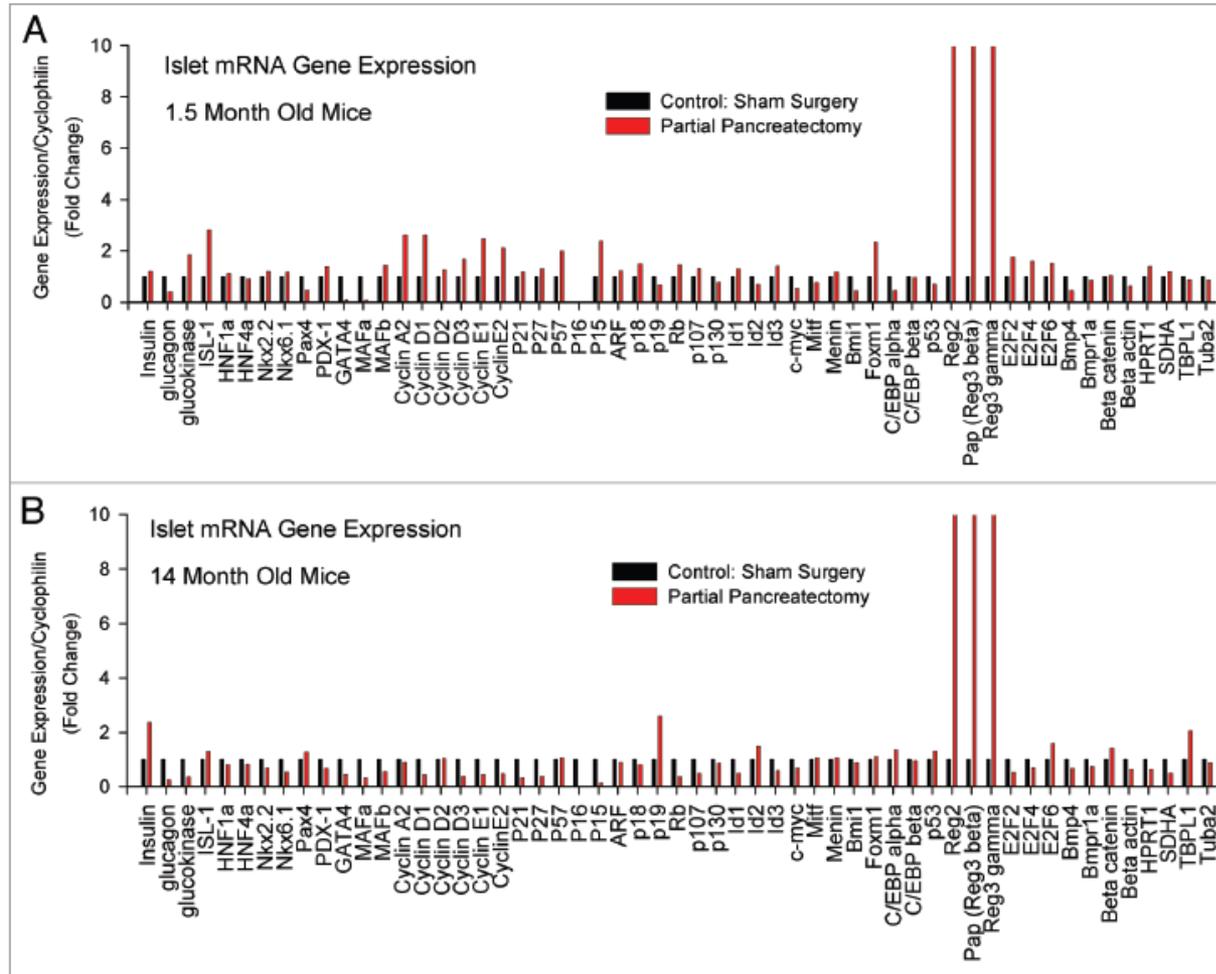
Gu Z. et al., Age, 2011

# MÉCANISMES MIS EN JEU



**Figure 1.** Aging is associated with distinct gene expression patterns in islets. Genomic microarray mRNA expression analysis of islets in the basal state, comparing islets from young mice (1.5 months of age) versus those from old mice (14 or 19 months of age). The 2 pair-wise arrays comprising in this data set (N2) represented the expression sets that exhibited the least exocrine contamination. (A) Heat map of the 91 elements of the PancChip microarray that were differentially expressed 1.5 fold change (FC) or more. Red: genes with higher expression in islets from young versus old mice. Green: genes with lower expression in islets from young versus old mice. (B and C) The most differentially expressed genes in islets from young versus old mice. (B) Genes that were expressed at higher levels in young mice. (C) Genes that were expressed at lower levels in young mice.

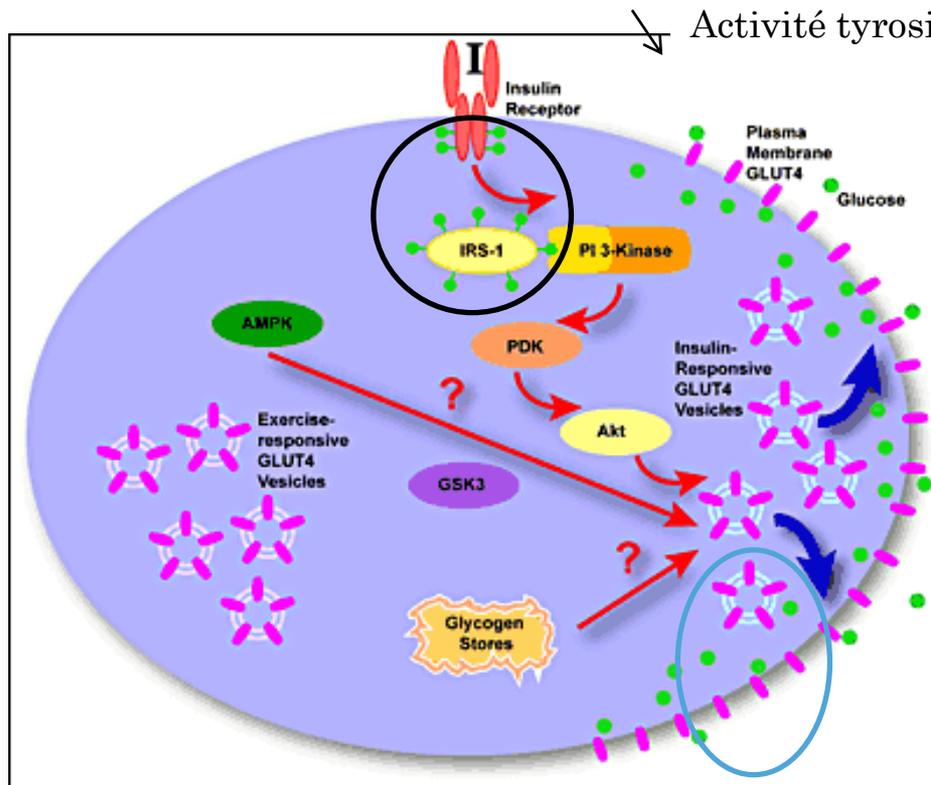
# MÉCANISMES MIS EN JEU



**Figure 2.** Partial pancreatectomy induces cell cycle component gene expression in islets from young mice but not in old mice. Candidate qPCR mRNA expression studies of islets after 50% partial pancreatectomy versus sham-operated controls. (A) Studies performed in young mice (1.5 months). (B) Studies performed in old mice (14 months). Results expressed as fold change from control.

# ALTÉRATIONS DE L'INSULINO-SENSIBILITÉ

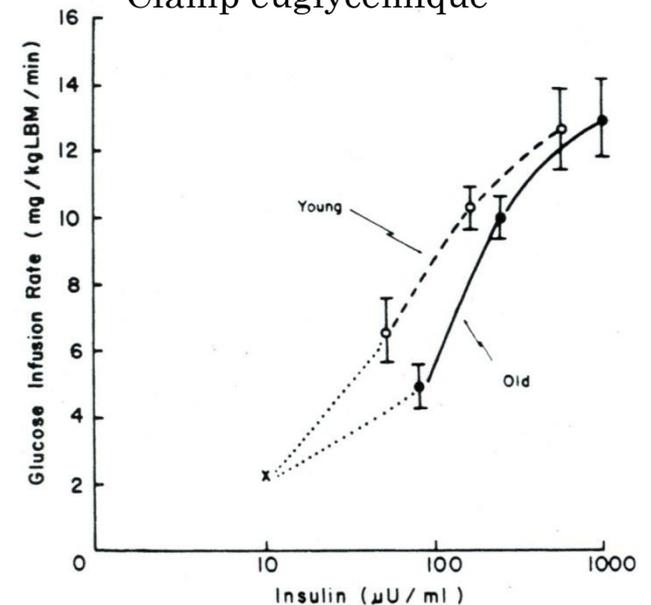
Insulino-résistance des tissus périphériques et du foie



↘ Activité tyrosine kinase du RI

↘ Nombre de GLUT-4 à la membrane  
↘ Expression du GLUT-4

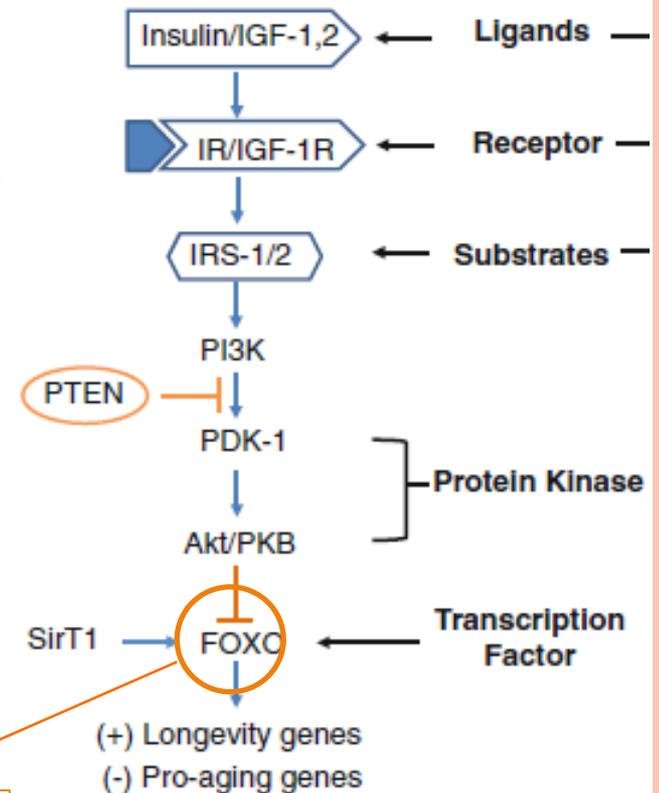
Clamp euglycémique



# MÉCANISMES MIS EN JEU

## ➤ Récepteur de l'insuline

Tissue	Phenotype	Glucose uptake?
Tissue-specific knockout:		
MIRKO	Dyslipidemic without diabetes, insulin-sensitive adipocytes	Decreased
FIRKO	Protection against obesity, enhanced longevity	Decreased
BAIRKO	Glucose intolerance without insulin resistance	ND
GIRKO	Insulin resistance and diabetes	Decreased

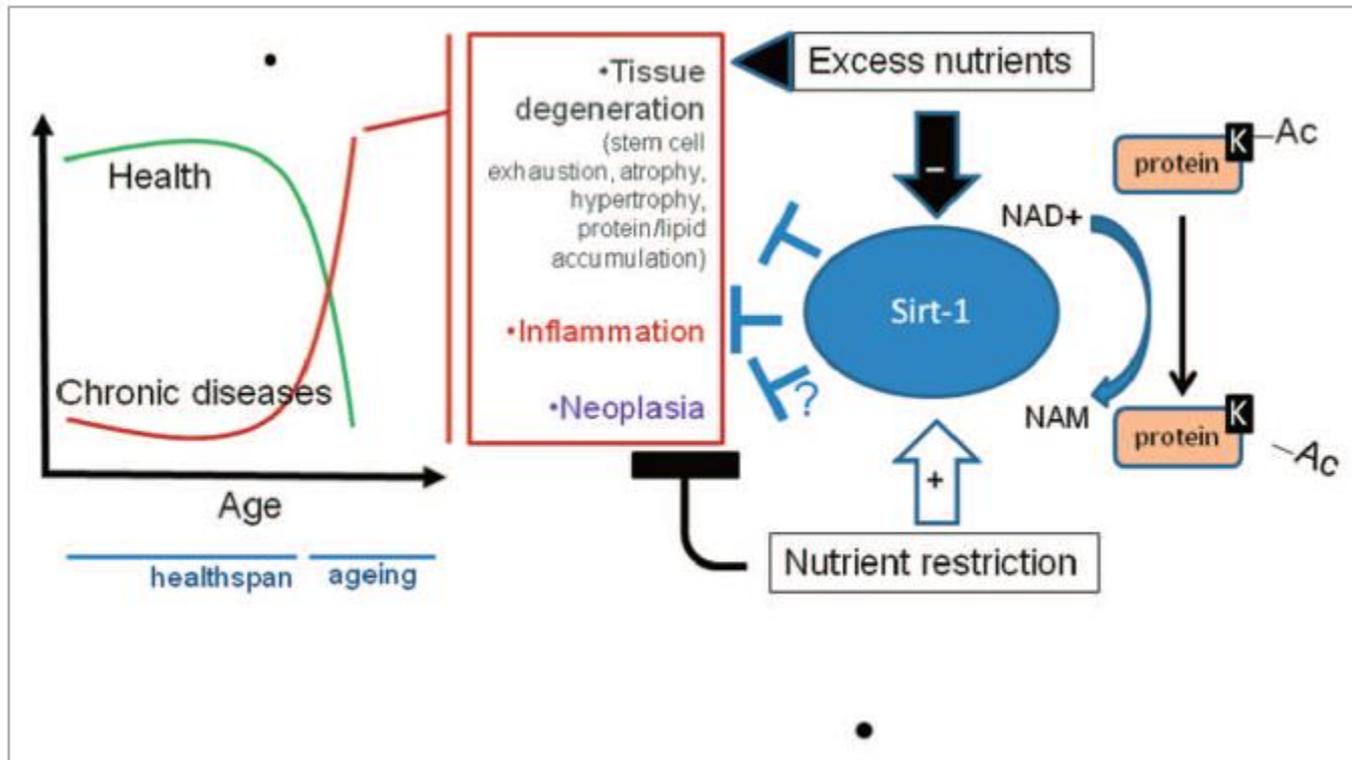


Rétention nucléaire de FOXO

Phosphorylation : séquestration dans cytoplasme

# MÉCANISMES MIS EN JEU

➤ Sirtuines: protéine déacétylase



→ Sirtuines connectent le métabolisme énergétique et l'espérance de vie

