Vieillissement et mitochondries

Pascale Leclercq
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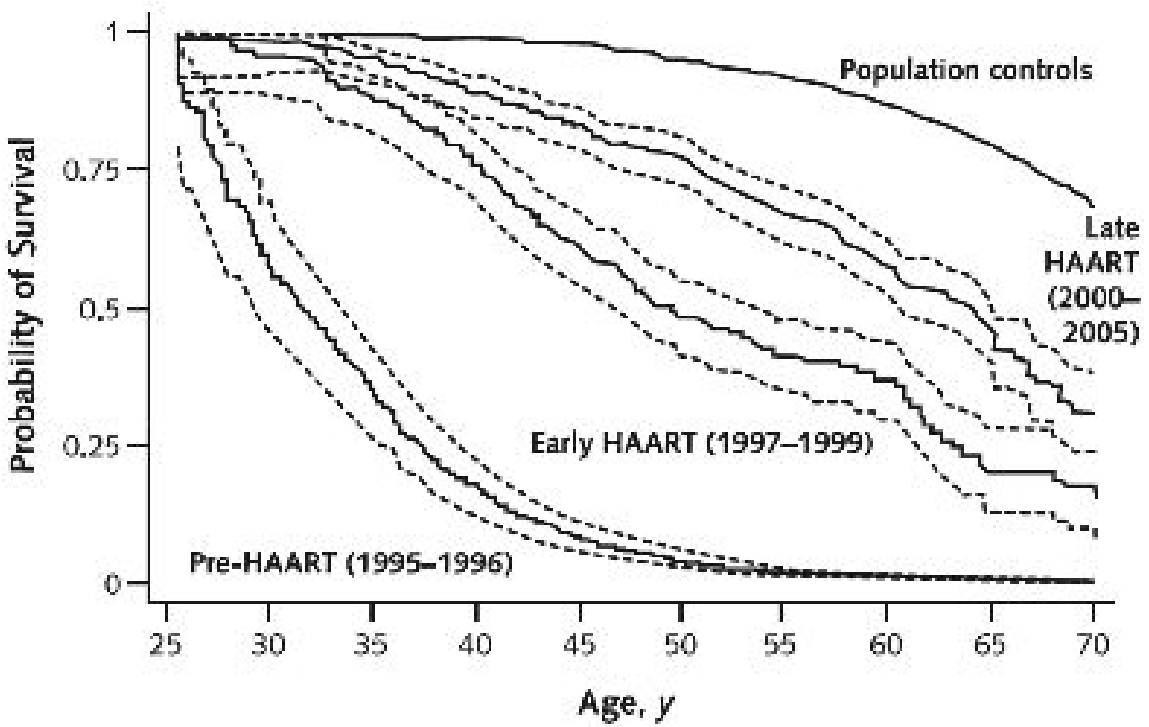
Espérance de vie

Survival from age 25 years



Cumulative survival curve for HIV-infected persons (without hepatitis C coinfection) and persons from the general population. Persons with HIV infection are divided into 3 calendar periods of observation. Dashed lines indicated 95% Cis. HIV – human immunodeficiency virus; HAART – highly active antiretroviral therapy.

Lohse N et coll., Ann Intern Med 2007; 146: 87-95

La mitochondrie

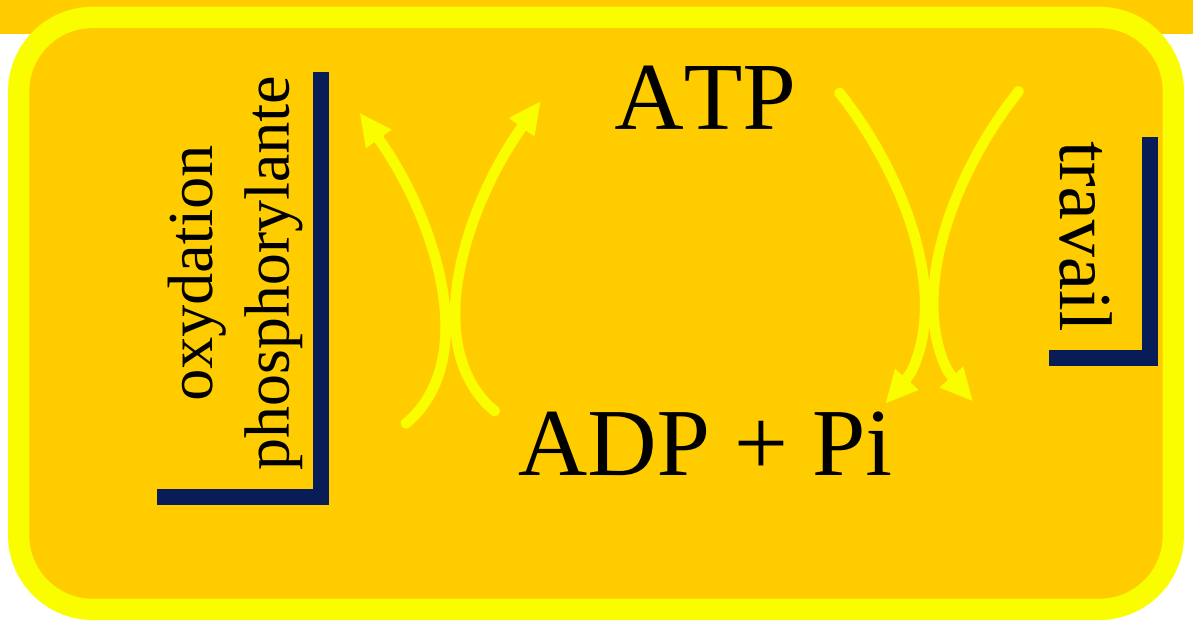
Système **producteur d'énergie**

Système **protecteur contre l'oxygène**

- fission contrôlée
- production de radicaux libres
- sensor de l'oxygène cellulaire

Système central dans l'**apoptose**

Système producteur d'énergie



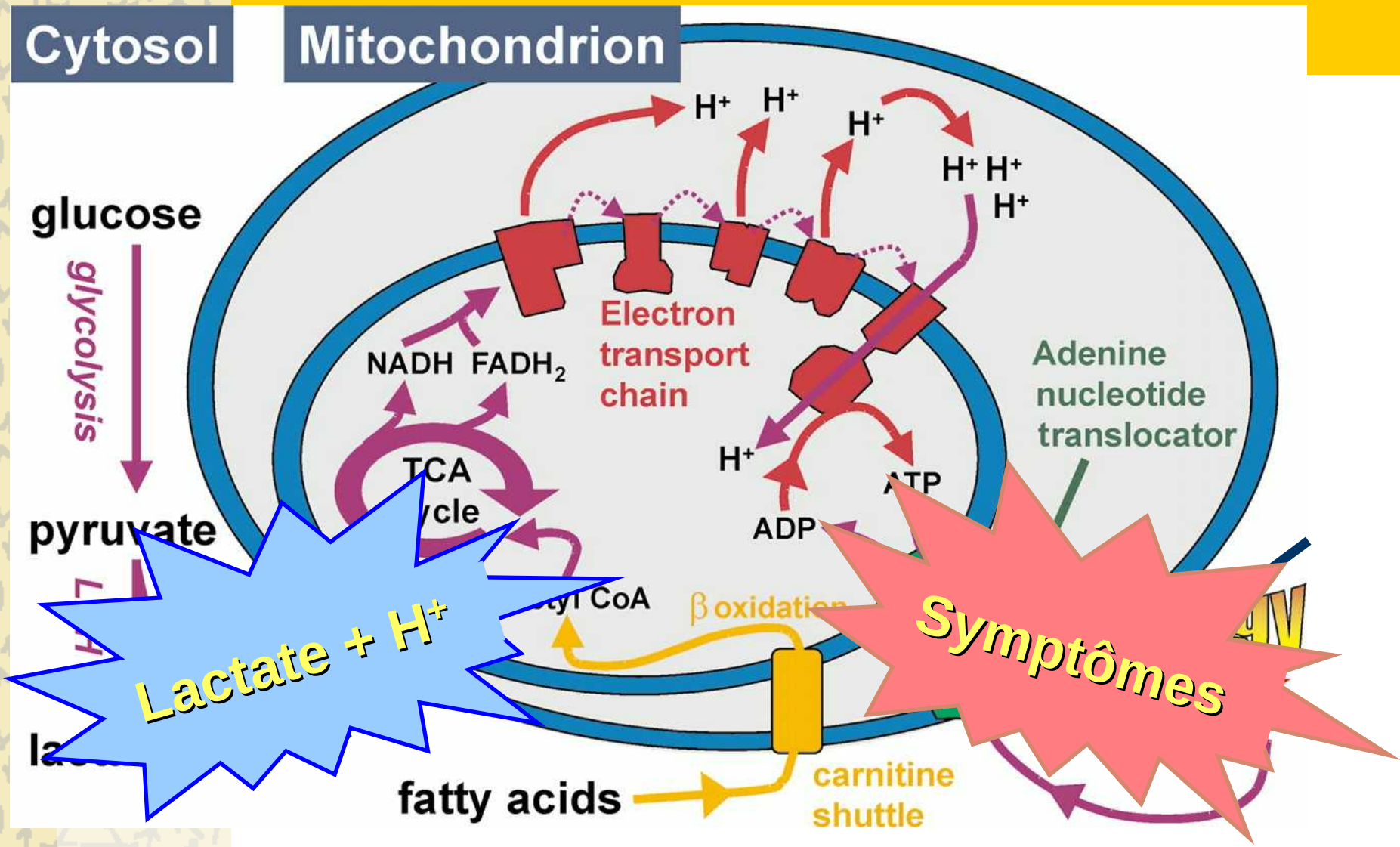
$$\frac{ATP}{ADP \times Pi}$$

turnover ATP = 70 kg / jour

Total nucléotides = 100g

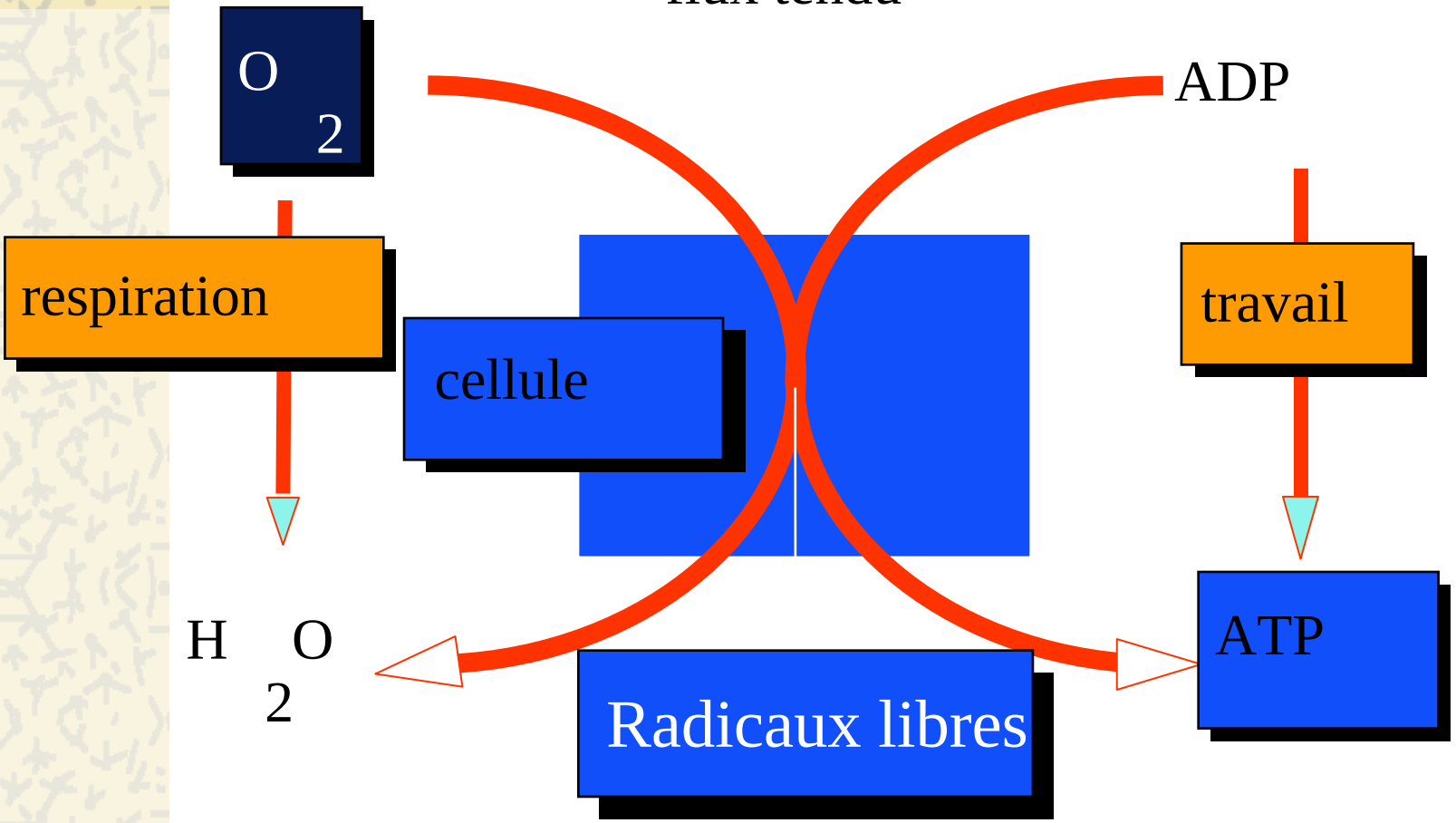
Autonomie = 2 - 3 min

La mitochondrie: fournisseur d ’ATP

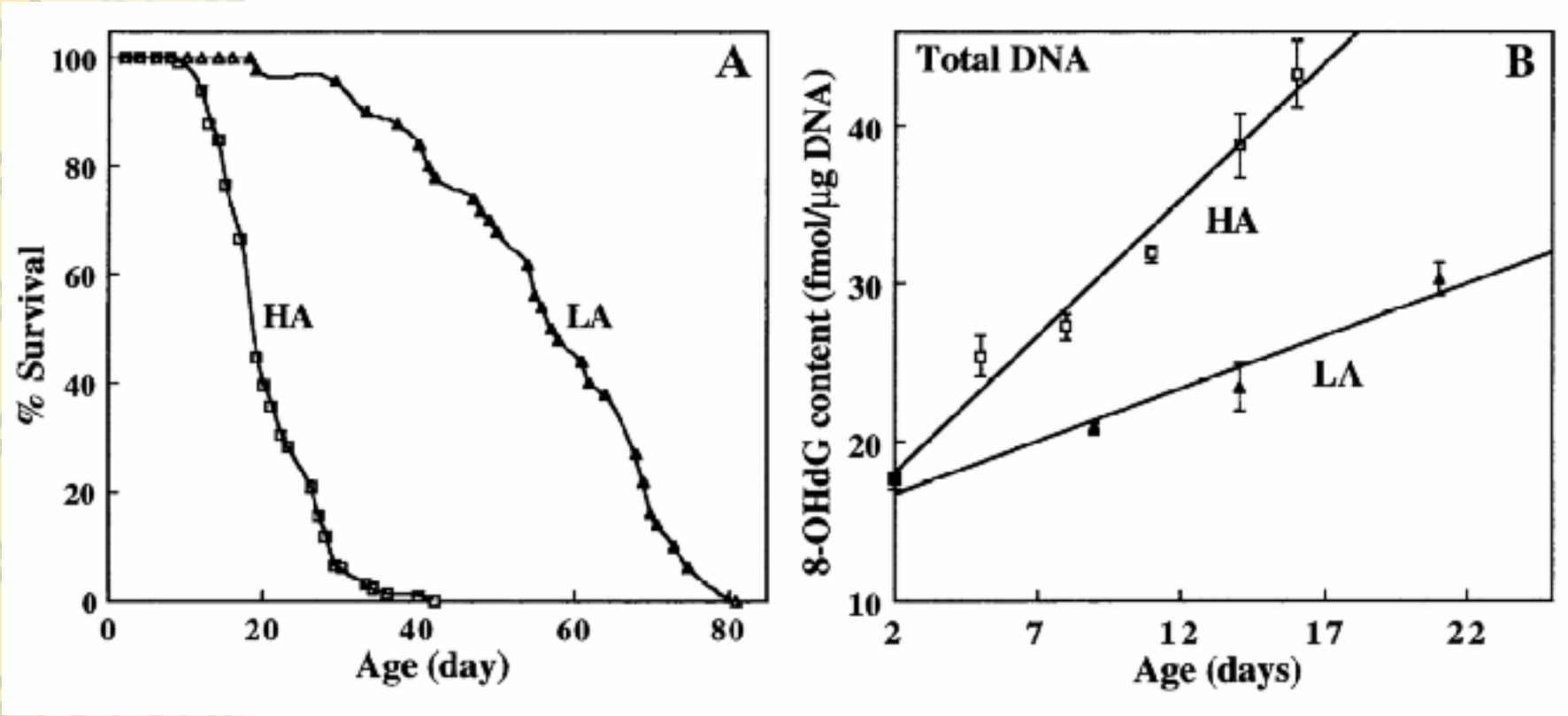


Système protecteur contre l'oxygène

"flux tendu"



Longйvitй et oxydation de l'ADN

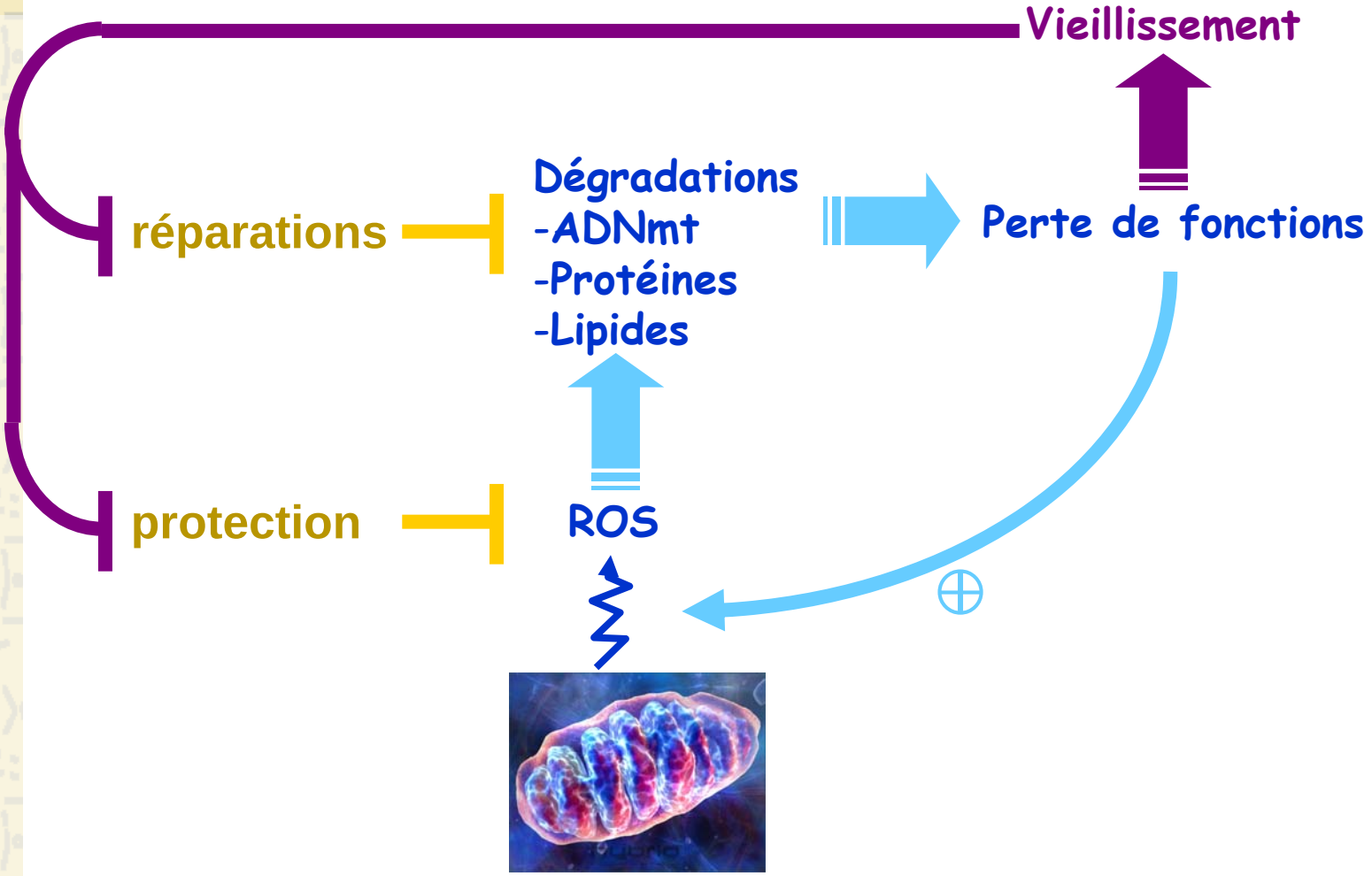


Mouches

HA: High level of activity
LA: Low level of activity

Agarwal *Proc Natl Acad Sci USA*, 1994

Mitochondrie et vieillissement (2)



Toxicité mitochondriale et ARV

- La toxicité mitochondriale

INRT inhibent la DNA polymérase virale…
mais aussi la DNA polymérase mitochondriale…
d'où une dysfonction mitochondriale

Hiérarchie d'effets dépend de entrée dans la cellule, de phosphorylation, de « sortie » de la chaîne de polymérisation
d4T, ddI > AZT > 3(F)TC, Abacavir, Tenofovir

Cliniquement le vieillissement concerne tous les organes
Les plus visibles: peau
Les plus limitants : muscle, cœur, poumons
Les plus inquiétants : cerveau
Les plus discrets ? Foie, rein, système immunitaire

Choix de montrer l'effet du vieillissement sur la fonction mitochondriale dans le muscle squelettique
(avec aide de Béatrice Morio, chercheur Unité Métabolisme Protéino-Energétique Clermont-Fd)

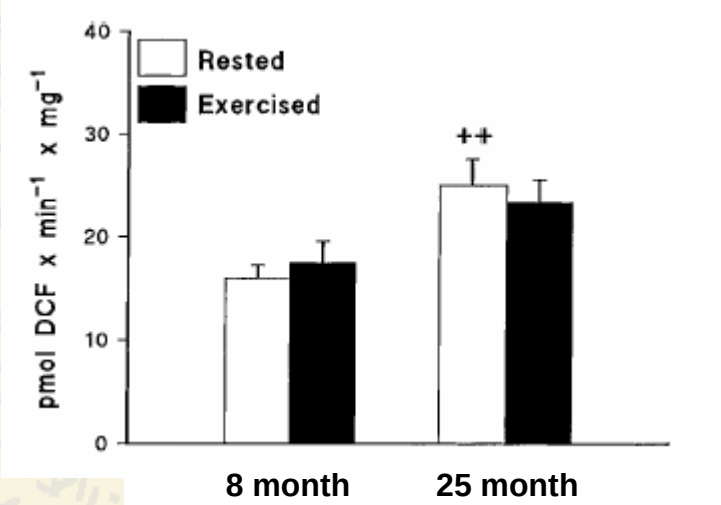
Production de radicaux libres (1)

Aging and acute exercise enhance free radical generation in rat skeletal muscle

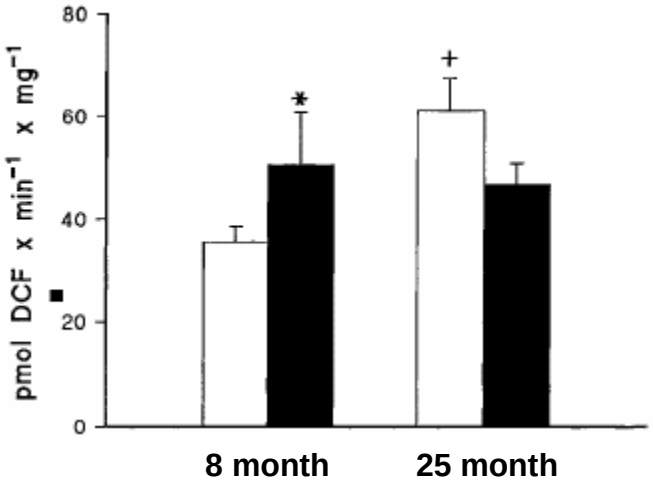
J. BEJMA AND L. L. JI

J.Appl. Physiol. 87(1):465-470, 1999

Mitochondrial H_2O_2 release in basal state



Mitochondrial H_2O_2 release in induced state (+ADP)



Production de radicaux libres (2)

Due to reverse electron transfer, mitochondrial H_2O_2 release increases with age in human vastus lateralis muscle although oxidative capacity is preserved

mechanisms of ageing and development

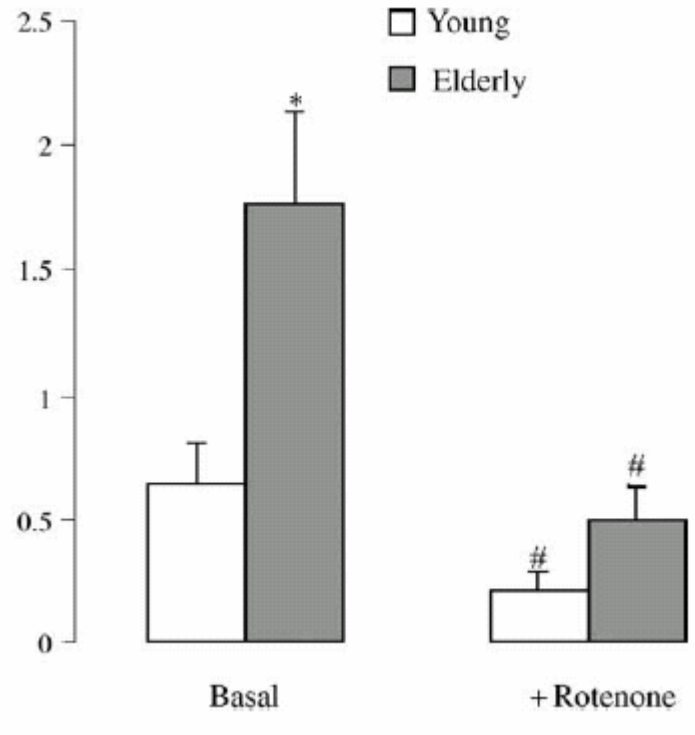
F. Capel[a], V. Rimbert[b], D. Lioger[b], A. Diot[a], P. Rousset[b], P. Patureau Mirand[a], Y. Boirie[b], B. Morio[b], L. Mosoni[a,*]

Effect of age on muscle mitochondrial enzyme activities

	Age groups		*T*-test
	Young	Elderly	
CS	22.6 ± 0.8	18.6 ± 2.7	NS
Complex II	1.1 ± 0.2	1.4 ± 0.1	NS
Complex III	3.0 ± 0.4	3.6 ± 0.3	NS
COX	5.5 ± 0.4	7.4 ± 1.4	NS

Activities are expressed in μmol min^{-1} g wet $tissue^{-1}$. Values are means ± S.E. of five measurements per age. CS, citrate synthase, COX, cytochrome *c* oxidase.

Mitochondrial H_2O_2 release



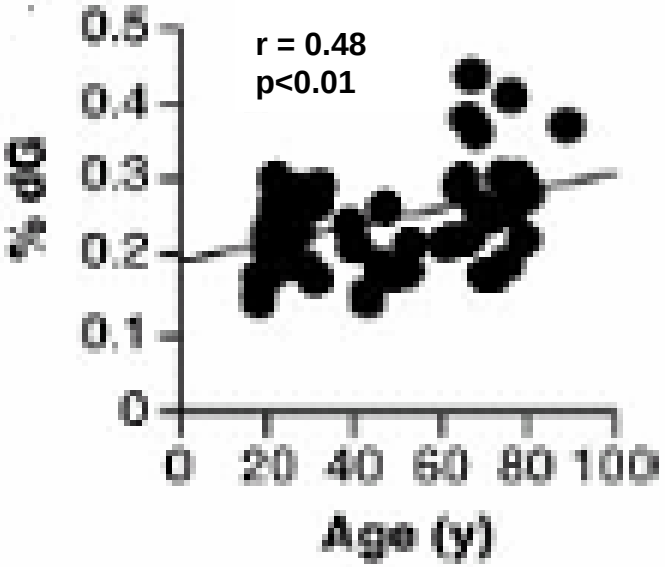
Production de radicaux libres (3)

Decline in skeletal muscle mitochondrial function with aging in humans

5618–5623 | PNAS | April 12, 2005 | vol. 102 | no. 15

Kevin R. Short*, Maureen L. Bigelow*, Jane Kahl*, Ravinder Singh†, Jill Coenen-Schimke*, Sreekumar Raghavakaimal*, and K. Sreekumaran Nair*‡

8-oxo-dG level



Production de radicaux libres (4)

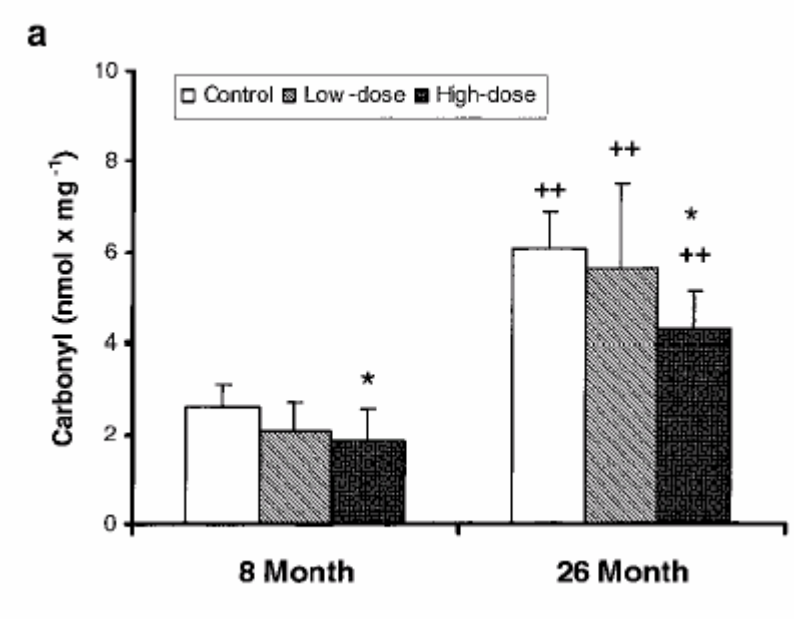
Chronic Ginseng Consumption Attenuates Age-Associated Oxidative Stress in Rats[1]

Ying Fu and Li Li Ji[2]

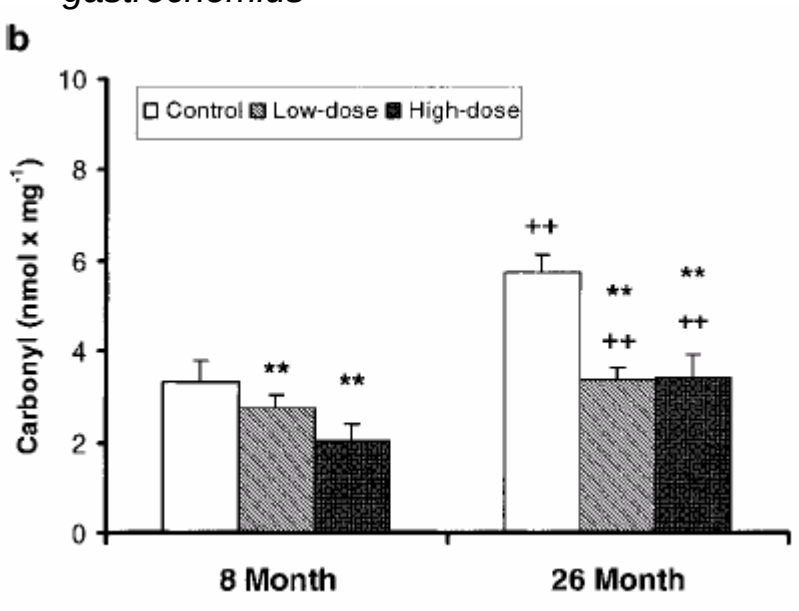
J. Nutr. 133: 3603–3609, 2003.

Protein carbonyl content

soleus



gastrocnemius



Fonctions oxydatives (2)

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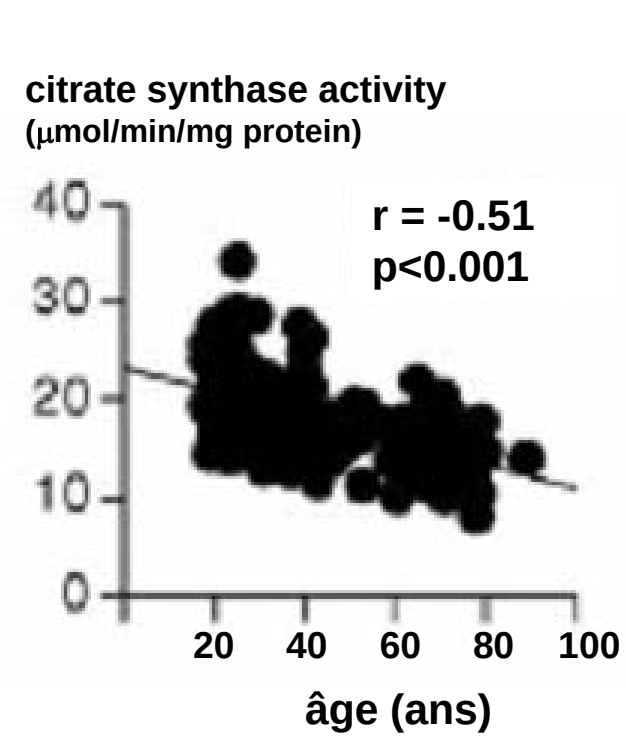

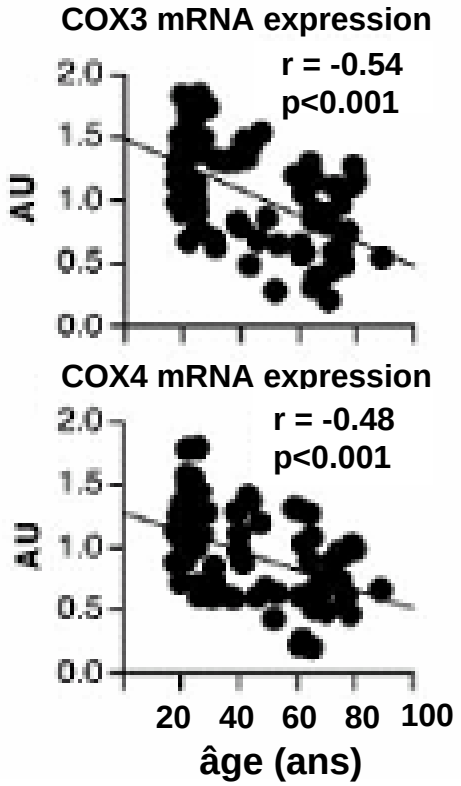

Biogenèse mitochondriale (1)

Decline in skeletal muscle mitochondrial function with aging in humans

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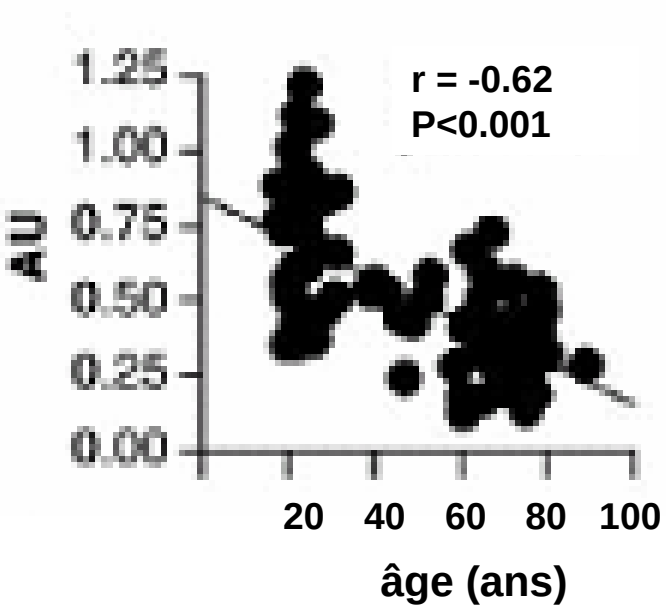
mtDNA abundance (ND1 gene probe)



Production d'ATP

Decline in skeletal muscle mitochondrial function with aging in humans

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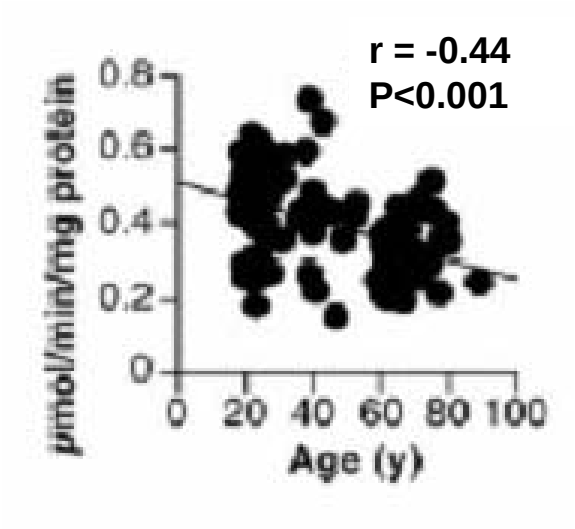
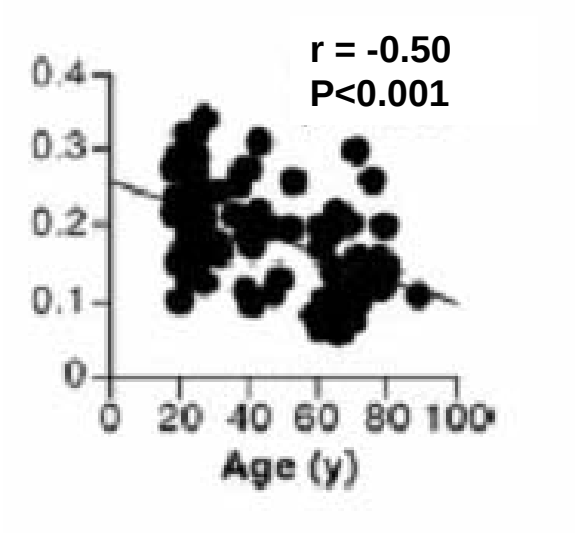
Kevin R. Short*, Maureen L. Bigelow*, Jane Kahl*, Ravinder Singh†, Jill Coenen-Schimke*, Sreekumar Raghavakaimal*, and K. Sreekumaran Nair*‡

Production d'ATP en glutamate/malate
Complex I



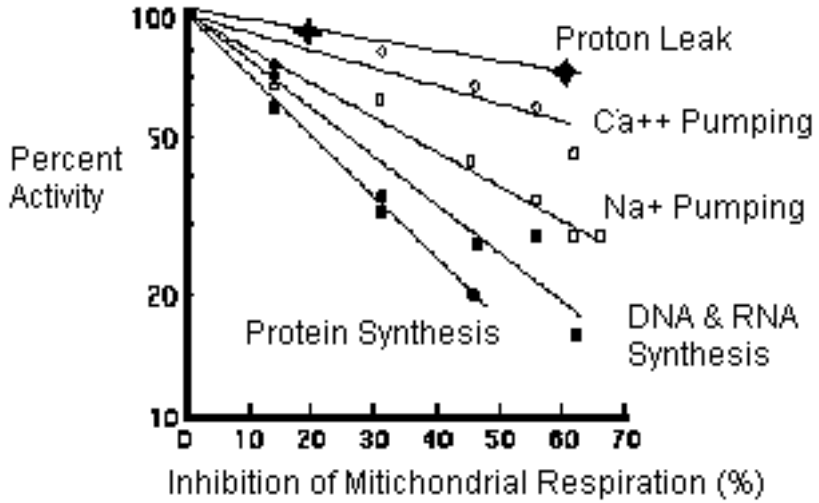
Production d'ATP en succinate + rot.
Complex II



⇒ **Couplage OXPHOS ?**

Conséquences cellulaires

Production d'énergie vs. voies métaboliques cellulaires



- Diminution de la production d'ATP
  - ⇒ diminution de la capacité contractile, du taux de renouvellement des protéines et des nucléotides (ADN, ARN)
  - ⇒ augmentation des risques de dégradation par les ROS

Les PBMC des patients VIH ont une diminution du potentiel de membrane mitochondrial (traités ou non) !

Sternfel.antivir ther 2007;12:769-78

Senescence cellulaire et VIH

Etudes de fibroblastes de patients VIH traités et de patients ayant une laminopathie génétique (progeria…)

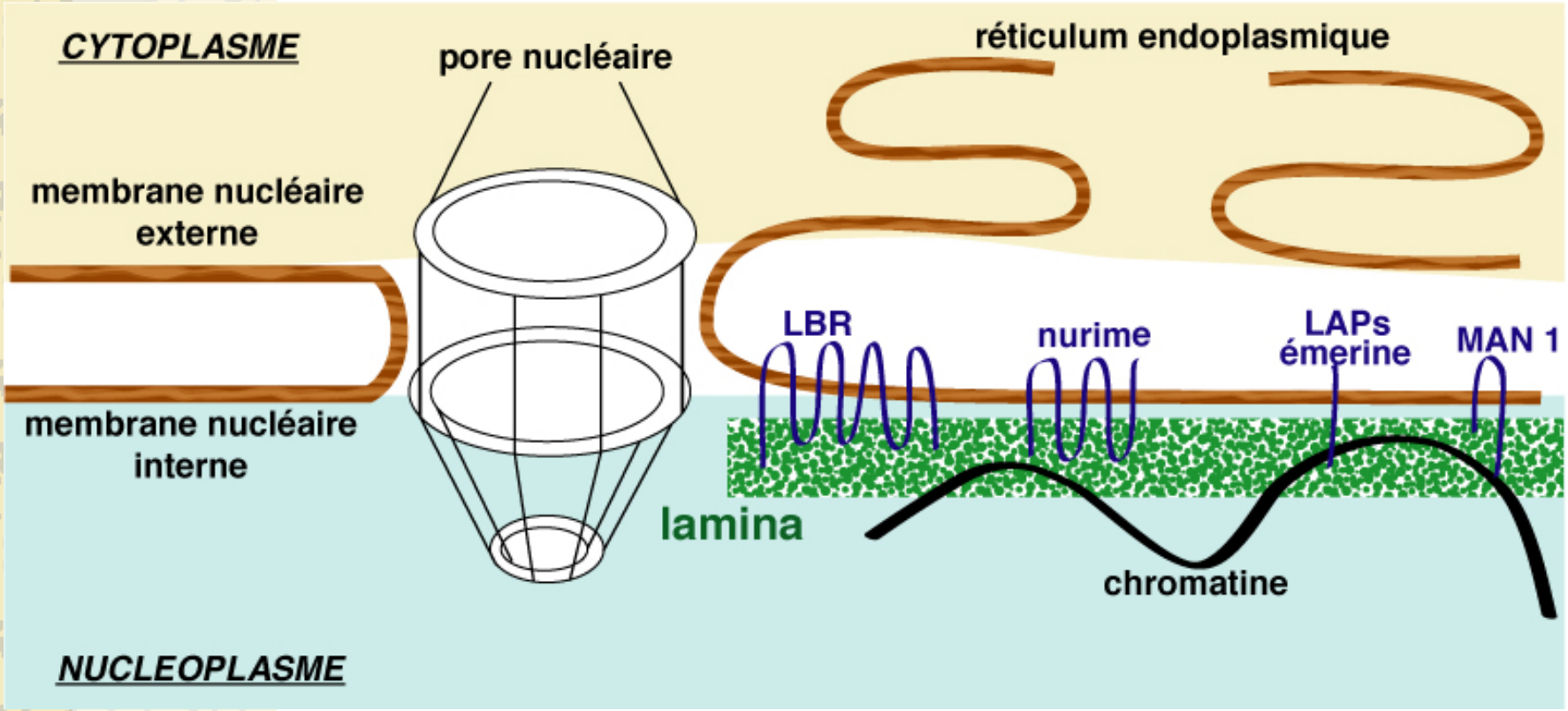
- dans les 2 cas
  - altérations nucléaires
  - altérations de la prolifération

  - accumulation de pré-lamina
  - augmentation stress oxydant
  - sénescence cellulaire prématurée

  •C'est probablement accumulation de pré-lamina farnésylée qui induit sénescence cellulaire

•*Caron. Cell Death Differ 2007*

L'enveloppe nucléaire



Importance de l'activité physique (1a)

Muscle fat oxidative capacity is not impaired by age but by physical inactivity: association with insulin sensitivity

Virginie Rimbert,* Yves Boirie,* Mario Bedu,† Jean-François Hocquette,‡ Patrick Ritz,§ and Béatrice Morio*

The FASEB Journal Published online February 20, 2004.

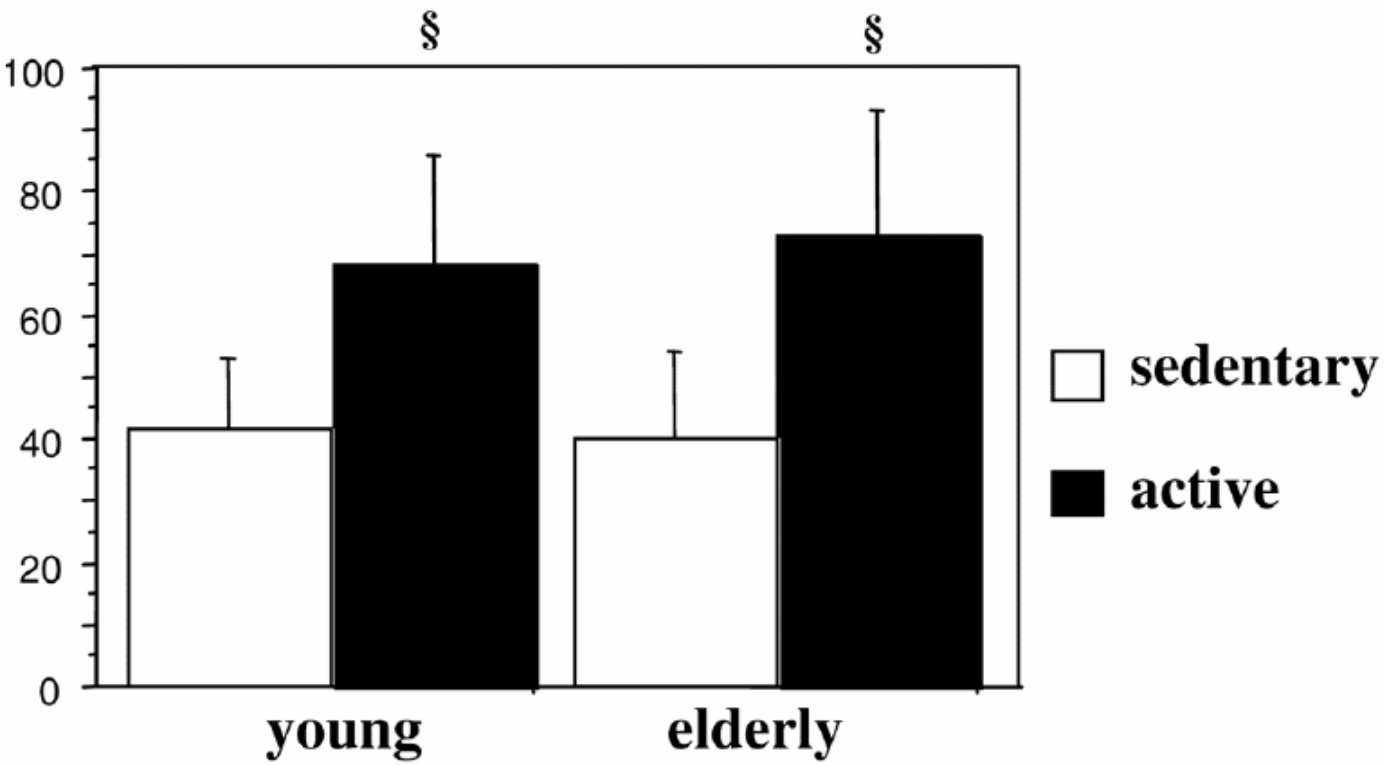
Subjects characteristics according to age and physical activity

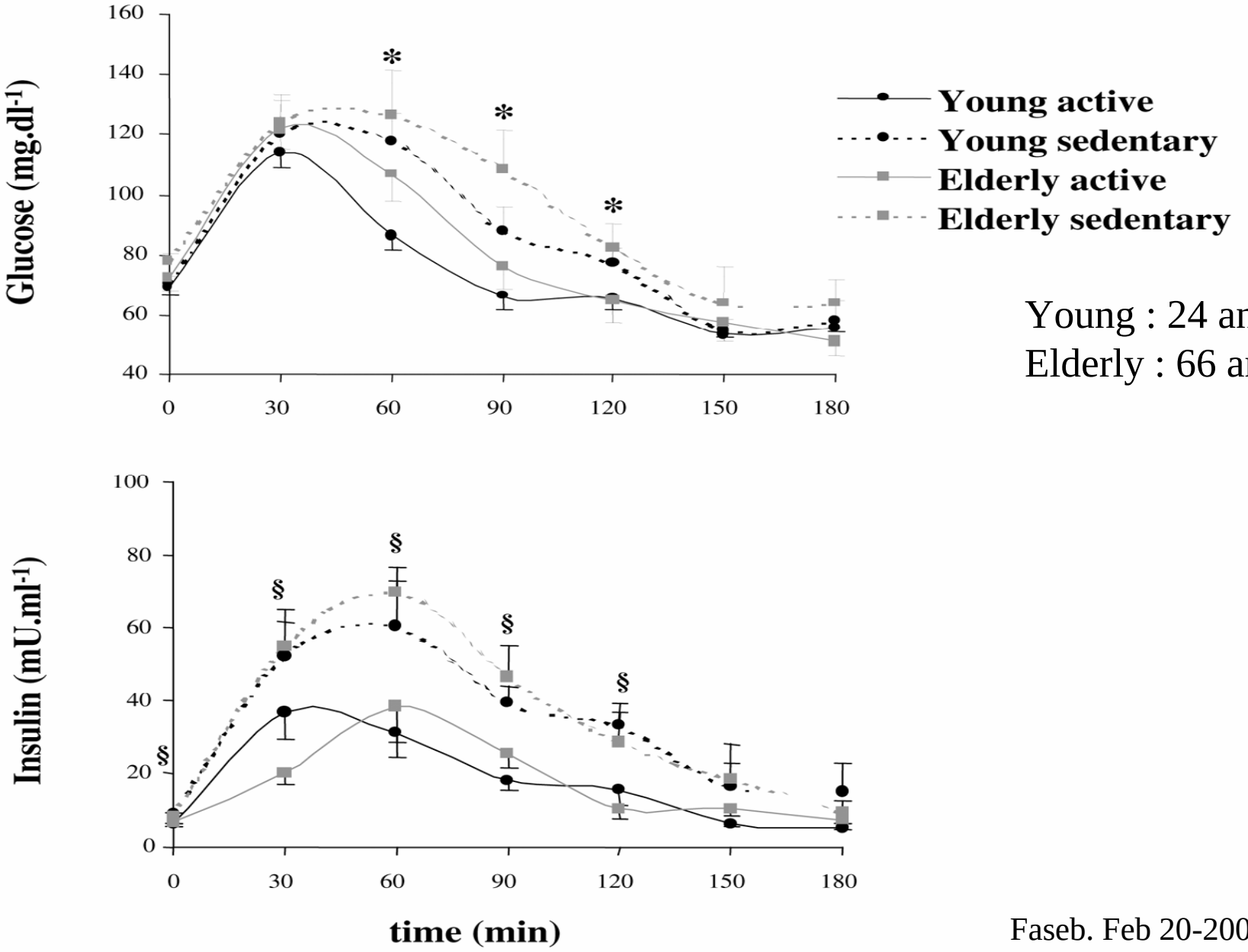
	Young		Elderly		ANOVA		
	Sedentary (n=10)	Active (n=6)	Sedentary (n=10)	Active (n=6)	Age	Activity	Age × Activity
Age (yr)	23.8±2.4	24.8±3.0	67.1±3.9	65.7±1.4	<0.0001	NS	NS
Height (cm)	177.6±6.4	182.3±2.1	172.0±6.9	168.0±2.4	<0.0001	NS	<0.05
BW (kg)	70.3±9.8	72.3±7.4	79.1±7.6	66.6±6.4	NS	NS	<0.05
BMI ($kg.m^{-2}$)	22.2±2.3	21.8±2.2	26.7±1.6	23.6±2.3	<0.001	<0.05	NS
%FFM	84.4±2.5	88.7±1.0	76.4±2.5	82.4±5.8	<0.0001	<0.0001	NS
%MuM	44.5±3.5	48.8±2.1	41.1±4.6	45.5±0.4	<0.05	<0.01	NS
FM (kg)	11.1±2.8	8.2±1.2	18.7±2.3	12.0±5.3	<0.0001	<0.001	NS
FM (%)	15.7± 2.5	11.2±0.9	23.6±2.3	15.9±2.1	<0.0001	<0.0001	NS
Truncal fat (kg)	4.2±1.1	2.7±0.5	10.1±1.3	4.4±1.0	<0.0001	<0.0001	<0.0001
Truncal fat (% FM)	37.9±3.0	33.5±4.0	54.3±3.1	40.4±13.2	<0.0001	<0.001	<0.05
VO_{2max} ($ml.min^{-1}.kg\ FFM^{-1}$)	45.8±3.8	62.4±4.1	35.7±3.3	50.7±4.9	<0.0001	<0.0001	NS

Results are means ± SD; BW, body weight; BMI, body mass index; FFM, fat-free mass; MuM, muscle mass; FM, fat mass; VO_{2max}, maximal oxygen uptake.

Importance de l'activité physique (1b)

Total oxidation rate of palmitate
(nmol palmitate.min^{-1}.g wet tissue^{-1})





Young : 24 ans
Elderly : 66 ans

Faseb. Feb 20-2004

Quelques concepts

- Le dysfonctionnement mitochondrial et en particulier une production inadaptée de radicaux libres est au centre des mécanismes du vieillissement
-Il y a un lien très fort entre vieillissement et voies de signalisation de l'insuline ; l'insulino-résistance ne modifie pas que la glycémie !
-Les mêmes concepts sont utilisés dans les maladies neuro-dégénératives…

-L'étude du fonctionnement mitochondrial reste difficile in vivo
-L'exercice permet de lutter contre le vieillissement musculaire
-Il va être difficile de faire la part des choses entre le vieillissement des patients et le rôle de la toxicité des ARV