



CHAIRE DE GÉNÉTIQUE ET PHYSIOLOGIE CELLULAIRE

Année universitaire 2013-2014

Pr Christine PETIT



# Le système auditif face à ses agresseurs

06 février 2014

**COURS** : Les agresseurs du système auditif : son, xénobiotiques, vieillissement... Aspects génétiques de la susceptibilité individuelle à ces agresseurs

**SÉMINAIRE** : Prédispositions génétiques aux maladies communes : de la causalité aux facteurs de prédisposition en interaction avec l'environnement  
Jean-Louis Mandel, *IGBMC, université Louis Pasteur, Strasbourg*

06 mars 2014

**COURS** : Le métabolisme de l'oxygène et la toxicité des espèces oxygénées activées, plaque tournante de l'action de nombreux agresseurs

**SÉMINAIRE** : Détection hors fréquence et réponses cochléaires fantômes  
Paul Avan, *laboratoire de biophysique sensorielle, université d'Auvergne, Clermont-Ferrand*

13 mars 2014

**COURS** : Détecteurs et effecteurs du stress oxydant : rôles dans le métabolisme et la signalisation. Le dialogue des organelles : la part des peroxysomes.

**SÉMINAIRE** : Les antibiotiques sont-ils autodestructeurs ?  
Patrice Courvalin, *unité des agents antibactériens, institut Pasteur, Paris*

20 mars 2014

**COURS** : Les moyens de défense : prévention et traitement

**SÉMINAIRE** : Acouphènes subjectifs : physiopathologie et éléments d'une prise en charge rationnelle  
Alain Londero, *Service ORL et CCF, hôpital Georges Pompidou, Paris*

3<sup>ème</sup> cours : 13 mars 2014

**Détecteurs et effecteurs du stress oxydant: rôles dans le métabolisme et la signalisation.**

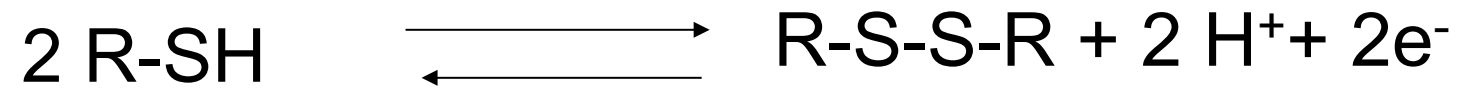
**Le dialogue des organelles: la part des peroxisomes.**

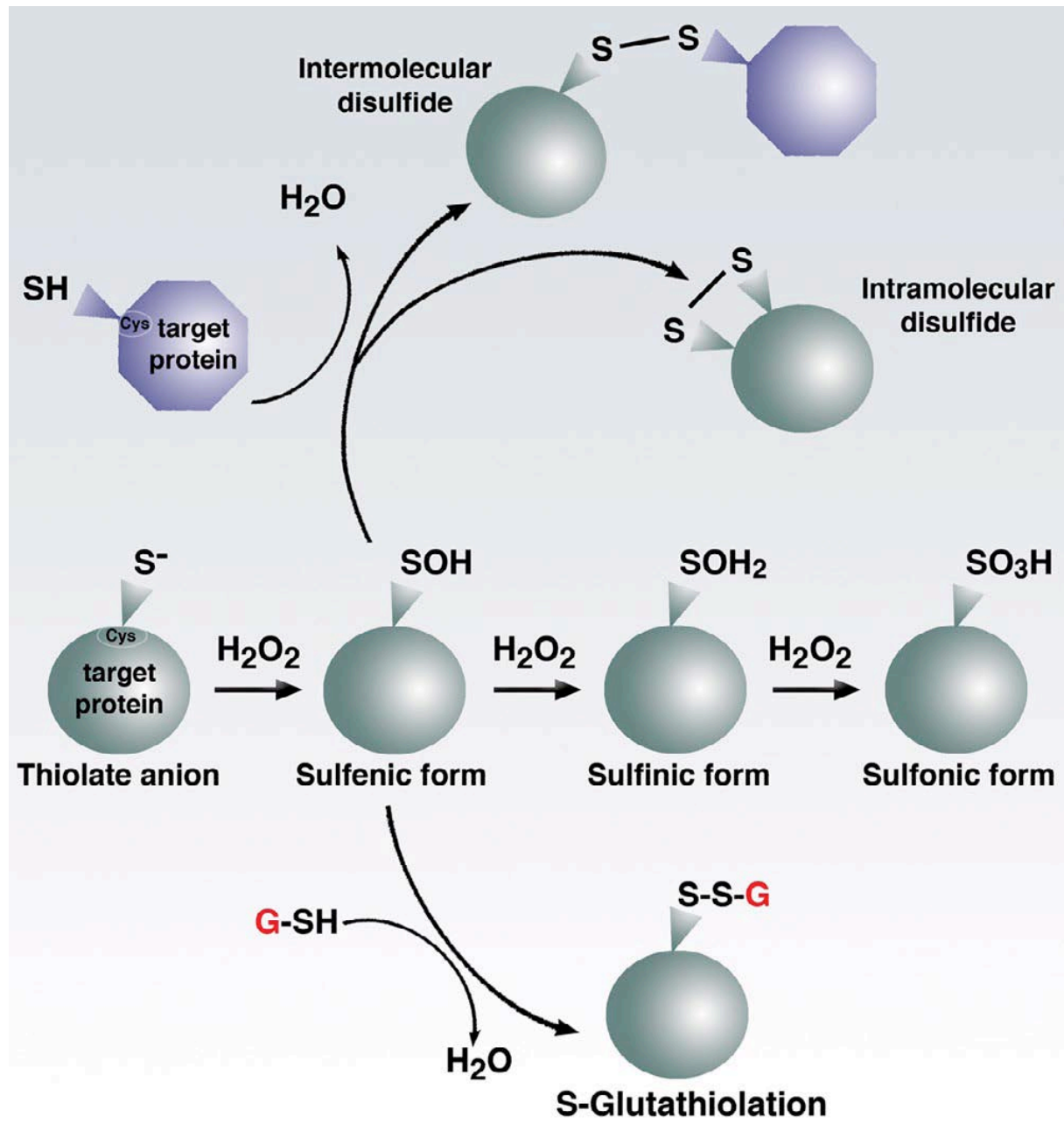
Séminaire:

**Patrice Courvalin** – Unité des Agents Antibactériens, Institut Pasteur, Paris

**“Les antibiotiques sont-ils autodestructeurs”**

# SIGNALISATION REDOX





# Produire de l' $\text{H}_2\text{O}_2$ (peroxyde d'hydrogène, eau oxygénée)

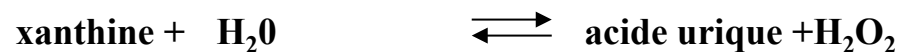
- **dismutation de l'anion superoxyde**: superoxyde dismutases: **SODs**  
cytoplasmique, mitochondriale, peroxysome, extra-cellulaire.



- **oxydation**

- **des acides gras à très longues chaînes ou branchés** dans le **peroxysome**  
(avec plusieurs autres oxydases dans cet organelle)

- **de la xanthine et l'hypoxanthine**:  
xanthine et hypoxanthine oxydase (**cytoplasme, peroxysomes**(*xanthine oxydase*))

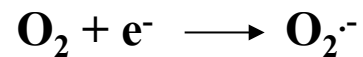


- **des monoamines**: monoamine oxydase (catabolisme de la sérotonine) (**mitochondrie**)

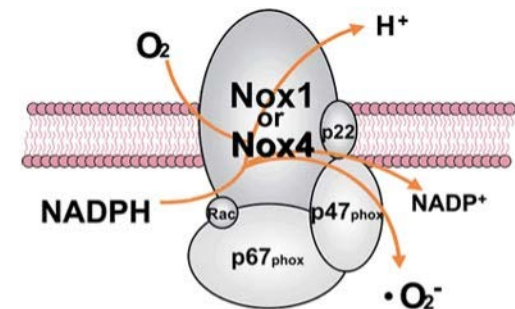
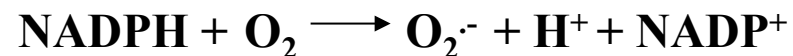
# Produire de l' $O_2^{\cdot-}$ (anion superoxyde)

## Réduction de l'oxygène moléculaire

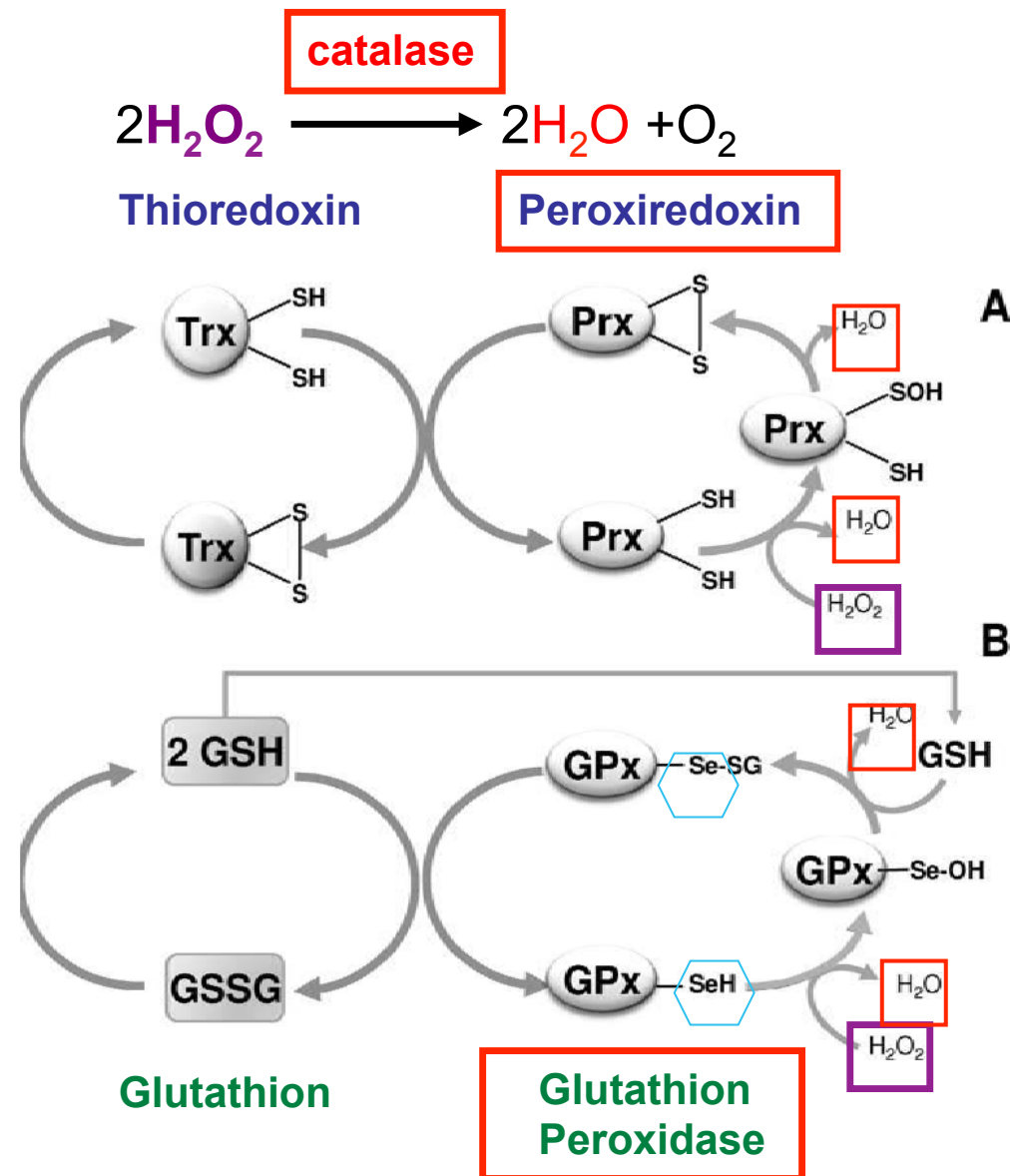
- *capture d'électrons par l'oxygène moléculaire (non enzymatique)*: dans la **mitochondrie** au niveau des **complexes I et III** (ubiquinone ou coenzyme A)



- *au cours de l'oxydation par les NADPH oxydases (NOX et DUOX) membrane plasmique et RE* ..NOX complexe

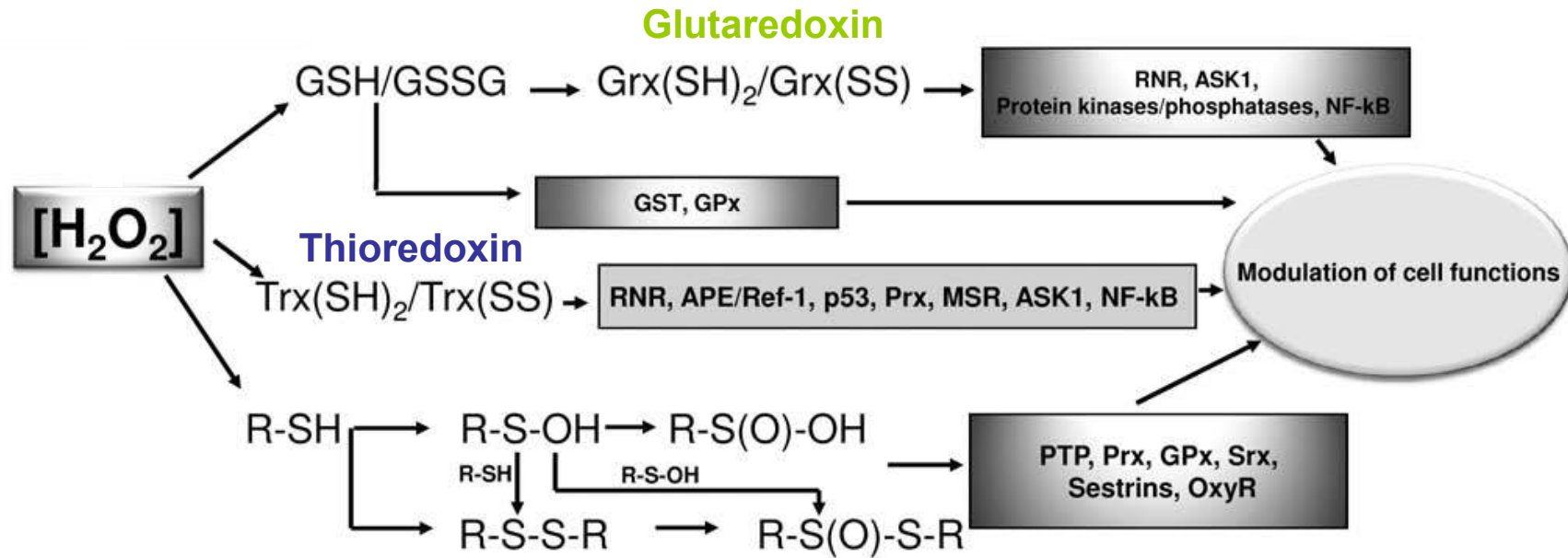


# REDUIRE l' H<sub>2</sub>O<sub>2</sub> en H<sub>2</sub>O (anti-oxydants)



# SIGNALISATION *via* H<sub>2</sub>O<sub>2</sub>

Signalisation thiol-disulfure (SH:SS) systèmes glutathion et thiorédoxine





# Le peroxysome et la signalisation REDOX

1. La découverte du peroxysome
2. Quelle est l'origine du peroxysome?
3. Ses caractéristiques, ses activités.
  - diversité et plasticité.
  - la prolifération du peroxysome et sa régulation à la lumière du débat qui persiste sur la biogenèse de l'organelle.
4. Le rôle du peroxysome dans la signalisation REDOX
5. Quel dialogue le peroxysome entretient-il avec les autres compartiments cellulaires dans la signalisation REDOX?
6. Maladies et atteintes du peroxysome (surdit ).

# Symposium on Renal Physiology

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## Electron Microscopy of the Kidney\*

JOHANNES RHODIN, M.D.

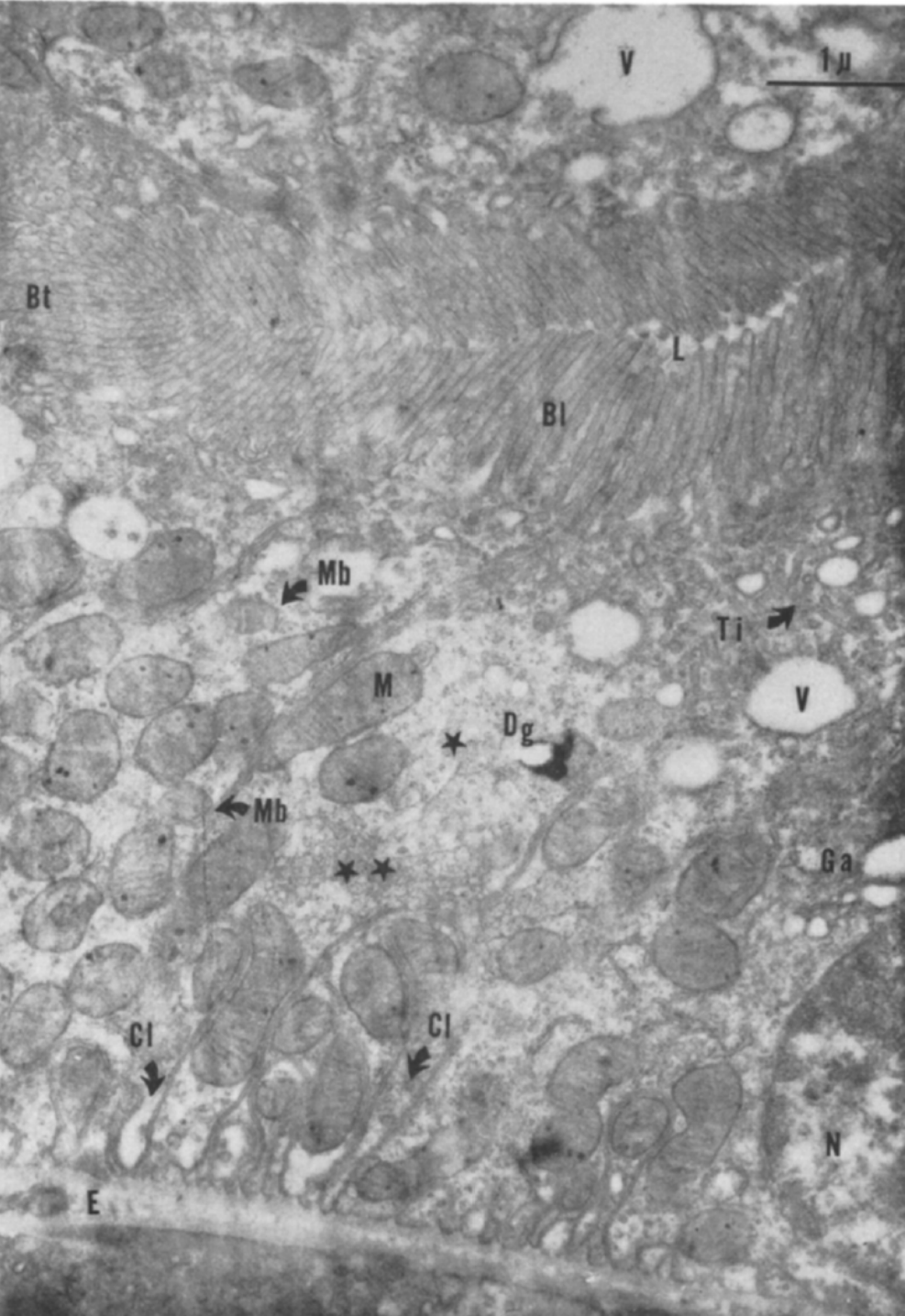
*New York, New York*

Department of Anatomy

Karolinska Institutet, Stockholm, Sweden

New York University-Bellevue Medical Center, New York

Rhodhin J - Am J Medicine 1958



# Peroxisomes (Microbodies and Related Particles)

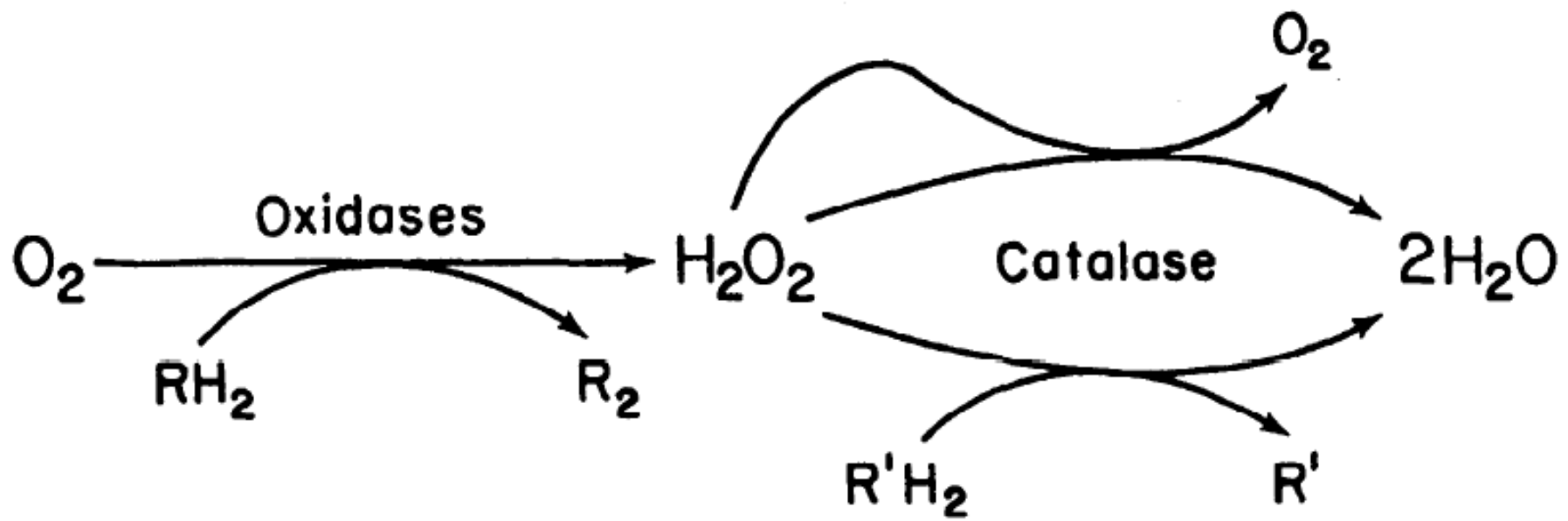
CHRISTIAN DE DUVE AND PIERRE BAUDHUIN

*Rockefeller University, New York City, and Department of Physiological  
Chemistry, University of Louvain, Belgium*

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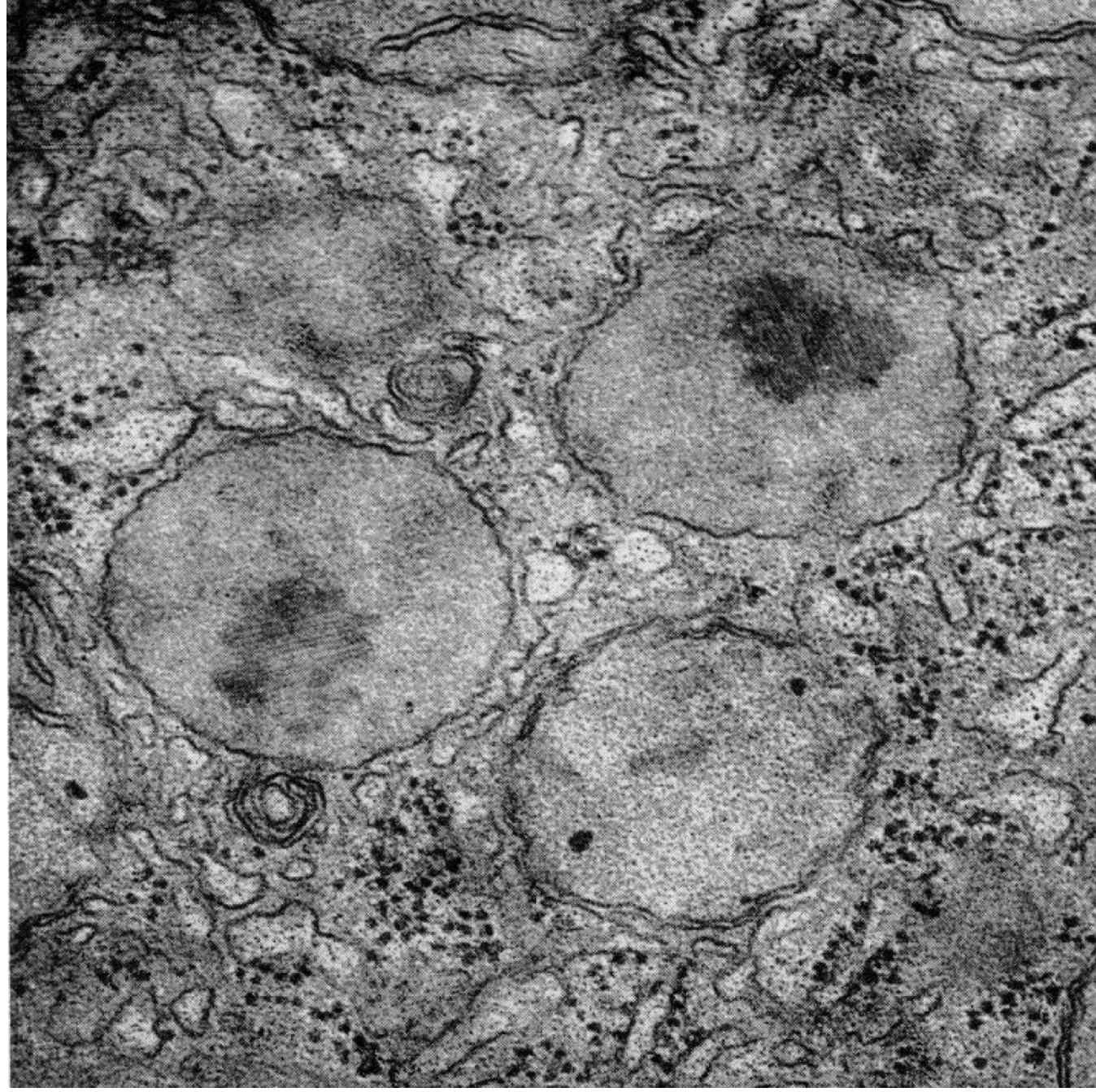
## HISTORICAL

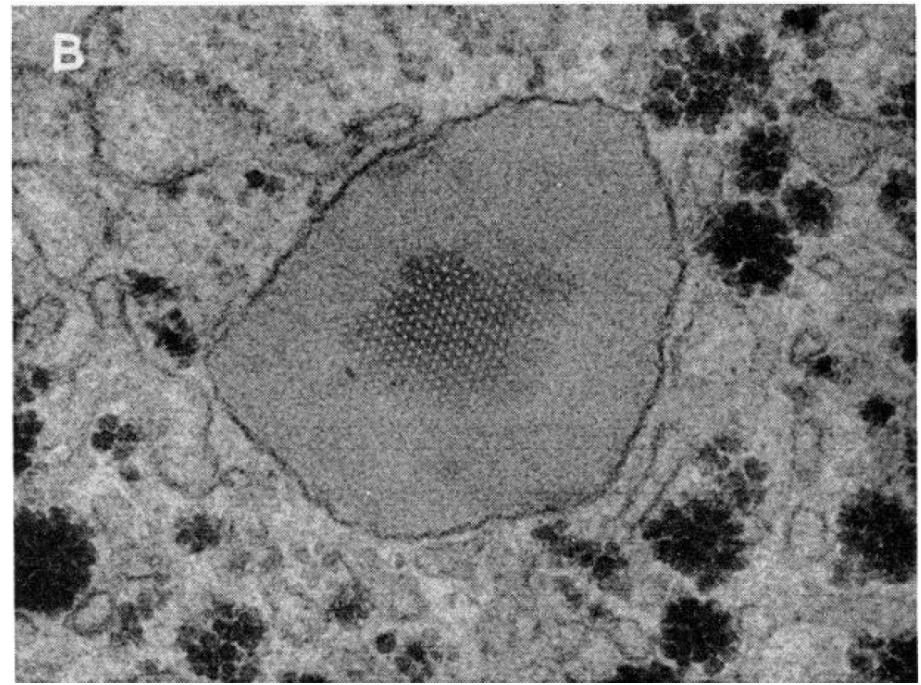
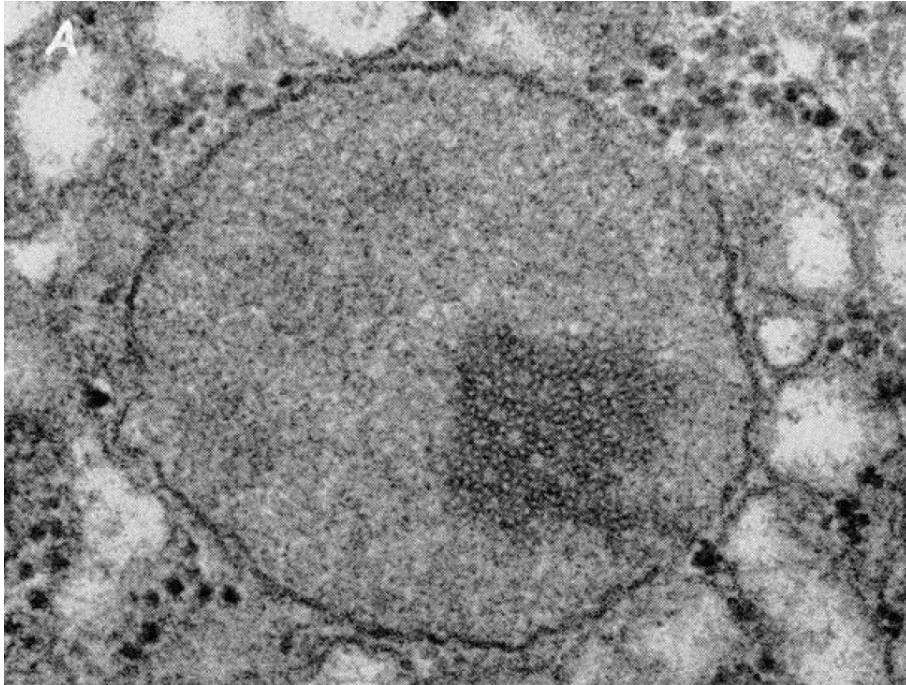
The term "microbody" was introduced into the electron microscope literature by Rhodin (109) in 1954 to designate a special type of cytoplasmic body present in the convoluted tubule cells of the mouse kidney, characterized by a single membrane and a finely granular matrix. Two years later, granules resembling the



Enzyme	Rat Liver		Rat Kidney		<i>T. pyriformis</i>	
	%	RSA	%	RSA	%	RSA
Protein	2.1	1	2.3	1	12.6	1
Catalase	56.7	27	35.6	15	46.0	3.7
Urate oxidase	56.2	27				
D-amino acid oxidase	40.6	19	31.1	14	46.3	3.7
L- $\alpha$ -OH-acid oxidase	32.1	15	22.4	9.7	56.6	4.5
L-amino acid oxidase			23.1	10		
Cytochrome oxidase or succinate dehydrogenase	0.9	0.43	1.8	0.78	9.6	0.76
Acid phosphatase	1.8	0.86	21.8	9.5	11.4	0.91

De Duve C & Baudhuin P – *Physiol Rev* 1966







## **EVOLUTION OF THE PEROXISOME**

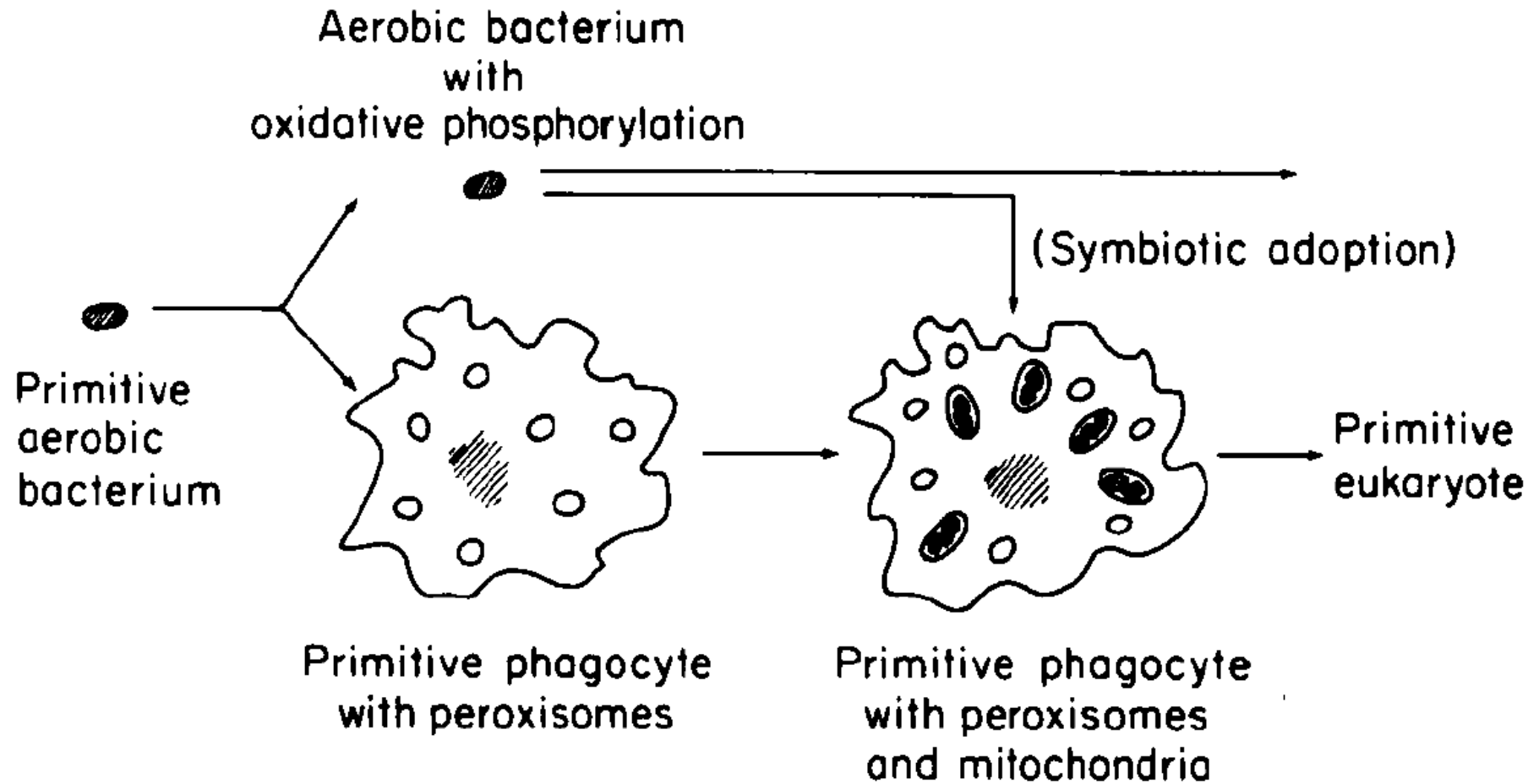
**Christian de Duve, M.D.**

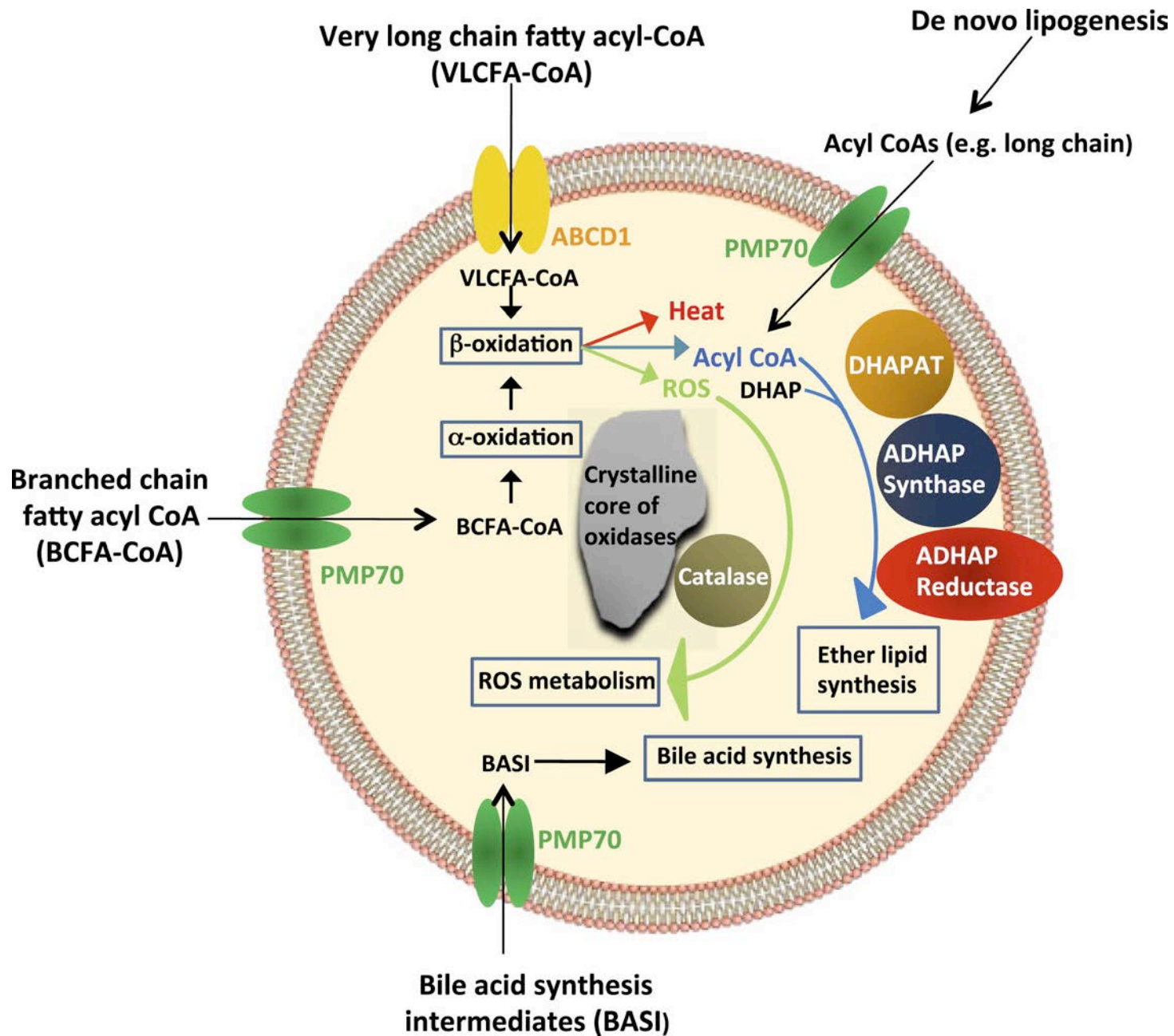
*The Rockefeller University, New York, and Université de Louvain, Belgium*

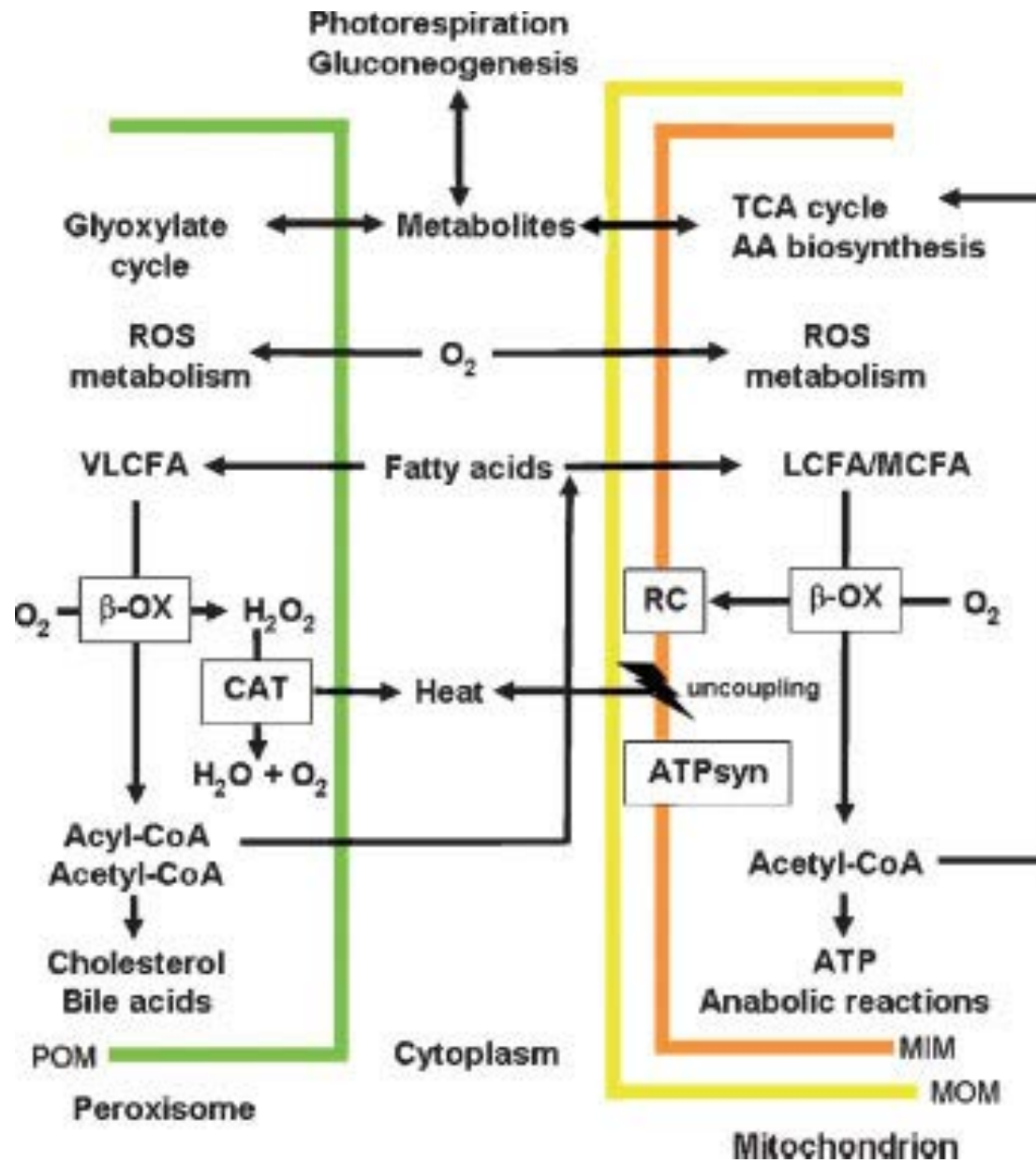
The work reported in this monograph has clearly established the presence of peroxisome-like particles in lower and higher representatives of both major biological kingdoms. Such findings invite speculation on the phylogenetic history of these particles, especially since some of the characters of peroxisomes label them as “primitive”, in both the literal and the figurative sense of the word. Some

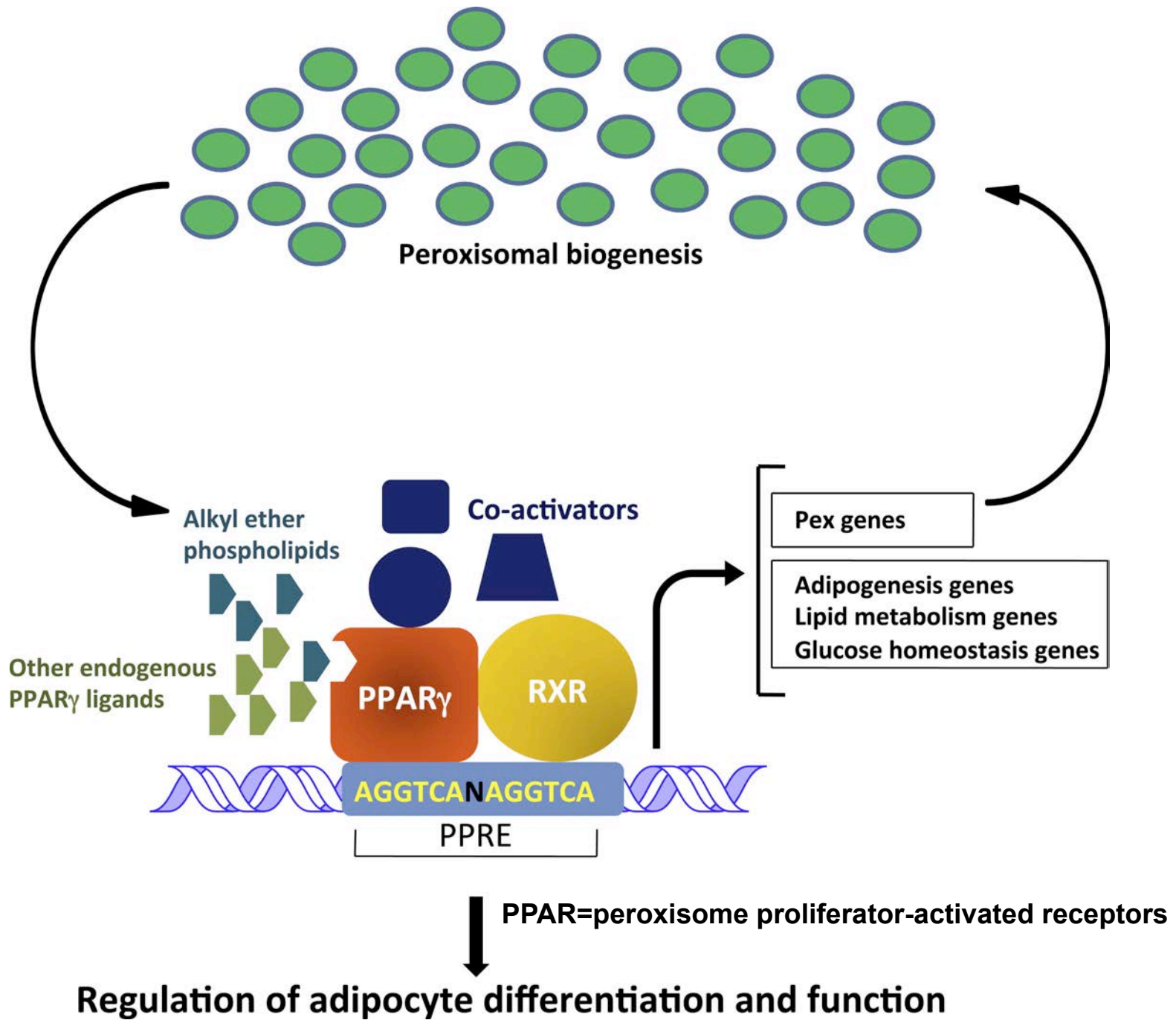
**Annals New York Academy of Sciences**

**168, 369-81, 1969**

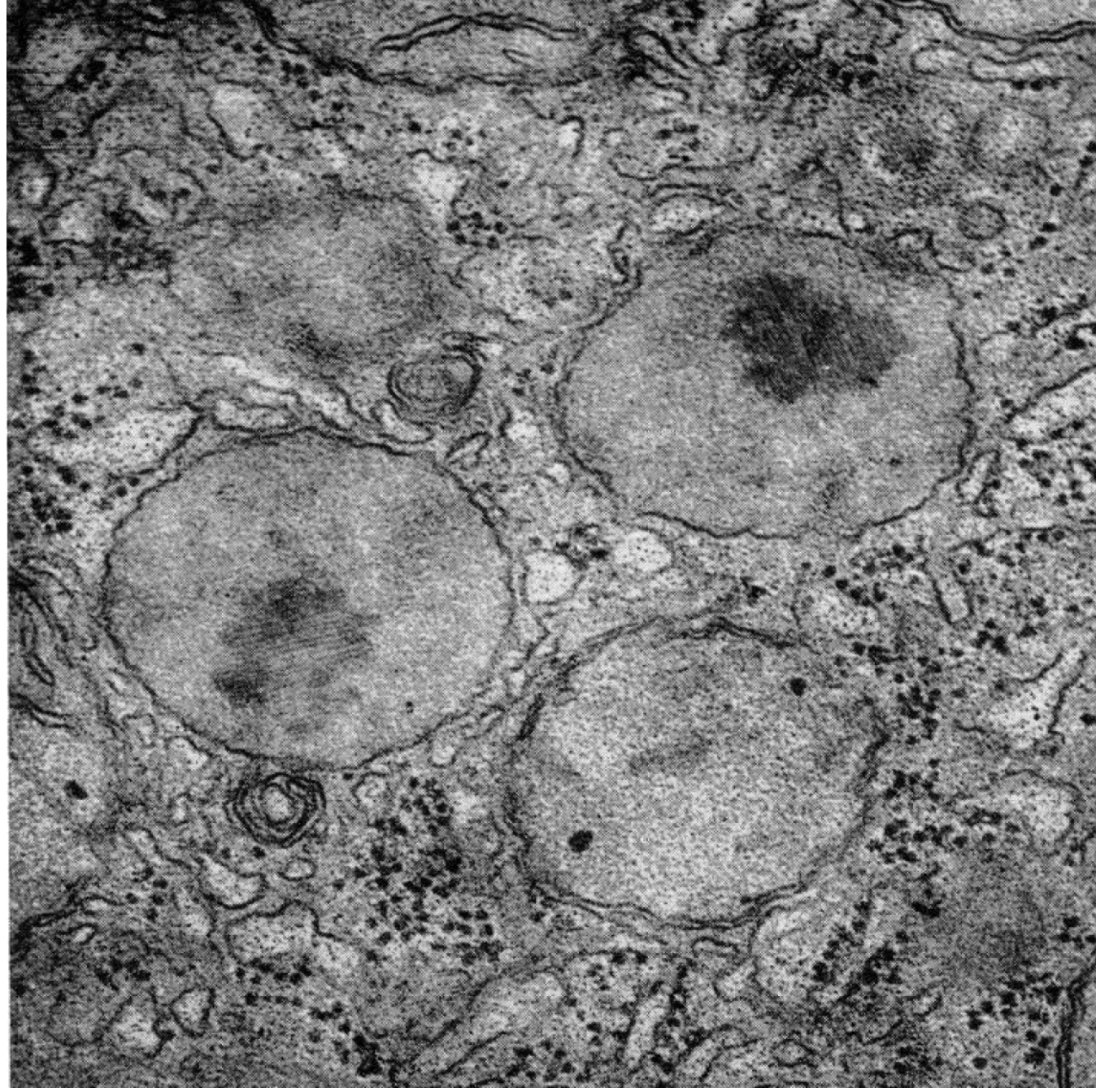








De Duve C & Baudhuin P – *Physiol Rev* 1966



## Enzymes du peroxysome qui génèrent des ROS

Enzyme	Substrate	ROS
(1) Acyl-CoA oxidases		
(a) Palmitoyl-CoA oxidase	Long chain fatty acids Methyl branched chain	H <sub>2</sub> O <sub>2</sub>
(b) Pristanoyl-CoA oxidase	fatty acids	H <sub>2</sub> O <sub>2</sub>
(c) Trihydroxycoprostanoyl-CoA oxidase	Bile acid intermediates	H <sub>2</sub> O <sub>2</sub>
(2) Urate oxidase	Uric acid	H <sub>2</sub> O <sub>2</sub>
(3) Xanthine oxidase	Xanthine	H <sub>2</sub> O <sub>2</sub> , O <sub>2</sub> <sup>•</sup>
(4) d-amino acid oxidase	d-Proline	H <sub>2</sub> O <sub>2</sub>
(5) Pipecolic acid oxidase	l-pipecolic acid d-aspartate,	H <sub>2</sub> O <sub>2</sub>
(6) d-aspartate oxidase	N-methyl-d-aspartate N-methyl-d-aspartate	H <sub>2</sub> O <sub>2</sub>
(7) Sarcosine oxidase	Sarcosine, pipecolate	H <sub>2</sub> O <sub>2</sub>
(8) l-alpha-hydroxy acid oxidase	Glycolate, lactate N-Acetyl spermine/ spermidine	H <sub>2</sub> O <sub>2</sub>
(9) Poly amine oxidase		H <sub>2</sub> O <sub>2</sub>
(10) Nitric oxide synthase	l-Arginine	•NO
(11) Plant sulfite oxidase	Sulfite	H <sub>2</sub> O <sub>2</sub>

From Schrader M. and Fahimi HD. *BBA* 2006

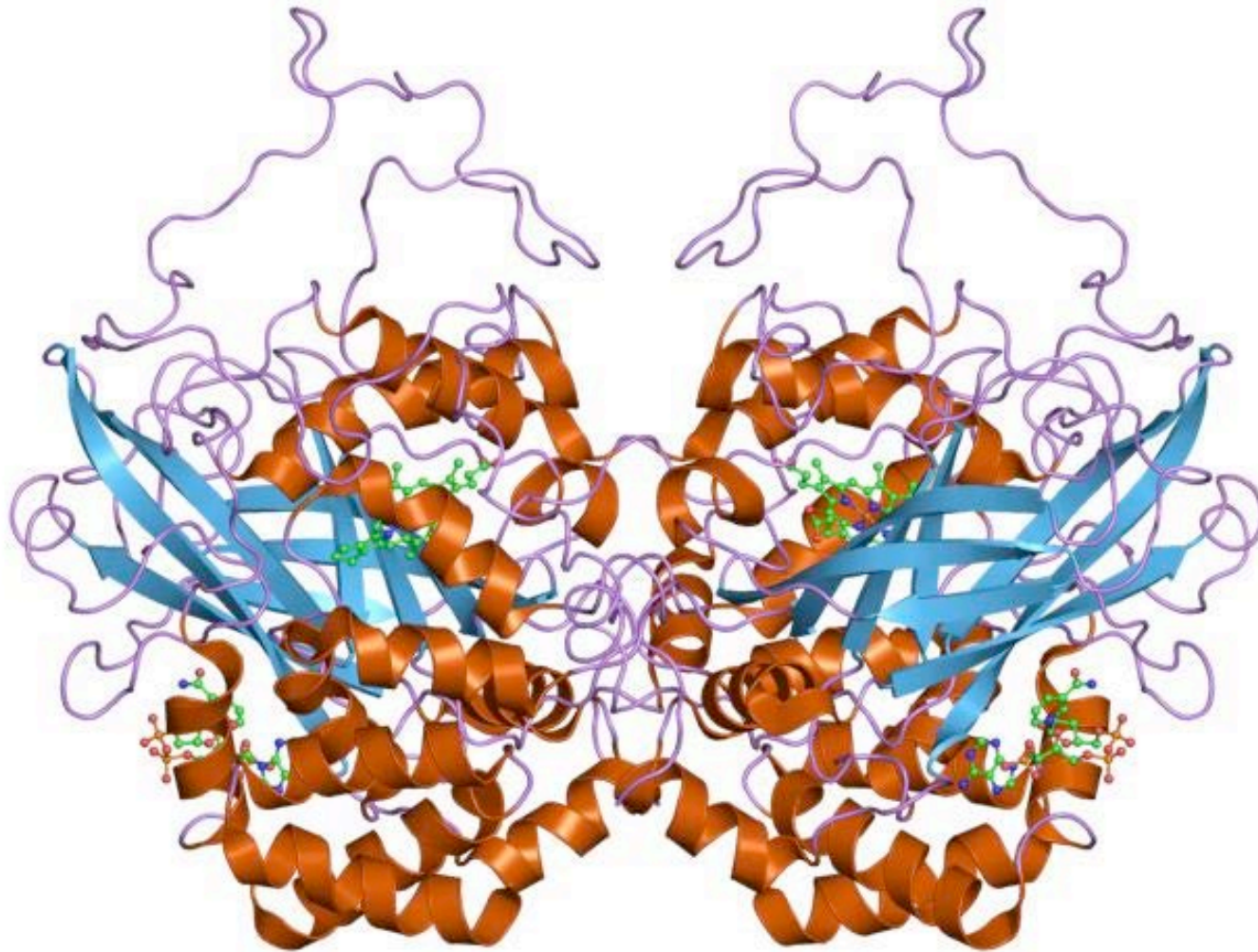
# D-Amino acid oxidase controls motoneuron degeneration through D-serine

Jumpei Sasabe<sup>a,1</sup>, Yurika Miyoshi<sup>b</sup>, Masataka Suzuki<sup>a</sup>, Masashi Mita<sup>c</sup>, Ryuichi Konno<sup>d</sup>, Masaaki Matsuoka<sup>e</sup>, Kenji Hamase<sup>b</sup>, and Sadakazu Aiso<sup>a</sup>

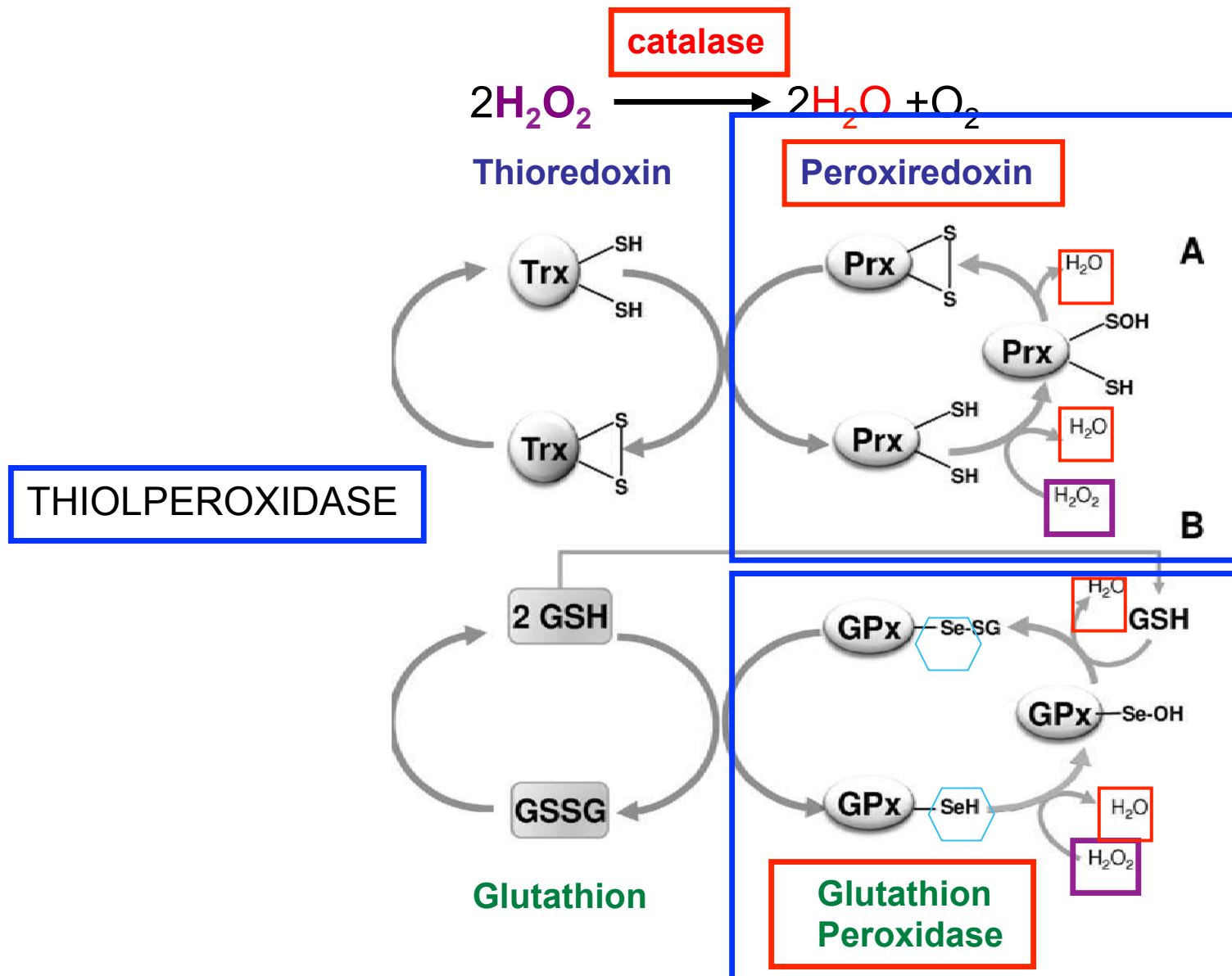
Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disorder involving an extensive loss of motoneurons. Aberrant excitability of motoneurons has been implicated in the pathogenesis of selective motoneuronal death in ALS. D-Serine, an endogenous coagonist of *N*-methyl-D-aspartate receptors, exacerbates motoneuronal death and is increased both in patients with sporadic/familial ALS and in a G93A-SOD1 mouse model of ALS (mSOD1 mouse). More recently, a unique mutation in the D-amino acid oxidase (DAO) gene, encoding a D-serine degrading enzyme, was reported to be associated with classical familial ALS. However, whether DAO affects the motoneuronal phenotype and D-serine increase in ALS remains uncertain. Here, we show that genetic inactivation of DAO in mice reduces the number and size of lower motoneurons with axonal degeneration, and that suppressed DAO activity in reactive astrocytes in the reticulospinal tract, one of the major inputs to the lower motoneurons, predominantly contributes to the D-serine increase in the mSOD1 mouse. The DAO inactivity resulted from expressional down-regulation, which was reversed by inhibitors of a glutamate receptor and MEK, but not by those of inflammatory stimuli. Our findings provide evidence that DAO has a pivotal role in motoneuron degeneration through D-serine regulation and that inactivity of DAO is a common feature between the mSOD1 ALS mouse model and the mutant DAO-associated familial ALS. The therapeutic benefit of reducing D-serine or controlling DAO activity in ALS should be tested in future studies.

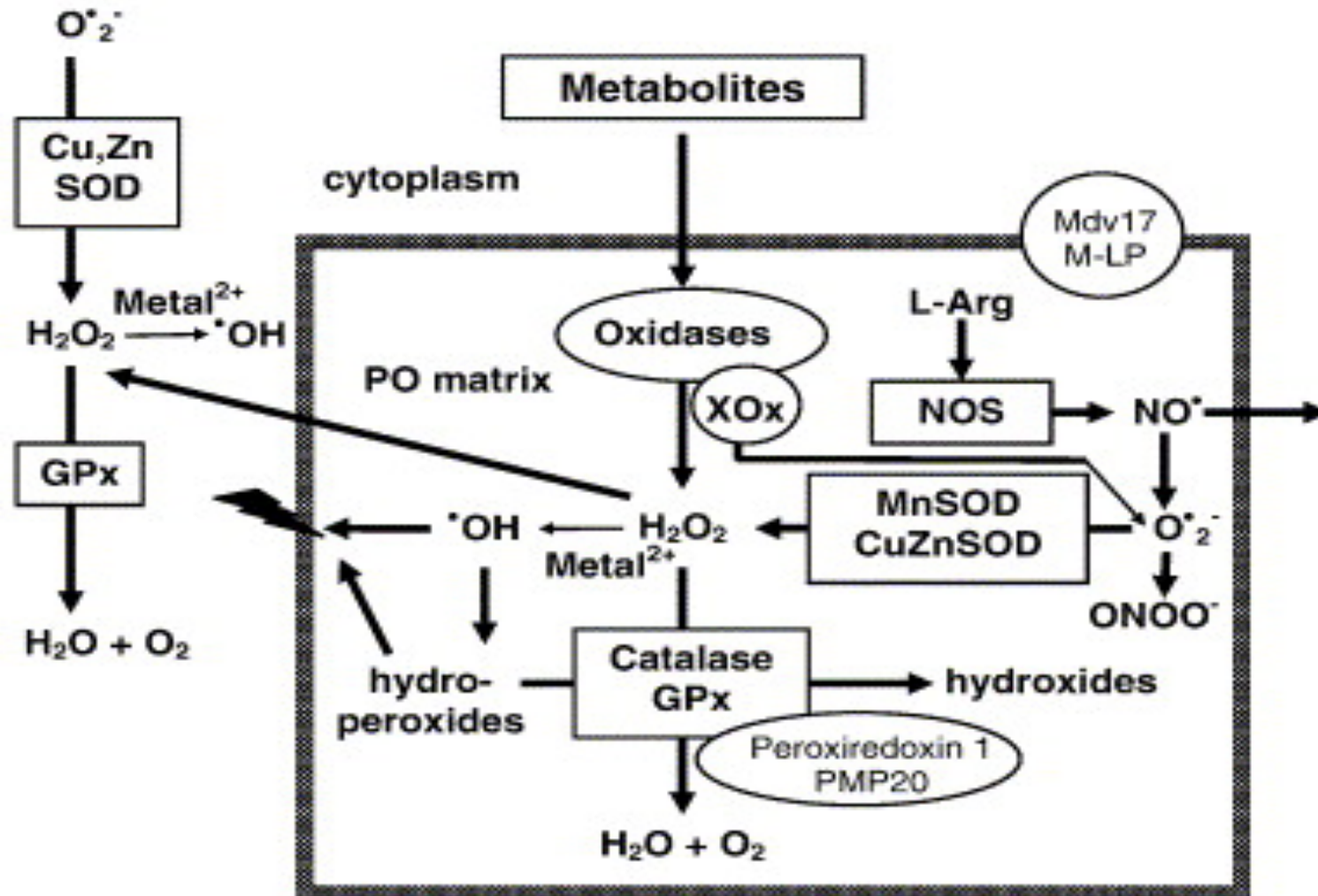


catalase



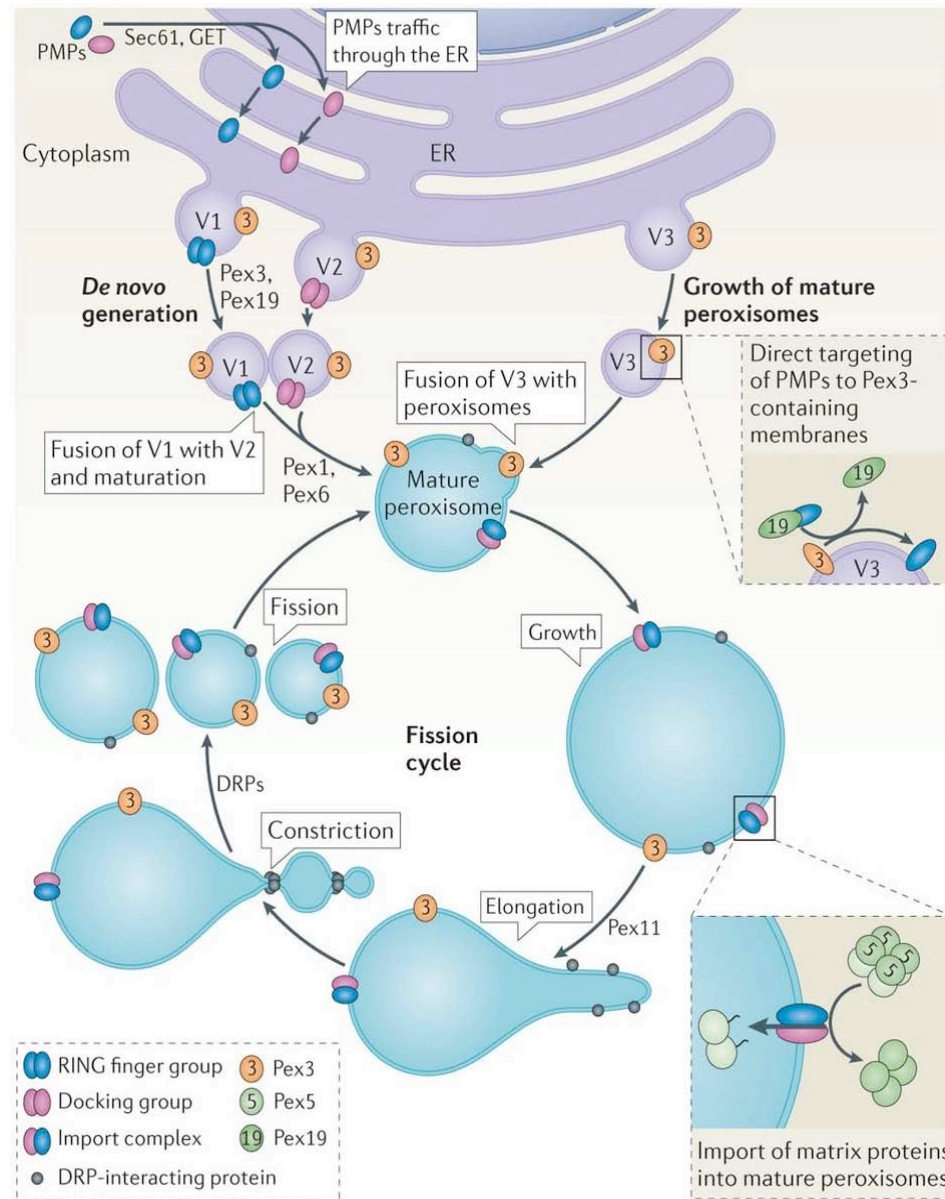
# REDUIRE H<sub>2</sub>O<sub>2</sub> en H<sub>2</sub>O (anti-oxydants)





Schematic overview of peroxisomal enzymes which produce or degrade ROS.

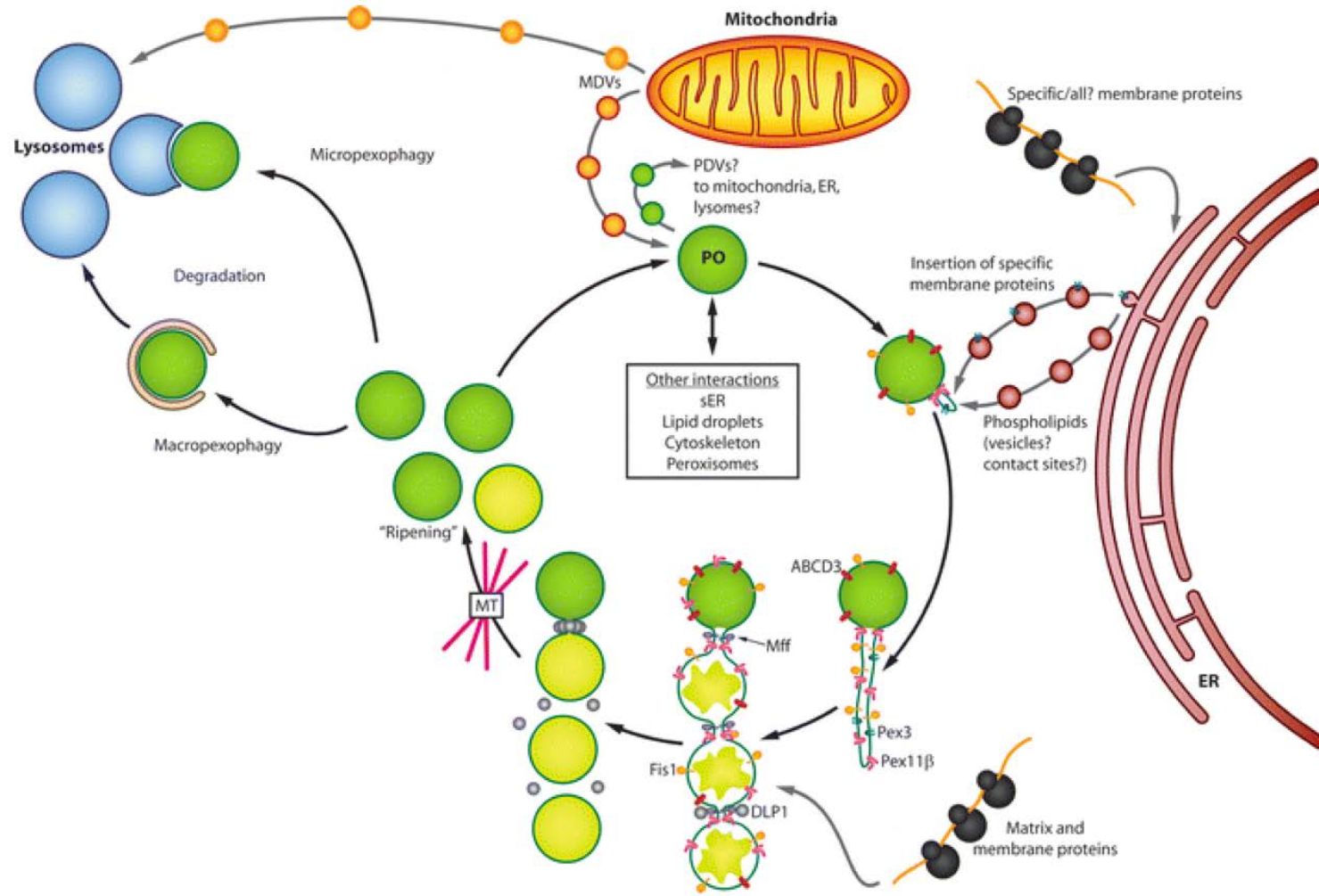
From Schrader M. and Fahimi HD. *BBA* 2006



Nature Reviews | Molecular Cell Biology

Peroxisomes can form through two pathways.

From Smith JJ. and Aitchison JD. *MOLECULAR CELL BIOLOGY* (2013)

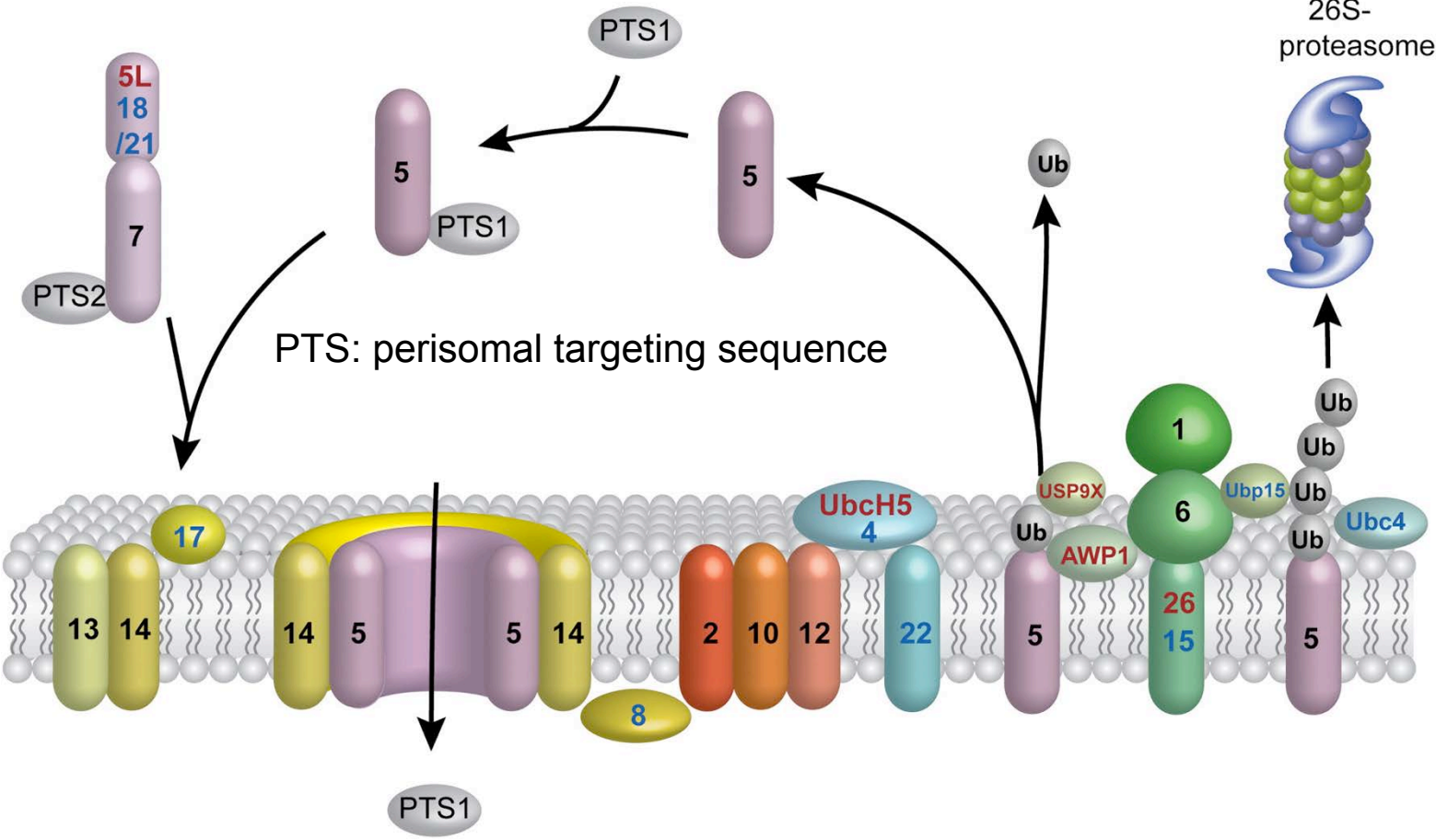


## REDOX SENSIBLE

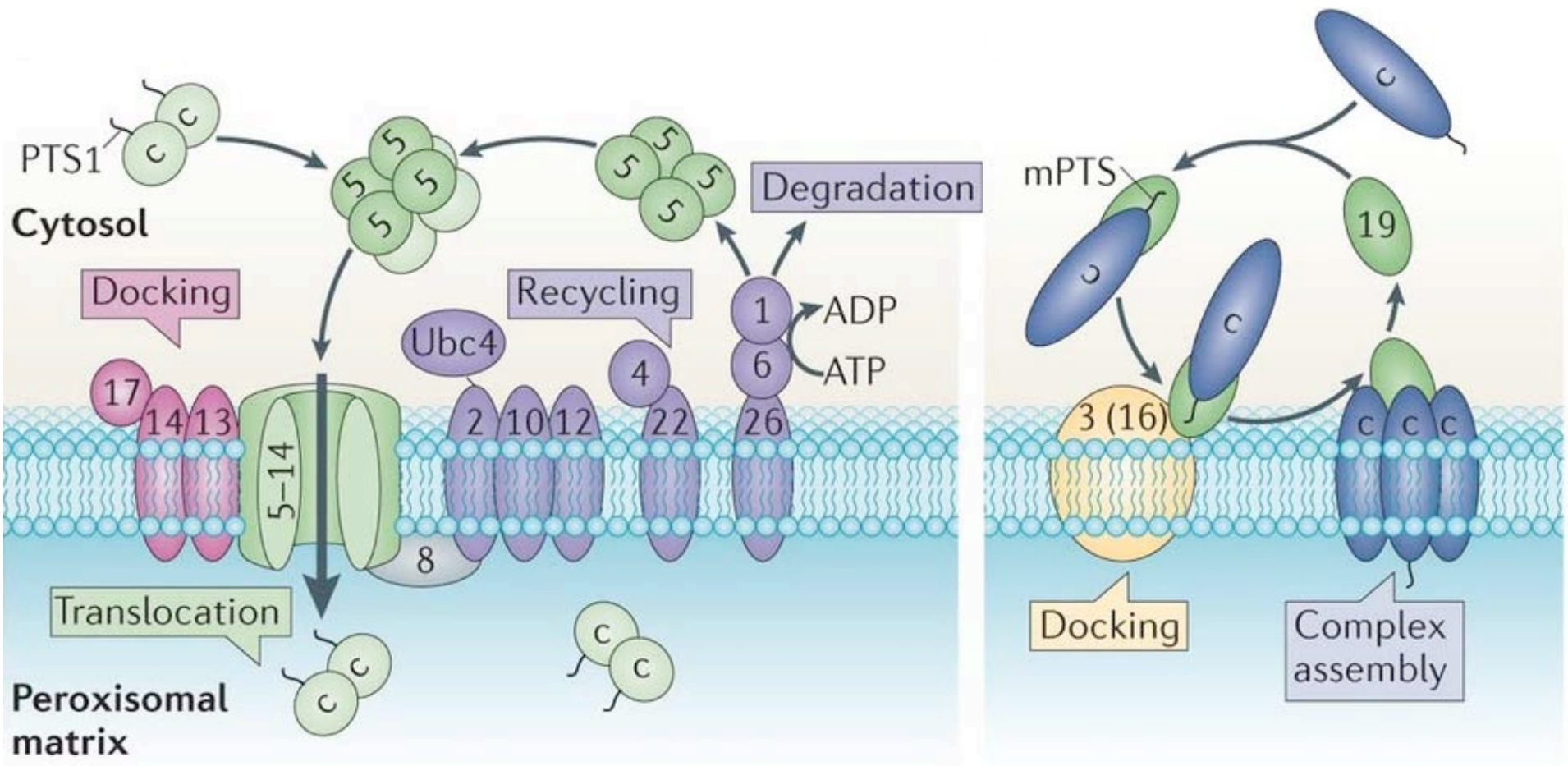
Model of peroxisome dynamics and interactions in mammalian cells.

From Islinger M. and Schrader M. . Histochem Cell Biol, 2012

# IMPORTATION DES PROTEINES MATRICIELLES

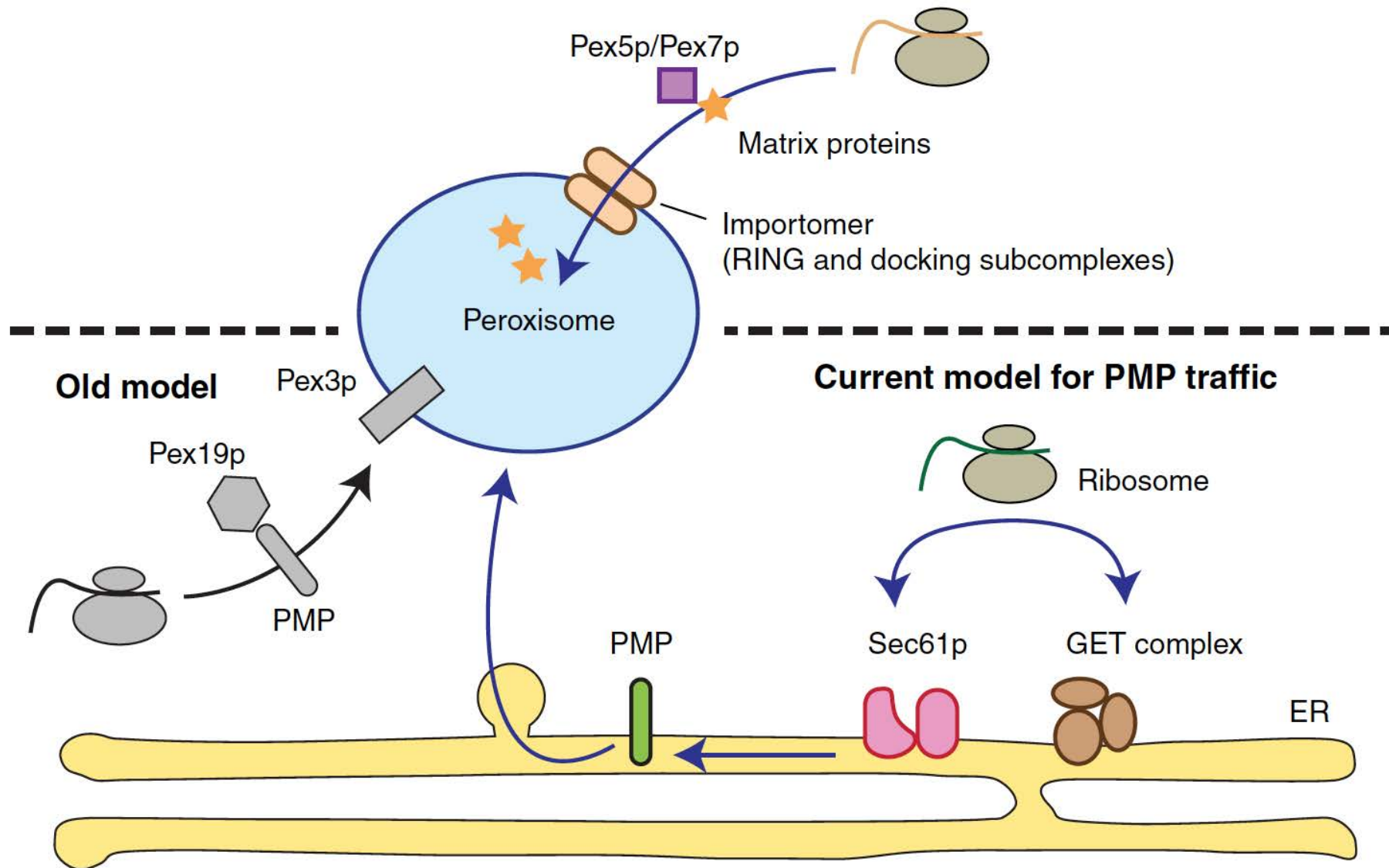


Composite model of peroxisomal matrix protein import. From Nagotu S. and Platta HW. *BBA* 2012



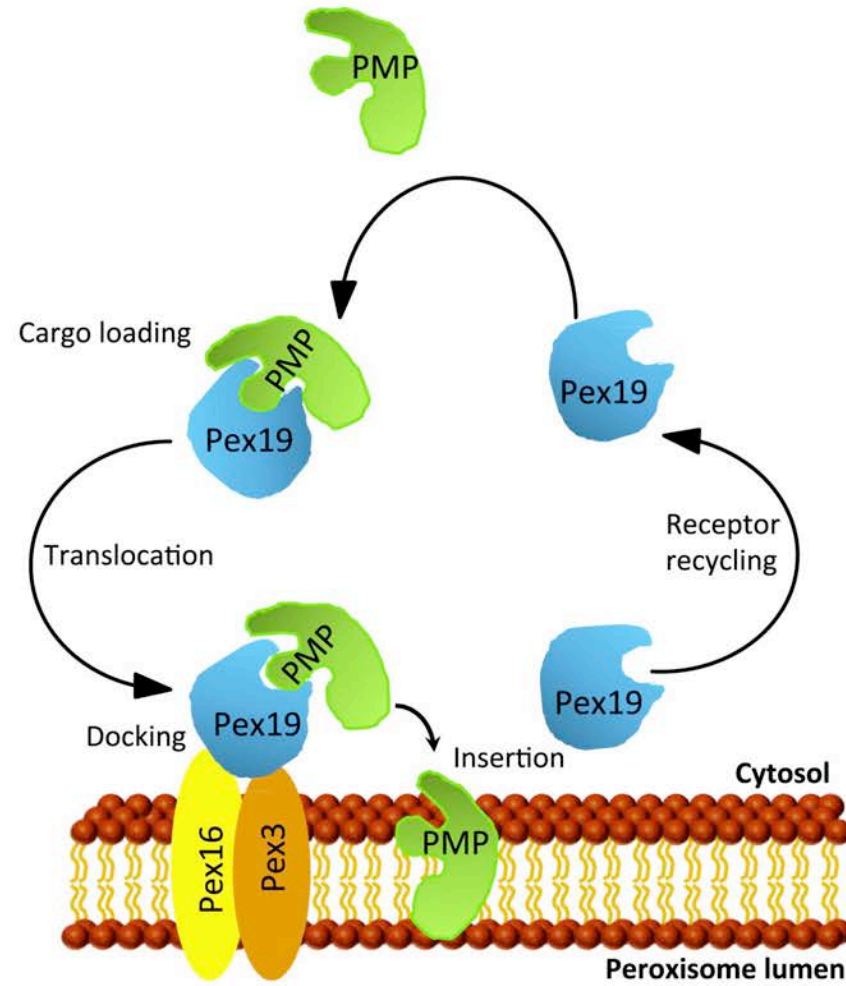
Direct targeting of proteins to peroxisomes

# Peroxisomal matrix protein traffic

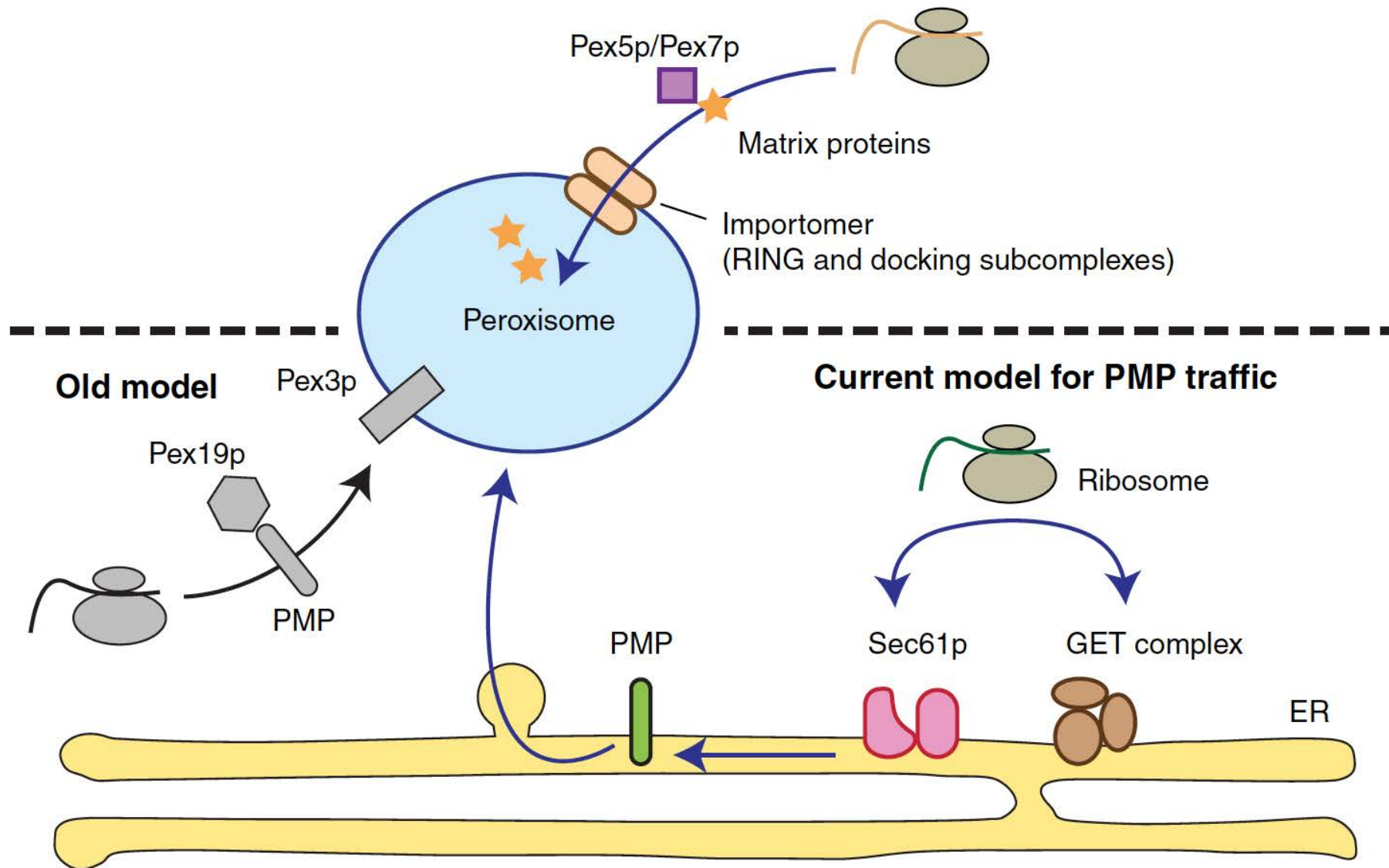




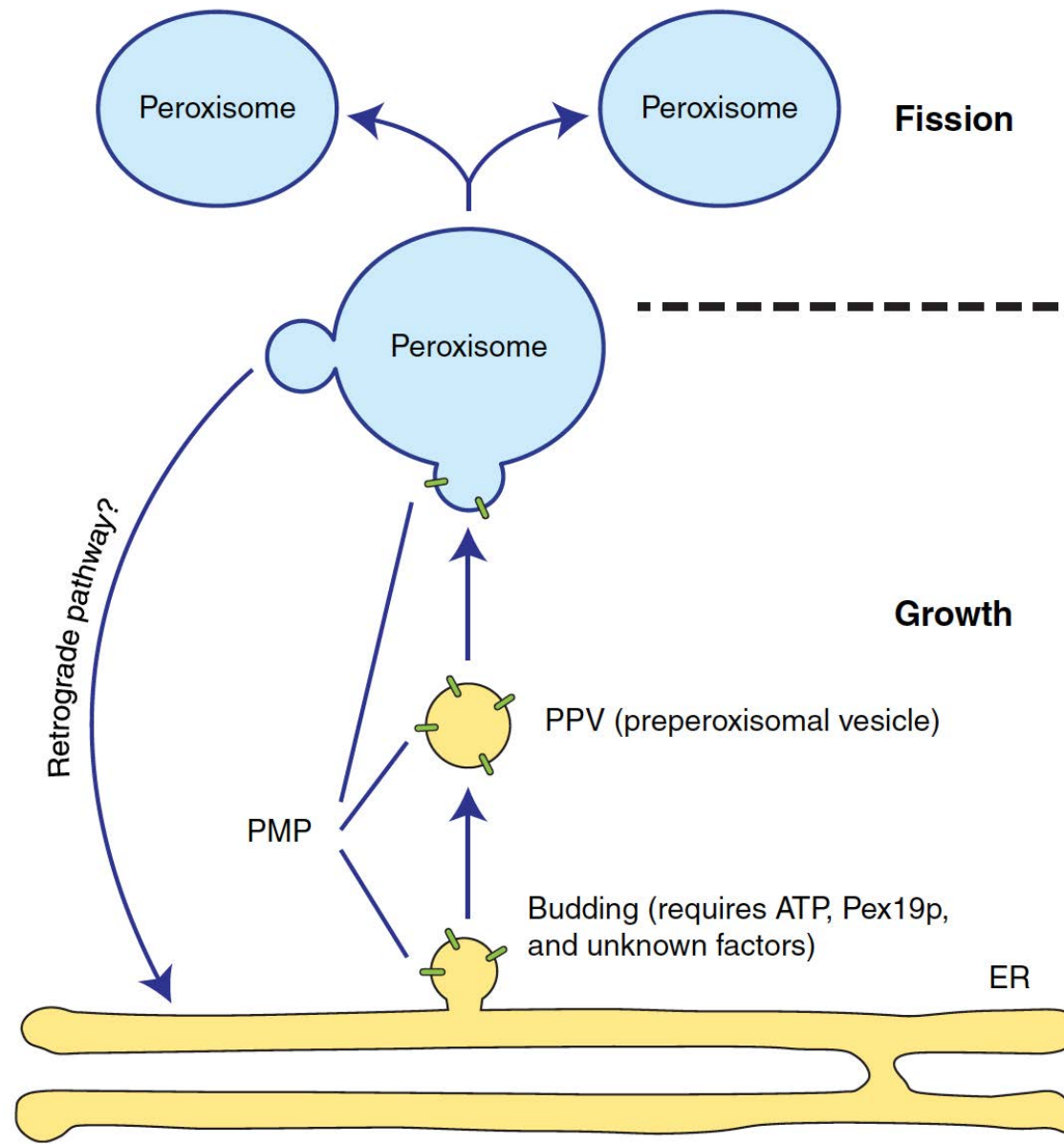
**B**

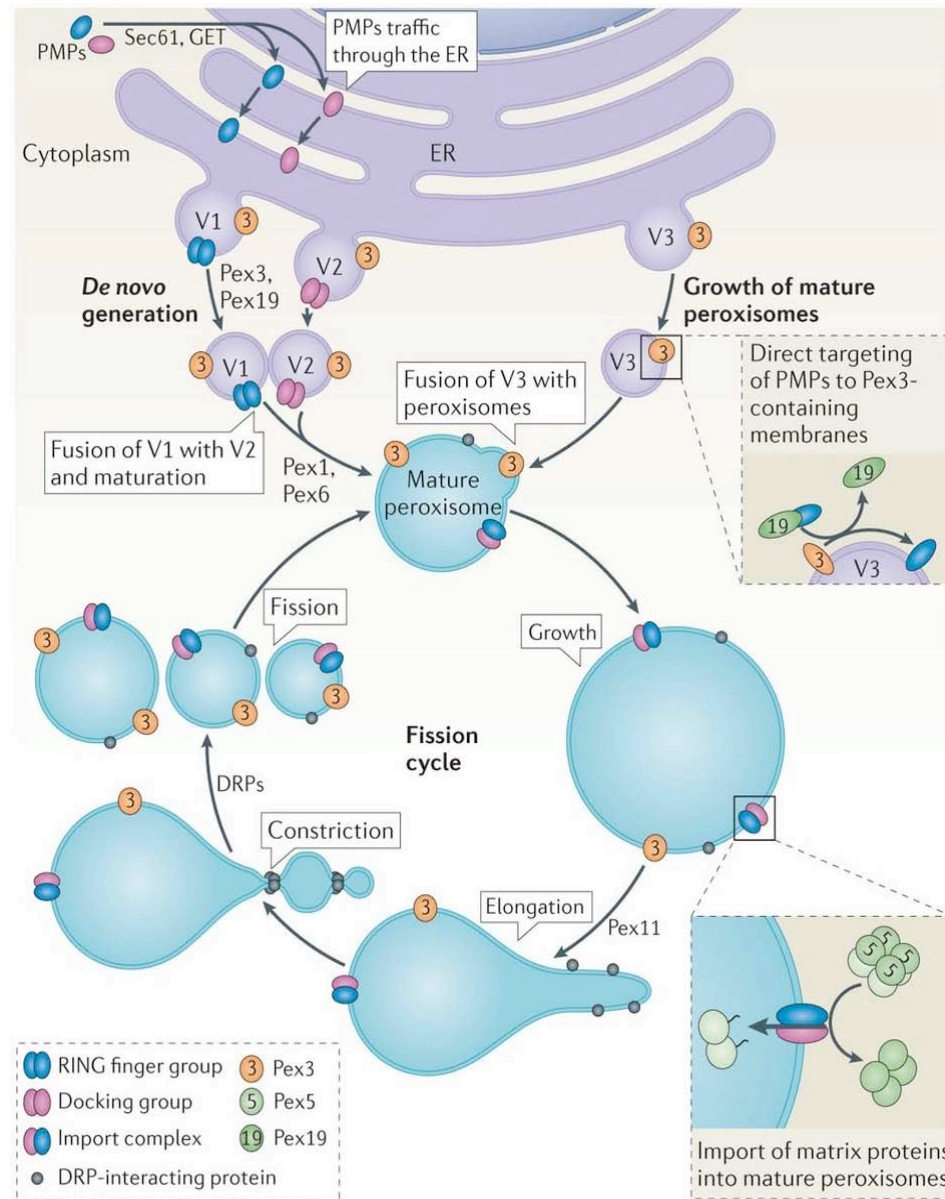


# Peroxisomal matrix protein traffic



Contribution of the endoplasmic reticulum to peroxisome biogenesis.

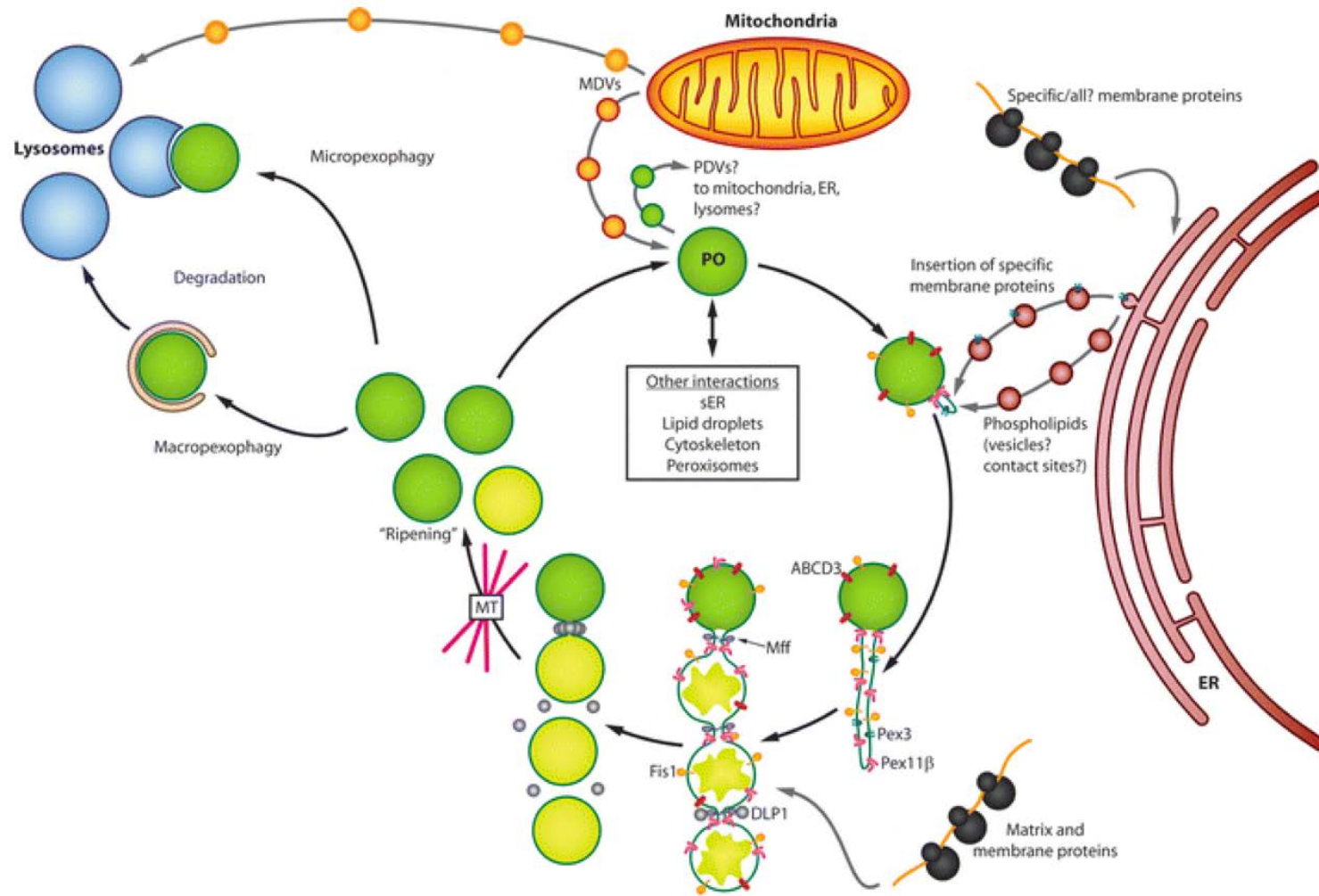




Nature Reviews | Molecular Cell Biology

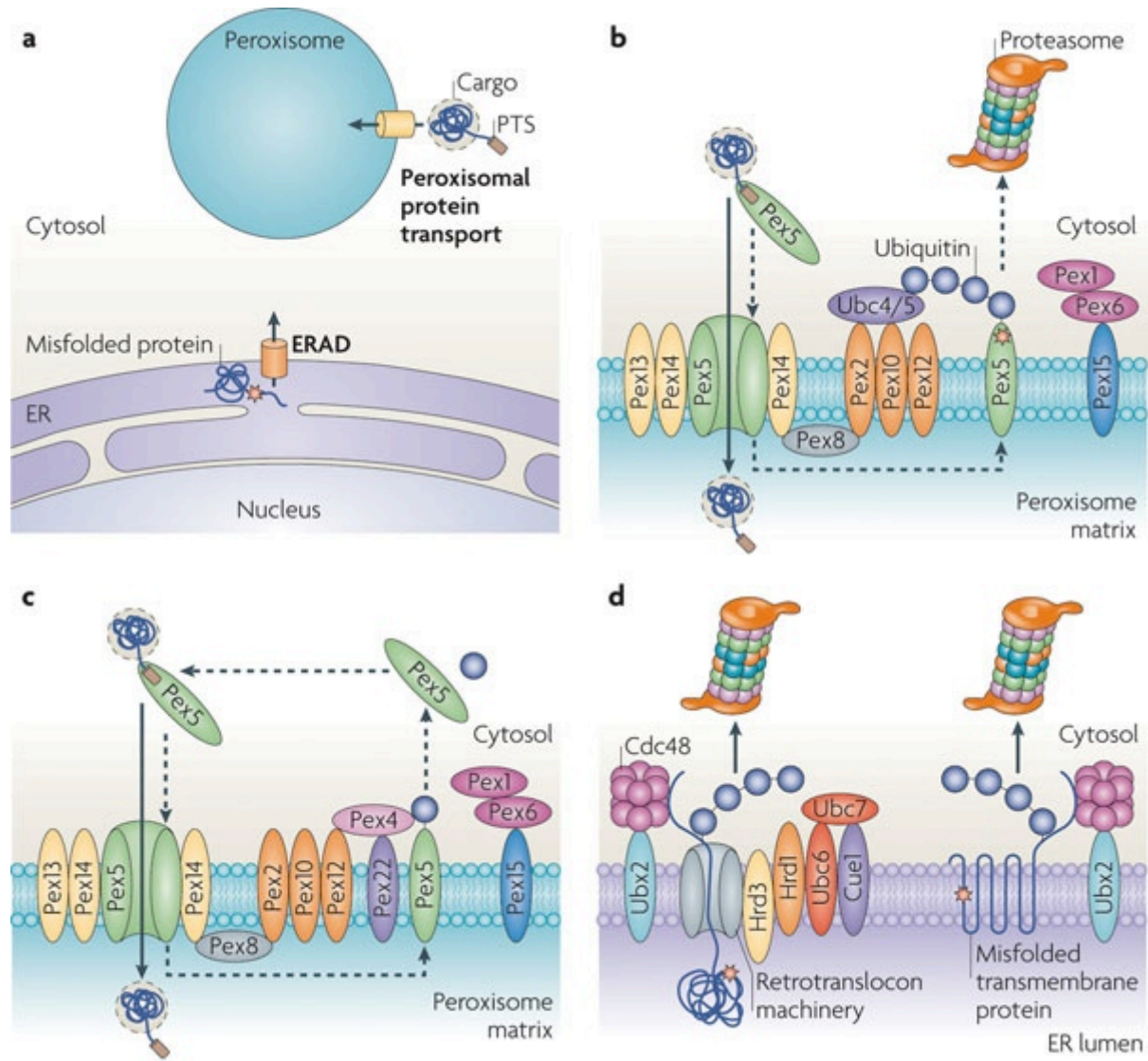
Peroxisomes can form through two pathways.

From Smith JJ. and Aitchison JD. *MOLECULAR CELL BIOLOGY* (2013)

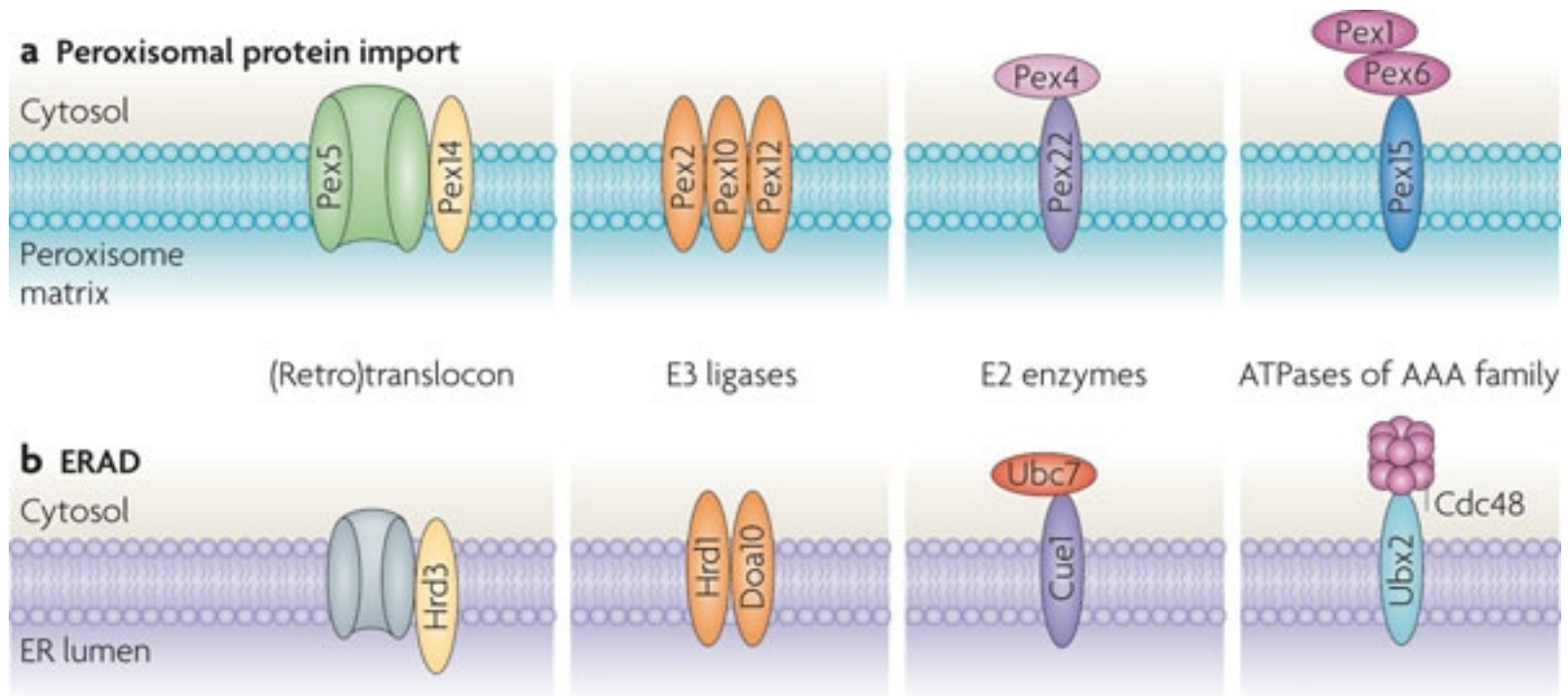


Model of peroxisome dynamics and interactions in mammalian cells.

From Islinger M. and Schrader M. . Histochem Cell Biol, 2012



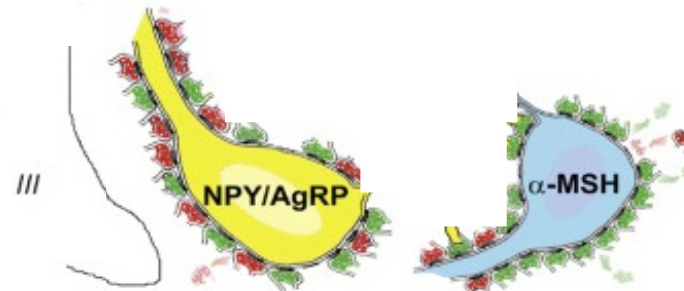
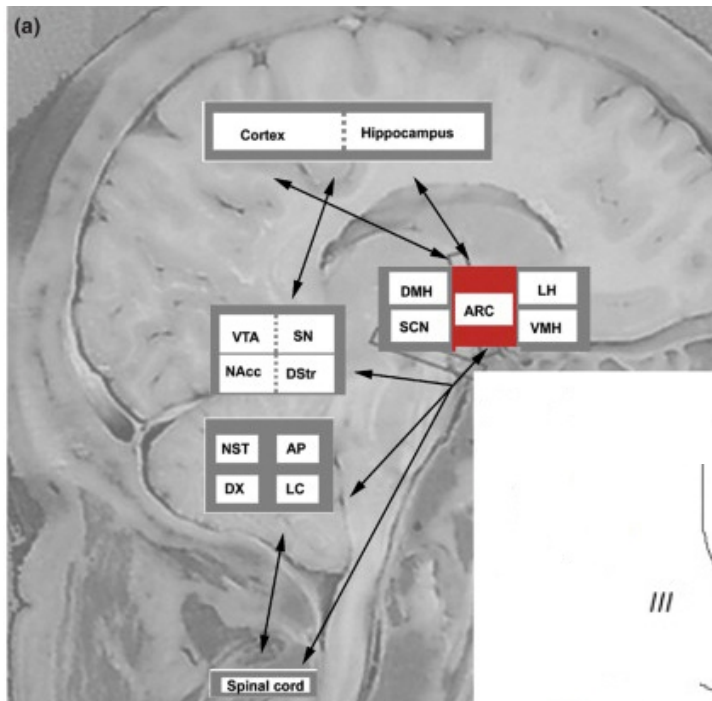
Peroxisomal protein import and ERAD in yeast.



Molecular parallels between ERAD and the peroxisomal import pathway.

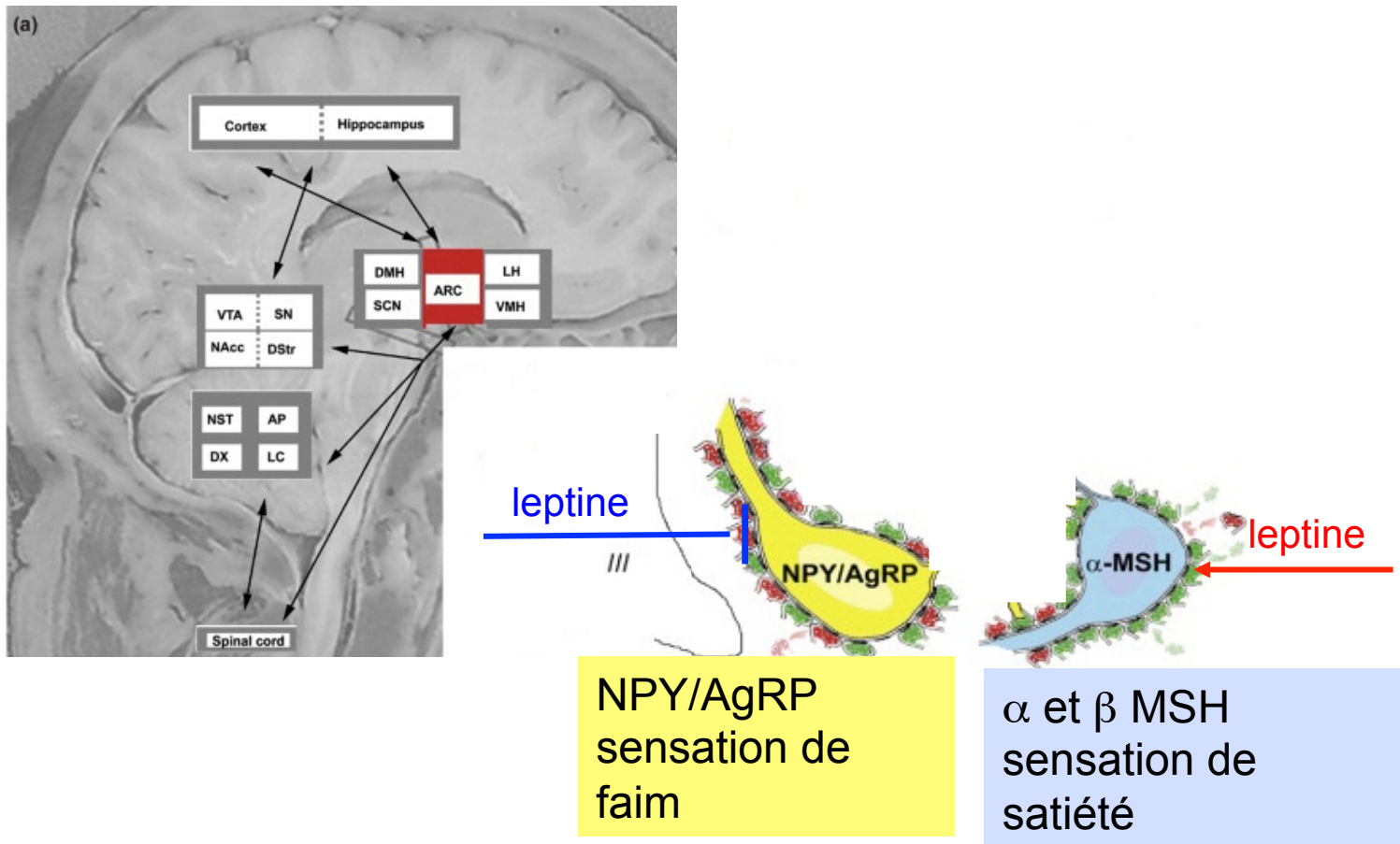
# HYPOTHALAMUS et ROS





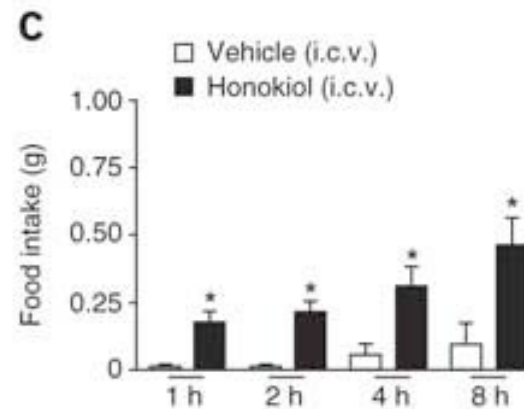
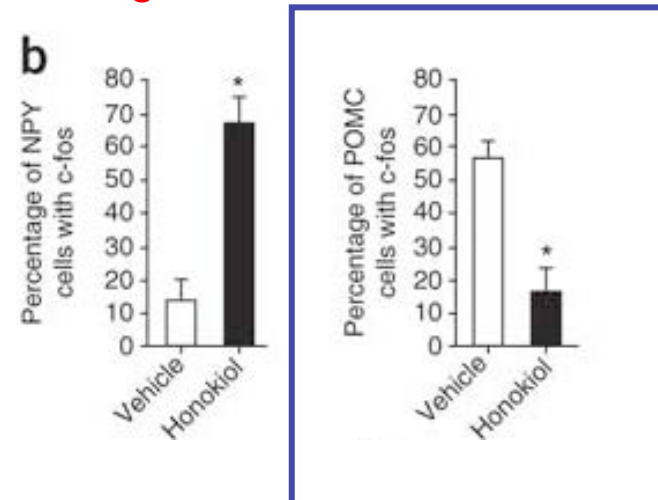
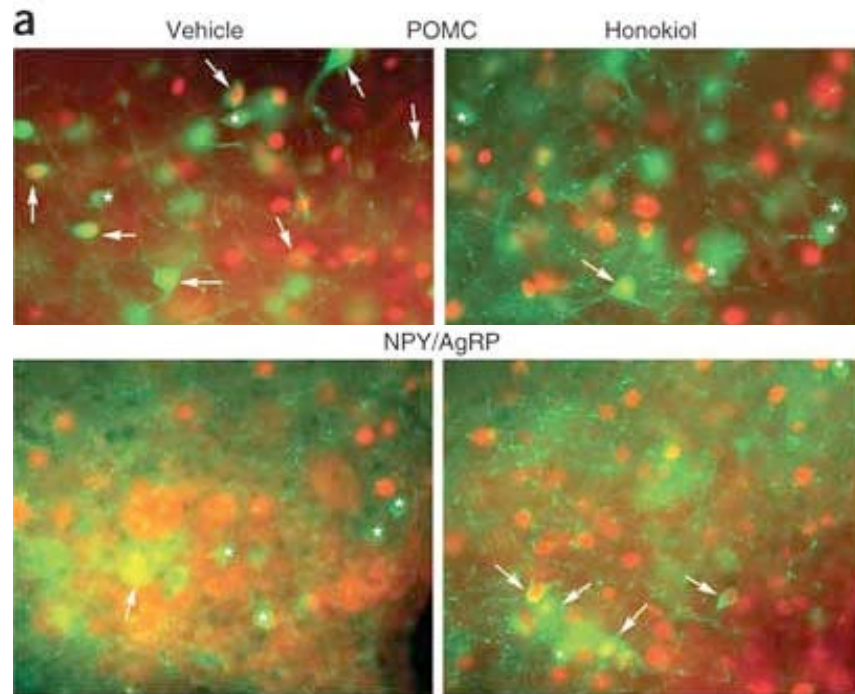
NPY/AgRP  
 Sensation de faim  
 Neurones NPY/AgRP  
 Orexigène, augmentation  
 de la prise nourriture

$\alpha$  et  $\beta$  MSH  
 sensation de satiété  
 Neurones POMCs  
 Anorexigène; baisse  
 de la prise nourriture



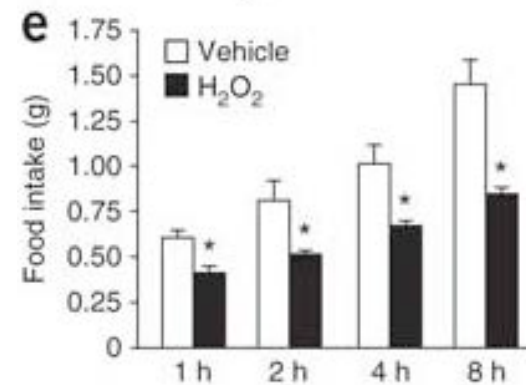
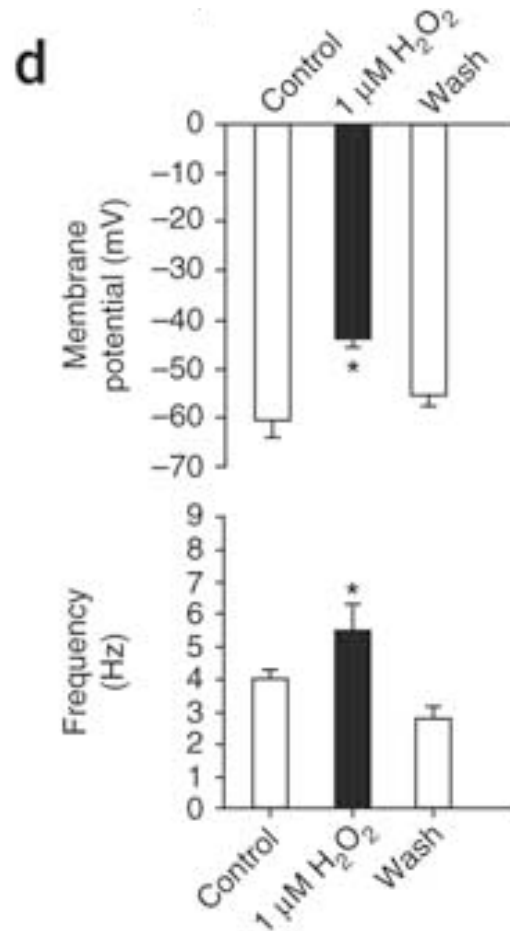
According to Horvath TL. and Diano S. *Trends in Endocrinology & Metabolism*, 2009

## Effet de l' Honokiol (piège les ROS) sur l' expression de c-Fos et la prise alimentaire chez des souris sauvages



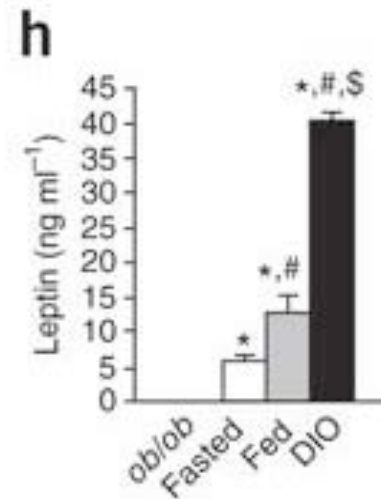
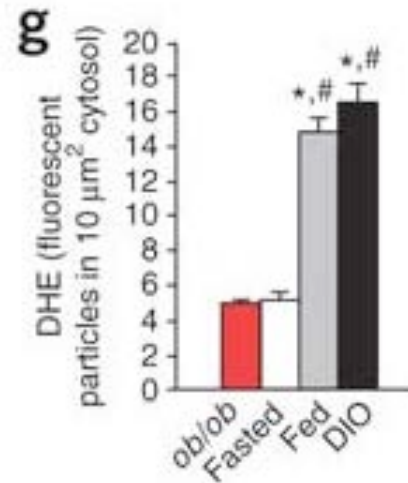
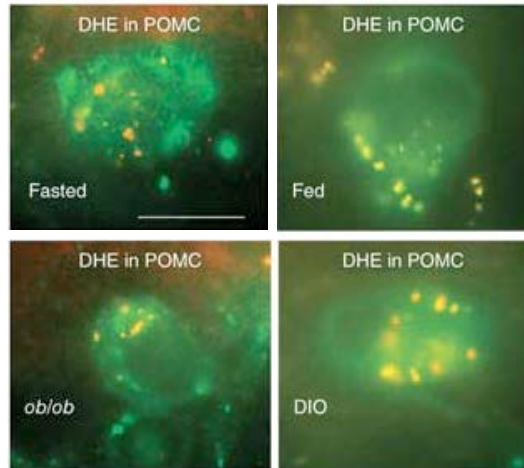
Free radicals' effect on the melanocortin system

## Effet de H<sub>2</sub>O<sub>2</sub> (augmente les ROS) sur l'activité électrique des POMCs et la prise alimentaire chez des souris sauvages

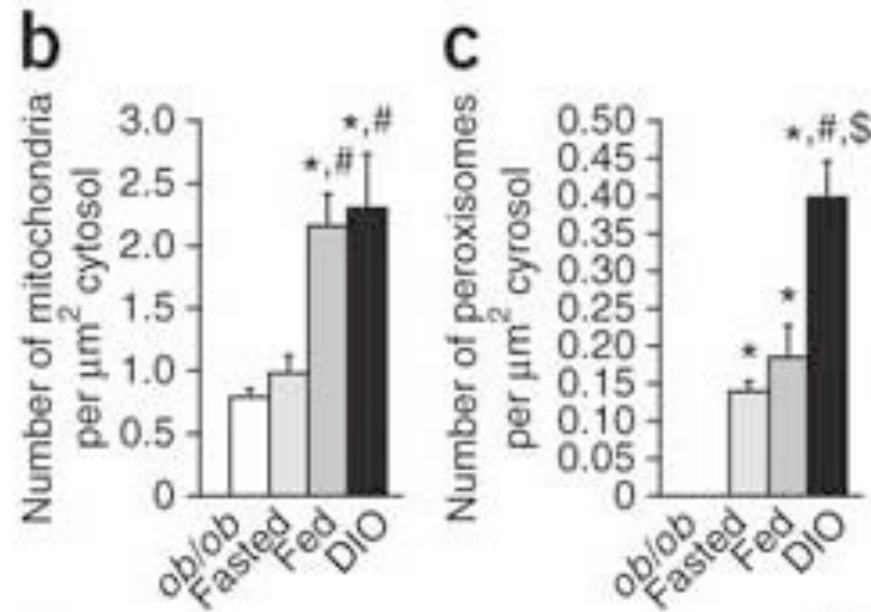
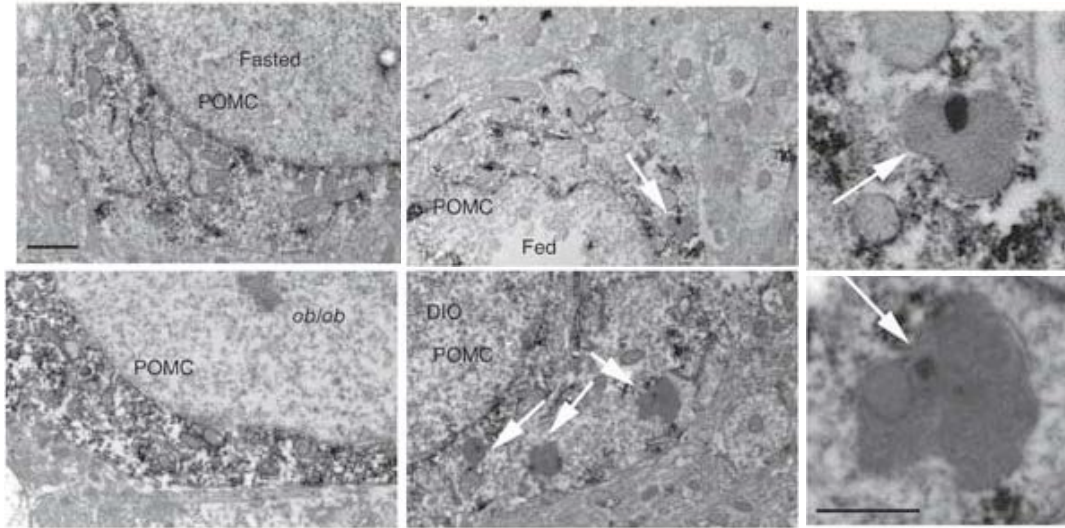


Free radicals' effect on the melanocortin system

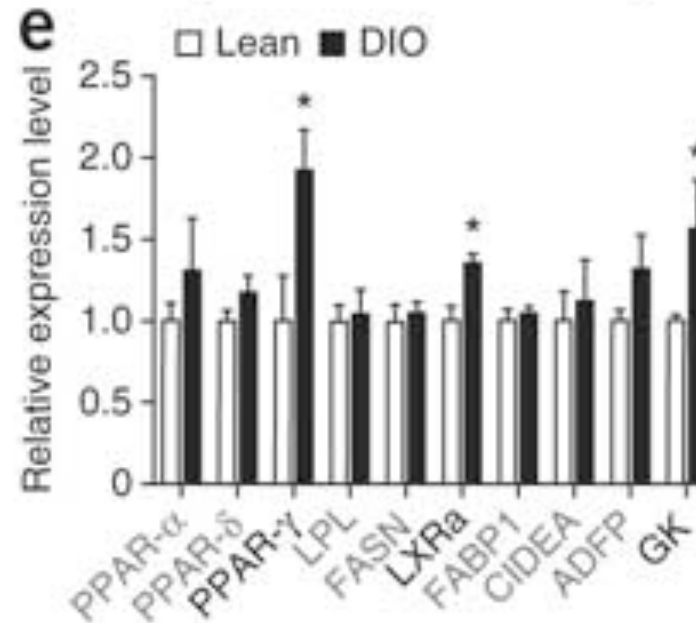
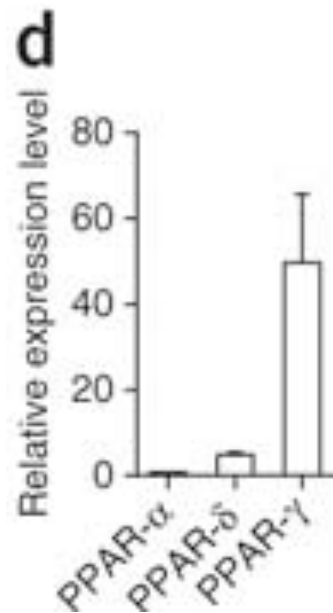
ROS dans les POMCs et taux de leptine:  
chez les souris DIO « diet-induced obesity » obèses par suralimentation:  
dissociation ROS/leptine



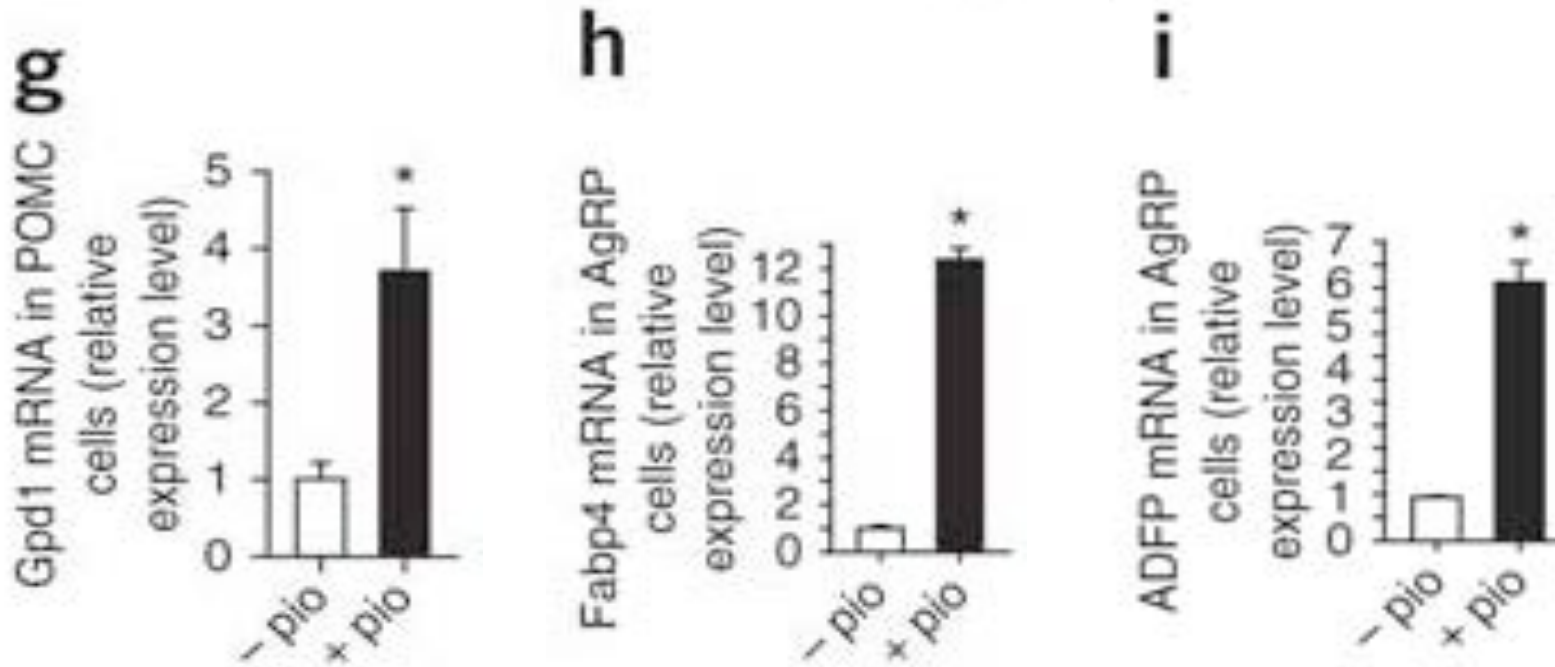
# Prolifération des mitochondries et des peroxysomes



# PPAR $\gamma$ et ses cibles (noyau arqué): les souris DIO

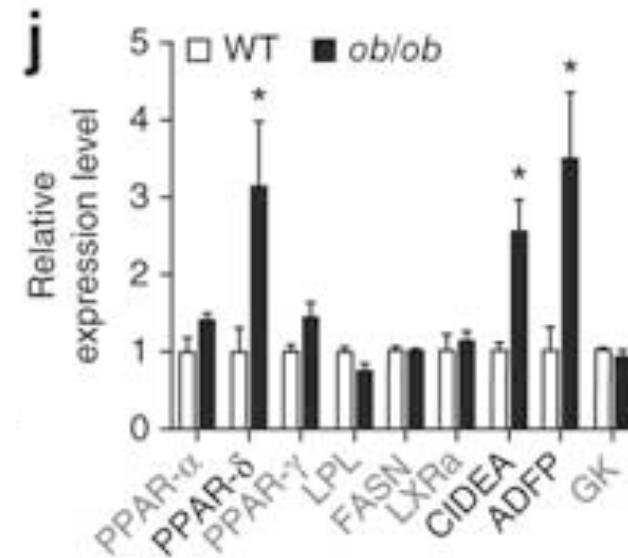
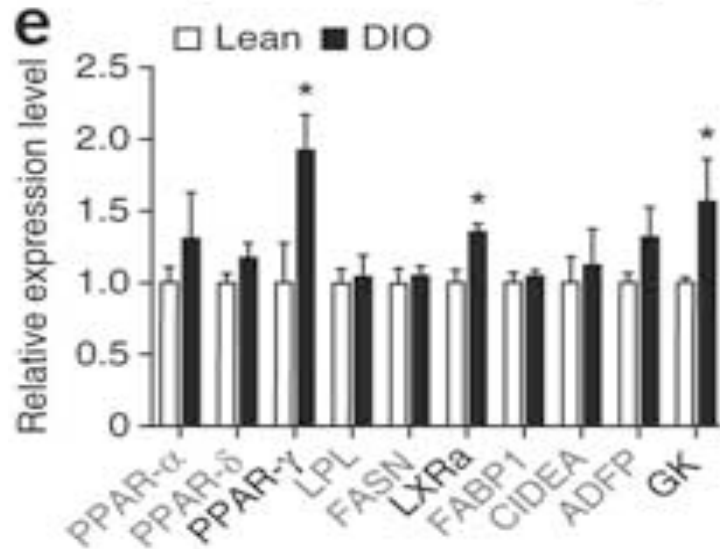


# Effet d'un agoniste du PPAR $\gamma$ –pioglitazon- sur les cibles de PPAR- $\gamma$ dans les lignées POMC et AgRP



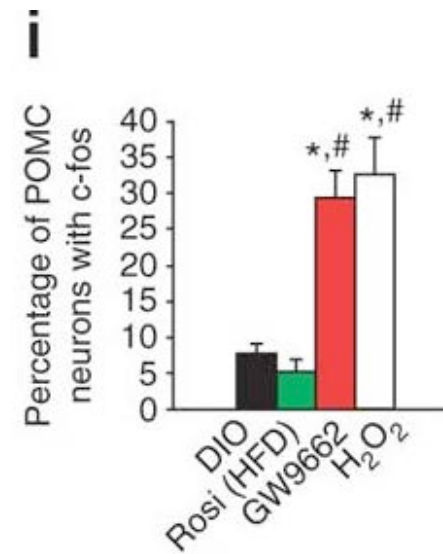
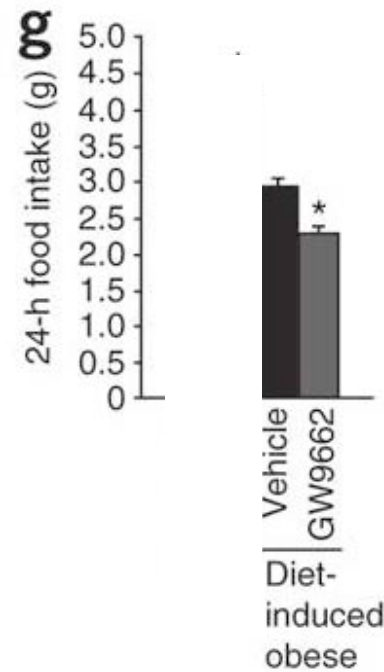
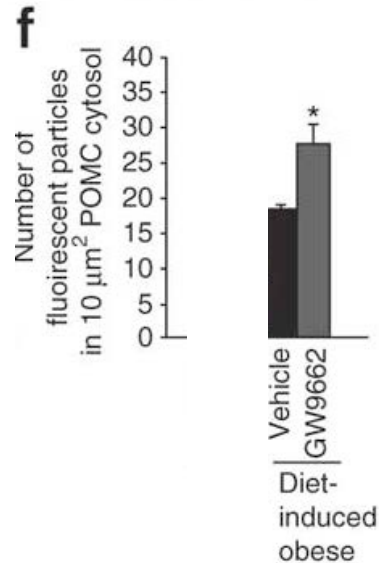
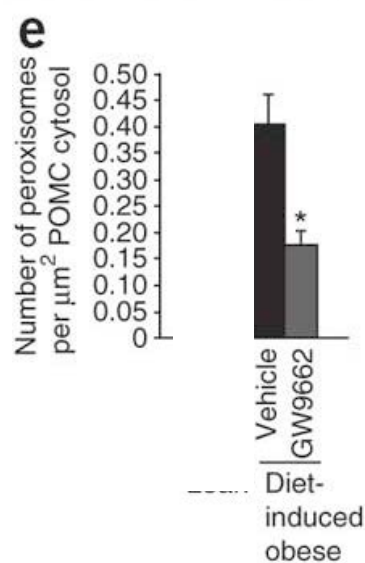
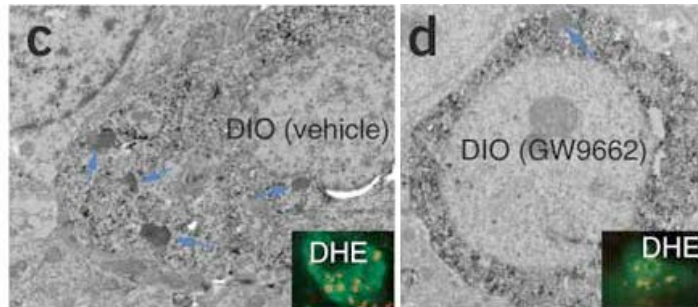


## Un profil de transcription différent dans le noyau arqué pour les PPAR et leurs cibles chez les souris obèses DIO et ob/ob

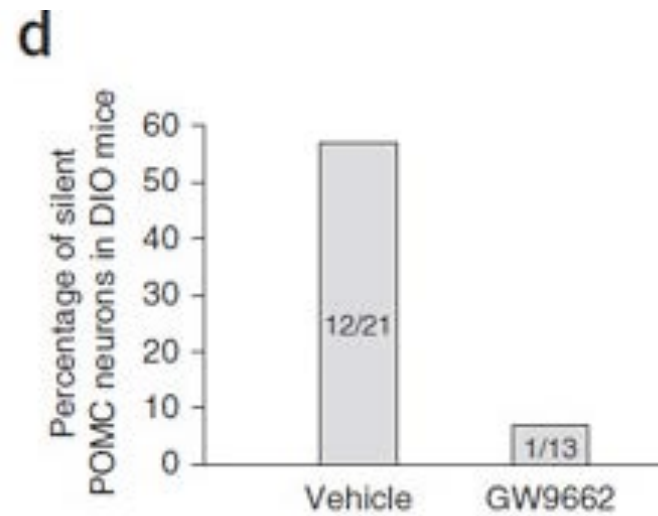
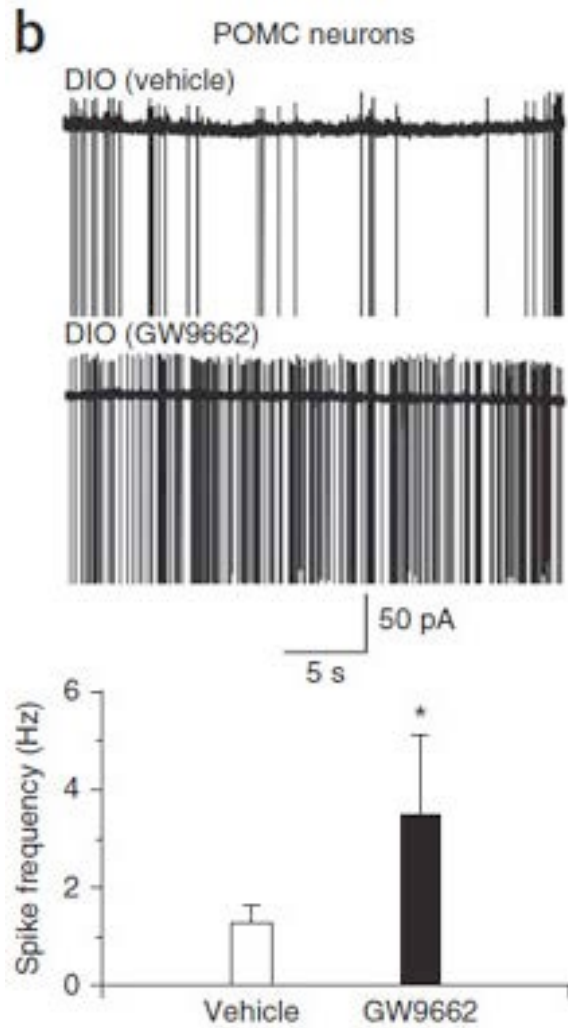


# PPAR $\gamma$ joue un rôle essentiel dans la résistance à la leptine des souris DIO et semble inhiber l'activité des POMCs

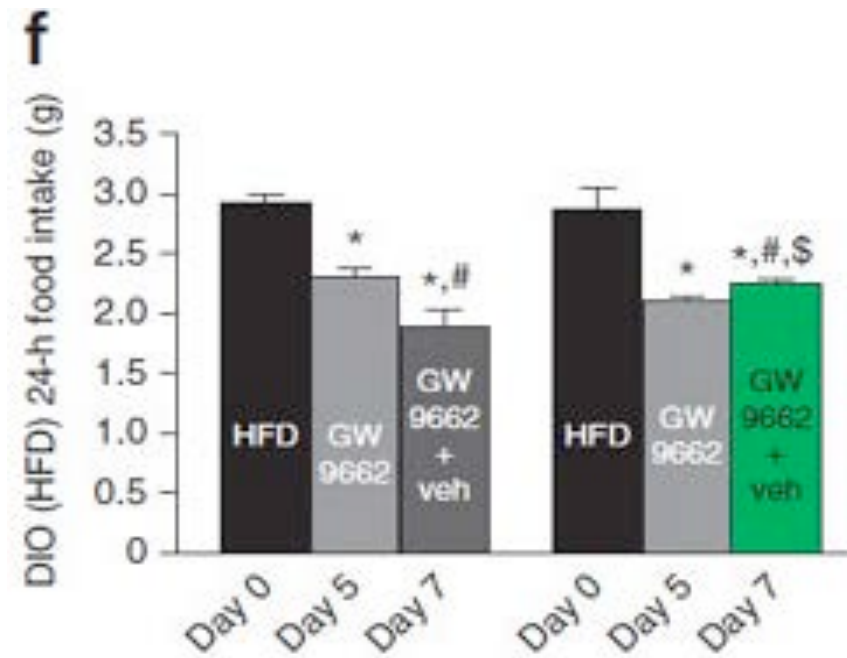
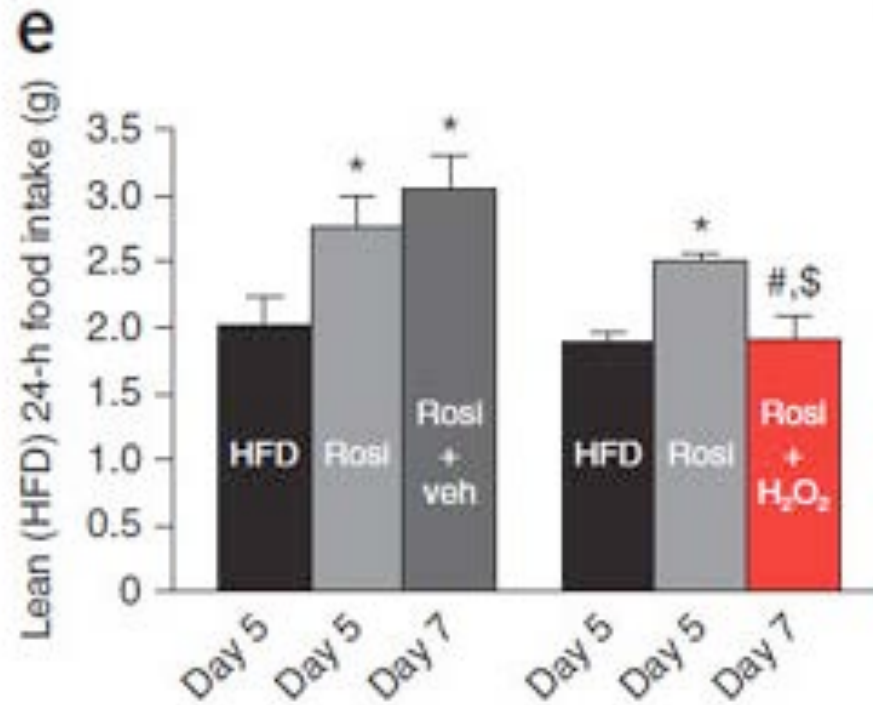
GW9662= antagoniste de PPAR $\gamma$



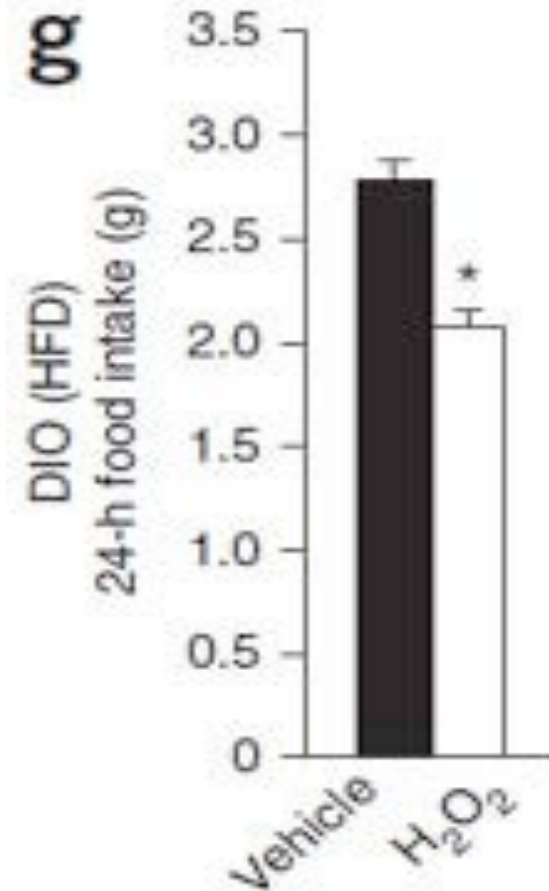
# PPAR $\gamma$ inhibe l'activité des neurones POMCs des souris DIO

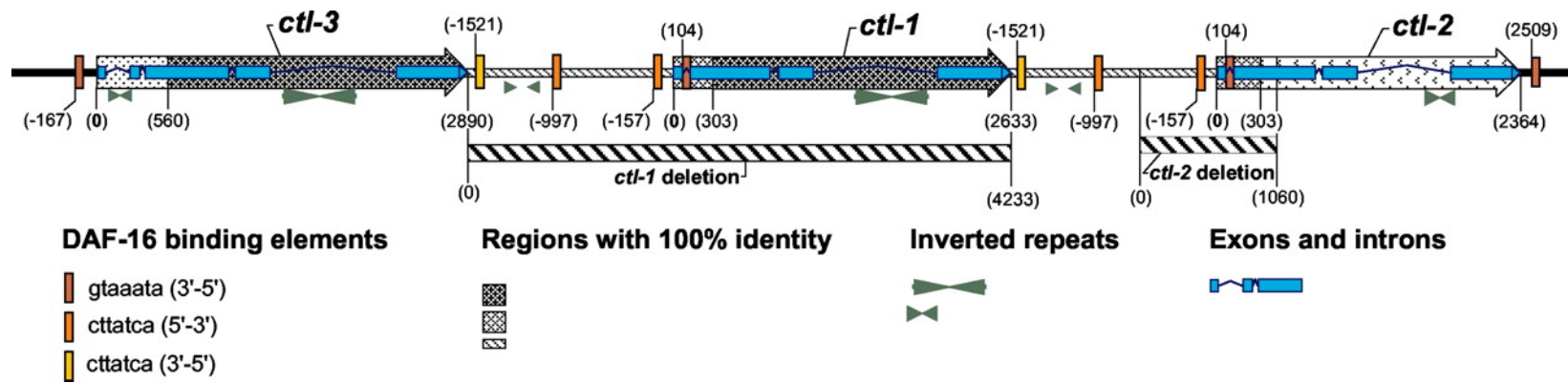


PPAR  $\gamma$  joue un rôle essentiel dans la prise de nourriture.  
Ce rôle chez les souris sauvages comme les souris DIO  
implique les ROS.



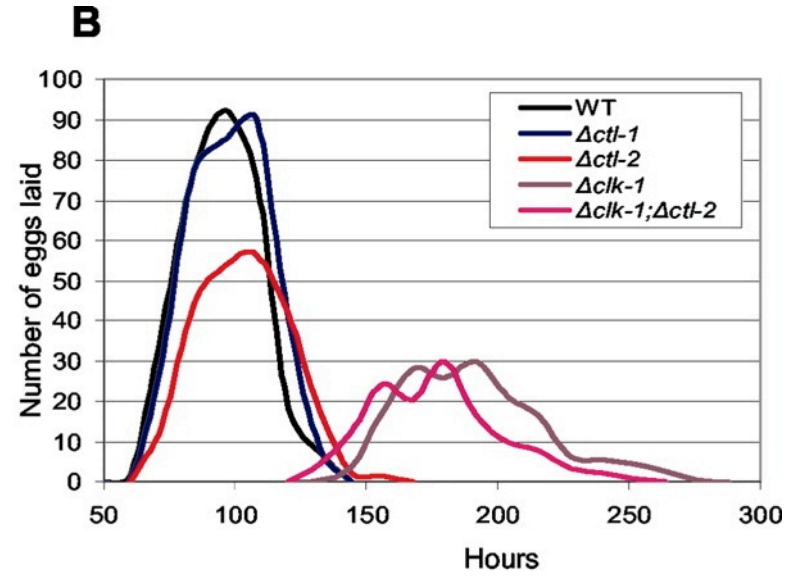
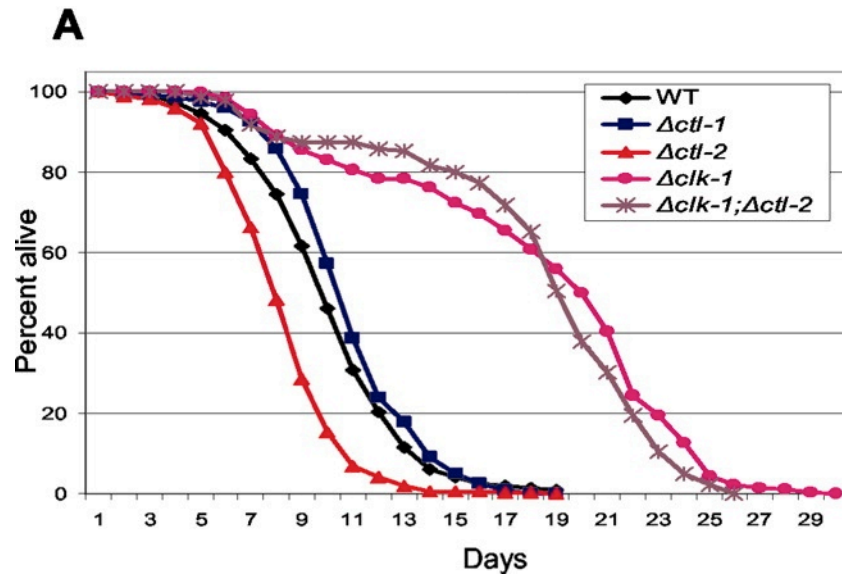
## Les ROS baissent la prise alimentaires chez les souris DIO





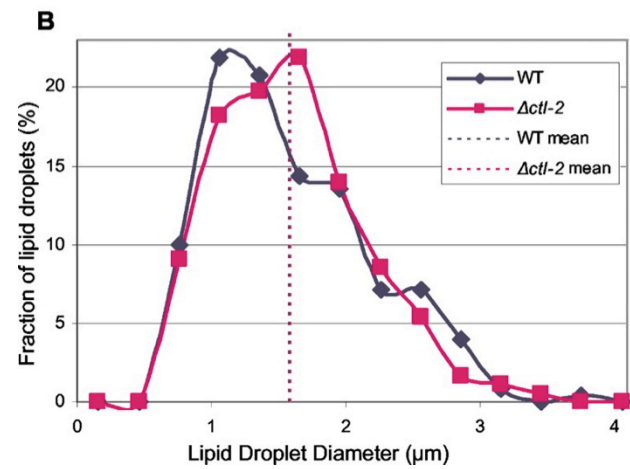
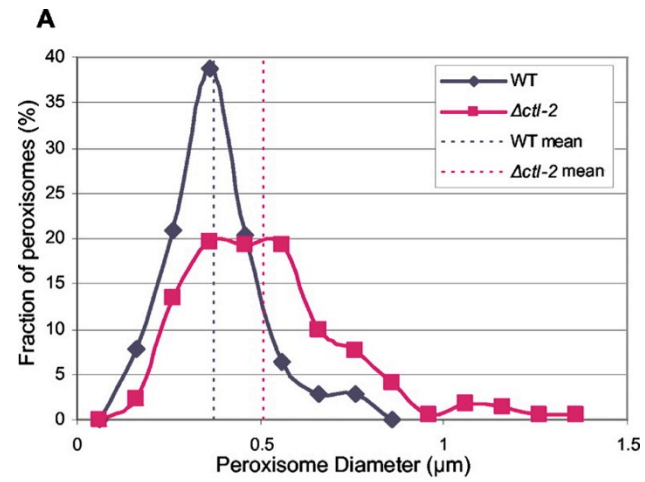
Structure of the *ctl* locus in the *C. elegans* genome.

From Petriv O I , and Rachubinski R A J. *Biol. Chem.* 2004



Effects of mutation of the *ctl-1* and *ctl-2* genes on life-span and egg laying capacity of wild-type and  $\Delta clk-1$  mutant worms.

From Petriv O I , and Rachubinski R A J. *Biol. Chem.* 2004

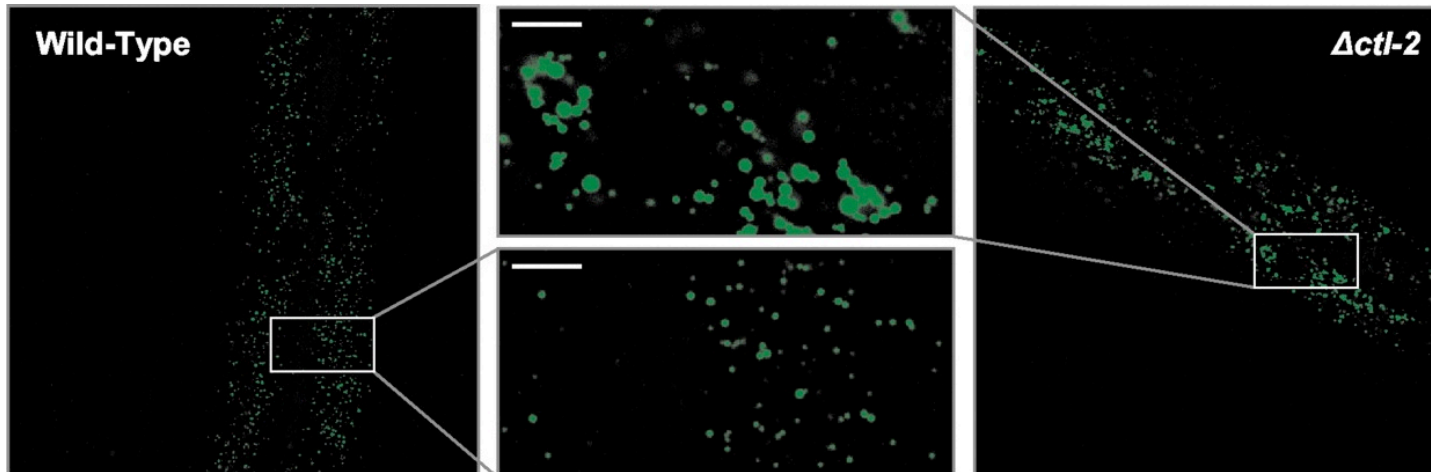


Cells of  $\Delta\text{ctl-2}$  mutant worms contain enlarged peroxisomes but lipid droplets of normal size.

From Petriv O I , and Rachubinski R A J. *Biol. Chem.* 2004

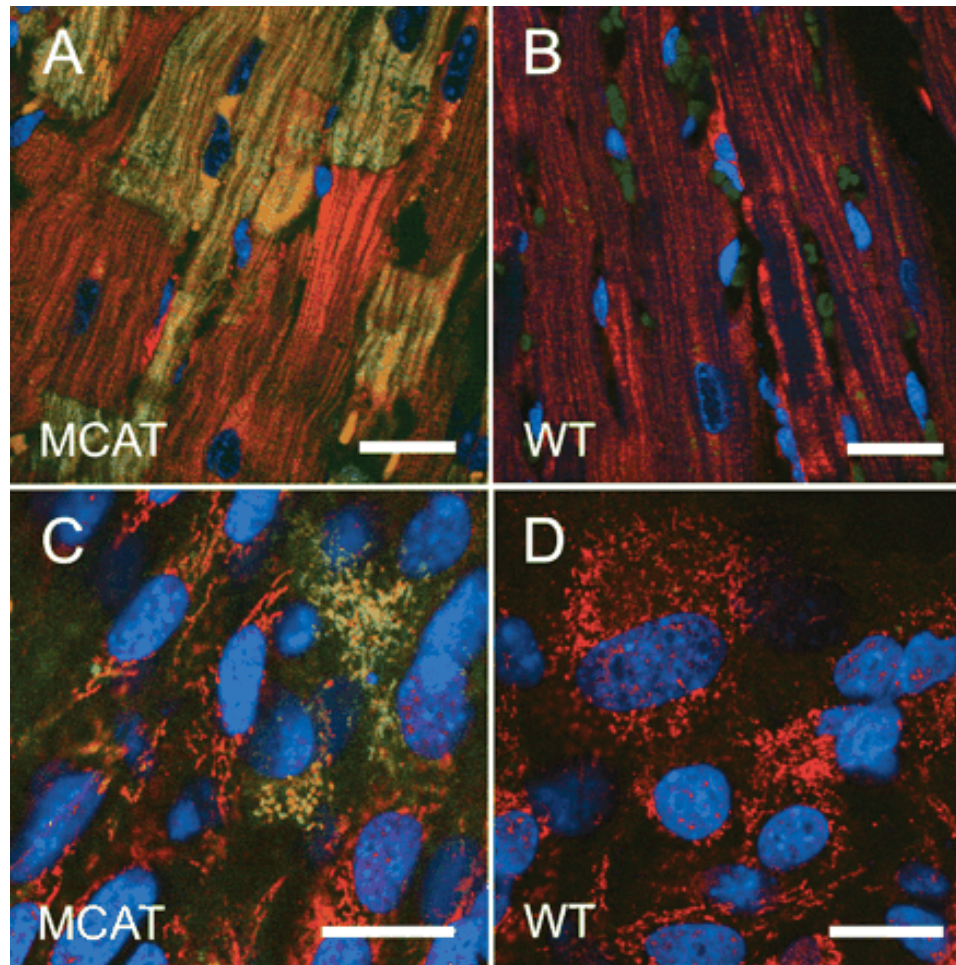
*jbc*





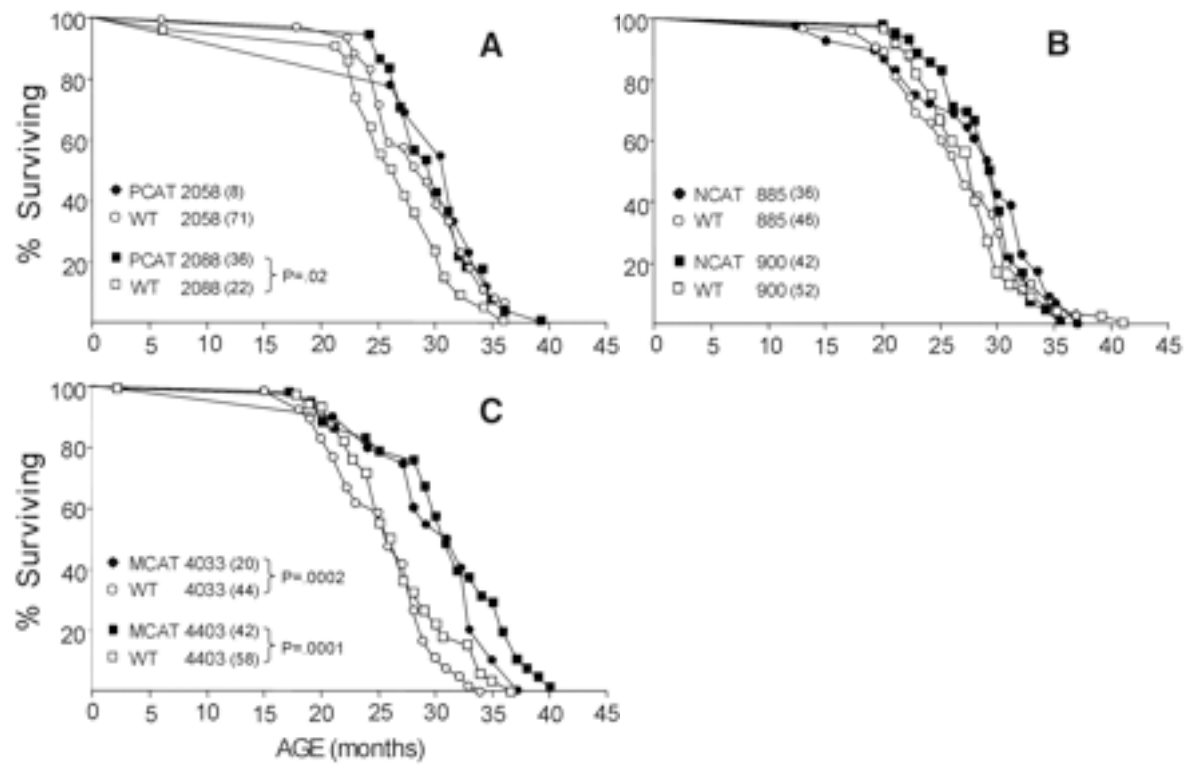
Peroxisomes exhibit altered morphology in  $\Delta$ ctl-2 mutant worms.

From Petriv O I , and Rachubinski R A J. *Biol. Chem.* 2004



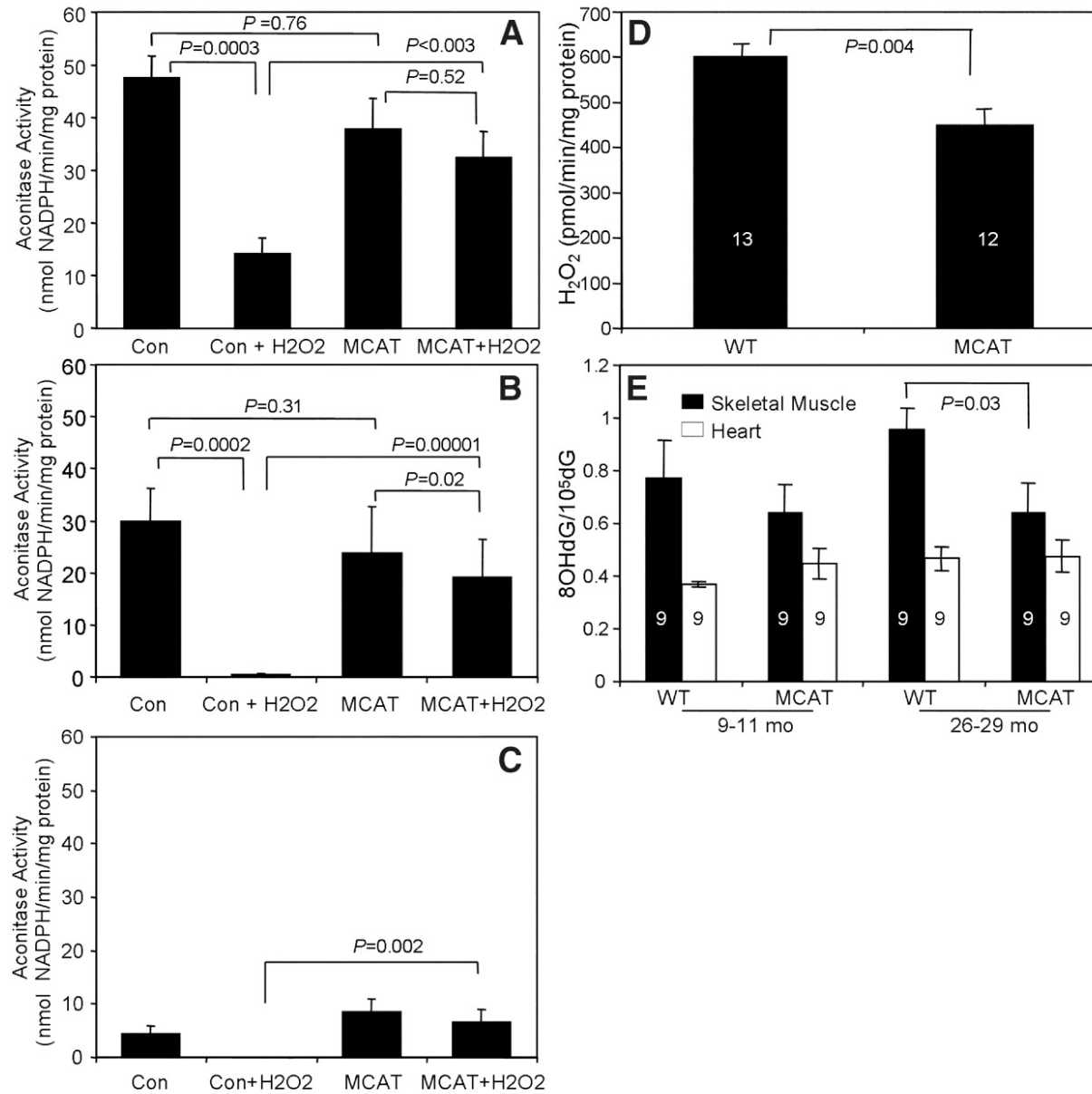
Mitochondrial localization of human catalase.

From Schriener SE. and Van Remmen H. *Science* 2005



Life span and catalase overexpression.

From Schriener SE. and Van Remmen H. *Science* 2005



Aconitase activity, ROS production, and oxidative damage