CHAIRE DE GÉNÉTIQUE ET PHYSIOLOGIE CELLULAIRE

Année universitaire 2013-2014

Pr Christine PETIT

COLLÈGE DE FRANCE 1530

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*

4ème cours : 20 mars 2014

Les moyens de défense: prévention et traitement.

Séminaire:

Alain Londero – Service ORL et CCF, HEGP, Paris

"Acouphènes subjectifs: physiopathologie et éléments d'une prise en charge rationnelle."

COLLÈGE DE FRANCE 1530

Plan du cours

I) Le peroxysome (suite)

- biogénèse des peroxysomes et contrôle de leur prolifération ;

- le peroxysome, senseur et effecteur du statut REDOX (biosenseurs)

- les maladies du peroxysome; ce que leur étude nous apprend sur les fonctions de cet organelle.

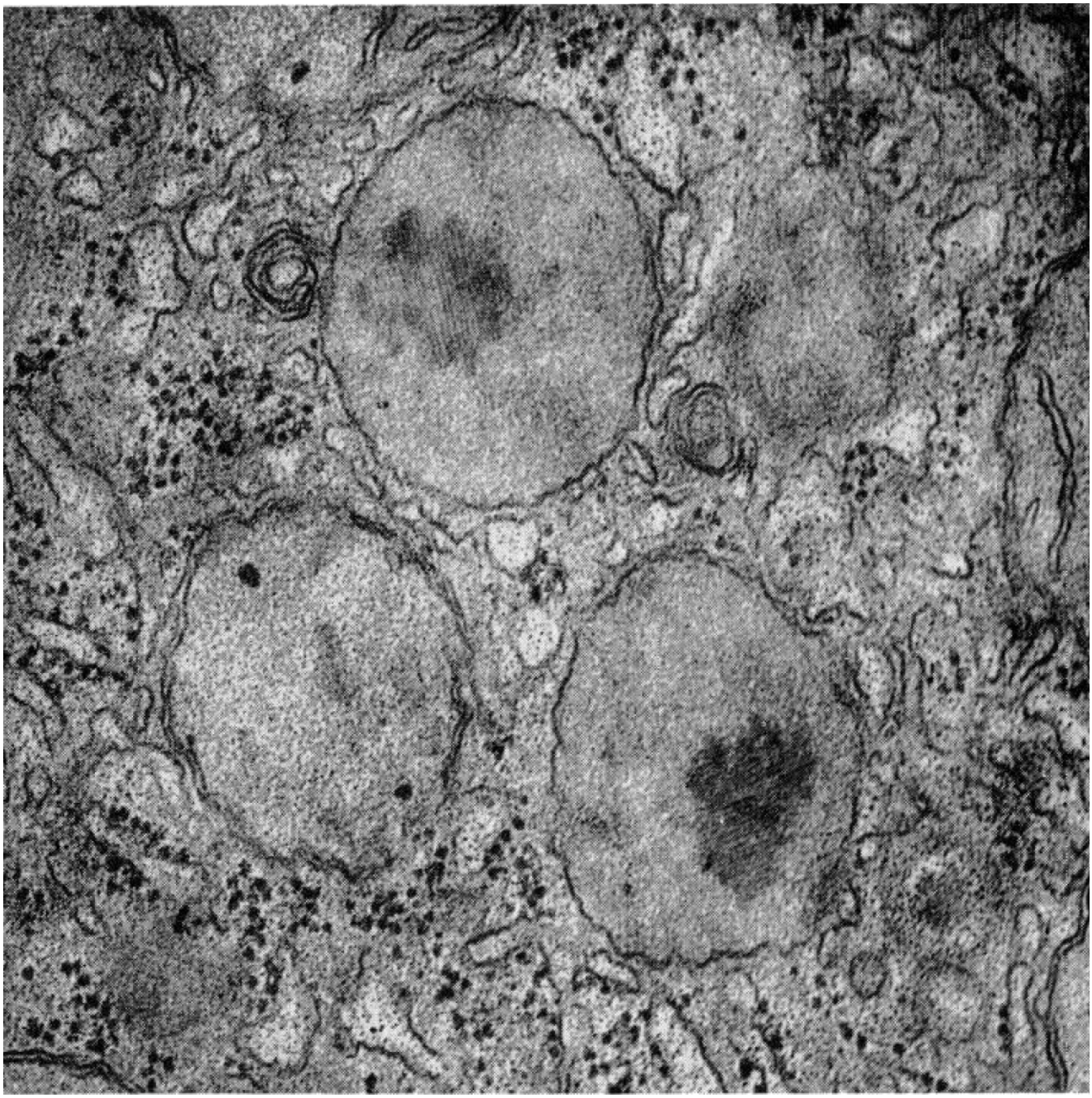
II) Prévention et traitement des atteintes auditives avec perturbation de l'homéostasie REDOX.

- la N-acétylcystéine.

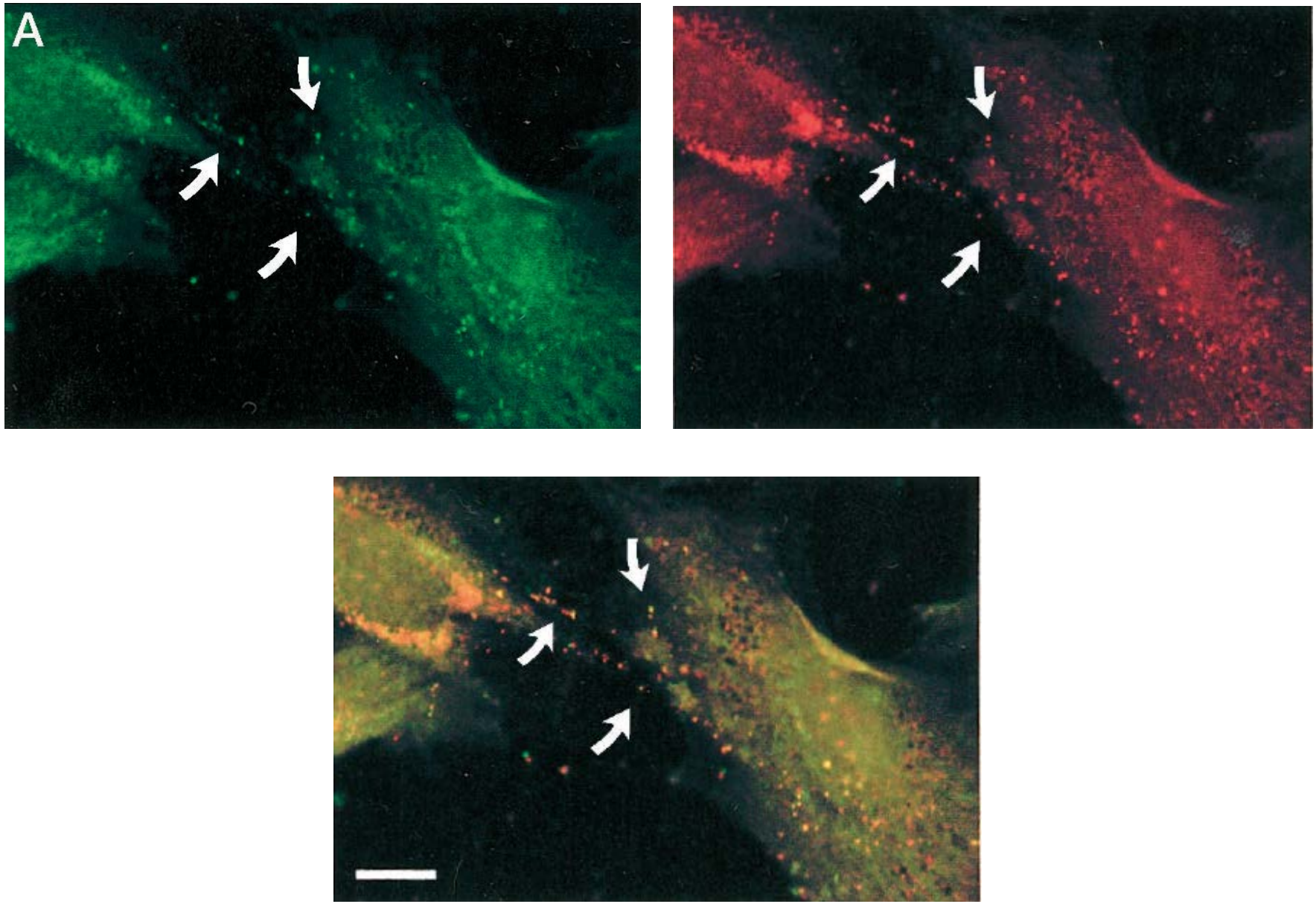
- la prévention par le pré-conditionnement sonore (le rôle des protéines de choc thermique)

- la diète calorique: de sa voie de signalisation au resveratrol.

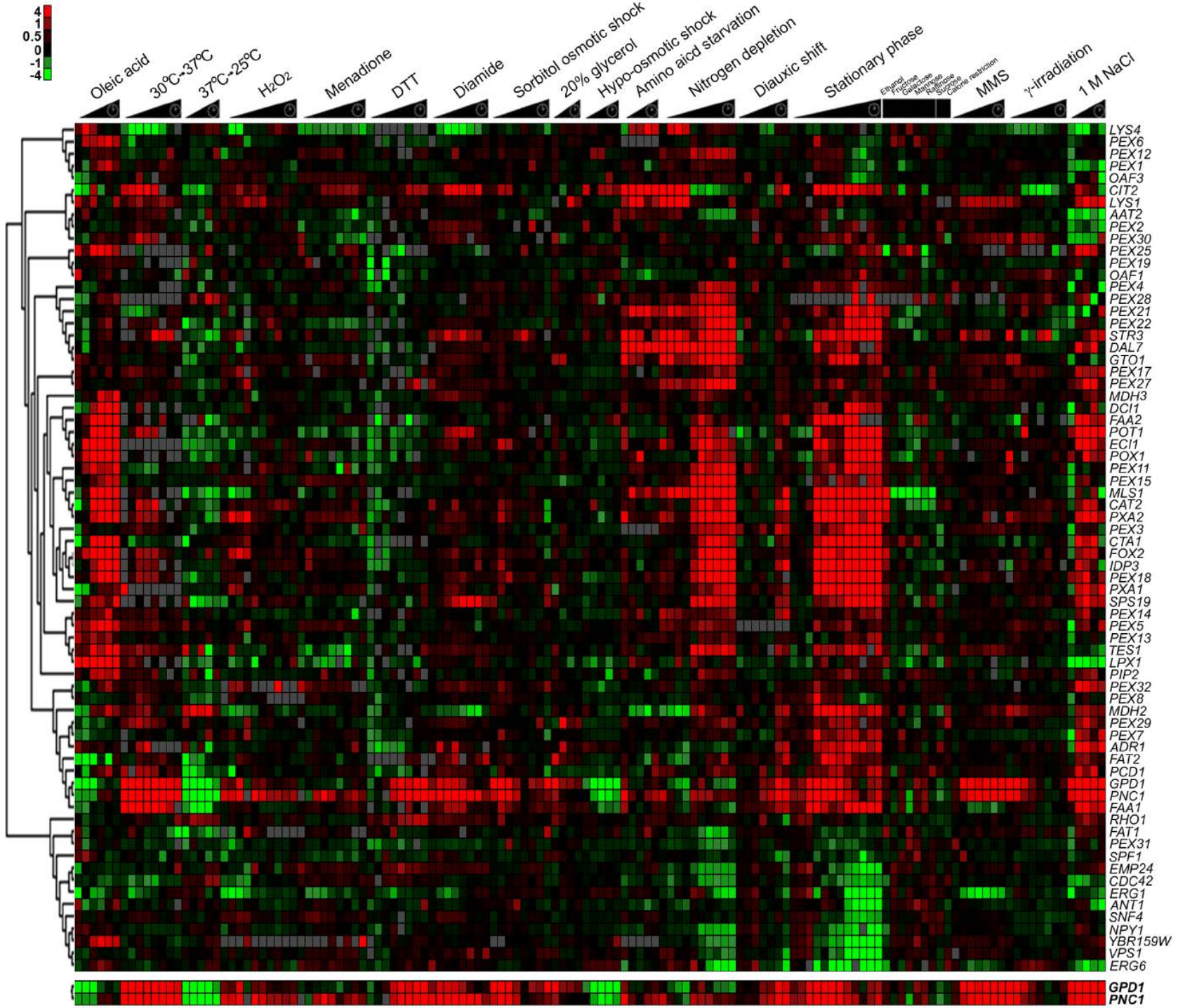
De Duve C & Baudhuin P – *Physiol Rev* 1966



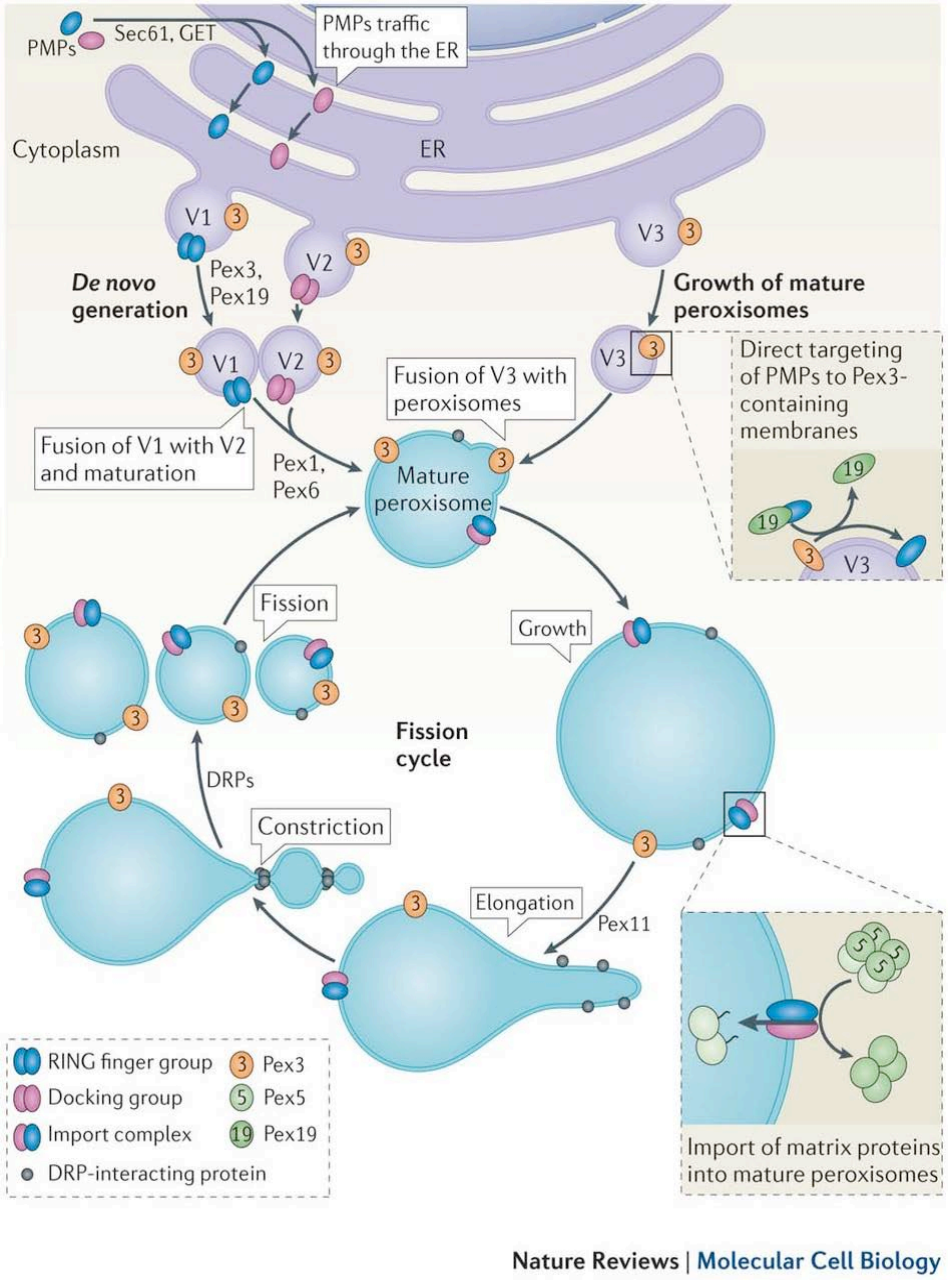
Co-localisation d' ATM et de la catalase en immunohistochimie.



Watters D… Lavin MF – *J Biol Chem* 1999



Jung S… Aitchison JD – *J Biol Chem* 2010



Peroxisomes can form through two pathways.

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

Expression of *PEX11β* Mediates Peroxisome Proliferation in the Absence of Extracellular Stimuli*

Michael Schrader **Stephen J. Gould**

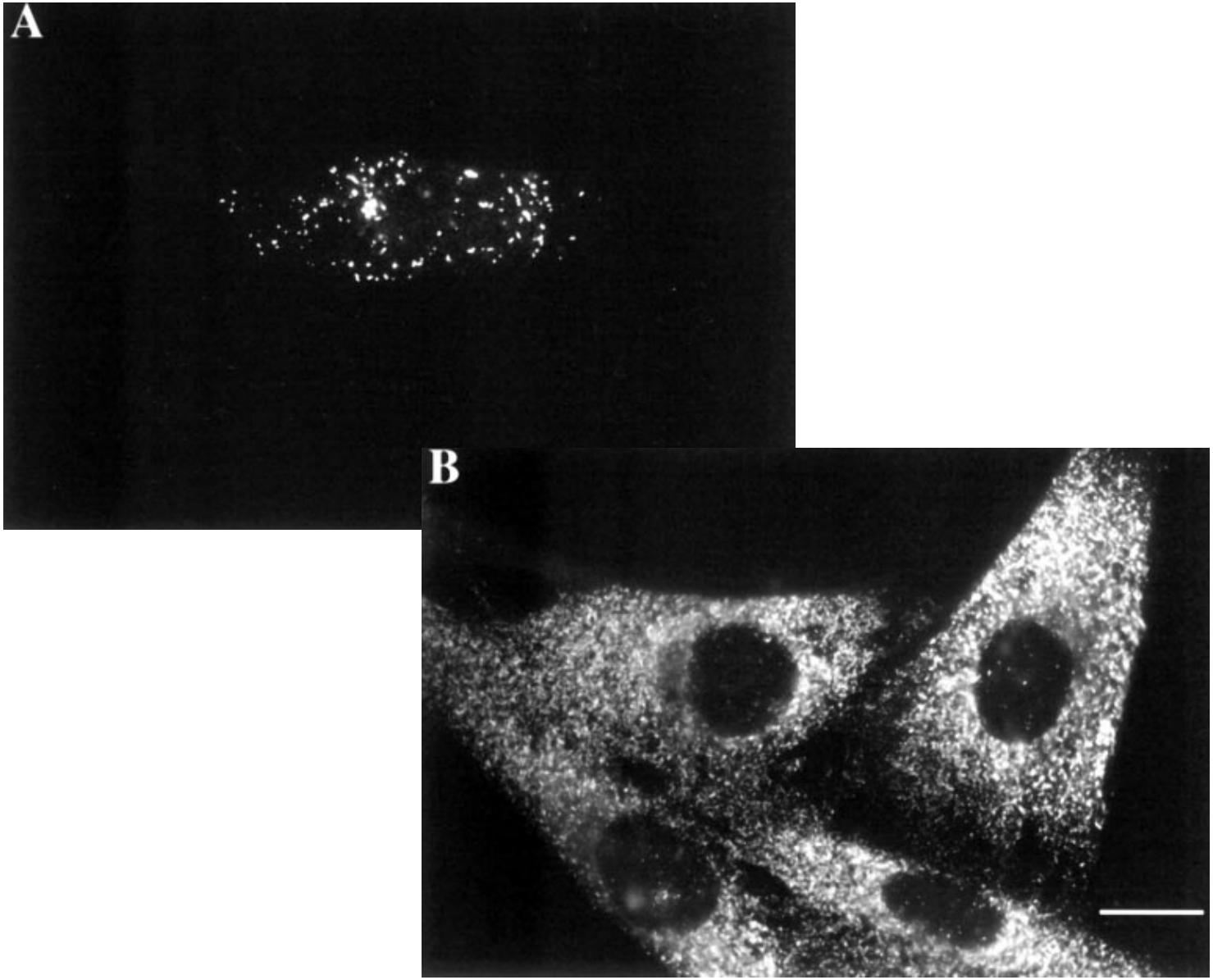
Johns Hopkins University School of Medicine

Mammalian cells typically contain hundreds of peroxisomes but can increase peroxisome abundance further in response to extracellular stimuli. We report here the identification and characterization of two novel human peroxisomal membrane proteins, PEX11α and PEX11β. Overexpression of the human *PEX11β* gene alone was sufficient to induce peroxisome proliferation, demonstrating that proliferation can occur in the absence of extracellular stimuli and may be mediated by a single gene. Time course studies indicated that PEX11β induces peroxisome proliferation through a multistep process involving peroxisome elongation and segregation of PEX11β from other peroxisomal membrane proteins, followed by peroxisome division. Overexpression of *PEX11α* also induced peroxisome proliferation but at a much lower frequency than *PEX11β* in our experimental system. The patterns of *PEX11α* and *PEX11β* expression were examined in the rat, the animal in which peroxisome proliferation has been examined most extensively. Levels of *PEX11β* mRNA were similar in all tissues examined and were unaffected by peroxisome-proliferating agents. Conversely, *PEX11α* mRNA levels varied widely among different tissues, were highest in tissues that are sensitive to peroxisome-proliferating agents, and were induced more than 10-fold in response to the peroxisome proliferators clofibrate and di(2-ethylhexyl) phthalate. Taken together, these data implicate PEX11β in the constitutive control of peroxisome abundance and suggest that PEX11α may regulate peroxisome abundance in response to extracellular stimuli.

THE JOURNAL OF BIOLOGICAL CHEMISTRY

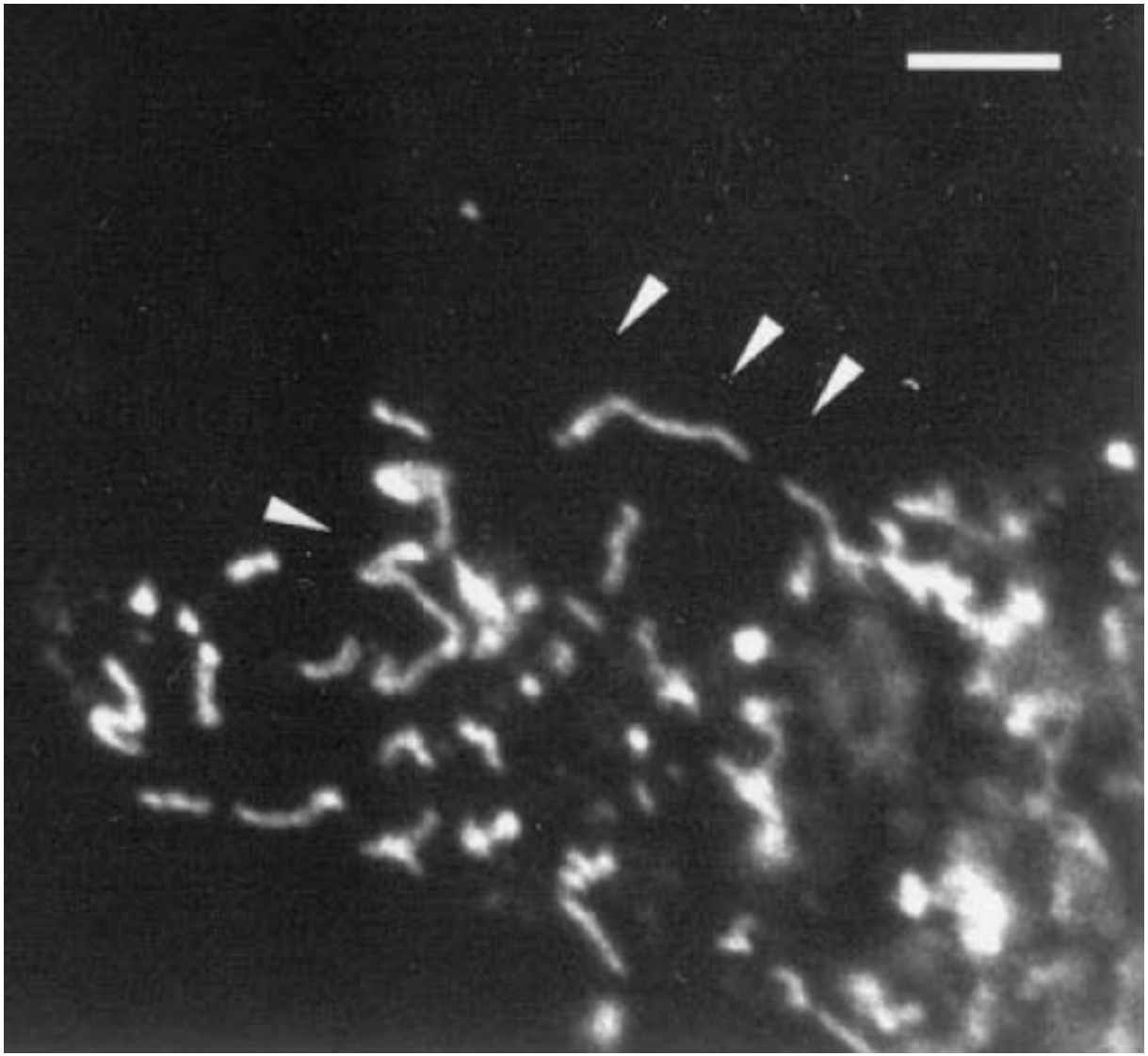
Vol. 273, No. 45, Issue of November 6, pp. 29607–29614, 1998

L'hyperexpression de *PEX11*β induit la prolifération des peroxisomes



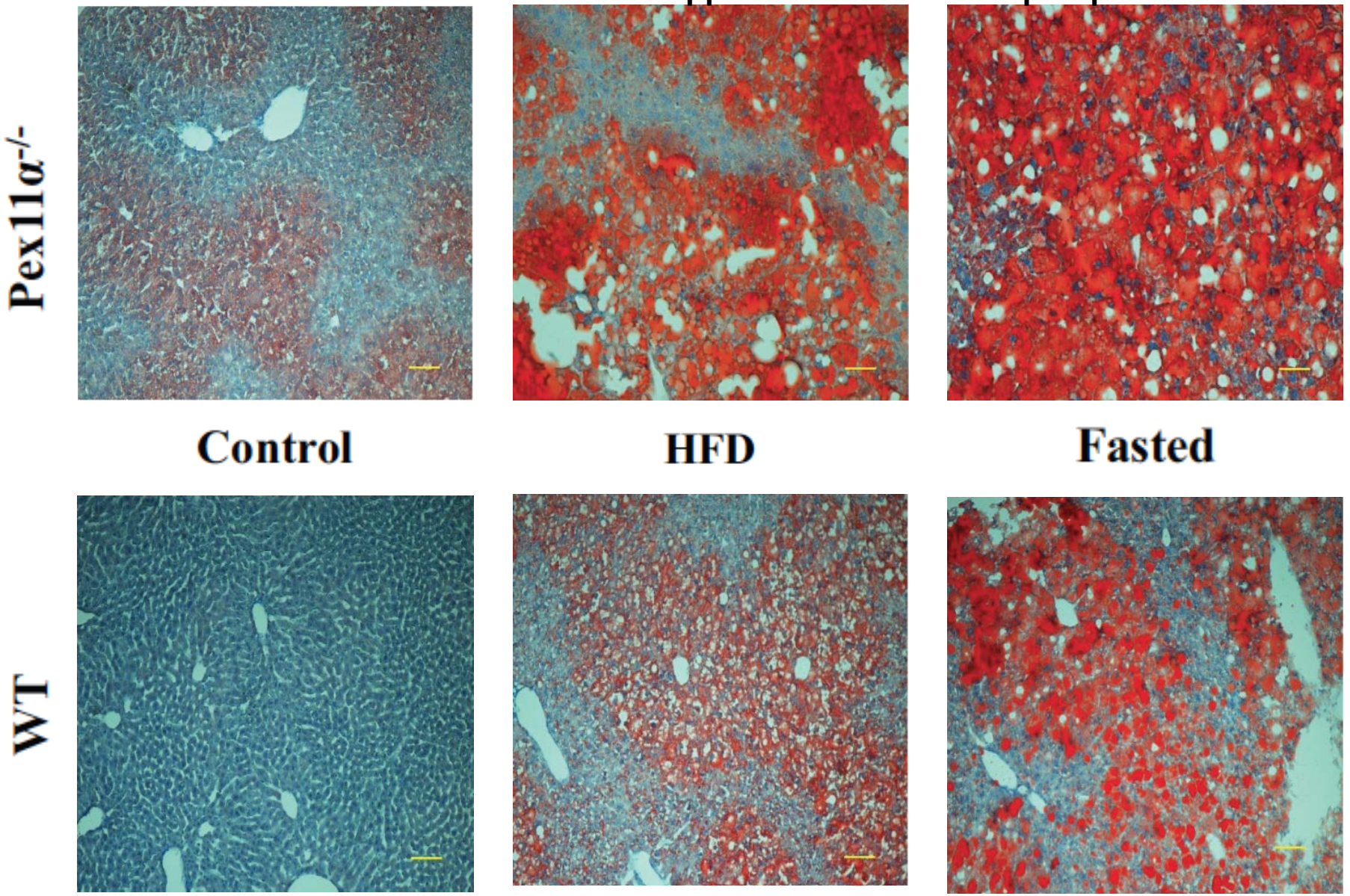
Schrader M… Gould SJ – *J Biol Chem* 1998

PEX11β induit l'élongation des peroxisome avant leur prolifération

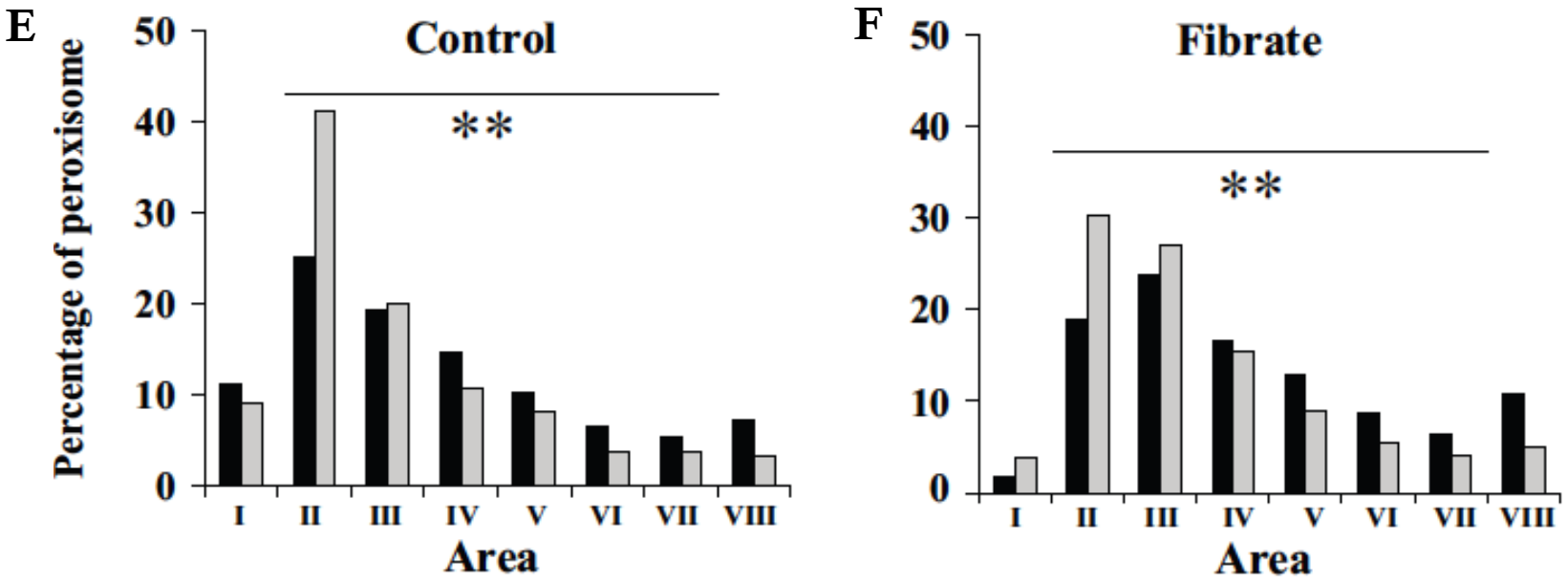


Schrader M… Gould SJ – *J Biol Chem* 1998

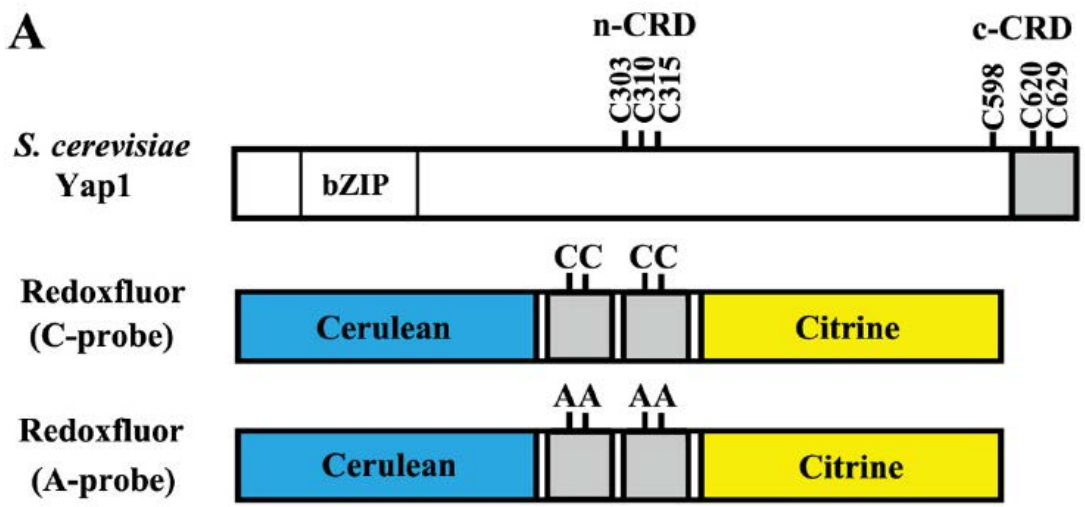
Les souris *Pex11α*$^{-/-}$ développent une stéatose hépatique.



Weng H… Iwai N – *Am J Physiol Endocrinol Metab* 2013

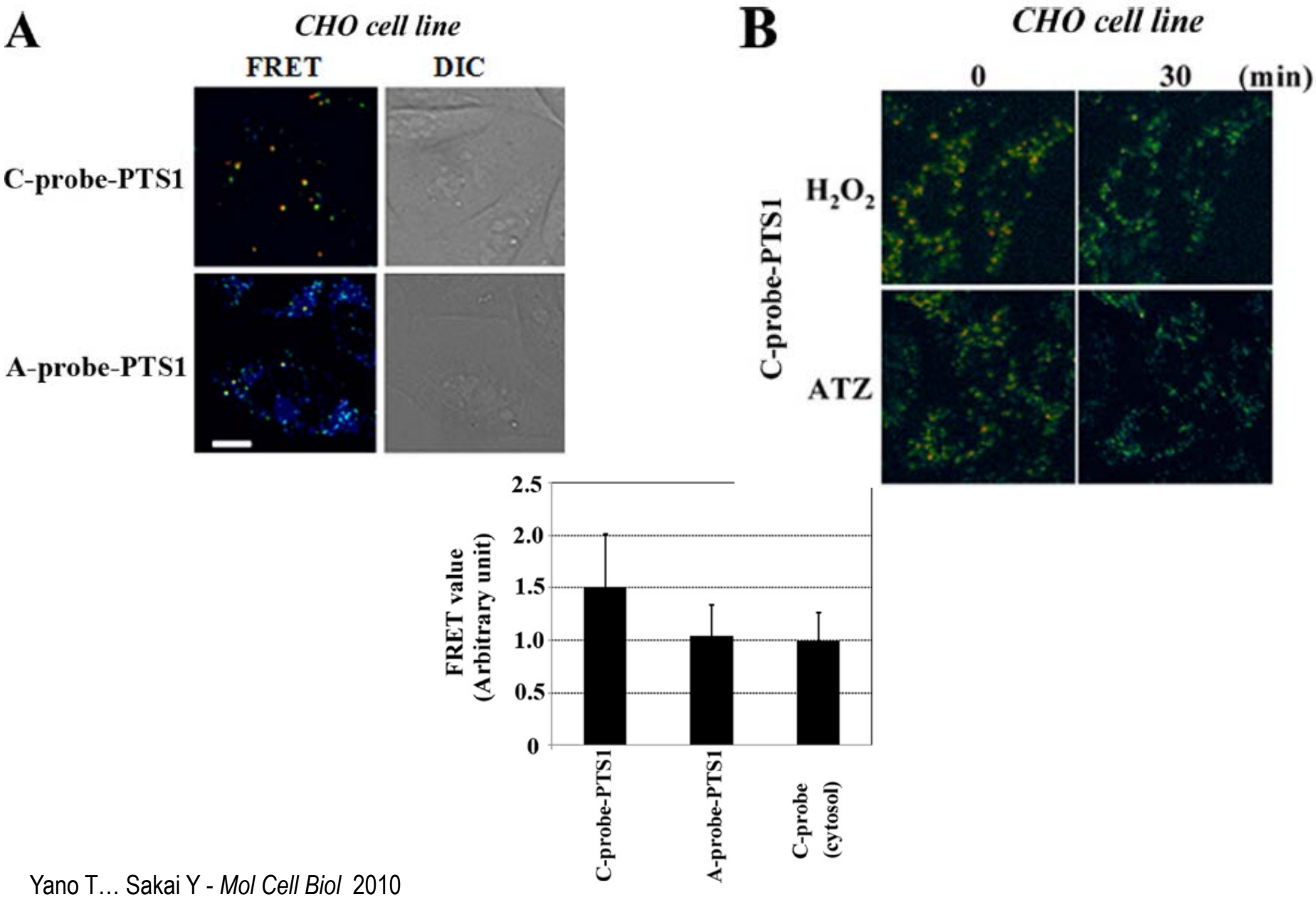


Weng H… Iwai N – *Am J Physiol Endocrinol Metab* 2013



Yano T… Sakai Y - *Mol Cell Biol* 2010

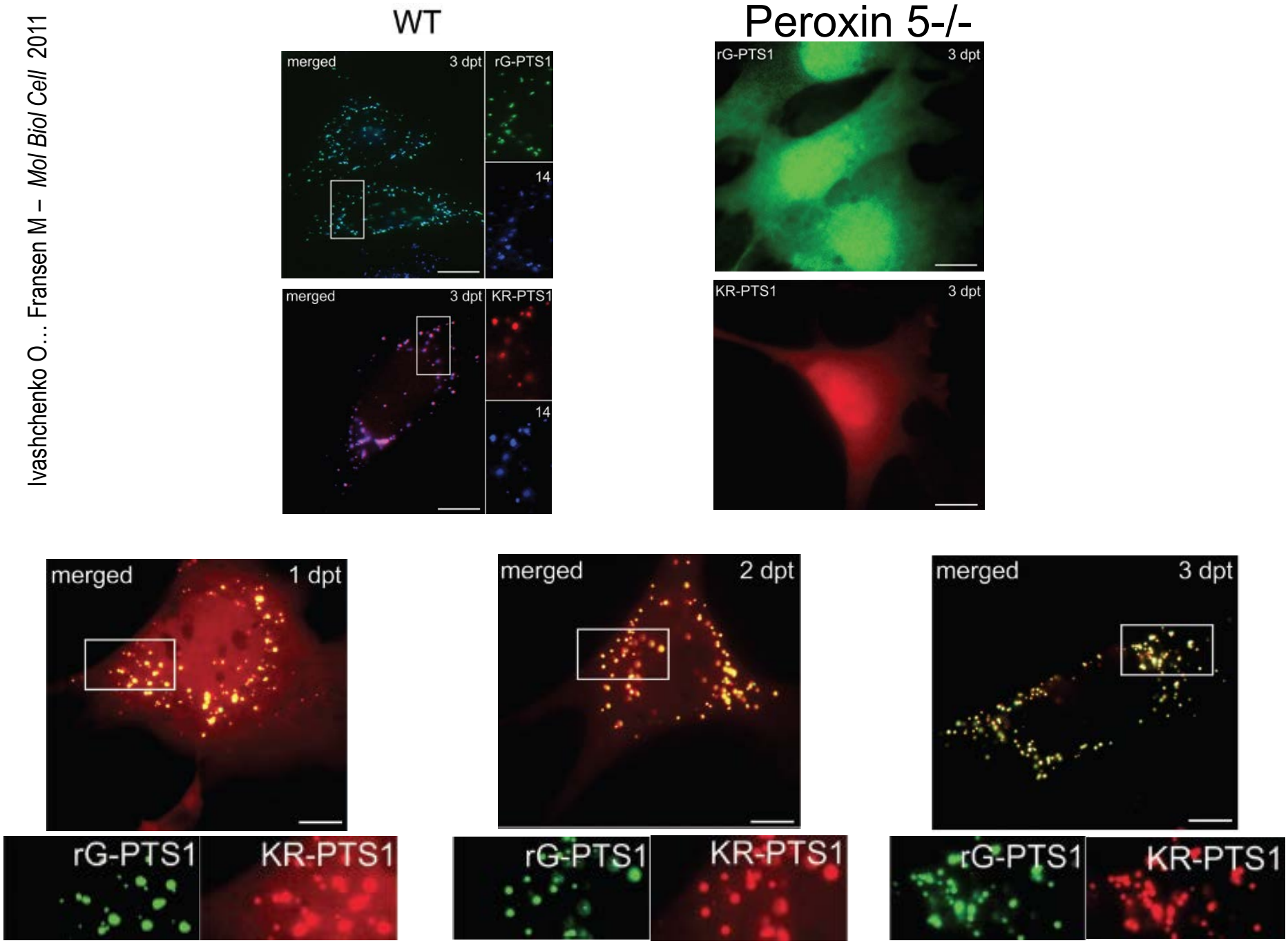
Ciblage de la sonde Redoxfluor dans les peroxysomes



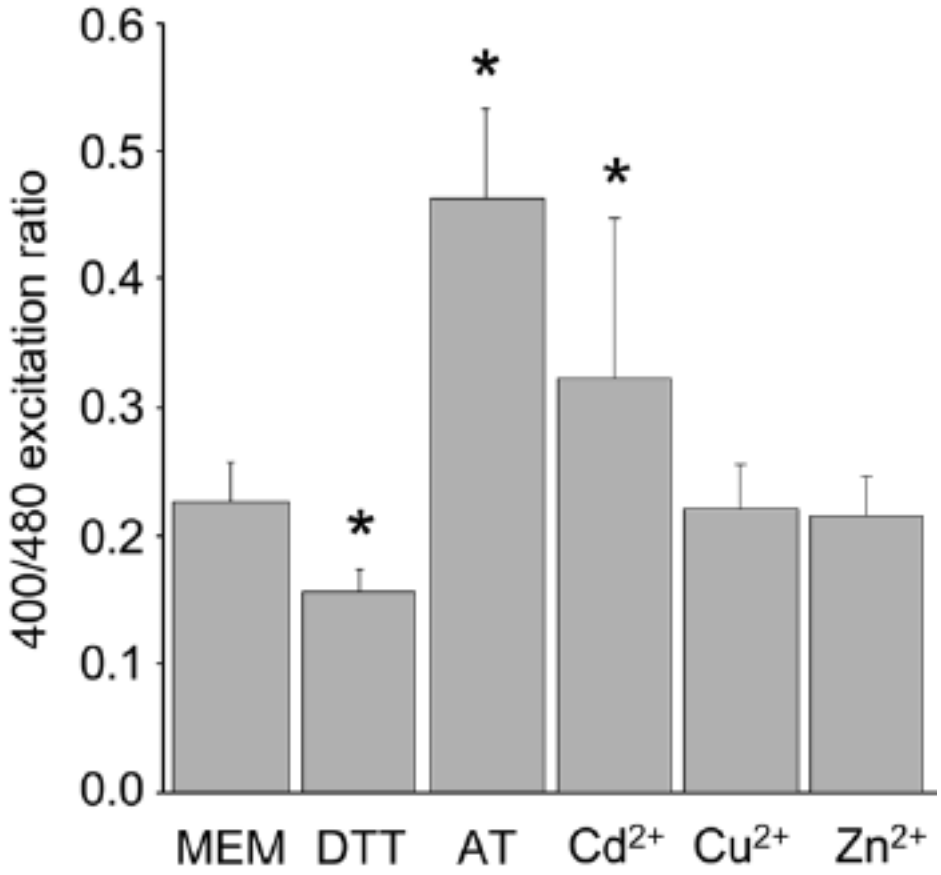
Yano T… Sakai Y - *Mol Cell Biol* 2010

roGFP2-PTS1 et KillerRed-PTS1.

Ivashchenko O… Fransen M – *Mol Biol Cell* 2011



roGFP2-PTS1 et oxydants/anti-oxydants



Ivashchenko O… Fransen M – *Mol Biol Cell* 2011

Le peroxysome: senseur redox

- **Prolifération**: peroxine 11p, 1ère cible redox identifiée

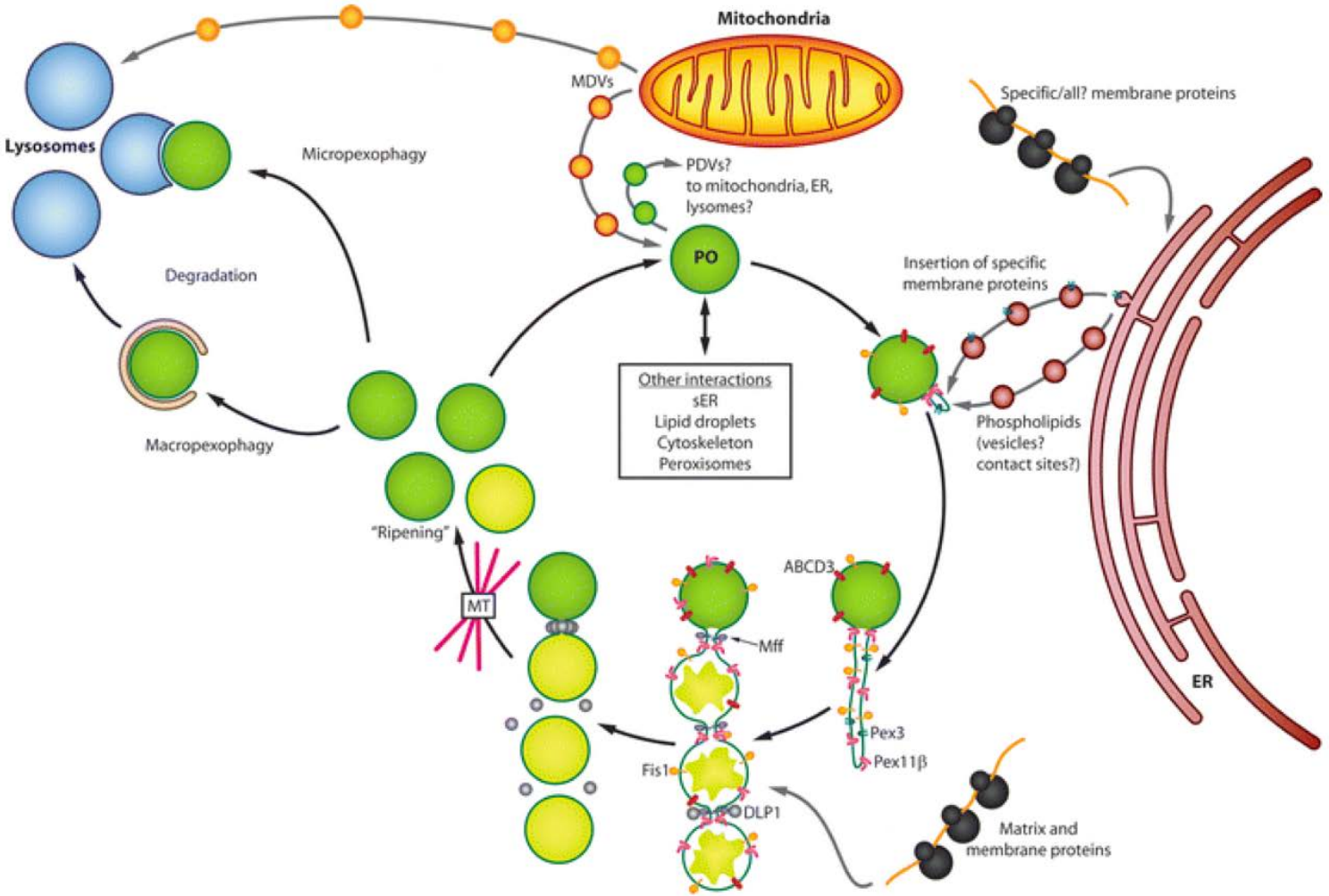
Redox-sensitive Homodimerization of Pex11p: A Proposed Mechanism to Regulate Peroxisomal Division

Pamela A. Marshall, John M. Dyer, Mary E. Quick, and Joel M. Goodman

University of Texas Southwestern Medical Center, Dallas.

Abstract. Pex11p (formerly Pmp27) has been implicated in peroxisomal proliferation (Erdmann, R., and G. Blobel. 1995. *J. Cell Biol.* 128: 509–523; Marshall, P.A., Y.I. Krimkevich, R.H. Lark, J.M. Dyer, M. Veenhuis, and J.M. Goodman. 1995. *J. Cell Biol.* 129: 345–355). In its absence, peroxisomes in *Saccharomyces cerevisiae* fail to proliferate in response to oleic acid; instead, one or two large peroxisomes are formed. Conversely, overproduction of Pex11p causes an increase in peroxisomal number. In this report, we confirm the function of Pex11p in organelle proliferation by demonstrating that this protein can cause fragmentation in vivo of large peroxisomes into smaller organelles. Pex11p is on the inner surface of the peroxisomal membrane. It can form homodimers, and this species is more abundant in mature peroxisomes than in proliferating organelles. Removing one of the three cysteines in the protein inhibits homodimerization. This cysteine 3 → alanine mutation leads to an increase in number and a decrease in peroxisomal density, compared with the wild-type protein, in response to oleic acid. We propose that the active species is the "monomeric" form, and that the increasing oxidative metabolism within maturing peroxisomes causes dimer formation and inhibition of further organelle division.

The Journal of Cell Biology.
Volume 135, Number 1, October 1996 123–137



REDOX SENSIBLE

Model of peroxisome dynamics and interactions in mammalian cells.

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

Le peroxysome: senseur redox

- **Prolifération**: peroxine 11p, 1ère cible redox identifiée

- **Biogenèse:** glutathion peroxydase-1, peroxirédoxine 5

Involvement of glutathione peroxidase 1 in growth and peroxisome formation in *Saccharomyces cerevisiae* in oleic acid medium

Takumi Ohdate [a,b], Yoshiharu Inoue [a,*]

Graduate School of Agriculture, Kyoto University

Saccharomyces cerevisiae is able to use some fatty acids, such as oleic acid, as a sole source of carbon. β-oxidation, which occurs in a single membrane-enveloped organelle or peroxisome, is responsible for the assimilation of fatty acids. In *S. cerevisiae*, β-oxidation occurs only in peroxisomes, and H_2O_2 is generated during this fatty acid-metabolizing pathway. *S. cerevisiae* has three *GPX* genes (*GPX1*, *GPX2*, and *GPX3*) encoding atypical 2-Cys peroxiredoxins. Here we show that expression of *GPX1* was induced in medium containing oleic acid as a carbon source in an Msn2/Msn4-dependent manner. We found that Gpx1 was located in the peroxisomal matrix. The peroxisomal Gpx1 showed peroxidase activity using thioredoxin or glutathione as a reducing power. Peroxisome biogenesis was induced when cells were cultured with oleic acid. Peroxisome biogenesis was impaired in *gpx1*Δ cells, and subsequently, the growth of *gpx1*Δ cells was lowered in oleic acid-containing medium. Gpx1 contains six cysteine residues. Of the cysteine-substituted mutants of Gpx1, $Gpx1^{C36S}$ was not able to restore growth and peroxisome formation in oleic acid-containing medium, therefore, redox regulation of Gpx1 seems to be involved in the mechanism of peroxisome formation.

Biochimica et Biophysica Acta 1821 (2012) 1295–1305

Absence of the peroxiredoxin Pmp20 causes peroxisomal protein leakage and necrotic cell death

Eda Bener Aksam [a], Helmut Jungwirth [b], Sepp D. Kohlwein [b], Julia Ring [b], Frank Madeo [b], Marten Veenhuis [a,c], Ida J. van der Klei [a,c,*]

Molecular Cell Biology, Groningen Biomolecular Sciences and Biotechnology Institute, University of Groningen, Haren, The Netherlands
Institute of Molecular Biosciences, University of Graz, 8010 Graz, Austria

We analyzed the role of the peroxisomal peroxiredoxin Pmp20 of the yeast *Hansenula polymorpha*. Cells of a *PMP20* disruption strain (*pmp20*) grew normally on substrates that are not metabolized by peroxisomal enzymes, but showed a severe growth defect on methanol, the metabolism of which involves a hydrogen peroxide producing peroxisomal oxidase. This growth defect was paralleled by leakage of peroxisomal matrix proteins into the cytosol. Methanol-induced *pmp20* cells accumulated enhanced levels of reactive oxygen species and lipid peroxidation products. Moreover, the fatty acid composition of methanol-induced *pmp20* cells differed relative to WT controls, suggesting an effect on fatty acid homeostasis. Plating assays and FACS-based analysis of cell death markers revealed that *pmp20* cells show loss of clonogenic efficiency and membrane integrity, when cultured on methanol. We conclude that the absence of the peroxisomal peroxiredoxin leads to loss of peroxisome membrane integrity and necrotic cell death.

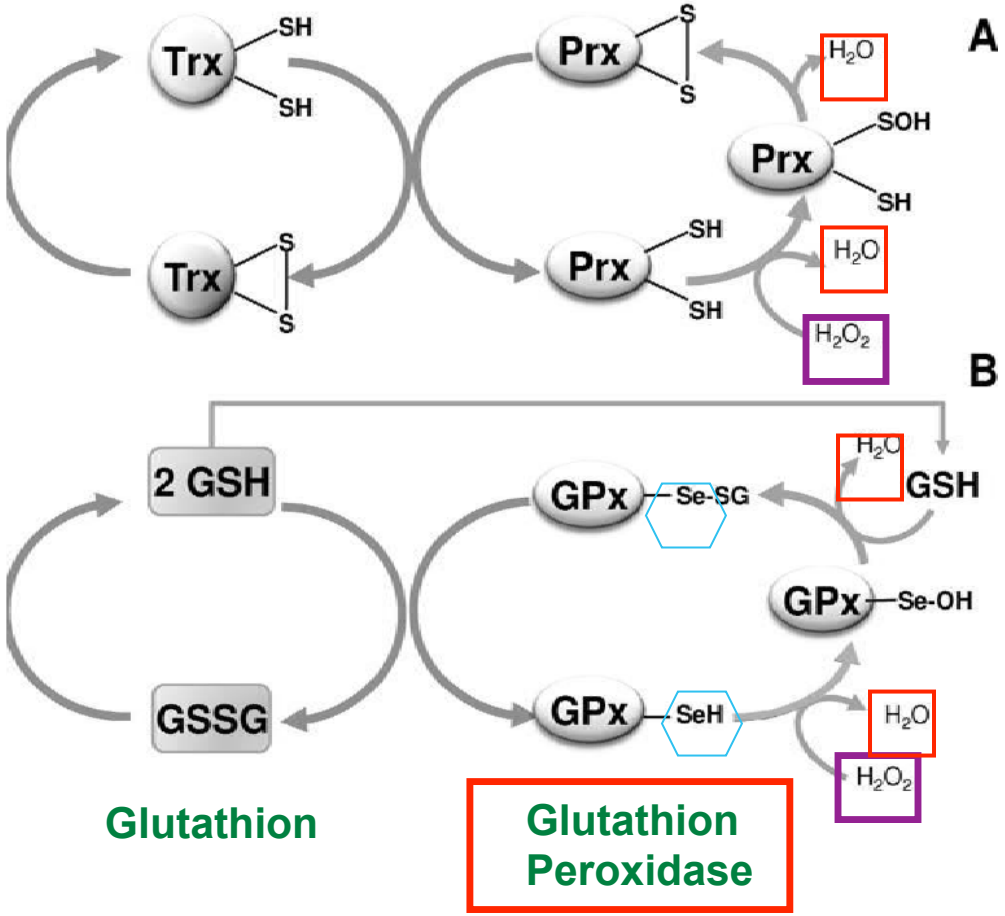
Free Radical Biology & Medicine 45 (2008) 1115–1124

REDUIRE H_2O_2 en H_2O (anti-oxydants)

catalase

$$2H_2O_2 \longrightarrow 2H_2O + O_2$$

Thioredoxin **Peroxiredoxin**



Glutathion **Glutathion Peroxidase**

Bindoli A… Forman HJ - *Antioxid Redox Signal* 2008

Le peroxysome: senseur redox

- **Prolifération**: peroxine 11p, 1ère cible redox identifiée

- **Biogenèse:** glutathion peroxydase-1, peroxirédoxine 5

- **Importation des protéines matricielles:** peroxine-5

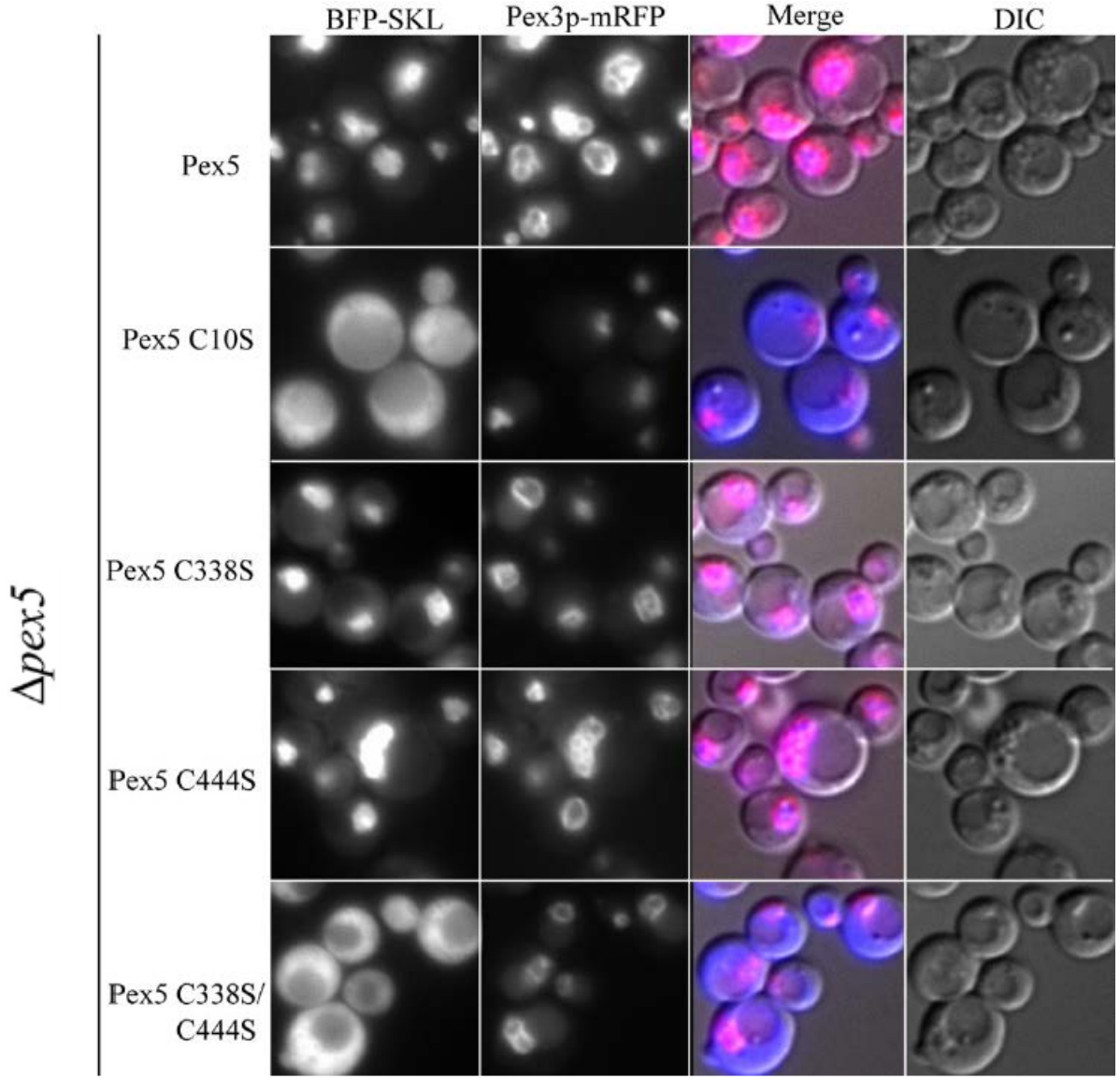
Redox-regulated Cargo Binding and Release by the Peroxisomal Targeting Signal Receptor, Pex5*

Changle Ma[1], Danielle Hagstrom, Soumi Guha Polley, and Suresh Subramani[2]

Background: Pex5 transports PTS1 proteins to peroxisomes, releases them there, and returns to the cytosol.
Results: Several steps of the import cycle are controlled by redox-sensitive oligomeric states of Pex5.
Conclusion: Cargo release from Pex5 is achieved by a redox-regulated oligomer to dimer transition of Pex5 and aided by Pex8.
Significance: This redox regulation of Pex5 function provides the first mechanistic view of cargo release.

From the Section of Molecular Biology, Division of Biological Sciences, University California, San Diego, La Jolla, California 92093-0322

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 288, NO. 38, pp. 27220–27231, September 20, 2013



Ma C… Subramani S -
J Biol Chem 2013

Le peroxysome: senseur redox

- **Prolifération**: peroxine 11p, 1ère cible redox identifiée

- **Biogenèse:** glutathion peroxydase-1, peroxirédoxine 5

- **Importation des protéines matricielles:** peroxine-5

- **Activité de certaines enzymes**: 3-Ketoacyl-CoA thiolase

The Crystal Structure of a Plant 3-Ketoacyl-CoA Thiolase Reveals the Potential for Redox Control of Peroxisomal Fatty Acid β-Oxidation

Ramasubramanian Sundaramoorthy[1], Elena Micossi[1,2]
Magnus S. Alphey[1], Véronique Germain[3], James H. Bryce[4]
Steve M. Smith[5], Gordon A. Leonard[2] and William N. Hunter[1]

Dundee Edinburgh UK *Grenoble Cedex, France Villenave d'Ornon* *Crawley Australia*

J. Mol. Biol. (2006) **359**, 347–357

Peroxisomal Plant 3-Ketoacyl-CoA Thiolase Structure and Activity Are Regulated by a Sensitive Redox Switch*[S]

Valerie E. Pye‡[1], Caspar E. Christensen‡, James H. Dyer§, Susan Arent‡[2], and Anette Henriksen‡[3]

Valby, Denmark

THE JOURNAL OF BIOLOGICAL CHEMISTRY
VOL. 285, NO. 31, pp. 24078–24088, July 30, 2010

Le peroxysome: senseur redox

- **Prolifération**: peroxine 11p, 1ère cible redox identifiée

- **Biogenèse:** glutathion peroxydase-1, peroxirédoxine 5

- **Importation des protéines matricielles:** peroxine-5

- **Activité de certaines enzymes**: 3-Ketoacyl-CoA thiolase

-**Ubiquitination: dégradation ou transport des protéines du peroxysome ?:** peroxine-5 (PTS-1), peroxine 18p (PTS-2) (via Pex7) cysteine

Peroxisome Senescence in Human Fibroblasts

Julie E. Legakis,* Jay I. Koepke,* Chris Jedeszko,† Ferdous Barlaskar,* Laura J. Terlecky,* Holly J. Edwards,* Paul A. Walton,† and Stanley R. Terlecky*‡

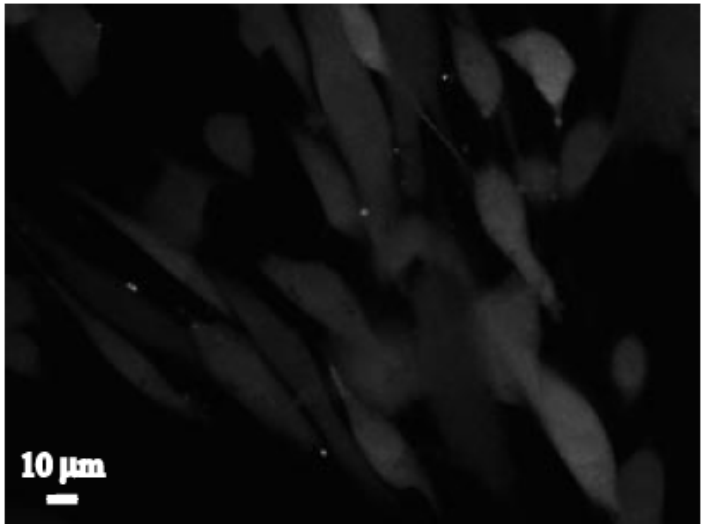
*Department of Pharmacology, Wayne State University School of Medicine, Detroit, Michigan 48201, and †Department of Anatomy and Cell Biology, University of Western Ontario, London, Ontario,

The molecular mechanisms of peroxisome biogenesis have begun to emerge; in contrast, relatively little is known about how the organelle functions as cells age. In this report, we characterize age-related changes in peroxisomes of human cells. We show that aging compromises peroxisomal targeting signal 1 (PTS1) protein import, affecting in particular the critical antioxidant enzyme catalase. The number and appearance of peroxisomes are altered in these cells, and the organelles accumulate the PTS1-import receptor, Pex5p, on their membranes. Concomitantly, cells produce increasing amounts of the toxic metabolite hydrogen peroxide, and we present evidence that this increased load of reactive oxygen species may further reduce peroxisomal protein import and exacerbate the effects of aging.

Molecular Biology of the Cell

Vol. 13, 4243–4255, December 2002

E



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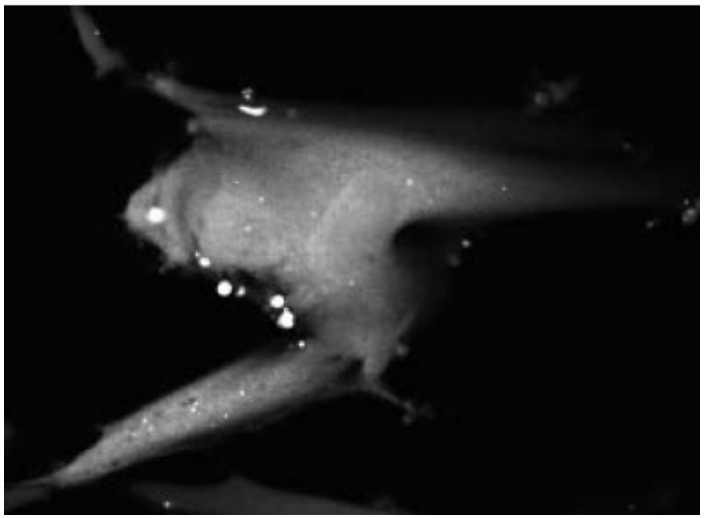
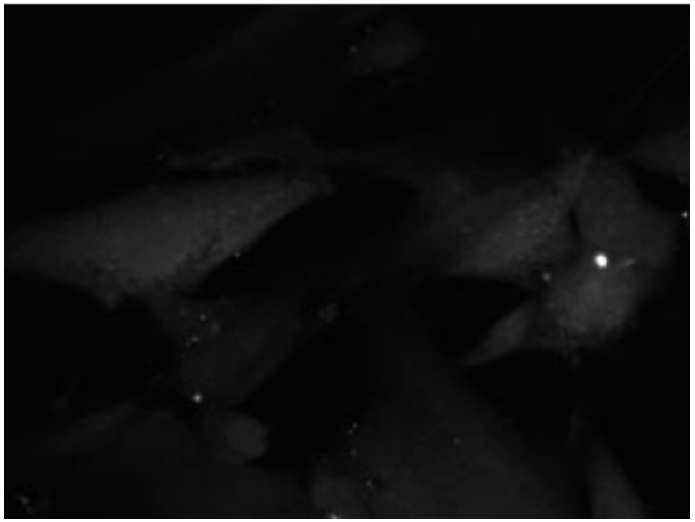
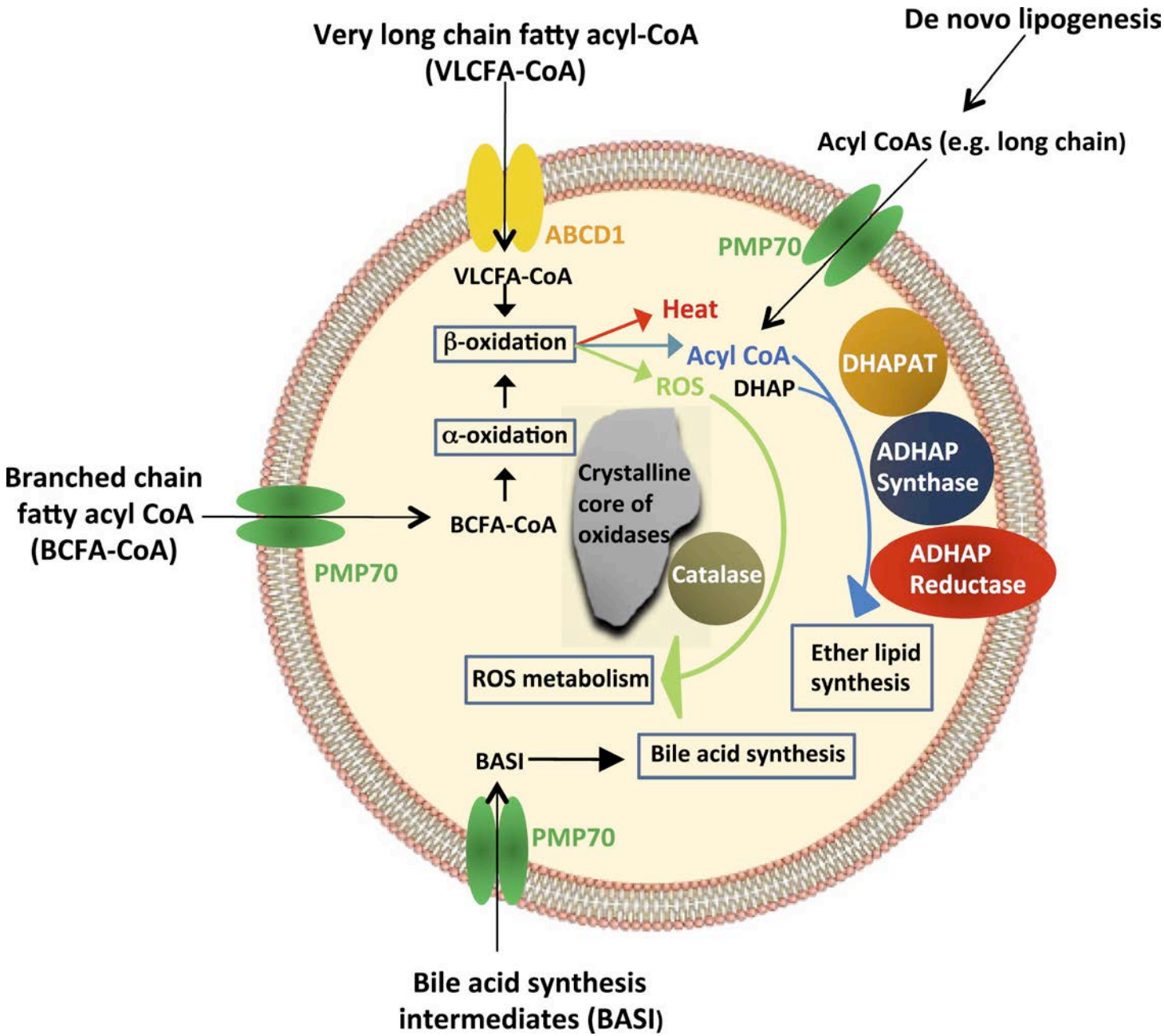


M



Legakis JE… Terlecky SR – *Mol Biol Cell* 2002

Maladies liées aux peroxysomes



Lodhi IJ & Semenkovich CF – *Cell Metab* 2014

Human brain peroxisome deficiencies and their pathologies

Disease	Peroxisome biogenesis disorders (PBD)				Single peroxisomal enzyme deficiency						
	Zellweger syndrome spectrum			RCDP type 1	X-ALD	PNALD	DBP deficiency	AMACR deficiency	Refsum disease	RCDP type 2	RCDP type 3
	ZS	NALD	IRD								
OMIM				215100	300100	264470	261515	614307	266500	222765	600121
Gene defect	*PEX 1,2,3,5,6,10,12, 13, 14,16,19 or 26*	*PEX 1,5,6,10, 12, 13, or 26*	*PEX 1,2,12 or 26*	*PEX 7*	*ABCD1*	*ACOX1*	*HSD17B4*	*AMACR*	*PHYH*	*GNPAT*	*AGPS*
Peroxisomes	Absence (or "ghost")	Absence (or "ghost")	Absence (or "ghost")	+	+	+ (abnormal)	+ (abnormal)	+	+	+	+
Clinical features											
Hypotonia	+	+	+	+		+	+			+	+
Craniofacial dysmorphy	+	+	+	+		+	+			+	+
Skeletal defect	+	+	+	+		+	+		+	+	+
Growth retardation	+	+	+	+		+	+			+	+
Mental retardation	+	+	+	+	+/−	+	+	+/−		+	+
Spasticity	+	+	+	+	+	+	+	+		+	+
Seizure	+	+	+	+	+	+	+	+		+	+
Retinopathy/vision failure	+	+	+	+	+	+		+	+	+	+
Hearing failure	+	+	+		+	+			+	+	+
Anosmia									+		
Neurological abnormalities											
Brain development											
Cortex malformation	+	+	+	+		+	+	+			
Neuronal migration defect	+	+	+	+			+				
Cerebellum malformation	+	+	+	+			+	+	+		
Brain degeneration											
Leukodystrophy	+	+	+		+	+	+	+/−			
Peripheral neuropathy	+	+	+		+/−	+	+	+	+		
Biochemical features											
Ether lipids (plasmalogens) ↓	+	+	+	+	+					+	+
DHA ↓	+	+	+	+		+					
VLCFA ↑	+	+	+		+	+	+				
Branched-chain fatty acids ↑	+	+	+	+		+	+	+	+		
Bile-acid intermediates ↑	+	+	+				+	+			
	Multiple impaired metabolic pathways				Impaired β-oxidation				Impaired α-oxidation	Impaired ether lipid biosynthesis	
Survival (-year-old)	<1	<10	Up to adulthood	<10	<10	<5	<2		Normal (under diet)	<10	<10
Approximative onset	Newborn[a]	Newborn[a]	Newborn[a]	Newborn[a]	Childhood	Newborn[a]	Newborn[a]	Adulthood	Childhood	Childhood[b]	Childhood[b]

Trompier D… Lizard G - *Biochimie* 2014

Disease	Peroxisome biogenesis disorders (PBD)			
	Zellweger syndrome spectrum			RCDP type 1
	ZS	NALD	IRD	
OMIM				215100
Gene defect	*PEX 1,2,3,5,6,10,12, 13, 14,16,19 or 26*	*PEX 1,5,6,10, 12, 13, or 26*	*PEX 1,2,12 or 26*	*PEX 7*
Peroxisomes	Absence (or "ghost")	Absence (or "ghost")	Absence (or "ghost")	+
Clinical features				
Hypotonia	+	+	+	+
Craniofacial dysmorphy	+	+	+	+
Skeletal defect	+	+	+	+
Growth retardation	+	+	+	+
Mental retardation	+	+	+	+
Spasticity	+	+	+	+
Seizure	+	+	+	+
Retinopathy/vision failure	+	+	+	+
Hearing failure	+	+	+	
Anosmia				
Neurological abnormalities				
Brain development				
Cortex malformation	+	+	+	+
Neuronal migration defect	+	+	+	+
Cerebellum malformation	+	+	+	+
Brain degeneration				
Leukodystrophy	+	+	+	
Peripheral neuropathy	+	+	+	
Biochemical features				
Ether lipids (plasmalogens) ↓	+	+	+	+
DHA ↓	+	+	+	+
VLCFA ↑	+	+	+	
Branched-chain fatty acids ↑	+	+	+	+
Bile-acid intermediates ↑	+	+	+	
	Multiple impaired metabolic pathways			
Survival (-year-old)	<1	<10	Up to adulthood	<10
Approximative onset	Newborn[a]	Newborn[a]	Newborn[a]	Newborn[a]

ZF= syndrome de Zellweger

NALD =adrénoleucodystrophie néonatale

IRD= maladie de Refsum infantile

RCDP type I: chondrodysplasie ponctuée rhizomélique de type 1

Trompier D... Lizard G - *Biochimie* 2014

	Single peroxisomal enzyme deficiency						
OMIM Gene defect	X-ALD	PNALD	DBP deficiency	AMACR deficiency	Refsum disease	RCDP type 2	RCDP type 3
Peroxisomes							
	300100 *ABCD1*	264470 *ACOX1*	261515 *HSD17B4*	614307 *AMACR*	266500 *PHYH*	222765 *GNPAT*	600121 *AGPS*
Clinical features							
Hypotonia	+	+ (abnormal)	+ (abnormal)	+	+	+	+
Craniofacial dysmorphy							
Skeletal defect							
Growth retardation		+	+			+	+
Mental retardation		+	+			+	+
Spasticity		+	+		+	+	+
Seizure		+	+			+	+
Retinopathy/vision failure	+/−	+	+	+/−		+	+
Hearing failure	+	+	+	+		+	+
Anosmia	+	+	+	+		+	+
	+	+		+	+	+	+
Neurological abnormalities	+	+			+	+	+
Brain development					+		
Cortex malformation							
Neuronal migration defect							
Cerebellum malformation		+	+	+			
			+				
Brain degeneration			+	+	+		
Leukodystrophy							
Peripheral neuropathy	+	+	+	+/−			
Biochemical features	+/−	+	+	+	+		
Ether lipids (plasmalogens) ↓							
DHA ↓	+					+	+
VLCFA ↑		+					
Branched-chain fatty acids ↑	+	+	+				
Bile-acid intermediates ↑		+	+	+	+		
			+	+			
	Impaired β-oxidation				Impaired α-oxidation	Impaired ether lipid biosynthesis	
Survival (-year-old)	<10	<5	<2		Normal (under diet)	<10	<10
Approximative onset	Childhood	Newborn[a]	Newborn[a]	Adulthood	Childhood	Childhood[b]	Childhood[b]

Human brain peroxisome deficiencies and their pathologies

Disease	Peroxisome biogenesis disorders (PBD)				Single peroxisomal enzyme deficiency						
	Zellweger syndrome spectrum			RCDP type 1	X-ALD	PNALD	DBP deficiency	AMACR deficiency	Refsum disease	RCDP type 2	RCDP type 3
	ZS	NALD	IRD								
OMIM				215100	300100	264470	261515	614307	266500	222765	600121
Gene defect	*PEX 1,2,3,5,6,10,12, 13, 14,16,19 or 26*	*PEX 1,5,6,10, 12, 13, or 26*	*PEX 1,2,12 or 26*	*PEX 7*	*ABCD1*	*ACOX1*	*HSD17B4*	*AMACR*	*PHYH*	*GNPAT*	*AGPS*
Peroxisomes	Absence (or "ghost")	Absence (or "ghost")	Absence (or "ghost")	+	+	+ (abnormal)	+ (abnormal)	+	+	+	+
Clinical features											
Hypotonia	+	+	+	+		+	+			+	+
Craniofacial dysmorphy	+	+	+	+		+	+			+	+
Skeletal defect	+	+	+	+		+	+		+	+	+
Growth retardation	+	+	+	+		+	+			+	+
Mental retardation	+	+	+	+	+/−	+	+	+/−		+	+
Spasticity	+	+	+	+	+	+	+	+		+	+
Seizure	+	+	+	+	+	+	+	+		+	+
Retinopathy/vision failure	+	+	+	+	+	+		+	+	+	+
Hearing failure	+	+	+		+	+			+	+	+
Anosmia									+		
Neurological abnormalities											
Brain development											
Cortex malformation	+	+	+	+		+	+	+			
Neuronal migration defect	+	+	+	+			+				
Cerebellum malformation	+	+	+	+			+	+	+		
Brain degeneration											
Leukodystrophy	+	+	+		+	+	+	+/−			
Peripheral neuropathy	+	+	+		+/−	+	+	+	+		
Biochemical features											
Ether lipids (plasmalogens) ↓	+	+	+	+	+					+	+
DHA ↓	+	+	+	+		+					
VLCFA ↑	+	+	+		+	+	+				
Branched-chain fatty acids ↑	+	+	+	+		+	+	+	+		
Bile-acid intermediates ↑	+	+	+				+	+			
	Multiple impaired metabolic pathways				Impaired β-oxidation				Impaired α-oxidation	Impaired ether lipid biosynthesis	
Survival (-year-old)	<1	<10	Up to adulthood	<10	<10	<5	<2		Normal (under diet)	<10	<10
Approximative onset	Newborn[a]	Newborn[a]	Newborn[a]	Newborn[a]	Childhood	Newborn[a]	Newborn[a]	Adulthood	Childhood	Childhood[b]	Childhood[b]

Trompier D… Lizard G - *Biochimie* 2014

Myelin peroxisomes – Essential organelles for the maintenance of white matter in the nervous system☆

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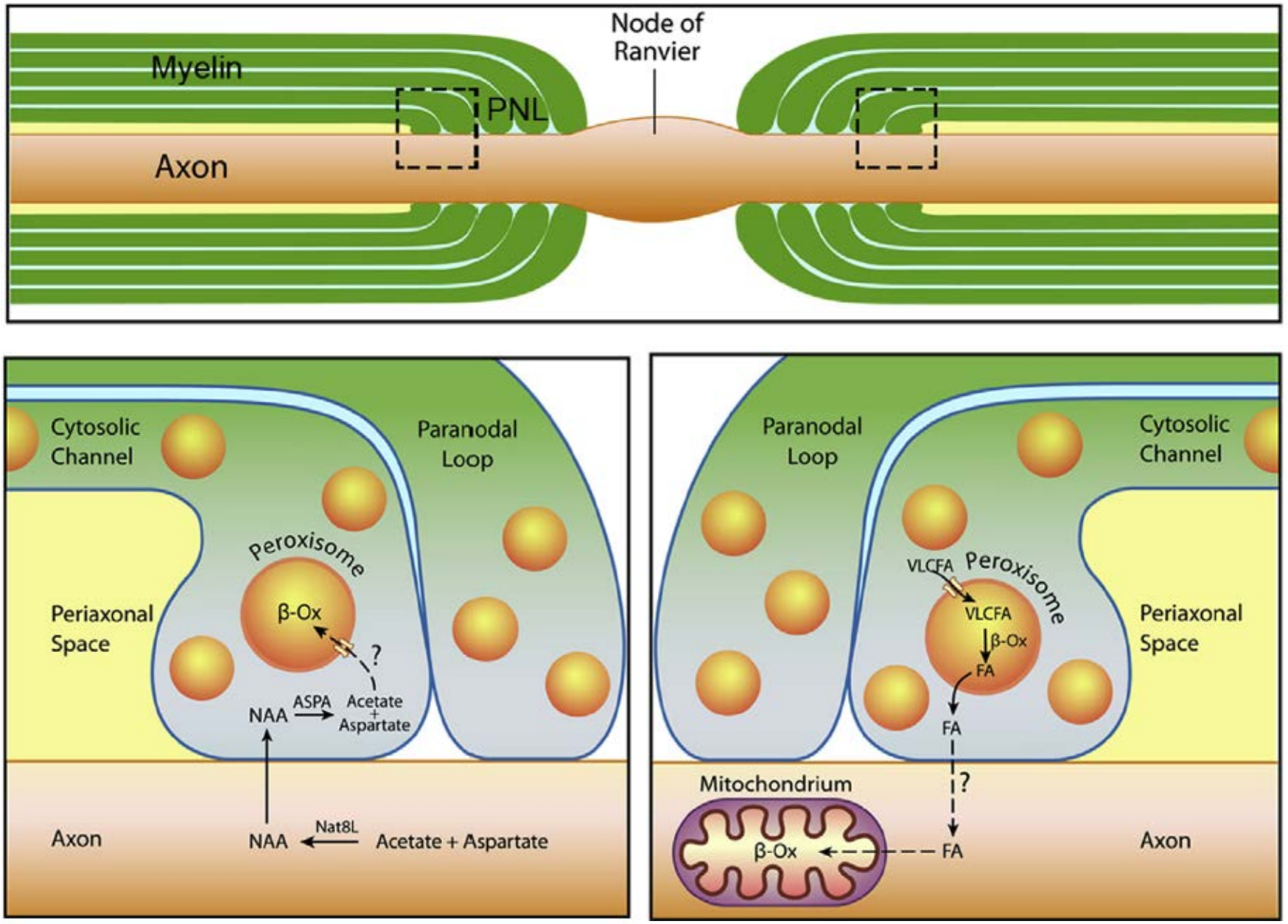
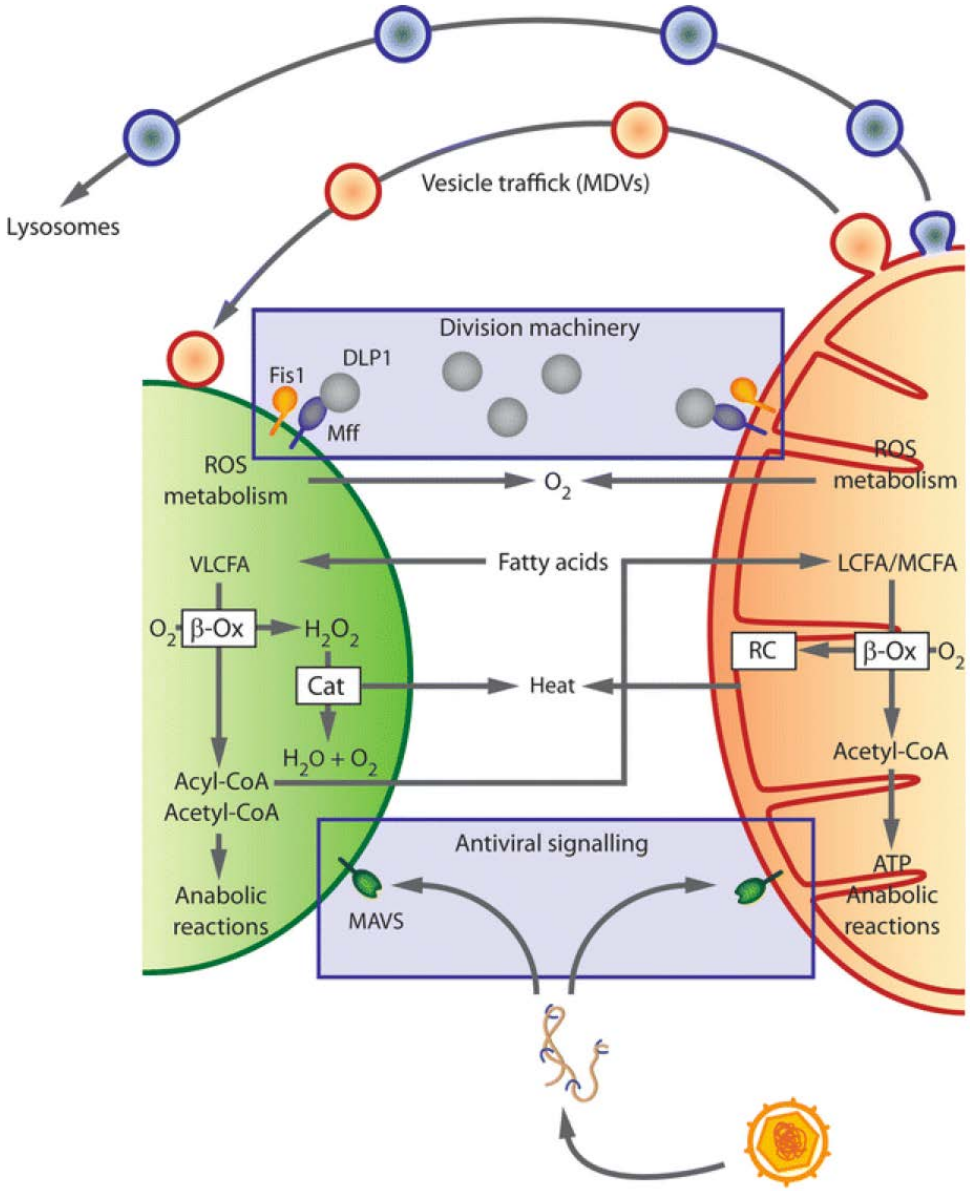
Peroxisomes are cellular compartments primarily associated with lipid metabolism. Most cell types, including nervous system cells, harbor several hundred of these organelles. The importance of peroxisomes for central nervous system white matter is evidenced by a variety of human peroxisomal disorders with neurological impairment frequently involving the white matter. Moreover, the most frequent childhood white matter disease, X-linked adrenoleukodystrophy, is a peroxisomal disorder. During the past decade advances in imaging techniques have enabled the identification of peroxisomes within the myelin sheath, especially close to nodes of Ranvier. Although the function of myelin peroxisomes is not solved yet on molecular level, recently acquired knowledge suggests a central role for these organelles in axo-glial metabolism. This review focuses on the biology of myelin peroxisomes as well as on the pathology of myelin and myelinated axons that is observed as a consequence of partial or complete peroxisomal dysfunction in the brain.

Biochimie 98 (2014) 111–118

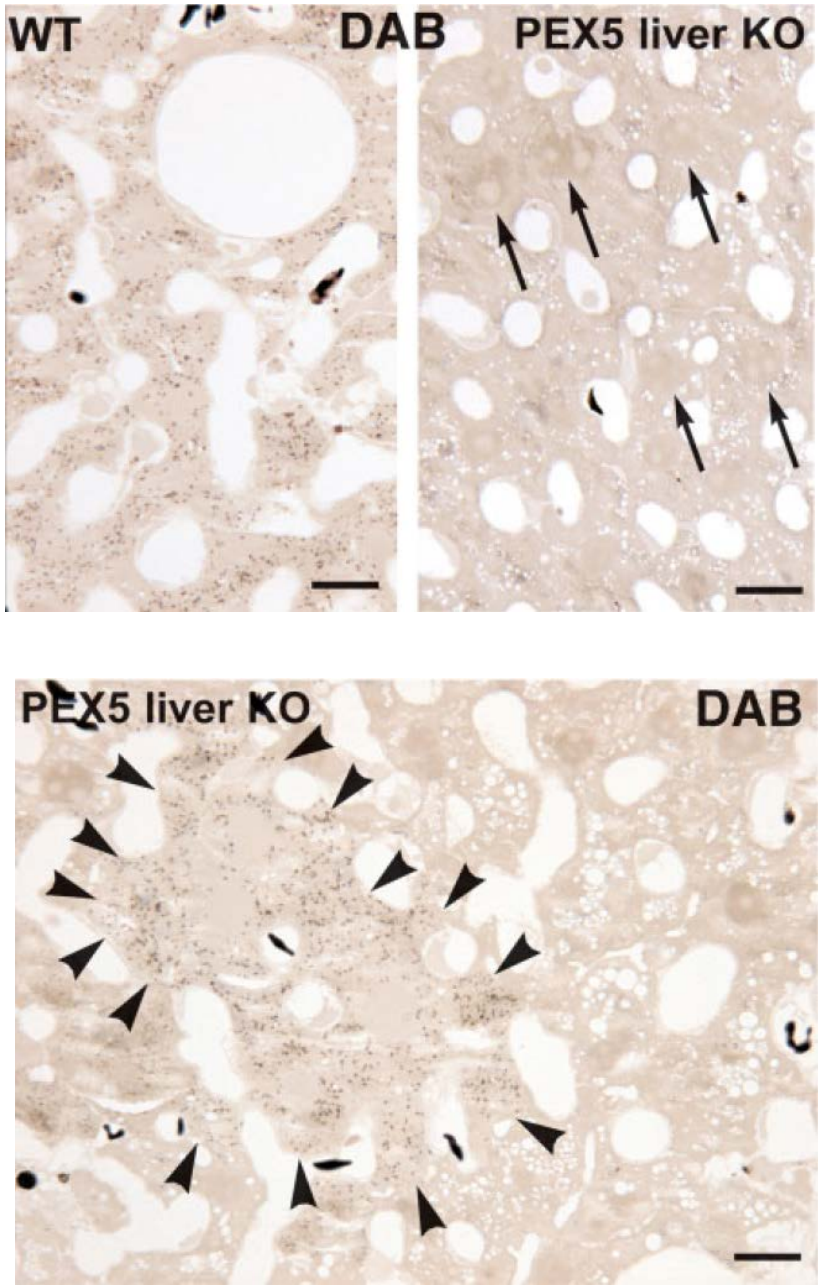


Kassmann CM - *Biochimie* 2014

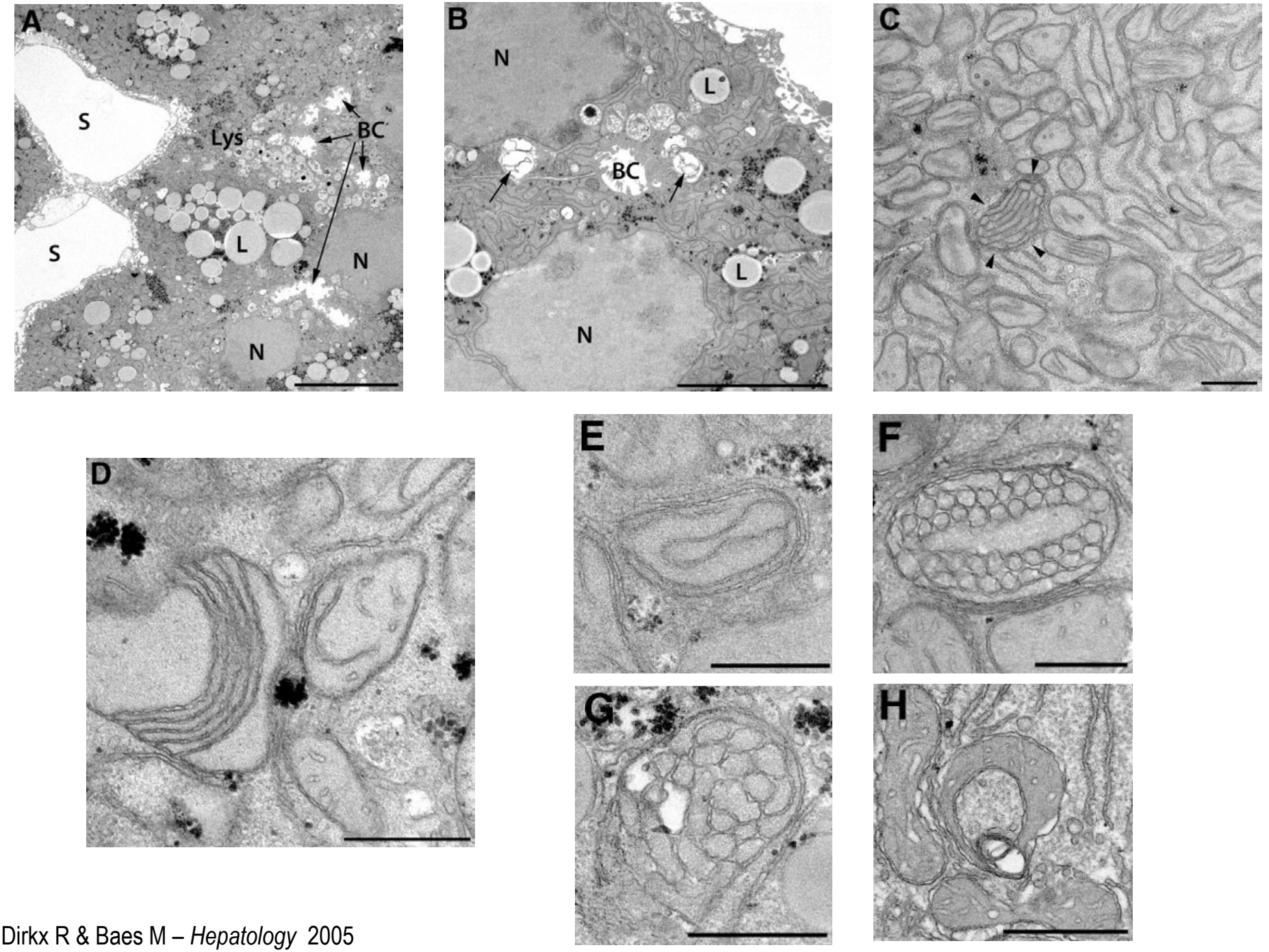


Interconnection between peroxisomes and mitochondria.

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



Dirkx R & Baes M – *Hepatology* 2005



Dirkx R & Baes M – *Hepatology* 2005

Plan du cours

I) Le peroxysome (suite)

- biogénèse des peroxysomes et contrôle de leur prolifération ;

- le peroxysome, senseur et effecteur du statut REDOX (biosenseurs)

- les maladies du peroxysome; ce que leur étude nous apprend sur les fonctions de cet organelle.

II) Prévention et traitement des atteintes auditives avec perturbation de l'homéostasie REDOX.

- la N-acétylcystéine.

- la prévention par le pré-conditionnement sonore (le rôle des protéines de choc thermique)

- la diète calorique: de sa voie de signalisation au resveratrol.

Thiol Redox Transitions in Cell Signaling: a Lesson from N-Acetylcysteine

Tiziana Parasassi[1,*], Roberto Brunelli[2], Graziella Costa[1], Marco De Spirito[3], Ewa K. Krasnowska[1], Thomas Lundeberg[4], Eugenia Pittaluga[1], and Fulvio Ursini[5]

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Università di Padova,

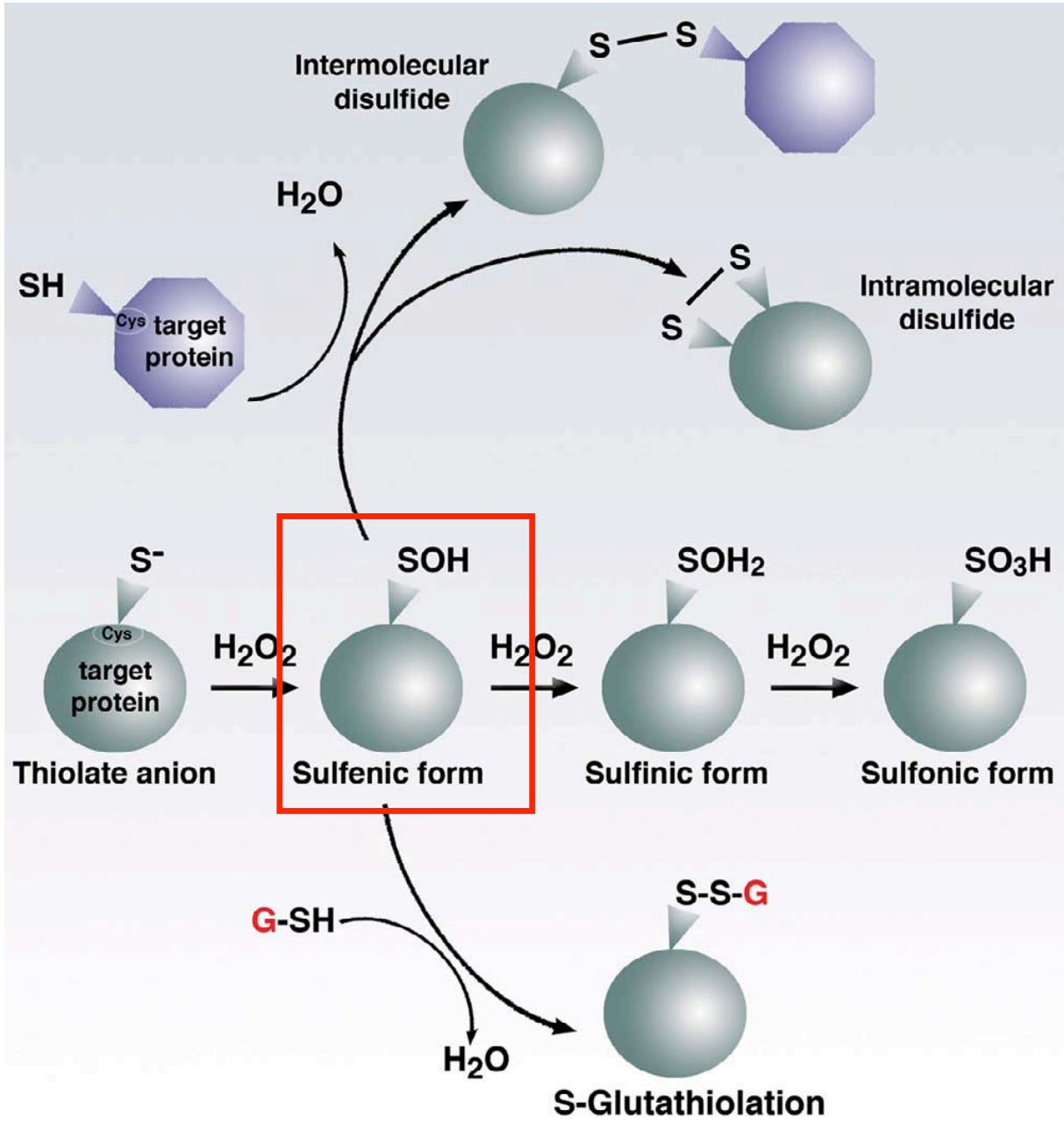
The functional status of cells is under the control of external stimuli affecting the function of critical proteins and eventually gene expression. Signal sensing and transduction by messengers to specific effectors operate by post-translational modification of proteins, among which thiol redox switches play a fundamental role that is just beginning to be understood. The maintenance of the redox status is, indeed, crucial for cellular homeostasis and its dysregulation towards a more oxidized intracellular environment is associated with aberrant proliferation, ultimately related to diseases such as cancer, cardiovascular disease, and diabetes. Redox transitions occur in sensitive cysteine residues of regulatory proteins relevant to signaling, their evolution to metastable disulfides accounting for the functional redox switch. N-acetylcysteine (NAC) is a thiol-containing compound that is able to interfere with redox transitions of thiols and, thus, in principle, able to modulate redox signaling. We here review the redox chemistry of NAC, then screen possible mechanisms to explain the effects observed in NAC-treated normal and cancer cells; such effects involve a modification of global gene expression, thus of functions and morphology, with a leitmotif of a switch from proliferation to terminal differentiation. The regulation of thiol redox transitions in cell signaling is, therefore, proposed as a new tool, holding promise not only for a deeper explanation of mechanisms, but indeed for innovative pharmacological interventions.

TheScientificWorldJOURNAL
(2010) 10, 1192–1202

Transitions REDOX pouvant impliquer la N-acétylcystéine (NAC)

1. NAC could be a free radical scavenger antioxidant. Although popular, this concept is extremely unlikely. NAC, in fact, does not fit the criteria to be a radical scavenger; in the presence of an oxidant-free radical, upon one-electron redox transition, the produced thiyl radical -S$^{\bullet}$ is still enough oxidant to propagate oxidative chain reactions. Moreover, the annihilating radical-radical interaction is limited by concentration of thiyl radicals and thus sulfur is just progressively oxidized[16].
2. NAC could directly reduce hydroperoxides in a nucleophilic displacement reaction. The criticism about this reaction resides in its low rate that renders it quite unlikely in a biological environment – as in the case of GSH[1]. Such a reaction will never compete with much more efficient removal of hydroperoxides by peroxidases, peroxiredoxins, and catalase.
3. NAC could be a substrate for GSH synthesis. Conflicting reports exist in the literature about a substantial GSH increase after NAC supplementation[17,18,19], which would lead to a lower redox potential of the GSSG/GSH couple. Moreover, an increase in the concentration of GSH, although changing the redox potential of the couple, would minimally, if at all, affect the actual concentration of hydrogen peroxide. This indeed depends on the nonreversible reaction of glutathione peroxidases, peroxiredoxins, and the related reductases and, eventually, on the continuous reduction of NADP from glucose oxidation. Thus, the option that an increase in GSH – due to NAC – could substantially affect the steady-state concentration of hydrogen peroxide through an increased activity of GSH peroxidases is extremely unlikely. Such a mechanism, instead, could be relevant only in cases of massive GSH depletion, such as in the peculiar case of the last phase of spermatogenesis[20]. The option of a nonenzymatic reaction of GSH is also already ruled out from the considerations in the previous point 2.
4. NAC could reduce protein disulfides. This is a possible mechanism of NAC action, although it has to compete with the much more efficient enzymatic systems encompassing thioredoxins and glutaredoxins, and the corresponding reductases (TrxR, GR). Nevertheless, also for these interactions, the key role is played by the specificity of protein-protein interactions kinetically driving the reaction. The option that NAC could reduce some specific disulfides sterically inaccessible to thioredoxins and glutaredoxins is therefore still open.
5. NAC could react with sulfenic acid derivatives in proteins. This event is chemically and biologically plausible. Notwithstanding that the "stable" sulfenic acid can only exist in hidden spots of the proteins, usually inaccessible to reducing substrates, the reactivity with NAC is still a reasonable option. Notably, this reaction would be in competition with GSH, but GSH accessibility is expected to be more limited than that of a small molecule such as NAC. When sulfenic acid derivatives are intermediates in the formation of intrachain or mixed disulfides, the reaction with NAC, in competition with the second thiol, would prevent the formation of the disulfide.

Parasassi T…Ursini F – *Scientific World J* 2010



Finkel T - *J Cell Biol* 2011

1 - **Prévenir la formation des espèces réactives de l'oxygène.**
Par la superoxyde dismutase, injectée par voie intra-péritonéale chez la souris (*Seidman MD, Shivapuja BG, Quirk WS 1993*)

2 - **Protéger par des antioxydants.**

- le plus puissant est le glutathion.

- les autres antioxydants sont le cuivre, le zinc, le manganèse, le sélénium, le fer (nécessaires à toutes les enzymes antioxydantes)

- les ubiquinones (production des ROS mais protège contre la peroxydation lipidique) et le cytochrome c (capte l'électron libre de l'anion superoxyde).

- la vitamine E (séquestre les radicaux libres) et la vitamine C (capte H_20_2 et OH)

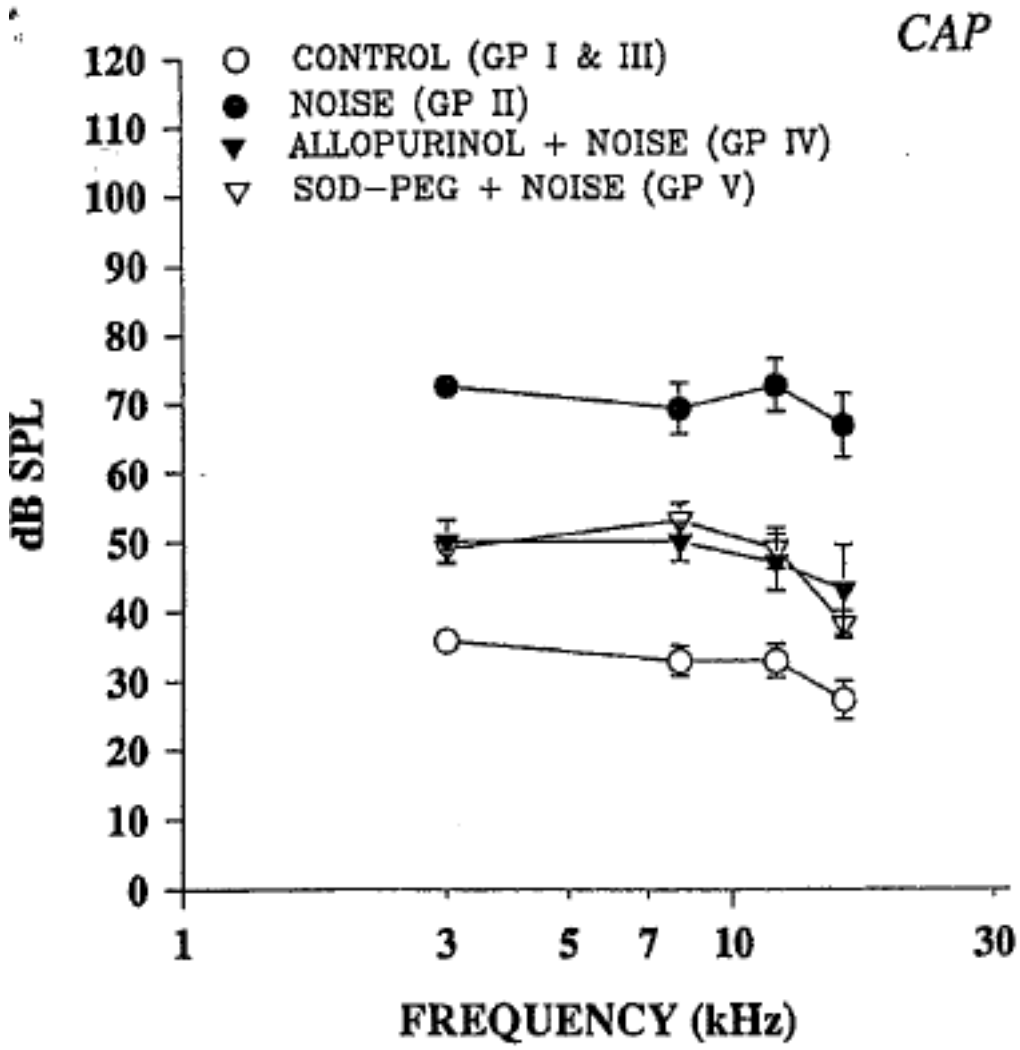
Les antioxydants de synthèse:

- N-acétylcystéine (association entre N-acétylcystéine (NAC) et alpha-phenyl-tert-butyl nitrone (HPN-O7)) et allopurinol

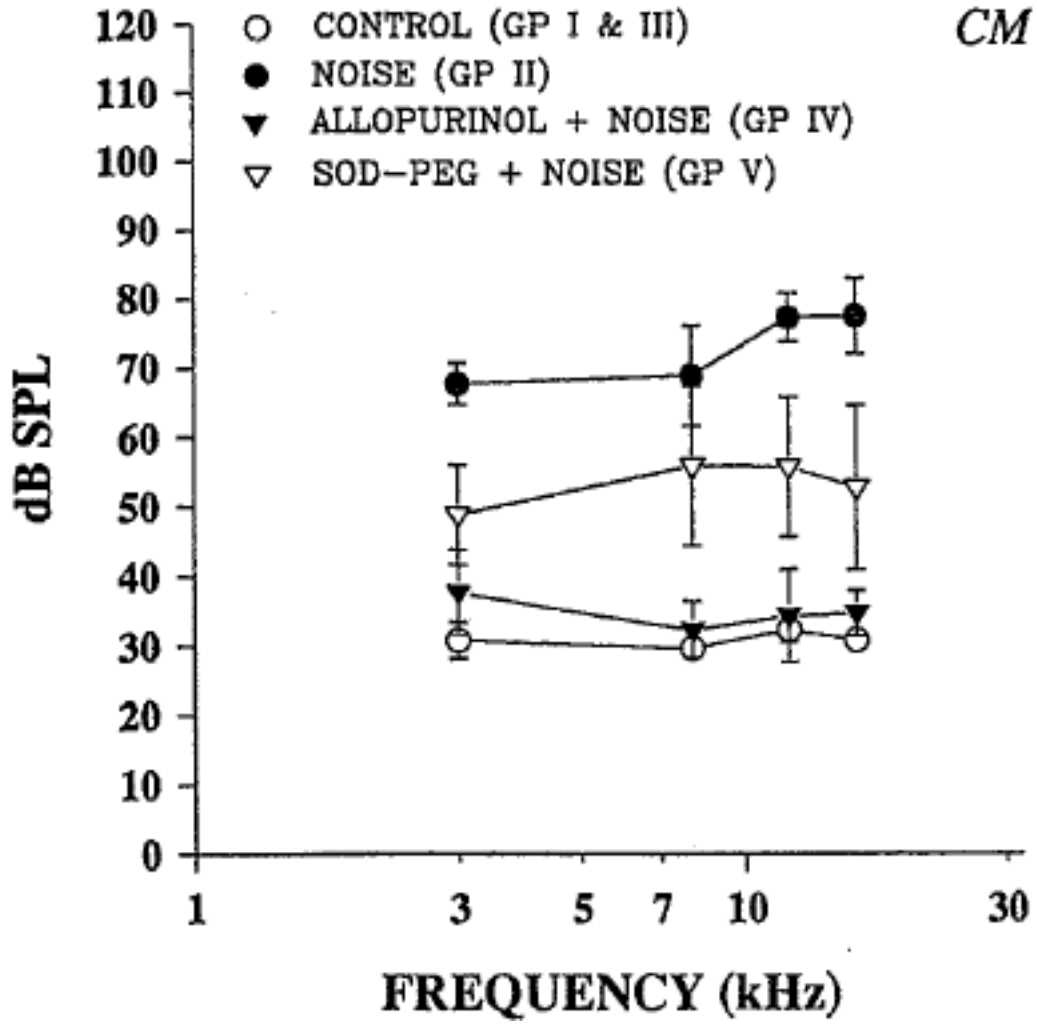
- Restriction calorique

- D-méthionine

- Ebselen



Seidman MD… Quirk WS - *Otolaryngol Head Neck Surg* 1993

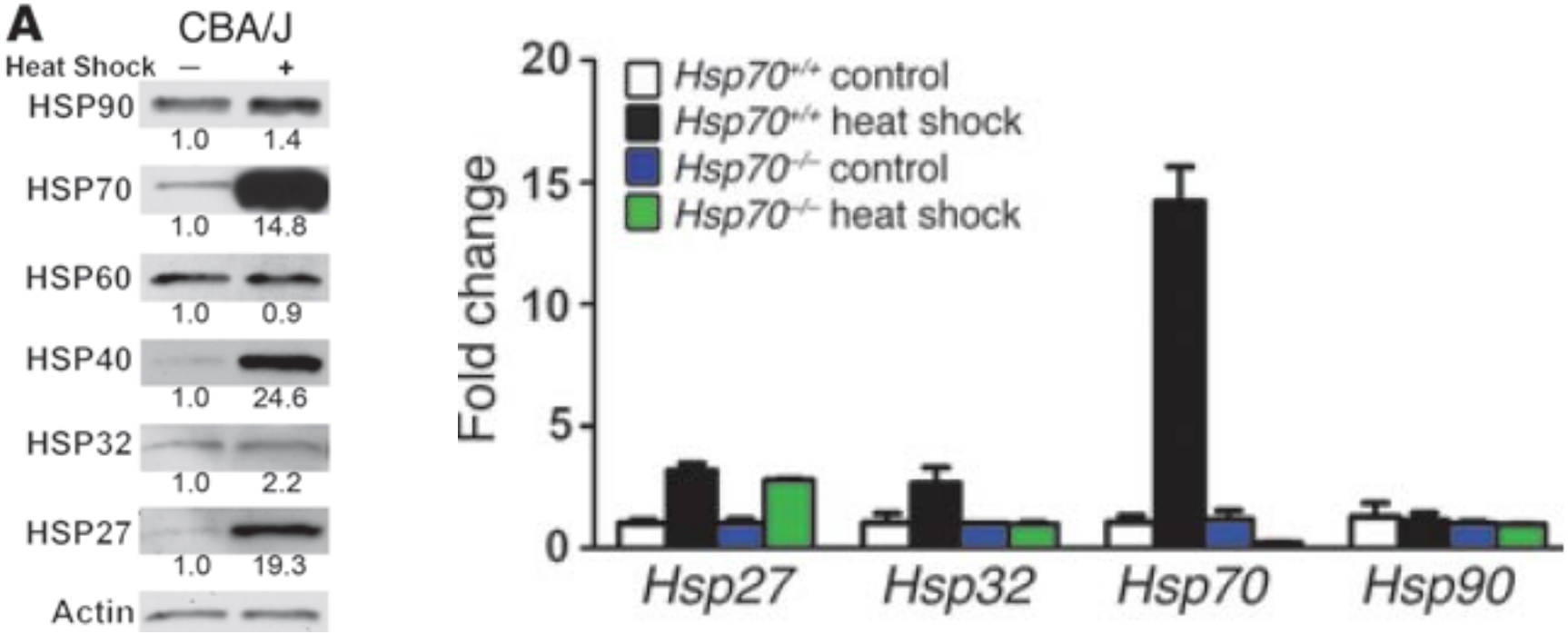


Seidman MD… Quirk WS - *Otolaryngol Head Neck Surg* 1993

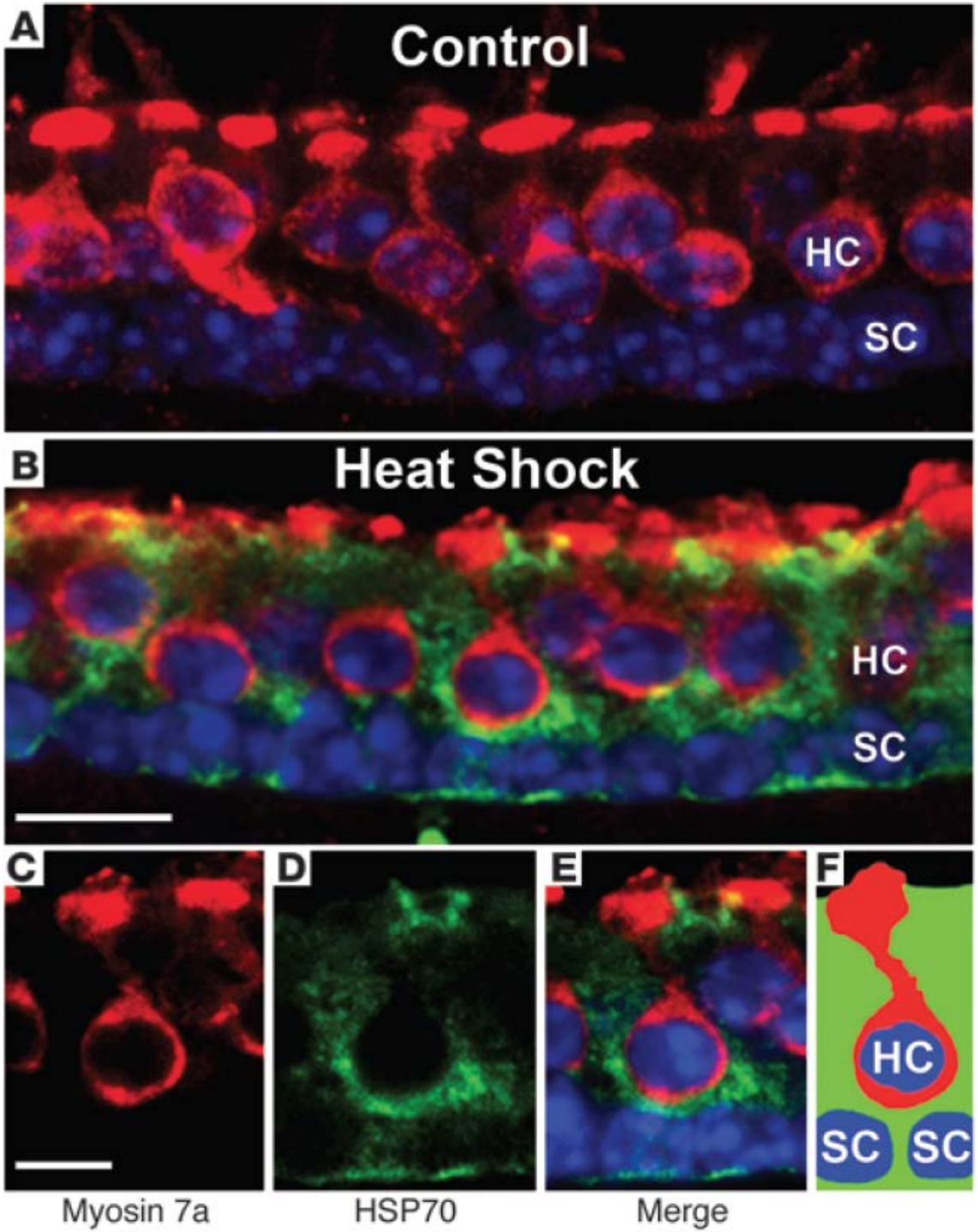
Inner ear supporting cells protect hair cells by secreting HSP70

Lindsey A. May,[1] Inga I. Kramarenko,[2] Carlene S. Brandon,[2] Christina Voelkel-Johnson,[2] Soumen Roy,[1] Kristy Truong,[1] Shimon P. Francis,[2,3] Elyssa L. Monzack,[1] Fu-Shing Lee,[2] and Lisa L. Cunningham[1]

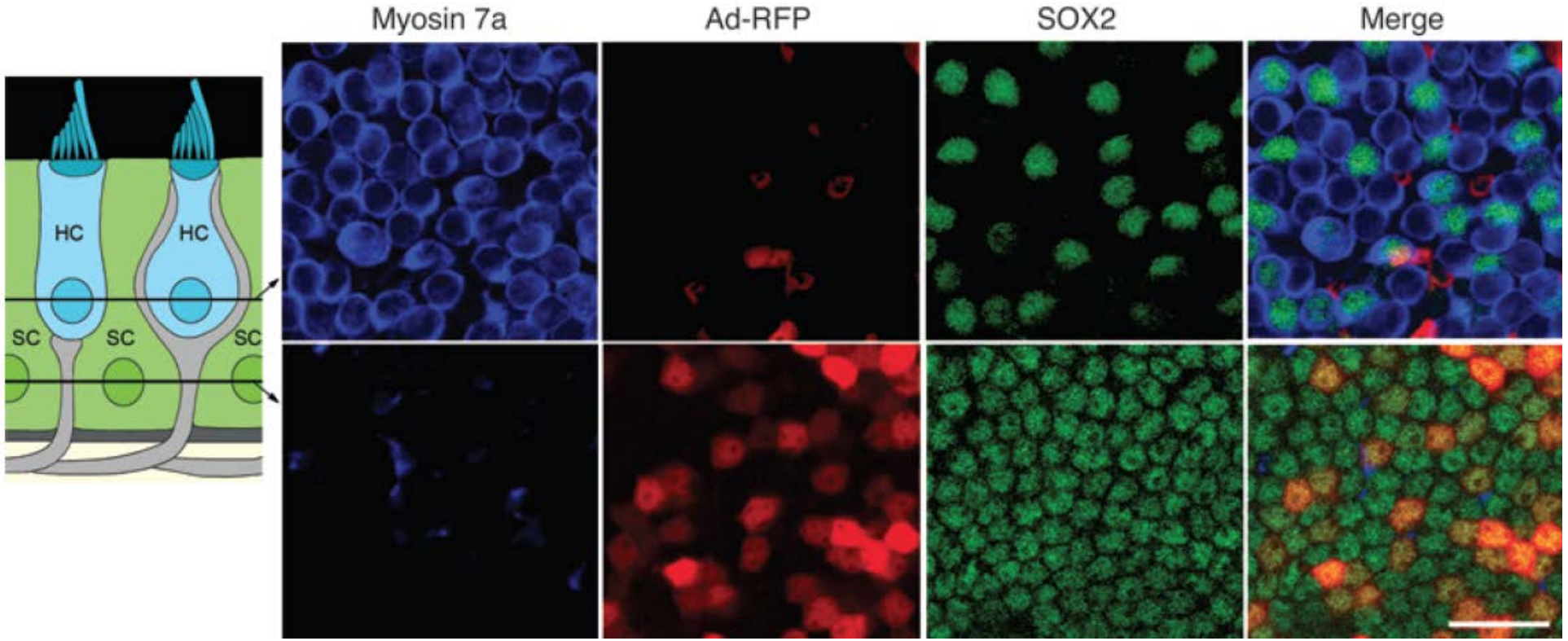
[1]National Institute on Deafness and Other Communication Disorders, NIH, Rockville, Maryland, USA.
[2]Medical University of South Carolina, Charleston, South Carolina, USA. [3]University of Virginia, Charlottesville, Virginia, USA.



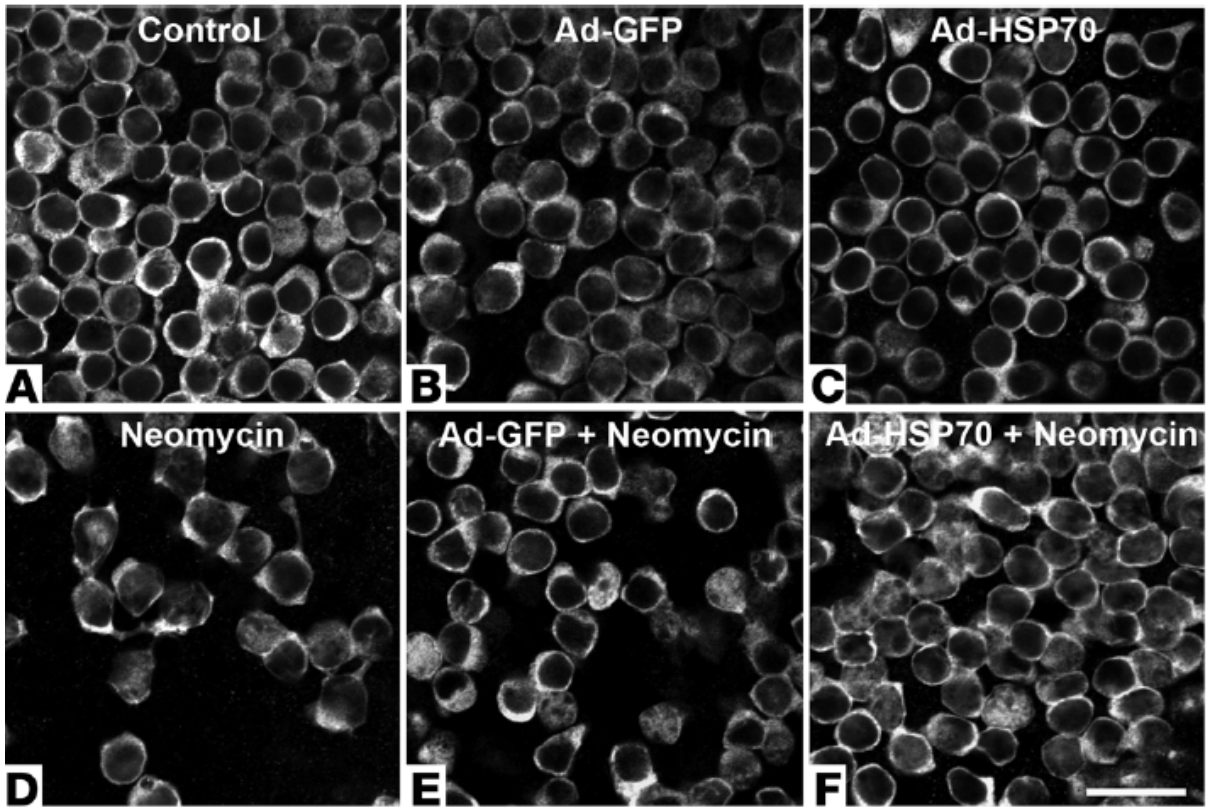
May LA… Cunningham LL - *J Clin Invest* 2013

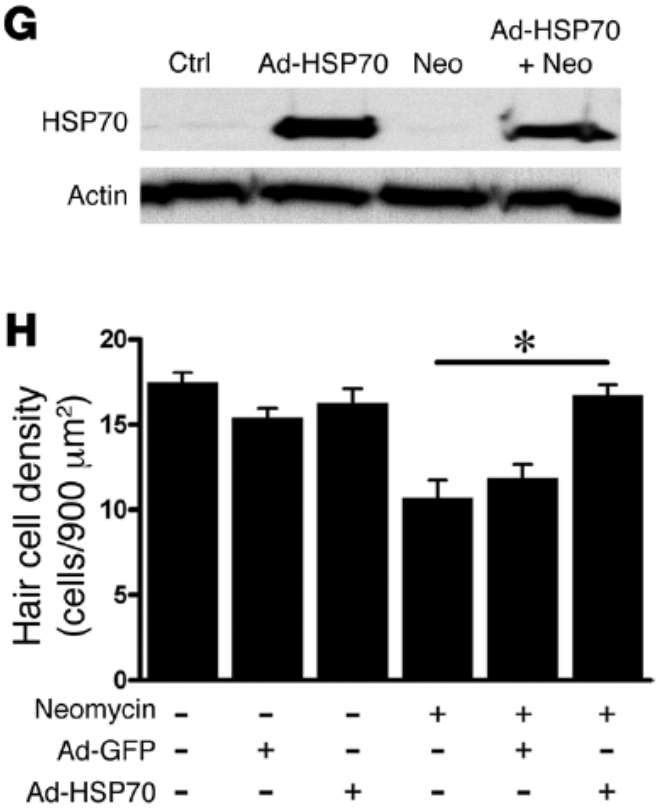


May LA... Cunningham LL - *J Clin Invest* 2013

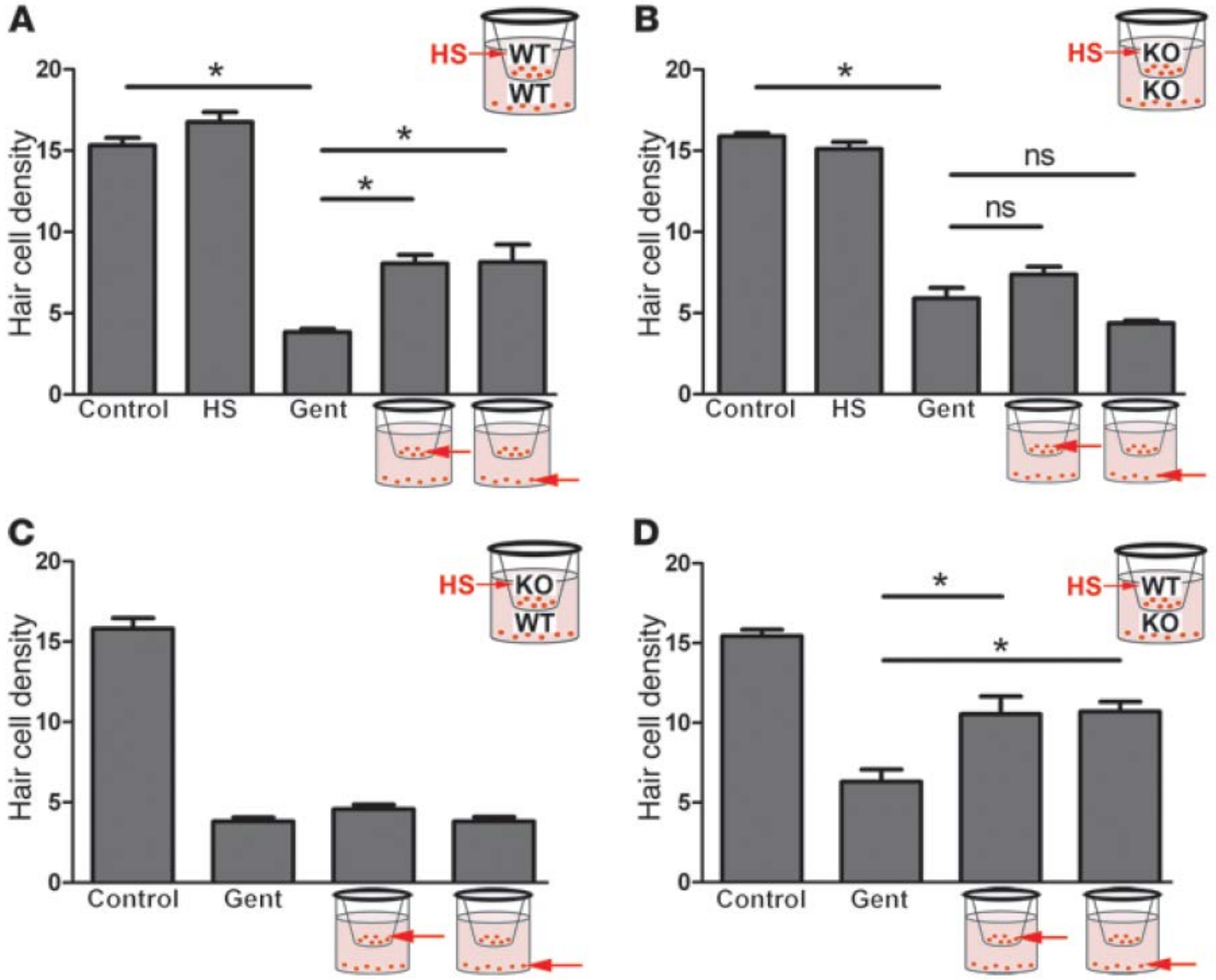


May LA… Cunningham LL - *J Clin Invest* 2013

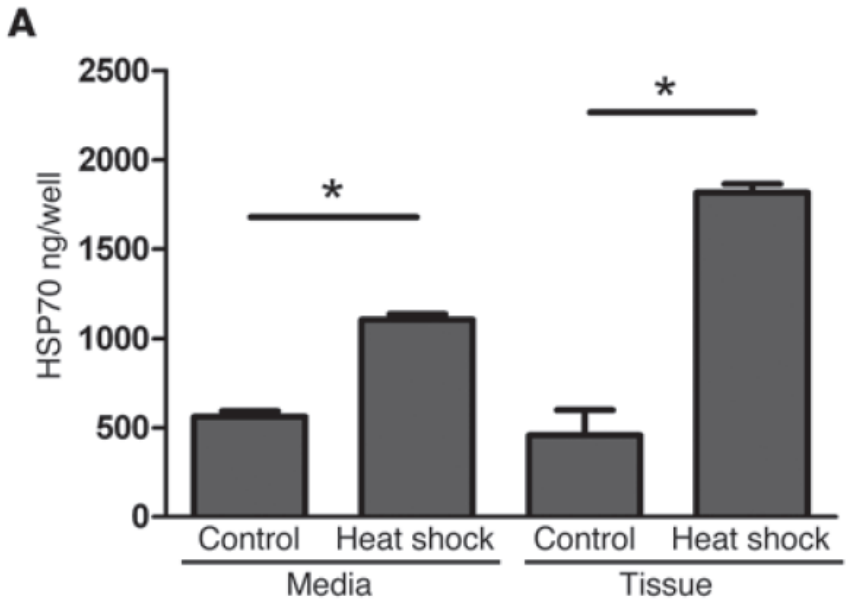




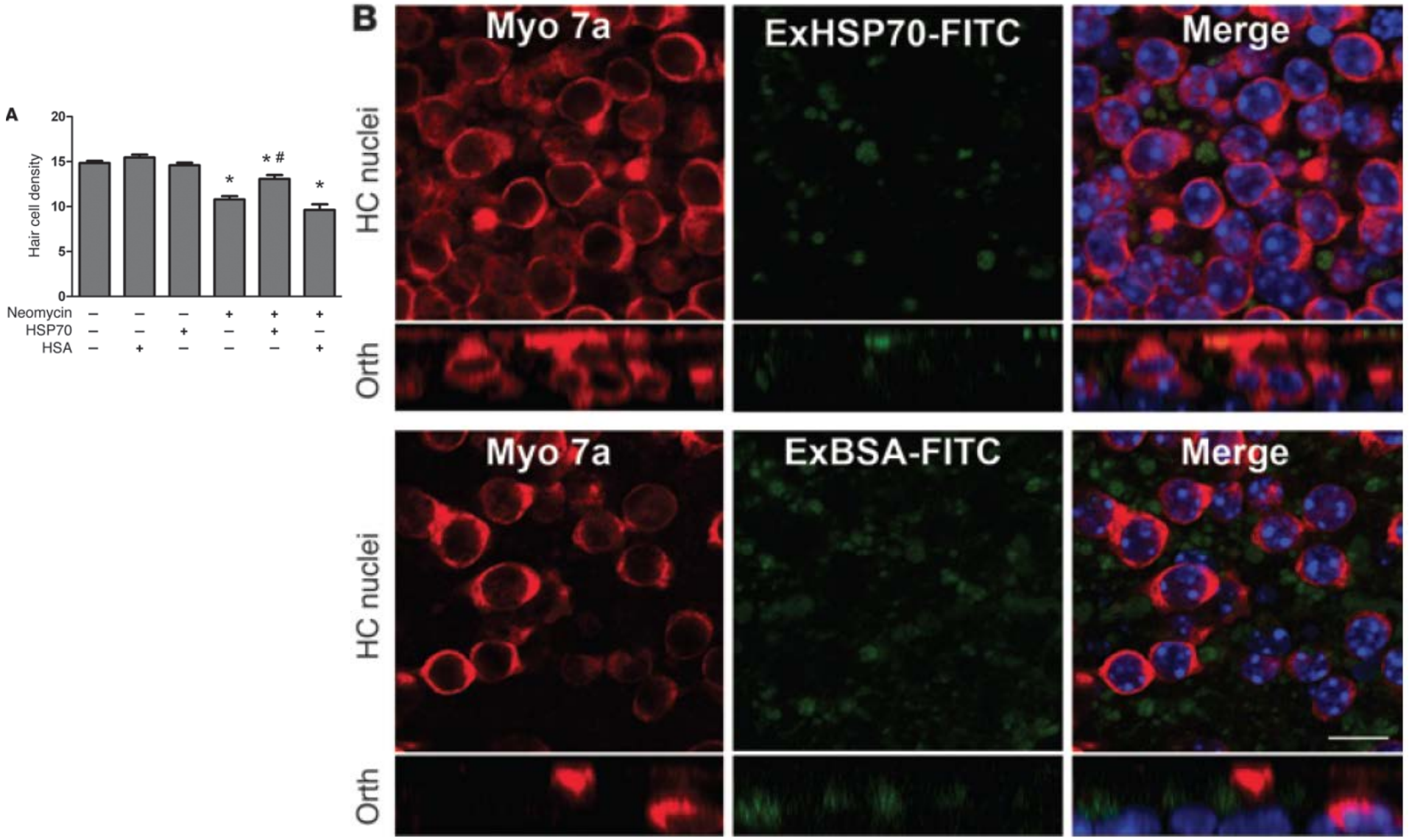
May LA… Cunningham LL - *J Clin Invest* 2013



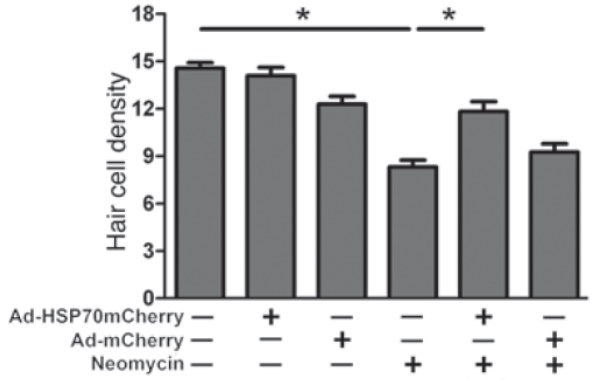
May LA… Cunningham LL - *J Clin Invest* 2013



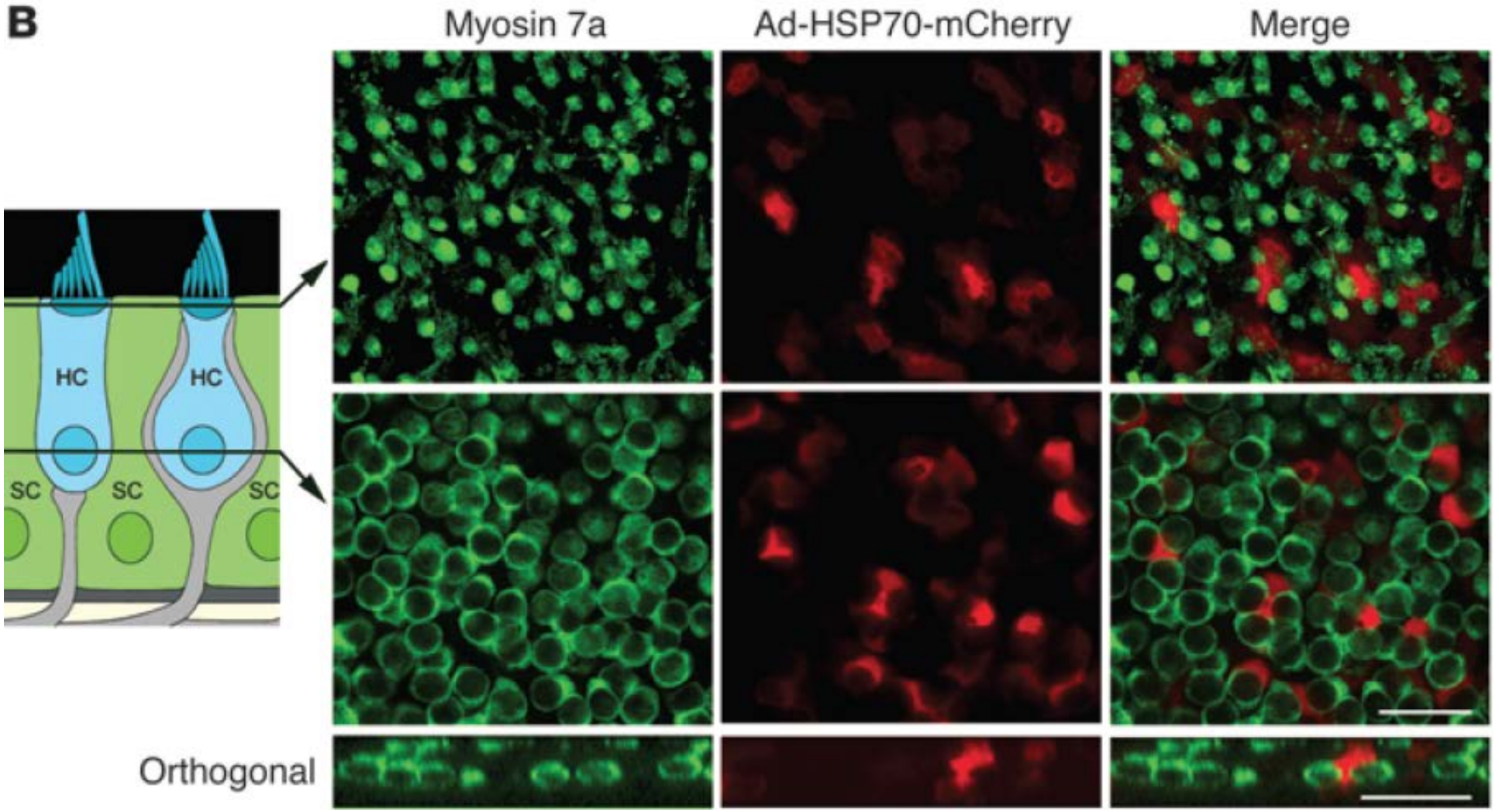
May LA… Cunningham LL - *J Clin Invest* 2013



May LA… Cunningham LL - *J Clin Invest* 2013



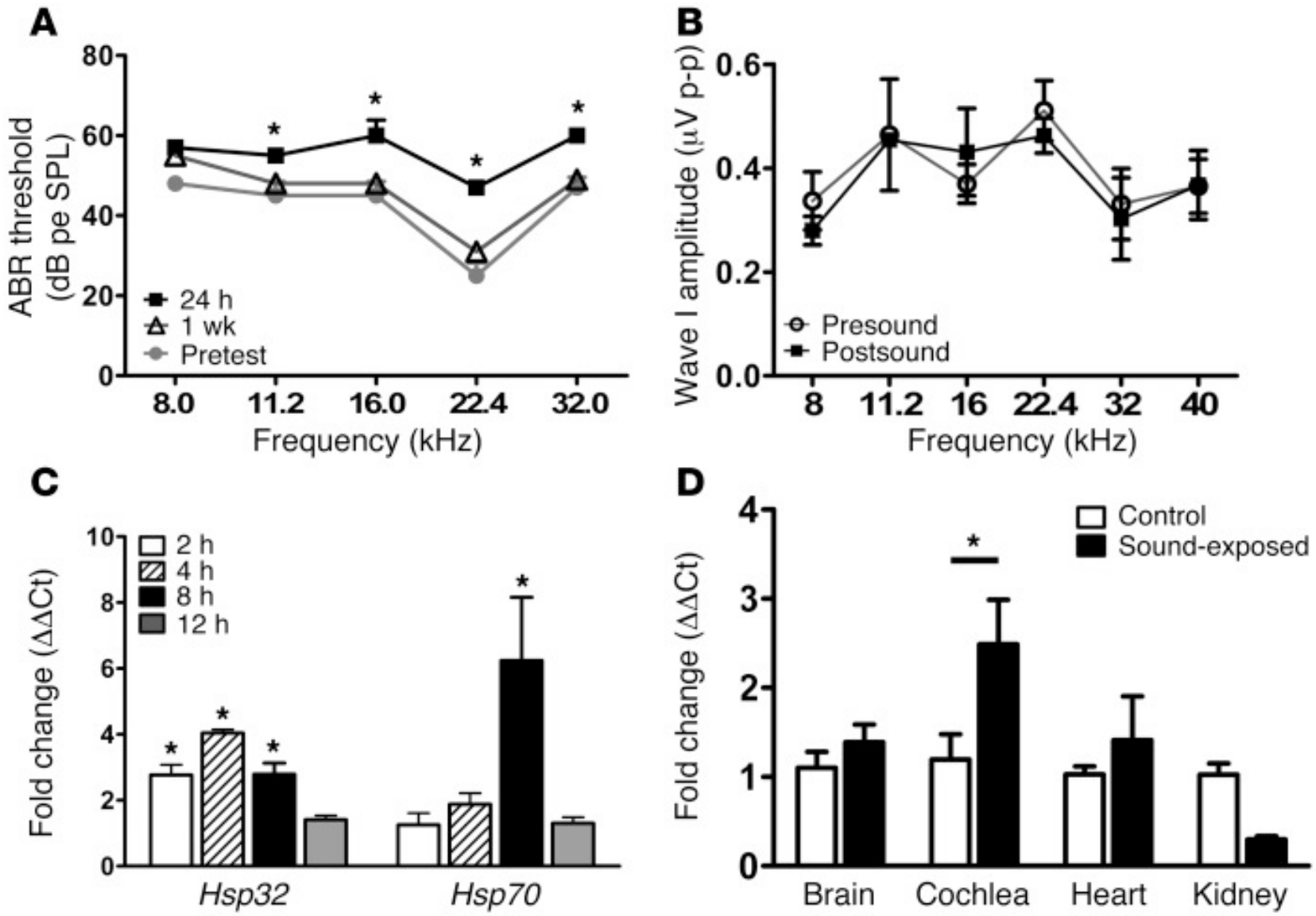
May LA… Cunningham LL - *J Clin Invest* 2013



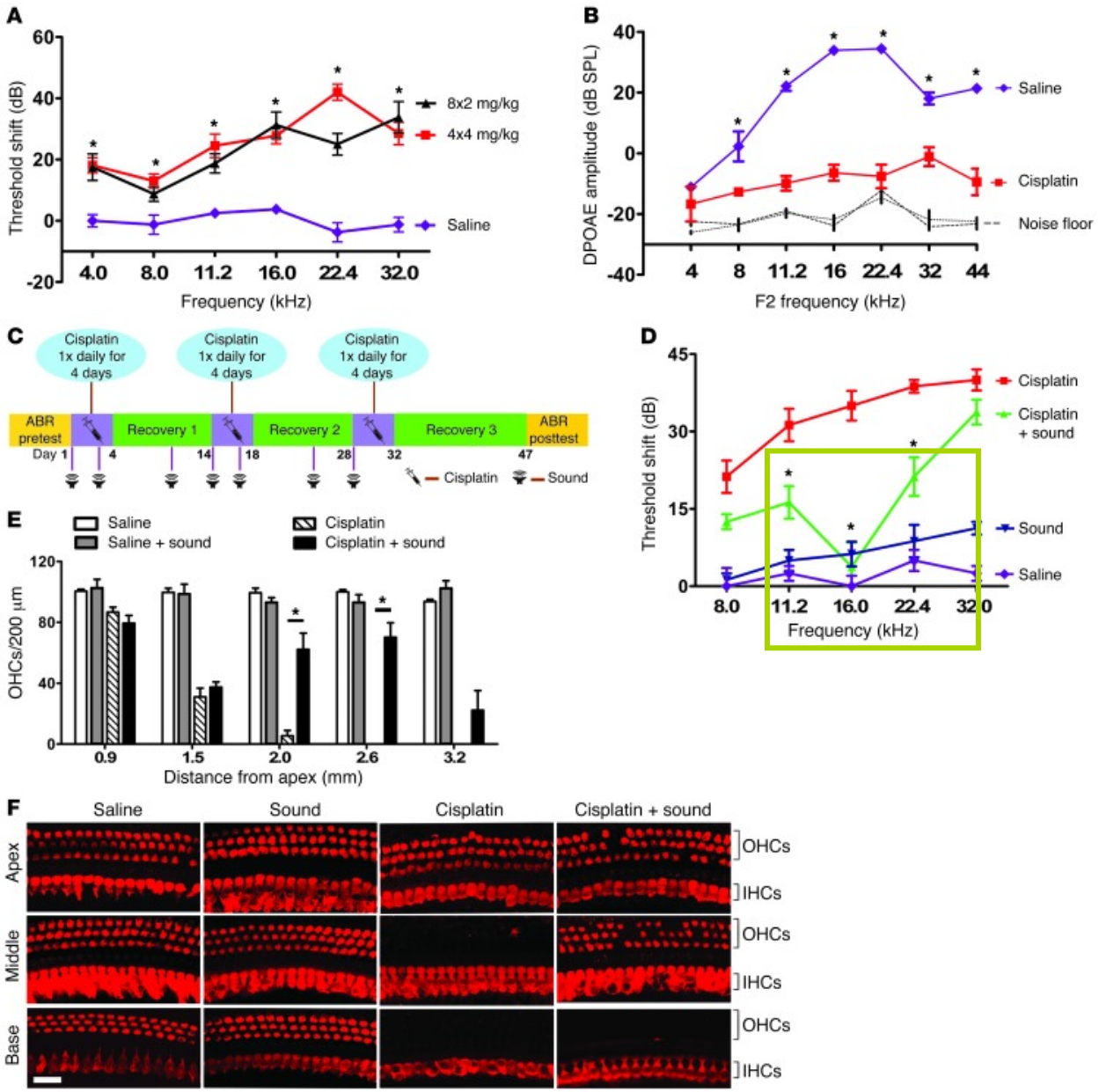
Sound preconditioning therapy inhibits ototoxic hearing loss in mice

Soumen Roy, Matthew M. Ryals, Astrid Botty Van den Bruele, Tracy S. Fitzgerald, and Lisa L. Cunningham

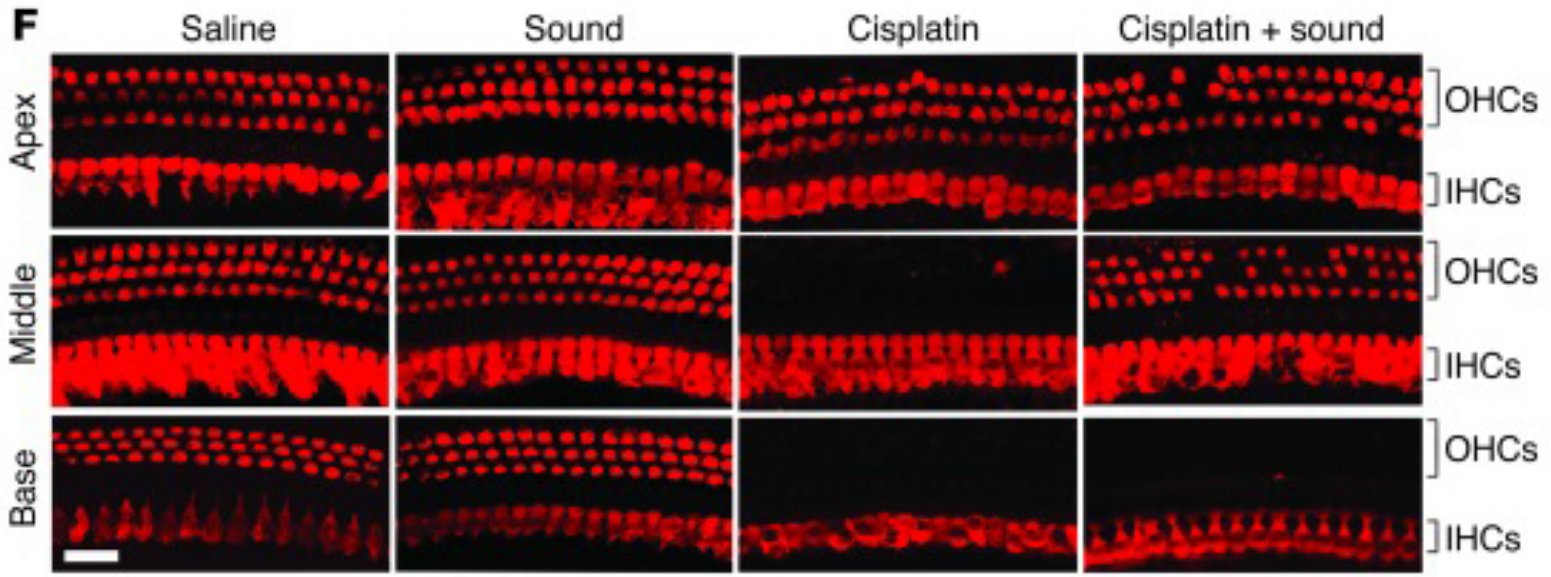
National Institute on Deafness and Other Communication Disorders (NIDCD), NIH, Rockville, Maryland, USA.



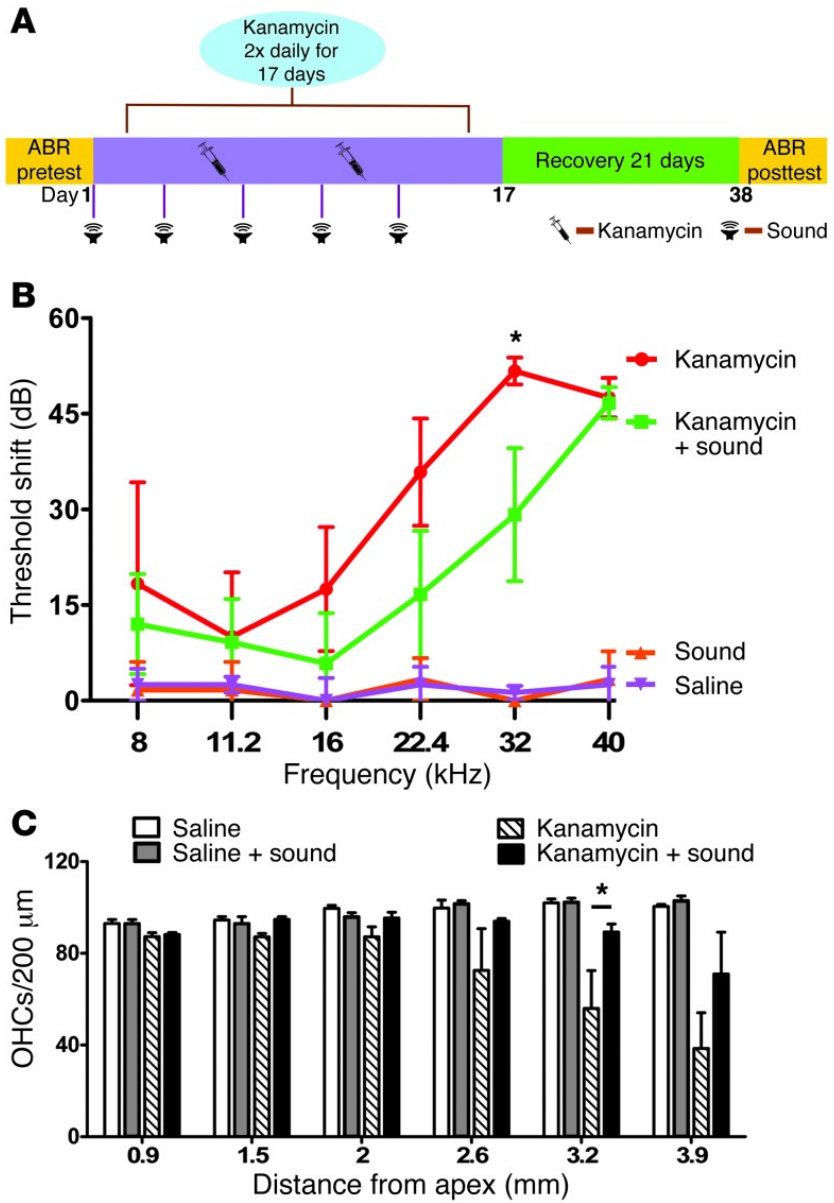
S. Roy, L.L. Cunningham, *The journal of Clinical Investigation* 2014



S. Roy, L.L. Cunningham, *The journal of Clinical Investigation* 2014



S. Roy, L.L. Cunningham, *The journal of Clinical Investigation* 2014



S. Roy, L.L. Cunningham, *The journal of Clinical Investigation* 2014

Sirt3 Mediates Reduction of Oxidative Damage and Prevention of Age-Related Hearing Loss under Caloric Restriction

Shinichi Someya,[1,3,5] Wei Yu,[2,5] William C. Hallows,[2] Jinze Xu,[4] James M. Vann,[1] Christiaan Leeuwenburgh,[4] Masaru Tanokura,[3] John M. Denu,[2,*] and Tomas A. Prolla[1,*]

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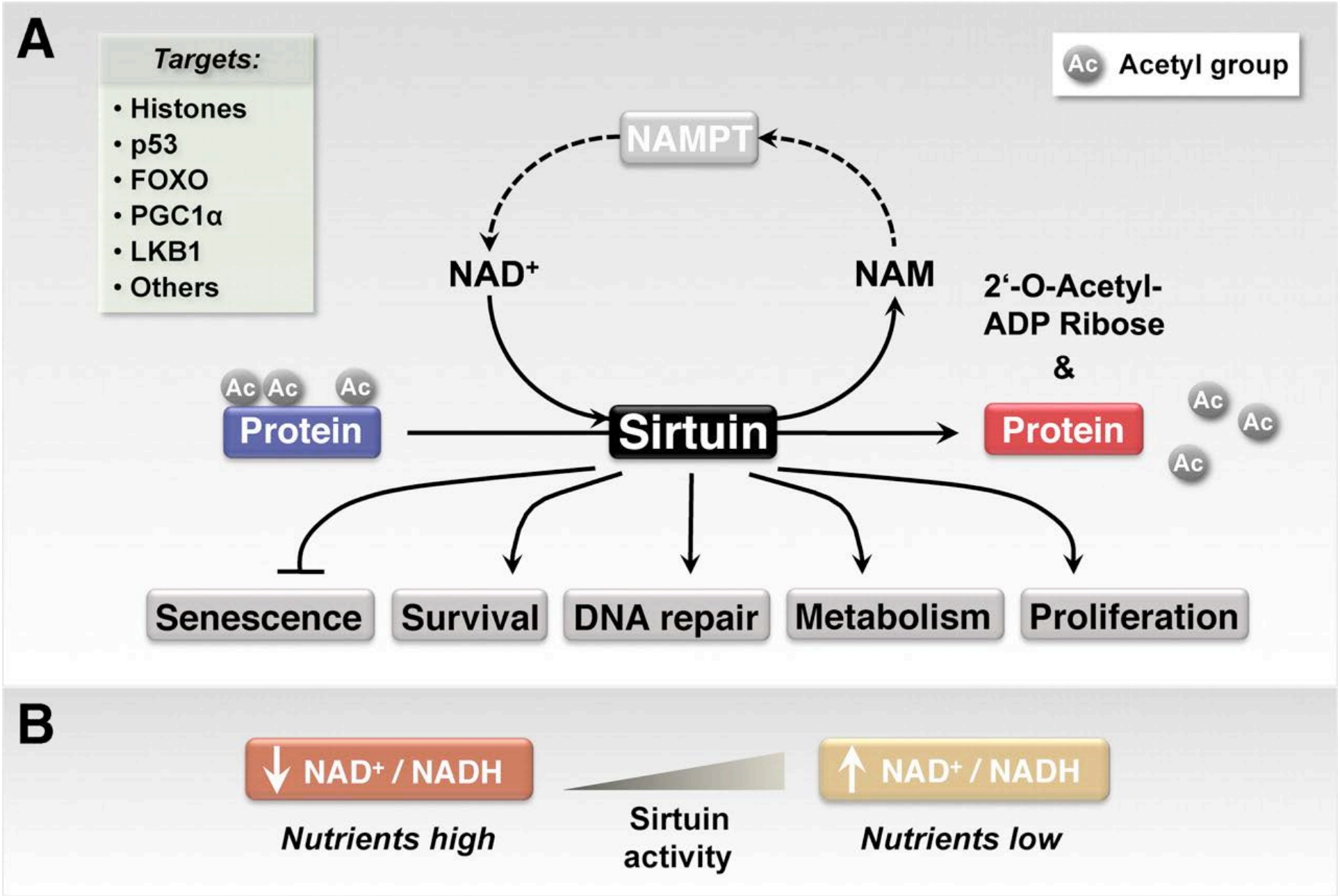
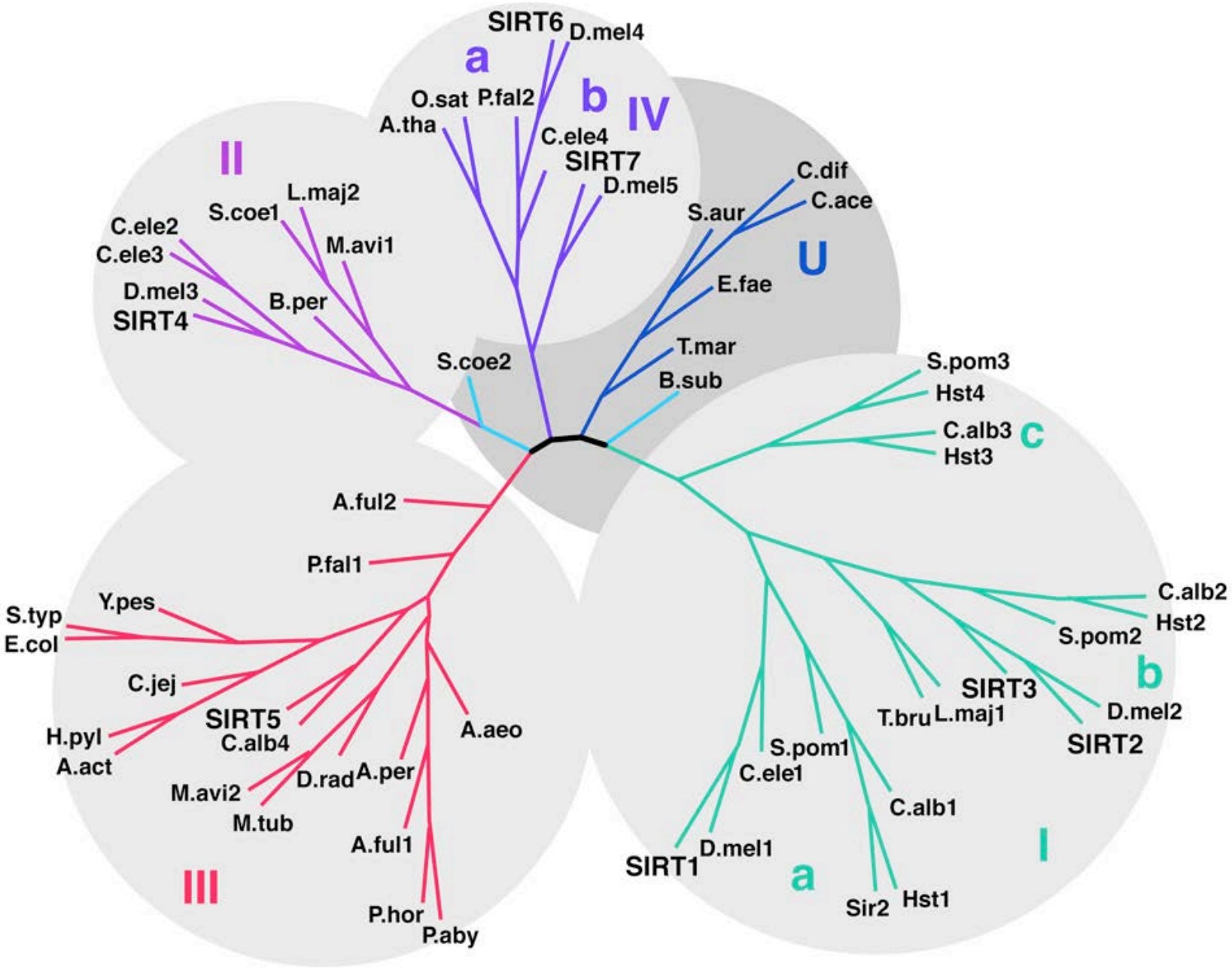
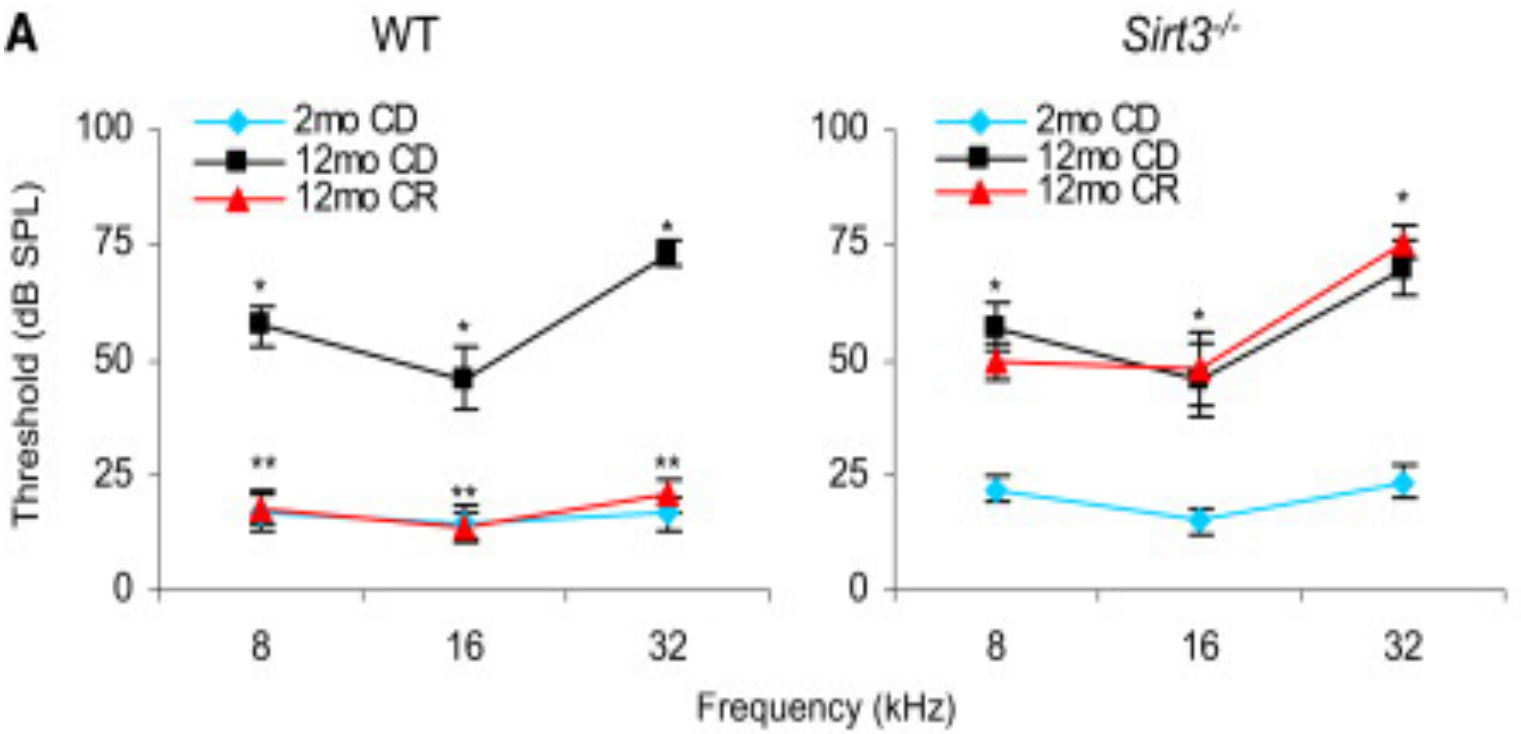
DOI 10.1016/j.cell.2010.10.002


A
Targets:
• Histones
• p53
• FOXO
• PGC1α
• LKB1
• Others
Ac Acetyl group
NAMPT
NAD+
NAM
2'-O-Acetyl-
ADP Ribose
&
Ac Ac Ac
Protein
Sirtuin
Protein
Ac
Ac
Ac
Senescence
Survival
DNA repair
Metabolism
Proliferation
B
NAD+ / NADH
Nutrients high
Sirtuin
activity
NAD+ / NADH
Nutrients low


SIRT6
D.mel4
a
b
IV
O.sat
P.fal2
A.tha
C.ele4
SIRT7
D.mel5
II
L.maj2
S.coe1
C.ele2
C.ele3
M.avi1
D.mel3
SIRT4
B.per
S.coe2
C.dif
C.ace
S.aur
U
E.fae
T.mar
B.sub
S.pom3
Hst4
C.alb3
Hst3
c
A.ful2
P.fal1
C.alb2
Hst2
S.pom2
b
SIRT3
T.bru
L.maj1
D.mel2
SIRT2
Y.pes
S.typ
E.col
C.jej
SIRT5
C.alb4
H.pyl
A.act
A.aeo
M.avi2
D.rad
A.per
M.tub
A.ful1
S.pom1
C.ele1
C.alb1
SIRT1
D.mel1
a
I
III
P.hor
P.aby
Sir2
Hst1

L'effet protecteur de la diète calorique à l'égard des effets de la stimulation sonore nécessite Sirt3



CD: controlled diet
CR: caloric restriction

Figure 1 CR Prevents AHL and Protects Cochlear Neurons in WT Mice, but Not in Sirt3 −/− Mice (A) ABR hearing thresholds were measured at 32, 16, and 8 kHz from control diet and/or calorie-restricted WT (left) and Sirt3 −/− (right) mice at 2 and 12 m...

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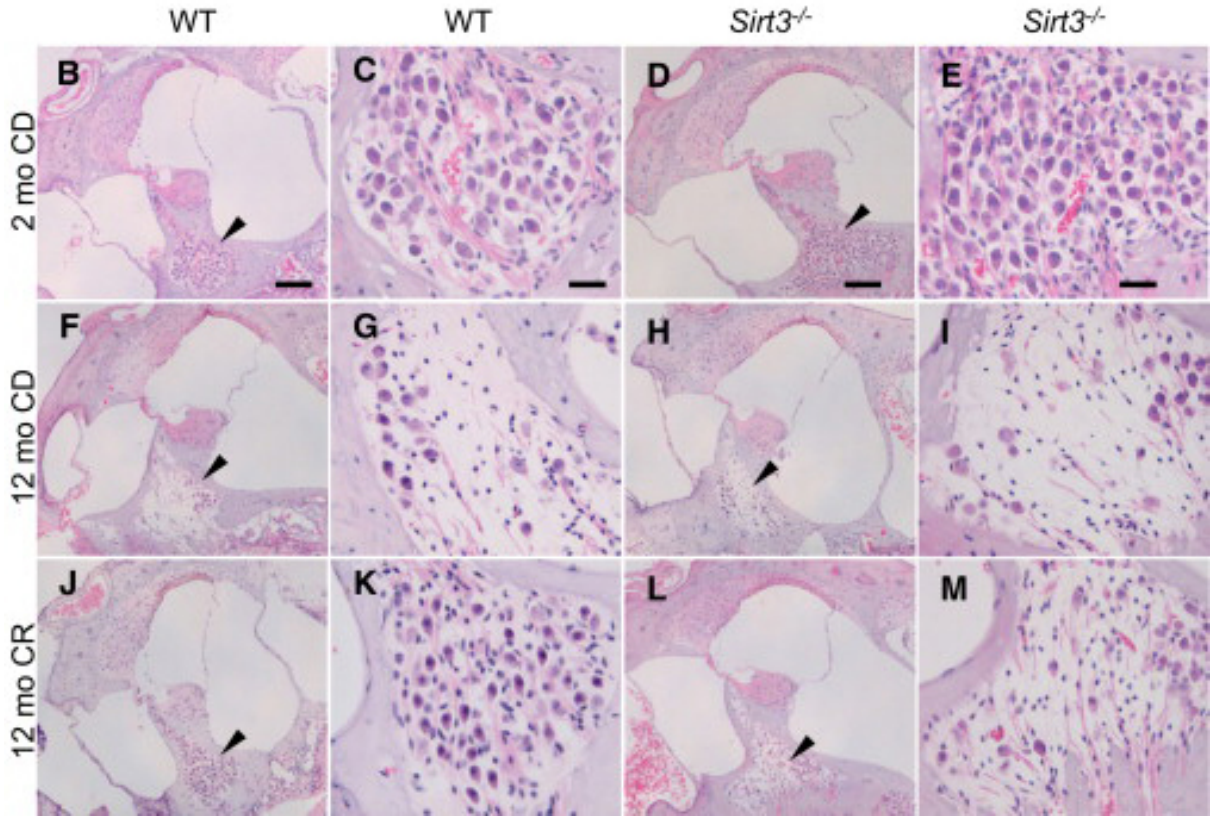
L'effet protecteur de la diète calorique à l'égard des effets de la stimulation sonore nécessite Sirt3



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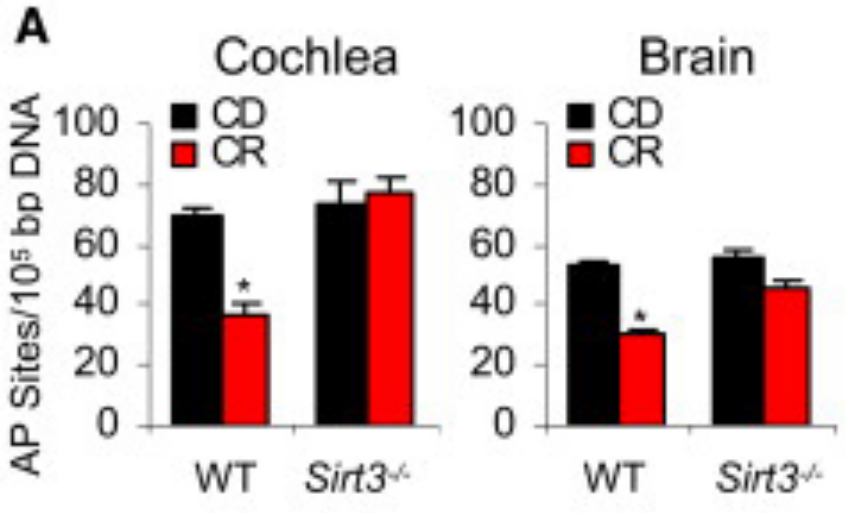

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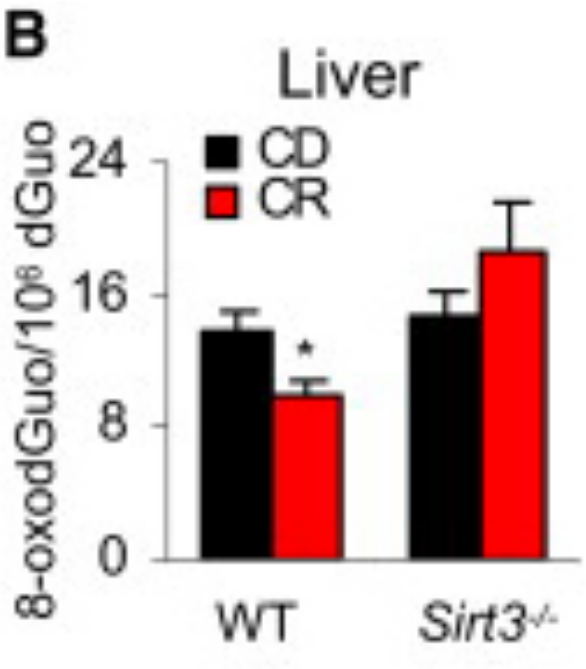

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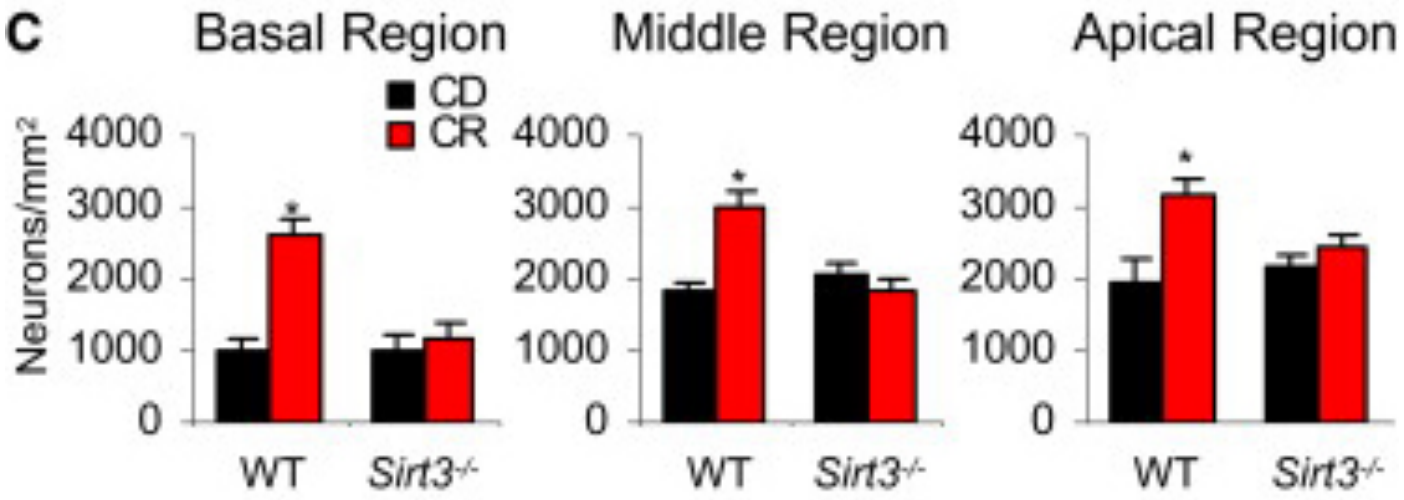

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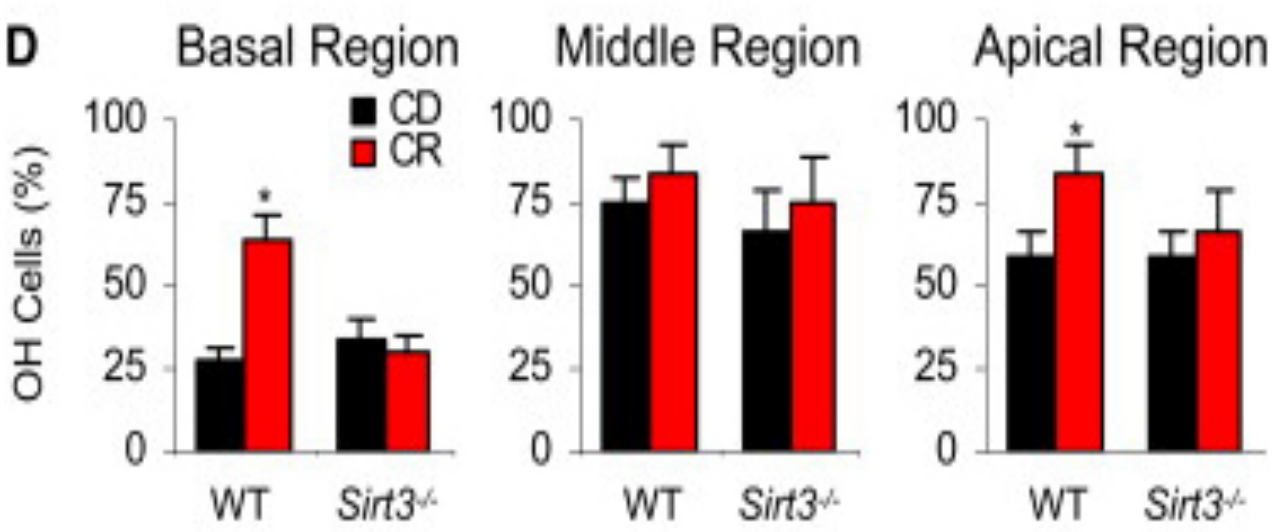

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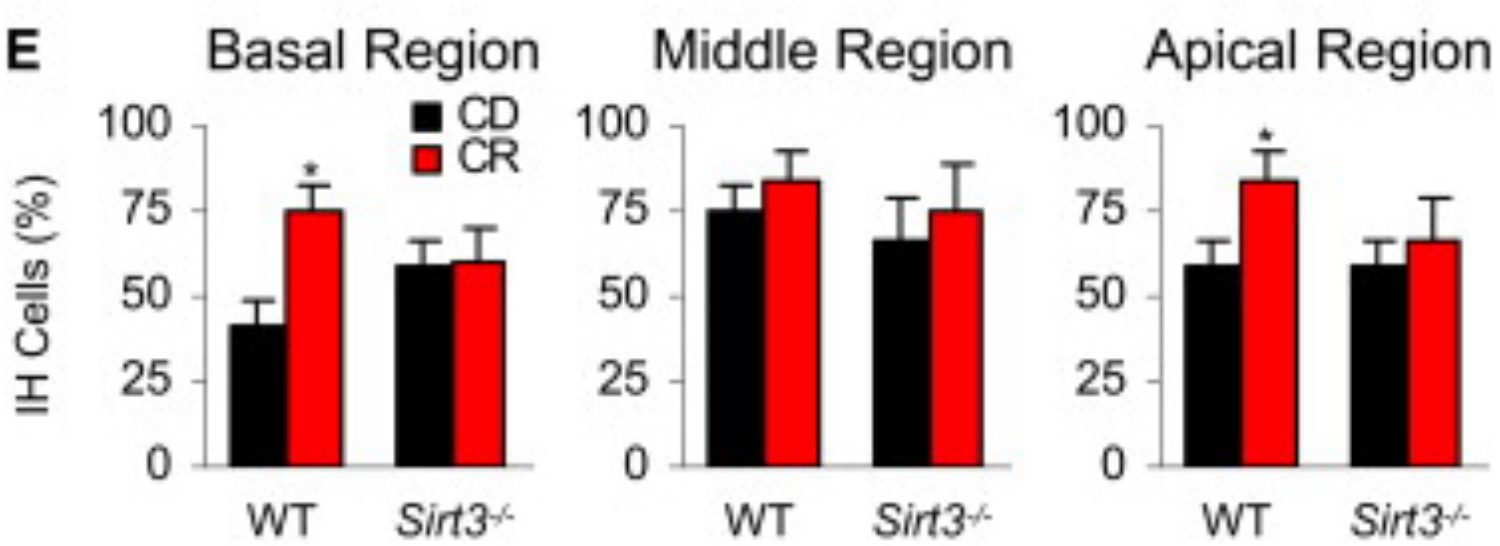

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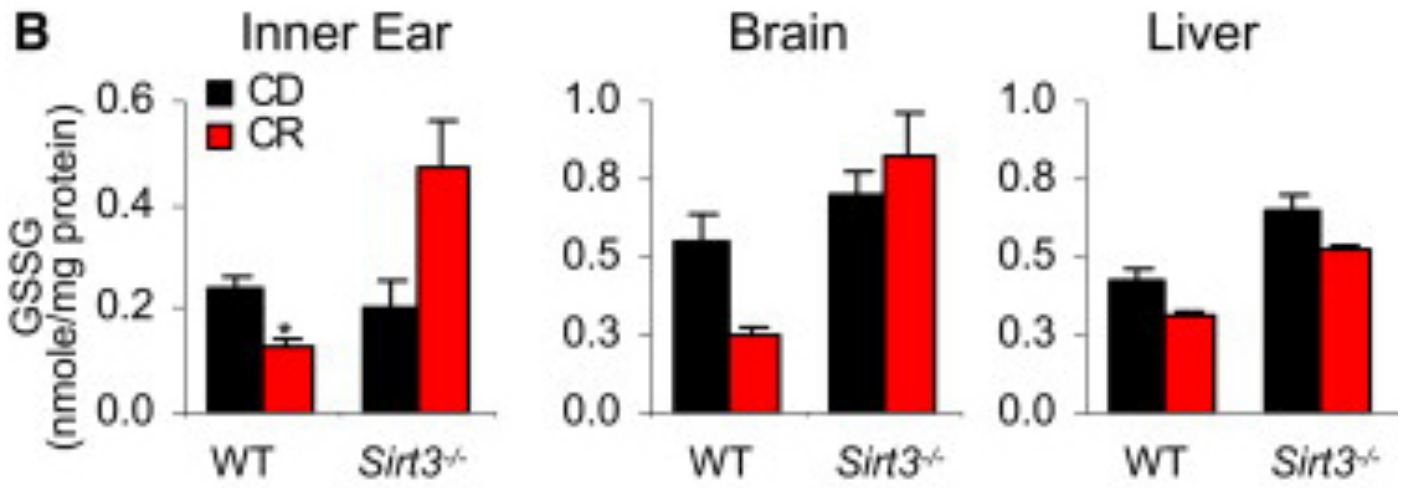
La diète calorique baisse le glutathion oxydé dans les mitochondries si SIrt-3 est exprimé



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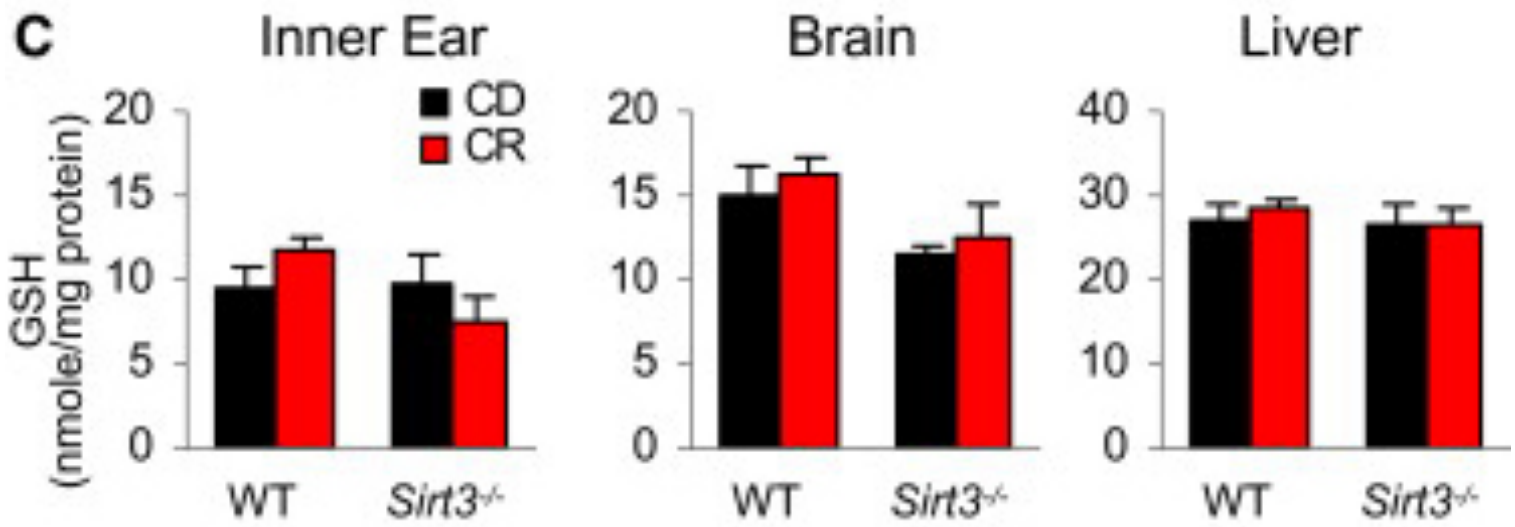

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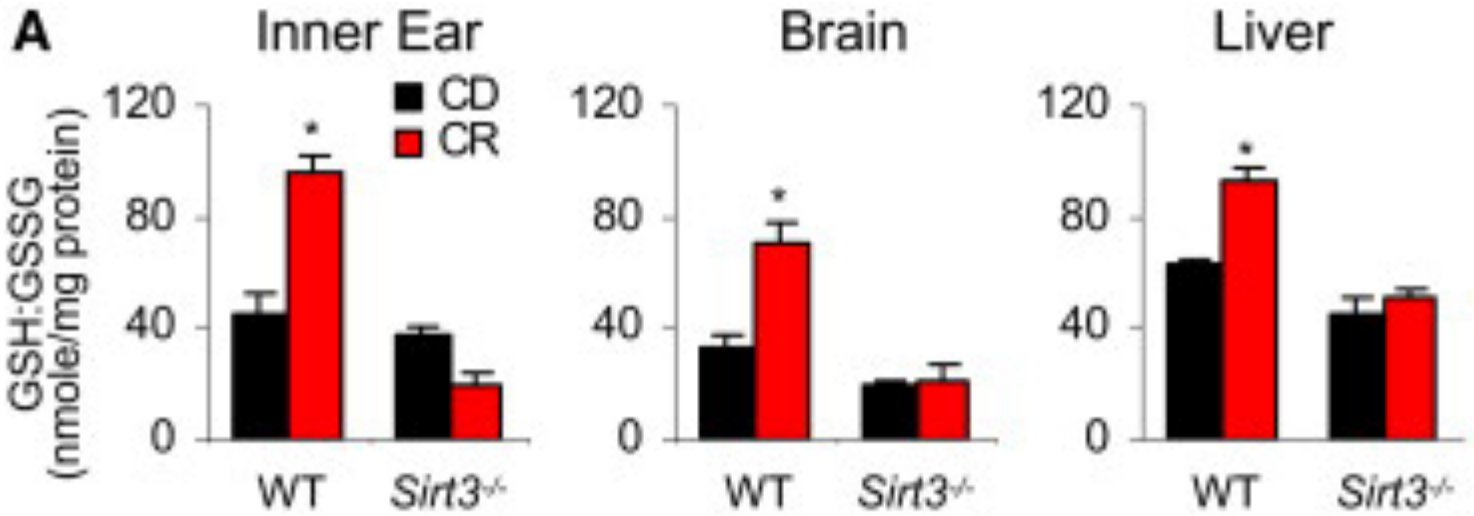

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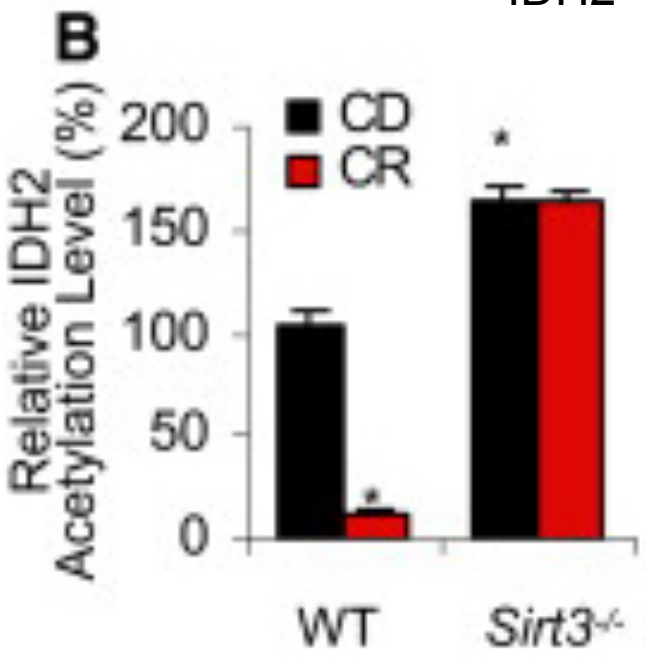
La diète calorique baisse le niveau de l'acétylation d'IDH2 si SIrt-3 est exprimé

IDH2=isocitrate déshydrogénase 2



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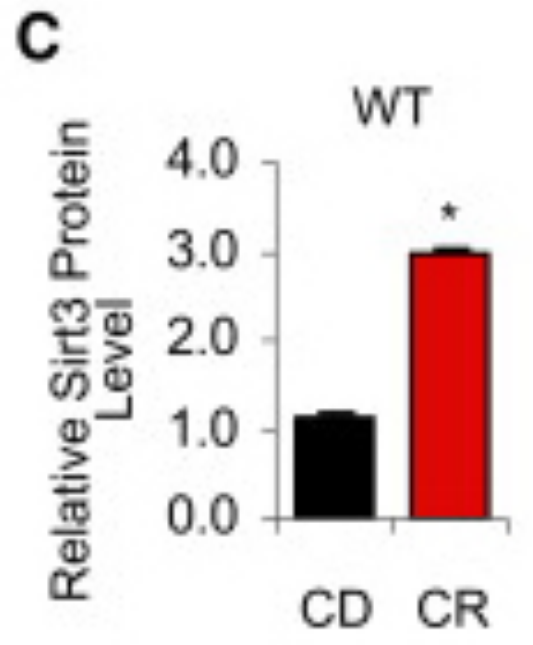
La diète calorique augmente le taux d'IDH2



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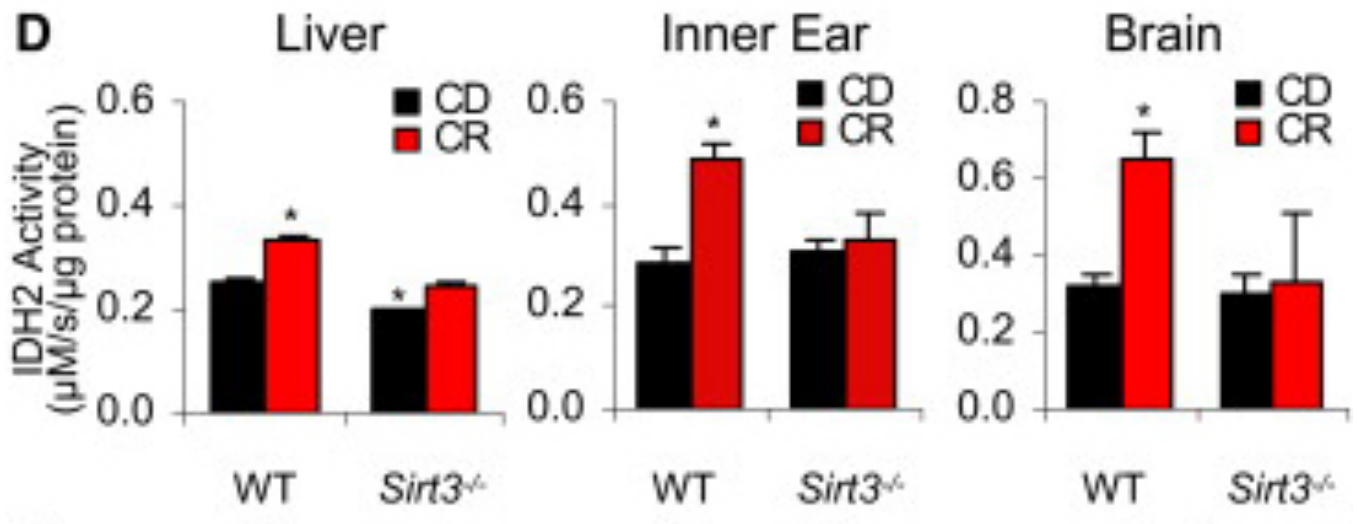

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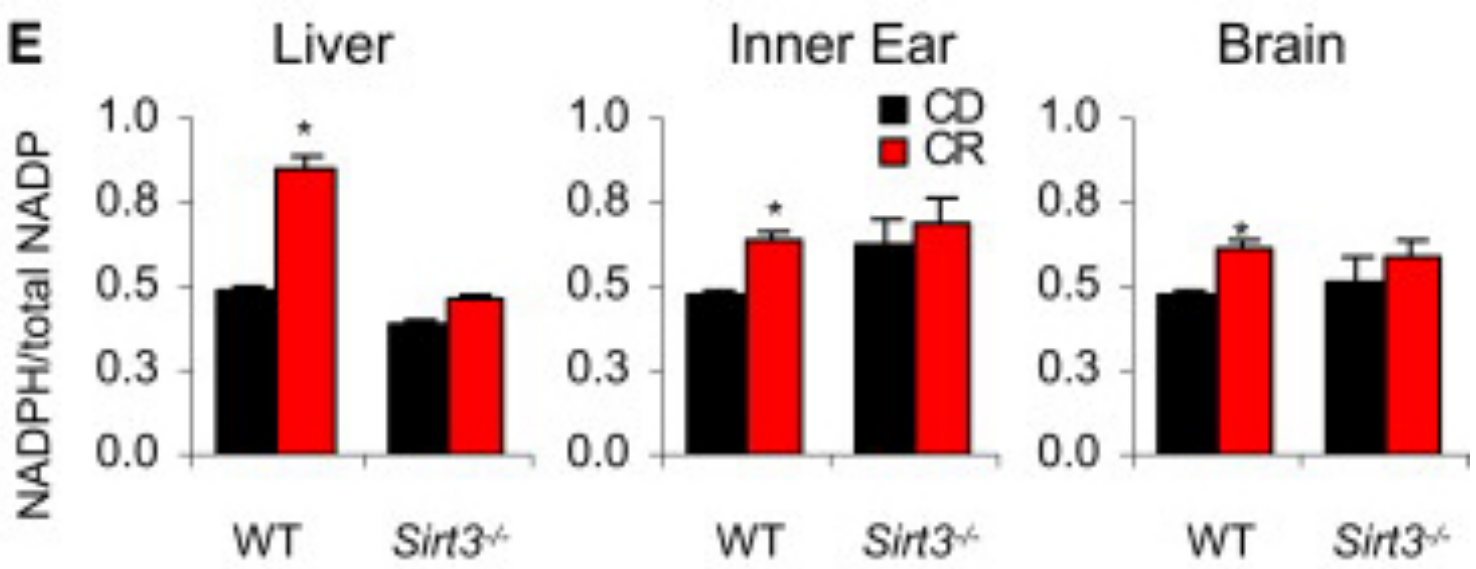
Le niveau de $NADPH_2$ est augmenté par la diète calorique si Sirt-3 est présent



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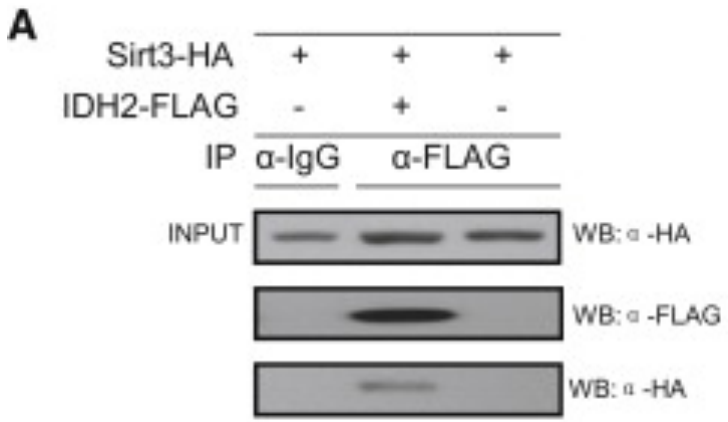

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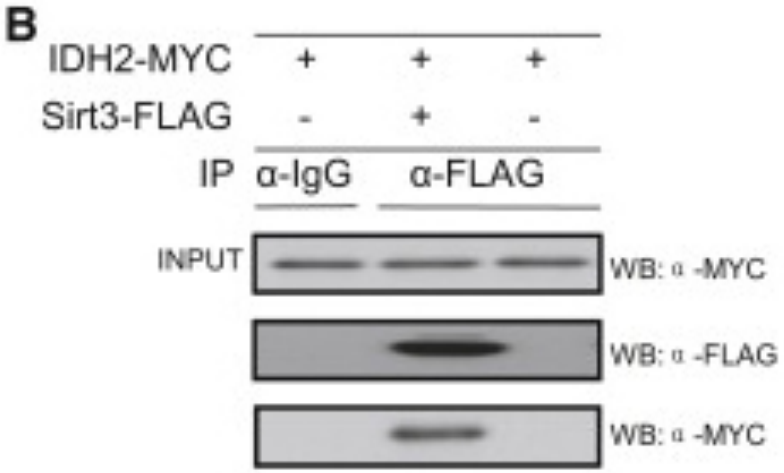

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L’hyper-expression de Sirt-3 ou d’IDH2 augmente le NAPDH et protège contre le stress oxydant

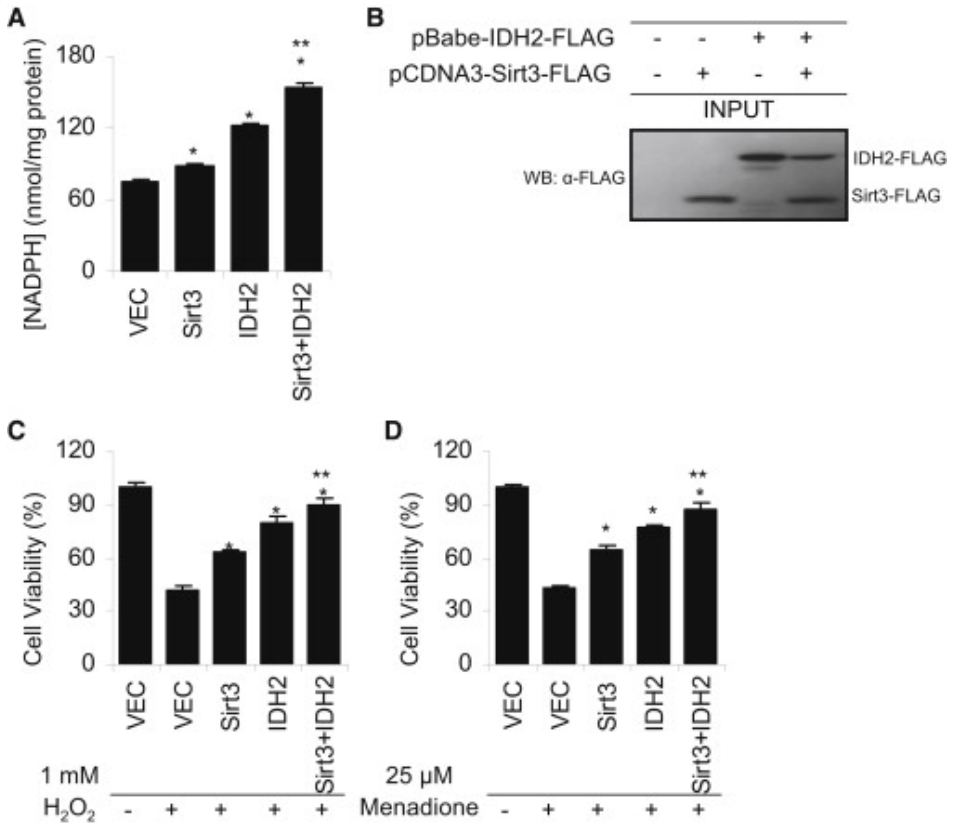

Figure 6 Overexpression of Sirt3 and/or Idh2 Is Sufficient to Increase NADPH Levels and Protects HEK293 Cells from Oxidative Stress (A and B) (A) NADPH concentrations were significantly increased when either Idh2 or Sirt3 or both were stably overexpressed...

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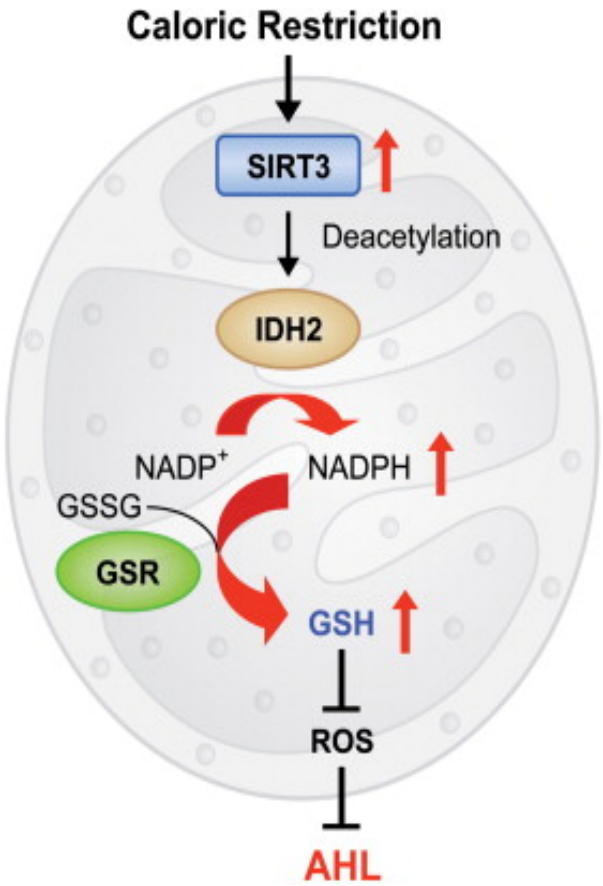

Figure 7 A Model for the CR-Mediated Prevention of AHL in Mammals In response to CR, SIRT3 activates IDH2, thereby increasing NADPH levels in mitochondria. This in turn leads to an increased ratio of GSH:GSSG and decreased levels of ROS, thereby resulting...

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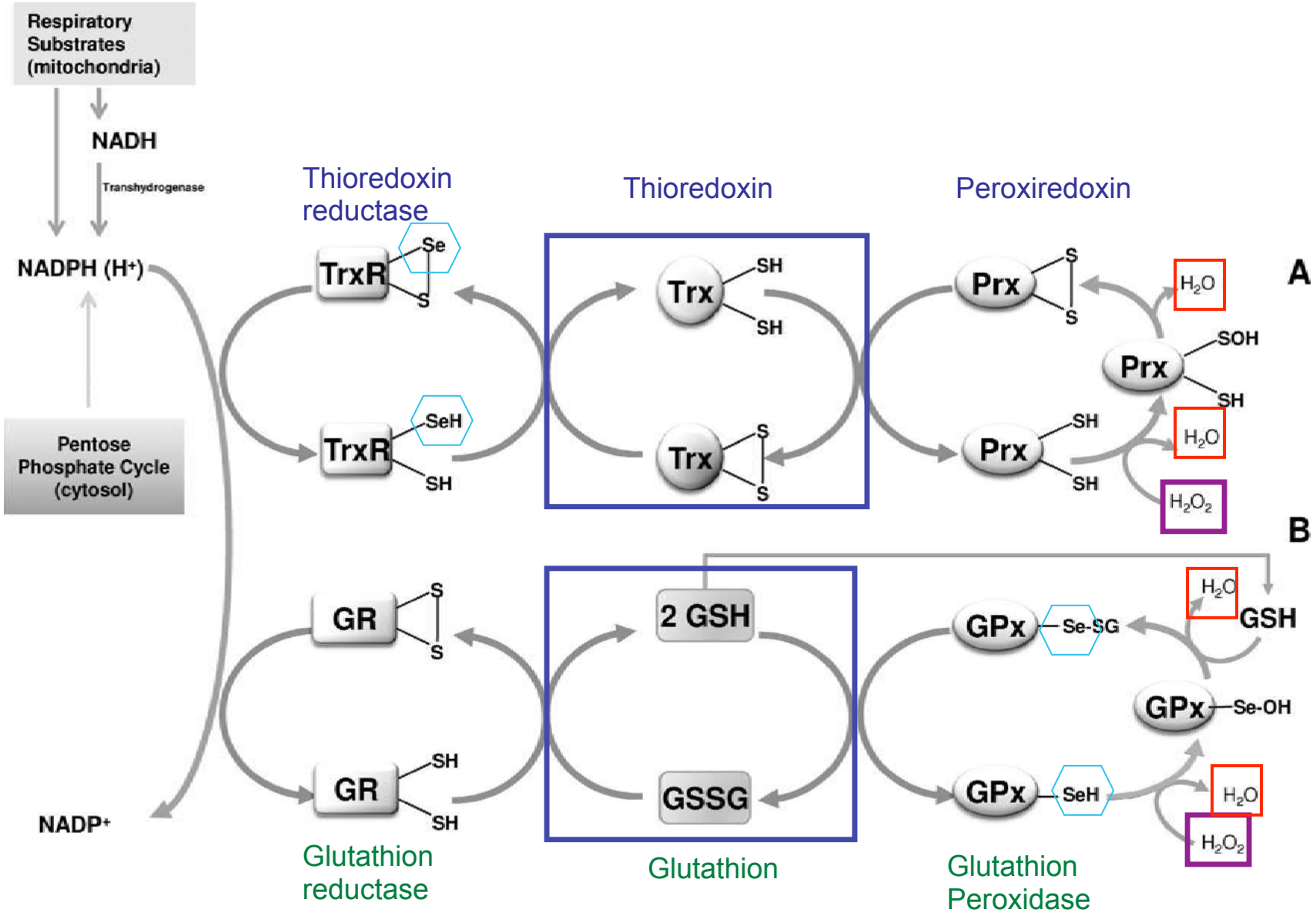
LA REDUCTION de H_2O_2 en H_2O (anti-oxydants)



Bindoli A… Forman HJ - *Antioxid Redox Signal* 2008