Cardiolipin Remodeling by ALCAT1 Regulates Dilated Cardiomyopathy Through Oxidative Stress and Mitophagy

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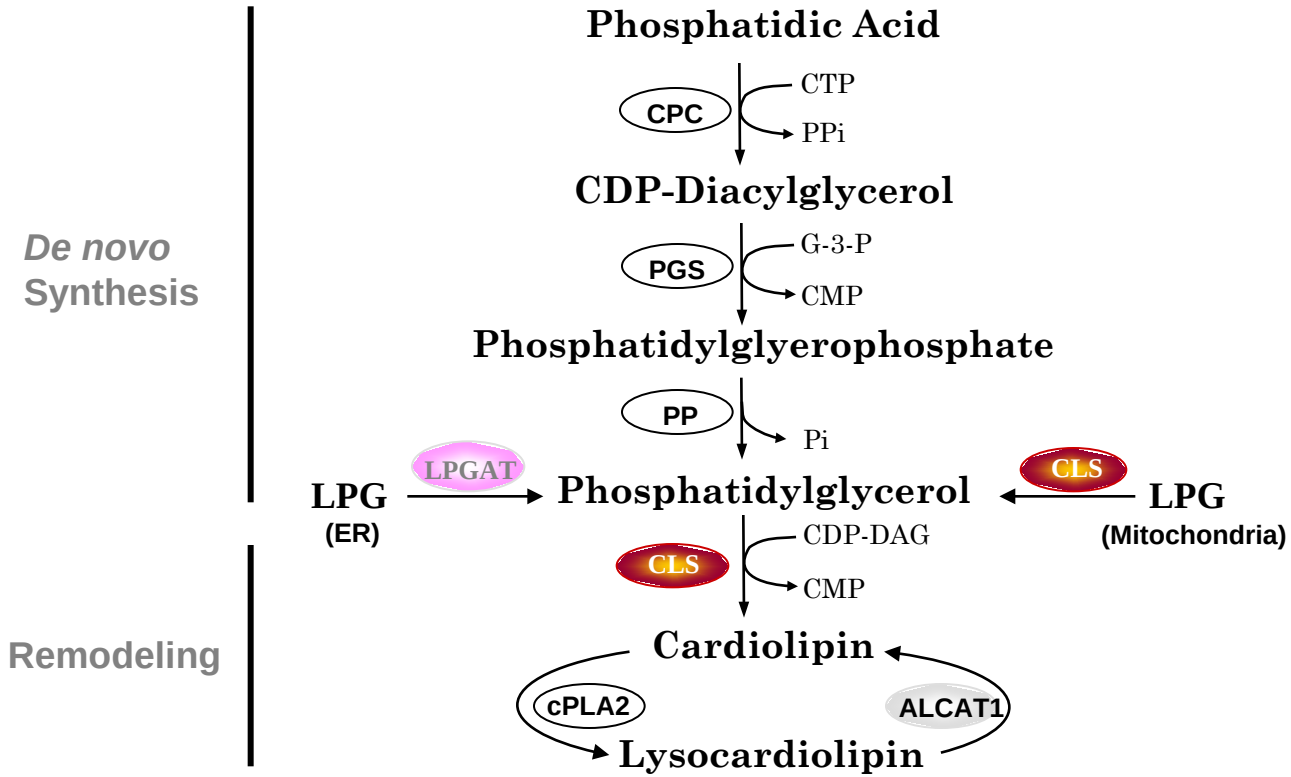
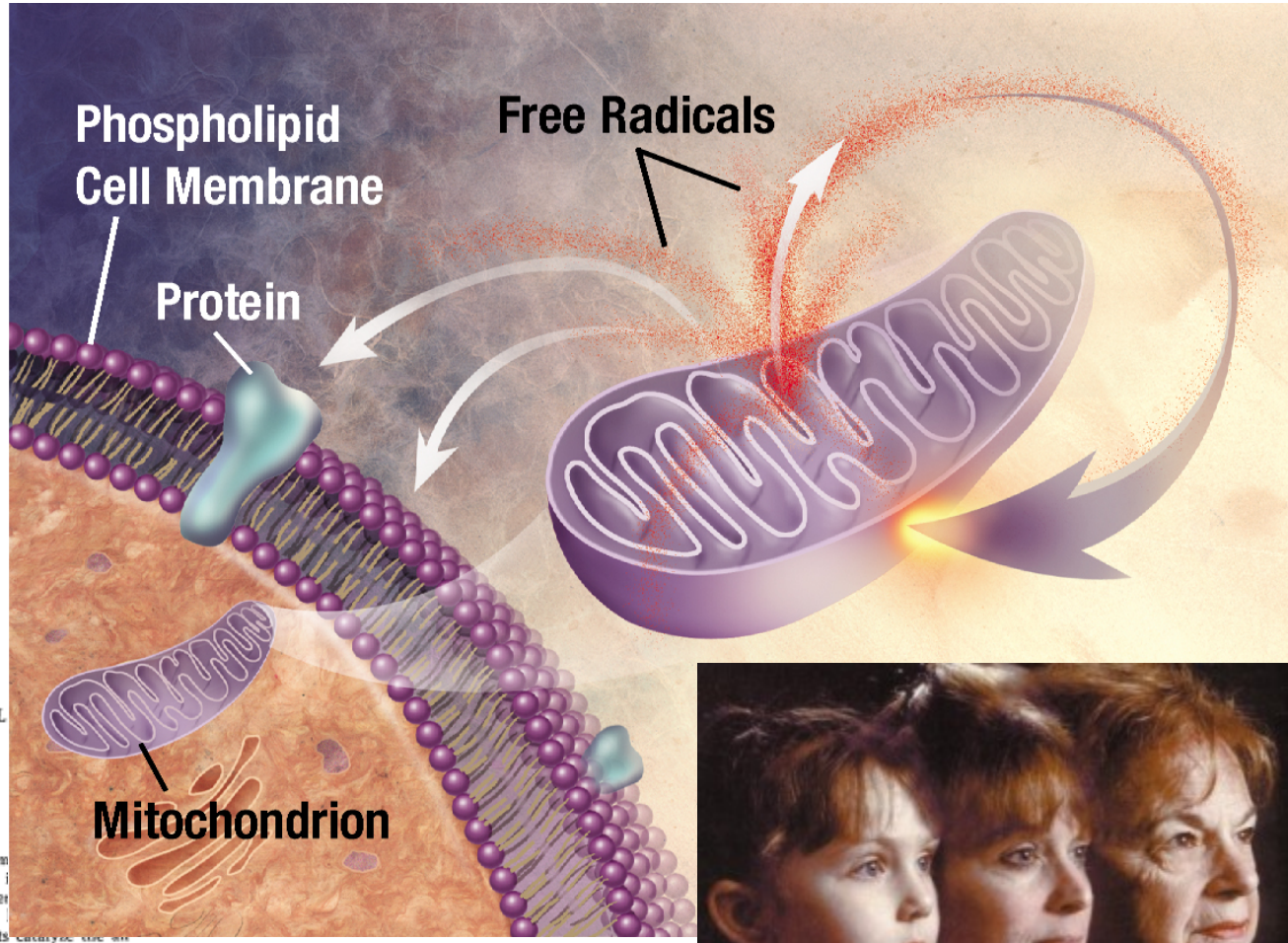
Cardiolipin Biosynthetic and Remodeling Pathways



Mitochondrial Theory of Aging

Dr. Denham Harman
(born February 14, 1916)



AGING: A THEORY BASED ON FREE RADICAL AND RADIATION CHEMISTRY

DENHAM HARMAN, M.D., Ph.D.

(From the Donner Laboratory of Biophysics and Medical Physics, University of California, Berkeley)

The phenomenon of growth, decline and death—aging—has been the source of considerable speculation (1, 8, 10). This cycle seems to be a more or less direct function of the metabolic rate and this in turn depends on the species (animal or plant) on which are superimposed the factors of heredity and the effects of the stresses and strains of life—which alter the metabolic activity.

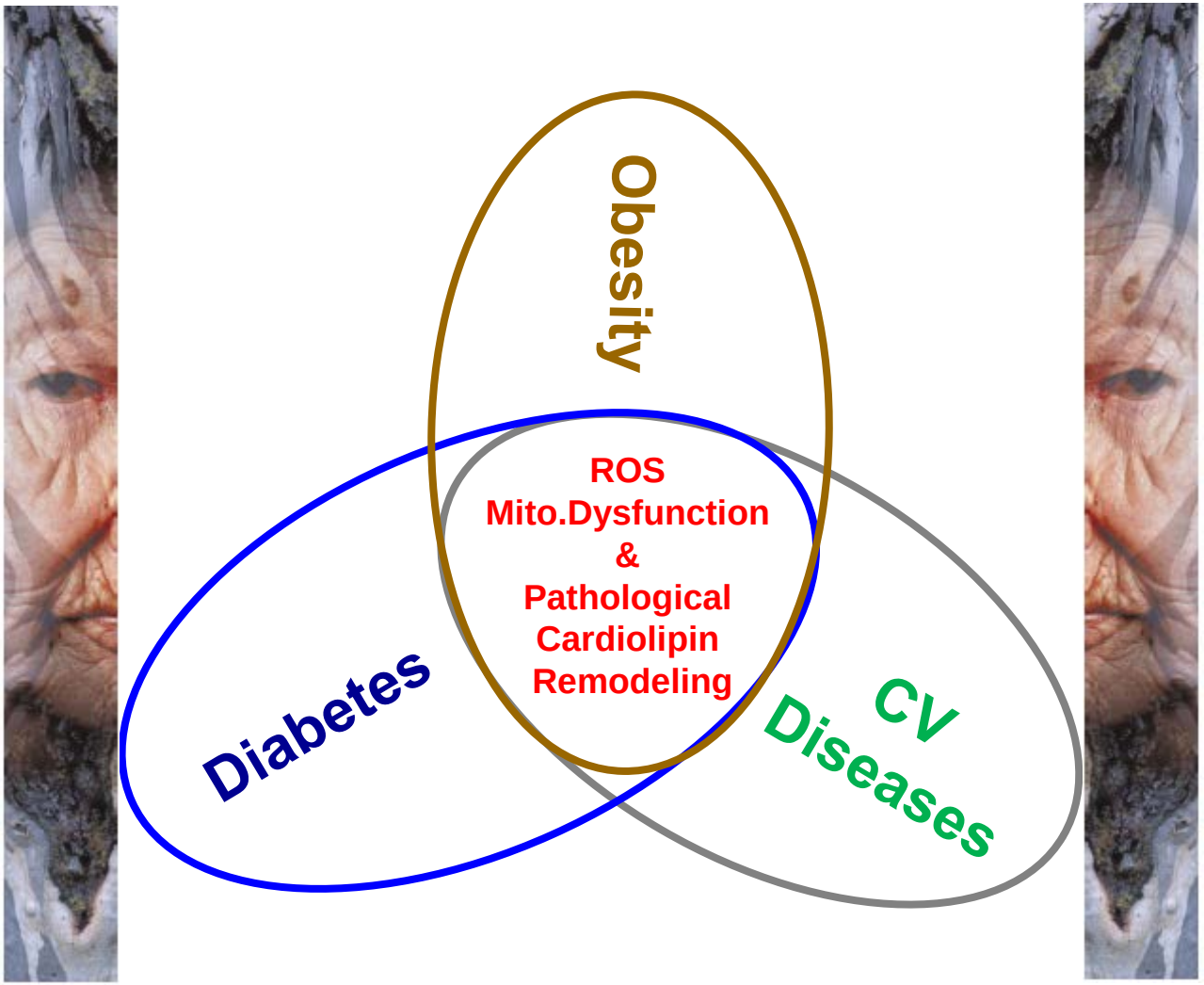
The universality of this phenomenon suggests that the reactions which cause it are basically the same in all living things. Viewing this

in the direct utilization of m
particularly those containing i
action of catalase on hydroge
follows from the fact that it
for many years that iron salts
oxidation of organic compounds (5, 6, 14, 15);
OH radicals are believed to be involved in these
reactions (13). Iron salts also catalyze the decomposition of hydrogen peroxide to water and
oxygen—a reaction that involves OH and HO_2
radicals (16). Further, recent studies in this
laboratory on the inactivation of rat liver cat-

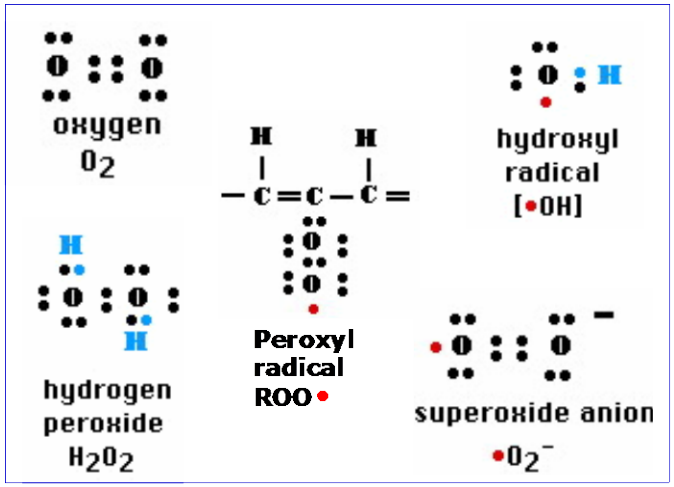
Harman, D (1956) *J. Gerontol.*11 (3): 298–300

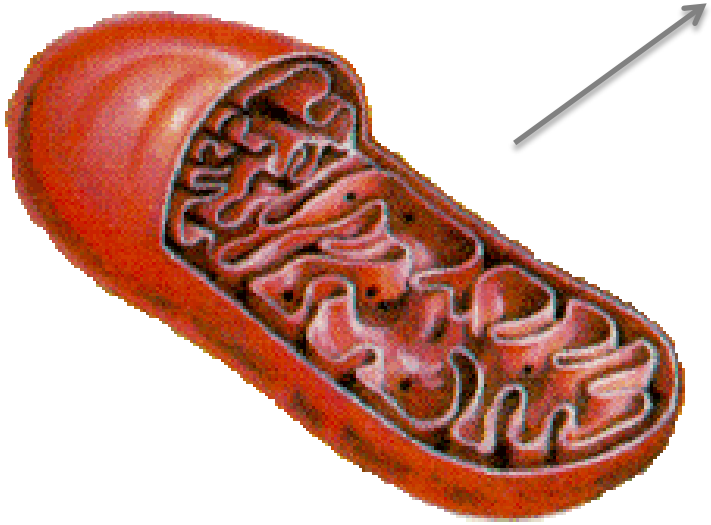
Harman, D (1972). "A biologic clock: the mitochondria?" *J. Am. Geriatrics Society* 20 (4): 145–147

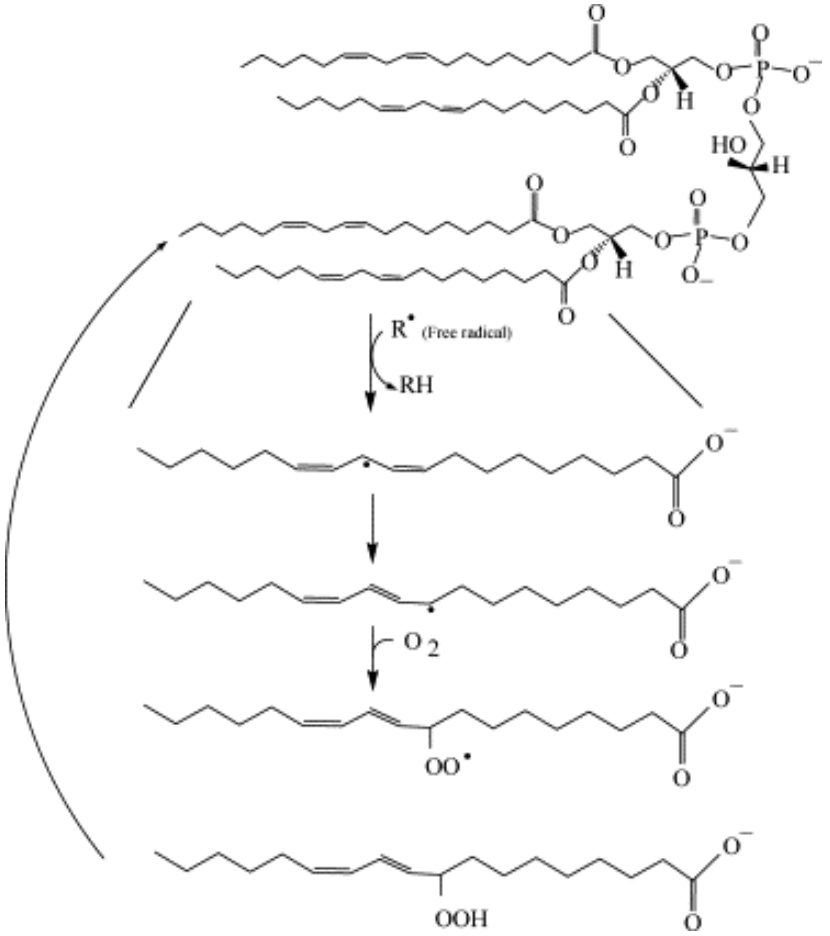
Pathological Remodeling of Cardiolipin Is a Common Defect in Aging-related Diseases



Oxidative Stress and Cardiolipin Peroxidation

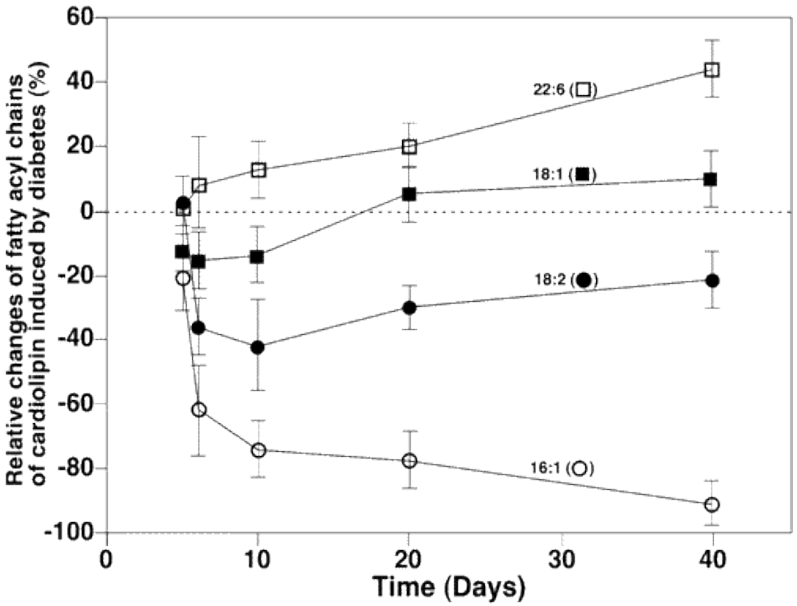






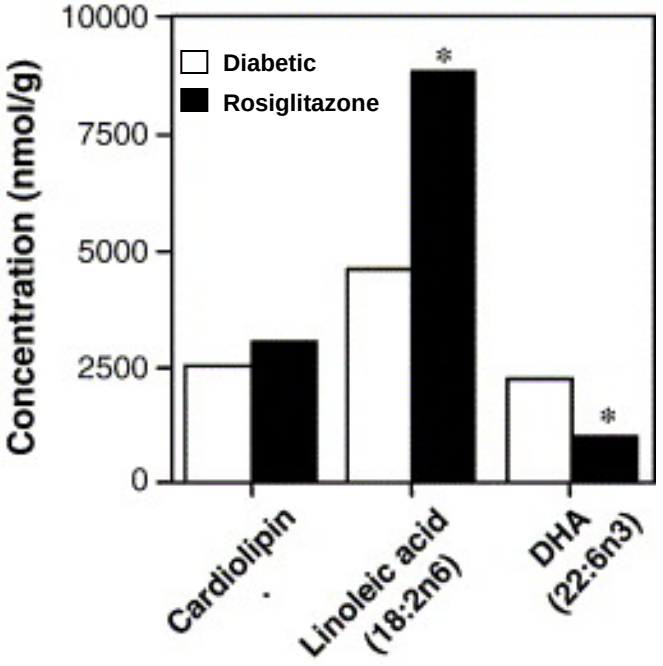
Diabetes and Obesity Increase DHA Content in Cardiolipin

STZ-Diabetic Mouse



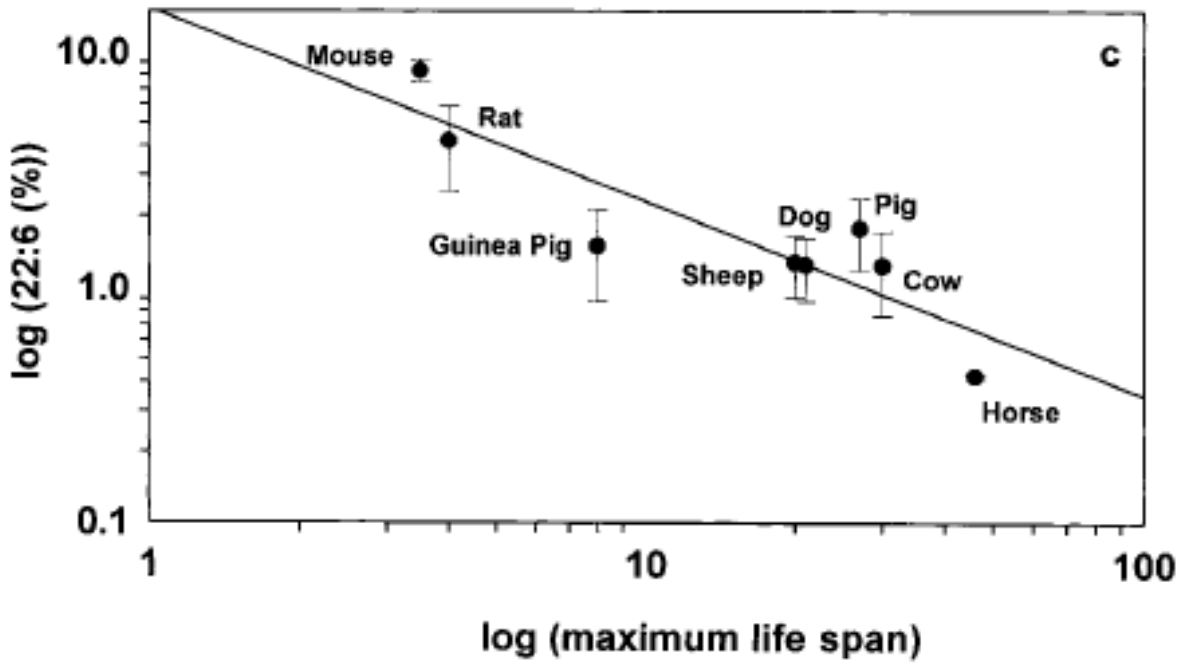
Han *et al, Biochemistry*. 2007 May 29;46(21):6417-6428.

Type 2 Diabetic Mouse



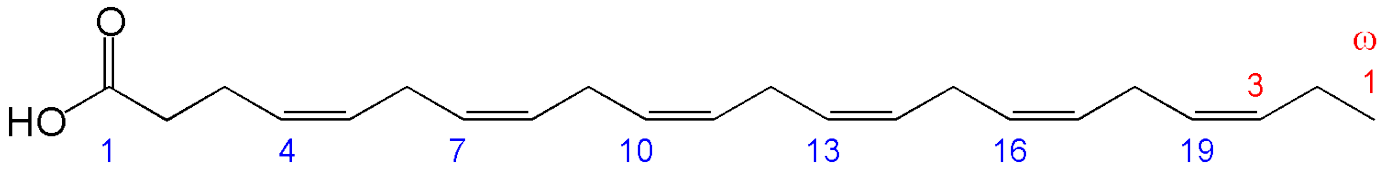
Pan et al, Vascul Pharmacol. 2006 Jul;45(1):65-71

Inverse Relationship between DHA Content in Cardiolipin and Lifespan

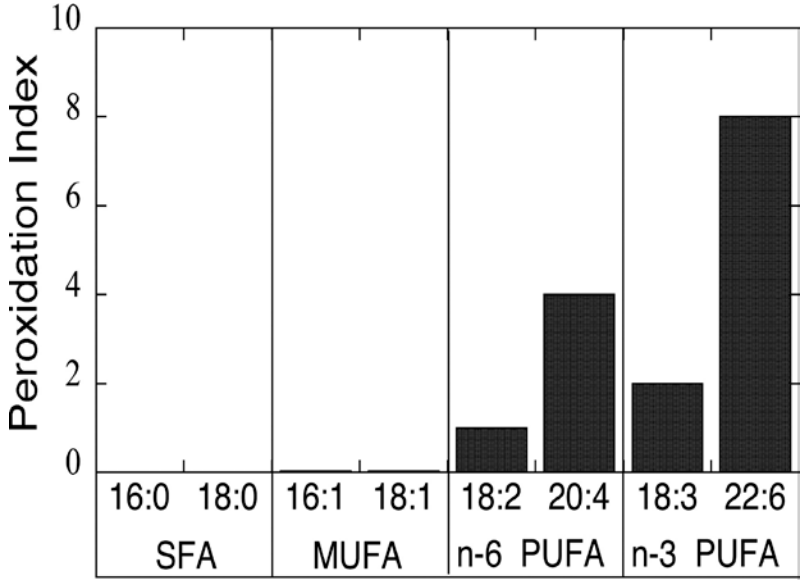


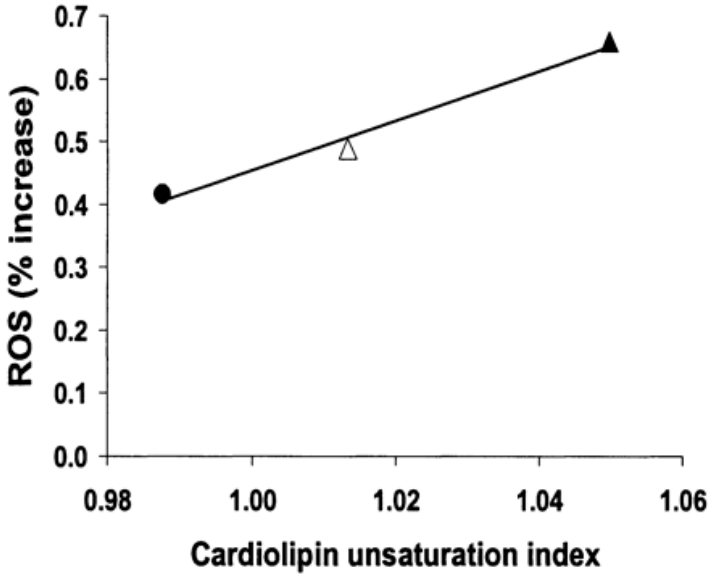
Journal of Lipid Research Volume 39, 1998

DHA Content in Cardiolipin Is Associated with ROS Production Rate



DHA (C22:6)

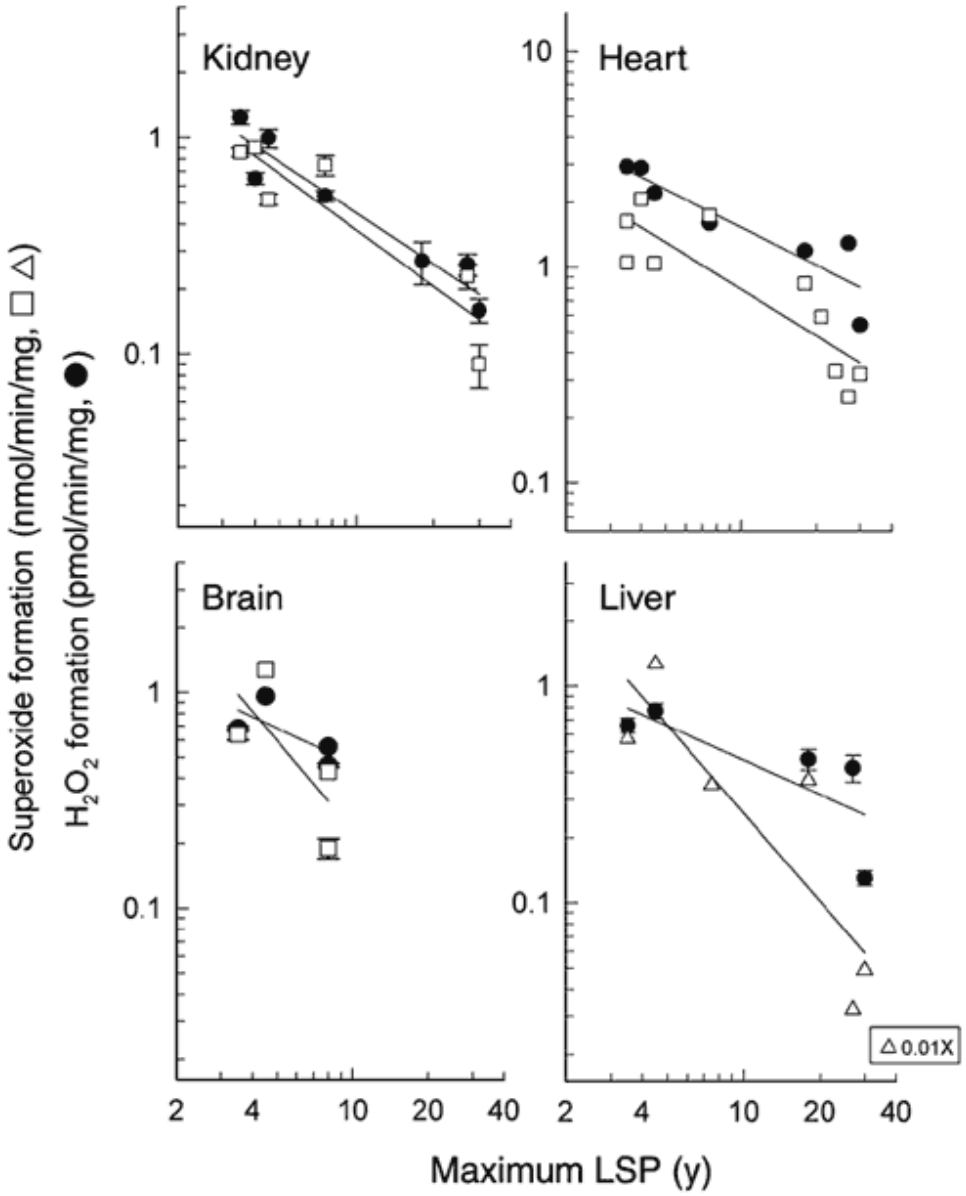




Physiol Rev (2007) 87: 1175–1213

Carcinogenesis (2002), 23 :11 1919-1926

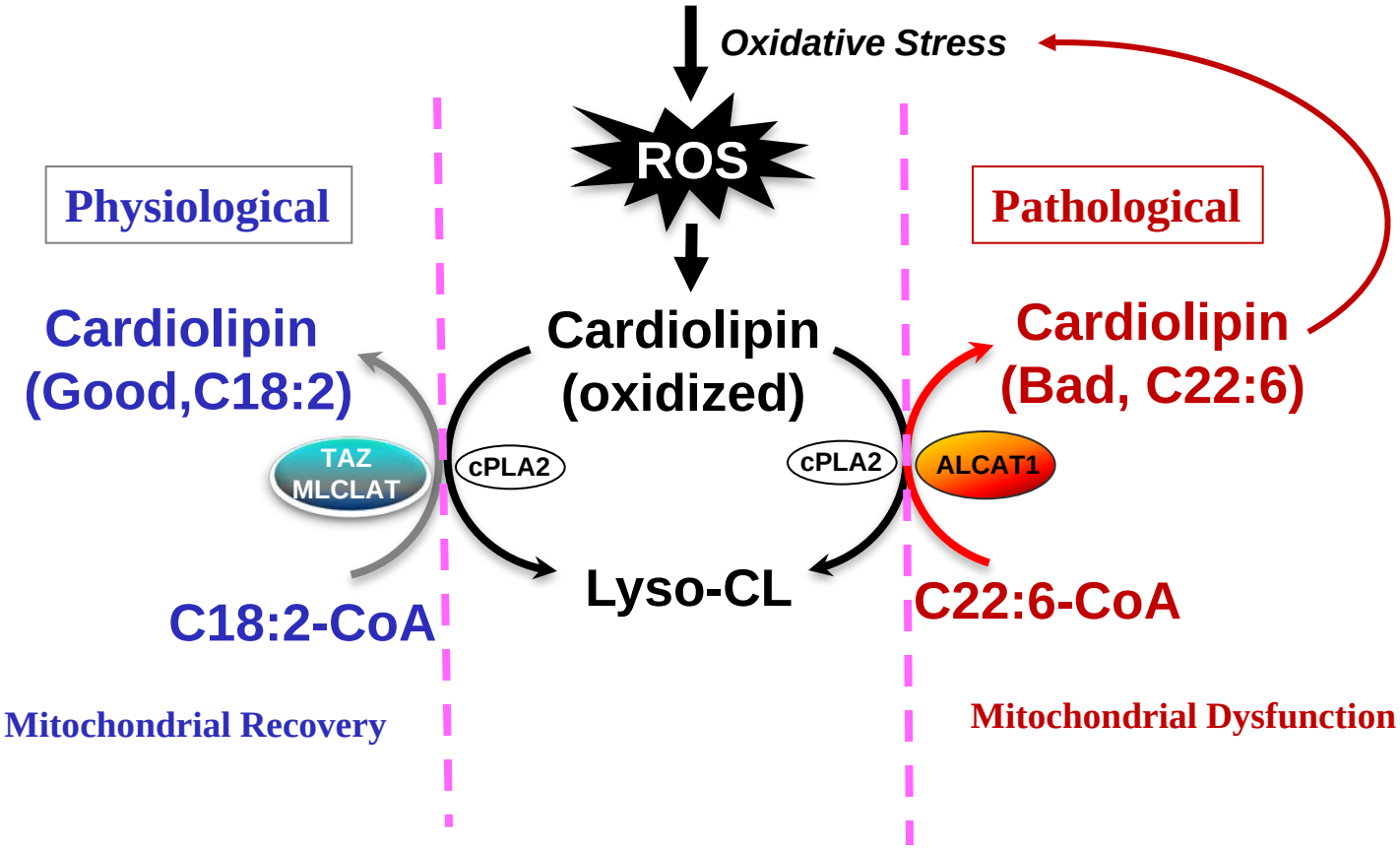
Inverse Relationship between ROS Production and Lifespan



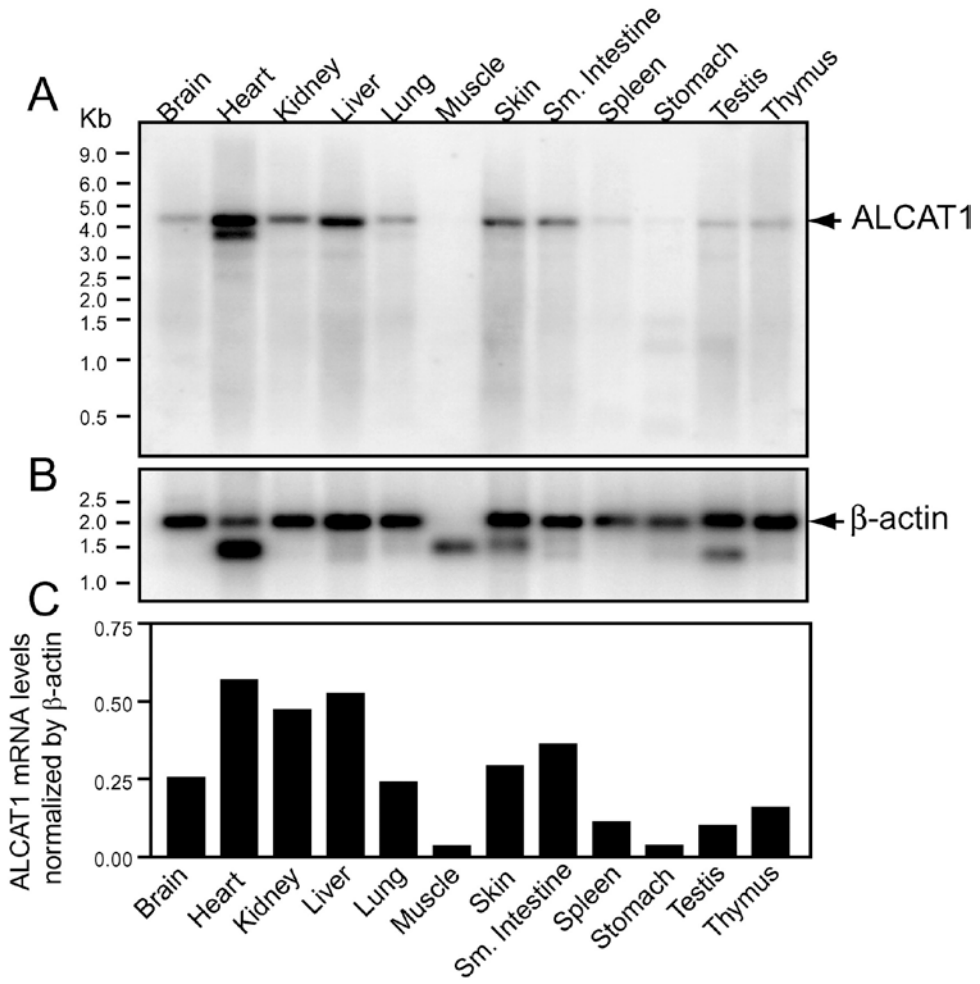
Nat Genet. 2004 Nov;36(11):1153-8.

Oxidative Stress, Metabolic Diseases, and Cardiolipin Remodeling

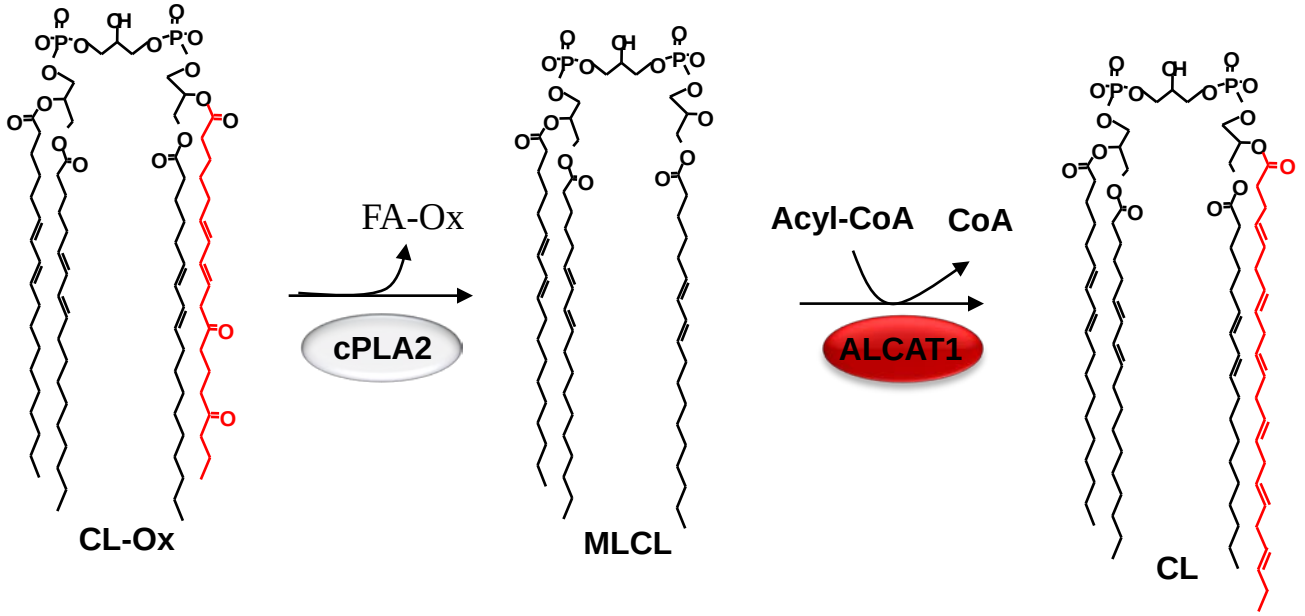
Diabetes, Obesity, and CV Diseases



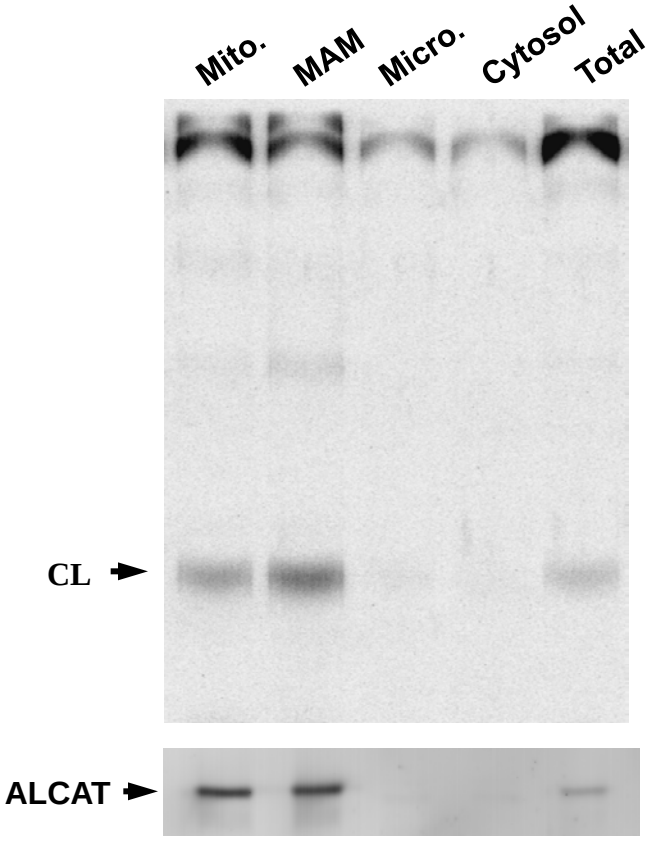
ALCAT1 Is Predominantly Expressed in Tissues with High Basal Metabolic Rate

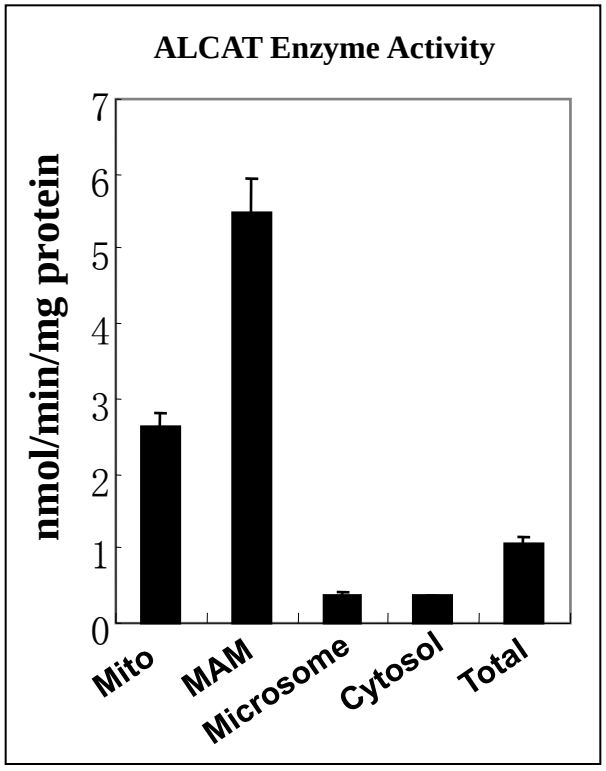


ALCAT1 Catalyzes Acylation of Lysocardiolipin



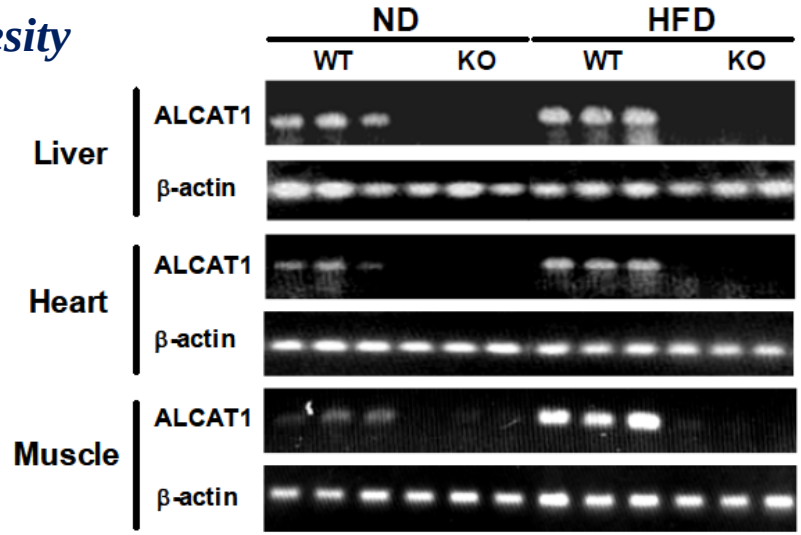
The Recombinant ALCAT1 Protein Is Localized in the Mitochondria-Associated Membrane (MAM)

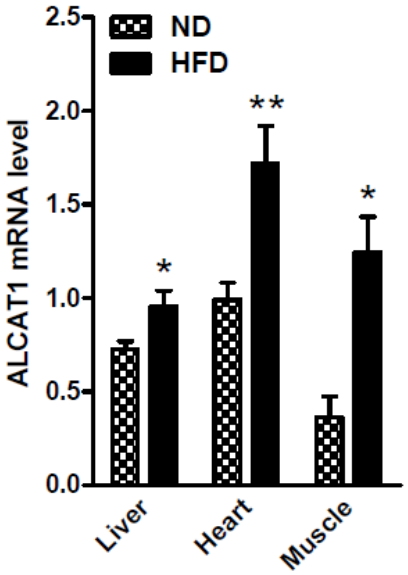




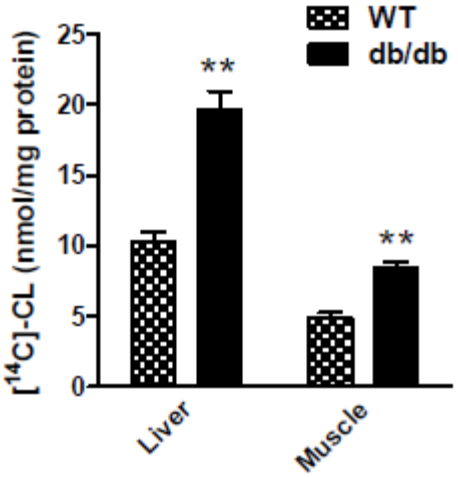
Up-Regulation of ALCAT1 Enzyme Activity and mRNA Expression by the Onset of Obesity, Diabetes, and Heart Disease

Obesity

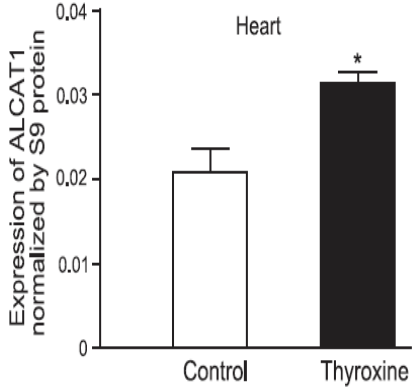




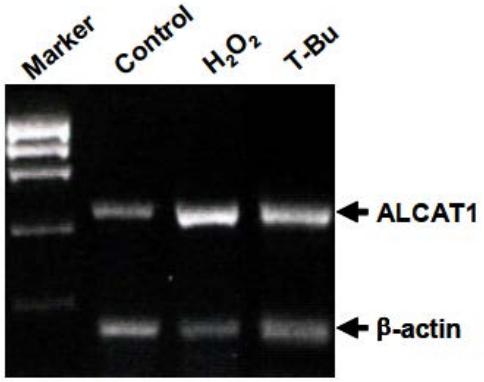
Diabetes



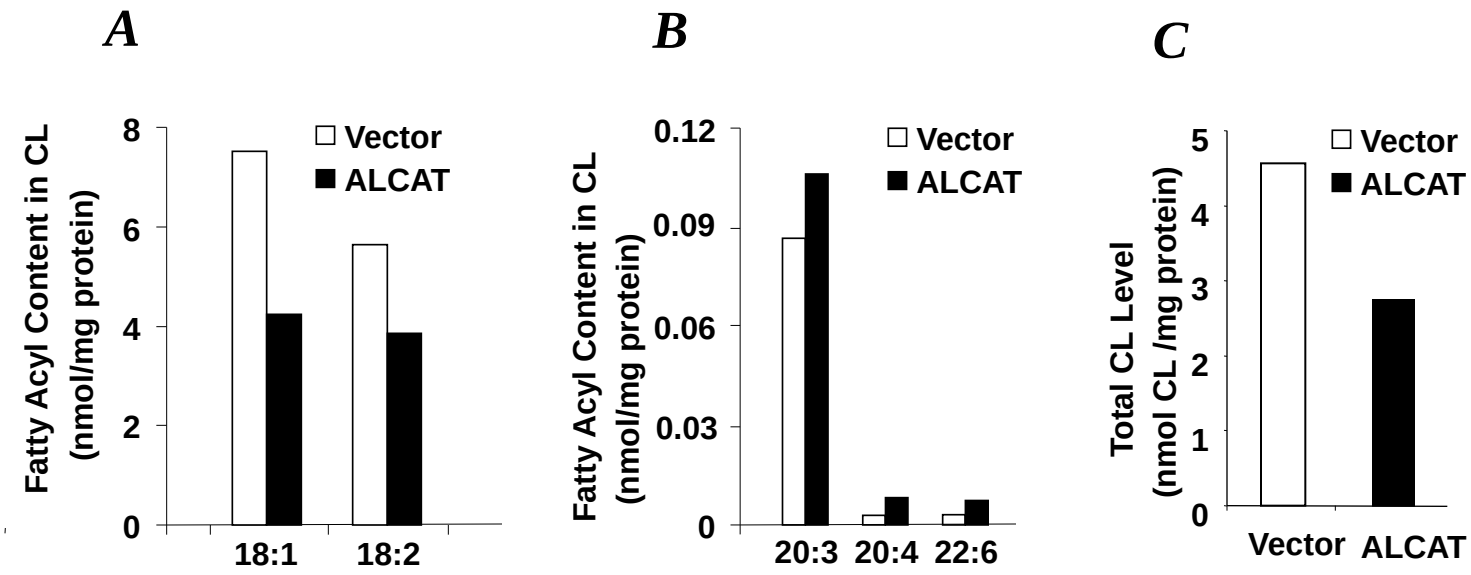
Cardiomyopathy



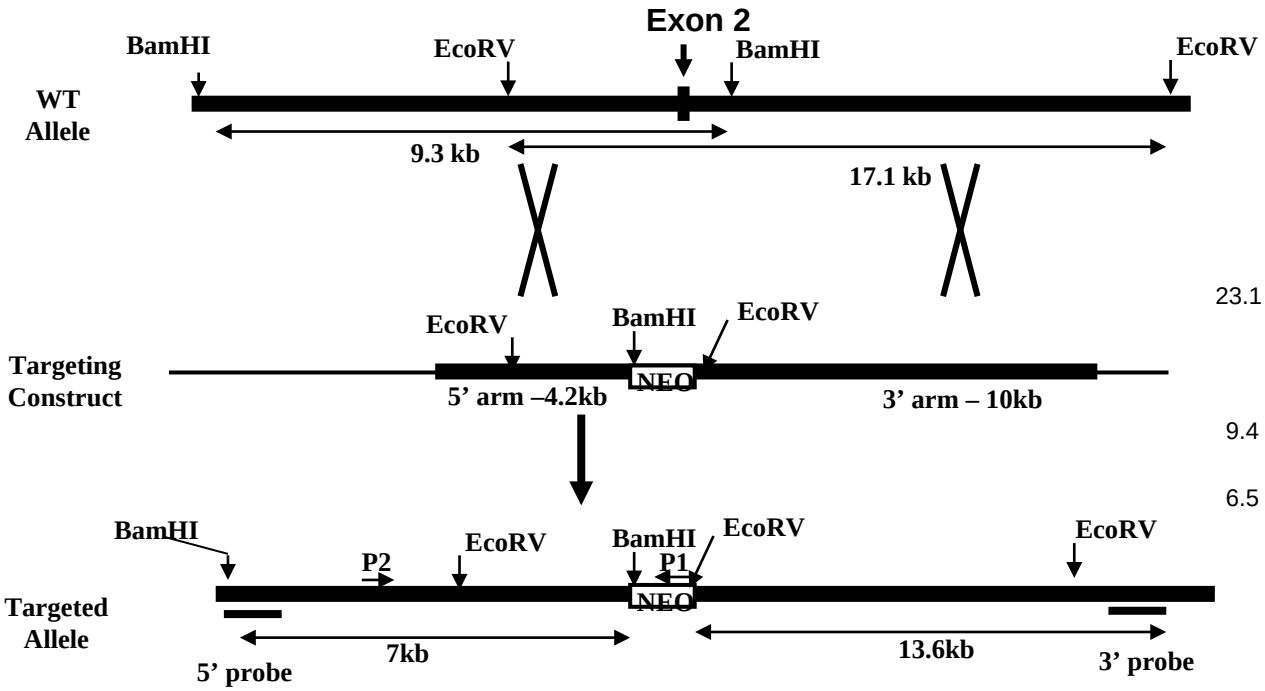
Oxidative Stress

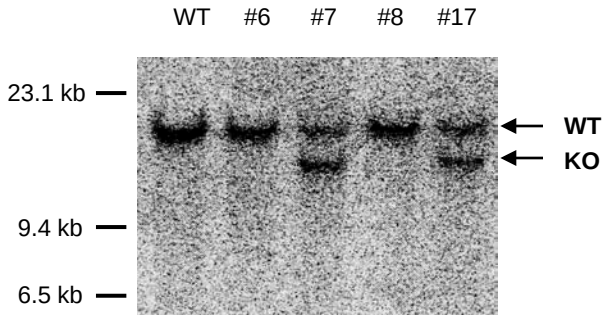


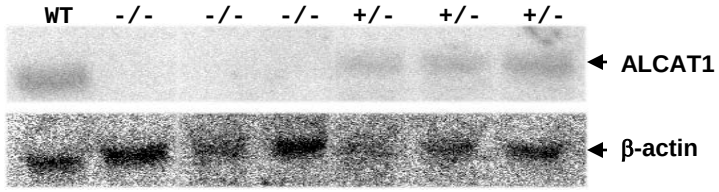
ALCAT1 Catalyzes Pathological Remodeling of Cardiolipin Commonly Associated with Diabetes and Obesity



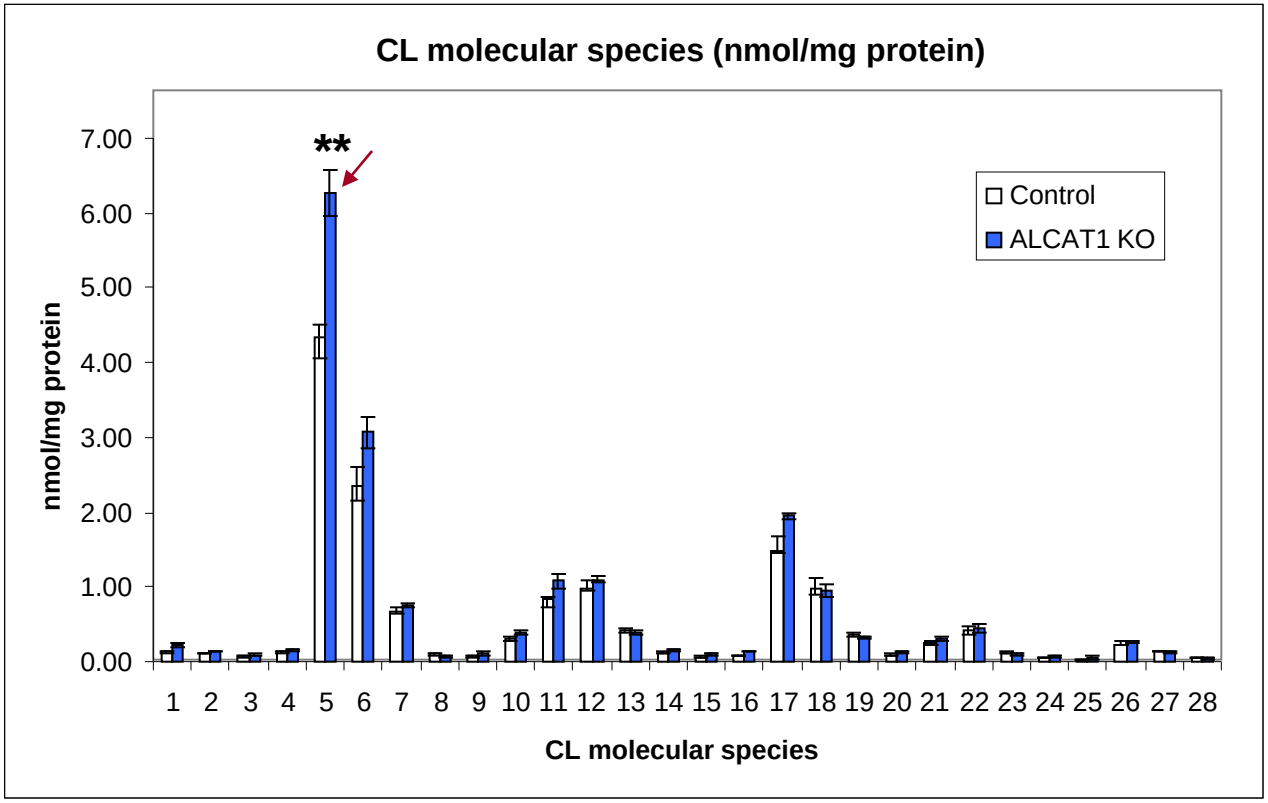
Generation of Mice With Targeted Deletion of ALCAT1 Gene







Increased Linoleic Acid Content in Cardiolipin in the Heart of ALCAT1 Knockout Mice



Column #	MOLECULAR SPECIES from primary MS
1	18:2-18:2-18:2-16:1
2	18:2-18:2-18:1-16:1, 18:2-18:2-18:2-16:0 (1:1)
3	18:2-18:1-18:1-16:1, 18:2-18:2-18:1-16:0 (1:1)
4	18:3-18:2-18:2-18:2
5	18:2-18:2-18:2-18:2
6	18:2-18:2-18:2-18:1
7	18:2-18:2-18:1-18:1
8	18:2-18:1-18:1-18:1
9	18:2-18:2-16:1-22:6
10	18:2-18:2-18:2-20:4, 18:2-18:1-16:1-22:6, 18:2-18:2-16:0-22:6 (2:2:1)
11	18:2-18:2-18:2-20:3
12	18:2-18:2-18:1-20:3, 18:2-18:2-18:2-20:2
13	18:1-18:2-18:2-20:2
14	18:1-18:2-18:2-20:1, 18:1-18:1-18:2-20:2 (1:1)
15	18:1-18:1-18:2-20:1, 18:1-18:1-18:0-20:3 (2:1)
16	18:2-18:2-18:3-22:6
17	18:2-18:2-18:2-22:6
18	18:2-18:2-18:2-22:5, 18:1-18:2-18:2-22:6 (1:1)
19	18:2-18:2-18:1-22:5, 18:2-18:1-18:1-22:6 (2:1)
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22	18:2-18:1-20:3-22:6, 18:2-18:2-20:2-22:6
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25	18:2-18:3-22:6-22:6
26	18:2-18:2-22:6-22:6
27	18:2-18:1-22:6-22:6
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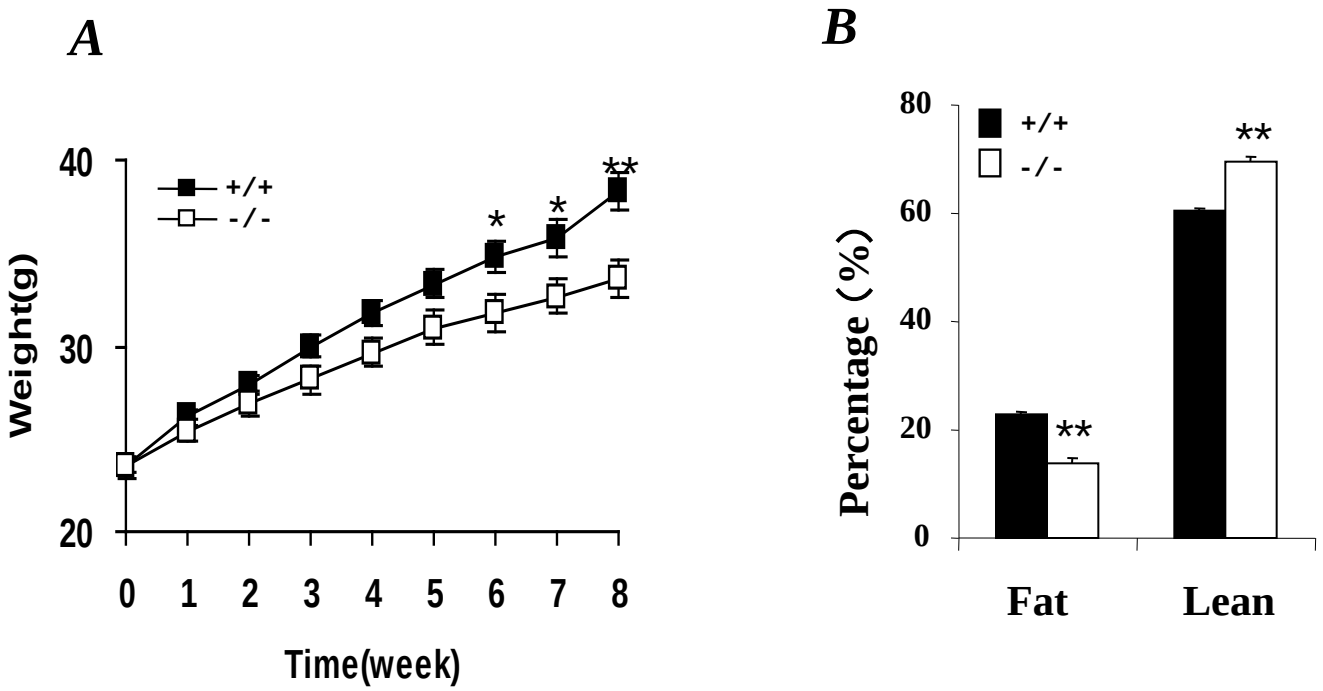
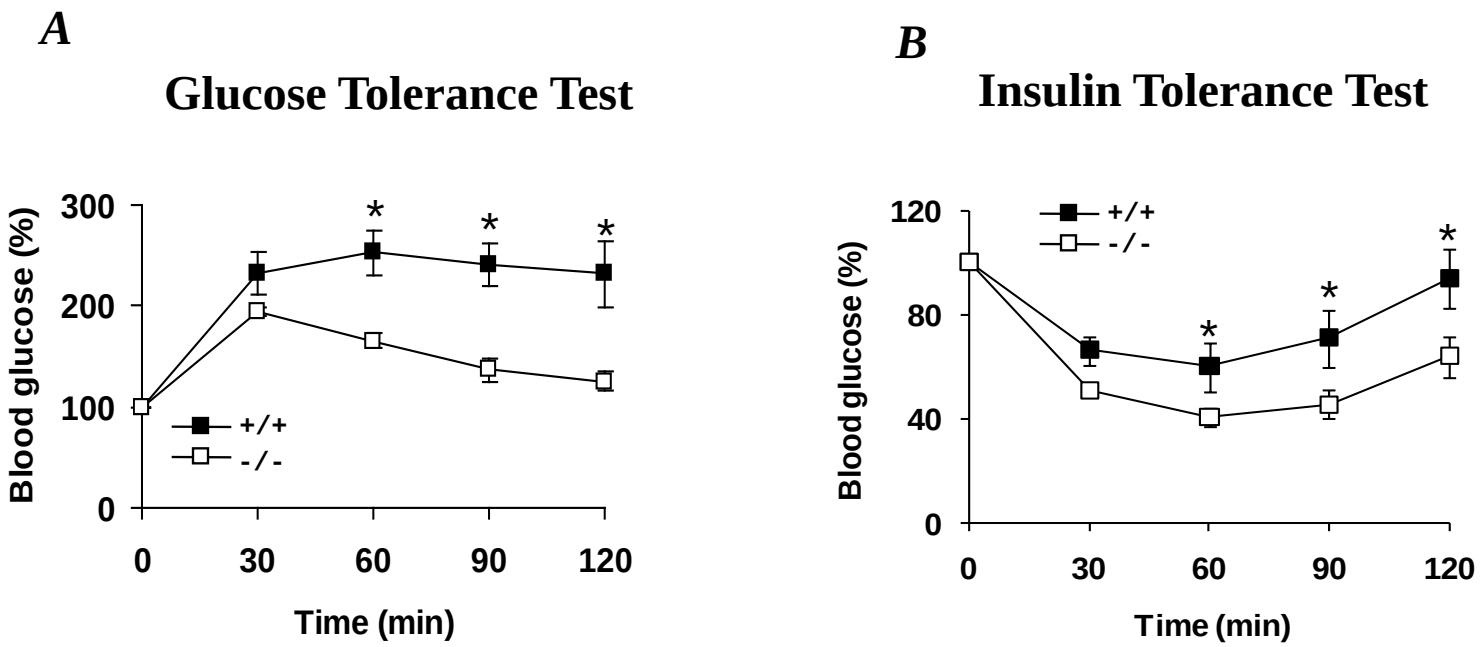
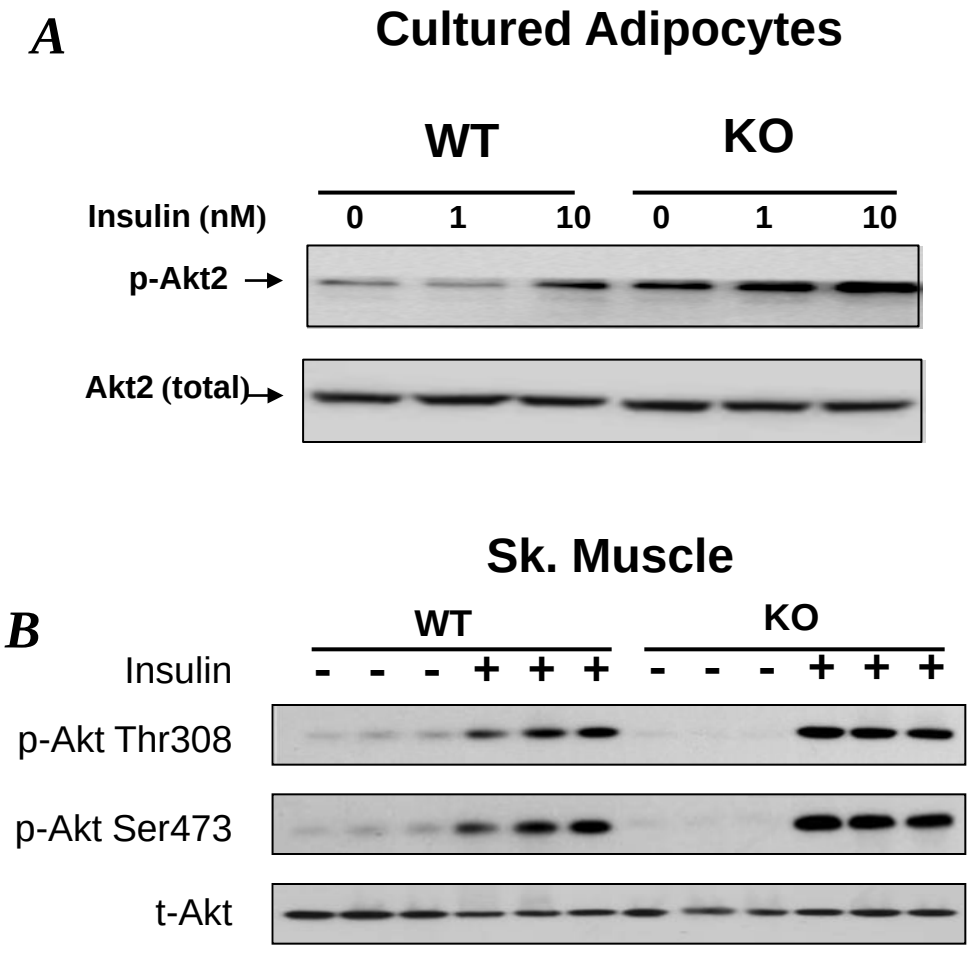
ALCAT Knockout Mice Are Resistant to the Onset of Diet-Induced Obesity



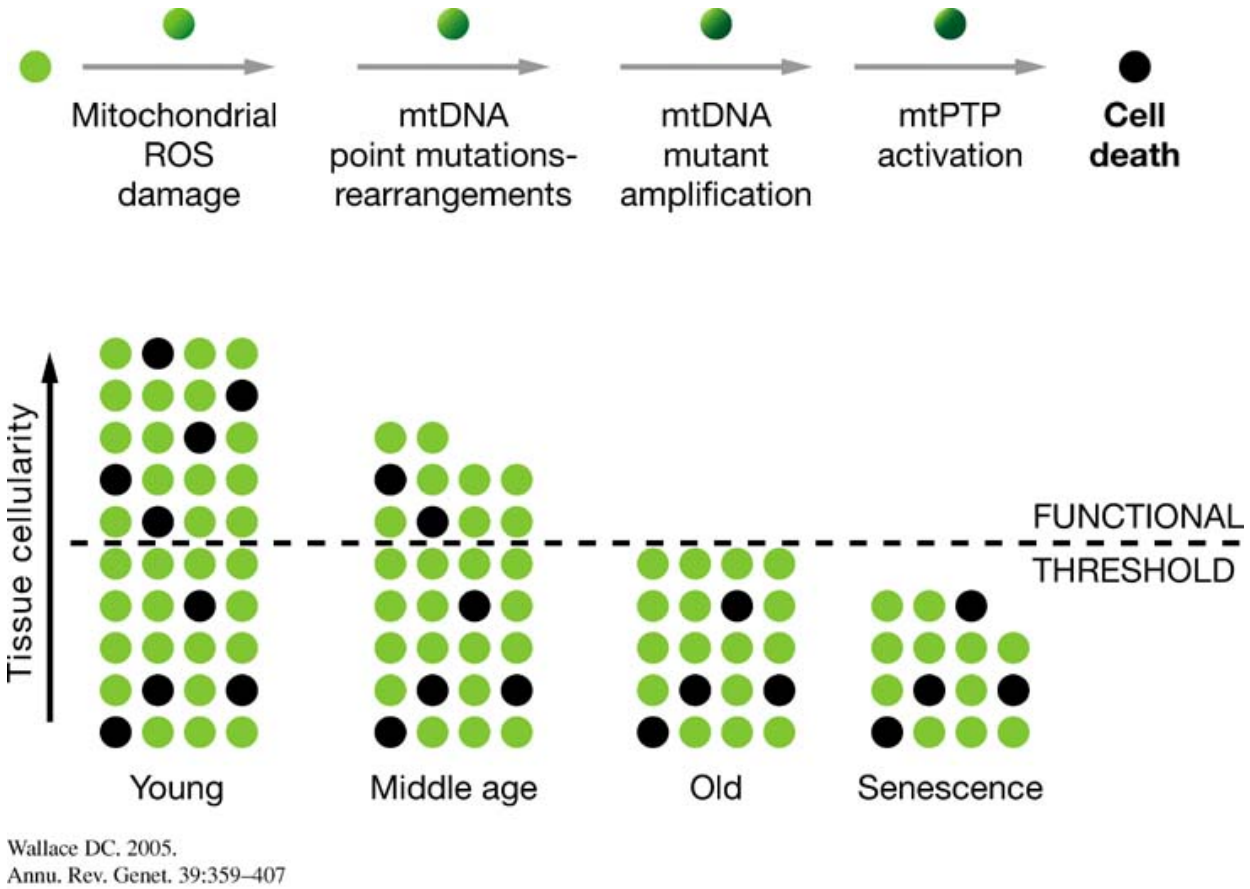
Improved Glucose Tolerance and Insulin Sensitivity in ALCAT1 Knockout Mice



ALCAT1 Deficiency Improves Insulin Signaling in ALCAT1 Knockout Mice

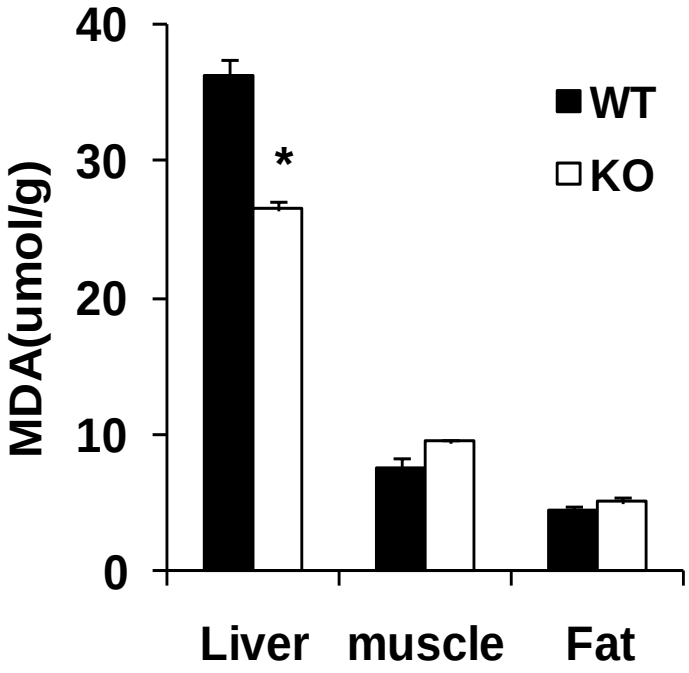


Oxidative Stress and Mitochondrial Aging

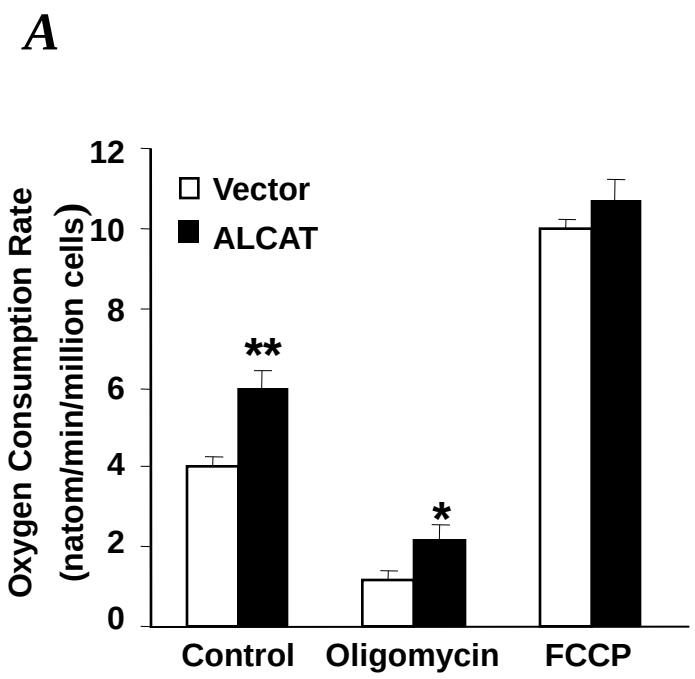


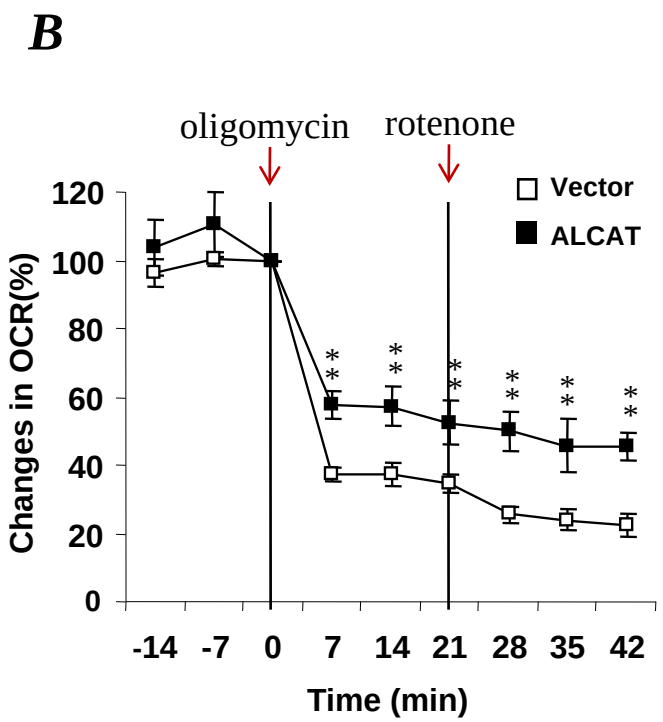
Wallace DC. 2005.
Annu. Rev. Genet. 39:359–407

ALCAT1 Deficiency Prevents Lipid Peroxidation In Liver

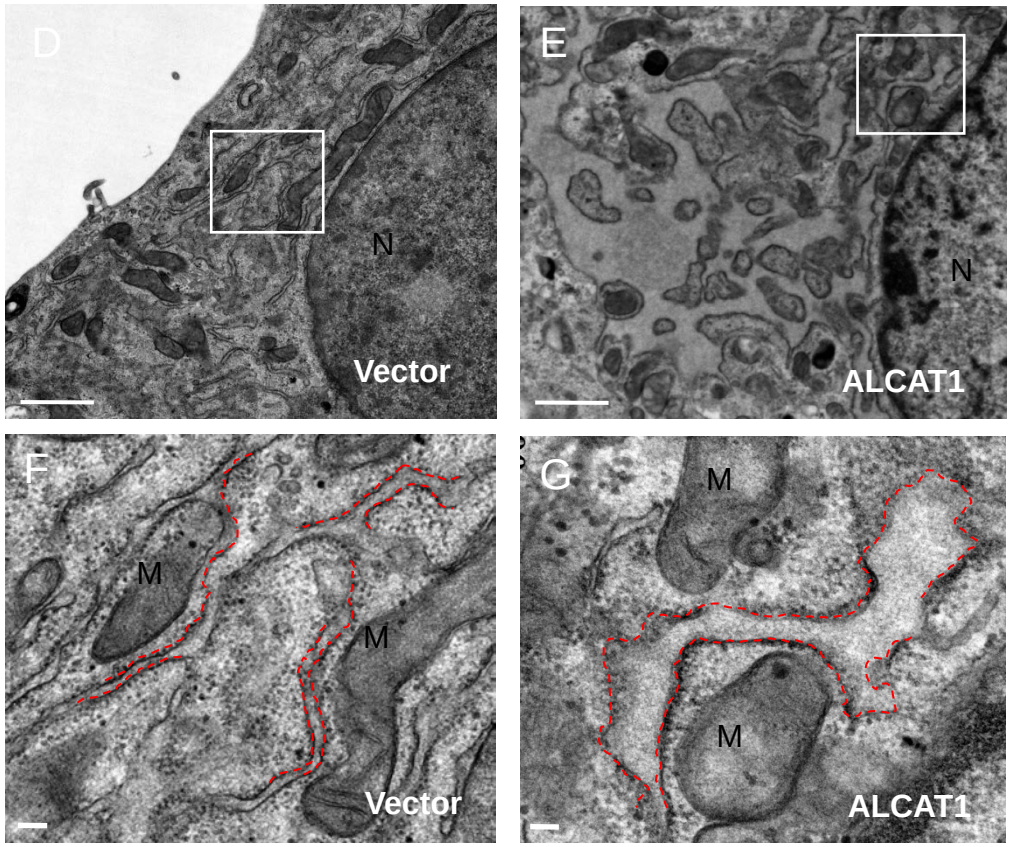


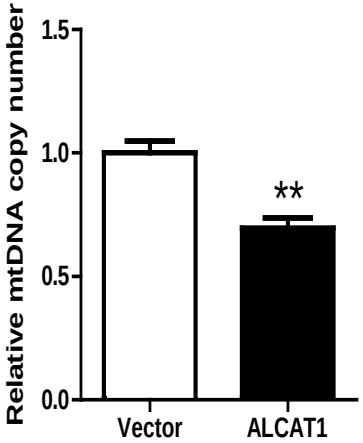
Overexpression of ALCAT1 in C2C12 Cells Increases Oxygen Consumption Rate and Mitochondrial Proton Leakage

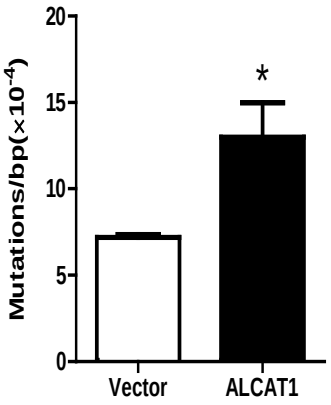




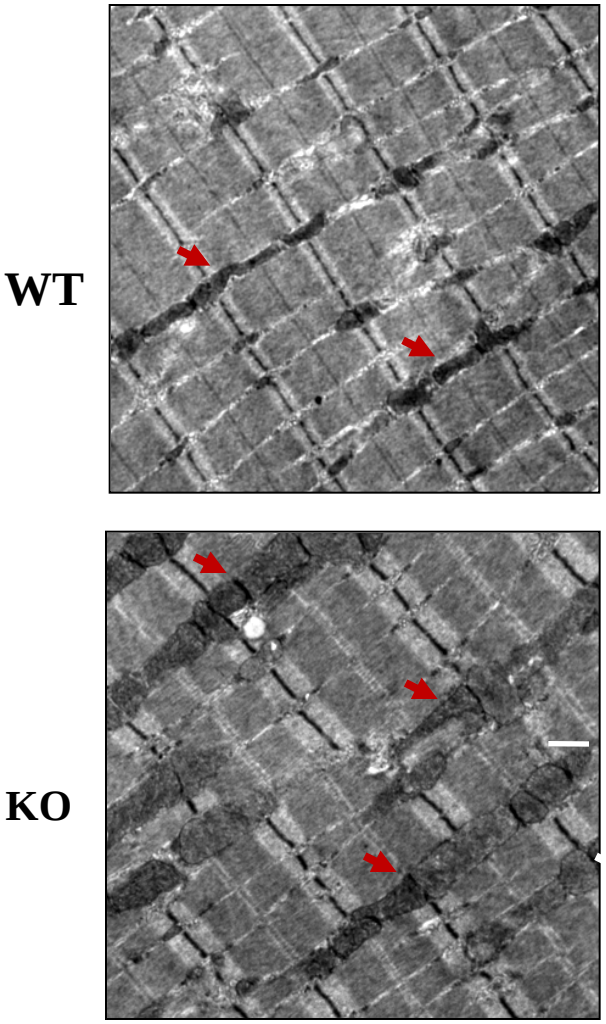
ALCAT1 Overexpression Depletes Mitochondrial Number and Increases Mitochondrial Mutation Rate in C2C12 Cells

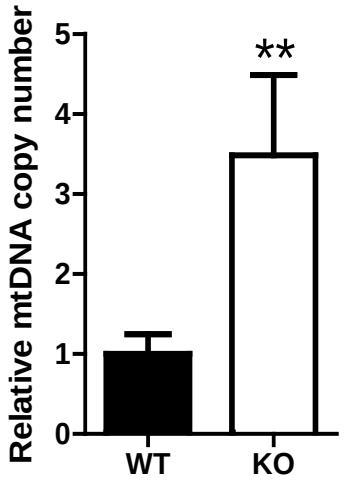


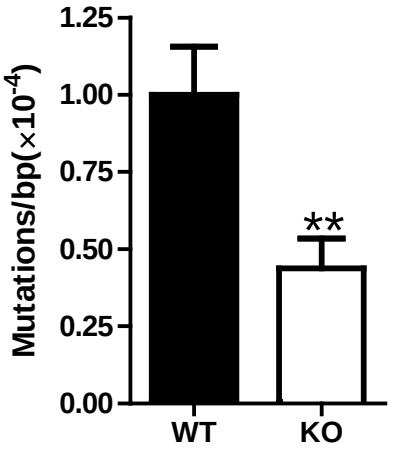




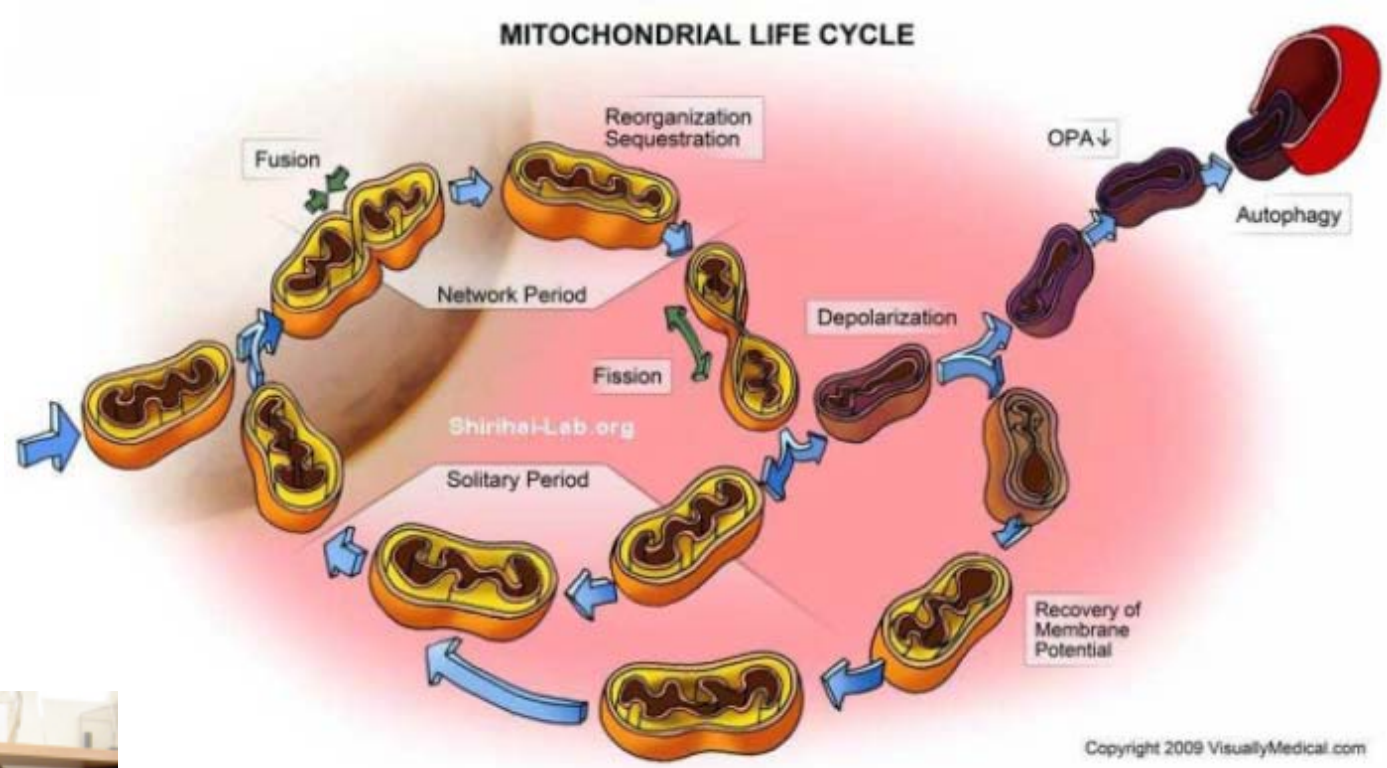
ALCAT1 Deficiency Increases Mitochondrial Number and Decreases Mutation Rate in Skeletal Muscle





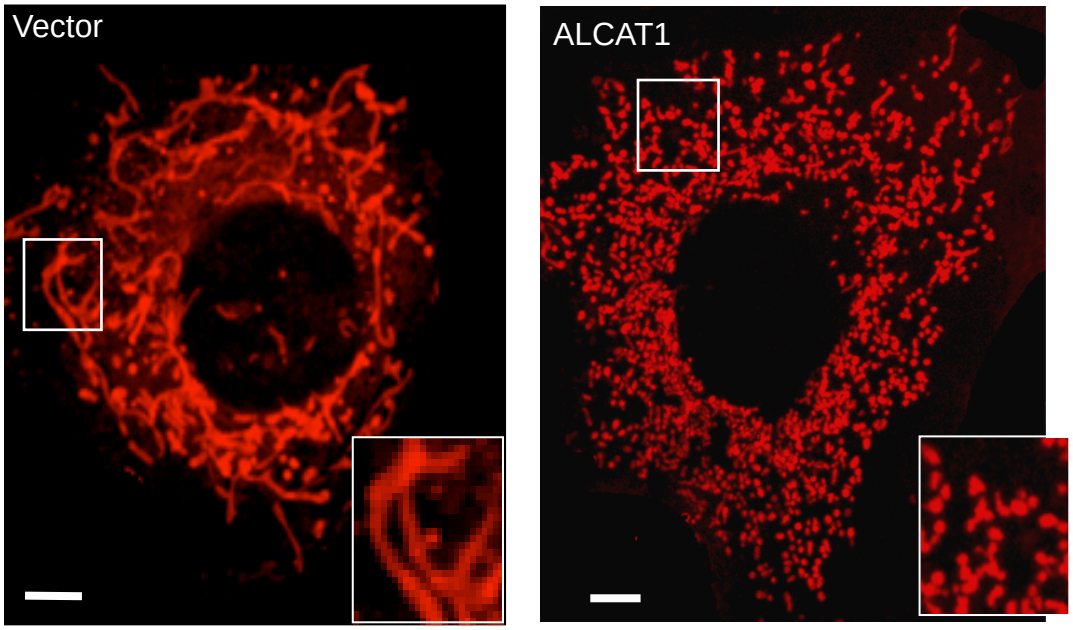


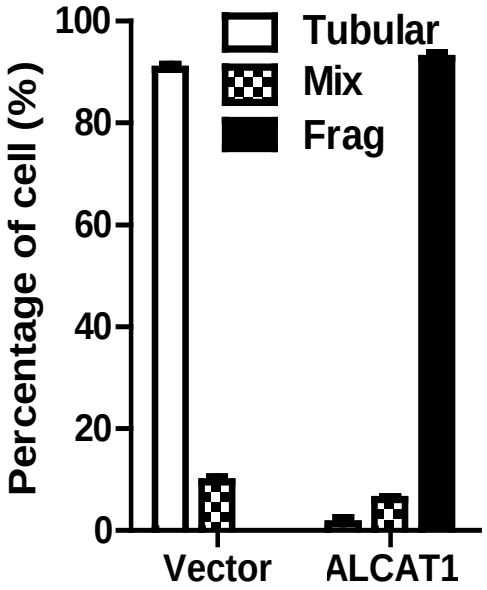
Mitochondrial Fusion and Fission in Quality Control



EMBO J 2008; (27): 433-446

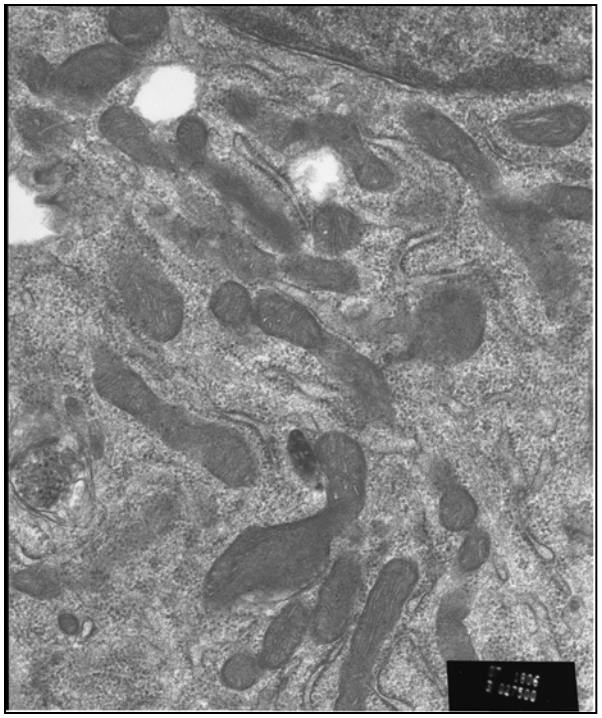
Overexpression of ALCAT1 in C2C12 Cells Causes Mitochondrial Fragmentation



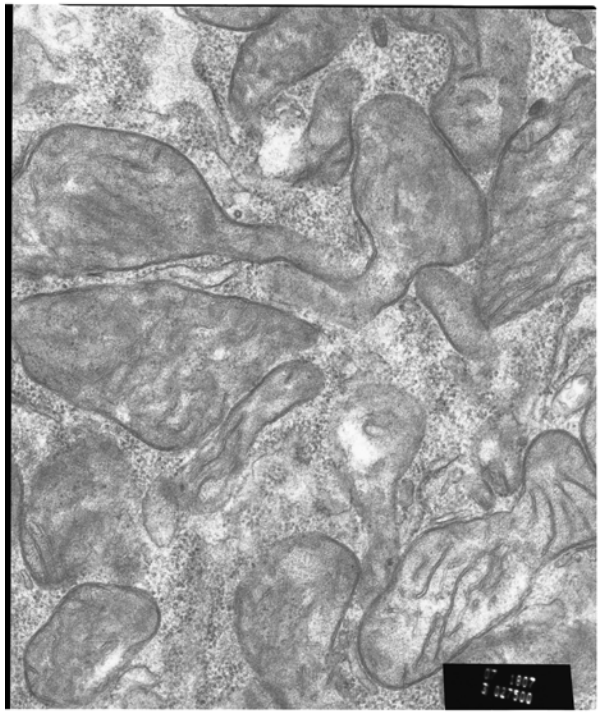


Overexpression of ALCAT1 in C2C12 Cells Causes Mitochondrial Swelling

VECTOR

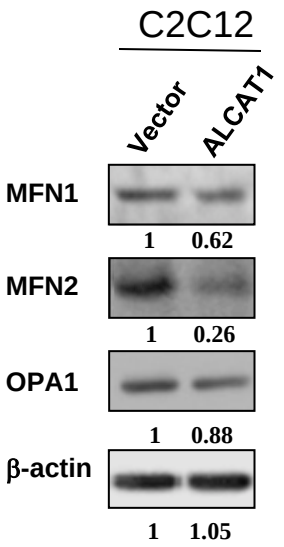


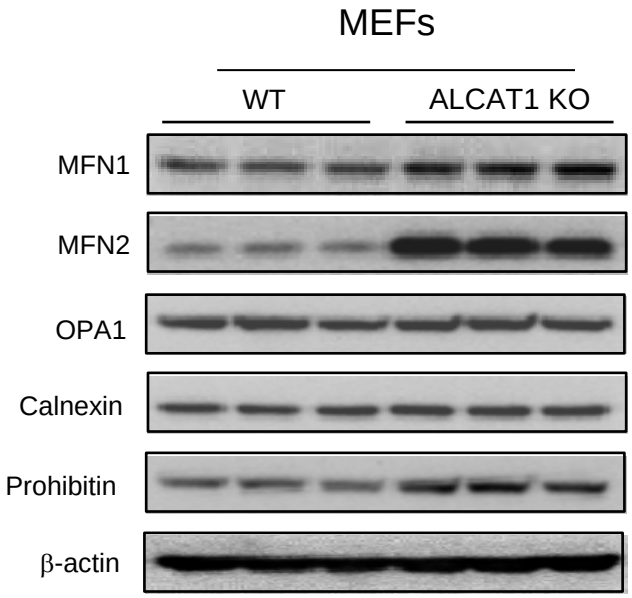
ALCAT1

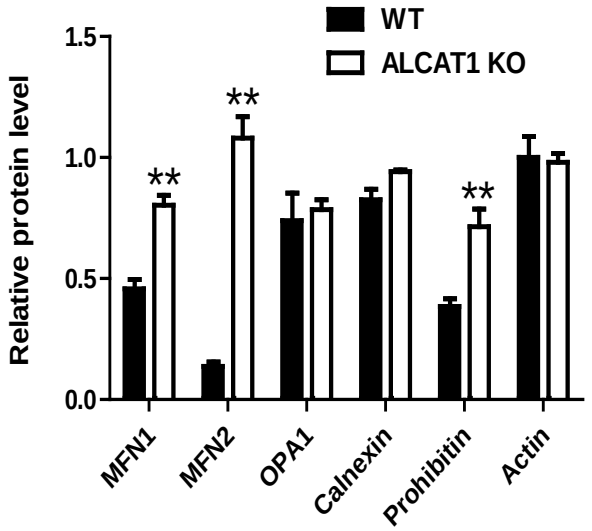


0.6 μM

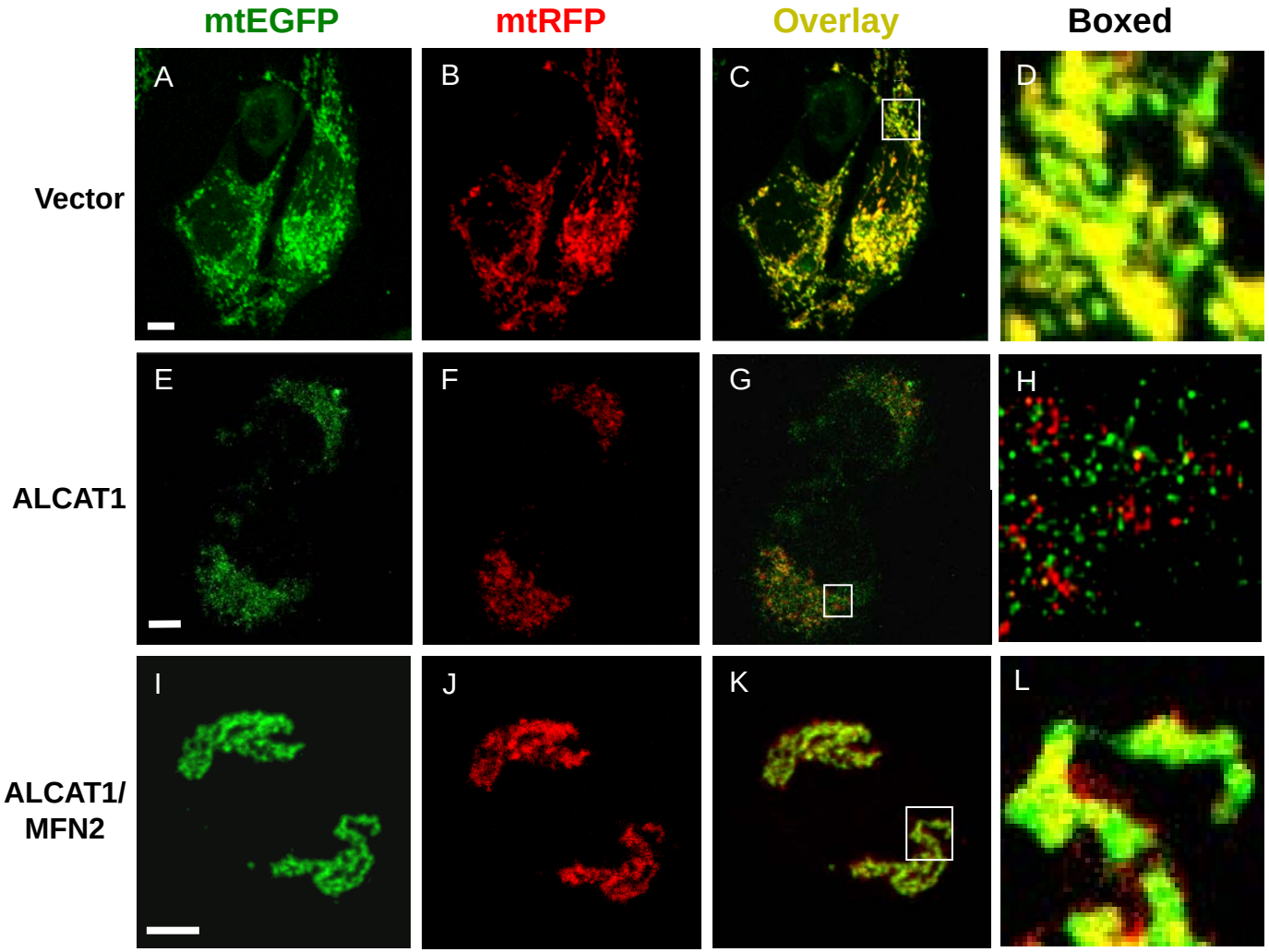
ALCAT1 Deficiency Increases Expression of MFN2 in MEF



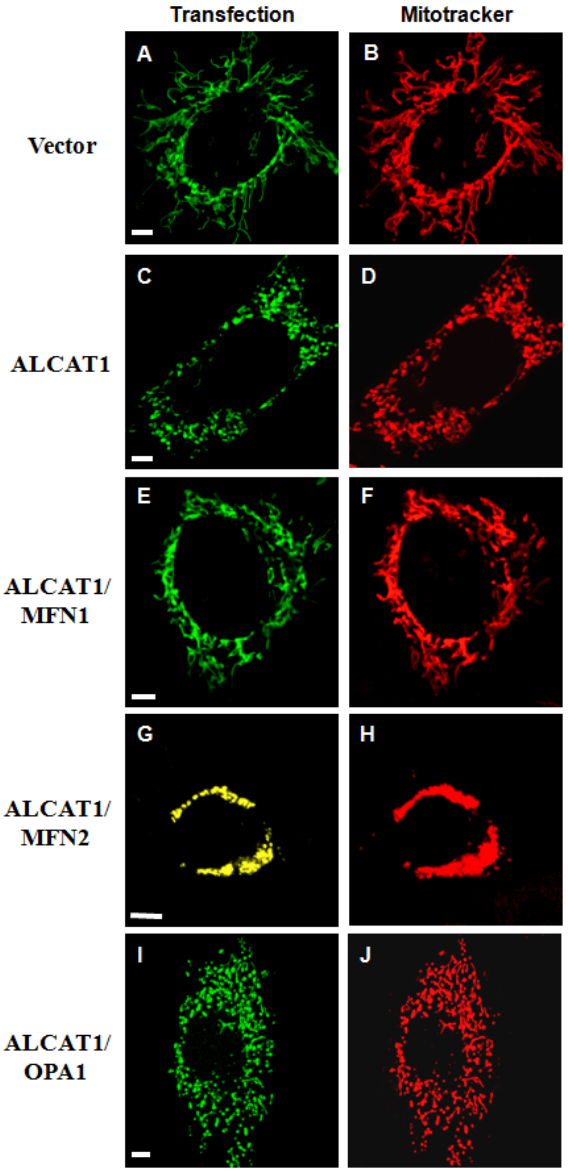




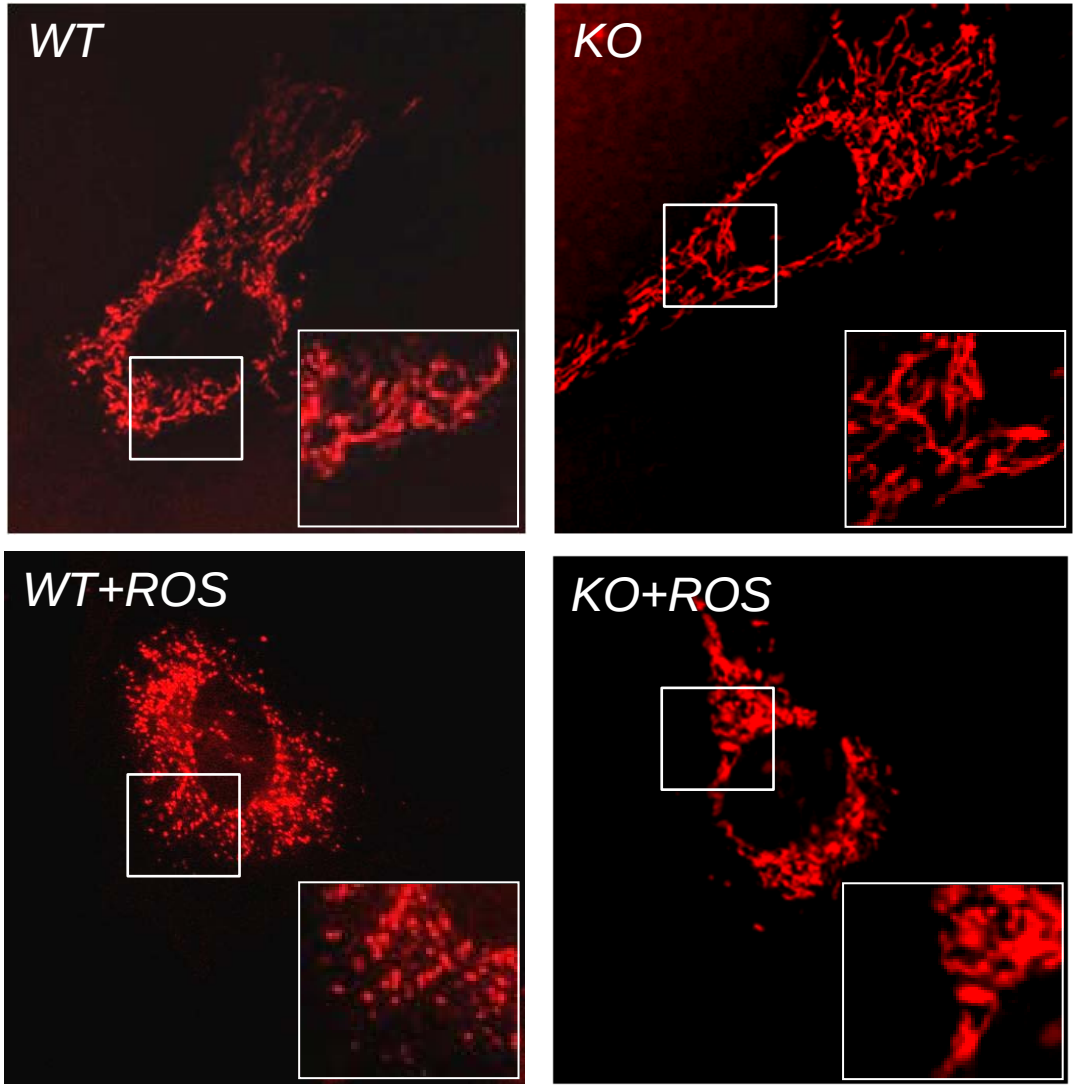
ALCAT1 Overexpression Imparis Mitochondrial Fusion



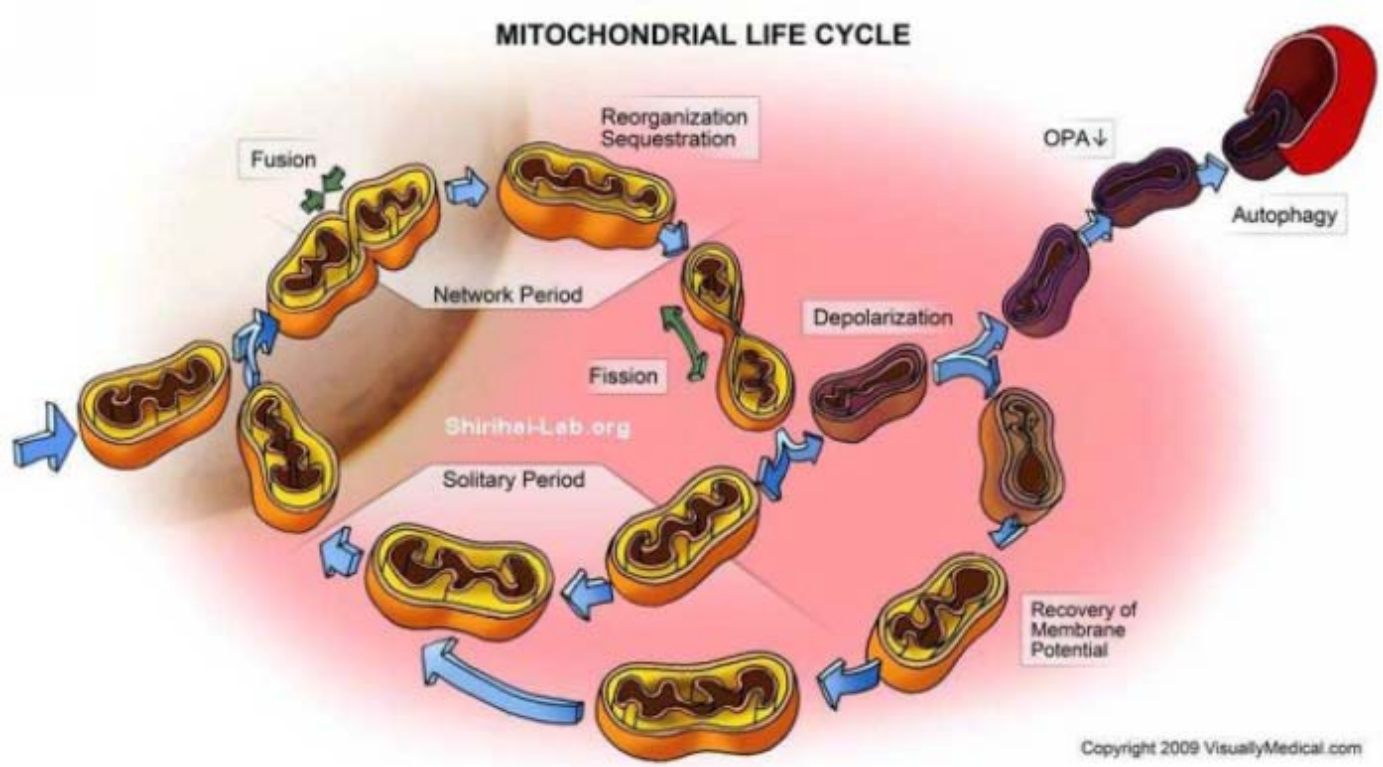
MFN1 and MFN2, but not OPA1 Rescue Mitochondrial Fusion Defects Caused by ALCAT1 Overexpression in C2C12 Cells



ALCAT1 Deficiency Prevents Mitochondrial Fragmentation in MEFs In Response to Oxidative Stress



Mitochondrial Fusion and Fission in Quality Control



The Working Model of ALCAT1 and Mitochondrial Dysfunction