Cours du 10-11-2014

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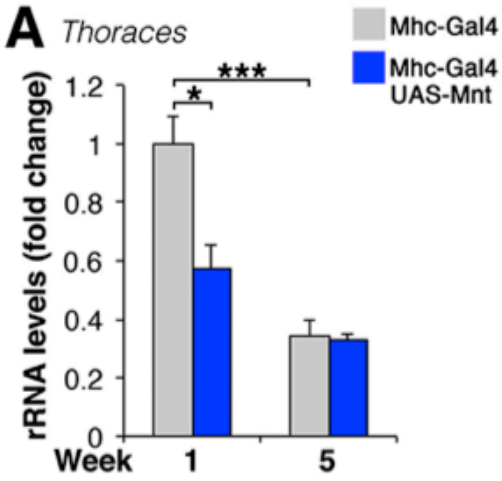
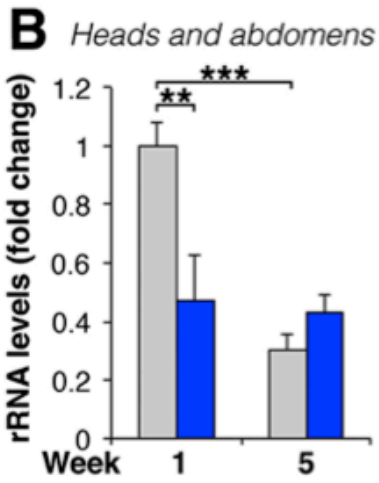
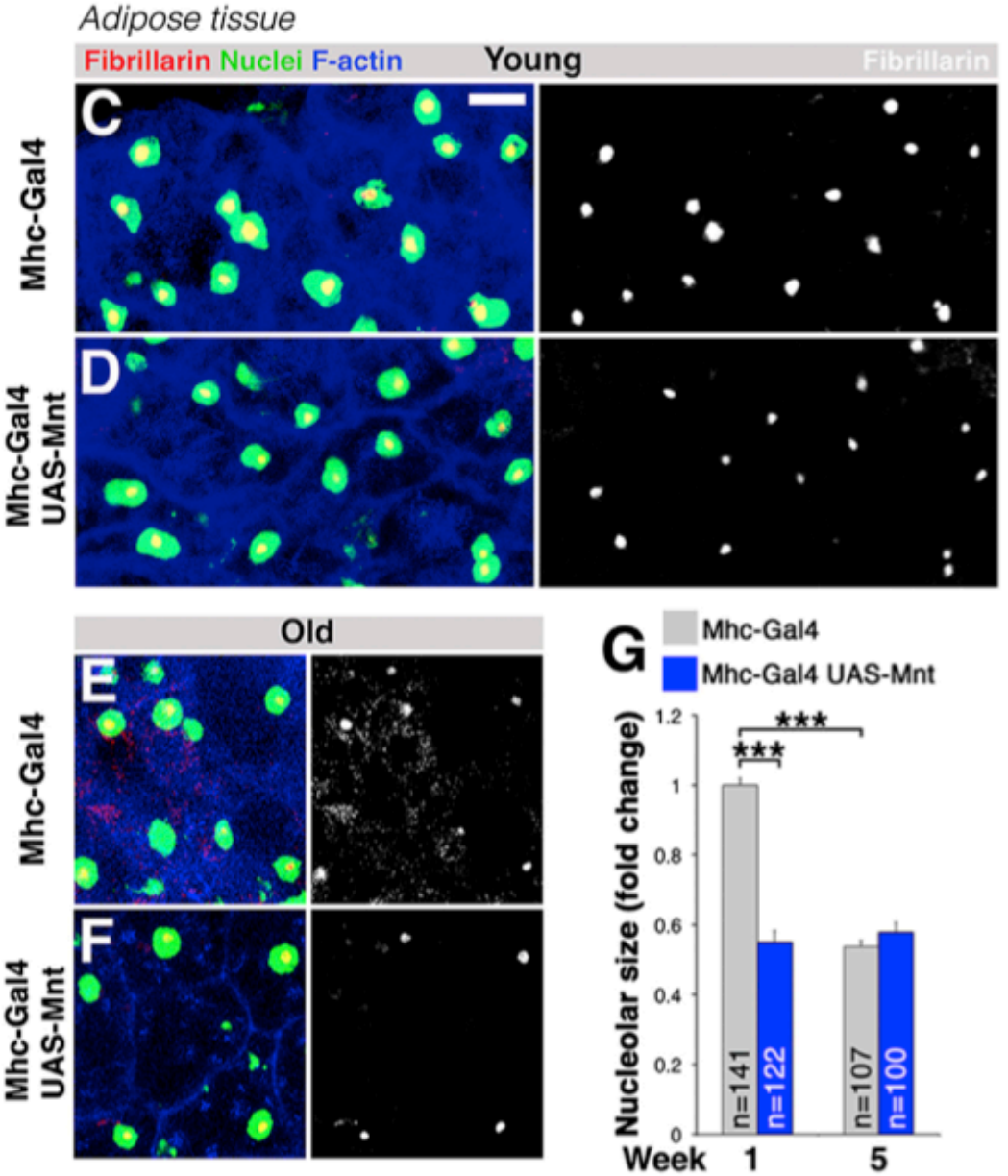
Cell Rep
2014 vol. 7 (5) pp. 1481–94







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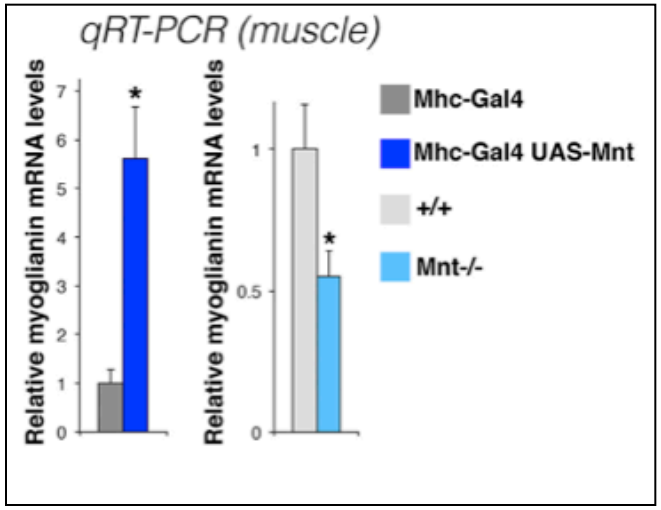

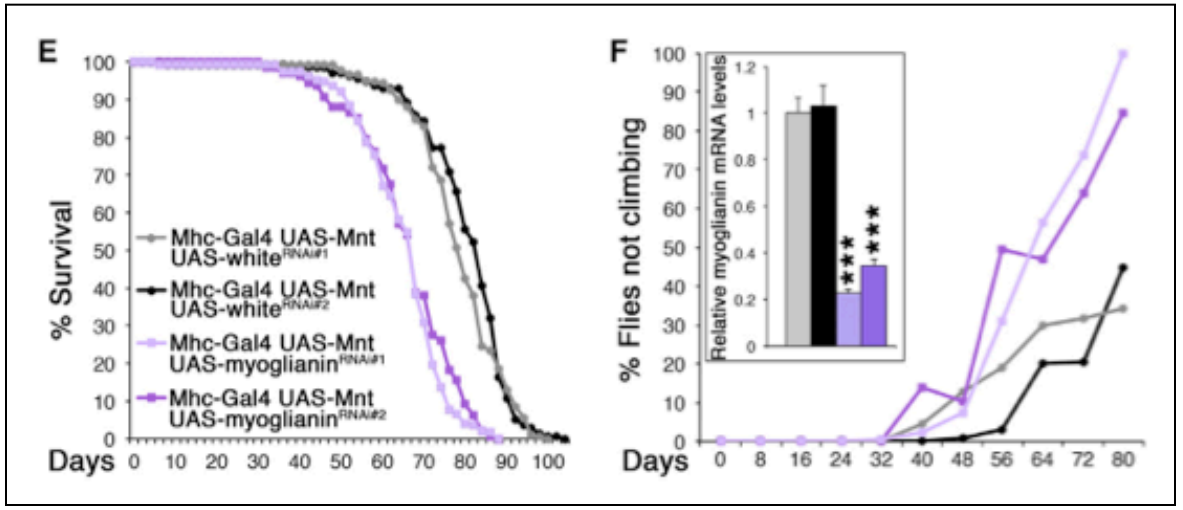

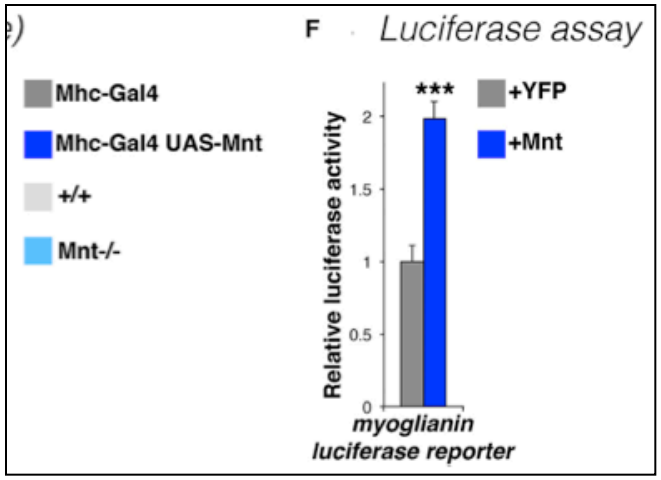

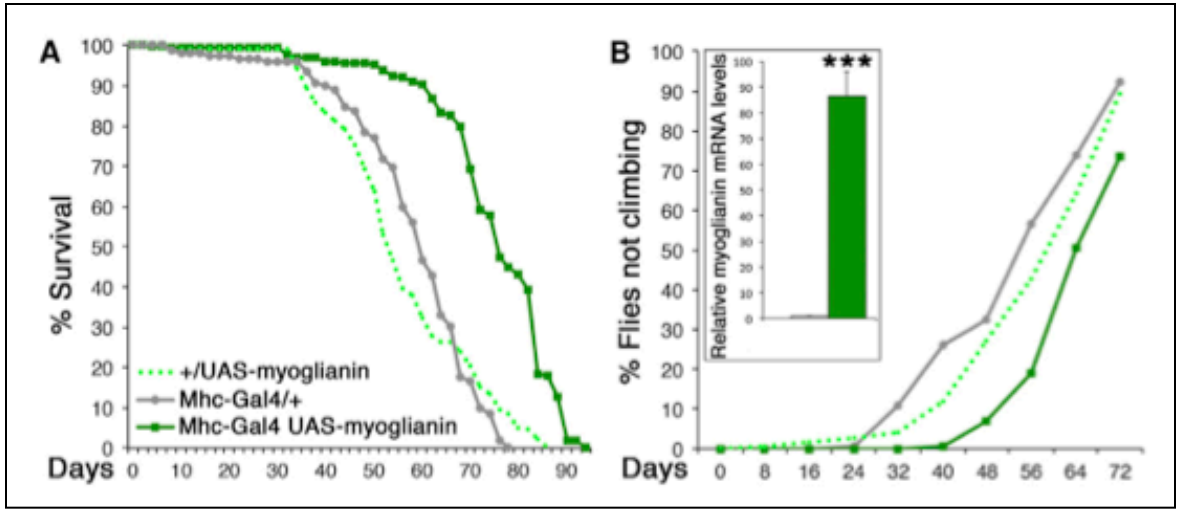

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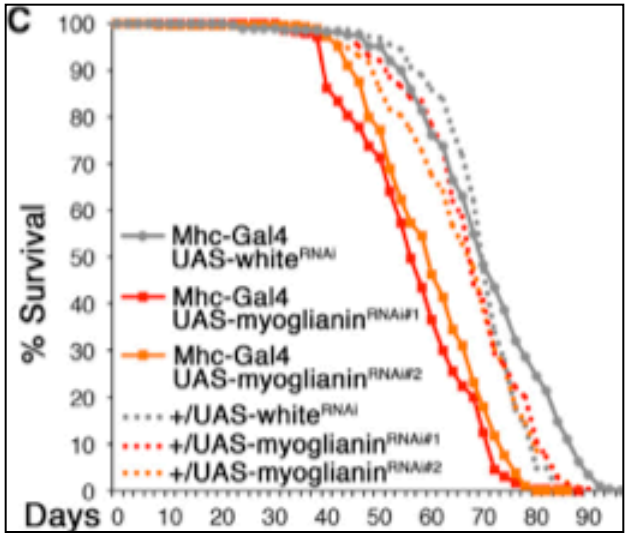

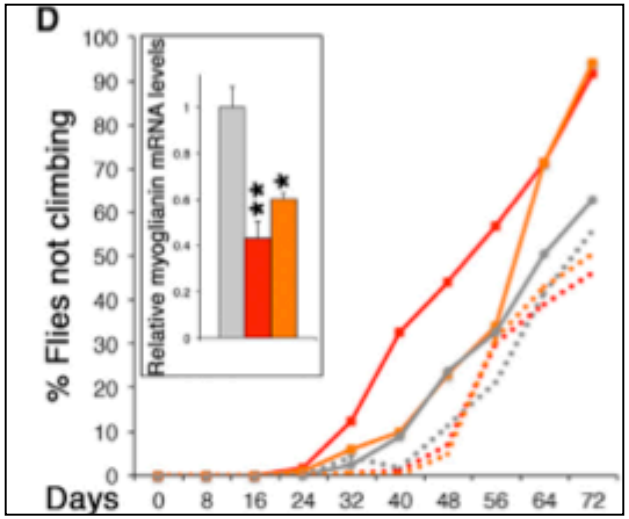

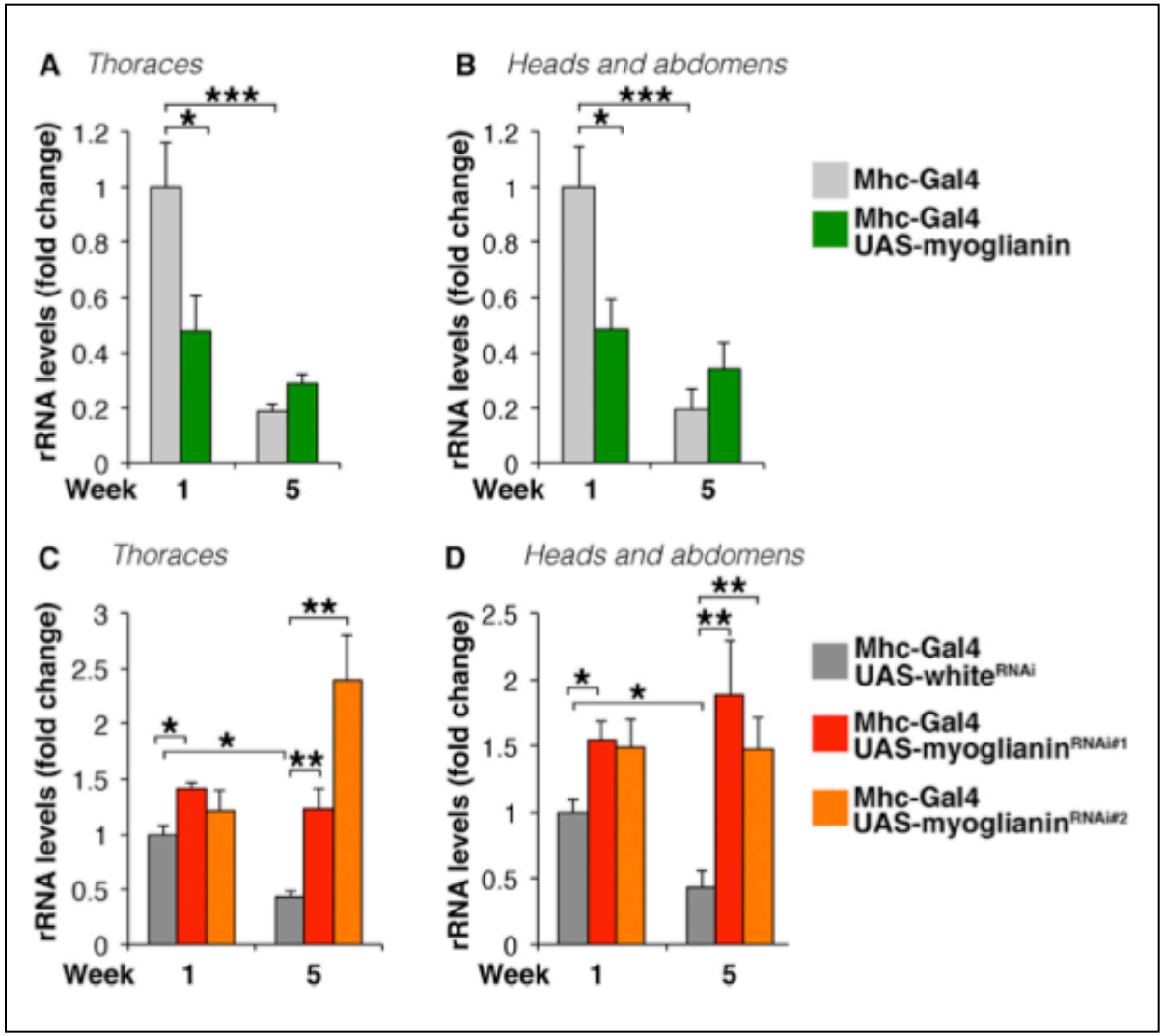

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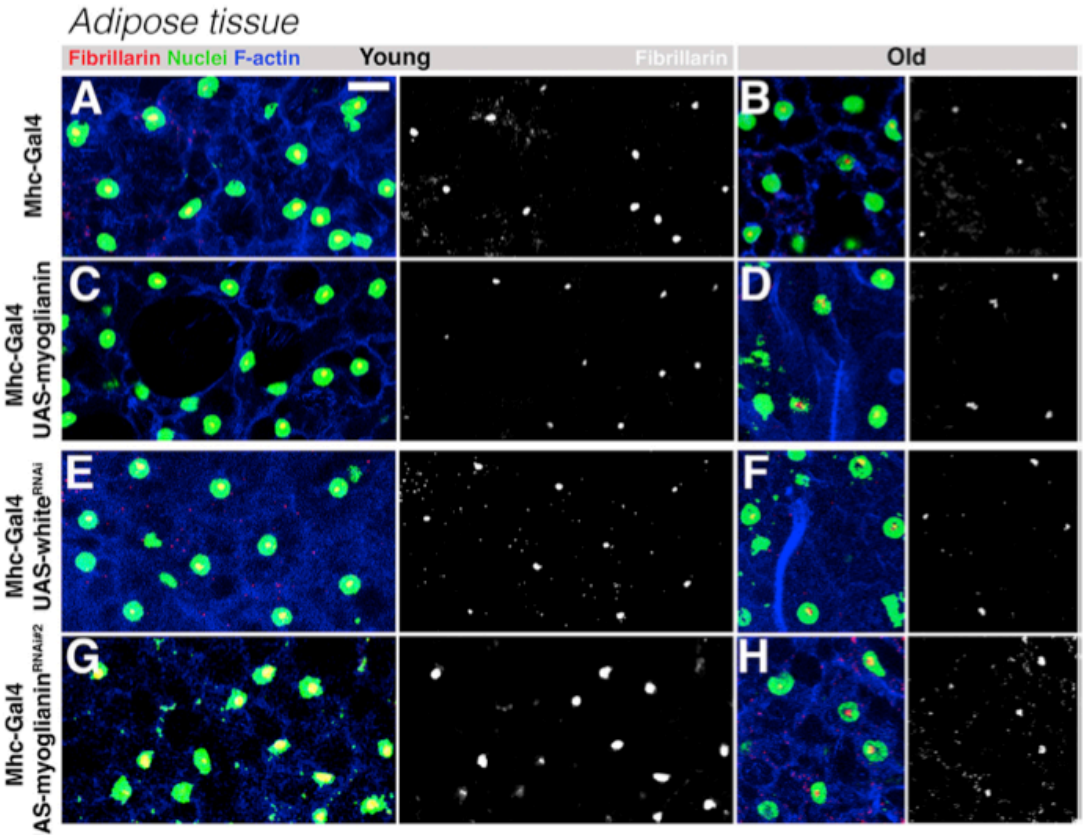

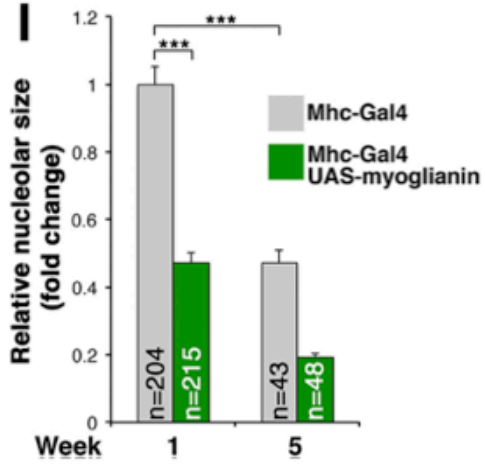

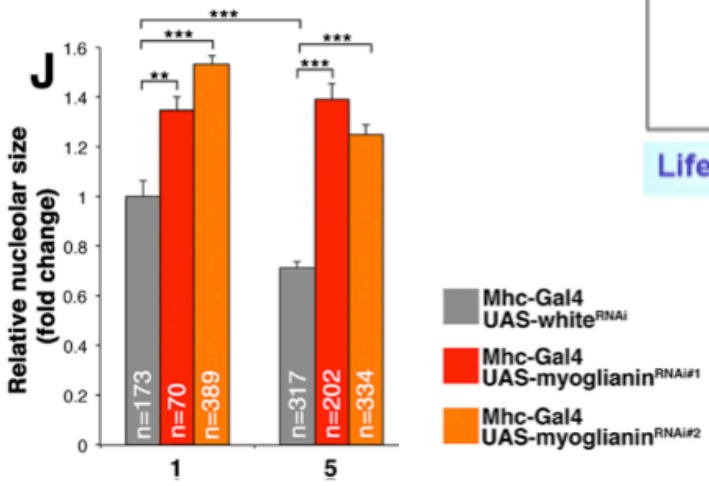

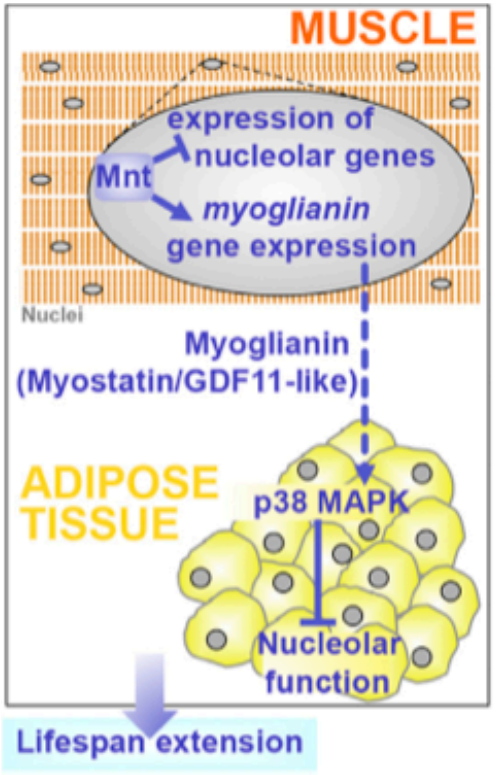

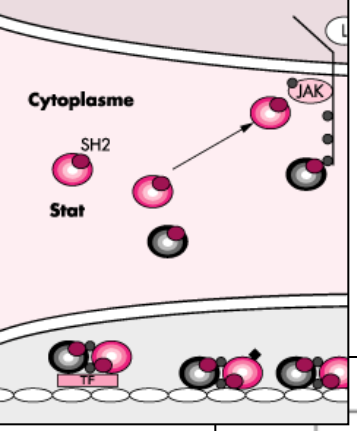

Heterochromatin formation promotes longevity and represses ribosomal RNA synthesis

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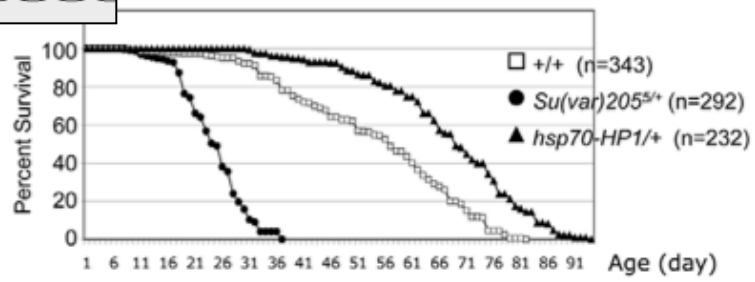

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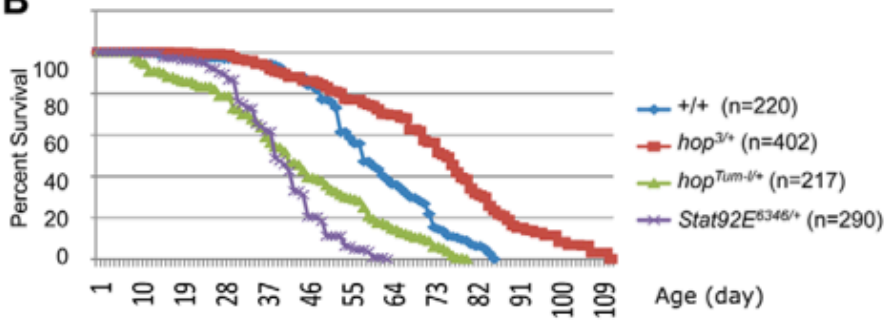

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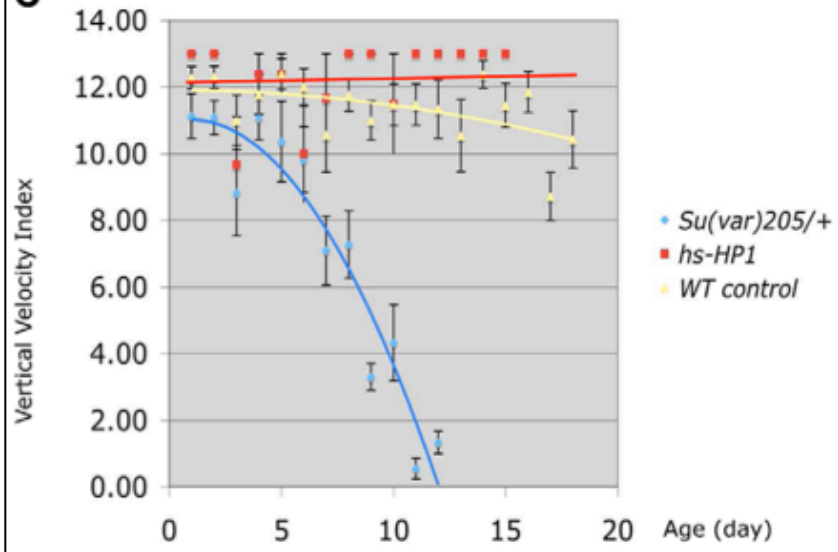

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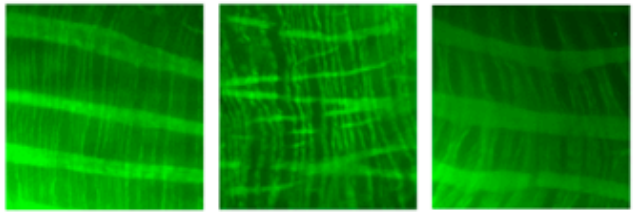

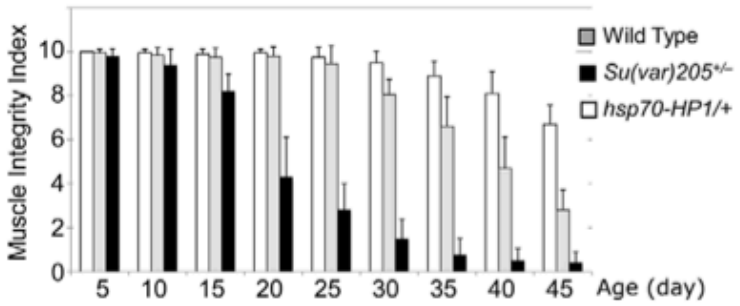

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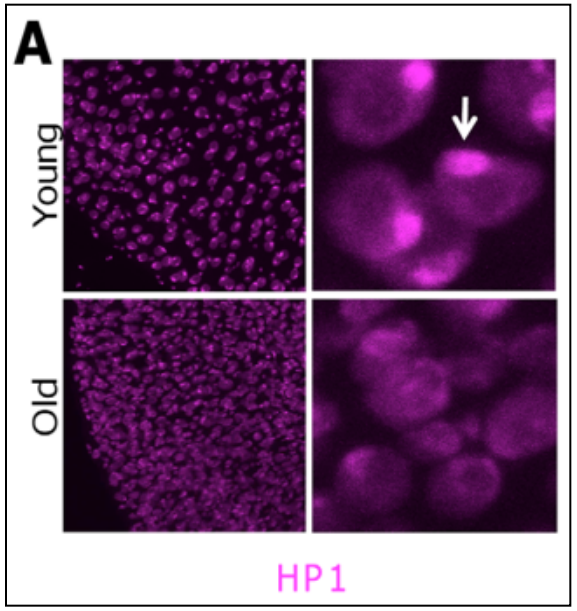

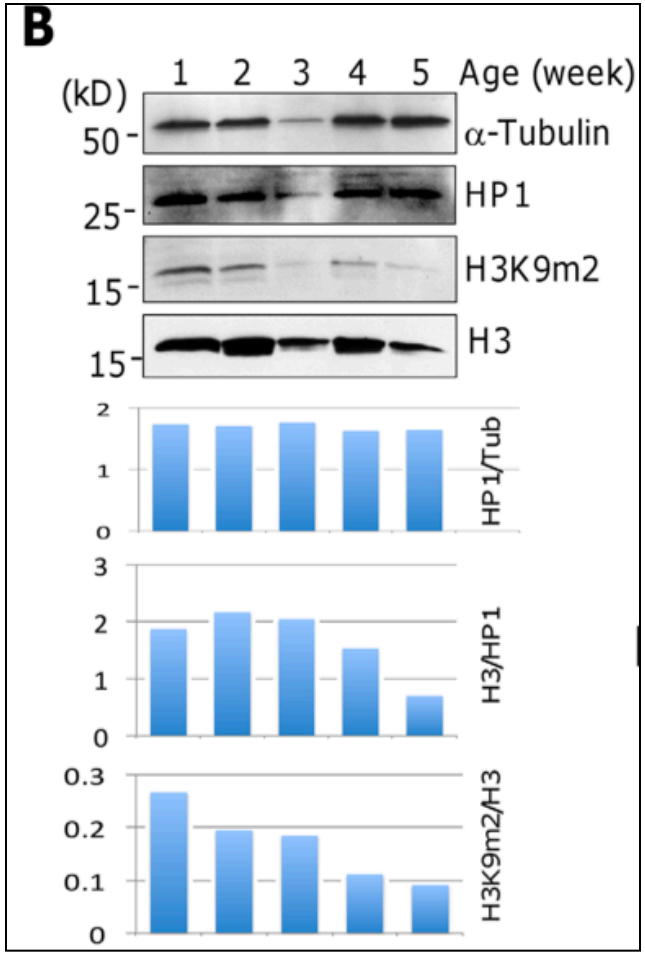

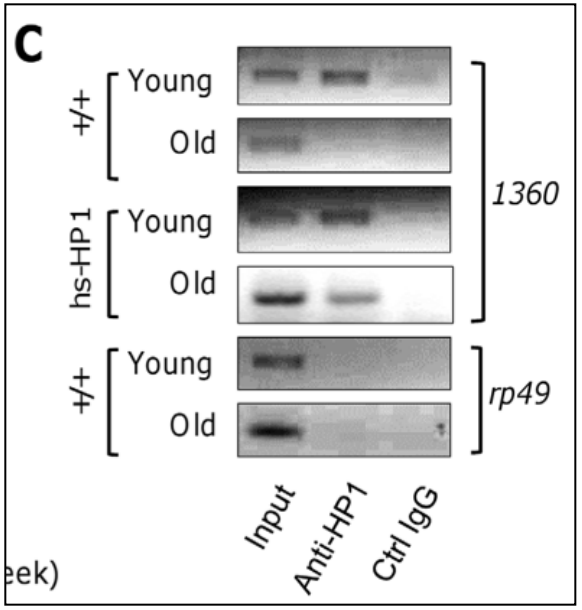

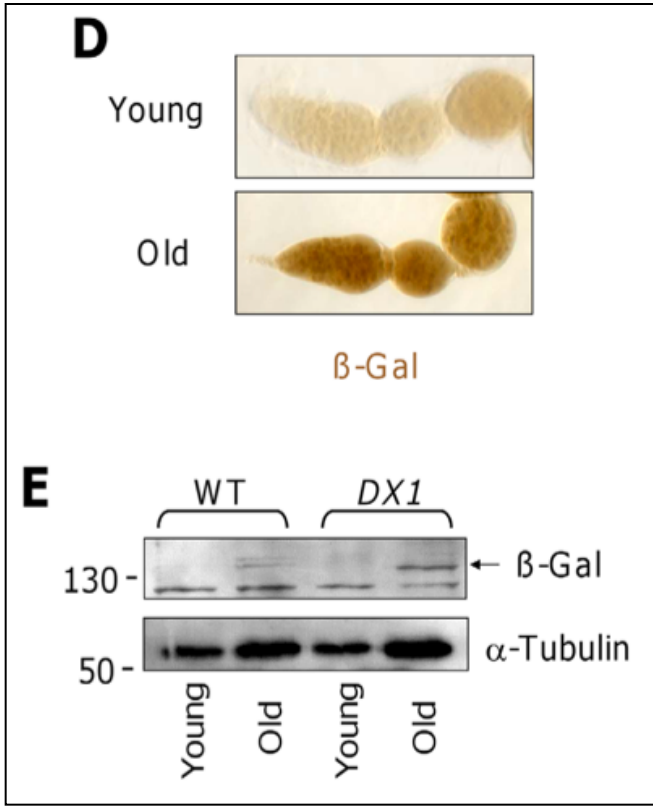

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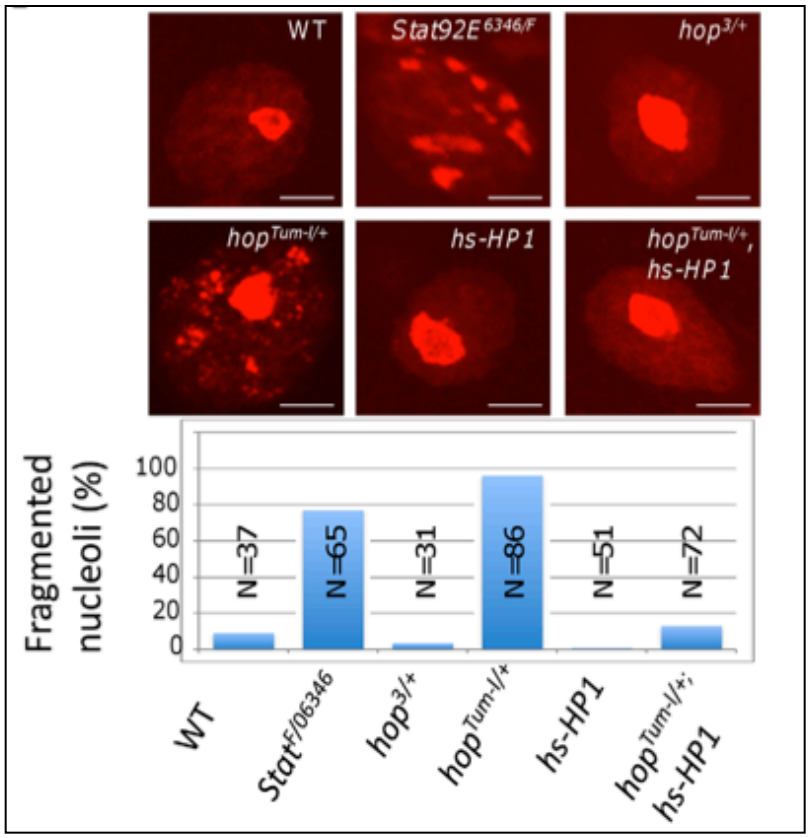

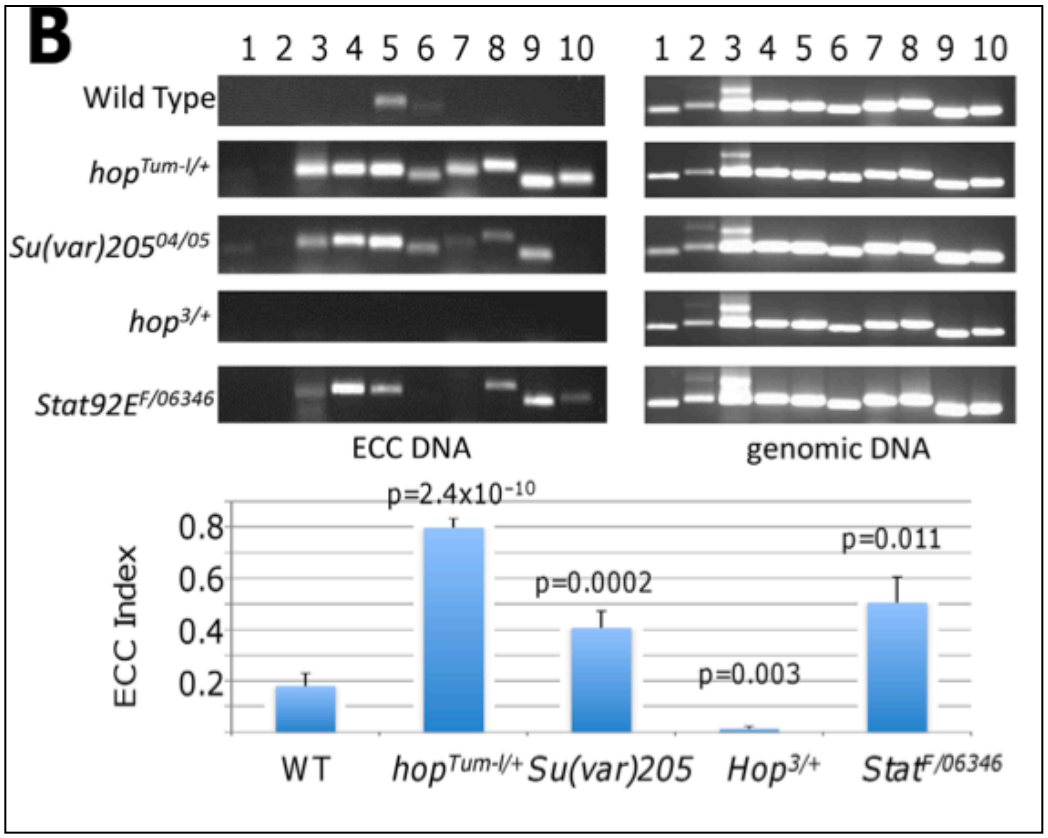

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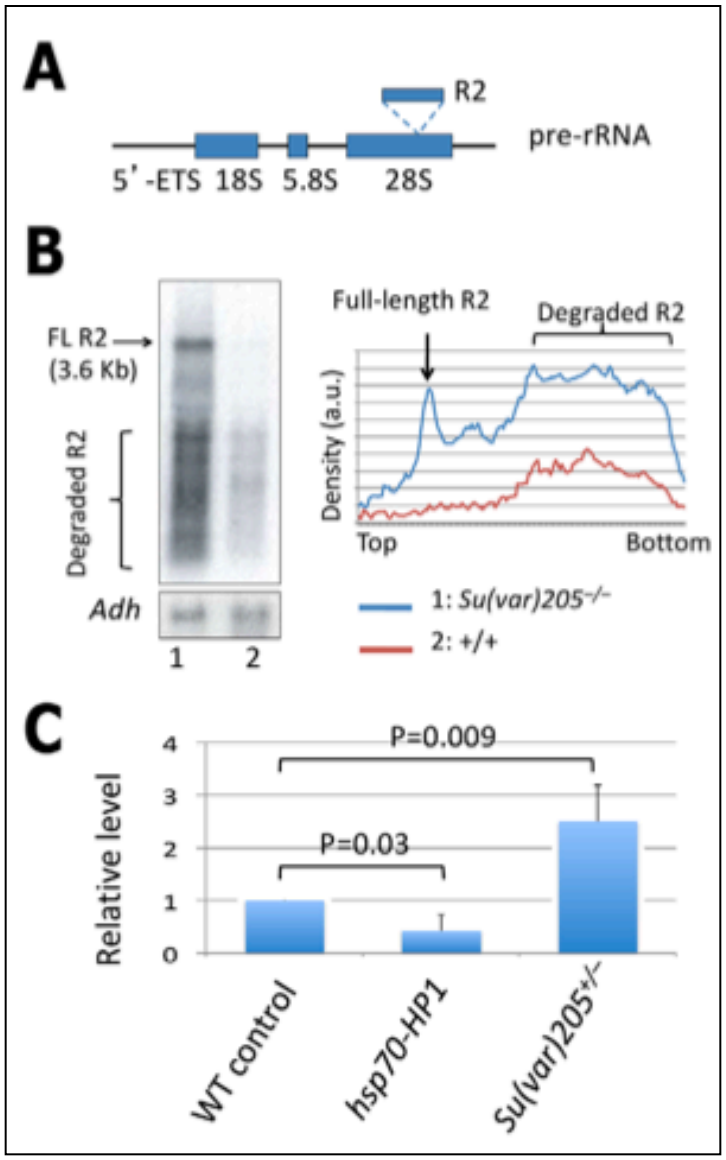

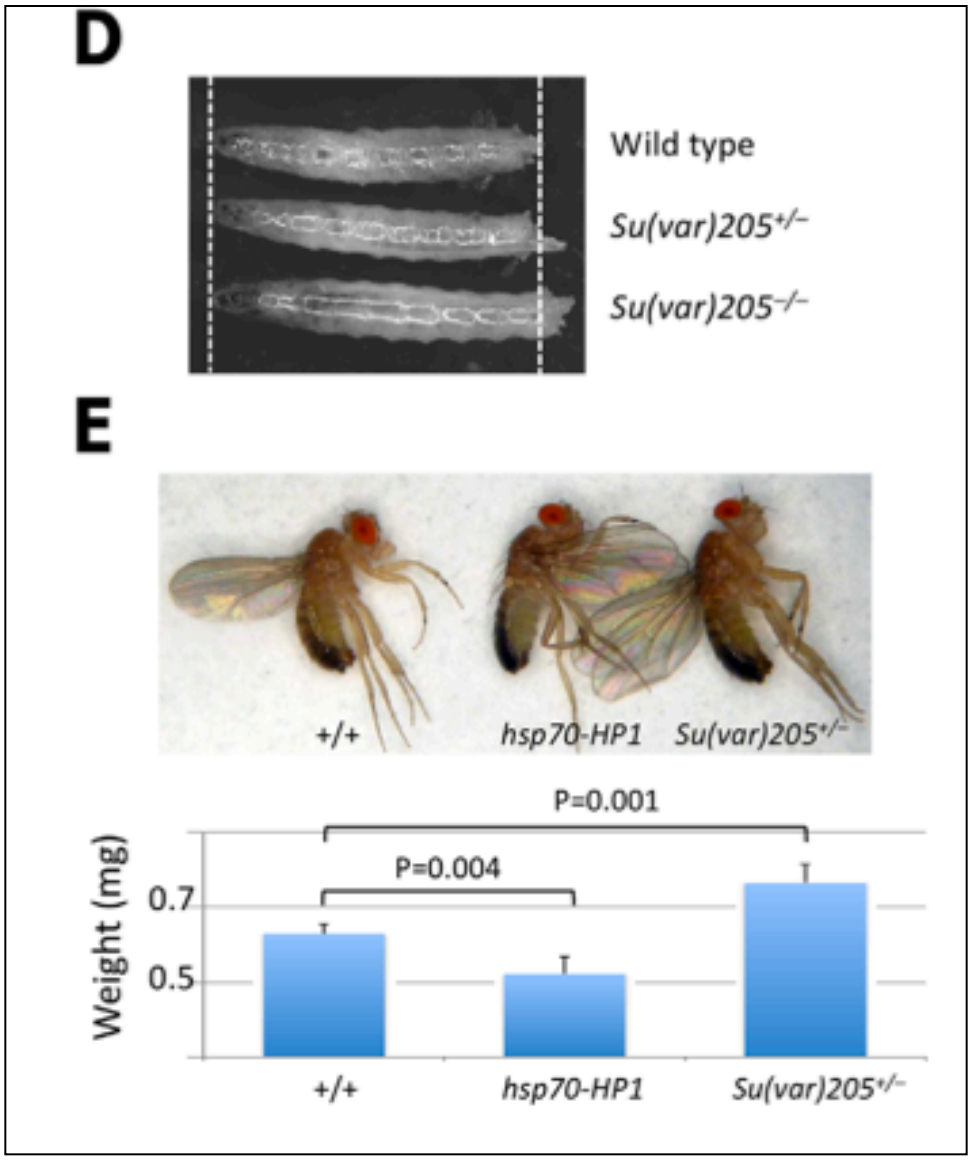

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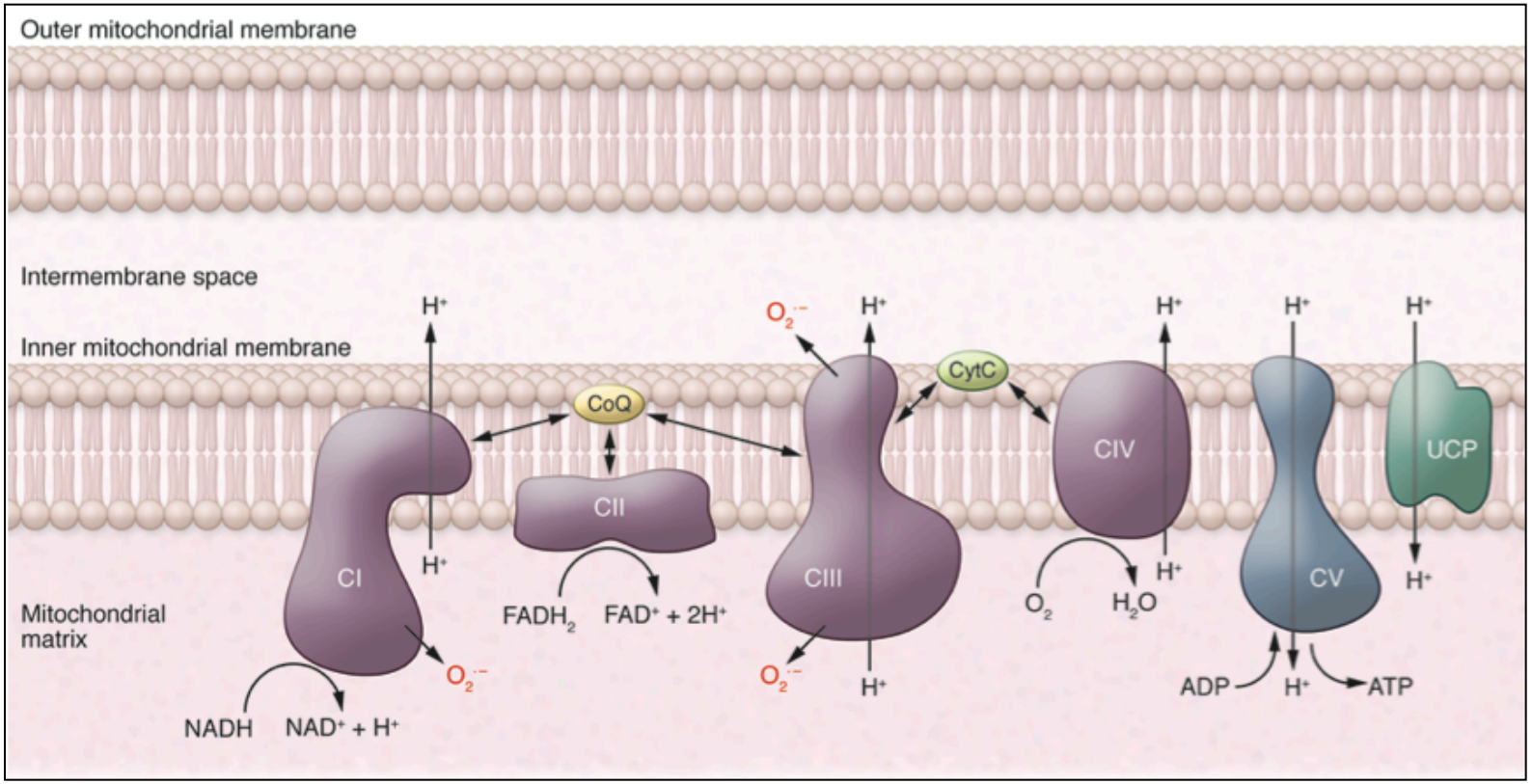

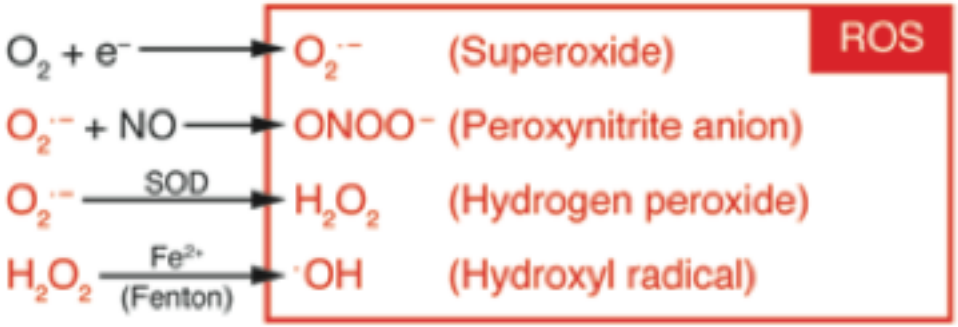

The Impact of Pathogenic Mitochondrial DNA Mutations on Substantia Nigra Neurons

The Journal of Neuroscience, June 26, 2013 • 33(26):10790–10801

Amy Reeve,[1,2] Martin Meagher,[2] Nichola Lax,[2] Eve Simcox,[1,2] Philippa Hepplewhite,[1,2] Evelyn Jaros,[3,4] and Doug Turnbull[1,2]

Table 1. Summary of the patient cohort used for this study including age, sex, genotype, major neurological features, the presence of extrapyramidal involvement and neuropathology of the SN

	MELAS 1 (m.3243 A>G)	MELAS 2 (m.3243 A>G)	MERRF 1 (m.8344A>G)	MERRF 2 (m.8344 A>G)	Single deletion 1
Age (years)	20	59	42	58	40
Sex	Female	Female	Female	Male	Female
Genotype	m.3243A>G	m.3243A>G	m.8344A>G	m.8344A>G	m.11756-15636
Disease duration (years)	10	33	24	18	37
Major neurological features	Ataxia, stroke-like episodes, cognitive impairment, deafness, encephalopathy	Ataxia, stroke-like episodes, epilepsy, dementia, deafness, encephalopathy, migraine, depression	Ataxia, deafness, myopathy, myoclonus, depression	Ataxia, epilepsy, peripheral neuropathy, myoclonus, areflexia	Ataxia, dementia, encephalopathy, depression, myopathy, CPEO, heart block
SN pathology	Normal neuronal density; pale neuromelanin in pigmented cells; α-Syn/LB: none	Intact neuronal population α-Syn/LB: none	Moderate loss of neurons in LMB, less pronounced in the UMB; α-Syn/LB: none	Intact neuronal population, mild to moderate neuropil microvacuolation; α-Syn/LB: none	Intact neuronal populations; mild to moderate vacuolation; α-Syn/LB: none
Presence of extrapyramidal involvement	No	No	No	No	No
Patient number[a]	Patient 6	Patient 1	Patient 8	N/A	Patient 11

Table 1. Continued

Single deletion 2	POLG 1	POLG 2	POLG 3	POLG 4	POLG 5
22	50	24	59	79	55
Female	Male	Female	Male	Male	Male
m.8469-13447	p.stop1240Gln and p.Ala467Thr with multiple mtDNA deletions	p.Ala467Thr and p.Trp748Ser with multiple mtDNA deletions	p.Gly848Ser and p.Ser1104Cys with multiple mtDNA deletions	p.Thr251Ile and p.Ala467Thr with multiple mtDNA deletions	p.Trp748Ser and p.Arg1096Cys multiple mtDNA deletions
18	22	4	37	26	40
Ataxia, seizures, intention tremor	Ataxia, epilepsy, dementia, peripheral neuropathy, myoclonus, encephalopathy, CPEO, myopathy, depression	Ataxia, epilepsy, dementia, encephalopathy, myoclonus, depression	Ataxia, dementia, peripheral neuropathy, areflexia, depression	Ataxia, myopathy, CPEO, dysphagia	Ataxia, cognitive decline, CPEO, myopathy, neuropathy, myoclonus, psychosis
Unknown	Severe neuronal loss; α-Syn/LB: none	Moderately severe neuronal loss; α-Syn/LB: none	Moderately severe neuronal loss; α-Syn/LB: extensive	Mild focally moderate cell loss; α-Syn/LB: extensive	Severe loss of UMB SN neurons; α-Syn/LB: none
No	No	No	Parkinsonian symptoms	No	No
N/A subject[b]	Patient 14	Patient 12	Patient 13	N/A	N/A

α-Syn, Synuclein; LB, Lewy body; LMB, lower midbrain; UMB, upper midbrain; CPEO, chronic progressive external ophthalmoplegia.

[a]From Lax et al. (2012a,b).

[b]Reported in Shanske et al. (1990).

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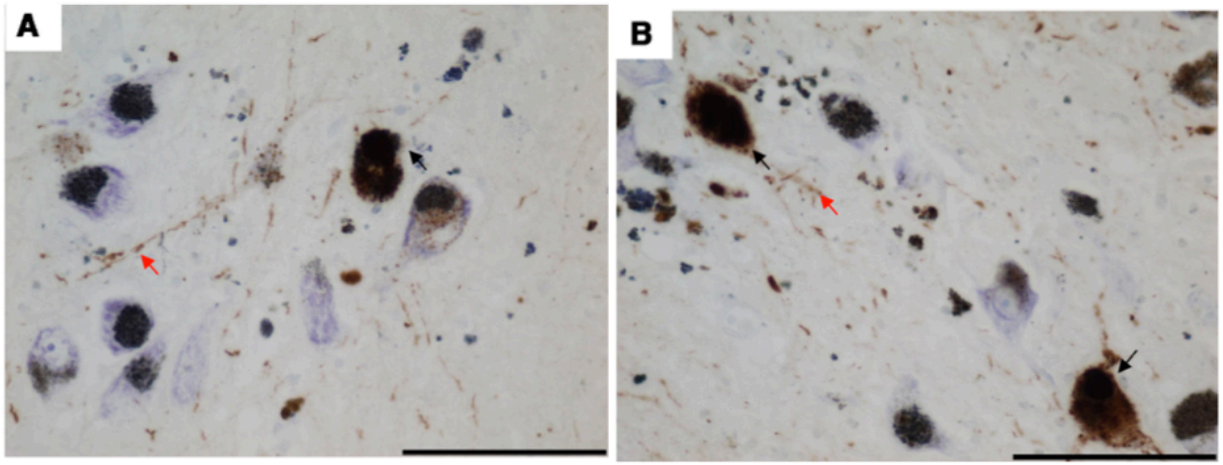

Figure 1. α-Synuclein immunoreactivity in SN of POLG patients, a marker of Lewy body pathology. ***A***, ***B***, Two of the five POLG/multiple deletion patients studied (***A***, POLG 3; ***B***, POLG 4) showed α-synuclein-positive Lewy body pathology within pigmented SN neurons. Pathology included Lewy bodies, pre Lewy bodies, cytoplasmic granular inclusions (black arrows), and Lewy neurites (red arrows). Sections were counterstained with CFV. Images were taken at a 40× magnification. Scale bar, 100 μm.

Table 2. Summary of control cases used in this study, including age, sex, post mortem delay, cause of death, and summary of the neuropathology report regarding the SN

Case	Sex	Age (years)	Post mortem delay (h)	Cause of death	SN pathology
Control 1	Male	48	—	—	—
Control 2	Male	53	—	Left ventricular failure due to ischemic heart disease	Normal
Control 3	Female	56	—	—	—
Control 4	Female	58	—	Lung cancer and Cushing's disease	Normal pigmentation with a small amount of extraneuronal neuromelanin
Control 5	Female	59	—	Bowel cancer	Normal
Control 6	Female	59	—	—	Mild neuronal loss with reduced neuromelanin
Control 7	Male	64	64	—	Normal
Control 8	Male	70	72	Metastatic prostate cancer	Mild age associated neuronal loss with some age related Lewy body pathology
Control 9	Female	69	16	Gastric cancer	Normal pigmentation with a small amount of extraneuronal neuromelanin
Control 10	Male	65	28	Respiratory failure due to acute bronchial asthma	Normal
Control 11	Male	55	41	Liver cancer	Normal
Control 12	Male	50	7	Coronary artery thrombosis	Normal

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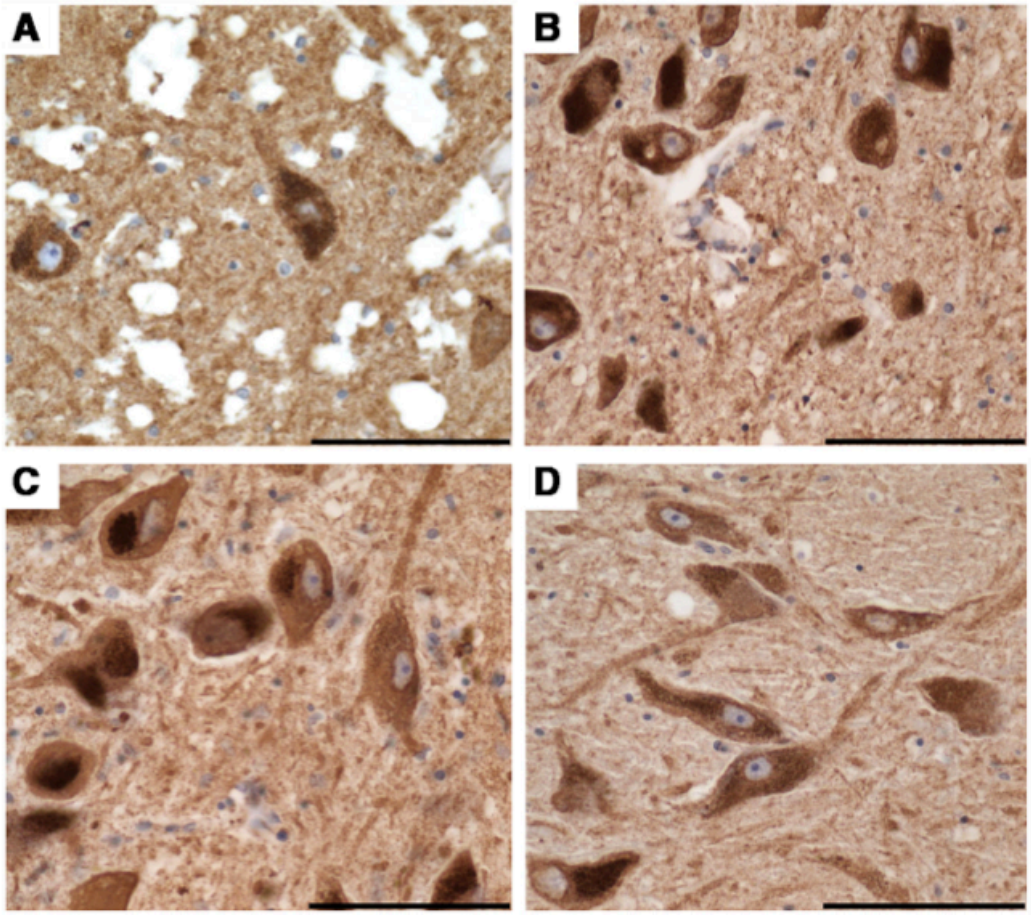

Figure 2. Porin immunoreactivity in SN neurons, a marker of mitochondrial density. All pigmented SN neurons in patients with mitochondrial disorders showed a uniform density of mitochondria, similar to controls. ***A–D***, Shown is KSS/single large-scale deletion patient 1 (***A***), m.8344 A>G point mutation patient (***B***), POLG/multiple deletion patients (***C***), and controls (***D***). ***A*** also highlights the microvacuolation that was widespread throughout the brain and mild to moderate within the SN of this case. Images were taken at a 40× magnification. Scale bar, 100 μm.

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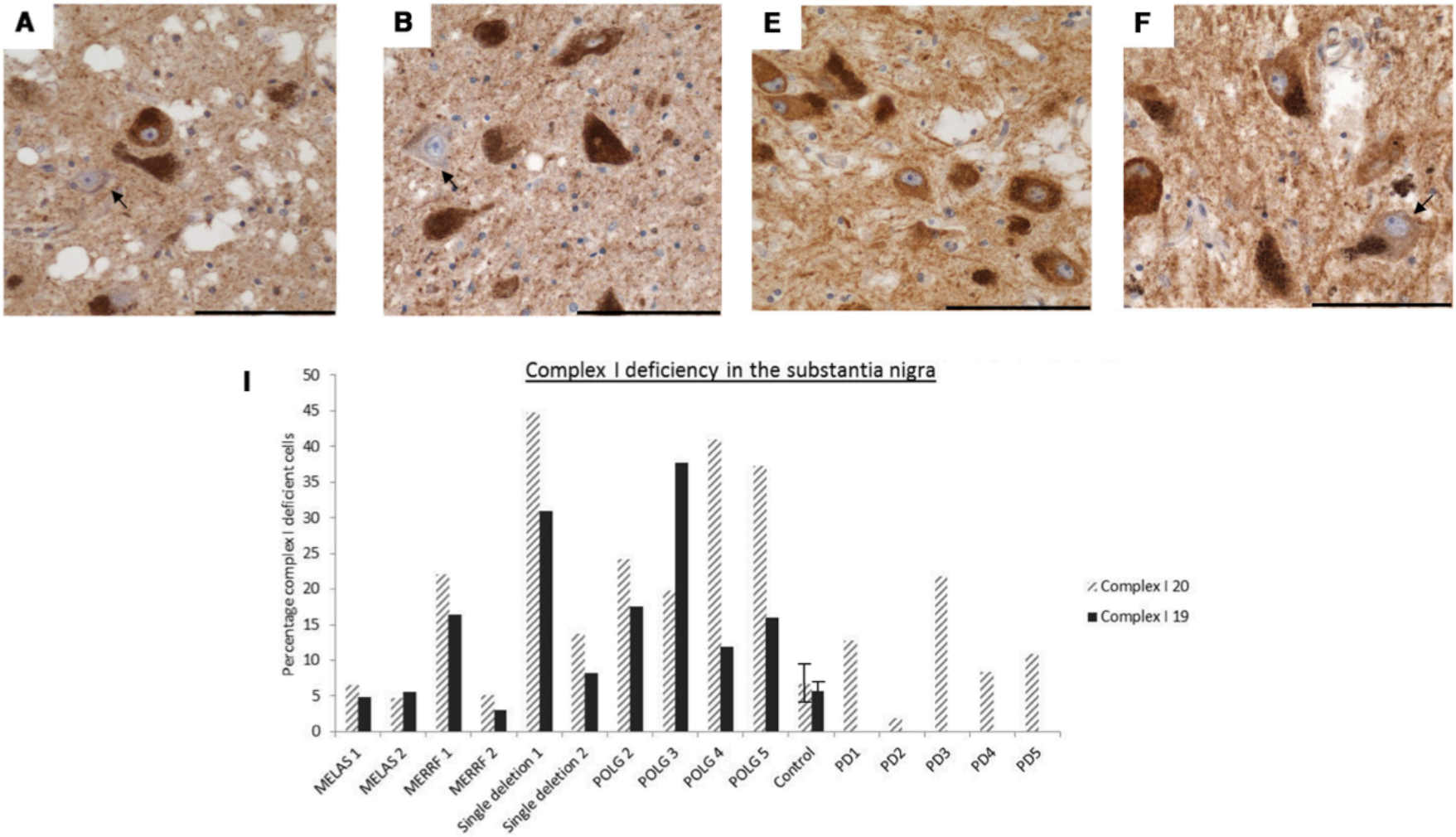

Figure 3. Complex I immunohistochemistry showing the variable degree of protein deficiency in SN neurons. Pigmented SN neurons with a deficiency in complex I subunits (arrows) were found in all cases and controls; however, the level of deficiency varied. ***A–H***, Images show staining for CI20 (***A–D***) and CI19 (***E–H***), and the arrows indicate neurons showing deficiencies for these proteins. (*Figure legend continues.*)

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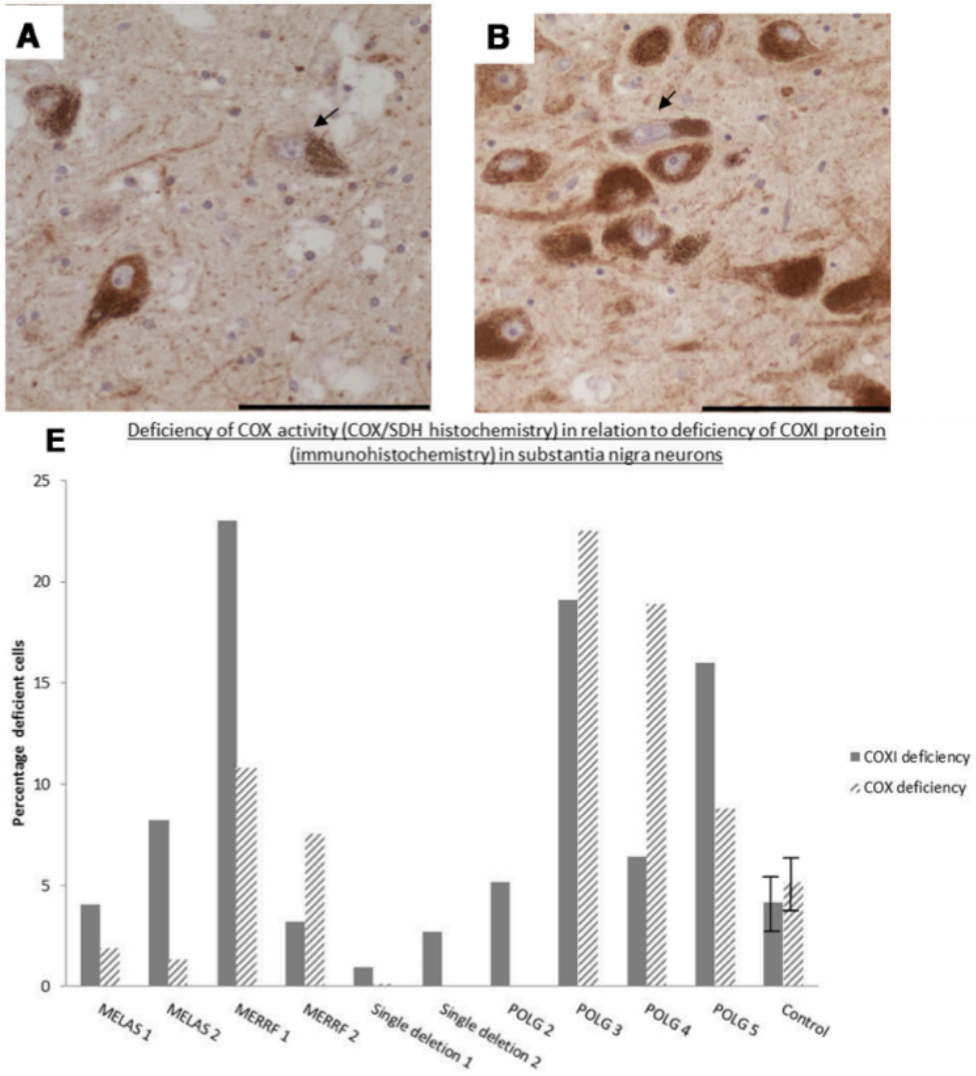
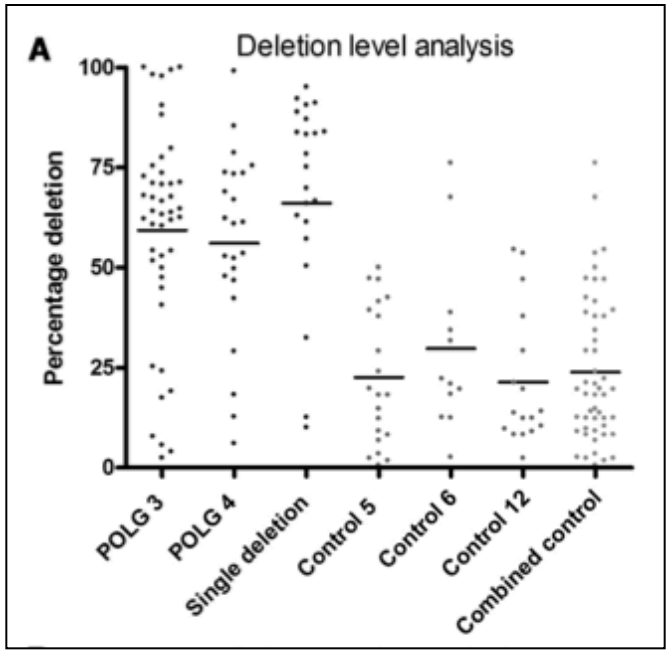
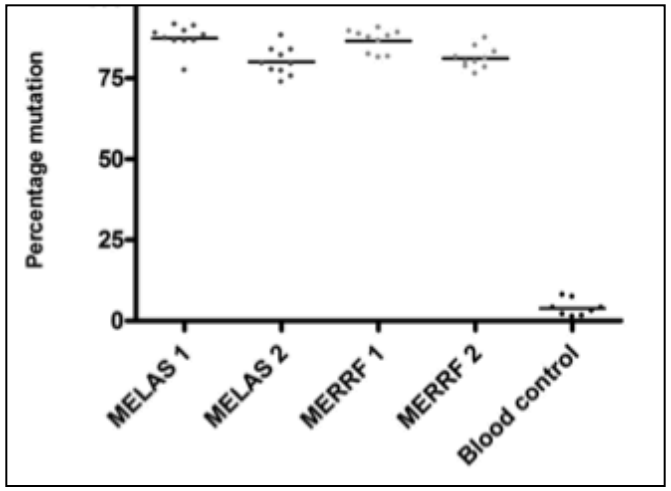


Figure 5. Deficiency in COX activity within SN neurons revealed by COX/SDH histochemistry. Respiratory (COX)-deficient neurons were found in the SN of all patients with mitochondrial disease and controls used within this study. However, the COX-deficient neurons (blue) were sparse in patients with KSS/single large-scale deletion (this patient had only one COX-deficient neuron; ***A***) and point mutations (***B***). POLG/multiple deletion patients (***C***) generally showed higher levels of COX deficiency than the patients with inherited defects. Few COX-deficient (*Figure legend continues.*)

Figure 6. SN neurons of patients with mitochondrial disorders show high threshold levels for mtDNA mutations. ***A***, Deletion levels within single SN neurons from POLG 3 ($n = 45$), POLG 4 ($n = 23$), and the KSS/single large-scale deletion patient 1 ($n = 23$) compared with controls ($n = 21$, 12, and 17, respectively). ***B***, Point mutation threshold levels for m.3243 A>G MELAS and m.8344 A>G MERRF patients were measured in single SN neurons and in blood cells of a normal control using pyrosequencing ($n = 10$).





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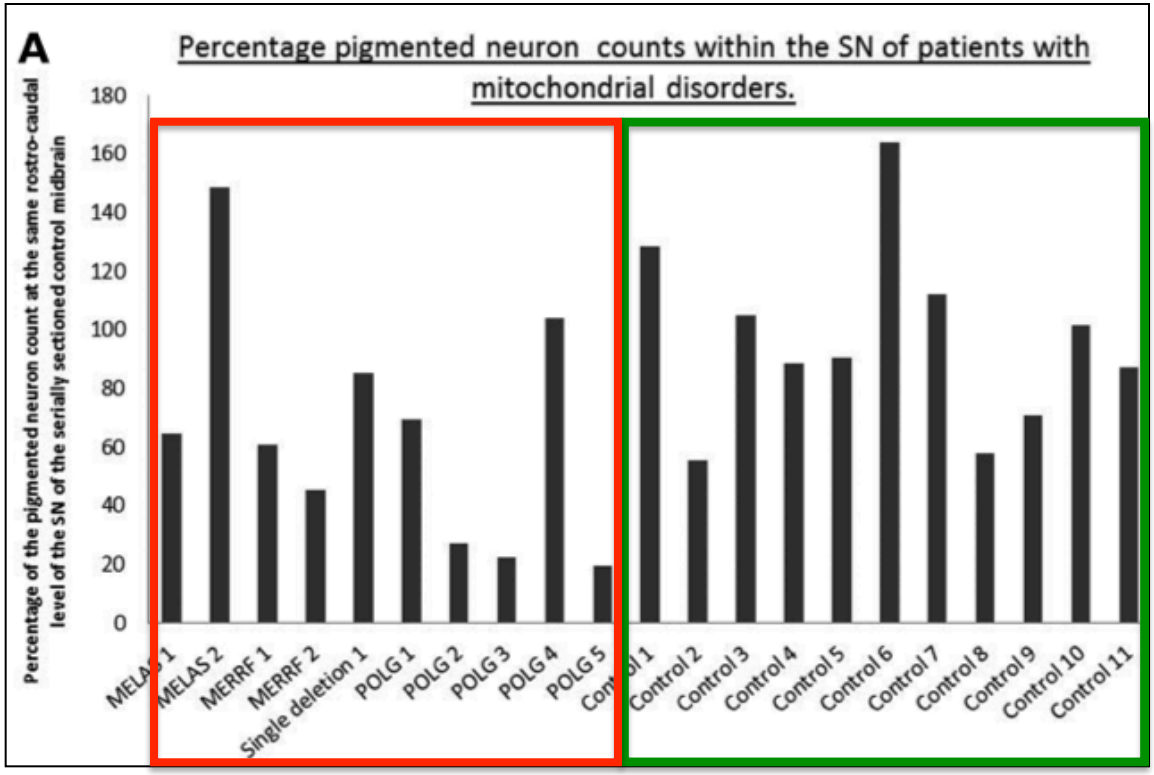

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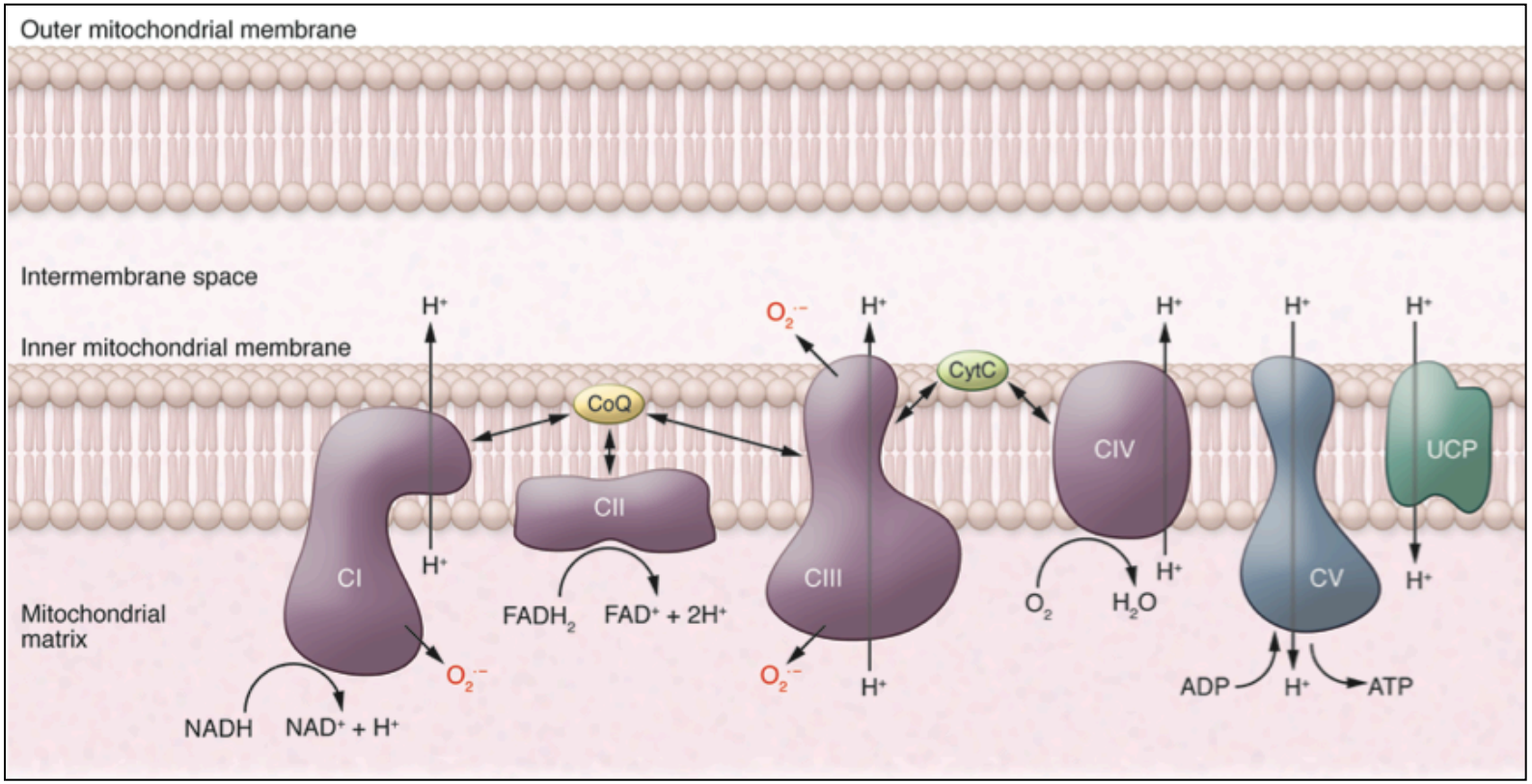
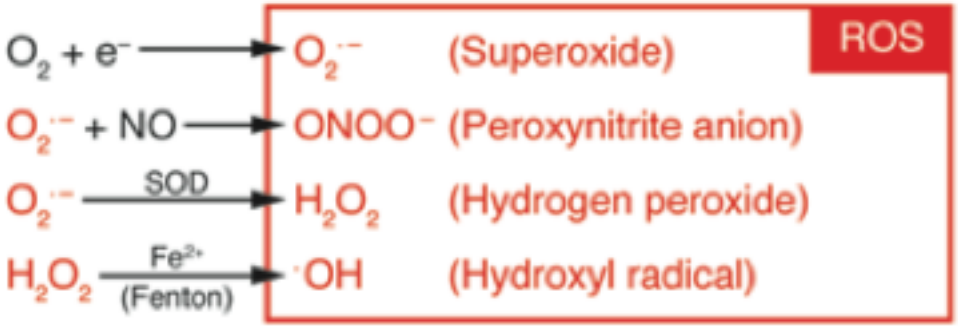
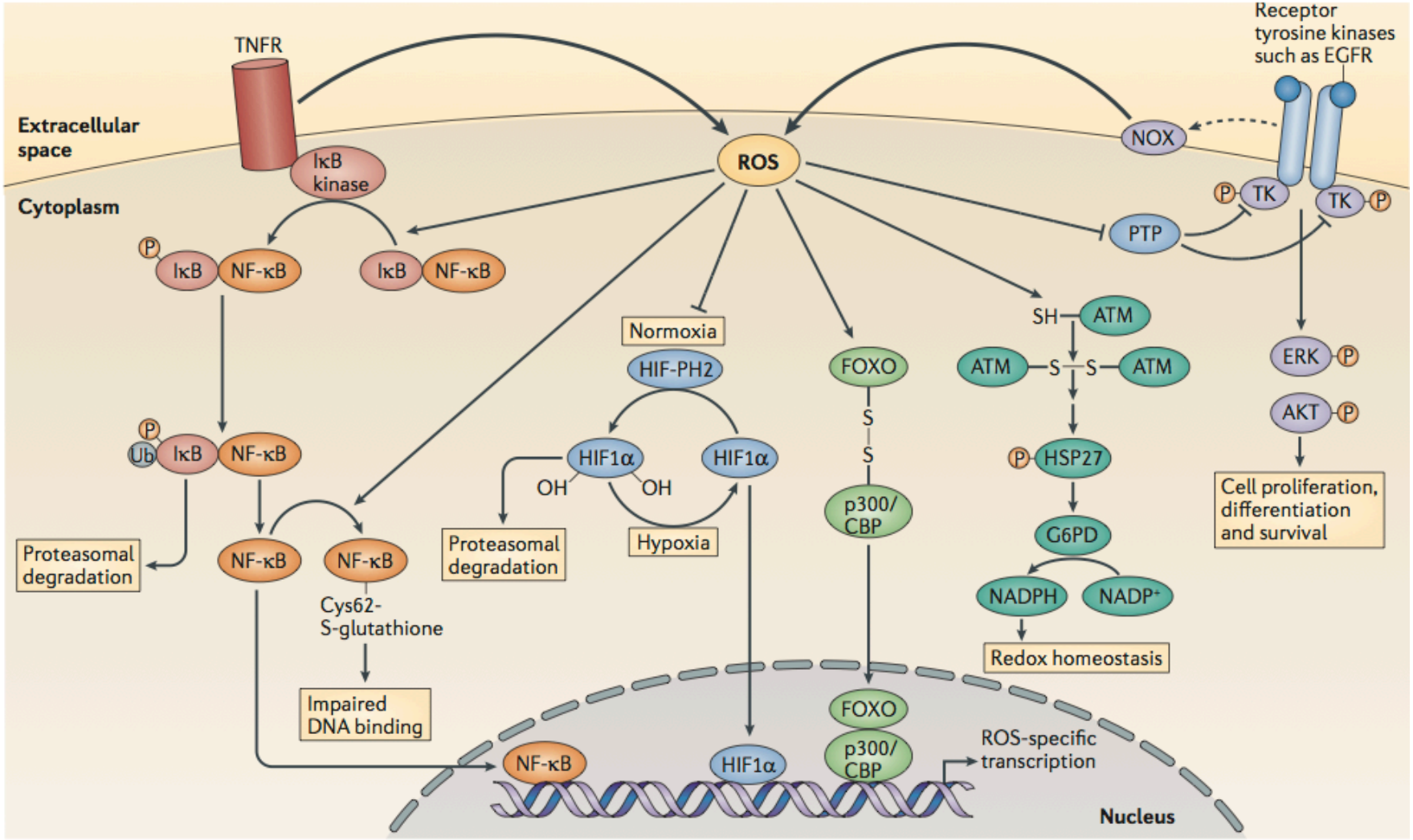




Beyond oxidative stress: an immunologist's guide to reactive oxygen species

Nathan C, Cunningham-Bussel A

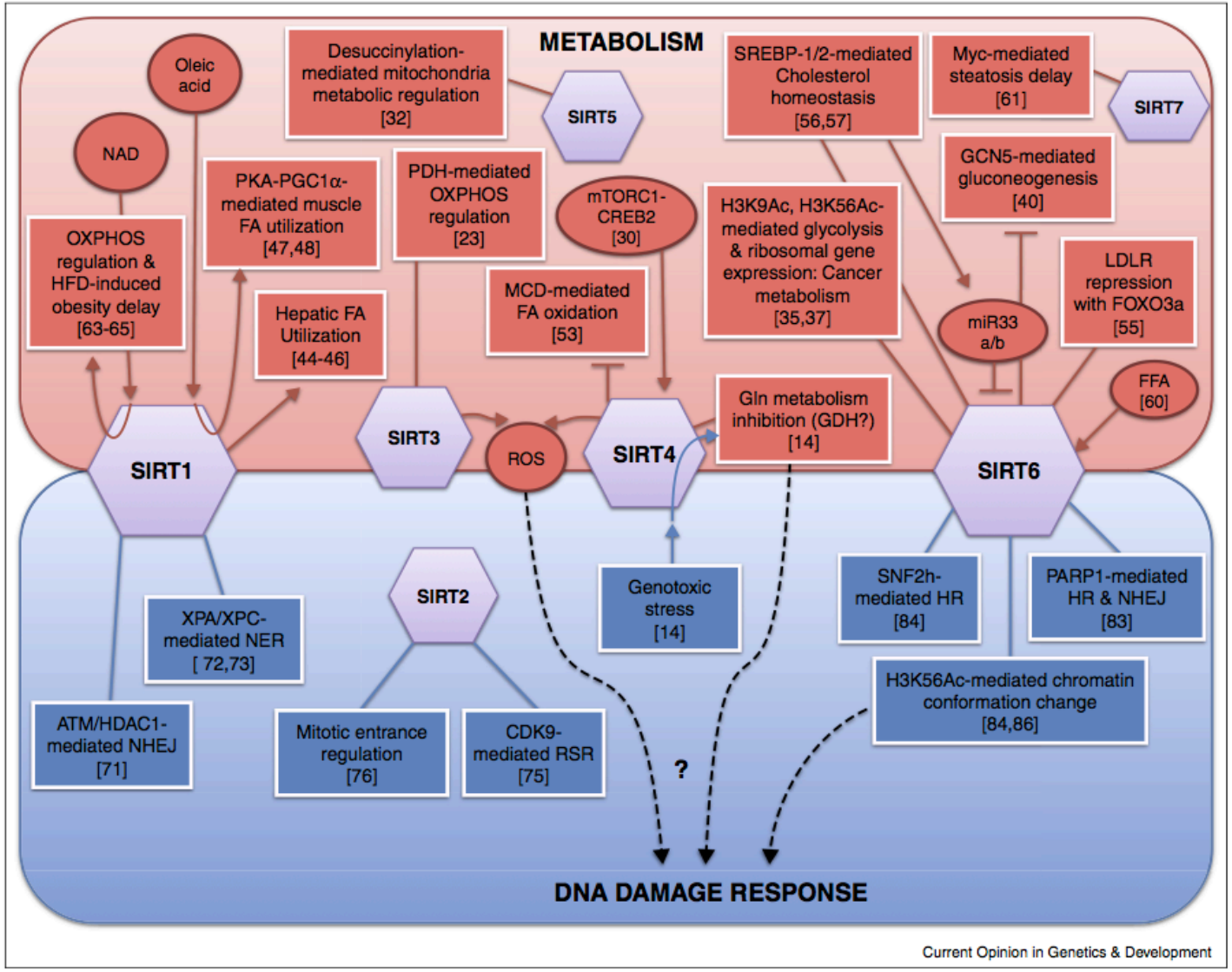
Nat Rev Immunol
2013 vol. 13 (5) pp. 349-61



Sirtuins, metabolism, and DNA repair

Current Opinion in Genetics & Development
2014 vol. 26C pp. 24–32

Choi J, Mostoslavsky R

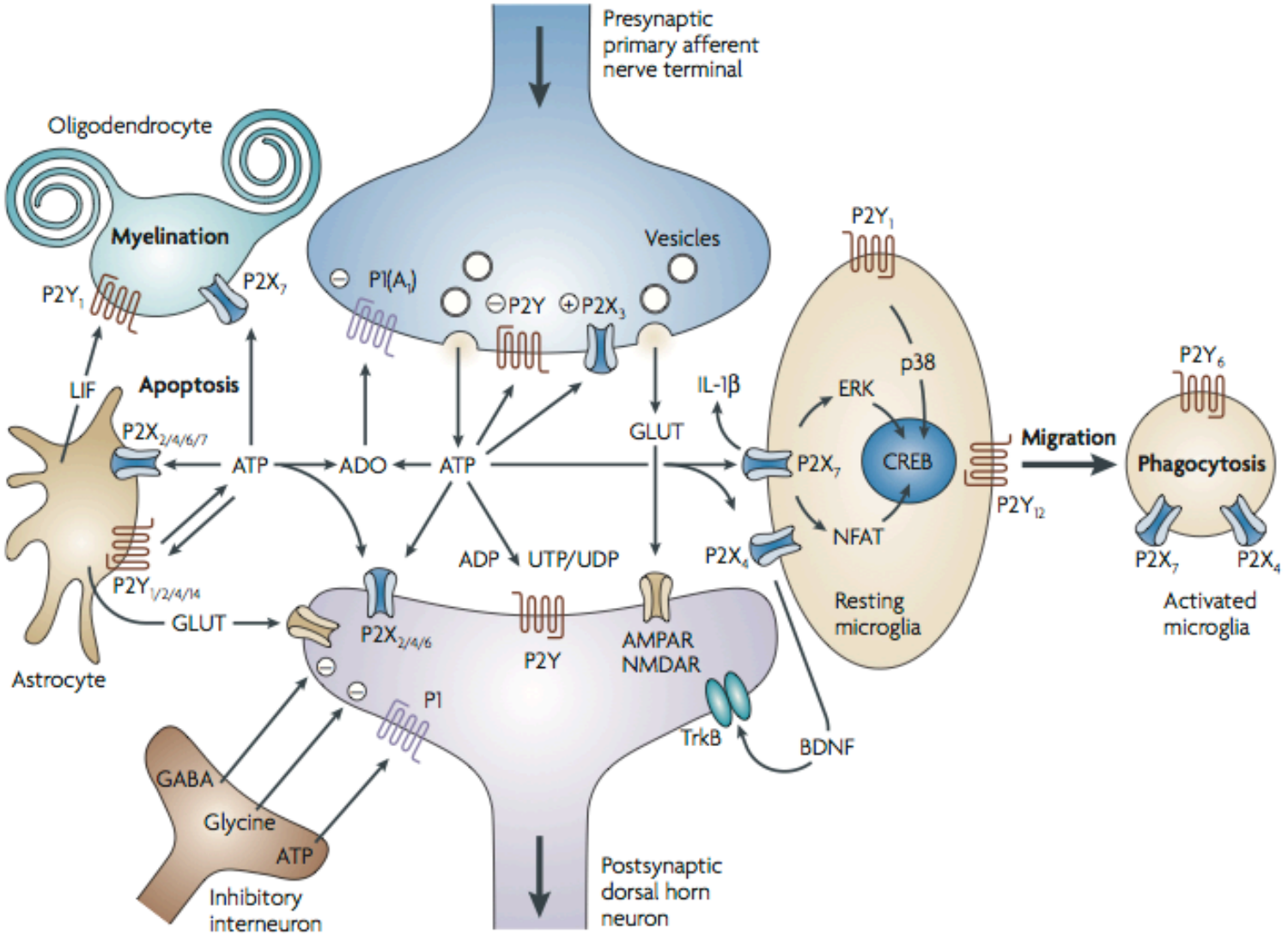


Sirtuins functions in metabolism and DNA repair. A diagram depicting the different functions for the mammalian sirtuins in cellular metabolism (red) and DNA repair (blue). Specific targets and biological roles are summarized.

Purinergic signalling and disorders of the central nervous system

Nat Rev Drug Discov
2008 vol. 7 (7) pp. 575-90

Burnstock G



Mitochondria: in sickness and in health

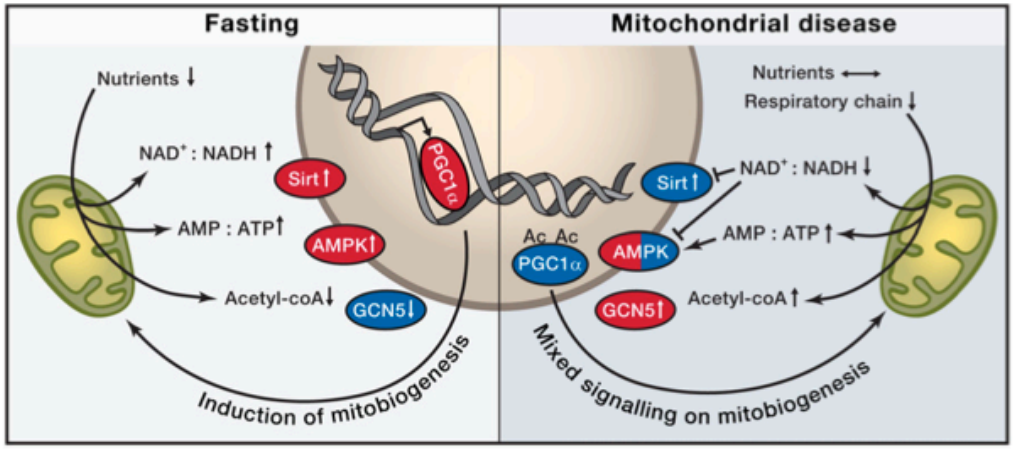
Nunnari J, Suomalainen A

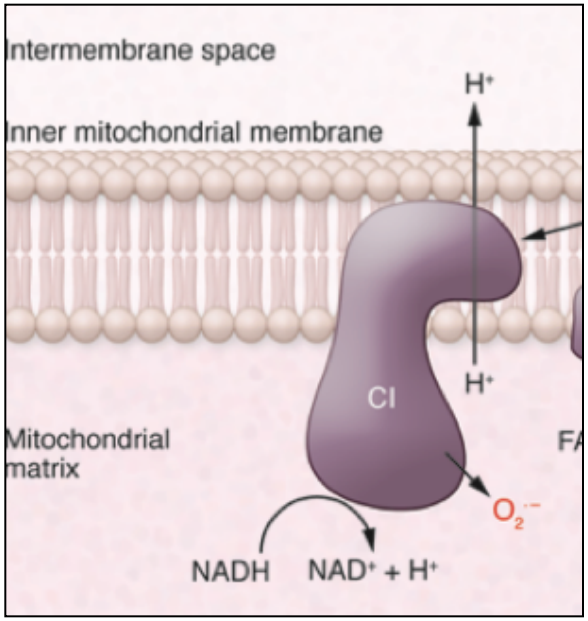
Cell
2012 vol. 148 (6) pp. 1145-59

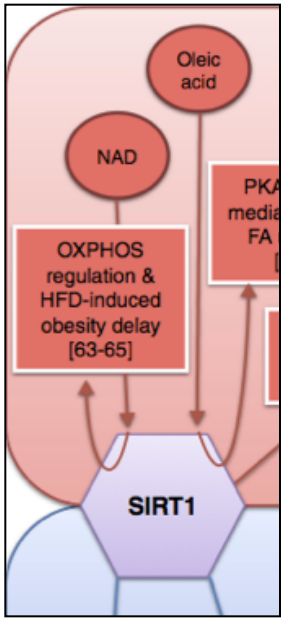
The role of mitochondria in aging

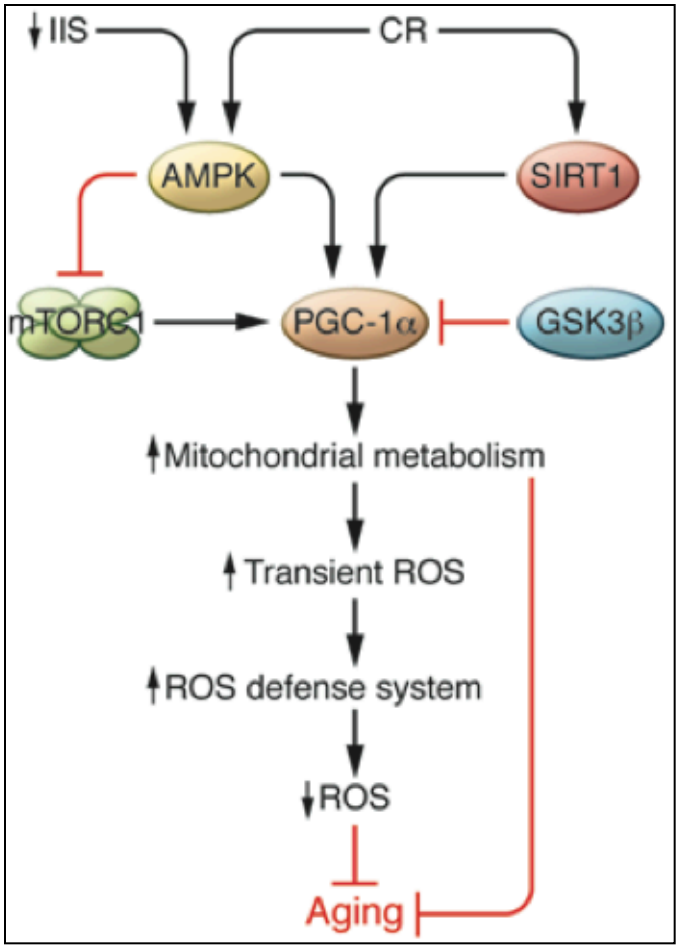
Bratic A, Larsson N

J Clin Invest
2013 vol. 123 (3) pp. 951-7









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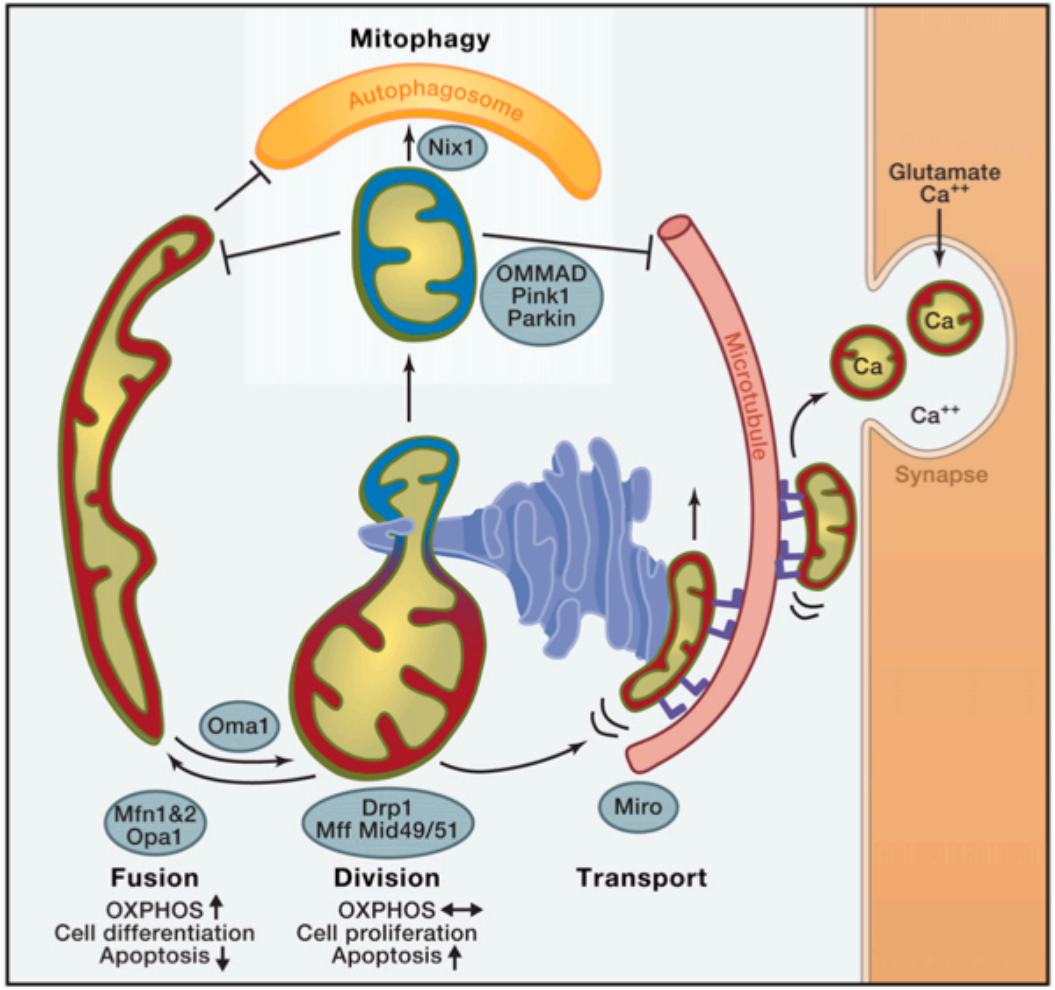


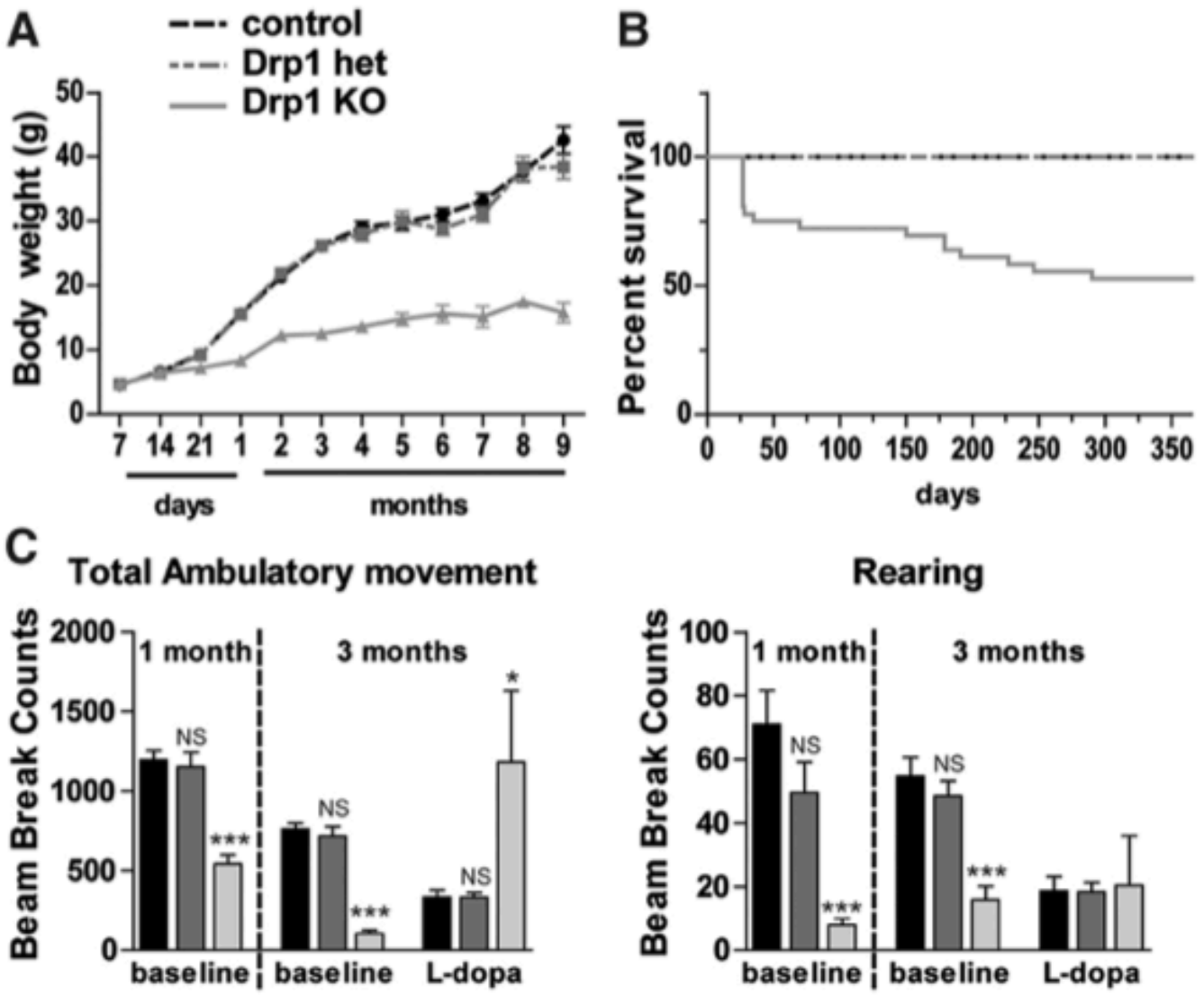
Figure 2. Roles of Mitochondrial Dynamics

Red: mitochondria with high membrane potential, with high oxidative phosphorylation (OXPHOS) activity. Blue: Mitochondria with low membrane potential. Mitofusin 1 or 2 (MFN1, MFN2) mediate mitochondrial outer-membrane fusion in a tissue-specific manner, and OPA1 (optic atrophy gene 1) mediates inner-membrane fusion. The zinc metalloprotease OMA1 proteolytically cleaves OPA1 under low membrane potential conditions, promoting fission. Mitochondrial dynamics factors 49 and 51 or mitochondrial fission factor (Mff) recruit DRP1 onto mitochondria at sites marked by endoplasmic reticulum tubules (ER), and DRP1 mediates mitochondrial division. In cultured cells, upon a decrease in mitochondrial membrane potential, PINK1 kinase recruits Parkin, a ubiquitin E3 ligase, which ubiquitinates several mitochondrial targets, including MFN1 and Miro, to facilitate the degradation of mitochondria via mitophagy. Parkin-mediated ubiquitination triggers OMMAD, outer-mitochondrial membrane-associated degradation—a proteosomal pathway that degrades ubiquinated OM proteins in a CDC48-dependent manner. OMMAD is probably cell type-dependent and may also function in quality control. In erythrocytes, mitophagy receptor Nix1 is involved in autophagosome recruitment. ER forms close contacts with mitochondria, essential for calcium regulation in cellular microcompartments. Miro (blue feet) is a mitochondrial receptor for kinesin via Milton that facilitates the transport of mitochondria on microtubules in a Ca^{2+}-regulated manner. Upon synaptic activity in neurons, influx of glutamate and Ca^{2+} halts mitochondrial transport via Miro to position them at sites of synaptic activity that require Ca^{2+} uptake and ATP.

Loss of mitochondrial fission depletes axonal mitochondria in midbrain dopamine neurons

J Neurosci
2014 vol. 34 (43) pp. 14304–17

Berthet A, Margolis EB, Zhang J, Hsieh I, Zhang J, Hnasko TS, Ahmad J, Edwards RH, Sesaki H, Huang EJ, Nakamura K



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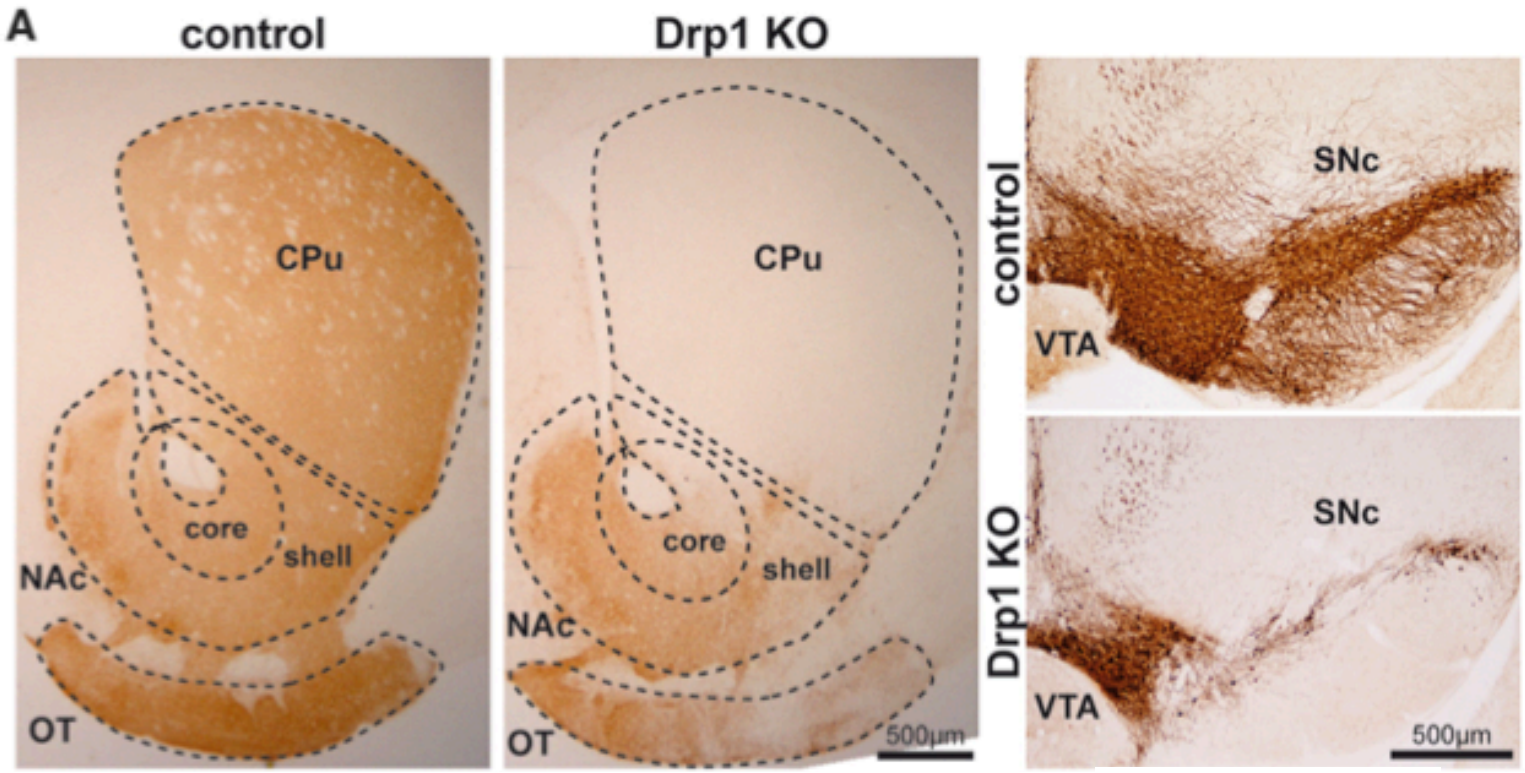

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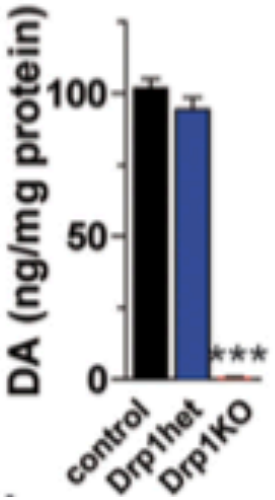

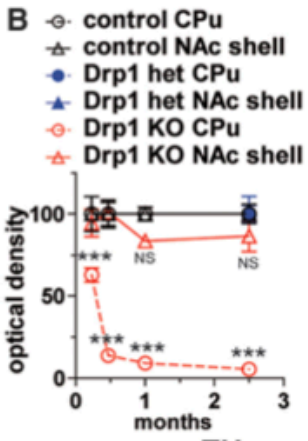

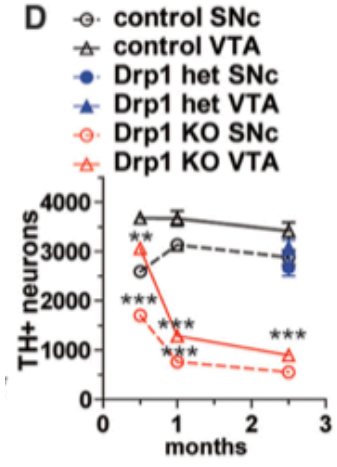

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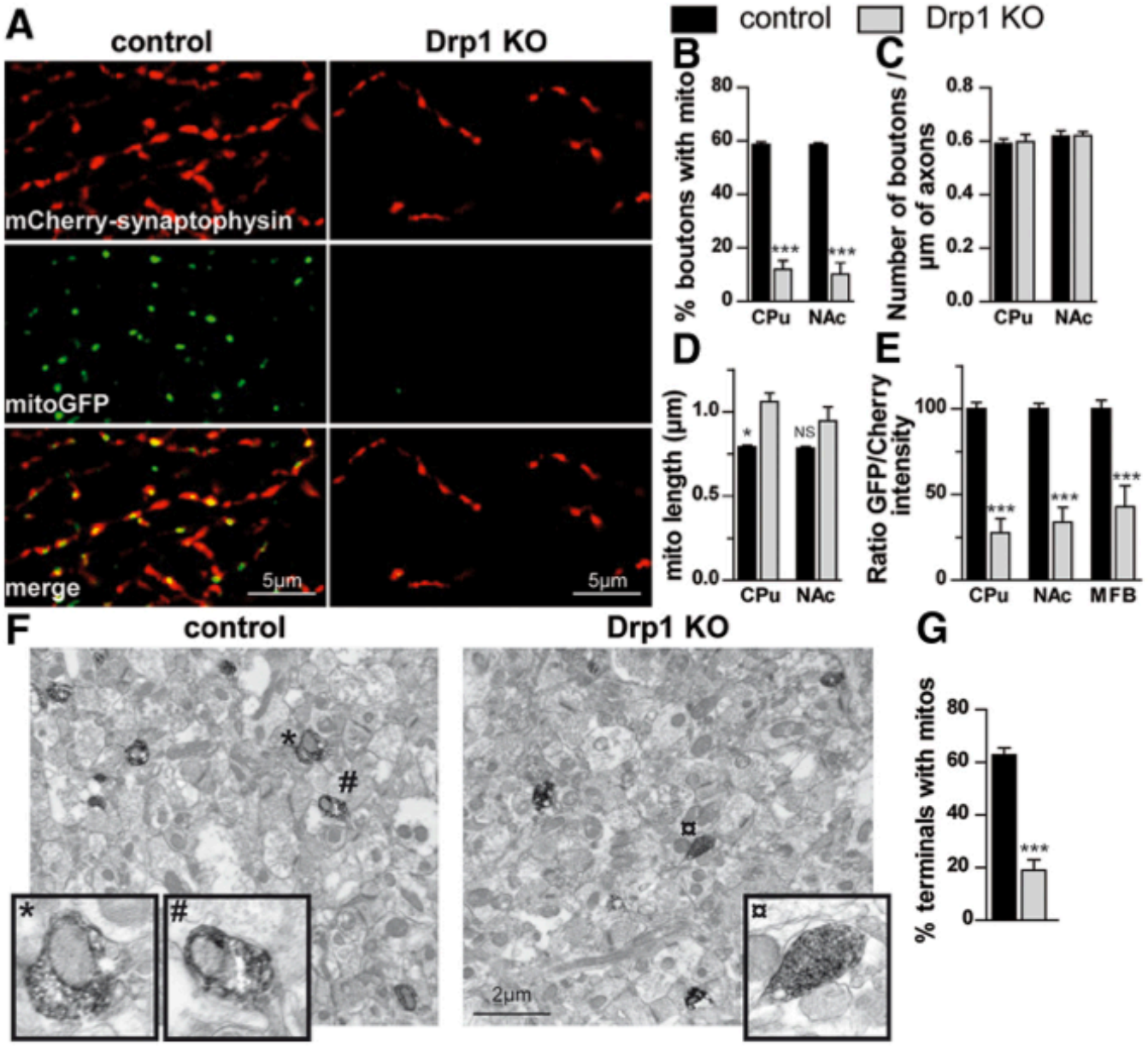

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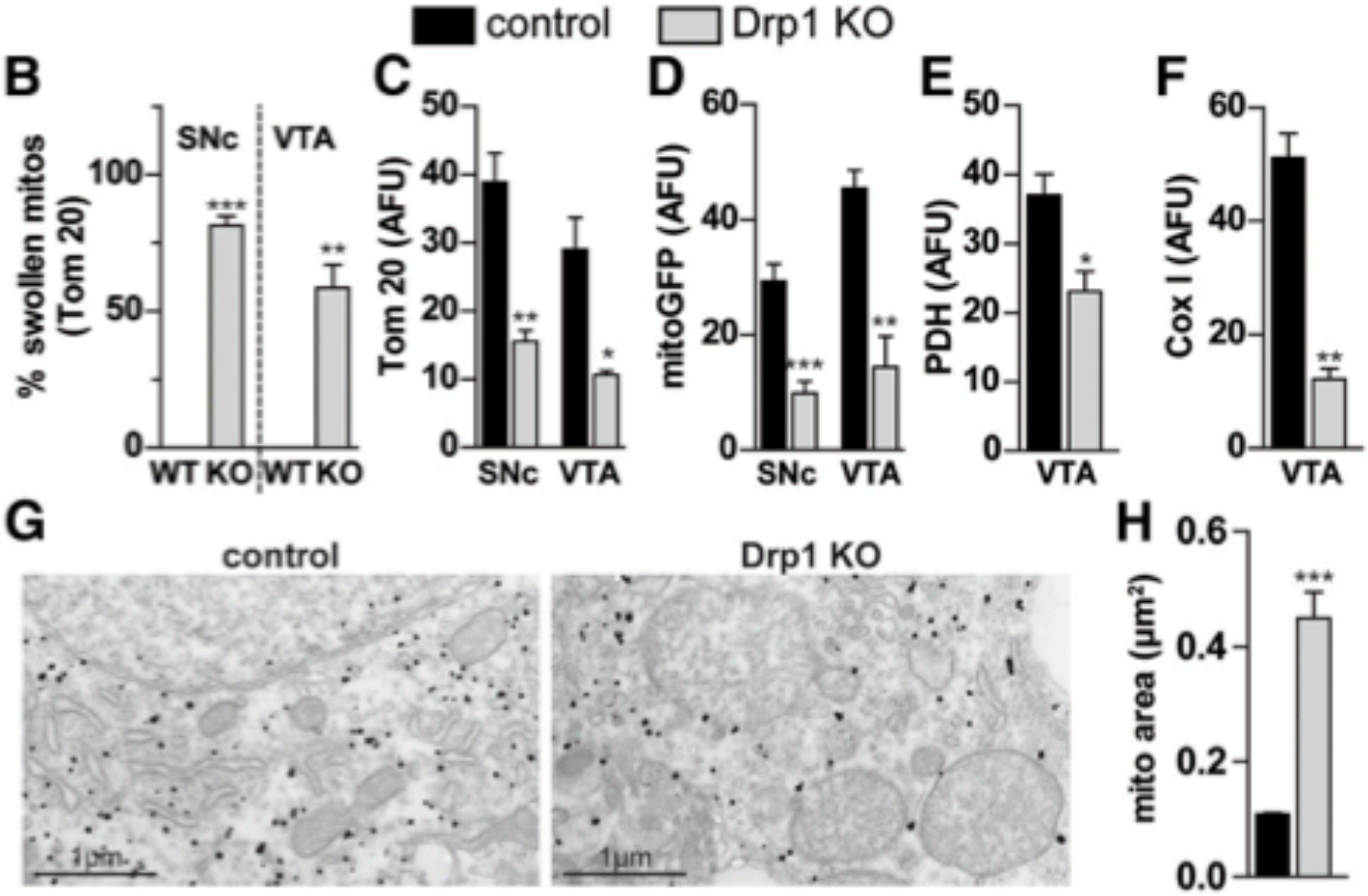

Figure 6. Loss of Drp1 disrupts mitochondrial morphology and decreases mitochondrial mass in DA neurons. ***A–F***, Mitochondrial morphology and mass in midbrain DA neurons from 1-month-old Drp1KO and control mice. ***A***, Loss of Drp1 causes mitochondria to become visibly swollen in most midbrain DA neurons (identified by TH staining, red). ***B***, Mitochondrial mass decreased upon determining the mean fluorescence (normalized to cell area) of neurons stained with Tom20 (***C***), AAVmitoGFP (AFU, arbitrary fluorescent units) (***D***), PDH (***E***), and cytochrome *c* oxidase I (Cox I; ***F***). Scale bars: 5 μm. Data show mean ± SEM, $^{*}p < 0.05$, $^{**}p < 0.001$, $^{***}p < 0.001$ by unpaired two-tailed *t* test, $n = 3–4$ mice per group, 36–76 cells quantified per mouse. ***G***, ***H***, Ultrastructural analysis at the cell body by immunogold staining against TH revealed larger mitochondria in Drp1KO mice than in controls. Scale bars: 1 μm. Data show mean ± SEM, $n = 3$ mice per group, 11–16 cell bodies quantified per mouse.

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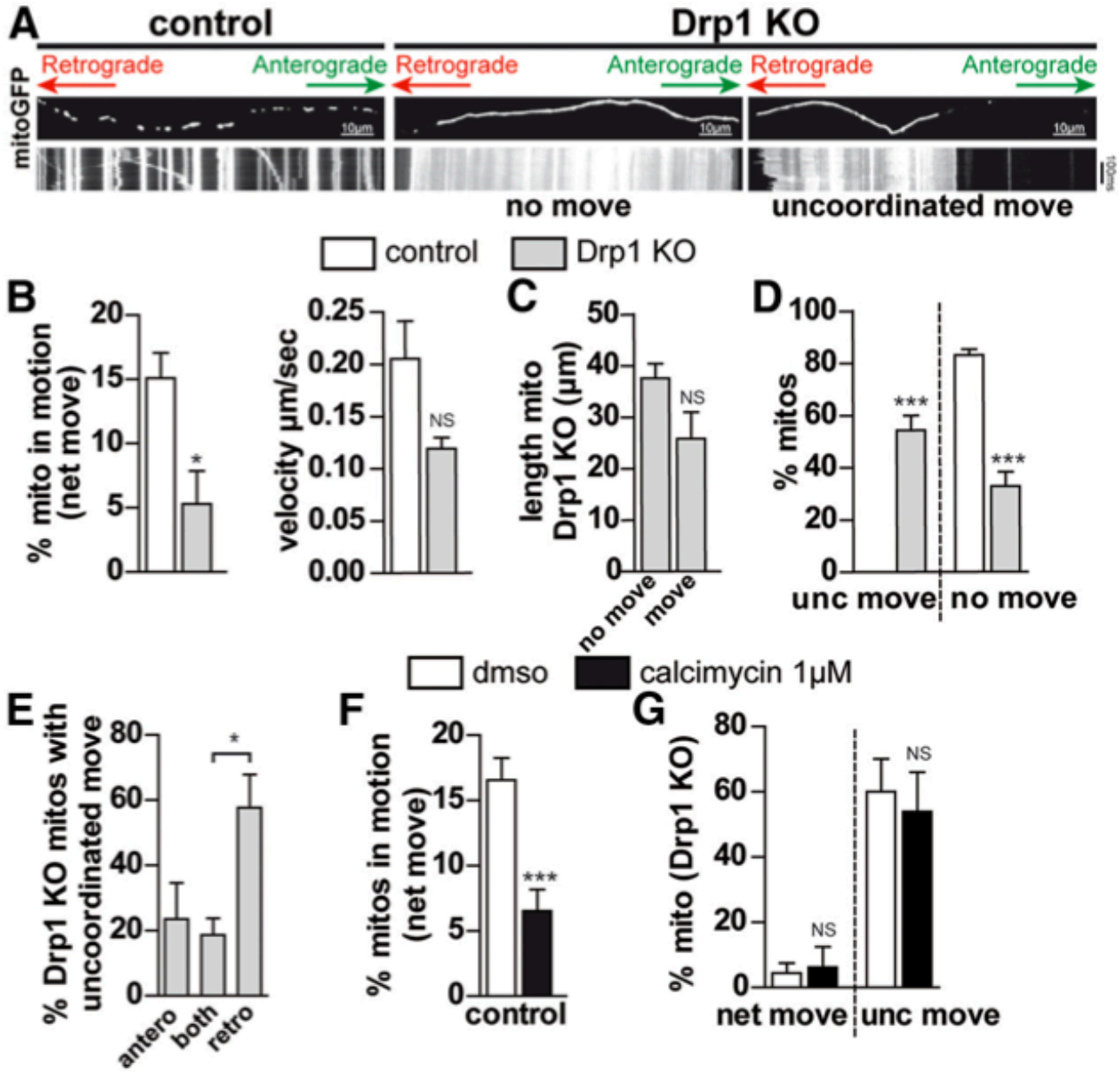

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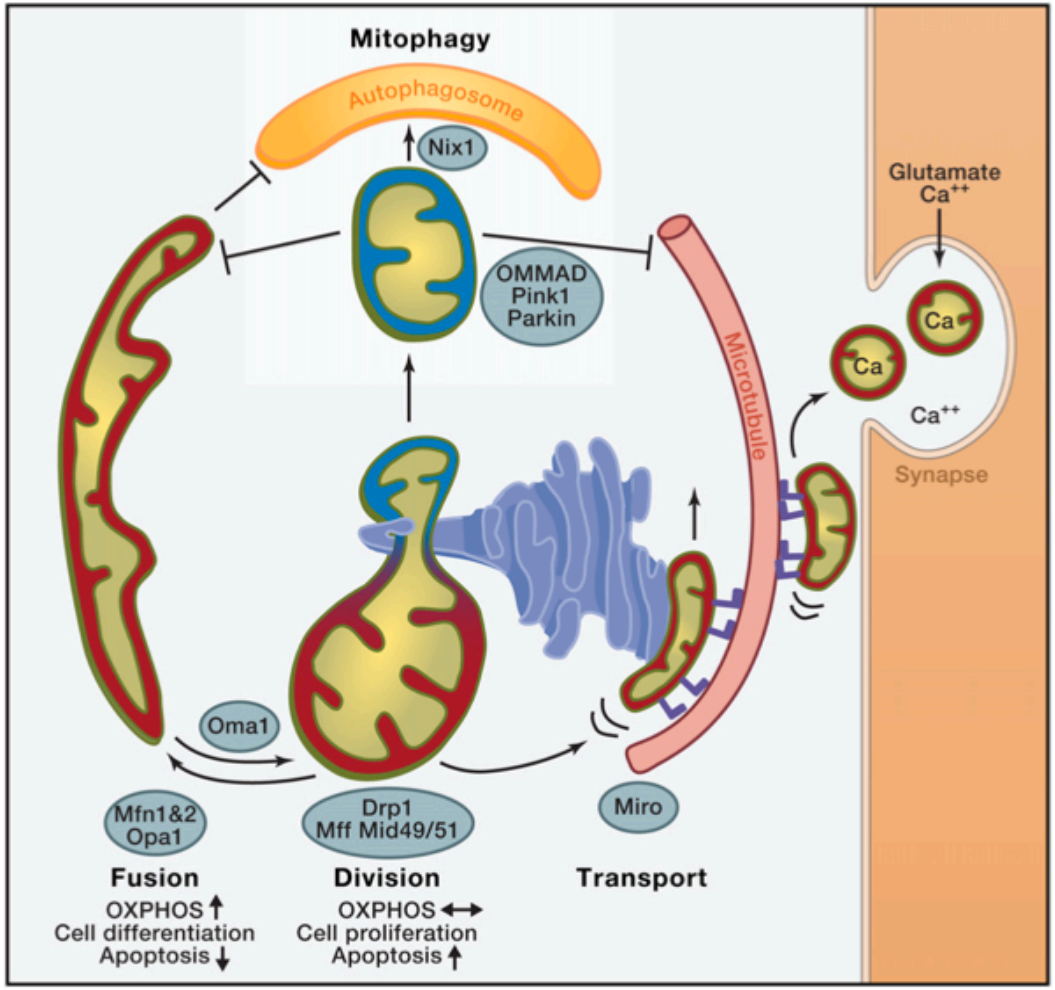

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