Cour 13-10-2014

DNA Damage and Its Links to Neurodegeneration

Neuron
2014 vol. 83 (2) pp. 266–282

Madabhushi R, Pan L, Tsai L

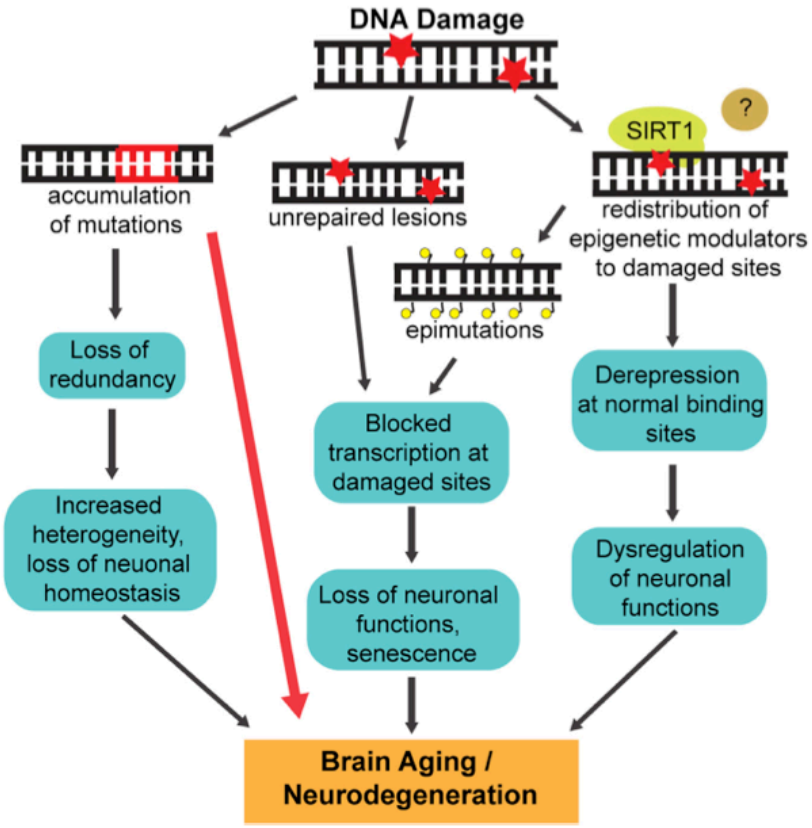


Figure 5. The Consequences of DNA Damage in Aging and Neurodegeneration

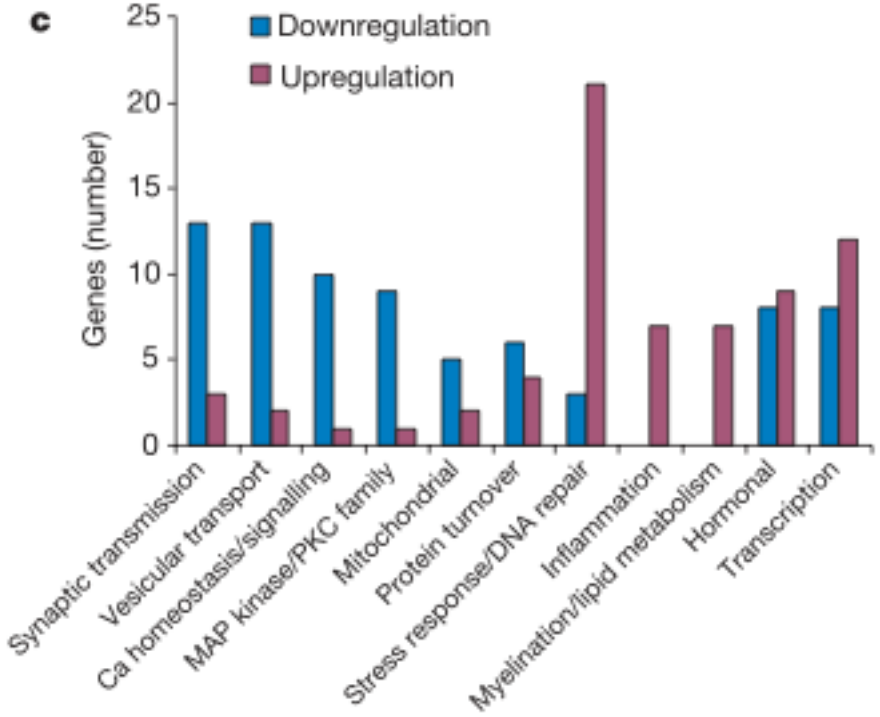
Left: erroneous repair of DNA damage can lead to the formation of mutations, which are irreversible and perturb tissue homeostasis in the nervous system by essentially promoting the formation of mosaics. Occasionally, mutations could occur in DNA repair factors (such as FUS, see text) and this can manifest in profound neurodegeneration (red arrow). Middle: in contrast, although reversible, the accumulation of unrepaired lesions due to decreased DNA repair activities can block the transcription of genes encoding for critical neural functions and downregulate their activity, leading to cognitive decline. Right: DNA damage also affects the epigenetic landscape. DNA damage-induced epigenetic changes can accrue over time as "epimutations" and affect gene expression. In addition, the redistribution of epigenetic modulators, such as SIRT1, can trigger global changes to the chromatin architecture, leading to large-scale transcriptional deregulation of their normally repressed targets, such as major satellite repetitive DNA.

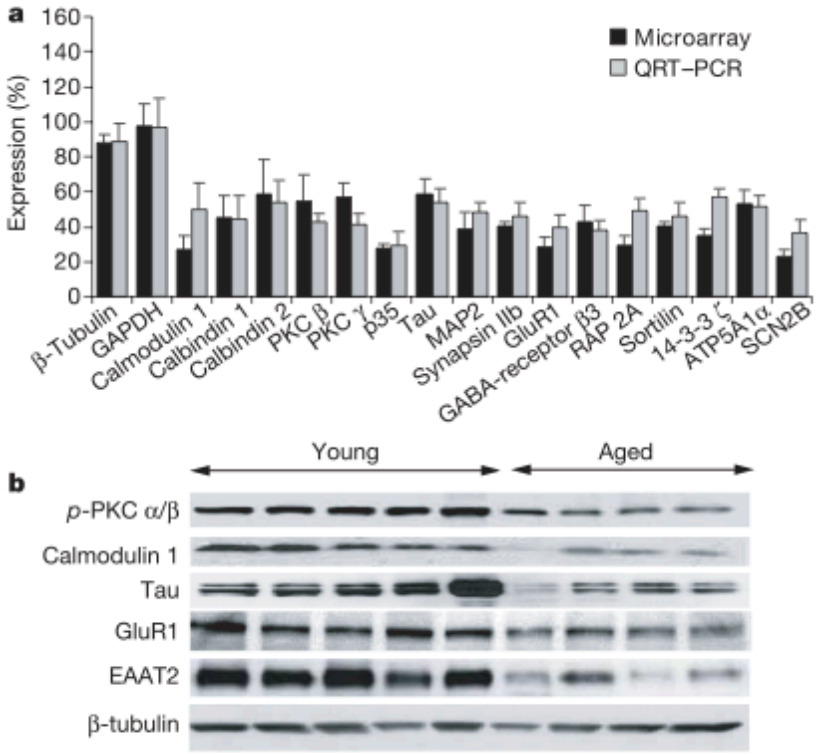
Gene regulation and DNA damage in the ageing human brain

NATURE | VOL 429 | 24 JUNE 2004 | www.nature.com/nature

Tao Lu[1], Ying Pan[1], Shyan-Yuan Kao[1], Cheng Li[2], Isaac Kohane[3], Jennifer Chan[4] & Bruce A. Yankner[1]

< 42 versus > 73





Gene regulation and DNA damage in the ageing human brain

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Synaptic function

Synaptic transmission	GluR1
	NMDA receptor 2A
	GABA A receptor β3
	GABA A receptor ∂
	Serotonin receptor 2A
	Voltage-gated Na channel II β (SCN2B)
	Voltage-dependent calcium channel β2
	Neurexin 1
	Synaptobrevin 1 (VAMP1)
	Synapsin II b
	γSNAP
	αSNAP
	RAB3A
	SNAP23
	Synaptophysin-like protein
Ca^{2+} homeostasis/signalling	Calmodulin 1
	Calmodulin 3
	Calbindin 1 (28 kD)
	Calbindin 2 (29 kD, calretinin)
	CaM kinase II α
	CaM kinase IV
	Calcineurin B α
	ATPase, Ca^{2+}-transporting, plasma membrane 2 (ATP2B2)
	ATPase, Ca^{2+}-transporting, plasma membrane 2 (ATP2A2)
	Regucalcin (senescence marker protein)
cAMP signalling	Phosphodiesterase 4D
	Adenylyl cyclase associated protein 2
Protein kinase C	PKCβ1
	PKCγ
	PKCζ
G protein signalling	Rap2A
	Regulator of G protein signalling 4
	G protein, q polypeptide (GNAQ)
MAP kinase cascades	MAPK1
	MAPK9
	MAPKK4
	Ras–GNRF
	MAPKK5
	14-3-3ζ
	p21 activated protein kinase (PAK1)
CdK5	CdK5, regulatory subunit 1 (p35)

Vesicular transport

	RAB1A
	RAB3A
	RAB5A
	RAB6A
	Kinesin 1B
	Sortilin 1
	Dynein (DNCH1)
	Dynamin 1-like
	Trans Golgi network protein 2
	Golgi reassembly stacking protein 2
	Phosphotidylinositol transfer protein β
	Clathrin, light polypeptide
	Kinesin 2
	VAMP3
Microtubule cytoskeleton	MAP1B
	MAP2
	Tau
	RAN binding protein 9

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Stress response	
Antioxidant	Nonselenium glutathione peroxidase
	Selenoprotein P
	Paraoxonase 2
	Cystathionine-beta-synthase
DNA repair	8-oxoguanine DNA glycosylase
	Uracil-DNA glycosylase
	Topoisomerase I binding protein
	Topoisomerase II β
	FK506 binding protein 12-rapamycin associated protein 1
Stress	Heat shock 70 kD protein 2
	Crystallin, alpha B
	Hypoxia inducible factor 1 α (HIF1 α)
	HIF-1 responsive RTP801
	Transglutaminase 2
	p53 binding protein 2
	Retinoblastoma-associated protein 140
	Retinoblastoma-like 2 (p130)
	Stress 70 protein chaperone
Metal ion homeostasis	Metallothionein 1G
	Metallothionein 1B
	Metallothionein 2A
	Haem binding protein 2
	Haemoglobin β
	Hephaestin
Inflammation	
	TNF-α
	C type lectin
	H factor (complement)-1
	Interferon, gamma-inducible protein 16
	Interferon regulatory factor 7
	Integrin α5
	Integrin β1

The genetics of early telencephalon patterning: some assembly required

NATURE | VOL 429 | 24 JUNE 2004 | www.nature.com/nature

Hébert J, Fishell G

Nat Rev Neurosci
2008 vol. 9 (9) pp. 678-85

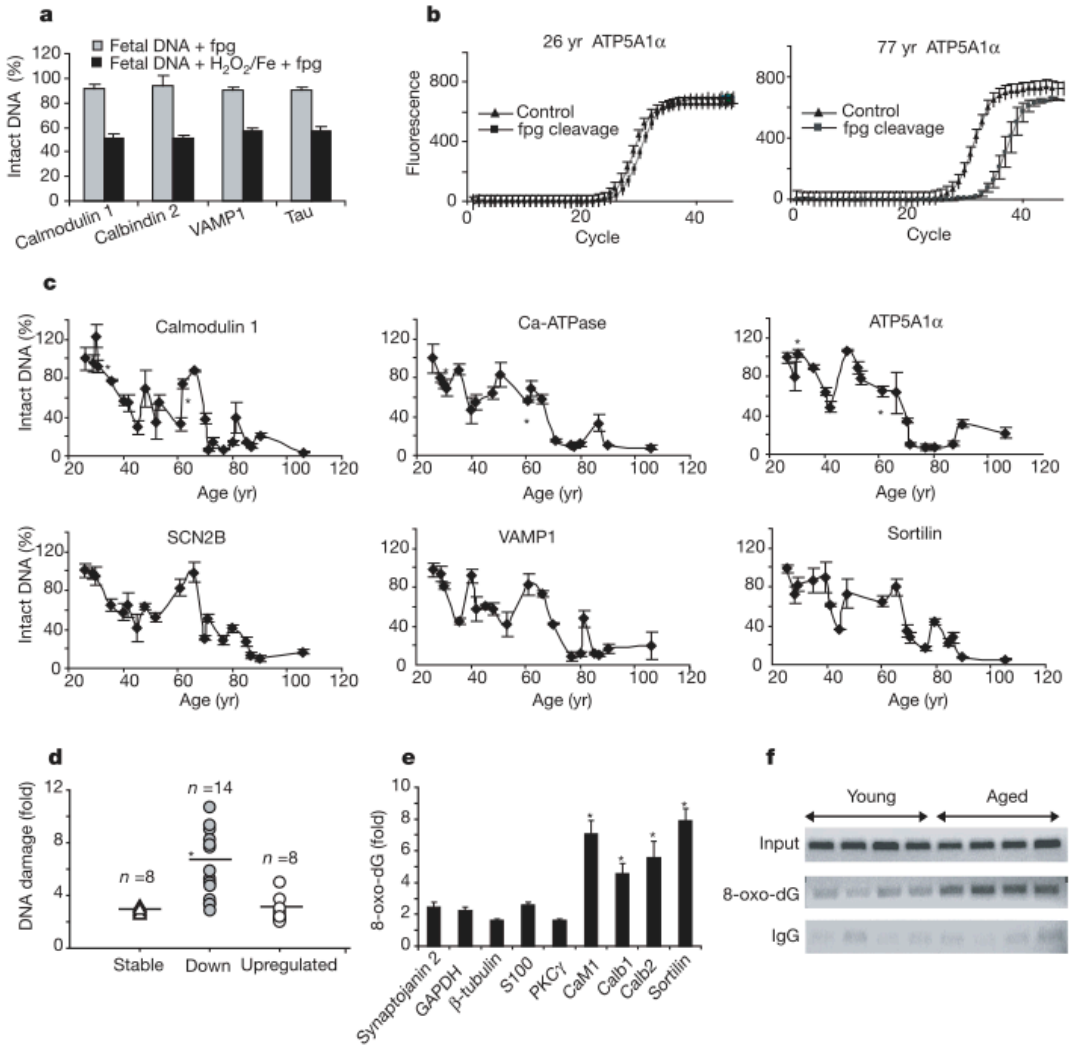

Figure 3 DNA damage in the ageing human cortex. **a**, Genomic DNA from fetal cortex does not exhibit significant DNA damage. DNA damage to the promoter regions of the indicated genes was assayed by cleavage with the endoglycosidase FPG and quantitative PCR. Intact DNA is the percentage detected by PCR following FPG cleavage relative to that in uncleaved DNA. **b**, Ageing increases oxidative DNA damage to the mitochondrial ATP synthase α (ATP5A1α) promoter. Shown are real-time fluorescence PCR curves from 26- and 77-year-old frontal cortical samples. Note the marked shift in PCR cycle number following FPG cleavage of 77 yr old DNA. Values in **a** and **b** represent the mean ± s.d. **c**, Time course of DNA damage in the ageing frontal cortex. DNA damage was assayed in the promoters of age-downregulated genes (calmodulin 1, Ca-ATPase, ATP5A1α, sodium channel 2β (SCN2B), VAMP1, and sortilin) in cortical samples from 26- to 106-year-old cases and normalized to the 26-year-old value (100%). Values represent the mean ± s.d.; $n = 3$. Asterisks indicate intracortical biopsy samples. **d**, DNA damage to promoters of genes that are stably expressed, downregulated or upregulated in the aged cortex. Shown is the fold increase in promoter DNA damage in aged cases (≥70 years old) relative to the youngest, 26-year-old case. Each point represents a gene (see 'DNA damage assay' in Supplementary Methods for gene identities). Asterisk indicates $P < 0.001$ relative to age-stable genes by analysis of variance (ANOVA) with post-hoc Student–Newman–Keuls test. **e**, Oxidative damage to gene promoters in the aged cortex. Shown is the fold increase in 8-oxoguanine (8-oxo-dG) incorporation into promoters of age-stable (GAPDH, β-tubulin and synaptojanin 2), age-upregulated (S100), and age-downregulated genes (calmodulin 1 (CaM1), calbindin 1 (Calb1), calbindin 2 (Calb2), sortilin and PKCγ). Asterisks indicate $P < 0.05$ relative to GAPDH. Values represent the mean ± s.e.m.; $n = 4$. **f**, Chromatin immunoprecipitation of the calmodulin 1 promoter with a monoclonal antibody to 8-oxoguanine in aged (≥73-year-old) and young (<40-year-old) cortical samples. Input DNA and non-specific IgG (IgG) controls are shown.

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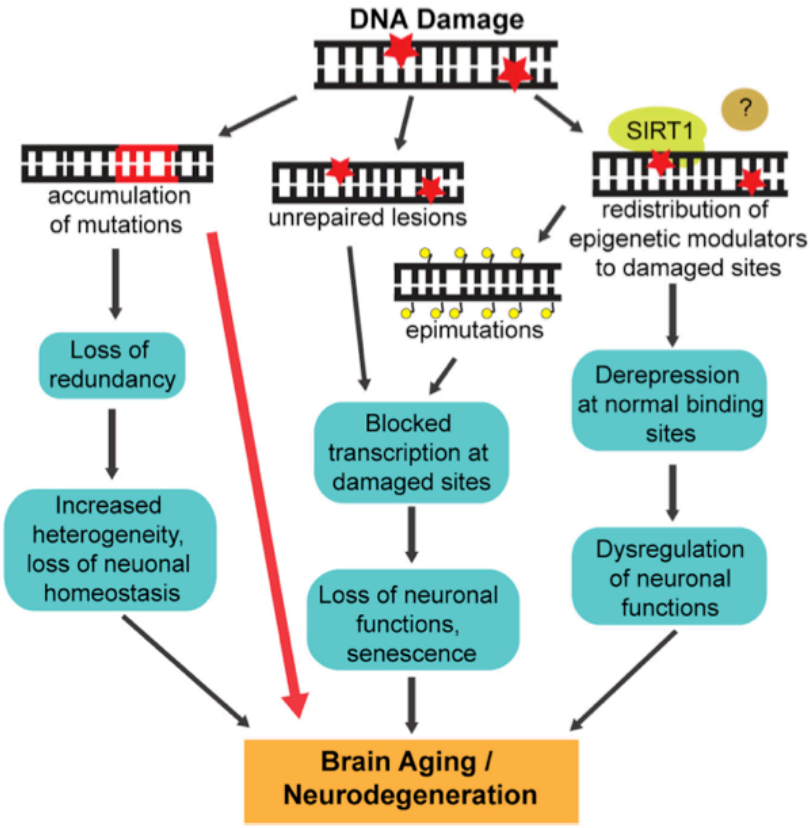

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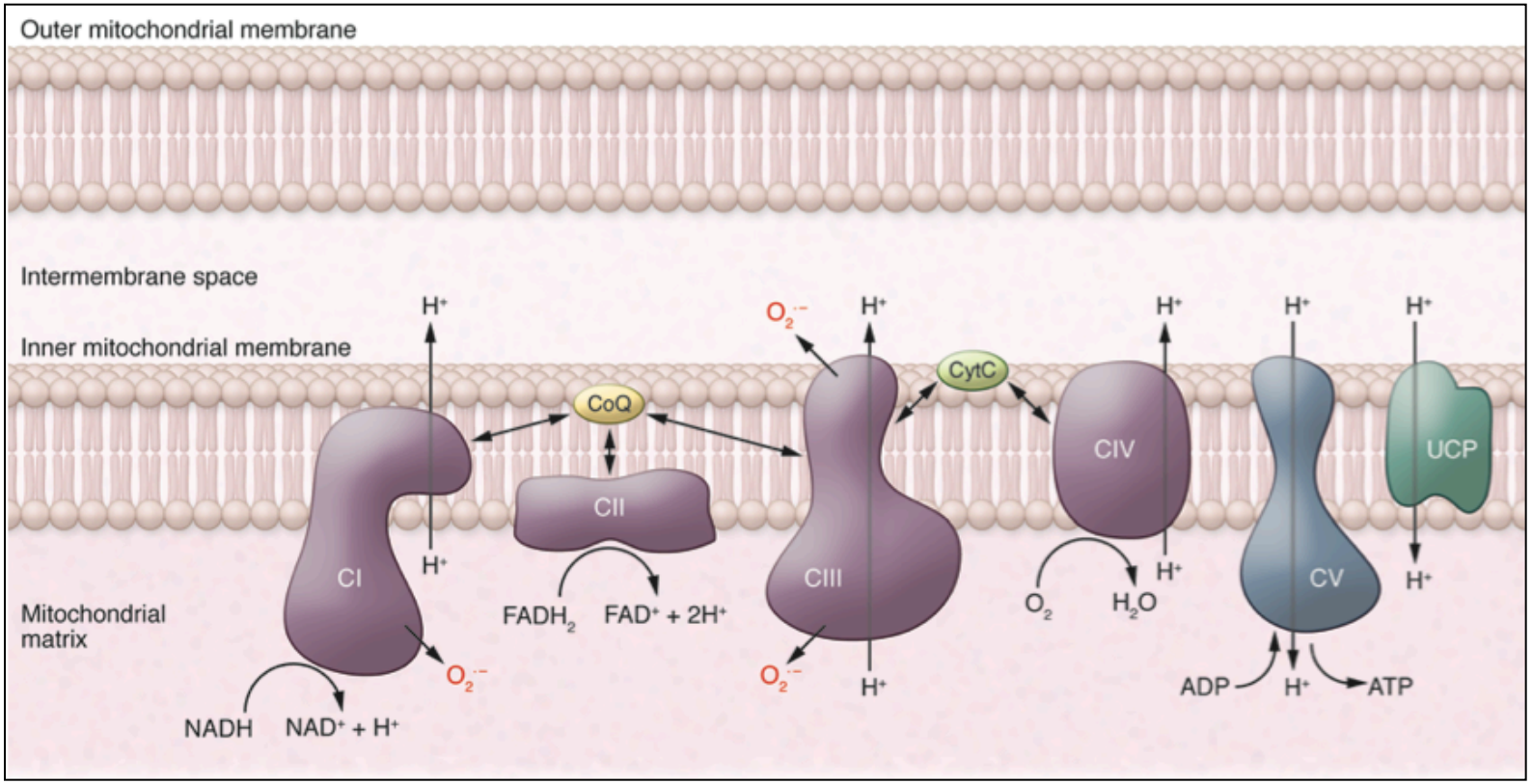
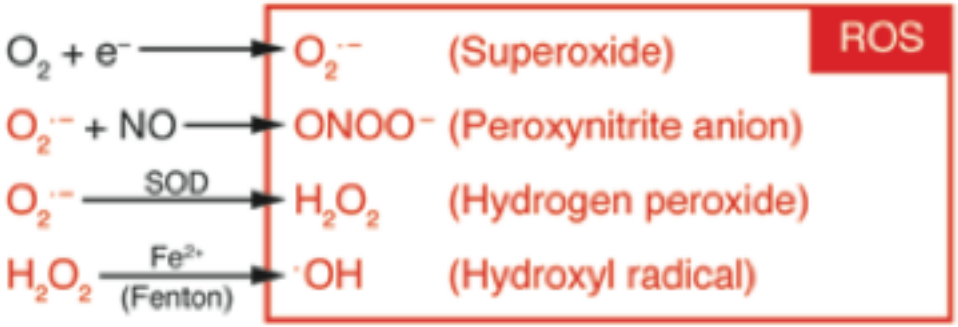
The role of mitochondria in aging

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

Bratic A, Larsson N

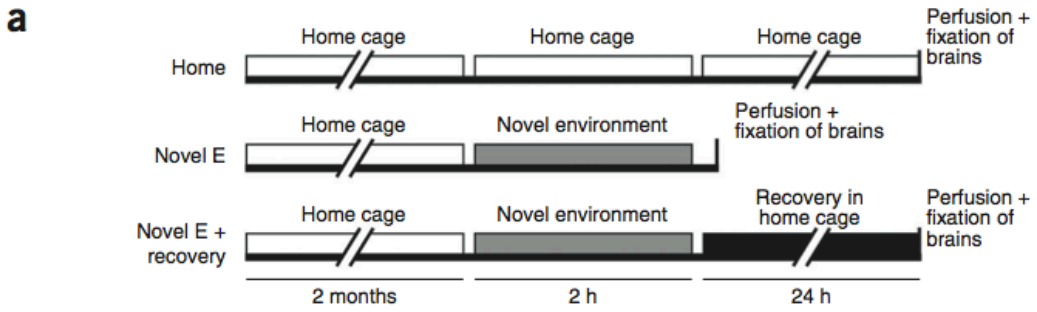


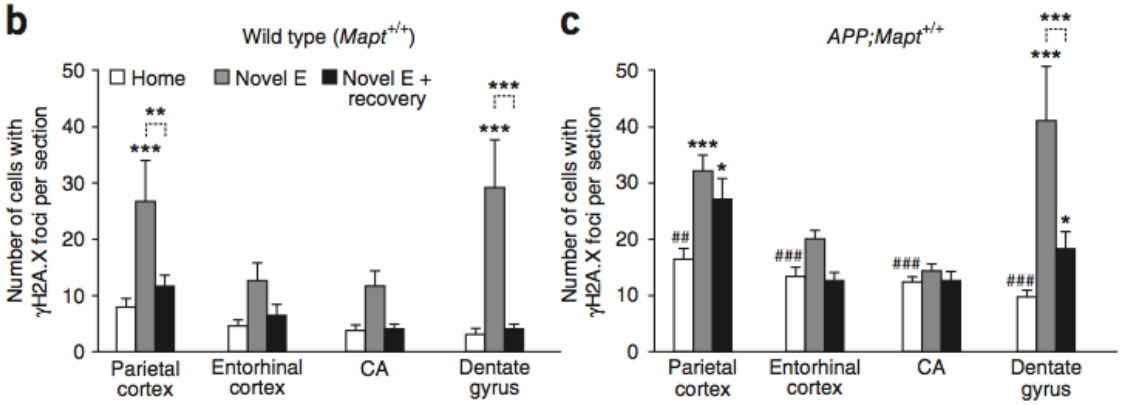


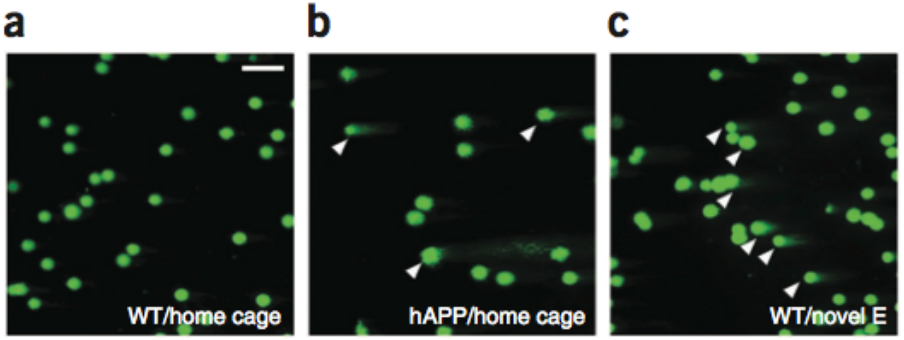
Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-β

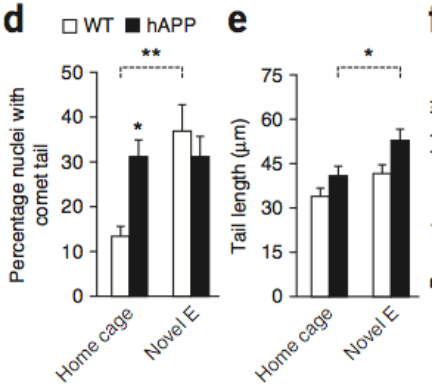
NATURE NEUROSCIENCE VOLUME 16 | NUMBER 5 | MAY 2013

Elsa Suberbielle[1,2], Pascal E Sanchez[1,2], Alexxai V Kravitz[1,2], Xin Wang[1], Kaitlyn Ho[1], Kirsten Eilertson[3], Nino Devidze[1], Anatol C Kreitzer[1,2] & Lennart Mucke[1,2]





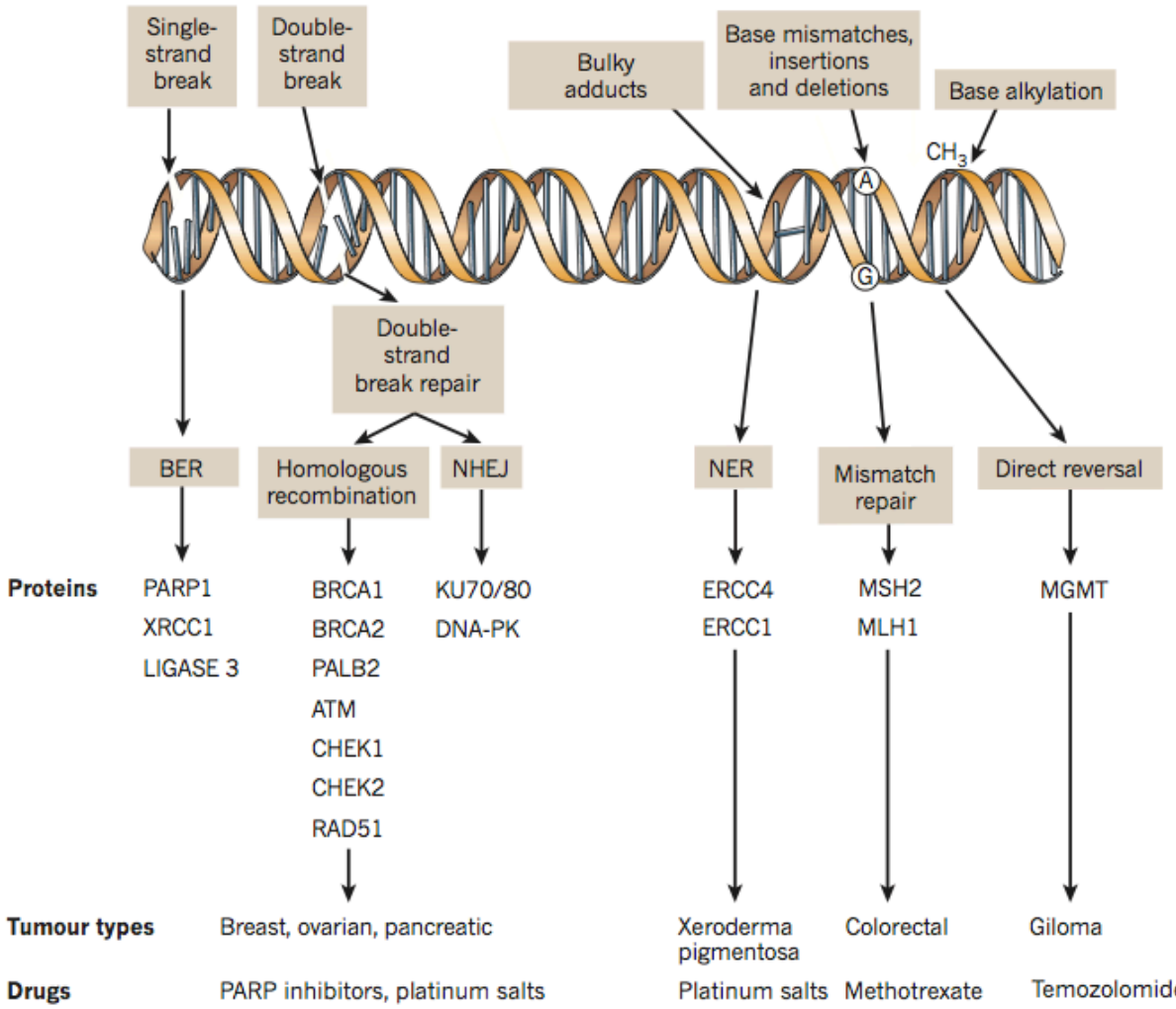




The DNA damage response and cancer therapy

19 JANUARY 2012 | VOL 481 | NATURE | 287

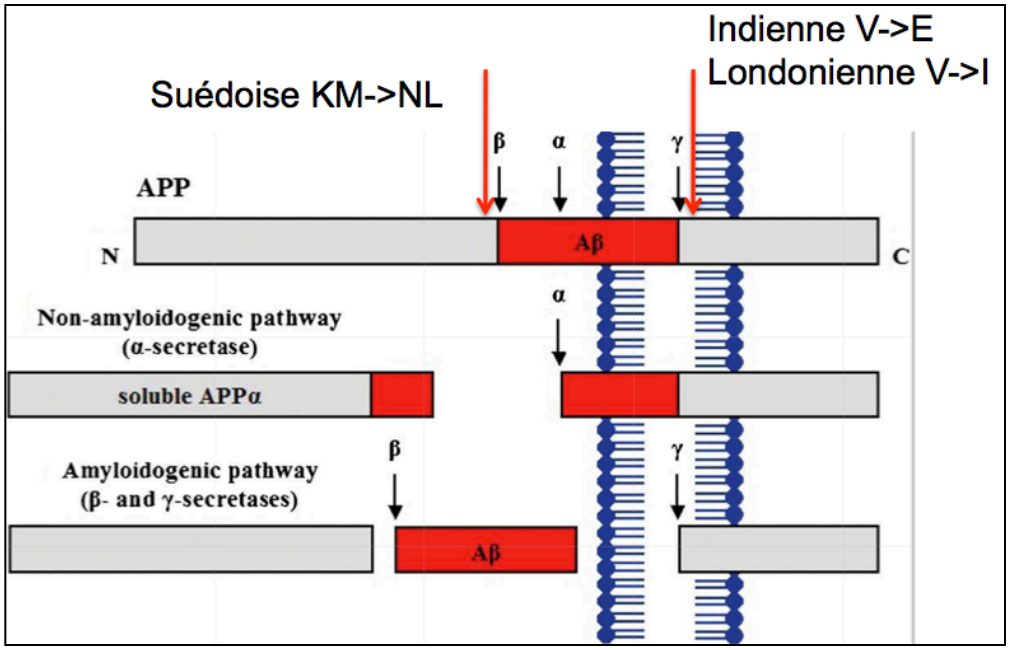
Christopher J. Lord[1]* & Alan Ashworth[1]*



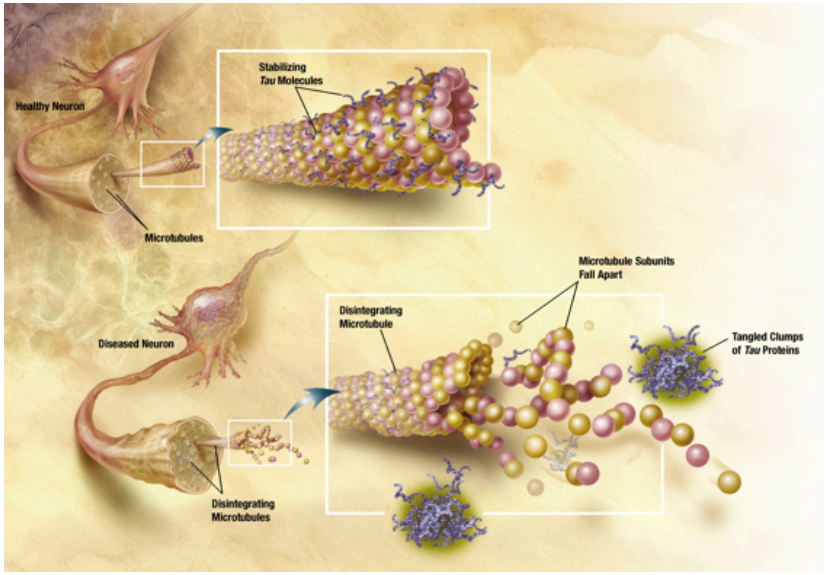
Clinics (Sao Paulo). 2011 June; 66(Suppl 1): 45–54.
doi: 10.1590/S1807-59322011001300006
PMCID: PMC3118437

Insights into Alzheimer disease pathogenesis from studies in transgenic animal models

Evelin L Schaeffer,[I] Micheli Figueiró,[I] and Wagner F Gattaz[I]



Tangles

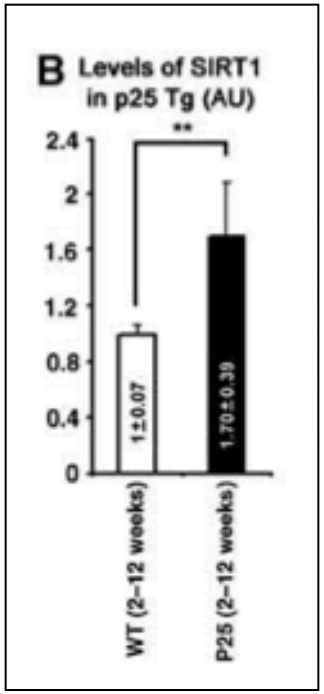


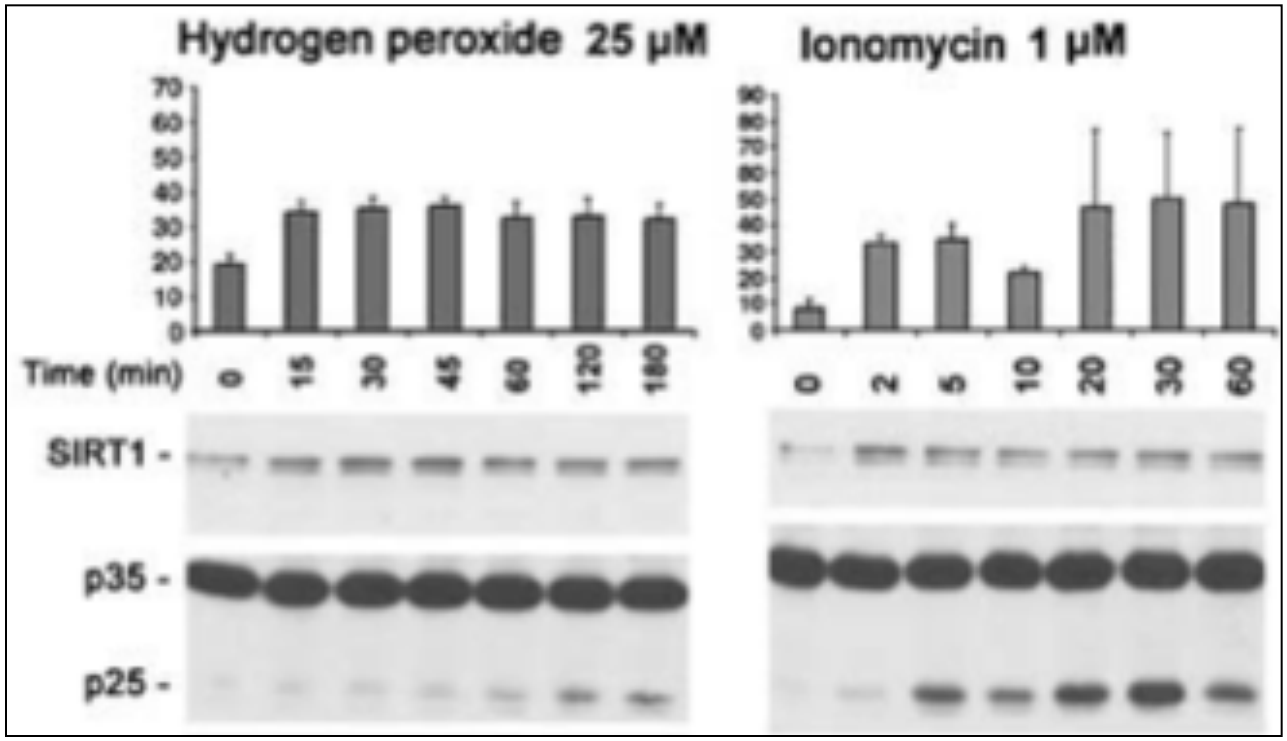
The Swedish mutation, which is located just outside the N-terminus of the Aβ domain of APP, favors β-secretase cleavage in vitro and is associated with an increased level and deposition of Aβ1-42 in AD brain. The Dutch and Iowa mutations, which are located in the Aβ domain of APP, accelerate Aβ1-40 fibril formation in vitro. The Dutch mutation is associated with cerebrovascular Aβ deposition—that is, CAA, resulting in cerebral hemorrhages and dementia in patients with AD, whereas the Iowa mutation is associated with severe CAA, widespread neurofibrillary tangles, and unusually extensive distribution of Aβ1-40 in plaques in AD brain. The Arctic mutation, which is also located inside the Aβ domain, makes APP less available to α-secretase cleavage and increases β-secretase processing of APP thus favoring intracellular Aβ production in vitro. The Arctic mutation is associated with severe CAA in the absence of hemorrhage, abundant parenchymal Aβ deposits, and neurofibrillary tangles in AD brain. The London mutation, which is located in the transmembrane domain of APP, as well as the PS1 and PS2 mutations alter γ-secretase cleavage and increase the Aβ1-42 level and/or the Aβ1-42/Aβ1-40 ratio in vitro. The London mutation is associated with extensive parenchymal Aβ deposition and abundant senile plaques and neurofibrillary tangles, as well as moderate CAA in AD brain. The Indiana mutation, which is also located in the transmembrane domain of APP, is associated with large number of neurofibrillary tangles and senile plaques, as well as mild CAA in AD brain.33 The Florida mutation, which is also located in the transmembrane domain of APP, affects γ-secretase cleavage causing an increased Aβ1-42 concentration and Aβ1-42/Aβ1-40 ratio in vitro.

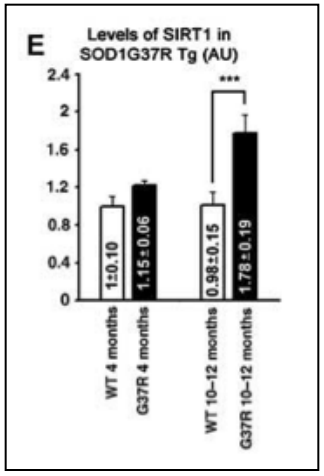
SIRT1 deacetylase protects against neurodegeneration in models for Alzheimer's disease and amyotrophic lateral sclerosis

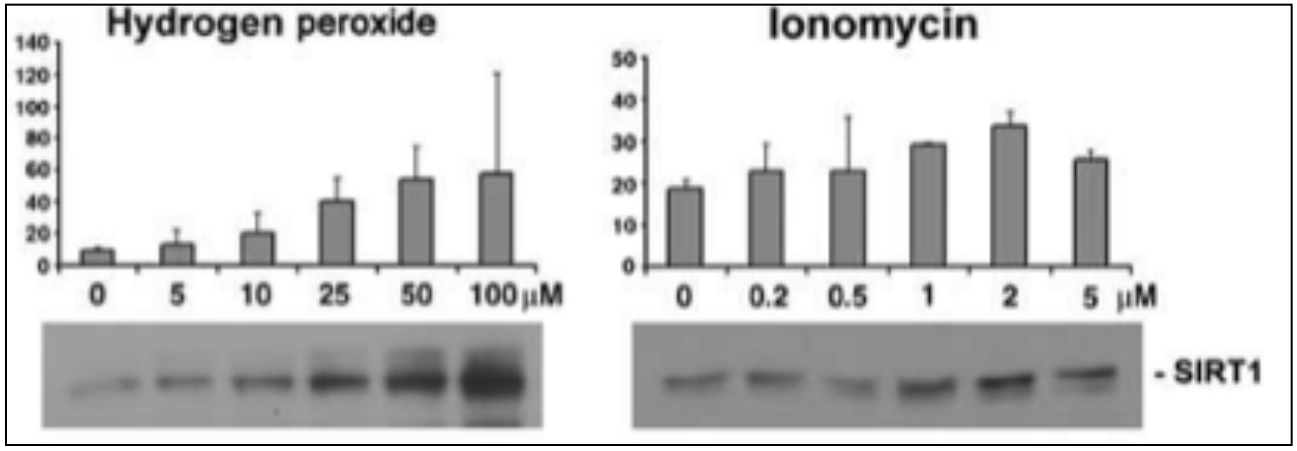
The EMBO Journal
2007 vol. 26 (13) pp. 3169-79

Kim D, Nguyen MD, Dobbin MM, Fischer A, Sananbenesi F, Rodgers J, Delalle I, Baur J, Sui G, Armour S, Puigserver P, Sinclair D, Tsai L









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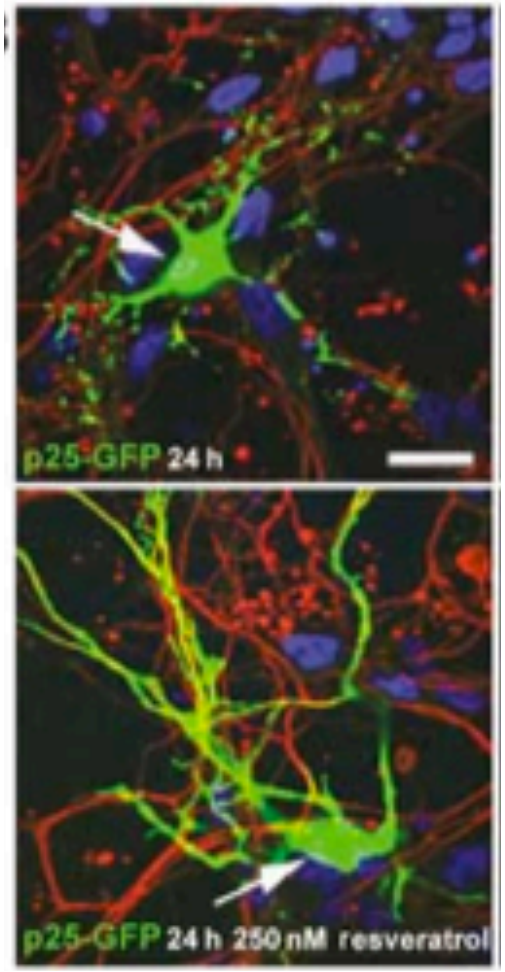

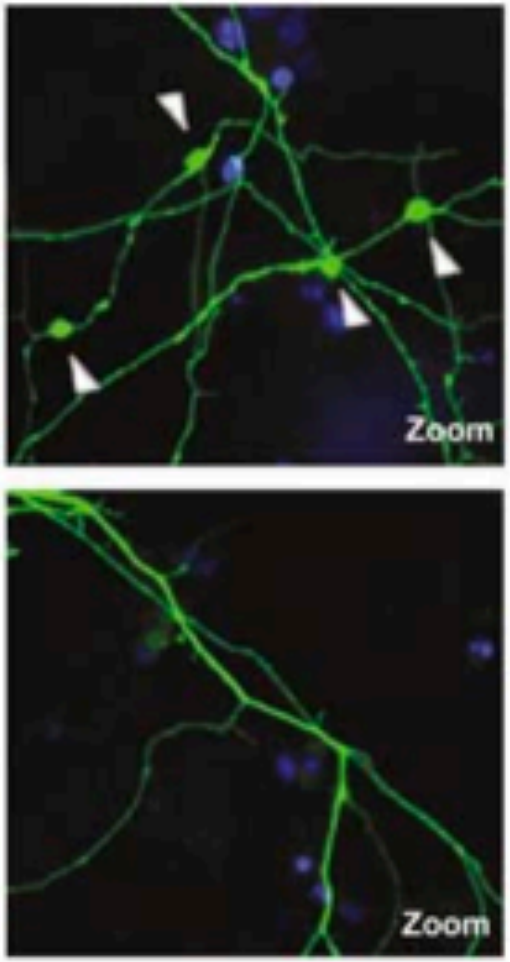

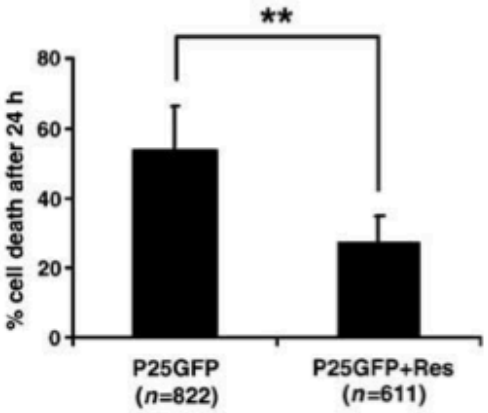

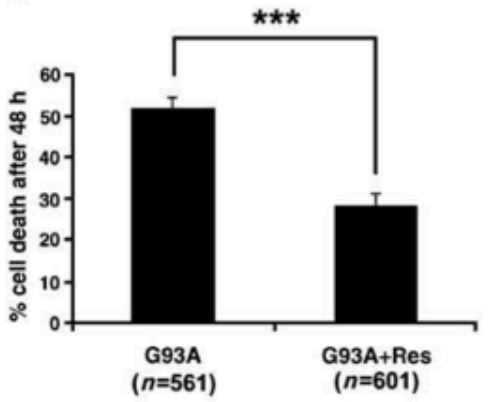

SOD mutée

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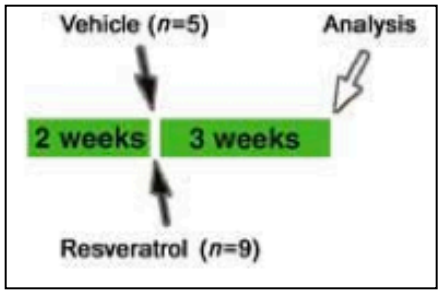

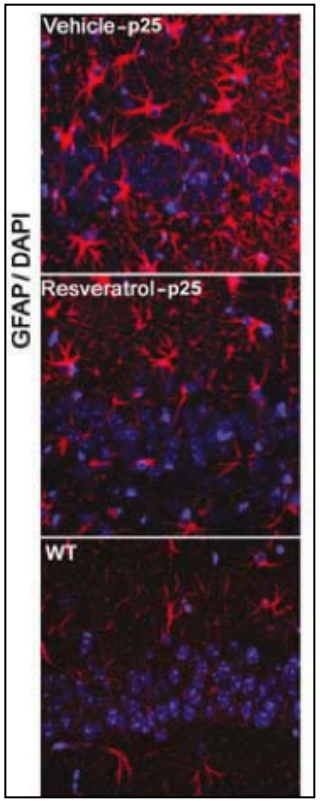

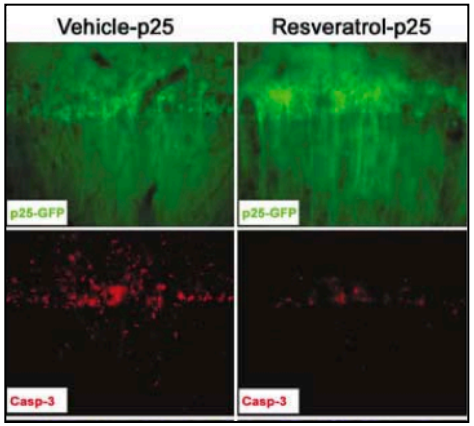

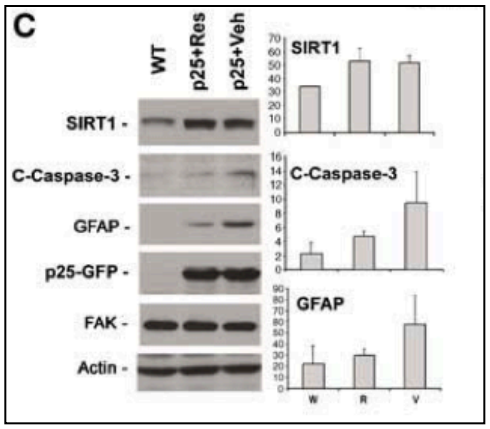

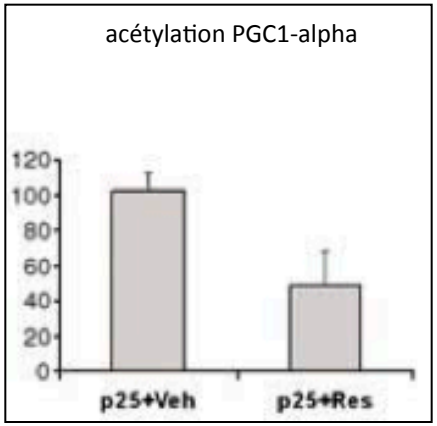

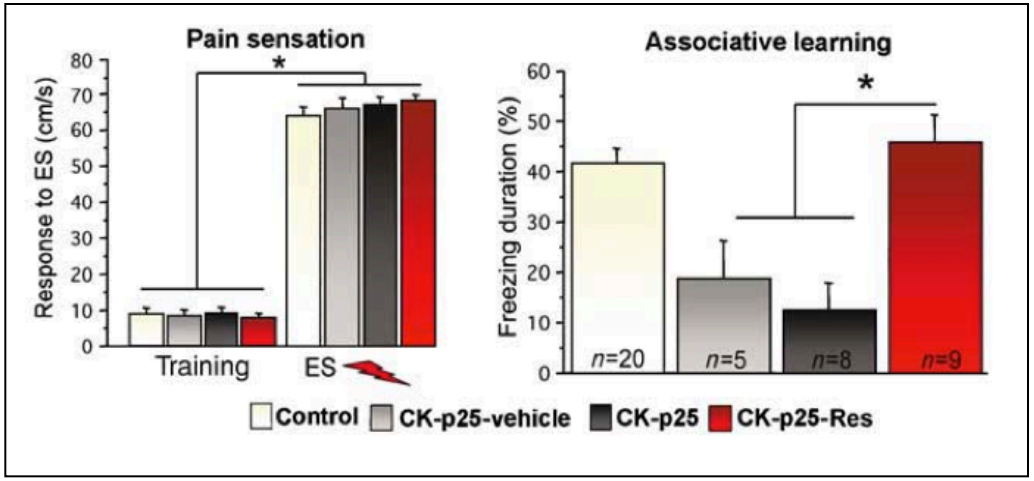

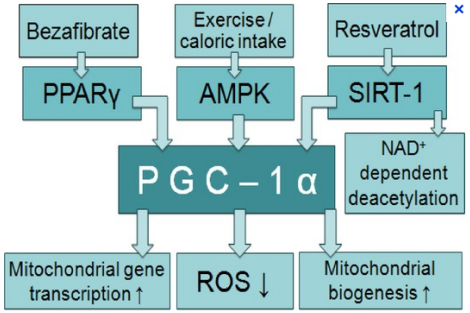

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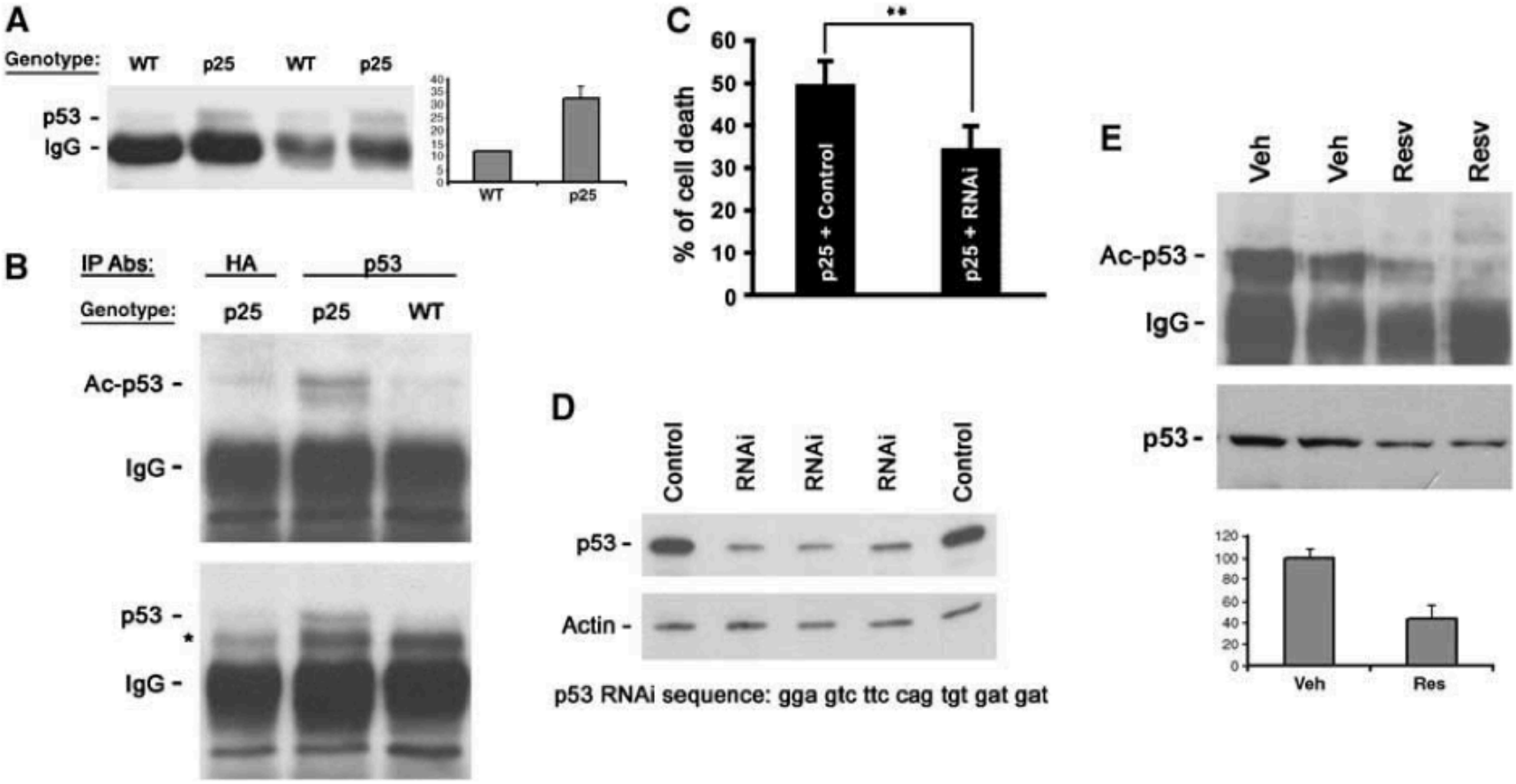
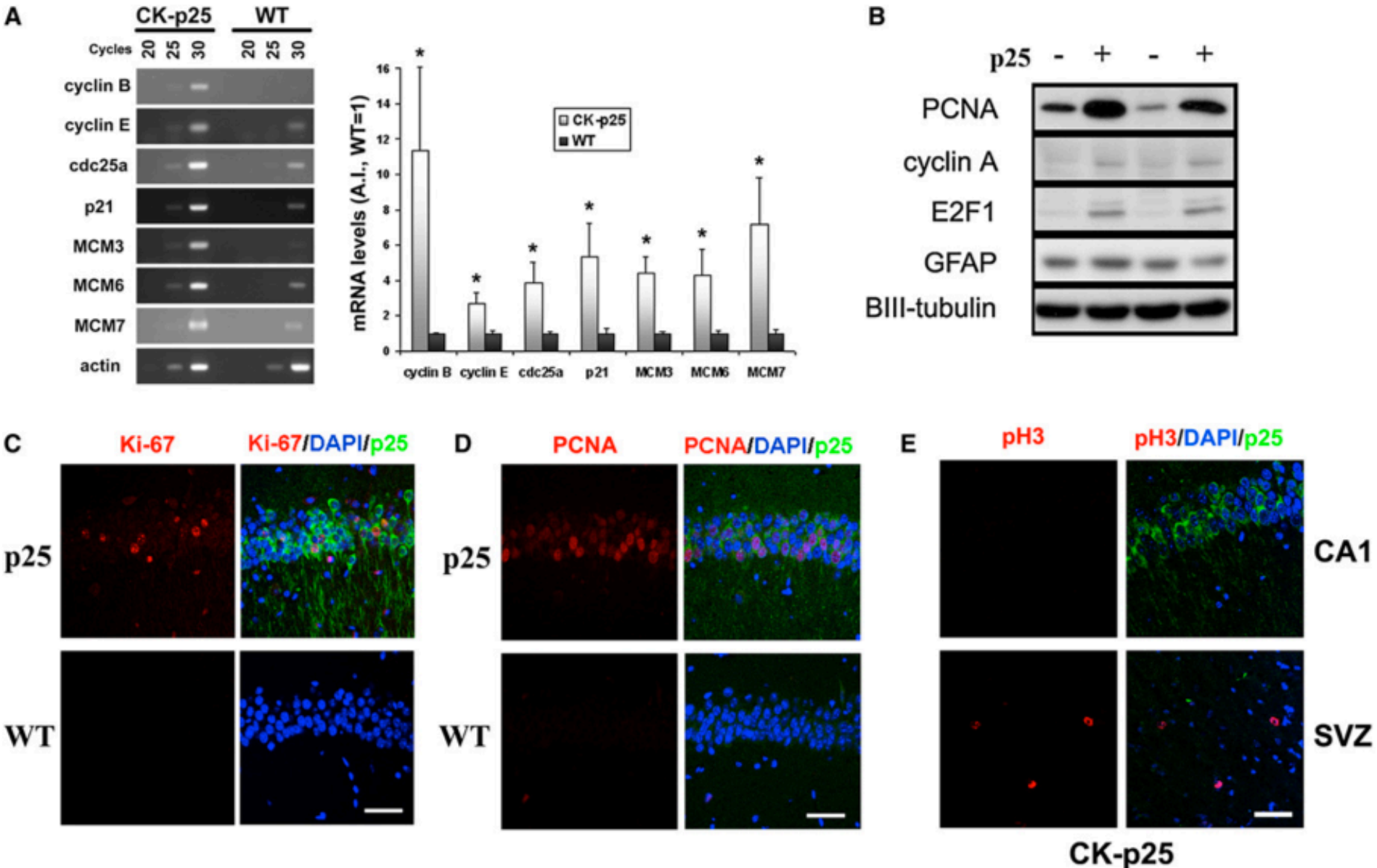


Figure 5 Acetylation of p53, a SIRT1 substrate, in p25 transgenic mice reversed by resveratrol. (**A**) Upregulation of p53 in p25 transgenic mice ($n=4$) detected by immunoprecipitation followed by Western blot. Densitometry analyses of p53 levels are shown on right. (**B**) Acetylation of p53 at lysine 382 in p25 transgenic mice ($n=3$) detected by immunoprecipitation, followed by Western blot. * Indicates nonspecific band. (**C**) P53 knockdown in p25-expressing primary hippocampal neurons rescues p25 neurotoxicity by 25%. $^{**}P(T \leqslant t)$ two tails: 0.001. (**D**) Efficient knockdown of p53 by RNAi in cell line transfected with p53. (**E**) Reduced acetylation of p53 at lysine 382 and downregulation of p53 in p25 transgenic mice ($n=3$) treated with resveratrol. Densitometry analyses of acetylated p53 levels is shown in the bottom panel.

Deregulation of HDAC1 by p25/Cdk5 in neurotoxicity

Kim D, Frank CL, Dobbin MM, Tsunemoto RK, Tu W, Peng PL, Guan J, Lee B, Moy LY, Giusti P, Broodie N, Mazitschek R, Delalle I, Haggarty SJ, Neve RL, Lu Y, Tsai L

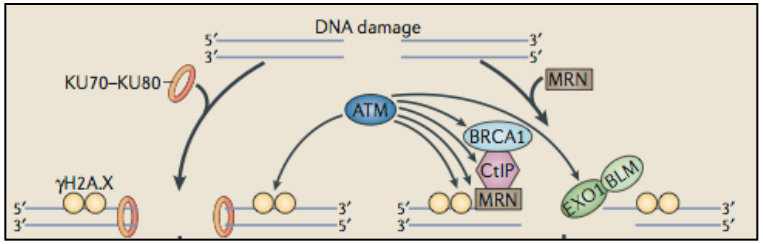
NEURON
2008 vol. 60 (5) pp. 803–17

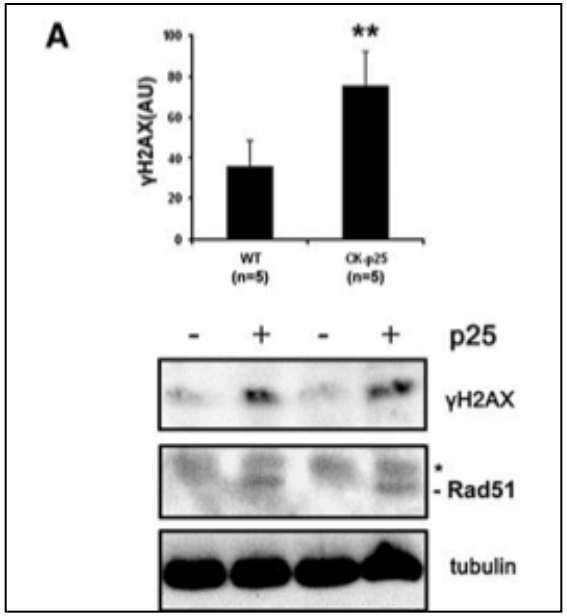


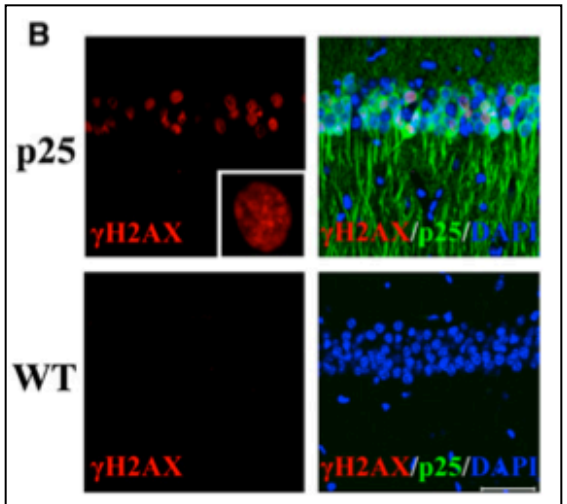
Charity begins at home: non-coding RNA functions in DNA repair

Dipanjan Chowdhury, Young Eun Choi and Marie Eve Brault

Nature Reviews Molecular Cell Biology
2013 vol. 14 (3) pp. 181–9







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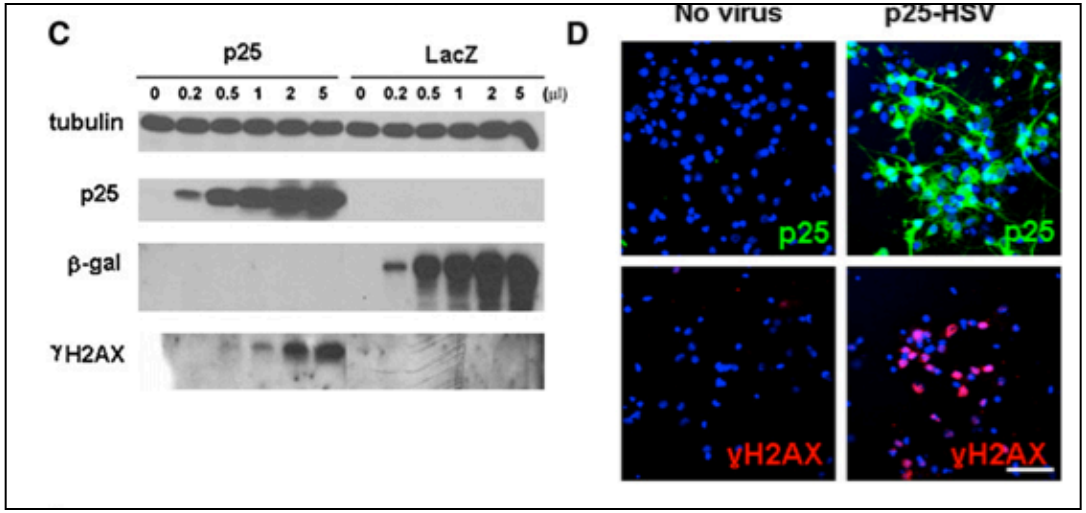

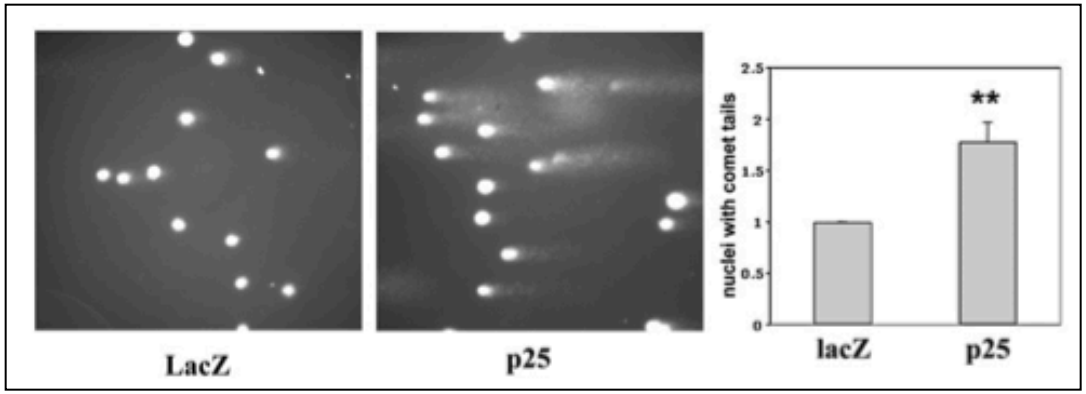

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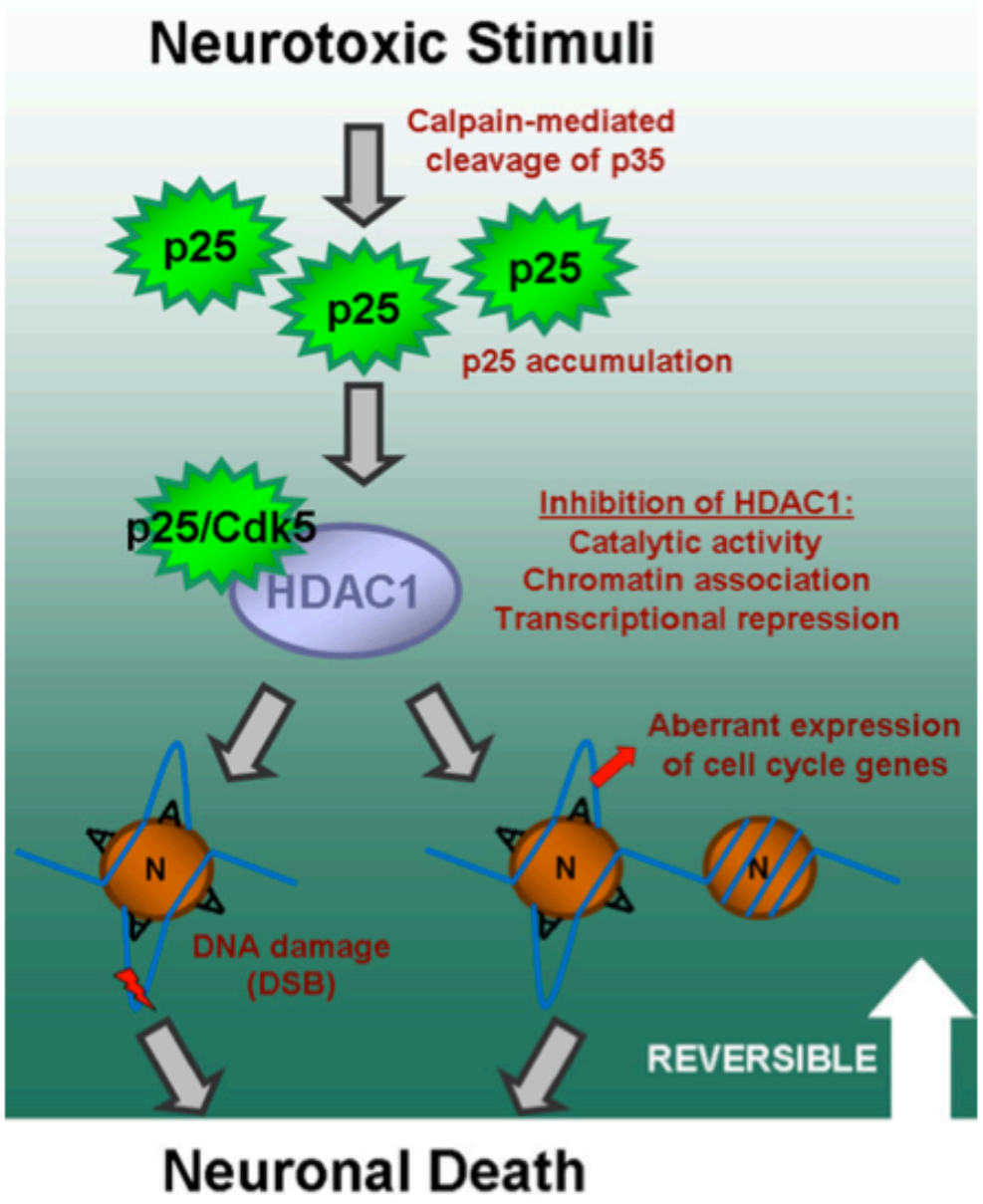

Figure 7. Schematic Model

Proposed model for p25-mediated cell death involving inhibition of HDAC1 activity, which leads to double-strand DNA breaks and aberrant cell-cycle activity. Neurotoxic stimuli such as ischemia result in p25 accumulation. This accumulation results in interaction with and inhibition of multiple aspects of HDAC1 activity, as shown in Figure 4, in a manner that is dependent on Cdk5, as shown in Figure 4E. Inhibition of HDAC1 results in DNA damage and aberrant expression of cell-cycle genes, which is likely associated with local histone deacetylation (Figure 4G; Figure 5; Figure S7) and which ultimately leads to neuronal death (Figure 3). The neurotoxic effects of p25 accumulation and downstream effects appear to be reversible before a certain period of induction (Figure 3C). Circles labeled "N" represents nucleosomes; "A" represents acetylation of histone tails. The nucleosomes with "A" represent acetylated nucleosomes and open chromatin loci, while the nucleosome at the far right represents a deacetylated nucleosome and closed chromatin locus.

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