COURS 2014-2015

6-10-2014

The Hallmarks of Aging

Cell *153*, June 6, 2013 ©2013 Elsevier Inc.

Carlos López-Otín,[1] Maria A. Blasco,[2] Linda Partridge,[3,4] Manuel Serrano,[5,*] and Guido Kroemer[6,7,8,9,10]

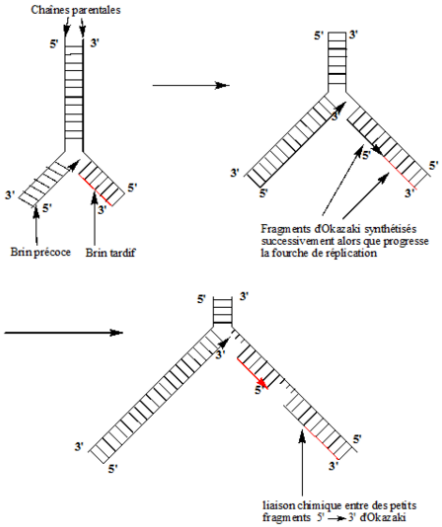
Figure 1. The Hallmarks of Aging
The scheme enumerates the nine hallmarks described in this Review: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular communication.

Breaking news: thinking may be bad for DNA

Karl Herrup, Jianmin Chen & Jiali Li

VOLUME 16 | NUMBER 5 | MAY 2013 NATURE NEUROSCIENCE

A study in this issue suggests that neuronal DNA double-strand breaks can result from natural behaviors. The breaks occur in the circuits that are activated and are enhanced in a model of Alzheimer's disease. The implications of this finding are far-reaching.



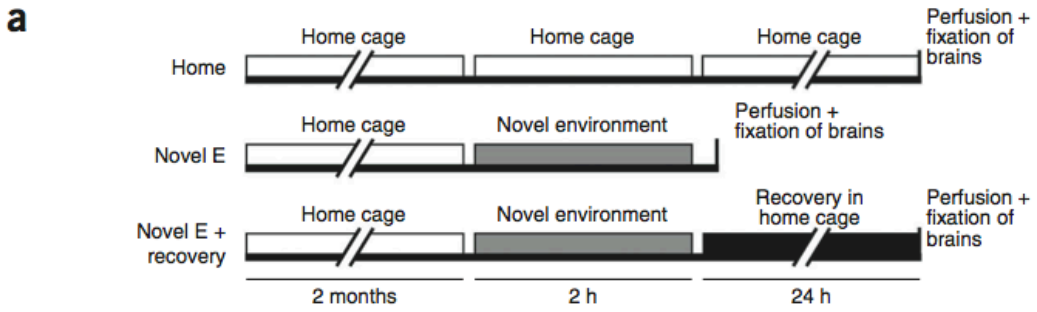
Marina Corral Spence

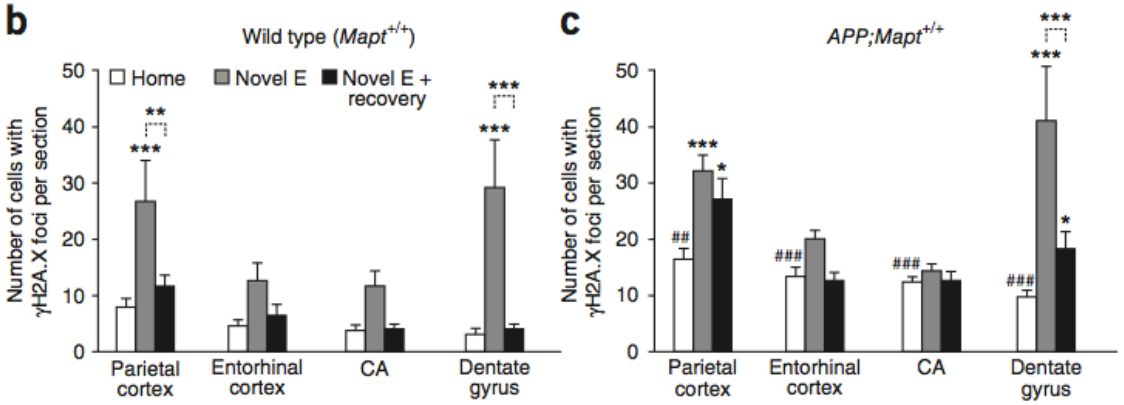
Figure 1 Giving your (neuronal) genome a break. The findings by Suberbielle *et al.*[1] suggest that while our neurons are at rest (left) their genomes are largely intact. However, during enhanced mental activity—either exploration (right) or other tasks—the number of DNA DSBs increases by twofold or more.

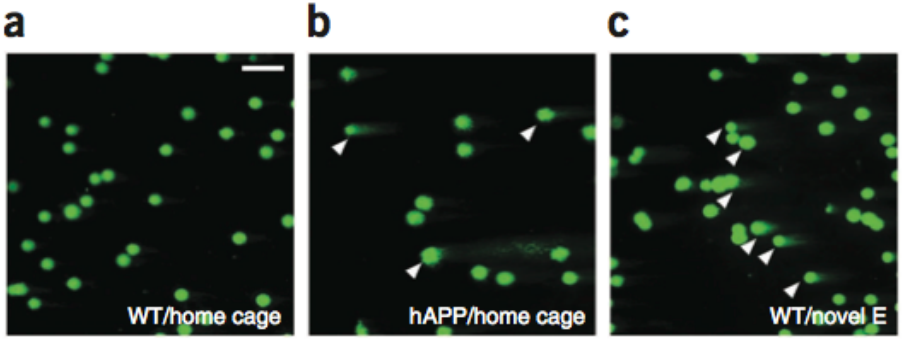
Physiologic brain activity causes DNA double-strand breaks in neurons, with exacerbation by amyloid-β

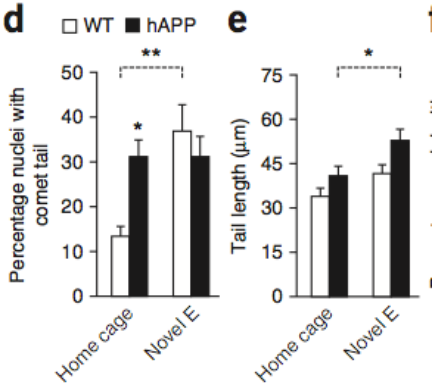
NATURE NEUROSCIENCE VOLUME 16 | NUMBER 5 | MAY 2013

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]





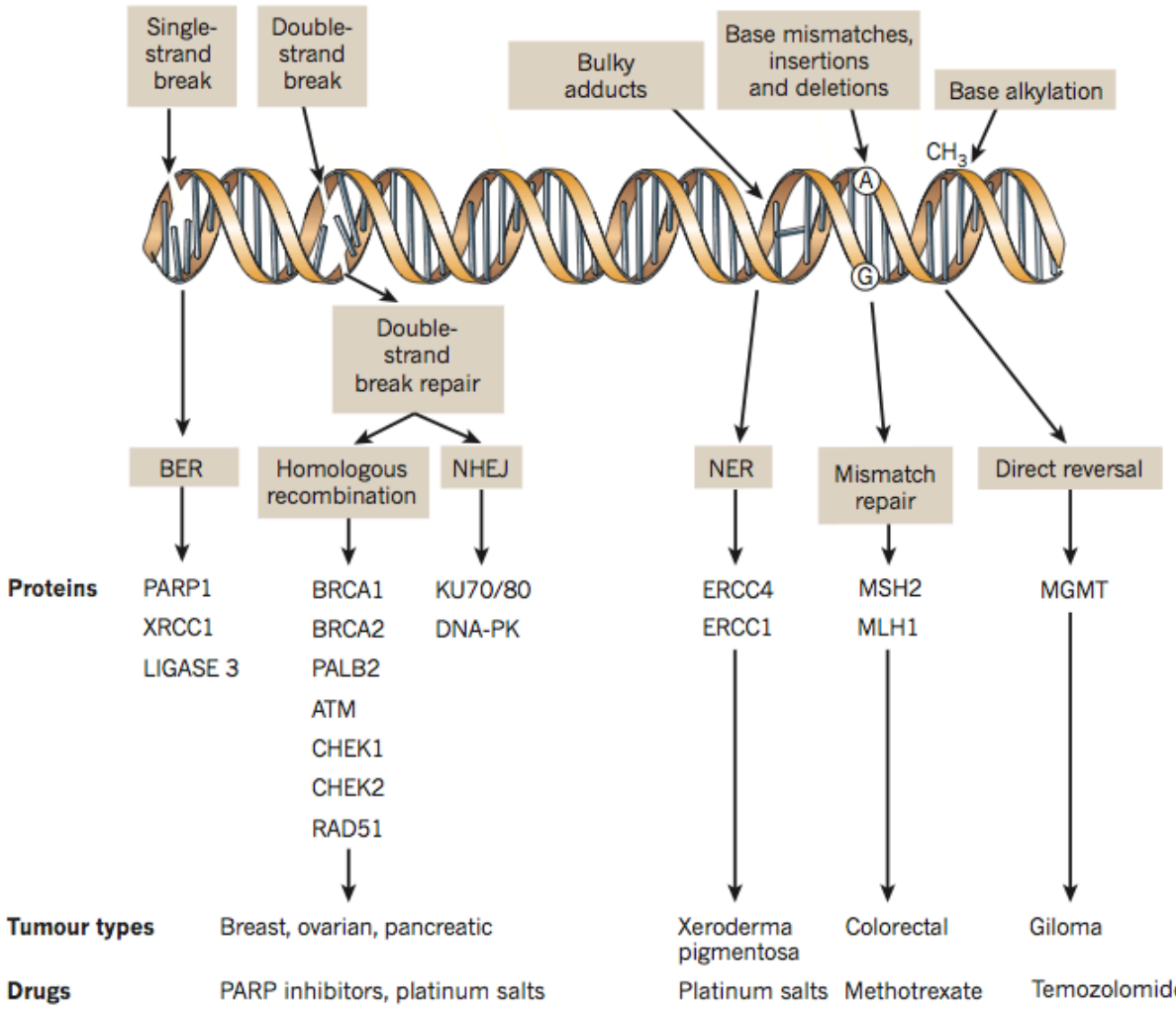




The DNA damage response and cancer therapy

19 JANUARY 2012 | VOL 481 | NATURE | 287

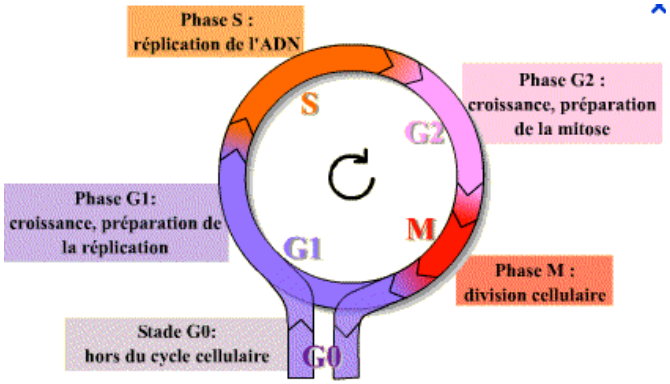
Christopher J. Lord[1]* & Alan Ashworth[1]*

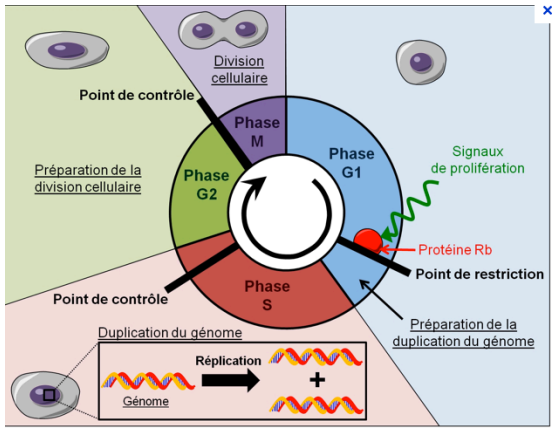


DNA strand break repair and neurodegeneration

Stuart L. Rulten*, Keith W. Caldecott**

DNA Repair 12 (2013) 558–567





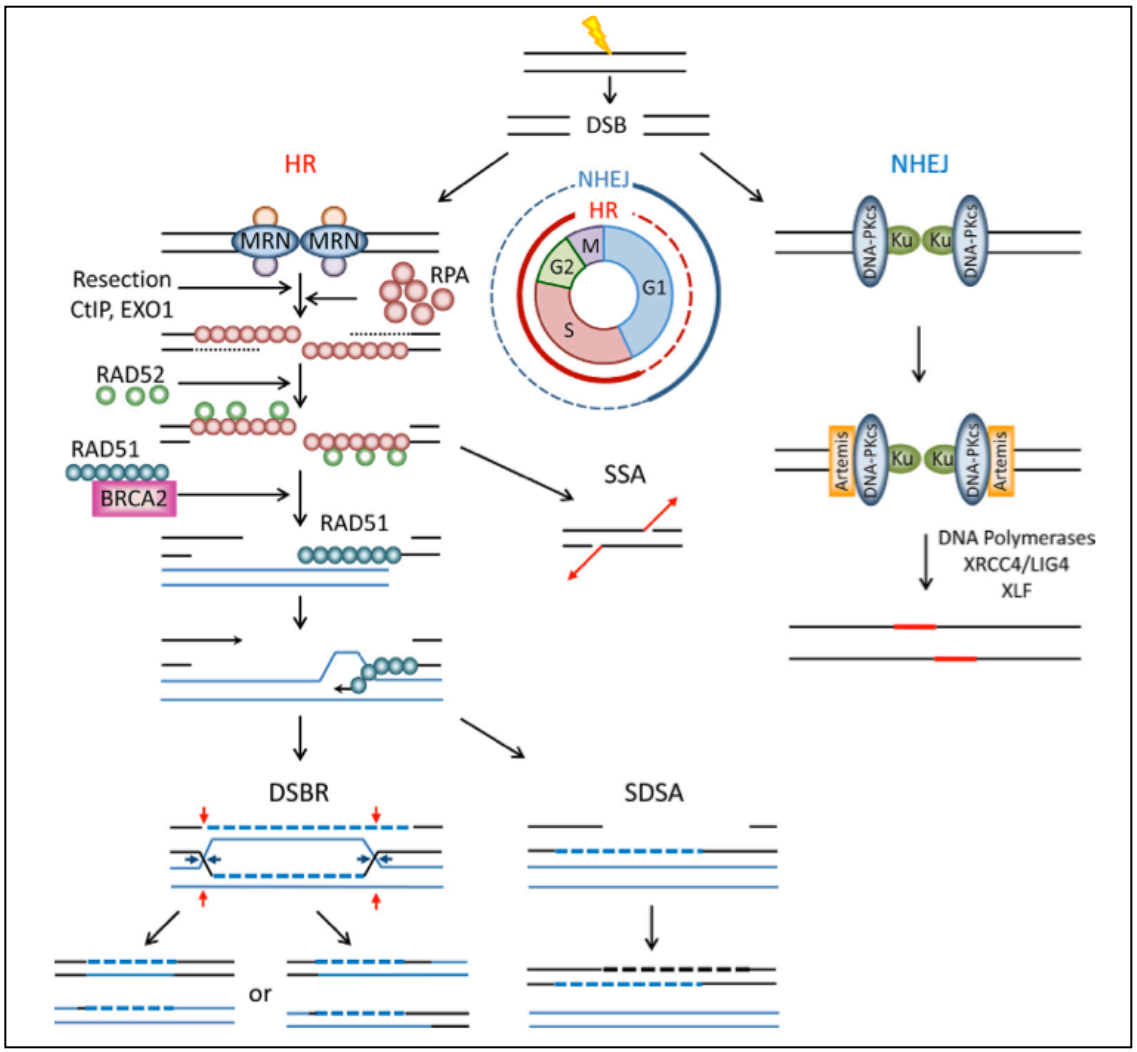
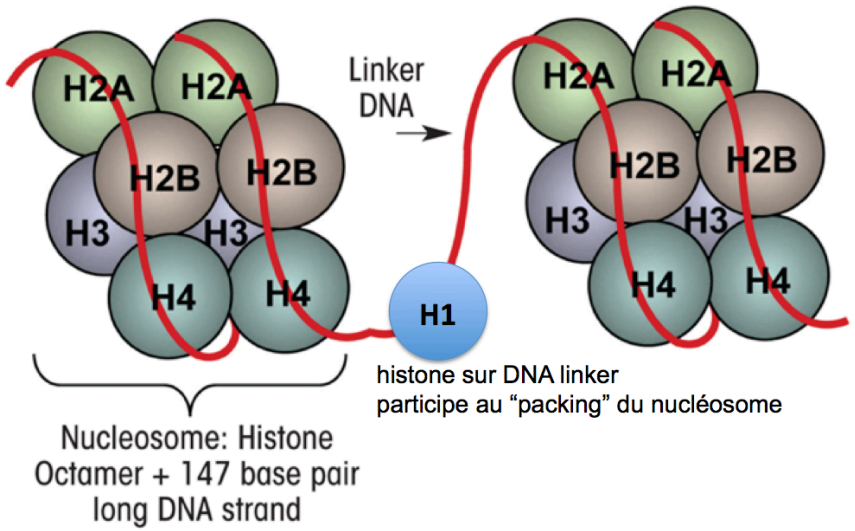


Fig. 4. Recombination pathways. DSBR is divided into two major pathways: HR and NHEJ. HR operates in dividing cells and in S phase, whereas NHEJ can function in both dividing and non-dividing cells and independently of cell cycle. HR has been proposed to be initiated by recognition of the DSB by the MRN complex (MRE11-RAD50-NBS1). The MRN complex associates with CtIP, which initiates 5′-3′ end resection to create the 3′ ssDNA overhang. Further resection is carried out by exonucleases (possibly EXO1), and the resulting ssDNA is stabilized by binding of RPA. RAD52 is recruited to RPA. The RAD51-BRCA2 complex then replaces the RAD52-RPA complex to form RAD51 nucleoprotein filaments, whereas, in SSA, RPA and RAD52 carry out the recombination process in a RAD51-independent manner. RAD51-coated ssDNA enables strand invasion of the intact homologous DNA region. In classic DSBR, the second DSB end can be captured by the D-loop to form an intermediate with double Holliday junctions, which can result in a non-crossover (cleavage at blue arrows) or a crossover (cleavage at blue arrows on one side and red arrows on other side) products. In SDSA, the newly synthesized strand is displaced to permit annealing to the other DSB end, resulting in a non-crossover product. NHEJ is initiated by recognition of the DSB ends by the Ku (Ku70/Ku80) complex, followed by recruitment of DNA-PKcs. DNA-PKcs activates Artemis, which generates terminal overhangs prior to ligation. To complete the process, DNA synthesis is performed to fill-in the gaps and end joining is carried out by XRCC4–LIG4 in collaboration with XLF. CtIP, C-terminal binding protein-interacting protein; DNA-PKcs, DNA-dependent protein kinase catalytic subunit; DSBR, DNA double strand break repair; HR, homologous recombination; NHEJ, nonhomologous end joining; SDSA, synthesis-dependent strand annealing; SSA, single-strand annealing; XRCC4, X-ray repair cross-complementing protein 4.

Epigenetics—Beyond the Genome in Alcoholism

Bela G. Starkman; Amul J. Sakharkar, Ph.D.; and Subhash C. Pandey, Ph.D.

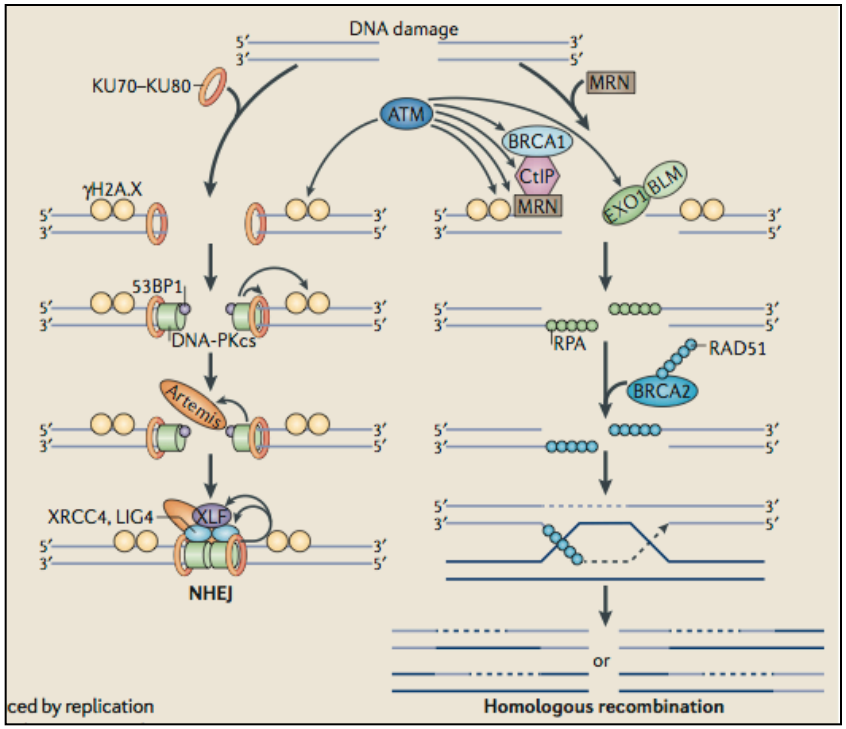
Alcohol Research: *Current Reviews*, Volume 34, Issue Number 3



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

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

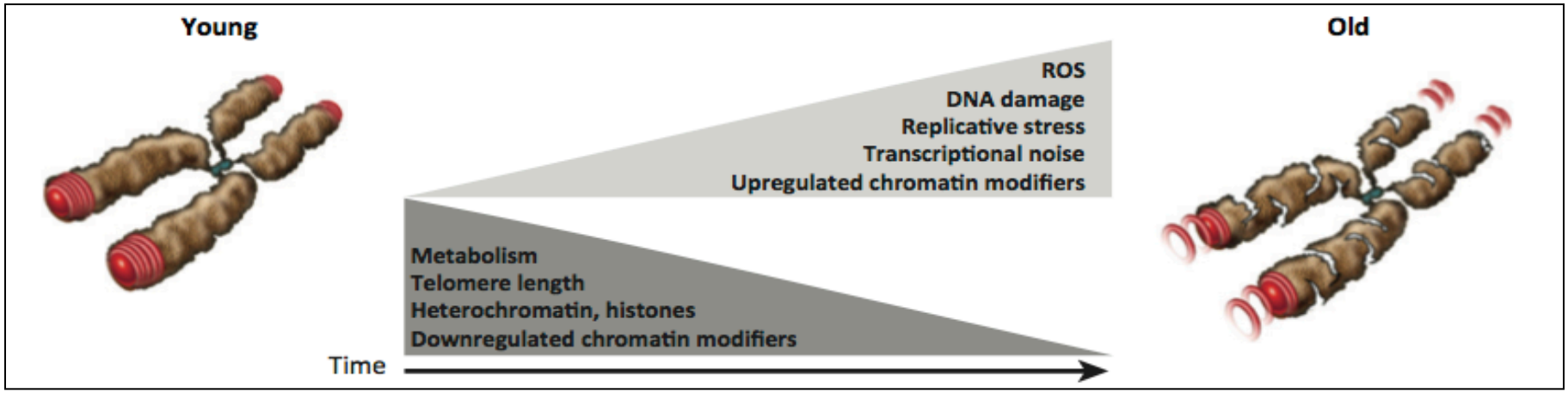
Dipanjan Chowdhury, Young Eun Choi and Marie Eve Brault



The great unravelling: chromatin as a modulator of the aging process

Roderick J. O'Sullivan and Jan Karlseder

Trends in Biochemical Sciences November 2012, Vol. 37, No. 11

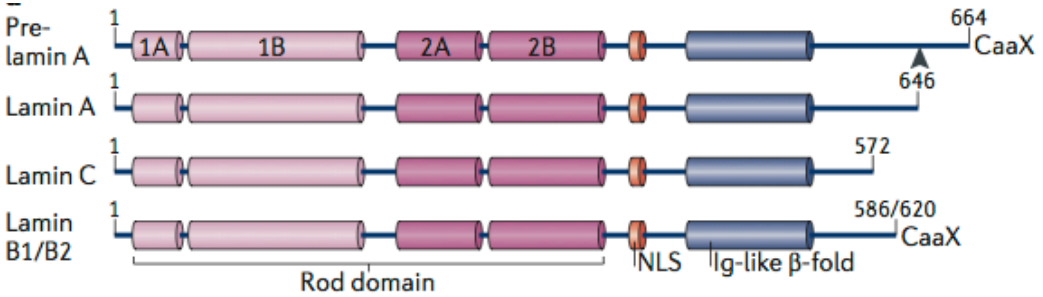


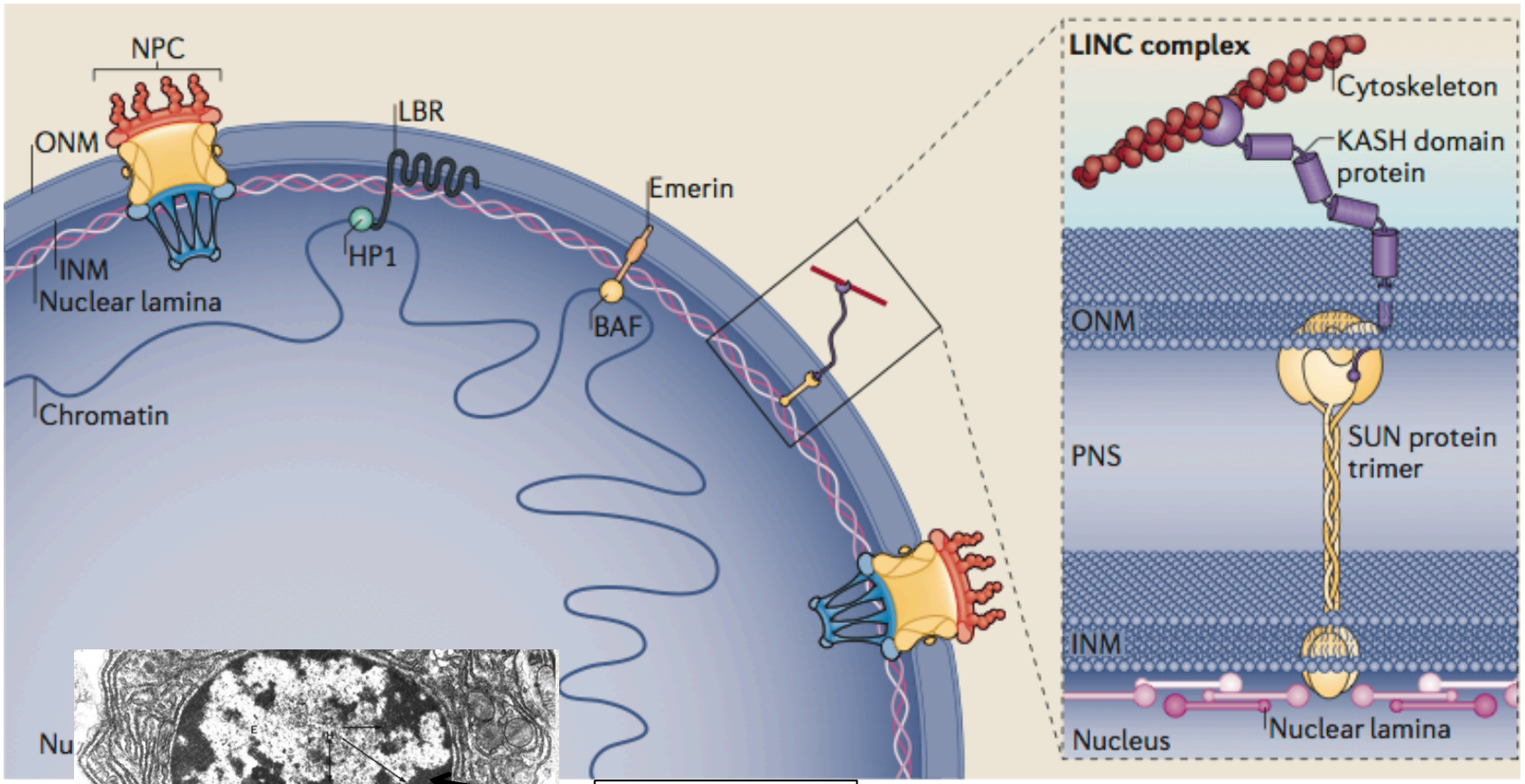
The nuclear lamins: flexibility in function

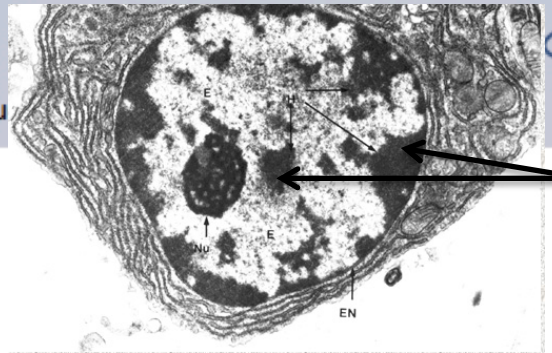
Burke B, Stewart CL

Institute of Medical Biology, 8A Biomedical Grove, Immunos 06-06, Singapore 138648. Brian.Burke@ imb.a-star.edu.sg

Nat Rev Mol Cell Biol
2013 vol. 14 (1) pp. 13-24







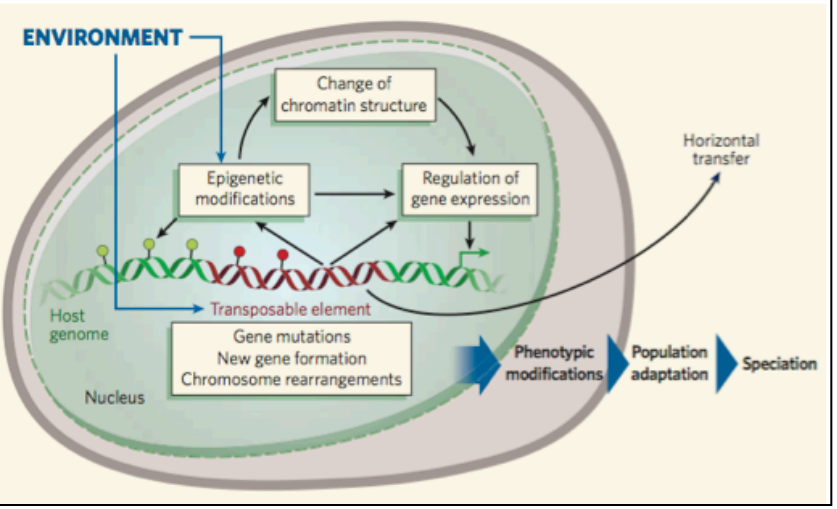
hétérochromatine

GENETICS

Junk DNA as an evolutionary force

Christian Biémont and Cristina Vieira

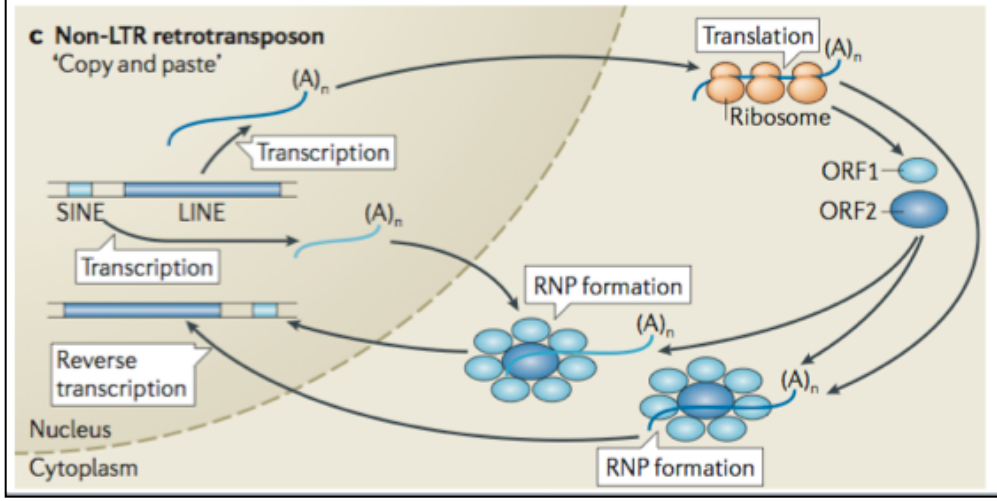
Vol 443|5 October 2006 nature



PIWI-interacting small RNAs: the vanguard of genome defence

Nat Rev Mol Cell Biol
2011 vol. 12 (4) pp. 246–58

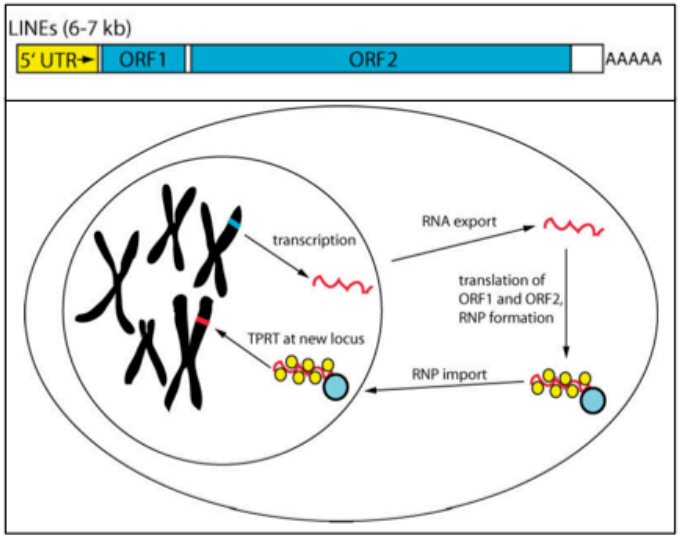
Siomi MC, Sato K, Pezic D, Aravin AA



LINE-1 retrotransposons: modulators of quantity and quality of mammalian gene expression?

Jeffrey S. Han and Jef D. Boeke*

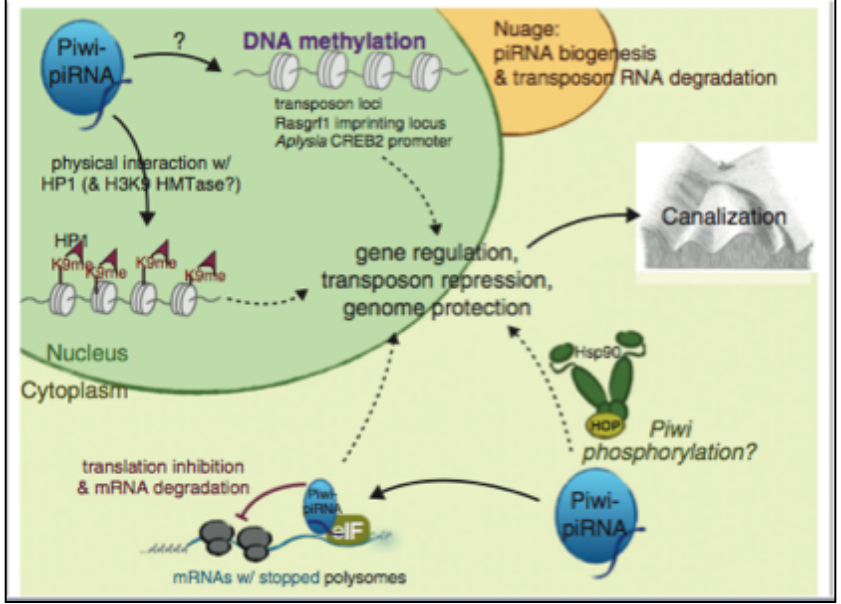
BioEssays 27:775–784, © 2005



Beyond transposons: the epigenetic and somatic functions of the Piwi-piRNA mechanism

Current Opinion in Cell Biology
2013 vol. 25 (2) pp. 190–4

Peng JC, Lin H



Mammalian non-LTR retrotransposons: for better or worse, in sickness and in health

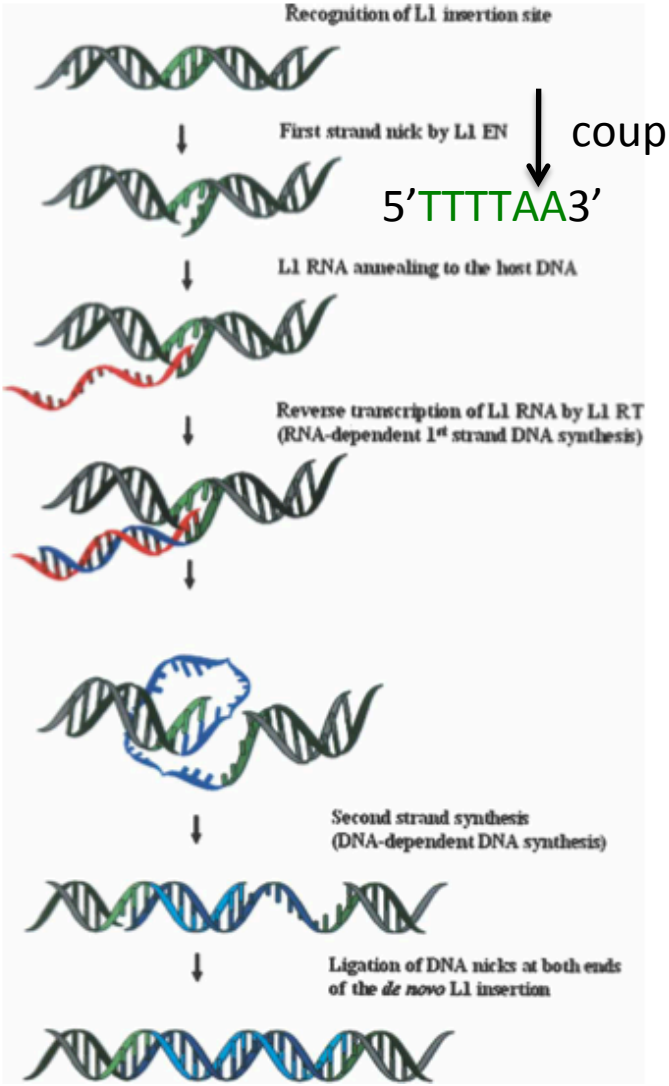
Belancio VP, Hedges D, Deininger P

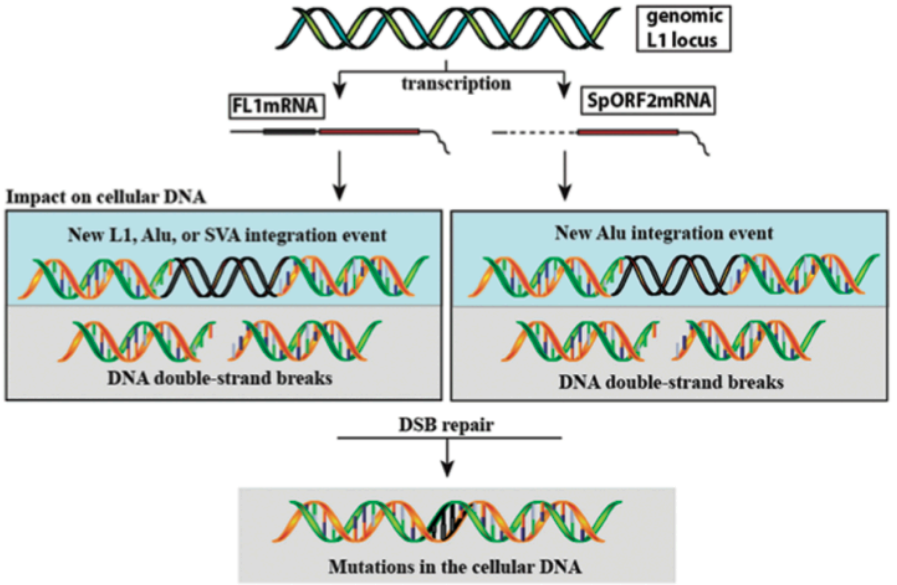
Genome Research
2008 vol. 18 (3) pp. 343-58

Somatic expression of LINE-1 elements in human tissues

Belancio VP, Roy-Engel AM, Pochampally RR, Deininger P

Nucleic Acids Research
2010 vol. 38 (12) pp. 3909-22





igure 8. A summary of the biologically relevant L1-related mRNA products and their respective impact on the host genome. Transcription of the inctional L1 locus results in the production of either the full-length mRNA (FL1mRNA), the splice ORF2 mRNA (SpORF2mRNA) or both. 'L1mRNA protein products can mobilize L1, Alu, and SVA elements, while SpORF2mRNA only produces ORF2 protein and as a result can only ssist Alu retrotransposition. Expression of either L1 mRNA can generate ORF2, which leads to introduction of DNA DSBs potentially resulting in ccumulation of mutations in the cellular genome.

Figure 3. Steps of the LINE-1 integration process. The L1 endonuclease domain encoded by the ORF2 protein loosely recognizes a consensus 5′-TTTTAA-3′ sequence (shown in green) in the genomic DNA and introduces a first-strand nick between the T and A nucleotides of the minus strand. The resulting free 3′ end of the host DNA is proposed to base-pair with the poly(A) tail of the L1 mRNA (shown in red) and serves as a primer for the first-strand cDNA synthesis (shown in blue) by the L1 reverse transcriptase that uses L1 mRNA as the template. This process is known as a target-primed reverse transcription (TPRT). Mechanistic details of the rest of the L1 integration process are not well defined yet. At some point during L1 integration, either L1 ORF2 or a cellular activity introduces a nick into the plus strand and the structure is resolved to utilize the 3′ end as a primer for the second-strand DNA synthesis (shown in light blue) by an unknown polymerase activity. Finally, the two nicks in the cellular DNA are repaired to complete the L1 integration event.

Activation of transposable elements during aging and neuronal decline in Drosophila

Li W, Prazak L, Chatterjee N, Grüninger S, Krug L, Theodorou D, Dubnau J

Nat Neurosci
2013 vol. 16 (5) pp. 529-31

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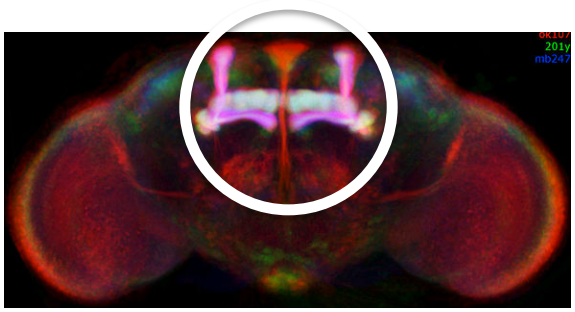
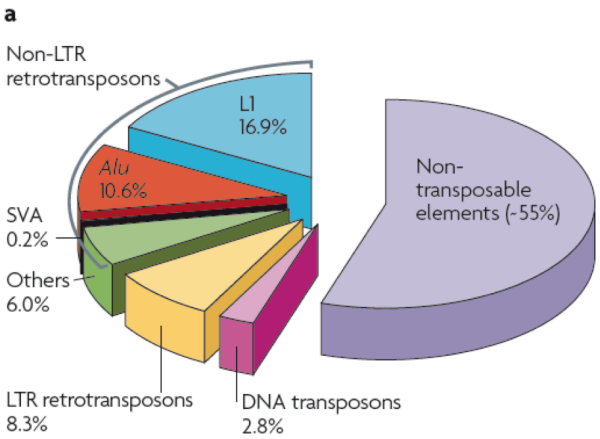
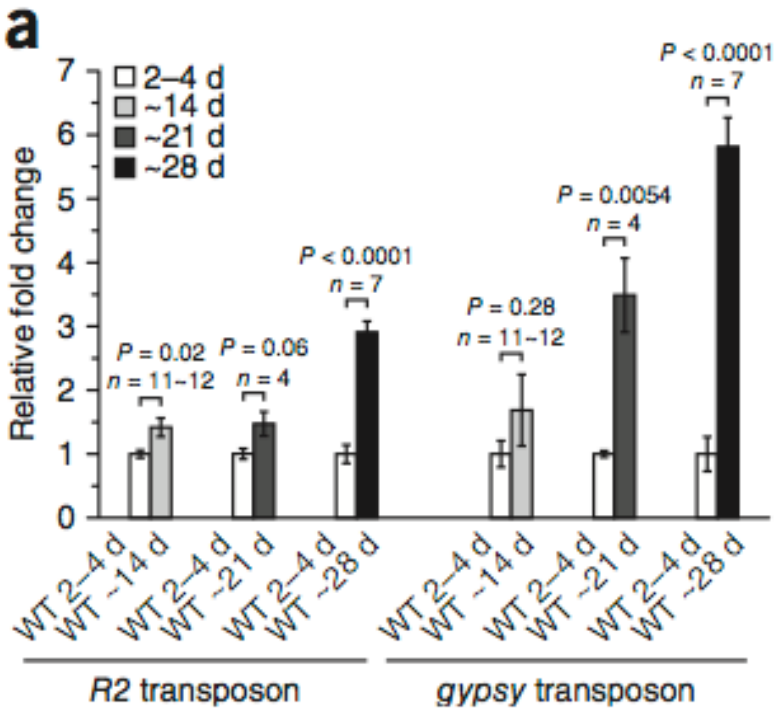
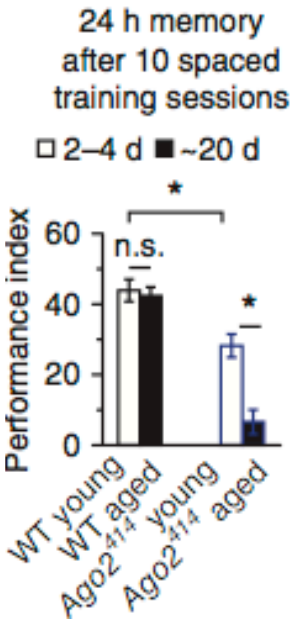
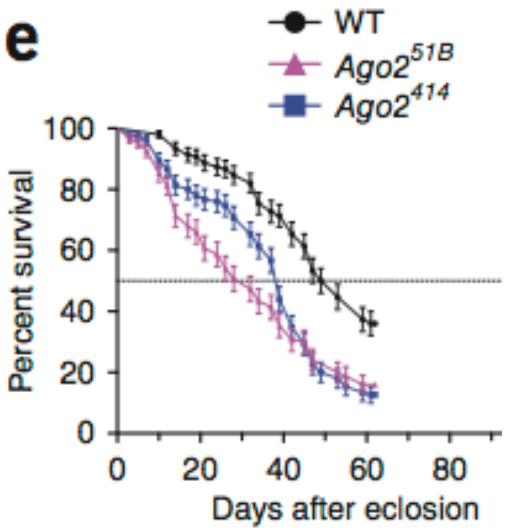


Cordaux @ Batzer, Nature Reviews genetics, 10: 691-703, 2009









The nuclear lamins: flexibility in function

Burke B, Stewart CL

Institute of Medical Biology, 8A Biomedical Grove, Immunos 06-06, Singapore 138648. Brian.Burke@ imb.a-star.edu.sg

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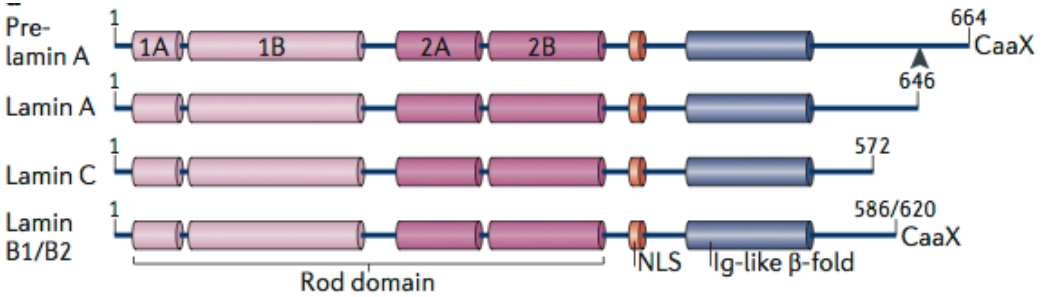
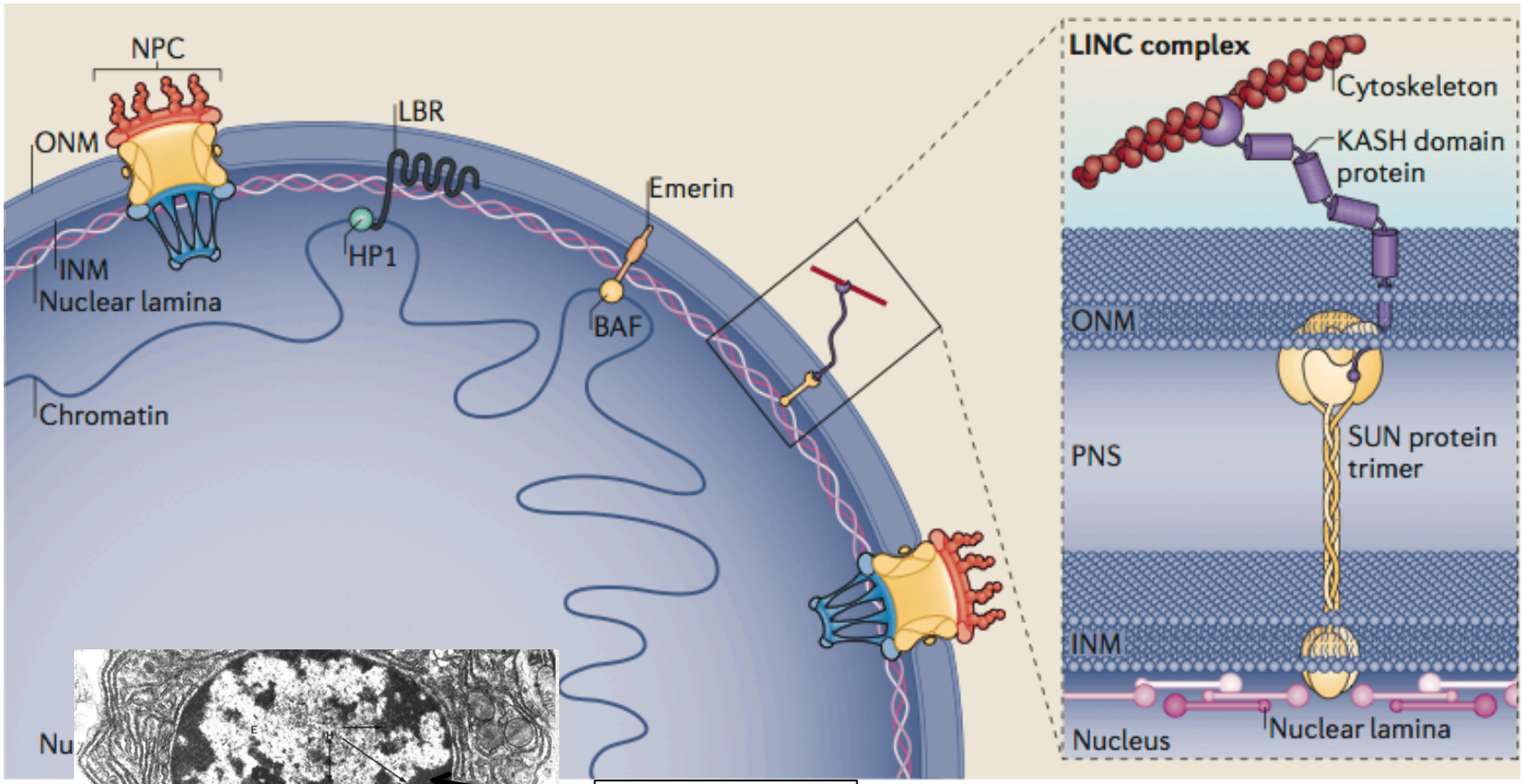
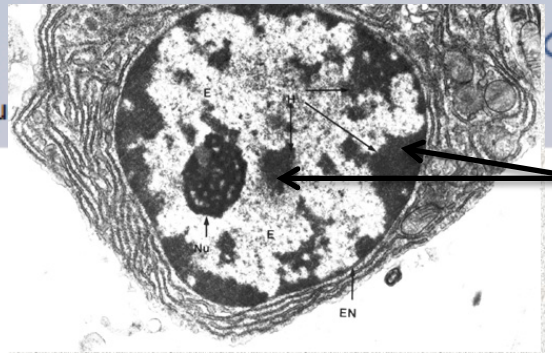




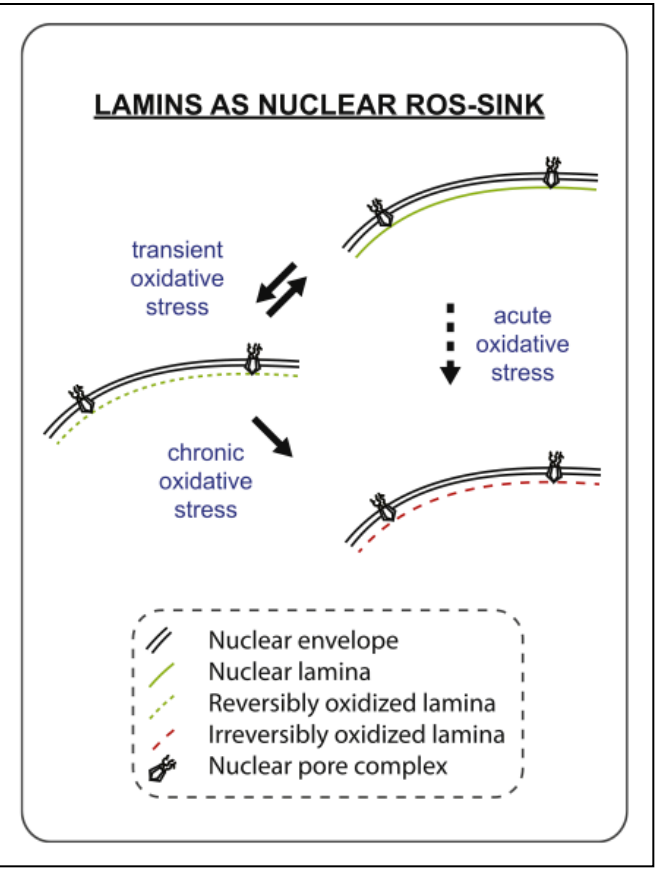


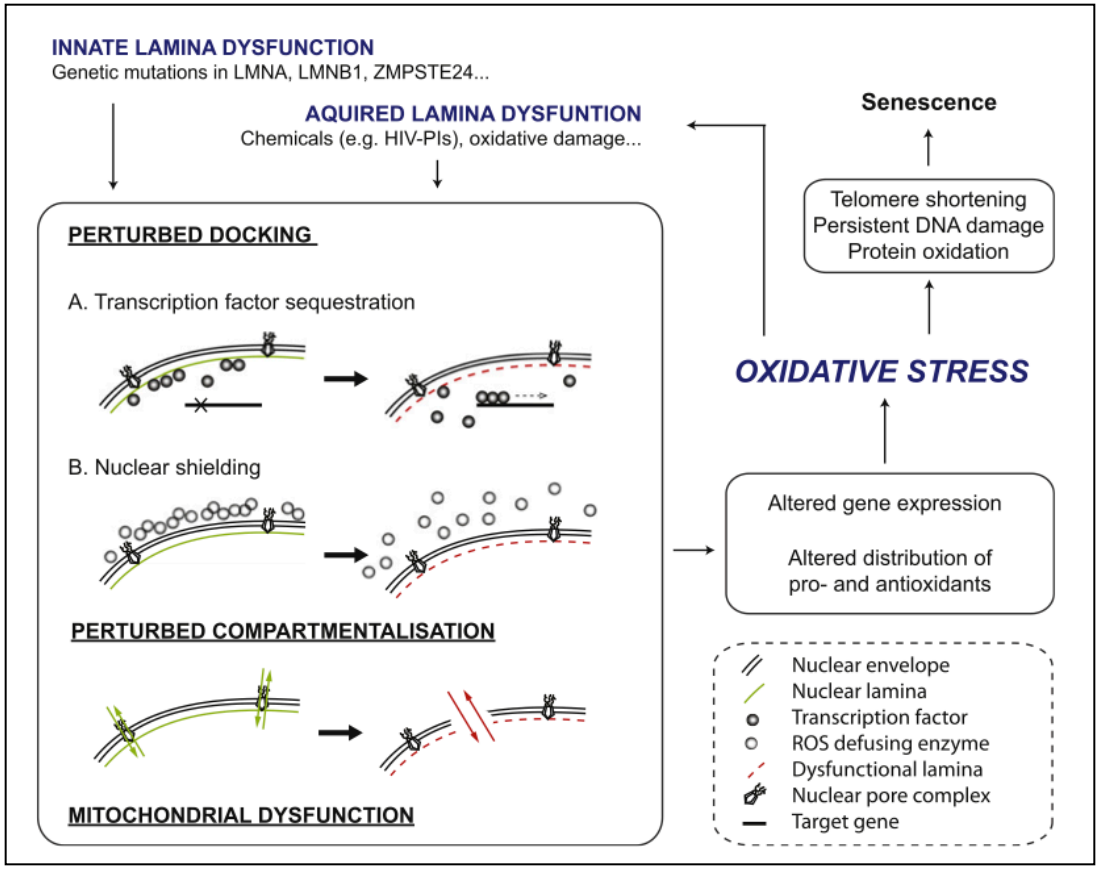
hétérochromatine

Lamins as mediators of oxidative stress

Tom Sieprath [a,1], Rabih Darwiche [a,1], Winnok H. De Vos [a,b,*]

Biochemical and Biophysical Research Communications 421 (2012) 635–639

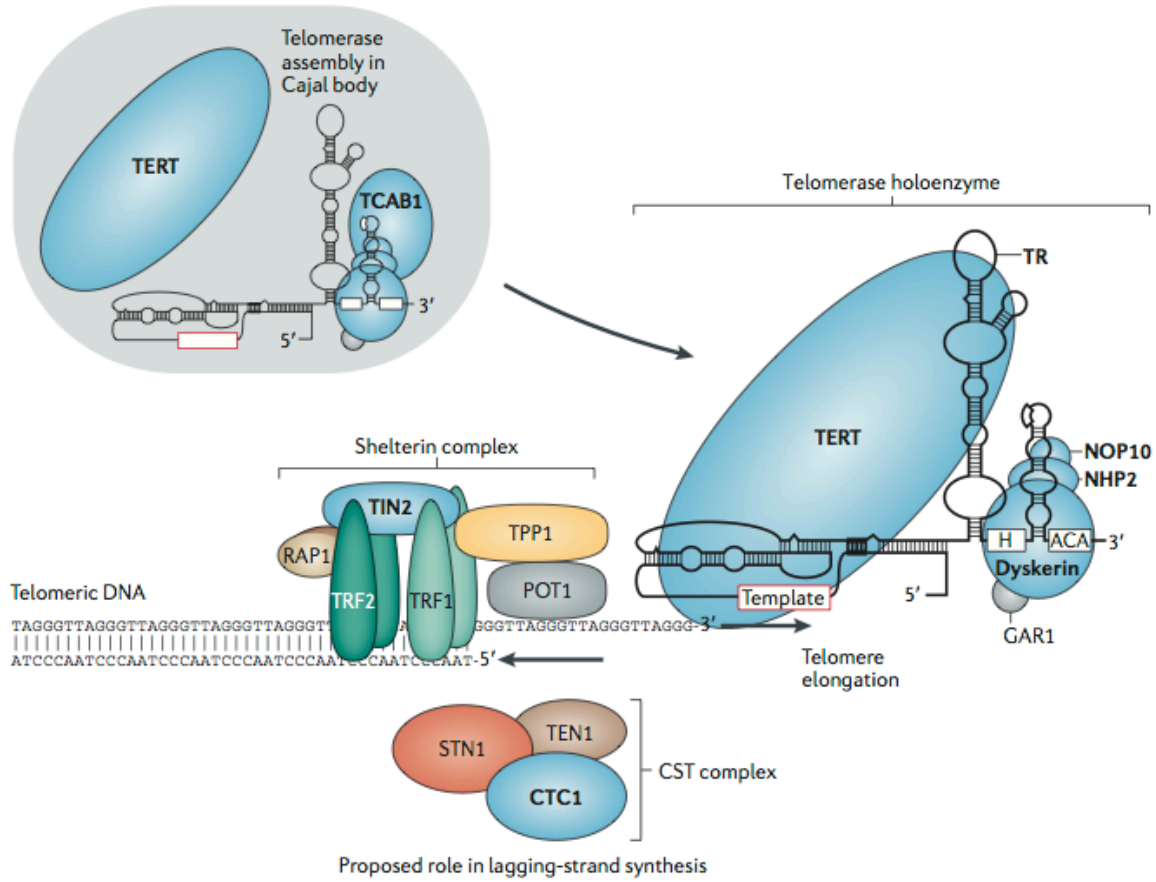




The telomere syndromes

Nature Reviews Genetics
2012 vol. 13 (10) pp. 693-704

Armanios M, Blackburn EH



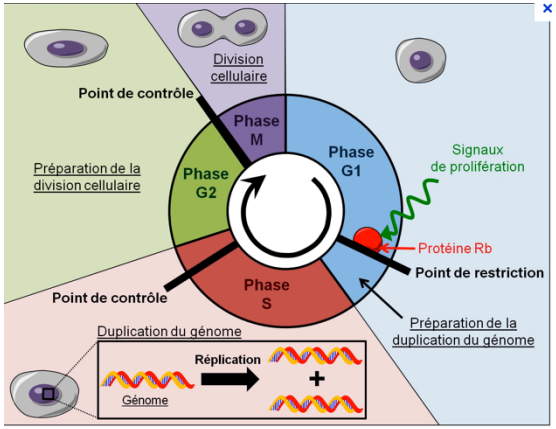
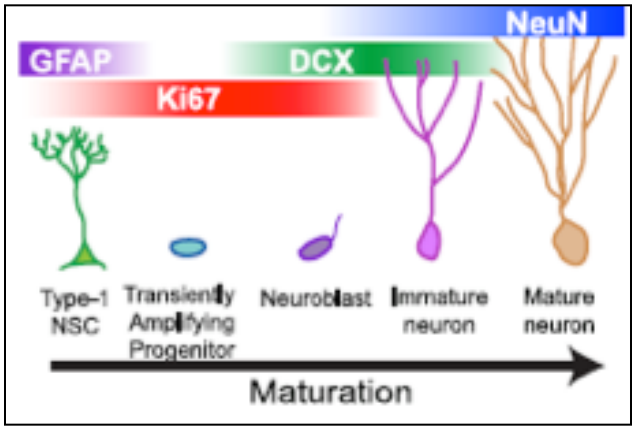


Figure 1 | **Telomerase and telomere components involved in human monogenic telomere syndromes.** Components for which mutations have been identified in telomere syndromes are indicated in bold type and shaded in blue. Shelterin complex components are made up of six component proteins — telomere repeat-binding factor 1 (TRF1), TRF2, repressor/activator protein 1 (RAP1), TRF1-interacting nuclear protein 2 (TIN2), TIN2-interacting protein 1 (TPP1) and protection of telomeres 1 (POT1) — which are essential for telomere protection and for regulating telomere elongation. The telomerase enzyme complex is comprised of TERT (the reverse transcriptase) and TR (the essential RNA component that contains a template for telomere repeat addition). TR contains a 3′ H/ACA box motif that binds the dyskerin protein, which is part of a larger dyskerin complex that also consists of NHP2, NOP10 and GAR1. Note that for simplicity, one dyskerin complex is shown per TR molecule, although two copies are now thought to bind each TR. Telomerase Cajal body protein 1 (TCAB1) binds a Cajal body localization motif in TR and has a role in TR trafficking and biogenesis. In the Cajal body, TR and TERT assemble into a functional holoenzyme complex. The CST complex has three components — conserved telomere protection component 1 (CTC1), suppressor of cdc thirteen 1 (STN1) and telomeric pathway with STN1 (TEN1) — which are thought to function in part in telomere lagging-strand synthesis. Figure adapted, with permission, from REF. 13 © (2009) Annual Reviews.

Notch1 Is Required for Maintenance of the Reservoir of Adult Hippocampal Stem Cells

Jessica L. Ables,[1] Nathan A. DeCarolis,[1] Madeleine A. Johnson,[1] Phillip D. Rivera,[1] Zhengliang Gao,[2] Don C. Cooper,[3] Freddy Radtke,[4] Jenny Hsieh,[2] and Amelia J. Eisch[1]

10484 • The Journal of Neuroscience, August 4, 2010 • 30(31):10484–10492



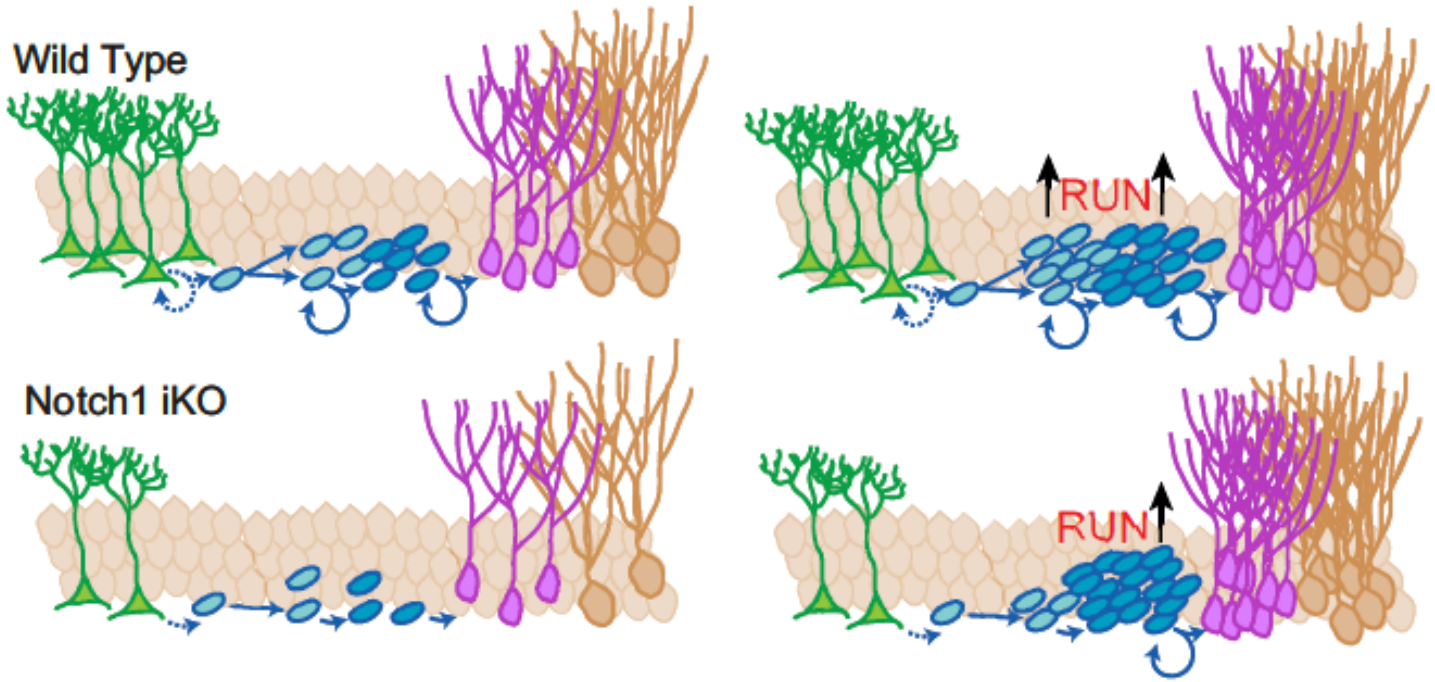
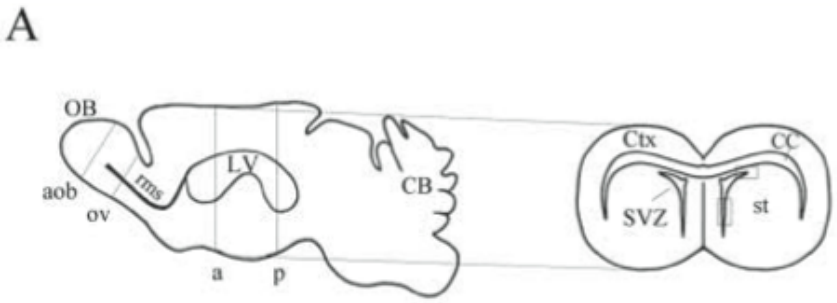


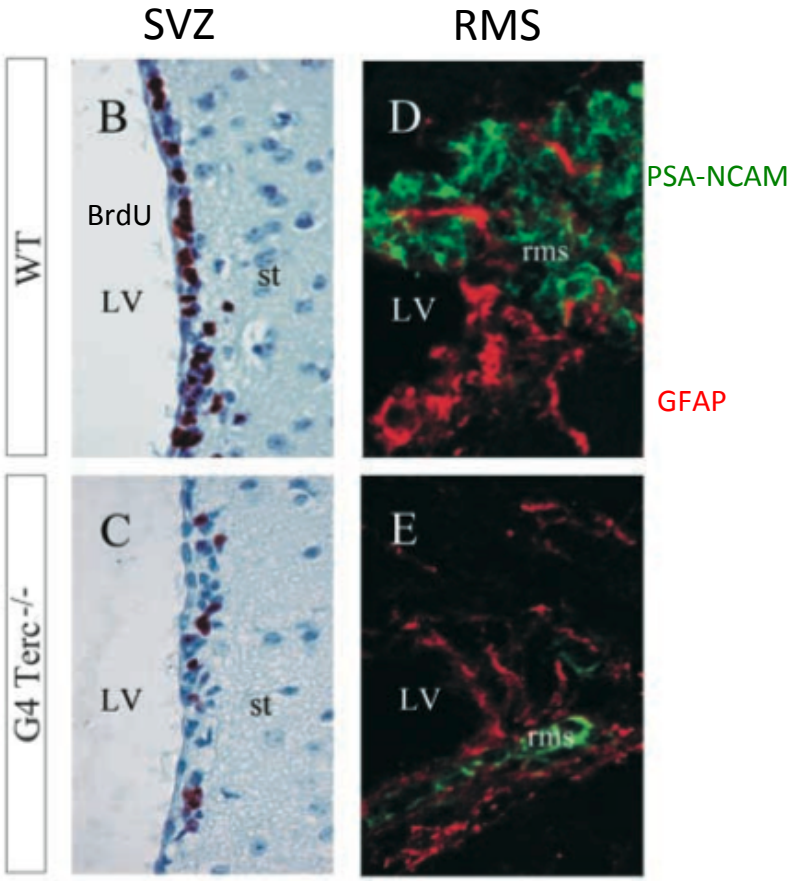
Figure 7. Proposed model of Notch1 in regulating adult neurogenesis under basal conditions and after physical activity. Without Notch1, self-renewal and expansion of nestin-expressing cells is disrupted and the net number of adult-generated dentate gyrus neurons is decreased. Physical activity increases adult-generated neurons in WT and Notch1 iKO mice by increasing neuroblast proliferation. However, physical activity does not rescue Type-1 NSC or TAP number in Notch1 iKO mice.

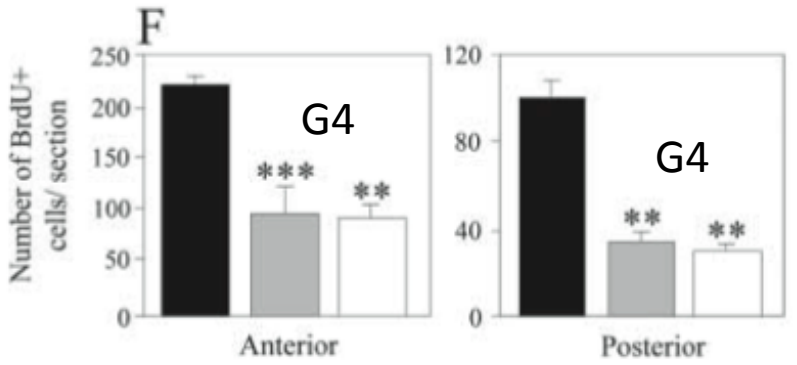
Telomere shortening and chromosomal instability abrogates proliferation of adult but not embryonic neural stem cells

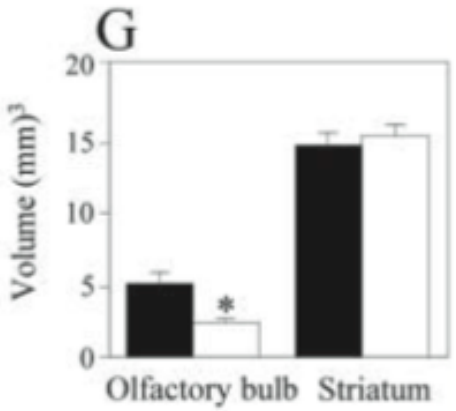
Ferrón S, Mira H, Franco S, Cano-Jaimez M, Bellmunt E, Ramírez C, Fariñas I, Blasco MA

Development
2004 vol. 131 (16) pp. 4059-70







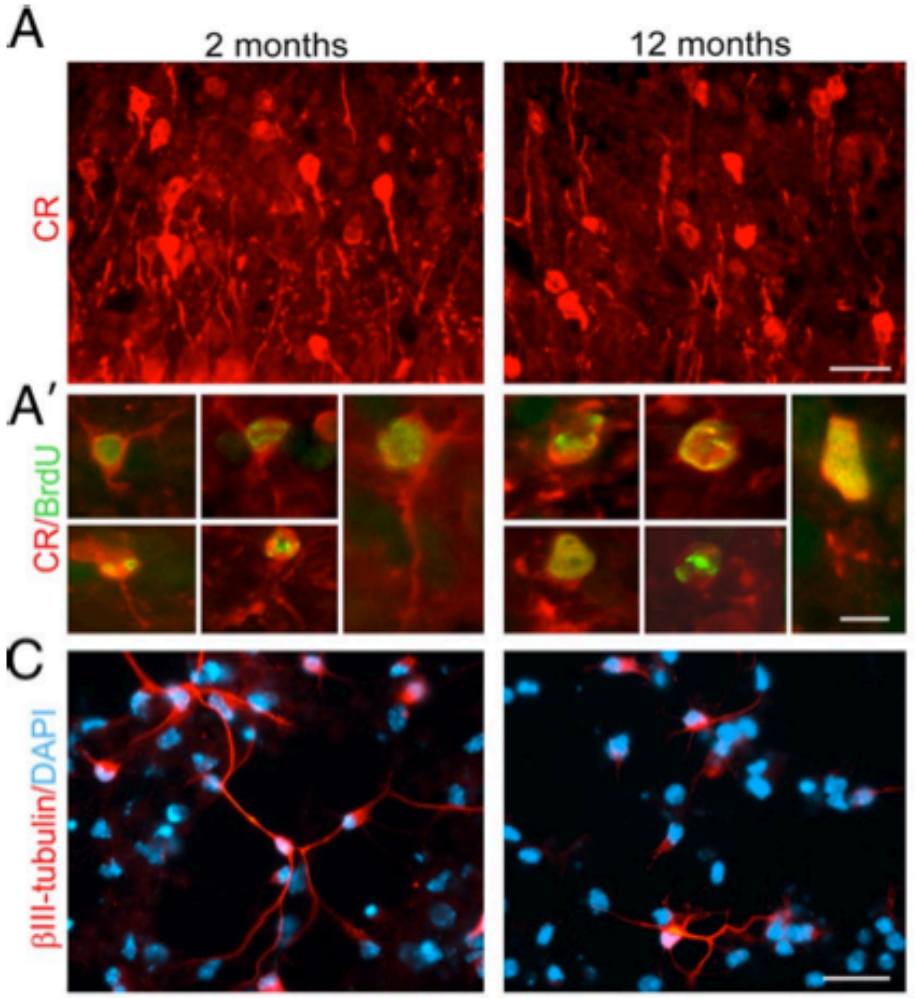


Telomere shortening in neural stem cells disrupts neuronal differentiation and neuritogenesis

J Neurosci
2009 vol. 29 (46) pp. 14394-407

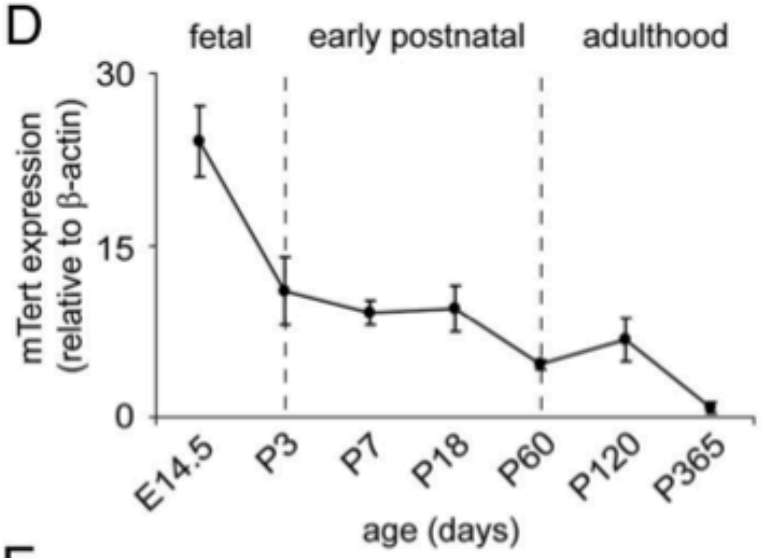
Ferrón SR, Marqués-Torrejón MA, Mira H, Flores I, Taylor K, Blasco MA, Fariñas I

LRC: labelled-retaining cells



B

	OB (granular layer)	
age (months)	2	12
LRC	43.9 ± 6.6	14.4 ± 1.8*
%LRC/CR	5.1 ± 0.6	1.6 ± 0.2**



E

	neurospheres	
age (months)	2	12
mTert expression (a.u)	2.2 ± 0.4	1.3 ± 0.3**
telomere length (a.u)	67.9 ± 3.2	52.5 ± 3.4*

The role of mitochondria in aging

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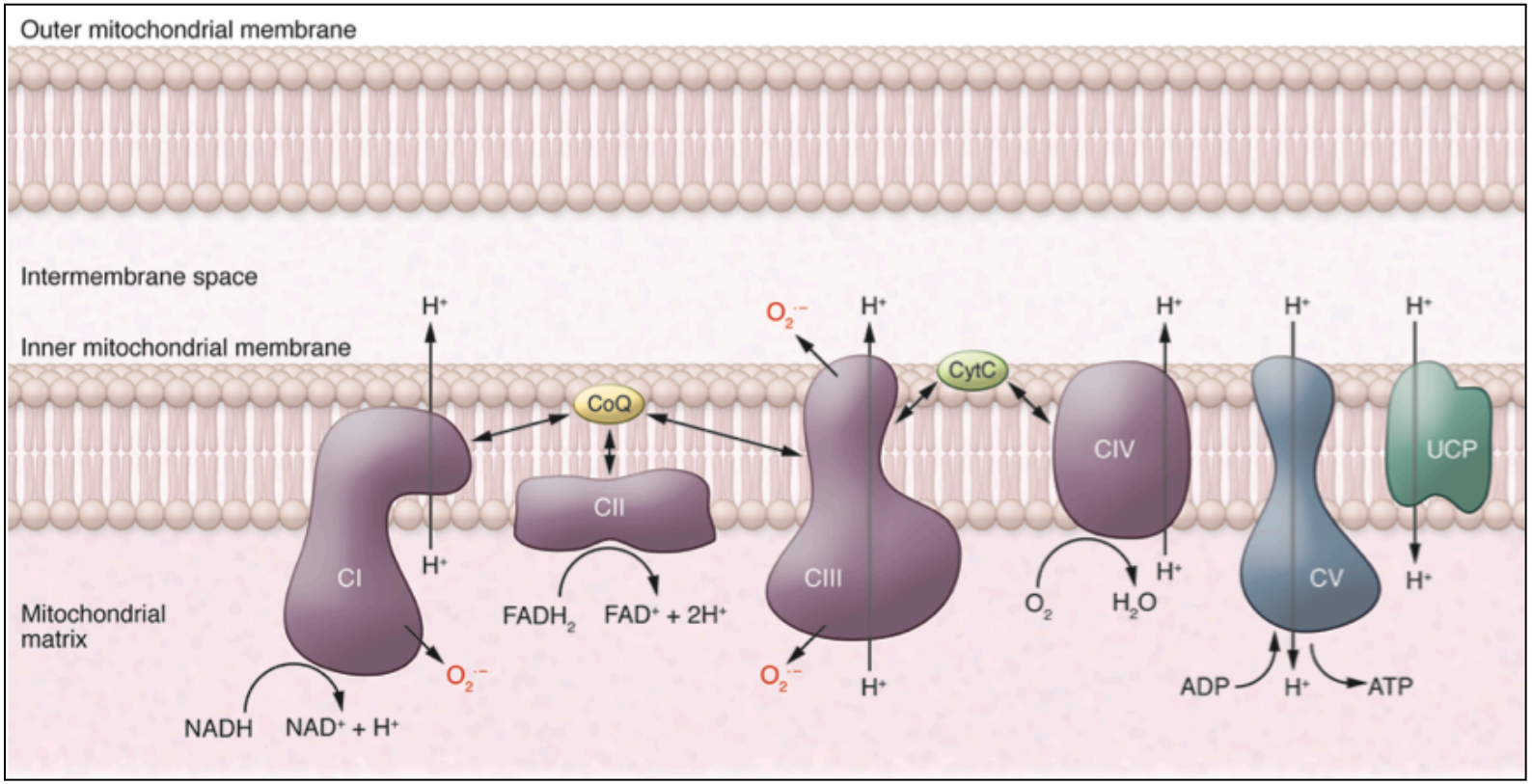

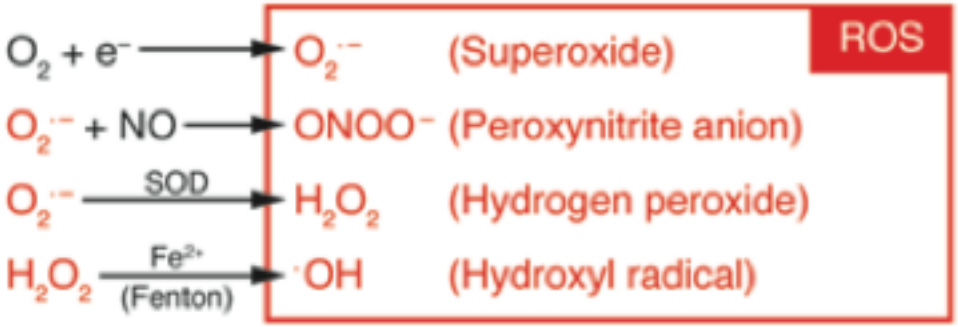

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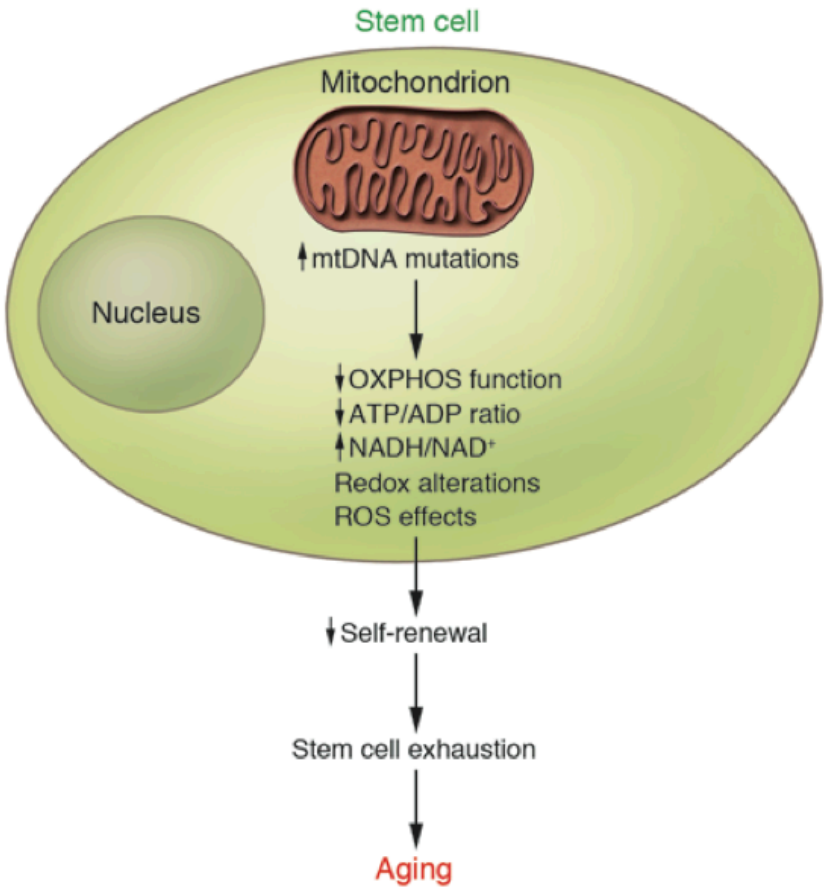
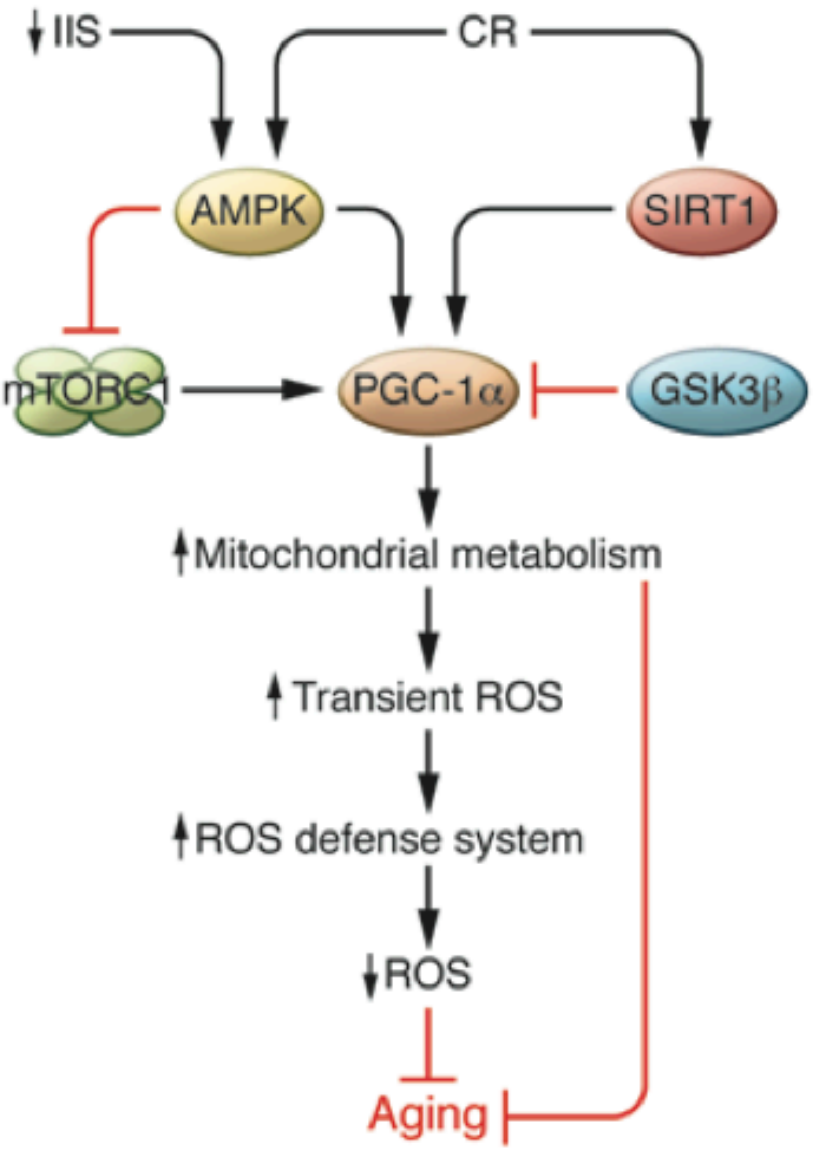


nutrient sensing calory restiction



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Nathan C, Cunningham-Bussel A

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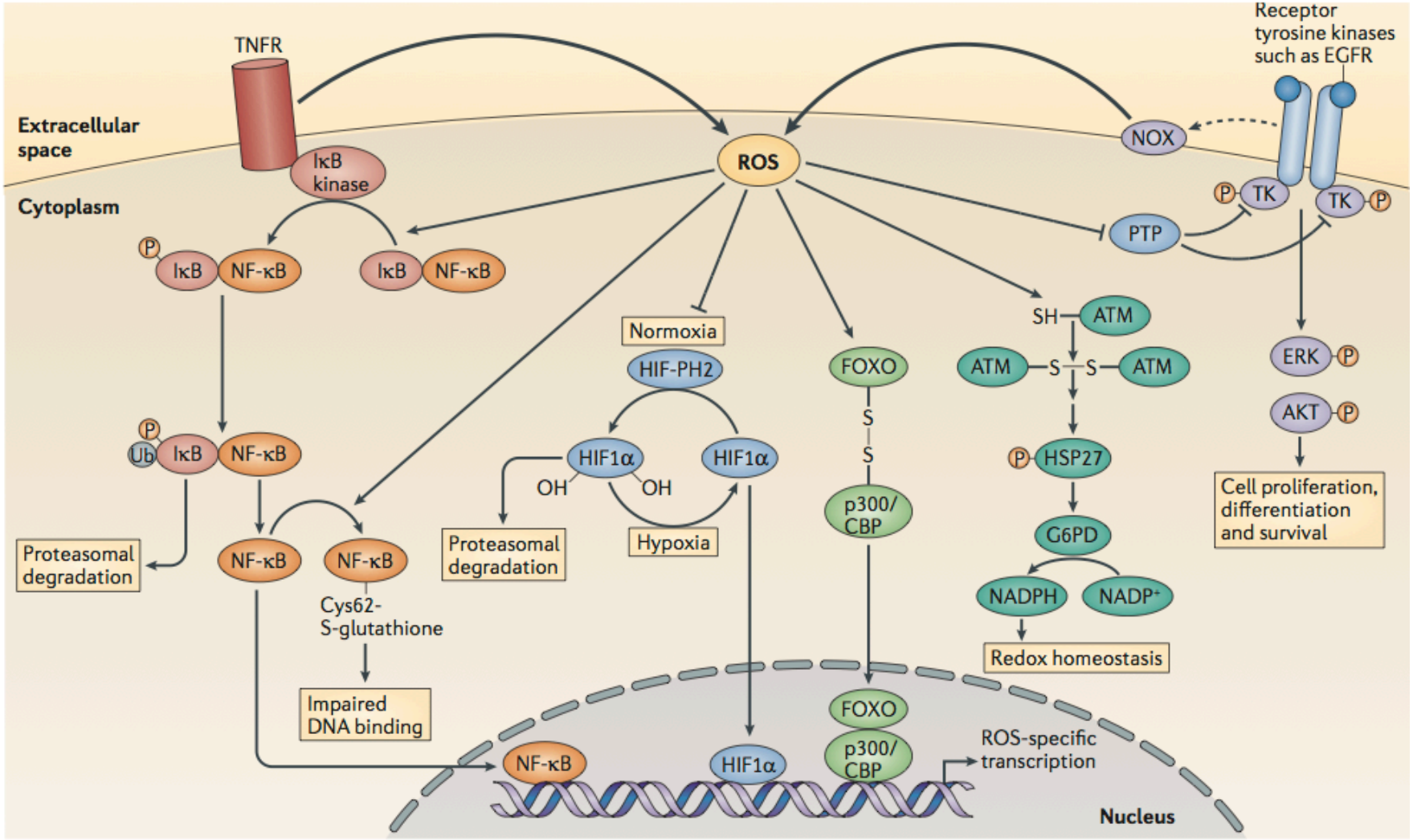

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