Cours du 28-10-2013

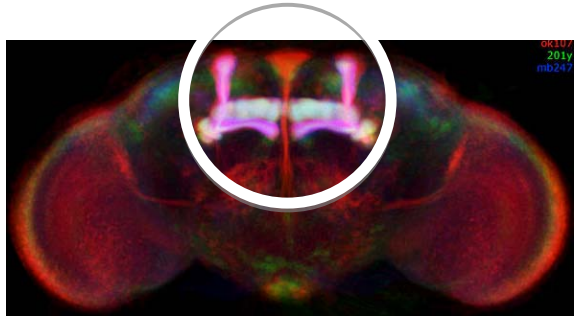
Longévité cérébrale

Activation of transposable elements during aging and neuronal decline in Drosophila

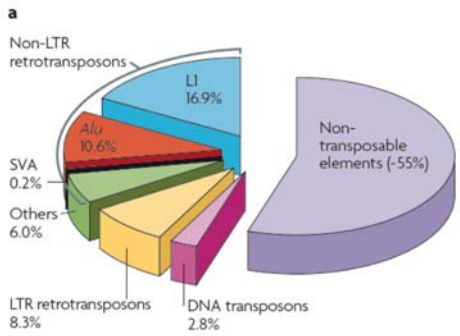
Li W, Prazak L, Chatterjee N, Grüninger S, Krug L, Theodorou D, Dubnau J

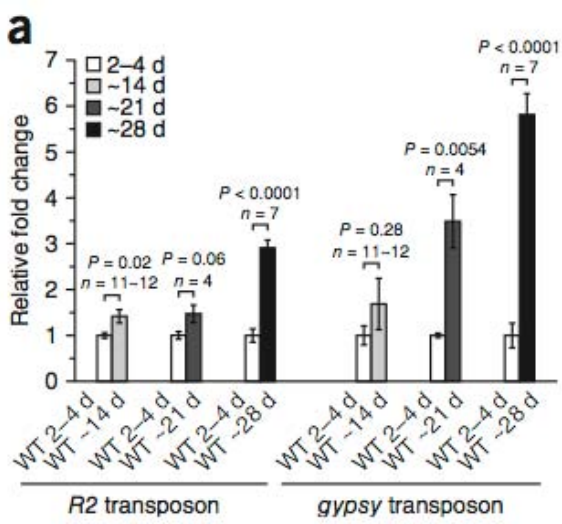
Nat Neurosci
2013 vol. 16 (5) pp. 529-31

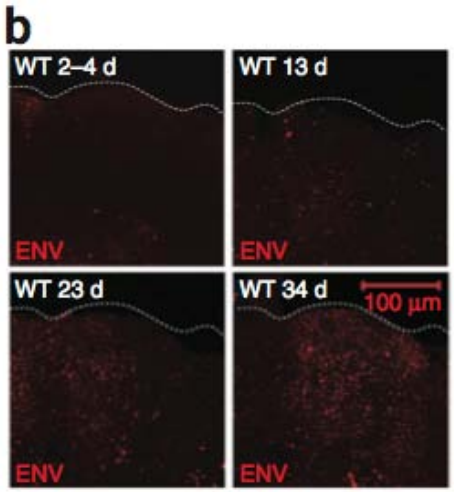
☆☆☆☆☆

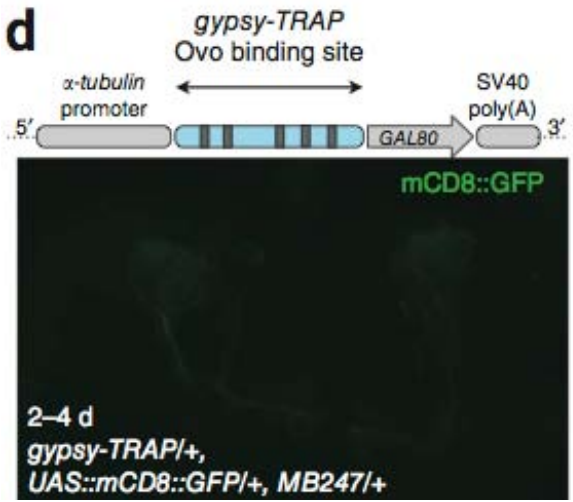


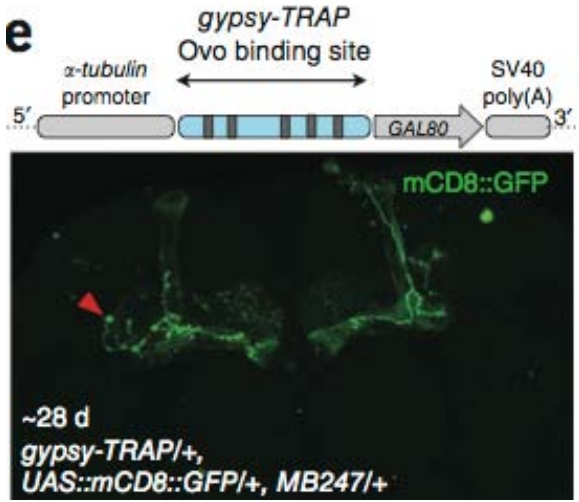
Cordaux @ Batzer, Nature Reviews genetics, 10: 691-703, 2009

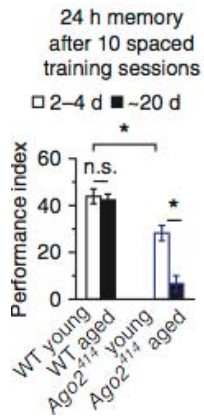


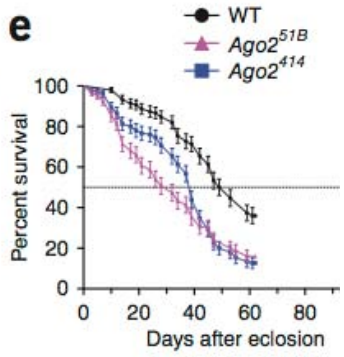












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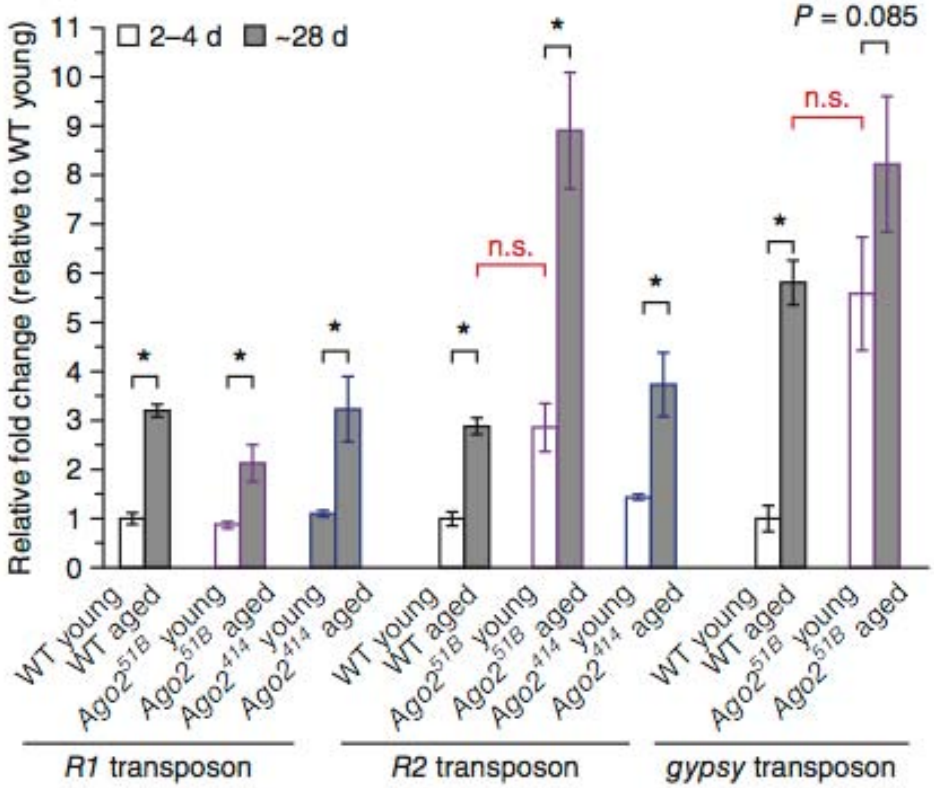
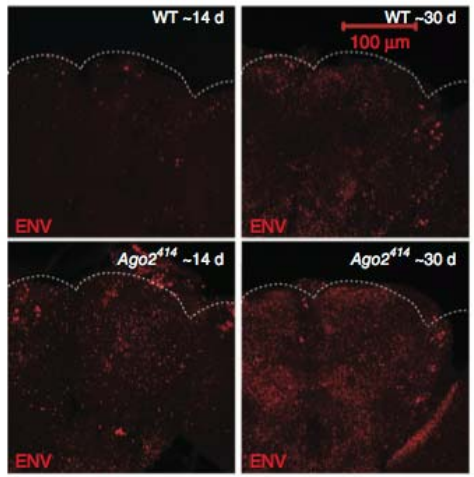
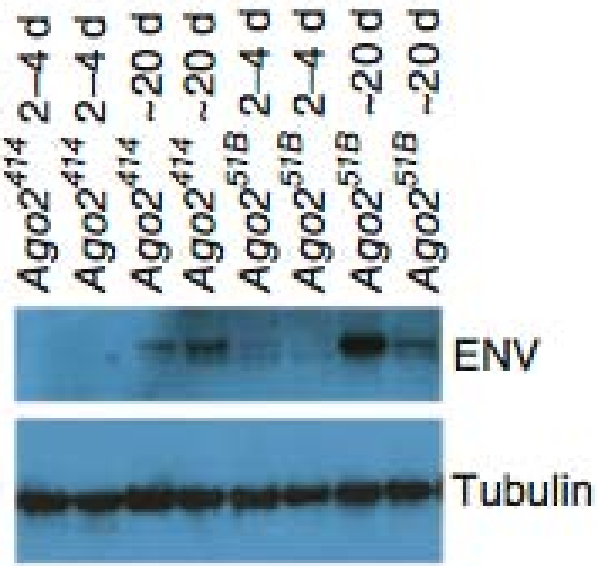
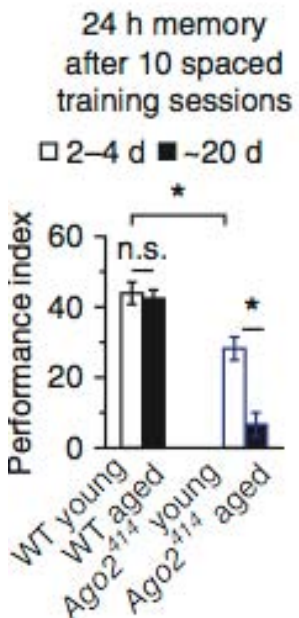
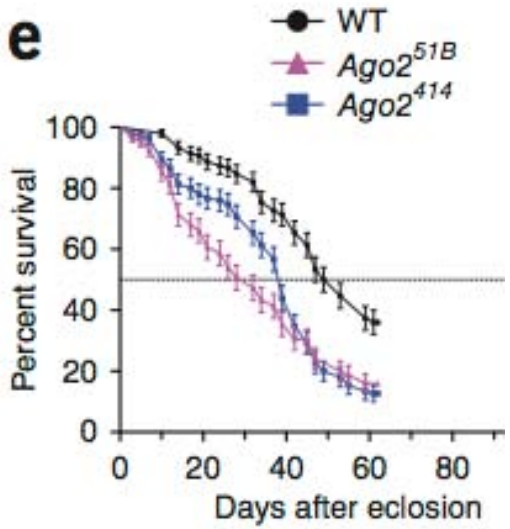






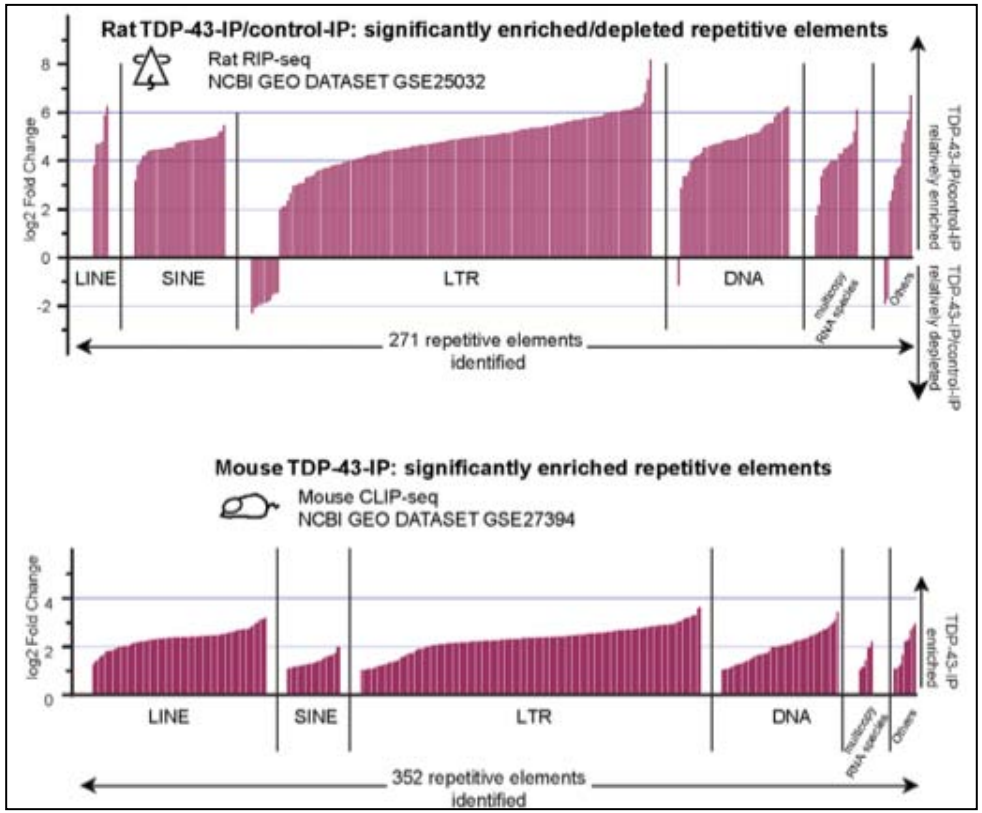


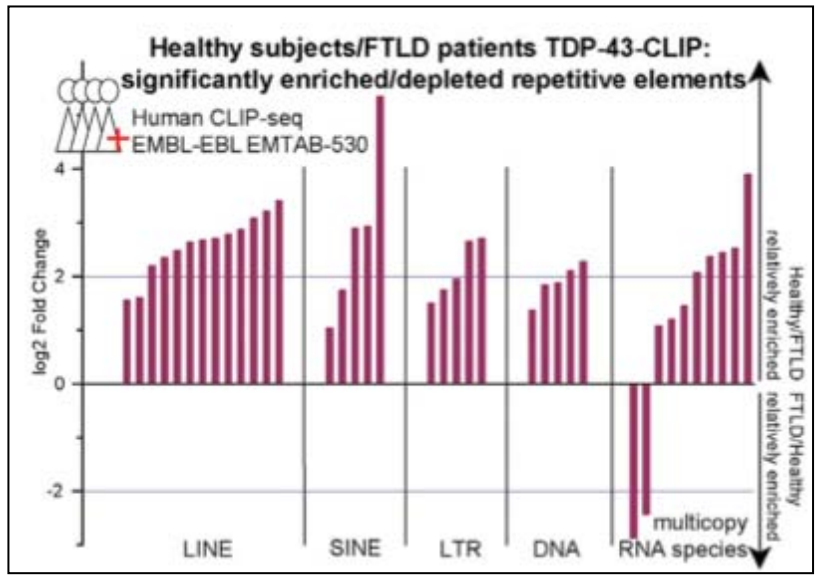


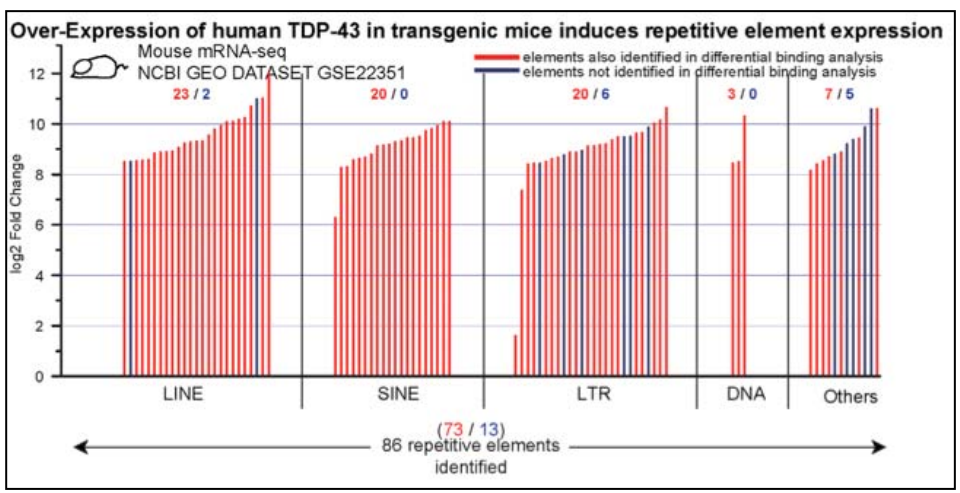
Transposable Elements in TDP-43-Mediated Neurodegenerative Disorders

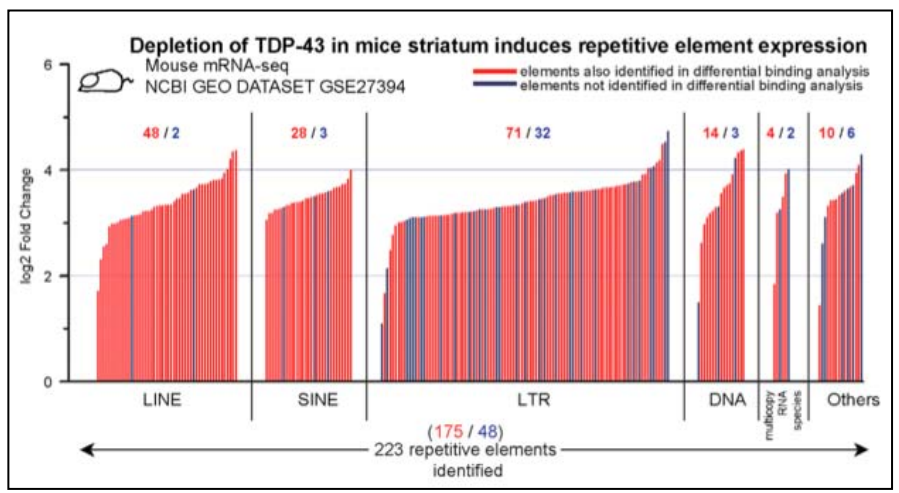
Wanhe Li[1,2☯], Ying Jin[2☯], Lisa Prazak[2☯], Molly Hammell[2*], Josh Dubnau[2*]

PLoS ONE
2012 vol. 7 (9) pp. e44099







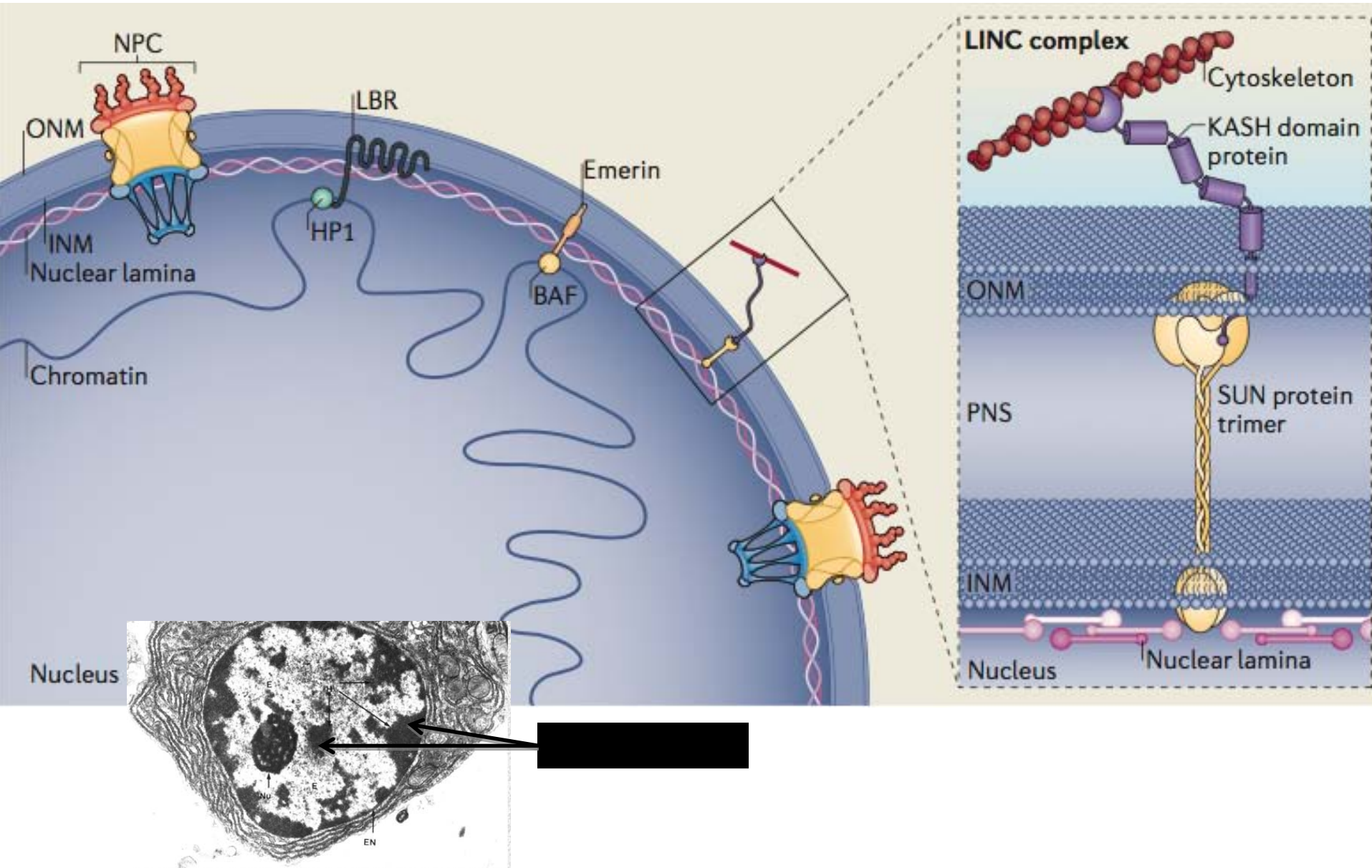


The nuclear lamins: flexibility in function

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



The nuclear lamins: flexibility in function

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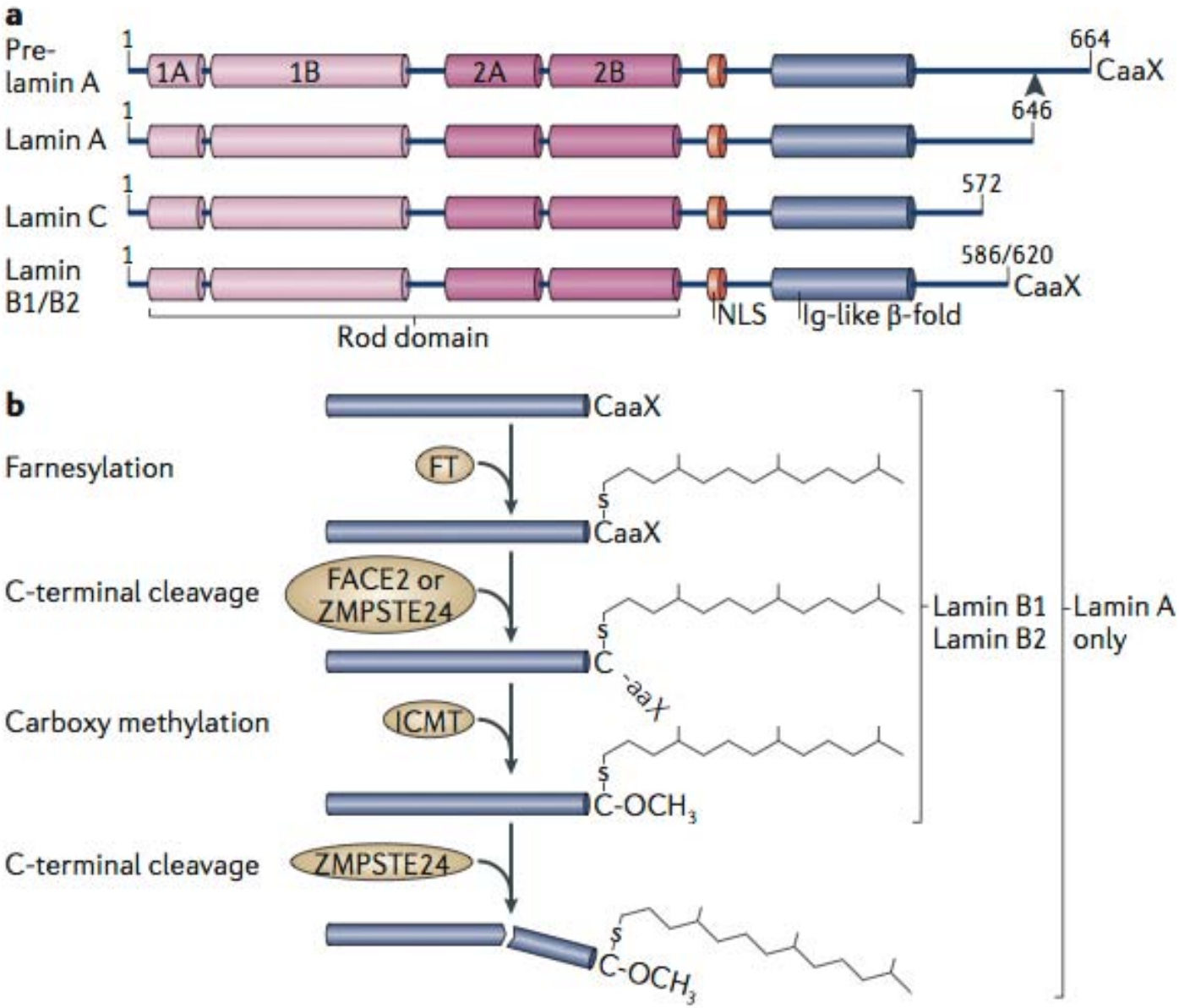
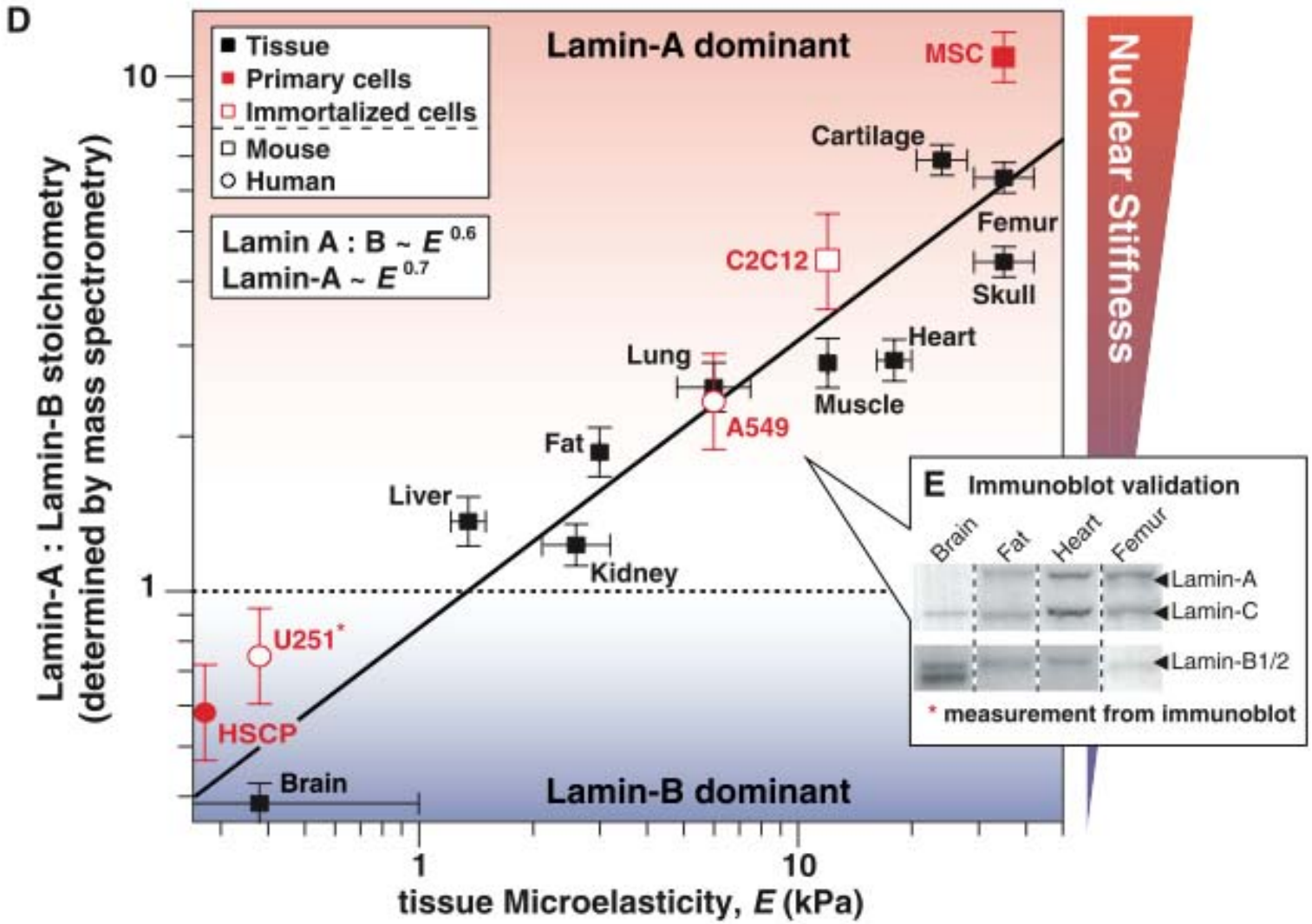


Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation

Science
2013 vol. 341 (6149) pp. 1240104

Swift J, Ivanovska IL, Buxboim A, Harada T, Dingal PC, Pinter J, Pajerowski JD, Spinler KR, Shin JW, Tewari M, Rehfeldt F, Speicher DW, Discher DE



Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation

Science
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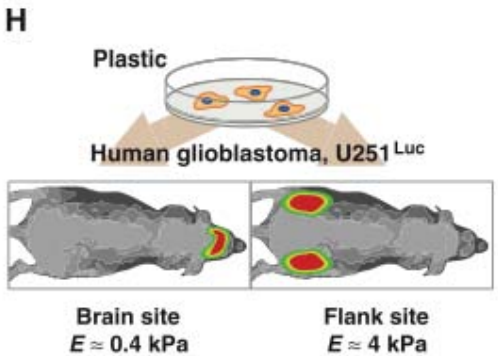
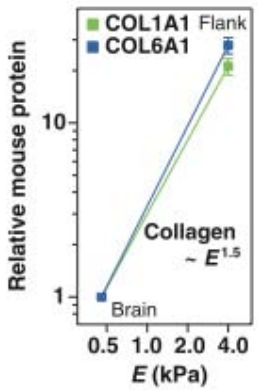
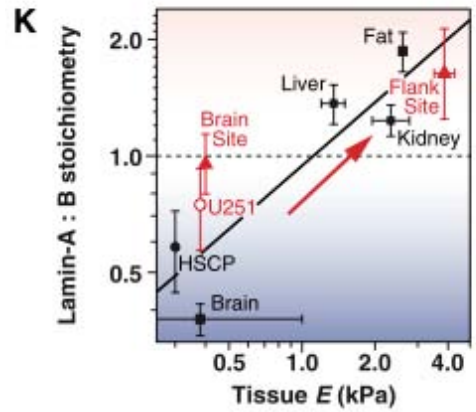
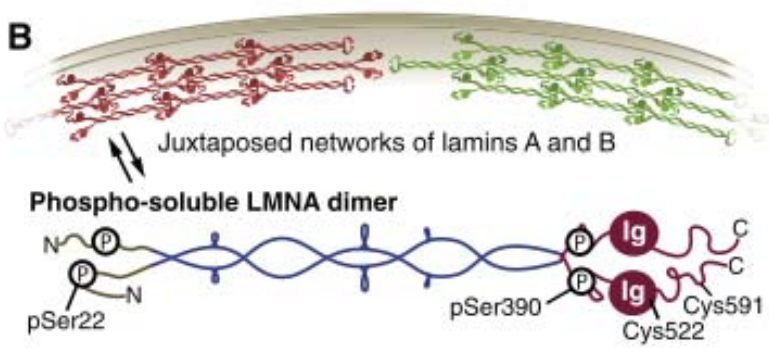
Swift J, Ivanovska IL, Buxboim A, Harada T, Dingal PC, Pinter J, Pajerowski JD, Spinler KR, Shin JW, Tewari M, Rehfeldt F, Speicher DW, Discher DE

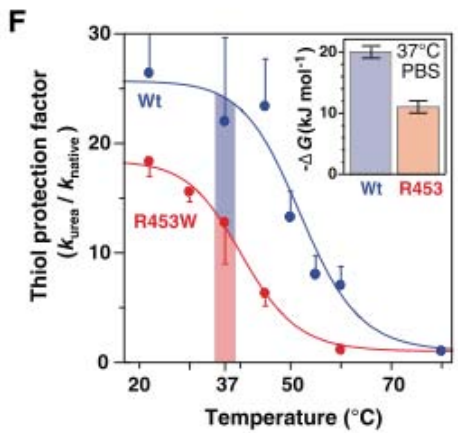
Collagen levels determine tissue stiffness and lamin-A levels respond in xenograft models









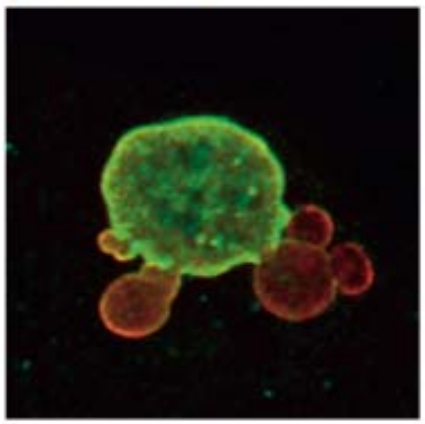


Nuclear lamin functions and disease

Butin-Israeli V, Adam SA, Goldman AE, Goldman RD

Trends Genet
2012 vol. 28 (9) pp. 464-71

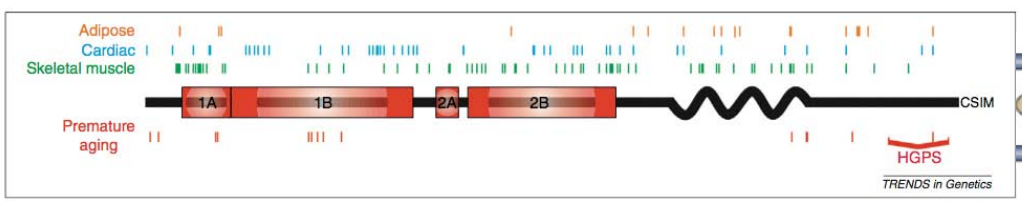
(a) HGPS

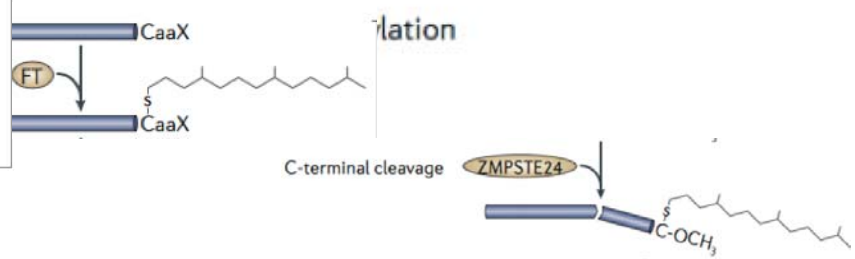


Lamin B

Lamin A

Syndrome/disease	Effects on *LMNA* gene and protein	Phenotype
Emery–Dreifuss muscular dystrophy (EDMD)	Autosomal dominant or recessive missense mutations in *LMNA* in various positions. Some may affect assembly of lamin A and interactions with associated proteins.	Progressive muscle weakness, cardiomyopathy.
Dilated cardiomyopathy, type 1A	Autosomal dominant missense mutations mostly in exons 1 *or* 3 of *LMNA*.	Cardiomyopathy with minimal effects on skeletal muscle.
Limb girdle muscular dystrophy (LGMD)	Autosomal dominant mutations in exon 1 of *LMNA*. The effect on lamin A is not known.	Skeletal muscle weakness and heart defects.
Familial partial lipodystrophy, Dunnigan type (FPLD2)	Autosomal dominant missense mutations in exons 8 and 11 of *LMNA*. Mainly affects the Ig-fold domain that may interfere with protein–protein interactions.	Loss of subcutaneous fat, insulin-resistance, diabetes, hypertriglyceridemia, and atherosclerosis.
Mandibuloacral dysplasia (MAD)	Autosomal recessive mutations: R527H, K542N, and A529V in the Ig-fold domain. Compound heterozygous mutations have also been reported. May interfere with protein–protein interactions.	Dental defects, lipodystrophy, atrophy of the skin on hands and feet, mandibular hypoplasia, acroosteolysis, alopecia, insulin resistance, progeroid features.
Hutchinson–Gilford progeria syndrome (HGPS)	Mostly spontaneous mutations (1824 C→T) in exon 11 of *LMNA*. This activates a cryptic splice donor site leading to the permanently farnesylated form of mutant lamin A called 'progerin' with a deletion of 50 amino acids near the C terminus. Alters lamin functions with respect to nuclear shape maintenance and chromatin organization.	Early-onset premature aging with alopecia, loss of subcutaneous fat, severe atherosclerosis, and cardiovascular disease leading to early death.
Atypical progeria syndromes (APS)	Various heterozygous missense mutations in *LMNA*, which are not associated with the production of progerin. These include heterozygous missense *LMNA* mutations, such as, P4R, E111K, D136H, E159K, and C588R.	Associated with different progeroid features including one or more of the following: short stature, partial alopecia, diabetes, lipodystrophy and mandibular hypoplasia, and cardiovascular disease.
Atypical Werner's syndrome (AWS)	Autosomal dominant mutations A133L mutation in *LMNA*. Effect on protein is unknown, but may lead to changes in protein–protein interactions.	Late-onset premature aging, atherosclerosis, sclerodermatous skin, premature grey hair.
Restrictive dermopathy (RD)	Mutations in exon 11 of *LMNA* and/or homozygous or compound heterozygous mutations in *ZMPSTE24*. These result in the formation of permanently farnesylated pre-lamin A.	Loss of fat tissue, tight skin, pulmonary hypoplasia, early lethality.
Charcot–Marie–Tooth disease, type 2B1	Autosomal recessive missense mutations in the lamin A rod domain that may affect lamin assembly.	Weakness and areflexia of lower limbs.
Generalized lipodystrophy	Autosomal dominant mutations I10T and heterozygous substitution in exon 1 c.29C→T, in *LMNA* with unknown effects on lamin A.	Lipodystrophy or lipoatrophy, may include diabetes and a progeroid phenotype.

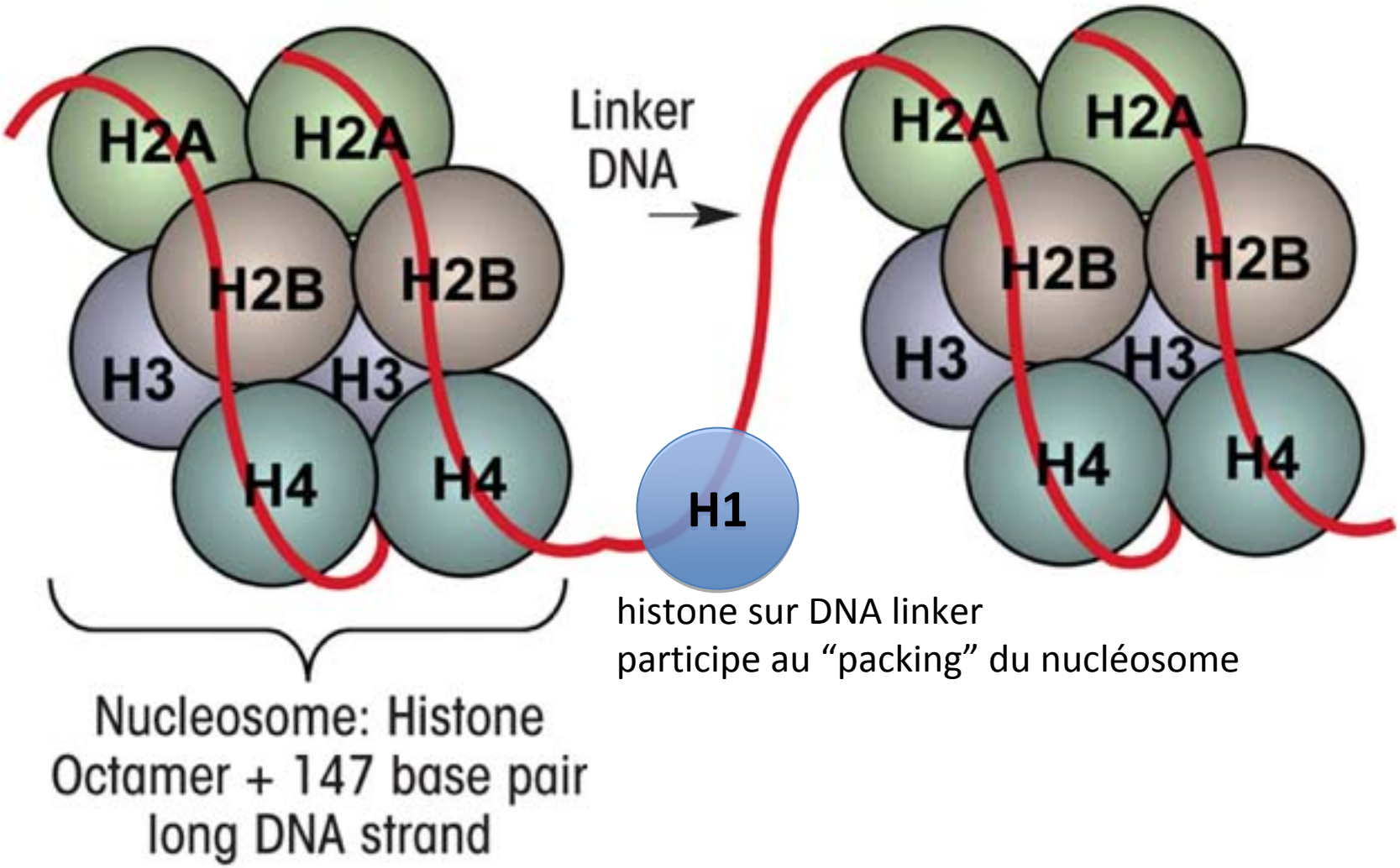




Epigenetics—Beyond the Genome in Alcoholism

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

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



histone sur DNA linker
participe au “packing” du nucléosome

Chromatin Remodeling at DNA Double-Strand Breaks

Brendan D. Price[1] and Alan D. D'Andrea[1,*]

1344 Cell *152*, March 14, 2013 ©2013 Elsevier Inc.

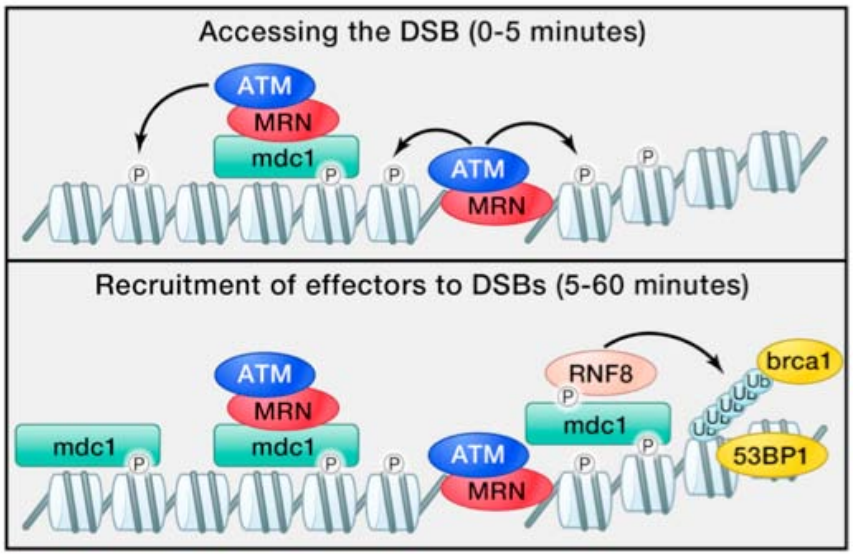


Figure 1. The Mechanism of DSB Repair

Top: ATM phosphorylates H2AX at DSBs, creating a binding site for the mdc1 protein. ATM-MRN complexes then associate with mdc1, promoting the spreading of γH2AX along the chromatin for hundreds of kilobases.

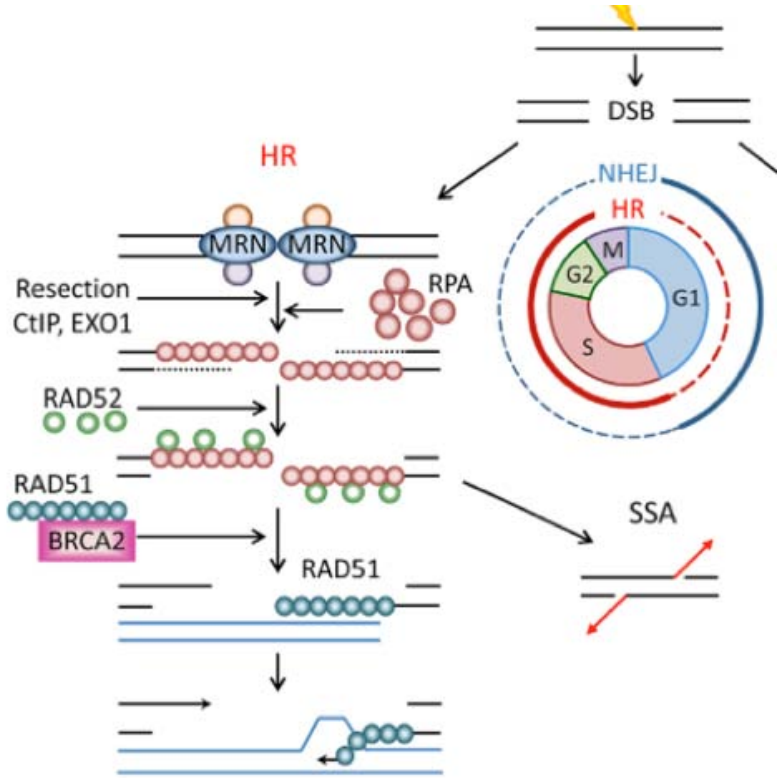
Bottom: mdc1 recruits multiple DSB-repair proteins, including the RNF8/RNF168 ubiquitin ligases, to sites of damage. Chromatin ubiquitination then facilitates loading of the brca1 complex and 53BP1 DSB-repair proteins.

P = phosphorylation, Ub = ubiquitination, MRN = mre11-rad50-nbs1 complex.

DNA strand break repair and neurodegeneration

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

DNA Repair 12 (2013) 558–567

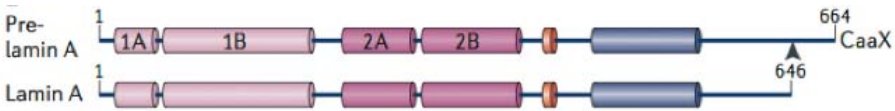


The nuclear lamins: flexibility in function

Burke B, Stewart CL

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

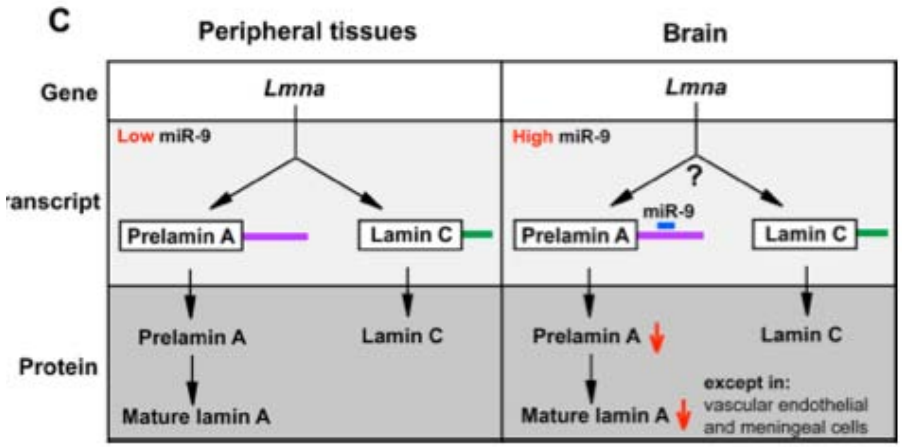
Nat Rev Mol Cell Biol
2013 vol. 14 (1) pp. 13-24

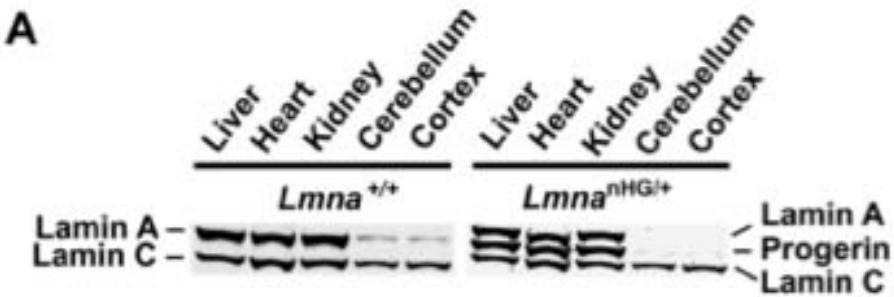


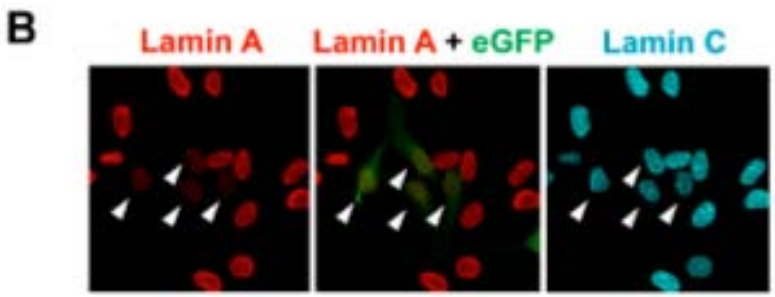
Understanding the roles of nuclear A- and B-type lamins in brain development

Young SG, Jung HJ, Coffinier C, Fong LG

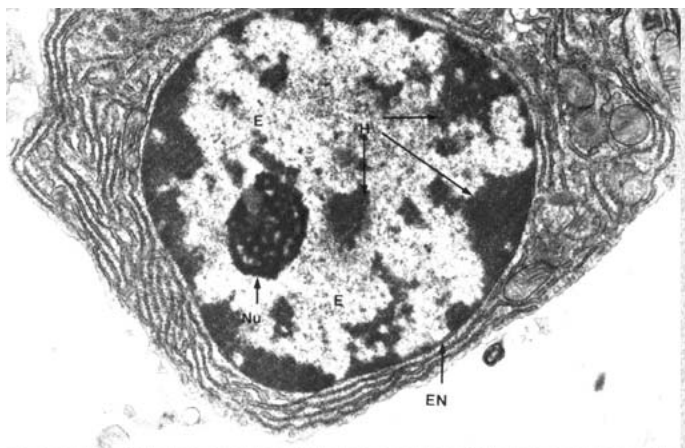
Journal of Biological Chemistry
2012 vol. 287 (20) pp. 16103-10







miR-9 represses
lamin A but not lamin C



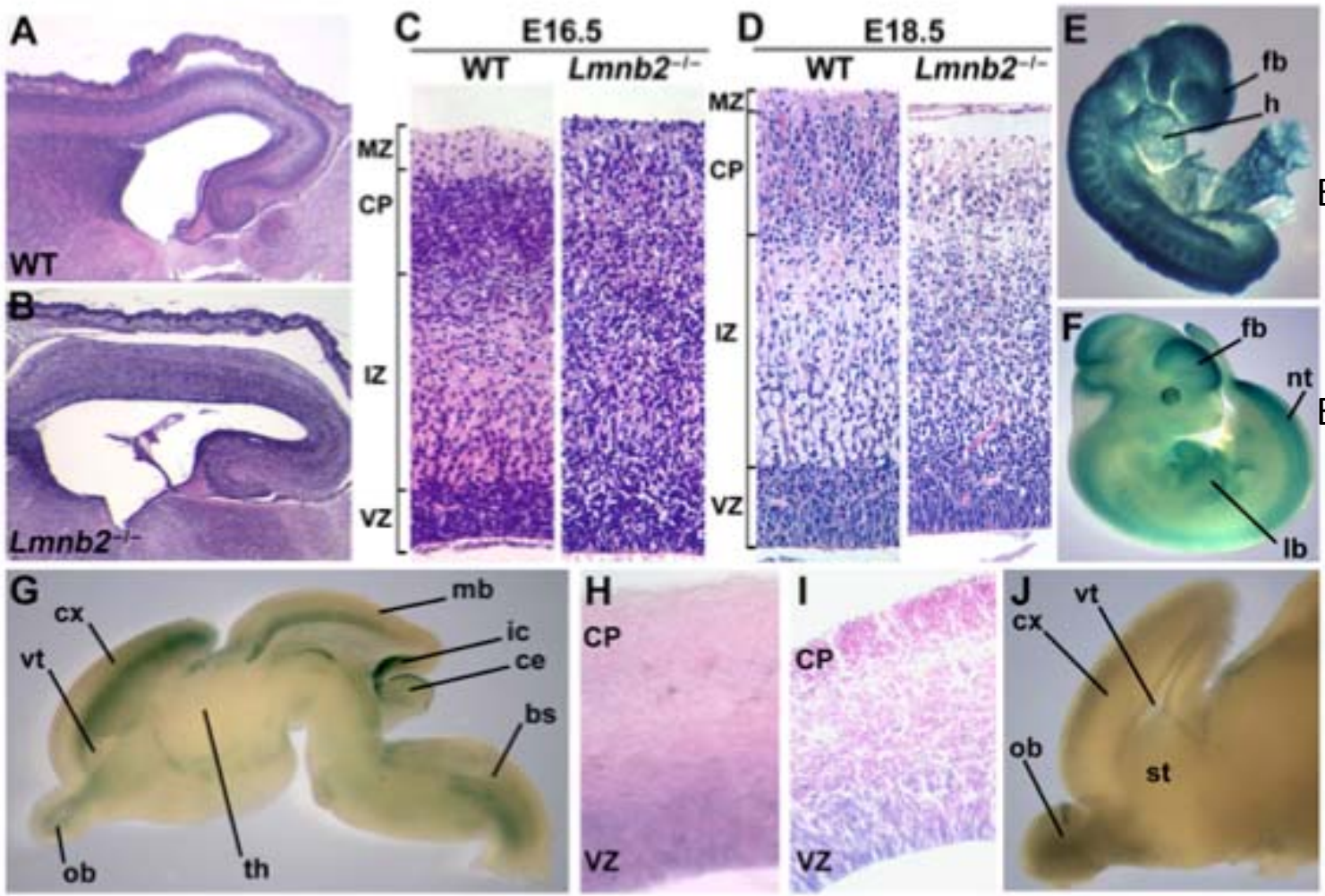
Abnormal development of the cerebral cortex and cerebellum in the setting of lamin B2 deficiency

Proc Natl Acad Sci USA
2010 vol. 107 (11) pp. 5076-81

Coffinier C, Chang SY, Nobumori C, Tu Y, Farber EA, Toth JI, Fong LG, Young SG

E16.5

E16.5



E8.5 Het

E11.5 Het

P0 Het

E16.5 Het

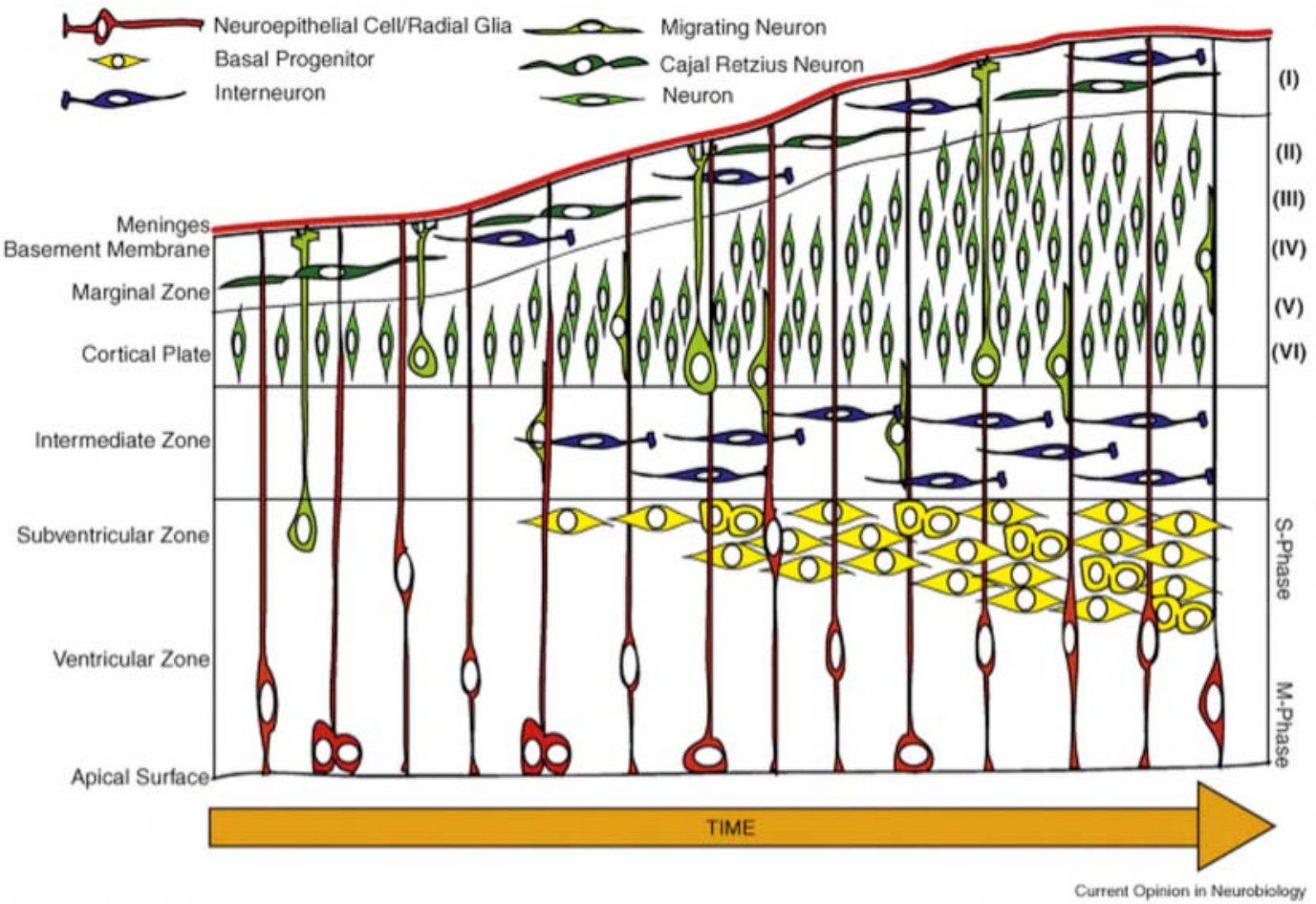
E16.5 Het

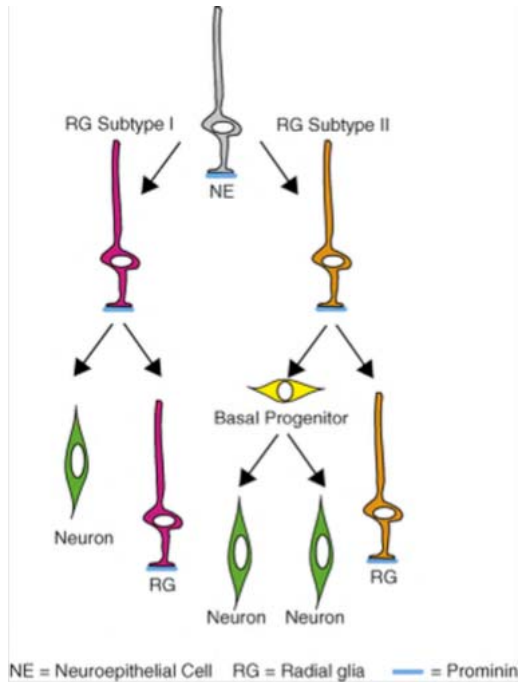
P0 Het

Stem cells niches during development--lessons from the cerebral cortex

Johansson PA, Cappello S, Götz M

Current Opinion in Neurobiology
2010 vol. 20 (4) pp. 400-7



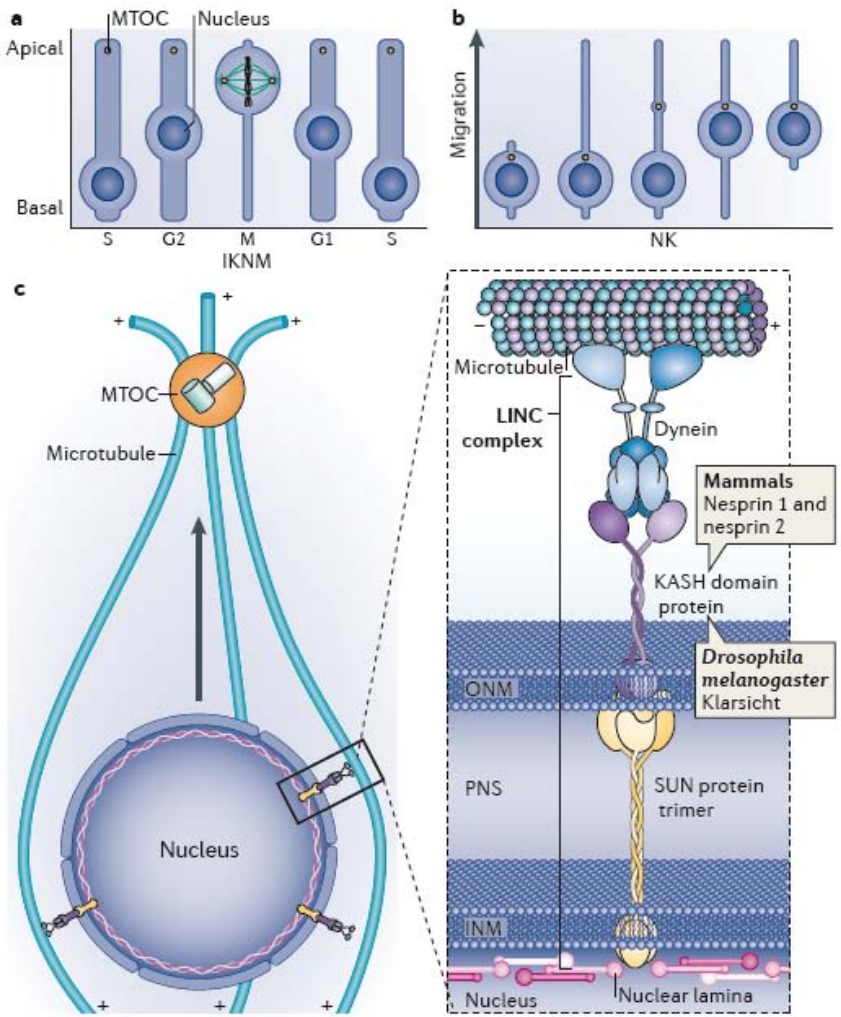


The nuclear lamins: flexibility in function

Brian Burke and Colin L. Stewart

NATURE REVIEWS | MOLECULAR CELL BIOLOGY

VOLUME 14 | JANUARY 2013 |



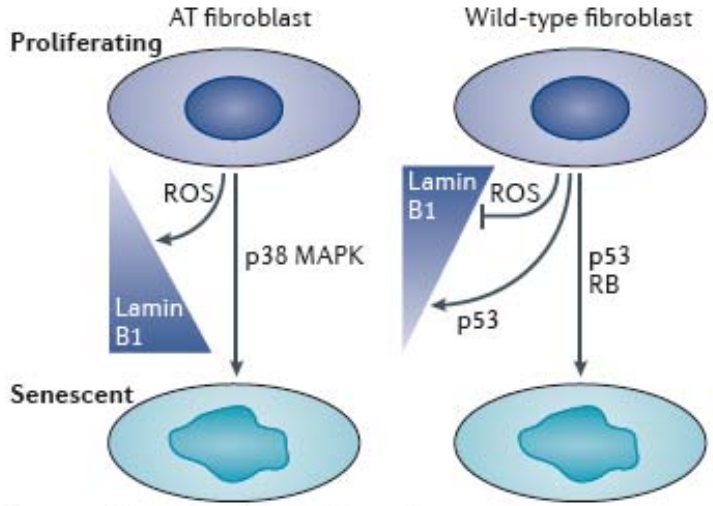


Figure 3 | **The role of lamin B1 and reactive oxygen species in cellular senescence.** In fibroblasts from patients with ataxia telangiectasia (AT), p38 MAPK-mediated premature senescence is associated with an increase in lamin B1 expression[140]. Upregulation of lamin B1 expression seems to be driven by reactive oxygen species (ROS) generation[140]. By contrast, replicative- and oncogene-induced senescence in wild-type human lung fibroblasts, which requires both p53 and retinoblastoma (RB), is associated with a p53-dependent reduction in lamin B1 expression[92,93]. In this case, ROS generation seems to inhibit the decline in lamin B1 levels[93]. Although the roles of lamin B1 in AT versus wild-type fibroblasts seem to be diametrically opposed, in both situations ROS generation is associated with increased lamin B1 levels[93,140].

The nuclear lamins: flexibility in function

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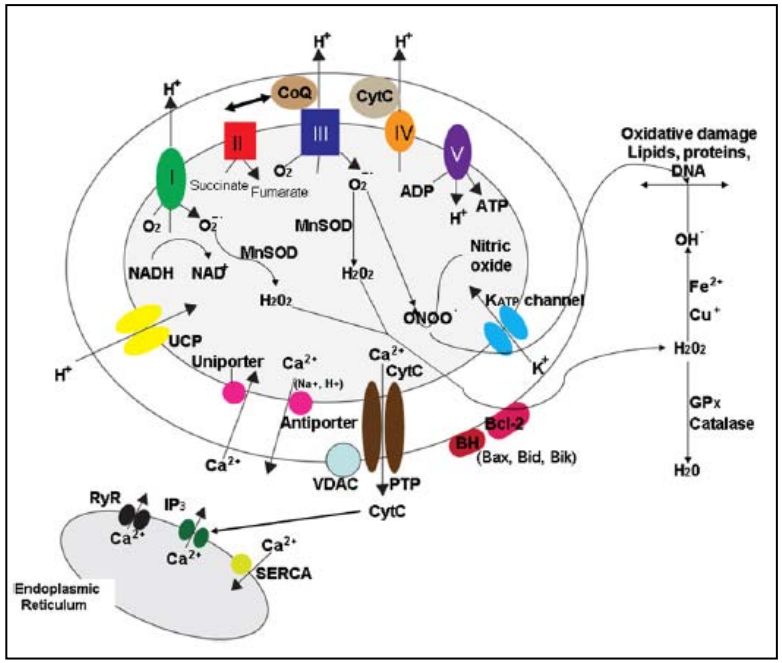
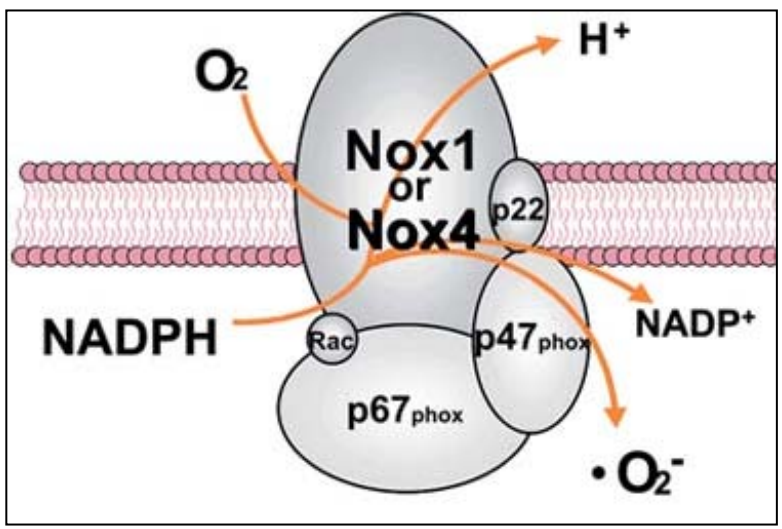
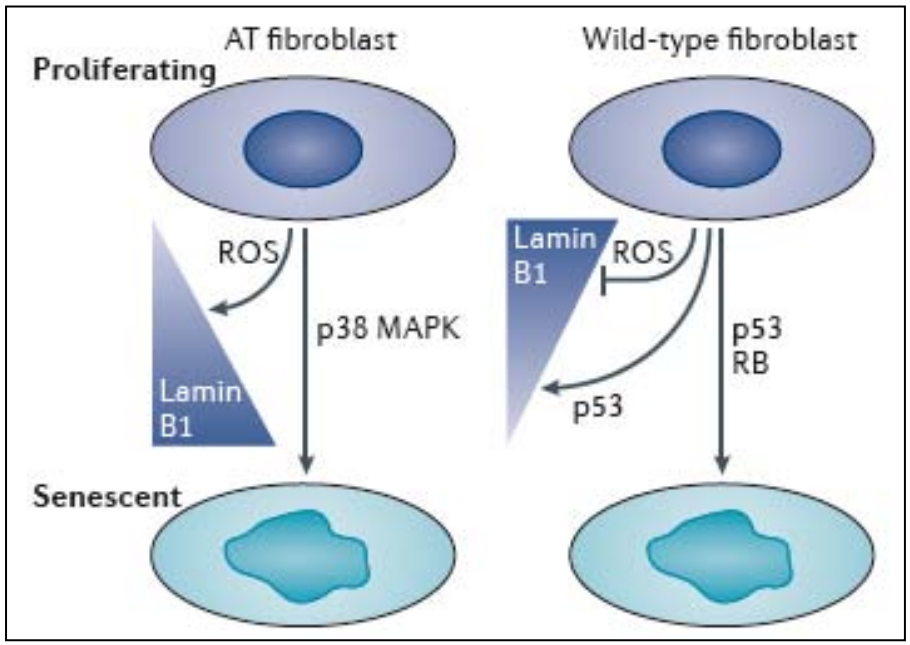
VOLUME 14 | JANUARY 2013 |



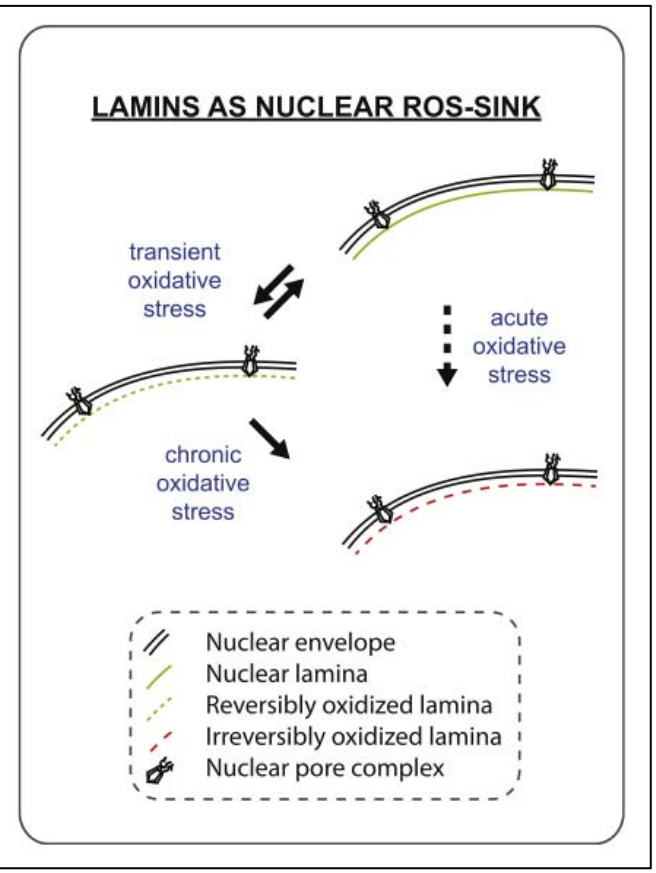


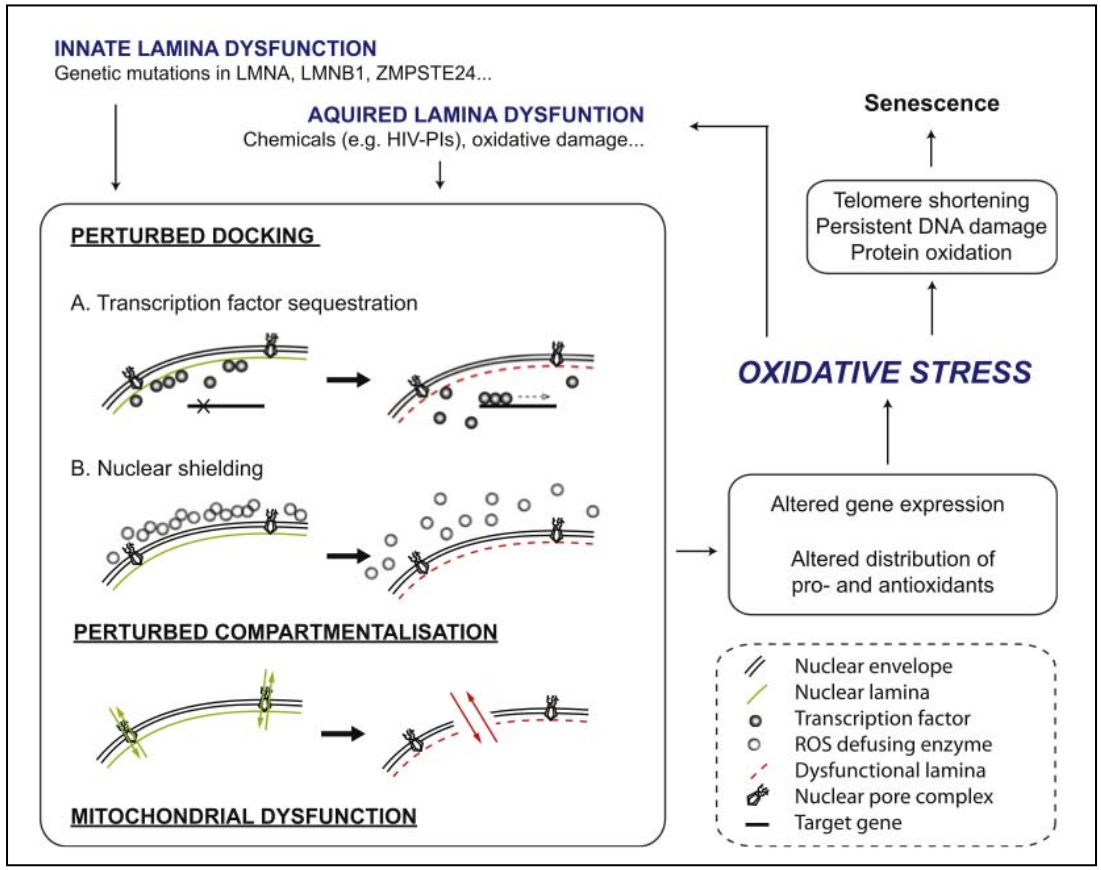


Lamins as mediators of oxidative stress

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

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





The Hallmarks of Aging

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

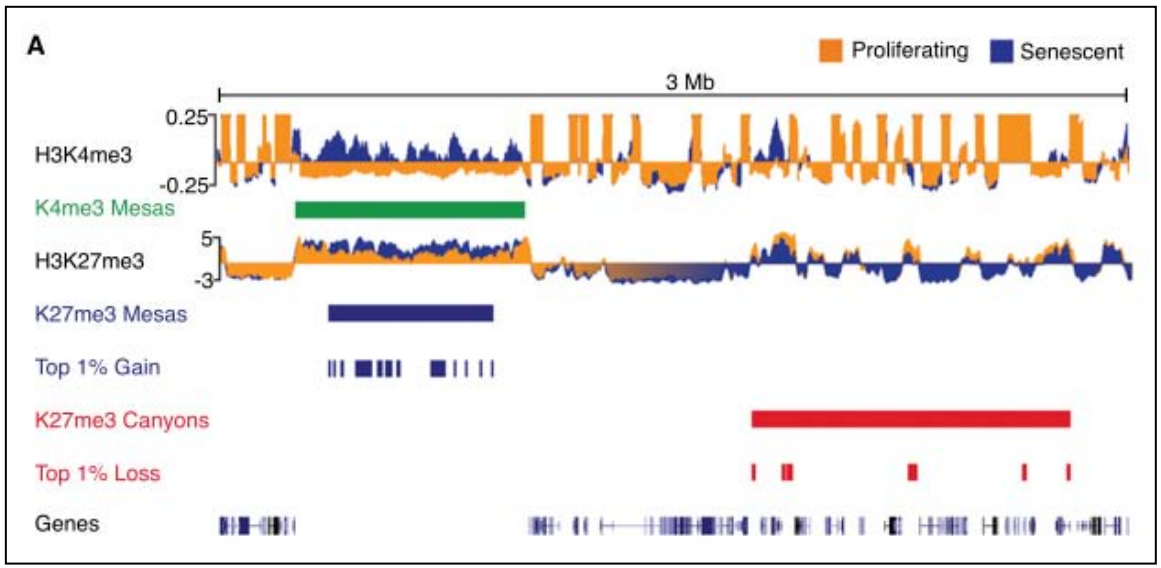
Carlos López-Otín,[1] Maria A. Blasco,[2] Linda Partridge,[3,4] Manuel Serrano,[5,*] and Guido Kroemer[6,7,8,9,10]

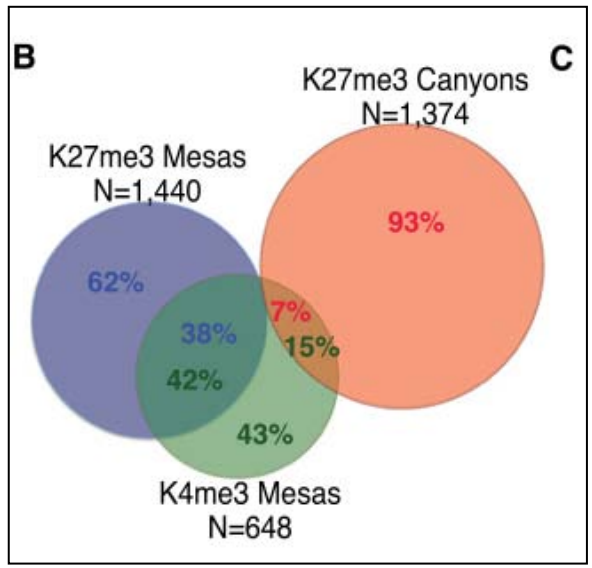
Figure 1. The Hallmarks of Aging
The scheme enumerates the nine hallmarks described in this Review: genomic instability, telomere attrition, epigenetic alterations, loss of proteostasis, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, and altered intercellular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

Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and the chromatin landscape

Parisha P. Shah, Greg Donahue, Gabriel L. Otte, et al.

Genes Dev. 2013 27: 1787-1799 originally published online August 9, 2013
Access the most recent version at doi:10.1101/gad.223834.113





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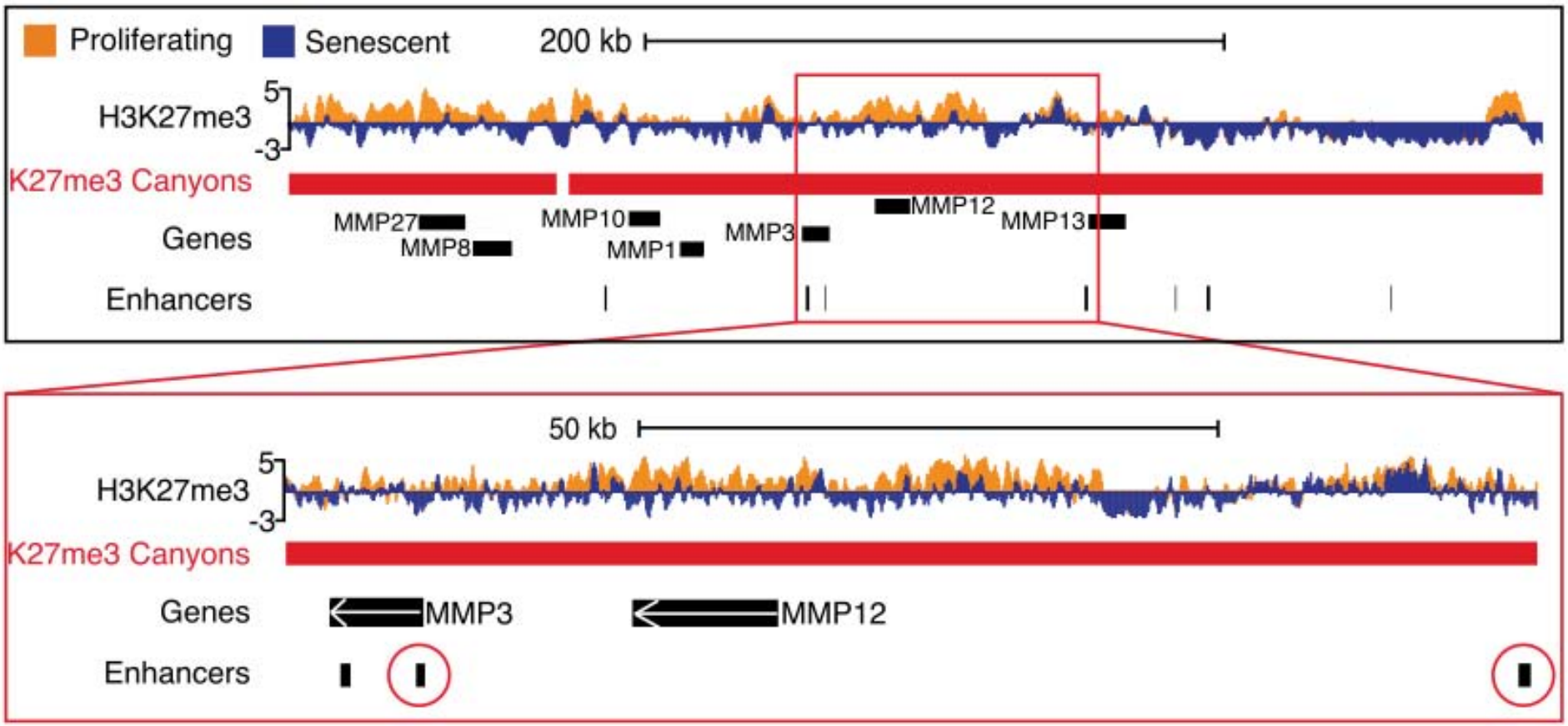

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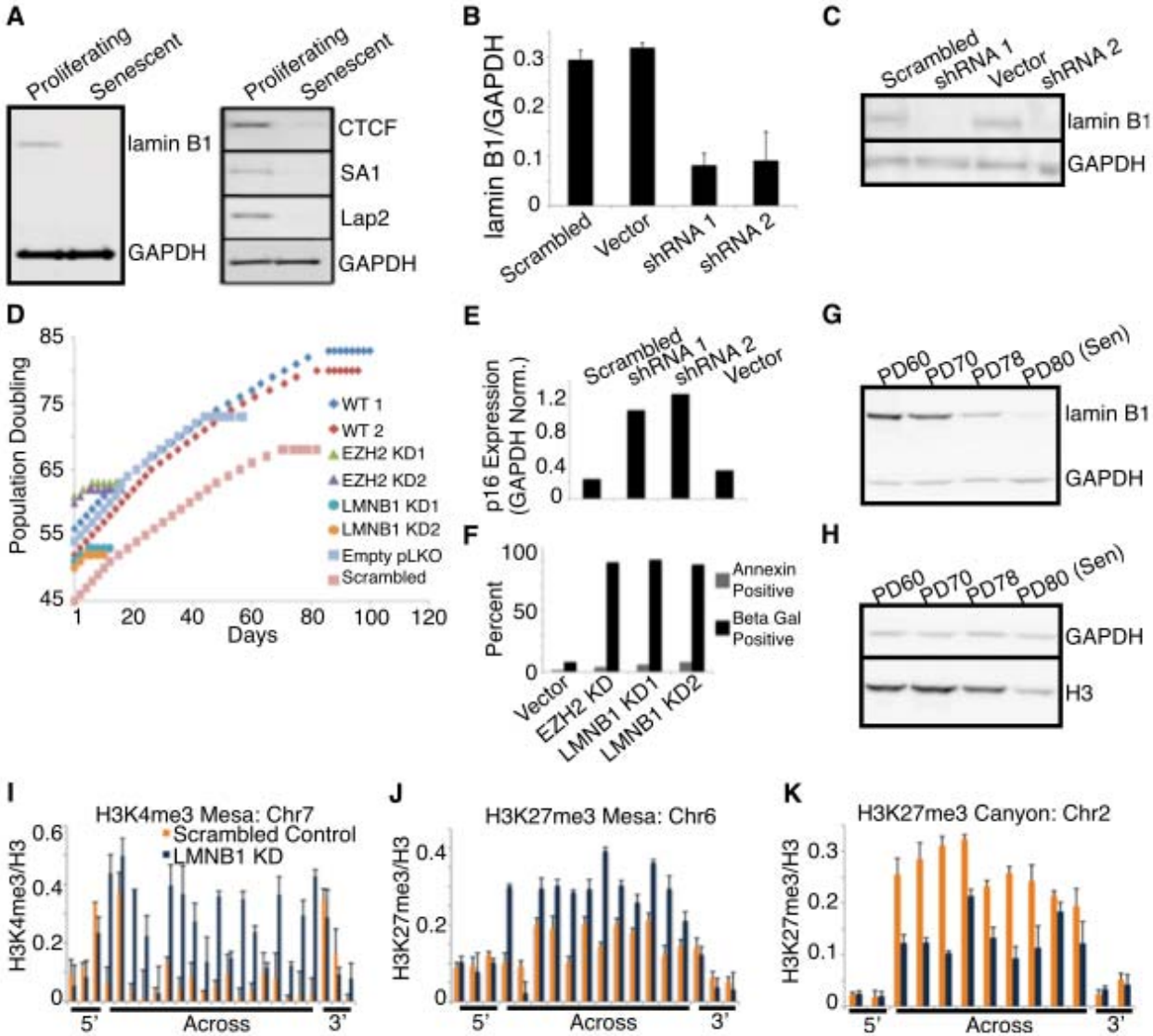

Functional Coupling between the Extracellular Matrix and Nuclear Lamina by Wnt Signaling in Progeria

Lidia Hernandez,[1,3,8] Kyle J. Roux,[4,8] Esther Sook Miin Wong,[5,8] Leslie C. Mounkes,[1] Rafidah Mutalif,[5] Raju Navasankari,[4,5] Bina Rai,[5] Simon Cool,[5] Jae-Wook Jeong,[6] Honghe Wang,[1] Hyun-Shik Lee,[2,9] Serguei Kozlov,[1] Martin Grunert,[5] Thomas Keeble,[5] C. Michael Jones,[5] Margarita D. Meta,[7] Stephen G. Young,[7] Ira O. Daar,[2] Brian Burke,[4] Alan O. Perantoni,[1] and Colin L. Stewart[1,5,*]

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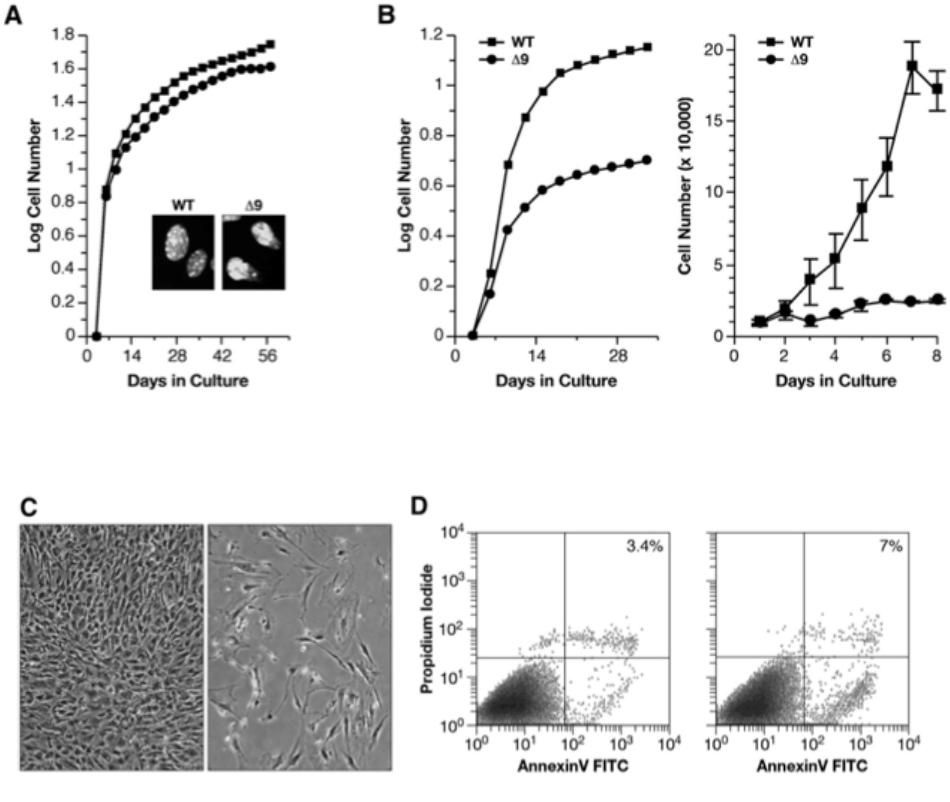
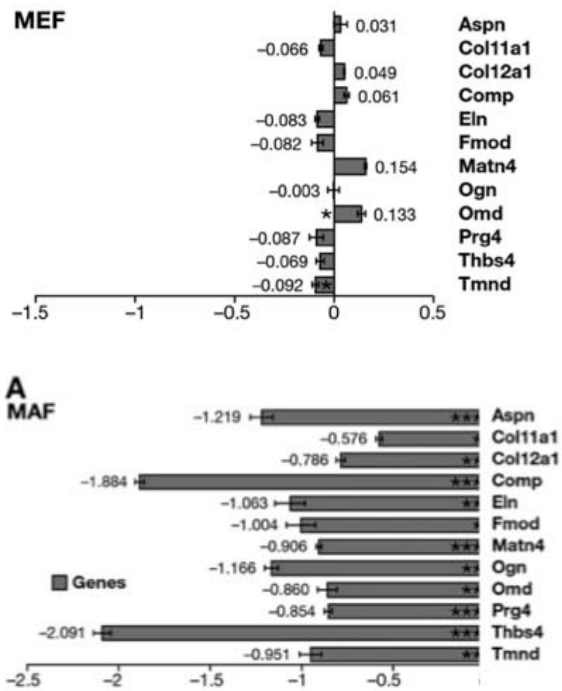
Embryonic

Postnatal





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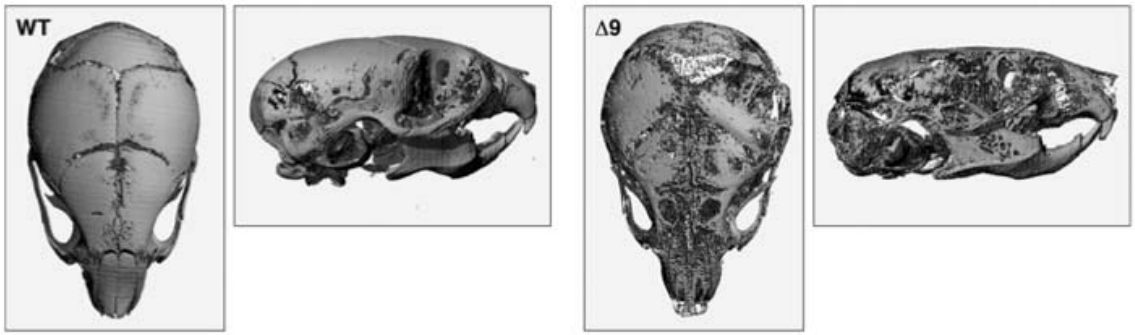

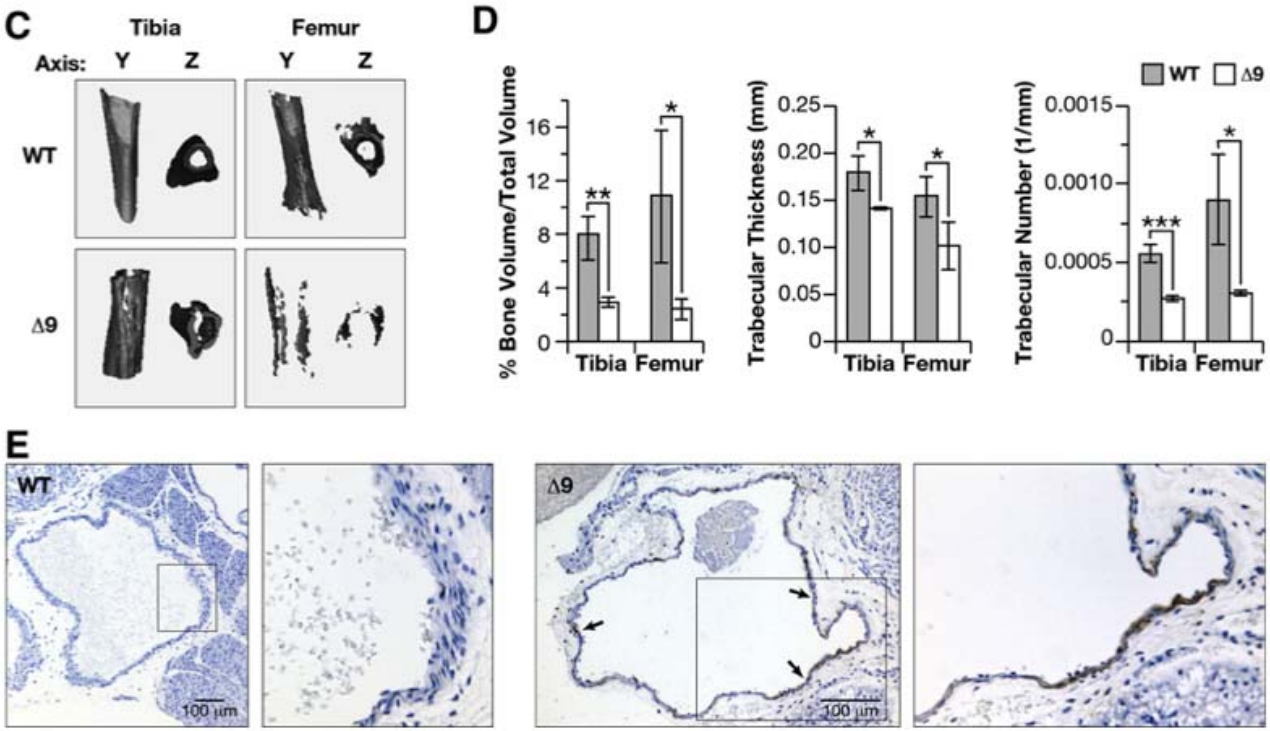

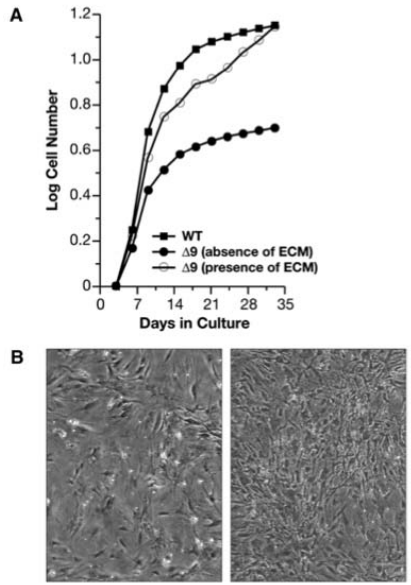

Figure 4. Δ9MAF Growth Is Rescued by WT Extracellular Matrix

(A) Growth curves of WT MAFs and of Δ9MAFs in the presence or absence of WT MAF ECM.

(B) Left panel Δ9MAFS at p4 with no ECM; right panel Δ9MAFs on ECM. Growth of Δ9MAFs on specific ECM components or with FTIs is shown in Figures S3A and S3B.

Wnt/β-Catenin Signaling: Components, Mechanisms, and Diseases

Bryan T. MacDonald,[1] Keiko Tamai,[2] and Xi He[1,*]

Developmental Cell 17, July 21, 2009 ©2009 Elsevier Inc. 9

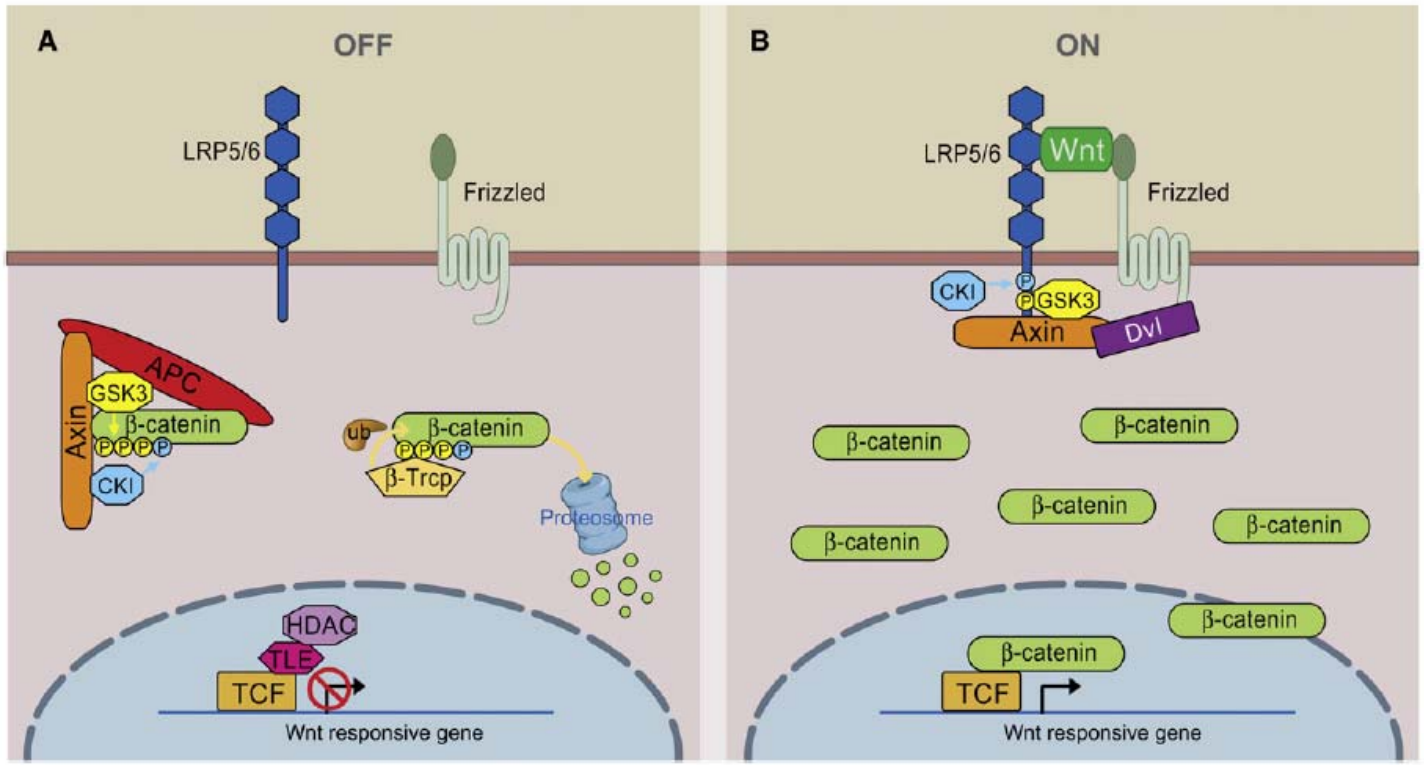

Figure 1. Overview of Wnt/β-Catenin Signaling

(A) In the absence of Wnt, cytoplasmic β-catenin forms a complex with Axin, APC, GSK3, and CK1, and is phosphorylated by CK1 (blue) and subsequently by GSK3 (yellow). Phosphorylated β-catenin is recognized by the E3 ubiquitin ligase β-Trcp, which targets β-catenin for proteosomal degradation. Wnt target genes are repressed by TCF-TLE/Groucho and histone deacetylases (HDAC).

(B) In the presence of Wnt ligand, a receptor complex forms between Fz and LRP5/6. Dvl recruitment by Fz leads to LRP5/6 phosphorylation and Axin recruitment. This disrupts Axin-mediated phosphorylation/degradation of β-catenin, allowing β-catenin to accumulate in the nucleus where it serves as a coactivator for TCF to activate Wnt-responsive genes.

Functional Coupling between the Extracellular Matrix and Nuclear Lamina by Wnt Signaling in Progeria

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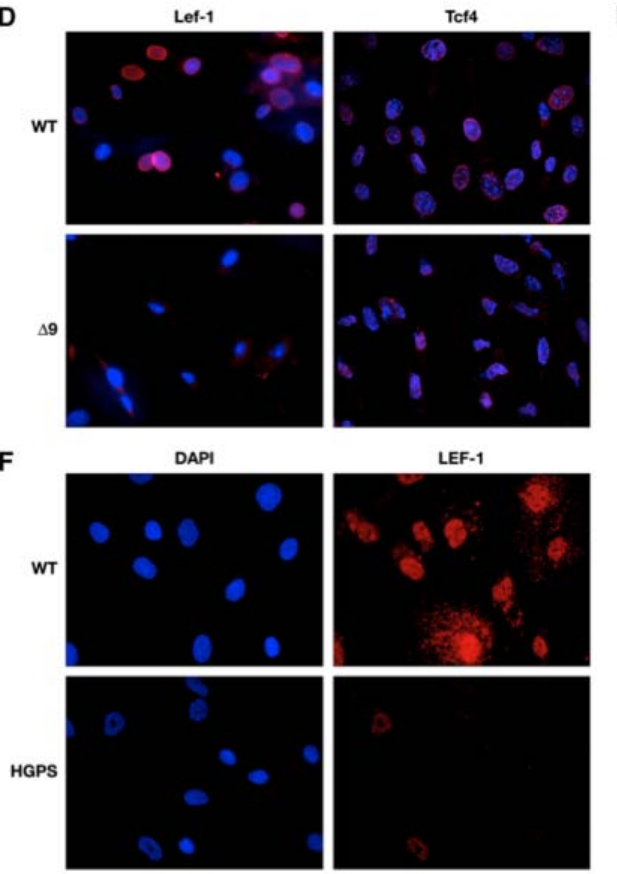

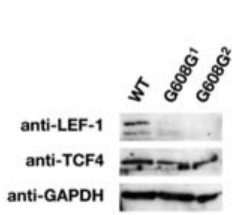

(D) Immunofluorescent detection of Lef1 and Tcf4 in WT and Δ9MAF nuclei counterstained with DAPI.
(E) Lef1 and Tcf4 detection by Western analysis of nuclear extracts of fibroblast lines from two progeric patients (Coriell #AG11498, AG06297).
(F) Immunofluorescence showing Lef1 in normal parental (WT- AG03512) and progeric (AG11498) fibroblasts, nuclei counterstained with DAPI.
Error bars are SEM.

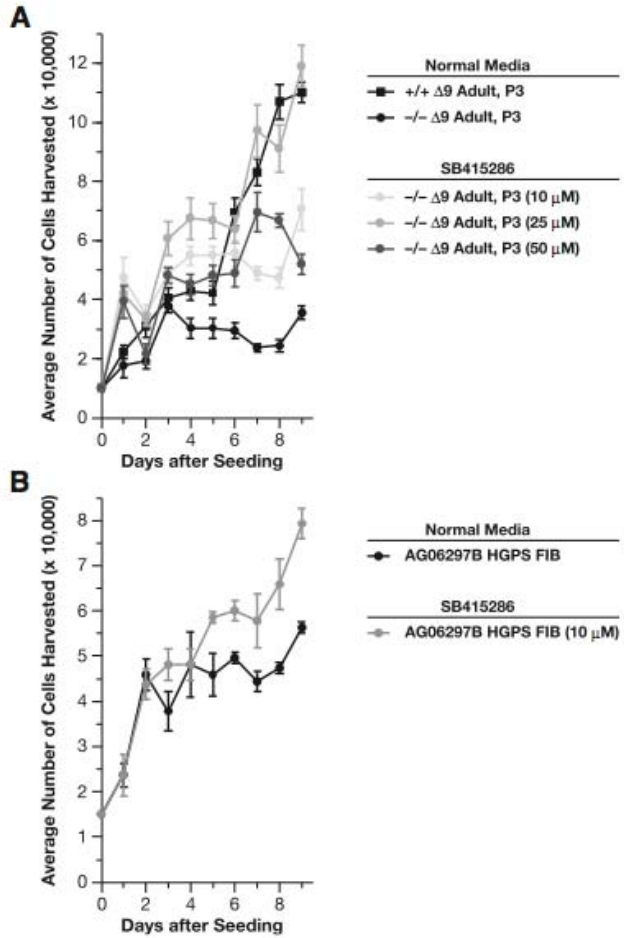

Figure 7. Cell Proliferation Is Enhanced by Gsk-3β Inhibition
(A) Treatment of Δ9MAFs with the Gsk inhibitor SB415286 (25 μm) rescues growth.
(B) Treatment of the progeric line AG06297 (10 μm SB415286) enhances growth.
Error bars are SEM.