Cours du 28-10-2013

Longévité cérébrale
Activation of transposable elements during aging and neuronal decline in Drosophila

Li W, Razak L, Chattarjee N, Grüniger S, Krug L, Theodorou D, Dubnau J

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

**a**

Non-LTR retrotransposons

- L1: 16.9%
- SVA: 3.6%
- Others: 6.0%
- Non-transposable elements (~55%)

**b**

Relative fold change

- WT 2-4 d
- WT 13 d
- WT 23 d
- WT 34 d

**c**

24 h memory after 10 spaced training sessions

- WT
- Agc2<sup>219</sup>
- Agc2<sup>211</sup>

Percent survival

- Days after occlusion
Activation of transposable elements during aging and neuronal decline in Drosophila

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

Nat Neurosci 2013 vol. 16 (5) pp. 529–31
Transposable Elements in TDP-43-Mediated Neurodegenerative Disorders

Wanhe Li‡, Ying Jin§, Lisa Prazak*, Molly Hammell*, Josh Dubnau*

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

Over-Expression of human TDP-43 in transgenic mice induces repetitive element expression

Depletion of TDP-43 in mice striatum induces repetitive element expression
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
The nuclear lamins: flexibility in function
Nuclear lamin-A scales with tissue stiffness and enhances matrix-directed differentiation

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

Collagen levels determine tissue stiffness and lamin-A levels respond in xenograft models.
# Nuclear lamin functions and disease

<table>
<thead>
<tr>
<th>Syndrome/disease</th>
<th>Effects on LMNA gene and protein</th>
<th>Phenotype</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dilated cardiomyopathy, type 1A</td>
<td>Autosomal dominant missense mutations mostly in exons 1 or 3 of LMNA.</td>
<td>Cardiomyopathy with minimal effects on skeletal muscle.</td>
</tr>
<tr>
<td>Limb girdle muscular dystrophy (LGMD)</td>
<td>Autosomal dominant mutations in exon 1 of LMNA. The effect on lamin A is not known.</td>
<td>Skeletal muscle weakness and heart defects.</td>
</tr>
<tr>
<td>Familial partial lipodystrophy, Dunnigan type (FPLD2)</td>
<td>Autosomal dominant missense mutations in exons 8 and 11 of LMNA. Mainly affects the Ig-fold domain that may interfere with protein–protein interactions.</td>
<td>Loss of subcutaneous fat, insulin-resistance, diabetes, hypertriglyceridemia, and atherosclerosis.</td>
</tr>
<tr>
<td>Mandibuloacral dysplasia (MAD)</td>
<td>Autosomal recessive mutations: R527H, K542N, and A629V in the Ig-fold domain. Compound heterozygous mutations have also been reported. May interfere with protein–protein interactions.</td>
<td>Dental defects, lipodystrophy, atrophy of the skin on hands and feet, mandibular hypoplasia, acroosteolysis, alopecia, insulin resistance, progeroid features.</td>
</tr>
<tr>
<td>Hutchinson–Gilford progeria syndrome (HGPS)</td>
<td>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. Ailts lamin functions with respect to nuclear shape maintenance and chromatin organization.</td>
<td>Early-onset premature aging with alopecia, loss of subcutaneous fat, severe atherosclerosis, and cardiovascular disease leading to early death.</td>
</tr>
<tr>
<td>Atypical progeria syndromes (APS)</td>
<td>Various heterozygous missense mutations in LMNA, which are not associated with the production of progerin. These include heterozygous missense LMNA mutations, such as, P44R, E111K, D136H, E159K, and C588R.</td>
<td>Associated with different progeroid features including one or more of the following: short stature, partial alopecia, diabetes, lipodystrophy and mandibular hypoplasia, and cardiovascular disease.</td>
</tr>
<tr>
<td>Atypical Werner’s syndrome (AWS)</td>
<td>Autosomal dominant mutations A133L mutation in LMNA. Effect on protein is unknown, but may lead to changes in protein–protein interactions.</td>
<td>Late-onset premature aging, atherosclerosis, sclerodermatous skin, premature grey hair.</td>
</tr>
<tr>
<td>Restrictive dermopathy (RD)</td>
<td>Mutations in exon 11 of LMNA and/or homozygous or compound heterozygous mutations in ZMPSTE24. These result in the formation of permanently farnesylated pro-lamin A.</td>
<td>Loss of fat tissue, tight skin, pulmonary hypoplasia, early lethality.</td>
</tr>
<tr>
<td>Charcot–Marie–Tooth disease, type 2B1</td>
<td>Autosomal recessive missense mutations in the lamin A rod domain that may affect lamin assembly.</td>
<td>Weakness and areflexia of lower limbs.</td>
</tr>
<tr>
<td>Generalized lipodystrophy</td>
<td>Autosomal dominant mutations 110T and heterozygous substitution in exon 1 c.29C→T, in LMNA with unknown effects on lamin A.</td>
<td>Lipodystrophy or lipatrophy, may include diabetes and a progeroid phenotype.</td>
</tr>
</tbody>
</table>

---

**Lamin B**

**Lamin A**

---

![Diagram](image)

- **HGPS**
- **LMNA**
- **C-term cleavage**
- **ZMPSTE24**

---

**Legend**

- Adipose
- Cardiac
- Skeletal muscle
- Premature aging
- 

---

**Diagram Notes**

- FT
- CaaX
- PREX2B
- ZMPSTE24
- MCT8
- C-cholesterol
Histone H1 participe au “packing” du nucléosome.
Chromatin Remodeling at DNA Double-Strand Breaks

Brendan D. Price and Alan D. D’Andrea

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

DNA strand break repair and neurodegeneration
Stuart L. Rulten*, Keith W. Caldecott**

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 S3BP1 DSB-repair proteins.
P = phosphorylation, Ub = ubiquitination, MRN = mre11-rad50-nbs1 complex.
miR-9 represses lamin A but not lamin C
Abnormal development of the cerebral cortex and cerebellum in the setting of lamin B2 deficiency

Coffine L, Chang SY, Nobumori C, Tu Y, Farber BA, Toth JM, Fong LG, Young SG

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

E8.5 Het
E11.5 Het
E16.5 Het
P0 Het
The nuclear lamins: flexibility in function

Brian Burke and Colin L. Stewart

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. Upregulation of lamin B1 expression seems to be driven by reactive oxygen species (ROS) generation. 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. In this case, ROS generation seems to inhibit the decline in lamin B1 levels. 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.
The nuclear lamins: flexibility in function

Brian Burke and Colin L. Stewart

NATURE REVIEWS | MOLECULAR CELL BIOLOGY
VOLUME 14 | JANUARY 2013
Lamins as mediators of oxidative stress

Tom Sieprath¹, Rabih Darwiche², Winnok H. De Vos²

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

LAMINS AS NUCLEAR ROS-SINK

transient oxidative stress

chronic oxidative stress

acutely oxidative stress

AQUIRED LAMINA DYSFUNCTION

Genetic mutations in LMNA, LMNB1, ZMPSTE24

INNATE LAMINA DYSFUNCTION

Chemicals (e.g. HIV-PIs), oxidative damage

PERTURBED DOCKING

A. Transcription factor sequestration

B. Nuclear shielding

PERTURBED COMPARTMENTALISATION

MITOCHONDRIAL DYSFUNCTION

OXIDATIVE STRESS

Senescence

Telomere shortening
Persistent DNA damage
Protein oxidation

Altered gene expression
Altered distribution of pro- and antioxidants

Nuclear envelope
Nuclear lamina
Reversibly oxidized lamina
Irreversibly oxidized lamina
Nuclear pore complex
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, Gabriela L. Otte, et al.

Genes Dev. 2013 27: 1797-1799 originally published online August 9, 2013
Access the most recent version at doi:10.1101/gad.229834.113
Lamin B1 depletion in senescent cells triggers large-scale changes in gene expression and the chromatin landscape

Parisha P. Shah, Greg Donahue, Gabrieli 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.229834.113
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 dx.doi.org/10.1101/gad.223834.113

A

[Image showing Western blot analysis for lamin B1, CTCF, SA1, Lap2, and GAPDH in proliferating and senescent cells.

B

[Graph showing lamin B1/GAPDH levels across different conditions indicated by bars with error bars.

C

[Image showing Western blot analysis for lamin B1 and GAPDH with bands corresponding to scrambled, shRNA 1, and shRNA 2.

D

[Graph showing population doubling over time with different cell lines and conditions.

E

[Graph showing p16 expression levels across different conditions.

F

[Graph showing percent Annexin V-positive and β-galactosidase-positive cells across different conditions.

G

[Image showing Western blot analysis for lamin B1 and GAPDH for cells in different conditions.

H

[Image showing Western blot analysis for H3 for cells in different conditions.

I

[Bar graph showing H3K4me3 and H3K27me3 across genes in Chr7 and Chr6.

J

[Bar graph showing H3K4me3 and H3K27me3 across genes in Chr6.

K

[Bar graph showing H3K27me3 across genes in Chr2.

Legends:

WT 1
WT 2
EZH2 KD
LMNB1 KD
Empty plKO
Scrambled

PD60
PD70
PD78
PD80 (Sen)

H3K4me3 Mesa: Chr7
Scrambled Control
LMNB1 KD

H3K27me3 Mesa: Chr6

H3K27me3 Mesa: Chr2
Embryonic Postnatal

A

B

C

D

MEF

Aspn
Col1a1
Col12a1
Comp
El1
Fmod
Matn3
Ogn
Omd
Prb4
Thbs4

A

MAF

-1.219
-1.884
-2.091
-0.906
-0.860
-0.854
-0.851
-0.851
-0.851

-0.576
-0.786
-0.804
-0.804
-0.804
-0.804
-0.804
-0.804
-0.804

-0.0061
-0.083
-0.082
-0.073
-0.069
-0.066
-0.064
-0.064
-0.064

0.049
0.061
0.154
0.133
0.069
0.031
0.069
0.069
0.069

0
0
0
0
0
0
0
0
0
Functional Coupling between the Extracellular Matrix and Nuclear Lamina by Wnt Signaling in Progeria

Developmental Cell 19, 413–425, September 14, 2010 ©2010 Elsevier Inc. 413

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 Δ9MAF specific ECM components or with FTIs is shown in Figures S3A and S3B.
**Developmental Cell**

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

Bryan T. MacDonald, Keiko Tamai, and Xi He

---

**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

Developmental Cell 19, 413–425, September 14, 2010 ©2010 Elsevier Inc. 413

(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 progeria patients (Cornell AAG11498, AG030297). (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.