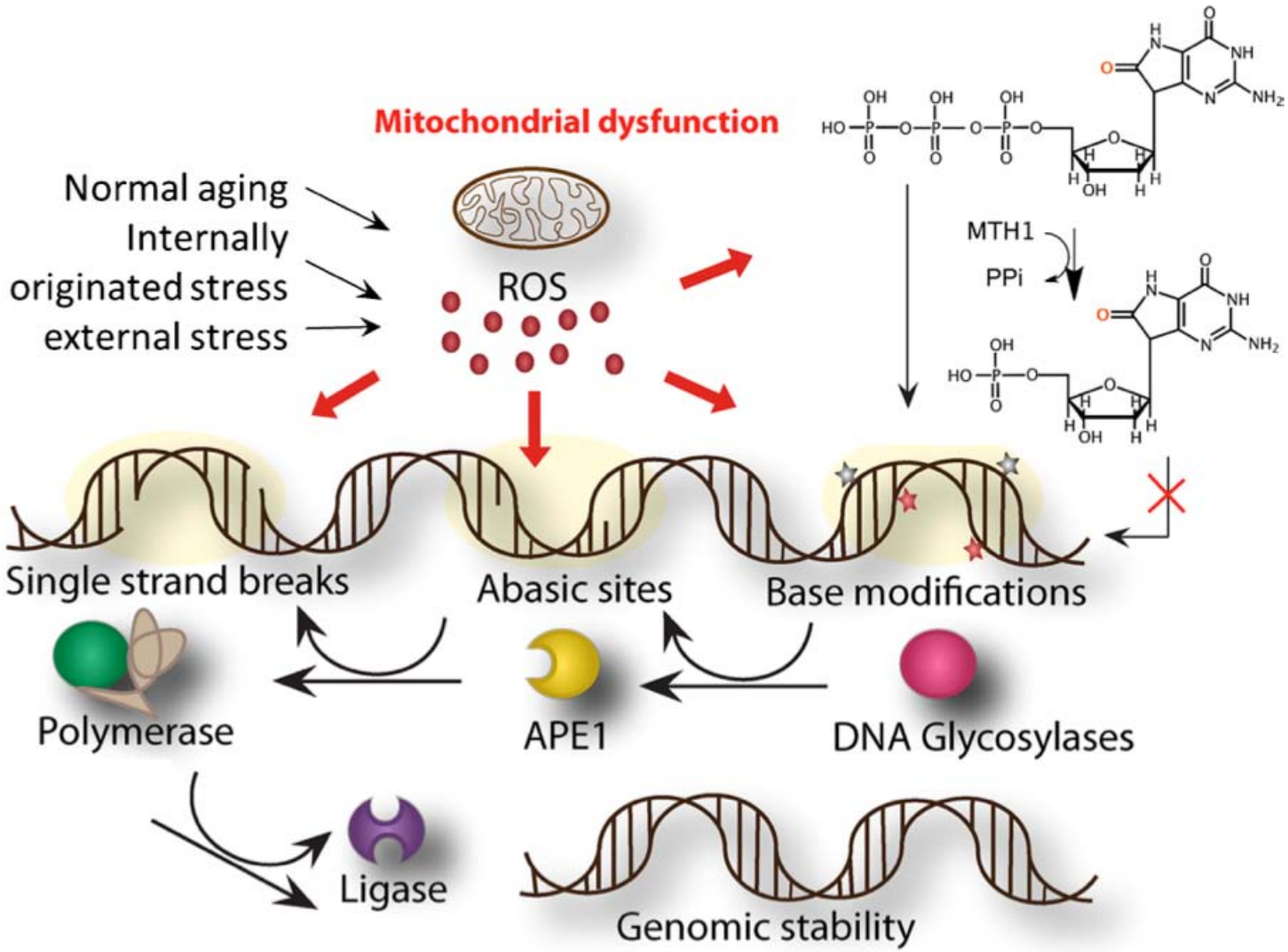
Cours du 14-10-2013

Longévité cérébrale

The role of DNA repair in brain related disease pathology

Chandrika Canugovi[a], Magdalena Misiak[a,b], Leslie K. Ferrarelli[a], Deborah L. Croteau[a], Vilhelm A. Bohr[a,*]

DNA Repair 12 (2013) 578–587

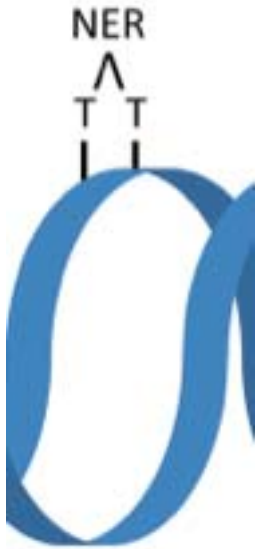


Oxidative damage repair of ROS-induced DNA damage in normal aging and neurological diseases. Amyloid beta precursor protein (AβPP) aggregates, α-synuc ts and ischemic reperfusion can cause mitochondrial dysfunction and increase cellular ROS levels. ROS damages DNA and generates various lesions including l cations, abasic sites and strand breaks. BER proteins repair these three varieties of damages in DNA. The multiple stages of BER are depicted. The base modificat eotide pools significantly contribute to the oxidative lesions in DNA. MTH1 converts oxidatively damaged dGTP into dGMP, which cannot be incorporated into l synthesis.

DNA repair mechanisms in dividing and non-dividing cells

Teruaki Iyama, David M. Wilson III*

DNA Repair 12 (2013) 620–636



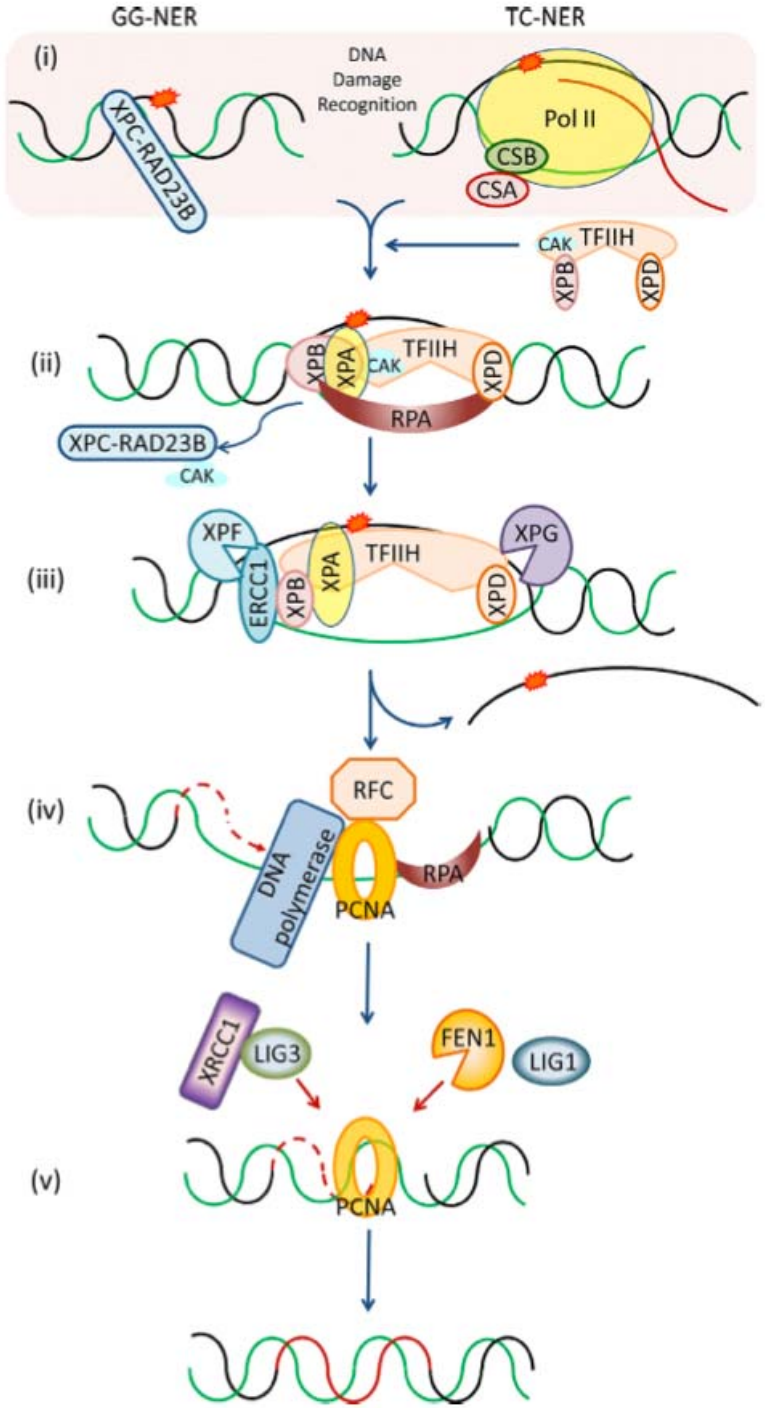


Fig. 2. Nucleotide excision repair pathways. Two subpathways of mammalian NER: GG-NER and TC-NER. (i) XPC-RAD23B recognizes DNA damage-induced structural change as the initiation step of GG-NER. TC-NER is initiated by stalling of an elongating RNAP at a blocking lesion on the transcribed strand within an active gene. After these initial recognition steps, GG-NER and TC-NER pathways involve many of the same protein components. (ii) Following recognition, the TFIIH complex is recruited. Through the activity of the helicase subunits, XPB and XPD, TFIIH promotes opening of the DNA duplex around the lesion, facilitating recruitment of XPA and RPA. (iii) The XPF–ERCC1 complex is recruited to the lesion via a direct interaction with XPA, while XPG is specifically engaged through an interaction with TFIIH. The two endonucleases, XPF–ERCC1 and XPG, are responsible for carrying out incision 5′ and 3′, respectively, to the DNA damage. (iv) After dual incision and removal of the damage-containing oligonucleotide fragment, a DNA polymerase carries out gap-filling repair synthesis in cooperation with RFC and PCNA. (v) Finally, the nick is sealed by either XRCC1–LIG3α or a FEN1–LIG1 complex. CAK, the cyclin-dependent kinase (CDK)-activating kinase; GG-NER, global genome-NER; RFC, replication factor C; RPA, replication protein A; TC-NER, transcription-coupled NER; TFIIH, transcription factor II H.

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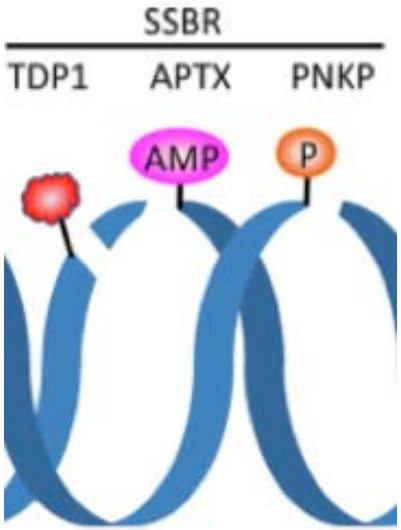
DNA strand break repair and neurodegeneration

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

DNA Repair 12 (2013) 558–567



TDP1: tyrosil-DNA phosphodiesterase
APTX: aprataxin
PNKP: polynucleotide kinase 3'-phosphatase

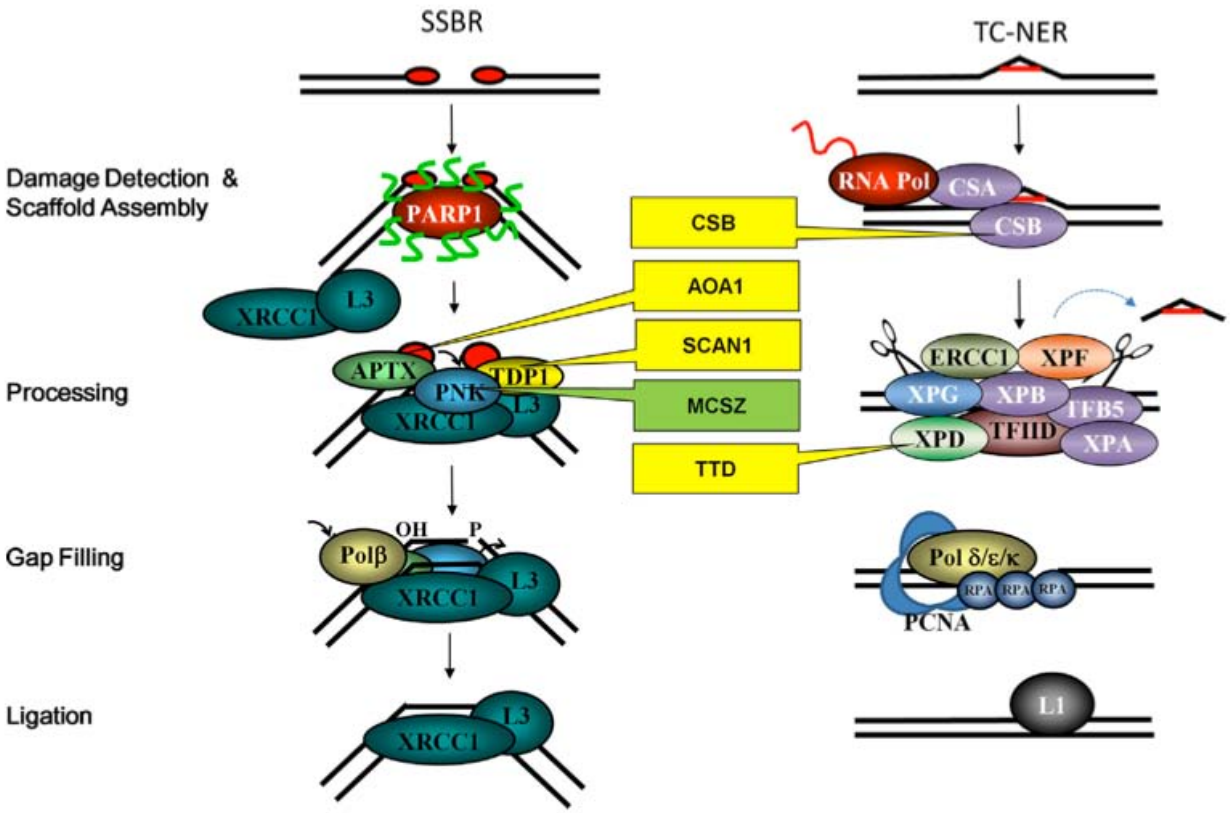
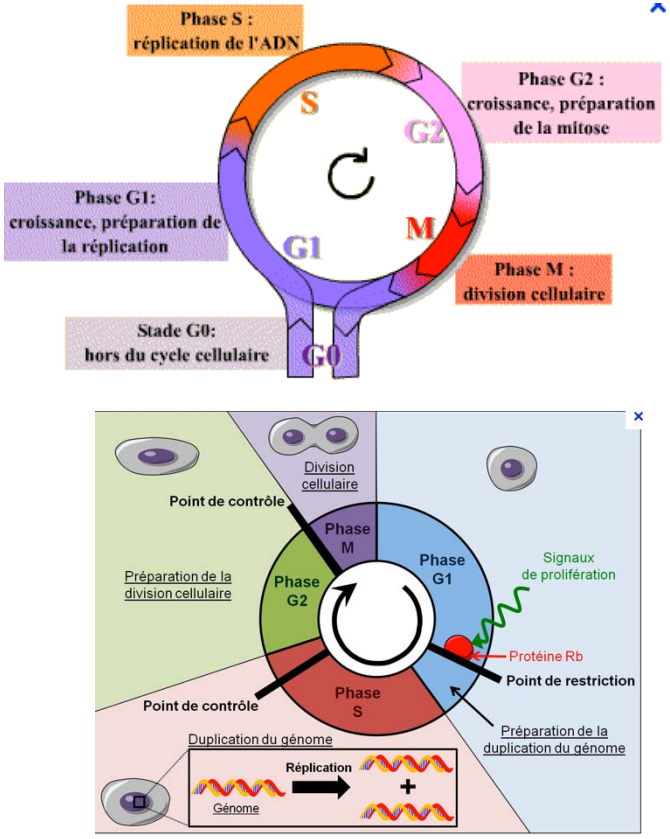


Fig. 4. Repair of single stranded lesions. Figure shows a simplified model for single strand break repair (SSBR) and transcription-coupled nucleotide excision repair (TC-NER). The green box shows a microcephaly (MCSZ) and yellow boxes show ataxias resulting from defects in the indicated proteins: Cockayne Syndrome, type B (CSB), ataxia with oculomotor apraxia 1 (AOA1), spinocerebellar ataxia with axonal neuropathy (SCAN1) and trichothiodystrophy (TTD). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

DNA strand break repair and neurodegeneration

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

DNA Repair 12 (2013) 558–567



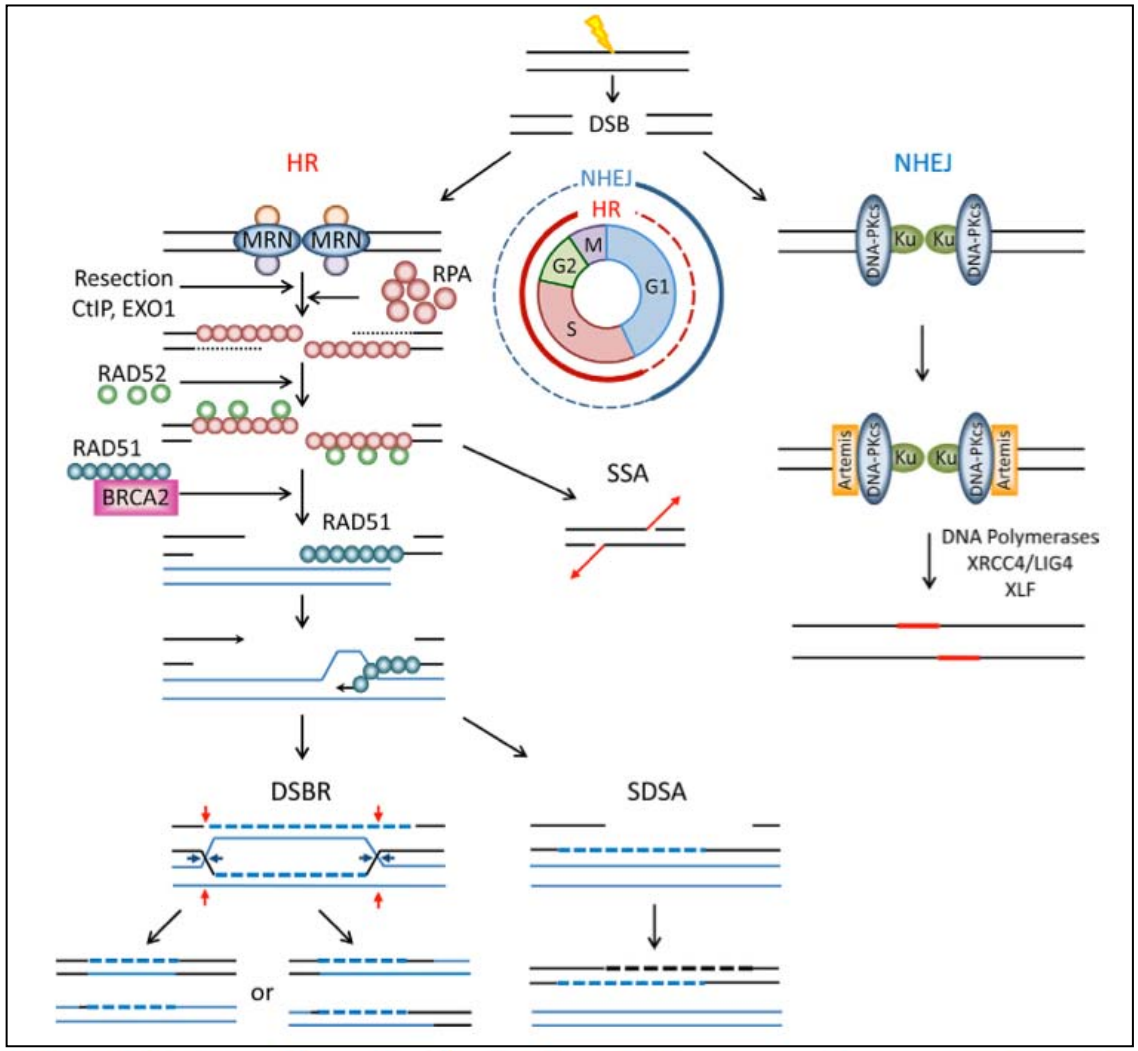
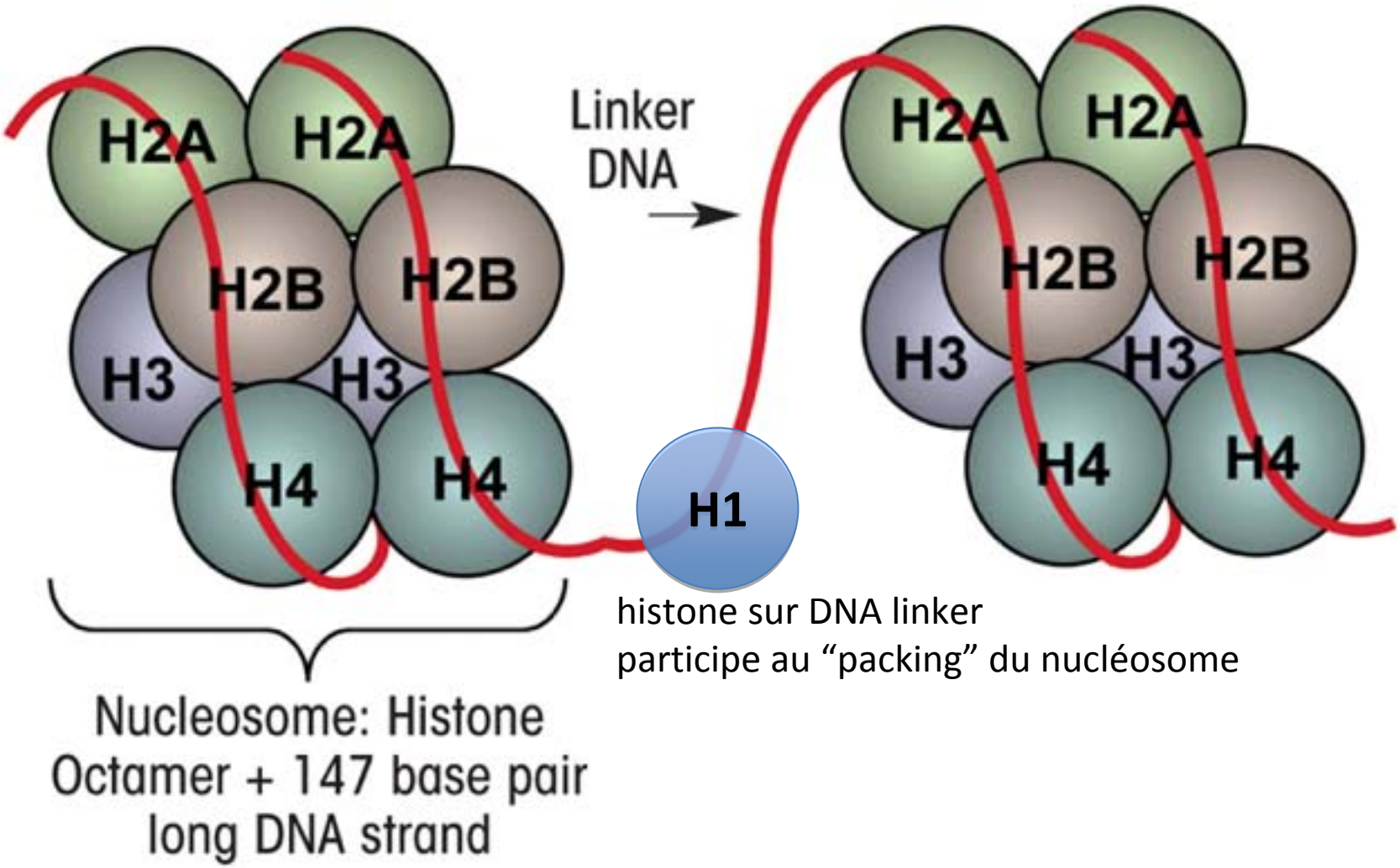


Fig. 4. Recombination pathways. DSBR is divided into two major pathways: HR and NHEJ. HR operates in dividing cells and in S phase, whereas NHEJ can function in both dividing and non-dividing cells and independently of cell cycle. HR has been proposed to be initiated by recognition of the DSB by the 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



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,*]

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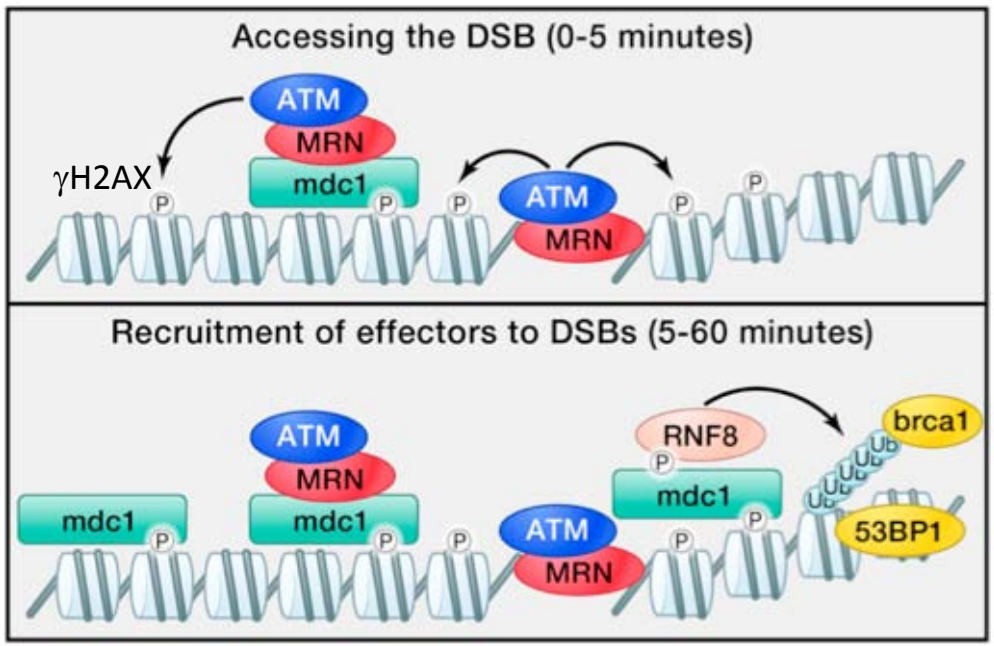

Figure 1. The Mechanism of DSB Repair

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.

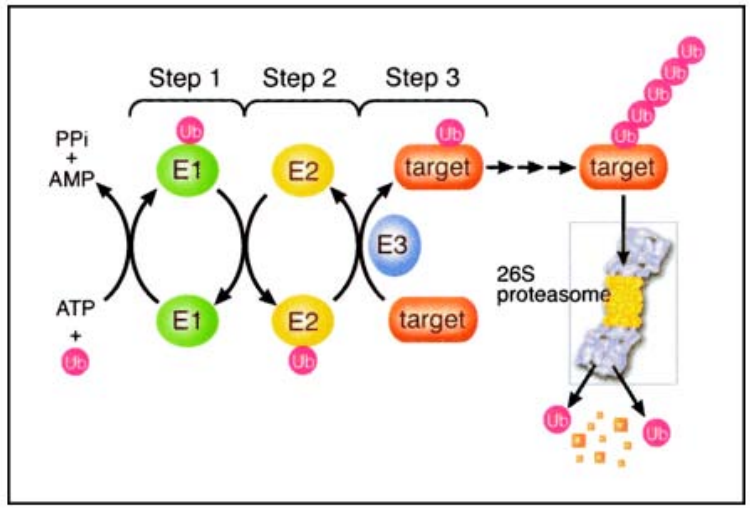

Fig 1.

The ubiquitin-proteasome pathway. Proteins marked with a polyubiquitin chain by the E1-E2-E3 enzymatic cascade are targeted for degradation by the proteasome. A ubiquitin-activating enzyme (E1) binds ubiquitin in an adenosine triphosphate (ATP) –dependent step. Ubiquitin is then transferred to a ubiquitin-conjugating enzyme (E2). A ubiquitin ligase (E3) helps transfer ubiquitin to the target substrate. PPI, pyrophosphate; AMP, adenosine monophosphate; Ub, ubiquitin. (Figure and legend adapted[30] and used by permission from Elsevier.)

DNA strand break repair and neurodegeneration

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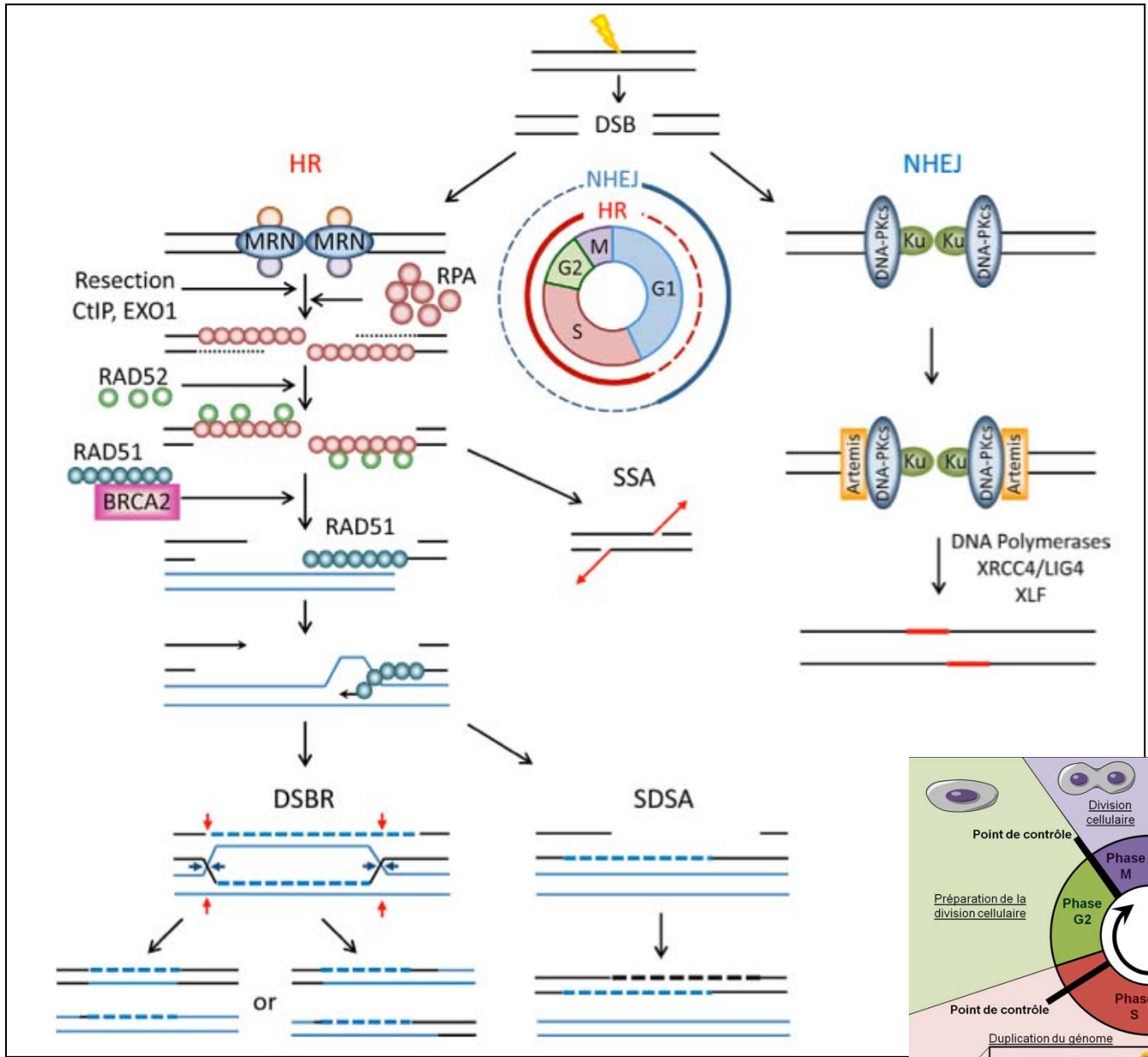
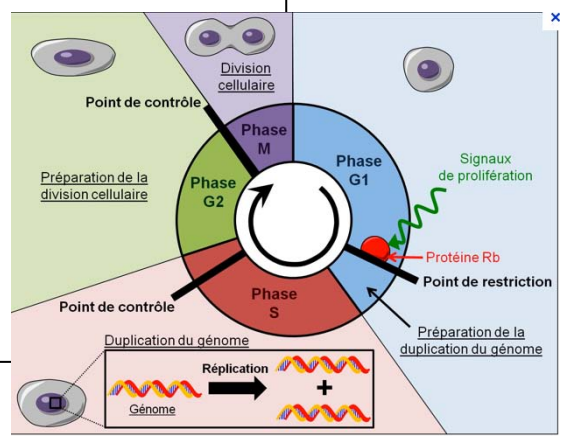
DNA Repair 12 (2013) 558–567





Chromatin Remodeling at DNA Double-Strand Breaks

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

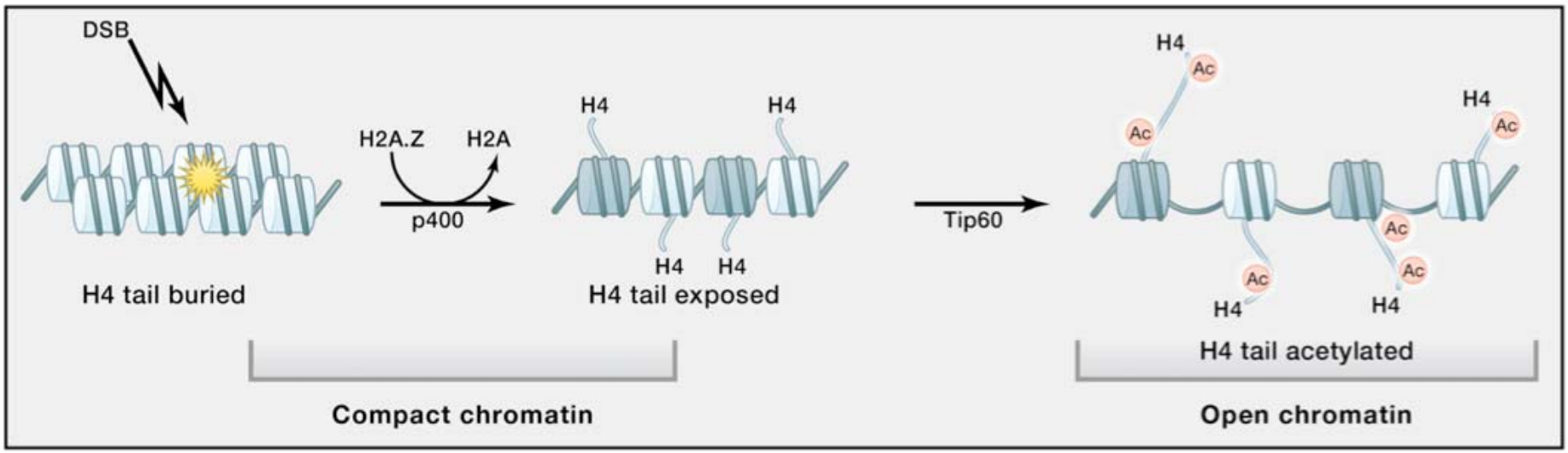
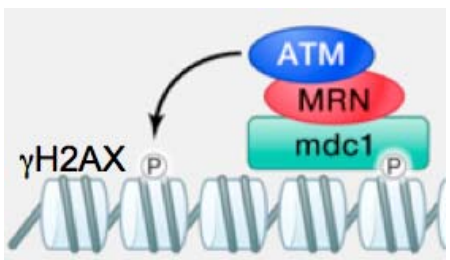


Figure 2. H2A.Z Exchange Drives H4 Acetylation

Exchange of H2A for H2A.Z alters interaction between the N-terminal tail of H4 and adjacent nucleosomes, exposing the tail to acetylation by Tip60. The combination of H2A.Z exchange and H4 acetylation functions to shift chromatin into the open, relaxed conformation required for DSB repair. H4 = histone H4 tail, Ac = acetylation.

? plutôt le contraire ?



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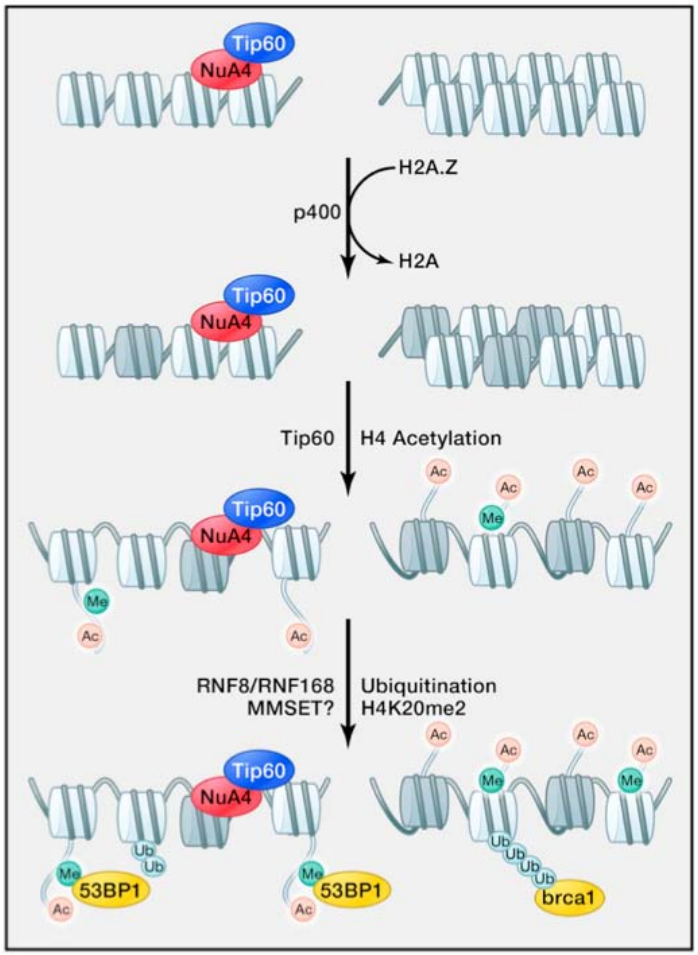
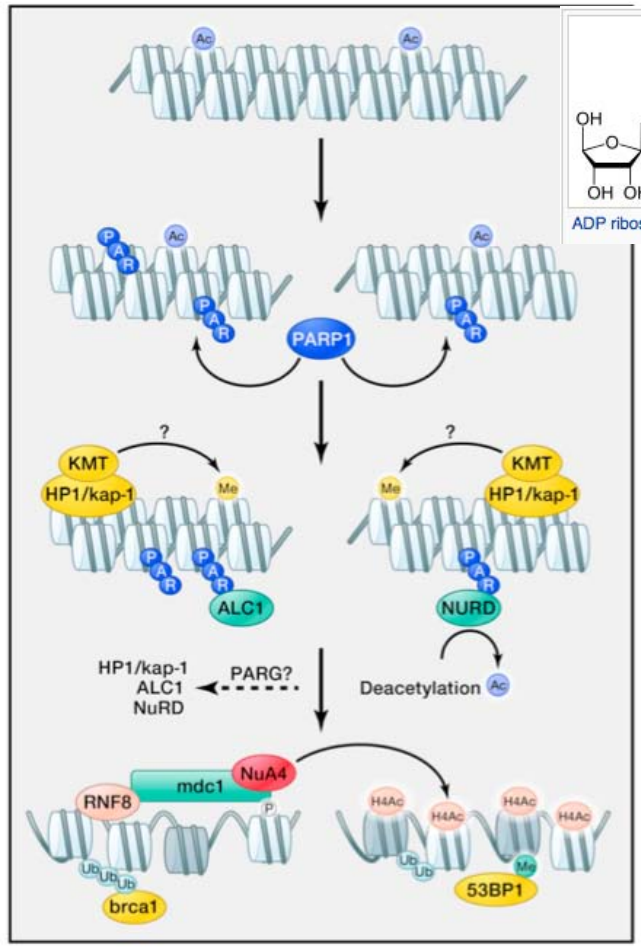


Figure 3. H2A.Z Exchange Drives Chromatin Changes that Direct Chromatin Modification at DSBs

H2A.Z exchange promotes H4 acetylation by Tip60, which in turn directs ubiquitination of the chromatin by the RNF8/RNF168 ubiquitin ligases. 53BP1 is then recruited to chromatin through interaction with H4K20me2. 53BP1 may utilize pre-existing H4K20me2 or require de novo methylation by MMSET. Whether ubiquitination promotes access to H4K20me2 is not yet known. Association of NuA4-Tip60 with mdc1 omitted for clarity. P = phosphorylation, Ac = H4 acetylation, Ub = ubiquitination, Me = H4K20me2.



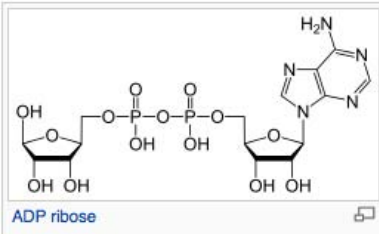


Figure 4. Creating Access to DSBs

Proposed chronological sequence of steps in remodeling of a DSB. Initial PARylation by PARP1 leads to rapid recruitment of NuRD and ALC1 (through interaction with PAR) and kap-1/HP1 complexes (possibly through interaction with PAR). Deacetylation of histones (including H2A, H3, and H4) by NuRD and proposed H3K9 methylation (by HP1/kap1-associated lysine methyltransferases [KMTs] including suv39h1 and G9a) create a temporary repressive chromatin structure with low histone acetylation and high density of H3K9me3. Subsequently, the HP1/kap1, ALC1, and NuRD complexes are rapidly released from the chromatin, potentially through dePARylation by PARG. Phosphorylation of γH2AX then recruits NuA4-Tip60, promoting the ordered remodeling of the chromatin through H2A.Z exchange, acetylation of histone H4 (H4Ac), chromatin ubiquitination, and modulation of H4K20me2. This creates a common chromatin template for DSB repair by either NHEJ- or HR-mediated repair.

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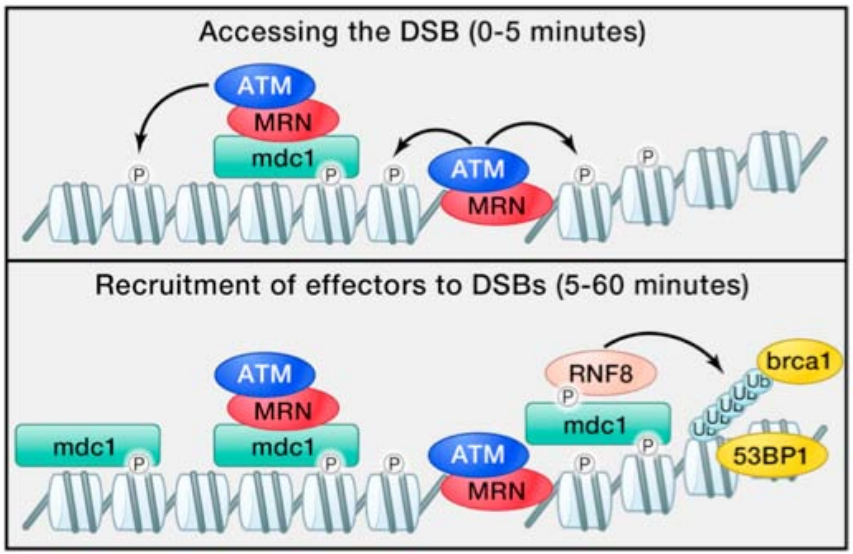

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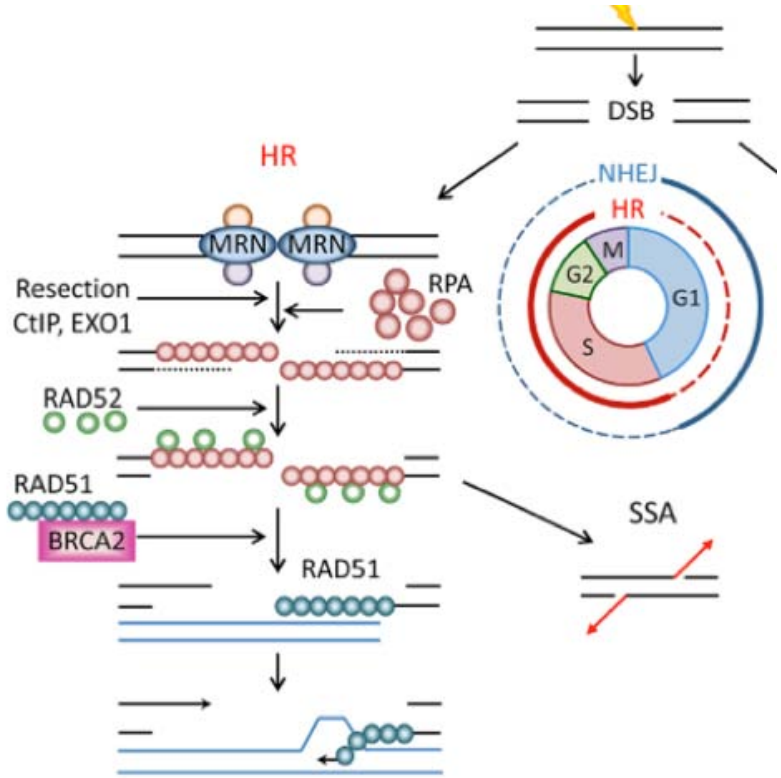
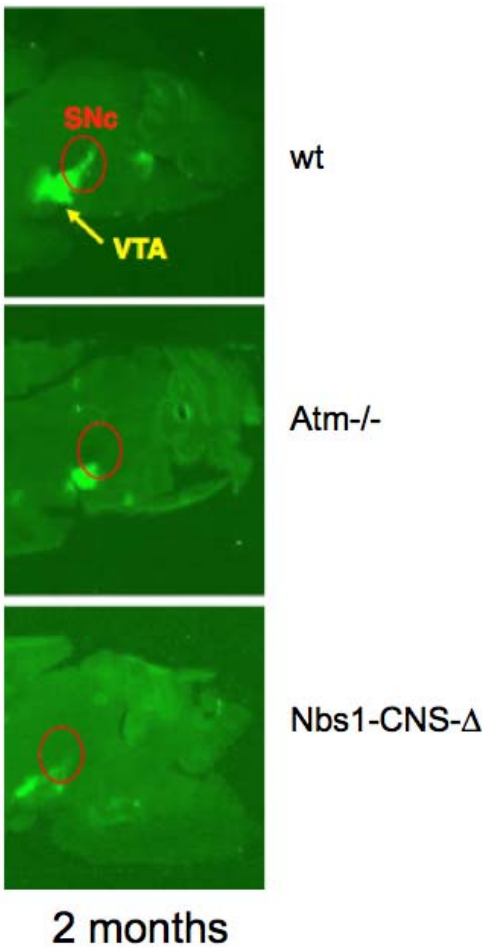
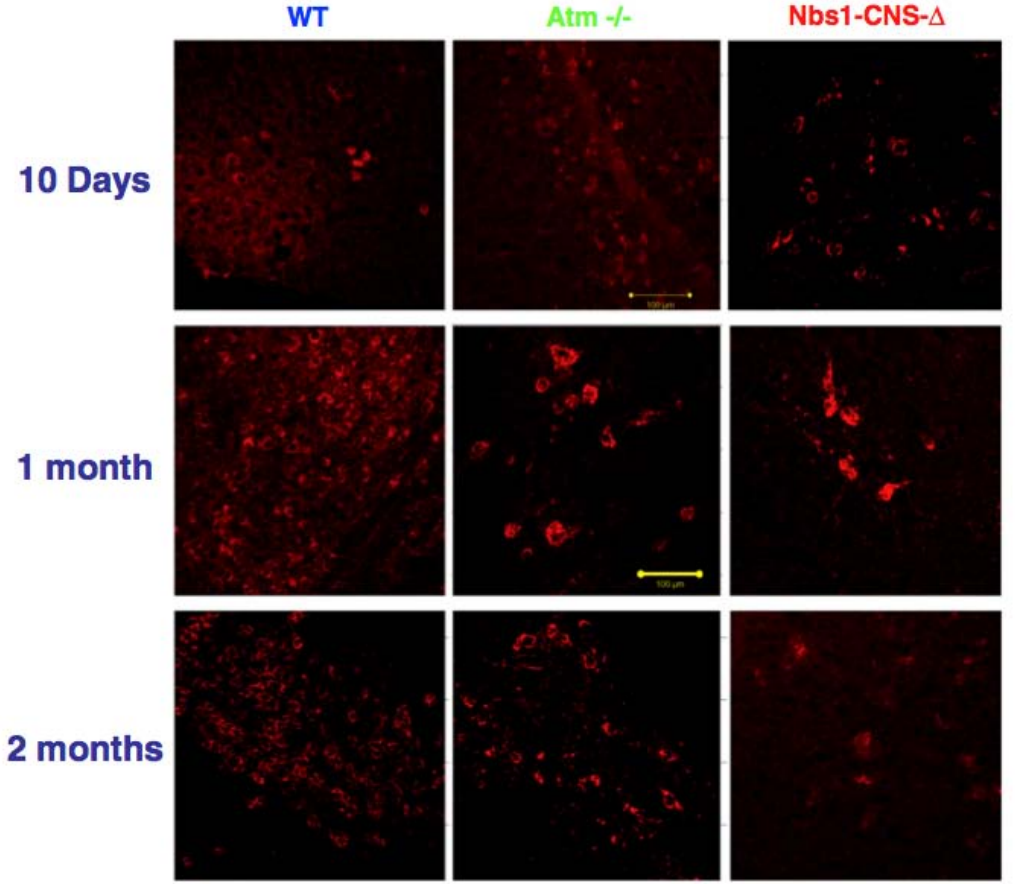


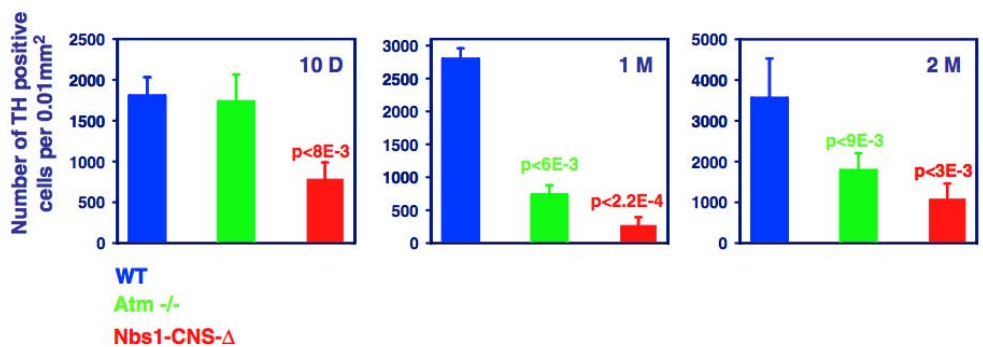
Malfunctioning DNA Damage Response (DDR) Leads to the Degeneration of Nigro-Striatal Pathway in Mouse Brain

Michal Kirshner · Ronit Galron · Dan Frenkel · Gil Mandelbaum · Yosef Shiloh · Zhao-Qi Wang · Ari Barzilai

J Mol Neurosci
DOI 10.1007/s12031-011-9643-y







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

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

Roderick J. O'Sullivan and Jan Karlseder

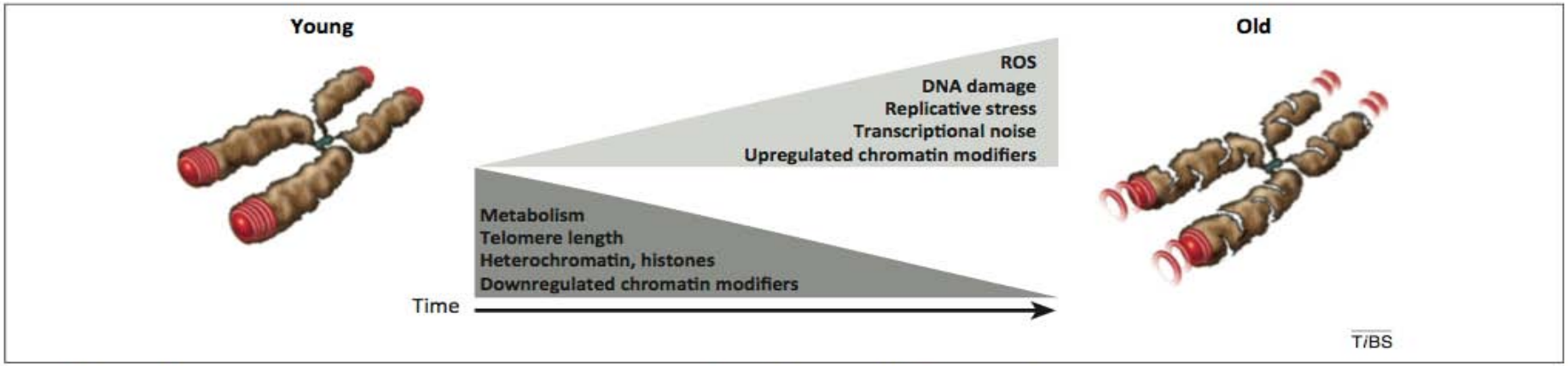
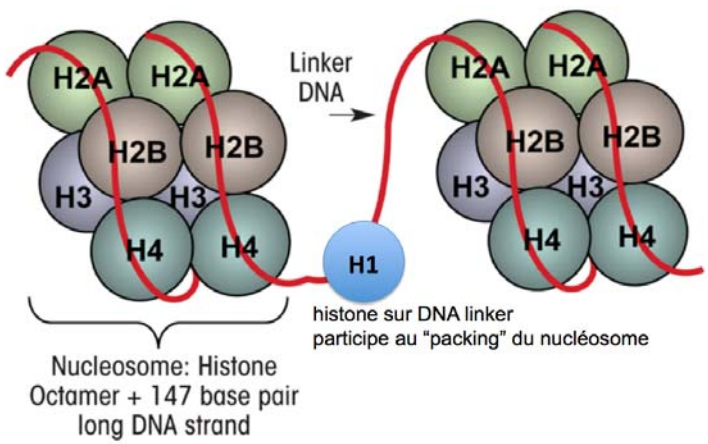


Figure 1. Aging is due to an increased disequilibrium in cellular homeostasis. The decline in metabolic rates and telomere shortening over time can contribute to structural and gene expression changes that are associated with aging. By contrast, chronic exposure to reactive oxygen species (ROS), DNA damage, and replicative stress can cooperatively cause elevated stochastic transcriptional noise. Structural changes in chromatin and the regulation of chromatin modifiers might be common denominators that underlie how these factors affect chromosomal stability and the cellular processes that drive the aging process.

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



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

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Table 1. Chromatin changes correlated with aging

Histone variant[a]	Change with age	Factors involved	Function	Organism[d]	Aging regimen
H3					
- H3.1, H3.2	down	SLBP, ASF1	Replication-coupled chromatin assembly	Hs, Sc	Rep Sen, Chron
- H3.3	up	HIRA	Transcription-coupled chromatin assembly	Hs	Rep Sen
H4	down	SLBP, ASF1	Replication-coupled chromatin assembly	Hs	Rep Sen, Chron
H2A					
- H2A.1	down	SWI, SNF	Chromatin assembly	Hs, Sc	Rep Sen
- H2A.2	up	SWI, SNF	Chromatin assembly	Hs	Rep Sen
- γH2AX	up	ATM, ATR	DDR Signaling	Hs, Mus	Rep Sen, OIS
Modification[b]	**Change with age**	**Factors involved[c]**	**Function**	**Organism**	**Aging regimen**
- H3K4me2/3	down	ASH-2, MLL-1 (KMT2A), WDR-5	Transcriptional activation	C.ele	Chron
- H3K9ac	up	TIP60 (KAT5), SIRT6?	Transcriptional activation	Hs, Mus	Rep Sen, Chron, HGPS
- H3K9me3	down up	SUV39H1/H2 (KMT1A/KMT1B), HP1α SUV39H1/H2 (KMT1A/KMT1B), HP1γ	Heterochromatin formation Transcription regulation/ DDR suppression	Hs, Dm Hs	Rep Sen, Chron, HGPS OIS
- H3K27me3	down	EZH2 (KMT6), JMJD3 (KDM6B), UTX-1 (KDM6A)	Transcriptional regulation	Hs, C.ele	OIS, Chron, CR
- H3K56ac	down	P300/CBP (KAT2A), HDAC1, SIRT2	DNA replication/DNA damage/transcription	Hs, Sc	Rep Sen, Chron
- H4K5ac	down	P300/CBP (KAT2A), SATB-1	Transcriptional activation	C.ele	Chron, CR
- H4K12ac	down	MYST4 (KAT6B), GCN5 (KAT2A), HDAC1	Transcriptional activation	Mus	Chron
- H4K16ac	up down	SAS2 (KAT8), SIR2 hMOF (KAT8), SIRT2	Telomere silencing/rDNA silencing Chromatin compaction (Mitosis/transcription)	Sc. Hs, Mus	Chron Rep Sen, Chron, HGPS
- H4K20me2	up	SUV420H1/H2 (KMT5A/KMT5B)	DNA damage/DNA replication	Hs	Rep Sen, Chron
- H4K20me3	down	SUV420H1/H2 (KMT5A/KMT5B)	Heterochromatin formation	Hs	Rep Sen, Chron

Replicative Senescence, Chronological aging

Oncogne-induced senescence

Hutchinson-Gilford Progeria Syndrom

Caloric Restriction

SIRT6 Recruits SNF2H to DNA Break Sites, Preventing Genomic Instability through Chromatin Remodeling

Debra Toiber,[1] Fabian Erdel,[2] Karim Bouazoune,[3] Dafne M. Silberman,[1,4] Lei Zhong,[1] Peter Mulligan,[1,5] Carlos Sebastian,[1] Claudia Cosentino,[1] Barbara Martinez-Pastor,[1] Sofia Giacosa,[1] Agustina D'Urso,[1,6] Anders M. Näär,[1,5] Robert Kingston,[3] Karsten Rippe,[2] and Raul Mostoslavsky[1,*]

454 Molecular Cell *51*, 454–468, August 22, 2013 ©2013 Elsevier Inc.

SUMMARY

DNA damage is linked to multiple human diseases, such as cancer, neurodegeneration, and aging. Little is known about the role of chromatin accessibility in DNA repair. Here, we find that the deacetylase sirtuin 6 (SIRT6) is one of the earliest factors recruited to double-strand breaks (DSBs). SIRT6 recruits the chromatin remodeler SNF2H to DSBs and focally deacetylates histone H3K56. Lack of SIRT6 and SNF2H impairs chromatin remodeling, increasing sensitivity to genotoxic damage and recruitment of downstream factors such as 53BP1 and breast cancer 1 (BRCA1). Remarkably, SIRT6-deficient mice exhibit lower levels of chromatin-associated SNF2H in specific tissues, a phenotype accompanied by DNA damage. We demonstrate that SIRT6 is critical for recruitment of a chromatin remodeler as an early step in the DNA damage response, indicating that proper unfolding of chromatin plays a rate-limiting role. We present a unique crosstalk between a histone modifier and a chromatin remodeler, regulating a coordinated response to prevent DNA damage.

The human LINE-1 retrotransposon creates DNA double-strand breaks

Gasior SL, Wakeman TP, Xu B, Deininger PL

Tulane Cancer Center and Department of Epidemiology, Tulane University Health Sciences Center, 1430 Tulane Ave., New Orleans, LA 70112, USA.

Long interspersed element-1 (L1) is an autonomous retroelement that is active in the human genome. The proposed mechanism of insertion for L1 suggests that cleavage of both strands of genomic DNA is required. We demonstrate that L1 expression leads to a high level of double-strand break (DSB) formation in DNA using immunolocalization of gamma-H2AX foci and the COMET assay. Similar to its role in mediating DSB repair in response to radiation, ATM is required for L1-induced gamma-H2AX foci and for L1 retrotransposition. This is the first characterization of a DNA repair response from expression of a non-long terminal repeat (non-LTR) retrotransposon in mammalian cells as well as the first demonstration that a host DNA repair gene is required for successful integration. Notably, the number of L1-induced DSBs is greater than the predicted numbers of successful insertions, suggesting a significant degree of inefficiency during the integration process. This result suggests that the endonuclease activity of endogenously expressed L1 elements could contribute to DSB formation in germ-line and somatic tissues.

J Mol Biol
2006 vol. 357 (5) pp. 1383-93

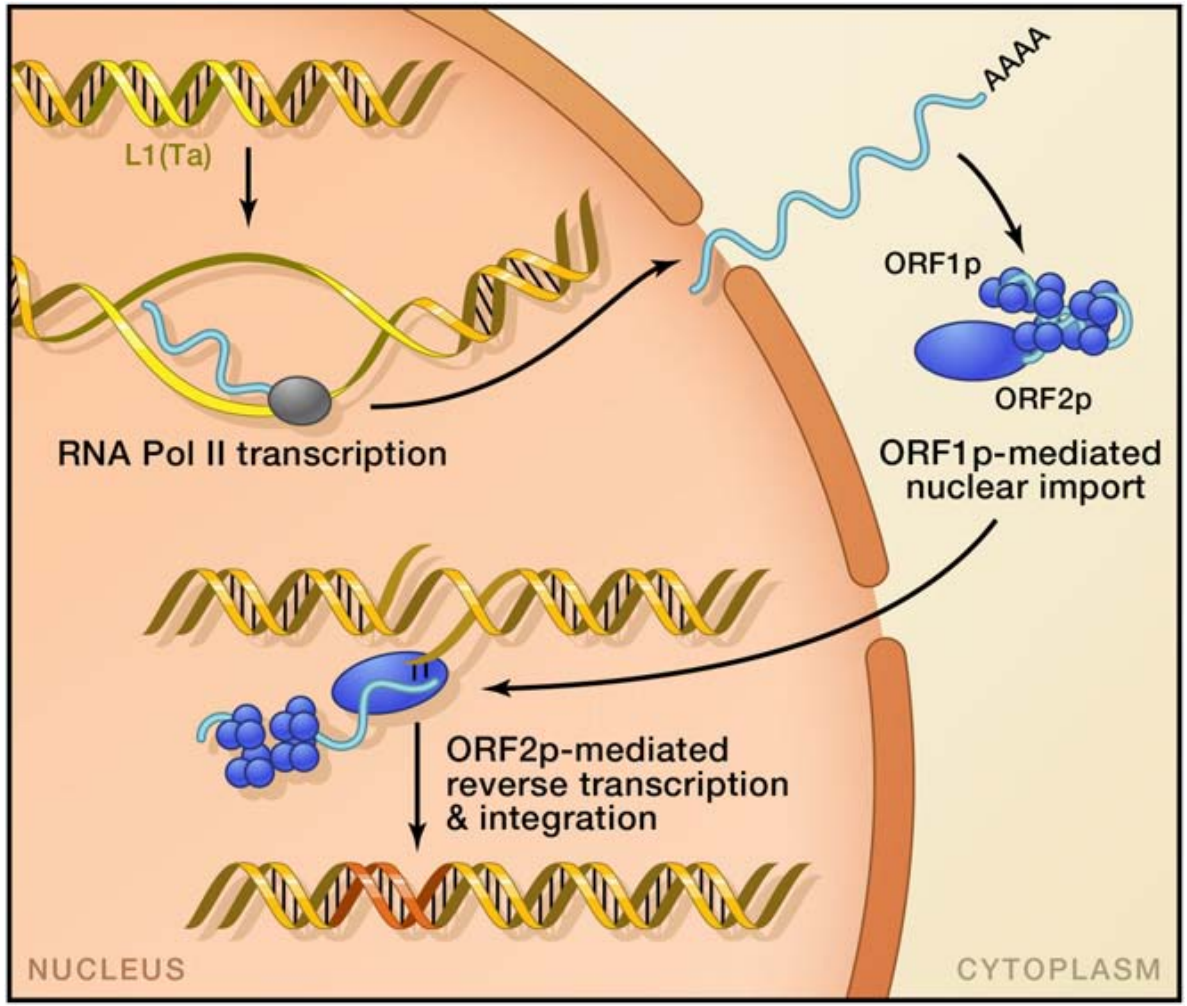
L1 mobile element expression causes multiple types of toxicity

Wallace NA, Belancio VP, Deininger PL

Tulane Cancer Center, SL66, and Department of Epidemiology, Tulane University Health Sciences Center, 1430 Tulane Ave., New Orleans, LA 70112, USA.

LINE-1 (L1) retrotransposons represent one of the most successful families of autonomous retroelements, accounting for at least 17% of the human genome. The expression of these elements can be deleterious to a cell. L1 expression has been shown to result in insertional mutagenesis, genomic deletions and rearrangements as well as double-strand DNA breaks. Also, L1 expression has been linked to the induction of apoptosis. These recent discoveries, in addition to correlations of L1 expression with cancer progression, prompted us to further characterize the effect of L1 expression on cellular viability. We show a marked decrease in the overall cellular vitality with expression of the L1 that was primarily dependent on the second open reading frame (ORF2). Both the endonuclease and reverse transcriptase domains of ORF2 can individually contribute to the deleterious effects of L1 expression. L1 decreases cellular viability both by the previously reported apoptotic signaling, but also by inducing a senescence-like state.

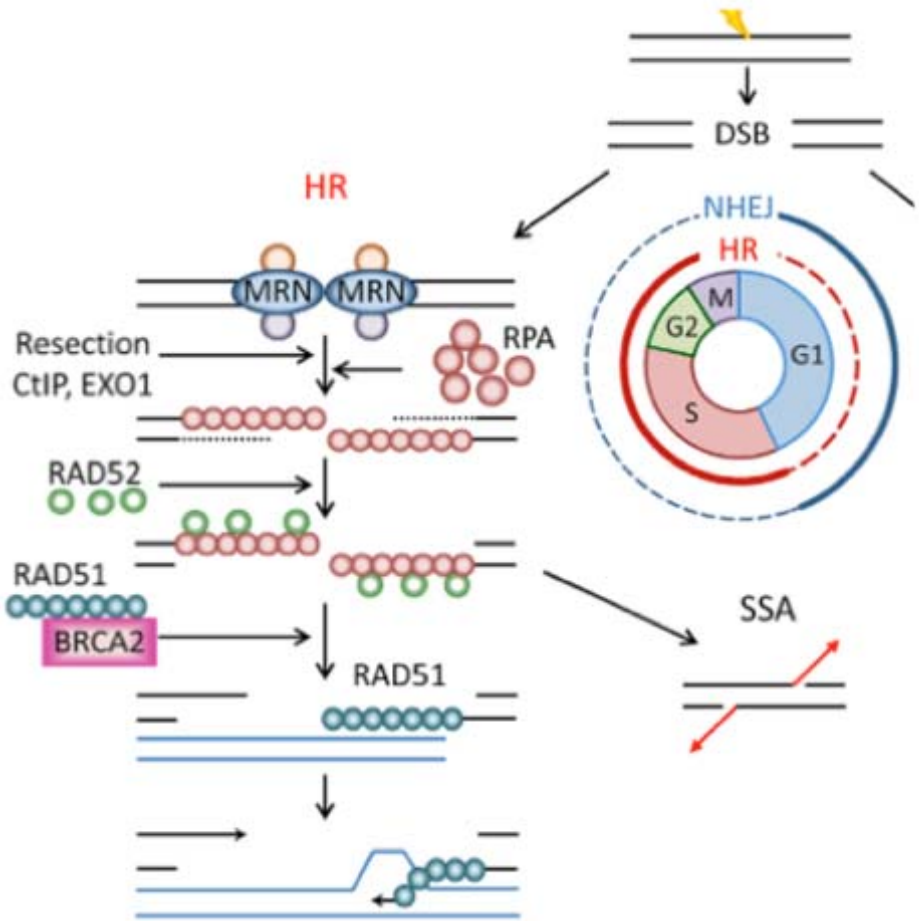
Gene
2008 vol. 419 (1-2) pp. 75-81



DNA strand break repair and neurodegeneration

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

DNA Repair 12 (2013) 558–567



Nucleosome remodelers in double-strand break repair

Andrew Seeber[1,2,4], Michael Hauer[1,3,4] and Susan M Gasser[1,2]

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