Activity DEPendent Transposition (ADEPT) and the Aging Brain

Andrew G. Newman[1], Paraskevi Bessa[1], V. Tarabykin[1,2], Prim B. Singh[1,3]*

[1] Institute for Cell and Neurobiology, Charité Universitätsmedizin Berlin, Charitéplatz 1, 10117 Berlin, Germany;
[2] Lobachevsky State University of Nizhni Novgorod, Nizhni Novgorod, Russia;
[3] Department of Natural Sciences and Psychology, Liverpool John Moores University, UK.
* Corresponding e-mail: andrew.newman@charite.de

Abstract. Neurons adapt to stimuli through activity dependent changes to their transcriptome, a process mediated by immediate-early gene networks. Recent findings that transcriptional activation of neuronal immediate-early genes requires the formation of controlled DNA double-strand breaks (DSBs) has come as a surprise and has profound implications for neuronal function, especially in the aging brain. Here we review recent literature surrounding the phenomena of activity-dependent DNA DSBs in neurons and how this process may be exploited by transposable elements (TEs) in both naïve and aging neurons. We hypothesize the existence of Activity DEPendent Transposition (ADEPT), where neuronal excitation is able to induce genomic rearrangements through either *de novo* integration of TEs or by homology-directed recombination of TE-derived repetitive sequences. Epigenetic drift may cause the magnitude of ADEPT to increase with age, leading to genome instability, which we suggest presages most, if not all, neurodegenerative diseases.

Keywords: Neurodegeneration, DNA repair, Epigenetics, Transposable Elements, Activity DEPendent Transposition (ADEPT), Genomic Plasticity

Introduction

It is well established that sustained neuronal activity can cause permanent transcriptional changes by stimulating expression of neuronal early response genes (Morgan and Curran, 1988, 1989). Such activity coordinates an integrated transcriptional response that changes cellular metabolism, ion channel expression, protein trafficking (Kaushik et al., 2014), neurotransmitter release and surface receptor expression (reviewed in Pérez-Cadahía et al., 2011). The persistent activation of neurons coincides with an exceptionally high metabolic rate and a higher sensitivity to DNA damage. It is estimated that the brain can metabolize from 20-50% of the body's consumed oxygen, yet has a lower capacity to neutralize reactive oxygen species compared to other organs (Barzilai, 2007; Magistretti and Pellerin, 1996). Accordingly, several neurodegenerative diseases and premature aging phenotypes have been linked to DNA repair genes, such as the ATM gene (Ataxia-Telangiectasia disease; Ziv et al., 1997), the TDP1 gene (Spinocerebellar Ataxia disease; Takashima et al., 2002), and the NBS1 gene (Nijmegen breakage syndrome; Zhu et al., 2001). Indeed there is a growing consensus that many neurodegenerative diseases are likely to result from deficiencies in DNA repair (reviewed in Barzilai et al., 2016; Canugovi et al., 2013; Jeppesen et al., 2011; Lardenoije et al., 2015; Madabhushi et al., 2014; McKinnon, 2009; Reynolds and Stewart, 2013; Ribezzo et al., 2016).

Given the emerging link between neuronal DNA damage and neurodegenerative disease it was surprising that several mutually-supporting lines of *in vitro* and *in vivo* evidence have shown that neuronal activity itself can result in DNA double strand breaks (DSBs). Put another way, the generation of DSBs are part of normal neuronal physiology (Burma et al., 2001; Crowe et al., 2006, 2011; Kasof et al., 1995; Rogakou et al., 1998; Suberbielle et al., 2013). The mechanism(s) by which activity induces DSBs has recently been elucidated. DNA DSBs are induced specifically at the promoters of a subset of neuronal early response genes by Topoisomerase IIβ (TopoIIβ), which allows the promoter to come in contact with an upstream enhancer (Madabhushi et al., 2015). Underscoring the requirement for DNA DSBs for proper neuronal function, inhibition of TopoIIβ activity reduces transcription of early response genes (Madabhushi et al., 2015).

Here we review the work on activity-induced DNA double strand breaks and genomic mosaicism in the context of aging neurons. In particular, we focus on two different, but related, aspects by which neuronal mosaicism occur during normal development and age-related disease. First, we discuss how DSBs are exploited by TEs during neuronal development to generate neuronal mosaicism. Second, how age-related drift of epigenetic mechanisms involved in regulating the DSB repair pathways exacerbates the development of neurodegenerative diseases.

DNA Double Strand Break Repair Pathways in Neurons

Canonical DNA double strand break repair follows one of two distinct pathways (Figure 1). The first is the error-prone non-homologous end joining (NHEJ) pathway, which is active throughout the cell cycle. NHEJ is both the primary DNA repair pathway of post-mitotic neurons as well as being required for differentiation of neural stem cells into post-mitotic neurons (Gao et al., 1998). Briefly, NHEJ involves recognition of the DSB site by components of the MRE11-RAD50-NBS1 (MRN) complex (Kim et al., 2005)

 doi:10.20388/OMP.003.0034

followed by rapid binding of a Ku70-Ku80 heterodimer, which holds the broken DNA ends in close proximity and also inhibits their end resection. Recruitment of DNA-dependent protein kinase DNA-PKcs to the DSB in turn recruits and activates end processing effectors ARTEMIS PNKP and APLF. Following end preparation the DSB is ligated by the DNA ligase IV/XRCC4/XLF complex (reviewed in Dabin et al., 2016; Madabhushi et al., 2014; McKinnon, 2009). Most NHEJ blunt ligations result in substitutions, insertions, deletions and translocations (Lieber, 2010). However, DSBs generated by neuronal activity (activity-dependent DSBs) can be repaired error-free by the NHEJ pathway due largely to the local enrichment of TDP2 (tyrosyl DNA phosphodiesterase-2), which is thought to protect transcription from halted topoisomerase IIβ activity (Gómez-Herreros et al., 2014; Madabhushi et al., 2015).

The second canonical DNA DSB repair pathway is the homologous recombination (HR) pathway (Figure 1), which is largely error-free and has a crucial role in dividing and meiotic cells. Classically, HR-mediated repair is thought to be restricted to S and G2 phases of the cell cycle, i.e., to dividing cells, and is relevant to the neurogenic progenitors of the ventricular and sub-ventricular zones of the developing brain. In dividing cells, HR maintains DNA sequence fidelity by employing a sister chromatid as a template for repair at the DSB (Helleday et al., 2007). In mammals, HR repair again involves the MRN complex in DSB recognition followed by 5′ to 3′ nucleotide end resection by BRCA1 C-Terminal interacting protein (CtIP). Following end resection, the 3′ single stranded DNA becomes bound by replication protein A (RPA) and Rad51 recombinase, facilitating strand invasion and homology search whereby the sister chromatid acts as an error free template to the damaged site (Takeda et al., 2007).

Evidence for a non-canonical mode of homologous recombination repair has emerged in recent years, whereby cells are able to use an RNA template to repair

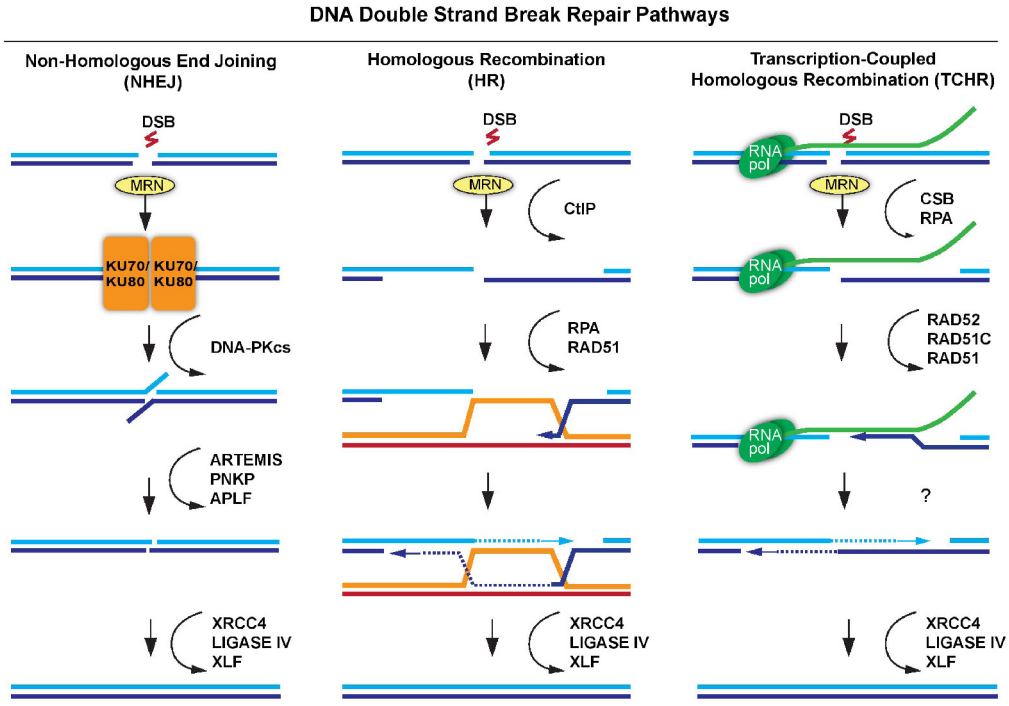

Figure 1. *Canonical DNA Double Strand Break Repair Pathways. Non-homologous End Joining (NHEJ) repair (**Left**) involves the recognition of the DSB by the MRE11-RAD50-NBS1 (MRN) (Kim et al., 2005) complex which facilitates recognition of DNA ends by the Ku70/Ku80 heterodimer. The Ku70/Ku80 heterodimer prevents end resection and hold DNA ends in close proximity. Next, the recruitment of DNA-dependent protein Kinase (DNA-PKcs) activates DNA end-processing effectors ARTEMIS, Polynucleotide kinase/phosphatase (PNKP) and Aprataxin and PNKP Like Factor (APLF). Processed DNA ends are then ligated by a DNA ligase IV complex containing X-Ray Repair Complementing Defective Repair In Chinese Hamster Cells 4 (XRCC4), and XRCC4-Like Factor (XLF, also known as Non-Homologous End Joining Factor 1 (NHEJ1)) (reviewed in Dabin et al., 2016; McKinnon, 2009). Homologous Recombination (HR) repair (**center**) involves the recognition of the DSB by the MRE11-RAD50-NBS1 (MRN) complex followed by end-resection mediated by BRCA1 C-Terminal interacting protein (CtIP) (Takeda et al., 2007). In dividing cells, 3′ single stranded DNA is bound by replication protein A (RPA) and Rad51 recombinase, which facilitate strand invasion and homology search of the sister chromatid (pictured) (Helleday et al., 2007). Following strand complementation, DNA ends are ligated by the XRCC4/XLF/DNA ligase IV complex. Transcription-Coupled Homologous Recombination (TCHR) repair (**right**). In G0/G1 cells, actively transcribed loci can also utilize HR repair by using RNA as a template. Following recognition of the MRN complex, TCHR repair is known to require the ATPase activity of Cockayne Syndrome B (CSB) followed by RPA loading to protect single stranded DNA. RNA-templated DNA repair then requires the loading of repair factors Rad51, Rad51C and Rad52/BRCA2, which utilize RNA as the template for DNA repair (Ohle et al., 2016; Wei et al., 2015, 2016a). Final end ligation of newly synthesized DNA is likely mediated by the same XRCC4/XLF/DNA ligase IV complex.*

a double strand break. While it has long been known that transposons can use RNA templates for DNA transcription (Baltimore, 1985), only recently has evidence emerged that host cells can make use of a similar mechanism. First observed in yeast (Keskin et al., 2014; Storici et al., 2007) and later in human (Shen et al., 2011; Wei et al., 2015) cells, DNA DSBs can be repaired using RNA as a template in cis or in trans. RNA-templated HR repair occurs in post-mitotic (non-dividing) cells, and is often the preferred mode of repair at actively transcribed loci (Ohle et al., 2016; Wei et al., 2015, 2016a) where it occurs in cis, termed here transcription-coupled homologous recombination (TCHR) repair. Transcription-coupled HR repair is still poorly understood. Following recognition by the MRN complex, TCHR is known to require the ATPase activity of the Cockayne Syndrome B (CSB) protein, which precedes loading of ssDNA-protective RPA and the repair factors RAD52 and RAD51C (Wei et al., 2015) (Figure 1). Recent work by (Ohle et al., 2016) has further elucidated that the presence of RNA-DNA hybrids is required for efficient DNA repair in yeast, as overexpression of RNAse H1 greatly diminishes efficiency and fidelity of DSB repair. While there is not yet evidence for TCHR repair in neurons, the existence of this pathway in other G0/G1 human cells sets a precedent of HR repair occurring in post-mitotic neurons.

Despite the fidelity of HR-mediated DNA DSB repair, there are cases when it can go awry. For example, errors in HR repair can occur when homologous sequences (such as repeats) flanking the DSB are allowed to anneal and recombine resulting in small deletions surrounding the DSB (Chen et al., 1997; Gardner et al., 1996). This can also occur between more distant ectopic locations in the genome (Pâques and Haber, 1999). Notably, it has been observed that unequal homologous recombination can occur between flanking long interspersed nuclear elements (LINEs) within a gene resulting in deletion of an entire exon (Burwinkel and Kilimann, 1998). Large scale LINE-LINE non-allelic homologous recombination has also been observed (Startek et al., 2015), the ramifications of which are discussed in the following section.

Transposable Elements in the Developing and Mature Brain

Transposable elements (TEs), also termed retrotransposons, are mobile genetic elements which have been estimated to comprise upwards of 40-50% of mouse (Chinwalla et al., 2002) and human (Venter et al., 2001) genomes. The majority of transposable elements are non-functional, as they are not under positive selection and accrue mutations over evolutionary time. Transposable elements are grouped into two categories; those containing a long terminal repeat (LTR) and those without (non-LTR) that are given in Figure 2. LTR containing transposons, typically called endogenous retroviruses (ERVs), result from past exogenous integration of retroviruses into the germ cell genome and comprise roughly 10% of mouse (Stocking and Kozak, 2008) and 8% of human (Cordaux and Batzer, 2009) genomes. Non-LTR transposable elements include LINEs, short interspersed nuclear elements (SINEs), and SINE variable-number tandem-repeat Alu SVA elements and collectively comprise ~35% of the mouse and human genomes (Friedli and Trono, 2015; Venter et al., 2001).

Despite the existence of substantial evidence for the reiterative exaptation of TEs as species-specific and even tissue-specific transcriptional enhancers (Elbarbary et al., 2016; Thompson et al., 2016), relatively few studies have examined the relationship between neuronal excitation and transposable elements. Here we coin a term Activity DEPendent Transposition, (abbreviated as ADEPT) which describes the genomic rearrangements caused by TEs upon neuronal activation. The arrangements are a result of either *de novo* integration of transposable elements or by homology-directed recombination of

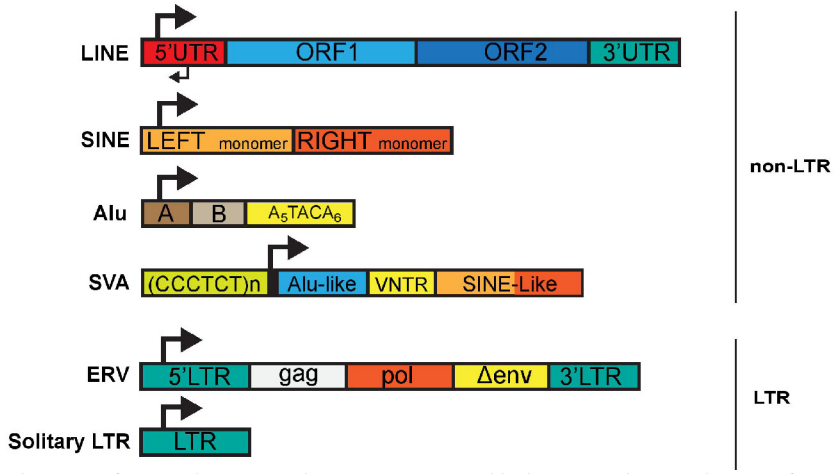

Figure 2. *Sequence architecture of mammalian LTR and Non-LTR transposable elements. Schematic diagram of non-LTR retrotransposons and LTR retrotransposons. Non-LTR transposons include Long INterspersed Elements (LINEs), Short INterspersed Elements (SINEs) such as Alu (primates) and SVA elements (primates). LTR retrotransposons are resultant of past exogenous viral integration and are comprised of 5′ and 3′ Long terminal repeats (LTRs) and retroviral ORFs gag, pol and a truncated or mutated env. Recombination between 5′ and 3′ LTRs deletes the internal region, leaving behind a solo LTR which harbors regulatory regions and transcription factor binding sites (TFBSs).*

 doi:10.20388/OMP.003.0034

repetitive sequences contained within the TEs. Given the implications of ADEPT for neuronal function in age-related disease, a description of the biology of TEs in the brain and how they are regulated is required. The next sections aim to provide that background. We also start with non-LTR retrotransposons because their role in generating neuronal diversity in the brain is better understood.

Non-LTR Retrotransposons and their Role in Generating Somatic Mosaicism in the Brain

LINEs are a class of non-LTR retrotransposon that are highly active in both the developing and the mature brain, and are thought to contribute to somatic variability between mature neurons. Of the roughly 500,000 copies of LINE in the human genome only ~100 remain functional (Beck et al., 2010). Importantly, autonomous LINEs encode a reverse transcriptase that facilitates transposition of non-functional (non-autonomous) LINEs or other SINE, SVA or Alu elements in trans (Dewannieux et al., 2003; Farkash et al., 2006). LINE1 variation in post-mitotic neurons between individual genomes long suggested that LINE1 retrotransposon activity generated neuronal diversity during neuronal differentiation (Muotri et al., 2005). This is further supported by the finding that LINE1 retrotransposons share the Sox2/TCF/LEF transcription factor binding site with the NeuroD1 promoter, a potent neuron-differentiation gene (Kuwabara et al., 2009). Unsurprisingly, the onset of LINE1 expression occurs simultaneously with activation of NeuroD1 in adult neurogenesis in the hippocampus. Moreover, it was found that 79 LINE1 loci were found within -6000 and +1000 base pairs of the transcription start sites of neuronally-expressed genes, which led to the speculation that the transcription factor binding sites embedded within LINE1 sequences provide a global regulatory system for adult neurogenesis in the hippocampus (Kuwabara et al., 2009). LINE1 expression also increases with exercise-associated adult neurogenesis (Muotri et al., 2009). Based on these observations it was suggested that LINE1 activity in neuronal progenitors generates somatic mosaicism and thus neuronal diversity (Baillie et al., 2011; Evrony et al., 2012). In support of this view, LINE1 mosaicism mirrors copy number variations (CNVs) where deletions of up to 1 MB are twice as likely to occur as duplications in 13-40% of human neurons of the frontal cortex (McConnell et al., 2013). Such mosaicism is likely to enhance neuronal diversity within the brain, which can be both beneficial and deleterious. With regard to the latter, LINE1 integrations have been shown to be increased in schizophrenia (Bundo et al., 2014; Guffanti et al., 2016), which further implicates schizophrenia as a developmental disorder.

Recent work by Wei and colleagues (Wei et al., 2016b) using high throughput genome-wide translocation sequencing (HTGTS) has shown a massive amount of non-random translocated DSBs in both wild-type and in DSB repair deficient XRCC4/tp53 KO NPCs. In both wt and XRCC4/tp53 mice the DSBs clustered around neuronal specific genes, including Lsamp, Npas3, Cdh13, Dcc, Nrxn1, Nrxn3 and Nfia. This clustering may account for the previous observation of LINE1 mosaicism and neuronal CNVs alluded to above, because increases in DSBs are known to increase LINE1 integration events (Farkash et al., 2006; Morrish et al., 2002).

We have obtained evidence that LINE1 expression also persists after neurogenesis and can be observed in pyramidal neurons of the mature cerebral cortex and hippocampus by RNA in situ hybridization (Figure 3, unpublished data). The probe used is against LINE1 ORF2 consensus RNA and is a good indicator of cells where LINE1 expression is permissive. However, Figure 3 cannot inform on *de novo* integration activity nor can the hybridization signal distinguish between fully intact (autonomous) and 5′ truncated (non-autonomous) LINE1 elements. Nevertheless, it begs the question: does continued LINE1 expression (Figure 3) contribute to genomic plasticity in neurons of the adult brain? We propose that it does and does so due to ADEPT (Box 1). The observation that that *de novo* LINE1 insertions have a preference for neuronal enhancers in hippocampal neurons (Upton et al., 2015), strongly indicates, we suggest, that these insertions result from ADEPT rather than developmental mosaicism generated by random *de novo* LINE1 insertions.

ADEPTATIONS

Transposable element (TE) insertion into the enhancer/promoter region of neuronal genes may cause either **ADEPT-mediated potentiation** or **ADEPT-mediated inactivation**.

ADEPT-mediated potentiation occurs when the transcription factor binding sites carried by the newly-transposed element enhance future activity-dependent transcription of the neuronal gene. **ADEPT-mediated inactivation** occurs when the insertion disrupts the enhancer/promoter architecture or endogenous regulatory sequences, resulting in a decrease or abolition of future activity-dependent transcription.

ADEPT-mediated inactivation is the more likely scenario. Some evidence for this comes from the study of older LINE1 and LTR elements that are inherited through the germ-line. They were found to be under-represented 5kb from gene promoters, which is most likely due to a negative effect of TE insertions on proximal gene expression (Medstrand et al., 2002).

At the network level, ADEPT-mediated inactivation may function as a 'hand brake' in assemblies prone to unstable (Hebbian) hyperexcitation by permanently disabling immediate-early gene activation in one or more neurons of the network. Accordingly, hyper-excitable neurons would generate more activity-dependent DSBs and thus have a higher probability of TE insertion. Since it is more likely that an insertion would disrupt immediate-early gene enhancer/promoter loci, Long Term Potentiation (LTP) in neurons with de novo integrations would be permanently disrupted returning the network to homeostasis. This mechanism might endow neural networks with a hard biological upper limit on coupled excitation and provide a stabilizing force in Hebbian plasticity.

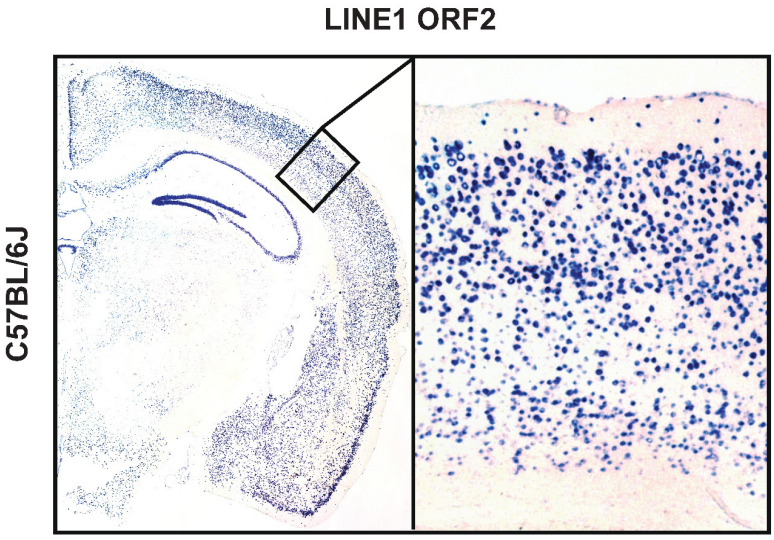

Figure 3. *LINE1 transcription persists in mature neurons. In situ hybridization using an antisense probe against a 791bp region of ORF2 of LINE1 in the adult (C57BL/6J) mouse brain. LINE1 transcripts are robustly expressed in the hippocampus and dentate gyrus as well as pyramidal cells of the neocortex. (For more details please see Methods.)*

Much of what we know about transposition in the brain comes from work on LINEs, albeit they comprise only a fraction of the non-LTR TEs. The SINE/VNRT/Alu SVA family of transposons are one of the most active transposons in humans and have a high rate of transposition in the brain, likely facilitated by LINE1 activity in trans (Baillie et al., 2011). ADEPT-mediated SVA insertions may be even more likely than ADEPT-mediated LINE1 insertions given that SVA family members are much smaller in size. Recent work showing increased expression of the B2 subfamily of SINE retro-elements in mature neurons upon stimulation (Lacar et al., 2016), which may or may not be related to the apparent exaptation of a SINE element as a transcriptional enhancer for callosal projection neurons (Tashiro et al., 2011), which is important for brain formation in mammals (Sasaki et al., 2008). Stimulation-evoked integrations of SVA elements in the neuronal transcriptome may significantly contribute to splicing capacity; there are ~1.4 million Alu elements interspersed throughout the human genome, each containing multiple donor/acceptor splice sites (Kreahling and Graveley, 2004).

Finally, outside of activity-dependent transposition, LINE1 expression in neurons might themselves induce DSB breaks at neuronal early response genes. There is evidence that LINE1 elements can increase DSBs frequency, without an increase in retro-transposition frequency (Gasior et al., 2006; Wallace et al., 2008). The relatively low abundance of fully functional LINEs capable of retro-transposition makes this scenario feasible if it runs under tight regulation. In summary, the evidence that implicates LINE1 in generating somatic mosaicism during neurogenesis is burgeoning. Preferential integrations of LINE1 into enhancer regions and up-regulation of SVA elements following stimulation suggests post-mitotic neurons have genomic plasticity, which we suggest is due to ADEPT. Similar observations have been made for LTR- retrotransposons, the endogenous retroviruses resident in the genome, which is discussed next.

LTR-Containing ERVs in the Brain

Endogenous Retroviruses (ERVs) are retrotransposons that contain Long Terminal Repeat (LTR)-and are descendants of integrations of exogenous viruses into germ cells. Their sequences are comprised of a typical viral architecture including 5′ and 3′ LTRs along with protein coding genes gag, pro, pol and sometimes env (Dewannieux and Heidmann, 2013) (Figure 2).

A large body of evidence has shown that ERVs are involved in the regulation of endogenous genes. As ERV LTRs contain the regulatory regions required for proviral transcription, often involving enhancers and many transcription factor binding sites (TFBSs), they harbour the capacity to autonomously recruit cellular transcription factors for maximum production of mRNA. In fact, ERVs have been more frequently exapted compared to other TEs and now constitute around 20-25% of functional transcription factor binding sites in mouse and human, including TFBSs for genes such as p53, Oct4, and Nanog (Chuong et al., 2013; Cordaux and Batzer, 2009; Sundaram et al., 2014; Thompson et al., 2016) . Studies determining which retro-elements are under positive selection infer that most exapted ERVs sequences are "solo" LTRs. This occurs by homologous recombination between repetitive sequences on 5′ and 3′ LTRs of a full length ERV. Accordingly, recombination between 5′ and 3′ LTR sequences deletes ERV internal regions (that encode retrotransposition machinery) (Belshaw et al., 2007), leaving behind a "solo" LTR, which contains the transcription factor binding sites. This has happened often, resulting in an estimated 577,000 "solo" LTRs in the human genome, comprising the majority of annotated ERV sequences (Friedli and Trono, 2015).

Evidence that ERV expression is involved in human brain development came from the observation

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that levels of ERV-derived transcripts are elevated in neuropsychiatric and neurodegenerative diseases. For example, HERV-K transcripts are elevated in the frontal lobe and serum of both symptomatic patients suffering from amyotrophic lateral sclerosis (ALS) and first degree relatives (Douville et al., 2011), leading to the suggestion that some individuals have inherited a highly active form of HERV-K. Experiments using transgenic mice expressing functional HERV-K env transgenes have recapitulated the human symptoms, however neurotoxicity was attributed to HERV-K env protein aggregation rather than genomic instability due to retrotransposition activity (Li et al., 2015). It was also reported that there were raised levels of DNA damage in HERV-K transgenic mice as measured by an increase in the number of γH2A.X positive nuclei, although this data has been questioned because γH2A.X foci are observed in senescent wild type neurons (Barral et al., 2014). HERVs have also been linked to several diseases such as schizophrenia (Frank et al., 2005; Suntsova et al., 2013), bi-polar disorder (HERV-K) (Frank et al., 2005), multiple sclerosis (HERV-W) (van Horssen et al., 2016) and sporadic Creuzfeld-Jakob prion disease (HERV-W, HERV-K, HERV-T) (Jeong et al., 2010).

Mouse studies have shed some light on the mechanisms by which ERV expression is regulated. The Intracisternal Alpha Particle (IAP) family of ERVs are particularly active in the mouse and has generated gene expression diversity between laboratory mouse strains, including alternative exonization of the protocadherin alpha gene cluster in neurons (Sugino et al., 2004). The epigenotype of IAP elements has been the focus of a recent study on the chromatin remodeler ATRX (Alpha Thalassemia/Mental Retardation Syndrome X-linked). IAP elements can be repressed by the ATRX gene product, which binds to chromatin of the repressed IAP elements through interactions with HP1 and H3K9me3 (Eustermann et al., 2011; Sadic et al., 2015). When neurons are stimulated, serine 10 adjacent to H3K9me3 can be phosphorylated giving rise to the complex modification H3K9me3S10ph (tri-methylated lysine 9 and phosphorylated serine 10 of Histone 3). Notably, phosphorylation of serine 10, which normally takes place during mitosis, causes strong steric hindrance to K9me3-binding proteins such as Heterochromatin Protein 1 (HP1) (Fischle et al., 2005) and causes ejection of HP1 from chromatin (Hirota et al., 2005). It is likely the same happens during neuronal stimulation, with the effect that HP1 is ejected leading to IAP expression (Noh et al., 2014).

Given the observation that transcription of ERVs is permissive following stimulation, it is highly likely that ADEPT may also occur with *de novo* integration of autonomous ERVs. While the number of autonomous ERVs in the human genome is believed to be extremely low, the abundance of repetitive LTR sequences throughout the genome may also contribute to ADEPT in the aging brain. A key mechanism, which will determine how ADEPT changes with age, is epigenetic regulation of TEs. These studies carry import because age-related epigenetic drift may enhance ADEPT, with clear consequences for neurodegenerative disease.

Epigenetic Control of Transposable Elements

While the promoter activity of transposable element sequences is frequently exapted for host cell use, full length TEs are typically silenced and packaged into heterochromatin. Transposable elements are usually marked by H3K9me3 (Bulut-Karslioglu et al., 2014; Karimi et al., 2011), H4K20me3 (Matsui et al., 2010; Mikkelsen et al., 2007) and DNA methylation (Hutnick et al., 2009; Sharif et al., 2016), although silencing pathways seem to be highly dependent on differentiation state.

For ERVs, host control stems from the co-evolution of the family of KRAB (Krüppel-Associated Box) Zinc finger proteins, which recruit co-repressor KAP1 (Krüppel Associated protein, also known as TRIM28 or TIF1β) and induce repressive histone H3 tri-methylation on lysine 9 (H3K9me3) via the methyltransferase SETDB1 (Matsui et al., 2010; Rowe et al., 2010) to silence the ERV. A subset of solo LTRs are marked by H3K9me3, suggesting LTR targeting by KRAB-ZFPs (Karimi et al., 2011). However, the majority of KRAB-ZFPs bind to and repress ERV internal regions (Ecco et al.; Rowe et al., 2010; Sadic et al., 2015). For an excellent summary of the evolutionary pressures between ERV repression and LTR exaptation for host cell use, see the review by Thompson et al., (2016). It has been known for some time that ERVs are involved in placental and early embryonic development (Lowe et al., 2007; Maksakova et al., 2013). A regulatory role for ERVs in various adult tissues has only recently been shown (Ecco et al., 2016). The relevance of ERV expression in the aging brain has yet to be explored.

Age-Related Changes in the Epigenome

A consensus is gradually emerging with regard to the changes in the epigenetic landscape of both heterochromatin and euchromatin during normal aging. In general, a loss of heterochromatin-specific epigenetic modifications is observed, coincident with a decline in levels of HMTases such as SUV39H1, its cognate histone modification H3K9me3 and chromatin-bound HP1 (Djeghloul et al., 2016; Larson et al., 2012). A more complex picture emerges in mammalian cells with the heterochromatin-specific modification H4K20 tri-methylation (H4K20me3). H4K20me3 has been shown to increase globally in Hutchinson–Gilford Progeria syndrome (Shumaker et al., 2006) and in aged rat liver tissue (Sarg et al., 2002). By contrast, aged human diploid fibroblasts show a near complete loss of H4K20me3 despite modest increases in H4K20me1 and H4K20me2 (O'Sullivan et al., 2010). A study examining the brains from the SAMP8 mouse model, where there is accelerated senescence, found no discernable difference in H4K20me3 levels in aged animals (Wang et al., 2010), but did observe decreases in H4K20me1 levels. It has been suggested that age-dependent global increase or decrease of H4K20me3 may be related to the pathway

taken to cellular senescence and is thought to explain the high variability across different cancer and cell lines (Zane et al., 2014). Repressive H3K27me3, sometimes found in combination with H3K4me3 in 'bivalent' domains, is also lost in aging, and is correlated with up-regulation of senescence-associated genes (Shah et al., 2013).

Mixed identity also occurs in aged euchromatin. H3K4me3, an epigenetic modification that is associated with active transcription, and typically found the transcription start site (TSS). H3K4me3 deposition becomes less specific with age in humans and mouse (Shah et al., 2013; Sun et al., 2014). Knockdown of enzymes responsible for H3K4me3 deposition can either promote or diminish longevity, largely due to tissue or context (Booth and Brunet, 2016). Euchromatic sequences marked by H3K4me1 normally include enhancers and sequences adjacent to H3K4me3-marked transcription start sites (Kim et al., 2010). During aging in both stem and differentiated cells, H3K4me1 distribution extends into genomic loci that show DNA hypomethylation with age (Fernández et al., 2015). Similarly, loss of H3K36me3, a mark associated with transcriptional elongation and splicing (Edmunds et al., 2008), is associated with shorter lifespan in S. Cerevisiae (Sen et al., 2015), C. Elegans (Pu et al., 2015), and in the SAMP8 mouse model (Wang et al., 2010). Notably, H3K36 methylation appears to regulate the association of NHEJ repair components to DNA, with loss of H3K36 methylation decreasing the association of NHEJ components to DNA (Fnu et al., 2011).

Aged cells also show depletion of DNA methylation at intergenic repeats normally packaged into heterochromatin (Cruickshanks et al., 2013; Heyn et al., 2012; Jintaridth and Mutirangura, 2010; Vanyushin et al., 1973), that is not observed in immortalized cells (Wilson and Jones, 1983). Conversely, aged cells display DNA hypermethylation in euchromatin, which occurs preferentially at bivalent chromatin domains (Rakyan et al., 2010) and at CpG island promoters of many cancer-related genes, resulting in their repression (Cruickshanks et al., 2013). Importantly, age-related loss of DNA methylation and heterochromatin at transposable elements precedes their de-repression, where aged or senescent cells show higher expression of TEs such as LINEs, SINEs and ERVs compared to youthful cells (Cecco et al., 2013; Djeghloul et al., 2016; Jintaridth and Mutirangura, 2010). The question then arises is: how would age-related drift of epigenetic modifications and concomitant de-repression of TEs augment ADEPT? The answer seems to be that age-drifted epigenetic landscape causes change in the choice of DNA DSB repair pathway, which is elaborated in the next two sections.

Epigenetic Maintenance of DNA Double Strand Breaks

What has become clear from recent work is that rapid transient heterochromatin compaction takes place, even within euchromatin, around double-strand breaks and is required for DSB repair. The epigenetic effectors involved in this transient chromatin compaction are part of a tightly ordered sequence of events described in a simplified form in Figure 4. For the sake of clarity some of the enzymatic activities and post-translational modifications have been omitted. For more detailed description see Dantuma and van Attikum (2016).

DSB repair-induced chromatin compaction follows a "lock, loosen, load" dynamic (Ayoub et al., 2009a; Burgess et al., 2014; Madabhushi et al., 2014). Briefly, following DSB recognition by the MRN complex in euchromatin, ATM is recruited to the DSB site, a process that also requires Tip60 acetyltransferase (Sun et al., 2010). A rapid transient heterochromatin state is induced where a KAP1/HP1/SUV39H1 complex is recruited and deposits H3K9me3 and extends outwards from the DSB site (Ayoub et al., 2009b; Ayrapetov et al., 2014). What induces the initial recruitment of the KAP1/HP1/SUV39H1 complex is unknown, however, it is presumed that the local assembly of a heterochromatin-like domain stabilizes the area surrounding the DSB and inhibits any ongoing transcription. The presence of H3K9me3 induces conformational change to Tip60, activating its acetyltransferase ability. Tip60 then acetylates, thereby activating, ATM kinase (Sun et al., 2005). Activated ATM phosphorylates γH2A.X, which can spread up to 1 megabase from the DSB site (Iacovoni et al., 2010). ATM also phosphorylates KAP1, which has the effect of ejecting the KAP1/HP1/SUV39H1 complex thereby dis-assembling the heterochromatin-like domain (Ayrapetov et al., 2014). The genomic region surrounding the DSB site is now "open" chromatin marked by γH2A.X, which provides a 'landing pad' for MDC1 (Stucki et al., 2005), which finally recruits DNA repair machinery.

Stabilization of the heterochromatin-like domain surrounding the DSB is likely to be enhanced by H4K20 mono-(H4K20me1), di-(H4K20me2) and tri-(H4K20me3) methylation generated by the NSD2 HMTase (Pei et al., 2011). H4K20 methylation is known to be important in chromatin stability (Evertts et al., 2013; Hahn et al., 2013) and in the case of H4K20me3, compaction (Lu et al., 2008). In DSB repair NSD2 is required for H4K20me2/3 accumulation at DSBs and thus the subsequent binding of 53BP1, a DNA repair effector that promotes the NHEJ repair pathway through antagonism of BRCA1 (Bunting et al., 2010; Zimmermann et al., 2013). It is possible that age-related increases in H4K20me1/2 may correspond with increased DNA repair, while loss of H4K20me3 may be more tightly linked to simultaneous loss of H3K9me3, given H3K9me3 appears to be pre-requisite for H4K20me3 deposition (Kourmouli et al., 2004).

It is still largely unclear how parental histone and DNA modifications are maintained following DSB repair, as following repair the cell is required to re-establish the pre-break epigenetic code peculiar to the genomic locus. This is confounded by the fact the histone variant H3.3 deposited at sites of DNA damage by HIRA (Adam et al., 2013), has been shown to be less able to receive the H3K9me3 modification (Loyola et al., 2006). Interestingly H3.3 variant is also deposited by HIRA in active gene bodies upon neuronal stimulation (Maze et al., 2015). It has also been observed that the histone chaperone DAXX deposits H3.3 at a subset of immediate

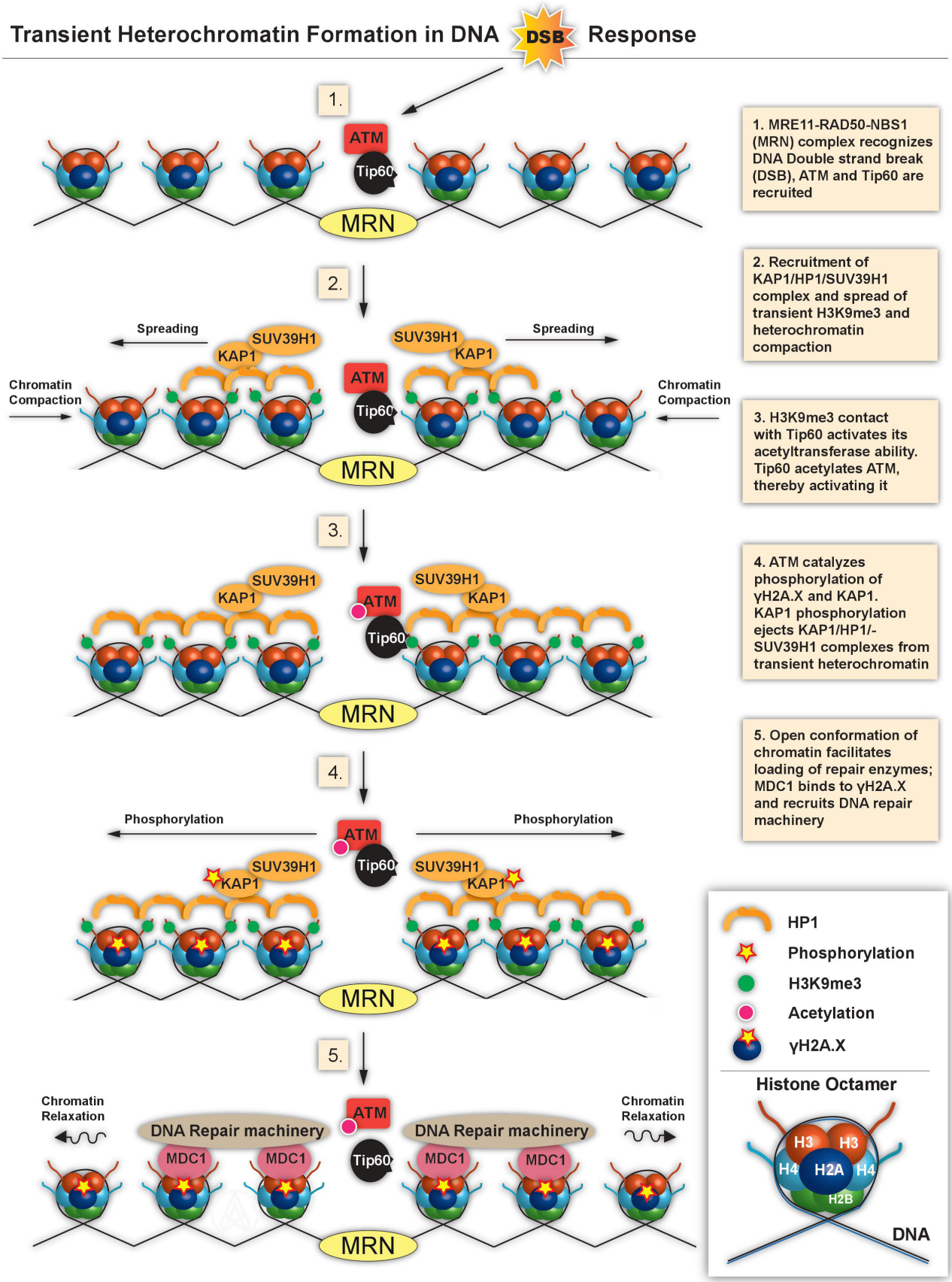

Figure 4. *Transient Heterochromatin Formation in the DNA DSB Response. Detection of DNA DSBs involves the transient formation of heterochromatin surrounding the DSB, which occurs even in euchromatin. (1) The DSB by the MRN complex. (2) KAP1/HP1/SUV39H1 is recruited to the DSB and H3K9me3 outwards, resulting in chromatin compaction. (3) The presence of H3K9me3 activates the acetyltransferase ability of Tip60, which acetylates and activates ATM kinase. (4) Activated ATM then spreads outward, phosphorylating KAP1 and histone variant H2AX. (5) Phosphorylation of KAP1 releases the transient heterochromatin state, while phosphorylation of H2A.X, which gives rise to the γH2A.X mark, serves as a landing pad for MDC1 which recruits DNA repair machinery.*

early gene promoters (Michod et al., 2012), a phenomena that may be tightly linked to neuronal activity-induced DSBs. Notably, over a human lifetime H3.3 becomes the dominant H3 isoform (compared to H3.1, H3.2,) in neuronal tissue (Maze et al., 2015), which is likely a direct result of a lifetime of neuronal transcription. Evidence also suggests that DNA modifications are re-established following DNA repair, as DNA (cytosine-5)-methyltransferase 1 (DNMT1) is known to be rapidly recruited to DSB repair sites (O'Hagan et al., 2008). Similarly, the DNMT1 co-factor UHRF1 (also known as Np95), is recruited to DSBs in dividing cells, and its presence can antagonize 53BP1 and NHEJ pathway selection (Zhang et al., 2016).

The aging Epigenetic Landscape Determines Choice of DNA Repair Pathway and Augments ADEPT

Local epigenetic landscape can dictate DNA DSB repair pathway choice by regulating both the duration and composition of DSB-associated transient heterochromatin-like domains (Clouaire and Legube, 2015). For example, the presence of SET can prolong the transient heterochromatin-like domain associated with DSB repair, which has the effect of locking in KAP1 and HP1 proteins and engagement of the NHEJ repair pathway, which can result in defective DSB repair (Kalousi et al., 2015). The composition of the transient heterochromatin-like domain is also important. The recruitment of HP1α and HP1β to the DSB are specifically found to favor homologous recombination (HR) repair by promoting end resection effectors, whereas the recruitment of HP1γ is known to prevent end resection, and its retention inhibits HR and favors NHEJ repair (Ayrapetov et al., 2014; Kalousi et al., 2015; Soria and Almouzni, 2013).

We suggest that in aged neurons, epigenetic drift causes a bias in DSB repair pathway, away from NHEJ towards HR repair (Figure 5). Neuronal loci that undergo activity dependent DSBs may be especially sensitive to epigenetic drift, as repeated repair to the same locus may result in a cumulative epigenetic scar in the form of orphaned histone or DNA modifications, as transcription factors compete with DNA repair enzymes (Moore et al., 2016). In aged neuronal chromatin, following the gradual loss of H3K9me3, adjacent repetitive sequences (TEs, LTRs or simple repeats) are moreover de-repressed and following an activity dependent DSB, an aged epigenome defers to transcription-coupled HR DNA repair. As a consequence, homologous recombination occurs between adjacent repetitive sequences. This phenomena has already been observed in C. Elegans, where the loss of H3K9me3 results in the transcription of repeats and the accumulation of unstable RNA:DNA hybrids and destabilizing RNA secondary structures called R-loops (Zeller et al., 2016). This age-associated ADEPT would most often result in frameshifts, deletions and altered exonizations. Local duplications may also occur, or the DSB may be exploited by autonomous transposable elements, such as LINE1 or HERV-K. In short, the tightly controlled neuronal early-response gene pathway will have been compromised, causing deleterious consequences for the neuron, ultimately leading to neurodegenerative disease.

In light of the foregoing discussion one of the key areas of future research will be to define the factors that augment age-related epigenetic drift and therefore likely to enhance ADEPT. One of these factors is environmental, namely inflammation which has been linked to neurodegenerative disease (Booth and Brunet, 2016; Faden et al., 2016; McGeer and McGeer, 2004; Pérez-Cerdá et al., 2016).

In particular, viral transactivation—where an exogenous viral infection results in trans-activation of resident ERVs, by stimulating transcription or modifying a protein product (Kolson et al., 1994; Michaud et al., 2014; Nellåker et al., 2006; Toufaily et al., 2011) - is an environmental factor that could affect epigenetic drift in neurons. Indeed, there is evidence that influenza viruses can transactivate HERV-W (Nellåker et al., 2006), an ERV known to be associated with multiple sclerosis, a disease largely restricted to northern latitudes. Given that exogenous viral infection is the primary stimulator of innate immunity and inflammation it is likely that repeated viral infection could be a primary cause of epigenetic drift in neurons. Clinical evidence for this may now be forthcoming as Alzheimer's disease, a notoriously heterogeneous disease, has been unified across mouse and man under a singular epigenomic immune response signature, where synaptic genes and regulatory elements are down-regulated and distinct immune genes and regulatory elements are up-regulated (Gjoneska et al., 2015).

Concluding Remarks

The generation of activity-dependent DSBs is a normal part of neuronal function. These breaks can either be generated by TEs or be utilized by them as new integration sites. Activity-DEPendent Transposition is distinct from developmental mosaicism caused by clustered high frequency DNA breaks during neurogenesis, as it is dependent on transcriptional activity at neuronal immediate-early genes. Transpositions are affected by epigenetic modifications associated with the TEs. Accordingly, ADEPT will be subject to changes in epigenetic landscape, which can be dramatically augmented during age-related epigenetic drift and de-repression of TEs. In this regard we suggest that age-related increases in ADEPT are a driving force in neurodegenerative disorders, especially in neuronal cell types that are particularly vulnerable to inflammatory and activity-dependent stress during an individual's lifetime.

Methods Summary

An RNA probe for a consensus sequence of LINE1 ORF2 was amplified from adult C57BL/6J cDNA

 doi:10.20388/OMP.003.0034

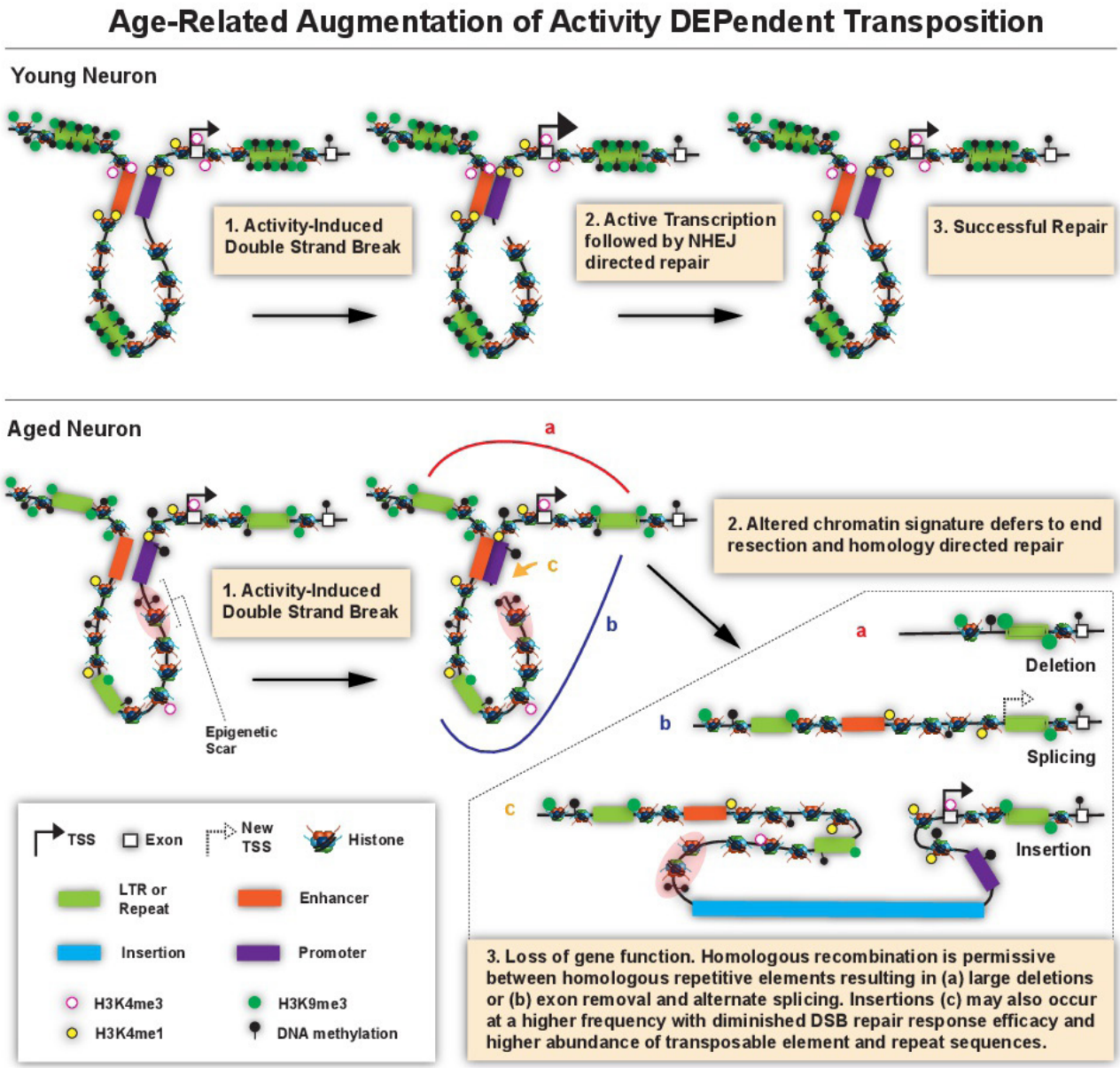

Figure 5. *Age-Related Augmentation of Activity DEPendent Transposition . In young neurons (top row), activity-dependent DNA DSBs occur in the enhancer/promoter region of immediate-early genes, which is a requirement for their expression. Following transcription, activity-dependent DSBs in young neurons are repaired without error by the NHEJ pathway, as described by Madabhushi et al., (2015). In aged neurons (bottom row), epigenetic drift leads to chromatin compartments being less well defined with regards to histone modifications and DNA methylation. Accordingly H3K4me1 and H3K4me3 are re-distributed and repetitive sequences are no longer repressed by H3K9me3 and DNA methylation, leading to their transcription and production of lncRNAs. In light of the epigenetic drift, DSBs generated in aged neurons are repaired by the homologous recombination (HR) pathway. HR repair uses the repeat-containing lncRNAs as a template, which results in recombination between repeats flanking the gene. Recombination between repeats would most frequently result in (a) deletions, as well as (b) alternative Transcription Start Sites (TSSs) or a change in splicing by exon removal, and (c) duplications or insertions into the enhancer/promoter region. (Figure modified from Newman et al. (2017) EMBO Reports).*

(Superscript II, Thermo Scientific) using primers FW: CAAGATCCAACACCCATTCATGA and RV: TTCCGCCAGAAGTTCTTTTATCC using GoTaq polymerase (Promega). The amplicon was ligated into a pGEM-T vector (Promega) and sequence verified. After linearization, an antisense RNA probe was transcribed from this template and in situ hybridization was carried out on adult C57BL/6J coronal cryosections using the methodology described in (Bormuth et al., 2013).

List of Abbreviations

ADEPT	Activity DEPendent Transposition
γH2A.X	Histone H2A.X variant phosphorylated at serine 139
53BP1	Tumor suppressor p53-binding protein 1
Alu	DNA repeat originally characterized by the Athrobacter luteus (Alu) restriction enzyme
ATRX	Alpha thalassemia/mental retardation syndrome X-linked
DAXX	Death domain-associated protein 6
DNMT1	DNA (cytosine-5)-methyltransferase 1
DSB	[DNA] Double strand break
ERV	Endogenous Retrovirus
H3.3	Histone H3 Variant 3
H3K4me1	Histone H3 lysine 4 mono-methylation
H3K4me3	Histone H3 lysine 4 tri-methylation
H3K9ac Histone	H3 lysine 9 acetylation
H3K9me3	Histone H3 lysine 9 tri-methylation
H3K36me3	Histone H3 lysine 36 tri-methylation
H4K20me1	Histone H4 lysine 20 mono-methylation
H4K20me2	Histone H4 lysine 20 di-methylation
H4K20me3	Histone H4 lysine 20 tri-methylation
HERV	Human Endogenous Retrovirus
HIRA	HIR (histone cell cycle regulation defective) homolog A
HP1	Heterochromatin Protein 1
HR	Homologous Recombination (DNA DSB Repair)
IAP	Intracisternal Alpha Particle
KAP1	Krüppel Associated protein, also known as TRIM28 or TIF1β
KRAB-ZFP	Krüppel Associated Box containing Zinc Finger Protein
LINE	Long Interspersed Nuclear Element
LTR	Long Terminal Repeat
NHEJ	Non-Homologous End Joining (DNA DSB Repair)
NSD2	Histone-lysine N-methyltransferase NSD2 (Nuclear SET domain-containing 2)
TCHR	Transcription-Coupled Homologous Recombination (DNA DSB Repair)
TE	Transposable Element
TFSB	Transcription Factor Binding Site
SETDB1	Histone-lysine N-methyltransferase SETDB1 (SET domain bifurcated 1)
SINE	Short Interspersed Nuclear Element
SUV39H1	Histone-lysine N-methyltransferase SUV39H1 (Suppressor of variegation 3-9 homolog 1)
SVA	SINE Variable-number tandem repeat Alu

 doi:10.20388/OMP.003.0034

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