Symposium

The Role of Transposable Elements in Health and Diseases of the Central Nervous System

Matthew T. Reilly,[1] Geoffrey J. Faulkner,[2] Joshua Dubnau,[3] Igor Ponomarev,[4] and Fred H. Gage[5]

[1]National Institute on Alcohol Abuse & Alcoholism, Bethesda, Maryland 20892, [2]Mater Medical Research Institute, South Brisbane Queensland, Australia, 4101, [3]Cold Spring Harbor Laboratory, Cold Spring Harbor, New York 11724, [4]University of Texas at Austin, Waggoner Center for Alcohol & Addiction Research and the College of Pharmacy, Austin, Texas 78712, and [5]The Salk Institute, Laboratory of Genetics, La Jolla, California 92037

First discovered in maize by Barbara McClintock in the 1940s, transposable elements (TEs) are DNA sequences that in some cases have the ability to move along chromosomes or "transpose" in the genome. This revolutionary finding was initially met with resistance by the scientific community and viewed by some as heretical. A large body of knowledge has accumulated over the last 60 years on the biology of TEs. Indeed, it is now known that TEs can generate genomic instability and reconfigure gene expression networks both in the germline and somatic cells. This review highlights recent findings on the role of TEs in health and diseases of the CNS, which were presented at the 2013 Society for Neuroscience meeting. The work of the speakers in this symposium shows that TEs are expressed and active in the brain, challenging the dogma that neuronal genomes are static and revealing that they are susceptible to somatic genomic alterations. These new findings on TE expression and function in the CNS have major implications for understanding the neuroplasticity of the brain, which could hypothetically have a role in shaping individual behavior and contribute to vulnerability to disease.

Introduction

Almost half of mammalian genomes are comprised of a class of repeat DNA sequences known as transposable elements (TEs) (Lander et al., 2001), where some TEs have the ability to mobilize and change locations in the genome. Other eukaryotes contain substantial proportions of TEs, making TEs a general feature of genomes across many organisms (Adams et al., 2000; Waterston et al., 2002; Gibbs et al., 2004; Nellaker et al., 2012). Yet, their roles in human health and disease and in genomic evolution are not well defined. Once considered "junk" or "selfish" DNA, TEs are now being appreciated for their specific functional roles in a variety of biological phenomena that can be both beneficial and pathological to the organism (Biémont, 2010). Barbara McClintock, who is credited with the discovery of TEs, first proposed two main functions: (1) insertional mutagens and (2) "controlling elements" that regulate the expression of nearby genes. McClintock's findings were not well accepted at the time of publication of her seminal work (McClintock, 1951). A large body of knowledge has accumulated over the last 60 years on TE biology (Britten and Kohne, 1968; Grimaldi and Singer, 1982; Boeke et al., 1985; Daniels and Deininger, 1985; Kazazian et al., 1988; Xiong and Eickbush, 1988b; Britten et al., 1989; Dombroski et al., 1991; Batzer et al., 1996; Moran et al., 1999). For example, Kazazian et al. (1988) discovered that hemophilia A resulted from a *de novo* insertion of a TE. This study was one of the first to demonstrate that a TE insertion in the human genome caused disease (Kazazian et al., 1988). However, a new interest in the function of TEs has resulted in part from large-scale genomic projects, such as the ENCyclopedia Of DNA Elements (ENCODE) and Functional Annotation of Mouse (FANTOM) projects. These studies showed that TEs are active in a highly cell type-specific manner and control their own cell-specific transcription as well as the transcription of neighboring genes (Faulkner et al., 2009; Djebali et al., 2012; Thurman et al., 2012). Finally, the advent of next-generation whole-genome sequencing approaches has identified major structural variation resulting from TE activity (Beck et al., 2010; Ewing and Kazazian, 2010; Huang et al., 2010; Iskow et al., 2010).

There are two major classes of TEs, distinguished by their mechanism of transposition (Levin and Moran, 2011). DNA transposons move via a cut-and-paste mechanism and are generally thought to be extinct in higher eukaryotes. Therefore, DNA transposons will not be discussed further in this review. However, RNA transposons (herein called retrotransposons or mobile elements) move via a copy-and-paste mechanism using RNA as an intermediate. Retrotransposons, namely, Long-Interspersed Elements (LINE1s), are the only known active and autonomous elements in the human genome (Beck et al., 2011). Other retrotransposon families include: Short-INterspersed Elements (SINEs), Alu and SVA elements. Retrotransposons with a long terminal repeat (LTR), such as endogenous retroviruses (ERVs), are also present in the human genome, but evidence has yet to be

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Correspondence should be addressed to either of the following: Dr. Matthew T. Reilly, National Institute on Alcohol Abuse and Alcoholism, National Institutes of Health, MSC 9304, Bethesda, MD 20892, E-mail: reillymt@mail.nih.gov; or Dr. Fred H. Gage, The Salk Institute, Laboratory of Genetics,10010 N Torrey Pines Road, La Jolla, CA 92037-1099, E-mail: gage@salk.edu.

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shown that ERVs have the ability to move (Moyes et al., 2007). Retrotransposition-mediated events in mammals are not only confined to germ cells, as once thought, but can produce somatic alterations in the brain and cancer (Muotri et al., 2005; Baillie et al., 2011; Solyom et al., 2012). That retrotransposons can generate neuronal somatic mosaics (Singer et al., 2010), creating genetic heterogeneity across neurons in the same individual, has wide-reaching implications for all areas of neuroscience (Muotri et al., 2005; Baillie et al., 2011; Perrat et al., 2013).

This review focuses on the recent identification of CNS-specific retrotransposons as generators of genetic heterogeneity, their regulation and function, and their role in health and diseases of the brain (Thomas et al., 2012). Many challenges remain, but new technologies for retrotransposon capture sequencing (Baillie et al., 2011) and single-cell TE analysis (Evrony et al., 2012) are opening up novel areas for discovery. However, retrotransposons may play a role in neurogenesis (Muotri et al., 2005; Coufal et al., 2009; Muotri et al., 2010), aging (Li et al., 2013), neurodegenerative diseases (Li et al., 2012), alcoholism (Ponomarev et al., 2012), and post-traumatic stress disorder (PTSD) (Ponomarev et al., 2010). The latest findings in these areas will be presented in a symposium at the annual Society for Neuroscience meeting in 2013.

Mobile elements, neuronal mosaicism, and evolution

Each cell in the body contains DNA, which instructs the cell and tissues to perform specific functions through the transcription of mRNA and translation of proteins. The DNA sequence within the nucleus has long been thought to be identical across different cell types within an individual, with the exception of the gene rearrangements in the immune system and in some cancer cells. The finding that L1 retrotransposons are active in somatic cells and have structural and functional consequences in neuronal genomes challenges the dogma that neurons are genetically stable entities (Muotri et al., 2005; Coufal et al., 2009; Baillie et al., 2011; Evrony et al., 2012; Perrat et al., 2013). The consequences of L1 activity in neurons resulting in neuronal mosaicism are evident throughout embryo development and in the adult brain (Thomas et al., 2012). This novel mechanism may contribute to genomic neuronal diversity across neurons in the same individual: the "one human, multiple genomes" phenomenon that has been demonstrated in a number of different cell types (Lupski, 2013). These findings on somatic retrotransposition in the brain offer a new paradigm to understand the unexplained variation seen in many psychiatric disorders that has evaded detection by conventional methods, such as genome-wide association studies (Manolio et al., 2009). Perhaps more generally important is the role of mobile elements in evolution, where they can be characterized as having a constructive role in genomic innovation rather than just being another random source of genetic variation (Heard et al., 2010).

L1s are one of the most ancient and successful innovations in eukaryotic genomes, comprising ~20% of mammalian genomes (Lander et al., 2001; Waterston et al., 2002; Gibbs et al., 2004; Nellaker et al., 2012). Active human L1s are ~6 kb long, harbor an internal polymerase II promoter, and encode two open reading frames (ORFs) (an RNA chaperone protein, ORF1, and an endonuclease and reverse transcriptase protein, ORF2), usually ending with a polyadenylic acid or short A-rich tail. They are the only autonomous transposable element known in the present-day human genome, encoding the essential machinery required to move within the genome. Upon translation, the L1 RNA assembles with its own encoded proteins (*cis*-preference) (Wei et al., 2001; Dewannieux et al., 2003) and moves to the nucleus, where an endonuclease makes a single-stranded nick and the reverse transcriptase uses the nicked DNA to prime reverse transcription from the 3′ end of the L1 RNA. L1-encoded proteins also provide the machinery to mobilize (in trans) nonautonomous retrotransposons (e.g., Alu and SVA elements) and other mRNAs that generate processed pseudogenes (Esnault et al., 2000; Wei et al., 2001; Kajikawa and Okada, 2002; Dewannieux et al., 2003; Hancks et al., 2012; Raiz et al., 2012). Reverse transcription frequently fails to proceed to the 5′ end, resulting in mainly truncated, nonfunctional *de novo* insertions. In addition, epigenetic and post-transcriptional silencing mechanisms exist to repress mobilization in somatic cells (Whitelaw and Martin, 2001; Slotkin and Martienssen, 2007; Chung et al., 2008; Czech et al., 2008; Ghildiyal et al., 2008; Kawamura et al., 2008; Garcia-Perez et al., 2010). However, there is evidence that some L1 insertions are functional. Human L1s structurally resemble those present in rodent and even invertebrate genomes, and a cultured cell retrotransposition assay has revealed that human L1s can retrotranspose in a variety of mammalian, nonhuman cell lines (Moran et al., 1996; Coufal et al., 2009).

Based on reverse transcriptase phylogeny, L1 elements are most closely related to the group II introns of mitochondria and eubacteria (Xiong and Eickbush, 1990; Cavalier-Smith, 1991). These studies revealed that the reverse transcriptase enzyme is extremely old and that retroelements can be viewed as relics or molecular fossils of the first primitive replication systems in the progenote. The origin of retroelements possibly traces back to the conversion of RNA-based systems, the "RNA World," to modern "DNA-based" systems. Current models suggest that these mobile introns of eubacteria were transmitted to eukaryotes during the initial fusion of the eubacterial and archaebacterial genomes or during the symbiosis that gave rise to the mitochondria, generating the modern-day spliceosomal introns (Zimmerly et al., 1995). Further acquisition of an endonuclease enzyme and a promoter sequence represented important steps in the evolution of L1 retrotransposons, providing autonomy for L1s to insert into many locations throughout the genome and provide the molecular machinery for mobilization of nonautonomous elements.

The apparent lack of function of retroelements in the genome has long puzzled scientists and inspired the concept of "junk DNA" to illustrate the idea that such sequences are mere evolutionary remnants (Ohno, 1972). However, the recognition that retrotransposons can actively reshape the genome is slowly challenging this terminology. Moreover, the mammalian genome has suffered waves of transposon bombardment, but the constant, single lineage of L1 history reveals that active, retrotransposition-competent L1 sequences were never absent from mammals' genomes during evolution, suggesting an inextricable link between L1s and their hosts (Levin and Moran, 2011). The relationship between transposons and their hosts is probably not entirely antagonistic, as several host genes have a high degree of homology to one or more transposable elements. For example, the sequence of paired box gene 6 (PAX6), a DNA-binding protein that regulates transcription, is derived from a transposase (Feschotte, 2008). In addition, the telomerase enzyme, responsible in most mammals for replication of the ends of chromosomes, is derived from retrotransposons (Nakamura and Cech, 1998). As described above, accumulating recent evidence in the literature points to a somatic function for L1 transcripts, involving cell proliferation, differentiation, and embryo development, although it is unclear how these different retrotransposons may be acting. Moreover, it is difficult to determine why the genome would need so many cop-

ies of retrotransposons and whether this expansion has any correlation with retrotransposition itself. The lack of an "apparent" cell function suggests that transposable elements are "selfish DNA," acting as parasites in the genome to propagate themselves (Orgel and Crick, 1980). The restricted activity of retrotransposons in germ or early embryonic cells apparently fits well with this concept because new insertions will be passed to the next generation. However, somatic insertions pose a conundrum because they will not be transmitted to the next generation. According to the symbiotic theory, it is advantageous to any transposable element to promote host mating, securing the propagation of the "master" elements to the next generation. From this perspective, it would not be surprising if advantageous insertional events in the brain, resulting in a better (cultural and social) fitness of the individual organism, also contributed to host mating. For example, Barsoum et al. (2010) showed that a transposable element promotes host sexual reproduction. This is the first empirical evidence of an association between a transposable element and sexual reproduction (Barsoum et al., 2010), which is congruent with a theoretical model proposed by Hickey (1982). Such a model requires the mechanism that allows retrotransposition in somatic cells to be similar to the mechanism existing in germ cells (i.e., that the factors involved in L1 mobilization in germ cells be related to the factors acting in the brain). Indeed, *in silico* data reported similarities between human brain and testes gene expression patterns (Guo et al., 2003, 2005). It has been proposed that the similarities in expression in human brain and testes may have very important implications for human speciation (Wilda et al., 2000; Graves, 2010). The emergence of new species during evolution might be the result of coordinated changes in many organ systems, and the organs associated with evolution would share a common set of regulatory genes. Although it has been proposed that genes in the Sox family in testes and brain share the same genetic origins, it seems unlikely that all other factors involved in L1 transcription would behave in the same way, contributing to the obvious differences observed in these two tissues. Although the role of transposable elements in human speciation and the hypothesis that the brain and reproductive organs coordinate this process are still highly speculative, the characterization of factors involved in the L1 retrotransposition in germ and brain cells will provide further insights into the evolution of these two organs.

If new L1 insertions in the brain are not passed to future generations, why would evolution conserve such a mechanism in the nervous system? Our hypothesis is that it is the propensity for L1 mobilization, rather than its consequences, on which natural selection may apply (Upton et al., 2011). Somatic retrotransposition may lead to the evolution of functional *de novo* regulatory elements more rapidly than by random accumulation of point mutations (Mukamel and Tanay, 2013), creating a greater potential for adaptation of beneficial genetic networks. As mentioned above, epigenetic modifications, particularly DNA methylation of CpG dinucletodies, are mechanisms used to suppress L1 mobilization. These potentially heritable epigenetic modifications may suppress deleterious L1 insertions, providing a buffer to allow further adaptation of L1 regulatory elements for the benefit of the host (Xie et al., 2013). This hypothesis is certainly speculative but might gain support by studying our own species. The human species has an enormous spectrum of phenotypic variation, despite being genetically quite homogeneous (Lander et al., 2001; Witherspoon et al., 2007; Henn et al., 2012). It has been proposed that a major portion of biological complexity in humans arises from regulation of the genome by the non-protein coding regions (e.g., epigenetic modifications and noncoding RNAs) (Carroll, 2008; Mattick et al., 2010). The diversity of behaviors, cultural practices, and languages that are not biologically inherited but have biological origins may have been important to control new resources or inhospitable territories. At the individual level, humans are also very diverse. Such variation can even be found in genetically identical twins. Recent studies have pointed to epigenetic variations during the life of monozygotic twins (Fraga et al., 2005). However, the idea that epigenetic modifications underlie many of the cognitive and sociobehavioral traits in humans is still highly speculative. The evolution of the CNS provided a notable selective advantage, as information about the environment could be processed rapidly and would allow organisms to more readily meet the challenges of ever-changing environmental conditions. Moreover, epigenetic modification allowed the nongenetic transfer of information or transmission of "culture" at an unprecedented magnitude (Jablonka and Lamb, 2007). Such specialization is highly dependent on the cognition levels acquired by the species, and cognitive levels are directly linked to the complexity of the neuronal network. Therefore, the advantages gained by retaining the mechanisms for somatic retrotransposition may outweigh the cost of a less plastic nervous system. We think that L1 retrotransposition may be part of a conserved core process responsible for generating genetic variability within germ and neural genomes. That is, the core molecular processes controlling L1 retrotransposition are conserved across organs (e.g., brain and testis) but result in different phenotypic cellular traits because of retrotransposition at varying loci, a principle known as pleiotropy (Wagner and Zhang, 2011). Such a process could evoke a facilitated, complex, nonrandom phenotypical variation on which selection would act. Therefore, transposable elements may play a constructive role in evolution and organogensis, where transposable elements could be coopted by their host as *cis*-regulatory elements and direct novel patterns of gene expression (Emera and Wagner, 2012; Wanichnopparat et al., 2013).

Techniques for mapping retrotransposons in the brain

The frequency, developmental timing, and functional consequences of endogenous L1 retrotransposition in the mammalian brain remain largely unclear. Until recently, experimental evidence supporting neuronal L1 activity was primarily supplied by (1) engineered L1 reporter assays, measuring mobilization of an EGFP tagged L1 (L1-EGFP) *in vitro* and *in vivo* (Ostertag et al., 2000; Muotri et al., 2005, 2009; Coufal et al., 2009), and (2) L1 copy number variation (CNV) assays based on TaqMan qPCR of genomic DNA extracted from human tissue (Coufal et al., 2009). These approaches enabled the laboratory of F.H.G. and others to make the seminal observation that L1 activation occurs in neuronal precursor cells and produces L1 CNV in the human body, enriched in the brain (Muotri et al., 2005; Coufal et al., 2009). Critically, *in vivo* 3D modeling using a transgenic L1-EGFP mouse revealed few GFP-positive clusters $>$1–2 cells, suggesting that most L1 activity occurred late in neuronal differentiation (Muotri et al., 2010). This view was reinforced by the finding that mouse and human neuronal precursor cells deficient for the L1 promoter repressor *MeCP2* exhibited higher L1-EGFP activity and L1 CNV than wild-type controls (Muotri et al., 2010). Together, these data highlighted a highly complex somatic genome mosaic in the brain (Singer et al., 2010), driven by L1 and with an apparent enrichment for the subgranular zone of the hippocampus, an established neurogenic niche (Eriksson et al., 1998).

Despite yielding intriguing and consistent data, several drawbacks are apparent for the L1-EGFP and L1 CNV assays. For instance, as an engineered system, epigenetic regulation of the L1-EGFP system may not exactly recapitulate regulation of endogenous L1s *in vivo*, potentially overstating their activity. Conversely, the addition of a 1.2 kb GFP reporter construct at the 3′ end of a tagged L1 element (Ostertag et al., 2000) may understate L1 activity in situations where L1 reverse transcription extends for <1.2 kb at a given integration site. Absolute quantification of L1 mobilization per cell using the L1 CNV assay, an approach that has indicated up to 80 somatic L1 copies per human neuron (Coufal et al., 2009), is confounded by the need to perform a plasmid "spike-in" as a reference control. It is also a possibility that L1 reverse transcription occurs in cytoplasmic foci without genomic integration. Thus, although these techniques provoked the key hypothesis that L1 mobilization occurred in neuronal precursor cells, more direct approaches, such as high-throughput sequencing, were required to precisely establish how often L1 mobilized during neurogenesis and, just as importantly, to determine which loci contained new L1 insertions.

Genomic mapping of somatic L1 variants in the brain is confounded by (1) high L1 copy number in genomic DNA (>500,000 L1 copies in the human reference sequence) and (2) the projected rarity of each individual L1 insertion. One way to overcome these issues is to perform targeted, deep sequencing of L1 integration sites. For instance, retrotransposon capture sequencing (RC-seq), an L1 mapping strategy based on sequence capture enrichment of L1 5′ and 3′ genomic junctions and applied to hippocampus and caudate samples from three individuals, reported several thousand somatic L1 insertions (Baillie et al., 2011). These occurred primarily in hippocampus, a trend strongly correlated with L1 CNV assay data obtained from the same samples (Baillie et al., 2011). Other approaches developed to study *Drosophila* transposable elements detected endogenous retrotransposition in purified neurons, with whole-genome sequencing (Perrat et al., 2013) and *in vivo* with a *gypsy*-TRAP reporter (Li et al., 2013), suggesting that a range of underexplored methodological options may yet be made available to study L1 mobilization in "bulk" human tissue samples.

However, the recent invention of single-cell genomic analysis techniques will likely prove decisive in counting somatic L1 insertions in neurons. In a recent landmark publication, Evrony et al. (2012) presented L1 mapping data from single neurons, using whole-genome amplification followed by targeted L1 sequencing. A total of 300 single neurons from the caudate and cerebral cortex were obtained from three normal individuals. Ninety-six candidate somatic L1 insertions were identified. Most of these candidates were deemed false positives after validation assays. However, one candidate somatic L1 insertion was successfully cloned. A full-length 6.1 kB L1 sequence was confirmed that contained all the characteristics of a retrotransposon: a target site duplication (TSD), a poly-A tail, and a 5′ transduction sequence. Four additional L1 insertions were validated by insertion site PCR at their 3′ end, but target site duplications could not be identified. Crucially, this was the first report of a validated somatic L1 insertion presenting TSDs in a human neuron, perhaps the best evidence presented thus far that L1 mobilization can occur in the brain.

The L1 mobilization rate reported by Evrony et al. (2012), perhaps as low as 1 in 300 neurons, contrasts with earlier calculations based on the L1 CNV assay (Coufal et al., 2009). It is, however, important to note that Evrony et al. (2012) did not evaluate hippocampal neurons, whereas other groups had previously reported major enrichment in this region (Coufal et al., 2009; Baillie et al., 2011), making it difficult to determine whether the discrepancy in L1 mobilization frequency estimates is the result of technical or brain regional differences. In addition, because brain samples in the studies of Baillie et al. (2011) and Evrony et al. (2012) were obtained from different individuals, biological variability could explain the discrepancies in L1 mobilization rate. That is, there may be biological heterogeneity in the rate of L1 mobilization across different populations of individuals. Further, because a range of environmental factors, including stress (Ponomarev et al., 2010; Hunter et al., 2012), alcohol (Ponomarev et al., 2012), and exercise (Muotri et al., 2009), can alter retrotransposon expression, variation in environmental exposures across individuals may contribute to the differences reported in the two studies. In any case, it is important to note that the adult human brain contains ~86 billion neurons (Azevedo et al., 2009). Based on the lower estimate of 1 new L1 insertion per 300 neurons, an extrapolation suggests that nearly 300 million distinct somatic L1 insertions would be found per brain. Therefore, even if lower estimates of new L1 insertions are correct, somatic retrotransposition could still potentially have a dramatic effect on the function of neurons.

Although others have found brain-specific L1 insertions to be enriched in genes involved in neurogenesis, even when correction for the unusual size of these genes was performed (Baillie et al., 2011), it remains unclear whether these mutations alter the function of the affected neurons. Moreover, although the full-length somatic L1 insertion found by Evrony et al. (2012) occurred in an intron of *IQCH*, a gene expressed in the brain, it was not determined whether host gene expression was perturbed. Future experiments guided by recent technical innovations are required to corroborate and build upon the two major reports of L1 mapping in the human brain published to date (Baillie et al., 2011; Evrony et al., 2012).

The transposon storm: from Barbara McClintock to Lou Gehrig

Barbara McClintock's dissociator and activator transposons explained unstable cellular inheritance of pigmentation patterns in maize (McClintock, 1951, 1984). McClintock referred to these transposons as "controlling elements" because their mobilization impacted the expression of nearby genes. Thus, even in McClintock's original work nearly 60 years ago, the potential for transposons to shape phenotypic outcomes was apparent, challenging the prevailing view that transposons were mere selfish DNA (Orgel and Crick, 1980). On the other hand, the unregulated activation of transposons, as seen for example with dysgenic crosses, reveals the powerful harmful impact of unregulated mobile elements (Pignatelli and Mackay, 1989; Jensen et al., 1995, 1999; Malone and Hannon, 2009). Indeed, animals and plants have evolved formidable surveillance mechanisms to detect and eliminate expression of transposons both in germline and somatic cells (Ghildiyal and Zamore, 2009; Czech and Hannon, 2011). The discovery that some transposable elements are actively mobile in brain (Muotri et al., 2005, 2010; Coufal et al., 2009; Baillie et al., 2011; Evrony et al., 2012; Perrat et al., 2013) thus raises two potential possibilities. The first, discussed above, is the notion that insertion of transposable elements may exert a controlling influence on flanking genes, causing a functionally relevant impact on the diversification of neuronal cell types or on the function of differentiated neurons. At the same time, however, we must consider the potential detrimental impact of unregulated transposon expression.

Transcripts from several *Drosophila* retrotransposons, such as R1 and R2 (which are LINE-like elements) and Gypsy (an LTR-retrotransposon), become highly expressed in head tissue during the course of normal aging (Li et al., 2013). In the case of Gypsy, a monoclonal antibody against the third Orf, which encodes the Env protein, also reveals a striking age-dependent accumulation of Env-immunoreactive puncta throughout neuropil and the "cortical" regions of the fly brain, which contain most of the neuronal and glial somata. In addition, age-dependent expression of Gypsy is associated with accumulation of *de novo* transposition events in neurons. This association was revealed using a "Gypsy-trap" reporter system in which a genomic hotspot for Gypsy integrations was incorporated into a transgenic construct such that insertions of Gypsy would inactivate expression of a Gal80 repressor (Li et al., 2013). Gypsy insertions thus turns off the repressor, allowing Gal4-mediated expression of a GFP reporter. This Gypsy-trap reporter revealed an apparently stochastic and sparse labeling of neurons that accumulated with advancing age.

In broad strokes, the finding that certain retrotransposons are active and even mobile in brain during aging is parsimonious with the observed mobility of L1s during mammalian neurogenesis (Muotri et al., 2005; Baillie et al., 2011) and of a number of transposable elements during *Drosophila* neurodevelopment (Perrat et al., 2013). On the other hand, the age-dependent increase in transposition in *Drosophila* brain that takes place after development is almost certainly occurring in terminally differentiated neurons because adult neurogenesis has not been seen in *Drosophila*. Thus, the observed age-dependent activation is mechanistically distinct from the transposition that normally occurs during development and neurogenesis. And, in contrast with the potential for a functionally relevant impact on normal neurophysiology with transposition during neurogenesis, two features of the age-dependent activation suggest detrimental consequences. First is the fact that both R1 and R2, unlike most LINE-like elements, exhibit target specificity in the genome. Both of these elements target unique locations within the 28s subunit of rRNA (Xiong and Eickbush, 1988a; Eickbush et al., 1997; Moss et al., 2011). In the case of R2, almost all insertions occur at the 28 s target site. Thus, unlike LINE 1 elements in mammals, R1 and R2 seem less likely to produce genetic heterogeneity that could functionally diversify neuronal physiology in a meaningful way. Because insertion of either of these elements is sufficient to inactivate the rRNA subunit, the accumulation of *de novo* insertions of R1 or R2 during aging would seem likely to have detrimental rather than beneficial consequences. A second observation that suggests disruptive effects is the time course of transposon activation. The expression of R1, R2, and Gypsy and the accumulation of *de novo* Gypsy insertions each begin in 2- to 4-week-old adults (Li et al., 2013), which is relatively late in the life span of *Drosophila*. Thus, the time course of transposon activation in the adult *Drosophila* brain is more consistent with an impact on age-related decline than on normal function.

However, there are cases where transposon activation in *Drosophila* is not purely antagonistic or detrimental to the organism. For example, non-LTR retrotransposons have been recruited to serve a telomerase function in *Drosophila*, which maintains genomic integrity (Zhang and Rong, 2012). Nonetheless, transposon activation in the germline has documented detrimental consequences for a number of reasons, including genomic instability, accumulation of deleterious mutations, toxic accumulation of protein or RNA products, and activation of DNA-damage induced apoptosis (Tanda and Corces, 1991; Sheen et al., 1993; Houle and Nuzhdin, 2004; Navarro et al., 2009). Two sets of findings provide indirect evidence that age-dependent activation of transposons in brain does indeed have a detrimental impact. The first comes from manipulations of the Chk2 signal that normally results in apoptosis after DNA damage and the second from disruption of *Drosophila* argonaute-2 (Chen et al., 2007; Klattenhoff et al., 2007; Chung et al., 2008; Czech et al., 2008; Ghildiyal et al., 2008; Kawamura et al., 2008).

The negative consequences of DNA damage resulting from transposon activation have been established in the germline. Paradoxically, blocking the DNA damage-induced signaling that normally leads to apoptosis can in some situations ameliorate the destructive effects of transposon activation in the germline. Disruption of Chk2-mediated signaling of DNA damage "tricks" cells into staying alive and actually suppresses the sterility caused by transposons (Chen et al., 2007; Klattenhoff et al., 2007). This same "trick" appears to ameliorate some of the effects of age in *Drosophila*, where disruption of the Chk2 ortholog in neurons is sufficient to extend life span (Li et al., 2013). Although the connection between the functional effects of disrupting Chk2 and retrotransposons is indirect, it is tempting to speculate that transposon activation contributes to age-dependent neurophysiological decline in part by induction of DNA damage leading to apoptosis.

A second line of evidence that is consistent with the interpretation that age-dependent transposon activation in brain is detrimental comes from manipulation of the *Drosophila* argonaute-2 gene. Argonaute proteins are guided by small regulatory RNAs to silence transposons that contain complementary sequences (Ghildiyal and Zamore, 2009; Czech and Hannon, 2011). In *Drosophila*, this cellular immunity against transposons in germline versus somatic tissue relies on different argonaute proteins that load distinct pools of small RNAs. Silencing of transposons in somatic tissues, but not germline, requires the *Drosophila* argonaute-2 gene (Chung et al., 2008; Czech et al., 2008; Ghildiyal et al., 2008; Kawamura et al., 2008). Thus, mutation of argonaute-2 in flies provides a means to unleash transposons in somatic tissues independent of age. Such mutations indeed lead to precocious expression of R1, R2, and Gypsy in young brains to levels normally seen only in older animals (Li et al., 2013). This expression is accompanied by rapid age-dependent memory impairment and shortened life span. Thus in flies, transposon activation appears to accompany normal aging, and precocious activation of these transposons correlates with more rapid neurophysiological decline. Such functional studies of transposon activation in mammalian brain during aging have not been reported, but there are a few lines of evidence that mobile elements may become actively expressed in patients with several different neurodegenerative disorders and in animal models of the disorders (Lathe and Harris, 2009; Jeong et al., 2010; Muotri et al., 2010; Coufal et al., 2011; Douville et al., 2011; Kaneko et al., 2011; Li et al., 2012; Tan et al., 2012). In the case of amyotrophic lateral sclerosis (Lou Gehrig's disease) and frontotemporal lobar degeneration, there is a link between transposon regulation and TAR DNA-binding protein-43 (TDP-43), which is one of the central players in the disease pathology (Li et al., 2012).

TDP-43 is an aggregation prone protein that plays a key role in a suite of neurodegenerative disorders (Cohen et al., 2011), including amyotrophic lateral sclerosis (Lou Gehrig's disease) and frontotemporal lobar degeneration, which is the second leading cause of dementia before the age of 65. TDP-43 is a multifunctional RNA-binding protein with roles in many aspects of RNA

regulation (Buratti and Baralle, 2010). Although it is not clear how TDP-43 malfunction kills neurons, many downstream impacts of TDP-43 proteinopathy have been elucidated. A series of studies made use of deep sequencing to identify RNA targets of TDP-43 in mouse, rat, and human neurons and characterized changes in transcriptional profiles in response to genetic manipulation of TDP-43 in mouse (Shan et al., 2010; Polymenidou et al., 2011; Sephton et al., 2011; Tollervey et al., 2011). Together, this literature identified thousands of RNA targets of TDP-43. Typically, TDP-43 binds to a UG-rich motif in long intron-containing transcripts. Many additional transcripts were found to be mis-regulated in mouse models of TDP-43 proteinopathy. Because of the difficulty of mapping repetitive reads (Treangen and Salzberg, 2012), each of these deep sequencing studies used analyses that focused on single copy annotated genes and excluded repetitive sequences, such as those that typically derive from transposons. More recently, new algorithms for analyzing multiple alignments of short sequence reads have been developed (Ji et al., 2011; Li et al., 2012), permitting a systematic analysis of transposon transcripts within these datasets. This analysis uncovered extensive binding of TDP-43 to RNA sequences derived from many transposons, including LINE, SINE, and LTR retrotransposons (Li et al., 2012). In a dataset that compared TDP-43 targets from healthy control cortex and cortical tissue from frontotemporal lobar degeneration patients (Tollervey et al., 2011), the binding between TDP-43 and its transposon targets was selectively and dramatically reduced (Li et al., 2012). Moreover, examination of transposon sequences (Li et al., 2012) in RNA-seq datasets from mice with disruptions of normal TDP-43 function (Shan et al., 2010; Polymenidou et al., 2011) revealed upregulation of many of the LINE, SINE, and LTR-retrotransposon transcripts to which TDP-43 normally binds. Taken as a whole, this meta-analysis raises the possibility that TDP-43 normally plays a protective role by binding to and silencing transposon transcripts.

The cellular mechanisms that lead to transposon activation in the brain during aging and with some neurodegenerative disorders are not understood. Furthermore, it is not known whether transposon expression is a cause or a consequence of aging or of neurodegenerative disease. Nevertheless, studies of dysfunctional activation of transposons during aging and neurodegeneration raise the provocative hypothesis that normally silenced transposons can become "awakened" (i.e., unsilenced, leading to increased expression and mobilization) in the brain during aging or with disease.

Activation of transposable elements in an animal model of PTSD and human alcoholism

There is much emerging evidence for the role of retrotransposons in regulation of brain function in health and disease. The availability of whole-genome sequences of multiple species (Adams et al., 2000; Lander et al., 2001; Waterston et al., 2002; Gibbs et al., 2004; Nellaker et al., 2012) and recent genome-wide projects, such as ENCODE (Dunham et al., 2012), greatly accelerated these research efforts, as information about the genomic location, diversity, and regulation of retrotransposons became available. Studies that use whole-genome approaches (e.g., microarray gene expression profiling and next-generation sequencing) can benefit tremendously from these new data on the function and localization of retrotransposons. A large portion of transcribed sequences (transcripts) used by these technologies are "unannotated" (i.e., corresponding to genomic locations with no protein-coding genes or repeated sequences, such as ribosomal proteins or retrotransposons). Most genomic studies usually discard these sequences from the analysis and focus on a small number of known protein-coding genes. An alternative is to take a systems genomics approach, focusing on the regulation of the transcriptome as a whole, including both coding and noncoding regions (Oldham et al., 2008; Ward and Kellis, 2012). One of the first coordinated efforts to investigate the role of TEs in the brain using a genome-wide approach was the study of central mechanisms underlying stress-enhanced fear learning (SEFL) in rats, which is an accepted model of PTSD in humans (Rau and Fanselow, 2009; Ponomarev et al., 2010). PTSD is a brain disorder that may develop after a person is exposed to one or more traumatic events. It is characterized by an exaggerated emotional reaction to mild stressors, and people who have PTSD may feel stressed or frightened even when they are no longer in danger. In the SEFL model, rats preexposed to a severe stressor of 15 foot shocks in one environment showed an enhanced freezing response to a single "reminder" foot shock in a second environment (Rau et al., 2005). This SEFL is similar to the disproportionately strong responses that PTSD patients show to reminders of the stressor. Gene expression profiles in the amygdala of SEFL rats were examined 3 weeks after the exposure to 15 foot shocks using Illumina microarrays. Using a clustering algorithm, several modules of genes coregulated by stress were detected, which corresponded to various functional and structural groups in the brain, including genes coexpressed in neurons and astrocytes. This finding suggested specific roles for these cell classes in the development of SEFL (Ponomarev et al., 2010).

One surprising finding was a statistically distinct module containing tightly coregulated transcripts with no annotations. Illumina probes were mapped to the rat genome using a combination of the UCSC Genome Browser and the RepeatMasker program that identifies the location of genomic repeats, including retrotransposons and showed that the majority of the unannotated microarray probes mapped to multiple locations in the genome that corresponded to LINE-1 retrotransposons. Furthermore, all these transcripts were highly upregulated in the basolateral amygdala of the SEFL rats compared with controls, suggesting that a single stress exposure could result in a long-term activation of retrotransposons. Retrotransposons are normally silenced by epigenetic mechanisms, including DNA methylation and modifications of histone tails, but can be expressed when the epigenetic silencing is released (Slotkin and Martienssen, 2007). Therefore, these results suggested that the increased expression of retrotransposons in SEFL rats was the result of a "passive" release of chromatin-mediated gene silencing. Interestingly, it was recently shown that acute restraint stress in rats inhibited expression of several classes of retrotransposons in the hippocampus through increases in repressive histone H3 lysine 9 trimethylation (Hunter et al., 2012). Therefore, there may be dynamic and opposing regulation of different types of retrotransposons depending on the magnitude and duration of the stressor as well as the brain region where they are expressed.

In another recent study, gene expression profiling in postmortem human brains of alcoholics and control cases using Illumina microarrays was conducted (Ponomarev et al., 2012). Alcoholism is a serious health problem that causes a large economic and disease burden (Grant et al., 2004; Rehm et al., 2009). Understanding the mechanistic changes in human brain after years of alcohol abuse is critical to understanding the disease and developing therapeutics to fight it. Similar to the previous study (Ponomarev et al., 2010), a systems genomics approach to transcriptome profiling was conducted and generated a systematic view of brain alterations associated with alcohol abuse. One of the

key components of this study was targeting differentially expressed retrotransposons in human alcoholic brain, including the central and basolateral amygdala and superior frontal cortex. Alignment of Illumina microarray probes to genomic retrotransposons using the RepeatMasker program showed that nearly 4000 probes could be mapped to one of three classes of retrotransposons (LINEs, SINEs, and LTRs) as well as DNA transposons. Gene clustering revealed that probes representing at least two TE classes (SINEs and LTR) were highly correlated (coregulated) across samples, forming several distinct gene modules. In addition, many probes mapped to several families of LTR-containing TEs, and these LTR modules were upregulated in alcoholics. Interestingly, the only Illumina probe corresponding to a currently "active" LINE-1 family, L1HS (ILMN_2291619) was also highly upregulated in alcoholic brain. Examination of DNA methylation at the LTR regions showed that, in alcoholics, these regions were less methylated, which is mechanistically consistent with the activation of these transposons because they are suppressed by methylation. This study showed that chronic alcohol abuse resulted in DNA hypomethylation and transcriptional activation of LTR-containing transposons and at least one family of LINE-1 TE.

Stress enhances alcohol drinking in animal models, and many alcoholics have had stressful events associated with their alcohol abuse (Becker et al., 2011; Sinha, 2012). Human alcoholism and PTSD are comorbid conditions, as many PTSD patients abuse alcohol (McCarthy and Petrakis, 2010). Based on the two studies described above and other literature, it can be concluded that stress and/or chronic alcohol may lead to transcriptional activation of TEs. Indeed, this is the first report suggesting that LTR-containing TEs may play a functional role in alcoholism (Ponomarev et al., 2012). These TEs represent a class of ERVs, most of which are nonfunctional remnants of ancient retroviral infections (Moyes et al., 2007). However, many human ERVs have retained functional promoters and the potential to encode viral proteins. Activation of ERVs has been linked to chronic diseases, including cancer, multiple sclerosis, and autoimmune disorders (Balada et al., 2009). An ERV-encoded glycoprotein, syncytin, can directly activate microglia and astrocytes and produce neuroinflammation (Antony et al., 2004). Microglial activation can result in neuronal degeneration (Crews et al., 2011), and compounds secreted by syncytin-activated astrocytes can produce cytotoxicity to oligodendrocytes and myelin degeneration (Antony et al., 2004), which is consistent with pathologies observed in alcoholics (Harper et al., 2003; Pfefferbaum et al., 2009; Zahr et al., 2011). Based on recent evidence that alcohol-induced neuroimmune responses are critical factors in alcohol addiction (Crews et al., 2011), these studies propose a potential role for ERVs in neuroinflammation and brain pathophysiology of human alcoholism. However, it remains to be determined whether ERVs play a causal role because it is not known whether altered expression of ERVs results in the expression of viral proteins and the initiation of the immune response in brain.

In addition to understanding the functional role of TEs in brain function, utilization of the emerging knowledge about the epigenetic regulation of TEs will enable a complete picture of TE regulation and function (Xie et al., 2013). TEs are tightly controlled and silenced by epigenetic mechanisms, and their expression patterns can be used as markers of epigenetic modifications without directly measuring epigenetic marks. Furthermore, detecting certain epigenetic changes may lead to hypotheses about TE regulation. There is substantial evidence suggesting the importance of epigenetics in stress-related disorders, including PTSD and alcoholism (Radley et al., 2011; Robison and Nestler, 2011), and this knowledge may be useful in better understanding the role of TEs in these conditions. In addition, many epigenetic therapeutics have been developed for non-CNS diseases. Therefore, epigenetic mechanisms could be targeted to alter the potentially deleterious effects of brain retrotransposons. Finally, examination of the effects of stress and alcohol on retrotransposons in additional regions of the brain is warranted. In particular, the hippocampus is an important target of stress and alcohol; both stress and alcohol decrease adult hippocampal neurogenesis (Dranovsky and Hen, 2006; Nixon, 2006). The majority of studies examining the function and expression of retrotransposons have been conducted in this region because neurogenesis in the hippocampus has been shown to substantially regulate the activity of retrotransposons (Muotri et al., 2005, 2009; Coufal et al., 2009; Muotri et al., 2010; Baillie et al., 2011).

Conclusions and future directions

The longstanding idea that neuronal genomes contain stable, unchanging DNA is now being challenged by mounting evidence that somatic retrotransposition occurs in neurons. This review has highlighted the evidence that retrotransposons, McClintock's "jumping genes," must now be considered as a viable source of genetic variability in the brain and in health and disease of the CNS. The advances in genomic technologies have enabled a deeper understanding of the role of retrotransposons in neuronal function and evolution. This is indeed an exciting time for what was once dismissed as genomic "parasites" or "selfish" entities of the genome.

The sheer abundance of retrotransposons in eukaryotic genomes begs us to reconsider their role in biology and in neuroscience in particular. Altered retrotransposon expression or function appears to be associated with stress, alcohol, neurodegeneration, and aging. However, we need to better define the functional consequences of these retrotransposons, which could lead to novel treatment strategies for a multitude of psychiatric and neurological disorders.

Finally, the evolutionary significance of retrotransposons, especially in the evolution of brain function, is paramount in understanding why nature has produced such a biological mechanism. Cross-species analysis of the function of retrotransposons in the brain will undoubtedly provide clues to their origin and their potential as drivers of genomic innovation.

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