NEUROSCIENCE

Early life experience shapes neural genome

Transposons accumulate in neurons of pups with lack of maternal care in mice

By **Saera Song**[1] and **Joseph G. Gleeson**[2]

The brain is constantly changing in response to environmental experiences throughout life. Mounting evidence from animal and human studies suggests that brain development and behavior are influenced by early life experiences. Several compelling experimental models have been developed to study the effect of early life experiences on the brain, such as stress, exposure to toxins, availability of nutrients, adversity, and quality of maternal care (*1*). The relationship between genes and environment on the brain and how they affect behavior has been a long-standing issue. Can the genome of individual brain cells be changed by environmental factors? If so, which types of genetic changes can result? What is the molecular basis of this genetic diversity? What are the physiological implications? On page 1395 of this issue, Bedrosian *et al.* (*2*) explore one possibility for how neuronal genomes can exhibit plasticity in response to environmental factors during early life, providing integrative evidence for the effect of early maternal care on the genomes of neurons.

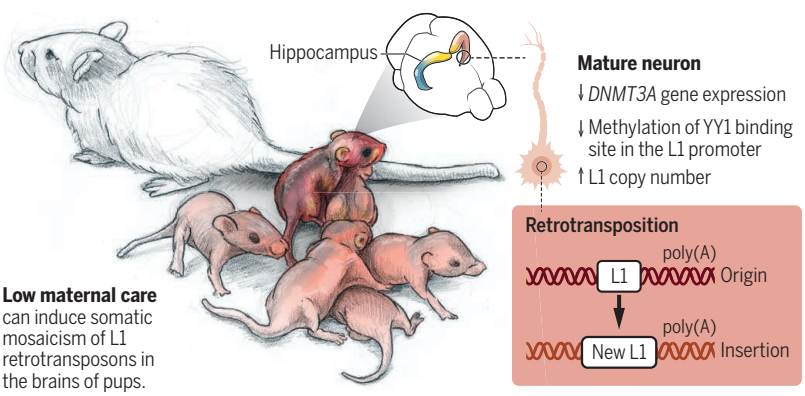
Somatic mosaicism is the phenomenon by which cells within an organism can have different genetic sequences. The brain exhibits extensive somatic mosaicism, and this is of particular interest because it can contribute to neuronal diversity and potentially expand the range of behavior of the individual (*3*). Mobile elements are DNA sequences that can change their position within the genome, either by a DNA-based (transposition) or RNA-based (retrotransposition) mechanism (*4*). Retrotransposition is one of the main forms of somatic mosaicism in the brain (*5*). Dividing cells, such as neural progenitor cells, may tolerate or even support increased levels of retrotransposition relative to other cells, resulting in neurons with unique genomes (*6*–*8*). Long interspersed element-1 (L1, also known as LINE-1) is the most abundant class of retrotransposon, comprising about 17% of the mammalian genome. L1 elements remain mobile in both human and mouse genomes throughout life. L1 elements are ~6 kb long, and the insertion of L1 into DNA during retrotransposition results in the generation of variably sized target site duplications, which flank the new insertion. It can be challenging to detect neuronal L1 retrotransposition events because individual events can be specific to a particular cell and can vary in frequency based on the brain region and/or cell type being assayed and the method of detection (*9*–*11*). Despite such challenges, it is now understood that somatic retrotransposition occurs in neurons of both humans and mice and can influence neural disease. These advances were achieved through the development of new experimental tools such as copy number quantitative polymerase chain reaction (PCR) assays, L1 reporter assays, and next-generation sequencing of bulk and single cells. Building on this previous work, Bedrosian *et al.* hypothesize that neuronal genomes can be influenced by environmental factors such as early life experiences.

Rodent pups receive maternal care as one of the first biological embedding experiences. Natural variations of maternal care can be assessed by monitoring licking and grooming behaviors, nesting patterns, contact time, and the type of posture in rodents (*12*). Bedrosian *et al.* developed a droplet digital PCR (ddPCR) assay to detect copy number of L1 retrotransposons in neuronal cell genomes. They demonstrated that pups reared under conditions of low maternal care for the first 2 weeks after parturition accumulate L1 retrotransposons. This L1 accumulation was observed in the hippocampus but not in the frontal cortex or heart, suggesting that they represent somatic mosaic events. The hippocampus exhibits plasticity, and it is highly sensitive to environmental stimuli, making it more likely to foster retrotransposition during early life (*7*). To further support the apparent inverse correlation of increased L1 copy number and decreased maternal care, the authors manipulated the effect of maternal care by separation, resulting in a compensatory increase in care that dams (female parents) provide to pups upon reunification. Maternal separation attenuated accumulation of L1 copies of pups reared with low-maternal-care dams. Moreover, a cross-fostering experiment showed better correlation of L1 copy number with the maternal care of the dam that reared the pups rather than the biological dam. As a potential mechanism, Bedrosian *et al.* also report that neuronal cells from pups that experienced low maternal care had reduced L1 promoter methylation on the binding sites of the transcriptional repressor protein, Yin Yang 1 (YY1), which correlated with reduced expression of DNA methyltransferase 3A (DNMT3A). Thus, the changes in retrotransposition may be regulated at the epigenetic level (see the figure). It will be interesting to measure the effect of these events on neuronal cell phenotypes and on the behavior of the offspring.

It is well established that maternal care can affect epigenetic control and changes in gene expression in the brain (*13*). The study

Maternal care alters genomic structure

Early life experiences such as maternal care affect DNA sequence in neurons of the hippocampus via L1 retrotransposition. The accumulation of L1 retrotransposons in the hippocampus of rodent pups reared with low maternal care might contribute to higher anxiety-like behavior in adulthood.



Low maternal care can induce somatic mosaicism of L1 retrotransposons in the brains of pups.

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by Bedrosian *et al.* brings new insight into this concept, demonstrating that plasticity in DNA sequences can change in response to environmental cues. More detailed analysis, including mapping of L1 insertion sites to demonstrate their integration into genomic DNA by single-cell genomic analysis from hippocampal neurons, is necessary to critically test this hypothesis. In addition, it will be interesting to examine the effect of other environmental challenges on L1 retrotransposition in the brain or to identify other types of somatic genomic variations in the brain that can result from environmental factors. However, caution is warranted in extrapolating these findings to humans. L1 is much more active in mouse than human brain, and there are higher numbers of active L1s in the average mouse genome (3000 to 4000) compared with human (~80 to 100) (*14*, *15*). Additionally, we still do not completely understand the biological and physiological consequences of L1 retrotransposition events. As in previous reports, higher anxiety-like behavior was observed in adult mice that were reared with low maternal care (*12*), and thus it would be interesting to investigate whether increased L1 copy number contributes to these behaviors. It is believed that mosaic DNA mutations can potentially alter the physiological properties of individual neurons, contributing to overall brain function, neural circuits, and behavior, although such changes could just as easily be maladaptive. Somatic mosaicism resulting from retrotransposition or other types of mutations may represent a bridge between environmental and genetic factors that create functional diversity among brain cells or the predisposition to brain disorders. With a further understanding of how environmental factors contribute to somatic mutations in the human brain, it may become possible to better predict risk and develop new treatments for neuropsychiatric disease. ■

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NEUROBIOLOGY

RNA targeting and translation in axons

Local translation of transcripts takes center stage in neuron growth and regeneration

By **Antonella Riccio**

Neurons are among the largest and most complex cells in nature, often extending very long axons, which in adult mammals, including humans, can reach up to one meter in length. These extraordinary morphological features pose a challenging problem as to how information codified in the nucleus can reach the periphery of the cell in a timely manner to respond to extrinsic stimuli. Similar to virtually all eukaryotic cells, neurons have adopted the strategy of localizing RNA asymmetrically. The nature of the transcripts targeted to dendrites and axons have been extensively studied, and they encode synaptic proteins, cytoskeleton components, ion channels, mitochondrial and ribosomal proteins, and proteins required for plasma membrane biogenesis. However, the mechanism underlying local translation has remained elusive. On page 1416 of this issue, Terenzio *et al.* (*1*) add a new piece to the puzzle and show that local translation to produce the protein mammalian target of rapamycin (mTOR) precedes the burst of protein synthesis associated with the regeneration of injured axons. mTOR is a serine/threonine kinase that plays a central role in regulating protein synthesis (*2*).

Peripheral localization of transcripts is a widespread phenomenon that mediates many cellular processes. In neurons, coding and noncoding RNAs are targeted to dendrites and axons, where messenger RNAs (mRNAs) are rapidly translated in response to extrinsic stimuli. Local protein synthesis has been shown to mediate synaptic development and plasticity in dendrites, whereas in axons, it is necessary for axon extension and steering in response to guidance cues (*3*). Although polyribosomes were visualized at the base of dendritic spines more than 30 years ago, the presence of the translational machinery in axons has been hotly debated. This was mostly because in axons, ribosomes are found close to the plasma membrane, which makes visualization by using classical microscopy techniques difficult. Because of their localization, it has even been proposed that axons may "borrow" ribosomes from surrounding cells, such as Schwann cells that produce the myelin sheath that coats axons (*4*).

Comparative analyses of RNAs localized in either dendrites, axons, or cell bodies showed expression patterns that only partially overlap and differ depending on cell type and developmental stage (*5*–*7*). Interestingly, transcripts that are highly expressed in cell bodies are not necessarily enriched in axons or dendrites, indicating that RNAs do not reach the peripheral compartments by passive transport but are sorted and delivered with an active mechanism. How are transcripts selected to be transported to axons? At least two mechanisms must be taken into account, one intrinsic to the RNA and dependent on its structure and a second related to the extrinsic signals that trigger transcript localization. Although the information necessary for RNA transport can be stored anywhere along the transcript, most elements that regulate mRNA targeting are found within the 3′ untranslated regions (UTRs). The first localization element of a neuronal transcript was identified in the 3′UTR of the mRNA encoding β-actin and was named "zipcode" because it was necessary for delivering the mRNA to axons in response to neurotrophins (*8*). A number of localization elements have since been found in the 3′UTRs of transported transcripts (*5*, *9*). Although the ribonucleotide sequences of localization elements described so far show little resemblance, it is possible that the folding of the RNA may form common secondary structures.

"Further understanding of the basic mechanisms underlying mRNA localization...will lay the foundations for developing new therapeutic approaches for many neural disorders."

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