Opinion

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RNA editing, DNA recoding and the evolution of human cognition

John S. Mattick[1] and Mark F. Mehler[2]

[1] ARC Special Research Centre for Functional and Applied Genomics, Institute for Molecular Bioscience, University of Queensland, St. Lucia, QLD 4072, Australia
[2] Institute for Brain Disorders and Neural Regeneration, Departments of Neurology, Neuroscience and Psychiatry and Behavioral Sciences, Einstein Cancer Center and Rose F. Kennedy Center for Research in Mental Retardation and Developmental Disabilities, Albert Einstein College of Medicine, Bronx, NY 10461, USA

RNA editing appears to be the major mechanism by which environmental signals overwrite encoded genetic information to modify gene function and regulation, particularly in the brain. We suggest that the predominance of Alu elements in the human genome is the result of their evolutionary co-adaptation as a modular substrate for RNA editing, driven by selection for higher-order cognitive function. We show that RNA editing alters transcripts from loci encoding proteins involved in neural cell identity, maturation and function, as well as in DNA repair, implying a role for RNA editing not only in neural transmission and network plasticity but also in brain development, and suggesting that communication of productive changes back to the genome might constitute the molecular basis of long-term memory and higher-order cognition.

Introduction

RNA editing is a process through which RNA base sequences are post-transcriptionally altered. RNA editing occurs in most, if not all, tissues but is particularly active in the nervous system, where it has long been known to play an important modulatory role, especially in the modification of transcripts encoding proteins involved in fast neural transmission, such as ion channels and ligand-gated receptors [1–3]. It is clear that RNA editing is a principal means by which environmental information can intersect with genetically and epigenetically encoded information, given that RNA is the product of the first and intimately involved with the second [4]. Although RNA editing has been a well-recognized phenomenon throughout evolution, there has been a dramatic increase in the incidence of RNA editing during vertebrate, mammalian and primate evolution, with humans exhibiting the highest levels of both edited and multi-edited transcripts [1–3].

Several different forms of editing occur in humans catalyzed by two classes of RNA editing enzymes [1–3,5]. The predominant form of RNA editing in mammals is adenosine-to-inosine (A-I) editing which is catalyzed by ADARs (*a*denosine *d*eaminases *a*cting on *R*NAs), of which there are three paralogs encoding ADAR1–3, all with preferential expression in the nervous system, with ADAR3 being expressed exclusively in the brain [1,2]. The general substrate for A-I editing appears to be double-stranded regions of RNA, but what determines the site selectivity of RNA editing of specific transcripts in different cells and tissues is not well understood [1–3].

RNA editing and gene–environmental interactions in the brain

There are at least three distinct ways that RNA editing can alter brain function in response to experience (i.e. learning) and contribute to the evolution of higher-order cognitive capacities. First, by selectively editing codons and splicing signals in protein-coding sequences involved in modulating fast neurotransmission and all stages of presynaptic vesicle release [1–3], ADAR enzymes can fine-tune the firing properties of neurons required for appropriate neuronal and neural network output and integration. Second, RNA editing can alter the processing, properties and target specificities of microRNAs (miRNAs) and the regulatory networks in which they participate [6,7] (see also below). Third, RNA editing can modify the sequences and biophysical properties of a vast array of other gene products, notably pre-mRNAs and the large numbers of non-coding RNAs known to be specifically expressed in the brain and to play roles in many functional and regulatory pathways, including epigenetic phenomena associated with learning [8–10].

Within brain, ADARs exhibit complex profiles of spatio-temporal regulation and dynamic changes in subcellular localization [3], and are themselves subject to alternative splicing [11]. Moreover, the activities of ADARs are modulated by environmental cues and modify signaling cues embedded within intracellular transduction pathways containing edited targets as seen in ADAR1/2 editing of the serotonin ($5\text{-}HT_{2C}$) transcript [3]. RNA editing is also modulated by genetic background as well as behavioral state, suggesting that this process might represent a hidden layer of regulatory and functional plasticity mediating gene–environmental interactions during neural state transitions [12]. Analysis of *Caenorhabditis elegans*, *Drosophila* and mouse ADAR mutants demonstrates that RNA editing is critical for the cognitive and behavioral correlates of nervous system function [3], and that loss of RNA editing predisposes to progressive neurodegeneration [3,13]. Furthermore, deregulation of ADAR activity and associated hyper- or hypo-editing of RNA transcripts is

Corresponding author: Mehler, M.F. (mehler@aecom.yu.edu).

0166-2236/$ – see front matter doi:10.1016/j.tins.2008.02.003 Available online 7 April 2008

associated with an increased risk of neurodegenerative diseases and cancer in addition to an elevated occurrence of neurodevelopmental as well as neuropsychiatric diseases [3,14,15].

The link between RNA editing and environmental cues is supported by the observation that inositol hexakisphosphate is complexed within the catalytic core of ADAR2, which strongly implies a connection to cell signaling pathways [16]. Moreover, there are well-characterized iconic examples of neural ligand-gated receptors, particularly glutamate and serotonin receptor subunits, that are edited to alter their coding sequence and splice isoforms, thereby modifying their biochemical and electrophysiological properties, presumably to fine-tune individual synaptic strength and other features of synaptic transmission and neuronal network connectivity [3]. Other molecules are also edited, including miRNAs [17–20] and other non-protein-coding RNAs (ncRNAs) [21–23], which can redirect the miRNAs to silence different targets [20]. Sites of RNA editing might also be sites of small nucleolar RNA-mediated RNA modification [24], suggesting that editing is used not only to alter the biochemical properties of proteins but also genetic and epigenetic regulatory networks, and that such networks could be extraordinarily complicated, especially in the brain.

RNA editing in Alu elements – evolutionary co-adaptation?

Recently, it was reported by several groups that A-I editing is much more abundant in humans than in mice, and that over 90% of this increased editing occurs in head-to-tail Alu elements in (mainly) noncoding regions of RNAs, that is, in UTRs of mRNAs, and in intronic and intergenic transcripts [21–23]. Alu elements represent a subclass of primate-specific SINEs (short interspersed nuclear elements) derived from 7S and tRNA sequences and spread around the genome by retrotransposition [25]. These repetitive elements entered the genome in three successive waves during primate evolution, with massive expansion in hominids to over one million copies that now comprise 10.5% of the human genome [25]. Although Alu elements have been exapted for many different functions [25], the observations that (i) editing is most active in brain and is important to brain function, (ii) humans show two orders of magnitude more editing than mice, (iii) most of the increased editing in humans occurs in Alu elements, which are primate specific and (iv) primates are the lineage which has experienced the highest evolution of cognitive capacities, raise the possibility that the predominance of Alu elements in the human genome might not be simply an accident of history but rather in large part the result of evolutionary co-adaptation of these sequences as a modular substrate for A-I editing, driven by positive selection for increased cognitive capacity.

This proposal is consistent with the observation that Alu elements are enriched in GC-rich regions of the genome (which are gene dense) and that this distribution is most likely because of positive selection [26]. If this is the case, Alu elements might have not only supplied the platform for accelerated penetration of RNA editing in the hominid lineage [27], but might also represent a central part of the functional programming of the ontogeny of neuronal circuitry, the plasticity of brain function and consequently higher-order cognition. The sheer number of these elements (~1 million) makes it difficult to assign an enriched association to any particular type of locus, and indeed the reprogramming of the editable portion of the genome required to support higher-order cognition might have been considerable, as evidenced by the range of transcripts that exhibit editing (see below).

RNA editing in brain development

If RNA editing represents a major molecular mechanism for mediating the interplay between the brain and the environment, what can we learn from the types of sequences that are edited? First, as noted already, it is evident that editing occurs in noncoding as well as coding sequences, indicating that editing can alter the spatiotemporal profiles of gene expression and functional regulation as well as the biophysical properties of gene products, a huge uncharted world to be explored. Indeed, the predominance of editing in noncoding sequences, not just in UTRs of mRNAs but also in other noncoding transcripts, suggests that Alu-based editing sites have been exapted primarily to alter regulatory networks rather than protein structure. A significant subset of the edited transcripts have been recorded simply as expressed sequence tags, many of which appear not to have any protein-coding capacity and to represent independent transcripts, processed intronic RNAs or antisense RNAs. Although there is only one documented case of RNA editing of a repetitive sequence element that has been shown to influence gene expression [28], many ncRNAs, including intronic and antisense RNAs, show precise expression patterns in the brain [10], suggesting a vast hidden layer of RNA-based regulatory transactions [29]. Moreover, some miRNAs are derived from Alu sequences [30] and are subject to ADAR editing [17–20], and recent results show that miRNA-mediated translational repression can be relieved by another class of editing enzymes, the APOBEC family members [31]. Given the abundance of miRNAs in the nervous system and their central roles in brain development [6,7], as well as the fact that many miRNAs are derived from introns [32] and that many are primate specific [33], RNA editing for regulatory purposes might be widespread, particularly if (as expected) it is the regulatory architecture that controls brain development and plasticity [6].

We analyzed the human RNA edited transcript databases [21–23], as well as an unpublished set (A. Athanasiadis, pers. commun.), and found that transcripts from loci involved in fast neural transmission represent only a small subset of the targets of A-I RNA editing. These targets (of which there are thousands) include many examples of transcripts from gene loci involved in nervous system development (Box 1), encompassing loci encoding proteins that modulate neural induction as well as those involved in three-dimensional patterning of the anterior portion of the evolving neural tube, including the forebrain (Box 1a). Editing is also observed in transcripts from loci involved in neural stem cell self-renewal, asymmetric cell division and modulation of proliferation (Box 1b) as well as those