Brain Cytoplasmic 1 RNA: Little Guy with a Big Role as a Repressor of Epileptogenesis

BC1 Regulation of Metabotropic Glutamate Receptor-Mediated Neuronal Excitability. Zhong J, Chuang SC, Bianchi R, Zhao W, Lee H, Fenton AA, Wong RK, Tiedge H. *J Neurosci* 2009;29(32):9977–9986. Regulatory RNAs have been suggested to contribute to the control of gene expression in eukaryotes. Brain cytoplasmic (BC) RNAs are regulatory RNAs that control translation initiation. We now report that neuronal BC1 RNA plays an instrumental role in the protein-synthesis-dependent implementation of neuronal excitation–repression equilibria. BC1 repression counter-regulates translational stimulation resulting from synaptic activation of group I metabotropic glutamate receptors (mGluRs). Absence of BC1 RNA precipitates plasticity dysregulation in the form of neuronal hyperexcitability, elicited by group I mGluR-stimulated translation and signaled through the mitogen-activated protein kinase kinase/extracellular signal-regulated kinase pathway. Dysregulation of group I mGluR function in the absence of BC1 RNA gives rise to abnormal brain function. Cortical EEG recordings from freely moving *BC1*$^{-/-}$ animals show that group I mGluR-mediated oscillations in the γ frequency range are significantly elevated. When subjected to sensory stimulation, these animals display an acute group I mGluR-dependent propensity for convulsive seizures. Inadequate RNA control in neurons is thus causally linked to heightened group I mGluR-stimulated translation, neuronal hyperexcitability, heightened γ band oscillations, and epileptogenesis. These data highlight the significance of small RNA control in neuronal plasticity.

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COMMENTARY

Most neuronal function in the CNS is highly dependent on glutamatergic excitation. When a rapid response is

needed, ionotropic glutamate receptors take charge and mediate the effect very efficiently. For more enduring responses, long-lasting modification of neuronal excitability and synaptic plasticity are necessary. In these cases, metabotropic glutamate receptors (mGluRs) are very useful for generating an intracellular second-messenger cascade of events that can culminate in the plastic changes required. Group I mGluRs, in particular, have been shown to serve important roles in synaptic plasticity processes that underlie both long-term potentiation and long-term depression. However, excessive activation of group I mGluRs can result in a long-lasting enhancement of network excitability, potentially leading to epileptogenesis (1). These mGluR-mediated plasticity processes are protein synthesis-dependent (2).

How does the system allow for localized plasticity to occur without always resulting in the pathologic network hyperexcitability underlying epilepsy? It appears that there are endogenous regulators in place that, in essence, put the brakes on the induced protein synthesis and thus, suppress excessive excitation. One such regulator is the fragile X mental retardation protein (FMRP), as discussed in a 2009 *Epilepsy Currents* commentary (3). The recent paper by Zhong and colleagues reveals yet another potent suppressor of this mGluR-induced pathway: brain cytoplasmic 1 RNA (BC1 RNA).

RNA was once, in the not-so-distant past, believed to serve primarily as a means to convert genetic code into proteins. Work done in recent years, however, has brought a wealth of information regarding the previously underappreciated roles of RNA. Specifically, small non-protein-coding segments of RNA have been found to be critical to higher organisms in the regulation of numerous cellular functions, such as helping to determine when and where specific genes are expressed and restricting the translation of certain proteins, thereby regulating synaptic plasticity. It is estimated that close to 98% of the human genome may code for these non–protein-coding RNAs (4).

What determines the impact of a given RNA on cellular function? How can a tiny bit of RNA modulate plasticity processes? Oftentimes, the influence of RNA on cellular function is highly dependent on location, location, location. (5). The dendritic colocalization of small RNAs and transitional machinery serve to compartmentalize the neuron, creating microdomains in which concentrations of key regulators and proteins can fluctuate in response to synaptic inputs and have a localized impact. Such localized modifications turn out to be essential for neuronal development in the immature nervous system as well as for the normal functioning of fully differentiated neurons and glia.

BC1 RNA is a brain-specific regulatory RNA whose expression is primarily localized to dendrites, where it serves to suppress the synthesis of certain proteins at the synapse by interfering with translation initiation (6). When scientists developed knockout mice to determine the significance of BC1 RNA, they reported that the mice were not only viable but at first glance appeared healthy (7). Subsequent studies revealed, however, that the animals were more anxious and displayed a diminished tendency to explore their surroundings (8). The current study by Zhong and colleague delves deeper into the physiologic impact of the absence of BC1 RNA.

Zhong and colleagues conducted a beautiful series of experiments using the BC1 RNA knockout mouse strain. The investigators examined both the cellular and network impact of the absence of BC1, combining in vitro and in vivo electrophysiological and molecular approaches and, most importantly, demonstrating the ability to reverse each of the observed abnormalities, thereby causally relating the deficient RNA, the enhanced group I mGluR physiologic responses, and the resultant phenotype. Comparing wild-type and mutant mice, they first demonstrated that mGluR-driven synthesis of synaptic proteins is enhanced in the BC1 knockout mouse. This finding correlated with an enhanced expression of ictal-length discharges that were dependent on group I mGluR activation and whose expression could be prevented with protein synthesis inhibitors. Functionally, this enhanced expression of discharges translated to a lowered seizure threshold that was manifested by the presence of audiogenic seizures, which were fatal in 23% of the animals. Here, too, the seizures could be prevented through the use of either group I mGluR antagonists or protein synthesis inhibitor. Finally, in nonconvulsing animals, EEG recordings revealed an increased presence of mGluR-dependent γ oscillations that were similarly sensitive to mGluR5 antagonist and to protein synthesis inhibitor (9).

These data reveal the delicate balance that exists between group I mGluR-mediated neuronal excitation and the protein-synthesis-dependent network plasticity that underlies the epileptogenic process. Activation of group I mGluRs drives an increase in protein synthesis, and if it is left unchecked, persistent ictal discharges may be expressed by the hippocampal network, leading to epileptogenesis (2). Fortunately, there are built-in roadblocks that titrate this effect and allow for some degree of excitation to come through without culminating in epilepsy. BC1 RNA is upregulated during times of increased activity (10), suggesting a compensatory effect that enhances its protective role during potentially epileptogenic events. In the absence of BC1 RNA, deficient endogenous regulation of group I mGluR-driven protein synthesis leads to epileptogenesis. The strength of this study by Zhong and colleagues is confirmation of the causative correlation between protein synthesis and the epileptic phenotype through the use of both protein synthesis inhibitors and mGluR antagonists.

A greater understanding the second-messenger pathways and endogenous control mechanisms involved in the epileptogenic process provides insights on the wide range of responses

evoked by similar insults (e.g., head trauma). Genetic variability in FMRP, BC1 RNA, or group I mGluRs among various individuals could potentially result in different levels of excitatory responses to similar provocations, and if the net excitatory response is enhanced, the outcome may be epilepsy. If so, targeting these pathways may provide novel therapeutic avenues for those patients whose seizures are mGluR-dependent.

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References

1. Merlin LR. Persistent changes in network excitability induced by group I metabotropic glutamate receptor activation: Impact on seizure expression and implications for epileptogenesis. In: *Encyclopedia of Basic Epilepsy Research* Vol. 1. (Schwartzkroin PA, ed.), Oxford: Academic Press, 2009:442–448.
2. Merlin LR, Bergold PJ, Wong RKS. Requirement of protein synthesis for group I mGluR-mediated induction of epileptiform discharges. *J Neurophysiol* 1998;80:989–993.
3. Merlin LR. The fragile X mental retardation protein: A valuable partner in the battle against epileptogenesis. *Epilepsy Curr* 2009;9:116–118.
4. Mattick JS. Challenging the dogma: The hidden layer of non-protein-coding RNAs in complex organisms. *BioEssays* 2003;25: 930–939.
5. Dahm R, Kiebler M, Macchi P. RNA localization in the nervous system. *Semin Cell Dev Biol* 2007;18:216–223.
6. Wang H, Iacoangeli A, Popp S, Muslimov IA, Imataka H, Sonenberg N, Lomakin IB, Tiedge H. Dendritic BC1 RNA: Functional role in regulation of translation initiation. *J Neurosci* 2002;22:10232–10241.
7. Skryabin BV, Sukonina V, Jorda U, Lewejohann L, Sachser N, Muslimov I, Tiedge H, Brosius J. Neuronal untranslated BC1 RNA: Targeted gene elimination in mice. *Mol Cell Biol* 2003;23:6435–6441.
8. Lewejohann L, Skryabin BV, Sachser N, Prehn C, Heiduschka P, Thanos S, Jordan U, Dell'Omo G, Vyssotski AL, Pleskacheva MG, Lipp HP, Tiedge H, Brosius J, Prior H. Role of a neuronal small non-messenger RNA: Behavioural alterations in BC1 RNA-deleted mice. *Behav Brain Res* 2004;154:273–289.
9. Whittington MA, Traub RD, Jefferys JGR. Synchronized oscillations in interneuron networks driven by metabotropic glutamate receptor activation. *Nature* 1995;373:612–615.
10. Muslimov IA, Banker G, Brosius J, Tiedge H. Activity-dependent regulation of dendritic BC1 RNA in hippocampal neurons in culture. *J Cell Biol* 1998;141:1601–1611.