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RESEARCH HIGHLIGHT

Expanding the AtLAS of non-coding RNA functions in the brain

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Long non-coding RNAs (lncRNAs) are diverse and often do not have a clear connection to specific physiological processes. In a recent paper in *Cell Research*, Ma et al. show that a novel lncRNA called AtLAS can affect social behavior in mice through regulation of the AMPA-type glutamate receptors (AMPARs).

Mice, like many mammals, have social hierarchies where there are dominant and subordinate individuals. The authors used a series of social dominance behavioral paradigms and screened for lncRNAs that were differentially expressed in the medial prefrontal cortex (mPFC) of dominant and subordinate mice.[1] Previous studies have shown that changes in the strength of synapses, or synaptic plasticity, in the mPFC underlie social dominance.[2] Out of this screen, the authors chose to pursue a lncRNA that was robustly decreased in dominant mice, an antisense long non-coding RNA of *synapsin II* (AtLAS).

In a series of experiments, the authors show that AtLAS is necessary and sufficient in the mPFC to suppress social dominance. Since AtLAS is an antisense RNA to *synapsin II* (*syn2*), an obvious mechanism of action is through the regulation of syn2 protein expression. Interestingly, AtLAS seems to differentially regulate two different isoforms of syn2, a and b. This isoform specificity is due to AtLAS interrupting the interaction of the RNA-binding protein CELF4 with the 3′UTR of *syn2b*, which increases *syn2b* and decreases *syn2a* mRNA expression through alternative polyadenylation. In dominant mice, the authors found that syn2b expression was downregulated and syn2a expression was upregulated. Transgenic mice in which syn2b was decreased in the mPFC displayed higher social dominance ranks relative to wild-type littermates. AtLAS seems to regulate social behavior through selective regulation of syn2b, but how does syn2b regulate behavior? The authors now make a jump to test whether AMPAR-dependent synaptic function is regulated by syn2b, with the rationale that the excitatory synaptic strength in layer V pyramidal neurons of mPFC is known to regulate social dominance.[2]

Overexpression of AtLAS decreased the amplitude of miniature excitatory synaptic currents (mEPSCs) in mPFC slices, which reflect the strength of single synapses. This data indicated that AtLAS regulates the number of AMPARs in synapses. Moreover, overexpression of syn2b resulted in similar changes in mEPSC amplitude. Since syn2b is expressed at synapses, the authors determined whether syn2b can directly associate with AMPARs. Interestingly, Syn2b but not syn2a associates with the AMPAR subunits GluA1 and 2. Finally, the authors used a membrane-permeable peptide to disrupt the syn2b-AMPAR interaction. Treatment with this peptide resulted in an increase in mEPSC amplitude in mPFC slices and strikingly, the mice with intraperitoneal injection of the peptide displayed higher dominance than the mice injected with a scrambled peptide.

This study is a tour-de-force, going from the identification of a differentially expressed lncRNA in social dominance to the elucidation of a potential molecular mechanism of action at synapses (Fig. 1). It is intriguing that a small change in the ratio of synaptic protein isoforms can have such a large impact on social dominance, a cognitively complex behavior. There are a number of questions posed by this work. How is AtLAS regulated transcriptionally and does neuronal activity play a role? Non-coding RNAs are emerging as important regulators of synaptic plasticity, behavior, and memory.[3] Gomafu, like AtLAS, is a lncRNA that regulates social behavior.[4] Knockdown of Gomafu increases the time spent on the edge of an open field, indicating increased anxiety-like behavior.[4] Transcription of ribosomal RNA (rRNA) seems to be necessary for memory formation in mice.[5] Additionally, rRNA transcription is negatively regulated by a nucleolar lncRNA dubbed LoNA, which is downregulated in response to learning.[6] Knockdown of LoNA also leads to an increase in rRNA and the protein component of ribosomes, and improved spatial memory performance. Intriguingly, production of these ribosome components is reduced in Alzheimer's disease (AD), and LoNA knockout rescues some memory deficits in the APP/PS1 mouse model of AD. Thus, the aberrant regulation of lncRNAs may play an important role in neurological diseases.[7] In another example, postmortem AD patient tissue shows elevated levels of the lncRNA BACE1-AS, which stabilizes *BACE1* mRNA leading to an increase in $A\beta_{42}$ peptide production.[8] Another lncRNA BC1 (BC200 in humans), modulates local mRNA translation in dendrites, and also increases translation of APP mRNA in a mouse model of AD, which leads to memory deficits.[9]

An important future direction will be to determine how syn2b regulates the expression of AMPARs at synapses. Synapsins are classically thought to regulate presynaptic vesicle release but not postsynaptic expression of receptors. The number of AMPARs at the synapse is tightly regulated by neuronal activity through numerous trafficking mechanisms that include insertion, removal and expression of receptor subunits.[10] Perhaps syn2b affects the trafficking of AMPARs through insertion or endocytosis. The isoform and brain region specificity indicate that this pathway may be unique to the mPFC, but it will be critical to determine whether AtLAS expression regulates synaptic function in other brain regions and in other forms of behavior. Finally, it remains unclear how the regulation of specific synapses in mPFC can have such profound effects on complex behavior. The challenge here will be to determine in vivo and at the circuit level how synaptic plasticity regulates the circuits that underlie social dominance.

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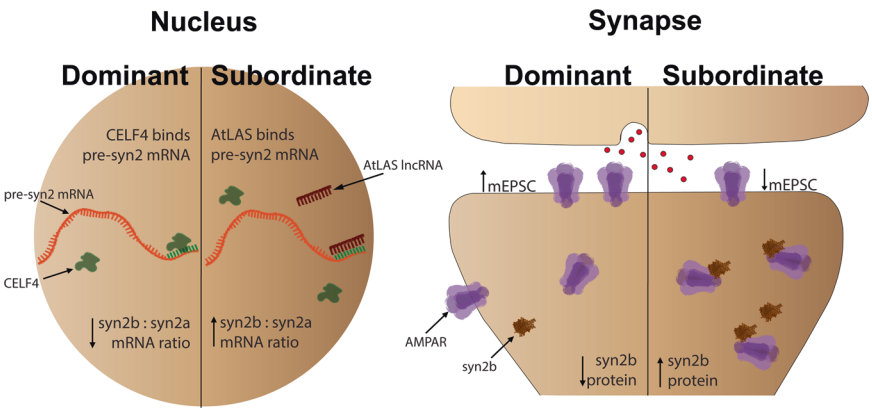

Fig. 1 AtLAS lncRNA regulation of social dominance in mice. Syn2b negatively regulates AMPAR presence in the synapses through a direct interaction with GluA1/2. The lncRNA AtLAS is an antisense to the *syn2* gene and interacts with the 3′UTR of *syn2b*, altering the expression of syn2 isoforms through alternative polyadenylation. Mice with low AtLAS expression and reduced levels of syn2b in the mPFC exhibit stronger synapses, which leads to dominant mice.

This study highlights the striking role that lncRNAs may play in regulating complex processes such as cognition and that non-coding RNAs are emerging as key regulators of many processes in neurons.[3] Human genetic studies show that many disease-causing mutations actually lie in non-coding regions of the genome.[7] Thus, studying the biology of non-coding RNAs will not only shed light on normal physiological processes, but also provide a more detailed atlas for how genetic mutations cause diseases.

ADDITIONAL INFORMATION

Competing interests: The authors declare no competing interests.

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