VIEWPOINT

No longer junk: Role of long noncoding RNAs in autism risk

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RNA acts as the intermediary between genes and proteins, but the function of pieces of RNA that do not code for protein has, historically, been less clear.Researchers have ignored these noncoding RNAs until recently for not complying with the central dogma of biology — that a straight line runs from gene to RNA (transcription) to protein (translation). However, noncoding RNAs are emerging as important regulators of diverse cellular processes with implications for numerous human disorders.

Extensive research has already examined the function of microRNAs, a category of small evolutionarily conserved noncoding RNAs about 22 to 24 nucleotides in length that target protein-coding genes in a sequence-specific manner. A plethora of microRNAs are important for brain function and neuropsychiatric diseases, **including autism**[1].

In the past decade, long noncoding RNAs (lncRNAs), which extend longer than 200 nucleotides, have emerged as additional important players in the control of gene expression. They fine-tune the expression of numerous genes and direct the activity of complex regulatory pathways, often in a cell- and developmental-stage-specific manner.

They are found in many places in the genome: within genes, near gene regulatory regions or by themselves (intergenic noncoding RNAs). lncRNAs may overlap with the genetic code for a protein or be expressed in the opposite, or antisense, direction.

In addition to the diversity in their biogenesis, lncRNAs exhibit an impressive versatility of molecular functions. These range from passive influence on the transcription of nearby genes to limiting expression to a paternal or maternal chromosome, a process called imprinting, and inactivating one copy of the X chromosome.

They also interact with chromatin-modifying complexes, which regulate gene expression by

changing the packaging of DNA, and with transcription factors that directly regulate gene expression. They may influence RNA splicing, stability and localization and play a role in the translation of RNA to protein and in protein activation. Finally, they may 'sponge' up certain microRNAs, thus blocking their function[2, 3, 4, 5].

Molecular multitaskers:

The ability of lncRNAs to engage in such molecular multitasking may allow them to link multiple risk factors for genetic disorders into functional networks. This makes them attractive candidates for autism spectrum disorders, which are characterized either by interactions of multiple genes or by disruptions in a single gene that influences numerous molecular pathways.

Whether whole-genome DNA sequencing data will reveal strong genetic links with lncRNAs, as it has for microRNAs, is not yet clear. One thing, though, remains certain: We can no longer overlook such a substantial and active chunk of the transcriptome and characterize it as 'junk' or 'transcriptional noise' if we hope to fully understand complex disorders such as autism.

In the past few years, studies have found alterations in lncRNAs in brains from people with autism, suggesting that they contribute to autism risk. For example, MSNP1AS, a lncRNA transcribed from a region of chromosome 5 that carries an autism-associated variant, is **elevated in the cortex of people with autism** who also carry the disease-related variant[6]. MSNP1AS may regulate moesin, a gene important for the structure of neurons' signal-receiving branches, or dendrites, and immune system activation.

Last year, a carefully conducted study identified numerous lncRNAs that are robustly **dysregulated in autism postmortem brain samples**[7]. Impressively, some disease-altered lncRNAs are found near important autism-linked genes such as **BDNF** and **SHANK2**.

Another lncRNA with potential implications for autism is LOC389023, which regulates **DPP10**, a gene linked to autism and other neurodevelopmental disorders. DPP10 controls the structure and function of neuronal junctions, or **synapses**, via its effects on potassium ion channels[3].

Last year, researchers used a similar approach to study the expression of lncRNAs in a mouse model of Rett syndrome[8]. One lncRNA (AK081227) that is expressed at abnormal levels in these mice controls the expression of its host protein-coding gene, the gamma-aminobutyric acid receptor subunit Rho 2 (GABRR2), which has also been linked to autism.

Additional reports have linked other lncRNAs to autism, such those that travel antisense to the **FMR1**[9, 10] and **UBE3A**[11, 12] genes. Mutations in these genes underlie **fragile X syndrome** and **Angelman syndrome**, respectively. Other studies have also uncovered a subset of lncRNAs expressed from the autism-linked **PTCHD1** gene[13] and the 7q31 chromosomal region[14].

In addition, the lncRNA ZNF127AS has altered expression in the brains of people with Prader-Willi syndrome[15]. On a similar note, a cluster of small nucleolar RNAs — which despite their name are a category of lncRNAs — are encoded by the paternally inherited microdeletion at 15q11.2 that is also linked to Prader-Willi syndrome[16].

Brain builders:

Previous work has identified a subset of lncRNAs that are important for regulating the birth of new neurons, or neurogenesis, and the process by which synapses adapt to experience, called synaptic plasticity.

Of particular importance is the finding that the intergenic noncoding RNA MALAT1, one of the most highly expressed lncRNAs in the brain, can regulate the formation of new synapses, or synaptogenesis. It does this by associating inside the nucleus with multiple RNA splicing factors and influencing the expression of autism-linked genes, such as **NLGN1**[17].

Intriguingly, there are several other links between MALAT1 and autism-associated factors. For example, beta-catenin — an important component of the WNT signaling pathway that has been linked to multiple neuropsychiatric disorders — activates MALAT1 transcription[18]. CREB, another transcription factor known for its role in activity-dependent gene expression, also binds to MALAT1. Notably, CREB may control MALAT1 transcription following exposure to the peptide hormone oxytocin, which has also been **linked to autism**[19].

MALAT1 and another lncRNA, BDNFOS, which has the antisense, or opposite, code to that of the autism-linked BDNF gene, are expressed in conjunction with neuronal activity[20]. On the other hand, GOMAFU, a lncRNA whose levels are dampened in postmortem brains from people with schizophrenia, is significantly suppressed following the activation of mouse cortical neurons[21].

Other lncRNAs run antisense to important synaptic plasticity-related genes, such as NRGN, CAMK2N1 and CAMKK1[22, 23]. lncRNAs are also associated with genes linked to changes in the synapse that occur after exposure to cocaine[24]. Interestingly, a novel subset of lncRNAs are expressed from the regulatory elements of genes, such as c-FOS and ARC, that regulate gene transcription in response to neuronal activity[25].

Adding to their important role in brain plasticity, lncRNAs are highly expressed during prenatal neurogenesis and are important for maintaining and differentiating the precursors to neurons: neural stem cells and neuronal progenitors[26, 27]. Of particular interest is the lncRNA EVF2, which runs antisense to the regulator gene DLX5,6 and plays a crucial role in the birth of **neurons that dampen brain activity**[28]. This adds another layer to the role of lncRNAs in cell-type-specific neuronal functions.

Despite these many threads, much more work is needed to determine the exact mechanisms of

action and the physiological significance of lncRNAs for autism and other neurodevelopmental disorders.

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