NEWS

MicroRNAs may play a role in autism, studies find

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Some small fragments of RNA are expressed differently in people with autism than in controls, according to two new studies. The findings unveil another layer of complexity in the genetics of autism.

These pieces of single-stranded RNA ? dubbed microRNAs or miRNAs ? have wide-ranging, subtle effects on the production of many different proteins without affecting a cell's underlying DNA code.

That may account for some of the widespread variation among people with autism, and even among family members who share genes, experts say.

“It's possible that microRNAs can have some kind of regulatory role over multiple targets and affect them a little bit differently in different people,” says **Kenneth Kosik**, co-director of the Neuroscience Research Institute at the University of California, Santa Barbara.

Since their discovery in 1993[1], miRNAs have been thought to play a significant role in brain development and neuronal signaling. Researchers have found altered miRNA expression in many neurological diseases, including autism-related disorders such as fragile X syndrome[2], Rett syndrome[3] and schizophrenia[4].

In July, Kosik and colleagues found, for the first time, that some miRNAs are also expressed differently in people with autism. Studying postmortem brain tissue samples of 13 people with autism and 13 controls, the team found that out of the 466 miRNAs analyzed, 9 are either up- or down-regulated in people with autism compared with controls[5].

In September, another team found that of 470 miRNAs analyzed, 9 are differentially expressed in people with autism, including 4 identified in the July report[6]. For their study, **Zohreh Talebizadeh** and colleagues from the University of Missouri-Kansas City looked at miRNA expression in cultured

blood cell lines from six people with autism and six controls.

In both studies, a computer algorithm predicted that a few of the differentially expressed miRNAs would target known autism-susceptibility genes. The July study?s list includes neurexin-1 (NRXN1) and SHANK3, and the August study points to **neuroligin-3**, **PTEN**, and two neurexin genes, NRXN1 and NRXN3.

If studies with larger sample sizes confirm these results, the next step is to confirm the target genes for the miRNAs. “For most miRNAs, the targets have not been confirmed yet,” says Talebizadeh. “We have a big task ahead of us.”

Multiple roles:

As part of a healthy cell?s operation, molecules of miRNA intercept mRNA on its way to the ribosome for translation, usually hindering the mRNA?s progress and reducing the amount of protein that?s churned out by the cell.

Human cells are thought to have about 500 miRNAs, and each can alter the translation of hundreds of different genes into protein; conversely, multiple miRNAs can target one gene. The same miRNA can also have different roles in different cell types.

miRNAs are strongly expressed in the nervous system and brain tissue, particularly in dendrites ? the long fibers that receive nerve signals.

In rats, some miRNAs appear to narrow the width of dendritic spines ? the nubs of fibers on a dendrite that receive signals at a synapse[7]. Spinal shriveling is prevented, however, when the synapse is exposed to brain-derived neurotrophic factor ? a growth factor that's found outside of the nerve cell and helps it survive and flourish.

This dynamic build-up and breakdown of dendritic spines is a hallmark of ‘synaptic plasticity? ? the ability of a synapse?s signal to change depending on its use. It?s one way that nerve cells learn. Scientists have long hypothesized that impairing normal synaptic plasticity might lead to schizophrenia or autism.

A study last year compared miRNAs in postmortem human brain tissue from 15 individuals with schizophrenia and 21 healthy controls and found that of 264 miRNAs analyzed, 16 are expressed at different levels in the schizophrenic group compared with controls. A few of the 16 also appear on the July study?s list of people with autism.

“It's kind of surprising to see that kind of overlap,” says **Diana Perkins**, lead investigator of the schizophrenia study and a professor of psychiatry at University of North Carolina, Chapel Hill.

“Autism and schizophrenia might be disorders of synaptic plasticity, and emerging data suggests that these microRNAs are very important in regulating synaptic plasticity, so it may be that that?s the common link,” she says.

Link to neurexin:

Another nod to a link between the two disorders is the importance of the neurexin genes that the microRNAs are predicted to target.

“I'm particularly happy about the neurexin finding, as it shows you a possible etiological overlap between schizophrenia and autism,” says Thomas Werge, director of the Research Institute of Biological Psychiatry at Copenhagen University Hospital.

In October, Werge and his collaborators found that deletions or duplications of the neurexin1 gene are about three times more prevalent in people with schizophrenia than in healthy controls[8].

“If you can show that microRNAs are regulating neurexin, and also seem to have altered expression in [autistic and schizophrenic] brains, that's of course very good news,” Werge says.

But there is another possible explanation: the differences in microRNA expression could be part of a compensatory mechanism, rather than the source of the disorder. “Is it a cause, an effect, or both? We just don?t know,” says Perkins.

Because the studies thus far have had small samples sizes, some experts caution against over-interpreting the results. “There's still the question of whether the findings coming out in these preliminary papers will be supported by other types of experiments that assess microRNAs in different ways,” says Werge.

Conducting those studies is easier said than done, however.

Postmortem brain tissue samples generally come from older adults whose brains may have naturally compensated for the disorder or been exposed to drugs since the onset of their illness.

What?s more, the brain begins to atrophy immediately after death, and can change dramatically within just a few hours. “God knows what might have happened in the brain since the person died,” Werge says. “It?s very, very important that that postmortem interval is highly identical in cases and controls.”

To get around these difficulties, one strategy is to use blood cell lines, which are easy to obtain from living people at any age. These cell lines and brain tissue share about 80% of all mRNA, but not much is known about their shared miRNAs. The kinds of miRNAs expressed in these cell lines, and the conditions under which they are expressed, may be vastly different from the scenario in

brain tissue.

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