How brain develops before birth is tightly controlled by RNA modification

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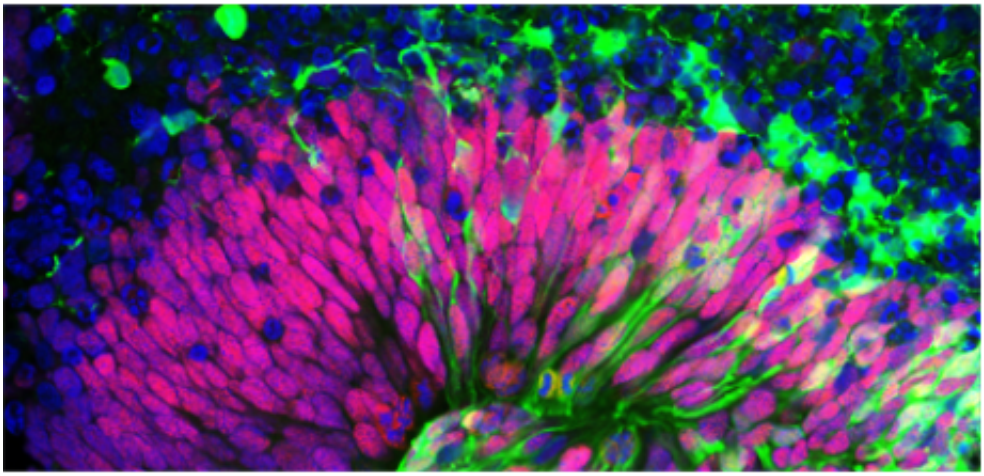

Human forebrain organoid labeled with Green Fluorescent Protein (green), neural stem cell marker SOX2 (red) and cell nuclei marker (blue). Credit: Xuyu Qian and Guo-li Ming, Perelman School of Medicine, University of Pennsylvania

A chemical tag added to RNA during embryonic development regulates how the early brain grows, according to research from the Perelman School of Medicine at the University of Pennsylvania. The findings are published this week in *Cell*.

Neuroscience professors Guo-li Ming, MD, PhD, and Hongjun Song, PhD, study the basic principles of how to make a working brain. "When this development goes awry, problems happen and may cause psychiatric

disorders in people," Song said. Ming and Song use animal models and organoids, also called mini-brains, made from human stem cells to relate their findings to conditions found in people.

In the last few years, scientists have discovered chemical modifications to messenger RNA (mRNA) across the genome at certain sites and found that these changes are dynamic, meaning that a specific chemical group is added and taken off by enzymes in a regular, patterned way. The chemical group studied in the *Cell* paper, m6A, is the most prevalent modification to mRNA in human cells.

"We asked: Is this another layer of regulation of gene expression?," Ming said.

The current thinking is that a tightly controlled molecular process guides the complicated development of the brain before birth—and that the process relies on a precise sequence of genes being turned on and off. However, even subtle mistakes in this process can become amplified later. Song likens this process to a train moving onto the wrong track and ending up miles and miles from its intended destination.

The classic view of this control is that DNA codes for RNA, guiding which proteins will be made by cells. However, mRNA can be modified along the way so that it can produce proteins with many variations. A new field called epitranscriptomics was born out of this knowledge.

The *Cell* paper is the first study of epitranscriptomics in the embryonic mammalian brain, and the key is m6A, a marker for molecules bound for disposal within the cell. Normally, m6A-tagged mRNAs are related to such processes as cell replication and neuron differentiation, and m6A-tagging promotes their decay after they are no longer needed.

If m6A is not added on the correct time schedule to a garbage-bound

molecule, the developmental train goes down the wrong tracks. Ming and Song surmise that this is because developing brain cells get stuck at an earlier stage because the m6A cues for taking out the cellular trash are misread or not read at all.

The researchers found that in a mouse model with depleted m6A, cell replication is prolonged, so that stem-cell differentiation, which normally reels out daughter cells in an orderly fashion, gets stuck. The knockout mouse develops less brain cells such as neurons and glia cells, and therefore has abnormal circuitry and a non-functioning brain.

"We used an organoid, a mini-brain, made from human induced pluripotent stem cells to relate the mouse knockout findings to humans," Ming said. "m6A signaling also regulates neuron development in human forebrain organoids."

Neuron development in the mini-brains that Ming has developed is similar to what happens in people, modeling fetal brain development up to the second trimester.

"We were surprised when we found that human stem cells had a greater number of m6A tags compared to mouse cells," Ming said. "Comparing the m6A-mRNA landscapes between mouse and human embryonic brain development showed us that human-specific m6A-tagging might be related to brain-disorder risk genes."

Many of the genes associated with genetic risk for certain conditions, such as schizophrenia and autism spectrum disorder, are only m6A-tagged in humans, not in mice, raising the possibility that dysregulation at this level of gene expression may contribute to certain human brain disorders.

In the near future, the team plans to look for m6A levels in brain tissue

donated by people who had psychiatric disorders, as well as if m6A regulates development and regeneration of the nervous system after birth.

Provided by Perelman School of Medicine at the University of Pennsylvania