NEWS

‘Outmoded’ mouse models of autism may still yield new advances

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In 2000, two of the most popular mouse models of autism were environmental ones: mice that had been exposed in the womb to a maternal immune response or to valproic acid, a seizure drug. Seven years later, a third set, an inbred strain of mice called BTBR, attracted followers after two teams reported unusual, autism-like features in the mice[1,2].

These three models remained the mainstay of autism research until about six years ago, when researchers began linking dozens of genes to autism. Since then, they have put many of the mutated genes into mice to try to understand the condition’s origins. They have learned, for example, that mutations in certain genes can cause subtypes of autism.

These days, the early environmental models seem quaint and imprecise compared with the genetic ones. And many autism researchers now eschew some of the older models.

“Now that we know so many causes of autism are related to genes, it seems counterintuitive to use models with an unknown cause of their behavior,” says **Jill Silverman**, associate professor of psychiatry and behavioral sciences at the University of California, Davis. “It would be wasteful to pursue models with unknown underlying pathology.”

Yet some researchers vouch for the mice’s promise in unraveling autism’s complexity, including its genetics.

“I like the single-gene models, but autism is not a single-gene condition, except in rare cases,” says **Valerie Bolivar**, director of the Mouse Behavioral Phenotype Analysis Core at the New York State Department of Health’s Wadsworth Center. “My bottom line is, we don’t throw any model out and we don’t rely on just one, because we’re so far from knowing anything really slam dunk yet.”

Bad smell:

The 2007 studies of BTBR mice showed that the mice seem disinterested in interacting with others. Subsequent reports showed that they also have strange patterns of vocalization, and bury marbles and groom themselves obsessively[3].

The reports fueled a “huge explosion” of studies involving BTBR mice, Bolivar says. Numerous teams have since replicated the mice’s autism-like behaviors, and the mice are readily available for purchase.

But as soon as the mice gained traction as an autism model, scientists discovered they had some concerning oddities. For instance, they spend less time sniffing their surroundings than control mice do. Odor is a key ingredient in mouse social interactions, and time spent sniffing other mice is one way researchers assess social behavior. BTBR mice’s disinterest in smell could explain their disregard for other mice.

This and other problems call into question the strain’s validity as an autism model, says **Mu Yang**, director of the Mouse NeuroBehavior Core at Columbia University.

The mice also lack a **bundle of nerves** called the corpus callosum that connects the brain’s hemispheres. This problem is seen in people with a rare condition called **agenesis of the corpus callosum**, about one-third of whom have autism. But it is not tied to any obvious autism-like features in the mice, researchers determined.

And yet some researchers still see promise in the mice.

“In terms of the anatomic abnormality that is most frequently seen in autism, a decrease in the size of the corpus callosum is the most common feature,” says **Elliott Sherr**, professor of neurology at the University of California, San Francisco.

Sherr says his team has unpublished data that fingers a mutation that may be responsible for the mice’s lack of a corpus callosum. But they did not find any mutations in the gene in people with autism, so the gene is unlikely to contribute to autism, he says.

Bolivar and her colleagues have also identified a genetic variant in the BTBR mice that may explain the animal’s lack of a corpus callosum. Mice with the mutation, in a gene called DRAXIN, do not develop a corpus callosum. Bolivar is exploring whether alterations in corpus callosum development contribute to the mice’s behavior.

Work on the mice may yet reveal combinations of genes that work together to contribute to autism, Bolivar and Sherr say. “There are single-gene causes of autism, and those make up about 20 percent of patients, but [then] there’s the other 80 percent,” Sherr says.

Real opportunity:

The valproic acid and immune response models have not suffered as dramatic a fall from grace as the BTBR mice have. That's in part because epidemiologic and mechanistic studies have linked in utero exposure to valproic acid, or to an immune response to infection, with autism.

Still, uncertainty clouds the infection model of autism. Several studies of autism recurrence among the siblings and cousins of people on the spectrum suggest that in utero factors specific to the mother play only a minor role in autism risk[4]. Maternal infection is one of the relevant factors because it is common enough for population studies to detect. (Valproic acid exposure is not.)

The molecular and behavioral features of both models are also difficult to reproduce. Study protocols vary by the dose, injection site and timing of the exposure. What's more, various strains of mice respond differently to the treatments.

Instead of throwing up their hands at this variability, however, researchers should study it, some experts say.

"This is a real opportunity to use that variability to tell us about the factors that contribute to susceptibility versus resilience," says **Kimberly McAllister**, director of the Center for Neuroscience at the University of California, Davis.

To make the infection model easier to reproduce, McAllister and her colleagues are developing rigorous guidelines, which she and her colleagues plan to publish later this year.

Others say it's useful to compare these models with mice that carry mutations linked to autism. Identifying similarities among the models may point to common pathways in the brain.

For instance, in a study published in November, researchers matched mice exposed to valproic acid in utero with two genetic mouse models of autism and identified **a faulty brain circuit** linked to social difficulties.

"My view is always not to put too many bets on any one model," says lead researcher **Vikaas Sohal**, associate professor of psychiatry at the University of California, San Francisco. "But when you find things that seem to be shared across models, then that seems really important to me."

Environmental exposure models might also prove useful when combined with genetic models. **Yong-Hui Jiang** and his team study mice with mutations in **SHANK3**, a strong candidate gene for autism. But **SHANK3 mice** typically show few autism features, so Jiang's team is exposing them in utero to a mock maternal infection.

"The question is whether we can use environmental modifiers to increase the [mutation's]

penetrance," says Jiang, associate professor of pediatrics at Duke University in Durham, North Carolina.

It's too soon to tell whether these latest efforts to redeem the older models will prove fruitful. But finding new uses for old models might be wiser than discarding them.

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