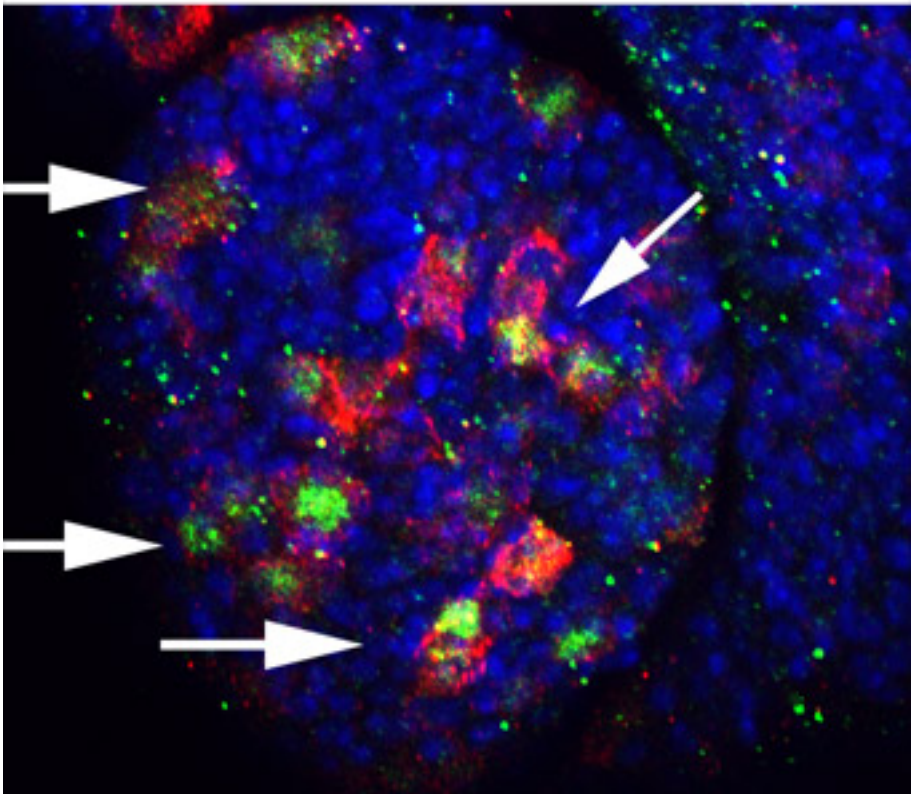
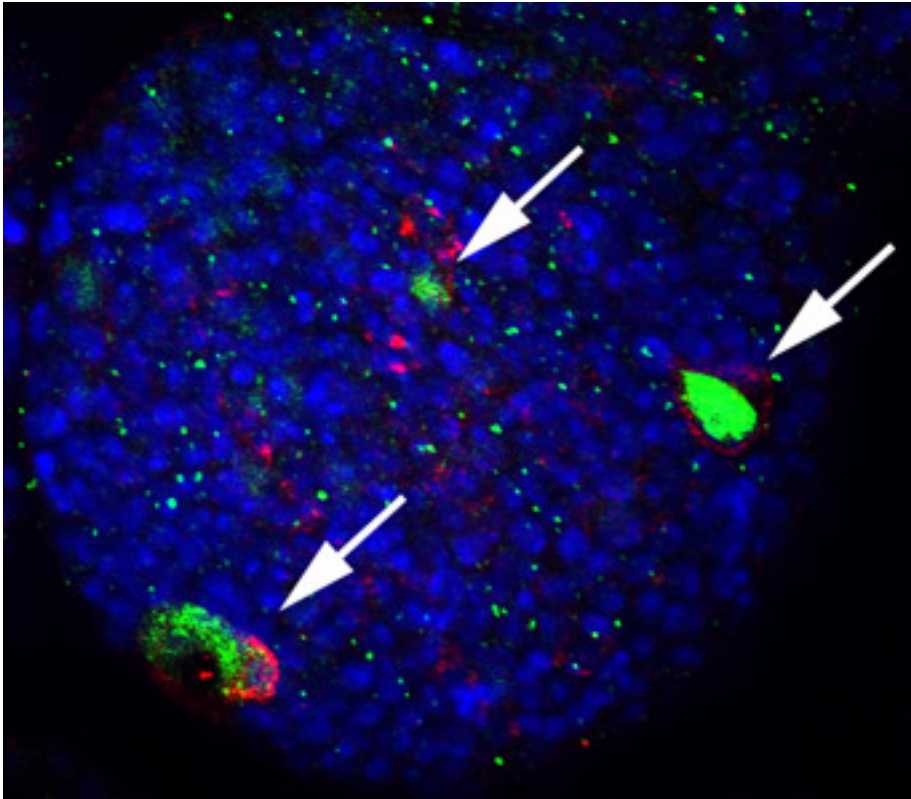


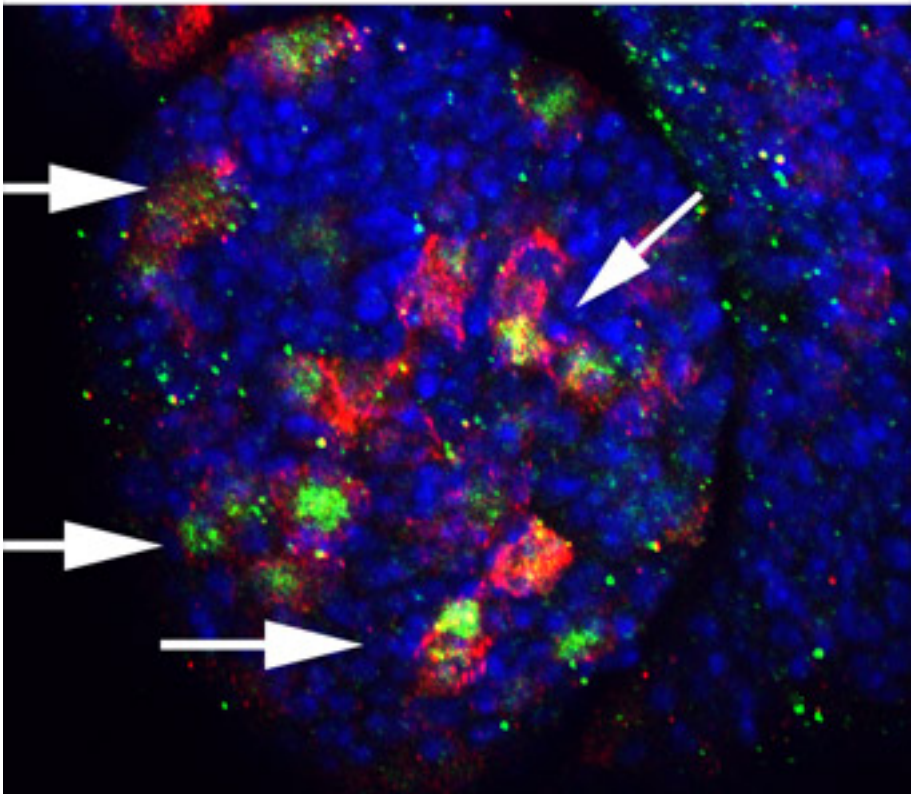
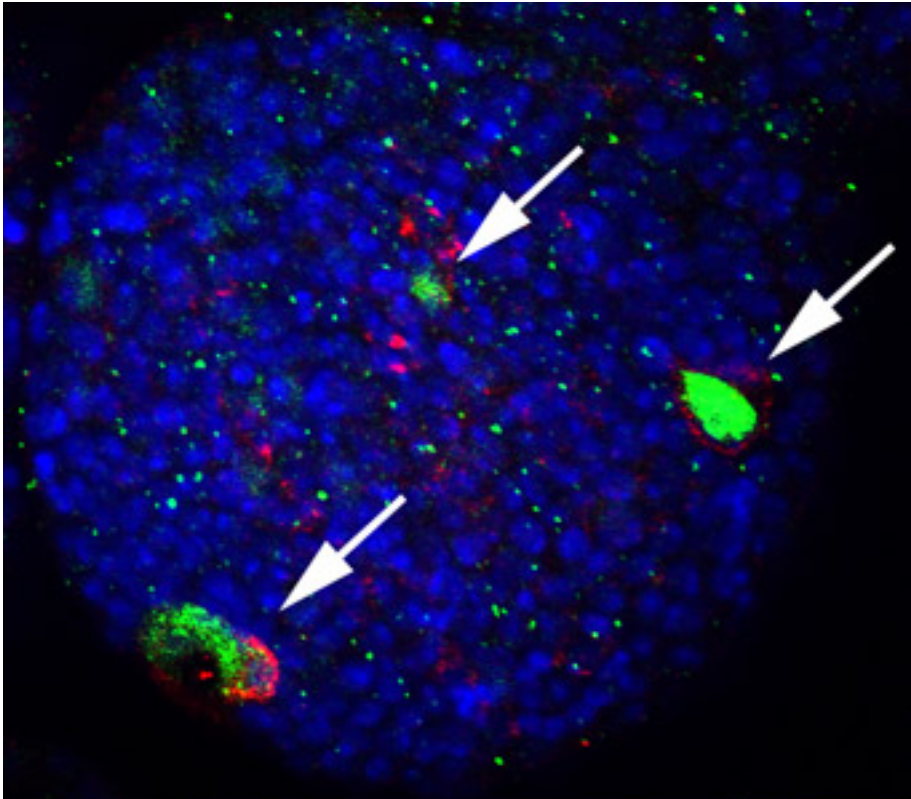
NEWS

Fragile X protein tied to snags in stem cell development

BY VIRGINIA HUGHES

13 SEPTEMBER 2010





Early explosion: Fruit fly larvae lacking the fragile X protein (above) have more brain progenitor cells than do controls (top).

The protein missing in fragile X syndrome is necessary for the proper development of neural stem cells — self-renewing cells that can differentiate into more specialized types, including neurons — according to a paper published in the August issue of *Human Molecular Genetics*¹.

The bulk of research on fragile X mental retardation protein (FMRP) has focused on its role at the synapse — the junction between neurons — and how disruptions to cell signaling might cause learning problems and autism-like behaviors. These efforts have led to **promising clinical trials** of drugs that act at the synapse.

The new work suggests that fragile X syndrome arises from glitches in early brain development that occur before synapses are formed, eventually leading to the signaling problems or to other defects.

"We are just at the beginning of this work, but I think it gives us a new handle on this disease, and perhaps on thinking of new therapeutic approaches at an earlier time in development," says **Daniela Zarnescu**, assistant professor of molecular and cellular biology at the University of Arizona.

In normal development, as nascent neurons lay down their connections, some connections are stabilized and form circuits, whereas others die.

In individuals with fragile X syndrome, however, this pruning process somehow goes haywire. For instance, by age 2, children with the syndrome have an **abnormally large caudate**, a brain region that is important for learning and memory. Studies of postmortem brain tissue from adults with the syndrome have also found denser neuronal projections in several brain areas compared with healthy controls².

A 2005 study first suggested that the overgrowth of neurons in the syndrome could begin with defects in neural 'progenitor' cells, which are more differentiated than stem cells, but still have the potential to turn into several types of brain cells. Researchers from the University of Helsinki found that progenitor cells cultured from mouse models of fragile X syndrome generate more neurons and fewer support cells, called glia, than do progenitor cells from healthy mice³.

However, a 2008 study found that brain tissue from a human fetus with the fragile X mutation has abnormal expression of several genes, but stem cells isolated from the tissue differentiate normally into neurons⁴. It's unclear whether these results undermine the proposed link between stem cells and fragile X syndrome, or are unique to this particular fetus.

Advanced technique

In August, Zarnescu's team reported stem cell abnormalities in fruit fly models of the syndrome. The researchers deleted FMRP from individual progenitor cells in fruit fly larvae and labeled the cells with a fluorescent protein tag. With this sophisticated technique — which is prohibitively expensive and time-intensive to perform in a mouse — they can trace the development of a single cell as it grows in normal tissue.

They found that a single progenitor cell lacking FMRP gives rise to up to 20 percent more neurons than does a control cell. These neurons survive to adulthood, and perhaps then disrupt circuits, Zarnescu says.

Another mouse study, published in April, finds that FMRP also regulates the number of adult progenitor cells and the formation of new neurons and glia in the adult brain⁵. The researchers found that, compared with controls, mice lacking FMRP have 53 percent more adult progenitor cells in the hippocampus, the site of memory formation.

Unlike the earlier mouse study of embryonic stem cells, however, these mutants have fewer mature neurons, and more mature glia, compared with controls.

This highlights important differences between embryonic and adult neural stem cells, says lead investigator **Xinyu Zhao**, associate professor of neuroscience at the University of New Mexico.

"The function of embryonic neurogenesis is to create the brain. The function of adult neurogenesis is plasticity — they're two very different things," Zhao says. It makes sense that FMRP is involved in both, she adds.

For instance, she notes, the large head size seen in people with the syndrome could be the result of too many neuronal connections in prenatal development, whereas the learning deficits might be the result of improper neuronal and synaptic maturation later on.

The effects on adult stem cells could also have implications for the cognitive decline in adults with fragile X, notes **Thomas Jongens**, associate professor of genetics at the University of Pennsylvania, who was not involved in the work.

The researchers analyzed brain tissue at two time points: when an adult stem cell first develops, and then four weeks later. At the first time point, the researchers saw a larger number of adult progenitor cells. At the second time point, however, they saw no difference between mutants and controls.

From this data, it's not clear whether the cells stabilize after four weeks, or continue to decline. "It would be neat to look at more time points," Jongens says. "Down the road, you might actually have

a deficiency of adult [progenitors] being produced, and that could tie into the learning and memory processes [involved in] aging."

References:

1.

Callan M.A. *et al. Hum. Mol. Genet.* **19**, 3068-3079 (2010) [PubMed](#)

2.

Irwin S.A. *et al. Am. J. Med. Genet.* **98**, 161-167 (2001) [PubMed](#)

3.

Castrén M. *et al. Proc. Natl. Acad. Sci. U. S. A.* **102**, 17834-17839 (2005) [PubMed](#)

4.

Bhattacharyya A. *et al. Stem Cells Dev.* **17**, 107-117 (2008) [PubMed](#)

5.

Luo Y. *et al. PLoS Genet.* **6**, e1000898 (2010) [PubMed](#)