



Pointing the way to normal

Tim Megraw studies microcephaly (literally “small heads”). In this rare congenital disease, the head is small because the brain does not develop to its normal size. Why? That’s what his research team is exploring.

Much as he would like to end microcephaly, his primary goal is to understand the birth of the brain – particularly the cerebral cortex, home of learning, memory, language and more.

“Rare diseases like this can tell us a lot about the normal processes of development,” said Megraw, associate professor of biomedical sciences. “This affliction is pointing the way to something basic about how the brain forms.”

In the May 31 *Trends in Cell Biology*, he provided an update on where it’s pointing.

“This paper proposes that MCPH (autosomal recessive primary microcephaly) is part of a spectrum of diseases that affect the brain,” Megraw said. “We synthesize the possible mechanisms for how stem cells in the brain are affected in MCPH and how we think it relates to these other syndromes.”

The other diseases are known in shorthand as MOPD II and SCKL. Megraw’s paper, co-written by postgraduate fellow James Sharkey and Biomedical Sciences



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Chair Richard Nowakowski, proposes that all three are centrosome-based.

The centrosome is crucial in cell division. A cell that's ready to divide typically has two centrosomes, each with a pair of interconnected centrioles. Ideally, when the cell divides, the genetic material is divided equally. But if those centrioles disengage at the wrong time, cells may start dividing too little or too much, or chromosomes may separate unequally. Last year, in research involving mice, Megraw's lab discovered that the protein Cdk5rap2 is required to regulate centriole replication. That work helped convince them that these microcephaly syndromes are centrosome-based.

But Megraw cannot pinpoint their exact cause. It could be related to cell division. Or to defective cilia, the hair-like structures produced by centrosomes. Or to DNA damage response. Linking these common features of MCPH to neural stem cell function during brain development remains the challenge.

"We have these pathways that repair our DNA when it's damaged," explained Megraw, whose work has been supported since September 2009 by a four-year, \$1.2 million grant from the National Institutes of Health. "And there are signaling pathways and mechanisms that will make sure that everything stops until it's fixed. Is there a connection between cilia and DNA damage response?" Those and other connections are the focus of continuing investigation.