Modeling epilepsy: A worm stands in for a human disorder

The elegant C. elegans *in closeup. EM by Juergen Berger, Max-Planck-Institut für Entwicklungsbiologie, Tübingen,Germany.*

A creature with exactly 302 neurons seems an unlikely stand-in for the human brain, which has ~100 billion neurons. Yet C. elegans, a nematode no bigger than the comma after this clause, may be a new model for epileptic seizures in humans, according to researchers at The University of Alabama in Tuscaloosa.

The laboratory of Guy Caldwell in the Department of Biological Sciences investigates the molecular basis of a devastating human brain malformation called lissencephaly, which has been traced to a gene called LIS-1. When LIS-1 is altered, neurons fail to migrate properly during brain development, resulting in a characteristic smooth appearance of the cerebral cortex. Children born with lissencephaly have severe mental retardation and frequent epileptic seizures. While only one in 30,000 live births results in a child with lissencephaly, epileptic seizures affect roughly two percent of the adult population, and are poorly understood.

The human gene, LIS-1, has an analog in C. elegans, worm lis-1. Indeed, C. elegans shares roughly half its genes with humans. Each worm has only 302 neurons, which operate in much the same way as human neurons using ion channels and neurotransmitters like dopamine, serotonin, and GABA. In work supported by an NSF CAREER Award, graduate student Shelli Williams identified worms with a mutated lis-1 gene. The loss of lis-1 function caused cytoskeletal defects that were lethal to large numbers of young C. elegans. However some "lissencephalic" worms survive to adulthood, and experience epileptic-like convulsions when exposed to seizure-inducing drugs.

Caldwell and colleagues say these convulsions mimic those seen in other worms with defects in the production of GABA, the most abundant inhibitory neurotransmitter in humans. In addition to seeing GABA-like convulsions in the lis-1 mutant worms, researchers found that transport vesicles containing GABA were mislocalized in neurons of lis-1 mutant worms. Defects in dynein, the molecular motor that drags GABA-containing vesicles to their proper destinations in neurons, were previously also linked to lissencephaly. Caldwell hypothesizes that lis-1 contributes to the function of this motor, and his lab is currently in hot pursuit of further dynein connections to seizures.

Searching for new genetic links to epilepsy is much easier to do in C. elegans than people, says Caldwell. Although worms are small creatures, scientists can apply powerful methods to rapidly identify genes and pathways associated with aberrant neuronal activity. u

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Defects in C. elegans LIS-1 Cause Both Cytoskeletal Defects and Epileptic Convulsions, S. N. Williams, C. J. Locke, A. L. Braden, K. A. Caldwell, G. A. Caldwell; Dept. of Biological Sciences, University of Alabama, Tuscaloosa, AL

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