Zebrafish enable scientists to study the migration of neurons that enable sexual maturity

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Scientists are watching a small group of neurons that enable sexual maturity and fertility make a critical journey: from where they form, near the developing nose, to deep inside the brain.

They believe their studies in the transparent embryo of the zebrafish will help explain why some neurons don't make it and enable better ways to help children who don't sexually mature as a result.

"They can go to the right place but take too long; delayed puberty suggests they got there late," says Dr. David J. Kozlowski, developmental geneticist in the Medical College of Georgia Schools of Medicine and Graduate Studies. "They can go to the wrong place. They can go to the right place and make the wrong connections, or not enough of them go to the right place. All sorts of things can go wrong and result in clinical defects."

Fortunately puberty problems due to central nervous system abnormalities are relatively rare, affecting about 1 in 40,000 females and 1 in 10,000 males, but they can be traumatic, says Dr. Lawrence C. Layman, an expert on delayed puberty who follows about 350 of these patients. Improved understanding and treatment could help scores of others as well by improving birth control and fertility treatments, he says.

To study one of the first things that can go wrong, Dr. Kozlowski, director of the Transgenic Zebrafish Core Laboratory, has teamed with Dr. Layman, chief of the Section of Reproductive Endocrinology, Infertility and Genetics in the MCG School of Medicine, and Dr. Nancy L. Wayne, reproductive neuroendocrinologist at the University of California, Los Angeles.

Boys typically begin puberty by age 10 or 11 and girls by age 8 or 9, when the hypothalamus in the brain begins releasing more gonadotropin releasing hormone, or GnRH, Dr. Layman explains. GnRH stimulates the pituitary gland to make follicle stimulating hormone and luteinizing hormone, which prompt ovaries to produce estrogen and eggs and testes to produce testosterone and sperm. But first, GnRH neurons must get to the brain. "This occurs very early in the life of a zebrafish, probably after the heart forms, at about 48 to 72 hours of life," says Dr. Kozlowski. "One class of patients Dr. Layman sees has Kallmann syndrome in which there is evidence that the GnRH neurons gets stuck about halfway. People want to know the molecular mechanism that allows these neurons to find the right place." Dr. Kozlowski is principal investigator on a new $1.4 million grant from the National Institutes of Health that should help.

The zebrafish embryo, which is transparent and develops outside the mother, is ideal for studying early development. Dr. Kozlowski's lab, in collaboration with UCLA's Dr. Wayne, made a transgenic fish whose GnRH neurons turn fluorescent green at birth for easy tracking. "We can put them under the microscope and image them for as long as it takes for these cells to get from point A to point B and ask how they got there," says Dr. Kozlowski. "Do they go straight there or take the long way? Then we can start asking questions about the signals that direct them and dissect out the genes expressed along the route which may function as road signs."

In live embryos, researchers are watching GnRH neurons as they first appear near the developing nose, then migrate with nearby olfactory neurons. "People actually think they use these olfactory neurons as the highway, which makes sense," says Dr. Kozlowski. "They are already there and moving to the brain. Why not follow the yellow brick road?" In fact, some patients with Kallmann syndrome, who have delayed puberty, also have impaired or no ability to smell, indications both neuron types may get off route.

Dr. Wayne uses tiny recording pipettes to measure the GnRH neuron's electrical activity as they travel. In cell culture systems at least, there is a known relationship between electrical activity in these neurons and their migratory activity. In zebrafish embryos, the researchers already know electrical activity in these neurons increases as they migrate into the brain. "What you want to know is which comes first. Do you have to be electrically active to move in the right direction or do you become electrically active as a consequence?" says Dr. Kozlowski. They want to change the neuron's route and see what happens to electrical activity, then change electrical activity and see what happens to the route.

They also are looking at genetic mutations, some of which Dr. Layman has identified in patients, to see what role they may play in misrouting neurons. "A mechanic has to know how a car works to fix it," says Dr. Kozlowski. "We want to understand what is under the hood that gets the neurons from point A to B. We want to know the mechanisms because that helps you understand how you might be able to fix it. It will also help you diagnose patients who have mutations in the road signs."

"You can try to figure out the genes that regulate migration, which gives you ideas about what genes to study in humans who don't have puberty," says Dr. Layman. "If we knew more genes involved, we could screen patients to see if we can find the mutations that cause problems.

"The understanding of what initiates puberty in humans is still not really known," he adds, and finding more genes involved in directing migration – even messing it up – will help. Current treatment for delayed puberty includes giving girls estrogen to help their breast develop and boys testosterone to enlarge the penis and scrotum (treatment won't enlarge the sperm- and hormone-producing testes). Expensive gonadotropin injections to stimulate ovulation in women and sperm production in men are needed for reproduction.

Source: Medical College of Georgia