Zebrafish expose tumor pathway in childhood muscle cancer

June 5 2018


Southwestern
Medical Center

Dr. Genevieve Kendall came to UT Southwestern because she wanted to work with zebrafish, which are an excellent model for studying childhood cancer. Because the young fish develop outside the mother's body, it's easy to insert human cancer-related genes into the fish genome, and drugs can be tested simply by adding them to the water. Credit: UT Southwestern

A popular aquarium fish may hold answers to how tumors form in a childhood cancer.

Muscle precursor cells called myoblasts are formed during normal fetal development and mature to become the skeletal muscles of the body. Rarely, a genetic error in which pieces of two chromosomes fuse together occurs in a cell related to this process and triggers those cells to multiply and behave abnormally. A particularly aggressive form of the muscle cancer rhabdomyosarcoma results.

The fused genes create an abnormal protein called PAX3-FOXO1, which blocks the normal maturation of muscle cells by inappropriately turning hundreds if not thousands of genes on and off. The exact mechanism by which PAX3-FOXO1 does this is not known.

Cancer researchers at UT Southwestern Medical Center developed a zebrafish model for the childhood cancer. To do this, Dr. James Amatruda's lab inserted the human PAX3-FOXO1 gene into the DNA of zebrafish. Using this new transgenic zebrafish, the researchers showed that the fused-gene DNA causes rhabdomyosarcoma that is similar to the human disease. They found it does this by turning on another gene, HES3, which leads to overproduction of the skeletal muscle precursor cells and allows for PAX3-FOXO1+ cells to survive during development

instead of dying.

Researchers (from left) Lin Xu, Genevieve Kendall, Collette LaVigne, and James Amatruda used zebrafish, which are surprisingly similar to humans in anatomy, physiology, and cancer susceptibility, to study the childhood cancer rhabdomyosarcoma. Credit: UT Southwestern

"There is a lot of interest in understanding the PAX3-FOXO1 block and in identifying treatments that overcome this block," said Dr. Amatruda, Associate Professor of Pediatrics, Internal Medicine, and Molecular Biology. "Such treatments could potentially cause the tumor to 'mature' and slow its growth without exposing the patient's normal tissue to the

side effects of chemotherapy and radiation."

Efforts to directly counter the effects of PAX3-FOXO1 have been unsuccessful, so the HES3 gene provides a potential back door for targeted treatment for this cancer.

Current treatments for rhabdomyosarcoma include surgery, chemotherapy, and radiation. Finding a drug that specifically targets part of the pathway initiated by the PAX3-FOXO1 gene fusion could improve survival rates as well as make treatments more tolerable for young patients.

The zebrafish model of rhabdomyosarcoma the researchers developed is particularly useful because few other options are available. "Gene fusions that function as transcription factors are notoriously difficult to model in animals, hence the limited availability of vertebrate animal models for this disease. Zebrafish are powerful models because their use provides insight into how cancer genes function during development and the fish are a platform for drug discovery efforts," said Dr. Genevieve Kendall, postdoctoral researcher and first author on the study.

The long-term goal of their work is to identify potential drugs for the most aggressive type of rhabdomyosarcoma tumor and to test these treatments in the zebrafish model. The new findings open the possibility of finding drugs that block HES3 or its downstream targets as a therapy for this cancer.

The research appears in the journal *eLife*.

Provided by UT Southwestern Medical Center