Zebrafish provide insights into causes and treatment of human diseases

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Zebrafish, popular as aquarium fish, now have an important place in research labs as a model organism for studying human diseases.

At the 2012 International Zebrafish Development Conference, held June 20-24 in Madison, Wisconsin, numerous presentations highlighted the utility of the zebrafish for examining the basic biological mechanisms underlying human disorders and identifying potential treatment approaches for an impressive array of organ and systemic diseases.

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD), while rarely fatal, can have a substantial negative impact on an individual's quality of life due to abdominal pain, diarrhea, vomiting, bleeding, and severe cramps. The causes of this chronic inflammatory disorder are largely unknown and existing treatments, usually anti-inflammatory drugs, are often not effective. In addition, IBD is often associated with increased risk of developing intestinal cancer.

Researchers from the University of Pittsburgh are using zebrafish to study the biological mechanisms that lead to intestinal inflammation, as often seen in IBD, providing additional understanding that may allow development of better therapies. Prakash Thakur, a research associate working with Nathan Bahary, M.D., Ph.D., described a mutant zebrafish strain that shows many pathological characteristics similar to IBD,

including inflammation, abnormal villous architecture, disorganized epithelial cells, increased bacterial growth and high numbers of dying cells in the intestine. "Most of the hallmark features of the disease are seen in this mutant. We are utilizing this fish as a tool to unravel fundamental mechanisms of intestinal pathologies that may contribute to intestinal inflammatory disorders, " Mr. Thakur said.

The fish have a genetic mutation that disrupts de novo synthesis of an important signaling molecule called phosphatidylinositol (PI). The lack of de novo PI synthesis, Mr. Thakur and his colleagues found, leads to chronic levels of cellular stress, particularly the endoplasmic reticum stress and, ultimately, inflammation. Drugs or other interventions targeting the cellular stress response pathway, rather than just inflammation, helped restore a healthy intestinal structure and increase cell survival in the fish intestine, suggesting this mechanism as a potential therapeutic target for patients with inflammatory disorders, including IBD.

Doxorubicin-Induced Heart Failure

Doxorubicin is a potent chemotherapy drug used to treat many types of cancer, including leukemia, lymphoma, carcinoma, soft tissue sarcoma, and bladder, breast, lung, stomach and ovarian cancers. Unfortunately, drug-induced cardiomyopathy is a common side effect and can lead to heart failure in cancer patients, not only during treatment, but months or years later.

"We hope to identify some drug which only blocks the side effect of doxorubicin but preserves the therapeutic effect," said Yan Liu, Ph.D., a postdoctoral researcher working in Dr. Randall Peterson's lab at the Massachusetts General Hospital.

Dr. Liu developed a zebrafish model of doxorubicin-induced

cardiomyopathy. The fish experience heart failure within two days of treatment with symptoms similar to those seen in humans, including fewer heart muscle cells, ventricular collapse, and ineffective heartbeats.

The researchers used the model to screen through thousands of potential drug compounds and identified two – visnagin and diphenylurea – that both improved cardiac function and reduced doxorubicin-induced cell death in the heart. Importantly, both compounds specifically protected heart tissue, but not tumor cells, from the toxic effects of doxorubicin. Both seem to act through the suppression of a particular signaling pathway, the c-Jun N-terminal kinase pathway, in the heart cells but not tumor cells.

Dr. Liu also reported promising preliminary results with mice showing reduced cell death and improved cardiac function, indicating that these compounds may also be active in mammals and giving hope for therapies that specifically treat doxorubicin's side effects without negating its anti-tumor activity.

Spinal Muscular Atrophy

Spinal muscular atrophy (SMA) is a group of progressive neurodegenerative diseases that affect the nerves in the spinal cord that control muscles, leading to weakness, movement difficulties, poor posture, and trouble breathing and eating.

SMA is linked to mutations in a specific motor neuron survival gene, SMN1. Though mouse studies have reported immature and ineffective synaptic connections between motor neurons and muscles, little is known about the molecular mechanisms leading to those problems or how they might be fixed.

Graduate student Kelvin See, working with Associate Professor

Christoph Winkler, Ph.D., at the National University of Singapore used zebrafish with activity-sensitive fluorescence to provide a visual readout of motor neuron activation. They confirmed that low SMN1 levels are associated with low neuronal influx of calcium ions, which play a critical role in triggering neurotransmitter release and thus stimulating the muscles. With their zebrafish model, Mr. See and Dr. Winkler also identified another gene with a similar effect, neurexin, which is important in synaptic structure but had never been implicated in SMA.

In a surprise discovery, the researchers found they could use the same sensor to see activation of a neighboring cell type called Schwann cells. "This gives us the unique opportunity to look at the role of SMN1 not just in motor neurons but also in the surrounding tissue," said Mr. See.

They saw reduced excitability in Schwann cells also, suggesting that a full understanding of SMA will require a broader view of the affected cell populations. Their results provide several new insights into the fundamental processes disrupted in SMA.

Acute T-cell Lymphoblastic Leukemia and Lymphoma (T-ALL/T-LBL)

Human acute T-cell lymphoblastic leukemias (ALL) and lymphomas (LBL) have high relapse rates in pediatric patients and high mortality rates in adults. Hui Feng, M.D., Ph.D., currently at the Pharmacology Department and Center for Cancer Research at Boston University School of Medicine, is using a zebrafish model of leukemia to search for promising targets for new molecular treatments for these diseases.

To date, studies have identified several biological pathways involved in ALL and LBL, all with a known oncogene in common called c-Myc. However, Myc is so common, involved in regulating more than 15

percent of all genes, that it is very hard to study.

"Because this is a huge list of downstream targets, it is very challenging to predict which genes in the pathway to target to treat Myc-related cancers," said Dr. Feng.

In work performed in collaboration with Thomas Look, M.D., at the Dana-Farber Cancer Institute, Dr. Feng is combining the power of zebrafish genetics with human clinical studies to hone in on potential genes of interest.

Using a fish strain that reliably develops T-cell lymphoma by two months of age, they identified a novel gene called DLST that is involved in metabolism and energy production in cells. Evidence from human cancer cell lines and patients indicate that abnormally high levels of the protein may be involved in the human disease as well.

Reducing DLST activity in the fish significantly delayed tumor progression and growth, suggesting it is a promising target for developing new therapies for ALL and LBL.

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