Fish shed light on human melanoma

June 18 2012

A transparent member of the minnow family is providing researchers at Weill Cornell Medical College in New York City with insight into human melanoma – a form of skin cancer – that may lead to new or repurposed drug treatments, for skin and other cancers.

The experiments will be reported at the "Model Organisms to Human Biology: Cancer Genetics" Meeting, June 17-20, 2012, at the Omni Shoreham Hotel in Washington, D.C., which is sponsored by the Genetics Society of America. The meeting will bring together investigators who study cancer-relevant biology in model organisms — such as fruit flies, yeast, fungi, worms, and mice — with investigators studying human cancer. Each session includes both speakers from the model organism research community and those focusing on human cancer research.

Each year in the United States, 8,700 people die from malignant melanoma. Yariv Houvras, MD, PhD, at Weill Cornell Medical College and Craig Ceol, PhD, at the University of Massachusetts Medical School, along with their colleagues, discovered that a previously-identified human gene, SETDB1, accelerated the progression of cancer when a copy of the gene was inserted into the zebrafish genome. This led researchers to believe that this gene may have a similar effect in humans. In fish with the human SETDB1 gene, melanomas appear earlier and spread faster, which is easily seen through the transparent skin of the zebrafish.

Zebrafish are valuable models for people. Their generation time is three

to four months, and each female lays hundreds of eggs every two to three days. In addition, researchers can easily manipulate its genes, many of which have human counterparts, and they can even see inside the developing embryos because they are transparent.

In the work that will be presented at the meeting on Monday, June 18, the researchers used the fish to probe a part of human chromosome 1 that is involved in melanoma. In humans, cancer gets underway when a sequence of genes mutate, including a key gene called BRAF. About 60 percent of human melanomas have a specific BRAF mutation, and a drug targeting mutant BRAF, Vemurafenib, was approved by the Food and Drug Administration (FDA) last year for the treatment of patients with metastatic melanoma. It's not unusual for cancers to have multiple genetic mutations, so the researchers reasoned that additional genes found in the amplified region on chromosome 1 could also drive melanoma.

And that's where the zebrafish came in. The researchers delivered SETDB1 into single-cell zebrafish embryos that already had BRAF mutations, and the resulting adult fish had the human gene in every melanocyte. They discovered that SETDB1 is a master regulator, playing an important role in the regulation of many other genes and accelerating the cancer. SETBD1 acts by altering regions of the genome using a biochemical process called methylation, and in doing so prevents many genes from being turned on and making their appropriate protein products.

Methylation of chromatin is an epigenetic change – that is, it doesn't alter the underlying DNA sequence. SETDB1 acts by binding to DNA and changing the methylation pattern, which it does at several thousand places in the human genome, according to the studies performed by Dr. Houvras and colleagues.

"This is a very exciting area. Many new connections are being made between chromatin-modifying enzymes and cancer," Dr. Houvras explains. The FDA has already approved a drug that inhibits DNA methylation, Decitabine, for a blood disorder called myelodysplasia. "Within the next few years drugs that inhibit histone methylation will be tested in clinical trials. These drugs may target SETDB1 and other histone methyltransferases and help treat specific cancers that rely on these pathways," Dr. Houvras notes.

The zebrafish may be easy to work with, however this project was anything but. The researchers scaled up their experiments to follow several thousand fish for six months. They performed over 35,000 individual observations, Dr. Houvras says, as they watched fish develop melanomas individually.

The role of SETDB1 in the cancer isn't black-and-white. In humans it's highly expressed in 5 percent of normal melanocytes, in 15 percent of benign nevi, and in 70 percent of malignant melanomas. Moles that overexpress the gene may be more likely to progress to cancer, the researchers speculate – which could be very useful information, and all thanks to the zebrafish.

Provided by Genetics Society of America