Fish Shed Light on Human Melanoma

_Zebrafish, a member of the minnow family, provides insight into melanoma, a form of human skin cancer_

BETHESDA, MD — June 15, 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 \textit{SETDB1} into single-cell zebrafish embryos that already had \textit{BRAF} mutations, and the resulting adult fish had the human gene in every melanocyte. They discovered that \textit{SETDB1} is a master regulator, playing an important role in the regulation of many other genes and accelerating the cancer. \textit{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. \textit{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 \textit{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 \textit{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.

\textbf{ABOUT THE MODEL ORGANISM TO HUMAN BIOLOGY MEETING:} The GSA MOHB Meeting has been held every other year since 2006. The GSA Board of Directors developed this meeting to enable basic research scientists studying genetic diseases in model organisms and scientists studying these diseases in humans to have a forum for discussion of their findings and to forge collaborative investigations.
ABOUT GSA: Founded in 1931, the Genetics Society of America (GSA) is the professional membership organization for scientific researchers, educators, bioengineers, bioinformaticians and others interested in the field of genetics. Its nearly 5,000 members work to advance knowledge in the basic mechanisms of inheritance, from the molecular to the population level. GSA is dedicated to promoting research in genetics and to facilitating communication among geneticists worldwide through its conferences, including the biennial conference on Model Organisms to Human Biology, an interdisciplinary meeting on current and cutting edge topics in genetics research, as well as annual and biennial meetings that focus on the genetics of particular organisms, including C. elegans, Drosophila, fungi, mice, yeast, and zebrafish. GSA publishes GENETICS, a leading journal in the field and an online, open-access journal, G3: Genes/Genomes/Genetics. For more information about GSA, please visit www.genetics-gsa.org. Also follow GSA on Facebook at facebook.com/GeneticsGSA and on Twitter @GeneticsGSA.