Surprising similarities between human and zebrafish tumors

October 7 2010, by Anne Trafton, MIT News

Most human cells have 23 pairs of chromosomes, the large bundles of DNA that store all of a cell's genetic information. However, scientists realized more than 100 years ago that tumor cells usually have extra copies of some chromosomes. This trait, known as aneuploidy, appears to give tumor cells a survival edge.

MIT biologists led by Professor Nancy Hopkins have now shown that aneuploidy also arises in tumors in zebrafish, which are increasingly used to study cancer biology. The finding, published last month in the *Proceedings of the National Academy of Sciences*, should help scientists identify cancer-promoting genes that could become targets for new drugs, said Hopkins.

Mice are the animals most commonly used to study cancer, but most of the mice genetically engineered to develop tumors do not usually produce highly aneuploid tumors. This is why zebrafish offer a useful model for studying this phenomenon.

Hopkins and her colleagues found that a gene called met, which is known to cause cancer, sits on a chromosome found in excess in zebrafish tumors.,Other researchers had previously observed met on a chromosome found in extra numbers in human cancer. "That already gives us reason to think the genes could be the same," said Hopkins, who is the Amgen Professor of Biology and a member of the David H. Koch Institute for Integrative Cancer Research at MIT.

Zebrafish cancer

Hopkins has been studying zebrafish since 1989, when she went to Germany on sabbatical and came back with enough fish to start a new colony in her lab at MIT. For 15 years she studied early zebrafish development, by mutating genes in zebrafish and tracking the resulting defects in embryos. She and her colleague, research scientist Adam Amsterdam, assembled more than 500 such mutations that affected early development when both copies of the gene were mutated.

Hopkins' lab manager, Sarah Farrington, who kept scrupulous records of the fish populations, noticed that some of the fish that carried mutations in a single copy of one of those 500 genes were dying early. With their colleague, Professor Jacqueline Lees, Hopkins lab researchers found that the fish were getting cancer, and the cancer-prone lines had mutations in genes that code for ribosomal proteins. The normal version of these proteins appears to suppress tumor development.

"It turned out that by accident, we had discovered a new class of cancer genes," said Hopkins.

After that discovery, Hopkins decided to determine whether the zebrafish tumors were aneuploid like human tumors. But she could not convince anyone to tackle the problem until two years ago when a new postdoctoral associate, GuangJun Zhang, arrived in her lab. Zhang had a long-standing interest in how cells maintain a normal amount of DNA and how chromosome numbers change in evolution. In his first experiment, he found that tumor cells taken from the fish had too many chromosomes.

However, techniques to distinguish zebrafish chromosomes by sight have not been developed, and so it was difficult to figure out which of the chromosomes were affected. The team enlisted help from the Koch

Institute's bioinformatics core facility. Koch research scientist Sebastian Hoersch, along with Zhang and Amsterdam, adapted a technique called comparative genome hybridization. This method involves mixing the DNA of tumor cells and normal cells and determining the ratio between the two. If the ratio for a given DNA sequence is not one to one, it means that chromosomal region has been gained or lost in the tumor.

Looking for patterns

While no two zebrafish tumors had exactly the same aneuploidy profile, the researchers did find recurring patterns, just as scientists have previously seen in human tumors. "If you looked at hundreds of patients with the same type of tumor, you could imagine it would be totally random, but that's not what is seen," said Amsterdam. "Some chromosomes are much more often overamplified while others are underrepresented."

In addition to whole chromosomes that are overrepresented or underrepresented, highly aneuploid tumors of fish and humans also have short segments of DNA that are amplified or deleted, called focal regions. The next step will be to use these regions to identify genes that are also focally amplified in human tumors and look for genes shared by fish and human cancers. The same approach may also be applied to whole chromosomes in the future.

It should not take long to find candidate genes that drive cancer in the two organisms, because fish and humans are close enough in evolution to have the same cancer genes, but far enough apart that the order of their genes is scrambled. Then, because the human and zebrafish genomes have both been sequenced, scientists can make a list of any genes that overlap between those two chromosomes. This could dramatically narrow the search for cancer genes — from the roughly 1,000 genes located on a given chromosome to a few dozen candidates.

That would represent a “major step forward” in the ability to identify potential cancer-causing genes, said David Langenau, assistant professor of pathology at Harvard Medical School, who was not involved in the research. “If there’s an amplification in a human tumor of 100 genes, and you find an amplification in zebrafish of 10 of those genes, you would focus on those 10 genes,” he said.

Once the researchers zero in on some promising genes, they plan to start doing experiments to figure out if shutting down gene expression inhibits tumor growth. The more cancer genes they can identify, the better, said Hopkins. “There’s a feeling that what you need in most cancers is a combination of drugs,” she said. “There will be several drivers, and you have to hit three or four of them to knock out the tumor.”

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