A new way to treat colon cancer?

10 October 2006

Researchers at University of Utah's Huntsman Cancer Institute have discovered a new target for possible future colon cancer treatments – a molecule that is implicated in 85 percent of colon cancer cases.

These findings were published online Oct. 6, 2006, in the *Journal of Biological Chemistry*.

By knocking out – that is, genetically disabling – a molecule called C-Terminal Binding Protein (CTBP) researchers were able to rescue zebrafish from the effects of a mutation in the adenomatous polyposis coli (APC) gene.

In humans, mutations in this gene long have been known to initiate a series of events that cause colon polyps, which eventually become cancerous. APC mutations play a role in 85 percent of colon cancers. The new findings mean CTBP also is involved in that proportion of colon cancers.

In zebrafish, APC mutations keep the intestine from developing properly. "In essence, knocking out CTPB promotes normal development of the intestine in zebrafish carrying an APC mutation," says David A. Jones, a University of Utah associate professor of oncological sciences and leader of the study.

In normal cells of both humans and zebrafish, the APC gene controls the amount of CTBP present by marking it for destruction. In tumor cells with mutated APC, CTPB is not destroyed; instead it accumulates in the cell.

One function of CTBP is to turn off the process that converts vitamin A into retinoic acid in the cell. Retinoic acid is essential in cell differentiation – the function that determines what type of cell forms and how long it lives. This study observed that in both zebrafish and human tissues with APC mutations, there are high CTBP levels and low capability to produce retinoic acid. In APC-mutated tissues in which CTBP had been "knocked out," retinoic acid production was restored.

Earlier studies in Jones' lab showed that lack of retinoic acid caused zebrafish intestines to form incorrectly, and that adding retinoic acid corrected the problems.

"Knocking out CTBP does exactly the same thing, and the logical conclusion is that it's because CTBP controls retinoic acid production," says Jones. "Since CTBP is a completely new target, we must now look for potential chemical agents that would work to block its actions. That could take three to five years."

Source: Huntsman Cancer Institute