MedicalXpress

Potential treatment target identified in an animal model of pancreatic cancer

July 1 2012

Detailed analysis of genes expressed in circulating tumor cells (CTCs) -- cells that break off from solid tumors and travel through the bloodstream -- has identified a potential treatment target in metastatic pancreatic cancer.

In a report that will appear in *Nature* and has received advance online publication, Massachusetts General Hospital (MGH) Cancer Center investigators describe finding increased expression of WNT2, a member of a known family of oncogenes, in CTCs from a mouse model of the deadly tumor and from human patients. The researchers were able to capture the CTCs -– present in the bloodstream at extremely low levels –- using a microchip-based device previously developed by members of the team.

"This proof of principle study is the first to show that, by studying both mouse and human pancreatic cancer cells captured with this device, we can dissect genes that are overexpressed in these cells and identify signaling pathways that allow them to survive in the bloodstream," says Daniel Haber, MD, PhD, director of the MGH Cancer Center and senior author of the Nature paper. "We also found that targeting a key step in these pathways can reduce metastatic potential, which is critically important for control of pancreatic cancer. This study would not have been possible without a way to isolate rare CTCs from both mouse models and human patients."

Using the second-generation version of the CTC-chip, developed in

collaboration with the MGH Center for Engineering in Medicine, the researchers first captured CTCs from mice genetically programmed to develop pancreatic cancer, one of the most deadly tumors since it is rarely diagnosed before spreading. Analysis of RNA expression levels in pancreatic CTCs, in primary tumor cells, and in normal pancreatic tissue identified several genes with significantly increased expression in the CTCs. One of these, WNT2, belongs to a family of developmental genes often overexpressed in cancer, and while the gene's expression in pancreatic tumors was higher than in normal tissue, WNT2 expression was significantly more elevated in both CTCs and metastatic cells.

Closer analysis of cells from several individual animals confirmed that WNT2 was highly expressed in pancreatic cancer CTCs and in metastases, but WNT2-expressing cells were found to be rare in primary tumors. Testing the consequences of WNT2 expression indicated that cancer cells expressing the gene were more likely to generate metastases, probably because of an improved ability to survive after dislodging from the primary tumor and entering the bloodstream.

The researchers tested several agents known to inhibit the activity of molecules in the WNT2 pathway their results implied was associated with pancreatic cancer and found that inhibition of TGF-beta activated kinase 1 (TAK1) prevented metastasis-associated activities in cultured CTCs. Knocking down TAK1 expression with RNA interference also reduced the development of metastasis in mice injected with WNT2-expressing CTCs. A significant percentage of tested CTCs from patients with metastatic pancreatic cancer were found to express WNT-related genes, along with other components of the signaling pathway associated with pancreatic cancer in the mouse model.

"The picture in more complicated in humans, since multiple WNTs are upregulated," Haber says. "But the TAK1 inhibitor we tested appears to have an effect on diverse WNT pathways involved in the survival of

pancreatic CTCs. We previously reported that TAK1 inhibition has promise for treating a genetically defined subset of colon cancers, and these findings now extend the relevance of the TAK1 pathway to suppression of blood-borne metastasis in pancreatic cancer. Considerable more work will be needed to fully understand the critical pathways involved, but it is our hope that TAK1 inhibitors will ultimately be developed for clinical testing."

Provided by Massachusetts General Hospital