Small molecules inhibit growth of human tumor cells

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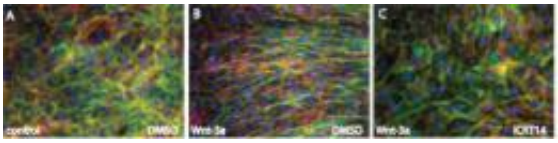

The impact of a small molecule that inhibits the Wnt pathway is shown in these panels of cultured cells seen under a microscope. Normal mouse mammary epithelial cells (panel 1) change shape when treated with Wnt-3a, a secreted molecule that activates the Wnt pathway (panel 2). Transformation of these cells can be blocked by a molecule called iCRT14 (panel 3). The cells are stained with □-catenin (in red), filamentous actin (in green) and DAPI (nuclear stain in blue). Credit: NYU School of Medicine

Researchers from the Cancer Institute at NYU Langone Medical Center have identified three novel small molecules that interrupt a crucial cellular communication pathway that regulates many aspects of development and cancer. The finding, published in the April 12, 2011 issue of the *Proceedings of the National Academy of Sciences* and featured on its cover, could provide the basis for innovative therapies for colorectal cancer and other diseases associated with aberrations in this pathway.

"Our study demonstrates that the three newly identified compounds are capable of blocking cell proliferation in cancerous human tumor biopsy cells," said Ramanuj DasGupta, PhD, assistant professor of

Pharmacology at NYU School of Medicine and the NYU Cancer Institute, and the scientific director of the NYU RNAi Core Screening Facility.

Dr. DasGupta and his colleagues identified the molecules as inhibitors of the Wnt signaling pathway. This pathway is of special interest to scientists because it controls many biological processes by promoting cell-to-cell communication. Many previous studies have shown that cancers in the liver, breast, skin, and especially the colon, are associated with abnormal signaling activity in this pathway. However, it has been difficult to find potential therapeutic agents aimed at the Wnt pathway.

"These molecules hold a lot of promise towards future Wnt-based drug development for cancer treatments," says Dr. DasGupta. "They may allow the compounds to be used for specific therapeutic purposes in humans to induce the death of Wnt-dependent or Wnt –addicted cancer cells and tumor tissues without affecting the growth and proliferation of normal healthy cells."

The scientists demonstrated that the molecules suppressed the activity of the Wnt signaling pathway—without disrupting other cellular functions—in human colon cancers from biopsies, in colon cancer cell lines, and in a mouse tumor-xenograft model. In all instances, the inhibitors stopped the proliferation of cancerous cells in the laboratory dish or in the mouse.

"To date, no therapies for the control of Wnt-driven tumors have been available for colon cancer, lung cancer, leukemia, and other forms of the disease caused by mutations in the Wnt pathway," said Robert A. Nagourney, MD, of Rational Therapeutics in Long Beach, California, who is one of the study's authors. "The findings in our human tissue model give us real hope that these compounds will have important implications in future clinical therapy and the development of an

effective Wnt inhibitor."

The Wnt pathway is complex and only partially understood. Wnt genes bind to receptors on the surface of cells, provoking a reaction (or a "signaling cascade") within the cell that ultimately allows various "downstream effector proteins" to go into action. One of these proteins, called β catenin, moves into the nucleus and oversees the activation of genes often associated with cell proliferation and other processes.

In the study, the researchers used an innovative, integrated screening platform combining RNA interference (RNAi) -technology and high-throughput chemical genetic screening to examine the potency of 14,977 compounds on the activity of the Wnt pathway. This targeted screening methodology helped identify the three promising novel inhibitors capable of blocking Wnt target genes in various mammalian cancer cell lines including human colon and breast cancer cells. Foster C. Gonsalves, PhD, first author of the study and post-doctoral fellow in Dr. DasGupta's lab, helped develop this technique.

"While more exploratory research of these promising compounds is needed, these small molecules identified in the RNAi screens can serve as prototypes for the development of future antitumor drugs targeting the Wnt signaling pathway in different Wnt-associated cancers," says Dr. DasGupta. "Similar RNAi-based integrated screening technology should be widely applicable to a variety of other signaling pathways implicated in human disease."

This study highlights the strength of high-throughput RNAi-based genome-wide or genome-scale modifier screens currently being performed at NYU's RNAi Screening Facility, according to Dr. DasGupta. The state-of-the-art functional genomic approach continues to help answer basic biological questions in cellular signaling and better define the Wnt pathway, he says.

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