Trends in Medical Research

ISSN 1819-3587

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Protein That Drives Survival of Gastrointestinal Tumors Identified

For patients with gastrointestinal stromal tumors, or GISTs, the blockbuster cancer drug Gleevec has been a reason to hope. Since the drug's introduction, survival rates have climbed dramatically and recurrence has fallen by two-thirds. But there's a downside: over time, many patients develop resistance to the drug. Now, scientists at Rockefeller University and Memorial Sloan-Kettering Cancer Center have identified a molecule that acts as a survival factor for gastrointestinal tumors, a finding that may lead to next-generation therapies that can pick up where Gleevec leaves off.

Gleevec was initially approved for fighting chronic myelogenous leukemia and it targets the BCR-ABL fusion protein that causes that rare blood disease. But Gleevec also inhibits the activated KIT receptor tyrosine kinase. Scientists have known that mutations in the gene that codes for KIT are responsible for development of GISTs, as well as other cancers such as melanomas, which makes Gleevec a potent treatment for GISTs.

Ping Chi, a Postdoctoral Fellow in C. David Allis' Laboratory of Chromatin Biology and Epigenetics at Rockefeller and a clinical fellow at MSKCC, and in collaboration with Yu Chen in Charles Sawyers' group at MSKCC, searched for GIST-specific genes to obtain better insight on the molecular events in GIST development. She focused on a group of cells in the gastrointestinal tract called interstitial cells of Cajal, or ICCs. GISTs arise from two specific populations of ICCs, myenteric and intramuscular; it's been known that KIT is highly expressed in these two types of ICCs, and these cells have been implicated as the cells that spur GIST formation.

By analyzing patient tumor samples stored at MSKCC, Chi and colleagues found that a protein called ETV1 is expressed in all GISTs at significantly greater levels than in any other type of tumor. Using RNA interference, in which small RNAs are deployed to prevent gene expression, Chi and her colleagues blocked ETV1 in GIST cell lines. The result was a decrease in cell division and an increase in cell death, findings that indicated that GISTs require ETV1 for growth and survival.

"We've shown that ETV1 is just as important as KIT in the development of gastrointestinal stromal tumors," says Chi. The findings have far-reaching implications, she says.

"About five percent of GISTs are KIT negative by immunohistochemistry," Chi says. "Because all GISTs express ETV1, we now have a very good biomarker for diagnosing GIST."

Chi and her colleagues were also interested in determining if ETV1 is required for normal growth of ICCs. They looked at the gastrointestinal tracts of genetically modified mice lacking the gene for ETV1 and observed significant loss of only myenteric and intramuscular ICCs, providing evidence of ETV1's role as a survival factor for the ICC-GISTs lineage.

The discovery by Chi and her colleagues also means that scientists now have a new therapeutic target. In addition to the risk of developing resistance to Gleevec, the drug must be given continuously because interrupting Gleevec treatment can cause GISTs to rapidly regrow.

"Now that we know ETV1's importance in GIST formation, we need to determine how the ETV1-driven oncogenic transcriptome is regulated," Chi says. "This opens possibilities for stopping GIST development when targeting of KIT fails."

"This work represents a remarkable collaborative effort from both sides of York Avenue wherein our combined strengths in signaling, mouse modeling, transcriptional regulation and chromatin biology came together to tackle complex mechanisms of cancer pathogenesis," says Allis, who is Joy and Jack Fishman Professor. "In addition to the gain-of-function KIT mutation, our results clearly show that cellular context, likely determined by transcription factor networks and chromatin landscape, also plays critical roles in oncogenesis."

Source: Nature, 2010; 467 (7317): 849 DOI: 10.1038/nature09409