Small-molecule inhibitors effectively targeted active colon cancer enzyme

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Researchers have identified two small-molecule inhibitors that effectively targeted the focal adhesion kinase (FAK), an enzyme present in certain cancers that helps tumors thrive and survive.

If the drugs are developed into oral therapeutic agents in the future, they could open up the potential for more effective and less toxic cancer therapies, according to research presented at The American Association for Cancer Research special conference on Colorectal Cancer: Biology to Therapy, held Oct. 27-30, 2010.

"It is well known that FAK is overexpressed in more than 89 percent of colon cancer tumors, helping these cancer cells survive and spread," said Vita M. Golubovskaya, Ph.D., associate professor in the department of surgical oncology at Roswell Park Cancer Institute, Buffalo, N.Y., and co-founder and senior scientist of CureFAKtor Pharmaceuticals. "We have found that targeting a specific site of FAK, called the autophosphorylation site, is an effective way to kill colon cancers cells, as it blocks FAK activation and its survival signaling."

Through prior research, Golubovskaya and colleagues identified a novel cancer therapy approach that targets the autophosphorylation site of FAK, known as Y397. Once it is "activated" the Y397 site acts as a controller that can "activate" additional cells of the FAK enzyme.

"Thus, our goal was to inhibit this Y397 site to block FAK activity," Golubovskaya said.

To do that, the researchers screened more than 140,000 small molecules from the National Cancer Institute database and identified several small molecules that could effectively target Y397. They then tested all of these molecules and found two that were the most potent at stopping colon cancer-cell growth: Y11 and Y30.

The effect of Y11 and Y30 were then tested on colon cancer cells. Compared with a commercially available inhibitor, Y11 and Y30 decreased the viability of all colon cancer cells in a time- and dose-dependent manner.

"Most companies target a site called the ATP binding site, which is very conservative, thus drugs developed to target this site are less specific and more toxic," Golubovskaya said. "Our inhibitors are very specific, inhibiting colon cancer survival and decreasing its viability and inhibiting tumor formation."

According to Golubovskaya, the next step is to test Y11 and Y30 in mice, eventually conducting pre-clinical studies with the goal in the future to use these drugs in patients after clinical trials.

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