Researchers develop synthetic compound that may lead to drugs to fight pancreatic, lung cancer

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Researchers at UT Southwestern Medical Center have identified a chemical compound that may eventually lead to a drug that fights cancers that are dependent on a particular anti-viral enzyme for growth.

The researchers are testing the compound's effectiveness at fighting tumors in mice. If it is successful, they will then work to develop a drug based on the compound to combat pancreatic and non-small cell lung cancer, two cancer types in which this particular enzyme, TBK-1, often is required for cancer cell survival.

"Our prediction is that TBK-1 is a good pharmacological intervention target for a subset of lung and pancreas cancers that are addicted to the activity of this enzyme. We believe there is a large population of cancer patients that could respond to inhibition of this activity," said Dr. Michael White, professor of cell biology and senior author of the study in the Feb. 18 issue of *Molecular Cell.*

The investigation, which lasted three and a half years, revealed how activation of the natural virus-fighting protein TBK-1 is hijacked in cancer cells to support growth and survival.

More than 250,000 compounds were screened to find one that would inhibit the enzyme's cancer-protection mechanism. The most effective, a compound called 6-aminopyrazolopyrimidine developed in collaboration

with pharmaceutical company Amgen, blocked TBK-1's effects in 40 percent to 50 percent of the non-small cell lung cancer and pancreatic cancer tissue cultures tested, reducing cancer growth. TBK-1 is activated by the Ras family of oncogenes, which are mutated in 40 percent of lung cancers and 90 percent of pancreatic cancers.

"We found a biological activity that some cancer cells need to be able to survive, and we found a way to turn it off," said Dr. White.

The next step, he said, would be ascertaining in rodents whether 6-aminopyrazolopyrimidine can permeate tumors, "hit the target and be effective." If the compound continues to demonstrate efficacy, researchers would begin work to develop a drug with the compound's properties for further testing.

The compound appears to migrate into all tissues of studied mice, but the UT Southwestern researchers don't know yet if it will penetrate solid tumors in the animal, "which is an incredibly important step in evaluating chemicals as drug leads," Dr. White said.

"We've illuminated the dark matter of regulation of an incredibly important oncogenic survival pathway. We've found a new regulatory arm of this pathway, and we've discovered you can inhibit it pharmacologically. That's target validation. The next step is to translate that target validation into development of a medicine," he said.

Provided by UT Southwestern Medical Center