Researchers discover Achilles' heel in pancreatic cancer

November 6 2008

UC Davis Cancer Center researchers have discovered a metabolic deficiency in pancreatic cancer cells that can be used to slow the progress of the deadliest of all cancers.

Published in the October issue of the *International Journal of Cancer*, study results indicate that pancreatic cancer cells cannot produce the amino acid arginine, which plays an essential role in cell division, immune function and hormone regulation. By depleting arginine levels in cell cultures and animal models, the team was able to significantly reduce pancreatic cancer-cell proliferation.

"There have been few significant advances in 15 years of testing available chemotherapy to treat pancreatic cancer," said Richard Bold, chief of surgical oncology at UC Davis and senior author of the study. "The lack of progress is particularly frustrating because most patients are diagnosed after the disease has spread to other organs, eliminating surgery as an option. We have to turn back to basic science to come up with new treatments."

Bold explained that average survival time for those diagnosed with pancreatic cancer is just four-and-a-half months, although chemotherapy can extend that prognosis up to six months.

"There is a dire need to find new options for these patients. While our findings do not suggest a cure for pancreatic cancer, they do promise a possible way to extend the life expectancies of those diagnosed with it,"

Bold said.

Bold and his colleagues hypothesized that pancreatic cancer cells lack the ability to produce arginine. In human pancreatic tumors, they measured levels of an enzyme — argininosuccinate synthetase — required to synthesize arginine.

The enzyme was not detected in 87 percent of the 47 tumor specimens examined, suggesting that the majority of pancreatic cancers require arginine for cell growth because of an inability to synthesize the amino acid.

The researchers then conducted further tests using pancreatic cell lines that represent the varying levels of argininosuccinate synthetase observed in human tumor specimens. Focusing on the lines with lowest levels, the researchers depleted arginine levels in cultures of pancreatic cell lines using arginine deiminase, an enzyme isolated from a Mycoplasma bacteria.

The enzyme was modified by adding polyethylene glycol chains to increase size and circulatory time.

The researchers found that exposing the pancreatic cancer cell lines to the modified arginine deiminase enzyme inhibited cancer-cell proliferation by 50 percent. They then treated mice bearing pancreatic tumors with the same compound and found an identical outcome: a 50 percent reduction in tumor growth. According to Bold, the current study represents a unique approach to cancer treatment in that it is one of the first to identify a metabolic pathway that can be leveraged to interrupt cancer growth.

"Instead of killing cells as with typical chemotherapy, we instead removed one of the key building blocks that cancer cells need to

function," Bold said.

Metabolic interruptions like this one are also being studied for their potential in treating cancers of the blood, such as leukemia and lymphoma. In those cases, depleting the amino acid asparagine may be used in slowing cancer-cell growth.

Bold and his colleagues are continuing their laboratory work on the effects of arginine deprivation on pancreatic cancer. They will next be looking for ways to increase pancreatic cell sensitivity to arginine deprivation.

The researchers have also begun designing human clinical trials in cooperation with the manufacturer of arginine deiminase, Polaris Pharmaceuticals.

"We're looking at whether we can combine this treatment with certain kinds of chemotherapy," Bold said. "This additional research is needed to inform the clinical work and move it forward more quickly. The better we understand this process, the more we can use it in the fight against pancreatic cancer."

Source: University of California - Davis