Researchers find oncogene is important in pancreatic cancer growth, spread

23 February 2010

(PhysOrg.com) -- Researchers at the Mayo Clinic campus in Florida have found that PKC-iota (PKCi), an oncogene important in colon and lung cancers, is over-produced in pancreatic cancer and is linked to poor patient survival. They also found that genetically inhibiting PKCi in laboratory animals led to a significant decrease in pancreatic tumor growth and spread.

The discovery, reported in the March 1 issue of Cancer Research, is especially encouraging, they say, because an experimental agent that targets PKCi is already being tested in patients at Mayo Clinic.

"This is the first study to establish a role for PKCi in growth of pancreatic cancer, so it is exciting to know that an agent already exists that targets PKCi which we can now try in preclinical studies," says the study's senior investigator, Nicole Murray, Ph.D., of the Department of Cancer Biology.

The drug, aurothiomalate, is being tested in a phase I clinical trial in patients with lung cancer at Mayo Clinic's sites in Minnesota and Arizona. Based on findings to date, a phase II clinical trial is being planned to combine aurothiomalate with agents targeted at other molecules involved in cancer growth.

Mayo Clinic researchers, led by Alan Fields, Ph.D., chair of the Department of Cancer Biology and a co-author of this report, discovered aurothiomalate in 2006 by screening thousands of Food and Drug Administration-approved drugs for their ability to inhibit PKCi signaling. The drug was once used to treat rheumatoid arthritis.

Dr. Murray stressed that this new study has not tested aurothiomalate against pancreatic cancer yet, but any treatment that targets this major cancer pathway offers a new avenue for therapy. "This is such a deadly disease. No standard treatment has shown much promise," she says. "New ideas and fresh, targeted therapies such as this are sorely needed."

Mayo researchers have led the field in understanding the role of the protein kinase C (PKC) family of enzymes as major players in cancer development and progression. Dr. Fields was the first to discover that PKCi is a human oncogene — an abnormal gene that cancer cells use to grow and/or survive. He found that PKCi is genetically altered and over-expressed in a majority of lung cancers, and that over-expression of the gene in tumors predicts poor patient survival. That led to his search for aurothiomalate and the current testing in patients.

Dr. Murray says she has also found that different members of the PKC family play distinct roles in colon cancer, which offers more opportunity for targeted treatment. In fact, animal studies show that use of a different drug, enzastaurin, significantly reduced the initial development of colon tumors, according to Dr. Murray. Enzastaurin targets PKC-beta (PKCb), which the Mayo team has shown is necessary for initiation of colon cancer, she says.

In the present study, the researchers looked at expression of PKCi in pancreatic cancer because tumor studies show that a different gene, KRAS, is mutated up to 90 percent of the time, and KRAS regulates PKCi. "KRAS has been very difficult to target therapeutically, which is why we are looking at molecules, such as PKCi, that convey signals downstream of KRAS that can be manipulated," Dr. Murray says.

They found that PKCi is highly expressed in most human pancreatic tumors they sampled, and that high PKCi expression predicts poor patient survival. Studying patient tumors, they found that patients whose tumors exhibited high PKCi expression had a median survival time of 492 days, compared to 681 days for low PKCi expression, and a reduced

five-year survival rate (10 percent versus 29.5 percent for low PKCi expression).

The researchers then genetically manipulated the expression of PKCi in pancreatic cancer cells. The results showed that PKCi is required for the growth of pancreatic cancer in both cell-based and animal models. "This is the first demonstration that pancreatic tumors require PKCi to grow and metastasize," Dr. Murray says.

The data suggest that aurothiomalate, which targets PKCi, may be effective against pancreatic cancer either alone or in combination with other treatments, such as conventional chemotherapy. "Aurothiomalate may inhibit pancreatic cancer alone, or it may sensitize pancreatic tumors to chemotherapy," she says. "It is possible that a number of cancer growth pathways will need to be targeted for an effective therapy."

The study was funded by the National Institutes of Health and the Mayo Clinic Foundation. The study's authors, which include investigators from Mayo Clinic in Rochester, Minn., declare no conflicts of interest.

Provided by Mayo Clinic