MedicalXpress

Scientists crack genetic code for form of pancreatic cancer

January 21 2011

Scientists at Johns Hopkins have deciphered the genetic code for a type of pancreatic cancer, called neuroendocrine or islet cell tumors. The work, described online in the Jan. 20 issue of *Science Express*, shows that patients whose tumors have certain coding "mistakes" live twice as long as those without them.

"One of the most significant things we learned is that each patient with this kind of rare cancer has a unique genetic code that predicts how aggressive the disease is and how sensitive it is to specific treatments," says Nickolas Papadopoulos, Ph.D., associate professor at the Johns Hopkins Kimmel Cancer Center and director of translational genetics at Hopkins' Ludwig Center. "What this tells us is that it may be more useful to classify cancers by gene type rather than only by organ or cell type."

Pancreatic neuroendocrine cancers account for about five percent of all pancreatic cancers. Some of these tumors produce hormones that have noticeable effects on the body, including variations in blood sugar levels, weight gain, and skin rashes while others have no such hormone "signal."

In contrast, hormone-free tumors grow silently in the pancreas, and "many are difficult to distinguish from other pancreatic cancer types," according to Ralph Hruban, M.D., professor of pathology and oncology, and director of the Sol Goldman Pancreatic Cancer Research Center at Johns Hopkins.

For the new study, the team investigated non-hormonal pancreatic

neuroendocrine tumors in 68 men and women. Patients whose tumors had mutations in three genes – MEN-1, DAXX and ATRX – lived at least 10 years after diagnosis, while more than 60 percent of patients whose tumors lacked these mutations died within five years of diagnosis.

The Johns Hopkins team, which previously mapped six other cancer types, used automated tools to create a genetic "map" that provides clues to how tumors develop, grow and spread.

Within the code are individual chemicals called nucleotides, which pair together in a pre-programmed fashion to build DNA and, in turn, a genome. Combinations of these nucleotide letters form genes, which provide instructions that guide cell activity. Changes in the nucleotide pairs, called mutations, can create coding errors that transform a normal cell into a cancerous one.

In the first set of experiments, the Johns Hopkins scientists sequenced nearly all protein-encoding genes in 10 of the 68 samples of pancreatic neuroendocrine tumors and compared these sequences with normal DNA from each patient to identify tumor-specific changes or mutations.

In another set of experiments, the investigators searched through the remaining 58 pancreatic neuroendocrine tumors to determine how often these mutated genes appeared.

The most prevalent mutation, in the MEN-1 gene, occurred in more than 44 percent of all 68 tumors. MEN-1, which has been previously linked to many cancers, creates proteins that regulate how long strands of DNA are twisted and shaped into dense packets that open and close depending on when genes need to be activated. Such a process is regulated by proteins and chemicals that operate outside of genes, termed "epigenetic" by scientists.

Two other commonly mutated genes, DAXX and ATRX, which had not previously been linked to cancer, also have epigenetic effects on how DNA is read. Of the samples studied, mutations in DAXX and ATRX were found in 25 percent and 17.6 percent, respectively. The proteins made by these two genes interact with specific portions of DNA to alter how its chemical letters are read.

"To effectively detect and kill cancers, it may be important to develop new diagnostics and therapeutics that take aim at both epigenetic and genetic processes," says Kenneth Kinzler, Ph.D., professor of oncology at the Johns Hopkins Kimmel Cancer Center and co-director of the Ludwig Center at Johns Hopkins.

The Johns Hopkins team also found that 14 percent of the samples studied contained mutations in a gene family called mTOR, which regulates cell signaling processes. Papadopoulos says that patients with tumors containing such alterations in the mTOR pathway could be candidates for treatment with mTOR inhibitor drugs.

"This is a great example of the potential for personalized cancer therapy," says Hruban. "Patients who are most likely to benefit from a drug can be identified and treated, while patients whose tumors lack changes in the mTOR pathway could be spared the side effects of drugs that may not be effective in their tumors."

Provided by Johns Hopkins Medical Institutions