Probing Pathways for Pancreatic Cancer

Pancreatic cancer is the fourth leading cause of cancer death worldwide, with a low survival rate that has not changed significantly for decades. Based on a collaborative effort by the International Cancer Genome Consortium, a recent study provides the most detailed picture yet of pancreatic cancer genomes and points to potential new therapies (Nature 2012;491:399–405).

Researchers analyzed tumors in patients with early pancreatic cancer who were undergoing pancreatectomy. The work included whole-exome sequencing and copy-number analysis on tumor and normal DNA from 142 patients, with additional analyses of 99 of the tumors. One of the challenges was to refine methods to analyze tumors that have small numbers of malignant epithelial cells, a problem that has been an obstacle in sequencing pancreatic tumor samples, says Andrew Biankin, MD, PhD, based at the Garvan Institute of Medical Research in Sydney, Australia, and a lead author of the study.

As with many other cancers that have been sequenced in depth, the pancreatic cancer genomes showed high variability. The 2,016 mutations identified in the subset of 99 tumors ranged in prevalence from 90% to just 1% of samples. The team found mutations in expected genes such as KRAS and SMAD, as well as in genes involved in DNA damage repair and modification of chromatin.

Additionally, the researchers found a pathway not previously seen in pancreatic cancer: mutations in genes such as SLIT2 and ROBO2 involved in axon guidance, the process by which neurons grow projections to target cells. This group of genes has recently been implicated in multiple other cancers, and Biankin notes that tumors often exploit genetic pathways that are important in development. In the case of pancreatic cancer, “we don’t know if they have hijacked these development mechanisms or are using the genes for other functions,” he says. Drugs targeting the axon guidance pathway have been investigated as therapies to promote neuronal regeneration.

Seeking to close in on driver mutations, Biankin and his team have generated more than 80 xenografts from the patient samples. They also are sequencing 40 cell lines created from the xenografts and are working with centers around the world to amass about 100 such cell lines.

Beyond the axon-guidance pathway, Biankin estimates that about 30% of pancreatic cancers might be treated by rescuing or repurposing existing drugs used for other conditions, or agents in clinical trials for other cancers.

Pursuing this approach, the Australian Pancreatic Cancer Genome Initiative and partners are launching the “Individualised Molecular Pancreatic Cancer Therapy” (IMPaCT) trial. IMPaCT will screen patients genetically and treat them with drugs targeting 1 of 3 actionable phenotypes: HER2 amplification, DNA damage repair defects, or responsiveness to EGFR inhibitors.

CT Scan Technique Boosts 3D Mammography

Computerized tomography (CT) can produce high-resolution, 3-dimensional (3D) images of the breast or other parts of the body. However, using CT scanning for screening would be a Pyrrhic victory: The high radiation exposure needed to get those images would pose a significant cancer risk.

A research team led by scientists at the California NanoSystems Institute (CNI) at the University of California, Los Angeles, has reported results that might take the “Pyrrhic” out of the victory. By combining phase contrast tomography with an algorithm developed by Jianwei Miao, PhD, they have produced high-resolution 3D images of breast tissue with radiation exposure that is less than that from today’s 2-dimensional screening mammograms (PNAS 2012;109:18290–4).

Standard CT scans depend on differences in radiation absorption to distinguish one type of tissue from another. Phase contrast tomography (PCT) distinguishes tissue types by how the electromagnetic waves of X-rays oscillate through them. The X-rays used in PCT have higher energy than those used clinically, but because less radiation is absorbed, the patient’s radiation dose is actually smaller.

GETTING A HIGH-RESOLUTION PCT image requires many X-rays from different angles, commonly referred to as views or projections. With CNI’s approach, far fewer views are needed because Miao’s “extra sloped tomography” (EST) algorithm accurately fills in the data that more views would ordinarily provide. As a result, Miao and his colleagues reported that the radiation dose is reduced by 74%. When 5 radiologists, blinded to the techniques, rated the resolution of images from a mastectomy specimen, they saw no difference between those created with more views and those that used the EST algorithm and fewer views.

However, this approach has hurdles to clear before it becomes a clinical reality. The experiment was conducted at the mammoth European Synchrotron Radiation Facility in Grenoble, France, which is about a half mile in circumference. Various groups are building more compact, room-sized synchrotrons capable of producing the same type of high-energy X-rays, but the machines aren’t available yet to hospitals and imaging centers. Given those engineering challenges and the need for patient trials of PCT mammography, Miao estimates that the approach may not be adopted by clinics for a decade or more.
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