Prostate Cancer Organoids Make Debut

Prostate cancer is notoriously difficult to culture in the lab, and many of the gene alterations that are instrumental in its growth are not represented in the few prostate cancer cell lines currently available.

Scientists have now for the first time grown "organoids," tiny 3-dimensional (3-D) structures composed of thousands of cells grouped together and arranged like an organ or tissue, from human prostate tumor biopsies. They have also correlated genetic mutations in the models with their response to various drugs (Cell 2014;159:176–87). A companion paper describes how to create healthy prostate organoids (Cell 2014;159:163–75).

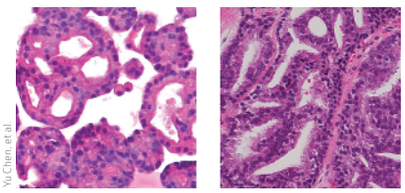
"This is a notable breakthrough for the prostate cancer field," says David Tuveson, MD, PhD, director of the Lustgarten Foundation Pancreatic Cancer Research Laboratory at Cold Spring Harbor Laboratory in New York, who was not involved in the study but is trying to grow organoids derived from pancreatic tumor samples. "This is the first system where you're able to study the biology of prostate cancer in a much more representative setting."

The clinical implications are profound, Tuveson adds, because prostate cancer is the most common cancer among American men.

In the new study, researchers used a 3-D culture method to grow six prostate cancer organoids derived from biopsies of patients with metastatic prostate cancer. A seventh organoid grew from a patient's circulating tumor cells. RNA sequencing revealed each organoid was molecularly similar to the metastasis from which it came.

According to the study's senior author, Yu Chen, MD, PhD, tumor organoids are not the same as benign organoids, in which multiple cell types mimic the normal organ. "In cancer, the organoid cells are more homogeneous," says Chen, a physician-scientist in the Genitourinary Oncology Service at Memorial Sloan Kettering Cancer Center in New York, NY.

Even so, each prostate cancer organoid was distinct from the others, containing unique mutations from each patient's tumor. Whole-exome sequencing revealed alterations such as *TMPRSS2–ERG* fusion, *SPOP* mutation, *SPINK1* overexpression, and *CHD1* loss. "These mutations are prostate cancer–specific, so there is a need for *in vitro* prostate cancer models to study them," says Chen.



Stained pathology slides of a prostate cancer patient's biopsy specimen (left) and of an organoid made from that tumor specimen.

Researchers used the organoids to test several approved and experimental prostate cancer therapies. The androgen receptor–amplified MSK-PCa2 organoid line, for example, was extremely sensitive to enzalutamide (Xtandi; Astellas Pharma) both *in vitro* and *in vivo*, whereas several other organoid lines were resistant.

Chen's team is now growing more organoids from patients with advanced prostate cancer. They plan to start large-scale *in vitro* testing to determine which drugs work best in different subgroups of patients.

"If we can identify molecular determinants of drug sensitivity and resistance, we can design more targeted clinical trials," Chen says. The long-term goal, he adds, is to optimize treatment by developing prostate cancer organoids derived from each patient's tumor and testing drugs on the organoid before they are given to the patient. ■

CRISPR Used to Create Mouse Models

Thousands of cancer-associated mutations have been discovered through tumor genome sequencing. A common strategy to study a particular mutation requires scientists to create and breed a strain of mice that carries the aberrant gene, a time-consuming and costly process.

A faster, less expensive method may now be possible, according to new research from the Massachusetts Institute of Technology (MIT) in Cambridge. Using a genome-editing system called CRISPR/Cas (clustered regularly interspaced short palindromic repeats/CRISPR-associated proteins) that protects bacteria from phage infections, scientists altered the tumor suppressor genes *Pten* and *p53* in about 3% of liver cells in mice. This was enough to produce tumors within 3 months, researchers reported (Nature 2014 Aug 6 [Epub ahead of print]).

"The beauty of this system is speed," says senior author Tyler Jacks, PhD, director of MIT's Koch Institute for Integrative Cancer Research. "The alternative process might take a year or more to get the same answer that we could get with this system in weeks."

This new method of cancer-model generation includes an enzyme called Cas9 that binds to and cuts DNA, and a short RNA guide strand that leads Cas9 to the DNA target.

MIT researchers used hydrodynamic injection to deliver a CRISPR plasmid DNA expressing Cas9 and single-guide RNAs to the liver that directly targeted *Pten* and *p53*. Cas9 snipped the DNA precisely where researchers engineered the break to occur. "When the break is improperly repaired, a mutation results, which is what we were aiming for," says Jacks.

Targeting of *Pten* and *p53* induced liver tumors that mimicked those caused by Cre-*LoxP* technology–mediated deletion of the two genes. In addition, researchers also used the CRISPR/Cas system to cut out the normal version of the β-catenin oncogene and replace it with a form containing activating mutations. The genetic switch was successful in about 0.5% of hepatocytes.

Being able to both replace a gene and mimic its deletion is important because cancer gene mutations fall into both categories, Jacks says. "Some are loss of function, some are gain of function. This editing ability is critical for accurately modeling certain types of cancer-associated mutations."

Injecting CRISPR components into veins in the tails of mice is an effective method for getting genetic material to the liver, a natural destination for foreign material filtered from the blood. Jacks's lab is now working on methods to deliver CRISPR components to other organs. From the long list of potential cancer genes, scientists will be able to rapidly evaluate the role