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.

Researchers used the organoids to test several approved and experimental prostate cancer therapies. The androgen receptor–amplified MSKPCA2 organoid line, for example, was extremely sensitive to enzalutamide (Xtandi; Astellas Pharma) both in vivo and in vitro, 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. Jack’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
each plays in tumor development and identify driver mutations.

“The faster we know the drivers, the faster we’ll be able to develop and test new medicines that are directed at the genes or the proteins produced by those mutations,” says Jacks.

In the future, he says, this genome-editing tool may even make it possible to correct cancer-causing mutations. “If you can do genome editing in vivo, which is what we’ve done, could you correct cancer-predisposing mutations in humans?” Jacks wonders. “That’s not going to happen tomorrow, but down the road, it’s not out of the realm of possibility.”

PD-1 Inhibitor Approved for Melanoma

The FDA’s accelerated approval of pembrolizumab (Keytruda; Merck) on September 4 will likely make a swift difference in melanoma care, according to several experts.

The drug, which turns off the immune modulator PD-1, was approved for use as a second- or third-line therapy, after the immune therapy ipilimumab (Yervoy; Bristol-Myers Squibb) no longer works, and, for BRAF V600-mutation–positive patients, developing resistance to a BRAF inhibitor.

Pembrolizumab shows a 24% response rate and causes fewer serious side effects than ipilimumab, and yields durable results in most patients who respond, says Jeffrey Weber, MD, PhD, a senior member and director of the comprehensive melanoma research center at the H. Lee Moffitt Cancer Center in Tampa, FL, who has led studies of pembrolizumab.

“It’s a major advance,” Weber says. The drug offers “great benefit for patients, humongous potential for combinations with other immune-therapies and other therapies, and it’s not very toxic—you can safely treat people in their 80s.”

Weber says his experience with pembrolizumab has been positive, and he predicts that the drug will soon be approved as a first-line therapy as well. However, he does not believe that oncologists will try pembrolizumab for first-line treatment or in other types of cancer until the FDA expands its use.

“I don’t think you’re going to see a lot of off-label use of such an expensive drug,” Weber says. Estimates suggest the drug will cost $125,000 a year.

Industry experts expect a second anti-PD-1 drug, nivolumab (Bristol-Myers Squibb), to follow pembrolizumab to market in the United States in a few months.

Bristol-Myers Squibb and its partner, Ono Pharmaceutical, filed suit in federal court against Merck the same day pembrolizumab gained FDA approval, claiming Merck violated its patents. Merck denies the charge and says it expects to win the challenge.

“Getting out of the gate first is a massive advantage” for Merck, says Rachel Webster, MSc, PhD, senior director of oncology with Decision Resources Group, a health care information company headquartered in Burlington, MA, which surveys doctors.

Oncologists are well informed about pembrolizumab and will be quick to use it, Webster explains. Once they get used to prescribing it, some might be less inclined to switch to nivolumab.

The real competitive advantage, Webster says, will come from winning approval in the first-line, or treatment-naive, setting, as well as in other cancers, such as non-small cell lung cancer and squamous cell carcinoma of the head and neck.

“The race,” she says, “has only just begun.”

Noted

• The U.S. Congress approved a stopgap measure to fund the federal government from October 1 through December 15. The measure will continue funding for the NIH and NCI at their 2014 levels. Congress will work to finalize the fiscal year 2015 budget after the November elections.

• Medivation and Astellas Pharma announced that the FDA approved Xtandi (enzalutamide) for the treatment of men with metastatic, castration-resistant prostate cancer (CRPC) who have not received chemotherapy. The drug was initially approved in August 2012 for use in patients with CRPC who had previously received docetaxel.

• AbbVie and Google’s biotech company Calico have agreed to partner and spend up to $1.5 billion to produce therapies for age-related diseases, including cancer. Calico will handle research and development, and AbbVie will be responsible for late-stage clinical trials and commercialization of products.

• General Electric received approval from the FDA to sell its 3-D breast-imaging devices in the United States. 3-D mammography combines X-rays taken from multiple angles to create more-detailed images than traditional mammograms. Until now, Hologic, which received FDA approval in 2001, has been the only company allowed to sell the machines in the United States.

• The Cancer Drugs Fund will get an extra £160 million (€265 million) and be extended to 2016 to help patients in England receive cancer medications that the country’s National Health Service would not ordinarily cover. The infusion of cash will bring the fund, which has helped more than 55,000 cancer patients since it was set up 4 years ago, to £280 million a year.

• Darmstadt, Germany’s Merck KGaA announced that it will buy Sigma-Aldrich of St. Louis, MO, for $17 billion. Merck KGaA, which operates under the umbrella brand EMD in the United States and Canada, creates high-tech products in the pharmaceutical and chemical sectors. Sigma-Aldrich develops and manufactures a range of life science products, such as chemicals, biochemicals, and equipment for life science research.

• For more news on cancer research, visit Cancer Discovery online at http://CDnews.aacrjournals.org.
CRISPR Used to Create Mouse Models


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