Identifying Cancer Mutations as Therapeutic Targets

By Anna Azvolinsky

Cancer therapies are increasingly targeting specific molecular pathways and mutations. Molecular testing to identify a mutation expressed in a tumor is becoming common both in clinical research and to gauge whether a patient is eligible for a Food and Drug Administration–approved therapy.

These molecular testing efforts have focused on well-defined pathways that drive tumor growth, such as the phosphatidylinositol 3-kinase (PI3K) and the human epidermal growth factor receptor 2 pathways. And yet researchers are just beginning to understand the genes and pathways important for progression of various tumor types.

Although a diagnostic screening test for a single molecular alteration is increasingly becoming common clinical practice, cancer researchers strive to go beyond this method to provide a wider picture of a tumor’s molecular landscape.

Importance of Single-Patient Studies

Although treatment with targeted therapies often works well initially, many patients develop resistance after chronic exposure to an agent that inhibits a cancer pathway.

“It is fairly well established that there are two major resistance mechanisms: acquired and adaptive resistance,” said Pau Castel, graduate student in the laboratory of José Baselga, M.D., Ph.D., medical oncologist and physician in chief at the Memorial Sloan–Kettering Cancer Center in New York. “[Patients treated with targeted agents who initially respond] tend to acquire adaptive resistance. Tumors are made up of a spectrum of clones and under targeted therapeutic pressure, one...
or several clones are selected that can overcome the drug’s inhibition, Castel said.

Baselga’s laboratory discovered a common mechanism by which advanced breast tumors with mutations in PIK3CA, the gene that encodes the alpha subunit of PI3K, treated with an inhibitor against PI3Kα, called BYL719, become resistant to the drug. Researchers identified the resistance mutation, loss of function of the tumor suppressor PTEN, by analyzing metastatic tumor samples of a trial patient who had a partial response for 7 months to BYL719 but who eventually died when her disease relapsed.

Castel and colleagues took samples from 16 tumors in the lung, liver, and other metastatic sites. They sequenced the genomes of tumors that had shrunk and the rest that had not responded to the drug and did so for metastatic tumor samples obtained before exposure to BYL719. The loss-of-function PTEN mutation occurred only in samples that had responded to the drug, but not in pretreatment samples from the same metastatic tumor. A similar analysis of nine more patients from the same trial identified the PTEN mutation in two more patients. Researchers presented the data at the 2014 annual American Association for Cancer Research meeting (abstract LB-327: “Loss of PTEN Leads to Clinical Resistance to the PI3Kα Inhibitor BYL719 and Provides Evidence of Convergent Evolution under Selective Therapeutic Pressure”).

“For those of us working on new therapy targets, a useful technique is to create a patient-derived xenograft mouse model using tumor samples,” said Castel. Researchers then study these models, including those made from lesions that relapsed after therapy, for response to clinically available and experimental therapies in the laboratory to understand which drug or combination treatments could work for patients with that resistance mutation.

“I think this methodology of analyzing a patient’s tumors directly to identify important mutations is a powerful tool—it’s a relatively fast approach,” Castel added.

Through focused efforts such as this, researchers are identifying the same mutations in different tumor types, and clinical trials are switching from tumor type-centric to mutation-centric. At Memorial Sloan–Kettering and other centers, so-called basket studies are being designed to enroll patients with a particular mutation, irrespective of the cancer they harbor, said David Solit, M.D., Memorial Sloan–Kettering medical oncologist and director of the center for molecular oncology.

“The cost of next-generation sequencing has declined significantly over the past several years, and it is now possible to use these large multigene assays as both clinical and research tools,” Solit said. However, he continued, few institutions have the resources to perform such tests, partly because insurance companies do not pay for genetic testing for most cancers.

It is early days for broad-access comprehensive sequencing, said Arul Chinnaiyan, M.D., Ph.D., director of the Michigan Center for Translational Pathology and professor of pathology at the University of Michigan in Ann Arbor. But he is optimistic that such efforts will become commonplace as costs of sequencing drop and research identifies more clinically important mutations for each tumor type.

“We are moving in this direction with new tools and clinical trials. We need to molecularly monitor patients longitudinally through the course of their disease and as they are exposed to various therapies. Just the primary tumor or archival material is not informative enough,” Chinnaiyan said.

Databases To Pool Data

Many efforts are under way to generate cancer genome sequencing and expression data as well as analytical tools to process and compare. The Cancer Genome Atlas, funded through the National Cancer Institute and the National Human Genome Research Institute, sequenced a spectrum of primary tumors and made the data publicly accessible. Since then, several analytical tools that pool data from different sources have emerged, allowing those interested to mine data for comparative analytics. Among the first was Chinnaiyan and colleagues’ Oncomine, which began as an academic project and is now licensed to
Life Technologies with free public versions as well as prescriber-only tools.

“The tool allows you to compare your own patient or laboratory data against public-domain data,” Chinnaiyan said. “It allows integration and analysis of all types of cancer -omics data, and both the databases and the analytical tools keep evolving.”

Similar types of free public tools include the cBioPortal from Memorial Sloan–Kettering and the Cancer Browser from researchers at the University of California, Santa Cruz.

Interinstitutional Collaborations
Employing these types of cancer genomic analytical tools in combination with laboratory experiments, Chinnaiyan, along with Charles L. Sawyers, M.D., of Memorial Sloan–Kettering, is leading a seven-institution effort funded by Stand Up to Cancer to identify the diversity of resistance mutations in patients with metastatic castrate-resistant prostate cancer that are acquired during therapy as well as those mutations that can, a priori, predict resistance to a therapy.

“The project is built around multi-institution data sharing and collaboration,” Chinnaiyan said. The goal is to sequence the tumors of 500 metastatic castrate-resistant prostate cancer patients. The team has sequenced 150 tumors so far, according to Chinnaiyan. Although setting up the infrastructure and communication took about 6 months, Chinnaiyan said that the academic institutions have now streamlined the data and analyses.

“This will probably be one of the first multi-institutional clinical sequencing cohorts put together,” Chinnaiyan said.

Such efforts are important to prevent overlap of efforts and to allow researchers to learn from each other’s studies.

“Our community in general will have to be more open to sharing large data sets as they are generated. There are powers in numbers. The only way to really validate results is to look across other large data sets and similar cohort analyses,” Chinnaiyan said.

Although the Cancer Genome Atlas has been instrumental, the data have not been that useful for identifying drug-resistance mechanisms. As clinical sequencing efforts continue, more clinical data are generated. Several organizations, including the American Association for Cancer Research and NCI, are in discussions to create bioinformatics resources, pooling such data, but this has yet to go beyond the discussion stage, according to Chinnaiyan.

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DQ (Physician Data Query) is the National Cancer Institute’s source of comprehensive cancer information. It contains peer-reviewed, evidence-based cancer information summaries on treatment, supportive care, screening, prevention, genetics, and complementary and alternative medicine. The summaries are regularly updated by six editorial boards. The following PDQ summaries were recently updated:

The PDQ Supportive and Palliative Care Editorial Board published a new summary about the preparation needed by health care providers, patients, and families for the transition to end-of-life care in advanced cancer. A comprehensive review of published literature was performed and the summary was reviewed by external experts in the field before final approval by the Editorial Board. The summary was posted on Cancer.gov on 07/015/2015. To review the summary, please use the following link: http://www.cancer.gov/cancertopics/pdq/supportivecare/transitiontoEOLcare/healthprofessional/page1/AllPages

The PDQ Genetics of Kidney Cancer (Renal Cell Cancer) summary was recently updated to include a new section on hereditary leiomyomatosis and renal cell cancer (HLRCC). HLRCC is an inherited syndrome characterized by cutaneous leiomyomatosis, uterine leiomyoma, and renal cell cancer. This section includes a description of the genetics, molecular biology, clinical manifestations, management, and prognosis of HLRCC. Future directions and therapies under investigation are also addressed.

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The PDQ Colorectal Cancer Screening summary was recently updated to include a new section on adherence to screening. This section states that there have been problems with screening adherence, especially in low income and uninsured people. There has been concern that some people may adhere less to screening with colonoscopy than with fecal tests. To review the summary, please use the following link:
http://www.cancer.gov/cancertopics/pdq/screening/colorectal/HealthProfessional/page1/AllPages#Section_259

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