Physician-scientist Timothy Chan

Summary

Investigators have sequenced the genome of adenoid cystic carcinoma, a rare and deadly head and neck cancer. The work sets the stage for the sequencing of additional rare cancers at Memorial Sloan Kettering.

Since the completion of the Human Genome Project in 2003, many researchers have turned their efforts toward sequencing the genomes of various kinds of cancer. Collaborative groups including The Cancer Genome Atlas (TCGA), a government-funded project created to accelerate our understanding of the molecular basis of cancer, have published genomic information on lung, ovarian, and colorectal cancers, among others.

Memorial Sloan Kettering has played a role in many of these multicenter efforts , sharing both tumor samples and the expertise of its clinician-scientists. But despite these efforts, these studies only examine a small fraction of the many different types of human malignancies. Now our investigators have performed complete sequencing and analysis of a large set of a rare head and neck cancer called adenoid cystic carcinoma (ACC), which is an aggressive form of salivary gland cancer.

“Sequencing rare cancers such as ACC is a great way for Memorial Sloan Kettering to take the lead in unraveling cancer genomics,” says Timothy A. Chan, a radiation oncologist and investigator in the Human Oncology and Pathogenesis Program (HOPP), and the senior author of the study, which was published online May 19 in *Nature Genetics*. “Just as we have the specialized knowledge and experience to treat rare cancers in the clinic, analyzing their genomics is an area where we believe we can make an important contribution.”

An Enigmatic Malignancy

ACC is one of the most difficult cancers to treat. Some patients are cured by surgery alone, but the disease can return or spread to other parts of the body, and no known chemotherapy agent is effective, although many patients are treated with radiation therapy. The cancer, which affects 800 to 1,000 people in the United States annually, can recur for as many as ten to 15 years after treatment.

Until the current study, little was known about the molecular changes that lead to these cancers. The investigators sequenced 60 matched pairs: the complete genomes or exomes of tumor samples from 60 patients along with normal tissue samples from those same 60 patients.

“By comparing the mutational landscape of tumors to normal DNA and comparing tumors with other tumors, you can determine which genes are mutated in these cancers and also how these tumors can differ from one another,” Dr. Chan explains.

The investigators found that ACC tumors could be divided into three general subtypes: those with mutations in PI3-kinase pathway genes, which encode enzymes involved in cell growth and proliferation; those with mutations in chromatin remodeling genes, which control how other genes are expressed; and those with mutations in a pathway called Notch, which also modifies gene expression.

Targeted therapies are already in development for these three types of mutations in other cancers, raising hope that clinical trials for ACC could start quickly.

Back to top ^

Quiet Genomes

The most surprising part of the discovery was that ACC tumors carry very few mutations when compared with most other solid tumors.

“We call these quiet genomes,” Dr. Chan explains. “Breast and lung cancer are very noisy, with about 100 times more mutations than ACC. This is one of the main reasons why targeted therapies for those cancers usually work for only a short time.”

Because ACC tumors have so few mutations, Dr. Chan and his colleagues expect that targeted therapies against them will be more effective than for many other cancers with similar mutations. He compares the number of mutations seen in ACC to the number in chronic myeloid leukemia, a type of blood cancer for which targeted therapies have been very effective.

“It is very unusual for a solid tumor to have so few mutations,” he adds.

Back to top ^

Focus on Rare Cancers

The study was a collaboration among researchers in HOPP, the Department of Radiation Oncology, the Head and Neck Surgical Service , the Computational Biology Program, and investigators from a multi-institutional collaboration, including the University of Pittsburgh Medical Center and the National Cancer Center in Singapore. Several cancer centers provided tumor samples.

“It’s great that we’ve set up the infrastructure to do this kind of genome sequencing and analysis here at Memorial Sloan Kettering, because we have a lot more diseases to study,” Dr. Chan notes. The team is already working with endocrinologist and HOPP investigator James A. Fagin to sequence other rare head and neck cancers, including Hurthle cell carcinoma.

Back to top ^

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