Researchers home in on genetic signature of esophageal cancer

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University of Rochester Medical Center researchers have pinpointed two genes that are amplified in the worst cases of esophageal cancer, providing data to support a new investigational treatment that targets those same genes.

The study, led by Tony Godfrey, Ph.D., a research associate professor of Surgery at the James P. Wilmot Cancer Center at URMC, was published by the journal Clinical Cancer Research. It explores the chromosomal abnormalities that influence poor survival rates of esophageal adenocarcinoma (EAC), the more common type of esophageal cancer which occurs at the junction of the stomach and esophagus.

Considered uncommon 20 years ago, the incidence of EAC has grown faster than any tumor type in the United States, Godfrey said. Health authorities believe high rates of obesity and gastroesophageal reflux disease (GERD) contribute to the rising numbers. And despite more awareness, early detection, and newer combinations of cancer therapies, overall survival of esophageal adenocarcinoma ranges from 70 percent to 80 percent for early-stage patients to only 5 percent to 20 percent for stage 3 or 4 patients. Since most cases are discovered when the cancer has already spread, EAC is often a devastating disease.

Until lately, the identification of gene targets for EAC had been limited by too few tissue samples and the inability of technology to provide a finely detailed map of gene mutations.

However, Godfrey's lab was able to collect tumors samples from 116 EAC patients, and then use modern molecular analysis tools – microarray technology -- to investigate the DNA in the tissue. The goal was to study known chromosomal regions associated with EAC and look for subsets of genes involved in malignancy that might also be markers of poor survival.

A better understanding of genetic markers is important because many modern cancer drugs, known as "targeted therapies," are designed to chemically inhibit or block the effect of oncogenes.

Prior studies on EAC had shown an extra copy of a DNA sequence in the 7q21 chromosome region. However, Godfrey and colleagues believe they are the first to map the region with fine enough resolution to identify six genes within the core of the amplified region, and to compare them to patient outcomes.

They further honed in on two genes, CDK6 and CDK4, and through laboratory experiments proved that both genes are critical for the growth of esophageal cancer cells.

Amin Ismail, Ph.D., the postdoctoral scientist in Godfrey's lab who led the research, explained that the two molecules appear to do exactly the same thing, however CDK4 is located elsewhere, in the 12q13 chromosome region, and although it is less frequently amplified compared to CDK6, its high expression in EAC may be attributed to other genetic alterations.

Researchers explored the activity of CDK4 and CDK6 both independently and in combination. They paid special attention to CDK6, which also has been associated with poor survival in T-cell lymphoma and two common brain cancers, gliomas and medulloblastomas. CDK6 is a known regulator of the cell cycle, and thus researchers theorized that if

they could shut down the CDK6 activity, the proliferation of cancer should also cease.

These experiments, Ismail said, led to the discovery that CDK6 is not acting completely alone, and that the combined over-expression of CDK6/4 was a more accurate marker of poor survival than the amplification of either gene alone.

Meanwhile, researchers knew that an experimental drug (known as PD-0332991) targeting CDK6/4 had been developed by Pfizer and Onyx, and was already being used in early clinical trials, showing promise against a range of cancers.

Therefore, the Wilmot research team tested PD-0332991 in the laboratory on esophageal cancer cells and discovered that, indeed, the drug halted CDK6/4 by inhibiting the entire cell-cycle process involved in malignancy.

"Our data provide direct evidence that CDK6 and CDK4 are strong predictors of poor survival, and that targeting those molecules is a viable treatment option," Godfrey said. "Although we still have more work to do, we are excited about the excellent progress in the effort to find better treatments for esophageal cancer."

The approach used by Godfrey and his team follows a classic example of another success story in cancer research. Decades ago scientists discovered that the protein HER-2 (human epidermal growth factor receptor 2) is frequently amplified in some breast cancers, causing them to become more aggressive. They reasoned that a drug was needed to effectively interfere with the HER-2 gene. That drug, known as Herceptin, was developed and then approved by the U.S. Food and Drug Administration in 1998 and is widely used today to boost the life expectancy of thousands of women. Interestingly, some patients with

EAC also take Herceptin, due to recent studies showing that HER-2 also is over-expressed in a subset of esophageal tumors.

Provided by University of Rochester Medical Center