Subtle molecular changes along the upper digestive tract could guide cancer therapy

June 30 2017

Based on a new molecular study of tissues biopsied from various parts of the upper digestive tract, researchers at Georgetown Lombardi Comprehensive Cancer Center have identified significant, if subtle, differences in gene mutations and other factors that could help in developing more tailored treatment options for cancer patients. This finding is notable because as the digestive tract winds its way down from the mouth to the rectum, a continuum of cancers can arise, each of which may be amenable to precision treatment.

In this study, the researchers focused primarily on small bowel adenocarcinomas (SBAs) and compared them with parts of the upper digestive tract that precede it and follow it - the gastroesophageal area and right-sided colon cancers, respectively. Each section of the gastrointestinal, or GI, tract plays a role in digestion of food and hence has distinct structural as well as molecular differences. The finding will be presented June 30, 2017, at the European Society for Medical Oncology gastrointestinal meeting in Barcelona, Spain.

"Our study was undertaken primarily because SBAs are greatly understudied, as well as increasing in incidence nationwide, and we wanted to determine what may make them unique," says Mohamed E. Salem, MD, assistant professor of medicine at Georgetown Lombardi, and principal investigator for the study. "We really didn't have good data on SBAs so we've been treating the tumors as if they were colon cancers and we really need to start treating them based on their unique properties."

The investigators looked at 4,278 tumor samples from a tissue repository of patients with GI tract cancers. The researchers were able to clearly identify 531 SBAs; 2,674 gastroesophageal cancers; and 1,073 ride-sided colon cancers. Using a variety of genetic sequencing techniques, they ascertained how well the genes were expressed, or "turned on" to make proteins. They also calculated what is called the tumor mutational load, or TML, which can be a marker for how responsive a tumor is to immunotherapy - which, paradoxically, could indicate that immunotherapy more effective when a higher TML is found.

The researchers found a set of frequently mutated genes in SBAs that could be helpful to clinicians when they are looking to use targeted therapies that work best in cancers with specifics mutations. In this case, KRAS, BRAF, BRCA2 and a few other genes were identified in SBAs. Mutations to these genes can affect the choice of therapy as well as how to better target the mutations.

Next, the investigators compared the SBA mutations with mutations in the two other parts of the GI tract and found higher and lower mutation frequencies across a wide array of genes. They were able to discern that SBAs were more like colon than gastric cancers.

More importantly, though, they found about a two-fold higher PD-L1 expression level for gastroesophageal cancers compared to right-side colon cancers but did not find such a marked difference between those tumors and SBAs. PD-L1 is often used as a marker to indicate if a cancer might be responsive to immunotherapy, and usually the higher the PD-L1 level, the more responsive a cancer would be to certain immunotherapies.

"With this study we now have what I think is one of the biggest datasets on SBAs," says Salem. "Previously, investigators studying the colon found very unique differences between the left and ride sides, and our

study therefore took advantage of those findings by exploring the differences between ride-sided colon cancers and SBAs. We now see a continuum of molecular changes that occur as these regions of the digestive tract transition from one area to the other."

The next step, says Salem, will be to try to correlate these findings with patient treatment outcomes, initially as a retrospective, or backward looking study, and then hopefully design a forward looking clinical trial to determine which treatments may be best for patients with SBAs.

Provided by Georgetown University Medical Center