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Cancer of the ampulla of Vater: analysis of the whole genome sequence exposes a potential therapeutic vulnerability

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Abstract

Background: Recent advances in the treatment of cancer have focused on targeting genomic aberrations with selective therapeutic agents. In rare tumors, where large-scale clinical trials are daunting, this targeted genomic approach offers a new perspective and hope for improved treatments. Cancers of the ampulla of Vater are rare tumors that comprise only about 0.2% of gastrointestinal cancers. Consequently, they are often treated as either distal common bile duct or pancreatic cancers.

Methods: We analyzed DNA from a resected cancer of the ampulla of Vater and whole blood DNA from a 63 year-old man who underwent a pancreaticoduodenectomy by whole genome sequencing, achieving 37× and 40× coverage, respectively. We determined somatic mutations and structural alterations.

Results: We identified relevant aberrations, including deleterious mutations of *KRAS* and *SMAD4* as well as a homozygous focal deletion of the *PTEN* tumor suppressor gene. These findings suggest that these tumors have a distinct oncogenesis from either common bile duct cancer or pancreatic cancer. Furthermore, this combination of genomic aberrations suggests a therapeutic context for dual mTOR/PI3K inhibition.

Conclusions: Whole genome sequencing can elucidate an oncogenic context and expose potential therapeutic vulnerabilities in rare cancers.

Background

Advances in treatments for cancer have generally come incrementally because novel treatments are subjected to large prospective randomized clinical trials. In these studies, several hundred patients are randomized to one treatment arm or another and the treatment associated with the best outcome is advanced. This method has worked well for relatively common cancers, including breast and colon cancers. This approach, however, falls short when one is faced with rare cancers such that prospective trials involving large numbers of patients are difficult or impossible to conduct. In these cases, oncologists may choose chemotherapy regimens because the rare tumor is thought to be similar to a more common cancer for which an accepted standard treatment exists. Such is the case with cancers of the ampulla of Vater. These cancers account for only 0.2% of gastrointestinal cancers and approximately 7% of periampullary tumors. Periampullary tumors arise from either pancreatic ductal epithelium, the distal common bile duct, the duodenal mucosa, or the ampulla of Vater. When resectable, ampullary cancers are treated like pancreatic cancers with a pancreaticoduodenectomy. When they present at an advanced metastatic stage, there is little information guiding choices for chemotherapy regimens. Although they represent a minority in such trials, patients with ampullary cancers are often included in clinical trials of patients with biliary tract cancers, so these patients are often treated with gemcitabine and cisplatin [1].

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