Genomics Paper

Key drug-targeting genes in pancreatic ductal adenocarcinoma

Name:

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Abstract:

Pancreatic ductal adenocarcinoma (PDAC) is a highly lethal type of cancer. In this study, we undertook a pairwise comparison of gene expression pattern between tumor tissue and its matching adjacent normal tissue for 45 PDAC patients and identified 22 upregulated and 32 downregulated genes. PPI network revealed that fibronectin 1 and serpin peptidase inhibitor B5 were the most interconnected upregulated-nodes. Virtual screening identified bleomycin exhibited reasonably strong binding to both proteins. Effect of bleomycin on cell viability was examined against two PDAC cell lines, AsPC-1 and MIA PaCa-2. AsPC-1 did not respond to bleomycin, however, MIA PaCa-2 responded to bleomycin with an IC50 of 2.6 μM. This implicates that bleomycin could be repurposed for the treatment of PDAC, especially in combination with other chemotherapy agents. In vivo mouse xenograft studies and patient clinical trials are warranted to understand the functional mechanism of bleomycin towards PDAC and optimize its therapeutic efficacy. Furthermore, we will evaluate the antitumor activity of the other identified drugs in our future studies.

INTRODUCTION:

Pancreatic ductal adenocarcinoma (PDAC), which is highly lethal and makes up to more than 80% of all pancreatic cancer cases, is a type of exocrine pancreatic cancer often found in the head of the pancreas. Based on study results from the GLOBOCAN project conducted by the World Health Organization (WHO), pancreatic cancer ranks as the 12th most common cancer in the world with the age-standardized rate (ASR) for incidence and mortality at 4.2% and 4.1%, respectively . Since surgical resection is still the only hope for a cure up to now, PDAC is usually treated with pancreatectomy, followed by adjuvant chemotherapy using gemcitabine or a combination of 5-flurouracil and leucovorin . Pancreaticoduodenectomy (Whipple procedure) is commonly adopted to treat tumors from the head of the pancreas; whereas laparoscopic surgery is ideal to treat tumors from the tail of the pancreas . Although advances in surgical instruments and techniques have significantly brought down the mortality rate for the pancreaticoduodenectomy procedure, the ASR for 5-year net survival remains less than 5% for PDAC patients.

Related Work:

Pancreatic carcinogenesis is a complex and complicated process. However, the rapid expansion of microarray and RNA-seq databases provides the possibility to systematically analyze the change of gene expression pattern during this process and identify key drug-targeting genes for pancreatic cancer. In the current study, we undertook a pairwise comparison of the gene expression pattern between PDAC tumor and its adjacent normal pancreatic tissue from 45 patients and identified *FN1* and *SERPINB5*, which encode fibronectin 1 (FN1) and serpin peptidase inhibitor B5 (Serpin B5, Maspin), respectively, as the key drug-targeting genes in developing novel therapeutic agents for PDAC. Our virtual screening showed that bleomycin and octreotide exhibit reasonably strong binding to FN1 and bleomycin, desmopressin, phosphonoacetic acid, cobicistat and oxytocin exhibit reasonably strong binding to Serpin B5, respectively. We evaluated the effect of bleomycin on cell viability of two PDAC cell lines, AsPC-1 and MIA PaCa-2, and bleomycin gave an IC_{50} of 2.6 μM towards the MIA PaCa-2 cells at 72h of treatment. However, further preclinical studies are warranted to confirm whether bleomycin, as well the other identified FDA-approved drugs, would indeed elicit its antitumor activity via FN1 and/or Serpin B5 under both *in vitro* and *in vivo* conditions and could be repositioned as a therapeutic agent for PDAC.