The somatic mutation profile in familial pancreatic cancer cases and KRAS negative sporadic cases includes potentially druggable genes.

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Introduction: The 5-year survival rate of patients with pancreatic ductal adenocarcinoma (PDAC) is around 5% as the majority of patients present with advanced and treatment resistant disease. PDAC is characterized by the presence of somatic KRAS mutations in around 95% of tumors and up to 76% also have somatic mutations in TP53. The presence of a KRAS mutation restricts the use of many targeted therapies and the majority of patients are treated with chemotherapy. Sporadic PDAC (SP) occurs worldwide at an approximate frequency of 7 in 100,000 and an estimated 4-10% of cases have familial pancreatic cancer (FPC). Primary tissue availability is severely limited in pancreatic cancer and therefore, the liquid biopsy is an invaluable tool to study tumor genomics in this disease. The somatic mutation profile in sporadic and familial PDAC cases was studies with the aim to identify potentially druggable mutations that can be exploited in the clinic.

Methods: cfDNA was isolated from plasma from PDAC cases using the Maxwell RSC ccfDNA Plasma Kit and quantitated. BEAMing was also performed for the detection of a KRAS mutation in plasma from 29 familial cases and 27 sporadic cases. Sequencing was performed in 14 sporadic and 18 familial cases using the TruSight15 panel (Illumina). Somatic mutations were identified using the Variant Interpreter analysis tool.

Results: Higher cfDNA levels in plasma was found in patients with locally advanced or metastatic disease compared to those with localized or benign pancreatic conditions. The concentration of cfDNA in plasma significantly correlated with overall survival (OS), i.e. patients with a lower concentration have a longer OS. The frequency of KRAS mutations detected by BEAMing in plasma was 59% in sporadic cases and 17% in familial cases. 71% of SP cases had KRAS/Tp53 mutations, whereas KRAS mutations were found in only 17% of FPC cases by panel sequencing. Although, TP53 mutations appeared at a similar frequency in FPC and SP cases (61% FPC vs. 71% SP). Mutations were found in the following potentially druggable genes in combination with TP53: KIT, AKT, PDGFR, ERBB2, PIK3CA and BRAF in familial PDAC and KRAS negative sporadic cases.

Conclusions: The level of cfDNA in plasma appears to be a prognostic indicator, independently of the detection of tumor specific mutations. FPC and KRAS negative sporadic cases harbor somatic mutations in TP53 in combination with potentially druggable mutations.

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