TITLE: Analysis of circulating free tumor DNA identifies potentially druggable somatic mutations in familial pancreatic cancer cases.

Julie Earl[1,2], Emma Barreto[1], Maria E. Castillo[1], Mercedes Rodríguez-Garrote [1,2], Vanessa Pachón[1,2], Reyes Ferreiro[1], Raquel Fuentes[1], Maria Villamayor[1], David García-Seisdedos[3,] Gloria Muñoz[3] and Alfredo Carrato[1,2,4]

[1]Molecular epidemiology and predictive tumor markers group, Ramón y Cajal Health Research Institute (IRYCIS), Carretera Colmenar Km 9,100. 28034. Madrid, Spain.

[2]Biomedical Research Network in Cancer (CIBERONC)

[3]Translational Genomics Core Facility, Ramón y Cajal Health Research Institute (IRYCIS), Madrid, Spain.

[4]Alcala University, Madrid, Spain

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, which restricts the use of many targeted therapies. An estimated 4-10% of cases have a familial background with an unknown genetic basis. Primary tissue availability is severely limited in pancreatic cancer. Therefore, the liquid biopsy is an invaluable tool to study tumor genomics. The somatic mutation profile was analyzed in sporadic and familial PDAC cases with the aim to identify potentially druggable mutations that can be exploited in the clinic.

Methods: cfDNA was isolated from plasma from patients with PDAC using the Maxwell RSC system (Promega) and BEAMing was performed for the detection of a KRAS mutation in 29 familial (FPC) and 27 sporadic PDAC cases (SP). Panel sequencing was performed in 14 sporadic and 18 familial cases using the TruSight15 panel (Illumina). Somatic mutations were idnetified using the Variant Interpreter analysis tool in the BaseSpace platform (Ilumina).

Results: The concentration of cfDNA in plasma significantly correlated with overall survival (OS), i.e. patients with a lower concentration had 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; 61% FPC vs. 71% SP. Mutations were found in the following potentially druggable genes in combination with TP53: KIT, AKT, PDGFR and ERBB2. Furthermore, sporadic cases that were negative for a KRAS mutation harbored potentially druggable mutations in the following genes: PDGFRA, AKT, ERBB2, PIK3CA, KIT, BRAF and ERBB2.

Conclusions: cfDNA is a valuable source of genomic information in PDAC cases where primary tissue samples are scare.
The level of cfDNA in plasma appears to be a prognostic indicator, independently of the detection of tumor specific mutations.
FPC cases harbor somatic mutations in TP53 in combination with potentially druggable mutations in genes such as KIT, AKT, BRAF, PIK3CA and PDGFR.