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New biomarkers: hERG1 and pancreatic cancer

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Pancreatic cancer (PC), and its most frequent form, the pancreatic ductal adenocarcinoma (PDAC) represents the tenth most common cause of death from cancer worldwide (Ferlay *et al*, 2013). While surgery remains the cornerstone of cure, pharmacological treatments, either as adjuvant to surgery or as definitive treatment for unresectable disease, have not substantially improved patients' outcome. Indeed, PDAC 5-year survival rate is still below 6%. Such a poor prognosis mainly relies on PDAC aggressive and invasive growth, which account for rapid development of distant metastases, as well as on the rapid onset of chemoresistance.

Traditional PDAC prognostic factors include tumour size and grade, lymph node status, resection margins and vascular or neural invasion. In the last years, many studies have been performed to identify novel biomarkers to predict clinical and therapeutic outcomes accurately, as well as to design a multimodal therapeutic strategy (Apte *et al,* 2004; Ansari *et al*, 2011). As shown in figure 1, several molecules have been widely investigated for their potential prognostic role.

However, none of the molecular markers described so far can be recommended for routine clinical use (Ansari *et al*, 2011). Therefore, the identification of novel biomarkers that accurately predict disease recurrence and patients' survival would substantially improve the identification of individual risk assessment and treatment selection.

In the last years, a new class of proteins has acquired increasing relevance in oncological research: the

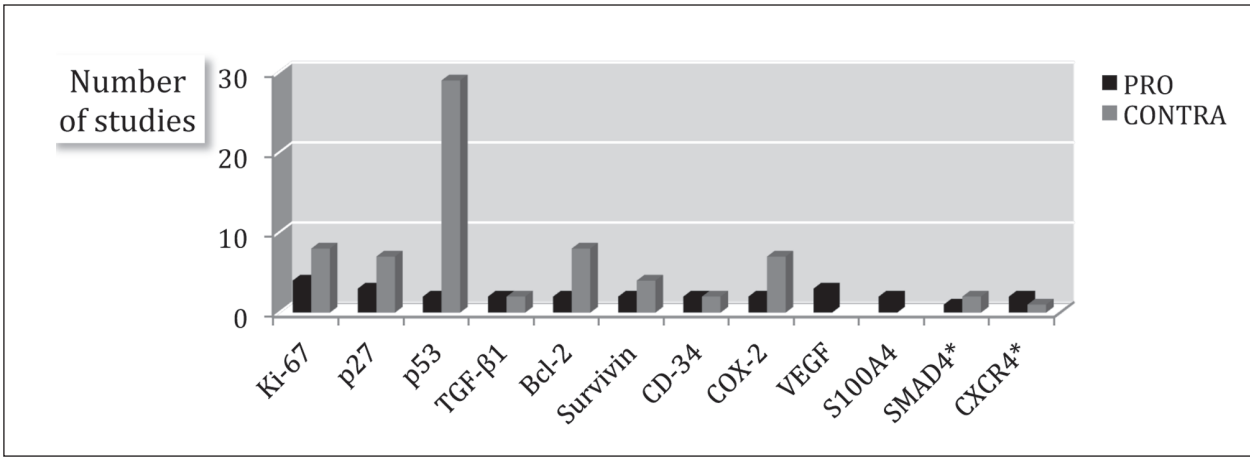

Figure 1. Potential prognostic biomarkers in PDAC. In black: studies suggesting that the molecule might serve as a prognostic biomarker. In grey: studies suggesting there is no evidence that the respective molecule might serve as a prognostic biomarker (Ansari *et al*, 2011; Kruger *et al,* 2014).

ion channels and transporters (ICTs). Indeed, ICTs control many "cancer hallmarks" in different types of human cancers and the blockage of their activity impairs the growth of different types of tumours, both *in vitro* and *in vivo*. A detailed characterization of ICTs in different cancer types is also allowing to exploit these proteins for diagnostic and patients' stratification purposes (Lastraioli *et al*, 2015).

Our group contributed to this topic, focusing on potassium channels encoded by the human ether à-go-go-related gene 1 (hERG1). hERG1 channels are over- and mis-expressed in a wide variety of human cancers and their activity is involved in the regulation of neoplastic cell growth and progression (Arcangeli, 2005). hERG1 has a clinical significance in colorectal cancer patients, where it contributes to identify at risk-subjects (Lastraioli *et al*, 2012), as well as in gastric cancer where it displays a negative prognostic impact in T1 stage patients (Crociani et al, 2014). Only very few studies examining the role of hERG1 in human PDAC have been produced: it was recently shown that hERG1 is expressed in pancreatic cancer (Zhou *et al*, 2012), and its expression is negatively regulated by miR-96 (Feng et al, 2014).

We analyzed hERG1 expression and role in PDAC surgical samples, in PDAC cell lines and primary cultures, as well as in Pdx-1-Cre, LSL-Kras-G12D/+, LSL-Trp53R175H/+ transgenic (KPC) mice. From our study it emerged that hERG1 dictates PDAC cell growth and migration, since it is physically and functionally linked to the Epidermal Growth Factor Receptor (EGF-R) pathway. We also provided evidence that hERG1 is switched on during pancreatic cancer progression as occurs in transgenic mice. In fact, mERG1 started to be aberrantly is expressed in ductal cells of Pancreatic Intraepithelial Neoplasia (PanIN) lesions, which arise in the pancreas of Pdx-1-Cre,LSL- KrasG12D/+mice, to reach high levels in adenocarcinomas of KPC mice. We finally tested the potential usefulness of hERG1 as a prognostic marker in PDAC, analyzing hERG1 expression in a cohort of 44 PDAC samples from surgically resected patients. We showed that: 1) roughly half of the primary PDAC samples over-express hERG1; 2) hERG1 expression correlates with EGF-R expression, and with 3) the proliferative index (measured through the Ki67 staining); 4) in TNM stage I and II patients, hERG1 positive-PDAC had a worse prognosis compared to the hERG1 negative.

The translatability of our data to the clinical setting is further sustained by the possibility of detecting hERG1 *in vivo*, using the α-hERG1-moAb as a tracer for in vivo imaging. In fact, the antibody, once labelled with Alexa-680, was able to detect hERG1-expressing tumors either when PDAC cells were injected into the pancreas of immunodeficient mice, or in KPC mice. This finding could have an immediate clinical fallout for the diagnosis and clinical follow up of PDAC, as well as for an early diagnosis of PDAC precancerous lesions.

Overall data here provided could qualify hERG1 as a candidate biomarker for diagnosis, treatment and patients' stratification in PDAC.

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