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Review

Drug resistance in pancreatic cancer: Impact of altered energy metabolism

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ABSTRACT

Pancreatic cancer is a highly deadly disease: almost all patients develop metastases and conventional treatments have little impact on survival. Therapeutically, this tumor is poorly responsive, largely due to drug resistance. Accumulating evidence suggest that this chemoresistance is intimately linked to specific metabolic aberrations of pancreatic cancer cells, notably an increased use of glucose and the amino acid glutamine fueling anabolic processes. Altered metabolism contributes also to modulation of apoptosis, angiogenesis and drug targets, conferring a resistant phenotype. As a modality to overcome chemoresistance, a variety of experimental compounds inhibiting key metabolic pathways emerged as a promising approach to potentiate the standard treatments for pancreatic cancer in preclinical studies. These results

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warrant confirmation in clinical trials. Thus, this review summarizes the impact of metabolic aberrations from the perspective of drug resistance and discusses possible novel applications of metabolic inhibition for the development of more effective drugs against pancreatic cancer.

1. Introduction

Pancreatic cancer is one of the most aggressive and deadliest malignancies. It is expected that by 2020 pancreatic ductal adenocarcinoma (PDAC) will surpass breast and colorectal cancer to become the second most common cause of cancer-related deaths (Rahib et al., 2014). Despite better understanding of its biology and pathogenesis, current treatment regimens are still insufficient (Wysocka et al., 2016). To date, only 5% to 25% of PDACs are eligible for resection, and even after this intervention median survival covers only 12–20 months and the 5-year survival does not exceed 20% (Oettle et al., 2007; Ahn et al., 2016). Given these poor statistics, there is a clear need to develop more effective pharmacological therapies (Wagner et al., 2004).

1.1. Pancreatic cancer chemoresistance

Chemoresistance is the major impediment for treating PDAC (Wang et al., 2016a). Currently, first and second-line therapy for PDAC chemotherapy relies on fluoropyrimidine- and gemcitabine-based regimen (Aroldi et al., 2016; Walker and Ko, 2014; Gall et al., 2015). The drug combination of Folinic acid, 5-Fluorouracil (5-FU), Irinotecan, and Oxaliplatin (FOLFIRINOX) is now considered a standard treatment in first-line setting, since it provided PDAC patients with a 4.3 month increase in overall survival when compared to gemcitabine alone (Conroy et al., 2011). Despite this progress, not all patients benefit from this intense therapy and clinicians are lacking predictive markers to help choosing which individual patient will benefit or when chemoresistance will occur. Potential biomarker candidates include determinants of drug metabolism and activity, such as the enzyme of 5-FU catabolism dihydropyrimidine dehydrogenase (DPD), and the target enzyme thymidylate synthase (TS) (Wang, 2014). For instance, Kurata et al (Kurata et al., 2011) demonstrated that PDAC cells with high TS and/or DPD levels are more resistant to 5-FU. However, high TS immunoreactivity did not significantly influence the OS of the patients with unresectable tumors, nor was an independent prognostic factor. Furthermore, in resectable patients, high TS expression levels were significantly correlated with a longer OS rate, vs lower OS for negative or low TS expression levels, suggesting a role for TS as a prognostic factor more than as a predictive biomarker (Caparello et al., 2016).

Data on potential biomarkers of resistance to platinum compounds in metastatic PDAC are also unclear. It has been demonstrated that cells able to repair platinum-DNA adducts present a profile of resistance to these drugs. The nucleotide excision repair system, which consists of at least 30 identified proteins, including ERCC1, play a key role in removal of damaged DNA (Chaney and Sancar, 1996). However, the clinical role of ERCC1 staining as a biomarker for resistance to platinum drugs is limited by methodological issues since the currently used ERCC1 antibodies are not specific to detect the unique functional ERCC1 isoform (Friboulet et al., 2013).

Cappelo et al. focused on carboxyl esterase-2 (CES2), which activates irinotecan into SN-38, evaluating *in vitro* and *in vivo* models as well as extensive analyses of genetic databases, proteomics and tissue microarrays. High expression of CES2 was associated with longer OS and PFS in resectable and borderline-resectable patients treated with FOLFIRINOX in the neoadjuvant setting (Capello et al., 2015). Remarkably, this is the first study reporting the associating of molecular features of pancreatic tumors and outcome of FOLFIRINOX treatment. However, the univariate and multivariate analyses were limited by the small number of patients included in the study (n = 22).

Gemcitabine (2,2-difluoro 2-deoxycytidine, dFdC) has been the standard of care for PDAC since 1997. This drug is a deoxycytidine analogue, whose cytotoxic activity is based on interference of DNA synthesis. Efficacy of gemcitabine-based therapy for PDAC is limited by emerging drug resistance, which can be intrinsic, or acquired after multiple treatment cycles, and is multifactorial (De Sousa Cavalcante and Monteiro, 2014). Resistance can indeed result from several molecular and cellular changes, affecting nucleotide metabolism enzymes, apoptosis pathway, drug efflux pumps, cancer stem cells or epithelial-to-mesenchymal transition (EMT) pathway, as well as up- or down-regulated expression of specific microRNA (miRNA) (Jia and Xie, 2015). For instance, Dhayat and collaborators suggested that consistent miR expression profiles (miR-21-5p, miR-31*, miR-125b-5p, miR-210-3p, miR-330-3p, miR-378a-3p, miR-422a and miR-486-5p) enhance proliferation by upregulating Bcl-2 expression in PDAC chemoresistant cells (Dhayat et al., 2015). Alterations in the nucleoside transporter-1 (hENT1), an important element in gemcitabine uptake, as well as various gemcitabine metabolism gene products, including deoxycytidine kinase and ribonucleoside reductase subunits M1 and M2 (RRM1 and RRM2), were also contributing factors in gemcitabine resistance (Nakano et al., 2007; Duxbury et al., 2004). Next, aberrant expression of genes associated with cellular survival and apoptosis have been implicated in gemcitabine resistance, such as for example the S100 family member S100A4, whose expression provokes resistance by regulation of the hypoxia-induced proapoptotic gene *BNIP3* (Erkan et al., 2005). Lastly, the phosphatidylinositol 3-kinase/Akt survival pathway has also been implicated in gemcitabine resistance (Bondar et al., 2002) along with integrin-linked kinase (ILK) (Duxbury et al., 2005).

In particular, ILK increases gemcitabine chemoresistance in PDAC cells due to a chemoprotective effect occuring in association with suppression of caspase 3 activity (Duxbury et al., 2005).

To overcome resistance modalities, several preclinical studies evaluated novel drugs alone and in combination with gemcitabine, and albumin-bound paclitaxel particles (nab-paclitaxel) revealed antitumor activity as a single agent and synergistic activity in combination with gemcitabine in murine models of PDAC (Von Hoff et al., 2013). Nab-paclitaxel is a nanoparticle albumin-bound paclitaxel, which achieves a higher tumor accumulation vs paclitaxel, both due to the lack of drug-sequestering solvent micelles and to albumin-mediated transcytosis (Yardley, 2013). The presence of albumin-binding proteins, such as secreted protein acidic and rich in cysteine (SPARC), which is overexpressed in the stromal fibroblasts surrounding PDAC, is another hypothesized mechanism to be responsible of the higher tumor accumulation of this drug (Desai et al., 2009). However, SPARC failed as a predictive biomarker and as a potential selection criteria for treatment with nab-paclitaxel (Von Hoff et al., 2013).

Additional studies showed that nab-paclitaxel improved the intratumoral concentration of gemcitabine, though the inactivation