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Pancreatic Cancer: What is the Role of ABC Transporters?

Beatrice Mohelnikova-Duchonova[1, 2*]

[1]Department of Toxicogenomics, National Institute of Public Health, Prague, Czech Republic
[2]Department of Oncology, Palacky University Medical School and Teaching Hospital in Olomouc, Czech Republic

Pancreatic carcinoma is one of the most severe forms of malignant disease with high mortality [1]. The etiology and molecular pathogenesis of the disease is still weakly understood [2]. The prognosis of patients remains very poor. Operative resection is the only therapeutic option with curative potential, but no more than 20% of patients have potentially operable tumors, and many of them experience recurrence of the disease despite the radical surgery [3]. Patients who received chemotherapy showed better survival than those who received only the best supportive care [4]. Despite this fact, resistance developed against anticancer drugs significantly limits their clinical use and influences the overall survival. Inter-individual differences in anticancer drugs pharmacokinetics and pharmacodynamics have been demonstrated. One of the most important mechanisms of the drug resistance is low accumulation of the drug in cancer cells caused by decreased uptake or increased efflux of the drug. The efflux is performed mainly by transmembrane ABC transporters [5]. The human family of ABC transporters has 49 members divided into 7 subfamilies (named ABCA - ABCG based on sequence similarities, [6]). Fourteen ABC transporters have been shown to contribute to the drug resistance in cancer cells, causing so called "multi drug resistance" (MDR) phenotype in cell lines and/or patients with various types of cancers (namely ABCA2, ABCB1/MDR1, ABCB4, ABCB11, ABCC1-ABCC6, ABCC10-ABCC12 and ABCG2/BCRP) [7].

Besides the well-known function of ABC transporters in the multidrug resistance to anticancer therapy there are important physiological functions of these proteins. It is clear that ABC transporters play an important role in all aspects of malignant disease: individual cancer susceptibility, tumor initiation and progression as well as the response of immunity system to tumor cells and the sensitivity of tumor cells to chemotherapy. The efflux of endogenous substrates and xenobiotics (including anticancer drugs) out of the cells presents the principal detoxification activity of ABCs.

Mutant K-ras activation and/or hypoxia of human pancreatic ductal epithelial (HPDE) cells led to induction of various ABC transporters [8]. Thus, ABCs could be important for both the pancreatic cancer onset and for the treatment outcome as well. Konig et al. [9] quantified the mRNA expression of nine ABCC family members and of ABCG2 in normal human pancreas and in pancreatic carcinoma (n=37). The expression of ABCC3 and ABCC5 mRNA was upregulated in pancreatic carcinoma samples. The authors suggested that ABCC3 and ABCC5 are involved in drug resistance of pancreatic tumors and analysis of their expression may contribute to the prediction of the chemotherapy outcome. ABCC5 mRNA expression in pancreatic adenocarcinoma cell lines significantly correlated with cellular sensitivity to 5-fluorouracil (5-FU) [10]. This result suggests that ABCC5 is expressed and functionally active and contributes to variable sensitivities of pancreatic adenocarcinoma cell lines to 5-FU. Further investigations using models that resemble human pancreatic tumors are necessary to prove a causative relation between expression and activity of ABCC5 and tumor resistance to 5-FU. *In vitro*, overexpression of the ABCB4 has been directly implicated in resistance to a spectrum of chemotherapeutic agents such as paclitaxel and doxorubicin [11,12]. ABCC10 mRNA levels were remarkably increased in doxorubicin-treated (MCF7) cells and its expression seems to be regulated in a TP53-dependent manner [13]. However, the nucleotides were not found to be transported by ABCC10 and nucleotide analogs are the most common pancreatic cancer therapeutics.

In conclusion, contributions of ABCs to chemoresistance of pancreatic cancer remain unknown. Similarly, their specific functions in other aspects of malignant disease, e.g. individual cancer susceptibility, tumor initiation, progression and the response of immunity system to tumor cells are not well understood. Based on the results of different studies, it is clear that some members of ABC transporters superfamily (e.g. ABCC1, ABCC3, ABCC5, and ABCC10) are possible genetic markers and targets for further validation studies on pancreatic carcinoma chemoresistance. A better understanding of genetic and molecular features of processes mediated by ABCs shall greatly improve pancreatic cancer treatment modalities. It remains an interesting field for future research to identify subgroups of patients who may benefit from specific anticancer drugs and "tailor" therapy to their "tumor profile".

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***Corresponding author:** Beatrice Mohelnikova-Duchonova, Department of Oncology, Palacký University, Czech Republic; E-mail: beatrice.mohelnikova@gmail.com

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