CYP3A5 mediates basal and acquired therapy resistance in different subtypes of pancreatic ductal adenocarcinoma.

Abstract:
Although subtypes of pancreatic ductal adenocarcinoma (PDAC) have been described, this malignancy is clinically still treated as a single disease. Here we present patient-derived models representing the full spectrum of previously identified quasi-mesenchymal (QM-PDA), classical and exocrine-like PDAC subtypes, and identify two markers-HNF1A and KRT81-that enable stratification of tumors into different subtypes by using immunohistochemistry. Individuals with tumors of these subtypes showed substantial differences in overall survival, and their tumors differed in drug sensitivity, with the exocrine-like subtype being resistant to tyrosine kinase inhibitors and paclitaxel. Cytochrome P450 3A5 (CYP3A5) metabolizes these compounds in tumors of the exocrine-like subtype, and pharmacological or short hairpin RNA (shRNA)-mediated CYP3A5 inhibition sensitizes tumor cells to...
these drugs. Whereas hepatocyte nuclear factor 4, alpha (HNF4A) controls basal expression of CYP3A5, drug-induced CYP3A5 upregulation is mediated by the nuclear receptor NR1I2. CYP3A5 also contributes to acquired drug resistance in QM-PDA and classical PDAC, and it is highly expressed in several additional malignancies. These findings designate CYP3A5 as a predictor of therapy response and as a tumor cell-autonomous detoxification mechanism that must be overcome to prevent drug resistance.