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Role of heat shock factor 1 in nab-paclitaxel sensitization in pancreatic ductal adenocarcinoma

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Background: Pancreatic ductal adenocarcinoma (PDAC) is primarily treated with chemotherapy, with first-line options including gemcitabine, 5-fluorouracil, and nab-paclitaxel (NP). However, drug resistance is a frequent occurrence and poses a significant challenge. Heat shock factor 1 (HSF1) is a key regulator of the proteotoxic stress response (PSR), and this HSF1-mediated PSR promotes tumor survival and contributes to drug resistance. Despite these established roles, the impact of HSF1 on the reaction to antimicrotubule agents such as NP in PDAC remains unexplored. It has been reported that HSF1 prolongs mitotic arrest under the antimicrotubule agent nocodazole through delaying Cyclin B1 degradation in lung and bone cancer, a process key in increasing antimicrotubule cytotoxicity. The objective of this study is to determine whether HSF1 modulates sensitivity to NP through prolonging NP-induced mitotic arrest in PDAC.

Methods: Drug sensitivity (IC50) to NP was evaluated in PDAC cell lines (PANC-1, MIA PaCa-2, PDCL-5, HPAFII, and Capan-2) using CellTiter-Blue® Cell Viability Assay. Relative HSF1 protein expression levels were measured via immunoblotting. The level of Cyclin B1, cleaved PARP, and phosphorylated HSF1 at Ser326 were analyzed following NP treatment using immunoblotting. HSF1 was knocked down using siRNA or lentiviral shRNA and rescued with exogenous lentiviral Flag-HSF1 full-length plasmids.

Results: In a panel of five human PDAC cell lines (PANC-1, MIA PaCa-2, PDCL-5, HPAFII, and Capan-2), relatively higher HSF1 expression was associated with reduced NP IC50 (p=0.008). NP IC50 was increased in PANC-1 cells following HSF1 siRNA knockdown. NP treatment induced HSF1 phosphorylation at Ser326, which correlated with Cyclin B1 expression and mitotic arrest at 12 hours in PANC-1 cells.

Conclusion: PDAC cell lines with higher basal HSF1 expression exhibit greater sensitivity to NP. The following studies will validate these findings in vivo and investigate the detailed mechanism by which HSF1 regulates antimicrotubular-induced mitotic arrest in PDAC.

Keywords: Pancreatic Cancer, Chemotherapy, Heat Shock Factor 1

