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11P
Profiling adaptive responses of renal cell cancer to cabozantinib in order to develop rational drug combinations

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Background: Functional adaptive responses (i.e. due to cellular machinery modulations) could contribute to targeted treatment resistance. We hypothesize that understanding tumor cell adaptive responses induced by cabozantinib (C) in renal cell cancer (RCC) cells could provide a rational basis for selecting treatment combinations and optimize drug doses and schedules.

Methods: We evaluated functional proteomic changes induced in VHL-mutated 786-O RCC cell line after in vitro exposure to low-dose C using reverse phase protein array (RPPA). A linear model analysis was performed on normalized intensity data from RPPA, in order to identify proteins and phosphoproteins undergoing significant treatment-induced changes. Then, we evaluated in vitro the efficacy of the interaction between C and drugs selected on the basis of RPPA analysis by mean of dose matrix tests.

Results: We exposed 786-O cells to HGF alone or in combination with C at 40 nM for 24 hours and then we performed RPPA analysis. Despite the low dose of C used, we observed a significant variation (i.e. with a log2 fold change for intensity of < 0.5 or > 1.5) in expression or phosphorylation of several protein targets. We observed inhibition of protein phosphorylation downstream of C targets (among which AXL, VEGFR–2, components of the PI3K/AKT/mTOR pathway and MEX1), which validates the cell model. Unexpectedly, we detected a significantly increased intensity signal for several protein targets involved in DNA repair process in RNA repair process (RBPP8, RPA32_pS4_S8, BABBAM1, BAP1, CDKN1A). We thus tested in vitro the association of C and inhibitors of the DNA repair proteins ATM, ATR and Wee1. We could observe that while the combination of C with KU60019 (an ATM inhibitor) is additive, the combinations of C with VE822 (an ATR inhibitor) or ML1785 (a Wee1 inhibitor) are synergistic in 2D and 3D cell culture.

Conclusions: Analysis of functional proteomic changes induced in vitro by C helped us to select targets for combination targeted therapy in RCC. Overall, our data suggest that cellular adaptive responses to drugs play a role in tumor resistance, and that elucidating them could help in designing drug combinations suitable for testing in the clinical setting.

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12P
The design and development of novel pentaranes: Paving the way to EMT inhibition in triple-negative breast cancer cells

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Background: Triple-negative cancer is characterized by a lack of expression of estrogen receptor α (ERα), progesterone receptor, and HER2/neu, which determines certain difficulties in the treatment of this molecular subtype of cancer. The development of drug candidates for triple-negative breast cancer is especially relevant. The work aims to design new type pentaranes (3-hydroxy-17(1)-hydroxysteraryl(aryl)-16,17-cycloalkano)–estra-1,3,5(10)-trienes) and to evaluate their biological activity against breast cancer cells.

Methods: The compounds tested were synthesized in ZIOC from commercial reagents using multistage procedures. Docking was performed by AutoDock Vina using a “rigid/flexible” docking approach. MCF-7 and MDA-MB-231 cells are obtained from ATCC.

Cell survival was assessed by the MTT test. ERα activity was analyzed by reporter analysis, protein expression was assessed using immunoblotting.

Results: A number of 16,17-cycloalkanoestratriene derivatives with a reduced binding affinity for the estrogen receptor α calculated by molecular docking have been obtained by multistage modification of estrone. The compounds showed weak activity as estrogen receptor alpha agonists on ERα-positive MCF-7 cells. The compounds inhibited the proliferation of triple-negative MDA-MB-231 breast cancer cells with micromolar IC50 values. The pentane T120S (3-hydroxy-17(1)-hydroxypropyl-16,17-cyclohexano)–estra-1,3,5(10)-triene) was selected as a hit. Cyclin D1 expression was notably downregulated in MDA-MB-231 cells after treatments with T120S. Analysis of signalling pathways revealed that compound T120S inhibits Slug, a key transcriptional factor in the epithelial-mesenchymal transition.

Conclusions: Novel pentaranes with low estrogenic potency and high activity against triple-negative breast cancer have been obtained. The epithelial-mesenchymal transition is considered a promising target for this class of compounds. The work was supported by RFBR, project 19-03-00246.

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13P
SY-5609, a highly potent and selective oral CDK7 inhibitor, exhibits robust antitumor activity in preclinical models of KRAS mutant cancers as a single agent and in combination with chemotherapies

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Background: Mutational KRAS activation drives oncogenic processes including aberrant cell cycle progression. CDK7 inhibition has been shown to target two fundamental processes in cancer: transcription and cell cycle control. SY-5609 is a CDK7 inhibitor in development in patients with solid tumors including pancreatic and lung cancers (NCT04247126). Here we report on SY-5609 preclinical activity in models of KRAS-mutant pancreatic ductal adenocarcinoma (PDAC) and non-small-cell lung cancer (NSCLC).

Methods: SY-5609 was evaluated as a single agent (SA) and in combination with chemotherapies. PDAC studies were done in RAS-mutant (7 KRAS, 1 NRAS) patient derived xenograft (PDX) models, and Panc-1 (KRAS-G12D) cells and xenografts +/- gemcitabine (Gem). NSCLC studies were done in A549 (KRAS G12S) cells and xenografts, and ST2972 (KRAS G12C) PDX tumors +/- docetaxel (Doc).

Results: In RAS-mutant PDAC PDX models derived from previously treated patients, SA SY-5609 (3mpk QD x28) induced regressions in 50% (4/8) of models and was well-tolerated (average body weight change [avg-BWC] 0%); regressions were sustained for >2 weeks (wks) after drug discontinuation. In Panc-1 cells, SY-5609 inhibited proliferation (IC50, 0.7nM) and was synergistic with Gem. In vivo, SA SY-5609 (3 mpk QD x21) and SA Gem (100 mpk QW) each induced partial TGI; the combination induced nearly complete TGI (97%) and was well-tolerated (avg-BWC +2%). Similar combination results (94.3% TGI) were seen with a SY-5609 dosing regimen of 3 mpk QD, other every wk for 28d. In A549 cells, SY-5609 inhibited proliferation (IC50, 10nM) and was synergistic with Doc. In vivo, the combination of SY-5609 (3 mpk) and Doc (5 mpk QW) enhanced TGI. In ST2972 tumors, SA SY-5609 (3 mpk QD x21) induced near complete regressions, and with Doc (10 mpk QW) induced complete regressions with no tumor regrowth for >4 wks post drug discontinuation. Both regimens were well-tolerated (avg BWC +3.6% to -6%).

Conclusions: SY-5609 shows robust antitumor activity in RAS-mutant PDAC and NSCLC preclinical models. Results support clinical evaluation of SY-5609 in combination with Gem in PDAC and Doc in NSCLC.

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