

Poster 09 Repurposing of the SP/NK1R-complex inhibitor Aprepitant in hepatic and pancreatic malignancies

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Background:

The SP/NK1R-complex plays a crucial role in tumor proliferation of various solid tumors. However, little is known about the mechanism involved in anti-tumor effects following antagonistic targeting of the receptor complex.

Methods:

We conducted bioinformatic analysis of RNA-Seq data sets comparing groups with low vs high NK1R expression. Cell proliferation/viability (MTT, scratch assays, colony formation) as well as apoptosis were investigated. Metabolic changes were analyzed using a SeaHorse Assay, ROS, NAD⁺/NADH, and MitoTracker staining. Key targets were analyzed by qPCR and western blotting. Pancreatic and hepatic cell models as well as 3D patient-derived organoids were used in the study.

Results:

GO analysis (KEGG DB) of patients with different NK1R expression levels (high vs low) revealed different gene expression profiles involved in mitochondrial functions (e.g., respiratory chain). In 2D and 3D cell models we found the anti-NK1R treatment to be highly effective in decreasing mitochondrial mass and generation of ROS. It is well-known that many tumors alter their metabolism under different oxidative conditions (i.e., "Warburg effect"). Mitochondrial activity is needed in energy generation but also participates in apoptosis signaling. Aprepitant is shown to change the morphology and function of mitochondria in tumor cells. Caspase signaling cascade, activated by Aprepitant, appears blocked by IAPs such as XIAP, indicating that SMAC mimetics could potentially sensitize for AP. In addition to anti-tumoral effects, autophagy signaling was increased following AP treatment. Indicating that other specific inhibitors (3-MA) would be useful in tipping the cell-balance towards cell death.

Conclusion:

The SP/NK1R-complex is a targetable pathway in hepatic and pancreatic malignancies. Selective inhibition of the receptor results in cytotoxicity involving different mechanisms, particularly involving mitochondrial functions or cellular metabolism. Co-treatment with SMAC mimetic, antioxidants or autophagy inhibitors are potentially sensitizing for Aprepitant mediated cytotoxicity.