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Transgenic Oncolytic Viruses and Ruxolitinib as Neoadjuvant Combination Therapy for Pancreatic Ductal Adenocarcinoma

Background: Pancreatic ductal adenocarcinoma (PDAC) is a highly invasive malignancy with poor prognosis and represents about 85 - 90% of all pancreatic cancers. PDAC is characterized by a dense stroma coupled with immunosuppression in a desmoplastic tumor microenvironment (TME). This makes PDAC resistant to radiation, chemotherapy and immunotherapy thus hindering successful treatment. Oncolytic viruses (OVs) such as vesicular stomatitis virus (VSV) are biological anticancer agents that replicate selectively within tumor cells. OVs are being explored in PDAC treatment because of their cell specific cytotoxicity and ability to improve immune activation within TME. OVs can be engineered with TME modulating genes to improve their efficacy. VSV has been shown to be effective against most PDAC cell lines but some are highly resistant to VSV. The Janus kinase - signal transducer and activator of transcription (JAK-STAT) signaling pathway has been implicated as a mechanism of resistance in these cell lines. The treatment of resistant PDAC cell lines with JAK1/2 inhibitors such as ruxolitinib has been shown to improve the sensitivity of some resistant cells to VSV infection. This research evaluated some transgenic VSV and ruxolitinib as potential neoadjuvant therapy for PDAC.

Methods: This study is based on an *in vitro* cell culture model. The cytotoxicity of transgenic VSV strains namely, VSV-GFP, VSV-Decorin, VSV-Relaxin, and VSV-PH20 against some PDAC cell lines were investigated. Furthermore, the effect of ruxolitinib treatment on different VSV infections in some PDAC cell lines was studied. In these experiments, cells were seeded in a 96-well plate at a density of 5,000 cells per well. After 24 hours and at 80-90% confluency, the cells were infected with different transgenic VSV at a multiplicity of infection (MOI) of 1 or 10 based on BHK-21 cells. Cell viability as a percentage of no viral treatment was analyzed by MTS assay using CellTiter-Glo® at 3 days post infection. Additionally, the invasiveness of some PDAC cell lines treated with VSV-Decorin and 5 μM ruxolitinib were assessed using the QCM™ 96-well cell invasion assay. All experiments and assays were done in triplicate.

Results: The results of viral cytotoxicity showed MiaPaCa2 cell line as the most sensitive at MOI of 1. Panc1, BX-PC3 and Capan1 cell lines were partially sensitive and HPAF-II cell line was resistant to VSV infection at MOI of 1. In the VSV-ruxolitinib treatment experiments, 5 μM ruxolitinib was the most effective for all VSV strains used on BX-PC3 cell line. In the KPC cell line, VSV-Decorin at MOI of 10 and 10 μM ruxolitinib was the most effective. For the HPAF-II cell line, the results of infection with VSV-Decorin at MOI of 10 and 5 μM/10 μM ruxolitinib were comparable in outcome. The cell invasion assay revealed an overall reduction of invasiveness in MiaPaCa2, AsPC-1 and HS766T cell lines with VSV-Decorin at MOI of 1 and in HPAFII with VSV-Decorin at MOI of 10.

Conclusion: This study showed that a combination of transgenic VSV strains coupled with ruxolitinib treatment was very effective in the infection of both sensitive and resistant PDAC cell lines. This shows great potential for oncolytic virotherapy in the neoadjuvant treatment of PDAC.