A NOVEL APPROACH TO TARGET TUMOR IMMUNE MICROENVIRONMENT AND IMPROVE CHECKPOINT IMMUNOTHERAPIES

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Background: Pancreatic cancer remains 3rd deadliest disease, with less than 7-10% survival rate. Little progress has been seen in patient's outcome due to high desmoplasia and chemo-resistance. Immunotherapy has shown promising results in cancers, except pancreatic cancer due to their characteristic fibrotic tumor microenvironment. The therapies are unable to penetrate fibrotic tumor leading to insufficient availability of therapeutic drugs at the tumor site. A recently identified mucin, MUC13 is aberrantly expressed in pancreatic tumors but not in normal pancreas, that makes it an excellent protein tumor target. This study is unique as it utilizes MUC13Ab for targeting the pancreatic tumor site and SPION nanoparticle system for delivering the stroma depleting drug (curcumin), which would help in improving immunotherapy response.

Methods: The inhouse generated MUC13Ab have been conjugated with our recently developed novel patented superparamagnetic iron oxide nanoparticles (SPIONS). Conjugation efficiency of the SPION-Anti-MUC13 particles was seen through cell uptake studies, by measuring fluorescence intensity, Prussian blue staining. Invasion assay and migration assay was carried out on KPC cells. We have used female C57BL/6J black mice, orthotopic mice model for investigating targeting efficacy of MUC13-SPION-CUR. Immune checkpoint therapy (PDL-1 and CTLA-4) was administrated along with MUC13-SPION-CUR and conjugated with fluorescent indocyanine green (ICG) dye for monitoring the tumor growth. Further, immunostimulatory effect of the nano formulation was done using flow cytometry.

Results: Our results showed that MUC13Ab conjugated SPIONS can efficiently internalize the PDAC cells. SPION-MUC13 using Indocyanine dye (ICG) specifically reached to the tumor site in an orthotopic syngeneic mouse model of PDAC as indicated by ICG fluorescence. Additionally, the combination formulation inhibited the tumor growth and showed more survival rate with CTLA-4. The combined treatment with CTLA-4 increased infiltration of total T cell population and CD8+T cells, reduced the population of myeloid-derived suppressor cells (MDSCs) by 43% (CD45+, CD3-, CD11b+, Ly6C high, Ly6G-) and T-Regulatory cells (Treg) by 23.8% (FoxP3+CD25+CD45+CD3+) in KrasG12D; LSL-Trp53R172H syngeneic mouse model of PDAC. Similar results were observed in SP-CUR-M13+PDL-1 group, which showed reduction in MDSCs (by 26.6%) and Tregs (by 0.1%) as compared with PDL-1 alone.

Conclusion: The formulation softens up the tumors for therapies that resulted in improved response to checkpoint immunotherapies in a pancreatic orthotopic mice model. Therefore, this study indicates high significance of MUC13-SPIONS-CUR for achieving pancreatic tumor specific delivery of drugs. This study has a potential to reduce morbidity and mortality caused by the disease and improve survival in patients.

Keywords: Pancreatic ductal adenocarcinomas, Tumor microenvironment, Nanodrug delivery system, Immune checkpoint inhibitors, Immunotherapy