TUMOR CELL- INTRINSIC EXPRESSION OF FGFR3 DRIVES ANTI-PDL-1 IMMUNOTHERAPY RESISTANCE IN A MURINE BLADDER CANCER MODEL

Erica Fleming-Trujillo*, Jeffrey Bloodworth, Anthony Fernald, Aubrianna Ramsland, Thomas Gajewski, Randy Sweis. *University of Chicago, Chicago, IL, USA*

Background Immune checkpoint blockade therapy has recently shown efficacy in treating advanced urothelial bladder cancer and anti-PD-1/PD-L1 therapy is currently the standard of care. However, most patients do not respond to these drugs and resistance mechanisms remain elusive. The non-T cell-inflamed tumor microenvironment phenotype correlates with poor prognosis and immunotherapy resistance. We previously found that activating mutations in Fibroblast Growth Factor Receptor 3 (FGFR3) were exclusive to non-T cell-inflamed bladder cancers. We investigated the impact of tumor cell-intrinsic FGFR3 activation on T cell infiltration and tumor responsiveness to anti-PD-1/PD-L1 in a murine model.

Methods We developed a syngeneic transplantable murine bladder cancer model using the MB49 cell line engineered to express FGFR3 with either the activating G370C mutation (FGFR3-G370C), a kinase-dead mutation K508M (FGFR3-K508M), a truncating mutation resulting in a secreted receptor (FGFR3-sec), or control. Mice were injected subcutaneously into flank and size was measured every 3 days along with PD-L1 therapy (BioXcell clone 10F.9G2). Tumors, draining lymph nodes, and spleens were harvested at endpoint for flow cytometry.

Results Tumors from mice inoculated with MB49-FGFR3-G370C cells showed diminished CD8+ T cell accumulation within the tumor and were resistant to anti-PD-L1 checkpoint blockade compared to MB49 controls. To determine if FGFR3-mediated immune resistance was dependent on FGFR3 kinase activity, MB49-FGFR3-K508M tumors were evaluated and unexpectedly found to be resistant to anti-PD-L1 treatment. Tumors with a secreted FGFR3 receptor (FGFR3-sec) retained responsiveness to anti-PD-L1 therapy.

Conclusions In a murine bladder cancer model, FGFR3 activation led to relative T cell exclusion and resistance to immune checkpoint blockade. The mechanism of resistance was not dependent on receptor kinase activity. Further studies are ongoing to determine the biochemical mechanisms of FGFR3-mediated immunotherapy resistance in bladder cancer.

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