639 PIK3IP1/TRIP IMMUNE REGULATION ON CD8+ T CELLS RESTRICTS ANTI-TUMOR IMMUNITY

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Background The signaling pathways involving phosphoinositide-3-kinases (PI3Ks) are highly conserved and tightly regulated to influence the activation, proliferation, and survival of all cell types. PI3K signaling plays a major role in T cell responses to antigen due to its position directly downstream of T cell receptor (TCR)/CD28 ligation.[1 2] Our lab has recently shown that the cell surface protein TrIP (Transmembrane Inhibitor of PI3K, gene name: Pik3ip1) has a distinctly high expression on T cells and is capable of downregulating PI3K signaling in CD4+ T cells, acting as a negative regulator of T cell immune responses.[3 4] These studies revealed that CD4+ T cells lacking TrIP expression exhibit a more Th1 inflammatory phenotype compared to WT T cells, both in vivo and in vitro.[3] These data have led us to propose that TrIP restricts the inflammatory activity of T cells more generally, including CD8+ T cells, and that targeting/knockout of this negative regulator may promote anti-tumor immunity.

Methods Using a conditional TrIP knockout mouse model developed in our lab, we have performed syngeneic tumor challenges in CD8+ T cell-specific TrIP knockout mice (TrIPfl/flE8icre). We have also characterized the tumor immune infiltrate of these mice to understand the impact of T cell-specific TrIP deficiency on the immune landscape.

Results Our data thus far show that CD8+ T cell-specific TrIP knockout mice (TrIPfl/flE8icre) are resistant to growth of syngeneic tumors. In addition to increased tumor resistance, we have also found that tumors harvested from our TrIPfl/flE8icre knockout mice contain twice as many infiltrating T cells compared to their WT counterparts. We also found that CD8+ T cells appeared to be the main drivers of this increased T cell infiltration, as their frequency was double that of the CD4+ population in tumors transplanted into TrIP KO mice.

Conclusions We describe data demonstrating that TrIP, a relatively novel PI3K inhibitor, plays a significant role in the anti-tumor immune activity of CD8+ T cells. Our that CD8+ T cell-specific TrIP knockout mice are resistant to tumor challenge and show more robust tumor CD8+ T cell infiltrate. With these data, we are excited to propose TrIP as a potential future immunotherapeutic target worthy of continued investigation.

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