## 1026 PIK3IP1/TRIP IMMUNE REGULATION ON CD8+ T CELLS RESTRICTS ANTI-TUMOR IMMUNITY

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**Background** The cancer immunology field has long been focused on understanding/optimizing T cell receptor (TCR) signaling to improve anti-tumor responses. Directly downstream of the TCR, the phosphoinositide-3-kinases (PI3Ks) play a major role in directing T cell responses.[1] Our lab has previously described a surface protein, TrIP(**Tr**ansmembrane **I**nhibitor of **P**I3K, gene name: *Pik3ip1*), is capable of regulating PI3K signaling further upstream than other known PI3K regulators.[3 4] Additionally, we have shown that TrIP protein expression is distinctly high on T cells and can negatively regulate T cell immune responses via its modulation of the PI3K pathway.[4] These data have led us to propose that TrIP regulation in T cells suppresses their inflammatory activity and that targeting/knocking out TrIP in $CD8^+$ T cells may improve anti-tumor response.

**Methods** Using our conditional TrIP knockout mouse model, we have performed syngeneic tumor challenges in $CD8^+$ T cell-specific TrIP knockout mice ($TrIP^{fl/fl}E8i^{cre}$). We have also characterized the immune infiltrate to understand the impact of T cell-specific TrIP deficiency on the immune landscape. Using TCR-transgenic TrIP KO mice, we have stimulated with varying affinity peptides to investigate how TrIP may alter activation/kinetics.

**Results** Our data show that $CD8^+$ T cell-specific TrIP knockout mice ($TrIP^{fl/fl}E8i^{cre}$) are resistant to growth of syngeneic tumors. In addition to increased tumor resistance, we have also found that tumors harvested from our $TrIP^{fl/fl}E8i^{cre}$ knockout mice contain twice as many infiltrating T cells compared to their WT counterparts. The increased T cell infiltration overwhelmingly driven by the $CD8^+$ compartment, and importantly don't display any increase in exhaustion. In our peptide studies, we have shown that TrIP expression loss from the surface of T cells is directly proportional to strength of stimulation (dose and/or affinity), whereby strong stim accelerated TrIP loss.

**Conclusions** We describe data demonstrating that TrIP, a relatively novel PI3K inhibitor uniquely expressed on the surface of T cells, plays a significant role in the antitumor immune activity of $CD8^+$ T cells. Our $CD8^+$ T cell-specific TrIP knockout mice are resistant to tumor challenge and show more robust tumor $CD8^+$ T cell infiltrate. Our affinity stimulation studies suggest TrIP's effects could be important for early activation events, so we are now working to employ tetramers to track the lymph node response as tumors develop to better understand our phenotypes. Nevertheless, we propose TrIP as an exciting novel immunotherapeutic target worthy of further investigation.

### REFERENCES

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