CONTEXT DEPENDENT EFFECTS OF TIGIT EXPRESSION ON CIRCULATING VERSUS INTRATUMORAL NK AND CD8 T CELLS IN MOUSE AND HUMAN SARCOMA MODELS

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Background TIGIT has been identified as a key inhibitory receptor on natural killer (NK), effector T, and regulatory T (Tregs) cells with implications for cancer immunotherapy and auto-immunity. Although TIGIT expression has classically been associated with exhaustion/dysfunction in NK and effector T cells, studies in HIV have demonstrated that TIGIT expression can also identify NK cells with enhanced functionality. Given the mixed results observed with TIGIT blockade clinically, we sought to characterize the differences in phenotype, proliferation, and function between TIGIT positive and negative NK and CD8 T cells in murine and human models of soft tissue sarcoma (STS).

Methods Human NK cells were flow sorted by TIGIT expression and co-cultured with cytokines and feeder lines. Human and murine NK cells were analyzed from the blood/spleen and tumors of mice and STS patients.

Results Following flow sorting, human TIGIT+ NK cells expanded over 7 days at a significantly higher rate in culture (10.45 vs 4.82 fold respectively, p=0.005). TIGIT+ NK cells also showed significantly less apoptosis (day 4, 12.8% vs. 20.8% and day 7, 15.3% vs 23.2%, p<0.05 respectively). In PBMC-derived NK cells from STS patients (N=8), we observed higher expression of CD69, Nkp46, and granzyme B in TIGIT+ compared to TIGIT- NK cells. However, these differences in activation marker expression dissipated in tumor-infiltrating NK cells. In our BALB/c K7M2 osteosarcoma (OSA) subcutaneous model, tumor infiltrating TIGIT+ NK cells expressed higher levels of NKG2A than TIGIT-. Unexpectedly, CD8+ T cells from peripheral blood of STS patients showed significantly higher expression of PD-1 and granzyme B (p=0.05 respectively) and higher expression of CD69 in TIGIT+ vs. TIGIT- subsets. These differences between TIGIT subsets also dissipated in STS-infiltrating CD8+ T cells, although PD-1 expression remained higher in the TIGIT+ subset. In murine K7M2 tumors, we also observed significantly higher PD-1 and TIM-3 expression (>90% for both, p<0.0001 for both) on TIGIT+ CD8 T cells.

Conclusions Overall, our results suggest that TIGIT+ NK and CD8 T cells display increased activation and decreased apoptosis peripherally which appears to be lost when in the STS tumor microenvironment. These data suggest tissue-specific effects of TIGIT on lymphocyte function with implications for how TIGIT block may be applied clinically.

Ethics Approval IRB Approved

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