ANTIBODY TARGETING NKG2D LIGANDS MICA/B TO UNLEASH ANTI-TUMOR IMMUNITY OF NK AND ILC1 CELLS

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Background Natural Killer (NK) cells, the founding member of innate lymphoid cells (ILCs), contribute to tumor control via direct cytolysis and secretion of immune-modulatory cytokines and chemokines. Despite well-characterized roles of NK cells, the involvement of other ILC family members in cancer is less understood. Recent reports indicate that solid tumors are populated by heterogeneous ILC subsets.1 The implication of such heterogeneity for anti-tumor immunity is not entirely clear.

MICA/B serve as ligands for the activating receptor NKG2D on NK and CD8+ T cells. Yet tumor-shed soluble MICA/B are shown to mediate immune suppression via multiple mechanisms.2 We designed a MIC-targeting antibody B10G5 which was shown to enhance anti-tumor immunity of NK and CD8+ T cells in a mouse prostate cancer model recapitulating MIC shedding (TRAMP/MICB).3 In this study we performed single-cell characterization of intra-tumoral ILCs from untreated and B10G5-treated TRAMP/MICB mice (figure 1) to better understand the effects of B10G5 on tumor immune contexture.

Methods We performed single-cell RNA sequencing of CD45+ immune cells from pooled tumors of TRAMP/MICB mice. The samples represent well-differentiated tumors of untreated mice (n = 7), poorly-differentiated tumors of untreated mice (n = 4), and tumors of B10G5-treated mice (n = 3) respectively. CD3-NK1.1+ cells were further sub-clustered into NK and ILC1 subsets, denoted based on their phenotypical and functional profiles. We also measured cytotoxicity of PBMCs from healthy donors stimulated with MIC/B10G5 complexes in vitro using calcein release assay.

Results TRAMP/MICB tumors were infiltrated by functionally heterogeneous NK and ILC1 subsets. The subsets exhibited distinct expression of genes related with cytotoxicity (GZMB, PRF1, TNFSF10) and immunomodulation (IFNγ, XCL1, CCL5), suggesting their capacity to engage in both cytolysis and immune modulation via diverse pathways. Notably, NK cells had higher perforin (PRF1) expression, whilst ILC1s exclusively expressed the death ligand TRAIL (TNFSF10). B10G5 treatment led to NK enrichment and increased heterogeneity of type I ILCs. Lastly, we showed that sMIC/B10G5 complexes enhanced cytotoxicity of PBMCs from healthy donors against tumor cells in vitro.

Conclusions Our data elucidated the functional heterogeneity of type I ILCs in prostate tumor microenvironment in a murine model, which has not been previously characterized. Moreover, we showed that targeting MIC with B10G5 could increase heterogeneity of type I innate lymphoid cells in vivo, which potentially contribute to better overall anti-tumor responses.

REFERENCES
