

1013 NKG2A EXPRESSION ON TUMOR REACTIVE CD8 T CELLS IS INDUCED BY IL-12

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Background Even though blockade of NKG2A interaction with its ligand HLA-E is a promising strategy to restore the function of cytotoxic T cells and induce tumor cell killing, several aspects of the NKG2A+ CD8 T cell biology remain to be understood to fully benefit from this therapeutic approach.

Methods To better define the nature of NKG2A+ tumor infiltrating CD8 T cells (CD8 TILs), we analyzed their phenotype in mismatch repair proficient (MMR-p) colorectal cancer (CRC) and head and neck squamous cell carcinoma (HNSCC). To further appreciate their role in the anti-tumor response, we analyzed NKG2A+ CD8 TILs by scRNA-seq and scTCR-seq and determined their spatial distribution by RNAscope. Finally, we investigated the signals regulating NKG2A expression by naïve CD8 T cells.

Results NKG2A was expressed by 10 to 15% of CD8 TILs. Among those, 3 distinct cell populations were observed, with the dominant population resembling the previously described CD39+CD103+ (DP) CD8 TILs. Analysis of our scRNA-seq and scTCR-seq dataset revealed that NKG2A expression identified DP CD8 TILs with a terminally differentiated cell state and high cytotoxic potential. Interestingly, there was a significant TCR repertoire overlap between NKG2A- and NKG2A+ DP CD8 TILs suggesting local induction of NKG2A expression. Using RNAscope, we demonstrated that, while NKG2A+ DP CD8 TILs can be detected in the stroma, those cells were enriched at the invasive margin and in the tumor bed where they might directly interact with HLA-E-expressing tumor cells. NKG2A+ DP CD8 TILs recognized tumor antigens, and HLA-E expression on tumor cells inhibited NKG2A+ DP CD8 functions. In contrast to previous results, we observed that TCR stimulation in the presence of IL-12 plays a central role in NKG2A induction by naïve CD8 T cells and their frequency was increased by TGF- β . IL-12, together with TGF- β , also potentiated the up-regulation of CD39, CD103 and PD-1 by CD8 T cells, inducing a phenotype similar to the DP CD8 TILs observed in tumors.

Conclusions Altogether, our work demonstrates that NKG2A is expressed by tumor reactive CD8 TILs in HNSCC and CRC. It also highlights that IL-12 promotes the expression of immunoregulatory molecules by CD8 T cells. While it might participate in the regulation the immune response during an acute infection, it can be detrimental to the anti-tumor response. Thus, in addition to blocking the NKG2A/HLA-E pathway, targeting soluble factors driving NKG2A up-regulation should also be considered to improve CD8 T cell functions in tumors.

Ethics Approval All surgical tumor samples and blood samples used in this study were obtained from individuals treated at the Providence Cancer Institute. All patients provided written informed consent. This study was approved by the Providence Portland Medical Center IRB (IRB protocol no. 06–108A) and was conducted in accordance with the ethics standards established by the Declaration of Helsinki.

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