

CHARACTERIZATION OF THE ANTI-TUMOR ACTIVITY OF MEMORY CYTOKINE ENRICHED NK CELLS AGAINST TUMORS WITH NEUROENDOCRINE FEATURES

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Background Small cell lung cancer (SCLC) is an aggressive neuroendocrine (NE) carcinoma with few treatment options. Although immune checkpoint blockade (ICB) is approved in combination with chemotherapy in extensive stage disease, only a subset of patients experience an improvement in overall survival. Studies suggest that a lack of response to ICB is partially attributable to low expression of MHC-class I. In a recent report, our group found that the lack of MHC-class I can be utilized to enable targeting by NK cells stimulated with an IL-15 cytokine superagonist (N-803). These findings led us to hypothesize that cytokine stimulated memory-like NK cells (M-ceNK) may be effective in targeting SCLC.

Methods M-ceNK are derived from an apheresis product from several healthy donors via culture in the presence of cytokines including N-803, IL-12, and IL-18; resulting M-ceNK were characterized by flow cytometry for expression of NK activating and inhibitory receptors as well as the intracellular expression of cytolytic mediators. Evaluation of the functional killing capacity of M-ceNK was assessed via 6-hour in vitro immune cytotoxicity assays against SCLC cell lines representative of each of the four molecular subtypes (ASCL1, NEUROD1, POU2F3, YAP1).

Results Flow cytometry assays showed that M-ceNK express high levels of activating receptors NKp30, NKp44, NKp46, low levels of inhibitory receptors KLRG1 and TIGIT, and elevated IFN- γ and Granzyme B production compared to healthy donor NK cells. Functional evaluation indicated that all SCLC models are highly susceptible to M-ceNK targeting, particularly at very low effector to target ratios (E:T). M-ceNK demonstrated a median of 69% lysis (range 35–89%) at an E:T ratio of 5:1 across 6 tumor models (DMS79, H69, H446, H1048, DMS114, H841) as compared to 2% lysis (range 0–58%) with NK cells isolated from peripheral blood of healthy donors. Analogously, NE models of prostate cancer (H660) and lung cancer (H720, H727) exhibited high susceptibility to targeting by M-ceNK exhibiting 66%, 42%, and 44% lysis, respectively.

Conclusions These data demonstrate the potential for M-ceNK based approaches for the treatment of NE tumors, including all molecular subtypes of SCLC. In the future, we aim to expand evaluation of the efficacy of M-ceNK to target additional tumor types that are refractory to ICB. Additional studies are ongoing to determine the contribution of low MHC-class I or other tumor ligands to the mechanism of action enabling lysis by M-ceNK in the context of NE tumor models.

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