TARGETING HLA-E POSITIVE CANCERS WITH A NOVEL NKG2A/C SWITCH RECEPTOR

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Background HLA-E is overexpressed by approximately 80% of solid tumors, including malignant glioblastoma and is emerging as a major check point turning of NKG2A+ CD8 T cells and NK cells in the tumor microenvironment and circulation. This axis operates side-by-side with PD-L1 to block both T and NK cells. Blockade of this suppressive pathway unleashes cytotoxic lymphocytes and prevents metastasis. This notion is supported by CRISPR screens in mice, identifying Qa-1 (the mouse orthologue to HLA-E) as a limiting factor for immunotherapy.

Methods We engineered a novel chimeric A/C Switch receptor, combining the strong HLA-E binding affinity NKG2A receptor’s ectodomain with the activating signaling of NKG2C receptor’s endodomain (figure 1A). We transduced NK-92 cells as well as primary NK and T cells with the A/C Switch and tested the efficacy against a battery of cancer cell lines with varying HLA-E densities (figure 1B, 1C). Cell viability, transduction efficiency, functional responses (CD107a, IFN-g, TNF-a) as well as target cell killing in vitro and in vivo were examined.

Results Our results showed that A/C Switch-transduced NK and T cells displayed superior and specific cytotoxic function and killing potential when challenged with tumor cells exhibiting medium to high HLA-E expression (figure 1D). In co-culture experiments with normal cells that are known to express low levels of HLA-E, A/C Switch T cells did not cause target cell death. We also observed that an equilibrium between A/C Switch transduction level and HLA-E expression governs the activity of the modified T cells, creating a therapeutic window to safeguard against on-target off-tumor toxicities. Furthermore, A/C Switch-expressing human T cells demonstrated enhanced anti-tumor function in a xenograft model of glioblastoma (figure 1E, 1F).

Conclusions NKG2A/C-switched cytotoxic cells display powerful and focused activity against tumor cells expressing medium to high levels of HLA-E, while sparing healthy cells. We propose that this novel A/C Switch receptor may operate alone to control tumor cells expressing high levels of HLA-E or in combination with other engineered specificities to overcome the suppressive NKG2A/HLA-E checkpoint.

REFERENCES

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