CO-TARGETING IMMUNE EVASION MECHANISMS TO IMPROVE CAR T-CELL THERAPY IN OSTEOSARCOMA

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Background: Immunotherapy using chimeric antigen receptor (CAR) modified T cells has the potential to improve outcome for children with recurrent or metastatic osteosarcoma. In a phase I trial, autologous HER2-targeted CAR T cells were safe with indicators of clinical benefit in a subset of pediatric patients with advanced HER2-positive sarcomas. However, improving the overall efficacy of CAR T cells to achieve sustained antitumor responses in a substantial proportion of patients requires a deeper insight into the tumor intrinsic resistance mechanisms to cellular therapy. We aim to systematically investigate and identify recurrent patterns of tumor adaptations in response to CAR T-cell therapy to enable strategic co-targeting of alternative surface receptors or upregulated oncogenic pathways to augment the therapeutic efficacy in osteosarcoma.

Materials/Methods: Osteosarcoma cells with variable surface expression of HER2 (U2OS, 143B, LM7 and two patient-derived lines) were treated with HER2-specific CAR T cells, Epha2-specific CAR T cells and IFN-γ in vitro. Surviving osteosarcoma cells were isolated and collected at 72 hours and analyzed for changes in the surface expression of a panel of critical oncogenic receptors and immune ligands using flow cytometry.

Results: In response to CAR T-cell treatment, decrease in the HER2 surface expression was observed in four of five osteosarcoma cell lines evaluated. In contrast, cell surface expression of the immunomodulatory ligand PD-L1 and the growth receptor tyrosine kinase c-MET increased across all cell lines post-treatment. There was no significant change in the expression of other surface receptors, including Epha2, EGFR and IGF-1R.

Conclusions: Osteosarcoma cells exhibit distinct and reproducible patterns of altered surface receptor expression in response to CAR T-cell therapy warranting further assessment of downstream signaling pathway dynamics, to be accomplished using reverse phase protein arrays. Additionally, we are currently evaluating the role of c-MET in tumor immune evasion in response to CAR T-cell therapy. We will subsequently develop further combinatorial approaches with blockade of putative resistance pathways, such as c-MET and its downstream signaling, using small molecules or further T-cell modifications to augment antitumor responses.