359 HYALURONIC ACID NANOGEL BASED CANCER VACCINE, IN COMBINATION WITH ADOPTIVE T CELL THERAPY TOTALLY SUPPRESSES ICI RESISTANT-TUMORS

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Background In this study, we questioned efficacy of combination therapy of newly developed cancer vaccines for tumors refractory to immune checkpoint inhibitors (ICIs) and adoptive therapy of TCR-T cells. We have developed a nano-sized hydrogel particles (nanogels) to create novel nanomaterials for biomedical applications. In particular, HANG; Hyaluronic Acid partially hydrophobized by a chemical modification with cholesteryl groups forms physically cross-linked NanoGel particles with a diameter of 30∼100 nm via self-assembly in water. HANG efficiently forms a stable complex with antigenic polypeptides (HANG-V) through hydrophobic interactions. Two murine tumor models, B16F10 melanoma and CMS5a sarcoma, both of which are known to be refractory to ICI therapy and adoptive T cell therapy of TCR engineered T cells were studied.

Methods The peptides, gp100 or CMS5a neoantigens, in DMSO were added to the HANG aqueous solution and the mixture was incubated for 24 h at room temperature. After 0.22 μm filtration, the antigen peptide concentration was quantified by reverse phase chromatography analysis.

Results HANG-V cancer vaccine (HANG and gp100 long peptides) with TLR agonist were subcutaneously injected to B16F10-bearing C57BL/6 mice on days 7, 11, 15 and subsequently administered with $CD8^+$ T cells obtained from Pmel-1 transgenic mice. B16F10 tumors more than 100 mm^2 became complete regression. This effect persisted for a long period without recurrence, by changing hair color of mice into white. Control non-vaccinated mice were all dead by day 25. The gp100-specific CTLs with effector phenotype and IFN-γ secretion, were observed with high frequency in LNs, spleen, PBMCs and TILs. Two months after last treatment of HANG-V, Ag-specific adoptive T cells were detected in circulating blood, which show effector memory/central memory phenotype. Furthermore, booster vaccination induces explosive expansion of these memory T cells. In similar experimental settings, BALB/c CMS5a tumor were treated with the HANG-V (HANG and mERK2 long peptides) plus TLR agonist with adoptive transfer of T cells from TCR transgenic DUC18, for CMS5a-specific mERK2 neoantigen, resulted in total suppression of tumor growth.

Conclusions HANG cancer vaccine (HANG-V) strongly enhances efficacy of adoptive TCR engineered T cell therapy against ICI refractory tumors leading to total tumor suppression. In addition, HANG-V induces potent and sustainable antigen-specific CTL systemically and intratumorally. Our studies may propose crucial insights for clinical application of HANG-V with adoptive T cell therapy for ICI-resistant and metastatic tumors with poor prognosis.

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