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

Hiroshi Shiku*, Fumiyasu Momose, Takashi Nakai, Kohei Yabuuchi, Toru Katsumata, Tsuyoshi Shimoboji. Mie University Graduate School of Medicine, Tsu, Japan; Asahi Kasei Corporation, Fuji, Japan

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 cholesterol 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 mm² 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.