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Targeted Anticancer Therapies

Tumor retargeting universal chimeric antigen receptor T cell (TRUE-CAR T) therapy in solid tumors

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Objective

The adoptive transfer of chimeric antigen receptor T cells (CAR-T cells) has demonstrated impressive clinical benefits in patients with hematological malignancies, however, no equivalent successes have been observed yet in solid tumors. The unsatisfactory outcome with solid tumors could be partly attributed to the lack of appropriate tumor-specific antigens. Here, we describes a novel strategy of tumor retargeting universal chimeric antigen receptor T cell therapy (TRUE-CAR T).

Methods

EGFRvIII antigenic peptide (EvIII) was conjugated with DSPE-PEG-Mal and was applied to construct fusogenic nanoparticles. Particle size, surface charge and stability of the nanoparticles were characterized. The antigen modification effect of EvIII-NP was evaluated through flow cytometry and confocal microscopy. In vivo anti-tumor effect and safety profile of TRUE-CAR-T were evaluated through tumor growth curve and tumor survival curve in subcutaneous and abdominal dissemination model of gastric cancer.

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Results

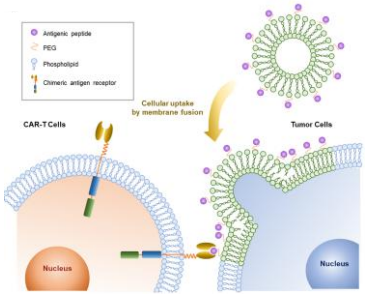

Fig.1 Schematic illustration of action mode of the cooperative target retargeted universal CAR T-cell (TRUE-CAR-T) therapeutic strategy, including: i) antigen peptides modified onto the tumor cell through F-AgNPs mediated membrane fusion; ii) antigen peptides modified on tumor cell membrane were recognized and bound by corresponding CAR-T cells, thus mediating the activation and antitumor effect of CAR-T cell therapy

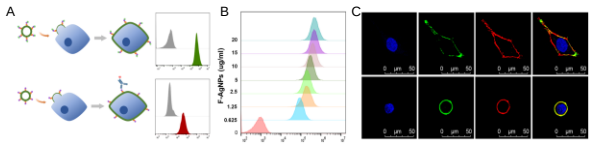

Fig.2 F-AgNPs mediated cell membrane modification. A, Flow cytometry histograms of tumor cells without treatment (grey), incubated with FAM-F-AgNPs (green) and incubated with F-AgNPs then detected by PE-antiEvIII mAb (red). B, Analysis of the dosage-effect relationship of F-AgNPs mediated antigen modification. C, Confocal fluorescent microscopic images of tumor cells MGC803 (upper) and MKN45 (lower) after F-AgNPs treatment. Nucleus: DAPI (blue); antigen peptide: FAM (green); and plasma membrane: DiI (red).

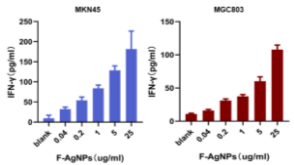

Fig.3 IFN-γ secretion of EvIII CAR-T cells after 24 h incubation with tumor cells (MKN45 and MGC803) treated by F-AgNPs of various concentration.

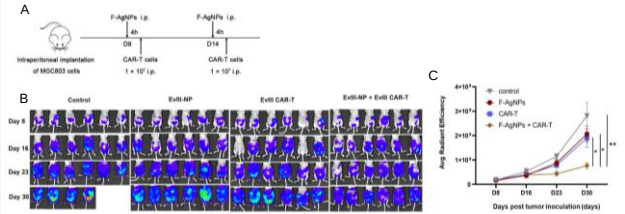

Fig.4 In vivo cooperative antitumor effect of F-AgNPs mediated TRUE-CAR-T cell therapy. A, Schematic illustration of treatment process of peritoneal metastasis tumor model. B and C, Tumor growth profiles (j-l) and survival curve (m) of micetreated with PBS, F-AgNPs, EvIII CAR-T, F-AgNP s+ EvIII CAR-T.

Conclusion

The TRUE-CAR T strategy possesses great clinical application potential with feasibility, universality and safety, providing new perspectives for CAR-T cells therapy in solid tumors.

Acknowledgements

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