RE-DIRECTING CAR-T CELLS AGAINST SOLID TUMORS
USING T-SIGN-MEDIATED ANTIGEN DELIVERY AND TUMOR MICROENVIRONMENT REPROGRAMMING

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Background Chimeric antigen receptor (CAR) T cell therapy has proven highly effective in the treatment of hematologic malignancies, however multiple barriers in the tumor microenvironment (TME) reduce its efficacy against solid tumors. Such barriers include an immunosuppressive TME, poor CAR-T cell trafficking and shortage of highly expressed tumor-specific target antigens. We recently demonstrated that Tumor-Specific Immuno-Gene (T-SIGN) viruses encoding multiple immunostimulatory mediators can reprogram the TME towards a pro-inflammatory phenotype, resulting in a markedly increased therapeutic efficacy of anti-EGFR and anti-HER2 CAR-T cells in an A549 human tumor xenograft and metastasis model. Here we further explored the potential of T-SIGN platform combination with CAR-T cells by developing different T-SIGN viral vectors for the simultaneous tumor-specific expression of CAR-T cell target antigens and immunostimulatory molecules.

Materials and Methods We used in vitro human tumor cell lines to assess the ability of T-SIGN viruses to induce expression of a range of chimeric CAR-T cell target antigens. Using CD19 as a model antigen, we quantified virus-encoded CD19 expression on tumor cell surface using flow cytometry. In vivo, T-SIGN-dependent tumor-specific CD19 expression was assessed by flow cytometry analysis of tumor cell suspensions from A549 subcutaneous lung tumor xenografts in NSG mice.

Results In multiple in vitro human cell culture models, T-SIGN virus infection led to efficient expression of chimeric CD19 antigen on the tumor cell surface that enabled effective antigen-specific tumor cytoxicty by anti-CD19 CAR-T cells. T-SIGN viruses with enhanced activity were also successfully generated by encoding immunostimulatory chemokines and cytokines together with chimeric CD19, enabling simultaneous tumor cell-specific CD19 antigen expression and enhancement of CAR-T recruitment and activity. In vivo, T-SIGN-dependent CD19 expression was demonstrated in intravenously dosed A549 human tumor xenografts, enabling future studies to optimize T-SIGN co-therapy with CAR-T cells directed against antigens otherwise not expressed in the tumor.

Conclusions Together, our data provide a proof of concept that T-SIGN viruses can re-direct CAR-T cells to act against solid tumors by enabling tumor-specific expression of cognate target antigens that are not endogenously expressed by the tumor cells. Further studies are ongoing to explore the full potential of synergistic combination of T-SIGN viruses and T cell therapy against solid tumors.

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