222-L PEMIGATINIB INCREASES THE EFFECTIVENESS OF EPCAM-CAR-T IN SQUAMOUS CELL CARCINOMA

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Background Chimeric antigen receptor (CAR) T-cell therapy has been generally more effective in hematological malignancies than solid tumors. Considering the complex tumor microenvironment that plays a role in regulating lymphocyte responses and promoting tumor growth, the response rates of CAR-T therapies in solid tumors could be improved by combining with other treatment modalities.

Aberrant fibroblast growth factor (FGF) receptor (FGFR) signaling plays a key role in proliferation and survival of malignant epithelial cells. This study examines the use of a FGF inhibitor in combination with CAR-T cells to target squamous cell carcinoma (SCC) cells in the presence of an extracellular matrix (ECM). The ECM in solid tumors can present a challenge for lymphocyte invasion and act as reservoir of FGF that can contribute to tumor survival and proliferation.

Methods Briefly, matrigel (6 mg/mL) was layered (50 µL/well) over A431-red target tumor cells expressing nuclear-localized mKate2 (red fluorescent protein). After 2h, epithelial cell adhesion molecule (EpCAM)-CAR-T cells were seeded over the matrigel layer. Tumor cell growth and CAR-T cytotoxicity were determined from real-time impedance and live cell imaging data collected on xCELLigence Real-Time Cell Analysis (RTCA) eSight. Pemigatinib (1 µM, 5 µM and 10 µM), an inhibitor of FGFR isoforms 1–3 sold under the brand name Pemazyre, was used to evaluate the role of FGFR signaling. Percent cytolysis was calculated from normalized cell impedance and imaging (red fluorescence) data using the formula [(1-(treated/control)*100].

Results A431 cells express EpCAM and the EpCAM-CAR-T cells effectively eliminate these tumor cells in cytotoxicity assays. Surprisingly, the CAR-Ts were ineffective (Effector:Target, E:T = 4:1) in the presence of matrigel. Since FGF signaling can promote the survival and proliferation squamous carcinoma cells, we tested the effect of Pemigatinib, a potent FGFR inhibitor. Pemigatinib reduced the proliferation of A431 cells with increasing concentrations tested. Assessment of CAR-T killing revealed an increase in percent cytolysis from the baseline (~6%) to ~20% in the presence of 5 uM Pemigatinib and ~40% with 10 uM Pemigatinib. Interestingly, complete elimination of A431 cells in invasion assays was achieved with very high E:T=20:1 and 1 uM Pemigatinib.

Conclusions The results suggest that Pemigatinib can be effectively combined with CAR-T therapies for solid tumors with aberrant FGFR signaling.

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