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703.CELLULAR IMMUNOTHERAPIES: BASIC AND TRANSLATIONAL

Development of a Novel Solid Tumor-Bearing Humanized Animal Model for Simultaneously Evaluating the Toxicity and Efficacy of Bispecific T Cell Engager

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The development of novel therapeutics for cancer immunotherapy is tightly restricted by using human samples to estimate the drug toxicity before moving to clinical trials. Currently numerous tumor-bearing animal models have been utilized to test the efficacy of anti-tumor drugs. However, the success rate remains low in the development of clinical treatment. One prominent reason is that the utilized animal models could not accurately predict the toxic response of human immune system to the drugs. Thus, establishing a predictive nonclinical animal platform that can detect potential unwanted toxicity to human patient will be critical for improving the safety of immune drug development. Previously, we have demonstrated a disseminated tumor-bearing humanized mouse model that can evaluate the toxicity and efficacy of bispecific T cell engager (BiTE). Here we aim to develop a novel tumor-bearing mouse model that can simultaneously evaluate the long-term efficacy against solid tumor in addition to cytokine level assessment. In this study, we co-engrafted disseminated and solid tumor cells to the same mice and compared with mice engrafted with disseminated tumor or solid tumor. Three donors were tested.

Method: Human triple negative breast cancer MDA-MB-231/Luciferase-2A-GFP (MDA) cell line is epidermal growth factor receptor (EGFR) positive and is labeled with luciferin. The cells were implanted into PBMC humanized NSG-MHC class I/II double knock out (DKO) mice via orthotopic injection into mammary fat pad (MFP, $5x10^6$ cells/mouse) and/or via intravenous (IV, $1x10^6$/mouse) injection. Disseminated MDA cells normally colonize lung of mice after IV injection. Following EGFRxCD3 BiTE dosing initiation, tumor burden in MFP and lung were evaluated by a in vivo Xenogen imaging system, and solid tumor volume in MFP was measured 2 to 3 times a week by a digital caliper. To evaluate the toxicity levels in response to EGFRxCD3 BiTE treatment, the level of inflammatory cytokine levels in serum of mice were analyzed by BD cytometric bead array. Clinical observations, body weight change, and human immune cell activation were also monitored for drug toxicity assessment.

Results: EGFRxCD3 BiTE treatment induced elevated human inflammatory cytokines in serum from humanized mice implanted with combined MFP and IV tumor. By comparison, the serum cytokine levels were low in mice implanted with MDA cells via MFP alone, suggesting that IV injection of tumor cells is required for cytokine production induced by EGFRxCD3 BiTE. MFP solid tumor continued to grow in the PBS control group and EGFRxCD3 BiTE treatments significantly inhibited solid tumor growth regardless the presence of IV implanted with MDA cells.

Conclusion: Without disseminated tumor, MFP solid tumor-bearing mice served as a model for efficacy but did not produce inflammatory cytokines after treatment with EGFRxCD3 BiTE. Combination of solid and disseminated tumor implantation provides a new tumor inoculation approach that can be used for simultaneously evaluating the toxic cytokine release and long-term efficacy of immunotherapy drugs. This is a promising preclinical platform to define optimal approaches for clinical cancer treatment.

Disclosures No relevant conflicts of interest to declare.

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