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A NOVEL IN VIVO PBMC HUMANIZED MOUSE PLATFORM FOR LONG-TERM ANALYSIS OF EFFICACY AND TOXICITY OF T CELL-BASED IMMUNOTHERAPY DRUGS

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Background Immune cell-based therapies, such as bispecific T cell engagers (BiTE), have been developed for treatment of malignancies. However, the current overall success rate of anti-tumor drugs during clinical development remains low. One prominent reason is that the existing animal models in preclinical studies often do not accurately predict the clinical outcomes. The differences between human and mouse immune systems hamper the development of new cancer therapeutic approaches. Herein, we developed a novel humanized mouse model with solid tumor that can allow long-term evaluation of the effectiveness and risk of unwanted toxicity for bispecific immune drugs.

Methods We utilized two human cancer cell lines in this study: 1) Breast cancer cell MDA-MB-231 (MDA, expressed EGFR); 2) B cell lymphoma Raji (Raji, expressed CD19). To establish the breast tumor model, MDA cells were implanted in NSG-MHC class I/II double knock-out (DKO) mouse via mammary fat pad (MFP) 2 days before humanized mice with human peripheral blood mononuclear cells (PBMCs). The same MDA cells were then intravenously (IV) implanted 3 days before EGFRxCD3 BiTE administration. Similarly, subcutaneous (SC) solid lymphoma model was established and treated with CD19xCD3 BiTE. Following BiTE dosing tumor burden was quantified by a Xenogen imaging system. To evaluate the toxicity levels in response to BiTE therapy, serum inflammatory cytokine levels were analyzed. Clinical observation, mouse clinical score, and body weight change were also monitored for drug toxicity assessment.

Results PBMC-humanized model with solid tumors were successfully established. Either MFP MDA tumor or SC B cell lymphoma could keep growing for more than one month in the mice. Low dose BiTE treatment did suppress tumor cell growth in the mouse lungs but did not inhibited solid tumor growth. Increased dosage significantly inhibited MFP or SC solid tumor growth. The mice with BiTE treatment exhibited elevated serum levels of human inflammatory cytokines. This cytokine production was dose-dependent and was associated with an increase of toxicity.

Conclusions This model provides a growth environment like that of the patients with solid tumor and can be used for both short-term and long-term data analysis of efficacy, toxicity, and dosing requirements of immunotherapy drugs. We emphasize that the solid tumor model using both IV and SC/MFP co-engraftment is a promising preclinical platform for simultaneously evaluating long-term efficacy and predictive safety of any T cell-based immunotherapies to define optimal approaches for clinical treatment.

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