ESTABLISHMENT AND APPLICATION OF A SERIES OF GENETICALLY ENGINEERED MOUSE DERIVED BREAST CANCER HOMOGRAFT MODELS

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Abstracts

Background Breast cancer is a complex disease which is defined by an intrinsic heterogeneity at the histopathological and molecular levels, as well as in response to therapy. It remains the second leading cause of cancer death among women worldwide despite advances in screening, detection and new therapeutic options. Therefore, it is important to establish relevant preclinical models to study new therapeutics and tumor biology. Genetically engineered mouse models (GEMMs) have been developed in order to understand the molecular, biochemical and cellular functions of oncogenes or tumor suppressor genes. However, the application of GEMMs is constrained due to the spontaneous nature of tumor onset and progression and high cost of breeding. Homograft tumor models, which are derived from and retain the histopathological and molecular features of GEMMs, can be used as faithful surrogates of human tumors.

Methods We generated a series of homograft tumor models from GEMMs overexpressing human epidermal growth factor receptor 2 (HER2, also known as ERBB2) or polyomavirus middle T antigen (PyMT) driven by the mouse mammary tumor virus (MMTV) promoter, or Simian Virus 40 T-antigen (SV40 Tag) under the promotion of the rat prostate steroid binding protein (C3(1)), which are commonly used GEMMs in preclinical breast cancer research.1 2 Models were generated by transplanting the mammary tumors into donor animals. Furthermore, we characterized the homograft tumors through histopathological analysis, immunohistochemical analysis, and immune profiling, as well as immunotherapeutic, cytotoxic and targeted therapy.

Results Nine breast cancer homograft models were developed from MMTV-ERBB2, MMTV-PyMT and C3(1)-Tag GEMMs, including six hormone receptor negative and HER2 positive models (mBR9013, mBR9026, mBR9027, mBR9028, mBR9029, mBR9030), one hormone receptor positive and HER2 negative model (mBR6174) and two triple negative models (mBR6004, mBR9014). Immune profiling of six models showed enriched macrophage infiltration in the tumor microenvironment. Immunotherapy treatment with anti-mPD-1 and anti-mCTLA-4 produced tumor growth inhibition (TGI) of 98% and 110%, respectively, in the triple negative model mBR9014, accompanied by tumor regression. HER2 targeted treatment with lapatinib produced robust response with TGI ranging from 48% to 97% in one HER2 negative and two HER2 positive models. Varying response to the cytotoxic treatments was observed among different models, with cisplatin producing robust response of TGI over 80% in all five of the tested models.

Conclusions We have generated and characterized a series of mouse breast cancer homograft models from GEMMs to facilitate both mechanistic investigation and preclinical testing of novel therapeutics.

Ethics Approval Animal experiments were conducted in accordance with animal welfare law, approved by local authorities, and in accordance with the ethical guidelines of Crown-Bio (Taicang).

REFERENCES

DEVELOPMENT OF PATIENT-DERIVED MODELS OF ESOPHAGEAL CANCER FOR GUCY2C-DIRECTED IMMUNOTHERAPEUTIC TESTING

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Background Esophageal cancer is the fifth most common cause of cancer-related death in the world1 with a 5-year survival rate of <20%.2 Current therapies result in high toxicity and low efficacy, with as many as 60% of esophageal cancer patients not responding to therapeutics.3 CAR-T cell therapy is a therapeutic that can selectively and robustly target cancer cells and eliminate bulky metastatic disease. Previous studies have shown preclinical success with CAR-T cell therapy targeting the human colorectal cancer antigen guanylyl cyclase C (GUCY2C).4 5 Interestingly, esophageal cancers arising from premalignant metaplasia resembling intestine (intestinal metaplasia, also known as Barrett’s esophagus) are highly prevalent and ectopically express GUCY2C. Thus, we hypothesize that GUCY2C will serve as an effective CAR-T cell therapy target in many esophageal cancer patients. However, the paucity of intestine-like human esophageal cancer models limits exploration of this hypothesis, necessitating development of suitable esophageal cancer models (figure 1).

Methods To develop esophageal cancer models for GUCY2C immunotherapy testing, esophageal cancer samples were collected at Thomas Jefferson University Hospital by endoscopic biopsy of treatment-naïve patients or by esophagectomy, primarily in patients previously treated with standard neoadjuvant therapy. Patient-derived xenograft (PDX) models were initiated from samples to establish in vivo models for immunotherapy testing. qRT-PCR, immunoblot, and immunofluorescence were performed to test for GUCY2C expression in primary and PDX specimens. Histopathology was performed to confirm retention of primary tumor features.

Results GUCY2C was present in only 2 of 6 esophagectomy samples. Interestingly, those patients with detectable GUCY2C were treatment-naïve, while neoadjuvant-treated patients lacked viable tumor, revealing neoadjuvant therapy as a significant barrier to esophageal cancer model generation. In contrast, of the 3 adenocarcinoma specimens collected by endoscopic biopsy in treatment-naïve patients, 2 express GUCY2C. To date, PDX models have been initiated from 6 total samples and successfully established for 3 samples. This 50% success rate may improve over time as PDX formation is often delayed in many models (>150 days). Importantly, established esophageal adenocarcinoma PDX models were histologically similar to their matched primary tumors and retained GUCY2C expression, integral to their validation as models of GUCY2C immunotherapy testing.
Abstract 739 Figure 1 GUCY2C expression during tumorigenesis in adenocarcinoma of the esophagus

Conclusions Several human esophageal adenocarcinoma models were successfully established, primarily from endoscopic biopsy of treatment-naive patients as neoadjuvant therapy proved to be a significant barrier. These models will be useful to explore GUCY2C-directed CAR-T cell therapies and other novel therapies targeting intestine-like esophageal cancer, prior to testing in early-phase clinical trials.

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Ethics Approval The study was approved by the Thomas Jefferson University Institutional Review Board (#18D.495) and Institutional Animal Care and use Committee (#01529).

REFERENCES


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