Background: Syngeneic tumor models have long been used in cancer research. The recent clinical success of anti-CTLA-4 and anti-PD1 antibodies contributed to increasing the interest around the use of syngeneic models to evaluate cancer immunotherapy. Surprisingly, although they were initially thought to be immunosuppressive, classic anticancer therapies, such as chemotherapy, targeted agents or radiotherapy, can promote antitumor immunity, thus synergizing with cancer immunotherapies. Suitable models in which to evaluate combination therapies are in great demand. Importantly, in the clinic it is still unknown why some patients respond to certain immunotherapies while others do not. We set out to utilize syngeneic models to address these questions.

Material and methods: Syngeneic cell lines models, such as B16, CT26, MC38, 4T1, were used to evaluate the efficacy of anti-PD1, PD-L1, and CTLA-4 antibodies. Tumors were collected and RNASeq was performed to identify biomarkers predictive of response.

Results: Crown has established a large collection of syngeneic models that covers most tumor types. Our models have been extensively profiled in vivo using anti-PD1, anti-PD-L1, and anti-CTLA-4 antibodies, providing necessary information for models selection and dosing for combination therapy. Mostly recently, we have generated detailed expression maps and mutational profiles for our syngeneic models, and we have identified transcripts from alternative gene spliced, and gene fusion using RNASeq. Our analysis indicated that a number of syngeneic models harbor mutations that may sensitize them to combination strategies of targeted agents and immunotherapy.

Using proprietary genetic signature algorithms, we have also identified in our mouse models a set of biomarkers that may be useful to predict response to different type of immunotherapies.

Conclusions: These data will enable researchers to select the appropriate model for combination studies with immunotherapies, based on the expression of specific targets. In addition, biomarkers of response identified using our predilection models can be used in predicting patient response in the clinic.

Methods

Animals and syngeneic models

Immunocompetent mice (such as C57BL6, BALB/c or C5H) were used to generate syngeneic models. Mice were innoculated at right lower flank with 0.1ml suspension of tumor cell in PBS therapeutic.

The treatments for the therapeutic study were started when mean tumor size reached 80-120 mm². Each group contained 6-10 tumor bearing mice.

Endpoints

Tumor volume was calculated using the formula: V(mm³) = (D x d²)/2, where D and d are the long and short diameters of the tumor, respectively. The tumor size was then used to calculate tumor growth inhibition (TGI). Tumors were collected for FACS and RNASeq analysis.

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