AACR Annual meeting 2021

Myeloid-dominated spontaneous tumor models as the tool for the evaluation of immune modulators

1654

Authors: Xianzhi Zhai[1], Yuying Yang[1], Haoxia Zhao[1], Jingjing Jiang[1], Mengyao Zhang[1], Fuyang Wang[1], Xuzhen Tang[1], Qunsheng Ji[1].1 WuXi AppTec, Shanghai, China
Corresponding Author: Qunsheng Ji. Email: ji_qunsheng@wuxiapptec.com

Background

Myeloid cells and their correlation with solid tumor progression have been widely recognized. As researchers are turning their interests to explore myeloid-related tumor models, spontaneous tumor models, which represent a natural development/progression of the tumor under a certain immune microenvironment, would be a valuable tool for such studies. Some traditional targeted drugs have been re-evaluated for their immune effects, for example, CDK inhibitors can trigger anti-tumor immunity beyond its cell cycle regulation.

Method

Animal resource:

APCmin and MMTV-PyMT animals were provided by GemPharmatech.

Model development:

APCmin mice were fed with a long-term high-fat diet to induce multiple intestinal adenomas. MMTV-PyMT can develop multifocal palpable tumors spontaneously 1-2 months. High-fat diet-induced C57BL/6 and congenic FVB were used as the control. The whole blood was collected for blood cell counting to evaluate anemia symptoms in APCmin model; Flow cytometric analysis of blood and tumor was conducted to evaluate the immune microenvironment of each model.

Drug treatment:

NSAID Celecoxib was dosed with 100 mg/kg, PO, QD for APCmin model; Immune modulators including checkpoint inhibitors (mAb CTLA-4: 10 mg/kg, IP, BIW; mAb PD-L1: 10 mg/kg, IP, BIW) and CDK4/6 inhibitor(Palbociclib: 100 mg/kg, PO, QD) were applied to evaluate their efficacy on MMTV-PyMT model.

Results

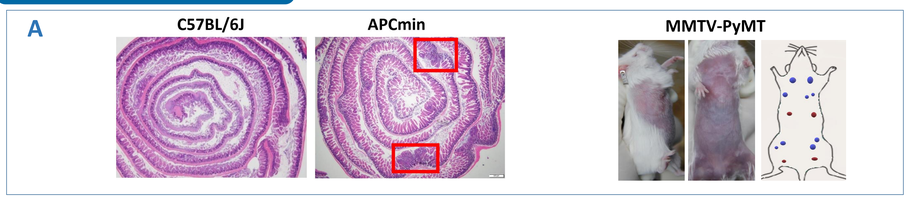

Fig 1 Phenotyping of 2 models compare with their congenic mice

A) H&E staining of small intestinal of APCmin at week 12; spontaneous breast tumors of MMTY-PyMT at week 6; B) blood cell counting analysis of APCmin from week 7 to week 20 as anemia indicator; C) Immune phenotyping of blood in each group (APCmin and C57BL/6; MMTV-PyMT and FVB). Two biological duplication for each measurement point, therefore average is calculated for plotting without SEM.

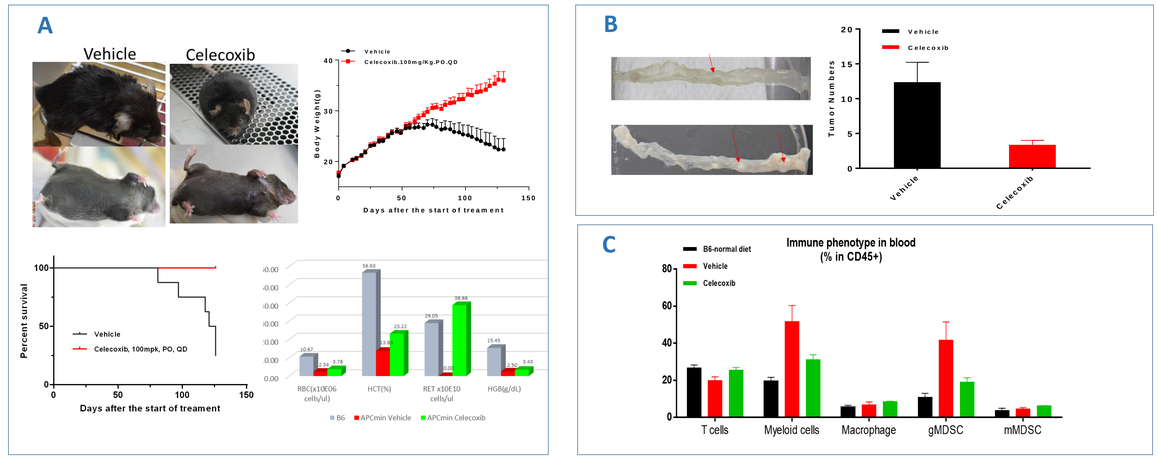

Fig 2 Celecoxib' efficacy study on APCmin model and the influence on the immune microenvironment

A) The basic physiological parameters in each group, including appearance(hair messy), anemia signature (pale skin), bodyweight, survival and blood cell counting. B)Total number of small intestinal adenomas. C) Immune phenotyping of blood in each group.

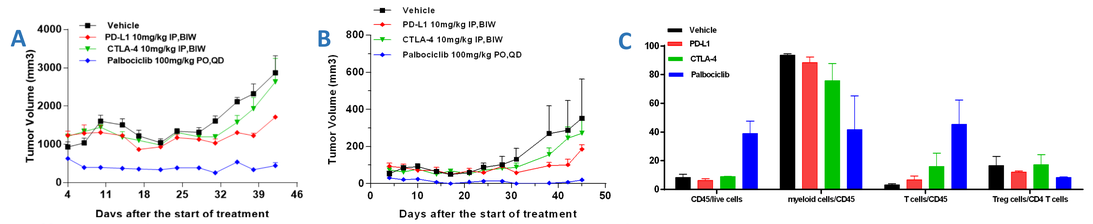

Fig 3 Efficacy study on MMTV-PyMT model and the influence on the immune microenvironment

A) The total tumor growth curve in each group (accumulation of all sites as tumor-volume of each mouse). B) The representative single-point tumor growth curve in each group (same location). C) Immune phenotyping of blood in each group.

Summary

- APCmin and MMTV-PyMT mouse models represented a myeloid-enriched(especially for gMDSCs) and low T cell infiltrated microenvironment compared to the congenic mice.
- Celecoxib reduced adenomas and alleviated the anemia symptoms on the APCmin model. The immune benefit was observed in the Celecoxib group with the reversal of myeloid cell elevation, especially the reversal of gMDSC compared to the vehicle group.
- Palbociclib showed the best curative effect on the MMTV-PyMT model compared to aPD-L1 and aCTLA-4. After Palbociclib treatment, a significant immune benefit was detected with the reversal of myeloid cell elevation and the increase of T lymphocyte infiltration.
- In summary, APCmin and MMTV-PyMT can be used as good tool models for the evaluation of myeloid-related immune modulators

Reference

Je-In Youn and Dmitry I. Gabrilovich. The biology of myeloid-derived suppressor cells: The blessing and the curse of morphological and functional heterogeneity. Eur J Immunol . 2010 November ; 40(11): 2969–2975
Laura Gómez-Cuadrado et al. Mouse models of metastasis: progress and prospects. Disease Models & Mechanisms (2017) 10, 1061-1074