AACR Annual meeting 2023

A tailored platform enables BRAF-targeted drug discovery and precision medicine

Hui Qi, Fuyang Wang, Bingrui Han, Xiaomin Wang, Xiangnan Qiang, Zhixiang Zhang, Qiangyang Gu- Oncology and Immunology Unit (OIU) WuXi AppTec

4988

Introduction

Mutation of BRAF, one of the most frequently mutated serine/threonine kinases, drives tumorigenesis via activating MAPK signaling across various tumor types. Expanded genomic and mechanistic studies over the past two decades have revealed the heterogeneity regarding BRAF mutation status and characterized a classification system for BRAF mutations based on their mode of action. Class I (V600 mutants) and class II (K601 mutants, G469A/V/R) BRAF mutants function as RAS-independent active monomers or dimers to amplify MAPK signaling, whereas class III (G466 mutants, D594 mutants, G469E, etc) mutants, which are kinase impaired or dead, promote MAPK signaling via enhanced RAS binding and subsequent CRAF activation. To date, combination therapies of BRAF and MEK inhibitors have been approved for treatment of patients harboring class I BRAF mutations, while viable therapeutic options for those with class II and III BRAF mutations are still ambiguous. Therefore, developing new drugs and personalized therapeutic strategies directing different classes of BRAF mutations, especially class II and III subtypes, have become vital in the war against BRAF-mutant tumors.

Methods

To enable BRAF-targeted drug discovery and precision medicine, we developed a tailored platform of patient-derived tumor xenograft (PDX) models based on the classification of BRAF mutations, which integrates whole exome sequencing (WES) for identification of mutant BRAF subtypes, with in vivo efficacy evaluation in the PDX models. Our panel covers all three classes of BRAF mutants, including V600E/G469A/G466V/G596R/D594N/G469E. Moreover, this platform faithfully recapitulates the responses of BRAF and MEK inhibitors, reported for treating BRAF-mutant tumors in preclinical and clinical studies, highlighting the potential translational values.

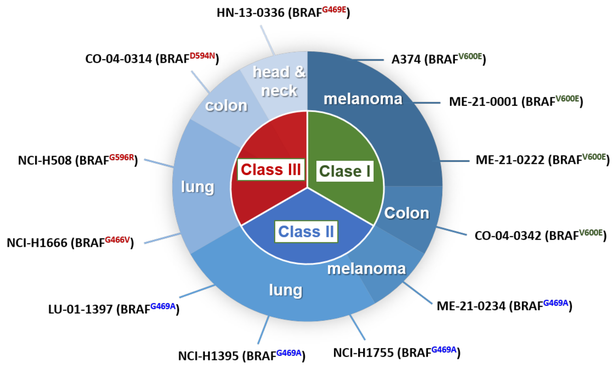

Figure 1 Classification of a panel of BRAF-mutated human cancer cell lines. BRAF mutations were identified by whole exome sequencing (WES).

Results

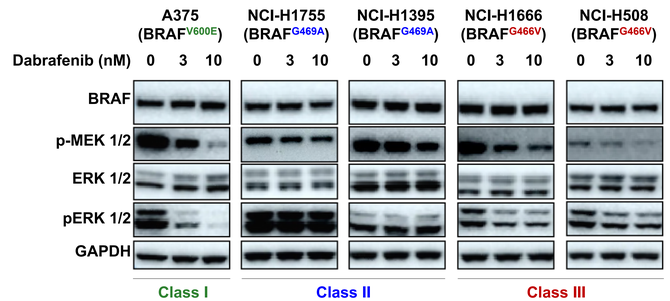

Fig. 2 MEK/ERK signaling in tumors with class I, but not class II and III BRAF mutants, are sensitive to BRAF inhibition. Inhibition of MEK/ERK signaling in a panel of cancer cell lines harboring indicated BRAF mutations exposed to Dabrafenib for 4 h at indicated doses.

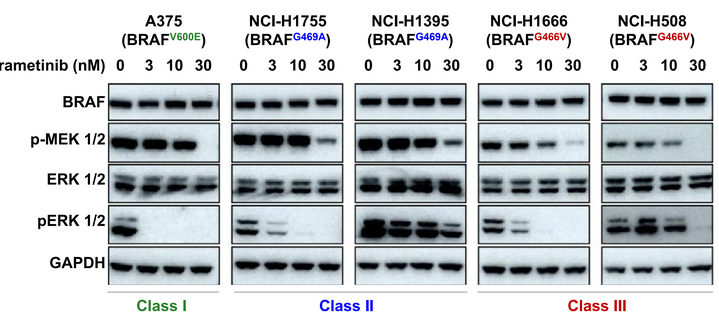

Fig. 3 MEK/ERK signaling in tumors with class II and III BRAF mutants are sensitive to MEK inhibition. Inhibition of MEK/ERK signaling in cell lines in (Fig. 2) exposed to Trametinib for 4 hr at indicated doses.

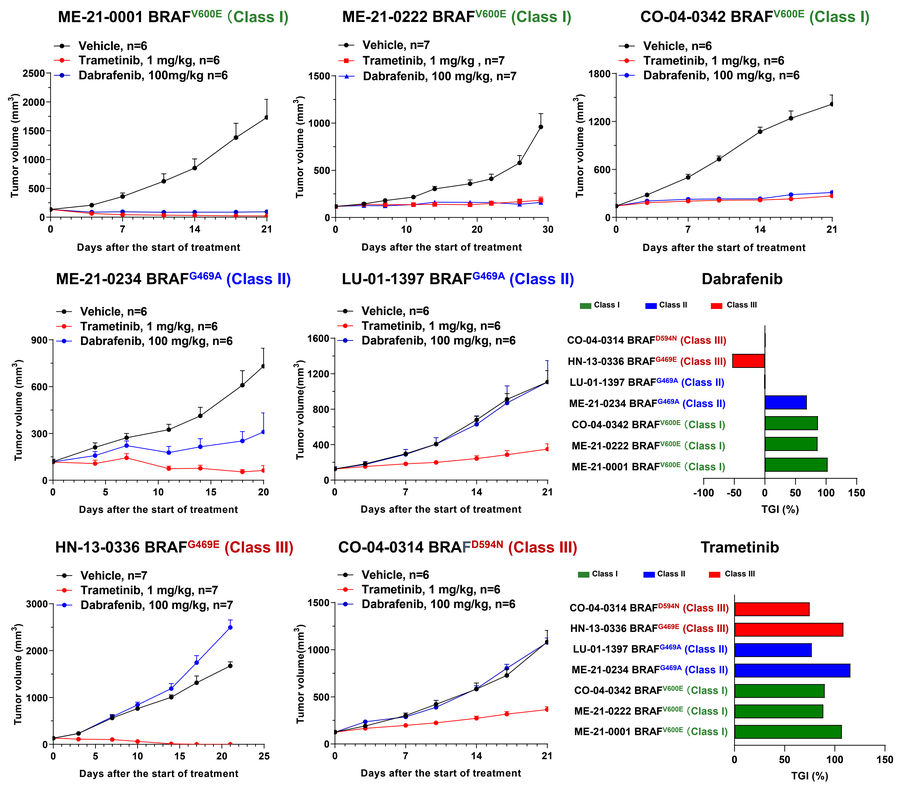

Fig. 4 Responses of a panel of BRAF-mutated PDX models to BRAF and MEK inhibition. PDX models harboring class I BRAF mutation were sensitive to both BRAF and MEK inhibition, while those with class II and III BRAF mutations were only responsive to MEK inhibition. Trametinib (1mg/kg) or Dabrafenib (100 mg/kg) were orally administered once a day.

Summary

- A panel of BRAF-mutated in vitro and in vivo tumor models were identified by whole exome sequencing and classified into 3 types based on their BRAF mutations. These different classes of BRAF mutations dictate cell sensitivity to BRAF and MEK inhibitors.
- Our study provides a tailored platform for discovery and development of novel BRAF inhibitors as well as clinically relevant precision medicine, which help lead to improved treatments for BRAF-mutated cancers, especially those with poor responses to standard clinical therapies.

References

1. Dankner M, Rose A, Rajkumar S, et al. Oncogene, 2018 Jun;37(24):3183-3199.
2. Yao Z, Yaeger R, Rodrik-Outmezguine V, et al. Nature. 2017 August 10; 548(7666): 234–238.
3. Kotani H, Adachi Y, Kitai H, et al. Oncogene, 2018 Mar;37(13):1775-1787.

药明康德 WuXi AppTec
Business contact: Declan Ryan, declan.ryan@wuxiapptec.com
Technical contact: oiu-bd-translation@wuxiapptec.com

Visit Booth #1427 to learn more

ONCO wuxi