A drug repurposing screen identified efficacious topoisomerase 2 (top2) inhibitors against mutant kras-driven colon cancer metastasis

Abstract Submitter: Jit Kong Cheong, Singapore*

Co-Authors: Yilong Zheng, Anya Ramanan, Andrea York Tiang Teo, Dominic Wei Ting Yap, Yang Lv, Gracie Wee Ling Eng

*Department of Biochemistry and NUS Centre for Cancer Research, Yong Loo Lin School of Medicine, National University of Singapore

Abstract

Colorectal cancer (CRC) is the third most common malignancy worldwide. It is projected to increase by 3.2 million new cases and account for 1.6 million deaths by 2040. Mortality is largely due to limited treatment options for patients who present with advanced disease. Oncogenic mutations in KRAS occur in approximately 30-50% of CRC, driving tumor progression and influencing efficacy of both cytotoxic and targeted therapies. Notably, KRAS-mutant and wild-type CRCs differed in the rate of disease progression and the pattern of metastatic involvement. KRAS-mutant CRCs, in particular, progress rapidly into metastatic disease and are associated with a higher cumulative incidence of metastases to lung, bone, and brain, which results in poorer prognosis. While the activating mutations of KRAS in CRC appear to dictate its metastatic potential as well as affinity for specific organs/tissues for tumor dissemination, the molecular mechanism(s) driving these defining features of metastatic CRC (mCRC) remains largely elusive.

We established an in vitro, three-dimensional HCT116 colon tumoroid model and showed that CRISPR-mediated knockout of the mutant KRAS (G13D) allele in HCT116 colon cancer cells upregulates cell adhesion molecules and dramatically reduces the abundance of non-tumoroid forming cells. Using the parental HCT116 colon tumoroids, we conducted a high throughput phenotypic screen with a unique collection of 978 FDA-approved drugs to identify compounds that specifically eliminates non-tumoroid forming HCT116 colon cancer cells. We demonstrate that topoisomerase 2 (TOP2) inhibitors are enriched in our drug screen and validated their anti-cell migration and invasion properties using orthogonal approaches, such as wound healing and extracellular matrix (ECM) transwell assays. Although TOP2 inhibitors have been shown to be efficacious against colorectal cancer and other solid tumors, their impact and mechanism-of-action on mCRC remains largely unknown. Our ongoing studies seek to elucidate their mechanism-of-action(s) on mutant KRAS-driven colon cancer cell migration and invasion.

Do you have any conflicts of interest?

No, I do not have a conflict of interest.