Cabozantinib overcomes ABCG2-mediated drug resistance in cancer

By
Prof. Zhe-Sheng (Jason) Chen
Professor
College of Pharmacy and Health Sciences, St. John’s University

Date: 10 July 2021 (Saturday)
Time: 9:30am (Hong Kong Time)
Zoom link: https://zoom.us/j/95824264674?pwd=MHIQUWdBZVZVJveTRsVkpONT1lZz09
(Meeting ID: 958 2426 4674 and Password: 65gEU9)

Abstract
Cabozantinib (CBZ, XL184) is a small molecule tyrosine kinase receptor inhibitor, which targets c-Met and VEGFR2. CBZ has been approved by the Food and Drug Administration to treat advanced medullary thyroid cancer and renal cell carcinoma. We evaluated the ability of CBZ to modulate the function of the ATP-binding cassette subfamily G member 2 (ABCG2) by sensitizing cells that are resistant to ABCG2 substrate antineoplastic drugs. We used a drug-selected resistant cell line H460/MX20 and three ABCG2 stable transfected cell lines ABCG2-482-R2, ABCG2-482-G2, and ABCG2-482-T7, which overexpress ABCG2. CBZ, at non-toxic concentrations, sensitized the ABCG2-overexpressing cells to mitoxantrone, SN-38, and topotecan. Our results indicate that CBZ reverses ABCG2-mediated multidrug resistance by antagonizing the drug efflux function of the ABCG2 transporter. The molecular docking analysis indicates that CBZ binds to the drug-binding site of the ABCG2 transporter. Recently, a new topotecan (TPT) selected non-small cell lung cancer (NSCLC)-resistant cell model NCI-H460/TPT10 with ABCG2 overexpression and its parental NCI-H460 cells were utilized to investigate the role of CBZ in drug resistance. The in vitro study also showed that CBZ, at a non-toxic concentration, could re-sensitize NCI-H460/TPT10 cells to TPT by restoring intracellular TPT accumulation via inhibiting ABCG2 function. In addition, the increased cytotoxicity by co-administration of CBZ and TPT may be contributed by the synergistic effect on downregulating ABCG2 expression in NCI-H460/TPT10 cells. To further verify the applicability of the NCI-H460/TPT10 cell line to test multidrug resistance (MDR) reversal agents in vivo and to evaluate the in vivo efficacy of CBZ on reversing TPT resistance, a tumor xenograft mouse model was established by implanting NCI-H460 and NCI-H460/TPT10 into nude mice. The NCI-H460/TPT10 xenograft tumors treated with the combination of TPT and CBZ dramatically reduced in size compared to tumors treated with TPT or CBZ alone. The TPT-resistant phenotype of NCI-H460/TPT10 cell line and the reversal capability of CBZ in NCI-H460/TPT10 cells could be extended from in vitro cell model to in vivo xenograft model.

Overall, our findings demonstrate that CBZ inhibits the ABCG2 transporter function and consequently enhances the effect of the antineoplastic agents that are substrates of ABCG2. CBZ may be a useful agent in anticancer treatment regimens for patients who are resistant to ABCG2 substrate drugs. In addition, the established NCI-H460/TPT10 xenograft model could be a sound clinically relevant resource for future drug screening to eradicate ABCG2-mediated MDR in NSCLC.

Biography
Professor Chen is the Director of the Institute for Biotechnology and a Special Advisor to the Provost for international students at St. John’s University. After obtaining his MD degree (Guangdong Pharmaceutical College) and BS degree in Toxicology (Sun Yat-Sen University), he had worked at CDC of Guangdong Province. He received his Ph. D degree from Kagoshima University in Japan. He conducted his postdoctoral training at Fox Chase Cancer Center. In 2004, he joined the College of Pharmacy at St. John’s University and was promoted to full Professor in 2010. He is an expert in the field of multi-drug resistance (MDR) following chemotherapy, with the goal of his lab being the development of more effective anticancer drugs. His research interests range from basic to clinical studies on drug resistance in cancers. Dr. Chen is an editor-in-chief of Recent Patents on Anticancer Drug Discovery (RPADD) and another two journals; an associate editor of several journals such as Frontiers in Oncology. He is also an editorial board member of 27 journals including Cancer Letters and a reviewer of more than 200 peer reviewed journals including Nature, and Nature Communications. His lab has been supported by USA NIH as well as pharmaceutical and biotech companies.

ALL ARE WELCOME

Enquiries: Dr Wei Zhao (wzhao42@cityu.edu.hk)