ABSTRACT

Charles University, Faculty of Pharmacy in Hradec Králové	
Training Workplace	Department of Pharmacology and Toxicology
Doctoral Degree Program	Pharmacology and Toxicology
Candidate	Yu Zhang
Supervisor	Assoc. Prof. RNDr. Jakub Hofman, Ph.D.
Advisor	
Title of Doctoral Thesis	Study of pharmacokinetic and pharmacodynamic mechanisms of drug resistance and their modulation in non-small cell lung cancer

Lung cancer represents one of the most threatening malignancies, which is attributed by its leading morbidity and mortality among all cancer types. Pharmacological interventions have played impressive roles in the clinical management of non-small cell lung cancer (NSCLC) with the outstanding improvements on patients' survival. Nevertheless, the inevitable emergence of drug resistance severely diminishes their efficacies.

Traditional chemotherapeutic drugs have been introduced in the treatment of NSCLC decades ago. Countless studies showed that the emergence of multidrug resistance (MDR) is deeply associated with two pharmacokinetic factors: (1) increased drug efflux via ATP-binding cassette (ABC) transporters and (2) enhanced drug deactivation by biotransformation enzymes, e.g., cytochromes P450 (CYPs). Previously, we and others have demonstrated that several novel targeted agents can synergistically modulate pharmacokinetic MDR by their interactions with ABC transporters/CYPs and their own anti-cancer activity. Thus, in the first part of our work, we characterized whether selected novel drugs used/intended for the NSCLC therapy could work as such dual-activity chemosensitizers. Four (tepotinib, sonidegib, talazoparib and encorafenib) out of seven tested drugs have gotten confirmed their MDR-modulating roles using in vitro, in silico as well as ex vivo models derived from NSCLC patients' tumor biopsies.

Epidermal growth factor receptor-tyrosine kinase inhibitors (EGFR-TKis) have revolutionized the pharmacotherapy of NSCLC. Numerous studies have described the mechanisms of drug resistance to EGFR-TKi therapy. However, their results are highly fragmented and lack the evaluation of their potential translation into effective resistance-combatting strategies. Thus, in the second part of this thesis, we aimed to provide a comprehensive view on this issue. Drug-resistant cell lines were established by at least 10 month-lasting stepwise selection with the first/second/third-generation EGFR-TKis (gefitinib, dacomitinib, osimertinib, respectively). Using various methodologies, including global proteomic analysis, we reported that (1) EGFR-TKi-resistant cell lines exhibit higher invasive levels than the corresponding EGFR-TKi-sensitive variants, (2) cross-resistance is the intrinsic feature of EGFR-TKis, (3) extracellular matrix (ECM)-related signaling, cancer stem cells (CSC)-related pathways, anti-apoptotic protein BCL-2 and efflux transporter ABCG2 universally participates in the development of EGFR-TKi resistance, (4) these signaling pathways/proteins could be the potential targets for synergistic reversal of EGFR-TKi resistance and (5) Hedgehog pathway as well as ECM-related signaling might be important for the lung carcinogenesis.

In conclusion, we have conducted a complex investigation on drug resistance and its modulation within NSCLC. We have provided important findings that might be eventually translated into the effective and safe drug combination regimens beneficial for NSCLC patients suffering from drug-resistant tumors.