Project title: A Groundbreaking Research Project aiming to Improve Cancer Diagnosis, Treatment, and Survival in Taiwan by National Cheng Kung University Hospital Program title: Improving survivals and quality of life of lung cancer patients via development of salivary diagnostics, anti-IL-6 nanodrugs and cost-effectiveness analyses in Taiwan

The Role of Exosome in Mediating Tumor Angiogenesis and Sensitivity to Targeted Therapy in NSCLC

Wei-Lun Huang[1], Chien-Chung Lin, Wu-Chou Su
黃偉倫，林建中，蘇五洲

Department of Internal Medicine, National Cheng Kung University Hospital, College of Medicine, National Cheng Kung University, Tainan, Taiwan.

Current research suggests that tumor-related extracellular vesicles play a significant role in paracrine signaling pathways, thus potentially influencing cancer progression via multiple mechanisms. EVs have also emerged as an important role in angiogenesis and cardiovascular homeostasis. And transferring EV's in the local tumour microenvironment contribute tumor progression and chemotherapy resistance. In our previous study, we successfully detected EGFR mutation DNA from saliva using Electric field–induced release and measurement (EFIRM) platform and we also demonstrated that most of the fragmented DNAs in saliva come from exosome. We hypothesized that tumor derived EV play a significant role in paracrine signaling pathways contributing the formation of malignant pleural effusion and drug sensitivity to EGFR-TKI in heterogeneous NSCLC. Our previous study highlighted that IL6-Stat3-VEGF pathway contributed progression of lung adenocarcinoma and formation of malignant pleural effusion. In current study, we found IL-6 and VEGF were enriched in exosomes derived from lung cancer cell and malignant pleural effusion. We further verified that cancer derived exosomes contribute to the formation of MPE by modulating vascular permeability using miles assay. We further extended the study to investigate the role of exosome in mediating EGFR-TKI sensitivity of lung cancer cell. We first verified PC9-derived EV could be uptake by EGFR wild type cell and EGFR mutant DNA and protein can be detected in recipient cell. We also found PC9-derived EV enhance sensitivity of gefitinib in EGFR wild type cell. And when we co-cultured EGFR wild type cell with PC9 cell, the sensitivity of gefitinib in EGFR wild type cell increase. However, when we added inhibitor of exosome secretion in co-culture system, the sensitivity was reversed. Our data showed cancer cell may induce angiogenesis via transferring the cytokine and growth factor in EV and we also found exosome from EGFR mutant cell can sensitize EGFR wild type cell which implied the diverse sensitivity in heterogeneous NSCLC. In the future, we will further identify the content of EV including miRNA, RNA, and protein which may contribute EGFR-TKI sensitivity. We plan to identify the potential biomarker in blood that can be used to predict response to EGFR-TKI. And we also plan to find the target that can be used to overcome EGFR-TKI sensitivity in heterogeneous NSCLC.