克服肺癌標靶治療的抗藥性

Overcoming drug resistance in targeted therapy of lung cancer

李日翔

台大醫院腫瘤醫學部

Lung cancers in Asia are characterized by frequent mutations in the oncogenic drivers, such as the epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK). Pre-clinical studies demonstrated that mutations of the oncogenic drivers trigger the development of lung tumors in vitro and in vivo. Inhibiting the activities of these driver mutation attenuate growth of lung tumors in vitro, in vivo, and clinically. Inhibitors for EGFR and ALK are among the standard therapies for advanced lung cancers harboring EGFR mutation or EML4-ALK translocation, respectively. Despite the success of these inhibitors, resistance to these inhibitors emerges in patients after months to years of treatment.

The EGFR T790M mutation accounts for about half of resistance to EGFR inhibitors. Several EGFR T790M specific inhibitors are under clinical development, and the results of some early phase clinical trials for these EGFR T790M specific inhibitors are encouraging. For EML4-ALK fusion lung adenocarcinoma under ALK inhibitor crizoitnib therapy, a second mutation on the ALK results in the resistance to crizotinib. Next generation ALK inhibitors induce promising clinical activities to overcome the resistance to crizotinib in these patients.