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Commentary

Losmapimod: A Novel Clinical Drug to Overcome Gefitinib-Resistance

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Lung cancer is the leading cause of cancer-related death for men and women in the world (Parkin et al., 2005), and epidermal growth factor receptor (EGFR) activation pathway has been implicated in tumorigenesis in non-small cell lung cancer (NSCLC), the most common type of lung cancer (85% of lung cancer cases) (Lynch et al., 2004; Paez et al., 2004). The discovery of EGFR-tyrosine kinase inhibitors (EGFR-TKIs), such as gefitinib and erlotinib, have led to the new era for clinical treatment on NSCLC patients who mostly harbors EGFR-active mutations including an in-frame deletion in exon 19 and the L858R point mutation in exon 21, which comprises more than 90% of EGFR-activating mutations (Lynch et al., 2004; Paez et al., 2004). However, it has been shown by many reports that patients are eventually developed drug-resistance caused by such as the secondary mutation (T790M) in the exon 20 of the EGFR gene (Kobayashi et al., 2005), activation of downstream signaling pathways (HGF-MET, loss of PTEN *etc.*) (Engelman et al., 2007). Until now, successful strategies by employing clinical agent to overcome these acquired resistance to EGFR-TKI have not been exploited.

On the other hand, recent reports have suggested that genomic instability, involving a tetraploidization leading to the cell survival, would be the cause of cancer cell growth (Hanahan and Weinberg, 2011; Vitale et al., 2007). Also it has been suggested that tetraploid cells are associated with multidrug resistance, leading to poor prognosis (Bakhoum and Compton, 2012; Lee et al., 2011). These resultant tetraploid cells can undergo asymmetric cell division or chromosome loss, leading to tumor heterogeneity (Zhang et al., 2014). Therefore, investigation for the identification of signaling pathway involved in tetraploidization might be an important approach to overcome EGFR-TKI drug resistance.

In this issue of *EBioMedicine*, Yeung et al. reported the evidence showing by immunohistochemistry and western blotting analysis that gefitinib activated p38 MAPK, one of the mitogen activated protein kinase (MAPK) superfamily, along with its downstream signaling YAP-MKK3/6-p38 MAPK-STAT3 pathway, and they also found that gefitinib could induce tetraploidization as demonstrated by flow cytometry for cell cycle analysis in the gefitinb-resistant NSCLC cells (Yeung et al., 2018). Most importantly, Yeung et al. have found novel evidence showing that losmapimod, a selective inhibitor of p38 MAPK, strongly suppressed gefitinib-induced tetraploidization associated with cancer cell growth. Further, knockdown of p38 MAPK by employing shRNA prevented tetraploidation and successfully inhibited geftinib-resistant lung cancer cell growth. *In vivo* study using an in-house generated gefitinib-resistant PDX mouse model showed that losmapimod effectively reduced gefitinib-resistant NSCLC PDX tumor volume and weight, thereby, confirming their argument that YAP-MKK3/6-p38 MAPK signaling is essential for the induction of tetraploidization that leads to gefitinib-resistance. Based on their novel findings, clinical use of losmapimod targeting p38 MAPK signaling through YAP-MKK3/6-p38 MAPK pathway might be a promising approach to overcome gefitinib-resistance in NSCLC patients. Further analysis by using specific inhibitors to validate these signaling mechanisms will be required in future studies.

Conflict of Interest

The author (YN) has no conflict of interest to declare.

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