Hepatocyte growth factor induces gefitinib resistance of lung adenocarcinoma with epidermal growth factor receptor-activating mutations.

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Lung cancer with epidermal growth factor receptor (EGFR)-activating mutations responds favorably to the EGFR tyrosine kinase inhibitors gefitinib and erlotinib. However, 25% to 30% of patients with EGFR-activating mutations show intrinsic resistance, and the responders invariably acquire resistance to gefitinib. Here, we showed that hepatocyte growth factor (HGF), a ligand of MET oncoprotein, induces gefitinib resistance of lung adenocarcinoma cells with EGFR-activating mutations by restoring the phosphatidylinositol 3-kinase/Akt signaling pathway via phosphorylation of MET, but not EGFR or ErbB3. Strong immunoreactivity for HGF in cancer cells was detected in lung adenocarcinoma patients harboring EGFR-activating mutations, but no T790M mutation or MET amplification, who showed intrinsic or acquired resistance to gefitinib. The findings indicate that HGF-mediated MET activation is a novel mechanism of gefitinib resistance in lung adenocarcinoma with EGFR-activating mutations. Therefore, inhibition of HGF-MET signaling may be a considerable strategy for more successful treatment with gefitinib.

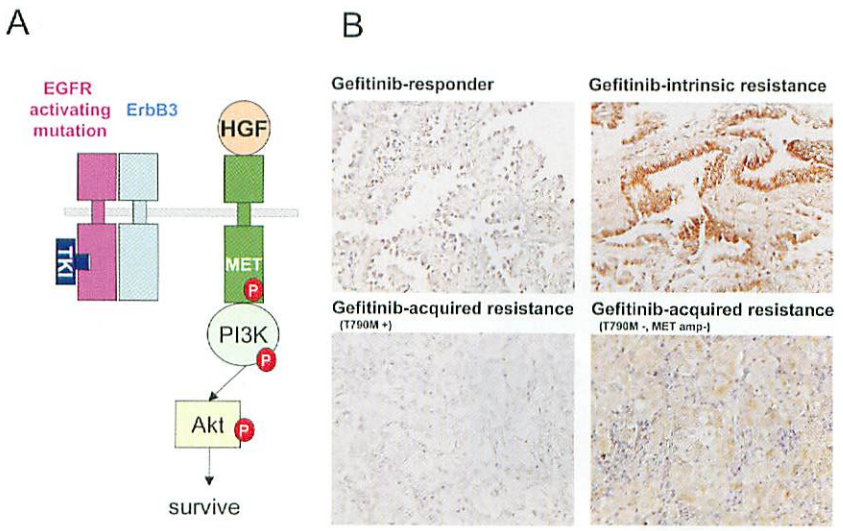

Figure A Signal transduction pathway of HGF-induced gefitinib resistance. HGF restores the phosphatidylinositol 3-kinase/Akt signaling pathway via phosphorylation of MET, but not EGFR or ErbB3. **B HGF expression in tumors from lung cancer patients.** Strong immunoreactivity for HGF in cancer cells was detected in lung adenocarcinoma patients harboring EGFR-activating mutations, but no T790M mutation or MET amplification, who showed intrinsic or acquired resistance to gefitinib.