THE IMPLICATIONS OF EPITHELIAL TO MESENCHYMAL TRANSITION AND NEUROENDOCRINE DIFFERENTIATION IN ACQUIRED RESISTANCE TO EGFR-TYROSINE KINASE INHIBITORS

Jin-Haeng Chung[1],Jin Kyung Rho[2], Xianhua Xu[1],Jong Seok Lee[3],Ho Il Yoon[3],Choon Taek Lee[3],Yun Jung Choi[2],Hye-Ryoun Kim[2],Cheol Hyeon Kim[2],Jae Cheol Lee[2]

[1]Departments of Pathology, [3]Internal Medicine, Seoul National University College of Medicine, Seoul National University Bundang Hospital

[2]Department of Internal Medicine, Korea Cancer Center Hospital

Background: Epithelial-to-mesenchymal transition (EMT), which was related with an acquired resistance to gefitinib, was found in the A549 lung cancer cell line. However, the clinical feasibility of this finding is still questionable because A549 cells also have K-ras mutation, and this mutation suggests a poor response to EGFR-tyrosine kinase inhibitors (EGFR-TKIs).

Design and Results: We found that EMT and neuroendocirne (NE) differentiation simultaneously developed in a lung cancer patient who had an acquired resistance to erlotinib. There were no known resistant mechanisms such as secondary T790M mutation according to the Scorpion test and the MET amplification that was done by performing fluorescence in situ hybridization (FISH), although the deletion mutation on exon 19 that was initially present in the patient's lung cancer was persistently detected by direct sequencing. We investigated the implications of these findings in the context of resistance to EGFR-TKIs with using the previously described A549 subline that has resistance to gefitinib and a newly generated HCC827 subline that has resistance to CL-387,785, an irreversible EGFR-TKI. The morphological and molecular maker changes compatible with EMT and NE differentiation were also found in both resistant cell lines by performing Western blotting and immunocytochemistry. The NE differentiation induced by treatment with cAMP and IBMX did not affect the sensitivity to gefitinib, while the EMT induced by TGF-β was related with a poor response to gefitinib and an increased capability for invasion and migration in both the A549 and HCC827 cells.

Conclusions: EMT should be considered as one of possible mechanisms for the acquired resistance to EGFR-TKIs in lung cancer cells.