Novel mechanisms of acquired resistance to EGFR-TKI in lung cancer

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Although epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs), were remarkably effective in patients with lung cancer, the patients eventually have acquired resistance to EGFR-TKIs within several years. To explore novel molecular mechanisms for the resistance, we previously established the gefitinib-resistant PC9M2 cells that were spontaneously derived from gefitinib-sensitive PC9 cells under the condition of low dose treatment of gefitinib. We found that expression of Wnt/β-catenin pathway-related molecules were up-regulated in PC9M2 cells compared with those of PC9 cells by analyzing time-course gene expression profiles using DNA microarray. We found that phosphorylation of GSK3 and the accumulation of β-catenin were increased in PC9M2 cells. We demonstrated that both the downregulation of β-catenin and treatment with an inhibitor for β-catenin partially restored the sensitivity to gefitinib in PC9M2 cells. Furthermore, we found that the accumulation of β-catenin in cytoplasm was promoted in xenograft tumors derived from PC9M2 cells compared with PC9 cell-derived tumors in which β-catenin was mainly localized at the plasma membrane. Targeting Wnt/β-catenin pathway may be useful for overcoming the acquired resistance to gefitinib.

EDUCATIONS AND POSITIONS

2004-2009	Nara Institute of Science and Technology, Japan, Ph.D.
2009-2010	Postdoctoral Fellow, Nara Institute of Science and Technology, Japan
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