The anti-tumor effects of resveratrol on NSCLC with resistance to gefitinib through VEGF suppression

부천성모병원 내과

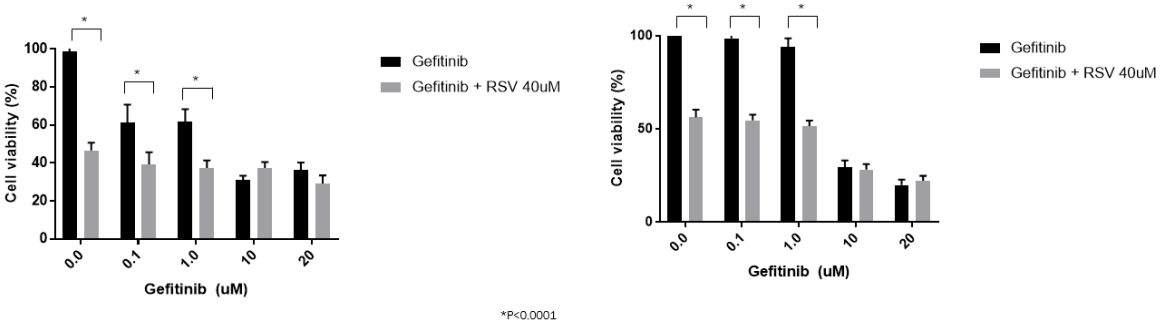
이정화, 강혜선, 이응구, 유지원, 김용현, 권순석

Background/Aims: The efficacy of Epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitors is significantly limited by various resistance mechanisms to those drugs. Vascular endothelial growth factor (VEGF) and EGFR inhibitors have become key therapies in lung cancer. Resveratrol (RSV, 3, 5, 4-trihydroxystilbene), a naturally polyphenolic phytoalexin has anti-inflammatory, anti-carcinogenic and angiogenesis regulating properties. The purpose of this study was to investigate the effect of RSV in gefitinib resistant PC9 (PC9/G) cell lines and establish if VEGF signaling may be a potential target.

Methods: Two cell lines, PC9 and PC9/G, were selected for this study. Cells were exposed to 0.1, 1.0, 10, 20 uM gefitinib (Gef) and/or 40 uM RSV. Cell viability was measured by MTT assay. The expression levels of target genes were examined with ELISA and western blot assay according to gefitinib and RSV treatment.

Results: To assess whether RSV could sensitize PC9/G cells to Gef. We evaluated the effects combination treatment of Gef and RSV on the proliferation of PC9/G cells. Compared with Gef teatment alone, Gef + RSV treatment was more potent growth inhibitory effects. Cell migration was more inhibited by Gef+RSV treatment than Gef alone. Western blot analysis showed that RSV repressed the expressions of VEGFR and multiple downstream protein kinases such as Akt, mTOR, and p70S6K. Survivin and cleaved PARP, apoptotic proteins, were enhanced after RSV + Gef treatment in PC9/G cells.

Conclusions: Our findings suggested that RSV combined with Gef had additional anti-tumor effects in PC-9/GR cells. Apoptotic effects was mediated by multiple mechanism involving suppression of VEGF expression via inhibition of PI3K/Akt/mTOR pathway.



*P<0.0001