Abstract

Role of tyrosine kinase-independent phosphorylation of EGFR with activating mutation in cisplatin-treated lung cancer cells

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Epidermal growth factor receptor (EGFR) mutation is one of the hallmarks of cancer progression and resistance to anticancer therapies, particularly non-small cell lung carcinomas (NSCLCs). In contrast to the canonical EGFR activation in which tyrosine residues are engaged, we have demonstrated that the non-canonical pathway is triggered by phosphorylation of serine and threonine residues through p38 and ERK MAPKs, respectively. The purpose of this study is to investigate the role of non-canonical EGFR pathway in resistance mechanism against cisplatin treatment. Wild type and mutated (exon 19 deletion) EGFR-expressing cells responded similarly to cisplatin by showing MAPK-mediated EGFR phosphorylation. It is interesting that internalization mechanism of EGFR was switched from tyrosine kinasedependent to p38-dependent fashions, which is involved in a survival pathway that counteracts cisplatin treatment. We therefore introduce a potential combinatorial therapy composed of p38 inhibition and cisplatin to block the activation of EGFR, therefore inducing cancer cell death and apoptosis.