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# TARGETING PROTEIN PHOSPHATASE METHYLESTERASE 1 TO INDUCE APOPTOSIS IN NSCLC CELLS THROUGH ITS UBIQUITYLATION AND PROTEASOMAL DEGRADATION

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**Protein phosphatase methylesterase 1 (PPME1) negatively regulates protein phosphatase 2A (PP2A) by demethylating its catalytic subunit. In our previous study, we found afatinib has antitumor activity in certain NSCLC cell lines by regulating Elk-1/CIP2A/PP2A/Akt pathway. Here, we found nintedanib, an inhibitor of angiokinase, can enhance the antitumor activity of afatinib by suppressing PPME1 expression. The detail mechanism of the synergistic effects is unclear. Therefore, we aim to characterize the mechanism for the antitumor effects related to PPME-1 inhibition. Four EGFR wild-type non-small cell lung cancer (NSCLC) cell lines were used *in vitro* to test the cytotoxicity of the combination treatment. The PPME1 expressions in NSCLC cells were significantly down-regulated by combined treatment. Flow cytometry, western blot, and caspase activity ELISA assay were used to detect the anti-tumor effects. PP2A activity assay, siRNA strategy, QPCR, and Co-IP assays were performed to determine the mechanism of combination efficacy. Furthermore, *in vivo* efficacy of combination treatment against xenografts tumors in nude mice were performed. The regulation of PPME1 was studied to analysis the levels of PPME1, demethylated PP2A, and ERK phosphorylation in IHC samples from NSCLC patients. Higher levels of PPME1 and demethylated PP2A were associated with poor survival in patients with NSCLC. Combination treatment increased the anti-tumor efficacy through PPME1 inhibition in a dose and time-dependent manner. Combination treatment showed synergistic apoptotic effect by enhancing PP2A activity and reducing phospho-ERK. Attenuated PPME1 accelerates antitumor activity that involved the ubiquitin-proteasome degradation process. Our results provide *in vitro* and *in vivo* evidences for the therapeutic potential of afatinib and nintedanib combination in EGFR wild type NSCLC treatment. Our findings disclose the therapeutic mechanism and suggest developing PPME1 inhibitor as a novel anti-cancer strategy.**

## Biography

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