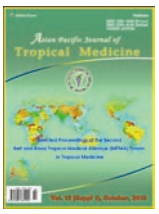

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A new double MEK/PDK1 inhibitor 9za retards cell cycle progression at G_0/G_1 phase and induces mitochondrial apoptosis in non-small cell lung cancer cells

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Objective: To identify the molecule mechanism of potential cytotoxicity and proapoptosis of 9za in non-small cell lung cancer (NSCLC) cells.

Methods: MTT assay, cell cycle detection kit, JC-1 staining assay were adopted to detect the cell viability, the cell cycle distribution and the mitochondrial membrane potential, respectively. Cell apoptosis was measured by Annexin V-FITC/propidium iodide apoptosis detection and the morphology was observed under a light microscope and the colorimetric TUNEL assay. Western blot was used to monitor the cell cycle-, apoptosis-related proteins and some proteins involved in the pathways.

Results: MTT assay showed that 9za significantly weakened the viability of NSCLC cells. Cell cycle analysis demonstrated that the low concentrations of 9za arrested the cell cycle at G_0/G_1 phase, which was further confirmed by the down-regulated levels of Cyclin D1, cyclin-dependent kinase 4 and cyclin-dependent kinase 6. In addition, Annexin V-FITC/propidium iodide apoptosis analysis, morphological observations and TUNEL assays revealed that the high concentrations of 9za could induce cell apoptosis. Furthermore, the JC-1 staining assay indicated that the mitochondrial membrane potential was reduced after 9za treatment. Western blot also manifested that 9za dramatically decreased the protein levels of the total Bcl-2, Cytochrome C in the mitochondria and BCL2 associated X in the cytoplasm. However, the levels of BCL2 associated X in the mitochondria, Cytochrome C in the cytoplasm, cleaved caspase-9, cleaved caspase-3 and the ratio of cleaved-PARP1/PARP1 showed the opposite trends. Moreover, the dose-dependently decreased phosphorylation levels of PDK1, protein kinase B, MEK and extracellular signal regulated kinase 1/2 following 9za treatment confirmed that 9za was indeed a double MEK/PDK1 inhibitor as we expected. Coadministration with PD0325901 or BX517 strengthened the cytotoxic and pro-apoptotic effect of 9za, verifying that 9za inhibited cell proliferation and induced cell apoptosis through the double MEK/PDK1 signaling pathways in NSCLC cells.

Conclusions: This study demonstrates that 9za could play the effect of cytotoxicity and pro-apoptosis *via* the dual MEK/PDK1 signaling pathways in NSCLC cells and provides certain experimental foundation for 9za as a new type of drug candidate against non-small cell lung cancer.

Keywords: 9za; Cytotoxicity; Cell cycle arrest; Mitochondrial apoptosis; Dual MEK/PDK1 signaling pathways; Non-small cell lung cancer

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