The Novel Synthetic YYK1 Triggers Cell Apoptosis through Induction of Oxidative Stress and Up-regulation of p38 MAPK Signaling Pathway in Human Leukemia HL-60 cells

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To discover the signaling pathways associated with YYK1-induced apoptosis in human leukemia HL-60 cells. YYK1-induced cytotoxic effect, cell morphological changes, decreased the cell number and increased reactive oxygen species (ROS) production and loss of mitochondrial membrane potential ($\Delta\Psi m$) in HL-60 cells. YYK1-induced apoptosis was confirmed by the terminal deoxynucleotidyl transferase dUTP nick end labeling (TUNEL) staining. Results from colorimetric assays and Western blot indicated that activities of caspase-7/-3, caspase-8 and caspase-9 were increased in YYK1-treated HL-60 cells. Western blot analysis showed that the protein levels of extrinsic apoptotic proteins (Fas/CD95, FasL and FADD), intrinsic related proteins (cytochrome *c*, Apaf-1, AIF and Endo G), the ratio of Bax/Bcl-2 and phosphorylated p38 MAPK were increased in HL-60 cells after YYK1 treatment. Cell apoptosis significantly reduced after pre-treatment with *N*-acetylcysteine (NAC; a ROS scavenger) or diphenyleneiodonium chloride (DPI; a NADPH oxidase inhibitor). Blockage of p38 MAPK signaling by SB202190 abolished YYK1-induced Fas/CD95 up-regulation and apoptosis in HL-60 cells. Taken together, we concluded that YYK1 induces both of extrinsic and intrinsic apoptotic pathways *via* ROS-mediated activation of p38 MAPK signaling in HL-60 human leukemia cells *in vitro*.