Microtubule Damaging Agents Induce Apoptosis in HL 60 Cells and G2/M Cell Cycle Arrest in HT 29 Cells.

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Abstract

Microtubule damaging agents (such as paclitaxel and nocodazole (ND)) have been used in the clinical cancer chemotherapy. However, the molecular mechanisms of these agents in the induction of anti-cancer activity are still unclear. In the present study, we demonstrated that 0.2 microM podophyllotoxin (PDP) induced the occurrence of apoptosis in human leukemic (HL 60) cells and cell cycle arrest at the G2/M phase in HT 29 cells. Our results suggest that the PDP-induced G2/M arrest in HT 29 cells was through the intracellular events including (a) inhibition of normal mitotic spindle formation, (b) elevation of cyclin B1/cdc2 kinase activity, (c) concomitant increases in cdc 25 A phosphatase and cdk 7 kinase activity, and (d) down-regulation of the wee-1 protein expression. On the other hand, activations of the caspases 3, 8, and 9, Bcl-2 hyper-phosphorylation, and increased leakage of cytochrome c from mitochondria into cytosolic fraction were detected in the PDP-treated HL 60 cells. These listed intracellular events were interpreted to lead to the apoptosis observed in PDP-treated HL 60 cells. We further demonstrated that activation of c-jun N-terminal kinase (JNK) signaling pathway may play an important role in the PDP-induced Bcl-2 phosphorylation and apoptosis in HL 60 cells as evidenced by the JNK specific anti-sense oligonucleotide experiment. Our results demonstrated that the occurrence of apoptosis or G2/M cell cycle arrest induced by microtubule damaging agents in different cancer cells was through independent mechanisms. The results from the present study highlight the molecular mechanisms underlying of the PDP-induced anti-cancer activity.