Activation of c-jun NH2-terminal kinase and subsequent CPP32/Yama during topoisomerase inhibitor -lapachone-induced apoptosis through an oxidation-dependent pathway.

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Abstract

ß-Lapachone (ß-Lap) has been found to inhibit DNA topoisomerases (Topos) by a mechanism distinct from that of other commonly known Topo inhibitors. Here, we demonstrated a pronounced elevation of H2O2 and O2- in human leukemia HL-60 cells treated with ß-Lap. Treatment with other Topo poisons, such as camptothecin (CPT), VP-16, and GL331, did not have the same effect. On the other hand, antioxidant vitamin C (Vit C) treatment effectively antagonized ß-Lap-induced apoptosis. This suggested that a reactive oxygen species (ROS)-related pathway was involved in ß-Lap-induced apoptosis program. We also found that c-Jun NH2-terminal kinase (JNK) but not p38 mitogen-activated protein kinase or extracellular signal-regulated kinase 1/2 was persistently activated in apoptosis induced by ß-Lap. Overexpression of a dominant-negative mutant mitogen-activated protein kinase kinase kinase 1 (MEKK1-DN) or treatment with JNK-specific antisense oligonucleotide or Vit C all prevented ß-Lap-induced JNK activation and the subsequent apoptosis. Only the expression of MEKK1-DN, not Vit C treatment, blocked the JNK activity induced by CPT, VP-16, or GL331. These results confirm again that ROS acts as a mediator for JNK activation during ß-Lap-induced apoptosis. Furthermore, we found that ß-Lap can stimulate CPP32/Yama activity, which was, however, markedly inhibited by the MEKK1-DN expression or Vit C treatment. Again, CPT-induced CPP32/Yama activation can be abolished by MEKK1-DN but not by Vit C treatment. Taken together, these results indicate that ß-Lap but not other Topo inhibitors triggers apoptosis signaling, i.e., JNK and subsequent CPP32/Yama activation are mediated by the generation of ROS.