Taxol-induced p34cdc2 kinase activation and apoptosis inhibited by 12-o-tetradecanoylphorbol-13-acetate in human breast MCF-7 carcinoma cells.

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Abstract

The p34cdc2 kinase is a highly regulated serine-threonine kinase that, when complexed with cyclins A and B, controls cell entry into mitosis. Recently, premature activation of p34cdc2 was shown to be required for apoptosis induced by a wide variety of agents. Here, we show that Taxol induced p34cdc2 kinase activity with a peak at 6 h in human breast carcinoma MCF-7 cells. We subsequently observed that the activation of CPP32/Yama protease as well as the cleavage of its substrate poly(ADP-ribose) polymerase occurred 9 h after Taxol treatment. Olomoucine, a potent p34cdc2 inhibitor, effectively prevented Taxol-induced p34cdc2 kinase activation and subsequent apoptosis. Furthermore, the treatment of cells with cyclin B1-specific antisense oligonucleotide also blocked Taxol-induced apoptosis, suggesting that cyclin B1-associated p34cdc2 kinase plays an important role in the induction of apoptosis by Taxol. 12-O-Tetradecanoylphorbol-13-acetate (TPA), a protein kinase C activator, was found to exert strong protection against Taxol-induced cell death in MCF-7 cells. TPA inhibited Taxol-mediated activation of p34cdc2 kinase by preventing the dephosphorylation of the Tyr-15 residue on p34cdc2 without altering the levels of Cdc2 and cyclin B1. In contrast, the ability of Taxol to enhance tubulin polymerization was not inhibited by TPA. These findings suggest that modulation of protein kinase C signaling can protect against Taxol-induced cell death by inhibiting p34cdc2 kinase activation.