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MODULATION OF CELL CYCLE-RELATED PROTEIN EXPRESSION BY RESVERATROL IN HUMAN LUNG CANCER CELLS

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Resveratrol (3,5,4'-trihydroxy-trans-stilbene), a phytoalexin found in grapes and wines is a potent antioxidant with cancer-preventive properties, the mechanism by which resveratrol imparts cancer chemopreventive effect is poorly defined. The aim of the present study was to further elucidate the possible mechanisms by which resveratrol exerts its anti-proliferative action in cultured human lung cancer cells. Resveratrol treatment of A549 cells resulted in a dose- and time-dependent inhibition of cell growth, which was associated with S phase arrest of the cell cycle as shown by DNA cell cycle analysis and induction of apoptosis as assessed by DNA fragmentation and cleavage of poly(ADP-ribose) polymerase protein. The immunoblot analysis revealed that resveratrol treatment causes inhibition of phosphorylation of retinoblastoma protein (pRB), and induction of tumor suppressor p53 and cyclin-dependent kinase (Cdk) inhibitor $p21^{WAF1/CIP1}$. Resveratrol also suppressed the Cdk2 and cyclin E-associated kinase activity without changes of their expressions. Our study suggests that resveratrol treatment of the cells causes inhibition of pRB phosphorylation and induction of p21 that inhibit cyclin E-Cdk2 and cyclin A-Cdk2 complexes, thereby imposing an artificial checkpoint at the S to G2/M transition of the cell cycle, that ultimately results in the apoptotic cell death. Thus, our findings suggest that resveratrol may be a potential chemotherapeutic agent for the control of lung cancer cells.