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SUPPRESSION OF HUMAN PROSTATE CANCER CELL GROWTH BY β-LAPACHONE VIA INHIBITION OF pRB PHOSPHORYLATION AND INDUCTION OF Cdk INHIBITOR $p21^{WAF1/CIP1}$

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β-lapachone, the product of a tree (*Tabebuia avellanedae*) from South America, is known to exhibit various pharmacologic properties, the mechanisms of which are poorly understood. The aim of the present study was to further elucidate the possible mechanisms by which β-lapachone exerts its anti-proliferative action in cultured human prostate cancer cells. We observed that the proliferation-inhibitory effect of β-lapachone was due to the induction of apoptosis, which was confirmed by observing the morphological changes and cleavage of poly(ADP-ribose) polymerase protein. DNA flow cytometric analysis also revealed that b-lapachone arrested the cell cycle progression at the G1 phase, which effects were associated with inhibition of phosphorylation of retinoblastoma protein (pRB) and enhanced binding of pRB and the transcription factor E2F-1. β-Lapachone also suppressed the cyclin-dependent kinases (Cdks) and cyclin E-associated kinase activity without changes of their expressions. Furthermore, this compound induced the levels of Cdk inhibitor $p21^{WAF1/CIP1}$ expression in a p53-independent manner, and p21 proteins induced by β-lapachone were associated with Cdk2. β-lapachone also activated the reporter construct of a p21 promoter. Overall, our results identify a combined mechanism involving the inhibition of pRB phosphorylation and induction of p21 as targets for β-lapachone, and this may explain some of its anti-cancer effects. [Supported by grant No. 2001-1-20700-005-3 from the Basic Research Program of the Korea Science & Engineering Foundation]