Z603 **Induction of Cell Cycle Arrest by Cyclic AMP in Tumor Cells through p53-Independent Transcriptional Regulation of Cdk Inhibitor p21WAF1/CIP1**

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cAMP is a negative growth regulator for many cells of epithelial origin. In this study, we have addressed the mechanism of cAMP-induced growth arrest in the p53-null PC-3-M prostate carcinoma and p53-mutant MDA-MB-231 breast carcinoma cell lines. In both cell types cAMP induced inhibition of cyclin E- and cdk2-associated kinase activity, hypophos-phorylation of the retinoblastoma protein, markedly enhanced binding of the retinoblastoma protein to E2F-1, and G1 synchronization. Growth arrest was associated with increased expression of the cyclin-dependent kinase inhibitor p21. cAMP induced p21 protein, mRNA and activation of a full-length p21 promoter-luciferase reporter construct. Analysis of deletion constructs of the p21 promoter indicated that the response to cAMP localized to the 93 base pairs proximal to the transcription start site. The histone acetyltransferase p300 has been shown to induce chromatin remodeling and activation of gene expression. A promoter-luciferase reporter construct of the 93 base pair region, p21-93-luc was activated by p300 and the combination of p300 and cAMP was synergistic. A p300 deletion construct did not activate p21 93-luc and expression of this truncated p300 completely blocked activation by cAMP. Inhibition of histone deacetylase with trichostatin A also induced p21 93-luc, and concentration-dependence curves were consistent with a shared mechanism of action for cAMP and trichostatin A. These data demonstrate that cAMP activates p21 transcription and suggest a molecular mechanism for cAMP-induced negative growth regulation.