TGF-beta-1 up-regulates cyclin D1 expression in COLO-357 cells, whereas suppression of cyclin D1 levels is associated with down-regulation of the type I TGF-beta receptor.

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Transforming growth factor-beta1 (TGF-beta1) inhibits cell growth in susceptible cells by interacting with a family of protein kinases that control cell cycle progression. In the present study, we investigated the effects of TGF-beta1 on cyclin D1 expression and activity in COLO-357 human pancreatic cancer cells. TGF-beta1 increased cyclin D1 mRNA and protein levels. Nuclear runoff transcription and protein synthesis inhibition by cycloheximide revealed that this increase was, in part, due to increased cyclin D1 mRNA synthesis. Despite its stimulatory effects on cyclin D1 levels, TGF-beta1 inhibited cyclin D1-associated kinase activity and the growth of COLO-357 cells. Furthermore, suppression of cyclin D1 expression with a cyclin D1 antisense cDNA resulted in loss of TGF-beta1-mediated growth inhibition in association with reduced induction of cyclin D1, p21(CIP)(1) and plasminogen activator inhibitor-1 (PAI-1). Concomitantly, there was a marked decrease in the levels of the type I TGF-beta receptor (TbetaRI). Our findings suggest that in some cell types cyclin D1 expression may be important for TGF-beta1-mediated signaling and that cyclin D1 may be involved in the transcriptional regulation of TbetaRI. Copyright 1999 Wiley-Liss, Inc.

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