Regulation of cyclin D1 expression in ES cells : the role of the Ras/MAPK pathway

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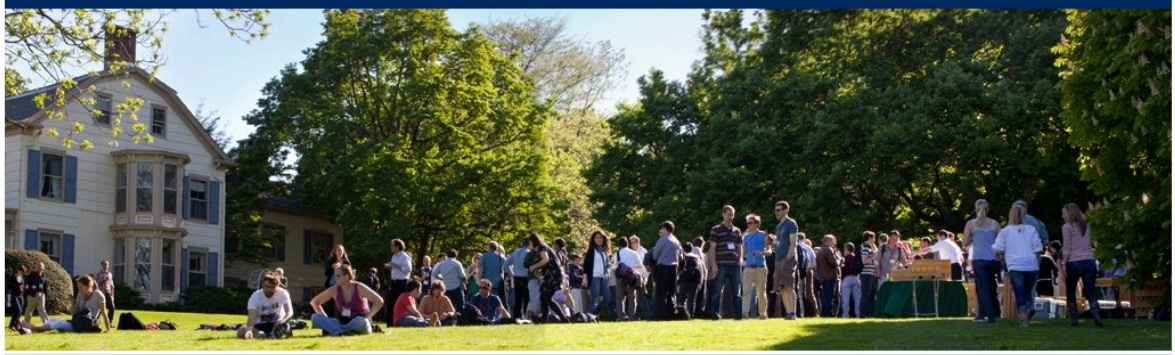

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Poster Abstract :

Regulation of cylin D1 expression in ES cells : the role of the Ras/MAPK pathway.

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The cellular machinery that is organized to collect extracellular signals and transduce them via tyrosine kinase receptors and the SOS-RAS-MEKK-MAPK pathay seems to be dedicated largely to driving RB phosphorylation. Cyclin D1 is likely to play a key role in this process as : (*i*) cyclin D1 expression is regulated by MAPK-dependent transcription factors (jun, fos, ets) and (*ii*) cyclin D1/CDK4 complexes are involved in RB phosphorylation during G1 phase of the cell cycle. The circuitry appears to be operative in virtually all cell types and its revelance is illustrated by its disruption in many types of human tumors. Using ES cells which express the *neo*^{r} gene driven off the *oct4* promoter (IOUD2 cells) so as to kill all spontaneously differentiating cells, we show that ES cells express low, although constant, evel of cyclin D1. This results from low activity of the cyl1 promoter. Promoter deletion analysis shows that this background activity originates from a proximal region of the promoter, and taht distal regions known to be involved in cyclin D1 expression in response to serum stimulation are not required. Treatment of IOUD2 cells with wortmannin (an inhibitor of RAS activation) or PD98059 an inhibitor of MEK) does not inhibit cyclin D1 expression. None of these inhibitors induce growth retardation. Induction of differntiation with retinoic acid (RA) up-regulates cyclin D1 expression, and distal - serum-responsive – elements of the cyl1 promoter are involved. Differentiating cells become sensitive to inhibitors of the Ras → ERK cascade. Both wortmannin and PD98059 inhibit cell growth and down-regulate expression of cyclin D1. Hence, cyclin D1 expression seems not to be regulated by the RAS → MERK → ERK phosphorylation in ES cells. This regulation is likely to be restored upon differntiation.