

# Cell Cycle Regulation: Mechanisms and Therapeutics

Premkumar E. Reddy

*Fels Institute for Cancer Research and Molecular Biology, Temple University School of Medicine,  
Philadelphia, USA*

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## **Abstract**

Cyclin-dependent kinase 4 (Cdk4) is an important regulator of G1/S cell cycle progression of mammalian cells. To understand the role of Cdk4 *in vivo* we generated strains of mice that either lack Cdk4 or express an activated form of this enzyme (Cdk4R24C), which cannot interact with the cyclin kinase inhibitor, p16INK4A. Cdk4R24C mutations that abolish the interaction of p16INK4A and CDK predispose humans to familial melanoma. Cdk4<sup>-/-</sup> mutant mice are viable but express defects in growth, fertility and are diabetic due to loss of insulin-producing islet cells. In contrast, CDK4 (R24C/R24C) mice exhibit growth advantage and their fibroblasts have a shorter cycle with high proliferative rates. The Cdk4 (R24C/R24C) fibroblasts fail to undergo senescence and are capable long-term growth in culture. Moreover, approximate 80% of Cdk4 (R24C/R24C) mice developed spontaneous tumors of varying cellular origin such as breast, pituitary, brain, skin, pancreas, liver, lung, testes, ovarian and hematopoietic tumors by 12 month. In addition, cdk4(R24C/R24C) mice are highly susceptible to TPA or DMBA carcinogen-induced tumors and Cdk4(R24C/R24C) mice developed skin tumors with average latency of 10-12 weeks. In contrast, wild type mice had a reduced frequency and latency of tumor formation. These studies indicated that the cdk4(R24C) mutation could exacerbate de-regulated Ras-pathways and accelerate tumorigenesis. In addition, Cdk4 (R24C/R24C) mice exhibit severe hyperplasia of the immune system and are highly susceptible to the development of hematopoietic malignancies. These results suggest that Cdk4 is an important modulator of cell cycle progression and abnormalities associated with this gene results in the development of abnormalities in multiple organs including the hematopoietic compartment.

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