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# The cyclin D1b splice variant: an old oncogene learns new tricks

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## Abstract

The function of cyclin D1 as a positive regulator of the cell cycle and proto-oncogene has been well established. Cyclin D1 elicits its pro-proliferative function early in G1 phase, through its ability to activate cyclin dependent kinase (CDK) 4 or 6. Active CDK4/6-cyclin D1 complexes phosphorylate substrates that are critical for modulating G1 to S phase progression, and in this manner promote cellular proliferation. Emerging data from a number of model systems revealed that cyclin D1 also holds multiple, kinase-independent cellular functions. First, cyclin D1 assists in sequestering CDK inhibitors (e.g. $p27^{kip1}$), thus bolstering late G1 CDK activity. Second, cyclin D1 is known to bind and modulate the action of several transcription factors that hold significance in human cancers. Thus, cyclin D1 impinges on several distinct pathways that govern cancer cell proliferation. Although intragenic somatic mutation of cyclin D1 in human disease is rare, cyclin D1 gene translocation, amplification and/or overexpression are frequent events in selected tumor types. Additionally, a polymorphism in the cyclin D1 locus that may affect splicing has been implicated in increased cancer risk or poor outcome. Recent functional analyses of an established cyclin D1 splice variant, cyclin D1b, revealed that the cyclin D1b isoform harbors unique activities in cancer cells. Here, we review the literature implicating cyclin D1b as a mediator of aberrant cellular proliferation in cancer. The differential roles of cyclin D1 and the cyclin D1b splice variant in prostate cancer will be also be addressed, wherein divergent functions have been linked to altered proliferative control.

## Background

Cyclin D1 is a focal point for integrating mitogenic stimulation with cellular proliferation [1,2]. Mitogenic signals typically induce increases in cyclin D1 mRNA expression and translation, thereby increasing the cellular pool of the protein product. The pro-proliferative function of cyclin D1 is mediated through its ability to regulate the cell cycle machinery, and excessive cyclin D1 expression and/or activity is a hallmark of several tumor types [3,4]. In addition, cyclin D1 has cell cycle-independent functions through its ability to modulate transcription factor action [5]. Given the importance of cyclin D1 in human disease, concerted effort has been directed at delineating the mechanisms by which cyclin D1 is dysregulated in cancer. In selected tumor types, cyclin D1 is overexpressed as a result of chromosomal translocation or amplification of the cyclin D1 (CCND1, PRAD) locus [1,6]. Intragenic somatic mutations of cyclin D1 are rare, but a polymorphism of cyclin D1 that occurs in a splice donor site has been epidemiologically linked to increased cancer risk or poor prognosis in a number of tumor types (reviewed in [7]). Recent functional analyses have revealed that the