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COMMENTARY

# PTEN, a general negative regulator of cyclin D expression

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The tumor-suppressor phosphatase with tensin homology (*PTEN*) is frequently mutated in many malignancies and is one of the most well studied tumor suppressor genes [1, 2]. PTEN, a lipid and protein dual phosphatase, plays a vital role in embryonic development, cell growth, apoptosis and cell migration. The well-known function of PTEN is phosphatidylinositol-3 ($PI_3$)-phosphatase, which functions as a negative regulator of the $PI_3$ kinase (PI3K) pathway. It is well established that PTEN regulates the G1-S transition by modulating the expression of cyclin D1 and $p27^{Kip1}$.

The passage of any cell through cell cycles is subtly modulated by a series of proteins, among which the main players in animal cells include cyclins, CDKs (cyclin-dependent kinases, positive regulators) and CDK inhibitors (negative regulators such as $p21^{Cip1}$ and $p27^{Kip1}$). Cyclin Ds are key regulators during the G1 phase and there are three types of cyclin Ds, D1, D2 and D3 in mammalian cells [3]. Although the phenotypic analyses of single cyclin D knockout mice revealed that each of the D type cyclins is sufficient to drive normal development of the majority of tissues [4], each cyclin D shows distinct and mutually exclusive expression patterns in mouse embryos and some organs of adult animals, indicating individual cyclin D may have their specific functions [5].

It has been documented that cyclin D1 is an important target of PTEN, which downregulates the expression and protein stability of cyclin D1 and inhibits its nuclear localization [6]. PTEN also reduces cyclin D3 levels in endometrial carcinoma cells [7]. Loss of PTEN occurs in a great portion of invasive germ cell tumors [8], while overexpression of cyclin D2 is frequently observed in germ cell tumors [9]. Considering that different cyclin D may have distinct functions, it is important to evaluate the effect of PTEN on other cyclin Ds.

In the study reported in *Oncogene* [10], we provided evidence that cyclin D2 is also an important target of PTEN. We found that the mRNA and protein levels of cyclin D2 were apparently higher in *Pten*-null cells than those in wild-type mouse embryonic fibroblasts (MEFs), and this elevated expression was suppressed by reintroduction of PTEN. We further defined a pathway involving GSK3β/β-catenin/TCF in PTEN-mediated suppression of cyclin D2 expression. Treatment of LiCl, an inhibitor of GSK3β, abolished the inhibitory effect of PTEN on cyclin D2 expression. TCF members could directly bind to the promoter of cyclin D2 and regulate its transcription in a CREB-dependent manner, indicating a novel mechanism whereby TCF and CREB cooperate in the regulation of cyclin D2 expression. These data also suggest a convergence of the PI3K pathway and Wnt pathway in the modulation of cyclin D2 expression. Significantly, we showed that the greater potential to overcome G1 arrest by loss of PTEN was at least partially contributed by the elevated level of cyclin D2. These findings together suggest that cyclin D2 is an important target of PTEN. Future studies are needed to determine how PTEN influences D2 protein stability and whether the subcellular localization of cyclin D2 is also regulated by PTEN.

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