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Review

New twist in the regulation of cyclin D1

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Abstract

Among the cell cycle-related mammalian cyclins, cyclin D1 is more closely connected with cell proliferation in response to extracellular signals than the cell cycle clock itself. Because both its mRNA and protein are labile, the intracellular abundance of cyclin D1 is thought to be largely regulated at the level of transcription. However, recent findings suggest that, in certain cell types, cyclin D1 is post-translationally regulated, and a disturbance of this regulatory mechanism induces aberrant entry into the cell cycle and proliferation, sometimes leading to diseases such as cancer. In this review, we summarize recent findings and discuss the physiological role and cellular function of the novel mechanism of regulation of cyclin D1 in terms of the control of cell proliferation.

Keywords: cancer; cell cycle; cell proliferation; cyclin D; cytoplasmic retention; degradation; E3 ubiquitin ligase; nuclear export.

Introduction: the finding of cyclin D1 and a classical mechanism of its regulation

Cell proliferation is the process that requires alternate genome duplication (S phase, DNA replication) and cell division (M phase, mitosis). S and M phases are separated by two gap phases, G1 and G2, and it is essential that G1-S-G2-M phases progress in this order (the cell cycle). The cell cycle is driven by a unique protein called 'cyclin', which activates its specific catalytic partner, cyclin-dependent kinase (Cdk), as a protein kinase. M phase is governed by the B-type cyclin-Cdk1 (Cdc2) complex (1–4), whereas the cyclin (and its partner kinase) that controls G1/S phase progression and transition of mammalian cells remained unknown before 1990.

In 1991, a novel mammalian cyclin was identified in three independent ways (5, 6): (i) a G1 target of growth factor stimulation (7), (ii) a cDNA capable of complementing yeast G1 cyclin deficiency (8), and (iii) a target of cancer-related chromosomal translocation (9). This cDNA was designated cyclin D1, and two related cDNAs isolated from different tissues were named cyclin D2 and D3. The three D-type cyclins were expressed in a tissue-specific manner; cyclin D1 is dominant in fibroblasts, macrophages, neurons, and muscles, whereas cyclins D2 and D3 are exclusively expressed in hematopoietic cells (7).

The function of cyclin D1 was first analyzed in cultured cells such as mouse fibroblasts and hematopoietic cell lines by ectopic overexpression or functional inactivation, showing that the level of cyclin D1-associated kinase (Cdk4 and 6) activity is the rate-limiting step in the progression of the G1 phase during the mammalian cell cycle (10–13). Subsequently, experiments with a series of cyclin D1-, 2-, and 3-deficient mice demonstrated that the functions of cyclin D1/2/3 and Cdk4/6 are actually important for progression of the cell cycle, although their roles are much more redundant *in vivo* than was anticipated (14–19) (Figure 1).

mRNA and protein of cyclin D1 are short lived, with a half-life of less than 30 min, and their expression is dependent on the presence of growth factors outside the cell (7). Therefore, the withdrawal of growth factors through serum deprivation rapidly reduces the level of both the mRNA and protein of cyclin D1. Although post-translational as well as transcriptional regulations are under the control of growth factors (see below), the rate-limiting step is the regulation of transcription, rather than protein degradation, from the specific promoter of cyclin D1, which is controlled by a growth factor-triggered signaling cascade. Among the known signal transduction pathways, it is reasonable to state and many researchers have actually found that the ras pathway plays an important role in transcriptional regulation of cyclin D1, presumably through the AP1 transcription factor (composed of Jun and Fos subunits) (20–23), although it is not excluded that other transcription factors (candidates include E2F, Sp1, Egr1, ATF, NFkB, STAT5, CREB, etc.) play an important role in transcriptional induction of cyclin D1 under the ras-mediated signals. In addition to the ras-signaling pathway, several transcription factors have been reported to control transcription of cyclin D1. β-Catenin functions downstream of the Wnt signaling pathway and directly activates the cyclin D1 promoter together with another transcription factor, TCF/LEF (24). Another example is that GATA3 directly acts on the cyclin D1 promoter in neuroblastoma cells (25). Tob (26) and jumonji (27) are both transcriptional regulators and specifically repress the activation of the cyclin D1 promoter.

In human tumors, cyclin D1 is frequently overexpressed due to an upregulation of transcription. In some tumors, the cyclin D1 gene is translocated, fused to another gene, and then transcriptionally activated in the presence of strong tis-

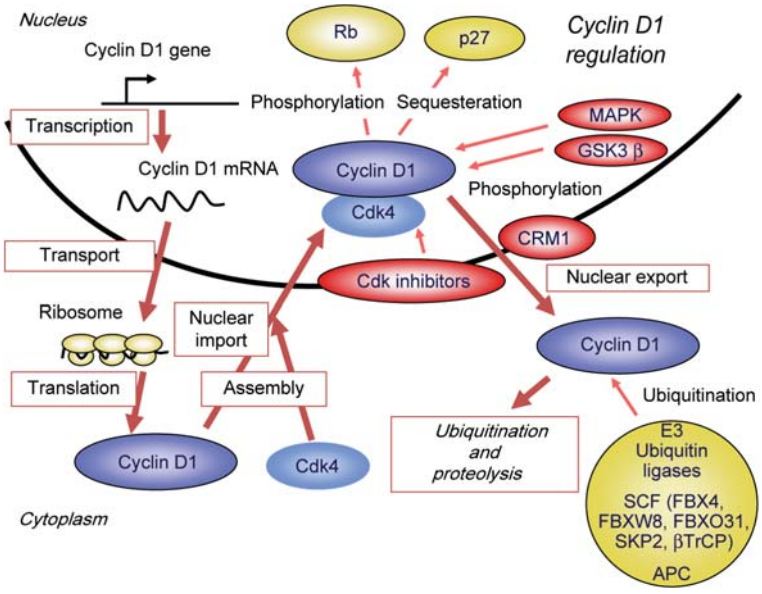

Figure 1 Overview of the regulation of cyclin D1.

sue-specific enhancer sequences, whereas in other tumors, the cyclin D1 gene itself is amplified (28). However, in some cases, cyclin D1 protein is overexpressed without any obvious genetic abnormalities, suggesting the upstream regulatory mechanism to be a target of tumorigenesis. These two events (the cyclin D1-gene amplification and the alteration of the upstream regulatory mechanism) are not mutually exclusive, and both types of mutations can actually occur in human cancer cells.

Regulation of the stability of cyclin D1

Cyclin D1 is a very labile protein, with a half-life of approximately 20 min (7), and is predominantly located in the nucleus (29), although some remained in the cytoplasm. The level of nuclear cyclin D1 fluctuates during the cell cycle, being high in the mid-G1 phase and decreasing upon entry into the S phase (29). These processes are dependent on the signals mediated by the extracellular growth factors.

In a post-translational regulation, phosphorylation of a specific residue (Thr286) located at the C-terminus of cyclin D1 (30) is an essential event. The phosphorylation of this residue triggers an association with the nuclear export receptor CRM1 and induces the translocation of cyclin D1 from the nucleus to the cytoplasm, where the protein is subsequently ubiquitinated and degraded by the proteasome. The deubiquitination enzyme USP2 antagonizes this process and facilitates the stabilization of cyclin D1 (31).

The kinase that phosphorylates Thr286 of cyclin D1 includes glycogen synthase kinase 3β (GSK3β) (32) and MAPK (ERK1/2) (33), both of which are regulated downstream of the Ras-mediated signaling cascade, but in a different manner (Table 1). In the absence of growth factors, ERK is not activated, but the activity of GSK3β is high; therefore, GSK3β seems to be a potential player in phosphorylation and subsequent degradation of cyclin D1 protein

Table 1 Post-translational regulators of cyclin D1 expression.

Regulators	Function	Reference
GSK3β	Phosphorylates Thr286	(32)
ERK1, 2	Phosphorylates Thr286	(33, 34)
$p38^{SAPK2}$	Phosphorylates Thr286	(35)
CRM1	Export to the cytoplasm	(36)
FBX4	A component of E3 ubiquitin ligase (F-box protein)	(37, 38)
αB-crystallin	A component of E3 ubiquitin ligase	(37, 38)
FBXW8	A component of E3 ubiquitin ligase (F-box protein)	(33)
FBXO31	A component of E3 ubiquitin ligase (F-box protein)	(34)
Skp2 (Fbxl1)	A component of E3 ubiquitin ligase (F-box protein)	(39)
APC3	A component of E3 ubiquitin ligase (APC/C)	(40)
β-TrCP	A component of E3 ubiquitin ligase (F-box protein)	(41)
USP2	A deubiquitinase	(31)

in this environment. However, as mentioned above, growth-factor deprivation rapidly reduces the level of cyclin D1 mRNA and the protein is hardly expressed. Therefore, phosphorylation and subsequent regulation of cyclin D1 protein by GSK3β could be a backup mechanism. The role of GSK3β in the regulation of cyclin D1 needs to be further investigated in terms of tissue specificity and cyclin D1-gene amplification. Once cells are stimulated with growth factors, ras is activated, followed by activation of the PI3 kinase (PI3K) pathways. PI3K activates Akt/PKB kinase, which leads to phosphorylation and inactivation of GSK3β, preventing degradation of cyclin D1 (32, 42, 43), and, together with the AP1-mediated transcriptional activation of the cyclin D1 promoter (20–23), facilitating the efficient accumulation of the cyclin D1 protein in G1. Ras also activates MAP kinase (ERK1/2), which phosphorylates Thr286 of cyclin D1 and subsequent degradation of cyclin D1 (33), which could explain why cyclin D1 is an unstable protein even in mid-G1. It is interesting that ras regulates both transcriptional and post-translational events in the control of cyclin D1 expression. But it seems likely that ras acts in favor of accumulation of cyclin D1 during G1 in proliferating cells (21, 22). However, given that the cellular response to activated ras varies depending on cell type, ras sometimes induces degradation of cyclin D1 through the MAPK pathway (44). Upon entry into S phase, however, downregulation and cytoplasmic localization of cyclin D1 is observed (29). In this setting, MAPK (ERK1/2) could play a central role in phosphorylation of cyclin D1 at Thr286 and subsequent nuclear export-mediated degradation (33). However, it remains largely unknown what makes the difference between early-to-mid-G1 phase and late-G1-to-S phase in terms of cyclin D1 regulation. It could be the qualitative alteration of MAPK because it is reported that MAPK translocates from the cytoplasm to the nucleus around mid-G1 (45, 46). In addition, osmotic stress induces phosphorylation of cyclin D1 by $p38^{SAPK2}$ MAP kinase and subsequent downregulation of the protein (35).

E3 ubiquitin ligases for cyclin D1

Several F-box proteins are reported to be involved in ubiquitination of cyclin D1 in the cytoplasm, all of which favor the interaction with phosphorylated cyclin D1. It is not known why many ligases are involved in cyclin D1 degradation. They do not seem redundant because they are activated and function in different situations (e.g., normal cell cycle progression and DNA damage response). More detailed investigation will be required to determine the specific roles and cellular functions of each ligase in terms of normal cell cycle, checkpoint control, cellular differentiation, and tumorigenesis (Figure 2).

FBX4

FBX4 forms a complex with SKP1 and CUL1, thereby generating an E3 ubiquitin ligase SCF^{FBX4}, but requires αB crystallin for efficient recognition of cyclin D1 as a substrate (37). Cyclin D1 forms a complex with $SCF^{FBX4\text{-}\alpha B\ crystalline}$ in cells treated with proteasome inhibitors and this interaction depends upon the integrity of the phosphorylation site Thr286 in cyclin D1. Both FBX4 and αB crystallin occur in the cytoplasm and are required for efficient downregulation of cyclin D1 expression *in vivo*. Knockdown of $SCF^{FBX4\text{-}\alpha B\ crystalline}$ ligase accelerates the progression through G1 in a cyclin D1-dependent manner and eventually induces the transformation of murine fibroblasts. The cyclin D1-FBX4 complex accumulates in the S phase. This is due not only to the phosphorylation of cyclin D1 by GSK3β but also to the phosphorylation of FBX4 at Ser12 by the same kinase, which facilitates dimerization of FBX4, SCF^{FBX4} activity,

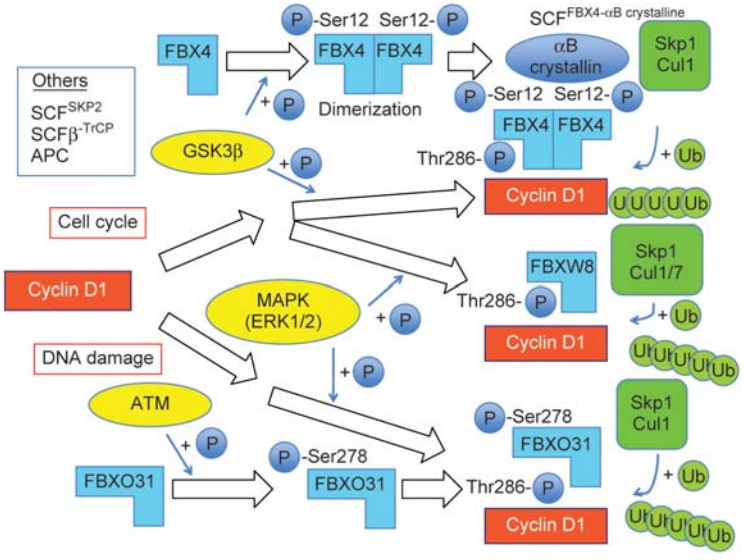

Figure 2 E3 ubiquitin ligases for cyclin D1.

and cyclin D1 turnover in the S phase (37, 38). The αB crystallin locus maps to chromosome 11 at q22.3–q23.1, which is frequently deleted in human cancer, and mRNA levels of FBX4 and αB crystallin are reduced in a broad spectrum of human tumors, which leads to cyclin D1 overexpression and tumor development (37). Furthermore, FBX4 was found to be mutated in human esophageal cancer (38). These mutations impair the phosphorylation, dimerization, or binding to the SCF complex of FBX4 protein, which ultimately leads to an increase in cyclin D1 and tumorigenesis.

FBXW8

In certain cancer cells, cyclin D1 is strongly destabilized specifically in the S phase. In these cells, the Ras/Raf/MEK/ERK MAPK signaling cascade plays an important role in phosphorylating Thr286 of cyclin D1. Actually, ERK/MAPK interacts directly with the D-domain to phosphorylate cyclin D1. In this scenario, FBXW8 in a complex with SKP1, RBX1 and either CUL1 or CUL7 functions as an E3 ligase to regulate the level of cyclin D1 (33).

FBXO31

Cells exposed to genotoxic stress undergo a DNA damage response and temporally arrest to perform various biological processes such as DNA repair, senescence, and apoptosis. During this period, cyclin D1 expression is downregulated by the ubiquitin-proteasome system, which plays an essential role in maintaining genomic stability. FBXO31 was originally identified by a genome-wide RNA interference screen as one of the factors required for oncogene-induced senescence. The FBXO31 gene is located at 16q24.3, a region frequently deleted in cancer cells, and is thought to be a putative tumor suppressor gene. DNA damage, especially double-stranded breaks, activates a serine-threonine protein kinase ATM, which in turn phosphorylates several substrates including FBXO31 at Ser278, resulting in the stabilization of this F-box protein and activation of SCF^{FBXO31}. Following γ-irradiation, which induces double-stranded breaks, cyclin D1 is phosphorylated through a MAP kinase (MEK-ERK) pathway but not by GSK3β. Expression of a phosphorylation-resistant cyclin D1 mutant (T286A) or knockdown of FBXO31 prevented cells from undergoing efficient arrest in G1 after DNA damage (34).

Other ligases for cyclin D1

Other ubiquitin ligases involved in cyclin D1 regulation include the SKP2-SCF complex (39, 47) and the anaphase promoting complex/cyclosome (APC/C) (40), both of which play an important role in the regulation of the cell cycle progression but at different points; G1-S transition and M phase, respectively (48). SKP2 forms a complex with SKP1 and CUL1 and induces ubiquitination of many regulators governing G1 progression, which include the Cdk inhibitor p27. It remains to be solved why SKP2-SCF ligase triggers degradation of both positive (e.g., cyclin D1) and negative (e.g., p27) regulators of the G1 cell cycle, but it seems that SKP2-SCF functions in favor of progression of the cell cycle. In the case of APC/C, transcription factor CCAAT/enhancer binding protein δ (C/EBPδ) upregulates the component (Cdc27 or APC3) of the APC/C ubiquitin ligase complex, resulting in the polyubiquitination and degradation of cyclin D1 in breast cancer cells. Furthermore, in prostate cancer cells, thiazolidinediones facilitates cyclin D1 degradation through the β-TrCP-SCF complex (41). It remains to be solved why cyclin D1 is targeted by so many ubiquitin ligases.

Retention of cyclin D1 in the cytoplasm

In proliferating cells, cyclin D1 accumulates within the nucleus. During progression of the cell cycle from Go, the expression of cyclin D1 is regulated at the level of transcription and newly synthesized cyclin D1 protein is readily transported into the nucleus (5, 6). Therefore, it seems likely that the nuclear transport of cyclin D1 protein is constitutive (not a rate-limiting step in these cells). Cyclin D1 does not have a canonical nuclear localization signal (NLS) and it is not entirely clear how the protein is efficiently transported into the nucleus (Figure 3).

Recently, however, cyclin D1 was found intact in the cytoplasm in certain mammalian cells, such as cardiomyocytes (49), neurons (50, 51), and hematopoietic stem cells (52). Mammalian cardiomyocytes irreversibly withdraw from the cell cycle soon after birth. Mitogenic stimulation of postmitotic cardiomyocytes still induces hypertrophic cell growth and upregulates the expression of cyclin D1 and Cdk4, but the cyclin D1-Cdk4 complex occurs predominantly in the cytoplasm. The cytoplasmic cyclin D1-Cdk4 complex is resistant to leptomycin B, an inhibitor of CRM1-dependent nuclear export. Interestingly, ectopic expression of a cyclin D1 mutant linked to the nuclear localization signal (cyclin D1-NLS), which is located in the nucleus even in cardiomyocytes, allows postmitotic cardiomyocytes to promote reentry into the cell cycle, suggesting that cardiomyocytes harbor a potential mitotic capability but the nuclear import of the cyclin D1-Cdk4 complex is inhibited in these cells (49).

Terminally differentiated neurons are another example of cells irreversibly withdrawn from the cell cycle. Although the level of cyclin D1 declines during the terminal differentiation of neurons, postmitotic neurons contain a significant amount of cyclin D1 protein in the cytoplasm. When DNA is damaged, the cyclin D1-Cdk4 complex is activated, which induces entry into the cell cycle leading to apoptosis. Ectopic expression of a cyclin D1-NLS mutant also induced apoptosis in neuronal cells, indicating that regulation of the subcellular distribution of cyclin D1 is important for neuronal cell death and survival (50, 51).

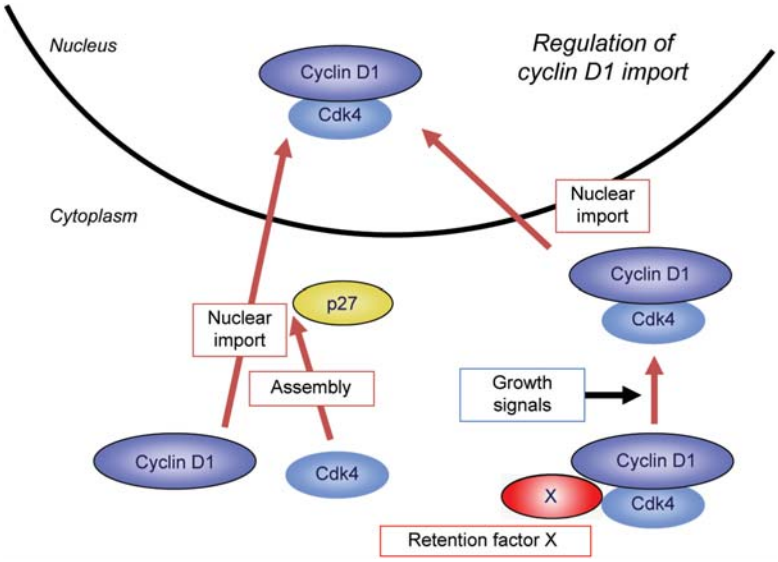

Figure 3 Regulation of the nuclear import of cyclin D1.

Hematopoietic stem cells (HSCs) are stored in the bone marrow in a noncycling state and seldom enter the cell cycle. In resting HSCs, cyclin D1 is maintained in the cytoplasm and, upon stimulation with cytokines, swiftly moves into the nucleus. Clustering in lipid rafts plays an important role in this process and the transcription factor FOXO and Cdk inhibitor $p57^{Kip2}$ are regulated in a similar manner (52).

Thus, evidence is accumulating that indicates the existence of a higher order regulatory system in activation of cyclin D1. However, the precise mechanism remains to be elucidated. In an attempt to clarify this issue, cyclin D1 mutants were isolated from a mixed population of randomly mutagenized cyclin D1 cDNA, which predominantly occurs in the cytoplasm. Analysis of these mutants shows that they harbor mutations in the cyclin box and lose capability to bind Cdk4, suggesting that interaction between cyclin D1 and Cdk4 might trigger the mechanism controlling the nuclear transportation of the cyclin D1-Cdk4 complex (53). However, the association with Cdk4 alone is not sufficient for cyclin D1 to be transported into the nucleus because the cyclin D1 mutant (T156A), which associates with Cdk4, still remains in the cytoplasm (30). Whatever the mechanism, detailed analysis will be required to obtain an overall picture of the cytoplasmic retention of cyclin D1 in stem and postmitotic cells.

Conclusion and future prospects

Cyclin D1 is overexpressed in a variety of cancers (28). The cause in most cases is assumed to be an upregulation of transcription due to chromosomal rearrangement and to an increase in transcriptional activators for the promoter of cyclin D1. However, recent findings show that the overexpression (and activation) of cyclin D1 also involves other mechanisms (54), including (i) blocking of the degradation of cyclin D1 (involving cytoplasmic exportation) and (ii) impairment of the nuclear import process. The former is demonstrated by the finding of a mutation in the FBX4 gene (38), and the latter mechanism is connected with the regulation of the proliferation of stem cells (52) and terminally differentiated postmitotic cells such as neurons (50, 51) and cardiomyocytes (49), suggesting that these newly identified regulatory mechanisms are physiologically highly important. In the forthcoming decade, we expect these new mechanisms to be clarified in a molecular biological manner, which might result in a new era of treatment for cancers (31), cardiovascular diseases, and Alzheimer's disease.

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