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Cyclin D Degradation by E3 Ligases in Cancer Progression and Treatment

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Abstract

D cyclins include three isoforms: D1, D2, and D3. D cyclins heterodimerize with cyclin-dependent kinase 4/6 (CDK4/6) to form kinase complexes that can phosphorylate and inactivate Rb. Inactivation of Rb triggers the activation of E2F transcription factors, which in turn regulate expression of genes whose products drive cell cycle progression. Because D-type cyclins function as mitogenic sensors that link growth factor signaling directly with G_1 phase progression, it is not surprising that D cyclin accumulation is dysregulated in a variety of human tumors. Elevated expression of D cyclins results from gene amplification, increased gene transcription and protein translation, decreased microRNA levels, and inefficiency or loss of ubiquitylation-mediated protein degradation. This review focuses on the clinicopathological importance of D cyclins, how dysregulation of Ubiquitin-Proteasome System (UPS) contributes to the overexpression of D cyclins, and the therapeutic potential through targeting D cyclin-related machinery in human tumors.

Keywords

D cyclin; E3 Ubiquitin Ligase; Protein degradation; Cancer

1. Introduction

Cell cycle defines the process through which cells duplicate their genome and divide into two daughter cells [1]. There are four phases of cell cycle: G_1, cell growth and generation of proteins required for DNA replication; S-phase, genome duplication; G_2, Gap phase to monitor fidelity of DNA replication; and M-phase, cell division [2, 3]. Progression through the cell cycle is catalyzed by cyclins and cyclin-dependent kinases (CDKs) [2, 4]. Cyclins can activate their cognate CDKs through the formation of heterodimers, which ultimately catalyze the phosphorylation of downstream genes to promote cell cycle progression. Due to

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their significance in regulating cell cycle progression, the activities of CDKs are tightly regulated by the abundance of cyclins and CDK inhibitory machinery like INK4, CIP and KIP family proteins [2, 5].

G_1 phase is unique as it regulates cell cycle re-entry in response to extrinsic factors such as growth factors, nutrients, and integrin-related adhesion signaling during G_1 phase [6]. The D-type cyclins along with their cognate CDKs, CDK4/6, are exquisitely sensitive to such extrinsic signals and serve to integrate such signals with cell division. Mammalian cells encode three D-type cyclins, D1, D2, and D3, with approximately 57% identity for the coding region among different isoforms, and 78% identity for the N-terminal "cyclin box" domain [7]. Moreover, D cyclins also possess a C-terminal phospho-degron and an Rb binding motif [8]. D cyclins heterodimerize with CDK4/6 to form kinase complexes, which phosphorylate and inactivate retinoblastoma (Rb) protein, leading to the release of the E2F transcription factors, thereafter, the expression of downstream genes to drive cell cycle progression [9] (Fig. 1).

The Restriction Point (R), analogous to "start" in budding yeast, occurs in late G_1 phase and represents an experimentally defined point where cells are committed to one round of cell division. Growth factor and nutrient signals are required for cells to reach R point. Molecularly, this reflects the assembly and activation of the D-type cyclin-CDK4/6 kinase and the initial phosphorylation-dependent inactivation of Rb. This initial Rb phosphorylation triggers an initial wave of transcription and activation of subsequent cyclin E-CDK2 and cyclin A-CDK2 kinases that drive G_1 to S-phase transition at which point cells are committed to finishing one round of cell division [10, 11]. Given the central role of D-type cyclins as sensors for various growth factors, it stands to reason that accumulation and activity of cyclin D-CDK4/6 kinase is dysregulated in a large fraction of human cancers [1, 2]. Elevated expression of D cyclins reflects gene amplification, increased gene transcription and protein translation, decreased microRNA expression, and inefficiency or loss of ubiquitylation-mediated protein degradation [2, 7]. This review will focus on the clinic-pathological importance of D cyclins, how dysregulation of Ubiquitin-Proteasome System (UPS) contributes to the overexpression of D cyclins, and the therapeutic potential through targeting D cyclin-related machinery in human tumors.

2. D cyclins and human cancers

2.1 Cyclin D1

Cyclin D1 is a direct target of mitogenic signaling cascades including epidermal growth factor receptor (EGFR) [12, 13], and phosphatidylinositol 3-kinase (PI3K)-Akt [14–16], and it is sensitive to transcription factors such as β-Catenin [17, 18], and nuclear factor-kappa B (NF-κB) [19, 20]. In addition, the CCND1 gene is amplified in a variety of human cancers including pancreatic cancer [21], non-small cell lung carcinoma (NSCLC) [22–24], breast cancer [25], head and neck squamous cell carcinoma (HNSCC) [26, 27], melanoma [28], endometrial cancer [29, 30], esophageal squamous cell carcinoma (ESCC) [31, 32], and colorectal carcinoma [7] (Table 1). CCND1 is dysregulated via chromosome translocation in mantle cell lymphoma (MCL) and multiple myeloma [33, 34]. Overexpression of cyclin D1 can also be driven through mutations in the 3'-untranslated region, resulting in reduced

mRNA degradation-mediated by microRNAs [35–39]. In addition, cyclin D1 levels directly correlate with tumor size, local invasion and metastasis as well as advanced clinical stages in human cancers [1, 2, 7]. These observations support cyclin D1 as an important prognostic indicator for patients with pancreatic adenocarcinoma, lung cancer, breast cancer, HNSCC, cutaneous melanoma, endometrial cancer, colorectal carcinoma, ESCC and MCL [7, 40]. Furthermore, its clinical importance highlights the therapeutic potential through targeting cyclin D1-CDK4/6 kinase complexes in human cancers [41].

2.2 Cyclin D2

Less is known about the contribution of cyclin D2 to tumor development and progression. Cyclin D2 is a downstream target of c-Myc and RUNX1/ETO oncogenes [42, 43]. Hyperactivation of proto-oncogenic signaling by these oncogenic factors accelerates cell cycle progression in part through increased cyclin D2 transcription. In addition, the CCND2 gene is amplified in glioblastoma and anaplastic astrocytoma, but without significant overexpression of cyclin D2 mRNA [44] (Table 1). In contrast, in gastric cancer, overexpression of cyclin D2 is the consequence of hypermethylation of CCND2 promoter [45, 46]. In addition to the aforementioned mechanisms, cyclin D2 mutations are identified in patients with acute myeloid leukemia (AML) [47]; these mutations, localize to the C-terminus, which contains sequences that direct ubiquitin-dependent degradation and thus the mutations appear to contribute directly to increased stability of cyclin D2 protein. In T-cell acute lymphoblastic leukemia (T-ALL), chromosomal translocations involving CCND2 locus and T-cell receptors have been revealed to account for the overexpression of cyclin D2 [48]. Furthermore, the stability of cyclin D2 mRNA is also regulated by microRNAs in thyroid carcinoma [49], NSCLC [50], prostate cancer [51], and oral squamous cell carcinoma [52]; insufficient expression or lack of those microRNAs also results in elevated cyclin D2 protein levels. Overexpression of cyclin D2 is associated with tumor invasion, metastasis and the prognosis in patients with colon cancer and gastric carcinoma [53–55].

2.3 Cyclin D3

Cyclin D3 is also implicated in human cancers of hematopoietic origin [56]. Genomic rearrangements of CCND3 locus are found in multiple myeloma and diffuse large cell lymphoma. In addition, several microRNAs like miR-4779, miR-212, miR-138, and miR-503 can destabilize cyclin D3 mRNA and block cell cycle progression in cell lines derived from colon cancer, T-cell leukemia/lymphoma, lung cancer, and hepatocellular carcinoma (HCC) [57–60]. Like cyclin D1, cyclin D3 protein degradation is determined by a C-terminal phospho-degron [61, 62]. However, the E3 ligase that directs phosphorylation-dependent and ubiquitylation-dependent degradation of cyclin D3 remains to be identified. Mutations at the conserved threonine (Thr283) occur at high frequency in Burkitt's lymphoma resulting in elevated cyclin D3 protein levels [56, 63]. In addition, dysregulation of cyclin D3 also occurs in HCC, gliomas, bladder carcinoma, prostate cancer and osteosarcoma, wherein cyclin D3 expression correlates with increased cell proliferation and tumor growth [53]. Although it remains to be established whether cyclin D3 or mutant cyclin D3 possesses the tumor promoting capability comparable to cyclin D1, it has been demonstrated to be indispensable for the maintenance of T-ALL [64].

3. Ubiquitylation-medicated protein degradation

3.1 Protein degradation via the UPS

Protein abundance reflects the balance of protein synthesis versus protein degradation [65]. Ubiquitin itself is a stable and highly conserved protein with 76 amino acids [66]. Ubiquitin is initially covalently conjugated through its C-terminal carboxylate group (glycine residue) to an available amino group of a lysine residue within substrate proteins. Additional ubiquitin molecules are linked through the utilization of one of seven internal lysine residues (Lys6, Lys11, Lys27, Lys29, Lys33, Lys48 and Lys63) [67]; the precise lysine linkage determines whether the substrate protein is destined for degradation in the 26S proteasome (e.g. Lys48) or for other fates (e.g. Lys63). Thus, different linkages and lengths of ubiquitin chains render diverse different biological functions [68, 69].

Protein ubiquitylation is catalyzed by the coordinated action of three enzymes: E1, ubiquitin-activating enzyme that produces an active ubiquitin using ATP hydrolysis to generate a thioester linkage between itself and ubiquitin molecule; E2, ubiquitin-conjugating enzyme that is both an ubiquitin receptor for E1 and an ubiquitin donor for substrates in concert with an E3; E3, ubiquitin ligase that binds to an E2 and its substrates to assist ubiquitin transfer from the E2 to a substrate or directly recognizes and conjugates ubiquitin to its targets [70–72] (Fig. 2). Currently, there are two E1s, approximately forty E2s, and more than six hundred E3s have been identified in human genome [73]. The E3 generally provides the specificity for this system, with each E3 specifically targeting a small subset of substrates. There are four groups of E3 ubiquitin ligases, including Really Interesting New Gene (RING), U-box, Homologous to E6-Associated Protein C-Terminus (HECT), and Ring-between-Ring (RBR).

3.2 Skp1-Cul1-F-box E3 ubiquitin ligases

RING E3 ubiquitin ligases have a conserved RING finger domain, which serves as the docking domain for E2s and facilitates the catalytic activity of ubiquitin ligases [74]. RING E3s are divided into four subgroups: Cullin RING ligases (CRL), Anaphase Promoting Complex/Cyclosome (APC/C), mono-subunit ligases, and Fanconi Anemia (FANC) E3 ligase [75–77]. G_1 to S-phase transition is in part regulated by Cul1 based RING E3 ligases; Cul1 functions as a scaffold protein for large molecular complex composed of Skp1, Cul1, Rbx1 (with the Ring box domain), and an F-box protein, which functions as a substrate specific adaptor, hence termed SCF complex.

F-box proteins are a family of proteins with an F-box motif that contains 40–50 amino acids and serves as a docking domain for protein-protein interaction [78]. In human genome, there are approximately 69 F-box proteins, which are categorized into three subfamilies: Fbxw (WD40 repeats as a substrate binding domain), Fbxl (leucine-rich repeats (LRRs) as a substrate binding domain), and Fbxo (with other substrate binding domains) [79]. There are 10 members of Fbxw proteins that are mainly involved in cell cycle regulation and tumorigenesis [80]. As for Fbxl proteins, there are 22 different members with LRR domains formed by 20–29 amino acids that are crucial for substrate recognition and integration [81]. Although without clearly defined C-terminal regions, Fbxo proteins have diverse binding

domains like proline-rich domains, cyclin box, zinc-finger, and so forth. Generally, different F-box proteins can target a specific group of substrates based on their unique ‘degron’ motifs.

3.3 Deubiquitinase (DUB)

Besides the enzymes catalyzing ubiquitylation, there is another group of enzymes termed DUB, which favors the recycle of ubiquitin and prevents it from 26S proteasome-mediated degradation. In human genome, there are about 100 DUBs that normally reside in proteasome [82]. The balance between ubiquitylation and deubiquitylation works in a Yin-Yang manner to control the intracellular abundance of ubiquitin and its substrates. Importantly, the recycle of ubiquitin benefits the cells through saving energy and facilitating the translocation of substrates in-and-out of narrow pores. DUBs specifically recognize their substrates based on the linkage of ubiquitin chain. Functionally, DUBs can trim or deubiquitylate the ubiquitin chains conjugated to their substrates, thereafter, change the stability, localization or functions of targeted proteins [83].

4. Ubiquitylation-mediated degradation of D cyclins

D cyclins are highly labile proteins with short half-lives ranging from 10–60 min depending on cell lines investigated [9, 14, 84–86]. As oscillating proteins, the ubiquitylation and degradation of D cyclins is cell cycle dependent, and these processes are normally regulated by the phosphorylation of D cyclins [14, 86] (Fig. 3). D cyclins are critical regulators of cell cycle progression from G_1 to S phase; therefore, their degradation mostly happens in late G_1 phase and early S phase [2, 87, 88]. However, some studies revealed controversial findings with cyclins D2 and D3 being ubiquitylated and degraded during G_2-M transition [84, 85]; additionally, there are also controversies regarding the importance of phosphorylation as an initiating event prior to the ubiquitylation of D cyclins.

4.1 Ubiquitylation and degradation of cyclin D1

Cyclin D1 is broadly expressed in a variety of mammalian cell types, with the notable exception in cells of hematopoietic origin. In the presence of mitogenic stimuli and abundant nutrients, cyclin D1 is synthesized; to perform its functions, cyclin D1 assembles with CDK4 or CDK6 to form a kinase complex; conversely, growth factor withdrawal or nutrient depletion compromises the formation of new cyclin D1-CDK4/6 complexes, leading to an immediate degradation of cyclin D1 in order to facilitate cell cycle exit [6]. Previous work demonstrated that cyclin D1 is phosphorylated at Thr286 during the G_1-S transition, and this phosphorylation in turn directs export of cyclin D1 from the nucleus to the cytoplasm where cyclin D1 is ubiquitylated and degraded by the proteasome [14, 89]. This entire regulatory process depends exquisitely upon Thr286 phosphorylation as mutation of the threonine acceptor results in a constitutively nuclear and stable cyclin D1 [89, 90]. Critically, Thr286 is mutated in a number of cancers including uterine and endometrial cancers [89, 91], and the expression of mutant alleles is sufficient to drive spontaneous cancers in mice [92], highlighting the true oncogenic potential of cyclin D1.

Glycogen synthase kinase-3β (GSK-3β) is the primary Thr286 kinase [14]. The activity of GSK-3β is regulated by Ras via PI3K-Akt signaling. This pathway is regulated by growth factor receptors that provide a direct link from growth factor signaling to the regulation of cyclin D1 stability and accumulation [93]. Critically, any cancer derived mutations that dysregulate signaling through Ras-PI3K-Akt-GSK-3β will directly impact and dysregulate cyclin D1, contributing to excess nuclear cyclin D1-CDK4/6 activity and this is a frequent occurrence in many cancer types independent of direct genetic alterations in the CCND1 locus [94–96]. In addition to GSK-3β, other Thr-286 kinases have been proposed including p38SAPK2 and ERK2 [97, 98], and Thr288 kinase such as mirk/Dyrk1b [99].

It is not uncommon that more than one E3 ubiquitin ligase mediates the ubiquitylation and degradation of proteins like the master regulators mediating cell cycle progression. For example, c-Myc can be ubiquitylated and degraded by more than one E3 ubiquitin ligases like Fbxw7, Skp2, CHIP, Fbxo29, etc. [100–103]. Ubiquitylation of cyclin D1 has been linked with E3 ubiquitin ligases including Fbxo4, Fbxo31, β-transducin repeat-containing protein (β-TrCP) and APC/C [87, 98, 104–106] (Table 2).

4.1.1 Fbxo4-mediated cyclin D1 degradation—Fbxo4 belongs to the F-box protein family with a conserved F-box domain [65]. Several substrates have been identified as Fbxo4 targets such as cyclin D1, Fxr1, Trf1, Peroxisome-Proliferator-Activated Receptor gamma (PPAR-γ), Mcl-1, and ICAM-1 [65, 107–113]. Structurally, Fbxo4 has four domains: C-terminal D domain for dimerization, F-box domain for interacting with Skp1, linker region, and N-terminal region for substrate recognition and interaction [95]. Like many other E3 ubiquitin ligases such as Skp2, Fbxw7 and β-TrCP, Fbxo4 normally forms homodimers in order to perform the E3 ubiquitin ligase function [107]. The dimerization of Fbxo4 is regulated by the phosphorylation of Ser12 in D domain, which is typically catalyzed by GSK-3β [114]. The significance of Fbxo4 phosphorylation is testified by data from mammalian cells with ectopically expressing S12A mutant that loses its dimerization capacity as well as E3 ubiquitin ligase activity.

Mass spectrometry screening revealed both Fbxo4 and αB-crystallin as binding partners of cyclin D1 in NIH3T3 cells [87]. Biochemical analyses demonstrated the interaction between Fbxo4 and cyclin D1 mainly depends on the phosphorylation at Thr286 in cyclin D1 and the presence of αB-crystallin. Like introduced above, cyclin D1 is commonly phosphorylated at Thr286 during G_1-S transition; not surprisingly, Ser12 phosphorylation of Fbxo4 also oscillates accordingly across the cell cycle, resulting in a prominent enrichment of the association of Fbxo4 with cyclin D1. Upon phosphorylation, cyclin D1 is transported from nucleus to cytoplasm where homodimerized SCF^{Fbxo4} complex ubiquitylates and targets cyclin D1 to proteasome for degradation [115]. With regard to the importance of cyclin D1 in cell cycle regulation, loss of function mutations in Fbxo4 lead to the accumulation of cyclin D1, cell cycle progression, cell proliferation, and eventually tumor development and progression.

Taking advantage of available human ESCC tumor samples, we screened and identified Fbxo4 mutations in these tumors, and defined the importance of Fbxo4 in ESCC development [1, 107]. In human ESCC, the majority of Fbxo4 mutations present in the N-

terminal region, for example, S8R, S12L, P13S, L23Q and G30N that undoubtedly disrupt the dimerization and activation of Fbxo4 without changing the ability for substrate recognition. In addition, it is as well revealed another mutation, P76T, which abrogates Skp1 binding and produces a dominant-negative form similar to the mutant with the deletion of F-box domain. Furthermore, the protein levels of cyclin D1 are elevated and accumulated in the nuclei in all ESCC samples harboring Fbxo4 mutations. The transformation phenotype related to cells expressing Fbxo4 mutants unquestionably supports that compromising the activity of cyclin D1 E3 ubiquitin ligase is oncogenic; therefore, Fbxo4 is defined as a tumor suppressor. However, in human HCC, it is identified a different mechanism how Fbxo4 activity is regulated. Sequencing analyses demonstrate four different Fbxo4 isoforms in HCC: α isoform with full length of amino acids, β isoform with 7 more amino acids encoded by code in intron5 and a sequence replacement of exon6, γ isoform without 168–245 nt in exon1, and δ isoform without exon6, among which only the α isoform can mediate the ubiquitylation and degradation of cyclin D1 [116].

These findings in heterozygous and knockout mice confirmed the tumor suppressor activity of Fbxo4. For example, Fbxo4−/− or Fbxo4−/+ mice can spontaneously develop diverse tumors including lymphoblastic lymphoma, extramedullary hematopoiesis/intense myeloid proliferation, hemangioma/angioinvasive tumor, dendritic cell tumor, histiocytic sarcoma, early myeloid tumor, mammary carcinoma, and uterine tumors [117]. Moreover, loss of Fbxo4 facilitates the development of N-nitrosomethylbenzylamine (NMBA)-induced papilloma in mice [118]. Importantly, loss of Fbxo4 also enhances the aggressiveness of melanoma in $Braf^{V600E/+}$ mouse models, highlighting the importance of Fbxo4 as a factor related to tumor progression [95].

4.1.2 Additional F-box E3 ubiquitin ligases for cyclin D1—

Fbxo31 is a senescence-related F-box protein. Under physiological conditions, Fbxo31 is highly expressed in brain and fat tissues, but its expression is low in stomach, pancreas and breast tissues as well as in bone marrow [119]. Under pathological conditions, Fbxo31 plays crucial roles in DNA damage response and tumorigenesis; however, the function of Fbxo31 varies in a context dependent manner in human cancers, for example, it has been detected that loss of heterozygosity of FBXO31 gene in HCC, prostate cancer, breast cancer and ovarian carcinoma [120]. A genome-wide RNA knockdown analysis revealed Fbxo31 is a key factor controlling BRAF-induced senescence in primary fibroblasts and melanocytes; moreover, overexpression of Fbxo31 can induce G_1 cell cycle arrest in a cyclin D1-depdendent manner [104]. Biochemical analyses found Fbxo31 directly interacts with cyclin D1, ubiquitylates and targets it to proteasome for degradation that requires the phosphorylation of cyclin D1 at Thr286. While another structural analysis demonstrated that cyclin D1 phosphorylation at Thr286 is not essential for its association with Fbxo31, and thereafter ubiquitylation by SCF^{Fbxo31} complex. Consistent with previous reports, T286A cyclin D1 mutant is mainly localized in the nucleus; however, this phospho-dead mutant can still be ubiquitylated by Fbxo31. These findings confirm that phosphorylation at Thr286 is important for nuclear exportation of cyclin D1, but it is not indispensable for Fbxo31-mediated ubiquitylation and subsequent degradation [121]. In addition, Fbxo31 can be induced by DNA-damage stresses like γ-irradiation, ultraviolet irradiation, X-ray irradiation,

oxidative stress or chemotherapeutic agents (etoposide, adriamycin, cisplatin or fluorouracil); under these conditions, cyclin D1 expression is compromised through Fbxo31-mediated degradation, resulting in cell cycle arrest.

β-TrCP is a WD40-repeat containing F-box protein. It regulates both physiological and pathological processes such as cell cycle progression, cell proliferation, signal transduction, and tumor development through targeting its substrates for ubiquitylation and degradation [122]. β-TrCP recognizes its substrates in a phosphorylation-dependent manner, through which a specific binding motif known as degron is phosphorylated at Ser or Thr, for example, DSGxxS sequence or its variants like DSG/DDG/EEG/SSG/TSGxxS/E/D [123]. β-TrCP possesses both tumor-promoting and tumor-suppressing properties because it can promote the degradation of both oncoproteins (β-catenin, YAP, and WEE1) and tumor suppressors (Bim EL, IκB, PDCD4, and CDC25A) [124, 125]. STG28 is a derivative of troglitazone that compromises cyclin D1 expression in a phosphorylation dependent but GSK-3β independent manner; instead, compound screening identified IKKα involved in nuclear exportation, and thereafter the degradation of cyclin D1 [105]. STG28 treatment elevates the expression of β-TrCP, but compromises the expression of Fbxo4, Fbxw8, Fbxw7 and Skp2, suggesting β-TrCP is an E3 ubiquitin ligase targeting cyclin D1 for ubiquitylation. Further biochemical analyses revealed $SCF^{\beta\text{-}TrCP}$ can ubiquitylate and degrade cyclin D1 after STG28 treatment. Cyclin D1 contains an unconventional recognition sequence (^{279}EEVDLACpT^{286}) that can be targeted by β-TrCP; this finding is convinced by mutational and modeling analyses [105]. Interestingly, besides STG28 treatment, nutrient depletion like glucose starvation also promotes cyclin D1 turnover in a β-TrCP-dependent manner, highlighting the physiological relevance of these findings.

4.1.3 APC/C-mediated cyclin D1 degradation—The CCAAT/enhancer binding protein delta (C/EBPδ) is a transcription factor that regulates many aspects of cell functions such as cell proliferation, differentiation, movement, and apoptosis [126]. The diverse functions of C/EBPδ are partially cell type and cellular context dependent. In human cancer cells, C/EBPδ compromises cyclin D1 expression in a proteasome-dependent manner [127]. Mechanistically, C/EBPδ induces the expression of Cdc27/APC3, a subunit of the APC/C complex, resulting in the ubiquitylation and degradation of cyclin D1 [106]. Previous report showed γ-irradiation can mediate the degradation of cyclin D1 depending on the RXXL motif or D-box [128]; moreover, this motif is also a conserved motif of APC/C targets, and it can be recognized by the Cdh1 coactivator. Mutational analyses verified the mutation of RXXL to QXXA successfully blocks the ubiquitylation and degradation of cyclin D1 mediated by Cdc27. Well-known APC/C targets include cyclin A and cyclin B1 that are involved in cell cycle transition from G_2 to M phase [129]; while cyclin D1 is one of the critical regulators for G_1-S transition; therefore, APC/C-mediated cyclin D1 degradation might not play important roles in normal cells. However, this mechanism may help maintaining mitotic viability in cells with Fbxo4 loss or mutations. Further investigations are required to dissect these potential and relative mechanisms.

4.1.4 Discrepancies in E3 ubiquitin ligases targeting cyclin D1 degradation—In addition to the above mentioned E3 ubiquitin ligases, there are additional E3 ubiquitin

ligases implicated in cyclin D1 ubiquitylation and degradation. For example, Skp2 and Fbxw8. Skp2 can form a SCF complex with Cul1 and Skp1 that controls the cell cycle transition from G_1 to S phase [130]. Well known substrates of Skp2 include p21 and p27 [131, 132]. Additionally, one previous study revealed that Skp2 can interact with cyclin D1 and knockdown of Skp2 leads to the accumulation of cyclin D1 [131]. Because both p21 and p27 can stabilize cyclin D1 [133], it is probable that cyclin D1 accumulation upon Skp2 knockdown is the consequence of reduced ubiquitylation and degradation of p21 and p27.

Fbxw8 is an F-box protein that utilizes Cul7. Cul7 indirectly associates with Skp1 in an Fbxw8-dependent manner, and Cul7 demonstrates a higher affinity with Fbxw8 than Cul1 [134, 135]. Biological analysis revealed similar phenotypes of placenta in Fbxw8−/− and Cul7−/− mice, suggesting Fbxw8 and Cul7 can form an E3 ubiquitin ligase complex in order to ubiquitylate and degrade their substrates. The levels of cyclin D1 are constant during S phase in normal cells, while its levels dropped dramatically during S phase. The alteration of cyclin D1 stability is mediated by Thr286 phosphorylation in a Ras-Raf-MEK-Erk signaling-dependent manner in these experiments. Biochemical analyses revealed Fbxw8 specifically associates with cyclin D1 in a phosphorylation-dependent way [98].

However, another study using transgenic mouse models introduced more challenges in E3 ubiquitin ligases that regulate cyclin D1 ubiquitylation and degradation [136]. In this study, several different transgenic mouse models were established with Fbxo4−/−, Fbxw8−/−, and Fbxo4−/− & Fbxw8−/− genotypes. However, no difference of cyclin D1 half-life was monitored in mouse embryonic fibroblasts (MEFs) derived from these transgenic mice, even with the knockdown of Fbxo31 and Skp2 in Fbxo4−/− & Fbxw8−/− MEFs. Although cyclin D1 protein levels are elevated, its regulation was proposed to be transcriptionally regulated in Fbxo31 knockdown MEFs. This is in sharp contrast to a majority of work demonstrating decreased rates of degradation of cyclin D1 in MEFs derived from Fbxo4 deficient MEFs under normal proliferating conditions as well as following a variety of cellular insults [1, 95, 117, 118]. The precise reason for these discrepancies remains to be discerned, but may reflect context-dependent and tissue-specific mechanisms.

4.2 DUBs and cyclin D1 degradation

4.2.1 Ubiquitin Specific Peptidase 2 (USP2)—

USP2 has been identified as a specific DUB for cyclin D1 [137]. USP2 directly interacts with cyclin D1 to perform deubiquitylation and thereby antagonize proteasome-dependent degradation of cyclin D1. Conversely, knockdown of USP2 dramatically shortens the half-life of cyclin D1 and compromises G_1-S transition and cell proliferation in human cancer cell lines. However, these effects are not significant in normal human fibroblasts or in cancer cells without cyclin D1 expression. An independent investigation demonstrated the effects of ML364, a small molecule inhibitor of USP2, on cyclin D1 expression. ML364, a reversible USP2 inhibitor with an IC50 of 1.1 μM, can effectively reduce cyclin D1 protein levels in a time- and dose-dependent manner in human cancer cells; mechanistically, ML364 promotes the ubiquitylation and the proteasome-mediated degradation of cyclin D1, leading to cell cycle arrest and reduced cell proliferation [138]. Consistently, other USP2 inhibitors like

lithocholic acid (LCA) derivative, LCAHA, and 3,3'-Diindolylmethane can also promote cyclin D1 degradation and cell cycle arrest in G_1 phase [139, 140].

4.2.2 USP22—USP22 is a highly conserved DUB from yeast to vertebrates. USP22 functions as a subunit of the human Spt-Ada-Gcn5-acetyltransferase (SAGA) transcriptional coactivator complex [141]. USP22 can alter chromatin structure and gene transcription through deubiquitylating histones H2A and H2B [142]. Elevated USP22 expression is correlated with aggressiveness of human cancer cells and cell cycle progression from G_1 to S phase. In addition to histones, cyclin D1 is also a direct target of USP22 [143]. USP22 function reverses cyclin D1 ubiquitylation; overexpression of cyclin D1 can partially rescue cell cycle arrest in USP22 knockdown cells. Consistent with this functional relationship, CDK4/6 inhibitors inhibit proliferation of cells with ectopic expression of USP22.

5. Targeting D cyclin-related signaling and cancer treatment

5.1 Targeting D cyclin-related CDK4/6 kinases

5.1.1 CDK4/6 kinase inhibitors—D cyclins are overexpressed in a variety of human cancers and elevated D cyclin levels are associated with tumor size, invasion, and metastasis. Although this would suggest that D cyclins are potential therapeutic targets, the fact that D cyclins do not have enzymatic activity makes directly targeting D cyclins a challenge [1, 2]. In contrast, highly specific CDK4/6 inhibitors have been developed, including PD-0332991 (palbociclib), LY2835219 (abemaciclib), and LEE011 (ribociclib), all of which are approved by U.S. Food and Drug Administration to treat patients with tumors [144, 145]. These inhibitors have IC50s in the nanomolar range and are being intensively investigated in biomedical studies and clinical trials to treat human cancers like pancreatic cancer, NSCLC, breast cancer, HNSCC, melanoma, endometrial cancer, ESCC, colorectal carcinoma, MCL, and multiple myeloma [1, 146]. The high potency of CDK4/6 inhibitors sets the stage for new therapeutic options for cancers with overexpression of D-type cyclins. CDK4/6 inhibitors are generally well tolerated with minimal side effects, while the most prominent one is neutropenia [147]. However, the development of resistance to CDK4/6 inhibitors is regarded likely inevitable. While there is much to be learned, some mechanistic insights regarding resistance to CDK4/6 inhibitors have been elucidated and are discussed subsequently.

5.1.2 Mechanisms of resistance to CDK4/6 inhibitors

1) Cell cycle-related mechanisms: Dysregulation of certain factors involved in the cell cycle machinery is a critical contributor to the development of resistance to CDK4/6 inhibitors. Loss of downstream target genes like Rb, Fizzy and Cell Division Cycle 20 Related 1 (FZR1) leads to the bypass of requirement of D cyclin-CDK4/6 for cell cycle progression [1, 148, 149]. In addition, overexpression or hyperactivation of factors directly or indirectly involved in cell cycle regulation are implicated the development of resistance to CDK4/6 inhibitors. Examples include the amplification of CDK4 [150], CDK6 [151], CCNE1/2 [152], CDK2 [153], E2F [154] CDK7, WEE1 and MDM2 [155], the loss of p16 [156], and the activation of HDAC [155].

2) Cell cycle-nonspecific mechanisms: Hyperactivation of mitogenic signaling, such as FGFR [157], PI3K-Akt-mTOR [158], and AP-1 [159], can promote the bypass of pathways for cell cycle progression, and the development of resistance to CDK4/6 inhibitors. Hormone-mediated ER activation is a driver of D cyclin-CDK4/6 activation in breast cancer cells. Loss of ER or PR in resistant tumors in preclinical studies and clinical trials indicates the alteration of ER or PR levels is correlated with the development of resistance [151]. Other mechanisms include the suppression of Smad3, the activation of autophagy, and the change of immune response [155, 160, 161].

5.2 Therapeutic vulnerability targeting degradation machinery for D cyclins

5.2.1 Targeting glutamine metabolism in tumors with dysregulated Fbxo4-cyclin D1—

The importance of glutamine as a key carbon source for many tumor types has recently been noted [162, 163]. Through a process termed glutaminolysis, glutamine is converted to glutamate, and this process is catalyzed by the glutaminase enzyme (GLS) [164, 165]. Glutamine can be utilized as an energy source, a nitrogen source, and a substrate-donor for glutathione synthesis. Recent work from a number of laboratories have demonstrated that oncogene-dependent transformation of normal cells to tumorigenic cells is associated with increased glutamine dependency. Such tumor cells require glutamine for survival and proliferation, and they are considered glutamine-addicted. Glutamine-addiction is associated with the dysregulation of tumor promoting oncoproteins such as c-Myc, N-Myc, ErbB2 or the inactivation of tumor suppressors like p53 and Rb [1, 166]. Glutamine-addiction of Rb deficient cells has broad sweeping implications given that Rb can be functionally inhibited by phosphorylation, an event mediated by cyclin D1-CDK4/6 kinases. This implies that cells with dysregulated cyclin D1-CDK4 would exhibit glutamine-dependency. Indeed, recent work revealed that oncogenic mutations in cyclin D1 driving its nuclear overexpression or inactivating mutations of the cyclin D1 E3 ubiquitin ligase, Fbxo4, can promote glutamine-addiction in mouse embryonic fibroblasts, and tumor cells derived from esophageal cancer [1].

Loss of Fbxo4 results in reduced cyclin D1 degradation and triggers a corresponding increase in CDK4/6 activity and a tumor prone phenotype in Fbxo4 deficient mice [117, 118]; for example, mice with the loss of Fbxo4 exhibit increased sensitivity to NMBA-induced gastrointestinal tumors [118]. Consistent with cyclin D1 as a critical Fbxo4 target, the NMBA-induced tumors are sensitive to treatment with palbociclib. With regard to glutamine metabolism in esophageal cancers, upregulation of GLS is observed in primary ESCC tissues, consistent with the findings that ESCC cells harboring dysregulated Fbxo4-cyclin D1 are glutamine-addicted [1]. Accordingly, the dysregulation of Fbxo4-cyclin D1 enhances the dependency of ESCC cells on glutamine in accordance with cell proliferation and growth. Furthermore, the dysregulation of Fbxo4-cyclin D1 not only drives glutamine-addiction through Rb inactivation and mTORC1 hyperactivation, but also promotes glutamine uptake as well as GLS expression [1].

Besides driving glutamine-addiction, loss of Fbxo4 or overexpression of cyclin D1 also compromises mitochondrial activity and oxidative phosphorylation, leading to deficient energy production [1]. These metabolic vulnerabilities make tumor cells with dysregulated

Fbxo4-cyclin D1-CDK4/6-Rb sensitive to combined treatment with CB-839 (GLS inhibitor) and metformin, leading to energy catastrophe and apoptosis in cell culture and in mouse xenografts. This pre-clinical study provides a potential therapy for various human cancers with cyclin D1 overexpression like pancreatic cancer, NSCLC, breast cancer, HNSCC, and melanoma, or tumors with Rb loss, such as, small cell lung cancer [167], and genitourinary cancers [168–170].

5.2.2 Targeting β-TrCP mediated cyclin D1 degradation—Troglitazone, rosiglitazone, and pioglitazone are synthetic ligands of PPAR-γ, and they are approved for treating type II diabetes [171]. In addition, all three compounds exhibit antitumor effects in pre-clinical studies and favorable outcomes in some clinical trials involving in thyroid carcinoma, glioma, prostate cancer, colon cancer, lung cancer, breast cancer, sarcoma, and melanoma [172, 173]. Although the molecular mechanisms remain undefined, troglitazone at high concentration can promote the ubiquitylation and degradation of cyclin D1 in breast cancer cells. STG28, a new PPAR-γ-inactive form of troglitazone, can effectively compromise cyclin D1 expression in a Thr286 phosphorylation-dependent manner [105]. STG28 can upregulate the expression of E3 ubiquitin ligase, β-TrCP, and promote the translocation of cyclin D1 into cytoplasm, where β-TrCP interacts with cyclin D1, enhances its ubiquitylation and degradation, highlighting the therapeutic potential of STG28 to treat human tumors with cyclin D1 overexpression.

5.2.3 Targeting USP2 and promoting cyclin D1 degradation—Another dimension of new therapies is through the development of inhibitors targeting deubiquitinating enzymes (DUBs) that antagonize ubiquitylation and degradation of cyclin D1. As such, various inhibitors have been developed based on the mechanisms how specific DUB performs its functions. However, it is critical to develop inhibitors with specificity that determines the efficiency and usability of these inhibitors. Several compounds have been shown to suppress the activity of USP2, which can promote the deubiquitylation and stability of cyclin D1 [137]. For example, LCAHA, ML364, and 3,3’-diindolylmethane (DIM), all of which can successfully suppress USP2, and enhance the ubiquitylation and degradation of cyclin D1, leading to reduced cyclin D1 protein levels [138–140]. Therefore, these compounds effectively block cell cycle progression from G_1 to S phase. Importantly, LCAHA can effectively antagonize the proliferative signals delivered by the presence of mitogenic stimuli in a cyclin D1 dependent manner.

6. Conclusion and future perspectives

As a central hub sensing extracellular stimuli and driving cell cycle progression, D cyclins act as a switch to integrate cell division with cell proliferation and growth. As such, D cyclins have critical roles in both normal and tumor cells. In general, the expression of D cyclins is dysregulated in various human cancers and cyclin D1 is regarded as an oncogenic driver in cancers including breast cancer, lung cancer, melanoma and HNSCC. Moreover, CCND1 gene, encoding cyclin D1, is broadly amplified with an incidence rate about 15–40% in human tumors. MCL has about ninety percent of CCND1 gene translocation with immunoglobulin heavy chain locus, while a small group of patients have the overexpression of cyclin D1 or cyclin D3. Although there are reports of CCND2 and CCND3 gene

amplification, the incidence rate is dramatic low comparing to that of CCND1 gene. Interestingly, CCND2 promoter is frequently methylated, leading to the loss of cyclin D2 in pancreatic, breast and prostate cancer, raising questions regarding its function in these tumors.

Currently, the best opportunity for targeting D cyclins is through inhibition of CDK4/6. High efficacy of CDK4/6 inhibitors endows them as favorable therapies for a variety of tumors with the overexpression of D cyclins. However, the development of resistance is one major challenge that cannot be overlooked. Opportunities to overcome resistance include: 1) combined treatment with inhibitors that target signaling pathways driving resistance (inhibition of mTOR or MEK signaling); 2) identification of alternative weaknesses that develop as a consequence of CDK4/6 inhibitor resistance (e.g. GLS inhibitors in Rb deficient tumors). It is critical to ascertain the molecular basis for acquired resistance to CDK4/6 inhibitors in order to develop new therapies. Additional opportunities may pertain to the molecular machinery related to ubiquitylation-mediated degradation of D cyclins. For example, targeting DUBs that antagonize cyclin D degradation. Further studies are required to investigate the detailed molecular mechanisms how DUBs control the ubiquitylation and degradation of D cyclins, especially, the structural analyses of DUBs that will facilitate the development of inhibitors with high specificity and potency. A collective understanding of cyclin D post-translational regulation will benefit patients with tumors harboring the overexpression of D cyclins.

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List of Abbreviations:

CDK	cyclin-dependent kinase
INK4	Inhibitors of CDK4
CIP/KIP	CDK interacting protein/kinase inhibitor protein
Akt	Protein Kinase B
Myc	MYC Proto-Oncogene, BHLH Transcription Factor
RUNX1/ETO	RUNX Family Transcription Factor 1
Cul1	Cullin 1
Skp1	S-phase kinase-associated protein 1
Rbx1	Ring-Box 1
Cdh1	Cadherin 1
p38SAPK2	Stress-Activated Protein Kinase-2
ERK2	Extracellular Signal-Regulated Kinase 2

CHIP	STIP1 Homology And U-Box Containing Protein 1
Fxr1	FMR1 Autosomal Homolog 1
Trf1	Telomeric Repeat Binding Factor 1
Mcl-1	Myeloid Cell Leukemia 1
ICAM-1	Intercellular Adhesion Molecule 1
YAP	Yes Associated Protein 1
WEE1	WEE1 G_2 Checkpoint Kinase
Bim EL	BIM-extra long
IκB	inhibitor of κB
PDCD4	Programmed Cell Death 4
CDC25A	Cell Division Cycle 25A
IKKα	Inhibitor of κB kinase α
ErbB2	Erb-B2 Receptor Tyrosine Kinase 2
mTOR	Target Of Rapamycin Kinase
MDM2	MDM2 Proto-Oncogene
HDAC	Histone Deacetylase
FGFR	Fibroblast Growth Factor Receptor
AP-1	Activator protein 1
ER	Estrogen Receptor
PR	Progesterone Receptor
MEK	Mitogen-activated protein kinase kinase

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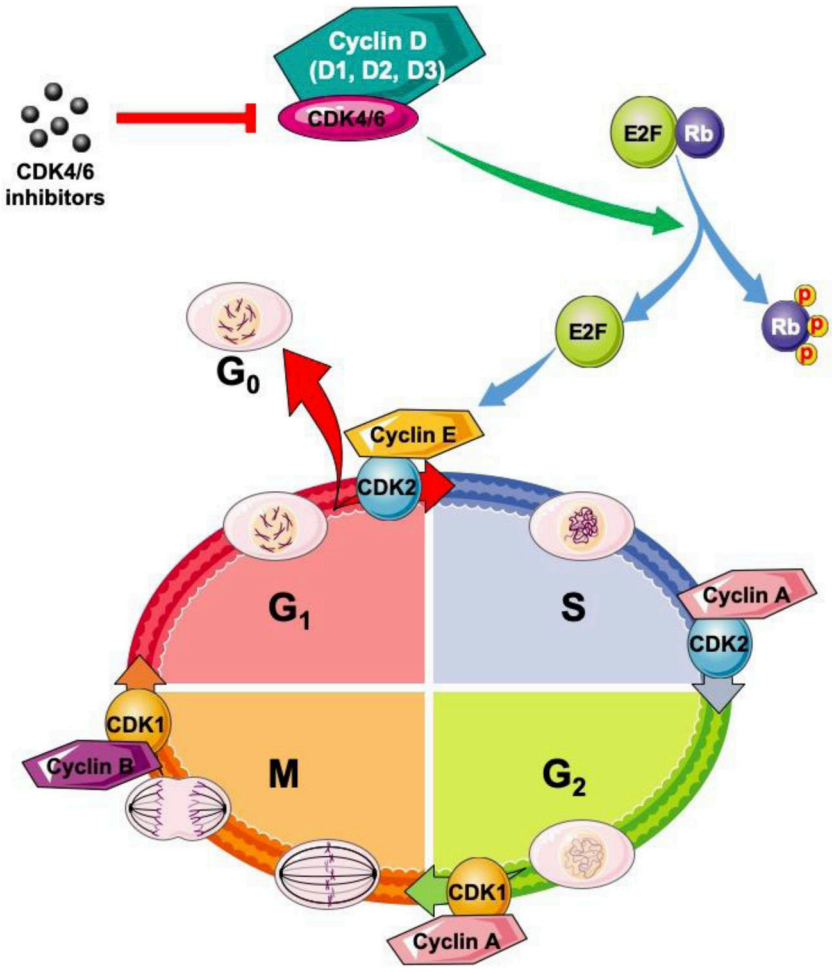

Figure 1. Schematic illustration of cell cycle regulation.

Cell cycle is divided into four phases: G_1 (gap phase 1), S (DNA synthesis), G_2 (gap phase 2), and M (mitosis). Cell cycle progression is regulated by cyclins and their cognate CDKs. As the important regulator of G_1 phase, CDK4/6 inhibitors have been developed, for example, PD-0332991 (palbociclib), LY2835219 (abemaciclib), and LEE011 (ribociclib) that are approved by U.S. Food and Drug Administration to treat human tumors.

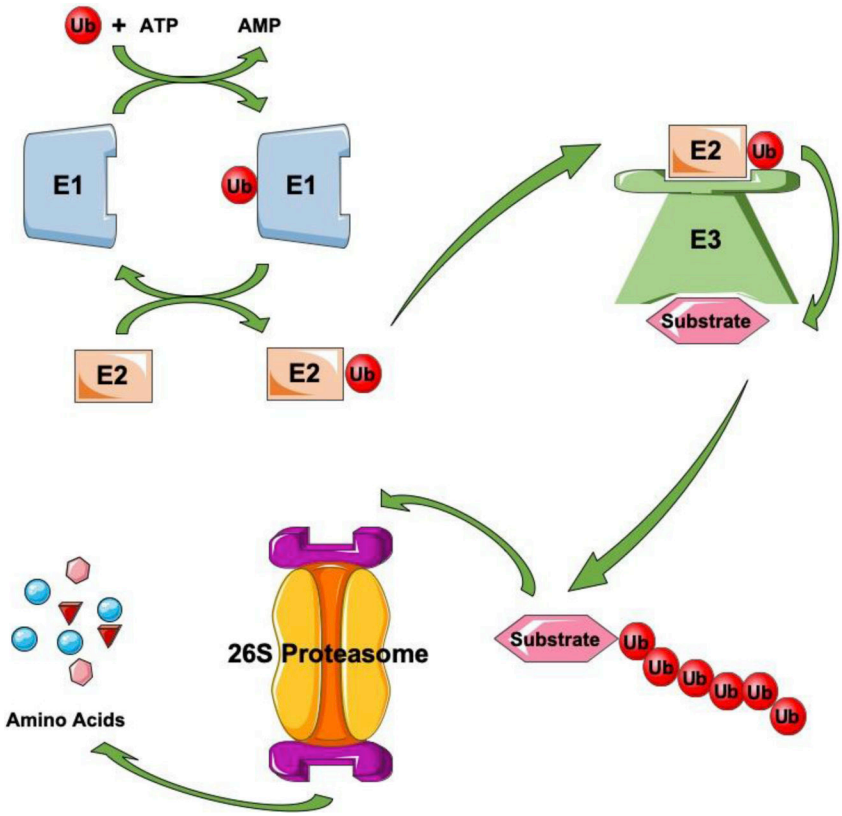

Figure 2. Ubiquitylation-medicated protein degradation.

Protein ubiquitylation is catalyzed by the concerted and coordinated action of three enzymes: E1, ubiquitin-activating enzyme that produces an active ubiquitin using energy to generate a thioester linkage between itself and ubiquitin molecule; E2, ubiquitin-conjugating enzyme that is both an ubiquitin receptor for E1 and an ubiquitin donor for substrates or E3s; E3, ubiquitin ligase that binds to E2s and its substrates to assist ubiquitin transfer from E2s to substrates or directly recognizes and conjugates ubiquitin to its targets. Polyubiquitylated proteins will be degraded in proteasome, a complex intracellular structure composed of multiple enzymatic complexes.

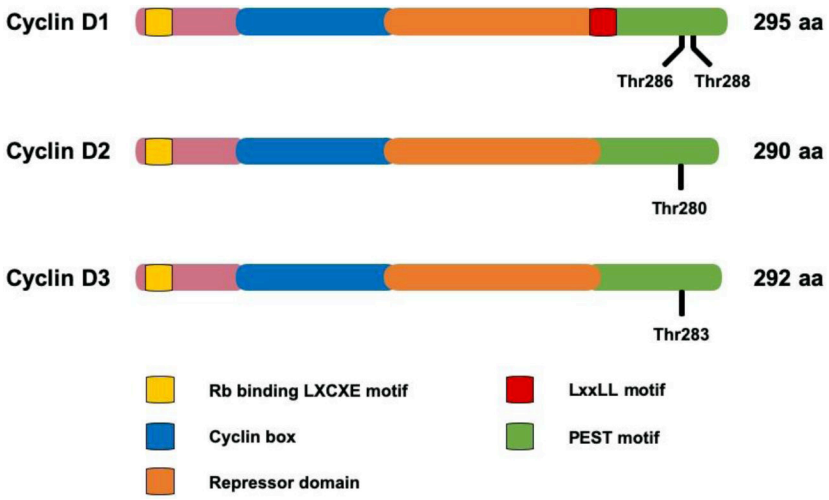

Figure 3. Illustration of phosphorylation sites of D cyclins.

As for phosphorylation-mediated degradation, the conserved sites for Thr286 in cyclin D1 are Thr280 in cyclin D2 and Thr283 in cyclin D3, respectively.

Table 1

Amplification and overexpression of D cyclins in human tumors

D Cyclin	Enzymes	Tumors	Incidence Rate	References
D1	*CCND1 Amplification*	ESCC	23–57%	[31, 32, 174]
		HNSCC	26–39%	[27, 175]
		NSCLC	5–30%	[22, 23]
		Endometrial cancer	26%	[29, 30]
		Melanoma	0–25%	[7, 28]
		Pancreatic cancer	25%	[7, 21]
		Breast cancer	15–20%	[22, 25]
		Colorectal carcinoma	2.5%	[7, 176]
	Overexpression	ESCC	42–87%	[177, 178]
		HNSCC	20–68%	[27, 175]
		NSCLC	18–76%	[24, 58, 179]
		Endometrial cancer	40–56%	[29, 30]
		Melanoma	30–65%	[7, 28]
		Pancreatic cancer	42–82%	[7, 21]
		Breast cancer	50–70%	[22, 25]
		Colorectal carcinoma	55%	[7, 180]
D2	*CCND2 Amplification*	Germ cell tumor	15.38%	[181]
		Adrenal carcinoma	12%	[182]
		Glioma	1.95–5%	[44, 181, 182]
		ESCC	0.58–5%	[181, 182]
		Lung SCC	1–4%	[181, 182]
		Colorectal carcinoma	0.97–3%	[181]
		Breast cancer	0.61–3%	[181, 182]
		Non-Hodgkin lymphoma	0.92%	[181]
	Overexpression	Lymphoplasmacytic lymphoma	100%	[183]
		B-cell chronic lymphocytic leukemia	85%	[183]
		Colon carcinoma	57%	[184]
		AML	47%	[183]
		Gastric cancer	26.2%	[55]
		Diffuse large B-cell lymphoma	10.6%	[185]
D3	*CCND3 Amplification*	Colorectal carcinoma	0.3–21%	[181, 182, 186]
		ESCC	1.78–10%	[181, 182]
		HNSCC	4%	[182]
		Gastric cancer	1.96–3%	[181, 182]
		Breast cancer	0.73–3%	[181, 182]
		Urothelial carcinoma	3%	[182]
	Overexpression	Thyroid carcinoma	72%	[187]
		Melanoma	20–42%	[188]
		B-cell chronic lymphocytic leukemia	20–41%	[189–191]

D Cyclin	Enzymes	Tumors	Incidence Rate	References
		Oral SCC	39%	[192]
		Colon carcinoma	21–35%	[184, 186]
		Breast cancer	30%	[193]
		Non-Hodgkin lymphoma	22%	[194]
		Renal cell carcinoma	16%	[195]

Table 2

Ubiquitylation-mediated degradation of cyclin D1

Enzymes	Cell Lines	Cell Cycle	Phosphorylation-dependency	References
E3 ubiquitin ligase				
Fbxo4	NIH3T3, MEFs, U2OS, MCF-7, TE8, TE10, TE15, 451Lu, WM793B, 1205Lu	G_1-S	Phospho-Thr286 mediated by GSK-3β	[87, 94, 95, 107, 117]
Fbxw8	HCT116, SW480, T98G	G_1-S	Phospho-Thr286 mediated by MAPK/Erk	[98]
Fbxo31	SK-MEL-28	G_1-S	Phospho-Thr286 mediated by MAPK/Erk	[104]
β-TrCP	LNCaP	G_1-S	Phospho-Thr286 mediated by IKKα	[105]
APC/C	MCF-7, MEFs	—	Phospho-Thr286 mediated by GSK-3β	[106]
Deubiquitinase				
USP2	HCT116, MCF-7, U2OS, PC3, 3T3-L1	G_1-S	—	[137, 139]
USP22	HCT116, MCF-7, U2OS, PC3, H1299, 2091	G_1-S	Not depending on Thr286 phosphorylation	[143]