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An Overview of Cyclin D1 (CCND1) over expression in MM

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Abstract

Multiple myeloma is a multifocal hematological disorder, which shows a proliferation of malignant plasma cells in the bone marrow, it represents approximately 1% of all malignancy, causing about 20% of deaths from hematological malignancies. Cyclin D1 is considered an important factor in the cell cycle control; dysregulation of cyclin D1 has an oncogenic role in multiple myeloma patients and can affect their prognosis. Amplification or overexpression of cyclin D1 plays pivotal roles in the development of a subset of human cancers including parathyroid adenoma, breast cancer, colon cancer, lymphoma, melanoma, Multiple myeloma and prostate cancer. Cyclin D1 overexpression is associated with human tumorigenesis and cellular metastases. Cyclin D1 also conveys cell cycle or CDK-independent functions. Cyclin D1 regulates activity of transcription factors, coactivators and corepressors that govern histone acetylation and chromatin remodeling proteins. The recent findings that cyclin D1 regulates cellular metabolism, fat cell differentiation and cellular migration have refocused attention on novel functions of cyclin D1 and their possible role in tumorigenesis.

Keywords: Cyclin D1, Tumorigenesis, Multiple myeloma.

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1. Introduction

One of the B-cell cancers that was discovered by the aberrant proliferation of malignant plasma cells was multiple myeloma (MM). Anemia, renal impairment, hypercalcemia, and osteolytic bone diseases are among the clinical manifestations of M.M. Patients' aberrant immunoglobulin production [1]. The term "cyclins" refers to a family of proteins that exhibit quantitative fluctuations throughout the cell cycle and cyclic expression. DNA replication and cell division are successively coordinated by cyclin production and the activation of their associated cyclin dependent kinases (CDKs) in the various cell cycle stages [2]. Tim Hunt and colleagues' research on fertilized sea urchin eggs, which showed an oscillating protein that was broken down after each division cycle, is where the discovery of cyclins began. Two distinct cyclins, referred known as cyclins A and B, were identified through additional research in various organisms (such as starfish, Xenopus, Drosophila, and S. pombe), and the initial functional investigations indicated that they were necessary for mitosis [3].

2. Types of Cyclins

The production of a class of proteins called cyclins and the subsequent activation of cyclin-dependent kinases (Cdks) are necessary for proper progression through the cell division cycle. The subfamilies (A-B-C-D-E-F-G-H) are scarce. E-type cyclins regulate entry into the S (DNA Synthesis) phase, A-type cyclins regulate entry into the G2 phase, B-type cyclins are important regulators of entry into mitosis (M), and C- and D-types aid entry into the cell cycle during the G1 (Gap 1) phase. Cyclin F and Cyclin A are comparable. Cyclin G is a p53 target that contributes to mitosis and genomic instability [3].

3. Types of cyclin D

- In 1991, it was discovered that cyclin D1, D2, and D3 (encoded by CCND1, CCND2, and CCND3, respectively) were G1 mitogen sensors specific to cell types [3].
- In solid tumors and malignant hemopathies, cyclin D1 is more commonly dysregulated than cyclins D2 and D3 [4].

4. Structure of Cyclin D1

The CCND1 gene, which is found on the 11q13 chromosome [6], encodes the 36-kDa protein [5] known as cyclin D1. A residual threonine that regulates nuclear export and protein stability, a domain for CDK binding or CDK inhibitor, a LxxLL motif that attracts coactivators, a PEST site for Cyclin D1 breakdown, and an RB protein binding section make up the Cyclin D1 protein Figure 1; [5] The greatest homology between the D-cyclins occurs in the cyclin box that mediates cyclin-dependent kinase (CDK) binding and is necessary for interaction with the CDK inhibitors p21,

p27 and p57 [6-7]. The region between the cyclin box and the C terminus contains domains that are responsible for transcription factor– cyclinD1 interactions and is relatively poorly conserved [7]. Through alternative splicing, cyclin D1b, a second human cyclin D1 isoform, is produced. For the first 240 amino acids, it is the same as the full-length, canonical cyclinD1 protein; however, it differs at the carboxy terminus, which means it is missing certain important interaction domains 69 [7]. While Cyclin D2 and D3 do not include (LLXXXL), Cyclin D1 does. In addition to moving between the nucleus and the cytoplasm, cyclin D1 has also been discovered near the cytoplasmic membranes at ruffles in migrating cells [7] or attached to the outer membrane of the mitochondria [6]. The cytosolic or membrane-bound forms of cyclin D1 carry out some of its carcinogenic activities, whereas the nuclear form carries out others [8-9].

5. Function of Cyclin D1

Cyclin D1 plays a role in both neoplasia and regular control of the cell cycle. One important regulator of G1 progression to S phase is cycline D1. In cell biology, cyclin D1 is essential for controlling cell migration, mitochondrial activity, DNA repair, and proliferation and growth [2].

*5.1. *Normal cell cycle and function cyclin D1*

The resting phase (G0) of a typical cell cycle occurs when the cell exits the cycle and ceases to divide. This is the point at which the cell cycle begins. The subsequent stage, known as the interphase, begins with G1 (gap 1), during which the cell grows larger. The process that makes sure the cell is prepared for DNA synthesis is managed by this G1 checkpoint [10]. DNA replication takes place during the second interphase phase, known as the S phase (synthesis). After that, the cell moves into the G2 (gap 2) phase, which guarantees that the cell is prepared for mitosis while it continues to grow. Cell development stops during the M phase (mitosis), and all of the cell's energy is directed toward the daughter cells' orderly division. To guarantee proper cell division and the creation of offspring cells with intact genomes, all of these processes—cell division, DNA replication, and cell growth—must occur in unison. The cell cycle is the series of processes that a cell goes through to replicate its genome, produce its other components, and ultimately split into two daughter cells Finger 2; [10].

Normal cell proliferation requires growth factors, which in turn regulate the activation of regulatory proteins that govern the cell cycle's progression through the G1 phase. Later on, the cells can overcome the G1 restriction point and advance through the cell cycle even without mitogens. An essential objective of cell cycle research has been to comprehend the molecular underpinnings of the G1 restriction point. E2F factor and retinoblastoma (Rb) protein have been identified as the restriction point's mediators. E2F family members are released when Rb and associated proteins are phosphorylated in the late G1 phase. These members subsequently control the transcription of genes required for the advancement of the S phase. Complexes of cyclin and cyclin-dependent kinase 3 (CDK3) phosphorylate Rb [10]. Cell division is facilitated by the sequential completion of DNA replication, which is made possible by the combination of distinct cyclins and subsequent CDK activation at specific cell cycle stages. These kinases are also responsible for the checkpoints that halt cell cycle progression, resulting in damage to DNA and abnormalities in the mitotic axle [10-11].

5.2. Amplification or Overexpression of Cyclin D1

Cyclin D1 overexpression is a characteristic of several carcinomas. For example, overexpression of Cyclin D1 or amplification of the CCDN1 gene sequence causes dysregulated CDK activity, changes in cell cycle regulation, circumvention of important cellular checkpoints, stimulated cell proliferation, and eventually neoplastic development [5].

5.3. Cyclin D1 play an important rule in some solid tumor

Such as hepatocellular carcinoma, overian cancer, lung cancer, melanoma, colorectal cancer, breast, prostate, thyroid, and cellular metabolism impacting the growth of cancer cells [5].

5.4. Cyclin D1 play an important role in some hematological malignancy

Numerous lymphoid and myeloid cancers, such as mantle cell lymphoma, multiple myeloma, acute lymphoblastic leukemia, and hairy cell leukemia, have been linked to cyclin D1. Additionally, B-cell chronic lymphocytic leukemia (BCLL) has been found to contain it [12].

5.5. CyclinD1 in mantel cell lymphoma

The clinical behavior of mantle cell lymphoma (MCL), a mature B-cell lymphoid tumor, varies from aggressive evolution in most individuals, which necessitates rapid treatment, to an indolent course that can be controlled with conservative approaches. The translocation t(11;14)(q13;q32), which results in cyclin D1 overexpression, is the first oncogenic event of MCL [10].

5.6. CyclinD1 in aute lymphoplastic leukemia

In ALL, cyclin D1 is overexpressed. The survival outcome for ALL was adversely affected by elevated cyclin D1 levels, indicating that this gene contributes to the malignant character of ALL [13].

*5.7. Cyclin D1 over expression in MM **

The primary characteristic of multiple myeloma (MM), the second most common tumor in the hematological system, is the clonal proliferation of cancerous plasma cells in the bone marrow.Forty percent of MM patients exhibit the double allele known as CCND1, which is primarily hyperdiploid [14]. The CCND1 gene expresses cyclin D1, a member of D1 cyclin family plays a role in the carcinogenesis and development and facilitates the transition from the G1 phase to S phase by controlling the transcription factor E2F-1 [15].

5.8. Unscheduled proliferation of myeloma cells

The dysregulation of cyclin D and the inhibitors of the INK4 family are the primary causes of the unplanned growth of myeloma cells. One of the main characteristics of MM is the dysregulation of cyclin D expression, which is typically brought on by translocations of the IgH locus. The most common translocation, t(11;14), causes cyclin D1 expression to be up regulated. A MAF transcription factor (c-MAF and MafB, respectively) is overexpressed in both t(14;16) and t(14;20) translocations, whereas MMSET is deregulated in t(4;14) translocations [16].

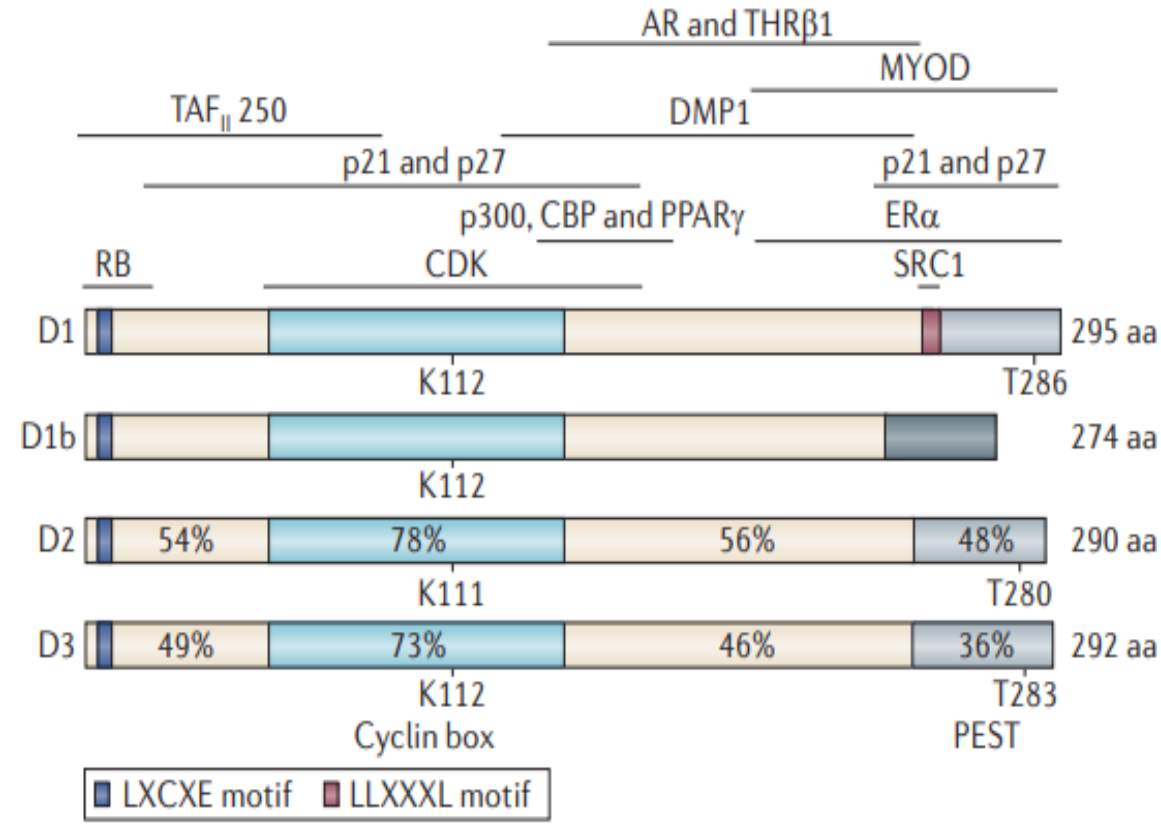
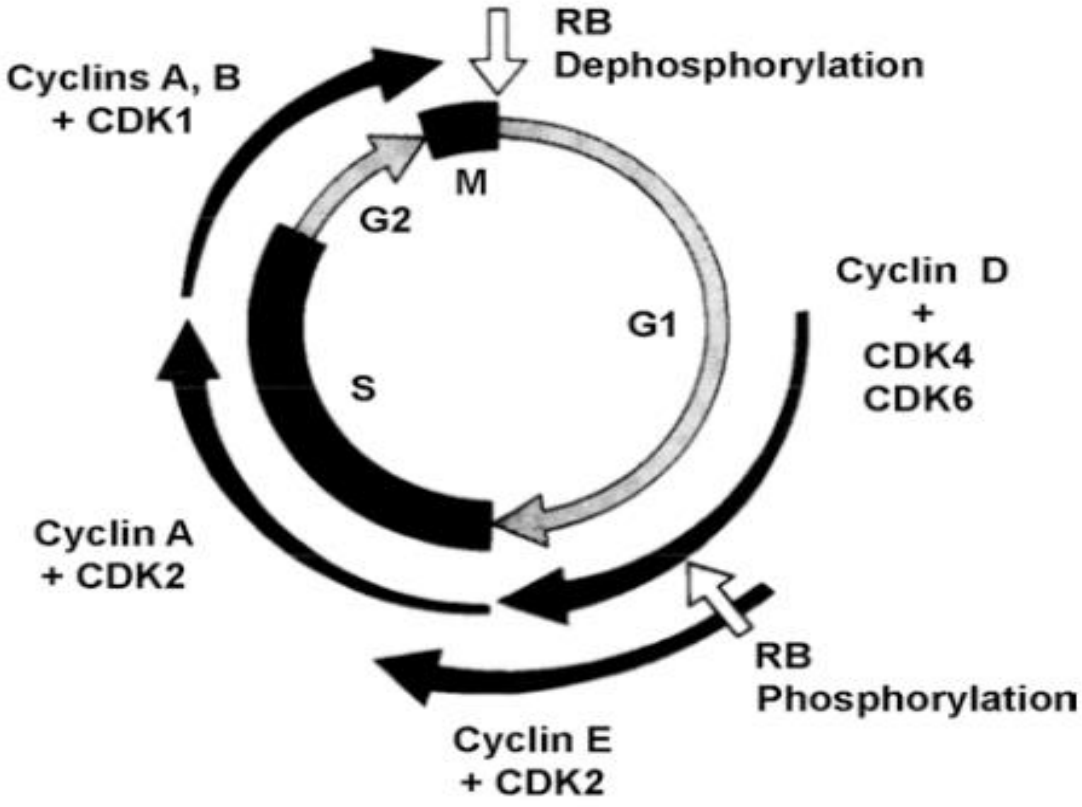
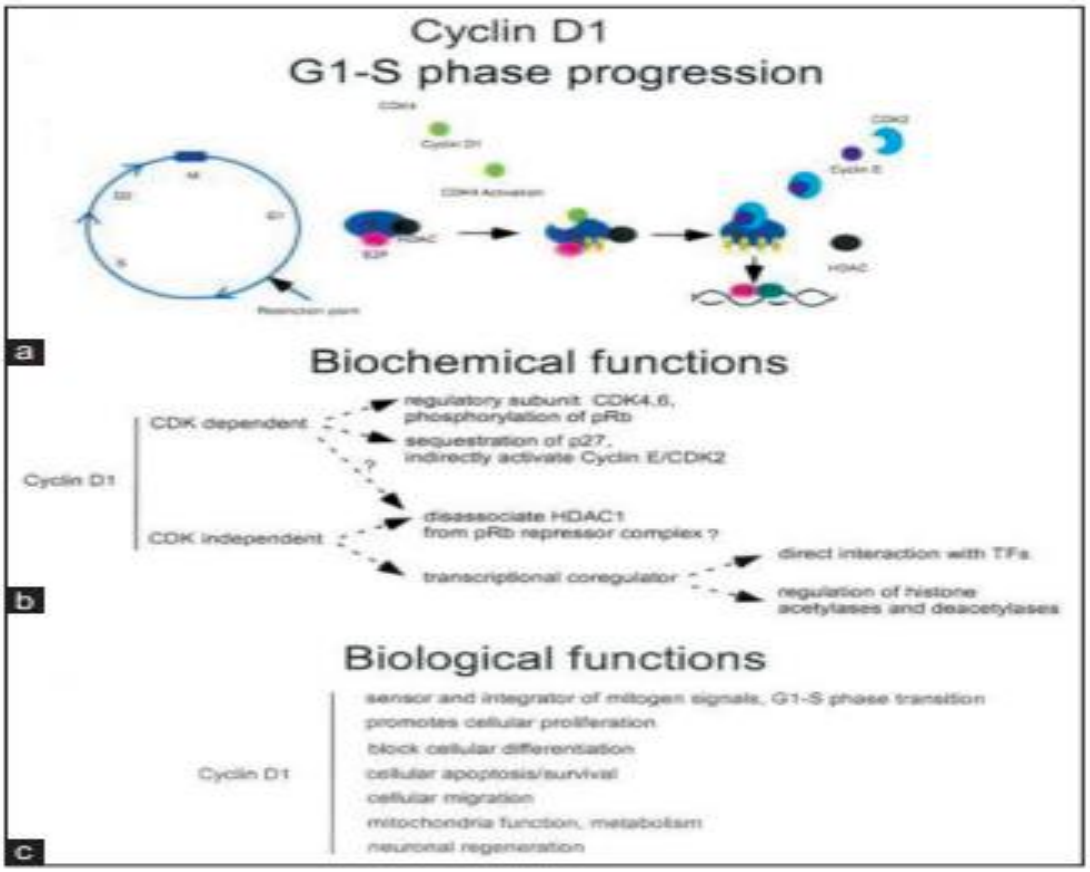


Figure (1): shows structures of D cyclins



Figuer 2: shows normal cell cycle



Figuer (3): Shows summary of Cyclin D1 function. (a)-Schematic representation of protein retinoblastoma phosphorylation by G1 phase cyclins, cyclin D, cyclin E. (b -and c) biological functions of cyclin D1 [10]

Cyclin D2 is then upregulated as a result of MAF family member overexpression and MMSET deregulation. The translocation t(6;14) is linked to an upregulation of cyclin D3 expression. Therefore, deregulation of cyclin D expression and, ultimately, the deregulation of G1/S transition are the outcomes of all these changes. Furthermore, hyperdiploid MM also has elevated cyclin D1 or cyclin D2 levels (16). Cyclin D1 is expressed biallelically in the majority of hyperdiploid malignancies. The trisomic chromosome 11, which contains cyclin D1 gene, may be source of this. Downregulation of some microRNAs (miRNA), such as miR-425, miR-152, and miR24, in hyperdiploid malignancies may be another route of cyclin D1 and cyclin D2 overexpression. Cyclin D1 is upregulated as a result of this downregulation. TACC3, FGFR3, and MafB, followed by a rise in cyclin D1 and cyclin D2. Eight TC (translocation/cyclin D) groups have been found in myeloma patients based on the ubiquitous overexpression of cyclin D genes and the spiking expression of genes altered by primary IgH translocations [16].

Therefore, it is evident that a common early oncogenic event in MGUS and MM is the dysregulation of a cyclin D gene. However, higher proliferation is rarely linked to abnormal cyclin D expression alone. The key to cell cycle progression is cyclin D–Cdk4/6's phosphorylation and inactivation of the Rb protein. Myeloma is also associated with elevated Cdk4 and Cdk6, in addition to cyclin D overexpression. In myeloma, several miRNAs that typically control the levels of Cdk4/6, like miR-29b and miR-34, are downregulated, which leads to an increase in Cdk4/6 expression. Even in the presence of CKIs, the Rb protein can be rendered inactive by the mutually exclusive pairing of cyclin D1–Cdk4 and cyclin D2–Cdk4/6 [16]. Crucially, it has also been reported that the Myc oncogene induces the production of D, E, Cdk2, Cdk4, and Cdk6, among other G1 phase cyclins, hence deregulating the cell cycle. 15% of newly diagnosed patients and 50% of patients with advanced myeloma exhibit elevated Myc expression as the disease progresses. This increase is linked to a bad prognosis for patients with myeloma and is brought on by intricate translocations involving the Myc gene [16-18].

5.9. Prognostic role of cyclin D1 in MM

Nonetheless, there is ongoing debate over the association between MM patients' prognosis and CCND1 overexpression. Soverini et al. [19] and Cook et al. [20] found that cyclin D1 overexpression was associated with a better prognosis of MM patients, whereas Sewify et al. [17] and Tasidou et al. [18] found that expression of CCND1 increased with the progression of MM, suggesting that MM patients overexpressing CCND1 have a poor prognosis. There are not enough evidence-based analyses on prognostic importance of cyclin D1 expression in MM because of complexity of the regulation mechanism of cyclin D1 in cell cycle.

5.10. Targeting cyclins in MM

Because Cdk4/6 plays a crucial role in controlling course of the MM cell cycle and because targeting other Cdks can have harmful consequences including myelosuppression and enteropathy, selective Cdk4/6 inhibitors appear to be

more appealing medicines [14]. Palbociclib (PD0332991) causes primary myeloma cells to go into G1 arrest by specifically inhibiting Cdk4/6 [16]. Although palbociclib alone does not cause apoptosis, it significantly increased myeloma cell death when combined with dexamethasone or bortezomib. Two distinct mouse models (MM1.S xenograft and 5T33MM model) were used to confirm palbociclib's anti-myeloma activity. These investigations showed that palbociclib makes tumor cells more susceptible to bortezomib death [16]. By competing with ATP for the ATP-binding site on Cdk4, another Cdk4/6 inhibitor, P276-00, also prevents the binding of cyclin D1 to Cdk4 [16]. P276-00 inhibits Rb phosphorylation before inducing a cell cycle arrest or caspase-dependent death in myeloma. Additionally, P276-00 sensitizes the MM cells to bortezomib by circumventing the survival and drug resistance signals that the BM niche provides. P276-00 causes apoptosis, which is likewise a consequence of transcriptional inhibition [16].

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