

Cyclin D1 and Chemotherapy Response

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ABSTRACT

Cyclin D1 is a protein that plays a role in the transition from the G1 to S phase of the cell cycle. Cyclin D1 expression has been found to increase in various malignancies and, in many studies, was associated with tumor growth, stage, lymph node involvement, distant metastases, and poor prognosis. Until now, studies on the association of cyclin D1 expression level with chemotherapy response have shown different results. An in-depth understanding of the cell cycle will allow doctors to develop target therapies that work when specific interventions are carried out at certain stages. Some studies reported that cyclin D1 expression was inversely related to chemotherapy response, while others showed opposite results. A significant number of studies have attempted to elucidate this ambiguous effect of cyclin D1. The suggested mechanism involves the difference of cancer cell types, the effect of chromosome instability in a few malignancies, trigger to an excessive DNA repair protein expression stimulus, and the response to DNA damage severity. The ambiguous effect of cyclin D1 towards chemotherapy was thought to arise from the difference in tumor type, chemotherapy agents used, and cell damage severity caused by cytostatics as per different research works. More in-depth research with parallel evaluation of other possible mechanisms such as DNA repair should elucidate the reason behind the inconsistent findings.

INTRODUCTION

Cyclin D1 is a protein that plays a vital role in the transition of the cell cycle from the G1 to S phase [1]. In the G1 phase, the cell will synthesize protein and cell organelles to prepare for the cleavage process in the next phase, the S phase. The cascade process from the G1 phase to the S phase is started by cyclin D1. It acts upon G1 phase progression through the activation of CDK 4 and CDK 6 pathways. This point is known as the starting point of cell growth and development (restriction point) [2]. Thus, the increase of cyclin D1 expression will shorten the G1 phase duration [3]. The expression of cyclin D1 is increased in various malignancies such as esophageal, breast, uterine, colon, lung, prostate, and head and neck cancers as well as lymphoma [1]. This expression was linked with tumor growth, cancer stage development, lymph node involvement, distant metastases, and poor prognosis [1,3].

Research on the effect of the cyclin D1 expression level on chemotherapy response has so far provided conflicting results. Akervall et al. [4] reported that nasopharyngeal cancer, which expresses cyclin D1, showed a favorable response to cisplatin/fluorouracil induction chemotherapy. The same phenomena were also observed in bladder cancer patients with distant

metastases treated with cisplatin and multiple myeloma patients receiving bortezomib [5,6]. On the other hand, other researchers have reported different results. The increase of cyclin D1 expression in germ cell tumor, pancreatic cancer, and head and neck cancer was shown to worsen the response towards cisplatin [7,8].

Therefore, a deeper understanding of the cell cycle would enable clinicians to develop targeted therapies that specifically intervene at a particular point in the cycle. One example of the implementations done by these findings is the recommendation by the FDA to use CDK4/6 inhibitor (Palbociclib) in breast cancer with positive estrogen or progesterone receptor and negative HER2. In this type of breast cancer, dysregulation of the cyclin D-CDK4/6 pathway has been proven to play a role in the growth of tumor cells [9]. This article will tackle questions on the relationship between cyclin D1 expression and chemotherapy response.

Cyclin D1

Cyclin D1 is one of many other proteins that are involved in the cell life cycle. The transition from the G1 to S phase requires the binding of cyclin D1 with CDK 4 and 6 [2,10]. In the G1 phase, a cell will synthesize the proteins needed for DNA replication and become more sensitive towards extracellular signals such as

adhesion molecules and growth factors. This particular point in the cycle is known as the starting point of cell growth and development, more commonly known as the restriction point. CDK 4 and 6 control the progression that occurs in the G1 phase [2].

The cyclin D1 protein is coded by the CCND1 gene located on chromosome 11q13. This gene consists of 13,388 nitrogen base pairs, which would translate to 295 amino acids. The half-life of the cyclin D1 protein within the tissue is 24 minutes [10]. The increase in the cyclin D1 level in healthy tissues as well as in their malignant counterparts stems from the gene expression of CCND1. Besides that, the rise in cyclin D1 gene transcription is influenced by some factors such as NF- κ B, B-catenin-dependent regulation, epidermal growth factor receptor (EGFR) expression, and PI3K [11]. Other than its binding with CDK 4 and 6, cyclin D1 has various biological functions, which are presented in **Table 1**.

Cyclin D1 that has been formed will degrade. The degradation is triggered by threonine (Thr286) phosphorylation by GSK-3 β at the tip of cyclin D1's C protein. However, this process will not occur on a cyclin D1 isoform. During the post-transcription process, a change can occur which will generate the cyclin D1 isoform cyclin D1b, instead of the normal cyclin D1. This happens because of the uncut intron 4 which then contributes to the change of the C molecule at the end of cyclin D1 [11].

Cyclin D1 And Cell Cycle

In the G1 phase, cells will prepare themselves for DNA replication. They will synthesize the protein needed for the replication so that cells are sensitive to extracellular signaling molecules, such as adhesion molecules or growth factors. This point is known as the start point of cell growth and development (restriction point). The progression in the G1 phase is controlled by CDK4 and CDK6 [12].

The bonding of cyclin D1 with CDK4 or CDK6 will activate enzymes that will phosphorylate Rb. The phosphorylation will activate Rb proteins so that they release their bonding with E2F, a transcription factor. It will ameliorate the repressive trait of E2F to cyclin E transcription. The increase of cyclin E transcription will be followed by the bonding of cyclin E with CDK2 that marks the next process of the cell cycle, the S phase [12,13].

Literature Selection

We searched articles from 3 electronic databases (PubMed, ScienceDirect, and Scopus) by using appropriate keywords and manual searching in search engines. The keywords used were "cyclin D1" or "CCND1", and

"chemotherapy response", as well as the synonyms. Then, we screened the articles by their abstracts based on the inclusion and exclusion criteria. The inclusion criteria were any analytic study, human subjects with any cancer, and the examination of cyclin D1 or gene CCND1 prior to chemotherapy. The studies published more than 10 years ago were excluded. Then, we eliminated double articles. The 5 full-text studies obtained were reviewed and summarized.

Cyclin D1 Chemotherapy Response

A few studies have tried correlating cyclin D1 with response to chemotherapy (**Table 2**). Some studies reported that cyclin D1 expression was inversely related to chemotherapy response, while others showed the opposite.

The rise in cyclin D1 expression was associated with cisplatin resistance. Cyclin D1 downregulation effort by RNA antisense can increase the sensitivity towards platinum chemotherapy agents and fluoropyrimidine. Meanwhile, the increase in cyclin D1 expression can be followed by the rise in transporter protein, which effluxes drugs out of the cell (MDR1 and MRP). This event can explain the reason behind the resistance to chemotherapy drugs [18]. Other cyclin D1 resistance mechanisms against cytostatics can be seen in **Table 3**.

Quite a few studies have attempted to elucidate this ambiguous effect of cyclin D1. One of the factors playing a crucial role in influencing cyclin D1's opposing forces on cytostatic drugs is the difference in cancer cell types. Nevertheless, the exact mechanism behind this idea is yet to be known [22]. Excessive cyclin D1 expression was reported to be causative of chromosome instability in a few malignancies (breast and head and neck cancers). This is caused by the forced transition of the cell cycle into the S phase, leaving virtually no time for the DNA repair process to take place [23].

Table 1. The function of Cyclin D1

Biological Function of Cyclin D1
Sensor and integrator of mitogen signaling, progression from G1 to S phase
Cell proliferation
Blocking cell differentiation
Cell apoptosis and survival
Cell migration
Metabolism
Neuron regeneration

Table 2. Studies of cyclin D1 and the response to chemotherapy

Author, Year	Subject	Marker	Regimen Treatment	Conclusion
Feng et al. [14] 2011	Stage III or IVa head and neck squamous cell carcinoma	CCND1	Cisplatin-based regimen	Low CCND1 expression more likely to respond to chemotherapy ($P < .001$) and had significantly better overall survival and disease-specific survival than high CCND1.
Bradford et al. [15] 2014	Advanced larynx cancer	Cyclin D1	Not clearly stated	Cyclin D1 expression not associated with response to chemoradiation ($P = .699$). However, higher cyclin D1 intensity expression was associated with poorer overall survival ($P = .0008$) and disease-specific survival ($P = .0147$).
Moreno-Galindo et al. [16] 2014	Stage III or IV squamous cell carcinoma larynx or hypopharynx	Cyclin D1	Cisplatin and 5-Fluorouracil	Cyclin D1 expression not associated with response to chemotherapy ($P = .341$).
Seiler et al. [5] 2014	Bladder cancer	CCND1 and cyclin D1	Platinum-based regimen or combination of Vincristine, Methotrexate, Leucovorin, Navelbine, or Vinflunine	High cyclin D1 expression in the metastasizing component predicts favorable response to adjuvant chemotherapy ($P = .008$).
Irawan et al. [17] 2020	Stage IV B of nasopharyngeal carcinoma	Cyclin D1	Cisplatin and 5-fluorouracil	Higher proportion of cyclin D1 positive (66.7%) was found in the responsive group compare with the non-responsive group (33.3%) ($P = .032$).

Table 3. Resistant mechanism of cyclin D1 to cytostatics

Author, Year	Resistance Mechanism	Explanation
Jirawatnotai et al. [19] 2012	BRCA2* and RAD51	Cyclin D1 is recruited alongside RAD51 and BRCA2 to DNA damage sites. BRCA2 displaces the ssDNA [†] -binding protein RPA by end resection and facilitates loading of RAD51 onto ssDNA. However, knockdown of BRCA2 decreased loading of cyclin D1, suggesting that BRCA2 is responsible for recruiting cyclin D1 to DNA [‡] damage sites. Cyclin D1 then helps to either recruit RAD51 or stabilize RAD51 on the repair foci, thereby contributing to DNA repair.
Sewify et al. [20] 2014	MDR 1§	Cyclin D1 levels showed a highly statistically significant positive correlation with MDR1 levels (R 0.8 and $P < .0001$).
Mohanty et al. [21] 2014	ATR-CHEK1¶ Pathway	In MCL**, the decreasing of CCND1 sensitizes TP53, which activates cell cycle checkpoints to stall DNA replication allowing time for DNA repair or induces apoptosis when damage is severe. Tumor cells lacking TP53 ^{††} function rely on the ATR-CHEK1 signaling for cell cycle checkpoints following DNA damage.

*BRCA2: breast cancer gene 2

†ssDNA: single-stranded DNA

‡DNA: deoxyribonucleic acid

§MDR1: multi-drug resistance gene

¶ATR-CHEK1: ataxia-telangiectasia-mutated-and-Rad3-related kinase-checkpoint kinase1

**MCL: mantle cell lymphoma

††TP53: tumor protein 53

On the other hand, excessive expression of cyclin D1 can also trigger an excessive DNA repair protein expression stimulus. Extreme RAD51 stimulus gives rise to DNA toxicity, which then causes DNA repair disturbance and DNA instability [23]. Richardson et al. [24] reported that unrestricted RAD51 expression induces genome instability due to aneuploid chromosome formation alongside chromosomal arrangement alteration.

Some research suggests a different cyclin D1 response to DNA damage severity. Severe DNA damage precipitated by chemotherapy or high-dose radiation will induce a prompt decrease of cyclin D1 levels, which then halts the start of phase S in the cycle. Thus, cell proliferation will cease, and cell death takes place. In the meantime, in less severe DNA damage, the damage caused is not enough to suppress cyclin D1 levels swiftly, enabling the cells to further replicate with cyclin D1 observed in the nucleus. Cyclin D1 has DNA repair activity and will mobilize its DNA repair protein expression, RAD51 [23].

Myklebust et al. [25] also reported that the increase of isoform cyclin D1a and cyclin D1b will have different responses to 5-fluorouracil. It is shown that in colorectal cancer that got 5-fluorouracil, the patients with cyclin D1a expression gave a better response than the ones with cyclin D1b expression. It could happen because of the imbalance between the ability of DNA repair and DNA synthesis [11].

CONCLUSION

Cyclin D1 holds the key in the transition from the G1 cell cycle phase to S1. Results about the association between its expression and chemotherapy response still showed conflicting results. From the literature review, the ambiguous effect of cyclin D1 towards chemotherapy is thought to arise from the difference in tumor type, chemotherapy agents used, and cell damage severity caused by cytostatics. However, more in-depth research with parallel evaluation of other possible mechanisms such as DNA repair is required to elucidate the reason behind the inconsistent findings.

Conflict of Interest

The authors declare that there is no conflict of interest concerning the publication of this paper.

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