Abstract

The objective of this paper is to discuss and put forward the various diversified roles of cyclin D1 in cancer. Neoplasia is defined by abnormal regulation of the cell cycle. Cyclin D1 could be a protein derived from the PRAD1, CCND1, or bcl-1 sequence on body 11q13 that is concerned in each traditional regulation of the cell cycle and pathologic process. Within the G1 (resting) part of the cell cycle, cyclin D1 in conjunction with its cyclin-dependent enzyme (cyclin-dependent kinase) partner is accountable for transition to the S (DNA synthesis) part by phosphorylating the merchandise of the metastatic tumor sequence (protein retinoblastoma) that then releases transcription factors vital within the initiation of DNA replication. Amplification of the sequence or overexpression of the cyclin D1 releases a cell from its traditional controls and causes transformation to a malignant composition. Analysis of those changes provides vital diagnostic information in oral carcinogenesis and is of prognostic value in several cancers. Data of cyclin D1’s role in malignancy at the assorted sites provide a basis on which future treatment directed against this molecule will proceed.

Keywords: Carcinogenesis, cyclin D1, DNA synthesis

Introduction

Normal cell cycle and cyclin D1

Cell division is a very important process in all living organisms. During the division of a cell, DNA replication and cell growth also take place. A normal cell cycle consists of resting phase (G0) where the cell leaves the cycle and stops dividing. It is with this stage that the cell cycle starts. The next phase is the interphase which starts with G1 (gap 1) where the cell increases in size. This G1 checkpoint controls the mechanism to ensure that the cell is ready for DNA synthesis. The second phase in the interphase is the S-phase (synthesis) where the DNA replication occurs. Then, the cell enters into G2 (gap 2) phase where the cell continues to grow and this G2 phase ensures that the cell is ready for mitosis. The M-phase (mitosis) is where the cell grows stops, and all the energies of the cell are focused on the orderly division of the daughter cells. All these processes, i.e., cell division, DNA replication, and cell growth, hence, have to take place in a coordinated way to ensure correct division and formation of progeny cells containing intact genomes. The sequence of events by which a cell duplicates its genome, synthesizes the other constituents of the cell, and eventually divides into two daughter cells is termed cell cycle.\[1]\n
Growth factors are mandatory for the normal cell proliferation, thereby governing the activation of regulatory proteins which control the transition through G1 phase of the cell cycle.\[2]\n
Later, even in the absence of mitogens, the cells can clear the G1 restriction point and progress in the cell cycle.\[3\]

Understanding the biochemical basis of the G1 restriction point has been an important goal of cell cycle research. Retinoblastoma (Rb) protein and E2F factor have been highlighted as mediators of the restriction point. Phosphorylation of Rb and related proteins during late G1 phase leads to release of E2F family members, which then regulate transcription of genes necessary for S-phase progression. Phosphorylation of Rb is carried out by cyclin/cyclin-dependent kinase 3 (CDK3) complexes.\[4,5\]

During G1 phase in most experimental systems, the D- and E-type cyclins are induced and bind to their respective CDK partners to form active Rb kinases.\[6\] In many cell types, cyclin D1 is the first cyclin to be upregulated by growth factors during G1 phase. Cyclin D1 is thought to be a key intracellular mediator of extracellular signals, such as mitogens, that regulate the cell cycle.

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The cyclins were named due to their intermittent, cell cycle - subordinate example of expression. The amalgamation of individual cyclins and ensuing cyclin-subordinate kinase (CDK) actuation at particular cell cycle stages facilitates the successive finishing of DNA replication leading to cell division. These kinases likewise underlie the checkpoints that end cell cycle movement accordingly leading to DNA harm and defects in the mitotic axle. Therefore, CDK movement is firmly managed at different levels through a few systems. These incorporate the abundance of the administrative cyclin subunits; their relationship with the synergist CDK subunit; initiating and repressing phosphorylation events, and the plenitude of individuals from two groups of CDK inhibitory proteins – the INK4 family which includes INK4A (otherwise called p16), INK4B (otherwise called p15 and CDKN2B), INK4C (otherwise called p18 and CDKN2C), and INK4D (otherwise called p19 and CDKN2D) and the CIP and KIP family which includes p21 (likewise known as CDKN1A), p27 (otherwise called CDKN1B), and p57 (otherwise called CDKN1C). The diagrammatic representation of the role of cyclin D1 in cell cycle is elicited below [Figure 1].

Deviation from normal

The oncogenic capacity of cyclin D1 has been established in various studies. It has been shown that the induction of cyclin D1 in breast cancer cell lines shortens G1 and results in an increase in the number of cells progressing through G1. This observation is supported by other studies demonstrating entry into S-phase is prevented by inhibiting cyclin D1 expression thereby suggesting that cyclin D1 is essential for G1 progression. Moreover, cyclin D1, along with cyclin E, is rate limiting for progress through G1 in various cell lines; cyclin D1 in early G1 and cyclin E in the late G1 phase of the cell cycle. Cyclin D1 plays a pivotal role in estrogen-induced breast cancer with estrogen action mediated through transcriptional activation of cyclin D1 and c-myc. This evidence suggests a critical role for cyclin D1 in human breast cancer cell cycle control. Given this role, overexpression of cyclin D1 may provide a growth advantage to the tumor cells and may also contribute toward resistance to endocrine therapy.

The oncogenic limit of cyclin D1 has laid foundations in different studies. It has been demonstrated that the impelling expression of cyclin D1 in breast cancer cell lines lessens G1 and results in an expansion in the quantity of cells advancing through G1. This perception is upheld by different studies showing that progression to S-stage is anticipated by repressing cyclin D1 expression consequently recommending that cyclin D1 is key for G1 progression. Cyclin D1 assumes an essential part in estrogen-actuated breast cancer with estrogen activity interceded through transcriptional initiation of cyclin D1 and c-myc. This proof proposes a basic part for cyclin D1 in human breast cancer cell cycle control. Given this part, overexpression of cyclin D1 may give a development preferred standpoint to the tumor cells and may likewise contribute toward imperviousness to endocrine therapy.

Figure 1: Summary of cyclin D1 function. (a) Schematic representation of protein retinoblastoma phosphorylation by G1 phase cyclins, cyclin D1 and cyclin E. Biochemical functions (b) and biological functions (c) of cyclin D1 are summarized. TF: Transcriptional factor (Adapted from: Minireview: Cyclin D1: Normal and abnormal functions. Endocrinology 145:5439-47)
The role of cyclin D1 has been voluminous. In this article, we will discuss in depth the role of cyclin D1 in human cancers.

**Discussion**

Cyclin D1 in human cancers:
- Mantle cell lymphoma
- Breast cancers
- Head and neck carcinomas
- Oropharyngeal cancers
- Hepatocellular cancers
- Colorectal cancers
- Lung cancers
- Skin cancers and sarcomas.

Increased cyclin D1 expression has been associated with various primary human tumors. The protein upregulation is more reliable in case of the tissue than the cell lines as other influences can cause the cells to proliferate faster and may upregulate cyclin D1 expression. The overexpression of the protein is usually associated with the amplification of the CCND1 gene, but this is not the case always. In some tumors, there is an increased cyclin D1 RNA and/or protein without apparent gene amplification, suggesting that other cellular genes (such as the Rb gene) may impact on the protein expression of cyclin D1, although all the mechanisms have not yet been satisfactorily elucidated. DNA amplification is the most frequent abnormality affecting the CCND1 gene. Furthermore, no major abnormality in the coding region of the cyclin D1 gene has been detected suggesting that it is the normal gene product that contributes to tumorigenesis.

**Role of cyclin D1 in mantle cell lymphoma**

All (centrocytic) lymphomas in a few studies have raised action of cyclin D1, even in cases in which no adjustment at 11q13 was found. For the most part, be that as it may, positive nuclear staining with monoclonal antibody to the cyclin D1 protein associates with intensification of the CCND1 quality and mRNA. It has been proposed that outflow of cyclin D1 by lymphocytes in the mantle zone hinders the limit of these cells to leave the cell cycle and to separate into full-grown plasma cells. This pathogenetic hypothesis is repudiated by a late finding of cyclin D1 protein expression in 26% of plasma cell neoplasms; nonetheless, the same study forms a foundation and a connection between mantle cells, plasma cells, and their comparing neoplasms. It has also been recognized the significance of chromosomes 11q13 translocation and expanded cyclin D1 expression in mantle cell lymphomas; later on, it might be lifted to a characterizing trademark, given the high sensitivity and relative specificity of this protein in mantle cell lymphoma contrasted and other B-cell neoplasms. Cyclin D1 protein expression and bcl-1 gene rearrangement have been distinguished as a key part in the analysis of the blastoid variation of mantle cell lymphoma and in addition in a substance firmly identified with mantle cell lymphoma—numerous lymphomatous polyposis.

**Role of cyclin D1 in breast cancer**

Overexpression of cyclin D1 has been associated with breast tumors that overexpress human epidermal growth factor receptor 2 which are usually estrogen receptor (ER) negative. Initially, it was suggested that CDK-dependent function of cyclin D1 only resulted in progression to G1 phase. This process caused cellular proliferation and lay behind its oncogenic potential. However, evidence from various clinical studies fails to support this hypothesis, and therefore, an alternative CDK-independent function resulting in tumorigenesis had been suggested. Since cyclin D1 is overexpressed preferentially in ER-positive breast cancer, it has been suggested that modulation of transcription through its action on ER probably underlies the oncogenic activity of cyclin D1 in breast cancer.

This hypothesis is supported by the findings that show the direct interaction between cyclin D1 and ER, which in turn activates ER-regulated genes in the absence of estrogen.

Cyclin D1 overexpression has been reported between 40% and 90% of cases of invasive breast cancer while gene amplification is seen in about 5%-20% of tumors. Although CCND1 amplification correlates well with the overexpression of the protein, high expression of cyclin D1 is not always secondary to gene amplification implying that other mechanisms contribute to maintain cyclin D1 overexpression. Various factors that could contribute to protein overexpression in breast cancer include estrogen and p53 through p21cip1 pathway (Figure 3).

**Role of cyclin D1 in head and neck cancers**

A range of 35%-64% of head and neck squamous carcinomas (squamous carcinomas in the oral cavity, skin cancers, and sarcomas) and in addition in a substance firmly identified with mantle cell lymphoma—numerous lymphomatous polyposis.
Role of cyclin D1 in oropharyngeal cancers

In roughly 30% of esophageal growths, overexpression of cyclin D1 has been illustrated, with a few studies demonstrating a relationship with expanded mortality. Furthermore, the ability of antisense to cyclin D1 to switch the cancerous phenotype of esophageal tumor cells gives solid supporting confirmation to the molecule’s role in diseases at this site. The group has exhibited a relationship between cyclin D1 protein and protein Rb (pRb) expression, a finding that is in accordance with the consequences of another study in a comparably high-frequency area. Although the outcomes support a relationship between cyclin D1, pRb staining, and aggressive behavior, the accurate way of this communication should be elucidated.

Role of cyclin D1 in hepatocellular carcinoma

Cyclin D1 gene amplifications explain only partially the frequent cyclin D1 protein overexpression encountered in hepatocellular carcinoma (HCC). As a sensor of mitogenic signals as well as during oncogenesis, cyclin D1 transcription, translation, or stability is under the control of several pathways such as Wnt/β-catenin, growth factors or GSK3β/AKT pathway, cytokines/Jak/Stat3 signaling, or even NFκB [Figure 4]. Despite the transcriptional activation of the cyclin D1 gene by nuclear β-catenin in normal or cancer cells, the link between β-catenin and cyclin D1 remains complex in HCC. Analyses of cyclin D1 transcript and protein level from human HCC samples have not shown a positive correlation between cyclin D1 expression and total or nuclear β-catenin as a result of amplification or mutation of its gene. Surprisingly, mice overexpressing hMet and truncated β-catenin do not require cyclin D1 expression for tumor development since it was shown that tumors grow faster in its absence (cyclin D1−/− mice). This can be potentially explained by compensatory expression and activity of cyclin D2 bound to CDK6 and successive overexpression of cyclin E1 and B1.

Role of cyclin D1 in colorectal cancers

Recent research throws light into the role of cyclin D1 in colorectal cancer although an initial report using cell lines suggested that cyclin D1 was not an important factor in colorectal adenocarcinomas. Overexpression of the protein is associated with early tumor progression, as well linked to be an independent prognostic factor. Adenomatous polyps and adenocarcinomas express increased nuclear immunostaining, but the respective adjacent normal or hyperplastic tissue had no expression. These findings apply to both sporadic and familial forms of colon cancer. Furthermore, as it has been demonstrated in the esophagus, antisense to cyclin D1 inhibits the growth and tumorigenicity of colon cancer cells.
Role of cyclin D1 in skin cancers

Compared to normal skin and benign lesions, cyclin D1 protein expression is significantly greater in various malignant skin tumors, including SCCs, melanomas, and malignant fibrous histiocytomas. Studies of chemically induced SCCs in mice also implicate cyclin D1 (and other G1 cyclins) in the process of carcinogenesis.

Role of cyclin D1 in sarcomas

Amplification of the cyclin D1 gene has been detected in a small percentage of a variety of sarcomas, but the increased cyclin D1 protein expression in at least some cases may be due to a mutant protein with greater stability.

Role played by cyclin D1 as a prognostic marker in head and neck cancer

Despite numerous studies done to find a marker that indicates the course of the disease and the expected outcome of a treatment protocol, head and neck cancer management still remains an unpredictable one with high mortality rate. The published data are full of evidence that cyclin D1 is an important marker for OSCC. Saawarn et al. found overexpression of cyclin D1 in oral cancer cases ranging from 39% to 83%. Angadi and Krishnapillai and Mishra and Das noted a uniformly increasing intensity in relation to the histopathological differentiation whereas Castle et al. found no correlation as recorded by Saawarn et al. By observing the expression of cyclin D1 in different stages, two major transitions were noted in normal mucosa that leads to oral cancer. The first is transformation of normal mucosa to premalignant lesion (PML), the second PML to OSCC. Evidence shows that the first transition induces cyclin D1 mRNA with no detectable cyclin D1 protein. The induction of mRNA is maintained with increased cyclin D1 protein accumulation in the second transition. Later stage cancers were significantly more likely to have overexpression compared to earlier stages, after adjusting for all other clinicopathological parameters in multivariate logistic analysis. This is in agreement with Sathyan et al. and Huang et al. who found that cyclin D1 overexpression was associated with stage but not with age of onset. Other studies have shown no significant correlation between cyclin D1 overexpression and clinicopathological factors. Site of the tumor was also a predictor of cyclin D1 overexpression with tongue tumors having an increased risk compared to other sites, supporting the findings of Haas et al. Cyclin D1 and E are G1 phase cyclins believed to participate in the pathogenesis of malignancy. Overexpression of CD1 has been reported to influence prognosis in SCC. The detection of prognostic markers is essential to specify treatment protocols and determine which patients need more aggressive surgery, adjuvant chemotherapy, or radiotherapy.

Conclusion

The review of literature on the presence and role played by cyclin D1 in various types of malignancies in different sites of the body indicates that it is a promising tumor marker which can aid in the diagnosis and predicting the prognosis of unpredictable tumors such as OSCC.

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Conflicts of interest

There are no conflicts of interest.

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