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Short Communication

Dual Roles of Cyclin D1 in Normal Physiology and Disease

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ABSTRACT

The rate of division and proliferation of a cell is determined by a complex sequential process known as the cell cycle. This process is directed by a family of numerous regulatory proteins known as cyclins, which are expressed at various phases of the cell cycle. Among the different cyclins, cyclin D1 is one such important cell cycle nucleoprotein that regulates the rate of mitotic division as well as many other biological mechanisms. In the recent years, however, cyclin D1 has shown abnormal expression within the cell cycle machinery and has been overexpressed in a wide variety of tumors, therefore implying that it might have an influence in the cell cycle aberration and can initiate oncogenesis. Hence, the emergence of cyclin D1 expression in cancer has indicated its significance as a tumor biomarker. In addition, cyclin D1 has also raised questions regarding its molecular role in many other pathologies apart from cancer as well, and so till date, it continues to be a topic of interest.

Keywords: Cyclins, Cyclin D1, Cell cycle, Cell cycle proteins, Tumor biomarker

INTRODUCTION

Cyclin D1 is a cell cycle proliferative marker protein that belongs to a family of cell cycle proteins known as cyclins. Cyclins are so named because they encompass a group of proteins displaying cyclical and a quantitative fluctuating pattern throughout the cell cycle. Cyclins play an integral role in regulation of the cell cycle and function as essential partners of a family of kinases known as cyclin-dependent kinases (CDKs) that play a critical role for cell cycle entry as well as progression. The CDKs are serine/threonine protein kinases activated at specific points in the cell cycle. They are critical for progression through cell cycle because their inactivation prevents mitosis. Cyclins activate and form complexes with cyclin-dependent kinases (CDKs) catalyzing progression through the cell cycle. Cyclin D1, a nucleoprotein, is part of the D-type cyclins forming a distinct subset within the cyclin family based on structural and functional criteria. Cyclin D1 along with CDK4/6 promotes progression through G1-S phase of the cell cycle through inactivation of the retinoblastoma (Rb) protein by phosphorylation. Cyclin D1 is encoded by the gene known as CCND1 gene, which is located in the chromosomal band 11q13. Apart from behaving as mediator of cell proliferation and DNA replication, cyclin D1 has also been implied in tumor progression as it has shown overexpression in various tumors. Hence, its expression in various tumors has sparked an interest on its role as a possible therapeutic target in various cancers.[1-3]

BACKGROUND

Cyclins were first discovered by Hunt *et al.* (1982) in fertilized sea urchin eggs and were revealed to be an oscillating protein degraded after each division cycle. About 16 mammalian cyclins have

been identified and have been denoted alphabetically as: A, B1, B2, C, D1, D2, D3, E, F, G1, G2, H, I, K, T1, and T2. Only five classes of cyclins are described in human cells, that is, cyclins A, B, C, D, and E. Cyclin D1 protein was first reported in 1991 by Motokura *et al*. Cyclin D1 forms one of the three isoforms of the D-type cyclins, that is, cyclins D1, D2, and D3. However, cyclin D1 shows more advanced cell cycle regulation than the other subtypes and also plays a role in cell cycle aberration leading to oncogenesis. Therefore, it is more prioritized than the other D- type cyclins.[3-5]

CYCLIN D1 IN HEALTH AND DISEASE

Cyclins are regulatory proteins mediating progression of eukaryotic cell through the cell cycle. Cyclins along with CDKs form complexes and are activated at specific stages of the cell cycle required mainly for progression through S phase and mitosis.[1,3]

Cyclins control various biological processes such as DNA replication, DNA damage repair, mitotic divisions, regulation of transcription, neuronal functions, renewal of stem cell population, cell proliferation, metabolic regulation, regulation of mitochondrial functions, immune cell maturation and development, erythrocyte development, and meiosis.[4-6]

Among cyclin family members, cyclin D1 is particularly important, as it is involved in regulation of natural biological processes in health and has also been demonstrated in the development of various diseases predominantly cancer. The roles of cyclin D1 in normal cell cycle machinery include control of cell migration of macrophages, cellular adhesion, regulation of transcription, regulation of stem cell renewal, growth regulation, mitochondrial activity modulation, DNA damage repair, cell proliferation, regulation of metabolism, cardiomyocyte proliferation, and hepatocyte cell proliferation. Genetic studies have demonstrated cyclin D1 to play a part in normal development of retina, components of nervous system, terminal alveolar breast bud development, promotes neural basal progenitors, etc. Cyclin D1 forms a holoenzyme with a cyclin-dependent kinase (CDK4/CDK6) that brings about phosphorylation of the Rb gene product pRB. The Rb protein (i.e., pRB), which is the product of the Rb gene, is a tumor suppressor gene, located on chromosome 13q and is a ubiquitously expressed nuclear phosphoprotein that plays a key role in the normal regulation the cell cycle. Overexpression of cyclin D1 promotes progression through the G1 phase of the cell cycle and overexpression of cyclin D1 promotes contact-independent growth.[1,5,7]

Apart from its role in normal cell cycle regulation, cyclin D1 also plays a role in aberrations in the cell cycle regulation. Cyclin D1 is frequently overexpressed in various cancers such as oral squamous cell carcinoma, oropharyngeal carcinoma, esophageal carcinomas, and breast carcinomas. Cyclin D1 is also expressed in tumors of odontogenic apparatus such as odontogenic cysts and tumors, salivary gland tumors, and potentially malignant oral disorders. Increased cyclin D1 expression paralleling with severity of lesions likely reflects the intense proliferative activity and invasiveness of these lesions. In general, cyclin D1 expression increased with increased grade of dysplasia in leukoplakia and OSCC. Hence, the severity of dysplasia increases with increased expression of cyclin D1 and can indicate a high risk for malignant transformation in these lesions.[8]

While it is unclear why cyclin D1 expression is frequently altered in human cancers, its overexpression can be influenced by multiple mechanisms such as genomic alterations, chromosomal instability, post-transcriptional regulation, and post-translational protein alterations. Due to its frequency of expression in various tumors, it is being considered as a therapeutic target considering its prognostic roles in various cancers. Therefore, various pharmacological agents are being formulated to target the control of cyclin D1 expression and its subsequent degradation, therefore establishing an alternative for control of cell proliferation.[9,10]

CONCLUSION

Even though cyclin D1 is associated with normal cell cycle regulation, it has also shown abnormal expression in various tumors, picking it apart from its other cyclin counterparts. However, a definitive etiological role of cyclin D1 is yet to be established on a more confirmatory basis in conditions such as oral potentially malignant disorders, odontogenic cysts and tumors, cardiovascular diseases, metabolic diseases, and urothelial carcinomas, its role as a prognostic target in certain tumors as cyclin D1 has shown a questionable significance. Till date, cyclin D1 still continues to be a mysterious entity and more approaches may help to unravel the puzzles surrounding it.

Declaration of patient consent

Patient's consent not required as there are no patients in this study.

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Conflicts of interest

There are no conflicts of interest.

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