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Cyclin D1: An Insight into its Physio-Pathological Role in Oral Squamous Cell Carcinoma

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Abstract

Cyclins and Cyclin dependent kinases (CDK's) are proteins which act as positive regulators of the cell cycle at its various check points. The different cyclins attain peak activity during different phases of cell cycle and Cyclin D1 regulates transition from G1 to S phase of mitotic cell cycle. Due to this crucial role in cell cycle regulation, cyclins play an important role in carcinogenesis. Deregulated or over-expression of Cyclin D1 may lead to shortening of G1 phase, increased cell proliferation and reduced dependency on growth factors leading to disturbance in the normal cell cycle control and tumour formation. This short communication is a brief review about its role in head and neck carcinomas.

Keywords: Cyclins; Cyclin D1; Oral squamous cell carcinoma

Neoplastic diseases have been defined as proliferative disorders characterized by an uncoordinated cell growth. To reach at a better understanding, it is of the utmost importance to have an in-depth knowledge of the mechanisms that control cell division [1].

The ability of a cell to duplicate into two daughter cells is one of the most fundamental properties that define life [2]. During cell cycle a cell goes through various phases viz. G0, G1, S, G2 and M. Following G1, S, G2 and M phases, the cell can start the cycle again by entering G1 or become quiescent by entering G0 or resting phase. G1 phase, where the cells undergo a period of growth and most cellular proteins, RNA membranes and other macromolecules are synthesized in preparation for DNA synthesis, is the only phase where the extracellular stimuli like growth factors can have an effect on the cell cycle [2,3]. There are various check points present in the cell cycle i.e. G1 /S and G2/M which ensure that each phase is completed before the next one is initiated [3]. Restriction Point is a point in late G1 phase which is the point of no return, because once the cell crosses this, it is committed to another round of cell cycle and is not affected by extrinsic influences like growth factors, mitogens etc [2].

The cell cycle progresses in a carefully coordinated manner and the orderly progression of cells through the various phases of the cell cycle is orchestrated by Cyclin dependent kinases (CDK's) which are activated by binding with another family of proteins called Cyclins. Both CDKs and Cyclins act as positive regulators of the cell cycle [2]. The cell cycle may be visualized as a relay race in which each lap is regulated by a distinct set of cyclins by activating cyclin dependent kinases (CDK), and as one set of Cyclin leaves the track, the next set takes over. The CDKs are expressed constitutively during the cell cycle in an inactive form, and require cyclins, which are synthesized during specific phases of cell cycle to bind with them and activate them. On completion of this task, cyclins decline rapidly. This cyclic nature of their production and degradation has led these proteins to be termed as 'Cyclins' [4].

Cyclins were first identified in marine invertebrates as proteins that accumulated at high levels following the fertilization of eggs and then underwent abrupt destruction during mitosis. Since, then, over 30 Cyclin sequences have been identified [3] and eight major classes of mammalian cyclins have been isolated, although within some classes, a number of subclasses exist. Therefore there are at least 11 cyclins termed as: A, B1, B2, C, D1, D2, D3, E, F, G and H [5]. The different cyclins attain peak activity during different phases of cell cycle. Cyclin D1-3, Cyclin E bind with CDK 4/6 and CDK 2 respectively, and regulate transition from G1 to S phase, whereas Cyclins A, B bind to CDK2 and CDK1 respectively and are most active during S and G2 phases where they regulate transition to the mitotic phase of the cell cycle [5]. In view of their crucial role in cell cycle regulation, cyclins have attracted considerable attention with regard to their putative involvement in oncogenesis [6].

The best characterized among the cyclins is Cyclin D1, a 45 kDa, 295 amino acid protein encoded by CCND1 gene located at chromosome 11q13 and has been reported with various other names like PRAD1 [1], Bcl-1 [7] and Exp2 [8].

Cyclin D1 appears to be important in the G1-S transition. Its synthesis begins in the G2 phase, reaches peak levels in the G1 phase and decreases in the M phase and is influenced by extracellular mitogenic signals like growth factors. The transition from G1 to S is believed to be an extremely important checkpoint in the cell cycle clock, guarded by the product of Rb protein which binds to transcription factor E2F. When a cell encounters growth signals, levels of the D1 cyclins go up and complex with CDK 4 and CDK 6, which get activated, and this complex of Cyclin D1/CDK4/6 phosphorylates Rb thereby releasing the transcription factors. This E2F is then able to function as transcriptional activator for genes important for entry into S phase and onset of DNA synthesis [2,3].

The deregulated expression or over-expression of Cyclin D1 may lead to shortening of G1 phase, increased cell proliferation and reduced

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dependency on growth factors [5] leading to disturbance in the normal cell cycle control and tumour formation [9,10]. Thus, overexpression of Cyclin D1 is thought to provide the tumour cells with a selective growth advantage [10]. Various mechanism of overexpression or dysregulation of Cyclin D1 are:

Gene amplification at 11q13 [6].

Chromosomal rearrangements and translocations (PRAD1, Bcl-1) [3].

Transcriptional i.e. upregulation of gene transcription [11] and posttranscriptional mechanisms [9].

Post translational stabilization of Cyclin D1 -GSK3β [12].

Retrovirus insertion [13].

Alteration in synthesis or stability of Cyclin D1 protein [14].

Cyclin D1 carries substantial evidence of its involvement in human oncogenesis and has been implicated in various types of malignancies [9] and Cyclin D1 gene amplification and overexpression of its protein products and mRNA has been reported in various tumours [3] of diverse histogenesis like breast carcinomas[6], Hepatocellular carcinomas [15], Colon carcinomas [6] Retroperitoneal soft tissue sarcoma [16] Oesophageal carcinoma [8,17]. Lung carcinoma [18] Head and neck carcinoma [13,17,19-28] and Oral carcinoma [2,21,29-55].

Immunohistochemical study of normal tissues revealed generally low levels of Cyclin D1 protein mainly restricted to the proliferative zones of some epithelial tissues which included stratified squamous epithelia of head and neck region, oral mucosa, epidermis, hair follicles, cervix, vagina, rectum and transitional epithelia of the urinary tract and lack of its expression in several tissues like lymph nodes, spleen and tonsils [6]. In tooth germ tissues it was expressed sporadically in inner and outer enamel epithelium, stratum intermedium, stellate reticulum but dental lamina showed little or no expression [29].

Various studies in head and neck squamous cell carcinoma has shown varying results. Callender et al., [21] reported Cyclin D1 oncogene amplification in approximately 30% of primary head and neck squamous cell carcinomas and amplification was also noted more in high grade, high stage and aneuploid tumours with a highly statistical correlation; suggesting Cyclin D1 amplification to be associated with aggressive tumours and highly proliferative neoplasms.

Gaffey et al., [23] showed an inconsistent association with 38% of head and neck carcinomas showing CCND1 gene amplification, but around 44% showing it's protein's over-expression; suggesting chances of some other mechanism for protein overexpression. Akervall et al., [11] showed that the patients with tumours strongly positive for Cyclin D1 and those with 11q13 rearrangements had poorer survival, however the correlation between these 2 variables was weak. Michalides et al., [10] reported overexpression of Cyclin D1 in 49% of 115 patients of head and neck squamous cell carcinomas studied, which was not associated with known prognostic factor like T and N stage, but tumors with Cyclin D1 reactivity recurred more frequently and in a shorter period of time; suggesting it to a novel marker for prognosis independent of other known markers. However, though Vora et al., [31] found 62% Cyclin D1 expression in 84 tongue carcinomas studied he reported an inverse correlation between Cyclin D1 expression and tumour grade.

Chetty et al., [25] reported Cyclin D1 expression in 29% of the 80 cases of oesophageal SCC, while Fracchiolla et al., [13] reported Cyclin D1 protein expression in 39% and gene amplification in 24% of the 58 cases of laryngeal Squamous cell carcinoma studied.

Castle et al., [32] reported that 77.8% of dysplastic pre cancerous lesions of oral mucosa stained positively with anti Cyclin D1 antibody in contrast to 55% cases of carcinomas. They suggested that increased expression of Cyclin D1 may occur early in tumour progression in oral carcinomas. Kuo et al., [33] reported cyclin D 1 expressuon in 73 of 88 (83%) cases of oral SCC. Saawarn et al., [34] in their study found positive reactivity to cyclin D1 in 45% cases of oralsquamous cell carcinoma and both nuclear and cytoplasmic staining was observed in all the cases of positivity. They found highest expression of cyclin D1 in Well Diffentiated Squamous Cell Carcinoma (WDSCC), followed by Moderately Diffentiated Squamous Cell Carcinoma (MDSCC) and Poorly Diffentiated Squamous Cell Carcinoma (PDSCC); again showing it to correlate with the higher grade and its ability to serve as a prognostic marker [34].

Other than being used as a prognostic marker, cyclin D 1 is may also be used as a target molecule in cancer chemotherapy as tumors over-expressing cyclin D1 has been found to be more sensitive to chemotherapeutic agent Rapamycin [56].

From this brief review we see that there a is wide variation and diversity in the reports available in the literature regarding levels and diagnostic prognostic significance of Cyclin D1 especially in oral Squamous cell carcinoma, which further opens a window of opportunity for advance discussion and research in this field regarding the role of Cyclin D 1 as a reliable prognostic marker.

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