MOLECULAR BASIS OF CELL CYCLE REGULATION BY CYCLIN : A SHORT REVIEW

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ABSTRACT

Eukaryotic cell cycle is under the control of Cyclin Dependend Kinase enzymes which is regulated positively by Cyclins and negati - vely by inhibitors of Cyclin Dependent Kinase (CDK). pRB, the fundamental component of cell cycle restriction point is phosphorylated and dephosphoryated by Cyclin Dependent Kinase enzyme. CDKI (p21) is transcriptionaly regulated by p53, which focus on the major role of Cyclin on cell cycle check point cascade. Dysregulation of normal cell cycle pathway can result in carcinogenesis.

Key words : Cyclin, dependend, kinase, cyclin, Phostho relation.

J Odontol Res 2016;4(1)5-7.

Introduction:

The progression of eukaryotic cell cycle is governed by a family of Cyclin-dependent kinases (CDKs), whose activity is positively regulated by sequential formation and degradation of a group of proteins called Cyclin[1]. Activation of specific Cyclin-CDK complexes results in a cascade of protein phosphorylation that is required for the passage through the key checkpoints in cell cycle. Therefore, dysregulation of Cyclin expression can result in the loss of control over cell cycle and ultimately result in tumour development. Cyclins are functionally divided into two groups. The G1 Cyclins (C, D1-D3, E), regulating the passage of cells through the G1 phase and their entry into the S phase, and the mitotic Cyclins (A, B) facilitating the cell through the mitotic phase. Through cell cycle progressions, Cyclin D/CDK4 and Cyclin D/CDK6 are the first complexes to become active, appearing during mid-to-late G1 phase. They are followed by Cyclin E/CDK2 complex in late G1 phase. Cyclin E/CDK2 complex is present in the cell cycle progressions until the cell completes the G1/S transition. Active CyclinA/CDK2 complexes drive S phase progression, and after the cell has entered G2 phase, Cyclin A trades its partner, CDK2, for CDK1. The G2/M phase transition heralds the appearance of Cyclin B-CDK1 [2,3].

II. Cell cycle regulation by Cyclin

Cyclin D is degraded through ubiquitin-proteosome pathway. During G1 phase of the cell cycle; Cyclin D binds to and activates CDK4, forming Cyclin

D-CDK4 complex. This complex has a critical role in the cell cycle by phosphorylation of the retinoblastoma susceptible protein (RB). The phosphorylation of RB protein is the on-off switch of the cell cycle. In the hypophosphorylated state, RB prevents cells from replicating by forming a tight inactive complex with the transcription factor E2F[4].

Phosphorylation of RB dissociates the complex and releases the inhibition on E2F transcriptional activity. Thus RB phosphorylation eliminates the main barrier of cell cycle progression and promotes cell replication. Hypophosphorylated RB present in or early G I phase binds to a protein complex that contains E2F and a subunit called DPI. E2F/DP1/RB complex binds to the promoters of E2F responsive genes. Bound to E2F/DP1/RB complex, such genes are silent because RB recruits Histone deacetylase, an enzyme that causes the compaction of chromatin and inhibition of transcription. When quiescent cells are stimulated by growth factors, the concentration of Cyclin D and Cyclin E will be elevated, resulting in the formation and activation of Cyclin D - CDK4 and Cyclin E-CDK2 at G1/S restriction point and causes phosphorylation of RB (Fig-1).

Hyperphosphorylated RB dissociates from the complex, activating the transcription of E2F target genes that are essential for the progression through S phase. These include cyclin E, DNA polymerase, thymidine kinase and dyhydrofolate reductase[4,5].

Cyclin A expresses from late G1 phase, reaches a maximum during S phase, and is degraded during mitosis just before the metaphase. Cyclin A-CDK2 complex regulates events in mitotic prophase. It is thought to be required, in association with CDK2 and CDC2 (cell-cycle division2), for DNA synthesis during the S phase and progression through the G2/M transition, respectively. Cyclin A has been implicated in cellular transformation by forming complexes with adenovirus E1A protein, transcription factors DP-1 and E2F, and the retinoblastoma protein. Ectopic expression of Cyclin A can lead to adhesion-independent cell proliferation and advance cell entry into S phase [6,7].

Cyclin A over expression is found in a wide variety of human tumors, like esophageal, non small cell lung cancer, hepatocellular, renal, breast, and prostate carcinomas as well as soft tissue sarcomas. Over expression of Cyclin A protein in oral Squamous Cell Carcinomas (oral SCC) could result from gene amplification, mRNA over expression and impairment of proteolytic degradation by a variety of molecular biological mechanism (e.g. oncogene activation, inactivation of tumor suppressor genes or growth factor stimulation) have been postulated as playing a role in oncogenesis of oral SCCs and other tumors[8].

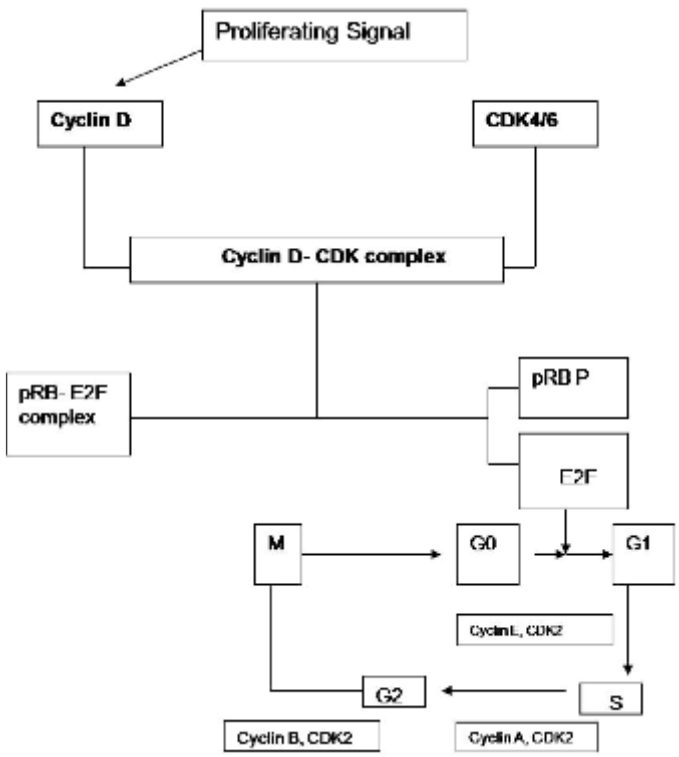
Cyclin dependent kinase inhibitors (CDKI). CDKI's in mammals fall in to two general families; the p21 family (p21Cip1/WAF1, p27Kip, and p57Kip2), and the INK4 family (p15INK4b, p16INK4a, p18INK4c, and p19INK4d). The CDK inhibitor p16 binds to CDK4 and CDK6 and inhibits phosphorylation of Rb, leading to G1 arrest [9]. Loss of p16 function has been demonstrated in a wide vari-

ety of human tumors, including oral and esophageal cancer. P21 acts on multiple Cyclin/CDK complexes to arrest the G1/S-phase of the cell cycle. This protein is frequently expressed in epithelial cells and may play a role in maintaining cells in a non-mitotic condition. p21 has been shown to be transcriptionally regulated by the tumor suppressor protein p53, providing an important possible explanation for P53 mediated cell cycle G1 arrest. p21 induction can also be accomplished by a p53 independent pathway. Over-expression of Rb protein has been shown to block p53-mediated apoptosis, and loss of Rb function has been shown to result in an induction of apoptosis in response.

III. Cyclin as a prognostic marker

Increased expression of cyclin is found in Oral squamous cell carcinoma and epithelial dysplasia. This is suggestive of the key role of mutated Cyclin in tumour progression[10]. Elevated expression of Cyclins, CDK2 and loss of p12DOC-1, p16INK4A and p27KIP1 may contribute to the multistep nature of oral carcino genesis. The mechanisms underlying Cyclin D1 over expression in cancer can be due to gene amplification, chromosomal translocation, and mitogenic stimulation of gene transcription. Cyclin D1 over expression has also been linked to increased risk of occult metastases and poor prognosis in oral cancer patient. Cyclins, the key regulatory proteins of cell cycle check point if mutated can lead to uncontrolled cell proliferation resulting in tumour formation as well as tumour growth. The expression of this molecule can be correlated with the prognosis of the tumour.

Fig.1: Flowchart depicting Cyclin in Cell cycle regulation.



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