

REVIEW ARTICLE

CELL CYCLE REGULATOR: CYCLIN DEPENDENT KINASE 10 AS POTENTIAL TARGET IN CANCER

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ABSTRACT

Cell cycle progression through each phase is regulated by series of kinase family, the cyclin dependent kinases (CDK). To understand this CDK machinery that controls normal cell cycles, by forming CDK/cyclin complexes thus assisting the identification of molecules or processes altered in tumor cell cycles. So far much has been said that de-regulation of cell-cycle control or inappropriate proliferation due to aberrant CDK activity is a common feature of most of the breast, gastric, Colorectal and testicular carcinomas. Literature shows that depending on the type of cancer, CDKs can be either upregulated or downregulated. One member of CDK family, a CDK10 attracted little attention until it was identified as a major element of resistance after therapy for breast cancer. Therefore, this review will provide an overview of this class CDK10 with a focus on its role in cell cycle and in various cancers.

KEYWORDS: Cell Cycle, Cyclin Dependent Kinase, CDK10, Cancer

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INTRODUCTION

The cellular processes such as cell cycle a series of tightly integrated events allow the cell to grow and proliferate¹. It is driven by protein kinases referred to as "Cyclin dependent kinases" (CDKs) whose serine/threonine-specific catalytic core, control the kinase activity and are only activated when bound by specific regulatory subunit "cyclin" (Figure 1). It plays critical roles in the control of cell-cycle progression, transcription, and neuronal functions². Human cancers are characterized by altered cell cycle regulation and a significant fraction of human cancers carry mutations that result in misregulation of CDK activity. They include overexpression of their cognate cyclins and inactivation of CDK inhibitors^[3].

CDK10/cyclin M complex modulates cellular growth and involved in many cancer which include breast cancer, colorectal, gall bladder tumour, nasopharyngeal, etc.^{4, 5, 6, 7}

DISCUSSION

Cell Cycle Regulators in the Cell Cycle: The division cell cycle consists of four coordinated processes (Figure 1 a): cell growth (G1 Phase), DNA replication (S Phase), distribution of the replicated copy of chromosomes to daughter cells (G2 Phase), and cell division (M Phase). DNA is synthesized during one phase of the cell cycle, and the replicated chromosomes are then distributed to daughter nuclei by a complex series of events preceding cell division. Progression between these stages is controlled by a conserved regulatory apparatus, which not only coordinates the different events but also links the cell cycle with extracellular signals that control cell proliferation⁸. Disturbances in cell cycle pathways by mutations in somatic cells make an important contribution to disease, and in particularly to cancer⁹. The cell cycle is a key target for tumorigenesis of many malignancies which can affect human health^{10, 11}. Defects in molecules that regulate the cell cycle have been implicated in cancer. Important molecules among these are p53, CDK inhibitors (such as p15, p16, p18, p19, p21, and p27), and Rb. They act to keep the cell cycle from progressing until all damaged DNA has been repaired^[12].

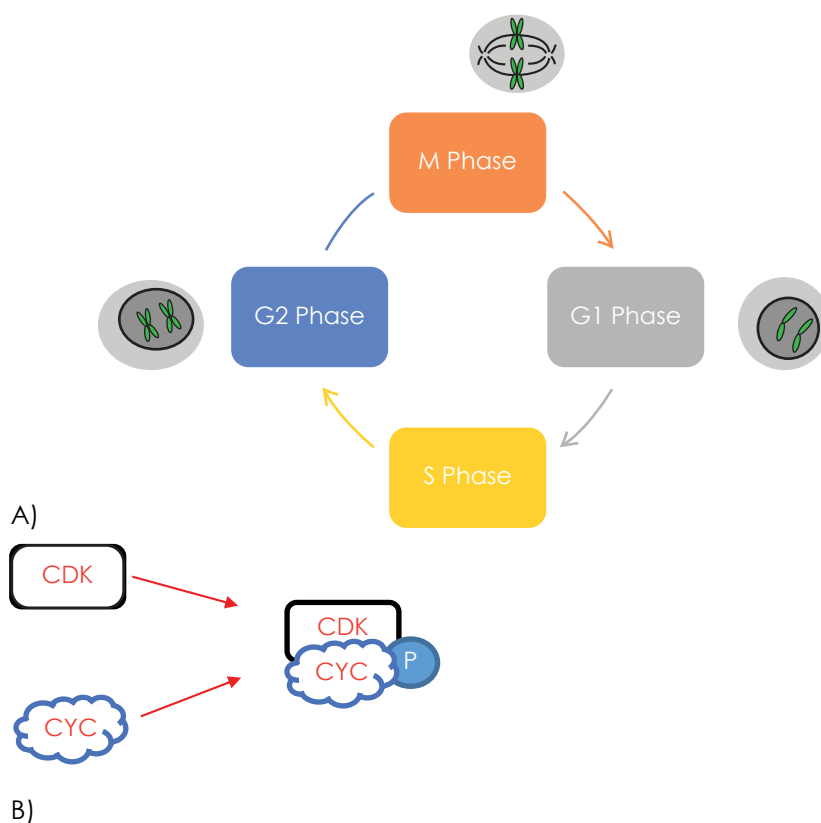


Figure 1: a) Schematic diagram of the cell cycle. M = Mitosis; G1 = Gap phase 1; S = Synthesis; G2 = Gap phase 2. b) Cyclin binds to CDK and control cell cycle processes through phosphorylation. P; Phosphorylation, Cyc; Cyclin, CDK; cyclin dependent kinases

Cyclin proteins bind to and activate their partner CDK (Figure 1b) and active kinase then phosphorylates a host of protein substrates within the cell. Phosphorylation of a specific set of proteins by CDK triggers the transition from one stage of the cell cycle to the next ^[13]. In somatic cells, movement through G1 and into S phase is driven by active form of the Cyclin D1, 2, 3/CDK4, 6 complex and the subsequent phosphorylation of retinoblastoma (Rb) protein. Once Rb is phosphorylated, the critical transcription factor, E2F-1, is partially released from an inhibited state and turns on a series of genes including cyclin A and cyclin E, they form a complex with CDK2 and cdc25A phosphatase. The later is able to remove the inhibitory phosphates from CDK2. The resultant cyclin E/CDK2 complex then further phosphorylates Rb, leading to a complete release of E2F and the transcription of multiple other genes essential for entry into S-phase and for DNA synthesis. Parallel to this, the c-myc pathway also directly contributes to the G1-S transition by elevating the transcription of genes for cyclin E and cdc25A. CDK activity is strictly dependent on cyclin levels which are regulated by ubiquitination and subsequent proteolysis. On mitogenic stimulation, cyclin D serves as an essential sensor in the cell cycle machinery and interacts with the

CDK4/6-Rb-E2F pathway. In addition to regulation by cyclins and phosphorylation/dephosphorylation of the catalytic subunit, CDKs are largely controlled by CKIs ¹⁴.

Role of CDK 10 in Cell Cycle: Cyclin-dependent kinases (CDKs) are a family of 20 serine/threonine kinases and their catalytic activities are modulated by interactions with cyclins and CDKs inhibitors (CKIs). Close cooperation between them is necessary for ensuring orderly progression through the cell cycle ^{15, 16}. CDK10 was discovered in early 1994 by sequence homology screening for CDK-related genes ^{17, 18}. It displays the central hallmarks of CDKs, bearing more than 40% sequence identity with CDK1 and other members of the family. Its closest paralog is CDK11, which promotes tumor cell proliferation ^{19, 20}. Early work established that CDK10 promotes cell proliferation and regulates transcription and development. CDK10 forms a complex with cyclin M to carry out its function²¹.

Role of CDK 10 in Cancer: A number of transcriptomic and proteomic studies report upregulation of CDK10 in cancer cells or in cells exhibiting exacerbated division, and/or downregulation of CDK10 in differentiated cells (Table1). For example, CDK10 was upregulated in tumour prostate specimens and

seminomas²². On the contrary, CDK10 was found to be downregulated in retinoic acid-treated retinoblastoma cells²³ and in butyrate-treated colon carcinoma cells²⁴. CDK10 mRNA and/or protein levels were found downregulated in biliary tract carcinomas²⁵, hepatocellular carcinomas²⁶ and

breast cancer tissues compared to adjacent noncancerous tissues²⁷. In the later study, the decreased CDK10 protein levels were associated with lymph node metastasis and unfavourable overall survival.

TABLE 1: STUDIES OF CDK10 IN VARIOUS CANCERS.

STUDY TYPE	PATIENT GROUPS	PRINCIPLE FINDINGS	REFERENCES
CASE CONTROL	20 PAIRED BREAST CANCER TISSUES AND ADJACENT NONCANCEROUS TISSUES.	CDK10 PROTEIN EXPRESSION WAS MARKEDLY DECREASED IN CANCER TISSUES COMPARED TO ADJACENT NONCANCEROUS TISSUES. FURTHERMORE, MULTIVARIATE ANALYSES INDICATED THAT CDK10 EXPRESSION MAY SERVE AS AN INDEPENDENT PROGNOSTIC FACTOR FOR SURVIVAL.	27
CASE CONTROL	189 POST-RESECTION GASTRIC CANCER PATIENTS AND 189 NON CANCER PATIENTS.	REDUCED CDK10 EXPRESSION INDEPENDENTLY PREDICTS A POOR PROGNOSIS IN PATIENTS WITH GASTRIC CANCER. IT CAN MAY SERVE AS A VALUABLE PROGNOSTIC MARKER AND A POTENTIAL TARGET FOR GENE THERAPY.	28
CASE CONTROL	12 BREAST CANCER SAMPLES AND 12 NON CANCER PATIENT.	COMPARED TO NON-CANCEROUS TISSUES, C1ORF63 EXPRESSION WAS ELEVATED IN TUMOR TISSUES. HOWEVER, C1ORF63 PREDICTS BETTER PROGNOSIS FOR BREAST CANCERS WITH ADVANCED TNM STAGE, AND THE UNDERLYING MECHANISM IS UNKNOWN. IN ADDITION, C1ORF63 IS CORRELATED WITH THE CELL CYCLE RELATED GENE, CDK10.	05
CASE CONTROL	47 TUMOUR SAMPLES AND 18 NORMAL SAMPLES.	RESULTS INDICATE THAT CDK10 PLAYS A CRUCIAL ROLE IN THE GROWTH AND SURVIVABILITY OF BILIARY TRACT CANCER, AND OFFERS A POTENTIAL THERAPEUTIC TARGET FOR THIS FATAL DISEASE.	29
CASE CONTROL	45 NASOPHARYNGEAL CARCINOMA SAMPLES AND 10 HEALTHY CONTROLS	FINDINGS IMPLICATE THAT ABERRANT METHYLATION OF THE CDK10 GENE PROMOTER OCCURS FREQUENTLY IN NASOPHARYNGEAL CARCINOMA, AND THAT REACTIVATION OF CDK10 MIGHT BE UTILIZED AS A NOVEL EPIGENETIC STRATEGY FOR THE TREATMENT OF NPC PATIENTS.	04
CONTROL	96 BREAST CANCER SAMPLES	THE UNMETHYLATED FORM OF CDK10, RASSF1A AND DAL-1 WAS DETECTED IN ALL THE SAMPLES ANALYSED.	30
CASE CONTROL	186 PRIMARY COLON TUMOUR SAMPLES AND 54 LIVER METASTASES	CDK 10 WAS FOUND TO BE OVEREXPRESSED IN BOTH PRIMARY COLON TUMOUR AND LIVER METASTASES.	31
CASE CONTROL	TISSUE SAMPLES OF COLORECTAL ADENOCARCINOMA AND MATCHED NORMAL COLON FROM 16 PATIENTS.	CDK10 IS OVEREXPRESSED IN HUMAN COLORECTAL CANCER TISSUES AND CELL LINES. HIGH CDK10 EXPRESSION IS ASSOCIATED WITH POOR SURVIVAL IN INDIVIDUALS WITH CRC. CDK10 KNOCKDOWN DECREASES CELL SURVIVAL AND PROMOTES APOPTOSIS IN CRC CELLS IN VITRO.	07
CASE CONTROL	128 SAMPLES OF PRIMARY GASTRIC TUMOURS AND 128 CONTROLS	CDK10 EXPRESSION MAY SERVE AS A NOVEL PROGNOSTIC BIOMARKER THAT HOLDS THERAPEUTIC PROMISE FOR GASTRIC CANCER.	32
CASE CONTROL	8 TISSUE SAMPLES OF GALL BLADDER CANCER PATIENTS AND 8 FROM HEALTHY CONTROL	INCREASED EXPRESSION OF C-RAF INDUCED BY DYSFUNCTION OF CDK10-CYCLIN M INCREASES CHEMORESISTANCE IN GALLBLADDER CANCER CELLS	06
CASE CONTROL	6 TESTICULAR CANCER AMPLES AND 5 NORMAL HEALTHY ADULTS SAMPLES	STARD7 (PRESENT ONLY IN THE NORMAL TESTES) AND CDK10 (PRESENT ONLY IN THE SEMINOMAS) COULD POTENTIALLY BE INVOLVED IN CELL DIFFERENTIATION AND GROWTH, AND THUS MAY SERVE AS POTENTIAL TARGETS FOR THERAPY OF PROGNOSTICATION OF SEMINOMAS	22

CONCLUSION

In conclusion, studies related to CDK 10 suggest that it may function as a prognostic marker in many different cancers. A number of studies report upregulation of CDK10 in cancer cells which are dividing rapidly and downregulation in differentiated cells. There is dire need to investigate the molecular mechanisms involved in the regulation of CDK10. This will not only help us to discover a therapeutic target against cancer but also prove to be a better diagnostic tool for different cancers.

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