Exploring CDKs, Ras-ERK, and PI3K-Akt in Abnormal Signaling and Cancer

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Abstract: Cancer or malignancy can be defined as abnormal growth and cell division. Malignancies spread, through metastasis invasion, or implantation into distant sites by which cancer cells can move through the bloodstream or lymphatic system to distant locations. The body cells follow the mitotic cell division process. Normal cell division occurs through the normal signal transduction through proto-oncogenes responsible for cell proliferation and differentiation. Mutation of these proto-oncogene leads to oncogene which can modify the gene expression and function through abnormal signal transduction, making uncontrolled growth of cells. The mitotic cell cycle is regulated by signal transduction through the cyclin-dependent kinases (CDKs), Ras-ERK, and PI3K-Akt. Abnormal signaling occurs through the mutation of these genes leading to cancer. The present review shortly reported the role of these proteins in abnormal signal transduction and cancer.

Keywords: CDKs, Ras-ERK, PI3K-Akt, abnormal signaling, and Cancer.

1. INTRODUCTION

Cancer means no answer to abnormal cell division and growth in an uncontrolled manner and can invade nearby tissues or other parts of the body through the blood and lymph systems and show metastasis. About 90.5 million people had cancer worldwide in 2015. In 2019, annual cancer cases grew by 23.6 million people and there were 10 million deaths worldwide, representing over the previous decade increases of 26% and 21%, respectively [1]. Therefore, cancer has been increasing day by day and genetic predisposition is one of the major factors. Frequent genetic or epigenetic alterations in cell cycle proteins or genes give rise to tumor development [2].

Cancer is predominantly called a disease of genome aberration though 5-10% of cancers are associated with inherited genetic mutations. Sometimes random mutations lead to the formation of tumors that may be benign and show less life-threatening characteristics. However, a tumor may become malignant due to driver mutations that make the tumor cancerous and potentially life-threatening. Cancer endues several characteristics that occur due to dysregulation of signal transduction pathways due to aberrant epigenetic or genetic function [3].

1.1. Abnormal Signal Transduction in Cancer

The aberrant activities of signaling proteins such as receptor tyrosine kinases, cyclin-dependent kinases, mTOR, ribosomal S6 kinase (RSK), mitogen- and stress-activated kinase (MSK), and mitogen-activated protein kinase (MAPK)-interacting kinase (MNK, Ras-ERK, and PI3K-Akt affect the cancer cells as well as other signal cascades that involve normal healthy cells, ECM proteins, immune system, blood vessels, etc. [4]. Tumorigenesis results due to the loss of fine balance between mitotic cell growth and cell death. When cells ignore the death signals like viral integration in DNA, activation of oncogenes, and DNA damage, the cell cycle progresses with all these aberrations to the next cycle thus dysregulating the adjoining cell signals in their way and thereby proceeding towards cancer. Thus abnormal cell signaling pathways become an integral part of cancer initiation and formation. Although several cancer treatments (chemotherapy, immunotherapy, radiation) could not specifically target cancer cells. Rather these therapies attack normal, healthy-growing cells adjacent to the cancer cells [5].

The majority of cancers occur as a result of aberrant cell cycle progression, triggered both by external and internal signals that determine normal cell function and control cell survival and growth. The unrestrained high rate of division, growth, proliferation, as well as differentiation of cancer cells, was mainly attributed to aggregation and accumulation of different anomalies which further facilitates abnormal cell signaling mechanisms and pathways [6]. To sustain and maintain their proliferative nature, cancer cells

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procured different mechanisms: these cells via autocrine mechanism undertake the stimuli to undergo rapid proliferative activity, these cells also possess the ability to trigger normal cells to secrete growth factors for their survival [7-8], alterations in the receptor structure were another way that makes the cancerous cells hyperactive even in a reduced level of growth factor [9]. Several molecular mechanisms, including genetic and epigenetic, regulate the cell cycle, resulting in the transformation of normal cells into tumors. Accumulating mutations in the DNA in response to replication errors or carcinogenic agents can result in tumor formation [2]. Known as passenger mutations, these mutations are not only associated with cancer initiation or progression but can also accelerate the development of cancer [5]. It is, however, the driver mutation that causes the tumor suppressor gene inactivation or activates the oncogenes, which causes the cells to break free from their orchestrated homeostasis and over-proliferate, become genetically unstable, become immortal, and begin metastasizing. Cancer cells bestow upon several mutational events which served as an additive advantage to the cells since both copies of the gene need to be mutated to manifest cancerous characteristics [10]. In cancer, tumor suppressor genes (TSGs) and oncogenes are critical regulators. In cancer, TSG mutations lead to proteins like p53 or pRB (retinoblastoma protein) becoming mutated and unable to regulate cell proliferation. In addition, the Ras gene, a proto-oncogene can lead to oncogenic Ras GTPases as a result of a gain of function mutation leading to uncontrolled cell division, which may lead to tumor development [11]. Cancer-related proteins or genes have also been linked to epigenetic dysfunctions, and oncogenesis is likely to be influenced by changes in the methylation state of certain gene promoters. Epigenetic dysfunctions have also been associated with cancer-related proteins or genes, where changes in the methylated status of promoters of certain genes play a role in oncogenesis [2]. Cancer progression is greatly impacted by epigenetically silenced cell cycle proteins such as CDK inhibitors, p16, or DNA damage repair enzymes. Several of these mutations are linked to unregulated signal transduction cascades that contribute to oncogenesis. Even though there are numerous signaling molecules and many signaling pathways that cause cancer to develop, Ras-ERK and PI3K-Akt – are mainly two key signaling pathways contributing initiation of cancer. These pathways cause metabolic changes, escalate cell proliferative activity, genetic instability, bypass programmed cell death, cellular polarity, metastatic activity, and more [2]. PI3K-Akt and Ras-ERK signaling pathways target several proteins or genes that are mutated during cancer progression. Several growth factors or cytokines stimulate these pathways to increase the growth rate of cells. Changes to the signaling cascades may make these pathways turn constitutive, that signals cells even in the absence of growth factors, directing their uncontrollable growth [12]. Ras is altered by mutations at codons 12, 13, and 61 that favor GTP binding, leading to the protein regulating both pathways through a molecular switch. The signaling pathway is constitutively activated in 30% of malignancies [13-14].

2. ROLE OF CYCLIN-DEPENDENT KINASES (CDKS)

The cell cycle is a wave of a coordinated string of specialized events of eukaryotic cells that results in an appropriate and controlled increase in cell number involving one parent cell to produce two daughter cells having similarity in shape and size and containing identical chromosomal sets. This phenomenon results in growth, division, repair, and regeneration as well as replacement of old, worn out, and damaged cells thus sustaining homeostatic balance [15]. Highly regulated molecular pathways, together with several regulators (positive and negative accelerators), tightly controlled the flow and progression of the cell cycle while yet retaining its fine-tuning. Checkpoints served as regulators that comprise proteins that portray as enzymes and their associated stimulating partners [16]. The checkpoints serve as control points that function to guide and surveil both external and internal conditions such as cell shape and size, growth factors, DNA architecture, and appropriate growth conditions of the cell. This eventually maintains cellular homeostatic equilibrium by assisting DNA replication and cell division meticulously and with accuracy. For cells to proceed through the mitotic cell cycle in a healthy homeostatic state, they must successfully pass each of the Cell Cycle checkpoints [6]. The key controllers of the highly regulated cell cycle are cyclins lacking fundamental enzymatic properties and Cyclin-dependent Kinases (CDKs) which co-occur in two forms [17]. In uncombined states, these proteins remain inactive whereas upon complexing with another class of proteins, cyclins, it acquires its kinase activity, thus becoming active.

The mitotic cell division cycle is regulated by two key classes of molecules, cyclins and cyclin-dependent kinases (CDKs), which are binary proline-directed serine-threonine-specific protein kinases consisting of positive regulatory subunit known as cyclin. The role of

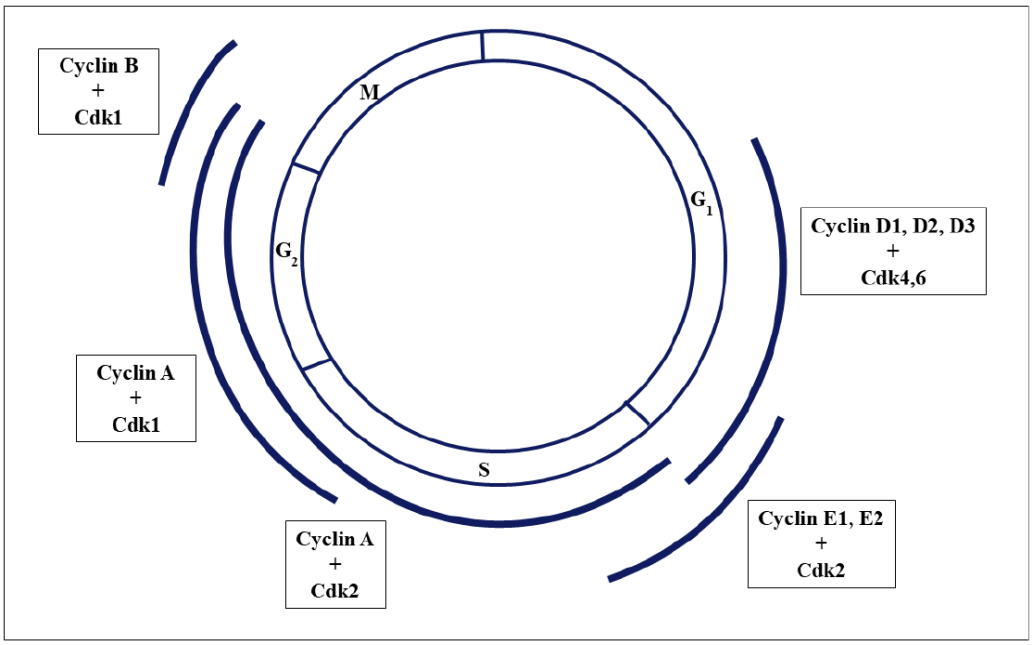

Figure 1: Cyclin-dependent kinase function in the mitotic cell cycle.

the CDKs is to control cell cycle progression through the phosphorylation of proteins that function at specific cell cycle stages (Figure **1**).

D-type cyclins (cyclins D1, D2, and D3) activate CDK4 and CDK6 for functions extending from mid-G1 to the G1/S-phase transition. E-type cyclins (cyclin E1 and E2) activate CDK2 for functions at the G1/S-phase boundary, probably extending into the early S-phase. Cyclin A activates CDK2 for functions extending from the G1/S-phase boundary and extending to G2. Cyclin A is known to interact with CDK1 as well; however, no specific function for this complex has been identified. Finally, cyclin B activates CDK1 at the G2/M-phase boundary with an activity that lasts until cyclin B is degraded during anaphase [18].

Each of the different CDKs-CDK1, CDK2, CDK4, CDK6, and cyclins-A, B, D, and E respectively paired up to function at distinct platforms of the cell cycle and are responsible to traverse different stages of the mammalian cell cycle [19-20]. The density of CDKs maintains a constant level throughout the cell cycle. Contrarily, cyclins develop and degrade at various phases, which modulates the activation of particular CDKs during the cell cycle. At varying phases of the cell cycle progression, active CDKs phosphorylate and activate their substrates. This controls the transcription of genes that produce different proteins needed for steady advancement to the next stage [21-22]. The Cyclin D and Cyclin E-Dependent Kinases keep an eye on the crucial point, or the Restriction point of the cell cycle during the G1 phase, which confirms and permits progression to the subsequent phase after satisfying the requirements and circumstances. Cyclin D interacts with CDK4/CDK6 to form cyclin D-CDK4/6 complex which when stimulated phosphorylates the retinoblastoma protein (pRB) and inactivates it. This inactivation of pRB subsequently releases transcription factor E2F which is a necessary event for the progression from G1 to S phase. CDK2-cyclin E and CDK2-cyclin A complex control G2 phase entry by regulating the synthesis of regulatory proteins necessary for DNA synthesis, thus promoting progression towards the G2 phase. Upon entry into the G2 phase, cyclin A-CDK1 and cyclin B-CDK1 aids in the start of the M phase and guide progression toward the M phase respectively. Furthermore, the G2 phase also facilitates FoxM1 phosphorylation which further plays a key role to acts as a transcription factor and transcribes genes encoding proteins of spindle assembly checkpoints [23]. The negative regulatory proteins, CDK Inhibitors (CKI), function as brake points and impede CDK activity by either interacting only with CDK or in a complex with cyclins to modulate CDK activity. Both the Cip/Kip family and the INK4 family are distinct groups of CDK inhibitors [23-24]. When CDKs are active, the ubiquitination apparatus ultimately destroys the Cyclins from the preceding phase, enabling escape from that stage and entry into the next [25].

CDKs is a molecular machine whose down-regulation results in obscuring various cell signaling

pathways through their aberrant activity by demilitarizing the checkpoints of the cell cycle and overruling various inhibitory mechanisms. Therefore, components of the CDK make a significant contribution to abnormal functioning in various ways.

2.1. Activation of CDKs

The CDKs require the removal of the phosphate group by other kinases known as phosphatase belonging to the Cdc25 family. Few Cdc25 family members have been identified as possible oncogenes whose transcriptional activation is mediated by the c-myc oncogene [26-27]. Ras/Raf/MEK/ERK signaling cascades via Elk transcription factor activation plays a major role in myc gene upregulation. This myc-gene which highly remains mutated among many cancer patients stimulates and hyperactivates cyclin-CDK complexes by instigating CDK Activating Kinase (CAK) and Cdc25 phosphatases [28].

There are very few reports of human malignancies brought on by modifications such as amplification and over-expression of CDK. The different anomalies in the functioning of CDKs were mainly attributed to protein mutations [29] amplification leading to overproduction in the level of CDKs. This finding has been investigated in different cancers such as melanoma, glioma, and sarcoma [16, 30].Through phosphorylating the carboxyl-terminal domain subunit of RNA polymerase II, a plethora of CDKs, notably CDK7, 8, and 9, couples cell cycle control with the general transcription factors. Since they directly govern the onset of transcription, CDKs take a role in the progression of the cell cycle from one stage to the next [31]. Therefore, abnormal CDKs contribute to incorrect gene transcription and influence the course of the cell cycle, ultimately resulting in cancer.

2.2. CDK Inhibitors (CKIs)

As a tumour suppressor, CKIs inhibit cells' growth by triggering the pRB gene. Several CDK inhibitors, including p15, p16, p21, and p27, block the formation of cyclin-Cdk complexes [28]. On the other hand, the p53 tumor suppressor gene controls the expression of the p21 gene. Therefore, p53-dependent tumor suppression is controlled by p21 [32]. Any damage in DNA structure is thus taken care of by the active participation of p21 which inhibits the CDKs responsible for initiating the G1 cell cycle [33]. Since any abnormality in CDK inhibitors is not controlled by the p53 protein and the cyclin-Cdkcomplexes dictate the progression of the cell cycle from one phase to the next even if any DNA replication error is present. Thus, the genomic integrity of the cells becomes compromised due to any abnormality present in the CDK inhibitors. So, we may conclude that any deviation in the CDKI functionality leads to tumorigenesis by inhibiting apoptosis [34].

2.3. Cyclin Proteins

According to several reports, abnormal characteristics as a result of mutated cyclin play a part in a variety of human cancers, including B cell lymphoma, gastric, and esophageal carcinoma, colorectal cancers, prostate cancers, etc. [16, 22, 35, 36, 37, 31]. Overexpression, hyperactivation, and hyper-expression of Cyclin D, CDK4 and CDK2, and anti-apoptotic genes respectively are characteristics of various human malignancies [31]. Again, it has been discovered that functional loss in Cyclin D1 is linked to a lack of normal cell cycle progression due to a major factor of genomic instability. Studies have proven that Cyclin D1 regulates the Rho-ROCK signal and the production of thrombospondin, leading to the malignant growth of cells and playing a predominant role in cellular motility, invasion, and metastasis, for example, cyclin D1overexpression is evident in human breast cancer [38] which might be due to Ras-mediated signaling pathways [39].

2.4. Checkpoint Proteins

The p53 is a tumour suppressor protein and also known as a cell cycle checkpoint protein that interacts with a certain DNA sequence that might elicit cell death or apoptotic induction. DNA double-strand breaks trigger the protein kinase ATM, which increases p53 phosphorylation by activating the ARF protein. By altering MDM2's ubiquitylation function, mutations in ATM or ARF lower p53's phosphorylation and activity, increasing the likelihood of tumours in those patients [40]. Although mutation in the p53 gene was initially discovered in SV40-transformed cells, it is now known to be the primary cause of several human malignancies, including more than 50% of lung carcinomas [41,42] as because the mutated version of the p53 gene inactivates the protein due to structural variations [43]. Studies of the literature on leukemia, breast cancer, gliomas, and sarcomas reveal reports of Mdm2 overexpression, a negative regulator of p53 [44-46]. The target genes of the p53-dependent pathway that arrests the cell cycle or encourages apoptosis include WAF1/Cip1, which function as CDK inhibitors, whereby mutation in WAF1 proteins contributes to the occurrence of breast cancers [47]. Another way that

oncogenes contribute to the production of stress signals is by activating INK4 family proteins, which regulate the activity of cyclin D-dependent kinases to inhibit the phosphorylation of RB family proteins. The RB protein remains inactive throughout the G1 phase of the cell cycle, inhibiting E2F activity, which is essential for the transcription of several G1-S transition genes. RB controls the functioning of P53 via the p53/RB /MDM2 complex. Many malignancies have reports of RB mutations or deletion [39].

3. RAS-ERK SIGNALING

The Ras-ERK signaling cascade can be activated by several mechanisms like BCR-ABL gene fusion, overexpression of receptor tyrosine kinases, and Myc. The BCR-ABL gene fusion that gives rise to the oncogenic fusion gene of tyrosine kinase Abl is associated mostly with patients of chronic myelogenous leukemia (CML) [48]. This BCR-ABL protein shows enhanced tyrosine kinase activity due to the presence of many protein-protein interaction domains like SH2, SH3, proline-rich sequences, DNA, and Actin-binding domains that can bind and phosphorylate many downstream proteins like Ras involved in different cellular signal transduction pathways. Ras gets activated by the formation of complexes with Grb-2, CRKL, Ras guanine nucleotide exchange factor, and SHC which thereby activate Raf (a serine-threonine kinase) which ultimately show anti-apoptotic effects [49]. Over-expression of receptor tyrosine with intrinsic kinase activities or mutation of the receptors like EGFR (Epidermal growth factor receptor), fibroblast growth factor receptor (FGFR), and platelet-derived growth factor receptor (PDGFR) can result in the constitutive function of Ras-ERK signaling and thereby phosphorylate many proteins like Bad, Bim, Caspase-9 and has a role in cell differentiation and apoptosis [13]. Amplification or gene-dosage of transcription factor Myc, which is a downstream target proto-oncogene of Ras-ERK pathway can amplify the genes associated with cell-proliferation, DNA replication and transcription, altered cellular metabolism and protein synthesis, activation of angiogenesis and suppression of immune responses by binding to the promoter sequences of genes that encode cell cycle proteins like G1/S cyclins, CDKs and G1 restriction point inhibitor proteins [2, 50].

4. PI3K-AKT SIGNALING PATHWAY

The PI3K-Akt signaling cascade can be activated by (a) Amplification or activating mutations of proteins like Akt, and the adaptor protein PIK3R1 [51]. Activated Akt acts as an important component in tumor development from several studies by regulating cell survival and proliferation and can act as an oncogene when overexpressed or mutated [52-53]. Akts also takes part in the inhibition of cell cycle inhibitors like KIP1(p27) and CIP1(p21) [2,10]. Akt can also regulate Wnt signaling by phosphorylating and inhibiting GSK3 proteins thereby regulating cell differentiation [54-55]. (b) Deletion or inactivating mutations of proteins like PTEN and INPP4B tumor suppressors that hydrolyze PI3K products such as phosphatidylinositol 3,4,5-trisphosphate (PIP3). PTEN inhibits the activity of Akt [52]. Several types of cancer have exhibited the loss of function of PTEN due to genetic alterations (mutations or deletions) or epigenetic regulations (promoter hypermethylation) [56-57]. (c) Mutations in the downstream proteins TSC1 and TSC2 that function as tumor suppressors hyperactivate PI3K-Akt signaling signaling by mTORC1. Hence TSC inhibition leads to hyperactivation of mTOR which acts as a chief mediator of cancer progression which becomes evident due to the loss of PTEN [58, 2, 10].

5. CONCLUSION

A deeper understanding of the molecular origins of cancer which are hyperactive in cancer cells might lead us to develop targeted treatments for cancer that will effectively kill the cancer cells sparing the normal ones. Hyperactivation of cyclin-dependent kinases may loss of the cell cycle control checkpoints which cause abnormal signaling-mediated cancer. The abnormalities in PI3K-Akt and Ras-ERK crosstalks may distort the signaling cascades forming a wide network of abnormal signaling meshwork and thereby resulting in subsequent anomalies in cellular activities. So, inhibitions of cyclin-dependent kinases, PI3K-Akt and Ras-ERK are taken as major targets in cancer therapy.

CONFLICT OF INTEREST

The authors confirm that there is no conflict of interest in the present study.

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