

The emerging role of CaMKII in cancer

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ABSTRACT

Ca²⁺/calmodulin-dependent protein kinase II (CaMKII) is a multifunctional serine/threonine kinases best known for its critical role in learning and memory. Recent studies suggested that high levels of CaMKII also expressed in variety of malignant diseases. In this review, we focus on the structure and biology properties of CaMKII, including the role of CaMKII in the regulation of cancer progression and therapy response. We also describe the role of CaMKII in the diagnosis of different kinds of cancer and recent progress in the development of CaMKII inhibitors. These data establishes CaMKII as a novel target whose modulation presents new opportunities for cancer diagnosis and treatment.

INTRODUCTION

Calcium ion (Ca²⁺) is a ubiquitous intracellular signal responsible for a broad range of cellular events, such as cell growth, cytoskeletal organization, regulation of synaptic transmission, and Ca²⁺ homeostasis [1-3]. The Ca²⁺/calmodulin (CaM)-dependent protein kinases (CaMKs) are multifunctional serine/threonine kinases whose activity are regulated through Ca²⁺ signaling [4]. Recent studies demonstrated that high levels of different isoform of CaMK, especially for CaMKII, expressed in several cancers such as lung [5], breast [6], prostate [7] and colon cancer [8]. CaMKII phosphorylates nearly 40 different proteins, including enzymes, ion channels, kinases, and transcription factors [9, 10] and plays a critical role in the regulation of proliferation, differentiation and survival of various cancer cells [5-8]. In this review, we will focus on the structure and biology properties of CaMKII, including the roles of CaMKII in the regulation of cancer proliferation and therapy response. The role of CaMKII as a biomarker in cancer diagnosis and the application of CaMKII inhibitors in cancer research will also be discussed in this review.

STRUCTURE AND ACTIVATION OF CaMKII

CaMKII is expressed as a multimeric protein, which

typically comprised of 12 subunits in most commonly observed physiological conditions [11]. Each of these subunits has an N-terminus catalytic domain, followed by a regulatory domain, and a C-terminus association domain responsible for multimerization (Figure 1). Like other kinases, the catalytic domain of CaMKII has an ATP-binding pocket that creates a microenvironment to lower the energy required to hydrolyze ATP, enhancing the rate of transfer for the γ phosphate from ATP to a target S/T and ejecting ADP [12]. The regulatory domain of CaMKII has a C-terminus Ca²⁺/CaM binding region and an N-terminus autoinhibitory region [13]. The autoinhibitory region contains most of the elements that are critical for regulation of CaMKII activity, including the post translational modification (PTM) segment for phosphorylation, O-linked N-acetylglucosamine (O-GlcNAc) modification, and oxidation [9, 14].

There are four different CaMKII genes, and each gene encodes a distinct CaMKII isoform (β , γ , and δ). All CaMKII isoforms appear to share common regulatory mechanisms and protein targets but differ in tissue distribution [15]. Under resting conditions, the catalytic domain is constrained by the autoinhibitory sequences on the regulatory domain, thereby inhibiting the activity of the enzyme [12]. When intracellular Ca²⁺-levels periodically rise during the cellular Ca²⁺-transient, Ca²⁺ binds to CaM and activates CaMKII by binding to the regulatory domain. The activation leads to the phosphorylation of adjacent CaMKII subunits at

Thr286 (for the α isoform) or at Thr287 (for the $\beta, \gamma,$ and δ isoforms). The phosphorylation of Thr287 has at least two effects on CaMKII. The binding affinity of CaM for the CaMKII regulatory domain increases by more than 1000-fold. Additionally, the negatively charged phosphate group at the Thr287 site precludes reassociation of the catalytic and regulatory domains, preventing autoinhibition even if Ca^{2+} falls and CaM dissociates from CaMKII. The autonomous activation of CaMKII by Thr287 phosphorylation will persist until the phosphate group is removed by a protein phosphatase [10, 16, 17].

Elevated reactive oxygen species (ROS) level upregulates CaMKII through direct and indirect ways. The regulatory domain of CaMKII contains a pair of redox-sensitive amino acids (Cys280/Met281 in the α isoform, Met281/Met282 in the $\beta, \gamma,$ and δ isoforms) that can be oxidized when exposed to elevated levels of oxidative stress. Like Thr287 autophosphorylation, Met281/Met282 oxidation prevents reassociation of the catalytic and regulatory domains even in the absence of Ca^{2+} /CaM binding either [10, 18]. And also oxidation may increase the sensitivity of CaMKII to activation by Ca^{2+} /CaM and the abundance of Thr287-autophosphorylated CaMKII by inactivating phosphatases [12].

The underlying mechanisms for CaMKII activation during hyperglycemia and diabetes through the addition of an O-GlcNAc modification was found in recent study.

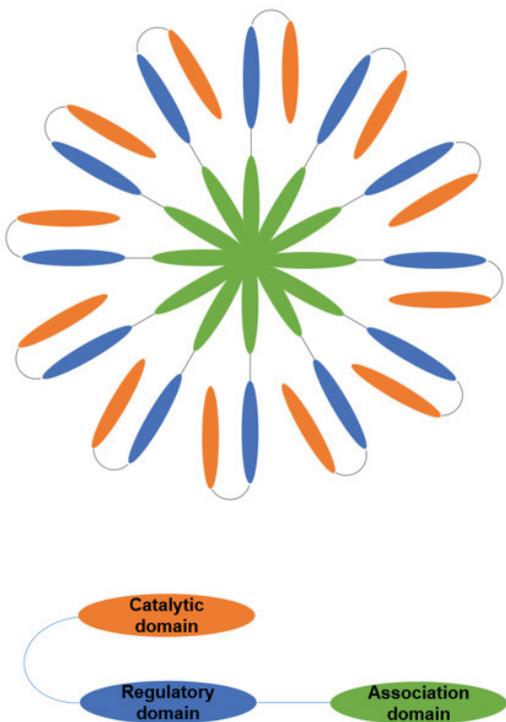


Figure 1: Schematic depiction of the Ca^{2+} /calmodulin dependent protein kinase II (CaMKII) structure. CaMKII holoenzyme is a dodecamer (top) and each monomer has the association domain, regulatory domain, and catalytic domain (bottom).

O-GlcNAc modification of CaMKII at Ser279 activated CaMKII autonomously, creating molecular memory even after Ca^{2+} concentration declines [19]. In addition, CaMKII can be activated via nitric oxide (NO)-dependent nitrosylation of Cys273 or Cys290, the exact mechanism is still unknown at present [20] (Figure 2).

THE ROLE OF CAMKII IN CANCER PROGRESSION

Cell proliferation

Some studies have implicated CaMKII as an important player in cancer cell proliferation. The pharmacologic inhibition of CaMKII in MG-63 and 143B human osteosarcoma cells by KN-93, a chemical inhibitor of CaMKII, resulted in an 80 and 70% decrease in proliferation, respectively. The in vivo administration of KN-93 to mice xenografted with human osteosarcoma cells significantly decreased intratibial and subcutaneous tumor growth. And the inhibitory effect of CaMKII was associated with increased p21^{CIP/KIP} gene expression, protein levels, and decreased the phosphorylation of retinoblastoma (Rb) protein and E2F transactivation [21]. In normal and neoplastic B-lymphoid cells, suppression of CaMKII prevented the excessive B-cell activating factor (BAFF) -induced aggressive B-cell malignancies. It appeared that human soluble BAFF (hsBAFF)-mediated cell proliferation and survival was Ca^{2+} -CaMKII-dependent [22]. In chronic myeloid leukemia (CML), cell proliferation specifically depends on activation of the CaMKII γ isoforms. CML cells undergoing terminal differentiation or growth arrest display a marked reduction of CaMKII γ autophosphorylation. Inhibition of CaMKII γ resulted in the suppression of myeloid leukemia cell proliferation. The inhibitory effect of CaMKII γ related to multiple signaling pathways, including mitogen-activated protein kinase (MAPK), signal transducer and activator of transcription 3(Stat3)/Stat5, and glycogen synthase kinase 3 β (GSK3 β)/ β -catenin pathways [23]. Recently, Monaco et al. [24] reported that inhibition of CaMKII activity resulted in an upregulation of CaMKIV mRNA and protein in myeloid leukemia cell lines. Conversely, expression of CaMKIV inhibited autophosphorylation and activation of CaMKII, and elicited G_0/G_1 cell cycle arrest, impairing cell proliferation. These data reveal a novel cross-talk between CaMKII and CaMKIV and suggest that CaMKII suppresses the expression of CaMKIV to promote leukemia cell proliferation. CaMKII γ promoted the cell proliferation via direct activation of nuclear factor kappa-light-chain-enhancer of activated B cells (NF- κ B) and multiple oncogenic signaling pathways in non-small cell lung cancer (NSCLC) was found by Chai et al. CaMKII γ could phosphorylate I κ B α kinase

β (IKK β) at Ser177/181 and functioned as a mediator of IKK β activation in NSCLC. In the meanwhile, CaMKII γ could directly or indirectly upregulate multiple signaling pathways such as extracellular signal-regulated kinase 1/2 (Erk1/2), protein kinase B (Akt1), Stat3, and β -catenin and involve in regulating the survival and proliferation of NSCLC cells [5]. In papillary thyroid carcinoma (PTC), CaMKII is activated by BRaf^{V600E}, Ras, and by RET/PTC. The activation of CaMKII subsequently leads to Erk activation and cell proliferation. Inhibition of CaMKII attenuates Erk activation and DNA synthesis in PTC cells [25]. Furthermore, the cell proliferation effects of CaMKII depend on the phosphorylated sites was found by Hoffman et al. [26]. They showed that the overexpression of a wild-type or Thr286 phosphomimic form of CaMKII increased proliferation rates of neuroblastoma and breast cancer cells, whereas overexpression of a Thr253 phosphomimic form significantly reduced proliferation rates in these cells.

Cell cycle effects

CaMKII involves in the cell cycle control with a complex manner and associates with multiple cell signaling pathways (Figure 3). In colon adenocarcinoma cells, CaMKII activates mitogen-activated/extracellular regulated kinase (MEK)/Erk, which is responsible for the phosphorylation and subsequent proteasomal degradation of cyclin-dependent kinase inhibitor 1B (p27^{Kip1}), thus causing the promotion of the S-G₂/M transition of cell

cycle progression [27]. In osteosarcoma cells, CaMKII α increases the phosphorylation of T-lymphoma and metastasis gene 1 (Tiam1) and its membrane localization, and then activates ras-related C3 botulinum toxin substrate 1(Rac1), inhibits the expression of p21^{CIP/KIP} and leads to a cell cycle progression [21]. In HeLa cells, CaMKII phosphorylates cell division cycle 25c (cdc25c) and enhances G₂/M transition. Treatment of a synchronous population of HeLa cells with KN-93 or the microinjection of AC3-I (a specific peptide inhibitor of CaMKII) resulted in a cell cycle block in G₂ phase [28]. In breast cancer cells, CaMKII triggers the export of breast cancer susceptibility gene 1 (BRCA1) from nucleus and decreases the BRCA1-dependent expression of p21^{CIP/KIP} [29]. Moreover, CaMKII also can stimulate Cyclin D1 expression via NF- κ B in breast cancer cells, which results in promoting of G₁/S transition [30]. In addition to the promotion of cell cycle progression, CaMKII also can block the cell cycle of different cancers. CaMKII may suppress cell cycle progression by stabilization of p53 via CaMKII-dependent phosphorylation of the RING-H2 type E3 ligase (Pirh2) in breast and lung cancer cell lines [31].

Invasion and metastasis

More and more evidences support the critical role of CaMKII in cancer invasion and metastasis. Daft et al. [32] demonstrated that the upregulation of CaMKII α was found in primary osteosarcoma tissues

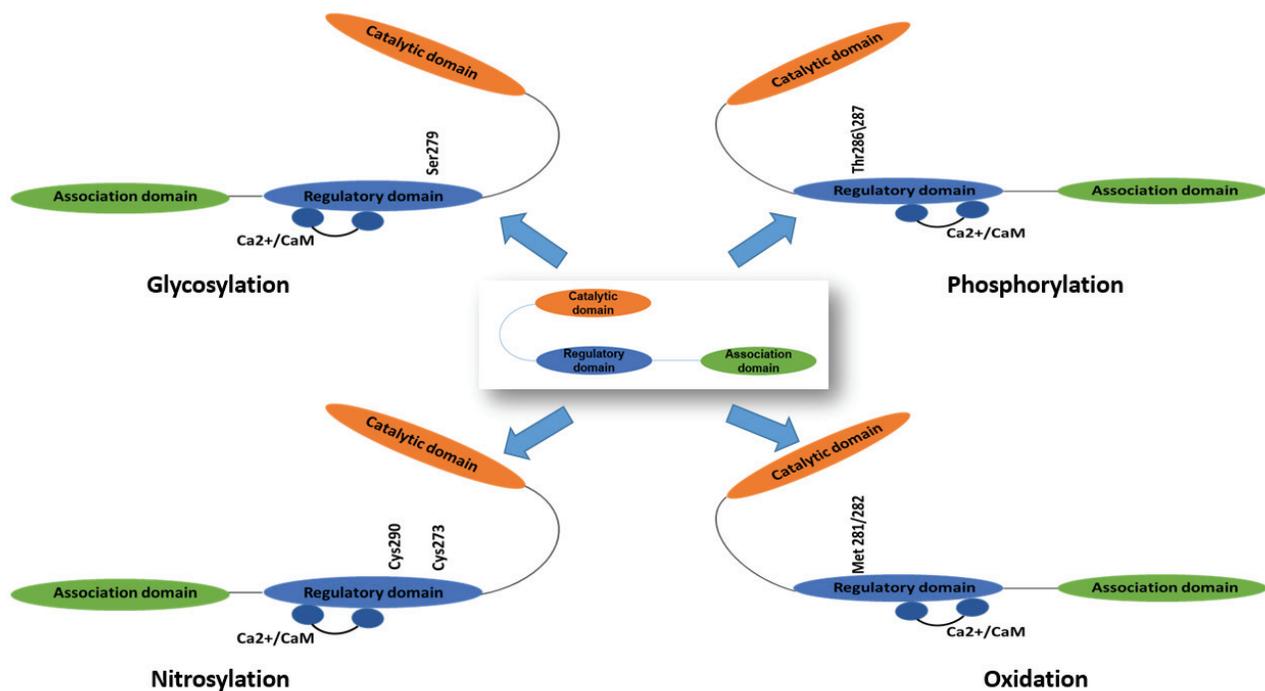


Figure 2: The activation mechanisms of Ca²⁺/calmodulin dependent protein kinase II (CaMKII). CaMKII could be activated by phosphorylation, oxidation, nitrosylation and glycosylation.

from patients and in aggressive osteosarcoma cell lines. The knockdown of CaMKII α decreases motility and invasion, whereas CaMKII α overexpression increases the tumorigenic properties of osteosarcoma cell lines in vitro. Wang et al. [33] found that the activation of CaMKII significantly increased cell motility and the capacity of wound healing in prostate cancer cell lines. The rate of wound closure was decreased by 80% after inhibition of CaMKII. Bourguignon et al. [34] showed that CaMKII involved in hyaluronan (HA)-CD44-mediated signaling and modulated the adhesion and migration of head and neck squamous cell carcinoma (HNSCC) cells. HA-CD44 binding induces the leukemia-associated Rho guanine nucleotide exchange factor (LARG)-specific RhoA signaling and phospholipase C ϵ (PLC ϵ) activity. The activation of RhoA- PLC ϵ stimulates inositol 1,4,5-triphosphate production, intracellular Ca²⁺ mobilization, and subsequently activates CaMKII, leading to phosphorylation of the cytoskeletal protein, filamin. The phosphorylation of filamin reduces its interaction with filamentous actin, promoting HNSCC cell migration. Li et al. [35] reported that apoptosis regulatory protein Siva1 inhibited stathmin's activity through CaMKII dependent phosphorylation of stathmin at Ser16 in breast cancer cells. The formation of microtubules and impedes focal adhesion assembly, cell migration, and epithelial–mesenchymal transition (EMT) were enhanced by Siva1 via the inhibition of stathmin. Cuddapah et al. [36] indicated that the interaction of CIC-3 and CaMKII played critical role in the invasion and metastasis properties of glioma cells. CaMKII phosphorylated CIC-3 at Ser109 and led to an increase in CIC-3 current. CIC-3 enhances migration of glioma cells, and pharmacological inhibition with NPPB2 demonstrates a requirement for chloride channels to support the glioma invasion. In addition, recent evidence elucidates that bradykinin increases human glioma cell motility. Bradykinin activates the bradykinin receptor B2 (B2R), leading to increases in Ca²⁺ and enhanced the migration of glioma cells. The action of bradykinin in glioma is related to Ca²⁺-activated Cl currents, which is modulated by CaMKII [37]. Umemura et al. [38] found another mechanism of CaMKII involving cancer cell invasion. They showed that store-operated Ca²⁺ entry (SOCE) promoted melanoma progression by enhancing cell invasion and metastasis through activation of Erk signaling via the CaMKII/Raf-1/Erk pathway, irrespective of the status of Braf. Najdi et al. [39] proposed that CaMKII involved in the auto-activating loop of Wnt and CaMKII, and skew the balance of T-cell factors (TCFs). Inappropriate activation of this signal pathway would contribute to the cause and aggressive behavior of colon cancer cells.

Apoptosis

The anti-apoptotic activity of CaMKII was found in recent studies. One anti-apoptotic pathway utilized by CaMKII is inhibition of caspase expression at the procaspase level and inhibition of caspase activation. Overexpression of CaMKII resulted in inhibition of procaspase-7 and procaspase-8 expression. And the activation of caspase-2, -7, and -8 could be prevented or diminished by overexpression of CaMKII [40]. Cohen et al. [41] reported that downregulation of ErbB could suppress the CaMKII signaling, which is coincident with the induction of apoptosis in breast and prostate cancer cells.

THE ROLE OF CAMKII AS A BIOMARKER IN CANCER DIAGNOSIS

The role of CaMKII as a biomarker in cancer diagnosis was evaluated in some studies. Epigenetic regulation of gene expression through changes in CpG methylation in the promoter plays pivotal roles during cancerogenesis. Kim et al. [42] found that normal breast cells and breast cancer cells had different CaMKII β promoter methylation status. Based on this result, they suggested the promoter methylations of CaMKII β can be used as a biomarker for the diagnosis of breast cancer. Mamaeva et al. [43] showed that the expression profile of CaMKII isoforms was tissue-specific and could be used as a biomarker to distinguish the origination of cancer cells. They examined the gene expression of the four isoforms of CaMKII: α , β , γ , and δ in prostate cancer cell line C4-2B, PC3, LNCaP, and DU145. Only C4-2B and PC-3 cells, which are both derived from bone metastases, express all four isoforms of CaMKII. In another study, expression profiling of primary tumor tissues from 12 colon and 12 rectal cancers was performed using oligonucleotide microarray analysis. Of the genes differentially expressed between colon and rectal cancer, CaMKII γ was one of the most significantly altered. CaMKII γ provides potential candidate for distinguishing between colon and rectal cancer [44]. In a recent study, Chai et al. [5] demonstrated that CaMKII γ was aberrantly expressed in human NSCLC tissues and correlated well with the degree of malignancy, and CaMKII γ could be used as a potential biomarker of malignancy for NSCLC. Cancer cachexia is a syndrome associated with malignant tumor disease defined by weight loss, asthenia and anorexia. Stephens et al. [45] indicated that CaMKII β directly involved in human cancer cachexia. The activation of CaMKII β appears to be a general marker of muscle wasting in human cancer cachexia.

THE ROLE OF CAMKII IN CANCER THERAPY

Therapy resistance

Cellular Fas-associating protein with a novel death domain (FADD)-like interleukin-1 β -converting enzyme inhibitory protein (c-FLIP), contributes to cancer therapy resistance has been demonstrated in some studies [46-48]. Yang et al. reported that the expression and phosphorylation of c-FLIP_L proteins was regulated by CaMKII [49]. When CaMKII activity was inhibited, c-FLIP expression reduced and the resistance glioma cells became sensitive to Fas-mediated apoptosis [50]. The similar results was also found in melanoma cells. KN-93 could sensitize resistant melanoma cells to TNF-related apoptosis-inducing ligand (TRAIL)-induced apoptosis via downregulated of c-FLIP proteins [51]. In addition, Rodriguez-Mora et al. [52] indicated that CaMK inhibitor could increase the treatment efficacy of doxorubicin, ionizing radiation, or photodynamic therapy in breast cancer cells. CaMKII participated in hydrogen

peroxide-induced Erk phosphorylation was considered to be the underlying mechanism. Riganti et al. [53] showed that the transient increase of Ca²⁺ may activate CaMKII, which in turn phosphorylated and activated the transcription factor hypoxia-inducible factors 1 α (HIF-1 α) in colon cancer cells. As a consequence of HIF-1 α nuclear translocation, P-glycoprotein 1 is overexpressed, intracellular accumulation of doxorubicin is reduced and cytotoxic effects of doxorubicin are prevented. These studies propose the critical role of CaMKII in cancer therapy resistance and targeting these pathways may provide novel therapeutic strategies in treatment of cancer.

Modulation of therapy efficiency

For patients with inoperable or disseminated neuroblastoma, one of the most actively employed treatment approaches is targeted radiotherapy using ¹³¹I-labeled metaiodobenzylguanidine (MIBG) [54]. The efficacy of ¹³¹I-MIBG therapy is related to norepinephrine transporter (NET), which activity is largely modulated through specific intracellular signaling cascades, and candidate pathways for its regulation including protein

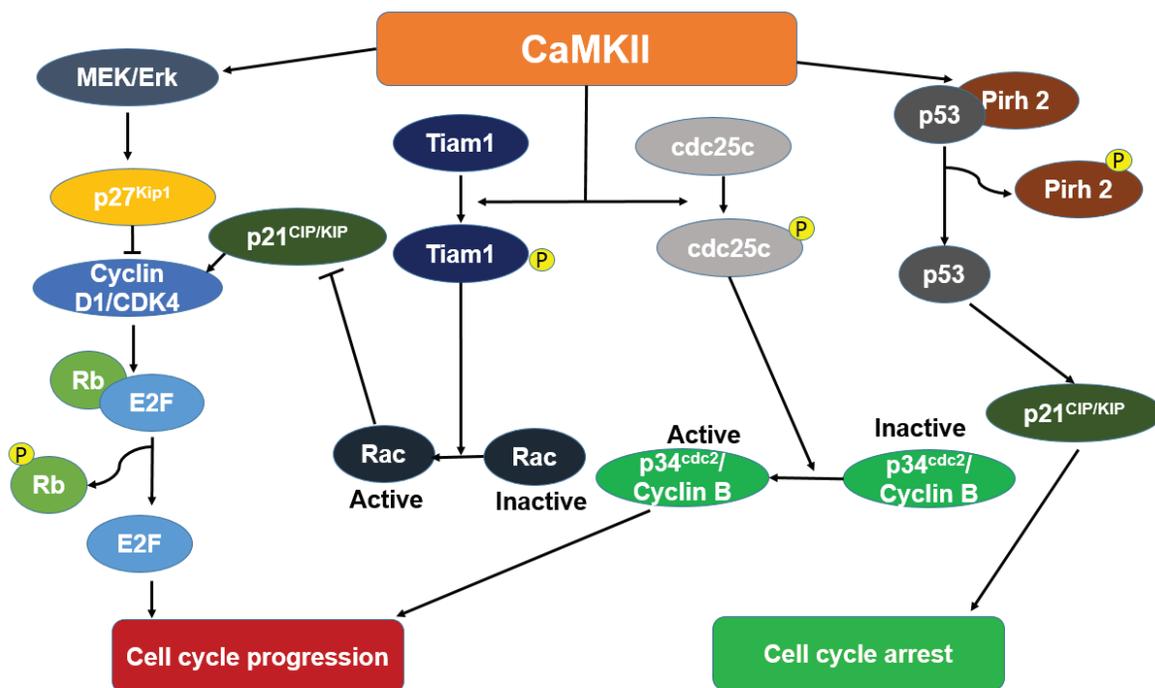


Figure 3: The proposed mechanisms depicting the cell cycle effect of Ca²⁺/calmodulin dependent protein kinase II (CaMKII) in cancer. CaMKII activates cyclin-dependent kinase inhibitor 1B (p27^{Kip1}) via the mitogen-activated/extracellular regulated kinase (MEK)/extracellular signal-regulated kinase (Erk) pathway. Activated p27^{Kip1} will then inhibit cyclin-dependent kinase 4 (Cdk4)/CyclinD1 complexes, and therefore retinoblastoma (Rb) phosphorylation and E2F activation, induce cell cycle progression. CaMKII phosphorylates T-lymphoma and metastasis gene 1 (Tiam1) and then increases the activation of ras-related C3 botulinum toxin substrate 1(Rac1). The activation of Rac1 inhibits the expression of p21^{CIP/KIP}. This leads to a cell cycle progression. CaMKII increases the phosphorylation of cell division cycle 25c (cdc25c) and activates p34^{cdc2}/Cyclin B, causes the cell cycle progression. CaMKII suppresses cell cycle progression by stabilization of p53 via CaMKII-dependent phosphorylation of RING-H2 type E3 ligase (Pirh2).

kinase C (PKC), mitogen activated protein kinase (MAPK), phosphatidylinositol-3 kinase (PI3K), and CaMKII [55]. Melittin, a water-soluble 26-amino acid peptide derived from bee venom of *Apis mellifera*, can exert toxic or inhibitory effects on many types of cancer cells [56-58]. Wang et al. [59] demonstrated that melittin potentiated the TRAIL induced apoptotic effects in human hepatocellular carcinoma cells by activating the CaMKII-transforming growth factor- β -activated kinase 1 (TAK1)-c-Jun N-terminal kinase (JNK)/p38 pathway but inhibiting the IKK-NF κ B pathway. Fucoidan, a fucose-rich polysaccharide, is isolated from brown seaweed such as *Cladosiphon okamuranus* and *Fucus evanescens*. Recent studies have reported its various biological activities including anti-inflammatory, anti-coagulant, and anti-cancer [60, 61]. Chen et al. [62] indicated that fucoidan treatment inhibited cell growth and induced apoptosis in breast and colon cancer through the promotion of endoplasmic reticulum (ER) Ca²⁺-dependent CaMKII phosphorylation. Additionally, fucoidan has been linked to the increase of ER-stress and release of Ca²⁺ intracellularly. Cytosolic Ca²⁺ binds to calmodulin to activate CaMKII signalling, leading to ER stress-induced cell apoptosis through activating the mitochondrial apoptosis pathway [63].

CAMKII INHIBITORS

During last two decades, a number of CaMKII inhibitors have been synthesized or found [14, 64]. Current knowledge about CaMKII control on physiological or pathological functions is largely based on the researches on these inhibitors. The most widely used inhibitor for study of cellular and in vivo functions of CaMKII has been KN-93 and KN-62. KN-93 and KN-62 share the same structural elements and mechanism of action. Inhibition by both is competitive with Ca²⁺/CaM and not competitive with ATP [14]. KN-93 and KN-62 have been found to induce cell cycle arrest in a variety of cancer cells. The G₁ and/or S phase arrest effect of KN-93 and KN-62 on K562 and HeLa cells has been reported [65, 66]. KN-93 decreased cyclin-dependent kinase (cdk) 4 activity by reducing Cyclin D1 levels and cdk2 activity by enhancing p27^{Kip1} expression, causing cell cycle blocked at the G₁ phase [67]. However, one of the limitations of KN-93 and KN-62 is low potency and absence of highly specific inhibition. KN-93 and KN-62 cannot discriminate between CaMKII and CaMKIV and also inhibit voltage-gated K⁺ and Ca²⁺ channels [68, 69]. Another limitation of KN-93 and KN-62 is that these compounds inhibit CaMKII activity by interfering with their binding to the Ca²⁺/CaM complex. However, once CaMKII has become activated (autophosphorylated), its dependence on further Ca²⁺/CaM binding is markedly diminished [17]. Thus, these compounds exert considerably less inhibition on CaMKII once it has become activated (autophosphorylated) [23].

CaMKII inhibitor 1 (CaMKIIN1), a peptide composed of 78-amino acids, functions as a potent and specific inhibitor of CaMKII and was investigated recently. Wang et al. [70] found that CaMKIIN1 could inhibit prostate cancer growth in vivo. The inhibition effect was attributed to the down-regulation of insulin-like growth factor 1 (IGF-1), ErbB2, and vascular endothelial growth factor (VEGF) downstream kinases PI3K/Akt, as well as the MEK/Erk-mediated signaling pathways. Cao et al. [8, 71] identified human CaMKII inhibitory proteins, hCaMKIIN α and hCaMKIIN β , which directly interacted with activated CaMKII and effectively inhibits CaMKII activity. hCaMKIIN α could inhibit human colon adenocarcinoma cell growth both in vitro and in vivo by arresting cell cycle at the S phase. The effect of hCaMKIIN α on cell cycle is correlated with up-regulation of p27^{Kip1} expression, which may be due to the inhibition of proteasome degradation of p27^{Kip1}. Moreover, hCaMKIIN α may suppress the activity of MEK/Erk, which is prerequisite to the inhibition of Thr187 phosphorylation and subsequent proteasomal degradation of p27^{Kip1}, causing the inhibition of S phase progression of cell cycle. For hCaMKIIN β , the cell cycle arrest effect was depended on the upregulation of p21^{CIP/KIP}, p53, and B-cell lymphoma 2 (Bcl-2)-associated X protein (Bax) and downregulation of Cyclin A, Cyclin D1, Cyclin E, Cyclin-dependent kinase 2 (CDK2), phosphorylated Rb, and Bcl-2 [72].

Other CaMKII inhibitors include some small molecules such as bosutinib, berberine, and berbamine. In contrast to other CaMKII inhibitors, which interfere with Ca²⁺/CaM complex formation, bosutinib directly targets the adenosine triphosphate binding site of CaMKII γ and exerts the CaMKII inhibition effect [73]. Berberine, which is an isoquinoline alkaloid, decreases phosphorylation of CaMKII and blocks subsequent MEK1 activation as well as p27^{Kip1} protein degradation in human hepatoma cells [74]. Berbamine is a structurally unique bisbenzylisoquinoline isolated from *Berberis amurensis*. It can specifically bind to the ATP binding pocket of CaMKII, inhibits its phosphorylation and triggers apoptosis of leukemia cells [75]. In addition, Berbamine could suppress the growth of liver cancer cells in vitro and in vivo through inhibited CaMKII phosphorylation and directly down-regulated CaMKII [76].

CONCLUSIONS

Strong evidences now show that CaMKII has emerged as a key nodal protein in the modulation of cell proliferation, cell cycle, invasion and metastasis, and therapy efficacy in variety of malignant diseases. These data establish CaMKII as a novel therapeutic target whose modulation presents new opportunities for cancer treatment. In this review, we also describe the role of CaMKII in the diagnosis of different kinds of cancer and

recent progress in the development of CaMKII inhibitors. Although our knowledge about CaMKII is advancing, major questions still remain. Due to the particularly elegant relationship between the structure and function of the kinase, CaMKII is able to translate a diverse set of signaling events into downstream physiological effects. If we hope to use this kinase deeply in cancer diagnosis and therapy, we also need improve the understanding of CaMKII activation mechanisms. Additionally, the development of clinically applicable CaMKII inhibitory drugs to test the clinical benefit of CaMKII inhibition is also very important in the future researches.

CONFLICTS OF INTEREST

None

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