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Review

The Emerging Roles of CIB1 in Cancer

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Key Words
CIB1 • Calcium • Integrin • Cancer • Tumor progression

Abstract
Calcium and integrin-binding protein 1 (CIB1) is an EF-hand calcium binding protein, which is involved in many cellular processes, including calcium signaling, cell survival and proliferation, cell migration, cell adhesion and apoptosis. A number of studies have found that CIB1 is ubiquitously expressed and is related to various human diseases, such as cancer, Alzheimer's disease (AD), cardiac hypertrophy and male infertility. The mechanism of CIB1 in human diseases is still not clear, although multiple functions of CIB1 are modulated by interacting with numerous interacting partners. As a calcium binding protein, the roles of CIB1 in calcium signaling by binding calcium or modulating some key modulators, such as calcineurin, integrin, inositol 1,4,5-trisphosphate receptor (IP_3R) and taste 1 receptor member 2 (TAS1R2). The tumor promoting mechanisms of CIB1 have been described in different aspects, including promoting tumor cell cycle and proliferation, inhibiting tumor cell apoptosis, and mediating tumor cell migration and angiogenesis. In addition, multiple functions of CIB1, such as neural development, taste or gustation functions, and virus infection are also elucidated. These recent advances have significantly expanded our understanding of the knowledge of CIB1 and highlighted the potential mechanisms of CIB1 in tumor progression.

Introduction

Calcium and integrin-binding protein 1 (CIB1, also known as calmyrin and KIP) is a 22 kD protein, identified originally as a binding partner of platelet integrin cytoplasmic domain alpha-IIb/beta3(αIIbβ3) [1], and later found to regulate αIIbβ3 activation [2, 3] and down regulate inositol 1, 4,5-trisphosphate receptor (IP_3R)-dependent calcium (Ca^{2+}) release [4]. As a calcium-binding protein, the structural properties of CIB1 are most closely related to calcineurin B (CnB) (57% sequence similarity to CIB1) and calmodulin (CaM)

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(56% similarity to CIB1) [1, 5]. Similar to these Ca^{2+} related proteins, as shown in Fig. 1, the human CIB1 contains four helix-loop-helix EF hand motifs, two C-terminal EF hand III and EF hand IV are responsible for Ca^{2+} and magnesium (Mg^{2+}) binding [1, 6-10]. However, CIB1 was found to bind two Ca^{2+} ions in a sequential manner with dissociation constants near 1.9 and 0.54 μM for sites EF-III and EF-IV, respectively. In contrast, CIB1 bound only one Mg^{2+} ion strongly to EF-III with dissociation constants about 120 μM [11]. Of note, CIB1 is usually found in monomeric form and distributed in both the nucleus and cytoplasm [12], and its subcellular localization might be influenced by association with its interacting partners and/or by Ca^{2+}/Mg^{2+} levels. Both Ca^{2+} and Mg^{2+} binding induce conformational changes which stabilize the higher structure of CIB1, leading to remarkable increases in the thermal stability of the proteins [11]. Yamniuk et al. identified that low affinity Ca^{2+} binding events that influence the structures of the N- and C-terminal extensions of CIB1 under high Ca^{2+} crystallization conditions [10]. Studies suggested that Mg^{2+}-CIB1 and Ca^{2+}-CIB1 exhibit a more ordered 4-EF-hand structure with smaller hydrodynamic radius than a highly flexible molten globule-like CIB1 (not bound to any metals)[6, 8]. A consensus sequence 5'-MGXXXS/T-3' at the CIB1 N terminus appears to be crucial for its myristoylation modification and plasma membrane localization [4, 7, 13, 14]. The myristoylation at the CIB1 N terminus might interfere with CIB1 cellular function [13, 15-17]. Stabler et al. showed that a myristoylated CIB1 that preferentially interacts with Presenilin 2 (PS2) [13]. The Ca^{2+}-myristoyl switch function of CIB1, and its ability to facilitate agonist-induced plasma membrane localization of SK1, a location where SK1 is known to trigger oncogenic signaling [15]. In addition, CIB1 myristoylation is also important in shuttling CnB to plasma membrane [16].

A number of studies have further indicated that CIB1 is ubiquitously expressed and is involved in various physiological and pathological processes, including apoptosis [18], cell survival and proliferation [19], cancer [20, 21], cardiovascular diseases [16], and Alzheimer's disease (AD) [22-24]. The precise mechanism between CIB1 and its various binding partners is not clear, although numerous associated proteins of CIB1 have been identified (Table. 1). In this review, we discussed the potential mechanism of CIB1 in Ca^{2+} signaling and paid more attention to tumor promoting effect of CIB1. Last but not least, some other functions of CIB1 were also involved in this article.

CIB1 and Ca^{2+} signaling

In general, intracellular Ca^{2+} signals result either from its release from the important intracellular stores (such as endoplasmic reticulum (ER) and endo-lysosome), or by activation of Ca^{2+}-conducting channels at the plasma membrane, including voltage-dependent Ca^{2+} channels (VDCCs), Na^{+}/Ca^{2+} exchanger (NCX), plasma membrane calcium-transporting ATPases (PMCAs), cyclic nucleotide-gated ion channels (CNGCs), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) and N-methyl-D-aspartate

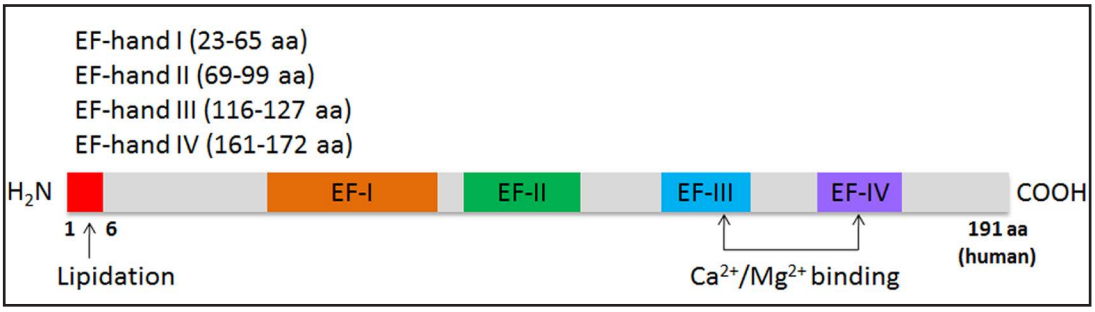

Fig. 1 The basic structure of human CIB1. The CIB1 contains four EF hand motifs, EF-I, EF-II, EF-III and EF-IV. The EF-III and IV of CIB1 are essential for Ca^{2+}/Mg^{2+} binding. The N-terminus (1-6 aa) of CIB1 is response for its myristoylation modification.

Table. 1 The important interacting partners and potential functions of CIB1.

Partners	Potential functions	References
αIIbβ3	platelet aggregation; cell migration; calcium signaling	[1, 2, 61]
FVIII	platelet aggregation	[24]
Rac3	cell migration	[66]
WASP	platelet aggregation; cell migration	[65]
FAK/PTK2	cell migration	[64, 70]
PAK1	cell migration; tumor growth	[67-69]
IP_3R	calcium signaling	[4, 8, 32]
TAS1R2	calcium signaling; taste or gustation	[4]
Plk2/Snk	cell cycle; cancer progression; DNA damage response; synaptic plasticity	[7, 39, 45]
Plk3/Fnk	cell cycle; cancer progression; DNA damage response; synaptic plasticity	[20, 39, 44, 46]
PKD2	tumorigenesis	[46]
SK1	cell proliferation; antiapoptosis; tumor growth	[15, 17, 49]
ASK1	antiapoptosis; calcium signaling;	[7, 57]
IFI6/G1P3	cell survival; antiapoptosis	[18]
UBR5/EDD	DNA damage response; tumorigenesis	[56]
DNA-PKcs/TRF2	DNA damage response	[53, 54, 56]
hTERT	telomere homeostasis; cancer cell proliferation	[53, 54]
SCG10/stathmin2	brain development	[72]
NBR1/BRCA1/ FEZ1	neural and brain development	[73]
PAX3	neurogenesis and myogenic differentiation	[75]
PS 1/2	apoptosis; AD	[13, 14, 22, 23]
EphrinA2	virus infection	[78]
Cn/CnB	calcium signaling; cardiac hypertrophy; valvular heart disease	[16, 25, 30, 79]

receptor (NMDAR) etc [4, 25-29]. Release of intracellular Ca^{2+} from ER store through IP_3R and/or ryanodine receptors (RyR) [25]. Endo-lysosomal Ca^{2+} stores, on the other hand, are mobilized by two-pore channels (TPCs) and transient receptor potential mucolipin-1 (TRP-ML1) [25-27].

The CIB1 belong to calcium-binding protein family, and serve important roles in Ca^{2+} signaling pathways by binding to Ca^{2+} and some key modulators. For example, CIB1 can interact with CnB and strongly enhances CnB membrane localization and activation [16, 30]. Calcineurin (Cn) was shown to associate with the L-type Ca^{2+} channel, which is the major mediator of Ca^{2+} influx from the sarcoplasmic reticulum by activating RyR_2 in cardiac myocytes [31]. The binding of CIB1 to αIIbβ3 is identified to inhibit phospholipase C (PLC)/IP_3 signaling [1, 2, 4]. Of note, CIB1 is also reported to inhibit the IP_3R-Ca^{2+} release channel [32]. Binding of CIB1 to the N-terminal region of IP_3R is reduced at low free [Ca^{2+}] and could be inhibited by mutations to EF hand-III or EF hand-IV, suggesting that Ca^{2+}-binding is the trigger for the CIB1-IP_3R interaction [7]. CIB1 interact with the intracellular C-terminal domain of rat sweet taste 1 receptor member 2 (TAS1R2) also reported to inhibit IP_3R-Ca^{2+} release [4]. Until now, two recognized intracellular Ca^{2+} signaling pathways, integrin-IP_3R-Ca^{2+} signaling and CD38-Ca^{2+} signaling have been established. CD38 is a multifunctional ectoenzyme that catalyzes the synthesis and hydrolysis of cyclic ADP-ribose (cADPR) from nicotinamide adenine dinucleotide (NAD^+) to ADP-ribose (ADPR) and nicotinic acid adenine dinucleotide phosphate (NAADP) [28, 33, 34]. Similar to integrin, a transmembrane CD38 also trigger intracellular Ca^{2+} signaling pathways [33]. In addition to IP_3, cADPR and NAADP are already identified as important intracellular Ca^{2+} messengers, which elicit intracellular Ca^{2+} flux from both ER and endolysosome [25, 33, 34]. CD38 act as a NAD^+ dependent enzymes, which catalyzing the synthesis of cADPR and NAADP to mediate ER-Ca^{2+} and lysosome-Ca^{2+} signaling, respectively [28, 34]. In addition to modulate IP_3R-Ca^{2+} signaling, CIB1 is possibly also implicated in CD38 triggering Ca^{2+} signaling pathway. As summarized in Fig. 2, In IP_3-ER-Ca^{2+} signaling, CIB1 acts as a partner of integrin, which affects the activation of PLC. As we known, IP_3 is produced by the activation of PLC and it acts on IP_3R to release Ca^{2+} from the ER stores. Besides, CIB1 also interact with the C-terminal domain of TAS1R2 to inhibit IP_3R-Ca^{2+} release. In CD38 triggering Ca^{2+} signaling pathway, it is interesting that whether CIB1 may also serve as an accessory protein of CD38, which synthesizes the second messengers, cADPR and NAADP. The synthetic cADPR and NAADP target to RYR and TPC/TRP-ML1, resulted in Ca^{2+} release from ER and endolysosome stores, respectively [25, 28, 34]. Furthermore, whether CIB1 is

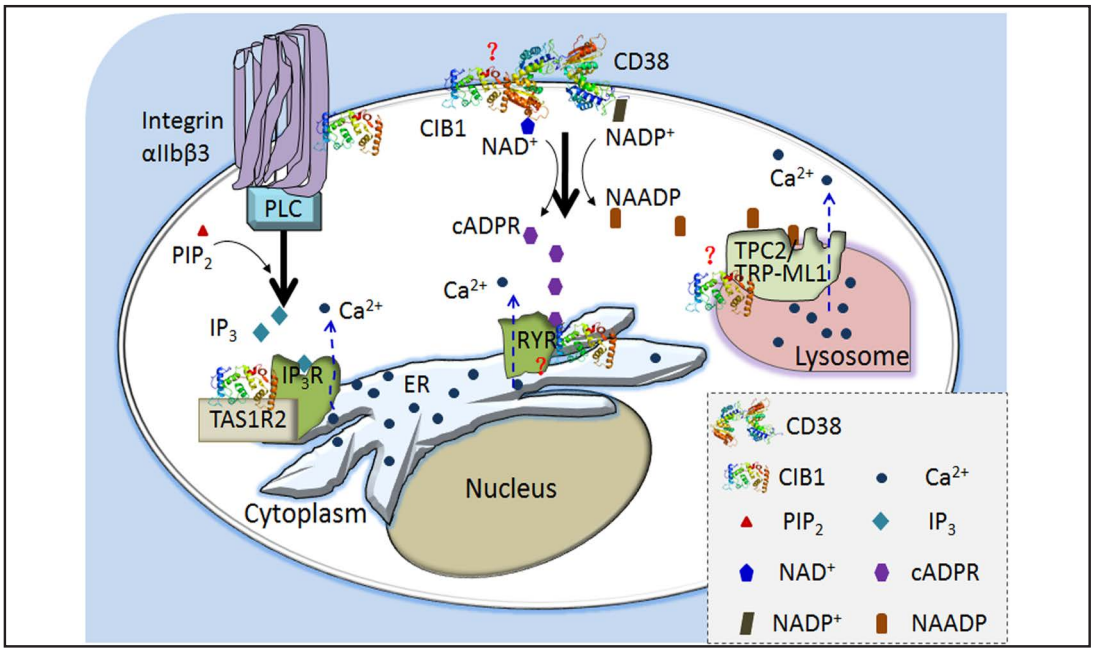

Fig. 2 The potential mechanism of CIB1 in intracellular Ca^{2+} signaling

Table. 2 The roles for CIB1 in tumor progression. Abbreviations: Acute myeloid leukemia (AML); colorectal cancer (CRC); hepatocellular Carcinoma (HCC); triple negative breast cancer (TNBC).

Tumor or cell types	Targets	Potential mechanism	References
MCF-7 cells	EDD, DNA-PKcs	DNA damage response; tumorigenesis	[56]
T47D breast cancer	FAK, PAK1	cancer cell migration	[69, 70]
H1299, MCF7 and HT1080 cells	DNA-PKcs, hTERT	telomere homeostasis; cancer cell proliferation	[53]
TMK-1 cells	G1P3	inhibit apoptosis	[18]
Melanoma or Lewis lung carcinoma cells	PAK1, ERK1/2	angiogenesis	[68, 71]
HeLa, MCF-7 and DU145 cells, lung cancer, AML,CRC	Ras, SK1	cell proliferation; antiapoptosis; tumor growth	[15, 17]
HCC and HepG2 cells	PAK1, ERK1/2 and ASK1	cancer cell proliferation	[42]
Breast cancer cells	PLK3	calcium signaling, cancer cell proliferation	[20, 44]
Breast, bladder, cervix and colorectal cancer	PKD2	tumor cell invasion, tumor growth and angiogenesis	[40]
Neuroblastoma and breast cancer cells	PI3K/AKT, MEK/ERK and PAK1	cancer cell proliferation	[43]
Kaposi's sarcoma	EphrinA2, ERK1/2	virus entry	[78]
Pancreatic cancer	DNA-PKcs, PLK3, Rac3, Pax3, PS2	cancer cell proliferation	[21]
TNBC cells	PI3K/AKT, MEK/ERK	cancer cell proliferation	[41]

also likely to affect the RYR and TPC/TRP-ML1 activity directly may be the result of further mechanism that have not yet been elucidated. Of interest, whether CIB1 and the modulators in these two signaling pathways synergistically modulating intracellular Ca^{2+} signaling are not clear. Whether CIB1 also affects some other Ca^{2+} channels on cell membrane (such as NMDAR, L-type Ca^{2+} channel and NCX) are still need further investigation. Several studies suggested that targeting Ca^{2+} signaling possible serve as a potential strategy in cancer therapy [35-38]. Thus, gaining better understanding of the relationship between CIB1 and these Ca^{2+} modulators remain an important area to investigate in the future study.

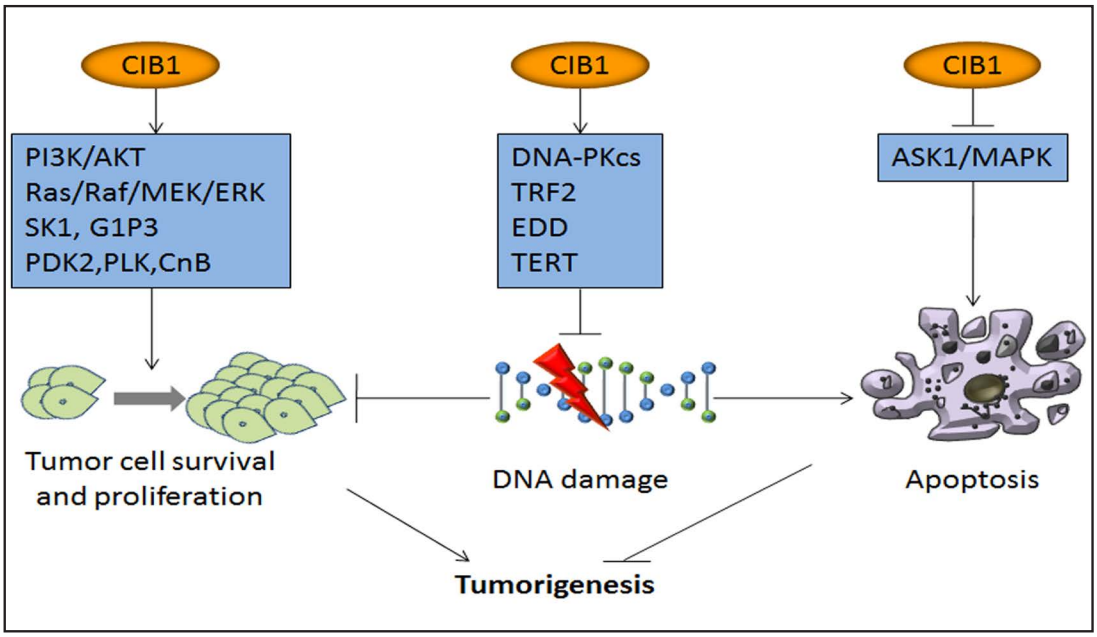

Fig. 3 The potential mechanism of CIB1 in tumorigenesis.

The potential roles of CIB1 in tumor progression

Recently, carcinogenesis of CIB1 is in the spotlight. Increasing evidence has suggested that CIB1 perform important roles in cell survival, cell proliferation, cell apoptosis and cell migration, thereby mediating tumor growth and angiogenesis [17, 20, 39-43]. CIB1 may serve an important role in tumorigenesis by regulating several kinase partners or oncogenic signaling (Table. 1, 2 and Fig. 3). The summary of these studies are described as below.

CIB1 and tumor cell survival and death signaling

Polo-like kinases (Plks), a family of serine/threonine kinases, have been shown to play key roles in regulation of cell cycle progression. So far, Plk1, Plk2, Plk3 and Plk4 proteins have been identified in the mammalian cells [20, 39, 44]. Plk2, also called serum-inducible protein kinase (Snk), is combined and inhibited by CIB1 [39, 45]. Plk3, also known as FGF-inducible kinase (Fnk), is coupled to the CIB1 in two-hybrid-analyses and coimmunoprecipitation assays [46]. The interaction between Plk3 and CIB1 might play a role in cancer progression. Later studies showed that CIB1 constitutively interacts with Plk3 and inhibits its activity in a Ca^{2+}-dependent manner, thereby contributes to the regulation of the cell cycle [20]. Protein kinase D2 (PKD2), a member of the PKD family of serine/threonine kinases, has been reported as a potential promoter for tumor growth and angiogenesis [40, 47]. Armacki et al. suggested that a novel splice variant of CIB1 (called CIB1a), which regulates tumor cell invasion, tumor growth and angiogenesis by mediating PKD-induced the secretion of vascular endothelial growth factor [40]. SK1 plays an important role in cell proliferation, protection from apoptosis, and oncogenic rat sarcoma (Ras)-mediated neoplastic transformation [15, 17, 48]. Study showed that CIB1 interacts with SK1 and promotes the translocation of SK1 from cytoplasm to plasma membrane, mediating activation of SK1 and in turn anti-apoptotic signaling through the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) pathway [15]. As we known, SK1 is a downstream mediator of oncogenic signaling by Ras since chemical inhibitors of SK or a dominant-negative SK1 attenuated Ras-induced neoplastic transformation [48, 49]. Besides, studies indicated that oncogenic Ras induced plasma membrane localization of SK1 [17, 50]. Thus, CIB1 serves as

an important effector of oncogenic signaling by Ras through the enhancement of subcellular localization of SK1 to the cell membrane [17]. Phosphatidyl inositol 3-kinase (PI3K) and extracellular regulated protein kinases (ERK) are involved in cellular functions such as cell growth, proliferation [51, 52]. CIB1 is also implicated in cell survival and proliferation by modulating PI3K/AKT and MEK/ERK oncogenic signaling [41, 42]. Leisner et al. have been identified that CIB1 depletion increased nuclear distribution of GAPDH by interrupting AKT and ERK signaling, leading to caspase-independent cell death and proliferation inhibition [43]. Besides, CIB1 can associate with the catalytic subunit of human telomerase reverse transcriptase (hTERT), stimulating telomerase activity and telomere lengthening [53, 54]. CIB1 is required for the association between telomeric repeat-binding factor 2 (TRF2) and DNA-protein kinase catalytic subunit (DNA-PKcs), the interplay of these three proteins may provide a mechanism for the recruitment of DNA-PKcs to telomeres [54]. The interaction between CIB1 and DNA-PKcs also affects DNA-PKcs related DNA damage [53, 55]. Moreover, being a binding partner of E3 ubiquitin-protein ligase UBR5 (EDD), CIB1 is a possible target for E3-mediated degradation and potentially involved in DNA damage signaling [56]. Study showed that CIB1 inhibits apoptosis signal-regulating kinase 1 (ASK1) activity both *in vitro* and *in vivo*, thereby negatively regulates stress-activated mitogen-activated protein kinase (MAPK) signaling pathways and apoptosis [57]. The mitochondria serve important roles in intrinsic apoptotic pathway [58, 59]. A mitochondrial localized G1P3 (also known as interferon alpha-inducible protein 6 (IFI6) or interferon-induced protein 6-16) has been shown to inhibit mitochondrial-mediated apoptosis in gastric cancer cell line TMK-1 cells [18]. This anti-apoptotic function is mediated by interacting with CIB1, thereby inhibit the depolarization of mitochondrial membrane potential, release of cytochrome c [18]. Although overexpression of CIB1 and/or PS2 promotes cell death *in vitro*, but no published data to confirm the role of CIB1 in cancer cell apoptosis [13, 18], further studies are needed to conclude the involvement in the anti-apoptotic activity. As summarized in Fig. 3, PI3K/AKT, Ras/Raf/MEK/ERK, Plks, PDK2, SK1 and G1P3 may be potential oncogenic signaling in CIB1-driven tumor progression. As an important effector of DNA damage signaling, CIB1 may effect tumor progression by regulating the function of DNA-PKcs, TRF2, EDD and TERT. Furthermore, inhibitions of tumor cells apoptosis by inhibiting ASK1/MAPK signaling are also involved in CIB1-induced carcinogenesis.

CIB1 and tumor cell migration and angiogenesis

Moreover, cell migration plays an essential role in tumor growth and metastasis. CIB1 is also involved in tumor metastasis by effecting tumor cell migration and spreading [7]. Until now, multiple studies have indicated that CIB1 serve important roles in regulating platelet integrin activity, cell adhesion and migration by interacting with at least six binding partners, including αIIbβ3, the coagulation factor VIII (FVIII), Wiskot-Aldrich syndrome protein (WASP), the small GTPase Rac3, P21-activatd kinases 1 (PAK1) and focal adhesion kinase (FAK). As a major adhesion receptors, integrin control many normal cellular processes, including migration, growth, differentiation, and proliferation [60]. Studies has suggested that CIB1 is coupled to cytoplasmic domain of αIIbβ3, thereby blocks αIIbβ3 activation and in turn platelet aggregation [1, 2]. Further study indicated that CIB1 could bind to all integrin complexes and act as a broad regulator of integrin function [3]. CIB1 also interacts with the FVIII in 227-336 regions, suggesting that CIB1 pay important roles in coagulation [24]. Base on the relationship between CIB1 and αIIbβ3, CIB1 is also involved in cell migration [61]. WASP binding to CIB1 affects the affinity of αIIbβ3 for fibrinogen (also called factor I), a soluble plasma glycoprotein is converted by thrombin into fibrin during blood coagulation [62-64]. CIB1 can bind to N terminus of the WASP and recruit it to αIIbβ3, increasing αIIbβ3-mediated cell adhesion in stimulated platelets [65]. Tsuboi et al. advanced that inhibition of WASP-CIB1 binding by streptolysin O decreases αIIbβ3 affinity for fibrinogen [65]. It is reported that CIB1 interacts with the small GTPase Rac3 and promotes αIIbβ3-mediated adhesion and spreading of cells through the fibrinogen receptor, such as αIIbβ3 [66]. As a downstream of Rac3, PAK1 is another key factor in cell migration. Multiple studies have indicated that

CIB1 is essential for PAK1 activation both *in vitro* and *vivo*, which further suggested that CIB1-PAK1 interaction is involved in cell migration [67-69]. Naik et al. suggested that CIB1 positively regulates cell migration and is necessary for the recruitment of FAK (also known as protein tyrosine kinase 2, PTK2, a key regulator in focal complex formation) to the focal adhesions. Furthermore, CIB1-induced cell migration is dependent on MAPK signaling and its function is attenuated by PAK1 [69]. Overexpression of CIB1 resulted in cell migration on fibronectin and ERK1/2 MAPK activation [69]. Moreover, by using Chinese hamster ovary cells as model, study showed that CIB1 induces cell migration by binding of FAK and increasing its activity. Overexpression of dominant-negative FAK and CIB1 inhibited cell migration completely [70]. Zayed et al. also found that CIB1 play a critical role in facilitating tumor growth and tumor-induced angiogenesis [68, 71]. As shown in Fig. 4, CIB1 can interact with the N-terminus of αIIbβ3 subsequent to integrin activation. CIB1 also bind to WASP and recruit it to αIIbβ3, which further promoting cell adhesion and spreading. The binding of CIB1 to FAK will also enhance FAK activation [64], and thereby triggering Rac3 and PAK1 induced adhesion and spreading.

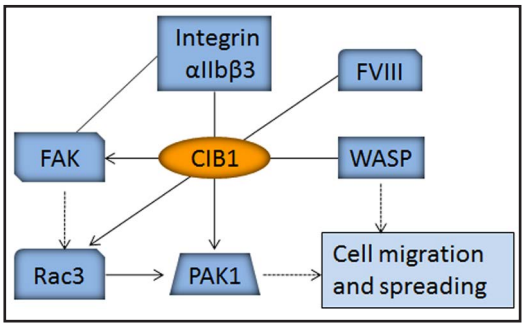

Fig. 4 The roles of CIB1 in cell migration.

In conclusion, CIB1 is widely up-regulated across a diverse range of human cancers. As an emerging potential oncogene [17], CIB1 may affect tumor progression by modulating various processes, including Ca^{2+} signaling, apoptosis, cell cycle and proliferation, cell migration and spreading, telomerase activity and DNA damage. Taken together, there are several potential mechanisms of CIB1 in cancer, including (i) promoting tumor cell cycle and proliferation, (ii) inhibiting tumor cell apoptosis, and (iii) mediating tumor cell migration and angiogenesis. Thus, CIB1 might become a good potential target for cancer therapy. Confirming the interaction mechanism between CIB1 and its interacting partners might provide the potential strategies for preventing cancers.

CIB1 and other pathological or physiological process

CIB1 is a versatile protein by interacting with more than 35 binding partners so far [7]. Of interest, CIB1 is involved in embryogenesis, neural development, AD etc. SCG10 protein (stathmin2), a microtubule-destabilizing factor, which is implicated in neuronal growth during brain development by tied up to the C-terminal of CIB1 and inhibited SCG10-mediated neurite outgrowth [72]. Whitehouse et al. have indicated that CIB1 interacts with NBR1 (named as next to BRCA1) and fasciculation and elongation protein zeta-1 (FEZ1) by using both the yeast two-hybrid assay and coimmunoprecipitation studies [73]. They also identified the subcellular co-localization of CIB1, NBR1 and FEZ1 proteins by immunofluorescence analysis, and speculated that the interactions between these proteins possible an important event in brain development [73]. A member of the paired class homeodomain family of transcription factors, paired box 3 protein (PAX3) [74], has been demonstrated to implicated in brain development by specifically fastening with CIB1 [75]. It is well established that Presenilin 1/2 (PS1/2) are important ageing genes. CIB1 has been demonstrated to fasten with PS2 and increase cell death [13]. By site-directed mutagenesis, Zhu et al. suggested that the interaction between CIB1 and PS2 is regulated by Ca^{2+} binding sequences in EF-hands III and IV [14]. Continues study showed that these binding appear to be in Ca^{2+} independent manner [22]. Moreover, the interaction between CIB1 and Fnk/Snk suggested that CIB1 play vital roles in synaptic plasticity [39]. Study has also demonstrated that CIB1 is associated with hTERT [53], and presented in human forebrain and altered distribution in AD brain [23], further suggesting that CIB1 might play important roles in AD [13, 14, 22, 23]. As

shown in Fig. 5, CIB1 control brain development by interact with a variety of partners, including NBR1, SCG10, FEZ1 and PAX3. CIB1 is involved in AD by modulating PS1/2, TERT and Fnk/Snk signaling. Moreover, CIB1 is also related to spermatogenesis. Down-regulation of CIB1 in the sperm of patients with oligoasthenozoospermia [76], reflected that CIB1 may be involved in male subfertility [19, 76]. CIB1 binds to TAS1R2 also suggested that CIB1 might be also effect taste or gustation functions [4]. CIB1 also serve as a potential effector molecule in virus infection, such as human herpes virus 8 and human immunodeficiency virus type-1 [77, 78]. It is demonstrated that CIB1 interacts with EphrinA2 (EphA2) and increase Kaposi's sarcoma-associated herpes virus infection in 293 cells [78]. CIB1 is high expressed in human and rat heart and necessary for cardiac hypertrophy [16, 30]. CIB1 and Cn expression was increased in atrial fibrillation atrial tissue, suggesting that CIB1 may be involved in the pathogenesis of valvular heart disease [79]. As we known, structure determines function. To get insight into the function of CIB1, the structure of CIB1 has been explored extensively by sequence analysis, nuclear magnetic resonance spectroscopy (NMR), circular dichroism or X-ray crystallography [6-8, 10, 80]. Thus, we believed that along with the further analysis of CIB1 structure, more and more CIB1 partners and the precise mechanisms for multiple function of CIB1 will be identified in the future.

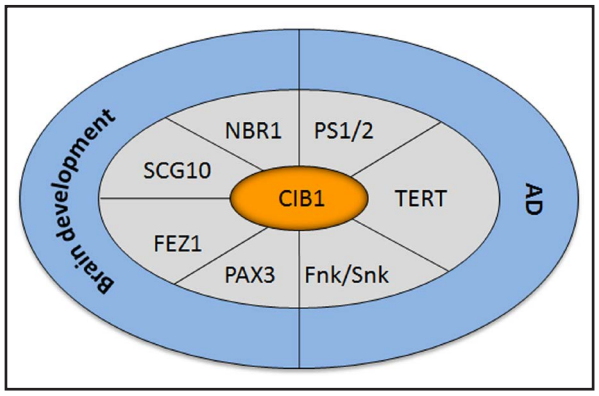

Fig. 5 The potential roles of CIB1 in brain development and AD.

Conclusion

In summary, as a multifunctional protein, CIB1 serving not only as a Ca^{2+} modulating protein, most surprisingly, but also as an important potential tumor promoting factor. Here we discussed the plausible mechanism of CIB1 in intracellular Ca^{2+} signaling conduction and paid more attention to an important pro-tumorigenic role for CIB1. The review of the signaling mechanism for CIB1 in tumor progression will highlight the great potential target for cancer therapy.

Abbreviations

CIB1 (Calcium and integrin-binding protein 1); αIIbβ3 (Integrin alpha-IIb/beta3); IP_3R (Inositol 1,4,5-trisphosphate receptor); RyR (Ryanodine receptors); CnB (Calcineurin B); CaM (Calmodulin); AD (Alzheimer's disease,); TPCs (Two-pore channels); TRP-ML1 (Transient receptor potential mucolipin-1); PLC (Phospholipase C); TAS1R2 (taste 1 receptor member 2); cADPR (Cyclic ADP-ribose); NAADP (Nicotinic acid adenine dinucleotide phosphate); Plks (Polo-like kinases); Snk (Serum-inducible protein kinase); Fnk (FGF-inducible kinase); PKD2 (Protein kinase D2); SK1 (Sphingosine kinase 1); ASK1 (Apoptosis signal-regulating kinase 1); IFI6 (Interferon alpha-inducible protein 6); hTERT (Human telomerase reverse transcriptase); DNA-PKcs (DNA-protein kinase catalytic subunit); EDD (E3 ubiquitin-protein ligase UBR5); FVIII (Coagulation Factor VIII); WASP (Wiskot-Aldrich syndrome protein); PAK1 (P21-activated kinases 1); FAK (Focal adhesion kinase); FEZ1 (Fasciculation and elongation protein zeta-1); PAX3 (Paired box 3 protein); PS1/2 (Presenilin); EphA2 (EphrinA2); HCC (Hepatocellular carcinoma).

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Disclosure Statement

The authors do not have conflict of interest.

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