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Physiological functions of CKIP-1: From molecular mechanisms to therapy implications

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ABSTRACT

The casein kinase 2 interacting protein-1 (CKIP-1, also known as PLEKHO1) is initially identified as a specific CK2α subunit-interacting protein. Subsequently, various proteins, including CPα, PAK1, Arp2/3, HDAC1, c-Jun, ATM, Smurf1, Rpt6, Akt, IFP35, TRAF6, REGγ and CARMA1, were reported to interact with CKIP-1. Owing to the great diversity of interacted proteins, CKIP-1 exhibits multiple biologic functions in cell morphology, cell differentiation and cell apoptosis. Besides, these functions are subcellular localization, cell type, and regulatory signaling dependent. CKIP-1 is involved in biological processes consisting of bone formation, tumorigenesis and immune regulation. Importantly, deregulation of CKIP-1 results in osteoporosis, tumor, and atherosclerosis. In this review, we introduce the molecular functions, biological processes and promising of therapeutic strategies. Through summarizing the intrinsic mechanisms, we expect to open new therapeutic avenues for CKIP-1.

1. Introduction

CKIP-1 is first identified as a specific CK2α subunit-interacting protein in a yeast two-hybrid screening and encompasses 409 amino acids (Bosc et al., 2000). It is also referred to as pleckstrin homology domain containing protein O1 (PLEKHO1). CKIP-1 possesses a pleckstrin homology (PH) domain at the N-terminus, a leucine zipper (LZ) motif at the C-terminus, as well as five proline-rich motifs throughout the protein. CKIP-1 seems to act as a regulatory protein to interact with various kinds of proteins and signals including CPα, PAK1, Arp2/3, HDAC1, c-Jun, ATM, Smurf1, Rpt6, Akt, IFP35, TRAF6, REGγ and CARMA1 through different domains, as shown in Fig. 1.

Here, we mainly summarize the molecular functions of CKIP-1 in cell morphology, cell differentiation and cell apoptosis, the involved biological processes including bone formation, tumorigenesis and immune regulation. We also introduce the potential role of CKIP-1 in the treatment of human diseases such as osteoporosis, tumor, and atherosclerosis.

2. Molecular functions

2.1. Cell morphology

The original identification and characterization of CKIP-1 result from the study of CK2 regulation twenty years ago (Bosc et al., 2000). CKIP-1 interacts with and recruits protein kinase CK2 to the plasma membrane (PM) via its N-terminal PH domain (Olsten et al., 2004), which is widely known as one of the phospholipid-binding domains. Interestingly, CKIP-1 is not a substrate of CK2. Besides, it has no direct influence on the kinase activity of CK2 (Canton et al., 2005). Instead, CKIP-1 functions to target CK2 to specific cellular compartments thereby facilitating phosphorylation of particular substrates (Olsten et al., 2004).

Actin-capping protein (CP) binds to and functionally caps free barbed ends, blocking their growth and shrinkage (Cooper and Sept, 2008). CKIP-1 interacts with and inhibits the capping activity of CPα through its CPI motif (133–193 amino acids). Detailed experiments identified that Arg155 and Arg157 in the CPI motif of CKIP-1 are the most important residues. CKIP-1 wild type (WT) but not R155E, R157E mutant can induce cell spreading (Canton et al., 2006). It is worth mentioning that CK2 phosphorylates the α-subunit of CPα on Ser9. The presence of CK2 increases the inhibitory effect of CKIP-1 on CPα (Canton et al., 2005).

P21-activated kinase 1 (PAK1) is a main downstream effector of Rho family GTPases Cdc42 and Rac1, and plays an important role in the regulation of cell morphology and motion (Manser et al., 1994). CK2 activates PAK1 through phosphorylation of PAK1 at Ser223 (Shin et al., 2013). In response to epidermal growth factor (EGF), CKIP-1 appears to

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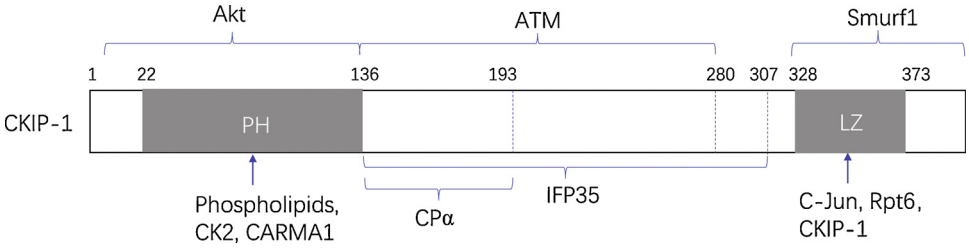

Fig. 1. CKIP-1 interaction regions with partners.
The CKIP-1 protein contains a N-terminus pleckstrin homology (PH) domain and a C-terminus leucine zipper (LZ) motif. CKIP-1 interacts with multiple moleculars such as CK2, phospholipid, CARMA1, Akt, ATM, CPα, IFP35, Smurf1, c-Jun, and Rpt6. This figure shows the diverse binding fragments of these proteins.

recruit CK2 and PAK1 to the PM and promote CK2 phosphorylation of PAK1 in a PI3K-dependent manner. Inhibition of either CKIP-1 or PI3K activity could block PAK1-mediated actin cytoskeleton dynamics and cell migration (Kim et al., 2015).

2.2. Cell differentiation

2.2.1. Myoblasts differentiation

In mouse myoblast C2C12 cells, CKIP-1 interacts with phosphoinositides via its PH domain and localizes at the plasma membrane (Safi et al., 2004). The Trp123 residue in PH domain plays a central role in this interaction (Olsten et al., 2004). Knockdown PI3K or co-expression of PI3K Δp85, a dominant negative mutant of PI3K, causes enrichment of CKIP-1 in the nucleus. Ectopic expressed CKIP-1 accelerates the first transient proliferative phase and induces muscle differentiation in response to insulin stimulation (Safi et al., 2004).

Plasma membrane localization of the Arp2/3 complex is also essential for muscle precursor elongation and fusion (Pollard and Borisy, 2003). CKIP-1 interacts with the Arp2/3 and recruits it to the plasma membrane. In addition to in vitro experiments, CKIP-1 depletion could influence cortical actin and myoblast fusion, regulate cell morphology and lamellipodia formation in mouse and zebrafish, in a PI3K-dependent fashion (Baas et al., 2012).

2.2.2. Mesenchymal stem cells (MSCs) differentiation

CCAAT/enhancer-binding protein a (C/EBPα) is a crucial adipogenic transcription factor (Wiper-Bergeron et al., 2003). The histone deacetylase 1 (HDAC1) is recruited to the promoter of C/EBPα to suppress its transcription during the early phase of adipogenesis (Yoo et al., 2006). CKIP-1 interacts with HDAC1 in the nucleus and through which inhibits C/EBPα transcription. Ectopic expression of CKIP-1 in an MSC-like cell line C3H/10T1/2 reduces the generation of adipocytes. MSCs derived from CKIP-1-deficient mice display enhanced adipogenesis upon induction. Moreover, CKIP-1-deficient mice show an increase in body weight and white adipose tissue gains when fed on a high-fat diet (Li et al., 2014). It is worth mentioning that MSCs can also differentiate into osteocytes, adipocytes, myoblasts and chondrocytes. Zhang et al. found that CKIP-1 can promote the differentiation of MSCs to osteocytes (Zhang et al., 2015). However, the effect of CKIP-1 in myoblasts differentiation and chondrocytes differentiation from MSCs remains elusive. The possible role of CKIP-1 in the self-renewal of MSCs requires further investigation.

2.2.3. Megakaryocytes differentiation

Megakaryocytes are derived from hematopoietic stem cells (HSCs). The differentiation of megakaryocytes can be positively and negatively regulated by transcription factors such as friend leukemia virus-induced erythroleukemia-1 (Fli-1, also known as transcription factor ERGB), c-Myb, c-Myc and GATA-binding factor 1 (GATA-1) (Dore and Crispino, 2011). K562 cells are usually considered as a pluripotent hematopoietic progenitors model which can be induced to differentiation (Leary et al., 1987). CKIP-1 expression is dramatically elevated upon PMA induced megakaryocytic diff ;erentiation in K562 cells. This change relies on the downregulation of GATA-1. Till now, GATA-1 is the only reported transcription regulator of CKIP-1. Besides, CKIP-1 can regulate the expression levels of Fli-1, c-Myb and c-Myc and on this account induce early megakaryocytic differentiation in vivo (Fan et al., 2017). However, the exact molecular mechanisms of how CKIP-1 regulated the expression of these transcription factors remain to be elucidated

Besides, CKIP-1 suppresses odontoblastics differentiation of dental pulp stem cells via BMP2 pathway and interaction with NRP1 (Song et al., 2018). And CKIP-1 can also promote early transdifferentiation of human lung alveolar epithelial type 2 (Morales Johansson et al., 2014).

2.3. Cell apoptosis

C-Jun, the core subunit of transcription factor activator protein-1 (AP-1), is a nuclear protein that constitutively binds to DNA (Shaulian and Karin, 2002). In response to cell death signal, CKIP-1 is cleaved by proapoptotic caspase-3 and then translocates from the PM to the cytoplasm and then the nucleus. C-terminal fragments of CKIP-1 bind to c-Jun and strongly repress AP-1 activity. Importantly, CKIP-1 overexpression promotes apoptosis by active caspase-3 through which forming a positive feedback loop between CKIP-1 and caspase-3 (Zhang et al., 2005).

ATM (Ataxia telangiectasia mutated) is a DNA-damage response kinase which belongs to PI3K family (Kastan and Lim, 2000). In response to DNA damage, ATM may promote p53 activity and stability by mediating phosphorylation of p53 on Ser15 (Khosravi et al., 1999). CKIP-1 could prevent p53 degradation induced by cycloheximide (CHX) treatment by directly binding to and activating ATM in SK-BR-3 breast cancer cells. Moreover, CKIP-1 could recruit ATM, a predominantly nuclear kinase, partially to the plasma membrane (Zhang et al., 2006).

As described above, CKIP-1 localized both at the plasma membrane and in the nucleus in response to CHX. It seems that the plasma membrane-localized CKIP-1 could form a complex with ATM and stabilized p53. Meanwhile, cleaved CKIP-1 translocated into the nucleus and bound to c-Jun. These two regulatory pathways synergistically promote cell apoptosis.

3. Biological process

3.1. Bone formation

Smurf1 (Smad ubiquitylation regulatory factor 1) is a HECT (homologous to E6AP C-terminus)-type E3 ubiquitin ligase which harbors important roles in diverse pathways through promoting the degradation of Smad1/5, MEKK2 and RhoA (Wang et al., 2003; Yamashita et al., 2005; Zhu et al., 1999). Smurf1 protein contains an N-terminal C2 domain, two middle WW domains responsible for substrate recognition and a C-terminal catalytic HECT domain. Previously, Lu et al. discovered that CKIP-1 could specifically bind to the linking region between the two WW domains of Smurf1. The WW domains linker includes totally 15 amino acids, among which six residues are required for the interaction with CKIP-1 and conserved across species. The critical residues for CKIP-1 binding are not identical between Smurf1 and Smurf2, which determines the specific activation of Smurf1, but not that of Smurf2, by CKIP-1. CKIP-1 enhances the affinity between Smurf1 and its substrates, such as Smad5 and MEKK2. This improves the ubiquitin ligase activity of Smurf1, promotes the degradation of

Smad1/5 and negatively regulates the BMP signaling pathway (Lu et al., 2008).

Furthermore, CKIP-1 interacts directly with Rpt6, one of the ATPase subunits of the proteasome 19S regulatory particle through its leucine zipper. CKIP-1 couples Smurf1 with Rpt6 to deliver the ubiquitylated substrates as well as Smurf1 itself to the proteasome for subsequent degradation (Wang et al., 2012). Importantly, mice lacking CKIP-1 show increased bone mass with age due to accelerated osteogenesis, and this is the first physiological evidence that CKIP-1 is an inhibitor of bone formation (Lu et al., 2008).

There still exist some questions. The ubiquitin proteasome system (UPS) is involved in almost all aspects of eukaryotic biology (Swatek and Komander, 2016). As far as we know, Smurf1 is the only UPS related E3 that can be regulated by CKIP-1. Are there any other E3s or dubs that can involve in the CKIP-1 mediated proteasome degradation cascades in some way? Is the interaction between Rpt6 and CKIP-1 a universal mechanism in UPS regulation?

3.2. Tumorigenesis

The serine/threonine kinase Akt plays a central role in cell survival and proliferation. Its activation is linked to tumorigenesis in several human cancers (Cheng et al., 2005). CKIP-1 could bind to Akt via its PH domain and exhibit Akt inhibitory function. Stable CKIP-1 expression causes Akt inactivation and cell growth inhibition in vitro and in vivo. Thus, CKIP-1 would be a candidate of tumor suppressor with Akt inhibitory function (Tokuda et al., 2007).

PI3K/Akt/mammalian target of rapamycin (mTOR) signaling increases the generation of Smurf1 in an mTOR-dependent manner. Notably, Smurf1 is a potential oncogene target in many kinds of cancer cells (Koganti et al., 2018). In colon cancer, CKIP-1 controls Smurf1 expression by opposing PI3K/Akt/mTOR signaling and enhancing Smurf1 autodegradation. Consistent with this, in human colon cancer tissues and cancer cell lines CKIP-1 is significantly downregulated which is correlated with colon cancer progression. Ultimately CKIP-1 overexpression inhibits cell growth and migration in cultured cells and nude mice model which are dependent on the downregulation of Smurf1 (Nie et al., 2014). Whether CKIP-1 deficiency in mice increases the susceptibility of tumor development needs further investigations in the future.

3.3. Immune regulation

3.3.1. Monocytes

Myeloid cells such as monocytes are key components of the innate immune system contributing to the maintenance of tissue homeostasis and the immune responses to pathogens (Gordon and Taylor, 2005). During monocyte immunity, Nmi (N-Myc interacting protein) can be stabilized through interacting with IFP35 (IFN-induced protein 35 kD) (Chen et al., 2000). CKIP-1 could bind to IFP35 and compete with Nmi for association. In this way, overexpress CKIP-1 destabilizes IFP35 via inhibiting IFP35–Nmi interaction and control cytokine signaling. Like Nmi and IFP35, CKIP-1 is significantly elevated in PBMCs (peripheral blood mononuclear cells) exposed to IFN-γ and IL-2. CKIP-1, Nmi and IFP35 form a delicate balance to adjust appropriate cytokine signal response mechanism (Zhang et al., 2007) (Table 1).

Transmembrane form of tumor necrosis factor (mTNF) can interact with its cognate receptors or agonistic antibodies to active the signaling in the ligand expressing cells. This “reverse signaling” pathway shows a fine tune control mechanism in the immune response (Watts et al., 1999). In THP-1 monocyte model cells, CKIP-1 mRNA and protein levels can be upregulated dramatically by LPS. CKIP-1 interacts with the N-terminal fragment of mTNF which induces a relocation from the plasma membrane to intracellular compartments. Thus, CKIP-1 exerts a pro-inflammatory role through interfering with TNF reverse signaling (Juhasz et al., 2013).

Table 1
CKIP-1 in immune regulation.

Cell types	Induce factors	Interacting proteins	Signaling	Intrinsic mechanisms	Molecular functions	Reference
Monocytes	IFN-γ/IL-2	IFP35	Cytokine	destabilize IFP35 through competition with Nmi	form a balance to adjust appropriate cytokine signal	Zhang et al., 2007
	LPS	N term mTNF	TNFα reverse	interact with and induces a relocation from PM to intracellular compartments	promote inflammation in monocytes	Juhasz et al., 2013
Macrophages	M-CSF	TRAF6	Akt	interacting with TRAF6 and suspending TRAF6-mediated activation of Akt	inhibits macrophage proliferation at the late stage	Zhang et al., 2014
	LPS/IFN-γ	–	NF-κB	pro-inflammatory genes activation in a NF-κB dependent manner	promotes pro-inflammatory in M1 macrophages	Chen et al., 2017
	IL-4/IL-13	–	JAK-STAT	inhibits anti-inflammatory genes by negatively regulating JAK1-STAT6	inhibits anti-inflammatory M2 macrophages	Chen et al., 2017
T cells	PMA/PKθ	REGγ CARMA1	NF-κB	interacts with proteasome activator REGγ and triggers Oct-1 degradation destroys the interaction between PKθ and CARMA1	decreases lipoproteins uptake and foam cell formation Inhibit NF-κB signaling in T cells	Fan et al., 2019 Sakamoto et al., 2014

3.3.2. Macrophages

During the inflammatory response, circulating monocytes give rise to mature macrophages, which then distribute in strategic tissues and play important roles in acute and subacute inflammation (Muller, 2011).

3.3.2.1. Proliferation. Macrophage proliferation is promoted by macrophage colony-stimulating factor (M-CSF)-induced Akt signaling (Hamilton, 2008). Glycogen synthase kinase 3β (GSK3β) is usually constitutively active in resting macrophages and can be suppressed by Akt-mediated phosphorylation in stimulated cells (Datta et al., 1999). In unstimulated cells, CKIP-1 is phosphorylated on Ser342 by GSK3β which triggers the polyubiquitination and proteasomal degradation of CKIP-1. Under the stimulation of M-CSF, GSK3β is inactivated, bring about the stabilization of CKIP-1 (Zhang et al., 2014).

The ubiquitin ligase TRAF6 (tumor necrosis factor receptor associated factor 6) promotes the K63-linked ubiquitination and plasma-membrane translocation of Akt (Yang et al., 2009). At the late stage after M-CSF stimulation, accumulated CKIP-1 inhibits macrophage proliferation by means of interacting with TRAF6 and suspending TRAF6-mediated activation of Akt. Lack of CKIP-1 leads to increased proliferation and decreased apoptosis of macrophages in vitro and in vivo (Zhang et al., 2014).

CKIP-1 is reported to interact with Akt and subsequently suppress its activity (Tokuda et al., 2007). In PMSCs, CKIP-1 binds to TRAF6 and through which antagonizes Akt activity (Zhang et al., 2014). These results enrich the mechanism by which CKIP-1 regulates Akt (Table 1).

3.3.2.2. Polarization. Macrophages exhibit phenotypic and functional heterogeneity and plasticity. M1 macrophages generally activated by interferon-γ (IFN-γ) or other microbial products (e.g. LPS) which represent the classically activated macrophages (CAM) on a pro-inflammatory state. M2 macrophages usually activated by the IL-4/IL-13 immune complex which represent the alternatively activated macrophages (AAM) on a contradistinctive anti-inflammatory state (Locati et al., 2013). M1 macrophages can serve as potent killers of pathogens, whereas M2 macrophages exhibit an immunosuppressive phenotype (Hamilton, 2008; Mantovani and Locati, 2009).

M1 stimuli (IFN-γ and LPS) induce nevertheless M2 stimuli (IL-4 and IL-13) suppress CKIP-1 expression in human and murine macrophage. CKIP-1 promotes pro-inflammatory gene activation in a NF-κB dependent manner. Meanwhile, CKIP-1 inhibits anti-inflammatory genes expression by negatively regulating JAK1-STAT6 activation. CKIP-1 regulates M1 and M2 inflammatory macrophage polarization by forming a double feedback loop which includes CKIP-1 and the key elements of the macrophage polarization pathways (Chen et al., 2017).

3.3.2.3. Transformation. Lipoproteins such as oxidized LDL (oxLDL) can be uptake by macrophages which is mediated by the lectin-like oxLDL receptor 1 (LOX-1). Subsequently, macrophages transform into foam cells. These lipid accumulation cells can release immune factors, initiate a series of immune responses, promotes plaque formation and thereby collectively contribute to atherosclerosis (Li and Glass, 2002).

CKIP-1 interacts with the proteasome activator REGγ and through which triggers the transcriptional factor Oct-1 for degradation (Fan et al., 2019). Oct-1 can induce the expression of LOX-1 (Chen et al., 2006). In this way, CKIP-1 decreases lipoproteins uptake and foam cell formation. In the knockout mice model, CKIP-1 deletion indeed accelerates atherosclerosis, and bone marrow transplantation from CKIP-1-deficient mice is sufficient to increase atherosclerotic plaque formation (Fan et al., 2019).

3.3.2.4. Migration. Preliminary integration analysis of genomics and proteomics in RAW264.7 cells suggests that CKIP-1 might be involved in the regulation of macrophage migration (Zhang et al., 2013). The physiological functions in vivo and regulation mechanisms are still worthy to be further detected.

3.3.3. T cell

Transcription factor NF-κB can activate lymphocyte and trigger immune responses (Vallabhapurapu and Karin, 2009). T cell receptor (TCR) induces phosphorylation of CARMA1 by PKθ, leading to the formation of CARMA1-Bcl10-MALT1 (CBM) complex in lipid rafts and then activates NF-κB signaling (Matsumoto et al., 2005). Through binding to CARMA1, CKIP-1 destroys the interaction between PKθ and CARMA1, and inhibits NF-κB signaling in both resting and PMA or constitutively actived PKθ induced Jurkat T cells (Table 1). The PH domain of CKIP-1 is essential for its interaction with CARMA1 and negative regulation roles. It is worth mentioning that stimuli CD3/CD28 which causes dissociation of CKIP-1 from lipid raft. Its inhibitory effect does not extend. Hence CKIP-1 subcellular localization appears to be critical for its function (Sakamoto et al., 2014).

4. Diseases

4.1. Skeletal disorders

4.1.1. Primary osteoporosis

Osteoporosis is causes of bone loss and bone microstructure damage, resulting in bone fragility and fracture increase. Primary osteoporosis, which mainly includes postmenopausal and senile osteoporosis, is the most common type of osteoporosis (Tarantino et al., 2017). CKIP-1-deficient mice undergo an age-dependent increase in bone mass as a result of accelerated osteogenesis and decreased Smurf1 activity (Lu et al., 2008). Besides, CKIP-1 expression is increased in the age-related bone specimens from either fractured patients or aging rodents (Liu et al., 2017a).

The $(AspSerSer)_6$-liposome-based bone tissue-specific delivery system has good affinity for the physiochemical features of the bone-formation surface than the bone-resorption surface. Using this system, osteogenic CKIP-1 siRNA was specifically delivered to the bone-formation surface and downregulated CKIP-1 expression efficiently, through which promoting the expression of osteogenic genes, increasing bone mass (Zhang et al., 2012). Since anti-osteoporosis bone synthesis drugs should be preclinically tested in animal models of osteoporosis before clinical trials, Guo et al. testified that cross-species CKIP-1 siRNA can promote osteoblast differentiation with enhanced bone microarchitecture in healthy human, rhesus monkey and rat (Guo et al., 2014). CKIP-1 is involved in multiple cell regulations, thus the osteoblasts specific system could have higher efficacy and less potential toxic side effects. Liang et al. demonstrated a real osteoblast-specific delivery system. The osteoblast-specific CH6 aptamer–functionalized lipid nanoparticles (LNPs) encapsulating achieves osteoblast specific delivery of CKIP-1 siRNAs and facilitates bone formation in OVX and healthy rodents (Liang et al., 2015).

In addition to direct siRNA delivery systems, MSCs implant using a chitosan/si-CKIP-1-biofunctionalized titanium can also significantly improve the osteogenic differentiation and result in dramatically enhanced Osseo integration in the OVX rat model (Zhang et al., 2015).

In aging male rats which suffered senile osteoporosis, CKIP-1 siRNA could increase bone mass and improving bone microarchitecture (Liu et al., 2017a). Taking together, knockdown of CKIP-1 expression seems to be a good therapy for both postmenopausal and senile osteoporosis.

4.1.2. Secondary osteoporosis

Secondary osteoporosis may ensue from several diseases, such as endocrine, hematological, gastrointestinal, rheumatic, and kidney disorders, or from medications such as glucocorticoids, anticoagulants, diuretics, and others (Tarantino et al., 2017). Glucocorticoid osteoporosis (GIO) is one of the most common secondary osteoporosis (Liu et al., 2018). Accompanied by extracorporeal glucocorticoid treatment, CKIP-1 is highly expressed by disrupting the Smad-dependent BMP

signaling pathway. Osteoblasts-specific CKIP-1-knockout prevents bone formation reduction during GIO development. Thus, targeting CKIP-1 can be a potential therapeutic strategy for GIO patients (Liu et al., 2017b).

4.1.3. Microgravity-induced osteoporosis

Exposure to low gravity environment can lead to weight and ground reaction force reduced, thus decrease the bone mass (Vico et al., 2000). Depletion of CKIP-1 could remiss microgravity-induced osteoporosis by affecting bone formation (Zhang et al., 2016). In addition, constrained dynamic loading combined with CKIP-1 knockout experiences a less loss of bone mass after four weeks of tail suspension compared with the wild type group (Han et al., 2018). This suggests an approach to the treatment of osteoporosis induced by microgravity in space.

4.1.4. Distraction osteogenesis

In addition to what mentioned above, distraction osteogenesis (DO) has become a widely accepted method for endogenous bone regeneration in oral and maxillofacial surgery (Konopnicki and Troulis, 2015). CKIP-1 silencing significantly inhibited apoptosis, but promoted osteogenic differentiation through promoted the expression of Wnt3a, β-catenin, and osteocalcin both in DO models in vivo and in cultured BMSCs in vitro (Zhou et al., 2017).

Taking together, CKIP-1 siRNA therapy may be a promising treatment option for various types of osteoporosis and osteogenesis. In addition to single CKIP-1 RNAi, either the CKIP-1–Smurf1 interaction or the CKIP-1–Rpt6 interaction might also be promising targets for the design of drugs.

4.2. Cancer

Over-activation of PI3K/Akt signaling leads to a competitive growth advantage and metastatic competence, and the dysregulation of PI3K/Akt signaling pathway have been broadly observed in human cancers (Hennessy et al., 2005). In HT1080 cancer cells, CKIP-1 represses Akt activation and inhibits cell growth in vitro and in vivo (Tokuda et al., 2007). CKIP-1 suppresses colon cancer progression through opposing PI3K/Akt/mTOR signaling and triggers Smurf1 to autodegradation (Nie et al., 2014). Similar to Nmi and contrast to IFP35, CKIP-1 inhibits the growth and Akt-mediated cell survival of Glc-82 lung cancer cells (Zhang et al., 2007). In non-Hodgkin's lymphoma, silencing of CKIP-1 promotes tumor proliferation and cell adhesion-mediated drug resistance via regulating Akt activity (Zhu et al., 2017). Moreover, CKIP-1 represses cell adhesion and proliferation and induces apoptosis in breast cancer MDA-MB-231 cells (Koskimaki et al., 2012). In addition, deletion of CKIP-1 is associated with the worse outcome of breast cancer patients associated with BRCA1 (Alvarez et al., 2016). Therefore, CKIP-1 functions mainly as a tumor suppressor.

However, CKIP-1 was reported to promote prostate cancer migration and proliferation by modulating PAK1 activity in RWPE-1 cells (Kim et al., 2015). Also, CKIP-1 promotes proliferation of human lung cancer H1299 cells (Chen et al., 2015). Since CKIP-1 can regulate numerous proteins in different cell types which are important in tumorigenesis (Table 2), it is not surprising that it might harbor complex function. However, in vivo evidence from CKIP-1 knockout mice to show whether it is a tumor suppressor or oncogenic factor is still lacking. More investigations are needed to clarify the profound mechanisms.

4.3. Cardiac hypertrophy

CKIP-1-deficient mice exhibit spontaneous cardiac hypertrophy with aging. Moreover, myocardial-specific CKIP-1 overexpression protects from cardiac hypertrophy induced by pressure overload. Besides, CKIP-1 expression was reduced in human heart failure (Ling et al., 2012). Therefore, CKIP-1 is close related to heart failure.

Table 2
CKIP-1 in different cancer cell lines.

Tumor types	Cell lines	Binding proteins	Intrinsic mechanisms	Molecular functions	Reference
Fibrosarcoma	HT1080	Akt	represses Akt activation	inhibits cell growth in vitro and in vivo	Tokuda et al., 2007
Colon cancer	HCT116, SW480	Smurf1	oppose PI3K/Akt/mTOR signaling and triggers Smurf1 autodegradation	suppresses colon cancer progression	Nie et al., 2014
Lung cancer	Glc82	IFP35	destabilize IFP35 through compete with Nmi	inhibits tumor cell proliferation and Akt-mediated cell survival	Zhang et al., 2007
Lymphoma	Raji, OCI-Ly8	Akt	regulating Akt activity	inhibits tumor proliferation and cell adhesion-mediated drug resistance	Zhu et al., 2017
Breast cancer	MDA-MB-231	–	–	represses cell adhesion and proliferation and induces apoptosis	Koskimaki et al., 2012
Prostate cancer	RWPE-1 cells	PAK1	binds and promote CK2 phosphorylation of PAK1	promote prostate cancer migration and proliferation	Kim et al., 2015

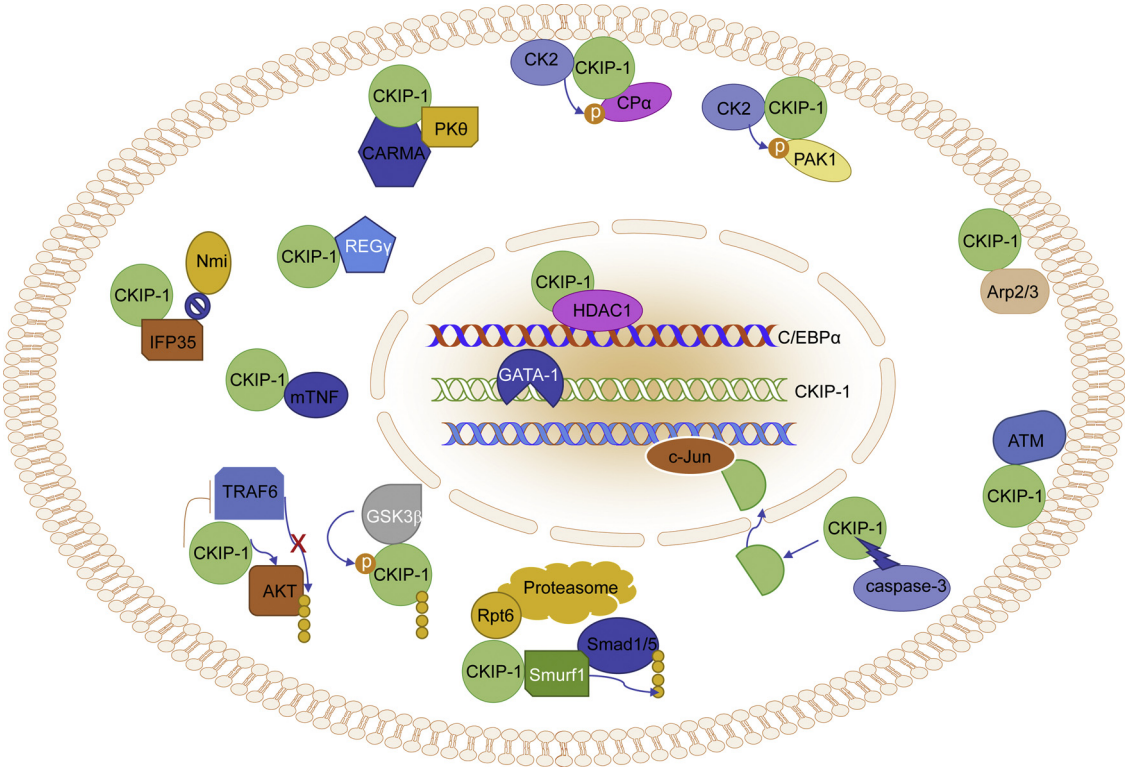

Fig. 2. The functional network of CKIP-1.
CKIP-1 has molecular functions and are involved in diverse biological processes. (1) cell morphology. CKIP-1 functions to target CK2 to the plasma membrane (PM) and facilitating phosphorylation of CPα and PAK1. (2) cell differentiation. CKIP-1 interacts with Arp2/3 and recruits it to the plasma membrane. CKIP-1 interacts with HDAC1 in the nucleus and through which inhibits C/EBPα transcription. The transcriptional factor GATA-1 can promote expression CKIP-1. (3) cell apoptosis. C-terminal fragments of CKIP-1 bind to c-Jun and repress AP-1. CKIP-1 interacts with ATM and stabilized p53 (4) bone formation. CKIP-1 binds to Smurf1 and Rpt6, and advances the degradation of Smad5. (5) Tumorigenesis. CKIP-1 could bind to Akt inhibit Akt. CKIP-1 enhances Smurf1 autodegradation. (6) Immune regulation. CKIP-1 binds to IFP35 and competes with Nmi. CKIP-1 interacts with the N-terminal fragment of mTNF. (Monocytes) CKIP-1 is phosphorylated by GSK3β and degradation. It can interactes with TRAF6 and suspends TRAF6-mediated activation of Akt. CKIP-1 interacts with the proteasome activator REGγ and diminish the degradation of Oct-1(Macrophages). CKIP-1 destroys the interaction between PKθ and CARMA1, and inhibits NF-κB signaling (T cells). This figure was prepared by Lin Fu. using the Biomedical PPT toolkit suite (www.motifolio.com).

HDAC4 is involved in the regulation of cardiac hypertrophy through its repression of MEF2 transcriptional activity (Ago et al., 2008). HDAC4 could be dephosphorylated by phosphatase 2A (PP2A) (Kozhemyakina et al., 2009). CKIP-1 could interact with both HDAC4 and PP2A to increase their interaction, thus promoting the dephosphorylation and nuclear retention of HDAC4 by PP2AC (the catalytic subunit of PP2A). By which, MEF2C activity is inhibited and protect cardiac hypertrophy (Ling et al., 2012). In addition, CKIP-1 P21A polymorphism is identified as a risk factor for chronic heart failure in a Chinese Han population (Li et al., 2017).This site might be a potential site which discards the interaction between CKIP-1 and HDAC4 or PP2AC.

After simulated microgravity, CKIP-1 mRNA and protein levels in hearts of mice and rhesus monkeys are significantly decreased. In CKIP-1 transgenic mice, CKIP-1 can inhibit the activity of HDAC4 and suppress cardiac atrophy induced by simulated microgravity in vivo (Ling et al., 2018).

Thus, modulating CKIP-1 may represent an effective therapeutic option for heart failure such as cardiac hypertrophy and cardiac atrophy induced by space flight.

4.4. Immune disorders

The definition of molecules and mechanisms associated with monocytes and macrophages may provide a basis for innovative diagnostic and therapies. CKIP-1 activates pro-inflammatory pathways and interferes with TNF reverse signaling induced apoptosis. As a consequence, it may be a promising target during local or systemic anti-TNF therapies (Juhasz et al., 2013). CKIP-$1^{-/-}$ mice spontaneously developed splenomegaly and bone marrow hyperplasia dominated by macrophages (Zhang et al., 2014). CKIP-1 regulates M1 and M2 inflammatory macrophage polarization. In LPS-mediated sepsis and TPA-mediated cutaneous, CKIP-1 exhibits inhibitory function which implies it as a new target for treatment of acute inflammation (Chen et al., 2017). CKIP-1 harbors a protective role during foam cell formation and atherosclerosis. Therefore, it can be a potential strategy for atherosclerosis treatment (Fan et al., 2019). In T cell-induced cell immune, CKIP-1 plays a unique role to keep resting T cells in a quiescent state or to prevent T cells from being activated by inadequate signaling. Dysfunction of CKIP-1 might constitutively activate NF-kB, leading to autoimmune diseases or malignant lymphomas, and CKIP-1 might be good therapeutic targets in autoimmune (Sakamoto et al., 2014). In addition, bioinformatics analyses revealed that potential biological functions of CKIP-1 are correlated with traditional Chinese medicine pattern of rheumatoid arthritis to varying degrees (Zhang et al., 2018). In osteoblasts from rheumatoid arthritis patients and collagen-induced arthritis (CIA) mice, CKIP-1 is highly expressed. TRAF2-mediated RIP1 ubiquitination requires CKIP-1 to activate NF-κB and induce inflammatory cytokines production in osteoblasts. Induction of osteoblastic CKIP-1 attenuates joint inflammation and reduces bone formation in CIA mice (He et al., 2019). We propose that further studies on CKIP-1 functions in immunity may contribute to more controlled therapeutic approaches.

Table 3
Subcellular localization of CKIP-1.

Interaction moleculars	Cell lines	Subcellular localization	Function	Reference
CPα	U2OS	PM	cell morphology control	Canton et al., 2005
PAK1	PC3	PM	cell morphology control	Kim et al., 2015
phosphoinositides	C2C12	PM	muscle differentiation	Safi et al., 2004
Arp2/3	C2C12	PM	muscle differentiation	Baas et al., 2012
HDAC1	C3H/10T1/2	Nucleus	MSCs differentiation	Li et al., 2014
c-Jun	SK-BR-3	Nucleus	induce cell apoptosis	Zhang et al., 2005
ATM	SK-BR-3	PM	induce cell apoptosis	Zhang et al., 2006
mTNF	THP-1	Cytoplasm	immune response	Juhasz et al., 2013

5. Discussion

CKIP-1 shuttles between the nucleus and the plasma membrane and functions at different subcellular compartments (Fig. 2). Although isolated CKIP-1 PH domain is predominantly localized in the nucleus, the C-terminus of CKIP-1 counteracted its nuclear localization (Xi et al., 2010). CKIP-1 can recruit CK2α, CPα, PAK1 and ATM to the PM. CKIP-1 localizes in the nucleus when interacts with c-Jun and HDAC1 in a truncated C-terminal or full-length form. Its subcellular localization is dependent on cell type and different physiological processes (Table 3).

Although multiple proteins are reported to interact with CKIP-1, the regulatory mechanism of CKIP-1 is still unclear. Diverse signals can induce the expression of CKIP-1 (Table 1) while the depth mechanism is not explicit. GATA-1 is the only reported transcriptional factor which directly binds to the promoter of CKIP-1 (Fan et al., 2017). GSK3β phosphorylates CKIP-1 on Ser342 which is essentials for the polyubiquitination and proteasomal degradation of CKIP-1 (Zhang et al., 2014). The E3 ligase which triggers this process is still unknown. Besides, whether CKIP-1 can be modified by other post-translational modifications (PTMs) such as methylation, acetylation still needs further consideration.

Conflicts of interest

The authors declare they have no conflicts of interest.

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