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Review Article

Significance of integrin-linked kinase (ILK) in tumorigenesis and its potential implication as a biomarker and therapeutic target for human cancer

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Abstract: Integrin-linked kinase (ILK), which is an ankyrin repeat-containing serine/threonine protein kinase, interacts with integrin β1 and the β3 cytoplasmic domain and phosphorylates integrin β1. ILK has multiple functions in cells, such as cell-extracellular matrix interactions, cell cycle, apoptosis, cell proliferation and cell motility, which are associated with the interacting partners of ILK and downstream signaling pathways. Upregulation of ILK is frequently observed in cancer tissues compared to corresponding normal tissues. Emerging evidence has demonstrated that ILK plays an important role in biological processes associated with tumorigenesis, including cancer cell proliferation, angiogenesis, metastasis, and drug resistance. Furthermore, inhibition of ILK expression and activity using siRNA or chemical inhibitors has shown a significant suppressive effect on cancer development and progression, implicating the potential of ILK as a target for cancer treatment. In this review, we summarized the functional role of ILK in tumorigenesis, with the expectation that targeting ILK could provide more evidence for cancer therapy.

Keywords: ILK, tumorigenesis, diagnostic and prognostic biomarker, therapeutic target

Introduction

Since its discovery in 1996 as an interaction partner of the β1 integrin cytoplasmic domain, ILK has been reported as a serine/threonine protein kinase, which plays a central role in fundamental processes, including the regulation of cell shape, motility, growth, survival, differentiation and gene expression [1]. Under normal conditions, ILK overexpression overrides the adhesion-dependent regulation of cell cycle progression and regulates cell growth and survival [2]. ILK regulates cell-cell adhesion and cell-matrix interactions through the loss of E-cadherin expression and increase in fibronectin matrix assembly [3]. Moreover, ILK modulates actin rearrangement, regulates chondrocyte shape and proliferation, and regulates the processes of myogenic differentiation [4-7]. In addition, ILK also inhibits anoikis and apoptosis through activation of phosphatidylinositide 3-kinase/protein kinase B (PI3K/AKT) signaling and stimulation of downstream anti-apoptotic pathways [8]. Since the discovery that overexpression of ILK induces the transformation of epithelial cells *in vitro* and *in vivo*, the important role of ILK in cancer proliferation, invasion, metastasis, angiogenesis, and chemoresistance has been extensively studied [9-14]. It is becoming clear that ILK exerts its biological functions through various signaling pathways, including PI3K/AKT, glycogen synthase kinase 3-beta (GSK3β), nuclear factor-kappa B (NF-κB), cell division control protein 42 homolog (Rac/Cdc42), mammalian target of rapamycin (mTOR), vascular endothelial growth factor (VEGF), and Snail1/E-cadherin [15-20]. More importantly, upregulation of ILK is frequently observed in human malignancies, and high ILK overexpression is associated with poor prognosis of cancer patients, suggesting its implication in cancer diagnosis and prognosis.

In this review, we summarized the physiological and pathological role of ILK in human cancer, including its biological functions, interaction

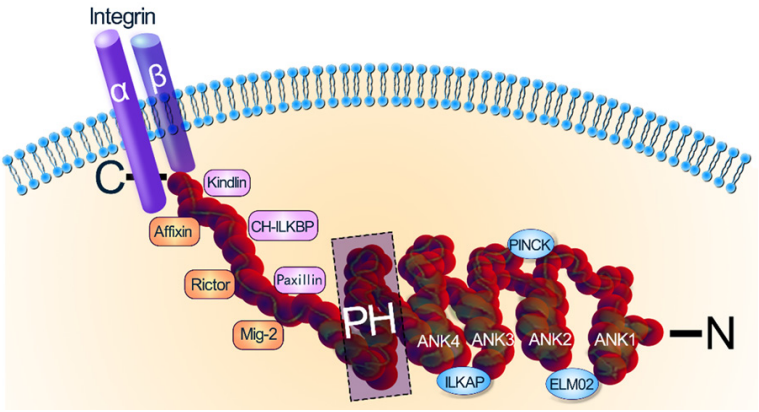

Figure 1. Structure and interacting proteins of ILK. ILK consists of three components: a COOH-terminal catalytic domain, a central pleckstrin homology (PH)-like domain, and an N-terminal domain. PINCH, ILKAP and ELMO2 interact with ILK via the N-terminal domain to modulate cell function. The C-terminal domain of ILK, which is the catalytic domain, directly interacts with Kindlin, Affixin, CH-ILKBP, Rictor, Paxillin and Mig-2. PH, pleckstrin homology; PINCH, particularly interesting new cysteine-histidine-rich protein; ILKAP, ILK-associated protein; ELMO2, engulfment and cell motility 2; CH-ILKBP, calponin homology domain-containing integrin-linked kinase (ILK)-binding protein.

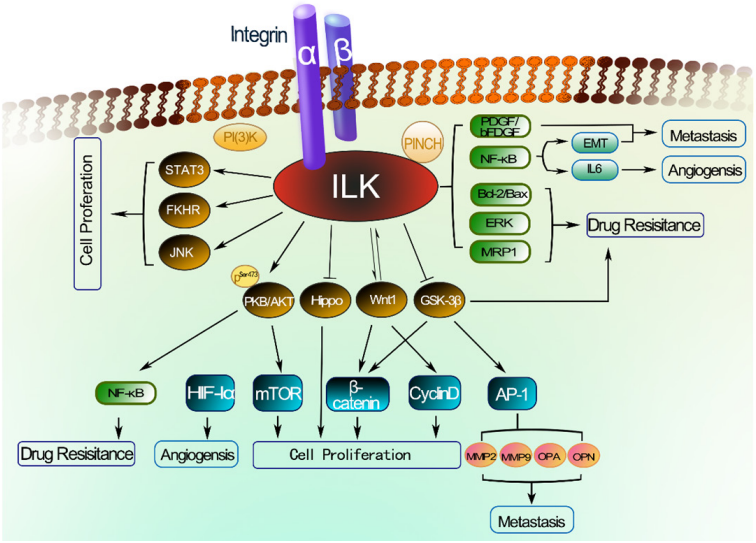

Figure 2. Role of ILK in regulating signaling pathways and cancer phenotypes. ILK is a central regulator of signaling cascades that control a series of biological processes that are crucial to cancer progression. ILK is activated by integrins and regulates downstream molecules, such as NF-κB, Hippo, Wnt1 and GSK3β. GSK3β, glycogen synthase kinase 3-beta; NF-κB, nuclear factor-kappa B; mTOR, mammalian target of rapamycin; STAT3, signal transducer and activator of transcription 3; FOXO1, forkhead box O1; JNK, c-Jun N-terminal kinase; PKB/AKT, phosphatidylinositide 3-kinase/protein kinase B; Wnt1, wingless-type MMTV integration site family, member 1; ERK, extracellular regulated MAP kinase; EMT, epithelial-to-mesenchymal transition; IL6, interleukin 6; PDGF, platelet-derived growth factor; HIF-1, hypoxia inducible factor 1 subunit alpha; MRP1, multidrug resistance-associated protein 1.

proteins, downstream signaling, and upstream regulation. Current progress on the development of specific small molecule inhibitors of ILK is described, and the potential of pharmacological inhibition of ILK for cancer treatment is discussed.

Structure and interaction proteins of ILK

ILK, which is localized on chromosome 11p15.5-p15.49 in humans [21], encodes a 59k serine/threonine protein kinase [1]. ILK consists of a COOH-terminal catalytic domain, a central pleckstrin homology (PH)-like domain, and an N-terminal domain consisting of four ankyrin-like repeats [22] (**Figure 1**). The main function of the ankyrin repeats is the regulation of protein-protein interactions [23]. Particularly interesting new cysteine-histidine-rich protein (PINCH), a widely expressed and evolutionarily conserved protein comprising five LIM domains, is a binding protein of ILK [24]. ILK-associated protein (ILKAP), a protein phosphatase 2C (PP2C) family protein phosphatase, binds to ILK to negatively regulate its downstream signaling [22]. Furthermore, engulfment and cell motility 2 (ELMO2) also interacts with ILK via the N-terminal domain to modulate cell polarity [25]. A PH-like domain in the central region mediates the interaction between ILK and 3'-phosphorylated inositol lipids, which is required for the PI3K-dependent activation of ILK [22]. The C-terminal domain, which is the catalytic domain of ILK, interacts with integrins [23], paxillin, a focal adhesion adapter protein [26], calponin homology domain-containing integrin-linked kinase binding protein CH-ILKBP [26], Affixin [27], Rictor [28], Mig-2 [29], and Kindlin [30, 31].

Table 1. Function of ILK in different cancers

Cancer Type	Observed Functions of ILK	Involved Pathway	References
Prostate cancer	Survival, Growth, Motility, Apoptosis	AKT	[81, 92]
Multiple myeloma	Angiogenesis, Survival	HIF-2α-ILK	[46, 93, 94]
Colorectal cancer	EMT, Proliferation, Invasion, Chemoresistance, Migration	NF-κB/p65	[16, 17, 55]
Pancreatic cancer	EMT, Proliferation, Migration, Invasion	MUC1-C	[11, 95]
Glioma cells	Proliferation, Migration, Invasion, Temozolomide resistance	Caspase3, E-cadherin, NF-κB, Cyclin D1	[14, 15, 96]
Bladder cancer	EMT, Proliferation, Morphology	ILK/PI3K/AKT	[97, 98]
Lung cancer	EMT, Migration, Invasion, Drug resistance	MRP1, NF-κB, MMP-9	[18, 52]
Gastric cancer	Growth, Migration, Survival, Multidrug resistance, Cell cycle	NF-κB, ERK1/2, E-cadherin, AP-1, MMP-2/9, Cystatin B, p-AKT	[54, 99, 100]
Tongue cancer	EMT, Proliferation, Migration, Invasion	AKT, GSK3β, MMP2, MMP9	[58]
Ovarian cancer	Migration, Invasion	Rac1, AKT	[101]
Breast tumors	Proliferation	PI3K/AKT	[102]
CLL	Proliferation	NF-κB	[103]
Thyroid cancer	EMT, Migration	AKT	[104]
OSCC	EMT, Growth, Metastasis, Adhesion	AKT, GSk3β	[105]
RCC	EMT, Migration, Invasion	Snail, Zeb-1	[59]
Retinoblastoma cells	Proliferation, Cytokinesis, Mitosis, Cytoskeleton dynamics	Unknown	[43]
Phyllodes breast tumors	EMT, Metastasis	E-cadherin, ZEB1, β-catenin, Twist, N-cadherin, Snail, Vimentin	[106]

CLL: Chronic Lymphocytic Leukemia; OSCC: Oral squamous cell carcinoma; RCC: Renal Cell Carcinoma.

Table 2. ILK expression in different cancers

Cancer Type	Comments	Methods	References
Prostate cancer	Overexpression of ILK in 57.1% of prostate cancer samples and 18.2% of benign prostatic hyperplasia (BPH) samples	IHC	[81]
Breast tumors	Greater ILK expression with increasing tumor grade	IHC	[106]
Colorectal cancer	Upregulated ILK mRNA and protein expression in primary CRC cells; high expression of ILK in 42.2% of primary CRC samples	IHC, WB, RT-PCR	[55]
ISCC	Increased expression level of ILK is associated with lymph node metastases and patient survival rate	IHC	[57]
CLL	ILK overexpression in patient samples, particularly in tumor cells harboring prognostic high-risk markers	IHC	[103]
NSCLC	Increased ILK overexpression in 46.4% of NSCLC tumors	IHC	[107]
Gastric cancer	ILK overexpression in 47.4% of gastric cancer tumor tissues	IHC	[108]
Breast cancer	Upregulated ILK1 mRNA expression in primary breast cancer tissues; 54.6% of patients are classified with ILK1 overexpression	IHC	[109]
Osteosarcoma	ILK overexpression is correlated with distant metastasis and it is an independent prognostic factor for poor overall survival	IHC	[47]
BTCC	Overexpression of ILK protein in BTCC tissue (53.6%)	IHC, RT-PCR	[110]
Pancreatic cancer	Increased ILK expression level in pancreatic cancer	IHC	[11]
CCRC	Upregulated ILK expression in high-grade CCRCs compared to low-grade CCRCs	IHC	[111]
RCC	ILK underexpression in normal cells and low-stage RCC cells and ILK overexpression in advanced and metastatic cells	IHC, WB	[59]

IHC, Immunocytochemistry; WB, Western blot; RT-PCR, Real-time PCR; ISCC, laryngeal squamous cell carcinoma; CLL, Chronic Lymphocytic Leukemia; NSCLC, Non-small cell lung cancer; BTCC, Bladder transitional cell carcinoma; CCRC, Clear cell renal carcinoma; RCC, Renal Cell Carcinoma.

Role of ILK in tumorigenesis

Since the discovery in 1998 that ILK overexpression induces tumorigenic transformation of epithelial cells *in vitro* and *in vivo*, which is accompanied by upregulation of fibronectin matrix assembly and downregulation of E-cadherin expression [12], accumulating evidence has demonstrated the role of ILK in the characteristics of cancer, including cell proliferation, cell survival, angiogenesis, metastasis and drug resistance (**Figure 2**), which is summarized according to different cancer types in **Table 1**. In addition to the findings that ILK is widely overexpressed in different cancers, ILK upregulation is more importantly associated with tumor grade and survival (**Table 2**). These results clearly indicate that ILK plays an important role in cancer development and progression.

ILK promotes cancer cell proliferation

Analysis of the expression pattern and regulation of ILK in mouse skin provided the first *in vivo* evidence of the role of ILK in the regulation of cell proliferation [32], and the effect of ILK on the proliferation of cancer cells has since become a popular topic. It has been reported that inhibition of catalytic activity of ILK suppresses tumor growth by inhibiting the PI3K/mTOR, signal transducer and activator of transcription 3 (STAT3) and forkhead box O1 (FKHR) pathways [33] or decreasing the phosphorylation of protein kinase B/AKT and GSK3β [34-36]. Similarly, knockdown of ILK with siRNA in colorectal cancer cells has been shown to decrease the expression levels of cyclin D1, Snail, matrix metallopeptidase 9 (MMP9) and fibronectin, and ILK intestinal knockout has been shown to result in a smaller tumor volume when mice are treated with azoxymethane and dextran sodium sulfate [37]. In addition, overexpression of ILK could stabilize β-catenin and increase β-catenin/Tcf transcriptional activity [38]. ILK cooperates with Wnt1 to stimulate the expression of β-catenin and cyclin D1 and accelerates breast tumor development [39]. In neuroblastoma cells, inhibition of ILK expression with an antisense oligonucleotide interferes with the regulation of ILK on PTEN (phosphatase and tensin homolog)-AKT signaling and tumor growth [40]. Additionally, ILK represses apoptosis and induces cell proliferation through regulation of the c-Jun N-terminal kinase (JNK) signaling pathway [41]. In human breast, prostate and colon cancer cells, ILK inhibits the Hippo pathway through inactivation of Merlin by direct phosphorylation of protein phosphatase 1 regulatory subunit 12A (MYPT1) [42]. Interestingly, Sikkema *et al.* found that ILK not only promotes cell proliferation but also regulates mitotic cytoskeleton dynamics and cytokinesis [43]. Therefore, ILK interacts with multiple pathways to affect cancer cell proliferation.

ILK increases tumor angiogenesis

Oxygen and nutrients are required for the growth and survival of mammalian cells. Angiogenesis occurs during development, wound healing, pregnancy and other physiological processes. However, angiogenesis is also an essential step in the conversion of a tumor from a benign to a malignant and metastatic phenotype. Tumor growth is a complex and multistep process involving recruitment of neighboring blood vessels or endothelial cells to deliver oxygen and nutrients into the tumor microenvironment to construct a favorable environment for tumor growth [44]. Tumors cannot grow beyond a critical size or metastasize to another organ without a sufficient nutrient supply [44]. VEGF, a secreted protein, is one of the most important proangiogenic factors involved in tumor angiogenesis [45]. The regulation of VEGF occurs at the gene transcription, translation, and posttranslation levels. Tan *et al.* found that ILK regulates VEGF expression by inducing hypoxia inducible factor 1 subunit alpha (HIF-1α) protein expression in a PKB/AKT- and mTOR-dependent manner and increases VEGF-stimulated blood vessel formation [19]. Additionally, overexpression of ILK in melanoma cells stimulates VEGF via NF-κB-mediated upregulation of interleukin 6 (IL-6), which is a pleiotropic cytokine closely associated with cancer development [20]. Genetic or pharmacological inhibition of ILK using siRNA or small molecule inhibitors has been shown to successfully decrease the expression and secretion of VEGF and suppress cancer progression [46-48]. ILK has been reported to be induced by hypoxia-inducible factor-2 alpha (HIF-2α) and VEGF and mediate their effect on angiogenesis in a positive feedback manner [46, 49].

ILK enhances the resistance of cancer cells to chemotherapeutic drugs

Overexpression of ILK could suppress stress-induced cell apoptosis [8] and regulate resistance to hyperthermia by inhibiting the activity of stress-activated protein kinase/c-Jun N-terminal kinase (SAPK/JNK) and p38 mitogen-activated protein kinase (p38 MAPK kinase) [50]. Moreover, knockdown of ILK makes cells more sensitive to EGFR inhibitors [51]. ILK is speculated to be associated with resistance to chemotherapeutic drugs in multiple cancer types. In pancreatic adenocarcinoma cells, overexpression of ILK increases gemcitabine chemoresistance by increasing phosphorylation of AKT and GSK3β, whereas inhibition of ILK induces apoptosis caused by gemcitabine [13]. Significantly greater expression levels of ILK have been observed in a gemcitabine-resistant subline derived from the lung cancer cell line A549 compared with the parental cells, and downregulation of ILK was shown to sensitize the cells to treatment by repressing epithelial-to-mesenchymal transition (EMT) and cellular drug efflux [52]. Similarly, ILK silencing has been reported to make A549 cells more sensitive to cisplatin, which is one of the most commonly used chemotherapeutic drugs for cancer treatment [53]. In gastric carcinoma SGC7901/DDP cells, not only AKT and extracellular signal-regulated kinase-1/2 (ERK) but also activator protein 1 (AP-1) and NF-κB pathways have been shown to be involved in the multidrug resistance caused by the upregulation of ILK [54]. Overexpression of ILK in glioma cells decreases the sensitivity to temozolomide, which is accompanied by the upregulation of the anti-apoptotic protein Bcl-2 and downregulation of the proapoptotic protein Bax [14]. Moreover, the expression correlation between ILK and markers of cancer stem cells, as well as the functional role of ILK in the sensitivity of cells to 5-FU and oxaliplatin, have been reported in colorectal cancer cells [55]. These findings support the important role of ILK in cancer chemoresistance.

ILK promotes cancer metastasis

Tumor metastasis is defined as the spread of cancer from one organ/site to distant sites. Metastatic cancers are largely incurable, and greater than 90% of mortality from cancer is attributed to metastasis [56, 57]. Identification of the key proteins and signaling pathways that promote cancer invasion and metastasis could facilitate the development of new treatment strategies. Emerging evidence has suggested that the expression level of ILK is closely correlated with cancer metastasis and poor prognosis (**Table 1**). For example, downregulation of ILK decreases N-cadherin, Vimentin, Snail, Slug and Twist expression levels, as well as cell migration and invasion in human tongue cancer cells [58]. A similar phenomenon has also been observed in adenoid cystic carcinoma of salivary glands and renal cell carcinoma [59, 60]. Recent studies have confirmed that NF-κB is crucial for the activation of metastasis mediated by ILK. In lung cancer, ILK stimulates matrix metalloproteinase-9 to promote cell migration and invasion through NF-κB [18]. Overexpression of ILK promotes cell migration and invasion of glioma cells, which is related to downregulation of E-cadherin via the NF-κB pathway [15]. Some studies have also reported that ILK could induce migration and invasion of colorectal cancer cells by promoting NF-κB-mediated EMT [16, 17].

Upstream regulation of ILK

ILK is regulated at the transcriptional level

The ILK protein is encoded by 15 exons, with the major transcriptional start site located 138 bp upstream of exon 1 and the translation initiation codon (ATG) located within the second exon. The *ILK* gene has the features of housekeeping genes, especially a TATA-less and GC-rich promoter region [61], and there are multiple transcription factor binding sites within the promoter, such as AP-2, Sp1 and NF-κB [62]. In NSCLC cells, PGE_2 stimulates cell growth through upregulation of ILK promoter activity, which is dependent on the binding of Sp1 to the *ILK* gene promoter [62]. Researchers have shown that rosiglitazone and metformin repress nasopharyngeal carcinoma (NPC) cell growth by reducing AP-2α-dependent ILK transcription [63]. Integrin αVβ3 has been reported to increase ILK promoter activity in human ovarian cancer, and the binding of Ets-1 to the second Ets DNA motif is critical for this process [64, 65]. A recent study demonstrated that KRAS regulates ILK expression through E2F1-mediated transcriptional activation, which induces KRAS expression as a regulatory loop to promote aggressive phenotypes in pancre-

atic cancer [66]. Moreover, it has been shown in the kidney that integrin α3 increases ILK expression via the Src/p-β-catenin/p-Smad2 regulatory axis [67]. ILK has also been shown to be activated by Twist, which is the conserved basic helix-loop-helix transcription factor, and mediates the effect of Twist in EMT and tumor metastasis [68]. In addition, hypoxia has been reported to stimulate ILK transcriptional expression in an HIF-1α-dependent manner, and ILK, in turn, induces HIF-1α expression in prostate and breast cancer cells [69]. However, it remains unclear which transcription factors are responsible for ILK transcription.

ILK is regulated at the posttranscriptional level

Recent studies have demonstrated that miRNAs can function as tumor suppressors or oncogenes in various cancers [70]. Researchers have shown that miR-542-3p inhibits *ILK* gene expression by binding to its 3'-UTR in oral squamous cell carcinoma cells [71], which has been confirmed in gastric adenocarcinoma cells [72]. It has been reported that miR-625 represses ILK expression by directly targeting its 3'-UTR to suppress lymphatic metastasis of human gastric cancer cells *in vitro* and *in vivo* [73]. Moreover, ILK has been shown to be targeted by miR-145, which functions synergistically with miR-143 to inhibit the growth of bladder cancer cells [74].

Protein modification of ILK

Although direct phosphorylation of ILK has not been reported, the kinase activity of ILK is not only stimulated by integrin and growth factors but also activated by PI3K via a PH-domain-mediated interaction with phosphatidylinositol 3,4,5-trisphosphate (PIP3) and regulated by the tumor suppressor PTEN (phosphatase and tensin homolog deleted on chromosome 10), which acts as an antagonist of PI3K signaling to dephosphorylate PIP3 to PIP2 [75, 76]. Moreover, ILKAP, a serine/threonine phosphatase of the PP2C (protein phosphatase 2C) family, has been shown to negatively regulate ILK activity and signaling [77].

Potential of ILK-targeting agents for cancer therapy

Chemotherapy is one of the standard treatment options for cancer patients. However, limited treatment efficiency, side effects and development of resistance to the current chemotherapeutic drugs remain serious challenges in the management of human cancer. For example, epidermal growth factor receptor (EGFR)-tyrosine kinase inhibitor (TKI) drugs have been shown to significantly prolong the lifetime of patients with non-small cell lung cancer [78, 79]. However, chemoresistance is a substantial obstacle in the use of the first-generation EGFR inhibitor drugs, and there are 3 generations of EGFR-TKI drugs [80]. Therefore, the development of novel strategies that target different oncoproteins or kinases to improve treatment outcomes is urgently needed. As summarized above, ILK is frequently overexpressed in cancer cells compared with the surrounding normal cells and plays a crucial role in regulating various cellular processes, including proliferation, survival, invasion, angiogenesis and metastasis, suggesting that ILK may be a promising target for cancer therapy.

The expression of ILK in cancer cells can be inhibited by antisense oligonucleotides and siRNA. Knockdown of ILK using siRNA or shRNA has been shown to markedly inactivate the PI3K/AKT pathway and repress EMT, tumor growth and metastasis of tongue and prostate cancer cells *in vitro* and *in vivo* [58, 81]. The antisense oligonucleotide targeting ILK has been reported to delay tumor formation of human ovarian carcinoma cells in nude mice [82] and exhibit a synergistic effect with either the Raf-1 inhibitor or the MEK inhibitor to kill glioblastoma cells [83].

By screening a compound library, Lee *et al.* identified N-methyl-3-(1-(4-(piperazin-1-yl) phenyl)-5-(40-(trifluoromethyl)-[1,10-biphenyl]-4-yl)-1H-pyrazol-3-yl)propanamide (compound 22) as an ILK inhibitor. This compound was shown to exert strong inhibitory effects on the proliferation of a panel of prostate and breast cancer cells through inactivation of the AKT pathway and inhibition of the transcription factor Y-box binding protein-1 (YB-1). More importantly, the *in vivo* treatment efficacy of compound 12 as a single agent used to suppress the growth of prostate tumor xenografts suggested its potential use as a lead compound to develop more I LK inhibitors [84]. Moreover, researchers have reported that treatment with QLT0267, a new ILK inhibitor, not only inhibits the kinase activity of ILK and PI3K/AKT signaling and leads to cell growth arrest *in vitro* but also sup-

presses tumor angiogenesis and reduces tumor volume of thyroid cancer and glioblastoma xenografts *in vivo* [85, 86]. In addition, the combination of QLT0267 with docetaxel has been shown to produce a synergistic effect in inhibiting the PI3K/AKT pathway and VEGF secretion, as well as in enhancing the treatment outcome in an orthotopic breast cancer model [87]. A recent study indicated that inhibition of ILK with QLT0267 could reduce acquired resistance to 5-FU and decrease the expression levels of EMT and cancer stem cell (CSC) markers in human colon cancer cells [55]. These findings suggest that ILK represents a valid therapeutic target for cancer treatment, and more ILK-targeting agents with improved efficacy and minimal toxicity need be developed to provide more therapeutic strategies for cancer treatment.

Conclusion and future perspectives

Since the discovery of ILK in 1996 as a new protein defined as a receptor-proximal protein kinase, its biological functions and mechanisms of activity have become popular topics in the fields of biochemistry and cancer biology. Accumulating studies have indicated that ILK plays an important role in various characteristics of cancer, including cell proliferation, migration, invasion, angiogenesis, chemoresistance and metastasis. ILK functions through multiple signaling pathways, such as PI3K/AKT, Hippo, NF-κB, ERK and Bcl-2. The expression of ILK is regulated at the transcriptional, posttranscriptional, and posttranslational levels. However, the role of ILK in some cancer types remains unclear, and more importantly, whether there are some crucial upstream regulators of ILK warrants in-depth investigation.

Cancer is a substantial threat to human life, and increasing numbers of patients have been reported to have drug resistance when treated with chemotherapeutic drugs for long periods of time [88]. Tumor metastasis remains largely incurable, and up to 90% of cancer-related deaths are caused by metastatic disease rather than primary tumors [89-91]. All of these factors cause more difficulties for the treatment of cancer and result in poor clinical outcomes. Therefore, the investigation of new targets for cancer therapy is urgently needed. ILK is overexpressed in tumors compared to adjacent normal tissues, and genetic and pharmacological inhibition of ILK has been reported to inhibit a series of oncogenic signaling pathways and suppress tumor development and progression in several cancer types. These findings support the potential of ILK as an ideal target for cancer therapy. Future studies should be performed to combine the *in silico* design of ILK-targeting lead compounds and function-oriented high-throughput screening, as well as drug repositioning, for the development of novel therapeutic strategies with improved efficacy and decreased toxicity to improve the treatment outcomes of this lethal disease.

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Disclosure of conflict of interest

None.

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