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Mechanisms and consequences of constitutive activation of integrin-linked kinase in acute myeloid leukemia

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ABSTRACT

Integrin-linked kinase (ILK) has emerged as a critical adaptor and mediator protein in cell signaling pathways that is commonly deregulated in acute myeloid leukemia (AML). This has led to the expectation that therapeutic targeting of ILK may be a useful option in treating leukemia. Although ILK can regulate many cellular processes, including cell differentiation, survival, migration, apoptosis and production of pro-inflammatory cytokines, its role in promoting AML is still unclear. However, its ability to mediate phosphorylation and regulate the important hematopoietic stem cell regulators protein kinase B (AKT) and glycogen synthase kinase-3β supports ILK as an attractive target for the development of novel anticancer therapeutics. In this review, we summarize the existing knowledge of ILK signaling and its impact on cytokines, paying particular attention to the relevance of ILK signaling in AML. We also discuss the rationale for targeting ILK in the treatment of AML and conclude with perspectives on the future of ILK-targeted therapy in AML.

1. Introduction

Acute myeloid leukemia (AML) is an aggressive heterogeneous hematological malignancy, characterized by a clonal expansion of immature myeloid cells [1]. Unfortunately, around 75% of AML patients who receive intensive chemotherapy experience a relapse within 2 years of remission [2]. Deregulated activation of integrin-linked kinase (ILK) is frequently associated with many human hematological and epithelial malignancies [3–6]. Despite the fact that ILK has a crucial role in the normal development and function of numerous tissues [7], its contribution to the pathogenesis of human AML is still a matter of debate. ILK activity is stimulated by adhesion of the cell to the extracellular matrix and by growth factors in a phosphoinositide 3-kinase (PI3K)-dependent manner [8,9]. Once activated, ILK can mediate various cellular functions that vary with cell context. However, through ILK downstream targets protein kinase B (AKT), glycogen synthase kinase-3β (GSK- 3β) and nuclear factor kappa B (NF-κB) [8–11], ILK can be linked to several tumorigenesis-related events including cell proliferation, adhesion, apoptosis, angiogenesis, migration, invasion and immune evasion [8,12,13]. In AML, activating mutations in the FMS-like tyrosine kinase 3 (FLT3) receptor or aberrant signaling of the PI3K/AKT pathway lead to an increased activation of ILK, but the mechanism behind that is still unclear [3,14]. In addition, the inhibition of phosphatase and tensin homologue (PTEN), a negative regulator of ILK, results in the expansion of bone marrow hematopoietic stem cells [15]. In mouse models, PTEN deletion and constitutive activation of Akt signaling gives rise to myeloid or lymphoid leukemia [15,16]. Collectively, these observations support the general concept that activated ILK signaling is associated with hematopoietic malignancies.

2. Integrin-linked kinase (ILK)

ILK was discovered in 1996, based on its interaction with the cytoplasmic domains of integrin-β1 and -β3 subunits [17]. It is a multifunctional intracellular adaptor and kinase that regulates several cellular processes, including cell proliferation, adhesion, survival, apoptosis, angiogenesis, migration and invasion [18–20]. ILK is expressed in most mammalian tissues and cells, with higher levels exhibited in cardiac and skeletal muscle. ILK is encoded by a single gene located on chromosomes 11p15 and 7 in human and mouse, respectively [21]. The ILK gene encodes 452 amino acids and consists of three conserved domains: the amino-terminal ankyrin repeat domain, a central pleckstrin-homology (PH)-like domain and a carboxy-terminal kinase catalytic domain that links the cell adhesion receptors, integrins and growth factors to downstream signaling pathways (Fig. 1). The ankyrin repeat domain enables ILK to bind with several adaptor

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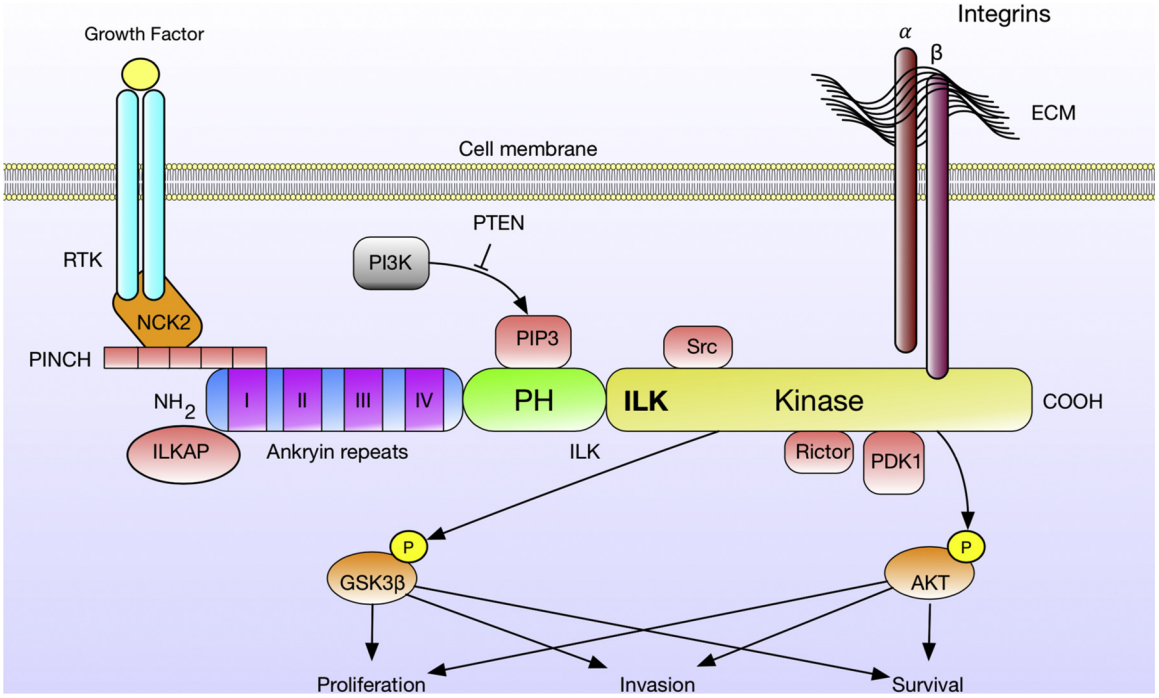

Fig. 1. ILK has a unique domain organization that supports its role as a multifunctional protein. It comprises an N-terminal domain that contains four ankyrin repeats, a central pleckstrin homology (PH)-like domain and a C-terminal kinase domain. ILK forms multi-complexes with several proteins. The N-terminal ankyrin repeats of ILK bind with PINCH and ILKAP. PINCH also joins ILK to non-catalytic (region of) tyrosine kinase adaptor protein-2 (NCK2), which associates with RTK and links ILK to growth-factor signaling. The middle PH-like domain of ILK interacts with PIP3 and is essential for PI3K-dependent activation of ILK. The C-terminal kinase domain of ILK binds to β1 and β3 integrins, as well as with several key proteins that are involved in cell signaling, including phosphoinositide-dependent kinase 1 (PDK1), AKT, Rictor and Src. The direct interaction between Rictor and ILK is important for phosphorylation of Akt at Ser473. ILK activity is antagonized by ILKAP and PTEN. Activation of ILK mediates the phosphorylation of many proteins such as AKT and GSK-3β, resulting in the regulation of downstream effectors that in turn modulate many biological processes such as survival, invasion and proliferation [84]. ECM, extracellular matrix.

proteins, including particularly interesting new cysteine-histidine-rich protein (PINCH), ILK-associated phosphatase (ILKAP) and PH-like domain, which interacts with five cysteine-rich repeats in Lin11, Isl-1 and Mec-3 (LIM). ILKAP is a serine/threonine phosphatase that negatively regulates ILK [22,23]. The PH domain binds with high affinity and specificity to phosphoinositides such as phosphatidylinositol 3,4,5-triphosphate (PIP3) [8]. ILK is also negatively regulated by PTEN, which inhibits ILK activity through dephosphorylation of PIP3 to phosphatidylinositol 4,5-diphosphate (PIP2) [24]. In accord with this, PTEN-deficient cells exhibit constitutive activation of ILK activity and a concomitant increase in the concentration of PIP3 [12,25]. Several adapter proteins network directly or indirectly with ILK through its interactions with PINCH or parvins [18,26,27]. The integrin-binding site in the catalytic domain of ILK facilitates interactions with actin through the formation of a complex signaling platform with PINCH and parvins [28,29].

Under homeostasis, ILK is most likely activated transiently, but since it acts as a biological switch for several signaling pathways, ILK must be inactivated to avoid abnormal signal transduction. However, in malignant cells in which ILK is constitutively activated, several signaling pathways could be amplified [30]. For example, ILK activates signaling pathways that impact on cell survival by mediating phosphorylation of AKT at serine 473 [9] and activation of NF-κB through p65 phosphorylation. ILK activation also results in phosphorylation of GSK3 at serine 9 of GSK-3β and serine 21 of GSK-3α, inhibiting their functions [31]. Moreover, ILK can indirectly activate selective transcription factors, including activator protein 1 (AP-1) and β-catenin, leading to cyclin D1 and matrix metalloproteinase-9 (MMP-9) stimulation [10,32,33]. Furthermore, a transcriptional co-activator of AP-1 and the JUN transcriptional co-activator, α-NAC, can be phosphorylated and regulated as a result of ILK activation [34]. It has also been shown that overexpression of ILK decreases the transcription of E-cadherin by increasing the expression of SNAIL1, which in turn accelerates invasion and metastasis of tumor cells [35,36].

3. ILK signaling in normal hematopoiesis

Knowledge of the role of ILK in hematopoiesis is primarily based upon empirical studies that investigate how PI3K/Akt, PTEN, GSK-3β and mTORC1 pathways regulate both normal and malignant hematopoiesis [15,37,38]. For example, PI3K signaling mediates the proliferation and survival of erythroid progenitors and controls erythropoiesis [39]. AKT regulates hematopoietic stem cell (HSC) fates during myelopoiesis, which is mediated by regulating the phosphorylation of the transcription factor CEBPA (C/EBPα) [40]. The inhibition of Akt leads to GSK-3β activation, which in turn inactivates CEBPA by phosphorylation and promotes eosinophil differentiation. In contrast, activation of Akt stimulates CEBPA and triggers neutrophil development [40]. PTEN phosphatase, a negative regulator of ILK and PI3K/Akt pathway, is vital in HSC functions. Inhibition of PTEN in the mouse results in several consequences in normal HSCs matched with leukemic stem cells (LSCs). The HSCs under PTEN deficiency proliferate and show a significant reduction in their retention in the bone marrow. Moreover, PTEN-deficient mice are characterized by genomic instability that leads to the development of myeloproliferative disorders and leukemias [15,16,41]. Emerging evidence is implicating GSK-3β as a central regulator of cellular HSC homeostasis and metabolism [38,42]. Previous studies have indicated that ILK decreases GSK-3β activity directly by mediating phosphorylation of serine 9 or indirectly through activation of Akt [8,31]. In addition, the expression of ILK and phosphorylation of GSK-3β are prominent in PTEN-deficient cells. These observations suggest that GSK-3β may function as a regulator of the HSC self-renewal process, which is dysregulated by PTEN deficiency and subsequent ILK hyperactivity. In addition, we have determined the

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