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Integrin-linked kinase (ILK) in hematologic malignancies: Bridging molecular mechanisms to therapeutic innovation

Omer Qutaiba B. Allela[1*], Abdulkareem Shareef[2], Ashishkumar Kyada[3], H. Malathi[4], Laxmidhar Maharana[5], Dinesh Puri[6,7], Harshit Gupta[8], Djamila Polatova[9], Hayder Naji Sameer[10], Ahmed Yaseen[11], Zainab H. Athab[12], Mohaned Adil[13]

[1]College of Pharmacy, Alnoor University, Mosul, Iraq
[2]Ahl al bayt University, Kerbala, Iraq
[3]Marwadi University Research Center, Department of Pharmaceutical Sciences, Faculty of Health Sciences, Marwadi University, Rajkot, Gujarat, India
[4]Department of Biotechnology and Genetics, School of Sciences, JAIN (Deemed to be University), Bangalore, Karnataka, India
[5]Department of Pharmaceutical Sciences, Siksha 'O' Anusandhan (Deemed to be University), Bhubaneswar, Odisha-751030, India
[6]Department of Pharmacy, Graphic Era Hill University, Dehradun, India
[7]Centre for Promotion of Research, Graphic Era Deemed to be University, Dehradun, Uttarakhand-248002, India
[8]Centre for Research Impact & Outcome, Chitkara University Institute of Engineering and Technology, Chitkara University, Rajpura, 140401, Punjab, India
[9]Scientific-Practical Medical Center for Pediatric Oncology, Hematology and Immunology, Tashkent, Uzbekistan
[10]Collage of Pharmacy, National University of Science and Technology, Dhi Qar, 64001, Iraq
[11]Gilgamesh Ahliya University, Baghdad, Iraq
[12]Department of Pharmacy, Al-Zahrawi University College, Karbala, Iraq
[13]Pharmacy College, Al-Farahidi University, Baghdad, Iraq

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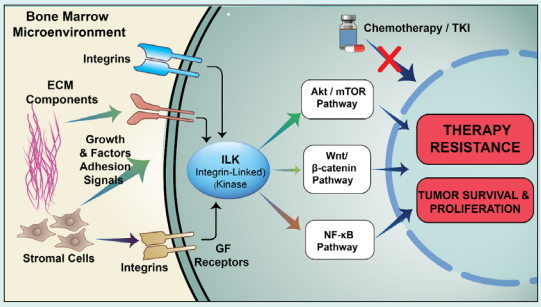
Abstract



Therapy resistance remains a formidable challenge in hematologic malignancies despite significant advances in targeted therapies. This comprehensive review examines integrin-linked kinase (ILK) as a critical molecular hub at the nexus of cell adhesion, signal transduction, and therapy resistance across leukemias, lymphomas, and multiple myeloma. Unlike in solid tumors, where ILK primarily drives invasion and metastasis, in hematologic malignancies it uniquely mediates microenvironmental protection and therapy resistance through distinct signaling networks. ILK functions as a central mediator connecting microenvironmental signals to intracellular survival pathways, with expression levels 5-20-fold higher in malignant cells compared to normal counterparts. Through systematic analysis of structural properties, expression patterns, downstream signaling, and microenvironmental interactions, we present compelling evidence for ILK as a promising therapeutic target capable of overcoming resistance mechanisms. Current data demonstrate that ILK inhibition simultaneously disrupts multiple survival pathways, sensitizes resistant cells to established therapies, and selectively targets therapy-resistant leukemic stem cells while sparing normal progenitors. This review provides a comprehensive framework for translating ILK-targeted approaches into innovative therapeutic strategies with significant potential to improve outcomes in treatment-refractory hematologic malignancies.

Introduction

Hematologic malignancies represent a diverse group of cancers affecting blood, bone marrow, and lymphatic tissues.[1,2] Despite remarkable advances in treatment approaches—ranging from targeted kinase inhibitors to revolutionary immunotherapies—therapy resistance

*Corresponding author: Omer Qutaiba B. Allela, Email: omerallela@alnoor.edu.iq

inevitably emerges in many patients, leading to relapse and disease progression.[3,4] The underlying mechanisms of this resistance are multifactorial, involving both intrinsic cellular adaptations and protective signals from the tumor microenvironment.[5,6] Recent evidence indicates that malignant hematopoietic cells exploit specialized niches within the bone marrow and lymphoid tissues, where they receive critical pro-survival signals that enable them to withstand therapeutic interventions.[7,8]

At the molecular level, integrin-linked kinase (ILK) has emerged as a pivotal orchestrator of these survival signals.[9,10] ILK serves as a multifunctional protein that links integrin receptors to downstream pathways driving cancer cell survival, proliferation, and migration.[9,11] While ILK's role in solid tumor progression has been extensively documented, its specific contributions to hematologic malignancies have only recently been appreciated.[9,10] Unlike solid tumors, where ILK primarily drives invasion and metastasis through epithelial-mesenchymal transition, in hematologic malignancies it uniquely mediates microenvironmental protection and therapy resistance through distinct signaling networks.[9,10]

The clinical significance of ILK in hematologic malignancies is underscored by its overexpression across various blood cancers and its association with poor prognosis.[9,10] ILK has been implicated in multiple resistance mechanisms, including those against Bruton's tyrosine kinase (BTK) inhibitors in chronic lymphocytic leukemia (CLL),[12,13] conventional chemotherapies in acute myeloid leukemia (AML), and even cutting-edge immunotherapies like chimeric antigen receptor (CAR) T-cells.[14-16]

Understanding ILK's role in hematologic malignancies requires examination of its molecular architecture, interaction partners, and the signaling networks it regulates. By dissecting these aspects, we can identify potential vulnerabilities and develop strategies to target ILK-mediated resistance mechanisms.

Molecular architecture and functional organization of ILK

Integrin-linked kinase possesses a sophisticated molecular structure that facilitates its diverse cellular functions.[17,18] ILK comprises three distinct domains, each serving specific roles in protein-protein interactions and signal transduction.[19,20] The N-terminal region contains four ankyrin (ANK) repeats that mediate interactions with several binding partners, most notably PINCH.[20, 21] This interaction creates a stable complex that is necessary for the assembly of focal adhesions and cell survival signaling pathways (Table 1).

Between the ankyrin repeats and the C-terminal domain lies ILK's pleckstrin homology (PH)-like domain.[17,22] This central region serves a crucial function by binding to phosphatidylinositol-3,4,5-triphosphate (PIP3), a lipid product generated by phosphoinositide 3-kinase (PI3K).[17] This interaction facilitates ILK's recruitment to the plasma membrane, enabling its activation and subsequent downstream signaling.[22]

Perhaps most intriguing is ILK's C-terminal pseudokinase domain, which resembles a serine/threonine kinase domain but lacks key catalytic residues typically required for enzymatic activity.[23,24] Despite its classification as a pseudokinase, this domain serves vital functions in protein-protein interactions. It binds to the cytoplasmic tails of β-integrins, creating a physical link between integrins and the actin cytoskeleton that influences cell shape, adhesion, and motility.

ILK's connection with several adaptor proteins that alter its activity and link it to various signaling networks further broadens its functioning (Fig. 1). ILK is connected to receptor tyrosine kinases (RTKs) and PI3K by NCK2 and insulin receptor substrate (IRS) proteins, creating a signaling axis that encourages cell survival and proliferation.[26-28] Conversely, ILK-associated phosphatase (ILKAP) binds to the ankyrin repeats of ILK and functions as a negative regulator by dephosphorylating downstream targets.[29,30]

Recent structural studies using crystallography and cryo-electron microscopy have provided deeper insights into the precise molecular interactions within the ILK pseudokinase domain[31] These studies reveal specific binding pockets and interface regions that can be targeted by small molecule inhibitors with improved specificity, facilitating the rational design of next-generation ILK inhibitors.[31,32]

ILK expression/role in hematologic malignancies

The ILK expression is significantly elevated across diverse hematologic malignancies compared to normal hematopoietic cells, suggesting its critical involvement in disease pathogenesis.[9] ILK expression is significantly elevated in multiple myeloma (MM), acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphoblastic leukemia (ALL), and lymphoid malignancies, such as diffuse large B-cell lymphoma (DLBCL), T-cell acute lymphoblastic leukemia (T-ALL), and CLL, according to quantitative analyses.[9,10]

Flow cytometry and immunofluorescence studies reveal that ILK levels are approximately 5-20-fold higher in malignant cells compared to normal bone marrow mononuclear cells.[23,24] In CML, ILK overexpression correlates with disease aggressiveness and resistance to tyrosine kinase inhibitors (TKIs).[9,10] K562 and KU812F cell lines show approximately 8.5-fold and 9-fold increases in ILK expression, respectively. Notably, imatinib-resistant CML cell lines (LAMA84R) exhibit even higher ILK levels (12-fold increase) compared to their imatinib-sensitive counterparts (LAMA84S, 7-fold increase), directly implicating ILK in TKI resistance mechanisms.[33,34]

Table 1. Structural and Functional Overview of ILK

Domain	Key features	Functional roles	Implications in hematologic malignancies
Ankyrin repeat domain (ARD)	Contains four ankyrin repeats	Mediates interactions with PINCH & parvin	Stabilizes focal adhesions, regulates cytoskeletal organization[20,21]
Pleckstrin homology (PH)-like domain	Binds PIP3, regulated by PTEN	Facilitates membrane recruitment and activation	Enables response to microenvironmental signals in bone marrow niches[17,22]
Pseudokinase domain	Lacks catalytic activity but binds AKT & GSK-3β	Regulates PI3K/AKT, β-catenin signaling	Drives survival, proliferation, and therapy resistance[23,24]
C-terminal domain	Integrin-binding, membrane localization	Transduces ECM signals to intracellular pathways	Enhances cell migration, invasion, and leukemic stem cell survival[23,25]

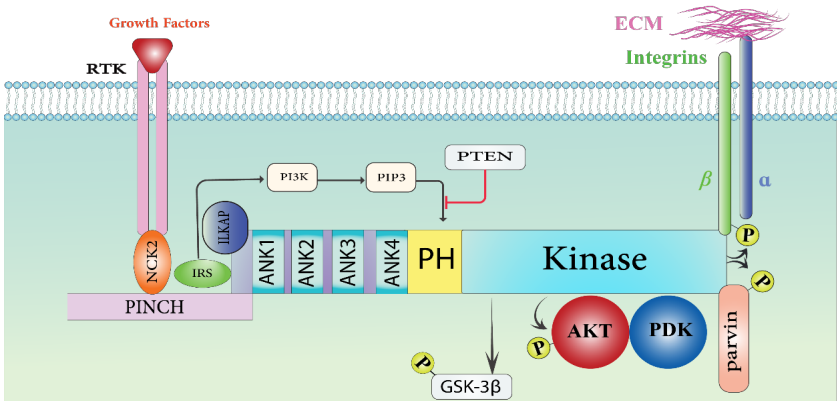


Fig. 1. The interaction between Integrin-linked kinase (ILK) occurs within cells. ILK contains three different domains: the Ser-Thr kinase domain at the C-terminal, four ankyrin (ANK) repeats at the N-terminal, and the pleckstrin homology (PH) motif between these two domains. The five LIM domains that make up Cys-His-rich protein (PINCH) interact with ILK's Ank1. ILK is coupled to PI3K and the tyrosine kinase receptor (RTK) by the adaptor proteins NCK2 and IRS. ILK's kinase activity is inhibited by the interaction between Ank1 and the associated protein (ILKAP). Through Phosphatidylinositol-3, 4, 5-triphosphate (PIP3), PI3K attaches itself to the PH domain of ILK. By dephosphorylating PIP3 and ILKAP, PTEN functions as a negative regulator of ILK activity. The cytoplasmic domain of beta integrin is one of the intracellular proteins that the kinase domain of ILK interacts with. ILK can phosphorylate PKB, GSK-3, and Parvin, and it can also interact with signaling proteins like Akt/PKB, PDK-1, and GSK-3.

Similarly, in AML, high ILK expression drives enhanced survival pathways and confers resistance to apoptosis-inducing chemotherapy agents. AML cell lines MOLM14 and NOMO-1 show 7.5-fold and 9.5-fold increases in ILK expression, respectively. This overexpression is particularly pronounced in FLT3-mutated AML, where ILK serves as a critical downstream effector of FLT3 signaling.[35-39]

Dysregulation of ILK in specific hematologic malignancies provides critical insights into its role in disease pathophysiology and therapy resistance. In CLL, ILK plays a crucial role in mediating resistance to Bruton's tyrosine kinase (BTK) inhibitors such as ibrutinib.[40,41] While these targeted agents achieve high initial response rates in CLL and mantle cell lymphoma, complete remissions are rare, and residual disease eventually leads to relapse.[42] Beyond acquired BTK mutations, resistance mechanisms involve the extrinsic protection conferred by the tumor microenvironment, with ILK serving as a critical mediator of this protection.[12,43-45]

In AML, ILK is essential for maximal Akt activation downstream of FLT3, a receptor tyrosine kinase frequently mutated in this disease.[46,47] Inhibiting ILK reduces stromal-induced Akt signaling and impairs leukemic growth in vivo, suggesting that ILK helps AML cells resist tyrosine kinase inhibitors.[48,49] Furthermore, ILK activation in AML triggers an IL-6/STAT3/NF-κB feedback loop, elevating IL-6 and IL-1β levels and fostering an immunosuppressive microenvironment.[50,51]

Multiple myeloma likewise leverages ILK-mediated adhesion mechanisms to evade therapy.[52,53] Cell adhesion-mediated drug resistance is associated with high VLA-4 expression on myeloma cells, and integrin interaction in the bone marrow niche activates the PI3K/Akt, MAPK, and NF-κB pathways, which shield myeloma cells from chemotherapy.[54,55] So, ILK serves as a critical mediator of these adhesion-induced survival signals, making it an attractive therapeutic target in this disease.[56,57]

On the other hand, in CLL, ILK overexpression enhances leukemia–stromal adhesion via integrin β1 signaling, resulting in Akt activation and GSK-3β inhibition, which together sustain NF-κB and β-catenin–dependent transcription of anti-apoptotic genes (BCL2, MCL1).[58] By enhancing carcinogenic feedback loops that sustain proliferation and cell cycle progression through CCND1 and β-catenin activation, ILK functions downstream of aberrant Notch1 and PI3K/Akt pathways in T-ALL. By suppressing Akt signaling and encouraging caspase-mediated apoptosis, blocking ILK highlights how crucial it is for preserving T-ALL cell survival.[59] ILK stimulates the development of the integrin–IKK–ILK complex, which promotes cytokine production, survival, and resistance

to apoptosis, and corresponds with constitutive NF-κB and STAT3 activity in DLBCL, particularly the activated B-cell (ABC) subtype.[60]

ILK downstream pathways orchestrating oncogenic signaling networks

ILK serves as a central hub in an intricate network of signaling pathways that collectively promote survival, proliferation, and therapy resistance in hematologic malignancies (Fig. 2).[22,61] This section provides an in-depth analysis of these downstream pathways, highlighting how ILK coordinates their activation and cross-talk to maintain malignant cell survival.[62,63]

PI3K/Akt pathway: the master regulator of cell survival

The PI3K/Akt pathway represents one of the most critical signaling cascades regulated by ILK in hematologic malignancies.[64] There is ongoing discussion on the exact mechanism by which ILK stimulates Akt phosphorylation. More recent research suggests that ILK largely acts as a molecular scaffold that moves Akt closer to its actual kinases, including mTORC2 or DNA-PK, despite prior research suggesting direct phosphorylation by ILK.[65] Research by McDonald et al. demonstrated that ILK directly interacts with Rictor, a defining component of mTORC2, facilitating the phosphorylation of Akt at Ser473.[66] Activated Akt phosphorylates and inactivates pro-apoptotic proteins including BAD and procaspase-9, while simultaneously promoting the expression of anti-apoptotic proteins such as Bcl-2 and Mcl-1.[67,68] These changes dramatically raise the apoptotic threshold, making malignant cells resistant to a wide range of therapies.[69,70] In AML, for instance, ILK-mediated Akt activation contributes to resistance against traditional chemotherapeutics like cytarabine and anthracyclines, while in CML it undermines the efficacy of TKIs such as imatinib.[69,71] Beyond its direct effects on apoptotic machinery, Akt activation by ILK also promotes mTOR

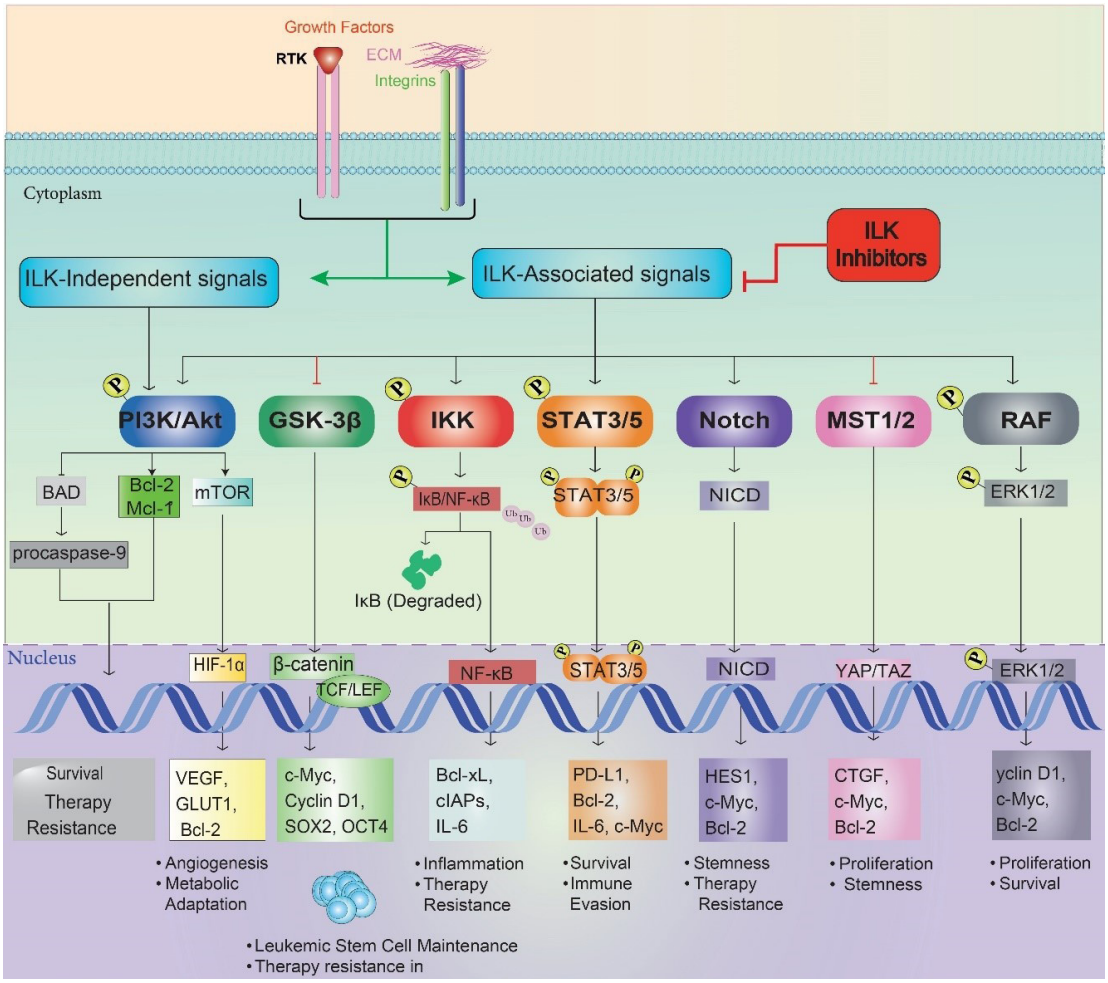


Fig. 2. Cross-talk between ILK-driven signaling pathways in leukemic cells. This network diagram illustrates the interconnected signaling pathways downstream of ILK, emphasizing cross-talk interactions that drive oncogenesis in AML and CML. ILK (center, gray) orchestrates signaling in the cytoplasm (e.g., PI3K/Akt, RAF, MST1/2) and leads to the nuclear translocation of transcription factors in the nucleus (e.g., ERK1/2, β-catenin, NF-κB, STAT3/5, HIF-1α, NICD, YAP/TAZ). Pathways are color-coded: PI3K/Akt (blue), Wnt/β-catenin (green), NF-κB (red), STAT (orange), MST1/2 (Hippo) (yellow), RAF/MAPK/ERK (pink), Notch (teal), and Hypoxia/HIF-1α (purple). Dashed gray lines indicate cross-talk, such as Akt enhancing RAF activity, β-catenin synergizing with YAP/TAZ for stemness, and NF-κB collaborating with HIF-1α for VEGF expression, highlighting the complexity of ILK-driven oncogenic networks.

signaling, driving protein synthesis and metabolic reprogramming that further enhance malignant cell survival.[72-74] This Akt-mTOR axis is particularly relevant in multiple myeloma, where it supports the excessive protein synthesis required by malignant plasma cells and contributes to proteasome inhibitor resistance.[75-77]

Wnt/β-catenin pathway: sustaining leukemic stem cells

ILK profoundly influences the Wnt/β-catenin pathway, which plays a crucial role in maintaining leukemic stem cells (LSCs) and promoting therapy resistance.[78,79] The primary mechanism involves ILK-mediated inhibition of glycogen synthase kinase-3β (GSK-3β) through phosphorylation at Ser9.[80,81] Inhibiting GSK-3β allows β-catenin to evade phosphorylation-dependent degradation, build up in the cytoplasm, and go into the nucleus, where it triggers the transcription of genes linked to survival, self-renewal, and stemness.[82,83]

This ILK-driven stabilization of β-catenin is particularly significant in the context of leukemic stem cells, which rely heavily on Wnt signaling for maintenance and self-renewal.[84] By enhancing β-catenin activity, ILK preserves the LSC population even in the presence of therapies that effectively eliminate bulk leukemic cells.[85] This mechanism helps explain the phenomenon of minimal residual disease and subsequent relapse observed in many patients with AML and CML.[86-88]

NF-κB signaling: inflammation and therapy resistance

ILK also plays a central role in activating NF-κB signaling, a pathway strongly associated with inflammation, survival, and therapy resistance in hematologic malignancies.[63,89] This pathway is particularly relevant in B-cell malignancies such as CLL and multiple myeloma, where constitutive NF-κB activation drives disease progression and therapy resistance.[90] In CLL, for instance, ILK-mediated NF-κB activation contributes to resistance against BTK inhibitors like ibrutinib, even in the absence of mutations in the drug's target.[91]

STAT signaling: a critical node in cytokine response

Beyond the three major pathways described above, ILK also regulates STAT (Signal Transducer and Activator of Transcription) signaling, particularly STAT3 and STAT5, which are critical mediators of cytokine responses in hematologic malignancies.[92] The ILK-STAT3 axis is particularly relevant in AML and certain lymphomas, where constitutive STAT activation drives disease progression.[48] Tabe et al demonstrated that coculture of leukemic cells with bone marrow stromal cells activates multiple signaling pathways, with ILK/STAT3 being a critical component.[48] When ILK is inhibited, STAT3 phosphorylation is reduced by approximately 60%, leading to decreased expression of STAT3 target genes, including MCL1, survivin, and cyclin D1.[46]

Notch signaling: maintaining stemness and differentiation block

In normal hematopoiesis, Notch signaling regulates the balance between self-renewal and differentiation of stem and progenitor cells.[93] In malignancies such as T-ALL and certain myeloid neoplasms, aberrant Notch activation contributes to differentiation arrest and maintenance of a stem-like phenotype.[94,95] ILK modulates Notch signaling through regulation of Notch1 and its downstream effectors Hes1 and Hey1.[46,96] Research by Tabe et al. revealed that ILK blockade significantly decreased Notch1 and Hes1 expression in leukemic cells cocultured with bone marrow stromal cells.[46,96] This cross-talk is particularly evident in T-ALL, where ILK activation enhances Notch signaling, contributing to maintenance of leukemic stem cells and therapy resistance.[97,98] By integrating Notch signaling with other pathways such as PI3K/Akt and Wnt/β-catenin, ILK creates a robust signaling network that sustains the malignant phenotype even under therapeutic pressure.[99,100]

Hippo pathway: controlling proliferation and organ size

The Hippo pathway, a conserved signaling cascade that regulates organ size and tissue homeostasis, represents another important downstream target of ILK in hematologic malignancies.[101] ILK influences this pathway by inhibiting MST1/2 kinases, which are the upstream regulators of the Hippo pathway.[102,103] This inhibition leads to reduced phosphorylation of YAP/TAZ, allowing them to accumulate in the nucleus and activate target genes involved in proliferation and survival.[104,105] In certain leukemias and lymphomas, dysregulation of the Hippo pathway contributes to uncontrolled proliferation and resistance to therapy, with ILK serving as a critical modulator of this process.[102,105,106] Targeting this ILK-Hippo axis could provide a novel approach to overcome therapy resistance, particularly in malignancies that show hyperactivation of YAP/TAZ signaling.[107,108]

MEK/ERK pathway: driving proliferation independently of Ras

In multiple myeloma and certain leukemias, ILK activates the MEK/ERK pathway independently of Ras mutations, contributing to cell proliferation and drug resistance.[109,110] The ability of ILK to stimulate MEK/ERK signaling provides malignant cells with an alternative mechanism to maintain proliferative signals even when targeted therapies inhibit upstream components of the pathway.[111,112] This is particularly relevant in the context of resistance to targeted therapies such as FLT3 inhibitors in AML or BCR-ABL inhibitors in CML, where activation of MEK/ERK through ILK can bypass the blockade of the primary oncogenic driver and sustain malignant cell proliferation.[113,114] blockade of ILK signaling suppressed ERK1/2 activation in leukemic cells cocultured with bone marrow stromal cells, indicating that ILK is an important upstream regulator of the MEK/ERK pathway in the context of the bone marrow microenvironment.[96,115] The ILK downstream pathways orchestrating oncogenic signaling networks has been summarized in Table 2.

Table 2. Summary of ILK downstream pathways in hematologic malignancies

Pathway	Key mechanism of ILK regulation	Primary molecular effects	Biological consequences	Representative malignancies / resistance contexts
PI3K/Akt	ILK facilitates Akt phosphorylation at Ser473 via interaction with mTORC2 (Rictor) or DNA-PK.	Activates Akt → Inhibits BAD, procaspase-9; Upregulates Bcl-2, Mcl-1; Activates mTOR.	Increased survival, anti-apoptosis, metabolic reprogramming, therapy resistance.	AML (resistance to cytarabine, anthracyclines), CML (imatinib resistance), Multiple myeloma (proteasome inhibitor resistance).
Wnt/β-catenin	ILK phosphorylates and inhibits GSK-3β (Ser9), preventing β-catenin degradation.	Stabilizes β-catenin → Nuclear translocation → Activation of stemness and survival genes (Cyclin D1, c-Myc, SOX2, OCT4, survivin).	Maintains leukemic stem cells (LSCs), promotes minimal residual disease and relapse.	AML, CML (stemness preservation, relapse origin).
NF-κB	ILK promotes IKK activation → IκB degradation → NF-κB nuclear translocation.	Transcription of Bcl-2, Bcl-xL, cIAPs; Cytokine induction (IL-6, TNF-α, IL-1β).	Inflammation, anti-apoptosis, therapy resistance, microenvironmental support.	CLL (resistance to ibrutinib), multiple myeloma.
STAT (STAT3/ STAT5)	ILK interacts with JAKs to enhance STAT3 Y705 phosphorylation and nuclear activity.	Induces transcription of MCL1, survivin, cyclin D1, PD-L1.	Promotes survival, proliferation, and immune evasion.	AML, lymphomas (constitutive STAT signaling, PD-L1-mediated resistance).
Notch	ILK upregulates Notch1 and downstream effectors Hes1 and Hey1.	Sustains self-renewal, inhibits differentiation.	Maintains stem-like phenotype, supports therapy resistance.	T-ALL, myeloid neoplasms.
Hippo (YAP/TAZ)	ILK inhibits MST1/2 kinases, reducing YAP/TAZ phosphorylation.	Increases nuclear YAP/TAZ → Activation of proliferation and survival genes.	Enhances proliferation, invasion, drug resistance.	Leukemias, lymphomas (YAP/ TAZ hyperactivation).
MEK/ERK	ILK activates MEK/ERK via RAF interaction or PI3K/Akt cross-talk, independent of Ras.	Stimulates ERK1/2 activation → Upregulates proliferation-related genes.	Promotes proliferation, sustains growth under therapy pressure.	AML (FLT3 inhibitor resistance), CML (BCR-ABL inhibitor resistance), multiple myeloma.

Potential interplay between ILK signaling and extracellular vesicles in hematologic malignancies

The relationship between the ILK and extracellular vesicles (EVs) is fascinating and has a big impact on how hematologic cancers behave. As messengers, EVs—tiny membrane-bound packets released by cells—transport proteins, RNA, and other substances between cancer cells and the milieu around them.[116] ILK-mediated pathways such as PI3K/Akt and NF-κB can be activated in recipient cells by integrins and associated signaling proteins found in EVs produced from malignant cells in hematologic malignancies. This activation increases the survival of cancer cells, fosters treatment resistance, and enables malignant cells to take advantage of their surroundings.[117] ILK also affects the cytoskeletal configurations necessary for EV biogenesis and release, which means it can control the amount and caliber of EVs generated by tumor cells, thus strengthening these feedback loops. EVs derived from acute myeloid leukemia and chronic myeloid leukemia cells, for instance, activate anti-apoptotic proteins like BCL-xl and start autocrine signaling that promotes growth and resistance to chemotherapy.[118] Additionally, EVs have the ability to rewire bone marrow niche stromal cells to take on a tumor-supporting phenotype by altering the extracellular matrix and secreting cytokines—processes that are closely related to ILK-driven integrin signaling. Therefore, there is a reciprocal relationship: EVs sustain ILK signaling in stromal cells and cancer cells, whereas ILK regulates EV generation and function. Leukemia progression, immunological evasion, and treatment resistance are all accelerated by this mutual interaction.[119] Targeting ILK may disrupt these EV-mediated processes to reduce microenvironmental protection and overcome drug resistance in hematologic malignancies. Both ILK and EVs have the potential to be biomarkers and therapeutic targets, bringing new approaches to better treatment results for patients with blood malignancies, because they are detectable and accessible in patient samples. Further investigation of this interaction will enhance comprehension and improve therapeutic approaches.[120]

Epigenetic regulation and hypoxia response

ILK also exerts profound influences on epigenetic mechanisms and cellular responses to hypoxia, two processes that significantly impact therapy resistance in hematologic malignancies.[121,122] Through regulation of histone deacetylases (HDACs) and DNA methyltransferases (DNMTs), ILK alters chromatin structure and gene expression patterns, contributing to the malignant phenotype and therapy resistance.[123-125]

The relationship between ILK and hypoxia response is particularly noteworthy. Under hypoxic conditions common in the bone marrow microenvironment, increased expression of hypoxia-inducible factor 1α (HIF-1α) enhances ILK expression and activation.[126,127] Reciprocally, ILK stabilizes HIF-1α through inhibition of its proteasomal degradation pathway, specifically by reducing PHD activity and preventing VHL-mediated ubiquitination.[128,129] This creates a positive feedback

loop that amplifies hypoxia-mediated signals and promotes adaptation to low oxygen conditions through upregulation of genes involved in glycolysis, angiogenesis, and cell survival.[130,131]

ILK modulates VEGF expression by promoting HIF-1α protein expression through PKB/AKT and mTOR pathways, hence enhancing VEGF-induced angiogenesis.[132,133] Moreover, mesenchymal stem cells co-cultured with myeloma cells in a hypoxic environment contribute to angiogenesis via the HIF-2α-ILK pathway.[131,134] In this situation, HIF-2α enhances ILK, hence augmenting mesenchymal stem cell-mediated angiogenesis in multiple myeloma.[131,135]

The ILK-HIF axis is particularly significant in leukemic stem cells located in hypoxic bone marrow niches, as it facilitates metabolic adaptations and confers therapeutic resistance.[136,137] ILK's capacity to modulate epigenetic processes and hypoxic responses affords malignant cells various protective layers against therapeutic obstacles, underscoring the intricacy of ILK-mediated resistance mechanisms.[61,138]

ILK in the tumor microenvironment and immune evasion

In addition to its intracellular signaling roles, ILK is essential in facilitating connections between malignant cells and the tumor microenvironment.[139] The bone marrow niche, characterized by its intricate network of stromal cells, extracellular matrix constituents, and soluble molecules, offers a protective environment for hematologic malignancies.[140] ILK functions as a vital intermediary in these protective relationships, converting adhesion signals into intracellular responses that enhance treatment resistance.[141]

Leukemic cells activate ILK and set in motion many downstream pathways that improve survival and resistance when they attach to stromal cells in the bone marrow or components of the extracellular matrix like fibronectin.[48] Cell adhesion-mediated drug resistance (CAM-DR) is a big problem when it comes to treating blood cancers, especially AML and multiple myeloma.[142,143]

More recent developments in bone marrow microenvironment modeling have shed light on the function of ILK in this setting.[144, 145] Anatomical and cellular details of the native bone marrow niche, including stromal cells, osteoblasts, and vascular elements, were faithfully reproduced in the three-dimensional organoid model created by Baryawno and colleagues.[146-148] Although it is usually difficult to sustain primary cells from various hematologic malignancies ex vivo, these organoids have effectively facilitated engraftment and survival of these cells.[149,150] The significance of the three-dimensional microenvironment was highlighted by these investigations, which demonstrated that multiple myeloma cells lost vitality quickly in typical liquid culture settings but maintained > 90% viability after 12 days in bone marrow organoids.[151,152] There is substantial evidence for a therapeutic window in a physiologically relevant environment, as these organoid models showed variable sensitivity patterns between malignant cells and normal hematopoietic progenitors when treated with ILK inhibitors.[153,154]

Not only does ILK affect conventional medication resistance, but it also affects immunotherapy failures. B-cell acute lymphoblastic leukemia and diffuse large B-cell lymphoma patients who undergo CAR T-cell therapy often experience remarkable remissions; yet, recurrence is common because tumor cells continue to elude immune clearance.[155] By enhancing integrin-mediated adhesion and activating survival pathways, ILK strengthens this immunological privilege and makes tumor cells less vulnerable to T-cell cytotoxicity.[17,156]

Additional roles for ILK in immune checkpoint inhibitor resistance have been uncovered in recent research.[157] In models of leukemia and lymphoma, it has been demonstrated that tumor cell ILK activation upregulates PD-L1 expression, which in turn contributes to immunological evasion and T cell exhaustion.[158,159] When used in conjunction with immune checkpoint inhibitors such as anti-PD-1 antibodies, ILK inhibition improves T cell activation and tumor regression.[160,161]

Therapeutic targeting of ILK in hematologic malignancies

In vitro studies

In vitro effectiveness of various small-molecule ILK inhibitors against hematologic malignancies is encouraging.[61] The three most researched inhibitors—Compound 22 (Cpd22), QLT0267, and OSU-T315—display different patterns of potency, selectivity, and mode of action.[162-164]

The MTT cell viability experiments reveal that Cpd22 is quite effective against chronic myeloid leukemia (CML) cell lines, with IC50 values varying between 235 and 500 Nm.[165] Even at dosages that cause severe cell death in leukemic cells, this inhibitor shows remarkable selectivity, maintaining normal cell viability.[49] It is worth mentioning that Cpd22 has the ability to circumvent existing resistance mechanisms. Its effectiveness is particularly demonstrated against imatinib-resistant CML cells (LAMA84R, IC50 = 300 nM).[165] In AML cell lines, QLT0267 shows good activity at dosages up to 3000 nM (3 μM), however it is more concentration-dependent than Cpd22.[166] Regardless, at 10 μM, normal bone marrow mononuclear cells retain 90% viability, demonstrating that QLT0267 retains selectivity for malignant cells.[167]

In the case of SUP-B15 (ALL) cells, OSU-T315 has strong activity, while in the case of MOLM14 (AML) cells, it demonstrates IC50 values of around 380 ± 40 nM.[168] Unlike other ILK inhibitors, OSU-T315 causes cells to die

in two distinct ways: via apoptosis and autophagy. This is quite intriguing.[49] The phosphorylation of Akt at Ser473 (80% reduction) and GSK-3β at Ser9 (70% reduction)—essential nodes in the PI3K/Akt and Wnt/β-catenin signaling cascades—is markedly reduced after 72 hours of treatment with 400 nM Cpd22.[164,169] Connected to these molecular occurrences are functional consequences, such as stem cell dysfunction, enhanced cell death, and cell cycle halt.[49,162] Molecular effects of inhibiting ILK include halting cell cycle progression, inducing cell death, interfering with β-catenin signaling, blocking NF-κB signaling, and preventing STAT3 activation.[47,48,170]

The combination of Cpd22 with imatinib demonstrates strong synergy (Combination Index = 0.45) in CML cell lines, significantly enhancing apoptosis induction compared to either agent alone.[171,172] Even more striking is the synergy observed between QLT0267 and dasatinib in imatinib-resistant CML cells (CI = 0.32), suggesting that this combination strategy may be particularly effective in the setting of established TKI resistance.[173,174] The mechanistic basis for these synergistic interactions involves complementary pathway inhibition.[22,61] While targeted therapies like TKIs primarily inhibit specific oncogenic drivers (e.g., BCR-ABL), ILK inhibitors simultaneously suppress alternative survival pathways such as PI3K/Akt and Wnt/β-catenin, preventing compensatory activation that often leads to resistance.[162,169] Additionally, ILK inhibition disrupts adhesion-mediated drug resistance by interfering with integrin signaling and microenvironmental protection.[48,175]

In vivo (pre-clinical) efficacy and translation to clinical studies

There is strong evidence from animal model research that ILK inhibitors work in vivo. In CML xenograft models, treatment with Cpd22 (10 mg/kg) significantly reduced tumor volume (around 70%) and increased survival time.[176] In AML xenograft models, QLT0267 (15 mg/kg) also improved overall survival and reduced tumor volume by 65%.[177] The combination of Cpd22 with imatinib reduced tumor volume by 85% in TKI-resistant rats, demonstrating that combination treatments are even more effective in vivo.[178]

Promising preclinical data have led to preparations for first-in-human clinical studies. Currently in late preclinical research with Phase I trials expected to start in 2025–2026, the most advanced contender is a modified form of Cpd22 with these enhanced pharmacokinetic characteristics.[179,180] With an eye toward safety, tolerability, and first efficacy, these initial studies will center on patients with relapsed/refractory CML and AML who have failed conventional therapy.[181]

Early safety evaluations in animal models are promising, despite the fact that pharmacokinetic factors and other toxicities pose obstacles to clinical translation.[169] No notable toxicities were seen in complete blood counts, liver enzymes, or renal function tests at doses that achieved powerful anti-tumor effects, suggesting that ILK inhibitors were usually well-tolerated at therapeutic doses.[182]

Particularly important is new research by UBC and BC Cancer (2023) showing that ILK inhibition especially targets dormant cancer stem cells that normal TKI treatment cannot sufficiently eradicate on its own.[183] Given most treatments that preferentially target actively dividing cells, these dormant cancer stem cells provide a significant obstacle in treating hematologic malignancies.[184] While preserving healthy stem cells, ILK inhibitors combined with conventional treatments efficiently sensitize these drug-resistant cancer stem cells, thus addressing a major unmet demand in the treatment of hematologic malignancies.[185] Overall, therapeutic targeting of ILK in hematologic malignancies has been summarized in Table 3.

While the preclinical evidence supporting ILK inhibition in hematologic malignancies is robust, successful clinical translation demands a strategic framework that integrates biomarker-guided patient selection, rational combination regimens, vigilant safety monitoring, and alignment with emerging therapeutic modalities. Recent advances now position ILK not only as a mechanistic linchpin of microenvironment-mediated resistance but also as a tractable node for precision intervention. The modified analog of Compound 22 (Cpd22)—optimized for enhanced bone marrow penetration, metabolic stability, and pharmacokinetic profile—is advancing toward first-in-human Phase I trials focusing on patients with relapsed/refractory AML and CML who have failed standard therapies, including TKIs.[181] Primary endpoints will assess safety, maximum tolerated dose, and preliminary efficacy signals such as reduction in minimal residual disease and leukemic stem cell depletion. Given the heterogeneity of ILK dependency across hematologic subtypes, predictive biomarkers are essential to enrich for likely responders. Emerging data support a composite biomarker strategy that includes ILK overexpression (≥ 5-fold vs. normal hematopoietic cells by qRT-PCR or IHC), phospho-Akt (Ser473) and phospho-GSK-3β (Ser9) as functional readouts of pathway activation, integrin β1/VLA-4 surface expression (particularly relevant in AML and multiple myeloma), and stromal adhesion signatures derived from bone marrow biopsies or circulating extracellular vesicles. These markers are being retrospectively validated and will be prospectively integrated into upcoming trials.[79]

Although ILK is ubiquitously expressed, malignant cells exhibit heightened dependency on ILK for survival and niche adhesion, creating a therapeutic window. However, chronic ILK inhibition may impair normal hematopoietic stem cell retention in the bone marrow niche, potentially leading to cytopenias or delayed hematopoietic recovery. To mitigate this, intermittent dosing schedules and short-course combination regimens are under evaluation.

Table 3. Therapeutic targeting of ILK in hematologic malignancies

Section	Category	Key Findings / Details
In vitro studies	Lead ILK Inhibitors	Compound 22 (Cpd22), QLT0267, OSU-T315
	Potency (IC50 Values)	-Cpd22:235–500 nM in CML; 300 nM in imatinib-resistant CML (LAMA84R) -QLT0267: Up to 3 μM in AML -OSU-T315: ~380 ± 40 nM in MOLM14 (AML); strong activity in SUP-B15 (ALL)
	Selectivity	Cpd22 and QLT0267 maintain normal cell viability (≥ 90%) at effective doses.
	Unique Features	-Cpd22: Active against TKI-resistant CML cells -OSU-T315: Induces apoptosis and autophagy simultaneously
	Molecular Mechanisms of Action	- Inhibits ILK-mediated phosphorylation of Akt (Ser473, −80%) and GSK-3β (Ser9, −70%) - Disrupts PI3K/Akt, Wnt/β-catenin, NF-κB, and STAT3 signaling - Induces apoptosis, cell cycle arrest, and loss of leukemia stemness
	Combination Synergy (In Vitro)	-Cpd22 + Imatinib:CI = 0.45, enhanced apoptosis in CML -QLT0267 + Dasatinib:CI = 0.32, synergy in imatinib-resistant CML - Mechanistic basis: dual inhibition of oncogenic and compensatory survival pathways, plus disruption of adhesion-mediated resistance.
Preclinical in vivo models	Efficacy in Animal Models	-Cpd22 (10 mg/kg): Reduced CML xenograft tumor volume by 70%, improved survival. -QLT0267 (15 mg/kg): Reduced AML xenograft tumor volume by 65%, extended survival. -Cpd22 + Imatinib: Decreased tumor volume by 85% in TKI-resistant rodent models.
	Stem Cell Impact	ILK inhibition sensitizes dormant leukemia stem cells resistant to TKIs, while sparing normal hematopoietic stem cells (UBC & BC Cancer 2023).
	Safety Profile (Preclinical)	No significant hematologic, hepatic, or renal toxicities observed at efficacious doses.
Clinical setting	Translation and Future Directions	- Modified Cpd22 analog advancing toward Phase I clinical trials (2025–2026) for relapsed/refractory CML and AML. - Early preclinical safety supports good tolerability and favorable pharmacokinetics.

Additionally, bone marrow–targeted delivery systems—such as nanoparticles functionalized with CXCR4 or CD44 ligands—are being developed to maximize tumor exposure while minimizing systemic toxicity. ILK inhibition holds particular promise in combinatorial approaches that disrupt both oncogenic drivers and microenvironment-mediated resistance: in CML, ILK inhibitors synergize with TKIs (e.g., imatinib, dasatinib) by overcoming stroma-induced survival signals; in CLL, combining ILK inhibitors with BTK inhibitors (e.g., ibrutinib) may prevent microenvironment-driven NF-κB reactivation; in AML, ILK blockade sensitizes leukemic stem cells to venetoclax or chemotherapy by suppressing β-catenin and MCL-1; in multiple myeloma, ILK inhibition disrupts VLA-4–mediated adhesion and reverses proteasome inhibitor resistance; and with immunotherapies, ILK inhibition downregulates PD-L1 and enhances CAR T-cell cytotoxicity, supporting trials combining ILK inhibitors with anti–PD-1 or CD19-directed CAR T-cell products.[16] These combinations are prioritized based on mechanistic synergy, non-overlapping toxicity, and unmet need in resistant/refractory settings. Collectively, the convergence of biomarker science, novel drug delivery, and rational polytherapy is transforming ILK from a compelling biological target into a viable clinical strategy. By simultaneously dismantling intrinsic survival pathways and extrinsic microenvironmental protection, ILK-targeted therapy offers a promising avenue to eradicate persistent disease reservoirs and improve long-term outcomes in high-risk hematologic malignancies.

Study limitations and challenges

There are a number of important obstacles that must be carefully considered when implementing ILK as a therapeutic target in clinical settings. The variable and context-dependent function of ILK in various hematologic malignancies is a major cause for worry. ILK inhibition is consistently effective against myeloid tumors, whereas its effects on lymphoid cancers are wildly inconsistent and contradictory.[186] Interestingly, ILK overexpression causes some B-cell lymphomas to develop less rather than more, indicating that ILK might act as a context-dependent tumor suppressor in particular situations. This basic biological difference suggests that ILK-targeted treatments won't work for everyone and that a malignancy-specific—and possibly even genetic subtype-specific—therapeutic approach is needed.[120]

Additionally, a crucial unresolved issue with immediate therapeutic relevance is the long-term effects of ILK inhibition on normal hematopoiesis. Strong, long-term ILK inhibition may result in hematologic toxicities that are not entirely represented in short-term preclinical models, such as cytopenias or compromised stem cell activity. The possibility of depleting normal hematopoietic stem and progenitor cells with extended treatment regimens is a legitimate safety concern that needs to be thoroughly assessed in long-term animal studies and eventually human trials, even though preliminary research indicates a therapeutic window exists.[186,187] Wider preclinical restrictions exacerbate these particular biology and safety issues. The majority of preclinical evidence comes from animal models and cell lines, which could not accurately represent the complexity of human disease.[188] The accuracy of standard mouse models is especially questionable because species-to-species variations in the bone marrow microenvironment are substantial. The need for more

physiologically appropriate models is highlighted by recent research employing humanized models, which indicates that human-specific microenvironmental variables can change the reliance of malignant cells on ILK signaling.[189] Beyond them, there are yet further obstacles. It is unclear how compensatory signaling pathway activation or other potential resistance mechanisms to ILK inhibitors itself work.[58] Additional optimization is needed to address pharmacokinetic issues, such as minimizing off-target effects and ensuring the best possible drug delivery to the bone marrow. Achieving consistent therapeutic responses is further complicated by the variation in ILK expression among patient populations, which may call for logical combination approaches.[58]

Translational strategies and future directions

Biomarker development for patient selection

To maximize the clinical impact of ILK-targeted therapies, robust biomarkers for patient selection and response monitoring are essential.[190,191] Several promising biomarker strategies are under development, including ILK expression levels, phospho-protein signatures, transcriptional profiling, and functional assays.[22,192] Initial studies suggest that patients with ILK expression ≥ 5-fold above normal controls may derive the greatest benefit from ILK inhibition.[33,193]

Preliminary validation studies suggest that high ILK expression combined with elevated phospho-Akt (Ser473) levels may identify patients most likely to respond to ILK inhibition.[194,195] Ongoing research aims to refine these biomarker approaches and integrate them into planned clinical trials.[196,197]

Novel delivery systems for ILK inhibitors

Optimizing the delivery of ILK inhibitors to malignant cells while minimizing systemic exposure represents an important approach to enhance efficacy and reduce potential toxicities.[22,198] Several innovative delivery strategies are under investigation, including nanoparticle formulations, antibody-drug conjugates, and bone marrow-targeted delivery systems.[199,200]

Recent innovations in nanoparticle-based drug delivery systems have shown particular promise for targeting ILK inhibitors to leukemic cells within the bone marrow microenvironment.[201,202] Zhao et al developed a novel bone marrow-targeted nanoparticle system that selectively delivers ILK inhibitors to malignant cells while minimizing off-target effects.[201] This approach significantly enhanced the therapeutic efficacy and safety profile of ILK inhibitors in preclinical models, suggesting potential clinical applications in the near future.[201,202]

Immune evasion mechanisms: The emerging role of ILK in immunotherapy resistance

An emerging area of interest is ILK's role in mediating resistance to immunotherapies, particularly checkpoint inhibitors and CAR-T cell therapy, which have revolutionized treatment for certain hematologic malignancies.[158,203] Recent research has revealed that activation of ILK in malignant B cells upregulates PD-L1 expression, therefore promoting immune evasion and resistance to checkpoint inhibitor treatment.[158] Particularly, the study conducted by Almasabi et al indicated that ILK expression correlates with PD-L1 expression and immune cell cytotoxicity in colorectal cancer, therefore implying its function in the tumor microenvironment and immune evasion mechanisms.

Furthermore, the study emphasizes how lowered PD-L1 expression caused by ILK gene deletion in PD-L1 positive cell lines suggests ILK might be a therapeutic target to stop immune evasion.[158]

In the context of CAR-T cell therapy, ILK activation in leukemic cells has been shown to enhance expression of adhesion molecules and anti-apoptotic proteins, creating a formidable barrier against CAR-T cell-mediated cytotoxicity.[48] Preliminary studies suggest that combining ILK inhibitors with CAR-T cell therapy may enhance CAR-T cell efficacy and durability, potentially addressing the significant challenge of relapse following initial CAR-T cell responses.[164,204]

Furthermore, ILK modulates the tumor immune microenvironment by influencing cytokine production and immune cell recruitment.[205] High ILK expression in AML blasts correlates with increased production of immunosuppressive cytokines such as IL-10 and TGF-β, creating an environment that inhibits natural killer cell and cytotoxic T cell functions.[206] Targeting ILK may therefore have the dual benefit of sensitizing malignant cells to therapy while simultaneously enhancing anti-tumor immune responses.[207,208] Overall, the central role of ILK in hematologic malignancies has been summarized in Fig. 3.

Conclusions

Integrin-linked kinase (ILK) has emerged as a critical mediator of oncogenic signaling and therapeutic resistance in hematologic malignancies. This comprehensive review has elucidated ILK's multifaceted roles in leukemias, lymphomas, and multiple myeloma, highlighting its potential as a therapeutic target. Several key findings and implications emerge from this analysis. ILK exhibits significantly elevated expression across diverse hematologic malignancies compared to normal counterparts, with quantitative studies demonstrating 5-20-fold increases in leukemic cells. This differential expression correlates with disease aggressiveness and treatment resistance, providing both a diagnostic marker and therapeutic opportunity. Targeting ILK exploits the higher dependency of malignant cells on this signaling hub, creating a therapeutic window that may minimize effects on normal tissues. ILK regulates multiple downstream signaling pathways essential for cancer cell survival and

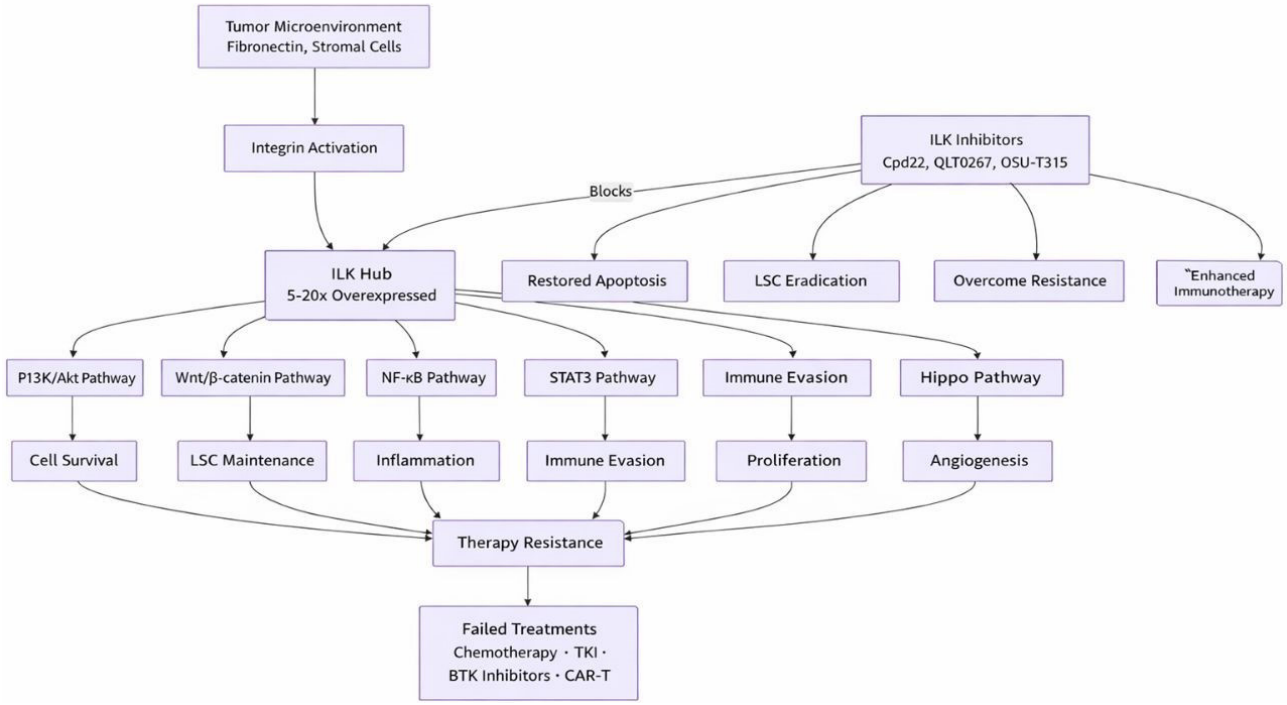


Fig. 3. The central role of ILK in hematologic malignancies. ILK is significantly overexpressed as a result of integrin activation by the tumor microenvironment. Thereafter, ILK acts as a molecular center, coordinating several pro-survival pathways that together create a therapy-resistant state. This network is simultaneously disrupted by the deliberate suppression of ILK, which overcomes resistance and makes cancerous cells more sensitive to other therapies.

therapy resistance. The unique ability of ILK to integrate inputs from the tumor microenvironment and receptor signals and transduce them to multiple effector pathways makes it a strategic target with significant potential to overcome therapy resistance. Preclinical evidence suggests that targeting ILK may be particularly effective in eliminating therapy-resistant leukemic stem cells (LSCs). A major challenge in treating hematologic malignancies is the complete eradication of the LSC population, which typically resists conventional chemotherapy and targeted therapy and can drive cancer recurrence. ILK inhibitors, by interfering with the Wnt/β-catenin pathway and disrupting microenvironmental connections, selectively target LSC viability while having minimal impact on normal hematopoietic progenitors. As our understanding of ILK biology continues to evolve, and as more potent and selective inhibitors enter clinical evaluation, targeting this critical signaling hub offers an innovative approach to addressing the persistent challenge of therapy resistance in hematologic malignancies. By disrupting both intrinsic survival pathways and microenvironment-mediated protection, ILK inhibition represents a promising strategy to improve outcomes for patients with these challenging diseases.

Review Highlights

What is the current knowledge?

Existing studies suggest ILK contributes to oncogenic signaling in leukemia and lymphoma, yet mechanistic insights and therapeutic relevance are limited.

What is new here?

We evaluate emerging ILK-targeted strategies, highlighting their translational potential for precision oncology in blood cancers.

Authors' Contribution

Conceptualization: Omer Qutaiba B. Allela.
Investigation: Omer Qutaiba B. Allela.
Supervision: Omer Qutaiba B. Allela.
Writing–original draft: Omer Qutaiba B. Allela, Abdulkareem Shareef, Ashishkumar Kyada, H. Malathi, Laxmidhar Maharana, Dinesh Puri, Harshit Gupta, Djamila Polatova, Hayder Naji Sameer, Ahmed Yaseen, Zainab H. Athab, Mohaned Adil.
Writing–review and editing: Omer Qutaiba B. Allela.

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