Gene Expression **2026** vol. 25(4) | e00027
DOI: 10.14218/GE.2026.00027

Review Article

CRKL: An Oncogenic Signaling Adaptor at the Convergence of RAS/RAP1 Pathways—A Pan-cancer Review with Perspectives from the IRS Adaptor Family

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Received: July 16, 2026 | **Revised:** August 22, 2026 | **Accepted:** September 21, 2026 | **Published online:** October 28, 2026

Abstract

CRKL is a non-catalytic Src homology 2 (SH2)/Src homology 3 (SH3)-domain adaptor protein implicated as an oncogenic driver across a wide range of human malignancies, yet existing literature is fragmented across tumor-type-specific studies of uneven evidentiary strength; evidence for CRKL is often conflated with studies of its paralog Crk, and directly conflicting functional findings in at least one cancer type remain unreconciled. This review synthesizes CRKL's structure and signaling mechanism across ten cancer types: breast, hepatocellular, non-small-cell lung, pancreatic, ovarian, gastric, laryngeal squamous cell, and colorectal carcinoma, cutaneous melanoma, and chronic myeloid leukemia (CML), framed against the Insulin Receptor Substrate (IRS) family as a conceptual precedent for adaptor-protein oncogenesis. In several solid tumors reviewed, CRKL overexpression or amplification shows a recurring signaling framework involving SH2-mediated docking onto activated oncoproteins coupled through its SH3 domains to C3G, SOS1, and DOCK180, driving RAS/RAP1-ERK signaling, proliferation, and MMP2/MMP9-dependent invasion, with overexpression generally associated with advanced stage and reduced survival. Hepatocellular carcinoma is a documented exception, where human-tissue and murine cell-line studies report opposing functional directions for CRKL. Evidentiary strength varies substantially across cancers: CML has the strongest translational evidence, with phosphorylated CRKL used as a pharmacodynamic biomarker of BCR-ABL kinase inhibition in clinical-trial and research settings, distinct from routine BCR::ABL1 monitoring; most solid tumors are supported by preclinical amplification, expression, and knockdown data; and immune-related associations with CRKL have been reported in melanoma, while a direct immune-evasion mechanism has been demonstrated in hepatocellular carcinoma; these relationships remain largely unexamined elsewhere. This review identifies concrete research gaps, including the unresolved CRKL-Crk relationship and the largely unpursued opportunity to target CRKL's SH2/SH3 interfaces therapeutically. Overall, CRKL emerges as a recurrently implicated oncogenic adaptor with strong mechanistic and translational support in selected settings, most notably CML, and a rational candidate for future drug discovery, rather than an already-established pan-cancer therapeutic target.

Keywords: CRKL; Adaptor proteins; Oncogenic signaling; Tumor invasion and metastasis; Chronic myeloid leukemia; Targeted protein-protein interaction therapy.
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How to cite this article: Abbasi MA, Munawar A, Khinsar KH. CRKL: An Oncogenic Signaling Adaptor at the Convergence of RAS/RAP1 Pathways—A Pan-cancer Review with Perspectives from the IRS Adaptor Family. *Gene Expr* 2026;25(4):e00027. DOI: 10.14218/GE.2026.00027.

Introduction

Receptor tyrosine kinase (RTK) signaling plays a central role in cell physiology and development, and its dysregulated activation contributes to the genesis and progression of many cancers. A typical RTK signaling pathway begins with growth factor binding, which promotes receptor dimerization, a process that varies considerably across RTK families.[1-3] This dimerization enables trans-phosphorylation of the receptor and recruitment of downstream signaling molecules, either directly to the receptor or indirectly

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through adaptor proteins, which lack enzymatic activity themselves but facilitate signal transduction, specificity, and amplification through scaffolding functions whose activity is temporally controlled by changes in adaptor expression and phosphorylation status.[3-5] Adaptor proteins fall into two structural classes[3,5,6]: Group A, membrane-linked docking proteins with multiple tyrosine phosphorylation sites, including Insulin Receptor Substrate (IRS), GRB2-associated binding protein (GAB), Src homology 2-containing protein (SHC), Fibroblast growth factor receptor substrate 2 (FRS2), and the Downstream of kinase (DOK) family; and Group B, comprising Src homology 2 (SH2)- or Src homology 3 (SH3)-domain-only adaptors such as NCK, GRB2, and CRK, which bind signaling partners without phosphorylation sites or membrane localization. Genes encoding several of these adaptor proteins are recurrently amplified in pancreatic, ovarian, lung, and breast cancers, are required for proliferation and survival in cell lines carrying these amplifications, and promote anchorage-independent growth and tumorigenesis when overexpressed, establishing several members of both classes as oncogenes in these cancer types.[7-17] This review focuses on the structure and function of adaptor proteins, the role of oncogenic adaptor proteins across different cancers, and the therapeutic implications of IRS and CRKL.

The objective of this review is threefold: to synthesize the structural and mechanistic basis of CRKL's oncogenic signaling across the ten cancer types reviewed here; to critically evaluate the strength and consistency of the supporting evidence for each cancer type rather than treating all findings as equally established; and to identify specific, actionable research gaps including the unresolved relationship between CRKL and its paralog Crk, and CRKL's largely unexamined role in the tumor immune microenvironment that currently limit translation of this biology into clinical benefit.

Unlike catalytically active oncoproteins, CRKL exerts its oncogenic function entirely through protein–protein interactions mediated by its SH2 and tandem SH3 domains, making it both a convergence point for multiple oncogenic signaling inputs (BCR-ABL, ALK, EGFR-resistant clones) and a structurally distinct and largely untapped therapeutic target.

Notably, the core RAS/RAP1-ERK-MMP-dependent invasion mechanism described throughout this review has remained consistent across more than a decade of subsequent studies in several cancer types, although important context-dependent contradictions, particularly in hepatocellular carcinoma (HCC), have also been reported. This shared mechanism is summarized in Figure 1.

Adaptor proteins as an oncogenic class: the IRS paradigm

Before turning to CRKL specifically, it is useful to establish, using a well-characterized precedent, that non-catalytic adaptor proteins can themselves function as bona fide oncogenes rather than as passive intermediaries of RTK signaling. The IRS family provides the clearest such precedent. IRS-1 and IRS-2, the best studied members of this family, are ubiquitously expressed cytoplasmic docking proteins first identified downstream of the insulin and insulin-like growth factor-1 receptor (IGF-1R) and later shown to relay signals from integrin, cytokine, and steroid hormone receptors as well.[18] Neither protein has intrinsic enzymatic activity; instead, each is built around a pleckstrin homology domain that localizes IRS proteins to the plasma membrane near activated receptors, and a phosphotyrosine-binding domain that docks onto the receptor's cytoplasmic tail. Receptor-mediated phosphorylation of C-terminal tyrosine residues then creates docking sites for SH2-domain effectors including PI3K (p85), SHP-2, GRB2, and the Crk/CRKL adaptors themselves, coupling receptor activation to the PI3K-AKT and RAS-ERK axes without any catalytic step occurring within IRS-1/2 itself. Despite this shared architecture, IRS-1 and IRS-2 diverge functionally in ways that matter for this review's central argument: IRS-1-null mice develop insulin resistance without progressing to overt diabetes, owing to preserved compensatory signaling, whereas IRS-2 loss produces a more severe, non-rescued phenotype,[19] foreshadowing a theme this review returns to for CRKL and its paralog CRK: structural similarity between adaptor family members does not guarantee redundant oncogenic function.

The oncogenic relevance of this scaffolding function is well established in breast cancer: IRS-1 and IRS-2 are broadly overexpressed in human breast tumors, and transgenic mice overexpressing either protein develop mammary hyperplasia progressing to tumorigenesis via AKT, ERK1/2, mTORC1, and Wnt/β-catenin signaling.[20] In the polyoma virus middle T mouse mammary tumor model, IRS-1 and IRS-2 have distinct roles in tumor progression: IRS-1 loss does not significantly affect primary tumor growth but enhances metastatic spread, whereas IRS-2 loss suppresses metastasis, underscoring that paralogous adaptors are not functionally interchangeable *in vivo*[21]; IRS-1 and IRS-2 are additionally implicated in hepatocellular, lung, pancreatic, and ovarian carcinomas, illustrating that scaffold-only proteins entirely lacking kinase activity can be sufficient to drive transformation, proliferation, and metastasis when aberrantly expressed.[18] This principle, an adaptor protein functioning as an oncogenic driver rather than a mere oncogenic accessory, is the organizing idea this review applies to CRKL. Structurally, CRKL is built on the same non-catalytic logic as IRS-1/2, but belongs to the second major structural class of adaptor proteins introduced above: rather than IRS's membrane-proximal, multiply-phosphorylated docking architecture, CRKL consists of a single SH2 domain flanked by two SH3 domains and functions without membrane tethering. Where IRS proteins integrate signals from receptors to which they are constitutively associated, CRKL is more promiscuous, recruited transiently to activated oncoproteins as diverse as BCR-ABL1, ALK, and EGFR, and, as the remainder of this review develops, is recurrently amplified or overexpressed across a broader range of solid and hematologic malignancies than the IRS paradigm alone would predict.

CRKL: structure, function, and expression

The CT10 regulator of kinase (Crk) family comprises adaptor proteins that participate in signal transduction. CrkI and CrkII are cellular isoforms, whereas Crk-like protein (CRKL) is a closely related paralog; these proteins are broadly expressed and conserved across eukaryotes.[22-24] Crk-family adaptors contain an N-terminal SH2 domain and one or more C-terminal SH3 domains.[22,25,26] They integrate signals from the extracellular matrix, growth factors, and oncogenic fusion proteins such as BCR-ABL1 and regulate migration,[27,28] invasion, adhesion, prolif-

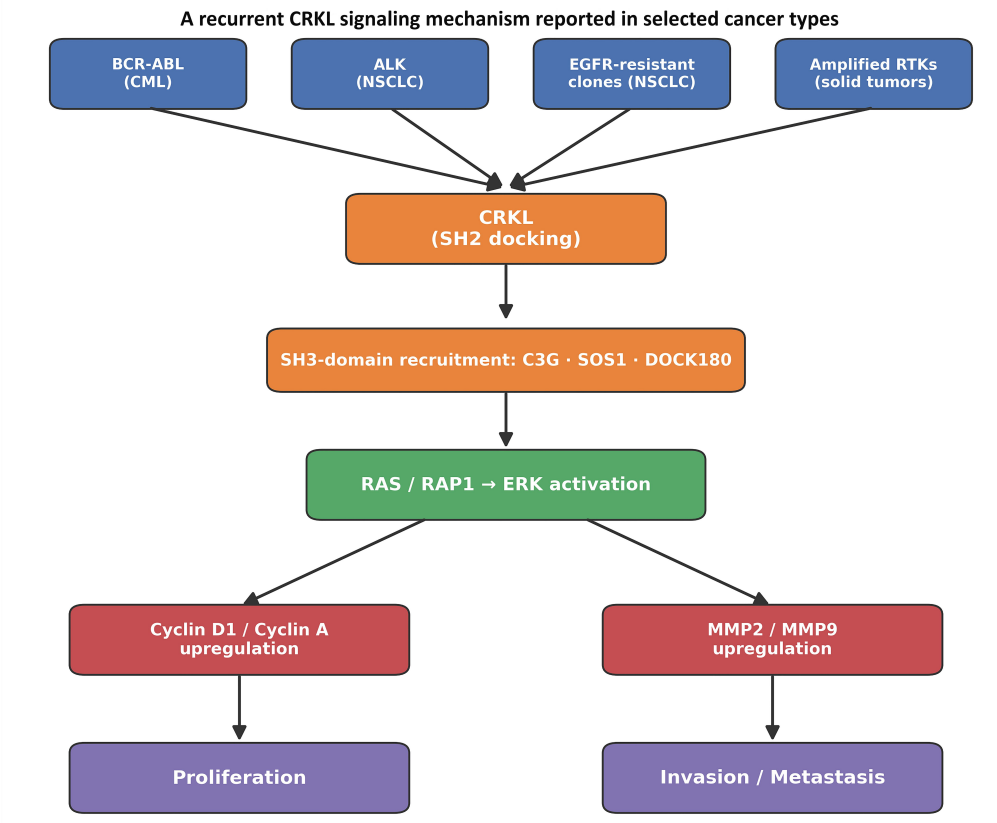


Fig. 1. A recurrent CRKL signaling mechanism reported in selected cancer types reviewed here: Src homology 2 (SH2)-mediated docking onto activated oncoproteins, Src homology 3 (SH3)-mediated recruitment of C3G (RAPGEF1), SOS1, and DOCK1 (DOCK180), and downstream RAS/RAP1-extracellular signal-regulated kinase (ERK) activation driving proliferative and invasive phenotypes in most, but not all, cancers examined; hepatocellular carcinoma is a documented exception, discussed in the main text. CML, chronic myeloid leukemia; NSCLC, non-small-cell lung cancer; RTKs, receptor tyrosine kinases.

eration, phagocytosis, and survival.[29-33] Within integrin signaling networks, Crk-family proteins function alongside adaptor families such as CAS, IPP, and CAP.[34] Integrins such as beta1 integrin lack intrinsic enzymatic activity; extracellular matrix binding induces conformational changes and initiates signaling through intracellular adaptors. CRKL contains one N-terminal SH2 domain followed by two SH3 domains (SH2-SH3N-SH3C).[24-26] The SH2 domain binds phosphotyrosine-containing motifs in docking proteins such as p130CAS (BCAR1), GAB proteins, and paxillin, whereas the N-terminal SH3 domain binds proline-rich motifs in proteins including SOS1, p85, C3G (RAPGEF1), and BCR-ABL1.[24,27,35-37] Early genomic studies identified recurrent amplification at chromosome 22q11.21 in lung adenocarcinoma, including high-level amplification in approximately 3% of 371 primary tumors and broader copy-number gain in an additional subset.[38] The minimal amplified region contains *CRKL*, ZNF74, THAP7, PI4KA, and LZTR1. *CRKL* amplification was also detected by fluorescence *in situ* hybridization in 3 of 84 non-small-cell lung cancer (NSCLC) cell lines, and associations between *CRKL* amplification and EGFR signaling were examined in primary tumors and NSCLC cell lines.[14,15] *CRKL*-amplified NSCLC cells depend on CRKL expression for proliferation and survival, and CRKL suppression induces apoptosis and inhibits growth *in vivo*.[14,15] Conversely, CRKL overexpression in immortalized, non-tumorigenic human airway epithelial (AALE) cells promotes anchorage-independent growth and cooperates with NF1 loss to induce tumors *in vivo*.[14] This transforming activity depends on the N-terminal SH3 domain. CRKL complexes with SOS1 and C3G activate SOS1-RAS-RAF-ERK and SRC-C3G-RAP1 signaling,[36,39,40] and CRKL overexpression increases ERK1/2 phosphorylation and RAP1 activity. These findings support roles for RAS and RAP1 signaling in CRKL-driven NSCLC proliferation. CRKL overexpression has also been associated with acquired resistance to EGFR-targeted therapy, with SOS1-dependent MAPK signaling implicated in gefitinib resistance. In genetically engineered mouse models, homozygous *Crkl* loss causes embryonic lethality with features resembling 22q11 deletion syndrome (DiGeorge syndrome).[41] For comparative context, several observations discussed below were generated using Crk rather than CRKL. Although the paralogs share substantial sequence homology and overlapping SH2/SH3 binding partners, they are not necessarily functionally interchangeable. In an MMTV-Crk transgenic breast cancer model, Crk promoted mammary tumor development after a long latency,[42] whereas *Crkl*-null mice

showed impaired BCR-ABL (p210)-mediated transformation of hematopoietic progenitors.[43] CRKL overexpression can transform fibroblasts in a RAS-dependent manner,[44] and CRKL is a major BCR-ABL substrate in chronic myeloid leukemia. Mutations that disrupt CRKL- or GRB2-binding sites reduce BCR-ABL transforming activity.[37,44] In neuroblastoma, ALK-activating mutations stimulate RAP1 through CRKL-C3G complexes.[45] Other Crk-family proteins are overexpressed in colon cancer, lung adenocarcinoma, and glioblastoma and have been linked to transformation, migration, and invasion.[34,46-49] Collectively, direct CRKL data in chronic myeloid leukemia (CML) and NSCLC, together with comparative evidence from Crk-family studies, support recurrent oncogenic functions for this adaptor family, while underscoring the need to distinguish CRKL-specific effects from those of Crk.

Structure of CRKL

The CRKL protein structure contains on SH2 domain that binds to p130CAS (also known as BCAR1), paxillin, GAB1 and BCR-ABL, and two SH3 domains (SH3N and SH3C) that interact with RAPGEF1, DOCK1, and SOS1. This domain architecture is summarized in Figure 2.

The role of CRKL in breast cancer: Breast cancer is the most commonly diagnosed cancer among women worldwide and remains a leading cause of cancer-related mortality in women.[50] Despite substantial improvements in prevention and treatment, including surgery, radiotherapy, and systemic therapy, metastasis remains a major clinical challenge; common metastatic sites include bone, lung, and liver.[51,52]

CRKL is a potential therapeutic target in breast cancer, functioning as a major signaling integrator in breast tumorigenesis.[22] CRKL protein expression is upregulated in breast cancer tissue relative to adjacent normal tissue, and this upregulation is associated with malignant proliferation.[53] High CRKL expression correlates with lymph node metastasis, tumor size, and advanced TNM stage, though it shows no clear association with estrogen receptor, ErbB-2, or progesterone receptor status. CRKL has been identified as a candidate proteomic marker in the breast cancer cell lines SUM149 and SUM190.[54] CRKL overexpression promotes cell spreading, lamellipodia formation, loss of adherens junctions, and colony dispersal in breast epithelial cells even in the absence of hepatocyte growth factor,[55] and promotes proliferation in the MDA-MB-435 cell line, which is now recognized as melanoma-derived.[53] In MDA-MB-453 cells, RNA interference-mediated CRKL knockdown significantly inhibited proliferation, while CRKL overexpression promoted malignant features via cyclin D1 (CCND1) induction and phosphorylated ERK (pERK) signaling.[53]

A study of microRNA regulation of bone metastasis in MDA-MB-231 breast cancer cells identified more than 100 differentially expressed microRNAs (miRNAs) between low- and high-metastatic sublines, several of which are implicated in tumor metastasis and invasion; because miRNAs typically act by binding 3′ untranslated region sequences of target messenger RNAs (mRNAs) to block translation or promote mRNA degradation, expression array and *in silico* target analysis identified CRKL as a common miRNA target in this system.[56,57] Independently of this miRNA regulation, CRKL is directly recruited downstream of BCR-ABL tyrosine kinase signaling and transforms fibroblasts[37,44,58]; fibronectin stimulates CRKL through integrin-mediated adhesion[59]; and in hematopoietic Ba/F3 cells, CRKL forms a complex with CBL and C3G to transmit signals controlling cellular motility.[60] CRKL promotes cell invasion and suppresses caspase-8-mediated apoptosis, a function shown to be important for distant metastasis,[61] acting as a downstream effector of Src family kinases in integrin-triggered cell migration.[62] Consistent with these mechanistic findings, an *in vivo* breast cancer bone metastasis model identified CRKL as a potential miR-429 target associated with metastatic behavior.[56] As in NSCLC, hepatocellular, and ovarian cancer, CRKL's contribution to breast cancer invasion converges on ERK-dependent signaling, suggesting a shared mechanistic logic across CRKL-driven tumors that is developed further in the Discussion. More recently, the deubiquitinase USP53 has been identified as a direct upstream regulator of CRKL stability in triple-negative breast cancer: USP53 is overexpressed in triple-negative breast cancer and correlates with poor prognosis, binds CRKL directly to stabilize it against proteasomal degradation, and thereby promotes proliferation, migration, invasion, and reduced chemosensitivity, providing a distinct upstream regulatory mechanism for CRKL accumulation in this cancer.[63]

The role of CRKL in hepatocellular cancer: HCC remains one of the most common and lethal malignancies worldwide. Its incidence continues to rise in many regions, and long-term survival remains poor despite advances in surveillance and systemic therapy. Hepatitis B virus infection, hepatitis C virus infection, alcohol-related liver disease, and metabolic dysfunction-associated steatotic liver disease remain major contributors to the global HCC burden.[64] Even when surgical resection and systemic therapies are available, recurrence and progression remain major causes of poor outcomes. Metastasis is a multistep process involving extracellular-matrix invasion, intravasation, dissemination, and colonization of distant sites.[33,65]

Protein-protein interaction analysis identified CRKL as a potential prognostic marker in hepatocellular carcinoma.[66] Differential network analysis identified a functional interaction between CRKL and the receptor tyrosine kinase FLT1 (VEGFR1), with both proteins correlated with the migratory capacity of HCC cells. In Mahlavu cells, FLT1 knockdown reduced CRKL phosphorylation, whereas CRKL reduction downregulated FLT1 expression, suggesting reciprocal regulation. Knockdown of either protein delayed migration without affecting proliferation and altered ERK signaling.[66] Immunohistochemical analysis showed that overexpression of CRKL and the CRKL-FLT1 complex was associated with shorter disease-free and overall survival, supporting their potential prognostic relevance in HCC.[66] FLT1 is targeted by several tyrosine kinase inhibitors used in HCC and other cancers, including cediranib, vatalanib, and sorafenib; however, this does not by itself establish therapeutic relevance for the CRKL-FLT1 interaction.

This oncogenic picture, however, is directly contradicted by an independent line of evidence using the murine hepatocarcinoma Hca-P cell line, a model developed specifically to mimic low- and high-lymph-node-metastatic-potential HCC *in vitro* and *in vivo*. In this system, CRKL overexpression efficiently inhibited proliferation, invasion, and migration of Hca-P cells,[67] while CRKL knockdown significantly increased proliferation, invasion, and migration, and increased the incidence and burden of ascites and lymph node metastasis in Hca-P-transplanted mice, leading the original

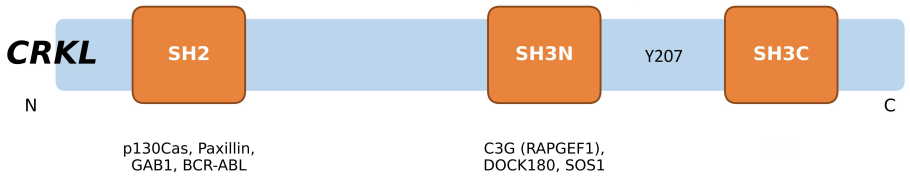


Fig. 2. Domain architecture of CRKL, showing the N-terminal SH2 domain and tandem SH3 domains (SH3N, SH3C) with their principal binding partners and the key phosphorylation site (Y207). SH2, Src homology 2; SH3, Src homology 3; SH3C, C-terminal SH3 domain; SH3N, N-terminal SH3 domain.

authors to conclude that CRKL functions as a repressor of tumor malignancy and lymph node metastasis potential in this model.[68] This is the opposite functional direction from the FLT1-associated findings described above, and we do not treat this as a minor discrepancy: whether it reflects genuine cell-line- or context-specific CRKL function, differences in the metastatic potential of the models used, or methodological differences between studies is not resolved by the available literature, and both findings are presented here rather than selecting the one that fits a uniformly oncogenic narrative. This pattern is consistent with more recent evidence from melanoma, where CRKL's prognostic association has itself required direct experimental interrogation rather than being assumed,[69] suggesting CRKL's functional output may not be uniform across all tissue contexts. This is treated as an open question in the Research Gaps section below rather than resolved in either direction.

Independently of the Hca-P data, other work supports an oncogenic role for CRKL in HCC: in HepG2 cells, CRKL knockdown reduced, and CRKL overexpression enhanced, cell proliferation and colony-forming ability, and CRKL was found to participate in miR-429-mediated regulation of metastasis, with re-expression of miR-429 repressing, and miR-429 silencing stimulating, HepG2 cell migration and invasion; CRKL up- or downregulation reproduced the effects of miR-429 silencing or re-expression, respectively, consistent with CRKL acting downstream of miR-429 in this pathway.[70] More recently, CRKL has also been directly implicated in HCC immune evasion: CRKL is significantly upregulated in anti-PD-1-resistant HCC, where it binds β-catenin and inhibits its proteasomal degradation, driving VEGFα and CXCL1 upregulation that promotes infiltration of tumor-associated neutrophils and suppresses CD8+ T-cell infiltration and function; blocking this CRKL/β-catenin/VEGFα/CXCL1 axis with bevacizumab or lenvatinib restored anti-PD-1 efficacy in preclinical models.[71] This makes HCC, alongside melanoma, one of two cancers in this review with direct evidence linking CRKL to anti-tumor immune evasion in HCC; melanoma has also shown associations between CRKL expression, immune features, and anti-PD-1 response, discussed further in the Research Gaps section below. Separately, CRKL has also been shown to enhance YAP transcriptional activity in liver cancer through direct binding and activation of the JNK/JUN signaling axis, adding a Hippo-pathway-linked mechanism to the FLT1/ERK and immune-evasion axes already described above.[72]

Taken together, the HCC literature reviewed here is not uniform: the majority of studies support a proliferation-, invasion-, and immune-evasion-promoting role for CRKL consistent with the pattern seen in the other cancers reviewed in this article, while the Hca-P model system reports the opposite with respect to proliferation, invasion, and migration. We present this conflict explicitly rather than resolving it.

The role of CRKL in lung cancer

Lung cancer remains a leading cause of cancer-related mortality worldwide, and non-small-cell lung cancer (NSCLC) is the predominant histologic subtype.[73] CRKL expression is increased in NSCLC tissues relative to adjacent non-tumor lung tissues and has been associated with poor differentiation, advanced pathologic TNM stage, nodal metastasis, increased proliferation, and shorter overall survival.[74] CRKL promotes cell-cycle progression through regulation of cyclin D1 (CCND1), cyclin B1 (CCNB1), CDK6, and retinoblastoma protein phosphorylation.[74,75] CRKL also promotes lung cancer cell invasion through ERK-MMP9 signaling. CRKL expression is higher in lymph-node metastases than in matched primary tumors, and CRKL overexpression increases invasion and MMP9 expression in HBE and H1299 cells.[76] MMP9 is an extracellular-matrix-degrading enzyme associated with tumor invasiveness. MMP9-neutralizing antibody treatment reduces CRKL-induced invasion, whereas CRKL overexpression increases AP-1 activity, c-Jun, ERK phosphorylation, and c-Fos occupancy at the MMP9 promoter. ERK inhibition suppresses MMP9 induction and invasion in CRKL-overexpressing cells, supporting an ERK-MMP9-dependent mechanism.[76] Genomic studies further identify *CRKL* as an amplified oncogene in lung cancer. RNA-interference-mediated CRKL knockdown in *CRKL*-amplified H1819 and HCC515 cells decreases proliferation, survival, cell-cycle progression, migration, and invasion, whereas the effects are less pronounced in H157 cells with little or no *CRKL* amplification.[15] CRKL amplification can activate SOS1-RAS-RAF-ERK and SRC-C3G-RAP1 signaling and promote cell adhesion and dispersion.[14] C3G forms complexes with CRKL downstream of anaplastic lymphoma kinase (ALK),[45] and CRKL is an ALK-dependent effector in EML4-ALK-positive NSCLC cells.[77] Thus, available evidence supports a role for coordinated RAS and RAP1 signaling in CRKL-driven NSCLC. More recently, vitamin

D-induced tsRNA-07804 was reported to suppress NSCLC progression by directly targeting CRKL, suggesting an additional small-RNA-mediated regulatory mechanism.[78]

The role of CRKL in pancreatic cancer

Pancreatic cancer is a major cause of cancer-related mortality and is characterized by poor long-term survival.[79,80] Its progression is driven by multiple dysregulated signaling pathways, and reliable biomarkers of biologic aggressiveness remain needed. CRKL protein overexpression has been reported in pancreatic cancer and is associated with increased proliferation and invasion.[81] Immunohistochemical analysis showed predominantly cytoplasmic and nuclear CRKL staining in pancreatic cancer cells, with higher expression in pancreatic ductal carcinoma than in normal tissue.[81] In CRKL-overexpressing pancreatic cancer cell lines, proliferation and invasion increase, the proportion of cells in S phase rises, and cyclin D1, cyclin A, and MMP2 expression is upregulated, suggesting promotion of G1-S cell-cycle progression and invasive capacity.[81] MMP2 facilitates tumor-cell invasion in pancreatic and other cancers.[82] CRKL is an adaptor within multiple signaling pathways,[24,44,60,83] and the MEK/ERK pathway is frequently activated in human malignancies.[84] CRKL-mediated RAS/RAP1-ERK activation has been demonstrated in NSCLC,[14,76] and MMP2 contributes to pancreatic cancer invasion.[85,86] Together, these findings suggest that CRKL may promote pancreatic cancer proliferation through cell-cycle regulators and invasion through MMP2 and ERK signaling, although the precise mechanisms remain incompletely defined. This proposed ERK-MMP2 axis is consistent with mechanisms described in other CRKL-associated epithelial cancers.

The role of CRKL in ovarian cancer

CRKL dysregulation has been implicated in epithelial ovarian cancer (EOC). CRKL expression is higher in EOC tissues than in benign epithelial ovarian tumors and normal ovarian tissues, although some studies have not found clear associations with tumor differentiation, histologic subtype, or clinical stage.[87] In SKOV3 cells, CRKL contributes to cell viability and signaling through DOCK180, C3G, and Rac; CRKL knockdown reduces viability, proliferation, and motility.[87,88] Other studies have reported increased CCR7 and CRKL expression in EOC tissues and cell lines, including A2780, HO8910, SKOV3, HEY, and ES2 cells, with CRKL expression associated with International Federation of Gynecology and Obstetrics stage and lymph-node metastasis and correlated with CCR7 expression.[89] Mechanistically, CRKL has been linked to activation of AKT and ERK signaling and increased MMP9 expression.[87,90] CRKL silencing reduces p-ERK, Snail, MMP9, and N-cadherin expression while increasing E-cadherin, consistent with effects on MAPK signaling and epithelial-mesenchymal transition.[87,89] CCL19 stimulation also increases p-CRKL and promotes CCR7-dependent epithelial-mesenchymal transition through ERK signaling.[89] Overall, these studies suggest that CRKL contributes to EOC proliferation, survival, migration, and invasion through interconnected ERK, AKT, MMP9, and epithelial-mesenchymal transition pathways.

The role of CRKL in chronic myeloid leukemia

CRKL was first identified as the major tyrosine-phosphorylated protein in neutrophils from patients with CML, established as a direct substrate of the BCR-ABL fusion tyrosine kinase that defines this disease.[91,92] Unlike the five solid tumors reviewed above, in which CRKL's oncogenic contribution has been established primarily through preclinical and correlative clinical studies, CRKL's role in CML has been functionally validated through targeted genetic approaches: mice carrying a null mutation at the *CRKL* locus show impaired BCR-ABL (p210)-induced transformation of hematopoietic progenitors,[43] and CRKL binds BCR-ABL directly to drive its transforming activity, with disruption of the CRKL-binding site reducing BCR-ABL transformation capacity by 2–3 fold.[37,44] Downstream, CRKL forms a complex with CBL and C3G to activate RAP1 and RAS/ERK signaling, promoting the proliferative and adhesive phenotype characteristic of CML blast cells.[58,60]

Critically, CRKL's role in CML extends beyond preclinical mechanism into translational and research-based use: in clinical-trial and translational research settings, phosphorylated CRKL (pCRKL) has been used as a pharmacodynamic biomarker of BCR-ABL kinase inhibition in patients treated with imatinib and second-generation inhibitors such as nilotinib; this is distinct from routine standard-of-care response monitoring in CML,[93] which relies on BCR::ABL1 molecular testing per current European LeukemiaNet (ELN) recommendations, not pCRKL measurement.[94,95] In a biomarker sub-study of the international phase I nilotinib trial, pCRKL/CRKL ratios in peripheral blood were used to establish a minimum effective dose for BCR-ABL inhibition and to characterize resistance mechanisms in imatinib-resistant CML and Ph+ acute lymphoblastic leukemia patients.[93] This makes CML the only malignancy in which a CRKL-related biomarker has advanced to clinical-trial and translational research use, a level of development not yet attempted in any of the solid tumors discussed above, though we note this reflects research and clinical-trial biomarker use rather than adoption as a routine, standard-of-care diagnostic assay; this distinction is developed further in the Research Gaps and Limitations sections below. This translational workflow is illustrated in Figure 3.

The role of CRKL in gastric cancer

The *CRKL* gene, located within the 22q11.21 amplicon also implicated in NSCLC (see above), is similarly amplified and overexpressed in gastric cancer, where it acts as a possible therapeutic target through effects on cell proliferation and invasion.[96] CRKL protein overexpression is detected by immunohistochemistry in gastric cancer tissue relative to adjacent normal mucosa, and functions, at least in part, through reciprocal regulation with miR-126: restoring miR-126 suppresses CRKL expression and inhibits gastric cancer cell proliferation, while CRKL overexpression promotes it.[97] More recently, CRKL overexpression has been independently validated as a prognostic biomarker in a cohort of 380 gastric cancer patients, and knockdown of CRKL in SGC-7901 cells suppressed proliferation and induced G0/G1 cell cycle arrest.[98] As in the pancreatic and hepatic sections above, CRKL's involvement in gastric cancer converges on cell-cycle regulation and proliferative signaling, reinforcing CRKL's role as a recurrent driver across gastrointestinal as well as thoracic and gynecological malignancies. Consistent with this, a large-scale molecular analysis of gastric cancer has identified a CDH1-mutant molecular subset with distinctive *CRKL* amplification, further supporting CRKL as a genomically defined driver within a specific gastric

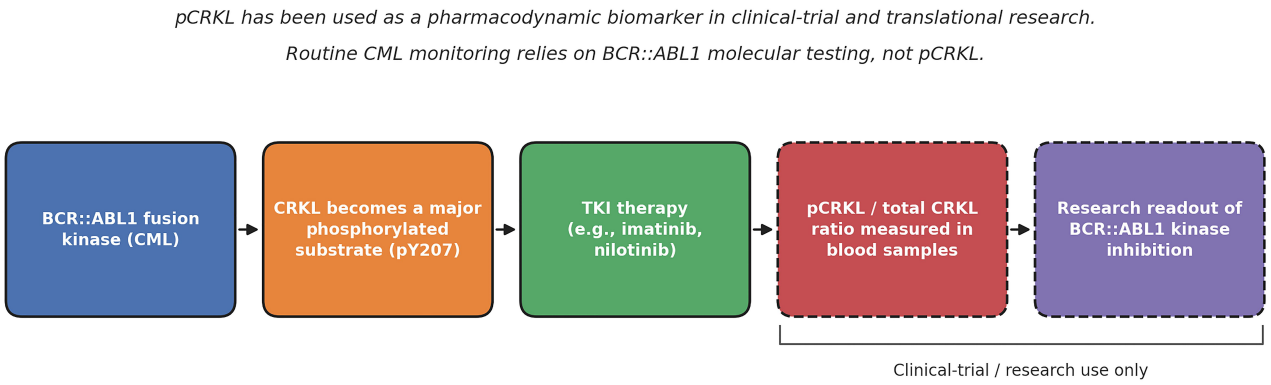


Fig. 3. Translational use of phosphorylated CRKL (pCRKL) as a pharmacodynamic biomarker of BCR-ABL kinase inhibition in chronic myeloid leukemia (CML), established in clinical trial and research settings rather than as a routine, standard-of-care diagnostic assay. BCR-ABL, breakpoint cluster region-Abelson; TKI, tyrosine kinase inhibitor.

cancer subtype rather than a uniform feature of the disease as a whole.[99]

The role of CRKL in colorectal cancer

Colorectal cancer now has direct CRKL-specific evidence, in addition to the Crk-family and combined Crk/CRKL data described below, though this evidence base remains smaller than that available for the other cancers reviewed in detail above. CRKL protein expression, assessed by immunohistochemistry, is significantly upregulated in human colon cancer tissue relative to adjacent normal mucosa and correlates with tumor differentiation, depth of invasion, and lymph node metastasis; CRKL knockdown in colon cancer cell lines inhibits proliferation, migration, and invasion, and reduces tumorigenicity in xenograft models, supporting a direct oncogenic role for CRKL in this cancer.[100] More recently, CRKL has been identified as a functional target of the microRNA miR-34b-5p in colorectal cancer: cancer-associated fibroblast-derived exosomal LINC00355 sponges miR-34b-5p, relieving its suppression of CRKL and thereby promoting epithelial-mesenchymal transition and chemoresistance, with CRKL knockdown reversing both phenotypes *in vitro*.[101] CRKL's role in colorectal cancer is not uniformly oncogenic, however: CRKL has also been identified as a direct binding partner of the tumor suppressor SASH1, and this SASH1-CRKL interaction inhibits epithelial-mesenchymal transition and metastasis in colorectal cancer, indicating that CRKL can participate in growth-suppressive as well as growth-promoting protein complexes depending on its binding partner.[102] Separately, CRK and CRKL promote SRC/FAK-driven epithelial-mesenchymal transition and colorectal cancer aggressiveness, and their combined loss reduces invasiveness, ERK1/2 phosphorylation, and chemoresistance.[103]

Independently of this CRKL-specific evidence, the Crk-family adaptor Crk (rather than CRKL) has also been reported as overexpressed in human colon cancer alongside lung adenocarcinoma and glioblastoma.[46-48] More recent work using colorectal cancer and glioblastoma cell models has directly compared Crk and CRKL within the same system, showing that Crk and CRKL must be depleted individually and in combination to reveal their distinct and overlapping contributions to tumor cell function, since single-protein knockdown of either paralog alone is insufficient to capture the full phenotype.[103,104] This makes colorectal cancer one of the few tumor types in which the Crk-versus-CRKL redundancy question has been directly tested, in addition to now having CRKL-specific expression, functional, and mechanistic data of its own.[100,101,103] Whether the combinatorial Crk/CRKL dependence observed in these comparative models generalizes to breast, hepatic, lung, pancreatic, ovarian, and gastric cancer is addressed further in the Research Gaps section below.

The role of CRKL in melanoma

CRKL is aberrantly expressed in melanoma, and bioinformatic analysis of melanoma data from The Cancer Genome Atlas shows that abnormal CRKL expression is associated with poor prognosis and correlates with immune-activated pathways, immune cell infiltration, and expression of immunoregulators.[69] Critically, CRKL expression was identified as a predictive biomarker for anti-PD-1 therapy response in melanoma patients, with low-CRKL-expressing patients showing greater responsiveness to anti-PD-1 therapy in an independent immunotherapy cohort.[69] Functionally, CRKL silencing in melanoma cell lines inhibits proliferation and invasion via the same ERK/MMP9 axis identified in the breast, hepatic, lung, pancreatic, gastric, and ovarian sections above, as well as via PI3K/AKT signaling, and additionally activates the NLRP3/caspase-1/GSDMD pyroptosis pathway, sensitizing melanoma cells to cisplatin chemotherapy.[105] Taken together, melanoma provides evidence associating CRKL with immune regulation and anti-PD-1 response, whereas a direct immune-evasion mechanism has been demonstrated in hepatocellular carcinoma.

The role of CRKL in laryngeal squamous cell carcinoma

CRKL copy-number gain within the 22q11 amplicon, the same region implicated in NSCLC and gastric cancer, has also been identified as a recurrent event in laryngeal squamous cell carcinoma (LSCC), where *CRKL* rather than the co-amplified MAPK1 gene appears to be the target oncogene.[106] *CRKL* copy-number gain correlates with strong nuclear CRKL

protein expression in primary LSCC tumors, and siRNA-mediated CRKL knockdown reduces proliferation and migration in LSCC cell lines, confirming a functional role for CRKL in this malignancy.[107] This extends the pan-epithelial CRKL-driven invasion pattern identified across breast, hepatic, lung, pancreatic, gastric, and ovarian cancer above to a sixth epithelial tumor type. The overall evidence for CRKL across the ten malignancies reviewed is summarized in Figure 4 and Table 1.[14,15,37,43,44,53,58,60,66-69,74,76,81,84,87-89,91-98,100-103,105-110]

Therapeutic implications of targeting adaptor proteins

Adaptor proteins lack tyrosine- or serine/threonine-kinase domains, which complicates conventional drug development. Established approaches to activated receptor tyrosine kinase pathways include small molecules targeting ATP-binding sites and monoclonal antibodies targeting extracellular receptor domains, but neither strategy directly applies to non-catalytic adaptor proteins. An alternative is to target protein-protein interactions.[111] Such interfaces were historically considered difficult to drug because they are often large and relatively flat, and short peptide fragments may have poor pharmacologic properties. However, protein-protein interfaces frequently contain discrete hotspot residues that contribute disproportionately to binding affinity and can be exploited therapeutically.[111,112] The BCL-2 family provides a well-established example: small molecules such as navitoclax (ABT-263) bind hydrophobic grooves in BCL-2-family proteins and disrupt protein-protein interactions that regulate apoptosis.[111,113] These advances support the broader feasibility of targeting adaptor proteins through their interaction interfaces. Compared with highly conserved kinase active sites, selected adaptor-protein interfaces may also offer opportunities for greater interaction specificity, although this potential must be demonstrated empirically for each target.

Although this general principle of targeting protein-protein interaction hotspots has so far been validated primarily using non-CRKL examples such as BCL-2/ABT-263, proof-of-concept work directly targeting CRKL itself actually predates much of this broader field. Peptides engineered to selectively block the first SH3 domain of Crk and CRKL disrupted their interactions with C3G, SOS1, and DOCK180,[114] and, when applied to primary blast cells from Philadelphia-chromosome-positive CML patients, strongly reduced proliferation by disrupting Bcr-Abl–CRKL complex formation and downstream MAPK activation.[115] These findings demonstrate that CRKL's SH2/SH3 interfaces are experimentally targetable using the same hotspot-targeting logic described above, despite CRKL's complete lack of catalytic activity. This approach has recently been revisited using modern peptide-antagonist methodology targeting the Crk/CrkL-p130Cas SH2-domain axis,[116] and the broader protein-protein interaction targeting field has continued to mature, most notably through targeted protein degradation approaches now reaching clinical use for other targets[117]; however, no CRKL-directed small molecule, stapled peptide, or targeted protein degrader has yet advanced to preclinical testing in any solid tumor model, despite the N-terminal SH3 domain (SH3N) being specifically required for CRKL-driven transformation in NSCLC. Given the precedent set by successfully drugging other non-catalytic scaffold proteins, together with this renewed methodological interest in the Crk/CrkL interaction surface,[116,118] CRKL's SH2/SH3 interfaces represent a rational, increasingly approachable therapeutic target that has not yet progressed beyond the preclinical stage, a gap addressed further in the Research Gaps section below. This comparison is summarized in Figure 5.

Discussion

The evidence assembled across the ten malignancies reviewed here — breast, hepatocellular, non-small-cell lung, pancreatic, ovarian, gastric, laryngeal, colorectal, melanoma, and chronic myeloid leukemia — converges, with one documented exception, on a broadly consistent picture. In most solid tumors examined, CRKL overexpression or amplification has been linked to the recurring signaling framework introduced in the structural overview: SH2-domain-mediated docking onto activated receptors and oncoproteins, coupled through tandem SH3-domain interactions with C3G, SOS1, and DOCK180, to drive RAS/RAP1-ERK pathway activation, cyclin D1/cyclin A-dependent proliferation, and MMP2/MMP9-dependent invasion. This mechanistic consistency, appearing independently in cancers as histologically and etiologically distinct as NSCLC and ovarian carcinoma, is the strongest argument the assembled literature makes for CRKL as a genuine cross-cancer oncogenic driver rather than a tumor-specific curiosity, and it is reinforced by Table 1, which shows CRKL overexpression associated with worse clinical outcomes: advanced stage, nodal metastasis, or reduced overall survival in the great majority of solid tumors for which prognostic data have been reported. The exception, discussed in detail in the hepatocellular carcinoma section above, is a murine Hca-P cell line study reporting the opposite, tumor-suppressive direction for CRKL; rather than treat this as an outlier to be set aside, we regard it as evidence that CRKL's functional output is not invariant across all cellular contexts, a point returned to below.

At the same time, this body of work has developed largely as parallel, tumor-type-specific literatures that have only recently begun to intersect. Three such intersections deserve particular emphasis. First, CRKL's original identification as the major tyrosine-phosphorylated substrate of BCR-ABL in chronic myeloid leukemia has, until recently, remained conceptually separate from its role in solid tumors, despite the fact that phosphorylated CRKL (pCRKL) has been used in clinical-trial and translational research settings as a pharmacodynamic biomarker of BCR-ABL kinase inhibition, distinct from routine standard-of-care BCR::ABL1 molecular monitoring,[93] a translational benchmark that no solid-tumor CRKL biomarker has yet approached. Second, the melanoma and hepatocellular carcinoma literatures have, for the first time in this review, connected CRKL overexpression to immune-related features and reduced anti-PD-1 responsiveness, with direct mechanistic evidence for immune evasion in HCC,[69,71] introducing an immunological dimension to CRKL biology that remains unexamined in the breast, lung, pancreatic, gastric, and ovarian sections above, despite checkpoint inhibitors now forming part of standard care in several of these same cancers. Third, the relationship between CRKL and its paralog Crk remains incompletely resolved: several of the foundational transformation studies discussed in the structural overview were performed with Crk rather than CRKL, and direct comparative work in colorectal

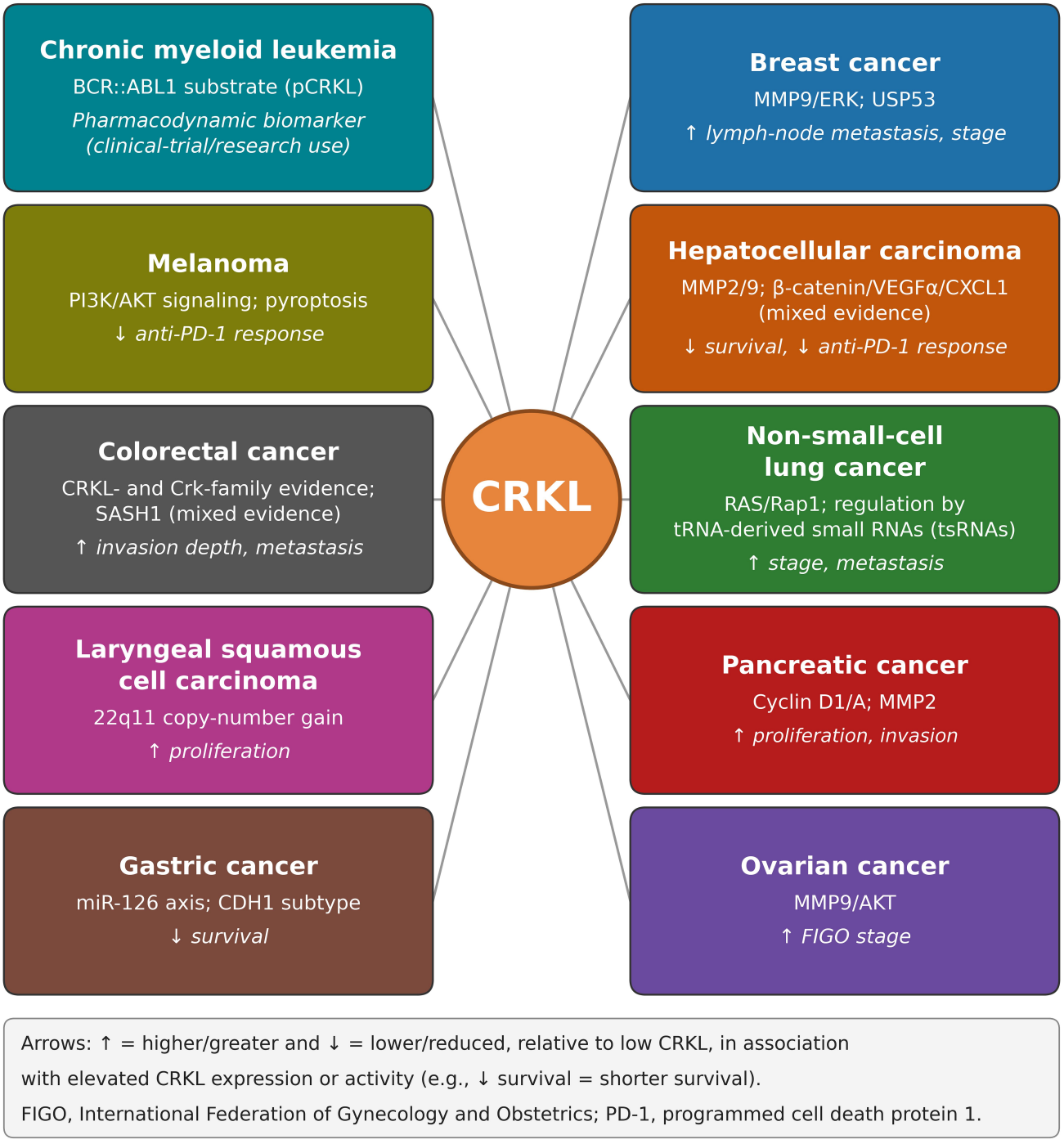


Fig. 4. Overview of CRKL involvement across the ten malignancies reviewed, showing the dominant downstream effector and clinical/prognostic association reported for each; note that evidentiary strength differs substantially by cancer type, and the colorectal cancer entry reflects both CRKL-specific and Crk-family evidence, the latter obtained from direct comparative Crk/CRKL knockdown studies. CML, chronic myeloid leukemia; FIGO, International Federation of Gynecology and Obstetrics; mets, metastases; NSCLC, non-small-cell lung cancer; reg., regulation; SCC, squamous cell carcinoma; tsRNA, transfer RNA-derived small RNA.

Table 1. Expression of CRKL in human cancers

Cancer type	Protein	Evidence type	Expression	Mechanisms of action	Clinical/prognostic association	References
Breast cancer	CRKL	mRNA/protein overexpression; IHC	↑	Malignant proliferation of breast cancer cells is promoted by high expression of CCND1 and p-ERK	Associated with lymph node metastasis, larger tumor size, and advanced TNM stage; no clear association with ER, ErbB-2/HER2, or progesterone receptor status.	[53]
Hepatocellular carcinoma	CRKL	mRNA/protein overexpression; IHC; functional knockdown (mixed direction; see main text)	↑	Mixed evidence: FLT1/ERK-linked studies report CRKL-driven proliferation and invasion, while an independent Hca-P cell line study reports the opposite, growth-suppressive direction (see main text for full discussion)	Majority of studies: overexpression linked to lower disease-free/overall survival. The Hca-P model reports an opposite functional effect	[66-68,108]
Lung cancer	CRKL	Genomic amplification (22q11.21); mRNA/protein overexpression; functional knockdown	↑	CRKL amplification/overexpression promotes proliferation and cell-cycle progression through CCND1, CCNB1, CDK6, and pRb, and promotes invasion through ERK-MMP9 signaling. CRKL also activates RAS and RAP1 pathways in NSCLC	Overexpression associated with poor differentiation, advanced p-TNM stage, nodal metastasis, and poor overall survival	[14,15,74,76,109]
Pancreatic cancer	CRKL	mRNA/protein overexpression	↑	CRKL overexpression promotes proliferation and invasion, with upregulation of cyclin D1, cyclin A, and MMP2; ERK signaling may contribute to the invasive phenotype	Clinical/prognostic correlation (survival, staging) not directly reported in reviewed studies; overexpression linked to increased proliferative and invasive capacity	[81,84,110]
Ovarian cancer	CRKL	mRNA/protein overexpression; functional knockdown	↑	CRKL contributes to ovarian cancer cell development and invasiveness through DOCK180/C3G, AKT/ERK signaling, and MMP9 induction	Associated with advanced FIGO stage and lymph node metastasis in epithelial ovarian cancer patients	[87-89]
Chronic myeloid leukemia	CRKL	Direct substrate identification; functional knockdown; clinical pharmacodynamic biomarker (routine research/translational use, not yet a standard-of-care clinical test)	↑	Major tyrosine-phosphorylated substrate of the BCR-ABL fusion kinase; forms a complex with CBL and C3G to activate RAP1 and RAS/ERK signaling, driving the proliferative and adhesive phenotype of leukemic cells	Phosphorylated CRKL (pCRKL) used as a pharmacodynamic biomarker of BCR-ABL kinase inhibition in clinical-trial and translational research settings (patients treated with imatinib and nilotinib); distinct from routine standard-of-care BCR::ABL1 molecular monitoring	[37,43,44,58,60,91-95]

Table 1. Expression of CRKL in human cancers (*continued*)

Cancer type	Protein	Evidence type	Expression	Mechanisms of action	Clinical/prognostic association	References
Gastric cancer	CRKL	Genomic amplification (22q11.21); mRNA/protein overexpression; clinical association	↑	CRKL gene amplified within the 22q11.21 region; reciprocally regulated by miR-126 to promote proliferation; CRKL knockdown induces G0/G1 cell cycle arrest	Overexpression independently validated as a prognostic biomarker in a cohort of 380 gastric cancer patients; associated with poor prognosis	[96-98]
Laryngeal squamous cell carcinoma	CRKL	Genomic amplification (22q11.21); protein overexpression; functional knockdown	↑	22q11 copy-number gain identifies CRKL, rather than co-amplified MAPK1, as the target oncogene; siRNA-mediated knockdown reduces proliferation and migration	Clinical/prognostic correlation (survival, staging) not directly reported in reviewed studies; overexpression linked to increased proliferative and migratory capacity.	[106,107]
Colorectal cancer	CRKL; Crk	mRNA/protein overexpression; functional knockdown (CRKL-specific; combined Crk/CRKL functional knockdown)	↑	CRKL overexpression correlates with differentiation, invasion depth, and nodal metastasis; CRKL knockdown inhibits proliferation, migration, and invasion; CRKL is a downstream target of the CAF-exosomal LINC00355/miR-34b-5p axis driving EMT and chemoresistance. Separately, Crk (rather than CRKL) is overexpressed in colon cancer, and combined Crk/CRKL knockdown reveals distinct and overlapping contributions not captured by single-protein depletion	CRKL overexpression associated with tumor differentiation, invasion depth, and lymph node metastasis; evidence base smaller than for other cancers in this table	[100-103]
Melanoma	CRKL	mRNA/protein overexpression; functional knockdown; bioinformatic prognostic/immune correlation	↑	Drives proliferation and invasion via ERK/MMP9 and PI3K/AKT signaling; silencing activates the NLRP3/caspase-1/GSDMD pyroptosis pathway and sensitizes cells to cisplatin	Associated with poor prognosis and reduced responsiveness to anti-PD-1 immunotherapy; correlates with immune-related features	[69,105]

AKT, protein kinase B; BCR-ABL fusion protein, breakpoint cluster region-Abelson; CAF, cancer-associated fibroblast; CBL, Casitas B-lineage lymphoma; CRKL, Crk-like protein; EMT, epithelial-mesenchymal transition; ER, estrogen receptor; ERK, extracellular signal-regulated kinase; FIGO, International Federation of Gynecology and Obstetrics; IHC, immunohistochemistry; mRNA, messenger RNA; NSCLC, non-small-cell lung cancer; p-ERK, phosphorylated ERK; PI3K, phosphoinositide 3-kinase; siRNA, small interfering RNA; TNM, tumor-node-metastasis.

cancer and glioblastoma indicates the two paralogs must be evaluated individually and in combination rather than assumed to be functionally redundant.[103,104,118]

Finally, CRKL's therapeutic potential remains underexploited relative to the strength of its mechanistic case. Unlike the receptor tyrosine kinases and cytoplasmic kinases that dominate targeted oncology, CRKL possesses no catalytic activity, and therefore cannot be inhibited by conventional small-molecule kinase inhibitors. Proof-of-concept peptide inhibitors targeting CRKL's SH3 domains demonstrated, more than two decades ago, that this limitation is not the same as undruggability,[114,115] yet this line of work has not been substantially extended using modern structure-guided or degrader-based approaches. Taken together, these three intersections—CML-to-solid-tumor biomarker translation, immune-microenvironment biology, and

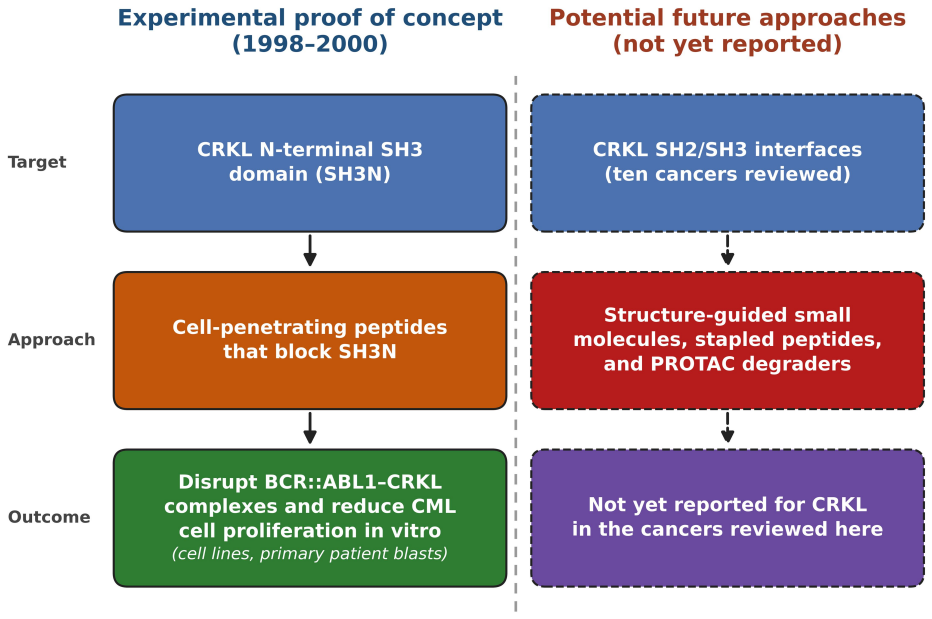


Fig. 5. Comparison of experimental proof-of-concept studies (1998-2000) with potential future approaches targeting CRKL. Left, cell penetrating peptides that block the N-terminal SH3 domain (SH3N) of CRKL disrupted BCR::ABL-CRKL complexes and reduced the proliferation of CML cell lines and primary patient blast cell intro; these were laboratory studies, not clinical validation, Right structure guided modalities that to our knowledge have not been reported for CRKL in the ten cancers reviewed here (dashed outlines and arrows denote hypothetical approaches). CML, chronic myeloid leukemia; PROTAC, proteolysis-targeting chimera; SH2, Src homology 2; SH3, Src homology 3.

Crk/CRKL paralog specificity—alongside the undrugged therapeutic opportunity define the research gaps addressed in the following section.

Research gaps and future directions

Despite more than two decades of work establishing CRKL as a recurrently amplified and overexpressed oncoprotein across ten cancer types, several gaps limit translation of this biology into clinical benefit.

First, CRKL's founding role as a BCR-ABL substrate in chronic myeloid leukemia has not been integrated with its solid-tumor biology in a single translational framework. Phosphorylated CRKL has been used as a pharmacodynamic biomarker of BCR-ABL kinase inhibition in clinical-trial and translational research settings in CML patients treated with imatinib and nilotinib, distinct from routine standard-of-care BCR::ABL1 molecular monitoring,[93] yet no equivalent phospho-CRKL biomarker assay has been developed or validated in any of the nine solid tumors discussed in this review, despite CRKL phosphorylation being mechanistically linked to invasion and proliferation in each of them. Developing and validating such an assay, analogous to its established role in CML, represents a concrete, near-term translational opportunity rather than a purely exploratory one.

Second, most studies to date examine either Crk or CRKL in isolation, rarely both within the same tumor model, and several foundational transformation studies frequently cited in CRKL reviews (including this one) were in fact performed with Crk, not CRKL. Direct comparative work in colorectal cancer and glioblastoma indicates the two paralogs are not simply redundant and must be assessed both individually and in combination to capture their full phenotypic contribution.[103,104] Systematic side-by-side knockdown/rescue studies across the remaining eight cancer types reviewed here are needed to determine whether this pattern generalizes.

Third, CRKL's role in shaping the tumor immune microenvironment is supported by association data in melanoma, where CRKL expression correlates with reduced CD8-associated immune activation and predicts poorer response to anti-PD-1 therapy,[69] and is mechanistically demonstrated in hepatocellular carcinoma, where CRKL drives tumor-associated neutrophil infiltration and suppresses CD8+ T-cell function via a β-catenin/VEGFα/CXCL1 axis, directly conferring anti-PD-1 resistance.[71] Whether this immune-evasive association extends to CRKL-amplified lung, breast, pancreatic, gastric, or ovarian tumors, several of which are already treated with checkpoint inhibitors in the clinic, is an open and clinically actionable question that, to our knowledge, has not yet been tested in any of these remaining cancers.

Fourth, although the CRKL–MMP invasion axis reported in several epithelial cancers in this review is mechanistically consistent, it has been demonstrated independently in each tumor

type rather than tested within a single comparative framework; whether the magnitude of CRKL's contribution to invasion is uniform across these tissue types, or varies with tissue-specific cofactors, remains untested. Colorectal cancer now has CRKL-specific expression and functional data of its own,[100,101] in addition to the combinatorial Crk/CRKL dependence already demonstrated in colorectal cell models,[103] but has not yet been directly tested for the MMP-dependent invasion mechanism emphasized in the other epithelial cancers reviewed here.[104]

Finally, although CRKL's lack of intrinsic catalytic activity has historically been treated as an obstacle to drug development, proof-of-concept SH3-domain-blocking peptides demonstrated more than two decades ago that CRKL's protein-protein interfaces are experimentally targetable, disrupting BCR-ABL–CRKL complexes and inhibiting proliferation of primary CML blast cells.[114,115]

This approach has not been meaningfully extended using modern modalities, including structure-guided small-molecule inhibitors, stapled peptides, or targeted protein degraders directed at the CRKL SH3 domain shown to be required for CRKL-driven transformation. Given the precedent set by successfully drugging other non-catalytic scaffold proteins, CRKL's SH2/SH3 interfaces represent a rational, largely unpursued drug-discovery target across all ten cancer types reviewed here.

Limitations

This review has several limitations that should inform how its conclusions are read. First, it is a narrative rather than a systematic review: no formal quantitative synthesis (for example, meta-analysis) was performed, no pre-registered search protocol was used, and publication bias toward positive findings cannot be excluded. Second, the density and quality of evidence vary substantially across the ten cancer types discussed. CML is supported by direct substrate identification, functional knockout studies, and a clinical-trial/translational research pharmacodynamic biomarker; NSCLC, gastric, laryngeal, breast, ovarian, hepatocellular, and pancreatic cancer are supported by genomic amplification and/or functional knockdown data at the cell-line or tissue level; melanoma is supported by bioinformatic and functional data specifically linking CRKL to immune evasion; and colorectal cancer now has CRKL-specific expression and functional data of its own, in addition to combined Crk/CRKL functional data. These differences in evidentiary maturity are summarized in the Evidence Type column of Table 1 and should be treated as integral to interpreting this review's conclusions, not as a secondary caveat.

Third, CRKL and its paralog Crk are structurally and functionally related but not interchangeable, and separating CRKL-specific from Crk-family evidence in the published literature is not always straightforward; where the original studies did not specify which paralog was examined, or where CRKL and Crk findings have been used comparatively in this review, we have attempted to flag this explicitly in the text, but residual ambiguity in the underlying primary literature cannot be fully resolved by a review article. Fourth, the hepatocellular carcinoma literature reviewed here contains a direct empirical contradiction between human-tissue and murine Hca-P cell-line findings regarding CRKL's functional direction; this is presented explicitly rather than resolved, and the broader possibility that CRKL's function is genuinely context-dependent across tumor types, rather than uniformly oncogenic, should be borne in mind when reading the mechanistic synthesis offered elsewhere in this review. Finally, CRKL-targeted therapy remains at an early, largely preclinical stage: with the exception of phosphorylated CRKL as a research and translational pharmacodynamic biomarker in CML, no CRKL-directed small molecule, peptide, or protein degrader has advanced to clinical development in any cancer, and the proof-of-concept peptide studies discussed in the Therapeutic Implications section demonstrate biochemical tractability of CRKL's interaction interfaces, not clinical or even preclinical therapeutic readiness.

Conclusions

The evidence reviewed here across breast, hepatocellular, lung, pancreatic, ovarian, gastric, laryngeal, colorectal, and melanoma, together with chronic myeloid leukemia, converges, with one documented exception in hepatocellular carcinoma, on a broadly consistent picture: CRKL functions not as a passive bystander of receptor tyrosine kinase signaling but as an active oncogenic node whose overexpression or amplification drives proliferation and invasion in most tumor contexts examined, and contributes to BCR-ABL-driven transformation in chronic myeloid leukemia. This consistency across most cancers reviewed is the strongest argument for CRKL as a genuine, cross-cancer oncogenic driver and a rational future therapeutic target; the conflicting Hca-P evidence in hepatocellular carcinoma is a reminder that this is a strong general pattern rather than an invariant rule. CML currently offers the strongest translational evidence in this review: phosphorylated CRKL has been used as a pharmacodynamic biomarker of BCR-ABL kinase inhibition in clinical-trial and research settings, a level of translational development not yet reached in any solid tumor discussed. CRKL's complete lack of catalytic activity, long treated as an obstacle to drug development, is increasingly recognized as a tractable feature rather than a dead end: protein-protein interaction interfaces stabilized by hotspot residues have been successfully drugged in other non-enzymatic oncoproteins, and early peptide-based proof-of-concept work shows CRKL's SH3 domains can be disrupted using the same logic. This remains evidence of biochemical tractability rather than clinical or advanced preclinical readiness, as no CRKL-directed small molecule, stapled peptide, or protein degrader has yet been developed or tested in any cancer model. Taken together, CRKL should be regarded as a recurrently implicated oncogenic adaptor with strong mechanistic and translational support in selected settings, most notably CML, and a rational candidate for future drug discovery, rather than as an already-established pan-cancer therapeutic target.

Acknowledgments

During the preparation of this work, the authors used Claude.ai to assist in the generation and visual development of explanatory figures. The generated material was subsequently reviewed, edited, and scientifically verified by the authors. The authors take full responsibility for the accuracy, integrity, and scientific content of the final figures and manuscript.

Funding

This research received no specific grant from any funding agency in the public, commercial or not-for-profit sectors.

Conflict of interest

The authors declare that they have no competing interests.

Author contributions

Conceptualization (MAA, AM), investigation (MAA, AM, KHK), writing – original draft (MAA, AM), writing – review & editing (MAA, AM, KHK), project administration (MAA), supervision (AM). MAA and AM contributed equally to this work. All authors read and approved the final manuscript.

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