MINI-REVIEW

Cortactin Expression in Hematopoietic Cells
Implications for Hematological Malignancies

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Cortactin is an actin-binding protein discovered in 1991 as an 80/85-kDa substrate of Src kinase. Cortactin was recognized to target actin structures in the cell cortex and to link cytoskeletal organization to signal transduction. Cortactin accumulates at sites of dynamic actin assembly, such as lamellipodia and invadopodia, localizes at the leading edge of migrating cells, and promotes secretion of matrix metalloproteinases (MMPs).

Cortactin has a hematopoietic-specific homolog termed hematopoietic cell-specific lyn substrate-1 (HS1). Both proteins are considered type II nucleation-promoting factors that have the ability to interact with the Arp2/3 complex and actin filaments to stabilize new actin branches, thus regulating actin polymerization and cell motility.

Cortactin is composed of 550 amino acids that form a multidomain structure: an N-terminal acidic domain, which binds the Arp2/3 complex; followed by 6.5 tandem repeat regions of 37 amino acids, mediating binding to filamentous (F)-actin; an α-helical domain of unknown function; a

SV2 lacks the fifth and sixth repeats (exons 10 and 11, respectively), generating proteins of 70 and 60 kDa, respectively.

The cortactin locus is often amplified in various tumors, such as human breast cancer and head and neck squamous cell carcinomas, and cortactin overexpression is generally associated with poor prognosis, invasion, and metastasis.

Cortactin is an actin-binding protein expressed in virtually all cell types. It regulates several cell functions, including adhesion and migration. Cortactin overexpression is associated with increased metastasis formation and worse outcome in different types of solid tumors, thus highlighting a critical role of cortactin in cancer progression. Mechanistically, this is due to increased invadopodia formation and matrix metalloproteinase secretion. Cortactin has been until recently considered absent in hematopoietic cells because these cells express the cortactin homolog hematopoietic cell-specific lyn substrate-1. However, many recent reports describe functional expression of cortactin in different hematopoietic cells, such as macrophages, dendritic cells, and lymphocytes. Of note, cortactin is strongly overexpressed in leukemic cell lines and primary patient-derived leukemic cells. In B-cell chronic lymphocytic leukemia, this is associated with poor prognosis and increased chemotaxis; in B-cell acute lymphoblastic leukemia, high cortactin levels correlate with treatment failure and relapse. Moreover, cortactin has been proposed as a diagnostic marker for non-Hodgkin B-cell lymphomas. This review summarizes current knowledge on cortactin expression in hematopoietic cells and discusses the functional implications for different hematological malignancies. (Am J Pathol 2020, 190: 958–967; https://doi.org/10.1016/j.ajpath.2019.12.011)
proline-rich segment with tyrosine, threonine, and serine residues prone to phosphorylation in response to several stimuli; and an Src homology 3 domain (SH3) at the C-terminal end, mediating interactions with a range of other adaptor proteins, such as zonula occludens-1, neural Wiskott-Aldrich syndrome protein, and Nck14 (Figure 1A). Cortactin activity is modulated by post-translational modifications in response to signaling pathways.
downstream of integrin-adhesion and cadherin-adhesion ligands and growth factor receptors \(^4\) (Figure 1B). The downstream kinases that phosphorylate cortactin include Src family kinases (Fer, Fyn, Syk, and Src), tyrosine kinases (Abl and Arg), and serine/threonine kinases, such as extracellular signal-regulated kinase (ERK) 1/2, p21 activated kinase 1, and protein kinase D.\(^4\) Cortactin phosphorylation sites for Src family kinases are mainly tyrosine 421, 466, and 482 in mice (421, 470, and 486 in humans) within the proline-rich domain (Figure 1B). Phosphorylation of these residues is proposed to activate the protein and induce cell migration, as cortactin mutants with these tyrosine residues changed to Phe or Ala (3YF/3YA) cannot be phosphorylated by Src and exhibited impaired cell migration.\(^9\)–\(^11\) Furthermore, ligation of the C-X-C motif chemokine receptor type 4 (CXCR4) by its ligand C-X-C motif chemokine ligand 12 (CXCL12) induced cortactin translocation from early endosomes to the cell surface and CXCR4 internalization, which was abolished by overexpression of a cortactin-Y421A mutant in HEK cells. In cortactin-Y421A-expressing cells, CXCL12 treatment also blocked CXCR4-mediated ERK activation, leading to inhibition of CXCR4-mediated chemotaxis.\(^12\)

Abl family kinases phosphorylated the same tyrosine residues as Src family kinases in response to platelet-derived growth factor, leading to cortactin translocation from a perinuclear region and colocalization with dynamin in F-actin—rich dorsal membrane ruffles in human fibroblasts.\(^13\) On the other hand, ERK phosphorylated human cortactin at S405 and S418, thus increasing accessibility of the SH3 domain, resulting in improved neural Wiskott-Aldrich syndrome protein binding to cortactin and increased cell motility and lamellipodial dynamics (Figure 1B). Of note, Src phosphorylation impaired this ability of cortactin previously phosphorylated by ERK, suggesting that the capacity of the cortactin-SH3 domain to bind neural Wiskott-Aldrich syndrome protein is subject to an on-off switch regulated by ERK and Src kinases.\(^14\) However, in head and neck squamous cell carcinoma, S405/418 and Y421 could be cophosphorylated without reciprocal influence of these phosphorylation events.\(^15\)–\(^16\) The p21 activated kinase 1 also phosphorylated cortactin at S405 and S418, leading to increased neural Wiskott-Aldrich syndrome protein binding without affecting Arp2/3- or actin-binding properties of cortactin.\(^17\) Protein kinase D phosphorylated human cortactin at S298, which increased Arp2/3 activation and cell migration.\(^18\)

In addition to phosphorylation, cortactin functions are also regulated by acetylation and deacetylation mediated by the histone-acetyltransferases p300/cyclic adenosine monophosphate (cAMP) response element-binding protein (CREB)-binding protein (CBP)-associated factor and p300 and the histone deacetylase-6 and sirtuin-1.\(^19\)–\(^20\) Given that the acetylation sites are within the tandem repeats region that regulates F-actin binding and that acetylation neutralizes charged lysine residues, acetylation diminishes the affinity of cortactin for F-actin, leading to decreased cell migration.\(^20\) Moreover, after treating podocytes with EX-527, a sirtuin-1 inhibitor, acetylated cortactin dissociated from actin fibers and translocated to the nucleus.\(^21\) However, the precise role of cortactin in the nucleus remains elusive. Post-translational modifications control many cell functions of cortactin. Thus, using pharmacologic inhibitors against kinases and deacetylases targeting cortactin is a novel approach to investigate the pathophysiological relevance of these cortactin modifications.

### Redundant or Specific Functions of Cortactin and HS1 in Hematopoietic Cells

There are still few studies describing cortactin functions in hematopoietic cells because cortactin has been until recently considered absent in most hematopoietic cells. However, recently, new evidence is emerging that cortactin is expressed in several hematopoietic cells (Table 1 and Figure 2).\(^14\)–\(^22\)–\(^34\) However, most studies remained descriptive, and many functions of cortactin in hematopoietic cells are yet to be unraveled. But why would there be the need of two homologs in hematopoietic cells, which, in theory, can fulfill the same functions considering that cortactin and HS1 share the same domain structure? And, vice versa, expression of HS1 has not been reported in cells, in which cortactin plays prominent roles, such as fibroblasts, endothelial cells, and epithelial cells. These are questions that need to be addressed in future studies. Below, this review summarizes current knowledge on cortactin functions in hematopoietic cells in comparison to HS1.

### Megakaryocytes and Platelets

Cortactin has been described to be important for human platelet aggregation, as it translocated to the platelet cytoskeleton and promoted F-actin polymerization after thrombin receptor engagement.\(^22\) On the other hand, HS1 in platelets mediates collagen receptor signaling, aggregation, and formation of thrombi.\(^35\) After phorbol-12-myristate-13-acetate stimulation, the human megakaryocyte (MK) cell line CMK up-regulated expression of cortactin, but not HS1, an effect also observed in murine bone marrow (BM)—derived MK after thrombin and IL-3 stimulation.\(^36\) However, in sharp contrast, mice with a platelet-specific cortactin knockout showed no overt effects on platelet aggregation or MK functions.\(^37\) In addition, cortactin/HS1 double knockout mice also showed no defects in platelet functions.\(^37\) The histone deacetylase-6 inhibitors tubastatin A and ACY1215 caused diminished levels of F-actin in human MK because of cortactin hyperacetylation, leading to changes in the distribution of MK organelles and consequently a strong decrease in proplatelet formation.\(^23\) Furthermore, depletion of cortactin by short hairpin RNAs in human MK necroplicated histone deacetylase-6 inhibition, leading to defects...
in proplatelet formation.\textsuperscript{23} Given that such effects were not observed in mouse MK, these findings may argue for species-specific effects of cortactin in platelets. Unfortunately, how HS1 affected human MK functions was not investigated. Thus, specific depletion of HS1 or cortactin together with HS1 in human MK should reveal whether HS1 also contributes to human platelet formation and aggregation or whether this is a unique feature of cortactin.

### Monocytes/Macrophages and DCs

In dendritic cells (DCs) and macrophages, cortactin plays a role in migration by controlling activation and stabilization of actin branches.\textsuperscript{9,24,26} Cortactin localized to sites of dynamic F-actin assembly, such as lamellipodia, invadopodia, and podosomes.\textsuperscript{38–40} Binding of Wiskott-Aldrich syndrome protein—interacting protein (WIP) to the SH3 domain of cortactin increased the efficiency of actin polymerization through cortactin-mediated Arp2/3 complex activation.\textsuperscript{41} In murine WIP-deficient splenic DCs, cortactin localization within podosome cores was impaired, causing random cortical protrusion formation, loss of DC polarity, and reduced motility.\textsuperscript{24} In addition, MMP-mediated extracellular matrix degradation was dependent on WIP binding to cortactin.\textsuperscript{42} In accordance, the use of the antigen-binding domain of Camelid heavy-chain antibodies specifically targeting the SH3 domain of cortactin\textsuperscript{13} impaired the formation of podosomes and invadopodia, migration, and the capacity to degrade extracellular matrix of human primary DCs and Tohoku Hospital Pediatrics-1 (THP-1) macrophages.\textsuperscript{26} In addition, in a murine model of peritonitis, histone deacetylase-6 deficiency showed impaired monocyte-derived macrophage recruitment into the peritoneal cavity and defective phagocytosis that was
accompanied by cortactin hyperacetylation and decreased interaction with F-actin.

On the other hand, HS1 but not cortactin was detected in murine BM-derived DCs; and cortactin expression was undetectable in murine BM-derived monocytes even after several days in culture. HS1-knockout BM-derived DCs showed disorganization of podosomes, altered lamellipodial dynamics, and impaired directional migration.44

Figure 2  Schematic representation of cortactin functions in different hematopoietic cells. Dotted arrows indicate translocation; green arrows, up-regulation; red arrows, down-regulation; dark red lines, inhibition. ac, acetylated; B-ALL, B-cell acute lymphoblastic leukemia; BCR, B-cell receptor; c-Cbl, c-Casitas B-lineage lymphoma; CTN, cortactin; CXCL12, C-X-C motif chemokine ligand 12; CXCR4, C-X-C motif chemokine receptor type 4; DC, dendritic cell; ECM, extracellular matrix; HDAC6, histone deacetylase-6; MΦ, macrophages; MHC-II, major histocompatibility complex class II; MK, megakaryocyte; MMP-9, matrix metalloprotease-9; P, phosphorylated; PMA, phorbol 12-myristate 13-acetate; PP2, 4-amino-5-(4-chlorophenyl)-7-(dimethyl)pyrazolo[3,4-d]pyrimidine; ROR-1, receptor tyrosine kinase-like orphan receptor-1; SDF, serum-derived factor; SEE, staphylococcal enterotoxin E; T-ALL, T-cell acute lymphoblastic leukemia; TCR, T-cell receptor; TP, thrombin receptor peptide; Ub, ubiquitin; WASP, Wiskott-Aldrich syndrome protein; WIP, WASP-interacting protein; ?, unknown mechanism.
Given that HS1 is also able to interact with WIP, HS1 and cortactin might be fulfilling similar roles in DCs. However, in human DCs and THP-1 cells, despite the presence of HS1, specific inhibition of cortactin-WIP interaction using cortactin nanobody 2 (CORNb2) impaired formation of podosomes, invadopodia, and migration, showing that HS1 was not able to compensate for loss of cortactin function, thus arguing for a non-redundant role of cortactin in human DCs. The discrepancy in cortactin expression in DCs could be explained by the different origins as isolated splenic DCs and BM-derived DCs are known to show functional differences.

B and T Lymphocytes and Natural Killer Cells

HS1 functions in B cells have recently been reviewed, and in normal, nonleukemic B cells, cortactin expression has been detected without testing any specific function. Cortactin functions in leukemic B cells are described in detail below.

In T cells, HS1 played important roles in T-cell receptor-mediated signaling, Ca²⁺ influx, nuclear factor of activated T-cells (NFAT)- and NF-kB-mediated gene transcription, and the formation of the immunologic synapse. Moreover, antigen-induced proliferation of HS1-deficient T cells was impaired. Cortactin was only studied in leukemic T-cell lines (see below).

In natural killer cells, HS1 was important for chemotaxis, cell adhesion, actin dynamics at the lytic synapse, targeted cell lysis, and transendothelial migration, processes that depended on HS1 phosphorylation at tyrosine residues 222, 378, and 397. Cortactin expression has been detected in human natural killer cells, without testing specific functional roles, which need to be analyzed in the future.

Granulocytes and Other Hematopoietic Cells

Polymorphonuclear cells are the most abundant cells in the bloodstream, and yet there is still a gap in knowledge regarding possible roles of cortactin in these cells. PubMed searches using the words eosinophils, mast cells, or basophils together with cortactin yielded no publication. Meanwhile, cortactin has been related indirectly to neutrophils as it regulates clustering of endothelial intercellular adhesion molecule 1 to enable neutrophil extravasation. However, in this study, cortactin was not detected in mouse bone marrow-derived neutrophils. Of note, neutrophil extravasation also depended on neutrophil HS1 that was required for proper Rac1, Rap1, and integrin activation, demonstrating that neutrophil HS1 and endothelial cortactin regulate the same process during neutrophil extravasation (ie, integrin—intercellular adhesion molecule 1 interactions), but in different cells.

In addition, the Btk inhibitor CC-292 inhibited bone resorption activity of monocyte-derived osteoclasts from multiple myeloma patients by reducing cortactin levels and impairing formation of the F-actin ring in the sealing zone.

Cortactin, a Metastasis Driver

Several studies have demonstrated that overexpression and amplification of the cortactin chromosomal locus is associated with worse pathologic parameters and metastasis, leading to poor prognosis in a variety of cancers. Metastasis formation occurs when cancer cells start migrating from primary tumors to secondary organs, a process requiring intravasation and extravasation that highly depends on actin cytoskeleton dynamics and cortactin. In breast cancer, this amplification has been associated with an increased risk of relapse and death in patients with estrogen receptor—negative disease. In head and neck squamous cell carcinoma, cortactin overexpression potentiated growth factor—induced signaling, leading to sustained ERK activation and cell proliferation, thus enhancing tumor cell motility and invasion.

Overexpression of cortactin in gastric carcinoma correlated with epidermal growth factor receptor up-regulation, proliferation, invasion, and cell migration. Cortactin overexpression in colorectal cancer patients was associated with invasion and lymph node metastasis, likely caused by enhanced epidermal growth factor receptor—ERK signaling. Moreover, Src-mediated cortactin hyperphosphorylation showed a strong correlation with extracellular matrix degradation, migration, and invasion of cancer cells from solid tumors. Cortactin phosphorylation on Y421 and Y466 allowed its association with Nck1 to recruit neural Wiskott-Aldrich syndrome protein and Vav2 to cortactin, thus promoting branched actin polymerization required for invadopodia assembly. During invadopodia maturation, cortactin also regulated matrix degradation by controlling the secretion of MMP-2, MMP-9, and membrane-type 1 (MT1)-MMP. Interestingly, examination of MDA-MB-231 breast cancer cells at different time points by live cell imaging revealed a multistep process in invadopodia: i) cortactin recruitment to membranes with extracellular matrix contact, ii) MT1-MMP accumulation and secretion at the region of cortactin localization, iii) matrix degradation at the invadopodia, and iv) subsequent cortactin dissociation from the area of MT1-MMP accumulation. Thus, cortactin in invadopodia regulated stimulated exocytosis of MMP-containing vesicles. However, further in vivo studies are needed to fully unravel cortactin functions in invadopodia and metastasis formation to propose cortactin as a potential target for cancer therapies.

Novel Functions of Cortactin in Leukemic Cells

As discussed above, cortactin overexpression in solid tumors is related to metastatic events and worsens the prognosis. In hematological cancers, several studies...
highlighted an important role of HS1 in leukemic cell migration and organ infiltration,\textsuperscript{5,20,30} and HS1 overexpression and hyperphosphorylation correlated with poor prognosis and lower survival rates.\textsuperscript{5} Thus, it was tempting to speculate that cortactin is overexpressed in leukemic cells with impact on disease progression. This idea was confirmed in recent studies showing that cortactin overexpression was related to disease progression and bad prognosis in different hematologic malignancies. For example, in B-cell chronic lymphocytic leukemia (B-CLL), expression of different cortactin isoforms was observed among B-CLL patients, including cortactin wild type (80/85 kDa) and SV1 (70/75 kDa), whereas in B cells from peripheral blood of healthy donors only the 70/75-kDa SV1 isoform was observed.\textsuperscript{27} Moreover, overexpression of the 80/85-kDa isoform of cortactin was associated with increased expression of negative prognostic factors, such as ZAP-70, CD38, and somatic hypermutations, in the Ig heavy-chain variable region.\textsuperscript{27} Another report from the same group showed that expression of cortactin in CLL B cells was related to MMP-9 secretion, motility, and invasion as these characteristics were significantly impaired after cortactin silencing.\textsuperscript{67} Because B-CLL patients with lymph node enlargement had increased levels of cortactin expression, they suggested a putative role of cortactin in the homing of CLL B cells. Intriguingly, leukemic B cells showed constitutive, high phosphorylation levels at the Y421 residue of cortactin under basal conditions, which was correlated with reduced MMP-9 secretion and migration in response to CXCL12.\textsuperscript{67} This cortactin phosphorylation was reverted after Src inhibition with 4-amino-5-(4-chlorophenyl)-7-(dimethylthethyl)pyrazolo[3,4-d]pyrimidine (PP2). Moreover, basal phosphorylation of cortactin at Y421 was significantly increased in receptor tyrosine kinase-like orphan receptor-1 (ROR1)-positive B cells from B-CLL patients.\textsuperscript{68} ROR1 is a surface receptor that plays important roles during organogenesis of skeletal and neural tissues,\textsuperscript{69} with its expression usually being restricted to embryonic development.\textsuperscript{31} In B-CLL cells stimulated with the ROR1 ligand Wnt5a, cortactin associated with ROR1 through its association of the cortactin/ROR1 complex to ARHGEF1 with its expression usually being restricted to embryonic development.\textsuperscript{31} In B-CLL cells stimulated with the ROR1 ligand Wnt5a, cortactin associated with ROR1 through its association of the cortactin/ROR1 complex to ARHGEF1 and RhoA activation, causing leukemic cell migration through ROR1-dependent, noncanonical Wnt5a signaling.\textsuperscript{58} Interestingly, the same group showed that HS1 could contribute to Wnt5a-mediated leukemic cell migration via ROR1-mediated activation of ARHGEF1 and RhoA.\textsuperscript{30} Silencing of both cortactin and HS1 displayed an additive inhibition of cell migration, suggesting nonredundant roles of the two proteins in this signaling cascade.\textsuperscript{58}

Also in B cells from CLL patients, cortactin was constitutively associated to the E3 ubiquitin ligase c-Cbl (c-Casitas B-lineage lymphoma),\textsuperscript{70} which regulates B-cell receptor-mediated signaling by ubiquitination of Lyn kinase.\textsuperscript{71} Given that both c-Cbl and Lyn are up-regulated in B-CLL, it is possible that their interaction with cortactin could impede c-Cbl activity to prevent Lyn degradation and promote B-cell receptor-mediated prosurvival signaling in CLL cells.\textsuperscript{70}

Cortactin expression has also been detected in non-Hodgkin B-cell lymphomas, such as hairy cell lymphoma and diffuse large B-cell lymphoma. Of note, mantle cell lymphoma cells, another non-Hodgkin B cell—lymphoma that in some cases might overlap in the clinical, morphologic, and phenotypic features with CLL,\textsuperscript{72} did not express cortactin.\textsuperscript{73} Thus, cortactin might be clinically relevant for the differential diagnosis of CLL, mantle cell lymphoma, and other non-Hodgkin B-cell lymphomas. On the other hand, in the Burkitt lymphoma cell line Namalwa, the multiple myeloma cell line U266, and the T-cell acute lymphoblastic leukemia (ALL) cell line CEM, recruitment of cortactin, focal adhesion kinase (FAK), Src, and ERK to focal adhesion complexes was observed after binding of vitronectin and fibronectin to α5β3 integrin, leading to proliferation and the secretion of MMP, which may provide the possible mechanism of enhanced leukemic cell invasion.\textsuperscript{33}

Expression of cortactin has also been reported in the leukemic T-cell line Jurkat and the antigen-presenting leukemic B-cell line Nalm-6 that were able to form an immunologic synapse in the presence of the superantigen staphylococcal enterotoxin E (SEE).\textsuperscript{14} Cortactin colocalized with F-actin and Wiskott-Aldrich syndrome protein at the immunologic synapse, suggesting a possible role for cortactin in immunologic synapse formation similar to HS1.

A recent study showed that cortactin is also overexpressed in ALL B cells from pediatric patients and in the B-cell acute lymphoblastic leukemia (B-ALL) cell lines RS4:11 and REH.\textsuperscript{32} In contrast to B-CLL cells, B-ALL cells only expressed the cortactin SV2 splice variant of 60 kDa.\textsuperscript{32} The reason for the isoform-specific expression pattern of cortactin in leukemic cells remains elusive. However, migration of 3T3 cells overexpressing specifically the cortactin SV2 variant was reduced compared with 3T3 cells overexpressing the cortactin wild type or SV1 isoform because of reduced affinity for F-actin as the SV2 isoform misses two repeats of the F-actin binding domain.\textsuperscript{7} Of note, using in vitro CXCL12-mediated transmigration and colonization assays, those B-ALL cells that colonized and transmigrated expressed the highest levels of cortactin, suggesting that high cortactin levels provide these cells with a migratory advantage.\textsuperscript{32} Moreover, in vivo leukemic xenotransplantation assays using immune-deficient mice revealed that only B-ALL cells with the highest cortactin levels infiltrated lungs, brain, and testes, a phenomenon that was significantly ameliorated using cortactin-depleted B-ALL cells.\textsuperscript{7} In agreement to the finding that cortactin was critical for CXCR4 trafficking in a murine model of calcineurin-deficient T-ALL cells,\textsuperscript{14} cortactin-depleted B-ALL cells also showed diminished expression of CXCR4 at the plasma membrane under basal conditions, suggesting that cortactin triggers CXCR4/CXCL12-mediated signaling.
in these cells to enhance transendothelial migration and organ infiltration.32 However, recycling dynamics after CXCL12 stimulation were similar in cortactin-depleted and control REH cells.32 These data are also clinically relevant as B-ALL patients with high cortactin expression showed a significant positive correlation with BM relapse, adenomely, and poor response to steroid therapy.32 Cortactin was up-regulated to a higher extent in these cells compared with HS1, suggesting that cortactin has a higher malignant potential in B-ALL cells, although this notion needs to be tested experimentally in the future.

Conclusions

Cortactin is an actin-binding protein that has been considered absent in most hematopoietic cells for many years. Nowadays, more evidence is arising pointing to prominent roles of cortactin in hematopoietic cells and especially leukemic cells. Although several of these functions might overlap with functions of the cortactin homolog HS1, other functions seem to be specific and independent of HS1. Certainly, many exciting discoveries regarding cortactin functions in different hematopoietic cells lie still ahead. Overexpression of cortactin in different types of leukemia, similar to solid tumors, has been associated with a worse outcome for these patients, suggesting that determining cortactin levels may help stratify high-risk patients and optimize their treatments. As cortactin apparently regulates invasive properties of leukemic cells, it can also be considered as a potential pharmacologic target for these malignancies. Therefore, it will be important to study in more detail the role of post-translational modifications, such as acetylations and phosphorylations, that regulate the subcellular localization and activity of cortactin. As the enzymes responsible for these modifications are druggable targets, this is an exciting new avenue to explore cortactin as target in hematological malignancies. In the future, clinical studies are needed to unravel the precise role of cortactin at different stages of leukemia progression and its usefulness as pharmacologic target in humans.

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