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Cortactin
A multifunctional regulator of cellular invasiveness

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Branched actin assembly is critical for a variety of cellular processes that underlie cell motility and invasion, including cellular protrusion formation and membrane trafficking. Activation of branched actin assembly occurs at various subcellular locations via site-specific activation of distinct WASp family proteins and the Arp2/3 complex. A key branched actin regulator that promotes cell motility and links signaling, cytoskeletal and membrane trafficking proteins is the Src kinase substrate and Arp2/3 binding protein cortactin. Due to its frequent overexpression in advanced, invasive cancers and its general role in regulating branched actin assembly at multiple cellular locations, cortactin has been the subject of intense study. Recent studies suggest that cortactin has a complex role in cellular migration and invasion, promoting both on-site actin polymerization and modulation of autocrine secretion. Diverse cellular activities may derive from the interaction of cortactin with site-specific binding partners.

Introduction

Cell movement is a critical cellular process that contributes to embryonic development, immune defense and wound healing. The actin cytoskeleton has long been known to be critical for various aspects of this process, including polarization, leading edge protrusion and cellular contraction (**Fig. 1**). Myosin-based contraction of unbranched actin filaments is closely connected to cellular traction formation and speed, and is critical for forward cell movement.[1,2] By contrast, dynamic branched actin assembly nucleated by the Arp2/3 complex is critical for other aspects of cell motility, including formation of protrusive motility structures and membrane trafficking to promote directional cell motility and secretion of extracellular factors (**Fig. 1**).

The identification of branched actin networks at the leading edge of migrating cells, along with the discovery of the Arp2/3 protein complex that is essential for nucleation of those networks,[3-6] led to a great deal of excitement in the cell motility field. Indeed, Arp2/3 activation by WAVE2 was found to be required for the first step of canonical cell motility: formation of leading edge protrusions known as lamellipodia.[7-10] Concurrently, the Src kinase substrate cortactin was shown to bind Arp2/3 complex,[11] serve as a cofactor for Arp2/3 activation, and to stabilize branched actin networks after they are formed.[12,13] In cells, cortactin localizes at sites of dynamic actin assembly and is favored as a marker for actin-rich motility protrusions such as lamellipodia and invadopodia.[14-16] Interestingly, in addition to Arp2/3 complex, cortactin binds to a large number of signaling, cytoskeletal and membrane trafficking proteins (**Table 1 and Fig. 2**) and links them to dynamic actin networks. Because of this linkage and the general role that cortactin plays in stabilizing branched actin networks,[13] a number of studies have examined the role of cortactin in migration and invasion. Overall, cortactin appears to be a strong promoter of cellular invasiveness, with multiple potential mechanisms.

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General Features of Cortactin

The gene encoding cortactin, CTTN (previously denoted EMS1), is located on the long arm of chromosome 11, in the 11q13 region that is frequently amplified in a number of cancer types.[17] Cortactin is ubiquitously expressed, except in most hematopoietic cells that instead express the homolog hematopoietic specific 1 (HS1).[18] Osteoclasts are a notable exception to this rule, expressing both HS1 and cortactin.[19] The mechanisms controlling cortactin expression are not well understood; however, an increase in cortactin mRNA has recently been shown to be downstream of hyaluronan (HA) binding to its receptor, CD44, through the activation of the NFκB pathway.[20] In addition, phospho-Stat3 was recently shown to bind the CTTN promoter and upregulate transcription.[21] In cancer, cortactin is frequently overexpressed, both as a consequence of gene amplification and by additional unidentified mechanisms.[17,22-25]

Cortactin contains the following key domains: an amino-terminal acidic domain, a tandem repeat domain, a carboxy-terminal proline-rich region that contains a number of phosphorylation sites and an SH3 domain (**Fig. 2**). The N-terminus of cortactin is critical for regulating branched actin assembly, via conserved interactions with the branched actin-nucleating Arp2/3 protein complex and with filamentous actin (F-actin) at the acidic and repeats domains, respectively.[11,26] Interestingly, recent structural studies found that cortactin alters the lateral and longitudinal contacts of actin subunits within an actin filament, suggesting that by changing the local conformation of filamentous actin

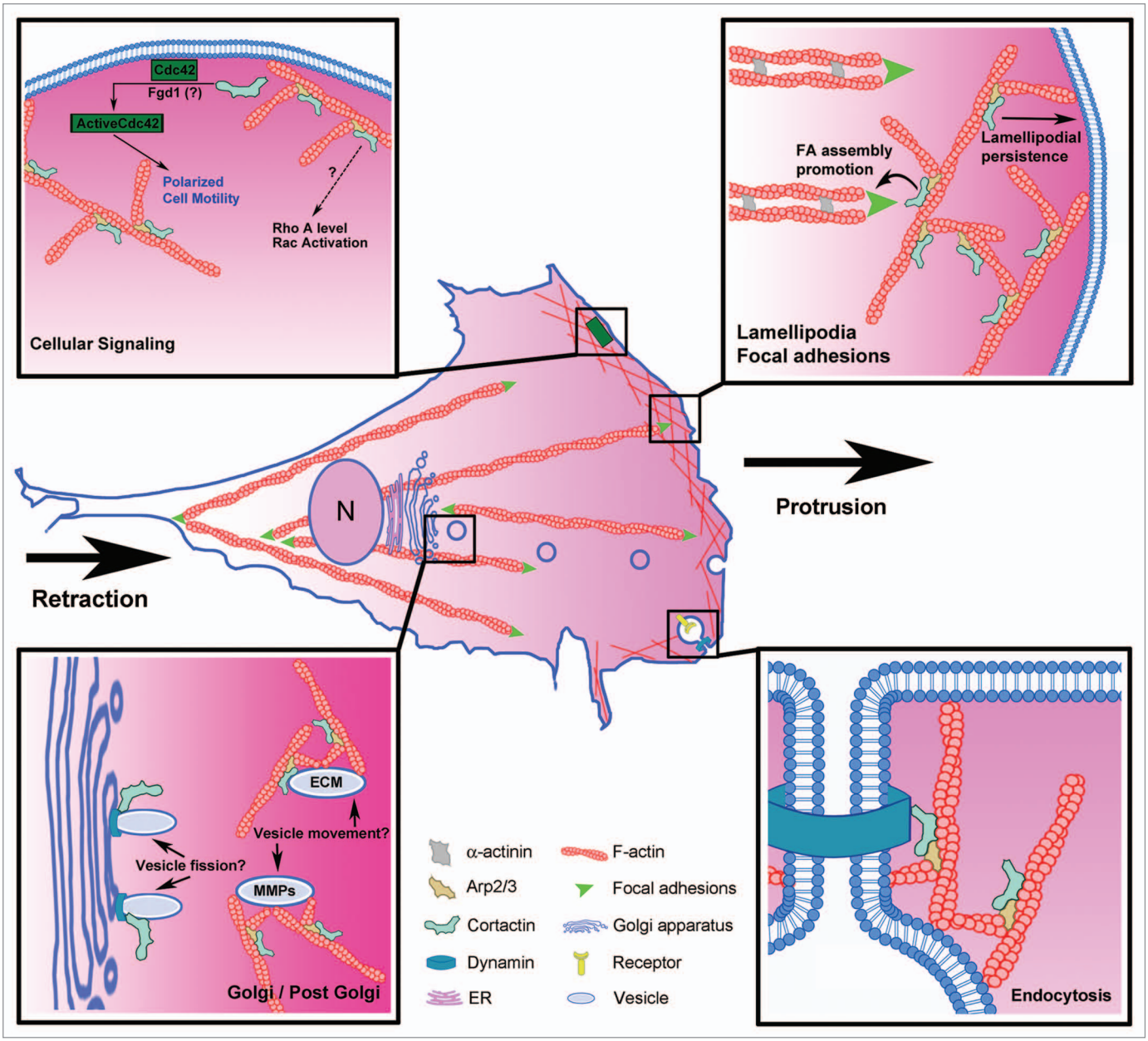

Figure 1. Regulation of cellular motility by branched actin and cortactin. Cell motility requires coordination of several processes, including protrusion of the leading edge lamellipodium, adhesion, contraction of actin bundles, and retraction of the rear of the cell. Depicted in the zoomed panels are mechanisms by which cortactin may regulate motility, including: promoting lamellipodial persistence, focal adhesion assembly, cellular signaling and secretion of autocrine factors.

cortactin might promote the exposure of new binding sites for Arp2/3 complex and thereby indirectly increase the affinity of Arp2/3 complex for the side of a mother actin filament.[27,28] The C-terminus instead allows cortactin to function as a scaffolding protein, since many cytoskeletal, membrane trafficking and signaling proteins bind to the C-terminal SH3 domain (**Fig. 2 and Table 1**) and can be bridged to the actin cytoskeleton through cortactin.[29]

Cortactin is evolutionarily conserved with members identified in a diverse array of species from sponges to mammals.[18] Although no cortactin gene exists in yeast, the protein ABP1 is thought to be a functional homolog based on its role in endocytosis and its ability to induce weak activation of Arp2/3 complex through interactions with both F-actin and Arp2/3 complex.[30,31] While orthologs exist in a number of species, they differ in the number of tandem F-actin binding repeats they contain, similar to the splice variants (discussed below). For example, Drosophila cortactin contains only four repeats.[32]

Cortactin function is altered through several different mechanisms including alternative splicing, phosphorylation and acetylation. The three major splice variants of cortactin, A, B and C, respectively contain 6.5, 5.5 and 4.5 of the cortactin repeats

Table 1. Table of cortactin binding partners

Cortactin binding proteins	Localization	Function	Binding site	References
Arp2/3	Located at branch points of actin filaments network	Actin nucleation	NTA	4, 11
Actin filaments	Cell cytoskeleton	Cytoskeletal polymer	Repeat regions	15
HDAC6	Cytoplasm	Deacetylase	Repeat region	36, 151
SIRT1	Cytoplasmic and nuclear	Deacetylase	Repeat region	37
Caldesmon	Filamentous distribution, lamella and lamellipodia	Actin binding protein, contraction	N-terminus	152
p120 catenin	Cell-cell junction, nucleus, membrane ruffles, actin halos associated with endocytic vesicles	Cell-cell adhesion via cadherin stability & trafficking	N-terminus	81, 153–155
Grb2	Cytoplasm, plasma membrane, lipid rafts, perinuclear region	Signaling adaptor	N-terminus	52, 156, 157
Met	Plasma membrane, dorsal ruffles, early endosomes and late endosomes	Receptor tyrosine kinase	?	52, 158
K^+ channel $K_v1.2$	Cortical cytoskeleton	Ion channel	?	159
PTP1B	Cytoplasmic face of endoplasmic reticulum	Tyrosine phosphatase	Tyr^{446}	160, 161
Nck1	Cytoplasmic, cell periphery, podosomes, invadopodia	Signaling adaptor	phospho-Y421, 466	162–164
Syk	Nucleus, cytoplasm, perinuclear region, plasma membrane at cell-cell contacts	Tyrosine kinase	?	53, 58, 165
Src family kinases (Src, Fer)	Cytoplasmic, plasma membrane, focal adhesions, podosomes, invadopodia	Tyrosine kinase	phospho-Y421, 466, 482	55, 56, 70, 71, 166, 167
ERK1/2	Nucleus, cytoplasm	Serine/Threonine kinase	S405, 418	57, 168–170
PAK1	Cytoplasm, plasma membrane, focal adhesions	Serine/Threonine kinase	S113	59, 170–173
CBP90	Cytosol, membrane and synaptic vesicles	?	SH3	33
ZO-1	Cell-cell junction	Tight junction adaptor	SH3	32
BPGAP1	Cytoplasm, plasma membrane	RhoA-GAP	SH3	174, 175
Hip1R	Present at all clathrin patches	Membrane trafficking	SH3	176
BK channels	Plasma membrane	Membrane excitability	SH3	177
ASAP1/AMAP1	Recycling endosomes, focal adhesions, invadopodia, podosomes	ARF6 GAP	SH3	129, 178–181
Abl/Arg	Cytoplasm, nuclear, plasma membrane	Tyrosine kinase	SH3	45, 60, 182, 183
N-WASp	Golgi, Podosomes and invadopodia.	Actin assembly	SH3	97, 184, 185
Dynamin2	Plasma membrane, trans-Golgi network, cell cortex, cortical ruffles	GTPase, Membrane trafficking	SH3	186–189
CortBP1/SHANK2	Within secretory granules (cytoplasm), membrane ruffles, neuronal growth cones, lipid rafts	Synaptic plasticity, adaptor protein, regulates Na^+/H^+ exchanger 3	SH3	190–195
FGD1	Cytoplasm, Golgi, cell cortex and membrane ruffles	Cdc42-GEF	SH3	196, 197
WIP	Perinuclear region, membrane ruffles	Adaptor protein, Actin binding/assembly, WASp stabilization	SH3	68, 198–200
Non-muscle myosin light chain kinase	Actin stress fibers, lamellipodia	Contraction	SH3	47, 201, 202
Missing in metastasis (MIM)	Plasma membrane, actin bundles, stress fibers, cytoplasm	Adaptor protein, Actin binding and regulation	SH3	203, 204
CD2AP	Cell membrane, endosomes, immune synapse (T cells)	Endocytosis (binds to Rab4 & c-Cbl)	SH3	205–210

List of Cortactin binding proteins

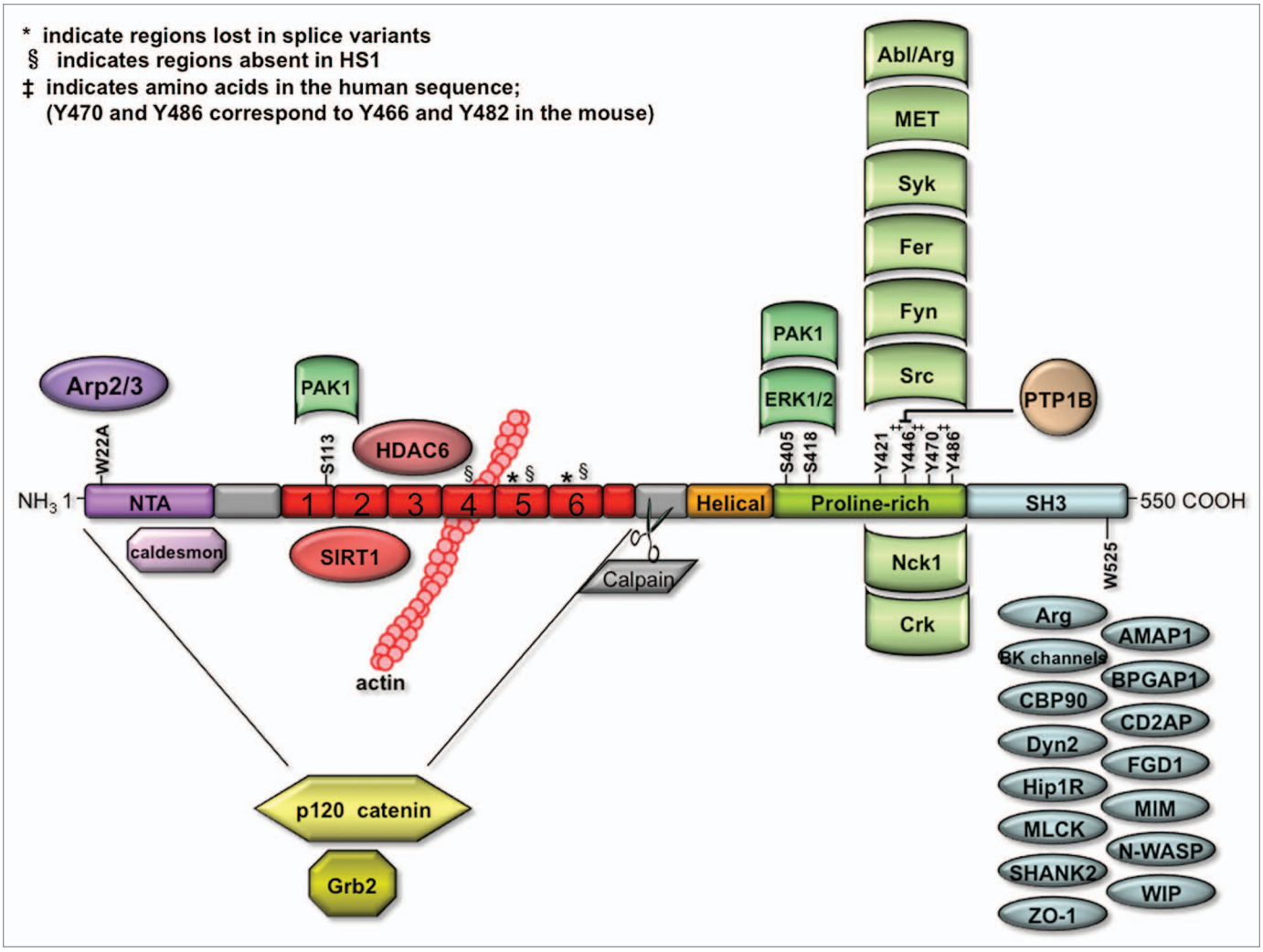

Figure 2. Cortactin domain structures. Schematic diagram of key cortactin domains and binding partners. The following abbreviations are used: NTA, N-terminal acidic domain and SH3, Src homology 3 domain. Proteins whose interaction with cortactin has been narrowed down to a particular domain are represented in the same color as the domain on cortactin. Interacting proteins shown in yellow bind the amino terminus of cortactin, which constitute the NTA + repeats domains. Amino acids that are essential for the interaction with key cortactin binding proteins, including W22 for interaction with Arp2/3 and W525 for interactions within the SH3 domain, are shown. The kinases known to phosphorylate cortactin are found above the respective sites they have been shown (or hypothesized) to phosphorylate.

domains.[33,34] Loss of the repeat domains via alternative splicing leads to both diminished binding affinity for F-actin, decreased localization to cellular cortical actin and decreased motility.[33-35] Acetylation can also occur within the tandem repeats region and regulates both F-actin-binding and cell motility.[36,37] A recent paper is suggestive for cortactin deacetylation being important in invadopodia function, as the cortactin deacetylase HDAC6 regulates both invadopodia activity and protein acetylation at invadopodia.[38]

Cortactin was originally identified as a substrate for Src tyrosine kinase (at Y421, Y470 and Y486 in the human sequence); however, it is a substrate for many different kinases (reviewed in refs. 39 and 40). An increase in phosphorylation of tyrosine, serine and/or threonine residues of cortactin is seen upon stimulation by numerous sources, including fibroblast growth factor (FGF),[41,42] epidermal growth factor (EGF),[43,44] platelet-derived growth factor (PDGF;[45]), thrombin,[46] sphingosine-1-phosphate,[47] homophilic ligation of E-cadherin,[48] bacterial phagocytosis[49] and integrin activation.[50] The downstream kinases involved in the phosphorylation of cortactin by these pathways include Src family kinases (Fer, Fyn, Syk and Src), tyrosine kinases (Abl and Arg, ErbB2 and c-Met), as well as serine/threonine kinases extracellular regulated kinase 1/2 (ERK1/2; at S405 and S418), p21 activated kinase 1 (PAK1; at S405/418) and protein kinase D (PKD; at S298).[16,45,51-59] Phosphorylation has been shown to be important for enhancing cortactin function in migration and invasion by altering the complement of proteins associated with cortactin.[43,44,60,61]

Many of the phosphorylation sites occur within the proline-rich domain, and may regulate binding to the adjacent SH3 domain (**Fig. 2**). In particular, Src kinase phosphorylation has been shown to inhibit accessibility of the SH3 domain,[57]

although this may be opposed by the binding of SH2-domain containing proteins, such as Nck1, to the phosphorylated tyrosine.[62,63] Indeed, in cells, tyrosine phosphorylation of cortactin has been shown to increase the binding affinity of the SH3 domain binding partner Dynamin 2.[64] By contrast, ERK phosphorylation increases accessibility of the SH3 domain resulting in increased N-WASp binding to cortactin,[57] which may account for Erk-regulation of cell motility and lamellipodial dynamics.[43] Likewise, PAK1 phosphorylation of the same sites in cortactin was shown to increase N-WASp binding to cortactin without affecting the Arp3- or actin-binding properties of cortactin.[54] It is likely that the Erk and Src phosphorylation events are not mutually exclusive in cells,[43] which may account for diverging models from in vitro biochemical experiments[57] and cellular studies.[64] In addition, a number of novel phosphorylation sites were identified by mass spectrometry,[65] including many in the amino-terminus; the regulatory kinases and functions of those novel sites remain largely unknown. Taken together, these data suggest that cortactin phosphorylation regulates the affinity and combination of binding proteins associated with cortactin.

Cortactin and the Actin Cytoskeleton

Virtually all of the cellular activities of cortactin, including cell migration and invasion, as well as localization, require association with Arp2/3 complex and the actin cytoskeleton.[11,12,35,66,67] Through this association, cortactin has been shown in vitro to regulate branched actin assembly by many mechanisms, including activation of Arp2/3 complex, stabilization of actin branches, enhancing activation of Arp2/3 complex by Wiskott-Aldrich Syndrome protein (WASp) family proteins and scaffolding of other actin regulators, such as N-WASp and WIP.[12,13,26,68] A function that is unique to cortactin and is thought to be important for regulation of actin dynamics is prevention of the de-branching of actin filament networks.[13] This function is likely to be particularly important in newly polymerized networks in cellular protrusions, since cortactin strongly localizes to such actin-rich structures and also has a high affinity for ATP-bound and ADP-P_i-bound actin.[66] Indeed, a recent study showed faster turnover of actin networks in cortactin-null cells compared with controls, as measured by fluorescence recovery after photobleaching (FRAP).[69] Recruitment of cortactin to sites of new protrusions and dynamic actin assembly occurs in response to many signals, including Rac activation,[70] and requires the presence of binding sites for the Arp2/3 complex and (to a lesser extent) F-actin.[11,12,66] In aggregate, these data suggest a role for cortactin in the regulation of newly polymerizing actin networks.

Cortactin in Cell Motility

The prominent localization of cortactin to the leading edge of migrating cells sparked an early interest in its potential function in cell migration. Indeed, numerous studies have demonstrated an important role for cortactin in the motility of diverse cell types, including fibroblasts, endothelial cells and a variety of carcinoma cell lines. Overexpression of cortactin has been shown to increase cell motility in transwell, scratch assays and single cell random motility experiments.[66,71-73] Likewise, knockdown of cortactin using si/shRNA approaches has been shown to decrease cell motility.[20,66,74,75] Recently, two groups generated and analyzed cortactin-null mouse embryonic fibroblasts (MEFs) generated from embryos containing FLOX-ed cortactin alleles and reported divergent results. One group reported a similar effect of cortactin knockout to the shRNA studies, with decreased migration in wound closure and single cell motility assays in cortactin-null MEFs, compared to controls.[69] By contrast, Tanaka et al. reported that cortactin loss did not affect MEF motility in wound closure and transwell migration assays.[76] It is unclear why no effect was evident in the latter study; however it is possible that the requirement for cortactin in efficient cell migration depends on the microenvironment. Indeed, in Drosophila, loss of the single cortactin gene diminishes border cell migration.[77]

The mechanism by which cortactin affects migration is not entirely clear (**Fig. 1**). Although cortactin is a prominent marker of lamellipodia, it is not essential for their formation.[66,69,75,78-80] Instead, cortactin affects the characteristics of lamellipodia, including their stability or persistence,[66,81] actin dynamics within the lamellipodia,[66,69] whether a dominant lamellipodium or multiple smaller protrusions are formed,[78] and PDGF-induced membrane ruffling[69] (**Fig. 1**). Furthermore, inhibition of lamellipodia formation by other mechanisms does not necessarily lead to decreased cell motility speed,[82] suggesting that lamellipodia may be more important for cell directionality rather than to drive cell motion.

A second potential mechanism by which cortactin might affect cell motility is via regulation of adhesion dynamics. In fibrosarcoma cells, cortactin was found to affect the rate of assembly of focal complexes.[66] Likewise, Lai et al. found that cortactin-null cells treated with PDGF had more prominent focal adhesions.[69] Interestingly, Boguslavsky et al. found that the cortactin-binding partner, p120-catenin, regulates both the assembly rate of focal adhesions and lamellipodial persistence, similar to cortactin.[66,81] Those similarities suggest both a partnership of the two molecules and a linkage between lamellipodial stability and adhesion formation. Cortactin has also been shown to affect the rate of cell spreading, an adhesion-dependent process.[60,81] As adhesions have been closely tied to cell motility speed,[83,84] and shown to be necessary for lamellipodial stability,[85-87] cortactin regulation of adhesions seems a likely mechanism of motility regulation.

A third, and not mutually exclusive, mechanism by which cortactin has been postulated to regulate cell motility is via activation of cellular signaling. Although generally cortactin has been thought to act as an effector of cellular signaling proteins, Lai et al. recently demonstrated a constitutive defect in cdc42 signaling and a defect in PDGF-induced Rac activity in cortactin-null MEFs.[69] Cortactin was also found to affect both the expression and activity of RhoA in head and neck squamous carcinoma cells (HNSCC).[88] Alteration in Rho GTPase activity could indeed affect multiple steps of motility reported to be regulated by cortactin, including adhesion dynamics (via Rho A) and lamellipodial activity (via Rac1). Alterations in cdc42 activity could

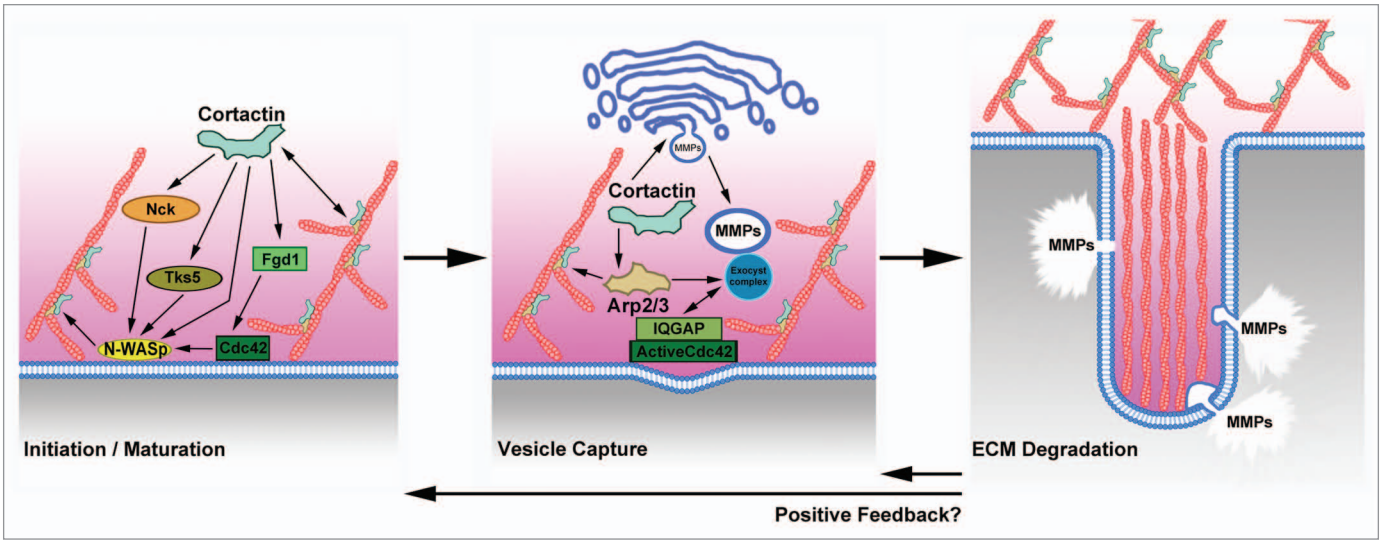

Figure 3. Model of cortactin function at invadopodia. Cortactin is thought to contribute to two major processes in invadopodia: (1) actin polymerization for initiation and/or maturation of invadopodia via activation of N-WASp via Nck, activation of cdc42 via Fgd1, and coactivation of Arp2/3 complex and (2) vesicular trafficking of matrix metalloproteinases to invadopodia via either regulation of post-Golgi trafficking or vesicle capture at invadopodia. Once ECM-degradation is established at invadopodia, they may become longer-lived due to positive feedback.

affect secretion of extracellular motility factors,[89] including matrix metalloproteinases (MMPs),[90,91] and extracellular matrix (ECM).[92]

Cortactin in Invasion-Extracellular Matrix Degradation: Invadopodia and Podosomes

While migration allows for lateral movement, invasion involves degradation of ECM to create space for tumor cell growth and movement. Dynamic changes in the actin cytoskeleton allow for the formation of specialized organelles used in ECM degradation: invadopodia and podosomes.[93,94] Invadopodia are actin-rich protrusions with associated concentrated proteolytic activity found on the basal surface of invasive carcinoma cells. Podosomes are similar structures, that are primarily found in normal cells that need to cross tissue barriers or remodel ECM, such as macrophages and osteoclasts. Although the two structures contain similar molecular machinery and have common functions of ECM degradation and motility,[93,94] recent studies have identified distinguishing features of invadopodia and podosomes, including the importance of Grb2 for podosome but not invadopodia assembly[95-97] and different dynamics of membrane activity between the two structures.[98]

Invadopodia are thought to form in stages, with actin assembly being triggered at basal membrane sites by growth factor and integrin-induced signaling,[97,99,100] followed by stabilization and matrix degradation[97,101] (**Fig. 3**). Cortactin is a key component of both invadopodia and podosomes, and is frequently used as a marker of those structures. Live cell imaging studies of invadopodia have found that cortactin is either recruited simultaneously with[61] or a few minutes before[101] recruitment of the transmembrane metalloproteinase MT1-MMP. Within 1–2 min after MT1-MMP recruitment, ECM degradation occurs, indicating rapid progression through these stages. It is currently unknown whether actin assembly occurs concurrently with or prior to cortactin recruitment.

An early study showed that neutralizing antibodies against cortactin block ECM degradation at invadopodia.[14] Numerous subsequent studies have reported that cortactin regulates both the number and activity of invadopodia and podosomes.[44,61,67,79,90,91,101-105] Mechanistically, there are two major processes by which cortactin is thought to regulate invadopodia: (1) by facilitating actin assembly at invadopodia initiation sites; and (2) by regulating membrane trafficking for the recruitment of ECM-degrading proteinases to invadopodia (**Fig. 3**). A role for cortactin in actin assembly at invadopodia is likely based on its general role in regulating Arp2/3 activity, as well as the potential to provide positive feedback through direct binding to the Arp2/3 activator N-WASp and upstream regulators including the cdc42 GEF, Fgd1 and Nck1.[63,97,106,107] Consistent with that idea, two recent papers demonstrated that cells expressing cortactin molecules with non-phosphorylatable mutations at the Src phosphorylation sites have reduced N-WASp activity, Nck1 recruitment and barbed end polymerization.[44,61] In addition, the phospho-mutant cortactin affected the lifetime of invadopodia, suggesting a role for cortactin in invadopodia maturation.[61]

Membrane trafficking is also a critical contributing process to invadopodia, as its function in ECM degradation relies on delivery of proteinases[94,108] (**Fig. 3**). In fact, "mature" invadopodia are often defined as those associated with ECM degradation.[61,101] Our laboratory identified a specific role for cortactin in regulating the secretion, cell-surface expression and localization to invadopodia of the matrix metalloproteases (MMPs) MT1-MMP, MMP-2 and MMP-9.[90,91] Consequently, the importance of cortactin in protein trafficking likely accounts for the larger defect

in ECM degradation than invadopodia numbers in cells lacking cortactin.[90,91] This statement is supported by the observation that the degradation defect in cortactin-deficient cells could not be overcome by overexpression of MT1-MMP, suggesting a block in secretion when cortactin is absent.[90,109] Similarly, in osteoclast podosomes, loss of cortactin was found to lead to selective inhibition of proteinase recruitment to actin-rich podosomes, and a block in formation of the mature sealing ring.[103] However, this point is controversial, as a previous study found a loss of the actin-rich podosomes themselves.[79]

Interestingly, the impact of cortactin loss on invadopodia, complete block in invadopodia-associated ECM degradation and reduction in invadopodia numbers, is similar to that of MMP inhibition by GM6001, TIMP2 or MT1-MMP siRNA.[91,101,108] At this point it is unclear whether the reduction in invadopodia numbers in cortactin-KD cells is the result of inhibition of actin assembly at invadopodia initiation sites or a decrease in invadopodia lifetime due to abolished positive feedback from ECM degradation. Live cell imaging using markers other than cortactin will be required to answer this question, if indeed these two functions are separable.

Cortactin in Membrane Trafficking

As noted above, one mechanism by which cortactin might regulate motility and invasion is through augmentation of membrane trafficking, via direct effects on actin polymerization and/or bridging membrane trafficking proteins to the actin cytoskeleton (**Figs. 1 and 3**). Generally, actin polymerization is thought to be critical for fission of vesicles, although fusion and tethering functions have also been noted.[110-112] Of note, cortactin and several cortactin binding proteins have been shown to be important for protein trafficking to and from the cell surface. For example, many studies have shown that cortactin regulates both clathrin-dependent and -independent endocytosis.[54,64,113-118] Interaction with SH3 binding partners, such as the Arp2/3 activator N-WASp and the membrane pinchase Dynamin 2, along with the actin cytoskeleton appears to be necessary and is regulated by kinases such as PAK1 and Src.[54,113] Of particular interest for cancer cell motility and invasion, cortactin expression levels were shown to affect ligand-induced internalization and downregulation of EGFR levels in HNSCC cells. Thus, cortactin-overexpressing cancers are likely to have increased EGFR levels via regulation of turnover.[119] However, as with many cortactin phenotypes, some studies have found no effect of cortactin expression changes on endocytosis[69,120] indicating that cellular context (either microenvironmental or cell-type) may dictate whether cortactin is essential for regulation of specific phenotypes.

With regard to exocytosis, fewer studies have been performed. We demonstrated that cortactin regulates the secretion of the gelatinases MMP-2 and MMP-9, MT1-MMP and apolipoprotein A1 from cancer cells. However, it is unknown at this point whether the block in proteinase secretion seen in cortactin-KD cells occurs secondary to defective transport from the Golgi[121] or post-Golgi carriers, or from lack of recruitment of vesicular carriers to invadopodia sites.[122] Both MMP9 and MT1-MMP have been localized to late endocytic/lysosomal compartments[108,123] and trafficking of MT1-MMP to invadopodia depends on the late endocytic v-SNARE VAMP7,[108] suggesting a potential point of regulation. However, at least in glial cells, MMP2 appears to reside in separate vesicles[123] from MMP9 and may therefore derive from a separate compartment. Furthermore, overexpression of cortactin that cannot bind SH3 partners leads to a block in trafficking from the trans-Golgi compartment,[121] suggesting another site where cortactin may be required for MMP trafficking. Finally, cortactin is considered to be an important scaffolding protein in dendritic spines and links to the exocyst protein Sec8/EXOC4 through its binding partner SHANK2 and PSD-95.[124,125] The exocyst complex has been shown to mediate tethering of post-Golgi vesicles to the plasma membrane[126] and regulate both cellular migration and invadopodia formation.[112,127] In addition, the cortactin binding partners N-WASp, Dynamin 2, FGD1 and ASAP1 all regulate both membrane trafficking and invadopodia function,[97,106,107,128,129] and are likely candidates to mediate the effects of cortactin at one or more membrane trafficking compartments (**Table 1**).

Cortactin in Cancer

Much of the interest in cortactin has stemmed from the early finding that the cortactin gene, CTTN, was amplified in HNSCC and breast cancers[130] as part of an amplification of the 11q13.3 region. Subsequently, cortactin overexpression has been found in many cancer types, including melanomas, ovarian, gastric, hepatic, colorectal and esophageal.[25,131-136] In 11q13-amplified cancer cell lines, cortactin expression is increased parallel with gene copy number, indicating that gene copy number and protein expression levels are "coupled."[74] In addition to gene amplification, cortactin expression is increased in many tumors by alternative means,[23,25] although the exact mechanism remains to be determined. The frequent, non-random increase in cortactin expression suggests that it provides a selective advantage to developing or progressing tumors.

Although a number of candidate genes exist in the 11q13 region, including several FGF family members and FADD,[137] cortactin and cyclin D1 have received the most attention. Cyclin D1 is a well known oncogene that is deregulated in many cancers and has been particularly associated with tumorigenesis in breast cancer.[138] Consistent with its role in cell migration and invasion, cortactin overexpression has been associated with tumor aggressiveness, regional and distant metastasis, poor patient prognosis and decreased patient survival. In HNSCC tumors, Rodrigo et al. reported that in the rare cases with independent amplification of cortactin and cyclin D1, cortactin amplification correlated most significantly to decreased patient survival.[24] Subsequent studies confirmed this finding at the protein expression level, finding that cortactin expression in laryngeal cancer predicts disease-specific mortality independent of cyclin D1 and FADD expression.[22,139] Furthermore, cortactin expression in HNSCC was found to predict local recurrence, disease-free survival and overall survival independent of EGFR expression status.[140,141] The fact that EGFR and cortactin expression are independent predictors of disease-free survival suggests that regulation of EGFR

by cortactin[119,142] is not the only mechanism by which cortactin promotes cancer aggressiveness. In other cancers, including hepatic,[25] breast,[143] esophageal,[133] ovarian,[132] melanoma,[136] gastric,[134,135] and colorectal,[131] cortactin expression and/or amplification has also been strongly associated with poor prognosis, often as an independent predictor of disease recurrence.

Experimental studies using mouse models have largely confirmed the prediction that cortactin promotes tumor aggressiveness. Unlike cyclin D1, transgenic expression of cortactin in the mouse mammary gland does not induce hyperplasias or tumors.[144] By contrast, overexpression of cortactin in established human carcinoma cell lines leads to aggressive in vivo behavior for multiple tumor types. In experimental metastasis assays, cortactin overexpression in breast and esophageal squamous carcinoma (ESCC) cells led to enhanced metastasis to the bone and lungs, respectively.[133,145] Likewise, cortactin-overexpression in hepatocellular carcinoma cells led to intrahepatic metastasis from orthotopic injection sites.[146] Using a semiorthotopic tumor model for HNSCC, our laboratory found that cortactin expression regulated invasiveness across a tracheal boundary in vivo and invasive behavior in vitro.[109] In addition to effects on cell motility and invadopodia activity, a mechanism by which cortactin might promote cancer aggressiveness is through regulation of cell-cell adhesions. However, since cortactin appears to promote rather than inhibit cell-cell junction formation and strength,[48,147] inactivation of cortactin may be required for promotion of epithelial-mesenchymal transition.[148]

In addition to regulating invasiveness, we also found that cortactin expression affected the size of HNSCC tumors.[109] For ESCC, but not breast or hepatocellular carcinoma, cortactin was also found to affect tumor size.[133,145,146] We speculate that tumor type or its local microenvironment may dictate whether cortactin only affects invasiveness or also tumor size. Removal of space constraints via proteolytic activity and altered angiogenesis have been postulated as mechanisms for the effects of other invadopodia proteins on tumor size, raising the possibility that cortactin may function similarly.[149,150] Alternatively, cortactin has also been shown to affect anchorage- and serum-independent growth[109,133] and to regulate cell cycle inhibitor levels[88] in squamous carcinoma cells. The mechanism by which cortactin alters these tumorigenic properties is a current area of investigation, but at least for serum independence it appears to be associated with the role that cortactin plays in autocrine secretion.[109] Regardless, it is clear that cortactin expression induces aggressive behavior in multiple cancer types, and in human cancers is a strong and independent prognostic marker of poor outcome. Future studies should focus on a better understanding of the molecular and cellular mechanisms by which cortactin influences tumor growth and metastasis.

Summary

Actin assembly serves a pivotal role in cell migration and invasion. Dynamic branched actin networks, nucleated by the Arp2/3 complex, provide the force for the formation of many cellular protrusions, including lamellipodia and invadopodia. They also serve as platforms for the assembly of signaling and membrane trafficking proteins at sites of vesicle formation and other branched actin-rich structures. The branched actin regulator, cortactin, may be particularly important in the latter process as it links the Arp2/3 complex to a variety of binding partners. Challenges for the future include identification of relevant protein complexes that regulate different cortactin-dependent cellular processes as well as determination of how tissue-specific contexts determine the outcome of cortactin and cortactin-binding partner interactions.

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