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Mini-review

Cortactin in tumor invasiveness

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Abstract

Cortactin is a cytoskeletal protein and src kinase substrate that is frequently overexpressed in cancer. Animal studies suggest that cortactin overexpression increases tumor aggressiveness, possibly through promotion of tumor invasion and metastasis. Recently, many studies have documented a role for cortactin in promoting cell motility and invasion, including a critical role in invadopodia, actin rich-subcellular protrusions associated with degradation of the extracellular matrix by cancer cells. Here, I review the evidence and potential mechanisms for cortactin as a critical mediator of tumor cell invasion.

Keywords: Cortactin; Tumor; Invasion; Migration; Invadopodia

1. Introduction

Cortactin was first identified as one of the major substrates for src kinase [1]. Because it localized to cortical actin structures, it was named cortactin [2]. At that time, little was known about its function, except that it bound to actin filaments, had an SH3 domain, and was phosphorylated in its C-terminus by src kinase [2]. Subsequently, the cortactin gene was found to be identical with Ems1 [3], a gene that is frequently overexpressed in breast and head and neck cancers due to its presence in the 11q13 amplicon [4]. 11q13 amplification has been frequently tied to poor prognosis, including association with higher pathological stage, lymph node and distant metastasis, and decreased survival [5–13]. Although many other genes are present within this amplicon, the consistent overexpression of cortactin in 11q13-amplified tumors along with its ubiquitous presence in cell motility structures, such as lamellipodia and invadopodia [2,3], have generated a great deal of interest in the role of cortactin in tumor invasion.

2. Domain structure and binding partners

Cortactin has four major domains of interest: the N-terminal acidic (NTA) and tandem repeats domains, and the C-terminal proline-rich and SH3 domains (Fig. 1). The N-terminus has generally been thought of as the actin assembly region of the molecule, as binding sites for the Arp2/3 complex and for actin filaments are found in the NTA and repeats domains, respectively (Fig. 1). These binding sites are both necessary and

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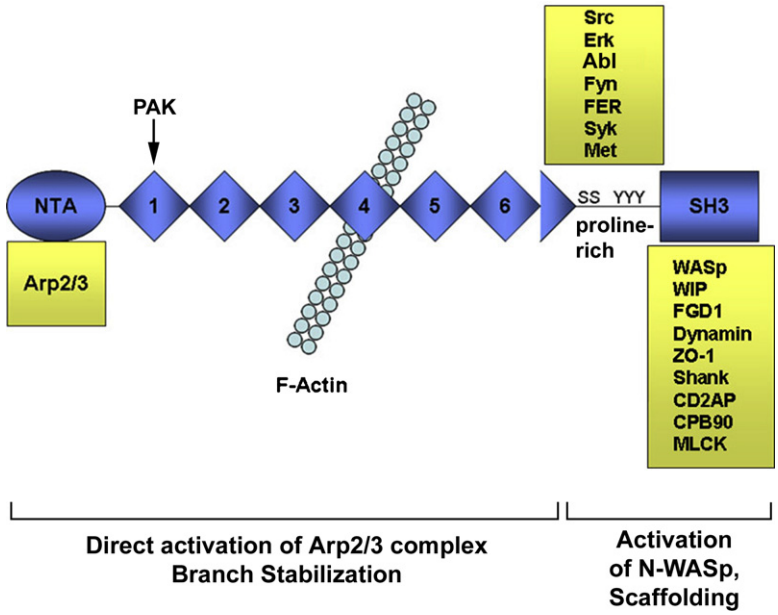

Fig. 1. Cortactin domain structure and binding partners. Cortactin domain structure is depicted in bright blue. Actin filaments (F-actin) are light blue. Cortactin-binding partners are indicated by labeling within the yellow boxes. The N-terminus of cortactin is composed of the N-terminal acidic (NTA) domain and the cortactin repeats (each repeat is represented by a numbered diamond) region. These two domains are notable for binding Arp2/3 complex and F-actin, respectively. The fourth repeat is depicted binding to F-actin, because it is essential for that interaction; however, the other repeat regions contribute to binding affinity [18]. In the C-terminus, the proline-rich region contains well-characterized serine and tyrosine phosphorylation sites. SS indicates the Erk S405 and S418 sites, whereas YYY indicates the Y421, Y466 and Y488 sites that are phosphorylated by src and the other tyrosine kinases indicated in the yellow box. Some of the cytoskeletal, membrane trafficking and signaling proteins that bind to the SH3 domain are indicated in the yellow box below it. Biochemical activities regulated by the N-terminus and C-terminus are indicated at the bottom of the figure. For a full listing of binding partners, see Table 1. Illustration by Emily Clark, Ph.D.

sufficient for direct regulation of Arp2/3-complex-mediated branched actin assembly (see next section) [14,15]. In addition, localization of cortactin to sites of dynamic actin assembly in cells is frequently mediated through the Arp2/3 and F-actin-binding sites [14,16–18], suggesting that cortactin is both a sensor and regulator of branched actin assembly. The C-terminus is generally thought to be the regulatory or signaling end of the molecule, as the proline-rich domain contains phosphorylation sites for a number of kinases and the SH3 domain mediates binding to a variety of other signaling proteins (Table 1). However, many cytoskeletal and membrane trafficking proteins also bind to the SH3 domain of cortactin (Table 1), suggesting a potential scaffold or regulatory role for cortactin in cytoskeletal arrangement and membrane trafficking. Many of these cortactin-binding partners, such as N-WASp, dynamin and WIP, bind each other via separate direct interactions, suggesting that they may function together in large multiprotein complexes.

3. Cortactin as a regulator of branched actin assembly

The role of cortactin in actin assembly remained elusive for almost a decade after its discovery, until it was identified as a binding partner for the Arp2/3 complex through mass spectrometry analysis [18]. The Arp2/3 complex is the molecular machine that nucleates branched actin filament networks in cells [19]. Branched actin provides structural support for the plasma membrane and provides the force for such processes as protrusion of lamellipodia, vesicle trafficking, pathogen motility and formation of cell–cell junctions [19]. Although the critical and strong activators of the Arp2/3 complex are members of the Wiskott–Aldrich Syndrome family of proteins (WASps) [19,20], cortactin promotes weak activation of Arp2/3-mediated branched actin nucleation by enhancing the key step of association of the Arp2/3 complex with the side of mother actin filaments [14,15]. This activity may indirectly enhance WASp-induced nucleation at a variety of