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Integration of signaling and cytoskeletal remodeling by Nck in directional cell migration

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Planar and apical-basal cellular polarization of epithelia and endothelia are crucial during morphogenesis. The establishment of these distinct polarity states and their transitions are regulated by signaling networks that include polarity complexes, Rho GTPases, and phosphoinositides. The spatiotemporal coordination of signaling by these molecules modulates cytoskeletal remodeling and vesicle trafficking to specify membrane domains, a prerequisite for the organization of tissues and organs. Here we present an overview of how activation of the WASp/Arp2/3 pathway of actin remodeling by Nck coordinates directional cell migration and speculate on its role as a signaling integrator in the coordination of cellular processes involved in endothelial cell polarity and vascular lumen formation.

Introduction

Tyrosine phosphorylation is an essential posttranslational modification enabling signaling cascades driving development and disease.[1] The status of tyrosine phosphorylation in metazoan cells is regulated by the interplay between protein tyrosine kinases and protein tyrosine phosphatases. A third, critical component of this signaling system consists of proteins containing the Src Homology 2 (SH2) domain.[2] This modular domain, consisting of about ~100 residues, binds the phosphorylated state of tyrosine and achieves selectivity for phosphopeptides through the specific recognition of the three to five residues C-terminal to the phosphotyrosine.[3] A subset of SH2 domain-containing proteins function exclusively as scaffolds that organize signaling networks by tethering relevant components or altering their subcellular distribution in such a way that facilitates their interaction.[4] A group of adaptor proteins contains, in addition to an SH2 domain, one or multiple copies of SH3 domains but no intrinsic catalytic activity. The SH3 domain is another important protein interaction module, about 60 residues long, that specifically recognizes proline-rich ligands and regulates intramolecular interactions, the local concentration/subcellular distribution of binding partners, and the assembly of multiprotein complexes.[5] The SH2/SH3 domain-containing adaptors, represented by Grb2, and the Crk and Nck (non-catalytic region of tyrosine kinase) families,[6] play critical roles in developmental programs and disease. Whereas all of these adaptors are involved in signaling to the cytoskeleton, here we focus on modulation of actin dynamics by Nck and briefly review recently discovered and emerging roles of this family in cellular migration and membrane trafficking.

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Nck Linking Tyrosine Phosphorylation with Localized Actin Polymerization

The Nck family of SH2/SH3 domain-containing adaptors, consisting of Nck1/α and Nck2/β (herein referred to as Nck),[7,8] is required during development[9] and involved in cytoskeletal remodeling underlying pathogen-host cell interactions,[10-13] T-cell receptor activation,[14] invadopodia formation,[15,16] cell adhesion and motility,[17-22] and intercellular junction organization in kidney podocytes.[23,24] The two protein isoforms share an overall ~68% amino acid identity[25] and their SH2 domains engage a common set of phosphopeptides with equivalent binding affinity.[26] Although Nck1 and Nck2 are believed to have mostly overlapping functions,[9] non-compensating roles depending on specific cellular and signaling contexts have been suggested.[20,27,28]

In addition to determining the architectural organization and morphology of cells, actin filaments (F-actin) provide support and protrusive force to the various structures involved in locomotion.[29,30] Recognized among the critical players in F-actin assembly, the Arp2/3 complex[30,31] binds preexisting filaments and directs nucleation of a branched actin network.[32-36] The activity of the Arp2/3 complex is intrinsically weak, and therefore, its full activation is dependent on the presence of nucleation promoting factors.[37,38] Type I nucleation promoting factors, typically represented by the WASp and WAVE protein families,[39] contain a conserved VCA (verprolin-homology, cofilin-homology, and acidic domain) region that engages both monomeric actin and the Arp2/3 complex.[38,40] Evidence from early studies suggested a model whereby Nck would promote Arp2/3-dependent actin polymerization through dissociation of the WAVE complex.[41] This model has been revised and it is now appreciated that full activation of WAVE does not involve complex disruption but requires the presence of coincident signals.[42] Notably, a pathway involving Nck-dependent recruitment/activation of the WAVE complex is involved in localized actin polymerization during pathogen-induced phagocytosis.[43] In addition, Nck is recruited

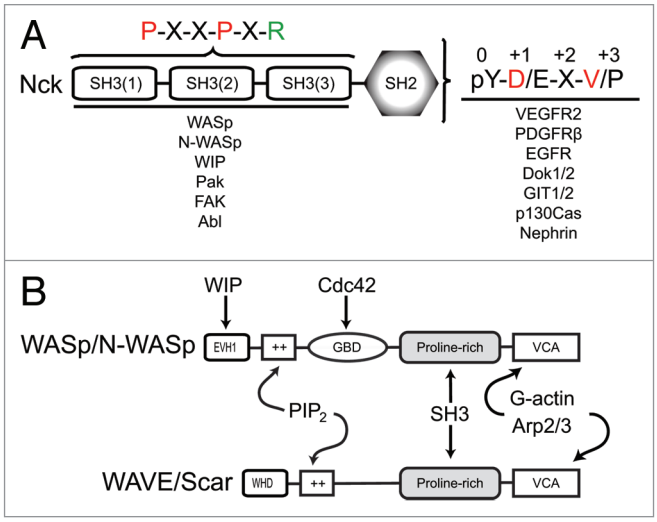

Figure 1. Representation of the structural domains of Nck, WASp/WAVE proteins and their critical interactions. (**A**) Nck consists of three N-terminal SH3 domains and a C-terminal SH2 domain. The consensus sequence of peptides found in proteins that bind Nck via SH2- or SH3-mediated interactions and well characterized Nck binding partners are shown. (**B**) Members of the WASP/WAVE families of nucleation promoting factors consist of a conserved C-terminus that enables interactions with G-actin and the Arp2/3 complex (VCA) and SH3 domains (proline-rich). Members from both families possess a polybasic motif (++) that mediates interaction/regulation by phosphoinositides. In cells, WASp proteins form a complex with WASp-interacting protein (WIP) whereas WAVE/Scar proteins are found as a complex that also includes Pir 121, Nap 1, Abi-1, and HSP300 (not shown).

to phagocytic cups and cooperates with Cdc42 in N-WASp activation downstream of Fcγ receptor clustering.[44]

WASp proteins act as integrators and coincidence detectors of signals from Rho GTPases, SH2/SH3 domain-containing adaptors, and phosphatidylinositol 4,5-bisphosphate (PtdIns(4,5)P_2).[37,45] Members of the WASp family are activated through relief of autoinhibition by a mechanism that involves allosteric regulation and oligomerization.[39] Pioneer studies showed that pathogens, including vaccinia virus[10,46] and enteropathogenic *E. coli*,[13] recruit Nck to promote localized, N-WASp/Arp2/3-stimulated actin polymerization. Clustering of Nck by a phosphopeptide from Tir, an Enteropathogenic *E. coli* effector protein, triggers actin tail formation in *Xenopus* egg extracts.[12] In living cells, an increased local concentration of membrane-targeted Nck SH3 domains leads to the formation of actin comets.[47] We showed that N-WASP recruitment/activation at the plasma membrane is elicited by a reciprocal interdependence between Nck and PtdIns(4,5)P_2.[48] Importantly, experimental evidence from our laboratory suggests that Nck provides a functional link between tyrosine phosphorylation and phosphoinositides in the activation of N-WASp.[48]

Recent studies also showed that Nck binding to WASp interacting protein (WIP) is essential for the recruitment of the WIP:N-WASp complex and full activation of localized actin polymerization.[49,50] Notably, using a combination of quantitative experimentation and computational simulations Mayer et al.[49] showed that the presence of WIP and the density of Nck molecules are crucial in activation of localized actin polymerization. Furthermore, their findings provide strong support for a model in which the Nck/N-WASP/Arp2–3 stoichiometry is 4:2:1.[49] Although research over the last decade has established Nck as a central player in the regulation of localized actin polymerization by the Arp2/3 complex, important questions remain unanswered: What is the identity and regulation of the protein complex recruited by Nck that bridges phosphotyrosine and phosphoinositides signaling? How is the WIP:N-WASp complex activated upon recruitment by Nck? What critical cellular processes are regulated and integrated by this important cytoskeletal pathway? We anticipate that future research combining proteomics, superresolution microscopy, and computational biology will bring about exciting new discoveries on Nck-dependent regulation of cytoskeletal remodeling. A representation of structural organization and major interactions of Nck and WASp/WAVE proteins are shown in **Figure 1**.

Spatiotemporal Coordination of Signaling During Directional Cell Migration by Nck

Directional cell migration involves the establishment of a front-rear axis of polarity, successive cycles of membrane protrusion, adhesion to the substratum, forward propulsion of the cell body, and disengagement of the trailing edge.[51] Morphological changes and asymmetric distribution of organelles, signaling and structural molecules underlie directional migration. For example, formation of new protrusions occurs at the cell front or lamellipodial edge whereas extension of lateral protrusion is limited during directional migration.[51] Similarly, signaling molecules including Rho GTPases, phosphoinositides, and polarity complexes are more abundantly localized and activated at the leading edge of crawling cells.[52] Endothelial cells exhibit planar polarity during migration and, therefore, the transition from apical-basal to planar polarity[52] is one of the initial, important processes in sprouting angiogenesis.[53]

As in the case of apical-basal polarity, regulation of front-rear polarity is dependent on the modulation of cytoskeletal remodeling and vesicle trafficking by proteins of the polarity complexes, including Crumbs, Par, and Scribble,[52,54] which are known downstream effectors of Rho GTPases. Using a combination of molecular genetics and quantitative live cell microscopy we showed that Nck is essential in the establishment of front-back polarity and directional migration of endothelial cells.[55] Our study uncovered new mechanistic insights whereby Nck integrates signaling by tyrosine phosphorylation with precise spatiotemporal activation of the Rho GTPases in the coordination of cytoskeletal dynamics. The loss of planar cell polarity caused by silencing of Nck was accompanied by the formation of simultaneous, multidirectional protrusions linked to mislocalized activation of Cdc42 and Rac. In addition, the activity of RhoA and myosin II phosphorylation were reduced in Nck-depleted endothelial cells. These exciting findings stimulate new hypotheses and will prompt further research to address outstanding questions: How does Nck contribute to regulation of the spatiotemporal activation of Rho GTPases? Does Nck modulate the distribution/activation of guanine nucleotide-exchange factors (GEF) or GTPase

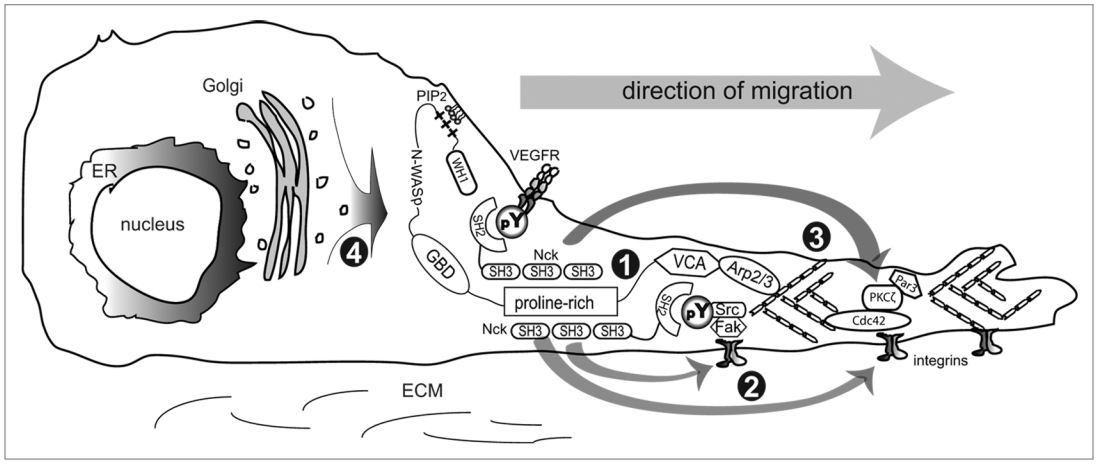

Figure 2. Cartoon highlighting known functions and hypothetical roles of Nck in the regulation of planar cell polarity and directional migration. (1) Nck stimulates Arp2/3-dependent polymerization of branched actin networks through activation of WASp/WAVE proteins, particularly at the leading edge/lamellipodium. (2) Nck links signaling by tyrosine phosphorylation induced by ligand-activated growth factor receptors and integrins with the cytoskeleton. Nck contributes to directional migration through the spatiotemporal regulation of Rho GTPases (only Cdc42 is represented) and stabilization of newly formed protrusions at the leading edge by strengthening cell-matrix adhesions. (3) Nck may play an indirect role in the differential distribution/activation of polarity complexes (only Par3/PKCζ is represented) at the leading edge through modulation of Rho GTPases. (4) Nck may also contribute to cell polarity through modulation of vesicular/membrane trafficking. The involvement of Nck in processes highlighted in 1 and 2 is supported by experimental data. The role of Nck in processes depicted in 3 and 4 remains speculative.

activating proteins (GAP)? Is the subcellular distribution and activity of the polarity complexes dysregulated by abrogation of Nck signaling? Below, we speculate on signaling mechanisms potentially modulated by Nck. A cartoon highlighting known functions and hypothetical roles of Nck in the regulation of cell polarity and directional migration are shown in **Figure 2**.

Modulation of the Subcellular Distribution/Activation of Rho GTPases and Polarity Complexes

Accumulating evidence suggests that myosin II contractility mediates the establishment of polarity in migrating cells by a mechanism that limits lateral protrusiveness through local depletion of β-Pix, a Cdc42/Rac GEF, and decreased Rac activation.[56,57] Inhibition/depletion of p21 GTPase-activated kinase (Pak), an important cytoskeletal effector downstream of the small GTPases Rac and Cdc42,[58] dislodges myosin IIA from the cell's edge and decreases adhesion maturation.[59] Nck directs the recruitment of Pak to the plasma membrane[60,61] and modulates VEGF-stimulated endothelial cell migration through a cellular mechanism that involves regulation of adhesion assembly.[62] Notably, the polarity protein Scribble interacts with integrin α5 and is required for endothelial polarization and directional migration.[63] Because Scribble forms a complex with β-Pix and its binding partner GIT[64] we speculate that the complex Nck-Pak-β-Pix-GIT,[65-67] known to be recruited to focal adhesions, contributes to the localization of Scribble to newly formed adhesions at the cell front. Conceivably, alternative mechanisms may involve the selective recruitment of GTPase activating proteins that spatially restrict the activation of Rac/Cdc42, as recently shown for SH3BP1, an exocysts interaction partner that facilitates the cycling of Rac between inactive/active states to enable the formation/stabilization of protrusion at the leading edge of migrating cells.[68]

Seminal studies by Hall et al.[69] showed that the wounding of a confluent monolayer of astrocytes induces polarized organelle distribution and protrusive activity of cells at the edge of the wound. These changes in morphology and architectural organization of cells are orchestrated by the polarized activation of Cdc42 and its downstream effector the polarity complex Par6/PKCζ.[69] During angiogenic sprouting elicited by angiopoitin-1, which induces collective and directional migration of endothelial cells, a signaling complex that includes β-catenin and Par3/Par6/PKCζ is recruited to the cell front to coordinate localized activation of Rac by Tiam1, a Rac-specific GEF.[70] Interestingly, this complex is also functional in adherens junctions where it might promote stabilization of cell-cell contacts.[70] Consistent with this notion, a recent study demonstrated full activation of the VEGFR at the sprout tip but not in the stalk cells in which inactivation the VEGFR is mediated by Tie2-dependent targeting of vascular endothelia phosphotyrosine phosphatase (VE-PTP) to cell-cell junctions.[71] Using a Cdc42 intramolecular Förster resonance energy transfer biosensor[72] we determined polarized activation of Cdc42 in control endothelial cells undergoing directional migration but not in unpolarized, Nck-depleted cells.[55] It has been reported that Nck binds directly to phosphorylated Tyr^{1214} within the activated VEGFR[73] and phosphorylated Tyr^{351} within Dok-R/Dok2,[74-76] an adaptor protein recruited to the activated Tek/Tie2 receptor. Furthermore, the Dok-R/Nck complex recruits and activates Pak at the cell membrane to drive angiopoietin-1 directed cell migration.[75] Collectively, these findings suggest that further research is needed to address important questions: Does Nck play a differential role in migration of sprout tip vs. stalk endothelial cells through the engagement of VEGFR vis-à-vis Tek/Tie2? Is the

activity of the Par3/Par6/PKCζ complex modulated by Nck? Research aimed at understanding the role of Nck in regulation of the subcellular localization and activity of polarity complexes is ongoing in our laboratory.

Powering Directional Migration through Ca^{2+} Flickers

An emerging concept in the field is that directionality of cell migration is also modulated by localized Ca^{2+} transients.[77] Persistent migration of endothelial cells depends on the spatiotemporal coordination of the activation of polarity protein complexes downstream of receptor tyrosine kinases[70,78] and integrins.[63] Elegant studies by Cheng et al.[79] showed that Ca^{2+} flickers occur more frequently at the leading edge of migrating cells and redirect cell polarization in response to a chemoattractant. Recent studies suggest that localized Ca^{2+} transients regulate critical processes during cell migration, including membrane protrusion, adhesion strength,[80] and focal adhesion dynamics.[81-85] What are the molecular mechanisms underlying the crosstalk between tyrosine phosphorylation and Ca^{2+} signaling during directional migration? Potential mechanisms of signaling integration are outlined below.

It is know that activation of tyrosine phosphorylation through integrins[86] and VEGFR[87] elicits Ca^{2+} transients in endothelial cells. Store-operated Ca^{2+} entry (SOCE) is a major Ca^{2+} regulatory pathway in non-excitable cells[88-90] and, importantly, its molecular components are involved in regulation of Rho-dependent cytoskeletal tension.[91,92] Ligand-activated VEGFR recruits phospholipase Cγ (PLCγ),[93] an enzyme that hydrolyzes PtdIns(4,5)P_2 to generate diacylglycerol and inositol-1,4,5-triphosphate (Ins(1,4,5)P_3). Increased cytosolic levels of Ins(1,4,5)P_3 stimulate endoplasmic reticulum Ins(1,4,5)P_3 receptors and SOCE.[88] Notably, Src-dependent phosphorylation of PLCγ plays a key role in stimulation of Ca^{2+} mobilization.[94] Silencing of the endoplasmic reticulum stromal interaction molecule 1 (STIM1), a critical component of SOCE,[90] abrogates VEGF-stimulated Ca^{2+} mobilization and cell migration.[87] Unpublished data from our laboratory show that silencing of Nck leads to a significant decrease in VEGF-induced Ca^{2+} transients in endothelial cells. Consistent with these findings, Nck depletion was shown to decrease Ca^{2+} mobilization in T-cells.[95] Importantly, the Nck binding partner GIT1 forms a complex with PLCγ and is required for Src-dependent activation of PLCγ, Ins(1,4,5)P_3 production and Ca^{2+} mobilization downstream of receptor tyrosine kinase and G protein-coupled receptor activation.[94] It is tempting to speculate that Nck regulates directional migration of endothelial cells during sprouting angiogenesis through modulation of SOCE and the generation of polarized Ca^{2+} flickers.

Vesicle Trafficking, Cell Polarity and Beyond: Is Nck Involved in Vascular Lumen Formation?

Three basic mechanisms have been proposed for lumen formation in tubular organs and networks, namely cavitation, hollowing, and focalized contact/membrane repulsion.[54,96] The establishment of apical-basal polarity is an absolute requirement for normal vascular lumen organization.[97] Although evidence for vascular lumen formation through cavitation is lacking, there is substantial support for lumenization of endothelial cords through hollowing[98] or focalized contact/membrane repulsion,[99] processes that may not be mutually exclusive. Regardless, the differentiation of apical vs. basolateral membrane domains entails coordination between the cytoskeleton and the membrane trafficking machinery.

Basic cellular mechanisms involving the establishment of cell-matrix contacts and cell-cell recognition are essential for symmetry breaking. These interactions provide essential spatial cues for the differentiation of membrane domains. Thus, the apical surface forms through the selective trafficking and delivery/fusion of vesicles containing apical proteins and lipids, particularly polarity complexes and phosphoinositides.[96] Vascular endothelial cadherin (VE-cadherin)-mediated cell-cell contacts are involved in apical-basal polarization of endothelial cells and vascular lumen formation through the recruitment of Par3/PKCζ to adherens junctions.[100] In humans, the stroke-predisposing disease cerebral cavernous malformation is characterized by vascular malformation and fragility caused by mutations in genes encoding the CCM protein family. CCM interacts with VE-cadherin and facilitates the assembly of cell-cell junctions and the recruitment of the polarity complex Par3/PKCζ.[100] Abnormalities in the vasculature in this disease arise from disorganization of adherens junctions, loss of cell polarity and altered lumenization.[100] Lumen formation also involves VE-cadherin-dependent vesicular trafficking of the sialomucin podocalyxin (PODXL), and anti-adhesive transmembrane protein, to areas of contact between adjacent endothelial cells.[99] Unpublished data from our laboratory show that control and Nck-rescued, but not Nck-depleted endothelial cells, developed a robust, well interconnected network of cords on Matrigel and tubes in collagen three-dimensional matrices. In addition, our findings suggest that Nck silencing reduces apical surface localization of PODXL which appears to remain trapped in cytoplasmic vesicles. These findings point to abnormal trafficking of PODXL to the apical surface and incomplete polarization as the underpinnings of impaired tubulogenesis observed in Nck-depleted cells.

Lumen formation in endothelial cells cultured in three-dimensional environments depends on the polarity complex Par and involves reciprocity between Cdc42 signaling and MT1-MMP proteolysis.[101] Notably, Nck silencing in a variety of tumor cells has been associated with decreased invasiveness and matrix degradation in vitro.[15,16,102,103] Nck interacts with phosphorylated cortactin,[15,104] an F-actin binding protein involved in regulation of tumor cell invasion and proteolysis of extracellular matrix components.[103,105-108] Our recently published studies show that Nck modulates the polarized activation of Cdc42 in migrating cells.[55] In addition, faciogenital dysplasia protein 1 (FGD1), a cortactin binding partner[109] and Cdc42 GEF involved in post-Golgi cargo trafficking,[110] has been implicated in invadopodia biogenesis and regulation of extracellular matrix remodeling.[111,112] Whether the cortactin/Nck signaling axis modulates the Cdc42/MT1-MMP reciprocity during vascular morphogenesis remains an unanswered question.

Concluding Remarks

We have highlighted the functional versatility of Nck adaptors in cellular processes requiring localized actin polymerization. Over the last decade we have gained a functional understanding of how Nck modulates localized actin polymerization through activation of the WAVE/WASp/Arp2/3 complex. Essential aspects including molecular composition, stoichiometry, and critical interactions among complex components have been elucidated. In addition, novel functions of this major pathway of actin remodeling in various cellular processes are becoming apparent. Recent findings underscore an emerging role for Nck in cellular adhesion and polarization, processes intimately involved in morphogenesis. Combination of advanced imaging, proteomics, and computational modeling/simulation will enable the testing of new hypotheses to uncover a cohesive picture of signaling integration by Nck in the coordination of cytoskeletal remodeling during development and disease.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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