JCB Mini-Review

Regulation of nucleocytoplasmic trafficking by cell adhesion receptors and the cytoskeleton

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It has become widely accepted that adhesion receptors can either directly activate, or significantly modulate, many of the signaling cascades initiated by circulating growth factors. An interesting recent development is the realization that adhesion receptors and their cytoskeletal partners can regulate the trafficking of signaling proteins between the cytoplasm and nucleus. Cell adhesion molecule control of nucleocytoplasmic trafficking allows adhesion to influence many cell decisions, and highlights the diversity of nuclear import and export mechanisms.

Introduction

Compartmentalization within mammalian cells offers a control mechanism over the elaborate array of signaling networks. Trafficking of signaling molecules between the cytoplasmic and nuclear compartments has important implications for the magnitude and specificity of gene expression. Adhesion, either to the extracellular matrix or between cells, strongly influences signaling events that have dramatic implications for the fate of the cell. An emerging theme is that cell adhesion molecules (CAMs)* elicit many of their actions through spatial control of signaling proteins. Although it is well known that a variety of structural, adaptor, and signaling molecules are localized to adhesion sites (Calderwood et al., 2000), recent studies have illustrated CAM-regulated localization of signaling molecules to membrane sites, mitochondria, and the nucleus, the latter being the focus of this mini-review.

Movement of macromolecules between the cytoplasmic and nuclear compartments is primarily mediated by the nuclear pore complex (NPC), importin/exportin family members, and Ran GTPase (Gorlich and Kutay, 1999). In the classical uptake pathway, importin-α recognizes a nuclear localization sequence (NLS), typically a series of basic residues within the cargo protein and complexes with importin-β. The latter protein docks and promotes translocation of the cargo-containing complex through the NPC. Once in the nucleus, the cargo is dissociated from the importin carriers by the action of GTP-loaded Ran. High levels of GTP-bound Ran in the nucleus and GDP-bound Ran in the cytoplasm are maintained by the selective localization of Ran guanine nucleotide exchange factors and Ran GTPase–activating proteins to the nucleus and cytoplasm, respectively. Alternatively, during export from the nucleus, exportin molecules such as chromosomal region maintenance protein (CRM)1 that recognize leucine-rich nuclear export signals form a complex with Ran-GTP and mediate transport to the cytoplasm. Thus, Ran maintains the directionality of nucleocytoplasmic trafficking. Although the majority of trafficking is Ran dependent, divergent mechanisms exist for both import and export due to the multiplicity of transport factors.

Recruitment into importin or exportin complexes before transport is influenced by anchor proteins in each compartment that mask transport signals within the signaling molecule (Cyert, 2001). Exclusion from the nucleus is often regulated by CAMs, as many transcription factor coactivators either bind directly to the CAM or localize to specialized adhesion sites. Alternatively, through alterations in the actin cytoskeleton, CAMs modify nuclear accumulation of cytoplasmic signaling molecules that are activated in response to growth factor stimuli. Adhesion has also been shown to regulate nuclear export of proteins such as c-Abl. In all scenarios, a common theme is that CAMs may regulate nucleocytoplasmic trafficking of signaling molecules, possibly by altering their interactions with anchoring proteins in nuclear and cytoplasmic compartments (Fig. 1).

Regulation of transcriptional proteins that interact with directly with CAMs

An exciting new dimension to adhesion receptor signaling has developed recently, based on direct connections identified between adhesion receptor cytoplasmic domains and proteins that are, or that regulate, transcription factors. The

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*Abbreviations used in this paper: APC, adenomatous polyposis coli; CAM, cell adhesion molecule; CRM, chromosomal region maintenance protein; ERK, extracellular signal-regulated kinase; JAB, Jun activation domain binding protein; LEF, lymphocyte-enhancer binding factor; LFA, lymphocyte function–associated antigen; LIM, Lin-11, Isl-1, and Mec-3; NLS, nuclear localization sequence; NPC, nuclear pore complex; SRF, serum response factor; ZO, zonula occludens.

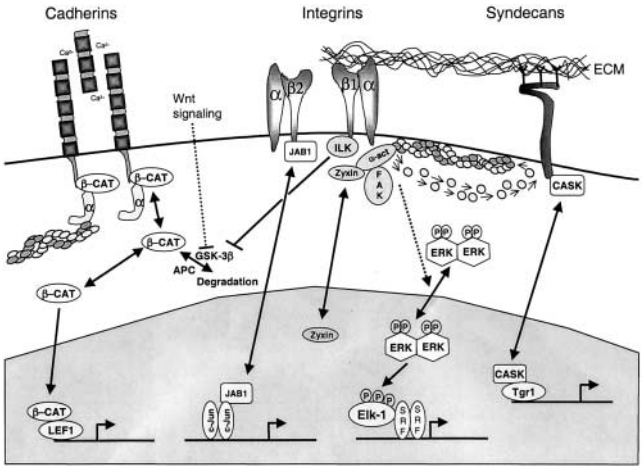

Figure 1. **Adhesion regulation of nucleocytoplasmic trafficking of signaling molecules.** CAMs regulate the nucleocytoplasmic trafficking by several mechanisms. Firstly, cadherins, β2 integrins, and syndecans directly act as cytoplasmic anchors for β-catenin, JAB1, and CASK, respectively. Nuclear accumulation of β-catenin may also be regulated by the integrin-linked kinase pathway. In the nucleus, β-catenin interacts with the TCF family member LEF-1 to regulate expression of genes, such as c-Myc and cyclin D1. JAB1 interacts with c-Jun containing AP-1 complexes, and enhances transactivation from AP-1–dependent promoters. CASK binds DNA in a complex with Tbr-1 to induce transcription of genes important in cerebrocortical development. Second, protein complexes associated with sites of adhesion act as sinks for a variety of proteins, for example zyxin, that contain LIM domains and traffic to the nucleus. Additionally, integrin-mediated adhesion and an intact actin cytoskeleton are important in controlling efficient ERK nucleocytoplasmic trafficking and phosphorylation of downstream transcription factors.

theme of transmembrane receptors directly acting on transcriptional regulators is a familiar one in the transforming growth factor β receptor/Smad, Jak/Stat, and Notch signaling fields, but until recently evidence for similar mechanisms among CAMs had been lacking.

The first reported example concerns calreticulin, a calcium-binding protein that binds to the conserved GFFKR sequence found in integrin-α cytoplasmic tails and that inhibits gene transcription mediated by steroid superfamily receptors, possibly by acting as a nuclear exporter distinct from CRM1 (Dedhar et al., 1994; Holaska et al., 2001). Thus, calreticulin could potentially shuttle between integrin adhesion sites on the cell membrane and the cell nucleus and regulate key events at both sites. An even more direct relationship between integrins and transcription has emerged in connection with lymphocyte function–associated antigen (LFA)-1, a β2 family integrin. A two-hybrid screen identified Jun activation domain binding protein (JAB)-1 as a protein that binds to the β2 cytoplasmic domain (Bianchi et al., 2000). JAB1 is also a known coactivator of the c-Jun transcription factor, and localizes both in the nucleus and at the cell membrane. LFA-1 engagement is accompanied by an increase in the nuclear pool of JAB1 and by enhanced activation of an AP-1–driven promoter. These studies demonstrate that JAB1 seems to directly convey information from ligated LFA-1 to control of gene expression in the nucleus.

Similarly, other reports have established direct linkages between transcriptional regulators and CAMs found at cell–cell junctions. CASK/LIN-2 is a membrane-associated guanylate kinase family member containing multiple protein binding domains. In rat brain, CASK is located both at synapses, where it binds to the transmembrane proteins neurexin and syndecan, and in the nucleus interacting with the Tbr-1 transcription factor. Localization of CASK is dependent on the relative levels of these cytoplasmic and nuclear anchors. High levels of Tbr-1 recruit CASK to the nucleus and trigger transcription of genes, including reelin, that are required for cerebrocortical development (Hsueh et al., 2000). In contrast, syndecan 3 acts as the transmembrane anchor and can shift the balance of CASK towards the cytoplasmic pool.

Some of the most compelling evidence for adhesion-associated molecules doubling as transcriptional regulators comes from studies on β-catenin. Compartmentalization of β-catenin is essential for it to fulfill its diverse roles (Ben-Ze'ev et al., 2000). β-Catenin interacts with E-cadherin at cell–cell contacts, with adenomatous polyposis coli (APC) and axin in the cytoplasm, and with lymphocyte-enhancer binding factor (LEF)-1/T cell factor in the nucleus. The transcriptional potential of β-catenin is enhanced upon activation of the Wnt signaling pathway through inhibition of APC/axin/glycogen synthase kinase 3β–mediated degradation of β-catenin. Hence, β-catenin accumulates in the cytoplasm and translocates to the nucleus where it acts in concert with LEF-1 to mediate gene transcription. Axin acts as a cytoplasmic anchor for β-catenin, as overexpression of axin in *Drosophila* germline clones titrates the β-catenin homologue, armadillo, out from the nucleus (Tolwinski and Wieschaus, 2001). Additionally, N-cadherin, E-cadherin, and α-catenin may all act to anchor β-catenin at cell–cell contacts, suppressing its transactivation potential, an effect that is dependent on expression levels rather than homophilic CAM interactions (Sadot et al., 1998; Simcha et al., 1998; Gottardi et al., 2001). The ramifications in vivo during development are that high cadherin levels decrease β-catenin signaling during dorsal axis formation (Fagotto et al., 1996). Furthermore, downregulation of E-cadherin levels is associated with an increase in motility and invasion of malignant epithelial cells. Integrins may feed into this pathway, as increased activity of the integrin-linked kinase promotes nuclear accumulation of β-catenin and mesenchymal transformation in mammary epithelial cells (Novak et al., 1998; Somasiri et al., 2001), raising the notion of cross-talk between integrin and cadherin signaling pathways.

Most evidence points towards importin-independent uptake of β-catenin into the nucleus. β-Catenin lacks a classical NLS, but may directly bind to the NPC via triple α-helix armadillo repeats, akin to those found in importins (Fagotto et al., 1998). Export of β-catenin is more complex, with support for both CRM1-dependent (mediated by APC, which also shuttles between compartments) and CRM1-independent export (Henderson, 2000; Wiechens and Fagotto, 2001). It is clear that LEF-1 and other molecules act as nuclear anchors by sequestering β-catenin in the nucleus (Simcha et al., 1998). Thus, nuclear APC competes with LEF-1 for overlapping binding sites in β-catenin and downregulates β-catenin signaling (Neufeld et al., 2000).

In summary, direct linkages exist between different CAMs and several transcriptional regulators. Often, the nucleocyto-

plasmic trafficking mechanisms used do not follow the "classical" pathway. Hence, understanding the mechanisms used by these signaling molecules will be an important area of future investigation.

Proteins found primarily at sites of adhesion that are capable of shuttling to the nucleus and regulating transcription

Specialized cell adhesion sites not only provide an architectural role in organizing cell structure and polarity, but also are dynamic units that may communicate through the nuclear trafficking capability of several adhesion-associated proteins. Hic5, a paxillin-related focal contact protein, can interact with the glucocorticoid receptor transactivation domain, and serves as a coactivator for this transcription factor (Thomas et al., 1999; Yang et al., 2000). Paxillin itself has a putative nuclear export sequence (LSELDRLLL) and may be able to traffic in and out of the nucleus (Thomas et al., 1999). Further examples are zyxin, lipoma preferred partner, and thyroid receptor interacting protein-6, all of which are predominantly localized to focal contacts but additionally shuttle to the nucleus (Wang et al., 1999; Petit et al., 2000; Nix et al., 2001). A common feature among this group is the presence of numerous Lin-11, Isl-1, and Mec-3 (LIM) domains, double zinc finger motifs that participate in protein–protein interactions. In zyxin and paxillin, the LIM domains are required for stable incorporation into focal adhesions (Nix et al., 2001). Hence, an interesting concept is that LIM domain–containing proteins may relay information from adhesion sites to the nucleus. The dual localization of many members of this class of proteins has been revealed by the identification of leucine-based nuclear export sequences and their utilization of the CRM1 export factor. Additionally, the focal adhesion protein, Cas-interacting zinc finger protein, also holds the ability to translocate to the nucleus where it regulates expression of matrix metalloproteinases (Nakamoto et al., 2000).

The notion of proteins shuttling from adhesion sites to the nucleus can also be broadened to include cell–cell junction proteins. The zyxin-related protein ajuba is found at cell–cell contacts, but can relocate to the nucleus upon inhibition of CRM1 activity or retinoic acid treatment. Nuclear entry is dependent on its LIM domains and results in differentiation of P19 embryonal cells (Kanungo et al., 2000). The membrane-associated guanylate kinase homologue, zonula occludens (ZO)-1, also moves between cell–cell contacts where it binds α-catenin and the nucleus in a cell density–dependent manner (Gottardi et al., 1996). In epithelial cells, nuclear ZO-1 interacts with a Y-box transcription factor and regulates expression of ErbB-2 in concert. Hence, nuclear ZO-1 may impact on epithelial differentiation and morphogeneis (Balda and Matter, 2000). Other proteins found at cell–cell contacts also have the potential to regulate transcription, including p120catenin, which partners the transcription factor Kaiso in the nucleus (Daniel and Reynolds, 1999). Also included are the p120catenin-related protein, the armadillo repeat gene deleted in Velo-cardio-facial syndrome (Mariner et al., 2000), and huASH1, a human homologue of a *Drosophila* protein that is a member of the trithorax group of transcriptional regulators of homeotic genes (Nakamura et al., 2000).

Clearly, numerous proteins found in adhesion sites are able to relocalize to the nucleus. It is possible that their incorporation into adhesion sites masks their accessibility to nuclear import factors. Whether turnover of adhesion sites regulates the localization and transcriptional potential of these proteins is intriguing. In many cases, the functional roles of these proteins in the nucleus remain unresolved; however, the very direct connections between the partners of CAMs and functional transcriptional regulators obviously represent a powerful channel for communicating information from the extracellular environment to the nucleus.

Adhesion and cytoskeletal modulation of nucleocytoplasmic trafficking of signaling proteins

Aside from proteins intimately associated with adhesion sites, engagement of CAMs and the subsequent formation of specialized F-actin structures also influence cytoplasmic pools of signaling molecules to ultimately regulate transcriptional events. In the Ras/extracellular signal-regulated kinase (ERK) pathway, ERK is sequestered in the cytoplasm through interactions with its upstream activator, mitogen-activated protein/ERK kinase, and with the phosphatases, PTP-SL and MKP-3 (Cyert, 2001). Upon activation, ERK is released from mitogen-activated protein/ERK kinase and homodimerizes before being imported into the nucleus (Cobb and Goldsmith, 2000). Normally, efficient activation of the Ras/Erk pathway is highly dependent on integrin-mediated cell anchorage (Howe et al., 1998). However, under conditions that ERK activation is forced in suspension, ERK accumulation in the nucleus remains anchorage dependent and requires an intact actin cytoskeleton (Danilkovitch et al., 2000; Aplin et al., 2001). Furthermore, the ability of active ERK to phosphorylate Elk-1 and enhance Elk-1 transcriptional potential is impaired in suspended fibroblasts. Together, these data suggest that adhesion regulates the ERK cascade at the level of both activation and nuclear accumulation (Aplin et al., 2001). One hypothesis here is that adhesion regulates the release of ERK from its cytoplasmic binding partners and/or homodimerization through an actin-organized scaffold. Interestingly, the ability of active JNK to phosphorylate nuclear transcription factors is not impaired in suspended cells (unpublished data).

ERK does not contain a classical NLS and its import factors are unknown, although trafficking occurs via Ran-dependent pathways (Cyert, 2001). Active ERK can be detected within nascent adhesion sites and laemellipodia (Fincham et al., 2000), raising the possibility of a direct line of communication from integrin adhesion sites to the nucleus. Control of ERK nucleocytoplasmic trafficking by integrins and the cytoskeleton is relevant to the adhesion requirement for cell cycle progression, and to prevent anoikis, a form of apoptosis that occurs when cells lose interactions with the ECM. Additionally, a feature of transformed cells is the disruption of the actin cytoskeleton that correlates with anchorage-independent proliferation. Thus, actin-dependent ERK nucleocytoplasmic trafficking may be a control mechanism that is overcome in cancerous cells, allowing proliferation in the absence of their normal extracellular environment.

An interesting converse example concerns the CRM1-dependent nuclear export of the tyrosine kinase c-Abl; this kinase is transiently activated when suspended fibroblasts are readhered to fibronectin (Lewis et al., 1996; Taagepera et al., 1998). c-Abl is able to associate with F-actin (Woodring et al., 2001) and is also found in nascent focal complexes, likely in complex with paxillin or Crk and $p130^{CAS}$ (Lewis et al., 1996). The interaction between c-Abl and F-actin has a negative effect on c-Abl kinase activity, and activity is enhanced in detached cells (Woodring et al., 2001) although the localization in a Crk–Cas complex may play a role in focal complex formation (Taagepera et al., 1998). This highlights a potential level of interplay that may exist between the actin cytoskeleton, focal complexes, and signaling molecules.

As an alternative to F-actin creating a scaffold for efficient signaling, an exciting and novel hypothesis has been proposed whereby some transcriptional events are directly dependent on the cellular levels of G-actin. This interesting model has arisen through a screen designed to identify activators of the serum response factor (SRF) (Sotiropoulos et al., 1999). Events that lead to the depletion of the G-actin pool result in activation of SRF, presenting the notion that G-actin may either be acting as a corepressor of transcription in the nucleus or as a cytoplasmic anchor for factor(s) that activate SRF.

Conclusions

There is increasing evidence for a role for CAMs in the regulation of nucleocytoplasmic trafficking, either directly by sequestering signaling molecules to adhesion sites, or through the formation of an actin-based scaffold. Thus, CAMs regulate the accessibility of signaling proteins to import factors, or in some cases have revealed novel import pathways. Adhesion control of nucleocytoplasmic trafficking has important ramifications not only for gene transcription events leading to developmental changes and cell cycle progression, but also for cytoplasmic changes, including actin organization.

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