Minireview

Cell adhesion molecule regulation of nucleocytoplasmic trafficking

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Abstract Cells undergo processes such as proliferation, differentiation, and survival based upon cues that they receive from their microenvironment. Extracellular matrix adhesion molecules, such as integrins and syndecans, and cell–cell adhesion molecules, including cadherins and Ig superfamily members, convey information about the environment to the cell. It is evident that cell adhesion molecules (CAMs) regulate a variety of signaling events. An emerging theme is that one level of CAM signaling control is through regulated nucleocytoplasmic distribution of molecules that either phosphorylate or co-activate transcription factors. In this manner, CAMs control transcription events that ultimately have a strong impact on cellular processes.

Key words: Integrin; Cadherin; Syndecan; CD44; Transcription; Proteolysis

1. Introduction

A key step in transcriptional regulation is the transit of signals generated at the cell surface from the cytoplasm into the nucleus. Much of our understanding of nuclear import and export mechanisms has been elucidated through the analysis of molecules containing consensus nuclear localization and export signals (NLS and NES). Importin and exportin adapter molecules recognize consensus NLS and NES, respectively, within target molecules and bind to the nuclear pore complex. Furthermore, adapter–target binding is regulated by the Ran GTPase [1]. Recent studies have highlighted a new function for many cell adhesion molecules (CAMs) in the regulation of nucleocytoplasmic trafficking. Many modes of regulation have been described including CAM interaction with molecules capable of transcriptional co-activation, CAM regulation of the nuclear accumulation of kinases, and proteolytic cleavage of CAMs to release fragments that are able to translocate to the nucleus (Fig. 1). Although many of the CAM-regulated signaling molecules utilize consensus NLS or NES, others do not contain such sequences and, in certain cases, nucleocytoplasmic trafficking may occur independently of Ran. Elucidating the mechanisms underlying CAM-regulated nucleocytoplasmic trafficking will aid our understanding of the role of adhesive interactions in controlling cell fate.

2. Cell adhesion site components with transcriptional co-activation potential

A direct method whereby CAMs regulate nuclear events is through the translocation of a signaling protein from an adhesion site to the nucleus upon CAM engagement. The integrin-interacting protein JAB1 (Jun activation domain binding protein 1) is also a co-activator of the transcription factor c-Jun. JAB1 associates with β2 integrins in lymphocytes and, upon $\alpha_L\beta_2$ engagement, translocates into the nucleus and enhances c-Jun-driven transcription [2]. JAB1 is also known to facilitate the degradation of the cyclin-dependent kinase inhibitor, p27 [3], an important cell cycle regulator that is down-regulated in an adhesion-dependent manner. Thus, integrin regulation of JAB1 localization has important implications for cell cycle progression.

Frequently, CAM expression level rather than engagement regulates the nucleocytoplasmic trafficking of signaling proteins by acting as a cytoplasmic anchor. E-cadherin is a homotypic cell–cell adhesion molecule that binds directly to β-catenin at adherence junctions. The cytoplasmic accumulation of β-catenin is prevented normally by an axin–APC–GSK-3β complex that mediates targeting of β-catenin for degradation [4]. However, under circumstances of inefficient β-catenin degradation, such as upon mutational inactivation of APC, β-catenin accumulates in the cytoplasm and translocates into the nucleus. Nuclear β-catenin acts as a co-activator for the transcription factor LEF-1 (lymphocyte enhancer binding factor-1) and regulates transcription of growth control genes such as c-Myc and cyclin D1 [5]. Cytoplasmic anchoring of CAM-interacting proteins is likely to be an important determinant in cellular processes. In colon carcinoma cells containing high levels of nuclear β-catenin, overexpression of cadherins titrates accumulated β-catenin away from the nucleus and reduces LEF-1-mediated transcription [6–8]. It should be noted that enhancing expression of β-catenin cytoplasmic anchors, such as axin, similarly reduces β-catenin transactivation potential [9]. In mammary epithelial cells, E-cadherin-mediated sequestration of β-catenin causes cell cycle arrest, suggesting that E-cadherin acts as a tumor suppressor through control of β-catenin nucleocytoplasmic distribution [10].

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Abbreviations: CAM, cell adhesion molecule; ECM, extracellular matrix; ERK, extracellular signal-regulated kinase; JAB1, Jun activation domain binding protein 1; LEF-1, lymphocyte enhancer binding factor-1; NES, nuclear export signal; NLS, nuclear localization signal

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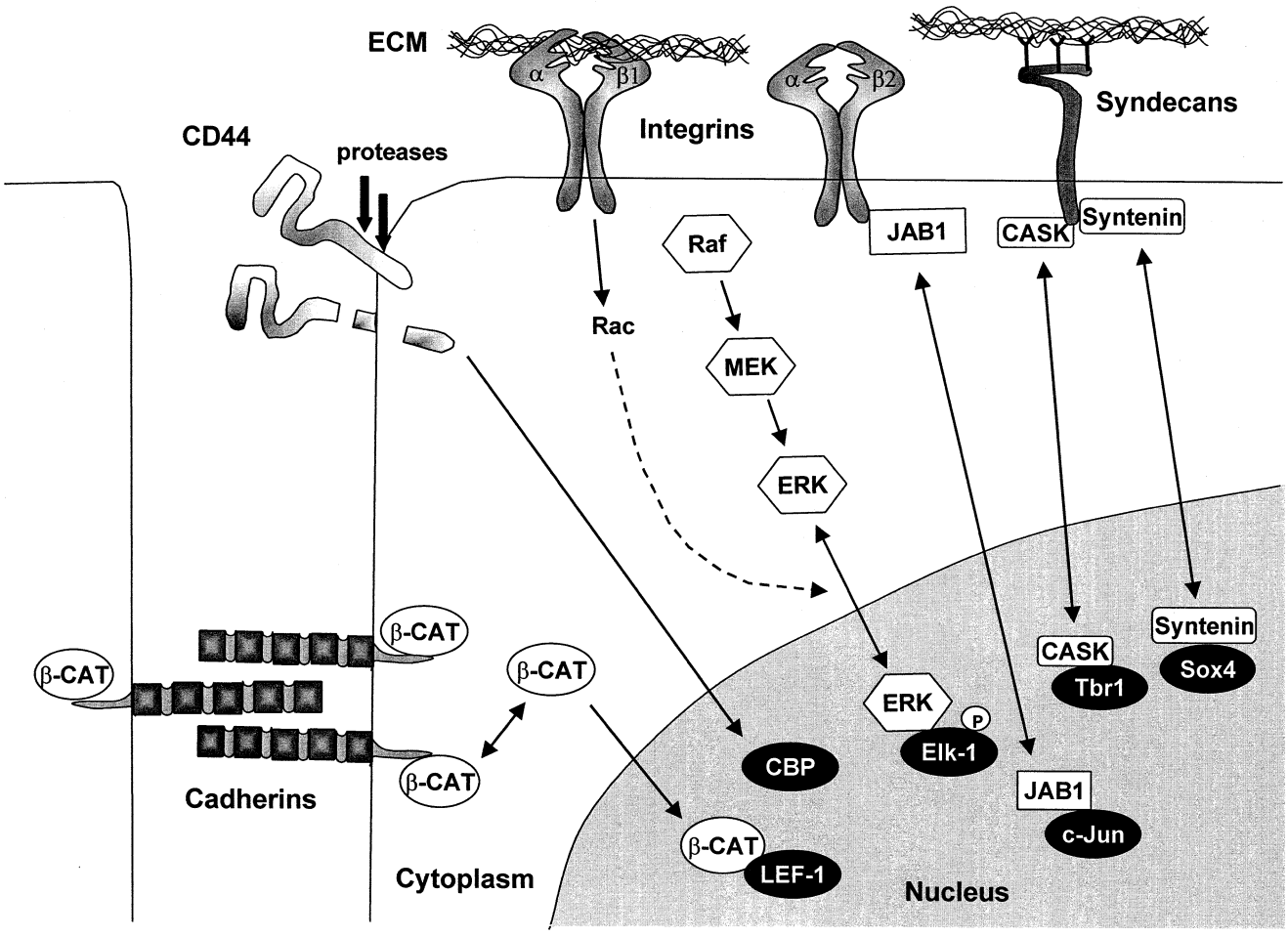

Fig. 1. Modes of CAM-regulated nucleocytoplasmic trafficking. CAMs regulate the nucleocytoplasmic trafficking of signaling molecules by different means. Engagement of integrins (such as $\alpha_L\beta_2$) can release integrin-interacting proteins (e.g. JAB1), which subsequently translocate to the nucleus and bind to transcription factors (for example, c-Jun). Additionally, integrin-mediated adhesion enhances nuclear accumulation of ERK and ERK-mediated phosphorylation of Elk-1, possibly via a Rac-dependent mechanism. Many CAMs can act as cytoplasmic anchors. Syndecans are able to recruit the PDZ domain-containing proteins, CASK and syntenin; cadherins bind β-catenin (β-CAT). CAM binding depletes the nuclear pool of these molecules with resulting decreases in transcription. Proteolytic cleavage of CAMs may also play a role in transcriptional events. Cleavage of CD44 initially in the extracellular domain and subsequently within the intracellular domain releases a CD44 fragment that translocates to the nucleus and enhances CREB binding protein (CBP)/p300-mediated transactivation potential.

A second example of a CAM acting as a cytoplasmic anchor is provided by syndecans. Syndecans are a family of transmembrane proteoglycans that, via their extracellular glycosaminoglycan chains, bind many extracellular matrix (ECM) proteins and growth factors. In addition, the cytoplasmic domains of syndecans bind directly to the PDZ domain-containing proteins CASK and syntenin, and recruit them to sites away from the nucleus [11,12]. In the nucleus, CASK interacts with Tbr, a transcription factor involved in forebrain development [11]. Syntenin interacts with Sox4 and may play a role in B cell development [13]. These studies indicate that the cellular levels of CAM are likely to dictate growth and developmental decisions.

Many additional proteins potentially perform roles both at cell adhesion sites and in the nucleus (see Table 1). A striking feature among several of these proteins is that their nuclear accumulation is often directed by LIM (Lin-11, Isl-1 and Mec-3) motifs, zinc finger-like structures that mediate protein–protein interactions [14]. However, the extent to which trafficking occurs directly from adhesion sites remains unclear. For example, paxillin has been reported to enter the nucleus from a perinuclear rather than focal adhesion pool [15]. Furthermore, the role that many of these proteins perform in the nucleus warrants further investigation.

3. Adhesion regulation of ERK nucleocytoplasmic distribution

Integrin-mediated adhesion to the ECM coordinates growth factor signaling events [35]. Signaling through Ras to the extracellular signal-regulated kinase (ERK) cascade is critical for cell cycle progression, a process that requires both ERK activation and subsequent nuclear translocation of activated ERK [36]. Adhesion to the ECM has recently been shown to promote efficient accumulation of activated ERK in the nucleus [37,38], an observation that does not extend to other mitogen-activated protein kinase subfamilies [39]. Furthermore, ERK nuclear accumulation is impaired in mouse embryo fibroblasts (MEF-β1del) in which the distal cytoplasmic portion of the β1 tail is mutated [40]. In addition to ERK nuclear localization, activation of the GTPase Rac is impaired in the MEF-β1del cells and notably ERK nuclear accumulation is recovered by expression of a constitutively active Rac.

Table 1
Adhesion site proteins with transcription potential

Protein	Role at adhesion site	Function in nucleus	References
Ajuba	Localizes to cell–cell junctions	Regulates differentiation of P19 embryonal cells	[16]
Calreticulin	Binds to the conserved GFFKR sequence of integrin α subunit cytoplasmic domains	Blocks steroid hormone receptor-mediated gene transcription. May act as a nuclear exporter	[17,18]
CASK/LIN-2	Binds to syndecan C-termini at neuronal synapses	Binds the transcription factor Tbr and mediates transcription of genes important for cerebrocortical development	[11]
CAS-interacting zinc finger protein	Binds to p130 Cas at focal adhesions	Regulates expression of metalloproteinases	[19]
β-Catenin	Binds to cadherins at cell–cell junctions	Interacts with the LEF-1 transcription factor	[6]
p120 catenin	Component of cell–cell contacts	Binds Kaiso, a putative transcriptional repressor	[20–22]
Four-and-a-half LIM domain protein 2 (FHL-2/DRAL)	Interacts with a variety of integrin cytoplasmic tails including α3A, α7A and several β subunits	Interacts with the promyelocytic leukemia zinc finger protein transcriptional repressor	[23,24]
Hic-5	A paxillin-related component of focal adhesions	Co-activator of glucocorticoid receptor	[25,26]
Jun activation domain binding protein 1 (JAB1)	Binds directly to the β2 integrin cytoplasmic tail	Co-activator of c-Jun-mediated transcription	[2]
Lipoma preferred partner	Found in focal adhesions and cell–cell junctions	Possible role in transcription	[27]
Paxillin	Major component of focal adhesions and is tyrosine-phosphorylated upon adhesion	May export polyadenylate binding protein and associated mRNA from nucleus	[15]
Syntenin	Binds to syndecans	Binds to the transcription factor Sox4 and regulates interleukin-5 signaling	[12,13]
Thyroid receptor interacting protein-6 (TRIP-6)	Localizes to focal adhesions	Possible transcription co-activator	[28,29]
Zonula occludens-1	Found at cell–cell contacts, interacts with β-catenin and α-catenin	Interacts with ZONAB, a Y-box transcription factor to regulate expression of ErbB-2	[30,31]
Zyxin	Localizes to focal adhesions	Possible role as transcription activator	[32–34]

Studies in myeloid leukemia cell lines have shown a role for Rho/Rho kinase-associated signaling in cytoplasmic sequestration of ERK localization and decreased ERK-mediated $p21^{Cip1}$ induction [41]. Such findings raise the notion of Rac and Rho acting in an antagonist fashion to regulate ERK localization [42]. Whether integrins and Rho family GTPases control ERK localization in an actin-dependent manner, through regulation of MEK1–ERK2 association [43], or by an alternative mechanism is not well established. Interestingly, parallels can be drawn between ERK and β-catenin nucleocytoplasmic trafficking. Both localize to the nucleus when highly expressed, are able to interact directly with nucleoporins in the nuclear pore complex, and are exported from the nucleus, at least in part, by the same proteins that act as cytoplasmic binding partners [44–46]. Given the importance of ERK nuclear activity for proliferation, understanding the mechanism whereby ERK nuclear accumulation is regulated by integrins is likely to provide important insight into disease states involving anchorage-independent cell growth.

4. Proteolytic release of CAM fragments that contain nuclear potential

An alternative mode of CAM regulation of nucleocytoplasmic trafficking is through proteolytic cleavage of the CAM. For several years, studies on the Notch receptor have illustrated the role of proteolysis in signal transduction. In this pathway, Notch is cleaved upon binding of its ligand and the release of an intracellular fragment ensues, which translocates to the nucleus and regulates transcription events involved in cell fate determination [47]. Recently, comparable mechanisms have been proposed whereby CAMs are cleaved to release either CAM fragments or interacting proteins that contain transcriptional potential.

CD44 binds matrix hyaluronan, links to the actin cytoskeleton, and plays an important role in a variety of cellular processes including lymphocyte homing and cell migration [48]. This CAM is sequentially cleaved, initially in the extracellular domain followed by a second cleavage close to the transmembrane-intracellular boundary [49]. Notably, the latter proteolytic event is blocked by an inhibitor of presenilin/γ-secretase, the same complex involved in Notch processing [42]. The final cytoplasmic fragment of CD44 is able to translocate to the nucleus and potentiate transactivation mediated by the co-activators CBP and p300. Interestingly, the cleaved CD44 C-terminal fragment enhances transcription of CD44. Thus, CD44 proteolysis may trigger its own turnover during migration, a finding of particular interest since CD44 cleavage products have been detected in primary tumor tissue [50].

Studies on E-cadherin also provide evidence for proteolytic cleavage of CAMs. Under conditions favoring apoptosis, E-cadherin is sequentially cleaved, first by a metalloproteinase and second by a presenilin/γ-secretase-like activity [51,52]. Release of the cytoplasmic E-cadherin fragment disrupts cadherin–β-catenin complexes leading to an increase in the cytosolic fraction of β-catenin. As discussed above, elevated cytosolic β-catenin levels are associated with increased β-catenin nuclear accumulation and LEF-1-mediated transcription, hence the implication is that presenilin-mediated proteolytic cleavage of E-cadherin may contribute to enhanced transcription of genes involved in survival. However, other findings show that presenilin deficiency leads to elevated β-catenin and cy-

clin D1 levels in primary fibroblasts and accelerated tumor formation in vivo [53,54]. Nevertheless, these studies highlight the emerging theme of proteolysis of CAMs and its possible involvement in regulating the localization and nuclear signaling of CAM fragments and CAM-associated proteins.

5. Summary

The localization of signaling molecules determines their ability to act as co-activators or to phosphorylate transcription factors. Thus, the ability of CAMs to alter the nucleocytoplasmic trafficking of signaling molecules is an important aspect of cellular decision-making processes. Altered localization of the signaling molecules is frequently associated with disease states, especially forms of cancer. Hence, understanding how CAMs regulate the nucleocytoplasmic trafficking of these signaling molecules will likely be key for understanding disease processes and provide the rationale for design of novel therapies.

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