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L1 and NCAM adhesion molecules as signaling coreceptors in neuronal migration and process outgrowth

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Neural cell adhesion molecules (CAMs) of the immunoglobulin superfamily engage in multiple neuronal interactions that influence cell migration, axonal and dendritic projection, and synaptic targeting. Their downstream signal transduction events specify whether a cell moves or projects axons and dendrites to targets in the brain. Many of the diverse functions of CAMs are brought about through homophilic and heterophilic interactions with other cell surface receptors. An emerging concept is that CAMs act as coreceptors to assist in intracellular signal transduction, and to provide cytoskeletal linkage necessary for cell and growth cone motility. Here we will focus on new discoveries that have revealed novel coreceptor functions for the best-understood CAMs — L1, CHL1, and NCAM — important for neuronal migration and axon guidance. We will also discuss how dysregulation of CAMs may also bear on neuropsychiatric disease and cancer.

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Introduction

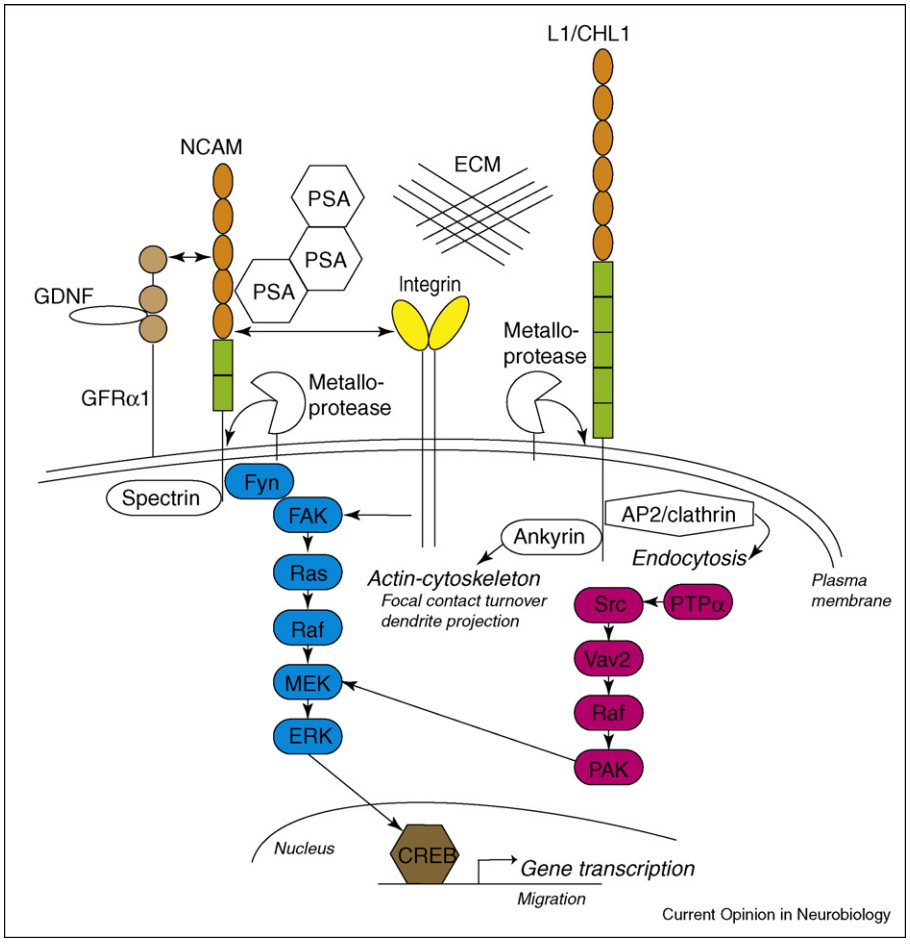
Neural cell adhesion molecules (CAMs) of the immunoglobulin (Ig) superfamily are complex transmembrane proteins capable of multiple molecular interactions mediated by their large and divergent extracellular regions, while their shorter cytoplasmic domains link reversibly to the actin cytoskeleton [1]. The L1 family of cell adhesion molecules (L1-CAMs) is comprised four structurally related transmembrane proteins in vertebrates: L1, Close Homolog of L1 (CHL1), NrCAM, and Neurofascin. L1-CAMs have six Ig-like domains and four to five fibronectin III repeats in their divergent extracellular regions and a more conserved cytoplasmic domain of ~100 residues that links to actin. Despite an overall similarity in structure, L1-CAMs share only 35–45% homology. The less closely related adhesion molecule, NCAM, was the first CAM identified and contains five Ig-like and two fibronectin type III repeats followed by a variably spliced cytoplasmic domain that produces two major transmembrane isoforms (180 and 140 kDa) and a glycophosphatidyl inositol (GPI)-linked isoform (120 kDa). The cytoplasmic domains of transmembrane NCAM isoforms link to the actin cytoskeleton by directly binding to spectrin. L1-CAMs and NCAM have long been known to signal intracellularly, but recent studies demonstrate that they act as coreceptors for integrins, growth factors, and receptors for repellent axon guidance molecules.

L1 and CHL1 as signaling coreceptors in cortical development

Cell migration and neurite outgrowth on extracellular matrix (ECM) protein substrates is potentiated by a functional interaction of L1 with β1 integrins. The interaction is mediated by a conserved RGD binding motif in the sixth immunoglobin-like domain and the third fibronectin type III repeat of L1 [2,3•], which serves to strengthen the adhesion of the cell to the ECM (Figure 1). L1 and β1 integrins associate with low affinity on the cell surface and activate a common intracellular signaling pathway. This pathway involves the sequential activation of the nonreceptor tyrosine kinase c-Src, phosphotidylinositide 3-kinase (PI3 kinase), Vav2 guanine nucleotide exchange factor, Rac1 GTPase, p21-activated kinase (PAK1), MEK, and the MAP kinases ERK1/2 [4,5] (Figure 1). The L1 and β1 integrin signaling pathway can converge with growth factor signaling pathways, culminating in increased ERK activation. For example, coincident activation of L1 and platelet-derived growth factor (PDGF) receptor causes sustained ERK activation, as opposed to transient activation in the case of L1 or PDGF signaling alone [6•]. Sustained ERK signaling upregulates the expression of integrins and Rac1 to increase cell motility. Since ERK is downstream of many receptor tyrosine kinases, such as IGF1, EGF, FGF, and Trk receptors, L1 convergent signaling may be a widespread neurodevelopmental mechanism.

ERK MAP kinases also feedback to L1 by modulating its linkage to the actin cytoskeleton. All L1-CAMs reversibly engage the actin cytoskeleton through a conserved motif FIGQ/AY in the cytoplasmic domain, which contains a crucial tyrosine residue required for binding the spectrin–actin adaptor ankyrin [7]. ERK, a serine/threonine protein kinase, was shown to indirectly induce tyrosine

Figure 1



NCAM and L1-CAMs as coreceptors in integrin and GDNF receptor signaling. Transmembrane isoforms of NCAM and L1/CHL1 activate distinct signaling pathways to regulate neuronal migration, axon growth, and dendrite projection, converging at the level of ERK1/2 MAP kinase. NCAM and L1-CAMs interact with β1 integrins to increase signaling and modulate adhesion to extracellular matrix (ECM) proteins. NCAM also associates with, and transduces signals from, the GDNF receptor GFRα1. PSA can be added post-translationally to the NCAM Ig5 domain, reducing NCAM interactions. L1 is endocytosed by binding to the AP2 clathrin adaptor at a sequence (RSLE) in the cytoplasmic domain of a neuronal L1 isoform. NCAM, L1, and CHL1 are each cleaved by ADAM metalloproteases releasing ectodomain fragments that may downregulate or stimulate CAM function. Rectangles: FNIII domains; ovals: Ig-like domains.

phosphorylation in the FIGQY motif in the L1 intracellular domain [8], thereby dissociating ankyrin and uncoupling L1 from the actin cytoskeleton. The tyrosine kinase responsible for FIGQ/AY phosphorylation remains elusive. Dynamic adhesive interactions controlled by phosphorylation/dephosphorylation of the ankyrin motif in L1 family members may enable a cell or growth cone to cyclically attach and detach from the ECM substrate or from neighboring cells, thus facilitating migration. Such cytoskeletal coupling induced by L1–ankyrin interactions has a crucial *in vivo* function in synaptic targeting. An L1 mutant mouse was engineered to contain a point mutation in the crucial tyrosine residue of the ankyrin-binding motif (Tyr1229His), which is also a human pathological mutation associated with mental retardation [9]. The L1–ankyrin deficient mouse displays defective topographic mapping of retinal axons to synaptic targets along the mediolateral axis of the superior colliculus regulated by the EphrinB/EphB guidance system. L1 cooperates with EphrinB/EphB to modulate adhesion of retinal cells to ECM *in vitro*, which could promote retinal axon branching important for mediolateral targeting or stabilize synaptic termination zones. Similarly, targeting of cerebellar granule cell axons to the Purkinje cell axon initial segment requires linkage to the cytoskeleton through the interaction of ankyrin with Neurofascin [10••].

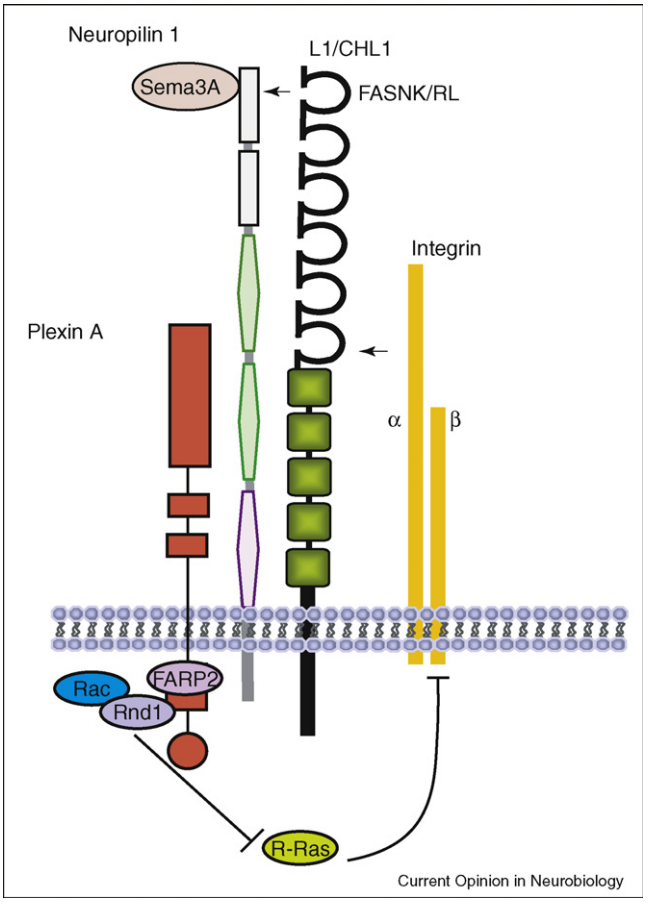
CHL1 plays a key role in neuronal positioning in caudal neocortical areas (visual and somatosensory cortex), where CHL1 is enriched compared to rostral areas [11••]. Analysis of CHL1-deficient mice revealed that

CHL1 acts to position deep layer pyramidal neurons in appropriate cortical laminae by facilitating radial migration of neuronal precursors. CHL1 functions coordinately with β1 integrins during the migration process, since haptotactic migration of embryonic cortical neurons is inhibited in the presence of integrin blocking antibodies *in vitro*. Cell-based assays implicate c-Src, PI3 kinase, and ERK1/2 in the CHL1–integrin signaling pathway [12]. Integrins have been shown to participate in the mechanism of radial migration of embryonic cortical neurons [13] but appear to function when expressed on radial glia, rather than on neurons [14]. Thus, a *trans* heterophilic interaction between CHL1 on neurons and β1 integrins on radial glia may transduce signaling in migrating cortical neurons responsible for correct laminar positioning. Other L1-CAMs might contribute to radial migration of neurons in different brain regions. In this regard, it is interesting that L1 and NrCAM double knockout mice exhibit a cerebellar phenotype consistent with impaired migration [15].

CHL1 is also required for directing apical dendrites of deep layer pyramidal neurons toward the pial surface in caudal cortical areas [11••]. Important in this context, CHL1 associates with NB3, a GPI-linked member of the TAG1/contactin/NB3 family of surface receptors, which like CHL1 is expressed in a low-rostral to high-caudal gradient in the developing neocortex [16]. Pyramidal neurons in NB3-deficient mice exhibit misoriented, often inverted, apical dendrites similar to those in CHL1 null mutants. However, NB3 mutant neurons do not show laminar displacement, suggesting that migration and dendritic orientation may be independently controlled. CHL1/NB3 clustering activates protein tyrosine phosphatase α (PTPα), which dephosphorylates and activates the Src family kinase Fyn. Both PTPα and Fyn are required for proper apical dendrite orientation of deep layer pyramidal neurons [17].

Semaphorin3A (Sema3A), a member of class-III Semaphorins, is a secreted protein that is involved in repulsive, and in some cases attractive, axon guidance, and dendrite projection. Interestingly, a Sema3A gradient in the developing cortex is required to maintain radial migration of embryonic cortical neurons [18•] and to attract their apical dendrites toward the pial surface [19]. However, Sema3A knockout mice show no obvious cortical lamination defects, suggesting the involvement of compensatory factors. Both CHL1 [20•] and L1 [21••] bind the Sema3A receptor, Neuropilin-1, via a conserved sequence in the Ig1 domain, and act as obligate coreceptors to mediate Sema3A-induced growth cone collapse and axon repulsion (Figure 2). The repellent response of L1/Neuropilin-1 involves signaling through focal adhesion kinase (FAK) and ERK, leading to disassembly of focal adhesions [22]. However, Sema3A-induced repulsion can be converted to Sema3A-induced attraction by homophilic binding of L1 on an apposing cell in *trans* with L1 complexed to Neuropilin-1 in the responding neuron [21••,23]. In this way, L1 and CHL1 acting as coreceptors with Neuropilin-1 in newly differentiating pyramidal neurons might promote the attraction of apical dendrites in response to local homophilic binding in the presence of the cortical Sema3A gradient.

Figure 2



L1-CAMs as coreceptors for Semaphorin3A signaling in axon repulsion and growth cone collapse. L1 and CHL1 associate with the Sema3A receptor Neuropilin-1 on the plasma membrane through conserved Ig1 domain motifs in L1 (FASNRL) and CHL1 (FASNKL) and with integrins through the Ig6 domain. PlexinAs are signaling coreceptors for Neuropilin-1. In response to Sema3A, the guanine nucleotide exchange factor FARP2 activates Rac1, which leads to the inactivation of R-Ras and integrins through binding of Rnd1 to PlexinA. This mechanism contributes to growth cone collapse and axon repulsion from Sema3A.

NCAM signaling and post-translational modification

Similar to L1-CAMs, NCAM regulates important aspects of integrin-dependent cell migration, axonal/dendritic outgrowth, and synaptic targeting. L1 and NCAM, both interact functionally with integrins and activate convergent signaling pathways leading to ERK MAP kinase

(Figure 1). However, they have different proximal signaling intermediates that differentially influence the cellular outcome [1]. Whereas L1 activates ERK through Src in a FAK-independent manner, NCAM induces the recruitment of tyrosine kinase Fyn to its intracellular domain, which in turn activates FAK, ERK, and the transcription factor cAMP response element binding protein (CREB), which stimulates neurite outgrowth (Figure 1). FAK is a key intracellular regulator of migration in non-neuronal cells, acting by increasing turnover of focal adhesive contacts at the cell's leading edge. In neurons, FAK is more important as a negative regulator of dendritic and axonal branching than migration outgrowth [24,25]. This may be because of the existence of multiple pathways that converge on FAK *in vivo*. NCAM signaling to ERK is more complex than L1–ERK signaling and involves interactions with different receptors. For example, NCAM signaling within lipid rafts is independent of the fibroblast growth factor (FGF) receptor, whereas a component of NCAM–ERK signaling in nonrafts is FGF receptor-dependent [26•]. The NCAM–FGR receptor pathway further differs by signaling through phospholipase Cγ and protein kinase C [27].

NCAM is also a signaling coreceptor for the glial cell line-derived neurotrophic factor (GDNF) receptor GFRα1, and functions by potentiating Schwann cell migration and neurite growth [28••]. GDNF signals in conjunction with NCAM and GFRα1 by activating FAK and Fyn. This activation decreases NCAM-dependent cell adhesion, illustrating a general principal that an optimal level of cell–substratum contact is needed for motility, with too much or too little impeding it. NCAM also mediates chemo-attraction of olfactory interneuron precursors to GDNF in the rostral migratory stream, but is not required for GDNF/GFRα1-mediated tangential migration of cortical interneurons [29].

An unusual mechanism that modulates NCAM-dependent cell adhesion during migration and synaptogenesis is provided by the polysialyltransferases PST and STX, which attach polysialic acid (PSA) to the fifth Ig-like domain of NCAM in a developmentally regulated manner. PSA is thought to act through steric repulsion between individual PSA clusters, thus increasing the distance between NCAM molecules on apposed cells. PSA attachment to NCAM globally regulates cellular responses to other factors by creating a permissive environment for cell migration. Deletion of PST and STX to prevent PSA attachment to NCAM inhibits the rostral migration of olfactory neuron precursors [30••], and also affects both tangential and radial migration of cortical precursors, resulting in aberrant positioning of neuronal and glial cells [31]. PST/STX deficient mice also display more severe axonal defects than NCAM-deficient mice because of gain-of-function effects [30••]. Premature removal of PSA from NCAM by endoglycosidase N treatment promotes synaptogenesis between GABAergic interneuron subpopulations and pyramidal cells in the visual cortex and regulates the onset of the crucial period of visual plasticity in adolescence [32]. On the contrary, surface levels of PSA–NCAM are upregulated in adult hippocampal neurons undergoing activity-dependent plasticity [33•]. Thus, PSA modification of NCAM at different places and times may regulate molecular interactions leading to either synaptogenesis or synaptic remodeling.

NCAM function can be downregulated by other mechanisms such as ectodomain shedding by ADAM (a disintegrin and metalloprotease) proteases (see [34]) and endocytosis by NCAM ubiquitylation [35]. L1-CAMs are also subject to ADAM-mediated ectodomain shedding and endocytosis by a clathrin-dependent mechanism (Figure 1). Ectodomain shedding of CAMs can downregulate CAM-dependent migration or neurite outgrowth [36], although in some cases it increases CAM activity by autocrine stimulation [37•]. Downregulation of NCAM function by ADAM-mediated shedding in cortical neurons decreases branching and neurite outgrowth *in vitro* [36], and inhibits branching and synaptogenesis of cortical interneurons in a mouse transgenic model excessive NCAM ectodomain [38]. Dysregulation of NCAM shedding may contribute to neuronal pathology in schizophrenia. Elevated levels of the entire soluble NCAM extracellular fragment have been described in affected brain regions and cerebrospinal fluid in schizophrenia [39].

Neural adhesion molecules and cancer

CAMs have gained much attention in cancer research because of their upregulation in human brain tumors. NCAM is strongly upregulated in many neuroblastomas, where it becomes post-translationally modified to PSA–NCAM, thus enhancing invasion of tumor cells [40]. Overexpression of L1 correlates with tumor progression and metastasis in certain neural tumors, most notably melanoma [41], while NrCAM is upregulated in high-risk neuroblastomas without N-myc amplification [42]. Cell adhesion molecule upregulation is likely to stimulate tumor cell invasiveness by signaling mechanisms that enhance migration. This probably involves cycles of cell attachment and deattachment regulated through signaling by dynamic interactions with the cytoskeleton, since purely increased adhesion would be expected to reduce rather than promote migration. The well-documented ability of L1-CAMs and NCAM to promote integrin-dependent cell migration through ERK MAP kinase could contribute to tumor cell invasiveness. Accordingly, antibody-based therapeutic strategies are being pursued to functionally inhibit homophilic and heterophilic interactions of cell adhesion molecules to curb tumor invasiveness [43].

Current research into the basic mechanisms of CAM regulation and their functions as coreceptors for integrins, growth factors, and repellent axon guidance receptors may become instrumental in discovering new therapeutic approaches in cancer research. In turn, tumor models may increase our understanding of the function for CAMs for the migration and process outgrowth in the developing nervous system. Differences in L1-CAM and NCAM signaling pathways during the development may generate distinct patterns of cortical connectivity in different neuronal populations or brain regions. Disruption of this signaling probably contributes to distinct developmental neuropsychiatric disorders that are associated with mutation or genetic polymorphisms in genes encoding L1 (X-linked mental retardation) [44], CHL1 (low IQ, speech, and motor delay) [45], and NCAM (schizophrenia, bipolar disorder) [39,46,47].

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