Cell Tissue Res (2012) 349:39–48
DOI 10.1007/s00441-012-1345-4

REVIEW

Role of L1CAM for axon sprouting and branching

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Received: 19 October 2011 / Accepted: 25 January 2012 / Published online: 28 February 2012

Abstract The central nervous system (CNS) has been traditionally considered as an organ that fails to regenerate in response to injury. Indeed, the lesioned CNS faces a number of obstacles during regeneration, including an overall non-permissive environment for axonal regeneration. However, research during the last few decades has identified axon sprouting as an anatomical correlate for the regenerative capability of the CNS to establish new connections. The immunoglobulin superfamily member L1CAM has been shown to promote the capability of neurons for regenerative axon sprouting and to improve behavioral outcomes after CNS injury. Here, we discuss the cell-autonomous role of L1CAM for axon sprouting in experimental rodent injury models and highlight the molecular interactions of L1CAM with ankyrins, ezrin-radixin-moesin proteins and the Sema3A/Neuropilin ligand-receptor complex in the context of axonal branching.

Key words L1CAM · CNS injury · Axon growth · Growth cone · Neural repair

This work has been supported by the Deutsche Forschungsgemeinschaft (SCHA 1261/4-1 to M.S.). M.F. is Senior Research Professor of the Hertie Foundation.

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Introduction

L1CAM, discovered in the mid-1980s (Rathjen and Schachner 1984), is the founding member of the L1CAM family. In mammals, this family consists in L1CAM, the close homolog of L1 (CHL1), the neuron-glial-related cell adhesion molecule (NrCAM) and neurofascin (Grumet et al. 1991; Volkmer et al. 1992; Holm et al. 1996). L1CAM is composed of a large extracellular region and a short cytoplasmic part, which is highly conserved in the L1CAM family. The extracellular domains are arranged as repetitive immunoglobulin-like (Ig-like) and fibronectin type III (FNIII) modules that allow complex molecular interactions with numerous ligands, including other neural members of the Ig-superfamily, integrins and extracellular matrix proteins (Friedlander et al. 1994; Ruppert et al. 1995; Montgomery et al. 1996; Malhotra et al. 1998; Oleszewski et al. 1999; Haspel and Grumet 2003). The intracellular domain of L1CAM mediates linkage to the actin cytoskeleton and the endosomal membrane system, thereby enabling axonal targeting, stabilization at the cell surface and dynamics of cell surface expression (Dahlin-Huppe et al. 1997; Hortsch et al. 1998; Kamiguchi et al. 1998; Dequidt et al. 2007; Herron et al. 2009; Lasiecka and Winckler 2011).

L1CAM participates in all steps during the establishment of neuronal connectivity including neuronal migration, axon growth, fasciculation and pathfinding and synapse formation and plasticity (Stallcup and Beasley 1985; Chang et al. 1987; Ohyama et al. 2004; Saghatelyan et al. 2004; Wiencken-Barger et al. 2004; Anderson et al. 2006; Godenschwege et al. 2006; Nakamura et al. 2006; Triana-Baltzer et al. 2006; Maness and Schachner 2007; Wolman et al. 2007; Li et al. 2008; Barry et al. 2010). Early during the neural development of mice, from embryonic stage 9.5 (E9.5) onwards, L1CAM is found on cell bodies of migrating neurons of the central nervous system (CNS), is strongly expressed on growing axons at

later developmental stages (Kallunki et al. 1997) and declines to more moderate levels at postnatal stages (Liljelund et al. 1994; Akopians et al. 2003). In the adult, L1CAM localizes also to presynaptic terminals in the hippocampus (Matsumoto-Miyai et al. 2003; Nakamura et al. 2006). In the periphery, myelinating Schwann cells express L1CAM only during embryonic and early postnatal development, whereas expression in non-myelinating Schwann cells persists into adulthood (Faissner et al. 1984).

The important role of L1CAM in the developing nervous system is further emphasized by more than 200 human gene mutations that cause a variety of neurological disorders referred to as L1 syndrome (Jouet et al. 1995; Kanemura et al. 2006; Schäfer and Altevogt 2010; Vos and Hofstra 2010). The broad clinical spectrum includes X-linked hydrocephalus, hypoplasia of the corticospinal tract, corpus callosum agenesis and mental retardation (Rosenthal et al. 1992; Jouet et al. 1993, 1994; Fransen et al. 1996). Similar phenotypes have been observed in L1CAM-deficient mice (Dahme et al. 1997; Cohen et al. 1998; Fransen et al. 1998; Demyanenko et al. 1999).

Research over the last few decades has revealed that L1CAM is dynamically regulated following brain lesion in various animal model systems. L1CAM has been proposed to reiterate its developmental role for axon growth in adults following injury. To date, genetically augmented expression of L1CAM in transplanted cells of various origins has been shown to improve functional recovery in experimental animal models of acute and chronic neurodegeneration (Bernreuther et al. 2006; Cui et al. 2009; Ourednik et al. 2009; Cui et al. 2011; Xu et al. 2011). This important issue has been addressed in recent reviews (Zhang et al. 2008; Lavdas et al. 2011). Here, we focus on the cell-autonomous role of L1CAM in axon sprouting. We summarize findings obtained in experimental CNS injury models and highlight molecular mechanisms related to L1CAM-mediated axon branching.

Role of L1CAM for axonal sprouting after experimental injury

Plastic remodeling processes, in particular axonal sprouting, are observed following brain damage and neuronal deafferentation (Deller et al. 2006). In the hippocampus, the regulation of L1CAM expression on sprouting axons has been investigated following entorhinal cortex lesion (ECL) or fimbria fornix lesion (Styren et al. 1995; Jucker et al. 1996; Aubert et al. 1998). ECL leads to lamina-specific deafferentation of granule cells in the dentate gyrus and evokes sprouting of commissural/associational and septo-hippocampal afferents (Deller et al. 1996, 2006). L1CAM expression progressively declines from 2 to 16 days after lesion when sprouting is most pronounced. Two months after ECL, L1CAM expression appears substantially increased on regrown unmyelinated axonal fibers and their presynaptic terminals (Jucker et al. 1996). This expression pattern suggests a role in maturation, stabilization and formation of synapses by reinnervating axon fibers, rather than the initiation of axonal sprouting. In contrast to these findings, sprouting cholinergic septo-hippocampal axons initially express L1CAM in the fimbria fornix lesion model but not upon target innervation. Conversely, L1CAM expression is maintained in sprouting sympathetic tyrosine-hydroxylase-positive axons (Aubert et al. 1998).

In experimental animal models of spinal cord injury (SCI) enhanced sprouting has been often correlated with improved behavioral outcomes (Weidner et al. 2001; Bareyre et al. 2004; Courtine et al. 2008; Goldshmit et al. 2008; Konya et al. 2008; Giger et al. 2011). Several studies have examined the role of L1CAM in axonal sprouting after SCI. L1CAM has been shown in rats to be upregulated on sprouting sensory axons, identified as small-diameter primary afferents containing the peptidergic marker calcitonin gene-related peptide (CGRP; Runyan et al. 2005). However, analyses of SCI in L1CAM-deficient mice from various laboratories have led to controversial results on the importance of L1CAM for the sprouting of CGRP-positive fibers. Reduced axonal sprouting has been reported in the dorsal transection SCI model (Deumens et al. 2007), whereas no effect has been observed in the extradural rhizotomy model (Runyan et al. 2007). In the contusion model of SCI, reduced sprouting of CGRP-positive fibers has been seen in L1CAM-deficient mice and they recover better from neuropathic pain than wild-type mice, which show increased sprouting of CGRP-positive fibers (Hoschouer et al. 2009). In contrast, corticospinal axons in L1CAM-deficient mice display enhanced sprouting following contusion injury to the spinal cord (Jakeman et al. 2006).

Different patterns of axonal sprouting have been recognized to occur, depending on the lesion model, age and genetic background of the employed rodent strains (Ma et al. 2004; Dimou et al. 2006; Kerr and David 2007; Lee et al. 2010; Li et al. 2010; Omoto et al. 2010; Jaerve et al. 2011). Nevertheless, the possible interaction of background strain and age in the L1CAM-deficient mouse has not been investigated as yet (Hoschouer et al. 2009). This is an important issue, because genetic background effects are known to influence phenotypic features of L1CAM-deficient mice, such as the development of hydrocephalus (Itoh et al. 2004; Tapanes-Castillo et al. 2010).

Together, the lesion studies in the hippocampus and in the spinal cord indicate that L1CAM does not stimulate axonal sprouting *per se* but does so with spatiotemporal specificity. In such a scenario, the role of L1CAM in regenerative axon sprouting might depend not only on the lesion model, genetic background and the age of the used animals but also on the different locations of the injury. Moreover, neuronal cell-type-specific L1CAM expression and accessibility of interaction partners known to regulate L1CAM-dependent axon growth might be critically involved.

L1CAM-mediated axon branching in vitro

L1CAM is known as a potent regulator of axon growth and branching both in vivo and in vitro. The in vitro effects have been observed when L1CAM has been either overexpressed in diverse types of primary neurons and/or offered as a substrate for developing neurons (Cheng and Lemmon 2004; Cheng et al. 2005; Hoffman et al. 2008; Moon and Gomez 2010; Schäfer et al. 2010b). In addition to studies in developing primary neuronal cultures, L1CAM overexpression has been shown to promote axonal branching in mature CA3 pyramidal neurons of organotypic hippocampal slice cultures. Dendritic branching appears unaffected in this in-vivo-like model system, both after overexpression of wild-type L1CAM and with mutant L1CAM carrying a missense mutation in the fifth FNIII domain, which causes mistargeting to dendrites (Schäfer et al. 2010b). Rescue experiments in cultivated L1CAM-deficient cerebellar neurons grown on a L1CAM-substrate indicate that pathological missense mutations affecting the extracellular domains impair neurite branching rather than neurite growth (Cheng and Lemmon 2004). Since impaired homophilic interaction appears to be an unlikely explanation, certain mutations might affect protein conformation or impair *cis*-interaction with heterophilic binding partners leading to altered association with the actin cytoskeleton (Cheng and Lemmon 2004).

Association of the cytoplasmic part of L1CAM with the actin cytoskeleton is known to depend on members of the ankyrin and ezrin-radixin-moesin (ERM) protein families. Various studies have implicated these two protein families in the regulation of L1CAM-dependent axon growth, targeting and branching.

L1CAM and ankyrins

Two members of the ankyrin-family, ankyrin B (*ANK2*) and ankyrin G (*ANK3*), have been shown to bind reversibly to the cytoplasmic domain of L1CAM and to mediate linkage of L1CAM to the actin cytoskeleton via the spectrin-based membrane cytoskeleton (Davis et al. 1993; Davis and Bennett 1994; Dubreuil et al. 1996; Bennett and Chen 2001; Nishimura et al. 2003; Hortsch et al. 2009; Fig. 1). In general, ankyrins are thought to stabilize L1CAM family members and compartmentalize them to distinct axonal compartments, including the axon initial segment and the nodes of Ranvier (Bennett and Lambert 1999; Bennett and Chen 2001; Huang 2006; Dzhashiashvili et al. 2007). Homophilic interaction of L1CAM has been shown to recruit ankyrins to its cytoplasmic domain (Malhotra et al. 1998). L1CAM-ankyrin binding is then controlled by the mitogen-activated protein kinase (MAPK) pathway-dependent phosphorylation of the FIGQY motif (Whittard et al. 2006), which is conserved in all L1CAM family members (Garver et al. 1997). Pathological L1CAM mutations located to this motif interfere with ankyrin binding (Needham et al. 2001). Phosphorylation of the

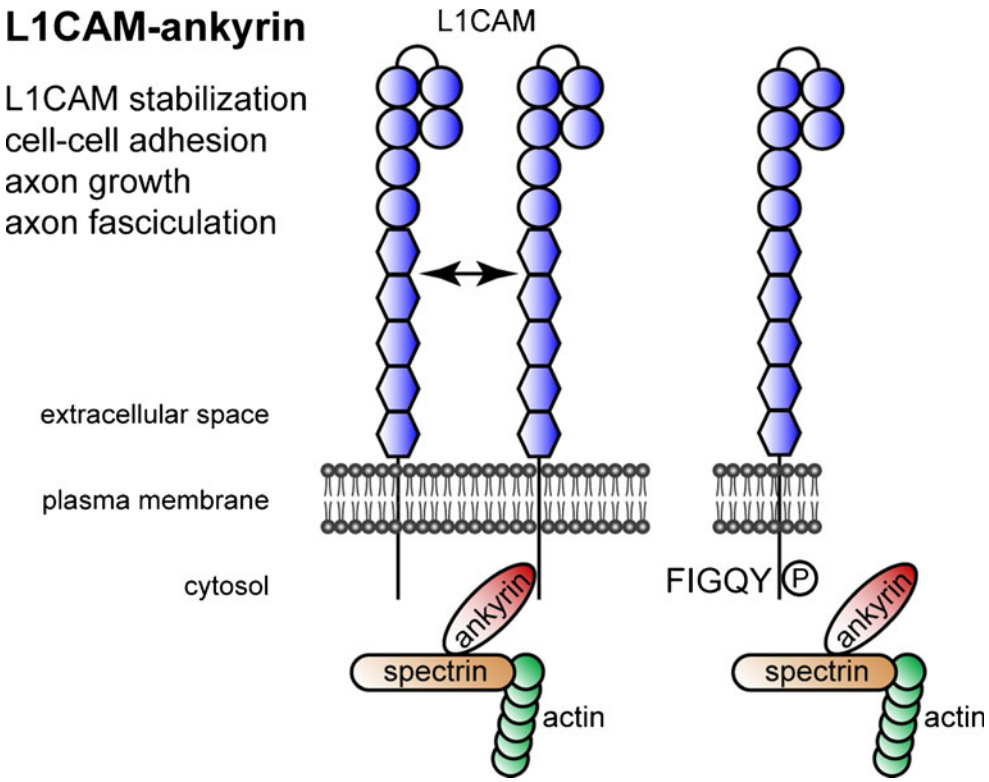

Fig. 1 Model for the ankyrin-mediated linkage of L1CAM to the actin cytoskeleton. Homophilic L1CAM binding (*cis*-binding indicated by *double-headed arrow*) leads to the recruitment of ankyrin. L1CAM-ankyrin interaction has been shown to stabilize L1CAM and to be engaged in cell-cell adhesion, axon growth and fasciculation. Binding of ankyrin is controlled by tyrosine phosphorylation of the FIGQY motif in the cytoplasmic domain of L1CAM

FIGQY motif abolishes ankyrin binding to L1CAM in a physiological manner (Fig. 1) and has been reported to promote axon growth (Gil et al. 2003; Whittard et al. 2006). In support of a stabilizing function of ankyrin, deletion of the ankyrin-binding region in L1CAM knock-in mice leads to the progressive loss of L1CAM expression (Nakamura et al. 2010). An additional transgenic mouse model has been generated carrying a point mutation of the Tyr1229 phosphorylation site in the ankyrin-binding region of L1CAM. The same point mutation has been earlier reported to constitutively enhance the endocytosis of L1CAM in vitro (Needham et al. 2001) suggesting reduced stability of cell-surface-expressed L1CAM. In Tyr1229His transgenic mice, disturbed topography of retinal axons including abnormalities in their interstitial branches (Buhusi et al. 2008) and impaired elongation and branching of interneurons have been observed (Guan and Maness 2010).

Whereas accumulating evidence indicates that ankyrin G is related to stationary behavior (Gil et al. 2003) and, together with its binding partner βIV-spectrin, maintains axonal polarization of L1CAM (Nishimura et al. 2007), the role of the L1CAM-ankyrin B interaction is less clear. Genetic ablation of ankyrin B in mice leads to reduced axonal levels of L1CAM, hypoplasia of axonal tracts and degeneration of the optic tract after completed target innervation (Scotland et al. 1998), all of which argues for similar functions of ankyrin B and ankyrin G for stabilizing L1CAM in the plasma membrane. On the other hand, ankyrin B, rather than ankyrin G, has been reported to colocalize with L1CAM in developing axons both in vitro (Boiko et al. 2007) and in vivo (Scotland et al. 1998), suggesting different modes of interaction. Furthermore, ankyrin B has been proposed to play a role in the dynamic behavior of L1CAM. The interaction of L1CAM with ankyrin B appears to induce neurite formation but not elongation and to couple L1CAM to retrograde actin flow (Nishimura et al. 2003). However, these results are partially contradictiory to the findings of Gil et al. (2003) and Cheng et al. (2005). The dynamic behavior of L1CAM in growth cones is well established (Kamiguchi et al. 1998; Kamiguchi and Lemmon 2000; Schaefer et al. 2002) and ankyrin B has recently been reported to be critically involved in the L1CAM-dependent increase of cyclic adenosine monophosphate (cAMP) in growth cones, thereby determining growth direction (Ooashi and Kamiguchi 2009). Thus, the axonal co-expression of L1CAM and ankyrin B, together with the proposed function of the L1CAM-ankyrin B interaction in neurite induction and growth cone behavior, suggests a regulatory role for L1CAM-mediated axonal sprouting following injury. To the best of our knowledge, protein expression regulation of ankyrins in the context of regenerative axonal sprouting has not been studied as yet. Investigation of axonal sprouting in the aforementioned mice models with disrupted L1CAM-ankyrin interaction should help to improve our understanding of L1CAM function in neural repair.

L1CAM and ERM proteins

The ERM protein family, comprising ezrin, radixin and moesin, is known to link filamentous (F-) actin to various transmembrane proteins (Fehon et al. 2010) including L1CAM (Dickson et al. 2002). Two ezrin-binding regions have been identified in the cytoplasmic domain of L1CAM and localize to a juxtamembrane region and the neuron-specific YRSLE region, respectively (Cheng et al. 2005; Sakurai et al. 2008; Fig. 2a). In vitro experiments have revealed a role of ERMs in the regulation of L1CAM-dependent axon branching (Dickson et al. 2002; Cheng et al. 2005; Sakurai et al. 2008). Neurons grown on a L1CAM substrate have been shown to display increased axonal branching and filopodia formation when disrupting ezrin-actin binding by dominant-negative ezrin (Dickson et al. 2002). Different effects have been observed following site-directed mutagenesis of the ezrin-binding regions of L1CAM demonstrating that ezrin is required for L1CAM-mediated axon branching (Cheng et al. 2005). Interestingly, the juxtamembrane ERM site appears to play a more important role for axon branching than the ERM binding to the RSLE region of L1CAM (Nakamura et al. 2010). In support of this notion, the juxtamembrane ERM-binding region in the cytoplasmic domain of CHL1, which lacks a second ERM-binding region, is required for axonal branching in cultured cortical neurons (Schlatter et al. 2008).

ERM-binding to the neuron-specific RSLE region of L1CAM overlaps with that of the μ2 subunit of the endocytosis adaptin complex AP-2 (Dickson et al. 2002; Cheng et al. 2005). Similar to the regulation of ankyrin binding by the phosphorylation of Tyr1229 in L1CAM, binding of ezrin and the μ2 subunit of AP-2 is abolished by phosphorylation of the Tyr1176 residue (Schaefer et al. 2002; Sakurai et al. 2008). Experimental evidence has been provided that the phosphorylation and dephosphorylation of Tyr1176 controls cycles of L1CAM endocytosis and cell surface trafficking in the advancing growth cone (Kamiguchi and Lemmon 2000; Kamiguchi and Yoshihara 2001; Schaefer et al. 2002). Double-immunolabeling has revealed distinct localizations of these ERM and AP-2 proteins in growth cones of cortical neurons suggesting the lack of competitive binding of these molecules to the cytoplasmic domain of L1CAM (Mintz et al. 2008). One possible explanation might be that lateral redistribution of L1CAM to distinct membrane microdomains allows association either with ERM or AP-2 proteins (Fig. 2b).

Whether interaction of ERM proteins with L1CAM is important for neural repair processes in the adult CNS is, to date, unclear. The modeling of transection injury has at least revealed the re-expression of ERM proteins in growth cones of sprouting neurites and their involvement in the regeneration of mature hippocampal neuronal cultures through interaction with L1CAM (Haas et al. 2004).

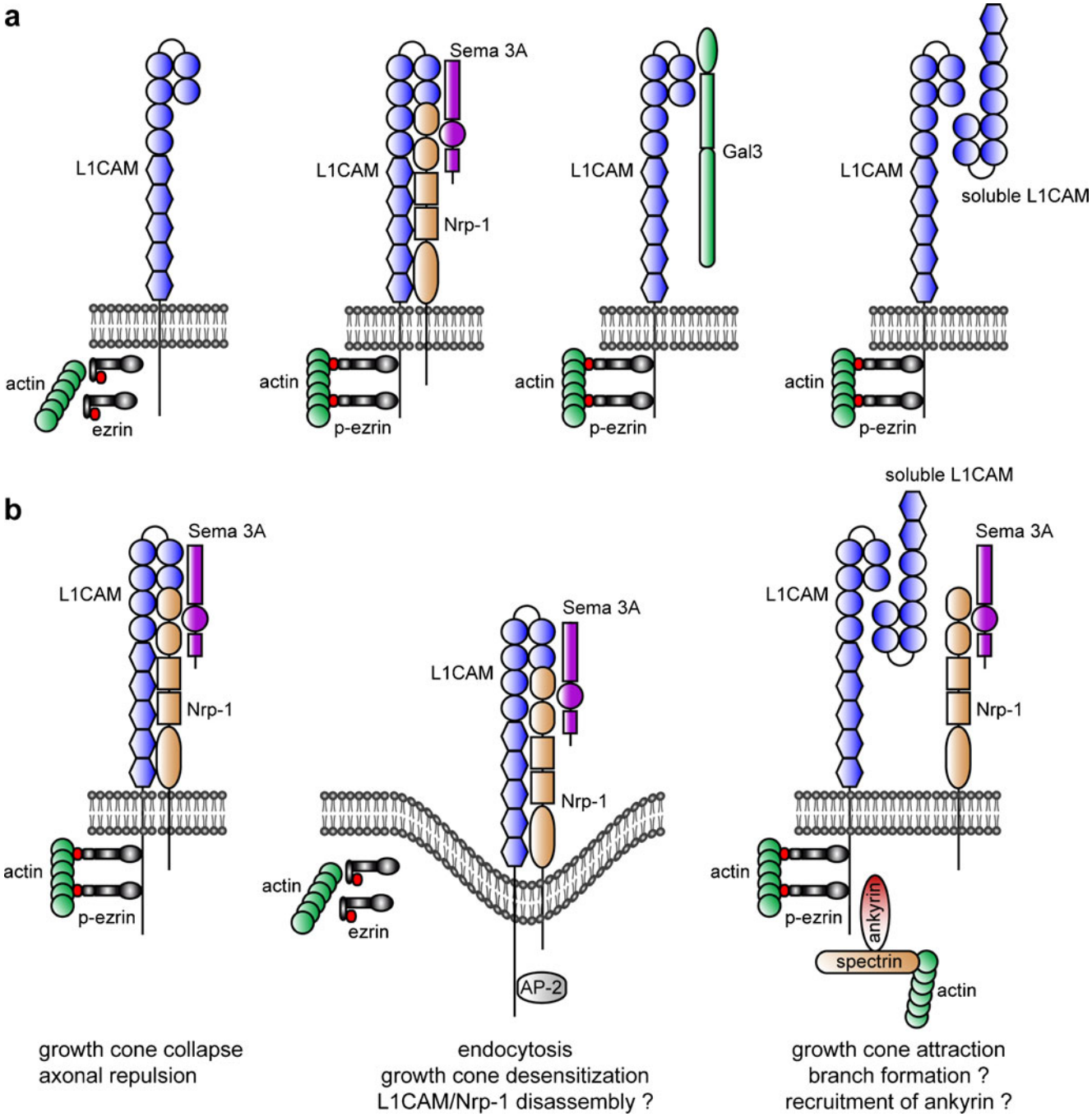

Fig. 2 Model showing various modes of intracellular interactions in response to extracellular ligand binding to L1CAM. **a** Semaphorin 3A (*Sema 3A*) binding to L1CAM/Nrp-1 or Galectin-3 (*Gal3*) binding to L1CAM or a homophilic L1CAM interaction leads to association of phosphorylated ezrin (*p-ezrin*) with the cytoplasmic part of L1CAM, thereby providing linkage to the actin cytoskeleton. **b** L1CAM/Nrp-1 mediate growth cone collapse and axon repulsion upon Sema 3A binding. Endocytosis of L1CAM/Nrp-1 might occur in membrane microdomains devoid of ezrin via interaction with the AP-2 complex (*AP-2*), which desensitizes for repulsive action of Sema 3A. Soluble L1CAM converts growth cone collapse to attraction and enables neuronal growth and branch formation, hypothetically involving the stabilizing function of ankyrins

More recently, the extracellular binding of the β-galactoside-binding protein Galectin-3 to hippocampal neurons has been identified to induce L1CAM-dependent axon branching (Diez-Revuelta et al. 2010). When offered as an immobilized substrate, Galectin-3 triggers the redistribution and co-localization of L1CAM, ERM and F-actin to discrete membrane sites at which axonal branches emerge (Diez-Revuelta et al. 2010; Fig. 2a). ERM proteins have also been

reported to co-localize in growth cones with another Ig superfamily member, the receptor protein called deleted in colorectal cancer (DCC), in response to the soluble DCC-ligand netrin-1, thereby mediating axon growth (Antoine-Bertrand et al. 2011). These findings are compatible with the hypothesis that ligand-receptor interactions can control axonal growth and branching via the redistribution of ERM proteins to the cytoplasmic part of transmembrane proteins such as L1CAM.

Supporting evidence for this hypothesis has been recently provided by Marsick et al. (2012). The authors report a rapid coincidental increase of L1CAM and phosphorylated ezrin in growth cone filopodia of dorsal root ganglion cells following neurotrophin stimulation. Conversely, depletion of L1CAM reduces filopodial levels of phosphorylated ezrin (Marsick et al. 2012). Earlier studies have highlighted the role of L1CAM in axonal responses to the soluble repulsive guidance cue Semaphorin 3A (Sema 3A). Work of Castellani and colleagues (2000, 2002) have uncovered that L1CAM is required for Sema 3A-mediated growth cone collapse. This effect has been attributed to an interaction of L1CAM and the Sema 3A-receptor Neuropilin-1 (Nrp-1) rather than plexin A, which also takes part in the transduction of Sema 3A signaling (Bechara et al. 2008). Moreover, the addition of soluble L1CAM-Fc protein to neuronal cultures, probably interfering with L1CAM *in cis*-binding to Nrp-1, converts Sema 3A chemorepulsion into attraction (Castellani et al. 2002; Fig. 2b). Dominant-negative ezrin also inhibits Sema 3A-mediated growth cone collapse (Mintz et al. 2008) suggesting a cooperative mode of interaction for L1CAM and ezrin in this process. Studies of growth cones of dorsal root ganglion cells indicate that Sema 3A induces the dephosphorylation of ERM proteins (Gallo 2008). This effect has also been observed in growth cones from cortical neurons. In addition, the dephosphorylation of ezrin causes enhanced internalization of L1CAM and Nrp-1 in these cells (Mintz et al. 2008). After the endocytosis of L1CAM/Nrp-1, ezrin has been hypothesized to become reactivated, thereby again stabilizing L1CAM/Nrp-1 in the plasma membrane and mediating their linkage to the actin cytoskeleton (Mintz et al. 2008).

Interestingly, L1CAM has been shown not only to interact physically with Nrp-1 (Bechara et al. 2008) but also to control the Sema 3A-induced internalization of Nrp-1 (Castellani et al. 2004). Ezrin-binding to the cytoplasmic domain of Nrp-1 has not been reported as yet. Thus, L1CAM-ezrin interaction might regulate Nrp-1 internalization in response to Sema 3A. Therefore, L1CAM-ezrin interaction might serve as an integrative step to regulate neurite growth and branching in response to Sema 3A via cell surface expression modulation of its own and Nrp-1. This mechanism likewise includes local rearrangements of the actin cytoskeleton and regulation by components of the focal adhesion kinase and MAP kinase cascade (Bechara et al. 2008). Additional mechanisms involved in the control of L1CAM cell surface abundance and recycling in growing neurons might relate to the partial ubiquitination and lysosomal degradation of L1CAM after endocytosis (Schäfer et al. 2010a). Further studies to dissect the regulatory mechanisms exerted by various protein kinases and associated signaling pathways that lie downstream of L1CAM might help to connect the role of this protein to neural repair processes in the damaged CNS.

Conclusions and perspectives

Since its discovery in 1984, substantial progress has been made in the understanding of the function of L1CAM in neurons and the developing nervous system. Mechanistic insights have been obtained into L1CAM-mediated axon branching in vitro, which might represent an anatomical correlate for axonal sprouting observed after CNS injury. The intrinsic role of L1CAM in regenerative axonal sprouting might, however, depend on the experimental lesion model, genetic background and age of the used model animals and on the cellular and molecular context of sprouting axons. Although the exact mechanisms of action are still incompletely understood, accumulating evidence indicates that L1CAM is important for the induction of a regenerative phenotype in neurons. As has become evident, the functioning of L1CAM and some of its interaction partners converges at the point of growth cone attraction and collapse. The unraveling of these mechanisms might represent a key step for the manipulation of axonal sprouting and promotion of neural repair in the adult CNS.

Acknowledgements We apologize to everyone whose work was not cited here because of space constraints.

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