L1 cell adhesion molecules as regulators of tumor cell invasiveness

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Fast growing malignant cancers represent a major therapeutic challenge. Basic cancer research has concentrated efforts to determine the mechanisms underlying cancer initiation and progression and reveal candidate targets for future therapeutic treatment of cancer patients. With known roles in fundamental processes required for proper development and function of the nervous system, L1-CAMs have been recently identified as key players in cancer biology. In particular L1 has been implicated in cancer invasiveness and metastasis, and has been pursued as a powerful prognostic factor, indicating poor outcome for patients. Interestingly, L1 has been shown to be important for the survival of cancer stem cells, which are thought to be the source of cancer recurrence. The newly recognized roles for L1CAMs in cancer prompt a search for alternative therapeutic approaches. Despite the promising advances in cancer basic research, a better understanding of the molecular mechanisms dictating L1-mediated signaling is needed for the development of effective therapeutic treatment for cancer patients.

A major obstacle in oncology is the early diagnosis and curative therapeutic intervention of locally invasive cancers that rapidly disseminate from the primary tumor to form metastases. The standard treatment for malignant tumors consists of surgical removal of the tumor mass followed by chemotherapeutic and radiotherapy in order to eradicate the remaining cancer cells. Despite such aggressive intervention, a population of resistant cancer cells often remains intact and is though to be the source of cancer recurrence. During the past decades, cancer basic research has focused on determining the molecular mechanisms underlying cancer initiation and progression that can provide a basis for the development of new and effective therapeutic treatments for cancer patients. An important finding was the discovery that cancer onset and progression and reveal candidate targets for future therapeutic treatment of cancer patients. With known roles in fundamental processes required for proper development and function of the nervous system, L1-CAMs have been recently identified as key players in cancer biology. In particular L1 has been implicated in cancer invasiveness and metastasis, and has been pursued as a powerful prognostic factor, indicating poor outcome for patients. Interestingly, L1 has been shown to be important for the survival of cancer stem cells, which are thought to be the source of cancer recurrence. The newly recognized roles for L1CAMs in cancer prompt a search for alternative therapeutic approaches. Despite the promising advances in cancer basic research, a better understanding of the molecular mechanisms dictating L1-mediated signaling is needed for the development of effective therapeutic treatment for cancer patients.

The L1 family of neural cell adhesion molecules (L1-CAMs), which is comprised of four structurally related transmembrane proteins L1, CHL1, NrCAM and neurofascin (Fig. 1), is now in the spotlight of cancer research due to their upregulation in certain human tumors. L1-CAMs are transmembrane molecules of the immunoglobulin superfamily, characterized by an extracellular region of six immunoglobulin-like domains and four to five fibronectin type III repeats, followed by a highly conserved cytoplasmic domain, which is reversely linked to the cell cytoskeleton through binding to ankyrin and ERM proteins (ezrin-radixin-moesin). Its multi-domain structure allows complex heterophilic interactions with diverse cell receptors, although homophilic interactions also have a crucial role in L1-CAMs mediated signaling.

A wealth of studies has revealed L1-CAMs as pivotal components for proper development of the nervous system through regulation of cell-cell interactions. L1-CAMs have critical roles in neuronal migration and survival, axon outgrowth and fasciculation, synaptic plasticity and regeneration after trauma.2 Neither CHL1 nor L1 is present on mature astrocytes, oligodendroglia or endothelial blood vessel cells in the brain, but CHL1 is upregulated in astrocytes upon injury2 and is present on oligodendroglial precursors.4,5 During neural development, L1 plays an important role in the migration of dopaminergic neuronal cell groups in the mesencephalon and diencephalon.6 In the cerebellum, L1 is required for the inward migration of granule neurons from the external granular layer and cooperates with NrCAM in regulating neuronal positioning.2 Similarly, CHL1 controls area-specific migration and positioning of deep layer cortical neurons in the neocortex.7 In addition to its role in neuronal precursor positioning, L1 plays a crucial role in axon guidance, which is governed by repellent and attractive response mechanisms directed by Ephrins and Semaphorins and their receptors (Ephs, Neuropilins, Plexins).2 The importance of L1-CAMs in the development and function of the nervous system is exemplified by developmental neuropsychiatric disorders that are associated with mutation or genetic polymorphisms in genes encoding L1 (X-linked mental retardation) and CHL1 (low IQ, speech and motor delay). Polymorphisms in L1 and CHL1 genes are also associated with schizophrenia, and NrCAM gene polymorphisms are linked to autism in some populations.2

Recent studies have described upregulation of L1 in a variety of tumor types. Overexpression of L1 correlates with tumor progression and metastasis in certain human gliomas,8 melanoma,9...
observed for epithelial ovarian carcinoma\textsuperscript{10} and colorectal
nostic factor, indicative of poor outcome for patients as
been pursued as both a biomarker and a powerful prog-
of colon cancers but not in the tumor mass.\textsuperscript{12} L1 is also
associated with micrometastasis to both lymph nodes and
bone marrow in patients bearing other cancers, suggesting
a potential role in early metastatic spread.\textsuperscript{11} L1 has now
been pursued as both a biomarker and a powerful prog-
ons in gliomas, L1 expression was shown to be over-
expressed in a small fraction of glioma cells, termed
glioma stem cells, which are capable of self-renewal and
generate the diverse cells that comprise the tumor.\textsuperscript{14} First
characterized in acute myeloid leukemia,\textsuperscript{15} cancer stem
methods that are laid down as "tracks" on the
extracellular matrix (ECM). These fragments can cause autocrine
activation of signal transduction pathways, promoting cell migra-
tion through heterophilic binding to integrins.\textsuperscript{20} Specifically, L1
is cleaved constitutively or inducibly by the ADAM family metal-
loproteases (a disintegrin and metalloprotease) ADAM10 and
ADAM17, which stimulates cell migration and neurite outgrowth
during brain development.\textsuperscript{20,21} In colon cancer, L1 colocalizes with
ADAM 10 at the invasive front of the tumor tissue, suggesting that
L1 shedding may play a role in cancer invasiveness.\textsuperscript{12} Similarly,
CHL1 is shed by ADAM8, which was reported to promote cell
migration and invasive activity of glioma cells in vitro and is
highly expressed in human brain tumors including glioblastoma
multiforme, correlating with invasiveness in vivo.\textsuperscript{22} Furthermore,
NrCAM, found in pancreatic, renal and colon cancers, is subject to
ectodomain shedding,\textsuperscript{23} but its function in regulating cell migra-
tion or invasion has not yet been studied.

Given the newly recognized roles of L1 in tumor progression,
a growing body of experimental studies has explored novel ther-
apeutic approaches targeting L1-CAMs. Antibody-based therapeutic
strategies are being pursued to functionally inhibit homophilic and
heterophilic interactions of cell adhesion molecules to suppress
tumor invasive motility. L1 monoclonal antibodies reduce in vivo
growth of human ovarian and colon carcinoma cells in mouse
xenograft models.\textsuperscript{13,24,25} L1 targeting using lentiviral-mediated
short hairpin RNA (shRNA) interference decreases growth and
survival of glioma stem cells in vitro, suppresses tumor growth, and
increases survival of tumor-bearing animals.\textsuperscript{14} These findings raise
the possibility that L1 represents a cancer stem cell-specific thera-
peutic target for improving the treatment of malignant gliomas and
other brain tumors. Cancer stem cells represent a potential target

![Figure 1. L1-CAMS: All have 6 Ig domains and 4–5 FN domains. The 186 kD Neurofascin isoform has a mucin-like Pro/Ala/Thr-rich (PAT) domain, while the 155 kD has only the 4 FN domains. RGD and DGEA motifs interact with integrins, while the FIGQ/AY motif binds to ankyrin. ERM binding sites are indicated. The RSLE motif in L1 recruits AP2/clathrin adaptor for endocytosis.](Image 276x545 to 568x728)
for future treatment of different cancer as these cells are believed to be responsible for cancer recurrence.26 Promoting cancer stem cell differentiation by drug treatment could potentially reduce stem cells properties of self-renewal and proliferation, leading to inhibition of tumor growth.

Inhibitors of metalloproteases that block L1-CAM shedding represent a potentially novel approach to curtailing tumor invasiveness. Chemical inhibitors of ADAMS are appealing for glioma therapy due to their diffusability, which circumvents blood-brain barrier limitations. Another novel approach involves the secreted axon repellent protein, Semaphorin 3A (Sema3A). L1-CAMs serve as co-receptors for Sema3A by cis binding in the plasma membrane to Neuropilin-1, important for repellent axon guidance.2 Interestingly, Sema3A inhibits invasiveness of prostate cancer cells27 and migration and spreading of breast cancer cells in vitro assays,28 and thus may also be mediated by L1-CAMs. Such an approach could be potentially useful in mitigating invasion of cancer cells in gliomas and other tumors that are known to express L1 and Neurilpins. However, effective strategies for some types of cancer can promote cancer progression in other types. For example, Sema3A has been shown to contribute to the progression of pancreatic cancer29 and colon cancer.30 Thus, it is imperative that the molecular mechanisms underlying L1-mediated signaling are understood in a tissue specific manner. Despite the promising advances in cancer basic research, much more research is needed to better design strategies for cancer therapy.

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