Chapter 12

Cell Adhesion Molecules in Neural Stem Cell and Stem Cell-Based Therapy for Neural Disorders

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1. Introduction

Neural stem/progenitor cells (NS/PCs), found in both the developing and the adult mammalian central nervous system (CNS), are a heterogeneous population of multipotent cells with the potential to self-renew by symmetric cell division or to differentiate into neurons, astrocytes and oligodendrocytes through asymmetric cell division (Gage, 2000; Alvarez-Buylla et al., 2001; Temple, 2001; Götz and Huttner, 2005). NS/PCs have been found in almost all regions of the developing mammalian CNS, including the basal forebrain, cerebral cortex, ganglionic eminence, hippocampus, cerebellum, neural crest and spinal cord (Temple, 2001). Throughout development, NS/PCs give rise to neurons and glial cell populations of the CNS. In the adult CNS, NS/PCs are mainly found in the subventricular zone (SVZ) and subgranular layer (SGL) of hippocampal dentate gyrus (DG) (Göritz and Frisén, 2012). The ependymal cells lining the central canal of spinal cord of the adult mouse could be another potential source of adult NS/PCs (Meletis et al., 2008). Because neurogenesis and gliogenesis occur during different stages of mammalian brain development, it was long assumed that neurons and glial cells in the CNS were generated from distinct precursor populations, known as early-embryonic, late-embryonic, and adult NS/PCs. However, abundant evidence has since now demonstrated that embryonic and adult NS/PCs are likely lineage-related. Neuroepithelial cells behaving as NS/PCs during very early developmental stages of the mammalian CNS give rise to radial glial cells around embryonic day 12 (E12). As the progeny of neuroepithelial cells, radial glial cells act as NS/PCs in the fetal and perinatal brain, and develop into astrocyte-like stem cells in the adult brains. Astrocyte-like adult stem cells function as stem cells to generate new nerve cells in the adult mammalian CNS. (Doetsch et al., 1999; Alvarez-Buylla et al., 2001; Merkle et al., 2004; Merkle and Alvarez-Buylla, 2006).

Evidence from recent studies indicates that NS/PC self-renewal and the time course of NSC fate determination are regulated by a combination of nuclear modifications, transcription factors and extrinsic signals from the stem cell microenvironment, also known as stem cell niche (Shi et al., 2008). Cell adhesion molecules (CAMs) located on the cell surface bind to the extracellular matrix (ECM) as well as other cells, thereby connecting cells with their surroundings. As important participants in cell-cell and cell-ECM interactions, CAMs have been shown to play essential roles in NS/PC development, including proliferation, differentiation, and migration, through extrinsic signals from the stem cell niche. Furthermore, many CAMs have been studied for the potential application in repair of CNS and peripheral nervous system (PNS) damage. Based on the role of CAMs in the NS/PC development and on the repair of nervous system, many researchers have investigated the possibility of combining CAMs and stem cell-based transplantation therapy to treat neural disorders and neural injury.

This chapter will discuss the most recent research in CAM functions in NS/PC development, as well as highlighting the applications and future potential of applying CAMs in stem cell-based therapy.

2. Cell adhesion molecules

CAMs are transmembrane proteins located on the cell surface through which cells bind or interact with other cells and the ECM surrounding them. CAMs normally contain three domains: an intracellular domain by which CAMs bind to cytoskeleton proteins, an extracellular domain that interacts with the ECM or other CAMs and a transmembrane domain (Chothia and Jones, 1997). Through these three domains, CAMs can transfer extrinsic signals from microenvironment or other neighboring cells and trigger diverse signaling pathways. Although CAMs can be classified by whether they are calcium-dependent or calcium-independent, most CAMs are categorized into four families: the immunoglobulin superfamily, the cadherins, the integrins, and the selectins (Brackenbury et al., 1981; Shapiro et al., 2007).

The complexity of structure and functions in the nervous system are achieved by the complex interconnections among its component cells. Many types of CAM interactions between various types of neural cells in the nervous system have been reported. Here, the classification and structure-function relationship of CAMs highly expressed in nervous system or play essential roles in nervous system will be introduced and briefly discussed.

2.1. Immunoglobulin superfamily cell adhesion molecules

Immunoglobulin superfamily cell adhesion molecules (IgSF CAMs) are a group of calcium-independent CAMs that share a common structural domain called immunoglobulin (Ig) domain. Members from IgSF CAMs have diverse binding activities and mechanisms of function. Certain IgSF CAMs interact through their extracellular domains with the same type of CAMs, a mechanism referred to as homophilic binding. Conversely, through heterophilic binding, other IgSF CAMs bind to different CAMs or to other cell surface proteins as well as

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soluble proteins in the ECM, Due to their structural and binding specificity, different IgSF CAMs have been shown to play distinct roles in the nervous system.

2.1.1. L1CAM subfamily

L1CAM subfamily proteins, which include L1, close homolog of L1 (CHL1), NrCAM, and Neurofascin, are one of the most well known groups of IgSF CAMs and are widely studied in the nervous system. L1CAM proteins can homophilically bind to themselves, and based on their structure, can heterophilically interact with many other IgSF CAMs (e.g. NCAM, TAG-1, and contractin), ECM molecules (e.g. laminian, tenascins, Src and extracellular signal-regulated kinases (Erk)), cytoplasmic proteins, including cytosketeton proteins such as ankyrins, and traffic proteins such as AP-2 (Maness and Schachner, 2007).

The extracellular domain of L1CAM proteins contains six Ig-like domains and four or five fibronectin type III (FNIII) repeats, followed by a transmembrane domain and cytoplasmic domain (Fig. 1A). The Ig1 domain of L1/CHL1 can bind neuropilin-1, an important component of the axonal guidance molecule semaphorin 3A (Sema3A) (Castellani et al., 2002). Similarly, NrCAM has been shown to bind neuropilin-2 to form a complex that mediates Sema3B and Sema3F signaling (Falk et al., 2005). Fluorescent bead aggregation and cell binding assays demonstrate the N-terminal of the L1 Ig1 domain is essential for L1 homophilic binding (Jacob et al., 2002). Through unique motifs in the Ig6 domains, L1 and CHL1 trigger Erk, mitogen-activated protein kinase kinase (MAP2K), phosphatidylinositol-3 kinase (PI3 kinase), and Src signaling pathway by interacting with integrins in some biological processes (Schaefer et al., 1999; Schmid et al., 2000). The intracellular domains of L1CAMs contain a highly conserved motif by which L1CAM proteins bind to ankyrins, a group of adaptor proteins linking integral membrane proteins to the cytoskeleton (Bennett and Baines, 2001). When the cytoplamic domain of Neurofascin is tyrosine phosphorylated, doublecortin (DCX) is recruited and mediates the binding of Neurofascin to microtubules (Kizhatil et al., 2002). An alternative splicing generates a motif YRSL in the cytoplasmic domain of L1 that mediate interactions between L1 and AP-2, a clathrin adaptor that triggers tyrosine-based signals for endocytosis (Kamiguchi et al., 1998). L1 was also shown to directly bind to membrane-cytoskeleton linking ezrin-radixin-moesin (ERM) proteins, through which L1 can bind to the actin cytosketeton and regulate axonal outgrowth and neuronal differentiation (Dickson et al., 2002). These structure-dependent interactions between L1CAMs and other ECM molecules, cytoskeleton proteins and cytoplasmic molecules suggests that are L1CAMs an essential component during the extrinsic signaling transduction regulating neurite outgrowth, axon growth, cell migration and differentiation (Maness and Schachner, 2007). Moreover, the intracellular domain of CHL1 directly interacts with synaptic chaperones Hsc70, CSP and alphaSGT, thereby regulating SNAP25 and VAMP2-induced exocytotic machinery (Andreyeva et al., 2010).

2.1.2. NCAM

Neural cell adhesion molecule (NCAM), also known as CD56, is a glycoprotein expressed on the cell surface of various cell types, including neurons, glial cells, and natural killer cells. NCAM is a unique member of IgSF CAMs because of its 27 alternatively spliced mRNAs and

its three major protein isoforms: NCAM-120, NCAM-140, and NCAM-180, so named due to their molecular weights (Reyes et al., 1991).

These three NCAM isoforms share the same extracellular domain, but vary in their transmembrane domains and cytoplasmic region. The extracellular domain of NCAM contains five Ig-like domains and two FNIII repeats, followed by a transmembrane domain in NCAM-140 and NCAM-180 isoforms, but a glycophosphatidyl (GPI) anchor linking to the cell membrane in NCAM-120 (Fig. 1A) (Chothia and Jones, 1997). NCAM-140 has a shorter intracellular domain compared to NCAM-180. The different domains of NCAMs have been reported to play distinct roles in binding activities and biological functions. The Ig-like domains have been shown to be essential for NCAM homophilic binding, and the FNIII repeats are involved in signaling that regulate neurite outgrowth. *Trans*-homophilic binding of NCAMs on different cell surfaces and *cis*-homophilic binding on the same surface have been observed, and both binding models play roles in neurite outgrowth (Walmod et al., 2004). Although the mechanism behind these binding models remains unknown, several studies have suggested that either Ig1 and Ig2 only or all five Ig-like domains are involved in NCAM *trans*-homophilic binding. Both Ig1 and Ig2, and Ig1 and Ig3 have demonstrated important roles in NCAM *cis*-homophilic binding (Frei et al., 1992; Ranheimet al., 1996; Atkins et al., 2004). The FNIII repeats bind fibroblast growth factor receptor (FGFR), which induces NCAM-mediated neurite outgrowth and plasticity. (Kiselyov et al., 2005). A PDZ-like sequence in the cytoplamic domain of NCAM-180 is required for NCAM-180-mediated activation of myosin light chain kinase (MLCK) (Polo-Parada et al., 2005). The intracellular domain of NCAM-180 has also been shown to be essential for the interaction between NCAM-180 and dopamine D2 receptor, by which NCAM regulates dopminergic signaling and behavior (Xiao et al., 2009). Non-receptor tyrosine kinase $p59^{fyn}$ has been found to interact specifically with NCAM-140, which activate $p59^{fyn}$ and focal adhesion kinase (FAK). The subsequent activation of c-Ras1 triggers the Erk signaling (Kolkova et al., 2000). Prion protein (PrP) can recruit and stabilize NCAM-140 on lipid rafts and regulate $p59^{fyn}$ to enhance neurite outgrowth (Santuccione et al., 2005). NCAM-140 also binds to GFRα, the glial-derived neurotrophic factor (GDNF) receptor, which regulates GDNF-mediated Schwann cell migration (Paratcha et al., 2003). Additionaly, the unique carbohydrate motif α-2,8-linked polysialic acid (PSA) on the Ig5 domain, observed only on NCAMs, has been found to negatively influence the homophilic binding of NCAMs as well as their interaction with heparin and heparin sulfate, due to the highly negative charge of PSA (Rutishauser and Landmesser, 1996). Through its inhibition of NCAM homophilic binding and reduction of cell adhesion during cell migration, PSA exhibits functions during many neural processes, including those related to learning and memory, and certain neurological disorders (Becker et al., 1996; Senkov et al., 2006; Stoenica L et al., 2006).

2.1.3. Nectins and Nectin-like molecules

Nectins and Nectin-like molecules (Necls) form another large IgSF CAM family, including four Nectins (Nectin-1, 2, 3, 4) and five Necls (Necl-1, 2, 3, 4, 5), and exhibit cell-cell adhesive functions in a wide range of tissues, including epithelia and neuronal tissue (Takai et al., 2003). All Nectins and Necls share the same structure domains, containing an extracellular

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domain with three Ig-like repeats, through which they play their roles in cell-cell adhesion activity, a single transmembrane region, and a cytoplasmic domain (Fig. 1A) (Sakisaka and Takai, 2004). Nectins and Necls can form *cis*-homo-dimers, and subsequently form *trans*-homo-dimers or *trans*-hetero-dimers through their extracellular Ig-like domains. (Sakisaka and Takai, 2004). Nectins can *trans*-interact with c-Src, to activate Rac and Cdc42 signaling (Shimizu and Takai, 2003)., Nectins can bind to F-actin-binding protein afadin through their cytoplasmic domain. Upon binding afadin, Nectins interact with α-catenin and cadherins, playing a role in forming cell-cell adhesion junctions and tight junctions in epithelial cells (Takai and Nakanishi, 2003). Nectins also regulate cell polarization through interacts with Par-3 via their intracellular domain (Takekuni et al., 2003). In addition, Necls interact with many important proteins, such as membrane-associated guanylate kinase Dlg3/MPP3, tumor suppressor DAL-1, CD44, platelet-derived growth factor (PDGF), and Nectins (Yageta et al., 2002; Fukuhara etal., 2003; Takai et al., 2003; Kakunaga S et al., 2004;).

2.1.4. TAG-1

TAG-1, also called TAX-1 (human) or axonin-1, a 135 kDa glycoprotein expressed on the developing axons, belongs to IgSF CAMs superfamily and plays important roles in neurite outgrowth and cell aggregation. TAG-1 has six Ig-like domains followed by four FNIII repeats and is anchored to the cell membrane by a GPI tail (Fig. 1A) (Furley et al., 1990). During development of the central and peripheral nervous system, TAG-1 is transiently expressed both as a soluble form and a GPI-anchored form (Karagogeos et al., 1991). Binding analysis revealed that FNIII repeats but not Ig domains are sufficient for homophilic binding, although both TAG-1 domains types can promote the neurite outgrowth (Tsiotra et al., 1996; Pavlou et al., 2002). The four amino-terminal Ig-like domains have been shown to be important for TAG-1 and neural glial cell adhesion molecule (NgCAM) *cis*-position binding, while the Ig5 and Ig6 domains have a strong inhibitory effect on TAG-1 and NgCAM binding (Buchstaller et al., 1996; Rader et al., 1996). L1 and NrCAM were shown to interact with TAG-1 through its Ig-like domains in the *trans*-position (Pavlou et al., 2002).

2.1.5. MAG

Myelin-associated glycoprotein (MAG) is expressed on the surface of oligodendrocytes in the CNS and Schwann cells in the PNS, and has been implicated in neuron-oligodendrocyte and oligodendrocyte-oligodendrocyte interactions in the CNS and glia-glia interaction in the PNS (Sternberger et al., 1979; Quarles, 1984; Martini and Schachner, 1986; Poltorak et al., 1987). Two MAG isoforms have been identified as small MAG (S-MAG) and large MAG (L-MAG). Similar to other IgSF CAMs, MAGs contain an identical extracellular domains composed of five Ig-like domains, a transmembrane segment, and two distinct cytoplasmic domains, which distinguish the S-MAG and L-MAG (Fig. 1A) (Salzer et al., 1987). MAG binds gangliosides, the most abundant sialylated glycoconjugates in the nervous system, which are important for neuron-oligodendrocyte interaction (Schnaar et al., 1998). MAG was shown to interact with the leucine-rich repeat (LRR)-containing GPI-linked Nogo-66 receptor (NgR), inducing the inhibition of neurite outgrowth (Fournier et al., 2001; Domeniconi et al., 2002).

There are many other IgSF CAMs, not to be introduced in this chapter, found in other mammalian body systems, such as intercellular cell adhesion molecule (ICAM-1, expressed on endothelial cells and cells of the immune system), vascular cell adhesion molecule (VCAM-1, expressed on blood vessels), platelet-endothelial cell adhesion molecule (PECAM-1, expressed on the surface of platelets, monocytes, neutrophils, and some types of T-cells).

2.2. Cadherins

Cadherins, a family of calcium-dependent CAMs, are the major architectural molecules mediating cell-cell adhesion of extracellular domains at intercellular junctions. The cadherin superfamily consists of four subgroups, including classic cadherins, protocadherins, desmosomal and unconventional cadherins, which share a similar structure with extracellular Ca^{2+}-binding domains, known as cadherin repeats (Angst et al., 2001). Although the homophilic binding of specific cadherin subtypes has been described frequently, several cadherin subtypes were also found to interact heterophilically (Ahrens et al., 2002).

2.2.1. Classic cadherins

In vertebrates, classic cadherins, including epithelial cadherin, neural cadherin, and placental cadherin and so on, have five extracellular cadherin repeats, a transmembrane domain, and a highly conserved intracellular domain (Fig. 1B) (Tepass et al., 2000). By binding to Ca^{2+} on the boundary between cadherin repeats, the extracellular domain is stabilized and undergoes homophilic interactions, which is essential for the adhesion function of cadherins (Nagar et al., 1996). Both *cis*- and *trans*-homophilic interactions were observed in classic cadherin-mediated cell adhesion (Zhang et al., 2009). Classic cadherins bind to two cytoplasmic proteins, p120-catenin and β-catenin, through the conserved intracellular motif (Tepass et al., 2000). The cadherin-β-catenin complex interacts with α-catenin and subsequently associates with actin, forming an adherin junction and a cell-cell signaling centre together with cytoskeletal and signaling molecules (Wheelock and Johnson, 2003; Drees et al., 2005). In addition to catenin proteins, classic cadherins have been observed to interact with many other molecules from various signaling pathways (Erez et al, 2005). For example, cadherin-mediated cell adhesion is involved in Wnt, Hedgehog, Ras, and RhoGTPase signaling (Stepniak et al., 2009; Watanabe et al., 2009; Heuberger and Birchmeier, 2010). Cadherin-catenin complex also interacts with receptor-type tyrosine kinases, such as FGFRs and epithelial growth factor receptors (EGFRs) (Mason, 1994; Perrais et al., 2007). Such crosstalk between cadherin system and other signaling pathways allow cadherins to play critical roles in diverse cell biological behaviors. In humans, there are 18 cadherins in the classic cadherin superfamily, of which epithelial cadherin (E-cadherin, or cadherin-1), is the most well studied member. As its name indicates, E-cadherin is expressed in developmental and adult epithelial tissues. The cytoplasmic tail of E-cadherin, containing a highly phosphorylated region, is essential for the function of E-cadherin in the formation cell-cell junction (Tepass et al., 2000). Neural cadherin (N-cadherin or cadherin-2) is broadly expressed in neuroepithelial cells during early embryonic and neonatal development, particularly in the nuclei and laminae, and neuroanatomical connections during late embryonic stages and early postnatal development (Redies and Takeichi, 1993). N-cadherin

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has been reported to play critical roles in the establishment of left-right asymmetry and synaptogenesis as well as catenin-mediated processes related to learning and memory (Benson and Tanaka, 1998; García-Castro et al., 2000). Placental cadherin (P-cadherin or Cadherin-3) is highly expressed in undifferentiated cells in epithelial tissues and human embryonic stem cells, and is a putative stem and precursor cell maker (Raymond et al., 2009).

2.2.2. Protocadherins

With more than 100 having been identified in mammals, protocadherins are the largest subfamily of cadherins (Hirano and Takeichi, 2012). Protocadherins can be further sorted into two groups, based on their genomic distribution: clustered protocadherins, whose coding genes are located on human chromosome 5 in tandem order, and consist of three gene subclusters Pcdhα, Pcdhβ and Pcdhγ, and non-clustered protocadherins, whose genes are distributed among different chromosomes and are divided into several subgroups, incuding δ-protocadherins (Vanhalst et al., 2005). The extracellular domains of protocadherins contain more than five cadherin motifs, which differ from the characteristic features of classical cadherins (Fig. 1B) (Sano et al., 1993). Unlike the highly conserved cytoplasmic tails of classic cadherins, the intracellular domains of protocadherins are variable, suggesting their diverse functions. Although protocadherins appear to display weaker cell-cell adhesion than classic cadherins, protocadherins show diverse biological functions in the CNS, including roles in neuronal differentiation and synaptogenesis (Hirano and Takeichi, 2012).

2.3. Integrins

Integrins are a group of cell surface receptors that form a large CAM subfamily. Integrins are heterodimeric glycoproteins consisting of two distinct subunits: an α-subunit and β-subunit that each penetrates the cell membrane once and has a short intracellular tail which is typically 40 to 70 amino acids long. Thus far, 18 α-subunits and 8 β-subunits have been identified and 24 $\alpha\beta$ combinations have been observed (Hynes, 2002). The extracellular domain of α-subunits, which generally are larger than 900 amino acids, is divided into four subdomains containing a ligand-binding N-terminal region including a sevenfold repeat, among which repeats 5, 6, and 7 contain a Ca^{2+}- binding structure. Half of the α-subunits contain an extra I-domain, which contributes a divalent cation-binding site and facilitates an interaction with IgSF CAMs (Fig. 1C) (Landis, et al., 1994). The ectodomains of integrin β-subunits are typically larger than 600 amino acids and contain 8 subdomains, including an N-terminal signal region as well as a metal-binding site that is directly involved in ligand-integrin interactions (Fig. 1C). The extracellular N-terminal of α-chain and β-chain form a ligand-binding $\alpha\beta$ headpiece (Fig. 1C). Through interactions between their extracellular domain and ECM ligands and other CAM family members, integrins can perform outside-in signaling to mediate cell response to its surrounding environment. Moreover, through their intracellular tails, integrins can also perform inside-out signaling, thereby relaying the intercellular cell state to the extracellular environment. Using both outside-in and inside-out signal transduction models, integrins not only aid in facilitating cell-ECM interactions, but also play roles in many other biological activities, including cell cycling as well as cell growth, survival, and differentiation.

2.4. Selectins

The selectin family of CAMs is a group of calcium-dependent transmembrane glycoproteins. Three selectins have been identified, including E-selectin (found on endothelial cells), L-selectin (found on lymphocytes), and P-selectin (found on platelets and endothelial cells). All identified selectins share a similar extracellular structure, composed of an N-terminal sequence, a calcium-binding lectin domain, an EGF-like domain, in addition to a non-conserved transmembrane domain, a non-conserved cytoplasmic tail and a differing number of consensus repeats (Fig. 1D). Selectins have been reported to play important roles in the immune system associated with inflammation and cancer progression (Barthel et al., 2007).

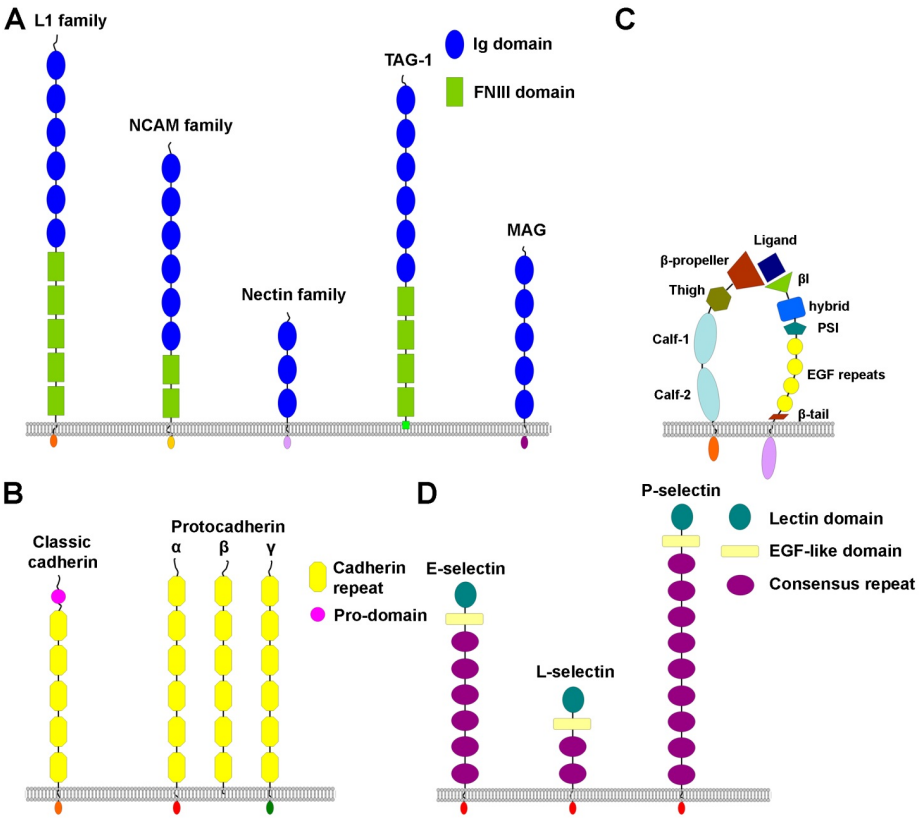

Figure 1. Schematic diagram of diverse domain structure of different CAM superfamilies. A. IgSF CAM proteins. B. Cadherins. C. Integrins. D. Selectins

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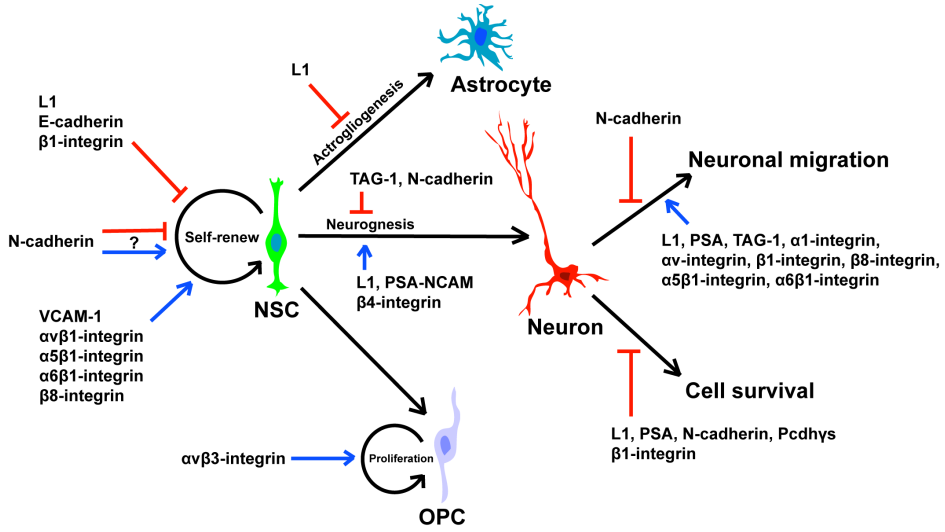

Figure 2. Roles of cell adhesion molecules in neural stem/precursor cell self-renewal, differentiation, cell survival and migration.

3. Cell adhesion molecules and neural stem/progenitor cell development

In the mammalian embryonic CNS, NS/PCs are found in almost all regions, and give rise to every type of neural cells, including various subtypes of neurons, astrocytes, and oligodendrocytes, forming the most complex and functional organ of the body (Temple, 2001). In the adult CNS, astrocyte-like type-B stem cells reside only in certain regions, namely as the subventricular zone (SVZ), from which stem cells migrate into olfactory bulb (OB) and differentiate into mature neurons, and the SGL of hippocampal DG, from which stem cells migrate and extend processes into the molecular layer of the hippocampus (Gage, 2000). Ependymal cells lining the central canal of adult mouse spinal cord can exhibit dramatic proliferation after spinal cord injury and give rise to newborn glial cells in the injured spinal cord (Göritz1 and Frisén, 2012). Many CAMs from different subfamilies are expressed in these neurogenic regions, although their functions have not been fully understood. Increasingly evidences suggest that CAMs are not only important for maintenance of the architecture and shape of stem cell niche, but also play essential roles in signaling transduction from the stem cell niche to regulate cell survival, proliferation, differentiation, and migration. Recent progress in NS/PC cell fate research indicates that stem cell maintenance and cell fate determination are regulated by a combination of epigenetic modulation, intrinsic transcription factors and extrinsic signals from the NS/PC niche (Shi et al., 2008). Transcriptional factors play essential roles in NS/PC fate determination by regulating multiple downstream gene expression in NS/PCs. However, the functions of these intrinsic factors are regulated by extrinsic cues

through various signaling pathways mediated by cell surface receptors and down-stream cellular signaling elements. Modulation of cell fate by such extrinsic cues provides an excellent mechanism for neural progenitor cells to adapt to the environment. As bridging molecules between extrinsic signals from neighbor cells or the ECM and intracellular transcriptional regulation, CAMs play critical roles during these processes.

3.1. Cell adhesion molecules regulate neural stem/progenitor cell self-renewal and proliferation

Self-renewal is essential for NS/PCs to perpetuate and maintain their population in an undifferentiated state, which is critical for the CNS development, learning and memory-related plasticity in adult animals as well as replacement for dead cell following injury. Recent studies showed that the NS/PC niche, comprised of ECM molecules, soluble factors, and cell surface molecules, is essential for NS/PC identification, maintenance of stem cell population, and preventing contact with differentiation stimuli and cell apoptotic signals (Doetsch, 2003; Miller and Gauthier-Fisher, 2009; Moore and Lemischka, 2006). Among the NS/PC niche molecules, CAMs play a critical role as transducers that mediate signaling between stem cells and their niche.

IgSF CAMs play diverse roles in the regulation of NS/PC self-renewal and proliferation through specific signaling pathways. L1 is highly expressed in the developing neurons of the cerebral cortex, hippocampus, and corpus callosum, with expression declining to low levels with maturation (Demyanenko et al., 1999). Reduced hippocampal neurons were observed in L1-deficient mice, suggesting that L1 may have a potential role in neurogenesis (Demyanenko et al., 1999). Although undifferentiated NS/PCs do not express L1, substrate-coated L1 inhibits the proliferation of cultured NS/PCs *in vitro* (Dihné et al., 2003). Further investigation using L1-deficient precursors suggests the mechanism by which L1 affects NS/PC proliferation is through heterophilic binding with unknown receptors (Dihné et al., 2003). Ectopic expression of L1 using human GFAP promoter in NS/PCs, or overexpression of L1 on the ESC-derived neural precursors resulted in an impaired proliferation *in vitro* (Bernreuther et al., 2006; Cui et al., 2010; Cui et al., 2011; Xu et al., 2011). Interestingly, L1 isoform 2 is expressed on the surface of human ESCs, in which it positively affects proliferation. Deletion of stable L1 decreased hESC proliferation, while L1 overexpression enhanced proliferation, suggesting the diverse roles of L1 on different cell types by different mechanisms (Son et al., 2011). In the adult CNS, VCAM-1 is expressed on the apical processes of type B astrocyte-like adult stem cells in the adult mouse SVZ, and has been reported to be essential for SVZ cytoarchitecture, maintenance of adult NS/PCs, and neuroblast chain migration (Kokovay et al., 2012). Blocking VCAM1 expression with VCAM1 antibodies disrupts position and cytoarchetecture of ependymal cells and type B cells in at ventricular surface. Further investigation demonstrated that VCAM1 maintains adult NS/PCs through NOX2 production of reactive oxygen species (Kokovay et al., 2012).

Neuroepithelial attachments at adherens junctions are critical for NS/PC maintenance and self-renewal. As essential molecules during the nervous system development, cadherins have been reported to play roles in neural tube, neuroepithelial layer and boundary formation, synaptogenesis, axon guidance and regulation of NS/PC behaviors. E-cadherin is expressed in the

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embryonic and adult ventricles, where NS/PCs reside, and in clonal stem cell colonies *in vitro*. Deletion of E-cadherin results in a reduction of NSC self-renewal, but an increase of neural precursor proliferation in vivo (Karpowicz et al., 2009). *In vitro* culture experiments provide further evidence that loss of E-cadherin reduces NSC self-renewal, while overexpressing E-cadherin results in an increased NSC number, due to the adhesion function of E-cadherin (Karpowicz et al., 2009). N-cadherin, which is highly expressed in the nervous system, appears to be important for maintenance of NS/PCs and cell proliferation. During neural tube development in zebrafish, N-cadherin was shown to restrict proliferation of neural precursors in the dorsal neural tube by regulating the cell cycle length (Chalasani and Brewster, 2011). Increased cell division and shortened cell cycle length, mediated by ligand-independent activation of Hedgehog signaling, were observed in the N-cadherin mutant, (Chalasani and Brewster, 2011). However, other studies have found opposing effects of N-cadherin. Knockdown of N-cadherin expression by *in utero* electroporation of shRNA targeting N-cadherin resulted in reduced β-catenin signaling, leading to increased cell cycle exit and enhanced premature neuronal differentiation. These effects could be rescued by introducing a stabilized active form of β-catenin (Zhang et al., 2010). Another *in vitro* study using fusion protein N-cadhsion-Fc (including extracellular domain of N-cadherin and Fc domain of IgG)-coated culture conditions demonstrated that N-cadherin-Fc promotes maintenance of the neural precursor cell lines P19 and MEB5, and promotes proliferation (Yue et al., 2010). In a more recent study in spinal cord, forkhead transcription factors Foxp2 and Foxp4 suppressed N-cadherin to promote the detachment of differentiating neurons from the neuroepithelium. Blocking Foxp2 and Foxp4 function in both mouse and chick enhances progenitor maintenance, implying that N-cadherin plays diverse in different systems and signaling pathways (Rousso et al., 2012).

Many integrins are expressed in neurogenic regions of the developing and adult mammalian CNS. Cultured neurospheres from newborn mouse forebrain express five major integrins, including α5β1-, α6Aβ1-, αvβ1-, αvβ5-, αvβ8-, and low levels of α6Bβ1-integrin. Antibody inhibition of α5β1- and αvβ1-integrins reduces NS/PC proliferation (Jacques et al., 1998). With the use of fluorescence-activated cell sorting, α5β1-integrin was shown to be highly expressed in multipotent NS/PCs and downregulated during neuronal differentiation, suggesting a role in maintenance of characteristic NS/PC features (Yoshida et al., 2003). α6β1-integrin, which is highly expressed in human NS/PCs, is used as a neural precursor cell marker, and was found to form a functional complex with laminin γ1, and netrin-4 on the NS/PC surface, that promotes cell proliferation (Hall et al., 2006; Staquicini et al., 2009). Antibody inhibition of β1-integrin signaling results in an increased population of abventricular dividing precursors, a phenomenon also observed in the neocortex of mice deficient in Laminin α2, a ligand of β1-integrin (Loulier et al., 2009). Although diminished proliferation was observed in cultured β1-integrin-deficient neural precursors, a small percentage of β1-integrin-negative cells survived and formed neurospheres normally, suggesting that β1-integrin is not required for maintenance of all NS/PCs (Leone et al., 2005). Further investigation has revealed that β1-integrin contributes to the maintenance of NS/PCs by activating MAPK signaling (Campos et al., 2004; Wang et al., 2011). β1-integrin interacts with Notch and EGFR signalling pathways, suggesting that ECM molecule or growth factor involvement may be important in β1-integrin-mediated

regulation of NS/PCs (Campos et al., 2006). β1-integrin is also involved in basic FGF (bFGF) and EGF-mediated proliferation of neuroepithelial cells (Suzuki et al., 2010). Moreover, the carbohydrate-binding protein Galectin-1 regulates proliferation of adult NS/PC through interactions with β1-integrin (Sakaguchi et al., 2010). Additionally, the FNIII domain 6-8 of ECM molecule tenascin-R inhibits NS/PC proliferation through interactions with β1-integrin, an effect that is eliminated with antibody inhibition of β1-integrin (Liao et al., 2008). PDGF stimulates proliferation of oligodendrocyte precursor cells (OPCs) through activation of αvβ3-integrin, which in turn activates PI3 kinase-dependent signaling pathway (Baron et al., 2002). Neurovascularization, regulated by αvβ8-integrin, plays essential roles during the CNS development (Proctor et al., 2005). Analysis of adult β8-integrin-deficient mouse brains shows abnormalities in the SVZ and RMS, with a smaller OB. Reduced proliferation of cells in the SVZ and RMS in β8-integrin-deficient brains and smaller neurospheres formed by β8-integrin-deficient NS/PCs reveal the important role of β8-integrin on NS/PC maintenance, potentially through transforming growth factor β (TGFβ) signaling (Mobley et al., 2009).

3.2. Cell adhesion molecules regulate neural stem/progenitor cell differentiation

In the mammalian CNS, different neural cell types arise and migrate in a precise temporospatial manner. During mouse brain development, neurons first arise around embryonic day 12 (E12), with neurogenesis peaking at E14 and ceaseing around E18. Astrocytes appear at approximately E18, with their numbers peaking in the neonatal period, and oligodendrocytes are generated after birth when the neurogenesis has largely subsided (Bayer and Altman, 1991).

In vitro cultured neural precursors showed enhanced neuronal differentiation, associated with a reduced astrogliogenesis and unchanged oligodendrocyte genesis whether cultured on substrate-coated L1, or co-cultured with L1-overexpressing fibroblasts (Dihné et al., 2003). Further analysis of different neuronal subtypes that differentiated from NS/PCs shows that L1 inhibits cholinergic neuron differentiation, but promotes differentiation of GABAergic neurons (Dihné et al., 2003). Under an *in vitro* culture system, ectopic expression of L1 in NS/PCs, or overexpression of L1 on the ESC-derived neural precursors promotes neuronal differentiation, but inhibits astrocytic differentiation (Bernreuther et al., 2006; Cui et al., 2010; Cui et al., 2011; Xu et al., 2011). L1 overexpression also resulted in an increased yield of GABAergic neurons after transplant into lesioned striatum (Bernreuther et al., 2006). Another important IgSF CAM PSA-NCAM, identified as a neural precursor marker, is expressed by NS/PCs in neurogenic regions in the developing and certain regions of the adult CNS, such as SVZ, hippocampus, and rostral migratory stream (RMS) (Seki and Arai, 1993; Bonfanti and Theodosis, 1994; Doetsch and Alvarez-Buylla, 1996; Alonso, 1999). Polysialic acid (PSA)-directed migration and differentiation of neural precursors are essential for mouse brain development. SVZ precursors migrate along the RMS towards the OB, where they differentiate into interneurons that do not express PSA. Interestingly, specific deletion of PSA from SVZ precursors using endoneuraminidase-N (Endo N) results in failure of migration and premature differentiation. Nestin-positive cells fail to migrate and develop neuronal cell features, such as long neurites. Furthermore, these cells are positive tyrosine hydroxylase (TH) (Petridis

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et al., 2004). Further investigation revealed that PSA-dependent differentiation requires cell-cell contact, facilitated by NCAM triggering p59fyn and MAPK p44/42 phosphorylation (Beggs et al., 1997; Petridis et al., 2004). Through a double-knockout of two PSA synthases ST8SiaII and ST8SiaIV, PSA was deleted, resulting in an increased number of glial fibrillary acidic protein (GFAP)-positive astrocytes both *in vitro* and *in vivo* (Angata et al., 2007). TAG-1 plays a role in inhibiting neurogenesis by interacting with amyloid β precursor protein (APP). TAG-1 and APP are co-localized in the neurogenic niche and neural precursors, and can bind to each other to release APP intracellular domain (AICD), triggering the APP signaling pathway to negatively regulate neurogenesis (Ma et al., 2008). Fe65 is also expressed in the neurogenic VZ and has been identified as a downstream element of TAG-1-APP signaling during regulation of neurogenesis (Ma et al., 2008).

The roles of cadherins on neural differentiation are still not well understood. Although neural differentiation appears to occur normally in N-cadherin-deficient mice (Kadowaki et al., 2007), a recent study knocking down N-cadherin expression by *in utero* eletroporation resulted in an enhanced neuronal differentiation, likely through β-catenin signaling as it can be rescued by introducing a stabilized active form of β-catenin (Zhang et al., 2010). Another study showed that bone morphogenetic protein 4 (BMP4) induces astrocytic differentiation of NS/PCs through PI3 kinase-mediated upregulation of N-cadherin (Kim et al., 2010).

β4-integrin plays an essential role in NS/PC differentiation. Under *in vitro* culture system, knockdown of endogenous β4-integrin inhibits cell differentiation and reduces of FGFR2 expression, while overexpression of β4-integrin in NS/PCs promotes differentiation (Su et al., 2009). The FNIII domain 6-8 of ECM molecule tenascin-R, through interactions with β1-integrin, promotes astrocytic differentiation, while preventing differentiation into neurons and oligodendrocytes; Conversely, epidermal growth factor-like (EGFL) domain of tenascin-R promotes neuronal differentiation, while reducing differentiation into astrocytes and oligodendrocytes, through interactions with β1-integrin that can be inhibited with application of β1-integrin antibody (Liao et al., 2008).

3.3. Cell adhesion molecules regulate neuronal migration

When NS/PCs give birth to neurons or glial cells, the differentiating or differentiated cells will migrate away from the stem cell niche to their appropriate location. In the developing CNS, specific neurons migrate in a specific pathway to reach their final destination in the brain. For example, in the developing cerebral cortex, the newborn neurons generated by radial glial cells in the embryonic VZ undergo radial migration along the long processes of radial glial cells, forming the different layers of cortical plate. Newborn interneurons generated from the ganglionic eminence also migrate in tangential path into the cortex without interacting with radial glial cells (Ghashghaei et al., 2007). In the adult CNS, NS/PCs from SVZ migrate along the rostral migratory stream towards the OB and from the SGL of hippocampus migrate a short distance into molecular layer (Ghashghaei et al., 2007). As cell surface molecules interacting with the surrounding environment, CAMs play essential roles in cell migration..

Overexpression of L1 using human GFAP promoter in NS/PCs promotes neuronal migration in *in vitro* neurosphere migration assays, and also enhances migration of transplanted cells in

the injured spinal cord (Xu et al., 2011). L1-overexpression in the neural precursors derived from ESCs also promotes migration into the lesioned CNS tissues (Bernreuther et al., 2006; Cui et al., 2011; Xu et al., 2011). The NS/PCs born in the adult SVZ express high levels of PSA-NCAM, and migrate along the RMS towards the OB and differentiate into interneurons. Increasingly evidence has demonstrated the importance of PSA in controlling NS/PC migration pattern, although PSA is not required for radial migration of interneurons within OB (Hu et al., 1996). SVZ precursors are unable to migrate when PSA expression is abolished, resulting in a smaller OB (Cremer et al., 1994; Hu et al., 1996; Angata et al., 2007). Expressed by hippocampal precursors in SGL, PSA is also required for the migration of newborn granule cells (Burgess et al., 2008). Although the mechanism by which PSA guides the NS/PCs is still not clear, it has been hypothesized that PSA regulates directed migration towards guidance cues. A recent study observing the effect of PSA on migration of OPCs showed that PSA-positive OPCs polarize and directly migrate towards concentration gradients of PDGF, while loss of the PSA tail of NCAM causes an altered migration pattern in response to PDGF gradients, indicating the PSA is involved in a regulatory network requiring environmental cues (Zhang et al., 2004). TAG-1 is expressed by cortical GABAergic interneurons and mediates their migration from the ganglionic eminence towards the developing cortex. Inhibition of TAG-1 function results in a remarkable reduction of GABAergic interneurons in the cortex (Denaxa et al., 2001).

Recently it was demonstrated that N-cadherin is involved in radial neuronal migration during cortical development. In N-cadherin conditional knockout mice, neuroepithelial and radial glial cells can not expand their cell bodies and processes to span the distance from the ventricular surface to the pial surface, which is essential for neuronal migration and cortical lamination, resulting in disorganization of the entire cortex (Kadowaki et al., 2007). Knockdown of N-cadherin expression by *in utero* electroporation reduced β-catenin signaling, causing enhanced premature neuronal migration, which can be rescued by introducing a stabilized active form of β-catenin (Zhang et al., 2010). A recent study showed that Rab GTPases-dependent endocytic pathways are critical for radial migration during the cortical development, through N-cadherin trafficking (Kawauchi et al., 2010). Deficiency in N-cadherin also causes mispositioning of neurons in the zebrafish neural tube (Lele et al., 2002). N-cadherin was also shown to regulate the directional chain migration of cerebellar granule neurons in zebrafish by continuously coordinating cell-cell contacts and cell polarity through the remodeling of adherens junctions (Rieger et al., 2009). Classic cadherins were also shown to regulate tangential migration of precerebellar neurons in the caudal hindbrain. N-cadherin, Cadherin-6, Cadherin-8, and Cadherin-11 are expressed in the migratory stream of lateral reticular nucleus (LRN) and neurons of external cuneate nucleus (ECN). Overexpression of two dominant negative constructs, a membrane-bound form and a cytoplasmic form, but not full length N-cadherin and Cadherin-11, inhibits LRN/ECN neuron migration, suggesting classic cadherins regulate contact-dependent tangential migration probably through their adhesive functions (Taniguchi et al., 2006). Additionaly, cadherins are also required for neural crest cells migration (Monier-Gavelle and Duband, 1997; Nakagawa and Takeichi, 1998; Borchers et al., 2001; Shoval et al., 2007).

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Integrins were also shown to control migration of neural precursors. During migration along the RMS, antibodies for specific integrins, such as α1-, β1-, and αv-integrins, inhibit neuronal migration during the stages at which they are expressed (Murase and Horwitz, 2002). β1-integrins-dificient progenitor cells exhibit impaired migration in different ECM substrates (Leone et al., 2005). Antibody inhibition of neurosphere-expressed α6β1-integrins results in inhibition of tangential chain migration of NS/PC *in vitro* (Jacques et al., 1998). The α6β1-integrin, laminin γ1, and netrin-4 complex was shown to be a promoter of NS/PC migration (Staquicini et al., 2009). Another study analyzing adult neural precursors from the striatum reveals that α6β1- and α5β1-integrins promote cell migration (Tate et al., 2004). β8-integrin has also been shown to be important for neural precursor migration. Selective deletion of β8-integrin expression in neuroblasts causes abnormal chain migration and a reduction in OB size (Mobley et al., 2009; Mobley and McCarty, 2011).

3.4. Cell adhesion molecules regulate cell survival

During embryonic and early postnatal development, approximately 50% of newborn neurons die due to apoptosis in almost every CNS regions. In adult the CNS, cell death mostly occurs in the regions of neurogenesis. For example, in the adult hippocampus, about 70% of newborn neurons die within three weeks after failing to form the functional connections with the existing neural circuits. CAMs have been shown to play essential roles during apoptosis signaling.

In the *in vitro* culture system, mouse or human L1Fc fusion proteins can protect cerebellar granule neurons from cell death induced by growth factor deprivation, staurosporine treatment, and oxidative stress (Loers et al., 2005). With the use of specific inhibitors of signal transduction molecules, PI3-kinase activity was shown to be important for the neuroprotective effect of L1. Moreover, protein kinase PDK1 and Akt were found to be potential downstream targets (Loers et al., 2005). In other *in vitro* assays, coated L1 had no effect on the extent of precursor cell death, measured by TUNEL staining (Dihné et al., 2003). Ectopic expression of L1 also showed no effect on cell death of ESC-derived neural precursors, suggesting diverse roles of L1 on different cell types (Bernreuther et al., 2006). PSA-NCAM is also involved in neuronal survival. After removal or inactivation of PSA using Endo N, impaired survival was observed in cultured cortical neurons. This effect of PSA has been shown to be involved the BDNF signaling pathway (Vutskits et al., 2001). In NCAM-deficient mice, increased cell apoptosis was observed in the SVZ and the RMS. Interestingly, increased cell death occurred in the PSA^+NCAM^+ neuroblasts, but not in PSA^-NCAM^+ astrocyte, suggesting that PSA-NCAM but not NCAM is important for cell survival (Gascon et al., 2007).

Cadherins, such N-cadherin and Pcdhγs, have also been found to be involved in neural cell survival. N-cadherin can enhance cell survival of both mouse spinal cord neurons and rat hippocampal neurons *in vitro* through pro-apoptotic protein Bim-related signaling pathway (Lelièvre et al., 2012). A cyclic peptide including a functional binding motif HAVDI in the extracellular domain 1 of N-cadherin promote *in vitro* survival of different population of CNS neurons, by binding to and clustering N-cadherin in neurons and thereby activating N-cadherin/FGFR signaling cascade (Skaper et al., 2004). Pcdhγs is proven to be involved in

neural cell survival. Abolishing Pcdhγs gene cluster results in the apoptosis of spinal interneurons, and retinal interneurons and ganglion cells, but the mechanism of Pcdhγs in cell survival is still unclear (Wang et al., 2002; Lefebvre et al., 2008).

Integrins also play a role regulation of cell survival. Cultured β1-integrin-deficient neural progenitors display high levels of cell death (Leone et al., 2005). Inhibition of phosphatidylcholine-specific phospholipase C in cultured neural cells results in a reduction of cell survival, associated with upregulation of β4-integrin and Rb protein (Lv et al., 2006).

4. Applications of cell adhesion molecules in stem cell-based regenerative therapy

Many CAMs have been investigated for pre-clinical studies in the treatment of neural injury and neurodegenerative disorders as their roles in CNS development and regeneration after CNS injury have been revealed. L1 has been reported to play important roles in neuronal survival and migration as well as neurite outgrowth and extension, axonal guidance and synaptic plasticity *in vitro* and *in vivo* (Hortsch, 1996). Thus, it has been studied as a target for the treatment of neurodegeneration and neural injuries. Application of soluble L1Fc to injured rat spinal cords significantly improved locomotor recovery compared to both the PBS-treatment group and the IgM antibody control group (Roonprapunt et al., 2003). Further analysis using biotinylated dextran amine for corticospinal axon labeling revealed that L1Fc promoted axonal growth (Roonprapunt et al., 2003). Another study using adeno-associated virus (AAV)-mediated L1 expression also promoted functional recovery including stepping ability and muscle coordination after mouse spinal cord injury (Chen et al., 2007). Increased regeneration of corticospinal tract axons and levels of 5-hydroxytryptamine (5-HT), an important neurotransmitter, were observed in the AAV-L1-treated spinal cord, along with a reduction of astrocytes and reduced expression of the neurite outgrowth-inhibitor and chondroitin sulfate proteoglycan NG2. Increased expression level of cyclic AMP, phosphorylated CREB, Rac1 and MAPK and a reduction of GTP-RhoA expression were observed in AAV-L1-treated spinal cord, revealing that exogenous L1 promotes functional recovery by triggering multiple signaling pathways (Chen et al., 2007). The reparative effects of L1 on spinal cord injury were achieved after acute application of L1. A separate study applying AAV-L1 alone, Chondroitinase ABC (ChaseABC) alone, which degrades chondroitin sulfates that inhibit neurite outgrowth, or a combination of AAV-L1 and ChaseABC to treat the sub-chronic spinal cord injury (Lee et al., 2012). Results revealed that when compared to the AAV-green fluorescent protein (GFP) injection control group, AAV-L1 treatment improves voluntary movements, while ChaseABC application enhances body weight support. Injection of the combination of AAV-L1 and ChaseABC results in improvement in both parameters, with increased densities of cholinergic and GABAergic terminals in motor neuron and enhanced synaptic rearrangements (Lee et al., 2012).

Polysialic acid (PSA) is a long linear homopolymer glycan carried by NCAMs that plays essential roles in PSA-NCAM-mediated activities, including cell-cell interaction and cell

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migration (Hu et al., 1996; Johnson et al., 2005). Numerous studies have used PSA to promote adult CNS or PNS repair. Expression of PSA at the lesion site can loosen scar tissue and reduce inhibitory interactions with growth cones. Thus, engineered overexpression of PSA on the astrocyte scar enhanced Purkinje cell axonal regeneration in the lesioned cerebellum of growth related genes L1/GAP-43 double transgenic mice (Zhang et al., 2007). Similarly, induced expression of PSA in the glial scar of injured spinal cords promoted regeneration of sensory axons (Zhang et al., 2007). PSA glycomimetics has also been reported to promote plasticity and functional recovery after spinal cord injury in mice (Mehanna, 2010). PSA was also applied in the study of regeneration following peripheral nerve injury. PSA glycomimetic promotes myelination and functional recovery after peripheral nerve injury (Mehanna et al., 2009). PSA-mimetic enhances Schwann cell proliferation and process elongation in vitro, which may be mediated by interaction with Schwann cell-expressed NCAM and FGFR (Mehanna et al., 2009).

Human natural killer cell glycan (HNK-1) is found on glycolipids and glycoproteins, including many CAMs, such as L1, NCAM, MAG, TAG-1 in the nervous system, and has been shown to play roles in cell recognition and adhesion (Morita et al., 2008). Application of HNK-1 mimic peptide in injured peripheral nerves resulted in larger motor neuron somata and enhanced axonal remyelination resulting in better functional recovery compared to the mice treated with a scrambled peptide (Simova et al., 2006). *In vitro* assays demonstrated that HNK-1 mimic peptide enhances neurite outgrowth and survival of motor neurons (Simova et al., 2006).

Due to the role of CAMs in the NS/PC development and repair of nervous system injury, many researchers have investigated the possibility of combining CAMs and stem cell-based transplantation therapy to treat neural disorder and neural injury models. As the most widely studied CAM associated with neural regeneration, L1 has been investigated as a potential candidate for stem cell-based therapeutic strategy for treatment of neurodegenerative diseases or regeneration after neural injury. Overexpresion of L1 in NS/PCs results in a reduced proliferation, enhanced neuronal migration and differentiation, as well as decreased astrogenesis using an *in vitro* culture system and enhanced migration and survival of grafted cell after transplantation into the injured spinal cord (Xu et al., 2011). Transplanted L1-overexpressing NS/PCs increased soma size and enhanced synaptic input to host motor neuron in the lesion site. Moreover, an increase in axons expressing tyrosine hydroxylase—a enzyme vital for the synthesis of catecholaminergic neurotransmitters—distal to the lesion site was observed in mice recipients of L1-expressing NS/PCs transplantation (Xu et al., 2011). Overall a significantly improved locomotor functional recovery was observed in mice transplanted with L1-expressing precursors when compared to mice transplanted with wild-type NS/PCs after spinal cord injury (Xu et al., 2011). The L1-overexpressing neural precursor derived from ESCs exhibits decreased cell proliferation *in vitro*, enhanced neuronal differentiation both *in vitro* and *in vivo* resulting in a diminished astrocytic differentiation *in vivo* without affecting cell death compared to wild-type cells (Bernreuther et al., 2006; Cui et al., 2010; Cui et al., 2011). Transplantation of L1-overexpressing ESC-derived neural precursors at the lesion site after spinal cord injury reduces glial scar volume, enhances graft size, promotes neuronal migration, and decreases the microglial/macrophage reaction in the lesion site, and thereby improves locomotor

functional recovery (Cui et al., 2011). In addition to application in treatment for spinal cord injury, L1-expressing NS/PCs have also been studied as potential candidates in neurodegenerative disease models, such as Huntington's and Parkinson's disease. In a quinolinic acid-induced Huntington's disease mouse model, L1-overexpressing neural precursors derived from ESCs generated more graft-derived GABAergic neurons in the lesioned striatum and improved locomotor functional recovery in rotation behavior test compared to the control mice transplanted wild-type cells (Bernreuther et al., 2006). In the MPTP-induced mouse model of Parkinson's disease, transplantation of L1-overexpressing ESC-derived neural precursors led to a better functional recovery in apomorphine-induced rotation test when compared to the mice treated with wild-type cells and vehicle-injected mice (Cui et al., 2010). Further morphological analysis revealed an increased number of dopaminergic neurons, leading to increased dopamine level in the striatum ipsilateral to the transplantation region of L1-expressing neural precursors (Cui et al., 2010). Due to the L1-mediated promotion of neurite outgrowth and neuronal survival by homophilic binding, NS/PCs overexpressing trimerized L1 extracellular domain and full length L1 were transplanted in to the injured spinal cord. The injured mice transplanted with NS/PCs overexpressing trimerized L1 extracellular domain and full length L1 exhibit improved functional recovery in locomotor behavior after spinal cord injury when compared to the group transplanted with only L1-overexpressing NS/PCs (He et al., 2012). The trimer-L1-expressing stem cells displayed enhanced reduction in glial scar volume in the lesion site and expression of chondroitin sulfates, preventing degeneration of corticospinal axons, promoting remyelination and enhancing regrowth of serotonergic axons (He et al., 2012). These results further demonstrated the potential application of L1-expressing NS/PC transplantation and could be of great therapeutic value. In cell replacement therapy, the transplanted cells need not only to be differentiated into proper cell types, but also to migrate into the injured region. In light of the effects of PSA on cell migration, researchers were motivated to attempt to overexpress PSA in transplanted stem cells. Ectopic expression of PSA on the ESC-derived neural precursors results in enhanced migratory ability after transplantation in the rodent striatum (Glaser et al., 2007).

Stem cell-based therapeutic applications have attracted a great deal of attention as multiple potential stem cell types were developed, particularly with the establishment of induced pluripotent stem cells (iPSCs). These stems cells seemed to provide near limitless potential in treating many human diseases. However, stem cell-based therapeutic applications for neurological disorders have faced many obstacles and setbacks, such as immunorejection, tumor formation, and low efficiency resulting from low cell survival, and failure to migrate and form functional neural connections with existing neural circuitry. Moreover, the molecular mechanisms that underlie NS/PC proliferation and differentiation into distinct cell types remain unclear. Nonetheless, advances in stem cell research and advantages of the combination of CAMs and stem cells in pre-clinical research, like enhanced cell survival, promoted cell migration, and increased neuronal differentiation, are encouraging. All these advantages suggest that CAMs have tremendous potential for application in stem cell-based cell replacement therapy for neurodegenerative diseases and spinal injuries.

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