TOPICAL REVIEW

Cell adhesion molecules in the neural development and plasticity

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Abstract

Cell adhesion molecules (CAMs) are cell surface glycoproteins mediating cell-cell and cell-matrix interactions which play a vital role in the embryonic development of the nervous system as well as in the maintenance and nerve regeneration in adults. In the central nervous system (CNS) three main CAMs, such as neural cell adhesion molecule (NCAM), L1 and N-cadherin have been characterized. In addition to their adhesive properties, CAMs are involved in cell migration, growth of axons, nerve pathways formation and synaptogenesis. The binding of CAMs can activate transmembrane-signalling reactions and thereby contribute to the initiation of cellular response in regulation of synaptic plasticity. CAMs play an important role in learning and memory. The role of CAMs in abnormal development and malignancies provide a wide field of research for diagnostic and therapeutic applications. ***(Ref. 36.)***

Key words: cell adhesion molecules, growth of axons, synaptic plasticity, nerve regeneration.

Cell adhesion molecules constitute a group of plasma membrane glycoproteins expressed on the surface of various cells that mediate cell-cell and cell-matrix interactions. These molecules play important morphoregulatory roles in the early stages of embryonal development. In the CNS three main CAMs have been characterized: neural cell adhesion molecule (NCAM), L1 and N-cadherin. All these molecules stimulate axonal growth during embryonal development as well as in the peripheral nerve regeneration. CAMs and other types of membrane proteins are localized in the phospholipid layer of the cell membrane, containing various cytoplasmic signaling molecules. In addition to their adhesive properties CAMs regulate cell migration, neurite outgrowth, fasciculation, synaptogenesis and intracellular signalization which are closely connected with activation of secondary messenger (Walsh et al, 1997). These different effects can be regulated by changes in the level of expression of specific CAMs, changes in their molecular isofoms, post-translational modification (glycosylation) and intracellular signaling. All these forms of regulations can be influenced by neural impulse activity (Doherty et al, 2000).

Function of CAMs

Cell-cell interactions mediated by CAMs are dynamically regulated during nervous system development. Their expression can be influenced by growth factors, intracellular signaling systems, hormones and neurotransmitters (reviewed in Fields and Itoh, 1996). Recent data show that CAMs support neurite outgrowth by increasing in calcium influx to the growth cone. Calcium is an important secondary mediator in the axonal growth cone region, which presents dynamic and specialized structure mediating axonal growth and guidance (Walsh et al, 1997). Influence of CAMs on axon pathfindings have been mainly studied in tissue culture where neuronal processes and growth cones are easily visualized. Growth cone movement is controled by the dynamic cytoskeletal changes including the transport of membrane bound vesicles from the perikaryon or generated within the growth cone by endocytosis. The ability of a CAM to activate cell signalling in some developmental stages may stimulate a cell migration, growth of axons and synaptic plasticity, while the same molecule in the other stage may serve to the stabilization of cell adhesion (Doherty et al, 2000).

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The work was supported by grant Vega 2/7235/20 from SAS.

NCAM was the first cell adhesion molecule structurally characterized (Brackenbury et al, 1977) and extensively studied. The cell surface glycoprotein is represented by several isoforms (NCAM 120, 140 and 180 kDa) that differ in their protein backbone and mode of attachment to the plasma membrane. NCAM belongs to the immunoglobulin superfamily which is involved in Ca^{2+}-independent cell-cell adhesion. One of the distinct structural features is, that NCAM carries a large amount of negatively charged sugar, polysialic acid (PSA) during embryonic and early postnatal life that modulates the adhesive property of NCAM. An important role of PSA-NCAM in the development of nervous system, mainly in the processes such as cell migration, growth of axons, fasciculation, nerve branching and synaptic arrangement have been well documented (Rutishauser and Landmesser, 1996). In the adult brain, the expression of PSA is limited, but it remains to be preserved in some regions (olfactory bulb, hippocampus, hypothalamo-hypophysial system), where structural and synaptic rearrangement is continued during the life. PSA can be removed from NCAM enzymatically by endoneuraminidase (endo-N). It has been documented, that NCAM with lower content of PSA is synthetized in astrocytes which was shown in primary cultures of cortical astrocytes (Minana et al, 1998). The expression of NCAM with lower content of PSA increases cell adhesion, and alternatively a higher content of PSA leads to the inhibition of cell adhesion due to decreased membrane apposition. Disruption of cell interaction enables a release and cell movement from the site of primary localization (Fukuda, 1996). As NCAM is a primary carrier of PSA in the developing embryo, mutant NCAM-deficient mice show PSA-deficiency as well (Cremer et al, 1994).

A higher interest in the biological significance of PSA encouraged the studies on the behavior of axons during their growth and innervation of the target tissues. It has been found that PSA reduces axonal fasciculation and thereby allowes the response to the variety of signals including those from their targets. In the development, as motor axons reach their targets they separate from the bundles and form intramuscular branches. When during this period PSA was removed by endo-N, the defasciculation and rearrangement of axons were prevented (Rutishauser and Landmesser, 1996). Removal of PSA leads to a reduction in the nerve branching, and thereby to a reduction in the number of synapses (Tang et al, 1994). PSA-NCAM is expressed on the surface of all growing axons. Later, when they are myelinized, this process is stopped which is related to the end of growth phase and the appearance of electrical signals (Charles et al, 2000).

CAM L1 is a transmembrane glycoprotein belonging to the immunoglobulin superfamily (200 kDa) of CAMs that is mainly involved in axonal growth and guidance. For this reason L1 is called a neuronal recognition molecule (Kenwrick et al, 2000) and has been identified in many species. In mammals, L1 is expressed predominantly on axons in CNS neurons as well as on Schwann cells of the peripheral nervous system. The molecule plays an important role also in the peripheral nerve regeneration. During the development L1 is involved in nerve cells adhesion, their interaction with Schwann cells, migration of neurons, axonal fasciculation and pathways formation. When L1 adhesion molecule is not expressed, or it is expressed in a mutant form, clear defects in axonal pathways in man and rodents have been observed (Kamiguchi et al, 1998). To date it is supposed, that L1 is the only CAM associated with a hereditary disease (Kenwrick et al, 2000). Adhesion molecule L1 is a part of dynamic molecular complex, which serves for the signal transduction into the cell and its cytoplasmic domain is linked to the cytoskeleton (Crossin and Krushel, 2000). Data obtained from in vitro studies showed that axon growth is impaired in L1-deficient neurons which indicates that the molecule acts as a growth cone receptor for signals inducing axonal extension (Lemmon et al, 1989). L1 can stimulate neurite outgrowth by activation of tyrosine kinase-linked receptors for fibroblast growth factors (FGFR) in neurons (Williams et al, 1994). Takei et al (1999) established that L1 functions in neurite extension, whereas NCAM plays a role only in growth cone protrusion. The expression of L1 is downregulated on axons with the start of myelinization.

N-cadherin is a CA^{2+}-dependent cell adhesion molecule with more potent effect on the axonal growth in the culture than L1 adhesion molecule (Bixby and Zhang, 1990). It has been documented that cadherins contribute to neural tube formation as well as CNS regionalization associated with development of brain nuclei, cortical layers, neural circuits and synapses formation (Redies, 2000). Recent data indicate that N-cadherin might promote axonal growth by direct interaction with FGFR in growth cone (Doherty et al, 2000). There are more members of cadherin family which are differentially expressed in the developing and mature brain. N-cadherin was identified as an integral part of synaptic complex and found to be a component of postsynaptic density. N-cadherin is a dynamic adhesion regulator between pre- and postsynaptic membrane and it may serve to the stabilization of synaptic connection. In the peripheral nervous system, Schwann cells express N-cadherin at their contact sites with unmyelinated axons, but no immunoreactivity is found on Schwann cell plasma membrane abutting the basal lamina**.** Expression of N-cadherin is increased during nerve regeneration (Shibuya et al, 1995)

CAMs and defects in their expression

Cell adhesion molecules are expressed in the early stages of embryonal development. The presence of NCAM and N-cadherin can be visualized during the neurulation, when neural tube is separated from the ectodermal surface (Hatta and Takeuchi, 1986). Deficit in N-cadherin expression leads to an altered neural tube closure, which is seen in cases of reduced expression of this molecule (Lagunowich et al, 1994). N-cadherin is ubiquitously expressed by the entire proliferative neuroepithelium. Blockage of N-cadherin by antibody injection results in a disruption of the neuroepithelium and formation of rosette-like structures which lead to the disorganization of the gray matter (Ganzler-Odenthal and Redies, 1998). Mutations in NCAM gene or cleavage of PSA during the development cause a defect in cell migration to olfactory bulb with subsequent reduction in its size. The dentate gyrus is also reduced in size in NCAM-deficient mice (Cremer et al, 1994). Alteration in the content and distribution of NCAM are also con-

nected with a defect in formation of the synapses. It has been suggested that PSA-NCAM has a potential role in learning and memory, as showed experiments in NCAM-deficient mice with impaired spatial learning. Similar deficits were observed in rats with enzymatic removal of PSA (Ono et al, 1994). Mutation in the human L1 gene leads to a complex clinical picture with mental retardation and other neurologic abnormalities, as well as variable degree of hydrocephalus (Kenwrick et al, 2000). These mutations are related to the cytoplasmic domain of L1, which contains binding region for the cytoskeletal protein ankyrin connecting various membrane proteins with the submembranous actin skeleton (Ide, 1996). Mutation of L1 gene in mouse results in a hypoplasia of corticospinal tract and vermis cerebelli that are associated with impaired space orientation and cognitive function (Kamiguchi et al, 1998).

CAMs and the synaptic plasticity.

Cell adhesion molecules are important constituents of synapses, which participate in building and maintaining synaptic structure during CNS development. By controlling of axons fasciculation, CAMs can regulate pathfinding and synaptogenesis with appropriate targets. CAMs that are involved in cell migration, axonal outgrowth and defasciculation during development, enable formation of new synapses or facilitate synaptic remodeling also in postnatal life. In adults synaptic plasticity is determined by definite physiological and pathological conditions, such as learning and memory and interruption of neuronal circuits, respectively. There are some evidence indicating the involvement of CAMs in synaptic plasticity and learning (Fields and Itoh, 1996). The first is a correlation between brain areas undergoing continuous neurogenesis with expression of embryonal form CAMs. Second, changes in CAMs expression or post-translational modification (glycosylation) detected during synaptic plasticity and learning. Third, blockade of long-term potentiation or learning results after exposure to antibodies or synthetic peptides against specific CAMs. Similarly, supressed NCAM expression in transgenic mice results in impaired learning. CAMs are involved in the control of synaptic plasticity by interacting with intracellular signaling reactions. Regulation of cytoskeletal dynamics by CAMs can participate in synaptic reorganization. The cytoplasmic domain of N-cadherin interacts with catenins which bind to the actin cytoskeleton, while L1 and NCAM are associated directly with ankyrin (Ide, 1996).

CAMs and nerve regeneration

Adhesion molecules play an important role in the nerve regeneration. After axotomy a decrease in NCAM and N-cadherin immunoreactivity was found, however, parallel with restoration of synaptic contacts and progressive reinnervation of the peripheral targets, there was an increase in mRNA for NCAM and N-cadherin (Squitti et al, 1999). Schwann cells significantly contribute to the nerve regeneration due to increased synthesis of CAMs, production of the basal membrane, that contains many extracellular proteins as well as by production of neurotrophic factors and their receptors (Fu and Gordon, 1997). Schwann cells in regenerating peripheral nerves express NCAM and L1 at the site of their contact as well as at the place of their contacts with axons (Martini, 1994). In adults on the regenerating peripheral nerve fibers no detectable amounts of L1, but a high levels of PSA was found (Bates et al, 1999). Recent studies show that CNS neurons also have the capacity to regenerate which is triggered by replacement of inhibitorial glial environment to peripheral nerve segment (Berry et al, 1988). Schwann cells present the major component which plays the role both in PNS and CNS regeneration by producing various functional substances. In addition to CAMs, Schwann cells utilize focal tight junctions to provide morphological stabilization of the contact with the elongated axons, as well as small gap junctions to facilitate traffic of substances between them (Dezawa and Adachi-Usami, 2000). In adult rats after a lesion of the hippocampal region, there was an increase in PSA-NCAM expression in the dentate gyrus (Miller et al, 1994). It is supposed that reexpresion of PSA in the denervated region may enable to the axon growth after transplantation as well as the reconstruction of the synaptic connections.

Age changes in the expression of CAMs

Ageing is accompanied by a decline in neurogenesis and a decreased expression in PSA-NCAM which was shown by a reduced number of PSA-NCAM positive cells within the hippocampus (Montaron et al, 1999). To the decline of neurogenesis contributes also elevated level of blood corticosterone. Suppression of corticosterone by adrenalectomy increased the neurogenesis and PSA-NCAM expression in the dentate gyrus of adult rats. When corticosterone was administrated to adrenalectomized rats, this effect was prevented. CAMs have been proposed to mediate neuronal plasticity during learning and memory. Spatial orientation impairment in aged rats seems to be associated with the decrease in PSA-NCAM expression. CAMs can also contribute to the development of age related pathology. It is supposed that PSA-NCAM participates in the pathogenesis of neurodegenerative (Alzheimer disease, multiple sclerosis) or psychiatric disorders (Barbeau et al, 1995; Cotman et al, 1998). PSA-NCAM is also expressed in certain tumors, such as small cell lung carcinoma, neuroblastoma and rhabdomyosarcoma (reviewed in Nakayama et al, 1998). PSA is an oncodevelopmental antigen expressed in tumors with a high metastatic potential, As PSA attenuates NCAM mediated cell adhesion it has been suggested that the presence of PSA in the tumor cells facilitate the detachment and metastatic migration of the tumor cells from the site of primary localization (Fukuda, 1996). Experiments using mice model of metastatic tumors showed, that cleavage of PSA on NCAM led to a decrease in number of metastases (Daniel et al, 2001). It is supposed that using of monoclonal antibodies against CAMs as well as synthetic peptidic or nonpeptidic analogs of the recognition sequences on their receptors may inhibit growth of tumors and provide a new strategy in their therapy (Huang et al, 1997).

References

Barbeau D, Liang JJ, Robitaille Y, Quirion R, Srivastava LK: Decreased expression of the embryonic form of the neural cell adhesion molecule in schizophrenic brain. Proc Natl Acad Sci USA 1995; 92: 2785—2789.

Bates CA, Becker CG, Miotke JA, Meyer RL: Expression of polysialylated NCAM but not L1 or N-cadherin by regenerating adult mouse optic fibers in vitro. Exp Neurol 1999; 155: 128—139.

Berry M, Rees L, Hall S, Yiu P, Sievers J: Optic axons regenerate into sciatic nerve isografts only in the presence of Schwann cells. Brain Res Bull 1988; 20: 223—231.

Bixby JL, Zhang R: Purified N-cadherin is a potent substrate for the rapid induction of neurite outgrowth. J Cell Biol 1990; 110: 1253—1260.

Brackenbury R, Thiery JP, Rutishauser U, Edelman GM: Adhesion among neural cells of the chick embryo. I. An immunological assay for molecules involved in cell-cell binding. J Biol Chem 1977; 252: 6835—6840.

Cotman CW, Heiler NP, Pfister KK, Soltesz I, Schachner M: Cell adhesion molecules in neural plasticity and pathology: similar mechanisms, distinct organizations? Prog Neurobiol 1998; 55: 659—669.

Cremer H, Lange R, Christoph A, Ploman M, Vopper G, Roes J, Brown R, Baldwin S, Kraemer Ph, Scheff S, Barthels M, Rajewsky K, Wille W: Inactivation of the N-CAM gene in mice results in size reduction of the olfactory bulb and deficits in spatial learning. Nature 1994; 367: 455—459.

Crossin KL, Krushel LA: Cellular signaling by neural cell adhesion molecules of the immunoglobulin superfamily. Dev Dyn 2000; 218: 260—279.

Charles P, Hernandez MP, Stankoff B, Aigrot MS, Colin C, Rougon B, Zalc B, Lubetzki C: Negative regulation of central nervous system myelination by polysialylated-neural cell adhesion molecule. Proc Natl Acad Sci USA 2000; 97: 7585—7590.

Daniel L, Durbec P, Gautherot E, Ruvier E, Rougon G, Figarella-Branger D: A nude mice model of human rhabdomyosarcoma lung metastases for evaluating the role of polysialic acid in the metastatic process. Oncogene 2001; 20: 997—1004.

Dezawa M, Adachi-Usami E: Role of Schwann cells in retinal ganglion cell axon regeneration. Prog Retin Eye Res 2000; 19: 171—204.

Doherty P, Williams G, Williams EJ: CAMs and axonal growth: a critical evaluation of the role of calcium and MAPK cascade. Mol Cell Neurosci 2000; 16: 283—295.

Fields DR, Itoh K: Neural cell adhesion molecules in activity-dependent development and synaptic plasticity. Trends Neurosci 1996; 19: 473—480.

Fu SY, Gordon T: The cellular and molecular basis of peripheral nerve regeneration. Mol Neurobiol 1997; 14: 67—116.

Fukuda M: Possible roles of tumor-associated carbohydrate antigens. Cancer Res 1996; 56: 2237—2244.

Ganzler-Odenthal SI, Redies C: Blocking N-cadherin function disrupts the epithelial structure of differentiating neural tissue in the embryonic chicken brain. J Neurosci 1998; 18: 5415—5423.

Hatta K, Takeichi M: Expression of N-cadherin adhesion molecules associated with early morphogenetic events in chick development. Nature 1986; 320: 447—449**.**

Huang YW, Baluna R, Vitetta ES: Adhesion molecules as targets for cancer therapy. Histol Histopathol 1997; 12: 467—477.

Ide C: Peripheral nerve regeneration. Neurosci Res 1996; 25: 101—121.

Kamiguchi H, Hlavin ML, Lemon V: Role of L1 in neural development: what the knockouts tells us. Mol Cell Neurosci 1998; 12: 48—55.

Kenwrick S, Watkins A, De Angelis E: Neural cell recognition molecule L1: relating biological complexity to human disease mutations. Hum Mol Genet 2000; 9: 879—886.

Lagunowich LA, Stein AP, Reuhl KR: N-cadherins in normal and abnormal brain development. Neurotoxicology 1994; 15: 123—132.

Lemmon V, Farr KL, Lagenauer C: L1-mediated axon outgrowth occurs via a homophilic binding mechanism. Neuron 1989; 2: 1597—1603.

Martini R: Expression and functional roles of neural surface molecules and extracellular matrix components during development and regeneration of peripheral nerves. J Neurocytol 1994; 23: 1—28.

Miller PD, Styren SD, Lagenaur CF, De Kosky ST: Embryonic neural cell adhesion molecule (N-CAM) is elevated in the denervated rat dentate gyrus. J Neurosci 1994; 14: 4217—4225.

Minana R, **Sancho-Tello M, Climent E, Segui JM, Renau-Piqueras J, Guerri C:** Intracellular location, temporal expression, and polysialylation of neural cell adhesion molecule in astrocytes in primary culture. Glia 1998; 24: 415—427.

Montaron MF, Petry KG, Rodriguez JJ, Marinelli M, Aurousseau C, Rougon G, Le Moal M, Abrous DN: Adrenalectomy increases neurogenesis but not PSA-NCAM expression in aged dentate gyrus. Europ J Neurosci 1999; 1: 1479—1485.

Nakayama J, Angata K, Ong E, Katsuyama T, Fukuda M: Polysialic acid, a unique glycan that is developmentally regulated by two polysialyl transferases, PST and STX, in the central nervous system: from biosynthesis to function. Pathol Internat 1998; 48: 665—677.

Ono K, Tomasiewicz H, Magnuson T, Rutishauser U: NCAM mutation ihibits tangential neuronal migration and is phenocopied by enzymatic removal of polysialic acid. Neuron 1994; 13: 595—609.

Redies C: Cadherins in the central nervous system. Prog Neurobiol 2000; 61: 611—648.

Rutishauser U, Landmesser L: Polysialic acid in the vertebrate nervous system: a promoter of plasticity in cell-cell interactions. Trends Neurosci 1996; 19: 422—427.

Shibuya Y, Mizogouchi A, Takeichi M, Shimamada K, Ide C: Localization of N-cadherin in the normal and regenerating nerve fibers of the chicken peripheral nervous system. Neuroscience 1995; 67: 253—261.

Squitti R, De Stefano ME, Edgar D, Toschi G: Effects of axotomy on the expression and ultrastructural localization of N-cadherin and neural cell adhesion molecule in the quail ciliary ganglion: an in vitro model of neuroplasticity. Neuroscience 1995; 91: 707—722.

Takei K, Chan TA, Wang FS, Deng H, Rutishauser U, Jay DG: The neural cell adhesion molecules L1 and NCAM 180 act in different steps of neurite outgrowth. J Neurosci 1999; 19: 9469—9479.

Tang J, Rutishauser U, Landmesser L: Polysialic acid regulates growth cone behavior during sorting of motor axons in the plexus region. Neuron 1994; 13: 405—414.

Walsh FS, Doherty P: Neural cell adhesion molecules of the immunoglobulin superfamily: Role in axon growth and guidance. Ann Rev Cell Dev Biol 1997; 13: 425—456.

Williams EJ, Furness J, Walsh FS, Doherty P: Activation of the FGF receptor underlies neurite outgrowth stimulated by L1, NCAM and N-cadherin. Neuron 1994; 13: 583—594.

Received October 17, 2001.
Accepted November 12, 2001.