Functional role of a glycolipid in directional movements of neurons*

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ABSTRACT

Migration of neurons from their site of origin to their final destination is a critical and universal step in the formation of the complex structure of the nervous system. The migratory process is thought to be governed in part by genetically and epigenetically defined sequences of signals which are interpreted by migrating cells. The molecular mechanisms that underlie neuronal migration have been the subject of intense investigation. As in other developmental processes, many molecules must participate in neuronal migration. Some molecules, such as cell adhesion molecules and motor proteins, may contribute to discrete steps in the migration act; others, like extracellular signaling molecules, may regulate the activation and/or termination of the migration program. In this article we review findings from our group that demonstrate the functional role(s) of a specific glycolipid in neuronal migration and neurite outgrowth in the developing and adult nervous system.

Key words: Glycolipid, Ganglioside, 9-O-acetyl GD3, Neuronal Migration, Neurite outgrowth, Development.

INTRODUCTION

In the developing central nervous system (CNS) most neuronal precursors are generated in specialized germinal zones adjacent to the ventricle, termed the ventricular zone. A wave of secondary neurogenesis occurs late in development, often in the perinatal period, and produces huge numbers of interneurons. Three primary sites of secondary neurogenesis have been described: the external germinal layer (EGL) of the cerebellum, the dentate gyrus, and the subventricular zone (SVZ) in the telencephalon. Both the dentate gyrus and the SVZ maintain a proliferative population of stem cells throughout life and give origin to neurons destined for the hippocampal formation and olfactory bulb respectively (Altman 1969a,b, Gage et al. 1998, Lois et al. 1996, Luskin 1993).

In general, after terminal mitosis, immature neurons migrate within the neuroepithelium until they reach the various structural primordia where subsequent maturation and final differentiation occurs. Two general modes of migration have previously been defined in the developing nervous system: radial and tangential neuronal migration. Radial migration involves movement of the neuron orthogonally to the pia surface and most of the neurons migrate associated to a special glia, the radial glia. Guidance along radial glia is a common mechanism for the formation of laminated structures, such as

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the cerebral cortex and the cerebellum (reviewed by Hatten 1999). This migration process is a complex developmental program involving a series of steps, including cell-cell recognition, cell-cell adhesion, cell motility, and finally detachment from the glial fibers once neurons reach their destination (Rakic et al. 1994).

Glial-directed neuronal migration has been well studied, but relatively less is known about a distinct mode of migration that occurs tangential to the pial surface. Tangential migration is a prominent developmental feature in both the cerebellum and the olfactory bulb (Luskin 1993, Luskin and Boone 1994, Lois et al. 1996), but has also been described in other regions as for instance the migration of the luteinizing hormone-releasing hormone (LHRH-) positive olfactory placode cells (Norgren and Lehman 1991), cortical interneurons (De Carlos et al. 1996, Anderson et al. 1997, Tamamaki et al. 1997), and neurons in the cerebral cortical subventricular zone (O'Rourke et al. 1997). In the cerebellum, neuronal precursors move tangentially from the rhombic lip to form the external granular layer. As the olfactory bulb forms, future interneurons are generated in the telencephalic SVZ and migrate into the bulb in a long tangential pathway. It has been shown that glial cells do not guide this class of neuronal migration. Rather, in the EGL it has been proposed that neuronal precursors migrate associated with axons (Hynes et al. 1986) and in the SVZ neurons move rapidly along one another in unique chain formations independent of radial glia or axonal processes, in a migration that persists into adulthood (Wichterle et al. 1997, Doetsch et al. 1997). Molecular studies have shown that the mechanism of migration involves the sialylated form of NCAM (neural cell adhesion molecule) and is guided, in part, by negative chemotropism (Hu et al. 1996).

GANGLIOSIDES AND CELL MIGRATION

In our laboratory we are interested in the study of molecules involved in neuronal migration and neurite outgrowth. In our studies we have identified a particular glycolipid, 9-O-acetyl GD3 recognized by a monoclonal antibody (Constantine-Paton et al. 1986) that is involved in neuronal migration and neurite outgrowth.

Results of numerous investigations of cell motility and axonal sprouting have suggested that gangliosides serve an important function in cell substratum interactions and neurite extension. Studies of these cell surface, sialic acid-bearing lipids have, in general, lagged behind those on similarly distributed proteins because of technical difficulties in their isolation and identification. Nevertheless, monoclonal antibodies directed against the carbohydrate moieties of gangliosides have become increasingly important aids in dissecting the biological function of these molecules. In our own earlier studies we described the monoclonal antibody JONES which recognizes a subset of acetylated gangliosides in the developing rat brain (Constantine-Paton et al. 1986). These acetylated gangliosides are associated with cell migration and axon elongation throughout the brain (Mendez-Otero et al. 1988, Schlosshauer et al. 1988, Mendez-Otero and Constantine-Paton 1990, Mendez-Otero and Ramón-Cueto 1994).

To better understand the role of these gangliosides in neuronal migration we have used the developing rat cerebellum as a model system. The development of the cerebellum is an example of a situation in which cell migration clearly plays a crucial role in the final architecture and, presumably, therefore in the physiology of the system. There are several waves of migration in this region. Prenatally, Purkinje cells, Golgi cells, and deep nuclear neurons originate in the ventricular zone and migrate into the body of the cerebellar anlage. This is a radial migration and quite likely takes place on radial glial cells although there is no direct evidence for this mechanism in this case. The deep nuclear neurons subsequently migrate away from the Purkinje cells to their final locations. Meanwhile, a second migration begins. A new stem cell layer known as the external granule (or germinal) layer (EGL) orig-

inates in the ventricular region at the caudal margin of the fourth ventricle (the rhombic lip). From here, the cells migrate over the outer (dorsal) surface of the developing cerebellum and, by the time of birth, have come to cover this surface completely (Altman 1969b, Altman and Bayer 1985 a, b, c). Postnatally this EGL gives rise to several types of neurons, but predominantly to granule cells, which make up 90% of the neurons of the cerebellum. These granule cells arise from the mitotic external granular cells and migrate inward from the pial surface past the layer of Purkinje cells and into the future internal granular cell layer (Altman 1972a, b, 1982, Rakic 1971, 1981). This postnatal migration of postmitotic but undifferentiated granule cells has been shown to follow the process of Bergmann glia, a particular type of radial glia found in the cerebellum (Rakic 1971,1981). The expression of 9-O-acetyl GD3 correlates particularly with regions and times of cell migration in the rat cerebellum. In the embryo (E14-18) the labeling is present extending from the ventricular to the pial surface of the cerebellar anlage and the immunoreactivity is distributed in a radially oriented pattern. Immunoreactivity is also present in the subpial region of the developing EGL, which, at this stage, begins its migration from the rhombic lip and is present as a densely packed zone of cell bodies in the caudal region of the anlage (Mendez-Otero et al. 1988). During the first two postnatal weeks the immunoreactivity for 9-O-acetyl GD3 is detected throughout the folium with a radially oriented pattern extending from the EGL and through the presumptive molecular layer corresponding to the migration of granule cells associated with the Bergmann fibers. The pattern of expression of 9-O-acetyl gangliosides in the developing cerebellum indicates that these molecules may play a role in neuronal migration *in vivo*.

To test this hypothesis we have investigated the expression of 9-O-acetyl gangliosides in two different types of cerebellar cultures prepared from dissociated postnatal rat cerebella. In the first type, cells are plated after dissociation under conditions where most of the glial cells develop a stellate morphology that anchors neurons but does not support their migration. In the second type of culture, cells are plated in a ratio of four neurons to one glia cell and under these conditions the predominant form of astroglia is an elongated form that supports the migration of granule neurons. Granule neurons express the gangliosides in both types of cultures. However, in cultures where the astroglial cells display the stellate morphology only a small proportion shows staining with the gangliosides. Cultures in which the glial cells assume the elongate morphology (radial glia) have a significantly higher number of Jones-positive astroglia (Mendez-Otero and Constantine-Paton 1990). We have also used cerebellar explants and slices from postnatal rat cerebellum in antibody perturbation assays to investigate the functional role of these ganglioside in granule cell migration. We found that although other receptor systems can support neuronal movement, blocking 9-O-acetyl GD3 reduces the rate of neuronal locomotion by approximately 66% (Santiago et al. 2001).

The migration of granule cells along the Bergmann glial fibers has been a useful model system to study radial neuronal migration. In rodents, this migration takes place during the first two postnatal weeks. These studies have implicated a number of molecules in steps of the migration process, for example, cell adhesion molecules, i.e., AMOG (Antonicek et al. 1987, Gloor et al. 1990) and astrotactin (Zheng et al. 1996); ion channels, i.e., NMDA receptors (Komuro and Rakic 1993) and Ca^{2+} channels (Komuro and Rakic 1992). In addition, studies of mutant mouse lines with defects in brain development have led to the identification of other molecules, including potassium channels in the case of weaver mutant (Patil et al. 1995); the extracellular matrix protein reelin in the reeler mutant (Caviness and Sidman 1973, D'Arcangelo et al. 1995, Hirotsune et al. 1995); p35, an activator of Cdk5 (Chae et al. 1997); and neuregulin and erbB receptors (Rio et al. 1997).

Our finding that 9-O-acetyl gangliosides play a

critical role in mediating neuronal migration in the cerebellum may also be relevant to neuronal migration in other regions of the developing nervous system. In this respect, we have shown that the expression of these gangliosides is not restricted to regions of radial neuronal migration but is also present in regions were tangential migration is taking place as for instance the EGL and the SVZ (Mendez-Otero et al. 1988, Mendez-Otero and Cavalcante 1996). Long tangential migrations are a prominent developmental feature in both the EGL and SVZ. It has been shown that glial cells do not guide this class of neuronal migration. Hynes et al. (1986) have suggested that in the prenatal migration en masse of EGL cells these cells migrate in close contact with axons that are present prior to the onset of migration and it appears that these axons serve as the substrate for EGL neuroblast migration and that axonal guidance of cell migration may be a general mechanism to be added to the previously studied guidance by glial cells processes.

We have investigated whether 9-O-acetyl gangliosides are also involved in tangential neuronal migration using the migration of the SVZ cells as a model. We have found that 9-O-acetyl gangliosides are highly expressed in the SVZ and along the route of tangential migration into the olfactory bulb during development (Mendez-Otero and Cavalcante 1996, Miyakoshi et al. 2001). Furthermore, the expression of these gangliosides persists in adult in cell chains similar to those showing immunoreactivity in developing animals (Mendez-Otero and Cavalcante 1996).

NEURONAL MIGRATION AND NEURITE OUTGROWTH

Cell migration is a ubiquitous event that occurs in all multicellular organisms to different extents and at different stages in their lifetime. Cell movements occur not only during development but also during wound healing, immune response, and tumor formation. The idea that axon extension is a form of cell migration in which the cell soma remains stationary was proposed many years ago (reviewed by Singer and Kupfer 1986) and has garnered support from findings that molecules that guide axons are also involved in cell migration.

We have investigated the role of 9-O-acetyl gangliosides identified by the Jones mAb in the elongation of neurites extended by neurons of embryonic rat dorsal root ganglia (DRG) explants growth *in vitro*. The behavior of individual growth cones was recorded using a time-lapse video-enhanced imaging system before and after the addition of antibodies that recognize specific gangliosides known to be expressed on these growth cones. It was possible to demonstrate that the advance of growth cones on laminin was halted in the presence of Jones mAb. This effect was partially reverted by washing the explants for several minutes with culture medium. Our findings show that 9-O-acetyl gangliosides may play an important role on the extension of growth cones and consequently influences navigation and pathway finding during development (Mendez-Otero and Friedman 1996, Araujo et al. 1997).

CONCLUSIONS AND PERSPECTIVES

The mechanisms by which ganglioside expression leads to neuronal migration and neurite outgrowth are still not defined. However, based on the data summarized in the previous sections and also in the literature (Cheresh 1987, Pande 2000, Armulik et al. 1999, Iwabuchi et al. 1998, Probstmeier and Pesheva 1999, Hakomori and Igarashi 1995, Lloyd and Furukawa 1998, Dulabon et al. 2000, Boldt et al. 1977, Tiemeyer et al. 1989) it is possible to suggest at least three mechanisms to explain the role of gangliosides (Fig. 1).

According to the mechanism illustrated in Fig. 1-I it is likely that specific gangliosides could interact with broadly distributed protein-based adhesion systems and favored subsets of moving cells or process that express these molecules. It is also possible to postulate a mechanism based on homophilic interaction between gangliosides located on adjacent membranes (Fig. 1-II). In addition, it has recently

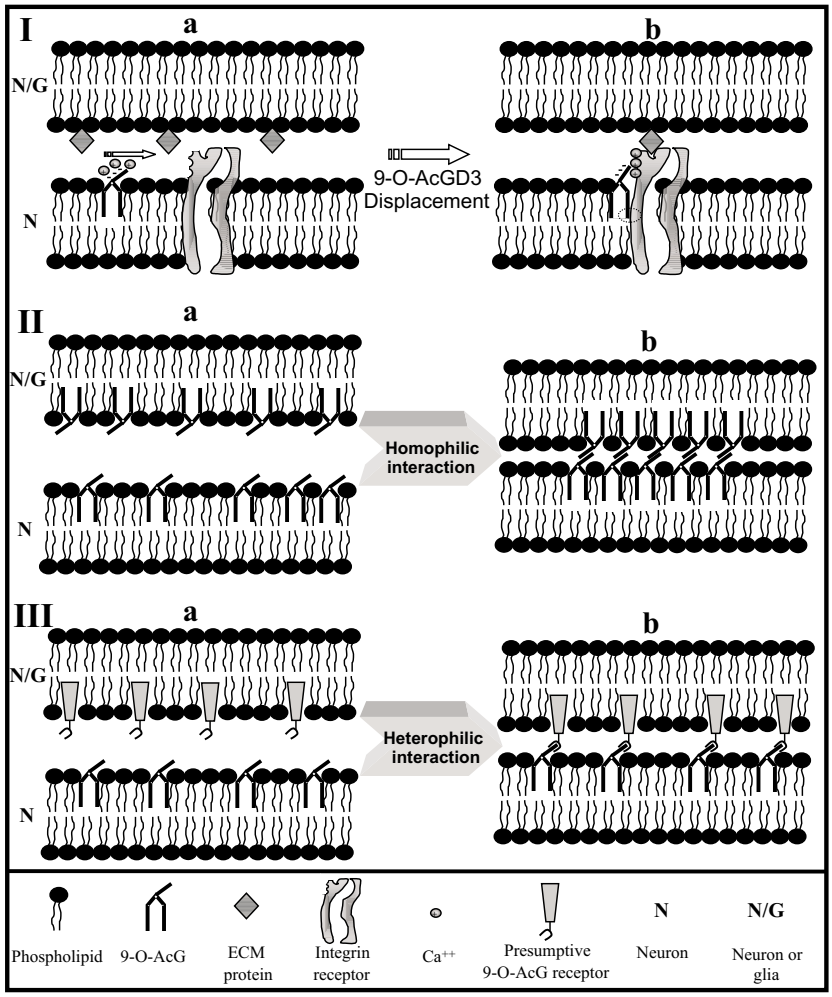

Fig. 1 – Schematic diagrams suggesting three possible mechanisms for 9-O-acetyl GD3 (9-O-AcG) action in gliophilic or neuronophilic neuronal migration. **I:** The ganglioside 9-O-AcG modulates the integrin receptor through a Ca^{++} dependent mechanism and/or by a direct interaction between the cerebroside moiety of the ganglioside and the integrin transmembrane helix (TMH). In a first stage **(a)**, the integrin receptor is inactive and there is no recognition of extracellular matrix (ECM) proteins. Later on **(b)**, the gangliosides in the adjacent membrane become laterally packed around the integrin receptor (represented on the scheme by only one ganglioside), providing an optimal Ca^{++} microenvironment for the activation and recognition of ECM proteins by this receptor. In addition, the gangliosides can interact directly with the integrin receptor through a conserved lysine located inside a 23 amino acids sequence at the carboxy-terminal of the TMH (outline). **II:** Homophilic interaction between gangliosides located at different cell membranes. In **(a)**, two cells containing 9-O-AcG randomly spread over the membranes. In **(b)**, the cells are interacting in a homophilic manner through a carbohydrate-carbohydrate interaction of the gangliosides. **III:** Heterophilic interaction between the gangliosides and a potential specific receptor. In **(a)**, a cell containing the ganglioside 9-O-AcG in the membrane and another cell expressing a presumptive receptor. In **(b)**, the cells are interacting by the way of a specific recognition between the ganglioside 9-O-AcG and its particular receptor. This interaction could trigger a specific cascade of reactions in both cells (not illustrated in the scheme).

been shown that selectins and/or galectins can function as receptors for specific gangliosides and this interaction could trigger a cascade of reactions in both cells (Fig. 1-III).

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RESUMO

A migração de neurônios de seus sítios de origem a seus destinos finais é uma etapa universal e crítica na formação da complexa estrutura do sistema nervoso. Admite-se que o processo migratório seja governado, em parte, por sequências de sinais definidas genetica e epigeneticamente que são interpretadas pelas células migrantes. Os mecanismos moleculares subjacentes à migração neuronal têm sido objeto de intensa investigação. Como em outros processos do desenvolvimento, muitas moléculas devem participar na migração neuronal. Algumas delas, como as moléculas de adesão e proteínas motoras, podem contribuir para etapas discretas no ato de migração; outras, como moléculas extra-celulares de sinalização, podem regular a ativação e/ou o término do programa de migração. Neste artigo nós revisamos achados de nosso grupo que demonstram o(s) papel (papéis) funcional(ais) de um glicolipídeo específico na migração neuronal e no crescimento de neuritos no sistema nervoso em desenvolvimento bem como no adulto.

Palavras-chave: Glicolipídeo, gangliosídeo, 9-O-acetyl GD3, migração neuronal, crescimento de neuritos, desenvolvimento.

REFERENCES

ALTMAN J. 1969a. Autoradiographic and histological studies of postnatal neurogenesis, IV: Cell proliferation and migration in the anterior forebrain, with special reference to persisting neurogenesis in the olfactory bulb. J Comp Neurol 137: 433-458.

ALTMAN J. 1969b. Autoradiographic and histological studies of postnatal neurogenesis. III. Dating the time of production and onset of differentiation of cerebellar microneurons in rats. J Comp Neurol 136: 269-294.

ALTMAN J. 1972a. Postnatal development of the cerebellar cortex in the rat. I. The external germinal layer and the transitional molecular layer. J Comp Neurol 145: 353-398.

ALTMAN J. 1972b. Postnatal development of the cerebellar cortex in the rat. III. Maturation of the components of the granular layer. J Comp Neurol 145: 465-514.

ALTMAN J. 1982. Morphological development of the rat cerebellum and some of its mechanisms. Exp Brain Res 6(Suppl): 8-46.

ALTMAN J AND BAYER AS. 1985a. Embryonic development of the rat cerebellum. I. Delineation of the cerebellar primordium and early cell movements. J Comp Neurol 231: 1-26.

ALTMAN J AND BAYER AS. 1985b. Embryonic development of the rat cerebellum. II. Translocation and regional distribution of the deep neurons. J Comp Neurol 231: 27-41.

ALTMAN J AND BAYER AS. 1985c. Embryonic development of the rat cerebellum. III. Regional differences in the time of origin, migration, and settling of Purkinje cells. J Comp Neurol 231: 42-65.

ANDERSON AS, EISENSTAT DD, SHI L AND RUBENSTEIN JLR. 1997. Interneuron migration from basal forebrain to neocortex: Dependence on Dlx genes. Science 278: 474-476.

ANTONICEK H, PERSOHN E AND SCHACHNER M. 1987. Biochemical and functional characterization of a novel neuron-glia adhesion molecule that is involved in neuronal migration. J Cell Biol 104: 1587-1595.

ARAUJO H, MENEZES M AND MENDEZ-OTERO R. 1997. Blockage of 9-O-acetyl gangliosides induces microtubule depolymerization in growth cones and neurites. Eur J Cell Biol 72: 202-213.

ARMULIK A, NILSSON I, VON HEIJNE G AND JOHANSSON S. 1999. Determination of the border between the transmembrane and cytoplasmic domains of human integrin subunits. J Biol Chem 274: 3703?-37034.

BOLDT DH, SPECKART, SF RICHARDS, RL AND ALVING CR. 1977. Interaction of plants lectins with glycolipid in liposomes. Biochem Biophys Res Commun 74: 208-214.

CAVINESS VS AND SIDMAN RL. 1973. Time of origin of corresponding cell classes in the cerebral cortex of normal and mutant reeler mice: an autoradiographic analysis. J Comp Neurol 148: 141-152.

CHAE T, KWON YT, BRONSON R, DIKKES P, LI E AND TSAI LH. 1997. Mice lacking p35, a neuronal specific activator of Cdk5, display cortical lamination defects, seizures, and adult lethality. Neuron 18: 29-42.

CHERESH DA. 1987. Ganglioside involvement in tumor cell-substratum interactions. In: GREENE MI AND HAMAOKA T., Eds, Development and recognition of the transformed cell, New York: Plenum Press.

CONSTANTINE-PATON M, BLUM AS, MENDEZ-OTERO R AND BARNSTABLE CJ. 1986. A cell surface molecule distributed in a dorsoventral gradient in the perinatal rat retina. Nature 324: 459-462.

D'ARCANGELO G, MIAO GG, CHEN SC, SOARES HD, MORGAN JI AND CURRAN T. 1995. A protein related to extracellular matrix proteins deleted in mouse mutant reeler. Nature 374: 719-723.

DE CARLOS JA, LÓPEZ-MASCARAQUE L AND VALVERDE F. 1996. Dynamics of cell migration from the lateral ganglionic eminence in the rat. J Neurosci 16: 6146-6156.

DOETSCH F, GARCIA-VERDUGO JM AND ALVAREZ-BUYLLA A. 1997. Cellular composition and three-dimensional organization of the subventricular germinal zone in the adult mammalian brain. J Neurosci 17: 5046-5061.

DULABON L, OLSON EC, TAGLIENTI MG, EISENHUTH S, MCGRATH B, WALSH CA, KREIDBERG JA AND ANTON ES. 2000. Reelin binds $\alpha 3\beta 1$ integrin and inhibits neuronal migration. Neuron 27: 33-44.

GAGE FH, KEMPERMANN G, PALMER TD, PETERSON DA, RAY J. 1998. Multipotent progenitor cells in the adult dentate gyrus. J Neurobiol 36: 249-266.

GLOOR S, ANTONICEK H, SWEADNER KJ, PAGLIUSI S, FRANK R, MOOS M AND SCHACHNER M. 1990. The adhesion molecule on glia (AMOG) is a homologue of the b subunit of the Na^+, K^+-ATPase. J Cell Biol 110: 165-174.

HAKOMORI S AND IGARASHI Y. 1995. Functional role of glycosphingolipids in cell recognition and signaling. J Biochem 118: 1091-1103.

HATTEN ME. 1999. Central nervous system neuronal migration. Ann Rev Neurosci 22: 511-539.

HIROTSUNE S, TAKAHARA T, SASAKI N, HIROSE K, YOSHIKI A, OHASHI T, KUSAKABE M, MURAKAMI Y, MURAMATSU M, WATANABE S, NAKAO K, KATSUKI M AND HAYASHIKI Y. 1995. The reeler gene encodes a protein with an EGF-like motif expressed by pioneer neurons. Nature Genet 10: 77-83.

HU H, TOMASIEWICS H, MAGNUSON T AND RUTISHAUSER U. 1996. The role of polysialic acid in migration of olfactory bulb interneuron precursors in the subventricular zone. Neuron 16: 735-743.

HYNES RO, PATEL R AND MILLER RH. 1986. Migration of neuroblasts along preexisting axonal tracts during prenatal cerebellar development. J Neurosci 6: 867-876.

IWABUCHI K, YAMAMURA S, PRINETTI A, HANDA K AND HAKOMORI S. 1998. GM-3 enriched microdomain involved in cell adhesion and signal transduction through carbohydrate-carbohydrate interaction in mouse melanoma B16 cells. J Biol Chem 273: 9130-9138.

KOMURO H AND RAKIC P. 1992. Selective role of N-type calcium channels in neuronal migration. Science 257: 806-809.

KOMURO H AND RAKIC P. 1993. Modulation of neuronal migration by NMDA receptors. Science 260: 95-97.

LLOYD KO AND FURUKAWA K. 1998. Biosynthesis and functions of gangliosides: recent advances. Glycoconj J 7: 627-36.

LOIS C, GARCIA-VERDUGO J-M AND ALVAREZ-BUYLLA A. 1996. Chain migration of neuronal precursors. Science 271: 978-981.

LUSKIN MB. 1993. Restricted proliferation and migration of postnatally generated neurons derived from

the forebrain subventricular zone. Neuron 11: 173-189.

LUSKIN MB AND BOONE MS. 1994. Rate and pattern of migration of lineally-related olfactory bulb interneurons generated postnatally in the subventricular zone of the rat. Chem Senses 19: 695-714.

MENDEZ-OTERO R AND CAVALCANTE LA. 1996. Expression of 9-O-acetylated gangliosides is correlated with tangential cell migration in the rat brain. Neurosci Lett 204: 97-100.

MENDEZ-OTERO R AND CONSTANTINE-PATON M. 1990. Granule cell induction of 9-O-acetyl gangliosides on cerebellar glia in microcultures. Dev Biol 138: 400-409.

MENDEZ-OTERO R AND FRIEDMAN JE. 1996. Role of acetylated gangliosides on neurite extension. Eur J Cell Biol 71: 192-198.

MENDEZ-OTERO R AND RAMÓN-CUETO A. 1994. Expression of 9-O-acetylated gangliosides during development of the rat olfactory system. Neuroreport 5: 1755-1759.

MENDEZ-OTERO R, SCHLOSSHAUER B, BARNSTABLE CJ AND CONSTANTINE-PATON M. 1988. A developmentally regulated antigen associated with neural cell and process migration. J Neurosci 8: 564-579.

MENDEZ-OTERO R, SCHLOSSHAUER B AND CONSTANTINE-PATON M. 1992. Role of acetylated gangliosides on neuronal migration and axonal outgrowth. In: LENT R, Ed. The Visual System from Genesis to Maturity, Birkhauser, Boston, MA 49-62.

MIYAKOSHI LM, MENDEZ-OTERO R AND HEDIN-PEREIRA C. 2001. The 9-O-acetyl GD3 gangliosides are expressed by migrating chains of subventricular zone neurons in vitro. Braz J Med Biol Res, in press.

NORGREN RB JR. AND LEHMAN MN. 1991. Neurons that migrate from the olfactory epithelium in the chick express luteinizing hormone-releasing hormone. Endocrinology 128: 1676-1678.

O'ROURKE NA, CHENN A AND MCCONNELL SK. 1997. Postmitotic neurons migrate tangentially in the cortical ventricular zone. Development 124: 997-1005.

PANDE G. 2000. The role of membrane lipids in regulation of integrin function. Curr Opin Cell Biol 12: 569-574.

PATIL N, COX DR, BHAT D, FAHAM M, MYERS RM AND PETERSON AS. 1995. A potassium channel mutation in weaver mice implicates membrane excitability in granule cell differentiation. Nature Genet 11: 126-129.

PROBSTMEIER R AND PESHEVA P. 1999. Tenascin-C inhibits β1 integrin-dependent cell adhesion and neurite outgrowth on fibronectin by a disialoganglioside-mediated signaling mechanism. Glycobiology 9: 101-114.

RAKIC P. 1971. Neuron-glia relationship during granule cell migration in developing cerebellar cortex. A Golgi and electromicroscopic study in Macacus Rhesus. J Comp Neurol 141: 283-312.

RAKIC P. 1981. Neuronal-glial interactions during brain development. Trends in Neurosci 4: 184-187.

RAKIC P, CAMERON RS AND KOMURO H. 1994. Recognition, adhesion, transmembrane signaling and cell motility in guided neuronal migration. Curr Opin Neurobiol 4: 63-69.

RIO C, RIEFF HI, QI P AND CORFAS G. 1997. Neuregulin and erbB receptors play a critical role in neuronal migration. Neuron 19: 39-50.

SANTIAGO MF, BERREDO-PINHO M, GANDRA M, COSTA MR, CAVALCANTE LA AND MENDEZ-OTERO R. 2001. Expression and function of ganglioside 9-O-acetyl GD3 in post-mitotic granule cell development. Mol Cell Neurosci, 17: 488-499.

SCHLOSSHAUER B, MENDEZ-OTERO R AND CONSTANTINE-PATON M. 1988. Developmental regulation of ganglioside antigens recognized by the JONES antibody. J Neurosci 8: 580-592.

SINGER SJ AND KUPFER A. 1986. The directed migration of eukaryotic cells. Ann Rev Cell Biol 2: 337-365.

TAMAMAKI N, FUJIMORI KE AND TAKAUJI R. 1997. Origin and route of tangentially migrating neurons in the developing neocortical intermediate zone. J Neurosci 17: 8313-8323.

TIEMEYER M, YASUDA Y AND SCHNAAR RL. 1989. Ganglioside-specific binding protein on rat brain membranes. J Biol Chem 264: 1671-1681.

WICHTERLE H, GARCIA-VERDUGO J AND ALVAREZ-BUYLLA A. 1997. Direct evidence for homotypic, glia-independent neuronal migration. Neuron 18: 779-791.

ZHENG T, HEINTZ N AND HATTEN ME. 1996. CNS gene encoding astrotactin, which supports neuronal migration along glial fibers. Science 272: 417-419.