Netrin-G/NGL interaction in elaborated neuronal circuits

Shigeyoshi Itohara,
RIKEN Brain Science Institute

Higher brain functions such as cognition, learning, language, attention, and emotion are attributed to the formation of highly complex and organized neural circuits associated with an increase in cerebral volume. The laminar structures of the cortex provide a fundamental basis for integrating information. Two pairs of a synaptic trans-neuronal ligand and receptor, namely netrin-G1/-G2 and netrin-G ligand (NGL) 1/2, have likely evolved by genomic duplication as vertebrate-specific genes, and have specific roles associated with the cortical laminar structures. Remarkably, the netrin-G1 and netrin-G2 genes are expressed in distinct neuronal circuits in a complementary manner. Loss-of-function studies of these genes in mice demonstrate that presynaptic netrin-G1 and netrin-G2, which are expressed in distinct neuronal pathways, constrain specific ligands NGL1 and NGL2 to a specific sub-domain of the dendrites of their target neurons, and thus contribute to determine circuit specificity within a single neuron. The lack of either netrin-G1 or netrin-G2 results in abnormal synaptic plasticity in a circuit-specific manner, and thus causes differential abnormalities in various behavioral domains. The retina also has highly elaborated laminar structures and serves as a mini-brain model. We revealed complementary expression patterns of netrin-G1/-G2 and NGL1/2 in the retina, similar to other brain areas. A lack of presynaptic netrin-G1 or netrin-G2 results in abnormal postsynaptic properties in a layer-specific manner. These findings indicate that netrin-G/NGL interactions contribute to laminar structure-dependent information processing.

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Shigeyoshi ITOHARA

Education and Degrees:

1972-1976 Yamaguchi University, BSc in Veterinary Medicine
1976-1978 Graduate School of Yamaguchi University, MSc in Veterinary Medicine
1987 Ph.D. from University of Tokyo

Research and Professional experience:

1978-1988 Researcher, National Institute for Animal Health (NIAH)
1988-1991 Postdoctoral fellow, Howard Hughes Medical Institute at MIT
1991-1993 Senior Researcher and then Laboratory Head, NIAH
1993-1997 Associate Professor, Institute for Virus Research, Kyoto University
1997-present Laboratory Head, Laboratory for Behavioral Genetics, RIKEN BSI

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THE ROLE OF ROBO RECEPTORS IN CORTICAL INTERNEURON MIGRATION

John G Parnavelas
Department of Cell and Developmental Biology, University College London, UK

We have been investigating the molecular mechanisms that guide the migration of cortical interneurons from their origin in the subpallial ganglionic eminences (GE) to the neocortex. Numerous molecules such as transcription, motogenic and neurotrophic factors have already been demonstrated to play important roles in their migration. Earlier studies have suggested that cortical interneurons express neuropilin (Nrp) receptors, which enable them to respond to the chemorepulsion produced by class 3 semaphorins (Sema3A and Sema3F) expressed in the striatum. This repulsive activity in the developing stratum creates an exclusion zone for migrating interneurons and channels them into adjacent paths, leading to the formation of their migratory routes into the cortex. However, we have discovered that interneurons in Robo1 null mice ($Robo1^{-/-}$) migrate through the striatum *en route* to the cortex. Our recent studies have indicated that Robo1 controls the migration of cortical interneurons by modulating their responsiveness to semaphorins. Specifically, we have found, using *in vitro* assays, that GE cells taken from $Robo1^{-/-}$ mice are markedly less responsive to Sema3A and Sema3F and this effect is not due to direct interaction between semaphorins and Robo1. Moreover, expression studies illustrated specific downregulation of semaphorin receptors (Nrp and plexin) in GE-derived cells of $Robo1^{-/-}$ mice. Biochemical studies also demonstrated that Nrp1 is able to directly bind to Robo1. Our data demonstrate that Robo1 modulates semaphorin-neuropilin/plexin signalling to steer interneurons around the stratum and into the cortex. We are currently trying to identify downstream molecules that may be involved in this interaction.

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CURRICULUM VITAE

Professor John G. Parnavelas

Department of Cell and Developmental Biology
University College London
Gower Street
London WC1E 6BT
UK

Telephone (020) 7679-3366
Fax (020) 7679-7349
E-mail j.parnavelas@ucl.ac.uk

UNIVERSITY EDUCATION:

1968	B.S., Physics, University of California at Los Angeles
1970	M.S., Biomedical Engineering, University of Southern California
1973	M.S., Biological Sciences, University of California at Irvine
1975	Ph.D., Anatomy, University of Rochester, New York

POSITIONS HELD:

1993-present	Professor of Neuroanatomy, Department of Anatomy and Developmental, Biology, University College London
1988-1993	Reader in Neuroanatomy, Department of Anatomy and Developmental Biology, University College London
1983-1988	Lecturer in Anatomy, Department of Anatomy and Embryology, University College London
1978-1983	Assistant Professor, Department of Cell Biology, The University of Texas Health Science Center, Dallas
1975-1978	Postdoctoral Fellow, Department of Anatomy and Embryology, University College London