



Multiple Biological Activities of Neuroglycan C, a Central Nervous System-specific Chondroitin Sulfate Proteoglycan

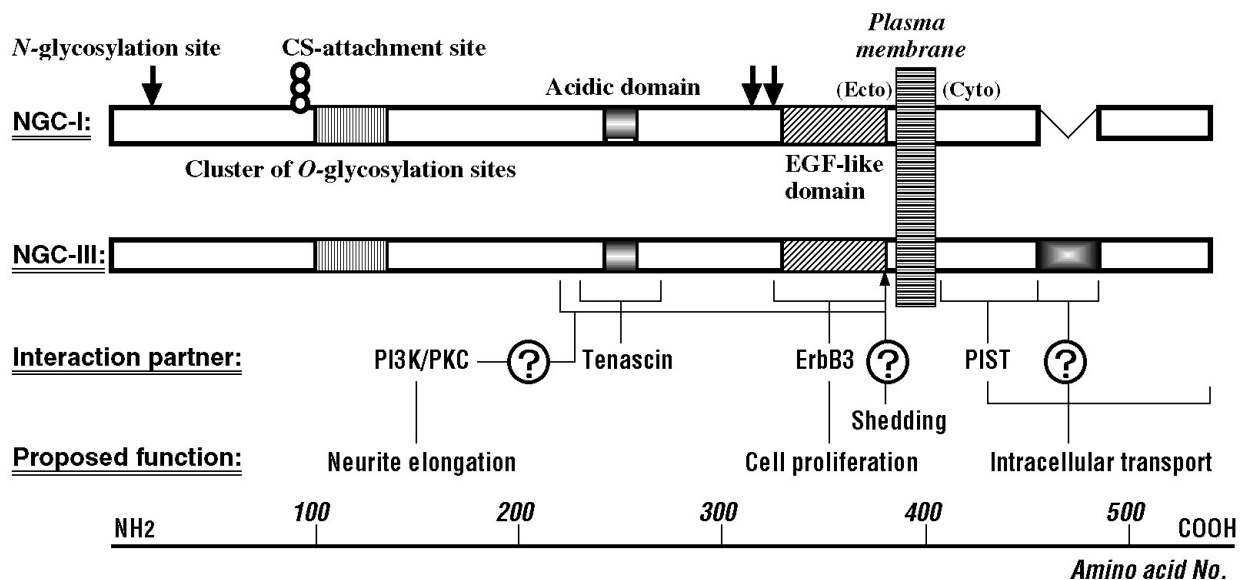
Atsuhiko Oohira

Department of Perinatology and Neuroglycoscience, Institute for Developmental Research, Aichi Human Service Center, Japan



Atsuhiko Oohira graduated from the Department of Chemistry, Nagoya University Graduate School of Science, Nagoya, Japan, under the supervision of Professor Sakaru Suzuki, and received his Ph.D. in 1974. The theme of his doctoral thesis was 'Biosynthesis of Cartilage Collagen'. He worked as a visiting scientist at the Department of Biochemistry (Prof. Paul Bornstein's Lab), University of Washing-

ton, Seattle, WA, USA, from 1980 to 1982, where he investigated the structure and function of heparan sulfate proteoglycans in the basement membrane. After coming back to Japan, he started a research project on proteoglycans in the central nervous system. He was made the Director of this Department in 1992, and has served concurrently as a Visiting Professor of Neurochemistry, Nagoya University Graduate School of Medicine, since 1999. His current research interests include the functional roles of nervous tissue proteoglycans and the therapeutic treatments of neonatal brain injuries.



Structure, interaction partners and proposed functions of two splice variants (NGC-I and NGC-III) of neuroglycan C (NGC). NGC-I is the major variant accounting for more than 90% of total NGC in the developing brain. CS, chondroitin sulfate; EGF, epidermal growth factor; PI3K, phosphatidylinositol 3-kinase; PKC, protein kinase C; ErbB3, an EGF receptor tyrosine kinase; PIST, PDZ domain protein interacting specifically with TC10.

Existence of multiple proteoglycan species is characteristic of the central nervous system (CNS). Of these nervous tissue proteoglycans, neuroglycan C (NGC) is exclusively expressed in the CNS, and is the only membrane-spanning chondroitin sulfate proteoglycan (CSPG) that exists mainly in association with the neuronal structure. NGC expression is developmentally regulated, higher in the developing brain. Three splice variants of NGC (NGC-I, -III and -IV) have been identified as CSPG in the brain. The entire core protein of mouse NGC-I (the major variant) consists of 509 amino acid residues plus a 30-residue signal peptide, and includes five structurally different domains; an N-terminal domain to which a chondroitin sulfate (CS) chain is attached, an acidic amino acid cluster, a single epidermal growth factor (EGF)-like module, a membrane-spanning segment, and a C-terminal cytoplasmic domain of 95 amino acids. All the splice variants have a common ectodomain, but NGC-III has a short peptide insert composed of 27 amino acid residues in the middle part of the cytoplasmic domain of NGC-I. NGC-IV has the shortest cytoplasmic domain with a peptide sequence different from those of other variants.

The ectodomain of the NGC core protein is modified post-translationally in various ways such as CS-glycosylation, *O*- and *N*-glycosylation, and probably phosphorylation. NGC exists in a proteoglycan form with a single CS chain in various regions of the developing CNS, while most NGC molecules exist

in a non-proteoglycan form in the mature cerebellum and retina. This indicates that NGC is a part-time proteoglycan.

NGC can bind at a high affinity to some molecules via a particular domain of the core protein; to tenascins via the acidic domain, to an EGF receptor ErbB3 via the EGF-like domain, and to PIST via the cytoplasmic domain. Some biological activities of NGC could be mediated by these molecular interactions. In fact, a recombinant peptide including the entire EGF-like module can stimulate proliferation of cells through autophosphorylation of the ErbB2/B3 heterocomplex. A recombinant peptide including the acidic domain and/or EGF-like domain stimulates neurite extension from primary-cultured neurons via the PI3K/PKC-signaling pathway, but a receptor of the peptide on neurons has not been identified. In addition, NGC could interact with a pronase, because release of the NGC ectodomain from the neuronal cell surface is inhibited in the presence of protease inhibitors including TIMP-3.

These molecular interactions may be implicated in some of brain functions. We have produced three mouse strains with a distinct NGC gene mutation; an NGC-null mutant strain, a strain with a low expression of NGC, and a strain expressing mostly a non-proteoglycan form of NGC. Behavioral analyses of these mutant mice suggest that NGC is really involved in some brain functions such as regulation of motor coordination.

Keywords : neuroglycan C, neurite elongation, proliferation, brain, gene mutation