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PTP ζ signaling and neural network formation

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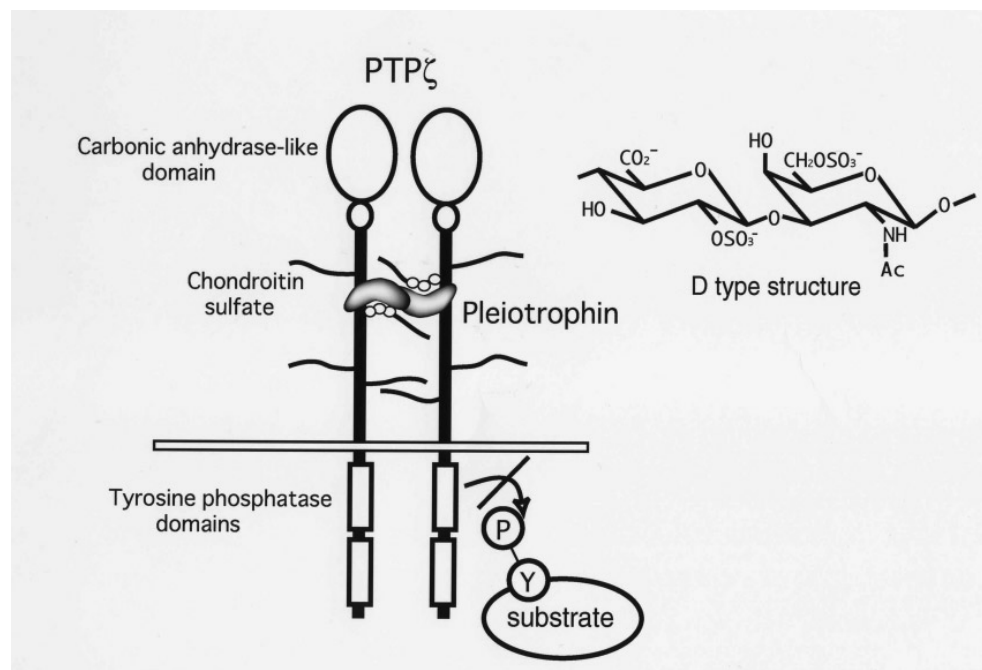
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Various aspects of the developmental processes of the brain are regulated by many extracellular matrix and cell surface molecules. Chondroitin sulfate proteoglycans are major components of the extracellular matrix in the brain, and play important roles in the neuronal migration, neurite extension and neural plasticity. Furthermore, it has been recognized that chondroitin sulfate proteoglycans are the major inhibitor of axonal regeneration after central nervous system injury.

PTP ζ is a brain-specific receptor-type protein tyrosine phosphatase, which is synthesized as a chondroitin sulfate proteoglycan. The extracellular region of this receptor is secreted as a soluble chondroitin sulfate proteoglycan, phosphacan/6B4 proteoglycan. These transmembrane and secreted forms are generated by alternative splicing. We identified pleiotrophin (PTN) as one of the major ligand of PTP ζ , in which chondroitin sulfate portion plays an essential role in ligand binding. PTN, also known as heparin-binding growth-associated molecule (HB-GAM), is an 18-kDa growth factor, which promotes neurite outgrowth and neuronal migration.

In order to reveal the roles of this signaling system in the brain development, we analyzed the expression of PTP ζ and PTN in the developing cerebellum. The expression of these molecules were dynamically regulated during development of cerebellum. While PTP ζ was expressed by Purkinje cells and Bergmann glia, PTN was produced by Bergmann

glia. Purkinje cells and the processes of Bergmann glia are closely associated, and it has been revealed that this cell-cell interaction plays important roles in the morphogenesis of Purkinje cells. Thus we hypothesized that PTP ζ -PTN signaling is involved in the morphogenesis of Purkinje cells. Using an organotypic slice culture system, we found that an aberrant morphology of Purkinje cell dendrites such as multiple and disoriented primary dendrites was induced by addition of the function-blocking antibodies against PTP ζ , chondroitinase ABC digestion, and addition of exogenous chondroitin sulfate preparations. The effects of chondroitin sulfate was structure-dependent, and GlcA(2S) β 1-3GalNAc(6S) disaccharide unit (D unit)-rich chondroitin sulfate strongly induced aberrant morphogenesis of Purkinje cells. The extracellular space between Purkinje cells and the processes of Bergmann glia were enriched with D unit-rich chondroitin sulfate. *In situ* hybridization analysis indicated that the uronyl 2-sulfotransferase gene, which is responsible for the production of D structure, was selectively expressed by Purkinje cells, and the expression level of this gene sharply increased during postnatal cerebellar development. Furthermore, biochemical analysis indicated that D unit-rich chondroitin sulfate strongly inhibited the binding of PTN to PTP ζ in the cerebellar slices, suggesting that this oversulfated structure plays important roles in the PTP ζ -PTN signaling during development of the cerebellar cortex.

Selected publications:

- (1) Maeda, N. et al. (2006). The binding of chondroitin sulfate to pleiotrophin/heparin-binding growth-associated molecule is regulated by chain length and oversulfated structures. *J. Biol. Chem.* 281, 4894-4902.
- (2) Maeda, N. et al. (2003). Heterogeneity of chondroitin sulfate portion of phosphacan/6B4 proteoglycan regulates its binding affinity for pleiotrophin/HB-GAM. *J. Biol. Chem.* 278, 35805-35811.
- (3) Tanaka, M., Maeda, N. et al. (2003). A chondroitin sulfate proteoglycan PTP ζ /RPTP β regulates the morphogenesis of Purkinje cell dendrites in the developing cerebellum. *J. Neurosci.* 23, 2804-2814.
- (4) Maeda, N. et al. (1998). Involvement of receptor-like protein tyrosine phosphatase ζ /RPTP β and its ligand pleiotrophin/heparin-binding growth-associated molecule (HB-GAM) in neuronal migration. *J. Cell Biol.* 142, 203-216.
- (5) Maeda, N. et al. (1996). 6B4 proteoglycan/phosphacan, an extracellular variant of receptor-like protein-tyrosine phosphatase ζ /RPTP β , binds pleiotrophin/heparin-binding growth-associated molecule (HB-GAM). *J. Biol. Chem.* 271, 21446-21452

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