Role of heparan sulfate proteoglycan in etiology of neurodegenerative disease

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Heparan sulfate proteoglycans (HSPGs) are one of the basic constituent of cell membranes and extracellular matrix. They intercept and regulate biological signals coming into cells, hence, playing an important role in various physiological and pathological cell functions. HSPGs have been identified to play important role in a development of mammalian nervous system, by modulating the axon guidance and synapse plasticity. On the other hand, altered turnover of HSPGs and/or their accumulation have been found in many neurodegenerative diseases, e.g., Alzheimer's disease (AD).

Glial cells are a main source of heparan sulfate and HSPGs detected in amyloid β (Aβ) deposits related to pathology of AD. The increased expression levels of cell surface HSPGs detected upon the stimulation with Aβ have been reported. Glial cells have been also found to express high levels of transglutaminase 2 (TG2). TG2 is a widely-expressed, calcium-dependent enzyme that catalyzes a formation of covalent bonds between certain proteins, resulting in formation of aggregates resistant to proteolytic cleavage.

Enzymatic function of TG2 seems to contribute to pathology or etiology of neurodegenerative disorders and might be at least partially regulated by HSPGs expressed by glial cells. In order to address this hypothesis, biochemical characterization of mouse glial cell lines was done. Staining with 10E4 antibodies showed high expression of HSPGs on cell surface. Western blotting using the antibodies recognizing HS-derived epitope revealed several bands suggesting the presence multiple types of transmembrane-type proteoglycans. The RT-PCR analysis and WB blotting with antibodies allowed identification of various syndecan and glypican species as putative candidates for interaction with TG2. Subcellular fractionation and immuncytochemical analyses showed that TG2-specific compartments were also specific for HSPGs suggesting possible interaction between those molecules.