



Endocytosis and Intracellular Degradation of Cell Surface Heparan Sulfate Proteoglycans

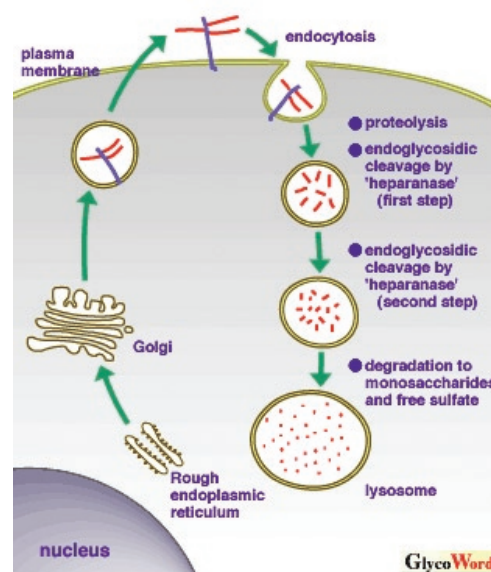
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Masaki Yanagishita obtained M.D. degree from the Keio University School of Medicine in 1973. After finishing his clinical training in Tokyo, he joined the postdoctoral program at the National Institutes of Health, Bethesda, in 1975. His initial study involved computerized characterization of molecular interactions between hormones and antibodies. While exploring possibilities in research directions, he was inspired by works on cartilage proteoglycans in Vincent Hascall's lab, and was drawn into the fascinating world of proteoglycans. He was especially interested in studying proteoglycans in non-cartilagenous tissues, which were not recognized very widely then. Ovarian granulosa cell culture system at his hand for endocrinology studies happened to provide an excellent system

studying biosynthesis and metabolism of multiple proteoglycan species. He focused his research interest on the biosynthesis and intracellular catabolism of cell surface heparan sulfate proteoglycans using metabolic radiolabeling of cell cultures combined with pulse-chase experiments. His major discoveries included demonstration of multiple, prelysosomal degradation pathways for cell surface heparan sulfate proteoglycans. The established scheme of intracellular degradation of heparan sulfate proteoglycans appeared to be general among animal cells. The studies also predicted the presence of endoglycosidic enzymes specific for heparan sulfate that are active in prelysosomal compartments. He moved to the Tokyo Medical and Dental University in 1996 as a professor of biochemistry. His laboratory now focuses on the research of heparan sulfate specific endoglycosidases (heparanase) and its medical significance.



Cell surface heparan sulfate proteoglycans (HSPGs) play diverse biological functions through specific molecular interactions with distinct classes of bioactive molecules, including growth factors and extracellular matrix molecules. However, the relative importance of each molecular interaction and its integration regulating cell functions have been difficult to evaluate. Studies elucidating metabolic turnover of cell surface HSPGs would shed light on the behavior of the molecules, thus, biological functions of the molecules.

Past studies on the metabolism of cell surface HSPGs using mammalian cell cultures in combination with metabolic radiolabeling experiments have elucidated that the endocytosis is the major metabolic pathway retrieving HSPGs from the cell surface. After endocytosis, HSPGs undergo two distinct intracellular processing pathways depending on their membrane anchoring structures. HSPGs with GPI-anchor, glypican family molecules, are processed like most other molecules that are endocytosed through a receptor-mediated endocytotic mechanism; quickly transported to lysosomes. On the other hand, HSPGs with transmembrane protein cores,

i.e., syndecan family HSPGs, undergo a unique degradation pathway; slow, stepwise degradation involving proteolytic degradation and prelysosomal endoglycosidic cleavage of HS chains. We have been focusing on the analysis of the latter degradation pathway, and identified a key degradation enzyme of HS, an HS-specific endo- β -glucuronidase, heparanase.

Recent genetic studies using *Drosophila melanogaster* and *Caenorhabditis elegans* have shed important light on the biological functions of HSPGs in growth factor signaling. These model organisms, thus, provide excellent experimental tools studying prototypical functions of HSPGs. They also provide interesting systems studying handling of HSPG molecules by the cell, since the organization of cell architecture, including that of Golgi apparatus and lysosome, in these organisms is distinct from those in higher organisms. The overall metabolic pathways for *Drosophila* HSPGs appeared similar to those observed for mammalian cells except the absence of heparanase activity, implicating widely conserved mechanisms for intracellular processing steps for HSPGs throughout the animal cells.

Keywords : heparan sulfate proteoglycan, metabolism, endocytosis, heparanase