29. Development of a novel glyco therapy / glyco diagnosis for cancer and viral diseases

Nobuto Koyama (Takara Bio Inc.)

Changes in oligosaccharide structure of glycoproteins are observed in cancer, inflammation, and viral diseases. The objects of our study are to elucidate the biological significance of the structure of *N*-linked oligosaccharides, and to develop a novel therapeutic tool or a diagnostic method for cancer and viral diseases. Our projects are summarized in 3 categories as follows

(1) Intracellular trafficking of glycoproteins and lectins: Annexin V is an animal lectin which recognizes a bisecting GlcNAc structure. We found that annexin V interacts with a molecular chaperon Hsp47 through its bisecting GlcNAc. Secretion of HBs antigen was selectively inhibited by gene transfection of GnT-III into HB611 cells. Glycomic approach revealed that oligosaccharide structures on adhesion molecules such as cadherin and integrins were selectively modified. These results suggest that bisecting GlcNAc affects the intracellular trafficking of certain kinds of glycoproteins.

(2) Oligosaccharide and hepatic stem cells: A rat hepatic stem-like cell line, RLE was found to express high levels of bisecting GlcNAc on its cell surface, and we are developing the method for separating hepatic stem cells by using E4-PHA lectin. RLE cells showed reduced expression of bisecting GlcNAc during differentiation, which suggests that bisecting GlcNAc and differentiation are closely related in hepatocytes.

(3) Modulation of oligosaccharide structures: The structure of *N*-linked sugar chain is related to tumor metastasis and proliferation of cancer cells. We analyzed the structure and function of GnT-III and GnT-V promoters with the object of searching substances for modulating the expression of these genes to utilize as drugs and supplements. Knockout/knockdown of fucosyltransferase 8 gene leads to growth retardation *in vivo* and *in vitro*. We found that trypsinogens and PAR-2 receptor are responsible for the mechanism. Thus, we intend to develop a cancer therapy by modulating the expression of glycosyltransferase genes.