

Japan Academy Prize to:

Naoyuki TANIGUCHI
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for “Pioneering Accomplishments in Glycobiology,
 Especially on the Significance of *N*-glycans in Disease”

***Outline of the work:***

Several years ago, the human genomic sequence was largely clarified, and biology entered the so-called post-genomic era. The genome merely provides a blue-print for living organisms but is insufficient for understanding functional details. Many proteins produced by genes must be modified further to be functional. One of the most important modifications is glycosylation. Over 60% of newly synthesized proteins must acquire sugar chains to become functionally active. Furthermore, work of Dr. Naoyuki Taniguchi and his colleagues have clearly shown that very tiny changes in the sugar chains can bring about completely opposite functions for the same protein(s), such as in metastatic capacity of cancer cells or the cellular cytotoxicity of antibodies. Glycoscience is now a rapidly developing field and no one can predict the extent of its influence for basic biology and medicine in the near future.

Dr. Taniguchi is the most prominent leader in this rapidly developing field. He purified many glycosyltransferases involved in the biosynthesis of N-linked sugar chains by methods developed by himself and characterized their biochemical properties. He then succeeded in cloning many genes that encode glycosyltransferases. He subsequently discovered many novel functions of sugar chains that have significant implications in the pathogenesis, diagnosis, and eventual treatment of medically important conditions such as cancer and emphysema.

Major Research Accomplishments**1. The discovery of cancer-specific sugar chains, purification and biochemical characterization of glycosyltransferases and cloning of their genes**

gamma-Glutamyl transpeptidase that degrades glutathione is highly activated in primary hepatomas. Dr. Taniguchi purified this enzyme from normal and tumor tissues. He discovered a novel sugar chain, bisecting GlcNAc, which was found specifically in hepatoma cells. He then identified and successfully purified an enzyme, GnT-III, which catalyzes biosynthesis of the bisecting GlcNAc, and cloned the GnT-III gene. He followed up this important work with subsequent purification and cloning of a series of related glycosyltransferases, GnT-IV, GnT-V, GnT-VI and Fut8.

2. Clarification for sugar chain functions by utilizing glycosyltransferase genes

GnT-V, which is highly expressed in metastatic foci of cancer under the control of transcription factor Ets-1, adds sugar chains to a serine proteinase, matriptase. The addition of sugar chains on matriptase results in an increase in its stability and enhances cancer metastasis. He also found that the basic region of GnT-V, distinct from the catalytic domain, has angiogenesis-promoting activity, which also contributes to proliferation of cancer cells. On the other hand, introduction of GnT-III gene into cancer cells with high metastatic potential resulted in suppression of metastasis with the addition of bisecting GlcNAc to E-cadherin and integrin. Cancer cells then form larger aggregates that reduce their metastatic potential. Thus, GnT-III and GnT-V act as a “good-guy” and a “bad-guy”, respectively, by minimal modification of the sugar chains of E-cadherin and integrin.

3. Clarification of underlying mechanism of the onset, diagnosis and treatment of diseases

Dr. Taniguchi made Fut8 knockout mouse and found that 70% of affected mice died within three days of birth while the survivors showed marked growth retardation and severe pulmonary emphysema. In those mice, matrix metalloproteinases (MMPs) 1, 9, 12, and 13 are highly expressed because the lack of the core fucose on the TGF-beta receptor (TGFR) causes loss of the suppressive effect of TGFR. As a result, collagen and elastin in the extracellular matrix are degraded and alveolar cell membranes are disrupted, resulting in severe emphysema. In humans, smoking is the major risk factor for emphysema (chronic obstructive pulmonary disease, COPD) but the pathogenetic mechanism remains unclear. Heterozygous Fut8 KO mice are highly susceptible to COPD when exposed to smoking compared to wild-type mice. In severe cases of human COPD patients, Fut8 enzyme activity is lower, suggesting that Fut8 is also involved in the onset of COPD.

The primary mode of action in antibody therapy against cancer, asthma and other conditions is the antibody dependent cellular cytotoxicity (ADCC). This activity involves binding of the Fc portion of IgG1 to the Fc gamma IIIa receptor on NK cells. The antibody IgG1 contains a sugar chain on Asn292 and deletion of the core fucose from the chain enhances ADCC activity by up to 100 fold. This is a major breakthrough for antibody therapy. For example, in the treatment of adult T cell leukemia and asthma, very small amounts of core fucose-deleted IgG1 against CCR4 and IL-5 receptors, respectively, have been reported to be dramatically effective. In the area of diagnosis, Dr. Taniguchi found that fucosylated haptoglobin may serve as an excellent bio-marker for diagnosis of pancreatic cancer because approximately 60% of patients with pancreatic cancer are positive and even in early stages, 30% of patients are positive.

In conclusion, Dr. Taniguchi is a champion in Japan who has led this field for the last several decades. He continues to be active and we can expect further contributions from him in the future as well. In 2001 Dr. Taniguchi was awarded the IGO (International Glycoconjugate Organization) Award which is internationally the most prestigious award in glycobiology. He is still the only recipient from Japan. He also received the IUBMB (International Union of Biochemistry and Molecular Biology) Medal in 2008 and the HUPO (Human Proteome Organization) Award in 2009 for his seminal and continuing contributions to research in glycobiology. In Japan, he was also awarded the Japan Medical Association Award in 2002, the Takeda Foundation Prize in 2002, and the Medal with purple ribbon in 2005.

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