



HOKKAIDO UNIVERSITY

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学 位 論 文 題 名
Title of Doctoral Dissertation

Comprehensive Glycomics for the Discovery of New Biomarkers
in Neurodegenerative Diseases
(神経疾患新バイオマーカーの探索のための総合的グライコミクス)

博士学位論文審査等の結果について (報告)
Results of Evaluation of the Doctoral Dissertation (Report)

The author hypothesized that central nervous system (CNS) disorders result from abnormalities in the processing of proteins and defective processing causes the accumulation of specific neuronal proteins. In addition, this abnormal protein processing of neuronal proteins can entail misfolding of proteins, consequently, altered post-translational modifications of newly synthesized proteins.

In most cases, scientists have chosen physical examination as diagnostic techniques for neurodegenerative diseases that targeted the levels of amino acids, small peptides and metabolic pathways in the brain. Moreover, clinical trials have been focused on lowering the levels of those molecules. All challenged by the unstable and single information, time consuming, and non-precise purifications of the targeted molecules with poor results.

In this study, the author performed research on comprehensive glycomics of human and transgenic mice of neurodegenerative diseases, viz., Alzheimer's, disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) using glycoblotting-assisted MALDI-TOF/MS analysis aiming at new biomarkers for complementary or alternative treatment strategies. The author published the first and the most comprehensive glycomes (*N*-, *O*-, and *GSL*-glycans), which succeeded in discovering potential disease specific biomarkers in neurodegenerative diseases.

From *N*-glycomics analysis, *N*-glycans were decreased in human frontal cortices of AD, PD, and HD cases when compared to the normal subjects. Core-fucosylated and bisecting-GlcNAc types of *N*-glycans was increased in human serum and cerebrospinal fluids (specifically in AD), and FUT8 and GnT III enzymes activities were increased in HD transgenic mice, respectively. The result confirmed the function of liver and pancreas are altered and neurodegenerative diseases share similar glycosylation effects as diabetic patients. Moreover, brain type *N*-glycans and major serum *N*-glycans sourced from IgG altered in neurodegenerative diseases.

The results of author's brain tissue *O*-glycomics showed a clear-cut difference in expression levels of mucin types of *O*-glycans between HD transgenic mice and control. Core 3 was increased and decreased in male and female, respectively, of HD transgenic mice. Besides, sialyl Tn was increased and core 1 was only detected in HD transgenic mice. The above-mentioned results confirmed that ST6GalNAc and C3GnT enzymes activities were increased. From serum HD transgenic mice, core 1 was decreased and core 2 was not detected in HD transgenic mice that confirmed the activities of C1GalT-I and C2GnT enzymes were reduced. Collectively, as the most widely recognized biomarkers, altered mucin types of *O*-glycans showed that CNS disorders sequel cancer complications.

This study also came up with potential ganglioside biomarkers. From HD transgenic mice, GD1a and GM2-NeuGc were the potential biomarkers in brain tissue and serum, respectively. Strikingly, it

was also demonstrated that GM1 and GM2 were found to be the biomarkers in human brain tissue and serum, respectively. Therefore, we believe that GSL-omics analysis for neurodegenerative diseases will definitely provide a benefit for the new era of drug discovery.

In conclusion, the author has discovered new and potential glycan-based biomarkers for the first time in neurodegenerative diseases, and these will contribute to the field of neuroscience and the future of drug discovery. Therefore, we acknowledge that the author is qualified to be granted the Doctorate of (Life Science) by Hokkaido University.