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学 位 論 文 内 容 の 要 旨
Abstract of Doctoral Dissertation

博士の専攻分野の名称　博士（**生命科学**）　　氏　名
Degree requested　Doctor of Life Science　Applicant name SOLOMON TEBEJE GIZAW

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)

Neurodegeneration is the umbrella term that can be applied to several conditions result in progressive loss of neuronal structure and function, and finally neuronal death. All those 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. Glycosylation is the most prevalent post-translational modifications of proteins in higher organisms essential to modulate a wide range of protein and lipid functions within or on extracellular surfaces of the cell. The atrophy of the neurons due to pediatrics and adulthood diseases of the CNS leads to aberrant glycosylation and the biosynthesis pattern of the available glycans is altered. Understanding the glycosylation pattern of *N*-, *O*-, and glycosphingolipids (GSL)-glycans, which is affected by either genetic or environmental cellular stressors, can be promising for an easy prognosis. Brain tissue, serum, and cerebrospinal fluids (CSF) specimens from neurodegenerative and age-related diseases have been validated for biomarker discovery. Moreover, direct glycan analysis of human serum without any protein identification represents a new and innovative approach to disease marker. As a first initiative, I have successfully profiled the presumptive compositions of total glycomes and quantified the total glycomes (*N*-, *O*-, and *GSL*-glycans) expressed in the brain tissue, serum, and CSF of neurodegenerative diseases using glycoblotting-assisted sample preparation combined with MALDI-TOF/MS analysis.

From mice brain tissue glycomics, I have found no significant difference in the amount of *N*-glycans expression levels between Huntington's disease (HD) transgenic mice (R6/2) and control mice (BCF1); however, in serum, *N*-glycans were found in decreased levels in HD transgenic mice. *N*-glycans were decreased in human brain tissues, but found in increased levels in human serum and cerebrospinal fluids. More pronouncedly, bisecting-GlcNAc and core-fucose were found decreased in Alzheimer's disease (AD), Parkinson's disease (PD) and HD of human brain tissues; however, these glycans were increased significantly in serum and cerebrospinal fluids of AD, female PD and Female HD. Human serum *N*-glycan expression levels have strongly correlated with the concentration of human serum Immunoglobulin G (IgG), but less pronouncedly with human CSF IgG, which encourage to suggest that the source of most of core-fucosylated, bisecting-GlcNAc and biantennary type of *N*-glycans was found to be IgG and, noteworthy, IgG used as a potential target for biomarker discovery.

Core 3 was found in increased levels in male and in decreased levels in both the striatum and cortices of female HD transgenic mice compared to the control group. Furthermore, serum levels of core 1 decreased and were undetected for core 2 for HD transgenic mice. *O*-glycans showed no significant difference in human serum of neurodegenerative diseases and the normal subjects. Sialyl T was the major mucin-type *O*-glycan in human serum of neurodegenerative diseases and normal subjects, but the expression level is highly sample dependent, which is more clinical effect. Sialyl T-focused reverse glycomics is needed.

The striatum HD transgenic mice displayed higher levels of GSL-glycans relative to those of the WT

mice. GD1a was drastically increased in the striatum of HD transgenic mice compared to the control mice. The higher levels of gangliosides in HD model mice might be due to inadequate amounts of hexosaminidase in lysosomal compartments, suggesting that HD transgenic mice experienced the same symptoms of GSL lysosomal storage disease. Total serum GSL-glycans, GM2-NeuGc in particular, were decreased in HD transgenic mice compared to the control group mice, in which my study provide further evidence demonstrating the alteration of liver functions due to the effect of HD. Gangliosides were found in decreased levels in human frontal cortex of AD, PD, and HD brain tissue (similar to the *N*-glycans), but in female PD. The decrease of gangliosides, particularly a-series gangliosides, resulted from the loss of neurons and brain shrinkage, which are the pathological hallmarks of neurodegenerative diseases. The reduction of GM1 in neurodegenerative diseases compared to the normal confirms the presence of membrane-bound Aß1-42 tightly bind to GM1 (GAß), which acts as a seed for amyloid, and exhibit early pathological changes of AD.

In conclusion, I have proved that total glycomes expression levels were found altered due to the accumulation of 'amyloid-like proteins' in neurodegenerative diseases in brain and circulation, which is favoring accumulation of aggregated proteins in the brain. As a result, neuronal death aggravated and subsequent perturbation of sugar metabolism which in particular reduced the concentration of brain specific *N*-glycans and gangliosides. Moreover, elevated non-physiologically aggregated proteins detected in peripheral tissues, serum, and CSF of neurodegenerative diseases; and aberrant and/or failure of glycosylation of these proteins altered the composition and expression levels of total glycomes.

Finally, I strongly certify that glycome-based analysis of neurodegenerative diseases are one of the down-to-earth and non-invasive approach towards the discovery of the most promising biomarkers in the next-generation neuroscience studies.