Summary of Doctoral Dissertation

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Title of Doctoral Dissertation

Human serum *N*-glycans as highly sensitive cancer biomarkers: Potential benefits and the risks
(高感度がんマーカーとしてのヒト血清*N*-グリカン：その潜在的な恩恵と危険性)

Apart from the cancer genome, deciphering posttranslational protein glycosylation alterations has been of critical importance as a promising target for discovering novel diagnostic and therapeutic agents. In the present study, the author performed large-scale glycomics research of human whole serum and purified IgG in Ethiopian breast cancer patients and matched controls using a glycoblotting-assisted MALDI-TOF/MS-based quantitatively analysis, aiming at identification of new biomarkers for early detection of breast cancer. With an overall quantitative up-regulation in all the breast cancer stages compared to NC, highest abundance of core-fucosylated, highly branched, and sialylated *N*-glycans with strong distinguishing power (AUC = 0.8-1) was clearly found in the earlier stage (stage I and II) patients. IgG-focused *N*-glycomic profiling further revealed increased fucosylation and agalactosylation of IgG glycoforms that could specifically discriminate stage-II patients from controls. Increased fucosylation and agalactosylation of IgG reduce its affinity with the Fc receptors and thus its effector function, a suggested mechanism allowing the tumor cells to escape from the immune system. By addressing serum and IgG *N*-glycosylation signatures of native black Africans for the first time, this study revealed novel candidate glyco-biomarkers markedly associated with early stage BC.

Using MALDI-TOF/MS- and HPLC-based quantitative approaches, the author extended his research by performing inter-ethnic serum *N*-glycome and sialic acid variations among US origin control, Japanese, Indian, and Ethiopian healthy volunteers in association with the identified glycan biomarkers, aiming to investigate the influence of confounding factors like ethnic variation (which is often overlooked in biomarker research). Informative findings of ethnic-associated variations in the serum *N*-glycans and free sialic acid were found with consistent highest abundance primarily demonstrated in the Ethiopian group compared to the other ethnicities.

Surprisingly, some of the *N*-glycans greatly elevated in the Ethiopian subjects have been identified as sensitive serum biomarkers of various cancers, implicating the critical impact of ethnic differences in human serum *N*-glycome variation, the ignorance of which may provide unclear and imprecise conclusion during diagnosis by using glycan-related disease biomarkers.