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Abstract of Doctoral Dissertation

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Title of Doctoral Dissertation

Study on Serum and Tissue Sulpho-N-glycomic Signatures in Early Detection of Breast Cancer

(乳がんの早期発見における血清および組織のスルホ-N-グリコミクス特性に関する研究)

Breast cancer (BC) is a major global health concern and the leading cause of cancer-related mortality among women. Early detection is vital to improving prognosis, yet current diagnostic methods lack sufficient sensitivity and specificity, particularly for identifying disease at early stages. Recent research has identified glycosylation—a post-translational modification of proteins and lipids—as a critical biomolecular signature of cancer. Among these, the sulfation of N-glycans represents a rare but functionally important modification associated with diseases. However, their detection has historically been limited due to their low abundance and susceptibility to ion suppression in conventional mass spectrometry.

To address these challenges, this study employed an advanced glycoblotting-based sulphoglycomics workflow, integrating high-throughput glycan enrichment, weak anion exchange (WAX) separation, and MALDI-TOF mass spectrometry, to investigate acidic N-glycan expression in both serum and breast cancer tissue samples collected from Ethiopian patients. A total of 96 serum samples (76 BC patients and 20 age-matched healthy controls) and tissue samples (35 tumor and 17 matched adjacent normal tissues) were analyzed. Internal standards were used for quantitative normalization, and multiple statistical tools, including t-tests, PLS-DA, and VIP score analysis, were applied for biomarker discovery.

The analytical method was initially validated using healthy serum, pooled breast cancer (BC) serum, and purified IgG, and further confirmed by MALDI-TOF/TOF MS and acid hydrolysis to ensure structural accuracy and specificity. Upon application to serum samples, a total of 13 distinct sulfated N-glycans were identified. Among these, seven mono-sulfated glycans were significantly upregulated in BC patients and exhibited strong diagnostic potential, with several achieving AUC values ≥ 0.8 in distinguishing early-stage breast cancer from healthy controls. Structural characterization revealed an enrichment of terminal Lewis-type epitopes, which are known to facilitate tumor–immune interactions and metastatic behavior. Additionally, increased levels of fucosylation and sialylation were observed, further underscoring the functional relevance of these glycan alterations in breast cancer progression.

In the tissue dataset, 36 acidic N-glycans were identified, including eight high-confidence tumor-associated biomarkers. Multivariate PLS-DA analysis demonstrated clear glycomic separation between tumor and adjacent normal tissues. Importantly, the tumor glycome was enriched in early-stage biosynthetic glycan structures, suggesting a shift toward immature or dysregulated glycosylation pathways

during tumor development. Comparison of tissue and serum profiles revealed partial overlap (9 shared glycans), with the majority of biomarkers being tissue-specific, indicating that serum and tissue glycomes reflect distinct yet complementary aspects of disease biology.

By preserving labile sialic acid and sulfate moieties, this platform enabled accurate characterization of native glycan structures, providing new insights into their diagnostic and functional significance in breast cancer. To our knowledge, this is the first study to perform integrated profiling of serum and tissue acidic N-glycans in breast cancer patients using a sulphoglycomics approach. The findings from this study reveal novel serum-derived non-invasive biomarkers and tissue-specific glycan signatures associated with breast cancer. Together, they offer promising tools for early detection and provide a molecular basis for future therapeutic targeting. These results underscore the critical importance of incorporating tissue-level glycomic profiling into cancer biomarker discovery pipelines, particularly for diseases with complex and heterogeneous glycosylation patterns such as breast cancer.