A Combined Shotgun and Targeted Mass Spectrometry Strategy for Breast Cancer Biomarker Discovery

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It is of highest importance to find proteins responsible for breast cancer dissemination, for use as biomarkers or treatment targets. We established and performed a combined nontargeted LC-MS/MS and a targeted LC-SRM workflow for discovery and validation of protein biomarkers. Eighty breast tumors, stratified for estrogen receptor status and development of distant recurrence (DR ś), were collected. After enrichment of N-glycosylated peptides, label-free LC-MS/MS was performed on each individual tumor in triplicate. In total, 1515 glycopeptides from 778 proteins were identified and used to create a map of the breast cancer N-glycosylated proteome. Based on this specific proteome map, we constructed a 92-plex targeted label-free LC-SRM panel. These proteins were quantified across samples by LC-SRM, resulting in 10 proteins consistently differentially regulated between DR+/DR- tumors. Five proteins were further validated in a separate cohort as prognostic biomarkers at the gene expression level. We also compared the LC-SRM results to clinically reported HER2 status, demonstrating its clinical accuracy. In conclusion, we demonstrate a combined mass spectrometry strategy, at large scale on clinical samples, leading to the identification and validation of five proteins as potential biomarkers for breast cancer recurrence. All MS data are available via ProteomeXchange and PASSEL with identifiers PXD001685 and PASS00643.

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