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Development of novel blood-based glycopeptide biomarkers for the diagnosis of cholangiocarcinoma

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Background & Objectives: Cholangiocarcinoma (CCA) is a highly aggressive malignancy arising from the bile duct epithelium. Despite advancements in diagnostic techniques, the diagnosis of cholangiocarcinoma (CCA) remains challenging. Currently, CA19-9 is the best available blood-based marker for detection of CCA, which has a sensitivity of 50-60% and a specificity of 80%. Moreover, individuals who are Lewis-antigen-negative (∼20% in some populations) have undetectable CA 19–9 levels resulting in false negative diagnoses. Therefore, there is a critical need for developing novel blood-based diagnostic approach for improving the sensitivity of diagnosis of CCA to improve clinical outcomes. Glycosylation, one of the most prevalent post-translational modifications, plays a crucial role in regulating biological functions such as cell-cell communication, protein folding and receptor signaling and is frequently dysregulated in cancer. Cell surface proteins, including glycoproteins, are overexpressed in CCA are likely to be shed into the blood and we investigated development of mass spectrometry-based methods to measure changes in glycosylation in patients with CCA.

Methods: Mass spectrometry data were acquired in parallel reaction monitoring mode using Orbitrap Eclipse Tribrid mass spectrometers. In addition, we tested the use of heavy glycopeptides for absolute quantitation of each glycopeptide. Mass spectrometry data were analyzed using Skyline to estimate glycopeptide abundance.

Results: First, we performed tandem mass tag-based quantitative proteomics and glycoproteomics of tumor tissues and serum collected from CCA patients using high-resolution mass spectrometry. From these experiments, a number of glycopeptides were found to be increased in abundance in CCA patients. We subsequently developed a targeted mass spectrometry–based assay to monitor four candidate glycopeptides derived from polymeric immunoglobulin receptor and aminopeptidase N to validate their performance in a large patient cohort from 269 patients with CCA and 100 healthy individuals.

Conclusion: We anticipate that this finding will lay the foundation for novel diagnostics that could benefit patients with this aggressive malignancy.