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Tissue proteome analysis for profiling proteins associated with lymph node metastasis in gallbladder cancer

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Abstract

Lymph node (LN) metastasis is the earliest sign of metastatic spread and an established predictor of poor outcome in gallbladder cancer (GBC). Patients with LN positive GBC have a significantly worse survival (median survival- 7 months) than patients with LN negative disease (median survival- ~ 23 months) in spite of standard treatment which includes extended surgery followed by chemotherapy, radiotherapy and targeted therapy. This study aims at understanding the underlying molecular processes associated with LN metastasis in GBC. Here, we used iTRAQ-based quantitative proteomic analysis using tissue cohort comprising of primary tumor of LN negative GBC ($n=3$), LN positive GBC ($n=4$) and non-tumor controls (Gallstone disease, $n=4$), to identify proteins associated with LN metastasis. A total of 58 differentially expressed proteins (DEPs) were found to be specifically associated with LN positive GBC based on the criteria of p value ≤ 0.05 , fold change ≥ 2 and unique peptides ≥ 2 . These include the cytoskeleton and associated proteins such as keratin, type II cytoskeletal 7 (KRT7), keratin type I cytoskeletal 19 (KRT19), vimentin (VIM), sorcin (SRI) and nuclear proteins such as nucleophosmin Isoform 1 (NPM1), heterogeneous nuclear ribonucleoproteins A2/B1 isoform X1 (HNRNPA2B1). Some of them are reported to be involved in promoting cell invasion and metastasis. Bioinformatic analysis of the deregulated proteins in LN positive GBC using STRING database identified 'neutrophil degranulation' and 'HIF1 activation' to be among the top deregulated pathways. Western blot and IHC analysis showed a significant overexpression of KRT7 and SRI in LN positive GBC in comparison to LN negative GBC. KRT7, SRI and other proteins may be further explored for their diagnostics and therapeutic applications in LN positive GBC.

Keywords Gallbladder carcinoma, Lymph node metastasis, Tissue proteomics, iTRAQ

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