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## SPECIALTY SECTION

This article was submitted to  
Molecular and Cellular Oncology,  
a section of the journal  
Frontiers in Oncology

RECEIVED 17 September 2022

ACCEPTED 13 December 2022

PUBLISHED 06 January 2023

## CITATION

Akhtar J, Jain V, Kansal R, Priya R,  
Sakhuja P, Goyal S, Agarwal AK,  
Ghose V, Polisetty RV, Sirdeshmukh R,  
Kar S and Gautam P (2023)

Quantitative tissue proteome  
profile reveals neutrophil  
degranulation and remodeling of  
extracellular matrix proteins in early  
stage gallbladder cancer.  
*Front. Oncol.* 12:1046974.  
doi: 10.3389/fonc.2022.1046974

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# Quantitative tissue proteome profile reveals neutrophil degranulation and remodeling of extracellular matrix proteins in early stage gallbladder cancer

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Gallbladder cancer (GBC) is an aggressive malignancy of the gastrointestinal tract with a poor prognosis. It is important to understand the molecular processes associated with the pathogenesis of early stage GBC and identify proteins useful for diagnostic and therapeutic strategies. Here, we have carried out an iTRAQ-based quantitative proteomic analysis of tumor tissues from early stage GBC cases (stage I, n=7 and stage II, n=5) and non-tumor controls (n=6) from gallstone disease (GSD). We identified 357 differentially expressed proteins (DEPs) based on  $\geq 2$  unique peptides and  $\geq 2$  fold change with p value  $< 0.05$ . Pathway analysis using the STRING database showed, 'neutrophil degranulation' to be the major upregulated pathway that includes proteins such as MPO, PRTN3, S100A8, MMP9, DEFA1, AZU, and 'ECM organization' to be the major downregulated pathway that includes proteins such as COL14A1, COL1A2, COL6A1, COL6A2, COL6A3, BGN, DCN. Western blot and/or IHC analysis confirmed the elevated expression of MPO, PRTN3 and S100A8 in early stage of the disease. Based on the above results, we hypothesize that there is an increased neutrophil infiltration in tumor tissue and neutrophil degranulation leading to degradation of extracellular matrix (ECM) proteins promoting cancer cell invasion in the early stage GBC. Some of the proteins (MPO, MMP9, DEFA1) associated with 'neutrophil degranulation' showed the presence of 'signal sequence' suggesting their potential as circulatory markers for early detection of GBC. Overall, the study presents a protein dataset associated with early stage GBC.

## KEYWORDS

gallbladder cancer, early stage, neutrophil degranulation, tissue proteomics, iTRAQ