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Proteomic profiling of cell line-derived extracellular vesicles to identify candidate circulatory markers for detection of gallbladder cancer

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Gallbladder cancer (GBC) is the sixth most common gastrointestinal tract cancer with a very low overall survival and poor prognosis. Profiling of cancer-derived extracellular vesicles (EVs) is an emerging strategy for identification of candidate biomarkers for the detection and prognosis of the disease. The aim of the study was to analyse the protein content from GBC cell line- derived EVs with emphasis on proteins which could be used as candidate biomarkers for the detection of GBC. NOZ and OCU-1 cell lines were cultured and EVs were isolated from conditioned media. LC-MS/MS analysis of total EV proteins led to the identification of a total of 268 proteins in both the cell lines. Of these, 110 proteins were identified with ≥ 2 unique peptides with ≥ 2 PSMs in at least two experimental and technical replicate runs. STRING (Search Tool for the Retrieval of Interacting Genes/Proteins) database was used to perform bioinformatics analysis of 110 proteins which showed 'cell adhesion molecule binding', 'integrin binding', 'cadherin binding' among the top molecular functions and 'focal adhesion' to be among the top pathways associated with the EV proteins. A total of 42 proteins including haptoglobin (HP), pyruvate kinase (PKM), annexin A2 (ANXA2), thrombospondin 1 (THBS1), were reported to be differentially abundant in GBC tissue. Of these, 16 proteins were reported to be differentially abundant in plasma and plasma-derived EVs. We infer these proteins to be highly important to be considered as potential circulatory biomarkers for the detection of GBC. To check the validity of this hypothesis, one of the proteins, haptoglobin (HP) as a representative case, was analysed in plasma by quantitative Enzyme-linked immunosorbent assay (ELISA) and we observed its increased levels in GBC in comparison to controls (p value= 0.0063). Receiver operating characteristic