Proteomic atlas of peritoneal tissue: sampling the “soil” for the metastatic seed in carcinomatosis

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Abstract

Peritoneal carcinomatosis (PC) occurs when the parietal and visceral peritoneum are involved with multifocal metastatic tumors, most commonly arising from abdominopelvic organ sites. The peritoneal cavity and its lining of mesothelial tissue serves as the ‘soil’ onto which metastatic cancer cells attach and grow during PC. In this study, we explored the use of liquid chromatography-tandem mass spectrometry (LC-MS/MS)-based proteomic assays on fresh frozen and formalin-fixed/paraffin-embedded (FFPE) peritoneal tissue samples, analyzed using an ultra-high resolution timsTOF mass spectrometer. The yield of unique proteins in peritoneal lining tissue was lower than that observed from similar studies of visceral organ tissue. Extracellular matrix proteins were present in high abundance, and may be contributory to cancer cell attachment and invasion in PC. We further quantified key signal transduction and metabolic proteins known to contribute to cancer progression, along with defined tumor suppressor and oncoproteins. Our findings represent a baseline catalog of the proteomic composition of the peritoneal lining, as a comparison dataset for future studies focused on alterations in pathologic states such as PC.

1. Introduction

Peritoneal carcinomatosis (PC) is a devastating late manifestation of cancer, in which the peritoneal cavity and its organ contents are infiltrated by metastatic tumors. Although PC can arise from nearly any primary tumor type, the most common sites of primary tumor origin are the digestive and gynecologic organs. However, PC can originate from non-abdominal primary tumors, as well as from the peritoneal lining itself, which is the case in peritoneal mesothelioma or primary peritoneal carcinomatosis[1]. PC is difficult to manage, due to limitations on diagnostic imaging of the peritoneal cavity[2,3], morbidity of peritoneal surgery[4], and limited efficacy of chemotherapy[5,6]. Unfortunately, most patients experience progression to bowel obstruction, malnutrition, cachexia and death despite aggressive therapy regimens.

Although the overall prognosis of PC is poor, advances have been made in utilizing cytoreductive surgery alongside systemic and regional chemotherapy to provide meaningful benefit to selected patients[6–8]. Depending on the primary tumor type and underlying tumor biology, some subgroups of patients can expect durable control of PC and long-term survival outcomes that exceed historical results with palliative chemotherapy alone[9]. Importantly, as the number of molecularly targeted therapies and immunotherapeutic options expands for cancer patients, patients with PC can hope to benefit as well[10–12]. In order to make these advances possible for patients, a thorough understanding of the peritoneal tumor microenvironment (TME) will be vital in the rational selection of therapeutic strategies.

Numerous technical approaches developed to investigate the peritoneal TME and the potential for targeted therapies have attained varying degrees of success. Biochemical and cytologic analyses are routinely utilized for diagnostic and palliative purposes in clinical practice, but have limited specificity and sensitivity for discerning the presence of cancer and provide little insight into molecular characteristics of peritoneal fluid or cells. Biochemical assessment has been augmented by molecular

techniques for biomarker quantification, for example the multiplex bead-based Luminex assay to accurately measure cytokine levels[13]. Additionally, flow cytometry has been employed to improve the sensitivity of cytologic assays[14] or to classify tumors by multiplex immunologic cell profiling[15]. More recently, high-dimensional transcriptomic data have been acquired in patients with carcinomatosis, providing key insights into the pathobiology of malignant peritoneal fluid[16].

While much progress has been made in analyzing the peritoneal fluid from patients with carcinomatosis, we know less about the solid tissue microenvironment in the normal and diseased peritoneal lining. Fluid analysis can be performed at the time of sampling for diagnostic or palliative purposes, but analysis of peritoneal tissue requires invasive procedures such as laparoscopy or surgical resection. This logistical barrier has slowed progress in understanding the peritoneal lining onto which tumor cells attach, implant and grow during PC. To overcome this knowledge gap, we collected non-neoplastic peritoneal lining samples in patients undergoing surgical procedures, utilizing this tissue to perform a proteomic assessment of the baseline state of the 'background' peritoneum. Proteomic methods hold distinct advantages over some of the aforementioned techniques, namely that they are cost effective and unbiased by upfront target specification[17–20]. The objective of this descriptive study was to create a baseline proteomic atlas for reference use in future studies employing this promising technology to characterize changes in the peritoneal microenvironment due either to disease state or therapeutic intervention.

2. Results

2.1 Proteome profiling of peritoneal FFPE and frozen tissue samples

Proteomics data from peritoneal tissues were acquired from 43 FFPE and 5 additional frozen non-neoplastic peritoneal tissue samples using an Evosep LC-timsTOF Pro2 mass spectrometer system. A total of 1,131 unique proteins were identified with high confidence among these samples of benign peritoneal tissues, with a per-sample ~ 500 from fresh frozen tissues, and 140 from FFPE samples (Fig. 1A). This is comparatively lower than the average yield obtained from visceral tissue samples in prior studies[19–21]. For instance, we were able to identify and quantify approximately 800 to 1,350 proteins per sample, and a total of around 3,000 proteins from FFPE needle biopsy samples collected from kidney transplant patients[19,20]. Using the same mass spectrometer equipment and analyzing data with the same software, over 4,000 proteins have been identified in healthy fresh frozen ovarian tissue (Fig. 1B)[22]. Our own laboratory has identified about 3,500 proteins in ovarian FFPE samples (data not shown). To rule out technical factors introduced by tissue processing (*i.e.*, formalin fixation and paraffin embedding) as an explanation for the low number of unique proteins identified compared to visceral tissue, we performed parallel analysis of frozen tissue and FFPE peritoneal tissue samples, finding no difference in the overall protein yield or number of identified peptides between the two techniques (**Supplemental**

Table). This suggests that proteomic results obtained from archival FFPE samples can reliably recapitulate the corresponding proteomic profile of freshly frozen tissue.

The 20 most frequently identified proteins in peritoneal tissue are listed in Table 1, the majority (13) of which are broadly defined as structural proteins, including desmoplakin, collagen, desmoglein-1, junction plakoglobin, annexin A2, actin, myosin-1, vimentin and titin. Among all 1,131 detected proteins, 1,123 were mapped by the Panther protein classification[23,24] and divided into 25 different categories according to protein class, and another 8 unmapped proteins were manually grouped into an 'unclassified' category as shown in Fig. 1C. The most frequently identified category (19%) includes diverse metabolite interconversion enzymes, consistent with their physiologically critical roles in maintaining cellular homeostasis and regulating various signal transduction pathways[25]. Although less frequently represented, a number of categories with proven roles in cancer development merit special attention, including defense/immunity proteins (4%)[26], extracellular matrix proteins (2.7%)[27], cell adhesion proteins (1.4%)[28] and cell junction proteins (0.3%)[29,30].

2.2 Tissue microenvironment of peritoneal carcinomatosis

Most commonly, peritoneal carcinomatosis occurs due to metastasis from visceral organs. In these cases, the peritoneal tissue is not the source of malignant cells, but rather the 'soil' onto which they are understood to implant and grow. We therefore scrutinized our data for key determinants involved in creating a permissive microenvironment for tumor progression. The mechanisms of peritoneal metastasis have been divided into five major steps[31]: invasion[32–39], intravasation[40–46], circulation[47–51], extravasation[45,46,52–56] and colonization[57–63], as shown in Table 2. We found several peritoneal proteins relevant to each of these steps, supporting the peritoneum-based "seed and soil" concept of peritoneal dissemination[64]. The identified frequency of each protein from 48 samples were as follows: fibrinogen (including chain α, β and γ, n = 49), plakoglobin (n = 43), Serpin (SERPINA1; n = 11), RAC1 (n = 4), CD44 (n = 3), Rap1 (n = 3), cathepsin B (n = 3), Fascin (n = 2), Tenascin (n = 2), MCAM (n = 1), cadherin-1 (n = 1), integrin (ITGA5; n = 1) and cortactin (n = 1).

Extracellular matrix proteins are major structural components of the TME, and we identified seven such proteins in peritoneal tissue samples with proven contributions to metastatic tumor establishment and progression (Table 3): COL1A1 (n = 31 cases), HSPG2 (n = 12), FN1 (n = 11), LGALS3 (n = 9), POSTN (n = 8), LAMA4 (n = 4) and TNC (n = 2). Collagen 1A1, as one of the top 20 most abundant proteins (Table 1), is especially notable as an important barrier to immune infiltration and potential contributor to immune evasion by peritoneal cancer[65]. Laminin[66], tenascin[67], periostin[68], fibronectin[69], heparan sulfate proteoglycan[70] and galectin-3[71] are further examples of quantitatively identified proteins that are known to contribute to cellular invasion, angiogenesis, epithelial-to-mesenchymal transition (EMT) and in some cases of immunosuppression and treatment resistance[72].

We next assessed whether proteomic output could be used to infer cell classification in the peritoneal TME, a concept that has been suggested previously[73]. Normal peritoneal tissue contains mesothelial

cells[74], fibroblasts, adipocytes, small blood vessels, lymphatics and immune cells[75,76] as listed in Table 4. Using the publicly accessible tissue/cell type-specific marker database[77,78], it is possible to identify cell types by comparing the known marker proteins from mass spectrometry results with the reference database[78,79]. Although true lineage-specifity from cell markers is uncommon, a comparison among samples of bulk data of cell type-enriched proteins identified here, such as calretinin, CD44/E-cadherin, LUM, COL1A2, CD36, FASN, CD14, MPO, S100A8 and S100A9, could allow for inferences regarding the relative proportions of key cell types in peritoneal samples. While this result demonstrates the potential utility of proteomic assays to supplement more resource-intensive modalities such as immunohistochemistry, flow cytometry, or single cell RNA-seq, it is recognized that spatial or singe-cell techniques are needed for validation of inferences derived from bulk data such as proteomics.

In particular, granulocytic markers including myeloperoxidase (MPO), S100A8 and S100A9 expression were found in high frequency in peritoneal tissue. The contribinution of granulocytes to peritoneal carcinomatosis has not been well characterized, and is an intriguing lead for follow-up studies to understand the potential contribution of these cell types to PC and its clinical sequelae[80]. Moreover, by simultaneously quantifying lineage-specific cell markers and their interacting proteins in the peritoneal tissue, important insights into the mechanisms governing the peritoneal immune microenvironment can be gleaned. For instance, surface proteins like galectin, HSP90, and S100A8/A9 within peritoneal tissue, are known to interact with glycans[81], Toll-like receptors[82], and RAGE receptors[83] from immune cells, respectively. A detailed assessment of these relationships could create opportunities to design rational immunomodulatory treatment strategies for PC.

2.3 Pathways potentially involving peritoneal carcinomatosis

To better understand the functional implications of the proteins in the peritoneal tissue context, KEGG[84] and REACTOME[85] pathway enrichment analysis was performed in Database for Annotation, Visualization, and Integrated Discovery (DAVID)[86]. Most identified proteins were mapped to metabolism, immune system, signal transduction, hemostasis, cellular response to stimuli in general, and neutrophil degranulation, cell cycle, and ECM-receptor interaction in particular (Fig. 3). Among these top pathways, several are relevant to ECM protein-involved processes such as ECM organization and focal adhesion. ECM-related physiological activities facilitate cancer metastasis and indeed, proteoglycans relevant to cancer progression were enriched in the top pathway list. Surprisingly, neutrophil degranulation was among the top-ranked enriched pathways in peritoneal tissue, providing validation to the cell classification results detailed above, and again raising questions regarding the potential contribution of granulocyte biology to peritoneal carcinomatosis[87].

2.4 Proteomic assessment of contributing factors to primary peritoneal carcinogenesis

Finally, we assessed the potential utility of proteomics in mechanistic studies of rare tumors intrinsic to the peritoneal tissue, such as peritoneal mesothelioma and primary peritoneal carcinomatosis. We focused our analysis on recognized oncoproteins, tumor suppressor proteins, and cancer biomarkers, along with cytokines and growth factors, which have a direct effect on promoting tumor growth and progression[88], secreted proteins suspected to facilitate tumor development[89] and membrane proteins of high relevance to carcinogenesis[90]. It is important to emphasize that this study measured the presence of normal proteins in normal tissue. We hypothesized that by demonstrating the utility of proteomic methods to detect these factors in the physiologic state, we could then utilize them in subsequent studies to detect alterations in these proteins in carcinomatosis, such as mutations or changes in expression level. Among the identified proteins, the numbers of potential intrinsic carcinomatosis factors are shown in Fig. 2 and **Supplemental Table**.

Specifically, 20 proto-oncoproteins identified in the peritoneal proteome have been previously linked to various cancers or known oncogenic pathways. Four such proteins—isocitrate dehydrogenase (IDH1; found in n = 2 cases)[91] collagen alpha-1(I) chain (COL1A1; n = 31)[92], Ras-related protein R-Ras (RRAS; n = 3)[93] and NAD(P)H dehydrogenase [quinone] 1 (NQO1; n = 2)[94] – warrant special attention due to direct evidence of their role in promoting ovarian cancer, which is widely hypothesized to share a common tissue origin together with fallopian tube and primary peritoneal cancer[95].

In addition, tumor suppressor proteins typically act as inhibitors of oncogenesis. Loss of function in tumor suppressor proteins due to mutations frequently contributes to the progression of cancer. 19 known tumor suppressor proteins were identified in the peritoneal proteome. Among these, cadherin-1 (CDH1)[96] and histone H1.3[97] may play an especially important role in primary peritoneal carcinomatosis, as is the case in ovarian carcinogenesis. Additionally, 157 potential cancer biomarkers were identified in the peritoneal tissue, based on prior studies evaluating their utility in screening, diagnosis or monitoring of many cancers, such as PRKDC (DNA-dependent protein kinase catalytic subunit) for breast cancer[98,99]. Again emphasizing ovarian cancer due to its relationship with primary and secondary peritoneal carcinomatosis, we identified COL1A1, collagen alpha-2(I) chain (COL1A2), and decorin (DCN), which have been studied as biomarkers in ovarian cancer and may play a similar role in primary peritoneal neoplasms[92,100].

Membrane proteins and secreted extracellular proteins were closely examined, given their involvement in cell-cell communication, signal transduction and cell-matrix interactions[101]. These interactions contribute to tumor cell attachment and invasion in metastatic sites, and include growth factors[102] and cytokines[103], along with their cognate receptors. We found 176 such proteins in peritoneal tissue samples, including the cell surface glycoprotein MUC18. Notably, while 205 secreted proteins were identified, only very small number of cytokines (n = 5) or growth factors (n = 6) were found, suggesting that they are either present in low frequency in peritoneal tissue, lost during tissue processing, or better assessed by methods other than proteomic assays.

3. Discussion

Cancer metastasis, responsible for the majority of cancer death[104], primarily occurs through the bloodstream, lymphatic system, and the serosal cavities (pleura or peritoneum)[1]. To better understand the latter route of metastatic spread, we undertook a descriptive study to define the potential of proteomic profiling to assess the peritoneal soil to which metastatic cells are proposed to attach, invade and form tumors[64,105–107]. This information could provide important insights into the mechanisms of peritoneal metastasis and inform the development of targeted therapeutics, assays for treatment monitoring, and strategies for preventing the downstream complications of carcinomatosis such as ascites, fibrosis or bowel obstruction.

The potential methodologic options for peritoneal analysis are numerous. Peritoneal fluid analysis is a prime example, and has been extensively studied by our group and others for example in defining the secretome of physiologic and pathologic peritoneal and pleural fluid[13]. Cytologic analysis, including flow cytometry and other molecular assays, have been performed to define the cellular constituents in the peritoneal and pleural fluid, which have contributed to our understanding of the presence and functional status of the immune cellular microenvironment/subsets of immune cells[13,108,109]. Transcriptomic methods in peritoneal fluid have also been reported, both as a means to diagnose metastatic cancer and to quantify cellular constituents of the peritoneal fluid and as a technique to yield options for targeted or immune therapy[16,110]. These methods have focused primarily on peritoneal fluid in the setting of pathology, whereas relatively little attention has been paid to the status of the background peritoneal lining, or the normal physiologic state of the peritoneal cavity, which represents a baseline point of departure for pathways of metastatic spread.

The development of tissue proteomic methodology holds a number of key advantages in addressing this knowledge gap. First, the techniques can be applied to archival tissue without need for special processing at the time of tissue acquisition[111,112]. Second, unlike cytokine or flow cytometry methods, the proteomic methods described here are not biased by target probe selection[18,111]. Third, the techniques are highly cost effective and repeatable, allowing for iterative sampling under different conditions at the time of diagnostic or therapeutic procedures[18,111]. For these reasons, we sought to define a baseline proteomic catalog of the peritoneal tissue for subsequent use in investigating disease states and therapeutic interventions. As shown here, proteomic methods hold great promise in understanding how the protein composition of peritoneal tissue may shift in cancer patients, impacting pathways critical to peritoneal cancer metastasis or ripe for exploitation in therapy design.

Not surprisingly, we found an abundance of stromal elements in our tissue biopsies. Collagen, together with other ECM proteins, facilitates cancer cell adhesion, migration and survival[70]. We identified several other potential tumor-promoting pathways that are known to facilitate cancer progression within the peritoneal cavity, through mechanisms such as cellular proliferation, migration, invasion, and tumor microenvironment modulation. The laminin subunit gamma-1 (LAMC1) signaling cascade, via activation

of the integrin β1/FAK pathway, promotes cell adhesion, migration, invasion, and survival while also facilitating preadipocyte differentiation to supply metastatic sites with fatty acids and support extracellular matrix (ECM) reorganization[113]. Similarly, ubiquitin-protein ligase E3 component n-recognin 5 (UBR5) drives tumor growth and metastasis by inducing chemokine and cytokine secretion, fostering immunosuppressive macrophage polarization. UBR5 has also been shown to sustain β-catenin-mediated signaling to enhance adhesion and colonization, as well as cellular proliferation through p53 regulation[114]. Myosin heavy chain 9 (MYH9) further reinforces β-catenin transcription via nuclear interactions, increasing resistance to anoikis and activating the Wnt/β-catenin signaling pathway, which accelerates tumor proliferation, migration, and invasion[115]. Additionally, the Hippo pathway, a key regulator of organ size and tissue homeostasis, is frequently dysregulated in metastasis, where YAP/TAZ activation promotes cell proliferation, epithelial-mesenchymal transition (EMT), cytoskeletal reorganization, and cytokine secretion, further modifying the tumor microenvironment and conferring stemness and chemoresistance[116]. Single-cell analyses of peritoneal metastases have confirmed diverse differentiation trajectories and drug resistance mechanisms, underscoring the adaptability of tumor cells in metastatic progression[117,118]. Collectively, these pathways create a metastatic niche, supporting tumor growth, dissemination and establishing peritoneal carcinomatosis.

Although we focused mainly on pathways relevant to peritoneal metastasis from visceral tumors, it is important to recognize the potential for proteomic assays to illuminate pathways of interest in primary tumors of the peritoneal cavity, such as peritoneal mesothelioma and primary peritoneal cancer. Because these diseases are exceedingly rare, very little is known regarding their pathogenesis and our findings could contribute to the understanding of carcinogenesis by serving as a baseline proteome against which pathologic datasets can be compared. Primary peritoneal cancer and malignant mesothelioma share several tumor-promoting pathways that drive their initiation and progression by disrupting tumor suppressor functions, enhancing proliferative signaling, and promoting invasive behavior[119]. The inactivation of key tumor suppressor genes, such as CDKN2A and NF2, removes critical controls on cell cycle regulation and contact inhibition, leading to unchecked cell division and tumor expansion[120]. Concurrently, activation of the PI3K/mTOR signaling pathway enhances cell survival, proliferation, and resistance to apoptosis, further supporting tumor growth[121]. The overexpression of mesothelin and its interaction with MUC16 (CA-125) facilitate tumor cell adhesion and peritoneal dissemination, increasing cancer cell survival and immune evasion[122]. Aberrant expression of glypicans (GPC1, GPC3) modulates key signaling pathways, including Wnt, Hedgehog, and FGF, promoting angiogenesis, proliferation, and invasion[123]. Additionally, Gremlin-1, a BMP antagonist, fosters an invasive tumor phenotype by promoting epithelial-to-mesenchymal transition (EMT), enhancing tumor cell migration, invasion, and resistance to apoptosis[124]. Collectively, we demonstrate that these molecular alterations are potentially measurable using proteomic techniques and thus represent candidate biomarkers for disease status and treatment response for future studies.

In addition to individual proteins, bioinformatic approaches allow for the definition of key cell types and pathways relevant to peritoneal physiology and pathology. Specifically, fibroblast and neutrophil

populations were identified based on cell-specific markers, which are important potential contributors to cancer progression and immune evasion[125]. Likewise, signaling transduction pathway enrichment analysis suggested the abundance of NOTCH and other signaling pathway elements that can support cell proliferation, self-renewal and survival. While some of these signaling pathways may be well established as contributors to peritoneal carcinomatosis[126–128], proteomics has the potential to identify new lines of investigation, such as the role of granulocyte biology in PC.

The number of unique proteins identified in peritoneal tissue was substantially lower than the published yield from previous studies on visceral organ tissue[129,130]. This was the case both for fresh frozen tissue, as well as FFPE tissue, and was stable across different protein extraction and MS/MS data collection strategies, such as longer retention time or peptide fractionation. Since the cellular constituency of the peritoneal lining should theoretically only include mesenchymal cells from the mesothelial lining and subjacent connective tissue, it is perhaps unsurprising that visceral organs, with their abundant diversity of cell types, would yield a much larger and more complex proteomic dataset. Another possible explanation would be that the presence of quantitatively abundant proteins, such as collagens, may crowd out signals from less prevalent protein constituents, analogous to the abundance of ubiquitous serum proteins hampering proteomic methods in peripheral blood samples[131].

Proteomic methods, while carrying distinct advantages of cost-effectiveness and repeatability, are not without their limitations. Proteomic data analysis is computationally intensive, and requires expert interpretation to prevent false attribution in protein identity[132,133]. Variability in tissue handling in the operating room or pathology laboratory, prior to fixation, is an unmeasurable contributor to experimental error[134,135]. Information about protein functionality, post-translational modifications, and protein-protein interactions may be lost in the sample processing and digestion steps[136]. Finally, spatial information is lost when tissue samples are homogenized for digestion and processing. For these reasons, proteomic studies are best considered as hypothesis-generating exercises that point researchers toward experiments for validating and mechanistically defining their implications.

In summary, we have demonstrated technical feasibility of peritoneal tissue proteomics to assess the peritoneal tumor microenvironment. By defining the baseline proteomic content of the peritoneal cavity, we have laid the foundation for future studies to quantify changes in primary peritoneal tumor development or metastatic progression in peritoneal carcinomatosis. We identified a number of potentially important structural proteins integral to tissue invasion, as well as cell types and pathways that could be exploited for therapeutic advantage. Ongoing studies contrasting the peritoneal tissue proteome in physiologic versus diseased states will generate mechanistic insights and ignite the search for biomarkers of disease status or treatment response in PC.

4. Methods

4.1 Ethics approval

This study was carried out in strict accordance with the principles of the Declaration of Helsinki and was approved by the Institutional Review Board (IRB) of the Allegheny Health Network (AHN) Cancer Institute (protocols: 2021-085-WPH, 2021-255-AHNMR, 2020-258-AGH, and 2022-116-AHNCI-AGH). Patients undergoing surgical procedures were counseled appropriately and informed consent was obtained for tissue biopsy for research use. All patient records and biological samples were de-identified prior to analysis to ensure confidentiality and adherence to ethical standards.

4.2 Peritoneal sample collection and processing

Peritoneal lining tissue samples were collected from patients (n = 43) undergoing surgery either for benign intra-abdominal indications or for treatment of localized tumors without peritoneal carcinomatosis. Tissue samples were subjected to immediate formalin fixation and paraffin embedding after dehydration and xylene clearing. After processing, the tissue samples were subsequently re-embedded into a paraffin block. The formalin-fixed paraffin-embedded (FFPE) blocks were then sectioned to 10 microns and 5 scrolls of tissue sample were collected and available for further analysis. In a subset of cases (n = 5), an aliquot of the tissue was separately frozen at -20°C instead of undergoing FFPE processing.

4.3 Preparation of frozen peritoneal tissue and FFPE samples

Scrolls from each FFPE sample were individually transferred to 1.5 mL conical microcentrifuge tubes with lock caps. Deparaffinization was performed by incubating the FFPE samples in xylene for 5 minutes at room temperature. Xylene was removed after centrifugation at 5,000 x g for 5 minutes and the deparaffinization step was repeated two more times. The resulting tissue pellets were rinsed twice with 100% ethanol and rehydrated using 95%, 70%, and 50% ethanol for 2 minutes each. Samples were subsequently dried in a Labconco CentriVap at 45°C for 10 minutes and then resuspended in an extraction buffer containing 100 mM TEAB pH 7.55 and 4% SDS. Samples were heated at 95°C for 60 minutes, followed by centrifugation, mechanical homogenization using a Bead Beating Grinder Homogenizer, and sonication using a Pulse ultrasonicator. This heating-centrifugation-homogenization cycle was repeated until the lysate became clear. The homogenized lysate was then centrifuged at 15,000 × g for 30 minutes, and the total protein concentration of the supernatant was measured using a NanoDrop One spectrophotometer with a reference setting of one A280 absorbance equal to 1 mg/mL of total protein.

Frozen tissue samples were transferred into 1.5 mL Kimble microcentrifuge tubes and placed on ice. Upon the addition of lysis buffer containing 50 mM Triethylammonium bicarbonate (TEAB) pH 7.55, 4% SDS and 1x Halt protease inhibitor cocktail (Thermo Scientific), tissue samples were homogenized with a disposable Kimble microtube-matching pestle. The samples were incubated at 95°C for 60 min in a digital heat block (Benchmark Scientific), and sonicated 20 times (3 sec on, 6 sec off) using a Fisher Scientific Sonic Dismembrator Model 705 sonicator. The heating and sonication steps were repeated

until no tissue chunks were observed. The tissue homogenates were centrifuged at 15,000 × g for 30 min. Protein concentration of the lysate was determined using Pierce BCA Protein Assay Kit.

For each frozen tissue or FFPE sample, 100 µg of protein was reduced with 10 mM dithiothreitol (DTT) for 1 hour at 56°C and alkylated with 55 mM iodoacetamide (IAA) for 30 minutes in the dark at room temperature. An additional 10 mM DTT was added to the lysate and incubated for 30 minutes at 56°C to stop over-alkylation. Protein samples were further processed using the ProtiFi S-Trap™ mini-MS sample prep kit according to the manufacturer's instructions. On-column digestion was performed using trypsin/LysC at an enzyme/protein ratio of 1:50 overnight at 37°C. Peptides were eluted by 0.2% formic acid (FA) and 80% acetonitrile, dried in a Labconco CentriVap at 45°C, and stored at -80°C until use.

4.4 Liquid chromatography-tandem mass spectrometry (LC-MS/MS) and protein identification

Peptides were resuspended in 20 µL of 0.1% FA, and their concentrations were quantified using a NanoDrop One spectrophotometer, as described above. Subsequently, 0.5 or 1 µg of available peptide digests was manually loaded onto an Evotip disposable trap column. Samples were then analyzed using a timsTOF Pro2 mass spectrometer (Bruker) coupled with a low-pressure nano-flow Evosep One LC system. Peptide separation was achieved using an 8 cm x 150 µm Evosep performance column (EV1109) packed with 1.5 µm C18 particles, with an LC gradient spanning 44 minutes.

The timsTOF Pro2 mass spectrometer was operated in DDA-PASEF (parallel accumulation-serial fragmentation) mode with the default 1.17-second duty cycle method (mass range, 100-1,700 *m/z*; mobility ($1/K_0$) range, 0.6–1.6 V·s/cm^2; accumulation and ramp times, 100 milliseconds; PASEF cycles, 10). The target intensity per individual PASEF precursor was set to 2,500 – 20,000. For data analysis, the acquired MS and MS/MS spectra were searched against a human protein database and common contaminants using MaxQuant v2.6.6.0[137]. The detailed search parameter settings are as follows: 20 *ppm* precursor mass tolerance, 20 *ppm* fragment ion mass tolerance, strict tryptic cleavage, a maximum of 2 missed cleavages, and a static modification of 57.02146 Daltons (carboxyamidomethylation) on cysteine, and a dynamic modification 15.99491 Daltons (oxidation) on methionine. All other parameters were set to default.

4.5 Statistical and bioinformatical analysis

The output file ProteinGroups.txt from MaxQuant v2.6.6.0 was imported into Perseus v2.1.3.0[138] using “Generic matrix upload” where protein intensity values were uploaded as “Main” columns and accession, description, taxonomy and gene name as “Text” string columns. Proteins that are only identified by a modification site, potential contaminants and reverse hits were removed from the data matrix.

The OncoKB[139] cancer gene (as of Nov 26, 2024) list including oncogenes and tumor suppressor genes was created and downloaded for analyzing potential cancer candidate gene in the identified peritoneum proteome. The lists of cancer biomarkers, membrane proteins and secreted proteins, cytokines, and

growth factors were generated from the Human Protein Atlas (HPA)[140] web portal to facilitate the data exploration in the identified proteome from peritoneum.

Declarations

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Author Contributions

The manuscript was written through contributions of all authors.K.X. and P. L.W. designed all experiments. Q. Z., C. S., X. P., Y. F., N. V., R. B., H. P., and E. G. performed the experiments. K.X., P. L.W., N. D., A. H. Z., V. D., D. L. B., A. D., K.X., P. L. W. analyzed data; Q. Z., K. X., P. L. W. wrote the paper. All the authors reviewed the paper and agreed for publication.

Data availability statement

The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Notes

The authors declare no conflicts of interest.

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Tables

Table 1 TOP20 abundant proteins

Peptides	Unique peptides	Intensity	MS/MS count	ID	Protein name	Gene name
183	183	7.65E+08	2970	P15924	Desmoplakin	DSP
110	110	3.05E+08	951	P12111	Collagen alpha-3(VI) chain	COL6A3
29	29	3.19E+08	903	Q02413	Desmoglein-1	DSG1
17	10	8.59E+08	843	P68871	Hemoglobin subunit beta	HBB
32	30	2.5E+08	842	P14923	Junction plakoglobin	JUP
16	12	6.54E+08	649	P69905	Hemoglobin subunit alpha	HBA1
28	28	2.06E+08	621	P07355	Annexin A2	ANXA2
30	2	5.83E+08	548	P62736	Actin, aortic smooth muscle	ACTA2
121	19	2.93E+08	498	P12882	Myosin-1	MYH1
45	38	1.26E+08	478	P08670	Vimentin	VIM
20	20	1.58E+08	455	P04406	Glyceraldehyde-3-phosphate dehydrogenase	GAPDH
303	303	71681000	445	Q8WZ42	Titin	TTN
15	15	5.46E+08	442	P06702	Protein S100-A9	S100A9
31	15	1.27E+08	435	P29508	Serpin B3	SERPINB3
25	25	8.54E+08	400	P02452	Collagen alpha-1(I) chain	COL1A1
73	65	90229000	384	P01024	Complement C3	C3
33	33	81197000	383	P12109	Collagen alpha-1(VI) chain	COL6A1
16	16	1.18E+08	382	P31944	Caspase-14	CASP14
28	1	1.27E+08	369	P63261	Actin, cytoplasmic 2	ACTG1
19	19	1.14E+09	362	P08123	Collagen alpha-2(I) chain	COL1A2

Note: As previously reported[141], protein abundances are estimated from the number of tandem mass spectrometry (MS/MS) spectra associated with each protein. The more MS/MS spectra detected for a protein, the higher its estimated abundance in the sample.

Table 2 Identified proteins involved in the known five key steps of cancer metastasis

Invasion	Intravasation	Circulation	Extravasation	Colonization
Cortactin	UPAR	Fibrinogen	Dock4	CEMIP
MENA	STC1	Osteopontin	Integrin	Prrx1
Fascin	Integrin	CD44	RAC1	ARHGAP15
Cadherin-1	MMP-9	ICAM1	IQGAP1	Endothelin1
Rap1	PDGF	Plakoglobin	Selectin	IL1
MIEN1	TGFB		IL22	Serpin
NOX	TRPM7		MCAM	Tenascin
RhoC	Cathepsin B			
Tks5	Selectin			

Note: The protein list here is incomplete due to the size limit of literature. The proteins colored in red are those identified in this work. Protein names for the abbreviations are as follows: MENA, Protein enabled homolog; Rap1, Ras-related protein 1; MIEN1, Migration and invasion enhancer 1; NOX, NADPH oxidase; RhoC, Rho-related GTP-binding protein; Tks5, SH3 and PX domain-containing protein 2A; UPAR, Urokinase plasminogen activator surface receptor; STC1, Stanniocalcin-1; MMP-9, Matrix metalloproteinase-9; PDGF, Platelet-derived growth factor; TGFB, Transforming growth factor beta-1 proprotein; TRPM7, Transient receptor potential cation channel subfamily M member 7; ICAM1, Intercellular adhesion molecule 1; Dock4, Dedicator of cytokinesis protein 4; RAC1, Ras-related C3 botulinum toxin substrate 1; IQGAP1, Ras GTPase-activating-like protein IQGAP1; MCAM, Cell surface glycoprotein MUC18; CEMIP, Cell migration-inducing and hyaluronan-binding protein; Prrx1, Paired mesoderm homeobox protein 1; ARHGAP15, Rho GTPase-activating protein 15; IL1, Interleukin 1

Table 3 Extracellular matrix proteins: exemplary factors potentially contributing to peritoneal carcinomatosis

Protein name	Gene name	Contribution to carcinomatosis
Collagen	COL1A1	Creates a barrier to prevent immune cells from reaching tumors
Laminin	LAMA4	Promotes tumor invasion and metastasis through activating YAP/TAZ signaling
Tenascin	TNC	Promotes cancer cell migration, proliferation, invasion, angiogenesis, and metastasis; Suppresses immune response
Periostin	POSTN	Promotes cancer cell growth, invasion, EMT and chemoresistance
Heparan sulfate proteoglycan	HSPG2	Plays important roles in cancer initiation and progression
Fibronectin	FN1	Enhances the tumor growth, angiogenesis and metastasis
Galectin-3	LGALS3	Contributes to cancer progression, EMT, immunosuppression, radio-resistance, and chemoresistance

Table 4 Identified markers for possible cell types from peritoneal tissue

Cell type	Markers
mesothelial cells	calretinin, WT1, CD44/E-cadherin
fibroblast	LUM, COL1A2, MMP2
adipocyte	CD36, FASN, LEP
macrophage	CD14, AIF1
B cell	CD20, CD27, CD43
T cell	CD3, CD4, CD8
eosinophil	CD13, CD14, CD15
neutrophil	MPO, CD33, S100A8, S100A9
NK cell	GNLY, CD56, NKG7
dendritic cell	CD1C, CD141

Note: Potential cell types from peritoneal tissues were included in this table. The proteins colored in red are those identified in this work. Note that cell-type-specific markers, such as genes or proteins, are not fixed and can vary based on development stages, their location within an organ or tissue, and the health state. Only partial cell type-specific markers were generated from databases singleCellBase and CellMarker 2.0. The known marker proteins identified in this work are highlighted in red.

Figures

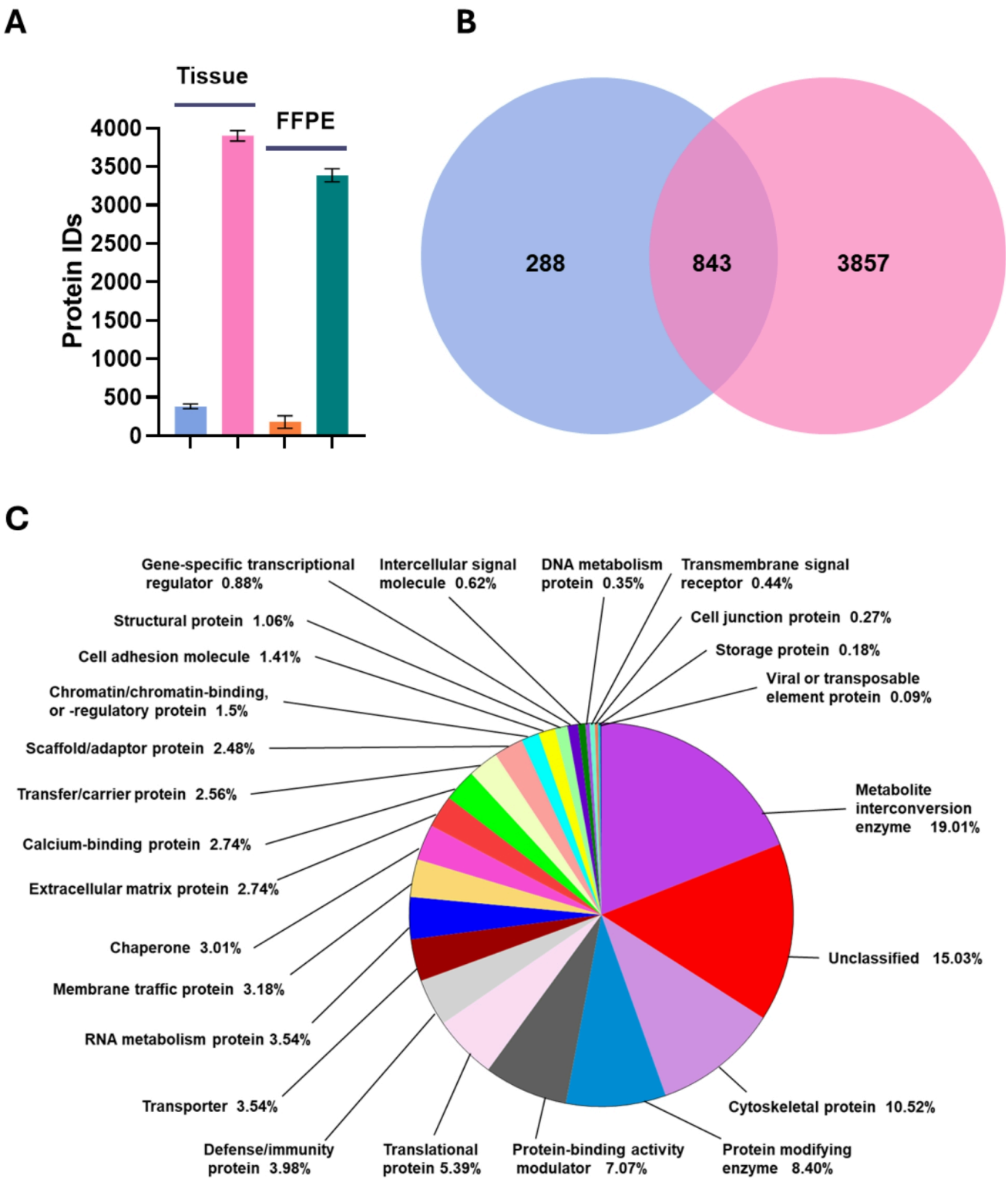

Figure 1

Proteomic characterization of peritoneal tissue. A. Low protein IDs from both fresh frozen and FFPE peritoneal tissues were observed using a high-resolution mass spectrometer. A) The average protein IDs found in fresh frozen peritoneal and ovarian tissues were colored in blue and purple, respectively. The average protein IDs found in FFPE peritoneal and ovarian tissues were colored in orange and green, respectively. The proteomic data for fresh frozen healthy ovarian tissues were obtained from 3

downloaded sample data sets (ProteomeXchange accession code: PXD033741), which were collected using the same timsTOF Pro mass spectrometer and reprocessed here by the same version of MaxQuant as described above. The proteomic data for FFPE ovarian tissues were collected and processed in the same way as all peritoneal samples. **B**) Venn diagram of peritoneal (blue) proteome overlapped with ovarian (purple) data. The total protein number of peritoneal tissue shares 843 proteins with ovarian proteome. **C**) Functional classification of the identified 1131 proteins by Panther classification system. A pie chart reveals 25 different functional classes of proteins as labeled in the figure where the ratio for each category was calculated. The protein classes include metabolite interconversion enzyme (215, the number shown in parenthesis is the identified protein categories), cytoskeleton protein (119), protein modifying enzyme (95), protein-binding activity modulator (80), translational protein (61), defense/immunity protein (45), transporter (40), RNA metabolism protein (40), membrane traffic protein (36), chaperone (34), extracellular matrix protein (31), calcium-binding protein (31), transfer/carrier protein (29), scaffold/adaptor protein (28), chromatin/chromatin-binding , or – regulatory protein (17), cell adhesion molecule (16), structural protein (12), gene-specific transcriptional regulator (10), intercellular signal molecule (7), DNA metabolism protein (4), transmembrane signal receptor (5), cell junction protein (3), storage protein (2), viral or transposable element protein (1) and a category “unclassified” (170 whereas 8 proteins were not able to be mapped by Panther classification system).

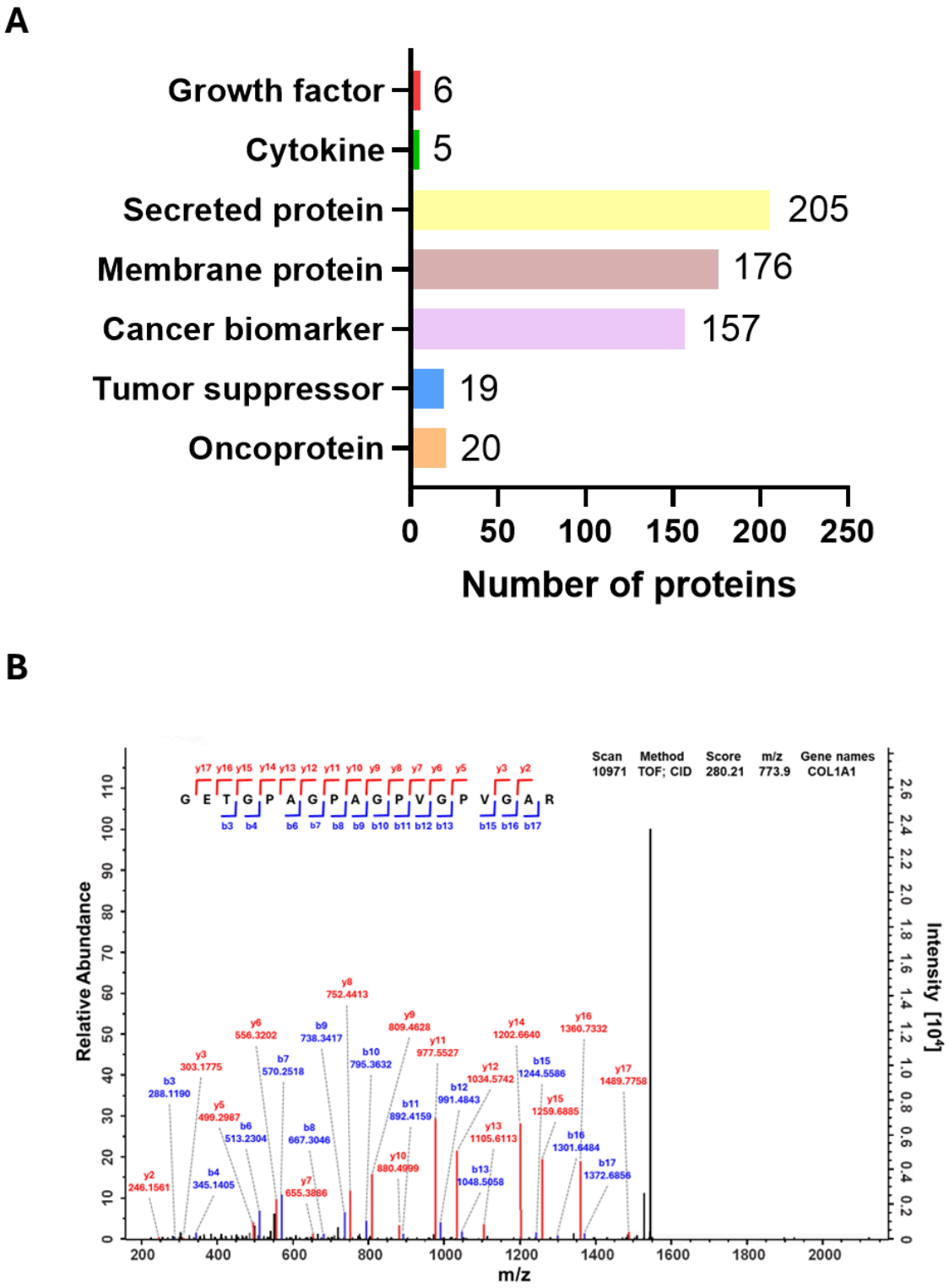

Figure 2

Potential contributing factors to peritoneal carcinomatosis. A) Protein category related to cancer development. The direct causative agents of peritoneal carcinomatosis include 20 oncoproteins, 19 tumor suppressors, and 157 cancer biomarkers. Some member from 5 cytokines and 6 growth factors is likely to promote cancer progression. Additionally, certain protein from 205 secreted and 176 membrane proteins may contribute to peritoneal carcinomatosis. Detailed list of all mentioned proteins is

summarized in Supplemental table. **B)**A representative peptide spectrum corresponding to sequence positions 1,070-1,087 of the potential oncoprotein collagen alpha-1(I) chain (COL1A1). The precursor peptide mass for this doubly charged peptide was measured with a mass error of 3.4564 ppm. The peptide posterior error probability (PEP) was 3.44E-296 (the lower PEP score, the higher confidence in the peptide identification) and the MaxQuant/Andromeda score was 280.21 (higher than 40 indicating confident peptide identification). The CID (collision-induced dissociation) fragmentation pattern shows almost uninterrupted *b*- (colored in blue) and *y*-ion (colored in red) series.

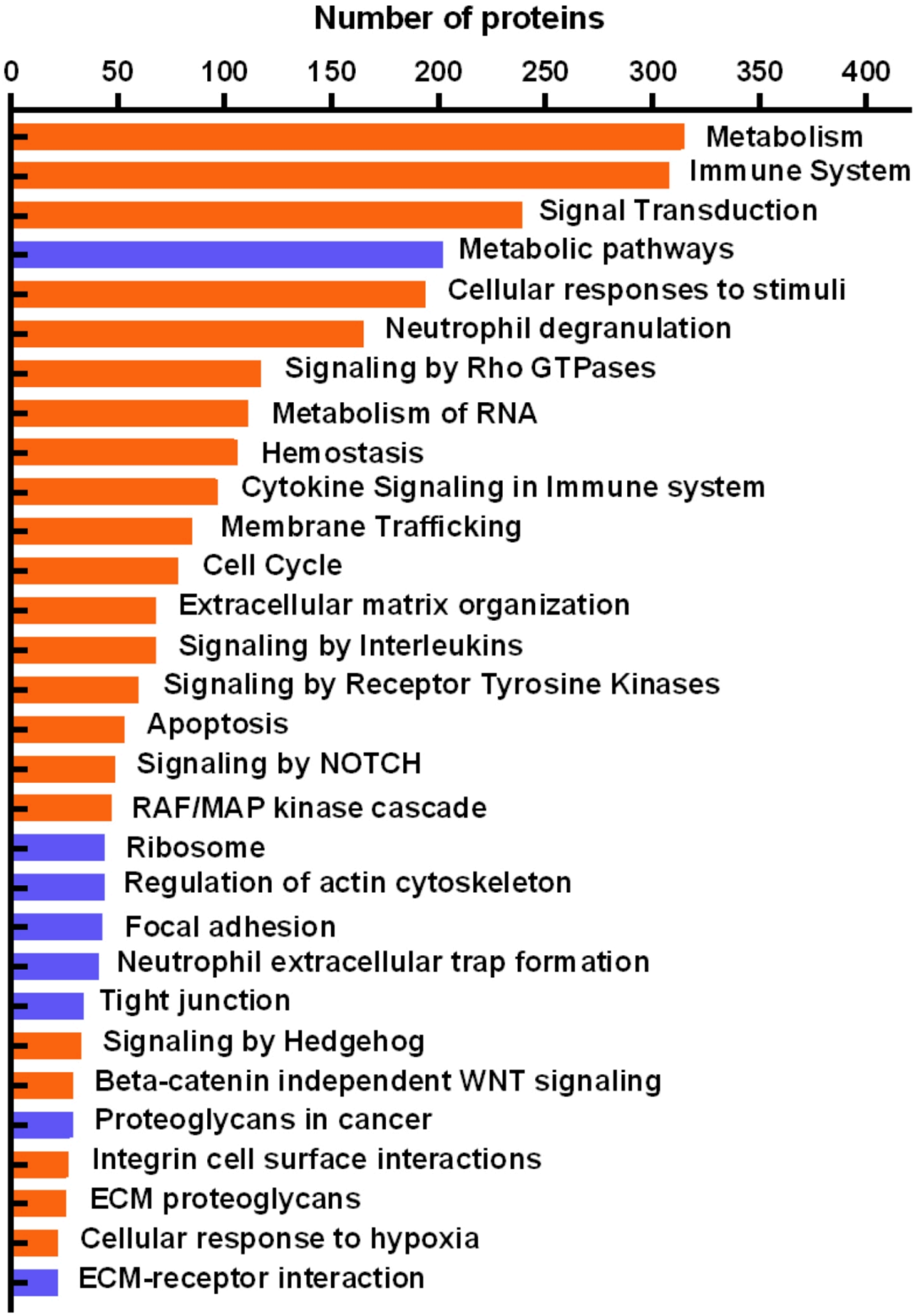

Figure 3

Reactome (orange) and KEGG (blue) pathway enrichment analysis using the DAVID database. The bar plot shows top 30 enriched pathways. The length of bars represents the number of proteins in the pathway. The majority of pathways involve metabolism (metabolic pathways and metabolism of RNA), immune system (Neutrophil degranulation and neutrophil extracellular trap formation), signal transduction (signaling by Rho GTPases, cytokine signaling, signaling by interleukins, signaling by receptor tyrosine kinases, signaling by NOTCH, RAF/MAP kinase cascade, signaling by Hedgehog, and Beta-catenin independent WNT signaling), and cell-cell interaction-related activities (Membrane trafficking, extracellular matrix organization, regulation of actin cytoskeleton, focal adhesion, tight junction, proteoglycans in cancer, integrin cell surface interactions, ECM proteoglycans and ECM-receptor interaction).

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- PeritonealProteomicsSupplemetalTables.xlsx