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Proteome alterations in pancreatic ductal adenocarcinoma

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Abstract

Proteins are the essential functional biomolecules profoundly implicated in all aspects of pancreatic tumorigenesis and its progression. While common genomic factors, such as KRAS, TP53, SMAD4, and CDKN2A have been well recognized in association of pancreatic ductal adenocarcinoma (PDAC), our understanding of functional changes at the proteome level merits further investigation. Malignance associated proteome alterations can be attributed to the convoluted outcomes from genetic, epigenetic and environmental factors in initiating and progressing PDAC, and may reflect on changes in protein expressional level, structure, localization, as well as post-translational modifications (PTMs) status. The study of localized or systemic proteome alterations in PDAC, as well as its precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN) and mucinous pancreatic cystic neoplasm, would provide unique perspectives in elucidating functional molecular events underlying PDAC. While efforts have been made, challenges still exist to comprehensively integrate much of the proteomic discovery to the perspectives gained from genomic studies in the context of biomarker discovery. Novel approaches and data from well-defined longitudinal clinical studies and experimental models are needed to facilitate the study of PDAC and precursor lesions for early detection and intervention.

Keywords

Pancreatic cancer; Proteomics; Mass spectrometry; Post-translational modification; Glycosylation

Introduction

In the United States, pancreatic cancer is the third leading cause of cancer death with a 5-year survival rate of 8%, and is predicted to be the second leading cause of cancer death by the year 2030 [1, 2]. Pancreatic ductal adenocarcinoma (PDAC) represents the vast majority of pancreatic cancers. This lethal disease is characterized by its poor prognosis and rapid

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development of drug resistance; and it is difficult to detect at early stages when treatments are most effective. Genomic studies have revealed common gene mutations in PDAC, including oncogenic activation of *KRAS* and the frequent inactivation of *TP53*, *SMAD4*, and *CDKN2A* tumor suppressors [3-6]. While KRAS mutations arise early in the natural history of PDAC, mutations in *TP53* and *SMAD4* are later events in cancer progression with higher frequency in invasive disease [7]. These genomic mutations can profoundly affect protein characteristics, function and interactions at various levels. However, changes in the genome and the transcriptome do not always correlate with proteome alterations at functional level [8]. Cancer cells and the surrounding microenvironment are directly influenced by their functional proteomes and associated biochemical processes. Malignancy-associated proteome alterations can extend beyond protein expressional changes and polymorphisms, and may include numerous post-translational and/or isoform changes that also impact specific signaling pathways and interaction of protein complexes in disease settings [9-11]. Such proteome alterations in cancer are dynamic and closely interplay with a reprogrammed metabolism that is required for tumor growth.

Currently, the knowledge of extended protein networks associated with PDAC tumorigenesis has lagged behind, in part, due to the enormous complexity, dynamic changes and high heterogeneity associated with the expanded proteome. Several PDAC associated protein families are found to be involved in the development and progression of PDAC. Mucins are a heavily glycosylated protein family that are frequently associated with epithelial mucosa. The abnormal expression, glycosylation, localization of various mucin molecules are correlated with PDAC and its progression [12-16]. Carcinoembryonic antigen-related cell adhesion molecules (CEACAMs) are another family of cell surface proteins that are implicated in facilitating tumor progression. CEACAMs 1, 5, and 6 have been linked with PDAC progression [17, 18]. While these two PDAC associated protein families[12-16] have been extensively studied, the investigation of the broader interactive protein changes and their roles in neoplastic progression, metastasis and chemoresistance of PDAC remain uncertain. There has been a knowledge gap in linking genetic, epigenetic and environmental factors to the broader proteome alterations for better understanding the complementary molecular events that are underlying pancreatic tumorigenesis. The study of localized or systemic proteome alterations in PDAC and its precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN) and intraductal papillary mucinous neoplasm (IPMN) / mucinous cystic neoplasm (MCN), would provide unique perspectives at a functional level to facilitate the earlier detection and intervention of this lethal disease.

MS based proteomics

Proteins are the essential functional biomolecules that participate in a vast array of physiological cellular activities, constituting ~50% of the dry mass of a cell [19] and reaching up to 60-80 mg/ml concentration in human plasma. Post-translational modifications (PTMs) of proteins add an additional layer of complexity to the protein, significantly affecting the folding, localization, activation/deactivation or stability of the proteins. Proteomics can deliver dynamic information such as protein turnover, protein interactions and status of PTMs, and thereby provide a real time picture of cellular function under biological conditions [9]. It represents an emerging paradigm in biomedical research in the

post genomic era, emphasizing functional changes, which are clinically highly relevant [9, 20, 21]. The advances in mass spectrometry and bioinformatics have enabled interrogation of a vast number of proteins and their PTMs in a complex biological sample at a global scale or using a targeted, highly specific fashion. The technologic advances in proteomic analyses permit reproducible, accurate, information-rich data sets that can be analyzed on their own or integrated with other “omics” data [9, 20].

In PDAC, proteomic efforts have investigated a variety of relevant clinical specimens, including pancreatic tissues, serum/plasma, pancreatic juice, cyst fluid, urine and bile fluid, with research goals spanning from mechanistic studies to elucidate complex pathways implicated in pancreatic tumorigenesis, to the discovery of protein biomarkers for early detection or as therapeutic targets [22-29]. These studies have pioneered the technology, generated important data sets and provided useful guidance for future PDAC study. However, challenges still remain in gaining the depth and breadth of a proteomics analysis to interrogate low abundant proteins with robust quantification, and to dissect the enormous and complex interactions and pathways embedded in the informatics rich data sets. In a proteomic analysis, while sample preparation strategies may vary due to individual study design and specimen type, the overall flow of shotgun proteomic analysis of clinical samples remains similar, as illustrated in Figure 1. Studies can be designed to elicit information with a variety of perspectives, such as protein expressional profiles, polymorphisms, status of PTMs, protein changes in subcellular compartments, and interactions between proteins and/or other biomolecules. Metaproteomics, which studies the proteomes of environmental sources, further extends the applications to explore the composition and functional changes in the gut microbiome, as relevant to pancreatic diseases. With improved sensitivity and resolution, investigation of proteome changes within a single cell is also becoming feasible. The information embedded in proteomic data is complex and enormous. The knowledge needed to comprehensively interpret an information-rich proteomic data set may extend beyond the sequence databases and knowledge bases that are currently available, as many disease-associated protein changes are post translational and/or have not been well defined, highlighting the technical challenges in analyzing proteomic data.

Alterations in PDAC proteome

The profound changes in protein expression in PDAC are driven by a variety of complex, multifaceted molecular events implicated in pancreatic tumorigenesis and disease progression. Many of the differential proteins identified in PDAC tissue by proteomics are involved in, not only cancer cells, but also protein-driven interactions between the cancer cells and the tumor stroma to orchestrate PDAC tumor growth, migration, angiogenesis, invasion, metastasis, and immunologic escape (Figure 2). PDAC is associated with enormous stroma, with fibroblasts, vascular endothelial cells, acinar cells and immune cells along with extracellular matrix (ECM). This underscores the importance of the tumor microenvironment in promoting pancreatic cancer progression and drug resistance. In fact, pancreatic cancer stroma may account for 50%-90% of the total volume of a PDAC tumor. The cross-talk between cancer cells and the surrounding microenvironment may induce production and secretion of stimulatory growth factors and cytokines by cancer and stromal cells to recruit vasculature or suppress immune surveillance and promote tumor development

[30, 31]. Such malignancy-induced phenomena are mirrored in the proteome alterations in cancer cells and the surrounding stromal cells in pancreatic cancer tissue, including fibroblasts, vascular endothelial cells, immune cells, and acinar cells. In-depth proteomic analysis of fibroblasts, vascular endothelial cells, and acinar cells isolated from tumor tissue has yet to be reported. Nevertheless, analysis of whole tumor tissues could reveal proteome alterations of these cellular and non-cellular components of the tumor microenvironment. For acinar cells, which are unique to pancreas, a number of exocrine pancreas digestive enzymes, including trypsin subtypes, lipase, carboxypeptidase, elastase, phospholipase, and amylase, are down-regulated in pancreatic cancer tissue, reflecting the possible replacement or destruction of acinar cell mass due to cancer [25, 32-34]. Activation of stromal fibroblasts into cancer-associated fibroblasts - a myofibroblast phenotype that promotes invasion of cancer cells, is evidenced by their functional changes driven by an altered proteome [35, 36]. Differential expression of proteins from vascular endothelial cells and immune cells are also observed, including thymocyte differentiation antigen (THY1 or CD90) - a biomarker for molecular imaging of PDAC [37], and galectins which are a family of proteins profoundly implicated in immune response and pancreatic cancer survival [33, 38-45]. The expression of Galectin-1 was inversely correlated with the survival of pancreatic cancer, suggesting that it could be a prognostic marker of PDAC [40, 45].

Proteins involved in wounding response and inflammatory pathways, such as apolipoproteins, SERPIN proteins, 14-3-3 proteins, S100A proteins, serum amyloid P-component, complements, gelsolin, lysozymes, and alpha-1-acid glycoprotein 1, to name a few, are largely over-expressed in PDAC tissue [25, 32-34]. As an integrated feature of PDAC, proteome alterations in extracellular matrix (ECM) are also involved in facilitating cancer growth by remodeling the ECM to promote invasion and angiogenesis. Many proteins involved in the ECM structure and organization are upregulated in pancreatic cancer tissue, including annexins, collagens, decorin, dermatopontin, EMILINs, fibrillins, fibrinogens, fibronectin, lumican, vitronectin, laminin, myosins, periostin, transgelins, transforming growth factor-beta-induced protein, versican, argins, integrins, cathepsins, and utrophin [25, 32-34], consistent with the persistent activation of pancreatic stellate cells that mediate stromal fibrosis through secretion of ECM proteins [46]. These proteome alterations in PDAC tissue are not only concurrent with the functional changes in PDAC, but strongly correlate with histological observations in pancreatic adenocarcinoma. The knowledge gained could be further assessed to inform the biomarker discovery and therapeutic target development. In addition to THY1 and galectins, several other proteins have been studied as potential PDAC biomarkers. Plectin-1 has been investigated as a molecular imaging marker for detection of primary and metastatic pancreatic cancer [47, 48]. Prolargin and osteoglycin were shown to be associated pancreatic cancer survival, and potential prognostic markers [40]. Gelsolin and TIMP1 were tested in plasma as a composite biomarker in separating the early stage PDAC patients from healthy controls and patients with chronic pancreatitis [49].

The functional alterations in PDAC tumor microenvironment create intense physical, oxidative and nutrient-poor stress for the cancer cells. In response, the PDAC tumors utilize various metabolic reprogramming mechanisms for survival, adaptation, and proliferation. This includes upregulation of proteins that increase glycolysis and biosynthesis, such as glucose transporter GLUT1 and other glycolytic enzymes [50]. One of the biosynthesis

pathways, pentose phosphate pathway (PPP) can be upregulated in PDAC tumors to provide sustain increased need of building blocks for ribose synthesis [10, 50]. The uptake of glucose and glutamine by cancer cells may fuel an increased glycan biosynthesis through hexosamine biosynthetic pathway (HBP), leading to the overall elevated level of glycosylation on many proteins in PDAC tissue [51]. PDAC cells are frequently addicted to glutamate for maintaining re-dox balance. Interfering the glutamine pathway of cancer cells might result in reducing cell proliferation and sensitizing chemo-resistant PDAC cells [52]. In addition, PDAC cells could utilize autophagy and micropinocytosis to overcome nutrient deprivation [53, 54]. All of these metabolic and functional changes in cancer cells and tumor environment dynamically interplay with and correspond to the proteome alterations in PDAC as the disease progresses.

PDAC-associated proteome alterations can extend beyond pancreatic tumor tissue. Analysis of relevant bodily fluids, such as blood and pancreatic juice or cyst fluids, reveals proteomic alterations that may represent a systemic or localized changes dependent, in part, on their proximity to the cancer site. The proteomic composition of these bodily fluids are dramatically different in association with their physiologic function. For example, plasma/serum represents the proteome of the circulating system, which includes many functional blood proteins and proteins shed from tissues, while pancreatic juice contains many secreted enzymes, and cyst fluid may include mucins and other tissue-derived proteins. The unique proteome differences originating from the physiological nature of these bodily fluids may determine a unique perspective in developing concentration-based protein biomarkers for bodily fluid detection, i.e. a novel and specific biomarker for a certain bodily fluid. More detailed discussion on the proteomic analysis of bodily fluid could be found in the literature [26].

Aberrant glycosylation in PDAC

Protein glycosylation can broaden the complexity and functionality of proteins and glycosylation changes have been implicated in pancreatic tumorigenesis. The glycan component of a mucin can make up more than 50% of its molecular weight and plays an important role in modulating the functionality of the protein in tumorigenesis, as well as cell-cell interaction within the tumor microenvironment. Among the most frequently occurring PTMs, aberrant glycosylation has been recognized as a hallmark associated with PDAC. In fact, CA 19-9, the current clinical biomarker for PDAC monitoring, is a glycosylation test that detects abnormal changes associated with sialylated Lewis antigen of mucins and other protein carriers (MUC1, MUC5AC and MUC16 are major carriers of CA 19-9) [12, 55-57]. Aberrant glycosylation changes can involve the structural modifications of glycan moieties, as well as the occupancy changes on protein glycosylation sites [58]. Altered glycoforms of MUC1, MUC4 and MUC5AC are observed early in pancreatic cancer progression (PanINs) to late stage metastatic disease [15], including the elevation of fucosylated core structures, fucose and Lewis antigen in the blood of PDAC patients [56].

Glycomic studies have also revealed a number of glycan structure changes associated with PDAC, including increased protein fucosylation and sialylation detected in serum [59], and several hyper-fucosylated glycoproteins, including triacylglycerol lipase and pancreatic

α-amylase, observed in cyst fluids from IPMN and MCN [60]. Recent reports also observed the occupancy changes on N-glycosylation of many PDAC associated proteins involved in TGF-β, TNF and NF-kappa-B pathways, including MUC5AC, CEACAM5, insulin-like growth factor binding protein (IGFBP3), and galectin-3-binding protein (LGALS3BP) [51, 61]. In addition, abnormal protein glycosylation can significantly affect the biochemical and mechanical properties of extracellular matrix (ECM), influencing the formation of cancer associated ECM, which promotes tumor cell migration and invasion [62-66]. Disruption of protein glycosylation through inhibition of N-glycosylation or the HBP pathway impacts the signaling cascade affecting expression of receptor tyrosine kinases (RTKs). Inhibition of glycosylation also enhances chemosensitivity of drug-resistant PDAC cells, underscoring the importance of glycosylation in perpetuating cancer survival [52, 67, 68]. While these studies open a window to explore the glycoproteome in PDAC, comprehensive analysis of intact glycopeptides or glycoproteins still remains a technical challenge. Much work remains to dissect on the complex mechanisms underlying the glycosylation events involved in PDAC.

Other protein PTMs in PDAC

In addition to the glycosylation discussed above, several common PTMs are also altered in the PDAC proteomes and contribute to the tumorigenesis, progression and metastasis. These PTMs may include phosphorylation, ubiquitination, sumoylation, and acetylation, playing pivotal roles in essentially all major signaling pathways implicated in PDAC. Three of these pathways are further discussed below (Figure 3).

In the RAS/MAPK pathway, which is activated in over 90% of PDAC, KRAS and other signal mediators are subject to multiple PTMs. Nascent K-RAS proteins are subject to 3 sequential PTMs at the C terminal (farnesylation, proteolysis and methylation) to gain affinity to the plasma membrane, which is required for its activity [69, 70]. The isoform K-Ras4A has additional palmitoylation to gain enhanced membrane affinity [71]. These PTMs are considered constitutional and are usually not affected by RAS activation status or disease condition [69]. However, these PTMs are required for the proper trafficking and localization of RAS into the membrane. Other PTMs of K-RAS, such as phosphorylation or ubiquitination, have been shown to result in membrane disassociation or enhanced K-RAS activity, respectively [69]. Phosphorylation and dephosphorylation of the multiple kinases and mediators in the RAS/MAPK pathway are pivotal in transmitting the extracellular signal to the cell nucleus to activate or modulate gene transcription. Gene mutations or PTMs leading to alterations in the phosphorylation can result in substantial impact in this signaling pathway and affect disease conditions.

Dysregulation of the TGF-β signaling pathway is very common at tumor initiation or during tumor progression of pancreas. It can act as tumor suppressing or tumor promoting, depending on the tumor stage and microenvironment. All signaling mediators in the TGF-β pathway are subject to extensive PTMs [72]. For TGF-β receptors, various PTMs, including phosphorylation and ubiquitination, are critical for the initiation and regulation of the signal transduction into the nucleus. The downstream SMADs are also subject to extensive and stringent regulation by multiple PTMs. Among the various SMADs in this pathway, SMAD4 is a critical common co-factor, which is deactivated in approximately 50% of PDAC.

The deactivation of SMAD4 in PDAC are usually the results of gene deletion, frameshift mutation, and single point mutation. Gene deletion and frameshift mutation can result in loss or reduced expression of SMAD4 protein. Most of the SMAD4 single point mutations found in PDAC cause a change in single amino acid that enhances affinity with ubiquitin (E3) ligase, and thus higher protein ubiquitination and accelerated degradation [73], leading to inhibition of transcriptional response of TGF-β.

Disabling immune checkpoints is emerging as a promising approach of immunotherapy for several types of cancer. The key T-cell checkpoint ligand, PD-L1, shows increased positivity in multiple cancers including PDAC [74, 75]. PD-L1 is subject to extensive regulation by PTMs. The stability of PD-L1 is extensively regulated by the ubiquitin/proteasome pathway [76]. Phosphorylation of PD-L1 by GSK3β increases its affinity to ubiquitin (E3) ligase, leading to degradation [77]. N-Linked glycosylation of PD-L1 creates a spatial barrier and disrupts GSK3β and PD-L1 interaction, leading to PD-L1 protein stabilization [77]. N-linked glycosylation of PD-L1 is also required for the proper interaction of PD-L1 and PD-1 [76]. These PTMs directly affect the functionality of PD-L1. Immunosuppression is very prominent in the progression of PDAC. However, recent results using checkpoint blockage have suggested that pancreatic cancer is resistant to this initial immunotherapy approach. Furthermore, the positivity of PD-L1 in PDAC is controversial in the literature, ranging from scarcely expressed to highly expressed in PDAC [74, 75, 78, 79]. The discrepancy on the PD-L1 staining between different studies could be in part attributed to the antibody used and the PTMs of PD-L1. In light of the complex PTMs of PD-L1, targeting PTMs of PD-L1 could represent a novel strategy to improve the effectiveness of immunotherapy for pancreatic cancer.

Proteome at early stages of PDAC

The precursors of pancreatic carcinoma may include PanIN lesions and pancreatic cystic neoplasms with malignant potential, such as IPMNs and MCNs. Both PanIN 3 and IPMN/MCN--with high grade dysplasia (both forms of *carcinoma in-situ*) show many similar molecular features with PDAC, including changes in the protein profile. Studies have shown that many differentially expressed proteins in PanIN 3 lesions, such as galectin 1, annexin A4 and A5, vimentin and laminin, are also concurrently dysregulated in PDAC tissue, suggesting that the dysregulation at functional level may start early prior to the development of invasive tumor [25, 33]. Oncogene *c-MYC* was identified as a prominent regulatory protein in the network of dysregulated proteins identified in PanIN 3 tissues. Such an observation from a proteome perspective, while preliminary, supports the pathological and genomic progression model of PanINs to PDAC [80-83].

In the proteomic study of pancreatic malignancy associated with cysts, one study suggested that the detection of protein family members of amylase, mucins, CEACAMs, and S100 proteins in cyst fluid might facilitate the discrimination of pancreatic cyst with malignant potential from benign lesions [84]. These proteins are among the proteins differentially expressed in PDAC. Systematic proteomic investigation of cystic tissue specimens obtained from surgical procedures or endoscopic ultrasound guided fine needle aspiration (EUS-FNA) have not been reported, but would provide useful insights and expand our understanding

on IPMN/MCN progression to pancreatic carcinoma. To date, the molecular details on the transition of proteomes and key protein networks at the early stages of human PDAC progression largely remain unclear. One of the major hurdles of clinical proteomic study on PDAC progression are the limited resources of clinically and pathologically well-defined specimens from patients with pre-cancer or early stage disease, as early detection of PDAC still remains a significant clinical challenge.

Confounding proteome changes

The changes in PDAC proteomes are multifaceted and can be convoluted by associated diseases or disease complications such as chronic pancreatitis, jaundice and diabetes [85-89]. Mounting evidence has shown that PDAC and chronic pancreatitis share many similar clinical and molecular features, and such similarities reflect in not only the tissue proteome but also the bodily fluids [34, 87, 88, 90-94]. As inflammation is a critical component of cancer progression, many inflammation-related proteins are concurrently overexpressed in the tissue lesions of both PDAC and chronic pancreatitis [34]. Fibrosis is one of the fundamental histological abnormalities observed in both PDAC and chronic pancreatitis [46, 95, 96]. Persistent activation of pancreatic stellate cells promotes fibrosis and enhances secretion of ECM components. As a consequence, proteins that are associated with ECM and stellate cells are frequently elevated in both PDAC and chronic pancreatitis [34]. In bodily fluids, the proteome and glycoproteome of plasma/serum of PDAC can be confounded by chronic pancreatitis, jaundice and diabetes due to the systemic proteome changes in the circulating system. The proteomes of pancreatic juice and EUS-FNA biopsies can be influenced by the level of obstruction of the main pancreatic ducts due to inflammation, jaundice or other non-cancerous diseases [97, 98]. While these confounding alterations pose a significant challenge in dissecting malignant signals for biomarker development, they may also be components of the complex mechanisms involved in pancreatic tumorigenesis, including inflammation, ECM remodeling, angiogenesis, fibrosis, immune response and diminishing of acinar cells.

Concluding remarks

While the signature mutations of PDAC, including near ubiquitous oncogenic mutations of *KRAS* and the frequent inactivation of *TP53*, *SMAD4*, and *CDKN2A* tumor suppressors have been well recognized [3-6], there is a need to collect sufficient data to define the cascading proteome alterations and functional drivers in PDAC. Such alterations may include changes in protein expression, amino acid sequence, PTM status, interaction networks and subcellular distribution associated with low- and high-grade dysplasia, at early and late stage PDAC. The discoveries from the emerging field of proteogenomics [99], which integrates genomic and transcriptomic information to enhance proteomic analysis, are expected to facilitate the interface and convergence of current understanding of pancreatic tumorigenesis from genomic and functional perspectives. The development of quantitative spectral library-based platform technology, such as SWATH [100], which affords enormous multiplex capability and records digital archive of a whole proteome for retrospective analysis, carries an exciting technological advance to assist clinical biomarker development. The development of databases and bioinformatics for metaproteomic analysis of human gut

microbiome has provided a powerful tool to interrogate the interplay of microbiota with host response at functional level. While exciting perspective has been demonstrated and increasing efforts have been made in exploring proteome alterations associated with PDAC and its progression, significant challenges exist. In addition to technical hurdles, the timeline and precise mechanism of PDAC progression from low-grade precursors (PanINs, mucinous cystic lesions) to invasive cancerous lesion are difficult to assess, and still remain vague. Heterogeneities associated with patients and specimen collection can also confound the analysis and data interpretation. Well-defined clinical longitudinal studies and experimental models are needed to provide well characterized samples for proteome analysis. The study of cancer stem cells and the presence of intra-tumoural heterogeneity in PDAC, which has direct implications for targeted or immunotherapeutic interventions, pose additional challenges for single cell proteomic analysis [101]. The co-existence of these challenges and knowledge gaps define the opportunities in current proteomic study of PDAC.

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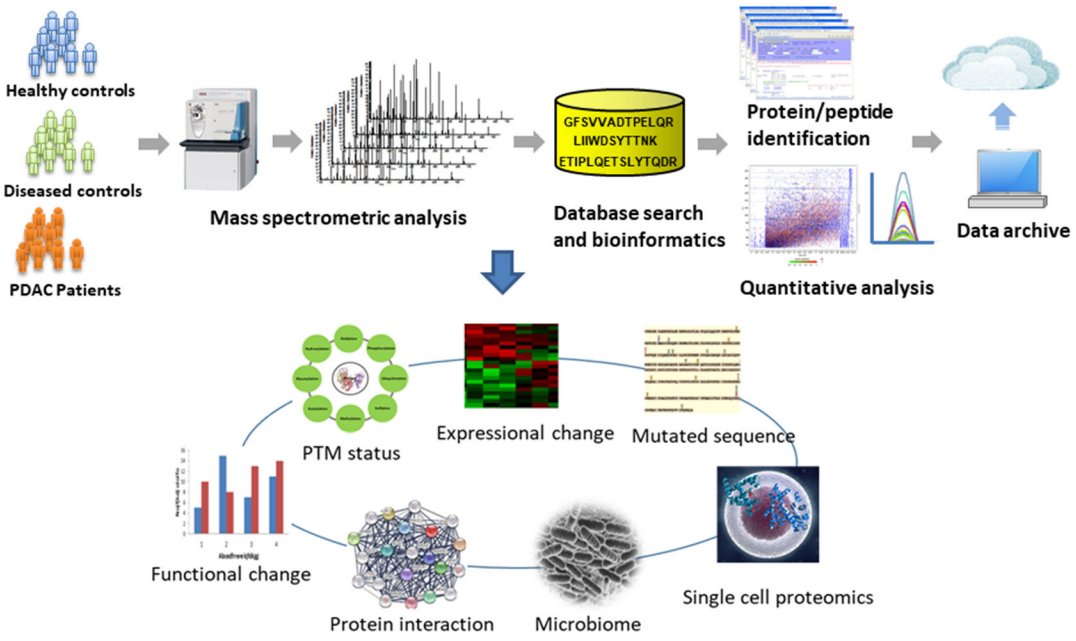

Figure 1.

A schematic illustration of proteomic work flow for comparative study of PDAC vs controls. Regardless study designs and specimen types, the platform typically consists of three modules, including sample preparation, LC MS/MS analysis and bioinformatics for data processing.

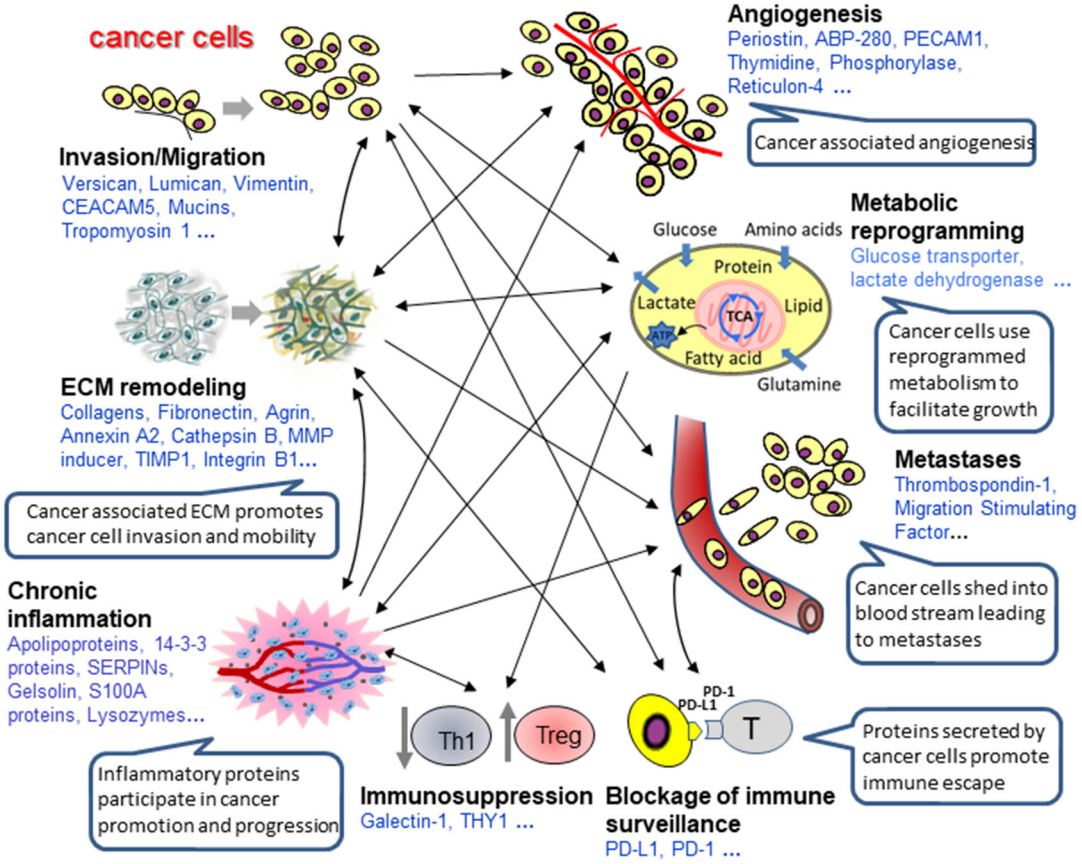

Figure 2.

Differential proteins in PDAC. Differential proteins identified in PDAC tissues are broadly involved in many aspects of tumorigenesis to facilitate cancer progression, including tumor growth, migration, angiogenesis, invasion, metastasis and immunologic escape, through orchestration of protein crosstalk between cancer cells and tumor microenvironment.

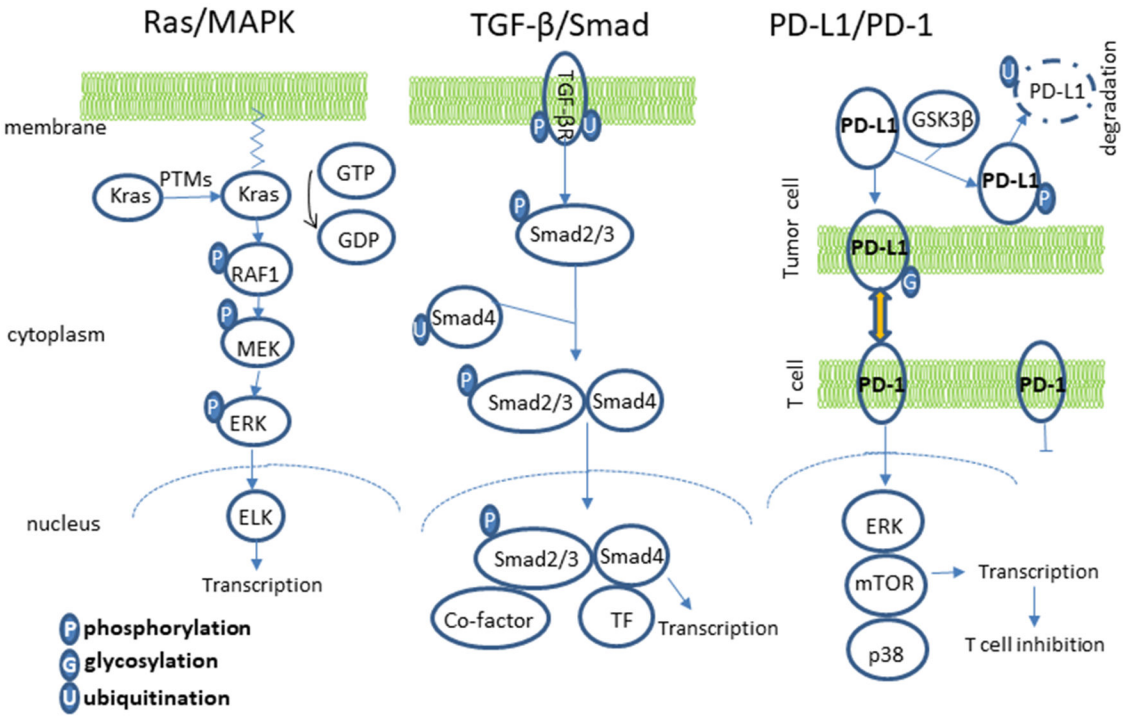

Figure 3.

PTMs in signaling pathways. PTMs play a pivotal role in regulating signaling pathways involved in pancreatic tumorigenesis and metastasis, including RAS/MAPK, TGF-β/SMAD and PD-L1/PD-1.