Review

Pancreatic Cancer- Secreted Proteins: Targeting Their Functions in Tumor Microenvironment

Anna Lisa Cammarota *, Antonia Falco, Anna Basile, Carlo Molino, Massimiliano Chetta, Gianni D'Angelo, Liberato Marzullo, Margot De Marco *, Maria Caterina Turco, Alessandra Rosati *

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Pancreatic Cancer- Secreted Proteins: Targeting Their Functions in Tumor Microenvironment

Anna Lisa Cammarota [1,°], Antonia Falco [1,°], Anna Basile [1], Carlo Molino [2], Massimiliano Chetta [3], Gianni D'Angelo [4], Liberato Marzullo [1,5], Margot De Marco [1,5,*], Maria Caterina Turco [1,5] and Alessandra Rosati [1,5,*]

[1] Department of Medicine, Surgery and Dentistry "Schola Medica Salernitana", University of Salerno, Baronissi (SA), 84081; Italy
[2] U.O.C. General Surgery, A.O.R.N. Cardarelli, Naples, 80131; Italy
[3] U.O.C. Medical and Laboratory Genetics, A.O.R.N., Cardarelli, 80131 Naples, Italy
[4] Department of Computer Science, University of Salerno, Via Giovanni Paolo II, 132, 84084, Fisciano, SA, Italy
[5] FIBROSYS s.r.l., University of Salerno, Baronissi (SA), 84081; Italy
* Correspondence: mdemarco@unisa.it (M.D.M.); arosati@unisa.it (A.R.)
° These authors equally contributed

Simple Summary: Pancreatic ductal adenocarcinoma requires a deeper understanding of its biology for effective therapies. This review focuses on connections between cancer- secreted proteins and tumor microenvironment (TME) and provides in this context a window on druggable molecular targets.

Abstract: Pancreatic ductal adenocarcinoma (PDAC) is a ravaging disease whose poor prognosis requires a more detailed understanding of its biology to foster the development of effective therapies. The unsatisfactory results of treatments targeting cell proliferation and its related mechanisms suggested to rather focus on the inflammatory tumor microenvironment (TME). Here, we discuss the role of cancer secreted proteins in the complex TME tumor-stroma crosstalk, to sched lights on druggable molecular targets for the development of innovative, safer and more efficient therapeutic strategies.

Keywords: pancreatic ductal adenocarcinoma; secretome; cell signaling; tumor microenvironment; small molecules; monoclonal antibodies

1. Pancreatic cancer Fact Sheet

The most common type of pancreatic cancer is the Pancreatic Ductal Adenocarcinoma (PDAC), which arises from the ductal epithelium of the organ. Around 70% of pancreatic cancers begin in the organ's head, and the majority start from the ducts that transport digestive enzymes (pancreatic ductal adenocarcinoma) [1,2]. The prevalence rate is 49.8 cases per million people, while the predicted global incidence rate is 58.6 cases per million people annually. Annual mortality is projected to be 57.7 per million persons. In the past 25 years, there has been a 55%, 63% and 53% increase in incidence, prevalence and death, respectively. While representing 1.8% of all malignancies, pancreatic cancer is responsible for 4.6% of cancer-related fatalities. Men have a somewhat greater incidence, prevalence, and fatality rate. By 2060, it is anticipated that pancreatic cancer deaths would have increased almost 1.97-fold.

Despite recent advances in surgical techniques and medical therapies, the median survival time for a pancreatic cancer patient at diagnosis is 4-6 months, with an 8% 5-year survival rate [3,4]. Pancreatic cancer is predicted to overtake colorectal, breast, and prostate cancer as the second leading cause of cancer death in the United States by 2030, surpassing colorectal, breast, and prostate cancer. In 2040, gastrointestinal cancers (pancreatic, liver, and colorectal cancer) are expected to be three of the four leading causes of cancer death. [3].

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The main reasons for such a poor prognosis can be found in the particularly complex anatomical region in which the tumor grows, as well as the fact that this tumor is usually diagnosed at an advanced stage in most patients. In fact, the survival curve of patients falls dramatically in the first year of follow-up from the moment of diagnosis; for this neoplasm, there have been no significant improvements in the last three decades, and the poor prognosis is substantially uniform at the international level [5,6].

Pancreatic cancer is a complex malignant tumor with a poor prognosis because it does not exhibit specific symptoms at an early stage, and even when they do appear, they are rather vague disorders that can be misinterpreted. For these reasons, the diagnosis is frequently made after the disease has spread. The only potentially curative treatment is surgical removal, but radical surgical resection of the tumor is indicated only in cases of intrapancreatic disease that does not extend to the retroperitoneum or transverse mesocolon and does not involve infiltration of the superior mesenteric artery, celiac tripod, or spleno-mesenteric-portal axis. For this reason, pancreatic cancer is only resectable in 10-20% of patients at the time of diagnosis, while it is locally advanced in 30-35% of patients due to infiltration of the large abdominal vessels, and metastases are already present in more than 50% of cases. However, even in the early stages, the prognosis is poor, as the median survival rates with surgery alone in this group of patients are in the order of 12 months, and the 5-year survival rate is between 5 and 10%. Median survival for stages III and IV is 10 and 6 months, respectively [7,8].

Differently from metastatic diseases in other tumor types (e.g. colon [9], gastroesophageal [10] head and neck [11] breast [12], lung [13] cancers) first-line treatment for metastatic pancreatic cancer is still chemotherapy [14]. Indeed, even though immunotherapies and/or targeted therapies for the majority of solid tumors have advanced quickly, progress in the treatment of pancreatic ductal adenocarcinoma has been unusually slow [15,16]. In this regard, researchers recently discovered novel players within the TME that can help improve therapeutic actions for various cancer therapies. A special emphasis here, has been placed on pancreatic cancer- secreted proteins, which are the primary source in developing and maintaining a cancer-friendly environment.

2. Proteins secreted by pancreatic cancer cells: messages sent to the neighborhood.

Cell communication in multicellular organisms allows cells to adapt their phenotypes and function. A number of secreted factors, soluble or associated to membranes, mediates critical molecular mechanisms involved in tissue and organism homeostasis. Proteins typically follow the conventional protein secretion pathway, which involves the endoplasmic reticulum (ER) and the Golgi complex. However, some proteins use alternative routes, such as unconventional protein secretion (UPS) pathways, induced by cellular stress such as nutrient deficiency, mechanical stress, inflammation, and ER stress. When the pathways leading to protein secretion - which mediate both short- and long-range signals - are dysregulated, disease pathogenesis is accelerated. In this context it is known that transformed cells are the source of distinct extracellular signals [17] that are captured by neighboring non-transformed stromal cells, influencing tumor development, metastasis, and even drug efficacy [18]. Moreover, tumoral secretomes provide a promising source of potential biomarkers useful in-patient management, and, in some cancers, there is a growing interest in intracellular proteins that have distinct and different functions when secreted, demonstrating how UPS pathways are still not fully understood [19]. In pancreatic cancer, mutated epithelial, acinar or ductal cells account for a small portion of the tumor mass, with the remaining made up of stromal cells and components. This reflects the significance of cell communication being hampered by pancreatic cancer cells, which collaborate in shaping a fibrotic and inflammatory microenvironment that promotes tumor establishment and progression [20].

Here, a literature search was conducted to find a comprehensive dataset that could illustrate the main biochemical pathway in which pancreatic cancer cells direct such a dramatic tissue transformation. We used PubMed to look for PDAC secretome studies. To maximize search specificity and sensitivity, the following keywords were used: “Pancreatic cancer,” “Pancreatic ductal adenocarcinoma,” and “secretome, extracellular protein and pancreatic carcinoma” and “tumor microenvironment”. Only studies involving pancreatic cancer- secreted proteins were included after further

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screening based on title and abstract. There were no restrictions on the type of study. Our studies primarily employ two methods for secretome analysis of pancreatic adenocarcinoma: mass spectrometry and the Enzyme-Linked ImmunoSorbent Assay (ELISA). Most mass spectrometry-based studies include secretome or proteome analysis of human [21–26], murine [27] or hamster [28] cell lines. On the other hand, most studies using ELISA analyzed serum from patients with hereditary predisposition [29] as well as advanced disease [30,31], and pancreatic cancer cell supernatant [22]. In addition, we included a recent review [32] resuming the use of novel protein biomarkers in early PDAC diagnosis, prognosis, and treatment response prediction, as well as the utility of possible biomarker combinations in diagnostic panels. Finally, an approach integrating meta-analysis of PDAC proteome and secretome MS data, used to identify potential disease biomarkers [33], was further considered (Table 1).

Table 1. Pancreatic cancer cells- secreted proteins dataset.

GENE NAME	REFERENCES
LGALS1, ENO2, SERPINA1, NMI, PRDX4	*Chung J.C., et al. 2008 [21]*
CP, LGALS3, MARCKS	*Brandi .J, et al. 2016 [22]*
GDF15, TGM2, LIF, MMP2	*Li X, et al. 2022 [23]*
SAA1, RC3H1, CCT8, ZNF518B, EXOSC8, IGF2, NPC2, HSP90AA1, PPIA, ENO1,	*Liu P, et al. 2019 [24]*
DNAJB11, PPT1, CTSD, CDH3, PLAU, LFNG	*Liu, P., et al. 2016 [25]*
GLRX3	*Jo J.H., et al. 2021 [26]*
PLEC	*Kelly KA et al. 2008 [27]*
MMP12, MMP10, LAMA5, WHAG, CPN1, THPH2	*Liu P., et al. 2020 [28]*
CXCL8, LCN2, MUC5AC	*Levink IJ.M., et al. 2022 [29]*
ULBP2, NAPA, TGFBI, RAB14, ULBP2, CP, RPL22, PURB, C1S, ANXA11, ERO1L	*Chang Y.T., et al. 2011 [30]*
ALCAM, ANG, AXL, BAG3, BSG, CCL24, CEACAM5, CEACAM1, CLU, COL18A1, EPCAM, HP, ICAM1, IGFBP2, IGFBP4, LCN2, LRG1, MMP2, MMP7, MMP9, MSLN, PARK7, PF4, PPBP, PRG4, SPARCL1, SPP1, TGFBI, THBS1, TIMP1, TNFRSF1A, VEGF	*Firpo M.A., et al. 2023 [31]*
THBS2, IGFBP2, IGF1, ENPP2, LRG1, TTR, APOE, ITIH3, APOA1, APOL1, TFF1, TFF2, TFF3, GDF15	*Kapszewicz M., et al. 2021 [32]*
ALB, ENO1, FN1, TF, LGALS1, APOE, CTSD, TPI1, GSTP1, PARK7, PRSS1, MSN, PGK1, ANXA5, PIN1, PKM, EEF1A1, THBS1, GSN, LGALS3, TIMP1, CFL1, FLNA, LGALS3BP, CALR, CLIC1, TAGLN2, LDHA, NME1, TKT, SFN, ALDOA, ENO2, PGAM1, ARHGDIA, ACTB, P4HB, ACTA1, AHSG	*de Oliveira G., et al. 2020 [33]*

The obtained dataset represented and summarized the coexistence of cytokines, growth factors, extracellular matrix proteins, proteases and protease inhibitors, membrane- and extracellular vesicle-associated proteins, and metabolic enzymes in the neoplastic *milieu* (Figure 1).

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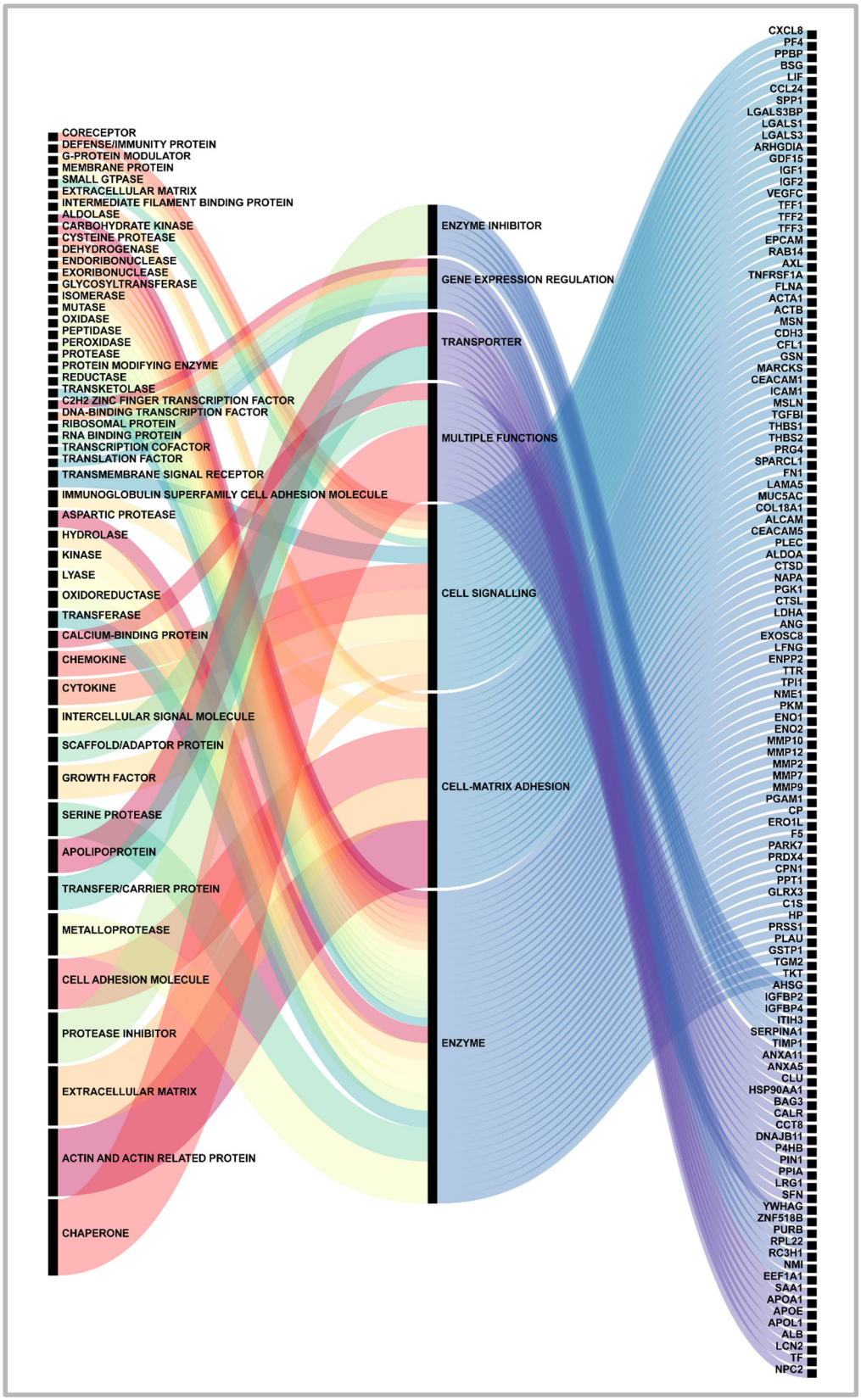

Figure 1. Proteins Functions- A Global Core Biodata Resource, Panther Classification System (https://pantherdb.org/, accessed in June 2023), classified the gene dataset for functions. Proteins secreted by pancreatic cancer cells (right column) were classified as having a general function (center column) or a specific function (left column). An Alluvial plot (https://www.mapequation.org/alluvial/, accessed in June 2023) was used to depict the classifications.

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To define protein clusters associated with main cellular processes, the dataset was analyzed in the GO biological processes 2023 database by using Enrichr (https://appyters.maayanlab.cloud/ accessed in June 2023) (Table 2). Proteins with a known function when secreted are then briefly discussed.

Table 2. Pancreatic cancer cells secreted proteins dataset Enrichr-Appyter online applications generated a downloadable table. The names of the genes were reported along with the p-values and q-values of significant terms in the chosen library. The q-value is an adjusted p-value calculated using the Benjamini-Hochberg method for multiple hypothesis testing correction.

Term	p value	q value	Overlaps genes
Extracellular Matrix Disassembly (GO:0022617)	7.05×10^{-09}	2.09×10^{-06}	*[MMP12, PRSS1, GSN, MMP7, MMP2, MMP9, MMP10]*
Regulation Of Apoptotic Process (GO:0042981)	2.42×10^{-11}	3.59×10^{-08}	*[HSP90AA1, GSTP1, ANXA5, PARK7, IGF1, CLU, MMP9, THBS1, ACTB, NME1, LGALS1, AXL, BAG3, CEACAM5, ARHGDIA, CFL1, ALB, PPT1, FLNA, CALR, PPIA, CTSD, TGM2]*
Neutrophil Chemotaxis (GO:0030593)	1.94×10^{-07}	2.88×10^{-05}	*[LGALS3, CCL24, CXCL8, SAA1, PPBP, PPIA, PF4]*
Carbohydrate Catabolic Process (GO:0016052)	4.19×10^{-09}	1.56×10^{-06}	*[LDHA, TPI1, PKM, PGAM1, PGK1, ENO1, ENO2]*

As a result of the analysis, it was possible to put in evidence a set of proteases responsible for extracellular matrix and cellular component disassembly. As previously reported, the acellular components of the pancreatic tumor mass, as well as their changes over time, drive the tumor's progression. In this regard, MMP-2 and MMP-9 (Matrix MetalloProteinases) gelatinases are abnormally and contemporarily up-regulated in pancreatic cancer [31,34], but the clinical relevance measured by the correlation between their expression and survival, metastasis, or tumor stage is debatable [35]. Instead, the expression of the matrilysin MMP-7 in tumor samples was linked to a poorer prognosis in patients [36] and an unfavorable pathologic response to neoadjuvant therapy [37]. Furthermore, the multifunctional zinc finger transcription factor YY1 (Yin Yang 1) has been shown to suppress stromelysin-2 (MMP-10), whose overexpression is a favorable independent prognostic factor in PDAC patients [38]. Finally, the secreted gelsolin, a scavenger of extracellular actin, has been recently reported for its involvement in attenuating DNGR-1-dependent dendritic cell-mediated anti-tumor immunity [39].

Some apoptosis-regulating proteins with very different biochemical functions have been also identified, and some of them have been linked to a role in pancreatic cancer. E.g., Hsp90AA1 (Heat Shock Protein 90 Alpha Family Class A Member 1) is one of the most abundant proteins expressed in the cells, which interacts with several secreted client proteins. Hsp90AA1 promotes tumor aggressiveness and chemoresistance by activating AKT through LRP-1 (Low-density lipoprotein Receptor-related Protein 1) [40]. Among other chaperones, PARK7 (Parkinson protein 7) [41] and PPIA (Peptidylprolyl Isomerase A) [42] are upregulated and secreted by cancer cells. While PARK7 has been described for its ability to counteract environmental oxidative stress [41], PPIA is known to act through CD47 and NF-kB pathway, thus promoting cell proliferation [43]. In addition, the extracellular chaperone Clusterin (CLU) has been shown to be a mediator of chemoresistance in pancreatic cancer [44]. The overexpression of the co-chaperone BAG3 (BCL2 Associated Athanogene 3) has also been described to be associated with pancreatic cancer aggressiveness [45], and its sera levels are measurable in pancreatic cancer patients [31,46]. Furthermore, a distinct function was described for secreted BAG3. Indeed, its interaction with IFITM2 (Interferon Induced Transmembrane Protein 2) on the plasma membrane can induce pro-tumoral cytokine release by macrophages [47] and

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fibroblasts [48], thus sustaining tumor growth. Another relevant protein in this context is the soluble GSTP1 (Glutathione S-Transferase Pi 1) able to catalyze the conjugation of many hydrophobic and electrophilic compounds with reduced glutathione. This activity plays a role in regulating oxidative stress, thus negatively affecting proliferation and upregulating apoptosis in PDAC cells, as demonstrated by knockdown experiments [49]. The transglutaminase-2 gene (TGM2) has been also identified as an important extracellular cross-linking enzyme involved in ECM turnover, and its levels were associated to a poor patient survival in pancreatic cancer patients [50]. Annexins dysregulation has also been reported as a common feature in several cancers [51], and, among them, soluble ANXA5 (Annexin A5) has been described for its activity in cell membrane resealing [52], an essential repair machinery which promotes survival in invasive cancer cells [53]. Insulin-like growth factor (IGF)-axis, which mediates survival signals essential for pancreatic cancer development and progression, belongs to traditional signaling molecules, and its crucial role was evidenced by the strong association between SNPs (Single Nucleotide Polymorphisms) in correlated IGF1R, IGF2R, and IRS1 genes with tumor response to therapy and disease stage [54]. Finally, AXL (a member of the TAM tyrosine kinase receptors) is present in our dataset. The AXL/Gas6 (Growth Arrest Specific 6) signaling pathway plays a role in tumor cell proliferation, and plasma detection of the AXL soluble form, obtained by an ADAM10/ADAM17 (ADAM Metallopeptidase Domain)-specific shedding mechanism, has been described as an early signature of PDAC [55], while its functions, likely relying on attenuating Gas6 functions in the TME, remain unknown [56].

An additional functional cluster of secreted proteins were linked to neutrophil chemotaxis. Tumor-infiltrating neutrophils indicate poor prognosis for patients and activated neutrophils can generate neutrophil extracellular traps (NETs) which are emerging in several cancers as a marker of cancer progression and immunosuppression [57,58]. As a first example, extracellular Galectin-3 (LGALS3), detected in the blood of PDAC patients [58], has been associated with neutrophils recruitment and inflammation exacerbation in several infectious diseases [59]. Indeed, given the similarities in the pathogenesis of inflammatory diseases and cancer, it is not surprising to find in the described pancreatic cancer- secreted proteins dataset molecules such as IL8 (CXCL8) [61], Eotaxin-2 (CCL24) [62], PPBP (Pro-Platelet Basic Protein) [63], and PF4 (Platelet Factor 4) [64] which are potent neutrophil chemotactic factors. Serum Amyloid A1 (SAA1) [65], another protein induced in pancreatic cancer cells, attracts neutrophils to the tumor nest by interacting with TLR2 (Toll-Like Receptor 2) [66].

Finally, altered carbohydrate catabolism has been recognized as the major metabolic alteration in pancreatic cancer [67], but the role of those enzymes in the pancreatic cancer *milieu* has not been fully elucidated yet. The evidence that secretory PKM (Pyruvate Kinase M1/2) promotes tumor angiogenesis by facilitating endothelial cell proliferation and new vessel formation via the PI3K/AKT and Wnt/-catenin signaling pathways provides some hints [68]. On the other hand, secreted PGK1 (Phosphoglycerate Kinase 1) has been shown to act on angiostatin levels, resulting in an anti-angiogenic and tumor suppressive function [69]. Finally, enolases, specifically the cell surface associated ENO1, have been identified as a pancreatic cancer neoantigen, promoting cancer cell survival and migration by coordinating with integrins and uPAR (Plasminogen Activator, Urokinase Receptor) [70].

Other proteins relevant in this context, but not included in Table 2, are: GDF15 (Growth Differentiation Factor 15), whose expression was positively correlated with poor survival in PDAC patients and whose downregulation inhibited PDAC tumor growth in vivo [71]; LIF (LIF Interleukin 6 Family Cytokine), a pleiotropic cytokine that regulates cell survival by interacting with its receptor LIFR/GP130 expressed on surrounding fibroblasts, thus promoting pro invasive phenotype [72]; VEGF (Vascular Endothelial Growth Factor) [73], which functions as an endothelial cell mitogen and is strongly linked to angiogenesis in pancreatic cancer; and TF (Tissue Factor), which, in its alternatively spliced form asTF, is released by cancer cells thereby triggering the activation of PI3K/Akt, MAPK, and FAK pathways through its interactions with $\alpha 6\beta 1$ and $\alpha v\beta 3$ integrins [74].

The list of proteins resulting from the analysis was used to screen the presence of pharmacologic molecules designed to interfere with their activity, to describe available candidates for therapeutic interventions in pancreatic cancer.

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3. Communications breakdown operated by small drugs.

The DGIdb (The Drug Gene Interaction Database, accessed in June 2023) was queried, screened and integrated with literature search for available molecules possibly having inhibitory activity on pancreatic cancer- secreted proteins illustrated above; obtained search results are thereby described.

The response to synthetic inhibitors of MMPs (MMPIs) were studied in the past decades in several solid tumors. However, despite the promising preclinical data, all trials were unsuccessful in tumor mass reduction or overall survival improvement [75].

Clusterin expression was challenged using the drug OGX-011, an antisense oligonucleotide that showed a potentiating effect of various FDA-approved anticancer chemotherapeutics during clinical trials [76]; any trial result for pancreatic cancer is still available [77].

Ganetespib (STA-9090) is a small molecule that interferes with HSP90 client protein binding, thus promoting the inactivation and degradation of the signaling proteins that regulate cancer progression. Unfortunately, a Phase II study carried out in refractory metastatic pancreatic cancer failed to prove its clinical efficacy [78]. More clinical trials as a neoadjuvant treatment and/or in combination with chemotherapy are expected [79].

The extracellular galectin-3 functions were shown to be targeted by RN1, an arabinogalactan polysaccharide isolated from the flowers of the Chinese ginseng plant (Panax notoginseng) which displayed antitumoral activity in PDAC in vitro and in vivo [80]. While the use of galectin inhibitors, such as belapectin (GR-MD-02), has been accepted as a novel therapeutic tool in liver antifibrotic therapy [81], clinical trials are ongoing to explore its utility in lung and head and neck cancer diseases (clinical trial: NCT02575404).

4. Communications breakdown operated by monoclonal antibodies.

The target specificity of monoclonal antibodies (mAbs) makes them powerful tools for a wide spectrum of biomedical and clinical application. As previously stated, the use of DGIdb was supported and integrated by a literature search to identify available mAbs able to bind and neutralize the secreted proteins here selected for discussion.

Xentuzumab, an IgG1 monoclonal antibody with high affinity for IGF-1 and IGF-2 currently tested in preclinical models for the treatment of advanced solid tumors, allowed the collection of several interesting data [82,83]. A phase I trial enrolling patients affected by different advanced solid tumors, including PDAC, allowed to verify its safety, tolerability and clinical manageability. On the other hand, in a phase II study in metastatic breast cancer, treatments with the Xentuzumab combined to everolimus and exemestane did not show significant impact on PFS (Progression Free Survival) [84].

Another strategy, aimed at neutralizing VEGF with the monoclonal antibody Bevacizumab, showed promising results in preclinical studies [85], but it did not show appreciable benefit when combined with gemcitabine in clinical trials [86]. Thanks to its high safety profile, trials were further extended to a third compound, erlotinib, but still without satisfying results [87].

Recently LIF, which seems to directly fuel oncogenic KRAS signaling, has been proposed as a therapeutic target in PDAC, thus providing a chance to develop a new tool able to overcome chemotherapy resistance in KRAS- targeted protocols. Indeed, in syngeneic mouse models of oncogenic KrasG12D-driven pancreatic adenocarcinoma, using LIF neutralizing antibodies, or only gemcitabine, had no effect on tumor growth, while the combined treatment was able to repress the tumor growth and improve the animal survival [88]. A recently completed first-in-human trial with a humanized anti-LIF mAb (MSC-1) in advanced solid tumors showed that the mAb was well tolerated and was able to extend the PFS of some patients [89]; a phase II study in PDAC patients is currently underway (D8151C00001).

In this context, the neutralization of extracellular BAG3 is another promising strategy supported by studies carried out in several murine preclinical models treated with an anti-BAG3 mAb, that showed its ability in reducing PDAC tumor growth as monotherapy [47,90]. but even more striking results were observed in combined treatments with the ICIs (Immune Check-point Inhibitors) anti-PD-1 [91] and anti-SIRP-alpha [92]. The ex vivo studies on mice tissues showed that combo treatments

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were able to promote an immunostimulatory microenvironment along with a significant reduction of cancer fibrosis [91–93]. Further refinements and developments of the anti-BAG3 mAb- based therapies could hopefully contribute additional evidence of efficacy and safety of combined treatments and could allow to tailor and diversify the protocols also for other solid tumors [94].

An anti-IL-8 antibody was also tested in a humanized mouse model of PDAC in combination with anti-PD-1. The treatment results in a significantly reduced tumor growth, as well as an increased innate immune response and type I cytokine expression in myeloid cells, that reveals a novel function of IL-8 antibody in myeloid cell "re-education" [95]. HuMax-IL8 was tested in a Phase I trial on solid tumors showing its safety and tolerability, while further studies are ongoing to evaluate the efficacy of anti-IL-8 treatments combined with other immunotherapies [96].

Another around the corner strategic perspective aims at targeting the asTF protein by First-In-Class humanized antibody which exerted a significant effect on tumor growth in an animal model, downregulating several gene function categories including focal adhesion, cell motility, cell proliferation, cytoskeleton, regulatory proteases and cell death, many of which are known to be TF-associated [97]. In this case, XB002, a novel, investigational ADC (Antibody Drug Conjugate), is currently being tested as single-agent and combination therapy in subjects with inoperable locally advanced, or metastatic, solid tumors in a Phase I trial; results are expected in late 2024 (NCT04925284) (Figure 2).

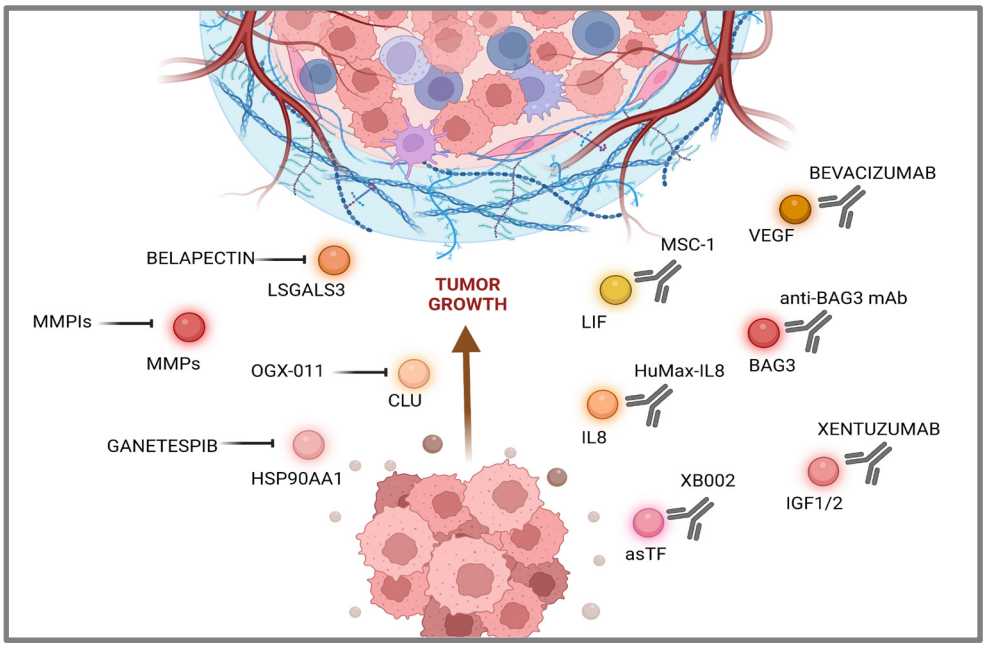

Figure 2. Druggable secreted proteins landscape in pancreatic cancer cells. Image was realized with Biorender.

5. Conclusion and Future directions

The abnormal production of secreted factors in malignant cells, via canonical and non-canonical pathways, has long been the key mechanism through which metabolic rewiring of cancer cells and neighboring non-malignant cells directs tumor progression [99]. With a focus on targeting pancreatic cancer- secreted proteins, we tried to summarize current and hopefully promising novel therapeutic approaches for the treatment of pancreatic cancer. The study, carried out by analyzing the data available in the literature, confirms the need for further efforts in selecting new molecular targets with lower toxicity risks along with the design of more appropriate, selective and specific therapeutic tools. Furthermore, a deep profiling of the tumor tissue proteome, as well as circulating proteins, using high-throughput technologies during the pre-treatment stage could help in tailoring personalized therapies, thus favoring the development of more effective therapeutic strategies for this fatal disease.

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Conflicts of Interest: AR, MDM, LM and MCT are shareholders of FIBROSYS s.r.l., an academic spin-off developing diagnostic and therapeutic tools related to BAG3 and its receptor. The remaining authors have nothing to disclose.

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