Microreviews in Cell and Molecular Biology
An undergraduate science journal
2023

Complexities in the Microenvironment of Pancreatic Cancer Cells Highlight the Difficulties in Developing Targeted Therapies.

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Key Words:
Pancreatic cancer, Tumor microenvironment, Exosomes, G-protein coupled receptors, DNA methylation

Pancreatic cancer is a devastating and frightening diagnosis to present to a patient. Pancreatic cancer is a disease that carries significant morbidity and mortality. Equally disheartening is the fact that few treatment options have long-term benefits. The only curative hope is a surgical intervention which is usually unavailable to most patients because of the advanced stage of the disease at the time of diagnosis. Unfortunately, surgical intervention carries significant morbidity and mortality as well. Conventional treatments such as chemotherapy and radiation are essentially palliative care. As we seek new and innovative treatment methods, we have to consider the nature of this aggressive and resistant tumor. Several factors involved in how pancreatic cancer develops make its resistance to treatment more difficult to overcome. In this series of papers, we look at several approaches currently being explored to understand better the nature of this devastating disease and its resistance mechanisms. We also present possibilities for future targets for new and unique therapies.

Introduction

Few diagnoses in clinical medicine present more frustration and challenges than the diagnosis of pancreatic cancer. Pancreatic cancer carries both high morbidity and high mortality. It is also a disease process with limited therapeutic success despite multiple treatment modalities(1). Pancreatic cancer has a 5-year survival rate of less than 5-8% worldwide. Cancer of the pancreas has the lowest relative five-year survival rate among all cancers(2). Approximately 75% of pancreatic cancer patients die within the first year(3). To make the statistics even worse, the average time between diagnosis and death is six months(4). Of great concern, pancreatic cancer, which is currently approximately the seventh leading cause of cancer deaths globally, is projected to move up to the second or third leading cause of cancer deaths within the next several years(5). The increase in pancreatic cancer deaths is not likely due to the increased incidence of pancreatic cancer but due to the lack of treatment progress compared to other forms of cancer. Pancreatic cancer is a disease that carries a poor prognosis at virtually all stages of the disease. Long-term survival is limited(6). Therapies have been very limited in their success.

There are multiple factors involved in the poor prognosis of pancreatic cancer. One of the primary causes of the poor prognosis is that the disease is relatively silent in its early stages and is rarely brought to the attention of medical providers until the disease is already advanced and metastatic(7). Currently, the only potentially curative treatment is surgical resection(8). Unfortunately, the surgical procedures used to treat pancreatic cancer carry high morbidity and mortality. Conventional chemotherapy and radiation therapy have been proven to be of limited value and are generally helpful in slowing the disease or palliative care. Targeted molecular therapy has also been of little value in treating pancreatic cancer. Begging the question of what other types of novel therapies may benefit in the future or might help deal with the failures of the current modes of treatment.

Several novel approaches have been attempted in other solid tumors. These approaches include gene therapy(9, 10), oncolytic virus therapy(11, 12), immunotherapies(13), and stem cell treatments. Unfortunately, to this point, the results in pancreatic cancer have been limited and disappointing. In the future, the microenvironment of pancreatic cancer cells and the unique molecular chemistry of this devastating disease must be more clearly understood.

The unique nature of the microenvironment of pancreatic cancer contributes to its significant virulence(14). In addition, there is a complicated interaction between the microflora of the gut with gastrointestinal malignancies. Intricate and complex genetic, molecular, and biochemical

interactions make pancreatic cancer difficult to treat clinically(10).

Recent Progress

Fang et al. (2023)(8) evaluated the effects of up-regulation of a subset of G-protein coupled receptors in the paper. G-protein coupled receptors are membrane proteins that act in regulating signal transduction from the outside of a cell to the inside of the cell. This group of membrane receptors works in various cellular processes and several signaling pathways. Their paper examined a subset of the G-protein coupled receptors, class C, group 5, and member A (GPRC5A). They looked at this receptor because it has variable effects across several different cancers where the receptor acts as an oncogene. In pancreatic cancer, this paper presented evidence demonstrating upregulation of the GPRC5A worked with the Hippo pathway. The Hippo pathway is a signaling path that acts in the regulation of apoptosis and cell proliferation. In addition, the Hippo pathway is a tumor-suppressing system. The core Hippo protein (Hpo) is a protein kinase that acts through a phosphorylation cascade of serine/threonine kinases. The paper points out that there is Hippo pathway dysregulation in pancreatic cancer. One of the cofactors in the Hippo pathway is YAP1 (yes-associated protein 1). YAP1 acts as an oncogene through its effects on cell proliferation, differentiation, and transformation through its impact on members of the notch signaling pathway and cycle-dependent kinase. One of the significant effects of YAP1 is to act in contact inhibition loss. This paper interestingly showed that GPRC5A regulated the expression of YAP1 at the transcription level but did not regulate it at the activity level. They also demonstrated that YAP1 knockout reversed the effect on pancreatic cancer cells. The final proposal was that the axis of GPRC5A-cAMP-CREB (cAMP response element binding protein, a cellular transcription factor) was crucial in the progression of pancreatic cancer.

Zhang et al. (2023)(15), in their paper on M2 macrophage-derived exosomes, discussed specific micro-RNAs and their effects on glutamine metabolism and pancreatic cancer. They pointed out that one of the critical factors in developing cancers, particularly pancreatic cancer, is the immune system dysregulation and alterations in metabolism in the tumor microenvironment. One of the essential immune cells in the tumor microenvironment is the macrophage. Of particular importance are the two primary macrophage subtypes, the M1 and M2 types. The M1 macrophage acts in promoting inflammation and has tumor-suppressive effects. The M2 subtype of macrophage affects to decrease inflammation and institute tissue repair. This paper looked at the second type of macrophage because of its tumor-supportive functions. They point out that several tumors have growth, malignancy, and metastasis processes that become upregulated by the effects of this M2 macrophage. Exosomes produced by the M2 macrophages act to release various mediators into the microenvironment of the tumor. The purpose of exosomes, in general, is to regulate various processes and interactions between different cell types in the microenvironment of a given cell(16). In addition, exosomes participate in a form of signaling between cells.

As part of the mechanism that the M2 macrophage uses to regulate tissue repair, induce cell growth, and modulate immune function, the M2 macrophages release small non-coding RNAs. These so-called micro RNAs act to control gene expression and have regulatory effects on mRNA. A number of the M2 macrophage-derived exosomes will carry micro RNAs, which serve to promote differentiation and growth in pancreatic cancer. Some of the other effects of these micro RNAs include that they act to induce angiogenesis, migration, and invasion by the pancreatic cancer cells. This paper looked at a specific micro-RNA that had not been evaluated. The miR-193b-3p micro RNA is upregulated in plasma exosomes from pancreatic cancer. There was no information, though, as to the effects of this miRNA on the tumor cells in pancreatic cancer. This paper determined that the target of this miRNA was a protein called TRIM62. This protein is a tripartite motif-containing protein. These proteins act in several cellular processes and help regulate immune function. This group of proteins acts in ubiquitination as an E3 ubiquitin ligase. In particular, the TRIM62 protein acts to modulate various immune functions. This paper demonstrated that the micro RNA miR-193b-3p acts via the TRIM62 protein to increase pancreatic cancer cells proliferation, invasion, and migration through glutamine uptake.

The overexpression of a primate-specific gene *MYEOV* was explored in the paper by Tange et al. (2023)(17). The report demonstrated poor survival with overexpression of this gene of unknown function. The myeloma overexpression gene is noted in several malignancies of various types. The protein that this gene encoded appeared to be consistent with a membrane-localized protein as it contained a distinct hydrophobic region at the C-terminal end. They also pointed out that it was difficult to clearly understand the biological role of this protein because it is a primate-exclusive gene that precluded the use of mouse models. The *MYEOV* gene expression was increased at the transcriptional level in pancreatic tumor tissues.

Furthermore, it was an independent indicator of poor prognostic disease-specific survival. Control of this gene appears to be regulated by methylation of its promoter region in nonmalignant tissues. Demethylation of this promoter leads to overexpression of *MYEOV* in the case of pancreatic cancer. The mammalian target of rapamycin complex 1 (mTORC1) is a protein complex that controls protein synthesis. This system functions by acting as a redox and energy sensor. The transcription-regulating pathway c-MYC is part of the *MYC* family of genes. These

genes code for proto-oncogenes and regulatory genes, which help control cell proliferation. This paper looked at the knockout effects of the *MYEOV* gene, which restored the expression of repressors of c-MYC and mTORC1 pathways. The *MYEOV* gene also affected the folate metabolism-related enzyme genes required for synthesizing amino acids and nucleic acids. The researchers demonstrated that *MYEOV* acted as an oncogene for pancreatic cancer.

The tumor microenvironment in pancreatic cancer with relation to long non-coding RNAs (lncRNA) was presented in the paper by Lu et al. (2023)(18). This paper discussed that the tumor microenvironment is a balance between immune cells and non-immune stromal cells. The stromal cells make up the connective tissue matrix which supports the structure of the tissue. This stromal matrix is particularly dense in the case of neoplastic tissues, particularly in the case of pancreatic cancer. The medical term is desmoplasia which refers to a dense network of malignant cells and background stromal cells intermixed with hyalinized tissue. This stroma is sclerotic in that it demonstrates an increased extracellular matrix composed of proteoglycans and glycosaminoglycans. Desmoplasia is a similar process to normal scarring in non-neoplastic tissue. In the case of pancreatic cancer, the network has a mixture of pancreatic cancer cells mixed with stromal cells and other various immunosuppressive cells, such as the M2 macrophage. There is an extensive array of immunosuppressive cells in this dense matrix.

Further complicating pancreatic cancer treatment resistance is poor T cell infiltration and activation in this matrix. The dense matrix is one factor that leads to the difficulties in therapeutic measures penetrating pancreatic cancer to have any beneficial effects. This paper used a database to look at various long non-coding RNAs and the dysregulation or mutation and any association with the progression of pancreatic cancer. Several lncRNAs, they pointed out, are involved in modulating the immune response in the tumor microenvironment and acting in tumor immunosuppression. They discussed that the regulation and mechanism of these lncRNAs, particularly in the relationship of the pancreatic cancer tumor microenvironment, were still unclear. Their paper aimed to look for a risk score model that could be prognostic.

In the final paper I evaluated in this series, Hagel et al. (2023)(19) looked at chimeric antigen receptor T-cell therapy in pancreatic cancer. Chimeric antigen receptor T-cell is a protein receptor engineered to target a specific antigen. These antigens allow the T-cells to be directed against a particular antigen on the tumor cell surface. Often T-cells are harvested from the patient's blood and modified to express a specific antigen receptor and target a surface antigen on a tumor. This paper discussed using the glycosylphosphatidylinositol linked membrane protein mesothelin (MSLN) as a target. This protein is overexpressed in many tumors and shows low expression in normal mesothelial tissue. They point out that the function of MSLN is unknown in normal mesothelial cells. They discuss that CAR T-cell therapy in pancreatic cancer showed intrinsic resistance because pancreatic cancer was particularly refractory. They hypothesize that this is likely due to multiple factors. One of the prime factors expected is poor penetration of T cells into the tumor mass, and T-cell dysfunction likely contributes. Again it is likely that the tumor microenvironment, which is resistant to T-cell infiltration, and the fact that there are multiple immunosuppressive modulating substances in the microenvironment, all contribute to resistance to this type of therapy. The authors also discussed factors intrinsic to the tumor that contributed to the lack of effect. These included antigen display by the tumor, expression of immune inhibitory substances, and inherent pancreatic cancer cell state that resists immediate killing. The authors used CRISPR-Cas9 screens against pancreatic ductal adenocarcinoma cells to identify some of the tumor's intrinsic factors. They were able to locate several antigen-dependent and antigen-independent mediators. One of the essential things they discovered was that most of the genes involved in the glycosylphosphatidylinositol membrane anchoring biosynthesis were lost in these pancreatic cells, thereby disrupting this particular pathway. They also pointed out intrinsic changes within the pancreatic cancer cells that disrupted the death cell receptor pathways. This research showed multiple antigen-dependent and antigen-independent mechanisms by which the pancreatic cancer cells avoided the CAR T-cell therapy.

Discussion

In this series of papers, we looked at the current state of research into pancreatic cancer. Five different approaches were presented in five separate articles. Illumination of some of the problems related to this disease's very nature makes it such a complex disease process to treat and clearly understand. These papers have interrelated themes that highlight the complexity and diverse nature of the problem of pancreatic cancer. It is clear from these papers that definitive treatment of pancreatic cancer will require a multipronged approach. Research in the future will require innovation and a clearer understanding of the complexities of this multifaceted disease.

In the paper by Fang et al. (2023)(8) article, they looked at increased G-coupled receptor protein GPRC5A in pancreatic cancer. They determined that a decrease in the receptor function inhibited tumors in vivo. They also discussed that it regulated YAP1 via the cAMP-CREB signaling axis. They determined that inhibiting the YAP1 expression reduced proliferation and migration in pancreatic cancer cells. The authors determined that disrupting the hippo signaling pathway prevented apoptosis and instigated cell proliferation. They pointed

out that this was a crosstalk model that may have benefits in future therapeutic targets. This research showed poor prognosis in pancreatic cancer with upregulation of the GPRC5A, and that knockdown inhibited cell proliferation and migration in pancreatic cancer cells in vitro. Using a nude mouse model, they showed that GPRC5A promoted pancreatic cancer growth in vivo. The paper presented mechanistic explanations of these effects through the dysregulation of the Hippo pathway. The YAP1 protein is the core protein of the Hippo pathway. The researchers examined the relationship between GPRC5A and YAP1 in pancreatic cancer cells. One of the strengths of this research was they looked at both normal tissues and adjacent tissues and compared those to pancreatic cancer cells. They demonstrated that YAP1 expression was positively related to GPRC5A expression. They also showed that there was downstream gene activation on several pathways.

Another strength of this paper was that it used both up-regulation and a knockdown of the YAP1 and compared this to GPRC5A up and down-regulation. They reported this as evidence of dysregulation of Hippo signaling by GPRC5A. The authors pointed out that overexpression of YAP1 only partially counteracted the effects of GPRC5A knockdown. They also discussed that when they downregulated YAP1, the result was only to reduce its expression without influencing GPRC5A expression. Research seemed to be contradictory and was not well explained in this paper. G-protein coupled receptors, in general, promote the generation of cAMP. GPRC5A knockdown decreased cAMP, and overexpression increased cAMP expression. The authors felt that this research showed that GPRC5A positively or negatively affected tumorigenesis based on expression levels and downstream regulatory molecules. They stated that GPRC5A promoted cancer progression regardless of the upregulation or downregulation and cells. This paper was somewhat confusing and unclear because it didn't clarify the mechanisms or functions of this G-coupled receptor protein. The authors point out that GPRC5A is markedly increased in pancreatic cancer compared to adjacent and normal tissues. They pointed out that GPRC5A functions differently in different cancers. The authors showed that crosstalk between the Hippo pathway and the GPRC5A-cAMP-CREB-YAP1 axis does have some function in pancreatic cancer progression. The limitations and biases are to what extent is this a factoring causation? And is it seen in the majority of cancers? It also demonstrated the difficulty of using CAR T-cell therapy, as discussed in the Hagel et al. (2023) paper. The complicated intrinsic nature of pancreatic cancer cells makes it difficult to find an antigen to target the cancer cells. In addition, there is a complex interaction between the multiple signaling pathways.

As pointed out in the paper by Zhang et al. (2023)(14), the crosstalk between M2 macrophage and pancreatic cancer cells via exosomes and the release of the miRNAs (miR-193b-3p) acts on the TRIM62 system to decrease ubiquitination of c-MYC. Crosstalk increases proliferation, migration, and invasion of the pancreatic cancer cells and glutamine uptake. Although this carries the potential therapeutic target by acting against the exosomes and the miRNA, it also points out the complexities of the alterations to the tumor microenvironment and its alteration of the immune response. The researchers began their investigation using a specific cell line SW1990 of human pancreatic cancer cells. They isolated macrophages from pancreatic tumors and identified M0 and M2 types of macrophages using surface markers. The SW1990 cells were then grown and a culture medium free of exosomes. The M2 macrophage increased proliferation, migration, invasion, and glutamine uptake. The authors subsequently isolated the exosomes produced by the M2 macrophage. The use of an exosome inhibitor reverses the effects of the M2 macrophage. Subsequent evaluations were done on the exosomes of both the M0 and M2 types. Measurements were taken of the micro RNAs from the exosomes. Expression levels of miR-193b-3p show the most significant increase. The miR-193b-3p was then transfected into exosomes, and these again demonstrated increased proliferation, migration, invasion, and glutamine uptake in the SW1900 cell line.

The research indicated that the miRNA was a primary factor in exosome communication inducing tumor expansion. The authors' analysis revealed that the target of the miR-193b-3p was the TRIM62 (tripartite motif-containing protein 62) protein. TRIM 62 is a protein that acts on protein binding activity, transcription co-activator activity, and ubiquitin-protein transferase activity. TRIM62 regulates the regulation of the miR-193b-3p effects. This research demonstrated that by silencing the TRIM62, which again promoted the proliferation, migration, invasion, and glutamine uptake by the SW1990 cell line. As for the confirmation, an inhibitor of miR-193b-3p inhibited proliferation, migration, invasion, and glutamine uptake and increased expression of TRIM62.

Further research showed that TRIM62 acts to induce c-Myc ubiquitination. The authors showed that overexpression of c-Myc reversed the TRIM62-inhibited proliferation, invasion, migration, and glutamine uptake in the SW1990 pancreatic cancer cell line. TRIM62 levels were significantly decreased in pancreatic cancer cells, and miR-193b-3p was increased considerably. Patients with high levels of miR-193b-3p or c-Myc had low survival rates. Those patients with high TRIM62 levels had higher survival rates. The authors predicted a correlation between the miR-193b-3p, TRIM62, and c-MYC levels and patient prognosis. A weakness in this study is that it was only in the SW1990 pancreatic cancer cell line. A further question

is whether other miRNAs have the same effects or contribute to the proliferation, migration, invasion, and glutamine uptake. This paper mentioned other miRNAs found in this group of exosomes but did not elucidate any further. A limitation of this study and needs to be investigated further.

The oncogene *MYEOV* in pancreatic cancer, investigated by Tange et al. (2023)(16), again pointed out the potential for a biomarker or a therapeutic target in treating pancreatic cancer. It pointed out complexities of the nature of pancreatic cancer in that the methylation of its promoter inhibits the expression of this gene in normal cells. Demethylation of the promoter was required to cause overexpression of this gene seen in pancreatic cancer. Increased gene expression is a prognostic factor for poor prognosis. Expression of the gene led to increased amino acid and nucleic acid production by activating folate metabolism genes in pancreatic cancer. The knockout of the *MYEOV* gene caused the restoration of repressors of c-MYC and mTORC1.The complicated gene expression demonstrates the highly complex nature of pancreatic cancer and its multiple intrinsic factors that make it resistant to numerous therapeutic measures. The authors of this study utilized The Cancer Genome Atlas (TCGA), a catalog of genetic mutations in cancer based on genome sequencing and bioinformatics, from the National Human Genome Research Institute and the Center for Cancer Genomics of the National Cancer Institute. This research showed that increased expression of *MYEOV* correlated with shorter disease-specific survival, worse recurrence-free survival, and progression-free survival. The database also showed that MYEOV expression is extremely low in normal tissues and upregulated in cancer tissues. There was overexpression of *MYEOV* in several different types of cancers. Expression of the gene was inversely correlated to methylation levels, and *MYEOV* expression was suppressed by DNA methylation both in normal pancreatic tissue and in some pancreatic cancer cells. They confirmed the effect of *MYEOV* on the proliferation of several pancreatic cancer cell lines by a knockdown of the gene, which showed a decrease in the proliferation. In addition, the authors showed that the knockdown of *MYEOV* led to the down-regulation of c-Myc and mTORC1 target genes. Activation of both c-Myc and mTORC1 contributes to tumor growth and survival by regulating folate metabolic activity. And again, this activity was downregulated by *MYEOV* knockdown. The authors pointed out that this suggested that *MYEOV* contributed to c-MYC and mTORC1 function in pancreatic cancer. One of the concerns with this research is that they noted that *MYEOV* promoter methylation is comparable in some pancreatic cancer specimens to normal pancreatic tissue. Although it was evident that some cancers that decrease methylation levels increased expression of *MYEOV*, this was not true for all pancreatic cancers. The authors concluded that suppression of *MYEOV* contributed to the poor prognosis of pancreatic cancer via activation of the folate cycle and the c-Myc and mTORC1 pathways. It is still unclear how the MYEOV protein acts to contribute to tumor progression.

In the paper by Lu et al. (2023)(17) again, they pointed out the complexities of the tumor microenvironment by looking at long non-coding RNAs. In addition, they looked at developing a predictive model based on this lncRNA. They created a risk score model to determine whether immunotherapy or conventional chemotherapy would better serve the patient. In their particular risk score model, they decided that based on eleven different lncRNAs, low-risk patients had a better prognosis and lower somatic mutation rates and responded better to immunotherapy. In the patients they determined to be high risk, they found better sensitivity to chemotherapy. The research points out the extreme complexity of the tumor microenvironment with considerations of micro-RNAs and long non-coding RNAs contributing to the modulation of the immune response to these types of tumors. The authors of this paper again utilized The Cancer Genome Atlas, Genotype-Tissue Expression, and International Cancer Genome Consortium databases as sources for their pancreatic cancer gene expression data. The researchers used several mathematical and statistical models to develop a predictive model for the lncRNAs.

The authors identified eleven tumor microenvironment-related lncRNAs, which they used to construct a risk score that showed good prognostic prediction ability. The purpose of this research was to find a risk score model that would allow lncRNAs to act as biomarkers for early diagnosis, develop targeted therapy in pancreatic tumors, and explore the pathogenesis of pancreatic cancer. These researchers also discussed the fact that the tumor microenvironment is crucial for developing new treatments. In their analysis, the authors found that lncRNAs are increased in immune cell activation, extracellular matrix, and collagen. They discussed that these lncRNAs promote T cell activation, extracellular matrix organization, regulation of T cell activation, collagen-containing extracellular matrix, and extracellular matrix structural constituents. These biological functions are essential in the pathogenesis of pancreatic cancer. In particular, they pointed out that interaction between immune cells in the tumor cells is crucial for tumorigenesis, local invasion, and distant metastasis. Collagen density affects tumorigenesis invasion and metastasis, and the extracellular matrix is essential in participating in various stages of carcinogenesis. The authors point out the limitations of this study in that all the data they evaluated were from open-source databases with limited samples.

Nevertheless, the authors emphasize the importance of the tumor microenvironment in developing and progressing

pancreatic cancer. The risk score model may show utility in predicting prognosis and response with various chemotherapeutic modalities. Indeed part of this analysis involved evaluating the potential effectiveness of different anticancer drugs depending on the stage of cancer development.

Finally, the authors of the paper by Hagel et al. (2023)(19) investigated the intrinsic tumor resistance in pancreatic cancer cells. To do this, they utilized a genome-scale CRISPR-Cas9 analysis in mesothelin (MSLN)-expressing pancreatic cancer cells. These researchers developed a chimeric antigen receptor (CAR) T-cell specific for mesothelin (MSLN). The first part of their experiments showed that loss of the MSLN eliminated the ability of the CAR T-cell they had developed to kill pancreatic cancer cells. MSLN is a glycosylphosphatidylinositol-anchored (GPI) membrane protein. The next phase of their experiments involved evaluating the GPI anchor function related to resistance to MSLN CAR T-cell killing. The author's experiments indicated that the GPI anchor biosynthesis or transfer machinery perturbation conferred resistance to the MSLN CAR T-cell killing.

Further observation showed that death receptor pathways FAS/FAD contributed to MSLN CAR T-cell killing, and TNF/NFκB promoted MSLN CAR T-cell evasion. In the final part of their investigations, they looked at the loss of the TFAP4 (a transcription factor activating cancer binding protein), which induces an increase in p65, a transcription factor NFκB. The study was well-done in showing the intricacies of avoiding T-cell killing by pancreatic cancer cells. The authors pointed out that their research may indicate a tumor cell-intrinsic state that might significantly affect CAR T-cell therapy for solid tumors.

Conclusions

The take-home message again is that the complex nature of pancreatic cancer will require a multipronged approach to any therapeutic measures. The tumor microenvironment is of prime importance in dealing with these tumors. The dense structural alterations in these tumors that inhibit both T-cell infiltration and infiltration of chemotherapeutic and other immunotherapeutic measures represent one facet of this complex issue. Alterations in the expression of various surface antigens on the pancreatic cancer cells and the presentation of various chemical modulators via exosomes from different cell types make this a further complicated problem. Both micro non-coding RNAs and long non-coding RNAs are modulators of the immune response and pancreatic cancer intrinsic gene expression. Crosstalk between pancreatic cancer cells and the stromal tissue surrounding the tumor cells makes this an extremely complex system that needs to be clearly understood if we intend to make significant advances in dealing with this deadly disease.

The tumor microenvironment is critical to many solid tumors, particularly pancreatic cancer(20, 21). This series of papers highlight different facets of this microenvironment and some current research involved in clarifying this complex system's nature. The documents by Fang et al. (2023)(8) and Hagel et al. (2023)(19) demonstrated the complex interactions between receptors on the surface of cancer cells and the microenvironment. Zhang et al. (2023)(15) and Lu et al. (2023)(18) pointed out the complex interaction between micro-RNAs and exosomes, which act in signaling between cells and the environment. All the studies showed the intricate interaction between the genetics of the cancer cells and the microenvironment. A much better understanding of the interactions between immune cells and pancreatic cancer cells will be critical in developing new treatments and directing focused immunotherapies against pancreatic cancer

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