Preface for Series: science on pancreatic cancer

Pancreatic cancer (PC) is the deadliest cancer. Despite recent progress on understanding the biology of PC, there are very limited treatment options for this aggressive cancer. The 5-year overall survival rate is less than 8%. The past few decades have seen an increase of PC-associated deaths. It is estimated that PC will be the second leading cause of cancer-related death by 2030 in the United States. Among all the options for PC, surgery remains to be the most effective treatment. However, less than 20% of PC patients are eligible for surgery, most patients had lost the opportunity for surgery as they presented with advanced stages at the time of diagnosis. For those patients with advanced PC, unfortunately, there is little, if any treatment was made available in the past few decades. In this special issue, we have eight expert review articles that cover cancer biology, tumor microenvironment and surgical resection of PC. This special issue aims to address the most recent research progress that have been made on understanding the initiation and progression of this deadly disease, in hopes of bridging the gap between basic science advances and clinical practice in PC.

The issue starts with an outstanding mini-review by Dr. Minoti Apte that summarized the current research progress regarding the role of pancreatic stellate cells (PSCs) in driving PC progression and discussed the potential therapeutic targets that mediate the crosstalk between PSCs and cancer cells. The interaction between PSCs and PC cells can be regulated by a variety of cytokines and exosomes. Co-injection of PSCs with PC cells led to larger tumor formation than PC cells alone. PC tumor cells induced activation of PSCs can produce large amounts of fibronectin, collagen, and cytokines resulting in pancreatic fibrosis and immunosuppressive microenvironment. Identifying PSCs as the major source of collagen and extracellular matrix (ECM) in PC microenvironment is critical on understanding the induction of desmoplasia, one of the hallmarks of PC. PSCs induced desmoplasia can establish a physical barrier to the delivery of chemotherapy and other targeted therapies. Meanwhile, PSCs can promote the mobility and metastasis of PC cells by inducing epithelial mesenchymal transition (EMT). Furthermore, PSCs contribute to immune-suppressive microenvironment by recruiting the infiltration of myeloid-derived suppressor cells (MDSCs) and mast cells, while suppressing the infiltration of cytotoxic $CD8^+$ T cells. These studies indicated that unravelling the underlying mechanism of the crosstalk between PC tumor cells and PSCs may facilitate the design of new clinical trials treating PC and translate the basic scientific discoveries into patient care.

The next review article by Dr. Takaori and colleagues discussed the difference in genetic profiles and biology characteristics between different PC mouse models. There are few reliable mouse models that can effectively trace the origins of pancreatic ductal adenocarcinoma (PDAC). In this review, they summarized the current molecular subtypes of PDAC, including the key molecular pathways that are involved in the development of PDAC. For example, KRAS, p53, SMAD4, and CDKN2A are the most common mutant genes that drive the initiation and progression of PC. But how these mutant genes promote the development of precursor lesions to PDAC remains undefined. They also discussed the genetic alterations and cellular origins of precursor lesions of PC. Another highlight of this study is that they compared the mouse model with organoid model, which showed wide applications in screening and developing potential new drugs for PDAC.

There are some exciting breakthroughs recently on cancer immunotherapy, which has emerged as a promising new treatment strategy for several cancers, such as melanoma, lung cancer, etc. But immunotherapy has limited survival benefit on PC. Dr. Qiang Shen and colleagues discussed the crosstalk between different cell types (tumor cells, stroma cells, myeloid cells, and immune cells) in tumor microenvironment that mediate the immune evasion of PC. Cytotoxic $CD8^+$ T cells can effectively suppress cancer cells, especially those with high tumor mutation burden (TMB). However, PC cells have a relatively low tumor mutation burden. With that being said, the quantity and quality of neoantigens that contribute to the initiation of adaptive immune response in PC are extremely low. Meanwhile, PC tumor cells can escape immune surveillance by establishing an immune-suppressive network with the stroma cells and myeloid cells in tumor microenvironment. Thus, different from some "immune-active" tumors like melanoma, PC is characterized with an "immune-suppressive" microenvironment. PD-L1 is recognized as a biomarker to predict the efficacy of immune-check point inhibitors. But the expression of PD-L1 in PC patients with KRAS mutation is comparable to those with wild type KRAS, which may explain the low response rate of PD1/PD-L1 treatment in PC. Thus, novel markers to predict the response to immunotherapy are warranted in PC.

Pancreatic neuroendocrine tumor (PNET) is the second most common PC that have totally different tumor behaviors

from PDAC. PNETs account for about 7% of total pancreatic tumors. Dr. Nancy Du and colleagues summarized the recent research progress on the biology and treatment strategies of PNETs. Meanwhile, they discussed the most common mouse models for PNETs, including GEMMs and xenograft models. PNETs include two subtypes, one is functional tumors which can produce hormones, and the other one is nonfunctional tumors which cannot produce hormones. About 45–60% of PNETs are nonfunctional tumors, which do not produce large amounts of hormones. Thus, most patients with PNETs are diagnosed at advanced stages with dismal prognosis.

Cancer metabolism is a hot topic that has drawn a lot of attentions in recent years. Researches of PC metabolism mainly focus on lipid metabolism, glutamine metabolism, and oncogenic signaling induced cachexia, which have led to the discovery of some key coordinators that regulate the metabolic network to fuel the rapid growth of PC. Dr. Jin Wang and colleagues discussed the aberrant metabolism and reprogrammed microenvironment that may dampen the efficacy of targeted therapies in PC. As a dominant genetic alteration in over 90% of PC, mutant KRAS signaling can drive the modulation of central metabolic pathway, resulting in increased glycolytic rates and enhanced lipogenesis, etc. Understanding the aberrant metabolic network and the underlying mechanisms is critical for identifying potential therapeutic targets and developing novel treatment strategies for this devastating disease. The researches mentioned above, along with emerging evidence that metabolic reprogramming plays a vital role in fueling the growth of PC with KRAS mutation, are creating innovative paths toward better treatment for PC.

Identifying the origins of PDAC is important for PC treatment, because ductal or acinar derived tumorigenesis has totally different genetic profiles, which may determine their response rates to different treatment options, especially targeted therapy and immunotherapy. Dr. Pei Wang and colleagues reviewed the current status on identifying the origins of PDAC. Ductal cells are believed to be the original cells that are responsible for initiating the process of PDAC, most of which have ductal morphology. However, recent studies showed that acinar cells are more vulnerable to KRAS and p53 mutation and are more likely to develop PanIN and subsequent PDAC. There are also evidences that demonstrated both acinar cells and ductal cells can develop PDAC under certain genetic profiles or external stimulation. What makes the situation more complicated is that acinar cells can transit to ductal metaplasia which may also be responsible for the initiation of PDAC. Although tumors derived from different cell lineage have different genetic context and biology functions, the histological characteristics are similar. Both groups can develop PDAC. But ductal derived PDAC are more invasive than that derived from acinar, and distant metastasis are more likely seen in ductal derived PDAC.

For those who have lost the opportunity for surgical resection, endoscopic therapy may serve as an alternative treatment option. The last two articles discussed the current advances on endoscopic therapy for PC. Dr. Mou's group compared the efficacy and safety between endoscopic ultrasound (EUS) guided biliary drainage (EUS-BD) and endoscopic retrograde cholangiopancreatography (ERCP) guided biliary drainage (ERCP-BD) by summarizing the results from randomized controlled studies (RCTs). The major endpoints of these studies are the efficacy and the incidence of complications. The efficacy was comparable between the EUS-BD and the ERCP group. But EUS-BD has lower incidence of treatment related complications such as pancreatitis and reintervention than that of the ERCP group, which indicates that EUS-BD should be applied as first-line treatment option for PC patients with obstructive jaundice.

EUS is widely used in PC diagnosis and treatment. EUS based radiofrequency ablation has emerged as a less invasive treatment option for advanced-stage PC patients. EUS shows its advantage over the traditional ERCP when it comes to biliary drainage, for the treatment of obstruction of jaundice, as ERCP has difficulty in reaching the papilla. Sun *et al.* summarized the current progress of endoscopic therapy in the treatment of PC patients at advanced stages. These patients may develop severe symptoms due to the growth of tumor mass, which include but not limit to jaundice, pain, etc. The aim of endoscopic therapy is to alleviate the symptoms caused by PC. Endoscopic therapy may improve the quality of PC patients by alleviating the symptoms, but it when it comes to improving the overall survival of PC, we still need novel therapeutic strategies.

The authors that contributed to this special issue are leading experts on this field. The editorial staff of *Annals of Pancreatic Cancer* appreciate their tremendous efforts in composing this special issue. I would like to close by congratulating all the authors. Their contributions are sparking a revolution of further understanding the biology of PC and charting novel paths toward more effective strategies for PC treatment.

Acknowledgments

Footnote

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