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Advances in Pancreatology: 2016

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This year progress has been made in understanding the mechanisms as well as the treatments for both pancreatic neoplasia and inflammatory pancreatic diseases. Advances in genetic sequencing, bioinformatics, and tissue procurement have resulted in more detailed descriptions of the molecular and functional changes that underlie pancreatic adenocarcinoma (PDA). As described in the review by Leach and Sinha (1), molecular analysis of this cancer in several studies has shown distinct patterns which were translated into meaningful categories. Thus, PDA can now be classified as featuring networks characteristic of: 1) Squamous neoplasms, 2) Early Development, and 3) Endocrine and Exocrine differentiation enriched. Molecular signatures of immune cells, most prominently B and T cells, resulted in another category, the Immunogenic Pancreatic Cancer phenotype. Distinct patterns of stromal cell activation were also observed. An exciting feature of these classifications is that they appear to correspond to patient survival. With this data in hand, it will be interesting to see whether these different tumors subtypes will exhibit distinct therapeutic responses.

In the review by Saluja and co-authors (2), advances in therapeutic non-surgical approaches that show promise for PDA are reviewed and include a history of the development of current therapies. Based on the molecularly determined pancreatic cancer phenotypes discussed above and by Leach and Sinha, there is reason to be hopeful that some of the newer approaches to therapy, such as enhancing drug access by reducing the barrier presented by the extracellular matrix, may be useful in select patient subgroups. The dramatic responses observed in melanoma with check-point inhibitors suggest that detailed knowledge of tumor antigens and well as local immunosuppressive mechanisms could greatly enhance future pancreatic cancer immune therapies. This contribution also summarizes preliminary studies on a drug known as Minnelide, a promising new compound that may have activity against a range of neoplasms, including PDA. Though the precise mechanism of action for this drug remains unclear as discussed by the authors, its effects on the stroma and deposition of extracellular matrix and cancer stem cells have been described in PDA animal models. A phase I study is being performed by the developers of Minnelide and data from this trial should be available in the near future.

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In Hartmann and Friess's overview of pancreatic surgery (3), issues related to inflammatory and neoplastic diseases are reviewed. As found with other illnesses, management of acute pancreatitis by a multi-disciplinary team at high-volume centers is associated with a lower risk of death from acute pancreatitis. Delaying surgical intervention by first using supportive therapy and then using invasive procedures in a step-wise manner with increasing levels of invasiveness has become central to the management of with suspected or documented infected pancreatic necrosis. Several short and long-term follow-up studies of different surgical approaches for the treatment of chronic pancreatitis pain have been completed and are reviewed. First, though there appears to be advantages of organ-sparing procedures (such as the Beger and Frey procedures which themselves seem to have similar outcomes) over the short-term with respect to pain relief and other parameters, in the long-term advantages of organ preservation approaches may be lost. Second, compared to pancreatoduodenectomy, duodenum preserving pancreatic head resections may result in a better quality of life. Third, the authors favor recent studies advocating for surgical intervention early in the course of chronic pancreatitis for those with pain and dilated pancreatic ducts. This review also commented on the challenges of managing pancreatic cystic neoplasms and underscored the importance of considering comorbidities using the Charlson comorbidity index or other such scales in selecting patients for surgery. Though the surgical approaches to pancreatic cancer remained similar over this review period, active discussion on the use of neoadjuvant (chemo or chemo-radiation therapy prior to surgery) remains an important topic of active but challenging investigation that has been expertly reviewed (4).

In Dr. Park's review (5) of clinical chronic pancreatitis (CP), genetic and other mechanistic advances are discussed, along with approaches to diagnosing and treating this disease. Though minor mutations in CFTR have been linked to pancreatitis, an important study he cites by Maleth and co-workers demonstrated that alcohol can selectively suppress the function and levels of this key transporter in pancreatic epithelial cells. Diagnosis of CP, particularly in those with early disease, continues to be a challenge. Trikudanathan and colleagues (cited by Dr. Park) showed a poor correlation between EUS features and pancreatic histology, raising questions about our current diagnostic criteria. Whether EUS elastography will lead to diagnose and detect chronic pancreatitis is still under study.

A role for long-term antioxidants in CP treatment has been the subject of a number of studies, but a consensus is lacking for benefit in part due to heterogeneity in both therapies and patient characteristics. High rates of osteoporosis in CP was again reported, but the etiology of this important disease complication remains unclear and correlation with serum vitamin D levels have been weak. Trials need to determine whether CP subjects with osteoporosis are also cigarette smokers because of the known effect of smoke toxins on bone mineralization and fracture risk. Finally, a multi-center consortium assembled and funded by the United States National Institutes of Health will examine relationships between CP, pancreatic cancer, and diabetes. In that context, Mohapatra and co-workers (6) provided an excellent summary relating diabetes to a recently described pancreatic exocrinopathy which is characterized by prominent pancreatic fibrosis, but lacks other features of chronic pancreatitis. Since fibrosis is known to underpin the development of other GI neoplasms, such as liver cancer, it is interesting to speculate response that this might contribute to the increased risk of pancreatic cancer in diabetics.

Dr. Elmunzer's review (7) on endoscopic approaches to pancreatic disease reviews issues related to diagnosing and treating pancreatic disease. He provides a practical and detailed discussion of the use of self-expanding metallic stents for the treatment of biliary obstruction caused by chronic pancreatitis. Development of other specialized technologies are also reviewed. Though surgical vs endoscopic drainage for CP are discussed in a manner similar to that in Friess's review on pancreatic surgery, the two authors provide contrasting views that may reflect their expertise and experience.

In the final contribution, Dr. Gukovskaya and co-authors (8) update our knowledge of the cellular and molecular mechanisms of pancreatitis. Known for their central role in degrading intracellular organelles, proteins, and lipids, autophagy is required for normal cell function. A series of studies has documented autophagic-lysosome dysfunction in experimental and human pancreatitis; the mechanism of the dysfunction remains under study. Changes in pancreatic acinar cell calcium signaling have longed been linked to the initiation of acute pancreatitis. Newly described inhibitors of calcium-entry can correct the disease-related calcium signals in model systems. They have now been found to reduce pancreatitis responses in experimental models and could be clinically useful. Finally, a large epidemiologic study showed a convincing decrease in pancreatitis risk for subjects receiving simvastatin. These findings are reminiscent of the growing body of data suggesting that statins substantially reduce the progression of chronic liver disease and raise the possibility that this class of drugs might have value with reducing disease severity or progression in recurrent acute or chronic pancreatitis.

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