Pathophysiology of Pancreatic Adenocarcinoma

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Abstract

Pancreatic ductal adenocarcinoma (PDAC), most common pancreatic epithelial malignancy, is found to have a poor prognosis as compared to other solid tumors and is believed to become one of the major cause of cancer related deaths in future. Most of cases which are being diagnosed are of people above 65 and 60% of these cases are at an advanced level. Moreover, 5 year survival rate is not more than 10%. PDAC is intrinsically resistant to chemotherapeutic drugs due to a dense stromal reaction which affects the delivery of drugs. So, surgery serves as the only treatment for early pancreatic cancer stages. For advanced and metastatic stage, treatment is in the form of adjuvant chemotherapy (with or without radiotherapy). There is a need to develop novel molecular markers for the clinical management of pancreatic cancer patients because the existing markers like CA19-9 shows some limitations, thus there is no marker available for routine use. Advancement in the field of molecular biology have increased our understanding on pathogenesis of pancreatic adenocarcinomas. Mutations in K-ras oncogene and tumor suppressor genes are found to have a link with pancreatic cancer.

Introduction

Pancreatic ductal adenocarcinoma is the most common type of pancreatic cancer, accounting for approximately 90% of the total cases.[1] PDAC is most common in Africans and Americans and occurs mostly between age of 60-80. Several environmental risks are also associated with this such as smoking, alcohol consumption, high calorie food, obesity, physical inactivity and so on. Chemicals such as DDT, gasoline and benzidine also increases the risk of pancreatic cancer.[2] Tumor in most of the pancreatic cancer are located in the head region of the pancreas (65%). These types of tumor causes pancreatitis and jaundice. some tumors are also present in body (15%) and the tail (10%) region of the pancreas and these ones show even worst prognosis.[3] PDAC is diagnosed at 2-4 cm and if it is located distally diagnosis is even more difficult.[4] Most PDAC tumors of head region metastases to stomach, duodenum, colon, peritoneum, gall bladder and jejunum. Tumors of tail region can invade into intestines, adrenal glands and spleen.

Histopathology

Pancreatic ductal adenocarcinoma are the epithelial gland-forming neoplasms in which dense fibrous tissue grows around the tumor and this phenomenon is known as desmoplastic reaction. The desmoplastic reaction associated with PDAC, consisting of lymphocytes, collagen and myofibroblasts, is responsible for its firm consistency. The extent of differentiation lies between well formed glands and non oriented cells either singly or in the form of solid sheets. The glands of PDAC grow in haphazard manner, disturbing the normal branching of benign glands.
The architecture of normal pancreas is acini around the ducts and these are distinguished by vessels. In case of infiltrating adenocarcinoma the glands are not properly organised and are found near to vessels but without interfering the acini.[5]

![Image](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6624347/#r2)

**Figure 1:** (A) Gross morphology of PDAC after axial slicing. (B) Histomorphology of PDAC.

**Immunohistochemistry and Cytology**

Many cytokeratins like CK 7, CK8, CK13, CK18, CK 19 and CK20 are expressed in PDAC. Many glycoprotein tumor antigens like, CA19-9, CEA, DUPAN-2, B72.3 and CA125 are also expressed in PDAC conditions. Expression of these glycoprotein tumor antigens are useful to distinguish between infiltrating adenocarcinoma and reactive glands. PDAC also shows the expression of high molecular weight glycoproteins like MUC1 and MUC5. Low power examination for cytology studies of pancreas includes its cellular composition, cellularity, cohesiveness and presence of mucin, inflammation and necrosis. High cellularity is done for well differentiated carcinoma so it is not important for poorly differentiated carcinoma. Smears prepared for such studies should only contain ductal cells. Cells in PDAC are arranged either in sheets or 3D clusters or occurs singly. In case of well differentiated carcinoma the arrangement is in the form of sheets whereas in poorly differentiated condition the cells occurs singly. In less differentiated carcinoma the nuclear to cytoplasmic ratio of the cells is high which results in increased nuclear density.

**Molecular genetics**

There are several genes which are responsible for the pathogenesis of pancreatic adenocarcinoma. Such types of genes fall under three categories: DNA mismatch-repair genes, tumor-suppressor genes and oncogenes. The most common genetic abnormality which occurs in most of the pancreatic adenocarcinoma is the mutation of Kras gene, wherein the Kras gene in converted to an oncogenic form and it occurs in only low grade PanINs (pancreatic intraepithelial neoplasia). Other abnormalities includes amplification of genes, shortening of telomerase, inactivation of tumor suppressor genes like SMAD4/DPC4, p16/CDKN2A and TP53, where alteration in p16/CDKN2A being the most common. Mutation in TP53 and SMAD4 occurs late in high grade PanINs. There are mutations in genes involved in Fanconi anemia pathway such as BRCA2 which encodes a proteins responsible
for the repair of DNA cross-linking damage is also associated with PDAC. A protein encoded by PALB2/FANCN gene interacts with BRCA2 protein, so a mutation in PALB2 also accounts for PDAC. Hereditary pancreatitis also imposes a risk of pancreatic cancer wherein mutations in SPINK1 and PRSS1 occurs. Along with the driver genes, some epigenetic changes also contributes in the development of PDAC. These changes includes dis regulation in histone modifications and DNA methylation.[6][7][8][9]

**Prognostic markers**

The prognosis of PDAC, with 5 year survival rate not more than 10%, is very poor as compared to other solid tumors. A prognostic marker, known as ROR2 (RTK-like orphan receptor 2), is important in terms of clinical management of pancreatic adenocarcinoma and can be potentially used as a therapeutic target. A certain type of cell population known as Cancer associated fibroblasts (CAFs) are responsible or the initiation and progression of the tumor. A cell membrane protein known as CD146 is found in many cancers including pancreatic adenocarcinoma. With an interaction with the cancer cells the CD146 expression in CAF is decreased which promotes tumor progression. Methylation of CDKN2A is associated with an enhanced risk of PDAC and can also serve as a prognostic marker.[10]

Expression of DDX3 and Nectin-2 are responsible for the poor prognosis of pancreatic cancer in patients. Their expression is generally higher in PDAC than in benign pancreatic tissues, normal pancreatic tissues and peritumoral tissues. Another prognostic marker, namely ezrin, is also responsible for the progression of PDAC.[11]

**Variants of PDAC**

There are a lot of PDAC variants (morphologically), out of which some shows almost same molecular pathogenesis, biological behaviour and prognosis and others have different prognosis and molecular background. Variants having same molecular pathogenesis are anaplastic carcinoma, adenosquamous carcinoma, micropapillary carcinoma, undifferentiated carcinoma having osteoclastic giant cells, large-duct type carcinoma and signet ring cell carcinoma of the pancreas. Whereas, medullary carcinoma, hepatoid adenocarcinoma and colloid carcinoma of pancreas are the variants showing different molecular pathogenesis. Adenosquamous carcinomas have 30% squamous component of the total tumor mass whereas glandular part is minimal. Though they show a similar pathogenesis, their molecular prognosis is even worse as compared to normal PDAC[12]. Anaplastic carcinomas also shows a poor prognosis than normal PDAC. Some of these carcinomas shows **SMARCB1** mutations.[13] Micropapillary carcinomas shows similarity to that of breast carcinoma and is made up of densely packed cluster of cells within the clefts.[14] signet-ring cell carcinomas are rare in nature and for its diagnosis more than 50% of the tumor must contain signet ring cells.[15] Large-duct type carcinoma forms large and dilated ducts and shows a similar survival rate of patients as classical PDAC.[16] Colloid carcinomas are often related to high grade intestinal type intra-ductal papillary neoplasms and contains extracellular mucin aggregates. These carcinomas shows GNAS and KRAS mutations and have 5 year survival
rate of 50% showing better prognosis as compared to classical PDAC. Hepatoid carcinoma is rare and shows similarity to hepatocellular carcinoma. It also exhibits mutations in Fign gene

![Image of variants of PDAC](https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6624347/#r21)

**Figure 2:** Variants of PDAC. (A) Histomorphology of adenosquamous pancreatic carcinoma. (B) immunohistochemistry of adenosquamous pancreatic carcinoma. (C) Histomorphology of anaplastic pancreatic carcinoma. (D) Immunohistochemistry of anaplastic pancreatic carcinoma. (E) Histomorphology of colloid carcinoma. (F) Histomorphology of colloid carcinoma.

Precursors of PDAC

Precursor lesions of Pancreatic ductal adenocarcinoma are classified into two groups: microscopic and macroscopic precursors.

Microscopic precursors include atypical flat lesions (AFL) and pancreatic intraepithelial neoplasia (PanIN). AFL are tubular lesions of small size which consists of flat to cuboidal atypical epithelia and are enclosed by reactive stroma.[17] PanIN are mucinous papillary intraepithelial neoplasms of small size (less than 0.5 cm in diameter). They can be further classified on the basis of grade of nuclear and cellular atypia as low grade PanIN or high grade PanIN.[18] Mutations in some genes are responsible for the induction of pancreatic intraepithelial neoplasia, wherein low grade PanIN includes KRAS mutations and high grade PanIN includes SMAD4 and CKN2A TP53 mutations.[19][20]
Macroscopic lesions include mucinous cystic neoplasms (MCN), intraductal tubulopapillary neoplasms (ITPN) and intraductal papillary mucinous neoplasms (IPMN). MCN are larger cysts that can be uni-locular or multi-locular, having thick and calcified cyst covering. These type of neoplasms occurs mostly in middle aged women and in the distal part of the pancreas. Low grade MCN consists of monolayer of mucinous epithelium cells with an underlying ovary like stroma. High grade MCN usually contains some papillary projections. KRAS mutations are shown by both low grade and high grade MCN whereas GNAS mutations are absent in these neoplasms.[21] ITPN is a rare PDAC precursor are connected to the duct system of the pancreas. Mostly they are high grade lesions and does not includes KRAS and GNAS mutations but shows PIK3CA mutations more frequently.[22] IPMN are large (more than 1cm in diameter) mucinous papillary intraepithelial neoplasms. They are classified on the basis of their site of origin as main duct, branch duct and combined duct and on the basis of their immuno-profile and histomorphology as gastric type, intestinal type, pancreatobiliary type and oncocytic type. Both GNAS and KRAS mutations are significantly more common in IPMN. More specifically, GNAS mutations occurs in intestinal subtype and KRAS mutations occurs in the gastric subtype. RNF43 mutations (normally coding for a protein having ligase activity) also occurs in IPMN.[23]

Future aspects

The main focus for future research in pancreatic cancer should be on biomarkers so that early diagnosis of the disease can be done. Also, certain markers which help to screen patients that are likely to respond to particular and specific therapies and treatments should be focussed upon. Recent research that has made the preclinical models available, which helps to summarise the complexity of this disease have made the discovery of novel targets and markers possible. A recent research on new sequencing technologies can be studied and exploited for novel treatments of pancreatic cancer. Understanding molecular pathways of pancreatic cancer should pave a way to develop novel therapeutics targeting only specific pathways for more specific result. Immunotherapy is one of the promising approach for the successful treatment of melanoma and is believed to become a therapeutic reality for the treatment of pancreatic cancer also. These immunotherapies may use vaccines, antibodies or oncolytic viruses.

References


