

Histological Structure of Pancreas in Chronic Pancreatitis and The Role of Pancreatic Stellate Cells

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ABSTRACT

Background: Chronic pancreatitis is a progressive inflammatory disease that causes damage and fibrosis of the parenchyma of pancreas, thus leads to endocrine and exocrine dysfunction.

Objective: The goals of this review were to analyze morphological alterations in pancreatic tissue during chronic pancreatitis and this analysis addresses the effect of pancreatic stellate cells (PSCs), on chronic pancreatitis, and collagen fiber deposition.

Results: This review also discussed the different immunohistochemical markers for PSCs. Alpha smooth muscle actin (α -SMA) is an excellent marker for activated PSCs. Transforming growth factor beta (TGF β) is an important profibrogenic cytokine that appears to act by stimulating collagen production by PSCs.

Conclusion: It was concluded that chronic pancreatitis caused a significant and progressive serious effects on the acinar cells, duct system, and islets of Langerhans in the form of intracellular vacuolations, decreased zymogen granules, pyknotic nuclei and thickening of the duct wall, and extensive fibrosis. It is hypothesised that during pancreatic injury, PSCs are activated and proliferated exhibiting positive staining for the cytoskeletal protein α -SMA, and synthesising amounts of extracellular matrix proteins, particularly collagen.

Keywords: Chronic pancreatitis, pancreatic stellate cells, fibrosis.

INTRODUCTION

Chronic pancreatitis is a very progressive inflammatory disease altering the pancreas' normal structure and functions. It can be preceded by episodes of acute inflammation in a previously injured pancreas, or as chronic disease with persistent pain or malabsorption. It is characterized by an irreversible damage to the pancreas as distinct from reversible changes in acute pancreatitis ⁽¹⁾. Chronic pancreatitis is the commonest cause of pancreatogenic diabetes followed by pancreatic neoplasia ⁽²⁾. Loss of endocrine function by beta-cells in the Langerhans islets is considered to be the main causative factor of diabetes mellitus, although several studies have also suggested insulin resistance as a possible additional mechanism ⁽³⁾.

Among the causes of chronic pancreatitis are excessive alcohol intake, autoimmune disorders, intraductal obstruction, idiopathic pancreatitis, tumors, ischemia, and calcific stones ⁽⁴⁾.

The relationship between etiologic factors, genetic predisposition, and progression of the disease requires further clarification. Also, recent research indicates that smoking may be a high-risk factor to develop chronic pancreatitis. In a small group

of patients, chronic pancreatitis has been shown to be hereditary. Almost all patients with cystic fibrosis have established chronic pancreatitis, usually from birth. Cystic fibrosis gene mutations have also been identified in patients with chronic pancreatitis but in whom there were no other manifestations of cystic fibrosis. Obstruction of the pancreatic duct because of either a benign or malignant process may also result in chronic pancreatitis ⁽⁵⁾. Most of patients with this disease have poor quality of life and the management is still mainly supportive.

General appearance and microscopic structure of pancreas:

Pancreas is surrounded by a very thin connective tissue capsule that invaginates into the gland to form septa, which serve as scaffolding for large blood vessels. Further, these septa divide the pancreas into distinctive lobes and lobules ⁽⁶⁾.

The bulk of the pancreas is composed of pancreatic exocrine cells and their associated ducts. Embedded within this exocrine tissue are roughly one million small clusters of cells called the islets of Langerhans, which are the endocrine pancreatic cells ⁽⁷⁾ (Fig. 1).



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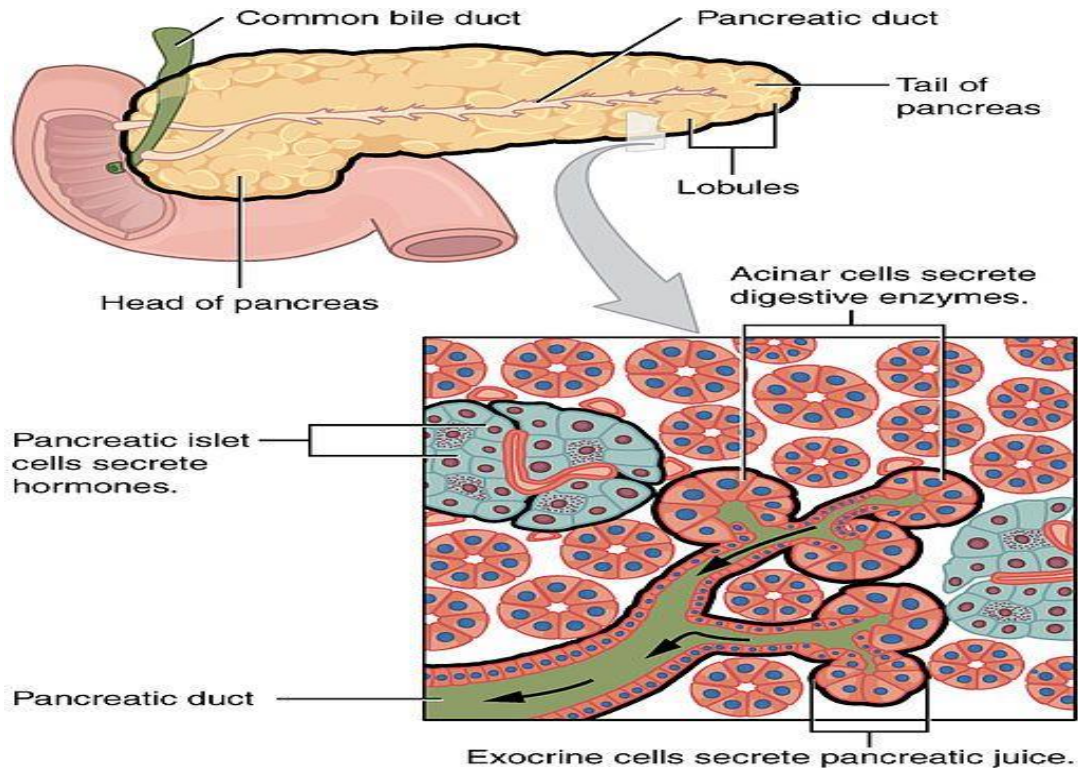


Fig. (1): Histological structure of the pancreas⁽⁸⁾.

The exocrine part:

The exocrine pancreas is formed of acini and duct system. It is classified as a compound tubuloacinous gland. The cells that synthesize and secrete digestive enzymes are arranged in grape-like clusters called acini. The acinar cells are tall,

pyramidal or columnar epithelial cells, with broad bases on a basal lamina and apices converging on a central lumen. In the resting state, numerous eosinophilic zymogen granules fill the apical portion of the cell. The basal portion of the cells contains one or two centrally located, spherical nuclei and extremely basophilic cytoplasm⁽⁹⁾ (Fig. 2).

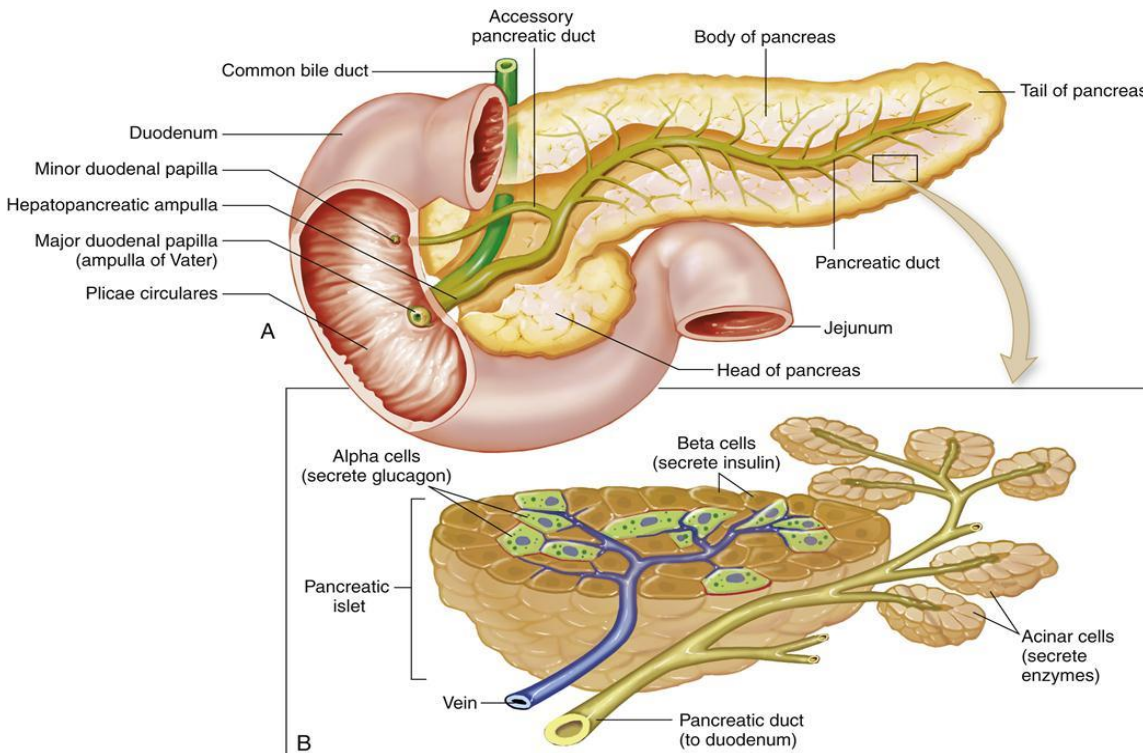


Fig. (2): Exocrine system of the pancreas⁽¹⁰⁾.

The duct system is formed of:

Intercalated ducts receive secretions from the pancreatic acini. They have flattened cuboidal epithelium that extends up into the lumen of the acinus to form what are called centroacinar cells ⁽¹¹⁾.

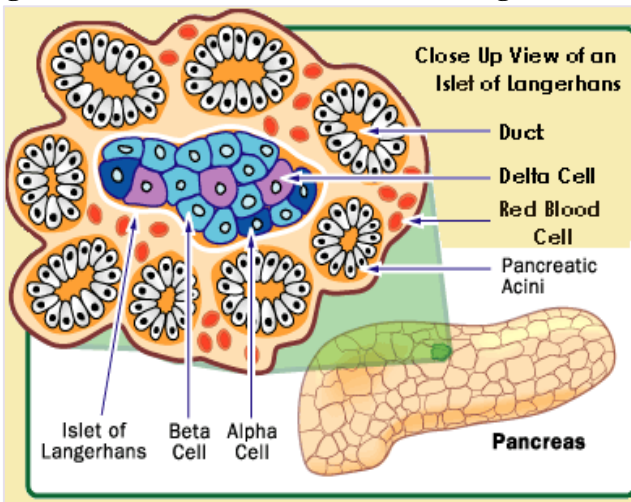
Intralobular ducts have a classical cuboidal epithelium and, as the name implies, are seen within the lobules. They receive secretions from the intercalated ducts ⁽¹²⁾. **Interlobular ducts** are found between the lobules within the connective tissue septae. They vary considerably in size. The smaller forms have a cuboidal epithelium, while a columnar epithelium lines the larger ducts. Interlobular ducts transmit secretions from the intralobular ducts to the major pancreatic duct ⁽¹³⁾.

Endocrine pancreas:

The endocrine portion is called pancreatic islets because it is separated from the cells of the exocrine pancreas by thin connective tissues ⁽¹⁴⁾.

The islets of Langerhans appear as pale staining spherical bodies among the serous acini. They are more in the tail region of pancreas and are made of branching cords of endocrine cells of the following types: Alpha (α) cells form 20% of the total population, they are large cells with eosinophilic granules found mainly at the periphery of the islet and secrete glucagon that increases blood glucose level. Beta (β) cells form 70% of the population, they are small cells with basophilic granules found mostly in the center and secrete insulin which decreases blood glucose level. Delta (δ) cells form 5% of the population; they secrete somatostatin which inhibits secretin of growth hormone, glucagon, and insulin ⁽¹⁵⁾ (Fig. 3). Other cell types are vasoactive intestinal peptide (VIP) secreting cells and mixed secreting cells (enterochromaffin cells) ⁽¹²⁾.

Fig. (3): Different cells in the islets of Langerhans ⁽¹⁶⁾.



Histopathological structure of pancreas in chronic pancreatitis:

Variable degenerative changes with loss of normal lobular architecture and necrosis of most acinar cells with altered ductal morphology, inflammatory cell infiltration and intense fibrosis. The degenerative changes observed affected not only the exocrine pancreas but also the endocrine portion. These changes were in the form of dilated congested blood vessels, extravasation, intracellular vacuolations, decreased zymogen granules, pyknotic nuclei and thickening of the duct wall.

Effect of chronic pancreatitis on collagen fiber deposition:

Fibrosis is a hallmark of chronic pancreatitis ⁽¹⁷⁾. Oxidative damage is believed to play a role in stimulation of pancreatic fibroblasts, leading to increased pancreatic fibrosis ⁽¹⁸⁾.

Mallory trichrome stained sections can reveal excess collagen fibers around the blood vessels, duct system, in between the degenerated pancreatic acini and within the islets of Langerhans. The pancreatic fibrosis can be referred to the generation of free radicals that in turn could activate the pancreatic satellite cells (PSCs).

Role of pancreatic stellate cells in pancreatic fibrosis:

Pancreatic stellate cells play a vital role in extracellular matrix formation. In experimental studies, it has been reported that the balance between newly synthesized extracellular matrix and its degradation is involved in regeneration process of the pancreas ⁽¹⁹⁾.

In normal pancreas, quiescent pancreatic stellate cells (PSCs) can be identified by staining for the cytoskeletal protein desmin, a stellate cell selective marker. PSCs are found in a periacinar location, with long cytoplasmic processes encircling the base of pancreatic acini (Fig.4).

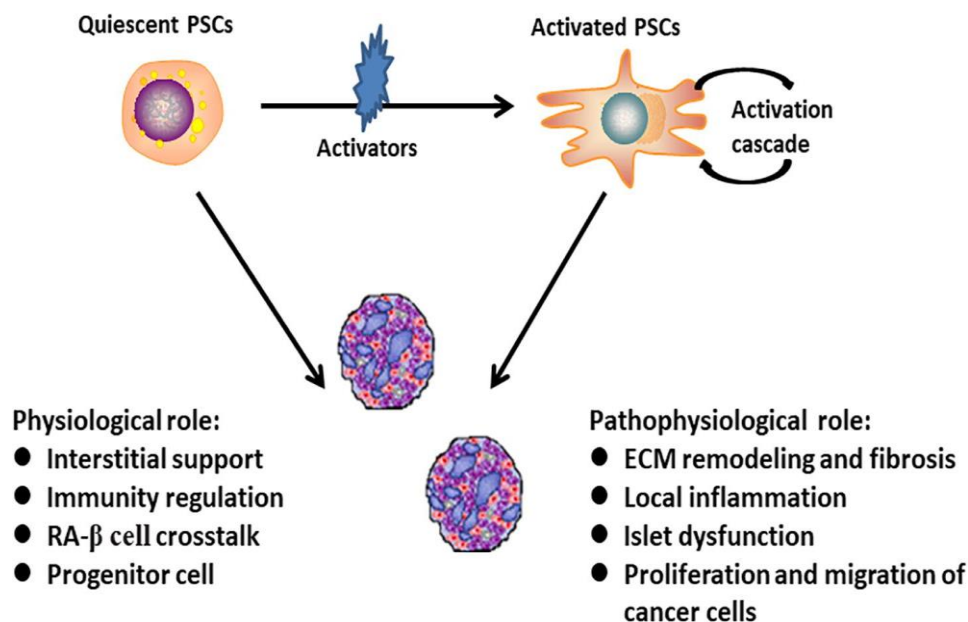


Fig. (4): Role of pancreatic stellate cells in pancreatic fibrosis⁽¹⁹⁾.

Alpha smooth muscle actin (α -SMA) is an excellent marker for activated PSCs⁽²⁰⁾. It is hypothesised that during pancreatic injury, PSCs are activated that is, they proliferate, transform into a myofibroblastic phenotype which exhibits positive staining for the cytoskeletal protein α -SMA, and synthesise and secrete increased amounts of extracellular matrix proteins, particularly collagen. Therefore, Omary *et al.*⁽²⁰⁾ reported a significant increase in α -SMA positive cells in cerulein model of chronic pancreatitis. Aoki *et al.*⁽²¹⁾ studied the pancreatic fibrosis and reported the presence of α -SMA positive cells in periductal, periacinar, and interlobular areas of pancreas that represented activated PSCs.

Transforming growth factor beta (TGF β) is an important profibrogenic cytokine that appears to act by stimulating collagen production by PSCs⁽²²⁾.

McCarroll *et al.*⁽²³⁾ and Gong *et al.*⁽²⁴⁾ demonstrated the up-regulation of TGF β mRNA levels in chronic pancreatitis, so it's suggested that the pancreatic cells could be a significant cellular source of TGF β in pancreatic fibrogenesis. The proposed mechanisms by which chronic pancreatitis occurs include the occurrence of acinar necrosis that lead to activation of cytokines as TGF β with subsequent activation of PSCs⁽²³⁾.

CONCLUSION:

It was concluded that chronic pancreatitis caused a significant and progressive serious effects on the acinar cells, duct system, and islets of Langerhans in the form of intracellular vacuolations, decreased zymogen granules, pyknotic nuclei and thickening of the duct wall, and extensive fibrosis. It is hypothesised that during pancreatic injury, PSCs are activated and proliferated exhibiting positive staining for the

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