PANCREAS ANATOMY, PHYSIOLOGY AND GENETICS

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Outline

Overview

Pancreatic Anatomy
- Gross anatomy
- Microanatomy

Pancreatic Physiology
- Acinar cell
- Duct cell
- Neurohormonal control
- Meals and system integration

Pancreatic Genetics
- Mendelian disorders
- Complex disorders
- Genetic test in interpretation

Questions

References
1. **Overview**

The pancreas is a vital organ that plays a central role in digestion and metabolism of nutrients. **Major functions** of the pancreas include: secretion of **digestive enzymes** into the duodenum for the breakdown of complex proteins, carbohydrates, lipids and nucleic acids, secretion of **bicarbonate** into the duodenum in order to neutralize the acidic chyme exiting the stomach, and secretion of **islet cell hormones** into the circulation to control systemic metabolism of nutrients after absorption.

2. **Gross Anatomy**

A. **Relationship of the Pancreas to other systems**

In the adult the pancreas lies **behind the peritoneum** of the posterior abdominal wall and is in an oblique orientation. The head of the pancreas is flanked by the duodenum on the right. The body is ventral to the **2nd-4th lumbar spine** (making it susceptible to blunt trauma) and dorsal to the stomach.

The **blood supply** to the pancreas can be quite variable, but comes, in general from branches of the gastroduodenal, superior mesenteric and splenic arteries. These form anterior and posterior arcades which supply the pancreatic head. The body and tail are supplied predominately by branches of the splenic artery.

**Venous drainage** of the pancreas is through the **splenic vein** and directly into the **portal vein**. More importantly, the portal vein courses through the pancreas and the splenic vein lies directly under the pancreas making them susceptible to injury (e.g. thrombosis) during episodes of severe acute pancreatitis. Thrombosis of the splenic vein cause the splenic blood to drain through the short gastric veins, which results in **gastric varices**. Treatment of bleeding varices is a splenectomy.

**Nervous innervation** comes from the sympathetic and parasympathetic nervous system. **Sympathetic** nerves arrive through the greater and lesser splanchnic nerve trunks which arise from the 5th to the 9th thoracic spine level. Sensory nerves travel with the parasympathetic fibers. **Parasympathetic** innervation is through the **vagus nerve**. Both systems travel through the celiac plexus (although some sympathetic fibers may travel through the superior mesenteric ganglion). There are also **interneurons** that travel from the myenteric plexus of the stomach and duodenum to innervate the pancreas. The pancreas has an extensive array of **intrapancreatic ganglion** and postganglionic fibers that innervate ductal cells, acinar cells and islet cells. The **sympathetic nerves and enteropancreatic interneurons are inhibitory**, the **parasympathetic are stimulatory**, and **pain** fibers travel with the **sympathetic** system.

**Question #1**
B. Duct System

The exocrine pancreas utilizes an elaborate duct system linking every acinar cell to the intestine. In most patients there is a **main pancreatic duct** which is derived from portions of the dorsal bud (duct of Wirsung) and ventral bud (duct of Santorini). The main duct projects into the duodenum at the major papilla (*ampulla of Vater*), which is protected by the *sphincter of Oddi*. In a minority of patients the two original duct system remains patent with the ventral pancreas draining through the minor papilla. Failure of the two pancreatic duct systems to fuse results in **pancreas divisum** (see below).

Pancreas Development

**Dorsal and Ventral Buds**

The pancreas develops from two outpouchings from the duodenum during the 5th week of life (Figure 2). The ventral and dorsal buds rotate and merge forming the body of the pancreas during the 7th week of gestation. The dorsal bud forms the body and tail of the pancreas whereas the ventral bud will form the pancreatic head.

**Ductal System Malformation**

The ductal systems usually merge and join the common bile duct and empty into the duodenum through the *ampulla of Vater* (major papilla). In ~33% of people the accessory duct is patent and empties through the *duct of Santorini* via the minor papilla (Figure 1, above).

**Pancreatic divisum** In 5-10% of people the ducts do not fuse (Figure 3). Thus, the majority of the pancreas must drain through the narrow minor papilla. This condition is often associated with recurrent acute
pancreatitis – usually if the patient also has a mutation in a pancreatitis susceptibility gene such as CFTR or SPINK1.

Pancreatic divisum is typically divided into there types.

Type 1 (classic) - no connection at all; occurs in the majority of cases: 70%
Type 2 (absent ventral duct) - minor papilla drain all of pancreas while major papilla drains bile duct; 20-25%
Type 3 (functional) - filamentous or inadequate connection between dorsal and ventral ducts: 5-6%

Common Channel Syndrome (not discussed).

In some patients an abnormally long common pancreatobiliary channel occurs (>10 mm in children) (1). The junction remains outside the duodenal wall and is lacks the normal sphincter. This may result in pancreatobiliary reflux and injury to the extrahepatic bile duct. Clinical presentation may present as a choledochal cysts (below) or recurrent acute pancreatitis.

Choledochal Cyst (not discussed)

Choledochal cyst often present in childhood with RUQ pain and jaundice, but it may be an incidental findings during ERCP. They are more often seen in Asian countries. Surgical removal is the treatment of choice. The incidence of carcinoma in these cyst is very high.

Choledochal cyst are divided into three types:

1. cystic dilations of the entire extrahepatic duct,
2. saccular dilatation of portions of the duct,
3. cystic dilatation of the intraduodenal duct (choledochocele).

(Intrahepatic dilation is Caroli's disease.)

Annular Pancreas - usually is a band of pancreatic tissue that completely encircles the second portion of the duodenum. It may cause duodenal stenosis. Annular pancreas is a rare finding (~3/20,000 autopsies). The ventral bud may become fixed and fail to rotate. This hypothesis is supported by the usual finding of the duct encircling the pancreas from anterior to posterior around the right side to join the common bile duct. Other variants are also seen. Annular pancreas is seen with other congenital defects including intestinal malrotation, cardiac defects, Meckel's diverticuli, imperforate anus, and spinal defects. It is common in Down's syndrome. The classic presentation in a vomiting infant is the "double bubble" sign.

Ectopic pancreatic tissue (not discussed)

Ectopic pancreatitis tissue (pancreatic rest) is relatively common on careful histologic examination (1-14% of autopsy cases), but less commonly of clinical significance. Ectopic tissue is usually seen in the stomach, duodenum, and jejunum, but foci of pancreatic tissue have been reported throughout the GI tract. Pancreatitis or pancreatic cancer may occasionally develop from ectopic pancreatic tissue.
Microanatomy of the Exocrine Pancreas

The functional unit of the exocrine pancreas is the acinus (Fig 4). The acinar cells form the terminal end of a duct. The acinar cells are oriented so that the zymogen granules (containing digestive enzymes, etc.) empty into the lumen. Each acinus is supported by a rich blood and nerve supply. The most proximal (intercalated) duct cells secrete bicarbonate-rich fluid.

![Figure 4. The acinus is an organized group of acinar cells that empty into a duct formed by duct cells. (Slide 14)](image)

Acinar Cells – digestive enzyme secretion

The acinar cells make up the vast majority of the pancreatic mass, about 80% of total. They are polarized epithelial cells that have the machinery to make huge amounts of proteins, process them, and to secrete them upon stimulation.

The key features are rich rough endoplasmic reticulum (RER), numerous mitochondria that tend to surround the nucleus and form a barrier between the apical and basolateral poles, and zymogen granules – the pre-activated pancreatic digestive enzyme storage units.

![Figure 5. The Acinar cell. A diagram of the acinar cell demonstrating a polarized epithelial cell with the basolateral surface on the left, and the duct lumen on the right. (see text.]

**Duct Cell – bicarbonate secretion**

The ductal cells make up less than 5% of the total pancreatic mass, yet are responsible for the large volume of bicarbonate-rich pancreatic fluid. The **intralobular ductules** penetrate the acinus and are composed of smooth low cuboidal cells (centroacinar cells). The **interlobular duct** is formed by pyramid-shaped cells. The cells lining the **main pancreatic duct** are similar to the interlobular cells.

The duct cells are polarized epithelial cells with a basolateral and an apical surface. The **CFTR** molecule is only normally only on the apical surface facing the duct lumen. During secretion the tight-junction protein claudin-2 (CLDN2) surrounds the duct cells (like a gasket). Claudin-2 forms channels that allow water and sodium to cross into the lumen to join bicarbonate, which is secreted through the CFTR channel. **Pancreatic bicarbonate secretion is derived from the centroacinar and terminal duct cells in the proximal (upstream) ducts.**

**Pancreatic Physiology**

**Acinar Cell**

The acinar cell is polarized (Figure 6) with the paranuclear region rich in rough endoplasmic reticulum (RER) and the apical pole (far right side) dominated by zymogen granules. The acinar cell is a protein-synthesis factory, with the digestive enzymes being synthesized in the RER, transported through condensing vacuoles, and stored as zymogens (inactive digestive enzymes) in the apical granules. The **mitochondria** are critical for synthesis of ATP, and also regulate calcium concentration. Receptors are located on the basolateral membrane (left side).

![Figure 6. Acinar cell biology](image)

**Figure 6. Acinar cell biology.** Excitation of the acinar cell receptors by hormones / neurotransmitters on the basolateral surface results in calcium signaling. The results are zymogens synthesis and zymogen granule secretion. Intracellular calcium levels are maintained at optimal levels by calcium pumps on the endoplasmic reticulum, mitochondria and plasma membrane powered by ATP. Zymogen production is monitored for protein misfolding (e.g. from mutations), then to the golgi for packaging, and to the apical membrane for secretion. High concentrations of calcium at the apical pole is a risk for premature enzyme activation either in the zymogen granules, or other vesicles (not shown).
Pancreatic zymogen secretion begins with activation of acetylcholine/other receptors on the basolateral cell membrane (Figure 6). Stimulation leads to activation of second messenger signal pathways and intracellular calcium release. This results in increase in apical calcium levels with exocytosis of the zymogen granules, and nuclear signaling for gene expression to make more zymogens beginning in the RER, with transport through the golgi (for sorting) and into new zymogen granules.

High calcium concentrations within acinar cells can trigger trypsinogen activation and acute pancreatitis. Calcium is used as a second messenger for zymogen secretion, and calcium levels oscillate during secretion. Sustained intracellular hypercalcemia from hyperstimulation or other causes leads to premature trypsin activation in the apical pole of the acinar cell.

Mechanisms of intracellular hypercalcemia.

- Extracellular hypercalcemia with pancreatic stimulation (2).
- Acinar cell hyperstimulation (3).
- Luminal bile salts (4).
- Alcohol (increases sensitivity to stimulation (5), mitochondrial damage (6)).
- Drugs

Recent research shows that mutations within proteins that are produced in large amounts, such as trypsin (PRSS1) or carboxypeptidase A1 (CPA) result in misfolding, and activation of the unfolded protein response (UPR). This results in stress signaling, and is associated with the development of chronic pancreatitis.

Pancreatic Enzymes – Types of enzymes (slide 19)

One of the major purposes of the pancreas is to synthesize digestive enzymes and deliver them to the intestine where they plan a critical role in digestion. The digestive enzymes are usually synthesized in an inactive form and together they are called zymogens. Most of the enzymes, >75% by weight, are proteases. Some of the major enzymes are listed below.

<table>
<thead>
<tr>
<th>Table 1. Major Pancreatic Enzymes</th>
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<tbody>
<tr>
<td><strong>ENZYME</strong></td>
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<tr>
<td><strong>Pancreatic Proteases</strong></td>
</tr>
<tr>
<td>Trypsin</td>
</tr>
<tr>
<td>Cationic trypsinogen (PRSS1)*</td>
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<td>Anionic trypsinogen (PRSS2)</td>
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<tr>
<td>Mesotrypsin (PRSS3)</td>
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<td>(Trypsin IV ?)</td>
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<tr>
<td>Chymotrypsin-like protease (ref 53)</td>
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<tr>
<td>Chymotrypsinogen C (CTRC)*</td>
</tr>
<tr>
<td>Caldecrin (8).</td>
</tr>
<tr>
<td>Elastase (unclear which form is secreted)</td>
</tr>
<tr>
<td>Elastase 2A, 2B</td>
</tr>
<tr>
<td>Elastase 3A, 3B</td>
</tr>
<tr>
<td>Carboxypeptidase A</td>
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<tr>
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<td>--------------------------------</td>
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<tr>
<td>Carboxyl Ester Lipase (CEL)*</td>
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<tr>
<td>Phospholipase A2</td>
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<tr>
<td>Pancreatic Alpha-Amylase</td>
</tr>
<tr>
<td>Nucleases</td>
</tr>
<tr>
<td>Pancreatic Ribonuclease</td>
</tr>
<tr>
<td>Deoxyribonuclease I</td>
</tr>
</tbody>
</table>

* Indicates the enzymes for which genetic mutations have been linked with risk of chronic pancreatitis.

The key enzymes are trypsin, which regulates all of the other digestive enzymes, amylase and lipase, which are synthesized in their active form (and are used diagnostically based on the enzyme activity). The lipases (with colipase and bile salts) are important for lipid digestion.

**Function of Digestive Enzymes (10)** (not covered in lecture)

Pancreatic digestive enzymes generally target at large, complex macromolecules whereas intestinal brush border enzymes target simple molecules.

The salivary glands and pancreas make α-amylases. Pancreatic α-amylase attacks the interior α-1,4-glucose linkage of complex carbohydrates and starches to produce short dextrins. The brush border enzymes cannot digest starches, but only dextrins by maltase and isomaltase, and simple sugars (e.g. sucrose).

Ninety-five percent of dietary lipids in western diets are triglycerides, which cannot be digested by brush-border enzymes. Pancreatic triglyceride lipase cleaves the majority of fatty acids from dietary triglycerides, usually at the sn-1 and sn-3 positions. Pancreatic triglyceride lipase is inhibited by dietary proteins and bile, but the activity is restored with colipase. Carboxyl ester lipase has a broad substrate specificity, and is important in digesting cholesterol esters and in the absorption of vitamin A. A critical role for the other lipases has not been demonstrated.

Pancreatic proteases and gastric pepsin digest all of the complex dietary proteins into short peptides and amino acids for further digestion and absorption in the intestine. The most abundant enzyme is trypsin, which is produced in three forms. The most abundant is cationic trypsinogen, coded by the PRSS1 gene. Anionic trypsinogen (PRSS2) and mesotrypsinogen (PRSS3) are similar to PRSS1 in that they all attack at exposed arginine or lysine residues within a peptide chain (i.e. an enteropeptidase). Other proteases are categorized by the amino acid side chain they prefer, by the part of the peptide chain they attach, and by the type of catalytic site.
**Enzyme Activation Cascade**

**Trypsin** is the key enzyme controlling zymogen activation. The zymogens are usually inactive when they are secreted from the pancreas into the intestine. When *trypsinogen* comes in contact with *enterokinase*, an activation peptide is cleaved from *trypsinogen* (trypsinogen activation peptide; TAP), resulting in active *trypsin*. Trypsin then activates itself and the other zymogens by cleaving their corresponding activation peptides and digestion begins.

**Figure 7. Zymogen Activation Cascade**

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<table>
<thead>
<tr>
<th>Zymogen</th>
<th>Trypsinogen</th>
<th>Enteropeptidase</th>
<th>Enzyme</th>
</tr>
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<tbody>
<tr>
<td>Trypsinogen</td>
<td></td>
<td>Trypsin</td>
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<tr>
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<td></td>
<td>Chymotrypsin</td>
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<tr>
<td>Proelastase 2</td>
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<td>Elastase 2</td>
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<tr>
<td>Proprotease E</td>
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<td>Protease E</td>
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<tr>
<td>Procarboxypeptidase B</td>
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<td>Carboxypeptidase B</td>
</tr>
<tr>
<td>Prophospholipase A2</td>
<td></td>
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<td>Phospholipase A2</td>
</tr>
<tr>
<td>Procolipase</td>
<td></td>
<td></td>
<td>Colipase</td>
</tr>
</tbody>
</table>
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**Acinar cell: protection from trypsin activation**

Since active trypsin has the potential of prematurely driving the pancreatic enzyme cascade while the pancreatic enzymes are still in the pancreas, a number protective mechanism are employed to protect the pancreas and the body from autodigestion.

1) All digesting enzymes, (except lipase and amylase), are synthesized in inactive "pro"-enzyme forms, 
2) The activating enzyme (enterokinase) is physically separated from the pancreas and located in the duodenum and jejunum, 
3) Digestive enzymes are compartmentalized in the acinar cells within zymogen granules, 
4) Intracellular calcium concentrations are low, limiting trypsin activation and survival 
5) The acinar cells synthesize pancreatic secretory trypsin inhibitor PSTI / SPINK1 along with the digestive enzymes. If trace levels of trypsin activation occur in the zymogen granules, then PSTI / SPINK1 inactivates trypsin. 
6) Trypsin is destroyed by chymotrypsin C (CTRC) (9) 
7) Trypsin activity outside the acinar cell leads to leads to protease activated receptor (PAR) activation which protects acinar and duct cells during acute pancreatitis (11) 
8) The duct cells secrete a large amount of bicarbonate-rich fluid to flush digestive enzymes out of the pancreatic duct (where calcium levels are high). 
9) High bicarbonate levels in the pancreatic duct maintain trypsin in a trypsinogen conformation (i.e. inactive). 
10) The liver produces two inhibitors found in the blood, α1-antitrypsin, and α2-macroglobulin, which immediately inhibit any trypsin that leaks out of the acinar cells or ducts.
Acinar Cell: Functional Reserve.

The pancreas has enormous protein (digestive enzyme) synthesis capabilities that greatly exceed the amounts required for normal digestion. More than 90% of the pancreas must be lost before significant steatorrhea develops! (10% of normal test meal response is 30K IU or 90K USP units, as used with current replacements.) Thus, signs and symptoms of pancreatic failure based on failed digestion occur too late to save the pancreas (13). However, other effects of pancreatic enzyme deficiency develop prior to gross steatorrhea.

DUCT CELL PHYSIOLOGY

CFTR and Bicarbonate Secretion.

Ductal cell secretion

Duct secretion is highly responsive to stimulation. Figure 9 shows that at low flow rates bicarbonate concentration in pancreatic juice is similar to plasma. With stimulation with secretin or vasoactive intestinal peptide (VIP) the fluid volume markedly increases, bicarbonate concentration increases and chloride decreases.

CFTR and Bicarbonate secretion

Ductal cell bicarbonate secretion has been studied extensively. The ductal cells secrete bicarbonate that is predominately derived from plasma (93%) rather than intracellular metabolism (7%). The key elements are shown in Figure 10. Secretion begins with opening begins and ends with opening of the CFTR. CFTR is both a chloride and bicarbonate conducting anion channel and conductance is independently regulated (14). Mutations in CFTR cause cystic fibrosis (of the pancreas).
**Figure 10.** Duct cell model (15). Bicarbonate (HCO$_3$-) enters through the sodium bicarbonate cotransporter (NBC) and exits through CFTR. The NaK pump keeps the intracellular sodium low so that there is a continual electrochemical force driving bicarbonate into the cell through NBC.

**Question 2**

**Control of Pancreatic Secretion**

In humans, the pancreas is primarily under neural control. Stimulatory input comes from multiple locations and is mediated by several different hormones and neurotransmitters.

Traditionally, pancreatic secretion has been organized into three phases based on the stimulant and mediators of pancreatic stimulation with various contributions from each.

- **Cephalic phase** (25%) is initiated by the sight and smell of food.
- **Gastric phase** (10%) is caused by distention of the stomach.
- **Intestinal phase** is caused by food in the intestine eliciting the release of secretin and CCK into the circulation where it stimulates sensory (afferent) vagal fibers.

The afferent vagal nerves synapse in the brainstem on interneurons which receive hormonal and neural input from other sites. These connect to the motor (efferent) neurons which project onto ganglia within the pancreas. The postganglionic fibers fan out to the acinar cells, duct cells (and islets) which together stimulate pancreatic secretion. In addition, there may be some direct nerve connections between the myenteric plexus of the stomach and duodenum to the pancreas.

**QUESTION 3**

**Integrated neurohormonal control of pancreatic secretion** (see (16))

(Not Discussed)

**Figure 11.** The nervous system controls pancreatic zymogen secretion. Most stimulatory nerves are cholinergic with extrinsic innervation via the vagus and subsequent intrapancreatic-cholinergic nerves. Vagal stimulation matches maximal meal-stimulated pancreatic secretion. CCK is clearly the most...
important hormone stimulating pancreatic secretion, but in man, at physiologic concentrations, CCK stimulates pancreatic secretion by stimulating sensory vagal and intrapancreatic nerves because there are almost no CCK receptor on acinar cells. Integration of the pancreatic secretory control mechanism through the nervous system allows pancreatic secretion to be continuously adjusted depending on the size of the meal, the meal content, the rate of digestion, and external factors. In times of sudden stress or fear the sympathetic nervous system will inhibit pancreatic secretion and divert the pancreatic (and other visceral) blood flow to muscles and other organs. Also, funneling stimulatory input through a central integrative site helps prevent pancreatic hyperstimulation, which can cause acute pancreatitis.

Feedback Regulation of Pancreatic Secretion.

Figure 12 summarizes the major pathways for stimulation and feedback inhibition of pancreatic bicarbonate and enzyme secretion. Duodenal acidification causes release of secretin, which stimulates vagal-vagal and duct cell receptors to activate pancreatic duct cells, which in turn secrete bicarbonate rich fluid. The bicarbonate neutralizes the duodenal acid and the feedback loop is completed.

Duodenal proteins cause a competitive reduction in free proteolytic enzyme activity thereby leading to an increase in free CCK-RF. The CCK-RF stimulates CCK release into the blood. At physiological concentrations, CCK acts through vagal-vagal pathways to cause acetylcholine-mediated pancreatic enzyme secretion. The pancreas continues to secrete proteolytic enzymes until the duodenal protein and CCK-RF is digested and the free duodenal proteolytic enzyme activity rises, thus completing another physiologic important feedback loop. CCK and secretion may also have some direct effects within the pancreas.

Meals and System Integration

- Normally, food empties slowly from the stomach over 18 hours (i.e. breakfast is not gone before lunch is added)
- Pancreatic exocrine secretion is at 100% capacity while food is emptying
- With the first meal, vagal stimulation drives pancreatic exocrine and endocrine secretion (CCK, secretin)
- Hind gut hormones (PYY, GLP-1) respond to nutrients by slowing gastric emptying and motility (PYY, “ileal break”), while GLP-1 enhances beta cell function and insulin secretion.
- Asynchrony between gastric emptying, nutrient digestion, absorption and insulin delivery may lead to poor glucose control
Pancreatic Genetics

Genetics - Key Points.

- Pathogenic genetic variants act by:
  - Altering protein expression
  - Altering protein location
  - Altering protein function
  - Loss of function
  - Gain of function
  - Change of function

- Pathogenic genetic variants cause disease by:
  - Altering normal development (congenital)
  - Altering function (congenital or acquired)
  - Altering responses to stress or injury (acquired)

Pancreatitis Genetic Risk.

- Pancreatitis is a complex genetic disease:
  - Strong underlying genetic risk of recurrent acute pancreatic injury (susceptibility).
  - Strong underlying genetic risk of progression to fibrosis, pain, diabetes, cancer. (disease modifiers)
  - Environmental factors such as alcohol and smoking accelerate and worsen pancreatic disease
- Early knowledge of the basis of increased risk could be used to improve diagnostic certainty, identify syndromes and target therapy.
- Genetics is predicted to change pancreatic disease management from treating end-stage symptoms to minimizing the disease!

Mendelian Genetics

Trypsinogen Regulation

Figure 13 – Trypsin-SPINK1 complex

There are three key mechanisms for regulating trypsin activity at the molecular level.

- Synthesis and storage of trypsin in an inactive form as trypsinogen.
- Regulation by calcium, the trypsin on-off switch. The trypsinogen molecule has two calcium binding sites, one formed by the trypsinogen activation peptide (TAP), and the second near the autolysis loop.
- During inflammation there is production of a specific trypsin inhibitor, pancreatic secretory trypsin inhibitor (PSTI) or serine protease inhibitor, Kazal type 1, (SPINK1).
The acinar cell prevents trypsin activation by maintaining low calcium concentrations. Loss of any of these protective mechanisms inside the pancreas (through mutations of trypsinogen or other protective molecules, or inappropriately high calcium concentrations) leads to zymogen activation, pancreatic autodigestion and **acute pancreatitis**.

**Mendelian: autosomal dominant**

**Hereditary Pancreatitis.**

Hereditary pancreatitis (HP) is an *autosomal dominant* disorder characterized by recurrent acute pancreatitis (RAP), chronic pancreatitis (CP) and (PC) pancreatic cancer. The age of onset varies from 1 to ~40 years of age, with a median of 10 years. About 80% of individuals with the disease-causing mutation have acute pancreatitis by age 20. Forty to 50% HP patients with RAP will develop CP, and ~ 40% of those with CP develop pancreatic adenocarcinoma by age 70 years of age, although multiple factors modify the risk (17, 18).

A. **Etiology.**

The mutation responsible for HP was identified in the cationic trypsinogen gene (*PRSS1*) located on chromosome 7 (19). This two most common mutations are R122H and N29I. These are gain-of-function mutations causing prematurely activated trypsin to avoid destruction. Recently, genetic variants in the non-coding region of the *PRSS1-PRSS2 locus* were found to decrease trypsinogen expression and reduce risk of pancreatitis (20). Thus, increased trypsin activity increases risk of pancreatitis, decreased expression decreases risk.

B. **Definition.**

Hereditary pancreatitis is a subtype of *familial pancreatitis*. Familial pancreatitis refers to the observed occurrence of pancreatitis in family members with a frequency greater than expected by chance, with or without a genetic defect. Hereditary pancreatitis is defined by an autosomal dominant inheritance pattern consistent with a single gene mutation in all affected family members. The majority of HP families will have a *PRSS1* gain-of-function mutation.

C. **Diagnosis.**

HP should be considered in children or young adults with unexplained RAP or CP, especially if they have a family history of pancreatitis or pancreatic cancer. Genetic counseling is strongly recommended before and after genetic testing, since the results have strong prognostic implications for the patient, their family and descendents.

D. **Clinical course.**

The clinical course is complex and highly variable. All of the complications seen in other forms of chronic pancreatitis are seen in hereditary pancreatitis. In a recent study from France in 189 patients reported that the mortality rate in these patients was *similar* to that of the general population *if* they did not develop pancreatic cancer (21). The risk for pancreatic cancer was increased by smoking and diabetes (21).
The results of an important international study of hereditary pancreatitis provides the following rates of complications (18).

The cumulative risk at 50 years of age:
- exocrine failure 37%
- endocrine failure 48%
- pancreatic resection for pain 18% (lower for females)
- pancreatic cancer 44.0% (at 70 years from symptom onset)

E. Treatment.

In general, treatment for HP is similar to treatment for other forms of acute and chronic pancreatitis. There are no proven medical treatments for hereditary pancreatitis, although there are case reports that antioxidants may be helpful in reducing the frequency and severity of symptoms. Endoscopic and surgical treatment of complications provide benefits similar to the benefits seen with similar complications in other types of chronic pancreatitis.

**Islet Autotransplantation.** There is growing use of *pancreatectomy and islet autotransplantation* in patients with hereditary pancreatitis. The primary indication is disabling pain in the young. The best outcomes (pain free and insulin free) are in patient with the highest yield of islets, which is before the inflammatory process has destroyed the islets. A more controversial indication is the fear of pancreatic cancer in adults. The concern is that there is a high frequency of precancerous lesions in the pancreas of these subjects that may be transferred back to the patient along with the islets. Furthermore, the islet cell yield is usually low in patients with long-standing disease. To date, no cases of pancreatic cancer have been reported in older patients with hereditary pancreatitis and islet autotransplantation.

**Sentinel Acute Pancreatitis Event (SAPE)**
CFTR Molecule

CFTR is a regulated anion channel that is expressed on the proximal (upstream) duct cells immediately adjacent to the acinar cells. CFTR opens with duct cell stimulation, with direct activation by cAMP dependent phosphorylation and gated by the binding of ATP to the nucleotide binding domains 1 and 2 (NBD1, NBD2). Recent research shows that the CFTR channel changes from a chloride-preferring anion channel to a bicarbonate-preferring anion channel with WNK1-SPAK activation (22, 23).

Mendelian Recessive

Cystic Fibrosis (of the pancreas)

Cystic fibrosis is a syndrome characterized by pancreatic insufficiency in infancy, elevated concentrations of sodium chloride in sweat, progressive pulmonary disease in childhood. Other common complications are meconium ileus, male infertility from congenital bilateral absence of the vas deferens (CBAVD) and liver injury. Specific and aggressive treatment of pancreatic insufficiency with pancreatic enzyme replacement therapy (PERT), good nutrition, antibiotic and lung therapy has changed the prognosis for survival from <5 years to >50 years. Because of the treatment successes by the pediatricians, about half of all CF patients are now adults.

A. Etiology.

Cystic fibrosis is an autosomal recessive disease caused by severe mutations in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. CFTR is an anion channel for chloride and bicarbonate that is expressed on epithelial cells of the airways, intestinal tract, bile ducts, pancreatic ducts and vas deferens and strongly contributes to fluid secretion. Cystic fibrosis is the syndrome

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**Figure 15.** SAPE Model. A) Normal pancreas conditions exist in patients who may have multiple risk factors. B) A stochastic event triggers the sentinel (initial) acute pancreatitis episode. This activates the immune system. Genetic and environmental variable may affect the healing process leading to C) features of chronic pancreatitis. This allows the features to be viewed in chronologic orders, and allows specific problems to be anticipated and managed.
caused by mutations that alter or destroy of function of the CFTR. Mutations are classified by their effect on channel function. Major mutations in both CFTR alleles are required for loss of nearly all CFTR function and classical clinical symptoms. Mutations in other genes (modifier genes) make symptoms on specific organs worse.

B. Genotype-phenotype correlations.

The overall clinical picture in an individual case depends on the nature of the combined CFTR mutations, modifier genes, and environmental factors. About 70% of Caucasian patients with cystic fibrosis have a 3 base pair deletion of the phenylalanine -coding codon 508 (ΔF508, F508del). If one or both of the chromosomes have a mild CFTR variant (Class 4 or 5, see table) then the patient will have mild or atypical CF. Atypical CF is when some of the organs affected by the CF syndrome remain fully functional. Indeed, cases of idiopathic recurrent acute pancreatitis or chronic pancreatitis may be atypical CF in which only the pancreas is effected.

Table 2. Classification for CFTR mutations, and pancreatic dysfunction. (not discussed)

<table>
<thead>
<tr>
<th>Class</th>
<th>Mutation (example)</th>
<th>Defect</th>
<th>Pancreatic Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>W1282X</td>
<td>Synthesis</td>
<td>severe</td>
</tr>
<tr>
<td>2</td>
<td>ΔF508</td>
<td>Maturation</td>
<td>severe</td>
</tr>
<tr>
<td>3</td>
<td>G551D</td>
<td>Activation</td>
<td>severe</td>
</tr>
<tr>
<td>4</td>
<td>R117H, (R75Q)</td>
<td>Conductance</td>
<td>mild</td>
</tr>
<tr>
<td>5</td>
<td>IVS8 5T</td>
<td>Abundance</td>
<td>mild</td>
</tr>
</tbody>
</table>

C. Diagnosis.

The consensus of a Cystic Fibrosis Foundation panel suggested a diagnosis of cystic fibrosis could be made by the presence of one or more characteristic clinical features, a history of cystic fibrosis in a sibling, or a positive newborn screening test result with confirmation by laboratory evidence of CFTR dysfunction(24). Furthermore, they suggest that either sweat chloride or nasal bioelectrical responses should be abnormal on two separate days before the diagnosis is confirmed by these one of these methods(24). Genetic testing is also commercially available to confirm the clinical diagnosis (two severe mutations must be identified), but these results cannot be interpreted apart from the clinical context and functional testing - especially in cases with atypical symptoms. Mutational screening of the entire CFTR gene should be considered in atypical cases.

D. Clinical features.

Cystic fibrosis is diagnosed within the first year of life in over 70% of patients, in over 85% by age of 5 years, but 8% remain undiagnosed until after the age of 10 years. Median survival is now over 40 years with >95% living past age 15 years (25). Life expectancy of newly diagnosed children of >50 years. Chronic pancreatitis is the most predictable feature (nearly 100% with <15% having residual function), with lung disease and digestive complications being more variable.

There are **three clinical syndromes**. (slide 42)

- **Classic CF**: pancreatic insufficiency, abnormal sweat chloride, progressive lung disease, meconium ileus, male infertility (CBAVD), liver disease.
**Atypical CF**: like CF but milder symptoms

**CFTR-Related Disorders**: (CFTR-RD)
- Recurrent acute & chronic pancreatitis (CFTR + SPINK1)*
- Pancreatitis, male infertility, chronic sinusitis (CFTR-BD**) 

* CFTR/SPINK1 genotypes represents a complex disorder
** BD, bicarbonate conductance defective.

E. Treatment.

The treatment of CF centers on providing adequate nutrition (PERT and a healthy diet), lung therapy (often provided by the family), and vigilance in treating pulmonary infections. PERT is often calibrated to symptoms of abdominal pain and/or stool consistency, while diet is calibrated to growth and BMI (> 22 in women and >23 in men) (26). Multidisciplinary care is needed, and should be coordinated with a CF Center.

New medical treatments are in trials with drugs classified as “CFTR Correctors” (27). These agents do not correct the genetic defect, but rather allow the CFTR molecule to survive, mature and function.

### Complex Genetics

#### Genetic Testing

- **Mendelian Disorders (HP, CF):**
  - Testing used to confirm or establish a diagnosis in the setting of disease symptoms.
  - Genetic counseling is typically recommended prior to ordering the test, and to explain results
- **Complex Disorders: (RAP/CP syndromes):**
  - Increases or decreases the likelihood that an equivocal pancreatic structural or functional test, or pancreatitis-like symptoms is a true positive.
  - Helps identifies pathogenic pathways leading to RAP, and alters the likelihood that specific complications will occur (e.g. rapid fibrosis).
  - May be useful in predictive disease modeling and personalized (individualized) medicine

#### Genetic Variants Related to Trypsin
Figure 16. Mutations in at least 5 different genes have taught us the importance of the regulation of trypsin inside the acinar cell (top) and duct (lower right). Hereditary pancreatitis (HP) is an autosomal dominant disorder with early onset of recurrent acute and chronic pancreatitis and risk of pancreatic cancer caused by mutations in the cationic trypsinogen gene (PRSS1) on chromosome 7. Note that acute pancreatitis can also be triggered by lipase + triglycerides (not shown).

**SPINK1 mutations.** (not discussed)

Pancreatic secretory trypsin inhibitor (SPINK1) is a specific inhibitor trypsin. The primary site of SPINK1 expression is the pancreatic acinar cell. SPINK1 is an acute phase protein, with minimal expression under normal conditions, but at high levels after pancreatic injury to minimize continued damage by trypsin.

Mutations in SPINK1 confer significant risk to the development of chronic pancreatitis. The most common high-risk allele, defined by SPINK1 N34S, is present in ~1% of populations worldwide (i.e. ~68,600,000 people). Homozygous SPINK1 N34S mutations are seen in people with early onset chronic pancreatitis, with the disease phenotype being typical chronic pancreatitis and no other organ involvement. Heterozygous SPINK1 mutations are benign unless the patient has a mutation in another trypsin-regulating gene such as CFTR.

Genetic testing for SPINK1 mutations is available. If testing is done in a person with recurrent acute pancreatitis, then it predicts progression recurrent acute pancreatitis to chronic pancreatitis. If testing is done in an asymptomatic patient and is positive for a SPINK1 mutation, then there is almost no prognostic significance since these mutations are so common.
Selected References:


Pancreas Anatomy and Physiology

Questions

1. The most common cause of major GI bleeding in the years following severe acute pancreatitis without a pseudocyst is:
   - a. splenic vein thrombosis
   - b. hemosusus pancreaticus
   - c. portal vein thrombosis
   - d. splenic artery aneurism

2. Which of the following neural system inhibit pancreatic secretion?
   - a. vagal nerves
   - b. sympathetic nerves
   - c. postganglionic parasympathetic nerves
   - d. all nerves passing through the celiac plexus to the pancreas

3. Which of the following pancreatic digestive enzyme is not activated by trypsin?
   - a. trypsinogen
   - b. proelastase
   - c. enterokinase
   - d. amylase

4. The duct cells provide protection from unregulated trypsin activity through
   - a. PSTI secretion
   - b. SPINK1 expression
   - c. Regulation of calcium concentrations
   - d. CFTR-linked bicarbonate secretion

5. Which of hormone or neural transmitter is a major inhibitor of pancreatic fluid secretion?
   - a. Peptide YY (PYY)
   - b. Cholecystokinin (CCK)
   - c. Secretin
   - d. acetylcholine

6. Sonic hedgehog (Shh) is important with respect to the pancreas because:
   - a. Expression is necessary for pancreatic bud development.
   - b. Shh upregulates PDX1
   - c. Shh expression and the Shh receptor are important in pancreatic cancer development.
   - d. Shh stimulates digestive enzyme secretion.
7. Shwachman-Diamond Syndrome is associated with
   a. abnormal sweat chloride levels
   b. Down’s syndrome
   c. Recurrent acute pancreatitis
   d. Recurrent infections
   e. Chronic pancreatitis

8. Trypsin activity is controlled in the pancreas by all of the following except:
   a. low cyclic AMP levels
   b. CFTR related fluid secretion
   c. CFTR related bicarbonate secretion
   d. Low calcium concentrations
   e. elevated SPINK1 expression
Pancreas Anatomy and Physiology

Answers


2. B. Sympathetic nerves are important for pain and for inhibition of pancreatic stimulation. Parasympathetic nerves include the vagus and postganglionic nerves. Both sympathetic and parasympathetic pass through the celiac plexus. (Reference: Gray's Anatomy: The Anatomical Basis of Clinical Practice, 40th edition (2008), 1576 pages, Churchill-Livingstone, Elsevier)

3. A. Amylase and lipase are the two major pancreatic digestive enzymes that are synthesized in an active form, and therefore have no activation peptide. Enterokinase is an brush-border enzyme and not a pancreatic digestive enzyme. Enterokinase has one substrate: trypsinogen, which it activates to trypsin. (reference: Whitcomb DC, Lowe ME. Human pancreatic digestive enzymes. Dig Dis Sci. 2007 Jan;52(1):1-17).


5. A. Peptide YY is a hind-gut hormone found in high concentrations in the terminal ileum. It is also known as the “ileal-break” because it potently inhibits fore-gut activity including gastric emptying, intestinal transit (not motility), and pancreatic secretion. PYY appears to act both locally and in the brain-stem, although the latter site appears to be most important in pancreatic physiology. The other factors are all stimulatory – and acetylcholine is not a hormone. (Reference: Deng X, Guarita D, Pedroso M, Kreiss C, Wood P, Sved A, et al. PYY inhibits CCK stimulated pancreatic secretion through the area postrema in unanesthetized rats. Am J Physiol Regul Integr Comp Physiol. 2001;281(2):R645-53)

6. C. Sonic hedgehog is expressed throughout the developing gut except where the pancreatic buds are developing because in inhibits pancreatic development. Pancreatic cancer expresses Shh and the Shh receptor, suggesting escape from normal control mechanism. (Reference: Hebrok M, Kim SK, St Jacques B, McMahon AP, Melton DA. Regulation of pancreas development by hedgehog signaling. Development. 2000;127(22):4905-13.)

7. D. SDS is an autosomal recessive disease caused my mutations in the SBDS gene on chromosome 7. It is the second most common cause of pancreatic insufficiency in children, but NOT acute or chronic pancreatitis. Down’s syndrome is associated with annular pancreas, but not SDS. Clinical features of SDS include; skeletal abnormalities, growth retardation and cyclic neutropenia (resulting in recurrent infections) and an increased risk for myeloid leukemia. (Reference: Cipolli M. Shwachman-Diamond syndrome: clinical phenotypes. Pancreatology. 2001;1(5):543-8)