Molecular Mechanism of Pancreatitis

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Pancreatic Function in Health

I. Inorganic Constituents

- Aqueous, isotonic to plasma
- Formed in duct cells
- Consists of electrolytes and water

  Cations= Na^+ , K^+

  Anions = Cl^-, HCO_3^-

- Electrolytes are secreted; H20 enters passively along the osmotic gradient
- Proportion of Cl and HCO_3 is dependent on the flow rate

  High Secretory rate $HCO_3 > Cl$

  Low Secretory rate $HCO_3 < Cl$

- Fluid is initially hypertonic but water movement into lumen dilutes it

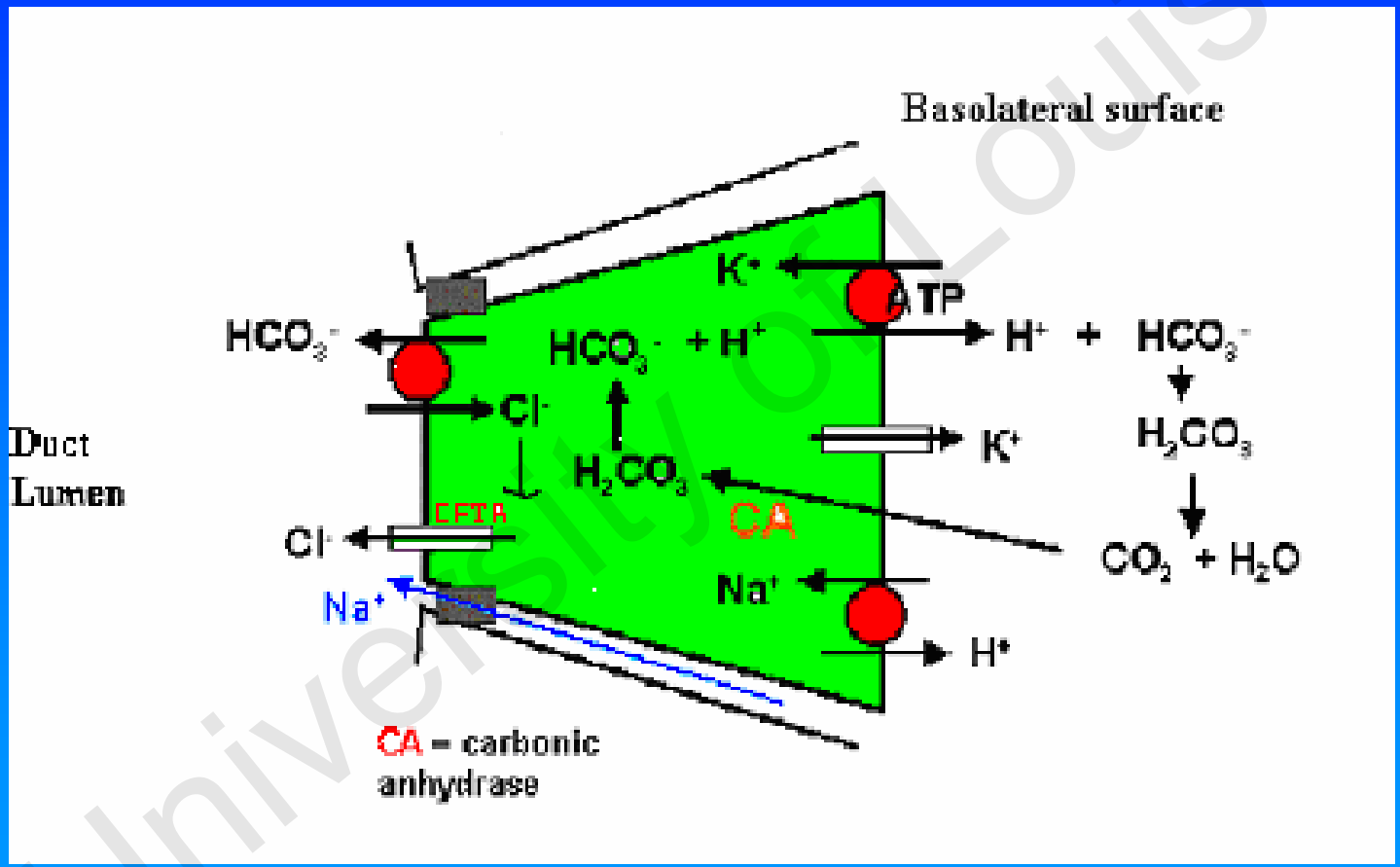
- Purposes of the water and ion secretions are to deliver digestive enzymes to the intestinal lumen and to help neutralize gastric acid emptied into duodenum

- Impaired secretion of ions and water causes impaired flow of proteins causing thick secretions to plug the ducts

Fluid secretion: Mechanism and Regulation

- Export of H^+ by Na^+/H^+ antiporter or H^+-K^+-ATPase
- CO_2 diffuses into cell
- Carbonic anhydrase catalyzes HCO_3 formation
- HCO_3 transported out in exchange for Cl^-
  Cl^- builds up in cell, exits by electrogenic channel =CFTR

Fluid secretion: Mechanism and Regulation



In Cystic Fibrosis

- Defective CFTR (Cl^- channel)
- HCO_3, Na^+, water secretion impaired
- Mucus buildup
- maldigestion due to duct obstruction, loss of enzyme delivery to duodenum

II. Organic Constituents

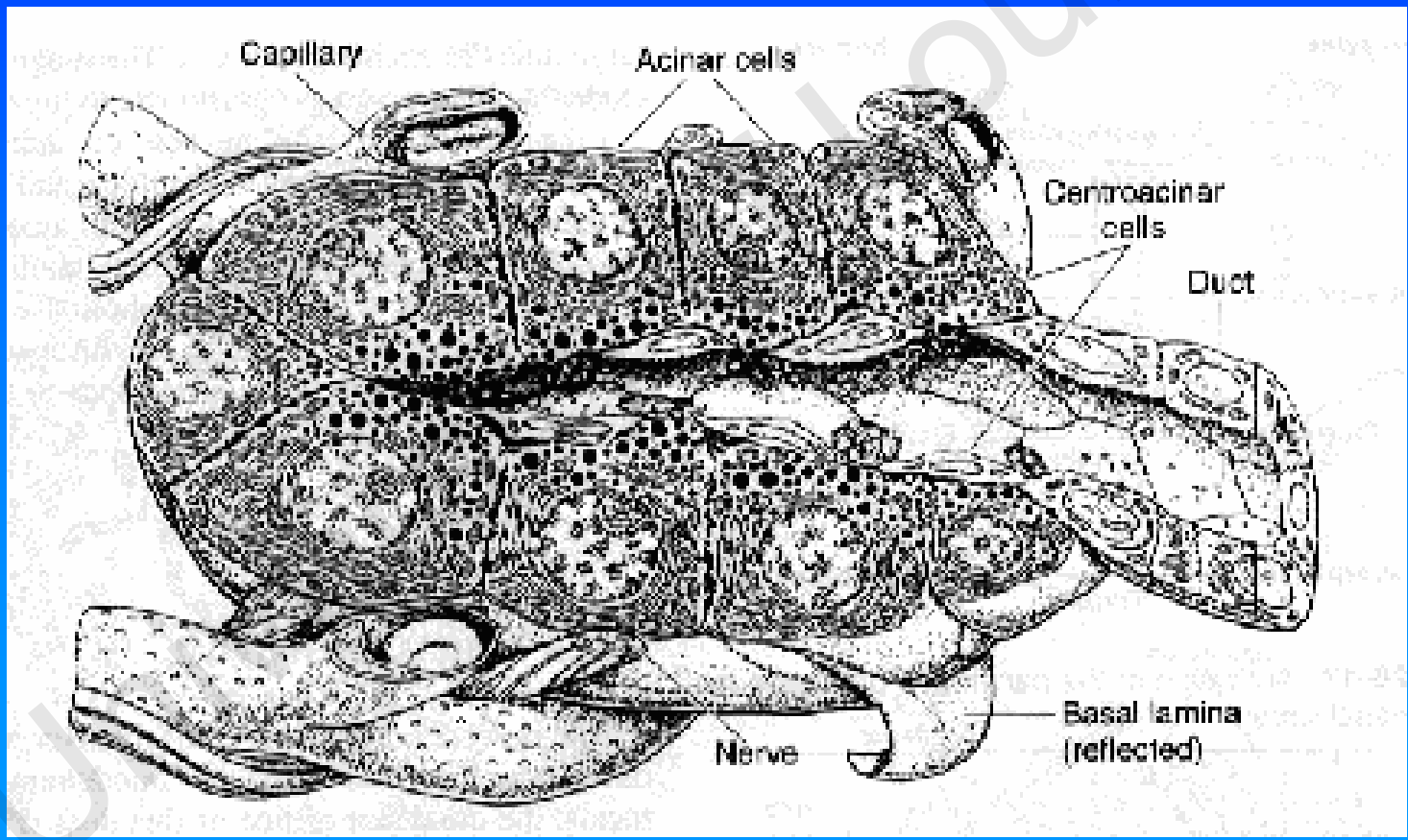
Digestive Enzymes
- Proteolytic Enzymes
- Amyolytic Enzyme
- Lipolytic Enzymes
- Nucleases

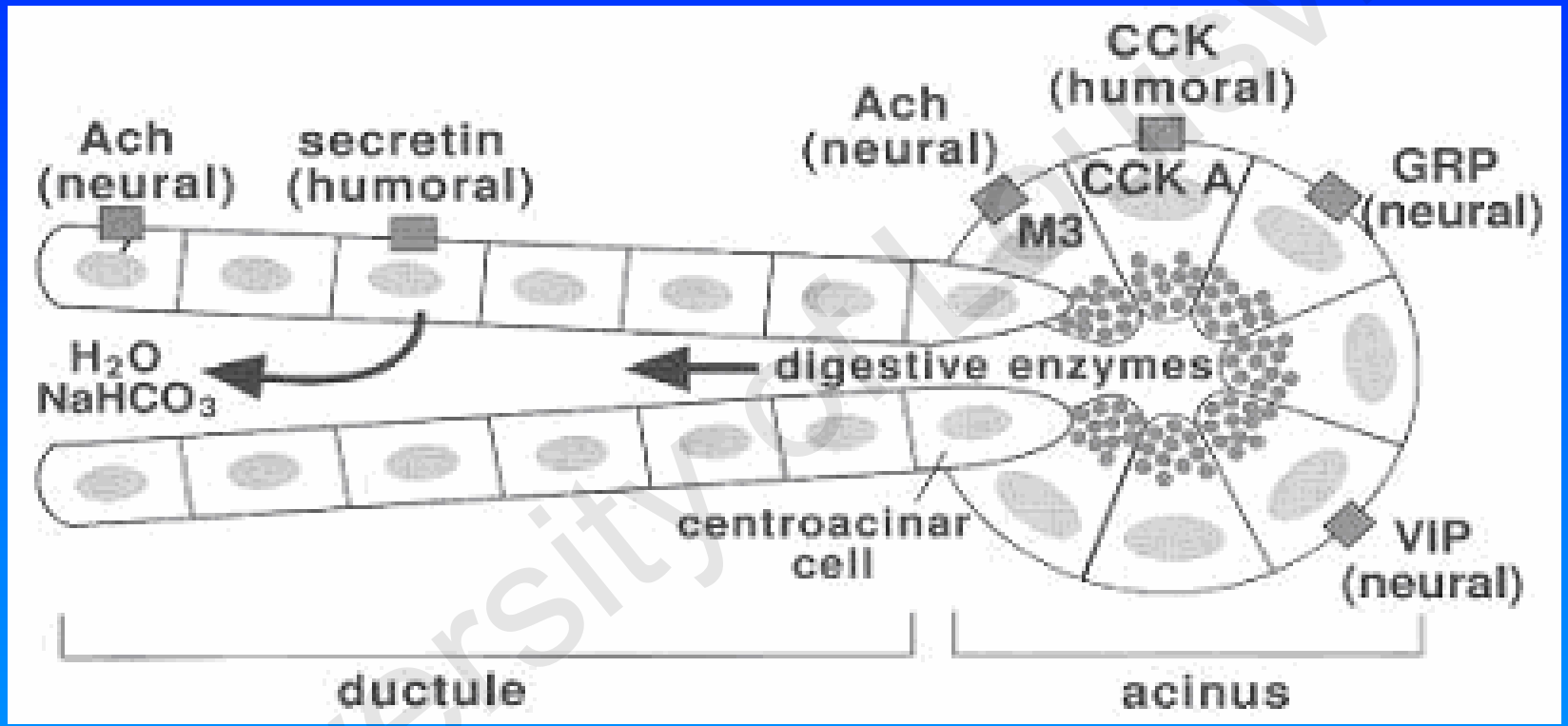
Trypsin Inhibitor

Some of the enzymes are present in more than one form (e.g. trypsinogen =cationic, anionic and mesotrypsinogen)

Enzyme Secretion: Mechanism and Regulation

Basic Secretory Unit = acinar cells.





Acinar cells

- Polarized

Panuclear region
- Rich in RER

Apical region
- Rich in Golgi apparatus and Zymogen granules

Rough endoplasmic reticulum (RER).

Synthesis of digestive enzymes occurs in internal space of the RER

Newly synthesized proteins undergo modifications (disulfide bridge formation, phosphorylation, sulfation, glycosylation.)

Processed proteins in the RER are transported to the Golgi complex

Golgi Complex

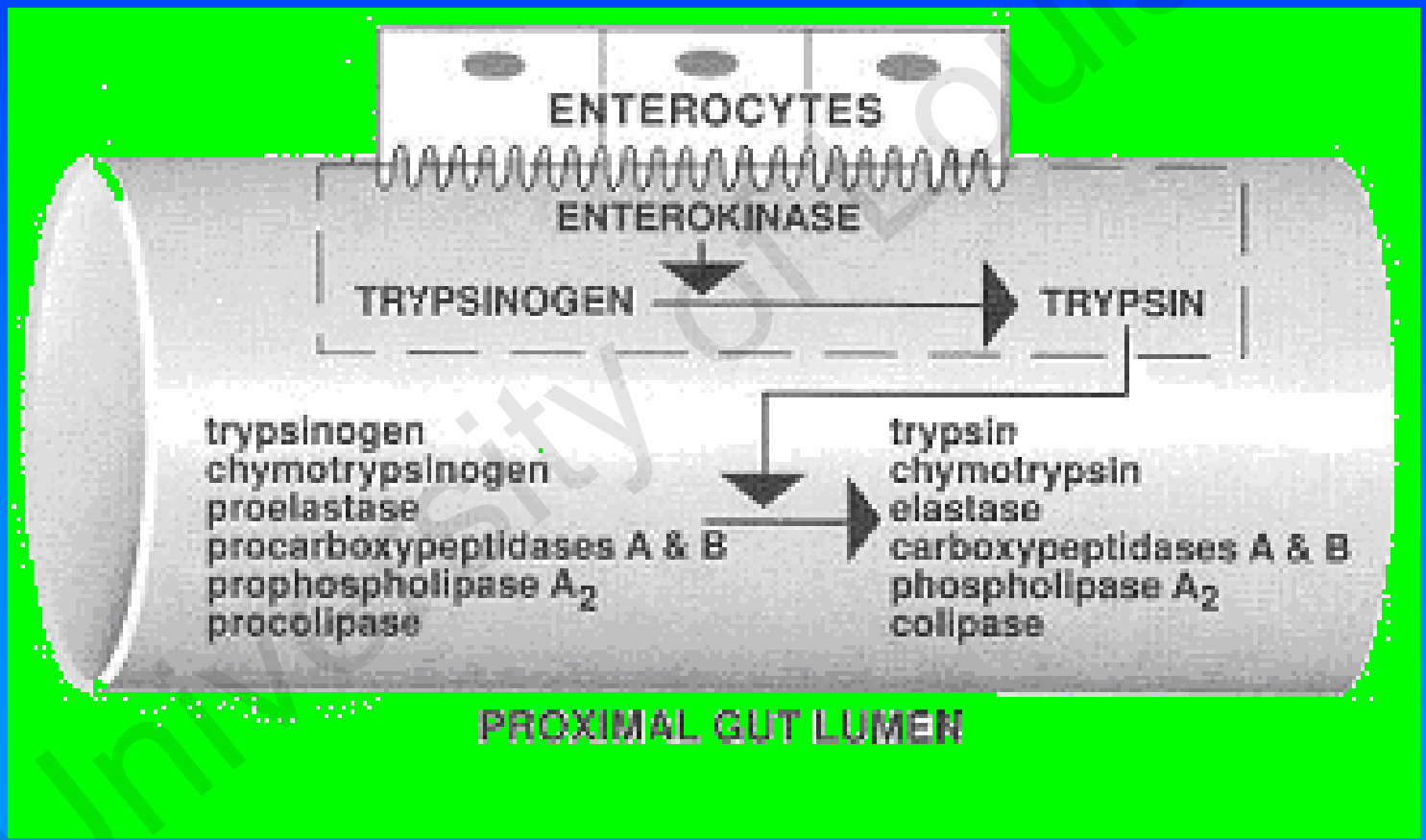
- Further post-translational modification (glycosylation) and concentration

- Sorting and targeting of newly synthesized proteins into various cell compartments.

- Digestive enzymes are transported to the zymogen granules.

- Lysosomal hydrolases are sorted to the lysosome.

Normal Activation of Pancreatic enzymes



Protective mechanisms against inappropriate zymogen activation

1. Synthesis of Digestive enzymes as proenzymes(except for Amylase and Lipase)

2. Remote activation in the duodenum.

3. Regulation of intracellular calcium content.

4. Separation of proenzymes and lysosomal enzymes in different intracellular compartments.

5. Transport and the separation of digestive enzymes from lysosomal hydrolases as they pass through the Golgi apparatus- important because Cathepsin B activates trypsin from trypsinogen.

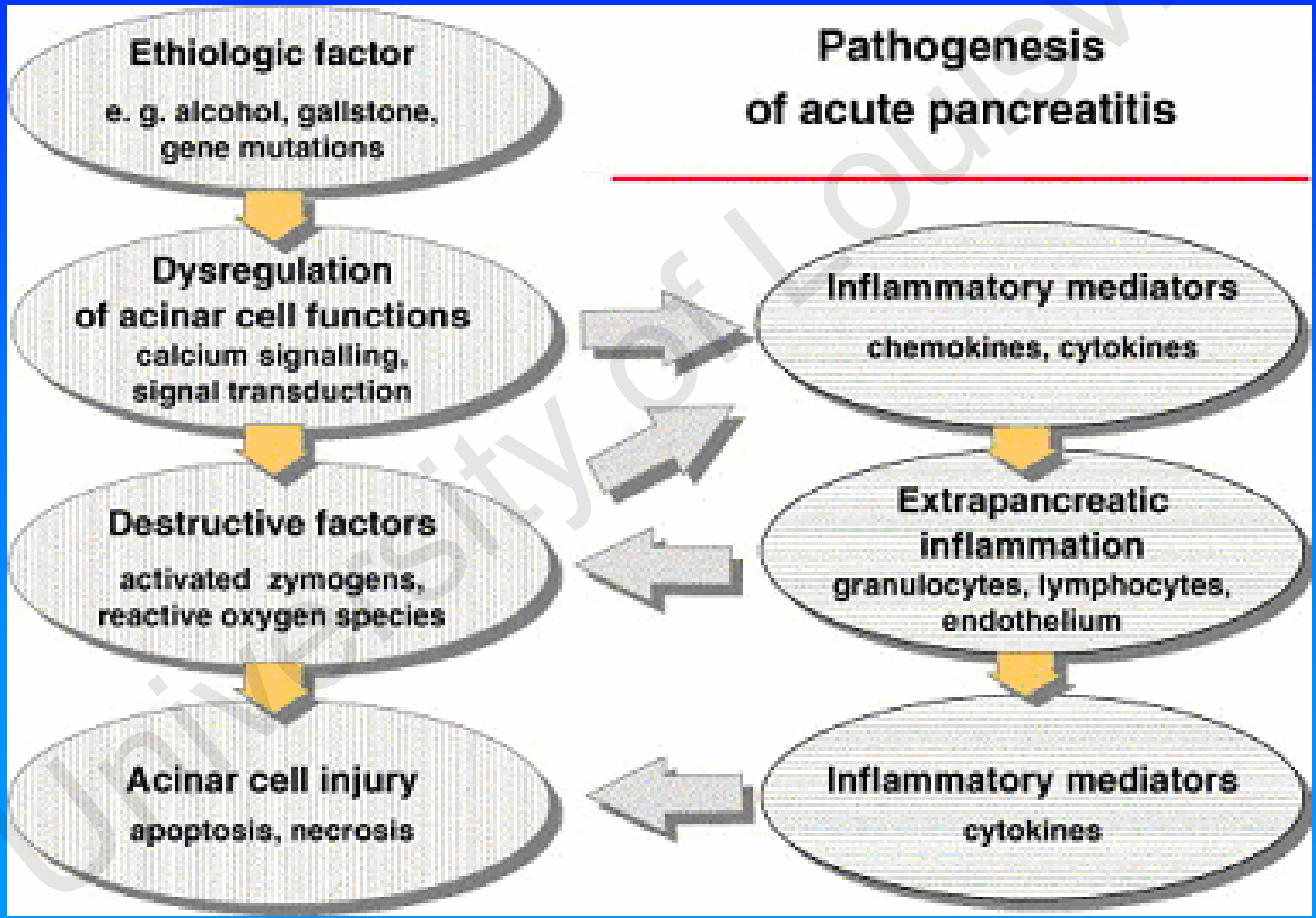
(Cathepsin B = lysosomal hydrolase)

5.Trypsin Inhibitors.

Normally, small amounts of trypsinogen are spontaneously activated within the pancreas, but intrapancreatic mechanisms quickly remove activated trypsin.

- Pancreatic secretory trypsin inhibitor (PSTI) binds and inactivates about 20% of the trypsin activity.
- Mesotrypsin, enzyme Y, and trypsin itself - other mechanisms (split and inactivates trypsin.)
- Nonspecific antiproteases such as alpha-1-antitrypsin and alpha-2 – macroglobulin

Overview of Pancreatitis



Basic pathogenetic mechanism
= Intracellular Zymogen activation

- Initial step is conversion of trypsinogen to trypsin in sufficient quantities to overwhelm normal mechanisms to remove active trypsin.

Trypsin

- catalyzes conversion of proenzymes to active enzymes.
- activate the complement and kinin systems.

Active enzymes autodigest the pancreas and initiate a cycle of releasing more active enzymes.

Two other features of experimental acute pancreatitis are

1. early blockade of the secretion of pancreatic enzymes while enzyme synthesis continues

2. disruption of the paracellular barrier of acinar cells and intralobular pancreatic duct cells
   - facilitates the extravasation of pancreatic enzymes from acinar cells and from the duct lumen into interstitial spaces.

This phenomenon may explain the rapid development of interstitial edema and the increase of pancreatic enzymes in the serum.

What causes Intracellular Zymogen activation?

The exact mechanisms by which diverse etiological factors induce an attack are still unclear.

Role of Disturbaces in Ca++ Signaling

Under physiological conditions, Ca++ is an essential second messenger in the stimulus-secretion coupling in exocrine pancreatic cells.

Various hormonal signaling -> increase the cytosolic free Ca concentration and regulates the exocytosis of digestive enzymes.

Under resting condition the acinar cells maintains a Ca++ gradient across the plasma membrane (low intracellular and high extra cellular concentration). This enables a rapid Ca++ release from intracellular stores in response to external and internal stimuli and regulates secretion of proteins.

An impaired cellular capacity to maintain Ca++ gradient has been identified as a pathophysiological characteristic in a secretagouge induced model of acute pancreatitis.

In experimental models where intracellular Ca stores were depleted by Ca - ATPase inhibition, withdrawal of extracellular Ca or complex formation with Ca chelators, intracellular protease activation in response to supramaximal hormone stimulation was greatly reduced or abolished.

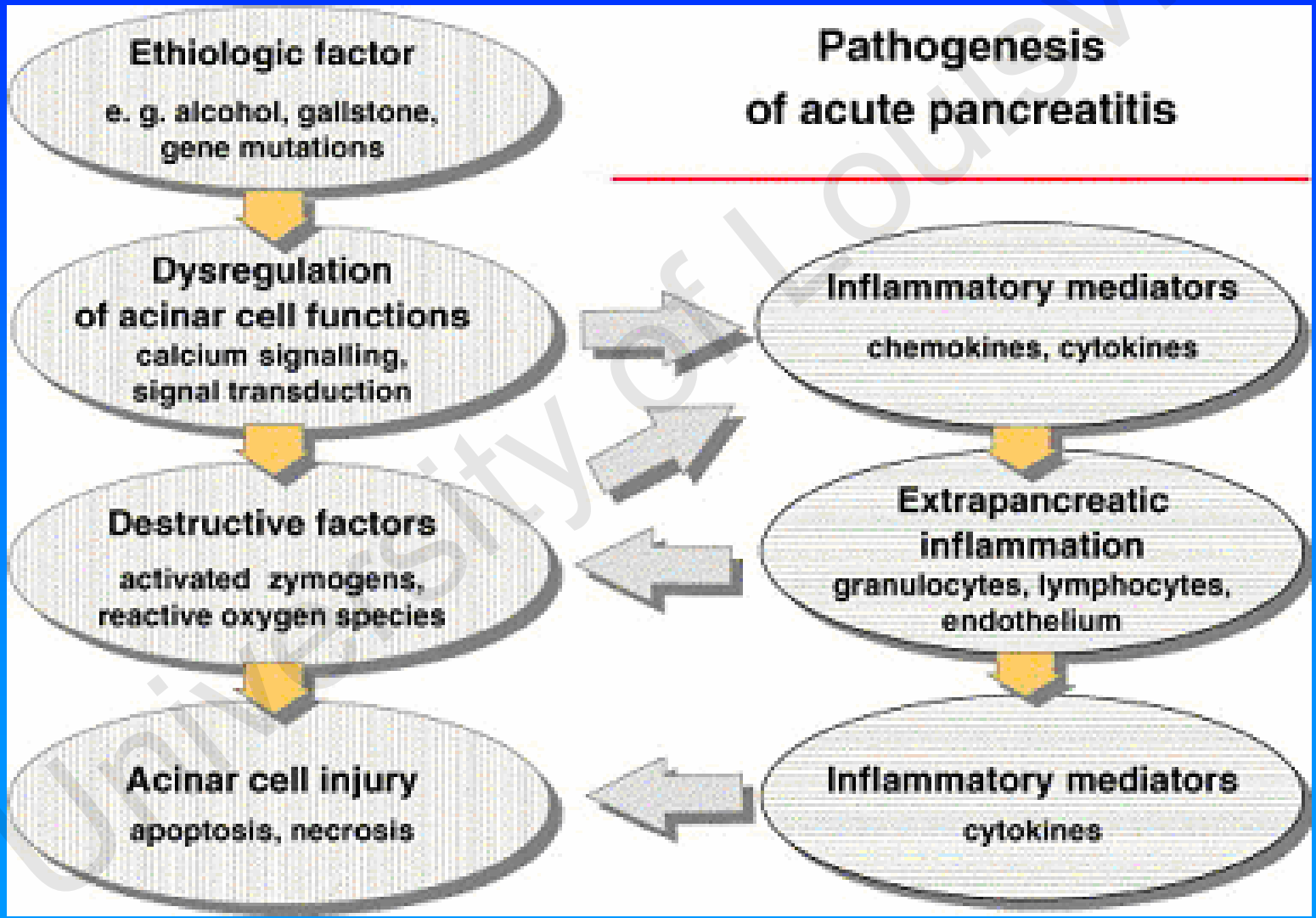
Pancreatitis induced by cerulean hyperstimulation and by pancreatic duct obstruction has been shown to cause a rise in intracellular Ca 2+ and a disruption of acinar cell Ca 2+ signaling.

This is associated with acinar cell vacuolization and the intracellular trypsinogen activation events that occur in early acute pancreatitis.

(Cerulean=CCK analogue)

Similar mechanisms may be involved in patients with hypercalcemia of endocrine causes and patients undergoing extracorporeal blood circulation for major cardiac surgery (exposure to supraphysiological concentrations of calcium).

Overview of Pancreatitis



Mechanisms of Zymogen Activation

Several pathways are likely to be involved in the intracellular conversion of pancreatic zymogens to active (mature) enzymes.

These include:
(1) Trypsinogen autoactivation to trypsin
(2) Cleavage of trypsinogen to trypsin by the lysosomal hydrolase cathepsin B (CTSB)
(3) Diminished activity of the intracellular pancreatic trypsin inhibitor

(4) Leakage of zymogens and lysosomal enzymes into the cytoplasm and subsequent proteolytic activation
(5) Shunting of zymogens into membrane bound compartments that contain active proteases
(6) Uptake and processing of secreted zymogens by endocytic pathways
(7) Enhanced susceptibility of zymogens to proteolysis because of oxidation or decondensation

The mechanisms that have received the most attention are

- Trypsinogen autoactivation
- CTSB activation of trypsinogen and
- Inappropriate activation of trypsinogen

(1) Trypsinogen Autoactivation

According to this theory,various stimuli lead to trypsinogen autoactivation and, therefore, a trypsin-induced trypsinogen activation represents the triggering event for acute pancreatitis

In a recent study, however, autoactivation of trypsinogen is *not* an initiating factor for the intrapancreatic proteolytic cascade.

(2) Cathepsin B (CTSB) Activation of Trypsinogen

- Cathepsin= lysosomal cysteine proteinase,
- Activates Trypsinogen
- One hypothesis predicts that CTSB plays an essential role in the molecular mechanisms responsible for the intracellular activation of trypsinogen.
- The largely circumstantial evidence for this 'CTSB/colocalization hypothesis' is based on the following observations:

(a) CTSB was shown to activate trypsinogen in vitro
(b) During the initial phase of acute pancreatitis, a redistribution of CTSB into a zymogen granule-containing subcellular compartment was detected
(c) In the experimental acute pancreatitis, lysosomal enzymes were detected in secretory organelles that also contained digestive enzymes, e.g. trypsinogen
(d) CTSB-deficient mice in which the *ctsb* gene had been deleted by targeted disruption was found 80% lower in the trypsin activity and 50% lower in pancreatic damage as indicated by serum activities of amylase and lipase, or by the extent of acinar tissue necrosis, after induction of experimental secretagogue-induced pancreatitis.

(3) Inappropriate Activation of Trypsinogen

Normally, trypsinogen becomes active only when it is secreted into the duodenum.

Pancreatic secretory trypsin inhibitor (PSTI) is present in secretory granules of acinar cells. It binds to the active site of trypsin in the ratio of 1: 1 and inhibits trypsin activities. The molar ratio of PSTI to trypsin is estimated to be 1: 10 . When more than 10% of trypsinogen is activated, this inhibitory mechanism is no longer effective.

Any disorders or agents that cause abnormalities in this natural protective mechanism can cause pancreatitis .

What happens after Inappropriate Enzyme Activation?

Pathophysiology

The pathophysiology of acute pancreatitis includes

- Local Changes
- Distant Effects
- Role of Imflammation

Local Effects

- Microcirculatory injury

- Leukocyte chemoattraction and release of cytokines

- Oxidative stress

- The release of pancreatic enzymes damages the vascular endothelium, the interstitium, and acinar cells.

Microcirculatory changes

- vasoconstriction
- capillary stasis
- decreased oxygen saturation
- progressive ischemia
- Increase vascular permeability and lead to edema of the gland

Vascular injury could lead to local micro-circulatory failure and amplification of the pancreatic injury.

It is uncertain whether ischemia-reperfusion injury occurs in the pancreas.

Distant Effects of Pancreatitis

Increased Intestinal permeability

During acute pancreatitis, this complex barrier consisting of immunologic, bacteriologic, and morphologic components barrier breaks down, which can result in local and systemic infection.

Penetration of the gut barrier by enteric bacteria is likely due to gut ischemia secondary to hypovolemia and pancreatitis-induced arteriovenous shunting in the gut.

SIRS

mediated by substances released into the circulation from the inflamed pancreas -activated pancreatic enzymes and cytokines

Can lead to multiple organ dysfunction syndrome (MODS).

Features include

Lungs - **ARDS**

Kidneys - **ARF (hypovolemia and hypotension)**

Heart - **Myocardial depression and shock (likely secondary to vasoactive peptides and myocardial depressants)**

Metabolic - **hypocalcemia, hyperlipidemia, hyperglycemia and hypoglycemia.**

Inflammation in Acute Pancreatitis

Proinflammatory mediators

-**TNF- α and IL-1**

-Knockout mice lacking receptors for IL-1 or/ and TNF- α have significantly improved survival when compared to wild-type mice.

-**IL-6**

Plasma levels of IL-6 correlate with hemodynamic abnormalities
Administration of IL-6 induces pyrexia.

PAF

In animal models intraperitoneal or intravascular injection can bring about or increase the severity of acute pancreatitis

PAF antagonists evaluated in experimental models

Lexipafant = PAF antagonist

In a recent study using a model of severe acute pancreatitis induced by infusion of bile salts into the pancreatic duct in combination with a supramaximal dose of cerulein administered intravascularly, treatment with lexipafant, a PAF antagonist had no effect on survival or local inflammation

Antiinflammatory mediators

IL-10

Experimentally, found to reduce the extent of inflammation as well as the mortality associated with acute pancreatitis.

Employing recombinant IL-10 in experimental models of acute pancreatitis, the animals were found to be protected to a significant extent.

Synthetic IL-10 agonist pretreatment in rabbits also lowers the extent of lung injury and mortality from this condition.

Two clinical trials involving IL-10 in post ERCP pancreatitis.

In both trials, patients received either recombinant IL-10 or placebo before ERCP.

One study reported no significant difference in clinical outcome between the two groups while other reported a significant protection by IL-10.

Therefore it is at present uncertain if IL-10 will reduce the severity of acute pancreatitis in patients with severe disease from other causes.

Gallstone Pancreatitis

Pathogenesis unknown.

Factors that may initiate gallstone pancreatitis include:-

- Reflux of bile into the pancreatic duct

- Obstruction of the pancreatic duct at the ampulla secondary to stone(s) or to edema resulting from the passage of a stone

Reflux of bile into the pancreatic duct could occur when

1. the distal CBD and PD form a *common channel* and a gallstone becomes impacted in the duodenal papilla.

2. Incompetent sphincter of Oddi injured by recent passage of a gallstone.

Experimentally, reflux of bile causes pancreatic injury. Mixtures of bile and pancreatic enzymes increase the permeability of the main pancreatic duct, which is associated with local parenchymal inflammation.

The common channel theory is somewhat problematic because pancreatic duct pressure is invariably higher than common bile duct pressure, making bile reflux unlikely.

Reflux of bile from the duodenum also is unlikely because pancreatitis does not occur in conditions with easily demonstrable reflux, such as after surgical sphincteroplasty or endoscopic sphincterotomy.

A popular opinion for the mechanism of gallstone pancreatitis

- an impacted gallstone in the distal CBD obstructs the pancreatic duct –> increases pancreatic pressure, thereby damaging ductal and acinar cells.

Experiments in the opossum support this theory

- ligation of the pancreatic duct causes severe necrotizing pancreatitis
- decompression of the ductal system within 3 days prevents progression to acinar cell necrosis and severe inflammation.

Alcohol related pancreatic disease

Acute Pancreatitis

- Does not cause pancreatitis directly
- Rather it lowers the threshold for initiatin of AP

-In vitro modules
ETOH added to pancreatic lobules with low dose CCK(0.1nm), zymogen activation was generated at level that were six fold higher than CCK alone and equivalent to levels generated by high dose CCK(10nm)

-In most cases except in those with mutations of trypsin or trypsin regulating genes, sustained intrapancreatic trypsin activation appears to require intra acinar hypercalcemia.

Effects of alcohol on the Pancreas

Pre-acinar and Intra-acinar

Pre-acinar cell effects

- Area Postrema
- One of the major targets of alcohol
- Dorsal vagal complex of the medulla oblongata.
- Incomplete blood–brain barrier
- Involved in vagal–vagal reflex

In awake (nonanesthetized) rats

- AP appears to be impaired specifically by chronic alcohol use.
- Leads to functional hyperstimulation of the pancreas because of loss of feedback regulation of vagal-stimulated pancreatic secretion.

Alcohol feeding protocol in rats

Within a short-term (approximately 2 weeks) marked changes in pancreatic responses to CCK and meals were elicited, resulting in pancreatic hyperstimulation and hypersecretion

Intra-acinar cell effects

1. Organnelle injury

Electron Microscopy -Significant changes in mitochondrial ultrastructure in rats

Mitochondria essential for

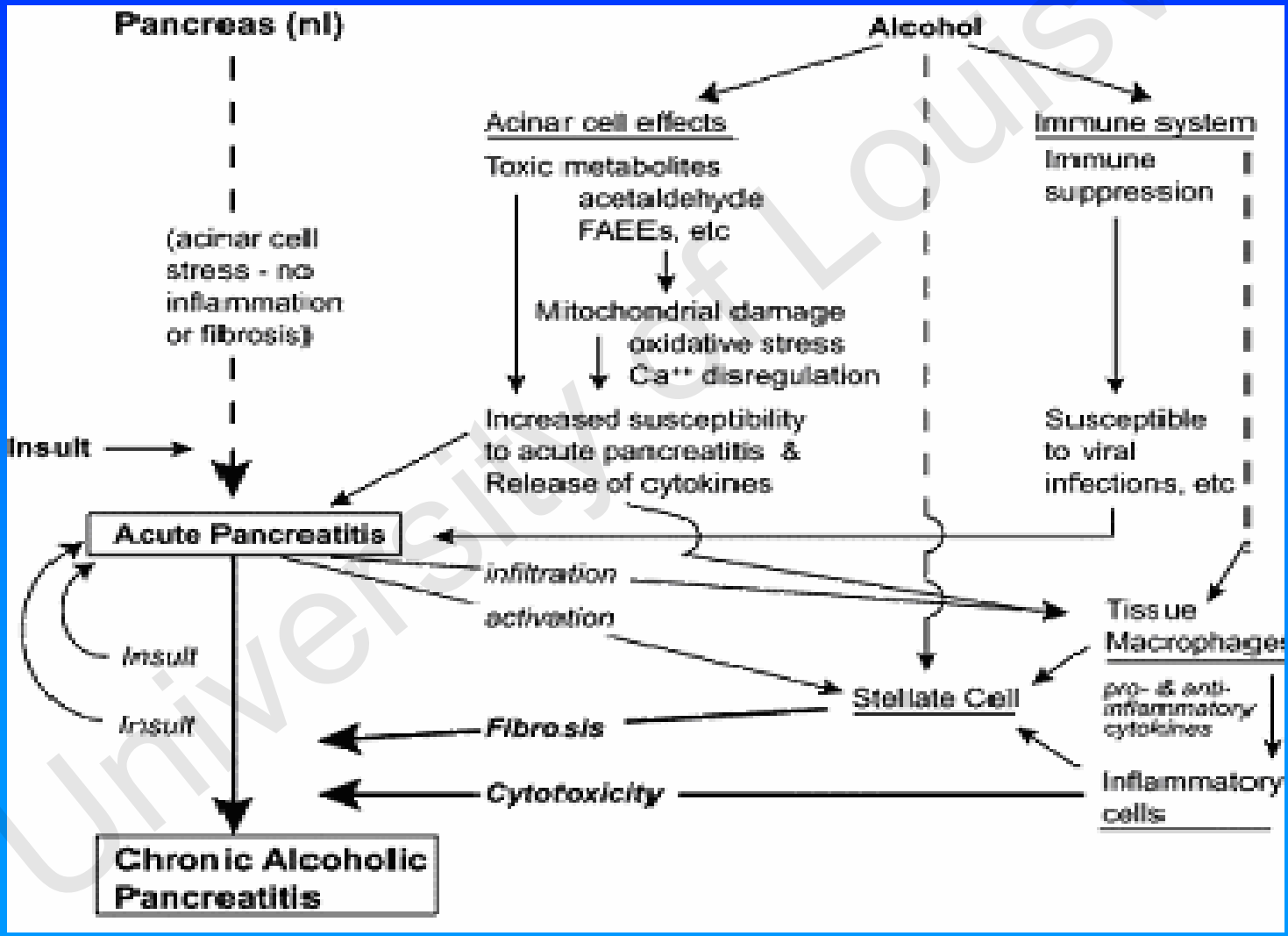
- generating the large amounts of ATP
- critical role in regulating intracellular calcium

2. Zymogen missorting

3. Regulation of the cholesterol esterase (CEL) genes
    - these enzymes help metabolize alcohol
    - also convert free fatty acids to fatty acid ethyl esters (FAEE), which appear to be a major factor in alcohol-associated acinar cell injury

4. Up-regulation of multiple stress-related nuclear factors, chemokines, and cytokines

Pathogenesis of alcoholic chronic pancreatitis



Theories, mechanisms, and models of alcoholic chronic pancreatitis

1. Necrosis –Fibrosis Sequence Hyopothesis
2. Duct –obstruction (Pancreatic Stone Protein)Theory
3. Leaky Duct Theory
4. Pathologic Adaptation in Digestive Enzyme Synthesis
5. Toxic Metabolite Theory
6. Altered Pancreatic Blood Flow
7. Mitochondrial damage
8. Fibrosis and Pancreatic Stellate Cells

Necrosis –Fibrosis Sequence Hyopothesis

Alcoholic pancreatitis begins as an acute process that progresses to chronic damage as a consequence of repeated acute attacks of pancreatitis.

Supported by clinical and experimental studies.

Sentinel acute pancreatitis event (SAPE) hypothesis model.

Importance of acute pancreatitis in activating the immune system (which is the mediator of chronic inflammation and fibrosis) and allows for the consideration of multiple risk factors to contribute to increase susceptibility, injury, severity of acute pancreatitis and modulation of the immune response.

Duct –Obstruction (Pancreatic Stone Protein) Theory

Suggested that alcoholic pancreatitis is caused by the blockage of small pancreatic ducts by protein plugs.

According to this hypothesis, the acini that secrete into ducts blocked by protein plugs would undergo fibrosis, and the protein plugs eventually would enlarge and calcify.

Content of the calcified protein plugs identified two pancreatic secretary proteins, called pancreatic stone protein (or lithostathine) and GP2.

Pancreatic lithostathine

- a protein that was thought to inhibit the deposition of calcium from pancreatic juice
- hypothesized that a decrease in the level of lithostathine would promote calcium precipitation and initiate development of protein plugs

More recent studies demonstrated that relative variations in the level of lithostathine mRNA do not correlate with the type of pancreatitis disease, and mRNA levels are unrelated to the presence of pancreatic stones.

In addition, studies have proven that this protein does not possesses physiologically relevant calcite crystal inhibition.

GP2

The most abundant zymogen granule membrane protein in the pancreas.

Suggested that chronic ethanol consumption may increases the release of GP2 into pancreatic juice and impair zymogen granule stability, which could favor protein plug formation.

HOWEVER many experts now believe that the plugs are a consequence, rather than a cause of acute pancreatitis and the chronic inflammatory process.

Leaky Duct Theory

Ethanol perfusion of the main pancreatic duct (ethanol 20% in milk, 10 mL/kg every 8 hours for 48 hours) was shown to increase ductal permeability.

Hypothesized tat after acute ethanol administration, enterokinase-activated pancreatic enzymes would leak from the duct into the gland and induce pancreatic damage.

Leakage of pancreatic enzymes into the interstitial space is more likely a consequence of obstruction and high pressure, or enzymatic breakdown of the pancreatic architecture, rather than a primary factor.

Pathologic Adaption in Digestive Enzyme Synthesis

Hypothesized that the risk of acute alcoholic pancreatitis might be higher if the proteolytic enzymes, especially trypsin, were upregulated.

In 1988, Ponnappa et al reported an increased pancreatic enzyme synthesis under chronic ethanol consumption

Confirmed and extended by others to include cathepsin B, but the animals on alcohol diets do not develop acute or chronic pancreatitis independent of other factors, so the relatively small (but statistically significant) increase in enzyme content cannot not explain acute or chronic pancreatitis.

Toxic Metabolite Theory

Alcohol can also be metabolized in the pancreas.

Oxidative metabolism of alcohol

Alcohol => acetaldehyde (alcohol dehydrogenase)

Acetaldehyde => acetate (acetaldehyde dehydrogenase.)

An alternative, nonoxidative pathway for ethanol metabolism in the pancreas involves the enzymes that convert alcohol and fatty acids to fatty acid ethyl esters (FAEEs)

Pancreas has a higher capacity to synthesize FAEEs than the liver.

FAEEs are cytotoxic, and excessive FAEEs may cause pancreatic edema, acinar cell vacuolization, and trypsin activation.

Chronic alcohol consumption itself upregulates the synthesis of several enzymes that catalyze FAEE production, including pancreatic cholesterol esterase, ES-10, and FAEESIII

Altered Pancreatic Blood Flow

Intravenous infusion of high-dose ethanol reduced pancreatic blood flow in dogs experimentally.

At clinically relevant blood ethanol concentrations, however, these changes in pancreatic blood flow were not detectable

This may be important in the context of acute pancreatitis when the pancreas is susceptible to pancreatic necrosis, and after chronic pancreatitis has developed, and the acinar cells are in a semihypoxic environment.

Fibrosis and Pancreatic Stellate Cells

Pancreatic fibrosis is a characteristic feature of alcohol-induced chronic pancreatitis.

Pancreatic stellate cells (PSC), similar to hepatic stellate cells located at the base of pancreatic acini

Studies indicate that PSCs are activated early in the course of pancreatic injury and are the predominant source of collagen in the fibrotic pancreas.

Pathogenesis of alcoholic pancreatic fibrosis may involve three pathways:

(1) a necroinflammatory pathway involving cytokine release and PSC activation,

(2) a non-necroinflammatory pathway involving direct activation of PSCs by ethanol and its metabolites such as acetaldehyde

(3) the generation of oxidant stress

Cystic Fibrosis Transmembrane Regulator (CFTR) Mutation and Chronic Pancreatitis

- Idiopathic Chronic Pancreatitis
  = Leading cause of Pancreatitis in non alcoholic adults

- In 1998 ICP was associated with muatations in the CFTR gene

- In a study of 27 patients with apparently idiopathic pancreatitis, 37 percent had at least one abnormal CFTR allele.

- Similar series of 134 consecutive patients with chronic pancreatitis attributed to a variety of causes,

  13 % had a CFTR mutation on one chromosome (compared to a frequency of 5 % among 600 local unrelated partners of persons with a family history of cystic fibrosis)

- Mechanism –outlined above

-CF pancreatic insufficiency Vs ICP

  - Early ductal plugging is common in both

  - Pancreatic inflammation is prominent in ICP whereas it is unusual in CF

-Since its discovery in 1989 roughly 1000 mutation identified.

CF- severe mutations (sev) i.e. ΔF508

- Eliminates nearly all CFTR function from the gene
- Causes CFTR to misfold, mislocalize or undergo accelerated degradation

CF-moderate variable (m-v) mutations

- Most common is 5T
- Others e.g. R117-7T,D1152H etc
- Reduce CFTR function by 10% to 30% and are assoc with variable clinical features.

-US CF patients

- 50% are ΔF508 homozygotes.(have low residual CFTR function,<2%)
- 40% are compound heterozygotes

-Risk of ICP

CF sev/- (Carrier) = Risk unknown*

Any CFTR compd Heterozygote =37 X Normal

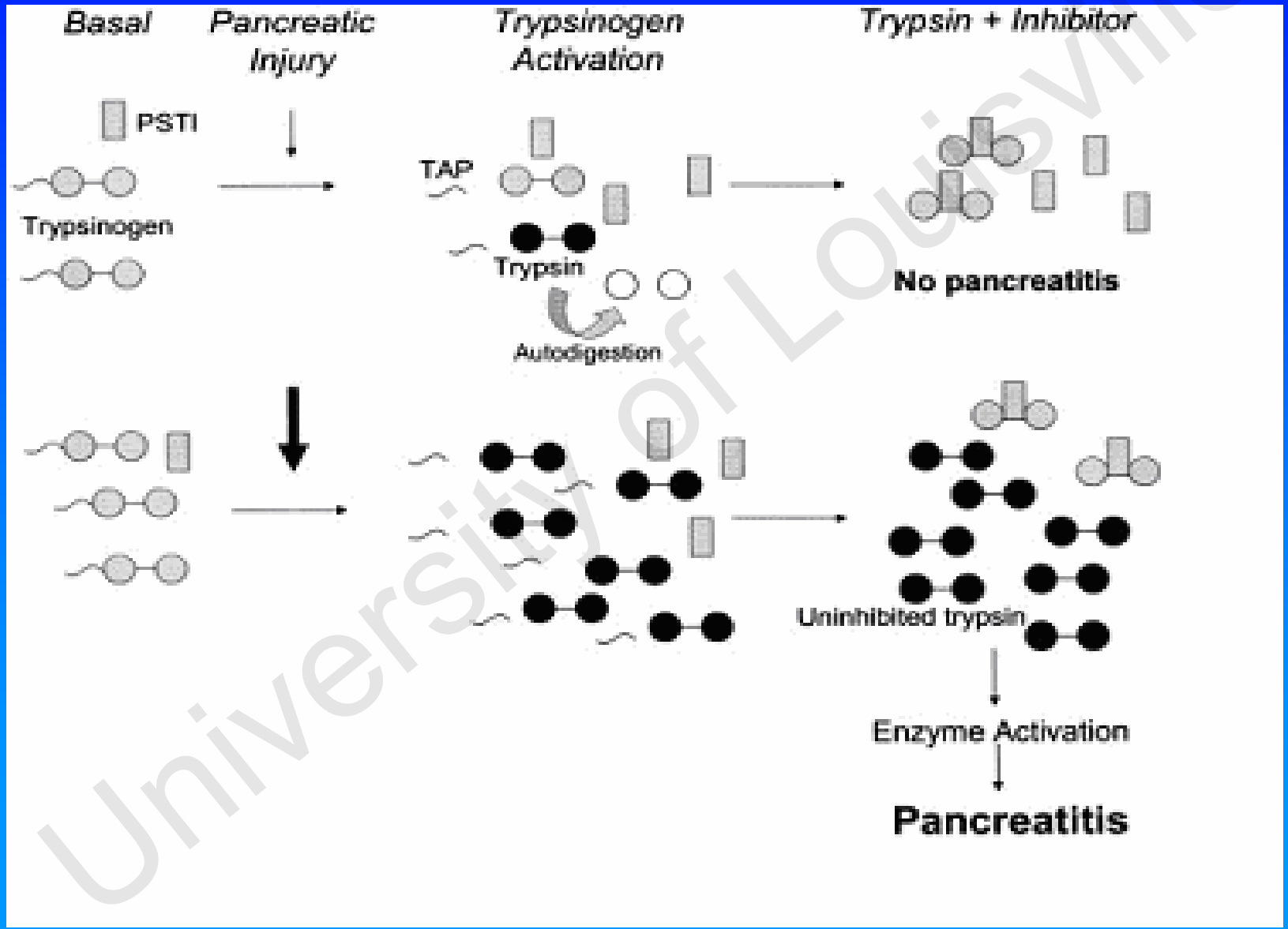
CF sev/CF m-v(5T) = 83 X N

*** p value insignificant in one study**

Most CFTR compound heterozygotes do not develop ICP.

Subsequent research identified that other factors influence the risk of pancreatitis in people who have ICP associated CFTR genotypes. (Role of PSTI)

Hereditary pancreatitis



Hereditary pancreatitis

In 1952, Comfort and Steinberg

First kindred with familial clustering of chronic pancreatitis and recognized that the risk of pancreatitis could be inherited

Since then, many more families with hereditary pancreatitis have been described worldwide

In 1996, Whitcomb et al discovered a mutation in the cationic trypsinogen (PRSS1) gene in several families with hereditary pancreatitis and established fact that specific genetic mutations increase susceptibility to acute and chronic pancreatitis .

In recent years, additional mutations in the PRSS1 gene associated with hereditary pancreatitis have been identified .

Because mutations in the cationic trypsinogen gene caused hereditary pancreatitis, it followed that mutations in the trypsin inhibitor, pancreatic secretory trypsin inhibitor (PSTI), also known as the serine protease inhibitor Kazal type 1 (SPINK1), might predispose individuals to pancreatitis.

More recently, several groups detected SPINK1 gene mutations in patients with alcoholic chronic pancreatitis and tropical calcific pancreatitis.

Cationic trypsinogen mutations and pancreatitis

Pathophysiology

Trypsinogen exists as three species

- **Anionic Trypsinogen**
- **Cationic Trypsinogen**
- **Mesotrypsinogen**

Patients with hereditary pancreatitis express mutations in the cationic trypsinogen gene

Trypsin is known to lose its activity spontaneously by autolysis. This mutation render a mutant resistant to autolysis.

Once an inappropriate activation of trypsinogen occurs and its levels exceed those of PSTI, the autoactivation process will not cease, which leads to the activation of other zymogens and acute pancreatitis.

In the late 1990s, two mutations in the protease serine 1 or cationic trypsinogen gene (PRSS1) were found to underlie some cases of hereditary pancreatitis

The active site of trypsin once activated from trypsinogen involves a serine residue at amino acid 200 . Active trypsin can be inactivated by cleavage at amino acid 122 .

R122H mutation

the arginine residue at position 122 that confers a trypsin-sensitive cleavage site is altered to a residue that is trypsin insensitive

N29I mutation

does not affect autocatalytic inactivation of human cationic trypsin but does lead to increased autoactivation of trypsin

PANCREATIC SECRETORY TRYPSIN INHIBITOR

PSTI is a member of a family of trypsin inhibitors that are expressed in the pancreas, intestine, prostate, and other tissues

PSTI originally was identified in the pancreas where it is synthesized and stored in zymogen granules of the acinar cell. It is secreted along with digestive enzymes upon stimulation of exocytosis.

(Gabexate= serine proteinase inhibitor)

THE FUNCTION OF SPINK1 IN PROTECTING THE PANCREAS FROM AUTODIGESTION

SPINK1 inhibits trypsin directly at the active catalytic site.

Incubation of equimolar quantities of trypsin with SPINK1 results in a complex that contains a covalent bond between the catalytic serine residue of the trypsin molecule and the reactive site of SPINK1

The inhibition of trypsin by SPINK1 is not permanent or irreversible.

Called temporary inhibition, and is thought to be physiologically important.

In the case of accidental activation of trypsinogen within the pancreas, SPINK1 inhibits trypsin activity, and the trypsin inhibitor complex is passed into the duodenum.

When the complex finally reaches the small intestine, the trypsin inhibitor complex serves as a substrate for trypsin, and the inhibitor molecule is degraded.

SPINK1 MUTATIONS

Different serine protease inhibitor Kazal type 1 mutations and genetic variants that have been detected in patients with chronic pancreatitis and may contribute to the development of chronic pancreatitis

Location	Sequence alteration	Amino acid	Prevalence
5'UTR	?53C > T	?	rare
Exon 1	2T > C	M1T	rare
Exon 1	41T > C	L14P	rare
Intron 1	IVS1?37T > C	?	common
Exon 3	101A > G	N34S	common
Exon 3	150T > G	D50E	rare
Exon 3	160T > C	Y54H	rare
Exon 3	163C > T	P55S	common
Exon 3	194G > A	R65Q	rare
Intron 3	IVS3+2T > C	?	rare
Intron 3	IVS3+184T > A	?	common
Intron 3	IVS3?604G > A	?	rare
Intron 3	IVS3?66–65insTTTT	?	common
Exon 4	199C > T	R67C	rare

Additional intronic variants have been identified that are not listed.

ASSOCIATION OF SPINK1 MUTATIONS WITH PANCREATITIS

Mutations in the SPINK1 gene were associated first with pancreatitis in children with idiopathic chronic pancreatitis (ICP).

Since then, several reports have confirmed that N34S mutations are associated with familial pancreatitis and idiopathic pancreatitis developing in childhood or adolescence

SPINK1 mutations, however, are not associated with typical hereditary pancreatitis, but rather a familial form.

SPINK1 mutations have been found in

- approximately 6% to 12% of patients with alcoholic pancreatitis
- at least one third of patients with tropical pancreatitis

Interestingly, the SPINK1 N34S mutation is fairly common in control populations, with a prevalence of 1% to 2%, which is much more common than any form of chronic pancreatitis.

Moreover, there is no clear difference in disease severity in individuals homozygous or heterozygous for the mutation.

Therefore, it appears that the N34S mutation is a disease-modifying mutation and, although, it clearly increases the risk of pancreatitis, it does not, itself, cause pancreatitis.

Autoimmune Chronic Pancreatitis

- an uncommon type of chronic pancreatitis with underlying autoimmunity .

-Many entities in the literature share the clinical features of AIP; e.g. primary inflammatory pancreatitis , lymphoplasmacytic sclerosing pancreatitis ,pseudotumorous pancreatitis , chronic pancreatitis with irregular narrowing of the main pancreatic duct, and nonalcoholic duct destructive chronic pancreatitis

Retrospectively, these names probably were describing AIP

-Although AIP is not a common disease, it is increasingly being recognized as knowledge of this entity builds up.

-Most of the cases have been reported from Japan-
May not be common in Japan only
May have been overlooked by physicians in other countries due to a lack of recognition and would regard these patients as ordinary acute or chronic pancreatitis, idiopathic chronic pancreatitis, or pancreaticobiliary malignancy.

Analogous to another disease entity of the pancreas, intraductal papillary mucinous tumor (IPMT)

- Pancreatitis in patients with an underlying autoimmune can be related to various causes, such as vasculitis or medications

- In contrast to these cases, AIP is a pancreatitis with an autoimmune pathogenesis that is characterized by a remarkable response to steroid therapy.

PATHOGENESIS

In the normal pancreas, carbonic anhydrase type II is located in the duct cells and lactoferrin exists in the pancreatic acini.

An autoimmune reaction against carbonic anhydrase type II or lactoferrin via Th1-type CD4+ T cells may have a role in the development of AIP.

C/F

- mean age 59.1 yr (range, 45–75 yr)
- male-to-female ratio was 15:2.

- Presenting symptom
  - Painless jaundice - (65%)
  - Nonspecific mild abdominal pain - (35%)
  - Weight loss - (35%)

- Presentation with typical severe abdominal pain of pancreatitis is rare.

In one study of 17 patients

- 60 % of the AIP patients were initially suspected of pancreaticobiliary malignancies
  (Five patients actually underwent laparotomy because malignancy could not be completely excluded.)

- Diabetes mellitus is often noticed in AIP with reports ranging from 42% to 76%

- Presentation for symptoms related to other autoimmune diseases, e.g. Sjögren's, PSC, IBD and retroperitoneal fibrosis.
  Other autoimmune diseases may not be detected at the time of diagnosing AIP, but may evidently manifest later along the course of the disease.

LABORATORY DATA

1. Pancreatic Enzymes
- mild elevation in serum amylase or lipase levels
- Only 3 (13%) of 17 cases revealed levels 3 times above the normal levels.

2. Liver Enzymes

Most (16/17) showed a cholestatic profile on liver function tests.

3. Hypergammaglobulinemia
- Elevated IgG and hypergammaglobulinemia
- IgG elevation or hypergammaglobulinemia reported in 37–76% of the patients in AIP

- IgG elevation can be seen in patients with alcoholic chronic pancreatitis and it may not be specific to AIP

- IgG4, a subtype of IgG, levels have been reported to be able to distinguish AIP from other pancreatic disorders with a high sensitivity (95%) and specificity (97%).

- In one study only 62.5% (5/8) had elevated IgG4 of patients

- Another report questioned the specificity of IgG4 and mentioned that IgG4 levels were similar among patients with AIP, pancreatic cancer, other types of chronic pancreatitis, and acute recurrent pancreatitis

4. Autoantibodies

Most commonly detected autoantibodies in AIP

- antilactoferrin antibody
- anticarbonic anhydrase II antibody

- The detection rate varies from 10% to 100%
- These antibodies require a special laboratory for measurement that are unavailable to many clinicians.
- May not be pathognomic to AIP because some report that it may be elevated in other types of pancreatitis

Histology

- medium sized and large interlobular ducts surrounded by the infiltration of inflammatory cells and fibrosis

- various degrees of parenchymal inflammatory changes - changes are heterogeneous and patchy

- inflammatory cells mainly composed of lymphocytes and plasma cells.

The lymphoplasmacytic infiltration is usually located in the subepithelial area with a relatively intact epithelial lining. This generates an infolding of the epithelium that compresses the ductal lumen into a star-like structure.

This process is analogous to PSC . This similarity was cited by a case report that named AIP "PSC involving the pancreas".

Interstitial fibrosis with acinar atrophy is another characteristic feature on pathology. When pancreatic fibrosis involves a large area, they commonly manifest as mass-forming pancreatitis

Radiology

CT Findings

- Diffusely enlarged pancreas without peripancreatic fat infiltration, phlegmonous changes, or pseudocysts.
- Some have described the CT findings of the diffusely swollen pancreas as "a sausage-like" appearance
- *Pancreatic parenchymal calcification or intraductal stones are rarely seen.*

MRI/MRCP

- Role of MRCP appears to be limited in diagnosing AIP because the entity is basically a "narrow-duct" disease.
- MRCP often fails to clearly delineate the pathology of the main pancreatic duct.

ERCP Findings

1. Pancreatic duct

-hallmark finding on direct pancreatogram is *diffuse or segmental irregular narrowing of the main pancreatic duct*

2. Bile duct

-The intrapancreatic portion of the common bile duct is narrowed in most patients.

- Distal CBD stenosis associated with AIP may be, due to the combined effect of extrinsic compression of the inflamed pancreatic head and the inflammatory changes of the CBD per se.

DIAGNOSTIC CRITERIA

Definite diagnostic criteria not fully established.

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(1) Radiologic imaging - diffuse swelling of pancreas, and segmental or diffuse irregular narrowing of the main pancreatic duct

(2) Laboratory data - elevated IgG, or detection of autoantibodies

(3) Histopathologic examination - lymphoplasmacytic infiltration, and fibrosis in the pancreas

For the diagnosis of AIP, all of the criteria are present or criterion 1 together with either criterion 2 or criterion 3. The presence of the imaging criterion is essential

In one experience, all of the patients (n = 15) who fulfilled the criteria responded to oral steroid.

TREATMENT

A detailed steroid schedule has not been not fully established at the present time

Prednisolone is usually initiated at 30–40 mg/day for 1–2 months, and tapered by 5 mg every 2–4 wk.

Some recommend a maintenance dose of 5–10 mg/day of prednisolone to prevent relapses without complete discontinuation of steroid .

Response to steroid therapy can be observed on imaging studies and lab findings.

Abnormalities observed on CT and direct pancreatogram , return to normal.

Obviously there is concern about further delay in the diagnosis of malignancy if weeks are spent trying steroid therapy.

The response to steroid therapy, can be observed within 2–4 wk by imaging studies, and AIP can be verified

If follow-up images do not reveal evident improvement, the diagnosis of AIP should undergo reevaluation and the possibility of exploratory laparotomy should be considered.

Temporary stents can be inserted into the bile duct in addition to the administration of oral steroid

While stenosis of common bile duct associated with ordinary chronic pancreatitis is notorious for its poor response to endoscopic intervention patients with AIP show resolution of the bile duct narrowing that allows the biliary stent to be removed mostly within 2–3 months.

The long-term prognosis of AIP is not well known.

In one report, 23 patients were followed up for a mean of 56 months and AIP relapsed in one patient

In one experience, one (1/17) patient relapsed at 16 months of follow up. Re-remission was achieved by challenging the patient with another trial of 40 mg of prednisolone and maintaining the patient on a maintenance dose of 10 mg.