Peering Into the “Black Box” of the Complex Chronic Pancreatitis Syndrome

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Disclosures

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The germ theory of disease states that some diseases are caused by microorganisms. These small organisms, too small to see without magnification, invade humans, animals, and other living hosts. Their growth and reproduction within their hosts can cause a disease.
Koch’s Postulates

Koch's Postulates:

1. The microorganism must be found in abundance in all organisms suffering from the disease, but should not be found in healthy organisms.

2. The microorganism must be isolated from a diseased organism and grown in pure culture.

3. The cultured microorganism should cause disease when introduced into a healthy organism.

4. The microorganism must be reisolated from the inoculated, diseased experimental host and identified as being identical to the original specific causative agent.

[Diagram showing the steps of Koch's postulates]

https://en.wikipedia.org/wiki/Koch%27s_postulates
• Based on the “Germ theory” of disease
  – One agent → Complex syndrome
• Based on the “Scientific Method” of Koch
  – Complex syndrome → one factor
• Based on clinicopathologic disease definitions
  – Syndrome, pathology-based (e.g. ICD codes)
• Results:
  – Progress in infectious diseases and simple genetics
  – Poor progress in complex* disorders
  – Little guidance for managing complex disorders

* Complex disorders: two or more factors are required. Can be gene x environment, gene x gene, etc. Individual factors may not be necessary nor sufficient to cause disease.
Germ Theory: Success & Failure

**Expected**

Sx

- Inflammation
- Pain
- Organ dysfunction

**Observed (if no “germ”)**

Sx

- Inflammation
- Pain
- Organ dysfunction

Germ Theory:

- symptom complex predicts single etiology

Germ Theory:

- A Paradigm Failure!
Chronic Pancreatitis:
  - Pancreatic inflammation
    - Scarring (80%)
    - Maldigestion (40%)
    - Diabetes mellitus (35%)
    - Pain (70% - 5 types)
    - Pancreatic cancer (15%)

Diagnosis and Treatment
  - Diagnosis: requires demonstration of irreversible damage
  - Methods: repeated CT, MRI, ERCP and/or EUS
  - Treatment: symptomatic, pain treatments, PERT, insulin

Summary: a hopeless, irreversible condition that is expensive to diagnose and treat.

*Whitcomb DC, Nature Reviews: G&H, 2012*
“chronic pancreatitis remains an enigmatic process of uncertain pathogenesis, unpredictable clinical course, and unclear treatment”
Complex Disease Syndrome

Studies based on symptoms

<table>
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<tr>
<th>Less severe</th>
<th>Disease Severity</th>
<th>More severe</th>
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<tr>
<td>Less severe</td>
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<td>Disease Severity</td>
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| Inclusion/Exclusion criteria

Best “evidence” with NNT>>1

“NO” evidence!
Complex Disease Syndrome: Outside of EBM

Mechanism 1
Mechanism 2
Mechanism 3
Mechanism 4

Non-responders
Highest cost

Inclusion/Exclusion criteria

Fraction of Population

Less severe  ←  Disease Severity  →  More severe
Acute Pancreatitis in 80% with the PRSS1 mutation

Chronic Pancreatitis in 50% with acute pancreatitis

Pancreatic Cancer in >40% with chronic pancreatitis.

• ~3000 patients (RAP/CP) and 1250 controls
• The strongest risk factor for CP is RAP.
• Half of CP patients do NOT drink excess alcohol

  • Alcohol alone is NOT sufficient to cause CP
  • Smoking is a strong risk factor for CP, and risk is multiplied by alcohol use

  • Genetic variants increase susceptibility to CP, severity of CP, and complications of CP.
Sentinel Acute Pancreatitis Event (SAPE)

- Patients have high-risk genes for years without evidence of disease
- Modifying factors appear to have minimal effect in asymptomatic people
- An “random” episode of acute pancreatitis clearly activates the immune system
- An active immune system can be influenced by modifying factors to drive all of the features of chronic pancreatitis.

Whitcomb Gastroenterology 2013;144:1292–1302
New Definition of CP

Original article

Chronic pancreatitis: An international draft consensus proposal for a new mechanistic definition

David C. Whitcomb a,b,c,*, Luca Frulloni d, Pramod Garg e, Julia B. Greer a, Alexander Schneider f, Dhiraj Yadav a, Tooru Shimosegawa g

- ‘Chronic pancreatitis is a pathologic fibro-inflammatory syndrome of the pancreas in individuals with genetic, environmental and/or other risk factors who develop persistent pathologic responses to parenchymal injury or stress.’ (essence)

- “Common features of established and advanced CP include pancreatic atrophy, fibrosis, pain syndromes, duct distortion and strictures, calcifications, pancreatic exocrine dysfunction, pancreatic endocrine dysfunction and dysplasia.” (characteristics)

Organizes genetic and environmental factors in response to the injury/inflammation/resolution/regeneration sequence.

The features within Stages D & E are not surrogates of each other

**Dx** is needed in Stages B, C and D.

**Rx** is aimed at Stages C and D (dashed lines), *symptomatic* Rx at Stage E

AP-RAP, acute pancreatitis and recurrent acute pancreatitis; CP, chronic pancreatitis; DM (T3c), diabetes mellitus Type IIIc or pancreatogenic diabetes mellitus; PDAC, pancreatic ductal adenocarcinoma; SAPE sentinel acute pancreatitis event
Nonspecific Biomarkers

(1) Non-specific
Pancreas Imaging
- EUS
- CT / MRI
Diabetes Mellitus
Pancreatic Insufficiency
Alcohol Use
Older Age
Typical Pancreatic Pain

(2) “Black Box”
Isolated or mild CP Features
“Pancreatopathy”

(3) Late outcomes
Other Diagnoses, or
“Classic CP Features”

(4) CP Progressive Pathway

A. “At Risk” Injury
Susceptibility factors

B. “AP-RAP”
SAPE, then RAP

Susceptibility to recurrence

Injury or stress

C. “Early CP”
CP biomarkers

Resolve

D. “Established CP”
Immune dysregulation
Acinar dysfunction
Islet dysfunction
Pathologic pain
Metaplasia

Fibrosis/sclerosis
Exocrine Insufficiency
DM (T3c)
Pain Syndrome
PDAC

E. “End Stage CP”

Therapeutic approaches
Progression pathways
Symptomatic and supportive treatment

Asymptomatic

Years

Days

Months

Months to Years

Remainder of life

Whitcomb DC. Pancreas. 2016. PMID: 27748718
• Patients with early signs and symptoms of CP, but who do not meet the criteria of “irreversible damage”
• This population of symptomatic patients includes:
  – True early CP
  – “Pancreatopathy” – often associated with DM, EPI
  – “Normal” variants on imaging studies (age, lifestyle)
• Must determine the mechanism of disease (i.e. why?)
• Must select the right biomarkers to make the diagnosis.
• New tools, exact context and diagnostic criteria are needed.
A. For **counseling** family members of affected subjects (rare – use Genetic Counselor)

B. For RAP **etiology** and **prognosis**

C. For **early diagnosis** and **prevention** of CP

D. For **management** of CP complications

E. For **research**
Genetic Variables

- Susceptibility
  - PRSS1/2 (risk and protective)
  - CFTR (5 classes)
  - SPINK1
  - CTRC
  - CAP1
  - CASR
  - CEL
  - CLDN1
  - GGT1
  - ABO
  - MCP1
  - MTHFR

- Modifier genes
  - Pain Genes
  - Phase I/II metabolism
  - Celiac
  - Dyslipidemia genes
  - Diabetes (multiple types)
  - Immune regulator genes
  - Other

Biomarkers

- AP/RAP
  - Amylase, lipase
  - CRP

- Imaging
  - CT
  - MRI / MRCP
  - EUS
  - ERCP

- Pancreatic function test
  - Secretin stimulation test
  - Serum trypsinogen
  - Fecal Elastase
  - Breath test / stool fat measures / others

- Pain measures
  - VAS
  - QOL

- Nutritional markers
  - Vitamin ADEK B12
  - Prealbumin, albumin
  - Weight, BMI Growth
  - Hemoglobin A1c, blood sugar,

- Experimental markers
  - Fibroscan
  - Urine biomarkers
  - Serum biomarkers

Partial List!!
Complex Pancreatitis Syndromes

Pathway

Alcohol pathway

Trypsin pathways

Acinar cell pathway

Duct cell pathway

Necrosis-fibrosis pathway

Gallstones
Hypertriglyceridemia
Obesity

Autoimmune pathway

Type 1
Type 2

ER Stress/UPR

First hit

Prolonged, heavy drinking/withdrawal [PRSS1-PRSS2 locus]

PRSS1-PRSS2 locus
PRSS1 (gain)
Hypercalcemia [alcohol +/- CASR-gain]

PRSS1-PRSS2 locus
CFTR/CFTR (bicarb. loss)*
CFTR (bicarb. loss)*
CASR (loss)

Moderate to severe acute pancreatitis
Widespread
Widespread
Near adipose tissue

Autoantigen?
Genetic/environmental factors–? activating injury

CPA1 (Witt NG 2013)

Second hit

Continued alcohol
Smoking
RAP
CLDN2 locus

RAP
SPINK1 (loss)
CTRC (loss)

Pancreatic necrosis
RAP

Continued inflammation
IgG4 (type 1)
GEL (type 2)

Fibrosis endpoint

Alcohol

Stellate cells (leukocytes)

Fibrosis

Whitcomb Gastroenterology 2013;144:1292–1302
Personalized Medicine for Pancreatic Disorders (ideal)

Current Approach

First Symptoms

Testing for 
Organ damage

Diagnosis made

Symptomatic 
Treatment

Patient is Disabled

Precision Approach

First Symptoms

Testing for 
Genetic Risk

 Diagnosis made

Preventative 
Treatment

Patient is much better
Conclusions

• Irreversible damage is irreversible!
• An ounce of prevention is worth a pound of cure
• Early CP is impossible to diagnose with the traditional definition of CP: *The new mechanistic definition is needed.*
• Signs of early CP are non-specific: *Clinical context, risk assessment and better biomarkers are needed to make an early Dx.*
• **New tools are needed to help busy clinicians.**
Any Questions?