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Commentary

Molecular Mechanisms of Driving the Pathogenesis of Acute and Chronic Pancreatitis

Helmut Fries*

Department of Transplantation Surgery, University of Bern, Bern, Switzerland

DESCRIPTION

Pancreatitis, a condition characterized by inflammation of the pancreas, can manifest in two primary forms: Acute Pancreatitis (AP) and Chronic Pancreatitis (CP). While both share the determining feature of pancreatic inflammation, they differ in their underlying pathophysiology, clinical outcomes, and molecular mechanisms. Understanding these molecular mechanisms is important for developing more effective therapeutic strategies and improving patient outcomes. This article will delve into the molecular processes that drive the development of both acute and chronic pancreatitis. Acute pancreatitis is a sudden inflammatory condition that can range from mild, self-limiting disease to severe, life-threatening complications. The molecular events that trigger acute pancreatitis are complex and involve multiple cellular pathways, including protease activation, inflammatory signalling, and oxidative stress.

Premature activation of pancreatic enzymes

One of the earliest and most critical events in acute pancreatitis is the premature activation of digestive enzymes within the pancreas. Normally, pancreatic enzymes are synthesized in an inactive form (zymogens) and are activated only when they reach the small intestine. However, in acute pancreatitis, various factors can cause these zymogens to become prematurely activated within the pancreas.

Endoplasmic Reticulum (ER) stress

ER stress and the Unfolded Protein Response (UPR) are central to the cellular response in acute pancreatitis. Under normal conditions, the ER is responsible for protein folding and processing. In acute pancreatitis, cellular stress due to enzyme activation, oxidative stress, or ischemia can lead to an accumulation of misfolded proteins. This triggers the UPR, which aims to restore cellular homeostasis by reducing protein synthesis and increasing the degradation of misfolded proteins.

Chronic pancreatitis: Molecular mechanisms

Chronic pancreatitis is a progressive and irreversible inflammatory condition characterized by pancreatic fibrosis, atrophy, and loss of exocrine and endocrine function. The transition from acute to chronic pancreatitis is thought to occur due to repeated episodes of inflammation and damage to pancreatic tissue. The molecular mechanisms underlying chronic pancreatitis are distinct but overlap with the events seen in acute pancreatitis.

Chronic inflammation and fibrosis

The characteristic of chronic pancreatitis is the persistent inflammation that leads to fibrosis, which progressively disrupts normal pancreatic architecture and function. The activation of Pancreatic Stellate Cells (PSCs) is a key event in this process.

Genetic mutations

Genetic mutations are implicated in the development of chronic pancreatitis, particularly in patients with hereditary forms of the disease. Mutations in genes such as *PRSS1* (which encodes trypsinogen), *SPINK1* (which encodes a trypsin inhibitor), and CFTR (Cystic Fibrosis Transmembrane Conductance Regulator) increase the risk of chronic pancreatitis.

Pancreatic ductal changes

In chronic pancreatitis, the ducts become dilated and obstructed due to the accumulation of proteins and inflammatory cells. This obstructive process leads to further tissue injury and inflammation. The ductal epithelial cells produce pro-inflammatory cytokines and chemokines that recruit immune cells, amplifying the inflammatory response.

CONCLUSION

The molecular mechanisms driving the development of acute and chronic pancreatitis are multifactorial and involve complex

Correspondence to: Helmut Fries, Department of Transplantation Surgery, University of Bern, Bern, Switzerland, E-mail: fri.helmtinsel@ug.ch

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interactions between enzymes, inflammatory mediators, genetic mutations, and cellular stress responses. In acute pancreatitis, premature activation of pancreatic enzymes and subsequent inflammatory cascades cause initial tissue injury, while in chronic pancreatitis, repeated injury and unresolved inflammation lead to fibrosis, pancreatic dysfunction, and eventual loss of endocrine and exocrine function. Further research into these molecular mechanisms is essential for developing targeted therapies to prevent, manage, and potentially reverse these debilitating diseases. Advances in understanding the intricate signalling pathways involved in pancreatitis offer hope for the development of more effective treatments, ultimately improving patient quality of life and reducing the burden of these disorders.