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Comparative Characteristics of the Course of Chronic Pancreatitis and the Development of Type 3C Diabetes Mellitus (T3CDM)

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Abstract: Chronic pancreatitis (CP) is a progressive fibro-inflammatory disease of the pancreas, characterized by persistent immune activation, acinar cell damage, and eventual endocrine dysfunction. Type 3c diabetes mellitus (T3cDM), a secondary form of diabetes resulting from pancreatic exocrine pathology, develops in the context of CP via a multifaceted pathogenic process. This review provides a comparative analysis of the clinical and molecular progression from CP to T3cDM. Key mechanisms include activation of the innate immune system (TLR4, NLRP3 inflammasome), chronic endoplasmic reticulum stress and unfolded protein response (UPR), apoptotic signaling in β-cells, and involvement of fibrogenic and pro-inflammatory pathways such as TGF-β/Smad, JAK/STAT3, PI3K/Akt, and MAPK. Epigenetic modifications and dysbiosis further amplify inflammation and fibrosis. The unique clinical features of T3cDM—distinct from types 1 and 2 diabetes—necessitate the development of personalized therapeutic approaches targeting inflammation, fibrosis, and microbiota. This work highlights the importance of early recognition of molecular biomarkers and signaling cascades for improved diagnostic and treatment strategies in pancreatogenic diabetes.

Keywords: Chronic pancreatitis; Pancreatogenic diabetes; TLR4; NLRP3 inflammasome; Fibrosis.

Introduction

Chronic pancreatitis (CP) is a progressive inflammatory-destructive disease of the pancreas, characterized by a persistent inflammatory process, the development of marked fibrosis, and the gradual loss of both exocrine and endocrine functions of the organ. In the pathogenesis of CP, a key role is played by recurrent injury to acinar cells, caused by premature intracellular activation of proteolytic enzymes, disruption of calcium homeostasis, and the development of endoplasmic reticulum (ER) stress [2].

These disturbances contribute to the structural and functional destabilization of the acinar epithelium, mitochondrial dysfunction, the release of lysosomal enzymes (particularly cathepsins), as well as the activation of apoptotic signaling pathways, including the release of cytochrome c and apoptosis-inducing factor (AIF) [10].

Collectively, these mechanisms establish a self-perpetuating inflammatory cascade, in which cellular damage products stimulate the recruitment of immune cells and the production of proinflammatory mediators such as IL-1β, TNF-α, and IL-6, thereby exacerbating tissue injury and promoting the chronicity of the process [13].

The connection between chronic pancreatitis (CP) and the development of pancreatogenic diabetes mellitus (type 3c diabetes, T3cDM) results from a complex interplay of multiple pathogenic mechanisms involving structural, immunological, and molecular-cellular changes.

Damage to the pancreatic islets in the setting of persistent inflammation is accompanied by infiltration of the tissue by immunocompetent cells, the release of proinflammatory mediators, and the development of fibrosis, leading to impaired insulin-secretory function of β-cells and their apoptosis [1].

Literature analysis

Key elements of the innate immune system, particularly Toll-like receptors (especially TLR4) and the multiprotein NLRP3 inflammasome complex, play a pivotal role in the initiation and chronic progression of the inflammatory process. Their activation in response to damaging signals triggers the release of cytokines such as IL-1β, IL-6, and TNF-α, which exert cytotoxic effects on β-cells, cause mitochondrial dysfunction, promote the activation of apoptotic cascades, and contribute to the progressive depletion of the cellular reserve [12].

In parallel, endoplasmic reticulum (ER) stress develops and intensifies in response to excessive production of inflammatory mediators, oxidative damage, and disruptions in calcium homeostasis. Activation of the PERK-eIF2α, IRE1α-XBP1, and ATF6 signaling pathways—collectively known as the unfolded protein response (UPR)—is initially aimed at restoring cellular homeostasis. However, under prolonged stress conditions, the UPR shifts into a pathological phase, marked by the expression of pro-apoptotic factors such as CHOP and BiP, leading to β-cell apoptosis, impaired insulin secretion, and the development of hyperglycemia [3].

Thus, the pathogenic link between chronic pancreatitis (CP) and type 3c diabetes mellitus (T3cDM) involves the coordinated activation of inflammatory receptors, cytokine responses, cellular stress mechanisms, and epigenetic regulators. This interplay leads to the progressive decline of pancreatic endocrine function and the development of a diabetic condition that is distinct from both type 1 and type 2 diabetes in terms of its origin and clinical features.

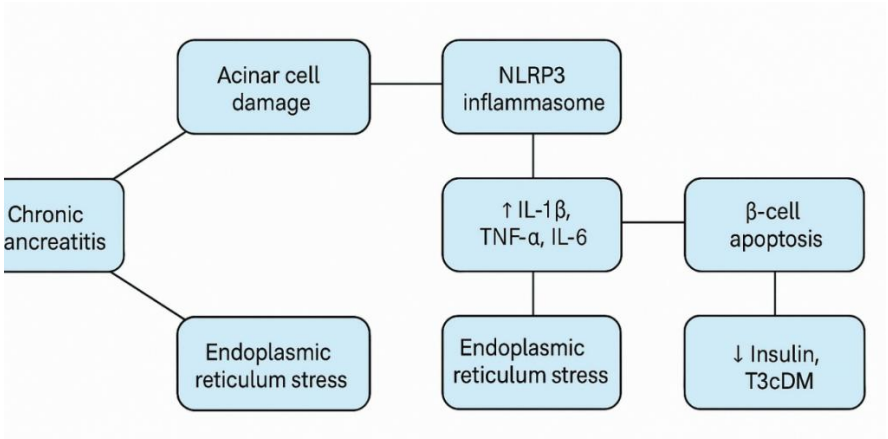

Fig. 1. Pathogenetic link between chronic pancreatitis and the development of type 3c diabetes mellitus (T3cDM) through the activation of inflammatory, stress-, and apoptosis-associated cascades.

The diagram illustrates the key mechanisms linking chronic pancreatitis (CP) with the development of pancreatogenic diabetes mellitus (type 3c diabetes, T3cDM). The central pathogenic elements include activation of the innate immune response (TLR4 and the NLRP3 inflammasome), production of pro-inflammatory cytokines, endoplasmic reticulum stress, and the unfolded protein response (UPR) signaling via PERK, IRE1α, and ATF6. These mechanisms ultimately lead to β-cell apoptosis and impaired insulin secretion.

Discussions

The clinical and pathogenetic progression of CP toward T3cDM can be conditionally divided into several phases. In the early phase, exocrine insufficiency predominates due to acinar cell destruction and reduced secretion of digestive enzymes. This phase is characterized by

steatorrhea, malabsorption, and weight loss, while blood glucose levels typically remain within the normal range [8].

In the transitional phase, as inflammatory and fibrotic changes progress, the islet apparatus becomes involved, leading to impaired glucose tolerance. Such patients exhibit episodes of postprandial hyperglycemia while maintaining relatively normal fasting glucose levels, indicating partial preservation of endocrine function [4].

In the final stage, overt T3cDM develops, characterized by marked reductions in insulin and other pancreatic hormone secretions. Unlike type 2 diabetes mellitus (T2DM), insulin resistance is typically mild, and the leading cause of glycemic instability is the deficiency of insulin, glucagon, pancreatic polypeptide, and somatostatin. This results in frequent glucose fluctuations, including severe hypoglycemic episodes, particularly during insulin therapy [11].

Furthermore, the lack of glucagon-mediated counterregulation aggravates hypoglycemic instability, necessitating an individualized approach to therapy and glucose monitoring. Contemporary studies confirm that patients with T3cDM represent a distinct clinical group differing from those with type 1 or type 2 diabetes in terms of both pathogenesis and therapeutic strategy [5].

At the molecular level, the progression of CP and the development of T3cDM are mediated by a complex activation of multiple signaling cascades and regulatory networks. A pivotal role in fibrogenesis is played by the TGF-β/Smad pathway, which induces the transcription of genes encoding type I and III collagen, fibronectin, and laminin. Activation of Smad2/3 via TGF-βRI/II receptors is associated with the proliferation and myofibroblastic transformation of pancreatic stellate cells (PSCs), contributing to the formation of a dense extracellular matrix [17].

Table 1. Key Signaling Pathways and Their Roles in the Pathogenesis of CP and T3cDM

Signaling Pathway	Key Molecules	Effect	Potential Therapeutic Targets
TGF-β/Smad	TGF-β1, Smad2/3, Collagen I and III	Activation of PSCs, extracellular matrix synthesis, fibrosis	TGF-βRI/II inhibitors, Smad3 inhibitors
MAPK (ERK, JNK, p38)	ERK, JNK, p38, transcription factors	Maintenance of inflammation and fibrosis	ERK, JNK, p38 inhibitors
PI3K/Akt	PI3K, Akt, PTEN	PSC proliferation, apoptosis suppression	PI3K inhibitors, PTEN restoration
JAK/STAT3	JAK1/2, STAT3	Cytokine production, inflammation	JAK/STAT3 inhibitors
PERK–eIF2α (UPR)	PERK, eIF2α, CHOP	β-cell apoptosis induction, decreased secretion	PERK inhibitors, CHOP inhibitors
IRE1α–XBP1 (UPR)	IRE1α, XBP1	Chronic ER stress, cell death	IRE1α inhibitors
NF-κB	IKK, p65, p50	Inflammation and cytokine production	NF-κB inhibitors (e.g., Bay 11-7082)
TLR4	TLR4, MyD88	Initiation of innate immune response	TLR4 antagonists
miR-21 / PTEN	miR-21, PTEN	Fibrosis via PTEN suppression	miR-21 antagonists
HDAC / Epigenetics	HDAC1/2/3, histone acetylation	Enhanced expression of inflammatory and fibrotic genes	HDAC inhibitors (e.g., vorinostat)
Microbiota / LPS / TLR4	LPS, SCFAs, TLR4	Enhanced inflammation and fibrosis	Probiotics, SCFAs, FMT

Additional signaling cascades are simultaneously involved, including MAPK (ERK, JNK, p38), PI3K/Akt, and JAK/STAT3 pathways.These pathways enhance the expression of pro-inflammatory mediators and maintain the activity of pancreatic stellate cells (PSCs), thereby promoting chronic inflammation and subsequent fibrosis [14].

Endoplasmic reticulum (ER) stress also plays a contributory role, characterized by the activation of UPR branches PERK–eIF2α and IRE1α–XBP1. While these pathways initially mediate the production of adaptive proteins, persistent stress leads to the upregulation of CHOP expression, β-cell apoptosis, and intensification of the inflammatory response [6].

Epigenetic mechanisms are also critically involved. In particular, hypermethylation of promoter regions of antioxidant and anti-inflammatory genes such as *SOD2* and *GPX1* reduces cellular defense mechanisms. At the same time, increased expression of miR-21 has been observed, which activates fibrogenic cascades by inhibiting *PTEN* and enhancing the PI3K/Akt signaling pathway [7].

Recent studies also highlight the role of gut microbiota in the pathogenesis of chronic pancreatitis. Dysbiosis is associated with elevated levels of circulating lipopolysaccharides (LPS), which activate TLR4 and trigger pro-inflammatory cytokine expression via the NF-κB pathway, exacerbating pancreatic tissue damage [9]. Furthermore, reduced production of short-chain fatty acids (SCFAs) such as butyrate impairs the anti-inflammatory activity of Treg cells and promotes fibrosis [16].

These processes are closely integrated with epigenetic regulation, including histone deacetylation via HDACs, which activate transcription factors such as NF-κB and STAT3, thereby amplifying inflammation and fibrosis [15].

Conclusions

Chronic pancreatitis (CP) and type 3c diabetes mellitus (T3cDM) result from a multifactorial pathological process involving persistent inflammation, immune activation, mitochondrial dysfunction, epigenetic alterations, and microbiota dysregulation. Comparative analysis of these processes shows that the progression of CP to T3cDM is accompanied by sequential activation of pro-inflammatory cascades, β-cell degradation, impairment of autophagy mechanisms, and a decline in pancreatic hormonal reserve. These mechanisms highlight the need for developing personalized treatment strategies, including targeted agents (JAK/STAT3 and TGF-β/Smad inhibitors), antifibrotic therapies, microbiota modulators, and epigenetic correctors.

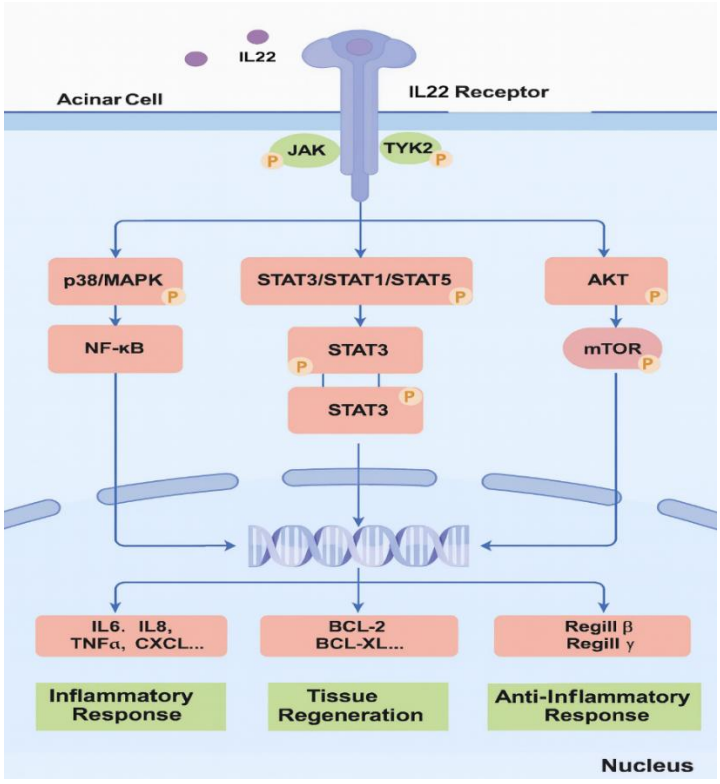

Fig. 2. IL-22 mediates tissue regeneration and anti-infective effects via the JAK/STAT signaling pathway in pancreatitis [18]

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