Új felismerések az akut pancreatitis patomechanizmusában
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New findings in the pathogenesis of acute pancreatitis

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ABSTRACT

Acute pancreatitis is a progressive inflammatory disease with a complex pathomechanism, which is only partially revealed. The mortality of the disease is unacceptably high, therefore there is an emerging necessity to develop specific clinical therapy to treat acute pancreatitis patients. In the recent years experimental results provided new insight into the disease development, which can be utilized in clinical therapy. Early subcellular events in pancreatic acinar and ductal cells, such as toxic intracellular Ca^{2+} overload and mitochondrial damage, and impaired pancreatic ductal fluid and bicarbonate secretion have been highlighted recently. In this brief review we will summarize these advances.

Introduction

Acute pancreatitis (AP) is the most common cause of hospitalization among non-malignant gastrointestinal diseases [1] and therefore it is a major healthcare problem worldwide. The most common causes of AP are heavy alcohol abuse and cholelithiasis [2], however other factors (such as genetic mutations) can play major role in the disease development, especially in children [3]. The disease mortality in severe cases - where multiorgan failure is prolonged - can reach 30-50% [4], moreover the therapy of AP is limited to supportive treatment without specific therapeutical targets.

Intrapancreatic activation of trypsinogen [5], the activation of nuclear factor κB (NF-κB) and the consequent upregulation of inflammatory mediators [6] have been shown to play an important role in the development and the progression of the disease. In addition to these observations, in the recent years several studies highlighted the crucial importance of intracellular Ca^{2+} overload and mitochondrial damage in the AP pathogenesis. Another important progression in the understanding of the disease pathogenesis is the recognition of the role of impaired pancreatic ductal function in the development of AP.

Intracellular Ca^{2+} toxicity in acute pancreatitis

Intracellular Ca^{2+} signaling is one of the major signaling pathways in the exocrine pancreas [7, 8] regulating the secretion of digestive enzymes in acinar cells, or the activity of several ion transporters and channels and therefore bicarbonate and fluid secretion in ductal cells. During physiological receptor stimulation Ca^{2+} is released from the endoplasmic reticulum (ER), which is the major Ca^{2+} store in non-excitable cells. These types of Ca^{2+} signals consist of repetitive, short lasting peaks, which have a strict spatiotemporal localization [9]. The spatial localization in acinar cells is maintained by the mitochondria, which form a belt-like structure in the apical perigranular region of the cells and buffer the released Ca^{2+} preventing its propagation to the basolateral area and the development of global Ca^{2+} elevations [10]. This unique organization of the mitochondria has been described in pancreatic ductal cells as well [11, 12]. The temporal localization of the released Ca^{2+} is achieved through the rapid Ca^{2+} reuptake into the ER by the sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA) and trough extrusion via the plasma membrane (PM) by the PM Ca^{2+} ATPase (PMCA). The operation of these pumps is ATP dependent. On the other hand prolonged agonist stimulation of the cells could empty the Ca^{2+} stores, therefore the cells need other source to maintain the stimulation. This source is usually the external Ca^{2+}, which can enter the cells via PM Ca^{2+} channels during a process called store operated Ca^{2+} entry (SOCE) [13].

The two proteins that mediate this process are the ER transmembrane Ca^{2+} sensor stromal interaction molecule 1 (Stim1) and PM Ca^{2+} channel Orai1. Lowering the Ca^{2+} concentration in the ER causes the translocation of Stim1 to the ER-PM contact sites, where it activates the Ca^{2+} influx via Orai1 (Figure 1.) [14]. This process is part of the physiological signaling however it can be toxic, if the proper regulation is damaged [15]. The intracellular Ca^{2+} overload will lead to premature activation of trypsinogen [5], mitochondrial damage, cell necrosis in acinar cells [16] and impaired bicarbonate secretion in pancreatic ductal cells [12]. In a recent publication Gerasimenko et al. demonstrated the inhibition of extracellular Ca^{2+} entry via Orai1 by a pharmacological compound called GSK-7975A prevents acinar cell necrosis *in vitro* (Figure 1.) [17]. This observation was further challenged by Wen et al., who have tested the effects of two Orai1 inhibitors (GSK-7975A and CM_128) in mouse and human pancreatic acinar cells *in vitro* and in three different *in vivo* pancreatitis model [18]. Both inhibitors prevented the Ca^{2+} overload of human and murine pancreatic acinar cells and significantly impaired pancreatic edema, inflammation and necrosis in all experimental models used. These results not just highlight the crucial role of Ca^{2+} toxicity in the AP pathogenesis, but also raise the possibility of targeted pharmacological treatment in AP. Although the possible application of Orai1 inhibitors have to be carefully investigated in experimental models to avoid potentially lethal side effects, such as severe immunodeficiency due to inhibited T cell function.

Mitochondrial damage and energetic breakdown in pancreatitis

Another hallmark of the AP pathogenesis is the mitochondrial damage [19]. The digestive enzyme synthesis of the acinar cells, or the ion and fluid secretion of the ductal cells require a lot of energy. To provide the sufficient amount of ATP both acinar and ductal cells are densely populated with mitochondria (see above). Under physiological conditions mitochondria buffer the released Ca^{2+}. However under pathophysiological conditions, the control over the Ca^{2+} signaling is lost, which will lead to mitochondrial Ca^{2+} overload. On the other hand the most common toxic factors that induce AP – such as bile acids, ethanol and its metabolites – have direct mitochondrial toxicity as well [12, 16, 20, 21]. Depending on the type of the damage, the mitochondria can induce cell death via two different pathways. Apoptosis is considered as the controlled form of cell death with characteristic subcellular changes (cell blebbing and shrinkage, nuclear fragmentation, chromatin condensation, chromosomal DNA fragmentation) and ATP dependence. During this process cytochrome c is released from the mitochondrial inner membrane electron transport chain leading to the activation of effector

caspases – the mediators of apoptosis. In contrast, necrosis is predominantly an unregulated mechanism of cell death that include loss of mitochondrial transmembrane potential ($\Delta\psi_m$), decreased ATP production, mitochondrial swelling, vacuolization, loss of plasma membrane integrity and crucially, leakage of the intracellular contents [22]. In this process a key step is the opening of the mitochondrial permeability transition pore (MPTP) induced by mitochondrial matrix Ca^{2+} overload. MPTP is a non-specific channel that forms in the inner mitochondrial membrane allowing passage of molecules under 1.5 kDa, causing loss of $\Delta\psi_m$ that is essential to ATP production [23].

During AP apoptosis and necrosis co-exists, although apoptosis seems to be less harmful due to the lower activation of the immune system [24]. However the available experimental and clinical data are controversial in this topic. Very recently Mukherjee et al. tested the effect MPTP inhibition on the severity of AP in rodent experimental AP models (Figure 2.) [25]. They have shown that the inhibition of MPTP with pharmacological compounds (two cyclosporine A derivate: DEB025 or TRO40303), or genetic deletion of the *Ppif* gene (that encodes cyclophylin D, a component of MPTP) significantly decrease the severity of AP in different independent models. These observations suggest that the MPTP inhibition might be potentially beneficial in the AP therapy. In a recent clinical study the efficacy and safety of TRO40303 (an MPTP inhibitor) have been evaluated for the reduction of reperfusion injury in patients undergoing revascularization for ST-elevation myocardial infarction (MITOCARE study) [26]. Although this study did not show any effect of TRO40303 in limiting reperfusion injury of the ischaemic myocardium, this therapeutical approach shall be tested on AP treatment as well. Another indirect evidence for this hypothesis has been provided by Judak et al., who showed that the supplementation of cellular ATP *in vitro* diminished the inhibitory effect of ethanol metabolites on the ion transport activities in isolated guinea pig pancreatic ductal cells [27]. These results suggest that the restoration of the cellular energy level can be beneficial in AP, which can prevent the cellular dysfunction and cell damage.

The role of pancreatic ductal secretion in the pathogenesis of AP

Until the recent years the research studies highlighted the role of pancreatic acinar cells in the AP pathogenesis, however nowadays it is well established that the pancreatic ductal epithelial cells play an important role in the physiology of the pancreas as well [7, 28]. The exocrine pancreas produces 2,5L of alkaline fluid daily, which washes the digestive enzymes into the duodenum. Changes that effects the ductal secretion affect the acinar cell function as well and can lead to serious diseases like cystic fibrosis [29]. Moreover our group demonstrated

that the autoactivation of trypsinogen is a pH dependent process, with increased activity in acidic environment, which means that HCO_3^- secretion prevents the untimely trypsinogen autoactivation [30]. These observations indicate that acinar and ductal cells don't function independently, but it is more likely that they create an acino-ductal functional unit, where they act as an integrated system and interact with each other during physiological secretion [31, 32]. Besides its physiological role, the ductal secretion seems to have pivotal role during the pathogenesis of AP as well. Insufficient electrolyte and fluid secretion by pancreatic ductal cells seems to lead to increased patient risk for pancreatitis [33]. These clinical observations have been supported by experimental data by Pallagi et al. [34]. They showed that mice with deletion of the Na^+/H^+ exchanger regulatory factor-1 that have selectively impaired ductal function develop more severe AP upon cerulein hyperstimulation, or intraductal administration of sodium taurocholate. In addition, we have shown that pancreatic epithelial fluid and bicarbonate secretion is significantly elevated in the absence of peripheral serotonin [35] (an important inhibitor of pancreatic ductal secretion [36, 37]), which might contribute to the decreased severity of AP in these mice [38]. Taken together these observations highlight the potential benefits of the correction of pancreatic ductal secretion in the treatment of AP.

Damaged cystic fibrosis transmembrane conductance regulator (CFTR) function in AP

CFTR Cl^- channel play an important role in the bicarbonate secretion of the pancreatic ductal epithelial cells into the ductal lumen (Figure 3.) [39]. It is also established that mutations of *CFTR* that impair bicarbonate permeability can increase the risk of AP [40]. Moreover experimental data suggest that CFTR function can affect the pathogenesis and severity of AP. DiMagno et al. showed that genetic deletion of *CFTR* in mice induce overexpression of proinflammatory cytokines, moreover these mice develop more severe AP [41]. Recently we investigated the role of CFTR in the pathogenesis of alcohol-induced AP in details and showed that indeed the *in vivo* pancreatic fluid secretion is markedly decreased in CFTR knockout mice (Figure 3.) [20]. These mice displayed more severe AP induced by intraperitoneal injection of ethanol and fatty acid. In addition, in pancreatic tissue samples from patients diagnosed with alcohol-induced AP the CFTR protein and mRNA expression were markedly decreased in small pancreatic ducts [20]. This mechanism also seems to be relevant in other forms of pancreatitis. In human pancreatic tissue samples Ko et al. described CFTR mislocalisation in alcoholic, obstructive and idiopathic chronic pancreatitis [42]. Our observations supported this observation, moreover we showed that this decrease is caused by the direct effects of ethanol and ethanol metabolites on CFTR expression (accelerated plasma

membrane turn over and decreased protein maturation due to impaired protein folding) [20]. The impaired fluid and bicarbonate secretion due to the CFTR mislocalisation could lead to decreased intraluminal pH, decreased wash out of the digestive enzymes and a protein rich ductal fluid [43]. These changes promote the formation of intraluminal protein gel, or plugs that are one of the earliest histological features of chronic pancreatitis [44, 45].

Conclusions and future perspectives

In this review we summarized the recent improvements in the understanding of the pathogenesis of AP. Evidences from different research groups suggest that sustained intracellular Ca^{2+} overload and mitochondrial damage with a consequent ATP depletion have key role in acinar and ductal cell injury during AP. This cell injury will lead to impaired secretion and premature activation of digestive enzymes and impaired ductal fluid and bicarbonate secretion. Experimental evidences suggest that the inhibition of cellular Ca^{2+} overload, or the prevention of mitochondrial damage might have clinical relevance in the AP therapy and shall be utilized in clinical trials and guidelines [3, 46-49]. An important conclusion from these results - which have already been utilized in a clinical trial [50] - is the emerging significance of the early cellular changes in AP. For effective therapy, patients with AP have to be diagnosed as early as possible and the assessment of severity is crucial in the management of the disease. Early recognition of severe disease may prevent serious adverse events and improve patient management as well as overall clinical outcome, therefore in this trial the authors aimed to develop a simple and accurate clinical scoring system that can stratify patients with AP during the first 6-12 hours of hospitalization according to their risk for severe disease course. Our observations also highlight the importance of the pancreatic ductal secretion and the wash out of the digestive enzymes from the lumen. Moreover Takacs et al. described that the luminal pH was significantly lower in patients with acute biliary pancreatitis vs. controls [51]. Dubravcsik et al. applied these experimental results to improve the outcome of biliary AP and designed a clinical trial to show whether early endoscopic intervention with the usage of preventive pancreatic stenting – and the restoration of the pancreatic ductal outflow - improves the outcome of acute biliary pancreatitis [52].

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Figure legends

Figure 1. Inhibition of Ca^{2+} overload is beneficial in experimental AP. A. Store operated Ca^{2+} entry (SOCE) is part of the physiological Ca^{2+} signaling. The two proteins that mediate SOCE are the endoplasmic reticulum (ER) transmembrane Ca^{2+} sensor stromal interaction molecule 1 (Stim1) and the plasma membrane (PM) Ca^{2+} channel Orai1. Exhaustion of the ER Ca^{2+} stores induces Stim1 translocation to the ER-PM contact sites, where it activates the Ca^{2+} influx via Orai1. However during AP the control over Ca^{2+} entry is lost, leading to toxic Ca^{2+} overload. **B.** Recent experimental data suggest that the inhibition of Orai1 and therefore the protection of the pancreatic acinar cells from sustained Ca^{2+} elevation are beneficial in AP.

Figure 2. Mitochondrial damage in AP. A. The most common pancreatitis inducing factors - such as alcohol and bile acid – induce mitochondrial damage and consequent ATP depletion in pancreatic acinar and ductal cells. The toxins can maintain sustained Ca^{2+} release, which can induce the opening of the mitochondrial permeability transition pore (MPTP), or damage the mitochondria directly. These changes induce cell death, which is a hallmark of AP. **B.** The genetic, or pharmacologic inhibition of MPTP can protect the mitochondria and decrease the cellular damage in AP.

Figure 3. Impaired CFTR function and pancreatic ductal bicarbonate secretion in AP. Under physiological conditions (left) CFTR is expressed on the luminal membrane of small inter/intralobular pancreatic ducts with the SLC26A6 Cl^-/HCO_3^- exchanger. The secretory function of these proteins maintains the alkaline intraluminal pH (pH_L) and washes out the digestive enzymes from the ductal lumen. During alcohol-induced AP (right) the function of CFTR is inhibited and the expression is decreased leading to impaired bicarbonate and fluid secretion and consequently drop in the pH_L. The washout of the activated digestive enzymes is insufficient. These changes together will increase the severity of AP.

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