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Review

The Pathogenesis of Pancreatitis and the Role of Autophagy

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Abstract: The pathogenesis of acute and chronic pancreatitis has recently evolved as new findings demonstrate a complex mechanism operating through various pathways. In this review, the current evidence indicating that several mechanisms act in concert to induce and perpetuate pancreatitis were presented. As autophagy is now considered a fundamental mechanism in the pathophysiology of both acute and chronic pancreatitis, the fundamentals of the autophagy pathway were discussed to allow for a better understanding of the pathophysiological mechanisms of pancreatitis. The various aspects of pathogenesis, including trypsinogen activation, ER stress and mitochondrial dysfunction, the implications of inflammation, and macrophage involvement in innate immunity, as well as the significance of pancreatic stellate cells in the development of fibrosis, were also analyzed. Recent findings on exosomes and the miRNA regulatory role were also presented. Finally, the role of autophagy in the protection and aggravation of pancreatitis and possible therapeutic implications were reviewed.

Keywords: pancreatitis; autophagy; mitochondrial abnormalities; ER stress; innate immunity; macrophages; fibrosis

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1. Introduction

The main etiologies of both acute (AP) and chronic pancreatitis (CP) are still gallstones and prolonged alcohol consumption. Their incidence is closely related to the prevalence of gallstone disease and alcohol abuse [1]. Alcohol abuse as a cause of pancreatitis requires consumption of ≥4–5 drinks per day over >5 years [2].

An additional risk factor is smoking, as several studies support an important role for either smoking alone or in combination with alcohol abuse [3–5]. The role of hypertriglyceridemia has also been established, as this is the third leading cause of acute pancreatitis [6,7]. It has been reported that approximately 15–20% of individuals with triglyceride levels over 1000 mg/dL will develop acute pancreatitis [8]. Other common etiologies of acute pancreatitis include complications of endoscopic retrograde cholangiopancreatography and autoimmunity, while in a small proportion of cases, no obvious factors can be identified and the term idiopathic pancreatitis is used [1,9]. Diabetes has been associated with an increased risk for pancreatitis [10–12]. Finally, medication-related pancreatitis is not a common cause, accounting for fewer than 5% of cases [13]. Drugs strongly associated with acute pancreatitis include azathioprine, 6-mercaptopurine, didanosine, valproic acid, angiotensin-converting enzyme inhibitors, and mesalamine [13].

A distinct group are patients where the first episodes of acute pancreatitis appear before the age of 35. Genetic abnormalities are found in nearly half of them [14]. Interestingly, a genetic mutation in claudin 2 may synergize with alcohol consumption in the development of pancreatitis, indicating the interplay between external and genetic factors in the pathogenesis of pancreatitis [15,16].

Chronic pancreatitis develops in about 10% of patients after the first episode of AP and in about 30% of patients with recurrent AP. Male sex and alcohol abuse are significant risk factors for the transition from AP to CP [17]. Chronic inflammation of the pancreas is caused by acinar and ductular cell injury driven by alcohol, smoking, hypercalcemia, genetic factors, or any combination of the above. It is distinguished from autoimmune CP, which responds to steroid treatment, obstructive CP, and infectious CP. Classic CP can be dominated either by fibrosis or by atrophy [18–20]. The relationship of ethanol and smoking to CP has been unequivocally proved. The amount and duration of ethanol consumption have been estimated to be either a median of 5.1 drinks/d or a consumption of up to 110–277 g ethanol/d over 5–25 years, similarly to AP [21–25]. As in AP, a synergy among genetic, immune, and environmental factors may be important [26–30]. Interestingly, post-mortem pathological studies of chronic alcoholics without a previous AP event in their medical history showed the presence of fibrosis and/or ductal calcifications in 47–68% of cases, indicating extensive CP that escaped undiagnosed [25,31,32].

The pathogenesis of both AP and CP is a complex process with many points that have not been fully investigated. Several mechanisms have been incriminated, such as acinar cell auto-digestion, mitochondrial abnormalities, and the involvement of immunity and inflammation. Recently, the role of autophagy has been recognized but not yet fully investigated. Therefore, in this review, we report an outline of the pathophysiology of pancreatitis, with a detailed presentation of the role of autophagy.

2. A Brief Overview of Autophagy

Autophagy is a degradation pathway that allows for the disposition of intracellular waste material including damaged organelles or intracellular pathogens. After lysosomal degradation, most of the final products can be recycled and re-used, supporting the energy system of the cell.

The term autophagy (a Greek word for self-eating) was introduced by Anselmier [33]. The modern concept of autophagy, however, started with the pioneer work of Christian René de Duve in the 1950s, when acid-phosphatase-positive granules were identified in the rat liver [34] and the term lysosome appeared for the first time [35]. The next important step came when the group of Oshumi described a series of fifteen autophagy-related genes (*Atgs*) involved in Saccharomyces cerevisiae autophagy [36]. Today, more than 40 *Atgs* have been identified [37]. The importance of autophagy led to the awarding of two Nobel Prizes for Physiology or Medicine, the first to Christian De Duve in 1974 and the second to Yoshinori Ohsumi in 2016 [38]. Historical landmarks of autophagy have been described by Ohsumi [39].

There are several stages in the pathway of autophagy. The initiation stage is followed by the elongation of the phagophore and the autophagosome formation, followed by fusion with lysosomes and degradation of cellular organelles, proteins, and lipids.

Initiation stage and phagophore formation. Autophagy inducers are responsible for the initiation stage. In reality, autophagy is a series of phosphorylations and dephosphorylations [40]. Three kinases are the main regulators of autophagy, namely the mammalian target of rapamycin (mTOR), the Unc-51 like autophagy activating kinase (ULK1), and the AMP-dependent protein kinase (AMPK) [41]. Autophagy inducers, such as starvation and increased levels of reactive oxygen species (ROS), repress mTOR and activate AMPK, which results in ULK1 activation [42]. Phosphorylation of ULK1 by mTOR reduces its activity, thus decreasing autophagy, while phosphorylation by the AMPK at a different site activates ULK1 and autophagy [43]. Upon induction of autophagy, the ULK1 complex is formed from the assembly of the ULK1, ATG13, FIP200, and ATG101 proteins [44,45]. Autophagy is also upregulated by p38 through inhibition of mTOR, while c-Jun N-terminal kinase1 (JNK1) and BNIP3 (BCL2/adenovirus E1B 19 kDa protein-interacting protein 3) disrupt the B-cell lymphoma 2 (Bcl-2)–Beclin1 complex, inducing autophagy [46,47]. Free Beclin1 binds to Vps34-Vps15 to increase autophagy through the formation of the class III PI3K kinase complex (PI3KC3), consisting of Vps34-Vps15-Beclin1 [48,49]. These complexes

lead to the formation of the autophagosome. Then, Vps34 produces phosphatidylinositol-3-phosphate to recruit the effector protein DFCP1, which promotes the development of the double membrane phagophore [50]. The phagophore is generated from the endoplasmic reticulum (ER) or Golgi membranes, mitochondria, and plasma membrane via endocytosis mediated by clathrin.

There are some additional points in the regulation of the initial stages of autophagy. AMPK can negatively regulate mTORC1, either directly through the phosphorylation of mTORC1 activity or indirectly by activating TSC2, which is a strong inhibitor of mTORC1 [51]. Recently, an additional mechanism for mTORC1 activation under energy-rich conditions was described. mTORC1 phosphorylates the protein Pacer, causing the disruption of the complex formed by the proteins Pacer, Syntaxin17 (Stx17), and the homotypic fusion and vacuole protein sorting (HOPS), thus inhibiting the autophagosome maturation mediated by this complex [52,53].

Two additional autophagy regulators have been described. The long non-coding RNA (lncRNA) NBR2 inhibits Beclin 1-dependent autophagy and attenuates the autophagy-induced cell proliferation [54], while Forkhead box O3 (FOXO3), a member of the FOXO subfamily of transcription factors, upregulates autophagy, acting on ULK1, Beclin-1, and LC3 [55].

Expansion (elongation). ULK1 phosphorylation leads to autophagosome formation. The critical step is the phosphorylation of ATG13, leading to the formation of the complex ATG5-ATG12, ATG16L1 [56,57]. This complex and the phosphatidylethanolamine (PE)-LC3 systems are critical for the elongation of phagophores [50]. Pro-LC3 cleaved by ATG4B leads to the generation of the cytosolic form of LC3 (LC3-I). Then, ATG7 processes LC3-I and ATG3 to be conjugated to PE and form LC3-II. The transformation of phagophores into autophagosomes requires the ATG12–ATG5–ATG16 complex and the PE-conjugated LC3II (ATG8) system. Autophagosomes contain materials or cellular organelles destined for degradation.

Autophagosome fusion to the lysosome. This is the final stage of autophagy that allows for the autophagy flux. The autophagosome does not contain hydrolases and the pH is neutral. Fusion with lysosomes forms autolysosomes during the so-called autophagic flux. Overproduction of autophagosomes faster than the flux rate or when flux is repressed will increase the levels of LC3 and p62 [58]. Components that are destined to lysosomal degradation are either labeled by ubiquitin or attached to receptors, such as sequestosome 1 (SQSTM1, also known as p62), and CALCOCO2 (calcium binding and coiled-coil domain 2). These receptors interact with LC3 to deliver the component into the autophagosomes [59,60].

A critical point for fusion to occur is the presence of soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) proteins localized in opposing membranes of the particles to be fused. Two SNARE complexes mediate the fusion of autophagosomes with lysosomes. The first consists of STX17-SNAP29-VAMP8 [61], and the second is composed of YKT6-SNAP29-STX7 [62]. For a complete fusion, additional proteins are also recruited, such as the HOPS complex, baculovirus IAP repeat containing ubiquitin-conjugating enzyme (BRUCE), and GRASP55, that bind to proteins of the lysosomal membranes, such as Rab-7 and Monensin sensitivity protein 1—Caffeine, calcium, and zinc 1 complexes (Mon1-Ccz1) [63]. ATG8 proteins also contribute to fusion protein recruitment, but they must be removed before final fusion [64]. Rab7 binds to FYCO1 (FYVE and coiled-coil domain-containing 1), ORP1L (oxysterol-binding protein-related protein 1L), and RILP (Rab-interacting lysosomal protein). In the next step, SM (Sec1/Munc-18) family proteins facilitate SNARE complex assembly and zippering. The zippering of these domains fuses the membranes, and SNAREs are now located on the same membrane [65]. The autophagosome–lysosome fusion process requires SNARE complex disassembly on post-fusion membranes [66].

Autophagosome degradation and recycling. After fusion, hydrolases that are active at acidic pH digest the different constituents. In lysosomes, the vacuolar ATPase (vATPase)

regulates the import of hydrogen ions to maintain the acidic pH. The same vATPase also induces the transcription factor EB (TFEB). TFEB is phosphorylated in starvation conditions, translocates to the nucleus, and induces the transcription of genes that promote autophagy, including LC3 and p62 [67,68]. mTOR activation decreases TFEB activity, and the autophagic machinery is repressed [69]. TFEB is also a controller of lysosomal biogenesis genes [70,71]. TFEB and ZKSCAN3 are major antagonistic factors during autophagy. ZKSCAN3 is the major transcriptional repressor of autophagy by targeting biogenesis and fusion of autophagosomes and lysosomes [72,73]. TFEB is also a controller of inflammation. Reduction of TFEB leads to exacerbation of inflammation [74]. After degradation, the breakdown products are moved back into the cytosol by lysosomal transporters and re-utilized by the cell [75].

Non-canonical forms of autophagy were reported as leading to similar fusion [76]. Several members of the *Atg* machinery are not used. Rab9-mediated autophagy functions in cells with *atg5* and *atg7* deletion. This non-canonical autophagy does not require ATG8/LC3 but is directly regulated by ULK1 [76]. By contrast, LAP is another form of non-canonical autophagy that does not require ULK1/2 but requires ATG8/LC3 conjugation instead and involves ATG5 and ATG7. LAP recruits LC3-II to the phagosomal membrane [77–79] and is taken up by macrophages through innate immune receptors, such as Toll-like receptors. In contrast to classical autophagy, the LAPasome is a single membrane vacuole. The term CASM (conjugation of ATG8 to single membranes) was introduced to describe these related pathways [80–82]. Detailed descriptions of the autophagy pathway have recently been published [66,83].

Figure 1 summarizes in a simplified diagram the various steps of autophagy.

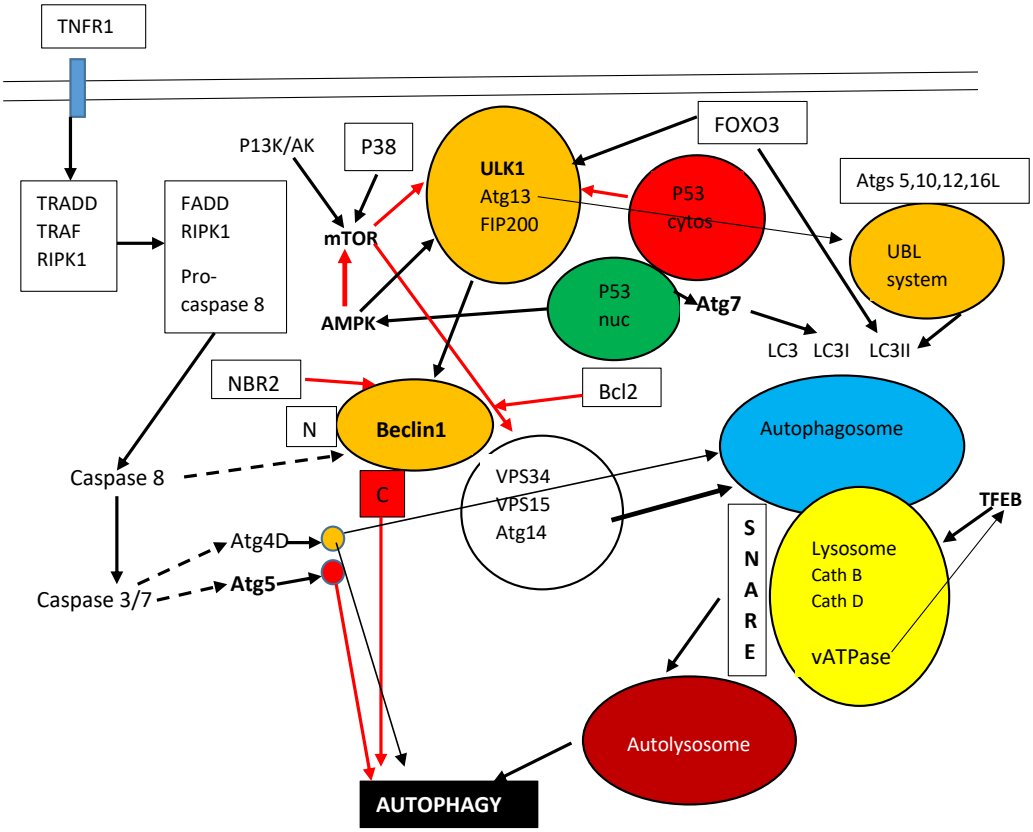

Figure 1. A simplified diagram of autophagy regulation. Black arrows: activation. Red arrows: inhibition. Intermittent arrows: cleavage. Certain pathways have been omitted for clarity. See text for more details. Bcl-2: B-cell lymphoma-2; FADD: Fas-associating protein with death domain; TRADD: Tumor necrosis factor receptor type 1-associated DEATH domain protein; RIPK1: Receptor Interacting Serine/Threonine Kinase 1.

The main regulators of autophagy are three kinases, namely the mammalian target of rapamycin (mTOR), the Unc-51 like autophagy activating kinase (ULK1), and the AMP-dependent protein kinase (AMPK). ULK1 and AMPK activation promote autophagy, while mTOR activation inhibits autophagy. Beclin 1 and Bcl-2 are important elements in the process. Activation of the TNFR1 leads to caspase 8 activation that cleaves Beclin 1, and the C-terminal fragment inhibits autophagy. The cleavage of Atg4D by caspase-3 generates a fragment, which increases autophagy. The effect of P53 on autophagy depends on localization. Cytoplasmic P53 inhibits autophagy, while nuclear P53 activates AMPK, increasing autophagy.

2.1. Mitophagy

A specialized form of autophagy that is pertinent in pancreatitis is mitophagy. It selectively degrades damaged mitochondria irrespective of the cause of damage [84,85]. Mitophagy is induced by two signal pathways, the PINK1 (PTEN-induced putative kinase 1)-PARKIN (parkin RBR E3 ubiquitin protein ligase) pathway and the PINK1/PARKIN-independent pathway [86,87]. PINK1 is aggregated into the inner mitochondrial membrane (IMM) in normal mitochondria through the activity of the TOM (translocase of the outer mitochondrial membrane) and TIM23 (translocase of inner mitochondrial membrane 23) proteins. PINK1 is cleaved by PARL (presenilin-associated rhomboid like). During severe oxidative stress, impaired mitochondria are not capable of PINK1 seggregation into the IMM. PINK1 associates with TOM and accumulates on the outer mitochondrial membrane (OMM) [88,89], where it recruits and activates Parkin from the cytoplasm [90]. Parkin ubiquitinates several OMM proteins, such as mitofusin 1 and mitofusin 2, voltage-dependent anion channel (VDAC), and Miro [91,92]. Cargo receptor proteins, such as p62, OPTN (optineurin), and CALCOCO2, bind to these OMM proteins to start autophagosome formation [91,93] and subsequent fusion with lysosomes. Mitophagy may be upregulated by phosphorylation of OPTN via the activation of TBK1 (TANK-binding kinase 1) [94,95].

PINK1/Parkin-independent mitophagy requires interaction of LC3II through the LC3-interacting region (LIR) with OMM proteins, such as FUN14 domain containing 1 (FUNDC1), NIP3-like protein X (Nix/Bnip3L), and Bcl-2/adenovirus E1B (Bnip3). The interaction leads damaged mitochondria to the autophagosomes and lysosomal fusion [86].

Details on mitophagy mechanisms have recently been published [96–100].

There are several other specialized forms of autophagy, but their role in pancreatitis has not been investigated [86].

2.2. Autophagy and Immunity

Autophagy is implicated in the regulation of the immune system [101,102], particularly in the regulation of innate immunity in macrophages [103,104]. Interestingly, there is evidence that high autophagic activity is implicated in acquired immunity as well because it maintains the differentiation and function of regulatory T (Treg)-cells [105] and γ δ T-cells [106].

2.3. Autophagy and Cell Death

Autophagy is mostly a protective cellular mechanism supporting cell survival. However, it may turn into a cellular death mechanism through its effect on apoptosis [107]. Autophagy is tightly related to apoptosis. These two pathways are affecting each other, being mutually exclusive [108]. Autophagy reduces the induction of caspase-dependent apoptosis, and apoptosis-associated caspase activation suppresses the autophagic process. Yet, autophagy may induce apoptosis or necrosis, while autophagy itself may degrade the cytoplasm, leading to autophagic cell death [109,110]. The balance between p53 and AKT/mTOR is crucial for the fate of cells [111]. Autophagy also induces a newly described mechanism of cell death named ferroptosis [112,113]. Many proteins vital for autophagy (like ATGs) also participate in ferroptosis. Additionally, activators of ferroptosis, such as

erastin, initiate autophagosome formation, while activation of autophagy led to ferroptotic death, possibly by increasing ferrous availability through ferritinophagy [114,115].

2.4. Autophagy and Inflammation

Autophagy is also implicated in the inflammatory response. Inflammasomes and autophagy affect each other. The same inhibitory mechanisms are involved, but they are regulated by different pathways. Autophagy could either repress the assembly of the nucleotide-binding oligomerization domain-like receptor family pyrin domain containing 3 (NLRP3) inflammasome [116] or eliminate active inflammasomes, particularly in macrophages [117]. In addition, the degradation of damaged organelles by autophagy does not allow for the production of more danger-associated molecular patterns (DAMPS) that would further activate NLRP3 inflammasomes [118]. DAMPS activation of NLRP3 leads to pyroptosis through the activation of procaspase 1 activation followed by the production of IL-1β and IL-18 [119]. This negative interplay between autophagy and inflammasome can become positive. Autophagy may induce NLRP3 activation by initiating NF-kB nuclear translocation, leading to pyroptosis [120,121].

3. Pathogenesis of Acute Pancreatitis

Various pathways have been implicated in the complex pathogenesis of AP. Thus, pathological calcium signal transduction, mitochondrial dysfunction, premature activation of trypsinogen in acinar cells and macrophages, endoplasmic reticulum stress (ERs), unfolded protein reaction (UPR), and autophagy impairment have been investigated mostly in animal models [122,123]. Earlier experimental evidence indicated that both acinar cells and ductal cells participate in the pathogenesis of acute pancreatitis. Recently, exosomes that contain proteins, nucleic acids, and lipids have been incriminated in the evolution of AP [124,125].

Abnormalities of intracellular organelles of acinar cells are the basis of the pathogenesis of acute pancreatitis in close association with abnormalities of water and electrolyte secretion by the ductular cells [126,127]. Pancreatic enzyme secretion is blocked in edematous and necrotizing pancreatitis models [128]. On the other hand, pancreatic fluid secretion is four- to five-fold increased at the early stages of pancreatitis, indicating that a defense mechanism is activated to attenuate the severity of the disease [129]. Secretin administration reduces the severity of cerulein-induced pancreatitis [130], a fact that supports the protective effect of this ductal hypersecretion, although this has been disputed [131,132]. The interplay between ductular and acinar cells is also supported by studies demonstrating that pancreatic duct obstruction alone can modify acinar cell membrane trafficking and the evolution of pancreatitis [133]. This is possibly due to the increased intraductal pressure, exposure of cells to bile acids, and acidification of the lumen [134–137]. An increased intraductal pressure can activate the mechanoreceptor PIEZO1 in the acinar cells to trigger the abnormal calcium signaling discussed below [135] in concert with inflammation and activation of the signal transducer and activator of transcription 3 (STAT3) pathway [138]. Acidification of the pancreatic lumen activates the transient receptor potential vanilloid 1 (TRPV1) in the sensory neurons and causes acute pancreatitis [134]. PIEZO1-mediated and TRPV1-mediated mechanisms of AP are considered to be the main underlying mechanisms for post-ERCP and gallstone pancreatitis [135,139]. Bile acids, on the other hand, can cause mitochondrial dysfunction and damage of the ductal cells [126] that exposes acinar cells to high bile acid concentrations, leading to their death [136,140,141].

These pathogenetic mechanisms are further analyzed.

3.1. Cellular Mechanisms Involved in AP Pathogenesis

3.1.1. Ca^{++} Signaling and Mitochondrial Dysfunction

Under normal conditions, Ca^{++} is released from the ER in association with zymogen exocytosis and production of ATP in the mitochondria [142]. This is only a transient increase in cytosolic Ca^{++}, as two ATP-driven calcium channels rapidly reduce the cytosolic calcium.

The smooth ER Ca^{++} channels (SERCAs) send Ca^{++} back into the ER, while the plasma membrane Ca^{++} channels (PMCAs) transport Ca^{++} out of the cell [142]. Protracted elevation of Ca^{++} concentration in acinar cells initiates activation of pro-inflammatory pathways, such as premature trypsinogen activation, activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB), and mitochondrial dysfunction leading to cell death [143–145]. Alcohol and bile acids can cause a sustained pathological cytosolic calcium elevation through the inositol 1,4,5-trisphosphate receptor (Ins (1,4,5) P3R) signaling pathway. Alcohol metabolites in the acinar cells open Ins (1,4,5) P3Rs, which are Ca^{++} channels located in the ER [146,147], thus increasing Ca^{++} release from the ER lumen [145,148,149]. Increased Ca^{++} concentration activates the calcium channel protein 1 (ORAI1) to further increase Ca entry into the cell from the outside, maintaining the lethal cellular calcium concentration [150,151]. On the other hand, ductal obstruction, as observed in post-ERCP and gallstone pancreatitis, increases Ca^{++} entry from the outside through the mechanoreceptor PIEZO1, as mentioned before [135]. Moreover, the high calcium concentration opens the mitochondrial permeability transition pores (MPTP), abolishing the membrane potential needed to generate ATP [145,152,153]. In turn, ATP depletion completes a vicious circle, maintaining the high Ca^{++} concentration by disrupting the ATP-dependent SERCAs and PMCAs' clearance of excessive calcium. ATP depletion also impairs other ATP-driven protective mechanisms, such as autophagy and the UPR [122,142], promoting, therefore, acinar cell necrosis.

3.1.2. Mitochondrial Dysfunction

Mitochondrial abnormalities of acinar cells are found in all forms and models of pancreatitis. They cause reduction of ATP synthesis, increased ROS production, and impairment of calcium transport [122,152,154–156]. In pancreatitis, there is permeabilization of the mitochondrial membrane due to a sustained opening of the MPTPs, the nonspecific channels crossing both IMM and OMM [157–159]. Opening of the MPTPs allows for the uncontrolled entry of water and solutes less than 1500 Da into the matrix, leading to inhibition of ATP synthesis and cellular necrosis. On the other hand, inhibition of the MPTP opening attenuates ATP depletion and acute experimental AP [152]. Not only mitochondrial Ca^{++} overload, but also increased reactive oxygen species (ROS) generation, cause MPTP opening. Peptidylprolyl isomerase D (cyclophilin D-CypD) is an essential mitochondrial protein around which the MPTPs are organized. CypD inhibition for any reason will block MPTPs' opening and prevent AP [122,154]. Individual mitochondria form a network that is involved in the mitochondrial activity [160]. In addition, abnormal mitochondrial membrane function releases mitochondrial contents into cytosol, including cytochrome c, which lead to cell death [161].

Aerobic metabolism in mitochondria generates most of the ATP, and only a small quantity is produced by glycolysis. In pancreatitis, anaerobic conditions predominate due to microvascular abnormalities and relative hypoxia of pancreatic tissues. Therefore, the generation of ATP is reduced and not sufficiently replaced by anaerobic glycolysis [30]. Acinar enzyme secretion and ductular bicarbonate production are also significantly reduced [140,162,163]. It should be noted that bile and fatty acids also inhibit ATP production from both sources in acinar and ductal cells [140,164].

An additional difficulty in the pathophysiology of pancreatitis is that current evidence indicates the formation of an interconnected system by different organelles in the acinar cell. Damage of one organelle can lead to failure of the entire network. Thus, the multiple organelle abnormalities found in acute pancreatitis resemble the chicken and egg problem, as it is difficult to dissect the different components responsible for the induction and evolution of AP [122,165]. This is best exemplified in the involvement of the endoplasmic reticulum in the pathophysiology of AP.

3.1.3. Endoplasmic Reticulum (ER) Stress

Mitochondria and ER are closely associated with membrane domains [166,167] providing the amount of calcium required for ATP generation [168,169]. Disruption of the ER–mitochondria interconnections leads to pathologic Ca^{++} signaling in the acinar cell and low ATP levels [168].

ER stress is the excessive accumulation of misfolded or unfolded proteins within the ER lumen observed when the capacity of the ER to eliminate these proteins is overwhelmed [170]. The pancreas is prone to ER stress because acinar cells produce a large quantity of proteins daily, such as trypsinogen, lipase, and several other lysosomal enzymes [171,172]. ER stress is found frequently in AP and can be triggered by hypoxia, alcohol consumption, Ca^{++} overload, and oxidative stress [173]. ER over-activation may be an important mechanism that initiates and exacerbates pancreatic injury [174]. During ER stress, acinar cells activate the UPR, which is a strictly controlled signaling pathway that blocks protein translation and synthesis. Meanwhile, the UPR also increases protein folding and the degradation of misfolded proteins, both of which relieve ER stress. UPR uses three functional pathways, namely the inositol-requiring enzyme 1 (IRE1), the activating transcription factor 6 (ATF6), and the protein kinase RNA-like ER kinase (PERK) pathways [175–177]. The downstream signals of the IRE1 and ATF6 pathways activate the transcription factors cATF6 and spliced X-box binding protein 1 (sXBP1). These transcription factors increase the synthesis of factors used for ER expansion and chaperones for protein folding [178,179]. They also induce autophagy to recycle misfolded proteins [180]. When UPR is overwhelmed, the apoptotic pathway is activated. On the other hand, the PERK pathway is the terminal response, where its downstream transcriptional factor CEBP homologous protein (CHOP) initiates apoptosis and inflammation [177,181–183]. UPR also activates the NF-κB inflammatory pathway, leading to exacerbation of acinar cell inflammation and cell necrosis. Therefore, NF-kB inhibitors, such as IL-10, can block ER stress, reduce pro-inflammatory cytokines, such as TNF-α, IL-1, and IL-6, and delay pancreatic inflammation [184]. CHOP can also induce autophagy, but, in the end, it promotes cell death during prolonged ER stress. Interestingly, 3-hydroxy-3-methylglutaryl-CoA (HMG-CoA) inhibitors, which are used in clinical practice, promote the UPR and may be used to prevent the recurrence of AP [185,186].

3.1.4. Trypsinogen Activation

Observations of pancreatic autolysis in postmortem studies made by the Austrian pathologist Chiari in 1896 [187] formed the basis of the long-held trypsin-centered theory of pancreatic injury.

Trypsinogen activation is the most widely studied pathogenetic mechanism of AP. Premature trypsinogen activation is inhibited by the presence of trypsin inhibitors and zymogen granule release [188]. Alcohol and bile acids stimulate the synthesis of lysosomal digestive enzymes and inhibit the release of zymogen granules at the apex of acinar cells. The lysosome and zymogen granules fuse with one another in the so-called co-localization process [165,188]. Lysosomal cathepsin B, in turn, activates trypsinogen, and both trypsin and cathepsin B are liberated [189]. Cathepsin B release leads to necroptosis, a regulated form of necrosis [190,191] that is mediated by the receptor-interacting protein kinases 1-3 (RIP1-RIP3) and the mixed lineage kinase domain-like (MLKL) pathway [192,193]. MLKL is phosphorylated and oligomerized by RIP3, and the oligomeres are translocated into the plasma membrane, where they cause membrane puncture and spillage of cellular contents [194]. Inhibition of the RIP1–RIP3 by the inhibitor of RIP1 necrostatin attenuates acinar cell injury and can be used as AP therapy [190,191,194]. Furthermore, GSK2982772, a novel RIP1 inhibitor, represses necroptosis and inflammation [195,196] and may be tested in AP treatment [194]. In addition, lysosomal membrane disruption activates caspase 3, which initiates apoptosis through mitochondrial release of cytochrome c [192,193].

Currently, premature trypsinogen activation in acinar cells is considered the central mechanism in the pathogenesis of AP [197]. Recent findings, however, indicate a more

complex problem as trypsinogen activation was also observed in macrophages [198,199], demanding further investigations. Macrophage activation of trypsinogen induced translocation of NF-kB and the production of inflammatory cytokines. Cathepsin B-knockout mice without trypsinogen activation in macrophages developed less severe pancreatitis compared to controls [198]. Moreover, another protease, cathepsin D, is expressed in pancreatic acinar cells and macrophages regulating disease severity by activating cathepsin B. Its effect is minimal in the early phase of pancreatitis and much greater in the later, inflammatory cell phase of the disease [200]. These findings challenge the long-held notion that premature trypsinogen activation occurs exclusively within the acinar cells.

Finally, the strongest support for the trypsin-centered theory comes from the identification of mutations in the trypsinogen gene PRSS1 in hereditary pancreatitis, an uncommon form of pancreatitis with autosomal-dominant inheritance [201].

Trypsin activation affects bicarbonate secretion in ductular cells as well. This was attributed to the activation of the basolateral protease activated receptor-2 (PAR-2) [202]. However, luminal administration of trypsin or PAR-2 activating peptide repressed bicarbonate production [203]. Similarly, the severity of experimental pancreatitis can be either reduced or increased after activation of PAR-2 [204–206]. Therefore, the matter requires further investigation. Mechanisms of acinar cell injury are summarized in Figure 2.

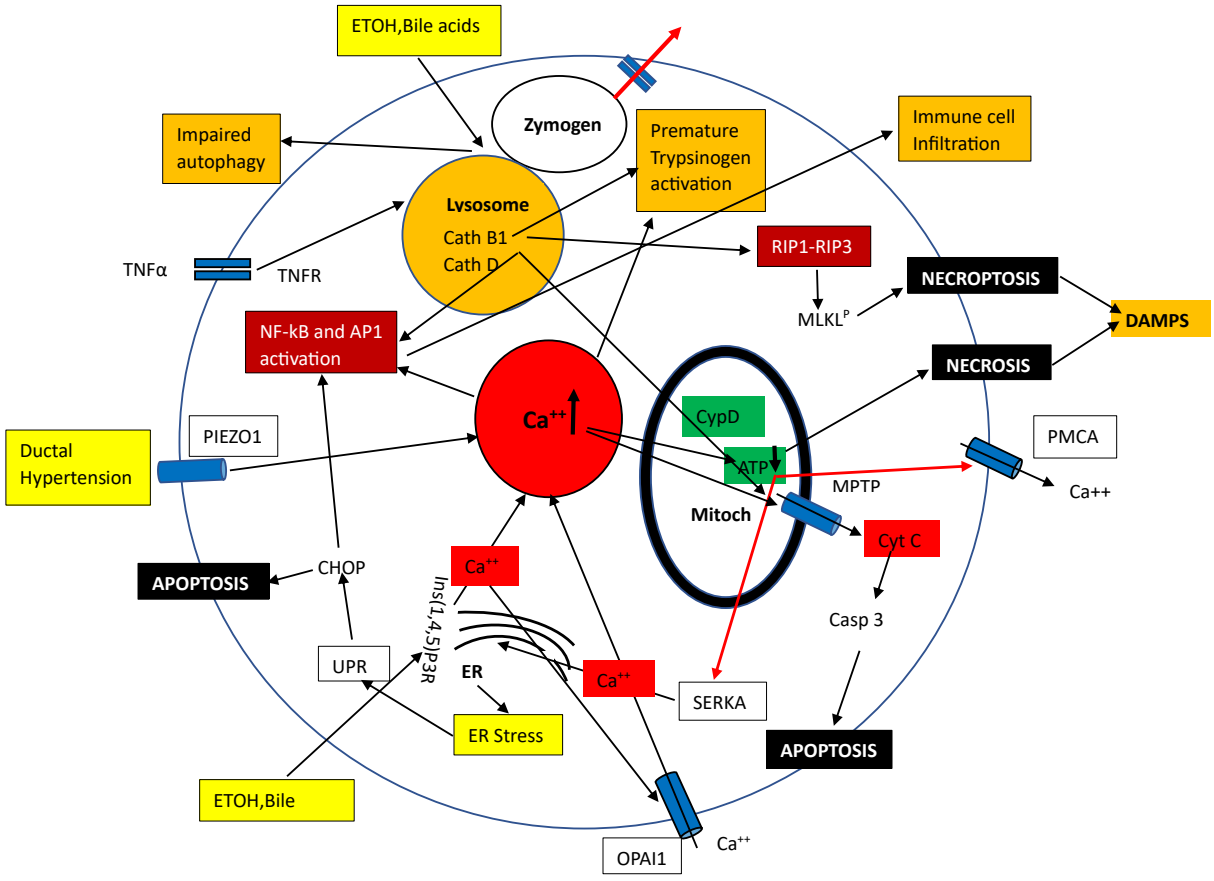

Figure 2. Pathogenesis of acute pancreatitis. Black arrows: activation. Red arrows: inhibition. ER: endoplasmic reticulum; MPTP: mitochondrial permeability transition pores; ATP: adenosine triphosphate; CHOP: CEBP homologous protein; DAMPS: damage associated molecular patterns; ETOH: Alcohol; SERCA: smooth ER Ca^{++} channels; PMCA: plasma membrane Ca^{++} channels; UPR: unfolded protein response.

ETOH and bile acid release cause acute pancreatitis through three mechanisms. (1) They increase Ca^{++} release from the ER via the InsP3R pathway. Ca^{++} overload increases the permeability of MPTP, leading to ATP depletion, which blocks SERCA and

PMCA and sustains Ca^{++} overload. Increased Ca^{++} overload activates trypsinogen and inflammatory signaling pathways but also causes mitochondrial dysfunction, leading to apoptosis and necrosis. (2) They inhibit the release of zymogen granules, which fuse with lysosomes, leading to impaired autophagy. Lysosomal cathepsin B causes premature trypsinogen activation and release of cathepsin B and trypsin into the cytoplasm. The released cathepsin B acts on the RIP3-RIP1-MLKL signaling pathway to promote RIP3-RIP1 necroptosis. It also leads to the release of cytochrome-c from the mitochondria, which activates caspase-3 and cell apoptosis. (3) They trigger ER stress and UPR, leading to CHOP expression and cell apoptosis. Necrotic or necroptotic cellular death liberate DAMPS. For details, see text.

3.1.5. Inflammation

Premature activation of digestive enzymes that occurs early in pancreatitis is not sufficient to explain several aspects of AP. This is because the inflammatory response in pancreatitis was reported to be independent of trypsinogen activation [188]. Therefore, other mechanisms, such as NF-kB and inflammasome activation, are now considered key pathogenic mechanisms in both acute and chronic pancreatitis [30,207,208]. Findings in models of chronic pancreatitis are quite interesting. The severity of fibrosis and the NF-kB activation of chronic inflammation are not mitigated in cathepsin-B-deficient- and trypsinogen-7-deficient mice, suggesting that inflammation is not dependent on trypsin activation in both chronic pancreatitis and AP [209].

The NF-kB implication. Like in most inflammatory conditions, the activation of NF-κB is an early event during pancreatitis observed within minutes after the initiation of the disease due to the constitutive presence of N-FκB in the cytoplasm of acinar cells before the initiation of AP [210,211]. Trypsinogen and NF-κB activation are independent from each other, but they follow similar kinetics [209], possibly due to their common activation by the intracellular Ca^{++} signaling [212,213]. However, models of experimental pancreatitis suggest an additional, complex involvement of NF-kB beyond the pro-inflammatory role. In fact, data suggest that NF-kB may even protect acinar cells [214–216]. Moreover, mice overexpressing active IKKβ kinase showed chronic infiltration of immune cells without acute pancreatitis, but administration of cerulein led to more severe pancreatitis [217]. These findings indicate that constitutive activation of NF-κB leads to an infiltration of immune cells, but pancreatitis only develops after an additional external noxious stimulant.

Another important transcriptional component in acinar cells is AP1 (activator protein 1). It controls pancreatic differentiation, cell death, and inflammation. Mice heterozygous for the orphan nuclear receptor NR5A2 develop an AP1-dependent pre-inflammatory state similar to early acute pancreatitis [218]. Interestingly, NF-kB and AP1 activity vary according to the etiology of pancreatitis. In cerulein models, an activation of both factors was described [219]. On the other hand, ethanol metabolites can either positively or negatively regulate NF-kB and AP1 depending on the presence of oxidative or non-oxidative alcohol metabolites in the pancreas [26,220]. Direct inhibition of NF-kB by certain agents, such as the peroxisome proliferator activator receptor gamma (PPAR-γ) ligand, pyrrolidine dithiocarbamate (PDTC), and calpain I inhibitor, can ameliorate experimental AP, but the clinical significance is still unknown [221].

The role of DAMPs. As a result of cell damage caused by injured acinar cells, damage-related molecular patterns (DAMPs) can be released that may aggravate pancreatic injury, leading to Systemic Inflammatory Response Syndrome (SIRS) [222,223]. This stage of hyper-inflammation is followed by a compensatory anti-inflammatory response syndrome (CARS), which is related to immunosuppression and is characterized by an overproduction of anti-inflammatory cytokines, such as TGF-β, IL-4, and IL-10 [224]. IL-10 inhibits the STAT3 pathway and the production of inflammatory cytokines [225]. The use of insulin-like growth factor 1 and IL-4, which enhance IL-10 production, have attenuated the damage in experimental AP [226,227]. However, it should be stressed that during CARS, patients with acute pancreatitis are susceptible to developing infection of pancreatic necrosis [228].

This idea was recently questioned, and a new approach was proposed where both SIRS and CARS start early and develop in parallel, as shown in severe pancreatitis induced by partial duct ligation with cerulein stimulation. Pancreatic macrophages promote inflammation and simultaneously induce a Th2-cell-mediated response via IL-18. The pro-inflammatory Th1 response was scarcely detectable in concert with the absence of IL-12, a cytokine released by M1-macrophage that regulates Th1 response. Regulatory T-cells were increased and anti-inflammatory M2 macrophages were dominant, while M1-macrophages were identified only in the necrotic areas. Inhibition of the NLRP3 inflammasome reduced both SIRS and CARS. Interestingly, both pathways are regulated by the NLRP3-inflammasome-derived IL-18 [229]. These findings, however, are not in agreement with data from other cerulein models of AP [230] and patients with severe acute pancreatitis [231], where IL-12 is detected and is a predictor of disease severity. This discrepancy may be due to different mechanisms in macrophage stimulation. In vitro activated macrophages after co-incubation with acinar cells did not secrete IL-12, in contrast to macrophage activation with LPS, which does induce IL-12 secretion [232].

DAMPs have a critical role in pancreatic inflammation. High mobility group box 1 (HMGB1) is a nuclear molecule constitutively expressed in almost every cell. HMGB1 may translocate to the cytosol under stress, and then it is released into the extracellular space where it functions as a DAMP with the ability to trigger inflammatory mediators [233]. The circulating HMGB1 levels in AP are increased and correlate with the severity of the disease both in humans and in experimental animal models [234–237]. In addition, the inhibition of HMGB1 protects from injury in models of AP [238–242]. In addition to HMGGB1, damaged pancreatic acinar cells release different intracellular contents, such as DNA, ATP, and heat shock protein 70 (HSP70), increasing NF-kB activation through TLR4 activation. ATP released by damaged cells also interacts with the purinergic receptor P2x7, inducing mitochondrial dysfunction. This is followed by intracellular K^+-depletion, which results in NLRP3 assembly, caspase-1 activation, and IL1β and IL18 secretion [234]. Moreover, the stimulation of intracellular nucleotide-binding oligomerization domain 1 (NOD1) by translocated bacteria from the gut microbiota is a crucial element to aggravate the inflammatory process in the pancreas.

The effects of DAMPs on macrophages were also investigated. Stimulator of interferon genes (STING) activation in macrophages by DNA derived from damaged acinar cells led to the overproduction of pro-inflammatory cytokines by macrophages in experimental AP [243]. In the absence of STING, macrophages did not overproduce cytokines, indicating a direct link between acinar cell DAMPs and the generation of proinflammatory cytokines.

The role of inflammasome activation. Patients with AP have elevated serum levels of pro-inflammatory cytokines, such as IL1β, TNFα, IL6, and IL18 [244]. The precursor forms of IL1β and IL18 cytokines are converted into an active form through the NLRP3 inflammasome. Two signals are required for the activation of inflammasomes. The first signal upregulates the inflammasome mRNA by NF-kB and the second signal initiates the activation of pro-caspase-1. The release of cathepsins from phagosomes into the cytosol may act as the second signal in inflammasome activation [245]. The NLRP3 inflammasome is activated during AP, and its components are required for pancreatic injury. The absence of caspase-1, caspase recruitment domain (ASC), or NLRP3 significantly reduced edema and inflammation in AP [246]. Another study using NLRP3-deficient mice found suppression of IL1β and prevention of the inflammatory cascade [247]. TLR4 involvement in the induction of AP has been reported. Administration of lactate to block TLR4 reduced the activation of NLRP3 inflammasome [248]. This finding agrees with clinical data showing an anti-inflammatory effect of Ringer's lactate solution used as a fluid replacement in patients with AP [249,250]. Other TLR4 modulators, such as carbon monoxide, produced similar results, indicating a clear role of TLR4 and the NLRP3 inflammasome in AP [251,252]. The NLRP3 inflammasome is also implicated in the development of lung injury secondary to pancreatitis through exosomal release. The plasma-derived exosomes trigger NLRP3 inflammasome activation and pyroptosis in alveolar macrophages, leading to ppulmmonary

dysfunction during AP [253]. A human study confirmed animal data. The report confirmed the presence of increased levels of AIM2 and NLRP3 inflammasomes in the early course of AP. Furthermore, AIM2 expression was increased in patients who developed moderate or severe AP [254].

Other factors connecting acinar cell damage and inflammation have been described. Histone deacetylase (HDAC) is one of these factors, as HDAC activity has been demonstrated to play a crucial role in the regulation of inflammation in AP. HDAC inhibition reduced trypsinogen activation, inflammation, and tissue damage in experimental AP [255]. Additionally, inhibition of Sulfiredoxin-1 (Srxn1) expression was reported to increase the production of ROS and induction of apoptosis. Inhibition also promoted inflammation by accumulating M1 macrophages and neutrophils in AP. Overexpression of Srxn1 reduced ROS and apoptosis in acinar cells [256].

Details of inflammatory mechanisms in AP have been published [29].

3.1.6. Role of the Immune System

Early in the course of AP, the pancreas is infiltrated by inflammatory cells. Macrophages and neutrophils are the first to reach the organ and contribute to the pancreatic damage phagocytosing necrotic tissue [257]. Pancreatitis is a sterile inflammation, and pathogen-associated molecular patterns (PAMPs) play no role, at least in the early phases. The activation of immune cells is mediated by damage-associated molecular patterns (DAMPs) that arise from acinar cell necrosis. DAMPs increase the nuclear translocation of the NF-kB family within infiltrating immune cells, leading to enhancement of the cytokine storm [198]. Injured acinar cells also release chemokines that recruit immune cells within minutes after the onset of disease into the site of injury [221,258] The monocyte chemoattractant protein 1 (MCP1) facilitates monocyte trafficking, while macrophage inflammatory protein 2α (MIP2α) and CXC chemokine ligand 1 (CXCL1) recruit macrophages and neutrophils [259,260]. Inhibition of chemokines and their receptors prevents pancreatic and distant organ injury in animal models [261–263]. Increased serum MCP1 levels correlate with severe acute pancreatitis in humans [264]. Neutrophilic NADP oxidase promoted oxidative stress and increased intra-acinar trypsinogen activation [265,266]. The infiltration of immune cells has been also associated with the prognosis of pancreatitis [267–269]. Macrophage infiltration better correlates with pancreatic damage and necrosis than the number of neutrophils because macrophages are required for the removal of necrosis and thus ameliorate pancreatic damage. Phagocytosing macrophages are found in almost all models of AP and CP [198,267,270,271]. Depletion of macrophages decreases disease severity and protects mice from cerulein-induced pancreatitis [263,267]. Macrophages also produce large amounts of IL1β, which is released by the gasdermin D pore complex from the cytosol into the extracellular space. Consequently, the cell undergoes pyroptotic cell death [272–274]. Macrophages at distant organs are also activated and contribute to distant organ damage in AP, although the mechanisms of distal organ injury have not been fully elucidated [264].

The role of neutrophil extracellular traps (NETs). Activated neutrophils use nuclear DNA and histones to form extracellular web-like structures called neutrophil extracellular traps (NETs) that participate in microorganism eradication. However, NETs can cause ductal obstruction, activate pro-inflammatory signals, and prematurely activate trypsinogen [275]. During experimental AP, NETs are produced in the pancreas, regulating organ inflammation and injury. NET levels are also increased in plasma from patients with AP [150,276].

NETs act as a double-edged sword, regulating, on the one hand, the protective innate immune response, but also precipitating in epithelial and tissue injury [277,278]. NETs are also associated with the severity of AP [279]. In septic AP, NETs kill invading pathogens [275] but also activate trypsinogen, mostly through the STAT-3 pathway [280]. NETs may also cause severe damage to other organs, such as the lungs, blood vessels, and kidneys [281,282]. NETs are implicated in thrombosis and participate, therefore, in

the hypercoagulability observed in the incipient stage of severe acute pancreatitis [280]. Additionally, NET formation increases macrophage recruitment by releasing chemokines.

As a consequence of these abnormalities in immune mechanisms, a paradoxical period of immunosuppression develops during AP. In patients with mild and moderate AP, there is a reduction in HLA-DR expression within the first few days of the disease, but this returns to near-normal levels within the first week [283]. In contrast, in patients with severe AP, the reduction of HLA-DR expression persists for a long period, and these patients may develop infectious complications [284]. A recent study reported increased activity of the PD1/PD-L1 system in severe pancreatitis, which was more pronounced in patients who develop secondary infectious complications [285]. Another serious consequence of the abnormal immune mechanisms in AP is the impairment of the intestinal barrier, leading to systemic bacterial translocation. In most AP patients, gut barrier failure occurs at the point of hospital admission [286], before the onset of multi-organ failure. Increased intestinal permeability has been observed even in mild disease, although it is more pronounced in severe disease [286–288], when patients are more vulnerable to infections [289]. A review of immunopathological abnormalities in AP has very recently been published [289].

Taken together, early protease activation as well as NF-κB and inflammasome activation are essential mechanisms of pancreatitis. These events occur in parallel during disease evolution and strongly influence each other. Recently, it has become clear that not only the activation of proteases and NF-κB play a critical role, but also the type of cell where these events take place. Pancreatitis is no longer a disease of acinar cells alone [26]. The role of inflammation and immunity is summarized in Figure 3.

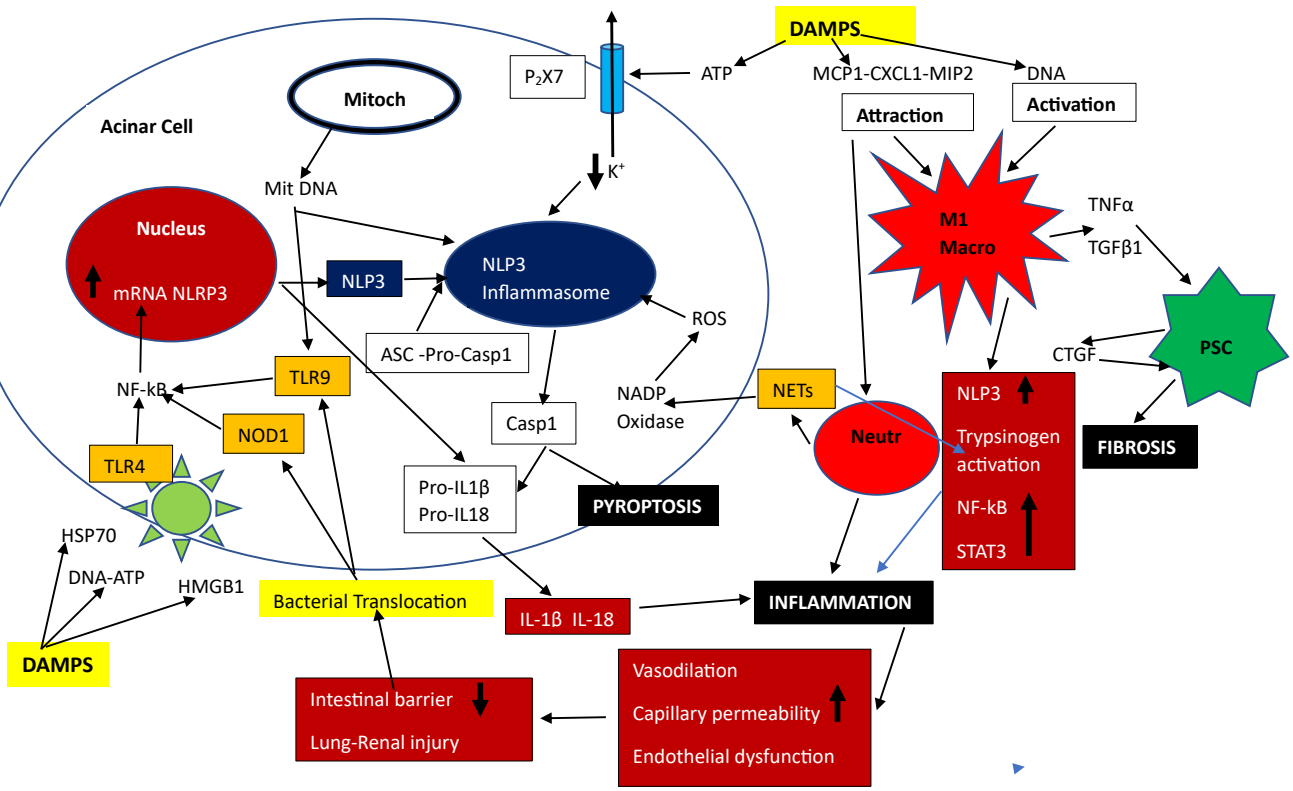

Figure 3. Inflammation in acute and chronic pancreatitis. *Black arrows: activation*. For more details, see text. LPS: lipopolysaccharide; HSP70: heat shock protein 70; HMGB1: high mobility group box 1; TLR4,9: toll like receptor 4,9; ROS: reactive oxygen species; ATP: adenosine triphosphate; NETS: neutrophil extracellular traps; NLRP3: NLR pyrin domain containing protein 3; ASC: caspase recruitment domain; NOD1: nucleotide-binding oligomerization domain 1; MCP1: monocyte chemoattractant protein 1; mtDNA: mitochondrial DNA; PSC: Pancreatic stellate cells; MIP2: Macrophage inflammatory protein-2.

DAMPs, such as HMGB1, HSP70, and ATP, are crucial for the promotion of acute pancreatitis and, indirectly, of chronic pancreatitis. They activate NF-kB through TLR4 and upregulate the mRNA and protein expression of NLRP3, leading to the assembly of the NLPR3 inflammasome in association with ASC and pro-caspase-1. In addition, bacterial translocation sustains inflammation through the NOD1. NLRP3 and casp-1 are activated by either ATP via its interaction with P2X7 and the resultant intracellular K^+-depletion or the ROS produced by NETs. Maturation of pro-IL1β and pro-IL18 leads to IL1β and IL18 secretion and inflammation. Some intracellular DAMPS, such as mitochondrial DNA, initiate NLRP3 inflammasome assembly and activation. Additionally, TLR9 senses intracellular bacteria and mtDNA with subsequent activation of NF-κB. Chemokines produced by injured acinar cells recruit and activate macrophages and neutrophils at the site of injury. Cytokines, such as TGFβ1, produced by macrophages activate PSCs to produce extracellular matrix initiating fibrosis in chronic pancreatitis. Neutrophils also release NETs, aggravating inflammation.

3.1.7. Exosomes and AP

Exosomes are vesicles secreted by various living cells that contain RNA and proteins (30–100 nm in size). In experimental pancreatitis, the number and content of the exosomes released to the peripheral blood from the pancreas are significantly increased. As mentioned before, pancreatic exosomes can reach the lung through circulation, where they are phagocytosed by alveolar macrophages, changing their phenotype from M2 to M1, which in turn aggravates the lung injury caused by AP [290]. Plasma-derived exosomes may activate lung NLRP3 inflammasomes to induce pyroptosis of alveolar macrophages in AP. Inhibition of these exosomes represses the pyroptosis of alveolar macrophages, attenuating the AP-induced lung damage [253]. The interplay between acinar cells and macrophages has been confirmed through analysis of microRNAs found in exosomes. Acinar cells activate macrophages through exosomes released in AP, which in turn promote acinar cell injury via apoptosis, necrosis, and autophagy [291]. Exosomes derived from different cells are not always detrimental in AP. Thus, exosomes derived from bone marrow mesenchymal stem cells (MSCs) have a protective effect on AP [292]. The specificity of exosomes in different cells and tissues should be further investigated [125].

3.1.8. Genetic Mutations

Several gene mutations are implicated in the pathogenesis of acute pancreatitis, such as mutations in protease serine 1, serine protease inhibitor Kazal type 1, chymotrypsin C, the cystic fibrosis transmembrane conductance regulator (CFTR), claudin 2, and calcium-sensing receptor genes [293]. Human genetic data indicate that premature activation or misfolding of pancreatic proteases play a central role in the onset of pancreatitis and progression to chronic pancreatitis [26]. A detailed presentation of these genetic mutations is beyond the scope of this review, but a paper is available that elegantly summarizes the genetics of acute pancreatitis [294].

4. Chronic Pancreatitis

4.1. Pathophysiology of Chronic Pancreatitis (CP)

Multiple mechanisms are involved in the pathogenesis of CP. Repeated insults to the pancreas by alcohol or tobacco or any other factor may lead to recurrent attacks of AP, which in turn activate pancreatic stellate cells (PSCs) and initiate fibrogenesis, ultimately resulting in chronic fibrosing pancreatitis. Interestingly, these recurrent attacks very frequently cause histopathological abnormalities in the pancreas in many patients, who remain asymptomatic, and only a few experience clinical disease [31,295–297]. After repeated episodes, areas of pancreatic necrosis are replaced by fibrotic tissue [298,299]. However, pancreatic necrosis is uncommon in patients with classic chronic pancreatitis.

Another theory is the “two-hit” model. After infiltration of the pancreas by macrophages and neutrophils during an episode of AP and the activation of pancreatic stellate cells

(PSCs), a second continuous insult, such as alcohol and tobacco and their metabolites, will promote fibrosis through activated immune cells [300–303]. However, most patients do not proceed to CP despite continuous use of these toxic factors. Earlier reports pointed to the role of ROS production by acinar cells and the subsequent activation of NF-kB [267]. ROS can promote the fusion of lysosomes and zymogen granules and the premature activation of trypsinogen [304,305]. This theory totally ignores the critical role of ROS production by macrophages. Finally, a ductal dysfunction has been connected to CP pathogenesis. Reduction of secretion of bicarbonate-rich fluid [306] favors the formation of protein plugs and ductal obstruction. Protein plugs are indeed described in chronic pancreatitis [298], but it is not clear if they are the cause or the result of CP.

The drawbacks of all of the theories presented above indicate that external factors are not sufficient to explain the development of CP. Whatever the pathogenesis of CP might be, its development leads to pancreatic exocrine insufficiency, diabetes mellitus, and an immune response that results in nerve abnormalities and chronic pain [307,308].

Mutations in several genes, such as the cationic and ionic trypsinogen or the pancreas-specific protease elastase 3b (*CELA3B*), have been implicated in the pathophysiology of CP to complete some of the missing points [16,26,309,310]. Therefore, it seems that a different "two-hit" model, where the first step is an underlying mutation and the second is the effect of toxic external factors, is a more comprehensive pathogenetic theory. The influence of external risk factors is very strong. In patients with CP, the pooled prevalence of alcohol as a risk factor is 65% compared to the risk factor of 61% of tobacco [17]. Smoking or alcohol abstinence reduces the risk of disease progression [311,312]. Alcohol toxicity is due to its metabolites [313,314] that cause the microcirculatory disturbances, which in turn mediate pancreatic acinar cell injury, resulting in fibrosis and chronic disease [172,315]. Recently, macrophages and pancreatic stellate cells are in the center of extensive investigation to clarify their role in the pathogenesis of CP [316].

4.2. The Role of Macrophages

Macrophages are the main inflammatory cells implicated in CP fibrosis [317]. Fibrogenesis in CP is induced when macrophages and other inflammatory cells are attracted by tissue damage and infiltrate the pancreas [318]. Necrosis and apoptosis of acinar cells can activate macrophages. Macrophages produce transforming growth factor-β1 (TGF-β1), platelet-derived growth factor (PDGF), and connective tissue growth factor (CTGF), which initiate activation and proliferation of the resident PSCs, which are transformed in mmyofibroblast-like cells (PMF) [319,320]. Activated macrophages create a positive feedback cycle through PSCs to secrete more cytokines [198,321]. Activated PSCs in turn induce M2 macrophages that play a significant role in angiogenesis and promote tissue fibrosis [322–325].

4.3. The Role of PSCs

PSCs are able to oxidize alcohol to acetaldehyde, leading to the generation of ROS and oxidative stress. As mentioned before, alcohol consumption damages the intestinal barrier and increases circulating levels of lipopolysaccharide, oxidized low-density lipoproteins, and TNF-α. All of them are potential activators of PSC in concert with TGF-β1 [326,327]. The resultant myofibroblasts secrete increased amounts of extracellular matrix proteins, thus mediating pancreatic fibrosis [328–330]. Mice overexpressing TGF-β1 develop spontaneous pancreatic fibrosis, indicating that TGF-β1 activates de novo PSCs [331]. Activated PSCs can also secrete CTGF, IL-1/16, and endothelin-1 (ET-1) and further promote the activation of PSCs through autocrine and paracrine signaling, which forms a vicious cycle [332]. At present, TGF-β is the strongest activator of PSCs. This effect is achieved by regulating the Smad2/3 signaling pathway [333,334]. This mechanism also influences the phosphorylation of three subtypes of the MAPK family, including c-Jun amino-terminal kinase (JNK), p38, and ERK [335–337]. All of these signals work in parallel, leading to pancreatic fibrosis [338–340]. While TGF-β1 is critical for promoting matrix deposition by

myofibroblasts, it fails to induce PMF proliferation, in contrast to PDGF, wwwwhich drove proliferation of PMFs isolated from CP patients [341]. PDGF also stimulated the production of a matrix with reduced potency compared with TGF-β1 [342]. PDGF itself is not capable of initial activation of PSCs [343].

CTGF is the third activator of PSCs. In CP specimens, CTGF and TGF-β1 were increased more than 20-fold [344]. It should be noted that CTGF expression in the pancreas is controlled by several cytokines, such as TGF-β1, Activin-A, PDGF, and TNF-α [345,346].

Additional external activators of PSCs are TNF-α, IL-1β, and Cyclooxygenase-2 (COX2). Incubation of PMFs with TNF-α increased α-SMA expression [342,347,348]. The COX2 downstream product Prostaglandin E2 stimulated PMF proliferation and the expression of matrix proteins and matrix metalloproteinases [349]. In a different model, ectopic expression of COX-2 in the acinar cells of rodents led to spontaneous CP, with deposition of ECM proteins [350]. PMFs are also sensitive to DAMPs. Rodent PMFs express TLRs 2, 3, 4, and 5, along with co-receptors CD14 and MD2 [351]. TLR2 and 4 are known receptors of high mobility group box 1 (HMGB1), heat shock protein 70 (HSP70), and fibrinogen, indicating that DAMPS are directly implicated in pancreatic fibrosis. In addition to DAMPs, acinar cell damage can directly activate PSCs. After trypsinogen activation, acinar cells liberate a large number of cytokines that activate PSCs and induce fibrosis [352–354]. Acinar cells in CP gradually change from columnar to flat and form a ductal structure expressing cytokeratin. This transformation is called acinar ductal metaplasia (ADM), and it is a promoter of fibrosis and an early event of pancreatic adenocarcinoma [355,356].

Two more factors that activate PCSs prove the complex nature of fibrosis development in CP. Hypoxia activates PSCs with the increased release of type I collagen, fibronectin, and vascular endothelial growth factor (VEGF) [357]. As mentioned before, high pressure in the pancreatic duct stimulates Piezo1 channel opening, leading to PCSs' activation and pressure-induced chronic pancreatitis. This mechanism may explain the fibrosis developed in biliary CP [358]. Details of the activation of PSCs were recently published [359,360].

In addition to the innate response mostly mediated by macrophages, several studies have demonstrated an involvement of adaptive immunity as well [361]. Increased clusters of CD4+ and CD8+ T cells in parallel with increased IL-10 levels have been reported in CP patients compared with healthy individuals [362]. Moreover, chronic pancreatitis specimens had more disease-specific regulatory T-cell subsets [363] and central chemokine receptor 7 (CCR7) positive memory T cells that persisted up to 3 years after pancreatic resection [364].

5. A Brief Synopsis of Forms of Cellular Death in Acute and Chronic Pancreatitis

1. Apoptosis was the first form of regulated cell death (RCD) to be described [365]. Apoptosis includes both external and internal pathways. The external pathway is initiated by death receptors (such as TNF receptors or Fas receptors) and mediated by the initiator caspase-8. Intrinsic apoptosis is initiated by MOMP, which leads to the release of mitochondrial proteins, such as cytochrome c, and diablo IAP-binding mitochondrial protein (DIABLO, also known as Smac), and subsequent activation of the initiator caspase-9 [366]. Both pathways lead to the activation of executionar caspases and cellular death.
2. Necroptosis. The regulated process of necrosis is called necroptosis. It is mediated by RIPs and MLKL, as mentioned before. Compared to apoptosis, necroptosis may be a more aggressive mode of cell death. Recent studies indicated that necroptosis may be the main mechanism of acinar cell death in AP [365,367,368].
3. Pyroptosis is the result of NLRP3 and other inflammasome activation. IL-37 protects against acinar cell pyroptosis in AP [369]. The activation of pyroptosis includes the caspase-1-dependent canonical pathway and the caspase-4/5/11-dependent non-canonical pathway. Caspases-3-7-8, implicated in apoptosis, also participate in the regulation of pyroptosis [370]. Caspases-1-4-5-11 directly cleave the gasdermin D (GSDMD) to produce N-terminal fragments. GSDMD forms pores in the plasma

membrane, followed by membrane rupture. It has been proposed that a shift from apoptosis to pyroptosis and necroptosis may explain why some patients with pancreatitis develop the necrotizing form of the disease [229,371].

4. Ferroptosis is a new RCD pathway that is an iron-dependent form of non-apoptotic cell death first described in 2012. It is induced by accumulation of peroxidized lipids and is regulated by glutathione peroxidase 4 (GPX4) and arachidonic acid lipid oxygenases [372]. Ferroptosis plays an important role in the death of acinar cells, at least in AP, associated with hypertriglyceridemia. NADPH oxidase 2 (NOX2) is a key point in the regulation of ferroptosis. The inhibition of ferroptosis and NOX2 attenuated the inflammatory response in a rodent model of AP and improved the outcome [373].

6. Autophagy in Pancreatitis

Autophagy is the cellular pathway for organelle, lipid, and protein degradation. It is the more efficient recycling machinery in nature [96].

Genetic models targeting autophagy have in part clarified the significant role of this system in the pancreatic pathophysiology. The role of autophagy was investigated in mice with pancreas-specific knockouts of mediators of autophagosome formation, the autophagy-related proteins ATG5 or ATG7. Genetic deletions of ATG5 or ATG7 or of the inhibitor of nuclear factor IκB kinase α (IKKα) result in ER stress and accumulation of dysfunctional mitochondria unable to generate ATP [178,271]. Moreover, the lysosome associated membrane protein 2 (LAMP2) deficiency increased the severity of cerulein pancreatitis [270,374]. Administration of the enhancer of autophagy trehalose significantly reduced trypsinogen activation and necrosis in a murine pancreatitis model [122]. Importantly, tissue from patients with pancreatitis showed abnormalities of autophagy similar to those in murine models [122,374–376]. These will be analyzed below. The AP models of IL-22 transgenic mice are a further indication of autophagy involvement in AP, as IL-22 can prevent the formation of autophagosomes through the Beclin-1 pathway, reducing the severity of AP [377]. An important aspect of autophagy in severe AP is the effect of autophagy on the integrity of intestinal barrier. Reduced autophagy in severe AP impairs tight and gap junctions and reduces the function of goblet and Paneth cells, leading to increased bacterial translocation and extra-pancreatic serious manifestations [370,378,379]. The increase in oxidative stress associated with the increased bacterial translocation will aggravate AP-associated lung injury and was attributed to decreased autophagy levels [380]. However, the opposite has also been reported, as excessive autophagy may also be connected to lung injury. It was recently shown that the nuclear translocation of Nrf2 reduced excessive autophagy in severe acute pancreatitis-related acute lung injury via the p62–Kelch-like ECH-associated protein 1 (Keap1)-NF-E2-related factor 2 (Nrf2) signaling pathway in mice [381].

Recent investigations have revealed more associations of autophagy and pancreatitis. Thus, an additional connection between zymogen exocytosis and autophagy has been reported involving SNARE proteins. Syntaxin 2 (STX-2), a SNARE protein of the acinar cell, blocked the fusion of zymogen granules with the plasma membrane and exocytosis and, at the same time, deregulated autophagosome formation by disrupting autophagy-related 16-like 1 protein (Atg16L1), an interaction with the clathrin heavy chain. This interaction is necessary to recruit membranes from acinar plasma membrane for physiologic autophagosome formation [382]. Notably, depletion of another SNARE protein, SNAP23, prevented the induction of AP by reducing trypsin activation of autolysosomes [383].

Xanthohumol (Xn), a natural prenylated chalcone compound isolated from hops, restored autophagy flux by inhibiting the AKT/mTOR pathway in experimental pancreatitis. This was associated with reductions in necrosis, inflammation, oxidative stress, and the severity of pancreatitis [384]. Experiments also indicated that Pancreatic Protein kinase C iota (PKCi) significantly increased pancreatic immune cell infiltration, acinar cell DNA damage, and apoptosis, but reduced sensitivity to cerulein-induced pancreatitis. *Prkci* dele-

tion in acinar cells resulted in p62 aggregation and loss of autophagic vesicles consistent with the disruption of autophagy [385].

Farnesoid X receptor (FXR) has been also implicated in pancreatitis. FXR is a ligand-activated factor that has an important role in the regulation of glucose, lipid, bile acid, and amino acid metabolism [386]. FXR is also an anti-inflammatory factor in several inflammatory diseases [387,388]. Nuclear FXR was considerably increased in the pancreas of patients with pancreatitis accompanied by a parallel increase in Oxidative Stress Induced Growth Inhibitor 1 (OSGIN1), which is the direct target of FXR in the exocrine pancreas. Deletion of the FXR in acinar cells caused severe pancreatitis, whereas pancreatic overexpression of *Osgin1* reduced the severity of pancreatitis. Stimulation of autophagic flux by the FXR-OSGIN1 axis was the mechanism through which FXR-OSGIN1 protected against pancreatitis [389].

A selective autophagic pathway called zymophagy is an early protective mechanism in AP preventing acinar cell death [390,391]. It may be induced by CCK-receptor hyperstimulation and may account for the self-limited form of AP [390].

The protective effect of canonical autophagy was reported in a recent study comparing canonical autophagy with the Ras-related protein Rab9-mediated non-canonical autophagy, which was not protective. These two forms of autophagy antagonize each other. Thus, Rab9 decrease as observed in rodent and human pancreatitis may be a beneficial response to boost canonical autophagy and mitigate disease severity [392].

Autophagy and autolysosomes are additionally involved in trypsinogen activation, as suggested by earlier reports. In a model of AP with *atg5* deletion, reduced severity of the disease paralleled reduced trypsinogen activation [393,394], a finding verified by a subsequent study [376]. Trypsinogen activation and the role of autophagy have been reviewed in detail [395,396].

6.1. Autophagy and ER in AP

ER is responsible for the synthesis and folding of proteins, the storage of Ca^{++}, and the regulation of Ca^{2+} concentration in cells [397]. Endoplasmic reticulum stress (ER stress) develops when the ER is overwhelmed by unfolded and misfolded proteins. Morphological changes in ER indicating ER stress, such as swollen ER, vacuolation, and loss of ribosomes, are observed at the early stage of AP [398,399]. ER is closely associated with autophagy. The major membrane source for the creation of autophagosomes is the rough endoplasmic reticulum, and both the initiation and maturation of autophagosomes have a close relationship with ER [179,400,401]. Autophagy will be interrupted, or the already impaired autophagy will deteriorate after the development of ER stress. Moreover, IL-1β released by macrophages can cause ER stress and liberation of large amounts of Ca^{2+} from ER into the cytoplasm, leading to both activation of trypsinogen and impaired autophagy in murine pancreatitis [402–404]. Alcohol consumption can also induce ER stress that impairs lysosomal proteases and lysosomal membrane proteins, such as LAMP2, leading to deranged autophagy and initiation of AP [405]. The deletion of IκB kinase α (IKKα) gene impaired autophagy and P62 accumulation, leading to ER stress and spontaneous pancreatitis [375]. With P62 gene deletion, all of these damages were mitigated, suggesting that autophagy impairment can indeed cause ER stress [176,406]. The ATG7 gene knockout model showed that autophagosomes are not formed in acinar cells, and autophagy flux is reduced while ER stress is increased [178]. Trehalose, which can increase autophagy activity and restore autophagy flux, reduces ER stress and trypsinogen activation, thus alleviating AP, as mentioned before [122]. In a different murine, it was also shown that reduction of autophagy aggravated AP and increased ER stress [407]. Taken together, these findings indicate that there is a reverse association between autophagy and ER stress. This is further confirmed by evidence suggesting that restoration of ER function could in turn promote autophagy and protect acinar cells. Thus, melatonin administration inhibited the EER stress and promoted autophagy, alleviating AP [408]. Finally, it should be noted that there is a synergy between UPR and autophagic pathways. Both UPR and autophagy aim

to restore ER function, as autophagy also degrades misfolded proteins, and the specialized form of reticulophagy removes damaged ER [405,409].

6.2. Autophagy and Mitochondria in AP

Mitochondrial dysfunction can lead to impairment of autophagy through the CypD-related MPTP opening. In some AP animal models, such as the cerulean and bile acid models, mitochondrial dysfunction in acinar cells is moderated through $Ca2^{++}$-dependent pathways [161]. $Ca2^{++}$-independent pathways may operate in other models, such as the Arginine-induced model of AP, where the opening of MPTPs is due to the decreased ATP synthase activity [410], while the MPTP opening in alcoholic AP is mediated by the reduction of Nicotinamide adenine dinucleotide (NAD) [354]. Finally, they all lead to continuous opening of the MPTPs, which is controlled by the mitochondria resident protein CypD [122,152]. Inactivation of CypD restores mitochondrial polarity and ATP synthase activity, proving that mitochondria regulate lysosomes and therefore autophagy in the pancreas [122,152,155]. In more detail, in the arginine model, free Arg in the mitochondria of acinar cells increased, and it was degraded through the ornithine pathway. The degradation product reduced ATP synthase, resulting in reduced autophagy, ER stress, and lipid metabolism disorders, ultimately leading to AP [122]. It was recently reported that loss of estrogen-related receptor γ (ERRγ) resulted in mitochondrial dysfunction and further increased autophagosome accumulation and ER stress in acinar cells [411].

In addition, impaired autophagy can also influence mitochondrial function through inefficient mitophagy, the selective autophagy of mitochondria [84,154]. Acinar cell survival depends on the efficient removal of damaged mitochondria. AP in mice induces mitophagy by up-regulating Parkin, an E3 ubiquitin-protein ligase that initiates mitophagy, as mentioned before [179,412]. Normal mitophagy may in part explain the mild course of AP in the majority of patients. However, the deletions of *atg5* and *atg7* genes inhibit mitophagy and lead to the accumulation of dysfunctional mitochondria [178,271], suggesting that the impaired autophagy observed in AP is finally accompanied by reduced mitophagy [354]. Recently, a new pathway for mitophagy was demonstrated in AP. Alterations of mitochondrial dynamics and subsequent mitochondrial dysfunction were shown early in the acute phase of mild pancreatitis. Moreover, it was shown that the vacuole membrane protein-1 (VMP1) is necessary in mitophagy, as VMP1 downregulation significantly reduced mitochondrial degradation [413]. Overproduction of ROS may also disrupt mitophagy, causing severe AP by activating the AKT/mTOR pathway [414]. So far, the results in human AP agree with the experimental findings.

6.3. Autophagy and Lysosomes in AP

The lysosome contains more than 60 acid hydrolases. It is protected from autoddegrradation by a glycocalyx of the membrane [415,416]. The lysosome is considered today to be an important coordinator of signals regulating cell growth, proliferation, and differentiation, in addition to its participation in the final stage of autophagy [417]. Cathepsins are the most important acid hydrolases of the lysosomes [418]. Dysfunction of the lysosomes can block autophagy through three mechanisms. The first mechanism is the impairment of the fusion of lysosomes with autophagosomes due to the defective function of the lysosomal membrane proteins, LAMP-1 and LAMP-2 [270,419,420]. This is an important mechanism of alcohol's induction of AP and CP. In murine pancreatitis, alcohol reduces LAMP-2 proteins, leading to the accumulation of autophagosomes in acinar cells and a shift from apoptosis to necrosis [374]. Patients with alcoholic pancreatitis also have local LAMP-2 depletion. Abnormal cathepsins are the basis of the second mechanism. Pancreatitis impairs the maturation of cathepsins in lysosomes of acinar cells, resulting in the accumulation of autolysosomes with undegraded material, including zymogen granules [395]. It should be noted that a reduction in enzymatic activities of cathepsins in pancreatic lysosomes has been reported in AP [421]. An imbalance between cathepsin L and cathepsin B may be the underlying reason. As mentioned before, cathepsin B converts

trypsinogen to trypsin, while cathepsin L degrades both trypsinogen and trypsin. Inhibition of cathepsin L may therefore lead to increased activity of trypsin and pancreatitis [376]. Inadequate synthesis of lysosomes leading to autophagy reduction and induction of AP is the third mechanism. Transcription factor EB (TFEB) is the central regulator of lysosome synthesis [70] and also a transcriptional factor of several autophagy-related genes [422,423]. TFEB is degraded in the cerulein model of AP, resulting in autophagy impairment [424]. Deletion of tfeb increased the severity of murine AP, while tfeb overexpression attenuated pancreatitis [425]. It should be noted that defective or aging lysosomes are phagocytosed by autophagosomes and fused with normal lysosomes for degradation through a process called lysophagy [426,427].

Recently, the importance of normal cathepsins was demonstrated in a double-knockout (DKO) model of cathepsin deficiencies. Cathepsin B/cathepsin D DKO mice showed cytoplasmic degeneration similar to atg5 KO mice. The autophagy markers LC3 and p62 accumulated, and the numbers of autophagosomes increased in the acinar cells. Moreover, these mice developed CP, indicating the significance not only of cathepsin B but also the significance of the combination with cathepsin D. Single KO mice for either cathepsin were normal [428].

6.4. The Role of miRNAs in Regulating Autophagy of AP

As mentioned above, there is an interplay between different organelles and autophagy in pancreatic acinar cells. Several microRNAs are involved in this interplay. Thus, miR155, miR141, miR-181b, miR-148a, and miR-375 contribute to the inhibition of autophagy initiation by inhibiting the expression of Beclin-1. The repressed expression of ATG12 and p62 and the downregulation of LAMP-2 by miR-148b-3p will also derange autophagy [429].

On the other hand, MiR-92b-3p was reported to attenuate inflammation and autophagy in cells incubated with cerulein by targeting tumor necrosis factor receptor-associated factor-3 (TRAF3) and repressing the p38 pathway [430]. An additional regulation of autophagy by miRNAs is via the calcium/calmodulin-dependent protein kinase II (CAMKII). It mediates the phosphorylation of its substrates in response to cytoplasmic Ca^{++} increase [431,432]. In addition, CAMKII is auto-phosphorylated after the entry of Ca^{++} into acinar cells and acquires Ca^{++}-independent activity [433]. CAMKII activity is necessary in one model of AP induced by nicardipine [432]. Pancreatic necrosis parallels the level of CAMKII, which is positively controlled by ATG7, suggesting that there is a connection between impaired autophagy and CAMKII-regulated necrosis in the pathogenesis of AP. The level of miR-30b-5p was negatively correlated with the levels of ATG7, indicating that the well-described impairment of autophagy is associated with low ATG7 and the subsequent necrosis of AP is mediated by the miR-30b-5p/CAMKII pathway [434].

6.5. Interplay of Autophagy and Inflammatory Response in Pancreatitis

Autophagy elimination through deletion of the genes atg5, atg7, lamp-2, or ikkα increases the inflammatory reaction associated with up-regulated production of cytokines, chemokines, and macrophage infiltration of the pancreas, as mentioned before [178,270,271,375]. Both inflammatory (M1) and fibrogenic (M2) macrophages are increased. M1 macrophages predominate in LAMP2-null mice with cerulein pancreatitis, while neutrophils are decreased, indicating a shift towards chronic inflammation [270]. In ATG5-deficient mice, autophagy blockade activates NF-kB, STAT3, and cJun N-terminal kkinases, all of which stimulate production of cytokines by acinar cells [435]. ATG5 deficiency also activates the IκB kinase (IKK)-related kinase (TBK1) and increases the infiltration by neutrophils and T-cells accompanied by PD-L1 upregulation, increased levels of type I interferon (IFN), and the IFN-regulated chemokine CCL5 [436]. As mentioned before, persistent ER stress is observed in mouse models of AP [437] and CP [438]. Autophagy suppression is one of the inducers of ER stress in experimental pancreatitis [178,271,439], but the mechanisms linking ER stress with defective autophagy, and the inflammatory response, are not clar-

ified as of yet [315,406,440,441]. Table 1 summarizes the main associations of autophagy with pancreatitis.

Table 1. Main studies on the role of autophagy in pancreatitis.

Original Studies	Outcomes	References
Deletions of Atg5 or Atg7 or of the inhibitor of nuclear factor IκB kinase α (IKKα)	ER stress and accumulation of dysfunctional mitochondria unable to generate ATP	[178,271]
Atg5 deletion	Reduced severity of the disease paralleled with the reduced trypsinogen activation	[393,394]
LAMP2 deficiency	Increased severity of cerulein pancreatitis	[270,374]
Administration of the enhancer of autophagy trehalose	Reduced trypsinogen activation and necrosis	[122]
Reduced autophagy in severe AP	Impaired tight junctions. Reduction of the function of goblet and Paneth cells. Increased bacterial translocation and extra-pancreatic manifestations	[370,378,379]
Zymogen exocytosis and autophagy. SNARE proteins	Block of the fusion of zymogen granules with the plasma membrane and exocytosis	[382,383]
Pancreatic Protein kinase C iota (PKCi) deletion	Disruption of autophagy. Increased sensitivity to cerulein-induced pancreatitis	[385]
Stimulation of autophagic flux by the FXR-OSGIN1 axis	Protection from pancreatitis	[389]
Increased zymophagy	Protection from pancreatitis	[390,391]
Rab9 decrease	Boost of canonical autophagy and mitigation of disease severity	[392]
Xanthohumol administration	Inhibition of mTOR. Restoration of autophagy. Reduction of pancreatitis severity	[384]
ER stress	Activation of trypsinogen and impaired autophagy	[402–404,407]
ROS overproduction	Mitophagy disruption. Activation of AKT/mTOR pathway. Severe AP	[414]
[407] Dysfunction of the lysosomes	Autophagy block. Pancreatitis	[376,395,419]
Deletion/degradation of TFEB	Autophagy impairment. Increased severity of pancreatitis.	[424,425]

The associations between autophagy and pancreatitis were recently reviewed [442].

7. Future Perspectives

Most pre-clinical studies focus on the regulation of the increased intra acinar calcium, and many ongoing clinical trials try to identify new agents for the treatment of AP. Despite the fact that pharmacological inhibition of the autophagy process offers a potential therapeutic strategy for AP, ongoing clinical trials are not existent, and only pre-clinical studies offer potential future clinical applications [443,444].

Inhibition of autophagy reduces AP severity [445] and alters the progression of experimental AP in mice [446]. Earlier studies showed that activation of the nuclear factor-κB pathway increases autophagy in pancreatic acinus cells, while inhibition of this pathway ameliorated AP [447].

Interleukin 22, a member of the Interleukin-10 family, is the most widely used agent in animal models. IL-22 is increased in experimental AP and in patients with AP. Administration of IL-22 reduced pancreatic inflammation and improved survival [448]. The protective effect of IL-22 on pancreatitis was mediated via the induction of Bcl-2 and Bcl-XL, which bind to Beclin-1 and subsequently inhibit autophagosome formation and the autophagic pathway [377]. A more recent study indicated that the beneficial effect of IL-22 is due to the activation of the AKT/mTOR pathway and subsequent inhibition of autophagy [449].

Spautin-1, an inhibitor of autophagy, was also shown to ameliorate acute inhibiting impaired autophagy and Ca^{2+} overload [431]. Moreover, a spautin-1 derivative, spautin-

A41, was described as a potent autophagy inhibitor. Mice treated with spautin-A41 were resistant to cerulein-induced pancreatitis due to the inhibition of autophagosome formation [450]. Interestingly, sitagliptin, a dipeptidyl peptidase-4 (DPP4) inhibitor recently associated with autophagy, ameliorated AP-induced acute lung injury. Sitagliptin protection was attributed to the reduction of excessive autophagy through the p62-Keap1-Nrf2 signaling pathway [381].

Clinical trials are required to verify in patients the significance of autophagy modulators.

8. Conclusions

The pathogenesis of both acute and chronic pancreatitis is a complicated process involving several pathways. The traditional theory of premature activation of trypsinogen into the acinar cells has been complemented by various signals in both acinar and ductal cells of the pancreas. Mitochondrial dysfunction and ER stress are prominent features of pancreatitis pathophysiology. Moreover, calcium signaling, exosome abnormalities, and the implication of mechanisms related to inflammation, innate immunity, and genetic predisposition have been clarified. Macrophages are recognized as important mediators of inflammation and innate immunity. MicroRNA regulation of inflammation has also been explored. Fibrosis induction by macrophages and pancreatic stellate cells are prominent characteristics of disease progression towards chronic pancreatitis. Most importantly, the role of autophagy and its specialized forms, such as mitophagy, are now at the center of interest. Autophagy has been associated with both protection and aggravation of experimental and human pancreatitis. It is the common denominator behind practically every mechanism involved in the pathogenesis of pancreatitis and a target for possible therapeutic interventions in this disease.

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