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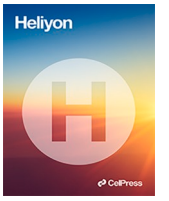

Review article

Long-chain fatty acids - The turning point between 'mild' and 'severe' acute pancreatitis

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ABSTRACT

Acute pancreatitis (AP) is an inflammatory disease characterized by localized pancreatic injury and a systemic inflammatory response. Fatty acids (FAs), produced during the breakdown of triglycerides (TGs) in blood and peripancreatic fat, escalate local pancreatic inflammation to a systemic level by damaging pancreatic acinar cells (PACs) and triggering M1 macrophage polarization. This paper provides a comprehensive analysis of lipases' roles in the onset and progression of AP, as well as the effects of long-chain fatty acids (LCFAs) on the function of pancreatic acinar cells (PACs). Abnormalities in the function of PACs include Ca^{2+} overload, premature trypsinogen activation, protein kinase C (PKC) expression, endoplasmic reticulum (ER) stress, and mitochondrial and autophagic dysfunction. The study highlights the contribution of long-chain saturated fatty acids (LC-SFAs), especially palmitic acid (PA), to M1 macrophage polarization through the activation of the NLRP3 inflammasome and the NF-κB pathway. Furthermore, we investigated lipid lowering therapy for AP. This review establishes a theoretical foundation for pro-inflammatory mechanisms associated with FAs in AP and facilitating drug development.

1. Introduction

Acute pancreatitis (AP) is an inflammatory disease with an increasing incidence rate. It has been reported that 34 individuals per 10,000 suffer from AP worldwide [1]. AP is caused by factors such as pancreatic duct obstruction, alcohol abuse, and hyperlipidemia. It triggers local or systemic inflammatory responses resulting from pancreatic acinar cell (PAC) death [2]. Mild acute pancreatitis frequently subdues on its own and resolves in 1–2 weeks. Moderately severe pancreatitis or severe acute pancreatitis can cause local complications and systemic organ failure with long periods of hospitalization and/or permanent organ dysfunction. Diffusion of the

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local inflammatory response is thought to be critical for in exacerbating AP progression. As such, identifying the factors that increase inflammation is imperative for the development of effective therapeutic drugs. There is ample evidence to suggest that the progression of hypertriglyceridemia-induced acute pancreatitis (HTG-AP) is more severe than that of AP caused by any other etiology [3].

Obesity-related physiological indicators, including body mass index, large abdominal circumference, elevated visceral fat levels and hyperlipidemia, are significantly linked to the incidence and severity of AP [4]. Catabolism of triglycerides (TGs) around the pancreas and in the bloodstream is believed to play a crucial role in the development of AP [5]. The initial stage of AP involves injury to the pancreatic acinar cells (PACs), triggering the release of pancreatic lipase into the peripancreatic region and bloodstream. Lipase release leads to TGs breakdown in both the bloodstream and peripancreatic fat. TGs are catabolized into fatty acids (FAs) and glycerol by lipase-induced hydrolysis. FAs modulate cell functions and can be divided into two categories based on the presence or absence of double bonds: saturated fatty acids (SFAs) and unsaturated fatty acids (UFAs). FAs can be classified based on the length of their carbon chains into short-chain fatty acids, medium-chain fatty acids and long-chain fatty acids (LCFAs). LCFAs are the main components of animal fats, participating in the functional regulation of cells and inflammatory responses. Palmitic acid (PA) is considered to be the primary long-chain saturated fatty acid (LC-SFA) that causes chronic inflammation in obese patients. Oleic acid (OA) and linoleic acid (LA), which are long-chain unsaturated fatty acid(LC-UFA), can mitigate the detrimental effects of PA [6]. PA hinder organelle functions, including those of mitochondria, autophagosomes, lysosomes, and the endoplasmic reticulum (ER), in PACs. As a result, PACs become more vulnerable to invasion in the AP. Moreover, PA can activate the NF-κB signaling pathway in macrophages and promote the inflammatory response involving the NLRP3 inflammasome [7]. Although LC-UFAs are widely recognized for their anti-inflammatory effects, high concentrations of LC-UFAs induce the necrosis of PACs, which increases the release of cell contents via cell membrane rupture. This, in turn, contributes to an amplified inflammatory response and hastens the development of AP [5,8,9]. Furthermore, fatty acid metabolites, such as fatty acid chlorohydrin and fatty acid ethyl esters (FAEEs) are involved in damaging PACs [10,11]. This paper provides a comprehensive analysis of lipase in AP, specifically examining the effects of PA and OA on Ca^{2+} overload, premature trypsinogen activation, protein kinase C (PKC) expression, ER stress, mitochondrial dysfunction, and autophagic dysfunction in PACs. Furthermore, this study outlines the diverse mechanisms through which PA induces M1 macrophage polarization by stimulating the NLRP3 inflammasome and the NF-κB pathway. Furthermore, we investigated lipid lowering therapy for AP. The potential of FA isoforms for predicting and treating AP is also briefly discussed.

2. Lipase catabolism in TGs mediates the onset and progression of AP

During AP, pancreatic enzymes leak from the injured PACs to the periphery of the pancreas, where they catalyze the catabolism of TGs. The storage and secretion of digestive enzymes in PACs are polarized and directional processes: digestive enzymes are released from the apical membrane into the lumen without touching the basement membrane side where fat is located [12]. However, in AP, this process is disrupted, and pancreatic enzymes in PACs pass through the basement membrane through exocytosis and leak into the periphery of the pancreas, where they contact peripancreatic fat [12–14]. Lipases, including pancreatic triacylglycerol lipase (PNLIP), pancreatic lipase-related protein 2, and carboxyl ester lipase (CEL), are the primary pancreatic digestive enzymes associated with peripancreatic lipolysis. PNLIP is critical for breaking down dietary fats, as well as peripancreatic fat [15]. Nevertheless, the participation of CEL in peripancreatic lipolysis depends on high concentrations of bile salts (>200 mmol/L), which are unavailable in AP [16]. In addition, CEL can break down only short six-carbon acyl chains [17] and is incapable of decomposing long-chain peripancreatic fat molecules [5,18]. Although CEL cannot mediate peripancreatic lipolysis, it mediates alcoholic AP by catalyzing the synthesis of FAEEs. The CEL inhibitor 3-benzyl-6-chloro-2-pyrone (3-BCP) alleviates FAEE-induced cytotoxicity [19]. Long-term alcohol consumption increases the content of fatty acid synthase in PACs [20], which catalyzes the synthesis of FAEEs from ethanol and intracellular FAs through a nonoxidizing pathway [21], resulting in the destruction of PACs and the onset of alcoholic AP. Although pancreatic lipase-related protein 2 hydrolyzes TGs in the absence of bile salts [16], it is rarely secreted and has a restricted function in lipolysis [22]. In addition to pancreatic lipase, adipose tissue also contains lipases, such as adipose triglyceride lipase (ATGL) and hormone-sensitive lipase (HSL) [23]. ATGL is the initial and rate-limiting lipase [24], and HSL is coregulated by glucagon, growth hormone, thyroid hormone, and epinephrine, which are involved in the hydrolysis of fat and the elevation of blood glucose levels. Although ATGL can be decomposed by trypsin during AP [15], ethanol can stimulate ATGL activity in obese mice to decompose peripancreatic fat and generate FAs, ultimately causing pancreatic injury [25]. ATGL is responsible for inducing alcoholic pancreatitis in obese individuals through lipolysis in the peripancreatic fat.

In addition to the breakdown of TGs derived from peripancreatic fat, lipase possesses the capacity to hydrolyze blood TGs. The process of lipase-induced TGs hydrolysis within the pancreatic vascular bed leads to the formation of FAs, a mechanism hypothesized to be one of the pathogenic pathways in HTG-AP [26]. Moreover, once AP is initiated, the release of lipase from PACs into the circulation could potentially trigger the breakdown of blood TGs and systemic lipolysis, thereby contributing to the overall systemic inflammatory response.

Lipases exert diverse functions in the onset and progression of AP. The breakdown of the TGs by PNLIP leading to AP exacerbation is a known phenomenon. CEL catalyzes the synthesis of palmitoleic acid and ethanol into FAEEs which in turn impairs PACs inducing alcoholic pancreatitis. Alcohol stimulates ATGL in the peripancreatic fat to participate in TGs catabolism, producing FAs that damage the PACs and induce obesity-alcoholic pancreatitis. These findings imply that abnormalities in the expression and functionality of lipase within pancreatic and adipose tissues, particularly in conditions such as obesity and alcohol dependence, may predispose individuals. Furthermore, HSL is a potential lipase implicated in systemic lipolysis, contributing to the development of AP under hormonal disruptions. The identification of lipase activity is crucial for assessing population susceptibility and formulating lipase-targeted therapies for AP treatment. Advancements in lipase activity assay technology provide a robust foundation for ongoing research in this

domain [27].

3. LCFAs cause acinar cell damage and death by inducing cellular events

Abnormal accumulation of LCFAs occurs through fat decomposition, which leads to destruction of the pancreas and its surrounding tissues. The utilization of the lipase inhibitor orlistat mitigated pancreatic damage in an AP mouse model [28,29]. LC-UFAs and LC-SFAs, produced via lipolysis, synergistically regulate cellular activity and inflammatory responses. For example, High concentrations of PA were cytotoxic to PACs. Conversely, OA alleviated lipid toxicity [30,31]. However, the impact of OA on PACs, whether protective or detrimental, is concentration-dependent [8,9,32].

3.1. *Typical manifestations of pancreatitis induced by LC-UFAs–mitochondrial dysfunction and Ca^{2+} overload*

High concentrations of LC-UFAs can cause mitochondrial dysfunction, which is a crucial step in damaging PACs. Beyond OA, various other LC-UFAs, including LA and docosahexaenoic acid (DHA), have the potential to induce Ca^{2+} overload in PACs at high concentration (Fig. 1a), resulting in ongoing opening of the mitochondrial permeability transition pore (MPTP) (Fig. 1b). This causes cytoplasmic components to enter the mitochondrial matrix, resulting in mitochondrial swelling and loss of membrane potential [33,34]. Furthermore, Ca^{2+} overload can induce mitochondrial dysfunction, subsequently leading to a surge in reactive oxygen species (ROS) production and a decrease in ATP synthesis. This ultimately results in premature trypsinogen activation. Upon its release, trypsin triggers autodigestion within and beyond PACs, including the mitochondria. Additionally, elevated levels of LA can impede the activation of mitochondrial complexes I and V [32]. The decrease in ATP production effectively disrupts the function of sarcoplasmic endoplasmic reticulum calcium-ATPases (SERCAs) and plasma membrane calcium ATPases (PMCAs), which are pivotal for removing Ca^{2+} from the cytoplasma, leading to Ca^{2+} overload [35]. Galactose supplementation has been demonstrated to mitigate this Ca^{2+} overload by supplying additional ATP to cells [36]. Research indicates that ROS can also induce persistent MPTP channel opening [34]. The activation of the MPTP channel is contingent upon cyclophilin D (CypD). Therefore, either CypD knockout or the application of a targeted small-molecule inhibitor (TRO40303) can offer protection against mitochondrial depolarization [37,38]. The mitigation of Ca^{2+} overload can be achieved through the inhibition of Ca^{2+} influx and release, as well as an increase in Ca^{2+} efflux. Melatonin has been shown to reduce pancreatic damage by upregulating SERCAs expression, thereby alleviating Ca^{2+} overload [39]. Research has indicated that dantrolene-mediated inhibition of ryanodine receptors (RyRs) effectively diminishes Ca^{2+} release from the ER in the granule region [40]. Furthermore, exposing PACs to caffeine inhibits 1,4,5-trisphosphate receptor (IP3R)-mediated Ca^{2+} oscillations [41]. Importantly, LC-UFAs do not appear to trigger Ca^{2+} release via the IP3R and RyRs pathways [8]. The potential mechanisms for Ca^{2+} overload induced by high concentrations of LC-UFAs could involve the inhibition of SERCAs and PMCAs functions, leading to a reduction in Ca^{2+} efflux. These findings warrant further investigation.

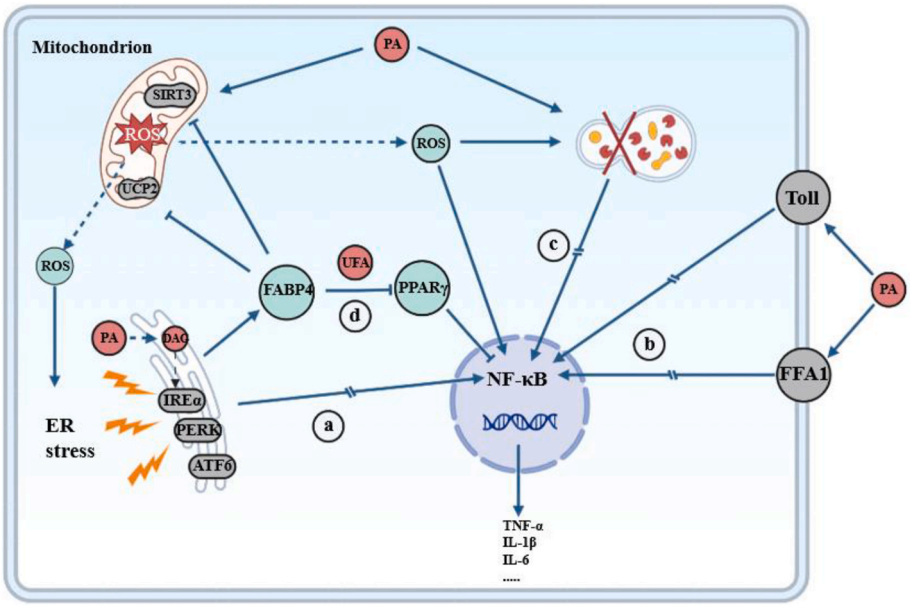

Fig. 1. Effect of high concentrations of OA on acinar cell function. (a) High concentrations of OA cause a continuous increase in Ca^{2+} levels, resulting in Ca^{2+} overload. (b) Continuous opening of the MPTP induced by high intracellular concentrations of Ca^{2+} causes mitochondrial dysfunction, decreased ATP production and disordered prothrombin secretion. (c) CN regulates premature trypsinogen activation. (d) OA regulates premature trypsinogen activation by upregulating PKC expression. (e) Cathepsin B released from lysosomes induces cell necroptosis and pyroptosis by stimulating RIP1-RIP3 and NLRP3.

3.2. LC-UFAs mediate impaired autophagy, premature trypsinogen activation, and death in PACs

Autophagy is a collective term for several pathways through which cytoplasmic materials are delivered to the lysosome and degraded by lysosomal hydrolases. This process involves organelles such as autophagosomes, lysosomes, and autolysosomes. Impaired autophagy leads to the premature trypsinogen activation associated with AP. The impairment of autophagy caused by mitochondrial dysfunction may involve damage to lysosomes through ROS generated by dysfunctional mitochondria or impaired delivery of hydrolases to lysosomes due to a decrease in ATP [42]. Furthermore, trypsinogen activation is regulated by both PKC and calcineurin (CN). High concentrations of LC-UFAs upregulate the expression of PKC, while Ca^{2+} overload induced by high concentrations of LC-UFAs mediates trypsinogen activation through CN [8,43–46] (Fig. 1c and d). During AP, there is a concomitant breakdown of polyamines, a natural anti-inflammatory substance. The reduction of polyamines activates cathepsin B, which in turn leads to the premature trypsinogen activation. Supplementing with the polyamine analog N(1), N(11)-diethylnorspermine and bismethylspermine can prevent the premature trypsinogen activation [47,48].

Sarah et al. have reported that increased levels of LC-UFAs can instigate cell necrosis [32], a phenomenon potentially attributable to the release of cathepsin B, which is triggered by damaged lysosomes. Furthermore, cathepsin B can cause necroptosis of PACs through the receptor-interacting protein kinase 1 (RIP1)–RIP3 pathway [49] (Fig. 1e). The inhibition of this RIP1–RIP3 pathway, either through genetic modulation or the use of necrostatin (an inhibitor of RIP1), can mitigate the severity of PACs injury. Consequently, this presents a potential therapeutic target for AP therapy [50]. The study of NLRP3 inflammasome-mediated cell death is a significant area of current research. The identification of the NLRP3 inflammasome in PACs provides a fresh perspective for investigating the role of LC-UFAs in acinar cell death, given that cathepsin B can activate the NLRP3 inflammasome, thereby triggering pyroptosis [51]. Furthermore, cathepsin B induces conformational alterations in the proapoptotic proteins Bax and Bid, which are situated within mitochondria and create pores on the mitochondrial membrane [52], which activates caspase-3/9 and ultimately triggers apoptosis. Although there are multiple modes of cell death, the preferred mode may be influenced by factors such as the concentration of LC-UFAs, the degree of trypsinogen activation, and cathepsin B leakage [50,52]. Given that different modes of death can exhibit varying degrees of proinflammatory effects, it is crucial to investigate the specific mode of cell death induced by LC-UFAs. Research has shown that the promotion of apoptosis can effectively mitigate inflammation in AP [53,54]. It is postulated that inhibiting pyroptosis and necroptosis in PACs could facilitate better control of inflammation in AP. The application of mimic peptides to inhibit NLRP3 inflammasome-mediated acinar cell pyroptosis may provide targeted therapies for AP [55]. Furthermore, Celastrol and baicalin have been found to inhibit necroptosis by reducing the activity of the RIPK1–RIPK3 pathway in mice with AP [56,57].

3.3. LC-UFAs participate in the development of AP through PKC expression

PKC plays a vital role in regulating multiple functions within the healthy pancreas and is involved in AP. PKC isoforms are associated with amylase secretion, trypsinogen activation, and NF-κB activation. Four subtypes of PKC, namely, PKCα, PKCδ, PKCε, and atypical PKCζ have been identified in PACs [8]. For instance, PKCα releases trypsin from the basolateral membrane, allowing it to enter peripancreatic tissue. Conversely, trypsin is not released from the apical membrane, which leads to entry into the pancreatic duct [58]. PKCδ and PKCε are involved in the activation of trypsinogen and the transcription factor NF-κB [46,59]. Once activated, PKCδ is translocated to the plasma membrane and participates in amylase secretion [60]. In AP, the expression of PKCα, PKCδ, and PKCε is upregulated under the stimulation of various LC-UFAs, whereas the expression of PKCζ is primarily influenced by DHA and arachidonic acid [8].

Low levels of LC-UFAs have a protective impact on PACs in AP mouse model. However, high amounts of LC-UFAs can induce AP-specific symptoms such as Ca^{2+} overload, premature trypsinogen activation, and expression of PKC. The mitigation of Ca^{2+} overload is vital for preserving the internal homeostasis of PACs. Previously, the exact pathways through which LC-UFAs instigate Ca^{2+} overload remained elusive. The inhibition of SERCAs and PMCAs functions present potential pathways that warrant further investigation. Currently, research into various types of cell death is a topic of significant interest. Premature trypsinogen activation leads to an increase in lysosomal membrane fragility and the release of Cathepsin B. This latter can trigger necroptosis and pyroptosis via the activation of both the RIP1-RIP3 pathway and the NLRP3 inflammasome. The identification of the NLRP3 inflammasome within the PACs implies that LC-UFAs may induce pyroptosis in this specific region. Furthermore, Sarah et al. have reported that high concentrations of LC-UFAs can provoke necrosis within the PACs [32]. Investigating the mechanisms behind PAC death is vital for managing the spread of inflammation. To mitigate the inflammatory response in AP, it is necessary to limit the occurrence of pyroptosis, necroptosis, and necrosis while simultaneously promoting apoptosis.

3.4. LC-SFAs induce PAC dysfunction by impairing autophagy

Impaired autophagy has been noted in the PACs of HTG-AP animal models, with LC-SFAs playing a pivotal role in this process [61]. The regulation of autophagy is largely dependent on key proteins such as mammalian target of rapamycin (mTOR) and AMP-activated protein kinase (AMPK) [62,63]. High concentrations of PA activate mTOR, thereby inhibiting the fusion of autophagosomes and lysosomes, which results in a decrease in autophagic flux. Mei et al. found that mice subjected to the HTG-AP model treated with the mTOR inhibitor rapamycin demonstrated a significant increase in autophagic flux [61]. Thioredoxin-interacting protein (TXNIP) expression escalates in response to stimulation of PA, inhibiting mTOR and fostering FA oxidation, and improving autophagy [64,65]. However, the over-upregulation of TXNIP induced by high concentrations of PA can lead to impaired autophagy and inflammatory responses [66]. Consequently, targeting TXNIP could offer a potential therapeutic avenue for the treatment of HTG-AP [67]. AMPK

mitigates mTOR activity via phosphorylation, thereby promoting autophagy [68]. Beyond regulating mTOR, AMPK plays a role in lipid metabolism. Activated AMPK augments the oxidation of FAs, thus inhibiting the accumulation of PA [69]. However, the expression of AMP-activated protein kinase precursor (*p*-AMPKα) was notably diminished in an obese mouse model of AP. The AMPK agonist, 5-aminoimidazole-4-formamide ribonucleotide (AICAR), activates AMPK to decrease lipolysis and alleviate necroptosis, thereby ameliorating AP [70]. Furthermore, research indicates that spermidine can both inhibit mTOR and activate AMPK, playing a role in activating autophagy and alleviating ER stress [71].

Alterations in the structure of the lysosomal membrane influence its functionality. A reduction in cholesterol content within this membrane impedes the fusion process between autophagosomes and lysosomes. PA diminished the cholesterol content within lysosomes by facilitating the transfer of cell membrane lipids to these organelles [72,73]. Furthermore, PA induced aberrant translocation of Bax from the ER to lysosomes. This process augments lysosomal permeability and compromises its functional integrity [74,75] (Fig. 2a).

ER stress and mitochondrial dysfunction significantly contribute to impaired autophagy. One such factor is the presence of ROS, which further exacerbates autophagy damage [76] (Fig. 2b). Moreover, a reduction in the ATP supply for the H^+ pump on the lysosome membrane results in an internal environment that becomes increasingly alkaline. This alkalinization impedes the hydrolysis of internal proteases [77]. The accumulation of PA metabolites, including diacylglycerols (DAGs), saturated phospholipids, and ceramides, within the ER induces stress, thereby escalating the damage to autophagy [78,79] (Fig. 2c). Treatment with 4-phenylbutyrate sodium (4-PBA) in an obese mouse model of AP has been shown to reduce ER stress and restore autophagy [61]. Trehalose, known for its ability to enhance the efficiency of autophagy, has been found to mitigate pancreatic injury and decrease the severity of AP in animal models. Consequently, trehalose shows potential as a therapeutic agent for treating AP [80]. However, the exact mechanism by which trehalose stimulates autophagy remains a subject of ongoing research [81].

3.5. *LC-SFAs activate ER stress, leading to acinar cell dysfunction and inflammation in AP*

Toxins such as ethanol cause ER stress by increasing the demand for protein synthesis and decreasing ER-processing ability [82]. Autophagy and the unfolded protein response relieve ER stress, but exceeding the ER stress threshold can trigger cellular inflammatory pathways. Precise regulation of ER stress is therefore essential for cellular homeostasis [83]. High concentrations of PA exacerbate CER-induced ER stress in PACs [30]. However, the molecular mechanism underlying PA-induced ER stress has largely not been elucidated. Sarnyai and colleagues speculated that metabolites of PA may alter membrane protein biological functions by affecting the morphology and fluidity of the ER membrane [84]. Intracellular metabolites of PA, DAGs, saturated phospholipids and ceramides, accumulate in the ER and are associated with structural damage [78,79]. Activation of the ER stress sensors IRE1α and PERK initiates a cascade of events that culminate in the manifestation of ER stress [85,86]. Furthermore, PA inhibits diacylglycerol acyltransferase 2 activity by stimulating ROS production, which is the essential enzyme in the synthesis of TGs, leading to diglycerol accumulation in PACs [87,88]. Low concentrations of OA promote the expression of diacylglycerol acyltransferase 2 (DGAT2) and carnitine

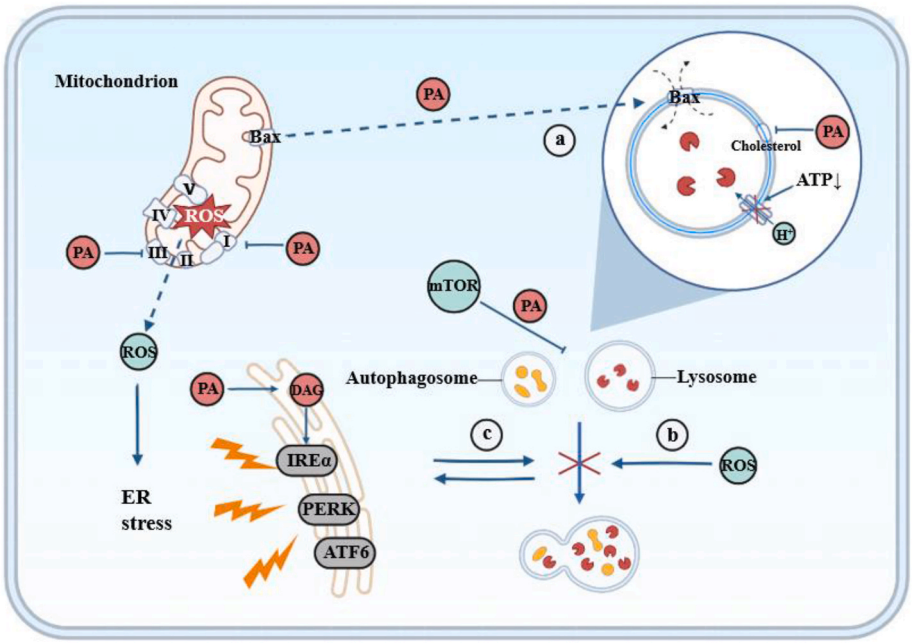

Fig. 2. Effect of SFAs on acinar cell function. (a) PA causes autophagy damage through lysosomal permeability, membrane composition and alkalization. (b) PA increases the production of mitochondrial ROS by inhibiting mitochondrial complexes I and III, which directly damages autophagy. (c) ER stress and autophagy injury can exacerbate each other.

palmitoyltransferase I (CPT1), which aids in the oxidation of FAs and the synthesis of TGs, thereby reducing production of intermediate products such as DAGs [87,89,90]. The polyphenolic antioxidant Urolithin A can restore the balance of mitochondrial fatty acid oxidation metabolism and reduce the production of intermediate products [91]. In contrast, PA induced the excessive release of ROS from mitochondria and autophagy dysfunction, which affects the ER function. Thus, PA aggravated PACs damage by triggering ER stress and disrupting autophagy. Mei et al. have demonstrated that the activation of AMPK can alleviate the autophagy disruption and ER stress induced by PA [61].

Ca^{2+} overload is a manifestation of compromised mitochondrial function. One mechanism through which SFAs impede mitochondrial function is by inhibiting complexes I and III [76]. PA had the capacity to induce mitochondrial dysfunction, ER stress, and autophagy damage, all of which contribute to abnormal PAC function. The adverse effects of PA on PACs appear to be amplified by AP-inducing factors. For instance, upon treatment with PA, PACs exhibited a transient surge in intracellular Ca^{2+} concentrations. However, co-administration of PA and caerulein led to a prolonged elevation in these levels [92]. The detrimental impact of PA on PACs appears to be exacerbated by AP causative factors. This may elucidate the heightened susceptibility and severity of AP observed in obese patients.

4. LCFAs regulate the differentiation of macrophages

Consuming a high-fat diet leads to obesity. LC-SFAs generated by the decomposition of stored saturated fat stimulate the polarization of M1 macrophages, contributing to chronic inflammation in obese individuals. Appropriate proportions of LC-UFAs in fat maintains a balanced proportions of M1 and M2 macrophages. In AP, necrotic adipose tissue leads to massive infiltration of M1 macrophages, amplifying inflammation and exacerbating organ injury in patients [93]. The product of lipolysis, LC-SFAs, are considered as a key factor mediating this process. PA stimulates macrophages transformation into an inflammatory phenotype and induces the secretion of proinflammatory factors and the suppression of anti-inflammatory factors in AP [94–96].

4.1. PA activates NF-κB signaling to mediate M1 macrophage polarization

The activation of the NF-κB signaling pathway is a pivotal mechanism that mediates M1 macrophage polarization. This process subsequently leads to the production of proinflammatory factors, including IL-1β, TNF-α, and IL-6 [97–100]. The Toll-like receptor (TLR) family is a crucial component in the activation of the NF-κB pathway. PA induces cellular oxidative stress and inflammatory responses by activating the TLR/NF-κB axis [101–103]. Hence, targeting TLR is considered a potential approach for mitigating the intensity of the inflammatory response in AP patients [102,104]. In addition, PA activates GPR40 receptors to induce an inflammatory response in macrophages [101], a proinflammatory mechanism that requires further investigation (Fig. 3a). Moreover, ER stress and

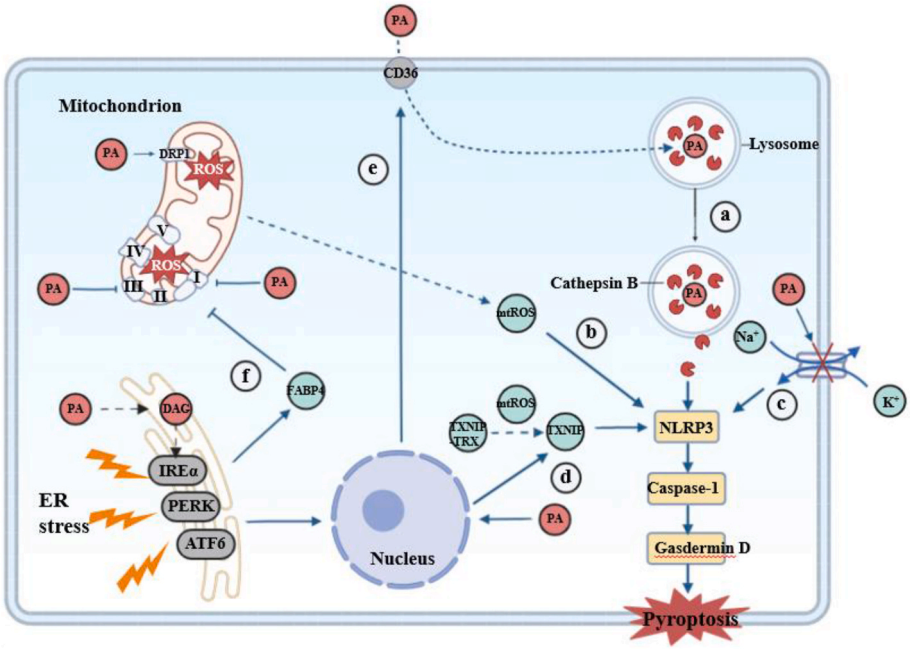

Fig. 3. PA mediates M1 macrophage polarization by activating the NF-κB signaling pathway. (a) PA stimulates the Toll and FFA1 receptors to stimulate a series of signaling pathways and ultimately activate NF-κB signaling. (b) Metabolites of PA cause ER stress, thus activating the NF-κB signaling pathway. (c) UFAs activate PPARγ and inhibit the NF-κB signaling pathway. ER stress causes increased expression of FABP4, which competitively binds to UFAs, resulting in PPARγ remaining inactive and unable to inhibit the NF-κB signaling pathway. (d) Autophagy injury activates the NF-κB signaling pathway.

lysosomal dysfunction are involved in the activation of the NF-κB pathway. On the one hand, the PA metabolites DAGs and ceramide accumulate in the ER, causing structural damage and activating IRE1α and PERK, which then stimulate cytokine production via the NF-κB pathway [85,86] (Fig. 3b). On the other hand, ER stress upregulates the expression of fatty-acid binding protein 4 (FABP4) [105,106], which competes with peroxisome proliferator-activated receptor (PPARγ) to bind UFAs, restricting the specific activation of PPARγ and disturbing mitochondrial function [7] (Fig. 3c). Moreover, FABP4 reduces the expression of sirtuin 3 (SIRT3) and uncoupling protein 2 (UCP2) [107], which in turn results in increased generation of ROS. Consequently, elevated levels of ROS are involved in the activation of NF-κB pathways. The polyphenolic antioxidant resveratrol can increase the expression of SIRT3, reduce the generation of ROS, and thereby inhibit the activation of NF-κB pathways [108]. Promotion of PPARγ activity significantly inhibits the activation of the NF-κB pathway [109]. Furthermore, PA induces lysosome dysfunction-related autophagy, eventually resulting in abnormal activation of the NF-κB pathway (Fig. 3d). PA induces and enhances NF-κB pathway activation through many mechanisms. Interference with these pathways in AP is difficult because changes in one pathway are compensated by other proinflammatory pathways. The most effective way to attenuate the inflammatory response to AP is to decrease the concentration of PA in blood and peripancreatic tissues, as well as to design related receptor (TLR, FFA) agonists. Furthermore, inhibiting the migration of macrophages to reduce their contact with activators is a feasible approach to suppress inflammation. The polyphenolic antioxidant chlorogenic acid reduced the serum and pancreatic levels of macrophage migration inhibitory factor in AP model [110].

4.2. PA activates the NLRP3 inflammasome to mediate M1 macrophage polarization

The NLRP3 inflammasome plays a crucial role in the macrophage response to microbial infections and cellular damage. Activation of the NLRP3 inflammasome occurs through two independent and parallel steps: priming and activation. The initial step entails boosting the mRNA and protein levels of NLRP3 and pro-IL1β by activating NF-κB [111]. After priming, activation of the NLRP3 inflammasome necessitates a second signal leading to oligomerization, caspase-1 activation, and the processing and release of IL1β and IL18 [112]. Caspase-1 plays a pivotal role in modifying inflammatory precursors and promoting the gasdermin-D induced pore formation within the cell membrane. The activation signal comprises lysosomal dysfunction, K^+ efflux, and mitochondrial dysfunction in AP. PA plays a role in priming and activating the NLRP3 inflammasome in macrophages [7,113]. The activation of NF-κB by PA has been previously detailed and will not be reiterated herein. This paragraph focuses on PA activation of the NLRP3 inflammasome mediating M1 macrophage polarization (Fig. 4a).

Lysosomal dysfunction results in the secretion of cathepsin B to activate the NLRP3 inflammasome [114]. PA and its metabolites are responsible for inducing lysosomal dysfunction in macrophages. PA penetrates macrophages through the cluster of differentiation 36 (CD36) to form fatty acid crystals and eventually lead to lysosomal dysfunction [115] (Fig. 4b). Furthermore, PA metabolites, DAGs,

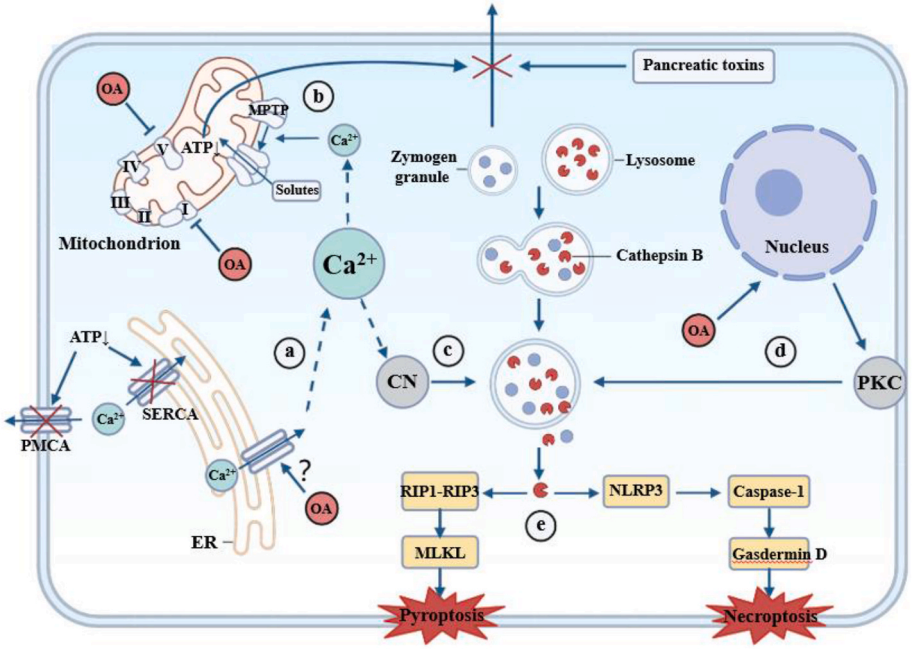

Fig. 4. PAs mediates M1 macrophage polarization by activating the NLRP3 inflammasome. (a) ER stress increases the expression of FABP4, which inhibits mitochondrial function, increases ROS production and hinders ATP production. (b) Phagocytized PA form crystals that damage lysosomes, which release cathepsin B to activate the NLRP3 inflammasome. (c) mtROS activate the NLRP3 inflammasome. (d) ER stress increases the expression of CD36 receptors. (e) mtROS stimulate TXNIP-TRX dissociation, and SFAs promote the expression of TXNIP. TXNIP stimulates the NLRP3 inflammasome. (f) PA caused Na^+-K^+-ATP dysfunction by affecting membrane components, and decreased K^+ influx activated the NLRP3 inflammasome.

saturated phospholipids and ceramides, activate ER stress, which in turn induces lysosomal dysfunction. First, ER stress triggers the transfer of Bax to lysosomes, resulting in lysosomal membrane instability. Second, ER stress can upregulate CD36 expression [116], which participates in PA transport and indirectly activates the NLRP3 inflammasome. Moreover, ER stress activates the NLRP3 inflammasome by increasing the overexpression of the TXNIP protein and directly or indirectly trigger increases in mitochondrial ROS levels [117,118]. Furthermore, PA modulates the expression of AMPK and components of the mTOR signaling pathway, thereby inhibiting autophagy. Additionally, PA diminishes the intracellular metabolism of FAs by impeding the activity of long-chain acyl-CoA synthetase, leading to an accumulation of PA within the cell [119,120]. Physiological concentrations of LC-UFAs can mitigate the activation of the NLRP3 inflammasome and pyroptosis by reducing ER stress, thereby mitigating the effects of PA [121].

Mitochondrial dysfunction and associated mitochondrial reactive oxygen species (mtROS) generation are correlated with the activation of the NLRP3 inflammasome [122]. The induction of mitochondrial dysfunction is among the mechanisms by which PAs activates the NLRP3 inflammasome. PA correlates with ATP accumulation by affecting prominent mitochondrial function, resulting in the abnormal accumulation of ROS (Fig. 4c).

PA induces dynamin-related protein 1 oligomerization (DRP1), which subsequently results in mitochondrial fragmentation and the generation of mtROS [123]. Furthermore, SFAs stimulate CD36 receptors to downregulate the expression of electron transport chain respiratory components [116] (Fig. 4d). In addition to its direct activation of the NLRP3 inflammasome, mtROS induce mitochondrial damage, resulting in the release of mitochondrial DNA into the cytoplasm and stimulation of the NLRP3 inflammasome assembly [124]. mtROS result in the dissociation of the TXNIP-TRX complex, whereby free TXNIP triggers the activation of the NLRP3 inflammasome [117,118,125] (Fig. 4e). Beyond the capacity of mtDNA to trigger inflammasome activation, mtDNA that has undergone ROS-mediated oxidation is equally capable of initiating this inflammatory response [126]. Epigallocatechin-3-gallate is a polyphenolic antioxidant extracted from green tea. It has the ability to reduce the production of mtROS in macrophages, thereby decreasing oxidized mtDNA and suppressing the activation of the NLRP3 inflammasome [127]. PA leads to mitochondrial dysfunction by mediating autophagy dysfunction and ER stress [128,129]. For instance, the inactivation of AMPK by PA adversely affects autophagy and stimulates the production of mtROS [128].

A decrease in the intracellular concentration of K^+, caused by K^+ efflux, is widely regarded as a common trigger for the NLRP3 inflammasome activation. PA increases the saturation of phosphatidylcholine in the macrophage membrane, which contributes to membrane and Na^+-K^+-ATP enzyme damage, thereby resulting in K^+ efflux [130] (Fig. 4f). ROS generation is frequently accompanied by K^+ efflux [131]. The interplay between these pathways is currently unclear, but it is possible that low intracellular K^+ concentration triggers ROS production or vice versa.

At present, therapy that targets the NLRP3 inflammasome pathway appears to hold significant promise. The pharmacological inhibition of this pathway may prove particularly beneficial for managing inflammation during the intermediate and advanced stages of AP. Liu et al. recently conducted a comprehensive review of existing literature on inhibitors that function by obstructing the formation of the NLRP3 inflammasome and proinflammatory effector molecules [132]. Inhibitors that interact with FA receptors and chelate FAs could potentially be effective strategies for mitigating AP inflammation. For example, LC-UFAs, including eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and other family members, have been shown to inactivate the NLRP3 inflammasome by reducing both its priming and assembly through the GPR120 and GPR40 cell-surface receptors [133,134].

4.3. The regulatory effects of LC-UFAs on macrophages need to be further explored

The established anti-inflammatory effect of LC-UFAs can effectively alleviate PA-induced macrophage activation at optimal concentrations. However, the anti-inflammatory effect of LC-UFAs is concentration dependent. High concentrations of LC-UFAs can decrease the integrity of the macrophage membrane, enhance DNA fragmentation and reduce mitochondrial transmembrane polarization, eventually leading to macrophage death. The proportion of cells undergoing apoptosis has been negatively associated with the LC-UFAs concentration, indicating limitations in managing the consequences of AP inflammation [135]. However, research investigating the influence of LC-UFAs on macrophages remains limited. This research is crucial as alterations in the concentrations of UFAs within peripancreatic tissue and serum may precipitate both early inflammatory responses and subsequent anti-inflammatory reactions.

5. Lipid lowering therapy

Reducing circulating TGs and FAs during the initial stages of HTG-AP can be advantageous for patients. The standard treatment protocol for HTG-AP typically incorporates the administration of fibrates, insulin, and heparin. Fibrates enhance lipoprotein lipase (LPL) activity while diminishing hepatic TG synthesis [136]. Insulin stimulates LPL, facilitating the metabolism of chylomicrons and very low-density lipoprotein, thereby reducing TG levels [137]. Furthermore, it inhibits HSL, which prevents the breakdown of TGs in adipose tissue and the overproduction of FAs. Heparin has the potential to reduce lipids by augmenting the breakdown of TGs [138]. However, it does not exhibit an inhibitory effect on HSL, which can lead to an overproduction of FAs [32]. Consequently, clinicians frequently employ a combination of these two methods. Plasmapheresis is another strategy for lipid reduction. However, its efficacy remains a subject of ongoing debate [139,140]. A notable limitation of these studies is the absence of measurements of FA levels.

In the context of HTG-AP, there is an impairment in FA oxidation and lipotoxicity can be mitigated by reestablishing this process. The administration of the neddylation inhibitor MLN4924 has been shown to restore pancreatic hnRNPA2B1 expression, thereby restoring FA oxidation and cell proliferation in mice treated with HTG-AP [141]. Furthermore, enhancing hepatic metabolism of FAs uptake can lead to a reduction in serum free FAs. PPARs play a significant role in lipid metabolism. Fibrates stimulate PPAR-α, which

inhibits TG synthesis and accelerates FA oxidation, thereby contributing to their lipid-lowering effects. In the liver, PPAR-γ facilitates FABP4-mediated uptake of free FAs and induces the expression of fatty acid synthase, further contributing to the reduction of serum free FAs [142]. The application of rosiglitazone, a PPAR-γ agonist, demonstrates potential in the treatment of AP [143,144]. The exploration of chelating agents tailored to specific FA isoforms, such as palmitoleic acid, presents a promising therapeutic avenue. The presence of Ca^{2+} in lactated Ringer solution has the capacity to chelate FAs, thereby reducing their concentration and subsequently mitigating inflammation. However, the clinical efficacy of lactated Ringer in treating AP remains a subject of debate [145–147]. The lipase inhibitor orlistat, utilized in the treatment of obesity, has been shown to mitigate the severity of the AP inflammatory response in various animal models [29,148], However, clinical trials are not feasible due to its administration via intraperitoneal injection. The use of LC-UFAs, such as omega-3 fatty acids, at an optimal dosage through oral or intravenous injection has demonstrated improved prognosis in AP. Nevertheless, high concentrations of omega-3 fatty acids can lead to cytotoxicity [8].

The rapid reduction of lipids, while simultaneously preventing the overproduction of FAs, is essential for effective treatment. The concentration changes in serum FAs can serve as a significant indicator of treatment efficacy due to their cytotoxic properties.

6. Conclusion

Research suggests that during AP, pancreatic lipase degrades TGs in both peripancreatic fat and blood, thereby triggering systemic inflammation. FAs, which are produced as a result of TG hydrolysis, are recognized as key mediators of this inflammatory response. However, there is a notable lack of research investigating the correlation between lipase levels, FA levels, PACs, and macrophage counts in patients with AP. This paper aims to offer a thorough review and analysis of existing research in relation to these factors.

PNLIP is believed to contribute to the deterioration of AP by breaking down peripancreatic fat. However, the onset and progression of AP are also influenced by adipose ATGL and HSL. For instance, the catabolism of TGs in adipose tissue can lead to high concentrations of UFAs. This process may be a key pathogenic mechanism underlying obesity-alcoholic pancreatitis. This article provides a comprehensive summary of the pathogenic pathways associated with high concentrations of LC-UFAs in PACs. It delves into an unexplored pathway that triggers Ca^{2+} overload. Additionally, it scrutinizes the mechanism through which UFAs induce acinar cell death. The review also discusses the impact of elevated LC-UFAs concentrations on the functionality and activity of macrophages. The deleterious effects of PA on PACs may be intensified in the presence of pathogenic factors associated with AP, potentially elucidating the susceptibility and severity of pancreatitis in obese patients. The activation of macrophages by PA is a pivotal element in the inflammatory response. The paper concludes with an overview of potential therapeutic agents for HTG-AP (Table 1). It should be highlighted that the concentration of FAs in serum significantly influences AP development, alongside TGs. The key to managing inflammation lies in limiting excessive FA production while swiftly reducing lipids. However, our study does not address more FA isoforms. Maria et al. delineate the differential proinflammatory and anti-inflammatory impacts of various FA isoforms on macrophages [101]. Recent research indicates that early serum palmitoleic acid levels in AP patients correlate with organ failure [149]. Furthermore, short-chain and medium -chain fatty acids are also crucial for the development of AP. Investigating FAs and their isoforms could provide insights into the pathogenesis of AP and facilitate the development of effective treatments.

Author declaration form

The construction of the main framework: QL, ZH, XG, YG. Collection of references: HZ, QL, ZH. Write manuscript: QL, ZH Critical revision of the manuscript: QL, JY. Drawing schematic diagram: XG, YG. All authors approved the final version of the manuscript.

Table 1
The table lists potential therapeutic agents and their mechanisms of action for HTG-AP.

DRUG	TYPE	THERAY PATHWAY	PMID
Galactose	Carbohydrate	Supply extra ATP via glycolysis cycle	29893744
Melatonin	Hormone	Upregulate SERCAs expression to improve Ca^{2+} overload	22687382
Rapamycin	Macrolide antibiotic	Improve autophagy and ER stress by inhibiting mTOR	32642911
Trehalose	Carbohydrate	Enhance autophagy efficiency	29907758
Omega-3 PUFAs	Unsaturated fatty acids	Inhibit the activation of NLRP3 inflammasome by inhibiting GPR120 and GPR40 receptor	23809162
Orlistat	Lipase inhibitor	Inhibit the breakdown of TGs in blood and peripancreatic fat	25579844
Urolithin A	Polyphenols	restore the balance of mitochondrial fatty acid oxidation metabolism	38116065
Resveratrol	Polyphenols	Increase the expression of SIRT3 and reduce the generation of ROS	33628394
Chlorogenic acid	Polyphenols	Reduced the serum and pancreatic levels of macrophage migration inhibitory factor	28919396
Epigallocatechin-3-gallate	Polyphenols	Reduce the production of mtROS and suppress the activation of the NLRP3 inflammasome in macrophages	34018522
N(1), N(11)-diethylnorspermine	Polyamine analog	Prevent the premature trypsinogen activation	21814793
Bismethylspermine	Polyamine analog	Prevent the premature trypsinogen activation	16400014
Spermidine	Spermidine	Inhibit mTOR and activate AMPK	21831529

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Data availability

No data was used for the research described in the article.

CRediT authorship contribution statement

Qiang Liu: Supervision. **Xinyi Gu:** Supervision, Investigation. **Xiaodie Liu:** Investigation. **Ye Gu:** Investigation. **Hongchen Zhang:** Investigation. **Jianfeng Yang:** Writing – review & editing. **Zhicheng Huang:** Writing – review & editing, Writing – original draft.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

AMPK	AMP-activated protein kinase
ATGL	Adipose triglyceride lipase
CEL	Carboxyl ester lipase
CD36	Cluster of differentiation 36
CN	Calcineurin
CypD	Cyclophilin D
DAGs	Diacylglycerols
DHA	Docosahexaenoic acid
ER	Endoplasmic reticulum
EPA	Eicosapentaenoic acid
FABP4	Fatty acid-binding protein 4
FAEEs	Fatty acid ethyl esters
FAs	Fatty acids
HSL	Hormone-sensitive lipase
HTG-AP	hypertriglyceridemia-induced acute pancreatitis
IP3R	Inositol 1,4,5-trisphosphate receptor
LCFAs	Long-chain fatty acids
LC-SFAs	Long-chain saturated fatty acids
LC-UFA	Long-chain unsaturated fatty acid
LPL	lipoprotein lipase
mTOR	Mammalian target of rapamycin
MPTP	Mitochondrial permeability transition pore
OA	Oleic acid
LA	Linoleic acid
PA	Palmitic acid
PACs	Pancreatic acinar cells
PPARγ	Peroxisome proliferator-activated receptor
PMCAs	Plasma membrane Ca^{2+} channels
PKC	Protein kinase C
PNLIP	Pancreatic triacylglycerol lipase
ROS	Reactive oxygen species

RyR	Ryanodine receptor
SERCAs	Smooth ER Ca^{2+} channels
SFAs	Saturated fatty acids
SIRT3	sirtuin 3
UCP2	uncoupling protein 2
TXNIP	Thioredoxin-interacting protein
TGs	Triglycerides
UFAs	Unsaturated fatty acids
3-BCP	3-benzyl-6-chloro-2-pyrone.

References

[1] M.S. Petrov, D. Yadav, Global epidemiology and holistic prevention of pancreatitis, Nat. Rev. Gastroenterol. Hepatol. 16 (3) (2019) 175–184.
[2] P. Szatmary, T. Grammatikopoulos, W. Cai, et al., Acute pancreatitis: Diagnosis and treatment, Drugs 82 (12) (2022) 1251–1276.
[3] X.Y. Lin, Y. Zeng, Z.C. Zhang, et al., Incidence and clinical characteristics of hypertriglyceridemic acute pancreatitis: a retrospective single-center study, World J. Gastroenterol. 28 (29) (2022) 3946–3959.
[4] W. Xia, H. Yu, Y. Huang, et al., The visceral adiposity index predicts the severity of hyperlipidaemic acute pancreatitis, Intern Emerg Med 17 (2) (2022) 417–422.
[5] P. Noel, K. Patel, C. Durgampudi, et al., Peripancreatic fat necrosis worsens acute pancreatitis independent of pancreatic necrosis via unsaturated fatty acids increased in human pancreatic necrosis collections, Gut 65 (1) (2016) 100–111.
[6] M.T. VAN Daal, G. Folkerts, J. Garssen, et al., Pharmacological modulation of immune responses by Nutritional components, Pharmacol. Rev. 73 (4) (2021) 198–232.
[7] J. Korbecki, K. Bajdak-Rusinek, The effect of palmitic acid on inflammatory response in macrophages: an overview of molecular mechanisms, Inflamm. Res. 68 (11) (2019) 915–932.
[8] Y.T. Chang, M.C. Chang, C.C. Tung, et al., Distinctive roles of unsaturated and saturated fatty acids in hyperlipidemic pancreatitis, World J. Gastroenterol. 21 (32) (2015) 9534–9543.
[9] B. Khatua, B. EL-Kurdi, K. Patel, et al., Adipose saturation reduces lipotoxic systemic inflammation and explains the obesity paradox, Sci. Adv. 7 (5) (2021).
[10] N. Franco-Pons, J. Casas, S.G. Fabri, et al., Fat necrosis generates proinflammatory halogenated lipids during acute pancreatitis, Ann. Surg. 257 (5) (2013) 943–951.
[11] J. Lee, J.W. Lim, H. Kim, Lycopene inhibits oxidative stress-mediated inflammatory responses in ethanol/palmitoleic acid-stimulated pancreatic acinar AR42J cells, Int. J. Mol. Sci. 22 (4) (2021).
[12] H.Y. Gaisano, M.P. Lutz, J. Leser, et al., Supramaximal cholecystokinin displaces Munc18c from the pancreatic acinar basal surface, redirecting apical exocytosis to the basal membrane, J. Clin. Invest. 108 (11) (2001) 1597–1611.
[13] P.P. Lam, L.I. Cosen Binker, A. Lugea, et al., Alcohol redirects CCK-mediated apical exocytosis to the acinar basolateral membrane in alcoholic pancreatitis, Traffic 8 (5) (2007) 605–617.
[14] L.I. Cosen-Binker, M.G. Binker, C.C. Wang, et al., VAMP8 is the v-SNARE that mediates basolateral exocytosis in a mouse model of alcoholic pancreatitis, J. Clin. Invest. 118 (7) (2008) 2535–2551.
[15] C. DE Oliveira, B. Khatua, P. Noel, et al., Pancreatic triglyceride lipase mediates lipotoxic systemic inflammation, J. Clin. Invest. 130 (4) (2020) 1931–1947.
[16] B. Khatua, R.N. Trivedi, P. Noel, et al., Carboxyl ester lipase may not mediate lipotoxic injury during severe acute pancreatitis, Am. J. Pathol. 189 (6) (2019) 1226–1240.
[17] E. Aubert, V. Sbarra, P. LE, J. Venin, et al., Site-directed mutagenesis of the basic N-terminal cluster of pancreatic bile salt-dependent lipase. Functional significance, J. Biol. Chem. 277 (38) (2002) 34987–34996.
[18] H. Fontbonne, L. Brisson, R.I.N.E.A. V, et al., Human bile salt-dependent lipase efficiency on medium-chain acyl-containing substrates: control by sodium taurocholate, J. Biochem. 149 (2) (2011) 145–151.
[19] W. Huang, D.M. Booth, M.C. Cane, et al., Fatty acid ethyl ester synthase inhibition ameliorates ethanol-induced Ca2+-dependent mitochondrial dysfunction and acute pancreatitis, Gut 63 (8) (2014) 1313–1324.
[20] R.H. Pf Tzer, S.D. Tadic, H.S. Li, et al., Pancreatic cholesterol esterase, ES-10, and fatty acid ethyl ester synthase III gene expression are increased in the pancreas and liver but not in the brain or heart with long-term ethanol feeding in rats, Pancreas 25 (1) (2002) 101–106.
[21] A.S. Gukovskaya, M. Mouria, I. Gukovsky, et al., Ethanol metabolism and transcription factor activation in pancreatic acinar cells in rats, Gastroenterology 122 (1) (2002) 106–118.
[22] T. Giller, P. Buchwald, D. Blum-Kaelin, et al., Two novel human pancreatic lipase related proteins, hPLRP1 and hPLRP2. Differences in colipase dependence and in lipase activity, J. Biol. Chem. 267 (23) (1992) 16509–16516.
[23] S. Wang, K.G. Soni, M. Semache, et al., Lipolysis and the integrated physiology of lipid energy metabolism, Mol. Genet. Metabol. 95 (3) (2008) 117–126.
[24] R. Schreiber, H. Xie, M. Schweiger, Of mice and men: the physiological role of adipose triglyceride lipase (ATGL), Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1864 (6) (2019) 880–899.
[25] X. Yang, L. Yao, L. Dai, et al., Alcohol predisposes obese mice to acute pancreatitis via adipose triglyceride lipase-dependent visceral adipocyte lipolysis, Gut 72 (1) (2022) 212–214.
[26] M. Qiu, X. Zhou, M. Zippi, et al., Comprehensive review on the pathogenesis of hypertriglyceridaemia-associated acute pancreatitis, Ann. Med. 55 (2) (2023) 2265939.
[27] S. Rajan, H.C. DE Guzman, T. Palaia, et al., A simple, rapid, and sensitive fluorescence-based method to assess triacylglycerol hydrolase activity, J. Lipid Res. 62 (2021) 100115.
[28] Y. Uchida, T. Masui, K. Nakano, et al., Clinical and experimental studies of intraperitoneal lipolysis and the development of clinically relevant pancreatic fistula after pancreatic surgery, Br. J. Surg. 106 (5) (2019) 616–625.
[29] K. Patel, R.N. Trivedi, C. Durgampudi, et al., Lipolysis of visceral adipocyte triglyceride by pancreatic lipases converts mild acute pancreatitis to severe pancreatitis independent of necrosis and inflammation, Am. J. Pathol. 185 (3) (2015) 808–819.
[30] K. Ben-Dror, R. Birk, Oleic acid ameliorates palmitic acid-induced ER stress and inflammation markers in naive and cerulein-treated exocrine pancreas cells, Biosci. Rep. 39 (5) (2019).
[31] J. Wu, G. Hu, Y. Lu, et al., Palmitic acid aggravates inflammation of pancreatic acinar cells by enhancing unfolded protein response induced CCAAT-enhancer-binding protein β-CCAAT-enhancer-binding protein α activation, Int. J. Biochem. Cell Biol. 79 (2016) 181–193.
[32] S. Navina, C. Acharya, J.P. Delany, et al., Lipotoxicity causes multisystem organ failure and exacerbates acute pancreatitis in obesity, Sci. Transl. Med. 3 (107) (2011) 107ra10.
[33] Correction: mechanism of mitochondrial permeability transition pore induction and damage in the pancreas: inhibition prevents acute pancreatitis by protecting production of ATP, Gut 68 (6) (2019) 1136.

[34] A. Habtezion, A.S. Gukovskaya, S.J. Pandol, Acute pancreatitis: a Multifaceted Set of organelle and cellular Interactions, Gastroenterology 156 (7) (2019) 1941–1950.
[35] D.N. Criddle, E. Mclaughlin, J.A. Murphy, et al., The pancreas misled: signals to pancreatitis, Pancreatology 7 (5–6) (2007) 436–446.
[36] S. Peng, J.V. Gerasimenko, T.M. Tsugorka, et al., Galactose protects against cell damage in mouse models of acute pancreatitis, J. Clin. Invest. 128 (9) (2018) 3769–3778.
[37] A. Haleckova, O. Benek, L. Zemanov, et al., Small-molecule inhibitors of cyclophilin D as potential therapeutics in mitochondria-related diseases, Med. Res. Rev. 42 (5) (2022) 1822–1855.
[38] M.A. Javed, L. Wen, M. Awais, et al., TRO40303 ameliorates alcohol-induced pancreatitis through reduction of fatty acid ethyl ester-induced mitochondrial injury and necrotic cell death, Pancreas 47 (1) (2018) 18–24.
[39] J. Huai, Y. Shao, X. Sun, et al., Melatonin ameliorates acute necrotizing pancreatitis by the regulation of cytosolic Ca2+ homeostasis, Pancreatology 12 (3) (2012) 257–263.
[40] A.I. Orabi, A.U. Shah, M.U. Ahmad, et al., Dantrolene mitigates caerulein-induced pancreatitis in vivo in mice, Am. J. Physiol. Gastrointest. Liver Physiol. 299 (1) (2010) G196–G204.
[41] W. Huang, M.C. Cane, R. Mukherjee, et al., Caffeine protects against experimental acute pancreatitis by inhibition of inositol 1,4,5-trisphosphate receptor-mediated Ca2+ release, Gut 66 (2) (2017) 301–313.
[42] A.S. Gukovskaya, I. Gukovsky, L.H. Alg, et al., Autophagy, inflammation, and immune dysfunction in the pathogenesis of pancreatitis, Gastroenterology 153 (5) (2017) 1212–1226.
[43] S.Z. Husain, W.M. Grant, F.S. Gorelick, et al., Caerulein-induced intracellular pancreatic zymogen activation is dependent on calcineurin, Am. J. Physiol. Gastrointest. Liver Physiol. 292 (6) (2007) G1594–G1599.
[44] A.U. Shah, A. Sarwar, A.I. Orabi, et al., Protease activation during in vivo pancreatitis is dependent on calcineurin activation, Am. J. Physiol. Gastrointest. Liver Physiol. 297 (5) (2009) G967–G973.
[45] K.A. Muili, S. Jin, A.I. Orabi, et al., Pancreatic acinar cell nuclear factor κB activation because of bile acid exposure is dependent on calcineurin, J. Biol. Chem. 288 (29) (2013) 21065–21073.
[46] E.C. Thrower, S. Osgood, C.A. Shugrue, et al., The novel protein kinase C isoforms -delta and -epsilon modulate caerulein-induced zymogen activation in pancreatic acinar cells, Am. J. Physiol. Gastrointest. Liver Physiol. 294 (6) (2008) G1344–G1353.
[47] N.E.N.M.T. Hyv, K.H. Herzig, R. Sinervirta, et al., Activated polyamine catabolism in acute pancreatitis: alpha-methylated polyamine analogues prevent trypsinogen activation and pancreatitis-associated mortality, Am. J. Pathol. 168 (1) (2006) 115–122.
[48] A. Uimari, M. Merentie, R. Sironen, et al., Overexpression of spermidine/spermine N1-acetyltransferase or treatment with N1-N11-diethylnorspermine attenuates the severity of zinc-induced pancreatitis in mouse, Amino Acids 42 (2–3) (2012) 461–471.
[49] G. Wang, F.Z. Qu, L. Li, et al., Necroptosis: a potential, promising target and switch in acute pancreatitis, Apoptosis 21 (2) (2016) 121–129.
[50] J. Louhimo, M.L. Steer, G. Perides, Necroptosis is an Important severity Determinant and potential therapeutic target in experimental severe pancreatitis, Cell Mol Gastroenterol Hepatol 2 (4) (2016) 519–535.
[51] L. Gao, X. Dong, W. Gong, et al., Acinar cell NLRP3 inflammasome and gasdermin D (GSDMD) activation mediates pyroptosis and systemic inflammation in acute pancreatitis, Br. J. Pharmacol. 178 (17) (2021) 3533–3552.
[52] R. Talukdar, A. Sareen, H. Zhu, et al., Release of cathepsin B in Cytosol causes cell death in acute pancreatitis, Gastroenterology 151 (4) (2016) 747–758.e5.
[53] Q. Zhang, C. Zhao, L. Zhang, et al., Escin sodium Improves the prognosis of acute pancreatitis via promoting cell apoptosis by suppression of the ERK/STAT3 signaling pathway, Oxid. Med. Cell. Longev. 2021 (2021) 9921839.
[54] J. Chen, J. Chen, X. Wang, et al., Ligustrazine alleviates acute pancreatitis by accelerating acinar cell apoptosis at early phase via the suppression of p38 and Erk MAPK pathways, Biomed. Pharmacother. 82 (2016) 1–7.
[55] Y. Lu, B. Li, M. Wei, et al., HDL inhibits pancreatic acinar cell NLRP3 inflammasome activation and protect against acinar cell pyroptosis in acute pancreatitis, Int. Immunopharm. 125 (Pt A) (2023) 110950.
[56] Q.Q. Liang, Z.J. Shi, T. Y, et al., Celastrol inhibits necroptosis by attenuating the RIPK1/RIPK3/MLKL pathway and confers protection against acute pancreatitis in mice, Int. Immunopharm. 117 (2023) 109974.
[57] Y.T. Huang, Q.Q. Liang, H.R. Zhang, et al., Baicalin inhibits necroptosis by decreasing oligomerization of phosphorylated MLKL and mitigates caerulein-induced acute pancreatitis in mice, Int. Immunopharm. 108 (2022) 108885.
[58] A.K. Fleming, P. Storz, Protein kinase C isoforms in the normal pancreas and in pancreatic disease, Cell. Signal. 40 (2017) 1–9.
[59] Y. Liu, J. Yuan, T. Tan, et al., Genetic inhibition of protein kinase Cε attenuates necrosis in experimental pancreatitis, Am. J. Physiol. Gastrointest. Liver Physiol. 307 (5) (2014) G550–G563.
[60] C. Li, X. Chen, J.A. Williams, Regulation of CCK-induced amylase release by PKC-delta in rat pancreatic acinar cells, Am. J. Physiol. Gastrointest. Liver Physiol. 287 (4) (2004) G764–G771.
[61] Q. Mei, Y. Zeng, C. Huang, et al., Rapamycin alleviates hypertriglyceridemia-related acute pancreatitis via restoring autophagy flux and inhibiting endoplasmic reticulum stress, Inflammation 43 (4) (2020) 1510–1523.
[62] B.K. Smith, K. Marcinko, E.M. Desjardins, et al., Treatment of nonalcoholic fatty liver disease: role of AMPK, Am. J. Physiol. Endocrinol. Metab. 311 (4) (2016) E730–E740.
[63] V.I. Korolchuk, S. Saiki, M. Lichtenberg, et al., Lysosomal positioning coordinates cellular nutrient responses, Nat. Cell Biol. 13 (4) (2011) 453–460.
[64] H.S. Park, J.W. Song, J.H. Park, et al., TXNIP/VDUP1 attenuates steatohepatitis via autophagy and fatty acid oxidation, Autophagy 17 (9) (2021) 2549–2564.
[65] H. Ao, H. Li, X. Zhao, et al., TXNIP positively regulates the autophagy and apoptosis in the rat müller cell of diabetic retinopathy, Life Sci. 267 (2021) 118988.
[66] W. Deng, Y. Li, Z. Ren, et al., Thioredoxin-interacting protein: a critical link between autophagy disorders and pancreatic β-cell dysfunction, Endocrine 70 (3) (2020) 526–537.
[67] Y. Liu, M. Li, C. Mei, et al., Thioredoxin-interacting protein deficiency protects against severe acute pancreatitis by suppressing apoptosis signal-regulating kinase 1, Cell Death Dis. 13 (10) (2022) 914.
[68] Y. Chun, J. Kim, AMPK-mTOR signaling and cellular Adaptations in Hypoxia, Int. J. Mol. Sci. 22 (18) (2021).
[69] C. Fang, J. Pan, N. Qu, et al., The AMPK pathway in fatty liver disease, Front. Physiol. 13 (2022) 970292.
[70] K. Wang, A. Zhao, D. Tayier, et al., Activation of AMPK ameliorates acute severe pancreatitis by suppressing pancreatic acinar cell necroptosis in obese mice models, Cell Death Dis. 9 (1) (2023) 363.
[71] P.B. Tirupathi Pichiah, U. Suriyakalaa, S. Kamalakkannan, et al., Spermidine may decrease ER stress in pancreatic beta cells and may reduce apoptosis via activating AMPK dependent autophagy pathway, Med. Hypotheses 77 (4) (2011) 677–679.
[72] H. Koga, S. Kaushik, A.M. Cuervo, Altered lipid content inhibits autophagic vesicular fusion, Faseb. J. 24 (8) (2010) 3052–3065.
[73] T. Yamamoto, Y. Takabatake, A. Takahashi, et al., High-fat diet-induced lysosomal dysfunction and impaired autophagic flux contribute to lipotoxicity in the Kidney, J. Am. Soc. Nephrol. 28 (5) (2017) 1534–1551.
[74] A.E. Feldstein, N.W. Werneburg, A. Canbay, et al., Free fatty acids promote hepatic lipotoxicity by stimulating TNF-alpha expression via a lysosomal pathway, Hepatology 40 (1) (2004) 185–194.
[75] A.E. Feldstein, N.W. Werneburg, Z. Li, et al., Bax inhibition protects against free fatty acid-induced lysosomal permeabilization, Am. J. Physiol. Gastrointest. Liver Physiol. 290 (6) (2006) G1339–G1346.
[76] N. Lin, H. Chen, H. Zhang, et al., Mitochondrial reactive oxygen species (ROS) inhibition ameliorates palmitate-induced INS-1 beta cell death, Endocrine 42 (1) (2012) 107–117.
[77] D.J. Yamashiro, S.R. Fluss, F.R. Maxfield, Acidification of endocytic vesicles by an ATP-dependent proton pump, J. Cell Biol. 97 (3) (1983) 929–934.
[78] A. Akoumi, T. Haffar, M. Mousterji, et al., Palmitate mediated diacylglycerol accumulation causes endoplasmic reticulum stress, Plin2 degradation, and cell death in H9C2 cardiomyoblasts, Exp. Cell Res. 354 (2) (2017) 85–94.

[79] S.K. Kim, E. Oh, M. Yun, et al., Palmitate induces cisternal ER expansion via the activation of XBP-1/CCTα-mediated phospholipid accumulation in RAW 264.7 cells, Lipids Health Dis. 14 (2015) 73.
[80] G. Biczo, E.T. Vegh, N. Shalbueva, et al., Mitochondrial dysfunction, through impaired autophagy, leads to endoplasmic reticulum stress, Deregulated lipid metabolism, and pancreatitis in animal models, Gastroenterology 154 (3) (2018) 689–703.
[81] H.J. Lee, Y.S. Yoon, S.J. Lee, Mechanism of neuroprotection by trehalose: controversy surrounding autophagy induction, Cell Death Dis. 9 (7) (2018) 712.
[82] J.S. Wu, W.M. Li, Y.N. Chen, et al., Endoplasmic reticulum stress is activated in acute pancreatitis, J Dig Dis 17 (5) (2016) 295–303.
[83] A. Gammelsrud, A. Solhaug, B. Dendel, et al., Enniatin B-induced cell death and inflammatory responses in RAW 267.4 murine macrophages, Toxicol. Appl. Pharmacol. 261 (1) (2012) 74–87.
[84] F. Sarnyai, M.B. Donk, T.Y.S.I.J. M, et al., Cellular toxicity of dietary trans fatty acids and its correlation with ceramide and diglyceride accumulation, Food Chem. Toxicol. 124 (2019) 324–335.
[85] R. Volmer, K. VAN DER Ploeg, D. Ron, Membrane lipid saturation activates endoplasmic reticulum unfolded protein response transducers through their transmembrane domains, Proc Natl Acad Sci U S A 110 (12) (2013) 4628–4633.
[86] N. Kono, N. Amin-Wetzel, D. Ron, Generic membrane-spanning features endow IRE1α with responsiveness to membrane aberrancy, Mol. Biol. Cell 28 (17) (2017) 2318–2332.
[87] J.H. Ahn, M.H. Kim, H.J. Kwon, et al., Protective effects of Oleic acid against palmitic acid-induced apoptosis in pancreatic AR42J cells and its mechanisms, KOREAN J. PHYSIOL. PHARMACOL. 17 (1) (2013) 43–50.
[88] S. Jung, M. Choi, K. Choi, et al., Inactivation of human DGAT2 by oxidative stress on cysteine residues, PLoS One 12 (7) (2017) e0181076.
[89] C.J. Nolan, C.Z. Larter, Lipotoxicity: why do saturated fatty acids cause and monounsaturates protect against it? J. Gastroenterol. Hepatol. 24 (5) (2009) 703–706.
[90] T. Coll, E. Eyre, R. Rodr Guez-Calvo, et al., Oleate reverses palmitate-induced insulin resistance and inflammation in skeletal muscle cells, J. Biol. Chem. 283 (17) (2008) 11107–11116.
[91] Y. Yang, Q. Hu, H. Kang, et al., Urolithin A protects severe acute pancreatitis-associated acute cardiac injury by regulating mitochondrial fatty acid oxidative metabolism in cardiomyocytes, MedComm (2020) 4 (6) (2023) e459.
[92] Y. Zeng, X. Wang, W. Zhang, et al., Hypertriglyceridemia aggravates ER stress and pathogenesis of acute pancreatitis, Hepato-Gastroenterology 59 (119) (2012) 2318–2326.
[93] N. Franco-Pons, S. Gea-Sorl, D. Closa, Release of inflammatory mediators by adipose tissue during acute pancreatitis, J. Pathol. 221 (2) (2010) 175–182.
[94] A. Shapouri-Moghaddam, S. Mohammadian, H. Vazini, et al., Macrophage plasticity, polarization, and function in health and disease, J. Cell. Physiol. 233 (9) (2018) 6425–6440.
[95] P.J. Murray, Macrophage polarization, Annu. Rev. Physiol. 79 (2017) 541–566.
[96] N.J. Pillon, K.L. Chan, S. Zhang, et al., Saturated fatty acids activate caspase-4/5 in human monocytes, triggering IL-1β and IL-18 release, Am. J. Physiol. Endocrinol. Metab. 311 (5) (2016) E825–E835.
[97] M.T. Nguyen, S. Favelyukis, A.K. Nguyen, et al., A subpopulation of macrophages infiltrates hypertrophic adipose tissue and is activated by free fatty acids via Toll-like receptors 2 and 4 and JNK-dependent pathways, J. Biol. Chem. 282 (48) (2007) 35279–35292.
[98] S. Huang, J.M. Rutkowsky, R.G. Snodgrass, et al., Saturated fatty acids activate TLR-mediated proinflammatory signaling pathways, J. Lipid Res. 53 (9) (2012) 2002–2013.
[99] R. Ahmad, A. AL-Roub, S. Kochumon, et al., The Synergy between palmitate and TNF-α for CCL2 production is dependent on the TRIF/IRF3 pathway: Implications for metabolic inflammation, J. Immunol. 200 (10) (2018) 3599–3611.
[100] X. Huang, L.Y. Chen, A.M. Doerner, et al., An atypical protein kinase C (PKC zeta) plays a critical role in lipopolysaccharide-activated NF-kappa B in human peripheral blood monocytes and macrophages, J. Immunol. 182 (9) (2009) 5810–5815.
[101] M.A. Hidalgo, M.D. Carretta, R.A. Burgos, Long chain fatty acids as Modulators of immune cells function: contribution of FFA1 and FFA4 receptors, Front. Physiol. 12 (2021) 668330.
[102] Q. Liu, L. Li, D. Xu, et al., Identification of novel immune-related targets mediating disease progression in acute pancreatitis, Front. Cell. Infect. Microbiol. 12 (2022) 1052466.
[103] L. Li, Q. Liu, C. LE, et al., Toll-like receptor 2 deficiency alleviates acute pancreatitis by inactivating the NF-kappaB/NLRP3 pathway, Int. Immunopharm. 121 (2023) 110547.
[104] Y. Wen, C. Han, T. Liu, et al., Chaiqin chengqi decoction alleviates severity of acute pancreatitis via inhibition of TLR4 and NLRP3 inflammasome: identification of bioactive ingredients via pharmacological sub-network analysis and experimental validation, Phytomedicine 79 (2020) 153328.
[105] H. Li, Y. Xiao, L. Tang, et al., Adipocyte fatty acid-binding protein promotes palmitate-induced mitochondrial dysfunction and apoptosis in macrophages, Front. Immunol. 9 (2018) 81.
[106] Y.M. Cho, D.H. Kim, K.H. Lee, et al., The IRE1α-XBP1s pathway promotes insulin-stimulated glucose uptake in adipocytes by increasing PPARγ activity, Exp. Mol. Med. 50 (8) (2018) 1–15.
[107] K.A. Steen, H. Xu, D.A. Bernlohr, FABP4/aP2 regulates macrophage redox signaling and inflammasome activation via control of UCP2, Mol. Cell Biol. 37 (2) (2017).
[108] Y. Rong, J. Ren, W. Song, et al., Resveratrol suppresses severe acute pancreatitis-induced microcirculation disturbance through targeting SIRT1-FOXO1 Axis, Oxid. Med. Cell. Longev. 2021 (2021) 8891544.
[109] M.K. Marimuthu, A. Moorthy, T. Ramasamy, Diallyl disulfide attenuates STAT3 and NF-κB pathway through PPAR-γ activation in cerulein-induced acute pancreatitis and associated lung injury in mice, Inflammation 45 (1) (2022) 45–58.
[110] T. Ohkawara, H. Takeda, J. Nishihira, Protective effect of chlorogenic acid on the inflammatory damage of pancreas and lung in mice with l-arginine-induced pancreatitis, Life Sci. 190 (2017) 91–96.
[111] N. Kelley, D. Jeltema, Y. Duan, et al., The NLRP3 inflammasome: an overview of mechanisms of activation and regulation, Int. J. Mol. Sci. 20 (13) (2019).
[112] A. AL Mamun, S.A. Suchi, M.A. Aziz, et al., Pyroptosis in acute pancreatitis and its therapeutic regulation, Apoptosis 27 (7–8) (2022) 465–481.
[113] S.A. Ferrero-Andr, A. Panisello-Rosell, J. Rosell -Catafau, et al., NLRP3 inflammasome-mediated inflammation in acute pancreatitis, Int. J. Mol. Sci. 21 (15) (2020).
[114] B. Cai, J. Zhao, Y. Zhang, et al., USP5 attenuates NLRP3 inflammasome activation by promoting autophagic degradation of NLRP3, Autophagy 18 (5) (2022) 990–1004.
[115] T. Karasawa, A. Kawashima, F. Usui-Kawanishi, et al., Saturated fatty acids undergo intracellular crystallization and activate the NLRP3 inflammasome in macrophages, Arterioscler. Thromb. Vasc. Biol. 38 (4) (2018) 744–756.
[116] D.H. Kim, Y.M. Cho, K.H. Lee, et al., Oleate protects macrophages from palmitate-induced apoptosis through the downregulation of CD36 expression, Biochem. Biophys. Res. Commun. 488 (3) (2017) 477–482.
[117] L. Xu, X. Lin, M. Guan, et al., Verapamil attenuated prediabetic neuropathy in high-fat diet-fed mice through inhibiting TXNIP-mediated apoptosis and inflammation, Oxid. Med. Cell. Longev. 2019 (2019) 1896041.
[118] R. Zhou, A. Tardivel, B. Thorens, et al., Thioredoxin-interacting protein links oxidative stress to inflammasome activation, Nat. Immunol. 11 (2) (2010) 136–140.
[119] W.L. Holland, B.T. Bikman, L.P. Wang, et al., Lipid-induced insulin resistance mediated by the proinflammatory receptor TLR4 requires saturated fatty acid-induced ceramide biosynthesis in mice, J. Clin. Invest. 121 (5) (2011) 1858–1870.
[120] V. Saraswathi, A.H. Hasty, Inhibition of long-chain acyl coenzyme A synthetases during fatty acid loading induces lipotoxicity in macrophages, Arterioscler. Thromb. Vasc. Biol. 29 (11) (2009) 1937–1943.
[121] Y. Qiu, Y.N. Shi, N. Zhu, et al., A lipid perspective on regulated pyroptosis, Int. J. Biol. Sci. 19 (8) (2023) 2333–2348.
[122] T. Pr Chnicki, E. Latz, Inflammasomes on the crossroads of innate immune recognition and metabolic control, Cell Metab 26 (1) (2017) 71–93.

[123] E. Zezina, R.G. Snodgrass, Y. Schreiber, et al., Mitochondrial fragmentation in human macrophages attenuates palmitate-induced inflammatory responses, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1863 (4) (2018) 433–446.
[124] J. Pan, Z. Ou, C. Cai, et al., Fatty acid activates NLRP3 inflammasomes in mouse Kupffer cells through mitochondrial DNA release, Cell. Immunol. 332 (2018) 111–120.
[125] C. Dostert, Pétrilli V, R. van Bruggen, et al., Innate immune activation through Nalp3 inflammasome sensing of asbestos and silica, Science 320 (5876) (2008) 674–677.
[126] K. Shimada, T.R. Crother, J. Karlin, et al., Oxidized mitochondrial DNA activates the NLRP3 inflammasome during apoptosis, Immunity 36 (3) (2012) 401–414.
[127] Z.L. Luo, H.Y. Sun, X.B. Wu, et al., Epigallocatechin-3-gallate attenuates acute pancreatitis induced lung injury by targeting mitochondrial reactive oxygen species triggered NLRP3 inflammasome activation, Food Funct. 12 (12) (2021) 5658–5667.
[128] H. Wen, D. Gris, Y. Lei, et al., Fatty acid-induced NLRP3-ASC inflammasome activation interferes with insulin signaling, Nat. Immunol. 12 (5) (2011) 408–415.
[129] P.K. Anand, Lipids, inflammasomes, metabolism, and disease, Immunol. Rev. 297 (1) (2020) 108–122.
[130] M.A. Gianfrancesco, J. Dehairs, L. L'Homme, et al., Saturated fatty acids induce NLRP3 activation in human macrophages through K(+) efflux resulting from phospholipid saturation and Na, K-ATPase disruption, Biochim. Biophys. Acta Mol. Cell Biol. Lipids 1864 (7) (2019) 1017–1030.
[131] A.J. Kowaltowski, N.C. DE Souza-Pinto, R.F. Castilho, et al., Mitochondria and reactive oxygen species, Free Radic. Biol. Med. 47 (4) (2009) 333–343.
[132] T. Liu, Q. Wang, Z. DU, et al., The trigger for pancreatic disease: NLRP3 inflammasome, Cell Death Dis. 9 (1) (2023) 246.
[133] D.Y. Oh, S. Talukdar, E.J. Bae, et al., GPR120 is an omega-3 fatty acid receptor mediating potent anti-inflammatory and insulin-sensitizing effects, Cell 142 (5) (2010) 687–698.
[134] Y. Yan, W. Jiang, T. Spinetti, et al., Omega-3 fatty acids prevent inflammation and metabolic disorder through inhibition of NLRP3 inflammasome activation, Immunity 38 (6) (2013) 1154–1163.
[135] T. Martins DE Lima, M.F. Cury-Boaventura, G. Giannocco, et al., Comparative toxicity of fatty acids on a macrophage cell line (J774), Clin. Sci. (Lond.) 111 (5) (2006) 307–317.
[136] N. DE Pretis, A. Amodio, L. Frulloni, Hypertriglyceridemic pancreatitis: epidemiology, pathophysiology and clinical management, United European Gastroenterol J 6 (5) (2018) 649–655.
[137] I.J. Goldberg, Lipoprotein lipase and lipolysis: central roles in lipoprotein metabolism and atherogenesis, J. Lipid Res. 37 (4) (1996) 693–707.
[138] N. Z Dori, N. Gede, J. Antal, et al., EarLy Elimination of Fatty Acids iN hypertriglyceridemia-induced acuTe pancreatitis (ELEFANT trial): protocol of an open-label, multicenter, adaptive randomized clinical trial, Pancreatology 20 (3) (2020) 369–376.
[139] L. Cao, Y. Chen, S. Liu, et al., Early plasmapheresis among patients with hypertriglyceridemia-associated acute pancreatitis, JAMA Netw. Open 6 (6) (2023) e2320802.
[140] J. Gubensek, M. Andonova, A. Jerman, et al., Comparable triglyceride reduction with plasma exchange and insulin in acute pancreatitis - a randomized trial, Front. Med. 9 (2022) 870067.
[141] W. Chen, Y. Wang, W. Xia, et al., Neddylation-mediated degradation of hnRNPA2B1 contributes to hypertriglyceridemia pancreatitis, Cell Death Dis. 13 (10) (2022) 863.
[142] H. Chen, H. Tan, J. Wan, et al., PPAR-γ signaling in nonalcoholic fatty liver disease: pathogenesis and therapeutic targets, Pharmacol. Ther. 245 (2023) 108391.
[143] B. Niyaz, K.L. Zhao, L.M. Liu, et al., Rosiglitazone attenuates the severity of hyperlipidemic severe acute pancreatitis in rats, Exp. Ther. Med. 6 (4) (2013) 989–994.
[144] S. Nie, X. Cui, J. Guo, et al., Inhibiting role of rosiglitazone in the regulation of inflammatory response and protective effects for severe acute pancreatitis in mice, J. Cell. Biochem. 120 (1) (2019) 799–808.
[145] E. DE-Madaria, J.L. Buxbaum, P. Maisonneuve, et al., Aggressive or moderate fluid resuscitation in acute pancreatitis, N. Engl. J. Med. 387 (11) (2022) 989–1000.
[146] B.U. Wu, J.Q. Hwang, T.H. Gardner, et al., Lactated Ringer's solution reduces systemic inflammation compared with saline in patients with acute pancreatitis, Clin. Gastroenterol. Hepatol. 9 (8) (2011) 710–717.e1.
[147] M. Lipinski, A. Rydzewska-Rosolowska, A. Rydzewski, et al., Fluid resuscitation in acute pancreatitis: normal saline or lactated Ringer's solution? World J. Gastroenterol. 21 (31) (2015) 9367–9372.
[148] S. Gea-Sorl, L. Bonjoch, D. Closa, Differences in the inflammatory response induced by acute pancreatitis in different white adipose tissue sites in the rat, PLoS One 7 (8) (2012) e41933.
[149] A.E. Phillips, A.S. Wilson, P.J. Greer, et al., Relationship of circulating levels of long-chain fatty acids to persistent organ failure in acute pancreatitis, Am. J. Physiol. Gastrointest. Liver Physiol. 325 (3) (2023) G279–G285.