Journal of Inflammation Research

Dovepress
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REVIEW

Signaling Pathways Involved in Acute Pancreatitis

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Abstract: Acute pancreatitis (AP) is a common digestive emergency with high morbidity and mortality. Over the past decade, significant progress has been made in understanding the mechanisms of AP, including oxidative stress, disruptions in calcium homeostasis, endoplasmic reticulum stress, inflammatory responses, and various forms of cell death. This review provides an overview of the typical signaling pathways involved and proposes the latest clinical translation prospects. These strategies are important for the early management of AP, preventing multi-organ injury, and improving the overall prognosis of the disease.

Keywords: acute pancreatitis, signaling pathway, calcium overload, endoplasmic reticulum stress, cell death

Introduction

Acute pancreatitis (AP) is one of the most common acute digestive disorders. Globally, the incidence of AP is 34 cases per 100,000 person-years, and the mortality rate is about 2 cases per 100,000 person-years.[1] Furthermore, the global incidence of AP has been steadily increasing. Modern medicine has developed a mature system in terms of diagnosis and supportive treatment. However, lacking targeted therapies challenges current management strategies, particularly in severe acute pancreatitis (SAP) cases. Acinar cell injury and systemic inflammation are considered to be the two basic features of AP. Acinar cell injury triggers a cascade of pathophysiological changes, including oxidative stress, mitochondrial dysfunction, endoplasmic reticulum stress (ERS), calcium overload, inflammatory responses, and various forms of regulatory cell death, such as apoptosis and autophagy. These mechanisms contribute to both localized pancreatic damage and systemic complications, including systemic inflammatory response syndrome (SIRS), sepsis, and multiple organ failure.[2] In severe cases, the fatality rate may reach 30% to 40%.

Recent studies have provided valuable insights into the molecular and cellular pathways underlying these pathological processes and new perspectives for disease management. This review aims to provide a comprehensive overview of these major pathophysiological mechanisms and their associated signaling pathways. Key signaling pathways associated with oxidative stress, calcium overload, and ERS have been identified as potential therapeutic targets. Clinical trials investigating targeted therapeutics are currently ongoing. Further, the inflammatory cascade mediated by various inflammatory factors such as cytokines, chemokines, and adhesion factors, as well as immune cell activation, is a key area of anti-inflammatory strategies. Recent advances in translational research are discussed, focusing on emerging therapeutic strategies targeting these pathways. These interventions may serve as key points for early AP management, prevention of multi-organ injury, and improved overall prognosis.

Calcium Ion (Ca^{2+})

As a second messenger, Ca^{2+} mediates intracellular signaling processes such as cell proliferation, differentiation, and metabolism.[3] Intracellular Ca^{2+} is mainly derived from the extracellular milieu and the endoplasmic reticulum

Received: 6 July 2024
Accepted: 25 January 2025
Published: 17 February 2025

(ER). Extracellular Ca^{2+} is primarily imported via store-operated calcium entry (SOCE), while Ca^{2+} is also released from the ER. Intracellular calcium balance is maintained by calcium channels, pumps, mitochondria, and calcium-storing organelles, including the ER.[4] A transient increase in Ca^{2+} in acinar cells activates the release of zymogen granules and simultaneously stimulates the mitochondria to generate ATP. Finally, Ca^{2+} is reabsorbed into the ER by smooth ER Ca^{2+} ATPase (SERCAs) and into the extracellular space by plasma membrane Ca^{2+} ATPase (PMCAs).[5] In the pathological state of AP, substances such as high levels of cholecystokinin (CCK), alcohol metabolites, and bile acids stimulate the inositol trisphosphate receptor (IP3R) and ryanodine receptor (RyR) signaling pathways,[6,7] promoting the release of a large amount of Ca^{2+} from the ER. Elevated Ca^{2+} levels activate the calcium release-activated calcium modulator 1 (Orai1) on the membrane, facilitating extracellular Ca^{2+} influx and disrupting calcium homeostasis in the pathological state.[4] Such a phenomenon where the intracellular Ca^{2+} level is abnormally elevated, exceeding the normal physiological requirements of cells and the regulation of cellular calcium homeostasis, is called calcium overload. Calcium overload can cause the continuous opening of the mitochondrial permeability transition pores (mPTPs) on the mitochondrial membrane, imbalance of the mitochondrial membrane potential and mitochondrial dysfunction, and impairment of ATP generation, resulting in the inactivation of SERACs and PMCAs, which are ATP-dependent and able to mediate the efflux of Ca^{2+}. This feedback loop exacerbates calcium overload by perpetuating mitochondrial dysfunction and impaired Ca^{2+} efflux mechanisms.[8] Moreover, a series of events like biliary AP and post-ERCP AP would cause increased pressure within the pancreatic duct, which can activate the pressure-gated Ca^{2+} channel (Piezo-Type Mechanosensitive Ion Channel Component 1, Piezo 1) on the cell membrane. These mechanoreceptors, located in ion channels of the cell membrane, facilitate Ca^{2+} influx upon activation[9,10] (Figure 1). Disrupted calcium homeostasis in pancreatic acinar cells leads to abnormal activation of digestive enzymes, mitochondrial damage, inflammatory responses, and other pathophysiological impairments.[11,12]

Abnormal Activation of Digestive Enzymes

Under normal conditions, pancreatic trypsinogen remains inactive and requires activation by enterokinase in the intestine. When the intracellular Ca^{2+} concentration is abnormally high, Ca^{2+} can directly promote the conversion of trypsinogen to trypsin, leading to the premature activation of trypsin in the acinar cells.[13,14] Calcium overload also activates Ca^{2+}-dependent protein kinases, such as protein kinase C (PKC), which phosphorylate downstream target proteins and facilitate the cleavage of inactive pancreatic enzymes.[15] Calcium upregulation can activate tissue proteinase B (a key lysosomal enzyme), activating trypsinogen to trypsin.[7] Trypsin is typically degraded by intracellular inhibitors to prevent excessive activation. In AP, mitochondrial dysfunction and insufficient ATP synthesis impair the inhibitory mechanisms that regulate trypsin activity. This inhibition system fails, allowing the active trypsin to continue exerting activity and aggravating autodigestion and pancreatic injury.

Mitochondrial Injury

Under specific conditions, mPTPs are transiently open to regulate the exchange of substances between mitochondria and the cytosol. MPTPs regulate mitochondrial membrane permeability, maintain intracellular calcium homeostasis and membrane potential, and preserve mitochondrial function.[16,17] When AP occurs, the intracellular calcium level in the acinar cells increases abnormally. Calcium overload activates mPTPs excessively, increasing mitochondrial membrane permeability and causing uncontrolled exchange of substances with the cytosol. The mitochondrial membrane potential drops and the ATP synthase cannot function normally, causing damage to mitochondrial function, impairment of ATP synthesis, and serious damage to cellular energy metabolism.[18] At the same time, open mPTPs allow Ca^{2+} to flow from mitochondria into the cytoplasm, further increasing intracellular calcium levels and continuing a cycle of mitochondrial and cellular damage. Excessive mitochondrial damage impairs mitophagy, leading to the accumulation of dysfunctional mitochondria that release reactive oxygen species (ROS) and pro-apoptotic factors.[19] At the same time, calcium overload interacts with the PKC pathway, activating inflammatory signaling cascades such as NF-κB and MAPK, which amplify local inflammation into a systemic response.[20]

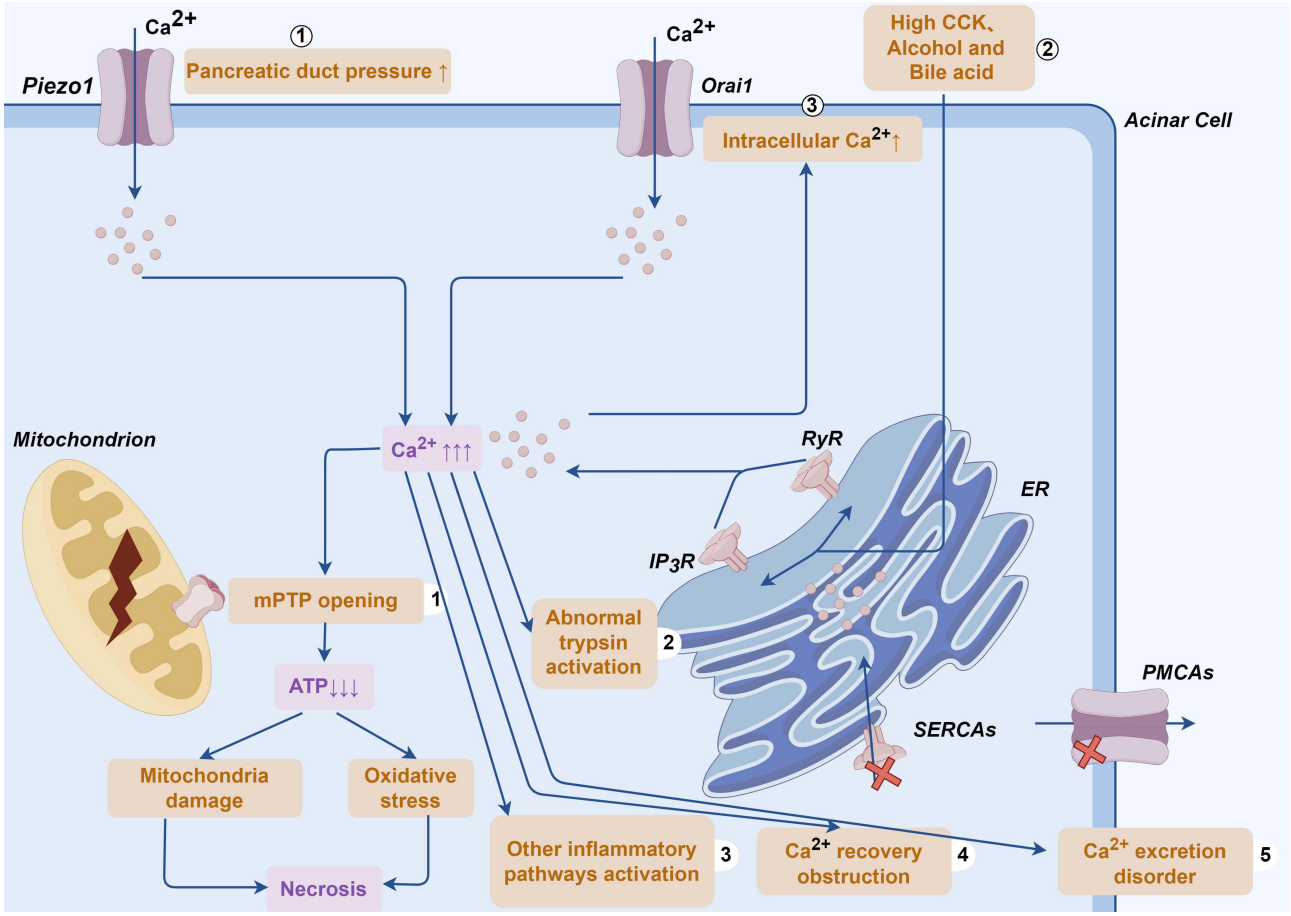

Figure 1 Calcium-mediated mitochondrial dysfunction and cell death in AP. In acinar cells, Piezo1 is a mechanosensitive receptor with cation channel properties, which is activated under conditions of increased pressure in the pancreatic ducts, promoting extracellular Ca^{2+} influx (1). High levels of cholecystokinin (CCK), alcohol, and bile acids lead to the release of calcium from the endoplasmic reticulum through IP3R and RyR-mediated pathways (2). The decrease in Ca^{2+} levels within the endoplasmic reticulum triggers the opening of Orai1, facilitating extracellular Ca^{2+} influx (3). This results in pathological elevation of calcium ions. The increase in calcium ion concentration leads to sustained opening of the mitochondrial permeability transition pore (mPTP), causing loss of the mitochondrial membrane potential [1]. This process leads to mitochondrial dysfunction, ATP depletion, and oxidative stress. These events further enhance and perpetuate pathological calcium toxicity, leading to the occurrence of other pathological processes, such as abnormal activation of trypsinogen [2], activation of inflammatory pathways [3], impaired calcium reuptake [4], and calcium efflux defects [5].
Note: This figure is originally drawn by Figdraw platform (www.figdraw.com).

Inflammatory Responses

In the early phase of AP, immune cells, primarily monocytes and macrophages, become activated. Calcium overload activates inflammatory pathways, including the NF-κB pathway and the NLRP3 inflammasome, leading to the release of pro-inflammatory cytokines such as IL-1β, IL-18, TNF-α, and IL-6, which exacerbate inflammation and pancreatic tissue damage.[20,21] Simultaneously, it enhances immune cell chemotaxis, promoting extensive inflammatory cell infiltration into the pancreas. Ca^{2+} upregulates intercellular adhesion molecules (ICAM-1, VCAM-1), facilitating inflammatory cell adhesion and infiltration into pancreatic tissue.[22] The accumulation of inflammatory mediators such as cytokines and ROS, along with extensive inflammatory cell infiltration, amplifies the inflammatory response, giving rise to pancreatic tissue injury and systemic inflammation.

Clinical Translation

Toxic calcium overload has revealed promising targets for therapeutic intervention in AP. Auxora (CM4620),[23] a selective Orai1 channel inhibitor, prevents calcium overload by blocking Ca^{2+} entry via Orai proteins. It has been verified to be effective in treating SAP and other systemic inflammatory conditions and is currently in clinical trials. Other Orai inhibitors, such as GSK-7975A and CM128, have demonstrated therapeutic efficacy both in human pancreatic acinar cells and mouse models of pancreatitis induced by taurolithocholate acid sulphate.[24] The mPTP inhibitor

https://doi.org/10.2147/JIR.S485804

TRO40303 can reduce calcium overload by safeguarding mitochondrial function and ATP generation, significantly suppressing local and systemic inflammation in cerulein-induced AP mice and ethanol- and palmitoleic acid-induced alcoholic AP mice.[25] Dantrolene specifically targets RyR receptors on the ER to alleviate the inflammatory response in bile acid-induced pancreatitis.[26] Caffeine inhibits IP3R and effectively mitigates the severity of palmitoleic acid plus ethanol-induced AP in experimental mice.[27] Certainly, the research and development of drugs remain in the early stages of animal experiments and clinical trials. Hence, intervention targeting calcium overload represents a promising therapeutic strategy for AP.

The Unfolded Protein Response (UPR) Pathway

During protein synthesis, the accumulation of misfolded or unfolded proteins in the ER induces ERS. Severe ER stress can compromise cellular protective mechanisms and trigger apoptosis.[28] Acinar cells, a type of highly secretory cells, can generate and secrete large quantities of proteins. The ER is a crucial site for synthesizing and folding pancreatic enzymes. Acinar cells are rich in ER content. Therefore, they are particularly susceptible to ER dysfunction. When common AP-inducing factors such as alcohol and fatty acids stimulate acinar cells, they undergo pathophysiological processes, including abnormal activation of digestive enzymes, oxidative stress, calcium overload, and mitochondrial dysfunction. These processes weaken protein synthesis while increasing energy consumption and demand for protein folding, thereby triggering ERS.[2,29] Currently, excessive ER stress is considered a key mechanism contributing to the progression of pancreatic injury. The UPR, an early "self-rescue mechanism" in ERS, can modify misfolded and unfolded proteins and alleviate their accumulation. UPR is mainly mediated jointly by three signaling pathways: Protein Kinase RNA-like Endoplasmic Reticulum Kinase (PERK), Inositol-requiring Enzyme 1 (IRE1), and Activating Transcription Factor 6 (ATF6).[28,30]

IRE1, ATF6 and PERK

IRE1, ATF6, and PERK are transmembrane proteins in the ER membrane that sense unfolded proteins. Each protein consists of three domains based on location and function: the ER luminal domain (sensing unfolded proteins), the transmembrane domain, and the cytoplasmic domain (possessing kinase activity).[30] The intracellular domain of IRE1 is composed of a kinase and an endoribonuclease. Upon ERS stimulation, IRE1α and IRE1β subunits dimerize and autophosphorylate, activating their RNase activity, which cleaves an intron from X-box binding protein 1 (XBP1) mRNA to produce spliced XBP1 (sXBP1). sXBP1 functions as a transcription factor that translocates into the nucleus and upregulates genes involved in ER function restoration, such as ER-associated degradation (ERAD) components and molecular chaperones like BiP[31–33] After receiving the stimulus signal, ATF6 undergoes translocation to the Golgi apparatus and is cleaved to the active transcription factor form (ATF6p50). ATF6p50, similar to sXBP1, translocates into the nucleus to regulate the transcription of downstream genes. The ATF6 pathway can alleviate the pressure of ER folding. However, continuous activation may lead to ER exhaustion and exacerbate cellular damage. Upon activation, PERK autophosphorylates and phosphorylates its downstream effector, eukaryotic initiation factor 2 alpha (eIF2α), reducing global mRNA translation initiation.[34] Simultaneously, it selectively enhances the translation efficiency of certain mRNAs, such as ATF4. ATF4 can activate the transcription of genes involved in amino acid metabolism, antioxidant responses, UPR, autophagy, and apoptosis, helping to balance cell survival and apoptosis[28,30,35] (Figure 2).

Signaling Crosstalk

UPR can regulate ER stress adaptation and cell apoptosis by interacting with other signaling pathways. Persistent IRE1α activation recruits the adaptor protein TNFR-related factor 2 (TRAF2), leading to the activation of the apoptosis signal-regulating kinase 1 (ASK1) pathway and its downstream target, JUN N-terminal kinase (JNK).[36,37] JNK activation by IRE1α promotes apoptosis and pro-inflammatory responses, exacerbating pancreatic injury. Furthermore, IRE1α also activates signaling pathways by binding to different adaptor proteins such as p38, extracellular signal-regulated kinase (ERK), and nuclear factor-κB (NF-κB).[33,38,39] Some reports indicate that PERK signaling can activate the transcription factors nuclear factor erythroid 2-related factor 2 (NRF2) and NF-κB, which regulate redox metabolism and inflammatory responses.[40,41] C/EBP Homologous Protein (CHOP) is the common downstream component of the IRE1, ATF6, and

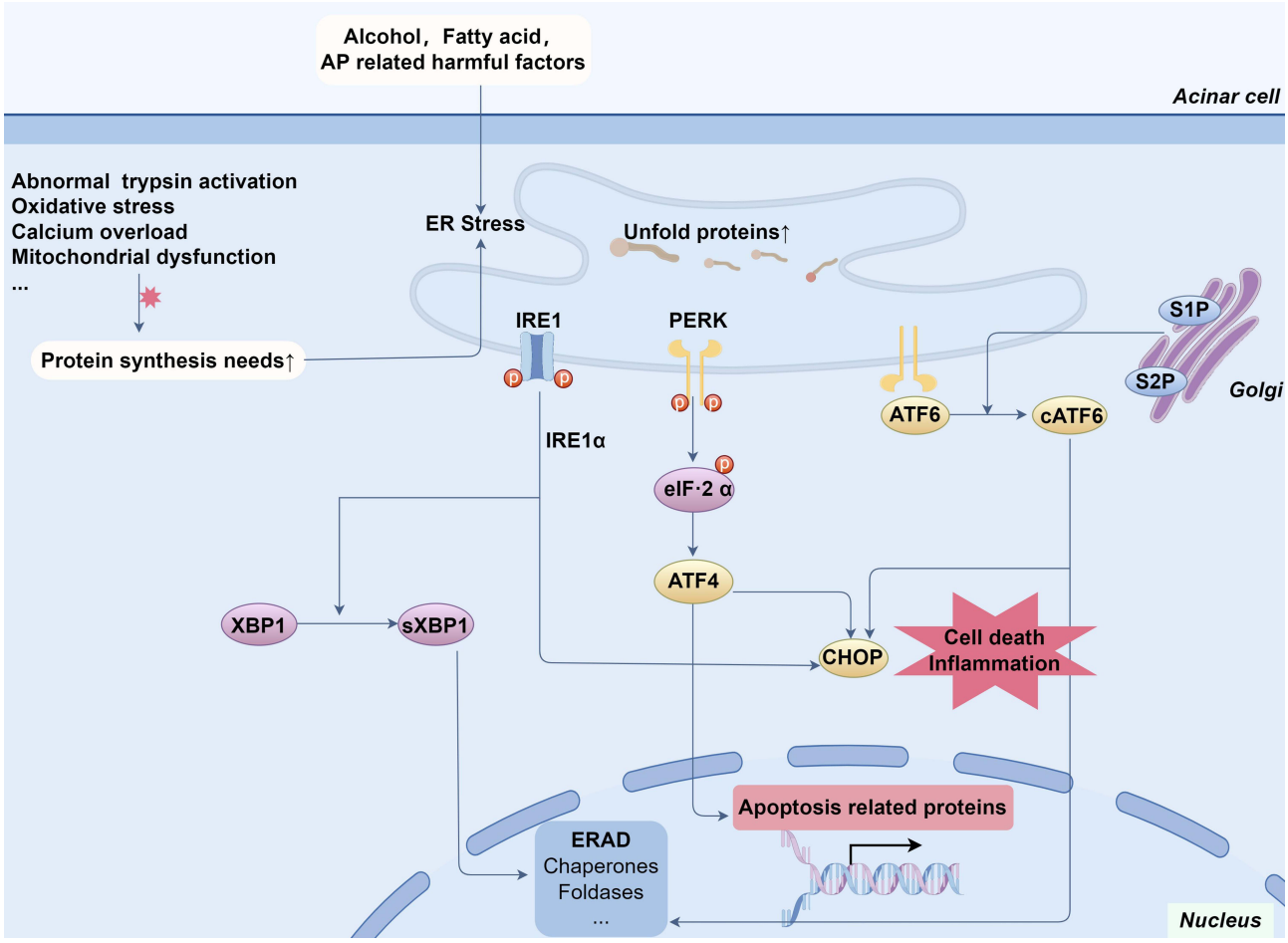

Figure 2 UPR Pathways act in AP. In acinar cells, pathological events such as abnormal enzyme activation, oxidative stress, calcium overload, and mitochondrial dysfunction all lead to an increased demand for protein synthesis. Meanwhile, alcohol, fatty acids, and other AP-related toxins act on acinar cells. These activities induce endoplasmic reticulum (ER) stress. This stress occurs when the demand for protein synthesis and the accumulation of misfolded or unfolded proteins exceed the ER's capacity to process them. IRE1, ATF6, and PERK sense misfolded proteins in the ER lumen. The effector protein of IRE1 splices X-box binding protein 1 (XBP1) to form spliced XBP1 (sXBP1). ATF6, under the action of the S1/2P protease complex in the Golgi, forms cleaved ATF6 (cATF6). These are transcription factors involved in ER expansion, molecular chaperone processes, and ER-associated degradation (ERAD), allowing the ER to restore its protein processing capacity. In extreme ER stress conditions, the three UPR pathways lead to apoptosis and inflammation mediated by CEBP homologous protein (CHOP).
Note: This figure is origintableally drawn by Figdraw platform (www.figdraw.com).

PERK signaling pathways. ATF4, ATF6, and XBP1 can all mediate its expression. CHOP upregulates apoptotic markers such as BAX, leading to selective apoptosis or necrosis.[42]

Clinical Translation

The UPR serves as a protective mechanism for cells. UPR activation restores ER homeostasis, enhances protein folding and processing, and exerting a protective effect. Nevertheless, sustained UPR activation may impair ER function, activate inflammation-related pathways, promote apoptosis and necrosis, and exacerbate the inflammation. Given this dual role, regulating UPR is considered a potential therapeutic strategy for AP. Fortilin reduces the signal of IRE1α during ERS, weakens UPR, and decreases the susceptibility of cells to apoptosis.[43] Statins (HMG-CoA inhibitors) can activate UPR and reduce the occurrence and severity of pancreatitis.[44] Simvastatin has been applied to treat patients with pancreatitis, and the clinical study indicates inflammation relief has been accomplished, but the researchers have not further explored the mechanism of action of this drug.[45] Irisin can upregulate the pro-survival UPR signal to alleviate the inflammatory response in rats with pancreatitis.[46] BiP inducer X (BIX) can enhance the function of BiP and protect cells from ERS-induced damage.[32] These drugs are currently in the laboratory research stage. In-depth exploration of the molecular

https://doi.org/10.2147/JIR.S485804

mechanism of UPR in AP can provide more targets for disease treatment. The development of experimental UPR-targeting drugs into clinical applications remains a key research focus.

Hypoxia-Inducible Factor-1α (HIF-1α)

HIF-1, a heterodimer composed of α and β subunits, is activated and highly expressed under hypoxic conditions. HIF-1α, the active subunit, regulates oxygen homeostasis, while HIF-1β, the structural subunit, is stably expressed in the cytoplasm.[47] In the normoxic environment, HIF-1α is ubiquitinated, retained in the cytoplasm, and undergoes proteasomal degradation.[48,49] Under hypoxic conditions, HIF-1α, the primary regulator of hypoxia adaptation, is stably expressed. After nuclear translocation, it binds to the hypoxia response elements on the promoters of corresponding genes and participates in the transcription of various downstream signal molecules related to hypoxia adaptation.[50,51]

Inflammatory diseases are characterized by hypoxia, resulting from increased oxygen consumption and insufficient supply due to tissue edema, vascular injury, and immune cell infiltration. When AP occurs, pancreatic microcirculation disorders and reduced blood flow induce local hypoxia. HIF-1α is stably and highly expressed in pancreatic tissues and contributes to pathogenic mechanisms, including mitochondrial dysfunction, oxidative stress, inflammatory responses, and cell death.[52]

Oxidative Stress

Acinar cells are exocrine cells whose functions primarily depend on mitochondria. Mitochondrial damage constitutes one of the significant pathological mechanisms of AP. In AP, extracellular injury induces intracellular calcium overload, leading to abnormal mPTP opening, impaired ATP synthesis, and subsequent cell injury.[53] Mitochondria serve as the primary source of ROS generation. Excessive ROS accumulation, exceeding the clearance capacity of the antioxidant system, triggers oxidative stress and damages cellular structures and functions. HIF-1α has a bidirectional regulatory interaction with oxidative stress. Under oxidative stress conditions, ROS stabilizes the expression of HIF-1α[49] and enhances the transcriptional activity of HIF-1α by activating signaling pathways like p38 MAPK and PI3K/Akt.[54–56] HIF-1α can exert a protective effect on acinar cells via its antioxidant mechanism, and it may also exacerbate the damage caused by oxidative stress. In the early stage of AP, HIF-1α can upregulate the expression of antioxidant genes such as HO-1, NQO-1, and SOD2, enhancing the ability of the pancreas to clear ROS.[57] It can also upregulate the vascular endothelial growth factor (VEGF) expression, promoting angiogenesis to improve local hypoxia, restore microcirculation, and alleviate oxidative stress.[58–61]

However, with the development of AP, the abnormal and excessive activation of HIF-1α might also intensify oxidative stress responses and mitochondrial damage. HIF-1α is capable of reducing the clearance activity of antioxidant enzymes and activating inflammatory responses through targeted regulation of the transcription of pro-inflammatory genes, such as IL1β and TNFα, activating the inflammatory responses of macrophages and neutrophils, thereby increasing the local accumulation of ROS;[62] increasing cellular glycolysis and shutting down the tricarboxylic acid cycle, thereby inhibiting the production of ATP;[63,64] increasing the level of the pro-apoptotic factor BAX through regulating the expression of Bcl-2 family proteins, which promotes the opening of mPTP, and releases apoptotic factors.[65–67] Knockout of the HIF-1α gene in AP models induced by a retrograde infusion of sodium taurocholate reduced intracellular Ca^{2+} concentrations and mitochondrial membrane potential in acinar cells. Oxidative and energy stress were alleviated, the proportion of apoptosis increased, acinar necrosis decreased, and pancreatic and other organ injuries were mitigated.[68]

Inflammatory Response

HIF-1α promotes the classical inflammatory response of AP by regulating the transcription of pro-inflammatory factors. Some studies suggest that HIF-1α downregulates immune responses, reducing tissue resistance to infections. Here are three specific manifestations of the former:

- Regulation of Pro-inflammatory Factors: HIF-1α regulates the transcription of pro-inflammatory factors within pancreatic cells and immune cells,[69] including TNF-α, IL-1β, and IL-6, which exacerbate local inflammation and spread systemically, causing multi-organ damage.
- Activation of Inflammation-Related Pathways: HIF-1α activates downstream pathways such as NF-κB, promoting the release of inflammatory mediators and exacerbating pancreatic tissue damage.[58,70] The HIF-1α/HO-1 pathway is also implicated in the process of ferroptosis. Research reveals that inhibiting HIF-1α can alleviate oxidative damage and mitigate ferroptosis, a form of regulated cell death associated with iron accumulation and lipid peroxidation. The key aspect of this section lies in influencing iron ion accumulation and lipid peroxidation by regulating the expression of HIF-1α and HO-1, thereby modulating the damage and death of pancreatic cells.[57] Yumei Ma et al demonstrated that HIF-1α regulates autophagy via the PPARγ-mTOR pathway, contributing to the inflammatory response in hyperlipidemic pancreatitis.[71]
- Coagulation Response: During the advent of AP, the body's coagulation function undergoes abnormality, ranging from localized intravascular thrombosis to disseminated intravascular coagulation. Some patients may endure extremely severe complications. The study carried out by Min-Jung Park et al[72] demonstrated that HIF-1α promotes coagulation via the HIF-1α-VEGF-TF cascade, disrupting pancreatic microcirculation and worsening local hypoxia. This feedforward mechanism not only enhances the stability of HIF-1α but also exacerbates the inflammatory response. Knocking out HIF-1α blocks coagulation and protects against pancreatitis.

Clinical Translation

In conclusion, HIF-1α is a key regulator in the onset and progression of AP. The bidirectional regulation between HIF-1α and oxidative stress offers potential therapeutic targets. Based on the distinct functions of HIF-1α during the early and late stages of AP, various treatment plans have been proposed at different times. Moderate activation of HIF-1α in the early phase of oxidative stress upregulates antioxidant genes, protecting against oxidative damage. In later stages, inhibiting excessive HIF-1α expression reduces inflammation and mitigates pancreatic damage. PX478 is a selective inhibitor of HIF-1α. ROS generation is reduced in the mouse AP model treated with PX478, and both AP injury and acinar cell necrosis are also alleviated.[52,57,73] Eliminating ROS through antioxidants to block the ROS/HIF-1α axis can reduce the abnormal activation of HIF-1α.[74–76] Combining antioxidants with HIF-1α regulators may minimize oxidative stress-induced tissue damage. The interaction between HIF-1α and pathways such as NF-κB and Nrf2 requires further exploration. Identifying the important nodes in the joint regulation of multiple pathways constitutes the key exploration focus in the future.

PI3K/Akt

Phosphoinositide 3-kinase (PI3K) is an evolutionarily conserved lipid kinase activated by protein tyrosine kinases, which phosphorylates the 3-OH site of phosphoinositide derivatives.[77] PI3K regulates various intracellular signal transduction pathways and is closely linked to diseases such as inflammation, autoimmune disorders, and cancer. Many studies have manifested that the PI3K signaling pathway, particularly PI3Kγ activation, plays a crucial role in AP pathogenesis. Specifically, PI3K is integral to regulating inflammation, oxidative stress, cell death, and calcium homeostasis.

Regulate the Inflammatory Reaction

The PI3K/Akt signaling pathway exhibits a dual role in modulating inflammatory responses. On the one hand, PI3K activation recruits inflammatory cells such as neutrophils and macrophages, exacerbating the inflammatory reaction within pancreatic tissue.[78,79] On the other hand, this pathway also has anti-inflammatory effects, capable of regulating the intensity of inflammatory responses by restricting the expression of pro-inflammatory genes.[80] Furthermore, the PI3K signaling pathway can interact with multiple signaling pathways to exert regulatory influences on inflammation. PI3K/Akt activates the IKK complex, promoting IκB phosphorylation and degradation, which induces NF-κB nuclear transcription and inflammatory factor release, driving immune cell recruitment and pancreatic acinar cell necrosis.[81–85] PI3K/Akt activates molecules like p38 and JNK on the MAPK pathway, enhancing inflammatory responses and regulating the activation and migration of immune cells,[86–88] facilitating immune cell infiltration and the release of inflammatory cytokines in AP, exacerbating pancreatic damage. Among the target genes of NF-κB, certain factors (such as Bcl-2 and TNF receptor-associated factors) can regulate the PI3K/Akt pathway, which can enhance the

expression and activation of the PI3K/Akt pathway and form a complex positive feedback regulatory network.[89] PI3K/Akt can also activate the Nrf2 pathway, suppressing inflammation by alleviating oxidative stress responses and inhibiting ferroptosis.[90–92] Moreover, the role of the PI3K/Akt pathway in influencing inflammatory responses is also manifested in regulating the activation, differentiation, and aggregation of immune cells. The Akt pathway regulates macrophage activation phenotypes via the PI3K/Akt/mTOR axis, influencing M1/M2 polarization.[93–95] Exosomal miR125b-5p inhibits polarization of M2 macrophages (the predominant type of macrophages involved in the pancreatic repair and regeneration process) through the PI3K/Akt pathway, worsening pancreatitis severity and promoting acinar-ductal metaplasia, which impacts pancreatic repair and regeneration.[96,97] Under the enhanced signal stimulation of the T cell receptor (TCR), PI3K/Akt is activated and further drives the effector T cell response.[98,99] Akt pathway activation influences neutrophil migration, modulating inflammatory and immune responses.[100,101]

Oxidative Stress

In AP, oxidative stress is a key factor in acinar cell death. The role of the PI3K/Akt pathway in oxidative stress regulation is complex. Once activated, it enhances antioxidant capacity but can also increase ROS production, intensifying oxidative stress and inflammation. PI3K can protect mitochondrial function and alleviate cell oxidative stress damage.[79,102] It can also interact with other signaling pathways to regulate oxidative stress. PI3K/Akt activates p38 MAPK, regulating cellular stress responses and promoting damage adaptation. PI3K/Akt can also activate the Nrf2 pathway,[86,103,104] which helps to elevate the expression levels of its downstream antioxidant factors, such as HO-1, GPX, and SOD. These antioxidant enzymes contribute to eliminating ROS and alleviating oxidative stress. By regulating antioxidant mechanisms to limit the expansion of inflammatory responses, the damage to acinar cells can be mitigated. Similarly, PI3K/Akt can activate the NF-κB signaling pathway, triggering inflammatory cascades that stimulate the release of inflammatory factors and ROS generation, forming a vicious cycle. The role of PI3K/Akt in AP is bidirectional, protecting pancreatic tissue by reducing oxidative stress and, at the same time, activating inflammatory pathways, enhancing oxidative damage, and aggravating the condition.

Cell Death

The PI3K/Akt pathway plays a vital role in regulating cell survival. It regulates cell apoptosis, necrosis, and autophagy in AP through different mechanisms, affecting the balance between the survival and death of acinar cells. Akt predominantly exerts an anti-apoptotic effect on cells. Akt can activate numerous anti-apoptotic proteins, such as Bcl-2 and Bcl-xL, and inhibit pro-apoptotic proteins, such as Bad, Bax, and Caspase-9, to prevent changes in mitochondrial membrane permeability and ultimately decrease cell apoptosis.[105,106] Under severe inflammation and energy stress in AP, PI3K/Akt regulates necrosis by modulating Ca^{2+} homeostasis and mitochondrial function. When PI3K/Akt is activated, it can enhance mitochondrial function, regulate mPTP, prevent impaired ATP generation, and alleviate cell necrosis from excessive ATP depletion.[102] PI3K/Akt inhibits autophagy by activating mTORC1, reducing autophagy-related cell death.[107] Similarly, PI3K/Akt can also activate other pathways to regulate cell survival. For example, it can trigger ERK and p38 MAPK in the MAPK pathway after PI3K/Akt activation, promoting cell proliferation and reducing apoptosis of pancreatic acinar cells.[108] P53, a key transcription factor in cellular stress responses, promotes apoptosis. PI3K/Akt can negatively regulate p53, inhibiting pro-apoptotic gene activation, reducing acinar cell apoptosis, and enhancing pancreatic cell viability.[109]

Calcium Homeostasis

As previously stated, calcium overload in acinar cells during AP is a critical factor leading to cell damage and disease progression. Knocking out the *PI3Kγ* gene or inhibiting PI3K suppresses calcium mobilization and reflux in acinar cells induced by supraphysiological doses of CCK.[110,111] The activation of the PI3K/Akt pathway regulates calcium homeostasis in acinar cells by modulating calcium pump activity, mitochondrial membrane permeability, and mPTP function. The PI3K/Akt pathway can facilitate intracellular Ca^{2+} storage and redistribution by regulating the activity of calcium pumps on the ER.[112] The PI3K/Akt pathway maintains the integrity of the mitochondrial membrane, protects the calcium absorption function of mitochondria, and can further preclude mitochondrial damage and energy depletion caused by calcium overload by inhibiting the excessive activation of mPTP.[102] The PI3K/Akt pathway can also interact with intracellular calcium homeostasis by influencing other pathways. PI3K/Akt can activate the mTORC1 pathway, which increases cellular energy metabolism, thereby maintaining calcium pump activity and reducing intracellular Ca^{2+} levels. A complex interplay exists between oxidative stress and calcium

overload. Oxidative stress can affect calcium channel and calcium pump activities, and calcium overload can also elevate ROS levels by damaging mitochondrial function. PI3K/Akt alleviates calcium overload by activating the Nrf2 pathway, increasing antioxidant expression, and reducing oxidative stress.

Clinical Translation

Taken together, the PI3K/Akt signaling pathway plays critical roles in AP, regulating inflammatory responses, oxidative stress, cell death, and calcium homeostasis. However, clinical translational research targeting this pathway is still in its early stages. Wortmannin, a PI3K inhibitor, has shown therapeutic potential on SAP rats through exposure to sodium taurocholate.[113] On treating SAP rats with Wortmannin, the activation of NF-κB and p38MAPK was significantly reduced, and the release of inflammatory factors was decreased, alleviating pancreatic tissue damage. Some other pathway inhibitors like Dactolisib (PI3K/mTOR inhibitor) and Triciribine (Akt inhibitor) have shown efficacy in cancer treatment but the application in AP has not been profoundly explored.[114,115] Current research on PI3K/Akt pathway inhibitors is focused on cancer. Given the complex pathological mechanism of AP and the multiple roles of this pathway in AP, its clinical translational research is still in its preliminary stage. Further research and clinical trials are essential to evaluate the feasibility and efficacy of targeting this pathway for AP treatment.

Jak/Stat

The JAK/STAT pathway is a key mechanism through which cells respond to external signals such as cytokines and growth factors. The JAK/STAT pathway, first identified in the interferon system, regulates cell growth, survival, proliferation, and differentiation.[116] It can be activated by various cytokines (interferons, interleukins, colony-stimulating factors, chemokines), hormones, and growth factors.[117] It participates in gene transcription and regulates numerous physiological activities, such as immune regulation, hematopoiesis, tissue repair, and apoptosis.[116] Mutations, component deficiencies, or abnormal JAK/STAT pathway activation can lead to pathological events such as inflammation, tumors, and autoimmune diseases.[118]

The JAK/STAT signaling pathway consists of three components: receptor-ligand complexes, Janus Kinase (JAK), and Signal Transducer and Activator of Transcription (STAT) proteins. It is recognized that JAK is a category of cytoplasmic tyrosine kinase featuring four subtypes: JAK1, JAK2, JAK3, and TYK2. Except for the fact that hematopoietic cells in the bone marrow and lymphocytes predominantly express JAK3, the remaining three types appear in all tissues.[119,120] Once activated, JAK can recruit and phosphorylate its downstream STAT proteins.[121] STAT is a signal-responsive transcription factor encompassing seven types (STAT1, STAT2, STAT3, STAT4, STAT5α, STAT5β, and STAT6).[122] Cytokines such as IL6, IL10, and TNFα can bind to cell surface receptors, triggering the corresponding activation of JAK and subsequently phosphorylating STAT proteins. STAT then translocates into the nucleus to regulate the target genes' transcription.

Inflammatory Reaction and Injury Repair

In AP, cytokines like TNF-α and IL-6 bind to cell surface receptors, activating the JAK/STAT pathway and regulating the inflammatory cascade. Different cytokines trigger different STAT proteins and exert distinct responses: IFN primarily activates STAT1; IL-6 activates STAT3 protein to promote the expression of pro-inflammatory factors and intensify inflammation; IL-10 also activates STAT3 but exerts an anti-inflammatory effect by inhibiting pro-inflammatory genes.[123] Hong Z. et al[124] have demonstrated that IL-6 and IL-6 trans-signaling can aggravate the inflammatory response in SAP via the JAK2/STAT3 signaling pathway and are closely associated with acute lung injury. Apart from cytokines, ROS can also activate JAK/STAT. In cerulein-induced AR42J cells, NADPH oxidase promotes the generation of ROS and increases the production of TGFβ1 by stimulating the activation of JAK2/STAT3 and MAPK, promoting the development of pancreatic inflammation.[125] Beyond the inflammatory response, the JAK/STAT pathway influences both damage and repair processes in acinar cells. STAT3 activation is associated with tissue damage and contributes to pancreatic repair by regulating cell death and regeneration pathways. IL-22, a member of the IL-10 family, primarily signals through STAT1, STAT3, and STAT5.[126,127] (Figure 3) IL-22 activates STAT to enhance the expression of anti-apoptotic genes like *Bcl-2* and *Bcl-XL*, reducing pancreatic cell death and thereby alleviating the damage of pancreatitis.[128] Moreover, IL-22-mediated STAT3 activation promotes the repair of damaged pancreatic tissue by enhancing the expression of specific proteins such as regenerative islet-derived protein 3 (RegIII) γ and RegIII β.[129] It can also control bacterial growth in intestinal epithelial cells and enhance intestinal barrier function, thereby regulating immune homeostasis during AP.[130,131]

Clinical Translation

The JAK/STAT pathway is a key signaling mechanism in most cells, with the JAK2-STAT3 pathway playing a central role. It also exerts a critical role in the pathogenesis of AP. Treatment with AG490, a classic JAK inhibitor, reduced IL-1β expression, alleviated tissue edema, and decreased inflammatory cell infiltration in pancreatic tissue.[132,133] Clinically, JAK inhibitors such as Ruxolitinib, Tofacitinib, and Baricitinib have been developed to target JAK1/2. These drugs alleviate acute inflammation by inhibiting JAK1/2 activity and reducing pro-inflammatory factor expression. Some STAT3 small molecule inhibitors (such as

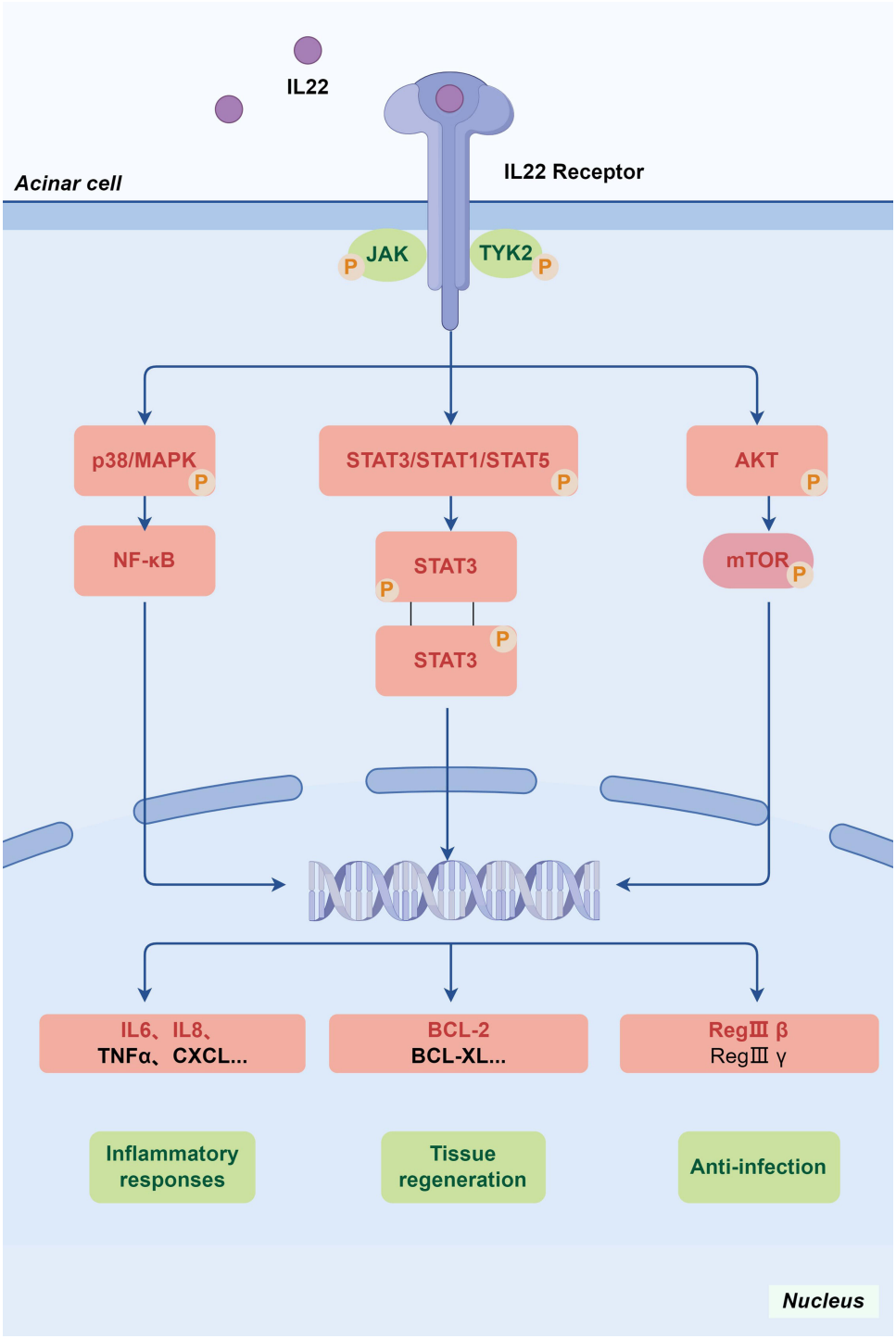

Figure 3 IL-22 mediates tissue regeneration and anti-infection through JAK/STAT pathway in AP.
Note: This figure is originally drawn by Figdraw platform (www.figdraw.com).

Stattic and HJC0152) reduce pancreatic and systemic inflammatory responses by blocking the transcription of inflammation-related genes.[134] These drugs are currently still in the research stages at the cellular and animal model level. Peptide YY, an inhibitory gastrointestinal hormone, reduces pancreatitis severity by decreasing STAT1 and STAT3 levels in acinar cells.[135] Furthermore, NF-κB and STAT3, which are regulatory hubs for immune and inflammatory responses, are activated sequentially to modulate the expression of other cytokines and pro-inflammatory or immune mediators after being activated by cytokines and growth factors.[136] Ping C. et al demonstrated that JAK1/STAT1 inhibitors suppress NF-κB activity, highlighting the interplay between the JAK/STAT pathway and other inflammation-related signaling pathways in driving inflammatory responses.[133] Furthermore, in light of the effect of IL-22 on the JAK/STAT pathway, the combined application of IL-22 and JAK inhibitors might regulate the inflammation and repair processes in AP more effectively. Overall, the JAK/STAT signaling pathway is involved in regulating inflammatory responses and repairing pancreatic cells during AP. Further research into the interactions between the JAK/STAT pathway and other signaling mechanisms could inform precise therapeutic strategies for AP.

Nuclear Factor-κB (NF/κB)

NF-κB is a well-established inflammatory signaling pathway that initiates inflammation in acinar cells.[137] Pathological stimuli in acinar cells, such as calcium overload, activate IKK, leading to IκB phosphorylation, p65/50 dimer release, and nuclear translocation. Activated NF-κB functions as a transcription factor, driving the expression of genes involved in inflammation and cell survival, releasing inflammatory factors, and regulating acinar cell apoptosis and necrosis.

The exacerbation of pancreatitis depends on the infiltration and dissemination of inflammation. NF-κB activation in inflammatory cells, especially macrophages, is central to pancreatitis progression. Inflammatory factors and damage-associated molecular patterns (DAMPs) act on the macrophage cell membrane's corresponding receptors, activating the downstream NF-κB pathway through mediating adaptor proteins. In the nucleus, NF-κB mediates the transcription of inflammation-related genes, promoting the secretion of mediators like chemokines, adhesion molecules, and inflammasomes. This aggravates inflammatory cell aggregation, local inflammation, and pancreatic necrosis. The main pathway is the TLR/MyD88 signaling pathway, which is also the major route for inflammasome generation. DAMP stimulation activates MyD88, a protein coupled with Toll-like receptors (TLRs), initiating inflammatory signaling cascades.[137–139] The ligand that also participates in activating the MyD88 protein is IL-1β. IL-1β is an active inflammatory factor transformed from the IL-1β precursor under the effect of the NLRP3 inflammasome.[140] It is produced in acinar cells through the activation of the NF-κB pathway and can simultaneously mediate the activation of other inflammatory cells, thereby forming an inflammatory positive feedback. Based on the above facts, it is well established that IL-1β significantly contributes to the severity of pancreatitis. Moreover, studies have indicated that transgenic rat model (elastase sshIL-1β) with overexpression of the IL-1β gene gradually lose pancreatic function after birth and eventually develop chronic pancreatitis.[141] Another initiating factor of pancreatitis is the abnormal activation of trypsinogen. Matthias S. et al demonstrated that abnormal activation of digestive enzymes in pancreatic exocrine cells also triggers zymogen granule endocytosis in macrophages via NF-κB.[142]

In the NF-κB cascade, regulating any factor affects pancreatitis progression. Mice with continuous overexpression of IKKβ manifest more severe pancreatic injury induced by caerulein.[143–145] Long-term activation of IKK2 leads to the loss of acinar cells and chronic fibrotic alterations in the pancreas.[144] The specific knockout of the mouse IκBα protein facilitates the nuclear translocation of Rel A (p65), upregulates serine protease inhibitor 2A (Spi2a), and impedes the progression of pancreatitis.[146] Upregulation of p65 expression and enhancing NF-κB pathway activation induces pancreatic inflammatory responses.[147] Nevertheless, some studies also disclose that selective truncation of the Rel A gene in acinar cells instead leads to severe pancreatic damage and even systemic complications involving multiple organ impairments.[148] Thus, the functions of NF-κB pathway components vary and cannot be generalized. For example, MyD88, coupled with TLR and IL1 receptors in inflammatory cells, serves as a necessary signaling intermediate for mediating NF-κB activation, whose deficiency results in severe pancreatitis in mice.[149] The above evidence indicates that the NF-κB pathway in pancreatitis has both protective and harmful effects.

Cell signaling pathways transmit external signals to elicit specific cellular responses. Understanding these pathways is essential for elucidating the pathophysiology of AP. This review focuses on six key signaling pathways, including Ca^{2+}, UPR pathway, HIF-1α, PI3K/Akt, JAK/STAT, and NF-κB, detailing their transduction processes in pancreatic acinar cells and their roles in the pathophysiology of AP. Key targets within these pathways offer potential for clinical translation. The characteristics described above are summarized in Table 1.

Table 1 Summary of Key Signaling Pathways Involved in Acute Pancreatitis: Mechanisms and Roles

Signaling Pathway	Key Molecules / Receptors	Main Function	Biological Processes Involved in AP
Calcium Signaling	Ca^{2+}, IP3R, RyR, Orai1, Piezo1, SERACs, PMCAs	Acts as a secondary messenger to regulate intracellular calcium fluctuations, influencing various cellular functions.	Abnormal activation of digestive enzymes mitochondrial injury, cell death and inflammation response.
UPR Pathway	PERK, IRE1, ATF6	Regulates the UPR to help cells cope with accumulated misfolded proteins in the endoplasmic reticulum.	ER stress, protein refolding, cell stress response, apoptosis and inflammation.
HIF-1α Pathway	HIF-1α	Regulates cellular adaptive responses under hypoxic conditions, promoting angiogenesis and metabolic reprogramming.	Oxidative stress, inflammatory responses, blood vessel formation and cell death.
PI3K/Akt Pathway	PI3K, Akt, mTOR	Regulates cell proliferation, survival, metabolism, and migration.	Oxidative stress, inflammatory responses, cell death and intracellular homeostasis regulation.
JAK/STAT Pathway	JAK family, STAT family, IL-22	Regulates immune responses, cell differentiation, and proliferation.	Immune response, inflammatory responses, tissue injury and regeneration and cell differentiation.
NF-κB Pathway	NF-κB family (p65, p50, etc.)	Regulates immune responses, inflammation, and cell survival.	Inflammation, immune response, cell death, tissue repair, immune cell activation.

Despite advances in understanding the mechanisms of AP, progress in translating this knowledge into clinical practice has been slow. Many mechanisms remain poorly understood, and several drugs have yet to complete clinical trials. Since human pancreatic tissue is difficult to obtain and biopsy, most studies have relied on animal models, resulting in limited progress in human-specific research. This highlights the need for further investigation. Future research should focus on areas such as elucidating the genetic diversity of human genes associated with key signaling molecules and defining the broader and more complex signal transduction pathways within acinar cells. Moreover, recognizing the interplay among signaling pathways in the pathogenesis of AP is critical for a more comprehensive understanding of its mechanisms. Such insights will guide the development of novel therapeutic strategies for this condition.

Data Sharing Statement

There are no data and no material associated with this manuscript.

Ethics Approval and Consent to Participate

There is no human subject, and this is a review, so there is no need for ethical approval and consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Funding

This review was supported by the Basic Public Welfare Research Program of Zhejiang Province (No. LGF19H160022) and Jinhua Municipal Science and Technology Bureau Key Project (No. 2023-3-091).

Disclosure

The authors declare no competing interests in this work.

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