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From micro to macro, nanotechnology demystifies acute pancreatitis: a new generation of treatment options emerges

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Abstract

Acute pancreatitis (AP) is a disease characterized by an acute inflammatory response in the pancreas. This is caused by the abnormal activation of pancreatic enzymes by a variety of etiologic factors, which results in a localized inflammatory response. The symptoms of this disease include abdominal pain, nausea and vomiting and fever. These symptoms are induced by a hyperinflammatory response and oxidative stress. In recent years, research has focused on developing anti-inflammatory and antioxidative therapies for the treatment of acute pancreatitis (AP). However, there are still limitations to this approach, including poor drug stability, low bioavailability and a short half-life. The advent of nanotechnology has opened up a novel avenue for the management of acute pancreatitis (AP). Nanomaterials can serve as an efficacious vehicle for conventional pharmaceuticals, enhancing their targeting ability, improving bioavailability and prolonging their half-life. Moreover, they can also exert a direct therapeutic effect. This review begins by introducing the general situation of acute pancreatitis (AP). It then discusses the pathogenesis of acute pancreatitis (AP) and the current status of treatment. Finally, it considers the literature related to the treatment of acute pancreatitis (AP) by nanomaterials. The objective of this study is to provide a comprehensive review of the existing literature on the use of nanomaterials in the treatment of acute pancreatitis (AP). In particular, the changes in inflammatory markers and therapeutic outcomes following the administration of nanomaterials are examined. This is done with the intention of offering insights that can inform subsequent research and facilitate the clinical application of nanomaterials in the management of acute pancreatitis (AP).

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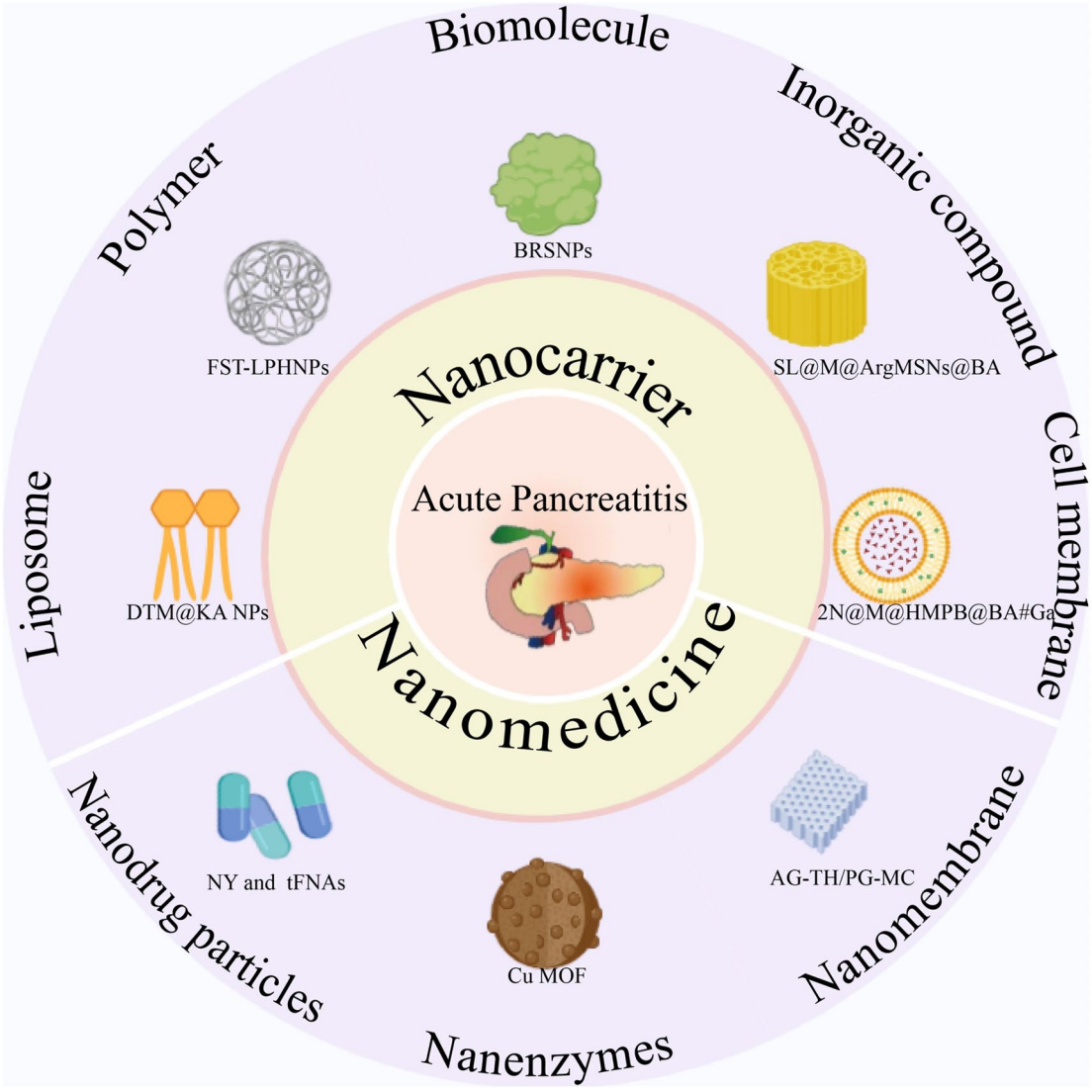
Graphical Abstract



Keywords Acute pancreatitis (AP), Nanotechnology, Nanomaterials, Nanocarriers, Nanomedicines, Therapy

Introduction

Acute pancreatitis (AP) is defined as a localized inflammatory response to the activation of pancreatic enzymes by a variety of etiologic factors and their action on pancreatic tissue, with or without functional changes in other organs [1–3]. The global incidence of AP ranges from 13 to 45 cases per 100,000 people, with a predominance of adults, and shows an increasing trend year by year [4–7]. Common causes are cholelithiasis, alcohol and hyperlipidemia [8, 9]. Additionally, less frequent causes encompass medication side effects, endoscopic retrograde cholangiopancreatography (ERCP), genetic predispositions and traumatic incidents [10]. The primary clinical manifestations are abdominal discomfort, nausea and vomiting and fever. In severe cases, hypotension and shock may also occur [3, 11], pathological alterations encompass interstitial inflammation as well as necrosis of the pancreatic tissue at the periphery [1]. The clinical severity of AP can be categorized into mild, moderate or severe. Mild AP is characterized by a self-limiting nature and typically not require specific intervention [8, 12], it is estimated that approximately 20% of patients with mild AP will progress to moderate or severe AP, with the development of localized complications such as pancreatic pseudocysts and encapsulated necrosis. In such patients, persistent organ failure and mortality rates of

10–20% have been observed [13, 14]. The current range of treatment options for AP is inadequate to meet the clinical needs of patients, underscoring the urgent need for the development of novel therapeutic modalities.

As we all know, nanotechnology is a scientific and technological field that employs the manipulation of individual atoms and molecules to fabricate and alter materials. It is concerned with the properties and applications of materials with structural dimensions in the range of 1–100 nm [15]. In recent years, nanotechnology has continued to evolve, extending from the domain of physical chemistry to the realm of biomedicine and achieving a significant degree of implementation. It has become a pivotal tool in the prevention, diagnosis and treatment of a multitude of illnesses [16–21], and plays a role in cell tracking and visualizing specific disease regions [22]. Nanomaterials can be altered in size, structure and other physical properties through processes including such as physical, chemical and biosynthesis methods [21, 22], giving it larger specific surface area, the ability to load drugs and a surface that can be used for other structural modifications [19, 23, 24]. The advent of rapidly evolving nanomaterials has opened up new avenues for therapeutic strategies in the treatment of AP. These strategies primarily revolve around the use of nanocarriers and nanodrugs, which have the potential to enhance drug safety, facilitate tissue penetration and enable targeted delivery [25–29]. At present, an increasing number of researchers have engaged in the treatment research of AP with nanomaterials. This review begins by examining the pathogenesis and current status of AP treatment. It subsequently searches and summarizes relevant literature on nanomaterials for treating AP. It then analyzes changes in inflammatory indexes and therapeutic effects after the application of nanomaterials. Finally, it analyzes the opportunities and challenges of nanomaterials for treating AP in the future.

Current research on the pathogenesis and treatment of AP

Mechanisms of AP

The etiology of AP is intricate, as is the pathogenesis. The specific mechanism remains unclear, but there is now a consensus among researchers and scholars that trypsin plays a role in digesting pancreatic tissue [30, 31]. Abnormal activation of trypsinogen is recognized as a significant pathogenetic mechanism in the development of AP. In normal physiological conditions, the rough endoplasmic reticulum of acinar cells synthesizes zymogen granules and lysosomes, which are then processed by the Golgi apparatus and stored in separate secretory vesicles. The apical region of the follicular cell is capable of cytosolizing zymogen granules, thereby maintaining a low concentration of these granules within the cell. Additionally, the presence of intracellular trypsin inhibitors prevents the premature activation of intracellular trypsinogen, which, if activated, could potentially lead to the development of AP [32, 33]. The synthesis of intracellular lysosomal and digestive enzymes is increased when cells are stimulated by substances such as alcohol and bile acids. Conversely, these toxic stimuli inhibit zymogen granule cytosolization, which results in an increase in intracellular zymogen granule and lysosome content [33–35]. The codomainization of zymogen granules and lysosomes occurs, and histone B within lysosomes activates trypsinogen under acidic conditions, resulting in its conversion to trypsin. Subsequently, lysosomal membrane rupture releases histone B and trypsin into the cytoplasm, where histone B then promotes RIP3. The formation of the RIP1 necroptosis complex through the mixed-series protein kinase structural domain (MLKL) signaling pathway results in the phosphorylation and oligomerization of MLKL protein molecules, leading to the rupture of the follicular cell membrane and necrosis, which ultimately causes AP [36–40]. In recent years, the calcium overload theory and the mitochondrial dysfunction theory, with pancreatic vesicles as the primary focus of investigation, have garnered significant attention within the scientific community.

Pathologic calcium signaling in pancreatic alveolar cells is mainly characterized by persistent, non-oscillatory, peak-to-plateau calcium signaling throughout the cell, also known as alveolar cell "calcium overload" [41, 42]. In typical physiological circumstances, cholecystokinin prompts the release of calcium from the endoplasmic reticulum through the inositol triphosphate (InsP3R) signaling pathway. The influx of calcium subsequently stimulates the generation of adenosine triphosphate (ATP) by mitochondria and the activation of apical secretory zymogen granules within follicular cells [43, 44]. Intracellular calcium overload resulting from alcohol, bile acids, and cholecystokinin stimuli represents a pivotal mechanism in the pathogenesis of AP. Calcium endocytosis reduces Ca^{2+} levels within the endoplasmic reticulum, thereby activating ORAI1 to facilitate Ca^{2+} influx from the extracellular milieu. Sustained calcium endocytosis culminates in intracellular calcium overload, which in turn induces mitochondrial membrane damage and mitochondrial dysfunction [45–47]. Normal mitochondrial membrane potential is essential for the maintenance of mitochondrial oxidative phosphorylation and ATP synthesis, in which the mitochondrial membrane permeability transition pore (MPTP) plays a pivotal role. The persistent influx of calcium ions into the cell results in an intracellular calcium overload, which in turn causes damage to the mitochondrial membrane and the opening of the MPTP. This alteration in the mitochondrial membrane potential subsequently leads to a reduction in

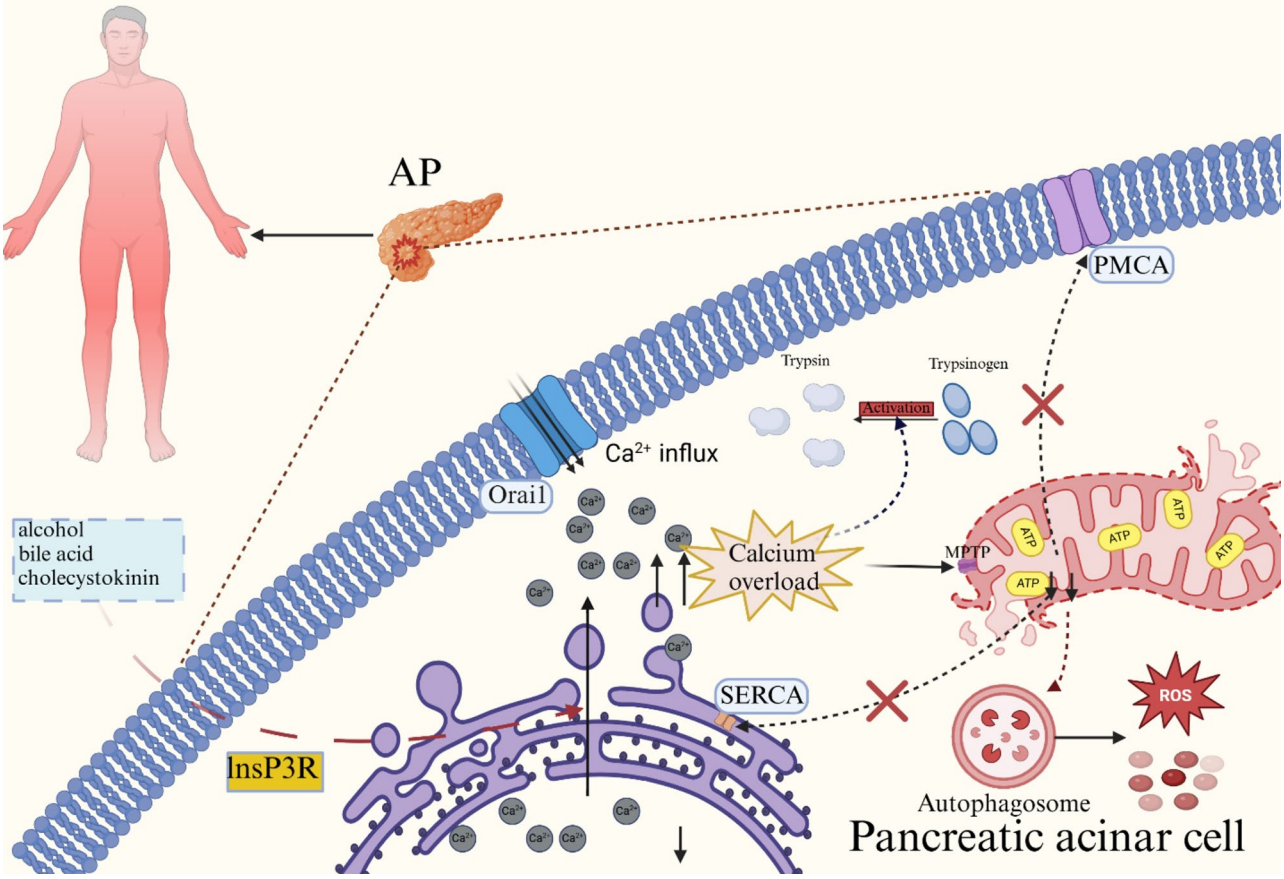


Fig. 1 Explanation picture of the AP Mechanism using the calcium overload theory and the mitochondrial disorder theory

ATP production. The reduction in ATP levels is insufficient to support the ATP-dependent transport of Ca^{2+} by the Sarcoendoplasmic Reticulum Calcium ATPase (SERCAs) and the Plasma membrane Ca^{2+}-ATPase (PMCAs). The transfer of calcium from the cell to the extracellular space results in a reduction in intracellular calcium transport, leading to intracellular persistent calcium overload. This ultimately causes the massive activation of digestive zymogens, which in turn leads to pancreatic auto-digestion [48–51]. Concurrently, mitochondrial dysfunction results in impaired cellular autophagy and the formation of autophagic vesicles with a distinct vacuolar structure. These vesicles produce reactive oxygen species and cytokines, exacerbating additional cellular damage (Fig. 1) [52]. Damaged cells produce tissue factor, heat shock proteins and other harmful factors, which activate NF-κB, MAPK, signal transducers and phosphatidylinositol-3-kinase inflammatory signaling pathways. This results in an elevated release of TNF-α, IL-6 and other similar inflammatory and chemokine factors, which then trigger the inflammation cascade that leads to the progression of a local inflammatory response into a systemic inflammatory response [53, 54]. Furthermore, the presence of mitochondria-associated endoplasmic reticulum membranes (MAM) induces endoplasmic reticulum stress, lysosomal damage, and impaired protein folding and post-translational modification within the endoplasmic reticulum. This, in turn, impairs cellular digestion and defense mechanisms, leading to cytoplasmic protein degradation and cellular necrosis [31, 55–58].

Novel therapeutics and challenges

In recent years, researchers have identified a number of drugs that can be used in the treatment of AP to address the pathogenic mechanisms involved. For example, Auxora is a novel selective inhibitor of the Ca^{2+} channel ORAI1, which prevents Ca^{2+} from entering the alveolar cells [59]. In a rat AP model, intravenous infusion of Auxora resulted in a notable reduction in the severity of AP-associated features, including vacuolization of the adenohypophysis, activation of necrotic cell signaling, pancreatic edema and adenohypophysis death, decreased myeloperoxidase activity and inflammatory cytokine expression in pancreas tissues. FMLF peptide was observed to induce an oxidative burst in human neutrophils and stimulate cytokine production in human PBMCs and rodent PAMs, suggesting that ORAI1/STIM1 channels play a role in the inflammation [60]. The

drug has successfully completed Phase II clinical trials in the United States. Compared to standard care, patients diagnosed with moderate AP who received Auxora exhibited a notable improvement in their symptoms, a reduction in the incidence of persistent systemic inflammatory response syndrome (SIRS), a lower rate of hospitalizations and a minimal prevalence of minor chromaturia adverse effects. These findings suggest that Auxora has the potential to provide personalized treatment pathways for patients presenting with AP-SIRS [61]. Moreover, additional researchers have substantiated that trehalose can be employed in the management of AP. Trehalose is a disaccharide that has been demonstrated to stimulate autophagic flux and autophagic vesicle clearance [62], which can inhibit the development of pancreatic necrosis, aberrant trypsinogen activation and inflammatory signaling pathways by enhancing the autophagic elimination of damaged mitochondria [31]. Aringenin is a naturally occurring dihydroflavonoid, derived predominantly from citrus fruits such as grapefruit and lemon. Some researchers have identified that naringenin can be modulated by PI3K/Akt [63], TLR4/NF-κB [64], MAPK/NF-κB [65]and other pathways to exert anti-inflammatory effects, reduce blood amylase (AMS) and lipase (LPS) levels and diminish the expression of inflammatory cytokines and the number of white blood cells (WBCs). This has the potential to effectively mitigate the damage of pancreatic tissue [66, 67]. Furthermore, emodin, ascorbic acid, α-tocopherol, β-carotene, baicalein, and other substances have been demonstrated to be effective in the alleviation of clinical symptoms and the mitigation of the condition and complications associated with AP [68–73].

While these drugs can be utilized for the management of AP, they are constrained by several factors, including poor chemical stability, low bioavailability, a short half-life and limited targeting capabilities [74–77]. Consequently, enhancing the stability, bioavailability and reducing the adverse effects of AP drugs have emerged as a prominent research area in recent years.

Advantage analysis of nanomaterials for AP treatment

Conventional drugs used to treat AP have been demonstrated to possess a limited capacity to selectively target the pancreas and effectively penetrate the blood-pancreas barrier (BPB) [78, 79], and most of these trypsin inhibitors are peptides with short half-lives [80]. It is frequently unfeasible to attain an optimal drug concentration within the pancreas, and the suboptimal tissue microenvironment of AP patients can influence both drug release and pharmacological activity [27], limiting the effectiveness of AP treatment [26, 27]. Nanomaterials offer several advantages over conventional drug formulations for the treatment of AP. Nanomaterials possess a structural size of 1–100 nm, which is characterized by a minor particle size, enormous specific surface area and good solubility. When vascular permeability is increased at the inflammatory sites of AP patients, nanomaterials with a small particle size can penetrate through the endothelial gap and selectively target pancreatic inflammatory tissues by traversing the blood pancreatic barrier, the cellular biofilm barrier and other body barriers [81, 82]. The large specific surface area endows it with the capacity to serve as an efficacious drug carrier. The utilization of nanoscale carriers has been demonstrated to augment the hydrodynamic radius of the drug, diminish its glomerular filtration rate and extend the drug's half-life [83, 84]. Nanomaterials can also be designed to possess the requisite functional characteristics to serve as nanomedicines for the treatment of AP. They can be modified in a variety of ways to enhance their targeting properties [85]. For example, nanomedicines can leverage alterations in the inflammatory microenvironment (e.g., pH, ROS and trypsin) or leaky vessel extravasation and inflammatory cell-mediated chelation (ELVIS effect)to achieve targeted release [86], thereby facilitating drug uptake, reducing the impact of the first-pass effect of the drug, improving bioavailability while decreasing toxicity and enhancing biosafety [85, 87–89]. The use of nanomaterials has been demonstrated to prolong the release of drugs by wrapping biofilms or fibrous proteins around the surface of the drug. This results in longer-acting blood levels and a reduction in the number of required administrations [20, 85, 90, 91].

Application of nanomaterials in the treatment of AP

Nanocarriers

Liposomal nanocarriers

Typical liposomes possess a bilayer membrane structure analogous to that observed in cell membranes. They are sealed spheres comprising a hydrophilic polar head and a hydrophobic nonpolar tail, which can be modified to facilitate the delivery of lipid-soluble, water-soluble and amphoteric drugs. They are extensively utilized as nanomedicine carriers [92, 93]. Kaempferol (KA) is a natural antioxidant in Traditional Chinese Medicine (TCM). A substantial body of evidence indicates that KA inhibits mitochondrial damage and exerts anti-inflammatory effects through the LPS-TLR4-NF-κB and IRE1-JNK-CHOP pathways. Consequently, it has been widely recognized as a potential treatment for inflammation [94–96]. However, KA is poorly soluble in water and fat solubility and is easily oxidized and less stable, which limits its therapeutic efficacy [97]. Some researchers have designed a novel thioketals (TK)-modified based on DSPE-PEG2000 liposomal nanocarriers (DTM@KA NPs), which enhances the bioavailability of KA while

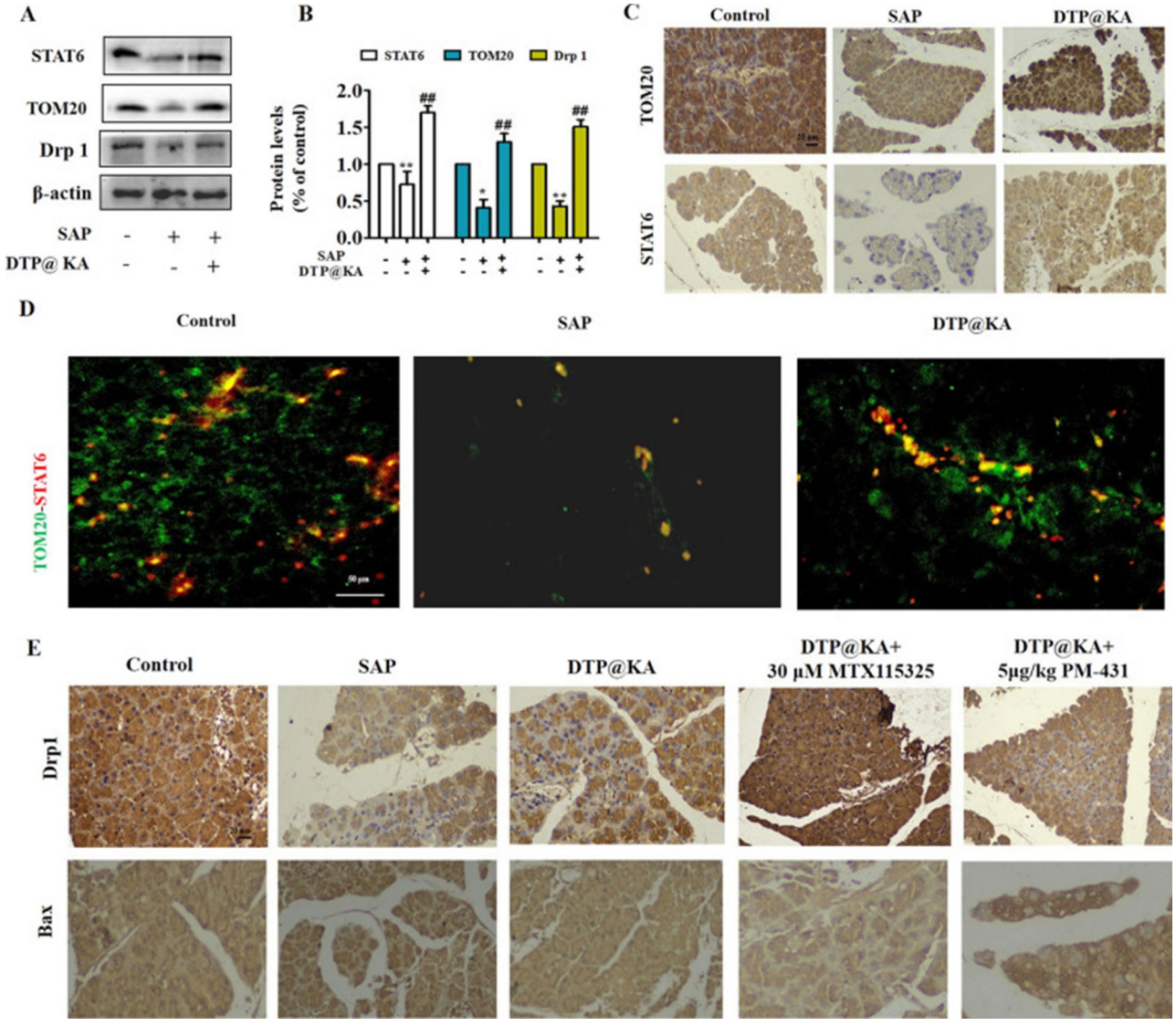


Fig. 2 DTP@KA NPs improved mitochondrial fission by activating TOM20-STAT6 signaling pathway. **A**. Protein expressions of STAT6, TOM20 and DRP1 in pancreas lysate. **B**. Quantitative analysis of STAT6, TOM20 and DRP1 protein expressions. **C**. Distributions and expressions of STAT6 and TOM20 in pancreas tissues. Scar bar = 20 μm. **D**. Co-localization and expressions of TOM20 and STAT6 with IF staining in pancreas tissues. Scar bar = 50 μm. **E**. IHC staining of DRP1 and Bax in pancreas tissues. Scar bar = 20 μm. Data represent the mean ± SEM of at least three independent experiments; $n = 5–8$/group. Significance: $p < 0.05$ and $p < 0.01$ vs. the control group; $p < 0.05$, $p < 0.01$ vs. the SAP model group. Reprinted from [98] with permission. Copyright © The Author(s) 2024

simultaneously reducing the incidence of toxic side effects. Results from the AP mouse model demonstrated that DTM@KA NPs exhibited favorable biological safety with minimal side effects in vitro and in vivo. Subsequent studies revealed that DTM@KA NPs facilitated STAT6-mediated mitochondrial precursor protein translocation by interacting with TOM20, and further promoted DRP1-dependent fission and Pink1/Parkin-regulated mitochondrial autophagy. Additionally, they enhanced lysosomal degradation, which facilitated the removal of damaged mitochondria from the PAC, thereby reducing inflammation and apoptosis (Fig. 2) [98].

Polymer nanocarriers

Polymeric nanomaterials encompass a range of synthetic and natural polymers. Synthetic polymers include PLGA, PEI, PEG and others. Natural polymers, such as chitosan (CTS) and sericin protein (SF), offer distinct advantages, including good biocompatibility, biodegradability, low cost and low toxicity [99, 100]. Festerone (FST) is a naturally occurring flavonol that has been the subject of several studies, which have identified a number of potential beneficial effects, including anti-inflammatory, antioxidant, anti-angiogenic and hypolipidemic properties [101–103], nevertheless, the material displays low water solubility and high permeability defects [104]. In

accordance with the aforementioned methodology, a research team prepared FST-loaded lipid polymer hybrid nanoparticles by conjoined ultrasonication and double emulsion (w/o/w) techniques. These nanoparticles exhibited a high level of loading and mucosal adhesion strength, enabling sustained in vitro release of FST [105]. Oral pretreatment with LPHNP containing FST provided protection for rats from L-arginine-induced SAP and multiple organ damage in the in vivo study. Additionally, this treatment resulted in a reduction in amylase and lipase levels compared with FST, LPHNP alone and the untreated group. Further biochemical analysis demonstrated a reduction in pro-inflammatory factors, including NLRP3, IL-1β, TNF-α and IL-6, were diminished, and a notable decrease in the observed inflammation in pancreatic tissue [105].

Biomolecule nanocarriers

In comparison to lipid and polymer carriers, biomolecule carriers demonstrate notable sensitivity to elevated amylase, protease and lipase levels in pancreatitis lesions. These compounds demonstrate greater specificity and offer distinct advantages in terms of half-life, stability, safety and manufacturing feasibility [106]. A research team has successfully developed a primary three-dimensional (3D) structure of a bilirubin-like DNA double helix by co-precipitation using silk fibroin as a carrier. It was collapsed into a nanoparticle (BRSNP), which could achieve targeted pancreatic tissue. In the presence of excess pancreatic enzymes (trypsin) at the AP site, the BRSNP was observed to release bilirubin, which demonstrated the ability to directly inhibit the production of cellular mitochondrial ROS. Additionally, bilirubin was observed to decrease malondialdehyde (MDA) levels and increase SOD levels in rats. The inhibitory effect of bilirubin on cellular mitochondrial ROS production, reduction in MDA levels and increase in SOD levels in rats has been demonstrated. Additionally, it activates the NRF2 pathway, increases HO-1, and thus inhibits the pro-inflammatory NF-κB signaling pathway. BRSNPs can target pancreatic tissues by reducing oxidative stress and pro-inflammatory cytokine expression, and impairing macrophage and neutrophil recruitment. The efficacy of BRSNPs in treating AP has been substantiated by evidence indicating that they can mitigate oxidative stress, diminish the expression of pro-inflammatory cytokines, and impede macrophage and neutrophil recruitment [20].

Inorganic nanocarriers

In comparison to lipid and polymer carriers, inorganic nanoparticles typically exhibit smaller particle sizes, narrower size distributions and surface chemistry well suited for ligand coupling [107]. 1,2-Bis (2-aminophenoxy) ethane-N, N, N, N, N′-tetra acetic acid (BAPTA-AM) is a hydrophobic membrane-permeable calcium chelator that can directly bind to intracellular Ca^{2+}, thereby eliminating cytoplasmic calcium overload at the root and blocking abnormal calcium-mediated sustained activation of trypsinogen at the source is interrupted by this mechanism, preventing the cascade of adenohypophysis cell death. However, the compound displays poor water solubility and a short half-life limit its clinical transfer [108]. A research team devised and synthesized an organosilicon precursor comprising a trypsin-cleavable arginine-based amide bond. It was incorporated into the framework of mesoporous silica to create trypsin-responsive organo-bridged MSNs (Arg-MSNs) for the effective encapsulation of a membrane-permeable calcium chelator, BAPTA-AM, to produce Arg-MSNs@BA. This approach was devised with the objective of facilitating the controlled release of drugs and rapidly eliminating intracellular Ca^{2+} overload during the initial stages of AP [109–111]. Arg-MSNs produced via a sol-gel process, exhibiting a small size, uniform size distribution, positive surface charge and exemplary storage stability properties, were then subjected to a series of modifications to create SL@M@Arg-MSNs@BA, which demonstrated immune evasion, inflammatory endothelial adhesion, transendothelial migration and precise targeting of injured cells [112, 113]. Upon arrival at the designated site, the core Arg-MSNs@BA in the AP mouse model responds to premature and massive activation of trypsin by rapid and direct biodegradation of its backbone, resulting in flexible payload release. The released BA will effectively chelate the overloaded Ca^{2+}, thereby restoring the cellular redox state by blocking the IκBα/NF-κB/TNF-α/IL-6 and CAMK-II/p-RIP3/p pathways. The MLKL/caspase-8,9 signaling pathways reduce the secretion of pro-inflammatory cytokines, block the inflammatory cascade and inhibit cell necrosis (Fig. 3). Additionally, they significantly reduce the adiposity of adipose tissue and lipase and amylase levels and restore pancreatic function [114]. Furthermore, the Arg-MSN backbone structure inhibits trypsin self-digestion while preventing tissue damage. This ultimately results in the inhibition and modulation of downstream local and systemic inflammatory responses, which disrupts the destructive cycle amplified by inflammation. This protective mechanism safeguards peripancreatic tissues and effectively reduces the risk of distal tissue damage [53].

Cell membrane nanocarriers

Cell membrane nanocarrier is a nanoparticle that has been coated with a partial or complete cell membrane. The surface of the nanocarrier mimics the properties of the source cells, carrying biological activity and homing effects. This enables the nanocarrier to replicate natural

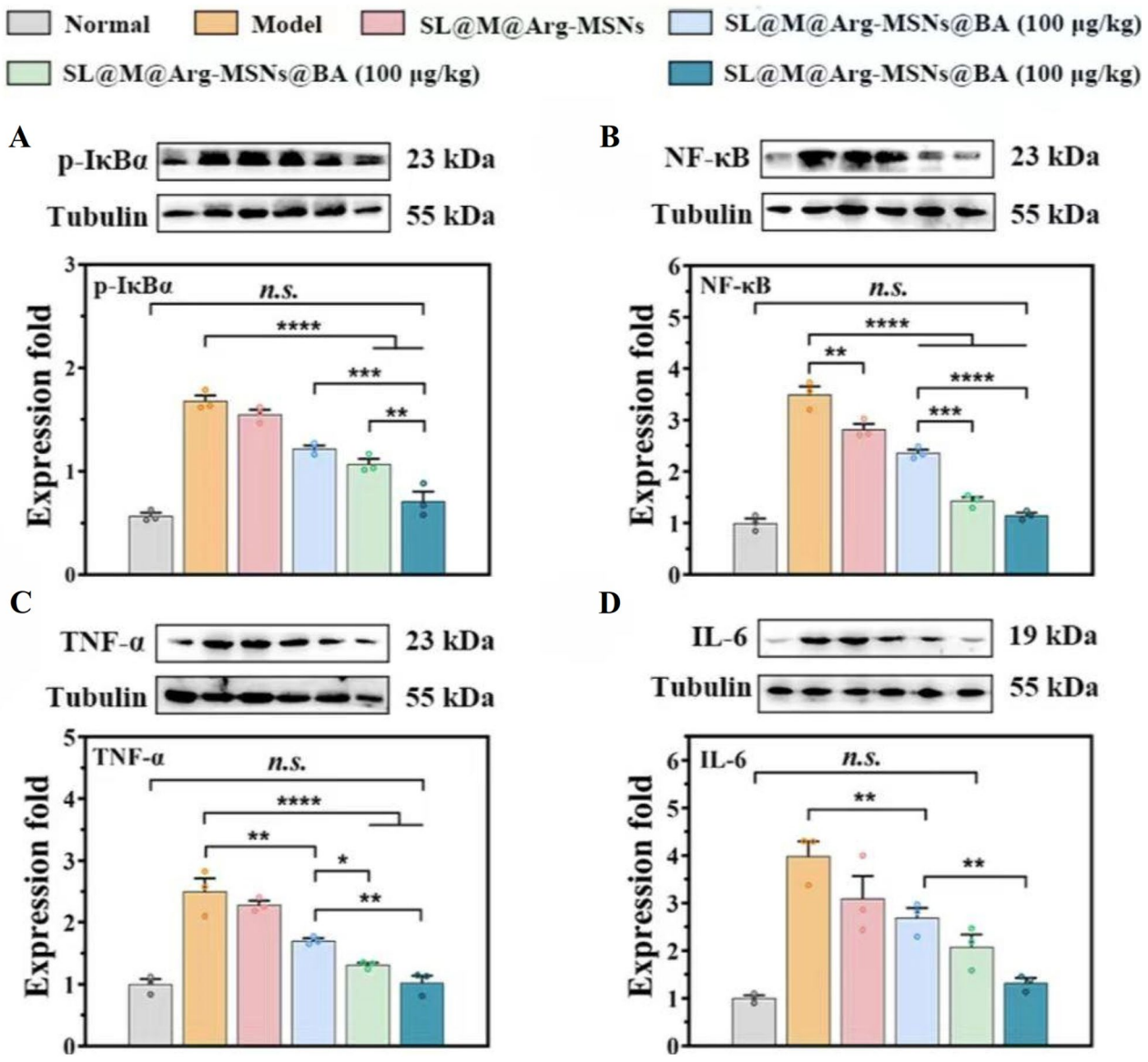


Fig. 3 SL@M@Arg-MSNs@BA reduces recruitment of mononuclear macrophages and neutrophils, inhibits the release of neutrophil extracellular traps, and promotes M2-macrophage polarization. Western blot analysis of (**A**) p-IκBα, (**B**) NF-κB, (**C**) TNF-α, and (**D**) IL-6 expression and their quantification of protein expression in the corresponding pancreas. $n = 3$. Data are shown as mean ± SEM. Reprinted from [114] with permission. Copyright © 2024 American Chemical Society

cellular interactions, effectively reducing the cytotoxicity and immunogenicity of nanoparticles. Additionally, the use of cell membrane nanocarriers improves the histocompatibility and bio targeting of nanoparticles. This makes them an effective drug carrier [115–117]. The aforementioned cells include red blood cells, macrophages, neutrophils, cancer cells, stem cells and others [118–120]. Pancreatitis is a severe inflammatory disease marked by the infiltration of the lesion by a substantial number of inflammatory cells, including neutrophils and macrophages [121]. In light of the aforementioned considerations, acid-responsive hollow mesoporous Prussian blue nanoparticles (HMPB-NPs) were developed for the co-delivery of the membrane-permeable calcium chelator, BAPTA-AM (BA) and the trypsin activity inhibitor, gabexate mesylate (GA). These nanoparticles were encapsulated with neutrophil membranes and partially surface-modified with N, N-dimethyl-1,3-propanediamine. In an AP mouse model, the agent demonstrated effective recruitment, trans endothelial migration and precise targeting of vesicular cells at the inflamed endothelium. Additionally, it inhibited endoplasmic reticulum stress (IRE1/XBP1 and ATF4/CHOP). Axis restoration was observed in impaired autophagy (Beclin-1/P62/LC3 axes), with a concomitant effective restoration of the cellular redox state and reduction in the proportion of

apoptotic cells. This resulted in the hindrance of alveolar cell autodigestion and restoration of pancreatic function [53].

In addition to cell membranes as nanocarriers, the "free-rider" strategy of drug-loaded inflammatory cells has become a hot research topic in recent years, mainly involving macrophages and neutrophils [122, 123]. The capacity of surviving inflammatory cells to respond to environmental changes is superior, enabling them to deliver therapeutic payloads with greater precision and dynamism. Furthermore, the heightened sensitivity of these cells to inflammatory signals increases the potential for targeted delivery of therapies to cell types. In addition, the large intracellular volume of live inflammatory cells allows them to accommodate more nanoparticles, resulting in enhanced loading capacity and drug-to-cell ratios. In addition, numerous drugs can be simultaneously introduced into inflammatory cells, promoting a combined therapeutic approach [124]. An investigator has developed a β-glucan-functionalized zinc-doxorubicin nanoparticle system (βGlus-ZnD-NPs). In mice with pancreatic ductal adenocarcinoma (PDAC), oral administration of βGlus-ZnD NPs resulted in positive targeting and transgression of microfold (M) cells, overcoming the intestinal epithelial barrier and undergoing phagocytosis by endogenous macrophages to produce βGlus-ZnD@Mϕ. As a hitchhiking cell carrier, βGlus-ZnD@Mϕ traverses the intestinal lymphatic system and gets into the circulation, and eventually accumulates in tumor tissues due to the tumor homing and "stealth" characteristics given by endogenous Mϕ (Fig. 4). Concurrently, the Mϕ of the hitchhiking βGlus-ZnD NPs are activated to produce MMP, which disrupt the proliferative matrix barrier of junctional fibers, promote the degradation of stromal fibrosis and differentiate towards an M-like phenotype. This process also promotes T-cell infiltration and ultimately remodels the TME from immune-suppressing to immune-primary, which induces apoptosis of the tumor cells and enhances the efficacy of PDAC therapy [125]. The "free rider" strategy of inflammatory cells carrying drugs provides a new approach for the treatment of AP. Figure 5 illustrates the preparation process of the different nanocarriers described above or the mechanism of action of the therapeutic APs. Table 1 shows the research progress of nanocarriers loaded with different drugs for the treatment of AP.

Liposomal, polymer, biomolecule and cell membrane nanocarriers are organic nanomaterials formed by covalent or non-covalent assembly of organic molecules [126]. They can be easily functionalized to precisely control their chemical composition, shape, size and surface properties, and have good biocompatibility, making them highly adaptable to various biomedical applications [127]. However, their mechanical strength and stability are low, and such limitations may be imposed by the requirement for high structural integrity and thermal stability in specific applications [128]. In addition, batch-to-batch variations in synthesis can affect reproducibility and scalability [129]. In comparison to organic nanomaterials, inorganic nanomaterials demonstrate superior chemical and structure stability, in addition to distinctive physicochemical attributes, including electrical, magnetic and catalytic properties [130]. However, the toxicity and low biocompatibility can trigger negative immune responses that prompt immune response and permanent toxicity, giving great challenges for clinical translation [131]. In addition, inorganic nanomaterials typically have limited biodegradability, leading to accumulation and presenting large venture over long periods of time [132].

Nanomedicine

Nanodrug particle

In addition to the loading or encapsulation of therapeutic AP drugs with various nanocarriers, drugs can be congregated into nanodrug particles through the influence of external forces. For example, selenium has been demonstrated to possess anti-inflammatory and antioxidant properties [133]. Selenium is directly converted into nano-selenium, which is not only a simple and efficient process that reduces drug toxicity, but also improves the shortcomings of poor drug solubility and bioavailability. Furthermore, it regulates the sustained release of the drug and guarantees its therapeutic efficacy [134, 135]. Similarly, a research team applied yttrium oxide nanoparticles (NY) to a mouse AP model and found that NY could potentially play a role in restoring mitochondrial and ER homeostasis through NRF2/NFκB pathway. This resulted in the effective reduction of plasma amylase and lipase levels, as well as a notable attenuation of mitochondrial stress and inflammatory markers. Additionally, inflammatory cell recruitment around damaged pancreatic follicular cells was inhibited, which contributed to a favorable therapeutic AP effect [136]. In addition to inorganic substances, biological macromolecules can also be directly assembled into drug nanoparticles. Tetrahedral framework nucleic acid nanoparticles (TFNAs) have been designed through the self-assembly of four single-stranded DNA (ssDNA) molecules, resulting in a three-dimensional cage-like structure [137–139]. A number of studies have demonstrated that TFNAs possess robust anti-inflammatory and anti-apoptotic properties [140–142]. A research team was able to achieve a notable reduction in amylase, lipase, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (CREA) and blood urea nitrogen (BUN) levels in mice with AP through the administration of TFNAs. This demonstrates that TFNAs can effectively inhibit inflammation and prevent pathological cell death [143].

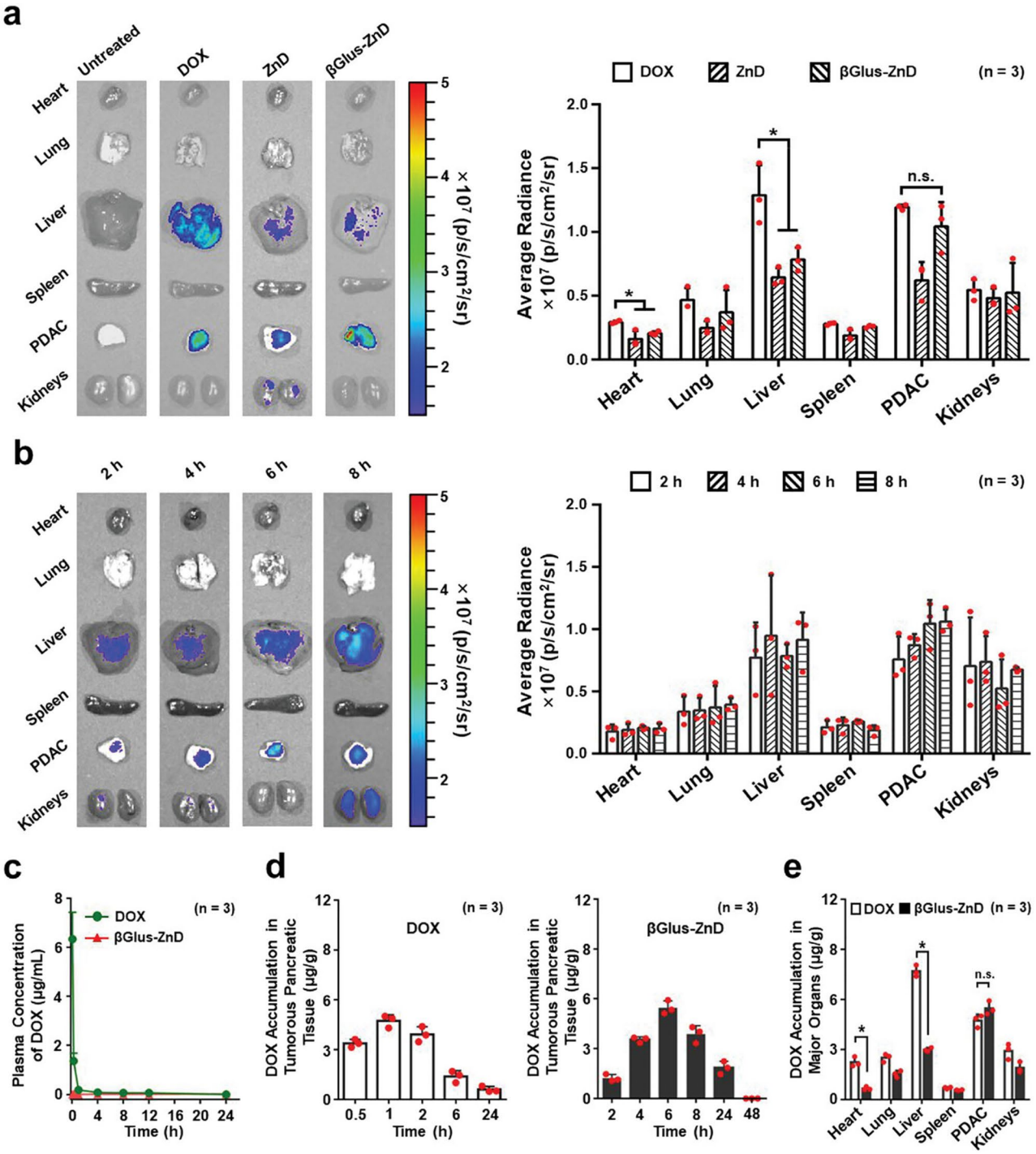


Fig. 4 In vivo biodistribution of ZnD/βGlus-ZnD NPs. **a**) Ex vivo IVIS images of fluorescence signals from DOX that accumulated in isolated major organs from test mice that had been treated using various modalities and their corresponding average radiances. **b**) Time-dependent fluorescence signals of DOX that accumulated in isolated major organs from test mice that had been orally treated with βGlus-ZnD NPs and their corresponding average radiances. **c**) Time course of DOX concentrations in plasma following treatment with i.v. DOX or oral βGlus-ZnD NPs. **d**) Time-dependent accumulation of DOX concentration in tumorous pancreatic tissues in test mice that had been treated with i.v. DOX or oral βGlus-ZnD NPs. **e**) Results of DOX accumulation in major organ tissues at 1 h (6 h) following i.v. DOX (Oral βGlus-ZnD NPs) administration. n.s.: not significant ($P > 0.05$). *: statistically significant ($P < 0.05$). Reprinted from [125] with permission. Copyright © 2023 Wiley-VCH GmbH

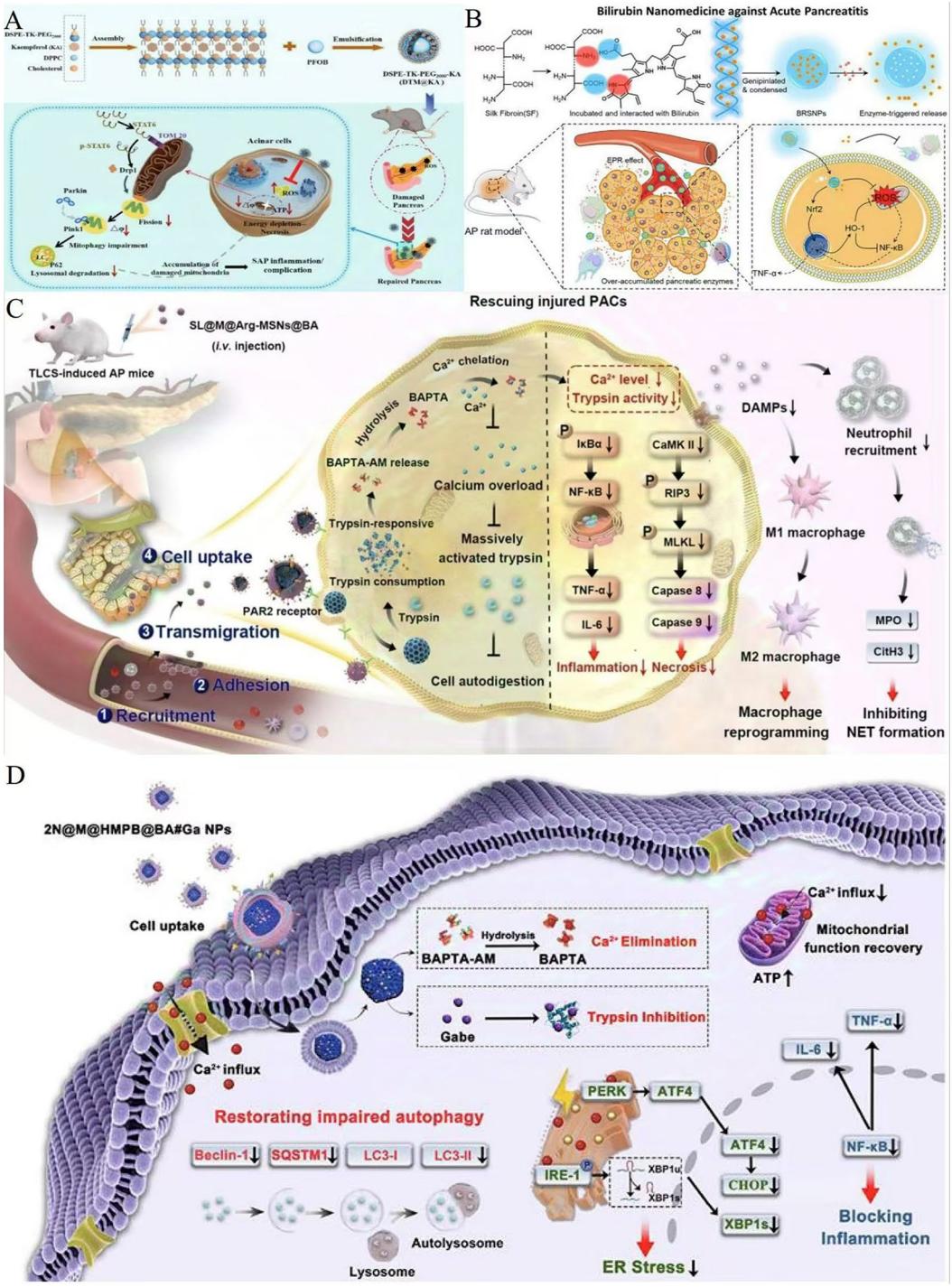


Fig. 5 The preparation process of the different nanocarriers described above or the mechanism of action of the therapeutic APs. (**A**) Schematic of study on DTM@KA NPs preparation and protective function as well as possible mechanism about mitochondrial function and oxidative stress regulated by TOM20-STAT6-DRP1-mitophagy signaling in experimental SAP. Reprinted from [98] with permission. Copyright © The Author(s) 2024. (**B**) Graph of bilirubin loaded silk fibroin nanoparticles (BRSNPs) for the experimental acute pancreatitis (AP) application. Reprinted from [20] with permission. Copyright © 2020 Elsevier B.V. (**C**) Schematic Representation Depicting the Fabrication Process of Biomimetic HMPB NPs and Their Therapeutic Mechanism in a Mouse Model of AP Induced by Sodium Taurocholate Retrograde Infusion. Reprinted from [114]with permission. Copyright © 2024 American Chemical Society. (**D**) Treatment mechanism diagram of the formulations 2 N@M@HMPB@BA#Ga. Reprinted from [53]with permission. Copyright © 2024 American Chemical Society

Table 1 The research progress of nanocarriers loaded with different drugs for the treatment of AP

Nano carrier	Drug	Characteristics	Ref.
Liposome	Kaempferol (KA)	Liposomes exerts profound impacts on damaging intracellular redox homeostasis by reducing GSH depletion and activating Nrf2, which synergizes with KA to reinforce the inhibition of inadequate fission, excessive mitochondrial fusion and impaired mitophagy.	[98]
Polymer	Fisetin (FST)	Polymer owns a high level of load capacity and mucosal adhesion strength, and it can achieve sustained in vitro release of FST.	[105]
Silk fibrin	Bilirubin	BRSNPs can be selectively delivered to inflammatory lesions in the pancreas and release bilirubin in an enzyme-responsive manner, reducing oxidative stress, decreasing the expression of pro-inflammatory cytokines, and impairing the recruitment of macrophages and neutrophils.	[20]
Mesoporous silica nanoparticles(MSN)	BAPTA-AM	MSN has a high loading content and surface modifications confer MSN inflammatory recruitment and precise PAC-targeting ability; after skeletal biodegradation, BAPTA-AM is released on-demand in injured PACs, resulting in elimination of intracellular calcium overload.	[114]
Macrophage membrane	Emodin(ED)	Macrophage membranes not only provide immune evasion, but also show a tendency to target inflammatory tissues with slow-release properties.	[121]
Neutrophil membrane	BAPTA-AM And Ga	The formulation exhibited efficient recruitment at the inflammatory endothelium, trans-endothelial migration, and precise acinar cell targeting, resulting in rapid pancreatic localization and higher accumulation.	[53]

Nanoenzyme

Natural enzymes are distinguished by their catalytic activity and substrate diversity. However, they remain susceptible to limitations, including high cost, poor thermal stability and a low recovery rate [144]. In comparison to natural enzymes, nanoenzymes exhibit tunable catalytic activity, high stability and biocompatibility, rendering them more suitable for bioassay and therapy [145]. Metal-organic frameworks (MOFs) represent a relatively novel class of porous solid materials. The diversity of metal nodes, connecting columns, and a vast range of coordination interactions in all potential orientations render MOFs the optimal alternative to natural enzymes. These have garnered significant research interest in the domain of catalysis due to the clarity of coordination networks, mesoporous structures and tunable porosities [146, 147]. A team of researchers has designed an optimized copper-based metal-organic framework nanoenzyme (Cu MOF) with special antioxidant activity. The activity of Cu MOF is at its greatest at pH 7.4 and 35 °C, and it displays considerable potential under physiological conditions. The majority of catalytic reactions associated with other nanoenzymes occur in acidic environments (pH < 5.0), which can lead to the denaturation of natural enzymes [148]. The newly developed compound displays remarkable excellent catalase-like activity and hydroxyl-removal ability. In addition, it scavenges ROS directly through its intrinsic enzyme. Furthermore, the Cu MOF displays antioxidant activity in AP, and also activates PINK1/PARK2-mediated mitochondrial autophagy (Fig. 6). This indicates that Cu MOF plays a role in mitochondrial autophagy-mediated inflammation and necrotic apoptosis in AP, in order to maintain mitochondrial homeostasis and attenuate inflammation [149]. Additionally, research indicates that the utilization of copper nanoparticles may potentially elevate the likelihood of developing neurological disorders [150]. Nevertheless, there is currently no consensus among medical professionals and toxicologists regarding the establishment of standardized methodologies for toxicological testing and analysis [132]. It is imperative to achieve a balance between efficacy and safety.

Nanomembrane

In complex pancreatic resections, the leakage of tissue fluid from medical trauma, accidents, and surgical treatments can result in significant complications, including acute necrotizing pancreatitis, hemorrhage, infection and mortality [151], the conventional techniques for wound closure, including suturing, ligating and cauterizing, are susceptible to stress concentrations that can result in secondary tissue trauma, capillary fragility and failure to seal pancreatic leaks. The use of traditional anti-leakage materials, such as fibrin glue and polyglycolic acid, has not demonstrated efficacy in enhancing tissue regeneration, wound healing, flexibility and adhesion at the pancreatic resection margin [152]. In response to these issues, a research team employed electrostatic spinning technology to develop a novel bilayer (AG-TH/PG-MC) multifunctional nanofiber membrane, wherein the inner layer consisted of a combination of sodium alginate (A), gelatin (G) and thrombin (TH), while the outer layer comprised a combination of polycaprolactone (P), gelatin (G) and mitomycin-c (MC). The elevated gelatin and alginate concentration within the internal layer diminishes fiber diameter and water contact angle. Furthermore, cross-linking enhances the membrane's hydrophilic properties, rendering it highly biodegradable and firmly adhering to tissue surfaces [153, 154]. The outer layer of MC has been demonstrated to possess antibiotic properties that reduce tissue adhesion by inhibiting fibrosis and vascular distribution. This effect can be observed within a few weeks. Furthermore, MC has been shown to inhibit fibroblast proliferation by downregulating TGFβ

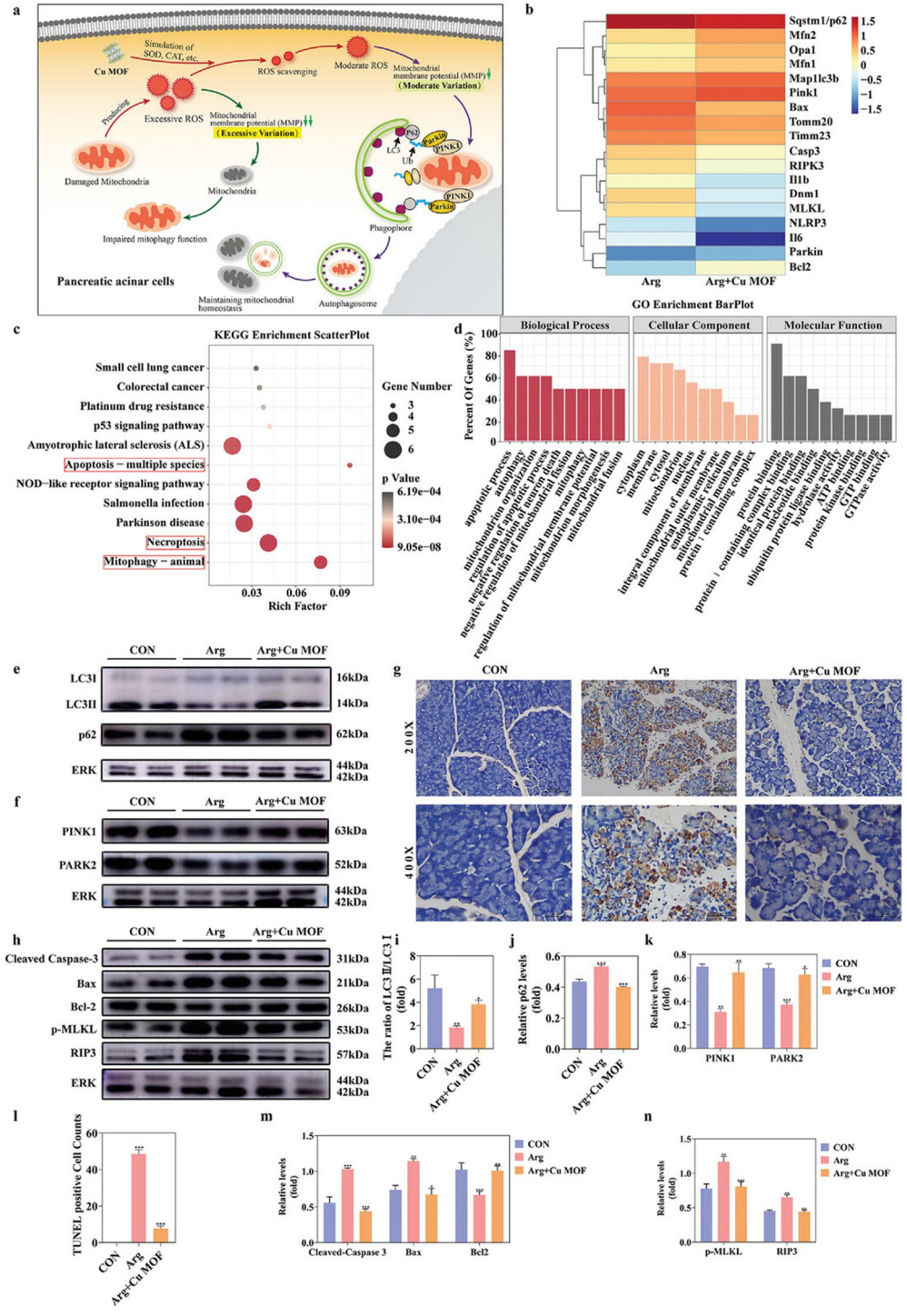


Fig. 6 Cu MOF regulated PINK/PARK-mediated mitophagy to control ROS-induced inflammation and necroptosis. **a**) Schematic diagram of the mitophagy, anti-inflammatory, and antioxidant mechanisms of Cu MOF. **b**) Heatmap of the differentially expressed genes. **c**) Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway terms. **d**) Significantly enriched Gene Ontology (GO) terms. **e**, **i**, **j**) Immunoblot analysis and quantification of P62 and LC3 in pancreatic tissues ($n = 3$). **f**, **k**) Immunoblot analysis and quantification of PINK1 and PARK2 in pancreatic tissues ($n = 3$). **g**, **l**) TUNEL positivity was revealed by immunohistochemical staining of pancreatic tissues and quantitative analysis ($n = 3$). Scale bar: 100 μm. **h**, **m**, **n**) Immunoblot analysis and quantification of cleaved caspase 3, Bax, Bcl-2, p-MLKL, and RIP3 in pancreatic tissues ($n = 3$). The data are represented as mean values, and error bars indicate SEM (mean ± SEM). n represents the number of samples for each group ($p < 0.05$; $p < 0.01$; $p < 0.001$; $p < 0.0001$). Reprinted from [149] with permission.

receptor expression and fibroblast apoptosis [155, 156]. The results of external biocompatibility and hemostasis tests demonstrated that the bilayer exhibited enhanced cell proliferation and effective hemostatic properties. Furthermore, in vivo studies and computerized molecular simulations revealed that the bilayer effectively covered the wound site, prevented suture breakage and leakage, inhibited bleeding and reduced postoperative tissue adhesion (Fig. 7). These findings suggest that the bilayer has a promising therapeutic potential in preventing pancreatic leakage in the postoperative period [157]. Figure 8 illustrates the preparation process of the various nanomedicines mentioned above or the mechanism of action of therapeutic APs. Table 2 shows different types of nanomaterials used for the treatment of AP.

Summary and outlook

AP is a severe, life-threatening inflammatory disease with an unclear pathogenesis. It is primarily characterized by inflammatory infiltration and oxidative stress. Previous reports on the treatment of AP have focused on the suppression of the inflammatory response and the prevention of oxidation of pancreatic tissue. The traditional therapeutic AP drugs have several limitations, including poor drug stability, low bioavailability and a short half-life. To date, there has been limited utilization of these techniques in clinical settings. The ongoing advancement of nanotechnology has resulted in the development of a plethora of novel multifunctional nanomaterials, which have been employed in a multitude of clinical studies pertaining to AP. These developments have yielded novel insights and approaches for the treatment of AP. Conventionally synthesized nanomaterials have several disadvantages, including the need for expensive equipment, the generation of toxic chemicals and the strict control of reaction conditions. In contrast, the production of bio-nanomaterials based on derivatives from natural organisms, microorganisms, microalgae, enzymes and plant extracts is biologically safer and represents a safe, efficient, environmental-friendly and favorable approach of obtaining nanomaterials. This approach has attracted considerable attention and interest within the scientific community. It is important to acknowledge that nanomaterials employed in AP therapy also possess intrinsic limitations. Nanomaterials for the treatment of pancreatitis have many challenges and opportunities on the way. First, despite the development of numerous nanomaterials for the treatment of AP, the majority have only been confirmed in rudimentary models, lack pathological and statistical data and have not been subjected to extensive, multicenter investigations. Second, although the high potential of nanomaterials, their long-term safety and toxicity in vivo need to be thoroughly investigated. Nanomaterials may elicit an immune response or accumulate in the body with potential toxic effects on healthy tissues. The future may see the advent of therapeutic systems based on combinations of multiple nanomaterials, with a particular focus on the in vivo distribution, metabolic pathways and potential toxic effects of novel nanomaterials. This will ensure safety in clinical applications and improve therapeutic efficacy while reducing the risk of toxicity by decreasing the number of single nanomaterials used. Third, it is necessary to establish a unified scientific evaluation system, improve multiple animal models, evaluation indices and test technology, and vigorously develop nanotoxicology to promote the clinical translation and safe application of nanomaterials.

With the continuous development of technology, artificial intelligence (AI), big data analytics, 3D printing technology, single-cell sequencing, spatial transcriptomics and other fields continue to emerge, nanotechnology can be combined with these fields to promote technological innovation. AI technologies, particularly machine learning and deep learning algorithms, have the capacity to process and analyze vast quantities of biomedical data in order to identify pivotal parameters in drug delivery. AI is capable of constructing predictive models based on known drug-target interaction data, with the objective of predicting new drug targets and assisting in the optimization of the design of nanocarriers. This is done with the intention of more efficiently incorporating specific biomarkers, with the ultimate goal of improving drug delivery and targeting in diseased tissues. The application of big data analytics can facilitate the identification of the behavioral patterns exhibited by nanomaterials in diverse biological environments. Furthermore, it can assist in the screening of materials with optimal biodegradability properties and in the development of kinetic simulations, which can be employed to predict biodegradability and to optimize drug release under a range of conditions. By means of big data analysis of patient-specific biological information, in conjunction with the application of AI, it is possible to develop personalized drug delivery solutions that are tailored to the individual patient, thereby advancing the concept of precision medicine.

It is similarly anticipated that nanomaterials will eventually receive policy support from governments, including the signing of bilateral or multilateral cooperation agreements and the establishment of cross-border cooperation mechanisms. Additionally, the formation of an international nanotechnology standards committee to develop unified nanotechnology standards and norms is envisioned, as is the establishment of an international forum on the ethics and regulation of nanotechnology for regular discussion and updating of nanotechnology ethical and regulatory policies. Furthermore, the creation of an international fund for nanotechnology education is proposed to support cross-border nanotechnology

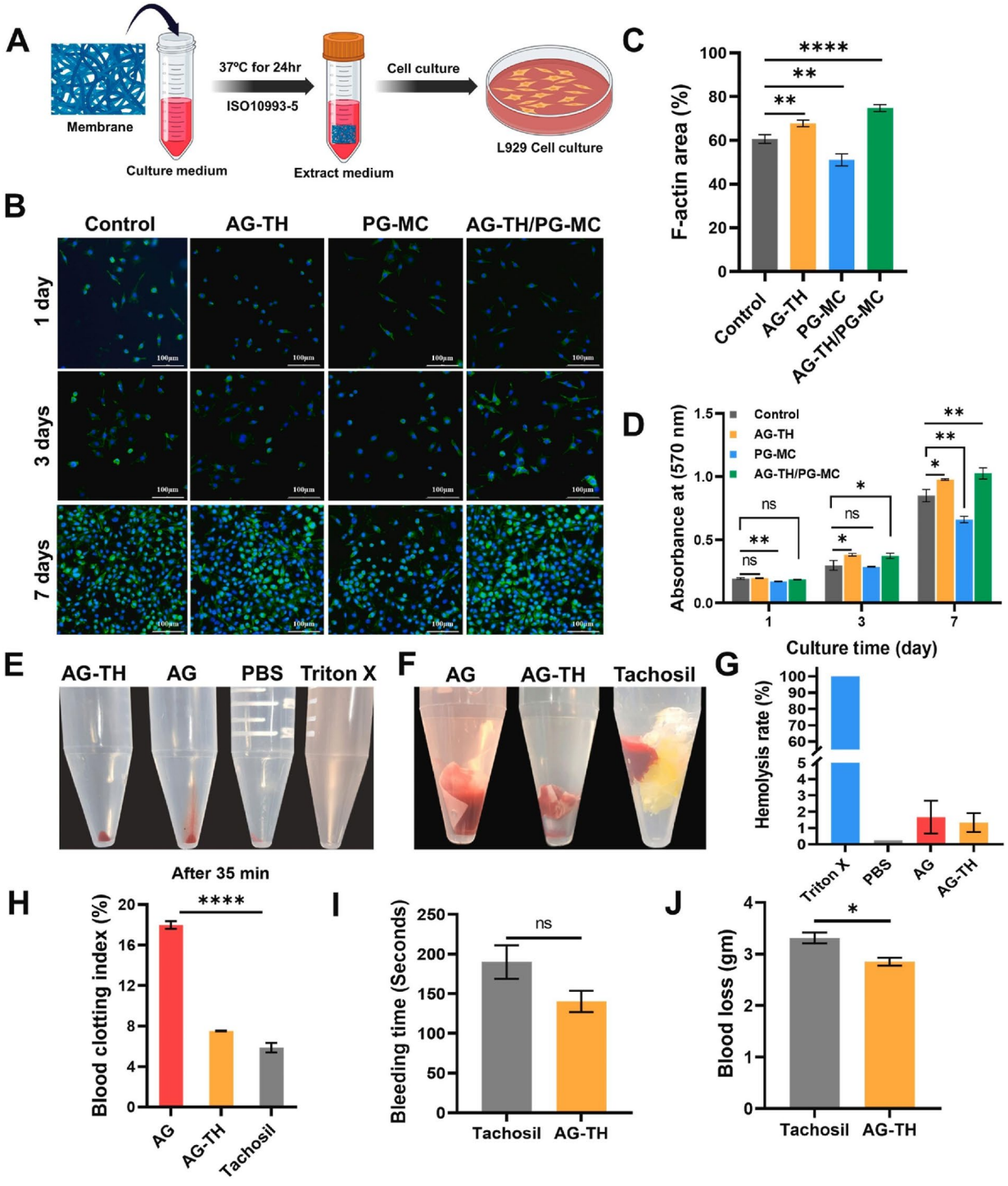


Fig. 7 (**A**) Samples extract preparation procedure and cell culture (**B**) Fluorescence microscope images of the L929 Fibroblast cell proliferation after 1, 3 and 7 days of culture. (**C**) F-actin are analysis of the L929 fibroblast cells after 7 days. (**D**) MTT cytotoxicity assay after 1, 3 and 7 days of culture. (**E**) Digital images of hemolytic activity of the composite membranes with PBS as a negative control and Triton x-100 as a positive control. (**F**) Digital images of the blood clotting formation on the samples. (**G**) Comparative blood hemolysis ratio analysis. (**H**) Blood clotting index (BCI) of the samples after 35 min. (**I**) Comparative bleeding time and (J) Blood loss analysis. Reprinted from [157] with permission. Copyright © 2024 Elsevier Ltd

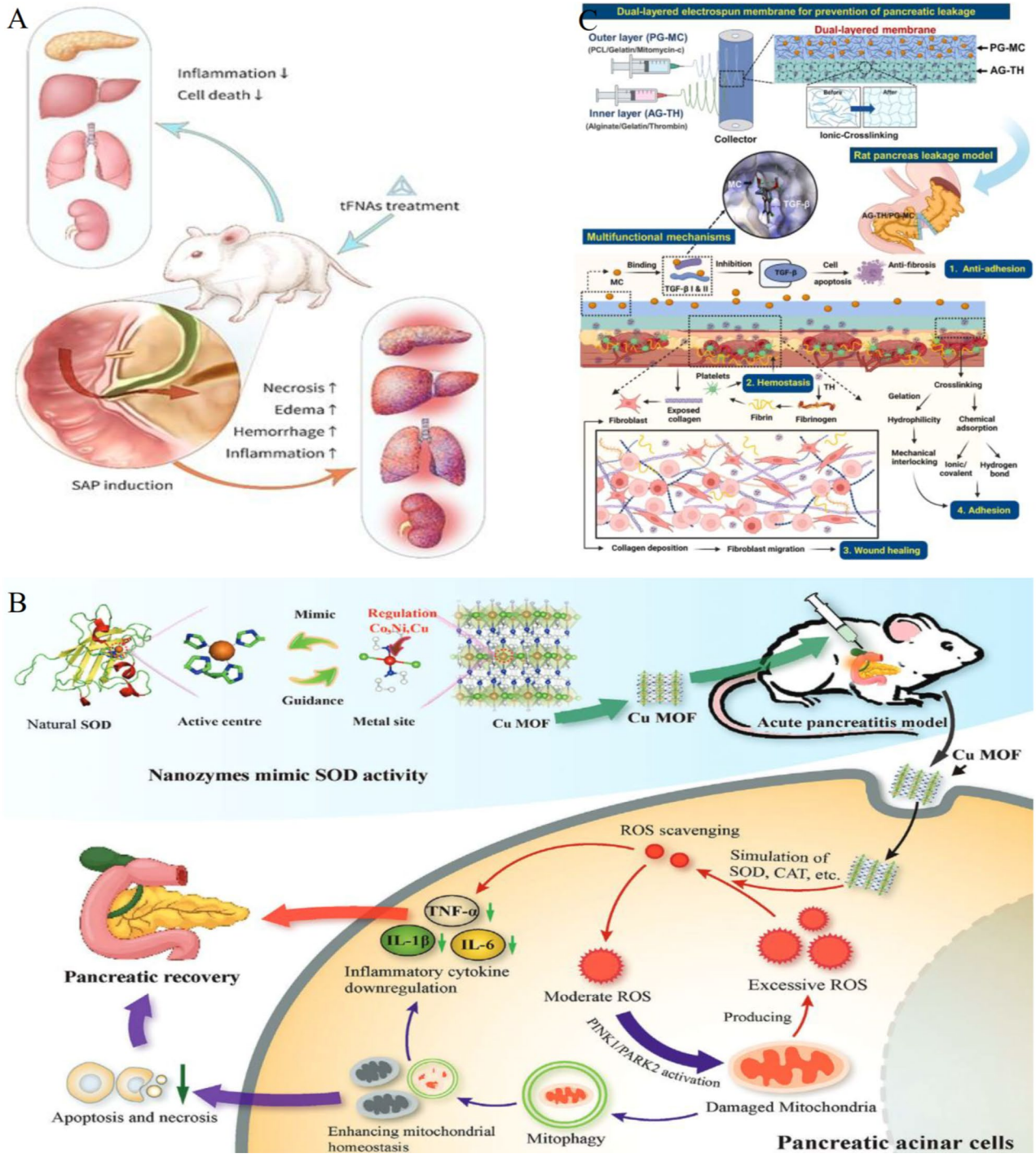


Fig. 8 (**A**)Schematic diagram of TFNAs in treating AP in mice. Reprinted from [143]with permission. Copyright © 2022 American Chemical Society. (**B**) Schematic diagram of Cu MOF nanozyme synthesis and its application in treating AP. Reprinted from [149] with permission. Copyright © 2024 Wiley-VCH GmbH. (**C**) Schematic illustration of the preparation of electrospun AG-TH/PG-MC dual-layered membrane and application in the rat pancreas leakage model and its multifunctional ability. Reprinted from [157] with permission. Copyright © 2024 Elsevier Ltd

Table 2 Different types of nanomaterials used for the treatment of AP

Types of Nanomaterials	Animal Model	Effects and Cellular Mechanisms	Ref.
Liposomes (DTM@KA NPs)	NAT; mice	DTM@KA NPs facilitated STAT6-regulated mitochondrial precursor proteins transport via interacting with TOM20 to further promote Drp1-dependent fission and Pink1/Parkin-regulated mitophagy with enhanced lysosomal degradation for removing damaged mitochondria in PAC.	[98]
Polymer (FST-LPHNPs)	L-arginine; mice	A reduction in NF-κB activity, amylase and lipase levels, and pro-inflammatory factors (NLRP3, IL-1β, TNF-α, and IL-6).	[105]
Silk fibrin (BRSNPs)	L-arginine; mice	Inhibition of cellular mitochondrial ROS production decreased malondialdehyde (MDA) levels and increased SOD levels in rats, as well as activation of the Nrf2 pathway and an increase in HO-1, which in turn inhibited the pro-inflammatory NF-κB signaling pathway.	[20]
Mesoporous silica nanoparticles (SL@M@ArgMSNs@BA)	Sodium Taurocholate; mice	Inhibit cell necrosis by impeding the IκBα/NF-κB/TNF-α/IL-6 and CAMK-II/p-RIP3/p-MLKL/caspase-8,9 signaling pathways.	[114]
Macrophage membrane (MVs-UIO-ED)	Cerulein; mice	Inflammation-targeting ability, with both alpha-amylase and lipase levels showing the most significant reductions.	[120]
Neutrophil membrane (2 N@M@HMPB@BA#Ga)	Sodium Taurocholate; mice	The formulation inhibited endoplasmic reticulum stress (IRE1/XBP1 and ATF4/CHOP axis) and restored impaired autophagy (Beclin-1/p62/LC3 axis), preserving dying acinar cells and restoring the cellular "health status".	[53]
Nano yttria (NY)	Cerulein; mice	NY can attenuate experimental AP by restoration of mitochondrial and ER homeostasis through Nrf2/NFκB pathway modulation, reducing of endoplasmic reticulum (ER) stress markers (BIP, IRE1 and Ero1-Lα), and molecular chaperones (Hsp27 and Hsp70)	[136]
Tetrahedral framework nucleic acids (TFNAs)	Sodium Taurocholate; mice	Decreased serum amylase, lipase, ALT, AST, CREA, and BUN levels, as well as decreased expression of the proteins Bax and caspase-3 associated with cell death and apoptosis.	[143]
Nanozymes(Cu MOF)	Arginine; mice	Effectively scavenges reactive oxygen species and attenuates apoptosis and necrosis of aden hypophysial cells by activating PINK1/PARK2-mediated mitochondrial autophagy pathway.	[149]
Nanomembrane (AG-TH/PG-MC)	Rat pancreatic leakage	The high gelatin and alginate content of the inner layer reduces fiber diameter and water contact angle, making it highly biodegradable and firmly adhering to tissue surfaces. The MC in the outer layer has antibiotic properties that reduce tissue adhesion by inhibiting fibrosis and inhibiting vascular distribution and can inhibit fibroblast formation by down-regulating the expression of TGFβ receptor and fibroblast apoptosis.	[157]

education and academic exchanges. It is recommended that the nanomaterials industry actively share their scientific research results, strengthen international exchanges and cooperation, and improve the international status and influence of the industry.

Abbreviations

AP	Acute pancreatitis
ERCP	Endoscopic retrograde cholangiopancreatography
RIP1	Receptor-interacting protein 1
RIP3	Receptor-interacting protein 3
MLKL	Mixed lineage kinase domain-like
InsP3R	Inositol 1,4,5-trisphosphate receptor
ATP	Adenosine triphosphate
MPTP	Membrane permeability transition pore
SERCAs	Sarcoendoplasmic Reticulum Calcium ATPase
PMCAs	Plasma membrane Ca^{2+}-ATPase
NF-κB	Nuclear factor-κB
MAPK	Mitogen-activated protein kinase
TNF-α	Tumor necrosis factor-alpha
IL-1	Interleukin-1
IL-6	Interleukin-6
MAM	Mitochondria-associated endoplasmic reticulum membranes
FMLF	N-Formylmethionine-leucyl-phenylalanine
PBMCs	Peripheral blood mononuclear cells
PASCs	Pancreatic stellate cells
ORAI1	Calcium release-activated calcium modulator 1
STIM1	Stromal interaction molecule 1
SIRS	Systemic inflammatory response syndrome
PI3K/AKT	Phosphatidylinositol 3-kinase/protein serine-threonine kinase
TLR4	Toll like receptor 4
AMS	Amylase
LPS	Lipase
WBCs	White blood cells
BPB	Blood-pancreas barrier
ROS	Reactive oxygen species
KA	Kaempferol
TCM	Traditional Chinese Medicine
IRE1	Inositol-requiring enzyme 1
JNK	c-Jun N-terminal kinase
CHOP	C/EBP homologous protein
TK	Thioketals
DSPE-PEG2000	Hydrophilic 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-[methoxy(polyethylene glycol)-2000
STAT6	Signal transducer and activator of transcription 6
TOM20	Translocase of outer mitochondrial membrane 20
DRP1	Dynamin related protein 1
PAC	Pancreatic acinar cell
PLGA	Poly-lactic-co-glycolic acid
PEI	Polyethyleneimine
PEG	Polyethylene glycol
CTS	Chitosan
SF	Sericin protein
FST	Festerone
LPHNP	Lipid polymeric Hybrid nanoparticle
SAP	Severe acute pancreatitis
NLRP3	NOD-like receptor protein 3
BRSNP	Bilirubin encapsulated silk fibrin nanoparticles
MDA	Malondialdehyde
SOD	Superoxide dismutase

NRF2	Nuclear factor erythroid 2-related factor 2
HO-1	Heme oxygenase-1
BAPTA-AM	1,2-Bis(2-aminophenoxy) ethane-N, N, N, N′-tetraacetic acid
CAMK-II	Calmodulin-dependent protein kinase II
HMPB-NPs	Hollow mesoporous Prussian blue nanoparticles
GA	Gabexate mesylate
XBP1	X box binding protein 1
ATF4	Activating transcription factor 4
P62	Protein sequestosome 1
LC3	Light chain 3
βGlus-ZnD-NPs	β-glucan-functionalized zinc-doxorubicin nanoparticle system
PDAC	Pancreatic ductal adenocarcinoma
M	Microfold
NY	Nanoparticles
ER	Endoplasmic reticulum
TFNAs	Tetrahedral framework nucleic acid nanoparticles
ssDNA	Single-stranded DNA
AST	Aspartate aminotransferase
ALT	Alanine aminotransferase
CREA	Creatinine
BUN	Blood urea nitrogen
MOFs	Metal-organic frameworks
PINK1	PTEN-induced kinase 1
PARK2	Parkinson Disease Protein 2
AG-TH/PG-MC	Alginate gelatin- thrombin/ polycaprolactone gelatin- mitomycin-c
MC	Mitomycin-c
TGFβ	Transforming Growth Factor beta
AI	Artificial intelligence
MMP	Matrix metalloproteinases

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Author contributions
W D: Writing-original draft and pictures. XY W and YY Z: Supervision; Validation. WC W, HJ H and ZD J: Writing – review & editing. All authors reviewed the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
All authors in the paper agree to be published.

Competing interests
The authors declare no competing interests.

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