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REVIEW

Nanotherapy for Pancreatitis: From Single-Cell Targeting Toward Multicellular-Coordinated Regulation

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Abstract: Pancreatitis constitutes a serious global health challenge characterized by a multicellular pathogenesis and limited therapeutic options. The recent discovery of different cellular pathogenic mechanisms and the emerging effectiveness of nanotechnology-based, cell-targeted therapies have provided promising therapeutic avenues for pancreatitis. However, the identification of effective cellular targets, the elucidation of nanotherapeutic mechanisms, and the multicellular-coordinated modulation remain fragmented and insufficiently defined. Here, we summarize recent progress in understanding pathogenic mechanisms from the perspective of different cell populations and analyze relevant nanotechnology-based approaches designed to target these cells in detail. By bridging different cellular pathogenesis with advances in nanotherapeutic design, this review offers a clear framework for cell-targeted nanotherapeutics across the disease progression, proposing pathological and methodological insights to guide the future development of multicellular-coordinated nanomedicines for pancreatitis.

Keywords: cellular pathogenic mechanisms, multicellular-coordinated regulation, nanotechnology, pancreatitis, target

Introduction

Pancreatitis is a common and potentially life-threatening gastrointestinal disorder.[1] In acute pancreatitis (AP), the overall mortality is approximately 1%,[2] but this value can increase dramatically to 30–40% in patients with organ failure, infected necrosis, and systemic inflammatory response syndrome (SIRS).[3,4] The most common etiologies include biliary obstruction, excessive alcohol consumption, hypertriglyceridemia, drug abuse and endoscopic retrograde cholangiopancreatography.[5–9] Existing clinical managements rely primarily on supportive care, including nutritional support, pain control, fluid resuscitation and infection prevention.[10,11] However, these therapeutic strategies remain insufficient to modulate the core cellular and molecular pathways underlying disease progression.

The pathophysiology of pancreatitis involves multiple cell populations and their intricate crosstalk (Figure 1).[12–20] The main cellular components include pancreatic acinar cells (PACs), which mainly synthesize and secrete digestive zymogens;[12] and pancreatic stellate cells (PSCs), which maintain extracellular matrix homeostasis.[15] Upon stimulation by factors such as alcohol abuse, biliary obstruction or metabolic disorders, these cells undergo injury and abnormal activation, thereby initiating and amplifying pancreatic inflammation. For example, Ca^{2+} overload in PACs induces premature trypsinogen activation, leading to autodigestion and tissue injury.[16] PSCs are activated and transform into myofibroblast-like cells, promoting fibrosis by through the secretion of TGF-β and collagen.[17] Additionally, the local injury environment recruits immune cells to the inflamed pancreas and amplifies the inflammatory response.[18–20] Injured endothelial cells facilitate immune cell extravasation and contribute to microvascular dysfunction.[21,22] Critically, intercellular crosstalk is a key mechanism in pancreatitis.[23–25] For instance, damaged PACs release damage-associated molecular patterns (DAMPs), which activates macrophages and exacerbates inflammation.[23]

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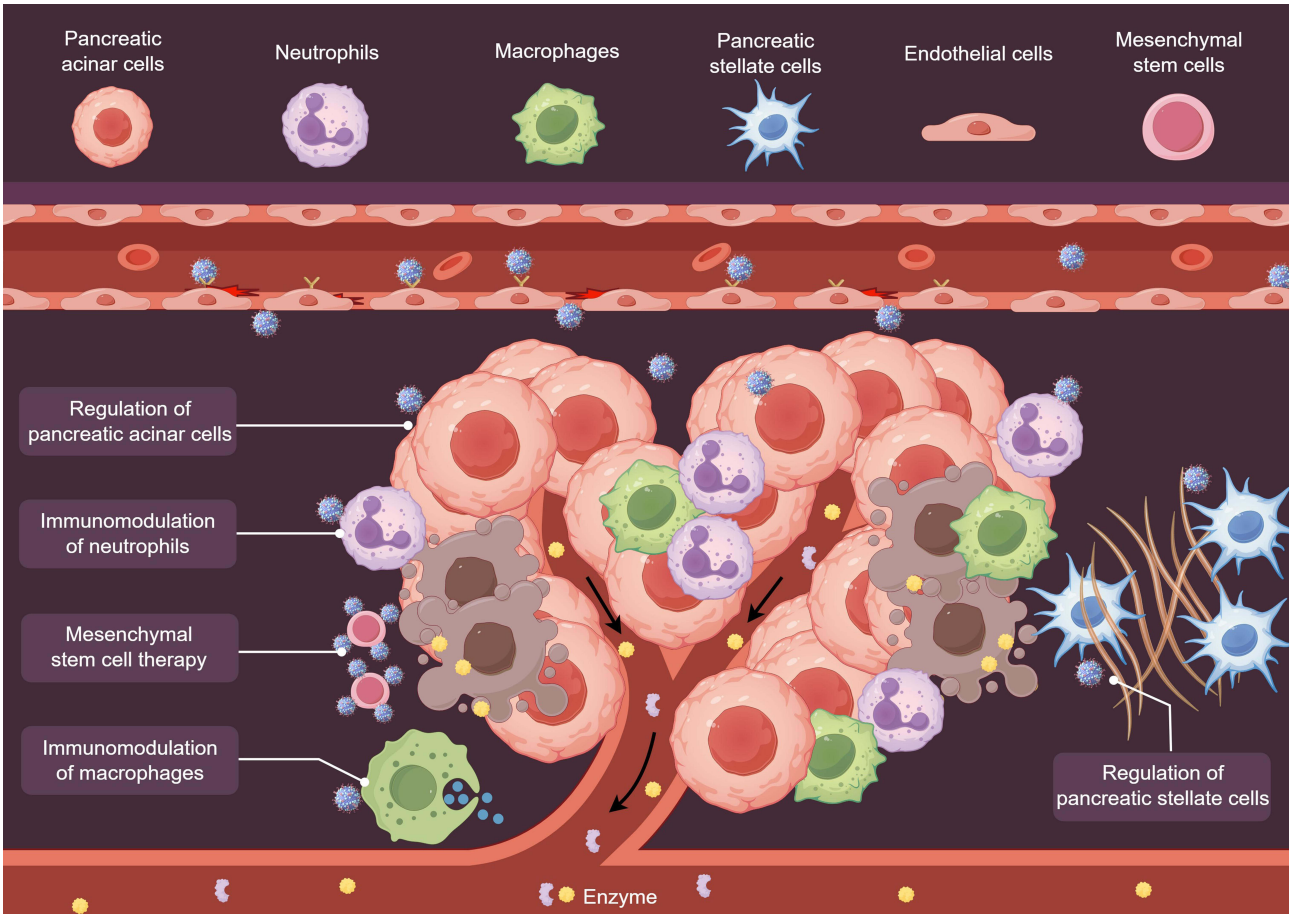

Figure 1 Schematic illustration of major cell populations involved in pancreatic inflammation and corresponding nanotherapies. Cell types include pancreatic acinar cells (PACs), neutrophils, macrophages, pancreatic stellate cells (PSCs), endothelial cells, and mesenchymal stem cells (MSCs). Nanotherapies target these cells through various mechanisms: regulating pathological events in PACs, immunomodulating neutrophils and macrophages, regulating activated PSCs to alleviate fibrosis, and leveraging MSCs as bioengineered platforms. Figure created by Figdraw.

Therefore, targeting these cell-specific events and their intercellular crosstalk holds significant promise for the development of effective therapeutic strategies for pancreatitis.

In recent years, various nanotechnology-based therapies have been developed to modulate cell-specific pathological processes in pancreatitis, demonstrating remarkable therapeutic efficacy in preclinical studies. Owing to their superior specificity and excellent biocompatibility, nanotechnology has emerged as a promising method for the targeted delivery of genes, peptides and small-molecule drugs for the treatment of pancreatitis.[26–30] In general, the current therapeutic mechanism of nanomaterials involves three main aspects: selectively modulating pathological events in distinct cellular populations, such as activating microenvironment-responsive drug release to confine its action to inflamed pancreatic niches;[27] correcting mitochondrial dysregulation in PACs, rebalancing inflammatory activation in immune cells, suppressing fibrotic reprogramming of PSCs and stabilizing endothelial barrier function;[28–30] and interrupting the intercellular inflammatory circuits that amplify inflammation-induced injury.[29] Together, these principles allow nanotechnology to achieve targeted regulation across different cellular compartments, enhance therapeutic specificity and suppress the multicellular inflammatory network underlying pancreatitis.

Although a considerable amount of research has been conducted in this field, current studies remain fragmented and lack integration across different cell populations. This review first summarizes the pathological mechanisms of major pancreatic cell types and corresponding nanotechnology-based therapeutics. It then discusses intercellular crosstalk and multicellular-coordinated nanotherapies, which refers to sequential or simultaneous modulation of key pathological nodes within distinct cell populations. By integrating cellular pathophysiology with nanomaterial design principles, this review bridges the current

fragmentation between mechanistic understanding and nanotherapeutic applications. The proposed multicellular-coordinated nanotherapy offers strategic innovation and guidance for the development of future nanomaterials that may affect pancreatitis management and provide insights into broader inflammatory diseases.

Relevant literature was identified through searches of PubMed, Web of Science, and Scopus using keywords related to pancreatitis, nanotherapy, nanomedicine, cell-target, drug delivery, and studies were selected based on their relevance to cellular mechanisms and nano-therapeutic strategies.

Cellular Mechanisms and Nanotherapeutic Strategies

Pancreatic Acinar Cell and Nanotherapies

Pancreatic acinar cell (PACs) plays a central role in driving the initiation and progression of pancreatic inflammation. A cascade of pathological events, including dysregulated calcium signaling, premature trypsinogen activation, endoplasmic reticulum (ER) stress, mitochondrial dysfunction, collectively contributes to PACs necrosis and enlarged inflammation (Figure 2).

Pathological Mechanisms in PACs

Pathological elevation of Ca^{2+} concentration in PACs is a critical early event that induces downstream premature activation of trypsinogen, mitochondrial dysfunction, endoplasmic reticulum (ER) stress. Under a physiological state, Ca^{2+} release from the ER initiates zymogen granule exocytosis and supports mitochondrial ATP synthesis.[31,32] The increased Ca^{2+} concentration is rapidly restored by two ATP-dependent transport systems: sarco/endoplasmic reticulum Ca^{2+}-ATPases (SERCA) return Ca^{2+} to the ER, and plasma membrane Ca^{2+}-ATPases (PMCA) extrude Ca^{2+} to the extracellular space.[33] Pathological stimuli, such as alcohol, disrupt this balance through the aberrant activation of inositol 1,4,5-trisphosphate and ryanodine receptors ($InsP_3R$), causing excessive ER Ca^{2+} release. Ca^{2+} depletion of ER subsequently triggers store-operated calcium entry (SOCE), which is mediated by stromal interaction molecule 1 (STIM1) and the calcium release-activated calcium channel protein 1 (ORAI1) channel complex, leading to sustained Ca^{2+} overloaded in PACs.[34–36]

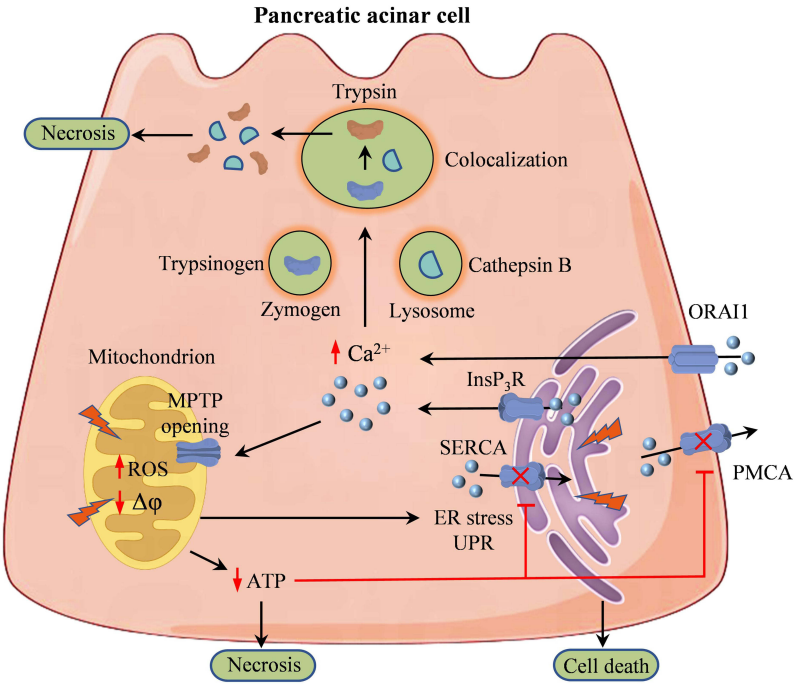

Figure 2 Pathological mechanisms in PACs. Pathological Ca^{2+} overload, driven by excessive ER Ca^{2+} release ($InsP_3R$) and sustained SOCE (ORAI1), disrupts Ca^{2+} homeostasis due to impaired SERCA and PMCA function. Elevated Ca^{2+} promotes aberrant colocalization of zymogen granules with lysosomes, enabling premature activation of trypsinogen. Concurrently, Ca^{2+} overload induces mitochondrial dysfunction, leading to ATP depletion and necrosis. In parallel, Ca^{2+} overload and ROS trigger ER stress and unfolded protein response (UPR), ultimately resulting in cell death. The red upward and downward arrows indicate upregulation and reduction, respectively; the red cross indicates blockade. Δφ represents mitochondrial membrane potential, lightning symbols indicate organelle stress or dysfunction.

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Sustained Ca^{2+} overload is a central trigger for the premature activation of trypsinogen. Under pathological conditions, Ca^{2+} elevation inhibits exocytosis of zymogen granules and promotes the aberrant colocalization of zymogen granules with lysosomes in PACs. The Cathepsin B (CTSB) in lysosomes directly cleaves trypsinogen into active trypsin inside the cytoplasm.[37,38] The activated trypsin further disrupts vesicular membranes, releasing CTSB into the cytoplasm and amplifying autodigestion.[38] Additionally, reduced cathepsin L activity limits trypsin degradation, further enhancing CTSB-mediated trypsinogen activation.[38,39] Furthermore, the excessive Ca^{2+} could activate the phosphatase calcineurin, which has been shown to promotes premature activation of trypsinogen.[40]

In addition, persistent cytosolic Ca^{2+} overload opens mitochondrial permeability transition pores (MPTP), leading to a collapse of the mitochondrial membrane potential, impaired ATP synthesis and a shift toward necrotic cell death.[41–44] Concurrently, electron transport chain disruption results in the overproduction of mitochondrial reactive oxygen species (ROS), which exacerbates oxidative damage to lipids, proteins, and mtDNA.[45] The resulting oxidative stress further promotes MPTP opening and activates key proinflammatory signaling pathways, including those involving NF-κB and the NLRP3 inflammasome, amplifying the release of cytokines such as IL-1β and IL-6.[46] This mitochondrial mtDNA acts as a DAMPs, activating the cGAS-STING signaling axis, thereby triggering a type I interferon response and perpetuating a vicious cycle of inflammation.[47–49]

Ca^{2+} overloaded, ROS accumulation and bile acids further cause ER dysfunction.[50–52] This induces the excessive accumulation of unfolded or misfolded proteins, leading to activation of the unfolded protein response (UPR). The UPR is mediated by inositol-requiring enzyme (IRE1), protein kinase RNA-like endoplasmic reticulum kinase (PERK), and activating transcription factor 6 (ATF6).[53–55] Under homeostasis, these sensors are sequestered by the chaperone GRP78. Misfolded protein accumulation triggers GRP78 dissociation and activates ER stress pathways: PERK-eIF2α reduces protein load while inducing ATF4,[54] IRE1-XBP1 enhances folding capacity,[55] and ATF6 promotes ER chaperone expression.[56] Under severe ER stress, this adaptive UPR transitions toward apoptosis, characterized by sustained PERK/ATF4-CHOP activation, ultimately leading to PACs death.[57]

Nanotherapeutic Strategies Targeting PACs

Current nanotherapies typically delivery Ca^{2+} chelators into PACs for scavenging excess Ca^{2+}.[26,27,58–60] For instance, Wang et al engineered a hollow Prussian blue nanoparticle and mesoporous organosilica nanoparticles camouflaged with biomembranes or peptides, achieving precise PACs targeting for 1,2-bis (2-aminophenoxy) ethane-N,N,N,N′-tetraacetic acid (BAPTA-AM) delivery (Figure 3A), which hydrolyzed intracellularly into active BAPTA to chelate overloaded Ca^{2+}.[26,27] As mentioned above, Ca^{2+} overload is an upstream pathological event, restoring Ca^{2+} homeostasis thus typically exerts regulatory effects on various downstream pathological events. For example, combined with the inhibition of trypsin activity using gabexate mesylate, the hollow mesoporous Prussian blue nanoparticles coordinately modulating ER stress and oxidative stress.[26] Fu et al developed BAPTA-AM loaded liposomal nanoparticles (BLNs) to eliminate Ca^{2+} overloaded, further interrupted the Ca^{2+}-ROS inflammation cascade and reduced cathepsin B-mediated zymogen activation.[58] Luo et al constructed a multifunctional cerium-based nanoplatform (MOF808@BA@CAT) that effectively inhibits ER stress in AP by restoring Ca^{2+} homeostasis and the enzyme catalase to mitigate oxidative stress, thereby suppressing the activation of the UPR.[59]

However, the dysregulated Ca^{2+} pathway is governed primarily by SOCE components such as STIM1 and ORAI1, for which selective small-molecule inhibitors such as CM4620[62] have already demonstrated clinical potential. Corresponding nanotherapies directly targeting these channels remain unexplored, possibly because of challenges in terms of subcellular delivery and limited formulation compatibility. Similarly, few nanotherapies directly target upstream activation nodes of premature activation of trypsinogen, such as lysosome-zymogen granule fusion and CTSB activation. This gap may largely arise from incomplete mechanistic understanding and safety concerns over disturbing essential lysosomal or proteolytic functions.[63] Conversely, current strategies regulating ER stress mainly focus upstream inducers rather than the UPR signaling pathway. Small-molecule inhibitors such as salubrinal[64] and guanabenz[65] have shown potential in modulating ER stress but are limited by poor bioavailability, tissue specificity and systemic toxicity.[50] Consequently, future nanotherapies will likely rely on the optimized targeted delivery of proven inhibitors or active molecules, as well as the modulation of established driving factors.

In terms of mitochondrial dysfunction in PACs, nanotherapies primarily involves the scavenge of ROS, inhibition of MPTP opening, improvement of ATP synthesis, and activation of mitophagy.[61,66–75] For instance, Yan et al developed hollow mesoporous manganese dioxide (MnO_2) nanoparticles loaded with cyclosporin A to inhibit MPTP opening of mitochondrial, thereby restoring the ATP supply and recovering Ca^{2+} homeostasis (Figure 3B and C).[61] Using the somatostatin analog octreotide to bind the SSTR-2 receptors on PACs, simultaneously inhibiting the activity of G protein-coupled adenylate cyclase and reducing intracellular cyclic adenosine monophosphate levels, thus suppressing trypsin secretion and activity (Figure 3D).[61] An engineered bio-heterojunctions (bio-HJs) scavenge ROS through electron transfer from Mo_2C to Au, increasing the Mo orbital and electron–hole separation, thus enhancing catalytic activities like those of SOD and CAT to eliminate ROS.[66] Wang et al reported an acid-responsive biomimetic nanozyme (MPBZC) composed of a Prussian blue core loaded with celastrol.[67] The system scavenges ROS via the superoxide dismutase (SOD) and catalase (CAT)-like activities of

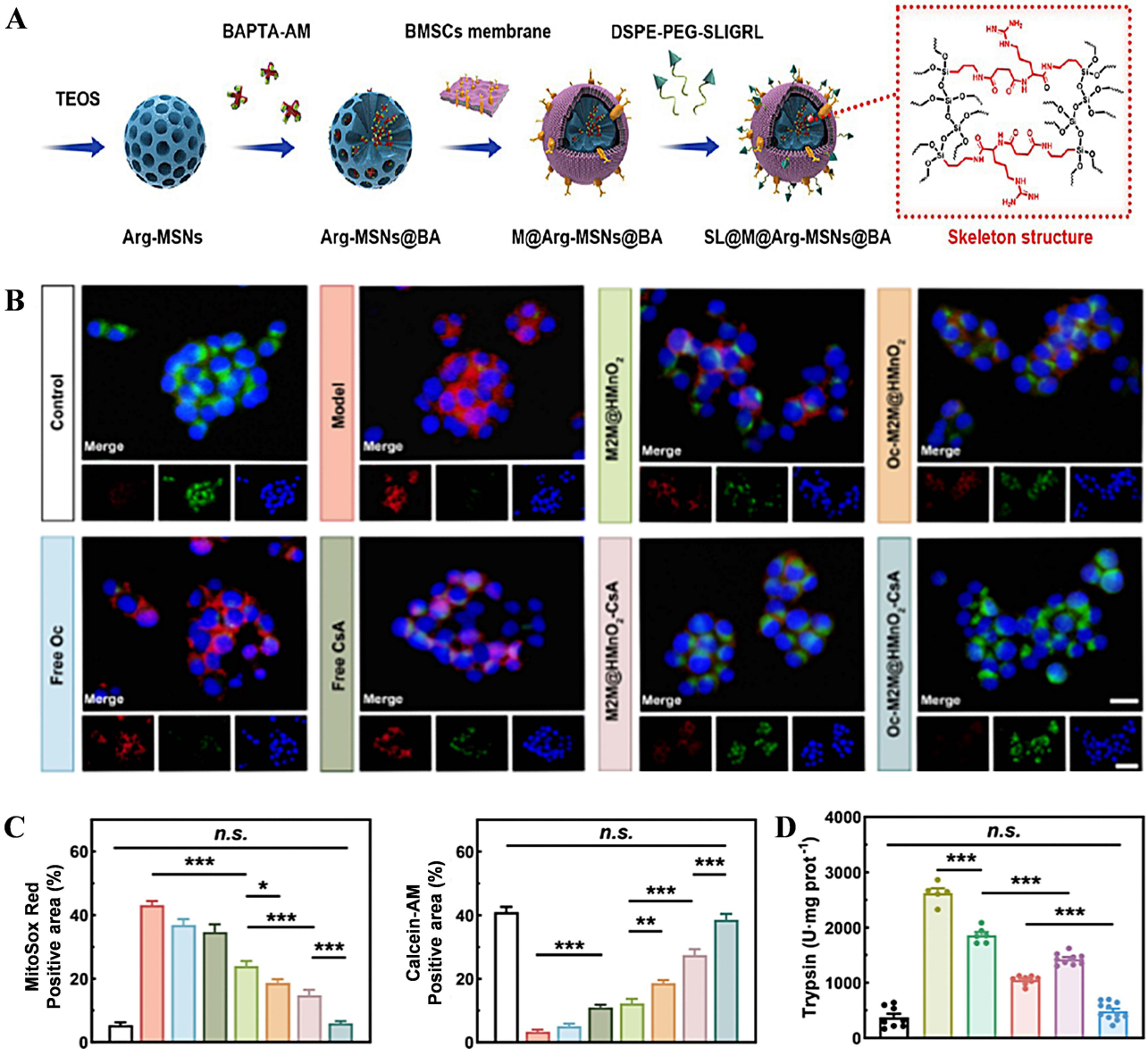

Figure 3 (**A**) Preparation of SL@Arg-MSNs@BA loaded with BAPTA-AM for direct chelation of Ca^{2+}. Reproduced with permission from reference.[27] Copyright 2024, American Chemical Society. (**B and C**) Analysis of MPTP opening status and mtROS in TLCS-stimulated AR42J cells with different treatments, scale bar: merge (20 μm).[61] (**D**) Trypsin levels in pancreatic tissue from each treatment group at 24 h.[61] Data are shown as means ± SEM. n.s.: not significant ($P > 0.05$). *p < 0.05, **p < 0.01, ***p < 0.001. Reproduced with permission from reference.[61] Copyright 2025, Elsevier.

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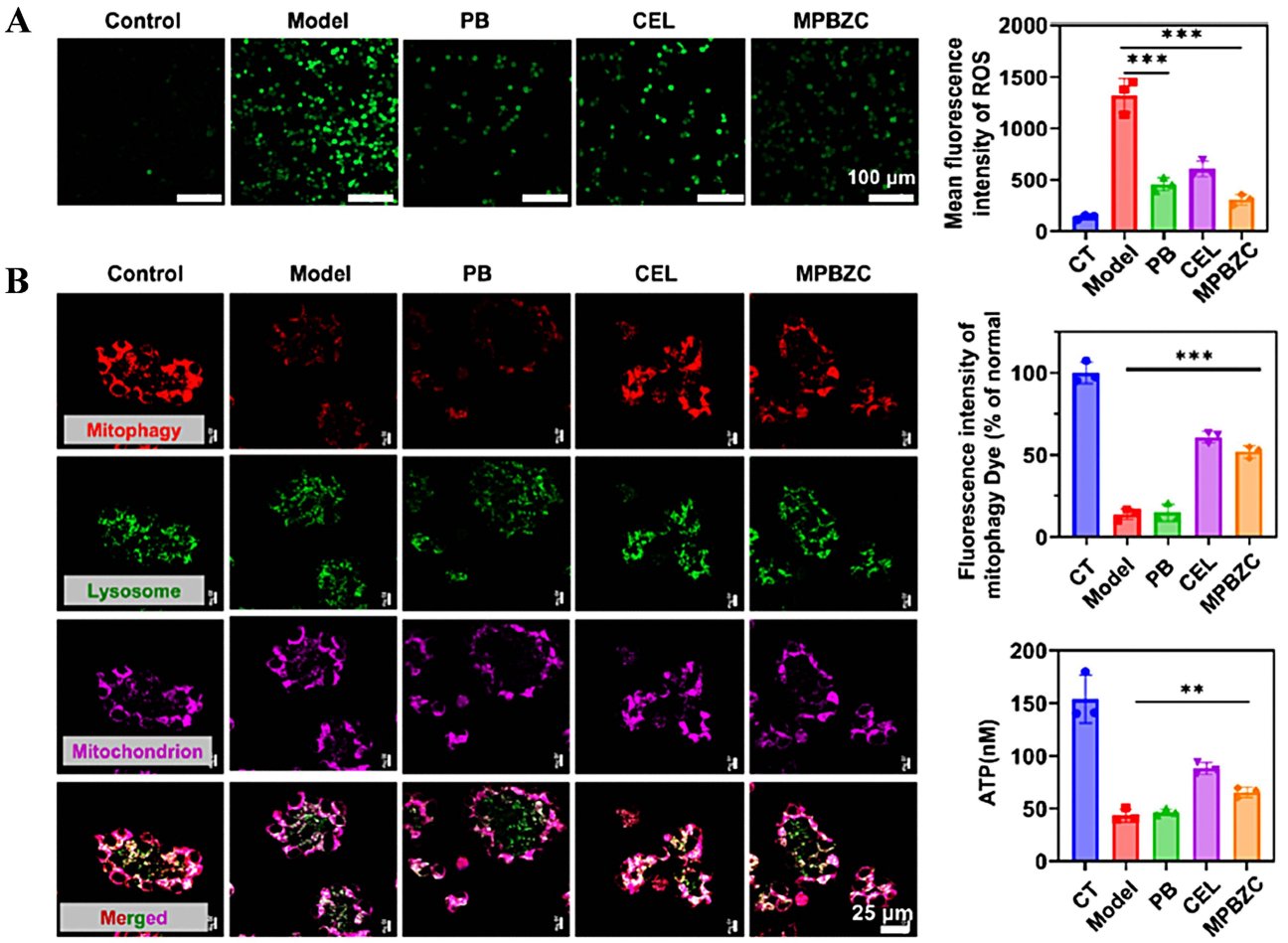

Figure 4 (**A**) ROS scavenging and semiquantification of fluorescence in response to treatment with PB, CEL, and MPBZC by dichlorofluorescein (DCF) measurement using confocal microscopy. (**B**) Evaluation of mitochondrial autophagy in response to different treatments. Mitochondrial autophagy is indicated by the red probe, and lysosomes are indicated by the green probe. Semiquantification of fluorescence to indicate mitochondrial autophagy levels in response to different treatments. Reproduced with permission from reference.[67] Results are presented as mean ± SD, n = 3. **p < 0.01, and ***p < 0.001. Copyright 2025, American Chemical Society.

Prussian blue and activates mitochondrial mitophagy through celastrol-induced Nur77 translocation, restoring autophagic flux and mitochondrial homeostasis (Figure 4A and B).[67]

The targeting strategies to PACs mainly includes biomimetic coatings with tannic acid,[29] octreotide,[61] lipids modifications,[66] macrophage membranes[67,68] and antioxidant properties.[75] These approaches enable nanoparticles to accumulate at inflammatory sites and enhance PAC recognition. Beyond these, ligand-receptor interactions (GPCR-targeting peptides) and microenvironment-responsive activation (pH, ROS, enzymes) could further improve specificity.[26,27,58–60] However, subcellular targeting–particularly mitochondria-directed delivery–remains underexplored but is crucial, as mitochondria serve as critical nodes integrating Ca^{2+} dysregulation, ER stress and oxidative stress in PAC injury. Future designs could incorporate mitochondria-targeting moieties such as triphenylphosphonium (TPP) or mitochondria-penetrating peptides to enhance selective accumulation within mitochondria. In addition, coupling mitochondria-targeting with microenvironment-responsive activation may further improve precision.

Immune Cells and Nano-Immunomodulation

Injured PACs release chemokines and DAMPs, which subsequently recruit many immune cells to the pancreatic tissue. These cells amplify local inflammation, tissue damage and fibrosis by releasing both pro- and anti-inflammatory mediators. Consequently, a greater understanding of the mechanisms of the main immune cells and corresponding nano-

immunomodulation, referring to nanotechnology-based regulation of immune cell activation and polarization, would offer significant guidance for developing immunomodulatory strategies.

Neutrophils

Neutrophils are pivotal effector cells in the early phase of pancreatitis, orchestrating a cascade of inflammatory amplification.[76] Chemokines released from injured PACs mediate the rolling adhesion and transmigration of neutrophils through the classical capture-rolling-adhesion-transmigration cascade.[77,78] Once infiltrating into pancreatic tissue, neutrophils initiate a respiratory burst to generate excessive ROS, which directly damage PACs, aggravate mitochondrial dysfunction and promote M1 macrophage polarization.[79,80] Moreover, activated neutrophils form neutrophil extracellular traps (NETs) through the p38/MAPK pathway.[79,80] Although NETs promote the trapping of pathogens, their DNA-histone-protease complexes obstruct pancreatic ducts and amplify tissue necrosis. Therapeutic strategies targeting NET formation, such as the DNase I-mediated degradation of DNA scaffolds, or blocking upstream pathways, such as the irisin-mediated inhibition of αV/β5 integrin signaling,[81] have been shown to significantly alleviate pancreatic edema, hemorrhage and necrosis.

Recent advances in nanotechnology have enabled the modulation of neutrophil-driven pathology through diverse strategies, including the suppression of infiltration,[82,83] ROS scavenging,[84] the inhibition of aberrant activation,[85] targeted clearance[86] and the restoration of dysregulated polarization.[84] For instance, a carbon monoxide-bound hemoglobin vesicle (CO-HbV) suppresses neutrophil infiltration by reducing pro-inflammatory cytokine production, attenuating endothelial activation, and inhibiting ROS-driven inflammatory amplification.[82] A single-cell atlas-inspired hitchhiking nanoreactor composed of hollow MnO_2 loaded with porphyrin ligands and conjugated to Ly6G antibodies enables ROS scavenging directly within neutrophils.[84] These nanoreactors inhibit both N_1 (proinflammatory) and N_2 (anti-inflammatory) polarization pathways, increase tissue oxygenation through O_2 generation, and attenuate inflammation without disrupting systemic redox homeostasis (Figure 5A and B).[84] Another biomimetic platform (PC@PLGA), designed by hybridizing platelet-derived vesicles with calreticulin-expressing cell membranes, presents an artificial aged signal that promotes macrophage-mediated nonapoptotic clearance of activated neutrophils, thus resolving inflammation (Figure 5C).[86]

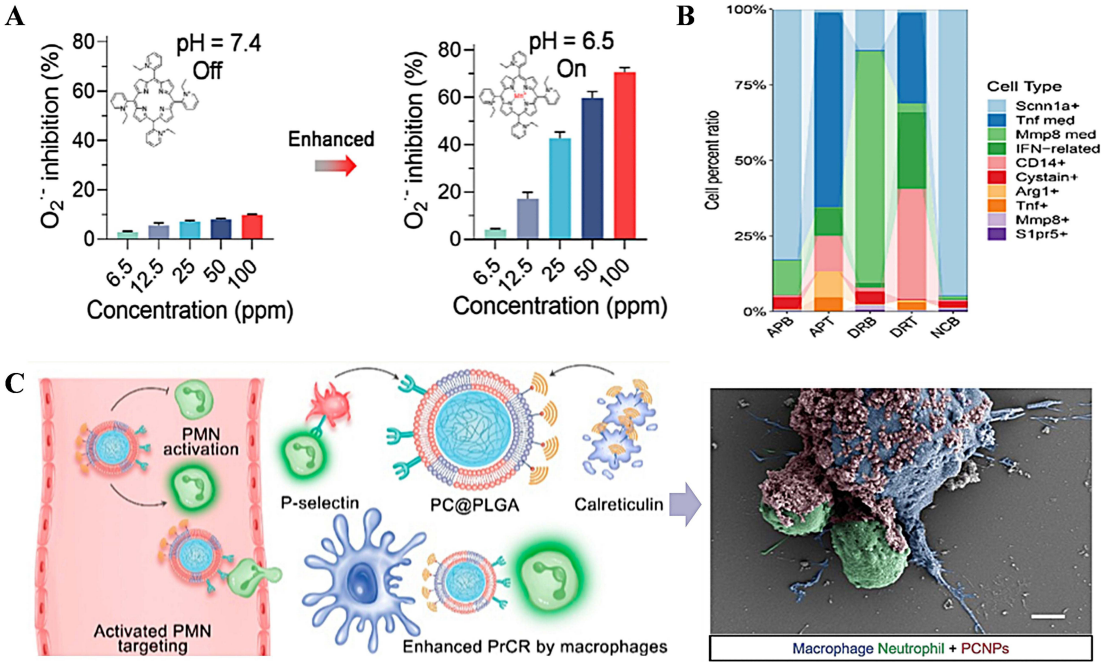

Figure 5 **(A)** The inhibition of $O_2^{\bullet-}$ at pH of 7.4 and 6.5 and **(B)** the proportion of each cell subgroup in each group. Reproduced with permission from reference.[84] Copyright 2025, Wiley-VCH GmbH. **(C)** The binding of PSGL-1 to P-selectin enables the anchoring of PC@PLGA on the activated neutrophils, whereas doxorubicin-induced CRT exposure results in an aged signal. Eventually, the artificial aged signal induced by PC@PLGA stimulates PrCR and prevents proinflammatory response and tissue damage, scale bar: 2 μm. Reproduced with permission from reference.[86] Copyright 2025, American Chemical Society.

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Despite these promising results, most existing systems function indirectly neutralizing inflammatory mediators or scavenging ROS rather than reprogramming neutrophil behavior at the transcriptional level. Moreover, their long-term safety, effect on host antimicrobial defense and potential to induce systemic immunosuppression remain insufficiently characterized. Future directions should emphasize temporally controlled nanotherapy aligned with the inflammatory phase, integrating multi-responsive platforms capable of NET degradation, redox modulation and immune signaling regulation. Such precise modulation could transform neutrophil-targeted nanotherapy from symptomatic relief to true disease interception.

Macrophages

Macrophages exhibit notable phenotypic plasticity and spatiotemporal heterogeneity throughout the course of pancreatitis.[87,88] In the early stage, injured PACs release monocyte chemoattractant protein-1 (MCP-1), which binds to CCR2 receptors on circulating monocytes and recruits them into pancreatic tissue, where they differentiate into proinflammatory M1 macrophages.[19] M1 macrophages recognize DAMPs via pattern recognition receptors such as TLR4, activating the NF-κB and MAPK signaling pathways.[89] This activation drives the secretion of proinflammatory cytokines, including TNF-α, IL-1β and IL-6, which exacerbate local inflammation and necrosis.[90] As inflammation resolves, macrophages gradually transition toward the anti-inflammatory M2 phenotype under the influence of IL-4/IL-13-STAT6 signaling and metabolic reprogramming. M2 macrophages promote tissue repair by releasing IL-10, TGF-β, and extracellular matrix components while facilitating efferocytosis to restore immune homeostasis.[91–94]

Given this central regulatory role, macrophage-centered nanotherapies have emerged as highly promising for restoring immunological balance in pancreatitis. Representative strategies include reducing recruitment,[95] modulating polarization,[85,96–99] restoring efferocytosis,[100] inhibiting PANoptosis[68,99] and regulating key signaling pathways.[29,101,102] For instance, β-glucan-conjugated PLGA nanoparticles (GNPs) loaded with amlexanox target macrophages via dectin-1 receptor-mediated endocytosis, inhibiting M1 polarization while promoting M2 differentiation through NF-κB inhibition and IL-4 upregulation (Figure 6A and B).[96] In another approach, the liposomal delivery of annexin A1 mRNA restored defective efferocytosis and suppressed the cGAS-STING pathway, thereby preventing PANoptosis and secondary necrosis (Figure 6C–E).[99] Lu et al developed FA@zein-CS, which targets inflamed pancreatic macrophages via CD44-CS binding and regulates them by responding to intracellular pH/GSH/ROS to release FA and zein degradation products for synergistic ROS elimination, thereby reducing oxidative stress and inflammatory factors.[103] These systems often integrate multiple functionalities, including ROS-responsive release, biomimetic membranes and hybrid metal-polyphenol coordination, to achieve precise nano-immunomodulation and enhanced therapeutic efficacy.[68,97,103,104]

The dynamic and context-dependent nature of macrophage polarization poses additional challenges for the temporal control and safety evaluation of nanotherapy. Moreover, the translation to clinical application is limited by uncertainty in off-target immune suppression and the lack of standardized models to evaluate macrophage–nanoparticle interactions. Future research should emphasize spatiotemporally adaptive systems capable of sensing local cytokine or redox gradients and responding with the programmed release of immunoregulatory payloads. Such intelligent nanotherapeutics could enable precise reprogramming of macrophages, offering durable resolution of inflammation and promoting tissue regeneration in pancreatitis.

Pancreatic Stellate Cell and Antifibrotic Nanotherapy

In a quiescent pancreas, pancreatic stellate cells (PSCs) contain lipid droplets and maintain extracellular matrix (ECM) homeostasis.[105,106] Upon exposure to stimuli such as alcohol and oxidative stress, PSCs transdifferentiate into myofibroblast-like cells that secrete large amounts of ECM components.[107] Key signaling axes driving activation include the TGF-β/Smad pathway, which potently induces collagen synthesis;[108] the PDGF/PDGFRβ and PI3K-AKT/MAPK pathways, which promote PSCs proliferation and migration;[109,110] and the NF-κB/JAK-STAT, which sustains inflammatory signaling.[111] The ROS and sphingosine-1-phosphate further amplify activation and stabilize the profibrotic phenotype.[111,112] Activated PSCs both overproduce matrix proteins (collagen I/III, fibronectin, and hyaluronan) and dysregulate matrix turnover via altered matrix metalloproteinase (MMP) balance, creating a feedback loop that recruits

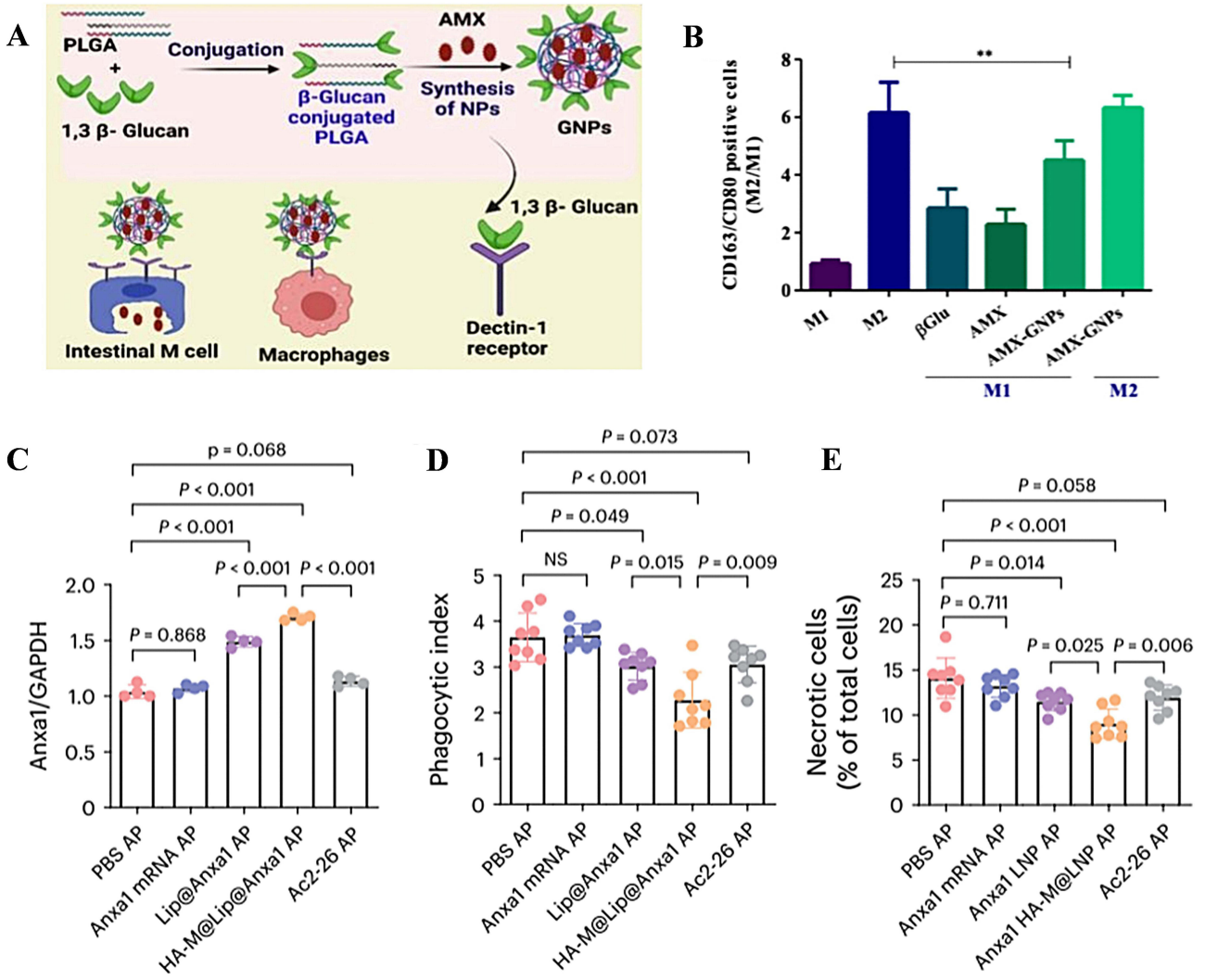

Figure 6 (A) Schematic and graphical representation of the synthesis of β-Glu-PLGA GNPs and their targeting mechanism to macrophage and **(B)** the ratio of CD163-and CD80-positive cells among M2 and M1 macrophages after drug treatment. Reproduced with permission from reference.[96] Graphs are presented as mean ± SEM, n = 3. **p < 0.01. Copyright 2025, Elsevier. **(C)** The quantification of Anxa1 expression and **(D)** Semiquantitative analysis of lesional efferocytosis and **(E)** the percentage of pancreatic tissue with necrosis. Reproduced with permission from reference.[99] Copyright 2024, Springer Nature.

profibrotic immune cells and progressively replaces parenchyma with fibrotic tissue.[113,114] Thus, PSCs activation is a pivotal, sustained driver of pancreatic fibrosis and a logical target for antifibrotic nanotherapy.

Nanotechnology offers a promising avenue for reprogramming PSCs and mitigating fibrosis through interference with multiple signaling and metabolic pathways. Current strategies focus mainly on inhibiting profibrotic activation, alleviating oxidative stress, and restoring ECM homeostasis. At the signaling pathway level, nanoparticles have been designed to block the PDGFRβ/ERK axis through pPB-mediated receptor competition,[115] modulation of the TGF-β/Smad cascade via the delivery of agents such as all-trans retinoic acid,[116] and the suppression of S1P/S1PR2 signaling using inhibitors such as JTE013.[117] Simultaneously, these nanomaterials mitigate oxidative stress using ROS-scavenging components[28,118,119] and restore ECM homeostasis by suppressing collagen cross-linking enzymes via siRNA delivery[28] (Figure 7A) or copper chelation.[116] Precise delivery to PSCs is achieved through both passive accumulation in fibrotic tissue and active targeting. Active targeting mechanisms rely on specific molecular recognition, including (1) vitamin A conjugation, which results in the overexpression of retinol-binding receptors on PSCs membranes (Figure 7B);[28] (2) PDGFRβ-targeting peptides that specifically interact with the upregulated PDGF on activated PSCs;[115] and (3) collagen-binding peptides that recognize exposed

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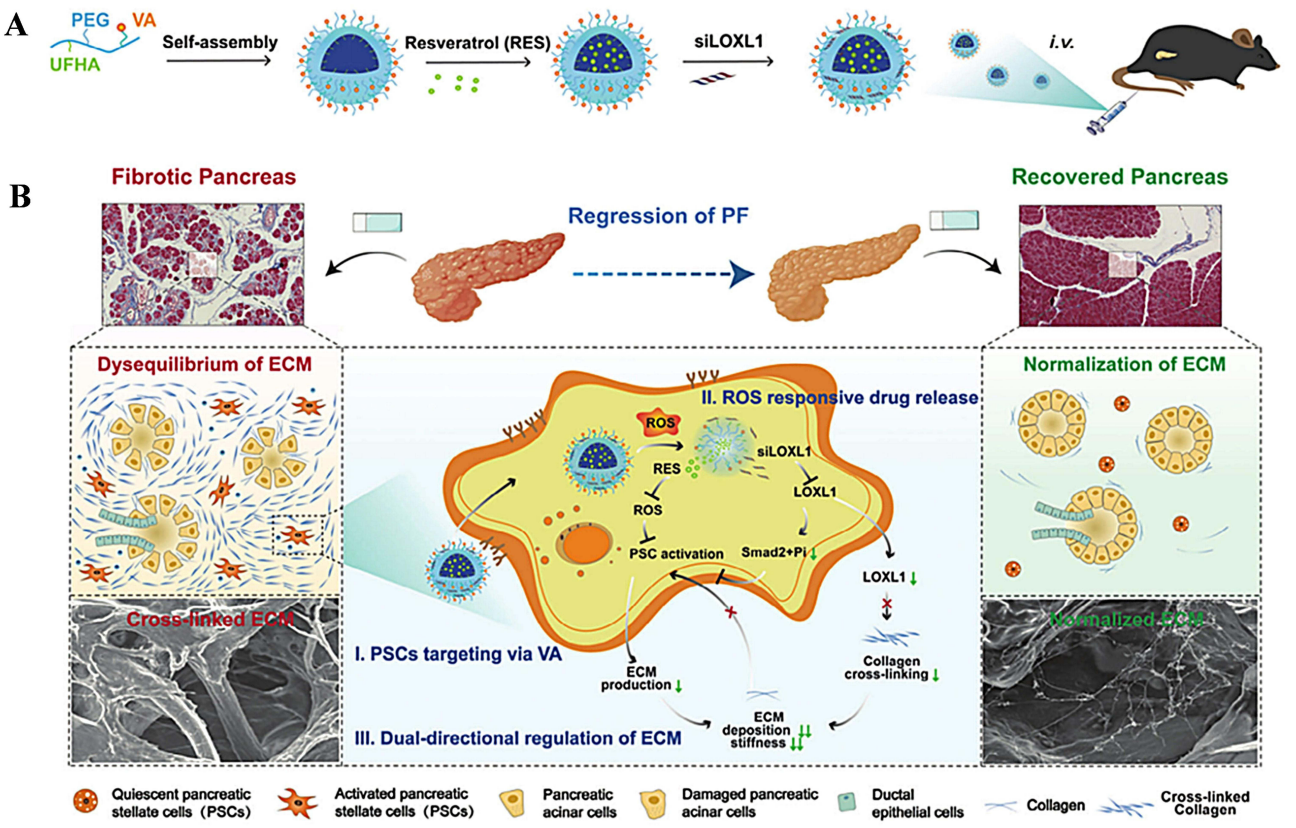

Figure 7 Schematic illustration of the preparation **(A)** and expected mechanism **(B)** of LR-SSVA toward ECM normalization for the regression of fibrosis. Reproduced with permission from reference.[28] Red crosses indicate inhibition, and downward arrows indicate decreased expression, activity, or ECM deposition. Copyright 2024, Wiley-VCH GmbH.

collagen fibers within fibrotic regions.[116,117] Biomembrane coatings are also implemented across diverse nanoplatforms and can be optimized for specific drug loading and release profiles.[115–120]

Nevertheless, challenges remain in achieving long-term and selective PSCs modulation. The phenotypic heterogeneity of PSCs across disease stages complicates targeting,[121] while the chronic nature of fibrosis requires sustained, safe exposure profiles that many nanomaterials have yet to demonstrate. Future research should focus on adaptive nanoplatforms capable of comodulating of metabolic and signaling cues and integrating antifibrotic drugs, redox regulators, and genetic payloads to achieve durable reversion of PSCs activation and restoration of pancreatic architecture.

Endothelial Cells and Nano-Targeted Strategies

Vascular endothelial cells play important roles in linking local pancreatic injury with systemic inflammation.[122] Pathological enzyme activation and cytokine release trigger endothelial activation, characterized by the upregulation of adhesion molecules such as E-selectin, ICAM-1, and VCAM-1, which mediate neutrophil and monocyte recruitment through rolling and transmigration.[123,124] Simultaneously, DAMPs and oxidative stress induce glycocalyx degradation and tight junction disruption, leading to vascular leakage and microcirculatory collapse.[123,124] Cold-inducible RNA-binding protein (CIRP) further destabilizes the endothelial barrier and promotes PANoptosis, a combination of pyroptosis, apoptosis, and necrosis-accompanied by mitochondrial dysfunction and ROS overproduction.[125–128]

Injured endothelium is characterized by the overexpression of adhesion molecules and enhanced vascular permeability, providing unique opportunities for nanoparticle accumulation and cell-specific targeting (Figure 8). Biomimetic nanocarriers, including neutrophil membranes,[129,130] macrophage membranes,[100,104] MSCs membranes[27] and platelet membranes,[131] have thus been engineered for the active recognition of and adhesion to inflamed endothelium. For instance, neutrophil membrane-coated nanoparticles target damaged endothelium through LFA-1/ICAM-1 and PSGL-1/P-selectin interactions, enhancing the

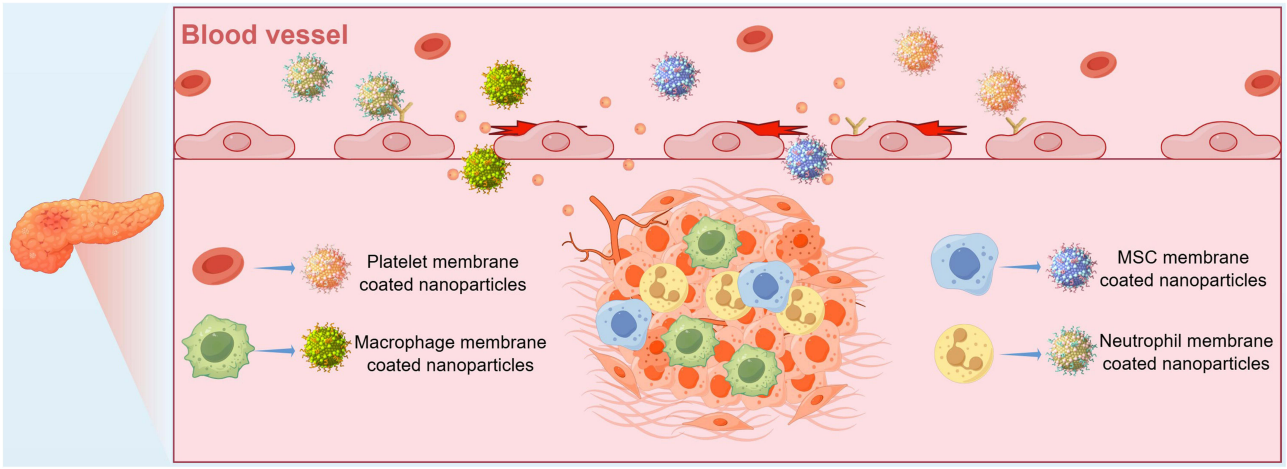

Figure 8 Schematic illustration of endothelial dysfunction and nanotechnology-based targets in pancreatitis. Pathological stimuli induce leukocyte infiltration and vascular leakage. Biomimetic nanoparticles coated with biomembranes actively adhere to inflamed endothelium via ICAM-1, P-selectin or GPIbα interactions, enabling targeted drug delivery. Figure created by Figdraw.

pancreatic accumulation of anti-inflammatory agents.[129,130] Similarly, the effects of MSCs membranes on natural inflammation-homing are mediated by the CXCR4/SDF-1 axis,[27] whereas platelet membrane-coated nanoparticles adhere to inflamed endothelium through GPIb-α and P-selectin.[131] Despite these advances, most strategies focus on targeting the inflamed endothelium for drug deposition rather than active repair of endothelial damage. The absence of nanotherapeutics designed to restore the glycocalyx or suppress CIRP/PANoptosis signaling remains a critical gap. Therefore, future development could prioritize multifunctional nanocarriers capable of sensing endothelial stress markers and sequentially releasing protective agents, such as antioxidants, tight junction stabilizers, or anti-CIRP peptides, while coordinating with targeted acinar and immune therapies.

Mesenchymal Stem Cells as Bioengineered Nanotherapeutic Platforms

Mesenchymal stem cells (MSCs) are multipotent stromal cells capable of differentiating into osteogenic and chondrogenic lineages while secreting diverse bioactive factors with anti-inflammatory and regenerative functions.[132,133] In recent years, the use of MSCs has emerged as a promising therapeutic approach for pancreatitis.[134,135] In general, MSCs can mitigate injury by suppressing proinflammatory cytokines, promoting regulatory T-cell expansion and releasing immunomodulatory mediators such as TSG-6 and prostaglandin E2.[136–138] These actions attenuate acinar necrosis and leukocyte infiltration in AP, whereas in chronic pancreatitis (CP), MSCs alleviate fibrosis by inhibiting TGF-β/Smad signaling and suppressing PSCs activation.[139,140]

In this review, we regard MSCs therapy as a nanotechnology-based approach primarily because of the application of MSCs-derived extracellular vesicles (EVs) and nanotechnology-based modifications. For instance, an MSCs-based exogenous nitric oxide (NO) delivery system was constructed by tethering ROS-responsive NO donor- loaded liposomes to MSCs with an MMP-responsive peptide linker, which acts as a cell booster to break through pathological barriers in treating CP (Figure 9A).[141] Hypoxia-preconditioned MSCs have been shown to transfer functional mitochondria through EVs, thereby restoring acinar metabolism and inhibiting MPTP opening, causing reduced necrosis and inflammation (Figure 9B–D).[142] Similarly, umbilical cord-derived MSCs display superior anti-inflammatory capacity; their derived exosomes can modulate inflammatory cytokines and inhibit acinar cell apoptosis by regulating Bax, Bcl-2, and caspase-3 expression in rats with traumatic pancreatitis.[143] Moreover, the incorporation of MSCs into decellularized hydrogels enhances their retention and engraftment in the pancreas, attenuating fibrosis and improving survival in murine models.[144] Current MSCs-based nanotherapies focus mainly on suppressing inflammation and inhibiting fibrosis; yet, optimizing in vivo persistence, immune compatibility, and targeted delivery remains crucial. Future work should emphasize engineered MSCs systems with surface nano-functionalization for guided homing and bioinspired EV mimetics to achieve controllable, reproducible, and clinically potential treatments for pancreatitis.

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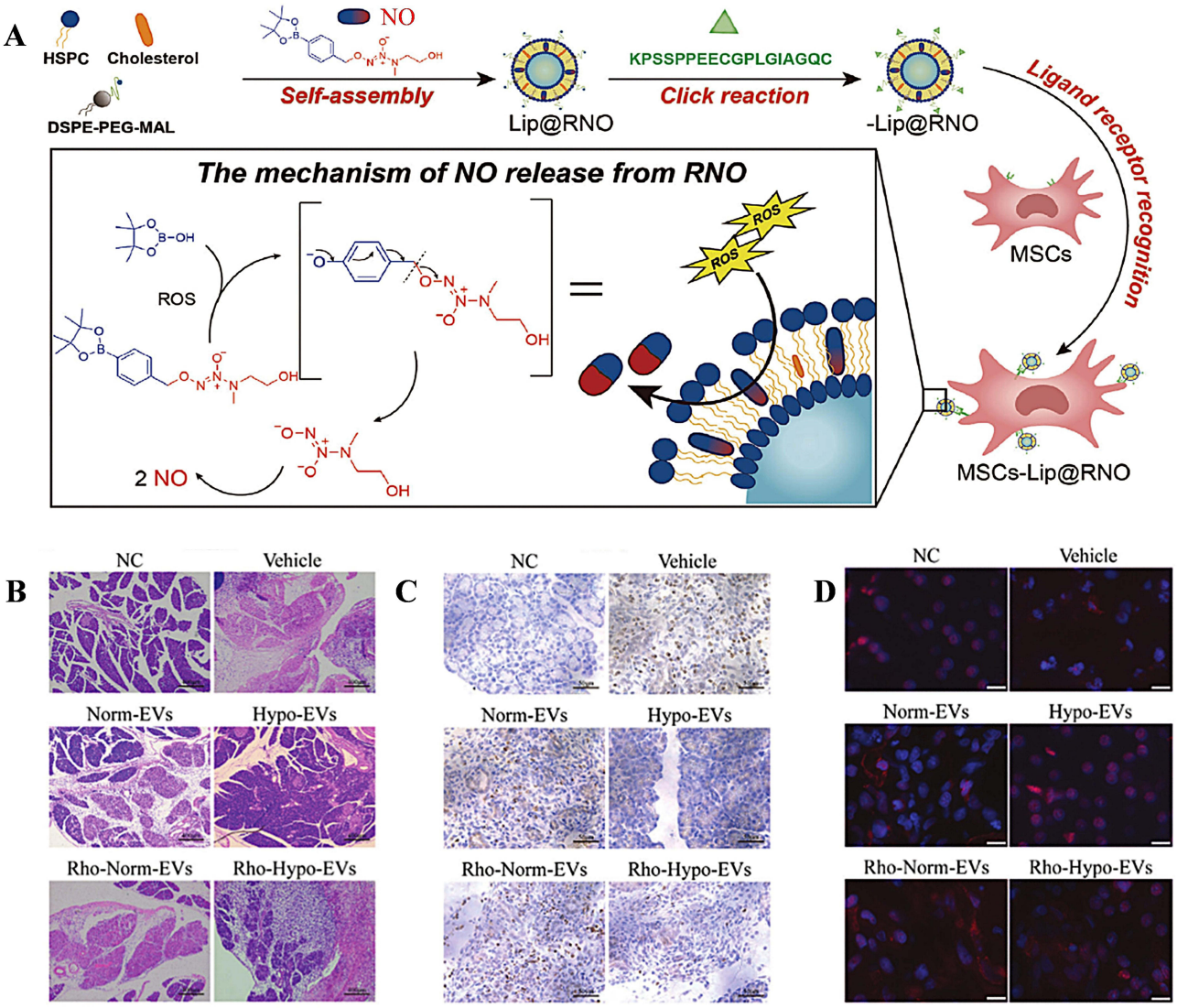

Figure 9 (A) Schematic illustration of the fabrication process of MSCs-Lip@RNO and its application in CP treatment. Reproduced with permission from reference.[141] Copyright 2025, Wiley-VCH GmbH. **(B)** H&E analysis of pancreatic slices, scale bar: 400 μm. **(C)** Immunostaining of pancreatic tissue for the neutrophil marker myeloperoxidase and **(D)** subcellular analysis of immunofluorescently labeled HMGB1 in pancreatic alveolar cells, scale bar: 50 μm. Reproduced with permission from reference.[142] Copyright 2023, Wiley-VCH GmbH.

Intercellular Crosstalk and Future Multicellular-Coordinated Nanotherapy

While we discussed the above cellular mechanisms and corresponding nanotherapeutic strategies from the perspective of individual cell types, pancreatic inflammation is driven primarily by intercellular crosstalk rather than isolated single-cell events in both AP and CP (Figure 10).[6,17,145] Injured PACs release DAMPs, chemokines and lipid mediators that activate resident and recruited immune cells, amplifying cytokine cascades and further promoting acinar injury.[145] Neutrophils exacerbate injury through ROS, proteases and the formation of NETs, which obstruct ducts, activate trypsinogens and aggravate PACs necrosis.[146] Activated macrophages polarize toward the proinflammatory M1 phenotype and secrete interleukin or tumor necrosis factor to promote PACs necroptosis and activate PSCs.[19] Endothelial injury further permits leukocyte extravasation and systemic inflammation to remote organs.[122] In addition, PSCs engage in bidirectional crosstalk with PACs and immune cells through paracrine signaling involving cytokines, SPHK1 and exosomal miRNAs, which amplifies PSCs activation, sustains inflammation and drives progressive fibrosis in CP.[17] This network reframes therapeutic goals from single-target inhibition to the interception of cross-cellular signaling nodes that promote inflammation or fibrosis.

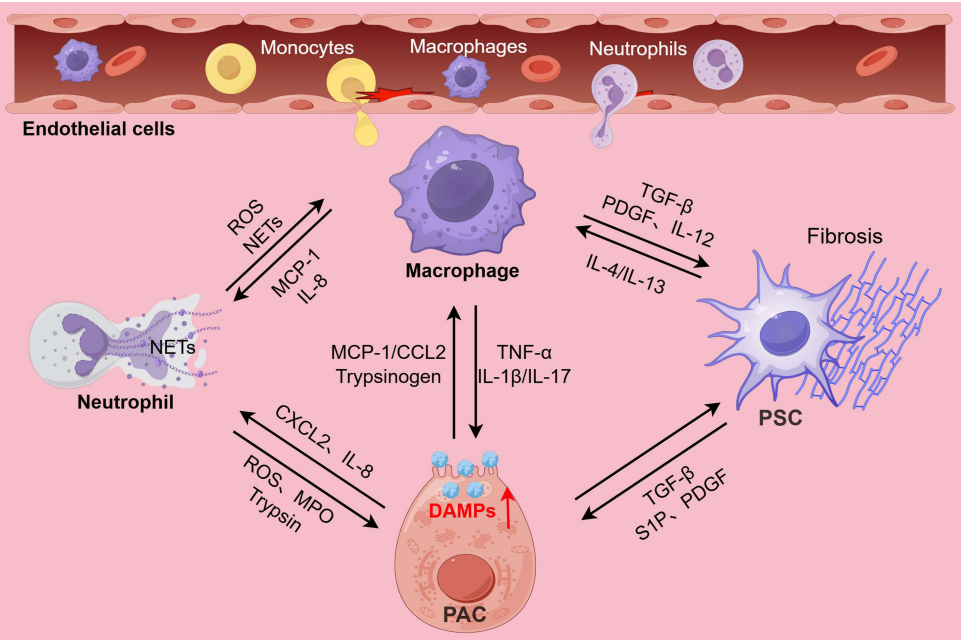

Figure 10 Schematic illustration of the intercellular crosstalk of different cells in pancreatic inflammation. Bold text is used to highlight cell types, and red upward arrows indicate increased release of DAMPs. Figure created by Figdraw.

There have been several recent reports of nanotechnology-based therapies that can be tailored to interrupt pathogenic intercellular circuits. For instance, Wang et al developed mitochondrial-targeted nanoparticles that scavenge mtROS in PACs, thereby preventing apoptosis and limiting mtDNA leakage.[29] This upstream control effectively blocks cGAS/STING activation in macrophages, suppresses M1 polarization, and reduces the secretion of proinflammatory cytokines. Beyond this strategy, numerous studies have shown that attenuating pathological events within PACs such as Ca^{2+} overload and mitochondrial dysfunction can mitigate immune cell recruitment and activation, ultimately reducing immune cell-driven inflammatory loops.[26,27] Nanoplatforms targeting immune cells or PSCs can also indirectly restore PACs function by suppressing inflammatory amplification.[83,116]

Despite these advances, current efficacy of multicellular nanotherapies largely stems from an extension of single-cell or single-target inhibition. It mainly relies on targeting upstream pathological events in one cell type to indirectly suppress downstream activation of other cellular events. However, because pancreatitis is driven by complex, interconnected cellular events, this design principle is not yet sufficient to block its amplifying inflammatory cascade. Therefore, future multicellular-coordinated nanotherapy could be further designed to regulate multiple cellular events in a spatiotemporally controlled manner, enabling sequential or simultaneous modulation of key pathological nodes within different cell populations. Such systems may incorporate staged targeting, stimulus-responsive activation, or multi-functional payloads to engage different cell populations during distinct phases in disease progression.

As a brief summary, Table 1 shows representative nanomaterials targeting distinct cell types and their mechanisms.

Limitations and Challenges of Nanotherapy for Pancreatitis

Despite significant progress in nanotechnology-based therapeutics for pancreatitis, several fundamental challenges still limit their application. One major issue arises from the intrinsic complexity of pancreatic inflammation, which is driven by dynamic interactions among different cell populations rather than by dysfunction of a single cell type. However, most currently reported nanotherapeutic strategies are designed to target individual cells, and therefore cannot fully interrupt the multicellular signaling networks that sustain inflammatory amplification and tissue injury. In addition, efficient delivery to the pancreas is restricted by the presence of the blood-pancreas barrier (BPB), a specialized vascular-stromal interface composed of endothelial cells, basement membrane structures, and surrounding extracellular matrix, which tightly regulates molecular transport into pancreatic tissue, leading to poor nanoparticle penetration and heterogeneous

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Table 1 Representative Nanotherapies Targeting Major Cell Types in Pancreatitis

Cell Types	Nanomaterials	Effects and Cellular Mechanisms	Ref.
Pancreatic acinar cells (PACs)	Mesoporous Prussian blue nanoparticle (HMPB NP)	Restoring Ca^{2+} homeostasis and inhibiting trypsin, further suppressing IRE1/XBP1 and PERK-ATF4-CHOP pathways	[26]
	Mesoporous organosilica nanoparticle (SL@M@Arg-MSNs @BA)	Trypsin-responsive release enables precise Ca^{2+} elimination while suppressing necrosis pathway: CaMKII-RIP3-MLKL	[27]
	BAPTA-AM liposome (BLN)	By eliminating Ca^{2+} overload, the Ca^{2+}-ROS-inflammatory cascade is blocked.	[58]
	Cerium-based MOF nanozyme (MOF808@BA@CAT)	Scavenging ROS and restoring Ca^{2+} homeostasis, autophagy (LC3/p62), and suppressing ER stress (GRP78-CHOP)	[59]
	Mesoporous manganese dioxide nanoparticle ($HMnO_2$ NPs)	Inhibiting MPTP opening and recovering ATP production, indirectly restoring Ca^{2+} homeostasis; Suppressing trypsin secretion via SSTR2-mediated inhibition of cAMP signaling	[61]
	Bio-heterojunction nanozyme (Mo_2 C-Au (MA))	Scavenging ROS combined with neutralizing enzyme, leading to disruption of the ROS-enzyme feedback loop and TLR4-ERK1/2-MAPK-MLCK signaling	[66]
	Biomimetic nanozyme (MPBZC)	Scavenging ROS via the SOD and CAT-like activities of Prussian blue and activating mitochondrial mitophagy through celastrol-induced Nur77 translocation	[67]
Neutrophils	CO-bound hemoglobin vesicle (CO-HbV)	Suppressing neutrophils infiltration by reducing pro-inflammatory cytokine and inhibiting ROS-driven inflammatory amplification	[82]
	Ly6G-conjugated MnO_2 nanoreactor (Pyp@APHM)	Scavenging ROS within neutrophils, thereby arresting neutrophil polarization and suppressing inflammation	[84]
	Biomimetic polymeric nanoparticle (PC@PLGA)	Targeting activated neutrophils and labels an artificial "aged" signal (calreticulin), thereby inducing PrCR to eliminate proinflammatory neutrophils	[86]
Macrophages	β-glucan PLGA nanoparticle	Targeting Dectin 1-expressing macrophages and enables trypsin-triggered release of Amlexanox to reprogram M1-to-M2 polarization via NF-κB inhibition	[96]
	Annexin A1 mRNA liposome	Restoring macrophage Annexin A1 expression to enhance efferocytosis and suppress PANoptosis-driven inflammatory signaling	[99]
	Polymeric nano-antioxidant (FA@zein-CS)	Targeting CD44-expressing macrophages and release of ferulic acid and antioxidants for ROS scavenging and inflammation suppression	[103]
Pancreatic stellate cells (PSCs)	Liposomal nano-drill system (LA-PC)	Inhibiting PDGF-BB/PDGFRβ-ERK signaling and inducing PSC quiescence to alleviate pancreatic fibrosis	[115]
	Liposomal nanoplatform (AT-CC)	Inhibiting PSC-mediated collagen production, and suppressing LOX-dependent collagen cross-linking	[116]
	Liposomal nanoplatform (JM-CC)	Inhibiting S1P/S1PR2-driven PSC activation	[117]
	Polymeric micelle (LR-SSVA)	Delivering resveratrol and siLOXL1 to eliminate ROS and inhibit LOXL1-mediated collagen cross-linking, thereby normalizing ECM homeostasis	[28]
Endothelial cells	Neutrophil membrane-coated PLGA polymeric nanoparticle	Targeting activated endothelium via leukocyte-like adhesion processes, and inhibiting NF-κB signaling	[129]
	Platelet membrane-coated mesoporous silica nanozyme (TMSN@PM)	Targeting injured endothelium via vWF-mediated adhesion, and scavenging excessive ROS	[131]

(*Continued*)

Table 1 (Continued).

Cell Types	Nanomaterials	Effects and Cellular Mechanisms	Ref.
Mesenchymal Stem Cells (MSCs)	MSC tethered NO liposome (MSCs-Lip@RNO)	Degrading fibrotic collagen via MMP activation, restoring microvascular perfusion and protecting MSCs from oxidative stress	[141]
	MSC-derived extracellular vesicle (EV)	Delivering functional mitochondria to acinar cells, thus restoring mitochondrial membrane potential and ATP production	[142]
	MSC-loaded hydrogel	Amplifying and sustaining paracrine secretion (HGF, TSG-6), and exerting anti-inflammatory and anti-fibrotic effects in pancreatitis	[144]
Multicellular intervention	Tungsten-based heteropolyacid nano-antioxidant (mTWNDs)	Scavenging mtROS in PACs, thereby preventing mtDNA release and suppressing macrophage cGAS-STING activation to disrupt the PAC-macrophage inflammatory crosstalk	[29]
	Neutrophil membrane-fused mitochondria (nMITO)	Targeting inflamed endothelium via β-integrin-ICAM 1 and transfer to PAC via TNTs; Restoring mitochondrial function and reducing macrophages and neutrophils infiltration	[83]

Abbreviations: BAPTA-AM, 1,2-bis (2-aminophenoxy) ethane-N,N,N,N′-tetraacetic acid; MPTP, mitochondrial permeability transition pore; ER, endoplasmic reticulum; SOD, superoxide dismutase; CAT, catalase; MOF, metal organic framework; PrCR, programmed cell removal; ECM, extracellular matrix; MMP, matrix metalloproteinase.

distribution.[29,147] Although strategies such as biomimetic coating, stimulus-responsive release, and inflammation-targeting ligands have been explored to improve pancreatic accumulation, overcoming the BPB in a controlled and reproducible manner remains a major obstacle for precise nanotherapy.

Moreover, the safety of most nanomaterials remains insufficiently understood, including potential toxicity, immunogenicity, and off-target effects associated with repeated administration or complex material compositions. The scalable and reproducible manufacturing of multifunctional remains technically challenging, and batch-to-batch variability may influence therapeutic performance as well as regulatory evaluation. Another important limitation is that commonly used animal models cannot fully reflect the pathological heterogeneity in human pancreatitis, which makes it difficult to accurately predict clinical efficacy. Furthermore, the regulatory approval of nanomaterials requires rigorous assessment of safety, pharmacokinetics, and long-term toxicity, posing additional challenges for multifunctional or biomimetic systems. As a result, most nanotherapies for pancreatitis are still confined to the preclinical stage. Therefore, future design should not only focus on improving therapeutic efficacy, but also on enhancing safety, scalability, and translational feasibility to enable clinically viable nanoplatforms.

Conclusions and Outlook

Pancreatitis constitutes a multifactorial and dynamically evolving inflammatory disease, in which dysregulated functions in epithelial, stromal, and immune cells drive tissue injury and systemic complications. Conventional therapeutic approaches aimed primarily at symptom control have long failed to address the underlying cellular and molecular dysfunctions. The recent convergence of cellular pathophysiology and nanotechnology-based therapeutics has reshaped pancreatitis management, offering new opportunities for precise intervention at both the cellular and molecular levels.

However, most currently reported nanotherapies primarily target a single cell type, which is often inadequate to effectively interrupt the amplifying inflammatory network. We therefore propose that future nanotherapy transition toward multicellular-coordinated regulation to modulate key signaling events in different cell populations. Several principles may guide the design of this nanotherapy. First, a hierarchical targeting strategy may be introduced, allowing nanoparticles to initially accumulate at sites of pancreatic inflammation and subsequently targeting cell populations with selectivity. Second, the activation should be governed by shared or cell-specific microenvironmental cues, such as the pH within the inflammatory milieu, calcium overload in acinar cells, thereby ensuring that its therapeutic functions are released only under appropriate pathological conditions. Third, loading multi-target drugs, such as berberine.[148] Finally, nanomaterials should adopt a modular architecture, such as layered shells, multi-compartment carriers, or differentiated release modules, to achieve a functional coupling among targeting, activation, and functions.

Notably, the pathological processes exhibit different temporal dynamics between AP and CP, which should be taken into account in the design principle of future nanotherapy. In AP, pancreatic injury is dominated by PACs stress, Ca^{2+} overload, mitochondrial dysfunction, and rapid immune activation. These features suggest that early interventions of multicellular-coordinated regulation should primarily target PACs and immune cells to prevent amplification of tissue damage. In contrast, CP characterized by persistent inflammation, activation of PSCs, extracellular matrix deposition, and progressive fibrosis, indicating that multicellular-coordinated strategies should shift toward modulation of PSCs and antifibrotic regulation.

While multicellular-coordinated regulation is promising, the inherent complexity of the required nanostructures often acts as a bottleneck for clinical translation. To promote clinical translation, future nanotherapy for pancreatitis should adopt a "translation-oriented design" strategy. At the material level, utilizing clinically validated biocompatible components to develop streamlined, modular platforms–integrating targeting, responsive activation, and therapy–can effectively orchestrate responses across diverse cell populations, while avoiding complex structures and components that hinder translation. On the translational front, it is essential to establish standardized evaluation frameworks, including consistent assessment of safety, pharmacokinetics, and therapeutic efficacy. In addition, more clinically relevant experimental models should be developed, and disease stage-specific study designs should be adopted to better reflect the heterogeneity of pancreatitis.

In conclusion, nanotechnology has transformed the therapeutic landscape for pancreatitis from symptom management to mechanism-driven, cell-targeted intervention. Despite the current translational challenge, the convergence of nanomaterial innovation, cellular biology and computational intelligence offers an unprecedented opportunity to achieve true precision therapy. Future success will rely on synergistic efforts across disciplines to develop intelligent, safe and clinically viable nanoplatforms. When realized, such advances may not only mitigate pancreatic inflammation but also reveal broader principles for treating complex inflammatory diseases through the use of cellularly informed nanomedicine.

Abbreviations

PACs, Pancreatic acinar cells; PSCs, Pancreatic stellate cells; AP, Acute pancreatitis; SIRS, Systemic inflammatory response syndrome; HMGB1, High mobility group box 1; DAMP, Damage-associated molecular pattern; ER, Endoplasmic reticulum; ATP, Adenosine triphosphate; SERCAs, Sarco/endoplasmic reticulum Ca^{2+}-ATPases; PMCAs, Plasma membrane Ca^{2+}-ATPases; SOCE, Store-operated calcium entry; STIM1, Stromal interaction molecule 1; MPTP, Mitochondrial permeability transition pores; ORAI1, ORAI calcium release-activated calcium channel protein 1; CTSB, Cathepsin B; mtDNA, Mitochondrial DNA; ROS, Reactive oxygen species; SOD, Superoxide dismutase; CAT, Catalase; UPR, Unfolded protein response; NF-κB, Nuclear factor-kappa B; NETs, Neutrophil extracellular traps; MCP-1, Monocyte chemoattractant protein-1; ECM, Extracellular matrix; CIRP, Cold-inducible RNA-binding protein; MSC, Mesenchymal stem cell; EVs, Extracellular vesicles; CP, Chronic pancreatitis; BPB, Blood-pancreas barrier; TNF-α, Tumor necrosis factor-alpha; BAPTA-AM, 1,2-Bis (2-aminophenoxy) ethane-N, N, N, N, N′-tetraacetic acid; TGF-β, Transforming growth factor beta; MMP, Matrix metalloproteinase; CHOP, C/EBP homologous protein; IRE1, Inositol-requiring enzyme 1; PERK, Protein kinase RNA-like endoplasmic reticulum kinase; ATF6, Activating transcription factor 6; XBP1, X-box binding protein 1; GRP78, Glucose regulated protein 78kD; IL, Interleukin; TLR4, Toll-like receptor 4; STAT6, Signal transducer and activator of transcription 6; ICAM-1, Intercellular cell adhesion molecule-1; VCAM-1, Vascular cell adhesion molecule 1; LFA-1, Lymphocyte function-associated antigen 1; PSGL-1, P-selectin glycoprotein ligand 1; CXCR4 CXC chemokine receptor type 4; SDF-1, Stromal cell-derived factor-1; GPIb-α, Glycoprotein Ibα; TSG-6, Tumor necrosis factor-α-stimulated gene 6; NO, Nitric oxide; cGAS-STING, Cyclic gmp-amp synthase–stimulator of interferon genes; SSTR-2, Somatostatin receptor 2; NLRP3, NOD-like receptor thermal protein domain-associated protein 3; ASK1, Apoptosis signal-regulating kinase; JNK, c-Jun N-terminal kinase; p38/MAPK, p38 mitogen-activated protein kinase; GSH, Glutathione; PDGF, Platelet-derived growth factor.

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.

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Disclosure

The authors report no conflicts of interest in this work.

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