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Original Research Article

Polystyrene Targeting Nanoparticles' Effect on Lung Injury in Severe Acute Pancreatitis

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Abstract

Background: Severe acute pancreatitis (SAP) has an acute onset and critical condition. It can mainly cause a pulmonary infection in patients. Whether polystyrene targeting nanoparticles play a role in lung injury in SAP remain unclear.
Objectives: To evaluate polystyrene targeting nanoparticles' (PTNs) effect on lung injury in severe acute pancreatitis (SAP).
Materials and Methods: Nanoparticles are characterized by a large unit surface area, high dispersion, tissue affinity, and adhesion, and are more conducive to bringing drugs into contact with tissues. In this study, SAP lung injury cells from alveolar lavage exfoliated cells under bronchoscopy were exposed to PTN to detect the proliferation of SAP lung injury cells, cycle and apoptosis, and nicotinamide adenine dinucleotide phosphate oxidase 2/reactive oxygen species/nuclear factor-kappa B (NOX2/ROS/NF-κB) expression.
Results: The compound PTN inhibited cell proliferation in SAP, and the degree of inhibition was positively correlated with the dose and the length of time. PTN inhibited the proliferation of SAP lung injury cells dose-dependently (5, 10, and 20 μmol/L) and arrested SAP lung injury cells in G2/M phase and increased cell apoptosis. In addition, PTN reduced NOX2, ROS, and NF-κB in SAP lung injury and downregulated interleukin-6, tumor necrosis factor-alpha, Janus kinase, signal transducer and activator of transcription, and interleukin-10 levels.
Conclusion: This study shows that polymer-targeted nano-drug systems regulate lung-damaged cell growth in SAP. PTN inhibits inflammation in SAP via regulation of NOX2/ROS/NF-κB.

Keywords

Lung injury, NOX2/ROS/NF-κB, nanoparticles, severe acute pancreatitis

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Introduction

Severe acute pancreatitis (SAP) has an acute onset and critical condition, which can cause organ failure in multiple organs throughout the body and has a high mortality rate. Common complications include inflammatory lung injury, which can cause respiratory system failure (Liu et al., 2023). It can mainly cause a pulmonary infection in patients. Treatments with symptomatic antibacterial and oxygen inhalation to improve ventilation only benefit some patients, and the mortality rate of patients remains high (He et al., 2022). Therefore, exploring the effective regulatory mechanism of acute pancreatitis lung injury is of great clinical significance for prevention and treatment. Pancreatic necrosis may lead to bacteremia, thus affecting intestinal mucosal barrier function and triggering a systemic inflammatory response, especially lung injury (Wu et al., 2021). Inflammation-related signaling pathways play an important role in acute pancreatitis lung injury, among which nicotinamide adenine dinucleotide phosphate oxidase 2/reactive oxygen species/nuclear factor-kappa B (NOX2/ROS/NF-κB) signaling is one of the earliest inflammatory signaling pathways discovered, and its molecular mechanism is highly conserved in different species (Ge et al., 2023; Sun et al., 2019; Xu, Luo et al., 2021). NOX2 activates NF-κB by producing ROS, thereby regulating inflammatory genes expression and participating in the amplification and maintenance of the inflammatory response (Mei et al., 2020). Abnormal activation of NOX2/ROS/NF-κB signaling will aggravate the pathological process of lung injury in acute

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pancreatitis, resulting in excessive release of inflammatory factors (such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF-α)) and further aggravating lung injury (Yang et al., 2021). Therefore, regulating the NOX2/ROS/NF-κB pathway may be a key strategy for treating acute lung injury pancreatitis.

In recent years, the targeting effect of nanomaterials has attracted attention to major diseases. As a targeted drug delivery system, polystyrene targeting nanoparticle (PTN) helps dissolve drugs that are difficult to dissolve (Li et al., 2020) and intervene in tissues and cells, easily penetrating cell membranes and epithelial cells barriers, thereby facilitating long-term drug delivery to target cells (Wang, Yuan et al., 2022) and reducing stimulation to other surrounding normal cells, thereby reducing toxic side effects. One of the characteristics of polymer targeting nanoparticles is that they have a large unit surface area and are dispersed. It has a high affinity and adhesion to the target tissue (Mei et al., 2020), which is more conducive to bringing the drug into contact with the target tissue (Hu et al., 2023), thus prolonging its circulation time in the body. Through the aggregation of PTN in target tissue cells, the therapeutic selectivity of drugs can be improved (Yang et al., 2021). The use of specific molecular targets to actively target tissues has become a research hotspot in targeted therapy in recent years (Zhu et al., 2021). However, the regulatory role of PTN and the NOX2/ROS/NF-κB pathway in SAP lung injury is unclear. Our results show that PTN can regulate the growth of SAP lung injury cells and regulate NOX2/ROS/NF-κB signaling through inflammatory effects. These findings provide important preclinical evidence and lay the foundation for clinical application.

Materials and Methods

Research Materials and Reagents Used

Polymer targeted nanoparticles (Xuchang Yuanhua Biotechnology Co., Ltd.); SAP lung injury cells were derived from alveolar lavage exfoliated cells under bronchoscopy in our hospital; culture medium (Gibco); fetal bovine serum (Invitrogen); cells apoptosis detection kit; reactive oxygen species detection kit; cycle detection kit; Western blot related reagents and antibodies NF-κB, signal transducer and activator of transcription (STAT), IL-10, IL-6, TNF-α, Janus kinase (JAK), glycogen synthase kinase-3 (GSK-3), and B-cell lymphoma-2 (Bcl-2). β-actin antibody was purchased from Cell Signaling Technology Company in the USA.

Cell Culture

The bronchoalveolar lavage solution was centrifuged (1,000 rpm, 10 min) to discard the supernatant, and cells were washed, resuspended, and cultured. When the degree of cell fusion reached more than 80%, they were digested and cultured by passage at a ratio of 1:3. They were divided into control and experimental groups (2.5, 5.0, and 10.0 μmol/L).

MTT Analysis of Cell Proliferation Inhibition Experiment

After the fusion of SAP, lung injury cells reached more than 80%. They were inoculated into culture plates, divided into groups, given different drug concentrations of polymer-targeted particles, set up duplicate wells, and continued to culture for 24, 48, or 72 h. MTT solution was added, and then dimethyl sulfoxide was added after washing, mixed thoroughly, and then the absorbance value was measured with a microplate reader.

The Propidium Iodide (PI) Method to Detect Cell Cycle Distribution

The PI method is a widely used technique in flow cytometry to detect and analyze cell cycle distribution. This method relies on the ability of PI, a fluorescent DNA intercalating dye, to bind stoichiometrically to the DNA content. Since the amount of DNA varies during different cycles, PI staining allows discrimination of cells in these phases based on their fluorescence intensity. Cells were first fixed and permeabilized. After staining with PI, the cells were analyzed using a flow cytometer, which measured the fluorescence intensity of each cell.

Apoptosis Analysis

After the fusion of SAP, lung injury cells reached more than 80%. They were inoculated into the culture plate, and 5 μL Annexin V-FITC and 5 μL PI were added to measure apoptosis by flow cytometry. The antibody was purchased from Cell Signaling Technology Company in the USA.

Western Blotting

The expression of inflammation-related proteins was detected. After the SAP lung injury, cells were treated with drugs for 2 h; cells were collected, processed with a RIPA kit, and protein was extracted. A BCA kit (Beyotime, Beijing, China) was used to prepare a protein concentration standard curve and detect protein concentration, in which proteins were added to sodium dodecyl sulfate-polyacrylamide gel electrophoresis (SDS-PAGE) for Western blot using primary antibody (dilution 1:1,000, CST, MA, USA) and secondary antibody (diluted at 1:1,000, CST, Danvers, MA, USA). The preprepared ECL solution was added to the membrane together with 20 μL of chromogenic reagent, then exposed in a chemiluminescence device, and the image was saved.

Data Processing

SPSS 27.0 analyzed the data and $p < .05$ indicated significance.

Results

Effect of PTN on Cell Proliferation

The morphology of PTN under electron microscopy is shown in Figure 1. Compared with the control group, PTN could dose-dependently inhibit severe acute respiratory syndrome at 24, 48, and 72 h. IC_{50} of pancreatitis lung injury cells is shown in Table 1.

Effect of PTN on Cell Cycle

PTN (5, 10, and 20 μmol/L) could dose-dependently cause lung injury in SAP after 24 h of administration. Cells are arrested in G2/M phase ($p > .05$). The specific characteristics are: reducing the distribution of cells in G1 phase and increasing the distribution in G2/M phase ($p < .05$), while affecting their distribution in S phase (Figure 2).

Effect of PTN on Cell Apoptosis in Lung Injury Caused by SAP

PTN induced apoptosis in a concentration-dependent manner (2.5, 5.0, and 10.0 μmol/L) for 24 h (Figure 3A) ($p < .05$).

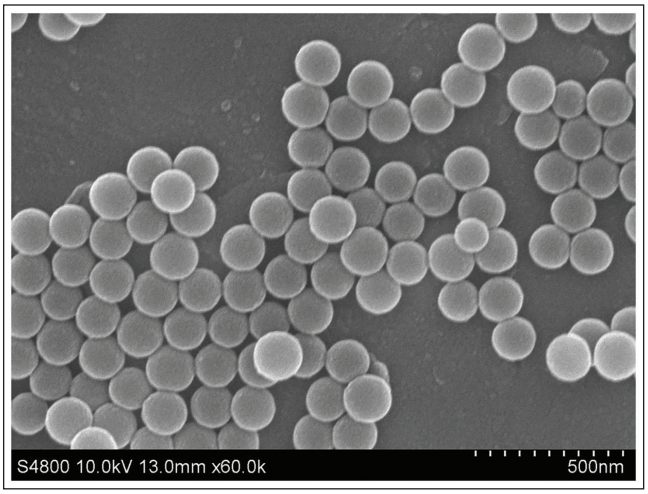


Figure 1. Electron Microscope Morphology of Polymer-targeted Nanoparticles.

Effects of PTN on NF-κB Protein Expression in Cells with SAP Lung Injury

Preliminary mechanism of action studies shows that PTN can simultaneously dose-dependently (5, 10, and 20 μmol/L) reduce intracellular NOX2, ROS, and NF-κB protein expression level in SAP lung injury cells (Figure 4).

Effects of PTN on NOX2/ROS/NF-κB Pathway-related Proteins in Lung Injury Cells Caused by SAP

Further study on the mechanism of action showed that PTN can significantly reduce the expression of inflammation-associated proteins in lung injury cells caused by SAP in a concentration-dependent manner (Figure 5).

Discussion

Lung injury in SAP is a difficult clinical problem. Inflammatory factors and inflammation-related pathways are involved in this disease (Owusu et al., 2018). By inhibiting inflammation-related pathways, inflammation can be effectively controlled, thereby reducing further aggravation of lung injury, which is of great help to the control and prognosis of the disease. At present, bronchoalveolar lavage is an important method to treat this disease. Obtaining lung-damaged cells through alveolar lavage and studying the mechanism of action of related drugs and small molecules on lung-damaged cells are important means and methods for this disease (Zhu et al., 2018). Accurate and effective targeted inhibition of inflammatory signaling pathways and pathway-related proteins is particularly critical in controlling the pathophysiological mechanisms of lung injury in pancreatitis (Wang, Liu et al., 2022; Wu et al., 2018).

The inflammatory cascade reaction refers to the process in which lysosomes and inflammatory vesicles are used to degrade their own damaged organelles and macromolecules. It is a method of cell necrosis and apoptotic programmed cell death (Kong et al., 2021). Due to the anti-inflammatory resistance, the body's response directly determines the body's stress situation. In recent years, researchers have continuously confirmed the existence of inflammatory cascade reactions in different SAP lung injury models through transmission electron microscopy, protein detection, and other methods (Hu et al., 2022). NOX2/ROS/NF-κB signaling participates in various inflammation-related diseases and its role in SAP

Table 1. Effects of Polyethylene Targeting Nanoparticles on Cell Proliferation in Severe Acute Pancreatitis (SAP) Lung Injury.

Concentration/time	0	1.25 (μmol/L)	2.50 (μmol/L)	5.0 (μmol/L)	10.0 (μmol/L)	20.0 (μmol/L)	40.0 (μmol/L)
24 h	100%	95.47%	89.52%	78.32%	70.23%	45.92%	23.35%
48 h	100%	93.26%	79.33%	64.83%	45.67%	39.16%	22.72%
72 h	100%	92.17%	62.51%	43.67%	38.74%	23.63%	21.24%

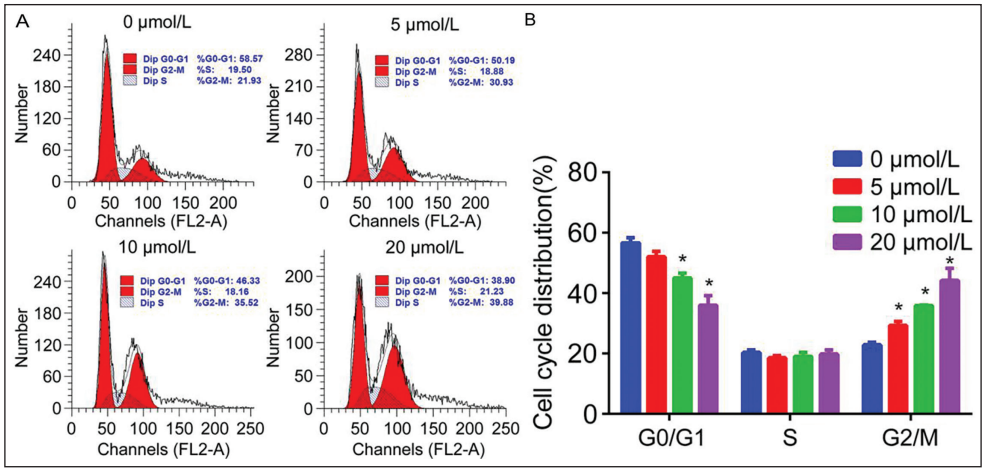


Figure 2. Effect of Polystyrene Targeting Nanoparticle (PTN) on Cell Cycle Distribution in Lung Injury Caused by Severe Acute Pancreatitis (SAP) ($x \pm SD$, $n = 3$): 24 h After Administration, PTN Can Dose-dependently Reduce the Risk of SAP. Inflammatory Lung Injury Cells Were Blocked in the G2/M Phase ($p > .05$).

Note: *$p < .05$ compared with the control group.

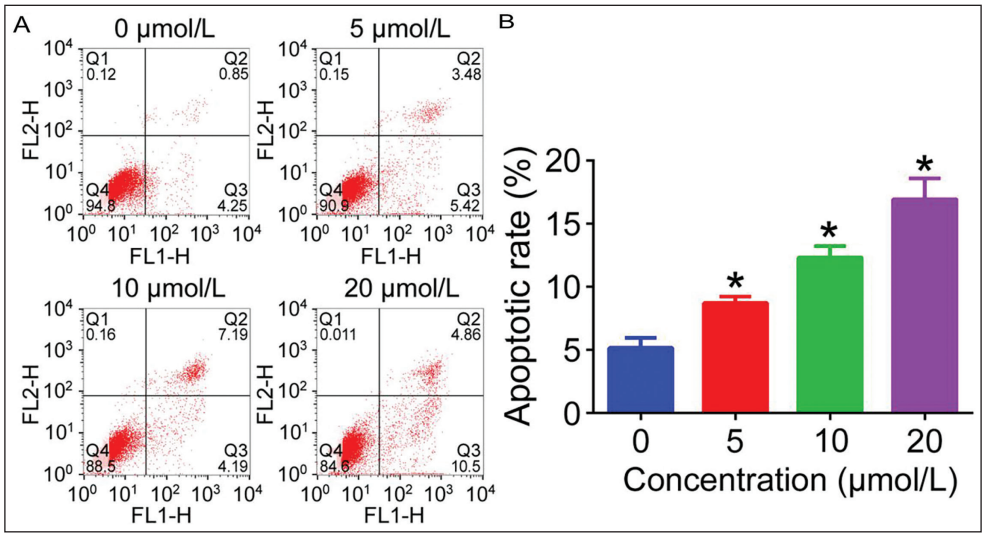


Figure 3. Effect of Polystyrene Targeting Nanoparticle (PTN) on the Apoptosis Rate of Lung Injury Cells in Severe Acute Pancreatitis (SAP) (mean ± SD, $n = 3$): PTN Can Increase the Severity of SAP in a Concentration-dependent Manner 24 h After Administration. Apoptosis Rate of Lung Injury Caused by Acute Pancreatitis.

Note: *$p < .05$ compared with the control group.

lung injury is particularly critical. However, it is still unclear how the NOX2/ROS/NF-κB signaling pathway can regulate cellular inflammation and the transformation of inflammation. SAP lung injury causes cytokine secretion, cell repair disorders, and lung tissue ischemia and hypoxia (Wang, Li et al., 2022). We first examined the effects of PTN on total, cytoplasmic, and nuclear NF-κB in cells with SAP lung injury. The results showed that NF-κB in these three locations was significantly reduced. This shows that the expression and intracellular distribution of NF-κB are regulated by PTN. Subsequently, the detection results of the reduced expression of NF-κB target proteins STAT and IL-10 also showed that PTN indeed inhibited the conduction of the NOX2/ROS/NF-κB pathway.

PTNs are currently the benchmark for tissue-targeted therapy and are also the most cutting-edge biomaterials. Preliminary results for tissue-targeted drug delivery show that they can penetrate intercellular gaps and barriers and improve drug targeting and cellular uptake function, which helps in drug absorption and targeted treatment (Zhang et al., 2022). PTN can increase the fluidity of target tissue cell membranes, interfere with protein metabolism, cell cycle regulation, and signal transduction in target tissue cells, thereby inhibiting or killing target tissue cells (Yang et al.,

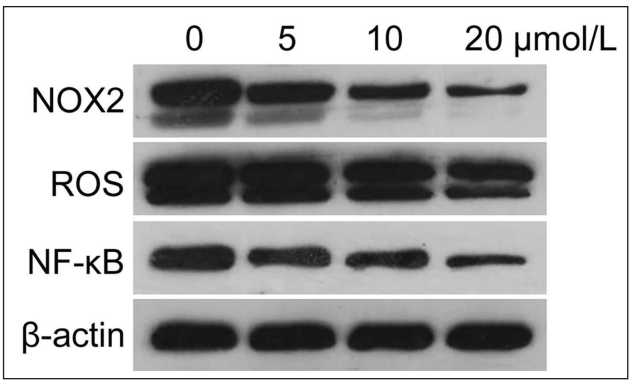


Figure 4. Effect of Polystyrene Targeting Nanoparticle (PTN) on Nuclear Factor-Kappa B (NF-κB) Protein in Cells With Severe Acute Pancreatitis (SAP) Lung Injury: Western Blotting Test Shows That PTNs Have an Effect on Nicotinamide Adenine Dinucleotide Phosphate Oxidase 2 (NOX2), Reactive Oxygen Species (ROS), and Nuclear Factor-Kappa B (NF-κB) in Cells with SAP Lung Injury. κB Protein Expression Was Significantly Downregulated.

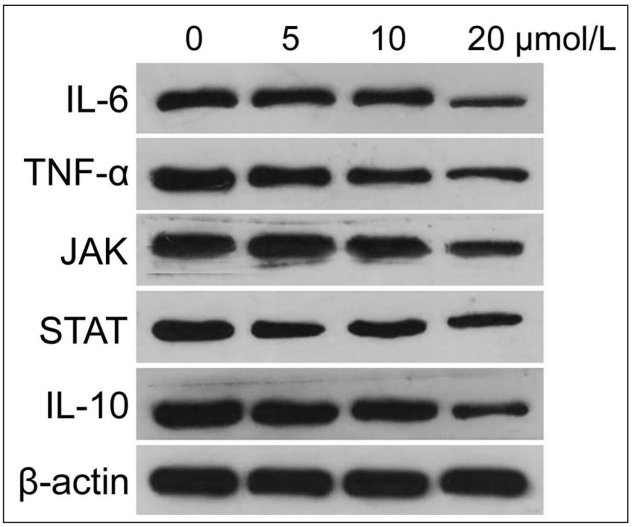


Figure 5. Effect of Polystyrene Targeting Nanoparticle (PTN) on Wnt/Nuclear Factor-Kappa B (NF-κB) Pathway-related Proteins in Severe Acute Pancreatitis (SAP) Lung Injury Cells ($x \pm SD$, $n = 3$): Western Blotting Test Results Show That PTN Can Decrease the Protein Expression of Inflammation-related Genes Interleukin-6 (IL-6), Tumor Necrosis Factor-alpha (TNF-α), Janus Kinase (JAK), Signal Transducer and Activator of Transcription (STAT), and Interleukin-10 (IL-10).

2019). PTN can also exert a competitive antagonistic effect, causing target tissue epithelial cells to lose their intercellular adhesion ability, inducing expression of anti-inflammatory and anti-target tissue factors, inhibiting target tissue growth, and promoting cell apoptosis. Studies have shown that PTN can reduce cell-endothelial cell adhesion (Xu, Wang et al., 2021).

The regulation of related signaling pathways is also an important way to regulate inflammation. NOX2/ROS/NF-κB signaling is involved in the pathological processes of various inflammations, cell proliferation, and apoptosis (Hegyi et al., 2020; Xu et al., 2023). It can accumulate in the nucleus of tissue cells, thereby forming inflammatory transcription cofactors to upregulate the expression of its target genes IL-6, TNF-α, and others, ultimately leading to lung injury in SAP (Wu et al., 2022; Zhao et al., 2023). In order to clarify the specific process of inhibiting the NOX2/ROS/NF-κB pathway, this study also detected related proteins IL-6, TNF-α, JAK, and NOX2-1 that affect the degradation and nuclear import of NF-κB. Activation of NOX2/ROS/NF-κB signaling can inhibit glycogen synthase kinase 3β activity and increase intracellular NF-κB levels. The increase in NF-κB levels causes NF-κB to enter the nucleus and bind the transcription factor, inducing the expression of downstream target genes (Ni et al., 2021). Although we have explored the mechanism *in vivo*, whether we can show the same results *in vitro* needs more verification. Next, we will elaborate on the model mice. The results show that PTN may reduce NF-κB through the following steps: reducing IL-6 and TNF-α expression.

Conclusion

In summary, PTNs inhibit the inflammatory response of SAP lung injury by directly regulating the NOX2/ROS/NF-κB signaling pathway. Our study suggests that PTNs have significant inflammatory regulatory effects on lung-damaged cells caused by SAP. Our research provides important evidence for therapeutic prospects in SAP lung injury. However, this study also has some shortcomings: (a) This study is an *in vitro* cell experiment, and its effect *in vivo* still needs to be verified. In future, the pharmacodynamics and pharmacokinetic properties of the nanoparticles *in vivo* should be further investigated through animal model experiments. (b) NOX2/ROS/NF-κB signaling has a complex regulatory network in inflammatory response. This study only preliminically explored part of the mechanism of this pathway, and further studies on other related signaling molecules and pathways are needed in the future to reveal the anti-inflammatory mechanism of PTN fully. (c) There are differences in inflammatory response and drug sensitivity among different patients, and further studies on the efficacy differences of PTN in different individuals are needed in the future to develop personalized treatment plans. In conclusion, this study provides a basis for the application of PTN in treating acute pancreatitis lung injury, but further studies are needed to overcome the existing limitations and promote their transformation into clinical applications.

Abbreviations

JAK: Janus kinase; NF-κB: Nuclear factor-kappa B; NOX2: Nicotinamide adenine dinucleotide phosphate oxidase 2; ROS: Reactive oxygen species; STAT: Signal transducer and activator of transcription; TNF-α: Tumor necrosis factor-alpha.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical Approval

This study was approved by the Ethics Committee of The Third Affiliated Hospital of Southern Medical University.

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Informed Consent

Not applicable.

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