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Commentary

Commentary on "Ultrasmall polyvinylpyrrolidone-modified iridium nanoparticles with antioxidant and anti-inflammatory activity for acute pancreatitis alleviation"

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Abstract

The purpose of this paper is to briefly summarize our team's recent studies on ultrasmall PVP-modified iridium nanoparticles (IrNP-PVP) for the treatment of acute pancreatitis. In an animal model of acute pancreatitis, IrNP-PVP expressed significant antioxidant and anti-inflammatory effects. This commentary will focus on previous research by our team on this novel material and discuss future research directions and possible challenges.

Keywords: Iridium nanoparticles, Acute pancreatitis, Antioxidant, Anti-inflammatory, Nanomedicine

Introduction

Acute pancreatitis (AP) can lead to severe body damage, including a systemic inflammatory response and multiorgan failure [1,2], and current therapies rely heavily on symptomatic treatment and supportive care, with a lack of targeted therapeutic strategies for specific pathologic processes [3,4]. In addition, existing treatment strategies are limiting in preventing the transformation of acute pancreatitis into a chronic form or reducing the risk of complications, highlighting the urgent need to develop more effective treatments and early interventions [5-7]. Promising applications of nanoenzymes in medicine include efficient bioassay tools, advanced drug delivery systems, and antimicrobial, anti-inflammatory and antioxidant agents [8-12]. They are able to mimic natural enzyme functions to treat diseases such as inflammatory disorders, while optimizing their design to enhance selectivity and biocompatibility [13-16]. However, challenges including safety assessment and evaluation of immune response need to be overcome before moving to clinical applications [17,18]. Recently, our research team published an article on ultrasmall polyvinylpyrrolidone-modified iridium nanoparticles that have significant antioxidant and anti-inflammatory effects and demonstrate therapeutic potential in an acute pancreatitis model. The purpose of this article is to summarize the core findings and challenges encountered in the original study, and to discuss the subsequent progress of our research efforts.

Discussion and Analysis

Original research

We synthesized a new ultra-small nano-enzyme IrNP-PVP by a one-step process, which is a promising artificial enzyme agent for the treatment of acute pancreatitis. We found that IrNP-PVP possesses multi-enzyme mimetic properties with catalase and peroxidase activities, which can effectively scavenge a variety of harmful free radicals such as H_2O_2, $\cdot O_2$, ·OH, and DPPH·, as well as scavenge ROS and RNS. Meanwhile, due to its excellent antioxidant and anti-inflammatory properties, IrNP-PVP showed a significant effect on the H_2O_2-induced oxidative damage in RAW 264.7 cells. Additionally, it exhibited significant cytoprotective effects against the LPS-induced inflammatory response in RAW 264.7 cells. *In vitro* cellular assays have demonstrated that IrNP-PVP has excellent clearance of ROS and reduction of cellular inflammatory factor levels. In addition, the ultra-small nanoenzymes IrNP-PVP show good biocompatibility and excellent hemocompatibility, and ICP-MS experiments have shown that they rapidly accumulate in pancreatic tissues and are rapidly eliminated with minimal potential impact on the organism. Moreover, the anti-inflammatory and antioxidant effects of IrNP-PVP on AP were further verified by HE staining of pancreatic tissues, serum inflammatory factor assay, and ROS staining of pancreatic tissues. Electron microscopic observation of mitochondrial and endoplasmic reticulum changes in pancreatic follicular cells and validation of mitochondrial function elucidated the therapeutic effect of the ultramicro nano-enzyme IrNP-PVP on AP. Our study promotes the possibility of further clinical applications of nanoenzymes in biomedical therapeutics and research, making iridium-based nanoenzymes with multiple enzyme mimetic properties therapeutic agents for the clinical treatment of oxidative stress and inflammation.

Research progress

An in-depth assessment of the physicochemical properties, stability, and behaviour of IrNP-PVP in different biological environments is essential to ensure its use as an efficient and safe nanotherapeutic agent. The diversity of biological environments - including different pH values, ionic strengths, protein concentrations, and enzyme activities - has a significant impact on the stability and functionality of nanoparticles [19-22]. For example, small changes in pH may affect the charge, solubility, and aggregation state of nanoparticles, which in turn alters the way they interact with cell membranes and affects their distribution and drug release behavior in the organism [23-25]. Specifically, the particle size and surface modification of IrNP-PVP determine its transport efficiency in the blood and intercellular matrix, as well as its ability to evade recognition and clearance by the immune system [26]. Therefore, it is particularly important to assess the stability and biocompatibility of these nanoparticles under specific conditions such as simulated blood, tumor microenvironments and inflammatory regions through laboratory studies that mimic the *in vivo* environment [27,28]. These studies require not only measurements involving chemistry and physics, such as dynamic light scattering (DLS) and transmission electron microscopy (TEM) to determine particle size and morphology, but also biological tests, such as cytotoxicity assays, cell phagocytosis assessments, and interaction analyses at the molecular level, in order to gain a comprehensive understanding of the biological behavior of IrNP-PVP [29,30].

In addition, long-term stability studies are equally indispensable, considering that nanoparticles may undergo physical and chemical changes in the biological environment over time [31]. This includes assessing the tendency of nanoparticles to aggregate during storage and *in vivo* circulation, the rate of release of active ingredients, and possible degradation products, which are directly related to their efficacy and safety [32,33]. To this end, meticulous monitoring of the chemical stability and morphological changes of IrNP-PVP using advanced analytical techniques, such as high-performance liquid chromatography (HPLC), mass spectrometry (MS), and atomic force microscopy (AFM), is an indispensable step [34-36]. These comprehensive characterization studies will not only optimize the design of IrNP-PVP and improve its performance in clinical applications, but also facilitate the standardization of its safety assessment process and accelerate its translation to the clinic [37,38]. Such a research approach ensures that all key factors related to the clinical application of nanoparticles are taken into account at the early stage of their development, laying a solid foundation for their successful application in healthcare [39,40].

Our study demonstrated that the ultrasmall nanoenzyme IrNP-PVP is safe and effective for *in vivo* application in mice, with antioxidant and anti-inflammatory effects. Therefore, there are potential prospects that can be used to treat various ROS and inflammation-related diseases such as acute kidney injury, acute liver injury, diabetic wounds and pancreatitis in a clinical setting [41-43]. Further, exploring the potential of IrNP-PVP nanoparticles in combination with other therapeutic drugs or treatments for the treatment of acute pancreatitis or other inflammatory diseases opens up a promising new pathway aimed at improving therapeutic efficiency and reducing adverse effects [44,45]. In this therapeutic strategy, IrNP-PVP not only serves as a platform for drug delivery and enhances the targeting and therapeutic efficacy of specific drugs but may also directly contribute to inflammation alleviation and tissue repair through its unique anti-inflammatory effects. For example, in the treatment of acute pancreatitis, IrNP-PVP could be designed as a carrier to carry drugs with potent anti-inflammatory effects to directly target damaged pancreatic tissues, thereby reducing systemic side effects and enhancing the concentration and persistence of therapeutic agents in the inflamed region. In addition, the combined use of IrNP-PVP and other therapeutic modalities, such as immunomodulators or biologics [46,47], can achieve a more comprehensive therapeutic effect by working together on the inflammatory pathway through multiple mechanisms. This multimodal therapeutic strategy not only contributes to the rapid relief of the acute inflammatory response, but also prevents, to some extent, the development of post-inflammatory fibrosis or other long-term complications [48]. Achieving this goal requires in-depth studies of IrNP-PVP interactions with various drugs and therapeutic approaches to ensure that the safety and efficacy of the combination are maximized. In summary, by combining IrNP-PVP with other therapeutic drugs or approaches, we can not only enhance the effectiveness of treating acute pancreatitis or other inflammatory diseases, but also provide patients with safer and more personalized treatment options. Further research in this area will provide valuable insights and new therapeutic tools for clinical care. Currently, based on the existing findings, our team is trying to combine IrNP-PVP with cellular vesicles and other combination therapies for inflammatory diseases. In our follow-up studies, we have made some important discoveries, for example, IrNP-PVP is also effective in the treatment of acute liver injury, infected wounds and so on.

However, we need to further explore the potential toxicity and immunogenicity of IrNP-PVP nanoparticles. In delving into the potential toxicity and immunogenicity of IrNP-PVP nanoparticles for medical applications, we must employ a multidimensional assessment strategy that involves not only rigorous laboratory testing but also complex biological modelling studies [49,50]. The aim of this comprehensive assessment is to reveal the mechanism of IrNP-PVP interaction with biological systems and its safety under different physiological conditions. A critical first step in the toxicity assessment is to perform an acute toxicity assay [51,52], which is implemented by administering a single high dose of IrNP-PVP to a model organism (usually a mouse or rat) over a short period of time. This experiment is designed to rapidly identify any immediate health risks or biological responses, such as cell death, organ damage, or acute inflammatory responses. Subsequently, chronic toxicity studies will evaluate IrNP-PVP for long-term or repeated exposures, which are more closely aligned with real-world applications in clinical therapy and can reveal long-term cumulative effects such as chronic inflammation, organ function decline, or risk of cellular degeneration [53]. The assessment of immunogenicity is equally complex and requires a detailed analysis of whether IrNP-PVP triggers a specific immune response, including antibody production or a cell-mediated immune response [54,55]. This requires an initial screening *in vitro* using human or animal immune cells, followed by *in vivo* validation by animal models to monitor for possible allergic reactions or autoimmune pathologies [56,57]. This assessment focuses not only on the immune activation capacity of IrNP-PVP itself, but also on the complex immune effects that may be induced when it is loaded. Through these comprehensive and detailed studies, scientists were able to systematically identify and assess the risks that IrNP-PVP may encounter in practical medical applications, providing a solid scientific basis for preclinical safety evaluation. Such studies not only help to optimize the design and application of IrNP-PVP, but also provide an important guarantee to protect patient safety and improve therapeutic efficacy.

The next work will focus on the signaling pathways and mechanisms of action by which IrNP-PVP's exert anti-inflammatory and antioxidant effects. Further investigation of the antioxidant and anti-inflammatory mechanisms of IrNP-PVP nanoparticles is essential to optimize their design and expand their range of medical applications. By delving into how IrNP-PVP affects intracellular signaling pathways and molecular mechanisms, we can gain a more precise understanding of the underlying causes of its anti-inflammatory and antioxidant effects. NF-κB is a transcription factor that plays a key role in regulating inflammatory responses. In its inactivated state, NF-κB binds to the inhibitory protein IκB in the cytoplasm. When cells are stimulated (e.g., by inflammation), IκB is phosphorylated and degraded, releasing NF-κB, which subsequently enters the nucleus and promotes the expression of inflammation-associated genes [58-62]. IrNP-PVP may inhibit the activation and intranuclear translocation of NF-κB by inhibiting the phosphorylation of IκBα and preventing its degradation. This reduces the production of inflammatory mediators such as tumor necrosis factor α (TNF-α), interleukin 1β (IL-1β) and interleukin 6 (IL-6), resulting in anti-inflammatory effects [63-65]. ROS is produced during cellular metabolism, and an excess of ROS can lead to oxidative stress and damage to cellular structures, including lipids, proteins, and DNA [66]. This is a many of the inflammatory and degenerative key pathological processes [67,68]. IrNP-PVP may have specific surface properties that allow it to scavenge ROS directly or reduce ROS levels by activating intracellular antioxidant enzymes such as superoxide dismutase (SOD) and glutathione peroxidase (GPx) [69,70]. This mechanism helps to reduce oxidative stress and protect cells from damage [71,72]. These speculations help us to further investigate the antioxidant and anti-inflammatory mechanisms of IrNP-PVP. It is also crucial to understand the behavior of IrNP-PVP in different biological environments, such as its distribution and metabolism in blood, inflammatory tissues or specific cell types. This information will help scientists to design more effective and safer nanoparticles that are targeted to improve their anti-inflammatory and antioxidant properties. Ultimately, these mechanistic insights could guide the development of novel therapeutic strategies for a variety of diseases, including autoimmune diseases, neurodegenerative disorders, cardiovascular diseases, etc., in which the antioxidant and anti-inflammatory properties of IrNP-PVP may play a key role [73-75]. These efforts will not only fill the existing knowledge gaps, but also further clarify whether these findings can be generalized to the treatment of other diseases. This will contribute to clinical translation and application.

Future Challenges

The clinical translation of IrNP-PVP is not only a technical and scientific challenge, but also a multidimensional strategic issue that requires fine planning and optimization on many fronts. Firstly, scaling up production means that a balance must be found between ensuring product quality while maintaining cost-effectiveness. Every step of the production process, from the selection of raw materials to the packaging of the final product, needs to take efficiency and environmental impact into account. This requires not only innovative production technologies, but also continuous improvement of existing processes.

On the regulatory front, the demonstration of the safety and efficacy of IrNP-PVP, as a novel nanomaterial, is critical to obtaining regulatory approval. This involves not only complex preclinical study design, but also transparent and detailed reporting of preclinical data [37,76]. The complexity of the regulatory pathway requires development teams to be familiar not only with international standards but also with the specific requirements of the target market [77,78]. In addition, ethical issues of nanotechnology, such as potential long-term environmental impacts and patient privacy concerns, need to be fully considered and addressed during the R&D process [79-81].

In terms of clinical trial design, choosing the right endpoint indicators and ensuring sufficient patient participation are key challenges [82]. Targeting IrNP-PVP for specific applications, such as the treatment of pancreatitis, may mean that innovative clinical trial designs need to be used to accurately assess its efficacy. In addition, transparency and communication during the patient recruitment process to ensure that patients fully understand the potential risks and benefits of the trial is essential to maintain public trust and obtain ethical approval [83,84].

In conclusion, the clinical translation of IrNP-PVP is a process involving complex scientific, technical, ethical, and regulatory challenges. It requires a multidisciplinary team working closely together to find innovative solutions while ensuring public and environmental responsibility. As the research progresses and the technology matures, the potential of IrNP-PVP to improve patient

outcomes becomes a reality, paving the way for future medical innovations.

Summary

Although nanoenzymes are able to mimic natural enzymes and offer advantages such as anti-inflammatory and antioxidant properties, their application still faces many challenges. These challenges include ensuring a safe range of dosages for use to protect biological systems, improving the selectivity and specificity of nanoenzymes to avoid non-specific reactions, safety in long-term applications and possible side effects, improving stability in different environments, and controlling nanoenzymes' activity precisely, among other issues. As scientific research progresses, it is expected that these challenges will be gradually overcome, thus expanding the prospects of nanoenzymes in different fields.

In sum, although we have made some progress in our work, a comprehensive understanding of IrNP-PVP nanoenzymes awaits future research. We are confident that, as our research continues, our work will have a profound impact on the entire field of nanoenzymes in medical applications.

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