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Application of Porous Molecular Crystals in Wound Healing

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Abstract

With the morbidity rate of chronic diseases like diabetes and cardiovascular disease increasing, the number of patients with chronic wounds caused by complications has increased significantly. Conventional wound dressings are incapable of resolving bacterial infection, sustained inflammation, and impaired tissue regeneration accompanying chronic wounds. Furthermore, antibiotic treatment and growth factor therapy in clinical practice encounter obstacles such as antimicrobial resistance and inadequate stability under physiological conditions. In response to these challenges, researchers have turned their attention to the realm of porous molecular crystals. However, research gaps still exist concerning the metabolism and long-term safety of these materials. This paper systematically reviews the research progress of Metal-organic frameworks (MOFs) in terms of antibacterial properties, anti-inflammation, and tissue regeneration. It also points out the research gaps in metabolism and long-term safety. Finally, it proposes that future research leverage AI tools to evaluate the biocompatibility and toxic effects of MOF-based hydrogel dressings, thereby promoting their clinical translation.

Keywords

chronic wounds; MOFs; antibacterial; anti-inflammatory; tissue regeneration

1. Introduction

In recent years, the morbidity rate of chronic diseases like diabetes and cardiovascular disease has been increasing. The number of patients with chronic wounds caused by complications (diabetic ulcer, vascular ulcer, pressure ulcer, etc.) is also increasing sharply. These chronic wounds account for a significant portion of the global healthcare burden. There are about 3 hundred million patients with severe injuries and 1 hundred million trauma patients. Furthermore, chronic wounds often occur secondary to diseases in the elderly. Thus, the elderly population is facing higher socioeconomic and medical pressures. This situation highlights the urgent need to develop new therapies.

Conventional wound dressings cannot solve effectively core challenges, including bacterial infection, sustained inflammation and impaired tissue regeneration. Antibiotics commonly used in clinical practice face the increasingly serious risk of drug resistance, and the application of growth factor therapy is limited due to poor stability and susceptibility to inactivation within the body. Thus, new technology for the effective treatment of chronic wounds is in urgent need.

Porous molecular crystals, especially Metal-Organic Frameworks, have shown great potential in wound healing due to the high specific surface area, adjustable channels and excellent designability. Now, scientists have successfully achieved the efficient loading of metal ions, drugs and bioactive molecules onto MOFs to achieve antibacterial and anti-inflammatory effects.

This paper starts from the mechanism of action of porous molecular crystals, and introduces the application of MOFs in antibacterial, anti-inflammation and tissue regeneration with examples based on the current research for a detailed introduction. The research of MOFs in wound healing is expected to solve clinical problems like chronic wound infection and difficult healing. The research also helps prevent serious consequences such as amputation caused by the deterioration of chronic wounds, reduce related medical risks and medical costs, and improve the quality of life for patients with chronic diseases, especially the elderly.

2. The Mechanism of Action and Application Strategies of Porous Molecular Crystals

2.1 Antibacterial Technology

Scientists often use drug delivery to achieve antibacterial effects. By taking advantage of the porous nature of MOFs, they load metal ions (Ag^{+}, Zn^{2+}, Fe^{3+}, Mn^{2+}, Pb^{2+}, Co^{2+}, Cu^{2+}, etc.), organic ligands (metal-organic compounds, aldehydes, phenols, acyl anilines and heterocyclic compounds) and nanozymes onto MOFs. It allows the MOFs to slowly release antibacterial ions, organic antibacterial agents, or by the dispersed nanozymes, catalyzing hydrogen peroxide to produce hydroxyl radicals. The hydroxyl radical can effectively kill bacteria and prevent the formation of bacterial biofilms [1]. One research group loaded silver nanoparticles onto MOF nanosheets and modified them with polyvinylpyrrolidone (PVP), resulting in PVP@MOF-Ag nanosheets. Through experiments, researchers found that this nanosheet releases silver ions when the temperature rises. These silver ions can induce the production of endogenous reactive oxygen species, thereby triggering oxidative stress in bacteria and achieving efficient antibacterial effects. Moreover, this antibacterial effect has been confirmed in experiments on mice [2]. Another research has proposed a multifunctional soluble microneedle array (Mem-DMOG@PCN-224 MNs). The array can simultaneously load antibacterial agents and bioactive small molecules. After penetrating the skin, the micro-needle rapidly dissolves the needle tip in the interstitial fluid of the skin, quickly releasing the antibacterial agent (meropenem) and drug-loaded metal-organic framework nanoparticles (DMOG@PCN-224 NPs), thereby achieving graded and multiple treatments for the wound through a single administration [3].

At present, the use of light energy in MOFs is also a popular research direction. Some MOFs (such as intrinsic photothermal MOFs) can generate heat at the active sites due to the strong local surface plasmon resonance effect of the metal ions when exposed to light, and this heat can then kill bacteria. Some MOFs can also act as effective photosensitizers. By combining with external light sources, they can generate reactive oxygen species (ROS) in situ, thereby selectively damaging the target tissue in the presence of oxygen molecules [1]. One research used Cu15%ZIF-8 as a bimetallic organic framework, taking advantage of the excellent light response ability of copper ions to enhance the photothermal and photocatalytic properties of wound dressings. The results showed that the photothermal conversion efficiency of MOFs significantly improved after the incorporation of copper ions, and Nar@Cu15%ZIF-8@Hydrogel showed stable photothermal cycling performance. In the photocatalytic experiment, this material significantly promoted the generation of ROS under the irradiation of 808 nm near-infrared light. This result demonstrated the excellent photodynamic effect of this MOF. Furthermore, in vitro experiments have confirmed that under near-infrared light excitation, Nar@Cu15%ZIF-8@Hydrogel exhibits broad-spectrum antibacterial activity through the release of metal ions and the synergistic effect of photothermal and photodynamic actions [4].

2.2 Anti-inflammatory Technology

MOFs achieve anti-inflammatory effects by loading anti-inflammatory drugs. One research has found that a biodegradable two-dimensional bimetallic MOF can generate a large amount of ROS under low-intensity medical ultrasound exposure to kill bacteria. Moreover, its nano-enzyme activity can be utilized to eliminate the ROS, thereby reducing the damage of ROS to human tissues. After the degradation of the MOF, the sustained-release copper-manganese ions form chelates with quercetin. Through metal-ion charge transfer, they exhibit superoxide dismutase and catalase-like effects, and by continuously adsorbing ROS, they reduce inflammatory responses. Furthermore, copper-manganese ions and quercetin have both osteogenic and antibacterial effects, thus they can continuously promote bone tissue repair. Currently, this achievement has been patented and can be used in clinical settings [5].

MOFs can also exert anti-inflammatory effects by adsorbing pro-inflammatory mediators (such as cytokines, nitric oxide (NO), ROS, etc.). One study has shown that the zirconium-based MOF-808 crystal, due to its porous structure and surface affinity, can effectively adsorb pro-inflammatory mediators such as NO, cytokines, and ROS. The study synthesized a zirconium-based MOF-808 and dispersed it in a hydrogel for application in a skin wound model. The results showed that this MOF effectively adsorbed pro-inflammatory substances such as ROS and NO, significantly alleviated chronic inflammation, and simultaneously promoted cell activation and proliferation, improving the healing quality [6]. Another study loaded silver nanoparticles, glucose oxidase and aptamers onto Cu-MOFs, and synthesized a multifunctional copper-based hybrid MOF. In the in vitro inflammatory model experiment of macrophages induced by lipopolysaccharide, the researchers found that the content of inflammatory factors in the cell supernatant was significantly reduced after treatment with multifunctional copper-based hybrid MOF. This result indicates that this MOF exerts anti-inflammatory effects by eliminating inflammatory factors [7].

2.3 Promoting Vascular and Tissue Regeneration Technology

Copper ions and zinc ions have the effect of promoting tissue repair and regeneration. Researchers often use these two ions to synthesize MOFs. Some researchers have developed a photothermal nanozyme based on copper-based metal-organic frameworks. The nanozyme is used to inhibit bacterial biofilms and promote chronic wound healing. The researchers have also loaded this nanozyme onto a gelatin methacrylate hydrogel microneedle system. This design utilizes the photothermal effect of near-infrared light radiation to activate the MOF to continuously release copper ions, thereby promoting collagen deposition and vascular regeneration. The MOF exhibits excellent biocompatibility and significantly accelerates wound healing [8]. In another research, a cerium-based composite nanozyme was prepared. This nanozyme integrated cerium nanoclusters (CeNC) and amino acids into the cobalt-based MOF framework. Experimental results showed that it could inhibit wound inflammation and promote angiogenesis, which is beneficial for promoting the healing of chronic wounds [9].

MOFs can also serve as a supporting framework, and simultaneously perform the functions of supporting and promoting tissue repair. In a study that utilized electrospinning technology to fabricate fiber scaffolds for promoting cartilage repair, researchers synthesized magnesium-gallic acid metal-organic framework nanoparticles (Mg-GAMOF) and introduced them into the core layer of the scaffold's core-shell fibers through coaxial electrospinning. The slow-release of magnesium ions can upregulate the expression of hypoxia-inducible factors, while the release of the anti-inflammatory molecule gallic acid (GA) alleviates the adverse effects of the inflammatory environment on the biological behavior of cells or tissues. The results show that MOF particles were successfully introduced into the fibers, achieving the controlled release of magnesium ions and GA. Meanwhile, the fibrous membrane of this scaffold shows no obvious cytotoxicity and supports the growth of bone marrow mesenchymal stem cells (BMSCs), macrophages (RAW 264.7), and chondrocytes derived from patients with osteoarthritis (OA). Compared with the fiber membranes without MOF, the fiber membranes loaded with GAG/MOF can better promote the differentiation of BMSCs into cartilage, induce RAW 264.7 to polarize into an anti-inflammatory M2 phenotype, upregulate the expression of hypoxia-inducible factors, and enable OA chondrocytes to transform from abnormal morphology to normal morphology. This experiment has been verified in mice [10].

3. Challenges and Development

Though MOFs show great potential, their clinical application still faces several key challenges.

Firstly, the long-term biological safety and metabolic mechanism of MOFs remain unclear. Some highly stable MOFs are difficult to degrade in the body. If the wound remains in the tissue for a long time after healing or is accumulated in the liver, spleen and other organs through the circulatory system, whether it will cause chronic inflammation, fibrosis or long-term immunotoxicity is currently lacking systematic toxicological data [11].

Secondly, the metabolic pathways and genotoxicity of MOFs are also unclear. There is a lack of sufficient research on the metabolic pathways, clearance half-life, and potential genotoxicity of the nanoscale fragments of MOFs in the body [11].

Finally, the control of the dose-time window is challenging. Metal ions have both antibacterial and angiogenic-promoting effects as well as cytotoxicity. How to achieve precise control of the dose-time window is a problem. If the release is too slow, it will be ineffective; if it is too fast or excessive, it will induce cell apoptosis or necrosis [11].

In response to these challenges, future research should focus on the development of MOF-based hydrogel skin wound dressings, systematic evaluation of their toxic effects and biocompatibility as antibacterial and anti-inflammatory dressings [11], and in-depth studies on their specific performance in the complex environment of the human body, thereby promoting the clinical application of MOFs in the treatment of chronic wounds. At present, AI is developing rapidly. Researchers can also use the existing data to establish evaluation models for big data and even establish clinical trial models for simulation experiments, thereby promoting the further development of the research.

4. Conclusion

In conclusion, this paper systematically reviews the three major application directions of MOFs in chronic wound healing: antibacterial, anti-inflammatory, and promoting tissue regeneration. Recent studies have shown that MOFs can exert therapeutic effects through various mechanisms such as drug delivery, light-responsive sterilization, ROS clearance, adsorption of pro-inflammatory mediators, and controlled release of metal ions to promote angiogenesis. Now multi-modal collaborative strategies (such as combined photothermal-photodynamic antibacterial therapy, and co-delivery of metal ions and anti-inflammatory molecules) have shown better efficacy than single therapy and are currently the main research mode of MOFs in the field of wound healing.

However, there are still significant limitations in the current research. Firstly, most of the experiments are still at the stage of being conducted in vitro or on small animal models, lacking relevant data for large animals and humans. Secondly, the long-term biological safety, in vivo degradation kinetics, and organ accumulation risks of MOFs have not been systematically evaluated. Furthermore, there is no standardized protocol for the optimal dosage of metal ions and the release time window, which limits the comparability among different studies and the potential for clinical application.

In response to the aforementioned challenges, future research should focus on the following directions. Firstly, researchers can consider developing MOF-based hydrogel wound dressings and systematically evaluate their toxicity effects and biocompatibility in complex physiological environments. Secondly, they can conduct in-depth studies on the metabolic pathways, clearance half-life, and potential genetic toxicity of MOFs and their degradation products in the body. Finally, by leveraging artificial intelligence tools, researchers can use the existing data to build a MOFs toxicity prediction model and a clinical trial simulation platform. These approaches can accelerate material screening, optimize the dose-time window, and reduce the clinical translation risk. Through the above efforts, MOFs-based dressings are expected to provide a safe and efficient new solution for the treatment of chronic wounds.

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Conflicts of Interest

The authors declare no conflict of interest.

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