Review
Research and Application of Metal–Organic Framework in Surface Modification of Biomaterials—A Review

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Abstract: Surface modification is one of the core technologies in the field of biomedical materials. The fundamental purpose is to enable the surface of biomass materials to have better biocompatibility to better meet clinical needs. A metal–organic framework (MOF) is composed of organic links and metal nodes. It is a type of new crystal porous material with important application potential. In recent years, it has been explored in the field of biomass materials. This review introduces the structure and synthesis of MOF and systematically combs, summarizes and evaluates the research and application of MOF in cardiovascular therapy, tumor therapy, bone tissue engineering and other scenarios, in order to provide reference and inspiration for subsequent researchers.

Keywords: metal–organic frameworks; surface modification; antibacterial performance; cardiovascular treatment; drug transmission

1. Introduction

Surface modification is one of the core technologies in biomedical materials. Its fundamental purpose is to improve the surface of biomass materials’ biocompatibility to meet clinical needs better. There are many parameters related to surface reactions, such as hydrophilic/hydrophobicity, surface energy, surface, functional group, surface charge, receptor position, molecular movement, roughness/texture, and spatial orientation of surface molecules. Surface modification aims to control the biological reaction properties on the surface of the biological material by changing these properties. Surface modification technology has been widely used in the surface modification of biological materials to improve their biocompatibility and material performance [1].

In recent years, metal–organic works (MOFs), also known as porous coordination polymers, have gradually deepened the research in the field of biomaterial surface modification (Figure 1). Their novel and attractive sub-organic framework (BioMOFs) has also caused great interest, bringing new opportunities to its application in a large number of biological and medical applications [2]. MOFs are a new type of crystal material composed of organic connectors and metal ions or clusters. Unlike the porous materials of traditional disorderly structures, MOFs have large surface area (generally 1000–10,000 m²/g), high pore rate, adjustable structure, and flexible customization [3]. These features make MOFs widely used in various scenarios, such as drug loading, cardiovascular treatment, bone tissue engineering, and tumor testing (Figure 2).

In this review, we firstly discuss the structure and preparation of MOFs, then systematically discuss the research on and application of MOFs in the medical field of cardiovascular treatment, tumor treatment, and bone tissue engineering, and finally provide a reasonable outlook for the lack of MOFs.
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2. Structures of MOFs

MOFs are assembled by a strong coordinate key between metal nodes/clusters and organic connectors, forming a co-organic hybrid crystal with ideal aperture and volume. An MOF itself forms an open framework through several metal units (M-L-M). The initial framework will expand to form porous nanoparticles (NPs) with gaps and grooves, so as to generate a high-level upper structure of one dimensions, two dimensions, three dimensions.
or four dimensions [4]. The structure of MOFs can be divided into four parts: form of metal clusters, organic linkers, NPs, and pores [5].

Tooba Rezaee et al. stated that MOFs can make polyte crystal particles with high surface area, and this may regulate its benefits by choosing appropriate metal ions and ligands. This is the unique feature of MOFs to make it an ideal medical science candidate material [6]. Subsequent researchers have found that by optimizing reaction parameters such as metal ions, organic ligands, metal and ligands, solvents, reaction time and other reaction parameters, they can obtain MOFs with different topological structures, forms, pores, volume and surface performance [5,7,8]. MOFs are crystalline powders filled with tiny-molecule pores, which have a unique structure: porous structures where metals are interconnected through organic connectors (Figure 3). As is currently known, the connection between MOFs and the surface of biomaterials usually does not occupy their own chemical structure, as this may alter their various characteristics, such as particle size, porous structure, potential, and even their unique framework structure distribution. The surface modification is often carried out by physical adsorption using material surface roughness, topological structure, hydrophobicity and other properties, or using the “double-sided tape” function of an adhesive transition layer, such as polydopamine film. The biomaterials that can be modified with MOFs are not limited to metals and their alloys: polymer or inorganic non-metallic materials can also be modified with MOFs, which mainly depends on the interface function required for implantation of lesions.

![Mental organic framework](image)

**Figure 3.** General schematic of MOFs and surface modification method of biomaterials with MOFs.

### 3. Preparation of MOFs

An et al. show that although the preparation and application of various biomolecule–MOF composite materials have made significant progress, there are still some challenges [9]. In terms of fixed strategies, although several methods have been developed, they all have their own advantages and disadvantages. For example, adsorption can usually maintain the high activity of biomolecules, but this approach is largely limited by biomolecular size and MOF aperture. In addition, the object molecules only have a weaker interaction with MOFs, and easily leak from the matrix. Due to the strong intensity of the covalent bonding, the covalent key can usually overcome this disadvantage. After synthesis, synthetic modification is an efficient technology that improves MOF performance. The specific method can be divided
into four groups: (i) biological coupling, (ii) package conversion, (iii) packaging and (iv) hybrid [10].

Lee et al. used a surface-anchored gel to synthesize a new type of large-molecule membrane through a surface-anchoring metal–organic framework (SURMOF). The surface-anchored gel (SURGEL) combines the possibility of modifying the height of the constructing block and the possibility of controlling the SURMOF’s synthetic network topology and membrane thickness, and the polymer has high mechanical and chemical stability. The porous bracket is used on the top of the membrane. It is mechanically stable and can easily transfer the membrane from the synthetic substrate to the final membrane bracket [10].

Hollow MOFs with only a shell may be used for efficient catalysis. In this work, a general sequential synthesis was employed to successfully create Hf-based hollow MOFs, such as UiO-66, MOF-808, and PCN-223. Etchants including monocarboxylic acids and H₂O are required to remove the interior of the MOFs to form hollow structures, while the different stability of the interior and surface of the MOFs partly resulting from surface epitaxy protection were responsible for the selective etching. Chen et al. found that PKA and concentration of monocarboxylic acids are the key, and water is also a necessary component to prepare this MOF [11].

Giliopoulos et al. reported a promotional method that built MOF@polymer function composite materials through the surface caused by the surface of the atom transfer radical polymerization (SI-ATRP). Unlike the traditional SI-ATRP, the covalent prices are anchored on the surface of the substrate. They first assembled on the surface of the MOF through the hydrogen bonding of the chain. Under the existence of the covalent price of the cross-linked monomer, the subsequent aggregation will string these polymer chains into a sturdy network, which physically restricts the MOF particles in the polymer shell. After that, the experiments of various polymers growing on the five MOFs of different metals (Zr, Zn, Co, Al, and Cr) prove the universality of this method, completely control the thickness, functions and layers of the shell layer, and still retain the inherent pore rate of MOFs. In addition, through reasonable selection of monomers, the wetness of UiO-66 can be continuously adjusted from super-water water to ultra-hydrophobic [12]. The general outline of the MOF fabrication methods is provided in Figure 4.

![Fabrication methods of MOFs](image)

(a) Hydrothermal/solvent thermal synthesis method  (b) Ultrasonic method
(c) Postsynthetic modification of MOF  (d) the etching of the UiO-66 MOF to form a hollow structure

Figure 4. General outline of the MOF fabrication methods.
4. Metal–Organic Frameworks for Surface Modification of Biomaterials

In order to provide better biocompatibility, corrosion resistance, and blood compatibility on the surface of biomaterials to meet clinical needs, surface modification methods are often used, and surface modification is also one of the core technologies in the field of biomedical materials. There are many parameters related to surface reactions, such as hydrophobicity, surface energy, surface potential, functional groups, surface charges, acceptor sites, molecular motion, roughness/texture, and spatial orientation of surface molecules. Surface modification is the control of the biological reaction properties on the surface of biomaterials by altering these properties. At present, surface modification technology has been widely applied in the surface modification of biomaterials to improve their biocompatibility and material properties [1]. The materials used for surface modification of biomaterials should have the following characteristics: stable attachment to the outer surface, appropriate stability under physiological conditions, release of loaded drugs at appropriate times, single-step (or several steps) acquisition under mild conditions, delayed degradation, improved blood compatibility, corrosion resistance, and biocompatibility.

MOF materials are receiving increasing attention in the biomedical field due to their porous structure, ease of design, and excellent biosafety and biodegradability. The use of porous crystal frameworks for surface modification of biomaterials to prepare new types of biomaterials has enormous potential [2]. Many studies have demonstrated the biocompatibility and biomedical applications of nano-MOFs, including the packaging of biological macromolecules, drug delivery, and other chemotherapy prospects. Thus, MOF is an ideal choice to be applied for surface modification of biomaterials. However, nano-MOFs still pose significant challenges to date, such as the limited stability of MOF particles or surface-anchored MOFs under physiological conditions. Although beneficial for in vivo applications (requiring removal from the body), this is the main limitation of bioactive coatings or cell culture applications [12]. Under these conditions, long-term stability and avoidance of potential cytotoxic metal ions are essential. MOF materials have certain applications in the fields of vascular stents, tumor therapy, and bone tissue engineering.

4.1. Cardiovascular Treatment

4.1.1. Existing Problems

The rapid development in medical technology in the past few decades has greatly affected cardiovascular stent materials, evolving from bare metal stents (BMS) that initially only the provided physical support to biodegradable metal stents [13].

Biodegradable metal stents have achieved significant success in clinical applications, but their rapid degradation rate and delayed surface endothelialization have always been bottlenecks in the further application of biodegradable metal stents. The long-term safety of cardiovascular stents caused by in-stent restenosis (ISR) and late stent thrombosis (LST) also urgently needs to be addressed [14,15].

Taking magnesium alloy as an example, it has excellent elastic modulus and tensile strength, negative charge during degradation, and also provides potential for antithrombosis. However, exposed magnesium alloy scaffolds often corrode quickly, dissolve quickly, and have insufficient endothelialization after implantation [12,16]. In order to improve the performance of magnesium alloy scaffolds, researchers have conducted extensive experiments from two aspects: changing material composition and surface modification.

In addition to improving the performance of magnesium alloy scaffolds through the above methods, Liu et al. provides us with another approach—using MOFs for surface modification of biomaterials [17]. The following mainly summarizes the research and application of MOFs in solving ISR and LST.

4.1.2. MOFs for ISR and LST

Nitric oxide (NO) secreted by endothelial cells (ECs) is a key signaling molecule in the blood circulation system and plays important roles in solving ISR and LST. NO itself is produced endogenously by a family of NO synthase enzymes, where it contributes...
to the regulation of immune response, neurotransmission, and vascular tension. The production of biological NO is crucial for the wound healing process, and exogenous NO supplementation has been proven to promote accelerated wound closure [18,19]. In situ generation of nitric oxide (NO) is considered a promising method for improving anticoagulant and anti-hyperplasia abilities [19]. Most nanoparticles used for gas transport exhibit varying degrees of cytotoxicity [20–22]. For MOFs, the use of highly biocompatible metals and/or ligands can easily reduce cell toxicity, and thus it is a better strategy for stimulating donor release of NO by preparing MOF coatings on the surface of biomaterials. The surface modification of other nanoparticle systems mostly involves complex processing methods, but MOF coating is simpler for NO release [23].

Harding et al. previously reported that copper (Cu)-based MOFs may induce the formation and decomposition of NO in S-nitroso mercaptan (RSNO), which is a unique NO donor compound in biogenesis. Copper-based MOFs have been shown to induce the direct release of NO from RSNO. Biological RSNO is considered a physiological reservoir of NO [24]. This phenomenon has led to the development of copper-based materials, aimed at generating local NO supply through the controlled decomposition of bioavailable RSNO, typically by containing simple copper salts or complexes. Copper-based MOFs have great potential as catalysts for NO generation and have recently emerged as components of antithrombotic coatings for cardiovascular implants [25].

Fan et al. used polydopamine as a linker and coating matrix to immobilize nanoscale copper-based metal–organic frameworks (nano-Cu-MOFs) on the surface of titanium. They found that the nano-Cu-MOF's immobilized coating had good NO and Cu²⁺ release capabilities. In the extracorporeal circulation model, this coating inhibits platelet aggregation and activation through the NO-cGMP signaling pathway, significantly reducing thrombosis. In addition, in vivo, nano-Cu-MOFs immobilized coatings can inhibit the proliferation of smooth muscle cells, smooth muscle cells (SMCs), and macrophages (MA), thereby reducing endometrial hyperplasia in vivo. This indicates that Cu-MOFs have significant potential in cardiovascular applications, and nano-Cu-MOF immobilized coatings provide a promising method for preparing multifunctional surfaces, which can solve LST and ISR problems through surface modification of cardiovascular stents [25].

Cu-BTC has been proven to be an effective catalyst for the conversion of blood-derived s-nitroso cysteine to nitric oxide and cysteine [24]. Zhao et al. used the layer-by-layer assembly method (LBL) to prepare copper-based benzo-1,3,5-tricarboxylic acid copper (Cu-BTC) surface-attached metal–organic frameworks (CuSURMOFs) for the generation of NO on alkali-activated titanium surfaces. By changing the number of LBL deposition cycles, control of surface chemistry and NO release can be achieved (Figure 5). It has been confirmed that the coating can decompose endogenous s-nitrosoglutathione (GSNO) to catalyze the generation of NO, and the resulting NO flux increases with the number of deposition cycles, demonstrating good catalytic durability. The appropriate deposition cycle of Cu-BTC coating has a significant promoting effect on EC proliferation, but an excessive deposition cycle provides excessive NO and leads to cell apoptosis. Further research has shown that coatings deposited over 10 cycles can effectively inhibit SMCs and MA, as well as inhibit platelet adhesion and activation. Cu-BTC coating prevents thrombosis in an arteriovenous shunt model and reduces intimal hyperplasia and inflammatory response in vivo after titanium implantation. It has been demonstrated that deposition of copper-based MOF coatings is an effective pathway for NO generation on titanium surfaces, indicating that this coating is suitable for surface modification of cardiovascular biomaterials to prevent thrombosis and intimal hyperplasia [26].

Zhang et al. developed a Cu MOF-based scaffold using M199MOF as an example, and embedded Cu MOF nanoparticles into polycaprolactone (PCL) fibers using electrospinning. Encapsulating Cu MOF nanoparticles in PCL can simultaneously enhance the stability of Cu MOF in serum and allow for long-term NO catalytic activity. In addition, the optimized concentration of Cu MOFs loaded into the stent significantly promotes EC migration and increases acetylated low-density lipoprotein (Ac-LDL) uptake, inhibits platelet adhesion and activation, and
significantly reduces acute thrombosis in arteriovenous shunt models. The results indicate that incorporating Cu MOFs into electrospun fibers is a promising method that can achieve the stable catalytic performance and long-term activity required for implanted materials [27].

![Figure 5. Schematic diagram of LBL deposition of Cu-BTC coating on alkali-activated titanium surface [26].](image)

MOFs are beneficial for gas transportation, and Furukawa et al. showed that the loading efficiency of MOFs can reach 95% [28]. The prodrugs are mediated through van der Waals force [29], electrostatic interaction [30], and coordination [31]. Zhou et al. conducted clinical trials to construct MOF-based gas transport platforms through both non-catalytic and catalytic pathways, and they found that MOFs can simulate the activity of specific enzymes. Hong et al. constructed a lanthanide metal–organic skeleton with one-dimensional nanochannels using a 1,3,5-benzenetricarboxylic acid (H$_3$BTC) ligand to bridge the helical chain secondary construction unit n(1,DEF = n,n-diethylformamide) [32]. The structural characterization showed that the complex is hexagonal space group P6122 in crystal form, has a one-dimensional triangular channel, and the water molecule cooperatively points to the center of the channel, which can improve the hemodynamic parameters and may be a better method to treat heart failure.

In another study, Melvin et al. investigated the application of a copper-based metal–organic framework—H$_3$ [(Cu$_4$Cl)$_3$(BTC)$_3$·(H$_2$O)$_{12}$]·7H$_2$O—where H$_3$BTCri = 1,3,5-tris(1H-1,2,3-triazol-5-yl) benzene [CuBTCri] was proven to be an effective catalyst for the generation of NO from small nitrothiols present endogenously in the blood. They successfully established a stable and active CuBTCri composite coating on medical catheters, which has the potential to reduce thrombosis and requires future in vivo trials. In the 72 h physiological saline flow rate experiment, the coating remained stable. In the blood compatibility test, no adverse reactions were observed compared to the control group, and minimal thrombus deposition occurred. CuBTCri within the coating produces NO in the presence of biologically relevant concentrations of NO donors after blood exposure. In addition, CuBTCri within the coating produces NO in the presence of biological NO donors, confirming the activity of MOF after exposure to blood. The stability and safety results of composite materials are promising, and future in vivo trials will be used to evaluate the effectiveness of this method in in vitro organ support and other medical devices involving blood biomaterial interactions [14].

4.2. MOFs for Tumor Treatment
4.2.1. Background

In terms of drug transfer, the large surface area and pore size of MOFs help package high-load drugs, and the high structure and functional flexibility of MOFs allow it to adapt to the shape, size and function of drug molecules.
In imaging applications, MOFs can be modified with chemical groups to uniquely influence the transfer of motion picture agents. MOFs also have the advantage that it can be used simultaneously as an MRI contrast medium and drug carrier, so it can be used simultaneously for diagnosis and treatment [33]. Therefore, in recent years, many studies have focused on the combination of MOFs and biocompatible polymers. The aim is to develop a more efficient and complex system than previous products and improve the quality of life of patients [34].

4.2.2. MOFs for Tumor Detection

UIO-66@Dopa-LB manufactured by Zhang et al. can not only achieve high image sensitivity (5 mm) for breast cancer tumors but also have excellent ability to detect early tumors (1–2 mm) [35].

In the experiments of Zhou et al., they found that a Zn-MOF-on-Zr-MOF-based aptassensor had high selectivity under various interference and was highly stable, reproducible and tolerated in serum [36]. Gu et al. also reported a new bimetallic ZrHf metal–organic framework (ZrHf-MOF) embedded with abundant carbon dots (CDs) (indicated as CDS@ZrHf-MOF) showing strong fluorescence and rich changes in amino function [37]. These experiments offer a new way to produce ultrasensitive and selective MOF-based bimetallic sensors that are expected to be used for early and sensitive testing of cancer markers and live cancer cells.

4.2.3. MOFs for Tumor Treatment

In clinical practice, chemotherapy is routine, but is still considered one of the most common cancer treatments. However, cancer drugs can have side effects such as nonspecificity, toxicity, poor solubility and unprepared control in the blood, so the effect of chemotherapy has not met people’s expectations. Therefore, with the development of nanotechnology, drug delivery systems (DDSs) are developing, which transport the necessary goods to the tumor site to achieve the goal of reducing possible damage to the body and improving the therapeutic effect [38].

There are still some challenges to increase the target capacity of the metal–organic framework (MOF) in tumor treatment and avoiding the removal and capture of the immune system. Liu et al. investigated promising cell membrane coverage and used it to synthesize new bionic cell membrane MOFs [39]. This coating can give excellent properties of various source cell membranes (red blood cell, immune cells, cancer cells, platelets, fusion cell membranes, etc.), such as long blood flow times, immune escape, and strong targeting capabilities.

Wen et al. point out that the fabrication of MOF-based low-toxicity and stimuli-responsive systems to stimulate colloidal stability needs to be further investigated. Currently, there are not enough studies on stable and biocompatible MOF-based stimuli-responsive NPs. To reduce the toxicity of NPs, it may be a better choice to select endogenous components such as organic compounds for the production of metal biomerings (BIOMOFs) using the “green” synthesis pathway [40]. Biomimetic amino acid enhancement can rapidly encapsulate or co-encapsulate a variety of proteins and enzymes into microporous MOFs with ultrahigh exercise efficiency. It has the properties of non-destructive, rapid encapsulation and controllable release independent of protein surface charge [41].

Zeolitic imidazolate framework (ZIF) is one of the metal–organic frameworks (MOFs). Porepolite mimazole skeleton (ZIFS) has drug capacity, release volume and decay rate [42]. ZIF-8 was primarily constructed by the pot method and can be used on drugs with large ZIF-8 pores in situ, improving drug loading capacity [43].

Its application features are the following: (I) higher biological safety; (II) decomposition into acidic solutions favoring the specific release of the medicinal product; (III) decomposition product Zn$^{2+}$ can generate active oxygen (ROS); (IV) Zn$^{2+}$ cofactor-catalyzed ribosase degradation reaction; and (V) cell autophagy induction (Figure 6) [44]. ZIF-8 can be used as part of a nanoreactor to prevent premature drug leakage and serve as a
self-sacrificing template. However, ZIF-8 is dispersed in water and tends to aggregate. Therefore, the surface of ZIF-8 is often modified by polyethylene glycol (PEG) or hyaluronic acid (HA) [43]. Active transfer of tumor cells in ZIF-8 surface ligand modification and bionic surface calcification of nanopotics [45,46] can also achieve long-term blood flow and immune escape, such as covering cancer cells [47] or red blood cell membrane essence [44,48].

In a recent study, researchers suggested more possibilities in the application of biomaterial surfaces through the surface modification of MOFs. Research by Shi et al. developed an in situ biomimetic mineralization strategy on a zeolitic imidazolate framework (ZIF) to build drug delivery systems with good cell compatibility, improved stability, and pH responsiveness. Using lysozyme (Lys) wrapped on the surface of Zn-based ZIF (ZIF-8), Lys/ZIF-8 strongly binds metal ions to promote nucleation and growth of bone-like hydroxyapatite (HAp) leading to formation of HAp@Lys/ZIF-8 composites, which have higher drug loading efficiency (56.5%), intelligent pH response to dose, cell compatibility and stability [26]. Fang et al. prepared zeolite-imidazolate framework-8 (ZIF-8)-coated ZnS nanoparticles for efficient gas amplification of cancer [49]. Yan et al. loaded a photosensitizer (chlorine e6, Ce6) and a ZIF8 coating layer into E. coli (MG 1655). Biomedication E.Coli@ZIF-8 can be selected by E. coli tumors to transport photosum and chemicals to cancer cells and induce high efficacy in vitro induce in vitro [46]. Another study found that more microporous structures were introduced into ZIF-8 modified by surfactants, which favored not only drug loading but also material degradation [50].

Figure 6. (A) Synthesis process of ZIF–8 nanocomposites. (B) Decomposition of ZIF–8 nanocomposites in cancer cells [44].
The above experiments show that MOFs have opened a new path towards intelligent pH-sensitive drug delivery systems and optical synergistic therapies [51]. However, existing studies have not paid enough attention to the nature of ZIF-8 itself, including possible mechanisms that affect tumor growth and long-term toxicity in the body. The clinical transformation of the ZIF-8 dating system requires additional internal and external studies of ZIF-8 [44].

Nanozymes have excellent catalytic properties in enzymatic modeling and play an increasingly important role in tumor diagnosis and treatment. Metal iron organic framework nanoparticles (MIL-101 (Fe) NPs) as nanozymes induce the death of cancer cells via catalytic endogenous substances in the tumor microenvironment [52]. Ma et al. synthesized nanozymes with degradable, microwave sensitivity and synthesized dual-mold imaging, and MTT and Medt combined anti-tumors were achieved [53]. Xue et al. used an MIL-100 metal–organic skeleton (MOF) by microwave-assisted synthesis and loaded doxorubicin (DOX) into MIL-100, effectively improving the shortcomings of DOX treatment [54,55]. The experimental results show excellent antitumor effects, and clinical experiments are expected.

Arcuri et al. synthesized an ultrasmall UiO-66 nanometer (NPs) with an average particle size of 25 nm, which could be a potential carrier for the treatment of gum cytoma therapeutics [56]. Trushina et al. prepared nuclear envelope structure UiO-66@SiO2/F127-FA drug delivery carriers for target cell uptake for cancer treatment. The silicone coating improves the colloidal stability of the composite material and prevents its load from being uncontrolled, while reducing overall porosity [57]. At the same time, according to research by Daniel Bůžek et al., zirconium-based MOFs (Zr-MOFs) represent a large class of water-resistant structures, and the most commonly used Zr-MOFs are UiO-66, because this MOF is robust and easy to synthesize, with many potential applications. However, UiO-66 is not as inert in aqueous dispersions as reported in previous literature, at 37 °C, i.e., at typical temperatures for biological and medical applications. UiO-66 accelerates decomposition when mixed with buffer (Figure 7) [58]. Therefore, there are still certain problems with the use of UiO-66 as a potential carrier for biological therapy.

Figure 7. The theoretical structure of UiO-66 [58].

Mitochondria play an important role in tumors and are one of the most important targets for cancer treatment [36]. The mitochondrial targeting function can improve the effectiveness of PDT through the initiation of mitochondrial membranes and internal apoptosis pathways [39]. Salame Haddad et al. reported a design of mitochondrial targeting MOFs, breaking through the bottleneck of free drug transmission in the body [59]. Zeng et al. designed an infused structurally dynamic MOF-based water gel. For the first time, MOF-based pharmaceutical carriers were subtracted by self-healing and shearing via coordinate keys [60]. In addition, Kato et al. investigated uremic toxins, in which NU-1000 almost completely revealed sulfate parameters in human leukocyte proteins [61]. These studies have significantly expanded the function of MOFs on drug loading systems.
4.3. Others

4.3.1. MOFs for Bone Tissue Engineering

Magnesium-based implants have attracted extensive attention in bone regeneration due to their similar elastic modulus to bone. The different volumes and compositions of gases released by magnesium implants, such as H₂, CO, and CO₂, have not shown long-term toxic effects on surrounding tissues, but there are clinical problems of complications such as wound rupture and osteolysis [12]. In response to such clinical problems, Polo et al. demonstrated in live animal studies that plasma electrolytic oxidation (PEO) coating was beneficial to bone formation in osteoporosis rats and had a higher level of bone maturation in later stages [62]. Khalili et al. used a zeolite imidazolic acid skeleton to electrospinning on the surface of AZ91 alloy, and they found that the degradation rate of the surface-modified implant was reduced by about 80% compared with the unmodified implant, and the cell adhesion and vitality were improved [63]. The above studies are of great significance in solving the clinical problems caused by magnesium-based implants [63].

Titanium alloys are also commonly used as orthopedic implants, and MOF coatings have greatly improved the antibacterial properties of titanium implants. Shen et al. prepared a composite coating of magnesium/zinc metal–organic skeleton (Mg/Zn-MOF) [64]. Tao et al. developed an MOF@Levo/LBL implant, and their internal and external experiments showed that this implant effectively inhibited bacterial adhesion, providing a variety of solutions for preparing multifunction titanium planting with strong antibacterial ability and enhanced bone formation, and has potential orthopedic application value [65].

In addition, MOFs in the surface modification of poly-l-lactic acid (PLLA) nanofibrous scaffolds [66] and electrospun asymmetric double-layer polycaprolactone/collagen (PCL/Col) membrane (Figure 8) [67] promoted osteogenic differentiation. In another study, after inducing bone defects of rabbit femoral bone, it is filled with UiO-66 nanomical material, has good cell compatibility and blood compatibility, and can stimulate the body to develop outside the body. The function of osteocytes is promoted for the healing process of key dimensions of bone defects [68].

![Figure 8. Schematic of fabrication of the PCL/Col/ZIF-8 composite membrane for bone tissue [67].](image-url)
MOFs show good bone-forming performance and antibacterial and anti-inflammatory capabilities in bone tissue engineering. However, existing research is concentrated on studying the role of MOF decomposition products and lacks discussions on MOF structure.

4.3.2. MOFs for Advanced Wound Care

Silk fibroin (SF) is widely used in skin-related wound care or monitoring [69]. Zhu et al. used a metal–organic framework composite system (MOF) as a bridge to expand the structural-functional multi-modification of SF, and prepared Dsilma-R@Z to enhance the mechanical strength of SF hydrogels while accelerating tissue healing and easily meeting the needs of conventional skin wounds [70].

Xiao et al. found that Cu-BTC showed a positive effect on skin healing of rodent skin wounds [71]. In 2020, researchers investigated and found that Cu-BTC [72] and cellulose-based biomaterials can release NO after forming a polymer network, which can be used as a wound dressing.

The combination of Zn$^{2+}$ and Cu$^{2+}$ in MOF further encapsulates the bioactive molecule. Along these lines, Chen et al. [73], encapsulating copper/zinc nicotinate MOF in alginate shells, significantly improved wound closure in models of infected skin defects, showing good antibacterial, antioxidant, and angiogenic properties. In addition, zinc supplementation of ZIF-8 has also been shown to be effective for wound healing in ZIF-8 hydrogel complex membranes [74].

4.3.3. MOFs for Biomolecule Protection

Enhancing the robustness of functional biomacromolecules is a key challenge in biotechnology that, if addressed, will enhance their applications in pharmaceuticals, chemical processing and biological storage. MOF is an emerging class of porous materials that can be constructed from biofriendly building blocks under physiological conditions. In addition, they are thermally and chemically robust and are synthesized using a modular approach that allows for fine-tuning of their pore shape, chemical functionality, and size. This unique set of properties suggests that MOFs are important materials as protective coatings for biomacromolecules.

Liang et al. applied the concept of biological calcification to MOFs, proposing to provide unprecedented protection of biomacromolecules by encapsulating biomacromolecules in a class of porous materials called metal–organic frameworks. Experiments have shown that proteins, enzymes, and DNA rapidly induce the formation of protective metal–organic framework coatings under physiological conditions by concentrating frame building blocks and promoting crystallization around biomacromolecules. The resulting biocomposites are stable in environments that decompose many biomacromolecules. This rapid and low-cost biomimetic mineralization process opens up new possibilities for the development of biomacromolecules [75]. Their work also illustrates how biomolecules from amino acids to enzymes directly trigger the formation of MOF crystals through a bionic mineralization process, overcoming the initial need for abiotic crystallizing agents. The strategy has also been successfully applied to thin films and patternized surfaces of proteins, and for the first time demonstrated that MOF materials (zeolite imidazolate framework or ZIF-8) can crystallize on the surfaces of the organisms Saccharomyces cerevisiae and the bacteria Micrococcus flavus. In both cases, the MOF forms a protective coating on the respective cell walls that protects the organism from the external environment while significantly maintaining cell life [76]. Their research group passed eukaryotic cells (yeast) first coated with β-galactosidase (β-gal) and then coated with crystalline metal–organic skeleton film. Thus, bioactive porous synthetic shells are produced, enabling cells to survive in oligotrophic environments. Beta-gal is an important component of the bioactive shell because it produces nutrients needed for cell viability (i.e., glucose and galactose) in nutrient-deficient medium (lactose group). In addition, porous MOF coatings perform other important functions, such as protecting cells from cytotoxic compounds and radiation, protecting non-natural enzymes (in this case beta-gal) from degradation and internalization, and allowing the
diffusion of molecules necessary for cell survival. The construction of bioactive coatings represents a conceptually new and promising approach to the next generation of cell-based research and applications [77].

Ha et al. have found that the development of exoskeletons may be beneficial in protecting cells from environmental stresses and cytotoxins. MOF exoskeleton coatings on mammalian cells were developed through a pot of biomimetic mineralization process. After opening the exoskeleton, individual cells are successfully protected from the cellular protease, or protease K, while maintaining a smaller scale of nutrient transport through the exoskeleton. In addition, important cellular activity mediated by transmembrane GLUT transporters is not affected by the formation of MOF exoskeletons on the cell surface. In short, there is the ability to control the entry of specific molecules into individual cells through the porous exoskeleton and provide cellular protection [78].

4.3.4. MOFs for Neural Interface Engineering

Electro-deposition of MOFs can be used for coating of conductive, implanted electrodes and sensors, and is expected to be applied in neural interface engineering. Electrochemical deposition of MOFs can be divided into three types: anodic electrodeposition (AED) cathodic electrodeposition (CED) and electrophoretic deposition (EPD). The first two methods are in situ synthesis of MOFs on the substrate, while EPD is a technique for deposition of presynthesized MOFs.

According to the different properties of MOFs, such as gas (liquid) absorption luminescence (photoluminescence) redox switch of metal ions and so on, different kinds of sensors can be prepared. The adjustable pore size and specific chemical interactions between the MOF interior surface and metal position provide an opportunity to improve the selectivity and sensitivity of MOF-based sensors. For most signal transduction schemes, it is necessary to integrate thin MOF films into devices. On the other hand, membrane equipment is easy to store, transport and recycle. In addition, the good mass transfer in the MOF film enables the analyte to be detected in real time. Gravitational optics and electrochemistry are the sensing mechanisms used in MOF thin film-based sensors.

The first sensor based on electrodeposited MOFs was proposed by researchers at the University of Leuven in 2009. In that paper, they demonstrated the modular growth of Cu-BTC by anodic electrodeposition on the electrodes of a quartz crystal microbalance (QCMB). In order to obtain a dense and smooth coating, the synthesis conditions were adjusted. Thus, the humidity of the flowing gas can be monitored by the adsorption of water into the Cu-BTC structure. The sensor exhibits good reproducibility when circulating between dry nitrogen flow and wet nitrogen flow [79].

The electrochemical behavior of Cu (II)-MOF (Cu-ybdc) was studied by Maria Cristina Cassani and others. Modification of a GC/Cu-YBDC electrode by AuNPs was successfully obtained by electrochemical reduction of Au (III) ions captured by propyl carbamate in the linking agent. The modified GC/Au/Cu-YBDC electrode has been tested as a nitrite sensor in 0.1 M PBS solution at pH 7.2, showing enhanced electrochemical detection of nitrite compared with GC/Cu-YBDC. The coexistence of copper and gold makes the LOD calculated by electron transfer kinetics faster at 5 µM, which is significantly lower than the maximum nitrite concentration allowed by the World Health Organization in drinking water [80].

Jing Lu et al. studied an electrochemical biosensor for measuring H2O2 released by H9C2 cardiomyocytes and Fe3O4 @ ZIF-8-MoS2 nanoenzymes exhibited excellent electrocatalytic activity for reduction in H2O2 due to its unique structure. They proved for the first time that AuNFs electrodeposited on Fe3O4 @ ZIF-8-MoS2 can play an important role in extracting the specific electrocatalytic performance of MMOF Fe3O4 @ ZIF-8 NPs. The electrochemical biosensor has high selectivity and good sensitivity in neutral solution, and has fast electrochemical response to H2O2 detection. The ultrawide linear detection range is 5 µM–120 mM, and the low detection limit is 0.9 µM. These characteristics enable real-time quantification of H2O2 secretion in living cells in strained and unstrained states. This
modified electrode can be used as a universal and powerful platform for drug evaluation to detect biomarkers of other diseases [81].

Ziqi Zhang and others prepared TiO$_2$ nanotubes with regular arrangement by anodic oxidation on the surface of titanium substrate. The composite coating of ZIF @ Nd and hydroxyapatite deposited by electrochemical deposition is more time-saving, environmentally friendly and controllable than the traditional production process [82].

5. Conclusions and Outlook

MOFs play an important role in the medical field and solve many potential clinical problems, but the nature of MOFs and the application mechanism are less researched. For example, the potential mechanism and long-term toxicity that affect the growth of tumor growth and the clinical transformation of the administration system require a lot of internal and external research.

In addition, we should pay more attention to the interaction between MOFs and cells in the body. For example, when MOFs are used in cardiovascular stents, it is necessary to pay more attention to the study of interaction with MOFs and myocardial cells.

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