Integrated design and application of stimuli-responsive metal–organic frameworks in biomedicine: current status and future perspectives

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In recent years, metal–organic frameworks (MOFs) have garnered widespread attention due to their distinctive attributes, such as high surface area, tunable properties, biodegradability, extremely low density, high loading capacity, diverse chemical functionalities, thermal stability, well-defined pore sizes, and molecular dimensions. Increasingly, biomedical researchers have turned their focus towards their multifaceted development. Among these, stimuli-responsive MOFs, with their unique advantages, have captured greater interest from researchers. This review will delve into the merits and drawbacks of both endogenous and exogenous stimuli-responsive MOFs, along with their application directions. Furthermore, it will outline the characteristics of different synthesis routes of MOFs, exploring various design schemes and modification strategies and their impacts on the properties of MOF products, as well as how to control them. Additionally, we will survey different types of stimuli-responsive MOFs, discussing the significance of various MOF products reported in biomedical applications. We will categorically summarize different strategies such as anticancer therapy, antibacterial treatment, tissue repair, and biomedical imaging, as well as insights into the development of novel MOFs nanomaterials in the future. Finally, this review will conclude by summarizing the challenges in the development of stimuli-responsive MOFs in the field of biomedicine and providing prospects for future research endeavors.

1. Introduction

In recent years, the utilization of stimuli-responsive nanomaterials as carrier vehicles in drug delivery and disease diagnosis has garnered considerable attention.1 It is well-known that conventional clinical therapies often entail inherent drawbacks such as rapid renal clearance, poor solubility, limited tissue cell uptake capability, drug cytotoxicity, low organismal bioavailability, and inadequate in vivo targeting.2,3 The advancement of responsive nanomaterials offers novel avenues for addressing the limitations associated with systemic administration of therapeutic agents, a premise substantiated by ongoing research endeavors. The paradigm of stimuli-responsive metal–organic framework (MOF)-based nanomaterials encompasses the capacity to elicit responses within biological systems via both endogenous stimuli, such as the microenvironmental cues present at pathological sites, immune reactions, pH variations, and ATP levels, as well as exogenous stimuli administered externally.4 These stimuli serve as triggers to initiate responses within MOF-based materials, thereby facilitating the controlled (with spatiotemporal precision) and targeted release of cargo encapsulated within the MOF-based framework.5 MOFs represent a class of hybrid porous polymeric materials composed of metal ions and organic molecules, also known as linkers.6 These materials, hailed as organic–inorganic hybrid constructs, possess distinctive attributes including high surface area, tunable properties, biodegradability, extremely low density, high loading capacity, diverse chemical functionalities, thermal stability, well-defined pore sizes, and molecular dimensions.7–10 The research
pertaining to MOFs has pervaded numerous domains, spanning from hydrogen storage, carbon capture, semiconductors, drug delivery systems, battery, electrochemical sensing detection, adsorbent material, soft nanobrush-directed growth, ammonia detection, biomedical imaging and sensing technologies, desalination of seawater, to ion separation, among various others.11–22 Organic–metallic structures, renowned for their versatile utility as crystalline materials, have garnered significant traction within the biomedical domain, manifesting advancements in both single and multiple stimuli-responsive systems. The fundamental principle lies in achieving controlled delivery of payloads post internal or external stimuli-induced responses. In the design and assembly of MOF structures, meticulous preparation on blueprints is imperative, as even minor alterations during the fabrication process can yield novel MOFs with distinct properties.23,24 The selection of appropriate MOF materials necessitates a reservoir of knowledge.

In biomedical research, stimuli-responsive MOFs play a pivotal role in the development of intelligent drug delivery systems and diagnostic platforms.25 Stimuli-responsive drug delivery systems (MOF carriers) can react to external stimuli such as pH, temperature, magnetic fields, light, and pressure signals, thereby inducing controlled release of therapeutic agents and targeted delivery to specific sites within the body.26,27 Additionally, these stimuli-responsive drug delivery systems can also respond to endogenous stimuli, such as temperature variations, active factors, and ATP levels, which are aberrant in diseased tissues compared to healthy ones.28 Through enhanced permeability, retention effects, and receptor–ligand affinity interactions, accumulation of MOF carriers at the diseased sites is achieved.29 MOFs, as nanomaterials, have the capacity to accumulate within highly porous vasculature of diseased tissues. However, such accumulation is often uncontrollable, rendering it ineffective for lesions lacking vascular alterations. To address this challenge, researchers have integrated concepts of active accumulation, timed, or controlled release characteristics into the design of MOFs.30 This responsive process involves changes in physicochemical properties and, comparatively, external stimuli-responsive systems offer superior spatiotemporal drug release, exhibiting greater potential for biomedical applications.31 In the diagnostic process of malignant tumors, MOFs exhibit characteristics of high sensitivity, broad recognition range, and clear visuality. The alteration of MOF shape and size can be achieved through modulation of precursor materials, bonding methods, and environmental conditions.32,33 As composite materials, MOFs require the combination of precursor substances and chelating ligands with different physicochemical properties to attain optimal performance. Numerous therapeutic MOFs have been reported in existing research, including titanium-based metal–organic frameworks, crystalline MOFs, nanosheet metal–organic frameworks, mixed-metal MOFs, iron-based metal–organic frameworks, and gallium-based metal–organic frameworks.13 When employed in tumor therapy, the nanoscopic properties of MOFs can orchestrate the formation of specific subcellular organelles at precise concentrations. Leveraging their tunability in dimensions, sizes, bonding, and surface modifications, MOFs exhibit targetability towards tumor lesions by surface compounds such as proteins, DNA, polymers, and nucleic acids.34,35 Tailoring MOF modification strategies according to diverse scenarios enables them to retain their targeting and responsive release properties even within complex microenvironments, thus expanding their scope of application. For instance, extensive research has been conducted on MOFs in immunotherapy for immune-related diseases and malignant tumors.36 In harnessing the stimulant-responsive properties of MOFs, biomedical researchers endeavor to pioneer innovative strategies for drug delivery, imaging, disease diagnosis, and treatment.37 Throughout this developmental journey, researchers also prioritize the design and augmentation of MOFs for enhanced targeting, thereby bolstering their utility within intricate microenvironments.

This article provides an overview of the advantages of stimuli-responsive MOFs and their potential in biological applications. It reviews recent design strategies for stimuli-responsive MOFs, including the selection of in vivo and in vitro stimuli sources, as well as the choice of metal ions and organic ligands. The common synthesis methods and their pros and cons, structural modifications, and functional enhancements are summarized. Additionally, we discuss the main types of stimuli-responsive MOFs in the biomedical field, elucidating their strengths and weaknesses through examples.38 Finally, based on existing research reports, we provide a summary of the biomedical directions of stimuli-responsive MOFs.

2. Design of stimuli-responsive MOFs

The synthesis and design of stimuli-responsive MOFs represent a dynamic and evolving frontier in materials science, holding significant value for biomedical applications. It is imperative to comprehend the characteristics, types, and interactions of metal ions and organic ligands within these stimuli-responsive MOFs. Subsequently, the controlled manipulation of suitable properties through judicious design is paramount to adapt to specific biomedical scenarios. Likewise, the selection of specific stimuli response during the initial design phase, tailored to impart desired functionalities, is essential to meet the requirements of distinct biomedical applications.13 Researchers have delved into various strategies for integrating stimuli-responsive components into MOF structures, including functionalization with pH-sensitive moieties, biologically signaling units, temperature-responsive linkers, and photoactive groups.39,40 These design principles enable precise control over MOFs’ response to external stimuli, fostering applications such as controlled drug delivery, biosensing, and imaging.

2.1 Endogenous versus exogenous stimuli

The tunable characteristics and responsiveness of stimuli-responsive MOFs, coupled with their versatility in responding to various stimuli, necessitate careful consideration in the design of stimulus sources. In biomedical applications, the
stimulus sources for stimuli-responsive MOFs can be categorized into endogenous versus exogenous stimuli. Studies have shown that endogenous stimulus sources mainly encompass biological systems, including biomolecules, pH, osmotic pressure, temperature, enzymes, and redox potential (Fig. 1). Under these endogenous stimuli, variations in MOF structure and function can manifest corresponding expression patterns within different physiological microenvironments. Designing MOFs responsive to endogenous stimuli presents unique advantages in targeted drug delivery and therapeutic interventions. The acidic microenvironment of tumors induces pH-responsive MOFs to undergo functional transformation, facilitating drug release at the site of lesion. Additionally, the redox gradient of intracellular oxidants such as peroxynitrite in tumors can trigger redox-responsive MOF transformations, leading to cargo release. Enzyme-responsive MOFs, leveraging high substrate specificity and catalytic properties, hold promise as an ideal responsive strategy. Enzymatic reaction-based MOFs undergo controlled degradation in the presence of specific enzymes, facilitating triggered drug release for precise therapeutic delivery. Endogenous stimulus-responsive MOFs, unaffected by temporal and spatial constraints within the body, undergo passive release upon entry into the human body. While this may enhance the targeting and biocompatibility of MOFs, it poses a challenge to their manipulability. Moreover, such targeting may become overly pervasive, necessitating structural modifications to enhance the discernment between diseased and healthy tissues.

The design of MOFs responsive to exogenous stimuli enables remote and non-invasive propulsion of localization, thereby controlling drug release and therapeutic activity. Exogenous stimuli-responsive MOFs respond to external factors such as light, temperature, pressure, and magnetic fields (Fig. 1). In contrast to endogenous stimuli, exogenous stimuli afford temporal and spatial control. This capability allows us to initiate direct cargo release at specific sites by activating MOFs, thereby maximizing therapeutic efficacy in diseased tissues. However, this spatiotemporally controlled delivery also confronts challenges related to the prolonged duration from MOF entry into the body to triggering by exogenous stimuli. Failure to achieve precise localization relative to healthy tissue poses a barrier to further therapeutic intervention. External stimuli sources typically entail higher costs, such as maintaining light sources, magnetic fields, and ultrasound, which are also considerations in the design process. Moreover, the selection of external stimuli sources is crucial. Studies have found that near-infrared laser (NIR) exhibits outstanding qualities in triggering processes of photothermal nanomaterials and photodynamic nanomaterials, including strong tissue penetration, low absorbance, and minimal tissue damage compared to other triggering light sources. Based on the research findings, when MOFs are irradiated in the region spanning from deep infrared to near-infrared light, they exhibit tunable emission characteristics. Additionally, they demonstrate high spatial resolution, excellent contrast, minimal cytotoxicity to live cells, and good penetration. These advantages hold significant implications for the advancement of photoacoustic imaging. Researchers utilize enzymatic activation pathways to ensure high specificity and selectivity by responding to substrates at multiple sites. Simultaneously, exogenous stimuli are introduced to minimize MOF-induced damage to healthy tissues. Combining endogenous and exogenous stimulus-response mechanisms within individual MOF systems can amplify overall reactivity, versatility, therapeutic efficacy, controllability, and multifunctionality in targeted delivery, imaging, and therapeutic applications. Complex dual-responsive MOF systems hold the potential to enhance spatiotemporal control over drug release, particularly within intricate biological environments, thereby offering promise in addressing pertinent challenges.

2.2 Metal ions and organic ligands

MOFs, crystalline nanoporous materials comprised of metal ions coordinated with organic ligands, also known as porous coordination polymers, represent a versatile platform for myriad biological applications. To tailor MOFs for diverse biological uses, various metal ions and organic ligands can be meticulously selected to confer distinct functionalities. Commonly reported metal ions include cobalt (Co), iron (Fe), zinc (Zn), chromium (Cr), and others. Additionally, alkali earth metal ions and lanthanide metal ions have also garnered attention to a certain extent. Conversely, organic ligands on the other hand encompass compounds such as dinitrophenylamine, isonicotinic acid, pyridine, and phthalic acid derivatives, typically forming MOFs through coordination bonds. The multifaceted platform of MOFs is profoundly influenced by the selection of metal ions and organic ligands, impacting their morphology, functionality, and responsiveness to stimuli, thus bearing significant implications for various biomedical applications. Alterations in the physicochemical properties of MOFs through inorganic metal ions and organic ligands contribute to enhanced drug loading capacity and applicability. Choosing different metal ions bestows upon MOFs distinct characteristics such as stability, biocompatibility, porosity, and stimuli responsiveness. The aforementioned common transition metal ions (such as zinc, copper, and iron)
portend diverse coordination geometries and redox activities. Zinc and magnesium ions, conversely, serve to mitigate cytotoxicity and enhance the biocompatibility of MOFs. Organic ligands adorned with specific functional groups can be custom-tailored to interact with biological targets seamlessly. Incorporating functional groups such as carboxylates, amines, or phosphonates can bolster drug loading capacity and facilitate targeted drug delivery. Modulating the structure and properties of organic ligands enables fine-tuning of MOFs' reactivity and responsiveness to stimuli. The regulation of crucial properties such as ligand acidity and basicity, hydrophobicity, and hydrophilicity enables control over drug release kinetics and the intensity of response to endogenous or exogenous stimuli. Following the synthesis of MOFs accomplished through the meticulous selection of metal ions and organic ligands, characterization and evaluation become imperative. Analytical techniques such as X-ray diffraction, spectroscopy, and microscopy aid in comprehending the crystal structure, porosity, and surface characteristics of MOFs post-synthesis and upon stimulus-induced transformations. This comprehensive assessment elucidates the structure–function relationship of stimuli-responsive MOFs and their behavior in response to stimuli.

3. Fabrication of stimuli-responsive MOFs

Once the meticulous design of synthesis parameters for stimuli-responsive MOFs is completed, it necessitates the adoption of rational synthesis methods. By considering specific stimuli such as pH, temperature, or biomolecules, guidance can be provided for the selection of both metal ions and organic ligands, crucial components, to attain the desired responsiveness and broad applicability of MOFs. The synthesis of ligand–metal salt mixtures (MOFs) typically requires temperatures around 273.15 °C, thus most synthesis methods involve heating. These sources of thermal energy generally come in the form of ovens, ultrasonic radiation, microwaves, electromagnetic radiation, potential, and mechanical energy, among others. According to existing reports, methods for synthesizing MOFs mainly include dry-gel conversion, microfluidic MOF synthesis, microwave-assisted synthesis, solvothermal method, hydrothermal synthesis, ionothermal synthesis, diffusion method, chemical synthesis, sonochemical synthesis, mechanochemical synthesis, and electrochemical synthesis (Fig. 2). The selection of synthetic pathways for MOF synthesis can profoundly influence its morphology, surface morphology, particle size distribution, structure, crystallinity, and surface area, thereby impacting its responsiveness and biomedical applicability. Similarly, in the preparation process, process parameters (such as reaction temperature, reaction time, environmental pressure, etc.), pH value, solvent characteristics, reagents, bonding substituents, and metal ion concentration are also crucial for MOF properties. The coordination synthesis process of MOFs through metal ions and organic ligands necessitates intricate procedures to control the preparation of well-defined structures. For instance, parameters related to the type of heat source and thermal energy during the production process can affect the porosity of MOFs. Although composed of the same synthetic raw materials including metal ions, organic ligands, and solvents, the resultant parameters such as yield, pore size, particle distribution, reaction time, and surface morphology vary among mixtures. Various external factors during synthesis such as hydrolysis and calcination, alongside internal factors, influence the sophisticated chemical reactions between organic and inorganic components, thereby altering the structure of MOFs. In this section, we will primarily focus on elucidating common synthetic methodologies for fabricating stimuli-responsive MOFs. Researchers devising synthesis strategies must consider factors such as low cytotoxicity, green synthesis principles, scalability, and reproducibility to ensure the translational potential of stimuli-responsive MOFs in biomedical applications ranging from drug delivery to biosensing. The stability of MOFs in aqueous solutions is crucial for their application in biological imaging platforms, where environmental stability becomes a paramount concern given the scenarios of bodily fluids. Enhancing the coordination bond strength between organic ligands and inorganic metal clusters can mitigate the degradation of MOFs in aqueous solutions or water vapor, a process wherein metal coordination ligands are substituted by water or hydroxyl ions. Researchers have discovered that MOFs constructed from Lewis acids (low-valence labile metal ions and azobenzene-based ligands) or hard Lewis acids (high-valence metal ions and carboxylate-based ligands) exhibit greater stability compared to those formed from soft Lewis acids and hard Lewis acids.

The dry-gel conversion (DGC) technique, as a recently developed technology, inherently possesses numerous advantages. DGC technology offers a plethora of benefits, including high yield, scalability, reduced reaction volumes, material savings, environmental friendliness, reproducibility, and the capability to synthesize various MOF structures. The DGC technique stands as a ubiquitous method for synthesizing MOFs, offering precise control over particle size, morphology, and surface area. Initially, a gel precursor solution containing solvents, metal ions, and organic ligands is prepared. Upon heating, the solution undergoes gelation through solvent evaporation or chemical cross-linking, leading to structural rearrangement and the formation of a solid gel. Subsequently, the gel is subjected to controlled drying conditions, often under vacuum or elevated temperatures, to remove solvents, resulting in a porous network structure of dried gel. The crystallization of MOF structures within the porous framework of dry gels, yielding high-performance MOF crystals, primarily entails two strategies. One such strategy involves vapor-phase transport (VPT), where amorphous porous dry gels transition into a crystalline state through exposure to volatile amines and water vapor. Alternatively, if the dry gel contains non-volatile amines, crystallization occurs via another approach known as steam-assisted crystallization (SAC), where crystals form in the presence of steam. DGC facilitates the incorporation of various functional groups and guest molecules into the MOF.
framework, thereby enhancing its potential for biomedical applications.

The sonochemical method, utilizing high-energy ultrasound ranging from 20 to 1000 kHz as a heat source to drive chemical reactions in the reaction mixture for the synthesis of MOFs, stands as a pioneering technique among early methods for MOF synthesis. Its primary advantages include rapid reaction kinetics, mild conditions, low cost, high yields, uniform particle distribution, short reaction times, scalability, environmental friendliness, economic efficiency, and low thermal degradation rates. Existing studies have reported the application of sonochemical synthesis in the fabrication of various MOFs such as HKUST-1, IRMOF-9, MIL-88, MOF-75, MOF-5 (IRMOF), PCN-6, and others. In the realm of sonochemistry, solvent ultrasound induces the formation of copious bubbles and voids. Within the acoustic field, precursor solutions undergo cavitation, whereby bubbles interact incessantly, influenced by alternating pressures, leading to their regular rupture. The accumulation of ultrasonic energy engenders locally elevated temperatures and pressures, fostering the uniform generation of MOFs. Remarkable cooling rates signify heightened reactivity of reactants, facilitating rapid energy dissipation conducive to the uniform crystallization of MOFs. Vaitsis et al. incorporated solvothermal and sonochemical
methods in the synthesis of zinc-based MOFs, resulting in smaller particle size of the MOFs due to reduced reaction time. They elucidated that process parameters such as reaction time, temperature, solvent ratio, and concentration significantly influence the surface morphology and particle size of MOFs during sonochemical synthesis. In their study, Qiu et al. employed sonochemical method for the first time in the preparation of fluorescent nanoporous metal–organic framework (NMOFs) crystals.

In addressing the commercialization challenges of MOFs, electrochemical synthesis emerges as a pivotal solution. Electrochemical synthesis can be categorized into direct or indirect strategies. In the direct approach, a continuous provision of metal ions from an electrolyte mixture dissolved at the anode in an electrochemical bath reacts with the conductive salt generated from the organic linkers. Consequently, MOF crystals are synthesized in proximity to the electrode. On the other hand, the indirect strategy involves the reduction and deprotonation (electrochemical-like reaction) synthesis of MOF crystals, followed by linker anchoring and surface modification to achieve the desired functionalities of MOFs. The primary advantages of electrochemical synthesis encompass short reaction times, rapid synthesis rates, low energy consumption, efficient utilization of linkers, high yields, mild experimental conditions, and avoidance of anions in metal salts. Notably, this method has been applied to MIL-100(Al), MIL-53(NH₂), AlMIL53NH₂, ZIF8, HKUST-1, and HKUST13, among others. Since the initial synthesis of porous MOFs through mechanochemistry in 2006, scholars have been captivated by its potential. Mechanochemistry involves the application of mechanical force to induce cleavage, accompanied by chemical repairs, constituting a blend of chemical reaction and physical phenomena. This approach boasts advantages such as solvent exclusion, environmental friendliness, scalability, and production of quantified fine particles. Studies have demonstrated the synthesis of HKUST-1, ZIF-8@alginateNPs, MOF-14, among others, through mechanochemical means.

Ionothermal synthesis typically occurs in water or organic solvents, but recent reports have also highlighted the utilization of ionic liquids (ILs). Upon heating a mixture of metal salts and organic linkers in an ionic liquid, self-assembly of MOFs occurs. Subsequently, solvent exchange, heat treatment, or vacuum processing is required to achieve further purification of the MOFs. Ionic liquids play a crucial role as solvents in the chemical transformations during ionothermal synthesis, possessing unique properties such as high solvation potential, virtually zero vapor pressure, excellent thermal stability, reproducibility, and cost-effectiveness.

The process of microwave (MW)-assisted synthesis entails dissolving a mixture of substrates in a suitable solvent, transferring it into a polytetrafluoroethylene container, and sealing it within a microwave apparatus. Heating under microwave irradiation (electromagnetic radiation of 1 to 104 mm) for 4 minutes to 4 hours in the microwave device facilitates a rapid nucleation process, yielding MOFs with uniformly distributed particle sizes. The energy transfer process may involve both ionic conduction and dipole rotation. The primary advantages of microwave-assisted synthesis include short reaction times, balanced heating, high purity, uniformity, high yields, low toxicity, monodispersity, green energy conservation, rapid heating, high potential for monodispersity control, and excellent selectivity. However, challenges lie in solvent selection for the dissolution of the substrate mixture and the reaction vessels used for loading, as they can influence the conversion between electromagnetic radiation and thermal energy. Recent studies have reported the microwave-assisted synthesis of various MOFs, including MOF-5, Fe-MIL-53, ultrathin nickel-iron-based trinmetallic MOF nanosheets with cobalt ion vacancies, Cr-MIL-100, and ZIF-8.

Temperature stands as a pivotal factor in the synthesis of MOFs, constituting a key aspect of conventional heating wherein mere elevation of temperature occurs without any additional reactions, defining what is known as the conventional synthetic pathway. The approach of elevating reaction temperature can be divided into solvent-thermal and non-solvent-thermal synthesis, each characterized by distinct temperature ranges. Solvent-thermal synthesis, also known as hydrothermal synthesis, involves heating the solvent within a sealed vessel to temperatures ranging from 80 to 260 °C, followed by a reaction period of 48 to 96 hours or even longer. Components such as cations, polymers, and surfactants within the mixture exert influence over the surface morphology and properties of MOFs. Noteworthy studies have demonstrated the synthesis of MOFs such as MIL-53(Fe) and MIL-101 through solvent-thermal methods. In non-solvent thermal synthesis, the solvent temperature within the reaction vessel exceeds the boiling point of water, facilitating further reactions at room temperature or even higher temperatures. This method, operating under pressures below or at the boiling point, eliminates the need for complex reaction apparatus, thereby simplifying the synthetic process. Studies have documented the synthesis of MOFs such as ZIF-8 (zeolitic imidazolate framework), MOF-177, HKUST-1, MOF-5, and others using non-solvent thermal methods.

Diffusion method, as a mild synthetic strategy, encompasses primarily three avenues: gas-phase diffusion (vapor diffusion method), gel diffusion, and liquid-phase diffusion. Gas-phase diffusion involves the mixing of reactants such as deprotonated organic ligands and metal ions in an open container with low-volatility solvents, followed by transfer into a sealed container containing easily volatile solvents. Highly volatile solvents permeate through the reaction medium, facilitating the formation of MOFs. In gel diffusion, the gel serves as both the diffusing and crystallizing medium, thereby mitigating diffusion and the deposition of larger materials. During the synthesis of MOFs via gel diffusion method, organic linker groups and metal ions are thoroughly mixed in a solution containing gel. The synthesis phase necessitates a prolonged reaction time, extending up to several weeks. MOFs are formed as a result of the reaction between reactants dissolved...
in the solvent. In the liquid-phase diffusion method, metal salts and organic ligands are added to an insoluble solvent and allowed to diffuse within the solvent. Emulating crystals, growth occurs at the interface of low-density solvent layers, where both metal salts and ligands can diffuse.

The application of microfluidic technology in MOF synthesis has enabled faster and more sustainable processes, meeting the ever-growing demands of industry and commerce. Initially, microfluidic technology synthesizes an aqueous phase of metal salts and organic ligands, resulting from the mixture of both components in solution. Subsequently, with the assistance of syringe pumps, droplets of the solution are continuously introduced into the organic phase, ultimately yielding MOFs. Microfluidic technology has been reported for the preparation of HKUST-1, ZIF-8, and MIL-100(Fe). Its advantages lie in its ability to produce more uniform, better crystalline, precisely controlled, and scalable production of MOFs. The reverse microemulsion method involves reacting substances confined within water droplets (restricted within reverse micelles), producing uniformly shaped and sized nano-MOFs. The synthesis process can adjust the micelle size to modify the morphology of MOFs, endowing them with exciting imaging properties.

Fig. 3 shows scanning electron microscopy (SEM) images of some of the MOFs mentioned in this review.

### 4. Modification of MOFs

MOFs, due to their tunable structures, dual-drug loading capability, precise volumes, high surface areas, and surface modifications, offer a versatile platform for biomedical applications. They hold a prominent position as one of the optimal candidates in the field of cancer therapy. Modification and functionalization strategies play a crucial role in adjusting the properties of MOFs to meet specific biomedical requirements. Post-synthetic strategies such as functionalization, covalent bonding, ligand exchange, guest encapsulation, lipid bilayer coating, post-synthetic modification (PSM), cell membrane coating, coordinated self-assembly, and surface modification enhance the desired characteristics of MOFs, including stimulus responsiveness, adaptability, and biocompatibility.

Covalently synthesized MOFs, through further modification and functionalization with specific functional groups attached to linking molecules, enable surface modification of MOFs. The materials required for modification and functionalization exhibit diversity, with the potential for multifunctionality by targeting either the inorganic nodes or organic linkers of MOFs. Functionalization achieved through coordination interactions involves the coordination of metal ions or ligands with functional groups or biomolecules, imparting specific functionalities to MOFs.

Surface modification techniques encompass surface coating, functional group grafting, and encapsulation of bioactive molecules such as drugs, enzymes, or imaging agents. Conjugated hydrophobic groups in MOFs possess hydrophobicity, facilitating selective diffusion of active molecules within the interfacial layer.

### 5. Classifications of stimuli-responsive MOFs-based nanomaterials

Stimuli-responsive MOFs in biomedicine exhibit dynamic behaviors in response to external stimuli, facilitating controlled drug delivery, imaging, and sensing by incorporating different stimuli-responsive groups or materials. External stimuli vary due to diverse materials such as glutathione (GSH), imidazole (pH), and porphyrin (light), encompassing oxidation–reduction, pH, light, ion, magnetic field, glucose, ATP, pressure, H2S, temperature, or enzymatic activities. Upon stimulus...
Table 1  Characterization of stimuli-responsive MOFs

<table>
<thead>
<tr>
<th>Composites based on stimuli-responsive MOFs</th>
<th>Type of stimulus</th>
<th>MOF composites preparation process</th>
<th>Trigger material</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>DOX@Fe@ZIF-8 hybridized nanoparticles 3,4-Dihydroxybenzaldehyde (DHBD)@UiO-66-NH₂/5-fluorouracil(5-FU)@carboxymethyl cellulose (CMC)/Ca²⁺/alginite (Alg.)</td>
<td>PH</td>
<td>A one-pot mineralization method solvothermal approach and the Schiff base reaction approach</td>
<td>ZIF-8</td>
<td>121</td>
</tr>
<tr>
<td>Folic acid-coupled chitosan-coated bi-MIL-88B MOF loaded with 5-FU</td>
<td>PH</td>
<td>Two-step secondary building unit (SBU) approach The solvothermal technique</td>
<td>UiO-66-NH₂</td>
<td>122</td>
</tr>
<tr>
<td>DOX@C/MOCZn-based metal–organic framework (MOF-5)/graphene oxide (GO)</td>
<td>PH</td>
<td>Straight-forward nano-precipitation technique</td>
<td>CMC</td>
<td>123</td>
</tr>
<tr>
<td>DOX@PCN-224-DNA UiO-66-350-phosphonic acid (H₂PA)-[Pt(NH₃)₄Cl₂(OH)₂]</td>
<td>PH</td>
<td>According to the previous literature. Competitive coordination of PO₄⁶⁻/H₂PO₄⁷⁻/H₃PO₄³⁻ to Zr⁴⁺</td>
<td>ZIF-90 (imidazoly)</td>
<td>125</td>
</tr>
<tr>
<td>Ibutopon [Ibu]@UiO-66-NH₂ Methotrexate (MTX)@Zif-90-O₂-DOX-NH₂-6-poly(ethylene glycol) modified folic acid (PEGFA) UiO-66-NH₂-5-FU@Zn-cpon-1</td>
<td>Ion</td>
<td>Impregnation method Mix, heat, cool and filter.</td>
<td>—</td>
<td>126</td>
</tr>
<tr>
<td>ZIF-8, Eu₃⁺, Tb₃⁺ (Eu³⁺ and/or Tb⁴⁺ ions)@gold nanoparticles (AuNPs, heater)</td>
<td>PH</td>
<td>The rapid room-temperature production Modified co-precipitation method</td>
<td>Lanthane ions (Eu³⁺ and Tb⁴⁺)</td>
<td>130</td>
</tr>
<tr>
<td>Fe₂O₃ nanorods@nanocrystals of Cu₃BTC₂ (HKUST-1) magnetic drug carrier</td>
<td>PH</td>
<td>Magnetic response</td>
<td>Fe₂O₃ nanorods</td>
<td>131</td>
</tr>
<tr>
<td>Magnetic nanoscale metal–organic frameworks (M-NMOFs) Perfluoropentane (PFP)@Fe/Cu-SS (MOF) Curcumin (CCM)@MOF-Zr DTBA (Zr₄-4',4'-dihydroxybenzonic acid)</td>
<td>PH</td>
<td>Redox</td>
<td>—</td>
<td>132</td>
</tr>
<tr>
<td>Rhodamine 6G fluorescent dye or DOX@Aptamer-NMOFs ZIF-90-Cas9 nanoparticles [Cu₃(ZnTepp)-H₂O₂] (NP-1)</td>
<td>ATP</td>
<td>Chemical synthesis</td>
<td>Aptamer-NMOFs</td>
<td>135</td>
</tr>
<tr>
<td>Water-stable UiO-68-azo (azobenzene groups)@β-CD Mn carbonyl modified PEGylated Fe(III)-based nanoMOF (MIL-100) coated magnetic carbon NPs (MCM@PEG-CO-Dox) The micelles of selenium-containing polymers (P)@ZIF-8@DOX</td>
<td>ATP and pH</td>
<td>One-step self-assembling method</td>
<td>AP-ZIF-90</td>
<td>141</td>
</tr>
</tbody>
</table>

recognition, MOF structures undergo reversible or irreversible changes, including molecular protonation, pore opening/closing, framework deformation, conformational alterations, or structural hydrolysis or cleavage, to control the release of cargo molecules such as drugs, contrast agents, or therapeutic proteins.¹¹⁸ The structural alterations are pivotal in modulating the kinetics of encapsulated drug release and selectivity. Controlled release mechanisms ensure targeted delivery, thereby mitigating off-target effects.¹⁶,¹²⁰ Crafting multifunctional stimuli-responsive ligand-coupled MOFs directs their potential interactions with biological entities such as cells or tissues post-cargo release. Modulating cellular signaling pathways, gene expression, or enzyme activity engenders the deployment of MOF delivery platforms to tumor sites.¹²⁶ Understanding the stimuli-responsive pathways of MOFs in biomedicine holds paramount significance in designing next-generation drug delivery systems, therapeutic agents, and biomedical devices with heightened efficacy and specificity. Table 1 shows the characterization of stimuli-responsive MOFs.

5.1 pH-Responsive

The investigation and application of pH-responsive metal–organic frameworks (MOFs) in drug delivery systems have garnered considerable attention, playing an indispensable role therein.¹²¹ Wang et al.¹ succinctly encapsulated the release mechanisms of pH-responsive MOFs, highlighting four key facets: protonation-induced coordination bond cleavage, pH-cleavable bonds, pH-sensitive materials, and host-guest
interactions. The sensitivity of coordination bonds to external pH variations and the pH fluctuations within the tumor microenvironment serve as triggers for controlled drug release. MOFs can be tailored with pH-responsive components, such as acidic or basic functional groups, to confer pH sensitivity (Fig. 4A and B). These functional groups and materials undergo protonation or deprotonation with pH changes, consequently leading to structural modifications or cargo release. Nanostructured MOFs, endowed with pH-responsive mechanisms through the incorporation of protonatable and deprotonatable materials and functional groups, facilitate the orchestrated release of therapeutic agents (Fig. 4C and D). In acidic environments, the organic ligands or functional groups within the MOF undergo protonation, inducing pH-triggered degradation and cargo release. MOF drug delivery systems responsive to pH gradients in physiological and acidic environments are exceptionally well-suited for cancer-related therapies. pH-responsive MOFs have shown promise in cancer treatment by enhancing drug efficacy, reducing systemic toxicity, and improving therapeutic outcomes. Research indicates that pH values associated with tumors generally trend lower compared to normal physiological environments, such as the tumor microenvironment (pH 5.7–7.8), lysosomes (pH 4.5–5.0), and endosomes (pH 5.5–6.0). Fine-tuning the organic chains within nanoMOFs enables pH-responsive degradation. Materials sensitive to low pH, unstable bonds, and MOFs undergo structural breakdown in acidic environments, triggering the release of loaded drugs. Among these,
materials sensitive to low pH encompass a spectrum of substances including chitosan (CS), DNA, carboxymethyl cellulose (CMC), glucose, polyketal, and gelatin polymers. Low pH-labile bonds, on the other hand, comprise a diverse array including amide, ester, imine, acetate, oxime, epoxy, Schiff base, imide, polycetal, benzylidene imine, polyketone, ether, hydrazone, and sulfonate bonds. Furthermore, low-pH-sensitive MOFs include MIL-100, UIO-66, ZIF-8, and DUT-66, among others. ZIF-8 is synthesized using 2-methylimidazole as an organic ligand under alkaline conditions. Under acidic environments such as those found in cancer, ZIF-8 undergoes protonation reactions with H+, leading to structural degradation and controlled release of loaded therapeutic agents. The conventional approach to pH-sensitive materials typically involves encapsulating them around the exterior of pharmaceutical agents, affording precise control over drug release while mitigating premature leakage of the medication. Research suggests that the acid-sensitive material chitosan (CS) possesses biocompatibility, rendering it suitable as a surface-modifying agent for nanoscale MOFs. Nano-MOFs adorned with surface-modified CS undergo protonation reactions in low pH environments, engendering a profusion of hydrogen bonds that form robust networks within the chains. The amino chains adopt an expanded random loop conformation, facilitating drug diffusion away from the MOF, thereby instigating drug release. Conversely, nanoscale MOFs undergo deprotonation reactions in higher pH environments, prompting skeletal contraction of the material. The term “pH-responsive cleavable bonds” refers to covalent bonds through which drugs are attached to MOF carriers, specifically selecting acid-labile bonds, which undergo cleavage in low-pH environments. Under acidic conditions, these covalent bonds undergo hydrolysis, triggering the selective release of therapeutically effective payloads within tumors, thereby reducing off-target effects.

In contrast to the proton-induced disruption of coordination bonds resulting in internal collapse of MOF frameworks between organic ligands and metal ion clusters, host–guest interactions occur between stimuli-responsive MOFs and loaded pharmaceutical agents. Host–guest interactions primarily encompass hydrogen bonding, electrostatic interactions, and π–π stacking interactions. MOFs such as CAU-8, UIO-66, ZJU-n, and MIL-n exhibit abundant functional groups, which undergo protonation as the pH decreases, thereby engendering electrostatic interactions. The physiological variations and pathological conditions correspond to diverse pH gradients, where host–guest interactions serve as the driving force to precisely regulate the release of loaded cargo in response to pH stimuli. Likewise, the encapsulation of loaded cargo at different locations within MOFs implies distinct hydrogen bonding conformational patterns, ultimately leading to varying rates of cargo release. By harnessing the pH gradients within biological systems, these MOFs can exert precise spatiotemporal control over the dynamics of drug release, offering potential solutions for the treatment of cancer and other ailments. In various phosphate-buffered solutions with pH values of 5.4 and 4.0, its structure dissipated, demonstrating its sensitivity to pH. Moreover, during the transition from pH 8.0 to pH 5.0, the release amount surged from 35% to 80%, underscoring its enhanced release performance at lower pH levels. The phenomenon of protonation-induced cleavage of coordination bonds, alongside the presence of pH-sensitive cleavable bonds, materials exhibiting pH responsiveness, and intricate host-guest interactions, has the potential to augment both biocompatibility and stability, all while preserving pH responsiveness. In a recent study, Cao et al. utilized the zeolitic imidazolate framework-8 (ZIF-8) loaded with doxorubicin (DOX) and iron (Fe), resulting in the preparation of DOX@Fe@ZIF-8 nanoparticles for the construction of magnetically actuated microbots based on MOF (MMRs). Under the manipulation of a magnetic field, pH-responsive drug release enables targeted cancer therapy. Moreover, MMRs exhibit significant potential for biomedical applications such as magnetic resonance imaging (MRI), ultrasound imaging, and monitoring. A comprehensive comprehension of the pH-responsive mechanisms inherent in metal–organic frameworks (MOFs) within the realm of biomedical applications stands as an indispensable cornerstone for the advancement of meticulously controlled kinetics in drug release and the creation of bespoke, targeted drug delivery systems tailored for the exigencies of biomedicine.

5.2 ATP-responsive
The development of adenosine triphosphate (ATP)-responsive metal–organic frameworks (MOFs) as drug delivery carriers for tumor therapy is rooted in the heightened energy demands of proliferating and growing tumor cells, which rely heavily on glycolysis for ATP production. The efficiency of ATP generation via glycolysis surpasses that of normal cells. The pathological upregulation of ATP during tumorigenesis provides novel insights into the design of ATP-responsive MOF drug delivery systems. ATP, as a ubiquitous high-energy compound in biological systems, serves as the primary energy currency by hydrolyzing phosphate bonds to generate requisite energy. The mechanism underlying ATP-responsive release primarily involves the formation of ATP aptamer complexes and the formation of ATP ion chelates. In the mechanism of ATP-aptamer complex formation, DNA forms stable ATP-binding DNA structures by specific binding to ATP-jelly column through two stacked G-quadruplex structures. ATP can also form ATP-aptamer complexes with DNA/RNA, facilitating drug release. For two adenosine residues that may stack between two short stems and the top G-quadruplex to form a pocket, they can bind ATP or adenosine ligands. Studies have shown that the construction of a cap-like (lock-like structure) structure through DNA/RNA duplex gate control and complementary DNA complexation can lock cargo in the pores of NMOF. When transported to an environment with strong ATP stimulation, the formation of ATP-aptamer complexes leads to the unlocking of the cap structure, resulting in drug release. Chen et al. ingeniously encapsulated fluorescent dye
Rhodamine 6G or anticancer drug actinomycin within metal-organic framework nanoparticles (NMOFs), subsequently employing complementary nucleic acids (including ATP aptamer sequences or ATP–AS1411 hybrid aptamer sequences) for drug entrapment. Upon transportation to ATP-abundant sites, NMOFs react with ATP to form ATP-aptamer complexes, leading to the unlocking of cap-like structures and cargo release.\(^{135}\) Compared to normal tissues, cancer cells exhibit ATP overexpression, and the AS1411 hybrid aptamer sequence can recognize nucleolin receptors on the cancer cell membrane.\(^{13}\) ATP-responsive NMOFs, equipped with targeted penetration and ATP unlocking mechanisms, enable precise therapy targeting cancer cells. The research conducted by Chen et al.\(^{135}\) also revealed that ATP–AS1411-gated NMOFs selectively penetrate MDA-MB-231 breast cancer cells, significantly enhancing cytotoxicity. When loaded with doxorubicin, NMOFs exhibited high cytotoxicity against cancer cells. Moreover, differences were observed in the cytotoxicity of doxorubicin loaded onto NMOFs gated by different mechanisms. Specifically, ATP–AS1411 aptamer-gated NMOFs and ATP aptamer-gated NMOFs were applied to MDA-MB-231 cells.\(^{135}\) After 5 days, the cell death rates of MDA-MB-231 cells were observed to be 55% and 40% respectively, while under the same conditions, the cell death rate of MCF-10A cells was only 10%.\(^{135}\) In future investigations on NMOF release, the scope of aptamer recognition could be expanded to include biomarkers such as VEGF, or novel unlockable cap-like structures could be designed.

ATP also exhibits remarkable coordination capabilities, owing to the presence of nitrogen atoms in the imidazole ring, benzene ring, and amino group.\(^{136}\) The ability of nitrogen atoms’ lone pair electrons to engage in coordination reactions with metal ions varies.\(^{152}\) The formation of ATP–metal ion complexes involves the competitive coordination of ATP with certain metals (competitive coordination mechanism) through the lone pair electrons of nitrogen atoms.\(^{153}\) In the mechanism of ATP–metal ion complex formation, ATP competes for the metal sites of MOFs, inducing the rupture of the MOF framework and subsequently facilitating the release of carried drugs.\(^{135}\) Yang et al.\(^{136}\) reported that in the microenvironment where ATP is present, there is competitive coordination between Zn\(^{2+}\) and ATP within the zeolitic imidazolate framework-90 (ZIF-90), leading to the collapse of ZIF-90 and subsequent release of pre-loaded cargo. Furthermore, they discovered the self-assembly of imidazole-2-aldehyde (2-ICA), Zn\(^{2+}\), and proteins to obtain ZIF-90/protein nanoparticles. The research investigated the application of ATP-responsive ZIF-90 in cytoplasmic protein delivery.

### 5.3 Hydrogen sulfide-responsive

The development of hydrogen sulfide (H\(_2\)S)-responsive MOFs arises from the observation of remarkably high levels of H\(_2\)S in colorectal cancer cells during research.\(^{154,155}\) The mechanism of H\(_2\)S-responsive MOFs involves a dual decomposition reaction between Cu\(^{2+}\) ions and S\(^2-\) ions within the MOF structure, leading to the formation of Cu\(^{2+}\) precipitates.\(^{137,136}\) The Cu\(^{2+}\) ions in the MOF are extracted, thereby forming functional ligands. Ma et al.\(^{137}\) synthesized a photosensitizer MOF nanoparticle for photodynamic therapy of cancer, where Cu\(^{2+}\) ions serve as metal nodes in the MOF. Under light conditions, when present in specific tumor microenvironments (i.e., colorectal tumors with elevated H\(_2\)S), Cu\(^{2+}\) ions are removed from the MOF metal nodes, triggering the release of signals and exciting the release of singlet oxygen (\(^{1}\)O\(_2\)) from the cells.

### 5.4 Ion-responsive

The ion-responsive MOFs represent a novel class of materials with promising prospects in biomedicine, particularly in drug delivery. These MOFs are designed to undergo structural alterations or exchange mechanisms based on specific ions present in the biological environment.\(^{76}\) The robust electrostatic interactions between the ion drugs and the MOFs enable precise therapeutic interventions.\(^{142}\) Notably, there exists a formidable electrostatic interaction between the therapeutic drug moiety and the framework of MOFs, giving rise to intrinsic attraction. Upon entering the organism, ion exchange occurs through biological fluids, stimulating the diffusion and release of drugs.\(^{77}\) While most MOFs exhibit electroneutrality (resulting from the binding of positively charged metal ions with negatively charged organic ligands), some may manifest positive or negative charge properties. Ion-responsive MOFs are crafted with tailored ligands and metal ions, capable of selectively interacting with common ions found in biomedicine (such as PO\(_4^{3-}\)/HPO\(_4^{2-}\)/H\(_2\)PO\(_4^{-}\), Mg\(^{2+}\), Pb\(^{2+}\), Ca\(^{2+}\), K\(^{+}\), Zn\(^{2+}\)/Ca\(^{2+}\)).\(^{13,157–159}\) The mechanism governing the release of cargo in ion-responsive MOFs involves three primary modalities: competitive coordination (serving as the driving force over the other two forms), anion exchange, and the formation of nucleic acid–metal ion complexes.\(^{160}\) Competitive coordination entails the release of ionic cargo being regulated by ions with high binding affinities, acting as switches for release, in competition with ions of lower binding affinities, ultimately controlling the on-demand release of drugs.\(^{161}\) Tan et al.\(^{162}\) employed a post-synthetic modification (PSM) method for the first time on UiO-66-NH\(_2\) (monodisperse zirconium MOF) to introduce positively charged quaternary ammonium salt (Q) modified straw. Subsequently, 5-fluorouracil (Fu) was encapsulated within the pores of UiO-66-NH\(_2\), with negatively charged aromatic hydrocarbons (CP5) supramolecularly coating it, serving as nanowalls for the nanocarrier.\(^{162}\) Zinc ions (Zn\(^{2+}\)), with high affinity, competitively bind to the CP5 supramolecules, thereby regulating the release of 5-Fu embedded within the pores of UiO-66-NH\(_2\), thus controlling the sustained release of 5-Fu. This study is crucial for the application of MOFs in the treatment of brain diseases, necessitating extremely low premature release rates and cytotoxicity. When the UiO-66-NH\(_2\) composite was placed in a standard physiological concentration of Zn\(^{2+}\) solution, the release rate of 5-Fu was 5%.\(^{162}\) The release rate and amount of 5-Fu increased continuously with the increase in Zn\(^{2+}\) concentration, indicating its excellent Zn\(^{2+}\) responsive behavior.

Anion exchange harnesses the preferentiality and differential coordination abilities exhibited when anions coordinate...
with metal cations, facilitating drug release. MOFs coordinate with drugs, and when anions (such as \( \text{PO}_4^{3-}, \ \text{H}_2\text{PO}_4^- \)) are introduced, they can preferentially coordinate with metal cations, thereby stimulating drug release.\(^{161}\) For instance, the O atom in \( \text{PO}_4^{3-} \) provides a lone pair of electrons, endowing it with strong coordination capabilities. Upon mixing with ion-responsive MOFs (such as ZIF-8 or Zr-based MOFs like UiO-66-NH\(_2\)), \( \text{PO}_4^{3-} \) interacts with the metal oxide clusters of the MOF, weakening the coordination system of the drug, resulting in MOF collapse.\(^{72,77}\) In the study conducted by Miriam \textit{et al.}\(^{163}\) the introduction of ZIF-8 particles into phosphate-buffered saline (PBS 10 mM) resulted in rapid degradation of ZIF-8. The research elucidated that the degradation mechanism involves phosphate, which exhibits high affinity towards Lewis metal centers, thereby altering the coordination equilibrium between \( \text{Zn}^{2+} \) ions and 2-methylimidazole (HMIM) in the solution. Disruption of this equilibrium leads to the formation of insoluble zinc inorganic salt particles and HMIM.\(^{157}\) Furthermore, the rate of ZIF-8 degradation is also correlated with particle size, with smaller particles indicating a faster degradation rate. Wang \textit{et al.}\(^{127}\) conducted a quantitative investigation into the drug-loading capacity of Zr-based MOFs (UiO-66-NH\(_2\)). In their study, ibuprofen was immersed into the porous structure of UiO-66-NH\(_2\) using a wet impregnation method. The fixation of ibuprofen within UiO-66-NH\(_2\) was achieved through hydrogen bonding between them, as well as \( \pi-\pi \) interactions of the dicarboxylic benzene rings.\(^{127}\) Subsequently, to mimic the acidic tumor microenvironment, the MOF was exposed to a phosphate-buffered saline solution (PBS, pH \( \approx 3 \)) for examination. The interaction between \( \text{PO}_4^{3-} \) in PBS and the metal oxide clusters led to the release of ibuprofen, demonstrating a drug-loading capacity of 55 milligrams per gram for UiO-66-NH\(_2\).\(^{72}\)

In the synthesis strategy of nucleic acid–metal ion composite systems, the nucleic acid-functionalized metal–organic framework nanoparticles (NMOFs), laden with drug cargo, covered by DNAzymes triggered by specific ions, are constructed through “click chemistry.” The enveloping DNAzymes possess metal ion-dependent and sequence-specific ribonucleic acid or nucleic acid bases\(^{159}\) (Fig. 5). Under specific circumstances, the formation of the nucleic acid–metal ion composite system occurs within the drug-loaded NMOFs.\(^{160}\) Subsequently, the nucleic acid caps dissociate, thereby regulating drug release. Chen \textit{et al.}\(^{159}\) have devised a covalent linkage system between DNAzyme sequences and NMOFs, with nucleic acids serving as anchoring points for stimuli-responsive behaviors, enveloping the NMOFs. The DNAzyme sequence exhibits specific metal-responsive characteristics, capable of forming nucleic acid complexes with Mg\(^{2+}\) or Pb\(^{2+}\), inducing catalytic cleavage of the covalent NMOFs system, thereby facilitating cargo release.\(^{159}\) This study reports the design of an Mg\(^{2+}\)/ATP-coordinated stimuli-responsive DNAzyme sequence covalently linked to NMOFs, demonstrating promising applications in the transfer of anticancer drug carriers, and holds potential for the development of novel stimuli-responsive MOF-based drug delivery systems.

### 5.5 Temperature-responsive

Temperature-responsive MOFs exhibit notable flexibility in research. The temperature gradient induced by elevated temperatures can delineate differences between diseased tissues and normal tissues.\(^{142,164}\) This disparity can induce the MOFs to possess targeting capabilities. While ensuring a thermally responsive reaction, the crystal topological structure of the MOFs also needs to be maintained, yet there remains a lack of observation regarding these nanoscale behaviors.\(^{165}\) As the temperature rises, the stability and interactions between the host and guest molecules in the MOFs decrease or become disrupted, and the affinity between temperature-responsive MOFs and active pharmaceutical ingredients weakens, accelerating the release of drugs from thermally sensitive MOFs.\(^{41}\)

Jiang \textit{et al.}\(^{166}\) delved into the realm of thermally responsive drug release utilizing biocompatible MOFs, investigating the \( \pi-\pi \) interactions between sodium dicyclofenac (DS) and the orthogonal-structured Zr MOF material (DS@ZJU-801). Due to the relatively loose interaction between the ligands of ZJU-801 and the drug, the \( \pi-\pi \) interactions can be disrupted upon heating, thereby achieving temperature-induced on-demand release. The study reported a drug loading capacity of DS@ZJU-801 reaching 41.7\%.\(^{166}\) When the temperature reached 60 °C, the drug release rate was 10.3 times higher compared to that at 25 °C, and approximately 3.4 times higher than at 37 °C. Balancing temperature control with the preservation of human tissues necessitates further investigation. Silva \textit{et al.}\(^{130}\) harnessed the adsorption capacity and thermal responsiveness of ZIF-8 crystals to synthesize a composite material, ZIF-8, EuxTby@AuNP, applied for the controlled release of caffeine (CAF) and 5-fluorouracil (5FU). In this composite, metal gold nanoparticles (AuNPs) act as nanoscale heaters, while Eu\(^{3+}\) and Tb\(^{3+}\) serve as temperature sensors within the material.\(^{130}\) The ZIF-8 crystals also exhibit biocompatibility and no detectable cytotoxicity. With the increase in temperature due to the exothermic adsorption of ZIF-8 crystals around AuNPs, a core–shell nanocomposite is formed, facilitating the eventual release of CAF-5FU. Under visible light, AuNPs absorb light, leading to a controlled release process by raising the temperature of the composite material. This novel, controllable ZIF-8, EuxTby@AuNP composite material demonstrates significant potential in the field of drug delivery.\(^{130}\)

### 5.6 Magnetically-responsive

The utilization of nano-magnetic MOFs encompasses unique physical and chemical properties, enabling novel functionalities such as magnetically responsive drug delivery within the context of anti-tumor therapy.\(^{83}\) Typically, iron-based magnetic materials are incorporated into nano-oxides for functionalization within MOFs.\(^{158}\) The carrier potential of magnetic MOFs, under the influence of an external magnetic field, precisely navigates to tumor sites owing to its robust magnetic responsiveness without inflicting harm upon the biological milieu\(^{109}\) (Fig. 6). Moreover, magnetic sorting post drug loading enhances targeting precision, offering controlled drug release by
manipulating the direction and frequency of the applied magnetic field.\textsuperscript{167} This characteristic heralds considerable promise for tumor-targeted therapy.\textsuperscript{13} Magnetic MOF carriers not only facilitate drug delivery but also serve diagnostic and therapeutic purposes in magnetic resonance imaging (MRI).\textsuperscript{157} The magnetically responsive delivery of targets driven by external magnetic fields plays a pivotal role in non-invasive power sources.\textsuperscript{37} Specifically, MOF-based magnetic-responsive structures have found successful applications in imaging-guided therapies and magnetic resonance imaging. In the study conducted by Zhang \textit{et al.},\textsuperscript{131} magnetic MOF composite drug carriers were fabricated utilizing Fe\textsubscript{3}O\textsubscript{4} nanorods (possessing magnetism) and Cu\textsubscript{3}(BTC)\textsubscript{2} nanocrystals (HKUST-1) as materials. This magnetic MOF carrier demonstrated magnetic targeting capability and high porosity for drug adsorption in the study, exhibiting considerable potential in drug delivery, magnetic resonance imaging, and magnetic separation.\textsuperscript{131} Current methods of drug administration typically require local injection or circulation through the bloodstream to reach the affected area and exert therapeutic effects. In order to concentrate medications at the site of pathology, researchers are increasingly exploring magnetically responsive drug delivery systems driven by external magnetic fields, aiming to significantly enhance targeting precision and reduce toxic side effects.\textsuperscript{168} Sharma \textit{et al.}\textsuperscript{132} ingeniously utilized magnetic nanoscale metal–organic frameworks (M-NMOFs) to deliver chemotherapy drug doxorubicin and photosensitizer methylene blue to the location of cancer cells for therapeutic purposes, with the M-NMOFs being completely degraded after fulfilling their mission. The ultra-supersuperparamagnetism of M-NMOFs allows for magnetically assisted sustained release to cancer cells. Furthermore, with the assistance of external magnetic force, the uptake of M-NMOFs by Panc-1 cell lines is further enhanced, amplifying the targeted cytotoxic effects of chemotherapy drugs and photosensitizers \textit{in vitro}.\textsuperscript{132}
Typically, these structures adopt a core–shell configuration, utilizing magnetic nanoparticles as the core and MOFs as the nano-carrier shell, designed for magnetically responsive drug delivery. Core–shell structures are commonly encountered in magnetically responsive drug delivery systems based on magnetic biomaterials, comprising a magnetic biomaterial core (such as metal oxides) surrounded by a MOF nano-material shell with specific pore structures. Researchers are actively harnessing magnetic biomaterials and MOFs to create efficient drug delivery systems. Magnetically responsive drug delivery is a unique technique influenced by an external magnetic field, enabling precise drug delivery to specific locations to enhance efficacy, while also enabling control of drug release through external magnetic fields. Importantly, magnetic structures based on MOFs serve a dual purpose, functioning as therapeutic systems for both magnetic resonance imaging and image-guided therapy. Zahra et al.’s study presents a multifunctional magnetic nano/micro MOF, wherein porous mesoporous MOF \( [\text{Cu}_3(\text{BTC})_2] \) serves as an anticancer drug carrier, while \( \text{Fe}_3\text{O}_4 \) nanoparticles act as \( T_2 \)-weighted MRI contrast agents. This magnetic composite material offers several advantages, including a large surface area, high drug loading capacity, significant mesoporous volume, biocompatibility, high transverse relaxivity \( (r_2) \), strong magnetic responsiveness, tumor cell-specific uptake, and inhibition of tumor cell viability.

5.7 Redox-responsive

The oxidation–reduction reaction MOFs exploit the significant disparity in oxidation–reduction concentrations between the tumor microenvironment and normal tissues to release drugs. Compared to normal tissues, cancerous tissues in the human body exhibit notably higher concentrations of reducible glutathione (GSH), laying the groundwork for the synthesis of nano-oxides using redox materials. Glutathione is a tripeptide abundantly released in tumor tissues, serving as an endogenous chemical agent. While cellular metabolic activity determines the levels of intracellular glutathione, tumor cells typically harbor higher concentrations of reduced glutathione (GSH), renowned for its biological reducing capability of disulfide bonds. Thus, integrating the reducing properties of glutathione into drug delivery systems initiates oxidation–reduction reactions, facilitating the efficient release of therapeutic drugs within cancer cells. In a study exploring the promotion of toxic lipid peroxide (LPO) generation at tumor sites, thus inducing ferroptosis in cancer therapy, He et al. introduced a composite MOF. This MOF was synthesized by incorporating perfluoropentane (PFP) into mesoporous MOF, followed by modification with polydopamine (PDA) and polyethylene glycol (PEG) to obtain PFP@Fe/Cu-SS metal–organic framework (MOF). PFP@Fe/Cu-SS MOF exhibited excellent stability and biocompatibility in vivo. Through redox reactions, PFP@Fe/Cu-SS MOF generated \( \cdot \text{OH} \) and inhibited the activity of glutathione peroxidase 4 (GPX4), preventing the exchange reaction between LPOs and GSH disulfide–thiol, thereby reducing the conversion of LPOs to LOH. Additionally, MOF could consume GSH through redox reactions, further inhibiting GPX4 activity. The study found that PFP@Fe/Cu-SS MOF increased LPO content at tumor sites through the Fenton reaction, effectively inhibiting the growth of xenograft Huh-7 tumor cells.
in mice.\textsuperscript{133,173} Interestingly, the study also mentioned that under near-infrared laser irradiation, liquid PFP transformed into microbubbles, serving as a $T_1$-weighted magnetic resonance imaging contrast agent and photothermal therapeutic agent. This represents a broader application of hybrid MOFs in biomedicine.

The ubiquitous mechanism of glutathione reaction-based MOFs primarily involves the cleavage of disulfide bonds.\textsuperscript{134,149} In the tumor microenvironment, an excess of glutathione triggers the disintegration of organic ligands containing these bonds, leading to the breakdown of the nanoscale framework and subsequent drug release.\textsuperscript{174} The complexity of organic ligands engenders the diversity of nanostructures, where exposure to glutathione induces the cleavage of covalent disulfide bonds, facilitating drug release through redox reactions.\textsuperscript{175} Modifying MOF surfaces with disulfide bonds is often a strategy for linking cargo and MOFs, as these bonds can be readily reduced and integrated into the organic chains of nano-oxides for targeted cancer therapy. In the study by Lei et al.\textsuperscript{134} on the application of novel redox reaction-based MOF-Zr(DTBA) carriers for tumor therapy, the preparation of redox reaction MOFs was achieved by introducing $4,4'$-dithiobisbenzoic acid ($4,4'$-DTBA) containing disulfide bonds as the organic ligand of MOFs. Researchers loaded the hydrophobic curcumin (CCM) onto MOF-Zr(DTBA) nanoparticles.\textsuperscript{134} These nanoparticles exhibited a higher drug release rate in the tumor microenvironment compared to normal tissues. Subsequent in vivo anti-tumor studies showed a significant increase in tumor tissue volume in mice treated with free CCM within 14 days. In contrast, there was no significant change in tumor tissue volume within 14 days in mice treated with CCM@MOF-Zr(DTBA) nanoparticles.\textsuperscript{134} The data showed tumor suppression rates of approximately 35.1% and 76.1% for the free CCM group and CCM@MOF-Zr(DTBA) nanoparticle group, respectively, indicating the efficient anti-tumor efficacy of the nanoparticles. The abundant glutathione in the tumor microenvironment can disrupt the disulfide bonds in $4,4'$-DTBA, leading to the collapse of CCM@MOF-Zr(DTBA) and controlled release of curcumin under redox reactions, expanding the horizon for drug carriers in tumor therapy.\textsuperscript{134} The abundance of GSH in tumor cells facilitates drug release through redox reactions, thereby minimizing side effects and enhancing therapeutic efficacy. Disulfide bonds (S-S) serve as redox reaction groups that are easily cleaved in the presence of GSH, making them excellent sites for constructing redox-responsive drug delivery systems exploiting the physiological differences between tumor and normal tissues.\textsuperscript{149}

5.8 Light-responsive

With the recent advancements in photodynamic therapy (PDT) and photothermal therapy (PTT), photosensitizers (PS) and light-responsive materials have experienced rapid development.\textsuperscript{170,176,177} Nano metal–organic frameworks (NMOFs) have emerged as one of the extensively researched PS in PDT, making them a key area of investigation for treating cancer through PDT, alongside photothermal therapy, antimicrobial therapy, and light-triggered drug carrier release.\textsuperscript{178,179} PDT involves the use of MOFs under near-infrared (NIR) or visible light to trigger the generation of reactive oxygen species (ROS) and free radicals, thereby implementing a localized treatment strategy.\textsuperscript{137,180,181} Light-responsive MOFs offer numerous advantages, including simplicity of operation, environmental friendliness, low energy consumption, and controllable temporal characteristics. Light-responsive MOFs also serve as carriers for drug delivery, enabling controlled release of therapeutic agents.\textsuperscript{182} Phototriggered drug release involves irradiation with specific wavelengths of light (non-invasive and spatiotemporal precision), thereby inducing conformational changes in MOFs, cleavage of chemical bonds, or photothermal conversion, resulting in on-demand release of therapeutic agents in target areas.\textsuperscript{183} In the design of light-responsive MOFs, the incorporation of light-active molecular ligands can enhance their reactivity. These photosensitive molecular ligands include azobenzene dicarboxylates (AZB), anthracene and its derivatives, porphyrins, indocyanine green (ICG), among others.\textsuperscript{184} (Fig. 7A). Existing reports mainly highlight light-responsive MOFs such as uiu-AZB and porphyrin-based MOFs. Among them, porphyrin-based MOFs and their derivatives stand out as exceptional photosensitizers (PS), generating abundant singlet oxygen ($^1$O$_2$) under light exposure.\textsuperscript{185} This species has the capability to disrupt molecular structures, thereby triggering the release or localized therapy mediated by the MOF carrier. $^1$O$_2$ itself exhibits remarkable oxidative reactivity and catalytic activity, garnering significant interest from researchers.\textsuperscript{175} With light-responsive MOFs introducing light irradiation, photoelectron transfer, or $^1$O$_2$ generation, resulting in surface and conformational changes, a plethora of possibilities emerges for biomedical applications.\textsuperscript{169} (Fig. 7B–D). Azobenzene dicarboxylates (AZB), serving as photosensitive agents, actively participate in the process of photoresponsive MOF drug delivery. Meenakshi et al.\textsuperscript{147} elucidated that the collapse of the MIL-125 (Ti) framework in light environments is attributed to the protonation of the carboxyl groups of BDC$^{2-}$ (1,4-benzene dicarboxylates). This further underscores the significance and potential of MIL-125 (Ti) in the realm of light-responsive stimuli.

External illumination can be classified into visible light (400–750 nm), near-infrared light (750–2000 nm), and ultraviolet light (UV, 200–200 nm) based on their wavelengths, each possessing unique advantages.\textsuperscript{182,186} Ultraviolet light, characterized by its high energy and strong biodegradability, exhibits relatively weak penetration, making it suitable for superficial applications. Photosensitive materials used under ultraviolet irradiation need to possess the capability of azobenzene functionalization, facilitating photosomerization reactions.\textsuperscript{186} Meng et al.\textsuperscript{138} have devised a water-stable zirconium metal–organic framework (Zr-MOF), UiO-68-azo, bearing photoresponsive azobenzene moieties, serving as a mechanized MOF platform for stimuli-responsive drug delivery (Fig. 7E and F). The azo functionalities on the surface of Zr-MOF are modified with $\beta$-cyclodextrin ($\beta$-CD) to form supramolecular complexes, thereby retarding drug release.\textsuperscript{138} Subsequent external stimuli,
such as UV irradiation or the addition of competitive agents, trigger the dissociation of the supramolecular complexes, leading to instructed drug release. Given that Rhodamine-B (RhB) dimensions are commensurate with the pores of UiO-68-azo and can diffuse through the triangular windows, researchers loaded RhB into UiO-68-azo to simulate drug loading. Subsequently, UiO-68-azo loaded with RhB is subjected to UV irradiation, causing dissociation of the stem β-CD rings from the MOF surface, thereby opening the supramolecular nanovalves and initiating controlled RhB release. Conversely, prior to UV irradiation, the supramolecular nanovalves are closed, preventing RhB release.
irradiation, RhB molecules firmly bind to the nano-sized pores of the mechanized MOF, preventing premature cargo release. Modulating the size of the UiO-68-azo azobenzene moiety, even down to the nanoscale, holds the potential to perpetually load more drugs, paving the way for the development of more valuable MOF drug delivery platforms.

The near-infrared (NIR) radiation possesses robust penetration capability, relatively weaker energy, diminished background signals, and enhanced biocompatibility.\(^{149}\) NIR has garnered extensive research interest in photothermal therapy and photodynamic therapy.\(^{49}\) Studies have reported higher photothermal conversion efficiency and target penetration in the NIR spectral range for photothermal therapy.\(^{187}\) Some MOFs exhibit antimicrobial properties as their metal ions dissociate under illumination. However, certain metal ions, such as Ag\(^+\) and Co\(^{2+}\), present potential toxicity to the human body. According to the study by Yao et al.,\(^{139}\) a drug delivery system was devised, involving the initial modification of polyethylene glycolated iron(III)-based nano-MOFs (MIL-100) through chelation with MnMn(CO)\(_5\)Br, followed by coating onto the surface of magnetic carbon nanoparticles (MCM@PEG-CO). The relatively facile synthesis of MCM@PEG-CO–DOX NPs was also employed for excellent biocompatibility.\(^{135}\) Eventually, MCM@PEG-CO–DOX NPs loaded with doxorubicin (DOX) constituted a comprehensive drug delivery system. The research findings indicate that MIL-100 enhances the drug loading capacity of the delivery system and facilitates a better fixation of carbon monoxide (CO) gas with the assistance of 4,4’-diamino-2,2’-bipyridine (DABPY).\(^{139}\) CO gas holds promising potential as an intervention therapy for malignant tumors. Within this drug delivery system, MCM@PEG-CO exhibits the capacity to generate photothermal effects under near-infrared light irradiation (808 nm laser).\(^{139}\) Upon NIR exposure, the heat generated by the magnetic carbon core intensifies, enabling not only photothermal therapy (PTT) but also responsive release of CO and DOX, thereby facilitating synergistic treatment of malignant tumor cells.\(^{139}\) Additionally, the dual-modal imaging capability of MCM@PEG-CO–DOX NPs, namely photoacoustic imaging (PAI) and magnetic resonance imaging (MRI), has been reported, enhancing its potential for biomedical research.

5.9 Multiple stimuli-responsive

Based on existing research on stimuli-responsive MOFs, part of the phenomenon arises from the alterations in pH and temperature in pathological microenvironments such as cancer cells, or the abnormal accumulation of ATP, GSH, and H\(_2\)S, leading to differential conditions compared to normal tissues.\(^{142}\) Leveraging these variances, specific stimulus responses can be chosen to achieve targeted drug release. Additionally, controlled release can be achieved by altering external conditions.\(^{13}\) Upon reaching specific locations, drugs fulfill biomedical applications such as disease treatment, tissue growth, and diagnostic imaging.\(^{167}\) Due to the complexity of the human body’s internal environment, enhancing drug delivery systems to trigger different responses or combining them with other therapeutic techniques, typically necessitates conditions responsive to multiple factors.\(^{188}\) Therefore, various stimuli-responsive MOF systems hold promise for achieving more precise disease treatment and diagnostic imaging. Zhou et al.\(^{140}\) devised a classic core–shell structured MOFs composite system (P@ZIF-8) for the loading and release of doxorubicin (DOX), with selenium-containing polymer micelles as the core and ZIF-8 as the shell. The selenium-containing polymer core undergoes reduction–oxidation reactions to decompose and release the drug, while the ZIF-8 shell collapses at low pH values, facilitating drug release.\(^{140}\) This enables P@ZIF-8 to release DOX under the dual stimulation of redox agents and pH, achieving therapeutic effects. The study also reported that achieving the desired 100% drug release rate from the ZIF-8 shell requires conditions with GSH (1 × 10\(^{-3}\) m) and pH below 4.2. In vitro studies demonstrated that both elevated pH and the addition of redox agents inhibited the release rate of DOX from P@ZIF-8 to varying degrees. The DOX released from the core needs to diffuse to the ZIF-8 shell before outward drug release, prolonging the overall release time. The P@ZIF-8 prepared in this study exhibits excellent loading capacity, biocompatibility, selectivity, and controllable release under the synergistic action of pH and redox agents, thus representing a promising system for intelligent drug delivery.\(^{140}\) The research on multi-stimuli-responsive MOFs has made remarkable progress in the treatment of certain specific diseases. For instance, Jiang et al.\(^{141}\) achieved notable results by employing a rapid self-assembly technique to fabricate ZIF-90 and investigating its loading of DOX (AP-ZIF-90@DOX) for the treatment of triple-negative breast cancer (TNBC). ZIF-90 was surface-modified with the Y1 receptor ligand [Asn6, Pro34]-NPY (AP) to obtain AP-ZIF-90 for targeted drug delivery to TNBC cell line MDA-MB-231. Compared to nano-ZIF-8, ZIF-90 exhibits excellent biocompatibility, good mitochondrial targeting, higher in vivo survival rates, negative zeta potential, lower hepatic and renal function side effects, and multi-stimulus responsiveness (ATP and pH dual responsiveness).\(^{141}\) The study demonstrated that AP-ZIF-90@DOX exhibited a release rate of 19.8% in PBS at 0.5 mM ATP and pH 7.4, while in PBS at pH 5.0 and additional 0.5 mM ATP (pH 5.0), the corresponding release rates were 21.7% and 70.2%, respectively. AP-ZIF-90@DOX exhibited inhibitory effects on MDA-MB-231 cells and enhanced targeted drug release.\(^{141}\)

6. Applications of stimuli-responsive MOF-based nanomaterials

6.1 Antitumor therapy

Stimuli-responsive MOFs materials have been widely researched in the field of tumor therapy, showing significant progress. Tumors, being one of the most severe threats to human life today, claim numerous lives every year. Current approaches to tumor treatment primarily encompass surgical intervention, radiotherapy, and chemotherapy.\(^{36}\) However, these interventions inevitably come with drawbacks. For instance, surgical procedures often fail to achieve complete excision, leading to tumor recurrence. Additionally, due to the lack of tumor targeting, radiotherapy and chemotherapy may result in poor treatment outcomes and damage to healthy tissues.\(^{143,189}\) However, this approach can cause extensive damage to the
body’s own organs. Researchers have identified differences between the tumor microenvironment and normal human tissues. Leveraging these differences, they explore and develop targeted drugs or carriers, enabling drugs to accumulate specifically at tumor sites. Stimuli-responsive MOFs in tumor therapy research primarily involve serving as carriers for targeted drug delivery, functioning as materials for photothermal therapy, acting as therapeutic agents themselves, or synergizing with anticancer drugs. MOFs carriers, when activated by specific stimuli in the local tumor microenvironment, trigger drug release, thereby accomplishing targeted therapy for tumors, elucidating the efficacy of tumor treatment (Fig. 8). As detailed earlier in various preceding sections of the article, a multitude of stimuli-responsive MOFs have been extensively researched in the field of tumor treatment, including temperature, ion, pH, ATP, and redox responsiveness. Furthermore, stimuli-responsive MOFs can also be modified to enhance their targeting properties by modifying their surface functional group or macromolecular structures. Following specific stimuli, MOFs carriers undergo physicochemical changes, with stimuli typically categorized as either intrinsic microenvironmental or external
Table 2  Biomedical applications of stimuli-responsive MOFs

<table>
<thead>
<tr>
<th>Biomedical applications</th>
<th>MOFs</th>
<th>Adding functional materials</th>
<th>Load cargo</th>
<th>Mechanism</th>
<th>Author</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimuli-responsive drug delivery system</td>
<td>Zeolitic imidazolate framework-8 (ZIF-8)</td>
<td>The ABA-type diselenide-containing triblock copolymer (PEG-PUSeSe-PEG)</td>
<td>Doxorubicin (DOX)</td>
<td>Targeted release of DOX by external redox agents and low pH stimulation</td>
<td>Zhou et al. 140</td>
</tr>
<tr>
<td>Platform for delivery of anticancer drug</td>
<td>MIL-100(Fe)</td>
<td>2-Butyl nitrite and trimethylsilyl azide</td>
<td>DOX</td>
<td>ATP-as1411 aptamer gates DOX release from NMOFs for treatment of MDA-MB-231 breast cancer cells</td>
<td>Chen et al. 135</td>
</tr>
<tr>
<td>NMOFs carriers responsive to external interventions</td>
<td>ZIF-8</td>
<td>CuS nanoparticles (NPs) and protoporphyrin IX (PPix)</td>
<td>DOX</td>
<td>Nanomaterials combined with therapeutic strategies such as photothermal, photodynamic and chemotherapeutic drugs</td>
<td>Yang et al. 193</td>
</tr>
<tr>
<td>Anti-tumor complex system combining drug delivery, PTT and PDT therapy</td>
<td>ZIF-8</td>
<td>Iridium dioxide nanoparticles [IrO₂ NPs] and bovine serum albumin-folate acid (BSA-FA)</td>
<td>Chlorin e6</td>
<td>Stimulation of responsive drug delivery at acidic pH and near-infrared light (NIR), as well as enhancement of PTT-PDT-mediated ROS killing of tumor cells</td>
<td>Deng et al. 194</td>
</tr>
<tr>
<td>NIR stimulated response to anti-tumor</td>
<td>MIL-100</td>
<td>Upconversion nanoparticles (UCNPs)</td>
<td>UCNPs</td>
<td>Fenton-response-based oxidative stress triggered by near-infrared light and calcium overload originating from intracellular acidification leads to mitochondrial dysfunction</td>
<td>Bao et al. 169</td>
</tr>
<tr>
<td>Stimuli-responsive drug delivery system</td>
<td>MOF UiO-66 beads</td>
<td>Gold nanorods (AuNR) and silica shell (SiO₂)</td>
<td>Iodine agents</td>
<td>Passive slow release and active fast release of iodine agent triggered by photothermal effect under NIR radiation</td>
<td>Han et al. 195</td>
</tr>
<tr>
<td>Skin repair</td>
<td>Copper–niacinamide (CuN)</td>
<td>Gelatin methacrylate (GelMA)</td>
<td>Basic fibroblast growth factor (bFGF)</td>
<td>Slow release of bFGF and NA under light stimulation promotes skin defect angiogenesis, re-epithelialization, collagen and elastin fiber deposition</td>
<td>Wang et al. 196</td>
</tr>
<tr>
<td>Treatment of methicillin-resistant Staphylococcus aureus (MRSA)</td>
<td>PCN-224</td>
<td>Poly-γ-glutamic acid (PGA)</td>
<td>Ciprofloxacin (CIP) and methylene blue (MB)</td>
<td>NIR irradiation triggers the production of PDT from single-linear oxygen (¹O₂) and the release of CIP sterilization</td>
<td>Xiang et al. 107</td>
</tr>
<tr>
<td>pH-Responsive release MOFs antibacterial system</td>
<td>B-UIO-66</td>
<td>Zn²⁺</td>
<td>Eugenol (Eu)</td>
<td>Under low pH stimulation, the coordination bond between eugenol and Zn²⁺ ions was broken, releasing eugenol</td>
<td>Wang et al.</td>
</tr>
<tr>
<td>PH stimuli-responsive drug delivery system</td>
<td>ZIF-8</td>
<td>Hyaluronic acid (HA)</td>
<td>Protocatechic acid (PCA)</td>
<td>Release of PCA in an acidic microenvironment suppresses the inflammatory response in the medulla oblongata and promotes type II collagen expression</td>
<td>Ding et al. 197</td>
</tr>
<tr>
<td>Dual-sensing fluorescence nanosensor (pH and phosphate)</td>
<td>PCN-224</td>
<td>Pyrazine groups of small molecule NP-HPZ</td>
<td>NP-HPZ</td>
<td>With decreasing pH and increasing phosphate levels, the ZrIV metal node in PCN-224 exhibits sensitivity to phosphorylation and is able to specifically coordinate with phosphate groups</td>
<td>Li et al. 198</td>
</tr>
<tr>
<td>MRI tumor imaging and tumor therapy composite platform</td>
<td>UiO-66(Zr)</td>
<td>-(COOH)₂</td>
<td>Mn²⁺</td>
<td>Reaching the tumor site and releasing cargo via the endosomal/lysosomal escape pathway</td>
<td>Meng et al. 199</td>
</tr>
<tr>
<td>MRI tumor imaging and tumor therapy composite platform</td>
<td>Fluorinated iron MOF (FIMOF)</td>
<td>Fluorinated iron MOF-TA nanoparticles (NPs)</td>
<td>Mn²⁺ MRI contrast agents and DOX ¹⁹FIMOF-TA NPs</td>
<td>Fluorinated ¹⁹F organic ligand and iron ion released, stimulated by excess glutathione in the tumor microenvironment, enhanced ¹⁹F MRI imaging signals, as well as decreased GSH, increased ROS, and GPX4 downregulation</td>
<td>Fan et al. 200</td>
</tr>
</tbody>
</table>

interventions.⁴⁶ Table 2 shows biomedical applications of stimuli-responsive MOFs.

Based on research reports, the tumor microenvironment typically exhibits lower pH, higher temperature, increased ATP abundance, and elevated GSH compared to normal tissues.¹¹⁶ These disparities can stimulate specific MOFs carriers to achieve drug release at predetermined sites.¹⁶¹ External interventions, usually administered artificially, such as light, magnetic fields, temperature, and ions, can also activate MOFs carriers. MOFs carriers responsive to external interventions need to accumulate at the tumor site before visualized drug release can occur.¹⁵¹ Drug release triggered by external stimuli offers greater controllability, including timing, spatial distribution, and dosage. Chen et al.¹³⁵ have devised a photothermal MOFs nanoparticle composite system (MOF@HA@ICG NPs) by synthesizing acidic hyaluronic acid, indocyanine green, and the metal–organic framework MIL-100(Fe) nanoparticles, applied in the realm of cancer therapy. MOF@HA@ICG NPs offer several unique advantages, including high payload capacity, enhanced cellular permeability, tumor cell targeting, ATP responsiveness, and functional nucleic acid gating (achieved through complementary nucleic acid hybridization with the cage-shaped ATP-AS1411 aptamer).¹³⁵ Upon loading doxorubicin onto MOF@HA@ICG NPs, they selectively infiltrate the
tumor cells (MDA-MB-231 cells). Upon recognition of the AS1411 aptamer by nucleolin receptors at the cell membrane boundary of tumor cells overexpressing ATP, the gate is unlocked, facilitating the selective release of doxorubicin, thereby effectively eradicating tumor cells.

Nanoparticles of metal–organic frameworks (MOFs) have been extensively studied as photothermal agents (PTAs), yielding promising outcomes in the field of biomedicine. Photothermal therapy (PTT), characterized by its non-invasiveness, spatial selectivity, and convenience, holds unique advantages in the realm of cancer treatment. Under light stimulation, MOFs nanoparticles absorb photons and subsequently convert them into heat, inducing tumor cell death. This approach is particularly enhanced under near-infrared (NIR) radiation, which offers superior penetration and photothermal conversion capabilities. Moreover, photodynamic therapy (PDT), another non-invasive treatment modality, can overcome the limitations of traditional combination chemotherapy. PDT operates under the influence of light, where photosensitizers (PS) undergo photoactivation, converting oxygen molecules into reactive oxygen species (ROS), singlet oxygen molecules ($^{1}O_2$), and superoxide radicals ($O_2^{-}$), initiating oxidative reactions that lead to tumor cell death. However, PDT suffers from several shortcomings, such as relatively low treatment efficiency and stability. Researchers have devised strategies to address these limitations by combining PDT with chemotherapy, yielding promising results. Studies have shown that the therapeutic efficacy of combining PTT with PDT surpasses that of PTT or PDT alone in treating tumor cells (Fig. 9). Yang et al. ingeniously utilized the versatile ZIF-8 as a carrier, co-loading polydopamine (PDA), copper nanoparticles, protoporphyrin IX, and doxorubicin to form an “all-in-one” composite drug delivery platform for cancer eradication research. This composite drug delivery platform integrates multiple therapeutic strategies, including photothermal therapy, photodynamic therapy, and chemotherapy, offering novel avenues for reducing tumor metastasis and recurrence.

### 6.2 Antimicrobial therapy

In the realm of biomedical applications, the utilization of responsive MOFs primarily revolves around photothermal reactions and photodynamic therapy triggered by light stimulation. The realm of antibacterial materials has witnessed extensive research on bio-materials based on MOFs. For instance, Han et al. have pioneered a composite material based on MOFs for iodine loading and release, thereby evaluating its antibacterial performance. In their selection of MOFs, the researchers emphasized the affinity for iodine agents. They opted for the MOF UiO-66 beads, enveloped with gold nanorods (AuNR) embedded in silica shell ($\text{SiO}_2$). This photosensitive material (AuNR@$\text{SiO}_2$@UiO-66) underwent a synthesis process involving amplification, continuous flow, and spray drying. Following iodine agent loading onto this composite MOF-based material, the process included passive slow release and active rapid release under near-infrared (NIR) radiation. NIR radiation triggered photothermal effects, resulting in temperature elevation, with the temperature of the loaded iodine MOF-based composite material reaching up to $274 \, ^\circ\text{C}$. Rapid heating acted as a “switch” to prompt iodine release, achieving antibacterial effects against both Gram-positive and Gram-negative bacteria in vitro. Research on stimuli-responsive MOFs as carriers for antibacterial agents is relatively scarce. However, the success achieved in tumor treatment by these materials has provided valuable insights for antibacterial therapy. This section primarily delves into phototherapeutic MOFs, building upon the preceding chapters. Of particular interest is a study reporting a phosphorescent MOFs composite system. Huang et al. combined highly porous MOFs with carbosymethyl chitosan (CMCS) to fabricate the HKUST-1@CMCS drug delivery composite system. Subsequently, antimicrobial active fumaric acid dimethyl ester was loaded onto HKUST-1@CMCS. Experimental results demonstrate that under phosphate stimulation, the HKUST-1@CMCS structure collapses, facilitating controlled, intelligent, and sustained release of the antibacterial agent. The combination of photoresponsive MOFs with other biomaterials enables the composite system to exhibit antibacterial properties under light stimulation. Niacinamide (NA), as a crucial vitamin in the human body, and copper, a trace element essential for human health, were synthesized into a copper–niacinamide (CuNA) donut-shaped metal–organic framework (MOF) by Wang et al. through a solvent thermal reaction. This CuNA MOF was then blended with gelatin methacrylate (GelMA) to form the CuNA-bFGF@GelMA composite hydrogel system. Remarkably, this composite system is a photosensitive hydrogel system, boasting high biocompatibility, porosity, water absorption capacity, flexibility, resilience, and excellent biodegradability. The study also attempted to load basic fibroblast growth factor (bFGF). Experimental findings demonstrate that the CuNA-bFGF@GelMA composite hydrogel system slowly releases bFGF and NA, facilitating the promotion of angiogenesis, re-epithelialization, collagen, and elastic fiber deposition in skin defects. Such attributes highlight the immense potential of this hydrogel system in the realm of biomedical applications. In the realm of antimicrobial research, the focal point lies in the prevention and treatment of multidrug-resistant (MDR) bacterial infections. MDR bacterial infections signify high mortality rates, making them the prime subjects of current antimicrobial therapeutic investigations. Xiang et al. ingeniously synthesized a hybrid nanocomposite material system, ZIF/PGA-C/M, by sensitively crosslinking zeolitic imidazolate framework-8 (ZIF-8) with poly-$\gamma$-glutamic acid (PGA), subsequently incorporating ciprofloxacin (CIP) and methylene blue (MB) (Fig. 10A). This composite exhibits excellent structural stability and biocompatibility, rendering it suitable for combating methicillin-resistant *Staphylococcus aureus* (MRSA). Remarkably, at a pH of 5.5, the drug release rates for CIP and MB reached 99.4% and 76.0%, respectively. Furthermore, the introduction of near-infrared (NIR) irradiation facilitated the generation of singlet oxygen ($^{1}O_2$), serving a photodynamic therapy (PDT) role. The ZIF/PGA-C/M composite system synergizes drug release with photodynamic action.
achieving a pronounced bactericidal effect against MRSA\textsuperscript{107} (Fig. 10B). This underscores the necessity of leveraging the intrinsic properties of MOFs to devise multifunctional composite platforms, thereby enhancing therapeutic efficacy. In another antimicrobial investigation, Wang \textit{et al.}\textsuperscript{187} devised a pH-responsive release MOFs antibacterial system (Eu@B-UiO-66/Zn). Their research unveiled that under acidic conditions (pH 5.8), Eu@B-UiO-66/Zn achieved a high release of eugenol, up to 80%, while exhibiting notable inhibition rates against \textit{Staphylococcus aureus} and \textit{Escherichia coli}, reaching 100% and 98.8%, respectively. By comparing the bactericidal rates between the Eu@B-UiO-66/Zn group and the Eu@B-UiO-66 group, researchers inferred a...
potential synergistic antimicrobial effect between Zn$^{2+}$ ions and eugenol. The additive antimicrobial effects exhibited by responsive MOFs composite systems represent a focal point for future research endeavors. Research has revealed that, in addition to Zn$^{2+}$, metal ions such as Ag$^+$ and Cu$^{2+}$ have the ability to disrupt bacterial cell membranes, thereby penetrating into the bacteria by compromising membrane integrity. Furthermore, these metal ions can disturb the surface potential of bacteria, impairing cell membrane integrity, and internally inhibiting protein synthesis, thus compromising cellular functions. Furthermore, the release of certain metal ions by MOFs (such as Ag$^+$ and Zn$^{2+}$) can disrupt ion balance, dismantle ion channels, and induce a
deficiency of essential metal ions crucial for bacterial growth. Some metal ions also have the capability to crosslink with DNA molecules, thereby compromising their structural integrity, leading to bacterial demise. Additionally, certain metal ions can disrupt oxidative respiratory chains, interfere with biological electron transfer chains, and engage in potent oxidative reactions, collectively undermining fundamental bacterial survival functions.

6.3 Tissue repair

The stimuli-responsive MOFs carrier can also load drugs that promote tissue repair, providing new inspiration for the development of tissue regeneration engineering. As a drug delivery platform, it responds to specific stimuli in the local microenvironment, achieving controlled release and therapeutic effects. This is a common working mechanism of stimuli-responsive MOFs drug delivery platforms. Tissue repair is often needed in situations such as tissue defects, tissue degeneration, and tissue degeneration. In existing research, an interesting study has been conducted to repair intervertebral disc degeneration by loading drugs onto pH-responsive MOFs. Ding et al. synthesized pH-responsive MOFs (ZIF-8), followed by loading protocatechuic acid (PCA) and encapsulating hyaluronic acid (HA) to obtain the drug-loaded composite platform. During intervertebral disc degeneration (IDD), the pH of the microenvironment within the intervertebral disc (IVD) typically decreases and progressively decreases with the worsening of the condition. In a rat model of intervertebral disc degeneration, it was found that the pH-responsive MOF composite platform released PCA when entering the acidic microenvironment. PCA inhibited the inflammatory response of the nucleus pulposus and promoted the expression of nucleus pulposus-specific markers (Aggrecan, Collagen II), leading to an increase in primary nucleus pulposus cells (NPCs). In NPCs treated with the pH-responsive MOF composite platform, the expression levels of ROS were significantly lower than in other groups. The expression levels of Aggrecan and Collagen II are generally positively correlated with the cellular activity of NPCs and negatively correlated with the occurrence and development of IDD. In conclusion, this MOF drug delivery platform upregulates the expression of Collagen II, suppresses inflammatory reactions in the IDD microenvironment, and delays the progression of IDD. This study provides new insights for future research directions in tissue repair and holds promise for further development in the field of tissue engineering. Furthermore, MOFs hold immense potential in promoting wound healing. Apart from serving as coverings for skin wounds, they can also be loaded with antibacterial drugs or endowed with photoreactive properties, enhancing wound resistance to infection and fostering skin regeneration.

6.4 Bioimaging

The evolution of diagnostic imaging plays a pivotal role in the early detection and precise visualization of neoplasms and masses. Following diagnosis, it holds significant importance in guiding therapeutic strategies, thereby contributing to enhanced patient survival rates. The integration of diagnostic imaging with molecular imaging has propelled the advancement of biological imaging. The introduction of stimuli-responsive MOFs enables the targeted release of imaging agents in response to specific pathological microenvironment stimuli, facilitating biological imaging. The potential of nanoscale MOFs in accomplishing disease diagnosis, treatment, and monitoring simultaneously holds significant promise for extending patient survival. Widely utilized as imaging agents in the field of biomedicine, nanoscale MOFs have been explored in various imaging modalities, including fluorescence imaging (FI), positron emission tomography (PET), magnetic resonance imaging (MRI), and computed tomography (CT). Among these, FI provides visual information on the distribution and content of biological molecules using optical probes. Its key features include multicolor detection, high sensitivity, non-ionizing properties, and excellent resolution. However, FI has limited tissue penetration capabilities. Li et al. ingeniously engineered a dual-sensing fluorescence nanosensor, PCN-NP-HPZ, by introducing pyrazine groups of small molecule NP-HPZ into the carboxyls of the metal-organic framework PCN-224. The pyrazine moieties endow specific detection of H+ ions (pH sensitivity). Meanwhile, the ZrIV metal nodes in PCN-224 exhibit sensitivity to phosphorylation, enabling specific coordination with phosphate groups. It was observed that in the early stages of Atherosclerosis in mice, there is a decrease in pH and an increase in phosphate levels. Remarkably, PCN-NP-HPZ is capable of simultaneously detecting both conditions. Besides monitoring the early progression of Atherosclerosis in mice, this approach holds promise for detecting inflammatory diseases through blood tests and could potentially be extended to various other pathological conditions. The advantageous attributes of nano-MOFs, such as their elevated hydrostability, low cytotoxicity, commendable biocompatibility, and biodegradability, render them valuable biomaterials. Nano-MOFs, through covalent bonding or physical adsorption of specific materials, acquire properties such as enhanced imaging signals (optical, chemical, or electrical) or the acquisition of biological target receptors (targeted recognition of cells or tissues) upon composite formation. MRI, as a widely used clinical imaging technique, offers non-invasive three-dimensional imaging with high spatial resolution. Unlike X-rays and CT scans, MRI does not entail radiation or ionization damage. Consequently, MRI, a commonly employed clinical technique, is often utilized for tumor diagnosis, spinal cord disorders, tumor efficacy evaluation, and more. However, its sensitivity is relatively lower compared to other imaging modalities.

MRI, under the influence of external strong magnetic fields, magnetic field gradients, and radiofrequency waves, detects proton absorption of radiofrequency (RF) energy in soft tissues at the site, generating specific radiofrequency signals and producing anatomical images with inherent contrast. Protons in water and fat, abundant with hydrogen atoms, are most commonly used for macroscopic polarization. The introduction of paramagnetic or superparamagnetic metal ions (such as
The organic ligands in nano-MOFs can coordinate with paramagnetic or superparamagnetic metal ions, yielding novel nano-MOFs imaging platforms. These novel nano-MOF contrast agents hold promise for enhancing MRI efficiency and applicability, thus bearing significant value for biological imaging. The strategy of utilizing paramagnetic Fe\(^{3+}\) to enhance MOFs is among the widely researched materials, frequently employed in MRI and cancer treatment.\(^{109,169,218}\) (Fig. 11). Meng et al.\(^{199}\) opted for nano-MOFs (UiO-66(Zr)-(COOH)\(_2\)) bearing carboxylic acid groups as cargo carriers. Synthesized via hydrothermal method using zirconium(iv) and 1,2,4,5-benzenetetracarboxylic acid (H\(_4\)BTeC \(>98\%\)) as precursors, these MOFs boast of nanoscale dimensions. Researchers ingeniously loaded Mn\(^{2+}\) MRI contrast agents and the anticancer drug doxorubicin (DOX) for tumor diagnostic and therapeutic investigations.\(^{199}\) The Mn\(^{2+}\)@DOX@MOF drug delivery platform, facilitated by endosomal/lysosomal escape pathways, adeptly ferries cargo to cancer cells, inducing demise of 4T1 breast cancer cells and impeding their growth and lung metastasis. The significance of inhibiting tumor metastasis lies in prolonging patient survival, given that over 90% of cancer-related deaths are associated with metastasis. Fortuitously, Mn\(^{2+}\)@DOX@MOF demonstrates therapeutic efficacy against both primary and metastatic 4T1 tumors.\(^{199}\) Moreover, the released MRI contrast agent (Mn\(^{2+}\)) selectively detects for precise diagnostics. Notably, the study proposes the synergistic coupling of tumor imaging and therapy facilitated by the presence of the contrast agent. Mn\(^{2+}\)@DOX@MOF not only treats tumors but also offers visual localization and anatomical signaling of carrier accumulation at tumor sites, enhancing the potential for monitoring treatment efficacy.\(^{199}\) Fan et al.\(^{200}\) synthesized fluorinated iron metal–organic frameworks (FIMOF) by employing iron ions and fluorinated organic ligands, resulting in FIMOF-TA nano-particles (NPs). These FIMOF-TANPs also exhibited stimuli-responsive activity and underwent research on 19\(^F\) magnetic resonance imaging (MRI) and synergistic therapy for tumors. While enhancing tumor therapeutic efficacy, they also provided tumor visualization effects.\(^{200}\) These NPs could respond to excess GSH in the tumor micro-environment and release fluorinated 19\(^F\) organic ligands and iron ions. Upon entry into tumor tissues, the magnetic dipole–dipole interaction between 19\(^F\) nuclei enhanced the signal of 19\(^F\) MRI imaging released by these fluorinated organic ligands.\(^{200}\) Furthermore, the occurrence of photothermal effects further enhanced the signal of 19\(^F\) MRI imaging, representing a responsive cascaded amplification for tumor imaging. As these NPs decompose and release, the generation of iron ions accompanies a decrease in GSH and an increase in ROS.\(^{200}\) Additionally, GPX4 downregulation and lipid peroxidation occur, leading to tumor cell death. This multimodal therapeutic composite platform paves the way for the biomedical application of stimuli-responsive MOFs.\(^{176,219}\)

Computed tomography (CT) involves the computational processing of multiple X-ray measurements taken from various angles to produce cross-sectional images of different layers of the body.\(^{220}\) In contrast to MRI, CT is considered favorable for patients with metal implants or pacemakers, as it does not pose any contraindications.\(^{214}\) Positron emission tomography (PET) is a nuclear medicine imaging technique that utilizes radioactive drugs (radiopharmaceuticals with attached radioactive isotopes) injected into the body, emitting positrons.\(^{221}\) When these positrons interact with ordinary electrons, they annihilate, emitting two gamma rays rosin opposite directions, creating highly sensitive, deep-penetrating tissue nuclear medicine scintigraphy.\(^{213}\) The gamma rays form a three-dimensional image, allowing observation of tumor cell metabolism and intra-body dissemination. Researchers are also endeavoring to develop MOFs as contrast agents for potential applications in CT and PET imaging directions. In recent years, significant progress has been made in the field of stimuli-responsive MOFs within biomedicine. Fig. 12 visually represents the number of publications on stimuli-responsive MOFs in PubMed over the years. Table 3 highlights several examples of MOFs used in

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**Fig. 11** (a) The upper diagram showcases T\(_2\)-weighted MRI images of Fe\(_3\)O\(_4@\)[Cu\(_3\)(BTC)\(_2\)] at various iron concentrations, while the lower diagram illustrates the distribution relationship between different iron concentrations and transverse relaxation time (1/T\(_2\)), with the relaxation rate (r\(_2\)) denoted by the slope. (Reproduced from ref. 109. Copyright 2023, Frontiers) (b) following the administration of MUP and FMUP to mice, the left panel exhibits pre- and post-injection T\(_2\)-weighted MRI images, with the tumor area delineated by the red dashed circle. The right panel presents the corresponding analysis of AT\(_2\) values pre- and post-injection. FMUP particles comprise a core of upconversion nanoparticles (UCNPs) enveloped by a carboxylic acid Fe(III) MOF shell. (Reproduced from ref. 169. Copyright 2021, Springer).

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biomedical applications, offering diverse perspectives for further exploration of their potential.

7. Challenges and future perspectives

In recent years, stimuli-responsive MOFs have garnered widespread attention in biomedical applications due to their unique advantages. Various types of stimuli-responsive MOFs require different triggers and exhibit diverse applications, necessitating the development of biomedical application strategies tailored to specific environments. Whether influenced by local pathological microenvironments within the body or external interventions, stimuli-responsive MOFs enable temporally and spatially controlled targeted release for therapy at predetermined locations. However, these internal or external stimulus responses also entail several limitations. Internally, there are challenges related to the inflexibility and controllability of in vivo stimulus responses. Externally, magnetic responsiveness requires a substantial amount of material, thermal responsiveness poses risks of skin damage, and photonic responsiveness suffers from inadequate light penetration. Addressing these drawbacks requires concerted efforts from researchers to enhance stimuli-responsive MOFs, aiming to develop materials with rapid responsiveness and high conductivity for improved biological applications.

The design, synthesis process, and modification strategies of MOFs play a crucial role in stimuli-responsive MOFs, as different tuning measures during preparation can significantly impact their physicochemical properties and structural functionalities. Therefore, it is imperative for researchers to explore novel synthesis processes and modification strategies to alleviate more restrictions on MOFs. For instance, extensive in vitro studies are necessary to assess various aspects such as cytotoxicity, immune clearance, colloidal stability, off-target accumulation, inadequate pharmacokinetics, biocompatibility, and biodegradability of MOFs to ensure their biological safety. The aim of improving the preparation process of stimuli-responsive MOFs is to enhance stability, prolong circulation time in the bloodstream, increase controllability of cargo release, enhance selective targeting, and improve uptake rates by specific cells. Additionally, researchers need to conduct further investigations into the metabolism mechanisms and pathways of MOFs both in vitro and in vivo. It’s worth noting that in vivo studies are fundamentally distinct from the simplistic in vitro cellular microenvironment systems. Moreover, the current research landscape predominantly focuses on in vitro studies, with only a few reports on in vivo studies. In the realm of biomedicine, the most extensively explored facet of stimuli-responsive MOFs research lies in their role as drug delivery platforms, particularly in the treatment of cancer. Presently, the administration route for MOFs research primarily involves intravenous injection, prompting inquiry into the feasibility of alternative administration methods to broaden their scope of application. With their exceptional catalytic functionalities, robust adsorption capacity, structural integrity, large surface area, multifunctionality, high porosity, and high drug-loading capacity, MOFs undeniably stand out as one of the

<table>
<thead>
<tr>
<th>Stimuli-responsive MOFs</th>
<th>Application direction</th>
<th>Advantages</th>
<th>In vitro/in vivo</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hierarchically porous UiO-66-NH₂</td>
<td>Antitumor therapy</td>
<td>pH stimulates response binding charge reversal and enhances co-delivery of chemotherapeutic agents</td>
<td>In vivo and in vitro (MCF-7/ADR and HepG2 cells)</td>
<td>222</td>
</tr>
<tr>
<td>Uio-68-N₄-DNA conjugates</td>
<td>Antitumor therapy</td>
<td>pH stimulates response binding charge reversal and enhances co-delivery of chemotherapeutic agents</td>
<td>In vitro</td>
<td>162</td>
</tr>
<tr>
<td>Ti₃C₂ MXene/Fe-MOFs composite (MXM)</td>
<td>Anti-infection</td>
<td>MXene nanosheets enhanced chemo-dynamic therapy (CDT) through near-infrared plasmonic excitons, which generated hot electrons transferred to the Fe⁻ moF surface, thereby promoting the Fenton reaction</td>
<td>In vivo and in vitro (E. coli, MRSA, and C. albicans)</td>
<td>177</td>
</tr>
<tr>
<td>Zeolitic imidazolate framework-8-capped ceria nanoparticles (CeO₂@ZIF-8 NPs)</td>
<td>Tissue repair</td>
<td>Inhibition of astrocyte activation and pro-inflammatory cytokine secretion to reduce oxidative damage</td>
<td>In vivo and in vitro (PC12 cells)</td>
<td>223</td>
</tr>
<tr>
<td>PVP-coated ceria (CeNPs)@ MIL-100 (CeM)</td>
<td>Tissue repair</td>
<td>The H₂O₂-responsive MOF-releasing cargo eliminates ROS from lesion areas and circumvents their oxidative damage to newborn neurons for the treatment of Alzheimer’s disease (AD)</td>
<td>In vivo and in vitro (PC12 cells)</td>
<td>224</td>
</tr>
<tr>
<td>Prussian blue (PB)@ZIF-8</td>
<td>Bioimaging</td>
<td>Unique core–shell dual moF structure for efficient multimodal imaging-guided synergistic chemo-thermal therapy</td>
<td>In vivo and in vitro (HeLa cells)</td>
<td>225</td>
</tr>
<tr>
<td>Temozolomide (TMZ)@ UiO-66-NH₂</td>
<td>Antitumor therapy</td>
<td>In the vicinity of the tumor site, TMZ is significantly released to achieve enhanced anti-tumor effects</td>
<td>In vivo and in vitro (U251 and SHG44 cells)</td>
<td>226</td>
</tr>
</tbody>
</table>
outstanding candidate materials in the field of drug delivery.\textsuperscript{55} Research findings have revealed commendable achievements of stimuli-responsive MOFs carriers in cancer drug release and biological imaging. However, within these advancements, some challenges have surfaced. Presently, stimuli-responsive MOFs in the antibacterial field are primarily photo-responsive, with antibacterial strategies such as PTT, PDT, or a combination of both. Existing research indicates a lack of studies on photo-responsive MOFs loaded with antibacterial drugs, presenting significant potential for expanding the biomedical applications of stimuli-responsive MOFs. This holds promise for providing a novel therapeutic strategy for the treatment of deep-seated infections or bloodstream infections. Similarly, there is a scarcity of research in tissue repair, but we can draw inspiration from studies aimed at delaying intervertebral disc degeneration. In modern medicine, the incidence of progressive diseases such as tumors is on the rise, prompting healthcare professionals to increasingly emphasize early diagnosis, metastatic extent, treatment efficacy assessment, and prognosis evaluation for such conditions. Consequently, the application of bioimaging using materials like MOFs has garnered growing attention. Stimuli-responsive MOFs loaded with specific agents provide optical or electrical signals during the imaging process. Stimuli-responsive MOFs, through effective and precise bioimaging techniques, offer high diagnostic accuracy for tumors, with their role as imaging contrast agents being widely researched. The utilization of stimuli-responsive MOFs in the development of various bioimaging technologies and collaborative therapeutic strategies for tumors demonstrates significant potential, offering researchers valuable insights into this field.

8. Conclusion

In summary, stimuli-responsive MOFs exhibit high porosity, facile functionalization, larger surface area, and enhanced drug-loading capacity. These attributes endow them with immense potential as drug delivery platforms, a potential that has yielded promising results in recent years. In future research on stimuli-responsive MOFs, researchers can explore broader aspects such as biocompatibility, responsiveness to stimuli, production processes, targeted drug delivery mechanisms, delivery routes, stability, and tunability under physiological conditions. Stimuli-responsive MOFs exhibit unique potential by controlling the spatiotemporal release of drugs in response to one or more stimuli within specific microenvironments, thereby achieving desired therapeutic outcomes. Researchers should focus on the orthogonality of various strategies to ensure precise targeted release of stimuli-responsive MOFs \textit{in vivo}. Moreover, stimuli-responsive MOFs can be combined with other therapeutic strategies; for instance, UiO-66(HF) MOFs have demonstrated high radiotherapeutic efficacy and drug transport capabilities. Traditional stimuli-responsive MOFs face several limitations that need to be addressed for successful clinical application. These include the low control over drug release in response to intrinsic stimuli, the poor penetration ability of light-responsive external stimuli, and the risk of skin damage from thermal stimuli. Selecting appropriate forms of stimuli and regulating their intensity are crucial for achieving high efficacy while ensuring biological safety. Developing “natural” synthesis processes and selecting endogenous components as modifying agents and functional linkers can significantly enhance biocompatibility. This approach could improve the stability, degradation, and reduction of side effects in normal organs for stimuli-responsive MOFs in \textit{in vivo} studies. Currently, research on stimuli-responsive MOFs in biomedicine remains limited, with even fewer studies focusing on \textit{in vivo} applications. Expanding \textit{in vivo} research could provide a solid foundation for clinical evaluation and application. Additionally, the primary administration route for stimuli-responsive MOFs is still intravenous injection, with other pathways being less explored. Researchers should investigate and validate alternative delivery methods to unlock the full potential of stimuli-responsive MOFs in biomedical applications.

In recent years, researchers have shown widespread interest in stimuli-responsive metal–organic frameworks (MOFs), achieving significant progress. Various stimuli-responsive MOFs, such as UiO-66 (zirconium-based), MIL-53 (iron-based), and ZIF-8, have demonstrated potential applications in biomedicine. Notably, ZIF-8, with its remarkable pH-responsive degradation, reacts to the acidic environment typically found in tumor tissues. This characteristic ensures precise drug release at the tumor site, thereby enhancing therapeutic efficacy while minimizing side effects. ZIF-8 has been extensively studied in tumor drug delivery systems and is considered one of the most promising materials. Additionally, ZIF-8 is an ideal candidate for applications in gene editing, biosensors, and antibacterial materials. Stimuli-responsive MOFs have overcome challenges associated with previous drug carriers, such as poor targeting, low drug solubility, and drug cytotoxicity. Their operational principles primarily involve the transportation of loaded cargo to specific sites within the structure, where stimuli trigger structural changes leading to cargo release and the acquisition of new functionalities. Additionally, external stimuli, primarily optical and magnetic signals, can trigger PTT or PDT. According to research reports, investigators are also striving to combine multiple stimuli or employ multimodal therapeutic strategies. This multimodal approach aims not only to enhance therapeutic efficacy but also to enable simultaneous diagnosis and treatment, thus representing a paradigm shift towards integrated healthcare solutions.\textsuperscript{115} We have summarized the latest advancements in the design, synthesis, and modification of MOFs in recent years, with the hope of overcoming more challenges in the future. The selection of internal and external stimuli, as well as metal ions and organic ligands, in MOF design routes needs to be tailored according to different application scenarios. Reported metal ions include Zr\textsuperscript{4+}, Tb\textsuperscript{3+}, Co\textsuperscript{2+}, Fe\textsuperscript{2+}, Mn\textsuperscript{2+}, Zn\textsuperscript{2+}, Cu\textsuperscript{2+}, and Eu\textsuperscript{3+}, all of which have been utilized in constructing stimuli-responsive MOFs.\textsuperscript{122,180} Over the decades of MOF development, various synthesis methods have been developed, including sol–gel transformation, microwave-assisted synthesis, diffusion method, solvothermal method, ionothermal synthesis, and mecanochemical
synthesis. Among these, microwave-assisted synthesis stands out for its high yield, high purity, and controllable particle size, surpassing other synthesis techniques. Through modification and functionalization, MOFs acquire new functional groups or adsorb new drug molecules, expanding their biomedical applications significantly. Stimuli-responsive MOFs possess unique properties, structural versatility, precise delivery, and responsive controlled release characteristics, making them highly suitable as carriers for drug delivery and bioimaging contrast agents. In biological imaging, MOFs function by targeting cells after being engulfed in the bloodstream, thereby exerting their imaging effects. Overall, researchers are dedicated to developing stimuli-responsive MOFs through environmentally friendly and reproducible synthetic routes, aiming to achieve combined diagnostic and therapeutic strategies for cancer diagnosis, treatment, and monitoring of efficacy and progression. Attention should also be paid to controlling issues such as early clearance rates and pharmacokinetics of MOF drug delivery platforms. Stimuli-responsive MOFs hold promise for expanding the biological application scope of nanomaterials and overcoming the limitations of existing drug carriers.

Data availability
No new data were generated or analyzed in support of this research.

Conflicts of interest
There are no conflicts to declare.

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