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Metal–organic framework-based smart stimuli-responsive drug delivery systems for cancer therapy: advances, challenges, and future perspectives

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Abstract

Cancer treatment is currently one of the most critical healthcare issues globally. A well-designed drug delivery system can precisely target tumor tissues, improve efficacy, and reduce damage to normal tissues. Stimuli-responsive drug delivery systems (SRDDSs) have shown promising application prospects. Intelligent nano drug delivery systems responsive to endogenous stimuli such as weak acidity, complex redox characteristics, hypoxia, active energy metabolism, as well as exogenous stimuli like high temperature, light, pressure, and magnetic fields are increasingly being applied in chemotherapy, radiotherapy, photothermal therapy, photodynamic therapy, and various other anticancer approaches. Metal–organic frameworks (MOFs) have become promising candidate materials for constructing SRDDSs due to their large surface area, tunable porosity and structure, ease of synthesis and modification, and good biocompatibility. This paper reviews the application of MOF-based SRDDSs in various modes of cancer therapy. It summarizes the key aspects, including the classification, synthesis, modifications, drug loading modes, stimuli-responsive mechanisms, and their roles in different cancer treatment modalities. Furthermore, we address the current challenges and summarize the potential applications of artificial intelligence in MOF synthesis. Finally, we propose strategies to enhance the efficacy and safety of MOF-based SRDDSs, ultimately aiming at facilitating their clinical translation.

Keywords Stimuli-responsive, Drug delivery, Metal–organic framework, Cancer therapy, Drug loading

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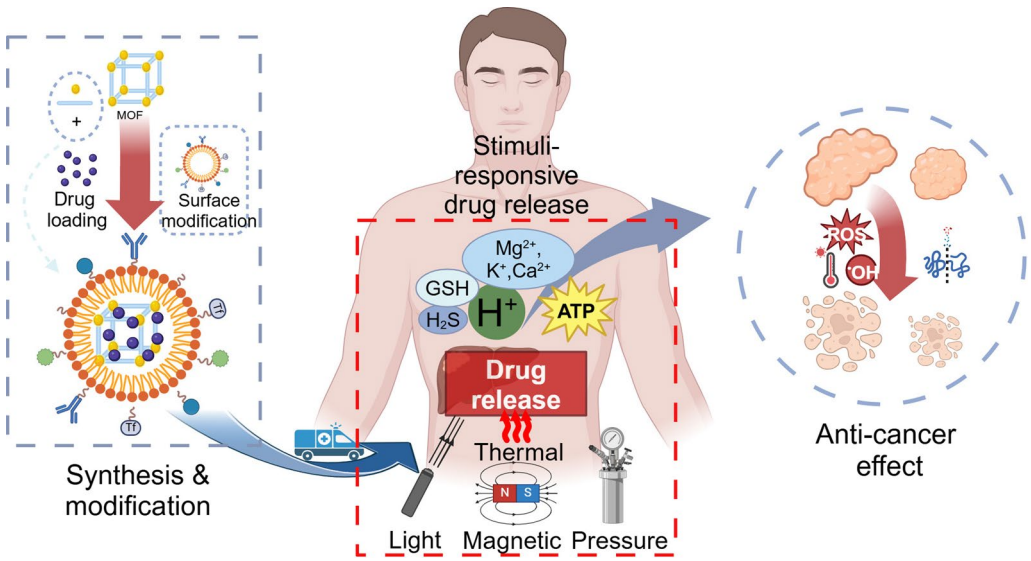
Graphical Abstract



Background

Cancer remains one of the major health problems threatening human survival [1, 2]. While chemotherapy is a primary non-surgical treatment for cancer, targeted therapy [3], immunotherapy [4], and other emerging methods have gradually become powerful tools against cancer. These treatment methods rely on drugs to kill tumors directly or serve as mediators for tumor treatment. Thus, the precision and concentration of drug distribution in the body are crucial for effective treatment and minimizing side effects. However, traditional drug delivery methods often lack tissue specificity, leading to poor targeting of tumor tissues and significant side effects.

To address the inherent limitations of traditional anticancer drug administration, such as undesirable side effects, poor pharmacokinetics, and adverse biodistribution [5], significant efforts have been made to explore novel drug delivery modalities [6]. Particularly, stimuli-responsive drug delivery systems (SRDDSs) show promising prospects [7–10]. SRDDSs can release drugs in response to certain stimuli. When introduced into the body, their chemical composition or physical structure undergoes a given transformation in response to certain triggers in the tumor tissue, and the loaded drug get released consequently consequently consequently, consequently, [11]. The triggers can be intrinsic, such as pH, glutathione (GSH), ions and adenosine triphosphate (ATP), which are localized in the tumor microenvironment (TME), or external, such as magnetic fields, temperature, pressure, and light, which can be manipulated intentionally to induce better spatiotemporal drug release, enhancing the efficacy and reducing toxicity, and have demonstrated greater potential for clinical application [12, 13].

Metal–organic frameworks (MOFs), also known as porous coordination polymers, which have been widely fabricated and applied for drug delivery since the initial application of loading ibuprofen [14], show great potential for anticancer applications. MOFs are organic–inorganic hybrid compounds with permanent porosity, formed by the self-assembly of metal ions or clusters with organic ligands through ligand bonds [15–18]. They are given the properties of a large specific surface area, tunable porosity, adjustable components and structure, easy synthesis, easy internal or surface functionalization, superior water solubility, special optical properties, multiple nano-enzymatic activities, excellent biodegradability, and good biocompatibility [19–23]. These properties make MOFs efficient hosts for various drugs [24, 25], allowing for extended release with tunable kinetics and improved bioavailability, meeting the demands of smart drug delivery systems.

Drug release can be effectively controlled by introducing MOFs as the carrier [26, 27], and more importantly, the degradation or structural changes of MOFs can be promoted by certain intrinsic and external features, achieving effective metabolism of MOF carriers and drug release [9]. Therefore, MOFs are promising candidates for developing SRDDSs.

Compared to other common nanoparticle platforms, MOFs offer distinct advantages. Unlike liposome-based platforms, MOFs exhibit superior drug loading capacity and tunable drug release properties. This is particularly evident in terms of drug loading capacity. For instance, liposomes have a drug loading capacity of only 0.4 wt%, whereas MIL-100, an iron-based MOF, can achieve a drug loading of up to 25 wt% for Bu, which is 62.5 times greater than liposomes [28]. This high drug loading capacity is a key advantage that enhances MOFs as drug delivery carriers. Another notable advantage of MOFs is the tunability of their structure, which provides controlled release capabilities when used as drug delivery systems. For instance, compared to other nanoparticles such as silica, gold, and lipid-based carriers, MOFs typically possess adjustable porosity and better structural flexibility, making them more suitable for encapsulating drugs and enabling their controlled release [29]. Furthermore, when designed as MOF-based SRDDSs, they demonstrate additional benefits in cancer therapy. For example, coupling nanoparticles or biomolecules to the surface of MOFs helps to realize the functionalization of MOFs, enabling various reversible drug loading manners, thereby improving targeting effects, stability, biocompatibility, and stimulus responsiveness [30, 31]; Moreover, various metal centers or organic ligands endow MOFs with different properties and functions, allowing the construction of multifunctional MOF nanoplatforms for cancer therapy [32, 33]. One of the most common applications involves leveraging the metal ions within MOFs to improve radiation efficacy, thereby enabling the combination of radiotherapy with other anticancer treatments, such as chemotherapy and immunotherapy. Furthermore, the organic ligands in MOFs can also be derived from materials with potential anticancer properties. For example, tetrakis (4-carboxyphenyl) porphyrin (TCPP), a photosensitizer used in photodynamic therapy (PDT), contains four carboxyl groups (-COOH) that strongly coordinate with metal centers such as hafnium ions (Hf^{4+}), facilitating the formation of a stable MOF. The resulting MOF not only possesses the radiotherapy potential imparted by Hf^{4+}, but also the photodynamic therapy potential conferred by TCPP, enabling a combination of radiotherapy and PDT [34]. Furthermore, by loading drugs, this MOF can integrate multiple therapeutic modalities, offering a versatile platform for more comprehensive treatment strategies. Building upon these advantages, MOF-based SRDDSs hold great promise as powerful tools to advance the development of cancer therapy.

As versatile drug delivery platforms, MOF-based SRDDSs can play various roles in different anticancer therapies, enhancing their targeting capabilities and achieving robust, comprehensive anticancer treatment [35–37]. In addition to traditional chemotherapy and radiotherapy, immunotherapy and targeted therapy have also shown excellent clinical efficacy in cancer treatment. Meanwhile, novel therapies such as PDT, photothermal therapy (PTT) [38], chemodynamic therapy (CDT) [39], and starvation therapy [40] are continuously being developed, with efficacy validated in vitro and in vivo. Most of these therapies rely on the corresponding therapeutic agents to exert their effects. MOF-based SRDDSs can effectively load these agents and bridge various anticancer therapies, contributing to better clinical outcomes. Therefore, as a promising emerging material in the field of cancer nanomedicine, MOF materials demonstrate substantial research value and considerable potential for application.

This review discusses the current status and unique challenges of MOF-based smart SRDDSs for various cancer treatments. It also summarizes the synthesis and modification of MOFs, types of MOFs for anticancer agent delivery, and various drug loading modes, proposing feasible strategies to improve clinical efficacy and biosafety.

The synthesis of stimuli-responsive MOFs

Hydro/solvothermal synthesis

Hydro/solvothermal synthesis is the most straightforward and widely used method. Its principle involves using high temperature and pressure to dissolve or partially dissolve substances that are insoluble or difficult to dissolve under normal temperature and pressure conditions in water or organic solvents. As the temperature increases under high pressure, the solution viscosity decreases, accelerating the diffusion and transfer of substances. This enhances reaction activity, which is advantageous for achieving reactions that are typically unattainable under normal conditions, thus promoting the generation of metal–organic framework compounds. The basic process begins with the following steps: (1) Selecting suitable metal ions and organic ligands; (2) Choosing an appropriate solvent, typically a high boiling point solvent that can dissolve the selected metal ions and organic ligands at a specific temperature, providing a stable environment for the synthesis reaction; (3) Mixing the selected metal ions and organic ligands in a certain proportion in the chosen solvent to form a precursor mixture.

The precursor mixture is then subjected to thermal treatment, usually in a high-temperature-resistant container (such as a stainless steel reaction vessel lined with polytetrafluoroethylene). When a certain temperature and pressure are reached, coordination reactions occur between the metal ions and organic ligands, initiating the formation of MOFs. As the reaction progresses, the

crystal structure of MOFs gradually grows and takes shape. For example, Scheidt et al. reported the synthesis of Urea MOFs synthesized by a solvothermal approach [41]; Corma et al. prepared coordinatively unsaturated MOFs by a modulated hydrothermal approach [42]; Su et al. reported a highly stable crystalline catalysts based on a MOF synthesized by solvothermal approach as well [43]. Recently, various modified methods have been put into practice. For example, Shelonchik and co-workers developed a photo-induced MOF synthesis method based on the traditional solvothermal method. This significantly shortened the synthesis time and allowed the preparation of four MOFs (Fig. 1) [44]. The prepared MOFs possessed photosensitizing properties and retained a large specific surface area, demonstrating their potential in the application of PTT.

In general, hydro/solvothermal synthesis is the most straightforward method with relatively simple operation, producing well-crystallized MOF products and facilitating the control of nucleation and growth rates. However, there are also notable drawbacks. Besides being energy-consuming and time-consuming, this method is prone to forming mixed crystals with different MOF structures, making separation extremely challenging.

Microwave-assisted synthesis

Unlike the thermogenesis mechanism in traditional hydrothermal synthesis, the principle of microwave-assisted synthesis involves converting electromagnetic energy into heat to facilitate reactions. Within the alternating electromagnetic field, polar molecules in the precursor (dielectric material) undergo coupling interactions in the microwave electric field, rapidly increasing the temperature of the reaction system. This, in turn, facilitates the bonding of metal ions with organic ligands.

The basic processes are as follows: Firstly, the selected organic substances and metal materials are placed in an organic solvent for ultrasonic dissolution. The obtained precursor solution is then subjected to microwave heating in microwave reaction equipment. The microwave's electric field exerts a torque on electric dipoles. Molecules with dipole moments (e.g., water) attempt to align these dipole moments with the electric component of the electromagnetic field, causing continuous rotation. The movement of these molecules generates thermal energy through molecular friction and dielectric loss. In this environment, coordination reactions occur between metal ions and organic ligands, leading to the formation of the crystalline structure of MOFs. Finally, these crystals are purified in an appropriate manner.

For example, Dong et al. prepared the MIL-53(Fe) through-microwave assisted synthesis with a considerably reduced duration compared with conventional solvothermal synthesis (15 h to 5-10 min) [45]. Moreover, Masel et al. produced MOFs with a shortened time and a more controllable particle size [46]. What's more, Schröder et al. reported a swift, size-controllable and morphology-controllable MOF synthesis assisted by microwave [47]. These examples highlight the advantages of microwave-assisted synthesis: time and energy efficiency, uniformity, and controllability over the size and morphology of MOF particles.

Electrochemical synthesis

The electrochemical synthesis method includes several specific synthesis approaches, such as anodic synthesis, cathodic synthesis, indirect bipolar electrodeposition, potential displacement method (electroplating replacement), and electrophoretic deposition. Among them, anodic synthesis and cathodic synthesis are the two most commonly used methods. The basic principle is that under the action of an external electric field, the target product is formed through self-assembly of metal ions dissolved at the anode or in the solution with organic

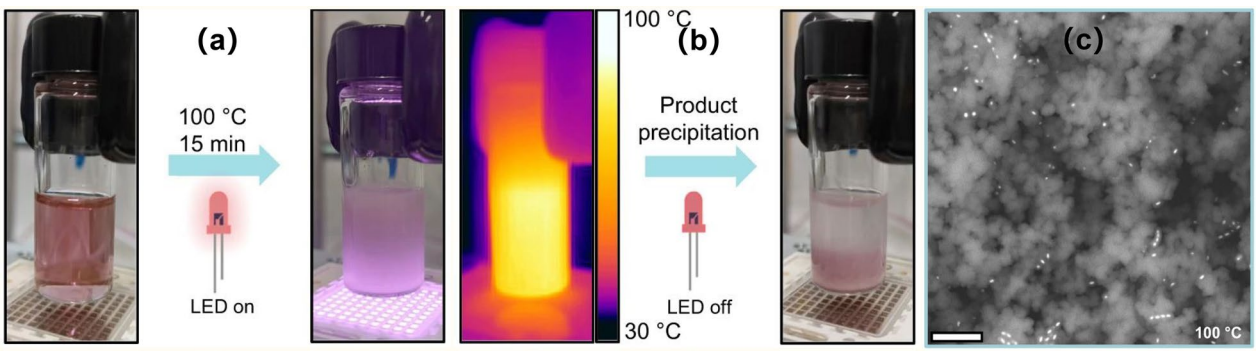


Fig. 1 Photothermal synthesis schemes of UiO-66 and its SEM image. **a** and **b** Photothermal synthesis schemes of UiO-66. **c** SEM image of synthesized UiO-66. The white scale bar size is 1 μm. Reproduced with permission [44]

ligands in the solution on the electrode surface. For anodic synthesis, the basic process consists of four stages: nucleation, cluster growth, coexistence, and separation. In this process, the metal source is the metal ions dissolved by anodic oxidation. Mueller et al. pioneered the anode synthesis method for MOFs. They used a copper plate as both the anode and cathode, and successfully prepared Cu-MOFs by applying electricity for 150 min in a solution containing 1,3,5-benzenetricarboxylic acid in methanol [48]. In comparison, the basic process of the cathodic synthesis method does not include a separation stage. Additionally, the metal source typically comes from externally added metal salts rather than anodic dissolution. Under the influence of an applied electric field, MOFs are formed through self-assembly with ligands. This method was first proposed by Li et al. for MOF-5 synthesis [49].Overall, the electrochemical synthesis method has several advantages: lower reaction temperature, faster reaction rate, greater energy efficiency, and the capability for continuous production. At the same time, the reaction process offers more adjustable parameters, allowing for better control over the shape and size of the products.

Mechanochemical synthesis

The fundamental principle of mechanochemical synthesis involves utilizing mechanical energy generated through compression, shear, and grinding to achieve chemical synthesis. Based on the grinding approach, mechanochemical synthesis methods used for MOF synthesis are generally classified into three types: dry grinding, liquid-assisted grinding, and ion-and-liquid-assisted grinding. The operational process typically includes material selection, mixing, grinding and reaction, and separation and purification.

In 2006, James et al. first reported the synthesis of MOFs through mechanochemical methods. They ground isonicotinic acid with copper acetate for 10 min without heating, ultimately obtaining efficient microporous $Cu(INA)_2$ [50]. Klimakow et al. employed a liquid-assisted grinding method to prepare HKUST-1 ($Cu_3(BTC)_2$) and MOF-14 ($Cu_3(BTB)_2$) [51]. Additionally, Beldon and his colleagues found that the synthesis of pillar-supported MOFs could be achieved by introducing ionic salts into a grinding system with liquid additives [52].

Mechanochemical reactions without grinding media and rotating screws have been previously reported, with researchers initially stirring samples by ultrasonic or sonic frequencies to prepare co-crystals [53, 54], and a similar approach to MOFs' preparation was utilized by Titi et al. [55]. They synthesized a variety of known MOFs and the ZIF-L framework, which had never been obtained in a mechanochemical setting before. This emerging approach has the potential to simplify sample preparation and scale up production.

Overall, the mechanochemical synthesis of MOFs has advantages such as high efficiency, cost-effectiveness, environmental friendliness, and the potential for large-scale industrial production. It is noteworthy that this method also provides an opportunity to utilize insoluble metal sources. However, it faces challenges such as controlling crystal structures and minimizing byproduct formation. Greater efforts are needed to improve its application in MOF synthesis.

Sonochemical synthesis

The sonochemical method has been increasingly employed for the swift synthesis of MOFs. Its fundamental principle involves the continuous generation and rupture of small bubbles in so-called "hot spots" under ultrasonic irradiation [56], thereby forming MOF nuclei in a relatively short period. The basic procedure involves introducing a mixture of metal salt and organic linker into a reactor equipped with an ultrasonic horn and sonicator bar. Ultrasonic waves are then generated through cyclic mechanical vibrations ranging from 20 kHz to 10 MHz. Under ultrasonic irradiation, small bubbles are continuously generated and ruptured in the hot spots, resulting in extreme local heating and high pressures. This process ensures an ample supply of energy, allowing for the generation of small and uniformly nucleated MOF crystals within a relatively short crystallization period [57]. Finally, the separation and purification are needed after the formation of MOF crystals.

Qiu et al. first demonstrated that rapid synthesis of MOFs can be achieved using the ultrasonic method [58]. Since then, sonochemistry has been widely used in MOF synthesis. Later that year, MOF-5 [59] and ZnBDC [60] were also successfully constructed using the sonochemical method. Furthermore, Ying et al. achieved ultrafast green synthesis of bismuth-MOF in aqueous condition using the sonochemical method [61]. As mentioned, sonochemical synthesis method possesses advantages such as rapidity, cost-effectiveness, environmental friendliness, uniform nucleation, and operability at room temperature. However, it also has certain drawbacks, namely, the resulting MOFs' structures exhibit a variety, leading to differences in material purity and making purification challenging.

Other methods

In addition to the commonly used methods mentioned above, there are several other techniques for synthesizing MOFs, such as microfluidic methods [62], room temperature synthesis [63], diffusion methods [64], microemulsion methods [65], spray-drying methods [66] and so

on. Here, we mainly outlined the microfluidic synthesis, room temperature conversion method and spray-drying methods.

Microfluidic synthesis

The basic principle of microfluidic synthesis of MOFs is to use microfluidic technology to precisely control the flow and mixing of liquids at the micron or nanometer scale, thereby improving the traditional MOF synthesis process. The introduction of microfluidic technology offers several advantages, including high controllability of reaction conditions, reduced material consumption, faster reaction speeds, and the capability for continuous production.

For example, Wu et al. designed a water-based continuous droplet microfluidic system for the large-scale production of ZIF-8 and MIL-100(Fe). By using this microfluidic system, they were able to complete the synthesis of MOFs in just 3 min, a remarkable reduction from the 300 min required by traditional hydrothermal synthesis. Additionally, studies showed that using the same raw materials, the introduction of the microfluidic system resulted in materials with greater uniformity and higher crystallinity [67].

Room temperature conversion synthesis

The basic procedure of the room temperature conversion method for MOF synthesis typically involves mixing a metal precursor solution with a ligand solution and stirring the mixture at room temperature. The size and morphology of the resulting materials can often be adjusted by changing the stirring time, speed, and the order in which the two solutions are mixed. This method is characterized by its low energy consumption and mild synthesis conditions.

Yan et al. successfully prepared UiO-66 membranes at room temperature by using $Zr_6O_4(OH)_4(OAc)_{12}$ clusters. This approach not only effectively reduced the synthesis temperature but also optimized the defect density in the UiO-66 framework [68]. Although this room temperature synthesis method has not yet been widely applied in drug delivery, further development of these methods could enhance their application in this field.

Spray-drying synthesis

Spray drying is an industrial technology designed for the rapid conversion of solutions into powders, which has recently been demonstrated to be applicable for the synthesis of new materials, including MOFs. The use of spray drying for MOF synthesis was first reported by Carne-Sanchez and their team [66]. They found that by directly spray drying MOF precursor solutions, typical HKUST-1 could be continuously and rapidly prepared. This method enabled the efficient, scalable production of dried spherical powders in a single step, significantly reducing manufacturing costs and production times. Spray drying thus holds great potential for the development and application of MOFs.

Figure 2 summarizes the main methods for MOF synthesis.

The classification of MOFs applied in SRDDSs for cancer therapy

Fe-MOFs

Due to their favorable characteristics, such as low toxicity, configurational flexibility, and biodegradability [69], Fe-based MOFs are among the earliest MOFs used for drug delivery. These Fe-based MOFs can respond to various physicochemical stimuli in the TME. For instance, the acidic environment of tumors can accelerate the disintegration of Fe-based MOFs. Rezaei et al. prepared nano MIL-100 top-down by sonication and used it to load the anticancer drug docetaxel (DTX) (Fig. 3) [70]. This carrier achieved a 57.92 wt% drug payload and exhibited pH-dependent release. Compared with the free drug, DTX delivered via the vector had a stronger cell-killing effect. In addition, modifying the surface of MOFs with pH-responsive coating is a promising strategy. Yang et al. prepared a pH-responsive Fe-based MOF that could release loaded doxorubicin (DOX) in the acidic TME [71]. Similarly, for Fe^{3+}-constructed Fe-based MOFs, the

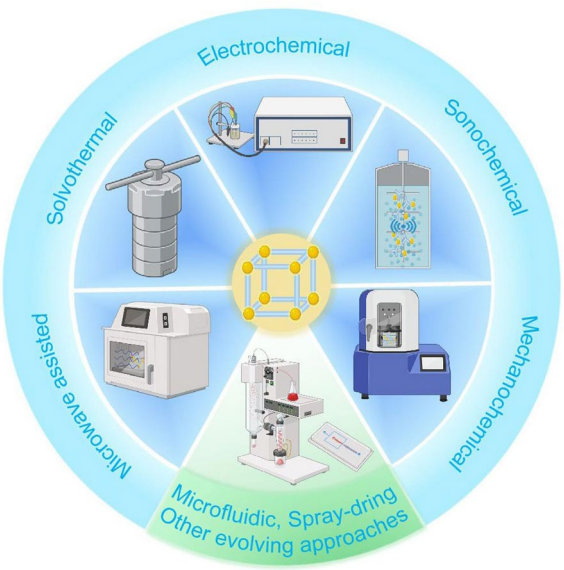


Fig. 2 Main methods for MOF synthesis. Solvothermal, microwave-assisted, sonochemical, electrochemical and mechanochemical synthesis are the most widely used methods, other methods such as microfluidic synthesis and spray-drying synthesis are also emerging and evolving

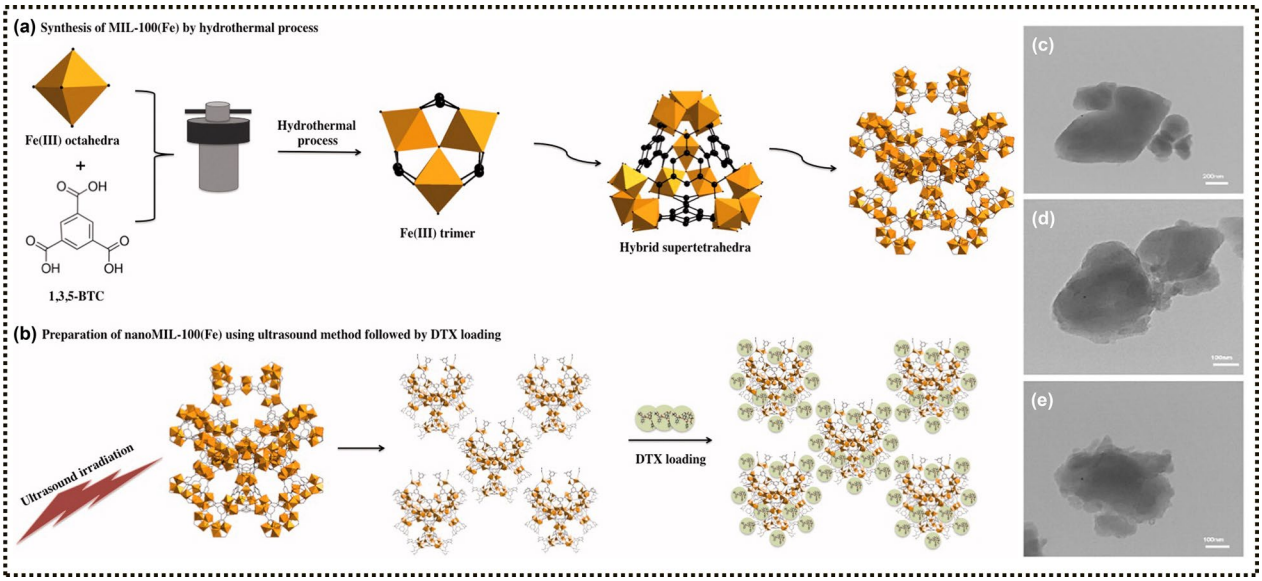


Fig. 3 Schematic steps from the synthesis of MIL-100(Fe) to DTX loading and the corresponding TEM images of products. **a** and **b** Schematic steps from synthesis of MIL-100(Fe) to DTX loading. **c**-**e** TEM images of MIL-100(Fe), nanoMIL-100(Fe), and DTX-loaded nanoMIL-100(Fe). Reproduced with permission [70]

glutathione (GSH) present in the TME can alter the oxidation state of Fe ions, leading to structural breakdown of MOFs and responsive drug release in the TME. Furthermore, Fe-based MOFs can respond to external physical stimuli. For instance, Xiang et al. prepared a DOX-loaded Fe_3O_4-MOF with magnetic field responsiveness [71]. Upon magnetic field intervention, the drug release significantly increased and accelerated. Consequently, iron-based MOFs are considered promising candidates for drug delivery systems. To date, a significant number of Fe-MOFs have been developed, with numerous members in the MIL-n family being Fe-based MOFs. Among them, MIL-100 is the most extensively researched.

Zn-MOFs

As one of the essential trace elements in the human body, zinc ions are considered to have low toxicity. Due to the diversity of zinc-based MOFs, their application in drug delivery systems is extensive. Many MOFs with zinc ions as metal centers are sensitive to low pH, where their acid-labile bonds degrade, leading to the release of encapsulated drugs. Hence, they serve as promising candidates for low pH-responsive drug delivery systems.

For instance, ZIF-8, constructed from 2-methylimidazole and Zn^{2+}, is an acid-responsive MOF. It remains relatively stable under neutral conditions (pH 7.4), but collapses under lower pH conditions [72]. Sun et al. [73] utilized ZIF-8 to package D-α-tocopheryl succinate, and the resulting D-α-tocopheryl succinate@ZIF-8 degrades rapidly in acidic environments due to ZIF-8's pH responsiveness, providing residue-free drug release for tumor chemotherapy. Similarly, another zinc-based MOF, DUT-32, is pH-sensitive and can be employed in drug delivery systems. Abazari et al. [74] proposed DUT-32 as a carrier for pH-responsive release of DOX and amoxicillin. Additionally, ZIF-8 can release drugs in response to glucose [75]. Furthermore, Zn-MOFs can release drugs through ATP response [76], ion response [77], or heat response [78]. MOF-5 and other members of the ZIF family, such as ZIF-11 and ZIF-90, are expected to show potential in drug delivery. In summary, the versatility of zinc-based MOFs, including ZIF-8 and DUT-32, offers a wide range of possibilities for pH-responsive and other stimulus-responsive SRDDSs.

Zr-MOFs

Zr-based MOFs are also considered to be qualified candidates for drug delivery due to their stability, low toxicity, and ease of nanoparticle formation. As the most extensively researched Zr-MOFs, UiO-66 also possesses the property of releasing its encapsulated drugs in acidic environments, which is supposed to be a result from the protonation of phosphates in an acidic medium. For example, Zhu et al. used UiO-66 nanoparticles as carriers for alendronate (AL) delivery and observed that the drug release percentage increased at lower pH levels, indicating that UiO-66 is pH-responsive. In addition to UiO-66, several other Zr-MOFs, such as UiO-67, UiO-68, NU-n, MOF-801, and MOF-802, hold potential for drug delivery applications and

warrant further exploration. Parsaei et al. synthesized a UiO-66-NH_2 based SRDDS for targeted delivery of quercetin to breast cancer cells. The UiO-66-NH_2 was synthesized using a sonochemical approach and a layer-by-layer assembly method following the synthesis of the Fe_3O_4-COOH magnetite core (Fig. 4a and c). With a considerable loading capacity, the attached quercetin showed pH-responsive release behavior (Fig. 4b). Additionally, researchers made preliminary confirmation of the anticancer effect and biocompatibility of the SRDDS by cellular experiments.

Furthermore, for better biocompatibility and tumor-target accuracy, Trushina et al. used SiO_2 as a shell and folate-conjugated pluronic F127 as surface modification of UiO-66 [80]. The synthesized UiO-66@SiO_2/F127-FA(folic acid) nanoplatform effectively targeted tumor cells, and the encapsulated DOX exhibited acid-responsive release characteristics. Figure 5a shows the TEM/STEM images of intact UiO-66 MOFs and elemental mapping. The intracellular distribution of the DOX-loaded MOF in MCF-7 and RAW 264.7 cells, shown in Fig. 5b, demonstrats effective tumor-targeted drug delivery.

Cu-MOFs

Copper, similar to zinc, is also one of the trace elements in the human body with important physiological functions, actively participating in normal metabolism. Consequently, Cu-MOFs are anticipated to exhibit excellent biocompatibility. Additionally, Cu-MOFs can respond to specific stimuli in the TME, such as low pH and high GSH levels. Wang et al. developed Cu-MOF-assisted PDT that leverages Cu(II)'s ability to react with GSH and deplete intracellular GSH, thereby enhancing therapeutic effects [81]. Shaabani et al. designed gelatin microsphere-encapsulated Cu-based metal–organic framework nanohybrids for methotrexate (MTX) delivery [82]. Currently synthesized copper-based MOFs, such as HKUST-1 and MOF-2/3, have demonstrated their potential applications in drug delivery systems [83]. Further research in this area is warranted to fully realize their capabilities.

CD-MOFs

CD-MOFs represent a novel class of MOFs synthesized using natural carbohydrates, specifically cyclodextrins, in combination with alkali metal cations. These materials are highly promising for oral or intravenous drug delivery systems due to their renewability, non-toxicity,

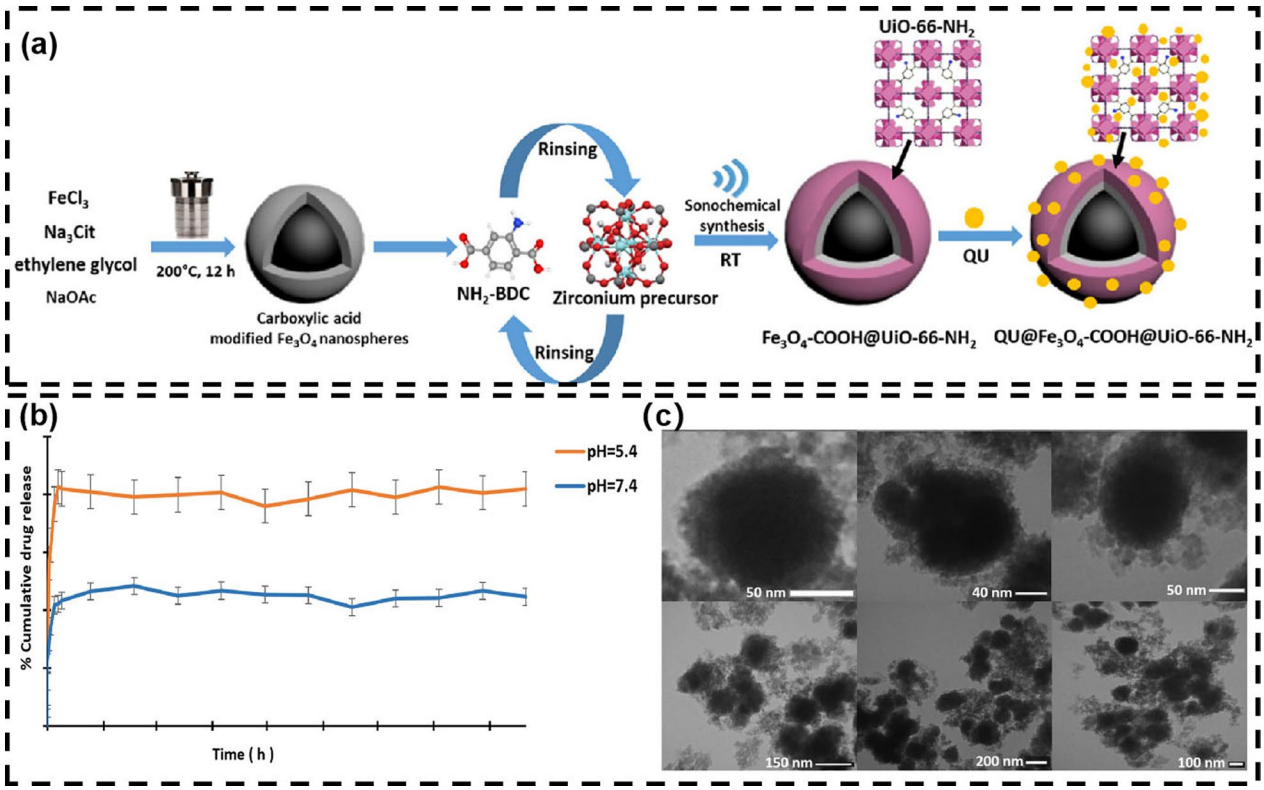


Fig. 4 Synthesis, drug release profile, and TEM images of QU@Fe_3O_4-COOH@UiO-66-NH_2 and QU@Fe_3O_4-COOH@UiO-66-NH_2. **a** Synthesis of QU@Fe_3O_4-COOH@UiO-66-NH_2. **b** QU drug release profile of QU@Fe_3O_4-COOH@UiO-66-NH_2 at two pH values of 5.4 and 7.4. **c** TEM images of Fe_3O_4-COOH@UiO-66-NH_2 (upper), QU@Fe_3O_4-COOH@UiO-66-NH_2 (lower). Reproduced with permission [79]

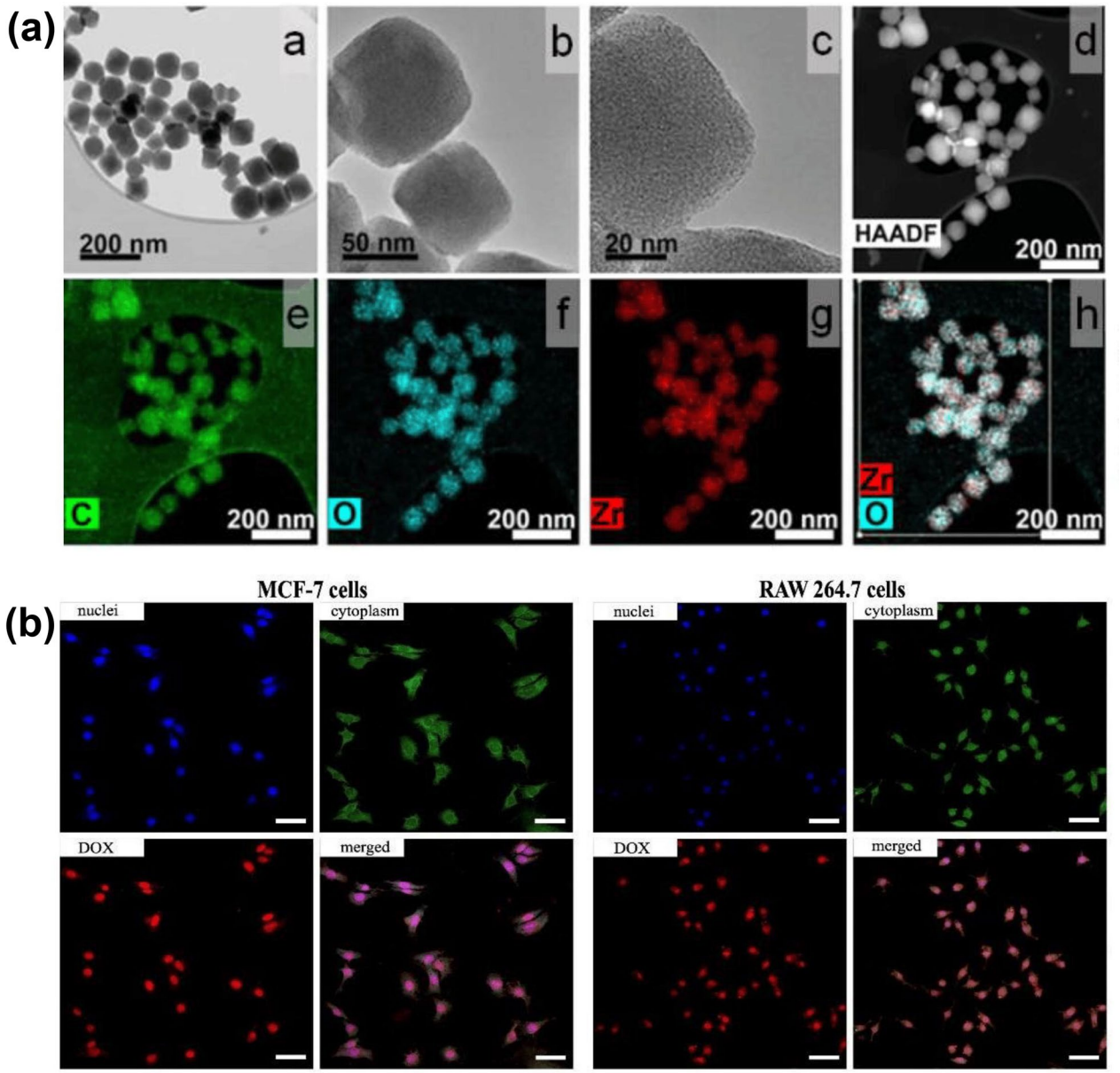


Fig. 5 TEM/STEM images and elemental mapping of intact UiO-66 MOFs, and the intracellular distribution of the DOX-loaded MOFs in target cells. **a** TEM/STEM images of intact UiO-66 MOFs and elemental mapping. **b** Intracellular distribution of the DOX-loaded MOFs in MCF-7 and RAW 264.7 cells after 2 h. Cell nuclei are in blue (Hoechst 33,258), cell cytoplasm in green (Calcein AM), and MOFs in red (DOX). Scale bar is 50 μm. Reproduced with permission [80]

and edibility. Smaldone et al. first reported the development of a renewable, highly symmetrical, porous, and ultra-high surface area edible MOFs [84]. This framework, named Cyclodextrin-based MOFs (CD-MOFs), is exclusively prepared from edible ingredients: potassium (K) ions, ethanol, and cyclodextrin. Further studies have explored the potential of CD-MOFs for drug delivery applications. For instance, Xue et al. developed a GSH-responsive CD-MOF for the delivery of doxorubicin (DOX), demonstrating the framework's ability to respond to specific biochemical stimuli [85]. Similarly, Singh et al. reported a pH-responsive CD-MOFs for delivering DOX, highlighting the versatility of CD-MOFs in responding to different environmental triggers [86]. The application of CD-MOFs in SRDDSs is still in its developmental stages, but their unique properties and the promising results from initial studies suggest significant potential for future advancements.

Continued research is needed to optimize CD-MOFs for clinical applications.

Other metals applied in MOFs for SRDDSs

MOFs composed of other metals such as Mn and Mg are also demonstrating significant potential in the development of drug delivery systems. These metal ions are essential to human physiology and exhibit a certain degree of biocompatibility, making them suitable for biomedical applications.

Additionally, they possess specific characteristics. Mn-MOFs are acid-sensitive materials that collapse rapidly in a weakly acidic environment, and especially, they can catalyze the decomposition of hydrogen peroxide (H_2O_2) to generate highly cytotoxic hydroxyl radicals. Therefore, it inherently possesses the potential to assist in inducing apoptosis in tumor cells. For instance, Yang et al. utilized Mn-MOFs to augment the efficacy of anti-PD-1 therapy in hypoxic tumors [87]. Mn(III) based MOFs have also been employed to enhance the efficacy of PTT for cancer therapy [88].

Mg-MOFs are increasingly recognized for their potential in drug delivery systems due to their biocompatibility, structural versatility, and unique physicochemical properties. The incorporation of magnesium into MOFs leverages these intrinsic benefits, making Mg-MOFs promising candidates for biomedical applications. And Mg-MOFs-74 has shown the ability to promote rapid pharmacokinetics for some drugs [89].

Intrinsic characteristics of tumors and MOF-based drug delivery systems

Since the proposal of "Hallmarks of Cancer", the characteristic features of tumors, such as self-sufficiency in growth signals, limitless replicative potential, sustained angiogenesis, deregulated cellular energetics, and tumor-promoting inflammation, have gradually come to light [90–92]. These features are the causes of tumor pathogenesis and, at the same time, are critical factors in cancer treatment. The unique TME formed based on these characteristics has become a focal point in cancer research. The TME comprises the extracellular matrix, blood vessels, and various cells. It evolves with the tumor's growth, acting as both a product of and a support system for tumor progression. It possesses characteristics such as mild acidity, hypoxia, a complex redox environment, overexpression of specific enzymes and proteins, elevated temperature, high ATP content, and vascular abnormalities [93–96]. Many of these characteristics have become targets for developing and improving cancer treatments [97–100].

MOF-based SRDDSs have emerged as promising platform that enhance the efficacy of cancer treatment while reducing side effects. These systems can effectively leverage the unique features of the TME for targeted drug delivery. For example, according to the Warburg effect, tumor cells primarily rely on the glycolytic pathway for energy [101], leading to a slightly acidic TME. While the normal extracellular pH is around 7.4, the extracellular pH in tumor tissues ranges from 6.5 to 6.8 [102, 103]. Some pH-responsive MOFs can deconstruct under low pH conditions, releasing encapsulated anticancer drugs in the acidic TME [104, 105]. Furthermore, metabolic dysregulation is one of the ten characteristics of tumors. Various organelles within tumor cells generate significant amounts of reactive oxygen species (ROS) during enhanced metabolic processes, leading to heightened oxidative stress. To counteract the destructive effects of oxidative stress, tumor cells accumulate reducing substances such as superoxide dismutase and GSH. Some MOFs can respond to ROS and GSH, enabling precise and controlled drug release in response to the oxidative stress and reductive environment within the TME [106, 107]. In addition, hypoxia is a common characteristic of aggressively growing solid tumors and a key factor in drug resistance. Hypoxia-responsive MOF drug delivery systems can target hypoxic tumor tissues and alleviate local hypoxia, thereby enhancing the effectiveness of various cancer treatments [108, 109].

Benefiting from the intrinsic properties of MOFs — such as high porosity, large surface area, tunable structure and pore size, diverse structural modifications, multiple drug loading modes, and moderate-strength coordination bonds—MOF-based SRDDSs demonstrate tremendous potential in cancer treatment. More importantly, their responsiveness to the TME allow for targeted and controlled drug release, improving therapeutic outcomes and minimizing side effects, and further enhance their potential for better cancer therapy. Figure 6 illustrates the main advantages of MOFs for developing SRDDSs based on their intrinsic structure, using ZIF-8 as a representative example.

Anti-cancer drug loading mode of MOFs

MOFs exhibit great potential for building anticancer drug delivery systems, largely due to their versatile drug loading modes. Currently, drugs can be incorporated into MOFs through four primary methods: (1) embedding within the pores of MOFs, (2) attaching to the outer surface of MOF crystals or covalently binding to the surface of MOFs, (3) encapsulating in situ into MOF crystals during synthesis, and (4) using the drug as a ligand to form MOFs directly with the metal-ion nodes (Fig. 7). These loading modes and their characteristics are summarized as follows:

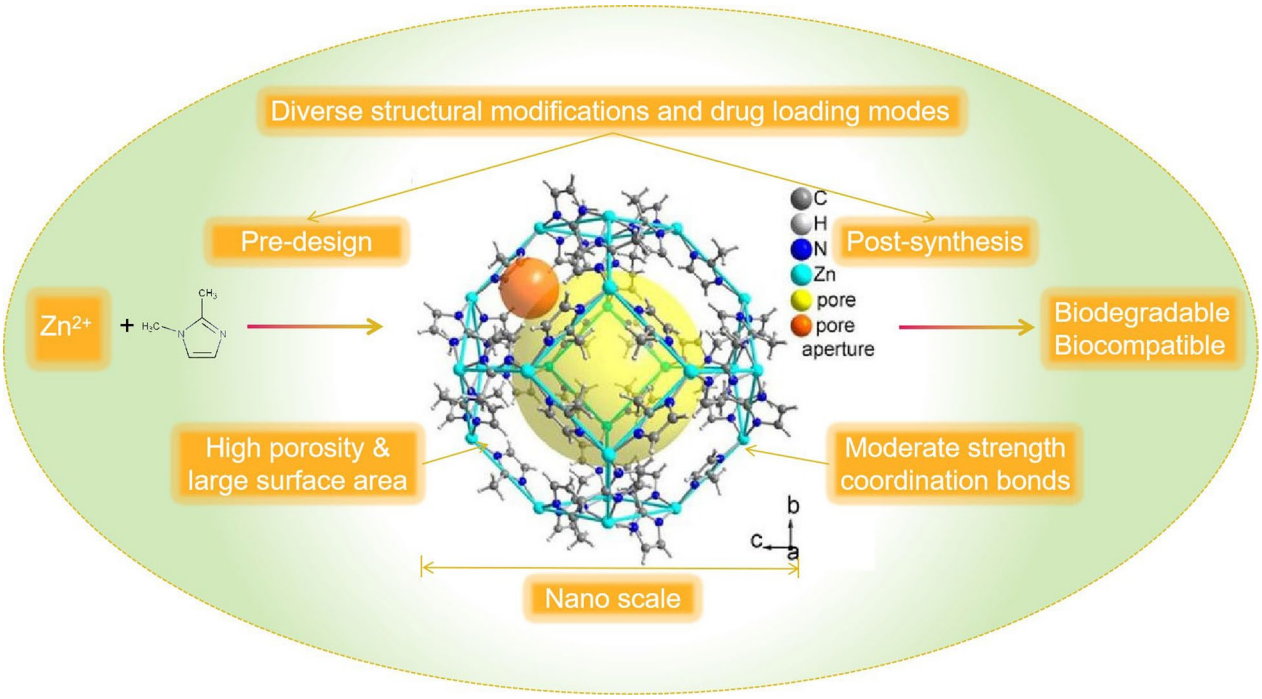


Fig. 6 Intrinsic advantages of MOFs for SRDDSs (Taking ZIF-8 as an example). Nanoscale size of ZIF-8 enables it to be passively targeted to tumor sites through EPR. High porosity and large specific surface area provide high drug loading potential, while the ease of pre-synthesis design and post-synthesis modification enhance its feasibility for drug loading. The moderate strength of coordination bonds imparts acid-degradable properties, and its biodegradability and biocompatibility make it suitable for in vivo drug delivery

Pore encapsulation

Pore encapsulation is the most direct and widely utilized method for drug loading in delivery systems [28, 110, 111]. By embedding drugs inside the pores of MOFs, the drugs are shielded from various disturbances in the body, thereby maintaining their stability and efficacy. In this loading mode, drug release is often triggered by the enlargement of MOF pores or the degradation of the MOF shell. This method ensures a controlled release, which can be finely tuned by manipulating the pore size and structural integrity of the MOFs.

Surface attachment

Surface attachment is also a common method to achieve drug loading [112]. This method does not impose strict requirements on the pore size of MOFs, making the immobilization process faster and easier [113]. Hydrogen bonding and π-π interactions are the main reasons for the host–guest attraction between the drug and the organic linker in MOFs. However, this method carries a higher risk of drug leaching, which also means that it may be more susceptible to TME stimulation for responsive release [114]. Covalent linkage is a special type of surface loading, which is more stable than the former. Drugs containing functional groups such as amino, carboxyl, phenol, thiol, imidazolyl, indolyl, and hydroxyl groups can form covalent linkages with organic linkers in MOF [115, 116]. These covalent bonds can break under specific stimuli, particularly low pH conditions in the TME, enabling responsive drug release.

In situ packaging

In addition to post-synthesis modification of MOFs, there is a strategy of directly loading the target drug during MOF synthesis [117, 118]. One of the advantages of this strategy is that the size of the drug will not be limited. However, the drug is exposed to the synthesis reaction environment, necessitating mild reaction conditions to prevent drug degradation. Although this method is promising, its current application is limited due to the stringent requirements for maintaining drug stability during synthesis.

Formation of bio-MOFs

In addition, for specific drugs such as biomolecules, drug loading can be achieved by incorporating the drug directly into the MOF assembly process [119]. Biomolecules, which often contain amino acids, peptides, and nucleobases with reactive chemical groups, can coordinate with various metals to serve as organic linkers for

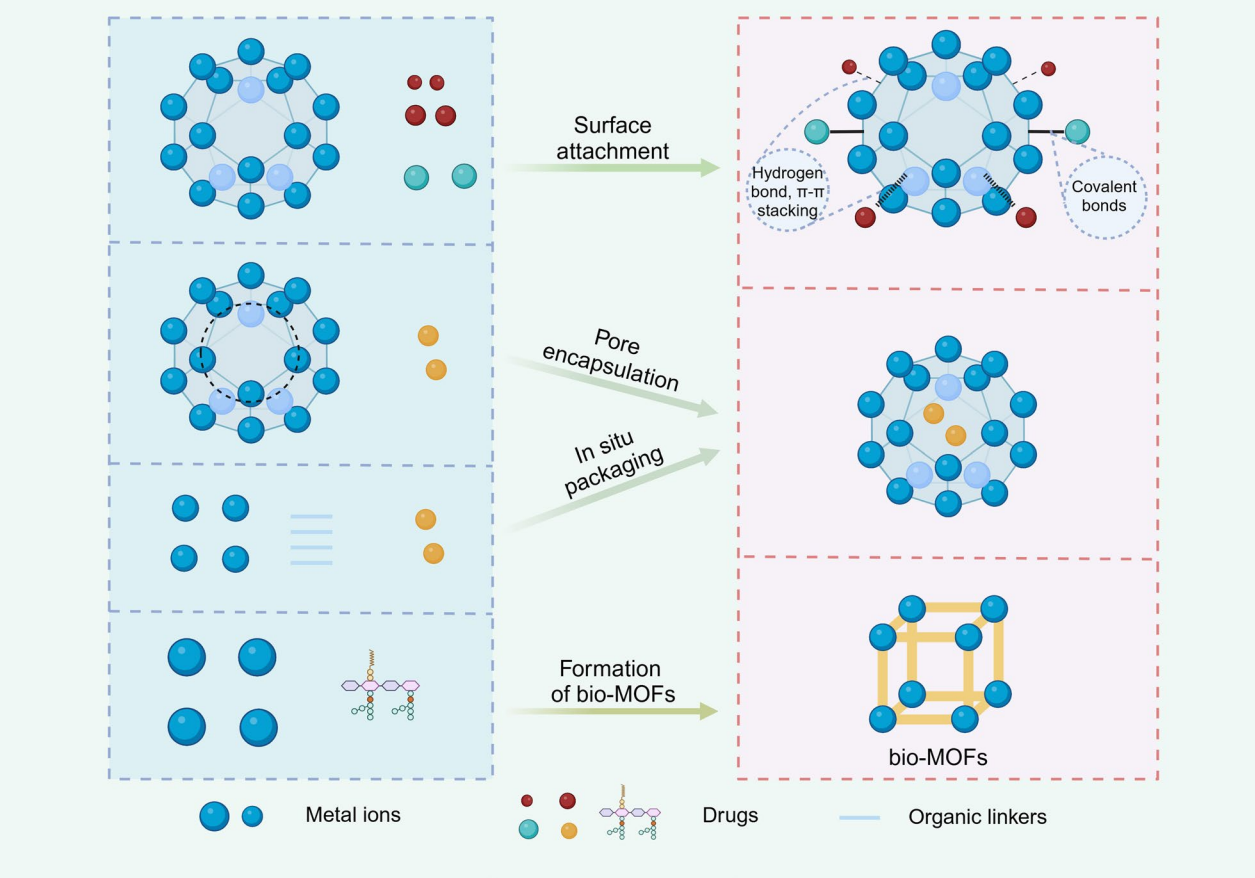


Fig. 7 Typical anticancer drug loading modes of MOFs. Drugs can be loaded onto MOFs through surface attachment by forming covalent bonds, hydrogen bonds, or π-π interactions with the MOFs. They can also be embedded within the pores or loaded in situ into the MOF's pores. Additionally, some drugs can act as ligands and form bio-MOFs with metal ions for loading purposes

MOF synthesis [120]. Although the application of bio-MOFs for SRDDSs remains limited, further exploration in this area is necessary to expand their potential.

The nature of MOFs themselves and the mode of drug loading collaboratively determine the response of drug delivery systems to different stimuli. Based on currently synthesized MOFs and established drug loading modes, MOF-based SRDDSs responsive to different types of stimuli have been developed. Common MOFs applied for anticancer drug delivery and the corresponding drug loading modes are summarized in Table 1.

Stimuli-responsive MOFs for anticancer drug delivery

Due to the inherent superior characteristics of MOFs and the distinctive properties of TME, MOF-based SRDDSs hold immense potential for enhancing targeted drug delivery to tumors. Additionally, MOFs can effectively load anticancer drugs through various reversible mechanisms, allowing for precise and controlled release. This potential is being rapidly explored and developed. In the following sections, anticancer drug delivery systems based on MOFs that respond to different types of stimuli will be summarized, and the mechanisms behind their stimuli-responsiveness will be elucidated.

pH-responsive MOFs

Among the various stimuli in the TME, pH is the most common and widely utilized one. The acidic nature of the TME provides an ideal target for designing pH-responsive drug delivery systems. These systems primarily respond to pH reduction, leading to structural changes and subsequent release of the loaded drugs. Common examples of pH-responsive MOFs include ZIF-8 [137], MIL-100/MIL-101 [115], UiO-66 [116]. Multiple mechanisms drive these materials to respond to pH changes. Here we summarize the prevalent major mechanisms for different loading modes (Fig. 8).

pH induced shell cracking

For drugs encapsulated in the shell of MOFs, pH can lead to the drug release by inducing the cracking of shells.

Table 1 Common MOFs for anticancer drug delivery

MOF	Drug	Loading mode	Drug loading	Target	Ref
ZIF-8	DOX	In situ packaging	10wt%	MCF-7 cells	[121]
ZIF-67	DOX, CuSe	Pore encapsulation, Surface attachment	20%	4T1 cells	[122]
ZIF-8	Rapamycin	In situ packaging	58.22%	MCF-7/ADR cells	[123]
ZIF-90	DOX, 5-Fu	Surface attachment, Pore encapsulation	13.6wt%, 36.35wt%	–	[124]
ZIF-8	Camptothecin	In situ packaging	15%	Hela cells	[125]
UiO-66-NH_2	Oxaliplatin	Surface attachment	10%	CT26 cell line	[126]
UiO-66	DOX	Pore encapsulation	6.2wt%	MCF-7 cells	[80]
UiO-66-NH_2	Quercetin	Surface attachment	53.9wt%	MDA-MB-231 cells	[79]
UiO-66	Acridine	–	10wt%	U251 glioblastoma cells	[127]
UiO-66	DOX	Pore encapsulation	55.9%	HeLa,HEK-293,PC12,HepG	[128]
UiO-66	Quercetin	Surface attachment	48.9wt%	MDA-MB-231 cells	[129]
UiO-66-NH_2	Temozolom-ide	Pore encapsulation	19.4wt%	Glioma cells	[130]
MIL-53(Fe)	5-Fu	Pore encapsulation	23wt%	MGC-803 and HASMC cells	[131]
NH2-MIL-53(Al)	DOX	Pore encapsulation	62.5%	HepG2 cells	[132]
MIL-100(Fe)	Cyclophosp-hamide	Surface attachment	56wt%	MCF-7 cells	[55]
MIl-100(Fe)	Methotrexate, col-lagenase enzyme	Pore encapsulation	50.3%; 91.74%	A-375 cell line	[133]
MIl-100(Fe)	DTX	Surface attachment	57.2wt%	MCF-7 cells	[70]
MIl-100(Fe)	Dacarbazine	In situ packaging	10.5wt%	A375 cell lines(melanoma)	[134]
MIL-101(Fe)	Curcumin	Pore encapsulation	56.3 wt %	HeLa	[135]
MIL-101(Fe)	Triptolide	Pore encapsulation	39.77 ± 1.24%	HepG2 cells	[136]

Many MOFs, such as ZIF-n and MIL-n series, are vulnerable to low pH. When entering the acidic TME, these SRDDSs released their drug responsively as the MOFs degrade, mainly due to the protonation-induced leakage of the coordination bonds between metal ions and organic ligands. For example, ZIF-8, constructed with 2-methylimidazole and Zn^{2+}, suffers degradation in acidic environment as 2-methylimidazole could be protonated and the coordination with Zn^{2+} weakened. Zhuang et al. developed a general synthetic route to encapsulate small molecules in ZIF-8 nanospheres for drug delivery [104]. In this SRDDS, ZIF-8 was used as the carrier and the shell of the anticancer agent camptothecin (CPT), and their experiments showed that ZIF-8 degraded at pH = 6 and lost its original size and shape. What's more, their in vitro experiment proved that the CPT-encapsulated ZIF-8 particles had an enhanced effect of killing MCF-7 breast cancer cells.

For the MIL-n series such as MIL-101-NH_2, similar degradation mechanisms apply. Li et al. synthesized a core–shell nanoparticle Fe_3O_4-NH_2@MIL101-NH_2 for pH-responsive DOX delivery [138]. They proved that the composite released DOX at a significantly higher rate in the simulated tumor cell microenvironment (pH 6.5) and the weakly acidic environment (pH 4.0) than in the simulated humoral environment (pH 7.4). This was attributed to the protonation of BDC-NH_2, leading to the decomposition of MIL101-NH_2. Meanwhile, they proved that this delivery system had low cytotoxicity and high biocompatibility by cellular experiments, which means it might be suitable for clinical application.

Many other acid-sensitive materials such as chitosan (CS), gelatin polymers, and carboxymethyl cellulose, also show structural changes in acidic environments, endowing drug delivery systems with pH-responsive characteristics. For example, CS contains active amino groups, which undergo protonation at low pH, forming abundant hydrogen bonds and leading to drug release. Based on this principle, Cao et al. prepared CS-coated biocompatible ZIF-90 for MTX delivery, successfully inhibiting the proliferation of liver, prostate, and gastric cancer cells [139].

Cleavage of the coordination bonds between drug and MOFs

For drugs loaded by forming covalent bond connections with MOFs, pH responsive release depends on the cleavage of the covalent bond in an acidic environment. As mentioned before, some groups in drugs can form covalent bonds with MOFs, but under acidic conditions, many of these bonds break, leading to drug release. For example, Cabrera-Garcia et al. developed novel drug delivery systems based on amine-functionalized MIL-100(Fe) and MIL-101(Fe) nano-MOFs containing covalently bonded CPT [115]. The drugs

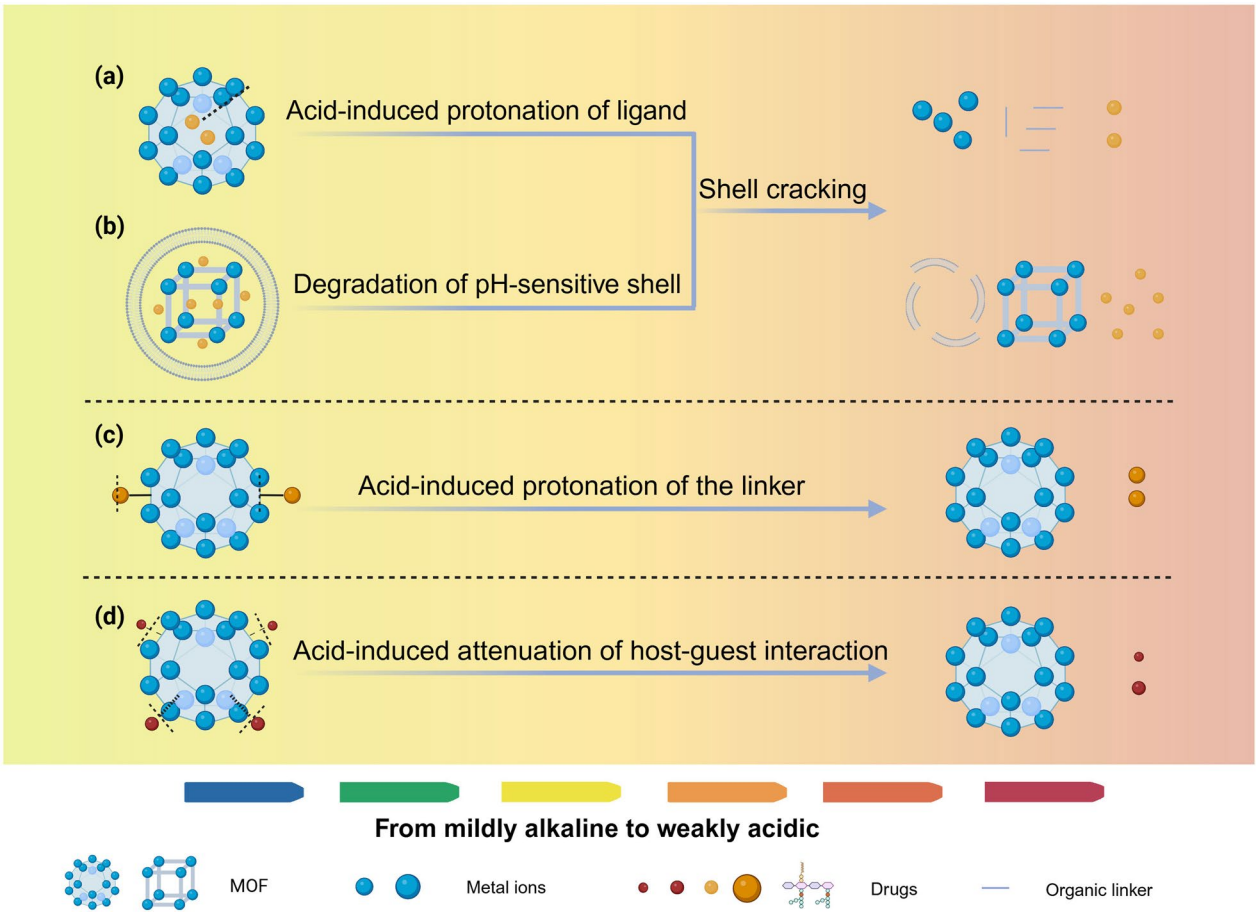


Fig. 8 Main mechanisms of pH-responsive anticancer drug release for SRDDSs. Shell cracking caused by acid-induced protonation of ligands (**a**) and the degradation of pH-sensitive materials (**b**). **c** Acid-induced protonation of the linker. **d** Acid-induced attenuation of host–guest interaction

were first esterified with linked chains, and these CPT prodrugs subsequently formed linkages with the MOFs through amide bonding or click chemistry. Drug loading significantly increased by introducing CPT into the MOF through covalent bonding. Moreover, this delivery system showed little or no drug autorelease at physiological pH, whereas it had a pronounced acid-stimulated drug release effect due to the instability of the covalent bonds in acidic environments.

What's more, Gupta et al. prepared a DOX-loaded UiO-66 coated with polyethylene glycol (PEG), where DOX formed covalent bonds with UiO-66 [116]. The FTIR spectra of DTX@UiO-66 showed a peak shift at 1706.8 cm^{-1}, indicating amide bond formation due to the conjugation of DTX with the carrier. In this DOX-bonded delivery system, low pH induced the leakage of the coordination bonds, resulting in the pH-responsive release of DOX. And they further validated the apoptosis-inducing potential of the synthesized drug delivery system in cellular studies.

pH-induced attenuation of host–guest interaction

For drugs loaded in SRDDSs with the contribution of host–guest interaction, they can also get released because of the attenuation of host–guest interaction under acidic conditions. For example, Dong et al. successfully loaded 5-Fu using MOFs-808 and NH_2-UiO-66 as the main carriers, supplemented with functional folate modification, to achieve the acid-responsive release of anticancer drugs [140]. Further experiments demonstrated that the carriers maintained their structural integrity at low pH, suggesting that the acid-responsive drug release was not due to the collapse of the MOF structure. Instead, it was attributed to the enhanced positive charge of the carriers and the weakened electrostatic interaction with the positively charged 5-Fu under low pH conditions.

Taking all of the above into account, the following mechanisms can be summarized: (1) Structural changes in MOFs themselves under acidic conditions; (2) Degradation of acid-sensitive materials; (3) Cleavage of coordination bonds linking MOFs and drugs, or attenuation

of host–guest interactions. These mechanisms can be applied individually or synergistically, enabling drug delivery systems to achieve enhanced pH responsiveness and more precise targeted release. However, despite the numerous mechanisms that can enable pH-triggered drug delivery platforms, and the inherent acidic nature of TME that offers significant potential for such mechanisms, the application of pH-responsive MOFs for smart anticancer drug delivery remains confined to the preclinical stage. Future clinical applications of MOF-based SRDDSs in cancer therapy could begin with the exploration of acid-triggered responses.

Redox-responsive MOFs

During heightened metabolic processes, tumor cells generate a large amount of ROS while also containing high concentrations of GSH to counteract them, thus creating an active and complex redox environment. Based on these characteristics, stimulus-responsive drug delivery systems primarily operate on the following principles: direct reaction with high concentrations of GSH, glucose-related redox reactions, and enzymatic reactions (Fig. 9).

GSH/H_2O_2 responsive

Specifically, in MOF-based SRDDSs, there are mainly two components capable of reacting with GSH: one is disulfide bonds, the other is GSH-sensitive materials.

Cleavage of disulfide bond Disulfide bonds can be formed between organic compounds and metal ions or between carriers and drugs, and can also be introduced into the coating layer. For example, Lei et al. developed a redox-responsive MOFs carrier, MOF-M(DTBA), for delivering the anticancer drug curcumin. They used 4,4′-dithiobisbenzoic acid (4,4′-DTBA) as an organic ligand, which was able to form a disulfide bond by connecting it to iron, aluminum or zirconium metal nodes. The disulfide bond in this carrier could be cleaved by GSH reduction, causing accelerated release of curcumin loaded in it. And experiments showed that the anticancer effect of CCM@MOF-Zr(DTBA) was much higher

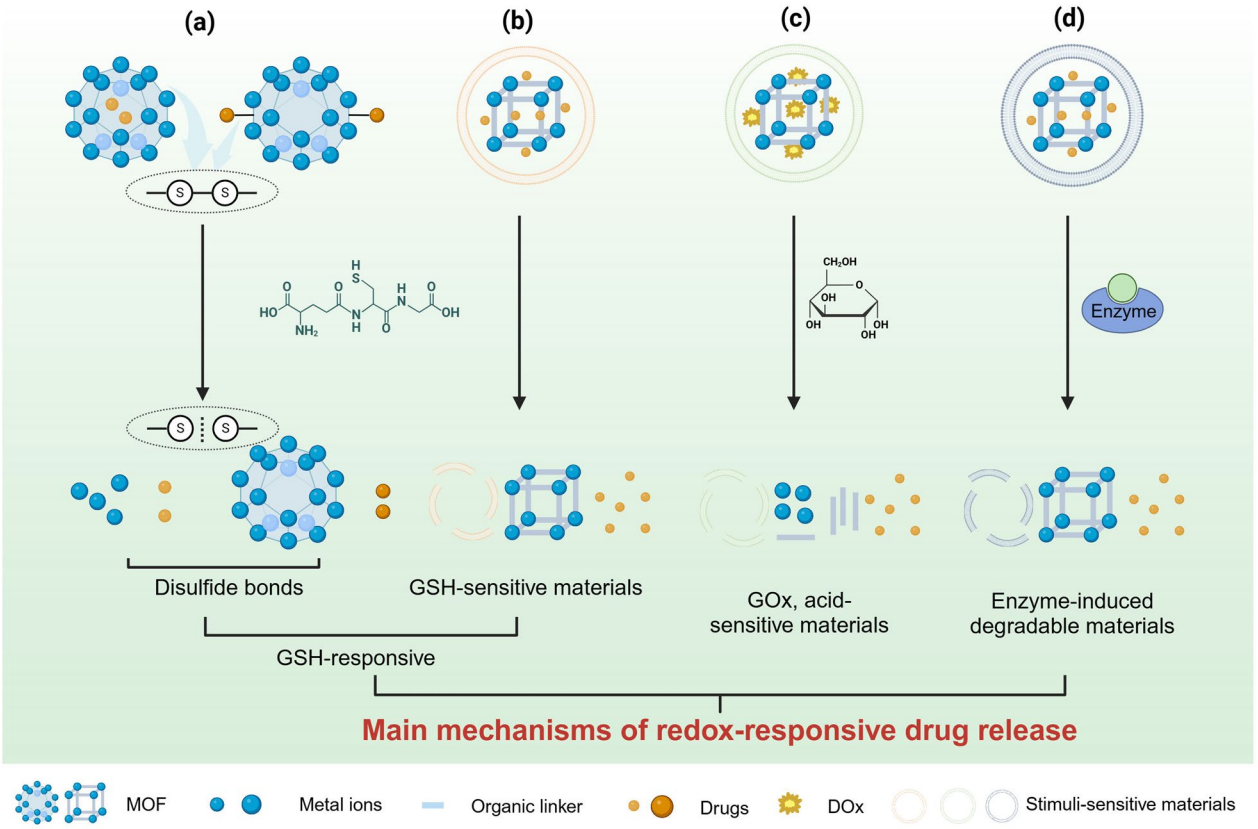


Fig. 9 Main mechanisms of redox-responsive anticancer drug release for SRDDSs. **a** and **b**GSH-responsive SRDDSs built by disulfide bonds and GSH-sensitive materials. **c**Glucose responsive SRDDSs. **d** Enzyme-responsive SRDDSs

than that of free CCM [106]. Similarly, Liu et al. synthesized an in situ polymerized MOF nanoparticle where disulfide bonds were used for surface modification of UiO-66 and connected to the prodrug CPT, making the delivery system GSH-responsive [141]. High GSH concentrations in tumor cells broke the disulfide bond, triggering CPT release and producing a tumor cell killing effect.

GSH-responsive materials Some materials contain no disulfide bond but can react with GSH directly through redox-active metal ions contained therein, such as Mn, Fe, Cu, or materials like MnO_2. Such materials can be designed as a shell for drug coating. Their metal ions or compounds can oxidize GSH, inducing degradation of the shell. Furthermore, they can consume excess GSH, altering the redox environment, thereby enhancing the efficacy of PDT and achieving a synergistic effect with various treatment modalities. For example, Wan et al. successfully achieved synergistic treatment combining chemotherapy, oxygen therapy, and PDT by synthesizing a Fe-TCPP NMOF coated with a $CaCO_3$ mineralized layer, where GSH reduced Fe^{3+} ions to trigger the release of active components [142]. What's more, Min et al. prepared a photosensitive porphyrinic Zr-MOFs coated with MnO_2, loaded with Apatinib [37]. Its shell reacted with GSH in the TME, decomposing and releasing the loaded Apatinib to exert its anti-angiogenic effect. Additionally, GSH was oxidized by manganese dioxide, significantly enhancing the cytotoxicity of PDT against tumors. This mechanism can be categorized as degradation of GSH-sensitive shells.

Similarly, a significant amount of H_2O_2 is present in the TME, serving as a trigger for redox-responsive drug release. For example, Huang and co-workers synthesized an oral drug loaded with an antioxidant prodrug based on CD-MOF, and the system had excellent H_2O_2 responsiveness and the release of therapeutic p-hydroxybenzyl alcohol correlated with H_2O_2 concentration [143]. Cellular experiments demonstrated that the system is biocompatible and in vivo tests showed its efficacy for treating Crohn's disease. In addition, H_2O_2-responsive MOFs can activate Fenton/Fenton-like reactions, enabling CDT. For example, Yang et al. achieved enhanced chemical dynamic therapy by combining chloroquine with nanoscale MOF, NH_2-MIL-88B (Fe), which possesses intrinsic peroxidase-like activity [144]. Redox-responsive SRDDSs not only enhance chemotherapy efficacy by releasing drugs but also directly or indirectly facilitate the efficacy of CDT or PDT, achieving synergy among multiple treatment modalities.

Glucose-responsive

Since the primary energy source for tumor cells is glucose, glucose-related redox reactions are also important targets. Zhang et al. encapsulated glucose oxidase (GOx) in MIL-100 and coated the nanoparticles with polydopamine-modified hyaluronic acid (HA) to achieve self-enhanced chemodynamic/starvation therapy [145]. The accelerated release of GOx under acidic conditions and its reaction with glucose to produce acid and H_2O_2, combined with the Fenton-like reaction of MIL-100 with H_2O_2, further enhanced the tumor killing effect. You et al. synthesized a dual enzyme-functionalized core–shell nanomotor based on ZIF-8 for PDT and starvation therapy of tumors [146]. The system was loaded with GOx for glucose-responsive self-accelerating cascade reactions. The results of MTT (Methylthiazolyldiphenyl-tetrazolium bromide) experiments showed that the system synergistically promoted enzyme-driven nanomotor activity, near-infrared light-triggered PDT, and GOx-induced starvation therapy under the bridge of enzyme-triggered biocatalytic reactions, achieving a strong tumor-suppressing effect.

Enzyme-responsive

TME contains a variety of enzymes, some of which such as proteases, phospholipases, hyaluronidase (HAdase) and glycosidases are expressed at higher levels than in normal tissues [147]. Enzymatic reactions are usually also redox reactions. Based on this, some drug-carrying systems can achieve redox-responsive release of drugs through enzymatic reactions. For example, Choe et al. utilized HA-encapsulated PCN-224 loaded with the anticancer drug DOX to achieve combined chemotherapy and PDT [148]. In this system, HA, which formed a ligand-bonded connection with MOF, enabled selective aggregation of drug carriers in CD44 overexpressing cancer cells and improves the accuracy of PDT while enabling responsive release of DOX in cancer cells. Experiments showed that HA effectively blocked the pore entrance of PCN-224. And after degradation by HAdase, DOX was released with the opening of the pore. Yang et al. designed a ZIF-8-based protease inhibitor delivery system in response to matrix metalloprotein enzyme [149]. In particular, the delivery system had bone-targeting and CD44-targeting features due to the modification of D8 and HA. And the protein inhibitor bortezomib encapsulated therein had clinically proven anticancer effects, which enabled the delivery system to achieve bone-targeted, enzyme-responsive anticancer therapy (Fig. 10). Cell proliferation assay showed that the drug complex had a better killing effect on tumor cells at the site of bone metastasis.

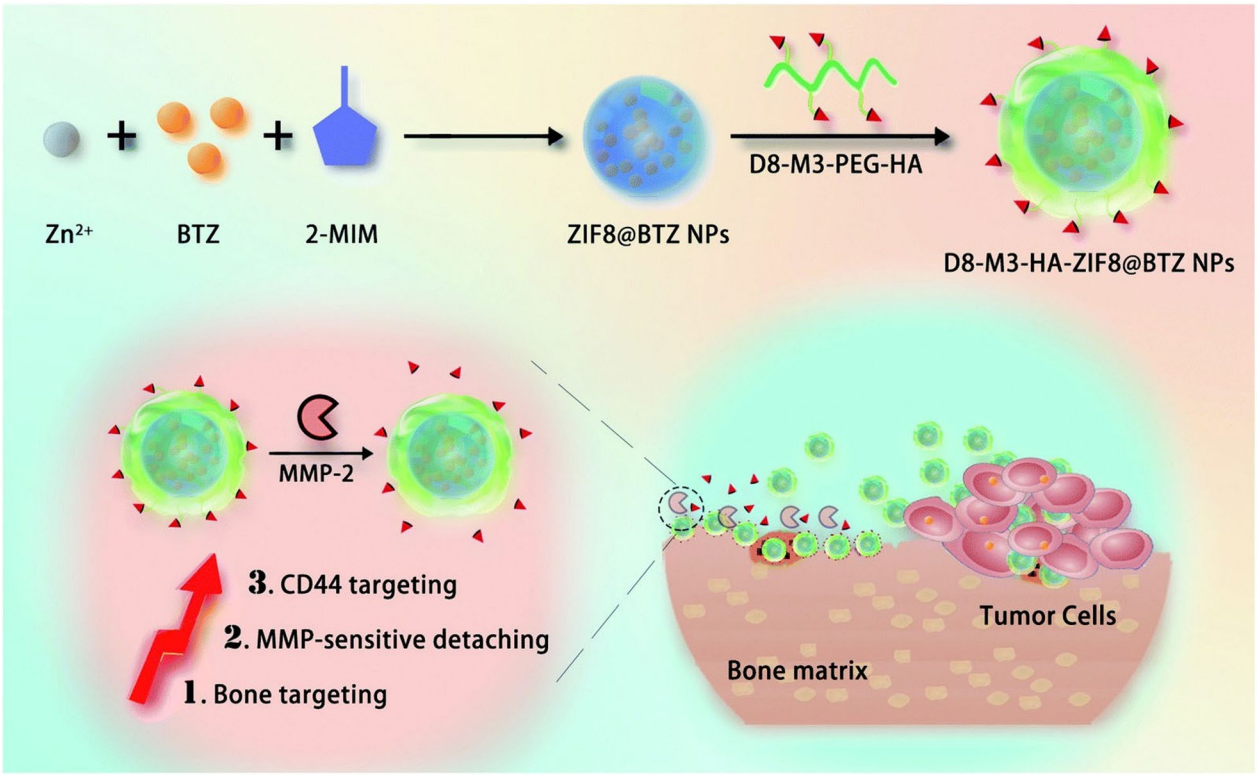


Fig. 10 Schematic representation of the synthesis of D8-M3-HA-ZIF8@BTZ and cascade targeting of tumor cells in bone metastases. Reproduced with permission [149]

ATP-responsive MOFs

ATP is a high-energy compound and serves as the "energy currency" in cellular activities, indispensable for the functioning of living cells. The active proliferation of cancer cells also heavily relies on ATP. Although research indicated that ATP synthesis in primary solid tumors may not be as active as commonly believed, and its production may even be lower than that of normal tissues [150], ATP remains the most important direct energy source for the proliferative activity of tumor cells, and the ATP content in the TME is significantly higher than that in normal tissues [151–153]. ATP in the TME still plays a crucial role in cancer cell proliferation [154]. Therefore, ATP depletion can inhibit the proliferation of cancer cells, making ATP depletion and ATP-targeted drug release have important applications in anticancer therapy [76, 155, 156].

The drug release responsive to ATP mainly occurs through two mechanisms: the formation of ATP-metal ion complexes and the formation of ATP-aptamer complexes. Due to the presence of lone pair electrons in the imidazole ring and amino nitrogen element of ATP, it can undergo coordination reactions with metal ions in solution. Since MOFs contain metal ion nodes, the competitive coordination between ATP and the metal ions in MOFs can lead to the breakdown of the MOFs framework, resulting in the formation of ATP-metal ion complexes. Based on this, Yang et al. utilized imidazole-2-carboxaldehyde and Zn^{2+} to self-assemble with proteins to form ZIF-90/protein nanoparticles. In the presence of ATP, the ZIF-90/protein nanoparticles degraded and released the proteins due to the competitive coordination between ATP and Zn^{2+} in ZIF-90. The encapsulated proteins include RNA hydrolase and the gene editing protein Cas9, where the cytotoxic RNase A effectively inhibited the growth of tumor cells, while Cas9 disrupted the expression of green fluorescent protein in HeLa cells. Therefore, this ATP-responsive protein delivery system was poised to advance protein delivery and CRISPR/Cas9 genome editing for targeted therapeutic interventions in diseases [76].

Another type of ATP-responsive mechanism is based on the formation of ATP-aptamer complexes, which can unlock nucleic-acid-derived gates. Based on this principle, the use of ATP-sensitive DNA-functionalized MOFs represents an effective approach for ATP-aptamer complex formation. When ATP-sensitive DNA-modified MOF systems come into contact with ATP-enriched culture medium, ATP interacts with the ATP-sensitive DNA, leading to the unlocking of the MOFs and the

release of therapeutic agents. For example, Chen et al. synthesized nanoparticles composed of nucleic acid-binding chain-modified metal–organic frameworks (NMOFs) and loaded them with the anticancer drug DOX. In the presence of ATP, the NMOF was unlocked by forming an ATP-aptamer complex, thereby releasing DOX, providing a platform for targeted delivery of chemotherapy drugs [157].

In summary, ATP-responsive MOFs present innovative strategies for cancer treatment by exploiting the unique properties of ATP in the TME. These systems can selectively release therapeutic agents in response to high ATP levels in cancer cells, thereby enhancing the specificity and efficacy of anticancer therapies.

H_2S-responsive MOFs

Hydrogen sulfide (H_2S) is an endogenous gas signaling molecule that plays a key role in many physiological processes, including inflammation, angiogenesis, nutrient supply, and blood flow regulation [158–160]. Existing studies have shown that in certain tumor tissues such as colon cancer, lung cancer,ovarian cancer and melenoma, there is higher levels of H_2S than normal tissue [161, 162]. This increased H_2S contributes to tumor angiogenesis as well as cancer cell invasion, migration, and proliferation [163]. Therefore, H_2S has become an important target for stimulus-responsive delivery of anticancer drugs. H_2S can competitively bind to metal ions in MOFs to form insoluble metal sulfides, leading to the disruption of the corresponding MOFs structure and the release of the loaded drugs. MOFs such as Cu-based MOFs can respond to the high concentration of H_2S in TME, enabling stimulus-responsive drug delivery. For example, Ma et al. employed zinc-metalated 4-methoxycarbonylphenyl porphyrin (ZnTcpp) as a photosensitive bridging ligand to construct a novel single-component MOF photosensitizer (PS). By introducing copper ions as metal nodes, they successfully constructed an H_2S-responsive Cu–Zn-MOF-based PS delivery system. Compared with other MOFs nanoparticle PS reported to date, this system provided the maximum PS loading. Upon reaching tumor tissues rich in H_2S, the copper ions in the system bind to H_2S, triggering the photosensitive effect, thereby providing a platform for achieving efficient and targeted cancer PDT [164].

Ion-responsive MOFs

In recent years, ion-responsive MOFs have been successfully developed. These MOFs facilitate drug release through ion exchange mechanisms. Ion-dependent switches for stimulus-responsive MOFs have attracted great attention, and many ions have been applied as stimulus signals for drug release, such as Mg^{2+}, K^{+}, Zn^{2+}, Ca^{2+}, $PO4^{3-}$, $HPO4^{2-}$, and H_2PO^{4-} [165]. The mechanisms of action for ion-responsive MOFs typically involve three main types. First, competitive binding. In this mechanism, ions with high binding affinity are utilized as stimuli for opening drug delivery system. They compete with materials of lower binding affinity, altering the MOFs' structure to release drugs. For instance, Tan et al. achieved Zn^{2+}-stimulated 5-Fu release by installing positively charged Q stalks on the surface of UiO-66-NH_2 via post-synthetic modification, loading drugs, and introducing negatively charged CP5 macrocycles to form gates of the nanocarriers through host–guest complexation. This drug delivery system exhibited extremely low premature release, gradually releasing drugs only with increasing Zn^{2+} concentration [166]. The second mechanism is anion exchange, where MOFs undergo structural changes due to the competitive coordination of metal ions by stronger anions, leading to the release of loaded drugs. Common anions with higher coordination ability, such as PO_4^{3-}, can competitively bind to the metal ions in MOFs. Some drugs, such as cisplatin [167] and ibuprofen [168], can achieve ion-responsive drug release through this mechanism [77]. For example, Lin et al. achieved burst release of cisplatin prodrug from modified UiO-66 in PBS solution, demonstrating potential for targeted drug release responsive to phosphate ions [167]. Another important mechanism involves the formation of nucleic acid/metal ion complexes, where the basic principle is that the lock formed by nucleic acid and substrate dependent on specific ions is opened in the presence of the corresponding ions, thereby triggering drug release. Tan et al. prepared an ion-responsive MOF-based DOX delivery system by loading DOX into MOFs and encapsulating it with metal ion-dependent DNAzyme/substrate complexes as locking units (metal ion = Mg^{2+} or Pb^{2+} ions). In the presence of Mg^{2+} or Pb^{2+} ions, the nucleic acid locking units cleaved off, resulting in DOX release. After that, they designed an ATP/Mg^{2+}-triggered DOX delivery system based on this, and its selective cytotoxicity against MDA-MB-231 cancer cells was further validated [169].

These stimuli mentioned above can be considered endogenous stimuli, playing an important role in stimulus-responsive drug delivery systems for anticancer therapy. In addition, MOFs responsive to exogenous stimuli are also increasingly applied in the design of SRDDSs. Figure 11 illustrates the main endogenous and exogenous stimuli involved in SRDDSs for anticancer therapy.

Light-responsive MOFs

In the past few decades, photosensitive nanoparticles have emerged as promising therapies for cancer, ranging from photodynamic therapy (PDT) techniques that

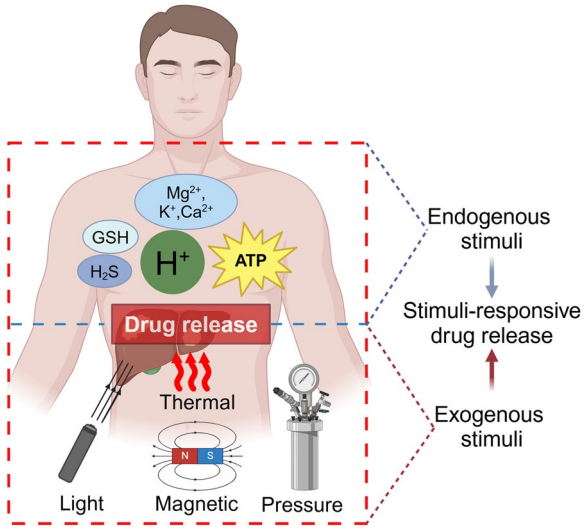


Fig. 11 Main exogenous and endogenous stimuli utilized by MOF-based anticancer drug delivery systems

are already in clinical use to anticancer drug delivery systems that are still in preclinical stages. Among these, light-responsive delivery systems are particularly notable for their ability to carry anticancer drugs and provide precise spatiotemporal control over drug release [170]. Many light-responsive drug delivery systems are loaded with both conventional anticancer drugs and photosensitizers to simultaneously kill cancer cells with chemotherapy and PDT, or PTT [171, 172]. Moreover, this combination can enhance therapeutic effects and shows promise for overcoming multidrug resistance in cancer treatment [38, 173]. In cancer therapy, the mechanism of light-responsive MOFs typically involves controlling the stimulus response through photothermal changes, conformational changes, and chemical bond cleavage under light exposure. Light-sensitive MOFs can be constructed by incorporating photoactive molecules or ROS, such as azobenzene dicarboxylate, TCPP, and indocyanine green (ICG), into their structure to facilitate chemotherapy, PDT, PTT, and fluorescence imaging [174–176]. For example, Zhu et al. prepared a DOX-loaded PPy@MIL-100 (Fe) system. Their findings indicated that the local temperature increase caused by the photothermal effect of PPy under near-infrared laser irradiation directly heated tumor cells while promoting thermal motion in the carrier lattice and increasing temperature-dependent molecular mobility, which triggered drug desorption and release. This enabled a synergistic effect between PTT and chemotherapy [177]. Similarly, Xu et al. constructed a ZnPc@ZIF-8 delivery system. In this delivery system, ZIF-8 was used as a carrier, and the loaded drug photosensitizer, zinc phthalocyanine was used to generate cytotoxic singlet oxygen under light irradiation to achieve tumor killing through PDT [178].

The selection of an appropriate light stimulus type is critical and requires careful consideration. Currently, ultraviolet (UV) light, visible light, and near-infrared (NIR) light are the main options. Most photochemical reactions rely on UV light as the trigger; however, UV light can cause more damage to biological tissues and has limited penetration, which significantly hinders the development of stimulus-responsive delivery systems based on UV light. In contrast, systems driven by NIR light have been rarely reported. However, due to its minimal effect on normal tissues and its ability to penetrate deeper into the body, NIR light offers greater potential for applications. Future research may focus on NIR-driven MOF-based delivery systems. Given the convenience of light-based stimuli in drug delivery systems and their great potential for multi-modal therapy, continuous research in this field is needed, and further clinical trials are highly anticipated.

Temperature-responsive MOFs

Temperature-responsive nanocarriers are materials that are sensitive to changes in temperature. MOFs serving as carriers for anticancer drugs, they are required to remain stable with loaded drugs under physiological temperature conditions and undergo structural changes to release drugs when the temperature changes. Since temperature elevation can serve as a stimulus, and PTT can achieve localized heating of tumors, temperature-responsive drug delivery systems based on MOFs are considered promising for combination with PTT. For example, Lin et al. synthesized two low-toxicity zinc-based porous MOFs (ZJU-64 and ZJU-64-CH_3) using zinc ions, carboxylate-based ligands, and adenine as raw materials. They achieved drug loading of the anticancer drug DOX through a simple impregnation process. In their study, ZJU-64 and ZJU-64-CH_3 exhibited low cytotoxicity, and drug release was significantly accelerated at 60 °C compared to physiological temperature (37 °C). Specifically, the release amounts of methotrexate loaded in ZJU-64 and ZJU-64-CH_3 at 37 °C for 72 h were approximately 1.5 h and 6 h, respectively, at 60 °C. This indicates that this SRDDS exhibits temperature responsiveness. Combining the low cytotoxicity and ideal drug-loading capacity of ZJU-64 and ZJU-64-CH_3, this drug delivery system has the potential for further practical application and provides a new approach for combining hyperthermia with chemotherapy to achieve better therapeutic efficacy [110].

However, the temperature increase required to trigger the response of such thermoresponsive MOFs is substantial, and the human body is often unable to withstand

such high temperatures. This significantly reduces their clinical applicability. Introducing temperature-sensitive materials and appropriately modifying the surface of MOFs can enhance the temperature responsiveness of MOF-based SRDDSs. One commonly used material for surface modification of smart materials is poly(N-isopropylacrylamide) (PNIPAM), a thermoresponsive polymer with a lower critical solution temperature (LCST) slightly below normal body temperature, allowing for potential "on–off" functionality in the human body [179]. For example, Nagata et al. integrated PNIPAM onto UiO-66 via a surface-selective post-synthetic modification technique, achieving controlled drug release in vitro [180]. At lower temperatures (25 °C), rapid release of guest molecules was observed, while minimal drug leakage occurred at higher temperatures (40 °C). This study provides valuable insights for further development of temperature-responsive MOF-based SRDDSs, and future incorporation of additional temperature-sensitive materials holds promise.

Pressure-responsive MOFs

In addition to the aforementioned stimuli, pressure can also serve as a stimulus for MOF-based SRDDSs. This change is typically induced by externally applied pressure. Currently, the basic mechanism of pressure-induced drug release in MOF drug delivery systems can be attributed to simple compression deformation of MOFs caused by external pressure, usually without involving changes in MOFs' topology and chemical properties. Jiang et al. achieved modulation of the drug release rate by controllable physical compaction to alter local pressure [181]. In their study, ZJU-800 was synthesized using a solvothermal approach, and a novel ligand, (2E,2'E)-3,3'-(2-fluoro-1,4-phenylene) diacrylic acid (F-H_2PDA), was introduced into the MOF to achieve a high drug-loading capacity. The results showed that the newly synthesized MOFs exhibited a satisfying loading capacity, negligible cytotoxicity, and most notably, pressure responsiveness. As pressure increased, the release rate of the loaded diclofenac sodium decreased. The emergence of this novel drug delivery system provides a valuable reference for further designing and preparing pressure-responsive drug delivery systems that meet practical needs. However, the application of pressure-responsive MOFs in drug delivery is still limited, and their use in stimuli-responsive delivery for anticancer drugs remains to be further developed.

Magnetically-responsive MOFs

Changes in magnetic fields are also important signals of exogenous physical stimuli. Magnetic-responsive nanoparticles have shown increasing potential in tumor therapy, mainly in tumor magnetic resonance imaging (MRI), magnetic-triggered hyperthermia and targeted drug release [182–184]. By introducing magnetic materials such as Fe_3O_4 into MOFs or directly using highly magnetic MOFs such as Fe-MIL-53-NH_2, the drug delivery system becomes magnetically responsive [185]. Meanwhile, various modifications are employed to enhance its drug-loading and imaging capabilities. To enhance targeted drug delivery to tumors, folic acid is often introduced, as folate receptors (FR) are usually overexpressed on the surface of some cancer cells, allowing selective absorption by FR-positive cancer cells and avoids absorption by normal tissues that do not express FR [131, 186]. For tumor imaging, highly magnetic MOFs can be used directly as MRI contrast agents, or fluorescent imaging agents can be introduced to achieve tumor fluorescence imaging [131, 186]. For example, Ebrahimi et al. synthesised $CoFe_2O_4$NPs@Mn-Organic Framework core–shell nanocomposites using a layer-by-layer method, where the anticancer agent DOX was loaded. And in vitro experiment showed that an external magnetic field significantly increased anticancer activity of th formulation (drug + MOFs), which confirmed its magnetic responsiveness.

Moreover, magnetic-responsive MOFs also demonstrate promising prospects in magnetic hyperthermia therapy and combined chemotherapy. For example, Xiang et al. developed a novel porous Fe_3O_4@C derived from MOFs for loading the anticancer drug DOX. This system achieved synergistic cancer therapy of MRI-guided magnetic-triggered hyperthermia and chemotherapy [184]. This system exhibited good biocompatibility, efficient MRI, on-demand DOX release triggered by a magnetic field, and synergistic therapeutic effects of magnetic hyperthermia and chemotherapy. Experimental results showed that DOX release triggered by an alternating magnetic field (AMF) was faster compared to conditions without AMF triggering. In vitro experiments demonstrated that AMF-triggered heating promoted the sustained release of DOX, resulting in its accumulation around CAL27 cancer cells, indicating the magnetic responsiveness of drug release. Further animal experiments showed that continuous magnetic hyperthermia combined with chemotherapy significantly inhibited malignant tumor growth with minimal side effects. Thus, this drug delivery system achieved efficient combined therapy of magnetic-triggered hyperthermia and chemotherapy, providing a preliminary experimental basis for the clinical application of magnetic-responsive MOF-based SRDDSs in precision cancer treatment.

In brief, various endogenous and exogenous stimuli can be the target of MOF-based SRDDSs. Common stimuli-responsive MOFs for anticancer drug delivery are summarized in Table 2.

Table 2 Common stimuli-responsive MOFs for anticancer drug delivery

Stimulus	Drug delivery system	Sensitive materials	Main mechanism	Drug	Drug loading	Target cell	Ref
pH	5-Fu@ZIF-8	ZIF-8	Protonation-induced breakage of the coordination bonds	5-Fu	45.4 wt%	-	[187]
	CCM@NZIF-8	ZIF-8	Protonation-induced breakage of the coordination bonds	Curcumin	12.7wt%	HeLa cell line; U14 cervical cancer model	[188]
	PEG-FA/(DOX + VER)@ZIF-8	ZIF-8	Protonation-induced breakage of the coordination bonds	DOX, verapamil	8.9%, 32%	B16F10 and MCF-7/A cells	[189]
	CCM@ZIF-8/HA	ZIF-8, HA	Protonation-induced breakage of the coordination bonds; pH-sensitive material	Curcumin	4.5%	HeLa cells	[190]
	CPT@ZIF-8@RGD	ZIF-8	Protonation-induced breakage of the coordination bonds	Camptothecin	15%	HeLa cells	[125]
	FA-PEG/CQ@ZIF-8	ZIF-8	Protonation-induced breakage of the coordination bonds	Chloroquine, diphosphate	18 wt%	HeLa cells	[191]
	3-MA@ZIF-8	ZIF-8	Protonation-induced breakage of the coordination bonds	3-Methylade-nine	19.798 wt %	HeLa cell	[192]
	UiO-66/Bi_2S_3@DOX	UiO-66/Bi_2S_3	Protonation-induced breakage of the coordination bonds	DOX	–	Hep G2, rat N1S1 liver tumor model	[193]
	Fe_3O_4@UiO-66-DOX	Electrostatic interactions between Fe_3O_4@UiO-66 and DOX	pH-induced attenuation of host–guest interaction	DOX	66.3wt%	HeLa cells	[194]
	PDA@CPT@MIL-53(Fe)	MIL-53(Fe)	Protonation-induced breakage of the coordination bonds	Camptothecin	43.07%	MCF-7 cell line	[195]
	MIL-53@CMC/GQDs	Hydrogen-bonding interaction between the polar groups of MIL-53@CMC/GQDs and DOX; π–π stacking interaction between the aromatic network of carrier and drug	pH-induced attenuation of host–guest interaction	DOX	–	MDA-MB 231	[196]
	5-Fluorouracil-GEM@MIL-100	MIL-100	Protonation-induced breakage of the coordination bonds	Fu, gemcitabine	78.5wt%, 74.5wt%	MCF-7 cells	[197]

Table 2 (continued)

Stimulus	Drug delivery system	Sensitive materials	Main mechanism	Drug	Drug loading	Target cell	Ref
	DHA-loaded Fe_3O_4@C@ MIL-100(Fe)	MIL-100	Protonation-induced breakage of the coordination bonds	Dihydroarte-misinin	80.5wt%	HeLa cells	[198]
redox	CCM@MOF-Zr(DTBA)	4,4′-DTBA	Cleavage of disulfide bond	CCM	78.7%	HeLa cells MDA-MB-231 cells	[106]
	Cisplatin-loaded ZrMOF-PAC	Poly(N,N′-bis(acryloyl) cystamine)	Cleavage of disulfide bond	CPT	25.1 μmol per gram of ZrMOF	A431 cells, U87MG human glioblastoma cells	[141]
	PCN-224@MnO_2	MnO_2	GSH-sensitive material	Apatinib	32.9%	4T1 cells	[37]
ATP	RhI-DOX@ZIF-90	ZIF-90	Formation of ATP-metal ion complexes	RhI and DOX	11 wt%	HCT116	[199]
	UiO-68/hydrogel	UiO-68	Formation of ATP-aptamer complexes	DOX	79.1 nmol mg − 1 for NMOFs/hydrogel hybrid	MCF-10A, MDA-MB-231 cells	[200]
Ion	UiO-66–350-PA-Pt	UiO-66	Anion exchange	Cisplatin	25.7 wt%	-	[167]
	NMOF-N_3	Mg^{2+}-ion-depende-nt DNAzyme	Formation of nucleic acid/ metal ion complexes	DOX	52.8 μmole DOX·gram-1 of NMOFs	MDA-MB-231	[169]
Light	PEGNH_2-UiO-AZB-F + 5FU	UiO-AZB-F	Photo-exfoliate upon isomerization of the incorporated ligand	DOX	20 wt%	HCT-116 cells	[201]
Tempera-ture	ZJU-64 ZJU-64-CH_3	–	Attenuation of host–guest interaction	MTX	13.45wt%, 10.63 wt%	PC12 cells	[110]
Pressure	ZJU-800	ZJU-800	–	Diclofenac sodium	58.8 wt%	PC12 cells	[181]
Magnetic	Fe_3O_4@C-PVP@DOX	Fe_3O_4	–	DOX	70%	CAL27 cells	[184]
Magneto-thermal	PNIPAM@IONPs@ UiO-66-NH2	IONPs, PNIPAM	Thermal induced conformational change of the PNIPAM	5-Fu	13.1 wt%	CT-26, 4 T-1	[202]

Multistimuli-responsive MOF-based drug delivery systems for multi-modality anticancer therapy

The TME is a complex environmental system in which numerous stimuli exist. Many of these stimuli can act independently or synergistically to influence the release of drugs from MOFs. Besides endogenous stimuli, exogenous factors such as light, temperature, magnetic fields, and pressure can also induce structural changes in MOFs within the TME context. Moreover, drugs released can achieve tumor therapy through different mechanisms. Consequently, multi-responsive MOFs are increasingly being applied in various anticancer treatments such as chemotherapy, radiotherapy, PDT, and PTT. However, despite the promising potential of numerous stimuli to trigger drug release, no stimulus-responsive MOF-based smart drug delivery systems have yet been used in human trials. This means that although research is progressing rapidly, the field is still in its early stages and significant efforts are required for clinical translation. Some key stimuli, through their combined effects, may hold the potential to advance stimulus-responsive drug delivery within the human body.

Low pH, as one of the fundamental characteristics of the TME, can not only induce structural changes in MOFs to release drugs by itself but also synergistically trigger the responsive drug release of MOFs in conjunction with various other stimuli. For example, many temperature-responsive MOFs are also pH-dependent. Lin et al. successfully loaded the anticancer drug MTX into the zinc-based MOFs Zn-TBDA by in situ embedding, demonstrating that the delivery system was pH- and temperature-responsive. In vitro experiments showed the release of MTX was significantly elevated at pH 6.5, 42 °C, and the 24-h release was about twice as much as that at pH 7.4 and 37 °C [203]. In addition, an H_2S/pH dual-responsive MOF was prepared by Zhao et al. [204], in which the carrier of the drug delivery system was Fe-ZIF-8, an iron-zinc bimetallic MOF-derived ferromagnetic nanomaterial. This MOF could be gradually decomposed in a mildly acidic environment, while the H_2S in the TME could strongly interact with the Zn and Fe therein, thus conferring the H_2S-responsive properties. Ultimately, the drug 5-Fu loaded on it could be released in the TME in a targeted manner. Another report suggested that Fe-ZIF-8 was a pH/liposome-responsive MOF, where drug release could be triggered in the presence of biocompatible liposomes and lower pH [205]. What's more, in redox-responsive SRDDSs, the majority of them could achieve accelerated drug release under acidic conditions [106, 107].

Pillararenes, a new class of synthetic supramolecular macrocycles, offer advantages such as rigid structure, electron holes, and easy functionalization, making them excellent candidates for responsive nanosystems. Many groups have prepared drug delivery systems based on MOFs with pillararenes nano-valves. Tan et al. prepared a smart cargo delivery system containing water-soluble derivatives of pillar [5] arenes (CP5), which demonstrated pH- and competitive binding agent-triggered drug release capabilities. [206]. They also designed a multi-stimulus-responsive "gated scaffold" and prepared a pH-, temperature-, and Ca^{2+}-responsive drug delivery system capable of loading 5-Fu by combining CP5 with UiO-66 [207]. Due to the relatively low pH and high Ca^{2+} concentration in bone tumors, this system was considered to have promising applications in bone tumor therapy.

In addition, there are many materials that can be used as gating systems to modify MOFs. For instance, β-cyclodextrin (β-CD) can be used as a gating molecule attached to MOFs. Zhang et al. achieved pH- and redox-responsive release of DOX by introducing β-CD into MIL-101, and in vivo and in vitro assays showed that the surface modification reduced the toxicity of the carried DOX to normal cells with satisfing anticancer effects [208].

Huang et al. designed a light/pH-responsive drug delivery system, Au@ZIF-8, enabling combined chemotherapy and PTT [209]. They first synthesized gold nanorods (AuNRs), then exchanged ligands with Zn^{2+} and 2-MIN with polyvinylpyrrolidone polymer to further promote coordination reactions in methanol, gradually growing ZIF-8 on the AuNRs (Fig. 12a). SEM (Fig. 12b), TEM (Fig. 12c and d), and EDX-elemental mapping (Fig. 12e) shows the surface morphology, internal structure, and elemental distribution of Au@ZIF-8. The core–shell configuration with AuNR as the core and ZIF-8 as the shell was clearly visible. Figure 12f shows the in vivo infrared thermal images of MCF-7 tumor-bearing mice after intravenous injection of Au@ZIF-8 or PBS buffer. This indicated the accumulation of the drug at the tumor site through this delivery system. Figure 12g and h respectively show the relative tumor volumes of mice in each group and the corresponding fluorescent images of live-dead staining cells for different groups. Compared to free drugs or carriers alone, the Au@ZIF-8/DOX delivery system achieved the best anticancer effect, especially under light irradiation.

Besides low pH-based multi-responsive systems, many other multistimuli-responsive delivery systems have been developed. For example, an ATP-Mg^{2+}-responsive MOF for loading DOX was prepared by Chen et al. [169]. Its responsiveness originated from the lock constituted by DNA scaffolds containing Mg^{2+}-dependent loops, which was unlocked only in the presence of ATP and Mg^{2+} ions, facilitating receptor-mediated endocytosis targeting and precise drug release (Fig. 13a). The lock formed

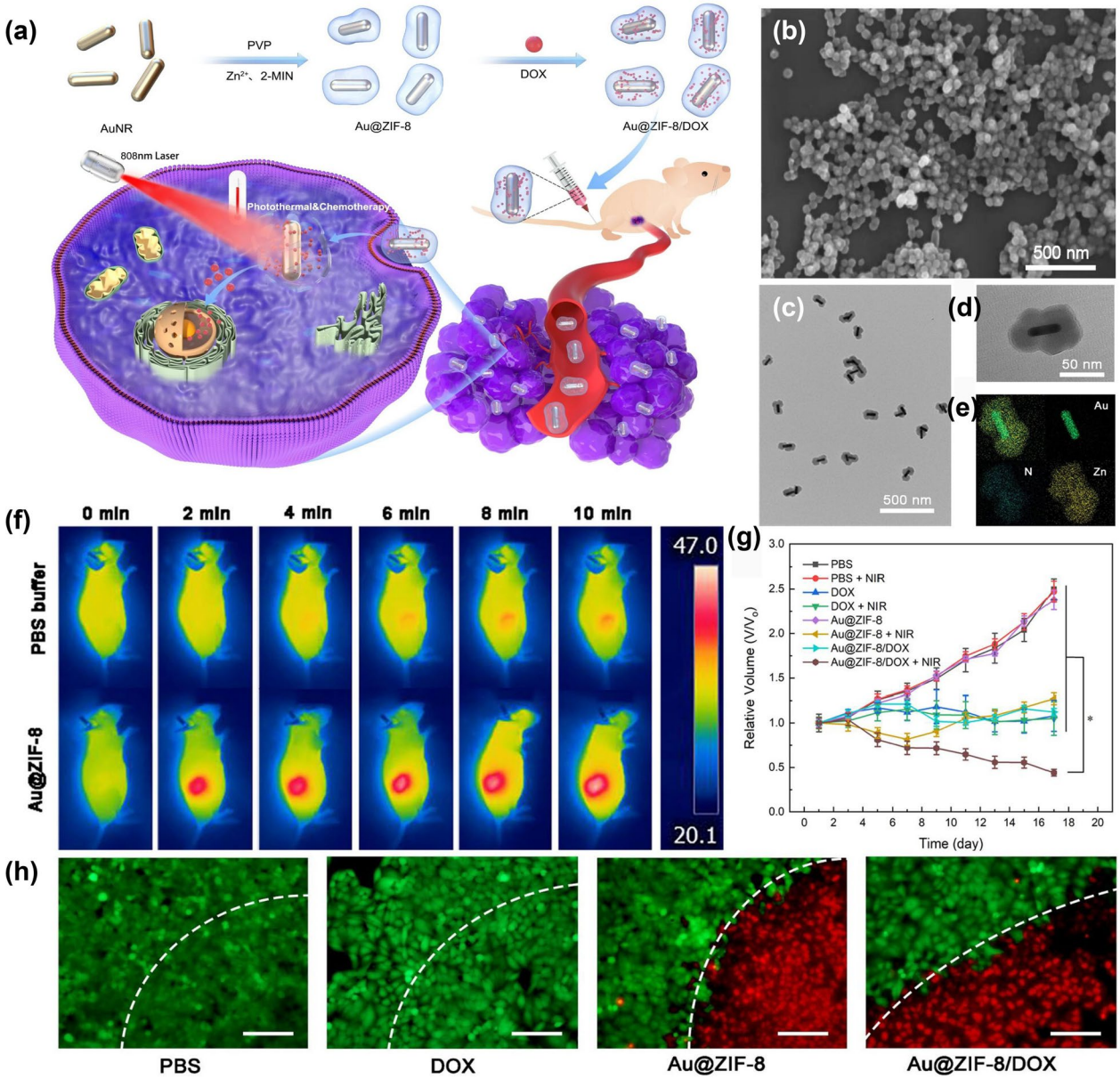


Fig. 12 Illustration of the synthesis and targeted anticancer process of Au@ZIF-8/DOX, along with the corresponding morphology, distribution, tumor targeting capability, and anticancer effects. **a** Schematic illustration of the synthetic procedure of Au@ZIF-8/DOX nanocomplexes for chemo-photothermal synergistic cancer therapy in vivo. **b** The morphology and distribution of Au@ZIF-8 indicated by SEM image. **c** and **d** Low and high magnified TEM image of Au@ZIF-8, **e** High magnified TEM image of Au@ZIF-8. **f** In vivo infrared thermal images of MCF-7 tumor-bearing mice after intravenous injection of Au@ZIF-8 or PBS buffer activated by 1 W/cm^2 808 nm laser for 10 min. **g** The relative tumor volumes of mice in each group. **h** The corresponding fluorescent images of live-dead staining cells for different groups. Scale bar: 100 μm. Reproduced with permission [209]

by the sequence-specific metal-dependent DNA enzyme sequences and the binding of the nucleic acid-modified chain attached to NMOF has also been applied to other drugs or dyes, showing good stimulus-responsive release (Fig. 13b and c). This encapsulation pattern holds promise for widespread application in multi-stimuli-responsive delivery of various drugs, thus achieving multiple anticancer effects.

Although multi-stimuli-responsive MOFs hold promise for achieving more precise anticancer drug delivery, their targeting specificity still falls short compared to ligand-receptor-based targeted delivery systems. Taking

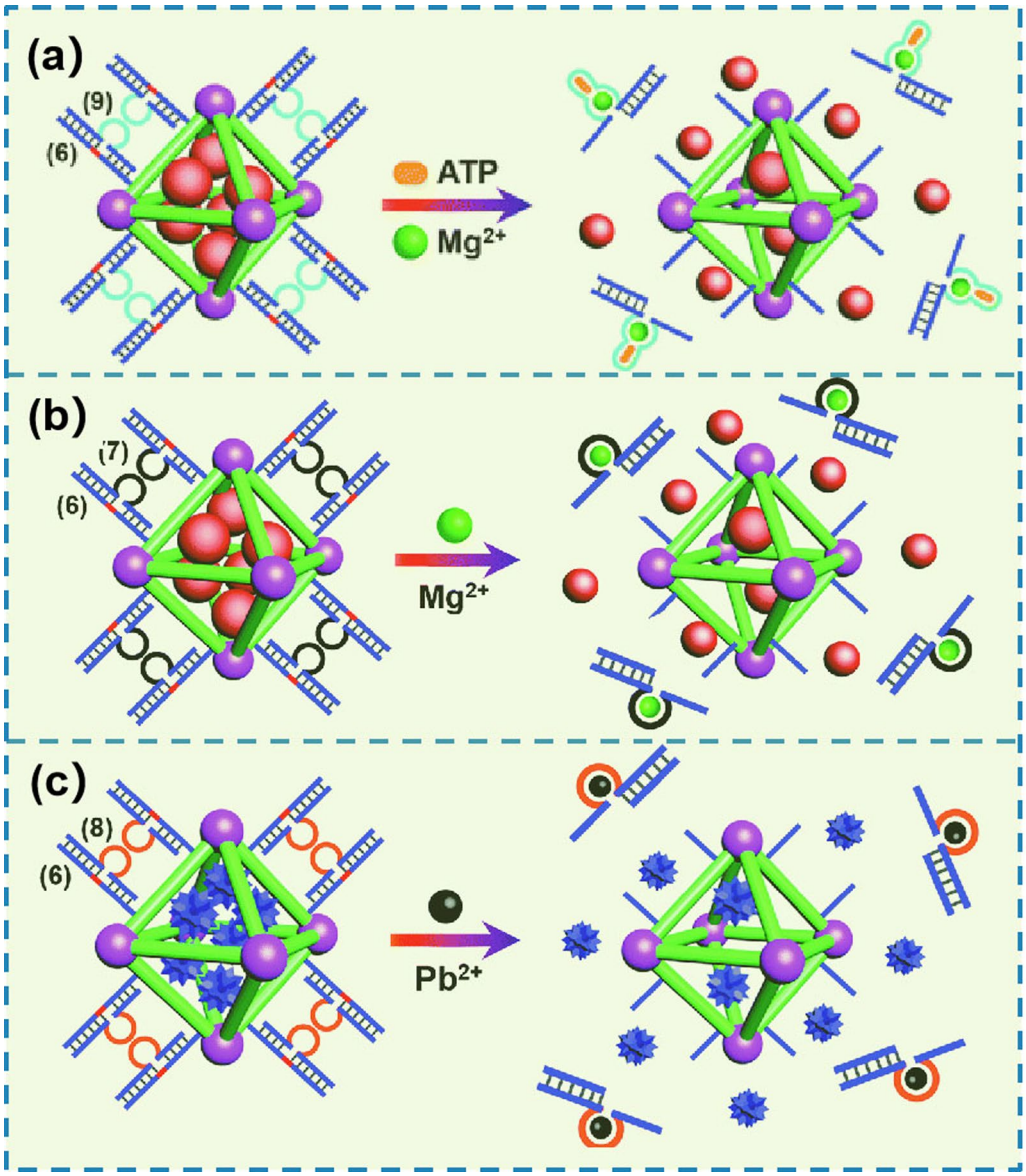


Fig. 13 Schematic loading and unloading of drugs carried by a series of NMOFs. **a** Loading of NMOFs with DOX and their capping with DNA scaffolds (6)/(9) where the strand (9) includes the Mg^{2+} ion-dependent loop with an integrated sequence of the ATP aptamer. Unlocking of the capping units via the cooperative cleavage of the lock, in the presence of ATP and Mg^{2+} ions. **b** Schematic loading and unloading of the Rhodamine 6G dye by capping the nanoparticles with the (6)/(7) duplexes that include the Mg^{2+}-ion-dependent loop, and the cleavage of the capping units by Mg^{2+} ions that activate the Mg^{2+}-dependent DNAzymes. **c** Schematic loading and unloading of the methylene blue dye by capping the nanoparticles with the (6)/(8) duplexes that include the Pb^{2+}-ion-dependent loop and the cleavage of the capping units by Pb^{2+} ions that activate the Pb^{2+}-dependent DNAzymes. (6), (7), (8), (9) represent four types of DNA scaffolds. Reproduced with permission [169]

the widely used FA-FA receptor targeting as an example, a variety of smart delivery systems have been developed that introduce FA to precisely target tumor cells expressing the FA receptor, enabling active targeting and accurate drug delivery through FA receptor mediation [210, 211].

In light of this, combining the advantages of MOFs, such as their high drug loading capacity and ease of surface modification, with targeting ligands (e.g., proteins, lipids, polysaccharides, or small biomolecules) conjugated to the surface of the MOF, could facilitate more precise accumulation of the drug delivery system in tumor tissues. Through localized stimulus-responsive release, this approach may ensure efficient and accurate drug delivery.

MOF based SRDDS in various modes of tumor therapy

MOF-based SRDDSs are playing an increasingly significant role in cancer therapy. These systems offer innovative perspectives for enhancing treatment efficacy by leveraging the unique properties of MOFs. Figure 14 summarizes the main methods for cancer therapy and the roles of MOFs in them. To date, a variety of MOF-based SRDDSs have been increasingly utilized in single or combined cancer treatment modalities, yielding promising therapeutic outcomes. Some of these are summarized in Table 3

Photodynamic therapy

PDT uses specific wavelengths of light to irradiate cancerous areas, triggering a photochemical reaction in photosensitizers (PS) delivered to the tissues. This reaction produces ROS, which induce the death of cancer cells, achieving an anticancer effect [231]. One of the key components, PS, can be transported by MOFs, enabling MOF-based SRDDSs to achieve tumor tissue-specific distribution and thereby mediating precise PDT. The key components PS can be transported by MOFs and lend MOF-based SRDDSs to achieve tumor tissue-specific distribution, thus mediating precise PDT.

For example, a GSH-responsive MOFs delivery system was constructed by Xia et al. for encapsulating nicorandil (Nic), which significantly enhanced the efficacy of PDT by reacting with GSH to generate nitric oxide (NO) production [232]. The drug Nic loaded in this system could react with a high concentration of GSH in the TME to release NO, a hypoxic photodynamic sensitizer. The NO promoted the formation of ROS, enhancing PDT efficacy and minimizing damage to healthy tissues. Guan et al. prepared a novel photosensitizer, 2I-BodipyPhNO_2@ZIF-90, by a one-pot method, using ZIF-90 as carrier for pH-sensitive PDT therapy. ZIF-90 was stable under neutral conditions, but under acidic conditions, 2I-BodipyPhNO_2 was released, resulting in the production of O_2 [233].

MOFs nanomaterials are used as intelligent carriers in the photodynamic therapy of cancers, mainly by acting as photosensitizer carriers, enhancing light absorption and energy conversion, and local targeted delivery, which can effectively achieve anti-cancer effects and reduce toxic side effects. MOFs nanomaterials can encapsulate photosensitizers through wrapping or chemical bonding, so as to effectively improve the stability of photosensitizers, avoid premature degradation or inactivation in vivo, and also change the physical and chemical properties of photosensitizers to achieve high enrichment of tumor sites [234]. In addition, some MOFs can be modified to have unique optical properties, which can effectively enhance the absorption of light and the efficiency of energy conversion, thereby promoting the production of more ROS by photosensitizers [235]. The surface of MOFs is linked to specific target molecules, such as antibodies, aptamers, or small molecule ligands, so that they can precisely recognize and bind to specific antigens or receptors on the surface of tumor cells, so as to specifically deliver photosensitizers to the tumor site. Although MOFs have many applications in photodynamic therapy, there are still few studies on their immunostimulatory effects in vivo and their interaction with the immune system. In addition, the actual effect of MOFs materials in enhancing drug delivery in vivo is still unclear, and their targeting still needs to be further studied and verified.

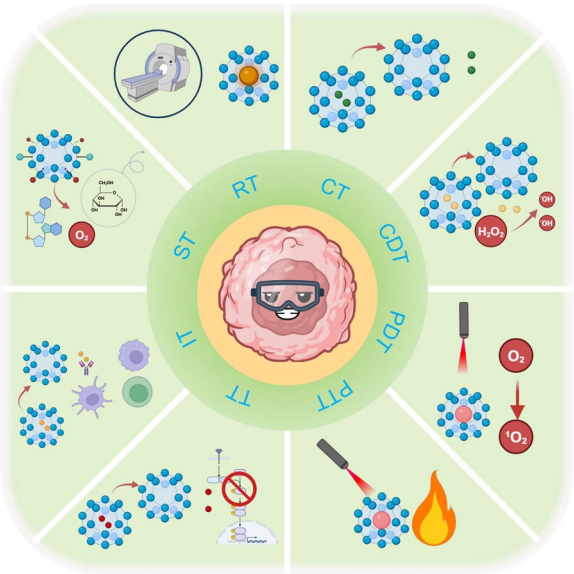


Fig. 14 Main methods for cancer therapy and the roles of MOFs in them. MOFs can load chemotherapy drugs for CT, while their metal ions can produce Fenton or Fenton-like reactions for CDT. MOFs can load photosensitizers for PDT, photothermal agents for PTT. MOFs can also be an carrier of small molecule targeted drugs and immunotherapy drugs for TT and IT. Additionally, MOFs can also load and protect GOx for ST and carry radiosensitizers to improve RT. *RT* radiotherapy, *CT* chemotherapy, *CDT* chemodynamic therapy, *PDT* photodynamic therapy, *PTT* photothermal therapy, *TT* targeted therapy, *IT* immunotherapy, *ST* stavation therapy

Photothermal therapy

PTT operates on the principle of converting light into thermal energy to generate thermal stress on tumor cells, thereby killing them [38]. Recent studies have focused on enhancing the efficiency of light-based localized heating, improving the selectivity for target tissues, and reducing heat dissipation from target tumors to minimize damage to surrounding healthy tissues. Incorporating

Table 3 MOF based SRDDS applied in various modes of tumor therapy

MOF	Drug	Drug loading	Stimuli	Treatment mode	Target cell	Tumor	Ref
MgAl-LDH/Fe-MOF/D-Man	MTX, DOX	28 and 21wt%	pH	Chemotherapy	MDA-MB 231 cells	Breast cancer	[212]
Aln-ZIF-8	DOX	0.65 μg/mg	pH	Chemotherapy	4T1 cells	Bone metastasis	[213]
CS/Bio-MOF	DOX	92.5%	pH	Chemotherapy	MCF-7 cells	Breast cancer	[214]
Fe_3O_4/Bio-MOF-13	DOX	15.6 wt %	pH/magnetic	Chemotherapy	MDA-MB-231 cell	Breast cancer	[215]
UCMOFs@D@5	DOX, 5-Fu	16.4 and 24.7 wt%	pH	Chemotherapy	Hela cells	Cervical cancer	[216]
MOF-801	5-Fu	70%	pH	Chemotherapy	SW480 cells	Colorectal cancer	[217]
Fe-ZIF-8	5-Fu	186 mg/g	pH	Chemotherapy	–	–	[204]
5-FU@bi-MIL-88B-FC	5-Fu	29.8wt%	pH	Chemotherapy	SW480 cancer	Colorectal cancer	[218]
Zr-MOF/AMC	MTX	36 mg/g	pH/GSH	Chemotherapy	HepG2 cells	Hepatoma	[219]
MIL-53@RB	TBSO-CPT	–	pH	Chemotherapy and CDT	MCF-7 cells	Breast cancer	[220]
(DOX + VER)@ZIF-8	DOX, Verapamil	~ 40.9%	pH	Chemotherapy and targeted therapy	MCF-7, B16F10	Multi-drug resistant cancer	[189]
AuNCs@MOF	DOX	12.25%,	pH	Chemotherapy and PDT	4T1 cells	Breast cancer	[221]
DOX-Cu-MOFs@Keratin	DOX	27.1% ± 2.6%	pH/GSH	CDT	A549 cells	Hepatic cancer	[222]
DOX@Cu–TCPP	DOX	33%	pH	Chemotherapy and PDT	4T1 cells	Breast cancer	[223]
RGD-mGZD	DOX, GOx	73%	pH	Chemotherapy and starvation therapy	U87 cells	Glioma	[224]
NH_2-MIL-88B-On-NH_2-MIL-88B	DOX	14.4 wt %	pH/GSH	Chemotherapy and CDT	4T1 cells	Breast cancer	[225]
DUCNP@Mn–MOF	3-F-10-OH-evodiamine	46%	pH	Chemotherapy and CDT	4T1 cells	Breast cancer	[226]
MOF(Fe)	TCPP	–	H_2S	PDT	CT26. WT cells	Colorectal cancer	[227]
SOR@ZIF-8@PDA (SZP)	Sorafenib	25.7%	pH	Chemotherapy and PTT	HepG2 cells	Hepatoma	[228]
ZIF-8	nivolumab	5.07 wt%	pH	Immunotherapy	MCF-7, 4T1 cells	Breast cancer	[229]
PCP-Mn-DTA@GOx@1-MT	GOx, 1-methyl-tryptophan	8.8% and 13.5%	pH, H_2O_2	Starvation therapy and immunotherapy	B16F10, 4T1 cells	Melanoma, Breast cancer	[230]

photothermal agents into metal–organic frameworks (MOFs) has emerged as a promising approach to achieving these goals. For example, Li and his colleagues delivered the phototherapy agent cyanine using ZIF-8 as a carrier and achieved acid-responsive release [236]. This allowed the photosensitizer to accumulate in acidic tumor tissues, exhibiting strong near-infrared absorption and high photothermal conversion efficiency, thus enhancing PTT. At present, the application of MOFs in photothermal therapy against tumors is still in the stage of animal experiments, especially in mice [237, 238]. Due to the inherent and significant differences between mice and humans in terms of immune system and tumor biology, animal models cannot adequately mimic the biological complexity of tumors in humans. Although the efficacy of MOFs in photothermal anti-cancer has been clearly confirmed in animal models, their clinical application effect is still unknown. In addition, due to the high heterogeneity of tumor tissues, the design of personalized nanomaterials for photothermal therapy of cancers still needs to be further explored.

Chemodynamic therapy

CDT is an innovative anticancer technology that leverages the TME to activate a Fenton (or Fenton-like) reaction, generating potent oxidizing hydroxyl radicals to selectively kill cancer cells [239]. Since its inception by Bu and Shi et al. in 2016 [240], more and more nanomaterials have been developed and applied to CDT in cancer treatment. MOFs are believed to be able to trigger an effective Fenton reaction and thus be used for chemodynamic therapy due to their unique structural features. MOFs can decompose under acidic conditions, thus providing effective metal ions for the Fenton reaction;

at the same time, the large number of adjustable pores allows MOFs to act as carriers for delivery of adjuvant or therapeutic agents to further enhance chemodynamic therapies or carry out a variety of combination therapeutic strategies. Furthermore, MOFs targeting the TME enable more precise delivery of drugs to the tumor tissues, which can improve the efficacy of CDT and reduce the inadvertent injury to the surrounding normal tissues. For example, Wang et al. developed a nanoplatform for delivering Mn^{2+} by decorating MnO_2 nanodots on ZIF-8-encapsulated glucose oxidase (GOx). This system enabled pH-responsive Mn^{2+} release, catalyzed H_2O_2 in tumor cells, and triggered a Fenton-like reaction that produces hydroxyl radicals to kill tumor cells [241]. At the same time, GOx in the platform consumed d-glucose, an essential nutrient for tumor cells, to produce H_2O_2, a precursor of hydroxyl radicals species, thus starving the cancer cells. Cytotoxicity tests demonstrated that this platform exhibited acceptable biocompatibility along with a significant cytotoxic effect on HeLa cells.

Stimuli-responsive MOFs have unique advantages as carriers for cancer chemodynamic therapy, which can effectively improve the stability and poor water solubility of some anticancer drugs by encapsulating them, so as to ensure that the drugs can better play a role in vivo. Stimuli-responsive MOFs are stimulated by the pH value of TME and GSH to achieve controlled drug release. In addition, the design of stimuli-responsive MOFs that respond to multiple factors of TME (e.g., pH, temperature, enzyme concentration) at the same time to further improve the anti-cancer effect is still needed. With the development of precision medicine, the effectiveness and targeting of cancer CDT based on personalized stimuli-responsive MOFs can be effectively improved by gene sequencing and proteomic analysis of tumor tissues to understand the molecular characteristics and heterogeneity of tumor cells.

Radiotherapy

In addition to chemotherapy, radiotherapy is another anticancer treatment that has been widely used in clinical practice [242]. It uses beams of intense energy, such as X-rays, to kill cancer cells. High doses of radiation, generated either externally or from particles implanted within the body, are focused locally on the tumor. It kills or inhibits tumor cell activity through a variety of mechanisms [243]. Although it is a well-established therapy, radiotherapy has significant limitations. It often relies on large radiation doses, which can harm surrounding normal tissues; at the same time, the limited absorption of radiation by tumor tissues significantly affects the tumor-killing effect.

MOFs, as drug-carrying platforms, present a promising solution to these challenges. They can be loaded with radiosensitizers to achieve strong X-ray attenuation capability and high X-ray absorption coefficients. Therefore, MOF-based SRDDSs are considered promising to improve the radiotherapy effect. For example, Pan et al. designed a MOF-based drug loading system, which was prepared by synthesizing Mn_3O_4 with a ZIF-8 cap under mild synthetic conditions and then modifying FA to the surface [244]. This system was responsive to ROS/GSH in the TME, and it exhibited a radiosensitizing effect, enhancing the efficacy of radiotherapy in cervical cancer. The MTT assay showed that the system could significantly enhance the inhibitory effect of radiotherapy on tumor cell activity. Stimuli-responsive MOFs can release radiotherapy sensitizers more precisely in response to TME or external stimuli, increasing drug concentrations at tumor sites and enhancing radiation sensitivity to cancer cells. Some stimuli-responsive MOFs are loaded with radiotherapy sensitizers containing high-atomic-number elements [245, 246]. These sensitizers can enhance energy deposition and generate more ROS when irradiated by X-rays, effectively killing tumor cells. Although stimuli-responsive MOFs are able to respond to specific stimuli, the specificity and sensitivity of their responses need to be further optimized in practical applications. There are multiple signaling molecular and physicochemical changes in the TME that may interfere with the accurate response of MOFs to radiotherapy-related stimuli. In tumor tissues, in addition to radiotherapy-induced local temperature changes, increased ROS, and other stimuli, there are similar signals generated by other physiological and pathological processes, which may lead to misjudgment of MOFs and inability to function precisely during radiotherapy. MOFs may also be insensitive to stimulation and unable to respond to radiotherapy stimulation in a timely and effective manner, affecting the therapeutic effect. In addition, the quality control standards for stimuli-responsive MOFs for cancer radiotherapy are not perfect, and further research is needed on how to further improve the quality consistency and stability.

Immunotherapy

Tumor immunotherapy is a therapeutic approach that enables the body to generate tumor-specific immune responses by active or passive means, leveraging the function of the immune system to inhibit and kill tumor cells [247]. This method boasts high specificity, good efficiency, and minimal harm to healthy tissues. More immunotherapy drugs are being developed, necessitating advanced drug carriers to enhance their delivery and efficacy [4].

With their innate advantages, MOFs can be used as excellent carriers to load immunotherapeutic drugs, such as antigens, small-molecule targeting drugs and immunomodulators, and achieving improved anticancer efficacy of immunotherapy. Recently, Liu et al. achieved GSH and pH-responsive release of immune checkpoint inhibitor CM-272 using MIL-53(Fe) as carrier [248]. Ingeniously, the responsive degradation of MIL-53(Fe) released the loaded drug and freed Fe^{3+} to generate ROS and O_2, ultimately achieving a combination of induced immunogenic cell death and ferroptosis. This approach effectively stimulated the immune response in vivo and modulated the immunosuppressive microenvironment, providing a viable strategy to enhance the efficacy of cancer immunotherapy. In another study, Zhao et al. developed a lysosome-targeted nanoparticle based on ZIF-8 for loading perforin and granzyme B, aiming to enhance the anticancer effect of T cells [249]. Due to the acidic degradation property of ZIF-8, the loaded proteins could be released and stored in the acidic environment of lysosomes. Once the major histocompatibility complex of tumor cells activated the T cell receptor, the therapeutic agents stored in the T cell lysosomes were rapidly released, leading to effective immunotherapy of tumors. At the same time, the immune-stimulating effect of chemotherapy (ISECT) is considered a potential alternative to traditional immunotherapy [250]. By utilizing a stimuli-responsive drug delivery system to achieve precise release of chemotherapy drugs, it also contributes to enhancing the immune therapeutic effect of ISECT. Overall, stimuli-responsive MOFs can serve as carriers for loading immune modulators, enabling their controlled release in response to TME signals. This enhances the activation of immune cells, thereby boosting the immune response against tumor cells [251–253]. They can also encapsulate immune checkpoint inhibitors (such as anti-PD-1 and anti-PD-L1 antibodies), releasing these inhibitors in response to TME signals. This blocks the immune checkpoint pathways, restores T cell-mediated anti-cancer activity, and enhances the immune system's ability to recognize and eliminate tumor cells [229]. Additionally, stimuli-responsive MOFs can help modulate the TME, clearing adverse factors that weaken immune therapy efficacy (such as hypoxia and high GSH levels), further enhancing immune treatment [254, 255]. Moreover, they can promote the release of intracellular antigens, facilitate cross-presentation, and activate immunity, thereby boosting the antigenic immune-stimulating properties [256, 257]. Lastly, MOF-based drug delivery platforms can enhance the efficacy of immunotherapy when combined with chemotherapy, PDT, and radiotherapy. Therefore, the application potential of MOFs in cancer immunotherapy is extensive, with considerable opportunities for further advancement. Current research predominantly focuses on loading chemical drugs and antigens into MOFs, while studies on the delivery of biological macromolecules (such as nucleotides and cytokines) remain limited. This gap should be addressed through further investigation to optimize synthesis methods, enhance loading efficiency, and improve the stability of MOFs, all while preserving the biological activity of the loaded substances. In addition, investigating the in vivo behavior of stimuli-responsive MOFs in immunotherapy is essential. Further studies are needed to develop reliable in vivo detection techniques, incorporating MRI or fluorescence imaging to monitor the location, response mechanisms, and drug release kinetics of stimuli-responsive MOFs in real time. Such advancements could significantly improve the diagnosis and treatment of diseases.

Targeted therapy

Targeted therapy is a cornerstone of precision oncology, which interferes with the growth, division and spread of cancer cells to achieve the purpose of tumor treatment [3]. Targeted therapy is sometimes called "molecular targeted therapy," and this therapeutic modality includes drugs such as Sorafenib, Lenvatinib, and Osimertinib, which act on specific molecular pathways critical to tumor progression. Targeted therapies offer higher specificity and fewer side effects compared to traditional chemotherapy; however, adverse and off-target effects remain a concern [258–260]. The integration of MOFs as drug delivery platforms in targeted therapy offers a solution to enhance drug selectivity and therapeutic precision. For example, Mete et al. developed a MOF-based delivery system using ZIF-8 loaded with Sorafenib for the treatment of hepatocellular carcinoma [261]. The delivery system achieved a 58% loading efficiency of Sorafenib and exhibited pH-responsive drug release. The acidic TME accelerated the release of Sorafenib and the degradation of ZIF-8, releasing zinc ions that contributed to the anticancer effect. This synergistic interaction resulted in a more potent anticancer response compared to Sorafenib alone, highlighting the potential of MOF-based systems to enhance the efficacy and precision of targeted cancer therapies.

The application of stimuli-responsive MOFs in tumor targeted therapy is based on their own stimuli-responsive properties and targeted modifications. Researchers can adjust the stimuli-responsive characteristics, targeting and biocompatibility of stimuli-responsive MOFs by selecting different metal ions, organic ligands and targeted modification methods to meet the needs of different cancer targeted therapies. In addition, in the targeted therapy of tumors, some stimuli-responsive MOFs can not only be loaded with targeted drugs, but also can be

used as contrast agents for magnetic resonance imaging or fluorescence imaging to monitor tumor changes in real time during targeted therapy of tumors, providing a basis for personalized tumor targeted therapy [262, 263].

Starvation therapy

Starvation therapy inhibits the growth of tumor cells mainly by restricting or depriving the conditions necessary for their survival, such as angiogenesis, nutrient acquisition, and metabolic pathways. Among them, depletion of glucose required for tumor metabolism is an important idea. GOx, a natural enzyme that depletes glucose, has been widely used in cancer starvation therapy [264]. However, GOx is inherently unstable and susceptible to environmental inactivation, so it needs proper carrier encapsulation. MOFs, as excellent carriers, can protect the enzyme activity and enhance the specificity of tumor tissue distribution. For example, Zhang et al. encapsulated GOx and the prodrug tirapazamine (TPZ) in erythrocyte-membrane-encapsulated ZIF-8. This delivery system achieved pH-responsive release of the enzyme and the drug with the help of degradation of ZIF-8 under acidic conditions [75]. The results of in vitro and in vivo studies showed that this system exhibited a powerful synergistic cascade effect in colon cancer therapy. GOx effectively consumed endogenous glucose and oxygen, thereby starving tumor cells; meanwhile, the intensified hypoxia converted the prodrug TPZ into highly cytotoxic free radicals in an acidic environment, which further induced cell apoptosis. Currently, MOF-based SRDDSs have been increasingly used in the combination of starvation therapy and other therapeutic strategies.

The rapid proliferation of tumor cells requires a large number of nutrients, such as glucose, amino acids, etc. Stimuli-responsive MOFs can be designed to inhibit nutrient uptake by tumor cells in response to specific stimuli in TME (e.g., low pH, high concentrations of GSH, etc.). Several stimuli-responsive MOFs can be loaded with enzymes or bioactive substances capable of depleting nutrient reserves within tumor cells [230]. Stimulated by TME, MOFs release these substances to accelerate the catabolism of nutrients within tumor cells. In addition, cancer starvation therapy with stimuli-responsive MOFs can be combined with other treatment modalities, such as photodynamic therapy, immunotherapy, to enhance the effect of tumor starvation therapy and achieve synergistic anti-cancer effects.

Challenge and further perspective

MOFs possess distinct advantages such as structural order, tunable porosity, and high drug loading capacity. However, several limitations currently hinder the clinical translation of MOF-based SRDDSs for cancer therapy. The most critical issues, safety and efficacy, remain challenging to verify due to the limited number of clinical trials related to MOF-based SRDDSs. RiMO-301 is currently the first and only MOF-based drug to have entered clinical trials [265]. This hafnium-based MOF has shown promising results in previously published clinical trial reports. Due to the high atomic number of hafnium (Hf), it efficiently absorbs X-rays and generates reactive oxygen species, thereby enhancing the effectiveness of radiotherapy while reducing the required radiation dose. Existing clinical trial data indicate that RiMO-301, with or without pembrolizumab, was well tolerated and demonstrated promising signs of efficacy in patients with advanced tumors treated with concurrent palliative radiotherapy (NCT03444714). Based on these encouraging results, a Phase Ib/IIa clinical trial has been initiated to assess the tolerability and efficacy of RiMO-301 in combination with hypofractionated X-ray radiotherapy and a PD-1 inhibitor (pembrolizumab or nivolumab) in patients with unresectable, recurrent, or metastatic head and neck cancer (NCT05838729). Similarly, in February 2024, a Phase I dose-escalation study of RiMO-401 in advanced tumors undergoing radiotherapy began (NCT06182579). However, it is important to note that in all three trials, the drug was administered via intratumoral injection, and the intended stimuli-responsive drug release system was not achieved. Therefore, clinical trials for MOF-based SRDDSs are necessary to further evaluate their efficacy and safety.

Additionally, the potential to combine MOFs with other nanoparticles to achieve multifunctional capabilities presents a promising avenue for enhancing tumor treatment through multiple pathways. Further systematic studies focusing on the structural modulation of MOFs themselves are also necessary to establish a theoretical foundation for designing drug delivery systems with better performance that better meet clinical needs and to create favorable conditions for further in vivo and clinical trials.

In vitro and in vivo safety

The primary and most urgent challenge in the clinical translation of MOF-based SRDDSs for cancer therapy is improving their biocompatibility, particularly addressing biotoxicity. Despite the potential of MOFs, the synthesis of biocompatible MOF-based SRDDSs with good stability remains underexplored.

As research on MOFs advances, there have been notable improvements in their biocompatibility [26, 266, 267]. Although no relevant drugs have been put into clinical use yet, more and more animal experiments have preliminarily verified the biosafety of MOF-based SRDDSs

[268–270]. Horcajada et al. reported the use of iron(III)-based MOFs for the efficient delivery of anticancer and antiretroviral drugs, and acute toxicity experiments were performed in rats at the maximum injectable dose. Different indicators (animal behavior, body and organ weights, and serum parameters) were evaluated three months after the injection and no significant abnormalities were observed, and no immune or inflammatory reactions were observed after nanoparticle injection; finally, in vivo subacute toxicity tests were also performed. No significant toxic effects were observed within ten days after dosing. This indicated that the drug delivery system has a relatively reliable biological safety [28].

Similarly, Cui et al. prepared a Fe-based MOF for carrying the anticancer drug 5-Fu, which demonstrated therapeutic efficacy and biosafety in mouse models. The delivery system exhibited tumor inhibition, and the model mice survived for over 40 days, indicating a degree of biosafety. As to whether it is safe and non-toxic to humans, further long-term in vivo and clinical trials are urgently needed [271]. Tian et al. designed a Cu-MOF nanoplatform for chemodynamic therapy. In vivo and in vitro experiments confirmed that the system had excellent breast cancer inhibition and minimal weight loss in the model mice, suggesting that it had a certain degree of biosafety [272].

In general, to improve biocompatibility, three viable strategies deserve to be noted. First, the biocompatibility of synthetic raw materials. The most important thing for MOFs is the selection of metal ions and organic ligands. The selection of human-acceptable alkali metals (i.e., K, Na, Ca, Mg, Fe, and Zn) as metal ion nodes and bioorganic ligands (including sugars, nucleobases, oligonucleotides/proteins, peptides, and amino acids) as the materials for the synthesis of MOFs can provide the basis for good biocompatibility, and at the same time, ensure the low toxicity of their metabolites. A good example is CD-MOFs. Cyclodextrins (CD), consisting of multiple α-D-glucopyranoses linked by a 1,4-glycosidic bond [273], have been approved by the U.S. Food and Drug Administration (FDA) as drug solubilizers and are safe for human use [274]. A number of cyclodextrin-containing drugs are already in clinical use, and CDs themselves have been found to be useful as drugs to treat atherosclerosis [275]. CDs can combine alkali metals to form metal–organic frameworks, mainly by coordinating metal ions using -OCCO- binding groups [276, 277]. CD-MOFs have higher drug loading efficiency and lower toxicity than mesoporous inorganic solids such as zeolites and silica [278]. He et al. designed a CD-MOF-based SRDDS loading DOX for lung cancer treatment and confirmed the anticancer activity of this drug-carrying system in animal experiments. Moreover, necropsy of the test mice was performed, and no damage to organs such as the heart, the liver, the kidney and the spleen caused by the drug delivery system was detected at the end of the experiment, which preliminarily verified its biological safety [279]. MOFs using biologically safe components are thought to be a viable approach for synthesizing SRDDSs with higher biosafety.

The second is the selection of "green" synthesis methods. The one-pot method is the most commonly used method for the synthesis of MOFs for high-volume production, but the separation of MOFs formed in one-pot reactions is still challenging, and the solvents used to separate the phases can lead to toxicity. Compared to solvothermal methods, hydrothermal methods are generally considered to be safer and more efficient. Ramos-Fernandez et al. synthesized ZIF -93 under aqueous conditions at room temperature in 80% pure yield. They reported that the material obtained had the same properties as the material synthesized with DMF as the solvent [280]. Such success cases suggested that we can pick a relatively biofriendly way to synthesize MOFs to reduce the mixing of toxic components during the synthesis process.

Third, "protective shell" coating and encapsulation. This approach increases the biocompatibility of the delivery system, improves its colloidal stability and prolongs the release cycle. For example, glucose [281], PEG [282], chitosan [283], hydrogels [284], erythrocyte membranes [285], phospholipid bilayers [286], GSH polymers [141] and sodium alginate [287] can be added as protective shells. The introduction of these materials improves biocompatibility. As the above methods are increasingly applied to the design of drug delivery systems, MOF-based SRDDSs are expected to eventually achieve clinical applications. Further improvement of biocompatibility requires more effort.

In vivo and clinical efficacy

So far, the effectiveness of MOF-based SRDDSs has been demonstrated in several in vitro experiments [288, 289]. However, there is still a significant need for improvement in related in vivo experiments, and clinical studies have yet to be conducted. Meanwhile, the mechanistic understanding on the absorption-distribution-metabolism-excretion (ADME) process of these drug delivery systems is insufficient, with a lack of comprehensive studies, which hampers the development and optimization of more effective MOF-based drug delivery systems. In the future, comprehensive mechanistic studies are urgently needed to establish a theoretical foundation for enhancing effectiveness. Two major challenges need to be addressed to improve efficacy:

First, ensuring that MOFs can stably carry drugs within the human body, minimizing spontaneous release and

"burst effects," is crucial. The stability of different MOFs varies significantly, for example, MIL-101(Fe) is less stable in phosphate buffer, whereas MIL-100(Fe) is stable in water but decomposes after a few days [28, 290]. What's more, many MOFs tend to degrade under low pH conditions, which can aid in the acid-responsive release of some drug delivery systems. However, it can also negatively impact the stability of other stimulus-responsive drug delivery systems. Additionally, designing orally administered MOF-based drugs to meet clinical needs and address low bioavailability is essential [291]. Therefore, systematic research into the stability and degradation mechanisms of various MOF carriers in both in vitro and in vivo settings is necessary. This could be achieved through the addition of protective shells or other surface modifications, as previously mentioned.

The second major point focuses on enhancing the accuracy and sensitivity of stimulus-responsive release. Multi-stimuli-responsive systems can achieve multi-level responsive release, combining low pH response with redox, temperature, or other responses to achieve more precise tumor-targeted delivery. Recent research conducted by Ge et al. realized the magneto-thermal response of drug delivery [202]. After the introduction of the magnetic material IONP and the thermosensitive material PNIPAM, the UiO-66-NH_2-based drug delivery system exhibited magneto-thermal responsive 5-Fu release, which was significantly accelerated in the presence of an alternating magnetic field and under the influence of high temperature. Further cellular experiments demonstrated that the delivery system exhibited good tumor killing with acceptable biocompatibility. This provides meaningful inspiration for the further development of multi-stimulus-responsive, multi-level-responsive drug delivery systems.

As one of the main features of TME, the study of hypoxia-responsive MOF delivery systems is still in its infancy despite their great potential for development and application. Zhang et al. first developed a hypoxia-responsive Cu-based MOF, a nanocarrier that could deliver drugs to deeper parts of the tumor and enable enhanced chemodynamic and sonodynamic anticancer therapy (CDT/SDT) [109]. In their study, the hypoxic microenvironment inside the tumor could cause the Cu-MOF/Ce6 to degrade and release Cu^{2+} and Ce6. Cu^{2+} could react with GSH, leading to GSH depletion and triggering Cu^{+}-mediated CDT via the Fenton-like reaction, and Ce6 achieved SDT under ultrasound irradiation. The synergistic effect of enhanced SDT/CDT could selectively kill MCF-7 cells, showing high efficacy, minimal invasiveness, and good biocompatibility. This delivery system provides a general strategy for the further development of hypoxia-responsive MOF delivery systems, which increases the dimension of stimulus response in TME, and offers a new idea for more comprehensive stimuli-responsive cancer therapy.

In general, exogenous stimuli responses are relatively more controllable but also have limitations. Exogenous stimuli responses are relatively more controllable but have limitations, such as the limited effectiveness of photothermal responses in deep-seated tumors and the need for large sample volumes for magnetic-responsive modalities. Internal stimulus responses are more widespread but also more complex. Therefore, developing new MOFs to achieve various stimulus responses, finding optimal response combinations, and enhancing anticancer therapy effectiveness are essential. Besides, some strategies have been demonstrated to increase the precision and efficacy of anticancer agents, such as "click to release" [292], in situ generation of active drugs from inert prodrugs in subcellular organelles [293], introducing"sacrificial" bonds [294], and using supramolecular nanovalves [295], which can also be applied in MOF-based SRDDSs.

Advantages and disadvantages of MOFs compared to other novel materials and their combined applications

MOFs present several unique advantages and challenges compared to other novel stimuli-responsive materials in the context of anticancer drug delivery such as liposomes, polymeric nanoparticles, and dendrimers [296–298]. Firstly, MOFs feature a high surface area, tunable porosity, and versatile functionalization capabilities, enabling precise control over drug loading and release in response to tumor-specific stimuli. Additionally, the modular structure of MOFs allows for the integration of targeting ligands, enhancing their potential for personalized drug delivery. These characteristics position MOFs as significant players in the field of drug delivery systems responsive to TME.

However, MOFs also face challenges, particularly concerning biocompatibility and biodegradability. Some MOFs may release toxic metal ions during degradation, raising concerns about their long-term safety. In contrast, materials such as hydrogels and liposomes have more well-documented biosafety profiles, making them more predictable in clinical applications [299, 300]. Moreover, the synthesis of MOFs can be more complex and costly, potentially limiting their scalability compared to other materials.

To overcome these limitations, the joint application of MOFs with other stimuli-responsive materials has been increasingly reported, showing promising potential to leverage the strengths of each material to enhance the efficacy of SRDDSs.

Hydrogels and MOFs: Javanbakht et al. developed a novel bio-nanocomposite hydrogel bead designed to navigate the digestive system, made of pH-sensitive carboxymethyl cellulose (CMC) wrapped with MOF-5, which successfully achieved pH-responsive release of 5-Fu [267]. This system achieved pH-responsive release of 5-Fu and demonstrated stability in the gastric acidic environment. Under intestinal conditions, the CMC/5-FU@MOF-5 exhibited controlled release, making it a promising oral drug delivery system.

Liposomes and MOFs: Cheng et al. developed a biomimetic nanoparticle platform for systemic and intracellular delivery of proteins. The protein carriers were encapsulated in ZIF-8 via self-assembly in an aqueous phase, and the nanoparticles were further decorated with the extracellular vesicle membrane. The system successfully overcame the problems of protein degradation and denaturation, poor cellular uptake, and inefficient transduction to the cytoplasm, achieving pH-responsive systemic and intracellular delivery of proteins [301].

Polymers and MOFs: MOF-polymer nanosystems have also been gradually developed for anticancer drug delivery. Shen et al. designed a ZIF-DOX/RA@DG nanosystem that encapsulates ribonuclease A (RA) and DOX using a microfluidic-assisted design, exhibiting a pH/enzyme dual response. And their in vivo experiments showed that the prepared polymer particles had good biological safety and were suitable for further therapeutic applications [302].

In conclusion, while MOFs possess distinct advantages over other materials in terms of structural versatility and stimuli-responsive drug release, their combination with other stimuli-responsive systems may offer even greater potential for precision tumor therapy. By leveraging the complementary strengths of MOFs and other materials, it is possible to design SRDDSs that enhance therapeutic outcomes while minimizing toxicity and improving safety profiles. The joint application of stimuli-responsive and tumor-targeting-capable materials with MOFs represents an important developmental direction that warrants greater attention from researchers, holding significant potential to enhance the tumor-targeting ability of drug delivery systems and improve therapeutic efficacy.

Modification of MOFs' structure

MOFs serve as a novel class of functional materials at the molecular level, enabling diverse control over structure and properties through the flexible assembly of inorganic–organic linking components. This characteristic provides the possibility to construct MOFs with various functionalities, meeting the demands of diverse SRDDSs. The deployment and manipulation of appropriately designed linkers within MOFs to achieve multifunctional dynamic structures with various stimuli-responsiveness pose a current challenge in MOF design and are crucial to overcome.

In theory, the bottom-up integration of molecules with structural dynamics into porous MOFs is feasible. Generally, three guiding principles exist for synthesizing stimuli-responsive MOFs: the size, shape, and structural symmetry of dynamic components; the availability of free volume in porous MOFs; and the chemical properties and inherent torsional barriers of binders or axes [303]. Conformationally flexible molecules such as molecular rotors [304], motors [305], and switches [306], can generate stimulus-responsive quasi-mechanical motions. Based on this, various response modes and drug delivery methods can be achieved by selecting and assembling molecular components with different characteristics to modulate the structure of MOFs themselves.

For example, Meng et al. reported the design and synthesis of a water-stable Zr-MOF with photoresponsive azobenzene groups. By attaching β-cyclodextrin to the surface of the MOFs via azobenzene stalks, further encapsulation of loaded cargo could be achieved. This drug delivery system could release cargo upon stimulation with ultraviolet light or the addition of a competitive agent, preventing premature release [306]. Tan et al. constructed a nanoscale intelligent cargo delivery system gated by carboxylated pillar [5] arene (CP5) switches, featuring pH and/or competitive binding agent-triggered cargo release functions with negligible premature release [206]. In this system, they introduced a negatively charged CP5 macrocycle that envelops positively charged pyridinium stalks via host–guest complexation, forming pseudo-rotaxanes as movable components of the mechanized nanocarrier, thus achieving drug encapsulation. Their comparative experiments suggested an important role for the CP5 supramolecular switch in regulating drug loading capacity. Moreover, MTT cell viability assays demonstrated negligible cytotoxicity of the novel functional materials before and after CP5 encapsulation. Therefore, this system held potential for clinical applications.

Another interesting coronal structure was used for surface modification of MOFs and showed great targeted delivery properties. Wang et al. constructed a coronal bio-MOF nanocarrier externally decorated with high-affinity apoferritin proteins to build a specific coronal structure [307]. The interior was loaded with protein-coated DOX particles (Fig. 15a and b), significantly increasing drug loading by fully utilizing the inner and outer surfaces of

ZIF-8. Notably, the nanoparticles exhibited significant pH-responsive properties due to the acidic degradation of ZIF-8 and decomposition of AFt proteins under low pH conditions. In addition, the loaded GOx catalyzed the oxidation of glucose to gluconic acid, enhancing the acidity and further accelerating the responsive release of DOX (Fig. 15c). Figure 15d shows the mechanistic illustration for the binding of DOX@AFt on the surface of BioMOF. Figure 15e presents the color STEM image of corona-BioMOF. The BioMOF nanocarrier had good biodegradability and biosafety, with immunofluorescence staining indicating tumor-specific distribution (Fig. 15f). Further in vivo experiments showed that the delivery system had great tumor-killing effects (Fig. 15g).

The composition and structural characteristics of MOFs fundamentally determine their properties and functionalities. To fully harness the potential of MOFs in clinical applications, it is essential to explore and understand the structure–property relationships of these materials, elucidate the underlying physical mechanisms that govern their functionality, and identify direct control methods for their design and construction. By optimizing the design, construction, and refinement processes of MOFs, researchers will be able to significantly enhance the efficacy and specificity of MOF-based SRDDSs.

MOF Synthesis assisted by artificial intelligence

Notably, with the rapid advancement in computational power, continuous improvements in algorithms, and the accumulation of high-quality data, the application of artificial intelligence (AI) in organic synthesis has shown increasing possibilities [308]. The design and synthesis of MOFs are also expected to benefit from AI assistance. A specific example is the use of ChatGPT as a chemical assistant to aid in text mining and MOF synthesis prediction.

In 2023, Omar's team reported their achievements in AI-assisted MOF synthesis. They introduced a ChatGPT chemical assistant that significantly advanced the extraction and analysis of MOF synthesis literature [309]. The resulting dataset of synthesis conditions can be utilized to construct predictive models for reaction outcomes, potentially elucidating the key experimental factors influencing the crystallization of MOFs.

Interestingly, they created a MOF chatbot capable of providing accurate answers based on text mining, facilitating access to the synthesis dataset through conversational interaction and bridging the gap between the fields of chemistry and computational data science. Furthermore, they leveraged the power of ChatGPT and Bayesian optimization to develop a multi-AI-driven system, accelerating the discovery of optimal microwave synthesis conditions, enhancing the crystallinity of MOFs, and improving their properties [310].

It is reasonable to anticipate that AI-driven stimuli-responsive MOFs for drug delivery will continue to emerge, with the potential for enhanced safety, drug loading capacity, and targeted responsiveness. In this era of AI development, MOF-based SRDDSs are poised for rapid advancement, and their clinical translation may also see accelerated progress.

Conclusions

Stimuli-responsive drug delivery systems, capable of responding to specific physicochemical factors in the tumor cite, are at the forefront of research aimed at enhancing anticancer drug efficacy and minimizing adverse effects. MOFs have emerged as promising candidates for SRDDSs due to their high drug-loading capacity, versatile structural tunability, various stimuli-responsive capabilities, and favorable biocompatibility. In this review, we have comprehensively summarized the synthesis techniques and classifications of MOF-based SRDDSs, highlighting their responsiveness to various stimuli. We also reviewed their applications across multiple cancer treatment modalities, identifying both the current advancements and the challenges faced in material preparation and clinical application. Furthermore, we discussed potential strategies for overcoming these challenges and summarized the latest developments in AI-assisted MOF synthesis, looking ahead to the progress of MOF-based SRDDSs for clinical practice. As the field progresses with the development of advanced MOFs and more comprehensive in vivo studies, MOF-based SRDDSs hold significant promise for clinical implementation, ultimately contributing to more precise and effective cancer treatments.

(See figure on next page.)

Fig. 15 Schematic illustration of the design and assembly process of the proposed corona-BioMOFs nanovehicle and its programmed therapy against breast cancer. **a** Assembly process of DOX@AFt. **b** Preparation steps of the corona-BioMOF nanovehicle. **c** Therapy process of corona-BioMOF in vivo. **d** Water-induced defect-based handle mechanistic illustration for the binding of DOX@AFt on the surface of BioMOF. **e** Color STEM image of corona-BioMOF. **f** Distribution of corona-BioMOF in tumor (Tu) and major viscera (He, heart; Li, liver; Sp, spleen; Lu, lung; and Ki, kidney) of MDA-MB-231 tumor-bearing mice at 24 h post intravenous injection with corona-BioMOF. **g** Photographs of tumor dissection. **h** Analysis of relative tumor volumes. Reproduced with permission [307]

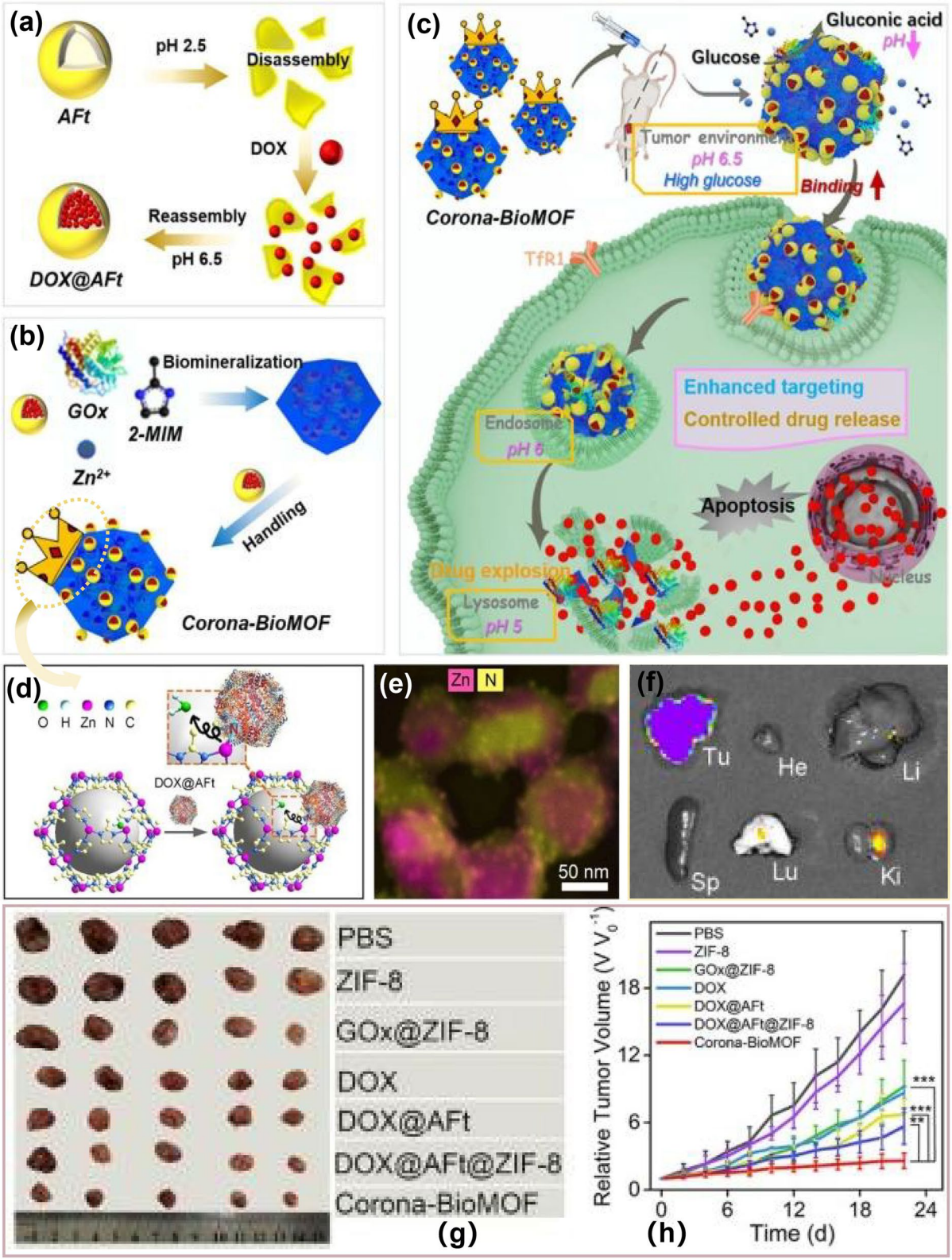


Fig. 15 (See legend on previous page.)

Abbreviations

SRDDSs	Stimuli-responsive drug delivery systems
MOFs	Metal–organic frameworks
GSH	Glutathione
ATP	Adenosine triphosphate
TME	Tumor microenvironment
EPR	Enhanced permeability and retention effects
PDT	Photodynamic therapy
PTT	Photothermal therapy
CDT	Chemodynamic therapy
DTX	Docetaxel
DOX	Doxorubicin
GSH	Glutathione
MIL	Materials of Institut Lavoisier
ZIF	Zeolitic imidazolate frameworks
AL	Alendronate
SEM	Scanning Electron Microscope
TEM	Transmission Electron Microscopy
STEM	Scanning transmission electron microscopy
FA	Folic acid
MTX	Methotrexate
CD	Cyclodextrin
H_2O_2	Hydrogen peroxide
ROS	Reactive oxygen species
CS	Chitosan
PEG	Polyethylene glycol
DTBA	Dithiobisbenzoic
CCM	Curcumin
TCPP	Tetrakis (4-carboxyphenyl) porphyrin
GOx	Glucose oxidase
HA	Hyaluronic acid
MTT	Methylthiazolyldiphenyl-tetrazolium bromide
NMOFs	Nucleic acid-binding chain-modified metal–organic frameworks
H_2S	Hydrogen sulfide
ICG	Indocyanine green
MRI	Magnetic resonance imaging
FR	Folate receptors
AMF	Alternating magnetic field
CP5	Carboxylated pillar [5] arenes
AuNRs	Gold nanorods
Nic	Nicorandil
NO	Nitric oxide
TPZ	Tirapazamine
SDT	Sonodynamic anticancer therapy
CMC	Carboxymethyl cellulose
RA	Ribonuclease A
AI	Artificial intelligence
UV	Ultraviolet
ISECT	Immune-stimulating effect of chemotherapy

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The authors declare no competing interests.

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