Review

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A Comprehensive Review on Metal–Organic Frameworks for Stimuli-responsive-based Drug Delivery: Recent Advances and Future Trends

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Abstract

Cancer treatment has witnessed the emergence of innovative stimuli-responsive nanotherapeutics aiming to overcome limitations associated with traditional drug delivery systems. Metal–organic frameworks (MOFs), a subset of inorganic nanomaterials, are known for their porous structures and versatile applications in integrated cancer diagnosis and therapy. Their noteworthy features include customizable porosity, diverse chemical configurations, adjustable sizes and shapes, and the potential for surface functionalization. The study delved into conventional cancer therapies, provided an overview of MOFs, and discussed various MOF synthesis approaches. Furthermore, this review explored the development of stimuli-responsive MOFs to enhance targeted drug delivery and bioimaging, improving the overall efficacy of cancer treatment, and investigated the applications of stimuli-responsive multifunctional MOFs in nanostructures activated by factors influencing precise drug delivery and bioimaging in cancers. pH, light, ions, temperature, magnetic field, redox reactions, and ATP contribute to the precise control of drug delivery and bioimaging processes. Designed multifunctional MOFs exhibit characteristic changes in response to external and internal stimuli, proving advantageous for drug release and bioimaging. Surface-modified MOFs with responsive features demonstrate excellent biocompatibility with noncancerous cells, efficient drug-loading capabilities, and nanocarrier-mediated targeted drug delivery to cancerous cells. Therefore, the innovative strategy of inorganic nanoscale MOFs with responsive properties holds significant promise for targeted therapeutic drug delivery and imaging across diverse malignancies. The growing interest in stimuli-activated MOFs will open new opportunities in cancer theragnostic applications.

Keywords: stimuli-responsive; metal–organic frameworks (MOFs); anticancer; bioimaging

Introduction

The standard treatments for cancer in clinical practice are surgery, radiation, and chemotherapy (CT). CT can be used on its own or in conjunction with other methods as the first line of treatment [1]. CT serves a

dual purpose in cancer treatment, as it can be employed to reduce tumor size before surgery or radiotherapy and inhibit the further proliferation of cancer cells once these initial treatments have concluded [2]. Although traditional approaches have shown clinical success in improving the survival rates of cancer patients, they face significant issues related to the nonspecific distribution of anticancer drugs to healthy and malignant cells [3]. The effectiveness of CT is ultimately limited due to its nonspecific drug delivery, resulting in various problems, such as severe side effects, inadequate drug distribution to targeted organs, and rapid clearance from the bloodstream (Fig. 1) [4]. This drawback of traditional CT underscores the importance of delivering anticancer drugs directly to the site of action. Considering that many cancerous growths develop gradually and are often only detected at advanced stages, there may be concerns that the reported statistics underestimate the true prevalence of the disease [5]. The growth of cancer is influenced by various factors. Supported by substantial research, smoking is one of the most prominent risk factors and has been linked to lung, head, and neck cancers. Chemicals commonly used in research laboratories and highly mutagenic substances like ethidium bromide serve as additional examples [6]. Furthermore, exposure to radiation, such as ultraviolet or X-rays, or infection with diseases, such as human papillomavirus (associated with cervical cancer) [7] or hepatitis C and B virus (linked to liver cancer), can lead to genetic material mutations. Congenital neoplasms represent a polygenic tumor formation [8]. This is due to DNA damage occurring at critical sites essential for initiating the cancer process during human evolution and hereditary changes in carriers of defective genes. Notable examples include inherited mutations in the BRCA1 gene [9] that predispose individuals to mammary and ovarian cancers and the RB1 gene responsible for retinoblastoma. Genetic predispositions, often called “genetic background”, can also increase the susceptibility to cancer development [10].

Cancer management has seen several treatments, but there are still many challenges. Therefore, it is crucial to continue making progress in medicinal therapy to treat cancer successfully. Current cancer therapy mainly comprises surgical resection, biological therapy, CT, radiotherapy, or a combination. However, anticancer drug delivery faces several issues, such as a lack of specificity, cytotoxicity, low solubility, and short half-life, significantly compromising treatment efficacy [11]. The significant mortality rate and substantial economic impact of cancer treatment on society are immense [12]. Hence, the scientific community recognizes the enormity of these challenges. Extensive research is underway to explore the possibilities of nanotechnology in cancer prevention and treatment within the medical field. Nanomaterials (1–100 nm) are utilized in diverse applications, employing nanocomposites. They offer numerous

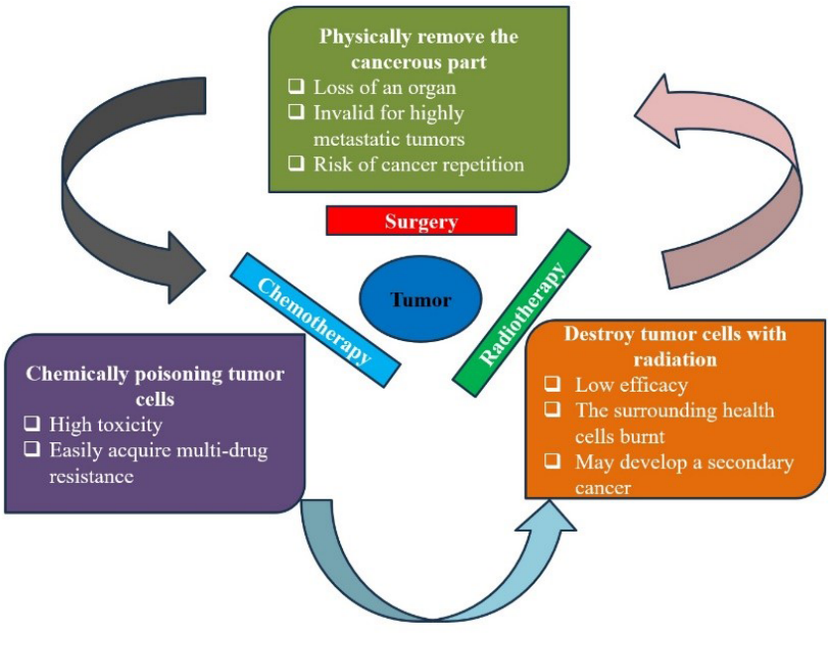

Fig. 1 Conventional methods and their disadvantages.

advantages, such as improved or enhanced drug solubility, promoting targetability, maximizing theranostic potential, and other factors that convincingly improve drug pharmacokinetics and therapeutic efficacy [13]. Nanomaterials, including lipid nanoparticles (NPs), polymeric nanocomposites, star polymers, colloidal micelles, nanodroplets, and organic nanocomposites, are used as drug carriers, particularly in the context of delivering anticancer therapeutics research [14]. Separately, these nanomaterials validate unique strengths and limitations. When extensively employed, liposomes consist of an aqueous essential encased by phospholipids and saturated fat. In addition to their biocompatibility, liposomes can be modified on their surface to enhance their targetability. Numerous studies have utilized liposomes for delivering anticancer drugs such as oxaliplatin and doxorubicin (DOX) [15]. Nevertheless, a significant obstacle in the clinical utilization of liposomes pertains to regulating their dispersion and elimination [13]. Food and Drug Administration approval has been granted for using albumin-based NPs in delivering paclitaxel (PTX) to treat various cancers, each with distinct characteristics and treatment approaches. Two notable examples are breast and nonsmall cell lung cancers. These polymer-based drug delivery systems (DDS) effectively deliver PTX to the target site in a controlled and sustained manner [16]. Numerous albumin-containing nanomolecule examples of such nanomaterials include ABI-008, ABI-009, and ABI-011, each of which has been explored for its potential applications in drug delivery, undergoing clinical trials due to their remarkable success [17], whereas poor drug-loading presents a significant obstacle to its commercial utilization [18]. Dendrimers, a unique class of polymeric macroparticles with a dominant core, branches, and terminal functional groups, have been employed as highly efficient probes for targeting cancer cells when loaded with aptamers [19]. The specific composition of the dendrimer effectively delivers DOX and methotrexate (MTX) to cancerous cells [20, 21]. Nevertheless, functional groups such as polyamidoamine and polypropylene imine on the outer surface enhance their harm to healthy cells, ultimately restricting their practical viability for commercial use [13]. Micellar NPs with a core-shell structure represent another nanoplatform. These NPs have garnered significant attention due to their biocompatibility and biodegradability, particularly their ability to target tumor cells. Researchers have explored the utilization of covalent bonding and the active targeting of tumors is facilitated by integrating peptides with sequences that bind to integrins and incorporating them into micelles [22]. In a separate study, the utilization of micelles composed of poly(N-isopropyl acrylamide) and poly(L-histidine) for encapsulating DOX has been proven effective in targeting therapy for hepatocellular carcinoma [23]. The clinical applicability of cationic polymers is restricted due to their potential interaction with cell membranes, resulting in toxicity [24]. In contrast, nanoemulsions comprise an aqueous phase, an emulsifying agent, and oil, offering several advantages over lipid-based NPs. These advantages include optical transparency, ease of manufacturing, and convenience [25]. The anticancer properties of PTX are enhanced when combined with spirulina polysaccharide in a nanoemulsion [26]. Furthermore, researchers have investigated its capacity to deliver drugs, including rapamycin, temozolomide, and bevacizumab, in the treatment regimen as a strategy for managing advanced melanoma [27]. Nanoemulsions have also been explored for immunotherapy by integrating immune-boosting features [28]. Although they offer numerous advantages, certain obstacles, such as the need for high temperature and pressure during production and susceptibility to instability during storage, underscore the importance of addressing these issues for clinical applications [25]. Therefore, it is necessary to develop a viable option for delivering anticancer treatments. In recent times, the effectiveness of tumor diagnosis and treatment has been greatly improved through the utilization of various inorganic NPs, such as gold NPs (AuNPs), superparamagnetic iron oxides, quantum dots, and carbon nanotubes. These NPs can enhance hyperthermia using alternative energy sources. They enable the targeted delivery of anticancer drugs to specific sites by loading or encapsulating them on nanostructure and nanocomposite surfaces [29]. Early-phase clinical trials involving these nanocomposites have encountered problems related to toxicity and stability [13]. Although surface modification of NPs can enhance their ability to target specific sites, identifying cancer-specific markers presents a considerable challenge. Furthermore, a stromal layer in solid tumors can restrict NP penetration, ultimately affecting their therapeutic effectiveness. Therefore,

the development of DDS that responds to stimuli activating drug release holds the promise of substantially enhancing the therapeutic capabilities of nanocomposites [30]. The tumor microenvironment (TME) exhibits changes in its physiological characteristics, such as increased acidity, low oxygen levels (hypoxia), and elevated levels of certain enzymes. Nanocomposites can react to these internal factors or external stimuli, such as temperature, magnetic field, and light. A comprehensive review of the existing literature has confirmed the substantial advantages of these intelligent nanoconjugates due to their ability to adapt during the drug transfer process [30, 31]. Effectively addressing a substantial portion of obstacles in drug delivery can be achieved through the utilization of stimuli-activated metal–organic frameworks (MOFs). The subsequent section will explore the idea of MOFs and their utilization as a framework that responds to stimuli.

Advancements in MOF Technology

Characteristics of MOFs

In brief, porous and nanoscale MOFs (NMOFs) represent an advanced category of frameworks constructed from porous organic systems, incorporating appropriate metal NPs and diverse linkers [32]. These innovative NMOFs are a porous framework that has garnered significant consideration due to their remarkable characteristics (Fig. 2), which are highly significant for various biomedical uses [33]. Numerous studies have emphasized that MOFs exhibit customizable porosity, unique catalytic capabilities, distinct topological structures, and many functional groups compared to other porous materials such as activated carbon, metal complex hydrides, and metal complex hydrides. Due to these attributes, MOF-based sensors offer outstanding performance in detecting target markers [34].

The ability of synthesized nanomaterials to capture and retain substances is crucial for making sensors. MOFs are particularly effective due to their large surface areas (200–10 400 m^2/g) [35]. Different MOFs have unique structures, resulting in varying surface areas, which are vital in designing highly sensitive sensors [36]. In summary, MOFs with innovative porous organic frameworks have broad surface areas that can be used for various applications, such as adsorbing and removing different contaminants and analytes. MOFs exhibit remarkable heat resistance. Research has demonstrated that MOFs can maintain their stability at temperatures as high as 573 K; in some cases, they can even withstand temperatures exceeding 773 K. The exceptional thermal steadiness of MOF materials permits their utilization in applications operating under elevated temperature circumstances [37]. In brief, MOFs can be fabricated using metal ions with lower oxidation states. Conversely, employing metal ions with higher oxidation states in the design of MOFs can enhance their thermal and chemical stabilities, particularly in sensor applications [38].

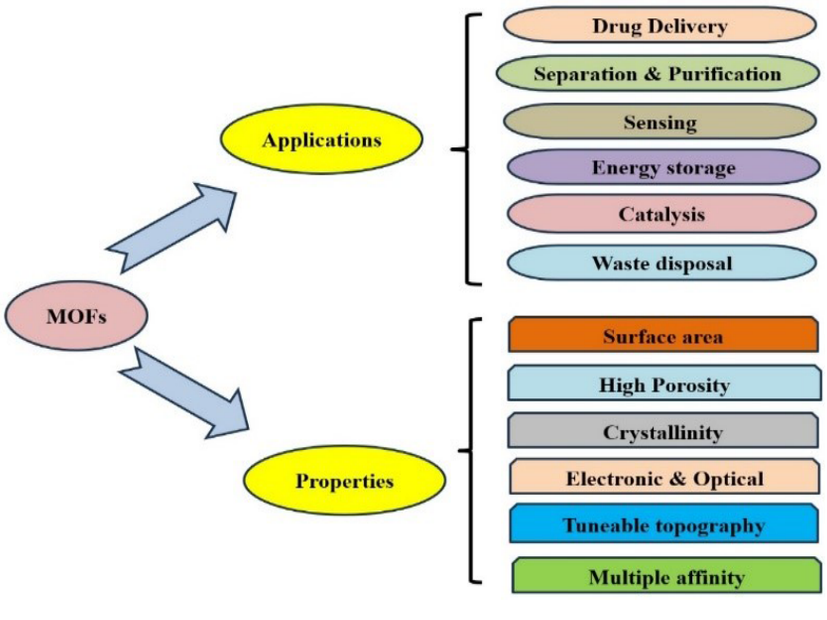

Fig. 2 Schematic representation of MOF applications and properties.

After exposure to severe conditions, zeolitic imidazolate framework (ZIF)-7 demonstrated exceptional chemical stability, retaining its structural integrity, especially when immersed in boiling dimethylformamide (DMF). Experiments involving ethanol or DMF confirmed the ability of ZIF-7 to undergo a reversible phase transformation, suggesting that its structure can maintain stability when subjected to heat and solvent treatments [39].

MOFs have demonstrated significant potential as innovative drug carriers due to their remarkable advantages. Compared to other porous materials, MOFs offer various benefits, such as high porosity and surface area, which enhance drug-loading, and the capability to readily alter their physicochemical parameters stems from the abundant presence of carbon base ligands and organic–nonorganic clusters [40]. Furthermore, anticipated functional groups can be incorporated into MOFs through postsynthesis modification [41, 42]. Additional advantages of MOFs include the efficient diffusion of substances through their pores to interact with encapsulated active compounds, moderate bond strength indicating decomposability, and an accurate structure beneficial for host-guest complexes. MOFs have established themselves as one of the most capable candidates for antineoplastic treatment [43].

Concept of multifunctional MOFs that can respond to stimuli

Stimuli-responsive MOFs can detect and respond to changes in their local environment and external signals. They react predictably by altering their physical and/or chemical properties [44]. These signals can be broadly categorized into two groups: endogenous stimuli, such as hydrogen potential, cellular constituents, and oxidation-reduction reactions, and external stimuli, such as light, magnetic flux, ultrasonography, and heat. The effectiveness of endogenous stimuli is particularly pronounced when distinctive features of the target site significantly deviate from those of normal tissues, as observed in cancer scenarios. These inherent tendencies prompt controlled drug release, improving the specificity of cancer cells [45]. Principally, pH-responsive nanocarriers have garnered significant attention in cancer therapy [46], in stark contrast to stimuli-activated MOFs. A noticeable pH difference between healthy and cancer cells can be ascribed to this phenomenon. In overview, alkalinity levels in the bloodstream and noncancerous cells generally are ~ 7.04, whereas the cancer location typically features a slightly acidic extracellular microenvironment from ~ 5.06 to 6.0. This acidic environment results from the increased glycolysis rate observed in cancer, leading to excessive lactic acid production. To ensure tumor cell survival, they expel this acid, creating an acidic surrounding environment [47]. pH variations have been effectively applied to target anticancer drugs using MOFs stable at pH 7.4 but decompose in an acidic environment. This decomposition process promotes drug release [44]. Redox-responsive MOFs release the drug when a redox reaction begins, making this approach particularly useful for targeting tumor cells with unique properties, which often feature reduced intracellular and oxidized extracellular environments [48, 49]. The redox potential inherent to cancer cells induces the mechanical breakage of MOFs, leading to drug release. Cancer cells exhibit significantly elevated glutathione (GSH) concentration levels in the cytoplasm, typically from 2 to 10 mmol/L. GSH is a reducing agent capable of oxidizing disulfide linkages commonly present in MOF structures. Specific ions, such as Mn^{4+} or Cu^{2+}, can also induce GSH oxidation [50, 51]. In contrast to the reducing intracellular environment, hydrogen peroxide (H_2O_2) generation in the oxidative extracellular environment plays a crucial role. However, most redox-responsive MOFs can effectively respond to GSH, but there are limited studies on composites with H_2O_2 responsiveness [51]. Redox-sensitive MOFs offer several advantages. First, they exhibit outstanding consistency in healthy cells, minimizing the risk of toxicity and adverse effects on cellular transport. Second, they exhibit a selective response to cancer cells, often with elevated GSH levels. Lastly, cytoplasmic drug release is generally more therapeutically beneficial than other potential release sites for carriers [52]. However, despite their promising sensitivity and precision, achieving the required specificity in redox reactions can be challenging due to the complex biological environment and the variability of cancer cells [53]. Nonetheless, there are drawbacks to endogenous stimuli-responsive systems, including limited flexibility and control and drug release that relies on MOF degradation [44]. Exogenous stimuli that can precisely control drug delivery, particularly magnetic field and light, have been extensively investigated from a DDS perspective. The amount of load

delivered can be checked by the strength of the stimulus, making it a good feature [47, 50]. Magnetic-responsive drug transmission is a unique and well-explored approach for achieving targeted drug delivery and controlling drug dissolution kinetics. This method includes the application of a layer of drugs onto a magnetically liable material [54]. Subsequently, this combined solution system can be directed to a specific site [47]. Researchers have shown great enthusiasm for MOFs that consist of magnetic metal ions and organic ligands. This enthusiasm arises from their inherited biocompatibility, manageable porosity, and intrinsic ability to bind covalently or noncovalently with active moieties. They are excellent templates for magnetic NPs synthesis [55, 56]. Nanomolecules based on iron oxide, covalently linked with active moieties, target cancer cells by applying an isolated magnetic field. However, most nanomolecules exhibit instability and nonspecific effects [55]. To address these drawbacks, researchers have recently explored the physical encapsulation of active moieties on NPs, demonstrating promising results. Furthermore, researchers have also extensively investigated Gd and Mn II-based DDS using a magnetic-responsive approach, and MOFs are employed for on demand drug release [57]. Researchers have investigated the role of light as an exogenous stimulus in controlled drug delivery applications and how it can be used to modulate drug release parameters [58]. Near-infrared (NIR) light is commonly used for this purpose due to its nondisruptive nature and excellent spatiotemporal control [59]. Upon light absorption, drug release is facilitated through different mechanisms: photochemical response, light-induced temperature response, ion-responsive release mechanism, etc. The initial mechanism encompasses a photochemical reaction, where covalent bonds connecting the drug and NPs are either directly disrupted or undergo a photochemical reaction. This process amplifies the release of the encapsulated drug within the structure [60]. In an alternative strategy called photoisomerization, light exposure prompts an arrangement-based conversion in a rotationally controlled bond, usually a double bond. When illuminated, these organic compounds undergo structural rearrangement, shifting from a conversion to a cis-configuration. This process disrupts their assembly, ultimately leading to drug release [61]. In a light-induced temperature response, a light-absorbing moiety transforms light energy into thermal energy, resulting in a substantial increase in temperature. If the temperature exceeds 44 °C, it can cause irreparable cell damage or even lead to cell death, primarily through cell membrane disruption, mitochondrial dysfunction, and impairment of RNA synthesis; healthy cells can disperse heat and regulate a consistent temperature via circulation, employing a mechanism different from that in tumor cells. This difference leads to the inhibition of controlling activities essential for tumor cell growth and propagation. As a result, this approach is widely employed in tumor therapy due to its minimal toxicity to normal body cells [62]. Photodynamic therapy (PDT) is a commonly used photothermal therapy (PTT) approach that relies on three key elements: NIR light, an ample supply of oxygen, and a photosensitizer (PS). Upon exposure to NIR irradiation, the PS is activated and alters the conversion of molecular oxygen (O_2) into nascent oxygen or reactive oxygen species (ROS), which leads to the formation of highly reactive oxygen intermediates, leading to the induction of programmed cell death, gangrene, or autophagy in tumor cells. PDT is a localized cancer control method that effectively removes malignant tumors while minimizing impairment to the surrounding healthy cells [63]. However, PDT might be constrained due to the intrinsic less water solubility of typical PS and limited optical penetration depth. To address these limitations, NMOFs based on photosensitive agents have recently been developed. These NMOFs are developed to be of the appropriate size with micropores that allow for elevated PS concentration with minimal self-quenching. Furthermore, their absorbent structures facilitate the carriage of ROS, ultimately resulting in enhanced PDT efficacy [64]. Although light-sensitive MOFs have several advantages, they face challenges related to limited penetration into materials. In contrast, magnetic-responsive MOFs require a substantial sample quantity [44]. Most MOFs are typically electrically neutral due to the balance of charges of both positive and negative nature associated with metal ions and ligands based on carbon. However, in specific cases, MOFs can exhibit either a positive or negative charge, introducing ionic properties. This approach is an innovative method for drug delivery [65]. In this context, an ionic drug incorporated into an ionic framework is established using ionic interactions.

Furthermore, diffusion and drug release are regulated through ion exchange in biological fluids, providing responsiveness to external stimuli [66]. The ion-responsive release mechanism primarily depends on three key components: fabrication of metal ion-nucleic acid complexes involves anion exchange, competitive binding, and synthesis, ensuring the originality of the content. In creating metal ion-nucleic acid complexes, click chemistry is employed to construct DNA enzyme-layered long-form NMOFs loaded with active pharmaceutical ingredients (APIs). By selectively isolating the stratum of nucleic acids in the presence of particular ions and facilitating drug release, a targeted extraction method can be employed. Anion exchange exploits diverse organic preferences, promoting drug release by facilitating the interaction between anions and metal cations. Conversely, in interfering binding, a highly binding ionic species is employed as a substitute to regulate drug release [67]. Hyperthermia is another extensively studied cancer therapy method involving the application of external forces or fields to induce localized heat, ultimately damaging or killing cancer cells. The thermal level change in noncancerous and cancer cells induced by elevated body temperature can be exploited to target and release antineoplastic drugs. Specific MOFs exhibit hyperthermia sensitivity, leading to a substantial improvement in drug release. This enhanced release may be due to MOF degradation or a weakened interaction between MOFs and APIs [68]. An additional ATP is an endogenous stimulus and a complex biotic molecule that is a vital energy source for various biological processes. Compared to the intracellular environment, where ATP concentrations are from 1 to 10 mmol/L, the extracellular ATP concentration is relatively low (typically ~ 0.4 mmol/L). Furthermore, cancerous cells exhibit significantly elevated intracellular ATP levels compared to noncancerous cells. This increase can be due to excessive glycolysis, rapid proliferation, and development. The TME, often characterized by hypoxia (induced by pressure), further contributes to substantially higher ATP levels (100–500 μmol/L) compared to healthy cells (10–100 nmol/L). This distinguishing feature potentially develops ATP-mediated DDS [68]. Hydrogen sulfide (H_2S) produced through enzymatic biosynthesis by cystathionine β-synthase is fundamental in various physiological and pathological processes. Its low levels offer cytoprotection due to its anti-inflammatory, antioxidant, and antiapoptotic characteristics. However, excessive H_2S generation is normally related to cancer. Therefore, correct monitoring and depletion of H_2S is essential to address this issue [69]. To enhance targeting precision, various DDS based on stimuli-responsive MOFs have been developed. In these systems, MOF surfaces are modified by incorporating supramolecular host molecules, serving as gates to facilitate host-guest complex formation. These interactions can be influenced by internal and external stimuli. This approach ultimately enhances the performance of DDS and improves their therapeutic effectiveness [46].

Applications of Stimuli-responsive MOFs in Cancer

MOFs present an exciting frontier in drug delivery. Their exceptional porosity, adjustable pore sizes, and diverse chemical compositions render them ideal for encapsulating and delivering therapeutic agents. A key advantage lies in their ability to finely modulate drug release kinetics, tailoring it to specific biological conditions. This precision facilitates targeted and sustained drug delivery, enhancing therapeutic efficacy while minimizing side effects. Furthermore, MOFs offer multifunctionality, integrating therapeutic agents, imaging tools, and targeting ligands within a single framework. This enables the development of theranostic platforms capable of simultaneously delivering drugs and monitoring treatment response. MOFs can also be developed to be biocompatible and biodegradable, ensuring safe clearance from the body. With their versatility, controllability, and compatibility, MOFs hold great promise in transforming drug delivery, paving the way for improved patient outcomes and enhanced therapeutic interventions.

pH-responsive MOFs

Sun et al. investigated a pH-responsive mechanism using a combination of hydroxylated ZIF-8 (HA-ZIF-8) for delivering tocopherol acid succinate (α-TOS). The synthesis process for α-TOS@ZIF-8 involved dissolving zinc nitrate hexahydrate [$Zn(NO_3)_2 \cdot 6H_2O$] and α-TOS in methanol with ultrasonic processing assistance. This solution was mixed with a methanolic solution of the organic linker, 2-methylimidazole.

The resulting compounds were mixed with a water-based solution of HA to produce HA/α-TOS@ZIF-8. These nanoplatforms exhibited impressive drug-loading ability (43.03 wt.%). As anticipated, the HA shell degraded upon exposure to hyaluronidase in the TME, revealing α-containing tocopherol succinate@ZIF-8. Subsequently, an acidic environment facilitated the breakage of ZIF-8, leading to drug release. The findings demonstrated minimal drug release at normal (physiological) pH, but under acidic conditions, 74% α-TOS was released within 74 h. Nanoplatforms prolonged circulation in the bloodstream due to their negative charge and enhanced tumor-specific accumulation via the CD44-mediated pathway. Substantial tumor growth inhibition was observed in *in vitro* studies on HeLa cells (with a 19.03% persistence rate) and *in vivo* studies on tumor-induced rats. In contrast, normal cells (L929) exhibited a significantly higher cell survival rate (85%). Overall, these biocompatible nanocomposites have the potential for targeted tumor-specific drug delivery on demand [70].

In a separate research endeavor, scientists developed luminescent –organicMOFs functionalized with folic acid (FA) amine and loaded with 5-fluorouracil (5-FU) for precise drug delivery to specific sites. To outline the synthesis process briefly, europium(III) nitrate hexahydrate [$Eu(NO_3)_3 \cdot 6H_2O$] solution, 2-amino-terephthalic acid ($H_2BDC\text{-}NH_2$), and DMF were mixed in a microwave device and heated to 91 °C. Subsequent quartzes were subjected to a mechanochemical synthesis. Subsequently, they connected FA to NH_2-Eu: TMU-62. Researchers observed that 53.8% of the drug payload was loaded with a remarkable 94.2% efficiency. The dissolution of metal-linked bonds activated the regeneration of carboxylic groups in acidic conditions, enabling the nanostructure to exhibit pH-controlled drug release characteristics. Specifically, it released < 55% of the drug at pH 6.8 and > 90% at pH 4.0 within 72 h (Fig. 3). Furthermore, this nanostructure has been proven nontoxic to normal cells (MCF-10A) and displayed a significant reduction in the proliferation of MCF-7 cancer cells compared to pure 5-FU in a manner dependent on the dosage. This effect was due to the binding of FOLA to folate receptors that are

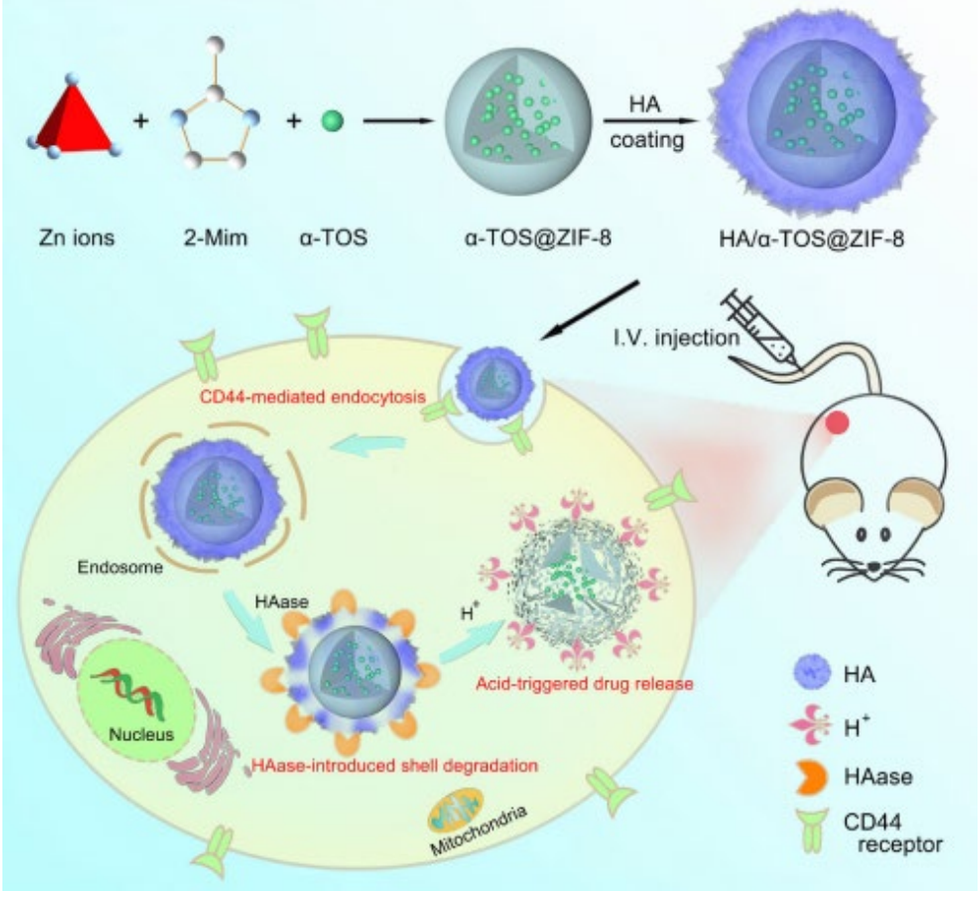

Fig. 3 Schematic representation of HA/α-TOS@ZIF-8 construction depicting pH-responsive α-TOS delivery. Reproduced with permission from Ref. [70] © 2019 Elsevier B.V.

overexpressed in cancer cells. To sum it up, FOLA@NH_2-Eu: TMU-62 can provide a synergistic benefit through its targeting capability and ability to release drugs in response to pH levels [71].

Liu et al. explored the use of a copper-based MOF denoted as $[Cu(L)]_n$, where H_2L is 1,4-bis(1,2,3-triazol-1-yl)terephthalic acid employed as a transporter for 5-FU. In their work, Cu(II) atoms at the core were bonded to tetradentate L2 ligands, and 5-FU was overloaded obsessed by nanocomposites through a straightforward adsorption method. The spectroscopical investigation established a 37.22% drug-loading rate. Interestingly, 5-FU release was nearly four times higher in acidic conditions (90%) compared to a neutral phosphate-buffered saline (PBS) solution with pH 7.4. This was due to the favored degradation of MOF in an acidic environment. The MOF composite exhibited exceptional biocompatibility and demonstrated significant anticancer activity against A549 and HeLa cell lines. To summarize, this synthesized MOF composite can be an effective carrier for cancer therapy [72]. In 2019, Song et al. developed zinc-based MOFs, specifically $[Zn_3(BTC)_2(Aml)(H_2O)_2](MeOH)_6$, where BTC is 1,3,5-benzene tricarboxylic acid and Aml is ammeline. The synthesis involved $Zn(NO_3)_2 \cdot 6H_2O$, ammeline, the organic linker H_3BTC, polyvinyl pyrrolidone, methanol, and water, which were subjected to ebb and detached through centrifugation. The resulting nanoplatform exhibited a moderate-high drug-loading capacity, with 36.82 wt.% for 5-FU. Only 23.9% of the drug was released at physiological pH, whereas 86.5% was released under acidic conditions, confirming a pH dependent drug removed outline. This was due to the breakage of NMOF due to a proton attack in an acidic medium, causing organic bond breakage. Synthesized MOF demonstrated compatibility with normal cells (HFL-1), whereas 5-FU-loaded MOF caused the death of 54% of tumor cells (HepG2). These nanomolecules can be effectively applied as drug transporters for controlled drug release based on pH in cancer treatment [73]. In current times, treatment modality has surfaced as a promising approach for addressing cancer due to its ability to enhance anticancer efficiency by targeting numerous drug battle pathways. Zhang et al. introduced a novel approach utilizing ZIF-90 to simultaneously transfer DOX and 5-FU. In ZIF-90 synthesis, zinc-containing nitrate was combined with tertiary butyl alcohol or 2-methyl-2-propanol, whereas instantaneously, 2-formylimidazole (ICA) and povidone (PVP) were solubilized in distilled water. The zinc nitrate solvent was combined with the ICA-PVP solution under ultrasonic conditions, leading to the formation of a precipitate separated through centrifugation. Subsequently, DOX was covalently attached to the exterior of MOFs through a Schiff base reaction, whereas 5-FU was encapsulated within the pores of the material. The study also involved assessing the drug-loading capacity and conducting *in vitro* drug release experiments. Results showed that the drug-loading capacity was ~ 36.35% for DOX and ranged from 11% to 13.5% for 5-FU by weight. Nanocarriers demonstrated a collapse in an acidic environment, leading to a quick release of > 95% for 5-FU and 91% for DOX, as opposed to the slower release observed in a usual physiological environment (5-FU: 44% and DOX: 20%). In summary, this codelivery approach of two anticancer agents holds the potential for a synergetic therapeutic consequence [74]. Evaluation of the drug transfer potential involved the assessment of amine-bonded MIL100 (Fe) and MIL101 (Fe) NMOFs. To synthesize amine MIL101 (Fe), a solution containing $H_2BDC\text{-}NH_2$ and ferric chloride hexahydrate ($FeCl_3 \cdot 6H_2O$) was dissolved in DMF and heated to 110 °C for 1 day. The resulting suspension underwent filtration, washing, and redispersion in ethanol, followed by centrifugation and drying. In contrast, in the fabrication of amine MIL100 (Fe), $FeCl_3 \cdot 6H_2O$ was combined with DMF and a specific amount of water and ethyl acetate. After aging, a solution of the ligand 1,3,5-tris(2-amino-4-carboxyphenyl)benzene was added to the mixture, which was autoclaved, and the resulting filtrate was collected. Nanostructured materials were further modified through covalent attachment of 20-S-camptothecin (CPT) precursor drugs. Based on the results, MIL101 nanoporous organic polymers could bind 18% of CPT, whereas MIL100 exhibited a binding capacity of 9% for CPT. CPT-loaded MIL101 (Fe) byproducts demonstrated enhanced intracellular absorption, resulting in a two- to four-fold improvement in drug release at pH 5. In contrast, the MIL100 derivative was minimally pretentious by acidic pH due to changes in its crystallinity, preventing drug-loading. Inferior cytotoxic effects were observed for the nanoconjugates when associated with free CPT. This can be due to the ester production of CPT within nanocomposites, which

reserved enzymatic cleavage, thus delaying comprehensive load release and subsequently reducing cell toxicity [75].

In supplementary research, Jia et al. established a potential of hydrogen-activated hollow mesoporous silica (HMS) encapsulated within ZIF-8 for drug transfer (DOX). Initially, they loaded DOX into HMS by dispersing it with an alcoholic mixture of HMS. The resulting precipitate underwent vacuum drying at 45 °C and lyophilized. Afterward, the dried residue was combined with a solution containing Hmim and zinc nitrate [$Zn(NO_3)_2$]. The mixture was centrifuged to separate DOX-loaded HMS@ZIF. HMS demonstrated a consignment loading capacity of 44% by weight. The resulting material was steady at physiological pH, leading to minimal drug release (3%). However, at lower pH levels (4–6), drug release ranged from 46% to 85%. Enhanced drug removal was due to the deprivation of MOFs. HMS@ZIF showed outstanding biocompatibility, as indicated by a high cell viability rate of 90%. In contrast, nanocomposites loaded with the drug demonstrated increased cytotoxicity compared to pure DOX when evaluated on HeLa cells. Furthermore, confocal microscopy revealed a distinct drug delivery pathway of DOX within HeLa cells when utilizing nanocomposites compared to using the drug on its own. This study thus opened up new possibilities for enhancing the efficient delivery of anticancer drugs [76]. Based on reports, poly(acrylic acid sodium salt) (PASS) NPs have shown a strong ability to load DOX through electrostatic interactions and exhibit pH-controlled drug release. However, these PASS NPs were developed to be unbalanced in aqueous environments, limiting their potential as drug transporters. To overcome this limitation, Ren et al. successfully synthesized polyacrylic acid-functionalized ZIF-8 NPs, which are designated the MOF, owing to their exceptional chemical and thermal durability and pH-responsive characteristics. The synthesis process encompassed generating PAA-Zn NPs by substituting Zn^{2+} ions on the surface of polyacrylic acid-functionalized silica (PAAS) NPs with Na^{+}. PAA-Zn NPs were introduced into a methanolic solution containing 2-methylimidazole (HMeIM) to produce PAA@ZIF-8 NPs. These nanocarriers exhibited an outstanding capability to incorporate DOX, achieving an impressive drug-loading efficiency of 95%. This remarkable drug-loading was due to a combination of electrostatic interactions and organic bonds. Furthermore, they observed a substantial 79.9% DOX release at pH 5.5, whereas 35.6% of DOX was released at pH 7.4 (Fig. 4), securing the pH sensitivity of the system. 3-

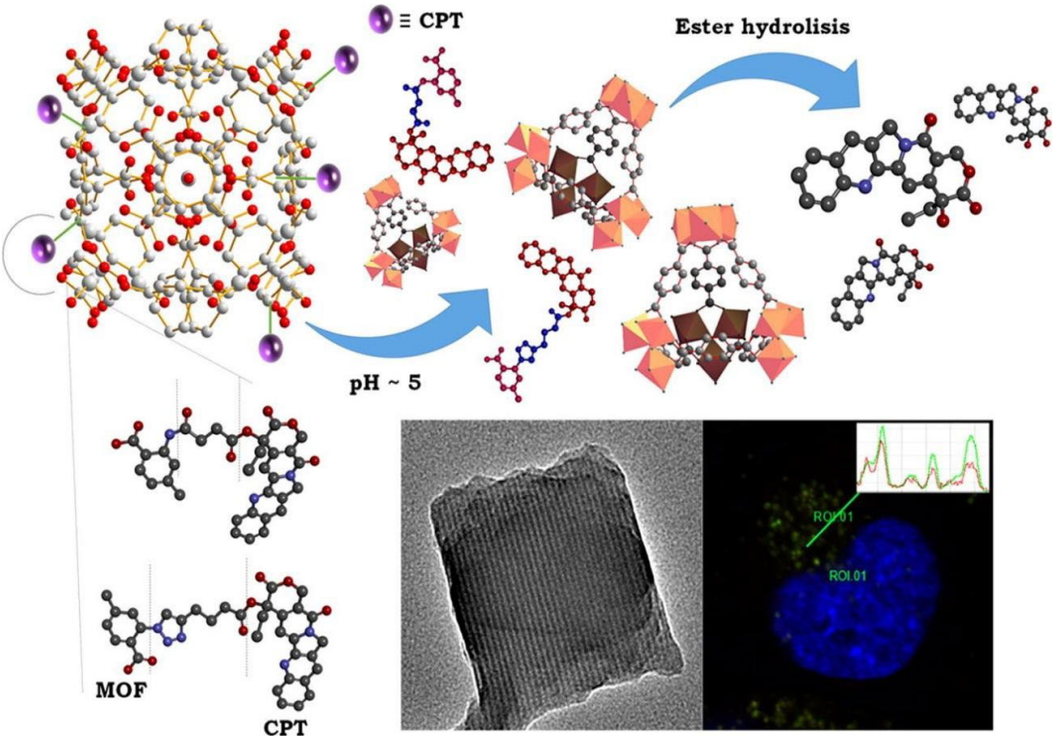

Fig. 4 Application of pH-responsive CPT-loaded NMOFs to target cancer treatment. Reproduced with permission from Ref. [75] © 2019 Elsevier B.V.

(4,5-Dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assays confirmed the biocompatibility of the drug-unloaded nanocompound. Upon testing DOX-loaded PAA@ZIF-8 nanocomposites, they demonstrated cell toxicity comparable to free DOX in MCF-7 breast cancer cells. Optical sectioning microscopy demonstrated the uptake of DOX-loaded PAA@ZIF-8 by breast cancer cells completed cellular absorption, leading to its eventual concentration within the cell nucleus. In general, this acid-responsive release feature holds the potential to facilitate customized anticancer drug delivery [77]. Kundu et al. developed a Gd(III)-based MOF called Gd-pDBI. This was achieved by adding pDBI-[1,4-bis(5-carboxy-1H-benzimidazole-2-yl]benzene to an aqueous solution of Gd(III) nitrate hexahydrate [$Gd(NO_3)_3 \cdot 6H_2O$]. They subjected this solution to sonication and high temperature treatment (72 °C), followed by crystal separation. The resulting MOF displayed outstanding thermal and water consistency and high porosity. In this study, mechanical breakage was employed to produce NMOFs. The nanomaterial demonstrated a 12% loading of DOX. The drug release profile was determined to be pH dependent, with only 22% of DOX released after 5 days at pH 7.4. In contrast, under acidic conditions, a higher release of 44% was observed. Cell culture studies on leukemia (U-937) cells revealed ~ 79.0% cell feasibility at a concentration of 0.3 g/mL. However, nanocomposites containing DOX exhibited markedly elevated cytotoxic effects, resulting in a mere 29% cell survival at equivalent dosage levels. Drug-free nanoplatforms presented no significant adverse effects on cell health, confirming their experimental applicability. Furthermore, *in vivo* investigations have proven the biocompatibility of the developed MOF [78]. Nanocomposite-containing tumor-associated antigens (TAAs) can be engulfed by antigen-presenting cells, making them highly promising in immuno-oncology. However, several challenges associated with TAA delivery include synthesis methodology, low payload efficiency, and inadequate stimulation of $CD8^+$ cytotoxic T lymphocytes (CTLs), leading to unsatisfactory therapeutic outcomes. To address these issues, Duan et al. industrialized MOFs by exploring lanthanide ions in conjunction with GMP as organic ligands. They also incorporated ovalbumin (OVA) into the framework and utilized Watson–Crick base pairing, an oligonucleotide containing unmethylated CpG sequences to enhance $CD8^+$ CTL responses. The maximum encapsulation efficiency for the antigen was 55% (w/w). The MOF structure disassembles at an acidic pH of 5.0, resulting in 60% antigen release, whereas there is negligible antigen release at pH 7.4. MTT assays confirmed the nanocomposite nontoxicity to cells. Administering the antigen and CpG simultaneously led to significant T-cell stimulation and cytokine secretion. Importantly, this simultaneous administration effectively suppressed tumor growth due to improved penetration of immune cells that can kill the tumor (Fig. 5) [79].

Redox-responsive MOFs

Zhang et al. initially developed redox-responsive MOFs for cancer treatment and chose ZIF-8 as the MOF due to its excellent biocompatibility. Cystamine (CA), a molecule containing disulfide bonds at its core and amide groups on the periphery, played a dual role as a redox-sensitive component and a linker. First, they synthesized ZIF-8 by mixing $Zn(NO_3)_2 \cdot 6H_2O$ and 2-methylimidazole in distilled water through magnetic stirring and detached the subsequent invention through centrifugation. They modified ZIF-8 with CA and loaded it with PTX. Interestingly, PTX release increased with the GSH concentration in the range of 0 to 15 mmol/L, from 10.9% to 48.8%, indicating the cleavage of disulfide bonds in the linker. They explored the impact of varying pH values while keeping GSH constant at 15 mmol/L on PTX release. As predicted, a reverse association between pH and PTX release was observed. After the pH changed from 7.4 to 5.5, the release increased from 48.8% to 78.6%, demonstrating its great potential for tumor-responsive drug delivery. Furthermore, ZIF-8 and ZIF-8/CA exhibited low cell toxicity, with AGS cell capability at ~ 80%. ZIF-8/CA@PTX displayed more cell toxicity related to free PTX. The difference in cell toxicity could be due to the hydrophobic nature of PTX, making it challenging to integrate into a cellular breakage. This challenge was overcome by the ammonium groups present in ZIF-8/CA@PTX, enhancing its water affinity and subsequent cell toxicity. The steady PTX release from ZIF-8/CA might also contribute to its superior performance compared to free PTX, which exhibited a sudden release [80]. Liu et al. developed a redox-responsive and cancer-targeted organic MOF called DCA-UiO-DTDP-FA, where DCA is for dichloroacetic acid,

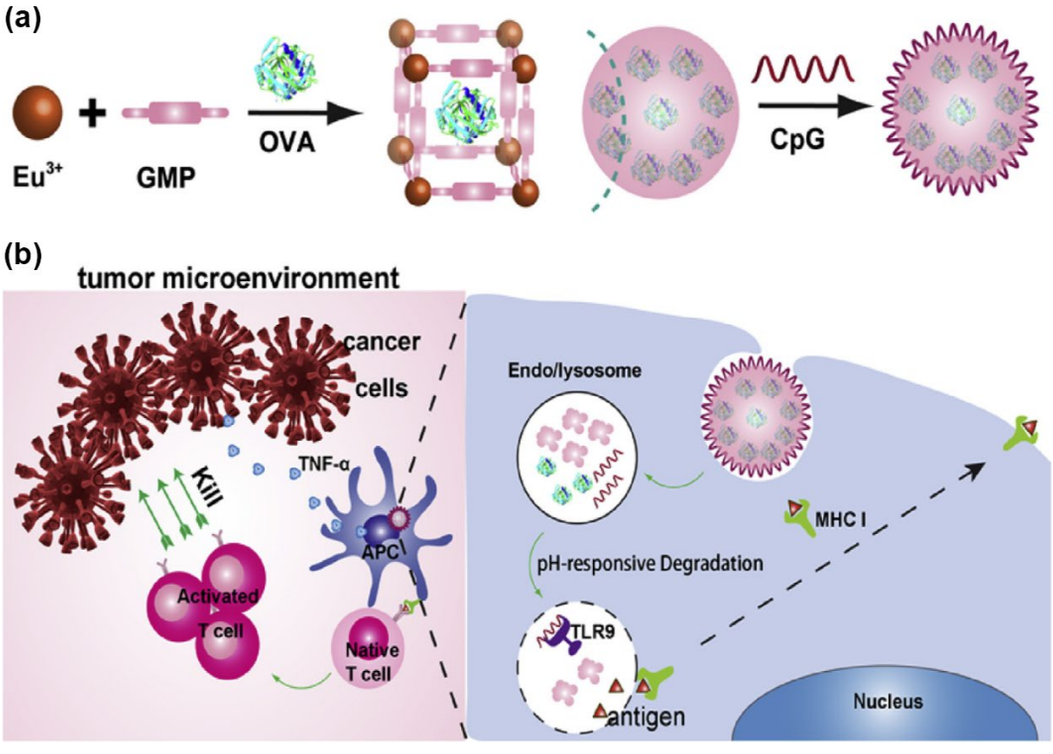

Fig. 5 Schematic illustration of OVA-encapsulated GMP/Eu fabrication and its application in pH-responsive drug delivery. Reproduced with permission from Ref. [79] © 2017 Elsevier B.V.

DTDP is 3,3′-dithiodipropionic acid anhydride, and FA is folic acid. The initial step involved the preparation of DCA-UiO-66-NH_2 MOFs by fraternization solutions of zirconium tetrachloride ($ZrCl_4$) and H_2BDC-NH_2 in DMF using the metal cation and binding agent, respectively. In this response, DCA was supplementary at 120 °C. Subsequently, the amino group of the MOF was coupled with dithiopropionic anhydride acid to conjugate oncotargeted elements, leading to DCA-UiO-DTDP synthesis. To design the 5-FU-loaded DCA-UiO-DTDP, 5-FU was loaded and modified by attaching FA to create 5-FU-DCA-UiO-DTDP-FA. This composite exhibited a high drug-loading efficiency of 31.6 wt.%. 5-FU release was evaluated using dithiothreitol (DTT), which simulates the effect of GSH. About 80% of the 5-FU was unbound in the presence of 10 mmol/L DTT, and the efficacy of 5-FU was potentiated by DCA. The 5-FU-DCA-UiO-DTDP-FA nanomaterial demonstrated higher cytotoxicity in MDA-MB-231 cells compared to a combination of pure 5-FU and DCA in cell culture assessments. Furthermore, drug uptake in cancer cells increased by modified MOF, targeting folate receptors that are overexpressed in malignant cells. Biocompatible and surface-modified MOFs are promising in future clinical applications [81].

Lei et al. developed oxidation-reduction-responsive MOFs (Fig. 6) utilizing zirconium ions (Zr) and bis(benzoic acid) disulfide (4,4′-DTBA) for the binding and delivery of curcumin (CCM). They synthesized MOF-Zr (DTBA) by reacting $ZrCl_4$ and 4,4′-DTBA in a combination of ultrasonic treatment of DMF and acetate. Significantly, they achieved a higher drug-loading capacity (11.08%) and drug encapsulation efficiency (78.07%) for CCM@MOF@Zr(DTBA). *In vitro* drug release assessments have proven the redox responsiveness of this structure. They observed 85% API release in the TME (pH 5.5 and 10 mmol/L GSH), whereas only

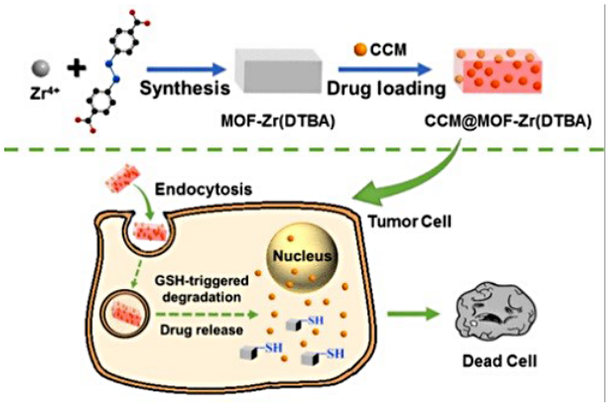

Fig. 6 Schematic illustration of redox-responsive MOFs. Reproduced with permission from Ref. [82] © 2018 American Chemical Society.

50% CCM was released under physiological conditions due to the cleavage of the disulfide bond in 4,4′-DTBA by GSH. Biocompatibility tests conducted on HeLa cancer cells (68.40%) and a breast cancer cell line (MDA-MB-231; 71.10%) confirmed the safety of MOF-Zr (DTBA). In comparison, advanced cytotoxic effects were observed with CCM@MOF@Zr(DTBA) compared to free CCM primarily because of enhanced cellular uptake. Chitosan-coated MOF encapsulated with zirconium (DTBA) exhibited an advanced tumor toxicity rate (76.10%) compared to free CCM (35.10%). This approach using redox-responsive MOFs for cancer drug delivery represents an innovative strategy for delivering anticancer compounds in a controlled manner [82].

Light-responsive approach

Lu et al. devised a hafnium (Hf)-porphyrin MOF responsive to light for application in light radiation therapy, precisely targeting head and neck carcinoma. The underlying hypothesis was that ligands originating from porphyrinoids within the UiO MOF structure would inhibit aggregation and self-quenching. The binding of these porphyrin agents with Hf centers was anticipated to enhance intersystem crossing, increasing ROS generation. Furthermore, the porous structure of the MOF would enable ROS diffusion into cancer cells. To create DBP-UiO, they conducted a solvothermal reaction using $HfCl_4$ and H_2DBP in DMF, resulting in 77% loading of DBP and 24.3% Hf content. DBP-UiO nanoplatforms demonstrated a significant production of oxygen radicals upon light exposure. These nanoplatforms accelerated the movement of newly generated oxygen across DBP-UiO by enhancing intersystem crossing through heavy metal Hf centers. Furthermore, when DBP-UiO was applied to SQ20B cancer cells at a 5 micro-MPS dose and irradiated for 15 min, a substantial improvement in PDT efficiency was observed. A single dose of DBP-UiO eliminated head and neck cancers in 50% of the tested mice. Developing efficient theranostic nanocomposites is crucial to avoiding undertherapy or overtherapy and enhancing therapeutic effectiveness [83]. In this perspective, Chen et al. developed a nanocomposite based on MOFs activated by PS and caspase activity. The nanocomposite comprised a porphyrin derivative known as TMPyP, a folate-targeting element, and a peptide labeled with dye. Caspases, enzymes stimulated only during apoptosis, were used for cell demise imaging. As a brief overview, TMPyP, a PS, was combined into the MOF structure using a single-step synthesis method, creating PS@MOF. Subsequently, a Cy3-labeled caspase-3 substrate peptide and H_2N-PEG-folate (FA) were chemically bonded to PS@MOF. This nanoprobe demonstrated stability in a PBS solution for up to 30 h, facilitating its uptake through folate receptor-mediated endocytosis in cancer cells. The nanoprobe significantly increased the quantum yield of singlet oxygen by 6.2 times, promoting cell apoptosis when exposed to laser irradiation. Furthermore, caspase-3 activation allowed real-time monitoring of therapeutic activity by cleaving the peptides and generating fluorescence. The nanoprobe exhibited good biocompatibility, with 95% HeLa cell viability after 8 h of incubation. However, after PS, MOF cytotoxicity was relatively high (53.91% apoptosis), surpassing normal PS (31.07% cell death). This increased phototoxicity was due to changes in the excitation level of the encapsulated TMPyP. In summary, the synthesized nanoprobe demonstrated promising multifunctional applications thanks to its good biocompatibility, outstanding phototoxicity, and high specificity for intracellular caspase activity [84]. Chen et al. conducted a study using the “ship in a bottle” technique with a lipophobic antineoplastic compound, topotecan, within MIL100 NMOF. They synthesized this NMOF using a microwave-enhanced hydrothermal synthesis method. Ferric chloride and trimesic acid were combined in purified H_2O and subsequently warmed at 130 °C for 360 s using a microwave at 400 W. Particularly, without irradiation, only 5% of the drug was released in water, whereas 13% and 28% of topotecan were released. Light radioactivity promoted drug release, and parallel results were found when the nanomolecule was treated in a PBS solution. In this case, light-delivered drug release reached 27%, whereas only 20% of drug release occurred without radioactivity. This effect was due to the separation of bonds between the drug and the complex, which facilitated separation and subsequent drug release. Furthermore, they conducted a cell line study to confirm the biocompatibility of empty MIL100 NMOFs and found no significant effect on human pancreatic cancer cell lines (MiaPaCa-2 and PANC-1) and A549 cells. That unmodified drug displayed concentration at 50% inhibition values of 0.4, > 25,

and 1.6 for MiaPaCa-2 cancer cells, a pancreatic cancer line, and a human lung adenocarcinoma cell line (A549), respectively. These drug-loaded nanocomposites exhibited enhanced cytotoxicity with IC_{50} values of 0.2, 2.4, and 2.5 for a MiaPaCa-2 cancer cell line, a pancreatic cancer cell line, and a human lung adenocarcinoma cell line, respectively. In another study by Zhang et al., the antitumor effects of PDT and DOX-loaded MOF porous organic polymer (PCN-224). They synthesized PCN-224, incorporating Zr^{4+} ions and tetra(4-carboxyphenyl)porphyrin derivatives, and subsequently modified it with a nucleic acid ligand specific to A549 bronchioalveolar carcinoma cells. The aptamer underwent additional modification with carboxyl groups and fluorescein at its terminals, enabling targeted delivery to A549 cells through PCN-224-DNA. Spectroscopic analysis revealed a DOX-loading efficiency of 50 μg/mg, and pH-activated DOX release was observed, with only 5% released at pH 7.4 and 45.0% released in an acidic medium (pH 5.0). When CT and PDT were combined, the cell viability for MCF-7 was significantly reduced to 45%. This marked a significant enhancement relative to the single laser treatment of DOX-loaded MOF (PCN-224). Therefore, DOX@PCN-224-DNA possesses notable site-specific targeting potential, and PCN-224 exhibited minimal toxicity to both cell lines [85].

Magnetic-responsive MOF-based approach

Sharma et al. developed iron carboxylate magnetic NMOFs to immediately transfer antitumor agents and PSs, specifically DOX and methylene blue (MB). Primarily, they synthesized NMOFs using a microemulsion method with sodium bis(2-ethylhexyl)sulfosuccinate (AOT) and DMF using the organic solvent. To create NMOFs, AOT was dissolved in distilled water, and *n*-butanol was mixed into the solution. $FeCl_3$ and NH_2BDC dissolved in DMF were introduced. The resulting nanocomposite was loaded with DOX and MB, with a loading efficiency of 0.69% and 4.3%, respectively. In their study, the release profiles of the two drugs exhibited differences. Initially, DOX showed a rapid release, possibly due to suppressing PS removal. However, after 4 days, drugs were released, with 95% of DOX and 72% of MB, indicating complete breakage of the MOF structure. NMOFs were replaced as an acidic medium, preventing the disruption of MB in the presence of a reducing agent. Furthermore, under the influence of the magnetic field, a substantial increase in the uptake of nanoencapsulated drugs was observed compared to free drugs. This enhanced uptake was due to the arrangement of drug-loaded NMOFs laterally the magnetic flux lines, which are important for the build-up of cancer tumor cells. Furthermore, upon light initiation, a substantial development in cell toxicity was observed, with ~ 25% cell feasibility. This improvement was due to the collaborative result of coencapsulated drugs, in contrast to free MB (90% capability), free and monoencapsulated DOX (71%–80% feasibility), and MB-loaded NMOF (~ 57% feasibility) in the Panc-1 cell line. Therefore, this specially considered material has the potential for site-specific and controlled cancer treatment [55]. Lu et al. established microwave-enhanced manganese-bisphosphonate nanomaterials with potential applications in theranostic. To fabricate these NCP carriers, a microwave-assisted synthesis reaction was employed using zoledronate and $MnCl_2$ in the presence of DOPA-sodium salt. These NCPs contained zoledronate as an antineoplastic agent and Mn^{2+} ions for magnetic resonance imaging (MRI). The compound was covered with lipids, PEGylated, and functionalized through anisamide (AA) to control drug release and provide site-specific targeting. This NCP complex had high drug-loading capabilities for zoledronate (63 ± 5)% and Mn^{2+} (13 ± 4)%. *In vitro* MRI demonstrated its potential as a T1 reducing agent. The consistency of functionalized nanocarrier particles was evaluated in a PBS solution with bovine serum albumin at a concentration of 5.0 mg/mL, and the granule size was unchanged, indicating excellent consistency. The *in vitro* drug release study revealed a 65% release rate for zoledronate. The lipid-encapsulated and PEGylated demonstrated an IC_{50} value of 6.4 μmol/L in MCF-7 cells, whereas lipid-coated, PEGylated, and functionalized nanocarrier particles (1@PEG AA) exhibited a lower IC_{50} value of 2.0 ± 0.9 μmol/L for the same cell line. For pancreatic cancer cells, IC_{50} values of 24 and 13 μmol/L were detected for 1@PEG and 1@PEG AA, respectively. This suggested that the functionalization of the nanocarriers led to enhanced efficacy in inhibiting cell growth, particularly evident in MCF-7 cells. The enhanced cell toxicity of 1@PEG AA was due to AA-mediated uptake in MCF-7 and AsPC-1 cells, making this polyfunctional compound a

promising platform for analyzing and controlling malignancies [86]. In another study, Li et al. developed magnetic organic–MOF NPs with a core–shell structure called Fe_3O_4-NH_2@MIL101-NH_2 for tumor therapy. These NPs have advantages such as easy separation and high drug-loading capacities. Researchers developed MOFs using Fe^{3+} as a metal form and BDC-NH_2 as a carbon-based ligand using microwave heating. DOX was employed as the model drug, and Fe_3O_4-NH_2, Fe_3O_4-NH_2@MIL101-NH_2, and MIL101-NH_2 were assessed for drug-loading capability, surface area, magnetic responsiveness, mesoporous content, *in vitro* release profiles, and cell toxicity. Among these, Fe_3O_4-NH_2@MIL101-NH_2 exhibited the highest drug-loading volume (48.75 ± 3.48), substantial superficial area (96.05 m^2/g), robust magnetic reaction (20.50 emu/g), and higher mesoporous quantity (22.07 cm^3/g). Drug release from Fe_3O_4-NH_2@MIL101 was slower compared to Fe_3O_4-NH_2@MIL101-NH_2, preventing sudden release. DOX was released to a limited extent in a simulated body fluid at pH 7.4. However, higher release percentages of 53% and 89% were detected in conditions simulating a cancer cell microenvironment and a mildly acidic environment (pH 4.0), respectively. This behavior was due to the breakage of MIL101-NH_2 in acidic conditions. Biocompatibility tests established the safety of these magnetic MOFs; however, DOX-loaded magnetic MOFs exhibited mild cell toxicity in HeLa cell lines, likely to slow drug release. Overall, Fe_3O_4-NH_2@MIL101-NH_2 demonstrated great potential for tumor targeting [87]. Ebrahimi et al. developed superparamagnetic core–shell nanomaterials known as the $CoFe_2O_4$NP@Mn–organic framework. They first fabricated cobalt ferrite ($CoFe_2O_4$) NPs using a coprecipitation method involving the addition of cobalt chloride tetrahydrate ($CoCl_2$•$4H_2O$) to $FeCl_3$•$6H_2O$ in the presence of nitrogen. These NPs were functionalized with thioglycolic acid and used to create $CoFe_2O_4$NPs@Mn-MOFs using the layer-by-layer technique. The resulting MOFs were loaded with daunorubicin, showing high crystallinity, thermal stability, and magnetic characteristics. The nanocomposites achieved a 75% ± 1.22% daunorubicin addition. The release profile demonstrated a two-phase *in vitro* drug release, with 38% removed in 1 200 s, followed by constant removal of 17% over 1 000 min. *In vitro* cell capability tests using MCF-7 cells showed that the drug-free formulation was biocompatible, whereas the drug-loaded formulation displayed increased cell toxicity. Furthermore, applying an external magnetic field reduced cell viability to 41% compared to blank MOFs. The outcomes suggested that the daunorubicin-loaded $CoFe_2O_4$@Mn-MOF, when subjected to a magnetic field, provided controlled release, biocompatibility, and improved site selectivity, making it an excellent drug delivery candidate [88].

Ion-responsive and temperature-responsive MOFs

Chen et al. delved into ion-responsive MOFs to investigate a DDS involving DOX-loaded into NMOFs adapted with a metal ion reliant on a DNAzyme/substrate complex. They started by treating amine-functionalized triphenyl carboxylic acid with $ZrCl_4$ to create porous NMOFs. They constructed DNA/NMOF complexes using connect chemistry and loaded DOX into these DNA-modified NMOFs. In accordance with existing literature, cancer cells overexpress ATP. As a result, researchers integrated an ATP aptamer onto a Mg^{2+}-dependent DNAzyme. What is intriguing is that the nucleic acid cap could be cleaved in the presence of Mg^{2+} or Pb^{2+} ions, activating drug release. As the concentration of Mg^{2+} ions increased, the fluorescence strength of the released DOX also increased. A similar effect was found for ATP at a constant Mg^{2+} concentration, highlighting the enhanced performance of NMOF. Although Mg^{2+} ions were required to begin the release process, the ATP binding worked in tandem to speed it. The improved penetration of the resulting NMOF was detected due to the aptamer targeting nucleolin, a biological marker associated with cancer cells. Furthermore, the targeted binding of NMOF had a selective effect on breast cancer cells (MDA-MB-231). All in all, this intelligent NMOF displays significant potential in anticancer drug delivery [89]. In a separate study, Lin et al. employed a solvothermal-assisted technique to develop dual MOFs, namely ZJU-64 and ZJU-64-CH_3. They utilized Zn^{2+} as the metal-positive ion and adenine as the binding agent to generate subordinate structure units connected using a carboxyl ligand. MTX was added onto these frameworks using a penetration method, with the drug to MOF weight ratio being adjusted to achieve maximum drug-loading, i.e., 13.45% and 10.63%, respectively, at an 8:1 ratio of drug to organic MOF, the decrease in drug-loading

noted for ZJU-64-CH3 was due to the existence of a methyl radical or group. Furthermore, both MOFs exhibited low cytotoxicity, as confirmed by MTT assays and cell cycle investigation. Furthermore, drug-loading and cell capability were 14.0% and 75.0% at 0.2 mg/mL, indicating substantial growth reserve. Under standard physiological circumstances, MTX-incorporated ZJU-64 and ZJU-64-CH_3 exhibited 54% and 23% drug release rates, respectively, after 3 days at pH 7.4. Under hyperthermia (60 °C), ~ 68.3% and 23.5% of drug release were detected for the respective MOFs within the preliminary 8 h, confirming thermal responsiveness. This substantial enhancement in drug release can be due to a disrupted host-guest complex. Therefore, the combination of less cell toxicity, outstanding drug-loading, and adjustable drug removal emphasizes the potential utility of both MOFs in therapeutic applications [90]. In 2019, Silva et al. intended core–shell NPs with temperature-responsive properties. In this study, they used ZIF-8, Eu^{3+} and/or Tb^{3+} ions, and AuNPs for adsorption, heating, and temperature monitoring, respectively. AuNPs formed on the core onto ZIF-8 were synthesized as a protective covering, with the shell improved by incorporating or chemisorbing lanthanide atoms. The resulting nanocomposite [namely (ZIF-8,EuxTby)@AuNP] was added through 5-FU. Particularly, the evaluation of photothermal presentation highlighted significant photothermal control with (ZIF-8,Tb20)@AuNPs at biological temperatures. *In vitro* drug release studies exposed a 29.5% 5-FU release in the early 10 min, followed by a controlled release at a rate of 0.7% per minute at moderate temperature, ensuring a precise and sustained drug release. *In vitro* cell toxicity assessments on RAW 264.7 cells confirmed the biocompatibility of these nanocomposites [91]. In summary, using temperature-responsive MOFs shows promise as a novel method for delivering anticancer agents for treating various cancers.

ATP-responsive MOF-based approach

Yang et al. developed a nanocomposite using ATP-responsive ZIF-90 to transport intracellular proteins and facilitate CRISPR/Cas9 genome removal (Fig. 7). Proteins play a vital part in regulating cell signaling, and Cas9 nuclease can alter the genetic code in mammalian cells, enabling the variation of genetic features. ZIF-90 nanocomposites with green fluorescent protein were synthesized by combining imidazole-2-carboxaldehyde and Zn^{2+} were utilized in conjunction with the protein. ATP activated the disassembly of ZIF-90/protein nanocomposites due to viable binding between ATP and Zn^{2+}, leading to protein release. Protein release was further enhanced with an increase in ATP concentration. Importantly, developed NPs exhibited high biocompatibility and low cytotoxicity when tested on HeLa cells. To assess the effectiveness of the nanocomplex, researchers designed the ZIF-90 to transport nanomolecules loaded with functional protein-targeted RNase A-NBC. In contrast to free RNase A-NBC, these protein-loaded nanomolecules demonstrated increased cell toxicity (cell characteristics reduced to 15%) against HeLa cells. To validate the role of ATP in releasing functional proteins, HeLa cells were pretreated with 2-deoxyglucose, reducing ATP levels. This action significantly reduced cell development and reduction, confirming the stimuli-responsive potential of the nanocomplex. Intracellular delivery studies

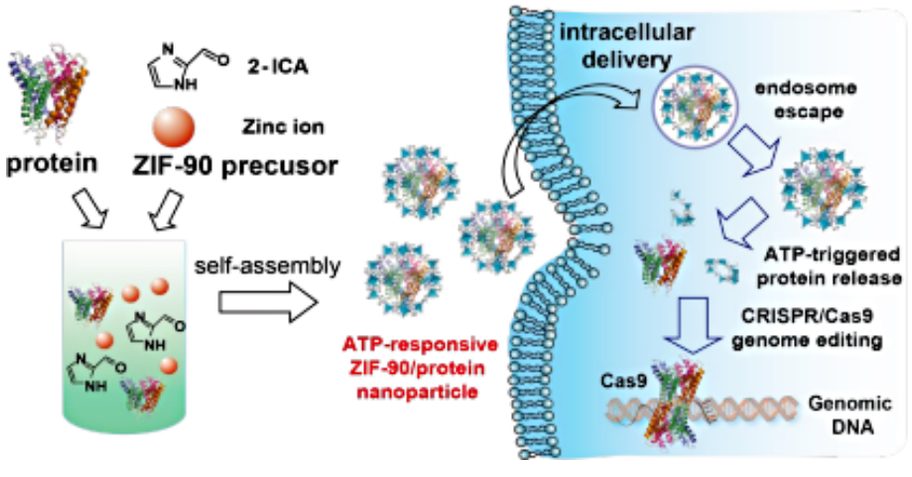

Fig. 7 Utilization of ATP-responsive ZIF-90 for cytosolic protein delivery and genome editing. Reproduced with permission from Ref. [92] © 2019 American Chemical Society.

demonstrated the ability of ZIF-90/protein NPs to transport various proteins into the cytosol. These findings underscore the possibility of ATP-responsive protein distribution and CRISPR/Cas9 genome editing as targeted approaches for addressing serious diseases such as cancer [92].

Pan et al. utilized ZIF-90 to design nanocomposites responsive to ATP, aiming to initiate a series of mitochondrial cascade responses for cancer therapy. ZIF-90 synthesis involved adding imidazole-2-formaldehyde to DMF and heating it to 50 °C. Subsequently, $Zn(COOH)_2•6H_2O$ in DMF was introduced, followed by trioctylamine and particle separation. In this study, CPT-thioketal complex (TK-CPT) and methoxy-substituted estradiol (2-ME) were encapsulated inside ZIF-90 and covered with a homologous cell membrane for tumor targeting. The drug-loading for TK-CPT and 2-ME was determined as 23.1% and 29.7%, respectively. An increase in ATP concentration correlated with enhanced drug release, as mitochondrial ATP efficiently degraded ZIF-90, resulting in 2-ME and CPT release. *In vivo* experiments demonstrated significant tumor growth inhibition in a mouse model, resulting in a cascade of reactions. 2-ME initially suppressed superoxide dismutase activity, leading to an upregulation of ROS. This, in turn, facilitated the conversion of the CPT bioprecursor to the active drug, inducing improved oxidative pressure and ultimately programmed cell death. The ZIF-90-based MOF possesses minimum cell toxicity, effective mitochondrial targeting, and promising therapeutic effects, making it a potential candidate for developing targeted therapeutic platforms. To assess the biocompatibility of ZIF-90, a cytotoxicity assay with 4T1 murine breast cancer cells showed 93.01% cell feasibility. Interestingly, TK-CPT- and 2-ME-loaded nanoparticles exhibited the lowest cell capability (30.04%), suggesting a synergistic effect compared to individual TK/2-ME-loaded nanoplatforms. The cell membrane also promoted endocytosis, enhancing targetability. The ATP-sensitive ZIF-90-based nanoplatform is a promising option for CPT delivery, combining low cytotoxicity, effective targeting, and a synergistic therapeutic effect [93]. Willner et al. designed MOFs responsive to ATP and metal ions to deliver an anticancer drug. In this process, amine-functionalized triphenyl carboxylic acid underwent treatment with $ZrCl_4$, resulting in NMOF formation. NMOF was further conjugated with metal-dependent DNAzyme/substrate pairs as locking elements. Furthermore, ATP aptamer arrangement was combined into the loop domain of the metal ion-dependent DNAzyme. Based on their hypothesis, the collaborative action of overexpressed ATP and Mg^{2+}/Pb^{2+} ions served as accelerators, unlocking NMOF and facilitating DOX release. Importantly, the ion and ATP concentration directly correlated with increased DOX release, confirming the stimuli-responsive potential of NMOF. *In vitro* cytotoxicity studies conducted on breast cancer cells (MDA-MB-231) and healthy epithelial breast cells (MCF-10A) affirmed the biocompatibility of DOX-free NMOF. In contrast, DOX-loaded NMOFs exhibited selective cytotoxicity to breast cancer cells due to the higher ATP expression and ion concentration. This suggested the possibility of NMOFs as a targeted drug transfer system for breast cancer treatment [89]. In 2021, Chen et al. developed a NIR fluorescence nanoprobe called RhI-DOX@ZIF-90. The nanocomposites were manufactured by reacting a solution of zinc acetate dihydrate in DMF with a solution containing two parts of ICA and DMF and DOX and RhI. Primarily, the nanoprobe existed in a nonfluorescent state. Upon encountering ATP, RhI-DOX@ZIF-90 underwent degradation, leading to DOX release and the restoration of RhI fluorescence. The nanosensor demonstrated its capacity to identify ATP at a concentration of 0.25–10 mmol/L, with a detection threshold of 0.10 mmol/L. The loading efficiency of DOX was ~ 11%. RhI-DOX@ZIF-90 displayed fluorescence when cultured with tumor cells, indicating a high ATP concentration. Importantly, nanomaterials displayed low cell toxicity to regular cells (FHC cells), whereas high cell toxicity cancer cells (HCT116) and reduced cell viability. Nanocomposites also showed the potential to accumulate in the mitochondria, improving drug delivery efficacy. *In vivo* studies revealed strong fluorescence signals concentrated inside the tumor compared to other body parts and tissues, confirming the accumulation of nanocomposites at cancerous sites. Animals treated with RhI-DOX@ZIF-90 exhibited significant reductions in tumor weight and volume. This nanoprobe demonstrated its efficacy as a valuable tool for initial cancer analysis and improving the effectiveness of anticancer drugs [94]. Zhang et al. designed a response to ATP self-digestion reaction to a nanosystem intended for anticancer treatment (Fig. 8). The process involved

incorporating glucose oxidase (GOX) into a ZIF via a one-step synthesis technique. Subsequently, the nanocomposites underwent a layering process via a metal–phenolic network (MPN) to generate GOX-incorporated ZIF within a metal polyphenol network. Specifically, with the presence of ATP, the magnetic polymeric NP shell underwent a transformation into ferric ions along with digallic acid, exposing GOX. GOX reacted with glucose to generate H_2O_2 through tannic ferric ion to Fe(II), catalyzing the Fenton reaction. This sequence produced a toxic radical (•OH) and Fe(III) from self-generated H_2O_2. Tannic acid facilitated the accelerated conversion of Fe(III) to Fe(II), enabling Fenton reaction-mediated chemodynamic therapy (CDT). The nanocomposites demonstrated 2% drug-loading. *In vitro* studies showed significant inhibition of 4T1 tumor cell proliferation compared to normal COS7 cells, indicating H_2O_2 production. Targeting potential was established through imaging studies in a 4T1 tumor-bearing mice model. Tumor-bearing mice treated with GOx@ZIF exhibited rapid tumor growth, whereas those treated with GOx@ZIF@MPN showed excellent tumor destruction [95].

Cheng et al. developed a nanosystem with mitochondrial targeting and ATP responsiveness to inhibit mitochondrial respiratory activity. They developed NPs of resveratrol (RES) encapsulated within a porous organic polymer (PCN) using a one-step synthesis technique, with 6.18% drug-loading into the nanomaterials. In the presence of ATP, external RES@PCN nanomaterials underwent

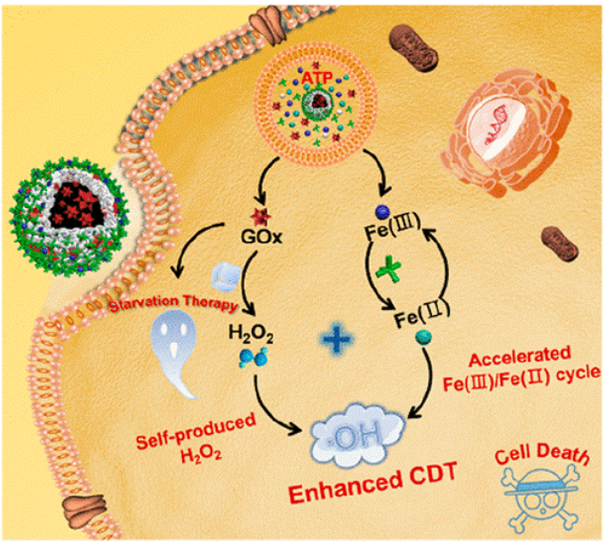

Fig. 8 Utilization of GOx@ZIF@MPN responsive to ATP in tumor ablation. Reproduced with permission from Ref. [95] © 2018 American Chemical Society.

significant changes and development. The increasing ATP concentration exacerbated this morphological change, indicating ATP-regulated PCN collapse. Without ATP, < 20% of RES was removed, avoiding undesirable effects from RES escape. Conversely, with the introduction of ATP within 5 h, RES release increased (> 80%), demonstrating ATP-sensitive sudden drug release. Quantitative investigation on CT26 cells revealed a 50% reduction in basal exhalation and ATP turnover, indicating effective inhibition of aerobic respiration by RES. Metabolic variations in tumor cells were further monitored using an ATP assay kit, confirming that nanocomposites (RES@PCN) decreased respiratory chain and ATPase action, activating inhibition of ATP-driven metabolism. Cell toxicity studies demonstrated that RES@PCN more effectively minimized cellular energy and inhibited tumor cell (CT26) propagation than regular cells (3T3). Imaging studies confirmed fluorescence at the tumor site, validating the nanocomposite transfer. *In vivo* experiments with C26 tumor-bearing mice showed an increased oxygen level, enhancing the outcome of oxygen-included photodynamic treatment. The RES@PCN cluster exhibited enhanced tumor growth related to RES due to increased solubility and enhanced permeability and retention outcomes. This study validated the efficiency of the proposed therapeutic method and laid the groundwork for future advancements in cancer therapeutic strategies [96].

H_2S-responsive MOF-based approach

Zhang et al. developed H_2S-responsive nanoplatforms called ZNNPs. The process involved separately dissolving ZM1068-NB and mPEG5000-PCL3000 in dimethyl sulfoxide. The ZM1068-NB mixture was subsequently mixed with the mPEG5000-PCL3000 solution during ultrasonication treatment. The resulting solution was added to distilled water, and ZNNPs were detached. To enhance tumor targeting, ZNNPs@FA nanocomposites were developed through a similar approach, employing a solution of mPEG5000-PCL3000-FA. The hypothesis suggested the possibility that the 4-nitrobenzoic ester moiety within ZM1068-NB might undergo a reaction with H_2S, leading to the formation of an enolic heptamethine cyanine. This compound would undergo keto-enol tautomerization to form ZM1068-ketone, resulting in NIR change (F1070 → F720) and a ratiometric photoacoustic (PA) response to H_2S. As

anticipated, the nanoprobes established outstanding responsiveness and sensitivity to H_2S. ZNNPs@FA effectively depleted intracellular H_2S, suppressing cancer cell migration (HCT116). The research also noted a decrease in H_2S levels in female nude mice bearing HCT116 tumors after ZNNPs@FA administration. The significant tumor destruction (89.03%) established the antineoplastic possibility of these nanomolecules [69]. In the study by Li et al., an H_2S-activated Cu-MOF called HKUST-1 was developed for combined H_2S-activated PTT and CDT targeting colon cancer. The synthetic process included introducing a mixture of 1,3,5-benzene tricarboxylic acid in DMF into a cupric nitrate [$Cu(NO_3)_2$] solution, and the resulting HKUST-1 was detached. Upon adding sodium hydrosulfide solution, HKUST-1 was stimulated, producing the photoactive complex CuS with a higher thermal change effectiveness (45.07%) designed for thermal imaging and PTT. HKUST-1 nanocomposites exhibited a horseradish peroxidase-mimicking activity, changing elevated H_2O_2 within malignant cells to cell toxicity •OH for CDT. *In vivo* investigation established important inhibition of colon tumor growth through minimal harmful effects on nearby normal cells. In an additional study, a varied metal-functionalized MOF NP PS was developed activated by H_2S in the TME for colon cancer. The mixed copper-zinc –organicMOF, denoted as {Cu_2(ZnTcpp)·H_2O}*n*(NP-1), was synthesized by employing zinc-metalated 5,10,15,20-tetrakis(4-methoxycarbonylphenyl) porphyrin as a linker through a hydrothermal process, whereas Cu^{2+} ions were introduced using a microemulsion method. Under normal physiological conditions, the fluorescence of MOF NPs was quenched by Cu^{2+} ions, resulting in a notable reduction in ROS production. However, in the presence of H_2S, Cu^{2+} ions were detached, exposing light-sensitive ligands. The nanocomposites exhibited remarkable selectivity and H_2S sensitivity. Confocal fluorescence microscopy investigations established the stimulation of these nanomolecules in HepG2 cells when exposed to H_2S. *In vivo* experiments conducted on HCT116 subcutaneous xenografts in nude mice demonstrated the effective elimination of tumors [97, 98].

Current Challenges and Prospects

MOFs for drug delivery pose both challenges and promising avenues for advancement. Recent studies underscore the effectiveness of multifunctional MOFs as stimuli–responsive carriers for releasing anticancer drugs and enabling bioimaging in cancer therapy. These MOFs have demonstrated efficiency, stability, and biocompatibility. However, challenges persist in stimuli-responsive anticancer drug delivery using MOFs, necessitating future solutions. Critical aspects such as the toxicological compatibility and biodegradability of each MOF necessitate thorough investigation. Metal ions such as $Fe^{3+,}$ Zn^{2+}, Zr^{4+}, Mn^{2+}, and Mg^{2+}, organic linkers such as terephthalic acid and trimesic acid, and bioactive coatings such as heparin are extensively used due to their low toxicity and enhanced biological properties. Future research should delve into these building blocks to create customized MOFs. Framework customization and synthesis approaches should prioritize enhancing dimensions, surface area, and morphology and integrating innovative features. Developing sustainable and green synthesis methods is imperative to address environmental concerns associated with current solvothermal conditions. Although MOFs as drug carriers for tumor therapy offer significant advantages, challenges such as early clearance, systemic toxicity, off-target accumulation, and unfavorable pharmacokinetics must be addressed. Biomimetic cloaking with the plasma membrane could potentially resolve these issues. Toxicity and biodegradation studies for MOFs are in their early stages, requiring comprehensive investigations into stability and degradation mechanisms *in vitro* and *in vivo*. To enhance clinical applicability, stimuli-responsive anticancer drug-loaded MOF formulations should be developed in various forms and administration routes. Adherence to stringent regulatory requirements is crucial for the commercial application of MOFs in cancer therapy and other biomedical applications. A MOF-based system for cancer treatment is currently undergoing phase I clinical trials, raising hopes for synergistic radiotherapy-radio dynamic therapy and immunotherapy. Concerted efforts by the scientific community are expected to overcome these challenges, This paves the way for the advancement of novel stimuli-responsive MOF platforms applicable to cancer therapy and various biomedical uses. In summary, the future of MOFs in drug delivery holds immense potential for transforming the landscape of therapeutic interventions. Through precision drug approaches, personalized therapeutics,

combination therapies, theranostic applications, bioresponsive materials, and continued advancements in biocompatibility, stability, scale-up, and translation, MOFs are poised to usher in a new era of targeted, efficient, and safe drug delivery for improved patient outcomes.

Conclusion

The growing prominence of stimuli–responsive heterogeneous surface-modified multifunctional NMOFs in cancer drug delivery and bioimaging is evident. MOFs exhibit unique characteristics such as elevated porosity, extensive surface area, efficient drug-loading, crystalline structure, biocompatibility, diverse functionality, flexible structure, and accurate architecture. These attributes make them well-suited nanocarriers for anticancer drug delivery and bioimaging applications. This review explored the utilization of stimuli-activated NMOF design in cancer therapy, focusing on targeted drug delivery and bioimaging. Diverse mechanisms for drug addition into MOFs, such as *in situ* entrapment, molecular bonding, less entrapment, surface immobilization, and others, are investigated within the framework of MOF-based systems. The design of multifunctional MOFs responsive to stimuli, which encompasses a range of factors, including temperature, redox potential, pH environment, enzyme levels, ions, pressure, magnetic field, and various endogenous and exogenous elements, is examined for stimuli-responsive drug transfer in cancer treatment. Incorporating metal elements such as Zn^{2+}, Cu^{2+}, CO^{2+}, Fe^{2+}, Mn^{2+}, Zr^{4+}, Tb^{3+}, and Eu^{3+}, along with suitable organic linkers, is documented in the construction of stimuli-responsive MOFs. These MOFs demonstrate advantages such as high stability, controlled release, low cytotoxicity, and improved anticancer efficacy. Stimuli-responsive multifunctional NMOFs exhibit notable efficiency in anticancer drug delivery, responding to chemical and physical stimuli. These surface-modified heterogeneous MOFs exhibit promising capabilities in cancer bioimaging, potentially reducing reliance on synthetic dyes and other potentially hazardous metal ions. This not only enhances therapeutic effectiveness but also improves diagnostic precision, positioning MOFs as valuable bioimaging agents for clinical applications. In summary, the stimuli-responsive capabilities of multifunctional NMOFs can enhance the efficacy of antineoplastic drugs by minimizing adverse impacts on healthy cells and the biological potential of MOFs contributes to the advantages of cancer therapy.

CRediT Author Statement

Jitendra H. Patil: conceptualization, writing, methodology, supervision, reviewing and editing the written content, and visualization. **Jayvadhan K. Patel:** conceptualization, methodology, drafting the original content, supervision, reviewing and editing, and contributing to visualization. **Ujashkumar A. Shah, Pravin O. Patil:** conceptualization and methodology. **Hardik H Goswami, Arjun S. Chaudhari:** reviewing, editing, and contributing to visualization.

Conflict of Interests

The authors disclosed no conflict of interest.

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