Metal-Organic Frameworks as Drug Delivery Systems for Tumor Targeted Treatment

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Abstract. Metal-organic frameworks (MOFs) are a class of porous crystalline materials composed of metal nodes and organic linkers, which have attracted great attention for various applications, especially in biomedicine. Tumor treatment often requires repeated, massive, prolonged drug therapy. Traditional drugs and their delivery systems are prone to the development of drug resistance and even concurrent cancers. So it is urgent to develop a new DDS. MOFs have shown promising potential in the DDS for tumor-targeted treatment, because of their large surface area, large pore volume, modifiable structure as well as functionality, and versatile drug loading and release mechanisms. In this review, the recent advances, and challenges of MOFs as DDS for tumor targeting treatment are summarized, focusing on the synthetic methods of promising MOFs, and the targeting strategies. Several recent studies of drug-loaded MOF NPs for the treatment are illustrated. Besides, the functionality proved for biocompatibility, biodegradability, and stability in vivo, the challenges and perspectives for future research and development were discussed. It is hoped that this paper can offer an overview and insights for researchers who are interested in MOFs as DDS for tumor targeting treatment.

Keywords: MOFs; tumor targeting; DDS; cancer treatment.

1. Introduction

Cancer is one of the leading causes of death globally, accounting for about 10 million deaths in 2020 according to the World Health Organization (WHO) [1]. Despite the advances in cancer diagnosis and therapy, such as surgery, chemotherapy, radiotherapy, immunotherapy, and targeted therapy, there are still many challenges and limitations in achieving effective and safe cancer treatment [2]. One of the major challenges is to deliver enough therapeutic agents to the tumor site while minimizing the damage to normal tissues and organs. Thereby, it is urgent to study novel drug delivery systems (DDS) that can improve the tumor targeting ability and therapeutic efficacy of anticancer drugs.

MOFs have shown promising potential as DDS for tumor targeted treatment, for their unique advantages over conventional DDS, such as polymers, liposomes, micelles, dendrimers, and nanoparticles. Porous structure allows MOFs for unparalleled drug loading through various interactions, such as surface adsorption and pore encapsulation, covalent binding, or using functional molecules as building blocks. They can also accommodate various drugs with different sizes, shapes, and properties, such as drugs of small molecules, proteins, and nucleic acids [3]. The organic ligands in MOFs are coordinated to the metal center, forming the framework, and they tend to be weak, which makes MOFs easy to degrade in the biogenic environment, bringing high biocompatibility and biodegradability. MOFs can realize controllable release under certain stimuli including pH, temperature, light, enzymes, as well as magnetic field. These stimuli can trigger the degradation or structural change of MOFs or the cleavage of linkers between MOFs and drugs, resulting in drug release. Stimuli-responsive drug release can improve therapeutic efficacy and suppress adverse effects by delivering them to the target site at the right time. Therefore, MOFs exhibit great potential as drug carriers for targeted therapy.

2. Design, Synthesis, and Functionalization of MOFs

2.1. Promising MOFs

Since the MIL-100(Fe) was applied in the biomedical field of DDS in 2008, many MOFs have been explored as DDS for various drugs. As DDS, for different drug applications and different treatments, varieties of the structures and characteristics are requested though, the common goals for MOFs as DDS are high biocompatibility, high drug loading capacity, controlled release, sustainability as well as balanced stability and biodegradability. As an excellent DDS for tumor targeting treatments, MOFs should also have high targeting efficiency and therapeutic efficacy.by now, the most studied MOFs are BioMIL-3, MIL-100, MOF-5, UiO-66 and Fe-MOF.

2.2. Design of MOFs

As an ideal DDS, the properties like biocompatibility, stability, functionality, sustainability, etc. should be taken into consideration when designing the MOF.

2.2.1. Biocompatibility and low toxicity

MOFs that are suitable for biomedical applications are often referred to as "BioMOFs". They usually consist of biocompatible components, such as light metal ions and organic linkers, that can be metabolized or excreted by the body and avoid toxicity or immunogenicity issues [4]. The selection of the components, size, and shape of MOFs can also affect their stability, degradability, biocompatibility, biodistribution, cellular uptake, and drug release. Some criteria for selecting MOFs for biomedical applications are as follows.

Components

The metal ions and organic linkers should be biocompatible and non-toxic. Commonly used metal ions used for BioMOFs are Zn, Mg, Fe, Cu, Al, Ca, Mn, Co, Ni, Cd, etc., organic linkers are carboxylates, phosphonates, sulfonates, and heterocyclic compounds [4]. Another way to reduce potential side effects is to use active pharmaceutical ingredients or various biomolecules such as amino acids, nucleobases, or sugars as building blocks for MOFs.

Size

The size of MOFs should be within 100 nm to decrease clearance by macrophages of the reticuloendothelial system and liver while reducing toxicity. Smaller MOFs can also penetrate deeper into tumor tissues and cells by enhanced permeability and retention (EPR) effects. Smaller MOFs also have higher specific surface areas (SSAs), which can improve the loading capacity and release rate.

Shape

The shape of MOFs should be spherical or near-spherical to avoid aggregation or phagocytosis. Spherical MOFs have better biodistribution and biodegradation than irregular ones [3]. The shape of MOFs can also influence their cellular uptake and endosomal escape mechanisms, for example, rod-shaped MOFs can induce membrane deformation and facilitate endosomal escape [4].

2.2.2. Balanced stability and biodegradability

Balancing the stability and biodegradability of MOFs for drug delivery is a challenging task requiring careful design and optimization of the structure, composition, size, and surface modification. The metal ion centers are bound by coordination bonds and ligands. In vivo, MOFs may be degraded due to the complex physiological and chemical environment and the influence of metabolites such as enzymes, leading to the premature release of drugs and reducing the efficacy of drugs. However, the overly firm structure may lead to slow or even difficult drug release and cause additional potential side effects due to the difficult degradation in the organism under unknown pharmacokinetics. Therefore, it is important and critical to balance the stability and biodegradability of MOFs in vivo. One possible way to achieve this balance is to choose appropriate metal ions and organic ligands that have moderate coordination strength and biodegradability, such as zinc, iron, copper, or zirconium ions and carboxylate, imidazolate, or amino acid ligands [5,6]. Another possible way is to control the

size of MOFs to enhance their stability in the bloodstream and their biodegradation in the lysosomes [7, 8]. A third possible way is to coat MOFs with biocompatible polymers, proteins, or lipids that can protect them from premature degradation in the physiological environment and facilitate their clearance from the body. Different drugs or biomolecules need to choose different MOFs and different targeting strategies. As for this property, there is no universal solution at present [6,7].

2.2.3. High drug loading and release

The surface area, pore size, and scale of MOFs are of great influence on drug loading and release High surface area usually leads to a larger volume yielding higher molecule loading. Also, with a larger pore size MOFs can load larger molecules. MOFs with small pores (less than 1 nm) can load small molecules such as indocyanine green, doxorubicin hydrochloride, 5-fluorouracil, caffeine, cidofovir, folic acid, calcein, and curcumin, when the size gets larger (more than 1 nm), larger molecules such as proteins, enzymes, DNA, RNA, and antibodies can be loaded [3,8]. Moreover, the pore size can affect the loading efficiency and the release kinetics of the molecules [8]. The scale or size of the MOFs can also affect their stability, solubility, biodistribution, and circulation time in the biological media [8, 9]. Smaller and spherical MOFs are often more stable, soluble, and biocompatible than larger and irregular MOFs [8, 9]. In addition, smaller MOFs can load more drugs per unit mass than larger MOFs because of the higher SSA and can release drugs faster than larger MOFs due to the shorter diffusion distance [8, 9]. However, the structural instability caused by large SSA and pore size can lead to the premature release of the drugs [8]. Furthermore, MOFs with regular structures tend to perform better in vivo due to critical effects and have higher biocompatibility, reduced toxicity, and can accumulate more effectively in vivo after drug release. Therefore, one should pay attention to the pore size, scale, and structure when designing to meet abundant drug loading and high release.

2.3. Synthesis of MOFs

The synthesis methods of MOFs play a crucial role in their structural and functional characteristics, when searching for suitable Bio-MOF for specific drug delivery, the synthesis method usually needs to be taken into account. By now, several conventional and matured methods have been widely used to synthesize MOFs including solvothermal, sonochemical, electrochemical, microwave-assisted, and mechanochemical synthesis. However, conventional methods often have common drawbacks such as high energy consumption, toxic solvent usage, poor morphology control, or low biocompatibility [10]. Recently, biosynthetic methods have emerged as an alternative approach that can overcome some of these limitations while producing MOFs with improved properties.

2.3.1. Conventional synthesis

Solvothermal synthesis

Involved heating a mixture of metal salt and organic ligand in a suitable solvent under high pressure and temperature, it usually produces high-quality crystals with fewer defects that are suitable for structure determination and drug loading. However, this method has drawbacks such as long reaction time, high energy consumption, use of toxic solvents, and difficulty in scaling up.

Mechanochemical synthesis.

Grinding or ball-milling the metal salt and organic ligands under ambient conditions is involved in this method [11]. It can produce MOFs with high yield, high purity, and high surface area without using toxic solvents and reducing energy consumption [12]. However, this method also has limitations such as low crystallinity, poor morphology control, and difficulty in loading drugs[12,13].

Microwave-assisted synthesis

This method involves heating a mixture of metal salts and organic ligands in suitable solvents under microwave irradiation and can produce MOFs with uniform size and shape, high crystallinity, and high porosity [13]. It can also enhance the drug loading and release performance of MOFs. However, this method has challenges such as high cost, safety issues, and the same difficulty in scaling up.

2.3.2. biomimetic synthesis

Biomimetic synthesis of MOFs is a method that mimics the natural biomineralization process and uses biomolecules as templates, precursors, or modifiers to produce MOFs with improved biocompatibility, biodegradability, bioactivity, and biofunctionalization [6]. It can be classified into four main strategies:

Directly using metal nodes as biomimetic active sites: Using metalloproteins or metalloenzymes as precursors or templates to form MOF nodes with biomimetic catalytic or recognition functions [4].

Bottle-around-ship strategy: Using biomolecules such as proteins or DNA as guests to form MOF shells around them through coordination bonds or non-covalent interactions [6, 8, 9]

De novo assembly strategy: Using biomolecules such as peptides or nucleic acids as building blocks to self-assemble into MOF structures through metal-mediated interactions[6].

Incorporation of biomimetic moieties in organic linkers: Using organic linkers that contain biomimetic functional groups such as amino acids or carbohydrates to form MOF structures with enhanced biocompatibility or bioactivity.

Biomimetic synthesis of MOFs can mimic the natural biomineralization process and produce MOFs with improved biocompatibility, biodegradability, bioactivity, and biofunctionalization, as well as offering green and sustainable synthesis routes avoiding the use of toxic solvents, high temperature, and high pressure [6]. However, this method also has many drawbacks. The synthesis is greatly limited by the availability and cost of biomolecules, including proteins, enzymes, DNA, and RNA, and can be affected by the stability and purity of biomolecules, making it difficult to control the size and structures. Sometimes, biomimetic synthesis of MOFs can pose potential risks for biosafety and biosecurity due to the possibility of contamination, infection, or misuse of biomolecules or biomimetic MOFs. It can also raise ethical and social concerns regarding the use of living organisms or their components for MOF production.

2.4. Functionalization and Surface Coating

There are mainly two ways applied to functionalize MOFs with therapeutic agents: pre-synthesis and post-synthesis. Pre-synthesis involves using drug molecules or biomolecules as building blocks to construct the MOF network. Post-synthesis involves modifying the surface or the pores of the MOF after its synthesis. Coating MOFs with biomaterials, such as polymers, proteins, lipids, or bioceramics can improve their stability and biocompatibility in the bloodstream and prevent premature drug release.

2.4.1. Pre-synthesis functionalization

Using functional molecules as building blocks to construct the MOF can improve the interaction, loading, and release of drugs or biomolecules by conferring different crystallinity, porosity, flexibility, stability, and topology. In general, the first step is to select suitable metal ions, organic linkers, and suitable functional building blocks that can react with the metal ions or organic linkers then, preparing the reaction mixture containing the metal ions, organic linkers, and functional building blocks in a suitable solvent. The following step is Heating or stirring the reaction mixture under controlled conditions to promote the self-assembly process and the formation of MOFs with functional groups.

However, this method also has some challenges such as the affinity and biocompatibility of the functional molecules, the stability of MOF structures, and possible resistance and adaptation of the tumor cells due to downregulation or mutation of target receptors or antigens and efflux pumps overexpression.

2.4.2. post-synthesis functionalization

Post-synthesis functionalization is the main way to modify the biocompatibility and targeting of MOFs as DDS [10]. It is commonly reported that coating MOFs with polyethylene glycol (PEG) and polysaccharides, targeting units, or cell membranes can improve the biocompatibility and targeted drug release ability of MOFs in vivo [8].

Coating with target units

The metabolome of tumor cells and normal tissue cells often show certain differences. Using these biochemical and physiological characteristics such as receptor overexpression, increased glycolysis, glutaminolysis, lipid synthesis, and production of metabolites brought by metabolic reprogramming, some tumor cells even express stress-induced molecules on their surface in response to DNA damage, oxidative stress, different targeting groups can be selected to target tumor cells through these characteristics [8]. Most studied targeting groups include folic acid, hyaluronic acid, glycyrrhetinic acid, and monoclonal antibodies. However, this method also has some challenges such as the affinity and biocompatibility of the targeting units, the stability of the coating layer, and the possible resistance and adaptation of the tumor cells due to downregulation or mutation of target receptors or antigens and efflux pumps overexpression [8, 10].

Coating with PEG

Certain coating materials such as PEG or hyaluronic acid (HA) can decrease the early degradation of MOFs by forming a shell on the MOF surface [9]. This can also reduce the nonspecific interactions with plasma proteins and immune cells, thus prolonging the circulation time and enhancing the accumulation of MOFs in tumor tissues [8, 10].

Mimicking cells

Although the surface modification of synthetic MOFs with PEG, targeting groups, or other biological macromolecules such as protein nucleic acids can effectively increase the biocompatibility and targeting ability of MOFs in vivo, MOFs as foreign bodies are still trapped and cleared by the immune system, resulting in a low half-life of drugs. Coating MOFs with cell membranes makes them biomimetic, which can camouflage and reduce the capture of the immune system and have higher targeting efficiency. Therefore, this strategy has a bright prospect [11, 13].

To build a mimicking cell MOF, different cell membranes need to be selected according to different target cells first. Commonly used cell membranes include blood cell membranes and cancer cell membranes, which can enhance the immune escape of MOFs and enhance tumor targeting through cell homology recognition. The second step is to isolate and purify the cell membrane under the activity and integrity of the protective membrane, which is still a difficult problem at present. Another key step is to choose a suitable method to coat the cell membrane on MOFs. Currently, the most used methods are co-extrusion and ultrasonic methods. At present, biomimetic MOFs constructed using various cell membranes are not mature enough, and the extraction and separation of cell membranes and multi-cell membrane fusion to enhance functionality are still in the early stage of experiments. It needs further study of the integrity and function of such MOFs in vivo, as well as their potential mechanism of degradation and carcinogenicity, more experiments are needed to understand their metabolic process in vivo.

3. Drug Capsulation and Targeted Release

In tumor treatments, therapeutic agents usually have many drawbacks such as rapid clearance from the body, but the main point has always been the medicine accumulation in normal tissue cells for lack of specificity, causing damage to healthy tissues and organs, as well as increasing the risk of infection or secondary cancers [8]. Under some circumstances, their reduced effectiveness over time even triggers drug resistance in cancer cells. With the help of a targeted drug delivery system (TDDS), drug distribution in specific tumor cells can be improved [8]. Tumor cells often overexpress certain receptors or antigens on their surface that can be recognized by specific ligands or antibodies. Some receptors or antigens can serve as biomarkers for tumor identification and targeting [10].

3.1. Drug Capsulation

Capsulation is the process of loading drugs or active molecules into MOFs. Capsulation can improve the drug loading capacity and efficiency, and protect the drugs from degradation or leakage[10]. Capsulation can also introduce functional groups or metal centers that can interact with drugs or stimuli to achieve controlled release. The commonly used capsulation methods include one-

step or multi-step capsulation, direct synthesis of drugs as precursors, or high-pressure capsulation [5, 7].

3.1.1. Surface adsorption

This method involves the synthesis of MOFs as the host, then activation and drug capsulation through adsorption. The drug molecules are dissolved in a suitable solvent and then added to the MOF powder. The drug molecules diffuse into the pores of the MOF and adsorb onto the internal surface through weak interactions such as van der Waals forces, hydrogen bonding, and electrostatic interactions. This method is mild and versatile but requires more steps and may result in low loading efficiency or poor release control. Many factors such as the nature of the solvent, the concentration of the drug molecules, and the surface area of the MOFs can influence the process.

3.1.2. Encapsulation

The one-step capsulation method is a process where the capsulation of the substance(s) is achieved in a single step, without the need for pre-forming the shell or the matrix [10]. For example, one-step emulsification is a process where oil-in-water or water-in-oil emulsions are formed by mixing two immiscible liquids with a surfactant. One-step electrospray is a process where microcapsules are formed by applying an electric field to a compound-fluidic jet. This method is simple and fast, can encapsulate multiple components, has good control of control the size and shape, but also has potential leakage of molecules during this progress and has poor stability, and is mainly limited to achieving specific properties or responses, such as stimuli-responsiveness, targeting, or imaging. Multi-step capsulations are achieved in multiple steps, involving pre-forming the shell or the matrix and then loading the substance(s) into it. For example, multi-step emulsification is a process where double or multiple emulsions are formed by two or more consecutive emulsification steps. Multi-step polymerization is a process where polymer microcapsules are formed by two or more consecutive polymerization steps. Compared with one-step capsulation, this method can enhance the stability of the microcapsules, and provide more functionalities, but also complex and time-consuming, sometimes it may damage molecules during the process, due to high temperature, pressure, or shear forces [10].

3.1.3. Other methods

Besides the most used capsulation methods as above, there are other methods like mechanochemical synthesis, direct synthesis, high-pressure encapsulation, covalent binding, and using functional molecules as building blocks. These methods can offer different advantages such as high yield, high purity, high loading capacity, high stability, and high functionality. However, they also have some challenges such as low crystallinity, poor morphology control, difficulty in loading drugs, difficulty in scaling up, and possible toxicity[10].

3.2. Targeted Release

The key point of MOFs as DDS is to achieve targeted drug release or loaded biomolecules. At present, the reported tumor targeting can be mainly divided into passive targeting, active targeting, and stimuli-responsive targeting.

3.2.1. Passive targeting

Passive targeting usually uses the characteristics of drug carrier composition, particle size, charge, and other characteristics to deliver to the targeted site through capillary interception or endocytic fusion or adsorption exchange of tissue cells [14]. This allows nanoparticles, such as MOFs, to pass through the gaps between endothelial cells and enter the tumor tissue. Moreover, tumor cells often have impaired lymphatic drainage that prevents the clearance of nanoparticles from the tumor tissue [8]. This leads to the accumulation and retention of nanoparticles in the tumor tissue known as the EPR effect, which leads to the accumulation of drugs with different particle sizes in different tissue cells.

3.2.2. Active targeting

Active targeting typically relies on the specific binding of ligands with high affinity to receptors on the cell membrane, which are often overexpressed in tumor cells [8]. Usually through adding directly with drugs or post-synthesis modification, the targeted biomolecules such as target peptides, anticancer peptides, polysaccharides, or antibodies are combined by covalent or electrostatic forces, the DDS can obtain active targeting ability and enhanced biocompatibility [11]. These ligands interact with cellular receptors to form complexes that induce drug assembly within target cells. These target groups bind to receptors on the cell membrane and activate endocytosis, bringing DDS into the cell for degradation due to the unstable structures under some conditions and with the assistance of some enzymes, thereby releasing the drug. For example, folate receptor (FR) is highly expressed on the surface of most tumor cells, usually 20-200 times higher than that of normal cell lines. FA can be used as a targeting molecule and has become a mediated drug delivery system to actively target tumors.

CD44 is a complex transmembrane adhesion glycoprotein that is recognized as a marker of cancer stem cells involved in tumorigenesis, progression, and metastasis, the receptor of which is usually overexpressed on the surface of almost all tumor cells. HA is a natural polysaccharide that can specifically recognize and bind to the CD44 receptor [16]. Curcumin (Cur) is a small molecule dove compound with good anti-tumor pharmacological effects. It can affect tumor proliferation and migration by regulating multiple signaling pathways of miRNA, lncRNA, and circRNA. Yang et al. reported the synthesis of a BIO-MOF using Cur and Zn as the core and coated with HA as the shell [15]. Doxorubicin (DOX) ·HCl was loaded on PDA by hydrogen bonding and π-π superposition, and the modified PDA was then successfully coated on Bio-MOFs NPS. The research showed partially released DOX causes damage to superficial tumor cells, and subsequently released positively charged Cur can progressively infiltrate the cell through electronic interaction, improving permeability [16]. The system has good morphology, structure, stability, and biocompatibility, and can efficiently enter tumor cells through folate receptor-mediated targeting. Under the stimulation of near-infrared laser, the rapid release of drugs and high temperature are achieved, to realize the synergistic multi-drug chemo-photothermal therapy for tumor cells. This system shows excellent anticancer effects both in vitro and in vivo and reduces the damage to normal tissues.

3.2.3. Stimuli-responsive targeting

Stimuli-responsive targeting refers to the targeting of nano-targeted drug systems on specific organs or disease sites according to the external or internal stimuli that can trigger the release of drugs from MOFs [14]. Stimulus-responsive DDSs have the advantages of timeliness of administration and excellent dose controllability, thereby improving the delivery effect and minimizing side effects.

At present, the targeted release of dual or multiple responses is becoming the focus of related research. For example, tumor cells often have abnormal pH and redox potential in their microenvironment or intracellular compartments. Tumor cells have acidic extracellular pH due to the production of lactic acid by glycolysis. They also have high intracellular glutathione (GSH) levels due to the activation of antioxidant pathways. These conditions can be used as stimuli for triggering the release of drugs from MOFs that are sensitive to pH or redox potential [14]. Li et al. recently prepared ZIF-8 nanoparticles using one-step synthesis and fabricated ZIF-2-PDA-PEG with pH and photothermal response loaded with baicalein (BA) using surface adsorption [15]. Hemolysis test showed that the prepared nanocellulars exhibited excellent biocompatibility. The investigators found BA uptake by tumor cells and ph-responsive controlled release of BA triggered by the acidic microenvironment of tumor cells and concluded that the tumor suppression efficiency of BZPP and NIR combined treatment was superior to that without 808 nm irradiation, indicating a synergistic PTT-CT effect of BZPP.

4. Applications of MOFs as DDS in Tumor Targeted Treatments

MOFs can be loaded with various drug molecules or biomolecules that can target tumor cells and induce antitumor effects. Some examples of drugs and biomolecules that have been loaded into MOFs are as follows.

4.1. Drugs

MOFs can be loaded with various drug molecules, such as doxorubicin hydrochloride, 5-fluorouracil, indocyanine green, caffeine, cidofovir, folic acid, calcein, curcumin. These drugs can have different mechanisms of action, such as DNA intercalation, antimetabolism, photothermal therapy, anti-inflammation, antiviral, targeting, fluorescence, or anti-oxidation [16]. MOFs can improve the loading capacity, stability, and release control of these drugs, as well as enhance their targeting and therapeutic efficacy [7].

Oleanolic acid (OA) has pharmacological activities such as hepatoprotective, hypoglycemic, lipid-lowering, antiviral, anti-tumor, and bacterial activities. It can act at different stages of tumorigenesis and inhibit tumor differentiation and metastasis. However, its hydrophobic nature is limited due to its oral efficacy and clinical application. Zhang et al. synthesized a novel hollow nanocages MOF-5 [17]. Reported the synthesis of the MOF-5 with a 3D hollow structure by solvothermal method. They used zinc as a fulcrum, terphenyl acid and five vinylamine organic ligands as a bridge, and input polyvinylpyrrolidone (PVP) as a structure guide. The human ovarian cancer SK-OV-3 was used to study the drug loading and release, cytotoxicity, and cellular uptake, results showed that OA-coated MOF-5 showed efficient drug release in cancer cells and significantly increased cell growth inhibition efficiency. Fe-MOF is a metal-organic framework material based on iron and organic ligands with the characteristics of porosity, high SSA, tunability, and biocompatibility, which can be used in DDS, can target specific cells or tissues by introducing functional groups or combining with other nanomaterials to improve the selectivity and efficacy of drugs. Moreover, it can control the release of drugs under external stimuli including pH, temperature, illumination, as well as magnetic fields, to achieve a precise response to the tumor microenvironment or pathological state. Ahmed et al. synthesized a dual-responsive Fe-MOF by the microwave-assisted method using $FeCl_3 6H_2O$ as the metal cluster and 2-aminoterephthalic acid (NH_2-BDC) as the organic linker (namely NH_2-Fe-BDC) with (DOX) loaded [18]. In addition, PEG-FA was coupled to the surface of MOF to serve as a targeting ligand for tumor biomarkers using post-synthetic modification technology. DOX was successfully loaded into the MOF and the efficiency of the MOF was approximately 97% with a load capacity of 14.5 wt%, the cumulative DOX release efficiency of the US was 44.4% and 90%, respectively. Experiments using FTR, TGA, and DLS analysis showed that the DDS had good thermal stability and suitable particle size. Ultrasound stimulation enhanced the release of DDS, and PEG-FA enhanced the biocompatibility and tumor targeting.

4.2. siRNA

siRNA is a type of RNA interference (RNAi) that can silence the expression of specific genes by degrading their mRNA. It can be used to target disease-related genes in cancer, such as oncogenes, tumor suppressors, or drug resistance genes which can be designed with site-specific chemical modifications using solid-phase synthesis, conjugated with targeting ligands of antibodies, peptides, or aptamers, to improve its specific delivery to tumor cells [19,20]. It has been explored for various types of cancer treatment, such as chemotherapy, immunotherapy, gene therapy, or combination therapy, can modulate the expression of genes involved in tumor growth, angiogenesis, metastasis, apoptosis, immune evasion, or drug response, has shown promising antitumor effects and safety profiles in preclinical and clinical studies [19,21]. Several siRNA therapeutics have been approved or are under development for cancer treatment. For example, siRNA targeting tumor necrosis factor-alpha (TNF-α) is a small interfering RNA that can silence the expression of TNF-α, a pro-inflammatory cytokine that promotes tumor growth and angiogenesis [20]. It can be loaded into

MOFs composed of tannic acid and iron ions by sonication. The MOFs can scavenge radicals and protect the siRNA from degradation as well as target tumor cells by recognizing the overexpressed folate receptors on their surface [16].

Cisplatin (DDP) is a mostly used chemotherapeutic treatment drug for hepatocellular carcinoma (HCC). Due to the serious off-target effects leading to some adverse effects and severe systemic toxicity, the clinical applications are limited, it even produces Multidrug resistance (MDR), resulting in a poor response in liver cancer patients to drugs, which greatly limits its application [22]. NOR1 participates in many biological processes including cell growth, differentiation, apoptosis, inflammation, and metabolism, showing great potential for cancer targeted therapy, and is over-expressed in HCC related to DDP resistance. Huang et al. structured a tumor-targeting, pH-stimulated drug/shRNA codelivery system (AR-NADR) [22]. They demonstrated that AR-NADR can efficiently deliver DDP and NOR1 shRNA to HCC cells and release them under acidic pH and near-infrared laser irradiation. The released DDP can kill the cancer cells by inducing DNA damage, while the NOR1 shRNA can inhibit the expression of NOR1, which enhances the sensitivity of cancer cells to DDP, and they evaluated the anti-HCC efficacy and biocompatibility of AR-NADR in vitro and in vivo, using a HepG2/DDP cell model and a tumor model. The results show that AR-NADR can significantly inhibit the growth of HCC cells and tumors while reducing the toxicity and adverse effects of DDP. So, AR-NADR is a promising strategy to overcome cisplatin resistance in HCC by achieving targeted delivery and synergistic combination therapy of DDP and NOR1 shRNA.

4.3. Peptides

Peptides are short chains of amino acids that have various biological functions, such as hormones, neurotransmitters, enzymes, or antibodies. They can act as anticancer agents by targeting specific receptors or mechanisms in tumor cells, such as apoptosis, angiogenesis, cell cycle regulation, or drug resistance [23]. Peptide therapy involves the injection of peptides that directly kill tumor cells or sensitize them to other therapies by disrupting their membranes, inhibiting their enzymes, activating their death receptors, or blocking their signaling pathways[19, 23]. Peptides can be loaded into MOFs and MOFs can protect peptides from degradation, enhance their stability and solubility, and control their release [23].

MG-132 is a peptide that can inhibit the proteasome, a complex of enzymes that degrades proteins in the cell. The proteasome participates in many cellular processes including cell cycle, apoptosis, and inflammation. By blocking the proteasome, MG-132 can affect these processes and induce various biological effects. One of these effects is the sensitization of cancer cells to ionizing radiation, which is a common treatment for cancer. MG-132 can enhance the radiosensitivity of cancer cells by interfering with the DNA damage response, the cell cycle arrest, and the apoptotic pathways. MG-132 can also inhibit the activation of NF-κB, a transcription factor that regulates the expression of genes related to immunity and inflammation. NF-κB is often overexpressed or activated in cancer cells and contributes to their survival, proliferation, and resistance to therapy. Therefore, MG-132 can potentially be used as an adjuvant agent to improve the efficacy of radiotherapy for cancer treatment. Yang et al. first synthesized an amino-modified MIL-88 with Fe as the central atom and then coated sequentially using MG132 and macrophage membrane [24]. Studies have found that MG132 can inhibit the proteasome, leading to changes in the ubiquitination and phosphorylation of some important proteins in colorectal cancer cells, thereby affecting epigenetic regulation, including histone modification and DNA methylation. These epigenetic changes can inhibit the proliferation, migration, and invasion of colorectal cancer cells, and enhance the sensitivity of colorectal cancer cells to radiotherapy and chemotherapy. The inhibitory effect of MG132-Loaded Fe-MOF on colorectal cancer metastasis was verified in a mouse model, and the possible molecular mechanism was analyzed. This novel nanocarrier can effectively improve the stability and bioavailability of MG132 while exploiting its influence on epigenetic regulation to improve the efficacy of colorectal cancer treatment.

5. Conclusion

MOFs have broad application prospects as new targeted drug carriers for tumor therapy, especially nano-MOFs, whose unique properties have become a recent research hotspot. Biomimetic MOFs covered with various cell membranes have higher biocompatibility than traditional MOFs. At present, the development of nanoscale multiple stimulus-responsive MOFs with active targeting is becoming a new trend. Some small molecule drugs, such as siRNA can make tumor gene silencing have higher specificity and better effect, the latest research used anticancer peptides also have better tumor cytotoxicity than monoclonal, simpler, and more convenient editing feasibility, the use of biological small molecule drugs to treat cancer is becoming a new research center. However, the pharmacokinetic mechanism of MOFs in vivo is still insufficiently studied, and its toxicity may be related to the reaction of compounds when they are degraded. It is still necessary to reduce the production cost of MOFs. How to ensure the repeatability of MOFs while using green synthesis, and how to customize different modification strategies for different tumor cells according to different drugs or biological macromolecules are still problems. At the end of the day, using machine learning and molecular simulation to study the metabolic and dynamic chemical structure of MOFs in vivo may lead to new practical guidance.

References

[1] Cancer - World Health Organization (WHO). (2022). Retrieved July 2, 2023.

[2] Cancer statistics, 2020 - PubMed. (2020). CA: A Cancer Journal for Clinicians, 70(1), 7–30.

[3] Liu W, Yan Q, Xia C, et al. Metal Organic Frameworks as Drug Targeting Delivery Vehicles in the Treatment of Cancer. Pharmaceutics. 2020; 12(3):232.

[4] Li, S., Zhang, Y., Xu, J., et al. BioMOF-Based Anti-Cancer Drug Delivery Systems. Nanomaterials, 2023, 13(5), 953.

[5] Wang, Z., Liu, J., & Zhou, HC. Metal-Organic Frameworks for Biomedical Applications: Current Status and Future Perspectives. Advanced Materials, 2020, 32(6), 1906068.

[6] Liu J, Qutub S, Khashab NM. Biocompatibility and biodegradability of metal-organic frameworks for biomedical applications. J Mater Chem B. 2021; 9(30):5925-5944.

[7] Lawson HD, Walton SP, Chan C. Metal–Organic Frameworks for Drug Delivery: A Design Perspective. ACS Appl Mater Interfaces. 2021; 13(6):7004-7020.

[8] Li C, Zheng L, Yang Y, et al. Metal–Organic Framework Nanocarriers for Drug Delivery in Biomedical Applications. Nano-Micro Lett. 2020; 12:103.

[9] Liang K, Ricco R, Doherty CM, et al. Biomimetic mineralization of metal-organic frameworks as protective coatings for biomacromolecules. Nat Commun. 2015; 6:7240.

[10] Saeb MR, Rabiee N, Mozafari M, Mostafavi E. Metal-Organic Frameworks (MOFs)-Based Nanomaterials for Drug Delivery. Materials (Basel). 2021; 14(13):3652.

[11] Cai M, Chen G, Qin L, et al. Metal Organic Frameworks as Drug Targeting Delivery Vehicles in the Treatment of Cancer. Pharmaceutics. 2020; 12(3):232.

[12] Wang Z, Li Z, Ng M, Milner PJ. Rapid mechanochemical synthesis of metal-organic frameworks using exogenous organic base. Dalton Trans. 2020; 49(45):16238-16244.

[13] Han, Y., Yang, H., & Guo, X. Synthesis Methods and Crystallization of MOFs. IntechOpen, London, UK. 2020.

[14] Munerato MS, Biguetti CC, da Silva RBP, et al. Inflammatory response and macrophage polarization using different physicochemical biomaterials for oral and maxillofacial reconstruction, Materials Science and Engineering: C, 2020, 107: 110229.

[15] Shanshan Gao, Ruihong Lv, Ning Hao, et al. Fabrication of pH/photothermal-responsive ZIF-8 nanocarriers loaded with baicalein for effective drug delivery and synergistic chem-photothermal effects,Colloids and Surfaces A: Physicochemical and Engineering Aspects,2023,668: 131401.

[16] Shasha Yang, Zhijuan Zhao, et al., Engineering Bio-MOF/polydopamine as a biocompatible targeted theragnostic system for synergistic multi-drug chemo-photothermal therapy, International Journal of Pharmaceutics, 2022, 623: 121912.

[17] Lei Zhang, Yan Chen, Rui Shi, et al., Synthesis of hollow nanocages MOF-5 as drug delivery vehicle to solve the load-bearing problem of insoluble antitumor drug oleanolic acid (OA), Inorganic Chemistry Communications, 2018, 96, 20-23.

[18] Ahmed Ahmed, Abdollah Karami, et al., pH and ultrasound dual-responsive drug delivery system based on PEG–folate-functionalized Iron-based metal–organic framework for targeted doxorubicin delivery,Colloids and Surfaces A: Physicochemical and Engineering Aspects,2021,626: 127062,

[19] Tong PH, Zhu L, Zang Y, et al. Metal–organic frameworks (MOFs) as host materials for the enhanced delivery of biomacromolecular therapeutics. Chem Commun. 2021; 57(93):12098-12110.

[20] Guo L, Zhong S, Liu P, et al. Radicals Scavenging MOFs Enabling Targeting Delivery of siRNA for Rheumatoid Arthritis Therapy. Small. 2021; 17(8): e202202604.

[21] Zhang Y, Zhang X, Wang F, et al. Functional peptides for siRNA delivery. Adv Drug Deliv Rev. 2016; 110-111:157-168.

[22] Huang, Y., Kou, Q., Su, Y. et al. Combination therapy based on dual-target biomimetic nano-delivery system for overcoming cisplatin resistance in hepatocellular carcinoma. J Nanobiotechnol, 2023 21, 89.

[23] Li CM, Haratipour P, Lingeman RG, et al. Novel Peptide Therapeutic Approaches for Cancer Treatment. Cells. 2021; 10(11):2908.

[24] Bu, Z., Yang, J., Zhang, Y., et al., Sequential Ubiquitination and Phosphorylation Epigenetics Reshaping by MG132-Loaded Fe-MOF Disarms Treatment Resistance to Repulse Metastatic Colorectal Cancer. Adv. Sci. 2023, 2301638.