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Review

Covalent organic framework-based nanoplatforms with tunable mechanical properties for drug delivery and cancer therapy

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ABSTRACT

Covalent organic frameworks (COFs) are emerging crystalline porous materials composed of covalently linked and periodically arranged organic molecules, which exhibit mechanical properties mediated by structural diversity. Meanwhile, the tunable mechanical properties of COFs have been widely applied in drug delivery and cancer therapy. Herein, we first summarize the regulation strategies of COFs with different mechanical strengths, such as structural dimensions, pore sizes, and host–guest interaction forces. Then, the remarkable achievements of COFs with different mechanical properties in drug delivery and cancer therapy in recent years are introduced. Finally, the mechanical strength regulation of COFs and the remaining challenges for biomedical applications are presented. This review provides a more comprehensive understanding of the application of COFs systems with tunable mechanical properties in the field of biomedicine, and promotes the development of interdisciplinary research between COFs materials and nanomedicine.

1. Introduction

Cancer has become one of the most serious health threats worldwide, causing millions of deaths annually from cancer-related diseases [1]. To date, the clinical treatment modalities are still dominantly chemotherapy, radiotherapy, surgical treatment, which suffer from high postoperative recurrence rates, severe toxic and side effects, unpredictable multidrug resistance [2–4]. Thus, researchers have made extensive efforts in nano-medicine to improve cancer treatments [5]. In recent decades, many different types of nanoparticles, including liposomes [6], mesoporous silica [7,8], quantum dots [9], metal nanoparticles [10], polymeric micelles [11], carbon-based materials [12], MXenes [13] and metal–organic hybrid nanomaterials [14,15], have been prepared for this purpose. However, all nanomaterial-based nanomedicines exist their limitations, such as low drug loading capacity, and undesirable long-term toxicity [16,17]. The design of new nanomedicine with high loading capacity, good biocompatibility and great therapeutic effects remains challenging.

As an emerging class of crystalline porous materials, covalent-organic frameworks (COFs) have been widely applied in various fields, such as gas storage and separation [18,19], sensing [20,21], catalysis [22,23], energy [24,25], optoelectronics [26,27], and others. In 2015, Yaghi et al. [28] first reported the COFs, which were synthesized by covalent bonds between molecular building blocks. During the past decades, various building blocks and synthetic methods were continuously developed to prepare COFs with different properties. The structure of COFs consists of periodically arranged molecular building blocks, mainly including light elements (C, H, O, N, and B) [29]. And COFs have many impressive characteristics, such as low density, large specific-surface area and porosity, adjustable pore size and geometry [30–32], highly efficient active sites, precisely tailored molecular building blocks [33,34], and tunable mechanical properties [35], as well as unique electronic and optical functions. Besides, the size of COFs can also be scaled down to nanoscale for nanomedicine-related applications in drug delivery and cancer therapy [36,37].

Nanosized COFs not only possess the properties of traditional nanoparticles, such as good dispersion, small volume and high bioavailability, but also retain the crystalline, porous features and tunable mechanical properties of COFs materials. Therefore, these properties make nano-COFs ideal drug carriers and nanomedicines for drug delivery and tumor therapy, endowing therapeutic agents with high loading efficiency, extending half-life time, enhanced cell uptake efficiency and cancer tissue enrichments, and minimal side effects [38]. In this review,

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we present the most recent progress of COFs with different mechanical characteristics as nanocarriers for drug delivery and cancer treatment (Table 1). First, the mechanical property regulation method of COFs is introduced. Next, COFs with various mechanical characteristics as nanocarriers for the delivery of chemotherapeutics, nucleic acids, proteins and multiple drugs are summarized. Then, the use of formulated COFs with unique mechanical structures for various strategies of tumor therapy, including chemotherapy, phototherapy, immunotherapy, catalytic therapy and synergistic therapies, is discussed. Finally, perspectives and challenges are summarized in anticipation that this review can provide guidance for future researchers to engineer and explore COFs with precise mechanical strength as novel drug delivery systems for antitumor applications.

2. Mechanical properties regulation of COFs

The properties of COFs are determined by the reactive and functional groups of their building blocks in their structures, such as mechanical strength mediated by rigid and flexible structures. Besides, the pore size and post-synthetic modifications of COFs can also affect their mechanical properties (Fig. 1). So far, the covalent bond connecting groups mainly include -B-O-, -C-N-, -C-C-, and -C-O-. In this section, mainly focus on the regulation strategies of the mechanical properties of COFs materials, which can be achieved through the structure, pore size and host–guest interaction [39,40].

2.1. Structure

The structure of COFs materials mainly includes two-dimensional (2D), three-dimensional (3D) and woven networks [52,53]. The morphologies of COFs have been reported in different shapes such as sheets, spheres, foams, cubes, rectangular prisms, and so on [54,55]. 2D planar COFs typically exhibit rigid structures and poor water dispersibility. 3D COFs are usually composed of non-planar building blocks, which exhibit some flexible properties [56]. COF materials with woven networks have good flexible properties, which have great application potential in the field of wearable devices [57]. Therefore, the planar and non-planar 2D and 3D structures of COFs materials can be adjusted to suit different applications. In 2015, Dichtel et al. [58] reported a series of boronate-based 2D COFs, which exhibited high thermal stability (500–600 °C). However, these boronate-based COFs were highly unstable toward trace of acid, alkali, alcohols and so on. The test results showed the degradation rate of 50% within 11 s and 90% in 1 min. To improve the hydrolytic stability of boric acid-based COFs, different strategies had been reported to adjust their mechanical properties by changing porosity and crystallinity. In 2018, Jia and co-workers [59] reported water-dispersible boric acid-based COFs (COF-1) as a biodegradable carrier for *in vivo* drug delivery. This nanosystem reduced rigidity and pore size, and enhanced stability through PEG-modified monofunctional curcumin derivatives assembly, amino functionalization, and chemotherapeutic drug loading, thereby efficiently delivering drugs to tumor sites and exerting good anti-tumor effects. In 2022, Zhao et al. [60] reported two new biomimetic COFs, NUS-71 and NUS-72, which were constructed from ellagic acid and two triboric acid ligands of different lengths, thus showing different structure-oriented ethylene affinities for carbon dioxide.

Table 1
Recent advances of COFs in drug delivery and cancer therapeutics.

Covalent linkage	COF material	Mechanical property	Biomedical application	Ref.
Imine	PI-COF-4, PI-COF-5	Flexible	Drug delivery	41
	PI-2-COF, PI-3-COF	Rigid	Drug delivery	42
	5-FU@TpASH-FA	Flexible	Drug delivery/ Chemo	43
	CuS@COFs-BSA-FA/DOX	Flexible	drug delivery/PTT	44
	F68@SS-COFs	Flexible	Drug delivery/ Chemo	45
	DiSe-Por-DOX	Flexible	drug delivery/PDT	46
	COF-808, COF-909	Rigid	PDT	47
	COF@ICG@OVA	Flexible	PTT/Immuno	48
	COF-606	Rigid	PDT/Immuno	49
Boronate ester	FITC-PEG-COF@Ins-GO_X	Rigid	Drug delivery	50
	ICG@COF-1@PDA	Flexible	PDT/PTT	51

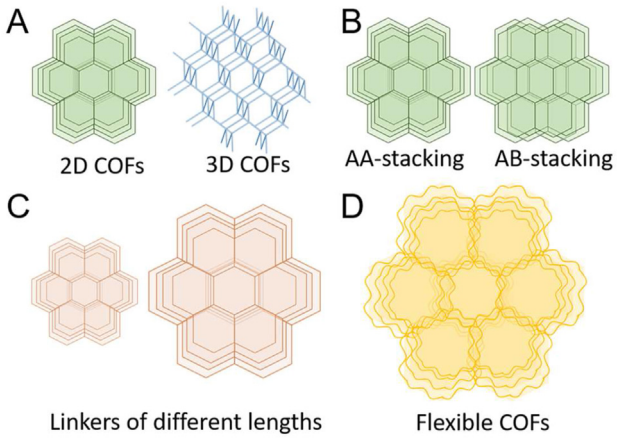

Fig. 1. Regulation strategies for the mechanical properties of COFs. (A) Structure of COFs in different dimensions (2D and 3D). (B) Layer-to-layer stacking of COFs structures in eclipsed (AA) stacking and staggered stacking. (C) Regulation of different linker lengths. (D) Synthesized from flexible building blocks.

2.2. Pore size

The pore size of COFs materials also affects their mechanical properties. Pore size of COFs materials can be tuned by varying lengths of linkers, which further determines their porosity. Therefore, the range of pore size exists micropores (<2 nm) and mesopores (2–50 nm). At present, the smallest pore size of COFs material (COF-6) has a pore size of 8.6 Å [61], and the largest pore size of COFs material (PC–COF) has a pore size of 5.8 nm [62]. The porosity of COFs depends not only on its pore size and geometry, but also on the arrangement of pores in the framework, which is further controlled by the way the layers are stacked. If all the atoms of adjacent layers are directly on top of each other, overlapping (AA) stacking results, while if the three connected vertices of a hole are located at the geometric centers of holes in adjacent layers, staggered (AB) stacking results. For instance, in 2020, Dai et al. [63] advanced a tandem transformation strategy for the preparation of covalent triazine framework with different mechanical features. Covalent triazine framework with eclipsed AA stacking structure exhibits more stable mechanical properties. In 2021, Cao and co-workers [64] prepared three COF isomers with different stacking pattern (eclipsed AA, staggered AB, and ABC stacking), resulting in different pore sizes. The ABC stacked COFs isomer had small pores but good stability.

2.3. Interaction force

In addition, the interaction force can also significantly regulate the mechanical properties of COFs, such as hydrogen bond forces, van der Waals forces. In 2011, Jiang et al. [65] introduced pore surface engineering into COF chemistry, which could not only regulate the pore size, but also change the interaction force, so that COFs had more stable mechanical properties. In 2023, Jiang and colleagues [66] constructed a series of hydrazone-linked COFs involving noncovalent hydrogen bonds, where the hydrogen–bonding interaction played critical roles in the COF mechanical properties. This work had demonstrated the regulation of structural flexibility and mechanical properties, the reversible transition between order and disorder, and the variety of host–guest interactions.

3. Mechanically tunable COFs for drug delivery

In the past few decades, nano-drug delivery system (DDS) has been developed rapidly and achieved many results. Nanomedicine is mainly based on organic, inorganic and composite nanomaterials, such as liposomes, polymer nanoparticles, dendrimers, mesoporous silica, metal nanoparticles, and metal–organic hybrid nanomaterials [67,68]. Furthermore, the mechanical properties of nanoparticles significantly affect nanomedicine delivery processes *in vivo*, including blood circulation, tumor enrichment, deep penetration, cellular uptake, and drug release. Nanoscale COFs have been widely studied in the field of drug delivery and anti-tumor due to their tunable mechanical properties, large specific surface area, high porosity, tunable pores, diverse functions, and easy modification. For example, by rationally adjusting the pore size and mechanical properties, the drug loading, cargo type, release rate and tumor treatment outcome of COFs can be controlled within a certain range to meet different needs. In this section, we mainly focus on recent advances in biomedical applications of COFs with different mechanical properties for chemotherapeutics drugs, nucleic acid, and protein delivery.

3.1. Chemotherapeutic drugs

Currently, chemotherapeutic drugs such as doxorubicin (DOX), cisplatin, paclitaxel, and 5-fluorouracil (5-FU) are still the main means of clinical cancer treatment. However, they suffer from low solubility, short half-life time, non-specific distribution and high toxic side effects., which affect their applications in cancer treatments [69,70]. In 2015, Yan et al. [41] synthesized two new flexible three-dimensional (3D) COFs (termed PI-COF-4 and PI-COF-5) with different pore sizes achieved by adjusting the size of the flexible molecular units. Both COFs showed good biocompatibility and high surface area (up to 2403 $m^2 g^{-1}$), endowing them with high ibuprofen loading efficiency and good release control (Fig. 2A). In 2016, Zhao et al. [42] reported two porous rigid 2D COFs with good stability and biocompatibility as drug nanocarriers, namely PI-2-COF and PI-3-COF. First, they systematically investigated the effect of pore size on the drug loading of captopril, ibuprofen and 5-FU with different molecular sizes. Then, as a typical drug, 5-FU performed a high drug loading (up to 30 wt%) and could be completely released *in vitro*, thus playing a good killing effect on MCF-7 tumor cells (Fig. 2B). From the above studies, it can be seen that the drug release rate of flexible COFs with smaller pores is faster. Besides, the 3D network of COFs materials with interspersed pores also exhibits efficient drug loading and sustained release properties.

An ideal drug loading strategy can not only improve the loading efficiency but also enhance the mechanical strength of COFs materials. In 2019, Lin et al. [71] reported a novel strategy to efficiently load DOX. Briefly, DOX was successfully encapsulated *in situ* into rigid COF-based nanocarriers *via* a one-pot method during preparation, which greatly simplified the drug loading process, increased the loading efficiency to 32.1 wt% and enhanced mechanical properties. *In vitro* and *in vivo* experiments showed that this nano-DDS exhibited effective cellular uptake effects, pH-sensitive release properties, good biocompatibility and enhanced antitumor efficacy. Bhaumik et al. [72] loaded cisplatin into the void spaces of rigid 2D crystalline COF nanomaterials through their interaction force and efficiently delivered drug against metastatic breast cancer cells. *In vitro* experiments demonstrated that this nano-DDS exhibited high drug loading efficiency and good therapeutic effect on triple negative breast cancer cells. In 2020, Huang et al. [73] facilely prepared flexible hollow COF nanospheres by heterogeneous nucleation growth. The obtained hollow COF nanoparticles could effectively encapsulate DOX due to its high specific surface area and porosity, and

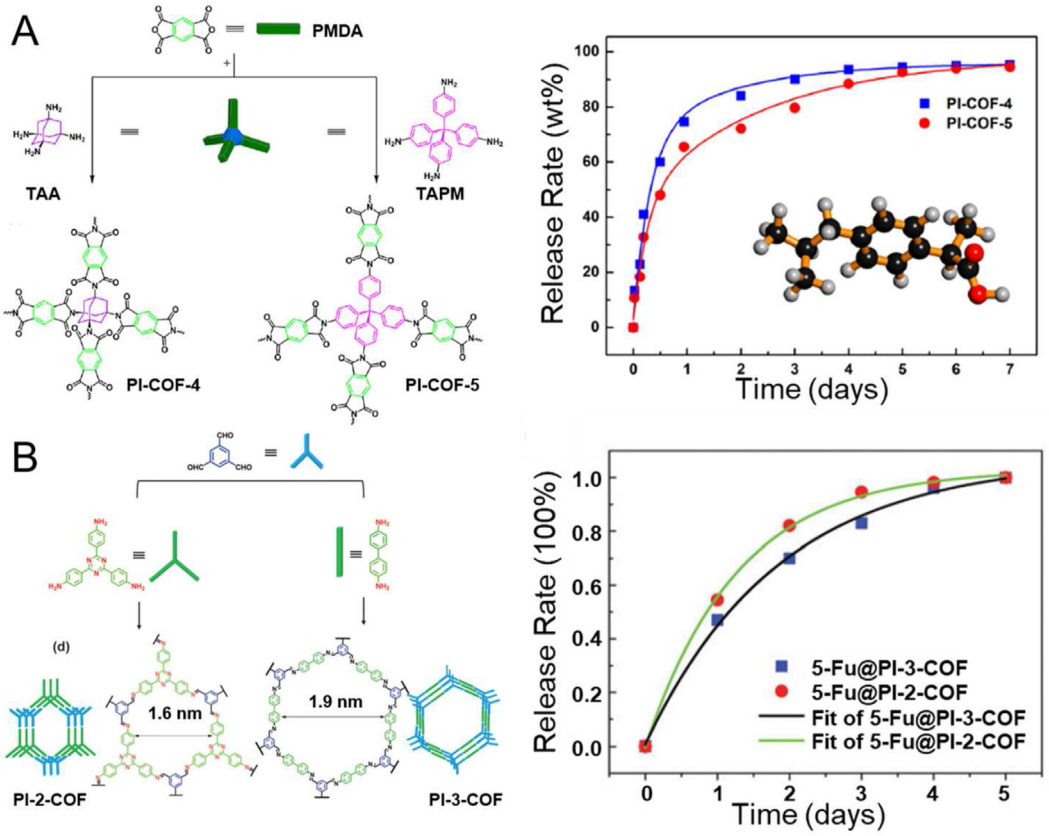

Fig. 2. COFs-based materials for drug delivery. (A) The synthesis process of two types of 3D porous crystalline PI-COFs and drug delivery performance of ibuprofen-loaded COFs. Adapted with permission [41]. Copyright © 2015, American Chemical Society. (B) Preparation and drug delivery performance of PI-2-COF and PI-3-COF with 2D structures. Adapted with permission [42]. Copyright © The Royal Society of Chemistry 2016.

performed a pH-sensitive release profile because of the acid-labile degradation. In addition, the loading of DOX could enhance the mechanical features and stability, endowing them with good antitumor ability *in vivo*. As drug carriers, COFs can effectively deliver drugs, and their tunable mechanical properties facilitate access to nano-delivery systems with excellent stability and specific degradation.

3.2. Nucleic acids and proteins

Nucleic acids, including deoxyribonucleic acid (DNA) and ribonucleic acid (RNA), are powerful laboratory tools that can efficiently inhibit the expression of targeted genes. However, their characteristics such as easy degradation, low transmembrane uptake, poor targeting, and potential safety hazards greatly limit the clinical application of nucleic acid drugs. Surface modification of COF nanoparticles with nucleic acids could increase their colloidal stability and interaction forces by providing steric and electrostatic hindrance to aggregation [74]. In 2021, Tang and co-workers [75] reported the rational design of a smart nucleic acid-gated COF nanosystem for cancer-specific imaging and microenvironment-responsive drug release (Fig. 3A and B). Cy5 dye-labeled single-stranded DNA (ssDNA) for mRNA recognition was adsorbed on the surface of DOX-loaded COF NPs. DOX loaded in the pores of COF NPs could strengthen the interactive force, as well as enhance their mechanical properties and stability, while the densely coated ssDNA could prevent the leakage of DOX from COF NPs and perform flexible properties. And *in vitro* experiments showed a tumor cell-specific delivery effect. This work offered a universal nanoplatform for cancer theranostics and a promising strategy for regulating the mechanical force between COFs and biomolecules. In 2020, Jia et al. [50] developed a glucose- and pH-based dual-response mechanical property smart-switchable insulin nano-COF carrier *via* Brønsted and Lewis-type (N:→B) complexation. In the hyperglycemic state, glucose was converted into gluconic acid under the catalysis of oxidase, and then ins were released after degradation due to the instability of boroxy-COFs under acidic conditions. Through the dual response of hyperglycemia and pH, COFs composites could effectively reduce blood glucose content to maintain normal blood sugar levels. In conclusion, due to the modifiability and structural diversity of COFs materials, they can not only protect easily degradable substances, but also achieve controlled release. Furthermore, this strategy can obtain nanosystems with *in situ* switching of mechanical properties.

Besides, COFs can also be used as delivery vehicles for a variety of drugs to achieve variable mechanical properties and synergistic effects. In 2022, Huang et al. [76] designed a space-time conversion carrier based on COF-coated mesoporous silica nanospheres (MSNs) and interlayered polyethyleneimine (PEI) layers with different mechanical properties for loading different cargos. Therefore, the programmed drug delivery could effectively mediate the sequential release of individual drugs, work synergistically with changes in nanoparticle surface charge, pull the extracellular matrix and inhibit drug efflux, thereby enhancing the chemotherapy effect of pancreatic cancer. This work suggested a space-time conversion strategy to achieve programmed multi-drugs delivery and represented a new avenue to the treatment of pancreatic carcinoma by overcoming extracellular matrix and drug reflux barriers.

4. COFs with different mechanical properties for cancer treatment

According to statistics, in 2021 alone, the number of new cancer patients in the world had reached about 19.29 million, and about 9.96 million people died of cancer-related diseases. This data suggests that effective cancer treatments are urgently needed [77]. At present, chemotherapy is still the mainstay of clinical cancer treatment. Immunotherapy is also emerging due to its specificity and high efficiency, but the high cost in the initial stage limits its development. In recent years, phototherapy, including photothermal and photodynamic therapy, has been widely studied due to its low invasiveness, high spatial selectivity, low toxicity and side effects, and broad-spectrum antitumor properties [78,79]. The following is an introduction to the research progress of regulating the mechanical properties of COFs materials in tumor therapy.

4.1. Chemotherapy

Traditional chemotherapy drugs lack tumor-specific targeting and can be distributed in various tissues and organs throughout the body, resulting in serious side effects and inefficient treatment. At least to some extent, COFs as nanocarriers for chemotherapy with high loading capacity and good biocompatibility can solve these problems. In addition, the tunable mechanical properties and pore sizes of COFs are beneficial for drug delivery into tumor cells and exert effective antitumor effects. In 2019, Chen et al. [80] reported a water-dispersible nano-sized COFs system prepared by a cyanine-assisted exfoliation strategy. This

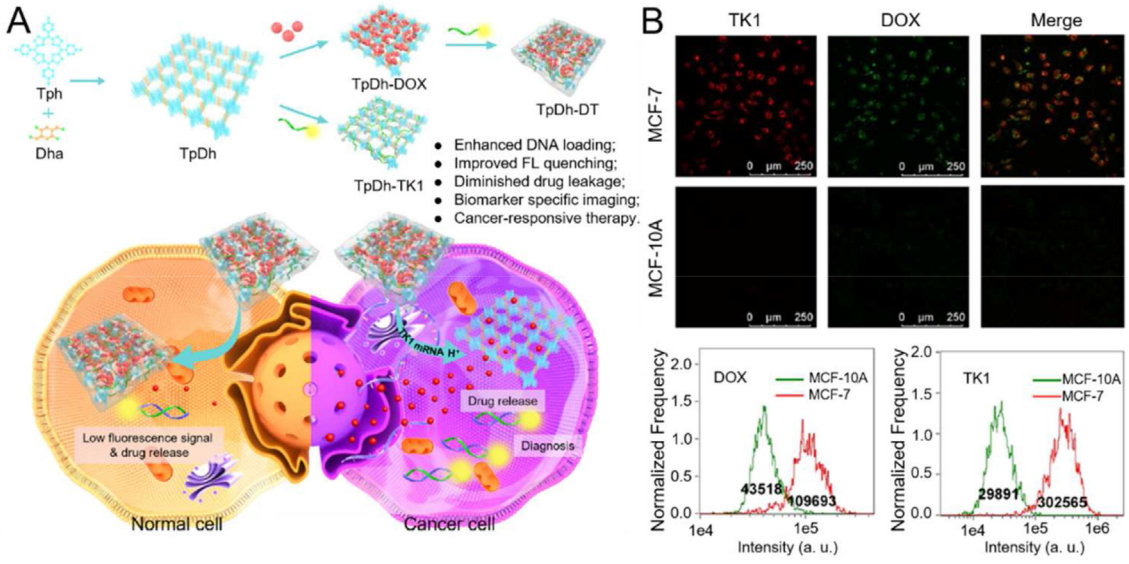

Fig. 3. Nucleic acids delivery. (A) A scheme for smart nucleic acid-gated COF flexible nanosystem for cancer-specific imaging and microenvironment-responsive drug release and (B) its delivery efficiency *in vitro*. Adapted with permission [75]. Copyright © 2021, American Chemical Society.

nanosystem was negatively charged and had flexible mechanical intensity, which was beneficial for improved blood circulation, enhanced permeability and retention-mediated tumor-targeting delivery therapy *in vivo*. The COFs-based nanocomposite could be further used as a drug delivery vehicle for loading the anticancer cis-aconityl-doxorubicin (CAD) prodrug. *In vitro* and *in vivo* experiments showed that the nanocomposites exhibited high drug-encapsulated efficiency and good anticancer effects.

Despite the afore-mentioned studies, COFs materials with tunable mechanical strength were promising in chemotherapeutic drug delivery for cancer chemotherapy. Their poor hydrophilicity, nonexistent targeting ability and premature drug leakage usually led to lower cellular uptake efficiency, severe systemic toxicity and discounts drug release at the target site, resulting in multidrug resistance and anti-tumor failure [81]. Therefore, it was urgent to develop COFs-based nanocarriers with strong targeting ability, good dispersion and stability, as well as precise release in tumor tissues. In 2017, Banerjee et al. [43] reported a targeted 5-FU@TpASH-FA system prepared by judicious postsynthetic modification steps. The postsynthetic modification not only yielded the desired cancer-cell targeting functions, but also facilitated exfoliation into COFs-based nanosheets with better flexibility and adjusted their pores for drug leakage. The obtained folic acid conjugated COFs platform could efficiently deliver 5-FU and continuously release drugs to the folate receptor overexpressed breast cancer cells through receptor-mediated endocytosis, which led to an obvious cancer death *via* apoptosis. In 2023, Li and colleagues [44] established a multifunctional nanoplatform (CuS@COFs-BSA-FA/DOX) based on COFs engineered with copper sulfide nanoparticles to synergize photothermal therapy (PTT), chemotherapy and chemodynamic therapy (CDT). The flexible PEI and BSA-FA layers were coated on the surface of CuS@COFs, which not only increased the cancer-targeting efficiency but also prevented the nonspecific release of DOX from CuS@COFs. The acidic tumor microenvironment and near-infrared light-mediated photothermal effect triggered the release of DOX for chemotherapy and simultaneously enhanced the CDT efficiency of CuS@COFs, thereby enhancing the PTT/chemotherapy/CDT synergistic effect. A variety of mechanical properties can satisfy tumor-specific responses, enabling efficient precision drug delivery and tumor therapy.

The tumor microenvironment (TME) can not only adjust the mechanical properties of COF to achieve precise tumor treatment, but also regulate the strength of the cell nuclear mechanics to enhance the antitumor effect. Compared with normal tissues or cells, TME exists some unique physical and chemical properties, such as acidic pH, hypoxia, reducing potential (reduced glutathione), high concentration of reactive oxygen species, and specific enzymes. Therefore, based on the characteristics of TME, intelligent responsive nanosystems can be designed and developed to precisely regulate the mechanical properties and achieve precise tumor therapy. In 2020, Zhang et al. [45] developed a facile strategy to prepare polyethylene glycol (PEG)-modified flexible redox-responsive nanoscale COFs (named F68@SS-COFs) for efficiently loading and delivering DOX by use of FDA-approved pluronic F68 and commercially available building blocks (Fig. 4A). The obtained F68@SS-COFs with moderate flexibility, controlled size, high stability, and good biocompatibility could not only achieve a very high DOX-loading content (about 21%) and very low premature leakage at physiological conditions but also rapidly respond to the tumor intracellular redox environment and efficiently release DOX to kill tumor cells. In 2022, Zhou et al. [46] developed a novel combined chemo/-photothermal/chemodynamic therapy using a pH/GSH/photo triple-responsive 2D-flexible COF drug carrier for passive target treatment of tumors with extraordinarily high efficiency. This nano-DDS was stable under normal physiological settings and could effectively accumulate in tumor sites. After entering tumor cells, the unique microenvironment of acidic pH and overexpressed GSH degraded the ultrasensitive nanosystem, promoting the release of DOX to specifically kill cancer cells. Meanwhile, the production of reactive oxygen species (ROS) was also significantly increased, thereby disturbing the redox balance of tumor cells. The highly extended flexible 2D structure endowed the drug delivery system with remarkable photothermal performance. The photothermal effect of external 808 nm laser irradiation further enhanced the degradation and drug release. In 2021, Jiang et al. [82] synthesized a hypoxia-responsive azo bond-containing flexible COF with nanoscale size to immobilize photosensitizers chlorin e6 (Ce6) and hypoxia-activated drug tirapazamine (TPZ). When this prepared COF entered a hypoxic environment such as tumor tissues, its structure ruptured and the loaded drugs were released. Moreover, upon near-infrared (NIR) light irradiation, Ce6 consumed oxygen to produce cytotoxic reactive oxygen species, leading to elevated hypoxia. The two-step hypoxic stimulation sequentially induced the flexible COF disintegration, released drugs and activated TPZ to generate massive biotoxic oxyradical (Fig. 4B). The physically connected cytoskeleton within the cell can transmit mechanical signals regulated by the microenvironment to the nucleus to obtain control of cell behavior and function. Microtubules are the hardest type of cytoskeleton, and the destruction of their structure directly affects the survival of tumor cells [83]. Therefore, in 2022, Herrero et al. synthetized a novel microtubule-destabilizing agent of PILA9, which can bind to the colchicine site of tubulin, disrupting the microtubule network and causing good cytotoxic effects [84]. However, COF, as an emerging biomaterial, has not yet been reported in this area and shows great potential.

4.2. Photodynamic therapy

Photodynamic therapy (PDT), as a promising treatment modality, has attracted considerable attention owing to its advantages of minimal invasiveness, high spatial selectivity, low side effects, and broad anticancer spectrum, which has also been applied in clinical cancer therapy. PDT employs photosensitizers (PSs) in tumor sites to absorb specific wavelength of light energy and excite oxygen to generate ROS (for example, $^1O_2$, ·OH, and $\cdot O_2^-$), resulting in cancer cell death [85,86]. However, the traditional PSs (such as porphyrin, boron-dipyrromethene (BODIPY) and their derivates) are restricted by their poor aqueous solubility, no tumor targeting and low bioavailability. While incorporation, modification, and loading PSs onto nanosystems can conquer these drawbacks and thus improve the antitumor efficiency. Significantly, the incorporation of flexible photosensitive molecules into ordered COFs nanomaterials can not only modify their mechanical properties but also enhance their photoactivity. For example, in 2019, Yuan and co-workers [51] aimed to demonstrate that the dispersion of NIR light-activated molecular dyes in nanocarriers could significantly improve their PDT anticancer ability. Therefore, they prepared a rigid 2D COF nanosheet to load PSs of indocyanine green (ICG) and subsequently coated it with polydopamine (PDA), namely ICG@COF-1@PDA. Interestingly, the absorption peak of loaded ICG was redshifted from 779 nm to 802 nm. Under a single 808 nm laser irradiation, the obtained flexible ICG@COF-1@PDA could achieve enhanced PDT efficiency, induce immunogenic cell death (ICD), elicit antitumor immunity in colorectal cancer, and exhibit 62.9% inhibition of untreated distant tumors. Besides, the flexible ICG@COF-1@PDA could efficiently prevent tumor metastasis and recurrence, providing a promising opportunity for the treatment of primary and metastatic tumors.

However, the loading of photosensitizers makes the mechanical properties of nanosystems uncontrollable, and it is difficult to avoid unnecessary toxic side effects due to leakage. Directly using photosensitizers with different mechanical strengths as linking units of COFs is also one of the current research hotspots. In 2019, Qu et al. [87] synthesized renal-clearable ultrasmall COF nanodots (2.9 nm) and used them as effective cancer therapy PDT agents. The COF nanodots were fabricated by a simple liquid exfoliation strategy of a porphyrin-based 2D rigid COF and modified by PEG to decrease mechanical intensity and improve physiological stability and biocompatibility. The well-isolated porphyrin molecules in the COF structure endowed them with a good

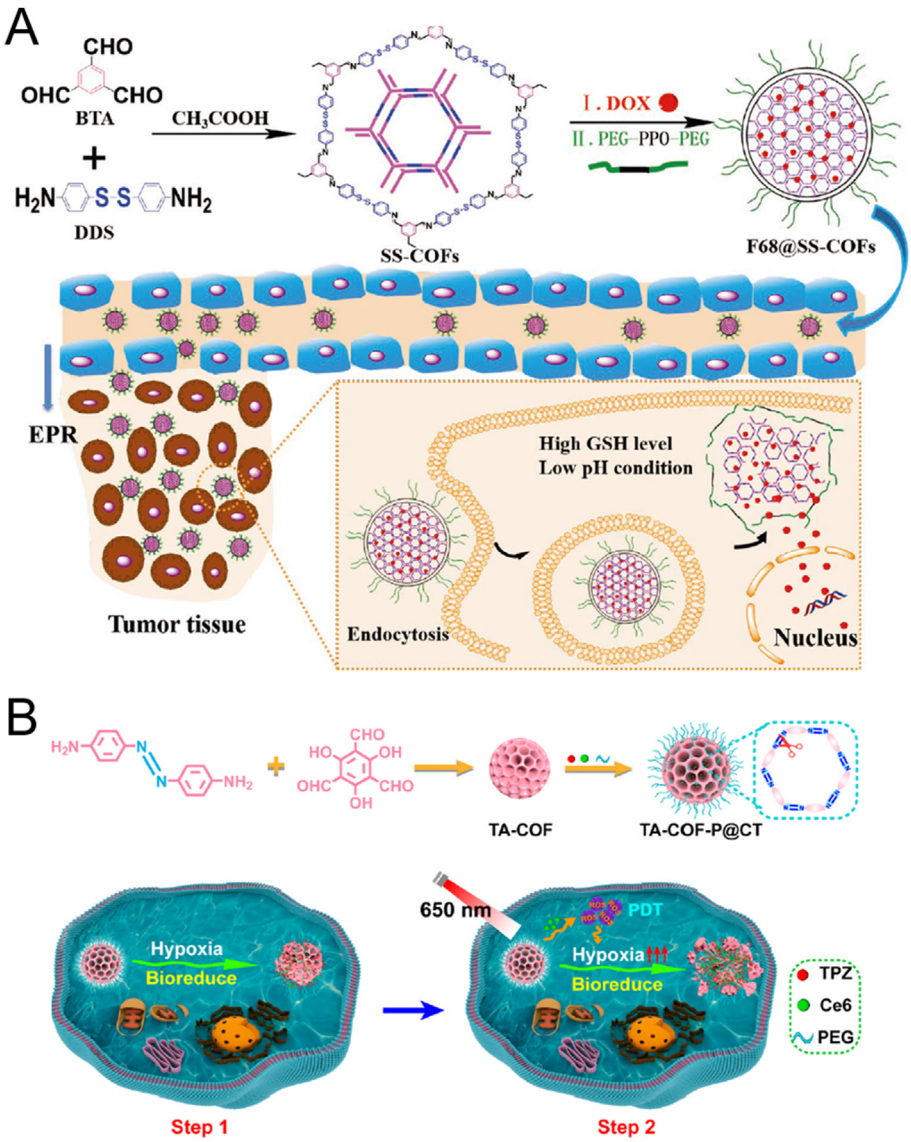

Fig. 4. TME-triggered specific drug delivery and tumor therapy. (A) Construction of reduction-responsive DOX-loaded COFs nanosystem containing disulfide bonds and its antitumor applications *in vivo*. Adapted with permission [45]. Copyright © 2020 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) A hypoxia-responsive azo bond-containing COF for effective combination cancer therapy. Adapted with permission [82]. Copyright © 2021, American Chemical Society.

ROS-yielding ability under 638 nm laser irradiation, leading to excellent PDT efficiency with good tumor enrichment. Particularly, due to their ultrasmall size and flexible PEG coating, the nanosystem could prolong circulation time and be cleared from the body through renal filtration without long-term toxicity *in vivo* (Fig. 5A). This work took advantage of the poor stability of 2D rigid COFs to prepare the PEG-modified COF nanodots with improved mechanical properties, good stability and excellent PDT performance, thus shedding new light on the advantages and disadvantages of the different mechanical material applications. In 2021, Tang et al. [88] developed a modification-facilitated exfoliation strategy for the one-step preparation of ultrathin 2D functionalized covalent organic framework nanosheets (COF NSs) with good flexible properties and enhanced dispersity and ROS generation ability. Compared with COF nanoparticles with higher rigid intensity, COF NSs performed better *in vivo* anti-tumor effects. Besides, the unique structure of COFs provides a potential design basis for their active functions. In 2019, Deng et al. [47] designed and synthesized two types of rigid COFs (COF-808 and COF-909) as PSs for efficient PDT *via* two inactive molecules (Fig. 5B). Compared with the bandgap energy of the inactive linker (2.79 eV), the bandgap energy of COF-909 was reduced to 1.96 eV, and its narrowed bandgap provides a suitable energy spectrum overlap, so that it could perform good PDT performance under 630 nm laser irradiation. The unique COFs properties with highly ordered rigid structure could also promote diffusion of both oxygen and release of ROS in cancer cells, resulting in significant tumor growth inhibition *in vitro* and *in vivo*.

4.3. Photothermal therapy

Photothermal therapy (PTT) uses external light (especially NIR light) to heat tumor cells and induce thermal damage to destroy tissues. PTT has been tried clinically but is not widely applied, in part because the high-intensity laser may damage normal tissues and cells. Nanoscale photothermal agents (PTAs), which convert light energy into heat, can reduce the required light power intensity while increasing tumor specificity, thereby preventing damage to surrounding normal tissues. During PTT treatment, when the tissue temperature rises above 41 °C, it may cause changes in gene expression patterns and generate heat-shock proteins, thereby reducing the damage to cells caused by thermal injury. When the temperature rises to 42 °C, irreversible tissue damage occurs, heating tissue to 42–46 °C for 10 min will result in necrosis of the cells. At 46–52 °C,

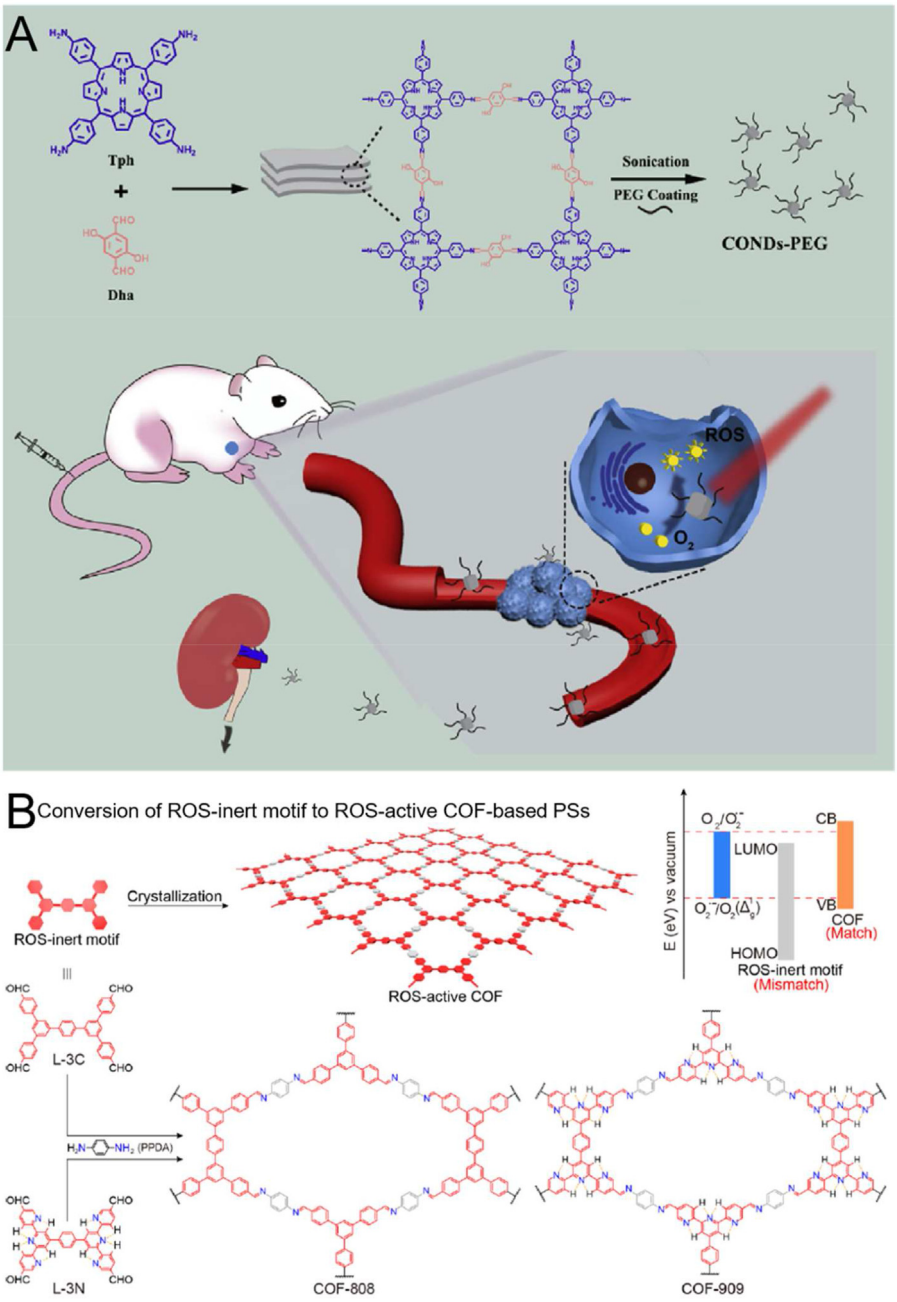

Fig. 5. Photosensitizer as COFs building blocks for photodynamic therapy. (A) Renal-clearable ultrasmall porphyrin-based 2D COF nanodots for efficient cancer PDT. Adapted with permission [84]. Copyright © 2019 Elsevier Ltd. All rights reserved. (B) Two types of COFs as PSs for efficient PDT *via* two inactive molecules. Adapted with permission [47]. Copyright © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

cells die rapidly due to microvascular thrombosis and ischemia. As tissue temperatures >60 °C, cell death occurs almost instantaneously due to protein denaturation and plasma membrane disruption [89].

At present, nanomaterials with high photothermal conversion efficiency mainly include conjugated polymers, plasmonic metal nanostructures, semiconductors, and ferromagnetic nanoparticles. Compared with closed porous systems that restrict heat flow, the open pores and mechanically adjustable COFs can quickly transfer the generated heat to the environment, and can realize customizable photothermal agents for COFs, so COFs materials have great potential for photothermal therapy. Currently, COF-based PTT can be mainly divided into two types: (1) COF composites loaded with PTAs (2) COFs materials with inherent photothermal properties. In 2019, Guo et al. [90] proposed a new strategy in which rigid COFs materials prepared by Schiff base condensation were transformed from neutral to positively charged COFs and finally into cationic radical frameworks, which allowed the redox centers within the frameworks to be superimposed on each other. The non-radiative relaxation process of NIR absorption and photothermal conversion could be enhanced through the charge transfer between the π-coupled rigid multilayer films. Under the irradiation of 808 and 1064 nm lasers, the photothermal conversion efficiency of the two cationic COF materials was respectively as high as 63.8% and 55.2%. Rigid 2D COFs were further modified with flexible PEG to reduce the mechanical intensity, and the particle size of the modified COFs was about 178 nm, which was suitable for biological applications, thus successfully realizing photoacoustic imaging and photothermal therapy in tumor-bearing mice under NIR light irradiation (Fig. 6A). In 2021, Jing and co-workers [91] synthesized a series of nanoscale COFs by integrating electron donor and acceptor linkers

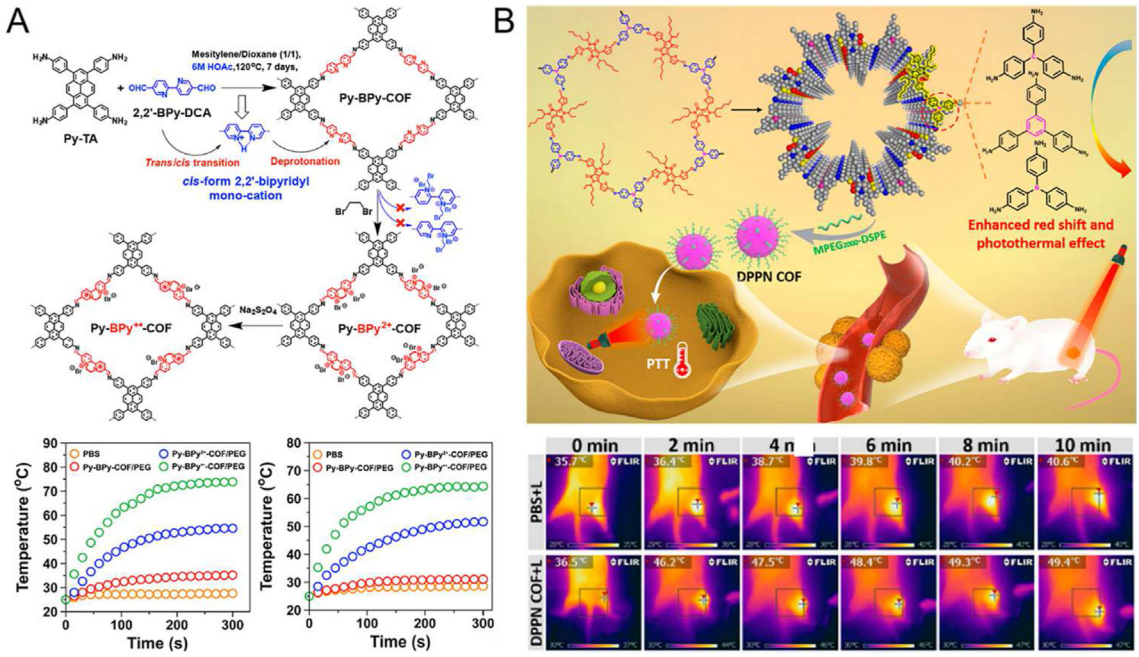

Fig. 6. COFs-based nanosystem with photothermal conversion performance for PTT. (A) Cationic radical COFs for effective cancer PTT. Adapted with permission [86]. Copyright © 2019, American Chemical Society. (B) NIR-II light-triggered COFs with donor–acceptor structure for PTT *in vivo*. Adapted with permission [91]. Copyright © 2021, American Chemical Society.

and modified with 1,2-distearoylsn-glycero-3-phosphoethanolamine-N-(methoxy-PEG) (mPEG-DSPE) to obtain flexible spherical COF materials. The donor and acceptor structure produced a narrow optical band gap, resulting in red-shifted absorption, which even covers the NIR-II biological window. Furthermore, the COF-based flexible materials exhibited excellent colloidal stability and photothermal conversion efficiency. The nanosystem demonstrated an efficient accumulation in tumor sites rapidly and a good PTT effect (Fig. 6B). The ingenious combination of organic radicals and unique electronic structures with COFs can endow COF materials with excellent optical and electronic functions, thereby opening up the biomedical applications of COFs materials.

4.4. Combined therapy

Owing to the heterogeneity and complexity of tumors, monotherapy usually faced many restrictions that made eradicating tumor tissue difficult. Combined therapy, however, could effectively overcome the shortcomings of monotherapy and further improve the therapeutic effect [92]. The versatility of COFs allowed different therapies to be easily combined on COF-nanoplatforms. In 2019, Chen et al. [93] synthesized rigid porphyrin-based COF NPs (COF-366 NPs) to control the orderly spatial arrangement of the photoactive building blocks and used them for antitumor therapy *in vivo*. COF-366 NPs could combine PDT and PTT under single-wavelength laser irradiation due to their unique rigid frame stack structure, and possessed photoacoustic imaging monitoring function, making the operation simpler and more convenient. Even in the face of large tumors, rigid COF-366 NPs achieved good phototherapeutic effects. This work opened a new avenue for phototherapy materials and expanded the application range of rigid COFs. Primary tumors could be effectively eliminated by phototherapy through generated ROS and heat. However, it was hard to prevent tumor metastasis and local regrowth. To resolve these problems, immunotherapy, which stimulated the inherent immune system, and induced an inflammatory response in tumor cells, could be a worthy option for cancer eradication. Immunotherapy by combining with other treatments such as phototherapy, chemotherapy., maximized the therapeutic effect compared to immunotherapy alone. For example, Pang et al. [48] in 2020 reported a flexible COF nanosystem loaded with ICG and chicken ovalbumin (OVA) (COF@ICG@OVA), which could ablate primary tumors under 650 nm and 808 nm laser irradiation with high photothermal conversion efficiency (35.75%) and ROS generation ability. Tumor-associated antigens were also produced after combinational PTT/PDT therapy. By further combining with anti-programmed cell death 1 ligand (PD-L1) checkpoint blockade therapy, it could effectively eliminate primary tumors and inhibit the metastasis of cancer cells by generating strong immune responses. Summarily, the post-modified 2D rigid COFs exhibited good flexibility properties and improved *in vivo* circulation and delivery efficiency (Fig. 7A). In 2021, Sun et al. [49] synthesized a serrated packing COF, COF-606, with excellent two-photon absorption (2 PA) property and photostability, its rigid framework structure largely avoided aggregation-caused quenching, therefore offering high ROS generation efficiency and used as a 2 PA photosensitizer for PDT in deep tumor tissue. COF-606-induced PDT was shown to be efficient in inducing immunogenic cell death, provoking an immune response and normalizing the immunosuppressive status for the first time. This made it possible to combine 2 PA-induced PDT using COF with programmed cell death protein 1 immune checkpoint blockade therapy. Such a combination led to strong abscopal tumor-inhibiting efficiency and long-lasting immune memory effects, standing as a promising combinatorial therapeutic strategy for cancer treatment (Fig. 7B).

5. Perspectives and challenges

COFs are an emerging class of highly controllable prepared porous materials with tunable mechanical properties, high surface areas and porosity, thus promising broad applications in drug delivery and antitumor applications. It can achieve enhanced stability *in vivo*, selective adsorption and release of drug molecules, as well as improved delivery efficiency by adjusting its pore size, surface chemical properties and mechanical intensity, thereby improving the bioavailability of drugs and anti-tumoral effects. In addition, COF can also achieve specific delivery of drugs and combined therapy and theranostics by adjusting surface mechanical intensity. COFs, however, are still in their infancy compared with other conventional nanomaterials. There are still many issues that need to be

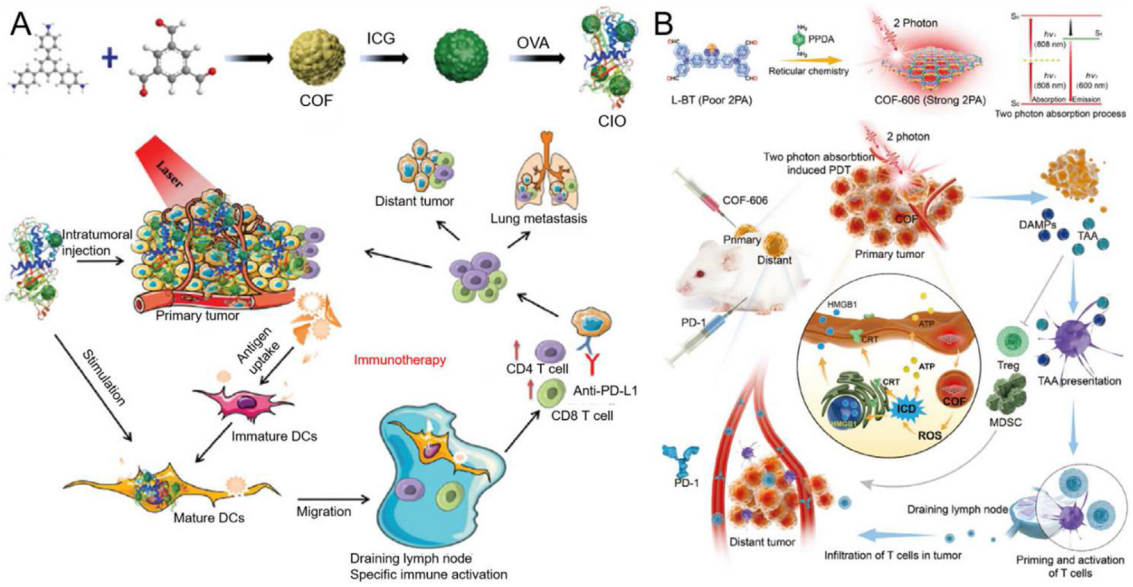

Fig. 7. The combination of photo-immunotherapy. (A) ICG and OVA-loaded COF nanosystem synergize with anti-PD-L1 to effectively treat cancer and prevent tumor metastasis. Adapted with permission [48]. Copyright © The Royal Society of Chemistry 2020. (B) The preparation and combination therapy of COF-606 with 2 PA property. Adapted with permission [49]. Copyright © 2021 Wiley-VCH GmbH.

addressed. 1) The stability of COF is very important for its application, but because its porous and mechanical properties are easily affected by factors such as water, solvent and temperature, its stability is poor, which affects its application in drug delivery and tumor application in therapy. 2) The preparation of COFs materials usually requires rigid building blocks and special experimental conditions, which to some extent limits the development of its large-scale preparation and commercial application. 3) As an emerging material, there is still a lack of in-depth research on its biocompatibility and mechanical properties, so more experimental verifications are needed. 4) The application effect of COFs with different mechanical strengths in drug delivery and tumor treatment still needs to be further verified and optimized, such as the interaction between COF and drugs and the stability of COF *in vivo*. 5) The mechanical strength of COFs nanosystems cannot be quantified and lacks regular guidance.

Even with the above challenges, nanomedicine based on mechanically tunable COFs for cancer therapy remains a very promising new growth area.

CRediT author statement

Liefeng Hu: Investigation, Software, Data curation, Writing - Original draft preparation. **Yonggang Lv:** Conceptualization, Funding acquisition, Investigation, Methodology, Project administration, Resources, Supervision, Validation, Writing review & editing.

Ethical approval

N/A.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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