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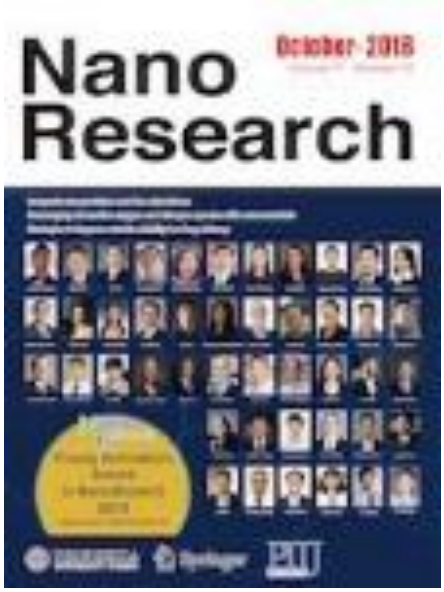

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Nanoformulation of metal complexes: Intelligent stimuli-responsive platforms for precision therapeutics

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ABSTRACT

Precision medicine is a potential effective therapeutic for various human diseases. Currently, metal complex-based drugs are being successfully used in clinical applications owing to diverse properties such as multiple redox states, photo-induced ligand exchange, and preferential ligand and coordination numbers, which facilitate drug design and development. However, drawbacks such as toxicity, lack of specificity, and severe side effects have hampered their therapeutic outcome. Therefore, innovative strategies for improving the specificity and pharmacokinetics of conventional metal complex-based therapeutic agents are required. Recently, nanotechnology, which provides a unique toolbox for developing effective and safer medicine, has attracted considerable attention, mainly because of their ability to reduce side effects and enhance drug loading efficiency and pharmacokinetics. Considering the promising chemical and physical properties of diverse nanostructures, nanoformulation of metal complexes can be used to effectively address the problems associated with current metallodrug complexes, especially those based on stimuli-responsive therapeutic strategies, with excellent spatial, temporal, and dosage control. In this review, we have mainly focused on the specificity and environment-responsiveness of metallodrug nanoformulations as therapeutics, and summarized the recent strategies being used for developing metal complex-functionalized intelligent nanoplatforms, which respond to various types of stimuli, including endogenous signals (pH, redox conditions, and enzyme activities) or external triggers (light irradiation and magnetic field manipulations). In addition, we have also discussed the potential challenges associated with use of metallodrugs and their nanoformulations as effective precision therapy with improved specificity and minimal side effects.

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1 Introduction

Currently, precision therapeutics in clinical practice has attracted considerable attention owing to their ability to effectively treat various diseases, including cancer, neurological disorders, cardiovascular diseases, as well as bacterial infections [1, 2]. Among the commonly used therapeutic agents, metal-based drug molecules have been widely used in clinics, mainly because of the diverse roles of metal ions in biological processes [1, 2]. Furthermore, some of these metal-based compounds exhibit advantageous properties such as specific metal-ligand interactions, multiple redox states, photo-induced ligand exchange, and preferential ligand and coordination numbers, which enables multiplex interactions with biomolecules such as DNA or proteins and interferes with cellular pathways, which underscore their therapeutic effects [3]. Currently, various drugs based on metal complexes (e.g., platinum, gold, and bismuth complexes) are being designed and developed for the treatment of diverse life-threatening ailments [4–7]. However, despite their success, the use of these metal complexes during treatment has been mostly associated with severe side effects such as toxicity and limited specificity [8, 9]. In addition, rapid clearance and short half-life in the circulatory system have largely affected their *in vivo* therapeutic efficacy [10]. Therefore, the development of new metallodrugs based on rational design of novel metal complexes with potent therapeutic effects, enhanced specificity, and improved pharmacokinetics still remains a significant challenge.

In recent decades, the remarkable advance of nanomedicine has attracted considerable attention and promoted the integration of metal complexes with nanomaterials for reduced side-effects and improved pharmacokinetics. These innovative platforms will significantly promote the application of precise and effective therapeutics for various diseases, mainly due to the unique physical and chemical properties of different nanoagents in terms of nanoscale size effect and high surface-to-volume ratio, which will allow efficient drug loading [11–16]. In addition, facile and versatile surface functionalization of nanoagents can improve the solubility as well as bioavailability of metallodrugs. Several nanoplatforms for drug delivery have been established by directly loading therapeutic metal complexes on the surface or in the cavity of nanostructures, mainly because of their ability to accumulate within diseased sites via enhanced permeability and retention effect (EPR effect) [17]. In spite of their initial success, the lack of specificity and uncontrolled drug release within targeted diseased sites remain challenging issues, which have significantly restricted their future clinical applications [18]. Effective and robust approaches, which can result in deposition of therapeutic payloads into targeted locations on demand with minimum off-target leakage are highly desirable and can be potentially used for designing precise therapeutics in clinics.

Extensive efforts have been made for merging precision therapeutics with biomedical practice. Inspired by the responsiveness of living organisms, stimuli-responsive nanoplatforms are emerging as feasible and promising strategies for precision therapeutics with excellent spatial, temporal, and dosage control [19, 20]. Basically, these innovative platforms will trigger payload (e.g., metal complexes) release or activation to exert cytotoxic effect in response to stimulation within targeted regions, thereby minimizing nonspecific off-target leakage and improving therapeutic efficacy. Until now, various stimuli-responsive therapeutic platforms, which are sensitive to endogenous properties of the diseased microenvironment, including pH gradient, redox potential, and enzyme activities, have been extensively investigated for treating neoplastic diseases. In addition, extracorporeal physical stimuli, including light and magnetic field can also be applied to facilitate investigations on their precise therapeutic effect on pathological situations (e.g., ischemia, inflammatory diseases, and infections) [18, 21–25].

Nanoconstructs functionalized with metal complexes for administering therapeutic agents have been extensively studied and discussed [17]. In this review, we have focused on the specificity and environment-responsiveness of metallodrug nanoformulations in disease treatment, and have summarized the latest advances on the integration of therapeutic metal complexes with various stimuli-responsive intelligent platforms, which respond to either endogenous signals (e.g., pH, redox conditions, and enzyme activities) or external triggers (such as light irradiation and magnetic

field manipulation) for precise therapeutic purpose. These approaches provide excellent means for more specific and effective treatment of various human diseases. Furthermore, we have also discussed the potential challenges in using metallodrugs and their nanoformulations for developing precise disease therapeutics with improved specificity and minimal side effects.

2 pH-responsive nanoplatforms for precise delivery of metal complexes

Among diverse environmental triggers, pH gradients have been commonly exploited for designing intelligent responsive therapeutic nanoplatforms. Compared to normal tissues, diseased sites display altered pH conditions. For example, tumors tend to have more acidic pH (with a median pH value of ~ 7.0) than normal tissue (pH ~ 7.4) [26]. Lactic acid overproduction, which mostly arises from elevated glucose uptake and reduced oxidative phosphorylation, is mostly responsible for the acidic microenvironment of tumors [27]. Furthermore, poor lymphatic drainage and insufficient blood supply also contribute to the acidic tumor microenvironment [28]. Such significant differences in pH between normal and pathological tissues have encouraged utilization of local pH as a natural trigger for controlled release of drugs at targeted areas to achieve high drug concentrations and minimize systemic exposure [29].

2.1 Approaches based on dissociation of pH-sensitive bonds

To obtain precise therapeutics based on pH-responsive nanoplatforms, one commonly used strategy involves utilizing the pH-sensitive bond, which can be cleaved under acidic conditions to allow targeted drug release within pathological regions. For instance, Gu and Xu et al. reported a supramolecular dendritic system with polyethylene glycol (PEG)ylated platinum derivatives coordinated to the carboxyl groups on the surface of the polymer. The polymer significantly enhanced the biodistribution and pharmacokinetics of platinum-based drugs in the bloodstream because of their stable nanostructure and the presence of the PEG shell. Upon internalization by tumor cells, the low intracellular pH within the tumor triggers rapid dissociation of the acid-sensitive coordinate bond and subsequent polymer degradation. Therefore, surface-functionalized platinum drugs can be released to exert antitumor effects. *In vivo* studies demonstrated that such systems can provide antitumor efficacy, which is comparable to that of clinically used cisplatin. In addition, they have minimal side-effects such as renal toxicity than platinum complex-based drugs. Furthermore, the encapsulated near infrared (NIR) dye allows tracking the fate of such theranostic nanoplatforms and monitoring real-time drug metabolism both *in vitro* and *in vivo* [30]. In addition to single drug delivery, pH-responsive nanoplatforms also exhibited potential for multidrug delivery in synergistic therapy. Nguyen and O'Halloran et al. used a polymer-caged nanobin (PCN) to achieve dual drug delivery of doxorubicin (DOX) and cisplatin (Fig. 1(a)). The PCN is composed of DOX-encapsulated core-structure, which is surrounded by a pH-responsive platinum prodrug loaded shell. Platinum complex release observed under acidic tumor environment can be attributed to the acid lability of the N α-acetylamido ligand, which detaches from the metal center after protonation by the acid. Simultaneously, protonation of the core structure of the liposome, which is composed of amine-modified lipids, leads to simultaneous DOX release. Thus, both drugs can be delivered to the diseased sites in a pH-controlled manner, following which they can synergistically enhance the overall cytotoxicity against cancer cells at reduced doses [31–33]. Recently, Wang's team has designed core-shell-corona nanoparticle $^{+}$NP/Pt@PPC-DA as a safe and effective strategy for delivery of therapeutic drugs for cancer, especially for those with drug-resistant properties. To facilitate rapid drug accumulation within drug-resistant cancer cells, positively charged core particle $^{+}$NP/Pt was prepared for efficient cellular uptake. However, under *in vivo* conditions, the positively charged nanoparticles are likely to be rapidly cleared from blood circulation due to nonspecific interaction with serum. To circumvent this issue, acid-sensitive polymer PPC-DA was decorated on the surface of $^{+}$NP/Pt particles. Exposure of $^{+}$NP/Pt@PPC-DA to slightly acidic conditions at pH 6.8 triggered the

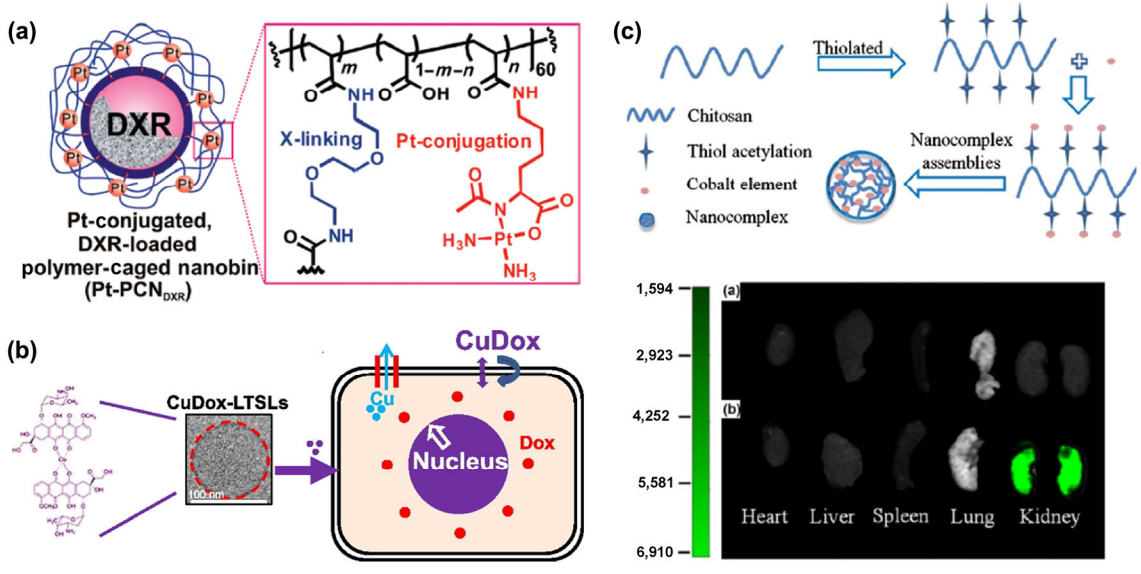

Figure 1 Illustration of pH-responsive platforms for precision therapeutics. (a) pH-sensitive polymer-caged nanobin. Reproduced with permission from Ref. [31], © American Chemical Society 2010. (b) pH-responsive copper-doxorubicin (CuDox) cargo loaded in lysolipid-based liposome. Reproduced with permission from Ref. [35], © Elsevier B.V. 2016. (c) Co(II) chitosan nanocomplex as pH-responsive renal fibrosis targeting drugs. Reproduced with permission from Ref. [36], © Taylor & Francis 2016.

degradation of PPC-DA amide bonds and generated positively charged groups, which subsequently lead to electrostatic repulsion to release positively charged $^{+}$NP/Pt. *In vitro* and *in vivo* studies on cisplatin-resistant tumor models demonstrated that $^{+}$NP/Pt@PPC-DA exhibited prolonged blood circulation and enhanced platinum-based drug accumulation in tumors. Furthermore, the pH response led to the release of positively charged $^{+}$NP/Pt nanoparticles and further promoted nanoparticle internalization by cisplatin-resistant tumor cells *in vivo*. In addition, $^{+}$NP/Pt rapidly released cisplatin in the intracellular environment, resulting in successful inhibition of cisplatin-resistant tumor growth in the murine xenograft model [34]. Apart from platinum complexes, copper-based complexes have also been applied for precise treatment of diseases. For instance, Farrara's team reported the delivery of a metallodrug complex (CuDox) via activatable liposomes (Fig. 1(b))[35]. The complexation of Cu^{2+} and DOX in liposomes can effectively extend drug retention in blood, maintain treatment efficacy, and reduce drug accumulation in sensitive tissues and organs such as the heart. The drug-metal complex is highly stable under physiological conditions and rapidly releases the drug in the acidic environment of lysosomes. Such rationally designed liposomes with drug-metal complexes can facilitate effective drug release in response to the tumor environment. Furthermore, the complexation of drug and Cu^{2+} in liposomes can minimize the side effect of clinically used DOX by reducing the formation of free radicals, which arise from the interaction of the drug with metal ions *in vivo*. In addition, the delivery of therapeutic metal complexes via pH-sensitive nanoplatforms has been used to target diverse pathological conditions such as renal fibrosis and chronic inflammation [36, 37]. Recently, Hu and coworkers reported chitosan cobalt nanocomplexes as pH-responsive renal fibrosis-targeting drugs (Fig. 1(c)) [36]. Chronic progressive kidney disease advances via tubulointerstitial fibrosis. Cobalt chloride has been reported to attenuate renal fibrosis. However, it exhibited obvious toxicity and caused unwanted damage to healthy tissue. Chitosan, a widely used natural drug carrier, possessed superior biocompatibility and coordination ability. The nanocomplex formed by chitosan and cobalt is stable in the circulatory system (pH 7.4) and accumulates in the proximal tubule. The pH-dependent cleavage of the coordinate bond between cobalt and chitosan under acidic conditions of lysosomes can trigger rapid drug release, exhibiting its potential as a kidney-targeting drug for renal fibrosis.

2.2 Approaches based on rupture of pH-sensitive carriers

In addition to bond dissociation, another commonly used strategy based on pH-dependent hydrophobic to hydrophilic transitions of nanocarriers have also been investigated for precise drug delivery via polymer matrix collapse. For instance, Nie and Wang et al. formulated a class of smart nanostructures with ultrasensitive size switching effect in response to pH change within the tumor microenvironment for enhanced tumor penetration and efficient *in vivo* drug delivery. The nanostructure was constructed through amphiphilic polymer-directed assembly of platinum-prodrug conjugated polyamidoamine (PAMAM) dendrimers, in which the amphiphilic polymer contained ionizable amine groups for rapid pH-responsiveness. The size of this nanostructure at neutral pH conditions (e.g., blood circulation) is ~ 80 nm. Once it enters the slightly acidic tumor environment (where pH is 6.5–7.0), the nanostructures undergo an obvious and sharp size transformation within a narrow range of acidity (less than 0.1–0.2 pH units) and dissociate instantaneously within seconds into the building blocks (~ less than 10 nm in diameter). This rapid size-switching will not only be beneficial for accumulation inside the tumor via enhanced permeability and retention effect, but will also improve tumor penetration. Further studies on both pH-sensitive and insensitive nanostructures of similar sizes, surface charge, and chemical composition were performed on both multicellular spheroids and poorly permeable BxPC-3 pancreatic tumor models. Results suggested that pH-triggered size switching is a viable strategy for improving drug penetration and therapeutic efficacy [38]. In another study, Wang and Du et al. reported a responsive nanocarrier, which is able to spatially target both tumor-associated macrophages and tumor cells for chemo-immunotherapy. To achieve optimum therapeutic efficacy, a system capable of delivering multiple therapeutic agents differentially to target cells was required. Therefore, they developed an immunostimulatory nanocarrier (BLZ-945SCNs/Pt), which could spatially target tumor-associated macrophages (TAMs) and tumor cells for cancer chemoimmunotherapy. At pH 6.7–6.8, the ionization of the amine groups on the amphiphilic polymer induced hydrophobic to hydrophilic transition and eventually lead to structure collapse of the carrier within the prevascular regions of tumor tissues, thereby enabling the concurrent release of both platinum-prodrug nano-conjugates and small molecule inhibitor BLZ-945 of colony stimulating factor 1 receptor (CSF-1R) of TAMs. In the extracellular environment, the released inhibitor can be incorporated by TAMs and result in TAM depletion in tumor tissues. The Pt-prodrug-containing small particles allow deep tumor penetration as well as specific intracellular drug release, thereby exerting cytotoxic effect against cancer cells. Further mechanistic studies revealed that the customized pH-sensitive co-delivery nanocarriers not only induced tumor cell apoptosis but also modulated the tumor immune environment and eventually augmented the antitumor effect of $CD8^+$ cytotoxic T cells through TAM depletion [39].

3 Redox-responsive nanoplatforms for metal complex activation

In addition to pH-responsive delivery of metal complexes, another well-established strategy for developing precise therapeutics involves the use of redox-responsive platforms, which utilize the local redox properties within diseased regions to activate metal complex agents. The concept of redox-responsive therapeutics arises from the steep reductive gradient between the extracellular and intracellular compartment of cells, and the accentuated upregulation of reductive species in cancer cells. The highly reductive environment in the intracellular milieu is mainly because of the presence of the glutathione tri-peptide, γ-glutamyl-cysteinyl-glycine (GSH), which is the most abundant small molecule reducing agent [40, 41]. The concentration of GSH is higher inside normal cells (~ 2–10 mM) than in the outside (~ 2–20 mM) [42]. Tumor cells have a higher reductive microenvironment than normal cells as their intracellular GSH concentration is four-times higher than that of normal cells [43, 44]. Based on this cancer-specific chemical cue, one common strategy involves utilization of the transformation of inert prodrug into its bioactive

form under reducing conditions. Recently, Lippard and Dai et al. devised a redox-sensitive delivery system based on soluble single-walled carbon nanotubes (SWNTs) and platinum (IV) prodrug. These SWNTs can effectively deliver the Pt(IV) prodrug into tumor cells. Under the reducing intracellular microenvironment of tumor cells, the Pt(IV) prodrug can be converted into cytotoxic Pt(II) species. Using this strategy, a substantial increase in cytotoxicity was achieved compared to cisplatin and the free Pt(IV) complex [45]. The Pt(IV) prodrug was conjugated to folate through an axial ligand for targeting folate receptors that are overexpressed on cancer cells. With the assistance of folate, the Pt(IV) prodrug can be effectively and specifically delivered into cancer cells, where it increased cell death by up to 9-fold compared to cisplatin [46]. Based on the strategy of intracellular reduction of Pt(IV), several groups have reported redox-sensitive nanosystems for tumor-specific and controlled drug delivery. Several studies have utilized the ligand dissociation property of Pt(IV) prodrugs under reducing environment for multidrug delivery to achieve synergistic treatment of diseases. For instance, Liang's team designed a dual drug backbone shattering polymeric nanomedicine (Fig. 2(a)) [47]. Demethylcantharidin (DMC), which can improve anticancer activity of DNA-damaging drugs without evident toxicity, was introduced to the Pt(IV) prodrug. The interaction between DMC and the Pt center, based on metal-ligand coordination, allowed precise control of drug ratio for optimizing therapeutic efficacy. Furthermore, the prodrug was further reacted with linker ethylenediamine and self-assembled into polymeric nanoparticles. Under reductive and acidic tumor microenvironment, the nanoscale polymers can be site-specifically chain-shattered through the transformation of Pt(IV) into Pt(II) and hydrolysis of the DMC precursor, releasing both drugs to exert synergistic antitumor effect in a controlled manner. Furthermore, an *in vivo* experiment on a high-fidelity patient-derived lung cancer model demonstrated the potential application of such personalized nanomedicines with precisely controlled composition in disease treatment. In addition, nano-scaled metal-organic frameworks (MOFs) have been also used for co-delivery of therapeutic metal complex prodrugs and siRNA to overcome drug resistance during cancer treatment (Fig. 2(b)) [48]. MOFs are emerging porous

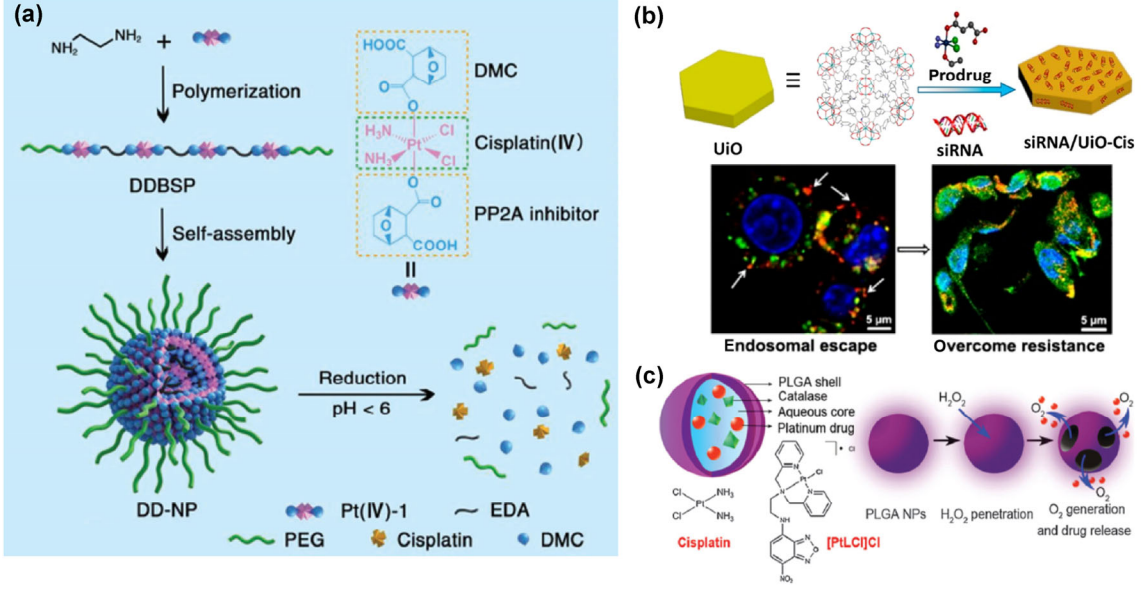

Figure 2 Schematic illustration of redox-responsive platforms for precision therapeutics. (a) Dual drug backbone shattering polymeric theranostic nanomedicine (DDBSP). Reproduced with permission from Ref. [47], © John Wiley & Sons, Inc 2018. (b) Redox-responsive MOFs (siRNA/UiO-Cis). Reproduced with permission from Ref. [48], © American Chemical Society 2014. (c) ROS-responsive PLGA NP structure and the mechanism of intracellular drug release. Reproduced with permission from Ref. [56], © Royal Society of Chemistry 2014. MOFs: meta organic frameworks; ROA: reactive oxygen species; PLGA, polylactic-co-glycolic acid; NP, nanopore.

materials that are constructed via self-assembly of molecular building blocks [49]. Typically, nanosized MOFs possess advantages such as well-defined pore aperture, high loading capacity, and intrinsic biodegradability. In addition, the size, composition, and morphology of engineered MOFs can be fine-tuned to optimize their properties for drug loading and controlled release, exhibiting the potential to serve as promising platforms for drug delivery and disease treatment [50]. For instance, Lin and coworkers designed an UiO MOF nanostructure with high porosity and surface binding sites. Redox-sensitive Pt(IV) prodrug and MDR-related gene silencing siRNA are efficiently loaded into UiO MOFs. The UiO carrier can protect siRNAs from nuclease degradation and enhance siRNA uptake, thereby improving MDR-related gene silencing effect and leading to an order-of-magnitude enhancement in the therapeutic efficacy of metallodrugs.

In addition to drug delivery, the redox-responsive drug delivery properties have also been combined with multi-modal imaging modalities for diagnosis and evaluation of therapeutic outcomes. Recently, Guo and Wang et al. reported superparamagnetic iron oxide nanoparticle (SPION)-based nanocomposites loaded with Pt(IV) prodrug as targeted theranostic agents for effective cancer treatment. In addition to the promising magnetic targeting and anti-proliferative properties, these intelligent platforms exhibited minimum toxic effect in normal cells. Importantly, unlike most commonly used chemotherapeutic agents such as cisplatin, which is prone to inactivation in the presence of GSH, these therapeutic platforms displayed increased cytotoxicity upon GSH treatment, suggesting a different mechanism of action of the nanocomposite compared to the well-established paradigm for Pt drugs [51].

In addition to the highly reductive properties, the redox environment in pathophysiological conditions is also characterized by high levels of reactive oxygen species (ROS), which accumulate in inflammatory tissues to create oxidative stress [52]. Accumulating evidence suggests that misregulation of ROS is associated with diverse diseases, such as cancer, atherosclerosis, and asthma [53–55]. Therefore, ROS-derived redox condition has been well-explored as a chemical trigger for stimuli-responsive therapeutics. For instance, Guo and He et al. proposed a ROS-responsive nanocarrier for controlled dual-release of Pt(II) drug and O_2 against cisplatin-resistant cancer cells (Fig. 2(c)). They used polylactic-co-glycolic acid (PLGA) nanoparticles as the degradable carrier, and platinum-based drugs together with catalase were incorporated into the particles as oxygen generating agents.

Facilitated by catalase, oxygen was generated when intracellular ROS penetrated the particles, leading to rupture of the carrier and subsequent release of encapsulated drugs. Furthermore, the generated oxygen relieved hypoxia-induced multidrug resistance and enhanced the efficacy of chemotherapy [56]. Similarly, Liu and Feng et al. reported a redox-sensitive liposome loaded with catalase and Pt(IV) prodrug for enhanced chemo-radiotherapy against tumors under hypoxic conditions. These systems can catalyze the decomposition of hydrogen peroxide produced by tumor cells, thereby acting as an oxygen source to relieve hypoxia and remarkably enhance the therapeutic efficacy of chemo-radiotherapy [57].

4 Enzyme-responsive nanoplatforms for controlled release of metal complexes

Although nanoplatforms responsive to pH and redox signals have been extensively investigated for controlled release and activation of metal complexes for precise therapeutics, the inherent pH gradient and presence of reductants in both healthy and diseased tissues may potentially compromise their specificity during treatment. Therefore, alternative approaches that allow more selective on-demand treatment in response to specific triggers in diseased sites are required. Recently, the enzyme-responsive nanoplatform has emerged as a promising option for precise delivery of metal complexes. Enzymes play critical roles in all biological and metabolic processes, and misregulation of enzyme expression and activity underpins the pathology of many diseases [58]. Using enzymes as triggers can be advantageous for developing therapeutics because of their ability to promote chemical reactions under physiological conditions [59, 60]. Furthermore, enzymes exhibit extraordinary selectivity for their substrates, which allows specific and

sophisticated therapeutic modality within desired biological targets [61]. In the past few years, a number of nano-scaled materials have been employed for designing enzyme-responsive systems, including polymers, phospholipids, and inorganic materials. The integration of nanomaterials with enzymatic responses can endow metal complexes with bio-specificity and selectivity, which are critical for biomedical applications. For example, Chen and coworkers have constructed a biocompatible DNA origami nanostructure for delivery of the anticancer ruthenium complex (Fig. 3). The unique tetrahedral DNA nanocages facilitate intercalation with the Ru(II) complex, enhancing the loading efficiency of therapeutic agents. Further conjugation with biotin allows specific cellular uptake of the DNA nanocarrier by HepG2 cells via receptor-mediated targeting. Moreover, unlike free Ru(II) complex or nanocage alone, this system can translocate to the cell nucleus upon internalization and is degraded in response to DNases, which leads to controlled drug release and subsequent induction of effective cell apoptosis through ROS-mediated signaling pathways [62].

5 Light-responsive platforms for precision therapeutics

Compared to intrinsic stimuli (e.g., pH gradient, redox environment, and enzyme activity) external stimuli (e.g., light trigger and magnetic field) also display advantages of user-defined control over time and space without interference from complex biological environments. Therefore, therapeutic platforms that respond to external stimuli will enable more precise temporally regulated release of therapeutic agents within a highly confined area of interest. Among diverse external stimuli, the light trigger strategy is gaining increasing attention because of its utility for on-demand therapeutics in well-delimited sites, which arise from the non-invasive and spatiotemporally precise mode of action after light irradiation [63–65]. Currently, various photo-sensitive therapeutic systems have been studied for light-responsive drug release, photodynamic therapy (PDT), and photothermal therapy (PTT) under living conditions [66–68]. Until now, the most widely used light sources for therapeutic purpose were based on ultraviolet–visible (UV–vis) light, the penetration depth of which has been limited by the absorption and scattering of endogenous molecules such as water, lipids, and proteins inside living systems [69–71]. Therefore, efforts for improving tissue penetration depth in deep subcutaneous pathological sites are urgently required. One of the key strategies for achieving deeper tissue penetration is the use of NIR light within the range of NIR window (e.g., ~ 650–1,350 nm). Light within this range exhibits

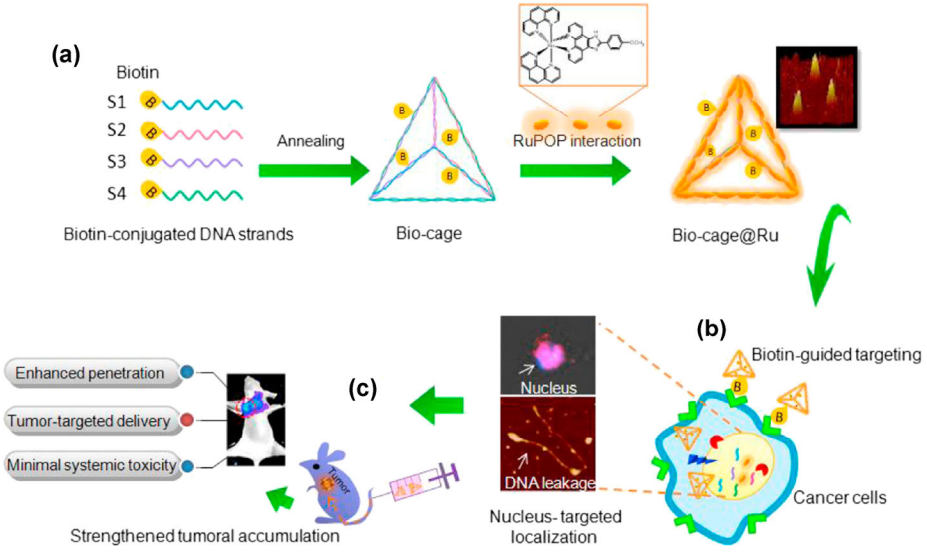

Figure 3 Enzyme-mediated precision therapeutics. Illustration of multifunctional Bio-cage@Ru nanostructure for enhanced tumor treatment and reduced systemic toxicity. Reproduced with permission from Ref. [62], © Elsevier B.V. 2016.

better tissue penetration depth (e.g., < 10 cm) than UV–visible light (e.g., < 1 cm) because of the lower absorption coefficient of water, lipids, and proteins. In addition, compared to short-wavelength UV–visible light, long-wavelength NIR light is expected to cause minimal photodamage to biomolecules, cells, and tissues. Toward this objective, an increasing number of drug molecules and bioprobes responsive to NIR light have been devised [72–74]. However, the laborious synthetic procedures, poor aqueous solubility, and limited accumulation within pathological area have restricted their future applications. Owing to the advances in chemistry and nanotechnology, certain novel nanomaterials (e.g., upconversion nanoparticles (UCNPs), gold nanoparticles, and carbon nanomaterials (CNMs)), which display large NIR absorption coefficients, have gained increasing attention because of their ability to absorb NIR light and facilitate the generation of bioactive species (e.g., drugs and ROS) for treatment of diseased sites situated in deep tissue [75]. Furthermore, these promising materials can act as useful platforms for integration of multiple functions in one single system, which can considerably promote simultaneous disease diagnosis, treatment, and *in vitro* and *in vivo* real-time imaging.

5.1 UV–visible light-mediated precision therapeutics

Currently, the most commonly used strategies for generating light-responsive therapeutics involve stimulation by UV–visible light, via which photolabile and photoactivatable moieties are triggered to induce controlled therapy as well as imaging at targeted sites. In this section, we will discuss rational drug design through controlled photo-release of bioactive molecules and activation of prodrugs by light irradiation.

5.1.1 UV–vis light-triggered drug-release

Carbon monoxide (CO) is known for its toxicity, which arises from its strong affinity towards hemoglobin.

However, recent studies revealed that it can also function as an important cell signaling mediator in response to stress and inflammation [76]. In addition, CO is known to exert protective roles through its anti-inflammatory, anti-apoptotic, and anti-proliferative properties [77]. However, its systemic toxicity and the requirement for precise control of the location, dosage, and timing of gaseous molecule delivery are two major challenges for controlled CO release. Photoactive CO-releasing metal complexes exhibit potential for intracellular CO delivery because of their ability to store CO in solid state, which can be liberated upon external light stimulation. However, these compounds may diffuse rapidly, which may lead to unwanted toxicity to healthy tissue [78]. The integration of CO-releasing complexes and nanomaterials is one of the promising strategies for achieving localized on-demand delivery of CO for therapeutic purposes. Therefore, considerable efforts have been devoted to this area [79–82]. For instance, Mascharak's group developed a nanocarrier based on mesoporous silica nanoparticles (MSNs) entrapped with a tailored photo CO-releasing molecule (CORM) for rapid eradication of human breast cancer cells through tractable light-triggered CO delivery [83]. Initially, this group prepared a photoCORM (fac-$[Re(CO)_3(pbt)(PPh_3)](CF_3SO_3)$), which could not only release CO upon illumination with low-power UV light (e.g., 305 nm, 5 $mW{\cdot}cm^{-2}$), but also exhibited "turn-off" fluorescence signal change upon release of the CO ligand. This provided a convenient strategy for tracking CO release event. Upon integration with MSNs, the photoCORM can be effectively internalized by live cells. In the presence of light stimulation, the fluorescence signal of the photoCORM rapidly decreased with CO release, which exerted cytotoxic effect on malignant cancer cells. Moreover, Ueno's group has developed a photoactive CO-releasing protein cage for dose-regulated delivery in living cells [79]. They have synthesized a composite of protein with photoCORMs (e.g., Mn-carbonyl complexes) by designing a protein mutant that can stabilize the CO-releasing complexes within the *in vivo* environment. Further studies revealed that the cellular uptake and light-induced (e.g., 456 nm light) CO-releasing properties of this protein cage activate nuclear factor-kB (NF-kB) and tumor necrosis factor a (TNF-a) in mammalian cells, which underscores the potential of protein cages in uncovering the role and mechanism of action of CO within living systems.

5.1.2 UV–vis light-triggered photo-activation of prodrugs

In addition to light-triggered release of gaseous

signaling mediators, an alternative approach in UV–vis light-mediated therapeutics involves photo-activation of prodrugs. In this case certain non-toxic photoactive metal complex-based prodrugs can be converted into their active form after light irradiation, which thereafter exert cytotoxic effect for therapeutic purposes [84]. Therefore, delivery of complexes with such properties will allow controlled prodrug activation within targeted diseased area after light stimulation. For instance, Frasconi et al. recently developed a MSNPs2 novel platform using covalent linkage between the Ru(II) complex and MSNPs (Fig. 4(a)). After light treatment, the Ru(II) complexes were rapidly released and transformed into cytotoxic aqua complexes, which subsequently formed monoadducts with DNA. In addition, paclitaxel formed caged-prodrug with the Ru(II) complex loaded on MSNPs during rational designing of chemotherapy medication. Paclitaxel can be released in a visible light-controlled manner to inhibit mitotic progression and cell proliferation during cancer treatment [85]. Furthermore, Xing et al. demonstrated a novel human serum albumin (HSA) protein-based nanocarrier, which combined the photoactivatable Pt(IV) antitumor prodrug for controlled release and fluorescent light-up probe for evaluation of drug action and efficacy (Fig. 4(b)). The constructed Pt(IV)-probe@HSA platform can be locally activated by UV irradiation to release the active Pt species, which led to enhanced cell death in both drug-sensitive A2780 and cisplatin-resistant A2780cis cell lines compared to the free prodrug molecules. Furthermore, the cytotoxicity caused by light-controlled drug release leads to apoptosis by activating caspase 3, a typical programmed cell death protease, which can be visualized using apoptosis-sensitive probes on the platform. This unique design offered a successful strategy for controlled drug delivery via biocompatible protein-based nanocarriers for enhancing therapeutic efficacy. In addition, it also provided real-time monitoring of antitumor drug efficacy at earlier stages, which may significantly benefit personalized cancer chemotherapy *in vitro* and *in vivo* [86].

5.2 NIR light-mediated precision therapeutics

Strategies based on light-triggered therapeutics have attracted considerable attention for their specificity and spatiotemporal precision. In most cases, the excitation sources for light-mediated therapeutics are based on radiations within the UV–vis range. Despite their initial success, short-wavelength light (e.g., UV–vis light) may have certain drawbacks such as limited tissue penetration and unwanted photodamage to cells and tissue [87, 88]. Hence, strategies that allow precise light-mediated therapeutics with deep tissue penetration and minimum phototoxicity are highly desired. Recently, an alternative strategy based on excitation via light within the NIR window (e.g., 650–1,350 nm) has emerged, which may meet clinical demands [89, 90]. Endogenous light absorbers such as water, lipids, and proteins exhibit minimum light absorption within the NIR window. This contributes to unique advantages of NIR excitation, such as

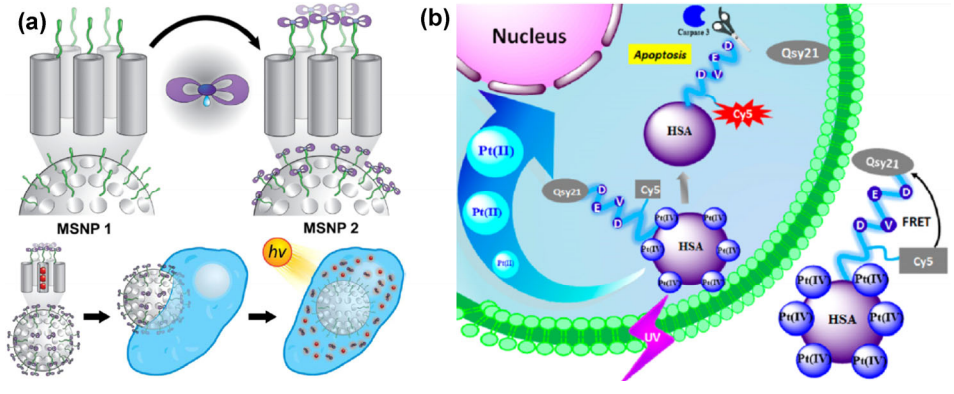

Figure 4 UV–visible light-mediated therapeutic strategies. (a) Scheme of visible light-controlled drug delivery through photoactivation of Ru(II)-dppz complex modified MSNs. Reproduced with permission from Ref. [85], © American Chemical Society 2013. (b) Human transport protein carrier for controlled photoactivation of antitumor prodrug and real-time intracellular tumor imaging. Reproduced with permission from Ref. [86], © American Chemical Society 2015.

deeper tissue penetration, minimal autofluorescence background, as well as limited light scattering or absorbance from endogenous biomolecules, and less photodamage, which are beneficial for light-mediated therapeutics in living systems. So far, several strategies have been used for effective therapy and imaging based on NIR-light mediated platforms [91, 92]. One frequently used method of NIR light-mediated therapeutics involves developing light-responsive drug delivery systems with precisely controlled drug release via light-promoted reactions. Another widely studied approach, PDT, is based on integration of nanocomposites with photosensitizers (PS) [93, 94]. In the presence of NIR light stimulation, PS molecules generate ROS owing to their unique photo-physical and photo-chemical properties, which can be used for treating diseases. In addition, another well-established method for light-induced therapeutics involves the application of PTT, which converts NIR radiation into heat after intense absorption by thermal-sensitive agents [95, 96]. In this section, we will briefly introduce the NIR-light mediated *in vitro* and *in vivo* precision therapeutic approaches for drug delivery, PDT, and PTT.

5.2.1 *NIR light-triggered drug delivery*

Currently, the most noteworthy light-mediated treatment approach is the NIR light-triggered drug delivery system, which is emerging as an effective technique for solid tumor treatment in recent years [97]. Typically, NIR light is used to either promote photochemical reaction of caged-drugs or for NIR-light induced heat generation for controlled drug delivery within diseased sites. Toward this objective, one commonly used method involves rational designing of prodrugs by integrating light-sensitive agents with multifunctional nanoplatforms. In the presence of light, the nanoplatform is activated, which induces structural changes in the prodrug, thereby effectively activating the prodrug for precision therapy. In addition, the nanoplatform can act as an intelligent carrier for enhancing treatment efficacy via the EPR effect and accumulate high doses of drugs within the targeted area. So far, various NIR light-responsive drug delivery platforms based on nanomaterials, such as UCNPs [98], CNMs [75] and gold nanomaterials [99, 100] have been extensively investigated for NIR light-mediated delivery of drugs.

Among various nanomaterials for NIR light-mediated therapeutics, UCNP, an unique rare-earth lanthanide-doped nanoplatform, has attracted much attention owing to its impressive photophysical properties [101–105]. Generally, UCNPs are able to convert low-energy NIR light irradiation (e.g., 808 or 980 nm, etc.) into high-energy UV or visible light [103, 106, 107]. The upconverted emissions within UV or visible window can effectively trigger the photo-release of bioactive molecules or the photo-activation of light-sensitive prodrugs [108–112]. For instance, recently, both Xing's and Lin's groups have independently devised novel UCNP-based NIR light-mediated delivery systems for light-controlled activation of Pt(IV) anticancer prodrug. Lin conjugated a newly designed Pt(IV) prodrug, trans,trans,trans-$[Pt(N_3)_2(NH_3)(py)(O_2CCH_2CH_2COOH)_2]$ to core-shell UCNPs (Fig. 5(a)). This photoactive system can not only display significant *in vivo* antitumor efficacy after 980-nm laser irradiation, but also act as multifunctional tri-modality imaging contrast agents for cancer treatment in living animals [113]. In contrast, a photo-sensitive Pt(IV) prodrug, trans, trans, trans-$[Pt(N_3)_2(py)_2(OH)(O_2CCH_2CH_2COOH)]$, together with an apoptosis sensing probe, were conjugated to silica-coated UCNPs by Xing's group (Fig. 5(b)). In the presence of light stimulation (980 nm), the Pt(IV) prodrug can be activated via upconverted UV emission to exert cytotoxic effect within cancer cells. Furthermore, caspases triggered by the cytotoxicity of the activated Pt drug can interact with peptide-based apoptosis sensing probes, which results in emission of fluorescence for real-time cell imaging and earlier evaluation of antitumor therapeutic efficacy [114]. Apart from photo-activation of prodrugs, another effective approach for controlling drug delivery in deep tissues depends on the photo-triggered release of biologically active molecules [115, 116]. For example, Xing's group recently demonstrated NIR light-mediated activation of cytotoxic Re(I) complexes using lanthanide-doped UCNPs. Typically, UCNPs can be used to activate the complex, with upconversion luminescence triggered by NIR. Upon NIR irradiation, the Re(I) complex can be locally activated to generate biologically active ROS and CO molecules. These

systems exhibited enhanced cytotoxicity against both drug-susceptible A2780 cells, demonstrating that NIR irradiation combined with this system can achieve potent photoactivated cytotoxicity while minimizing unwanted photodamage to cells [109]. In another study, Wu and coworkers fabricated a light-responsive drug delivery system by loading mesoporous silica-coated UCNPs with DOX (Fig. 5(c)). To achieve light-controlled release and prevent non-specific drug leakage, photo-sensitive Ru(II) complexes are grafted on the surface of nanoparticles as molecular valves [115]. After the NIR light trigger, upconverted emissions from UCNPs induce the cleavage of molecular valves on particle's surface, thereby allowing on-demand release of loaded drugs in a light-dependent manner. In addition to the strategies based on photo-triggered release and photo-activation of prodrugs, the heat produced by specific NIR light-sensitive materials has been also widely investigated as an alternative approach for light-mediated drug delivery. Generally, the rational design involved using nanomaterials with unique optical properties, which enabled the absorption of NIR light and converted them into heat. The locally produced heat increases the temperature of the surrounding diseased area, leading to rapid drug release from the nano-carrier. So far, a variety of light-to-heat transducers such as AuNPs [117], CuS [118], and Pd@Au [119] have been reported for heat-induced drug delivery. For example, Sun and co-workers constructed a platform for NIR light-induced dual drug release via the photothermal effect of polymeric carrier loaded with indocyanine green

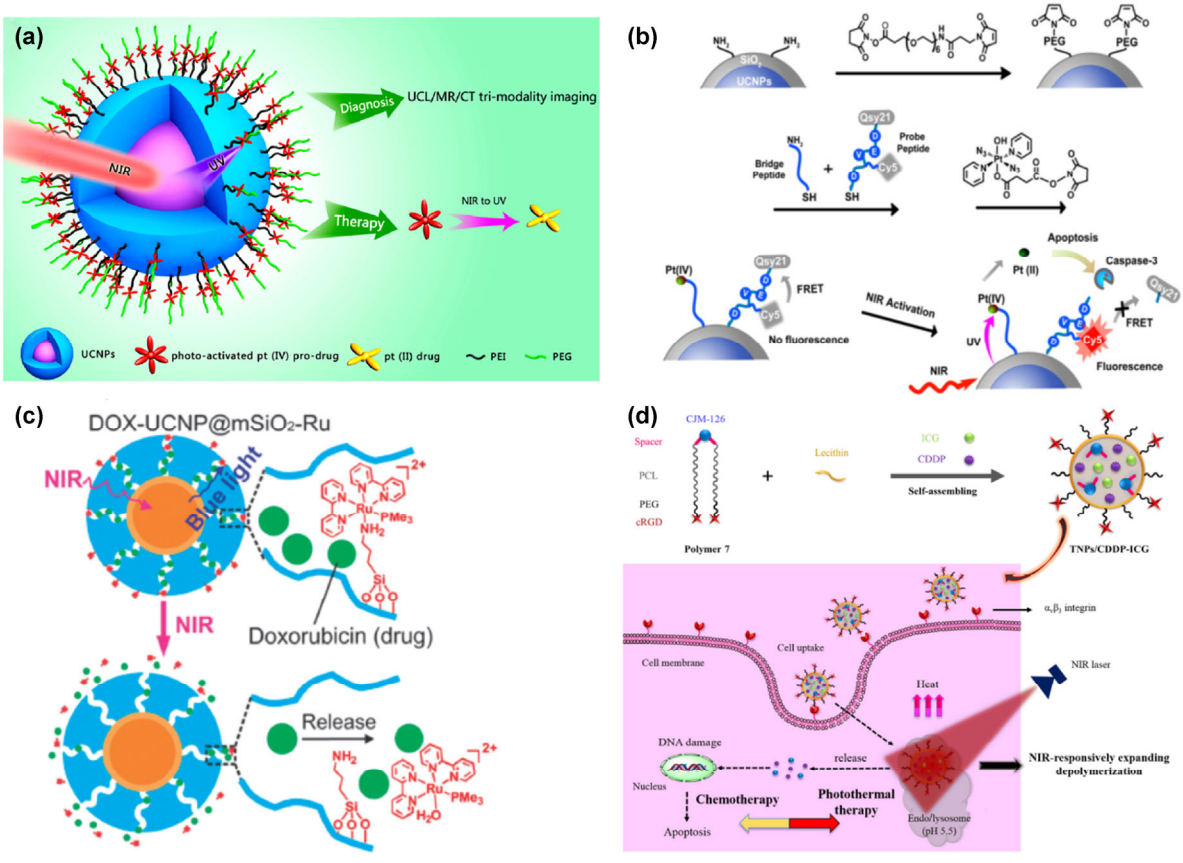

Figure 5 NIR light-triggered drug delivery strategies. (a) Scheme of NIR light-mediated UCNPs nanoplatform for Pt(IV) prodrug-based therapy and multimodal imaging. Reproduced with permission from Ref. [113], © American Chemical Society 2013. (b) Pt(IV) prodrug photoactivation by 980-nm light and intracellular monitoring of apoptosis. Reproduced with permission from Ref. [114], © John Wiley & Sons, Inc 2014. (c) Upconverted blue luminescence triggers cleavage of Ru complexes and release of doxorubicin from DOX-UCNP@mSiO$_2$-Ru nanoparticles. Reproduced with permission from Ref. [115], © Royal Society of Chemistry 2015. (d) NIR-responsive binary-drug loaded photothermal conversion nanoparticles for drug delivery. Reproduced with permission from Ref. [120], © IOP Science 2018.

(ICG) dye (Fig. 5(d)) [120]. The NIR light-sensitive ICG allows light to heat conversion, which accelerated the expanding depolymerization of nanoparticles when exposed to 808 nm NIR light. Subsequently, the loaded drugs, DOX and CDDP, can be released after degradation of the nanoparticles to exert cytotoxic effect. Yeh's group recently developed oligonucleotide-assembled Au nanorods for NIR light-triggered dual drug delivery. In their design, single-stranded DNAs were assembled onto the surface of Au nanorods. The complementary DNA strands, which were conjugated to the Pt(IV) prodrug, were hybridized. The resulting double stranded DNA sequences facilitated the loading of DOX. Upon heating by 808-nm NIR light, dehybridization of double-stranded DNA lead to rapid release of both drugs within the intracellular environment for effective cancer treatment [117]. In addition to drug release, light-responsive nano-formulated complexes can also regulate cellular events [121]. For instance, Qu and coworkers have developed an intelligent spiropyran-upconversion nanoparticle (SP-UCNPs) based on light-activatable nanosystems for accurate spatial and temporal regulation of zinc signaling in living cells. By varying the duration of NIR irradiation, the magnitude of zinc released can be easily manipulated to regulate downstream biological events, such as protein activity. This promising strategy can precisely control the specific signaling pathways of metal ions while minimizing cellular damage and facilitating advanced manipulation of cellular dynamics.

5.2.2 *NIR light-triggered PDT*

NIR light-mediated drug delivery systems have been recognized as effective approaches for treating diseases. In addition to the methods based on the light-activatable prodrug or photo-triggered drug release, PDT is another well-established therapeutic modality, which relies on photosensitizers to produce ROS (e.g., hydrogen peroxide, hydroxyl radical, and singlet oxygen) after light irradiation ROS are usually associated with oxidative stress and cellular damage caused by their reaction with cellular components such as DNA and proteins [122–125]. Compared to traditional therapeutic modalities (e.g., chemotherapy), PDT displays unique advantages, especially in cancer therapy owing to its intrinsically non-invasive nature, safety, and spatiotemporal precision after light treatment. Therefore, PDT has been developed as a promising therapeutic approach for effective cancer treatment and has been approved by the FDA [126].

Currently, a variety of metal complex-based photosensitizers (e.g., ZnPc, Ir complexes etc.) have been developed owing to their efficiency in singlet oxygen generation [127, 128]. For instance, Huang's team developed a novel Ir(III) complex containing phosphorescent polymer dots (Pdots). The excited state energy transfer from Pdots to molecular oxygen facilitated optical sensing of oxygen with high sensitivity. In addition, upon 488-nm light stimulation, these Pdots are capable of generating singlet oxygen for effective inhibition of tumor cells *in vitro* [129]. Despite the initial success, their extensive use in clinics is restricted by two challenges. First, most PS molecules applied in PDT are hydrophobic, which may lead to limited accumulation within diseased sites due to their lack of aqueous solubility. To circumvent this problem, various carriers based on nanomaterials have been developed to deliver PS agents to targeted diseased area with improved PDT efficacy. Limited tissue penetration is another drawback of traditional PDT, as most PS agents only respond to short-wavelength light. To circumvent these problems, extensive efforts have been made to explore the feasibility of NIR light for PDT, mainly because of their ability to penetrate deeper in tissues, which may significantly improve the safety of PDT treatment by effectively reducing light-induced cytotoxicity in living systems. Although various NIR light-responsive PS molecules have been developed for PDT in clinics, some drawbacks, including laborious synthesis procedures, poor aqueous solubility, and limited accumulation in diseased area, have restricted their application in deep-tissue therapeutics. In recent years, various types of nanomaterials with large extinction coefficient in the NIR window, including organic NPs (e.g., polymeric NPs [130, 131], liposomes [132]) and inorganic NPs (e.g., carbon-based NPs [133], gold-based NPs [134], and UCNPs [135]), have been extensively investigated for PDT applications both *in vitro* and *in vivo*.

As a promising candidate, lanthanide-doped UCNPs,

which are able to convert NIR light into broad UV/visible emission, can act as a powerful tool to overcome the major limitations of current PDT strategies by using NIR light illumination. For instance, Zhang and coworkers were the first to report 980-nm light-triggered PDT in living cells using UCNPs as light transducers to activate PS agents [136]. Similarly, Gu and Cui et al. have also demonstrated *in vivo* deep-tissue PDT using NIR light-triggered UCNPs. Typically, a well-established metal complex-based photosensitizer, ZnPc, is loaded on to UCNPs via the surface functionalized polymer chitosan (Fig. 6(a)). This system not only displayed significant *in vivo* antitumor efficacy after 980-nm laser irradiation, but also acted as multifunctional upconversion luminescence (UCL) imaging contrast agents for cancer treatment in live animals [137]. Furthermore, Zhang's team developed an intelligent UCNP-based PDT strategy. In their design, two photosensitizers, ZnPc and MC540, were incorporated into one single UCNP platform (Fig. 6(b)). Upon NIR light stimulation, the upconverted emissions (e.g., at ~ 540 and ~ 660 nm) activated both types of PS molecules, thereby significantly enhancing PDT efficacy. In addition, surface coating with tumor-targeting ligands such as folic acid imparted the UCNP platform with effective tumor accumulation ability, which is important for NIR light-mediated *in vivo* PDT treatment [138].

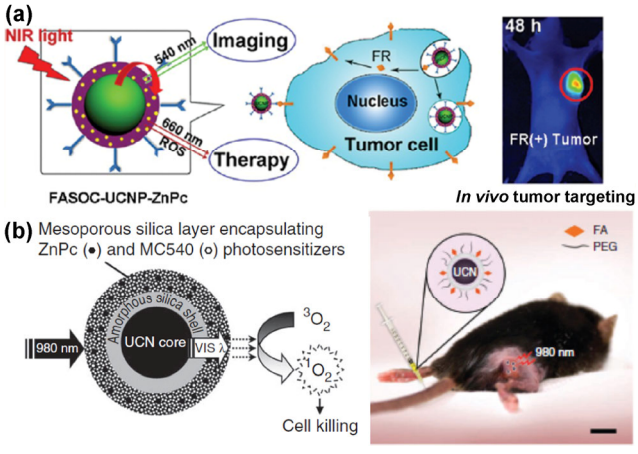

Figure 6 NIR light-mediated PDT strategies. (a) FA/PEG-modified UCNPs@mSiO$_2$ loaded with ZnPc and MC540 for PDT. Reproduced with permission from Ref. [137], © American Chemical Society 2012. (b) FA and ZnPc modified FASOC-UCNP-ZnPc nanoconstruct for PDT and simultaneous UCL imaging applications. Reproduced with permission from Ref. [138], © Macmillan Publishers Limited, part of Springer Nature 2012.

5.2.3 *NIR light-triggered photothermal therapy*

Over the past decade, NIR light-mediated drug delivery and PDT therapeutic approaches have been extensively studied for effectively treating diseases. In addition, another promising therapeutic modality, PTT, has also attracted considerable attention in recent years. Basically, PTT utilizes photothermal conversion agents (PTCAs) to locally convert NIR light into heat. The localized heat generation leads to overheating of diseased sites, which facilitates damage of surrounding biological species and causes subsequent cell death [139]. Generally, the ideal PTCAs possess the following advantages: 1) strong NIR light absorption; 2) excellent photothermal conversion efficiency; 3) good biocompatibility and biodegradability. So far, various promising PTCAs, including inorganic nanomaterials [140–143] and organic polymers [144, 145], have been developed for effective NIR light-triggered PTT treatment *in vitro* and *in vivo*. For instance, Chao's team recently developed gold nanoparticles with Ru(II) complexes grafted on the surface of nanoparticles (Fig. 7(a)). The Ru(II) complexes that displayed strong NIR absorption were utilized as antenna molecules to effectively harvest NIR photons, which considerably improved the photothermal efficiency of the Au nanomaterials *in vitro* and *in vivo* [146]. In addition to their successful application in cancer treatment, metal complexes also exhibit efficient antimicrobial activity against bacterial infections via various mechanisms, including damage to bacterial cell walls, and photothermal inactivation [147–150]. For instance, Chen and Wang et al. proposed an *in situ* synthesis strategy for graphene oxide (GO)-wrapped gold SERS tags by using Ru(bpy)/GO nanohybrid as the Raman reporter (Fig. 7(b)). This nanomaterial may serve as a multifunctional platform, which allows sensitive Raman imaging of both Gram-positive (e.g., *Staphylococcus aureus*, etc.) and Gram-negative (e.g., *Escherichia coli*, etc.) bacteria. In addition, effective photothermal eradication of both types of bacteria can also be achieved with NIR light treatment. Furthermore, the correlation between SERS signal intensity and bacteria survival rate enables simultaneous monitoring of light-triggered antimicrobial efficacy [151].

Although these nanomaterials based on inorganic structures exhibited good therapeutic effects, concerns

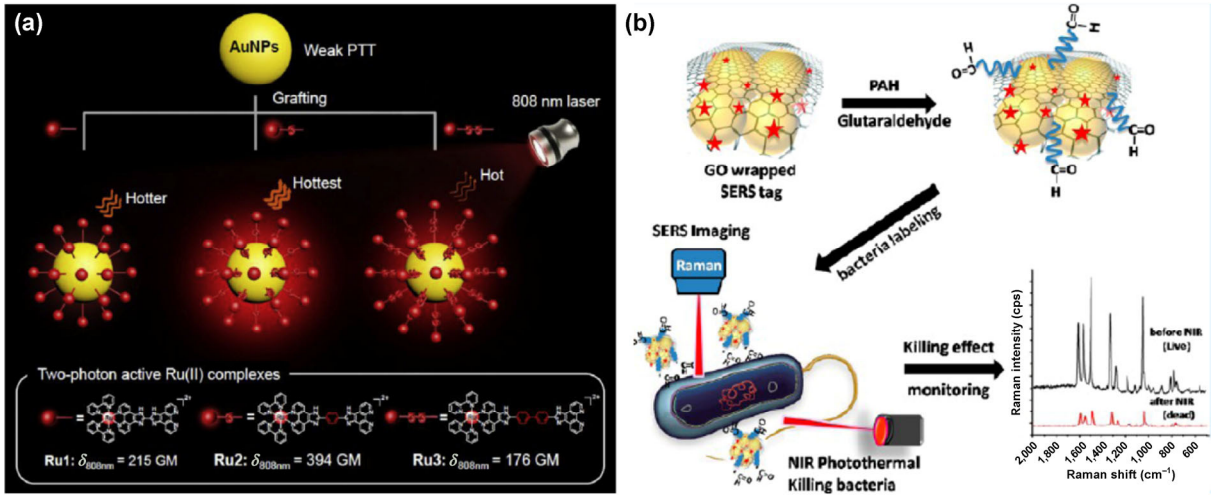

Figure 7 NIR light-mediated PTT strategies. (a) Illustration of gold nanoparticles grafted with Ru(II) complexes for PTT. Reproduced with permission from Ref. [146], © Elsevier B.V. 2015. (b) Au@Ru(bpy)/GO for PTT and simultaneous SERS imaging applications. Reproduced with permission from Ref. [151], © American Chemical Society 2014. PTT, Photothermal therapy.

over their non-biodegradable properties and long-term biosafety may potentially restrict their future applications *in vivo* and in clinics. Therefore, several types of PTT materials such as NIR dye-loaded liposomes [152], polymers [153], and micelles [95, 154] have been extensively studied over the past decades. For instance, Zhang and Sun et al. have demonstrated a facile and feasible approach for enhancing 808-nm photothermal conversion effect of d orbit transitions of Cu(II) ions using Cu-carboxylate complexes. The coordination with carboxylate groups significantly enhances the splitting energy gap of Cu(II) and the capability of electron transition, which improves absorption in the NIR region. Further loading of the cupreous complex into biocompatible chitosan NPs enabled photothermal therapy of human oral epithelial carcinoma (KB) cells *in vitro* and *in vivo*. These nanoplatforms not only inhibited tumor growth through effective PTT, but the released cupreous complexes also served as chemotherapeutic agents for tumor treatment [155].

6 Magnetic stimuli-responsive platforms for precision therapeutics

Although light-responsive therapeutic approaches have enabled precise therapeutic intervention for several diseases, the use of high power laser has raised safety concern because of its potential damage to tissues. Therefore, alternative stimuli-responsive strategies with minimum damage to biological samples are required for developing precision therapeutics [156]. Similar to light, magnetism constitutes an external non-invasive method of activation that has attractive capabilities, as it can be controlled in a temporal and spatial manner. In addition, magnetic stimuli have been considered to be a promising option for designing precision therapeutics owing to the fact that magnetic fields rarely interact with the patient's body compared to other traditional stimuli, e.g., pH and light [157]. Currently, various strategies based on magnetically-responsive systems have been reported mainly because of their ability to achieve magnetically-guided targeting and hyperthermia-induced drug release in an alternating magnetic field [158–160]. Typically, magnetic guidance can be obtained by focusing an external magnetic field on the targeted diseased site during the administration of magnetically-responsive nano-systems. The interaction between the magnetic field and nano-system facilitates the targeting and accumulation of nanocarriers within the diseased regions [161, 162]. Furthermore, once the carrier reaches the biological target in the region of interest under the influence of an external oscillating or alternating magnetic field (AMF), the magnetically-active nanosystems can act as transducers to produce

heat in the surrounding environment for controlled drug release or thermal therapy [163]. By combining these properties, a broad spectrum system for on-demand drug delivery has been proposed. For instance, Janiak and Kunz et al. reported manipulation of CO-gasotransmitter release via a magnetic signal. As a proof-of-concept, a CORM (e.g., [RuCl(CO_3)-(l-DOPA)]) was conjugated to a nano-magnet (Fe_2O_3 nanoparticles) as a precursor of CO-gasotransmitters (Fig. 8(a)). Upon heating within AMF, the locally increased temperature facilitated the rapid CO release from the Ru(II) complex within targeted region [164]. In addition, Zhang and coworkers developed a multifunctional theranostic platform for precise therapy and simultaneous magnetic resonance imaging (MRI). In their design, β-cyclodextrin (β-CD) was conjugated to the silica shell surface of a core-shell magnetic mesoporous silica nanoparticle (Fe_3O_4@MSN) as a gatekeeper for a Pt(IV) prodrug (Fig. 8(b)). Upon administration, the nanoparticles accumulated at cancerous regions via magnetic targeting and enhanced EPR effect. Once internalized by the tumor cell, the reducing microenvironment induced the reduction of the Pt(IV) prodrug and removed the gatekeeper β-CD, thereby promoting the release of loaded anticancer agent DOX for precision therapy. In addition, the magnetic properties of the nanoparticles enabled simultaneous magnetic resonance imaging (MRI) imaging modality for theranostic purpose [165]. In another study, Kim and Ishikawa et al. designed a magnetically active theranostic platform for effective treatment of cancer. For ensuring the potential biosafety of conventional inorganic magnetic nanoparticles, the platform was based on polymeric nanoassembly loaded with simple magnetic metal complexes (Fig. 8(c)). The simple complex Fe(Salen) acted as an antitumor agent owing to its intrinsic antitumor activity. Furthermore, the ubiquitous magnetic properties of this versatile complex endowed the nanoassembly with favorable magnet-guided targeting ability and MRI imaging modality. Importantly, the magneto-thermal properties triggered the release of encapsulated dual drug (Fe(Salen) and DOX) for precise drug delivery to achieve enhanced tumor treatment *in vivo*, demonstrating its potential as a theranostic platform in future preclinical applications [166].

7 Concluding remarks

Currently, metal based therapeutic agents are being widely used in clinical application for the treatment of diseases. Rationally designed metallodrugs with

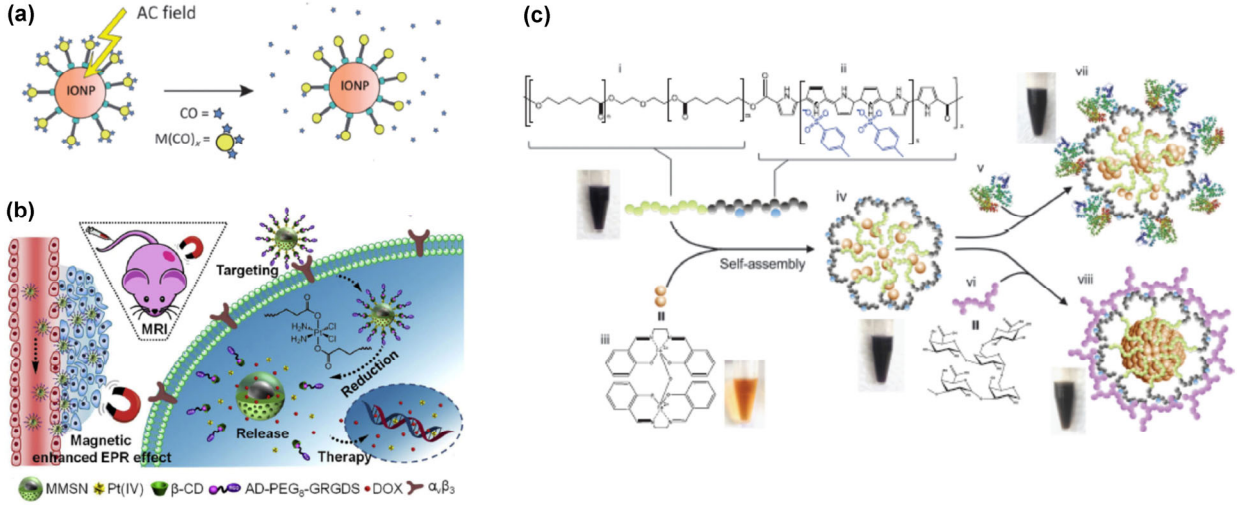

Figure 8 Magnetic stimuli-mediated precision therapeutics. (a) Illustration of induced CO-release from CORM-functionalized IONP using an alternating magnetic field. Reproduced with permission from Ref. [164], © Royal Society of Chemistry 2013. (b) The design and proposed mechanism of the multifunctional MMSNs for tumor-targeted MRI and precise therapy. Reproduced with permission from Ref. [165], © Elsevier B.V. 2016. (c) Preparation of Fe(Salen)-loaded polypyrrole (ppy)-polycaprolactone (PCL) core–shell nanoassembled composites for a single-drug anticancer platform. Reproduced with permission from Ref. [166], © Macmillan Publishers Limited, part of Springer Nature 2017.

potent therapeutic efficacy, as well as high specificity and minimal toxicity, are highly desired, and they play important roles as precision medicine. Unfortunately, most of the currently used metallodrugs have drawbacks of limited specificity, inevitable toxicity, and adverse side effects. Therefore, new alternative metallodrugs, which address the limitations of currently used therapeutic agents are essential to achieve the goals of precision therapeutics. In this review, we have mainly focused on the specificity and environment-responsiveness of metallodrug nanoformulations in disease treatment and have summarized the well-established strategies used for the development of metal complex-functionalized smart nanoplatforms, which respond to different types of external and internal stimuli. Despite the initial success of these stimuli-responsive therapeutic strategies, the application of metallodrugs as precision medicines is still a far cry.

First, despite the clinical success of currently available metallodrugs, these therapeutic agents possess drawbacks such as lack of specificity, inevitable toxicity, and side effects. Therefore, development of new drugs based on metal complexes with desired properties such as efficient therapeutic efficacy, broad-spectrum disease suppression, enhanced specificity, and minimal side effects are required. These subjects are among the top priorities of different research fields including biochemistry, molecular biology, pharmacology, and medicinal chemistry.

Second, although the currently used metallodrugs can be used effectively for disease treatment, detailed information regarding their active structure and behavior in biological environments is lacking. To completely utilize the potential of metallodrugs and optimize therapeutic activity while minimizing size effects, it is necessary to understand the fate of the metal complex once it enters the body. To what extent will the metal complex undergo ligand exchange or dissociation? How much does the designed ligand affect this process? Are the toxicological properties of metal complex predictable based on the knowledge of metal speciation in body? What role does oxidation state of metal ions play in this? Although these questions have been raised previously, most of them still remain unanswered. Therefore, further understanding of the mechanism of action of metal drugs and speciation of drugs both in transit to cells or inside cells are still required. An in-depth understanding of metallodrugs in terms of their mechanism of action and structure-activity relationship can significantly facilitate the development of more novel metallodrugs with potent therapeutic effects as well as minimal side effects.

Third, in addition to their therapeutic effect, certain metal complexes are also known for their versatility in molecular imaging (e.g., magnetic resonance imaging, single photon emission computed tomography, and positron emission tomography) [167]. The use of multifunctional therapeutic metal complexes for biomedical imaging may open up a new window for theranostic agents, which will allow simultaneous disease diagnosis and personalized treatment within one single molecular platform for future clinical practice.

In addition, although a large number of nanostructures has been currently demonstrated to significantly improve therapeutic efficiency and reduce the side effects of the currently used metallodrugs, most of these nanoplatforms, especially for inorganic nanomaterials, face inevitable challenges because of potential biosafety issues, such as non-biodegradable properties and side effects of long-term accumulation inside living system post-administration [168]. Although numerous studies have reported that the biocompatible surface coating (e.g., polymer and silica,) can reduce the toxicity of inorganic nanomaterials in living systems, their long-term safety in clinics is still being cautiously investigated. Therefore, development of alternative biodegradable and safe therapeutic nanoagents, such as biodegradable polymer or carbon-based nanomaterials, and protein-based nanocarriers, are urgently required as stimuli-responsive therapeutic nanoplatforms for precise treatment of diseases in the near future.

Furthermore, despite the initial success of stimuli-responsive nanoplatforms in precision therapeutics, further understanding of the spatial and temporal pattern of biological stimuli are essential for more effective and precise therapy. For instance, examples of misrelated enzyme activities in diverse diseases, and even at different stages of one particular disease, are abundant [169]. Therefore, better spatiotemporal

Table 1 Representative examples of light-responsive platforms for precision therapeutics

Wavelength range	Wavelength	Delivery system	Size	Mode of action	Loading capacity	Loaded complex	Ref.
UV light	305 nm	MCM-41	100 nm	Drug release	0.97%	Re(I) complex	[83]
UV light	365 nm	HSA NPs	200 nm	Photoactivation of prodrug	4.10%	Pt(IV) complex	[86]
Visible light	456 nm	protein assembly	12 nm	Drug release	—	Mn(I) complex	[79]
Visible light	—	MCM-41	120 nm	Photoactivation of prodrug	—	Ru(II) complex	[85]
Visible light	488 nm	polymeric NPs	19 nm	PDT	8%	Ir(III) complex	[128]
NIR light	980 nm	UCNPs	65 nm	Photoactivation of prodrug	2.60%	Pt(IV) complex	[113]
NIR light	980 nm	UCNPs	35 nm	Photoactivation of prodrug	3.50%	Pt(IV) complex	[114]
NIR light	980 nm	UCNPs	118 nm	Drug release	6.14%	Re(I) complex	[109]
NIR light	980 nm	UCNPs	92 nm	Drug release	0.76%	Ru(II) complex	[115]
NIR light	808 nm	polymeric NPs	88.9 nm	Drug release	9.52%	cisplatin	[120]
NIR light	808 nm	AuNPs	38.5 nm (*H*) × 9.5 nm (*W*)	Drug release	—	Pt(IV) complex	[117]
NIR light	980 nm	UCNPs	50–60 nm	PDT	Up to 10%	ZnPc	[137, 138]
NIR light	808 nm	AuNPs	45.0 ± 1.5 nm	PTT	—	Ru(II) complex	[146]
NIR light	785 nm	GO	192.8nm	PTT	—	Ru(II) complex	[151]
NIR light	808 nm	Chitosan NPs	89nm	PTT	—	Cu(II) complex	[155]

comprehension of enzyme activity pattern will be beneficial for the development of precise and effective therapeutic modalities.

To summarize, nanoformulation of metal complexes by integrating the diversified properties of stimuli-responsive nanoplatforms and metal complexes provides an opportunity for improving the current metallodrugs with novel therapeutic modality for precise treatment of human diseases. We envision that the development of novel metallodrugs and their integration with these intelligent therapeutic platforms endowed with environment-responsive features will largely facilitate the development of efficient and precise therapeutic approaches that will benefit human health in the future.

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