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Review

Stimuli-responsive nanocarriers for drug delivery, tumor imaging, therapy and theranostics

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Abstract

In recent years, much progress has been motivated in stimuli-responsive nanocarriers, which could response to the intrinsic physicochemical and pathological factors in diseased regions to increase the specificity of drug delivery. Currently, numerous nanocarriers have been engineered with physicochemical changes in responding to external stimuli, such as ultrasound, thermal, light and magnetic field, as well as internal stimuli, including pH, redox potential, hypoxia and enzyme, *etc*. Nanocarriers could respond to stimuli in tumor microenvironments or inside cancer cells for on-demanded drug delivery and accumulation, controlled drug release, activation of bioactive compounds, probes and targeting ligands, as well as size, charge and conformation conversion, *etc*., leading to sensing and signaling, overcoming multidrug resistance, accurate diagnosis and precision therapy. This review has summarized the general strategies of developing stimuli-responsive nanocarriers and recent advances, presented their applications in drug delivery, tumor imaging, therapy and theranostics, illustrated the progress of clinical translation and made prospects.

Key words: nanoparticles, stimuli-responsive, tumor microenvironment, diagnosis, theranostics, clinical translation

Introduction

Since the discovery of the enhanced permeability and retention (EPR) effect and impaired lymphatic drainage of tumors [1], nanocarriers have been regarded as promising drug delivery vehicles to tumors [2-5]. In general, nanocarriers in the range of 10 to 200 nm are more likely to be accumulated in solid tumors by passively extravasation from the hyperpermeable tumor blood vasculature [6] and the dynamic openings [7]. Nanocarriers provide a versatile platform for loading a wide range of payloads, including imaging agents, nucleic acids, anticancer drugs, photosensitizers and antibodies, *etc*., to improve the diagnostic and therapeutic outcomes [8,9]. By incorporating bioactive compounds inside nanocarriers, it could avoid enzymatic degradation and undesired exposure to healthy organs, maintain drug activities, as well as alert the half-life in blood circulation, tumor accumulation and biological performance. Until now, several types of nanocarriers have been engineered for drug delivery in oncology [10, 11], including dendrimers, metal nanoparticles (*e.g*., iron oxide nanoparticles), polymeric micelles, liposomes, inorganic nanoparticles (*e.g*., silicon nanoparticles), and cell membrane-based nanoparticles *etc*. Currently, some nanocarriers have been approved for cancer treatment in clinic, for instance, the doxorubicin-incorporated PEGylated liposome (*i.e*., Doxil®) is approved for handling Kaposi's sarcoma and ovarian cancer.

Nanocarriers are supposed to deliver bioactive compounds (*e.g*., imaging or therapeutic agents) to tumor tissues or cancer cells for achieving improved diagnostic and therapeutic efficacy. However, it meets several barriers during circulation or in tumors [12], such as protein corona, degradation, burst release or leaking of cargos, and recognition and clearance by

the reticuloendothelial system (RES) *etc.* Several strategies have been applied to address this, including applying PEG shell for achieving stealth effect [13], decorating with targeting moieties or charge conversion materials for improved cellular internalization [14], multistage drug delivery [15], introducing hydrophobic units or cross-link the core to increase the stability, adding specific molecules to escape from RES, *etc.* Although the PEGylated nanocarriers exhibited advantages in prolonged circulation, improved drug solubility and reduced side effects, the delivery efficacy of most nanocarriers is still quite low, which requires further improvement [16]. Therefore, strategies for tumor-specific drug delivery have been exploited, mainly including stimuli-responsive nanocarriers [17], and ligand-installed nanocarriers [2], while both were developed to improve the precision of drug delivery but with different focus. The stimuli-responsive nanocarriers are mainly functionalized to delivery, release and activate cargos in specific regions (*e.g.*, tumor microenvironments or intracellular spaces of cancer cells) by responding to internal/external stimuli, *e.g.*, pH, enzymes, *etc.* [18, 19], while the ligand-installed nanocarriers are mainly applied to promote the specific internalization between nanocarriers and specific cells, *e.g.*, cancer cells, tumor vascular endothelial cells [2], *etc.* The stimuli-responsive nanocarriers could specifically delivery cargos into tumor microenvironment or cancer cells, while the ligand-installed nanocarriers could specifically target cancer cells that highly expressing receptors. From the application view, the stimuli-responsive nanocarriers have attracted broad attention, as the stimuli could be existed/generated in most of the tumors, while the cancer cell-specific receptors were reported to be expressed only on partial cancer cells (*e.g.*, the expression of Her2/neu was only found in less than 25% of breast cancer patients) [20], which may require preselection of receptors for the application of ligand-installed nanocarriers. It is possible to develop nanocarriers with stimuli-responsive functions for controlled drug release, and with ligands on their surface for targeting cancer cell. In addition, nanocarriers have also be functionalized for cancer theranostics, as the combination of diagnostics and therapy was generally referred as "theranostics" [16, 21], which could be achieved by loading both diagnostic and therapeutic compounds inside the same nanocarriers [22].

The stimuli-responsive nanocarriers have been rationally designed and developed by considering different pathological profiles in normal tissues, intracellular compartment and tumor microenvironment, to increase drug delivery specificity, efficacy and biological activities (Figure 1) [23-29]. In general, the nanocarriers could response to external stimuli, including magnetic field, temperature (*i.e.*, thermal), ultrasound, light (*e.g.*, laser) and electronic field, *etc.*, and internal stimuli, including pH, ATP, H_2O_2, enzyme, redox-potential, and hypoxia *etc.*, while the stimuli could be appeared in tumor microenvironment or inside cancer cells (Figure 1). The stimuli-sensitive functions facilitate on-demand or controlled drug release, promoted tumor accumulation, ligand exposure, drug or probe activation, nanoparticle structure or size conformation, charge conversion, as well as signaling in specific positions, sensing of special pathological factors/molecules, tumor-specific diagnosis and theranostics (Figure 1). Moreover, the external force (*i.e.*, stimuli) could also alert the biological performances of nanocarriers, for example, the external magnetic field could increase the accumulation of magnetic nanocarriers in tumors. Furthermore, the stimuli could also be applied to provoke biological activities of certain prodrug-formulated nanocarriers in diseased regions/cells for precision therapy. In addition, the stimuli-responsive nanocarriers were reported to overcome multidrug resistance in cancer treatment [30].

This review has summarized recent progress and achievements in nanocarriers that responsive to external or internal stimuli, presented different stimuli-sensitive strategies and their applications in drug delivery, tumor imaging, therapy and theranostics. In the following sections, the clinical translation of stimuli-responsive nanocarriers has been illustrated, and finally the perspectives were made.

External-responsive nanocarriers

The external stimuli, mainly including thermal, magnetic field, electronic field, ultrasound and light, could affect the fate of nanocarriers inside the biological systems. With the external stimuli, it facilitates enhancing the accumulation of nanocarriers in desired regions with outer forces (*e.g.*, magnetic field), controlled release, intracellular drug delivery, as well as activated imaging and therapy. There are several advantages of applying external-stimuli for drug delivery to tumors: (1) it could precisely control the location and intensity of given external stimuli (*e.g.*, magnetic field, laser irradiation); (2) the external stimuli could be added or removed depending on the treatment requirement; (3) multiple external stimuli could be overlaid for achieving multifunction in cancer theranostics; (4) the possibility to provide multi-times or continuous (*e.g.*, several hours or days) stimuli for drug delivery and therapy. However, the externally-directed triggers would be impractical for

accessing and treating the metastatic lesions, when their location is uncertain. Here, the application of external stimuli-responsive nanocarriers will be discussed in this section.

Ultrasound-responsive nanocarriers

Ultrasound is a type of high-frequency sound waves, which could affect nanocarriers for controlled drug release at diseased sites (*i.e.*, tumors). The intensity of ultrasound could be adjusted for different applications. At low ultrasound frequencies (< 20 kHz), it could be applied for imaging, while it could be applied for disrupting nanocarriers to release cargos or enhancing the permeability of cancer cell membrane at high ultrasound frequencies (> 20 kHz) [31]. Until now, several microbubbles have been commercialized, such as Albunex, Optison, Definity, Imagent, Levovist and Sonazoid *etc* [32]. However, the large size (1-10 μm), short half-life and low stability of microbubbles limit their access to vascular compartments in tumor tissues and deep penetration. Several size switchable microbubbles (*i.e.*, from microbubbles to nanobubbles) [33], or nanocarriers have been engineered for ultrasound imaging [34], ultrasound-triggered drug delivery [35-37], and ultrasound-triggered cancer theranostics (Table 1), including nanobubbles [38], calcium carbonate ($CaCO_3$) nanoparticles [39], liposome [40], nanodroplets [41], vesicles [42] and nanoparticles [43], *etc*. Generally, the ultrasound-sensitive nanocarriers are incorporating gas or contrast agents [44], including air, N_2 and perfluorocarbons, *etc*., or generating gas in biological environment [45-47], such as $CaCO_3$ nanoparticles [39].

The ultrasound-responsive nanocarriers could be applied for tumor ultrasound imaging, which is safe, low cost and widely applied in clinic, and providing images with high spatial resolution. The gas and contrast agent (*e.g.*, perfluoropentane) incorporated nanocarriers [48], as well as nanoparticles that could generate gas (*e.g.*, CO_2) in biological environment [34, 49], have demonstrated tumor-specific imaging at high resolution and intensity. In another strategy, the porphyrin microbubbles (1-10 μm) could be converted into nanobubbles (5-500 nm) for tumor ultrasound imaging (Figure 2) [33]. Besides, ultrasound could also be applied for triggering controlled release of cargos (*e.g.*, imaging probes, anticancer agents) from nanocarriers at desired tumor sites [42, 50]. For example, the phase changeable, polymeric nanodroplets could be generated for tumor imaging and doxorubicin release due the collapse of microbubbles when responding to the low-intensity focused ultrasound [41]. Moreover, the ultrasound-responsive property could be applied for enhancing the tumor accumulation and intracellular delivery of bioactive compounds (*e.g.*, siRNA, DNA) [51]. Because ultrasound could increase gap in tumor vasculature wall (*i.e.*, disrupting of vascular integrity) to facilitate extravasation of drug delivery systems to malignant tissues, as well as enhance cellular uptake by cancer cells [52-54]. However, the large size of ultrasound-sensitive nanocarriers may limit their penetration across tumor tissues, due to the weak penetration of large nanocarriers [6]. In addition, the drug- loaded, ultrasound-sensitive nanocarriers could further be applied for cancer therapy [55], imaging- guided therapy [56-58], and theranostics [39, 59].

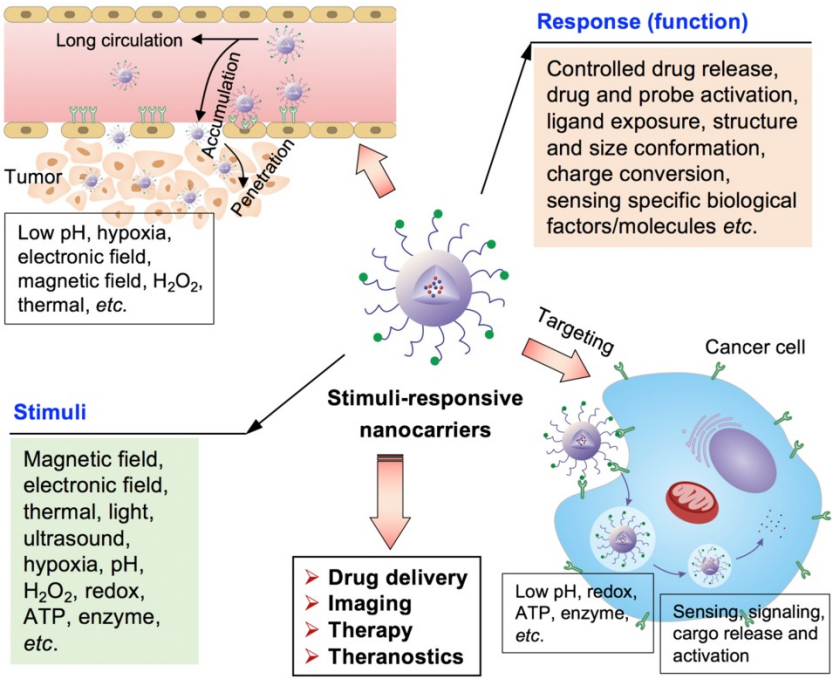

Figure 1. The stimuli-responsive nanocarriers for drug delivery to tumors towards precision imaging, effective therapy and theranostics. The nanocarriers could accumulate and penetrate tumors, and target cancer cells for achieving different applications and functions by responding to the external and internal stimuli.

Thermal-responsive nanocarriers

The temperature-sensitive nanocarriers have also been widely applied for drug delivery and dealing with cancer. Generally, the nanocarriers are designed to be stable in normal regions with temperature up to 37 °C and sensitive to higher temperature (> 40 °C) with significantly changes in their properties by responding to the

narrow temperature shift. Until now, several thermal-sensitive nanocarriers have been formulated (Table 2), including liposomes [63-65], polymeric micelles [66-70], nanocomposites [66, 71], nanocapsules [72], nanogels [73-76] and vesicles [77, 78], *etc*. The thermal-sensitive nanocarriers is generated with materials that could undergo physicochemical properties variation associating with temperature change [71, 79]. The temperature-sensitive materials are mainly including poly(N-isopropylacrylamide) (PNIPAM) [80, 81], poly(N-inyl isobutyramide) (PAMAM) [82], poly(2-oxazoline) (POxs) [83], and poly [2-(2-methoxyethoxy) ethyl methacrylate] [PMEOMA] [84], *etc*. Besides, another strategy for achieving thermal-sensitivity is to incorporate thermal-unstable materials inside nano-carriers. For instance, the NH_4HCO_3 incorporated liposome could generate CO_2 after giving local hyperemia (42°C) to make liposome swollen and collapse [64], leading to drug release for efficient intracellular drug delivery (Figure 3).

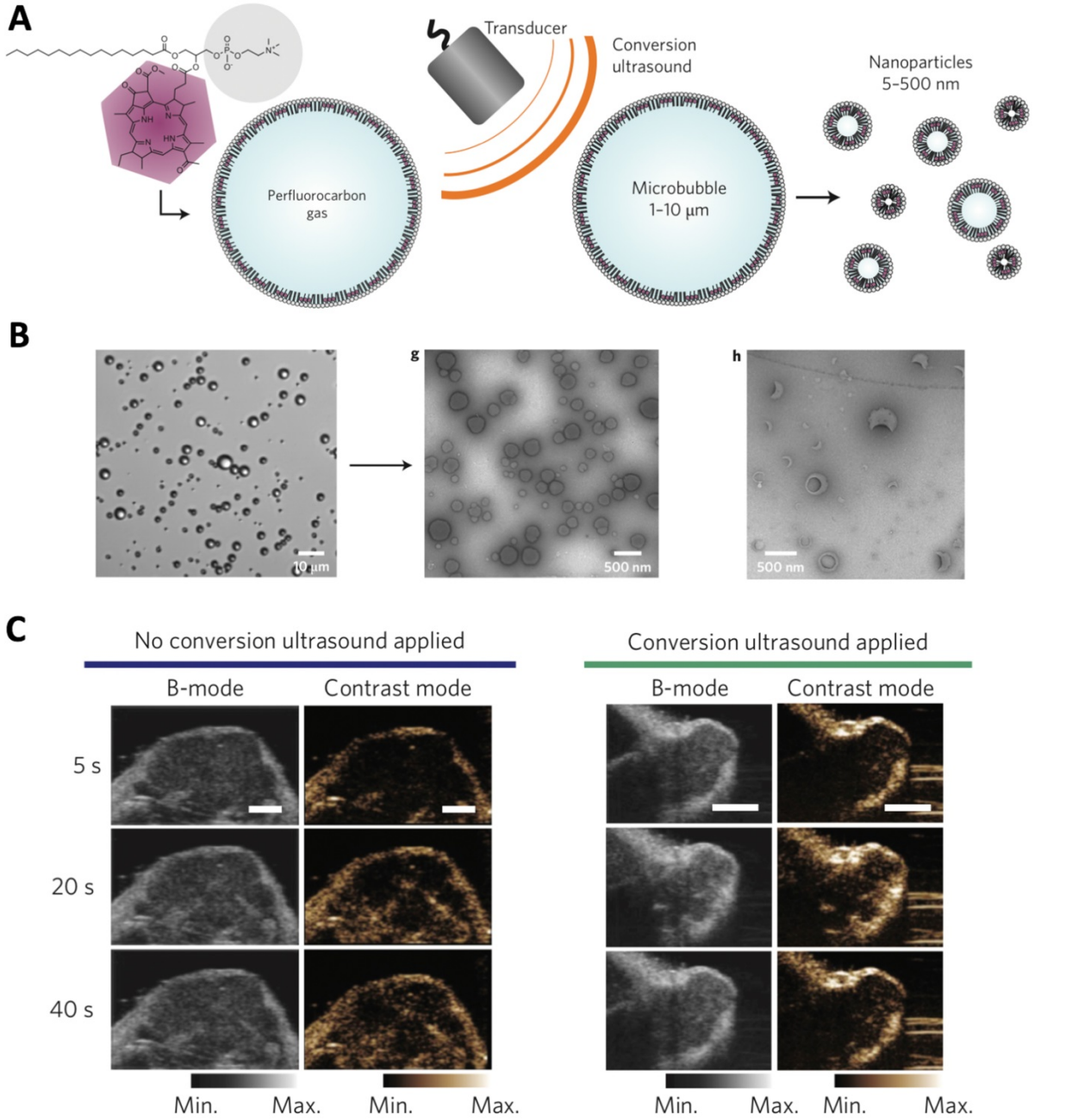

Figure 2. The ultrasound-triggered conversion of microbubbles to nanoparticles for multimodality tumor imaging. (A) Illustration of ultrasound-triggered conversion of porphyrin microbubbles to nanobubbles. **(B)** Confirmation of the conversion of microbubbles to nanobubbles with ultrasound stimuli by microscopy. **(C)** Ultrasound imaging of tumors by using no conversion ultrasound (left) and by administration of conversion nanoparticles (right). Adapted with permission from ref. [33], copyright 2015 Springer Nature Publishing AG.

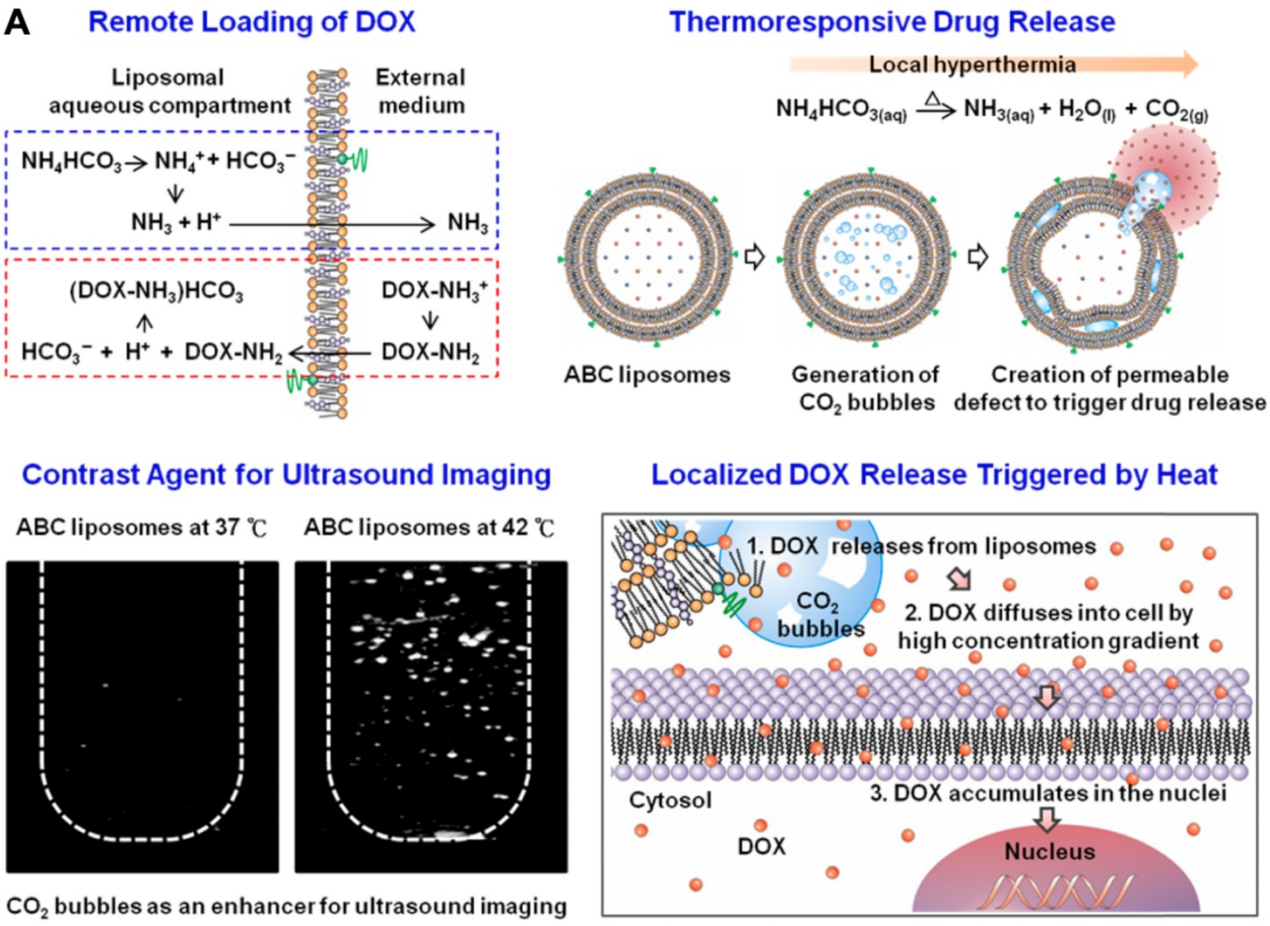

Figure 3. Thermal-sensitive nanocarriers for drug delivery. (A) Thermal-sensitive liposomes (*i.e.*, ABC liposomes) for molecular imaging, drug delivery and controlled drug release. **(B)** Cellular uptake of thermal-sensitive liposomes, control liposomes (*i.e.*, AS liposomes) and free doxorubicin. Adapted with permission from ref. [64], copyright 2013 American Chemical Society.

Table 1. Representative ultrasound-responsive nanocarriers

Nanocarriers	Ultrasound-sensitive strategy/materials	Cargos	Applications	Ref.
Converting microbubbles	Converting porphyrin microbubbles to nanoparticles by ultrasound	Porphyrin and perfluorocarbon gas	Ultrasound imaging	[33]
$CaCO_3$ nanoparticles	The $CaCO_3$ could generate CO_2 in the acidic tumor microenvironment	Doxorubicin	Tumor ultrasound imaging, drug release and tumor therapy	[39]
Nanobubbles	CO_2 gas-generating polymeric nanoparticles	-	Ultrasound Imaging	[34]
Liposome	Perfluorocarbon for ultrasound-sensitive	Doxorubicin, gold nanospheres	Cancer imaging, photothermal-chemotherapy	[60]
Liposome	Containing NH_4HCO_3 to generate gas in tumors	Docetaxel and NH_4HCO_3	Dual ligand targeted triplex therapy, and ultrasound imaging	[61]
Nanorattles	Perfluoropentane for ultrasound-sensitive	Perfluoropentane	Ultrasound and photoacoustic imaging, photothermal therapy	[48]
Nanodroplets	Perfluorocarbon	$ZnF_{16}Pc$, IR dye, perfluorocarbon	Tumor multimodal imaging and therapy	[62]
Gas vesicles	Genetically encoded gas nanostructures from microorganisms	Gas	Ultrasound and multimodal imaging, molecular biosensors	[44]

Table 2. Representative thermal-responsive nanocarriers

Nanocarriers	Thermal-sensitive strategy/materials	Cargos	Applications	Ref.
Liposomes	The incorporated NH_4HCO_3 could response to local hyperemia for drug release	Doxorubicin, NH_4HCO_3	Temperature-controlled drug release	[64]
Nanoscale vesicles	The temperature-sensitive leucine zipper peptide in the wall of vesicles could open pores for cargo release	Doxorubicin	Temperature-triggered drug release	[87]
Micelles	PMEEECL-*b*-POCTCL diblock copolymer displays phase transition at temperature above its LCST for cargo release	Nile Red, doxorubicin	Thermal-triggered drug release, efficient drug delivery to cancer cells	[67]
Nanogels	PNIPAM grafted chitosan nanogels response to temperature for drug release	Curcumin	Temperature-triggered drug release, intracellular drug delivery	[73]
siRNAsome	With siRNA-SS-PNIPAM to form vesicles responding to temperature higher than LCST	Doxorubicin, siRNA	Against multi-drug resistant cancer cells	[78]
Polymersomes	Thermal-sensitive PNIPAM gel in side pH-sensitive polymersomes	Doxorubicin	Dual-thermal, pH-responsive drug release, tumor therapy	[88]
Complexes	PEI-g-PMEOMA-*b*-PHEMA) polymers for temperature sensitive gene delivery	pDNA	Gene therapy of tumors	[84]
Nanocapsules	Forming Pluronic/PEI with high temperature to load siRNA, which could be released inside cancer cells with cold shock	siRNA	Enhanced intracellular siRNA delivery to HeLa cancer cells	[72]

The thermal-sensitivity nanocarriers could be applied for gene and drug delivery by using thermal-sensitive polymeric materials [63, 85, 86], which could shift from hydrophilic to hydrophobic for forming nanocarriers. In a recent study, the siRNA-SS-PNIPAM conjugates could form siRNAsomes by self-assembly at higher temperature (> 32°C) than the lower critical solution temperature (LCST) for phase transition [78]. In another study, the nanocarriers with PNIPAM on the surface formed micellar networks (*i.e.*, aggregates) at temperature higher than LCST, while disassociated to each other at low temperature [75]. In this way, the thermal-sensitive nanocarriers could also be applied for plasmid DNA (pDNA) condensation [84], folding proteins [77], and incorporating hydrophobic anticancer drugs (*e.g.*, doxorubicin) [66]. Besides, it could be applied for controlled releasing cargos in diseased regions with local hyperemia [64, 67, 85]. For instance, the doxorubicin could be released from the lipid-peptide vesicle by responding to mild hyperemia [87], as the peptides in the wall of vesicles could open pores at high temperature (42.5°C). In another case, the Nile Red and doxorubicin could be release from the polymeric micelles by responding to the thermal-stimuli, where the poly(γ-2-(2-(2-methoxyethoxy)ethoxy)ethoxy-ε-caprolactone)-*b*-poly(γ-octyloxy-ε-caprolactone) (PME EECL-*b*-POCTCL) diblock copolymer displayed phase transition at temperature above its LCST (38 °C) [67]. The thermal-sensitive polymeric micelles displayed higher cellular uptake at high temperature (42.5°C) than at normal temperature (37 °C), as well as lower survival than free doxorubicin as tested on MCF-7 cancer cells. Although with much advances in developing temperature-sensitive nanocarriers, only limited thermal-sensitive materials are existed, which requires further development. The thermal-sensitive temperature of some materials and nanocarriers was neither in the range of biological systems (*e.g.*, 37-42°C), nor could be simply shifted to another desired temperature. It further has to point out that some thermal-responsive nanocarriers were developed with non-biodegradable polymers (*e.g.*, PNIPAM), which may be difficult for clinical translation. Thus, development of biodegradable and thermal-sensitive materials would be a future direction. In addition, the accumulation of nanocarriers in tumors is still critically important for achieving pinpoint thermal-triggered drug release and therapy.

Magnetic-responsive nanocarriers

The magnetic-responsive nanocarriers have been engineered, as the magnetic nanoparticles has intrinsic tropism to magnetic field for tumor targeting, while it also could generate local hyperthermia under an alternating magnetic field for triggering drug release and tumor ablation. Until now, several magnetic-responsive nanocarriers have been formulated (Table 3), including magnetic nanoparticles [89, 90], liposomes [91], superparamagnetic iron-oxide nanoparticles (SPIONs) [92], polymeric micelles [93], albumin nanocapsules [94], magnetic nanocarriers [95, 96] and magnetic nanogels [97], *etc.* Generally, nanocarriers are incorporating magnetic materials for achieving magnetic-sensitivity, which are mainly including iron oxide nanoparticles (*e.g.*, Fe_3O_4 nanoparticles) [98], iron oxide hybrid nanoparticles (*e.g.*, graphene/Au/Fe_3O_4 hybrids) [99], and other magnetic nanomaterials (*e.g.*, $ZnFe_2O_4$) [100]. The incorporated magnetic materials also could be applied for tumor imaging by magnetic resonance imaging (MRI) [92, 101, 102]. Besides magnetic materials, the contrast agents [103], anticancer drugs [101, 104], plasmids [100], antibodies [98] and photosensitizer [91], could also be incorporated inside the magnetic-sensitive nanocarriers for achieving multiple functions or multimodal therapeutic effects. Moreover, the nanocarriers could be engineered for passive tumor targeting through the EPR effect [105], as well as be installed with targeting moieties (*e.g.*, folic acid) for active targeting cancer cells [94].

Table 3. Representative magnetic-responsive nanocarriers

Nanocarriers	Magnetic-responsive strategy/materials	Cargos	Applications	Ref.
Multifunctional magnetic nanocarriers	Magnetic field guided tumor targeting of SPIOs-loaded nanocarriers	SPIOs, doxorubicin	Tumor-targeted therapy	[95]
Albumin nanocapsules	Magnetic guided tumor targeting	Fe_3O_4, hydrophilic drugs	Targeting cervical cancer cells	[94]
Magnetic nanoparticles	Nanoparticles response to the alternating magnetic field for geldanamycin release and effective apoptotic hyperemia to kill cancer cells	Geldanamycin, amine-functionalized $Zn_{0.4}Fe_{2.6}O_4$	Nanoparticle-mediated resistance-free apoptotic hyperthermia for kill cancer cells	[89]
Mesoporous iron oxide nanoparticles	Burst gas generation and on-demand drug release upon high-frequency magnetic field exposure	Iron oxide nanoparticles, paclitaxel, perfluorohexane	Tumor active targeted thermos-chemo-therapy	[107]
Polymeric micelles	Generate magnetic hyperthermia and controlled drug release	$La_{0.7}Sr_{0.3}MnO_3$, doxorubicin	Effective breast cancer theranostics	[93]
Multifunctional hybrid nanoparticle	Produce localized heat under an alternating magnetic field, which triggers the release of the loaded drug	Fe_3O_4, Au, carbon dots, doxorubicin	Photothermal therapy of melanoma tumor	[115]
Liposomes	Induce local hyperthermia by response to alternating magnetic field	Magnetic nanoparticles, rhodamine, photosensitizer	Ultimate hyperthermia and photodynamic therapy combined tumor ablation	[91]
Nanoparticles	Generate heat in response to an alternating current magnetic field	Fe_3O_4 nanoparticles, doxorubicin	Tumor active targeted therapy by magnetic hyperthermia and chemotherapy	[116]
Magnetic nanogels	Magnetic hyperthermia	Iron oxide nanoparticles, doxorubicin	Prostate cancer therapy by hyperthermia and chemotherapy	[97]
Porous magnetic microspheres	Produce thermal energy and trigger the vaporization of liquid perfluorohexane	Iron oxide nanoparticles, perfluorohexane	Tumor treatment by activating droplets vaporization	[103]
Magnetic nanoparticles	Localized hyperthermia kills tumor cell preferentially	Iron oxide nanoparticles	Treating primary and metastatic lung malignancies	[109]

The interaction between magnetic nanocarriers and magnetic field facilitates the magnetic-guided accumulation of nanocarriers in tumors, while a typical approach is to locate a permanent magnetic field in malignant tissues after administration [94]. For example, much higher level of SPIONs and doxorubicin-loaded nanocarriers in tumors have been achieved with external magnetic field-guided tumor targeting, leading to effective tumor ablation [95]. In this way, it could be applied for promoting the accumulation of a myriad of bioactive compounds in tumors, including genes, anticancer drugs, and imaging probes [106]. Besides, the alternating magnetic field-triggered hyperthermia could induce on-demand release of cargos from the magnetic-sensitive nanocarriers in diseased regions (*i.e.*, tumor or cancer cells) [105, 107, 108]. Using hyperthermia to cleave the thermosensitive bonds , the magnetic nanoparticles could release the heat shock protein inhibitors (*i.e.*, geldanamycin), which could block the protective function of heat shock proteins to induce resistance-free apoptosis for effective tumor ablation (Figure 4) [89]. This magnetic-sensitive nanocarriers would facilitate treating tumors that resistant to hyperthermia therapy, and overcoming multi-drug resistant (MDR) of cancers. Moreover, the hyper-thermia generated by magnetic-sensitive nanocarriers could further be applied for tumor ablation [90, 100], as hyperthermia could induce apoptosis of cancer cells. For example, the magnetic-responsive nanocarriers have been developed with $ZnFe_2O_4$ inside the core and decorated with cationic polymers of polyethyleneimine (PEI) to interact with plasmids on the surface [100]. It facilitated cellular uptake of plasmids by the adipose-derived mesenchymal stem cells (MD-MSCs), which could migrate to tumors guided by an alternating magnetic field for effective therapy. Besides primary tumors, the magnetic-responsive nanocarriers have also demonstrated high potential for treating metastatic tumors (*e.g.*, lung metastasis) [109]. Furthermore, the magnetic-sensitive nanocarriers could be applied for tumor theranostics [110], as it could probe tumors by MRI or other imaging modalities, and remotely and non-invasively eradicate tumors with the generated hyperthermia in the alternating magnetic field [111]. For example, the PEGylated MoS_2/Fe_3O_4 nanocomposites (MSIOs) made through a two-step hydrothermal method, have demonstrated high potential for tumor diagnosis by T_2-weighted MR imaging and photoacoustic tomography (PAT) imaging, and magnetic-targeted effective photothermal ablation of tumors [112]. Meanwhile, it further allowed both T_1- and T_2-weighted MR imaging of tumors by doping Mn into the core of Fe_3O_4@MoS_2 nanocomposites (*i.e.*, multifunctional nanoflowers) [113]. Some other bioactive compounds, such as photosensitizer chlorin e6 (Ce6), could also be incorporated into the magnetic-sensitive nanocarriers for multi-functional cancer theranostics [96]. In addition, the superparamagnetic materials in magnetic-responsive nanocarriers could be extensively employed as a target moiety for improved tumor therapy, which is comparable to the decoration of active targeting moieties. As presented in a recent study, the paclitaxel (PTX) and SPIO-loaded poly(lactic-co-glycolic acid) (PLGA) nanocarriers have been engineered for tumor passive targeting by EPR effect, active targeting of $\alpha_v\beta_3$ integrins on cancer cells with RGD ligands (RGD), magnetic field (*i.e.*, 1.1 T) guided tumor targeting (MT), and the combination of magnetic targeting and active targeting (RGD+MT) (Figure 5A)

[114]. Accordingly, both RGD and magnetic targeting drastically exhibited much higher tumor accumulation (*i.e.*, 8-fold increase) of nanocarriers than passive targeting, leading to effective tumor ablation and improved survival rates of colon CT26 tumor-bearing mice, while the combination of magnetic targeting and active targeting demonstrated the best performance in tumor ablation than other groups (Figure 5B,C). Notably, higher accumulation in tumors and lower deposition in livers/lungs have been achieved by magnetic field-guided targeting nanocarriers than the RGD-installed nanocarriers, demonstrating the promise of magnetic targeting approach. Overall, the magnetic field guided-targeting strategy requires tumor-specific drug delivery, as it may also affect normal organs/tissues that distributed with magnetic nanocarriers when exposed to the alternating magnetic field. In addition, the generation of hyperthermia requires high level of magnetic-sensitive nanocarriers in diseased regions, which should be located in the alternating magnetic field. This approach may facilitate treating tumors located in partial regions of the body (*e.g.*, legs, feet and arms, *etc.*), due to safety consideration.

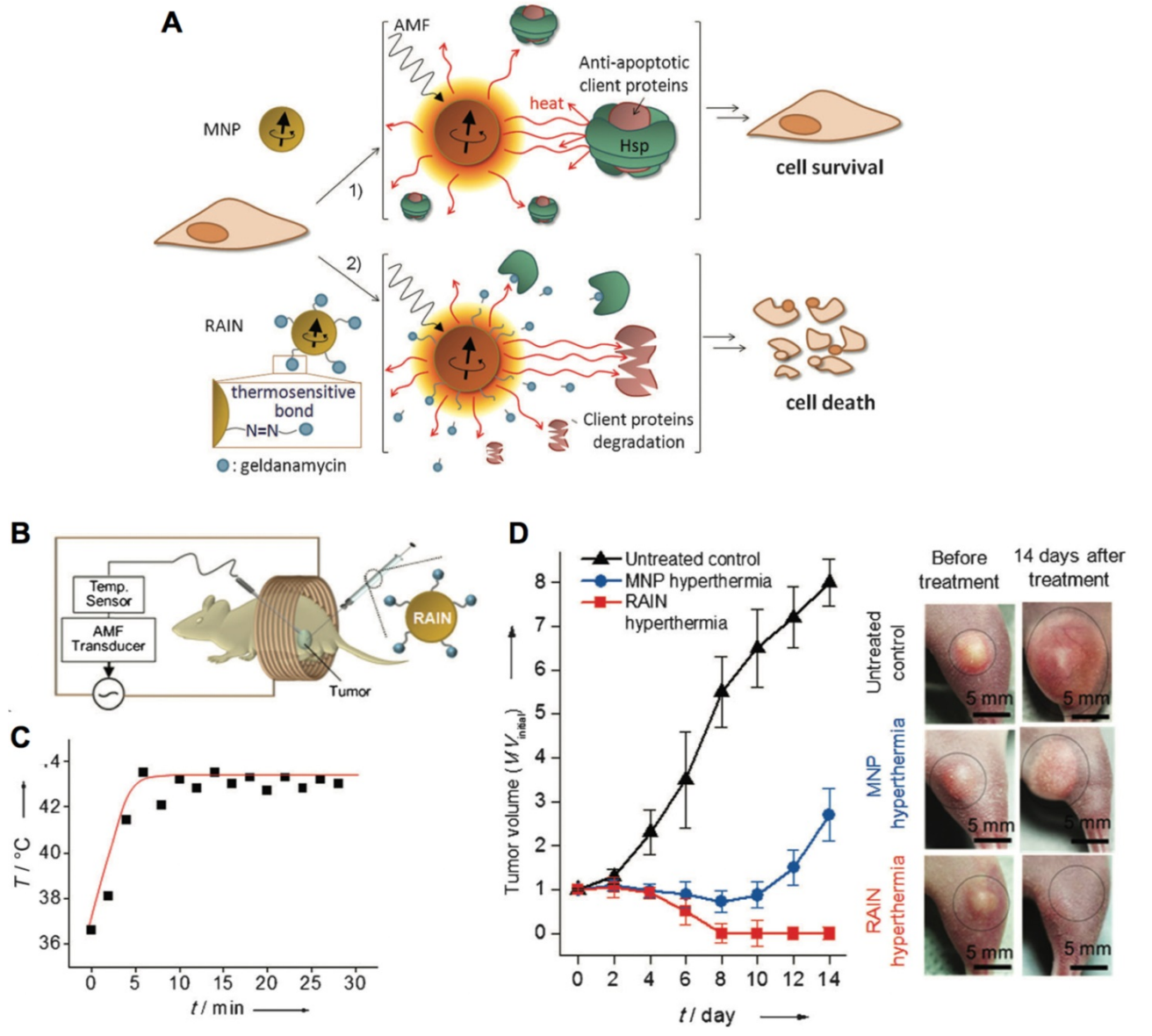

Figure 4. Magnetic-responsive nanocarriers for tumor therapy. (A) Schematic illustration of resistance-free apoptosis-inducing magnetic nanoparticles (RAIN) for cargo release and killing cancer cells. **(B)** Illustration of applying magnetic-sensitive nanocarriers for tumor treatment in an alternating magnetic field. **(C)** The temperature profiles in tumors. **(D)** The anti-tumor efficacy by magnetic-sensitive nanocarriers with hyperthermia. Adapted with permission from ref. [89], copyright 2013 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

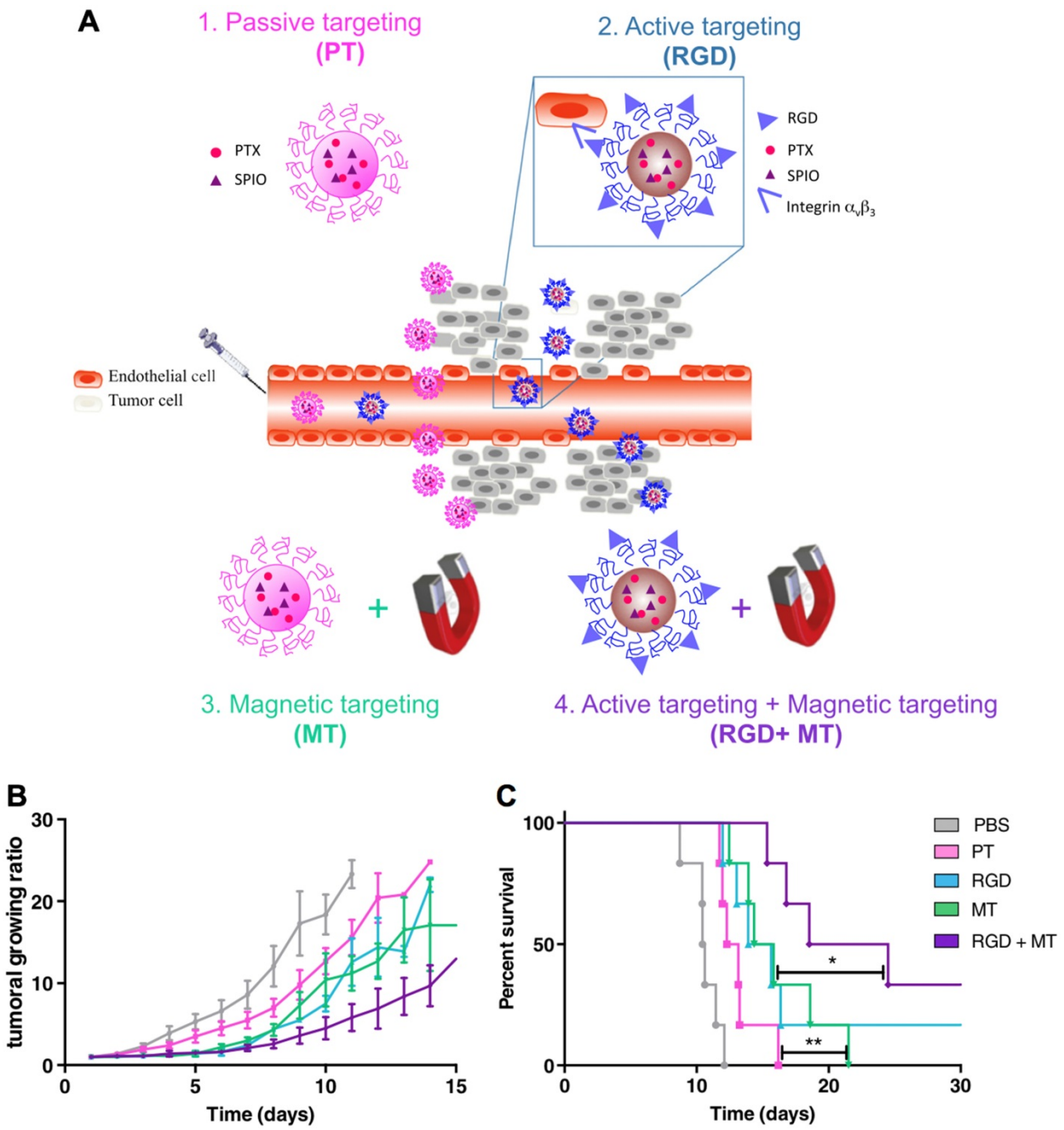

Figure 5. Nanocarriers for magnetic targeted tumor therapy. (A) Illustration of paclitaxel (PTX) and SPIO-loaded nanocarriers for tumor passive targeting (PT), active targeting of $\alpha_v\beta_3$ integrins with installed RGD ligands (RGD), magnetic field (1.1 T)-guided tumor targeting (MT), and combination of magnetic targeting and active targeting (RGD+MT). **(B,C)** The tumor growth ratio (B) and survival rates (C) of CT26-tumor bearing mice. Adapted with permission from ref. [114], copyright 2014 Elsevier B.V.

Light-sensitive nanocarriers

Nanocarriers that could responsive to light have also been extensively developed, as light is an attractive stimulus with the possibility to adjust the irradiation wavelength, power and affecting area [117]. In general, the light irradiation, such as UV-Vis and near-infrared light (NIR), could remotely affect the light-sensitive nanocarriers in biological systems (*e.g.*, cancer cells, or tumors). Meanwhile, the light-triggered tumor therapy could be precisely conducted by control the range of irradiation to avoid or minimize potential harm to normal organs and tissues. Until now, several light-responsive nanocarriers have been exploited (Table 4), including polyion complex vesicles (PICsomes) [118], polyplexes [119, 120], nanoparticles [121, 122], polymeric micelles [123, 124], upconverting nanoparticles (UCNPs) [125,126], polymersomes [127,128], liposomes [129, 130], nanogels [131], nanorods [132], and nanorattles [48], *etc.* Meanwhile, the cargos/materials with light-response function could be applied for constructing light-sensitive nanocarriers, such as photosensitizers (*e.g.*,

IR780) [133], gold nanocomposites (gold nanoparticles) [134], UCNPs [123], organic molecules (*e.g.*, azobenzene) [135], graphene [131], carbon nanotubes [136-138], and two-dimensional (2D) transitional metal nanomaterials (*e.g.*, MoS_2, WSe_2 and WS_2) [139, 140], *etc*. Nanocarriers could response to light for several activities: (1) alert the conformation of certain molecules, such as azobenzene, spiropyran, dithienylethene and diazonaphthoquinone *etc.* [141]; (2) cleave the light-sensitive chemical bonds for nanocarriers disassociation [123]; (3) trigger release of therapeutics from nanocarriers in diseased regions [130]; (4) light-activated imaging (*e.g.*, photoacoustic imaging) or imaging-guided therapy [142-146]; (5) generate singlet oxygen (O_2^1), also referred as reactive oxygen species (ROS) for photodynamic therapy (PDT) [147, 148], and photothermal effect for tumor ablation by photothermal therapy (PTT) [149, 150].

Nanocarriers could also be formed or assembled by responding to light, due to change the hydrophilic-hydrophobic balance or structure conversion of light-sensitive materials. Recently, the light-sensitive nanoparticles were formed by using 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-*N*-carboxy(polyethyl ene glycol) (DSPE-PEG) to incorporate spiropyran in visible or dark conditions, and disassociated responding to UV irradiation due to the conversion of SP to merocyanine (MC) [121]. The photo-switching nanocarriers demonstrated high potential for loading different bioactive compounds for UV-Vis triggered drug release, including paclitaxel, docetaxel and doxorubicin *etc.*, as well as for cancer therapy [151]. The light-switching function also could be applied for inducing reversible aggregation of nanoparticles (*e.g.*, vesicles) [152]. However, the short wavelength of UV-Vis may limit their applications. Therefore, the NIR light-sensitive nanocarriers have also been engineered for controlled drug delivery [153], and penetrating into deep tissues [154]. For example, the IR-780-incorperated polymeric micelles could response to NIR for doxorubicin release [155]. Besides, the light-sensitive nanocarriers facilitate intracellular delivery of bioactive compounds, including genes [120], photosensitizers [118], and anticancer drugs [124], *etc*. In a recent study, the photosensitizer Al(III) phthalocyanine chloride disulfonic acid (AlPcS2a)-incorporated polyion complex vesicles (PICsomes) could sensitive to laser irradiation for endosome escape and drug release, exhibiting much stronger photocytotoxicity than that of AlPcS2a [118]. In another strategy, by co-administration of photofrin, it could also induce photochemical internalization (PCI) for achieving endosomal escape of nanocarriers to improve the therapeutic effects of camptothecin [124]. Moreover, the light-triggered endosome/lysosome escape also plays an important role in transferring genes into cytoplasm, as genes could be degraded in the late lysosomes to lose activity. For example, the light-responsive, three-layered polyplex micelles have been developed with polycationic polymers to condensate pDNA and load dendrimer phthalocyanine (*i.e.*, photosensitizer), demonstrating efficient systemic gene transfection by light-triggered PCI for endosomal/lysosomal escape (Figure 6) [119].

Table 4. Representative light-responsive nanocarriers

Nanocarriers	Light-responsive mechanism/materials	Cargos	Applications	Ref.
Polyion complex vesicles (PICsomes)	Light-triggered release of photosensitizer, photochemical internalization	Al(III) phthalocyanine chloride disulfonic acid (AlPcS2a)	PDT of tumors, photoinduced cytoplasmic delivery of drugs	[118]
Three-layered polyplex micelles	Dendrimeric photosensitizer for light-responsive endo-/lysosomal escape	pDNA, photosensitizer	Light-induced systemic gene transfer for tumor therapy	[119]
Micelles	Using NIR light excitation of UCNPs to trigger dissociation of micelles	$NaYF_4$:TmYb UCNPs	NIR light-triggered cargo release	[123]
Nanoparticles	Spiropyran for UV-Vis light responsive	Rhodamine B, coumarin 6, calcein, Cy5, paclitaxel, docetaxel, doxorubicin	Light-triggered drug delivery and tissue penetration	[121]
Nanoparticles	Photosensitizer Ce6 for light- triggered size reducing, and generation of O_2^1 (ROS)	Camptothecin, Ce6	Enhanced tumor penetration for combined therapy	[159]
Liposome	Porphyrin for light-responsive phototherapy	Doxorubicin, porphyrin	Chemotherapy and phototherapy of tumors	[129]
Lanthanide-doped UCNPs	Dithienylethene photo-responsive molecules	Er^{3+}/Yb^{3+} and Tm^{3+}/Yb^{3+} doped NaYF4 UCNPs	NIR light remote-control to drive the reversible photo-switching reactions	[125, 126]
Cell membrane-based nanocarriers	Indocyanine green (ICG) for photothermal therapy	Doxorubicin, ICG	NIR-triggered drug release and tumor active targeted photothermal and chemotherapy	[160]
Vesicle	The structure change of azobenzene makes disassociation with β-CD	β-CD, azobenzene	Mimic for cell aggregation	[152]
Nanogel	Graphene for light-triggered photothermal effects	Doxorubicin, graphene	Theranostics of lung cancer	[131]
Nanorods	Gold nanorods for thermal sensitivity	DNA, doxorubicin	Treatment of multidrug resistant cancer cells	[134]
Carbon nanotubes	Photothermal effects of carbon nanotubes	Doxorubicin	Photothermal and chemotherapy of tumor	[138]
2D transitional metal nanomaterials	Photothermal effects of MoS_2	Doxorubicin	Photothermal and chemotherapy of tumor	[139]

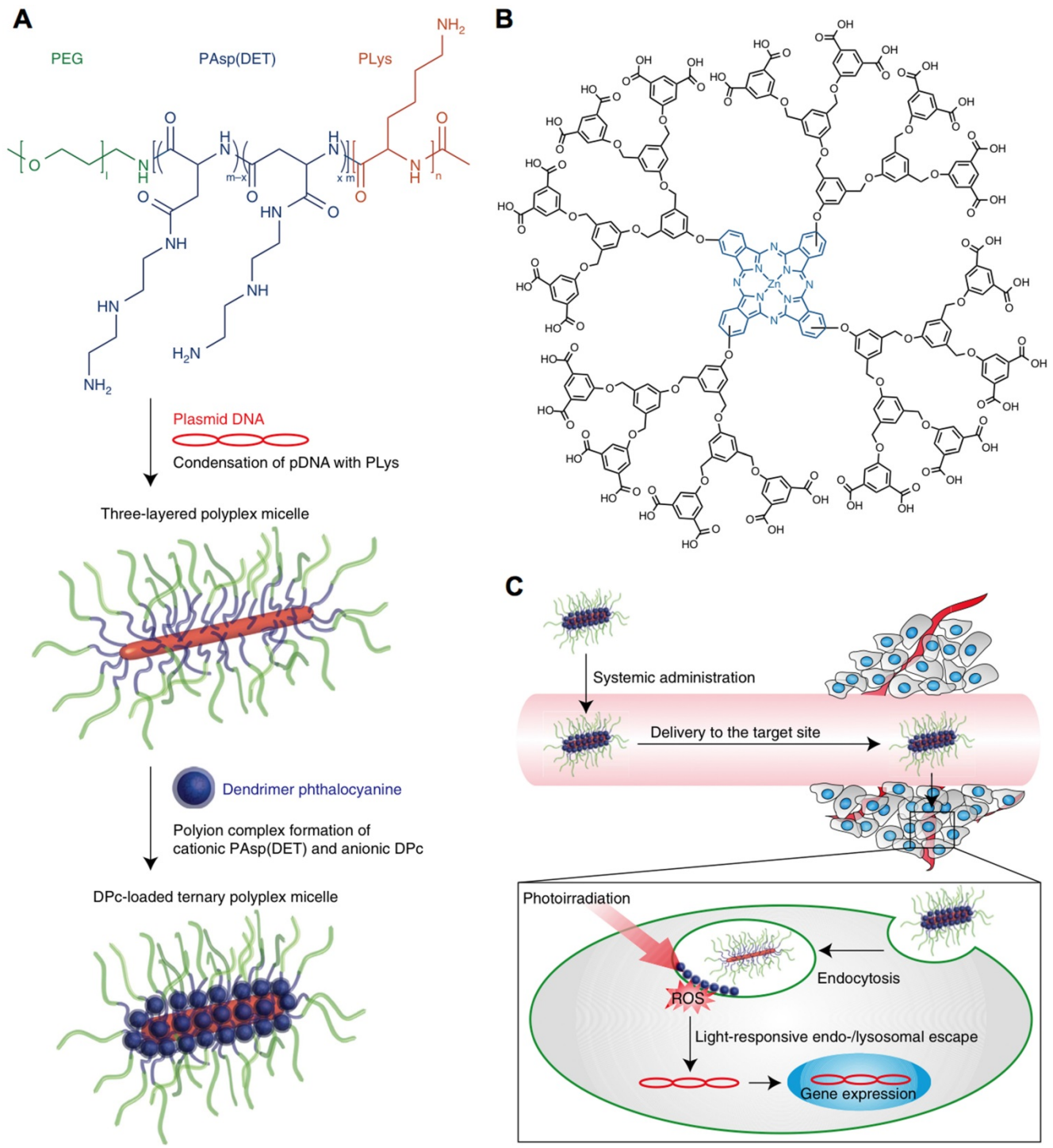

Figure 6. Schematic illustration of light-responsive nanocarriers for gene transfer. (A) Preparation of pDNA and photosensitizer-loaded nanocarriers. **(B)** Chemical structure of photosensitizer; **(C)** Light-triggered endo-/lysosomal escape for gene transfection inside cancer cells. Adapted with permission from ref. [119], copyright 2015 Springer Nature Publishing AG.

Furthermore, the light-sensitive nanocarriers could further be activated for imaging-guided tumor therapy [156, 157] and theranostics [60, 156], which could figure out the cut-edge of tumors for precisely irradiation by PTT or PDT. In addition, the light-sensitive nanocarriers could be applied for tumor ablation, as a result of light-triggered generation of ROS and photothermal effect [130, 156], or combined with other bioactive agents (*e.g.*, anticancer drugs) for multimodal cancer theranostics [155, 158]. It has also demonstrated high efficacy for treating MDR cancers [134]. In general, the light- sensitive nanocarriers have demonstrated high potential for drug delivery, controlled drug release and cancer theranostics, especially tumors that could be accessed by light/laser due to the limitation of light penetration.

Internal stimuli-responsive nanocarriers

Specific biological factors in tumor microenvironment or inside cancer cells, such as enzymes, ATP, low pH, redox-potential and hypoxia, *etc*., could be specific triggers for controlled drug release, endosome/lysosome escape, prodrug activation, tumor specific imaging and therapy [161]. The internal triggers are intrinsically existed in tumor microenvironment or inside cancer cells. However, they usually show poor specificity and heterogenetic distribution in tumors, which may affect the efficacy of internal stimuli-sensitive nanocarriers. In this section, recent advances in nanocarriers responding to internal stimuli, mainly including pH, hypoxia, redox and enzymes, for tumor theranostics will be focused.

pH-responsive nanocarriers

The pH-responsive nanocarriers have been extensively exploited, due to the nature of low pH inside the organelles (*e.g.*, lysosomes and endosomes) of cancer cells and in tumor microenvironment. In general, the pH in cytoplasm, blood and normal tissues is almost around pH 7.0 to 7.4, while it exhibits approximately pH 6 to 4 in endosomal/lysosomal organelles, and pH 6.5 to 6.8 in tumor microenvironment [162]. Thus, the pH-responsive in tumor microenvironment could be applied for controlled drug release or prodrug activation, while keep the "stealth effect" of nanocarreirs in normal regions (*e.g.*, in blood circulation) without leaking of cargos. This would decrease the risk of exposure normal organs (*e.g.*, heart) to the toxic cargos (*e.g.*, doxorubicin), and specifically deliver them to tumors for achieving high therapeutic performance. Until now, several types of pH-sensitive nanocarriers, including $CaCO_3$ nanoparticles [163, 164], calcium phosphate (CaP) nanocarriers [165-167], inorganic nanoparticles or crystals [168-170], polymer-drug conjugates [171, 172], polymeric micelles [173-175], liposomes [176], polymersomes [177], nanogels [178- 180] and dendrimers [181], *etc*., have been exploited for imaging, intracellular drug delivery, charge conversion, and controlled drug release in tumor- microenvironment [172, 182]. Meanwhile, several pH-sensitive polymers have been synthesized for fabricating nanocarriers with pH-responsibility [183, 184], including poly(2-(pentamethyleneimino) ethyl methacrylate) (PC6A), poly(2-(hexamethyleneimino) ethyl methacrylate) (PC7A), poly(β-amino ester) (PAE), polysulfadimethoxine (PSD), poly(L-histidine) (PHis), poly(4-vinylbenzoic acid) (PVBA), 2,3-dimethylmaleic anhydride (DMMA), poly(N,N-dimethylaminoethyl methacrylate) (PDMAEMA), poly(N,N-diethylamino-2-ethylmethacrylate) (PDEAEMA), poly(N'-(N-(2-aminoethyl)-2-aminoethyl) aspartamide) [PAsp (DET)], poly(2-diisopropylaminoethyl methacrylate) (PDPA), poly [(2-N-morpholino) ethyl methacrylate] (PMEMA), poly(4-vinylpyridine) (P4VP), poly (glutamic acid) (PGlu) [185], poly (methacrylic acid) (PMAA), poly(L-aspartic acid) (PAsp) and poly(2-vinylpyridine) (P2VP) (Figure 7). Meanwhile, certain pH-sensitive chemical bonds have also been applied for drug conjugation, confirmation/ size change and charge conversion, *etc*. (Figure 8), which facilitate pH-triggered drug release, and disassociation of nanocarriers inside cancer cells or in tumor microenvironment [186].

Compared to cytoplasm with an almost neutral pH (pH 7.2), the pH in endosomal/lysosomal organelles was around pH 6 to 4. Generally, nanocarriers enter into cancer cells through the pathway of endocytosis, which requires endosome/lysosome escape to avoid further degradation in late lysosomes with low pH. Currently, several intercellular pH-triggered nanocarriers have been engineered for liberating cargos inside cancer cells [187]. The pH-triggered charge conversion nanocarriers have also been engineered for intracellular drug delivery, where the neutral or negative charged nanocarriers could turn to be positively charged by responding to low pH in endosomes/lysosomes for disrupting endosomes/lysosomes, due to the protonation of the cationic materials [188, 189]. The pH-triggered charge conversion could be obtained with certain chemical groups, such as citraconic anhydride, 2,3-dimethylmaleic anhydride (DA), cis-aconitic anhydride, carboxy dimethylmaleic anhydride (CDM) and cis-4-cyclohexene-1,2-dicarboxinic anhydride, *etc.* The charge conversion strategy facilitates intracellular delivery of antibodies [190], proteins [189, 191], siRNA [192, 193], and DNA [194], as well as enhancing the tumor accumulation of nanocarriers [195], *etc.* As presented in a recent study, the pDNA-loaded nanocarriers (HA-NPs) were innovated by using PAsp(DET) for formulating cationic PAsp (DET)/pDNA condensates and endosome escape, as well as installing hyaluronic acid (HA) for active targeted gene therapy of cancer [196]. The HA-NPs could selectively internalize with CD44 receptors overexpressed on B16F10 melanoma cancer cells and tumor vascular endothelial cells to prompt preferential intracellular delivery of pDNA payloads, and block the CD44-angiogenic signaling for pursuit of inhibited tumorigenesis, leading to effective ablation of primary tumor and lung metastasis. Besides, the endocytosis procedures could be visible with probe-loaded, intracellular pH-sensitive nanocarriers. For example, the endocytic pH-sensitive nanoparticles has been reported, which could

specifically probe early endosomes or late endosomes/lysosomes with different pH-sensitive groups [197, 198], and even probe early endosomes (pH 6.0) at single-organelle resolution [199]. Moreover, the intracellular pH could trigger controlled drug release from nanocarriers [200-203]. With one example, the cRGD-decorated polymeric micelles that self-assembled from epirubicin- conjugated block copolymers through hydrazide bonds, could specifically delivery and release epirubicin inside cancer cells for effective tumor ablation [204].

Functional nanocarriers could also response to the low pH in tumor microenvironment for cancer-specific theranostics. Firstly, the pH-sensitive nanocarriers could incorporate different types of imaging probes for tumor-selective imaging and diagnosis. For instance, the pH-sensitive polymeric micelles incorporating fluorescence dye could specifically probe several types of solid tumors, due to the specific exposure of dyes in tumors, while the diagnostic selectivity could be promoted higher by installing targeting moieties (*i.e.*, cRGD) on the surface of micelles [20]. The nanocarriers could further be utilized for fluorescence imaging-guided surgical resection of tumors [206]. Considering the limited penetration of optical imaging, the pH-sensitive nanocarriers have been exploited for tumor imaging by MRI [207, 208]. For instance, the Mn^{2+}-doped, polymer hybrid CaP nanocarriers (PEGMnCaP) have been developed with intratumoral pH-triggered contrast amplification for MR imaging of tumor malignancy (Figure 9A), as the released Mn^{2+} could

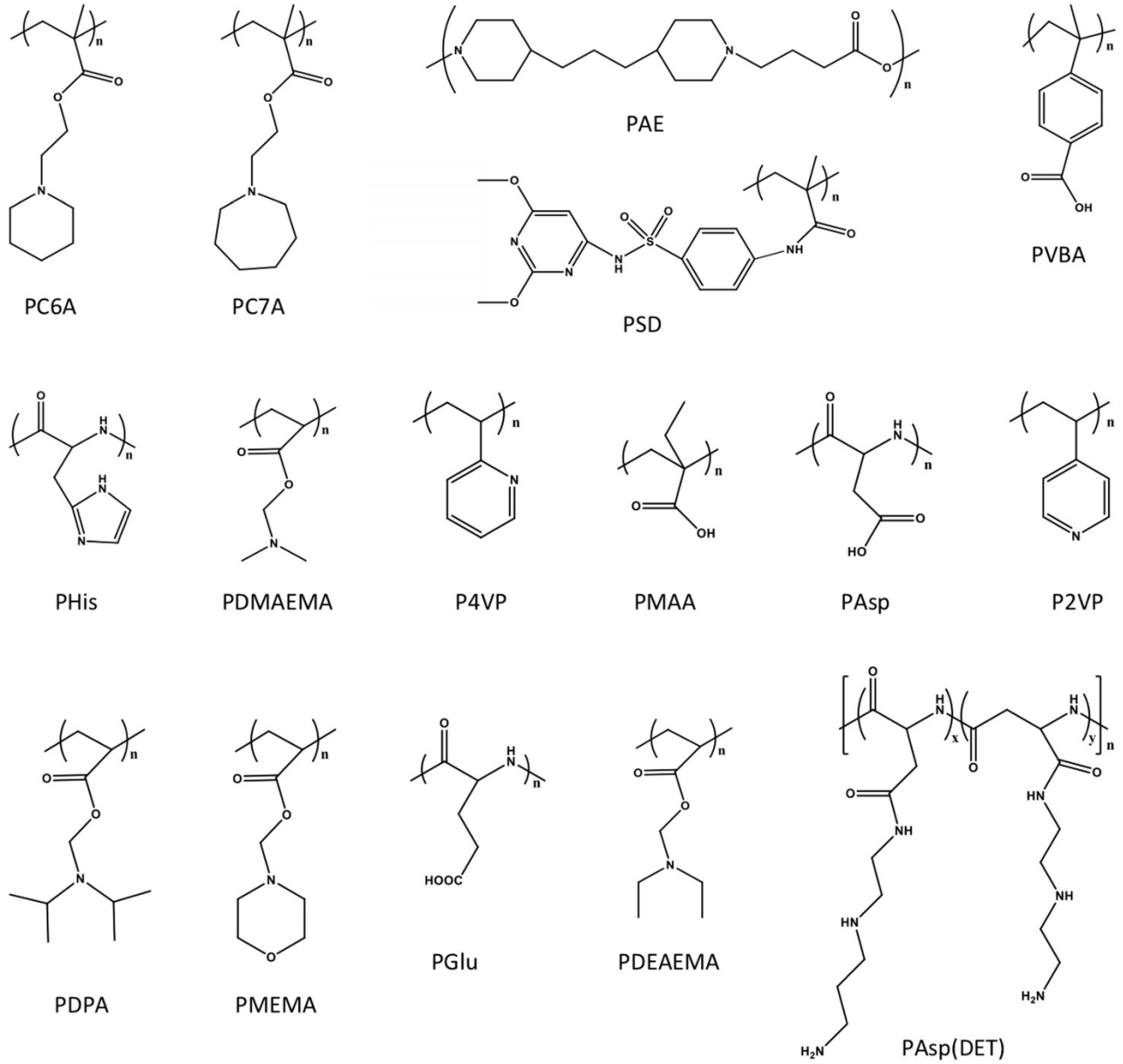

Figure 7. The intracellular or tumor microenvironment pH-responsive polymers have been applied for engineering pH-sensitive nanocarriers.

bind to surrounding proteins to boost much higher relativities. It could specifically and sensitively amplify the contrast in tumors for accurate two- and three-dimensional MR imaging (Figure 9B). The PEGMnCaP could also distinguish hypoxia in tumors with even higher contrast enhancement than the surrounding tumor regions, as more Mn^{2+} were released in hypoxic regions with lower pH, while the hypoxia imaging was confirmed by immunostaining of hypoxia (Figure 9C) and checking the lactate level in the detected hypoxia regions (Figure 9D). It further accurately probed ultra-small liver metastasis (Figure 9E), which was difficult to be detected by conventional CAs. The pH-triggered MR imaging of solid tumors could be further applied for imaging-guided tumor neutron capture therapy [165]. For example, the pH-sensitive block copolymer hybrid CaP nanocarriers further demonstrated high performance in cancer theranostics by incorporating Gd-DTPA for tumor diagnosis and promoted gadolinium neutron capture therapy (GdNCT) [165, 208]. Besides, the intratumoral pH could also trigger size switching for improved penetration of nanocarriers [186, 209], as comparable large size of nanocarriers benefits long circulation, while small size benefits intratumoral penetration [6, 210]. For instance, the polymeric micelles have been self-assembled with platinum (Pt)-drug conjugated, pH-sensitive poly(ethylene glycol)-*b*-poly(2-azepane ethyl methacrylate)-modified polyamidoamine dendrimers (PEG-*b*-PAEMA-PAMAM/Pt) (Figure 10A). It could be disassociated into small size of polymer-drug conjugates by responding to tumor pH for deep penetration in tumors, exhibiting improved therapeutic efficacy (Figure 10B-D) [211]. Moreover, nanocarriers could response to pH for surface charge conversion in tumor microenvironment [212, 213], as neutral or negative charged nanocarriers holds the "stealth effect" during long circulation, while positive charged nanocarriers are more likely to internalize with cancer cells. Regarding this point, the surface of polymeric micelles were designed to switch from neutral charge at blood pH 7.4 to cationic at tumorous pH 6.5, which could maintain their "stealth effect" during circulation and increase internalization with cancer cells for improved tumor accumulation [195]. By tumor pH-triggered surface conversion, nanocarriers could also be applied for tumor-specific molecular imaging [214]. In addition, by conjugating ligands (*e.g.*, biotin) to tumor pH-sensitive polymers, it was applied to hide the targeting ligands inside the PEG shell during circulation (*i.e.*, pH 7.4) and present ligands in tumor microenvironment (*i.e.*, pH <7.0) [215], to avoid unspecific internalization and uptake of ligands during circulation, as well as improve tumor active targeting efficacy [216]. The ligand-installed, pH-sensitive nanocarriers were reported to target tumors and spontaneous metastasis with effectively suppressed tumor growth [202].

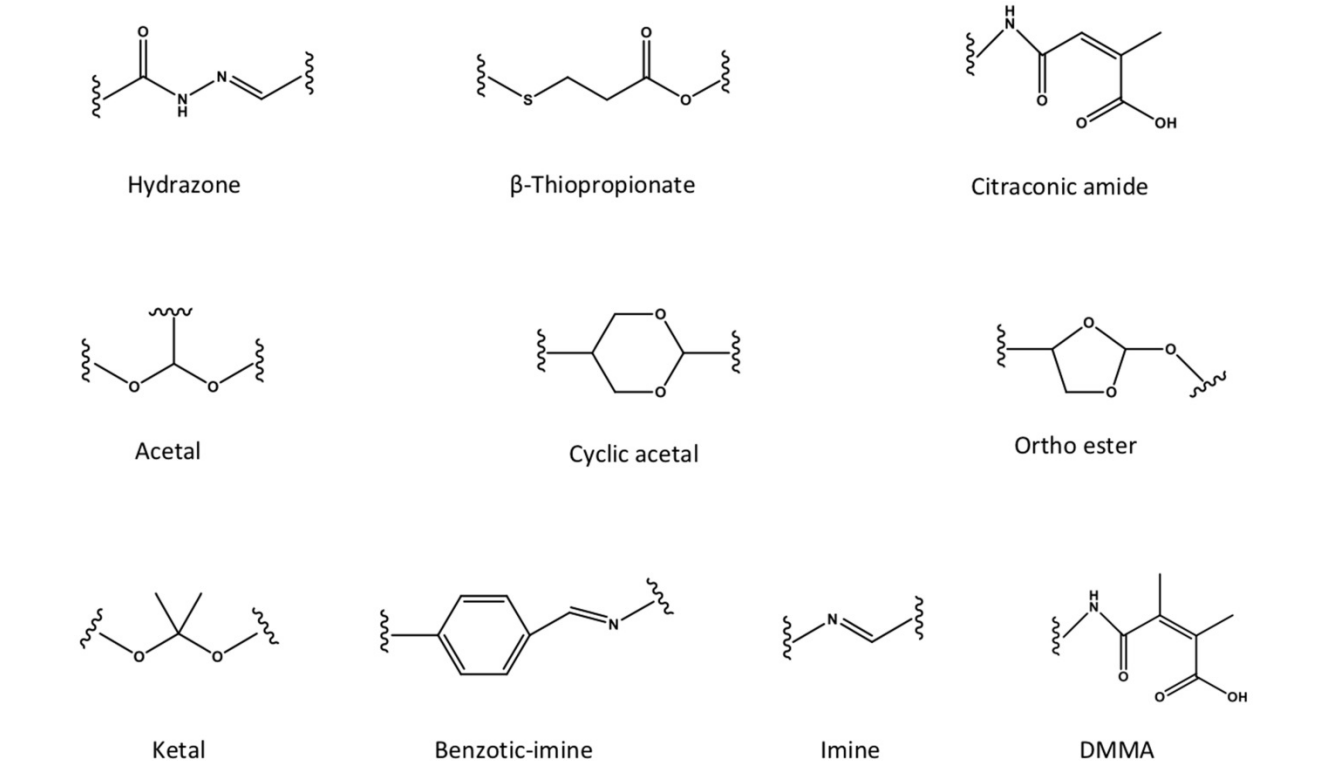

Figure 8. The pH-responsive chemical bonds have been utilized for developing pH-sensitive nanocarriers.

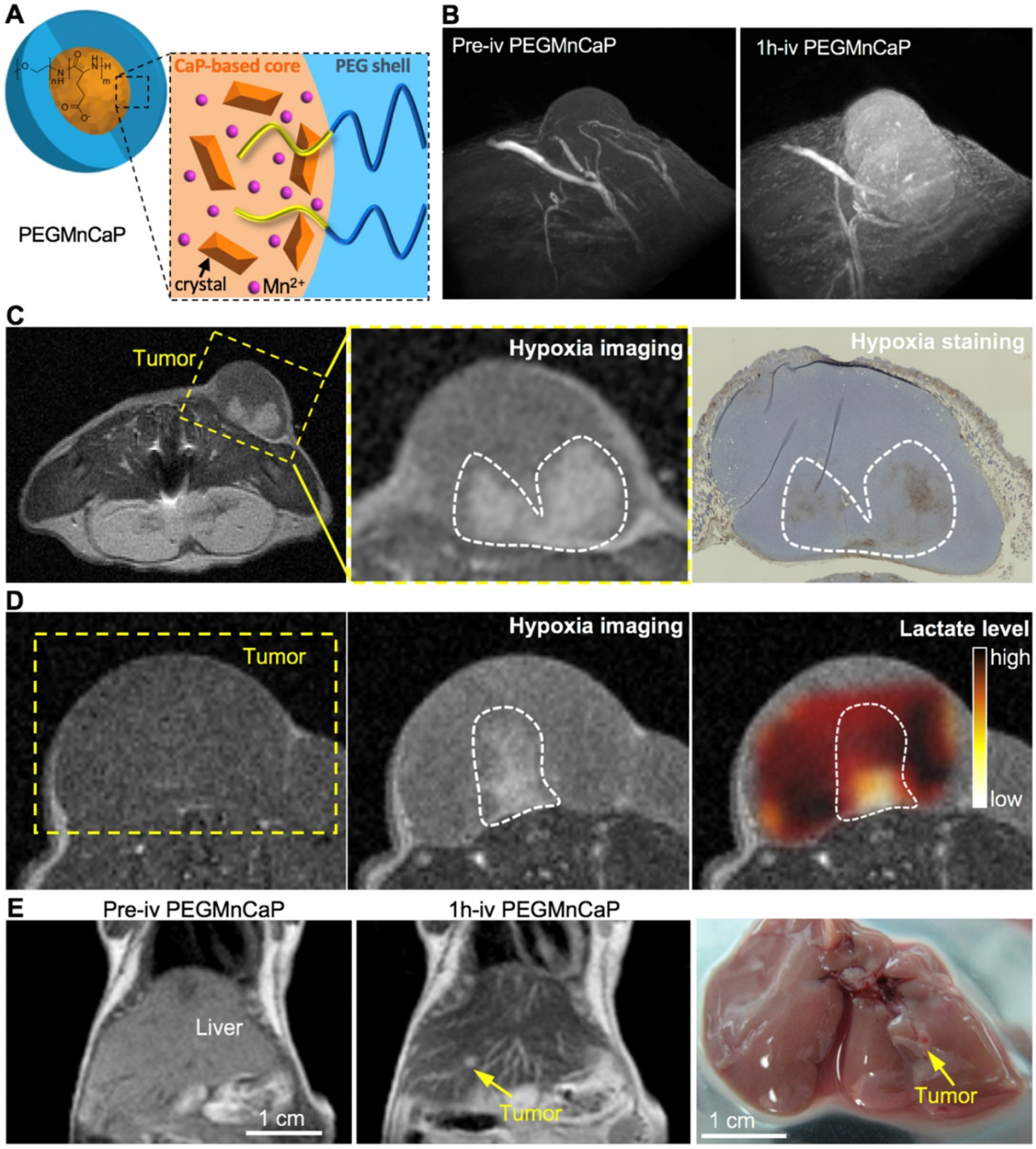

Figure 9. The pH-responsive PEGMnCaP nanocarriers with contrast amplification ability have been developed for MR imaging of tumor malignancy. (A) The composition and characterization of Mn^{2+}-doped PEGMnCaP. **(B)** PEGMnCaP specifically enhanced the contrast in C26 tumors for three-dimensional (3D) MR imaging. **(C,D)** PEGMnCaP probed hypoxia in tumors as confirmed by immune-staining of hypoxia (C) and chemical shift imaging (CSI) of lactate (D). **(E)** PEGMnCaP for precisely MR imaging of 1-2 mm ultra-small metastasis in liver. Adapted with permission from ref. [205], copyright 2016 Springer Nature Limited.

Hypoxia-responsive nanocarriers

The poorly vascularization inside solid tumors is likely to form hypoxia (low oxygen level), which plays an important role in cancer progression, such as locoregional spread and distant metastasis [217]. The promoted malignant phenotype by hypoxia has negative impact on prognosis and therapy and leads to resistance to standard therapy (*e.g.*, radiotherapy, chemotherapy). Therefore, several strategies have been utilized for treating hypoxic tumors, mainly including increasing the oxygen level and using hypoxia activatable prodrugs, *etc* [218]. Until now, several types of nanocarriers have been engineered for drug delivery to hypoxic tumors (Table 5) [219], including liposomes [220], silica nanoparticles [221], upconversion nanoparticles (UCNPs), layer-by-layer nanoparticles [222], nanovesicles [128], polymeric micelles [223], polymersomes [224], albumin nanoparticles [225], cell membrane coated metal organic framework (MOF) [226], solid-state sensors

[227], polymeric probes [228], and polymer hybrid CaP nanoparticles [205], *etc.* Meanwhile, different cargos could be loaded inside the hypoxia-activation nanocarriers, ranging from imaging agents (*e.g.*, contrast agents), prodrugs (*e.g.*, dihydrochloride (AQ4N)), anticancer drugs (*e.g.*, doxorubicin), siRNA and photosensitizers (*e.g.*, ICG), *etc.*, demonstrating high performance in hypoxic tumor imaging and effective therapy by overcoming drug resistance [229].

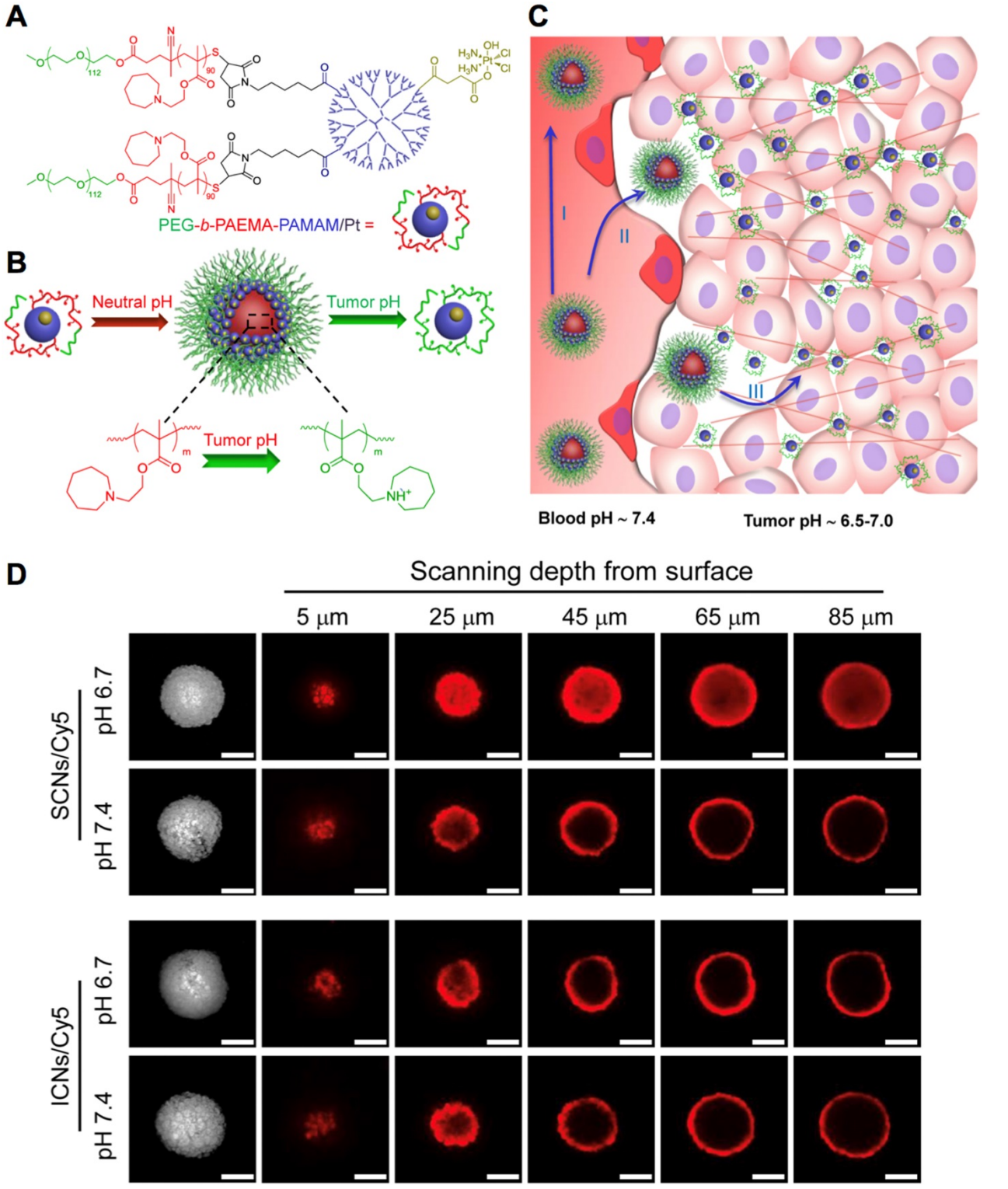

Figure 10. The pH-responsive nanocarriers for tumor therapy. (A) The structure of pH-sensitive polymer-drug conjugates. **(B)** Illustration of pH-dependent self-assembly and disassociation of PEG-*b*-PAEMA-PAMAM/Pt nanocarriers (SCNs/Pt) at different pH. **(C)** Illustration of pH-triggered disassociation of SCNs/Pt nanocarriers in tumors. **(D)** The penetration of SCNs/Pt nanocarriers in BxPC3 pancreatic cancer spheroids. Adapted with permission from ref. [211], copyright 2016 American Chemical Society.

Table 5. Representative hypoxia-responsive nanocarriers

Nanocarriers	Magnetic-responsive strategy/materials	Cargos	Applications	Ref.
Liposomes	The prodrug of banoxantrone dihydrochloride (AQ4N) could be activated in hypoxic environment caused by PDT	Ce6, AQ4N	Cancer therapy	[230]
Silica nanoquencher	Azo monomer; cell-penetrating poly(disulfide)s (CPD) coated silica nanoquencher (BS-*q*NP) (CPD-protein@BS-*q*NP)	Antibody (Cetuximab), fluorescent dye	Hypoxia-triggered protein release and fluorescence imaging	[231]
Upconversion nanoparticles (UCNPs)	Oxygen indicator $[Ru(dpp)_3]^{2+}Cl_2$ for hypoxia detection as UCNPs provided the excitation light of $[Ru(dpp)_3]^{2+}Cl_2$ by upconversion process at 980 nm	$[Ru(dpp)_3]^{2+}Cl_2$, UCNPs	Imaging hypoxic regions or oxygen changes in cells and zebrafish	[229]
Nanoparticles	The photosensitizer of ICG-mediated PTT induced hypoxia, which then activated the prodrug of TPZ	TPZ, ICG	Tumor therapy by PDT and chemotherapy	[232]
Nanoparticles	The shift from hydrophobic to hydrophilic of 2-nitroimidazole that grafted to polymers in light-activated hypoxia	Doxorubicin, light-sensitive polymer	Hypoxia-triggered drug release, tumor	[233]
Nanoparticles	PEG-azo(azobenzene)-PEI-DOPE block copolymer	siRNA	siRNA delivery and tumor RNAi	[234, 235]
Nanoparticles	Layer-by-layer nanoparticles with a pH-sensitive layer for targeting of tumor hypoxia	Sulfonated polystyrene beads or carboxylated quantum dots	Systemic tumor targeting	[222]
Cancer cell membrane coated MOFs	The porphyrinic MOFs could generate toxic ROS for PDT and cause hypoxic regions for activating TPZ	Porphyrinic metal organic framework, TPZ	Tumor targeted PDT and chemotherapy	[226]
Nanovesicles	The light irradiation of Ce6 induced hypoxia for oxidation bioreduction of 2-nitroimidazole in polymers and activation of TPZ	Ce6, TPZ	Tumor fluorescence imaging and therapy	[128]
Polymeric micelles	The metronidazole (MN) grafted in polymers could change hydrophobicity in hypoxic conditions for drug release	Doxorubicin	Tumor chemotherapy and radiotherapy	[236]
Polymersomes	The PLA (polylactic acid)-azobenzene-PEG is sensitive to hypoxia	Gemcitabine, hypoxia- sensitive dye "Image-iT"	Tumor imaging and drug delivery	[224]
Albumin nanoparticles	With hypoxia-sensitive azobenzene linker to covalently bridge photosensitizer Ce6-conjugated HSA and oxaliplatin prodrug-conjugated HSA	Oxaliplatin prodrug, Ce6	Tumor chemotherapy and photodynamic therapy	[225]
Mesoporous silica nanoparticles	The Ce6-dopped mesoporous silica nanoparticles were decorated with PEG and glycol chitosan by hypoxia-sensitive azobenzene linker	Oligonucleotide (CpG), Ce6	Cancer immunotherapy	[221]
Solid-state sensors	Iodide-substituted difluoroboron dibenzoylmethane-poly(lactic acid) (BF_2dbm(I)PLA) solid-state sensor material	BF_2dbm(I)PLA	Tumor hypoxia optical imaging	[227]
Polymeric probes	Poly(N-vinylpyrrolidone)-conjugated iridium-(III) complex (Ir-PVP) and poly(ε-caprolactone)-*b*-poly(N- vinylpyrrolidone) (PCL-PVP) nanoparticles	Iridium (III) complex	Optical imaging of tumor and metastasis	[228]
Polymer hybrid CaP nanoparticles	Tumor pH-triggered release of Mn^{2+} from CaP to boost higher contrast enhancement in hypoxic tumor regions	Mn^{2+}	MR imaging of solid tumors, hypoxia and metastasis	[205]

The tumor hypoxia could be targeted with hypoxia-responsive and some pH-sensitive nanocarriers, since hypoxic tumor regions are generally associated low pH due to the glycolysis of glucose and production of H^+ and lactate [237]. The major strategy is utilizing hypoxia-sensitive nanocarriers, which are generally constructed with hypoxia-sensitive materials or derivates, *e.g.*, 2-nitroimidazole [238-240], nitroimidazole [241-243], metronidazole [236], azobenzene [244-246], nitro-benzene derivatives [223] and iridium (III) complexes, *etc*. Hypoxia could trigger cargo release from the hypoxia-sensitive nanocarriers, *e.g.*, the incorporated antibody (*i.e.*, Cetuximab) could be released from the silica nanoparticles in hypoxic tumors due to the cleavage of the hypoxia-sensitive cross-linkers (*i.e.*, Azo monomer) [231]. In another study, the nanocarriers were prepared with hypoxia-sensitive 2-nitroimidazole and light-sensitive conjugated polymers for generating ROS and local hypoxia after laser irradiation, to trigger doxorubicin release for enhanced synergistic anticancer efficacy (Figure 11) [233]. The hypoxia-sensitive nanocarriers also facilitate molecular imaging of tumors and metastasis. For example, the nanoscale probes with oxygen level-sensitive iridium (III) complexes have demonstrated high potential for optical imaging of tumors and metastatic lesions [228, 247]. Besides, some nanocarriers could delivery hypoxia-activatable prodrugs [*e.g.*, tirapazamine (TPZ) and banoxantrone (AQ4N), *etc*.] to hypoxic tumors for enhanced therapy, while some photosensitizers could be co-loaded to generate hypoxia by laser irradiation for prodrug activation. For instance, the ICG and TPZ-incorporated liposomes with iRGD as targeting moieties could target both normoxic and hypoxic cancer cells, while the irradiation of ICG by NIR laser could produce extra hypoxia activate TPZ for enhanced therapy [232]. In another example, the vessel-disruptive agents (*i.e.* 5,6-dimethylxanthenone-4-acetic acid) and TPZ incorporated, platelet membrane-coated nanoparticles could disrupt tumor blood vasculatures to promote drug accumulation for improved hypoxia-sensitive therapy [248]. In addition, some pH-sensitive nanocarriers have also be applied for treating tumor hypoxia [249], *e.g.*, the pH-sensitive nanoparticles formed by layer-by-layer procedure could target hypoxic tumors for fluorescence imaging with the incorporated QDs [222]. So far, the hypoxia- sensitive nanocarriers have exhibited much progress in drug delivery to hypoxic tumor for molecular imaging and improved therapy. However, some underlying problems would be addressed in future studies, such as modulating hypoxic tumor microenvironment, increasing drug

penetration and oxygen level, and clinical translation of hypoxia-responsive nanocarriers.

Redox-responsive nanocarriers

The redox-responsive nanocarriers have been widely applied for drug delivery due to the significantly different reduction potentials and capacities in tumors, *e.g.*, the glutathione (GSH) level inside cancer cells (2-10 mM) is remarkable higher than that in normal regions (2-10 μM). Until now, several redox-sensitive nanocarriers have been engineered (Table 6), including nanocapsules [250], mesoporous silica nanoparticles [251], polymer-drug conjugates [252], polymersomes [253], polymeric vesicles [254], polymeric micelles [255-257], nanogels [258], gold nanoparticles [259] and hybrid nanoparticles [260], *etc*. The disulfide bonds could be cleaved into sulfhydryl groups by GSH [261], while the diselenide bonds (Se-Se) are also sensitive to redox potential [262], but with lower bond energy than that of disulfide bonds [263]. Moreover, the H_2O_2-responsive nanocarriers have also been developed for tumor therapy [264, 265], including for treating hypoxic tumors [266] and multidrug resistant tumors [267].

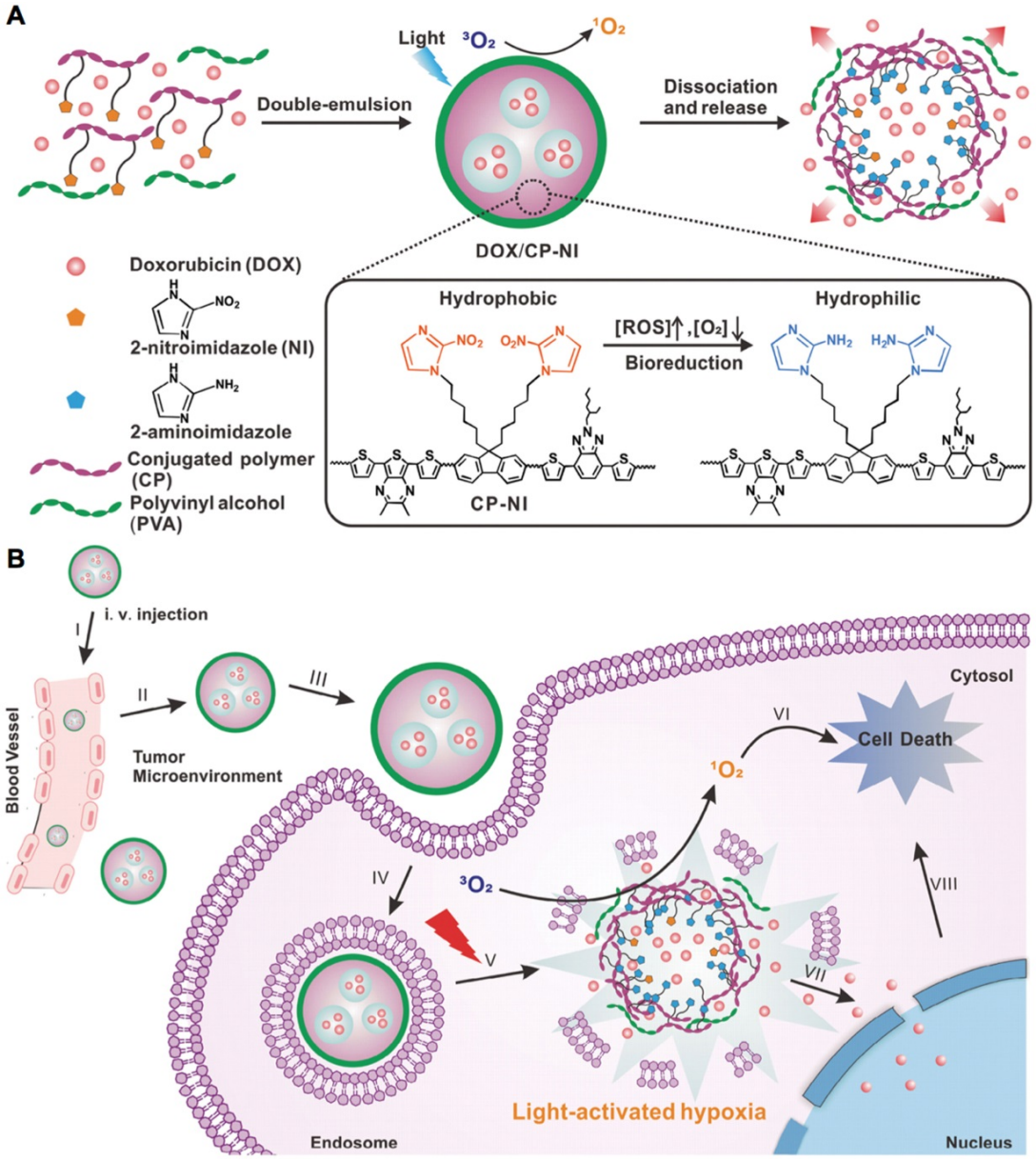

Figure 11. Schematic illustration of light-activated hypoxia-responsive nanocarriers. (A) Preparation of nanocarriers. **(B)**Nanocarriers generated ROS to induce local hypoxic environment, which triggered drug release to enhance the synergistic anticancer efficacy. Adapted with permission from ref. [233], copyright 2016 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim.

Table 6. Redox-responsive nanocarriers for cancer theranostics

Nanocarriers	Redox-responsive mechanism/materials	Cargos	Applications	Ref.
Nanocapsules	Disulfide bonds response to DTT) and GSH	Carboxyfluorescein	Redox-potential triggered drug release inside cancer cells	[250]
Mesoporous silica nanoparticles	Disulfide bonds	Fluorescence dye	Cell-specific targeting and redox-sensitive drug release	[251]
Mesoporous silica nanoparticles	Disulfide bonds	Doxorubicin	Controlled drug release and tumor active targeted therapy	[275]
Polymer-drug conjugates	Disulfide bonds	^{10}B-based sodium borocaptate	Efficient tumor targeted therapy, deep penetration, GSH-triggered drug release	[252]
Polymeric vesicles	Oxidation of the central-block sulphide moieties to sulphoxides and ultimately sulphones by H_2O_2	-	The first example of use oxidative conversions to destabilize nanocarriers	[276]
Polymersomes	Disulfide bonds in poly (trimethylene carbonate-co-dithiolane trimethylene carbonate)	Doxorubicin	Lung cancer chemotherapy	[253]
Micelles	Disulfide bonds	Camptothecin	GSH-triggered drug release inside cancer cells for effective tumor therapy	[124]
Micelles	Se-Se bonds	Rhodamine B	GSH-triggered cargo release	[263]
Micelles	Disulfide bonds	siRNA	Cross-linked micelles with improved stability for siRNA delivery	[271]
Dendritic nanoparticles	Disulfide bonds	Cisplatin, fluorescence dye	Tumor theranostics	[277]
Cationic vesicles	Reduction of Fe^{3+} to Fe^{2+} by GSH	Anticancer drugs and siRNA	Redox-responsive nanocarriers for drug/siRNA co-delivery	[254]
Nanogels	Disulfide bonds	Camptothecin	Tumor therapy	[258]
Nanoparticles	Diselenide bonds	Paclitaxel	GSH-triggered drug release and tumor active targeted therapy	[278]
Nanoparticles	Catalase-response to H_2O_2	Catalase, photosensitizer of methylene blue	Light-triggered, H_2O_2-responsive release of cargos for treating hypoxic cancer cells	[267]
Polyphosphazene nanoparticles	Cross-linking by disulfide bonds	Doxorubicin	Redox-responsive chemotherapy and photothermal therapy	[279]

The redox-sensitive nanocarriers could trigger cargo release inside cancer cells [268], as some bioactive compounds were conjugated to nano-materials through the disulfide bonds [252, 269] and the drug-loaded cavities in some nanocarriers (*e.g.*, mesoporous silica nanoparticles) were sealed by disulfide bonds [251]. The redox-sensitive strategy could also be applied to detach the surface shell [270], and cross-link the core to increase the stability of nanocarriers [271, 272]. In another strategy, the cationic vesicles were formed by chelating of Fe^{3+} with amphiphilic piliararene, exhibiting GSH-triggered release of incorporated doxorubicin and siRNA from the collapse vesicles, as a result of GSH-induced reduction of Fe^{3+} to Fe^{2+} inside cancer cells [254]. Besides, the redox-responsive function could trigger the disassociation and degradation of nanocarriers inside cancer cells, as some nanocarriers were cross-linked by redox-sensitive bonds to increase the stability [271, 273]. The disulfide bonds cross-linked polymer nanocapsules could be disassociated by responding to GSH and dithiothreitol (DTT) [250]. Meanwhile, nanocarriers prepared by polymers with diselenide bonds (Se-Se) could also response to environmental redox-potential (*i.e.*, GSH, H_2O_2) for controlled disassociation of nanoparticles and release of cargos [263]. Moreover, the redox-responsive nanocarriers facilitate intracellular delivery of bioactive compounds into cancer cells to overcome the cellular barriers, such as siRNA [254] and sodium borocaptate (BSH) [255], *etc.* For one example, the BSH-polymer conjugates have been engineered by conjugating with disulfide bonds for tumor boron neutron capture therapy (BNCT), because of the poor cellular uptake of clinically approved ^{10}B-compounds (*e.g.*, BSH) and the limited effective distance almost within diameter of cancer cells (Figure 12A-C) [252]. The BSH-polymer conjugates have significantly promoted the intracellular delivery of BSH, slightly extended the half-life in blood circulation and highly enhanced the tumor accumulation for deep penetration in tumor tissues and significant tumor therapy by BNCT (Figure 12D-F). Furthermore, the morphology of redox-sensitive nanocarriers may affect the intracellular delivery of cargos. Therefore, nanocarriers with different morphologies have been self-assembled with camptothecin and polymers through the disulfide bonds, including spheres, smooth disks, vesicles, and staggered lamellae [274], while the staggered lamellae ones demonstrated the most efficient cellular internalization than others. In addition, the redox-responsive nanocarriers demonstrated high potential for treating hypoxia tumors. For example, the Cy5.5-deoxybouvardin (RA-V) conjugates incorperated nanocarriers could target cancer cells by cRGD ligands, as well as release RA-V for intracellular fluorescence imaging and inducing apoptosis of cancer cells [266].

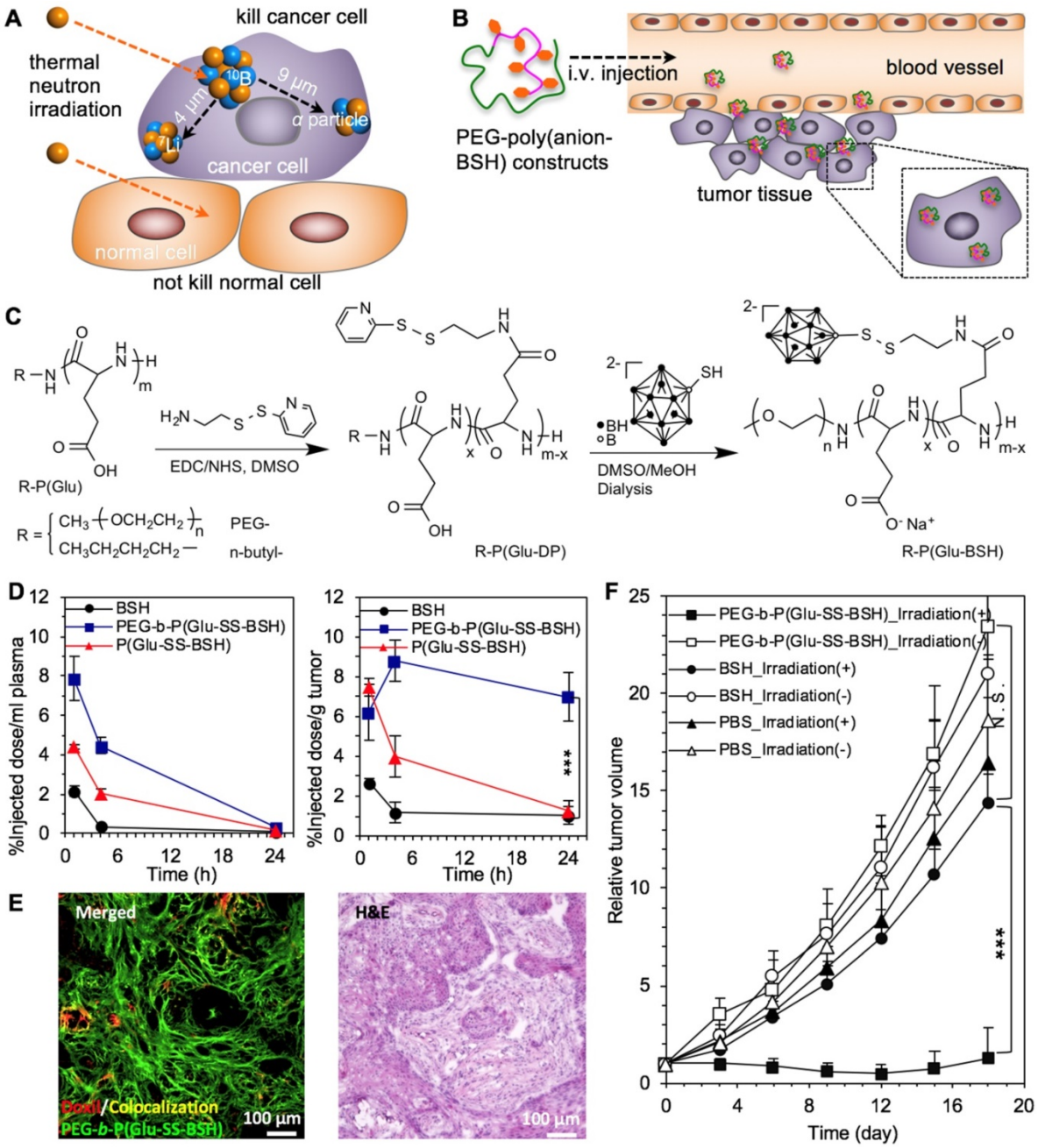

Figure 12. The redox-responsive nanocarriers for drug delivery to tumors toward effective therapy. (A,B) Illustration of boron neutron capture therapy (A) and nanocarriers for tumor BNCT (B). **(C)**The synthesis of redox-responsive polymeric nanocarriers. **(D)** Plasma clearance and tumor distribution of BSH and BSH-polymer conjugates. **(E)** The deep penetration of BSH-polymer conjugates in BxPC3 pancreatic tumors. **(F)** Boron neutron capture therapy of solid tumors with the polymer-boron cluster conjugates. Adapted with permission from ref. [252], copyright 2017 Elsevier B.V.

Enzyme-responsive nanocarriers

Enzymes play an important role in biological reactions, while the unregulated expression of certain enzymes in neoplastic conditions could be triggers for enzyme-responsive drug delivery. Several enzyme-responsive nanocarriers have been engineered for achieving controlled release of cargos in tumors and cancer cells [280, 281], prodrug/ligands activation, as well as morphology change, mainly including mesoporous silica nanoparticles [282, 283], dendrimers [284], magnetic nanoparticles [285, 286], polymeric micelles [287] and liposomes [288, 289] *etc.* As shown in Table 7, nanocarriers could response to several upregulated enzymes in tumor microenvironment and cancer cells [290], which are mainly including oxidoreductases (*e.g.*, peroxidases) [291], transferases (*e.g.*, creatine kinase) [289], and hydrolases, such as matrix metalloproteinases (MMPs) [292-294], human recombinant caspase 3 [295], proteinase K [60, 296], intestinal protease [286], cathepsin B [297] and trypsin [298, 299] *etc.*

Table 7. Enzyme-responsive nanocarriers for cancer theranostics

	Bond type	Enzyme	Reaction	Occurrence	Materials	Cargo	Ref.
Hydrolases	Peptide bonds	α-Chymotrypsin	Hydrolyze peptide amide bonds	Pancreas	Hollow mesoporous silica/poly(L-lysine) particles	Fluorescein and cytosine-phosphodiester-guanine oligodeoxynucleotide (CpG ODN)	[283]
		Human recombinant caspase 3	Hydrolyze peptide bonds only after an aspartic acid residue	Cytoplasm	Hyaluronic acid coating caspase 3 loaded pure drug nanoparticles	Paclitaxel	[295]
		Cathepsin	Hydrolyze glycyl phenylalanyl leucyl glycine tetra-peptide	Lysosome	PEGylated lysine peptide dendrimer-gemcitabine conjugate	Gemcitabine	[284]
			Hydrolyze tetrapeptide glycyl phenylalanyl leucyl glycine tetra-peptide	Lysosome	Amphiphilic biodegradable triblock N-(2-hydroxypropyl methyl) acrylamide copolymer-gadolinium- paclitaxel-Cyanine5.5 conjugates	Paclitaxel	[297]
		Elastase	Hydrolyze peptide amide bonds of elastin	Tumor	PEGylated pDNA-nanoparticles	Nucleic acid	[306]
		MMPs	Hydrolyze peptide amide bonds of extracellular matrix proteins	Participate in tissue remodeling and metastasis	Low molecular weight protamine and conjugated it to PEG-PCL nanoparticles	Paclitaxel	[307]
			Hydrolyze peptide amide bonds of extracellular matrix proteins	Participate in tissue remodeling and metastasis	MSNs-Peptide-BSA-LA@DOX	Doxorubicin	[293]
			Hydrolyze peptide amide bonds of extracellular matrix proteins	Participate in tissue remodeling and metastasis	Brush peptide-polymer amphiphiles composed fluorescent nanoparticle	Fluorescence dye	[294]
			Hydrolyze peptide amide bonds of extracellular matrix proteins	Participate in tissue remodeling and metastasis	Micellar nanoparticles with a surface comprised of MMP-substrates and a hydrophobic paclitaxel core	Paclitaxel	[292]
			Hydrolyze peptide amide bonds of extracellular matrix proteins	Participate in tissue remodeling and metastasis	Phenylboronic acid conjugated human serum albumin grafted mesoporous silica nanoparticles	Doxorubicin	[282]
		Thrombin	Hydrolyze peptide amide bonds of fibrinogen	Participate in haemostasis, thrombosis, cell signaling, fibrinolysis and inflammation	Layer-by-layer assembly of poly(2-oxazoline)-based materials	Thrombolytic agent	[308]
		Thermolysin	Hydrolyze peptide amide bonds containing hydrophobic amino acids.	Produced by *Bacillus thermoproteolyticu*	Poly(L-glutamic acid) star polypeptides using PPI dendrimers as initiators.	Rhodamine B	[309]
		Trypsin	Hydrolyze peptide amide bonds	Pancreas	Bola-like cationic diphenylalanine nanocarriers	Doxorubicin	[298]
			Hydrolyze peptide amide bonds at C terminal of lysine and arginine	Produced by the pancreas, activated in the small intestine	Protamine/ sulfatocyclodextrin supramolecular nanoparticles	Trisodium salt of 8-hydroxypyrene-1,3,6-trisulfonic acid (HPTS)	[299]
		Proteinase K	Hydrolyze peptide bonds	Candida albicans	Methotrexate-conjugated magnetic nanoparticles and glycine coated magnetic nanoparticles	Glycine and methotrexate	[296]
			Hydrolyze peptide bonds	Candida albicans	Polytyrosine nanoparticles	Doxorubicin	[60]
	Ester bonds	Acetyl-cholinesterase	Hydrolyze acetylcholine and other choline esters	Present in neuromuscular junctions	Poly(ethylene glycol)-block-poly(acrylic acid) with myristoylcholine chloride	Nile red	[310]
		Phospholipase	Hydrolyze lipids	Present in human digestive system, intracellular compartment and extracellular spaces	(R)-1-O-hexadecyl-2-palmitoyl-snglycero-3-phosphocholine	Antitumor ether lipids	[301]
			Hydrolyze phosphoric acid monoester in peptide sequences	Participate in signal transduction and protein activity	ATP coated Ag nanoparticles	Silver nanoparticles	[311]
	Glycosidic bonds	α-amylase	Cleaved α-1,4 glycosidic bond	Present in saliva	Hydroxyethyl starch based 10-hydroxy camptothecin (10-HCPT)-HES and 5-FU-HES conjugates	Paclitaxel	[312]
		β-Glucuronidase	Hydrolyze complex carbohydrates	Present in lysosome, necrotic tissue, and some solid tumor types	β-glucuronidase-responsive prodrugs with the potent monomethyl auristatin E linker	Monomethyl auristatin E	[313]
Oxidoreductases	Azo compounds	Azoreductase	Reductive azo compounds	Colon bacteria	Copolymers of 2-hydroxyethyl methacrylate (HEMA) and methyl methacrylate (MMA), and terpolymers of HEMA, MMA, and methacrylic acid	Ibuprofen	[291]
Transferases	Phosphorus-containing groups	Creatine kinase	Phosphorylate hydroxyl group in peptide sequences	Regulate cellular pathways	Liposome based DSPE-PEG2000-TAT	Paclitaxel	[289]

The enzyme-sensitive nanocarriers could be utilized in the following aspects: (1) Activating prodrugs, probes and ligands by cutting the enzyme-sensitive bonds between the bioactive compounds and protective groups; (2) Degradation or disassociation of nanocarriers through enzyme-triggered cleavage of polymer backbones, charge conversion of nanomaterials and disassembly of nanoparticles; (3) Direct cleaving the conjugation between nanocarriers and drugs; (4) Enzyme-triggered physical disruption of nanocarriers; (5) Enzyme-triggered controlled release of cargos. For achieving enzyme-sensitive function, several factors should be considered for rational design nanocarriers: (1) The recognition and accessibility of enzymes to the sensitive groups/substrates in nanocarriers; (2) The threshold of the substrates that responding to enzymes, which should ensure the enzyme-triggered reaction; (3) the influence of physiological conditions and the physicochemical properties to the enzyme-sensitivity.

The specific enzyme-triggered cargo release allows drug delivery to tumors and avoids cargo exposure during circulation, which could maintain the activity of bioactive compounds, while avoid causing sides effects to normal organs/tissues. For enzyme-triggered drug release, the cathepsin could cleave the hydrolyze peptide bonds in gemcitabine-conjugated dendrimer nanocarriers inside lysosomes to liberate gemcitabine and cationic dendrimers, leading to lysosome escape and intracellular gemcitabine delivery [284]. In another study, the hyaluronic acid coated and prodrug-loaded nanoparticles could specifically release paclitaxel inside cancer cells by affecting the hydrolyze peptide bonds with human recombinant caspase 3 [295]. Besides, the prodrugs/probes could be activated by enzymes in tumors, as the prodrug strategy is generally applied to protect the activity of drugs, probes and ligands during circulation to increase the diagnostic or therapeutic specificity [301]. In one example, the protease-activatable nanoprobes have been developed by combining fluorescent dye and Fe_3O_4 nanocrystals through MMP-9 [302], which could turn "ON" the fluorescence for tumor imaging when the peptide substrates linkers were cleaved by protease. In another case, the MMP9-activatable doxorubicin prodrug-loaded nanocarriers were developed (Figure 13A,B) [300], to combine with combretastatin A4 (CA4)-loaded nanocarriers for cancer synergistic treatment. The CA4-loaded nanocarriers could disrupt tumor blood vasculature and selectively enhance MMP9 expression in tumors to promote the accumulation of doxorubicin (Figure 13C), leading to effective treatment of 4T1 and C26 tumors (Figure 13D,E). Moreover, the enzyme-responsive nanocarriers could be applied for tumor specific imaging, e.g., the MMP-responsive iron oxide nanoparticles have specifically enhanced the T_2-weighted contrast in tumors for diagnosis by MRI [285]. Furthermore, the enzyme could uncap the surface shell (*e.g.*, peptides) of nanocarriers to improve their accumulation in tumors. For example, the nanocarriers self- assembled by paclitaxel-conjugated block copolymers and enzyme-recognition peptide shell, could change the morphology due to the cleavage of peptide shell by MMP, leading to high accumulation of the polymer-drug conjugates in tumors [292]. In addition, the enzyme-responsive function could be applied for disassociation of nanocarriers. The azobenzene-linked amphiphilic diblock copolymers have been applied to form polymeric micelles, and micellar architecture could be disrupted by responding to azoreductase and nicotinamide adenine dinucleotide phosphate (NADPH) [303]. It demonstrated high potential in the arena of colon-specific drug delivery, as azoreductase is existed in human intestine. The enzyme-triggered degradation of nanocarriers into small size structures would improve the penetration of drug delivery systems throughout the tumor's interstitial spaces. For instance, the 100 nm nanoparticles could be reduced to 10 nm by responding to proteases (*i.e.*, MMP-2) in tumor microenvironment, which effectively enhanced the diffusion of drugs into the tumor's dense collagen matrix, while maintained long circulation for achieving EPR effect [304]. Overall, the enzyme-sensitive nanocarriers have demonstrated high potential in tumor diagnosis [285, 286], as well as treating primary and metastatic tumors [293, 294, 305].

Multimodal-responsive nanocarriers

In addition, nanocarriers have also been engineered with multiple stimuli-responsive functions, facilitating multistage drug delivery, as well as achieving higher specificity and efficacy. For example, nanocarriers responding to both intracellular pH and GSH have been developed for promoted intracellular drug delivery [314]. In another study, the developed platinum drug delivery nanocarriers could response to intracellular GSH for disassociation, and response to intracellular low pH for controlled drug release [277]. Indeed, the multiple stimuli-responsive nanocarriers hold high potential in achieving long circulation, high tumor accumulation, deep penetration in tumor tissues, internalization with cancer cells and endosome escape, *etc.* Thus, several multiple stimuli-responsive nanocarriers have been engineered for delivery cargos to tumors [315-321]. In one example, the multiple stimuli-

responsive nanocarriers could be discharged into small nanoparticles by responding to the low pH in tumor microenvironment, and then the platinum prodrugs in the small nanoparticles were activated by GSH for promoted penetrating and treating the poorly permeable pancreatic tumors [209]. In another example, the nanocarriers made by γ-glutamyl-based polymer–drug conjugates (PBEAGA-CPT) conjugates could response to both γ-glutamyl transpeptidase (GGT) and GSH have been developed [322], which could convert to be positive charged nanomaterials by responding to GGT for internalization with cancer cells and by responding to GSH inside cancer cells to release CPT (Figure 14A-C). The multimodal responsive polymer-drug conjugated nanocarriers have demonstrated high efficacy in transcytosis, extravasation, internalization with cancer cells and deep tumor penetration, leading to effective supression of subcutaneous HepG2 tumors (Figure 14D-F). In general, it is sophisticate for developing multiple stimuli-responsive nanocarriers, and also difficult to maintain the multiple functions in biological systems. Thus, nanocarriers with single or dual stimuli-responsive functions have been more focused [49, 323]. For instance, the polyphosphazene nanocarriers with pH- and redox-sensitivities have been engineered for tumor multimodal imaging- guided chemo-photodynamic therapy [324-326]. Here nanocarriers for multiple stimuli-triggered drug delivery were briefly introduced, as each stimuli- responsive function has already been discussed above.

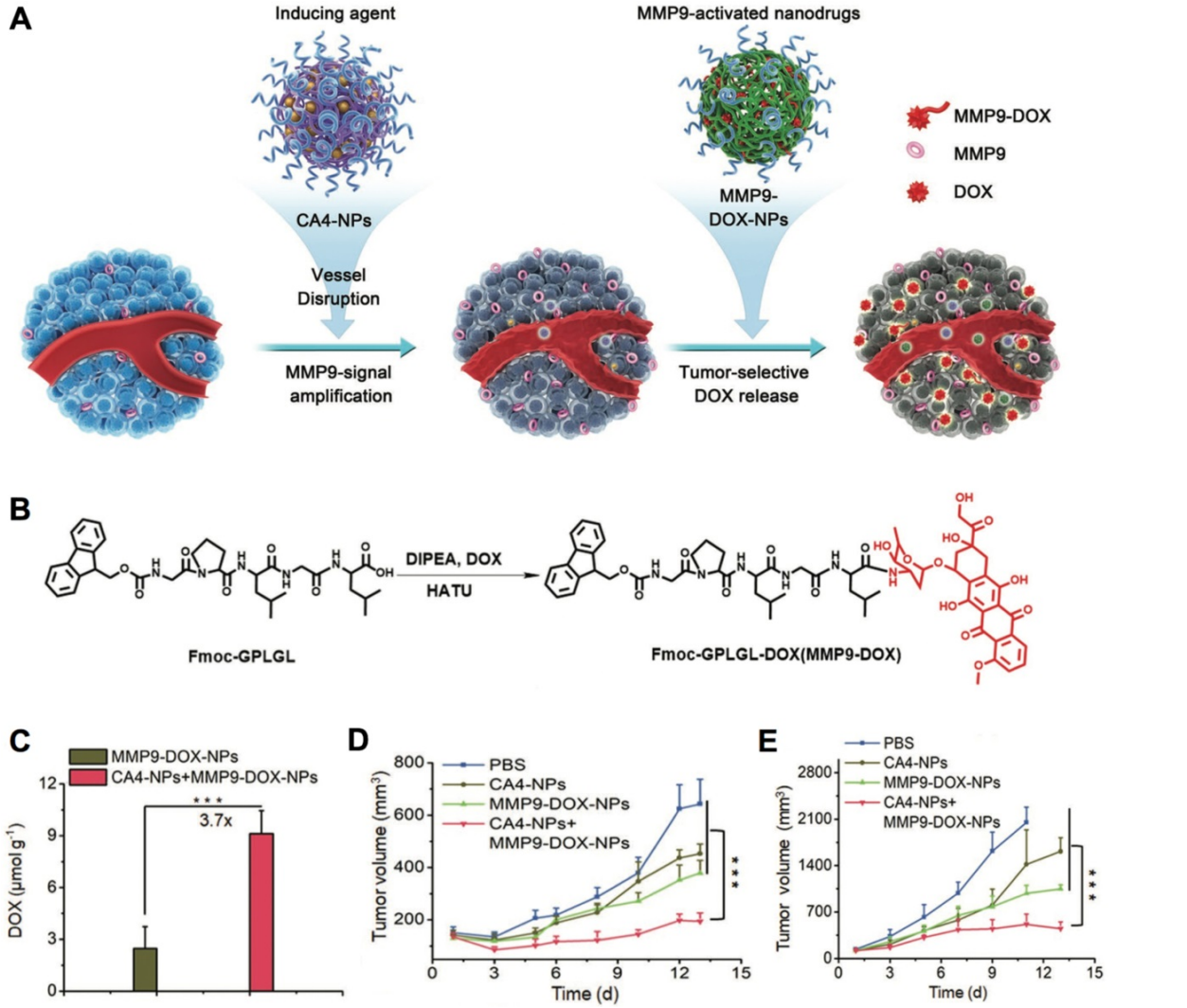

Figure 13. Enzyme-responsive nanocarriers for cancer therapy. (A) Schematic illustration of nanocarriers incorporating combretastatin A4 nanodrug (CA4) plus MMP9-activatable doxorubicin prodrug for tumor therapy. **(B)** The chemical structure of MM9-activatable MMP9-activated doxorubicin prodrug. **(C)** The distribution of doxorubicin in tumors. **(D,E)** Tumor inhibition rate in 4T1 (D) and C26 (E) tumor models. Adapted with permission from ref. [300], copyright 2019 John Wiley & Sons, Inc.

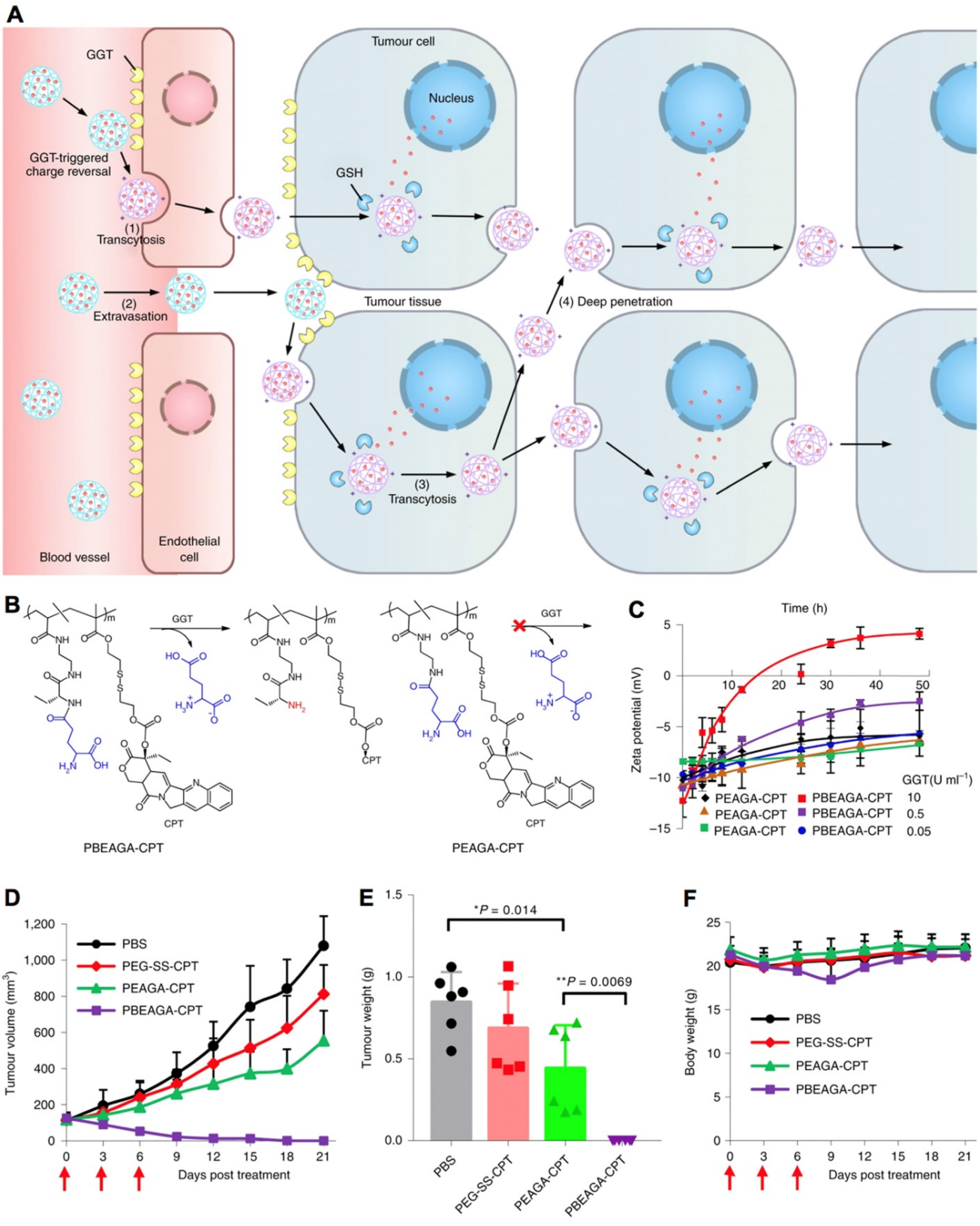

Figure 14. Multimodal-responsive polymer-drug conjugated nanocarriers. (A) Illustration of the cationization-initiated transcytosis-mediated tumour penetration for transendothelial and transcellular transport of nanocarriers. **(B)** The structures of GGT-responsive cationizing PBEAGA-CPT conjugates and the non-GGT-responsive PEAGA-CPT conjugates. **(C)** The zeta potentials of the nanocarriers. **(D-F)** Antitumor efficacy of polymer-drug conjugated nanocarriers against subcutaneous HepG2 tumors, where the tumor growth rate (D), tumor weight (E) and bodyweight (F) were measured. Adapted with permission from ref. [322], copyright 2016 Springer Nature Limited.

Table 8. Clinical translation of stimuli-responsive nanocarriers

Stimulus	Nanocarriers	Cargo	Indications	Clinical status	Reference
Magnetic	Iron oxide magnetite	Iron oxide nanoparticles	Prostate cancer	Phase I	NCT02033447
	Iron and carbon (MTC-DOX)	Doxorubicin	Unresectable hepatocellular carcinoma	Phase II and III	NCT00034333
			Hepatocellular carcinoma	Phase I and II	NCT00054951
			Liver metastasis	Phase I and II	NCT00041808
Temperature	Liposomes (ThermoDox)	Doxorubicin	Recurrent regional breast cancer	Phase I and II	NCT00826085
			Liver tumor	Phase I	NCT02181075
			Pediatric refractory solid tumor	Phase I	NCT02536183
		Doxorubicin combined with high Intensity focused ultrasound (HIFU)	Painful bone metastases, breast carcinoma, non-small cell lung cancer, small cell lung cancer, adenocarcinoma	Phase II	NCT01640847
		Doxorubicin combined with standardized radiofrequency ablation	Hepatocellular carcinoma	Phase III	NCT02112656
pH	Polymeric micelles (NC6300)	Epirubicin	Solid tumor, soft tissue sarcoma, metastatic sarcoma, sarcoma	Phase I and II	NCT03168061
Secretory phospholipase A2 (sPLA2)	Liposomes (LiPlaCis)	Cisplatin	Advanced or refractory solid tumor, metastatic breast cancer, prostate cancer and skin cancer	Phase I and II	NCT01861496

Clinical translation of the stimuli-responsive nanocarriers

The advances in stimuli-responsive nanocarriers have led to clinical translation of several formulations. As shown in Table 8, there are six nanocarriers responding to magnetic, temperature, pH and secretory phospholipase A2 (sPLA2), are under clinical translation. Two magnetic-sensitive iron-based nanocarriers, iron oxide magnetite, and doxorubicin-loaded iron and carbon (MTC-DOX), are under clinical trial for treating cancers. The iron oxide magnetite was conducted Phase I clinical trial to evaluate safety, retention and distribution after injection, which final score is for treating prostate cancer in men by thermal ablation. Three clinical trials have been applied for MTC-DOX, including Phase II and III studying the safety, tolerance and efficacy (survival time) on treating unresectable hepatocellular carcinoma (NCT00034333); Phase I and II evaluation of prohibiting hepatocellular carcinoma progression after injection with external magnet (NCT00054951); and Phase I and II studying on liver metastasis (NCT0 0041808). Besides, the thermal-sensitive doxorubicin-incorporated liposomes (ThermoDox) have been applied for the following three clinical studies: Phase I and II studying the maximum tolerated dose, safety, pharmacokinetics and hyperthermia effects in patients with recurrent regional breast cancer (NCT00826085); Phase I investigation of doxorubicin release from liposome by focused ultrasound in liver tumors (NCT02181075); and MRI and high intensity focused ultrasound (HIFU) combined study to determine doxorubicin release in pediatric refractory solid tumor (NCT02536183). The clinical trial of ThermoDox has also be designed to evaluate the safety and efficacy by combining with HIFU on several tumors (Phase II, NCT01640847), *e.g.*, painful bone metastases, breast carcinoma, non-small cell lung cancer, small cell lung cancer and adenocarcinoma; as well as study the efficacy on treating hepatocellular carcinoma combined with standardized radiofrequency ablation (Phase III, NCT02112656). Moreover, the pH-responsive, epirubicin-loaded polymeric micelles (NC6300) have entered Phase I and II study (NCT03168061) for evaluating the dose, activity and tolerability in patients with soft tissue sarcoma. In previous preclinical clinical study, NC6300 could reduce the cardiotoxicity of epirubicin by conjugating to polymers through pH-sensitive bonds (*i.e.*, hydrazone) [327], and exhibited better therapeutic effect (10 mg/kg based on epirubicin) on treating hepatocellular carcinoma [328]. The preclinical evaluation has provided positive evidences for further clinical evaluation. In addition, the secretory phospholipase A2 (sPLA2)-sensitive, cisplatin-incorporated liposomes (LiPlaCis) have entered Phase I and II to study the safety, tolerability and sensitivity on patients with advanced breast cancer and metastatic breast cancer (NCT01861496). Although with progress, the clinical translation of stimuli-responsive nanocarriers still encountered several barriers: (1) the differences between animal tumor models and tumors in patients, as tumors in patients are more heterogeneity and complicated; (2) the toxicity, biosafety and biodegradability of nanocarriers should be addressed; (3) the stable stimuli-responsive function *in vivo*; (4) the tumor accumulation and therapeutic efficacy of stimuli-sensitive nanocarriers should be proved in clinical trial; (5) the factors that influence the stimuli-responsive properties *in vivo* should be clarified; (6) the right dose and administration way should be studied, *e.g.*, intravenous injection (*i.v.*), intraperitoneal injection (*i.p.*). Therefore, future work would focus on clinical translation of the stimuli-sensitive

nanocarriers, and optimizing the formulations from lessons of clinical trial.

Conclusion

The nanocarriers bring novel strategy for delivery bioactive compounds to tumors. The stimuli-sensitive nanocarriers provide high specificity and multiple functions in drug delivery, including controlled release, alerted tumor accumulation, switch "ON-OFF" activities, as well as promoted diagnostic and therapeutic accuracy and efficacy. Besides, the rational design of stimuli-nanocarriers has considered their biological manners in tumor microenvironment and cancer cells to maximize the efficacy and minimizing the adverse effects to normal organs and tissues. Until now, numerous external and internal stimuli-sensitive nanocarriers have been developed, exhibiting better outcomes than the conventional formulations. The stimuli-responsive systems could be widely applied for diagnosis, probing, sensing and therapy tumors and other diseases, such as cardiovascular diseases, *etc*. Moreover, maintaining the stimuli-sensitivity in large scale produced nanocarriers would be potential challenge. Furthermore, although with extensive studies on stimuli-sensitive nanocarriers, only a few formulations have entered clinical translation, which requires future extensive works on clinical translation. In addition, considering the heterogeneity of tumors, the molecular imaging would be applied for screening the stimuli-responsive nanocarriers in tumors and patients, to predict and study the sensitivity and responses [329]. Meanwhile, the stimuli-responsive nanocarriers may also be combined with antibodies for tumor immunotherapy [330, 331]. Overall, the development of nanocarriers responding to external and internal stimuli in diseased regions would promote the advent of "magic bullets" for tumor precision diagnosis and therapy in future.

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Competing Interests

The authors have declared that no competing interest exists.

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