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REVIEW

Size-transformable nanotherapeutics for cancer therapy



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Abstract The size of nanodrugs plays a crucial role in shaping their chemical and physical characteristics, consequently influencing their therapeutic and diagnostic interactions within biological systems. The optimal size of nanomedicines, whether small or large, offers distinct advantages in disease treatment, creating a dilemma in the selection process. Addressing this challenge, size-transformable nanodrugs have surfaced as a promising solution, as they can be tailored to entail the benefits associated with both small and large nanoparticles. In this review, various strategies are summarized for constructing size-transformable nanosystems with a focus on nanotherapeutic applications in the field of biomedicine. Particularly we highlight recent research developments in cancer therapy. This review aims to inspire researchers to further develop various toolboxes for fabricating size-transformable nanomedicines for improved intervention against diverse human diseases.

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1. Introduction

The rapid development of nanotechnology has enabled broad applications in biomedical research, with nanomedicine offering new opportunities for tumor treatment¹. Compared with traditional small molecule drugs, nanomedicine boasts several advantages: 1) The nanoscale drug carrier endows it with enhanced permeability and retention (EPR) properties. This feature enables nanotherapeutics to selectively accumulate at tumor sites, thereby realizing passive targeting ability; 2) The long circulation time in the body, resulting from the size effect, prevents rapid drug elimination, enhances drug molecule stability, and circumvents degradation by the body; 3) Active targeting is achieved through carrier modification, further improving the enrichment efficiency of nanomaterials at tumor sites; 4) Integration of multiple imaging and treatment methods into a drug delivery system enables multi-modal diagnosis and treatment². In 1995, The US Food and Drug Administration (FDA) granted its first approval to the anti-tumor nanotherapeutic doxorubicin liposome (Doxil) for treating Kaposi's sarcoma and multiple myeloma³. In 2005, the nanoparticle formulation of albumin-bound paclitaxel was approved for treating breast cancer and non-small cell lung cancer⁴. Subsequently, more nanomedicine carriers such as dendrimer macromolecules, nanogels, and polymer micelles have been developed and entered clinical settings⁵. Currently, more than 1000 nanomedicines are being tested in clinical trials⁶. Although nanodrugs have made great progress in the past ten years, they often do not perform well in clinical trials, leading to poor clinical translation. The main hurdle to the clinical conversion of nanomedicine is the low drug delivery efficiency, which is attributed to: 1) poor tumor accumulation efficiency; 2) low cellular uptake efficiency; 3) difficulty in achieving lysosomal escape in cells. A growing body of research has identified that the current level of nanodrug delivery to the target is inadequate, and the extent of accumulation and penetration at the tumor site significantly impacts intratumoral delivery⁶.

There are many important factors that impact the efficiency of drug delivery, such as surface charge, coating, shape, and ligand⁷. Among these attributes, size plays a pivotal role in nanomedicine, with a crucial impact on therapeutic delivery^{8,9}. The effectiveness of nanotherapeutic delivery relies on achieving both substantial accumulation and efficient penetration in tumor tissues, which are essential for reaching the site-specific treatment window and ensuring optimal treatment effectiveness¹⁰. Studies have indicated that cellular responses mediated by nanoparticles are contingent on size, as size can exert a substantial impact on their blood circulation duration, tumor delivery, and penetration^{11,12}. Nanoparticles smaller than 5 nm can be eliminated through the kidneys, whereas those between 10 and 20 nm are quickly absorbed by the liver from the bloodstream. Particles larger than 200 nm are trapped in the splenic sinusoids or identified and removed by the reticuloendothelial system (RES). Consequently, nanoparticles within the 20–200 nm range are likely to remain in circulation for an extended period. Thus, size is a pivotal factor influencing the effectiveness of tumor-targeted drug delivery, including blood circulation, biological distribution, tumor localization and penetration, uptake by cells, and trafficking at the subcellular level¹³.

Numerous studies have demonstrated a close correlation between the size of nanomedicines and their anti-tumor efficacy^{14,15}. In general, the diameter of the nanomedicine is designed based on the aperture of leaky tumor blood vessels¹⁶. Although there may be differences due to varied tumor models, the characteristic pore size of subcutaneous tumors typically varies between 200 nm and

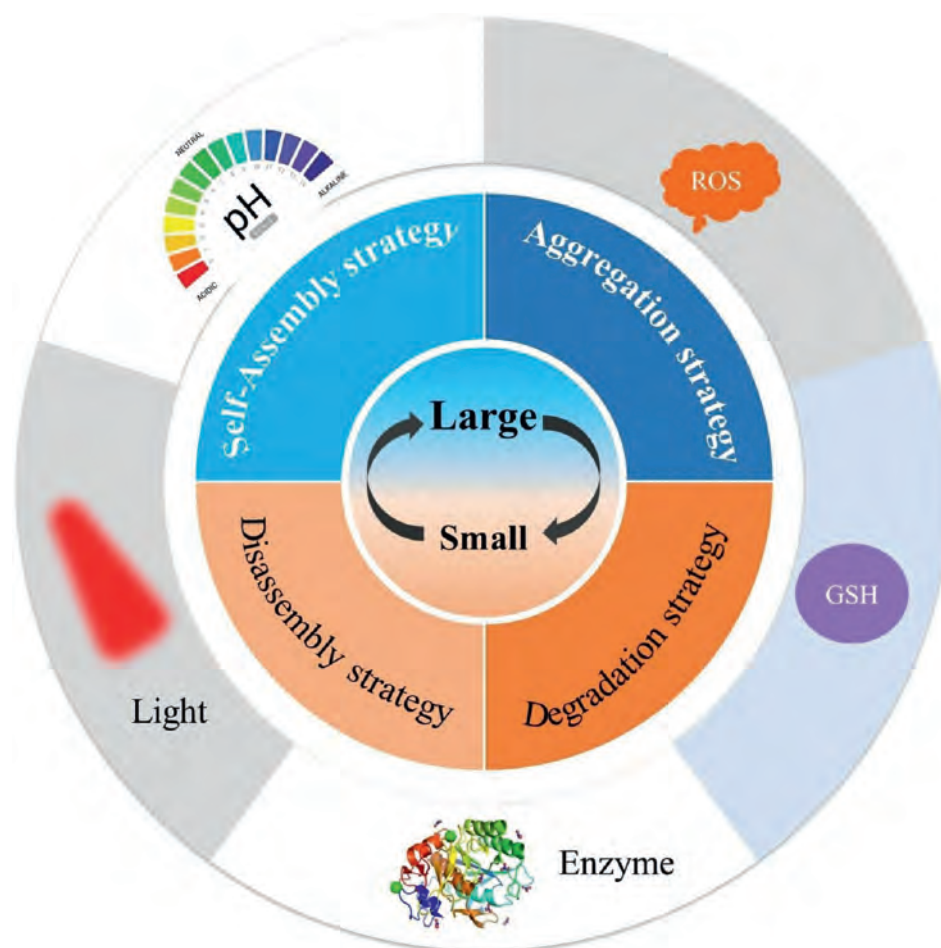
1.2 μm . In tumors that grow in the skull, such as brain gliomas, the size is further reduced¹⁷. However, nanotherapeutics face the problem that size-dependent tumor accumulation and penetration ability cannot simultaneously be optimized due to a prerequisite intricate balance. With the distinctive structure and conditions of tumor tissues, the inherent size of nanoparticles complicates efficient drug delivery. Large nanoparticles tend to remain in tumor tissues better than small nanoparticles^{18–20}. On the contrary, small nanoparticles boast higher level of permeability^{21,22}. To overcome this dilemma, the development of nanocarrier systems with adjustable size is of high therapeutic impact to leverage both effective retention and permeability concurrently.

After nanodrug reaches the tumor zone, substantial nanoparticles can effectively stay in the proximity of the tumor yet face obstacles in penetrating the dense matrix^{23,24}, while small nanoparticles can efficiently penetrate the tumors. But under the elevated interstitial fluid pressure within the tumor, small nanotherapeutics can easily be pumped back into the bloodstream^{25–27}, greatly undermining the delivery efficiency. Therefore, constructing a size conversion nanomedicine carrier with optimal delivery efficiency for improved anticancer efficacy represents the major challenge in nanotechnology-enabled drug delivery systems.

A variety of size-transformable nanomedicines has been reported with the aim of addressing the drawbacks mentioned above^{28–32}. In this review, we summarize two types of size-transformation nanosystems for different medical applications in tumor therapy and imaging. Specifically, we cover the strategies used to switch the size from small to large and large to small. They are divided into 4 subcategories: self-assembly strategy, disassembly strategy, aggregation strategy, and degradation strategy (Scheme 1). These strategies include enzymes, pH changes, light exposure, redox reactions, temperature variations, and more, which enable leveraging their respective unique advantages in enhancing drug delivery, payload release, cellular uptake, and improving tumor imaging. Size-transformable nanodrug strategies offer significant therapeutic advantages, such as enhanced tumor targeting, improved drug accumulation and retention, deep tissue penetration, and controlled drug release. Self-assembly and aggregation strategies capitalize on increasing particle size to avoid rapid clearance and extend retention times, while disassembly and degradation strategies leverage size reduction for deeper tumor penetration and rapid clearance. However, these strategies also present challenges: complex synthesis, stability issues, potential toxicity, and difficulties in achieving precise control over size transformation and drug release. Addressing these challenges through further research is essential for optimizing these strategies for clinical applications (Table 1). Finally, the contemporary challenges and outlook of size-transformable nanomedicines are discussed.

2. Strategies from small to large

The large size of nanodrugs can extend tissue retention and attenuate exocytosis rates from cells, making them well-suited for prolonged imaging and effective treatment³³. Furthermore, specific large nanoparticles are superior to smaller counterparts in terms of enhanced theranostics^{34,35}. Numerous studies have explored strategies involving self-assembly and aggregation to concurrently enhance the accumulation and penetration of nanoparticles^{36,37}. This involves employing initially small nanoparticles for deep penetration, followed by their transformation



Scheme 1 Schematic illustration of the size-transformation strategy in cancer therapy.

into large nanomaterials to increase retention once deep within the tumor, triggered by specific stimuli. These stimulations are associated with internal factors such as tumor heterogeneity, categorized as hypoxia, a slightly acidic microenvironment, and the specific upregulation of enzymes. Additionally, external stimuli including light and temperature are leveraged to craft intelligent, size-aggregable nanomedicines. In response to either external or internal stimulation, the initial relatively small nanoparticles can engage in interactions through click reactions, self-assembly, electrostatic interactions, or phase transitions, ultimately leading to the formation of aggregations.

2.1. Self-assembly strategy

Nanodrugs can self-assemble into different kinds of assembly through hydrophobic–hydrophilic interaction³⁸, electrostatic interaction³⁹, and hydrogen bonding interactions⁴⁰, and π – π stacking effects⁴¹. These noncovalent interactions are the main factors for spontaneous self-assembly. Hence, changing these intermolecular forces is key to designing size-transformable nanodrug. Many subfields of research are focused on tumor-specific microenvironments and external stimulation such as enzymes, pH, redox, and lasers. Once the internal or external stimulation affects the nanodrug, the initial small-sized nanodrug will transform into a large size.

2.1.1. Enzyme-induced

The enzyme induction strategy shows considerable potential owing to its high specificity in selecting substrates and the varied expression of enzymes across various organs/tissues⁴². Tumors, in particular, exhibit numerous specifically upregulated enzymes, including hyaluronidase (HAase), matrix metalloproteinase (MMP)⁴³, legumain⁴⁴, gelatinase⁴⁵, furin⁴⁶, and caspase3/7⁴⁷, among others. Enzyme-induced self-assembly capitalizes on the inherent characteristics of nanocarriers. FAP- α , an exclusive enzyme present in cancer-associated fibroblasts, functions as a prolyl oligopeptidase with specificity to cleave proline from the adjacent amino acid. As a tumor biomarker, it has been extensively used⁴⁸. Zhao et al.⁴⁹ developed a diagnostic system with a size-switchable mechanism activated by FAP- α . This system comprises GTDTKTGPAKLTVFC (Cy) TDTG (molecule 1, Fig. 1A). Size transformation occurs through the cleavage of Gly–Pro–Ala (GPA), stimulating the release of proline and forming plentiful β -sheet fibrils. The morphological transition resulted in a 24-fold retention time increase compared to free drugs. Furthermore, the nanofibers enhanced imaging sensitivity considerably and could function as nanoprobe to expand the tumor detection limit to as tiny as 2 mm, portending an innovative way for the early diagnosis and screening of tumors.

As depicted in Fig. 1B, Hao Wang's research team⁵⁰ designed a tumor-selective cascade-activatable self-detained system (TCASS) for both tumor imaging and drug delivery. In this

Table 1 The strategies, categories, advantages, and disadvantages of size-transformation nanomedicine.

Strategy	Category	Advantage	Disadvantage
Self-assembly	Enzyme induced;	High specificity in selection, good biocompatible, and retention time;	Some enzymes in other nontarget sites, relatively long reaction time;
Disassembly	pH-induced;	High sensitivity, short reaction time;	Unstable, the uncertainty of biological distribution;
	Redox-induced;	Fast response speed;	The uncertainty of biological distribution
	Light-induced;	Precise control, non-invasive trigger, spatial selectivity;	Limited penetration depth, potential tissue damage;
Aggregation strategy	Biological orthogonal crosslinking;	High specificity, improved targeting and retention;	Complex synthesis, potential for immune response;
	Electrostatic interactions;	Simple and versatile;	Interference with biological processes;
Degradation strategy	Chemical bond break;	Multi-functionality, minimized off-target effects;	Complex design and synthesis, degradation and stability issues;
	Onion peeling strategy;	Enhanced stability, sequential release;	Potential drug loss, complex synthesis;
	Surface-binding strategy;	Simplicity in design, controlled release;	Limited drug loading capacity;

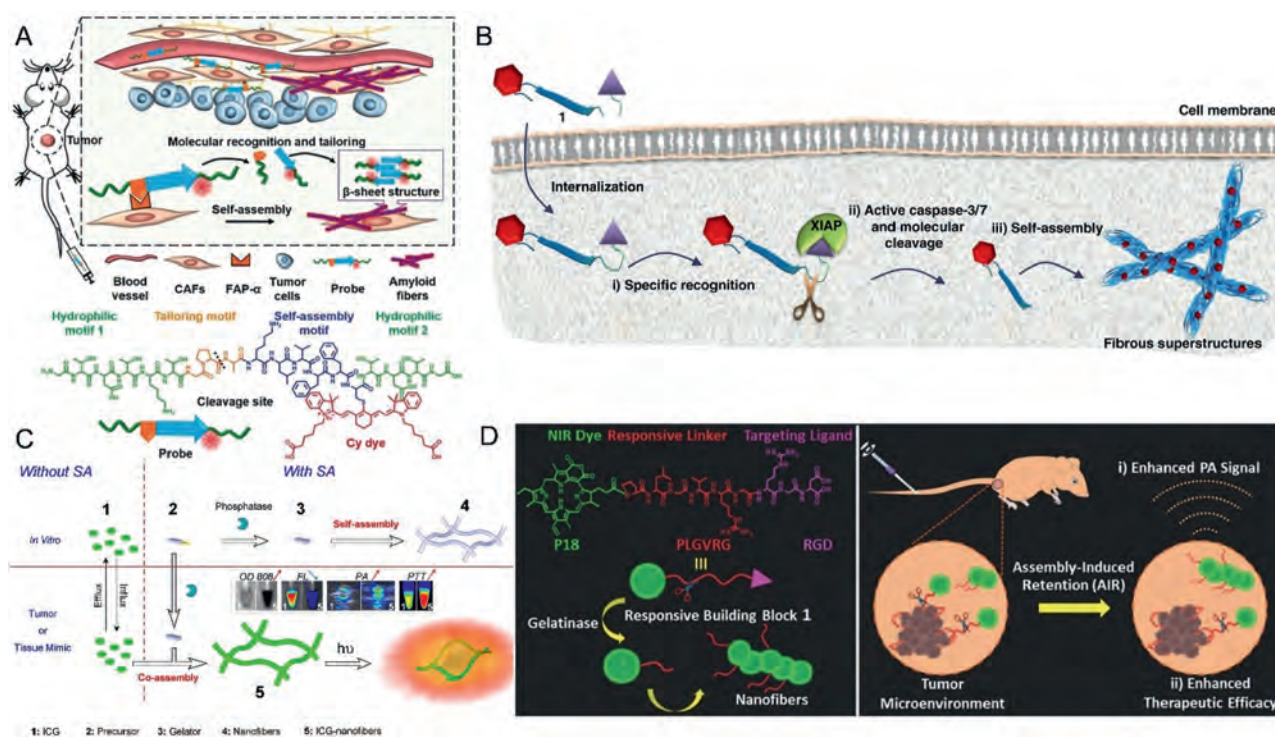


Figure 1 (A) Schematic of *in situ* self-assembly of nanofibers guided by cancer-associated fibroblasts (CAFs) for heightened tumor imaging, accompanied by the chemical structure of the probe featuring four motifs. Reprinted with permission from Ref. 49. Copyright © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) The process entails the specific identification, molecular cleavage, and on-site self-assembly of molecule 1. Initially, the X-linked inhibitor of apoptosis protein (XIAP) specifically recognizes molecule 1. Subsequently, the activated caspase-3/7, triggered by the identification process, cleaves the molecules. Following this cleavage, the molecules undergo rapid self-assembly *in situ*, forming fibrous β-sheet superstructures. Ultimately, these nanostructures made of β-sheets are crucial in enhancing the accumulation and retention of functional molecules within the tumor tissue. Reprinted with the permission from Ref. 50. Copyright © 2019 Springer Nature. (C) The Schematic of the enzyme-triggered supramolecular coassembly of compounds 1 and 2. Reprinted with the permission from Ref. 52. Copyright © 2015 American Chemical Society. (D) Illustration depicting the structural arrangement of compound 1 and its adaptive self-assembly into nanofibers within tumor sites, highlighting the amplification by stimulated emission of radiation (AIR) effect. Reprinted with the permission from Ref. 45. Copyright © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

system, small molecule peptides are engineered for the specific recognition and targeting of X-linked inhibitors of apoptosis protein (XIAP), a protein significantly elevated in tumor cells. The interaction with XIAP triggers caspase-3 activation, enabling molecular shearing and self-assembly into nanofiber structures that enhance the accumulation and retention in tumor sites. Furthermore, TCASS exhibited metabolism similar to small molecules, allowing for rapid clearance from the kidneys and liver and mitigating systemic toxicity. Responsive to enzymatic stimuli, TCASS improves the therapeutic effectiveness of conventional chemotherapy drugs while abrogating their adverse effects. By coupling with contrast agents, the specificity and sensitivity of imaging agents are markedly improved, demonstrating excellent imaging performance in a human bladder cancer model. This study provides a novel tumor targeting mechanism, accelerating the application of nanodrugs and opening new avenues for basic research and clinical translation of nanodrugs.

Alkaline phosphatase (ALP), an enzyme overexpressed in stem cells and certain cancer cells that rapidly converts ATP into adenosine, has been identified as a cancer biomarker for over half a century ago⁵¹. Huang et al.⁵² established a co-assembly strategy instigated by endogenous phosphatase, leading to the formation of tumor-specific nanofibers incorporating indocyanine green (ICG) for cancer therapy. Utilizing coordinated intermolecular interactions, the size-transformable nanofiber brought about significant alterations in the near-infrared absorbance of ICG, which in turn, enhanced its crucial photoacoustic and photothermal performance. The enzyme-guided co-assembly process and its therapeutic capabilities were successfully demonstrated *in vitro*, live cells, tissue-mimicking models, and *in vivo* (Fig. 1C). 4 h post intravenous injection, the ICG uptaken by tumor notably elevated to $15.05 \pm 3.78\%$ ID/g, a 25-fold increase compared to free ICG. This yielded a high tumor-to-normal tissue (*T/N*) ratio (>15). Finally, this nanosystem effectively eliminated tumors, demonstrating high-precision treatment.

MMP-2 (matrix metalloproteinase-2) and MMP-9 (matrix metalloproteinase-9) are members of the matrix metalloproteinase family⁵³. Their roles in cancer progression involve enzymatically degrading the extracellular matrix (ECM), detaching cancer cells from the primary tumor. This process enables the migration of cancer cells to distant sites, where they form metastatic lesions⁵⁴. These enzymes are frequently overexpressed in the tumor microenvironment and selectively cleave peptide substrates with the sequence of PLGVRG. Zhang et al.⁴⁵ devised a peptide sequence, P18-PLGVRGRGD, capable of self-assembling into nanofibers within the tumor. This design amplified both photoacoustic (PA) signal and therapeutic effects (Fig. 1D). Transmission electron microscopy (TEM) validated nanofiber formation in P18-PLGVRGRGD buffer solution when incubated with MMP-2/9. The Purpurin 18 molecules overlapping and π - π stacking interactions between the molecules gave rise to nanofibers with a width of 3.8 nm. Leveraging a small hydrophilic RGD peptide ligand facilitated the targeted delivery of nanofibers to $\alpha v \beta 3$ integrin on the cancer cell membrane. MMP cleavage of the PLGVRG linker enhanced the molecule's hydrophobicity, reducing steric hindrance and facilitating self-assembly into nanofibers with the near-infrared dye P18 in the tumor. Ultimately, as the anhydride groups on P18 underwent gradual hydrolysis, the hydrophilicity of the gel-like molecules increased, leading to nanofibers degradation and subsequent clearance of P18 from the solid tumor. Following injection of P18-PLGVRGRGD, within 10 h, the amount of P18 at the tumor site was almost 7-fold greater

than the control group. Concurrently, an elevated photoacoustic signal was observed with tumor inhibition. This suggests that assembly-induced retention can amplify the tumor-targeted imaging capabilities of P18 and subsequently enhance the effectiveness of photothermal therapy (PTT).

2.1.2. pH-induced

Rapidly proliferating cancer cells display increased glycolytic activity, leading to an acidic extracellular pH (pHe) in tumors compared to normal tissue⁵⁵. The pHe of tumor tissue is approximately 6.8–7.2, whereas normal tissue has a pHe of around 7.4⁵⁶. Within tumor cells, the pH levels in the nucleus (5.0–5.5) and lysosomes (4.5–5.0) can be further reduced⁵⁷. Recently, diverse strategies have been identified for creating pH-responsive nanocarrier systems with size transformation potential. In contrast to the aggregation induced by enzymes, pH-induced reactions provide swift responsiveness and heightened sensitivity. Histidine can be protonated at pH 6.5, an acidic condition frequently employed for constructing pH-responsive nanocarriers⁵⁸. As shown in Fig. 2A, Yang et al.⁵⁹ developed an in-situ peptide-based self-assembling nest-like host for non-invasive implantation in tumor regions for homing therapy of drugs. The peptide was comprised of four segments: (1) a hydrophobic aromatic bispyrene module, (2) a hydrogen-bonding peptide KLVFF module derived from A β , selected as the peptide scaffold for the formation of β -folded fibers with enclosed hydrophobic domains, (3) polyethylene glycol as a hydrophilic chain, and (4) a pH-sensitive peptide sequence. Initially, in a phosphate buffer solution BP-KLVFF-His6-PEG self-assembled into nanoparticles, manifesting green fluorescence due to bispyrene aggregation. The nanoparticles were administered intravenously to mice with tumors, accumulated at the tumor site *via* the EPR effect, and then transformed into nanofibers attributed to changes in hydrophilic/lipophilic balance triggered by the acidic tumor microenvironment, thus forming a nest-like host with a β -folded structure. The host enveloped the tumor area, extending a retention of up to 96 h, enabling the binding and concentration of guest molecules, including doxorubicin (DOX), Nile Red (NR), and ICG that were embedded into the hydrophobic regions of the β -folded nanofibers. 96-h post intravenous injection, the tumor exhibited significant accumulation of NR, with a fluorescence intensity 7.5-fold greater than the free NR group. Concurrently, ICG and DOX molecules were concentrated in tumor sites, facilitating effective chemotherapy and photothermal therapy, respectively. This innovative approach laid the foundation for creating tumor-specific hosts that can accumulate therapeutic drugs under pathological conditions, prolonging retention and sustained release.

Han et al.⁶⁰ developed a hybrid peptide responsive to extracellular tumor acidity, designed to undergo geometric shape transformation to enhance tumor internalization and improve photodynamic therapy (Fig. 2B). Under physiological conditions, this hybrid peptide self-assembles into nanoparticles. However, within the acidic tumor microenvironment, the acid-sensitive group 2,3-dimethylmaleic anhydride detaches from the hybrid peptide, and can detach, resulting in ion-complementary restoration among hybrid peptides and the formation of rod-shaped nanoparticles. Their results showed that the pH-triggered size transformation of the hybrid peptide accelerated its internalization into tumor cells, prolonged tumor retention, enhanced photodynamic therapy, and reduced side effects. These findings support the effectiveness of the size transformation strategy based on the acidity of the tumor microenvironment in improving therapeutic delivery efficiency.

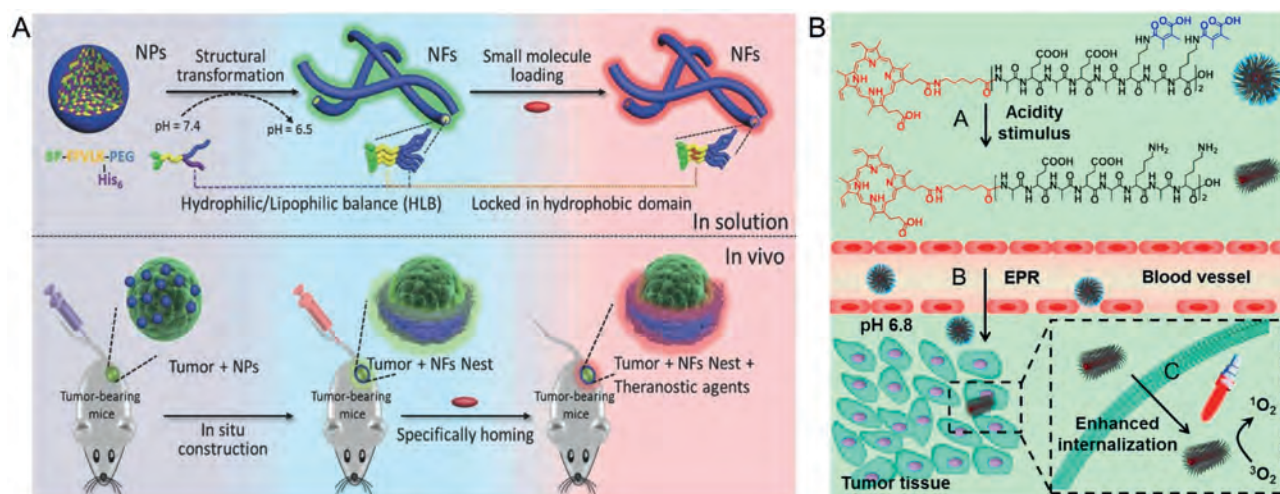


Figure 2 (A) Illustration depicting the composition of the molecule, the mechanism behind shape transformation, and the strategy for drug homing. Reprinted with the permission from Ref. 59. Copyright © 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) Schematic depiction of an acidity-triggered size transformation leading to enhanced photodynamic therapy (PDT). Reprinted with the permission from Ref. 60. Copyright © 2017 American Chemical Society.

2.1.3. Redox-induced

The heightened proliferation of aggressive tumors leads to elevated levels of oxidative stress in both tumor tissues and cells, manifested by increased levels of reactive oxygen species (ROS)⁶¹. In response to oxidative stress, there is a concomitant increase in the oxidative-reductive environment within tumors⁶². For instance, the glutathione (GSH) level inside tumor cells rises to enhance antioxidant capacity, combat oxidative stress, and regulate cell differentiation, proliferation, and apoptosis⁶³. Research indicated that GSH concentrations in tumor regions, especially intracellularly, can reach ~2–10 mmol/L, whereas in normal tissues, it ranges from ~2 to 20 μ mol/L^{64,65}. Disulfide bonds are chemical groups that can be reduced to thiol groups by GSH response making them valuable in drug delivery systems that exploit redox environments⁶⁶. Guo et al.⁶⁷ developed a PEG-dithiothreitol (TGA)-NapFFKY delivery system responsive to redox conditions. The disulfide bonds are cleaved in the presence of a high concentration of glutathione, decreasing hydrophilicity. Consequently, hydrophobic interactions and hydrogen bonding are enhanced, promoting the formation of β -folds and facilitating the transition to nanofibers. Compared to free DOX, the DOX-laden nanotherapeutic exhibited decreased systemic toxicity, with a lower half-maximal inhibitory concentration and an elevated apoptosis rate in tumor cells (2.4-fold higher), indicating a synergistic effect of self-assembling nanofibers with chemotherapy. Moreover, this nanosystem with shape-shifting capabilities enabled efficient systemic administration of DOX by overcoming the poor solubility encountered during intravenous delivery of nanofibers, resulting in increased effective drug concentration within tumor cells (Fig. 3A).

In the majority of cancer cells, there is an overproduction of ROS in the vicinity of mitochondria^{68–71}. Drug delivery systems featuring ROS-responsive bonds have been extensively investigated⁷² and can achieve oxidative stress-induced size-transformation. ROS triggers the size transformation of Polymer-Peptide Conjugates (PPCs), which interact with mitochondria and demonstrate high efficacy in tumor treatment⁷³. PPCs consist of (1) a ROS-cleavable sulfone-linked polyethylene glycol (PEG)

coupled to a β -sheet forming peptide KLVFF, (2) a cytotoxic peptide KLAK specifically targeting mitochondria, and (3) a PEG main chain. PPCs nanoparticles can enter cells and target mitochondria. Given the excess ROS production around mitochondria in cancer cells, the sulfone linker can be cleaved, leading to the shape transition of nanoparticles to nanofibers (Fig. 3B). The exposed nanofibers at the KLAK positions heightened interactions with mitochondria involving multiple binding sites and cooperative effects, resulting in targeted cytotoxicity against cancer cells and effective tumor suppression *in vivo*.

2.1.4. Light-induced

The photo-induced approach offers advantages such as non-invasiveness, remote operation, and simplicity⁷⁴. Recently, photothermal response strategies have garnered considerable attention owing to their precision, non-invasiveness, environmental friendliness, remote control, and convenience⁷⁵. Commonly, photosensitive therapy materials incorporate photo-responsive groups like nitrobenzene, diazo, or diazenyl groups, and acrylic groups⁷⁶. Regarding light-induced polymerization strategies, photosensitive polymers integrate photoreactive groups such as azobenzene, spirogyran, triphenylmethane, or cinnamyl. These groups exhibited reversible structural changes upon exposure to UV–Vis light^{77–80}. Cheng et al.⁸¹ reported light unstable gold nanoparticles (AuNPs) modified with dinitroimidazole (DA) at the end of the ligand PEG₅₀₀₀ (MW = 5000), can covalently crosslink under 405 nm laser irradiation. As illustrated in Fig. 4A, upon 405 nm laser excitation, the surface dinitroimidazole on particles first converted to a carbene that subsequently formed covalent bonds through C/H, C/C, O/H, and X/H (X = heteroatom) on the ligands of adjacent AuNPs, yielding aggregation of AuNPs. The robust coupling among the aggregated AuNPs *in vivo* caused an effective shift of the surface plasmon resonance peak of 20.5 nm AuNPs toward the near-infrared region. This enabled the use of small AuNPs for not only improved photoacoustic imaging but also efficient photothermal therapy of malignant tumors.

As shown in Fig. 4B, Liu et al.⁸² developed a nano-drug, IP@NPs@M, coated with a thin film, which boasted

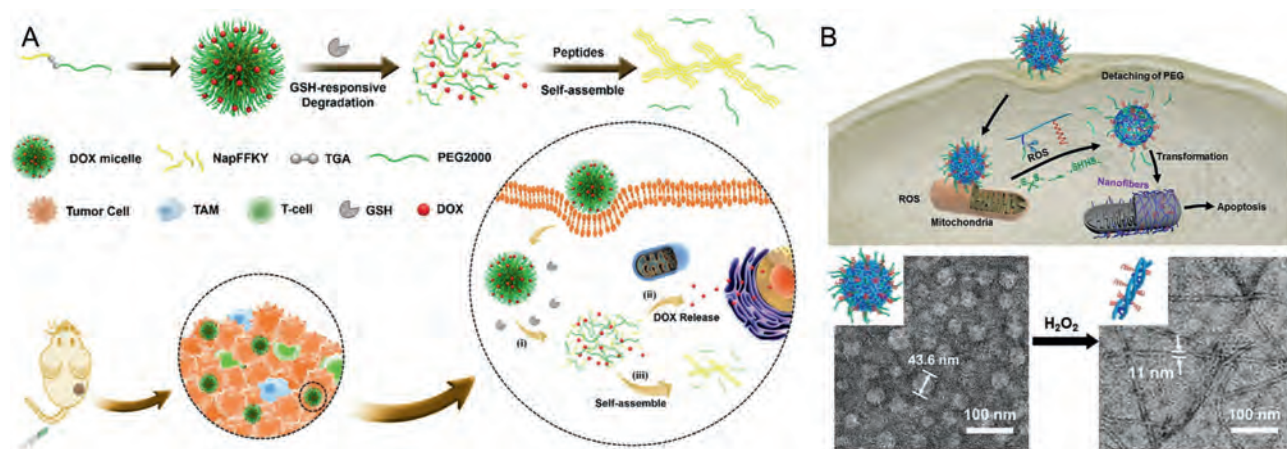


Figure 3 (A) Schematic representation illustrating the intracellular restructuring of a GSH-responsive drug delivery system on transitioning from micelles into nanofibers. Reprinted with the permission from Ref. 67. Copyright © 2020 American Chemical Society. (B) Schematic of ROS-induced size-transformation with shape transition from nanospheres to nanofiber. Reprinted with the permission from Ref. 73. Copyright © 2019 American Chemical Society.

morphological transformation and light-responsive properties. Under laser irradiation, the photosensitizer can produce ROS, leading to a change in the hydrophilicity of bilirubin. This change caused the nanoparticles to transition from a spherical to a fibrous shape, significantly improving drug retention at the tumor site. Due to the morphological and size transformation, the combination therapy of PDT, chemotherapy, and immunotherapy elicited

remarkable efficacy by markedly suppressing tumor growth and reducing metastasis. Ma et al.⁸³ reported a novel nano-drug, DEVD-DLPA@C3 NPs for caspase-3 responsive tumor treatment. This nanosystem was composed of a dual amphiphilic peptide (DEVD-DLPA) with a diacetylene moiety and a mitochondria-targeting photosensitizer (C3) (Fig. 4C). DEVD-DLPA@C3 NPs increased drug delivery efficiency by actively

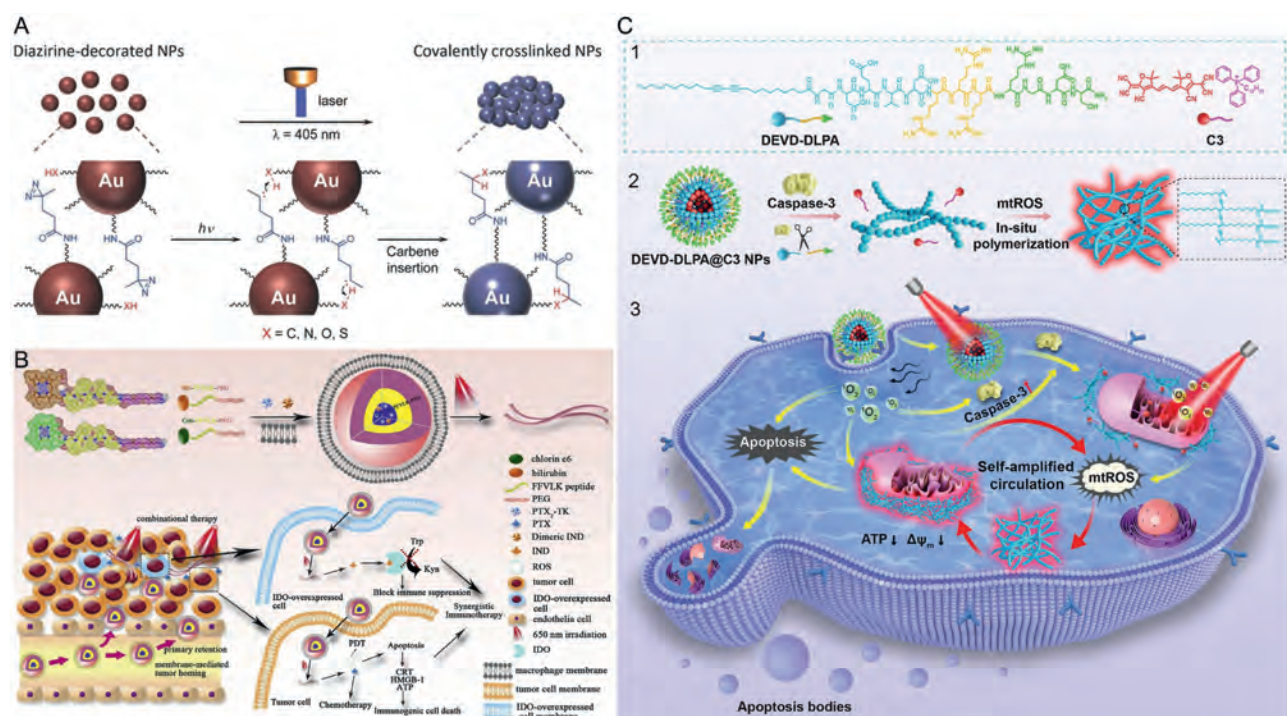


Figure 4 (A) Illustration depicting the light-triggered assembly of dendritic gold nanoparticles (dAuNPs). Reprinted with the permission from Ref. 81. Copyright © 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) Schematic illustration depicting the change of IP@NPs@M nanoparticles from spherical micelles to nanofibers under 650 nm laser irradiation. Reprinted with the permission from Ref. 82. Copyright © 2020 Elsevier. (C) 1. The compositions of DEVD-DLPA and C3. 2. Illustration depicting the morphological transition from nanoparticles to nanofibers. 3. Schematic illustration portraying photodynamic therapy (PDT) triggered *in situ* intracellular polymerization, resulting in mitochondrial ROS burst and self-amplified circulation of tumor therapy. Reprinted with the permission from Ref. 83. Copyright © 2022 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

targeting tumor cells through an affinity interaction with the RGDS peptide and integrins. Under laser irradiation, the generated ROS initiated the apoptotic process, demonstrative by overexpression of caspase-3 and the release of photosensitizer. Upon a second laser irradiation, free photosensitizer on mitochondrial generated singlet oxygen, disrupting the mitochondria and causing a mitochondria ROS (mtROS) burst. Significantly, the ROS produced *via* photodynamic action and the mtROS burst cleaved DEVD-DLPA by caspase-3, leading to the transformation of spherical NPs into elongated nanofibers through efficient *in-situ* polymerization. This transformation resulted in a more severe mtROS burst, thereby maximizing the effectiveness of the nanomaterial.

2.2. Aggregation strategy

In addition, some research groups have designed smart nanoparticles that aggregate in response to both external and internal stimuli, including pH, light, and enzymes. When subjected to these stimuli, initially small nanoparticles aggregated through interactions such as click reactions, electrostatic interactions, or phase transitions, resulting in the formation of larger nanoparticles.

2.2.1. Biological orthogonal crosslinking

Due to the simplicity and speed, click reactions are often employed in enzyme-induced size transformations. Typically, functional groups capable of undergoing click reactions, such as azides and alkynes⁸⁴, thiols and maleimides⁸⁵, and 1,2-dithiolanes and cyanides^{86,87}, are decorated on the surface of nanoparticles. Upon exposure and interaction of these chemical groups following

enzyme cleavage reactions, rapid aggregation occurs, yielding the formation of larger nanoparticles. As shown in Fig. 5A, Ruan et al.⁸⁸ proposed a strategy for enhancing the retention of chemo drugs for brain tumors using an asparagine endopeptidase-triggered gold nanoparticle aggregation platform. This platform consists of gold nanoparticles modified with Ala-Ala-Asn-Cys-Lys (AuNPs-AK) and gold nanoparticles modified with 2-cyanobenzothiazole (AuNPs-CABT). AuNPs-AK is hydrolyzed by asparagine endopeptidase in glioma cells, exposing the 1,2-dithiolane on the nanoparticle surface. Subsequently, it engaged in a click cycloaddition reaction with neighboring cyanide groups on AuNPs-CABT, leading to the aggregation of AuNPs. This approach improved the retention of gold nanoparticles, attributed to hindering nanoparticle efflux into the bloodstream. Efficiency in treating gliomas is enhanced when doxorubicin (DOX) is attached to AuNPs-A&C through a pH-sensitive linker. Compared to the saline group, DOX-conjugated AuNPs-A&C increased the average survival time by 288% in mice, as assessed with multi-spectral optoacoustic tomography for effective *in vivo* imaging. This study offered a strategy to enhance nanoparticle accumulation in tumors and improve therapeutic outcomes for tumors.

3. Electrostatic interactions

Surface charge is commonly employed for nanoparticle stabilization, and nanoparticles with a positive charge can form cross-links with those carrying a negative charge^{89–91}. Nam et al.⁹² produced amine-functionalized AuNPs with a positive charge and modified them with a pH-sensitive citramide group to invert the surface charge of the AuNPs. The citramide moiety remains

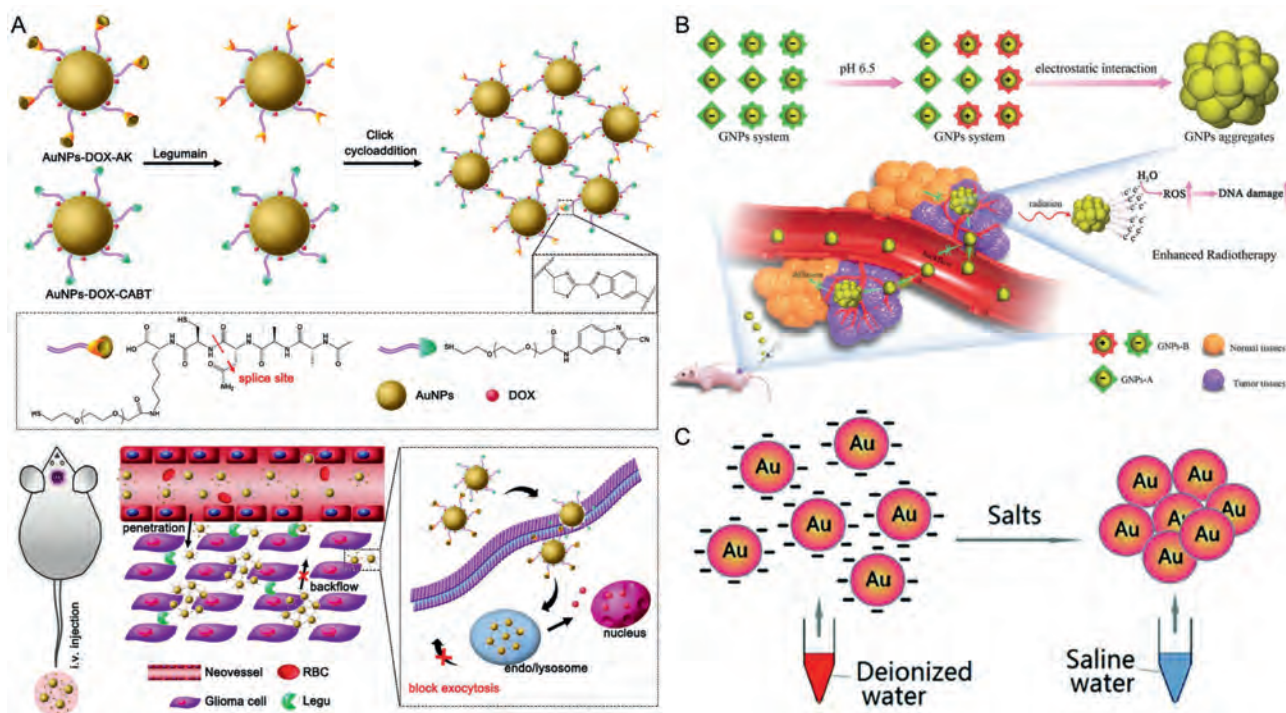


Figure 5 (A) Schematic illustration represents the legumain-induced aggregation and composition of AuNPs-DOX-A&C. Reprinted with the permission from Ref. 88. Copyright © 2016 American Chemical Society. (B) Diagram illustrating the behavior of the AuNPs system *in vivo* after intravenous injection, showcasing enhanced tumor retention and increased radiotherapy (RT). Reprinted with the permission from Ref. 83. Copyright © 2019 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (C) Schematic of the salt-induced aggregation of AuNPs that bear a negative charge with citrate. Reprinted with the permission from Ref. 95. Copyright © 2016 The Royal Society of Chemistry.

stable under neutral or alkaline conditions but undergoes hydrolysis to citric acid at pH values below 7.0. Consequently, when the terminal functional group transitioned from a carboxylic acid anion to a protonated amine, the surface molecules acquired a positive charge. Subsequently, the negatively charged, unhydrolyzed AuNPs can crosslink with the positively charged AuNPs. In addition, a strategy based on the acid-triggered small AuNPs was proposed by Zhang et al.⁹³ for the aggregation of AuNPs within tumors. The resultant AuNPs aggregates served as radiation sensitizers in both *in vivo* and *in vitro* applications (Fig. 5B). The AuNPs improved the accumulation and retention of AuNPs in cells and tumor sites, resulting in a notable enhancement in the radiation sensitization effect for tumor radiotherapy. This was substantiated by studies using DNA breakage and comet assays, where the sensitivity enhancement ratio (SER) for the AuNPs system was much higher (1.730) compared to the single AuNPs system (1.16) in MCF-7 cancer cells. *In vivo*, anti-tumor investigations also demonstrated that the AuNPs system bolstered the sensitivity of MCF-7 tumor transplants to radiotherapy. Additionally, the aggregation of AuNPs enhanced the signal of photoacoustic imaging *in vivo* of small AuNPs. This research provided novel strategies and insights for developing nanoparticle aggregates to boost the efficiency of radiation sensitivity in nanosystems for cancer radiotherapy.

4. Screening electrostatic effect-induced aggregation

Electrostatic repulsion plays a crucial role in the colloidal stability of nanoparticles, inhibiting their aggregation⁹⁴. Sun et al.⁹⁵ developed a method for inducing the aggregation of AuNPs through salt in biological environments, creating an effective and biocompatible near-infrared photothermal transducer for cancer photothermal therapy (PTT) and PA/PT imaging (Fig. 5C). The *in situ* formation of AuNPs depot through salt-induced aggregation exhibited strong near-infrared absorption due to plasmon coupling between adjacent AuNPs, achieving a remarkably high photothermal conversion efficiency of 52%, enabling the photothermal elimination of cancer cells. Interestingly, the *in situ* aggregated AuNPs depot in the tumor can simultaneously perform tumor PA/PT imaging and PTT. These findings offered a straightforward and effective approach to developing a smart, biocompatible, and efficient near-infrared photothermal sensor for PT/PA imaging and PTT.

5. Strategies from large to small

As discussed earlier, the relationship between nanoparticle size and intratumoral behavior is impacted by elevated interstitial fluid pressure and the dense matrix commonly found in solid tumors^{24,25}. These factors hinder thorough penetration and uniform distribution of nanoparticles within the tumor^{96,97}. Hence, reducing nanoparticle size is essential to enhance penetration. Furthermore, the size of nuclear pores (reported to be ~10 nm, expanded to as much as 39 nm)⁹⁸ restricts the size of nanoparticles that can target the nucleus. Shrunken nanoparticles not only maintain a compact size for improved penetration but also influence various other characteristics, including drug release, secondary distribution, and rapid renal clearance^{99–101}. Thus far, a diverse array of nanoparticles has been explored using two strategies: reassembly and degradation. These strategies are enabled by endogenous pH, elevated enzyme levels¹⁰², redox reactions, and exogenous physical-chemical stimulation.

5.1. Reassembly strategy

5.1.1. pH-induced

Block copolymers (BCPs) serve as a highly versatile platform for designing smart nanosystems¹⁰³, and their applications in cancer therapy have made significant progress^{104,105}. There is ongoing interest in investigating the morphology and responsiveness of BCP-based nanosystems to fully utilize their therapeutic potential. As shown in Fig. 6A, Cao et al.¹⁰⁶ constructed a biodegradable block copolymer assembly with pH-responsive behavior, which changed in size to form smaller, highly penetrable cationic nanocarriers under low pH conditions. This was achieved by modifying imidazole domains in flexible poly(carbonate) to a pK_a of ~6.5, enabling pH-induced changes in BCP amphiphilicity and charge reversal under tumor microenvironment pH conditions. The dynamic alterations in size and adjustable surface charge of this biodegradable nanocarrier offered optimal physicochemical characteristics for accomplishing targeted drug delivery and facilitating deep penetration at tumor sites.

2,3-Dimethylmaleic anhydride (DMA) undergoes a reaction with different amines to produce acidic amines. These acidic amines then undergo further reactions and decomposition into an amine and DMA under weak acidic conditions¹⁰⁷. As shown in Fig. 6B, Li et al.¹⁰⁸ developed a PCL-CDM-PAMAM/Pt formulation that switched size from 100 to 5 nm in the acidic pH environment within tumors. This structural change greatly promoted tumor penetration and cellular uptake of the therapeutic drug. The internalized prodrugs further released cisplatin to kill cancer cells intracellularly. The *in vivo* antitumor efficacy of this nanodrug system was confirmed in low-permeability pancreatic cancer, metastatic tumors, and drug-resistant tumors, highlighting its adaptability and wide applicability in cancer therapy. DMA, in addition to its direct decomposition to decrease size, displays an additional feature of charge reversal for the creation of smaller nanoparticles (as shown in Fig. 6C)¹⁰⁹. Sun et al.¹⁰² constructed a core-satellite nanostructure system, denoted as MSN-Fe-CAuNC (MFA), comprising mesoporous silica nanoparticles (MSN) and cysteamine-functionalized gold nanoclusters (CAuNC). Iron ions (Fe^{2+}) were employed as bridging ions coordinated with amino groups. The ionic ligands are sensitive to acidic pH, allowing the core-satellite structure to dissociate in the tumor microenvironment, leading to volume reduction. Achieving substantial size reduction and altering the charge are crucial for facilitating penetration and uptake by cells within tumors. Although pH-triggered methods exhibit sensitivity and specificity due to the prevailing acidic conditions and presence of proton, acidic and hypoxic areas are frequently located distantly from blood vessels. This poses a notable challenge for pH-induced size reduction strategies¹¹⁰. Ma and colleagues¹¹¹ have developed a multi-functional dual-component peptide nanomedicine capable of size-shifting in response to the changing forces of intermolecular interactions within the acidic conditions of the tumor microenvironment. They utilized two peptides, C12-K(Dye)EEEGRGDS (PA1) with a negative charge and CKKK-SS-DOX (PA2) with a positive charge, which self-assembled through electrostatic interactions and hydrophobic forces (Fig. 6D). These self-assembled dual-component nanoparticles (PP NPs) possessed an appropriate size and near-neutral charge, prolonging circulation time and stability *in vivo*. Upon reaching the tumor tissue, PA1 and PA2 responded to the tumor microenvironment pH and laser irradiation, leading to their reassembly into smaller nanoparticles. *In vitro* and *in vivo* investigations using near-infrared fluorescence

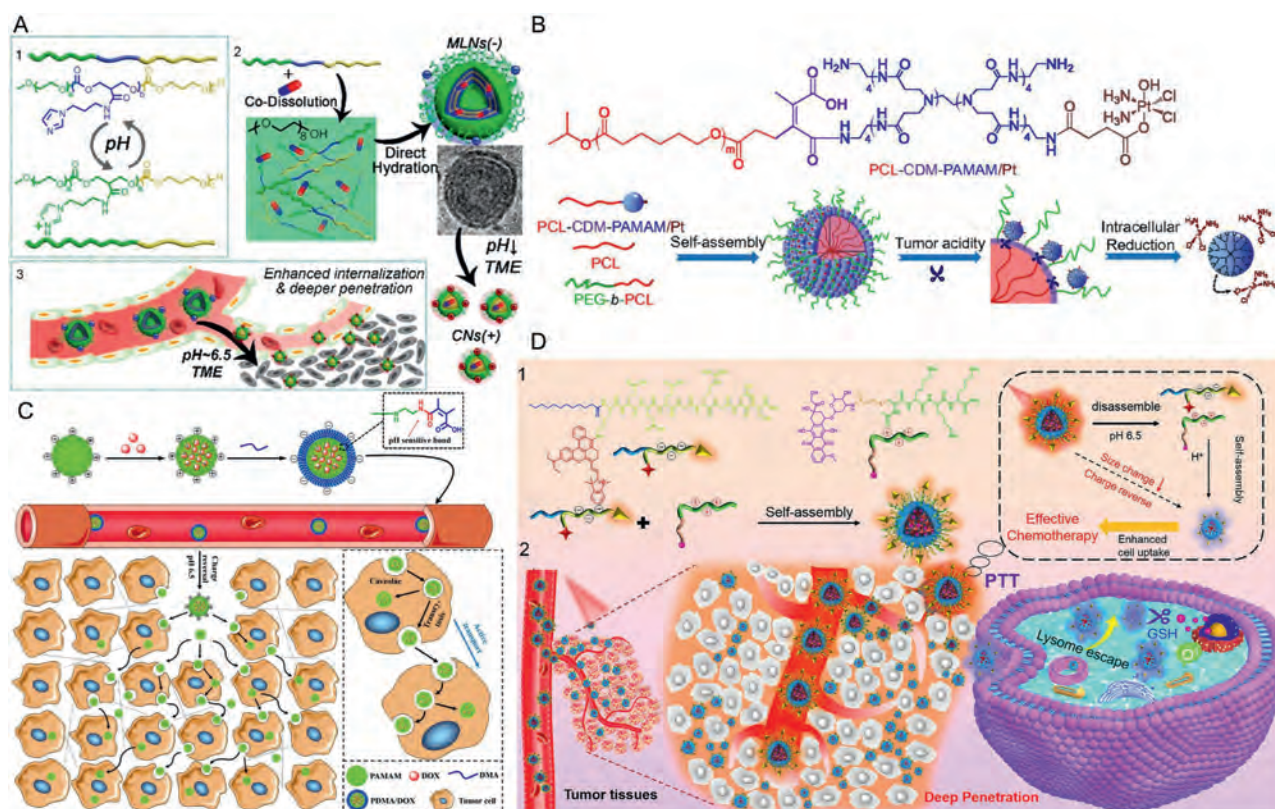


Figure 6 (A) 1. The chemical structure of PEG-TMCI-TMC terpolymers and the protonation of imidazole moieties induced chemical transformation at low pH. 2. Drug-loaded multilamellar nanovectors (MLNs) are generated through direct hydration and undergo structural reconfiguration at low pH, resulting in their transformation into cationic nanovectors (CNs). 3. The anticipated mode of action of MLNs *in vivo* involves the localized pH reduction in the tumor microenvironment, thereby enhancing the internalization of CNs and improving tumor penetration. Reprinted with the permission from Ref. 106. Copyright © 2018 American Chemical Society. (B) The chemical structure of PCL-CDM-PAMAM/Pt and the process of self-assembly and structural changes of iCluster/Pt in tumor responses. Reprinted with the permission from Ref. 108. Copyright © 2016 National Academy of Sciences. (C) Schematic representation of the structure of DMA-based nanomicelles and the illustration of pH-responsive size shrinkage. Reprinted with the permission from Ref. 109. Copyright © 2020 American Chemical Society. (D) 1. Diagram depicting the creation of multifunctional two-component nanoparticles (PP NPs) facilitated by electrostatic interactions between PA1 and PA2. 2. Illustration of the tumor-targeting and size-transformable characteristics of PP NPs for enhanced tumor penetration and efficient photochemical combined anticancer therapy. Reprinted with the permission from Ref. 111. Copyright © 2022 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim.

imaging showed that the transformed smaller nanoparticles were readily taken up by tumor cells and penetrated the tumor effectively. Crucially, the disassembled PP NPs demonstrated phototherapeutic effects comparable to those of intact PP NPs and exhibited superior chemotherapeutic efficacy in the deeper regions of tumors. PP NPs integrated fluorescence imaging, tumor targeting, tumor penetration, and phototherapy, leading to promising *in vivo* anti-tumor effects.

5.1.2. Redox-induced

Given the crucial role of GSH levels in both cytoplasm and tumor tissues, their influence is also evident in approaches that trigger size reduction^{112,113}. As shown in Fig. 7A, Guo and colleagues¹¹⁴ designed a nanomicelle structure using polyethylene glycol-co-poly(lactic acid) (PEG-PLA) and polyethyleneimine modified with 2,3-dimethylmaleic anhydride (PEI-DMA). These components were linked by disulfide bonds, resulting in the formation of PEG-PLA-S-S-PEI-DMA (PELESS-DA). Upon reacting with the high concentration of GSH inside cells, the PEI shell detached. Moreover, the significant decrease in size enabled the shrunken

nanoparticles to enter the cell nucleus, subsequently facilitating the release of the DOX. Nuclear delivery ensured the drugs efficacy against its target, preventing exclusion from the cells by drug efflux proteins, a critical aspect in nuclear-targeted chemotherapy drug delivery. Similarly, Wang et al.¹¹⁵ designed and synthesized PSPD/P123-Dex hybrid nanomicelles (Fig. 7B). Under conditions of high intracellular GSH concentration, the nanomicelles with a size of 120 nm significantly shrank to ~30 nm for P123-Dex. Owing to its ideal small size and the aid of dexamethasone, P123-Dex facilitated the transport of encapsulated DOX into the cell nucleus, leading to considerable cytotoxic effects.

6. Light-induced

The optical and photothermal properties of photosensitizers can be harnessed to design nanoscale drug carriers with size-transforming capabilities¹¹⁶. As shown in Fig. 7C, Chen et al.¹¹⁷ integrated the benefits of photo-responsiveness and shape transformation in the design of a nanodrug utilizing the BF2-azadipyromethene (aza-BODIPY) dye. Because of the favorable photothermal property of

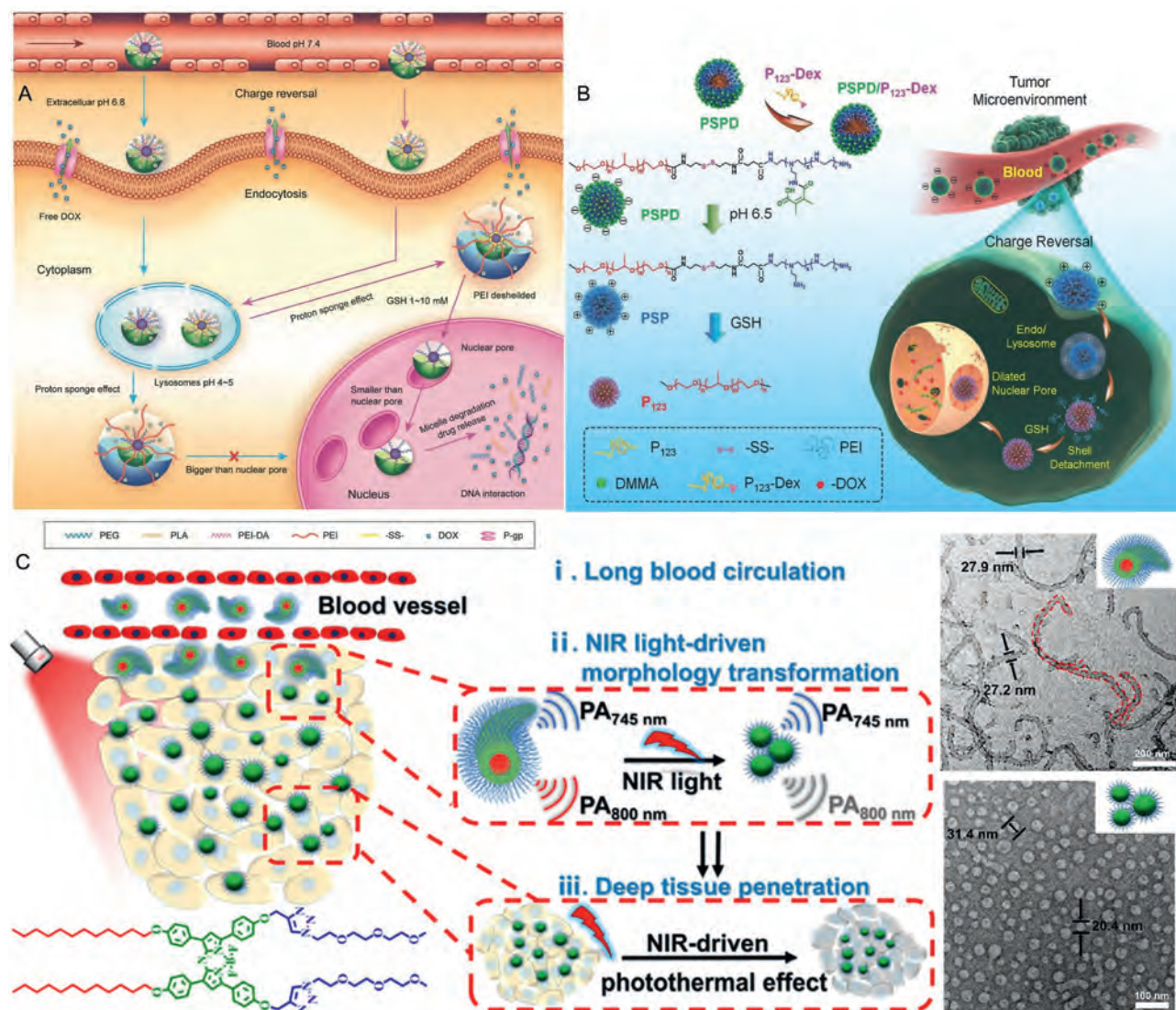


Figure 7 (A) Schematic illustration of the nuclear entry mechanism of size-shrinking polymer micelles (PELESS-DA) overcoming multidrug resistance (MDR). Reprinted with the permission from Ref. 114. Copyright © 2015 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (B) Schematic illustration of the hybrid micelle PSPD/P123-Dex-mediated synergistic size strategy for anticancer drug delivery. Reprinted with the permission from Ref. 115. Copyright © 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (C) 1. Schematic illustration of amphiphilic Aza-BODIPY-1 transforming from nanofibers to micelles under near-infrared light irradiation. 2. Long circulation of nanofibers in the blood-stream and deep penetration of spherical micelles into tumors. Reprinted with the permission from Ref. 117. Copyright © 2020 American Chemical Society.

aza-BODIPY nanoclusters, the thermodynamically stable fibrillar aggregates can undergo a transformation into a metastable spherical micelle. Elevating the temperature extended the circulation time of these aggregates by 7.6-fold. Moreover, under NIR stimulation, the nanofibers can effortlessly and rapidly convert into smaller nanoparticles without the need for additional groups, enabling deeper tumor penetration. The size-shrunk 1-NPs can infiltrate solid tumors effectively through photothermal effects, inhibiting tumor growth. Continuous monitoring of alterations in photoacoustic (PA) signals at distinct wavelengths using PA imaging identified the *in vivo* transformation from 1-NFs to 1-NPs in morphology. Hence, the NIR laser-induced, *in-situ* size transition from aza-BODIPY dye-1 into aza-BODIPY dye-1 with dual-state aggregation presented a robust treatment strategy for extended circulation and enhanced tumor penetration.

6.1. Degradation strategy

6.1.1. Chemical bond break

Wang et al.¹¹⁸ illustrated a dendrimer-drug conjugate that penetrated deeply into PDA tumors *via* a cellular uptake mechanism and phagocytosis induced by γ -glutamyltransferase (GGT) (Fig. 8A). Using a ROS-sensitive linker, they covalently attached camptothecin (CPT) to polyamidoamine (PAMAM) dendrimers, followed by surface modification with glutathione to synthesize dendrimer-drug conjugates. Once delivered to the periphery of PDA tumors, the overexpression of GGT on vascular endothelial cells or tumor cells triggered the γ -glutamyl transfer reaction of glutathione, producing the original amine. The positively charged conjugate underwent rapid internalization through endocytosis mediated by vesicles and subsequent transcytosis, facilitating its deep penetration into the

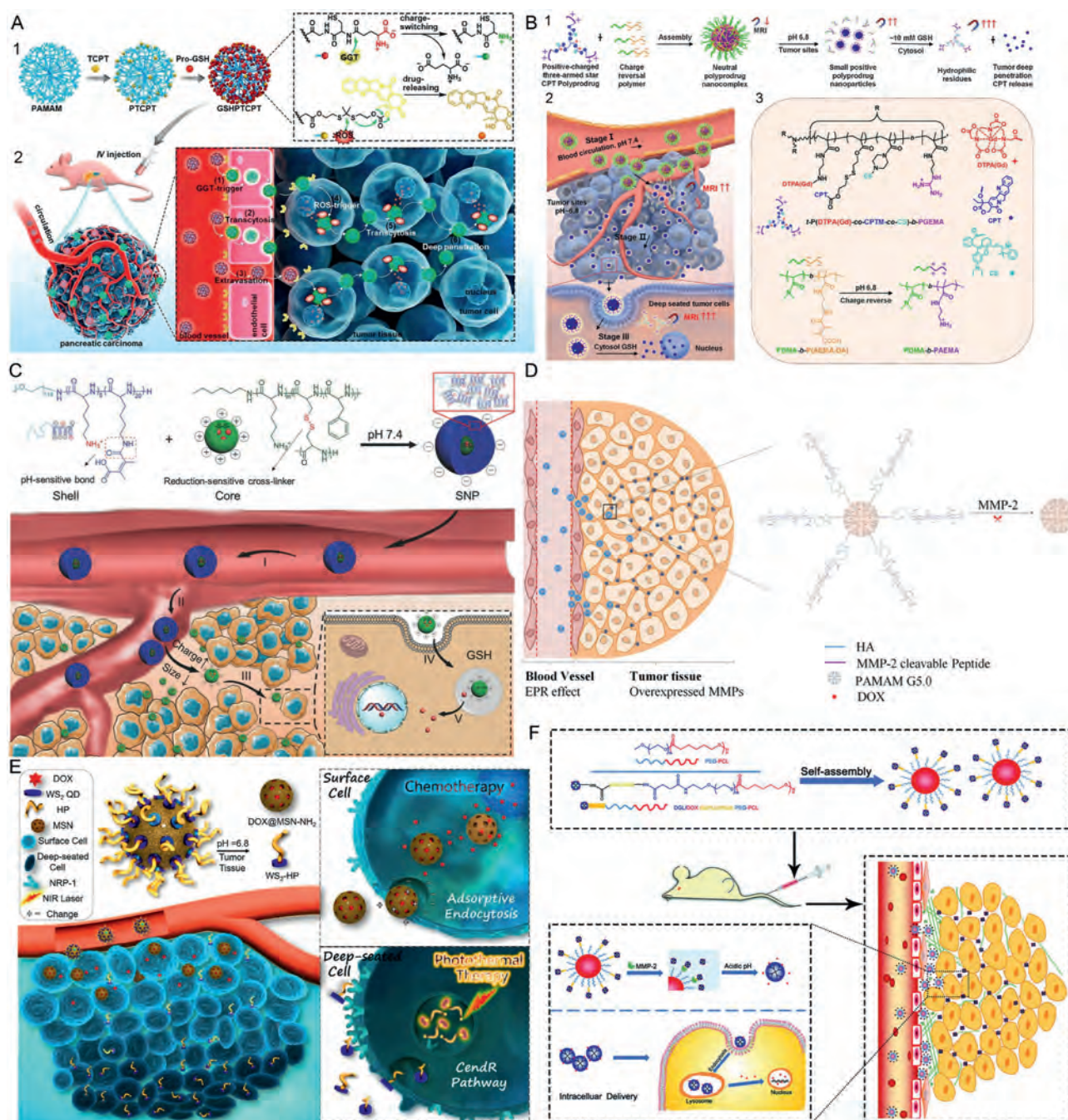


Figure 8 (A) Diagram illustrating the preparation of nanomedicines and the process of charge reversal catalyzed by GGT. 2. The positive charge is rapidly internalized *via* vesicle-mediated endocytosis, enhancing deep penetration into the tumor stroma. Reprinted with the permission from Ref. 118. Copyright © 2020 American Chemical Society. (B) Self-assembly and disassembly process of positively charged three-arm star-shaped multifunctional prodrug *t*-P(DTPA(Gd)-*co*-CPTM-*co*-CS)-*b*-PGEMA. 2. *In vivo* evaluation of SPNs for drug delivery with deep tumor penetration monitored through progressively enhanced magnetic resonance (MR) signals. 3. Structures of all polymers. Reprinted with the permission from Ref. 119. Copyright © 2020 American Chemical Society. (C) Shell-core nanoparticles (SNP) can achieve size reduction in reaction to the tumor's acidic pH. Reprinted with the permission from Ref. 120. Copyright © 2017 Wiley-VCH Verlag GmbH & Co. KGaA, Weinheim. (D) MMP-2 is highly expressed in the extracellular matrix of tumor cells, triggering the contraction of HA-pep-PAMAM from 200 to 10 nm, enabling its deep penetration into the tumor tissue. Reprinted with the permission from Ref. 121. Copyright © 2017 American Chemical Society. (E) Schematic illustration of the acid-labile nano-platform rapidly degrades into positively charged DOX@MSN-NH₂ and small-sized WS₂-HP, enhancing their tumor-penetrating abilities. Reprinted with the permission from Ref. 124. Copyright © 2017 American Chemical Society. (F) Accumulation and size reduction schematic of DGL/DOX@PP at the tumor site to surmount biological obstacles and penetrate deep into the tumor. Reprinted with the permission from Ref. 125. Copyright © 2018 The Royal Society of Chemistry.

tumor stroma. Following ROS cleavage inside cells, active CPT was released throughout the tumor. Compared to gemcitabine, the first-line chemotherapy drug used for the treatment of advanced pancreatic cancer, dendrimer–drug conjugates demonstrated superior anti-tumor activity in diverse mouse tumor models, including patient-derived pancreatic ductal adenocarcinoma (PDA) xenografts and *in situ* PDA tumor model.

Hao et al.¹¹⁹ developed a stimuli-responsive multi-prodrug nanoparticles (SPNs), which were assembled from negatively charged coronas and positively charged multi-prodrug cores connected by disulfide bonds within the core, displaying a high payload of camptothecin (CPT). As shown in Fig. 8B, upon accumulation in tumor sites, SPNs disassembled to release small sizes of positively charged SPNs. These nanoparticles effectively infiltrated tumor cells, facilitating the release of substantial amounts of the parent CPT drug in the reducing cytoplasmic environment. Meanwhile, the multi-prodrug cores of SPNs, labeled with the magnetic resonance imaging contrast agent DTPA (Gd), served as a means to monitor the cascading degradation and biodistribution of SPNs, with the subsequent intracellular release of CPT. Size-switchable SPNs demonstrated noticeable tumor penetration and significant tumor suppression, making them promising candidates for precision diagnosis and treatment using endogenous activation.

6.1.2. Onion peeling strategy

The strategy of stripping the nanoparticle's outer shell layer to form smaller nanoparticles is referred to as the "onion-peeling" strategy. Recently, Chen et al.¹²⁰ developed shell-stacked nanoparticles (SNPs), which exhibited a significant size reduction in acidic tumor tissues (from ~145 to 40 nm) with a surface charge reversal from -7.4 to 8.2 mV (Fig. 8C). This design aimed to boost the penetration and uptake of nanoparticles by cells in deep tumor tissue. The disulfide cross-linked core maintained particle stability, preventing undesired drug release until the outer shell was shed. This facilitated the cleavage of more exposed disulfide bonds, accelerating intracellular drug release. SNPs achieved a penetration depth of ~1 mm in A549 lung cancer xenografts, which was ~4-fold greater than in non-transformed lung cancer. SNPs loaded with DOX (SNP/DOX) exhibited a marked antitumor effect, nearly eliminating tumors, highlighting the significance of designing dual-transformable nanodrugs with changes in both size and charge. Han and colleagues¹²¹ proposed a collapsible drug delivery system utilizing tumor microenvironment-responsive polysaccharide-modified dendrimers. As displayed in Fig. 8D, hyaluronic acid (HA) was attached to the surface amino groups of polyamidoamine (PAMAM) using an MMP-2-cleavable peptide (PLGLAG) via a click reaction. The initial size of these nanoparticles is ~200 nm, but upon exposure to MMP-2, they underwent swift and substantial size alterations due to the cleavage of PLGLAG, which dissociated into their dendritic structural blocks (with a diameter of ~10 nm). The rapid shrinkage promoted extravasation and accumulation of nanoparticles within tumors, improving their permeability and retention, thereby facilitating rapid diffusion and penetration of the nanoparticles.

6.1.3. Surface-binding strategy

The surface-binding strategy involves attaching small nanoparticles to the surface of large nanoparticles, creating a nanocomplex with a raspberry-like structure^{122,123}. Within tumor tissues, the interconnected small nanoparticles can be quickly liberated as responsive ligands or molecules to the unique tumor microenvironment. Compared to the onion-like peeling strategy,

surface drug loading can impart new functionalities to small nanodrugs, enhancing drug release rate and drug loading. Nevertheless, this also increased the intricacy of construction and preparation. Lei et al. devised a stimulus-responsive "Cluster Bomb" comprising mesoporous silica nanoparticles (MSN) adorned with penetrating and tumor-homing peptide-modified quantum dots (QDs) (Fig. 8E). Under normal physiological conditions, the azo bond, which acted as a linker between MSN and QDs, remained stable; however, it became markedly unstable under pH 6.8. Subsequently, the small-sized quantum dots can enhance tumor penetration and be used for photothermal therapy in deep tumors¹²⁴. Cun et al.¹²⁵ constructed a size-switchable nano-platform based on an onion peeling strategy. This size-switchable nano-platform (DGL/DOX@PP) was produced by coupling small dendritic poly-L-lysine (DGL) with poly (ethylene glycol)-poly(ϵ -caprolactone) micelles using MMP-2-sensitive peptides (Fig. 8F). Initially, DGL/DOX@PP exhibited a nearly neutral charge and a size of 100 nm, enabling it to leverage the EPR effects. Following extravasation from tumor vasculature, DGL/DOX small nanoparticles responded to MMP-2 in the tumor microenvironment, rapidly releasing drugs from DGL/DOX@PP. The alteration in particle size significantly improved nanoparticle penetration into multicellular spheroids (MCSs) and tumors. Their results proved that size-switchable nano-platform outperformed small particles and non-switchable nanoparticles in suppressing tumor proliferation in 4T1 tumor-bearing mice. This adaptable nano-platform can offer a multifaceted strategy for modulating the tumor microenvironment and enhancing tumor penetration.

7. Reversible size-transformation

Research on reversible size-transformation aims to combine the benefits of both large nanoparticles and small nanoparticles for more efficient drug delivery, garnering increasing attention. Tumor microenvironment (TME)-responsive nanosystems represent a class of advanced nanomaterials designed for precise anticancer drug delivery¹²⁶. Jia et al.¹²⁷ present an innovative size- and morphology-switchable nanodrug that responds to both the acidic TME and near-infrared (NIR) laser irradiation, with the goal of effective tumor destruction and inhibition of metastasis. The nanoagent comprises melittin (MEL), a cytolytic peptide; cypate, an NIR-absorbing molecule; and hyaluronic acid (HA), a tumor-targeting polymer. At a neutral pH of 7.4, the MEL/Cypate@HA complexes form negatively charged nanospheres (~50 nm), ideal for prolonged systemic circulation. Upon reaching the tumor site, the acidic TME induces the transformation of these nanospheres into net-like nanofibers, which inhibit tumor cell movement and enhance the retention of the nanodrug for MEL-based chemotherapy. Additionally, NIR laser irradiation during cypate-mediated photothermal therapy degrades the nanofibers back into smaller nanospheres (~25 nm), enabling deeper tumor penetration of MEL and leading to effective tumor eradication. Hypoxia, a common characteristic of most solid tumors, leads to significant resistance to chemotherapy and immunotherapy¹²⁸. Wang et al.¹²⁹ introduce a tumor-acidity and bioorthogonal chemistry-mediated nanosystem designed to overcome hypoxic resistance and enhance chemio-immunotherapy. The system uses poly(2-azepane ethyl methacrylate), which responds rapidly to tumor acidity, and efficient bioorthogonal click chemistry to form large aggregates in tumor tissue, enhancing accumulation and retention. Another acidity-responsive group, maleic acid amide, responds more slowly, causing the aggregates to gradually dissociate into ultrasmall

nanoparticles. These nanoparticles penetrate the tumor more effectively, delivering doxorubicin (DOX) and nitric oxide (NO) to hypoxic tumor tissue, offering a novel strategy for enhanced tumor accumulation and penetration.

8. Major challenges of size transformable nanodrugs

While significant progress has been made in advancing size-transformable nanoparticles, numerous challenges remain, requiring further optimization and innovative solutions. First, there is the issue of off-target effects for internally triggered size-transformable nanosystem. The same stimuli that trigger size transformation could be present in other tissues, leading to undesired transformations and off-target adverse effects^{29,130}. Therefore, developing nanosystems capable of accurately and specifically converting in target region are of considerable impact. Second, the protein corona could shield all the responsive components of nanodrugs. Once nanomedicines entered blood circulation, they will be quickly coated by the protein corona¹³¹, masking responsive ligands (*e.g.*, enzymes and pH-responsive ligands) that are crucial for size-transformed nanodrug. Third, light can serve as a predominant external stimulus to regulate transformations. However, due to the limited tissue penetration capability of nanoparticles (NPs) within deep tissues¹³², effectively regulating their size can be challenging. Therefore, there is an urgent need to explore innovative convertible nanosystems using alternative external stimuli with stronger tumor-penetrating capabilities, such as ultrasound, X-rays, and magnetic fields, to further fortify transformation within deep tissue. Fourth, the reactive time of the size-transformable nanoparticles in the tumor microenvironment is crucial. Due to the elevated interstitial pressure in tumor sites, nanoparticles entering the tumor region are susceptible to being expelled back into the blood vessels, yielding poor retention time¹³³. Sensitivity and response time are critical factors in developing size-adjustable nanoparticles. As mentioned above, pH-triggered responses offer rapid and highly sensitive reactions, whereas the enzymatic reaction time with substrates may not be as swift. Enzyme-induced aggregation often occurs over a timeframe of 12–24 h, during which a considerable portion of the initial nanoparticles might be eliminated before aggregation initiates. Fifth, the intelligent design of size-transformable nanoparticles has the potential to remodel the tumor microenvironment¹³⁴, including the formation of extracellular matrix (ECM) structures like nanofibers. While such remodeling holds promise for enhancing drug delivery and efficacy, it also presents risks. Disruption and remodeling of the ECM can facilitate tumor migration and metastasis. Additionally, premature vascular normalization, resulting from this remodeling process, poses challenges for nanoparticles relying on passive tumor targeting through the enhanced permeability and retention (EPR) effect¹³⁵. Achieving an optimal balance in both the degree and timing of microenvironment remodeling is therefore crucial to maximize the therapeutic benefits of size-transformable nanoparticles while mitigating unintended consequences.

9. Outlooks and future directions

Integrating the benefits of both large and small nano delivery systems has emerged as a promising strategy in cancer therapy. A plethora of approaches have been developed to create size-switchable nanocarriers responsive to diverse internal factors

such as pH, enzymes, ROS, GSH, salts, lactate, and hypoxic environments as well as external stimuli like light and light-induced ROS/thermotherapy. These size-switchable nanotherapeutics, capable of adjusting their size under specific conditions, offer a range of advantages. They can enhance therapeutic efficacy by facilitating deep tumor penetration, prolonging retention times in targeted sites, controlling drug release, increasing intracellular uptake, reducing extracellular efflux, and even modifying or enhancing inherent physicochemical properties. Therefore, advancing innovation and creating more efficient nanocarriers are crucial for the future of nano-formulation development. Recently, smart transformable nanomedicines, capable of altering their physicochemical properties in response to internal and external stimuli, have emerged, offering the potential to overcome various barriers and enhance treatment efficacy. Additionally, there is increasing awareness that the substantial disparity between pre-clinical animal tumor models and clinical cancer patients profoundly affects the clinical translation of nano-formulations. Lastly, ensuring the scalability of production and the reproducibility of nanomedicines is essential for their clinical application. Here are the key points and challenges for future focus:

- (1) Clinical translation discrepancy: Addressing the significant gap between findings in preclinical animal models and the realities of clinical cancer patients to enhance the clinical translation of nano-formulations.
- (2) Scalability and reproducibility: Ensuring the ability to scale up production and maintain the reproducibility of nanomedicines for clinical application.
- (3) Integration of dual strategies: Many existing size-transformable nanoparticles primarily focus on either size reduction or enlargement. Future designs should aim to integrate both strategies to optimize tumor penetration and prolong retention time at tumor sites.
- (4) Simplicity in nanoparticle structure: Complex material structures may introduce additional variables, potentially obscuring the relationship between material properties and efficacy and limiting clinical application prospects. Therefore, future research and development should prioritize size-transformable materials with simple structures and excellent biocompatibility.

In conclusion, the size of nanoparticles plays a crucial role in enabling deep penetration and targeted delivery in cancer therapy. Therefore, careful consideration of the physicochemical properties and composition of nanoparticles is essential in the design of nanomedicines to achieve optimal antitumor effects. Moving forward, there is anticipation for the development of nanomedicines with straightforward structures, intelligent size-transformable capabilities, and high targeting efficiency, all of which hold promise for improving cancer therapy outcomes.

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Author contributions

Teng Ma: Conceptualization, Investigation, Writing — original draft, Writing — review & editing, Methodology, Visualization. Tuyen Ba Tran: Writing — review & editing. Ethan Lin: Writing — review & editing. Stephanie Hunt: Writing — review & editing. Riley Haveman: Writing — review & editing. Kylie Castro: Writing — review & editing. Jianqin Lu: Conceptualization, Funding acquisition, Project administration, Resources, Supervision, Writing — review & editing.

Conflicts of interest

The authors declare no conflict of interest.

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