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Review article

Stimuli-responsive peptide assemblies: Design, self-assembly, modulation, and biomedical applications

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ABSTRACT

Peptide molecules have design flexibility, self-assembly ability, high biocompatibility, good biodegradability, and easy functionalization, which promote their applications as versatile biomaterials for tissue engineering and biomedicine. In addition, the functionalization of self-assembled peptide nanomaterials with other additive components enhances their stimuli-responsive functions, promoting function-specific applications that induced by both internal and external stimulations. In this review, we demonstrate recent advance in the peptide molecular design, self-assembly, functional tailoring, and biomedical applications of peptide-based nanomaterials. The strategies on the design and synthesis of single, dual, and multiple stimuli-responsive peptide-based nanomaterials with various dimensions are analyzed, and the functional regulation of peptide nanomaterials with active components such as metal/metal oxide, DNA/RNA, polysaccharides, photosensitizers, 2D materials, and others are discussed. In addition, the designed peptide-based nanomaterials with temperature-, pH-, ion-, light-, enzyme-, and ROS-responsive abilities for drug delivery, bioimaging, cancer therapy, gene therapy, antibacterial, as well as wound healing and dressing applications are presented and discussed. This comprehensive review provides detailed methodologies and advanced techniques on the synthesis of peptide nanomaterials from molecular biology, materials science, and nanotechnology, which will guide and inspire the molecular level design of peptides with specific and multiple functions for function-specific applications.

1. Introduction

Taking the role as one of the basic substances of life activities, peptides are mainly involved in many physiological processes directly or indirectly. Connected by amide bonds between amino acids with different arrangements, peptides have rich designability and diverse structures. Based on the self-assembly property of peptides, it is possible to design and assemble peptide nanomaterials with different morphologies, and the modifiability of amino acid side chains also provides a broad application prospect for self-assembled peptide (SAP) nanomaterials [1–3]. Usually, the self-assembly behaviour of peptides could be triggered by internal or external environmental stimuli, so the engineering and exploitation of stimuli-responsive peptide nanomaterials (SRPNs) is an important part of advancing peptide nanomaterials for biomedical and tissue engineering applications [4,5].

The self-assembly of SRPNs often requires an external agent to stimulate specific sites in the peptide as a driving force. Temperature, pH, metal ions, solution type, and others can trigger the self-assembly behaviour of peptides. In addition, the modification of peptides also can achieve the response to specific substances [6–9]. Based on the designability, modifiability, and environmentally friendly synthesis methods of peptides, the design of SRPNs that can be used in different environments provides more options for the development of biomedicine. However, the fixation of peptide elements limits the development of their functional diversity to a certain extent, as a result of which, take full advantages of the richness of amino acid side chain groups and the

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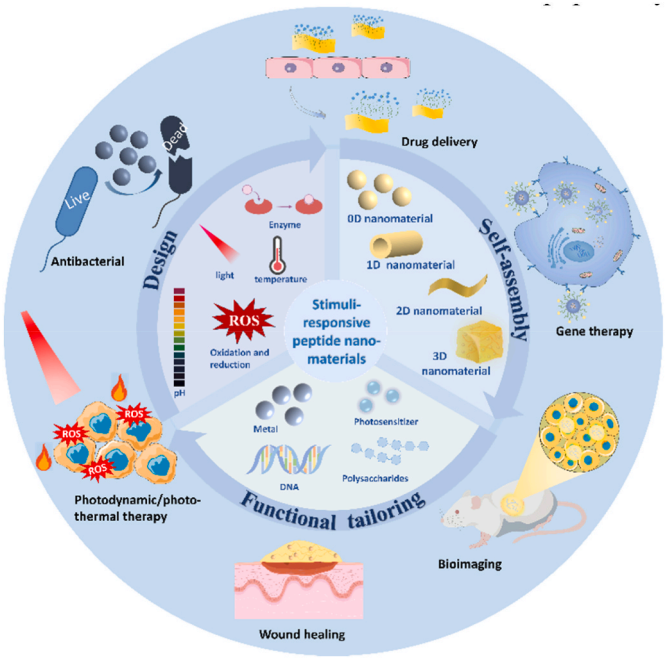
modifiability of peptides to functionalize peptides is particularly important [10–12]. It is possible to search for suitable materials for the peptide functionalization to synthesize SRPNs can undergo behavioural changes triggered by the conditions such as pH, temperature, enzymes, reactive oxygen species (ROS), and light [13–16]. The stimuli-responsive properties are important for biomedical applications such as drug delivery, tumor diagnostics, bioimaging, and biosensors [17–19].

Designing different SRPNs based on different biomedical needs have strong pertinence, enabling rapid and accurate locate and specific behavioural changes under the stimuli. For example, the microenvironment around malignant tumors is often acidic, with the increasing of specific proteins, enzymes, and other substances. Firstly, on the basis of this characteristic of the tumor microenvironment (TME), the design of SRPNs to achieve drug release, photothermal therapy (PTT) or imaging guidance under the stimulation of the TME has a broad application prospect [13,20,21]. Secondly, the production of excess ROS in the inflammatory microenvironment provides a clear target for the ROS-based SRPNs. In addition, the modification of SRPNs using DNA or RNA achieves genetic delivery *in vivo* and induces programmed apoptosis in diseased cells from the inside [22]. More importantly, SRPNs are able to achieve different dimensions of peptide nanomaterials under the influence of the target stimuli. The SRPNs with large dimensions tend to have a higher specific surface area and have a more difficult process in entering cells or tissues. Previous studies have indicated that temperature or pH stimulation enabled the transition between peptide nanofibers (PNFs) and peptide nanoparticles (PNPs) to be more adaptive to physiological environments [23]. The morphological change of the peptide nanomaterials in response to a stimulation is beneficial for promoting SRPNs to enter and aggregate at the targeted sites, thus enabling better functions and therapy efficiency.

Biomedical applications of peptide-based nanomaterials have been well described in past years, but there are few articles on the summary of the design of SRPNs. In this review, taking stimuli-responsive peptides (SRPs) as the starting point, the design of peptides to the self-assembly and functionalization of SRPNs to the construction of peptide systems are discussed in detail. In addition, the biomedical aspects of SRPNs for drug delivery, gene therapy, phototherapy, antimicrobials, wound healing, and wound dressing are summarized (Scheme 1). The work comprehensively covers the triggering factors of peptide self-assembly (PSA), the characteristics as well as the advantages and disadvantages of peptides in different dimensions, the functionalization of peptides by different materials, and the broad applications of SRPNs in biomedicine. This review is expected to provide more valuable ideas and guidance for promoting the applications of SRPNs in biomedicine and tissue engineering.



Scheme 1. Overview of the molecular design, self-assembly construction, functional modulation, and biomedical applications of SRPNs.

2. Design of stimuli-responsive peptides (SRPs)

It is easy to chemically modify peptides by adding specific functionalized components to form SRPs that are responsive to external and internal stimuli [24]. SRPs can be assembled into nanostructures of different sizes and shapes when subjected to single or multiple stimuli. When subjected to single or multiple stimuli, SRPs can self-assemble, disassemble, or change size and shape based on chemical bonding. From the preparation point of view, SSRPNs are characterized by simple preparation, and nanomaterials can be easily designed to respond to a single environment. However, the complexity of the human environment usually requires SRPNs to respond to multiple triggers. Dual or multi-stimulus response can combine endogenous and exogenous stimuli and show greater precision and controllability in targeted delivery. In addition, dual or multi-stimulus responses not only respond to a single stimulus targeted by the drug, but also show enhanced effects when multiple stimuli are triggered simultaneously. Thus, the effect of single stimuli-response as well as dual and multiple stimuli-response on peptide nanocomponents is discussed in this section.

2.1. Single stimuli-responsive peptide nanomaterials (SSRPNs)

SSRPNs can be prepared by cross-linking the peptide with a functional connector or by a simple coupling reaction or ring-opening polymerization (ROP) reaction. When affected by pH, GSH, and ROS, the designed SRPNs change accordingly. In this section, we demonstrate the molecular design and synthesis of different types of SSRPNs.

2.1.1. pH-responsive peptide systems

The acidity of pathological tissues such as inflammation or tumors is often lower than that of healthy tissues and blood [25]. The pH-sensitive nanomaterials can carry therapeutics that undergo solubilization or dissolution to achieve targeted delivery of drugs to the target tissues, when the pH of the environment changes. In addition, SRP-based hydrogels can be modified with special functionalization and are able to increase the biocompatibility of the hydrogels for specific purposes. For example, Qian and co-workers designed an SAP nanomaterial that loaded with drugs based on a peptide (SKDEEWHKNNFPLSP) and tetraphenyl vinyl for cancer therapy [26]. The designed peptide could specifically recognize vascular endothelial growth factor receptor 2 (VEGFR2) and self-assemble into α-helical reversible structure in an acidic environment. The peptide couplings self-assembled into PNPs in a neutral environment, and the PNP-to-PNF morphology transition occurred under the influence of low pH in the TME, turning on *in vivo* targeting to improve delivery and therapeutic efficacy (Fig. 1a). In another example, a pH-responsive peptide (C16-VVAEEE) was designed, which could self-assemble into SAP hydrogels in acidic cellular microenvironment [27]. The C16 alkyl chain relied on hydrophobicity to enhance the self-assembly ability, the tripeptide fragment VVA formed a *β*-sheet conformation through hydrogen bonding with the alkyl group, and the carboxyl groups in the side chain and C-terminus of the peptide sequence EEE acted as pH-responsive portions. Therefore, C16-VVAEEE could gather to pathological tissues with blood circulation and self-assembled into nanofibers that could winding to form hydrogels when stimulated by a slightly acidic environment.

In addition, L-Phe-L-Phe (FF) and its derivatives can self-assemble into different nanostructures under different conditions [28].

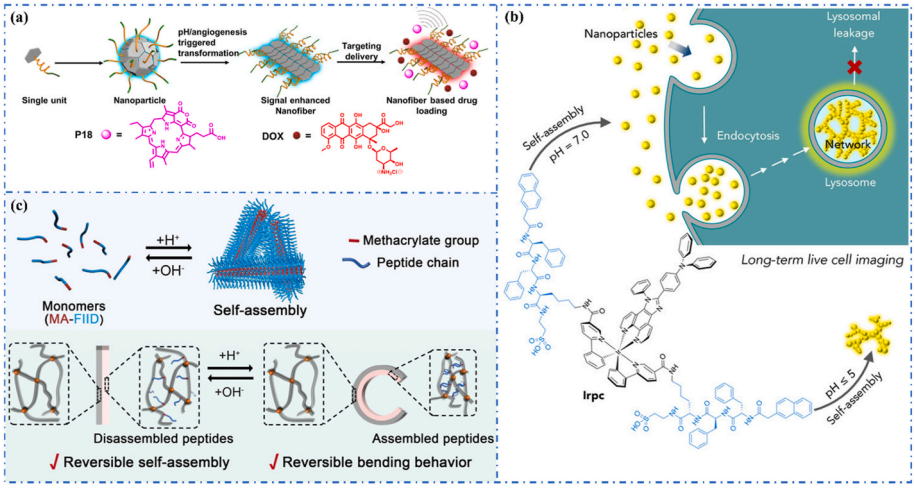


Fig. 1. Design of pH-responsive peptide nanomaterials: (a) Low pH affects PSA morphological transformations [26]. **(b)** Schematic representation of endocytosis transport in pH-responsive self-assembly of Irpc [29]. **(c)** Reversible PSA in response to pH [30]. Adapted with permission [26], Copyright 2018, American Chemical Society; adapted with permission [29], Copyright 2021, Wiley-VCH; adapted with permission [30], Copyright 2023, Wiley-VCH.

Considered the acidic environment of the lysosome, Jin et al. selected a biocyclic metallo-iridium (III) (Ir) with aggregation-induced emission (AIE) properties as the core to connect two carboxyl groups to form an Irc complex [29]. Naphthalene-phenylalanine-phenylalanine-lysine (NapFFK) is connected to the core Ir (III) to realize π-π interaction, promote PSA to form the complex Irpc, and achieve long-term fluorescence imaging in lysosomes. (Fig. 1b). The Irpc was dispersed large NPs at pH 7.0–8.0 and transformed into small particles at pH 6.0. In the lysosomal microenvironment (pH 4.0–5.0), the small molecular particles were connected into a network of NPs, which facilitated the realization of lysosomal endocytosis. Therefore, this peptide-based nanoprobe with good biocompatibility enabled long-term lysosomal imaging.

The formation and dissociation of pH-dependent PSA exhibit excellent reversibility, which provides a driving force for the volume of peptide-based hydrogels to undergo contraction and expansion. For example, Bao and co-workers reported the design of a pH-sensitive peptide (MA-FIID), which has both a hydrophobic end and a pH-sensitive aspartic acid [30]. The MA-FIID peptide was loaded into poly-N-isopropylacrylamide (PNIPAM) backbone, constructing both bilayer and non-homogeneous hydrogel through using the peptide dissociation and re-assembly under different conditions (Fig. 1c). The self-assembly and dis-assembly of the MA-FIID peptide in response to pH stimulation provided the impetus for reversible bending and stretching of these peptide-containing hydrogels, providing a novel approach for the production of smart hydrogel materials.

In another case, Pahovnik et al. developed a biodegradable pH-responsive peptide hydrogel [31]. The hydrogel was mainly based on L-glutamic acid (Glu), and three types of SAP hydrogels (P(Glu), P (Glu-co-Phe), and P(Glu-co-Lys)) were formed by cross-linking Glu with L-cystine or copolymerizing Glu with L-lysine or L-phenylalanine through the principle of equimolar ratio. It was found that changes in pH affected the buffer uptake of the hydrogels. Unlike P(Glu-co-Lys) hydrogels, which exhibited a high uptake of buffer at pH values less than 4 or greater than 9, the hydrogels with P(Glu) and P(Glu-co-Phe) became more absorbent with increasing pH.

2.1.2. *Enzyme-responsive peptide systems*

Enzymes are indispensable basic substances for maintaining normal life activities of organisms, and their catalytic reactions are characterized by high efficiency, mildness, specificity, and high sensitivity. Abnormal enzymatic overexpression is common in the pathologic tissue microenvironment of a variety of diseases, including matrix metalloproteinase (MMP) and hyaluronidase (HAase). Enzyme-responsive systems have received increasing attention due to their mild reaction conditions and low side effects [32], which are incorporated into polymers, proteins, or drugs to realize the applications in the fields of targeted drug delivery, disease diagnosis, controlled release, and enhanced cell permeation [33,34].

The promotion of bone healing through local delivery of growth factors (GFs) with osteoinductive activity is an easy and effective way, but this approach faces great challenges in treating some complex clinical fractures. Therefore, Qi et al. constructed a peptide nanocapsule delivery platform for delivering bone morphogenetic protein-2 (BMP-2) GFs (Fig. 2a) [35]. Uniformly sized BMP-2 nanocapsule (n(BMP-2)) shell was formed on the surface of BMP-2 by *in-situ* free radical polymerization using 2-(methacryloyloxy)ethylphosphorylcholine (MPC) as the monomer and bisacryloylated VPLGVRTK peptide as a cleavable cross-linker. After n(BMP-2) was injected into the body, it was passively targeted and accumulated to the fracture site through blood circulation. The shell of the n(BMP-2) nanocapsule would be degraded by MMP (mainly MMP-2 and MMP-9), releasing BMP-2 to accelerate fracture healing. The animal experiments demonstrated that this enzyme-responsive peptide-based n(BMP-2) revealed low irritation, excellent bone repair properties, and *in vivo* high stability.

In another study, Fores et al. demonstrated a catalytically growth supramolecular hydrogel (CASH) [36]. An amphiphilic diester heptapeptide HE^2 was designed with one heptapeptide H remaining after hydrolysis of the two ester groups (Fmoc-GFFYGHY). In addition, phosphate group was used to modify the tyrosine of heptapeptide H to obtain HP^2 (Fmoc-GFFpYGHpY), which released the heptapeptide H under the catalytic action of alkaline phosphatase (AP). Meanwhile, the heptapeptide H could self-assemble into nanofibers, which continue to grow and self-assemble into hydrogels over time (Fig. 2b). It is novel to synthesize hydrogel through biocatalytic initiation and location of enzymes, which is a significant step towards the development of localized self-assembly strategies that mimic the growth and reproduction behaviour of cells.

The integration of drugs with MMP-responsive peptides for enzyme-responsive drug release is also a potential way for disease therapy. Li and co-workers designed a simple and flexible strategy to prepare enzyme-responsive vectors (called WINNER) for precise delivery of extracellular functional protein drugs (Fig. 2c) [37]. The shell of WINNER was composed of phosphatidylcholine (PC) (50.5 %–58.3 % filling ratio) and MMP-2 enzyme-responsive peptide (VPLGVRTK) for protecting internal protein drug. The shell of WINNER protected it from being taken up by

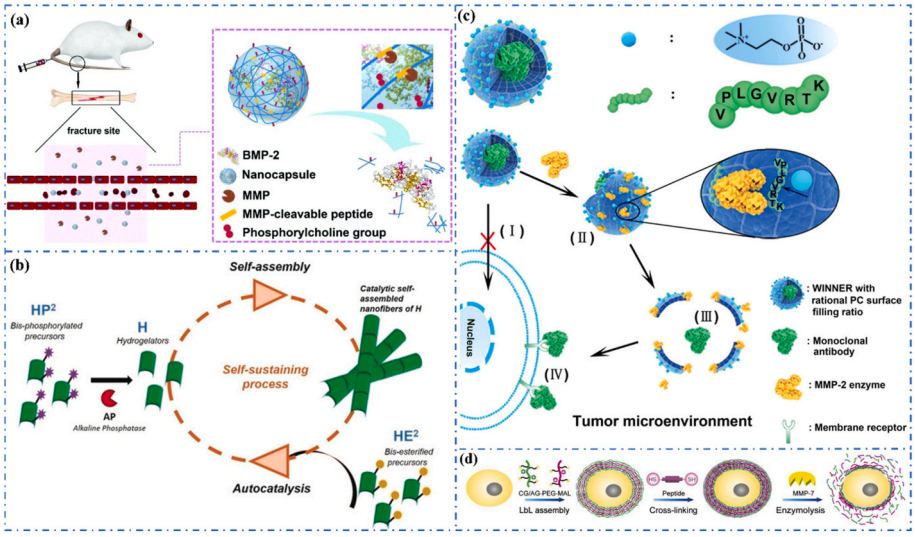


Fig. 2. Design of enzyme-responsive peptid nanomaterials: (a) Composition of enzyme-responsive peptide capsule n(BMP-2) and its use for bone repair [35]. **(b)** Peptide H autocatalyzed and self-assembled into hydrogels [36]. **(c)** MMP-responsive peptide vectors for enzyme-responsive drug release [3]. **(d)** Enzyme-responsive nanoshells for on-demand release [38]. Adapted with permission [35], Copyright 2019, Royal Society of Chemistry; adapted with permission [36], Copyright 2020, Wiley-VCH; adapted with permission [37]. Copyright 2019, Wiley-VCH; adapted with permission [38], Copyright 2019, Elsevier BV.

normal cells. Upon the accumulation at the tumor site, the overexpressed MMP-2 was specifically recognized by the enzyme site of the outer shell, which helped the vector to release the internal functional protein drug outside the cell and bind to the receptor on the surface of the tumor cell to achieve effective inhibition of tumor growth.

In addition, thin and stable membranes or semi-permeable hydrogels encapsulating the cells can reduce the immune and increase the cell activity. Nanoshell encapsulation is more efficient compared to other approaches. For example, enzyme-responsive peptide nanoshell has been synthesized to encapsulate HeLa cells and human bone marrow mesenchymal stem cells (hMSCs), inducing enhanced efficiency for cancer therapy [38]. The highly stable enzyme-responsive nanoshell was composed by the self-assembly of oppositely charged polyethylene glycol (PEG)-gelatin layer-by-layer (LBL) and cysteine-capped peptide linkers (sequence CGGPLGLAGGC) (Fig. 2d). When the enzyme-responsive nanoshell was transported to the tumor site, highly concentrated MMP-7 induced the cleaving of enzyme-responsive peptide, followed by dissociation of the PEG-gelatin shells, and promoted the releasing of HeLa cells and hMSCs.

2.1.3. ROS-responsive peptide systems

ROS is a class of oxygen-derived chemicals (e.g., hydroxyl radicals,

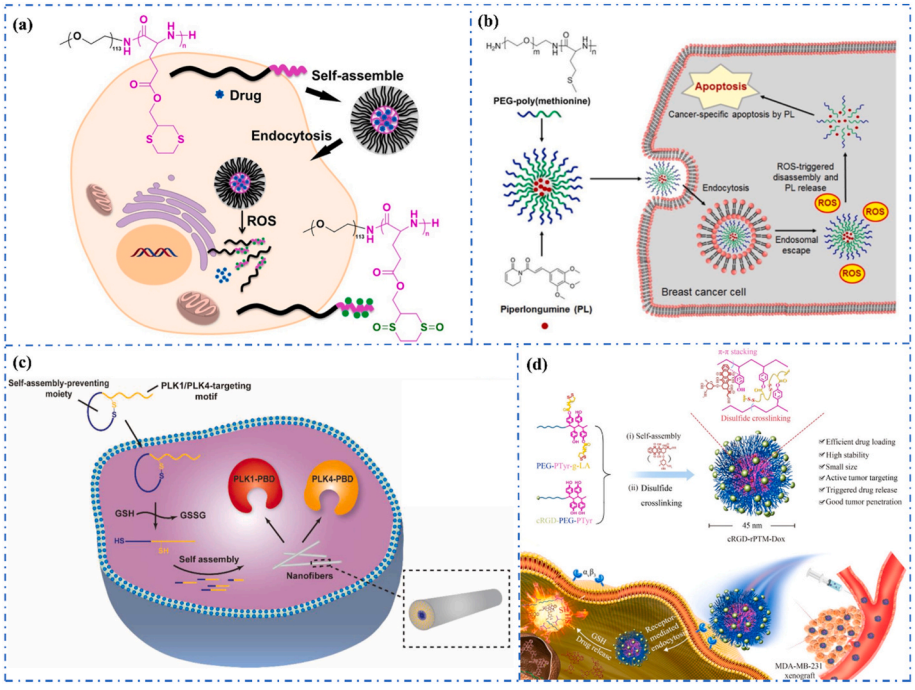


Fig. 3. Design of ROS-responsive peptide nanomaterials: (a) ROS-responsive drug release with mPEG-b-PDTG micelles [41]. **(b)** ROS-responsive PEG-P(Met) micelles [42]. **(c)** SAP nanofiber as nanomedicine for ROS-induced cancer cell death [43]. **(d)** ROS-responsive cRGD-rPTM for targeted delivery of adriamycin [44]. Adapted with permission [41], Copyright 2019, Elsevier BV; adapted with permission [42], Copyright 2020, Elsevier BV; adapted with permission [43], Copyright 2019, Wiley-VCH; adapted with permission [44], Copyright 2018, American Chemical Society.

hydrogen peroxide, superoxide, *etc.*) produced in the body, which have an irreplaceable role in pathological processes and physiological metabolism. When ROS is overproduced in cells or tissues, it usually leads to oxidative stress effects that disrupt cellular homeostasis, thus affecting a range of pathological conditions [39,40].

A number of ROS-responsive peptide systems have been designed and synthesized based on the elevated ROS levels in pathological tissue cells. For instance, Zhang et al. designed a novel peptide block copolymer (mPEG-*b*-PDTG) containing thioether for drug delivery [41]. The amphiphilic peptide-polymer conjugate could self-assemble into micelles in aqueous medium using amino-terminated PEG methyl ether ($MPEGNH_2$) as an initiator (Fig. 3a). The sulfide ethers on the side chains of mPEG-b-PDTG were oxidized to thioethers in the presence of hydrogen peroxide (H_2O_2), leading to the disintegration of the formed peptide-polymer micelles. Therefore, when the mPEG-b-PDTG micelles entered into pathological tissue cells, the oxidation of overproduced ROS triggered their disintegration, releasing the drug for treatment. In a similar study, Quan and co-workers prepared a ROS-responsive polymer for safe and effective delivery of antioxidant piperlongumine (PL) for the treatment of human breast cancer cells [42]. PEG was doped into poly (methionine) (P(Met)) and self-assembled with PL to form nanomicelles with a core-shell structure (PL-PEG-P(Met)) (Fig. 3b). The high expression of ROS in cancer cells caused the hydrophobic Met residues in the P (Met) peptide micelles to be oxidized to hydrophilic Met sulfoxide or sulfone, which further led to the cleavage of the micelles. The released PL could induce the apoptosis in cancer cells by causing the cells to overexpress ROS.

Comparatively, reducing secretions such as GSH provide another possible way for detecting and killing bacteria. In the TME, GSH is at least ten times higher than in healthy tissues. Notably, Yang et al. synthesized a cyclic peptide precursor that is capable of responding to reduced GSH for the synthesis of ROS-responsive supramolecular nanodrugs [43]. After the cyclic peptide precursor enters the cancer cells, the disulfide bonds are reduced by the high intracellular concentration of GSH, which leads to the PSA into nanofibers (Fig. 3c). This bioactive nanofiber could specifically bind to Polo-like kinases (PLK1 and PLK4), which led to the apoptosis of human cervical cancer cells. It was an effective anticancer nanomedicine for the treatment of cervical cancer.

In addition, Song et al. designed a ROS-responsive polytyrosine micelle (cRGD-rPTM) based on PEG-b-poly(L-tyrosine) lipoic acid (PEG-*b*-PTyr-LA) coupling, which exhibited a small size and robustness with adriamycin loading and highly efficient targeting delivery properties (Fig. 3d) [44]. When the peptide micelles reached the TME, cRGD could selectively bind specifically to the integrin αvβ3 and αvβ5 for targeted delivery. When it entered into the tumor cells and was affected by the high concentration of GSH, the disulfide bonds in the nanomicelles were reduced, releasing drug, which had a more prominent therapeutic effect on breast cancer.

2.1.4. *Temperature-responsive peptide systems*

In addition to a number of endogenous stimuli, exogenous stimuli can make different effects on PSA. Temperature has been widely studied as an influencing factor for peptides to undergo structural changes and self-assembly [45]. For example, The Barker group designed two elastin-like peptides (ELPs) (sequence (VPGXG)n, where X is any amino acid except proline) di-block (A80-I60, P40–I60) [46]. When the temperature was increased successively to reach the transition temperatures of I60, A80, and P40, I60 firstly underwent collapse to form a micellar shell. Then A80 peptide was detached from fibrinogen, and finally P40 shrank to form microscale clusters. This PSA system allowed triggering of *in-situ* release behaviour in response to the temperature stimulation.

Interestingly, Lim et al. designed a peptide platform for the development of temperature-responsive elastin peptide amphiphiles (ELPAs) [47]. As shown in Fig. 4a, the ELP sequences were inserted into the building blocks and the N-terminus was coupled with a linear RGD for self-assembly. Elevated temperatures higher than the transition temperature (Tt) resulted in rapid aggregation of the peptide conjugates. When the temperature was less than Tt, the peptide conjugates underwent a slow dissolution behaviour. In addition, α-helical peptides were also attached to the N-terminus to form ELPAs for the self-assembly, which underwent rapid dis-assembly when the temperature was elevated to greater than Tt. This peptide platform exhibited great potential for developing applications related to temperature response.

In another case, Basheer et al. designed di-block copolymerized peptides based on elastin-based protein peptides (EBPs) with low critical

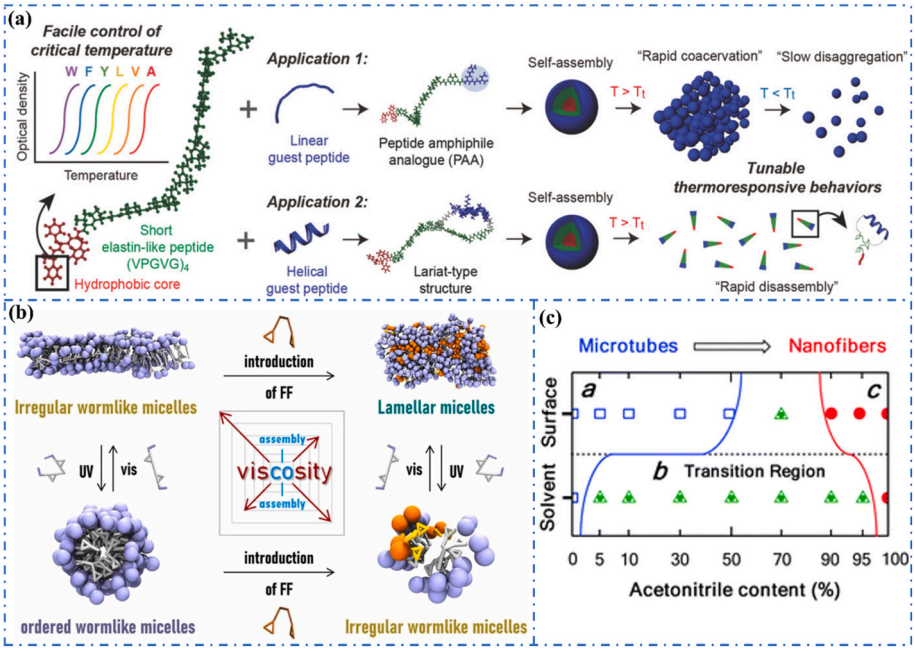


Fig. 4. (a) Thermo-responsive ELPAs with different structures [47]. **(b)** Reversible self-assembly morphology of photo-responsive peptides under UV and reversible light irradiation [54]. **(c)** Acetonitrile-induced SAP structure from microtubules to nanofibers [60]. Adapted with permission [47], Copyright 2018, Wiley-VCH; adapted with permission [54], Copyright 2023, Elsevier BV; adapted with permission [60], Copyright 2011, Royal Society of Chemistry.

temperature (LCST) and resilin-based protein peptides (RBPs) with high critical temperature (UCST) (LCST < UCST) [48]. The temperature was adjusted to study the changes of the PSA behaviour of the EBP-RBP di-block. It was found that when the temperature was lower than LCST and UCST, EBP remained hydrated, and RBP was aggregated, resulting in the self-assembly of the di-block copolymer peptide into micelles or vesicles. At the temperature higher than LCST and UCST, EBP and RBP showed opposite behavior and the nanostructure was reversed. This temperature-responsive copolymeric peptide can self-assemble into different nanostructures under the stimulation of temperature.

2.1.5. Photo-responsive peptide systems

Among many exogenous stimuli, photo-stimulation is non-invasive and highly spatio-temporally selective, therefore has become one of the hot topics in the last years [49,50]. Many photo-responsive molecules respond to light by forming or breaking bonds, which triggers a change in geometry [51]. For example, Pal et al. achieved self-assembly of peptides (NVFFAC) from 1D nanofibers to 2D nanosheets using UV irradiation [52]. Xie et al. created an antibacterial system using trigeminal β-cyclodextrin (tri-β-CD) and an electro-positive peptide containing an azobenzene side chain. Both of them underwent dynamic self-assembly to form microscale lamellar structures with high surface potentials [53]. Under UV irradiation, the interaction between azobenzene and tri-β-CD was weakened to form small, stable nanospheres. This system with controllable photo-responsive PSA provided a new idea for the preparation of antimicrobial materials.

In the work of Wang et al., biazophenylalanyl-alanine (FA) allowed the self-assembly of irregular nano-networks [54]. As shown in Fig. 4b, the irradiation with UV light converted the morphology of micelles from network state to regular wormlike micelles. After switching to visible light irradiation, the morphology was reversed. After adding diphenylalanine (FF) to FA, the morphology of micelles was transformed from irregular network state to lamellar state. The irradiation with UV and visible light also achieved a reversible shift in micelle morphology.

Xiang et al. designed a photo-responsive peptide (DDFFFKK) with high aggregation tendency [55]. The presence of dipeptide (KK) resulted in the inability of the PSA in water, and KK was removed under light irradiation, which triggered the PSA to further form SAP hydrogels. Meanwhile, they designed the photo-responsive peptide, Fmoc-KDFFFNBKK, which realized precise spatiotemporally controllable photo-responsive hydrogels. In addition, controlling the time of irradiation could regulate the mechanical strength of the formed hydrogels and expand their applications in biomedical fields.

2.1.6. Other stimuli-responsive peptide systems

Obviously, the aforementioned pH, enzyme, ROX, temperature, and light stimuli have impacts on the PSA. Besides these factors that can modulate the behavior of peptides, there are other factors that can trigger the changes in the PSA behavior, such as the ionic response, solvent response, and others.

Numerous peptides can self-assemble with metal ions into nanostructures of different morphologies through ligand-binding interactions. The introduction of metal ions into the peptide systems can stimulate conformational changes of peptides, leading to significant changes in the properties and performance of peptide nanomaterials [56,57]. The Ulijn group designed a co-assembly nanostructure of the tripeptides FFD and GHK, and proved that the PSA behavior can be affected by metal ions [58]. Due to the electrostatic interactions, the co-assembled FFD-GHK conjugates formed the nanoribbon structure in water. Upon the addition of Cu^{2+}, the peptide was stimulated to complex with Cu^{2+} and the SAP structure was changed from nanoribbons to nanofibers, which entwined to form a hydrogel. Additionally, to investigate the effect of different metal ions on the PSA, Cienfuegos and co-workers added Cs^{+} and Ca^{2+} to Fmoc-FF peptide solutions, respectively [59]. The peptides in the solution with added Cs^{+} self-assembled into uniformly sized nanorods and then nanorods aggregated into fibers. In both cases, finally peptide hydrogels could be obtained. However, the mechanical strength of the hydrogel formed by adding Cs^{+} was much weaker than the hydrogel formed in the presence of Ca^{2+}. This is ascribed to the fact that Cs^{+} tends to stabilize the water-solution interface, which attenuates hydrophobic interactions and facilitates the formation of metastable intermediates. In contrast, Ca^{2+} destabilizes the water-solution interface and increases hydrophobic interactions, leading to the PSA into larger fiber aggregates and the formation of hydrogels with higher mechanical strength.

Dipeptide FF can self-assemble into nanotubes or nanofibers. Huang et al. explored the self-assembly behavior of FF in different solvents [60]. They found that the structural transition of PSA from microtubes to nanofibers was more likely to occur in the aqueous phase with acetonitrile as the co-solvent (Fig. 4c). When the proportion of acetonitrile was increased to the point where the solvent was pure acetonitrile, the microtubule content gradually decreased to disappear, and uniformly sized nanofibers were obtained.

2.2. Dual and multi stimuli-responsive peptide systems

Clearly, SSRPNs offer significant advantages for controlled and specific applications. However, due to the complexity of the microenvironment at the target sites, the single stimuli-response may not accurately achieve desired results [61]. In consequence, many researchers have been working on the development of dual or multi stimuli-responsive peptide nanomaterials (DSRPNs or MSRPNs) to achieve more precise treatments.

Among all DSRPNs and MSRPNs, pH/ROS-responsive system is one of the keen of researchers. For instance, Yue et al. designed hybrid NPs based on hydrophilic PEG and a peptide copolymer (PEG-D-PC) of L-cysteine containing thiol side chains [62]. The hybrid NPs exhibited a PEG corona capable of shedding and a dynamic disulfide bond cross-linking core. It can be loaded with the anticancer drug camptothecin (CPT) for cancer therapy, as shown in Fig. 5a. The size of the formed NPs decreased dramatically and the zeta potential increased under the influence of TME. The disruption of disulfide bonds by highly concentrated GSH could precisely and effectively release and accumulate CPT to improve the anticancer efficiency. In another case, Zhao and co-workers designed a pH/ROS dual-responsive DOX-loaded carboxymethyl chitosan nanogel (CMCSN) that modified by angiopeptide-2 (ANG) for targeted treatment of glioblastoma (GBM) (Fig. 5b) [63]. ANG acted as a bifunctional peptide that specifically recognized low-density lipoprotein receptor-related protein 1 (LRP-1), which is highly expressed on the BBB and GBM. After the DOX-ANG-CMCSN was ingested by tumor cells, the nanogel was cleaved and DOX was released for anticancer treatment due to its sensitive response to pH and GSH.

Beyond pH/ROS-based DSRPNs, pH/enzyme-based DSRPNs are also important for biomedical applications. For instance, Shuai et al. prepared a dual-responsive nanocarrier loaded with anti-PD-1 antibody (aPD-1) and the chemotherapeutic drug paclitaxel (PTX) [64]. This dual-responsive nanocarrier with azide-PEGPAsp as the shell wrapped the PTX in the center of the micelle. As shown in Fig. 5c, MMP-2 overexpressed in tumor tissues recognizes and cleaves the MMP-2-sensitive peptide (Mal-GGPLGVRG-Pra-NH2, releasing aPD-1 into the tumor cells. In addition, low pH stimulated the NPs to release PTX. Therefore, the pH/enzyme-based DSRPNs realized the release of two drugs sequentially on demand, giving full play to the synergistic anticancer effect of both drugs.

In addition to the combination of the above endogenous stimuli, the combination of internal and external stimuli has also been widely studied, among which the peptide nanomaterials that responsive to the pH/temperature dual-stimuli have attracted more attention. Shi et al. prepared a series of polypeptide-containing amphiphiles (PPCAs) with good gelling ability using PEG and poly(L-glutamic acid) derivatives as temperature- and pH-sensitive fractions, respectively [65]. It was shown that the PPCAs exhibited a reversible sol-gelation transition when there

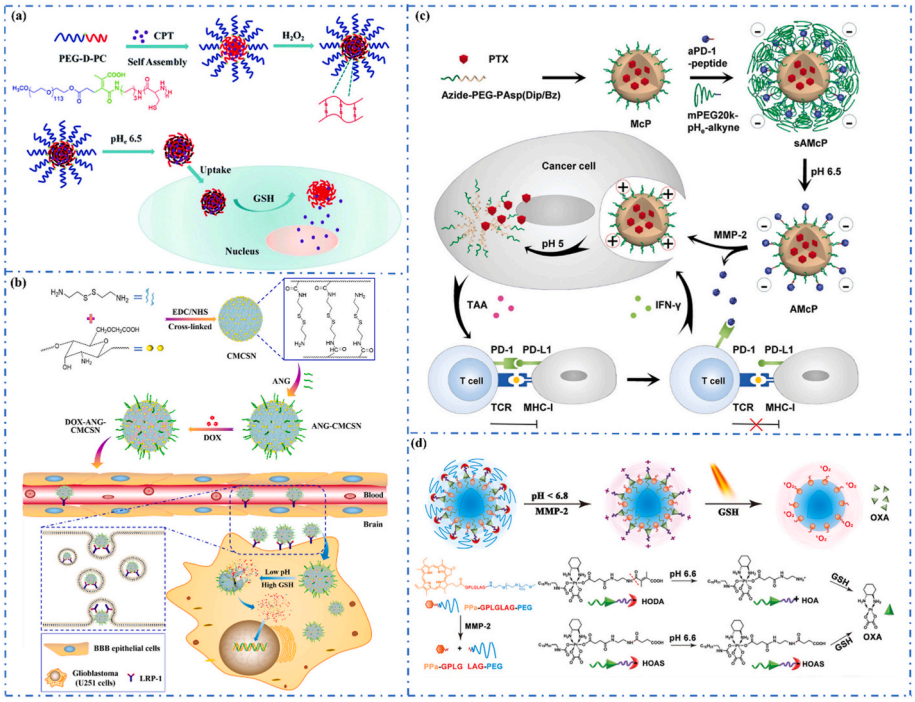


Fig. 5. Design of DSRPNs and MSRPNs: (a) pH/ROS dual-responsive PEG-D-PC for *in vivo* drug release [62]. **(b)** pH/ROS-responsive DOX-ANG-CMCSN nanogel for targeted drug delivery [63]. **(c)** pH/enzyme dual-responsive nanocarrier for tumor therapy [64]. (**d**) Light/pH/enzyme multi-responsive prodrug vesicle for tumor therapy [66]. Adapted with permission [62], Copyright 2018, Royal Society of Chemistry; adapted with permission [63], Copyright 2021, American Chemical Society; adapted with permission [64], Copyright 2020, Wiley-VCH; adapted with permission [66], Copyright 2019, Wiley-VCH.

was only a single variable of the pH. At pH 7.4, the sol-gel transition temperature of the hydrogels ranged from 10 to 70 °C. When the pH was between 6.5 and 7.4, it had a significant effect on the gelation temperature of PPCAs, which gelled at 37 °C. This study provided useful ideas for realizing physiologically relevant dual pH/temperature-responsive peptide hydrogels.

Table 1
Summary on the molecular design, structure, responsive properties and applications of SRPs.

Type	Peptide	Structure	Responsive	Application	Ref.
SSRPNs	SKDEEWHKNNFPLSP	NPs	pH	Specific recognition of VEGFR2.	[26]
	C16-VVAEEE	NFs	pH	Induction of apoptosis in HEK293 cells	[27]
	NapFFK	NPs	pH	Promotes endocytosis uptake	[29]
	MA-FIID	Hydrogel	pH	Provides power for reversible bending and telescoping	[30]
	P(Glu), P(Glu-co-Phe) and P(Glu-co-Lys)	Hydrogel	pH	Improves uptake of buffers	[31]
	Bisacryloylated VPLGVRTK	Nanocapsules	Enzyme	systemic delivery of growth factors	[35]
	Fmoc-GFFYGHY	NFs	Enzyme	Catalyzes self-sustained growth of hydrogels	[36]
	VPLGVRTK	NPs	Enzyme	Binds specifically to MMP-2	[37]
	CGGPLGLAGGC	Nanoshell	Enzyme	Binds specifically to MMP-7	[38]
	Boc-Glu-OtBu	Nanomicelles	ROS	Self-assembling into nanomicelles loaded with drugs to treat tumors	[41]
	P(Met)	Nanomicelles	ROS	Low-toxicity ROS-responsive drug carriers	[42]
	C-1	NFs	GSH	Inhibition of PLK1 and PLK4	[43]
	cRGD	Nanomicelles	GSH	selectively bind to αvβ3 and αvβ5 receptors on cancer cells	[44]
	$(VPGXG)_n$	Nanomicelles	Tmperature	Carriers of proteins or drugs for *in situ* release	[46]
	ELPAs, RGD, α-Helical peptide	NPs	Tmperature	Temperature-regulated changes in peptide self-assembly behavior	[47]
	EBP-RBP	Nanomembranes or vesicles	Tmperature	Changes to the nanostructure	[48]
	$^{N}VFFA^{C}$	NFs and NSs	Light	Changes to the nanostructure	[52]
	AMPs	NSs	Light	Photocontrols Cationic antimicrobial	[53]
	FA, FF	Nanomicelles	Light	Photocontrol of peptide self-assembly morphology, viscosity	[54]
	DDFFFKK, FmocKDFFFNBKK	Hydrogel	Light	Formation of hydrogels in response to light	[55]
	FFD-GHK	Nanoribbons and NFs	Metal ion	Prepares hydrogels	[58]
	Fmoc-FF	Nanospheres and NFs	Metal ion	Prepares hydrogels of different strengths	[59]
	FF	Microtubes and NFs	Solvent	Controls peptide self-assembly structure	[60]
DSRPNs	PEG-D-PC	NPs	pH/GSH	Releases drugs in a high GSH environment	[62]
	ANG-2	Nanomicelles	pH/GSH	Increases tumor targeting and BBS	[63]
	Mal-GGPLGVRG-Pra-NH_2	Nanomicelles	pH/Enzyme	Binds specifically to MMP-2	[64]
	Poly(l-glutamic acid)	Hydrogel	pH/Temperature	Changes in sol-gel transition temperature	[65]
MSRPNs	GPLGLAG	vesicles	Light/Ezyme/GSH	Binds specifically to MMP-2	[66]

Inspired by the advantages of the dual stimuli-response, researchers have further developed MSRPNs. Currently, chemoimmunotherapy can only be used in a small percentage of patients. To break through this limitation, Zhou et al. developed a prodrug vesicle that could be stimulated in the TME by integrating oxaliplatin (OXA) and PEG-modified photosensitizer (PS) [66]. As shown in Fig. 5d, the prodrug vesicles circulated with the blood to the tumor site, and MMP-2 targeted the recognition peptide to strip the PEG crown of the prodrug vesicles. Under the influence of the acidic microenvironment of the tumor, its surface charge was transformed from negative to positive to achieve the accumulation in the tumor cells. In the presence of laser irradiation and large amounts of GSH, the OXA release was precisely realized. These results suggest that MSRPNs are a type of more precise and promising materials.

The above sections introduce the molecular design, self-assembly, nanostructures, and stimuli-responsive properties of various peptides. To make it more clear, here a table (Table 1) is presented to summarize the key information that shown in these important cases.

3. Self-assembly of peptides into various stimuli-responsive superstructures

Peptides are composed of several amino acids connected through the amide bonds. By arranging and combining amino acids, peptides with different lengths and types are obtained. The SAP structure is usually formed by noncovalent interactions, including electrostatic interactions, hydrophobic interactions, van der Waals forces, as well as hydrogen bonds and π-π interactions due to aromatic amino acid residues [67–69].

Peptides are identifiable in a variety of sequences and structures and can self-assemble into nanostructures of different shapes by regulating intermolecular or intramolecular interactions. For example, 0D PNPs, peptide nanospheres and peptide quantum dots (PQD), 1D PNFs, peptide nanowires (PNWs), peptide nanotubes (PNTs) and peptide nanorods (PNRs), 2D peptide nanosheets (PNSs) and peptide nanoribbons, and 3D hydrogels and other structures. Peptide nanostructures with different morphologies play different roles in peptide-based hybrid nanomaterials. The 0D nanomaterials PNPs, nanospheres and PQDs with small size and small specific surface area can be easily taken up by cells and have greater advantages in information transfer and as drug carriers into cells and tissues [70]. Compared to 0D nanomaterials, 1D nanomaterials such as PNFs, PNWs, PNTs, and PNRs possess longer structures, providing abundant active sites for the attachment of other materials. In addition, 1D nanomaterials can connect two materials with no binding force to prepare hybridized nanomaterials. The huge surface area of 2D nanomaterials provides richer active sites for the attachment of other materials, and the excellent functionalization ability makes them have inestimable application prospects in various fields of biological and material science, such as biosensors, photothermal diagnosis and treatment, *etc.* [71,72]. 3D hydrogels can provide macroscopic visual observation. Also the rich pore structure makes it easier to load drugs or biomolecules for delivery into the body [73]. Nanostructures of different dimensions also have their corresponding defects.0D nanomaterials are small in size and cannot be easily combined with other materials. 1D nanomaterials are less malleable and deformable. 2D nanomaterials have poor edge active sites compared to 0D [74]. 3D hydrogels and scaffolds are larger, less accessible and more difficult to prepare. Therefore, the selection of nanostructures with appropriate dimensions is essential.

SRPNs modulate self-assembly behavior by altering peptide properties (e.g., changing peptide surface charge) or cleaving unstable or responsive bonds, further realizing biomedical applications that meet specific needs. A large number of switchable peptides are triggered by microenvironmental pH, which is usually the result of protonation and deprotonation of amino acids [75]. Reversible α-helix to β-sheet or β-sheet to α-helix transitions can be realized by processing pH-responsive peptides. Meanwhile, the effect of temperature on peptide self-assembly should not be underestimated. Increasing temperature weakens the hydrogen bonding effect and enhances the hydrophobic effect. This can cause peptide self-assembly to shift from a specific morphology to other morphologies. Elevated temperature usually disrupts the peptide secondary structure, thereby rendering it non-functional [76]. Metal ions interacting with the side chains of different amino acids can induce a shift in peptide conformation from the unfolded to the folded state [77]. Enzymes can act as one of the triggers for peptide alterations. Peptides are cleaved or degraded by enzymes in the microenvironment to promote the functioning of peptide nanomaterials. In addition, peptides are modified at strategic positions using luminescent moieties to form light-responsive peptides. Under light irradiation, the structure or function of the peptide is altered.

Peptides and polypeptides have strong self-assembling ability and can be controllably self-assembled into nanomaterials of different dimensions. Self-assembled nanostructures based on peptides and peptide conjugates have the advantages of good stability, precise selectivity, excellent biocompatibility, and low cytotoxicity, which have exhibited broad application prospects in drug delivery, bioimaging, clinical disease treatment, antibacterial materials, and tissue engineering [78,79].

3.1. 0D peptide nanomaterials

Peptides have excellent self-assembly capabilities and can easily form PNPs, PNSs, and PQDs, which are widely used as nanocarriers for drug delivery and cancer therapy [3,80,81]. The excellent properties of peptide nanomaterials have attracted increasing attention in collagen-mimicking nanomaterials. Xiao et al. demonstrated that when the triple-helix peptide $G(PRGPOG)_5$ with an aromatic group at the N terminus and the single-chain peptide EOG-10 were mixed at room temperature [82]. Due to π-π stacking and electrostatic interactions, the peptide self-assembled into uniformly sized PNSs. This peptide-triggered self-assembly of collagen-mimetic peptides with good biocompatibility revealed potential applications in the biological fields.

Artificial viruses are capable of producing high gene transcription levels in cancer cells. Cao and co-workers designed several peptides to mimic the shell of artificial viruses based on the Nap-FFGPLGLAG $(CK_m)_nC$ (Nap = naphthalene) peptide sequence by changing the values of m and n (Fig. 6a) [83]. Interestingly, the designed $(CK_5)_2C$ or $(CK_3)_3C$ peptides self-assembled into stable PNP structure smaller than 10 nm under the influence of hydrophobic interactions and π-π stacking. By further co-assembly with genetic components, artificial viruses were formed for gene delivery and transcription, which have been used to selectively deliver therapeutic nucleic acids to cancer cells for highly effective gene therapy.

Through the stimulations, 0D peptide nanomaterials with specific functions can be created. For instance, Sun et al. designed an acrylamide monomer with the KLAKLAKKLAKLAK peptide sequence (KLA peptide acrylamide). The spherical micelles composed of pro-apoptotic peptide-polymer amphiphilic molecules self-assembled into NPs under the induction of light-initiated polymerization [84]. The size of the NPs formed in this way could be adjusted by changing the length of the hydrophilic and hydrophobic building blocks. In another example, Li and co-workers prepared a metal nanomedicine for anti-tumor treatment by combining short peptides containing histidine, metal ions, and PS [85]. In the presence of Zn^{2+}, multiple noncovalent interactions of short peptides and PS co-assembled into metal nanomedicines to achieve rapid release of drugs in the TME.

3.2. 1D peptide nanomaterials

1D peptide nanomaterials have unique advantages such as high stability, elongated shape, excellent biocompatibility, and adjustable chemical and physical properties, and functions, which are beneficial to improving tissue adhesion and prolonging blood circulation. They are ideal building blocks for preparing functional composite materials for

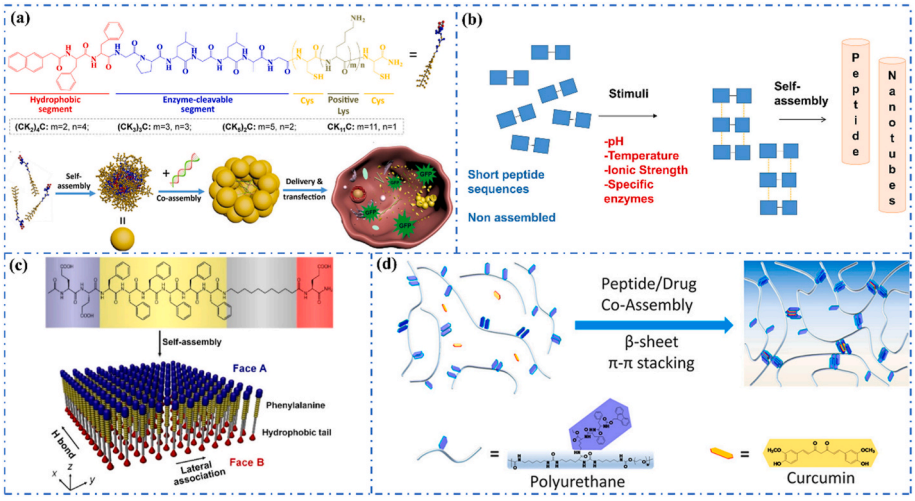


Fig. 6. Self-assembly of peptide into various superstructures: (a) Self-assembly of designed peptide molecular sequences into artificial viruses for genome release and transfection [83]. **(b)** Self-assembly of short peptides into PNTs in response to various stimuli [91]. **(c)** Self-assembly of F6C11 into Janus PNSs [97]. (**d**) Co-assembly formation of peptide/drug hydrogel for tumor therapy [103]. Adapted with permission [73], Copyright 2022, Elsevier BV; adapted with permission [91], Copyright 2018, Elsevier BV; adapted with permission [97], Copyright 2017, American Chemical Society; adapted with permission [103], Copyright 2019, American Chemical Society.

bioimaging, tumor therapy, gene delivery, wearable biosensors, and others [86,87]. 1D peptide superstructures mainly include PNFs, PNWs, PNTs, and PNRs.

In the work of Wei and colleagues, a half-sequence ion complementary peptide RATEA16 (CH_3CO-RATARAEARATARAEA-$CONH_2$) for PSA was developed [88]. The peptide RATEA16 has a stable β-sheet secondary structure and self-assembles into PNFs with a diameter of 70.3 nm and a length of 273 nm. When encountering blood, it quickly formed a 3D network gel structure to stop bleeding. The peptide RATEA16 with excellent biocompatibility can be developed as an ideal hemostatic agent during surgery.

Recently, Raganato et al. reported for the first time the L, D-octapeptide-dextran conjugated compound DEX_{29}-$(L_VD_V)_4$ block conjugate [89]. The strong hydrogen bonds and hydrophobic interactions of the $(L_VD_V)_4$ linear peptide promoted the self-assembly of the conjugated compounds to grow into 0.10–1 μm PNWs. The created PNWs with dextran properties assembled in this way revealed good hydrophilicity, biocompatibility, and non-toxicity, presenting high potential for biomedical application.

PNTs have excellent high aspect ratio and surface area that play an important role in mediating drug delivery and cell interactions. Meanwhile, tubular NPs have a larger contact area with target cells and can better adhere to cells [90]. Laverty et al. studied the self-assembly behaviour of FF motifs, in which the carboxyl-terminal FF motif (NH_2-FF-COOH) has the ability to self-assemble into PNTs in solution, ascribing to the hydrophobic, π-π stacking, and hydrogen bonding interactions between adjacent phenyl groups of the molecule [91]. In response to stimuli such as pH, temperature, ionic strength, and enzymes, the β-sheet secondary structure was formed and self-assembled into PNTs (Fig. 6b). PNTs formed by the self-assembly of FF exhibited sufficient antibacterial ability to eradicate bacteria in the form of biofilms that infect a variety of patients.

In addition, Zhang et al. used the homologous sequence KLVFFA of amyloid-β (Aβ) peptide in the brain and the mimic peptide COG1410 of the apo E receptor binding domain to construct a unique apolipoprotein E mimic peptide (MOP) to synthesize PNRs [92]. MOP has inherent self-assembly ability, and its self-assembly behavior was affected by the pH value and ionic strength of the solution. In acidic and neutral environments, MOPs were induced to self-assemble into spheres. When the pH was adjusted to 9, the NR structure with a size of 50 × 100 nm was observed. In Na_2SO_4 solutions with different concentrations, the aspect ratios of the generated NRs were different. Compared with spherical nanostructures, such rod-shaped nanostructures could penetrate the blood-brain barrier better, the designed PNRs enhanced the efficiency of MOP delivery to the brain, improved the abnormal metabolism of Aβ, and effectively solved key issues in the treatment of Alzheimer's disease (AD).

3.3. 2D peptide nanomaterials

2D peptide nanomaterials have a large specific surface area and abundant surface functional groups, so they are easier to combine with other nanomaterials for functional regulation [93,94]. In addition, 2D peptide nanomaterials have flexible and controllable surface functions, as well as excellent biodegradability and biocompatibility, and have been widely used in the fields such as biomedicine and environmental science [95].

PNSs and peptide nanoribbons are typical 2D peptide superstructures that bridge the gap between low dimensions and 3D materials. Peptides rich in tyrosine and phenylalanine tend to form 2D PNSs and peptide nanoribbons [96]. For instance, Stevens et al. dmonstrated the synthesis of single-layer Janus PNSs with a thickness of approximately 5 nm by manipulating the PA (F6C11) containing hexaphenylalanine, hydrophobic tail, and glutamic acid in two dimensions (Fig. 6c) [97]. The hydrogen bonds provided by the hexa-phenylalanine fragment in the F6C11 induced the peptide to form β-sheets in the x-axis direction, while the aromatic interactions caused the β-sheets to stack in the y-axis. In addition, the alkyl tail enhanced the hydrophobic effect on the x-axis and y-axis, and finally assembled PNSs with highly ordered structures. In another study, Albert et al. designed a phenylalanine-rich peptide (EEFFFFFFFFFF) to combine with DNA to form a diblock conjugate (DP) [98]. The PSA was induced by adding DP to 1,1,1,3,3,3-hexafluoroisopropanol (HFIP) and then injecting the solution into phosphate buffer solution (PBS). Experimental results indicated that the DP self-assembly produced PNSs with an average thickness of 5.1 ± 1 nm. The glutamic acid residues in DP reduced the hydrophobic interaction, and the abundant hydrogen bonds and π-π stacking provided by the large amount of phenylalanine formed 2D nanosheets. This approach was further utilized to design DNA1-peptide-DNA2 triblock conjugates by presenting two different DNA sequences on opposite surfaces, which self-assembled into Janus hybrid nanosheets successfully.

In addition, Castelletto et al. prepared an aromatic peptide CapNFF

by capping the N-terminus to the FF dipeptide through acetic anhydride reaction [99]. The PSA was performed in a mixed solution of water and acetonitrile, and a free-floating nanosheet lamellar structure was observed, which was the result of intermolecular interaction forces driven by π-π stacking.

3.4. 3D peptide nanomaterials

Self-assembled peptide 3D nanomaterials are mainly hydrogels and aerogels. Under certain conditions, peptides self-assemble to form ultra-long nanofibers, which then engage in wrapping to construct 3D hydrogels. Hydrogel, as a unique carrier, effectively improves the release of biologics and provides mechanical support, with great advantages in promoting tissue regeneration, drug delivery, and wound healing [100,101].

Sun et al. prepared a class of diphenylalanine-based biphenyl tripeptide compounds with different C-terminal amino acids [102]. The designed peptides, such as BPAA-FFG, BPAA-FFA, BPAA-GFF, and BPAA-AFF, all could form nanofibers and nanoribbons with different lengths under certain conditions for high-density winding and overlapping to form hydrogels. This is a result of the influence of hydrogen bonding, π-π stacking, and spatial site resistance.

Drug-carrying hydrogels have promising biomedical applications. Zhang et al. hybridized PEG-modified Fmoc-FF peptide with polyurethane, in which the Fmoc-FF peptide self-assembled to form β-sheet nanostructure [103]. The added curcumin assembled with the Fmoc-FF peptide by π-π stacking to form a hybrid hydrogel (Fig. 6d). The hydrogels prepared bythe peptide-polymer exhibited strong self-healing properties and had good prospects for the applications in tissue engineering and biomedicine.

Han et al. developed a functional peptide hydrogel for encapsulating exosomes and ensuring stable and sustained release of exosomes [104]. The self-assembled PA, GTAGLIGQ, was linked to cardioprotective peptide (GHRPS) via GG peptide to generate the PA-GHRPS. Simultaneous modification of PA-GHRPS using Nap-FF increased the solubilization of the PA-GHRPS in water and allowed its self-assembly to form hydrogels. The hydrogel carriers could improve cardiac function after myocardial infarction by reducing the inflammation, avoiding myocardial fibrosis, and prolonging the retention time of exosomes in the body compared with exosome treatment alone.

4. Functional tailoring of SRPNs

Peptides can be combined with other materials through covalent and non-covalent interactions for targeted functionalization of nanomaterials, in order to improving the biocompatibility and reducing the cytotoxicity of nanomaterials [105]. This part presents the hybridization of peptides with metals and metal oxides/sulfides, DNA/RNA/PNA, polysaccharides, PS, and other materials for functional modulation of SAP materials.

4.1. Functional tailoring with metals and metal oxides/sulphides

Metal NPs are available for surface modification of various biomolecules for specific functional tailoring [106]. Metal/peptide hybrid nanomaterials formed by the combination of metals with peptides exhibited wide applications, such as cell imaging, tissue engineering, phototherapy, and drug delivery [107,108].

Gold NPs (AuNPs) with the properties of inertness and non-toxicity are relatively safer than other metal NPs, and thus have been extensively studied by researchers [109]. For example, Borglin and co-workers used a peptide (JR2EC) with a dual stimuli-response of Zn^{2+} and MMP-7 to prepare a high signal-to-noise biochemical contrast agent for multiphoto-induced luminescence (MIL) [110]. Zn^{2+} was removed by chelators after stimulating the peptide to self-assemble into a four-helix bundle, and the AuNPs achieved suspension. The release of MMP-7 resulted in the elimination of JR2EC and aggregation of AuNPs, significantly enhancing the MIL signal.

AuNPs have been considered to be a promising PTT agent for cancer therapy. Yang et al. synthesized AuNPs@PNPs by coating method for targeted therapy of prostate cancer [111]. The peptide (sequence: CREKA-YPFFK (Nph)) self-assembled after being stimulated by serum alkaline phosphatase (ALP) (Fig. 7a). Compared with the unassembled groups, the retention period of AuNPs@PNPs in the tumor site increased by about three times. In addition, as a PTT agent, the designed AuNPs@PNPs could effectively increase the tumor temperature *in vivo* under near infrared (NIR) irradiation. In another study, Chen et al. used a mixture of peptides (CALNNKKKK and CALNNKKKKGRGD) functionalized AuNPs (GNPs@peptide) and silica nanoparticles (MSNs) to construct a stimuli-responsive drug delivery system (Fig. 7b) [112]. The negatively charged carboxylated MSNs were bound to positively charged GNPs@peptide via electrostatic interactions, preventing premature drug leakage. In the microacidic environment of lysosomes, the MSN surface charge reversed, leading to the removal of GNPs@peptide and the targeted release of drugs.

In addition to AuNPs, other metals are often used to modify peptides. For example, in the work of Li et al., multifunctional peptides (MFP) encapsulated silver NPs (MFP@AgNPs) were used for *in vivo* antimicrobial purposes [113]. The peptide consists of MMP cleavable sequence (PVGLIG), antimicrobial peptide (tachyplesin-1), and the target peptide (PGP-PEG), which bound to AgNPs via electrostatic interactions (Fig. 7c). The formed MFP@AgNPs exhibited antibacterial activity against both Gram-positive and Gram-negative bacteria. Upon reaching a slightly acidic environment, MFP was dissociated, releasing tachyplesin-1, which induced synergistical antimicrobial effects besides the effect of AgNPs. The time to sterilization was shortened by 4-fold. Furthermore, in order to reduce chemoresistance and decrease the recurrence rate of hepatocellular carcinoma (HCC), Xia and co-workers synthesized platinum nanocluster assemblies (PT-NA) using platinum nanoclusters (PtNCs), pH-sensitive polymers, and the HCC-targeting peptide SP94 (H2N-SFSIIHTPILPLGGC-COOH) (Fig. 7d) [114]. The HCC-targeting peptide prompted the entry of PT-NA into HCC cells by mediating endocytosis. In the acidic microenvironment, the PT-NA dissociated and accelerated the release of Pt ions. PtNCs had more robust stability and were not affected by ATP-binding cassette transporter proteins. Therefore, the sustained release of Pt ions promoted DNA platinization, induced DNA damage, and killed HCC cells.

Apart from mono metals, metal oxides/sulfides can also be functionalized to modify peptide-based nanomaterials. For example, Yang et al. designed a pH/temperature dual-responsive nanogels (NGs) for drug (rapamycin, RAPA) delivery and magnetic resonance imaging (MRI) fluorescence imaging [115]. The system was coupled to the surface of an anti-collagen type IV peptide (KLWVLPK) to form a nanogel (RAPA/Fe_3O_4@NGS-Col IV) for targeted drug delivery. The presence of magnetic Fe_3O_4 cores conferred imaging capabilities to the nanogels and further weighted the MRI resolution. Moreover, the surface hydrophobicity of the magnetic NPs increased the loading of hydrophobic drugs. Thus, the dual-responsive multifunctional NGs achieved RAPA-targeted release and inhibited neoplastic endothelial neoplasia more efficiently than non-targeted NGs.

In a previous report, Zhao and co-workers constructed a multi pH/enzyme/redox stimuli-responsive fluorescent porous $pSiO_2$ nanocarriers ($pSiO_2$-GSSG NSs) with high drug storage capacity [116]. The carriers were formed by the combination of amino-functionalized silica ($pSiO_2$), oxidized glutathione (GSSG), and fluorescent ZnO QDs. GSSG was attached to the $pSiO_2$ nanospheres via an amide bond, and the aminated ZnO QDs were covalently coupled to the carboxyl group of the GSSG side chain. Through the decomposition of ZnO QDs in an acidic environment, the amide and disulfide bonds were cleaved by proteinase K and GSH, respectively, leading to the detachment of ZnO QDs and the controlled release of the drug. Additionally, the aminated ZnO QDs emitted yellow fluorescence under UV irradiation, which could be used as a potential

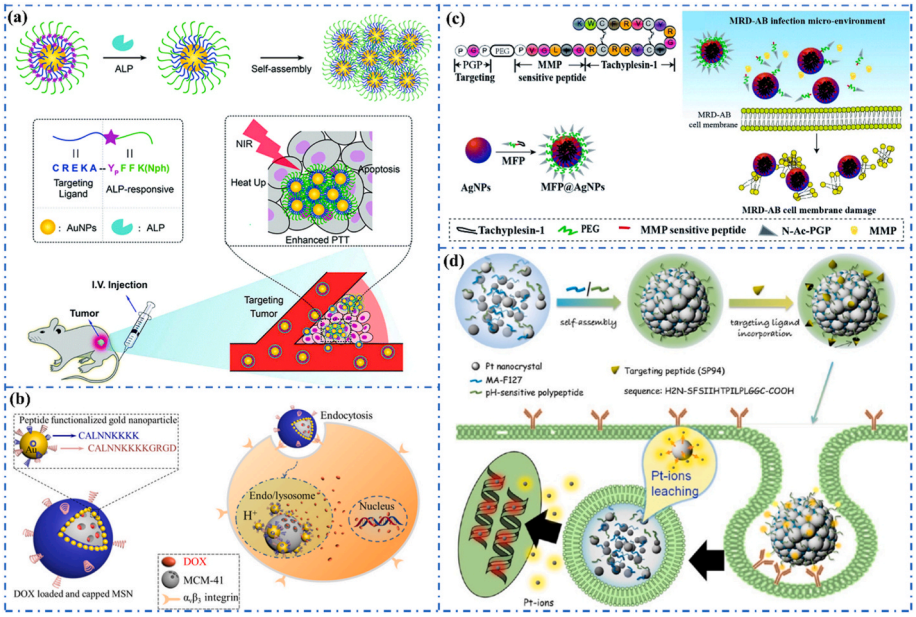


Fig. 7. Functional modulation of peptide nanomaterials by metals: (a) Synthesis of AuNPs@PNPs for targeted tumor PTT [111]. **(b)** AuNPs and MSNs-modified RGD peptide for targeted cancer therapy [112]. **(c)** MFP@AgNPs for enhanced antibacterial application [113]. **(d)** Pt-NA hybrids for targeted HCC uptake and killing [114]. Adapted with permission [111], Copyright 2018, Royal Society of Chemistr; adapted with permission [112], Copyright 2016, American Chemical Society; adapted with permission [113], Copyright 2020, Royal Society of Chemistry; adapted with permission [114], Copyright 2016, American Chemical Society.

fluorescent probe to in-situ monitor drug release from the pores.

In addition, Chen et al. designed a thermo-sensitive CuS-based diagnostic micelle to encapsulate aminoflavonoids (AFs) for targeted treatment of triple-negative breast cancer (TNBC) [117]. The micelles were formed through the functionalization of CuS NPs by the thermo-sensitive amphiphilic block copolymer poly (acrylamide-acrylonitrile)-PEG (PAAmAN-PEG), which was then coupled with the tumor-targeting ligand, GE11 peptide (YHWYGYTPQNVIGGGGC). The temperature increasing of CuS NPs under NIR irradiation not only triggered PTT, but also induced the transition from hydrophilic to hydrophobic PAAmAN fragments possessing a high critical temperature (~38 °C), accelerating drug release. In addition, CuS NPs had photoacoustic imaging properties, which allowed real-time monitoring of anti-tumor effects of peptide nanomaterials.

4.2. Functional tailoring with DNA/RNA/PNA

DNA and RNA are biomolecules that maintain the normal immune response of the body, which have irreplaceable roles in cell proliferation and differentiation and in the transmission of information through the processes of replication, transcription, and translation [118]. Previously, they have been widely used in nanotechnology, clinical diagnostics, and therapeutics [119].

DNA-based peptide nanohybrids with size and structural controllability and excellent biocompatibility are promising delivery vehicles [120]. Peptide Nucleic Acids (PNAs) are a class of DNA analogs in which the sugar-phosphate backbone is replaced by a peptide backbone.PNAs are not electrostatically repulsive to DNA and RNA, resulting in high stability and excellent specific recognition. In particular, PNAs have stable and effective RNA target recognition. PNAs targeting tumor-associated microRNAs (miRs) have been shown to have potent antitumor effects both *in vivo* and *in vitro*. Gupta and co-workers developed a miR-210 inhibition strategy for MGγPNA with very high DNA/RNA affinity by modifying antisense γPNAs [121]. ^{MG}γPNAs were coupled with pH-low insertion peptides to encapsulate them in poly (propylene glycol-glycolide-co-glycolide) (PLGA) NPs for cellular delivery. The experimental results showed that MGγPNA could be effectively released by the delivery t PHLIP has a weak interaction with the cell membrane at normal pH. However, pHLIP folds and inserts into the cell membrane in a low pH environment, promoting cellular uptake of NPs. The experimental results showed that ^{MG}γPNA could be effectively released by the delivery through PLGA NPs and showed a significant inhibition effect on tumor growth. It provided a powerful means to treat cancer by targeting miRs.

Nucleic acid aptamers are oligonucleotide sequences that have the advantages of easy synthesis and modification, low toxicity, and high specificity. They can be coupled with peptides and drugs to enhance cell penetration and perform targeted therapy [122,123]. For example, Tan et al. constructed an aptamer-peptide conjugate containing DOX (APPC-DOX) [124]. The conjugate composed of an anti-heat shock protein 70 (HSP70) peptide (P8: SPWPRPTY or P17: YCAYYSPRHKTTF) and a MUC-1 aptamer with the ability to recognize the transmembrane glycoprotein mucin (MUC-1) (Fig. 8a). The obtained results indicated that the designed APPC-DOX not only had excellent targeting ability to drug-resistant breast cancer cells overexpressed MUC-1, but also enhanced the sensitivity of DOX to cancer cells and significantly reduced the toxicity of DOX.

4.3. Functional tailoring with polysaccharides

Among polymers, polysaccharides have excellent biocompatibility and biodegradability, making them highly attractive for peptide conjugation [125]. In view of the uniqueness and complementarity of polysaccharides and peptides, polysaccharide-peptide conjugates (PPCs) have been extensively studied to be developed as multifunctional biomaterials. PPC nanomaterials have shown wide applications in antibacterial, tissue engineering, and drug delivery [126–128].

Fucose-based nanomaterials are often used to develop drug nanocarriers for treatment of cancer and cardiovascular diseases. Lu et al. combined fucoidan and cationic peptide (protamine) via electrostatic interactions, which self-assembled into dual stimuli-responsive PNPs after loading DOX for inhibiting metastatic breast cancer cells (MDA-MB-231) (Fig. 8b) [129]. Fucoidan targeted the P-selectin of MDA-MB-231, which under trypsin and acidic environment could undergo charge conversion and volume expansion, releasing DOX and effectively inhibiting the growth of MDA-MB-231.

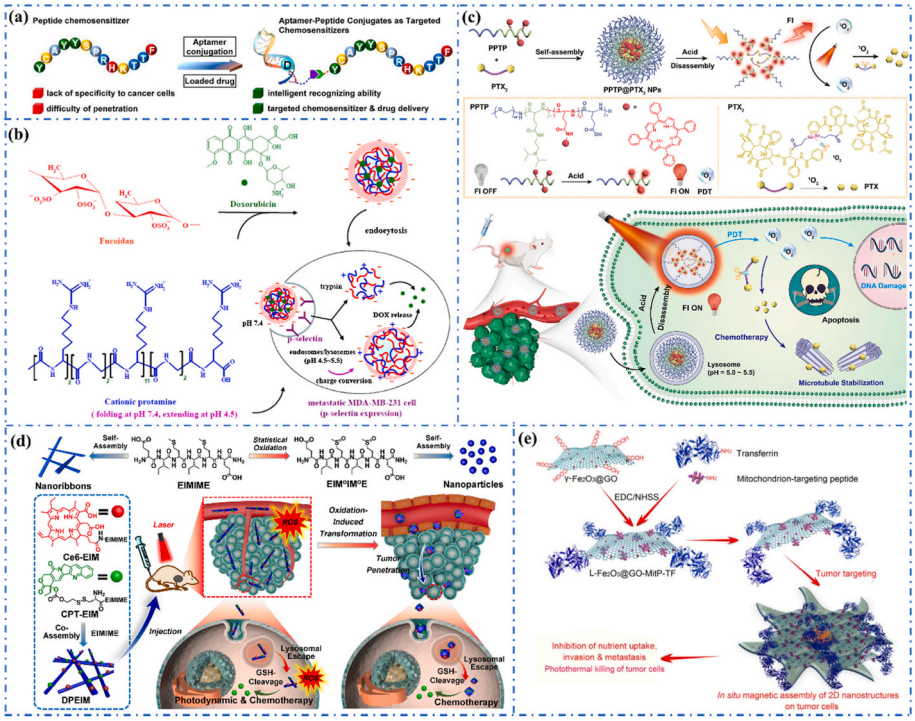


Fig. 8. (a) DNA-modified peptide for enhanced drug delivery [124]. **(b)** Dual SRPNs the modified with polysaccaride for cancer therapy [129]. **(c)** PPTP@PTX2 NPs for combined PDT and CT of tumor [137]. (**d**) Oxidation-responsive peptide nanocells that modified with PS for combined PDT and CT of tumor [138]. (**e**) Synthesis of L-Fe_2O_3@GO-MITP-Tf for tumor targeting and treatment [140]. Adapted with permission [124], Copyright 2021, American Chemical Society; adapted with permission [129], Copyright 2017, Elsevier BV; adapted with permission [137], Copyright 2022, American Chemical Society; adapted with the permission [138], Copyright 2021, Elsevier BV; adapted with the permission [140], Copyright 2020, Springer.

Nanomaterials based on cellulose and antibacterical peptides (AMPs) have good solubility and biodegradation sensitivity. In a work by Weishaupt and colleagues, 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO)-oxidized nanofiber cellulose (TONFC) and AMP were combined to form pH-responsive nanocomposites with antibacterial properties via self-assembly [130]. When the pH value of the solution was higher than the pKa of the carboxyl group, and the ionic strength was low, the positive charges on the surface of *Lactococcus* bacteria combined with the large number of negative charges provided by TONFC, resulting in an increase in the radius of the fibrils and a decrease in fiber flexibility. Compared with *Lactococcus aureus*, TONFC-*Lactococcus aureus* biocomposites showed stronger antibacterial activity against *Bacillus subtilis* and *Staphylococcus aureus*. α-Lactose specifically recognized liver cancer cells and played a crucial role in mediating the endocytosis.

Recently, Meng et al. used casein hydrophobic peptide (CHP) to modify CS and synthesized a set of Pickering emulsifier CS-CHP NPs (NPs3-1, NPs1-1, NPs1-3) with a wide range of HLB values [131]. The CS-CHP NPs revealed better emulsifying ability, antioxidant properties, and high stability. Meanwhile, the emulsion type could be converted from O/W to W/O, showed pH- and CO_2/N_2-responsiveness, and efficiently treated curcumin at different pH. The encapsulation and smart release provided a new way for improving drug delivery.

4.4. Functional tailoring with photosensitizers (PSs)

In recent years, photothermal nanomaterials integrating multifunctionality have provided excellent conditions for targeted diagnosis and therapy in medicine [132]. Photothermal nanomedicines combining photosensitizers and peptides have been considered as promising therapeutic agents for cancer phototherapy [133]. Photochemical stability and safety are prerequisites for use as photosensitizers [134].Stimuli responsive nanomaterials combining photosensitizers and peptides are able to accurately respond to the microenvironment and change accordingly, providing excellent efficacy in targeted delivery and accumulation of drugs and multifunctional imaging [135].

Ther functionalization of peptide nanomaterials with PSs can achieve precise drug release and improve the therapeutic efficiency of phototherapy. For example, in a work by Le and colleagues [136], monoblock ELP was conjugated to the PS (TT1) and co-assembled with diblock ELP (dbELP) to generate targeting NPs. TT1 generated $^1O_2$ under the light irradiation, which oxidized the Met residues in the monoblock ELP, making the ELP hydrophilic, thereby triggering the dissociation of NPs. In addition, TT1 interacted with phenylalanine in dbELP through π-π interactions, inducing the generation of smaller-sized NPs, achieving deeper penetration, and obtaining effective anti-cancer treatment. In another report, Zhang and colleagues designed polyglutamic acid-based dual-responsive PNPs for combined treatment of TNBC polyglutamic acid with PDT and CT [137]. Tetraphenylporphyrin (TPP) was used as a PS, and N, N-diisopropyl ethylenediamine (DPA) was jointly connected to the peptide skeleton to form intracellular pH-responsive peptide (PPTP). PPTP and paclitaxel dimer the drug (PTX2) self-assembled to form biodegradable PNPs (PPTP@PTX2NPs) (Fig. 8c). After intravenous injection, the PPTP@PTX2 NPs passively accumulated at the tumor site and were taken up by tumor cells. They were activated in an acidic environment, released and restored the TPP fluorescence signal, and generated singlet oxygen ($^1O_2$) under 660 nm laser irradiation, stimulating PTX2 to return to PTX. Therefore, the synergetic effect of PDT and CT significantly inhibited the growth of 4T1 TNBC tumors.

Interestingly, Yu et al. designed and synthesized an oxidation-responsive peptide nanocells (DPEIM) containing two hexapeptides with Met residues (EIMIIE, EIIIME, and EIMIME) [138]. It was obtained by co-assembling with the PS Ce6, named as the CPT (Fig. 8d). The incorporation of Ce6 into polypeptides generated ROS *in-situ* under the laser irradiation, achieving PDT and the oxidation of Met, which further led to the transformation of the scaffold morphology and improved the

tumor penetration rate. The large amount of GSH in tumor cells made CPT to interact with the polypeptide. The disulfide bond between them was broken, and CPT was released to achieve synergistic treatment of PDT and CT. In a similar study, Hu et al. assembled a core-shell structure using poly(2-methacryloyloxyethylphosphocholine) (PMPC), enzyme-responsive peptide GFLG, and poly-L-lysine with Ce6 [139]. The peptide bundle that loaded with gemcitabine (GEM) enabled the combined PDT and CT of cancer.

4.5. Functional tailoring with other active materials

In addition to the above-mentioned materials that can combine with peptides to enrich the functions, there are also some other materials that have good binding capabilities with peptides, such as graphene and its derivatives (graphene oxide (GO), reduced graphene oxide (rGO)) have a large specific surface area and abundant surface functional groups. Polypeptides can be easily combined with them through noncovalent interactions to present great application potential in biomedicine.

Liu et al. synthesized large-size magnetic nanosheet (L-Fe_2O_3@GO-MITP-Tf) of 0.5–1 μm using GO containing γ-iron oxide (γ-Fe_2O_3@GO), tumor-targeting protein transferrin (TF), and mitochondrial-targeting peptide (MITP) (Fig. 8e) [140]. Nanosheets targeted tumor cells and self-assembled *in-situ* on the surface of tumor cells to form a 2D structure. The large-sized 2D magnetic assembly inhibited the uptake of nutrients by tumor cells and reduced the possibility of tumor cell metastasis. In addition, under the stimulation of NIR, the 2D PSA effectively responded to NIR radiation, produced a photothermal effect, significantly damaged mitochondria, and induced cancer cell death. In another report, Zhang et al. connected the apoptotic peptide $(KLAKLAK)_2$(KLA) to the GO surface through the formation of disulfide bonds, and then loaded DOX through π-π interactions and hydrogen bond interactions, and finally coated with bovine serum albumin (BSA) to form an anti-cancer nanosystem with dual pH/GSH-response (DOX@GO–SS–KLA/BSA) [141]. After the DOX@GO–SS–KLA/BSA entered into cancer cells, the disulfide bonds between the peptide and GO were broken, releasing KLA. In the presence of a large amount of GSH, the GO-based drug carrier could easily and quickly release DOX in a weak acid environment to achieve synergistic anti-cancer treatment.

In the above sections, we introduced and discussed the functional tailoring of peptide-based nanomaterials with various components to enhance the stimuli-responsive abilities of SRPNs. To make it more clear, we summarize the important details that could be useful for readers to understand the cases, as shown in Table 2.

5. Biomedical applications of SRPNs

Compared to non-peptide nanomaterials, peptide-based materials have excellent biocompatibility, bioactivity and biodegradability, and reduced rejection. Specific interactions between amino acids lead to highly ordered and stable assemblies. Peptides are allowed to self-assemble into different nanostructures. Rationally designed amino acid sequences allow combinations of different functions within a single molecule, such as stimulus responsiveness, enabling the self-assembly of peptides or assembly with other materials into multifunctional nanomaterials, which is a great advantage for nanomaterials [142]. SAPNs are capable of undergoing conformational and chemical changes in response to stimuli, and have been widely used in biomedicine as drug carriers, imaging agents, anti-tumor, antimicrobial and tissue repair, among other uses. In this section, we focus on the biomedical applications of SRPNs in drug delivery, bioimaging, gene therapy, PTT/PDT, antibacterial biomaterials, wound healing, and wound dressing.

5.1. Drug delivery

Over the last years, drug delivery technology has achieved great progress, but traditional drug delivery still faces many problems, such as premature drug leakage, inability to target lesion identification, and slow drug release [143,144]. Peptide-based drugs have been permitted for the treatment of diseases such as cancerous tumors and gastrointestinal disorders. The utilization of emerging nanomaterials for delivery of small molecule drugs is an effective way. Generally, nanocarriers can be functionalized by targeting portions to specifically recognize with specific organs or diseased cells [145].

SRPNs act as drug delivery carriers, delivering drugs to the vicinity of diseased cells and releasing them on demand as influenced by the microenvironment of the diseased cells, increasing the specificity and

Table 2
Summary of functional regulation of SRPNs.

Peptide	Functional part	hybridized structure	Responsive	Application	Ref.
JR2EC	AuNPs	NPs	Enzyme/Zn^{2+}	Preparation of biochemical contrast agents with high signal-to-noise ratio	[109]
CREKA-YPFFK(Nph)	AuNPs	NPs	Enzyme	Enhances PTT effect on the different expression levels of ALP in cells	[110]
CALNNKKKK, CALNNKKKKGRGD	AuNPs	NPs	pH	Stimuli-responsive drug delivery systems	[111]
PVGLIG, tachyplesin-1, PGP-PEG	AgNPs	NPs	Enzyme/pH	antibacterial	[112]
H_2N-SFSIIHTPILPLGGC-COOH	PtNCs	Nanocluster	pH	Induces DNA damage and kills cancer cells	[113]
KLWVLPK	Fe_3O_4	Nanocells	Temperature/pH	Image-guided therapy and Inhibits neoplastic endothelial regeneration	[114]
GSSG	ZnO QDs	NSs	Enzyme/pH/GSH	Acts as a fluorescent probe to monitor drug release	[115]
YHWYGYTPQNVIGGGGC	CuS NPs	Nanocells	Temperature	Photoacoustic imaging, combination of CT and PTT	[116]
pHLIP	γPNAs	NPs	pH	Induces apoptosis and necrosis	[121]
SPWPRPTY, YCAYYSPRHKTTF	MUC-1 aptamer	ApPC	–	Targeted chemical sensitizers and anticancer agents	[124]
Fish protein	Fucoidan	NPs	Enzyme/pH	Inhibits breast cancer cell metastasis	[129]
AMP lactostreptococcal	TONFC	NFs	pH	Biocomposites with high antimicrobial activity	[130]
CHP	CS	NPs	pH	Changes emulsion hydrophilicity type	[131]
ELP, dbELP	TT1	NPs	Temperature/ Light	PS delivery and PDT	[136]
polyglutamic acid	TPP	NPs	pH/Light	Combined CT and PDT for breast cancer	[137]
EIMIIE, EIIIME and EIMIME	Ce6	scaffold	redox	Responds to ROS, transforms stent morphology	[138]
GFLG and Poly-l-lysine	Ce6	Nanocells	Enzyme/Light/pH	Co-delivery of anticancer drugs and pro-apoptotic peptides in tumor cells	[139]
MITP	γ-Fe2O3@GO	NSs	Light	Forms 2D structure to inhibit nutrient uptake by tumor cells	[140]
$(KLAKLAK)_2$	GO	nanospheres	pH/GSH	Co-delivery of anticancer drugs and pro-apoptotic peptides in tumor cells	[141]

effectiveness of drug delivery. Compared with inorganic nanomaterials, peptide nanocarriers have good stability, membrane penetration, biocompatibility, and low cytotoxicity.

Drug nanocarriers with deformable size can be flexibly regulated according to the spatial size of tumor tissues to achieve effective crossing of barriers and preservation of tissue interstitial space. Chen and co-workers designed shell-stacked NPs (SNPs) using stimuli-responsive shell separation technique [146]. Methoxy PEG-blocked poly-L-lysine (mPEG113-*b*-PLL25/DMMA) with charge reversal property was stacked by electrostatic interactions to form a shell layer (Shell-DMMA). The inner shell was cross-linked by disulfide bonds. After accumulating in the acidic environment of tumor tissue, SNP effectively achieved a significant size reduction and effective charge reversal at the tumor site (size reduction from around 145 to 40 nm and surface charge reversal from −7.4 to 8.2 mV) (Fig. 9a). Within the cell, the disintegration of disulfide bonds accelerated drug release and improved anti-tumor activity. SNPs with deformable size and charge reversal could deliver drugs to deeper tumor sites with significantly improved anti-tumor effects. It is a reliable carrier for deep delivery of peptide nanomedicines.

The development of stimuli-responsive drug carriers is a good strategy in order to fulfill drug penetration and effective release in the body. Xue et al. designed a novel albumin-like drug nanocarrier based on zwitterionic poly(glutamatyl lysine-*co*-cysteine) (p(EK-*co*-C)) peptide scaffolds to form a novel albumin-like drug nanocarrier with positive and negative charges on the surface [147]. Under the TME, the polymer could effectively recognize the poly(salivary acid) over-secreted on the tumor cell membrane, and targeted the tumor cells for drug delivery (Fig. 9b). Amphipathic ionic EK peptide had properties similar to plasma proteins. It was internalized by tumor cells by reducing the recognition of the reticuloendothelial system to prolong blood circulation. The albumin-like nanocarrier could be broken down by enzymatic digestion. It accelerated the release of DOX in tumor cells and improved the anti-tumor efficiency. Meanwhile, it did not gather in large quantities in normal cells. Therefore, the nanocarrier exhibited good biosafety,

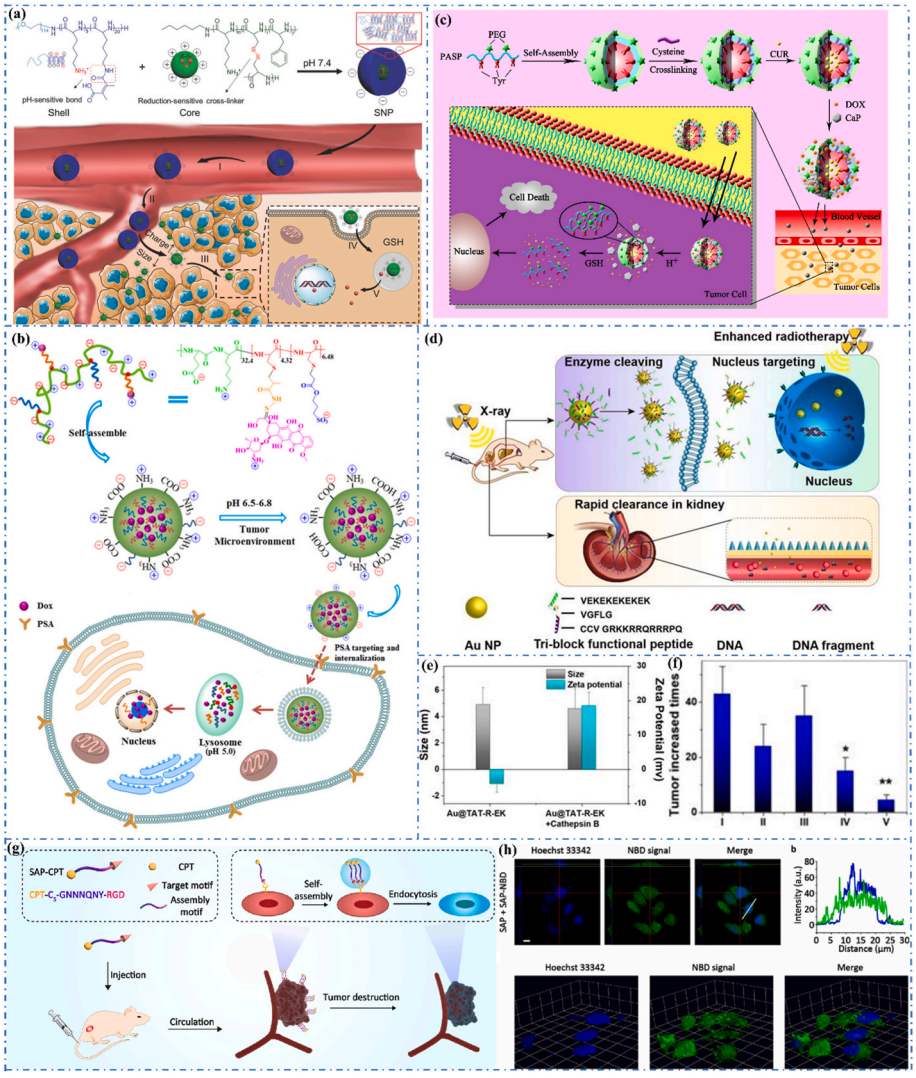


Fig. 9. SRPNs for drug delivery applications: (a) TME-stimulated SNPs for targeted drug delivery [146]. **(b)** Peptide drug nanocarriers for pH-triggered tumor targeting [147]. **(c)** pH/GSH-responsive CPPT@CaP-CD NPs for drug release [148]. **(d)** Schematic representation of the accumulation of Au@Tat-R-EK NPs in tumor tissues and nuclei to enhance radiotherapy *in vivo* [149]. **(e)** Hydrodynamic size and zeta potential of Au@Tat-R-EK NPs with and without histone B treatment [149]. **(f)** Fold increase in relative tumor weight at day 14 in different groups. (I: Control; II: X-ray; III: Au@Tat-R-EK; IV: Au@Tat-I-EK + X-ray; V: Au@Tat-R-EK + X-ray) [149]. Adapted with permission [149], Copyright 2020, IYYSPPING. **(g)** Schematic representation of SAP-CPT molecular design and self-assembly targeting of tumor cells [150]. **(h)** Fluorescence imaging of SAP-CPT molecules entering cells [150].Adapted with permission [132], Copyright 2017, Wiley-VCH; adapted with permission [133], Copyright 2020, American Chemical Society; adapted with permission [134], Copyright 2021, Elsevier BV, adapted with permission [149], Copyright 2020, IYYSPPING, adapted with permission [149], Copyright 2020, IYYSPPING, adapted with permission [149], Copyright 2020, IYYSPPING, adapted with permission [150], Copyright 2021, Elsevier BV, adapted with permission [150], Copyright 2021, Elsevier BV.

degradability, and low cytotoxicity, and could be utilized as a promising carrier for tumor-targeted drug delivery.

Li et al. prepared a novel type of dual pH/redox stimuli-responsive peptide-calcium phosphate hybrid co-loaded PNPs by a simple green polymerization method [148]. Cross-linked methoxy PEG-g-polyaspartic acid-tyrosine (CPPT) polymers self-assembled into stimuli-responsive NPs with Ca^{2+} and PO_4^{3-} in water. The hybrid NPs encapsulated curcumin (CUR) in the hydrophobic core provided by tyrosine (Tyr), and loaded DOX on the hydrophilic part of the micelle and the calcium phosphate (CaP) shell to form spherical drug-loaded NPs (CPPT@CaP-CD) (Fig. 9c). The presence of PEG shell reduced the non-specific cellular uptake and prolonged the circulation time of the NPs in the bloodstream. The presence of disulfide and CaP shell prevented drug leakage. Upon reaching the tumor location, the CaP layer was dissolved under the influence of pH. Simultaneous protonation of polyaspartic acid (PASP) led to structural instability of the NPs, releasing DOX and CUR. When the NPs entered the cytoplasm with high GSH concentration, the disulfide bond was cleaved and CUR was further released. Thus, the dual pH/redox-responsive CPPT@CaP-CD allowed effective drug release in the acidic and low-oxygen microenvironment of tumors, which is promising in the field of targeted drug delivery.

Compared with conventional sensitizers, SRPNs possess greater penetration and highly internalized target tissues. In the study of Ding et al. triple-block functional peptide-modified ultrasmall Au NPs were prepared (Au@Tat-R-EK NPs) for cancer radiotherapy (Fig. 9d) [149]. One of the Tat peptides (GRKKKRRQRRRPQ), a powerful cell-penetrating and nuclear-targeting peptide, was linked to the Au NPs. the GFLG peptide could be cleaved by histone B for linking the Tat and zwitterionic antifouling peptides (EKEKEKEKEK). The prepared Au NPs exhibited superb stability, histone responsiveness and nuclear targeting. Upon encountering histone B, GFLG was selectively cleaved to expose the Tat peptide, and the zata potential of Au@Tat-R-EK underwent a shift from negative to positive. This change enhanced its selective uptake by tumor cells (Fig. 9e). Subsequently, Au@Tat-R-EK enters the tumor cells and precisely targets the nucleus for accumulation. In combination with X-rays, they exhibited excellent sensitization for radiotherapy. The results of the *in vivo* radiotherapy assay demonstrated that the Au@Tat-R-EK NPs + X-ray group showed the slowest tumor growth compared to the control group, with only 4.5-fold expansion of the tumor volume at day 14. Au@Tat-R-EK NPs mediated up to 90 % of the radiotherapy, significantly prolonging the survival time of the mice (Fig. 9f).

In vivo self-assembly of peptide-based nanomaterials is a promising diagnostic strategy. Compared with conventional CT, peptide drug coupling (PDC) drugs offer advantages such as improving drug targeting and reducing adverse effects. Wang and colleagues prepared a PDC drug (SAP-CPT) for *in vivo in situ* self-assembly strategy to improve drug penetration into tumor cells [150]. SAP-CPT consisted of the targeting RGD peptide, GNNNQNY peptide, and the drug molecule camptothecin (CPT) (Fig. 9g). The SAP-CPT drug targeted the cancer cell receptor αVβ3, which then formed nanoclusters *in situ* and entered the cell via endocytosis. Intense fluorescent signals were observed in the cytoplasm and nucleus (Fig. 9h) Compared with the monomeric SAP-CPT drug, the assembled SAP-CPT drug had an enhanced ability to enter tumor cells. In addition, compared with conventional PDC drugs, SAP-CPT drugs were successfully aggregated by self-assembly, which improved the cell penetration rate and achieved corresponding excellent therapeutic effects.

5.2. Bioimaging

Bioimaging is a non-invasive imaging technique for observing the behaviors of living organisms over a period of time, providing visual evidence for in-depth understanding of biological processes and drug effects, and playing an irreplaceable role in clinical diagnosis and treatment [151]. SRPNs are capable of target binding to diseased sites, improving the stability and accuracy of imaging.

Fluorescent imaging has contributed greatly to the exploration of complex biological systems. Organic fluorophores and green fluorescent proteins (GFPs) have been more widely used in biomedical applications. Two-photon absorption (TPA) fluorescence imaging is also promising in diagnostics and biomedicine due to its excellent spatio-temporal resolution [152]. But for GFP, getting into the cell and stabilizing its role is more complicated. For this reason, Kong et al. designed a cyclic peptide with the sequence of Fc-YYGCGPGRC, by combining a cell-penetrating peptide (CPP) with di-tyrosine [153]. This peptide could self-assemble into biologically active pH-responsive NPs. When the phenolic group of Tyr was deprotonated, the NPs emitted bright green fluorescence, which could effectively penetrate the cell membrane and enter the cell to create function (Fig. 10a). In addition, tyrosine-based peptides had good biocompatibility, endosomal escape ability, and low cytotoxicity. There is great potential in biomedical applications such as monitoring and tracking biological processes.

Bioprobes constructed based on the AIE-responsive molecular fluorophores have been reported to be able to monitor signalling components in real time and keep abreast of therapeutic effects. It is beneficial for NIR image-guided cancer surgery [154]. Qian and co-workers modified functional peptide ST and tumor acid-activating peptide TD on the surface of a nanocarrier, constituting an STD nanomicelle (STD-NM) for targeted therapy and imaging [155]. Among them, ST consisted of the pH-triggered targeting peptide STP (sequence: SKDEEWHKNNFPLSPG), a responsive peptide junction (sequence: DEVD), and the AIE molecule TPE (tetraphenylethylene). This nanomicelle remained 'invisible' and stable in the normal environment *in vivo*, whereas it could be stimulated and activated in the microacidic environment of the tumor and revealed an 'activated' state (Fig. 10b). The drug-encapsulated STD-NM showed controlled drug release capability. In addition, the AIE-based two-photon imaging to monitor the apoptotic process *in vivo* was also successfully realized, enabling a precise assessment of the *in vivo* therapeutic effect.

Imaging of cancer cells due to nonspecific aggregation of imaging probes in some specific metabolic organs, such as kidney and liver, remains a great difficulty. Previously, An et al. designed a NIR peptide probe, TER-SA (RGDRDDRDDPLGYLGFFC(Cy)), with tumor-specific efflux inhibition (TER) effect [156]. It specifically recognized αvβ3 integrins overexpressed in renal cancer cells, specifically cleaved by MMP2/9 in the TME. The residues self-assembled into PNFs *in-situ* at the lesion site. Improved signal-to-noise (S/N) ratio for high-performance imaging of human renal cell carcinoma (RCC) (Fig. 10c). The tumor was completely resected, reducing the postoperative recurrence rate and improving patient survival. The NIR peptide probes based on TER strategy could accurately identify RCC and tumor boundaries. It is a promising approach to achieve tumor imaging of metabolic organs.

Contrast agents responding to TME are important in monitoring tumor therapy. Among them, T1&T2 dual-mode MRI has high sensitivity and accuracy. Chen et al. designed an MMP-9-responsive nanocellulose (PMPSD) that could be used for quantitative tumor imaging [157]. As shown in Fig. 10d, superparamagnetic iron oxide (USPIO) was aggregated and the nanocolloid acted as a T1 contrast agent. In the presence of MMP-9, the MMP-9-sensitive peptide (Fmoc-GPLGL) was cleaved, dissociating the nanocolloid and transforming it into a T2 contrast agent. The T1/T2 transition enabled the visualization of MMP-9 concentration (Fig. 10e). In addition, PMPSD revealed excellent photothermal properties. As shown in Fig. 10f, the anti-tumor effect of PMPSD plus MMP9 combined irradiation treatment was the best. The higher the concentration of MMP9 in the tumor, the better the anti-tumor effect. Therefore, the designed PMPSD exhibited the ability of T1-T2 dual--mode imaging to monitor drug release and realize PTT/CT combination therapy.

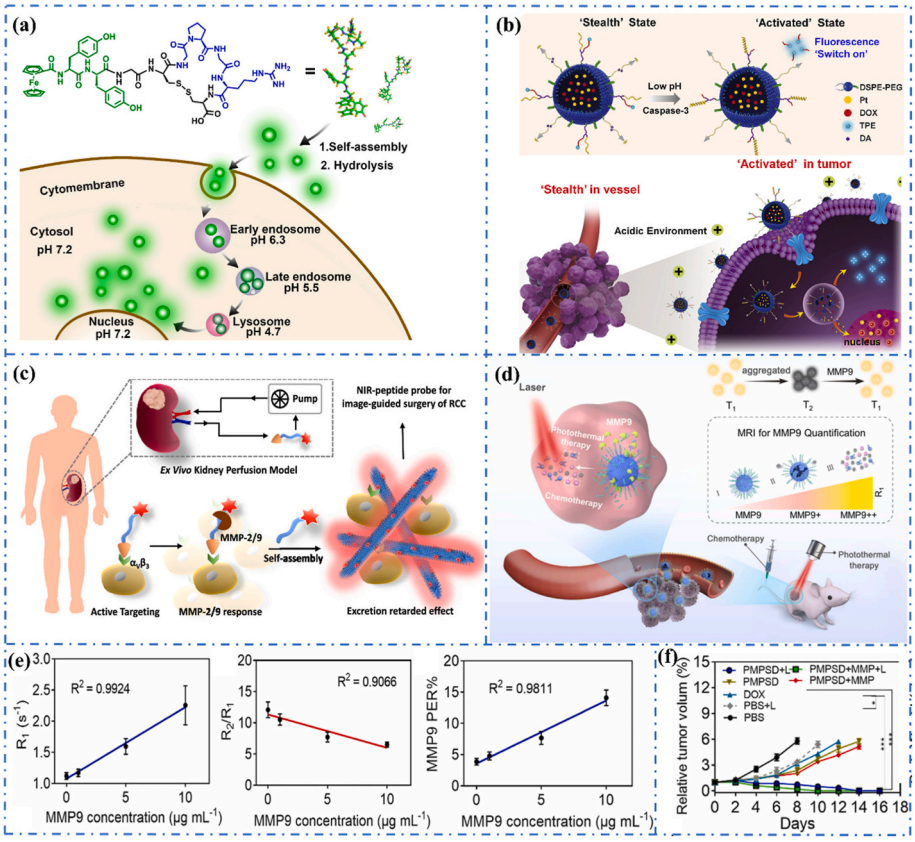


Fig. 10. Bioimaging application of SRPNs: (a) Self-assembled pH-responsive Fc-YYGCGPGRC PNPs for cell imaging [153]. **(b)** pH-responsive STD-NM AIE-based two-photon imaging of tumor [155]. **(c)** Enzyme-responsive NIR PNF probe for imaging of RCC [156]. **(d)** MMP-9 responsive peptide nanocolloids for MRI and PTT or tumor [157]. **(e)** Relationship of MMP9 to R_1, R_1/R_2, and the positive expression rate of MMP9 in tumors. **(f)** *In vivo* antitumor efficacy as of relative tumor volum ($R_1 = 1/T_1$, $R_2 = 1/T_2$).Adapted with permission [153], Copyright 2020, American Chemical Society; adapted with permission [155], Copyright 2018, Elsevier BV; adapted with permission [156], Copyright 2020, American Chemical Society; adapted with permission [157], Copyright 2022, Elsevier BV, adapted with permission [157], Copyright 2022, Elsevier BV, adapted with permission [157], Copyright 2022, Elsevier BV.

5.3. Gene therapy

Gene therapy treats at the genetic level by introducing exogenous normal genes into target cells through gene transfer technology. With high efficiency and high selectivity, it provides an effective way for cancer treatment. Conventional gene delivery vectors have the disadvantages of difficult preparation, poor targeted drug delivery, and lower biosafety [158]. In recent years, stimuli-responsive nanocarriers have been rapidly developed. Highly selective and specific targeted delivery and controlled gene release behavior can be achieved, improving the overall efficiency of gene therapy [159].

Conventional treatments for glioblastoma (GBM), such as CT and radiotherapy, have drawbacks like insufficient drug delivery and off-target drug delivery [160]. Nanotechnology-based small interfering RNA (siRNA) is a promising therapeutic modality for the treatment of GBM. However, due to the complexity of brain structure, purely targeted strategies are still unable to meet therapeutic needs of GBM. Liu et al. designed a novel charge-converting biomimetic siRNA delivery nanoplatform with a three-layer core-shell structure [161]. This was a nanocomposite (Ang-RBCm-CA/siRNA) encapsulated by vasopeptide-2-modified erythrocyte membrane (Ang-RBCm), which avoided siRNA from immune attack and facilitated the penetration of the BBB. When it reached the vicinity of tumor cells, the weak acidity in the microenvironment triggered a negative-to-positive charge shif, which induced erythrocyte membrane lysis and accelerated siRNA release in tumor cells (Fig. 11a). The nanocomplexes yielded excellent anticancer therapeutic effects in therapeutic experiments in mice harboring human GMB *in-situ* and did not produce other side effects. Overall, this novel multifunctional biomimetic nanocomplex possesses good biocompatibility, excellent BBB permeability, and targeted delivery ability. This study provides a powerful way for GBM-targeted gene therapy.

Notably, Shi and co-workers designed a highly stable ROS-responsive siRNA nanomedicine (3I-NM@siRNA) [162]. The functionalization of Angiopep-2 peptide (Ang-3I-NM@siRNA) was utilized for targeting GBM. When the Ang-3I-NM@siRNA reached the TME, it enabled to actively penetrate the BBB targeting into brain tumor cells. In the presence of a large amount of ROS, the phenyl borate changed into a hydrophilic compound, leading to the effective release of siRNA and the realization of targeted therapy (Fig. 11b). As verified by *in vivo* experiments in mice, the nanomedicine functionalized with Angiopep-2 peptide had excellent BBB penetration ability, brain tumor targeting ability, and excellent siRNA release ability. This study provides a safe and efficient strategy for brain tumor gene therapy, possessing also the potential to treat other tumors and brain diseases.

Gene release can be controlled through space or time to improve the transfection efficiency. Park and co-workers used a CPP (DS4-3) and coupled with a disulfide-bonded cross-linked PEI (ssPEI) to form a multimer (SPD) [163]. SPD was complexed with bovine serum albumin (BI) NPs loaded with IR780 to form a dual stimuli-responsive nanocomplex (BI-SPD). Upon entry into breast cancer cells, this nano-assembly was subjected to 808 nm laser irradiation, which locally thermally triggered the escape of SPD multimeric endosomes. The disulfide bond was broken in the cytoplasm containing a large amount of GSH, releasing the DNA plasmid for gene expression (Fig. 11c). 4T1 cell line experiments showed that the transfection efficiency of BI-SPD was

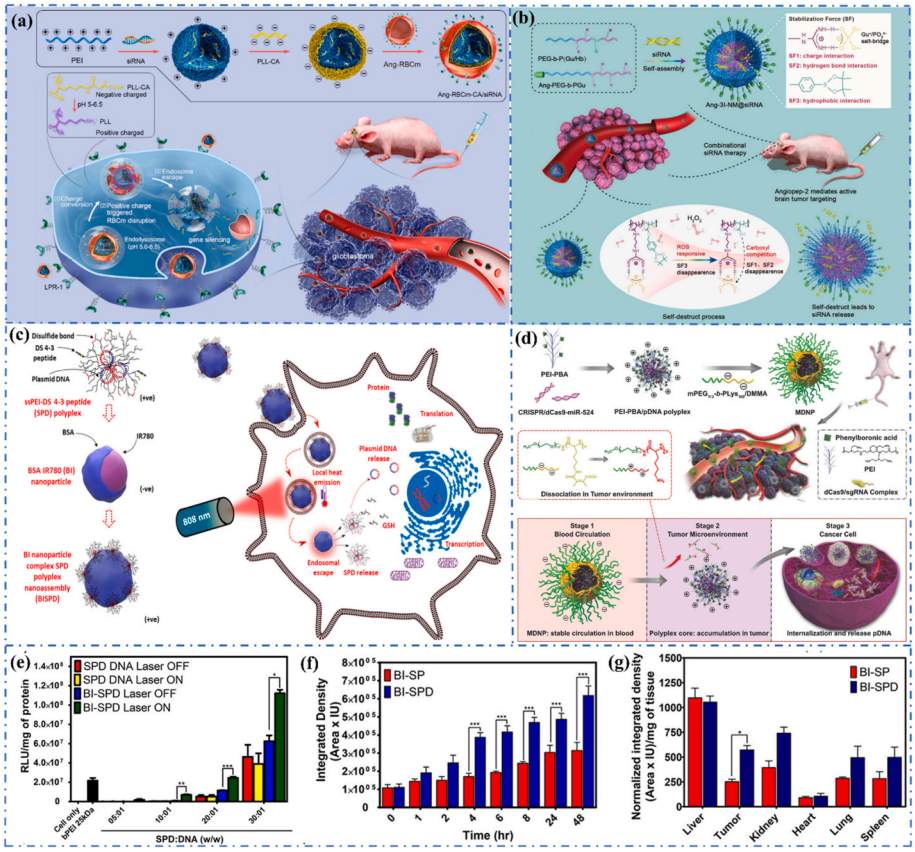


Fig. 11. Gene therapy applications of SRPNs: (a) Ang-RBCm-CA/siRNA loaded with siRNA for treating U87MG human glioblastoma [161]. **(b)** ROS-responsive 3I-NM@siRNA for siRNA release [162]. **(c)** Thermo-responsive gene release of BI-SPD by 808 nm laser irradiation [163]. **(d)** pH-responsive MDNP for multistage delivery of genes to tumor cells [164]. **(e)** Relationship of luciferase gene expression in BI-SPD-treated cells with external laser irradiation and laser intensity [164]. **(f)** Combined density maps of tumor regions after BI-SP and BI-SPD treatments [164]. **(g)** Normalized integrated density plot of the various organs from the BI-SP and BI-SPD nanoassembly treated 4T1 tumor mice [164]. Adapted with permission [161], Copyright 2020, American Chemical Society; adapted with permission [162], Copyright 2019, Wiley-VCH; adapted with permission [163], Copyright 2019, Elsevier BV; adapted with permission [164], Copyright 2018, American Chemical Society; adapted with permission [164], Copyright 2018, American Chemical Society; adapted with permission [164], Copyright 2018, American Chemical Society; adapted with permission [164], Copyright 2018, American Chemical Society.

two-fold higher than that of SPD multilinkers alone (Fig. 11e) BI-SPD-treated 4T1 tumor-bearing mice showed an increased fluorescence intensity and a significantly higher accumulation of nano-assemblies compared to BI-SP (Fig. 11f and g). This nanocomposite did not cause significant toxicity to surrounding healthy tissues and was highly stable and cell-penetrating. Under laser irradiation, the endosomal escape of multimers was accelerated, resulting in a 4-fold increase in the transfection rate.

Nuclease-inactivated clustered regularly interspaced short palindromic repeats (CRISPR)-associated protein 9 (dCas9) can be targeted to almost any location in the genome with the help of short guide RNAs for precise and efficient gene expression without interrupting the host genome. The anti-cancer approach of CRISPR/dCas9 still faces great challenges in effective targeted delivery. To address this problem, Liu et al. constructed a multistage delivery NP (MDNP) with a core-shell structure for enhancing tumor targeting of the CRISPR/dCas9 system (Fig. 11d) [164]. When MDNP was transported in the bloodstream and reaches the acidic microenvironment of tumor tissues, the DMMA groups in the shell decompose and the shell structure was disrupted. The core cationic polymer was exposed, enhancing the accumulation of the complex in the tumor tissue. The overexpression of sialic acid in cancer cells bound to PBA in the polymer, enhancing the intracellularization of the cationic polymer. Therefore, MDNP achieved efficient multi-stage delivery and inhibited tumor growth effectively, providing an effective strategy for gene therapy based on the CRISPR/dCas9 system.

5.4. PDT/PTT

Traditional cancer treatments have unavoidable damage to the human body and are associated with more side effects and even disease recurrence. Phototherapy is a relatively new minimally invasive cancer treatment with low toxicity to healthy tissues and minimal damage to the human body, which is divided into PDT and PTT.

PDT relies on specific wavelengths to activate PS to generate ROS and oxidize target cells, causing apoptosis or necrosis and thus the death of tumor cells [165]. The traditional PS for clinical application has the disadvantages of poor water solubility, poor biocompatibility, and low bioavailability, which limit the use of PDT in clinical medicine [166]. In contrast, peptide-based nanomaterials have been widely used as PDT agents due to their good biocompatibility and degradability, low cytotoxicity, as well as structural and functional diversity [167]. The use of SRPNs increases the selectivity and efficiency of PDT while at the same time eliminating side effects.

To address the problems of poor PS accumulation and short retention time, Sun et al. designed a novel highly sensitive PEGylated PS-PNF (termed PHHPEG6 NF), which exhibited fast and efficient tumor aggregation and could be used for PDT tumor imaging [168]. As shown in Fig. 12a, the nanofibers could rapidly and efficiently aggregate in the TME of tissues, inducing the generation of singlet oxygen ($^1O_2$), which improved the PDT efficiency. In addition, since $PHHPEG_6$ PNFs had different fluorescence signals before and after PDT. These PNFs could monitor the whole process of PDT, which had obvious advantages in

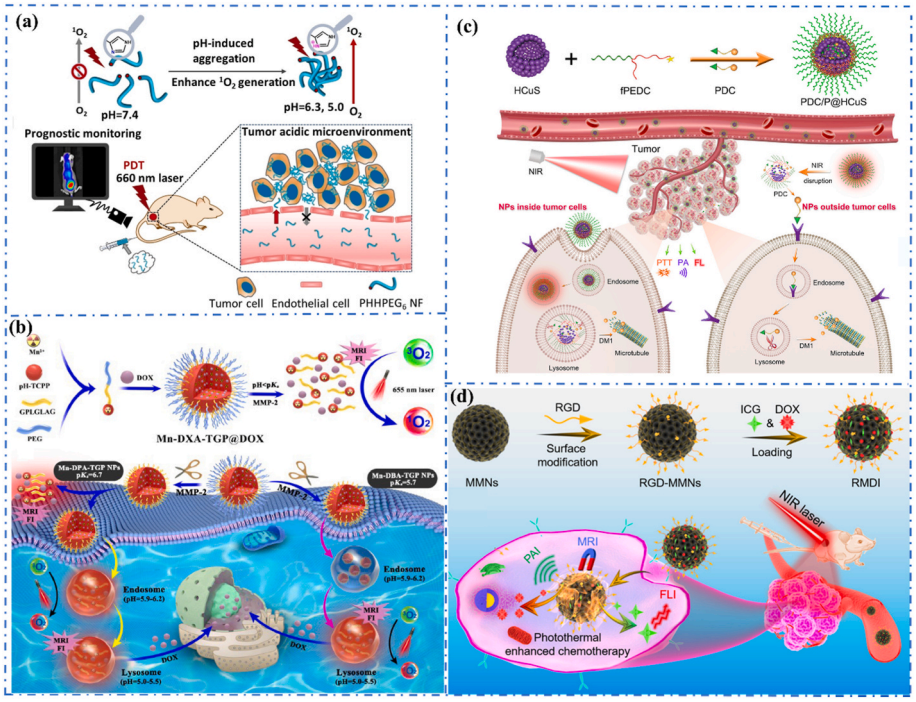


Fig. 12. PDT/PTT applicationS of SRPNs: (a) pH-responsive PHHPEG6 PNFs for enhanced PDT and postoperative detection [168]. **(b)** pH/enzyme-responsive Mn-DXA-TGP@DOX NPs for FI/MRI-guided PDT/CT of cancer [169]. **(c)** Design of pH/reduction-responsive DC/P@HCuS NPs for PTT of tumor [175]. (**d**) pH/photo-responsive NPs for PA/MR/FL imaging-guided PTT/CT of tumor [176]. Adapted with permission [168], Copyright 2022, Wiley-VCH; adapted with permission [169], Copyright 2023, Elsevier BV; adapted with permission [175], Copyright 2019, American Chemical Society; adapted with permission [176], Copyright 2021, American Chemical Society.

PDF tumors. In clinical trials of PDT, the development of PS with AIE properties utilizing fluorescenT imaging-guided PDT has improved the therapeutic efficiency.

To address the tumor specificity of PS, Xu et al. designed a series of pH-responsive PS with different pKa for PDT of TNBC [169]. Tetrakis (4-carboxyphenyl)porphyrin (TCPP) derivatives were grafted onto PEG by the MMP-2-sensitive peptide (GPLGLAG) and chelated with Mn^{2+}, and finally self-assembled into MRI-capable NPs (Mn-DXA-TGP@DOX) that could be loaded with DOX. As shown in Fig. 12b, the NPs were recognized and activated in the acidic environment of the tumor. The presence of a large amount of MMP-2 effectively recognized GPLGLAG peptides, allowing NPs to efficiently aggregate in tumor cells. Under laser irradiation, singlet oxygen was generated and DOX was released. Therefore, the DSRPN nanoplatform exhibited tumor-targeting functionality and the ability to load DOX. Dual-modal image-guided combined PDT/CT with FI and MRI were realized for the treatment of breast cancer.

Bacterial cornea is one of the leading causes of corneal blindness. PDT treats bacteria by killing them through oxidative stress. However, increasingly bacteria are becoming resistant to conventional PS. For this reason, Yao et al. designed an MMP-responsive supramolecular NPs (MMP-S NPs) [170]. They were constructed from an adamantane (Ad)-capped MMP-sensitive peptide (YGRKKKRRQRRR-GPLGVR-G-EEEEEEE) and a β-CD prodrug (β-CD-CE6). The negatively charged EEEEEE peptide shell prevented the NPs from adhering to healthy corneal cells. Upon arrival in the keratitis microenvironment, MMP-9 protease severed the peptide chain and the EEEEEE peptide shell was removed. The exposed cationic peptide effectively facilitated the penetration and accumulation of MMP-S NPs, which bound to *P. aeruginosa* pseudomonas cells and largely eliminated corneal inflammation. Further, the therapeutic effect of MMP-S NPs on keratitis was verified using mice. By generating ROS through in-situ activation using 660 nm light, the cell membrane was disrupted and the structure of the cornea was largely normalized. Therefore, the designed MMP-S NPs could be a viable antimicrobial alternative to target inflammatory cells and improve the antimicrobial performance of PDT.

PTT is a cancer treatment method in which a photothermal agent (PTA) is irradiated by a laser, which converts light into heat energy and kills cancer cells using high temperature [171]. PTT destroys pathological tissues without damaging normal tissues and has the advantages of high selectivity, low drug resistance, and low side effects, which enables local non-invasive treatment of solid tumors [172,173].

The overexpression of P-glycoprotein (P-gp) is one of the main causes of multi-drug resistance (MDR) in cancer cells, and stimuli-responsive nanomedicines can bypass P-gp and overcome MDR to some extent. Ding et al. prepared a NIR-responsive NO-releasing peptide nanocomposite, PNOC-PDA, using PNOC obtained from the coupling of poly(L-cysteine)$_{20}$-poly(ethoxymethylene)$_{45}$(PC) to the thermos-sensitive NO donor SnO, and then wrapping bionic polydopamine (PDA) around the peptide micelles [174]. It was able to convert absorbed NIR light into heat and release NO to optimize CT. The high intracellular concentration of NO gas could promote the eradication of cancer cells by PTT, realizing the synergistic effect of mild PTT, NO gas therapy, and CT, and improving the therapeutic effect. In addition, the expression level of P-gp in MCF-30/ADR cells under different conditions was measured by protein blotting, and compared with the control group, the expression level of P-gp in the cells treated with PNOC was significantly reduced, indicating that the released NO gas could effectively inhibit the expression of P-gp in MCF-30/ADR cells and reduce the MDR.

In addition, Sun et al. constructed hybrid NPs for pH/reduction-responsive bimodal imaging [175]. As shown in Fig. 12c, hollow mesoporous copper sulfide NPs (HCuS) were coupled with a fluorescently labelled amphiphilic copolymer (fPEDC) loaded with a targeting molecule peptide-drug coupling (cRGD-SMCC-DM1, PDC) to form a nano-complex with targeted therapeutics (PDC/P@HCuS). Under NIR irradiation, the PDC/P@HCuS exerted excellent fluorescence and photoacoustic imaging properties. Induced by pH and redox stimulation, the PDC/P@HCuS successfully induced drug release at the tumor site,

realizing dual-modal imaging and combined PTT/CT of tumor, which is promising in image-assisted cancer therapy.

Recently, Lin et al. designed a dual pH/photo-responsive nano-diagnostic agent based on melanin-encapsulated magnetic NPs (MMNs) and introduced RGD peptide, DOX, and indocyanine green (ICG) for biologically/physically dual-targeted treatment of U87 MG tumors (Fig. 12d) [176]. Under the influence of external magnetic field and RGD, the nano-diagnostic agents accumulated at the tumor site, enhancing photoacoustic imaging/MRI as well as PTT. In addition, targeted release of DOX and ICG was achieved under the influence of NIR light illumination as well as the acidic microenvironment of the tumor. Both *in vivo* and *in vitro* experiments demonstrated the complete ablation of U87 MG tumor cells by this dual stimuli-responsive nano--diagnostic agent with low recurrence rate and biotoxicity, achieving synergistic effect of PTT and CT.

5.5. Antibacterial/antimicrobial biomaterials

With the rapid development of nanotechnology, nanomedicines show great advantages in antibacterial applications, such as improving the bioavailability of drugs, reducing side effects, and inhibiting the formation of biofilms, reducing bacterial resistance, *etc.* [177]. And the stimuli-responsive nanomaterials largely improved the effectiveness of biocides [178].

Chronic lung infections caused by bacterial biofilms are the main cause of death in cystic fibrosis (CF) patients, with *Pseudomonas aeruginosa* being the main bacterial source [179]. In order to reduce bacterial biofilm resistance and better drug penetration, Gao et al. designed a cluster NP (AZM-DA NP) encapsulating azithromycin (AZM) through electrostatic interactions [180]. When the NPs reached the infected lung tissues, they were decomposed by the acidic microenvironment, and the positively charged PAMAM-NPs were released, which could effectively improve the permeability of the bacterial biofilm and enhance the internalization of AZM. Therefore, AZM-DA NPs were a promising anti-biofilm nanoplatform with better antibacterial activity than free AZM and were able to slow down the development of bacterial resistance.

For better biofilm removal and accelerated healing of chronic wounds, Wang et al. designed a pH-responsive antibacterial hydrogel based on octapeptide (IKFQFHFD) [181]. In addition, the photothermal agent cypate and the pre-collagen component proline were added to the hydrogel to form a nanofiber network. Upon reaching the vicinity of the infected tissue, the hydrogel dissociated IKFQFHFD with an antibacterial peptide (ABP) molecular structure in an acidic environment, and the loaded cypate could be released on demand in the pathological environment of chronic wounds to disrupt the extracellular polymeric substances (EPS), which produced PTT under NIR (808 nm) in irradiation to achieve a better biofilm removal effect. Proline could promote the formation of collagen and ECM as well as cell proliferation and angiogenesis, achieving rapid healing of chronic wounds (Fig. 13a). This method realized the synergistic effect of antibacterial hydrogel, PTT, and proline, which hold great potential in antibacterial and accelerated chronic wound healing.

Short antibacterial cycles of PTT can exhibit excellent broad-spectrum antibacterial capacity for the efficient treatment of multidrug-resistant (MDR) bacterial infections. Du et al. introduced a photothermite (cypate) into a functionalized probe with gelatinase response for NIR fluorescence imaging and localized PTT of methicillin-resistant *Staphylococcus aureus* (*MRSA*) infections (Fig. 13b) [182]. The nanoprobe (named AUNS-APT-Cy) was centered on a photothermal gold nanostar (AuNS) of the heptapeptide CPLGVRG-Cy complex and *MRSA*-recognizable aptamer (APT). The ATP enabled the nanoprobe to be targeted to reach the *MRSA*-infected microenvironment, and in the presence of gelatinase, Cy with its photothermal effect and NIR properties would cleave the peptide CPLGVRG and turn on NIR fluorescence imaging *in-situ*. Therefore, the designed nanoprobe could be targeted to

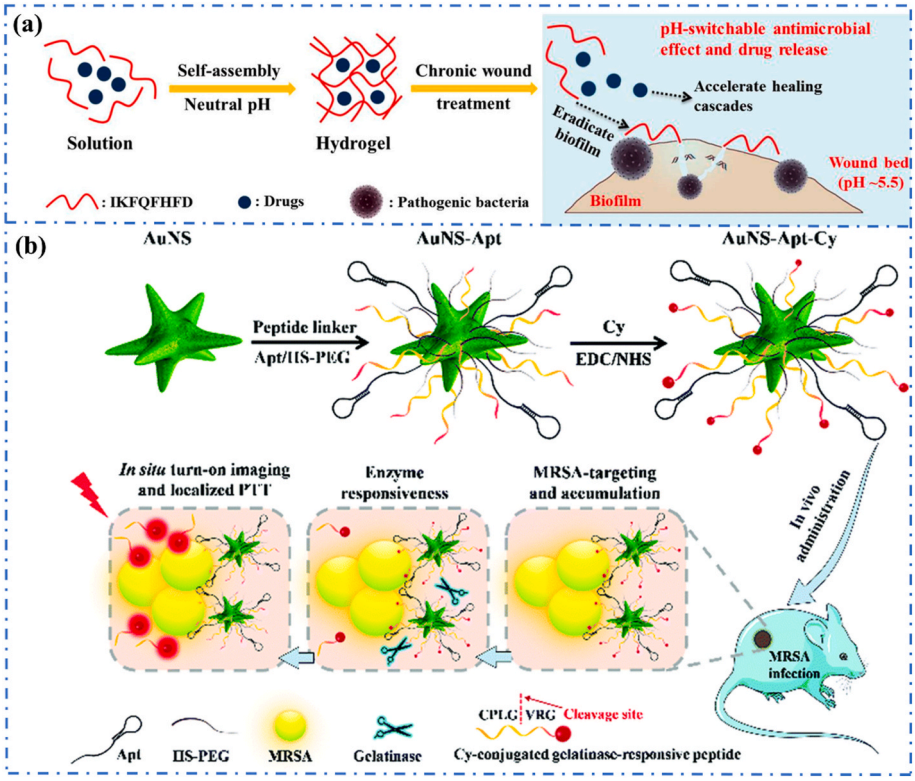


Fig. 13. Antibacterial applications of SRPNs: (a) pH-induced antimicrobial IKFQFHFD nanofiber networks for wound healing [181]. **(b)** AuNS-Apt-Cy nanoprobes for in-situ fluorescence imaging and localized PTT for MRSA infection [182]. Adapted with permission [181], Copyright 2019, American Chemical Society; adapted with permission [182],Copyright 2020, Royal Society of Chemistry.

accumulate at the *MRSA* infection site, which reduced the thermal damage to healthy tissues and achieved *MRSA*-specific therapy and localized PTT.

Based on the good biocompatibility and spectral antibacterial properties of ABPs, and the photothermal activity of PDA Andoy et al. designed an antibacterial agent based on PDANPs and an ABP (CWR11), which targeted and killed bacteria through multiple coordinated mechanisms [183]. Upon reaching the bacterial location, NIR laser stimulation induced localized heating of the PDANP-CWR11 nanosystems to kill the bacteria, and the adverse effects on the surrounding healthy tissue cells were reduced by lowering the critical temperature for bacterial inactivation. In addition, the morphological results showed that the PDANP-CWR11 nanosystems revealed excellent properties of specifically targeting to disrupt the mechanical integrity of the outer membrane of *E. coli*.

5.6. Wound healing

In general, wound healing is a complex long-term biological process characterized by multiple phases, including hemostasis, inflammation, proliferation, and tissue remodeling [67]. Chronic wounds that are not treated in a timely manner have a high morbidity rate, and in severe cases can even lead to patient death [184]. Highly biocompatible SRPNs have the ability to self-assemble and change in structure in response to the physiological environment. They enable functionalized control at different stages of wound healing and facilitate wound treatment.

Diabetic wounds are difficult to heal due to excessive oxidative stress and persistent inflammation. To promote diabetic wound healing and skin regeneration, Shi et al. prepared a micelle with the ability to transform the oxidative wound microenvironment into a regenerative microenvironment (P311@PEPS) [185]. The P311@PEPS was synthesized based on the self-assembly of P311 peptide and PEG-block-poly (propylene sulfide) (PEPS), which is ROS-responsive. Excess intracellular ROS stimulated the sustained release of P311 peptide from this micelle, which attenuated the inflammatory response as well as accelerated epidermal cell migration. This study provides a simple and efficient ROS-responsive SRPN system for wound healing.

In another work, Wang and co-workers developed an injectable ABP hydrogel (named as FHE), which is self-healing and thermo-sensitive (Fig. 14a) [186]. FHE consists of a reaction of peptide (ε-poly-L-lysine, EPL), oxidized sodium hyaluronate (OHA), and Pluronic F127 (F127), and was gel-forming at 37 °C, which could be used to deliver bioactive exosomes. Adipose mesenchymal stem cell exosomes (AMSCs-exo) were loaded into the hydrogel by electrostatic interaction with EPL. In a weakly acidic environment, the Schiff base bond was broken and exosomes were released. The *in vivo* and *in vitro* experiments demonstrated that the FHE@exo hydrogel accelerated the cell proliferation and migration, promoted angiogenesis, and exhibited potent skin regeneration compared to FHE or exosomes alone. This study provides a new idea of controlled-release exosomes and the application of responsive hydrogel for synergistic repair of chronic wounds.

Adhesive functionalized hydrogels are considered for the treatment of endometrial injury. Xu et al. prepared a series of thermo-sensitive, adhesive hydrogels based on heparin-modified poloxamer (HP) and EPL [187]. The hydrogels were used to encapsulate the cell growth factor, KGF, to repair damaged endometrium (Fig. 14b). By adjusting the EPL content in the EPL-HP hydrogel, the rheological and adhesion properties could be altered. After a series of studies, the EPL-HP hydrogel containing 90 μg/mL EPL (EPL-HP-90) revealed strong adhesion and drug release ability. After 8 h of intrauterine administration treatment, more KGF was absorbed by the endometrium. After 3 days, the damaged endometrium was obviously well repaired. Therefore, the endometrial epithelial cells, glands, and vasculature were significantly enhanced after the treatment of damaged uterus with the KGF-EPL-HP-90 hydrogel. It has a great ability to repair the damaged uterus.

In another report, Suo and co-workers designed an AMP hydrogel based on HA [188]. This hydrogel was crosslinked by AMP (sequence: $KK(SLKL)_3KK$), which triggered the release of AMP upon acidic stimulation for the treatment of chronic wound infections (Fig. 14c). The

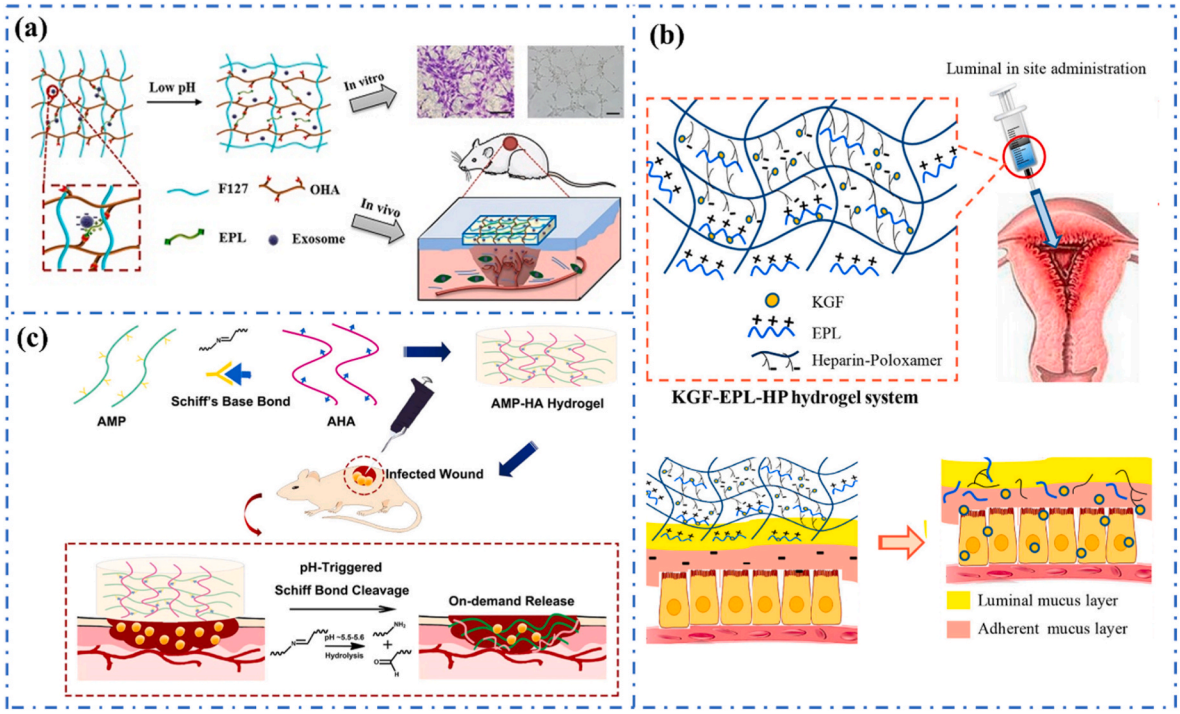


Fig. 14. Wound healing of SRPNs: (a) Thermo-responsive FHE/exosome hydrogels for diabetic wound healing [186]. **(b)** Thermo-responsive KGF-EPL-HP hydrogel for endometrial injury [187]. **(c)** pH-responsive AMP-HA hydrogel for wound healing [188]. Adapted with permission [186], Copyright 2019, Ivyspring International Publisher; adapted with permission [187], Copyright 2017, American Chemical Society; adapted with permission [188], Copyright 2021, American Chemical Society.

created AMP-HA hybrid hydrogel possessed higher mechanical strength and exhibited excellent antibacterial activity both *in vivo* and *in vitro*. This study opens up options for the development of functional wound dressings.

Suitable immunomodulatory biomaterials play a crucial role in tissue repair. In order to dynamically regulate the immune function of macrophages, Wang et al. designed a photo-responsive hydrogel nanocomposite based on HA, in which acrylated HA (HA-AC) macromolecular chains were used to encapsulate macrophages in an HA-based ECM by cross-linking with MMP cross-linking peptides (GCRDVPMSMRGGDRCG) [189]. The coupling of RGD peptides to HA-AC was realized in the presence of UV light. Photo-controlled RGD coupling activated macrophage αvβ3 integrins, which further enhanced the polarization of anti-inflammatory macrophages. This study presented a controlled pathway to promote tissue repair by modulating immune cells.

5.7. Wound dressings

Wound dressings are used to cover wounds and act as a physical barrier against external infection [190,191]. Traditional wound dressings, such as cotton gauze and bandages, have the advantage of economic and easy to handle. However, neoplastic cells and tissues adhere to them and frequent changes tend to cause secondary trauma and pain to patients [192,193]. Novel SRPNs can respond to different stimuli and make changes, revealing high biocompatibility and degradability as wound dressings. When combined with certain functionalized reagents, they can be dressed for different wounds and accelerate wound healing.

An ideal wound dressing should have excellent cytocompatibility and antibacterial properties. Rezaei and co-workers synthesized thermosensitive, antibacterial CS hydrogels by loading different concentrations of AMP (named AMP-TCTS) [194]. The formed hydrogel had a gel time of 15 min at 37 °C and could be used as an antibacterial wound dressing for humans. The experimental results showed that the AMP-TCTS hydrogel containing 16 μg/mL AMP exhibited strong antibacterial activity against both standard strains and drug-resistant *Acinetobacter baumannii*. This hydrogel has a high potential for use as a wound dressing against drug-resistant bacteria.

In recent years, 2-acrylamido-2-methylpropane sulfonic acid (AMPSA) with pH-dependent swelling behavior has been used for wound dressings. Malik and co-workers designed a highly absorbent hydrogel based on polyaspartic acid and AMPSA with glucose- and pH-sensitive properties [195]. Polyaspartic acid and AMPSA gave the hydrogel high water absorption properties, which were able to absorb and swell rapidly in acidic and alkaline environments. Therefore, in the environment of wound infection, the hydrogel as a wound dressing absorbed more bacterial exudates. In addition, in the treatment of skin healing, the hydrogel encapsulated the GHK-Cu peptide at a high rate of 72.8 % with a 24 h release rate of 88.46 %. This is an effective wound dressing for treating skin wounds and diabetes.

Furthermore, Wu et al. prepared a biodegradable and pH-sensitive peptide-based hydrogel loaded with triclosan for antibacterial wound dressing [196]. This pH-dependent swelling peptide-based hydrogel showed great potential for drug release and wound dressing applications compared to conventional biodegradable hydrogels.

In another report, Wang et al. developed a hydrogel with antibacterial and excess ROS scavenging capabilities [197]. The hydrogel consisted of $_{DL}$-dithiothreitol, PEG diacrylate (PEGDA), and phenylboronic acid-modified ε-polylysine (EPL-PBA), which were progressively mixed and then irradiated by blue light to generate a hydrogel *in-situ*. The addition of EPL-PBA gave the hydrogel better water absorption and antibacterial properties. In addition, the hydrogel could respond to excessive ROS. As a chronic wound dressing for diabetes, the hydrogel not only exhibited good biocompatibility and excellent antimicrobial properties, but also promoted the wound healing by modulating the inflammation and collagen deposition.

In the above sections, we presented some cases on using SRPNs for various biomedical applications. It is clear that the functionalization of peptide nanomaterials with different functional components enhanced the stimuli-responsive properties of materials, and promoted their wide applications that related to the stimuli-responses specifically. To make it more clear, we present a table (Table 3) to summarize these details of SRPNs in biomedical applications.

6. Clinical status of peptide nanomedicines

Currently, more than 80 peptide drugs are available on the market worldwide, about 150 peptide drugs are in the clinical development stage, and hundreds of other peptides are in the preclinical research stage. Notably, the first to be approved for clinical gene therapy was p53-based [198]. According to the report, more than half of people with cancer are caused by mutations or dysfunction of the p53 oncogene. Therefore, regulating and replacing the abnormal p53 gene is an effective way to treat cancer cells [199]. Chen et al. used disulfide bonds to cross-link CPP (CR_8C) and C-KLA (TPP) to synthesize a bifunctional peptide (xPolyR_8-KLA(TPP)) that efficiently concentrates the p53 gene for loading and delivery [200]. The xPolyR_8-KLA(TPP)/p53 complex was internalized, the disulfide bond was disrupted, releasing C-KLA (TPP) and p53 gene. Cancer cell apoptosis was induced through both C-KLA(TPP) and p53 gene pathways. The apoptosis and necrosis rate of cells cultured with xPolyR_8-KLA(TPP)/p53 was about 45.5 % compared with cells cultured with other vectors.

However, before peptide nanomedicines can be used in humans, a large number of clinical trials need to be put in place to test the tolerance of the human body to the drug as well as the actual effects of the drug. More than 2000 clinical trials have been conducted based on therapeutic peptides. For example, the BLP25 lipopeptide (STAPPAHGVTSAPDTRPAPGSTAPP) vaccine is MUC1-specific, and the L-BLP25 cancer vaccine has been evaluated in a phase III trial for the treatment of unresectable stage III non-small cell lung cancer [76]. Cell-penetrating peptide (CPP, D-JNKI-1) used to block the jun-N-terminal protein kinase (JNK) pathway has been shown to be an effective modality as a prophylactic and therapeutic treatment for acute cochlear injury. Patients with severe acute hearing loss treated with D-JNKI-1 had a significant therapeutic effect in the clinical trial mentioned in the report by Meyer et al. [201]. In clinical practice, the coupling of targeted peptides with chemotherapeutic agents and specific proteins has been rapidly developed. Mahalingam and colleagues developed a targeted prodrug (Mipsagargin) consisting of a peptide substrate specific for prostate-specific membrane antigen and 12ADT with TG [202]. Mipsagargin was evaluated for safety and the TG-targeting strategy was explored in clinical trials for the treatment of advanced solid tumors. The results of the clinical trials demonstrated that Mipsagargin was well tolerated and had excellent anti-tumor activity, and showed significant efficacy in the treatment of hepatocellular carcinoma.

In summary, many peptide-based nanomedicines have been developed with excellent experimental results in in vivo and *in vitro* experiments. Some peptide-based therapeutics have been approved by the U.S. Food and Drug Administration (FDA). Peptides as therapeutic agents have attracted widespread attention. In order to better apply peptide-based drugs in practice, multiple issues that may be encountered during clinical use need to be explored in depth. Therefore, the development of peptide nanodrugs with efficient clinical effects is still a very long way to go.

7. Conclusions and perspectives

In summary, we summarized recent advances in the molecular level design and controlled synthesis of stimuli-responsive peptides, and provided detailed discussions on the functional modulation of SRPNs. Different arrangements of amino acids provide diversity in peptide design. Meanwhile, the abundant amino acid side chains provide the

Table 3
SRPNs for biomedical applications.

Application	Peptide	Additive	Structure	Responsive	Ref.
Drug delivery	poly-l-lysine	Methoxy PEG	NPs	Redox/pH	[146]
	p(EK-co-C)	DOX	NPs	pH	[147]
	g-polyaspartic acid-tyrosine	methoxy PEG, Cysteine, and CaP	NPs	Redox/pH	[148]
	GRKKKRRQRRRPQ	Au NPs	NPs	Enzyme	[149]
	RGD, GNNNQNY	CPT	nanocluster	specific recognition	[150]
Bioimaging	Fc-YYGCGPGRC	–	NPs	pH	[153]
	DEVD, ST, and TD	DSPE-PEG, Pt	nanomicelle	pH	[155]
	RGDRDDRDDPLGYLGFFC(Cy)	–	NFs	Enzyme	[156]
	Fmoc-GPLGL	USPIO, PEG	NPs	Enzyme	[157]
Gene therapy	PLL-CA	Ang-RBCm, PEI,and siRNA	NPs	pH	[161]
	Angiopep-2	siRNA, PEG	NPs	ROS	[162]
	DS4-3	ssPEI, BI,DNA	NPs	GSH	[163]
	poly-l-lysine	DMMA,PEG, PEI-PBA, miR	NPs	pH	[1464]
PDT	$PHHPEG_6$	PEG	NFs	pH	[168]
	GPLGLAG	PEG, TCPP, and Mn^{2+}	NPs	Enzyme	[169]
	YGRKKKRRQRRR-GPLGVRG-EEEEEE	Ad, andβ-CD-CE6	NPs	Enzyme	[170]
PTT	poly(l-cysteine)	PDA, SnO, polyoxyethane	Nanocells	Light	[174]
	cRGD	HCuS, and fPEDC	NPs	Redox/pH	[175]
	RGD	MMN, and ICG	NPs	Light/pH	[176]
Antibacterial/antimicrobial biomaterials	poly-l-lysine	PAMAM, DA, and PEG	NPs	pH	[180]
	IKFQFHFD	Cypate and proline	Hydrogel	pH	[181]
	CPLGVRG-Cy	APT, AuNS and Cypate	Nanoprobes	Enzyme	[182]
	CWR11	Pd NPs	NPs	Light	[183]
Wound healing	P31	PEPS	Nanocells	ROS	[185]
	ε-Poly-l-lysine	OHA, and F127	Hydrogel	pH	[186]
	EPL	heparin-modified poloxamer	Hydrogel	Temperature	[187]
	$KK(SLKL)_3KK$	HA	Hydrogel	pH	[188]
	GCRDVPMSMRGGDRCG, RGD	HA-AC	Hydrogel	Light	[189]
Wound dressings	AMP	β-glycerolphosphate disodium salt pentahydrate, CS	Hydrogel	Temperature	[194]
	Polyaspartic acid, GHK-Cu	AMPS	Hydrogel	pH	[195]
	GGGGGGGK	AAC	Hydrogel	pH	[196]
	ε-Poly-lysine	$_{DL}$-dithiothreitol, PEGDA, and phenylboronic acid	Hydrogel	Light	[197]

basis for combining peptides with other materials. The stimulations of internal and external environment can trigger different structures and behaviors of peptides, which make it possible to synthesize SSRPNs, DSRPNs, and MSRPNs with different dimensions and specific stimuli-responses. In addition, in order to broaden the biomedical applications of SRPNs, special functional tailoring of SAP nanomaterials can be achieved by using substances such as metals, nucleic acids, polysaccharides, PS, and other substances to couple with peptides. Given the functional tunability of SAP nanomaterials, they show promising applications in the fields of drug delivery, bioimaging, gene therapy, phototherapy, antimicrobials, as well as wound healing and dressing.

Although the design and preparation of SRPNs as well as their functional tailoring have been widely discussed and developed in the past years, their applications in biomedical fields still faces some challenges. Here we would like to give some suggestions. Firstly, it is particularly important to develop simple, green, and controllable PSA platforms for the preparation of functionalized SRPNs from the perspective of synthetic methodologies. Secondly, although peptides have good biocompatibility, for *in vivo* applications, peptides need other chemicals for the modification due to the complex physiological environment. Therefore, the biocompatibility and the stability of SRPNs *in vivo* need to be evaluated and tested in the long term. Thirdly, despite the low cytotoxicity of peptides, chemicals coupled to peptides may have an impact on normal tissue and cell survival. Thus, designing SRPNs still requires further studies on their biodegradation and the toxicity of the degraded products to ensure a stable safety profile in the human body. Fourthly, there are needs to enhance the exploration of the PSA behavior in cancer cells, which will be beneficial to gain useful insights into the intelligent transformation of SRPNs in specific environments *in vivo*. Fifthly, at this stage, mature methods and technologies for real-time feedback of the PSA process *in vivo* and real-time monitoring of cancer therapy are still lacking. SRPNs were drug-loaded via covalent and non-covalent modalities. In order to promote cell internalization and tumor site accumulation, it is necessary to create more active sites and enhance their targeting ability of SRPNs. Finally, due to the complexity of the TME, more specific stimuli-responsive mechanisms must be developed to improve the safety and therapeutic efficiency of SRPNs for effective and clinical cancer therapy.

Declaration of competing interest

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

Ethics Approval and Consent to Participate

☒The authors declare that they have no known conflict of interests.

Declaration of interests

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

CRediT authorship contribution statement

Rongqiu Mu: Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Danzhu Zhu:** Writing – review & editing, Writing – original draft, Visualization, Conceptualization. **Sama Abdulmalik:** Writing – review & editing, Writing – original draft. **Suranji Wijekoon:** Writing – review & editing, Writing – original draft.

Gang Wei: Writing – review & editing, Writing – original draft, Visualization, Supervision, Funding acquisition, Conceptualization. **Sangamesh G. Kumbar:** Writing – review & editing, Writing – original draft, Visualization, Funding acquisition, Conceptualization.

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