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Tumor Microenvironment-responsive Self-immolative Polymers for Cancer Imaging and Therapy

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Abstract Self-immolative polymers (SIPs) have recently emerged as a distinct class of stimuli-responsive materials that undergo programmed domino-like degradation in response to specific biochemical triggers. The unique biochemical characteristics of the tumor microenvironment (TME) include acidic pH, elevated glutathione (GSH) levels, excessive reactive oxygen species (ROS), dysregulated enzymes, and hypoxia. TME-responsive SIPs have attracted significant attention for precise cancer imaging and therapy. By integrating labile linkages and modular structural design, these polymers can amplify weak biochemical signals into robust responses, enabling controlled drug release, signal amplification in imaging, and multifunctional theranostics. Compared with conventional responsive systems, SIP-based nanoplatforms offer enhanced sensitivity, tunable degradation kinetics, and the potential for sequential or cascade activation. In this review, we provide a comprehensive overview of the design principles, activation mechanisms, and functional applications of TME-responsive SIPs. We highlight representative strategies for their use in targeted drug delivery, tumor imaging, and synergistic therapeutic approaches and discuss the incorporation of emerging modalities such as near-infrared II (NIR-II) imaging and combination immunotherapy. Finally, we outline the major challenges and opportunities for advancing SIP-based nanomedicines for clinical translation and offer perspectives on how this rapidly evolving field may reshape the future of precision cancer diagnosis and treatment.

Keywords Tumor microenvironment; Self-immolative polymers; Stimuli-responsive polymers; Drug delivery systems; Theranostics; Cancer therapy

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1 INTRODUCTION

Cancer continues to pose one of the greatest global health concerns, necessitating the development of effective diagnostic and therapeutic approaches to improve treatment efficacy and patient survival. Despite advances in chemotherapeutics, immunotherapy, and imaging technologies, many anticancer agents are not clinically translated owing to systemic toxicity, poor pharmacokinetics, limited tumor selectivity, and inadequate accumulation at disease sites.[1] To overcome these challenges, several nano-based delivery systems have been ex-

plored for cancer imaging and therapy, including liposomes,[2] polymer micelles,[3] dendrimers,[4] inorganic nanoparticles,[5] and polymer-drug conjugates.[6] However, each class of carrier presents intrinsic limitations, such as instability, cytotoxicity, poor biodegradability, and unpredictable drug release, which limit their long-term clinical utility.[7] In this context, self-immolative polymers have emerged as a distinct class of stimuli-responsive materials that undergo controlled cascade depolymerization in response to specific biochemical or physiological triggers. When engineered to respond to the unique biochemical features of the tumor microenvironment (TME), such as acidic pH, elevated glutathione (GSH), reactive oxygen species, or enzyme overexpression, self-immolative polymers (SIPs) enable highly selective spatiotemporally regulated drug and probe release.[8,9] The ability to deliver precise therapeutics along with real-time imaging makes TME-responsive SIPs a transformative cancer theranostics platform.

A tumor microenvironment is crucial for cancer progression, therapeutic resistance, and metastasis.[10] Compared to healthy tissues, tumors exhibit a unique biochemical and biophysical milieu characterized by acidic extracellular pH, elevated levels of GSH and reactive oxygen species, hypoxia, abnormal enzyme activity, and a dense extracellular matrix.[11,12] These hallmarks not only facilitate tumor survival and immune evasion but also provide exploitable triggers for designing smart delivery systems. Harnessing TME-specific cues can facilitate localized activation of therapeutic agents, reduce systemic toxicity, and improve therapeutic efficacy and imaging precision.[13] Although conventional nanocarriers have been adapted with responsive linkers and coatings to exploit these advantages, their responses are often incomplete or suffer from premature leakage and limited control over the release kinetics. Owing to their unique end-to-end depolymerization mechanism, self-immolating polymers provide an amplified and highly controlled release profile, which makes them ideal for TME-responsive theranostic applications.[14]

SIPs have emerged as a distinct subclass of stimuli-responsive materials in this rapidly evolving field. After a single triggering event, SIPs are programmed to undergo cascade depolymerization from end to end rather than responding in a stoichiometric manner.[8] By amplifying weak stimuli, self-immolation achieves efficient signal amplification, sustained drug release, and highly sensitive imaging. Under physiological conditions, SIPs retain structural integrity but disassemble completely upon stimulus activation, thus influencing spatiotemporal release profiles in an unprecedented manner.[15] These properties uniquely position SIPs as chemical amplifiers within the tumor milieu, amplifying subtle TME cues for therapeutic and diagnostic effects. In recent years, tumor microenvironment-responsive SIPs have demonstrated remarkable potential in both cancer imaging and therapy. By tailoring their end-cap motifs, backbone chemistry, and degradable linkages, researchers have developed systems capable of tumor-selective activation, controlled drug release, real-time imaging, and synergistic theranostics.[16] These advances highlight the versatility of SIPs in overcoming long-standing barriers such as poor drug stability, inefficient tumor accumulation, and limited imaging sensitivity.

In this review, we highlight the recent advances in the design and application of TME-responsive self-immolative polymers for cancer imaging and therapy. First, we summarize the fundamental design principles and triggering mechanisms governing self-immolative depolymerization. We then describe how different TME triggers, such as pH, reactive oxygen species (ROS), GSH, H_2S, and enzymatic activity, were harnessed to achieve tumor-selective activation. Particular emphasis was placed on strategies that integrate therapeutic payloads and imaging agents within a single SIP-based platform to enable spatiotemporally controlled cancer theranostics. Finally, we outline the current challenges, translational considerations, and future directions required to enhance the clinical realization of SIP-based nanotheranostics (Fig. 1).

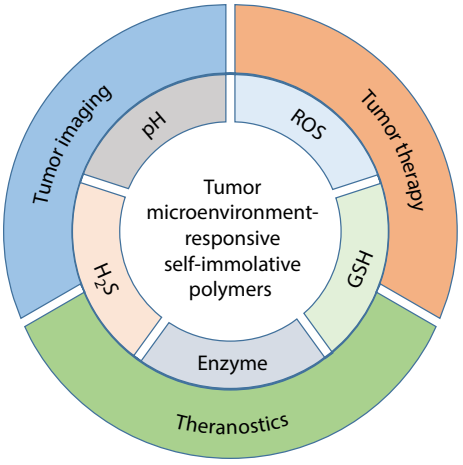

Fig. 1 Schematic representation of TME–responsive self-immolative polymers (SIPs), where pH, ROS, H_2S, and enzyme triggers induce cascade depolymerization, enabling amplified tumor imaging, controlled drug release for tumor therapy, and integrated theranostic applications.

2 DESIGN PRINCIPLES OF TME-RESPONSIVE SELF-IMMOLATIVE POLYMERS

The core design of TME-responsive SIPs involves matching the molecular trigger to a specific biochemical cue in the tumor milieu, such as acidic pH, elevated ROS or GSH, aberrant H_2S levels, or overexpressed enzymes, to achieve selective depolymerization within malignant tissues.[17–20] For pH-responsive SIPs, acid-labile motifs, such as hydrazone, *cis*-aconityl, acetal/ketal, or *ortho*-ester linkages, are often incorporated as terminal or pendant triggers that undergo hydrolysis or protonation-driven rearrangement in the mildly acidic extracellular tumor space (pH=6.0–7.0) or within endo/lysosomal compartments (pH=5.0–6.0).[21,22] ROS-responsive SIPs exploit the overproduction of hydrogen peroxide and peroxynitrite in tumors by embedding thioketal, boronic ester/boronate, or thioether groups that undergo oxidative cleavage to unmask the self-immolative unit and propagate head-to-tail depolymerization.[23,24] By contrast, GSH-responsive SIPs leverage the high intracellular reductive potential of tumors (up to 10 mmol/L cytosolic GSH) using disulfide, diselenide, or telluride linkages that are rapidly cleaved by thiol-disulfide exchange, releasing the capping group and initiating depolymerization cascades.[25,26] Enzyme-

responsive SIPs use peptide or ester substrates tailored to tumor-overexpressed proteases (*e.g.*, matrix metalloproteinase-2 (MMP-2), matrix metalloproteinase-9 (MMP-9), cathepsin B (CTSB), and legumain) or esterases; cleavage of these peptide/ester linkers at the polymer terminus unlocks the self-immolative backbone.[27,28] Finally, hypoxia-responsive SIPs employ azo-, nitroimidazole-, or quinone-based triggers that are reductively cleaved by hypoxia-inducible nitroreductases or one-electron reductases in oxygen-deficient tumor cores, thus selectively releasing the depolymerization initiator in hypoxic regions.[29]

A successful SIP integrates these stimulus-labile triggers with an electronically tuned self-immolative backbone (*e.g.*, poly(benzyl carbamate), poly(quinone methide), or poly(thiocarbonate)) to ensure rapid domino-type depolymerization after trigger activation, while maintaining kinetic stability at physiological pH=7.4. Fine control over the electronic properties of the linker, such as electron-withdrawing substituents to accelerate β-elimination), steric environment, and polymer hydrophilicity/hydrophobicity modulate both the degradation rate and bio-distribution.[30–33] Moreover, the heterogeneity of TME features often necessitates multi-responsive or cascade-activation SIPs, in which orthogonal triggers, such as pH, ROS, enzymes, or hypoxia, act sequentially or synergistically to improve activation specificity while minimizing off-target degradation.[34] These strategies illustrate how a deep understanding of TME pathophysiology can be directly translated into rational molecular designs for SIPs that achieve precise tumor-selective activation, predictable depolymerization kinetics, and improved therapeutic indices.

2.1 Molecular Structure and Self-degradation Mechanism

Self-immolative polymers are architecturally programmed macromolecules composed of repeating "self-immolative units" that remain kinetically stable until unmasked at a terminal end-cap.[8] Their molecular frameworks are poly(benzyl carbamate), poly(benzyl ether), poly(benzyl carbonate), hemiacetal-containing poly(phthalaldehydes), and more recently, metathesis-driven 1,6-enyne-based chains that feature nucleophiles or electron-donors bearing benzyl or heteroaryl motifs whose liberation triggers a cascade of head-to-tail bond scission.[35,36] Upon cleavage of the stimuli-responsive endcap (*e.g.*, by enzymes, pH, ROS, reductants, UV, or thermal triggers), the newly exposed aniline, hydroxyl, thiol, or alkene groups initiate stepwise transformations such as 1,6-aza-quinone-methide elimination, intramolecular cyclization–elimination, hemiacetal fragmentation, or metathesis-driven ring closures.[37,38] Each cleavage event liberates the next latent unit, driving head-to-tail depolymerization into discrete low-molecular-weight fragments, such as quinone-methides, CO_2, cyclic thiols, or bicyclopentene derivatives.[33] This one-stimulus-many-response behavior functions as a molecular amplifier, sharply contrasting with conventional degradable polymers, whose scission is random and stoichiometric. Recent innovations, including modular multi-stimuli "logic-gate" endcaps and post-polymerization click-installed termini/capes, have diversified SIP architectures and enabled precise spatial and temporal control over degradation kinetics.[39] This molecular programmability increases their involvement in biosensing activities, signal amplification, drug release systems, and materials with adaptive properties as well as bioimaging platforms.

2.2 pH-responsive SIPs

pH-responsive SIPs have emerged as a new generation of crucial stimuli-responsive materials for the controlled release of drugs, based on the capacity of the polymer chains to depolymerize *via* an end-to-end mechanism in the presence of a single environmental trigger.[40] As a result of the depolymerization mechanism of the polymer chains, efficient drug release is realized as the polymer chains are broken into smaller molecules. Owing to the progressive nature of the acidification pathway within the cellular compartment, pH-responsive SIPs are crucial for intracellular drug release.[41] The main disadvantage of the initial design of SIPs is the poor pH selectivity within the physiologically relevant pH range of 7.4 to 5.0.[42] The initial design of SIPs focused on modifying the end-cap reactivity. As a result of the initial design of SIPs, there were challenges with poor pH selectivity within the physiologically relevant pH range. Recent designs for pH-responsive SIPs have focused on the utilization of acid-labile motifs and self-immolative backbones.[43] As a result of the utilization of the acid-labile motifs and the self-immolative backbones within the design of pH-responsive SIPs, efficient release of the drug is realized as the bonds are broken *via* the pH-triggered mechanism.

Recent breakthroughs also show that the kinetics of depolymerization and stability of SIPs could be controlled in a fine manner through backbone and side-chain engineering. Thus, glyoxy-amide-based SIPs containing a series of tertiary amine side chains display efficient rates of depolymerization in mildly acidic environments while maintaining stability at physiological pH, thus facilitating efficient intracellular delivery of active payloads.[44] Gillies *et al*. reported pH-responsive self-immolative nanoparticles based on poly[*N*,*N*-(diisopropylamino)ethyl glyoxylamide-*r*-*N*,*N*-(dibutylamino)ethyl glyoxylamide], in which the disassembly threshold (pH=7.0–5.0) could be precisely regulated by pendant amine composition. These nanoparticles remained stable in circulation, but underwent rapid depolymerization (about 60%–80% within 2 h) under acidic conditions, resulting in effective peptide release and enhanced endosomal escape.[45] Mechanistically, protonation of tertiary amine pendants at mildly acidic pH destabilizes the polymer backbone, facilitating end-cap cleavage and subsequent 1,6-elimination along the glyoxylamide units. This cascade depolymerization resulted in rapid nanoparticle disassembly and synchronized peptide release, demonstrating the kinetic advantages of self-immolative systems over conventional acid-labile carriers.

Beyond pH responsiveness, multifunctional SIPs have been developed to integrate tumor-associated biochemical cues. Tumor-acidic-milieu-responsive self-immolative amphiphilic poly(ferrocenes) undergo complete depolymerization to form cascade-release glutathione-depleting azaquinone methide and aminoferrocene, thereby amplifying intracellular oxidative stress and effectively inhibiting tumor growth *in vitro* and *in vivo* (Fig. 2).[46] Furthermore, by integrating phenylboronic acid ester and ferrocene units into a single amphiphilic backbone, these nanoparticles translate elevated intratumoral oxidative stress into a self-propagating degradation process that amplifies local pH modulation and reactive oxygen

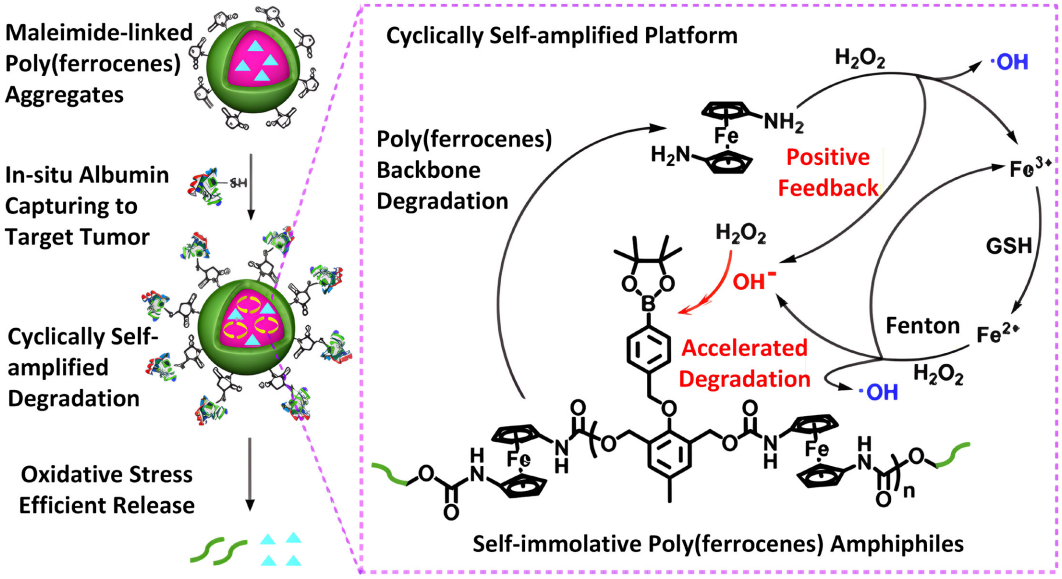

Fig. 2 pH-responsive SIP nanoplatforms that undergo acid-triggered end-cap cleavage in the TME, initiating cascade depolymerization and amplified therapeutic release (Reproduced with permission from Ref. [46]; Copyright (2023), American Chemical Society).

species production, leading to selective tumor accumulation, accelerated cargo release, and superior antitumor performance *in vivo*.[46]

2.3 ROS-responsive SIPs

The increased levels of ROS within the tumor environment act as a specific trigger for activating ROS-sensitive SIPs through traceless depolymerization and the effective release of cargo into cells.[47,48] Hydrogen peroxide (H_2O_2), one of the major ROS species, is typically present in tumor tissues at concentrations of approximately 50–100 μmol/L, which are higher than those in normal tissues. Depending on the ROS-sensitive motif used in the design, ROS-sensitive SIPs are divided into two classes: sulfur-based and sulfur-free systems. The use of sulfur-based bonds, including thioacetal, ketal, thioether, selenium, and diselenide groups, leads to the depolymerization of these systems upon exposure to ROS or oxidative stress (commonly ≥50 μmol/L H_2O_2 under tumor-relevant conditions). This leads to the destabilization of these drug delivery systems and effective release of cargo into cells. Selenium-based bonds are more sensitive to ROS and are preferred over their disulfide-based counterparts because of their lower bond dissociation energies.[49] The use of aryl- or benzyl-boronic ester-based bonds and peroxalates leads to the depolymerization of these systems upon exposure to ROS and oxidative stress.[50–52] The use of these bonds leads to depolymerization of these systems.

Recent studies have shown that ROS-responsive SIPs hold great promise for intensifying ROS-mediated oxidative damage and disrupting redox homeostasis in the TME in an unprecedented manner. The ROS-activatable self-immolative mitoxantrone prodrug was shown to exhibit ROS-mediated activation under tumor-relevant ROS levels (≥50 μmol/L H_2O_2) and self-amplified fragmentation of the tumor backbone, resulting in specific drug delivery and ROS amplification to enhance chemotherapy efficacy while reducing side effects.[53] Upon oxidation of the ROS-sensitive linker, the terminal protecting group is cleaved, exposing an electron-donating unit that initiates head-to-tail depolymerization. This cascade process amplified drug release beyond stoichiometric cleavage, enabling enhanced intracellular mitoxantrone accumulation specifically under tumor-relevant oxidative conditions, while remaining relatively stable in normal physiological environments. Accordingly, ROS-responsive SIP prodrugs have been designed to combine ROS-mediated activation and self-propagating depolymerization to generate ROS and chemotherapy through positive feedback loops to induce irreversible redox imbalances and trigger cancer cell apoptosis.[54] Our group developed a ROS-responsive cinnamaldehyde-derived poly(thioacetal) that showed improved self-amplified shattering chain fragmentation to enhance ROS generation and immunogenic cell death (ICD) under oxidative conditions (about 100 μmol/L H_2O_2) to produce chemo-immunotherapy through improved activation of dendritic cells and cytotoxic T cells.[55] In addition, self-immolative polymer-based ICD inducers have recently proven to be highly potent candidates for cancer immunotherapy through modulation of the cellular redox status. Therefore, ROS-responsive SIPs represent the oxidative branch of redox-responsive systems discussed in this review.

Generally, these types of systems have been specifically designed to induce cascade depolymerization upon detection of tumor-related cellular oxidative and reductive environments, such as increased ROS (50–100 μmol/L H_2O_2) and glutathione levels (2–10 mmol/L intracellularly). This increases oxidative stress in cancer cells. This self-immolative reaction is expected to induce the rapid release of ICD inducers, leading to further disruption of mitochondria, increased ROS production, and the release of damage-associated molecular patterns (DAMPs) such as calreticulin and high mobility group box 1 (HMGB1). As a result, cancer cells undergo immunogenic apoptosis, while dendritic cells mature and cytotoxic T cells become activated (Fig. 3).[56] In summary, these studies show that self-immolative polymers can combine precise redox regulation with immune activation, providing a promis-

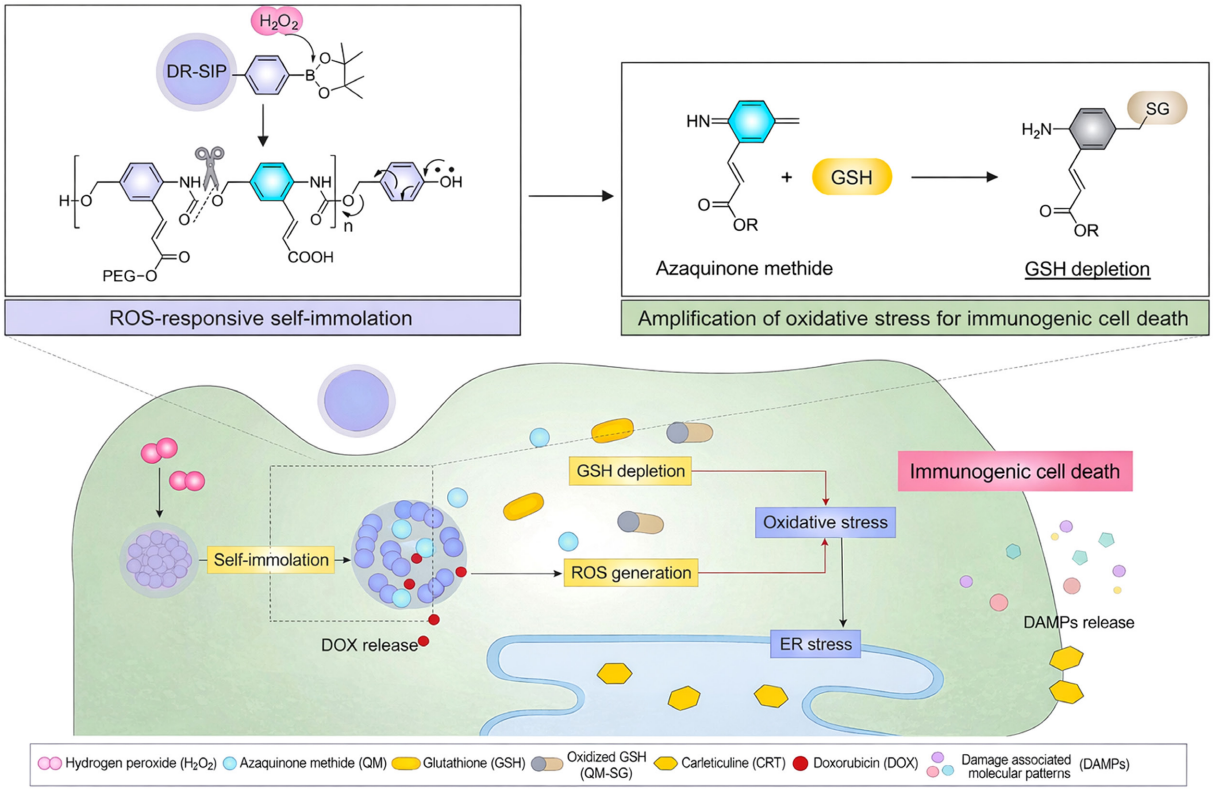

Fig. 3 An ROS-responsive SIP enables cascade depolymerization, redox amplification, and enhancement of anticancer efficacy by translating elevated intratumoral ROS into oxidative stress (Reproduced with permission from Ref. [56]; Copyright (2023), Elsevier).

ing platform for synergistic cancer immunotherapy. Here, ROS-responsive systems correspond to oxidative redox triggers, whereas GSH-mediated activation is discussed separately as the reductive (GSH-responsive) branch in the next section.

2.4 GSH-responsive SIPs

Intracellular glutathione (GSH), which is typically elevated 2–10-fold in many solid tumors relative to normal tissues, is a key reducing metabolite that drives redox homeostasis and frequently contributes to multidrug resistance (MDR) by detoxifying reactive species and promoting drug efflux. GSH-responsive SIPs represent the reductive branch of redox-responsive systems, in which thiol-mediated activation is primarily driven by intracellular glutathione. Intracellular GSH concentrations in tumor cells are generally in the range of 2–10 mmol/L, whereas extracellular levels are typically <10 μmol/L. SIPs platforms have exploited this biochemical hallmark to achieve selective activation of tumor cells.[57] The most widely used motif is the disulfide linkage, which undergoes rapid thiol-disulfide exchange with cytosolic GSH, typically at concentrations of 5–10 mmol/L, triggering main-chain depolymerization or cleavage of pendant linkers, thereby releasing conjugated drugs or imaging probes. For example, poly(disulfide)-based prodrugs can simultaneously scavenge intracellular GSH and unleash the active drug payload. Our group has designed an amphiphilic doxorubicin (DOX)-conjugated poly(disulfide) (PSSD) whose dense S—S bonds consume intracellular GSH, disrupt redox balance, and promote cascade depolymerization-assisted DOX liberation in MDR breast-cancer models, with depolymerization observed under 10 mmol/L GSH conditions within approximately 30–60 min, leading to significantly reduced IC_{50} values and pronounced tumor growth inhibition *in vivo*.[58]

Furthermore, recent advances have demonstrated that redox-responsive self-immolative polyprodrugs can exploit intracellular GSH and oxidative stress for cascade-amplified cancer therapies. In this context, the term "redox-responsive" refers to systems integrating both oxidative (ROS-mediated) and reductive (GSH-mediated) activation mechanisms. Yuan *et al*. reported a dual-polymer system in which a ROS-degradable poly(thioacetal) polyprodrug containing cinnamaldehyde-depleted GSH (within the 2–10 mmol/L intracellular range) elevated oxidative stress, thereby amplifying endogenous ROS levels. This redox amplification subsequently triggered head-to-tail depolymerization of a second ROS-responsive self-immolative polyprodrug, enabling efficient doxorubicin release and resulting in pronounced antitumor efficacy in murine models.[59] Xu *et al*. reported the synthesis of an amphiphilic, ferrocene-grafted self-immolative block copolymer prepared through a polycondensation strategy followed by post-polymerization functionalization (Fig 4). In their design, an acid-responsive trigger enabled the polycondensation of a side-chain-linked ferrocene monomer, after which an isocyanate-terminated poly(ethylene glycol) (PEG) segment was introduced to yield the amphiphilic self-immolative polymer. Under acidic conditions (pH=6.5–6.8, representative of the tumor extracellular environment), the polymer undergoes degradation *via* a cascade self-immolation process, leading to the formation of azaquinone methide (AQM) intermediates, concurrent release of ferrocene, and payload libera-

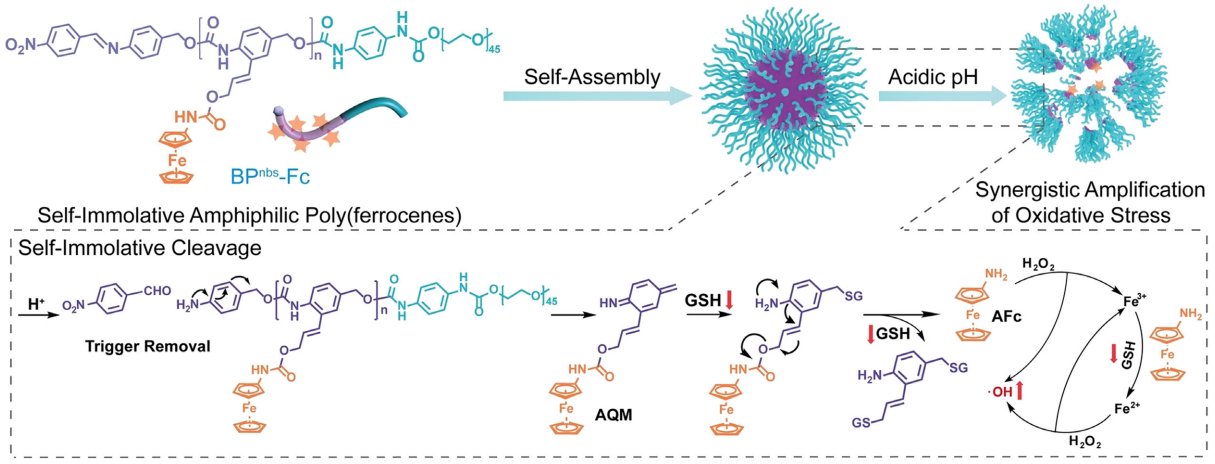

Fig. 4 SIP systems that deplete glutathione by inducing intracellular reduction of disulfide or related linkages, and trigger amplified drug release to overcome multidrug resistance (Reproduced with permission from Ref. [44]; Copyright (2023), Wiley-VCH GmbH).

tion. The generated AQMs consumed intracellular glutathione (GSH), whereas ferrocene participated in Fenton-like reactions with endogenous hydrogen peroxide, typically present at 50–100 μmol/L in tumor tissues, collectively inducing ferroptotic cell death in cancer cells. Significant tumor growth inhibition was demonstrated *in vivo* using the developed polymer system in 4T1 tumor-bearing mice.[44] A number of biomedically relevant self-immolative polymers, including poly(benzyl carbamate), poly(benzyl carbonate), and polyglyoxylate, were developed by Gillies *et al*., showing that hydrophobic core properties play a critical role in aqueous stability, drug loading, and cytotoxicity.[8,60,61] GSH-associated redox modulation has been demonstrated to be a promising strategy for designing smart self-immolating polymer therapeutics.

Mechanistically, GSH-responsive SIPs act not only as stimulus-triggered depots but also as redox modulators; by locally depleting GSH, they amplify oxidative stress and can resensitize resistant tumors to chemotherapy, creating synergistic effects when combined with ROS-generating agents, photodynamics, or radiotherapy.[54] Current challenges include balancing linker stability in the blood versus rapid intracellular cleavage, optimizing hydrophobic/hydrophilic block design for high loading and endosomal escape, and translating these redox-triggered depolymerizable systems into scalable, clinically safe formulations. Overall, the combination of self-immolative backbones with GSH-labile linkages represents a robust strategy to exploit tumor redox imbalance for precision imaging and combination therapy.

2.5 H_2S-responsive SIPs

The abnormal distribution of hydrogen sulfide (H_2S) as a pathological biomarker and signaling gasotransmitter is linked to cancer progression. Basal H_2S levels in tumor tissues are typically higher than those in normal tissues; however, the concentration is rarely sufficient to affect therapeutic outcomes or activate prodrugs effectively. In addition to detecting H_2S, SIPs that respond to H_2S are capable of enhancing their signal locally to trigger domino-like polymer degradation, allowing ultrasensitive imaging and potentiated therapy.

The poly(thiocarbamate)s used in this design are based on benzyl-thiocarbamates and are end-capped with triggers that are H_2S-cleavable. Upon nucleophilic attack by H_2S, the terminal capping group is removed, resulting in the release of carbonyl sulfide (COS), which is rapidly hydrolyzed to H_2S by the ubiquitous enzyme carbonic anhydrase (CA). Because of this feedback loop, the local H_2S concentration exponentially increased, accelerating the depolymerization of the PTC backbone into 4-aminobenzyl alcohol and PEG fragments. In our recent study, we engineered an amphiphilic variant (H_2S-PTC-PEG) that self-assembled into about 110 nm nanoparticles (SNP) capable of encapsulating either an H_2S-responsive hemicyanine fluorogenic probe (p-Cy) or an H_2S-activatable doxorubicin prodrug (p-DOX). The resulting SNP p-Cy achieved a detection limit of about 20 nmol/L for H_2S in buffer, which is seven-fold more sensitive than the free probe, permitting real-time visualization of orthotopic colorectal, liver, and lung metastatic lesions as small as about 2 mm and even submillimeter pulmonary micrometastases in mice. Parallel SNP p-DOX formulations exploited the surge of polymer-derived H_2S to disrupt mitochondrial cytochrome-c-oxidase and depress ATP production and efflux pump (P-gp) activity, thereby overcoming MDR and markedly suppressing the growth of MCF-7/ADR xenografts, lung metastases, and breast cancer patient-derived xenografts (Fig. 5).[62]

To further broaden tumor selectivity beyond endogenous H_2S abundance, we introduced a bioorthogonal pre-targeting click-activated SIP nanocarrier (CONP). In this two-step strategy, trastuzumab-tetrazine (T-Tz) first labels HER2-positive cancer cells and the subsequent systemic delivery of CONP composed of an isocyanide-capped PTC (NC-PTC-PEG) plus an H_2S-responsive amplifier polymer (NO_2-PTC-PEG)—undergoes cycloaddition with the surface-bound T-Tz, liberating COS that is enzymatically converted to H_2S. The burst of H_2S then triggers NO_2-PTC-PEG to depolymerize in a self-propagating fashion, producing further H_2S, thereby converting a sparse antigen signal into a robust chemical stimulus. This cascade enabled potent fluorescence recovery of a quenched $CyNO_2$ probe, high-contrast imaging of heterogeneous HER2-positive xenografts, and superior suppression of tumor growth when loaded with a doxorubicin prodrug while minimizing off-target toxicity.[63]

H_2S-responsive self-immolating polymers have emerged as

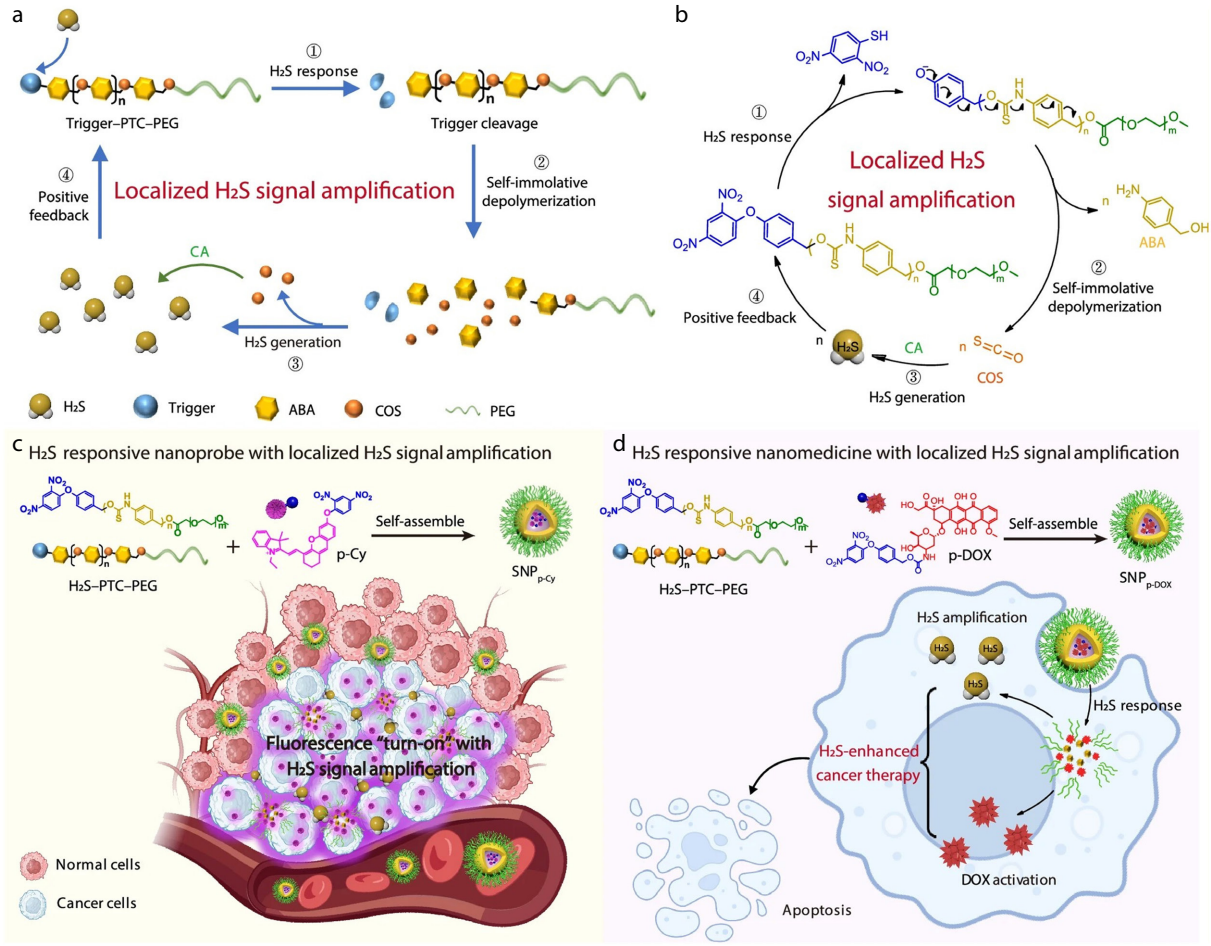

Fig. 5 H_2S-responsive SIP nanoplatform for tumor imaging and therapy. (a) H_2S-triggered end-cap cleavage initiates self-immolative depolymerization; (b) Released COS is converted into H_2S, enabling localized signal amplification; (c) p-Cy-loaded nanoparticles afford amplified fluorescence imaging; (d) p-DOX-loaded nanoparticles enable cascade-activated cancer therapy (Reproduced with permission from Ref. [62]; Copyright (2024), Springer Nature, CC BY-NC-ND 4.0).

promising macromolecular donors that can deliver gasotransmitters to specific sites in pathological microenvironments. An acrylate-caged poly(thiourethane) (PTU) self-immolating polymer was developed to initiate hydrogen sulfide release in the presence of Cys/Hcy, targeting biomarkers closely correlated with neurodegenerative diseases. Carbonyl sulfide (COS) is generated when Cys or Hcy is added to the PTU backbone, resulting in end-to-end depolymerization, which is then converted to H_2S by carbonic anhydrase. The polymer was self-assembled into biomimetic nanoparticles *via* CTAB-assisted self-assembly and coated with red blood cell membranes to make them more stable and biocompatible. When exposed to Cys/Hcy, these core-shell nanoparticles exhibited negligible hydrolytic degradation, but they rapidly depolymerized and released H_2S.[64] Importantly, controlled intracellular H_2S delivery effectively mitigated oxidative stress and mitochondrial damage in BV-2 microglial cells under Alzheimer's disease-relevant conditions. This study highlights the potential of pathology-responsive self-immolative PTU platforms as advanced macromolecular H_2S donors for neuroprotective applications.

2.6 Enzyme-responsive SIPs

Activity-linked labeling of enzymes using SIPs represents an emerging strategy for translating enzymatic activity directly into molecular signal amplification. Enzyme-responsive SIPs enable the direct conversion of enzymatic activity into amplified labeling signals through depolymerization cascades. Sahabat *et al.* reported activity-linked SIP probes, in which enzyme-mediated cleavage of terminal capping groups by penicillin G-amidase or the catalytic antibody Ab38C2 initiates end-to-end depolymerization, generating multiple reactive azaquinone methide intermediates that covalently label the active enzyme (Fig. 6). Following the enzymatic cleavage of the terminal capping group, the exposed aniline intermediate undergoes rapid 1,6-elimination, generating multiple azaquinone methide intermediates along the polymer backbone. Because each catalytic event triggers the depolymerization of the entire chain, significant signal amplification is achieved, ensuring that labeling reflects enzymatic activity rather than simple protein abundance. The system is inherently fluorogenic because enzymatic uncaging restores π-conjugation in the released aniline units, allowing fluorescence-based detection in conjunction with mass spectrometry.[65] Although background fluorescence from hydrolyzed intermediates remains a consideration, this work underscores the utility of enzyme-responsive SIPs as powerful plat-

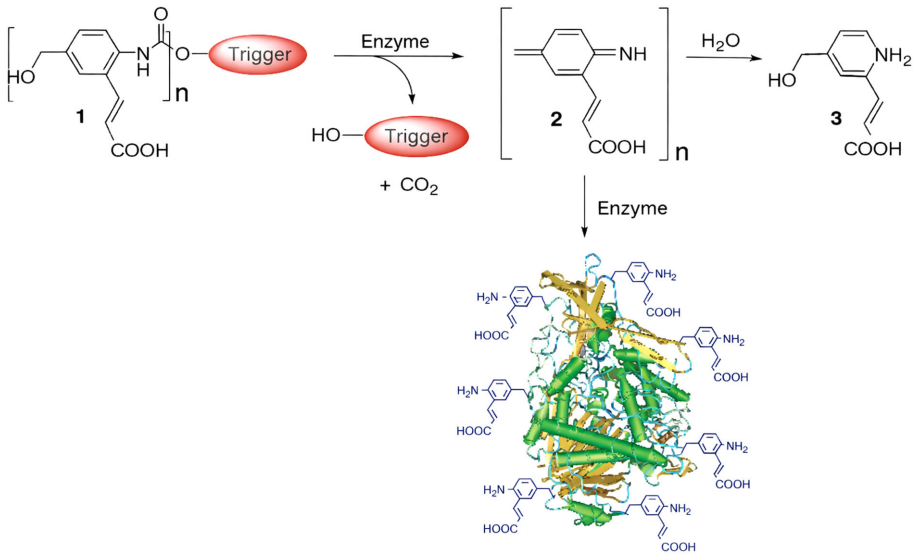

Fig. 6 SIPs with enzyme-dependent depolymerization triggered by tumor-associated enzymatic cleavage are capable of amplifying signals based on activity and selective release of payloads (Reproduced with permission from Ref. [65]; Copyright (2009), American Chemical Society).

forms for activity-based enzyme profiling and molecular signal amplification. In addition to enzyme profiling, aberrantly expressed enzymes within pathological microenvironments, particularly proteases such as matrix metalloproteinases, cathepsins, esterases, and γ-glutamyl transpeptidase, have been widely exploited to trigger SIP prodrugs and nanotheranostics with high spatial precision.[28,29] Typically, enzyme-cleavable linkers are incorporated to expose a triggering motif upon site-specific cleavage, initiating domino-like depolymerization or backbone disassembly that releases conjugated drugs, photosensitizers, or imaging agents.[66] This strategy enables rapid and efficient payload liberation under biologically mild conditions, while minimizing off-target toxicity. Owing to their intrinsic catalytic efficiency, substrate specificity, and compatibility with physiological environments, enzymes offer uniquely advantageous triggers for SIP activation, providing a biomimetic and selective approach for amplified signal generation and precise drug delivery in diseased tissues such as cancer and inflammation.[67,68]

Furthermore, enzyme-responsive self-immolative systems provide an effective strategy for dynamically controlling cell-cell interactions. A recent study by Chad *et al*. demonstrated that an artificial cell-surface marker incorporating a β-glucuronidase-cleavable self-immolative linker, multivalent adamantyl recognition units, and a bioorthogonal dibenzocyclooctyne (DBCO) handle was engineered and efficiently installed on living cell membranes *via* strain-promoted azide–alkyne cycloaddition. The modified cells selectively assembled with β-cyclodextrin-functionalized partners through non-covalent host-guest interactions, inducing proximity-dependent biological responses, such as actin cytoskeleton remodeling and suppression of cancer cell proliferation and migration. Notably, enzymatic activation triggers rapid self-immolative decomposition of the marker, leading to cell disassembly and full restoration of native proliferative and migratory behavior.[69] The work presented here highlights enzyme-responsive self-immolative platforms as versatile chemical biology tools for reversible and on-demand regulation of intercellular interactions, which are relevant for the study of cellular communication and engineering of dynamic cellular assemblies. Enzyme-responsive SIPs offer sharp on-site activation, minimal off-target leakage, quick and easy diagnostics, and therapeutic integration. In addition, there are continued challenges, such as refining trigger specificity in healthy tissues, tuning the depolymerization kinetics of polymer scaffolds for efficient release *in vivo*, and increasing biodegradability and translational scalability.

3 TME-RESPONSIVE SELF-IMMOLATIVE POLYMERS FOR TUMOR IMAGING

The TME is characterized by a complex network of biochemical and biophysical abnormalities, including acidic extracellular pH, high GSH and ROS levels, overexpressed enzymes, and hypoxic conditions.[70–72] These specific features drive tumor growth and resistance to therapy but also provide exploitable cues for the design of smart, activatable imaging agents. Among the emerging strategies, stimulus-responsive intelligent polymers have received considerable attention in the last few years as a new generation of TME-responsive materials because they can convert subtle biological events into amplified chemical or optical responses.[73,74] SIPs induce a head-to-tail depolymerization cascade when triggered by specific TME stimuli, releasing reporter molecules or fluorescent fragments in an event that amplifies the signal.[75] This self-propagating disassembly mechanism allows precise spatiotemporal control and enhanced imaging contrast within the tumor tissues.[33] Recent progress in this field has yielded a diverse range of SIP-based probes responsive to pH, redox gradients, and enzyme activity, offering versatile platforms for tumor visualization through fluorescence, chemiluminescence, and multimodal imaging platforms.[76,77]

3.1 Fluorescence Imaging

Fluorescence imaging is considered to be one of the most effective approaches for visualizing tumor progression and therapeutic response. However, its clinical translation remains hampered by poor signal-to-background ratios, limited tissue pene-

tration, and lack of probes that respond selectively to TME cues. The traditional form of fluorophores, based on the concept of always-on, is usually characterized by nonspecific activation and quick photobleaching, resulting in high background fluorescence and limited diagnostic accuracy. In contrast, TME-responsive SIPs provide a promising strategy for overcoming these challenges by combining conditional activation with signal amplification. In these systems, fluorescence is quenched during circulation. However, it is quickly rebuilt in association with a terminal triggering stimulus, such as hypoxia, acidity, enzyme activity, or redox imbalance, detaching the terminal triggering group, thereby initiating a cascade of depolymerization. Each triggering event can liberate multiple fluorophore-containing fragments, amplify the emission intensity, and improve detection. Such sensitivity. Autocatalytic disassembly allows SIPs to function not only as molecular amplifiers for diagnostic imaging, but also as dynamic probes for monitoring therapeutic activation and fate within tumors.

Recent studies have demonstrated the ability of a rational combination of self-immolative chemistry and TME-responsive motifs to generate highly specific and bright fluorescence signals for real-time cancer visualization. As an illustration, Shao *et al*.[78] fabricated an azobenzene-capped self-immolative block copolymer that is non-emissive in circulation but can depolymerize under hypoxic conditions through enzymatic reduction of the azo bond to release fluorescent subunits selectively in tumor tissues. In this design, enzymatic reduction of the azo linker removed the terminal stabilizing group, initiating head-to-tail backbone depolymerization and releasing multiple fluorogenic fragments per triggering event. This cascade activation significantly enhanced the fluorescence intensity in hypoxic tumor regions compared with normoxic tissues, thereby improving tumor-to-background contrast. Similarly, Jeon *et al*.[56,77] demonstrated a ROS-responsive self-immolative polymer that activates oxidative stress and generates powerful fluorescence, as well as therapeutic radicals that can induce immunogenic cell death, demonstrating the dual diagnostic and therapeutic capabilities of SIPs. In another elegant example, Zong *et al*.[62] developed an H_2S-triggered self-immolative poly(thiocarbamate) (PTC) that not only releases an near-infrared (NIR) fluorophore upon activation, but also generates carbonyl sulfide, which is enzymatically converted into additional H_2S to drive further depolymerization, creating a self-amplifying feedback loop that enables ultrasensitive tumor imaging. Beyond organic dyes, Smith *et al*.[45] introduced lanthanide chelates containing self-immolative polymers, whose depolymerization restores metal-based luminescence, enabling deep tissue and vascular imaging with reduced background interference. Grolman *et al*.[79] reported depolymerizing self-immolative lanthanide-chelate polymers that switch on metal luminescence after trigger cleavage, enabling vascular/tomographic contrast with programmed circulation and subsequent rapid excretion.

Furthermore, Sagi *et al*. reported a self-immolative polyurethane system engineered to undergo rapid end-to-end depolymerization upon the removal of a terminal trigger group. The polymers were constructed using urethane-linked aromatic repeat units that enabled efficient 1,6-elimination and decarboxylation reactions, resulting in complete chain unzipping after a single cleavage event. Importantly, the incorporation of fluorogenic units into the polymer backbone allowed direct visualization of the depolymerization process. When capped with a protein-responsive butanone moiety, enzymatic activation by bovine serum albumin initiates head-group removal, triggering cascade degradation and the release of highly fluorescent amine products, highlighting the potential of self-immolative polymers as signal-amplifying platforms for fluorescence imaging and sensitive biomolecular detection.[80] In addition, SIPs provide a powerful framework for fluorescence imaging by converting a single biochemical trigger into a cascade depolymerization event that releases multiple fluorogenic units, thereby achieving intrinsic signal amplification.[80] In contrast to conventional activatable probes that generate stoichiometric fluorescence responses, SIP-based systems undergo head-to-tail backbone fragmentation after trigger cleavage, resulting in enhanced fluorescence when the trigger is activated, with an improved signal-to-background ratio and sensitivity.[80] This concept has been further extended to tumor-specific imaging by integrating hypoxia-responsive motifs into self-immolative block copolymer architectures.[78] Under oxygen-deficient conditions, enzymatic reduction of hypoxia-labile azo linkers induces detachment of hydrophilic shielding blocks and initiates cascade depolymerization of the SIP backbone, leading to rapid and selective amplification of fluorescence within hypoxic tumor regions (Figs. 7a and 7b).[78] Together, these studies demonstrate that combining trigger-responsive chain-shattering polymers with hypoxia-activated self-immolative block copolymers enables highly sensitive and spatially confined fluorescence imaging, highlighting SIPs as versatile molecular amplifiers for visualizing tumor-associated microenvironmental cues.

3.1.1 Polymer degradation-activated probes

The accurate acquisition of molecular information from tumor-associated biomarkers requires imaging probes that respond selectively to pathological cues while maintaining low background signals in complex biological environments. Although fluorescent probes offer high spatial and temporal resolutions, conventional polymeric imaging systems often suffer from nonspecific activation and persistent background fluorescence caused by premature probe turn-on and off-target accumulation.[81–84] To overcome these limitations, small-molecule chemical labeling has emerged as an effective alternative to fluorescent protein tagging for *in vitro* and *in vivo* protein studies, offering improved specificity and reduced steric interference.[65] Probes based on enzyme activity are even more selective, as they take advantage of the catalytic production of reactive intermediates, including quinone methides, to perform targeted labeling.[85] Simultaneously, SIPs have facilitated the creation of degradable lanthanide-based vascular imaging agents that offer a long duration of circulation and micro-CT contrast and completely break down to excrete small molecules during end-cap cleavage. This enhanced degradation system addresses the toxicity issues related to long-circulating systems of contrast agents and underscores the flexibility of SIPs in medical imaging applications.[79] Furthermore, recent efforts have sought to construct dual-responsive degradation probes in which ortho-

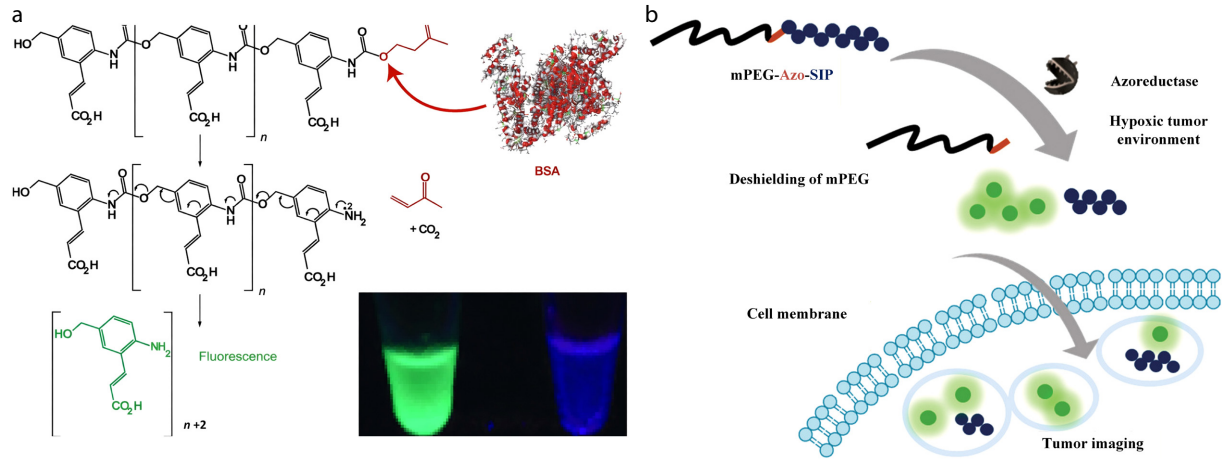

Fig. 7 Enzyme- and microenvironment-activated fluorescence amplification based on self-immolative polymers. (a) Enzymatic cleavage (*e.g.*, BSA) removes the terminal protecting group to initiate cascade depolymerization and release fluorogenic reporters (Reproduced with permission from Ref. [80]; Copyright (2008), Wiley-VCH GmbH). (b) Tumor-associated internalization and activation enables localized fluorescence turn-on in cancer tissues (Reproduced from Ref. [78]; Copyright (2022), Wiley-VCH GmbH).

gonal triggers, such as pH and hypoxia, act together to amplify degradation kinetics. For example, polymeric assemblies bearing azobenzene–imidazole conjugates display hypoxia-induced cleavage followed by acidic-accelerated self-immolation, yielding rapid fluorescence "turn-on" at the tumor site.[86] Despite this progress, the majority of systems are currently limited to first near-infrared window (NIR-I) emission, which has low tissue penetration. Therefore, subsequent SIP probes need to be extended into the second near-infrared window (NIR-II) window and utilize biodegradable backbones to reduce long-term toxicity, enabling translational imaging applications.

3.1.2 Signal amplification imaging principles

A distinguishing feature of SIP-based imaging systems is their signal-amplification capabilities. Unlike conventional activatable probes that rely on a one-to-one stoichiometric response, SIPs enable "chain-reaction" amplification, where a single triggering event induces depolymerization of the entire backbone and liberates multiple signaling units. This chemical amplification mechanism mirrors biological signal transduction and markedly enhances the detection sensitivity and imaging contrast. Self-immolative comb polymers (reported by Shabat *et al.*) are an effective signal-amplification approach, in which one event at the polymer head activates head-to-tail depolymerization to release multiple units of reporters in sequence along the polymer backbone. By incorporating cleavable side reporters into each repeating unit, this architecture overcomes the steric limitations of dendritic systems and enables an amplified fluorescence output from one molecular recognition event, making it highly attractive for sensing and imaging applications.[30] Furthermore, recent advances have highlighted the integration of self-immolative polymers with advanced photophysical strategies to achieve amplified and stimuli-responsive tumor imaging. For example, Wang *et al*. developed conjugated poly(fluorene-*alt*-benzothiadiazole) (PFDBt-BIMEG) donors that can be used in energy transfer switching to switch the real-time ratiometric fluorescence under tumor-relevant redox conditions.[87] Additionally, with self-immolative depolymerization linked to chemiluminescence or photoacoustic (PA) capabilities, hybrid SIP systems allow deep-tissue visualization according to optical diffusion depth.[88,89] These efforts collectively demonstrate that combining self-propagating chemical amplification with advanced photophysical mechanisms holds promise for precise, high-sensitivity tumor imaging in complex biological environments.

3.1.3 Fluorogenic SIPs for tumor tracking

Fluorogenic SIPs are a rapidly developing TME-sensitive imaging agent capable of real-time tumor tracking with minimal background interference. These systems are optically silent in systemic circulation but become fluorescent. Response to environmental stimulation, for example, enzyme cleavage, redox reactions, or bioorthogonal ligation, through which the emission of a reaction is spatially confined. Recent progress in bioorthogonal chemistry has provided efficient routes for the construction of fluorogenic SIPs with high temporal and spatial resolution.

Gerti *et al*. reported tetrazine-trans-cyclooctene (Tz-TCO) click-based fluorogenic probes that achieve rapid *in situ* activation and high signal-to-noise imaging in live imaging cells and *in vivo* tumor models.[90] Additionally, Xu *et al*. produced a live-cell fluorescence-activated Tz probe targeted at the lysosome within minutes, demonstrating its potential for bioorthogonal imaging.[91] Incorporating such bioorthogonal motifs into self-immolative polymer architectures pioneered by Shabat *et al*. as powerful signal-amplification platforms enables the development of hybrid SIP systems that remain optically silent until tumor-microenvironment-triggered depolymerization unmasks reactive fluorogenic units.[92] Despite these advances, challenges related to *in vivo* polymer aggregation and metabolic clearance persist, underscoring the need for next-generation fluorogenic SIPs emphasizing biodegradable backbones, red-shifted emission beyond 1000 nm, and multimodal integration with PA or magnetic resonance imaging (MRI) for clinically translatable tumor visualization.

3.2 Chemiluminescence Imaging

Chemiluminescence (CL) imaging has become one of the most effective strategies for visualizing ROS in biological systems, of-

fering a naturally high signal-to-noise ratio without the need for external light excitation. Classic small-molecule CL probes are typically characterized by short emission lifetimes and very limited signal strengths, thus limiting their application to long-term and cumulative ROS monitoring *in vivo*. The development of self-immolative polymers could offer a solution given that one chemical triggering event can result in a cascading depolymerization process, liberating multiple signal units. Embedding chemiexcitable motifs in self-immolative backbones allows the resulting CL-active SIPs to produce amplified, long-lasting light emissions by marrying the sensitivity of chemiluminescence with the signal amplification offered by polymeric systems.[88]

Recent research has demonstrated that the incorporation of self-immolative polymers into CL nanoparticle platforms can circumvent the intrinsically short emission lifetime of conventional CL probes. Upon ROS-mediated activation, the SIP-based nanoparticles undergo stepwise head-to-tail depolymerization. Through this process, high-energy intermediates are continuously produced, and resonance is transferred to the encapsulated hydrophobic dyes *via* resonance energy transfer (CRET), as illustrated in (Fig. 8). This domino-like degradation process enables a single ROS-triggering event to produce multiple CL emission cycles, resulting in sustained high-contrast signals lasting several hours. Compared with small-molecule CL donors, SIP-based configurations provide higher ROS sensitivity, better signal retention, and superior *in vivo* imaging performance, enabling the precise delineation of ROS-rich inflammatory zones across multiple disease models.[88] Beyond this, depolymerization enhances the luminescent response and promotes substrate turnover efficiency to nanomolar detection limits.[77] By combining self-immolative chemistry with peroxyoxalate-driven luminescence, these designs amplify slight biochemical alterations in the tumor microenvironment into massive photon bursts, thus enabling the detection of early tumor growth-associated oxidative stress.

In addition to ROS, hypoxia- and pH-responsive SIPs have been engineered to trigger chemiluminescence under characteristic tumor conditions. For example, oxygen-depleted regions of solid tumors have been targeted with hypoxia-activated nitrobenzyl-caged SIPs coupled to 1,2-dioxetane phosphors, enabling high-contrast imaging of hypoxic cores.[93,94] An acidic environment within the TME causes acid-cleavable carbamates or imine linkers in the SIP backbones to depolymerize and release CL precursors or energy-transfer donors. As pH-triggered cleavage triggers chain reactions, chemiluminescence is amplified, providing visual feedback on intratumoral acidity.[95] In these hypoxia- and pH-responsive systems, stimulus-mediated cleavage of the terminal protecting group initiates cascade depolymerization of the SIP backbone, resulting in the sustained generation of chemiexcitable intermediates rather than single-emission events. This domino-type amplification prolongs the emission lifetime and enhances the sensitivity under tumor-relevant conditions, distinguishing SIP-based chemiluminescent platforms from conventional small-molecule CL probes. A key advantage of SIP design is that it can incorporate a variety of TME-responsive motifs, such as GSH-cleavable disulfides and enzyme-sensitive peptides, enabling multimodal chemiluminescent sensing in complex tumor biochemistry.

Furthermore, Self-immolative amplification contributes to prolonged luminescence lifetime and improved photon yields. Conventional CL reactions typically suffer from short emission durations owing to rapid substrate depletion; however, SIP-based systems overcome this by continuously generating CL precursors through a domino-like depolymerization process. For example, a recent study found that polycarbonate-based SIPs activated by TMEs depolymerize upon exposure to H_2O_2, releasing multiple light-emitting units.[96] As a result of this molecular amplification, persistent lumines-

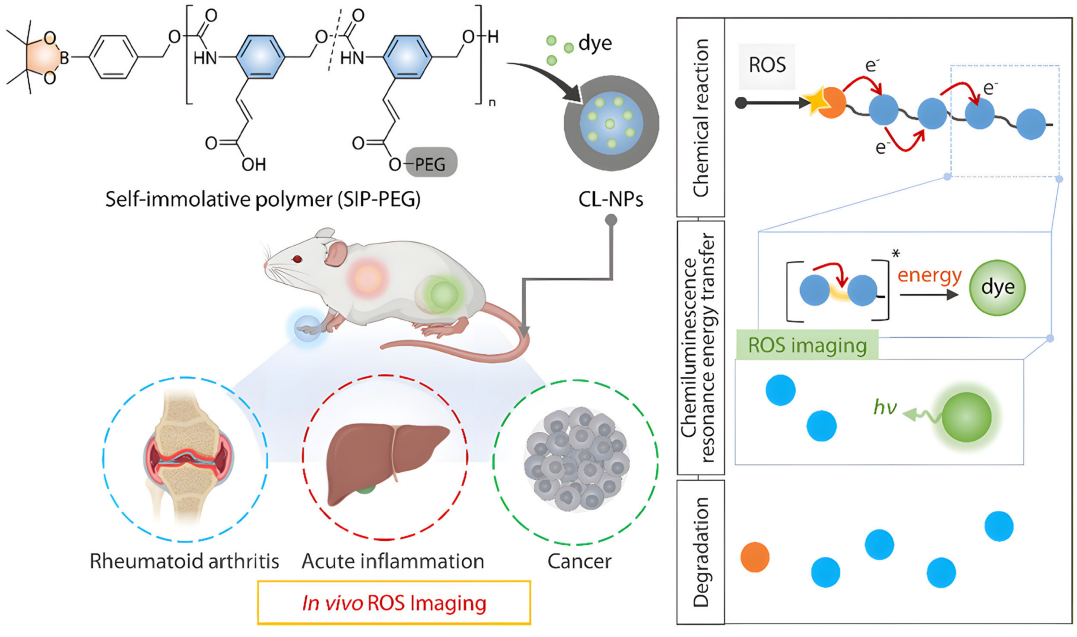

Fig. 8 Chemiluminescent SIP nanoparticles in which ROS-triggered cascade depolymerization generates sustained light emission for long-term, background-free *in vivo* imaging (Reproduced with permission from Ref. [77]; Copyright (2022), American Chemical Society).

cence can be produced for over 30 min, allowing for time-resolved tumor imaging with minimal interference. By varying the trigger sensitivity, backbone rigidity, and substitution pattern, the SIP architecture can be tailored to the activation kinetics and emission profiles to meet specific diagnostic requirements.

To translate CL imaging from preclinical models to clinical practice, it is necessary to rationally engineer SIP backbones with higher quantum yields, improved biocompatibility, and optimized pharmacokinetics. Combining SIPs and nanocarrier architectures (*e.g.*, micelles, dendrimers, polymeric nanoparticles) could further stabilize CL precursors and enhance tumor accumulation *via* the enhanced permeability and retention (EPR) effect.[97] Furthermore, integrating multiplexed CL systems responsive to distinct TME cues may provide a comprehensive view of tumor heterogeneity by simultaneously monitoring the pH, redox state, and enzyme activity. SIPs based on TMEs will become versatile molecular amplifiers for chemiluminescence imaging, bridging the gap in diagnostic sensitivity and clinical applications.

3.3 Multimodal Imaging Platforms

Multimodal medical imaging plays a central role in cancer diagnosis and therapeutic monitoring. However, the performance of conventional contrast agents is often constrained by either rapid systemic clearance or long-term tissue accumulation and toxicity. In particular, vascular imaging by CT and MRI requires exogenous agents with sufficiently long blood circulation time, a feature not attainable with the clinically used small-molecule iodinated or Gd^{3+} chelates.[79] Although macromolecular and nanoparticle-based contrast agents improve pharmacokinetics, their poor degradability and potential for long-term organ retention remain major concerns. SIPs offer a compelling alternative by combining prolonged circulation with complete stimulus-triggered depolymerization into excretable small molecules.[98] Recent research has demonstrated that lanthanide-containing SIPs, such as self-immolative polyglyoxylamides bearing pendant Gd^{3+} chelates, function as effective blood-pool contrast agents for micro-CT and MRI.[99] These systems exhibit tunable depolymerization kinetics through rational end-cap design, enabling stable vascular contrast for up to one hour followed by rapid renal clearance after imaging. Importantly, despite the high doses required for micro-CT, these polymeric chelates showed good *in vivo* tolerability, highlighting the unique ability of SIPs to reconcile the imaging efficacy with biosafety.

Self-immolative polymers have emerged as a powerful bridge between rapidly clear-ring small-molecule probes and non-degradable nanoparticles, enabling TME-responsive multimodal imaging. Amphiphilic self-immolative block copolymers self-assemble into micellar nanoparticles that undergo cascade depolymerization in response to acidic pH and elevated ROS levels, generating reactive azaquinone methide (AQM) intermediates that covalently trap intracellular thiol-containing substrates.[100] This triggered disassembly activates fluorine-19 nuclear magnetic resonance/magnetic resonance imaging (^{19}F NMR/MRI) signals and enables ^{19}F/^{1}H dual-modality imaging, whereas *in situ* covalent conjugation of DOTA-Gd moieties with thiol-rich biomacromolecules affords prolonged ^{1}H MR contrast retention in tumors. Such covalent trapping-assisted signal amplification provides a general strategy for long-term, stimuli-activatable imaging using self-immolative polymer platforms (Fig. 9). Recent research has extended these principles to more complex tri-modal or cascade-activated SIP nanocarriers, advancing diagnostic precision and treatment monitoring. Liu *et al*. introduced an ROS-cleavable SIP micellar platform co-loaded with iodinated aromatics and porphyrin derivatives for concurrent CT/PA/FL imaging, in which oxidative stress in tumors triggered polymer depolymerization and a sharp "turn-on" of both optical and X-ray contrast.[101] Furthermore, sequence-defined self-immolative and degradable amphiphiles have been engineered into "digital micelles," enabling label-free, multimodal tracking and quantitative biodistribution analysis by MALDI mass spectrometry and imaging.[102] Collectively, these studies establish SIPs as versatile and mechanistically distinct platforms that bridge the gap between small-molecule probes and conventional nanoparticles, offering unprecedented opportunities for tumor-responsive, multimodal imaging, and theranostic applications.

3.4 Mechanisms for Improving Imaging Sensitivity and Specificity

Achieving high imaging sensitivity and specificity remains a central challenge in cancer diagnostics owing to the biological complexity and heterogeneity of the TME. SIPs that respond to TMEs provide a molecular framework that is capable of amplifying biochemical signals while minimizing background interference. They rely on a "cascade disassembly" mechanism to rapidly and completely release imaging agents or signal-generating molecules after being triggered by a single stimulus.[103] Self-amplified responses improve the signal-to-noise ratios (SNRs), enabling the detection of early stage or microscale lesions that would otherwise remain undetected using conventional activation probes. Furthermore, the modular nature of SIPs enables precise integration of multiple stimuli-responsive triggers (*e.g.*, pH, ROS, GSH, hypoxia, or enzyme-responsive linkers), thus enabling spatially and temporally precise activation control. Such systems ensure that the imaging signal is exclusively "turned on" in malignant regions, thereby reducing the systemic background and off-target activation.[104,105] For example, research has reported a renewable-resource-based chain-shattering polymer synthesized *via* ADMET polymerization, in which amphiphilic triblock copolymers incorporate repetitive, enzyme -labile azobenzene units directly into the backbone. Enzymatic reduction of azobenzene motifs triggers a self-immolative cascade leading to main-chain fragmentation into small, non-toxic products, distinguishing this system from conventional end-to-end depolymerizing polymers and highlighting its potential for enzyme-responsive delivery and imaging applications. Additionally, ROS-sensitive self-immolative constructs built around thioketal or related ROS-cleavable motifs have been used to translate oxidation events in tumor microenvironments into amplified near-infrared fluorescent and photoacoustic outputs by releasing or unquenching NIR chromophores upon cascade depolymerization.[106] Beyond simple fluorogenic "turn-on" behavior, self-immolative scaffolds have also been adapted to produce amplified chemiluminescent readouts and other modality-switched signals, demonstrating how one triggering event can drive a cascade emission suitable for ultrasensitive detection.[88]

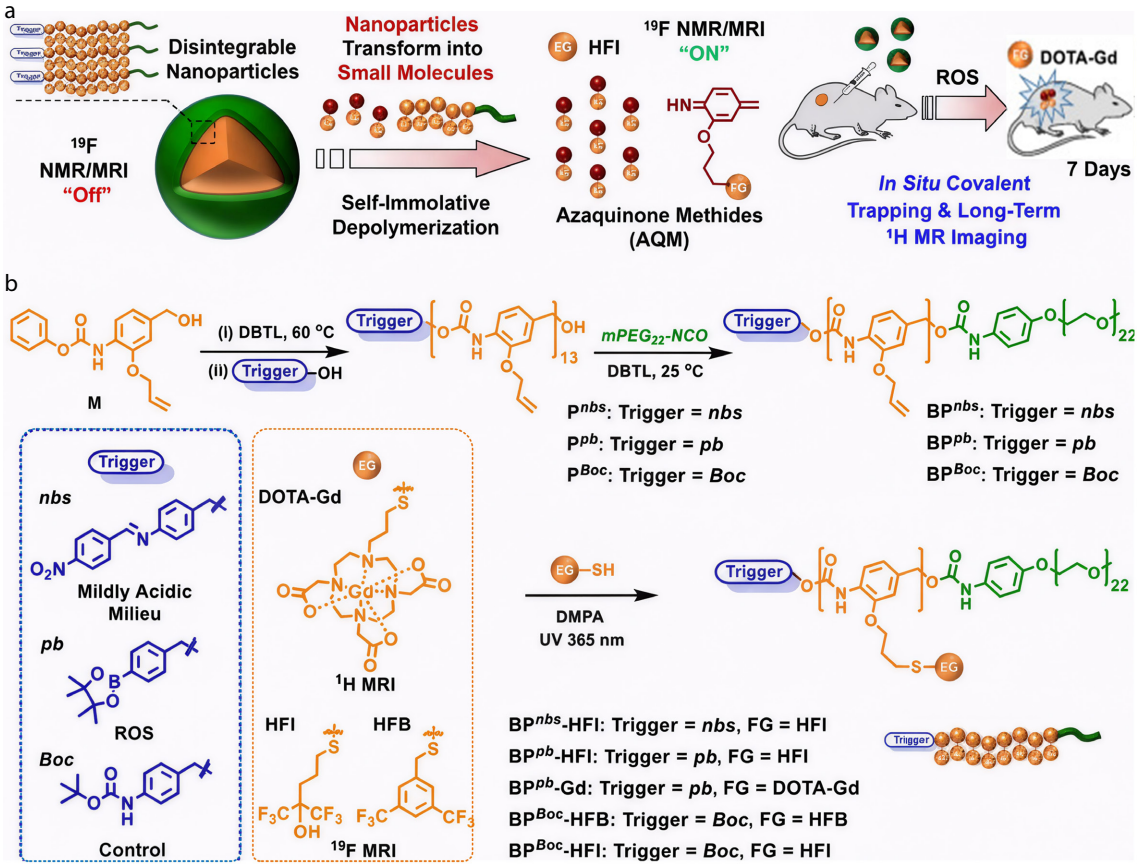

Fig. 9 (a) TME-triggered cascade depolymerization of self-immolative nanoparticles under acidic and ROS conditions generates AQM intermediates, leading to nanoparticle disassembly and thiol-mediated activation of $^{19}F/^{1}H$ dual-modality MR imaging with prolonged retention; (b) Multifunctional self-immolative polymers bearing HFI, HFB, and DOTA-Gd side chains with orthogonal acid and ROS-responsive triggers enable programmable depolymerization and multimodal imaging (Reproduced with permission from Ref. [100]; Copyright (2020), Elsevier).

The autocatalytic or head-to-tail depolymerization characteristics of SIPs ensure that even low-abundance stimuli are converted into large, measurable outputs, narrowing the sensitivity gap between molecular events and *in vivo* imaging readouts.[92] Moreover, specificity can be improved by integrating orthogonal gating designing SIPs that require two or more TME cues (for example, pH plus reductive potential, or enzyme activity plus hypoxia) to trigger disassembly, thereby confining activation to tumor loci and reducing off-target signals.[107] For example, several groups have reported dual- or multi-stimuli-responsive polymeric reporters (pH/GSH or hypoxia/enzyme combinations) and self-immolative block copolymers that remain quiescent until the intended intracellular milieu is encountered, improving *in vivo* contrast and minimizing premature leakage.[46] In invasive metastatic models, protease-activated (MMP-sensitive) polymeric reporters that release fluorophore-labeled fragments only after site-specific proteolysis provide superior imaging contrast, showing the importance of spatially restricted SIP activation for more accurate diagnostics.[108] Taking advantage of these activation-specific approaches, recent efforts have focused on fine-tuning the photophysical processes that underlie signal generation to maximize the optical output while minimizing background interference. In addition to activation logic, energy transfer and quenching mechanisms also contribute significantly to the improvement of the SIP-based sensitivity. Incorporating Förster resonance energy transfer (FRET) or photoinduced electron transfer (PET) motifs allows efficient "on-state" emission when the polymer is intact.[109] For example, when QSY21 and Cy5 were combined in a FRET-paired SIP in circulation, no fluorescence was detected, but once enzymatically activated in tumor tissue, intense NIR-II fluorescence was observed.[110,111] By improving the contrast and minimizing photobleaching and autofluorescence artifacts, this built-in signal gating improves the imaging fidelity under complex conditions *in vivo*. Furthermore, SIPs allow for the integration of energy transfer systems that are capable of adjusting the emission wavelength or lifetime in a dynamic manner to provide outputs that are ratiometric or time-gated. For deep-tissue visualization, such methods are particularly useful for overcoming the scattering and absorption challenges.[112]

Nanostructural engineering plays a critical role in the imaging precision, signal amplification, and rational polymer design. In systemic circulation, stimuli-responsive SIPs are commonly assembled into nanoscale architectures, including micelles, vesicles, and nanogels, which stabilize the imaging payloads. This nanostructure disassembles or shrinks when exposed to tumor-specific triggers, thereby improving tissue penetration and intratumoral diffusion.[113,114] By enhancing the signal through fragmentation, robust "turn-on" contrast can be achieved with little interference from the

background.[115] Furthermore, poly(urethane) frameworks with ROS-cleavable linkers enhance the activation selectivity of the oxidative TME, resulting in an enhanced fluorescence signal and higher tumor-to-normal tissue ratios.[106] In addition to demonstrating strategies for improving imaging sensitivity, specificity, and biocompatibility using SIP-based nanostructures, these multiscale designs demonstrate how SIP-based nanostructures can overcome the traditional trade-offs between these properties. In summary, SIP-based imaging systems enhance the sensitivity and specificity by converting subtle tumor-associated biochemical cues into amplified diagnostic outputs through controlled cascade depolymerization.

4 TME-RESPONSIVE SELF-IMMOLATIVE POLYMERS FOR PRECISION TUMOR THERAPY AND DIAGNOSIS

4.1 Chemotheraputic Drug Delivery

SIPs have emerged as a powerful class of TME for chemotherapy delivery owing to their ability to undergo cascade depolymerization upon exposure to disease-associated triggers. By coupling amphiphilic or hybrid polymer architectures with enzyme, pH, or redox-labile initiating units, SIP-based nanoparticles can remain stable during circulation and rapidly disassemble in the TME to release cargos. Several studies have demonstrated that enzyme-triggered polymer unzipping enables precise control over nanoparticle disassembly, allowing efficient drug liberation in response to tumor-associated enzymes while minimizing premature leakage. In addition, hybrid polyester SIP nanoparticles have been shown to integrate favorable biodegradability with self-immolative behavior, achieving controlled drug release kinetics that are well-aligned with pathological conditions in solid tumors.

SIP-based nanoassemblies have emerged as versatile platforms for TME-responsive chemotherapy delivery, thereby enabling controlled disassembly and efficient drug release. For example, Ren *et al*. demonstrated that in cancer cells, immunogenic micelles capable of capturing CD8 + T-cell epitopes and adjuvants undergo intracellular disassembly, enhancing antigen cross-presentation and antitumor responses, highlighting the potential of stimulus-responsive carriers in tumor therapy.[116] Similarly, Ergene *et al*. reported that side-chain-engineered SIPs exhibited potent and selective antibacterial activity through the rapid generation of bioactive species upon triggering, illustrating how chemical design can modulate release kinetics and bioactivity.[117] Activation of self-immolative side chains exposes reactive intermediates that initiate backbone fragmentation, enabling the rapid release of bioactive species. Compared with non-immolative analogs, these polymers demonstrated accelerated degradation kinetics and enhanced biological efficacy following stimulus exposure. Kumar *et al*. demonstrated enzyme-activated polymer unzipping to induce complete nanoparticle disassembly, with amphiphilic nanoassemblies providing more uniform and efficient cargo liberation than polyelectrolyte complexes.[118] Furthermore, Hybrid nanoparticles composed of self-immolative poly(ethyl glyoxylate) and poly(D,L-lactic acid) demonstrated tunable, stimuli-responsive drug release, where the rate and extent of degradation and release depended on the polymer ratio and triggering stimulus. *in vitro* assays highlighted the influence of both the stimulus and formulation on cytotoxicity.[89] Furthermore, self-immolative polymersomes (SIPsomes) were fabricated from amphiphilic block copolymers containing hydrophobic blocks capable of head-to-tail cascade depolymerization upon stimulus-triggered cleavage of the terminal capping moieties.[119] By incorporating visible light, UV light, or reductive-sensitive end caps, SIPsomes disassemble into water-soluble fragments, enabling the controlled co-release of encapsulated drugs and regulated permeability to protons, oxygen, and enzymatic substrates. This modular design also allows the execution of programmable enzymatic reactions following the OR, AND, and XOR logic gates (Fig. 10). These findings establish SIP-

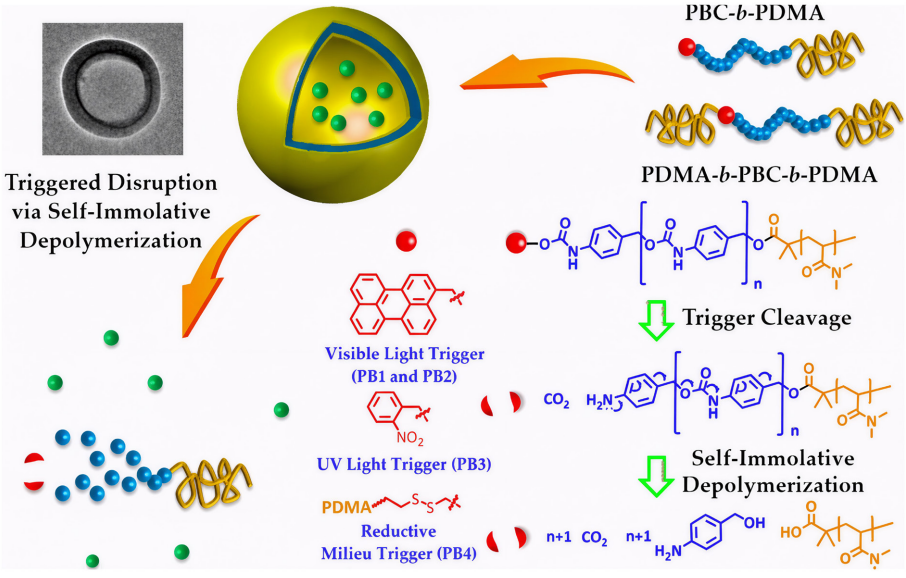

Fig. 10 Self-immolative polymersomes enabling stimulus-triggered unzipping, programmable permeability, and logic-gated (OR/AND/XOR) drug release for precision chemotherapy (Reproduced with permission from Ref. [119]; Copyright (2014), American Chemical Society).

somes as versatile, stimulus-responsive nanocarriers with the potential for precision chemotherapy delivery and advanced therapeutic programming. Collectively, these studies highlight that SIP-based chemotherapeutic systems enable stimulus-amplified drug release with improved kinetic control and tumor selectivity compared with conventional degradable carriers.

4.2 Combination Therapy Platforms

Single-modality therapies based on TME-SIPs often fail to achieve complete tumor eradication, owing to the multifactorial nature of malignancies and intratumoral heterogeneity. Chemotherapy alone suffers from MDR and systemic toxicity, while photodynamic therapy (PDT) and photothermal therapy (PTT) are restricted by oxygen dependence and limited tissue penetration, and immunotherapy is frequently compromised by the immunosuppressive TME. To overcome these intrinsic limitations, combination therapy platforms that integrate two or more therapeutic strategies or combine therapy and diagnostic imaging within a single SIP construct have emerged. Such systems exploit the unique ability of SIPs to undergo stimulus-triggered, domino-type depolymerization in response to endogenous cues (*e.g.*, pH, ROS, hypoxia, or redox gradients), thereby coordinating spatially and temporally controlled release of multiple payloads. TME-responsive SIPs amplify therapeutic efficacy while minimizing off-target effects by coordinating co-delivery, sequential activation, and synergistic interactions between modalities. Our recent research showed that ROS can trigger a self-amplifying poly(thioacetal) polymer that releases cinnamaldehyde (CA) when endogenous ROS cleave thioacetal groups, thereby increasing ROS levels *via* mitochondrial dysfunction and accelerating polymer degradation. In this cascade, immunogenic cell death (ICD) of tumor cells is induced, while side chains conjugated with an IDO-1 inhibitor (1-MT) reverse the immunosuppressive TME for synergistic cancer immunotherapy. Upon self-assembly into nanoparticles, the amphiphilic polymer exhibited ROS-sensitive degradation *in vitro* and *in vivo*, leading to potent antitumor activity and immune memory against tumor recurrence (Fig. 11a).[120] Building on this approach, we also developed an ROS-responsive self-immolative polyprodrug nanoparticle (SIPN) encapsulating a tumor-specific ROS inducer ($NCyNH_2$) and doxorubicin (DOX).[48] Endogenous ROS triggers polyprodrug degradation, releasing DOX and NCyNH2, which are further activated by NAD(P)H quinone dehydrogenase 1 (NQO1) to generate additional ROS, amplifying drug release. This self-amplifiable mechanism enhances intratumoral drug activation and selectivity, achieving efficient tumor suppression with minimal off-target toxicity. These studies demonstrated that ROS-triggered self-amplifying polymeric systems provide a versatile platform for precise, amplified therapeutic effects *via* synergistic immuno- and chemotherapeutic strategies (Fig. 11b).

Furthermore, recent advances in SIPs have demonstrated their potential as multifunctional platforms for targeted and responsive cancer therapies, integrating both therapeutic delivery and diagnostic imaging using a single stimuli-responsive system. Xie *et al*. demonstrated a glutathione (GSH)-responsive SIP nanoparticle (DSS-BEN) that co-delivered a therapeutic miRNA (miR-34a mimic) and a polyamine analog (BENSpm). Upon activation by elevated concentrations of glutathione, SIP was cleaved, releasing the co-delivered compounds, which resulted in a synergistic effect in cancer therapy by concurrently regulating metabolism and genetic targets.[121] The most recent study by Zhang *et al*. expanded the field of theranostics to include a self-immolative, fluorinated nanotheranostic system for ^{19}F NMR/MRI-guided photodynamic therapy. In this design, TME-triggered fragmentation not only restored ^{19}F MRI visibility, but also released photosensitizers simultaneously, thereby allowing real-time image-guided therapy.[122] Taken together, these studies underscore the flexibility of SIPs as intelligent multimodal platforms that allow self-amplifying, cascade-responsive, and feedback-regulated therapy. Despite these meaningful advances, challenges persist, such as uniform activation in heterogeneous TMEs, finding a balance between stability and responsiveness, and simplifying synthesis to enable scalable clinical translation. Future efforts should focus on the integration of SIPs with TME cues, employing modular click-type chemistry, and incorporating real-time imaging modules to precisely guide adaptive and synergistic precision oncology. Additionally, TME-responsive self-immolative combination platforms demonstrate how cascade depolymerization can coordinate multimodal therapeutic activation with spatial and temporal precision, thereby enhancing the synergistic efficacy while minimizing systemic toxicity.

4.3 SIPs Hydrogel Delivery Platforms

SIPs represent a distinct class of macromolecules that undergo end-to-end depolymerization in response to specific triggers such as variations in pH or exposure to light.[92] Owing to this programmed disassembly, SIPs have emerged as versatile stimuli-responsive materials with broad utility in signal amplification, biosensing, controlled drug delivery, and advanced material engineering.[123] Initial demonstrations of self-immolation were largely limited to oligomeric or dendritic structures; however, subsequent developments have expanded the scope to include linear, cyclic, graft, hyperbranched, and network-type architectures.[124] The capacity of SIPs to be finely tuned towards diverse external stimuli offers unique opportunities for the design of degradable hydrogels.

Recent studies have demonstrated that SIPs enable hydrogels to undergo precisely programmed stimulus-triggered degradation through cascade depolymerization mechanisms. Dual-responsive systems combining catechol-metal ion cross-linking with self-immolative backbones exhibit gel disassembly and payload release *via* either pH-induced cross-linking dissociation or thiol-triggered end-to-end depolymerization, highlighting orthogonal degradation pathways.[125] In a bio-inspired approach, vesicular assemblies formed through polyvalent polyelectrolyte interactions were shown to disassemble upon polymer unzipping, releasing encapsulated gelators that subsequently induced hydrogel formation, thus coupling polymer destruction to network construction.[126] Side-chain immolative poly(benzyl ether) systems further expand hydrogel design by enabling post-polymerization functionalization and reductive disassembly of graft networks and organogels into their constituent components.[127] Concurrently, self-immolative poly(thioesters) derived from amino acids are synthesized through photocrosslinking to generate hydrogels that are degraded by rapid unzipping under physi-

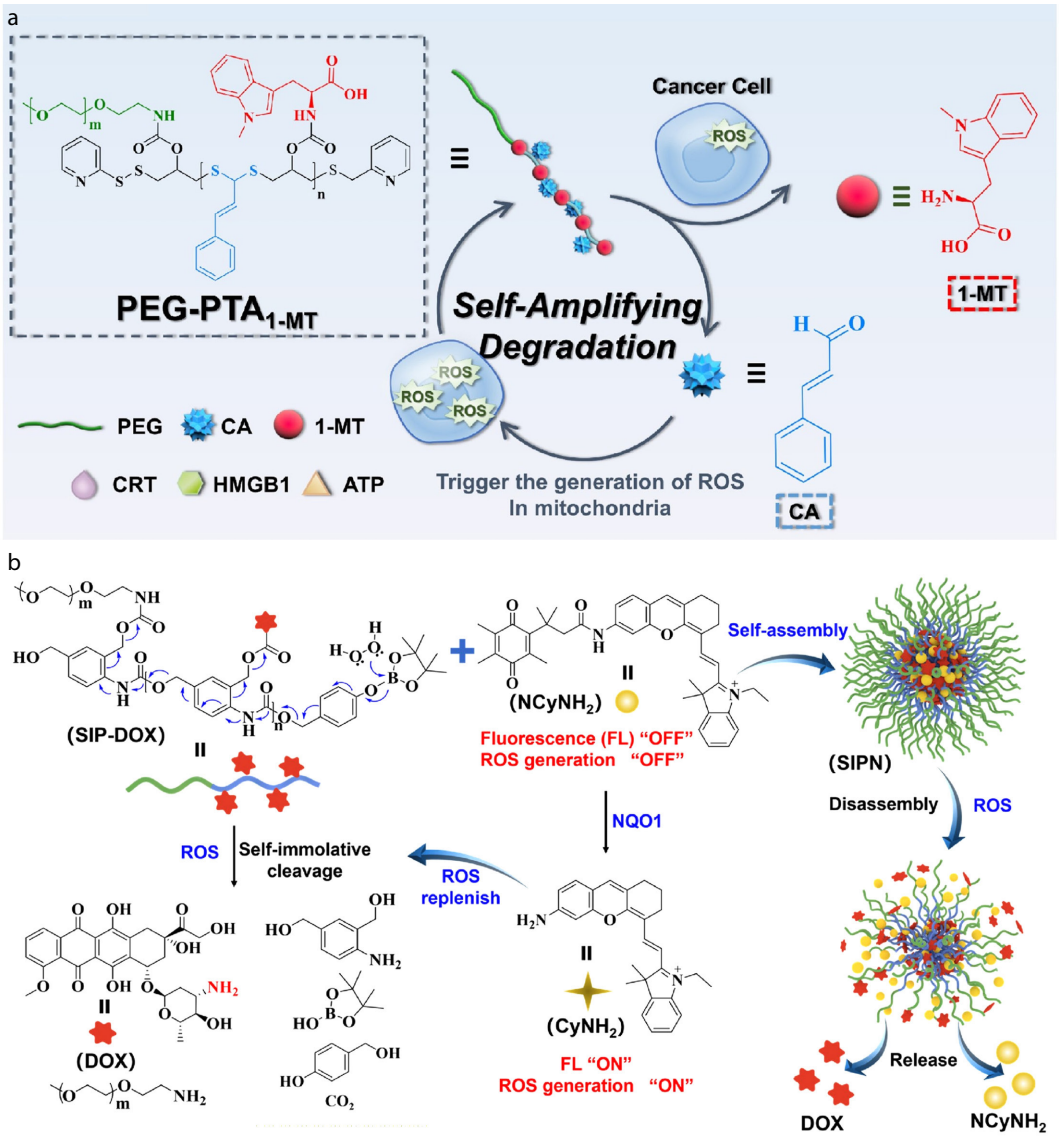

Fig. 11 (a) Chemical structure of PEG-PTA$_{1\text{-MT}}$ and its intracellular ROS-triggered self-amplifying degradation mechanism (Reproduced with permission from Ref. [120]; Copyright (2022), Elsevier). (b) Structure of SIP-DOX and NCyNH$_2$ and schematic illustration of ROS-responsive NCyNH$_2$-loaded SIP-DOX nanoparticles (SIPN) enabling efficient drug loading and controlled self-immolative release for cancer imaging and therapy (Reproduced with permission from Ref. [48]; Copyright (2022), Elsevier).

ological conditions.[128] Collectively, these advances have established SIP-based hydrogels as highly versatile, degradable materials with tunable responsiveness, efficient network dissolution, and significant potential for biomedical, sensing, and recyclable-material applications.

Self-immolative hydrogels (SIHs) composed of poly(ethyl glyoxylate) (PEtG) hydrogel materials exhibit considerable potential for the development of hydrogel materials with amplified rates of degradation upon demand and high pre-trigger material stability.[61] The development of hydrogels with a high gel content, large levels of water uptake, and appropriate tissue-relevant material properties was achieved by incorporating light-responsive end-capped PEtG with PEG cross-linked networks. Notably, hydrogel degradation and small-molecule release could be reversibly switched on and off by alternating light irradiation and dark storage, demonstrating precise temporal control over network disassembly and drug release (Fig. 12a). Furthermore, Deng *et al*. reported a click-activated self-immolative polymer hydrogel in which selective cleavage of terminal end-caps initiates cascade depolymerization, enabling rapid and amplified gel degradation in response to a single triggering event.[8] This reversible degradation pattern can be used for precise timing control over hydrogel stability and drug release, further highlighting the possibilities for designing programmable drug delivery devices using self-immolative hydrogels, as depicted in (Fig. 12b). Water-soluble SIH was also synthesized using SPAAC, which was expected to enable gelation upon injection for subsequent drug delivery applications.[129] To gain further control over both gelation and degradation processes, dendritic SIH was designed for drug delivery applications using carbosilane dendrimers as bifunctional cross-linkers, according to

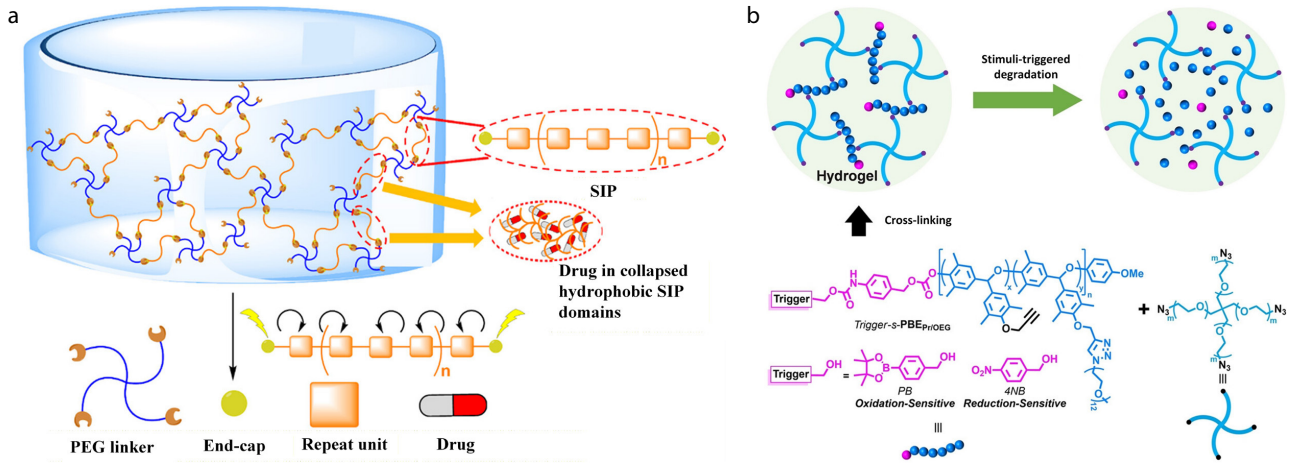

Fig. 12 Stimulus-responsive self-immolative hydrogels with programmable degradation. (a) Light-triggered end-cap cleavage induces cascade depolymerization of poly(ethyl glyoxylate) hydrogels, enabling reversible on–off degradation and controlled release (Reproduced with permission from Ref. [61]; Copyright (2023), American Chemical Society). (b) Schematic illustration of the click-triggered self-immolative polymer degradation and cascade depolymerization mechanism (Reproduced with permission from Ref. [8]; Copyright (2024) Wiley-VCH GmbH, CC BY 4.0).

Muñoz-Sánchez *et al*.[130] They employed CuAAC for SIH synthesis, where different types of azide-functionalized polymers, including those with non-cleavable and self-immolative segments, were compared using non-cleavable and self-immolative fragments. Collectively, these studies establish SIHs as versatile material platforms in which degradation, mechanical performance, and therapeutic release can be predictably engineered, offering significant potential for responsive biomaterials, controlled drug delivery, and smart hydrogel systems. These findings establish self-immolative hydrogels as programmable biomaterials, in which degradation, mechanical integrity, and therapeutic release can be precisely synchronized through cascade-triggered polymer unzipping.

4.4 Other Drug Delivery Platforms

In addition to conventional micellar and vesicular assemblies, TME-responsive TME SIPs have been exploited to construct a variety of supramolecular and hybrid nanostructures capable of programmable and stimuli-controlled drug release. The intrinsic degradability of SIPs enables structural disassembly and concomitant release of encapsulated payloads upon exposure to specific physiological cues, including mildly acidic pH (6.5–6.8), intracellular glutathione (2–10 mmol/L), and elevated reactive oxygen species (typically 50–100 μmol/L H_2O_2 in tumor tissues), thereby enhancing therapeutic precision. Moore *et al*. demonstrated this concept through the fabrication of programmable SIP-based microcapsules *via* interfacial polymerization, where fluorescent dyes encapsulated within the cavities were released upon stimulus-triggered cleavage of SIP linkages, leading to rapid shell rupture and cargo release within minutes under the applied triggering conditions *in vitro*.[131] Stimulus-mediated cleavage of SIP linkages destabilizes the polymeric shell through head-to-tail depolymerization, leading to rapid structural collapse and synchronized cargo release. This behavior highlights the mechanical amplification capability of self-immolative polymers in confined architectures, such as microcapsules. Similarly, Liu *et al*. designed amphiphilic block SIP micelles composed of polybenzoyl carbamate backbones incorporating distinct stimuli-labile end-caps, which allowed the controlled release of chemotherapeutics, such as doxorubicin (DOX) and camptothecin (CPT), in response to visible or ultraviolet light and reductive environments.[119] Based on this concept, Molla *et al*. designed amphiphilic polyurethane-based self-immolative polymers with redox-sensitive self-immolative groups on the hydrophobic backbone and triethylene glycol groups as hydrophilic segments. The synthesized amphiphilic SIPs self-assemble to form micelles with the ability to encapsulate drugs *via* π-π stacking, hydrogen bonding, and hydrophobic interactions. At a slightly acidic pH between 6.5 and 6.8 (tumor extracellular pH range), the tertiary amine groups of the micelles underwent protonation to enhance their uptake by cells, whereas the higher concentration of GSH in tumor cells (2–10 mmol/L intracellularly, compared with <10 μmol/L extracellularly) activated the self-immolation of the micelles to release the encapsulated drugs.[132–134]

Modern studies have also adapted these ideas into multi-drug and hybrid nanocarrier designs to control drug release kinetics in space and time. Gilliés *et al*. designed nanocarrier hybrids made of fast-degradable self-immolative PEtG and slow-degradable lactic acid (PLA), developing a system in which drug release occurs in sequence according to differences in degradation rates under UV or reducing conditions, closely mimicking the pharmacokinetic profiles of drug combinations that have different release profiles, that is, different kinetics of release are required in drug combinations.[89] In another study, Such *et al*. designed nanocarrier hybrids made of different ratios of fast degradable self-immolative poly[*N*,*N*-(diisopropylamino) ethyl glyoxylamide-*r*-*N*,*N*-(dibutylamino)-ethyl glyoxylamide] (P(DPAEGAm-*r*-DBAEGAm)) and a pH-sensitive PEG-*b*-(2-diisopropylaminoethyl methacrylate) copolymers, in which drug release kinetics can be accurately modulated according to different ratios of diisopropylamino and dibutylamino side groups, showing that nanocarrier composition can control drug release kinetics according to different ratios of diisopropylamino and dibutylamino side groups, showing that nanocarrier composition can control

drug release kinetics according to different ratios of diisopropylamino and dibutylamino side groups, showing that nanocarrier composition can control drug release kinetics.[45] In addition, research conducted by Langer *et al*.[135] described a light-responsive self-immolative polycarbonate (LrPC) conjugated with 4,5-dimethoxy-2-nitrobenzyl (DMNB) side chains. These constructs were co-assembled with U. S. Food and Drug Administration (FDA)-approved poly(DL-lactic-*co*-glycolic acid) (PLGA) to provide nano-constructs for photoinduced degradation and drug release. Despite these advances, several challenges remain before SIP-based drug delivery systems can be clinically translated. For instance, the synthetic complexity of multicomponent SIPs, degradation rate in heterogeneous TMEs, and biocompatibility of degradation products are important factors in advancing drug delivery systems involving SIPs. Furthermore, the assembly stability of drug delivery systems involving SIPs in the blood circulation, off-target effects, and scaling synthetic protocols are important factors in advancing drug delivery systems involving SIPs. Future research on drug delivery systems involving SIPs should focus on integrating multiple stimuli in tumor microenvironments, such as redox potentials, pH, and enzymatic activity, as described above in this review. Together, these alternative SIP-based architectures expand the design space of programmable nanomedicines by coupling structural disassembly with amplified stimulus responsiveness across diverse supramolecular platforms.

5 TME-RESPONSIVE SIPS IN THERANOSTICS (IMAGING-GUIDED THERAPY)

5.1 Imaging-Therapeutic Integrated Platform Design

Theranostic systems are molecular or nanoscale structures that combine diagnostic imaging with therapeutic intervention in a single system. TME-sensitive SIPs provide an efficient and unique platform because they combine molecular sensing and therapy in a self-amplifying depolymerization mechanism.[31] In contrast to the usual polymer-drug conjugates, which depend on the controllable release of drugs through diffusion or cleavage of a single bond, SIPs are cleaved through cascade depolymerization activated by just one triggering event and are rapidly unzipped at the backbone. This domino-dependent signal amplification, increased sensitivity to pathological cues, and effective payload release makes SIPs especially ideal for responsive imaging-based cancer treatment.[33]

The rational design of SIP-based theranostic platforms is based on the rational inclusion of TME-labile chemical motifs such as disulfide, boronate ester, imine, or enzyme-cleavable linkers responding to endogenous tumor signals, such as increased glutathione concentration, reactive oxygen species, acidic pH, hypoxia, or aberrant enzymatic activity.[136] When activated, self-immolative depolymerization can release both imaging reporters (*e.g.*, fluorogenic reporters or MRI contrast reporters) and therapeutic payloads (*e.g.*, chemotherapeutics, photosensitizers, or immunomodulators).[76] This synchronized activation enables a direct correlation between diagnostic readouts and therapeutic response, facilitating real-time monitoring of drug release, tumor penetration, and treatment efficacy while minimizing off-target toxicity.

Recent advances in self-immolative polymer nanotheranostics have enabled the rational integration of tumor microenvironment-responsive drug release with high-field imaging capabilities, exemplified by a glutathione-activated platform designed for ultrahigh-field (UHF) MRI-guided hepatocellular carcinoma therapy.[137] A glutathi-one-responsive self-immolative polymer nanotheranostic platform (CA4@SIPD) chelated with Dy(III) was developed for UHF MRI-guided hepatocellular carcinoma therapy.[138] The disulfide-containing polymer undergoes tumor-associated GSH-triggered cascade depolymerization, enabling efficient and controlled release of the vascular-disrupting agent combretastatin A4 while simultaneously degrading the carrier. Owing to the high magnetic moment and fast electron relaxation of Dy(III), CA4@SIPD exhibited markedly enhanced weighted contrast performance under UHF MRI conditions. This platform integrates microenvironment-responsive drug delivery with high-performance UHF MRI, allowing real-time tumor visualization and synchronous therapeutic monitoring and highlighting the potential of self-immolative polymers in next-generation imaging-guided cancer theranostics. Furthermore, to address the challenges of long circulation, deep tumor penetration, and efficient intracellular drug release in solid tumors, a zwitterion, star-shaped auto-degradable nanoarchitecture was engineered *via* a layer-by-layer block copolymer strategy, yielding about 25 nm electroneutral nanoparticles with high DOX loading, excellent serum stability, and prolonged blood circulation (>72 h).[139] This system undergoes synergistic enzyme-triggered self-degradation in endolysosomal compartments, enabling efficient intracellular drug release, deep tumor penetration, and effective pancreatic tumor suppression *in vivo*. Integrated NIR imaging further confirmed stable tumor accumulation and retention, highlighting its promise as a stealth theranostic platform for hard solid tumor treatment.

5.2 Real-time Monitoring of Drug Release and Tumor Regression

The capacity to monitor the release of the drug and regression of the tumor in real time is a characteristic of TME-responsive SIPs in theranostics. In contrast to traditional nanocarrier methods that are based on passive accumulation or prolonged degradation of the matrix, SIP-based systems convert a single biochemical stimulus into a cascade depolymerization reaction, which allows systematic activation of the therapeutic part and amplification of the diagnostic signal. This unzipping mechanism can contribute to the direct conjugation of polymer degradation with optical, magnetic, or nuclear imaging outputs, thus delivering a quantitative and time-resolved readout of the dynamics of drug release in tumors.[40,128]

In typical SIP-based theranostics, tumor-associated stimuli, including acidic pH, elevated GSH, ROS, or aberrant enzymatic activity, cleave a terminal trigger group and initiate head-to-tail depolymerization.[77] The resulting release of multiple reporter units per triggering event affords intrinsic signal amplification, enabling the sensitive detection of polymer disassembly *in vivo*. Fluorogenic SIPs of quenched near-infrared (NIR) dyes or aggregation-induced emission luminogens have been commonly used in imaging the intracellular release of drugs, where recovery of fluorescence is related to depolymerization rates and cytotoxicity.[76] Similarly, redox-respon-

sive SIP prodrugs carrying doxorubicin or mitoxantrone have been shown to exhibit GSH or ROS-dependent fluorescence turn-on, quantitatively predicting intracellular drug release and therapeutic outcome.[33]

In addition to fluorescence imaging, SIPs have been integrated with MRI, PA, and positron emission tomography (PET) to enable deep tissue and longitudinal monitoring of treatment response. For example, disulfide-containing SIP nanotheranostics doped with paramagnetic ions undergo GSH-triggered depolymerization, simultaneously releasing chemotherapeutics and generating MRI contrast agents *in situ*.[60] Longitudinal imaging revealed that signal enhancement temporally coincides with maximal drug release and tumor regression, establishing a direct causal relationship between molecular activation and macroscopic therapeutic outcomes.[76,77] Chemiluminescent SIPs further extend this capability by eliminating the need for external excitation, allowing background-free visualization of ROS-amplified depolymerization and treatment-induced oxidative stress.

Notably, imaging feedback with therapy can be integrated to allow SIP-based systems to be active and adaptive treatment systems, rather than passive carriers. SIP theranostics can now provide early indicators of therapeutic response by correlating signal kinetics with tumor growth inhibition, and can be used to optimize the dose. However, there are still difficulties in overcoming intratumoral heterogeneity, reducing interference by the accumulation of nonspecific probes, and compatibility with clinically relevant imaging windows including NIR-II, MRI, and PET. Further developments in logic-gated SIP designs, multimodal signal integration, and quantitative pharmacokinetic modeling are likely to continue to improve real-time "see-treat-verify" strategies and enable faster clinical translation.

5.3 Overcoming Penetration Depth and Sensitivity Limitations

Although having potential in cancer theranostics, their clinical translation is traditionally limited by inadequate penetration into tumor tissue and poor imaging sensitivity, especially in large and dense or hypoxic solid tumors.[96,31] This abnormal tumor vasculature, elevated interstitial fluid pressure, and high-density extracellular matrix (ECM) all limit the deep diffusion of nanoscale carriers and limit therapeutic activation and diagnostic signal generation to the perivascular tissue. Thus, these physical and functional barriers are important factors that need to be addressed to ensure the full effectiveness of SIP-based platforms.[31].

An effective strategy involves the design of transformable SIP nanostructures that undergo size or charge modulation in response to TME cues.[96,111] In circulation, SIP assemblies are typically engineered as stable nanoparticles (about 80–120 nm) to prolong blood residence time. Upon exposure to acidic pH, ROS, or tumor-specific enzymes, cascade depolymerization induces disassembly into ultra-small fragments (<30 nm), enabling enhanced diffusion within tumor cores and a more homogeneous intratumoral distribution.[140] Charge-reversible SIPs further exploit tumor acidity to switch from neutral or anionic states to cationic species, thereby promoting cellular internalization and penetration through the negatively charged ECM.[140,141] Complementary approaches incorporate ECM-modulating agents or enzymatically degradable linkers within SIPs to locally soften stromal barriers, thereby facilitating deeper transport of both therapeutic and imaging components.

Simultaneously, signal attenuation and sensitivity loss in deep tissues require a combination of amplified and multimodal imaging techniques to overcome this lack of advantages. Traditional fluorescence and PA techniques are limited in terms of penetration depth because of light scattering and absorption.[32] To address this, SIPs have been engineered to generate amplified outputs or secondary signals upon depolymerization, such as gas generation, catalytic ROS production, or the release of high-relaxivity MRI contrast agents.[142] Multimodal SIPs systems that incorporate fluorescence or PA with MRI, CT, or ultrasound offer complementary depth and spatial resolution, warranting reliable tumor delineation on both spatial scales. Notably, SIPs operating in the NIR-II window (1000–1700 nm) significantly reduced tissue scattering and autofluorescence, enabling deeper imaging and more accurate monitoring of drug release and tumor response.[143]

This is further enhanced by the penetration capabilities of SIP-based theranostics using external energy sources. SIP can be remotely activated by ultrasound, X-ray, and NIR, and ultrasound can be used in combination with TME-responsive depolymerization to induce the spatial control of drug delivery to deep-seated tumors. Additionally, self-immolative signal amplification ensures that even weak biochemical cues in poorly perfused tumor regions are translated into robust diagnostic outputs. Future SIP designs are expected to integrate depth-adaptive responsiveness, precise size or charge conversion kinetics, and biodegradable backbones that depolymerize into renally clearable fragments, thereby minimizing long-term accumulation. The convergence of these strategies is essential for overcoming penetration and sensitivity barriers, ultimately enabling precise, deep tissue, and image-guided cancer therapy.

6 CONCLUSIONS AND PERSPECTIVES

SIPs with TME responses have emerged as a powerful and versatile class of materials for precision oncology, bridge-building between molecular-level tumor sensing, and targeted therapeutic interventions. In addition to their modular structure and tunable self-degradation kinetics, SIPs are highly selectively activated within tumor tissues based on several TME stimuli, such as pH, ROS, GSH, enzymes, and hypoxia, thereby maximizing therapeutic efficacy and minimizing off-target effects. Over the past decade, SIPs have evolved from simple degradable backbones to sophisticated platforms capable of synergistically integrating multiple functions, including real-time imaging, controlled drug release, and multimodal therapies. This evolution reflects the increased appreciation of the dynamic and heterogeneous nature of the TME and the need for polymeric systems that can adapt to complex chemical and physical cues.

Tumor imaging with TME-responsive SIPs has demonstrated substantial improvements in sensitivity and specificity. By exploiting "turn-on" fluorescence caused by degradation, fluorogenic SIPs enable precise tumor localization. CL-based SIP platforms minimize background interference while enhancing the signal-to-noise ratios by eliminating the need for ex-

ternal excitation. Multimodal imaging systems can be used to visualize anatomical and functional structures by combining near-infrared fluorescence (NIRF), photoacoustic imaging (PA), magnetic resonance imaging (MR), and positron emission tomography (PET). Several approaches have been used to improve the resolution and accuracy of SIP-mediated tumor imaging, including signal amplification *via* cascading polymer degradation, selective enzyme and ROS activation, and the rational modulation of polymer hydrophobicity and charge. Combined, these innovations demonstrate the importance of SIPs as versatile molecular probes for noninvasive, high-fidelity tumor detection.

Therapeutically, TME-responsive SIPs enable spatiotemporally regulated drug release profiles that match the physiological conditions of the tumor microenvironment. Combination therapy platforms that incorporate chemo-immunotherapy or photothermal/photodynamic therapy expand therapeutic efficacy through synergistic mechanisms using pH-, ROS-, and GSH-responsive SIP micelles and prodrugs. Because of their localized, sustained release, hydrogels and other SIP-based delivery matrices reduce systemic toxicity and improve patient compliance. A single SIP construct, theranostics, integrates imaging and therapeutic functions to offer real-time monitoring of drug release, tumor regression, and therapeutic responses, making it possible to tailor treatment regimens based on the needs of individual patients. Additionally, advances in polymer design, such as the development of self-amplifying and hierarchical degradation systems, have addressed the classical limitations in tissue penetration depth, signal intensity, and systemic stability, thus extending the clinical application of SIP-based platforms.

Although significant progress has been made, several challenges remains before TME-responsive SIPs can realize their full translational potential. In particular, improving trigger selectivity to better discriminate between tumor and normal tissues is essential for minimizing off-target activation. Rational tuning of end-cap sensitivity and backbone electronics is critical to reduce premature depolymerization during systemic circulation while preserving rapid activation within the TME. Additionally, enhancing the *in vivo* stability through optimized nanostructural design and hydrophilic–hydrophobic balance may improve pharmacokinetics and tumor accumulation. Addressing these design parameters is pivotal for translating SIP platforms into clinically viable precision oncology systems.

BIOGRAPHY

Youyong Yuan received his Ph.D. degree in Polymer Chemistry and Physics from the University of Science and Technology of China in 2012. He subsequently conducted postdoctoral research in the Department of Biomedical Engineering at the National University of Singapore from 2012 to 2017. He joined the School of Biomedical Science and Engineering, South China University of Technology, in 2017, where he is currently a full Professor. He leads a research group focusing on biomaterials and drug delivery, bioorthogonal chemistry, and tumor microenvironment-responsive nanomedicine for precision cancer imaging and therapy.

Conflict of Interests

The authors declare no interest conflict.

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Graphical Abstract

Tumor Microenvironment-responsive Self-immolative Polymers for Cancer Imaging and Therapy

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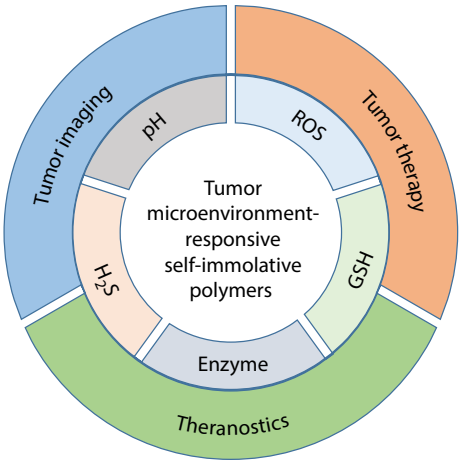
Tumor microenvironment-responsive self-immolative polymers (SIPs) undergo cascade depolymerization triggered by pH, ROS, GSH, H_2S, and enzymes. This amplified response enables enhanced tumor imaging, controlled drug release, and integrated theranostics, providing precise spatiotemporally regulated platforms for cancer diagnosis and combination therapy.



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