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Ultrasound-activated mechanochemical reactions for controllable biomedical applications

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ABSTRACT

Intramolecular bonds in small organic molecules, macromolecules, and organic-inorganic hybrids are broken or formed by ultrasound-activated mechanical force that can be applied with spatial and temporal precision for contactless external control of mechanochemical reactions. Ultrasound featuring non-invasiveness, high tissue penetration, and spatiotemporal controllability has shown great potential in controlling the activation of mechanochemical reactions such as chemical bond scission, natural enzyme activation, and catalytic radical generation for targeted drug or gene therapy. Here, we comprehensively summarize the latest research and future trends in ultrasound-activated mechanochemical reactions for smart biomedical applications. First, the mechanism of ultrasound-activated mechanochemical reactions will be outlined. Then, the types of mechanochemical reactions will be carefully discussed. After that, the representative biomedical applications have been summarized from a unique perspective. Finally, we systematically emphasize the current challenges and future outlooks to guide the rational design of ultrasound-activated drug release over conventional drug-loaded therapies. We believe that this review will substantially facilitate the progression and widespread utilization of ultrasound-activated mechanochemical reactions in biomedical applications.

1. Introduction

Intramolecular bonds in small organic molecules, macromolecules, and organic-inorganic hybrids are broken or formed by mechanical force that can be integrated with spatial and temporal precision for external control of mechanochemical reactions [1–3]. As one kind of mechanical wave, ultrasound (US) oscillates periodically at frequencies beyond 20 kHz that are over the range of human hearing [4–6]. The US featuring the advantages of non-invasiveness, high tissue penetration, and spatiotemporal controllability has shown great potential in control activation of mechanochemical reactions such as chemical bond scission [7,8], natural enzyme activation [9], and catalytic radical generation for targeted drug or gene therapy [10,11].

Ultrasound can exhibit two main biological effects, including mechanical effects and cavitation effects [12,13]. The mechanical effect is the main effect of ultrasonic waves, which can promote the movement of molecules in the tissue, produce a stimulating effect on cells, and change the permeability of cell membranes [14–16]. In addition, ultrasound has a heat-generating effect caused by the transfer of acoustic energy, raising the temperature in the medium [17,18]. The cavitation effects result from the oscillation of the bubble under intermittent sound pressure, and the resulting bubble rupture exerts a shear force on the surrounding medium [19]. The shear force can disrupt drug delivery vectors, generate highly reactive free radicals, and produce interactive effects, such as enhanced drug permeability and sonodynamic therapy [20–22].

Recently, researchers have paid close attention to controlled drug carrier switches, prodrug conversion, releasing or activating gases,

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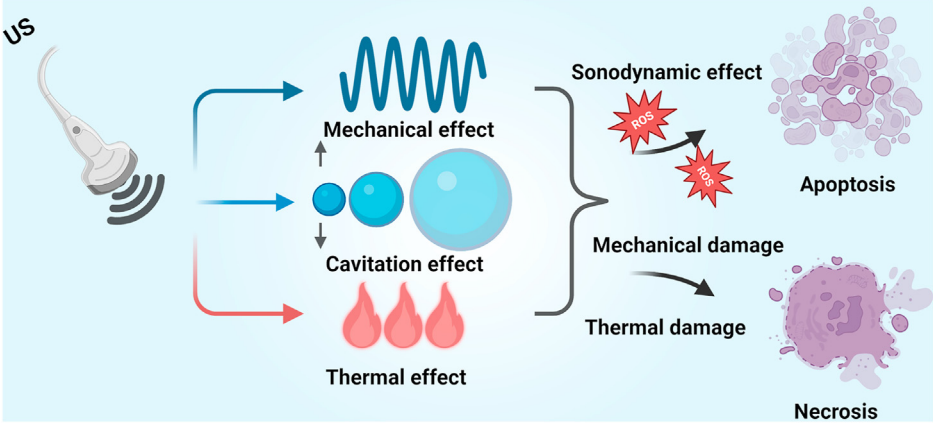


Scheme 1. The biological effect mechanisms of ultrasound.

activating mechanically sensitive ion channels [23], *in situ* synthesis in vivo, and many other application fields with the synergy of ultrasound [24–26]. Based on these ultrasound-activated mechanochemical reactions, ultrasonic treatment systems provide a viable exception because they lead to mechanical and chemical events through unique acoustic phenomena [27,28]. For these treatment systems, separate ultrasound, including high and low-intensity ultrasound, can directly result in the chemical bond scission or formation [29,30]. Microbubbles or other bubble-generating nanoplatforms synergistic with ultrasound could enhance the mechanical chemical reactions [31–34]. Additionally, some precursor molecules, in response to reactive oxygen species, can be activated by ultrasound-synergistic sonosensitizers [35–37]. This trend has been supported largely by a shift toward integrating ultrasound with smart systems, which benefit from the advantages mentioned above of ultrasound [38,39].

This timely review comprehensively summarizes the significant progress in the past five years and future trends in ultrasound-activated mechanochemical reactions for smart biomedical applications. First, the mechanism of US-activated mechanochemical reactions in mechanical, cavitation, thermal, and sonodynamic effects will be outlined. Subsequently, the types of mechanochemical reactions, including covalent and non-covalent bond scission, will be carefully discussed. Thereafter, the representative biomedical applications have been summarized with a unique perspective on intelligently controlled carrier switches, prodrug conversion, releasing or activating gases, activating mechanically sensitive ion channels, and synthesis in vivo. Finally, we systematically highlight the current challenges and future outlooks to guide the rational design of ultrasound-activated drug release over conventional drug-loaded therapies, for instance, those designed to be combined with small pharmaceutical molecules. This cutting review is believed to substantially stimulate the development and widespread utilization of ultrasound-activated mechanochemical reactions in future biomedical applications.

2. Mechanisms of US-activated mechanochemical reactions

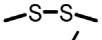
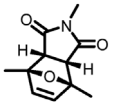
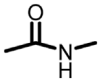
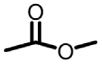
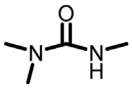
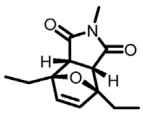
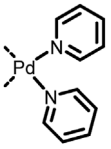
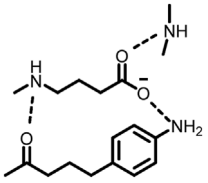
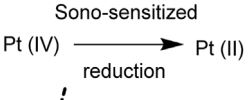
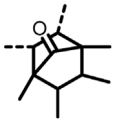
US-activated mechanochemical reactions refer to chemical reactions that are initiated, accelerated, or otherwise influenced by the application of US. The physiological parameters of necrosis or tumor microenvironment, such as pH, ROS, and glutathione, invariably differ from those of the normal cells and tissues [12,40]. The heterogeneity of these physiological variations motivates the development of intelligent, controlled, and targeted drug release systems [24,41]. The US is a bio-favorable mechanical wave that has displayed practical significance in biomedical fields. Extensive research has revealed that US stimulates cavitation, pyrolysis, sonoporation, sonoluminescence, and other biophysical and chemical effects [30,42]. Of the various advanced techniques explored so far, the US-responsive smart materials are of particular interest due to their desirable features. For instance, US-responsive smart materials are noninvasive and nonionic, delivering mechanical waves that can penetrate underlying tissue with negligible attenuation [43,44]. The ultrasonic wave can generate mechanical vibration, caviation effect, and sonodynamic effect that can activate drug, cause certain predetermined reactions in the molecular structure, break the homeostasis of the drug carrier which result in controllable therapeutic effects (Scheme 1) [45,46]. This section will discuss the mechanisms, reactions, etc (Table 1).

2.1. Mechanical effect

The mechanical effects of US primarily refer to the mechanical actions and effects generated when US propagates through a medium. These effects are based on the properties of ultrasonic waves and their interaction with materials. As US propagates through a medium, it causes mechanical vibrations of the medium's molecules, creating high-frequency regions of compression and rarefaction, forming longitudinal and transverse waves of US. These vibrations can lead to a variety of mechanical effects. A typical mechanical action is a radiant force, which means that applying ultrasound to an organism through a fluid with a sound speed of c is the same as applying a steady-state force to the same entity [59].

The Herrmann group proposed an unprecedented mechanochemical responsive platform capable of release of furan-containing organic molecules, a fluorophore with the furylated group, and the furosemide, and the furylated doxorubicin in an on demand sequentially-controlled manner. This was possible thanks to the US-induced controllable breakage of the disulfide-centered polymers. Ultrasound acts on sulfhydryl-terminated polymers to form Michael-type adducts, which then lead to the formation of Diels−Alder (DA) adducts of furylated drugs and acetylene dicarboxylic acid derivatives. This process activates the release of small-molecule drugs through the reverse DA reaction (Fig. 1a and b) [47]. The Zheng group made a surprising discovery that advanced the use of ultrasound stimulation in medicine. They found that dihydroethidium (DHE) can generate ROS when activated by US, transforming it into ethidium (EB). The excited DHE reacts with O_2 to produce $\bullet O_2^-$ and EB, while the ground-state DHE reacts with $\bullet O_2^-$ to generate EB and •OH. Moreover, EB can induce DNA damage, leading to both oxidative stress therapy and chemotherapeutic effects simultaneously. This discovery presents the opportunity for glutathione-acted release of DHE in tumor tissues, creating a special kind of prodrug that is not dependent upon ROS as an initiator but can react to US excitation, directly release curative drugs, and even induce ROS production. This discovery has already been applied in the field of tumor therapy (Fig. 1c–f) [60].

Table 1
The mechanochemical bonds, reaction, biomedical application of ultrasound-activated controllable biomedical applications.

Chemical Bond	Reaction	Application	Reference
	Diels-Alder reactions	Release of the small-molecule drug	[47]
	Aromatic isomerization rearrangement reactions	Selectively triggered release of therapeutic drug with fluorogenic	[48]
	Microbubble-induced amide bond breaking	Noninvasive cavitation-enhanced ultrasound to facilitate drug delivery	[48]
	Breakage of ester bonds	Ultrasound-Induced Targeted Drug Delivery	[49]
	Ultrasound-induced amide bond breaking	Visualization of targeted drug therapy triggered by low-intensity ultrasound	[50]
	electrocyclization	Ultrasound-induced cascade drug release	[51]
	Cycloelimination of 1,2-dioxetane	Visualization of chromaticity changes in ultrasound-activated PDMS membranes	[52]
	isomerization reaction	Ultrasound-induced continuous controlled release of cargo	[53]
	metal coordination reaction	Ultrasound-activated drug release	[54]
	hydrogen bonding force	Highly efficient drug-carrying capacity	[55]
	liposome package	Dual-programmed deep-tissue acoustic power-iron prolapse-induced immunotherapy	[56]
	reduction reaction	ultrasonically responsive electron transfer pathway	[57]
	open-loop reactions	Ultrasonic activation of CO gas release	[58]

Furthermore, there are mechanisms based on an adaptor that can specifically combine with thrombin and inhibit its catalytic performance. Through US-induced inertial cavitation, the interactions between the adaptor and the thrombin are destroyed, regaining the enzyme's ability to facilitate the conversion of fibrinogen into fibrin (Fig. 1g–l) [61]. The Herrmann group proposed an innovative concept that sets apart the design of linear polymers from traditional ones. They manipulate the polymer's structural arrangement to control the US-induced release of drugs that are covalently bound to the polymer matrix. This approach involves mechanoresponsive disulfide crosslinked microgels and DA adducts of furylated molecules with copolymerized acetylene dicarboxylic acid. The selected microgels markedly minimize ultrasonication times compared with linear polymeric chains and effectively protect the cargo through ultrasound activation that generates inertial cavitation at 20 kHz.

2.2. Cavitation effect

The phenomenon of gas- or vapor-filled cavities (bubbles) forming or becoming active within a medium exposed to an ultrasonic field is referred to as cavitation effect, in which bubbles are compressed by positive pressure and expanded during negative pressure [62]. The cavitation effect is classified as non-inertial or inertial based on the oscillation amplitude [63]. The recurrent oscillation and expansion of the bubbles without breaking, which happens at a relatively low sound intensity, is known as non-inertial cavitation. In contrast, inertial cavitation, termed collapse cavitation, happens when bubbles are created by cavitation vibrating violently under higher intensity ultrasonic waves, ultimately bursting or collapsing. Cavitation effects are extensively used in the biomedical field, including targeted drug delivery, enhancing the delivery of therapeutics across biological barriers, sonothrombolysis, and

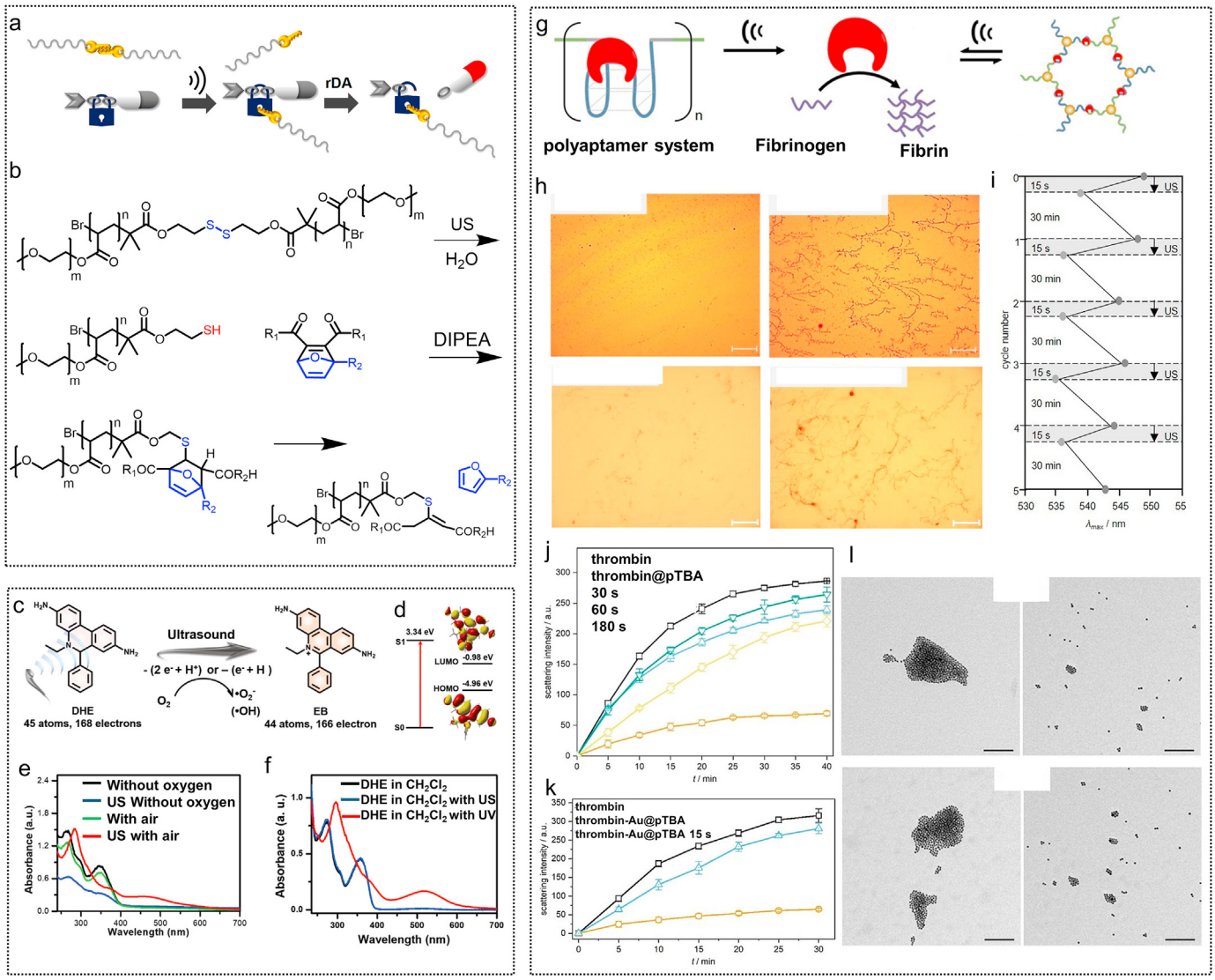


Fig. 1. Representative examples of US-activated mechanochemical reactions for drug activation. (a–b) US-induced covalent bond scission of polymer mechanochemical S—S bonds to activate drugs [47]. Copyright 2020, American Chemical Society. (c) Scheme of the US-activated ROS and EB. (d) Theoretical calculation for excited state energy of S_1 and HOMO/LUMO orbital of DHE. (e–f) UV–vis spectra of DHE in aqueous state upon US irradiation (1.0 MHz) in air or N_2 atmosphere, respectively; and in CH_2Cl_2 solution upon US irradiation (1.0 MHz) or UV irradiation [60]. Copyright 2023, WILEY-VCH. (g) Split aptamer-conjugated Au NPs for inhibiting thrombin activity. (h) Optical microscope images of different group-treated fibrinogen. Scale bar: 50 μm. (i) The reversibility of the disassembly and reassembly of thrombin@Au@TBA_{15} (20 kHz) induced by US was examined, with five cycles of disassembly and reassembly (each involving 15 s of US and a 30-min recovery period) monitored using UV–vis spectroscopy. Real-time light scattering spectra of fibrinogen solution (j) with thrombin (control) and thrombin@$pTBA_{15}$ treated with US for 0, 30, 60, and 180 s, respectively, and (k) with thrombin, thrombin@Au@TBA_{15} treated with US for 15 s. (l) TEM images for aggregated (left) and dispersed (right) Au NPs with US in cycle 1 and cycle 5. Scale bar: 100 nm [61]. Copyright 2021, WILEY-VCH.

cancer treatment [64]. One of the key applications is in drug delivery.

Ultrasound's spatiotemporal controllability, biocompatibility, and feeble attenuation in tissues have steadily advanced the field of intelligent drug delivery platforms with its vast potential for remote activation [65–68]. The latest technology for ultrasound-triggered payloads is based on encapsulated microbubbles. Currently, the development of mainstream carrier technology mainly follows two categories: microbubbles and phase-change nanodroplets. Microbubbles fulfill an essential role in the transportation and release of nanoparticle loads or chemicals upon ultrasound stimulation. The research on microbubbles spans nearly 30 years, initially used as an ultrasound contrast agent and more recently as a controllable targeted drug carrier and on-demand release system utilizing medically relevant ultrasound. Yao et al. developed an innovative synergistic mechanism based on functionalized polymers to enable tunable activation with biocompatible focused US by utilizing gas vesicles that respond to pressure as mechanochemical transducers [48]. Critical to the above methodology is a pressure-responsive air-filled protein nanostructure to transform low-frequency acoustic to mechanical force and then selectively trigger the release of therapeutic drug molecules with fluorogenic pass through a furan–maleimide Diels–Alder covalent structure (Fig. 2a).

Microbubbles could also be used to disperse nanoparticles in multiple media. Nanodroplets were vesicles including a core of phase change material that could be modified by functional drugs. Suitably scaled microbubbles can also mechanochemically trigger the release of small aminocoumarin molecules upon ultrasound stimulation (Fig. 2b). Current mainstream research considers that noninvasive cavitation-enhanced ultrasound could produce sufficient agitation to create open spaces in biofilms to facilitate drug delivery and high efficiently kill the bacterial biofilm.

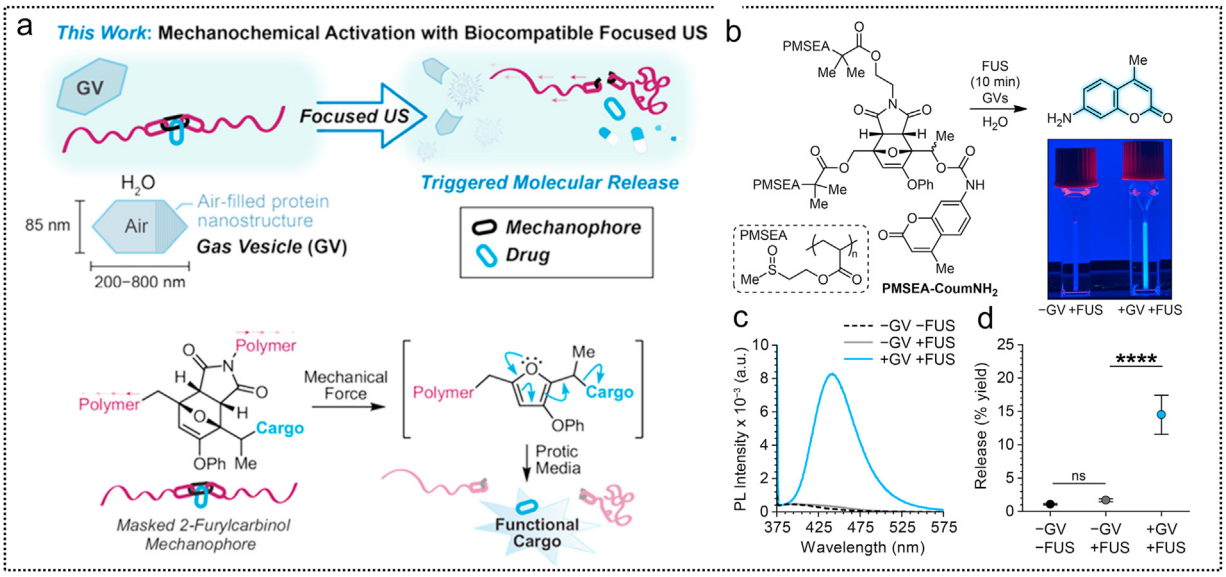


Fig. 2. Biocompatible focused US and gas vesicles (GVs) activated mechanochemical reactions in physiological conditions. (a) Mechanism schematic utilizing GVs with acoustic-mechanical regulator functionality to achieve mechanochemical activation of the functionalized polymer in physiological conditions using a biocompatible FUS, which triggers the release of the molecular payload. (b) Example demonstrating the use of biocompatible FUS to mechanochemically trigger the release of small aminocoumarin molecules. (c–d) Illustration of aminocoumarin release by photoluminescence (PL) spectroscopy [48]. Copyright 2023, National Academy of Sciences.

2.3. Thermal effect

During the propagation of ultrasonic waves in the medium, some of the acoustic energy will be absorbed by the medium and transformed into heat. Moreover, ultrasound cavitation can lead to thermal effects, which are exhibited two forms. One is the continuous thermal effect arising from the sustained oscillation of cavitation bubbles, which can lead to thermal energy deposition in the sound field region. The other is the instantaneous thermal effect when the cavitation bubble suddenly collapsed [10].

2.4. Sonodynamic effect

US is applied to the target area that can penetrate deep into tissues without being absorbed significantly and activate sonosensitizers that generates reactive oxygen species (ROS) and other free radicals [6]. ROS can induce oxidative stress in cells, leading to cell death that result in tumor inhibition. sonosensitizers and US-induced inertial cavitation can both generate ROS. Sonosensitizers can shift from ground state to excited state after absorbing ultrasonic energy. When the excited sonosensitizers returns to the ground state, the energy released causes the surrounding O_2 to produce a large number of ROS, which can initiate a cascade of biochemical reactions, including breaking DNA, shrinking cytoskeleton, and mitochondrial membrane potential reduction. In the end, these physiological processes ultimately lead to cancer cell damage or even apoptosis [63].

Considering the serious side effects associated with the non-targeted nature of conventional chemotherapeutic drugs, the Jiang group proposed a radically different strategy than the traditional one, based on the development of an US-activated liposome with prodrug-loaded CPBSN38L including the sonosensitizer chlorin (Ce6) and the prodrug PBSN38 [49]. After CPBSN38L incrementally aggregating in the tumor microenvironment and uptaking by the tumor cells, US excitation causes the Ce6 to rapidly generate a large amount of intracellular ROS. ROS-responsive cascade activation of PBSN38 leads to cell apoptosis and the subsequent release of the active SN38 (Fig. 3a–e). Furthermore, the researchers also proved therapeutic US-induced scission of urea bonds for drug release. Such transformations have been demonstrated to be initiated by ·OH in the interior of cavitation bubbles and then the cavitation occurring on a two-phase (bubble−liquid) interface. Upon stimulation with 1 MHz low-intensity therapeutic US, the urea bonds covalently linked with primary amines can be selectively cleaved, and the free methylene blue (MB) is controllably released in a physiologically relevant microenvironment or tumor lesion tissue [50]. Moreover, due to the hydrophobic MB, this interface-confined reaction can be conducted with little interference from the hydrophilic reductant in solution, which allows for a novelty “agent of US” strategy with superior efficiency and selectivity (Fig. 3f–j).

3. Types of mechanochemical reactions

3.1. Covalent bond scission

Covalent bond-based drug-carrying presents a prevalent strategy to construct drug molecules with controlled and precise targeted release [69–71]. It is worth noting that this strategy is centered on breaking covalent bonds by US stimulation. Drug molecules can be effectively concentrated on tumor tissue, and once the drug's molecular target is reached, the active drug is released in time [14,72]. After all, we prefer to avoid premature release of the drug into other normal tissues or organs, causing drug leakage and damage to the organism [73–76]. Huo et al. reported a release strategy of secondary cascades containing a disulfide bond polymer carrying the anticancer drug camptothecin (CPT). Irradiation with US caused the unstable S-S bond to split, and the disulfide transformed into thiols, activating an intramolecular *5-exo-trig* cyclization, liberating, and then triggering the CPT from the carbonate [77]. This cascade strategy advances the exploration of US-induced activation and release of drugs for developing smart biomedical applications. Kim et al. demonstrated an efficient elastomeric polydimethylsiloxane (PDMS) network to realize spatiotemporal controllable mechanophore activation by utilizing high-intensity focused ultrasound (HIFU) as a remote and non-invasive energy source to drive the mechanical-to-chemical transduction. The molecular sites of the bisvinyl joint in the naphthopyran mechanophore effectively passed mechanical force to the mechanophore's C–O pyran bond to induce ring-opening reactions for electrocyclization (Fig. 4a and b) [51]. Subsequently, Kim

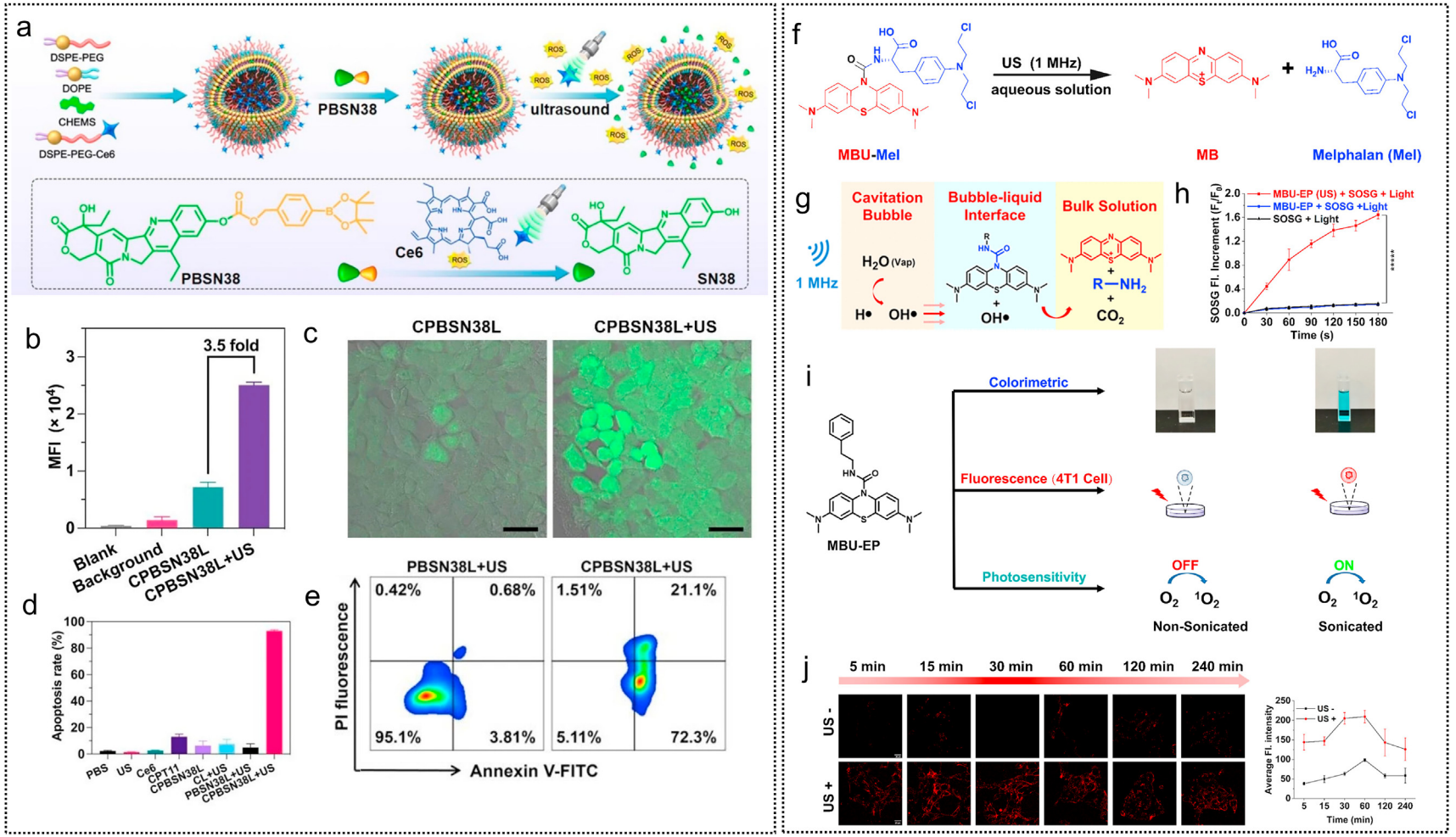


Fig. 3. Scheme of the US-induced prodrug-loaded delivery process and transformation. (a) Scheme of the US-induced prodrug-loaded liposome for targeting therapy. (b–c) Quantitative results of the flow cytometry analysis and confocal laser scanning microscopy (CLSM) images of the intracellular ROS levels in MC38 colon adenocarcinoma cells after different treatments. (d–e) Flow cytometry analysis of cell apoptosis [49]. Copyright 2024, Springer Nature. (f–g) Schematic of the US-induced transformation of MBU-Mel and proposed urea-bond scission mechanism. (h–i) US-controlled generation of oxygen in a single linear state. (j) Fluorescent images demonstrate of MBU-EP in 4T1 cells by sonication or without sonication activation [50]. Copyright 2022, American Chemical Society.

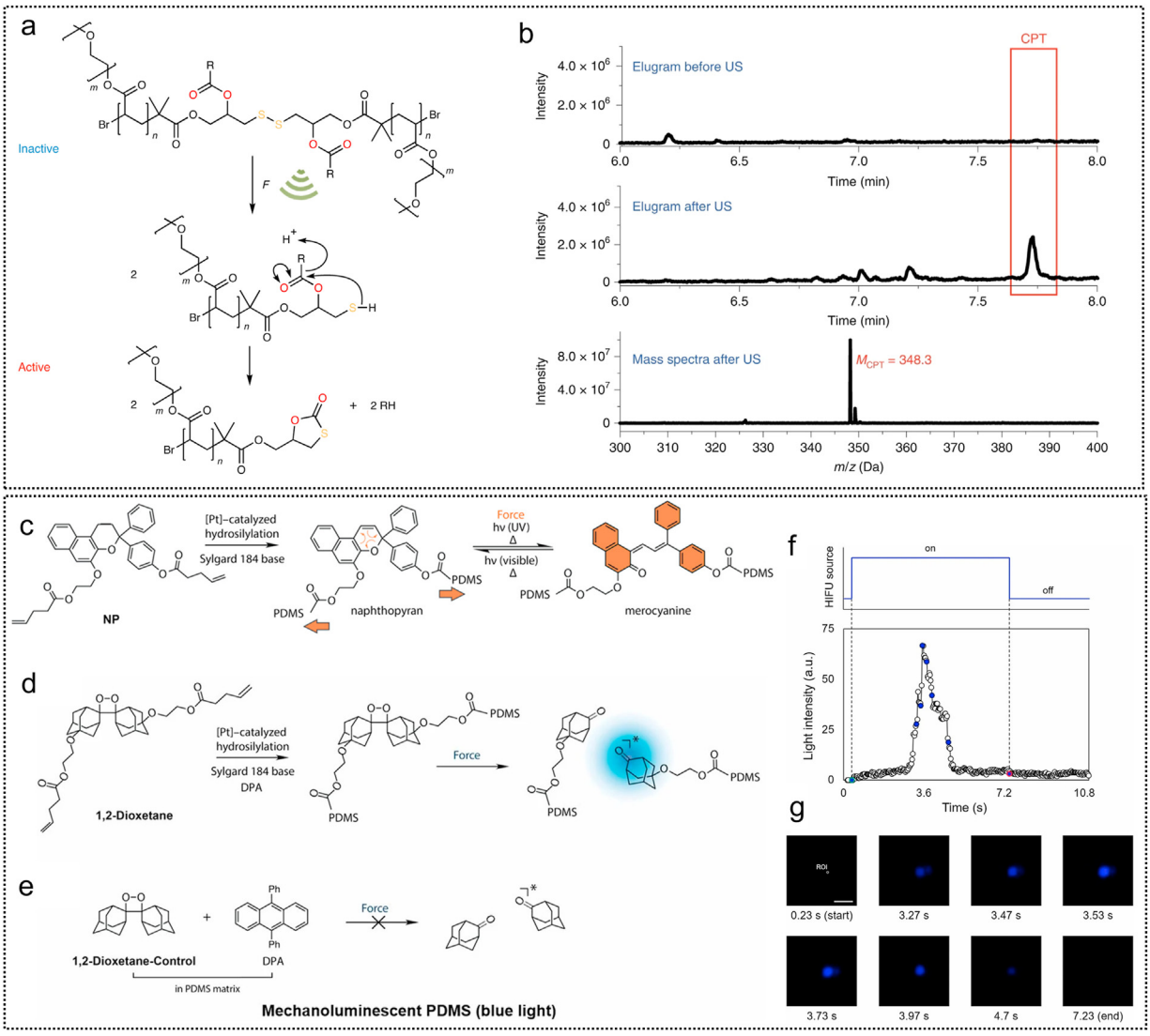


Fig. 4. Display of covalent bond breaking to release cargo under ultrasonic stimulation. (a) US excitation cleaves disulfide polymers spawning a 5-*exo*-trig cyclization and then releases CPT from its β-carbonate linker. (b) Mass spectrometry proved that CPT was produced after ultrasound [51]. Copyright 2021, Springer Nature. (c–e) Synthesis of chromic PDMS materials and isomerization reaction upon US mechanical force. (f–g) Plot of the generated blue-light intensity and optical images versus time [52]. Copyright 2019, National Academy of Sciences.

et al. first envisaged US-triggered polymeric mechanical carriers and biosystem-compatible platforms by utilizing HIFU as a remote controllable energy source to propel the spatio-temporal mechanical--to-chemical conduction in mechanoresponsive polymers [52]. Both the isomerization of NP and the cycloelimination of 1,2-dioxetane were realized utilizing mechanical energy delivered from HIFU excitation, resulting in visual chromaticity variation on functionalized PDMS films (Fig. 4c–g).

Meanwhile, Hu's group designed a general and efficient modular mechanophore system based on adaptive spontaneously decomposed sheltered 2-furylcarbinol derivatives. When subjected to a contactless mechanically triggered stimulation in a moderate environment, this system allows the selective control of bond breaking and the release of a covalently linked molecular payload [53]. Besides, they established structure−property relationships based on the reactivity characterization of 2-furylcarbinol derivatives that trigger the mechanically controllable release of diverse functional cargo (Fig. 5a). Shi et al. showed a US-responsive release platform based on a continuously controlled release mechanism. This was achieved through a mechanical force-activated cyclization that induced the rupture of disulfide-bearing cargo molecules linked through a b-carbonate linker. This bifunctional theragnostic approach allows visual tracking of drug release within the cell (Fig. 5b).

3.2. *Non-covalent bond scission*

The ultrasound-triggered approach due to mechanical forces is based on the scission of the covalent bond between the carrier and the drug [78–80]. Besides covalent bonds, non-covalent interactions can also be used to design a platform for activating drugs using ultrasound. Therefore, under low-level mechanical forces, responsive effects can be triggered, such as hydrogen bonds and mechanical force-induced conformational changes [81]. The mechanical breakage of hydrogen bonds is observed in the mechanical unfolding of proteins and serves as a remarkable example. For instance, Kung presented a star-shaped supramolecular coordination cage structure with numerous intermolecular hydrogen interactions that respond to ultrasonication-activated mechanical shear force. This structure uses polymer-branched bipyridine as ligands for assembling an octahedral Pd^{II}_6 $(TPT)_4$ supramolecular cage containing ibuprofen and progesterone drugs inside its hydrophobic nanocavity. When ultrasound is applied to the aqueous solution, the caged polymer is activated by shear force and ruptures to release the drug

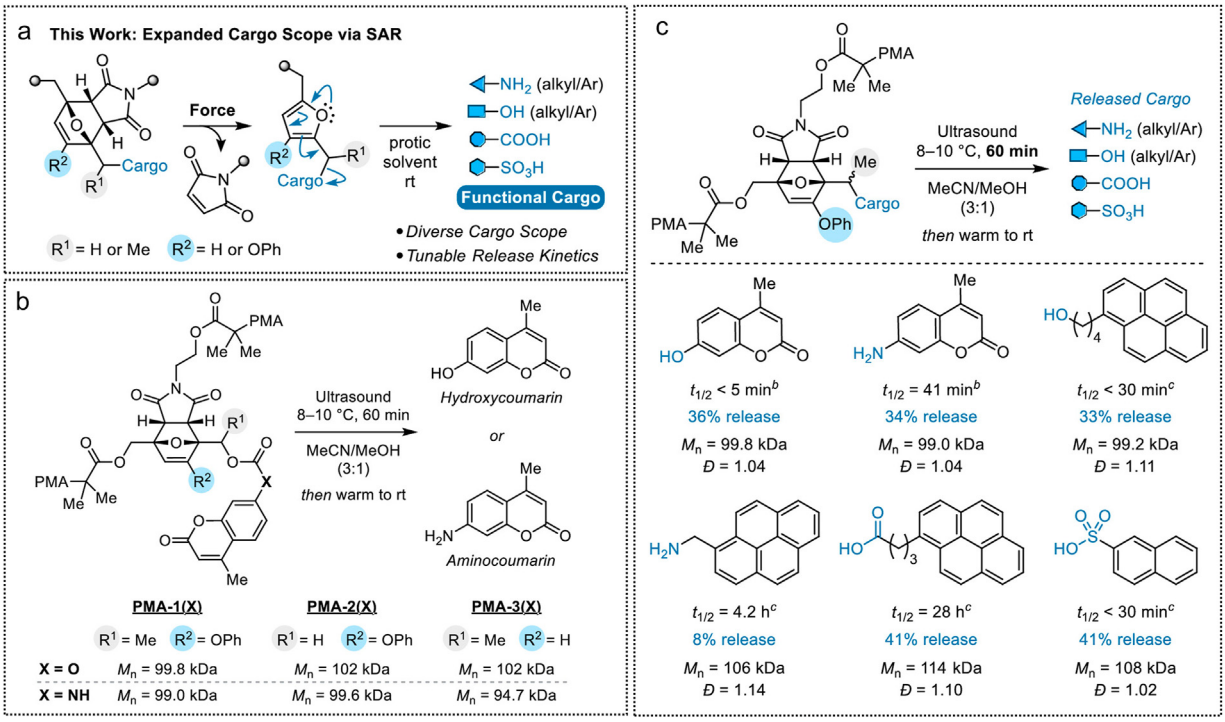


Fig. 5. Examples display mechanically triggered molecular release cargo. (a) US-triggered controllable release functional cargo via a cascade Retro-DA/Fragmentation isomerization reaction. (b) US-triggered Mechanical activation of the release of fluorescent cargo. (c) Mechanically triggered cargo release with α-methyl/phenoxy substitution [53]. Copyright 2021, American Chemical Society.

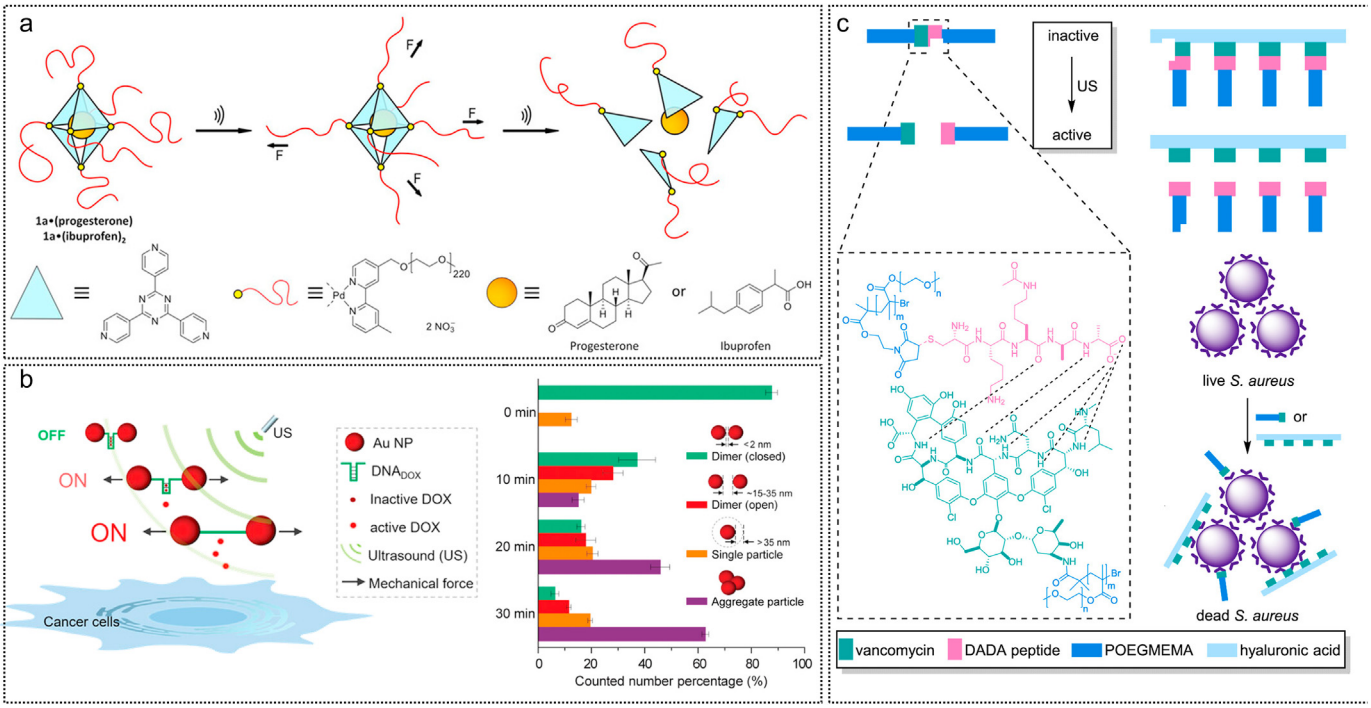


Fig. 6. Schematic representation of the ultrasonic activation response to several noncovalent bond scission. (a) Ultrasound activation induces fragmentation of the cage and releases non-covalently bound cargo [54]. Copyright 2021, WILEY-VCH. (b) Ultrasound-controlled release of DOC selectively inhibits cancer cells through activating dimerization nano-switches [82]. Copyright 2022, WILEY-VCH. (c) Glycopeptides to kill Gram-positive bacteria by ultrasound-controlled activation of surface binding and inhibition of the cell wall [55]. Copyright 2022, American Chemical Society.

(Fig. 6a) [54].

Huo et al. conceptualized a mechano-nano-switch to selectively activate the anti-cancer drug doxorubicin (DOX) via ultrasonication. This switch was based on mechanochemistry using two gold nano-particles (AuNPs) as a transmitter medium of mechanical shear force. Double-stranded DNA chains connected the two AuNPs acting as a force-sensitive mechanophore. Upon US stimulation, the nano-switch, integrated with DOX, became extended, breaking the specific noncovalent

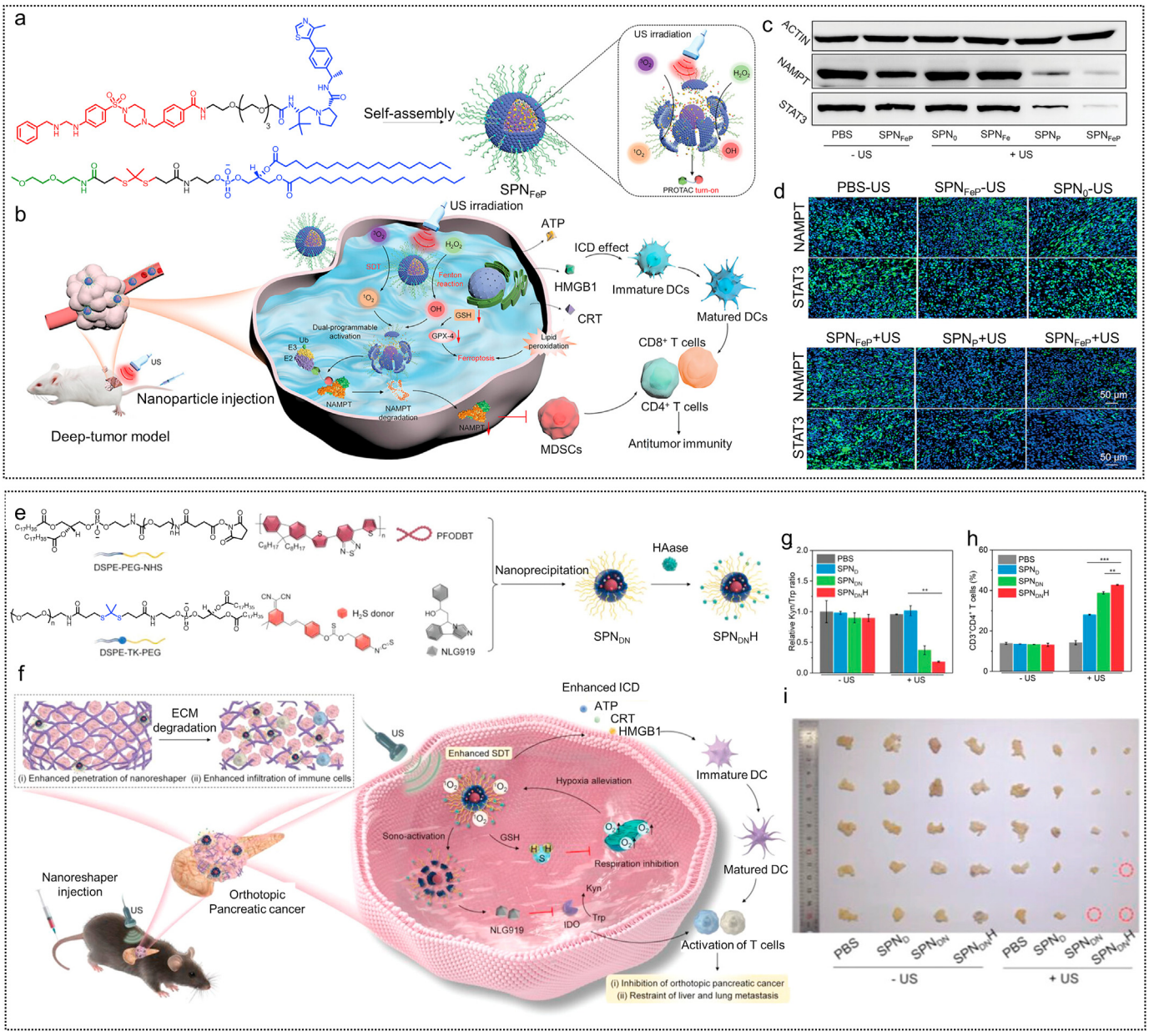


Fig. 7. Schematic illustration of Ultrasound-activated smart drug delivery and release. (a–b) Mechanisms and concepts of dual-programmable semiconducting polymer for deep-tissue tumors therapy. (c) The expression of GPX-4 in CT26 cells. (d) CRT immunofluorescence staining images of CT26 cells [56]. Copyright 2024, WILEY-VCH. (e–f) Mechanisms and concepts of multiply remodel tumor microenvironment for potent immunotherapy through ultrasonically responsive of orthotopic pancreatic cancer. (g–h) Kyn/Trp ratio analysis for treated before and after Ultrasound-activated panc02 cells (n = 5). (i) Tumor images of orthotopic pancreatic cancer-bearing mice [100]. Copyright 2023, WILEY-VCH.

interactions between the drug and the DNA, causing DOX to be activated and released (Fig. 6b) [82]. A similar design concept was used for US activation of vancomycin, which showed the development of mechanophore-centered linear chains, resulting in an increase in drug potency through mechanochemical dissociation (Fig. 6c) [55].

4. Biomedical applications

Ultrasound biomedicine, a unique interdisciplinary field involving materials science, chemistry, and clinical medicine, is dynamically and rapidly evolved. Ultrasound's spatiotemporal controllability, superficial attenuation in tissue [83–85], and biocompatibility [86–90] have steadily progressed the field of intelligent drug delivery platforms with its vast potential for controllable remote activation [91–96], which hold a tremendous deal of potential for overcoming the intricate obstacles that prevent efficient drug delivery in disease therapies. These innovative approaches, ranging from ultrasound-responsive nanoparticles [97], switchable nanocarriers, and ultrasound-induced prodrug conversion, provide a comprehensive strategy for boosting therapeutic results and drug penetration in a variety of diseases [98]. However, it's still in its exploration stages. Considering the high level of interest in this field, it is essential to propose new ideas and applications [99]. In the next sections, we will cover the use of ultrasound in medicine.

4.1. Intelligently controlled carrier switches for drug release

Wang's group presented a semi-conducting polymer named nano-PROTAC (SPN_{FeP}), which achieved ultrasound and tumor microenvironment synergy, facilitating a dual-programmable response for deep-tissue sonodynamic-ferroptosis-based immunotherapy [56], this

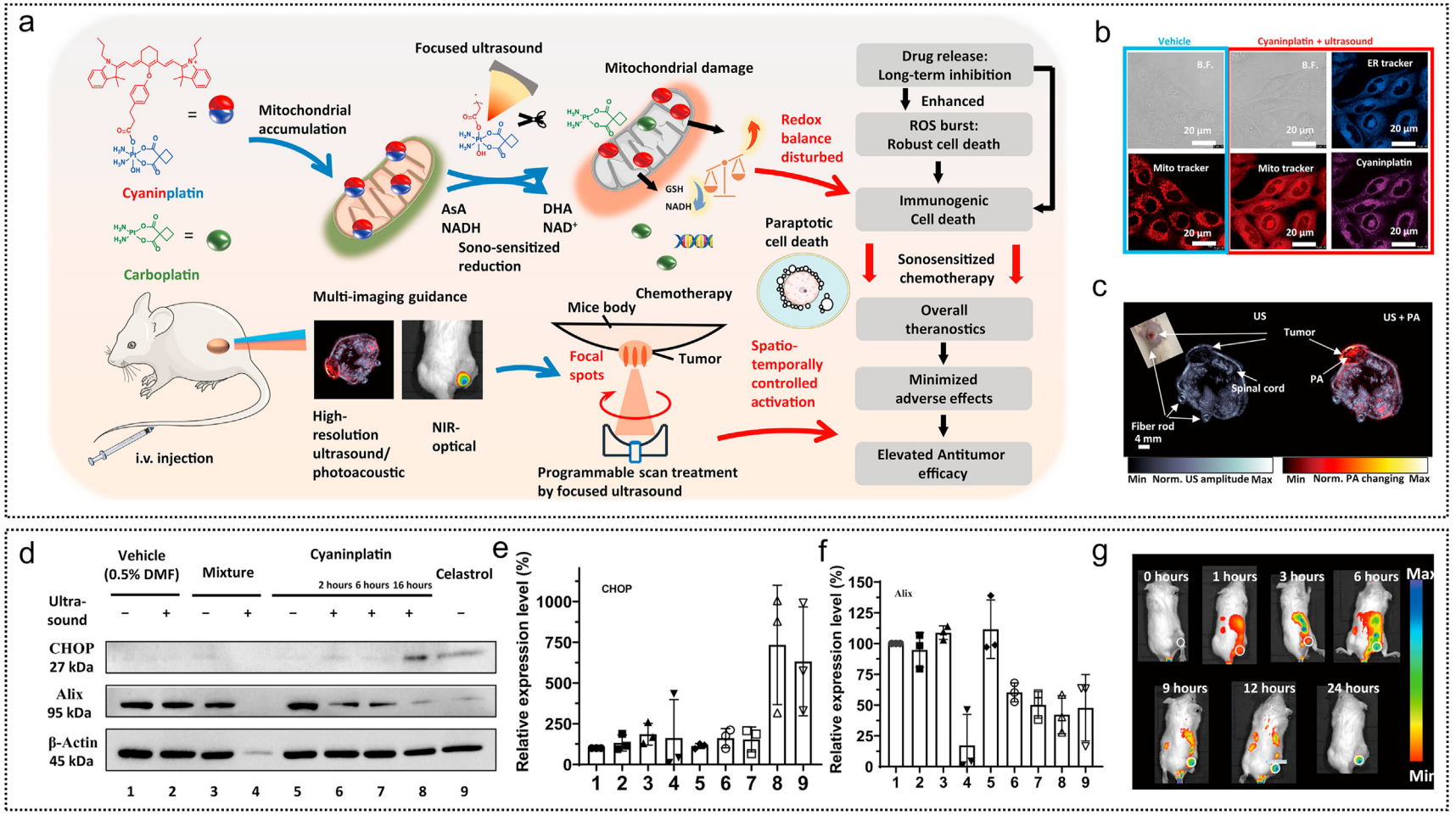


Fig. 8. Schematic illustration of prodrug conversion for drug activation. (a–f) Focus on ultrasound-activated Cyaninplatin to induce apoptosis in cancer cells and multimodal imaging-guided therapy. (g) NIR optical imaging to verify tumor accumulation of Cyaninplatin [57]. Copyright 2023, AAAS.

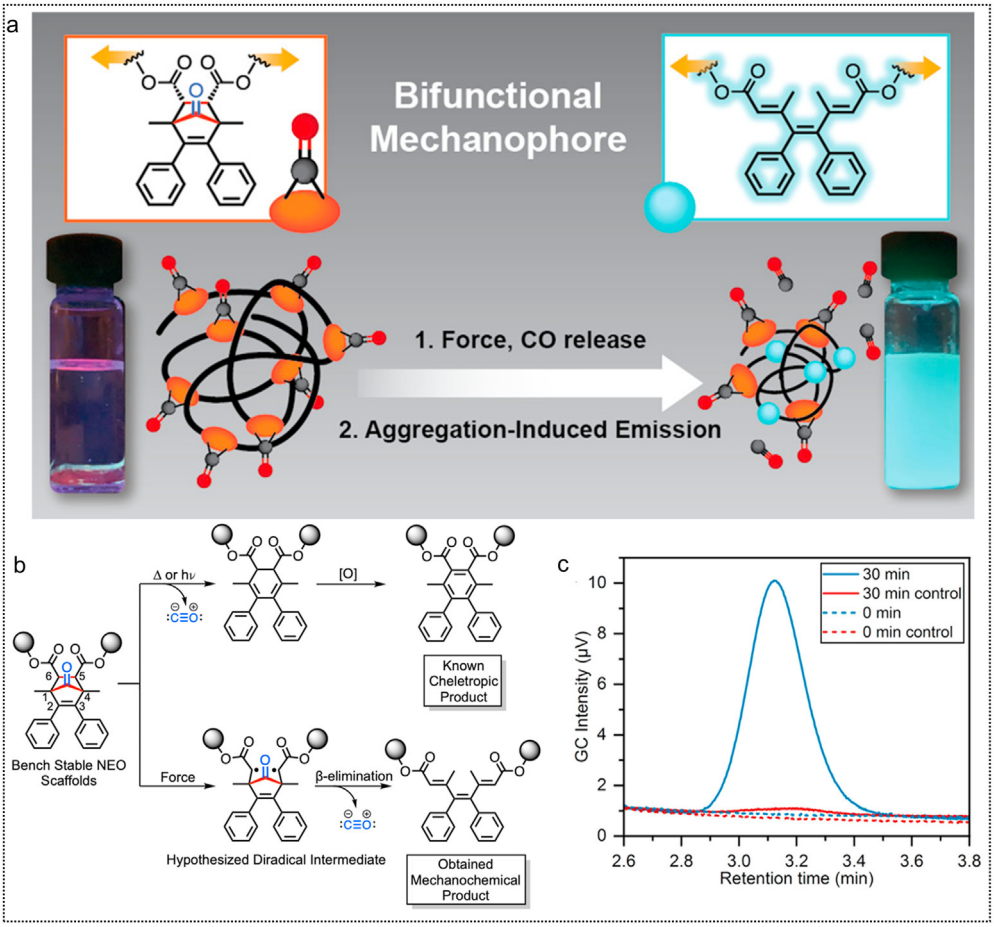


Fig. 9. Scheme of ultrasonically activated gas release. (a–b) Ultrasound mechanically triggered CO release. (c) GC-TCD quantification of CO release [58]. Copyright 2022, American Chemical Society.

approach not only induces ferroptosis and immunogenic cell death (ICD) but also stimulates the controlled release of PROTAC molecules into tumor tissues. The activated nano-PROTACs effectively suppress the activity of nicotinamide phosphoribosyl transferase (NAMPT), thereby preventing the infiltration of myeloid-derived suppressive cells (MDSCs) into tumors and enhancing antitumor immunity (Fig. 7a). Moreover, ultrasound has the advantage of being precise and controllable, as shown by Li's group with the creation of a sono-activatable $SPN_{DN}H$ to precisely target drug delivery and the remodeling of tumor tissue microenvironment to enhance anti-tumor immunological response [100]. The $SPN_{DN}H$ includes $^1O_2$-responsive units encapsulated in a semiconducting polymer (PFODBT), a H_2S donor, and NLG919 encapsulated in the nanoparticle core, along with chemical modification of hyaluronidase on the surface. This dense extracellular matrix (ECM) substrate leads to multiple remodeling of hypoxia and immunosuppressive pathways, resulting in an effective anti-tumor effect via the synergy of SDT with immunotherapy (Fig. 7b).

4.2. Prodrug conversion for drug activation

Liu et al. presented a molecular paradigm utilizing a US-activated Pt ionic (IV) prodrug that attains targeted delivery of Pt (II) ions chemotherapeutics through an ultrasonically responsive electron transfer pathway. After US treatment with precise and remote spatiotemporal control, there was a significant reduction of mitochondria-targeted Pt (IV) ions, leading to the delivery of carboplatin. This reduction process also resulted in the simultaneous depletion of intracellular reductants, reinforcing ROS-triggered apoptosis. This synergistic treatment not only led to a rapid release of Pt (II) ion therapeutics but also overcame drug resistance by circumventing the antioxidant defense system (Fig. 8a) [57]. Researchers developed a real-time, rapid, and noninvasive treatment system designed to improve sperm cell motility via ultrasound irradiation at 40 MHz and 800 mW. The results of single-cell analysis of sperm cells, conducted using droplet microfluidics, show that US irradiation led to a 266 % increase in the motility of relatively immotile sperm cells, with 72 % of initially immotile sperm exhibiting a swimming velocity of over 5 μm s^{-1}. These exciting results allow a real-time, rapid, and noninvasive clinical program for increasing sperm cell viability as an alternative to more invasive treatments in the most challenging cases of assisted reproduction and improving assisted reproduction outcomes (Fig. 8b).

4.3. Release or activate gases for diagnosis or treatment

Sun's group developed a non-scissile bifunctional mechanophore based on US-activated mechanochemical reaction including norborn-2-en-7-one (NEO). The innovation point is the release of carbon monoxide (CO) after pulsed US stimulation, with a release efficiency of 58 %, corresponding to a release of 154 molecules of CO per chain (Fig. 9) [58].

4.4. Activate mechanically sensitive ion channels

Sorum et al. studied the sub-millisecond activation kinetics of the mechanosensitive K^+ channel TRAAK in response to mechanical stimulation [101]. They found that ultrasound and mechanical stimulation have a similar effect on the channel, as revealed by single-channel recordings. They noted that ultrasonic energy is transmitted to TRAAK via the membrane tension, which in turn boosts channel opening. They also

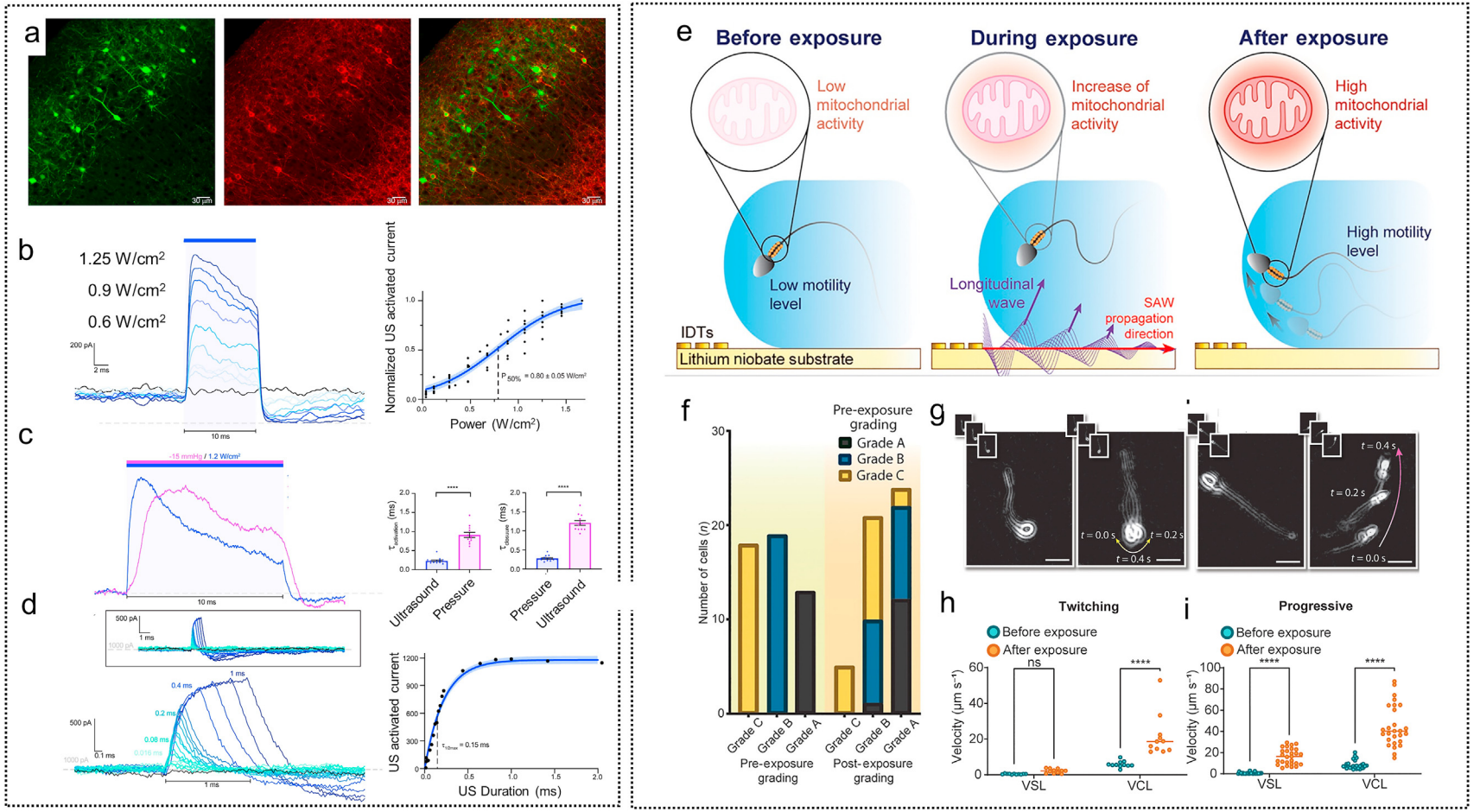


Fig. 10. Schematic diagram of ultrasound activates physiologic microenvironmental alterations. (a) Confocal fluorescent images of a juvenile mouse cortex in utero. (b–d) Relationship between ultrasound and current and pressure channels [101]. Copyright 2021, National Academy of Sciences. (e) Schematic diagram of the interdigital transducers used to analyze the effects of ultrasound on sperm cells and transducer. (f) Comparison of the number of spermatozoa of each motility class was counted before and after ultrasound irradiation. (g) High-speed imaging of twitching and progressive states. (h–i) Two-way AnOVA-matched values of twitching and progressive states [102]. Copyright 2024, AAAS.

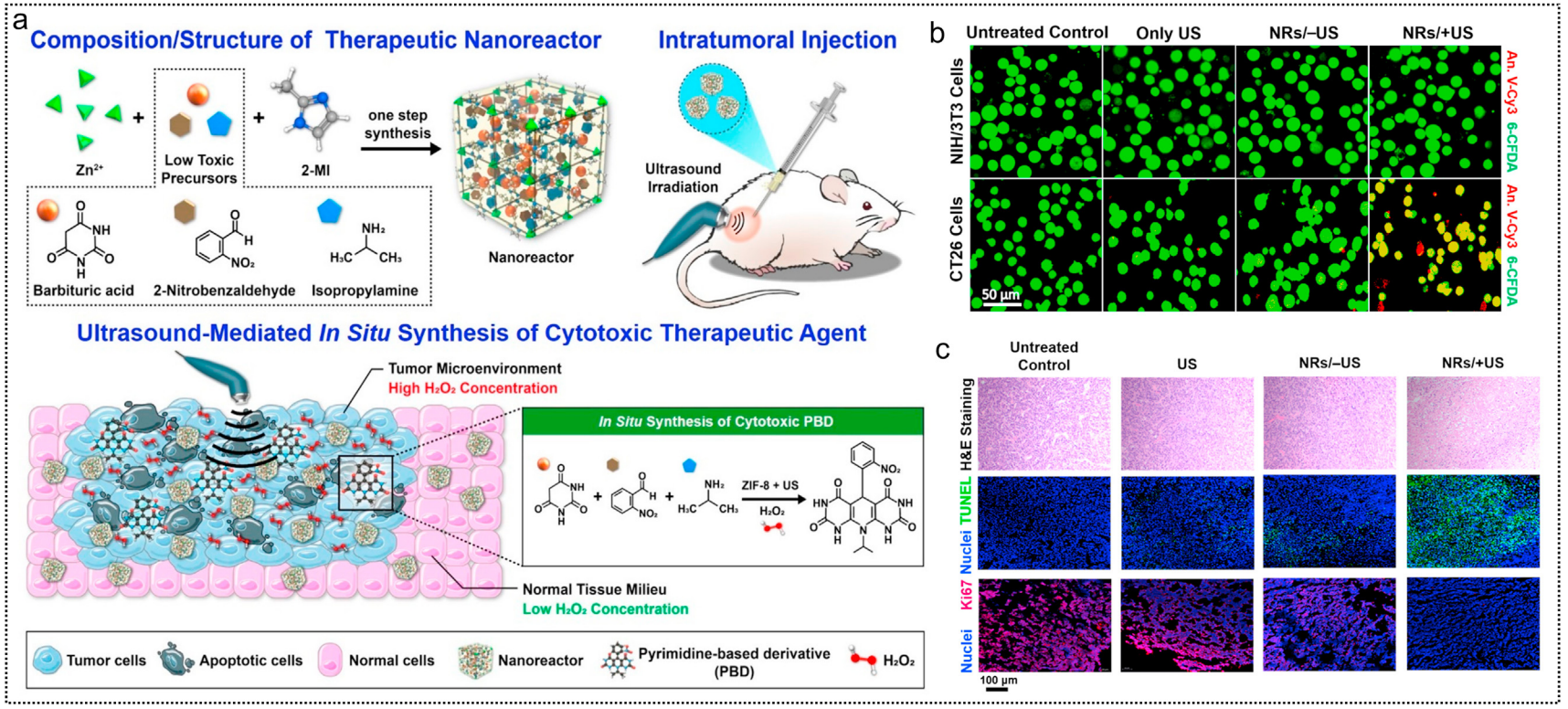


Fig. 11. Schematic diagram of the *in situ* transformation of drugs at a tumor site. (a) Schematic of *in situ* synthesis of Cytotoxic PBD. (b) Cytotoxicity and cell apoptosis of synthesized PBD. (c) Results of histological analysis [103]. Copyright 2022, American Chemical Society.

discovered that TRAAK expressed in neurons can be modulated by ultrasound. These results suggest that US can modulate TRAAK activity, making it a potential tool for acoustic neuromodulation (Fig. 10) [102].

4.5. *In situ synthesis in vivo*

Siboro's group reported a nanoreactor (NR) that can be utilized for the *in situ* synthesis of antitumor drug precursors, consisting of a zinc-based zeolitic imidazolate salt framework. These NRs were injected intratumoral in a tumor-bearing mouse model and then US was used to activate NRs *in situ* synthesis [103]. The US helps the drug-carrying NRs platform penetrate into the tumor tissue to eradicate it and cover the lesion entirely. However, only the tumor tissue with higher H_2O_2 concentrations can access the antitumor drug, hindering anti-tumor research. The proposed approach specifically binds to tumor targets *in situ* with minimal in vivo toxicity, which is potentially a promising biocompatible strategy for precision chemotherapy (Fig. 11).

5. Outlooks and perspectives

Over the past few decades, research has shifted its focus to the biomedical field and the pharmacology of disease as more and more researchers recognize the unique advantages of ultrasound-activated drug release over conventional drug-loaded therapies. For example, US-active drugs are designed to be combined with small pharmaceutical molecules. As a result, the design and fabrication of smart drug carriers with ultrasound controllability is a hot research topic.

The numerous research examples discussed in this review demonstrate the mechanism of ultrasound activation, types of mechanochemical reactions, and medical applications. The mechanism of action of ultrasound activation mainly consists of covalent and non-covalent forces induced by ultrasound, cavitation effects, and acoustic kinetic activity. At the same time, ultrasound is mainly responsible for breaking covalent bonds and rearranging reactions by inducing, for example, the breaking of disulfide bonds, ether bonds, etc. Based on these in-depth studies of the mechanisms and responses to ultrasound activation, researchers have also developed a range of ultrasound-activated drugs and other treatments.

Despite the unique advantages and promising applications of ultrasound for controlled drug release and drug activation, there are still some challenges to overcome at this stage. Firstly, under the premise of ensuring biosafety, basic laboratory research should try to use clinical ultrasound equipment. At the same time, efforts should be made to improve the mechanical force response efficiency of carrier materials to high-frequency ultrasound. Secondly, most current research focuses on conceptual innovations, which is quite far from the routine clinical application of ultrasound modulation of drug activity. In addition, many studies have demonstrated that nanostructures possess high ultrasound response efficiency. Combining them with traditional polymer systems to construct new drug delivery systems with simple processes and sensitive mechanical forces will also be the next key research direction worth pursuing. Thus, to further expand the innovations of ultrasound diagnostic techniques and the scope of sonochemistry, and pave the rock-solid way for future ultrasound intelligent medical application-driven advancements, fundamental inquiries require to be addressed.

- Further exploration of what additional and potential response mechanisms are selectively altered by ultrasound waves?
- What innovative strategies can be implemented to optimize ultrasound systems to further increase the energy efficiency?

It should be focused on integrate novel fabrication and synthesis methods, such as ultrasound assisted with 3D printing, achieving integration of intelligent materials for medical use that enable large-scale manufacturing, precise control, and rapid availability.

To conclude, ultrasound-activated mechanochemical reactions for intelligent and precise biomedical applications offer both opportunities and challenges. Based on the progress experienced by ultrasound medicine, more intelligent and targeted precision will be further developed and advanced.

CRediT authorship contribution statement

Maocheng Zuo: Writing – original draft, Investigation, Data curation. **Rong Xiao:** Writing – original draft, Conceptualization. **Fangxue Du:** Writing – review & editing, Writing – original draft, Conceptualization. **Chong Cheng:** Writing – review & editing, Supervision, Conceptualization. **Raul D. Rodriguez:** Writing – review & editing, Supervision, Conceptualization. **Lang Ma:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization. **Bihui Zhu:** Writing – review & editing, Writing – original draft, Conceptualization. **Li Qiu:** Writing – review & editing, Writing – original draft, Supervision, Conceptualization.

Declaration of competing interest

Given her role as editorial board member of this journal, Prof. Li Qiu was not involved in the editorial review or the decision to publish this article and had no access to information regarding its review.

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References

[1] S. Mateti, M. Mathesh, Z. Liu, T. Tao, T. Ramireddy, A.M. Glushenkov, W. Yang, Y.I. Chen, Mechanochemistry: a force in disguise and conditional effects towards chemical reactions, Chem. Commun. 57 (9) (2021) 1080–1092.
[2] R.T. O'Neill, R. Boulatov, The many flavours of mechanochemistry and its plausible conceptual underpinnings, Nat. Rev. Chem 5 (3) (2021) 148–167.
[3] Z. Shi, Y. Hu, X. Li, Polymer mechanochemistry in drug delivery: from controlled release to precise activation, J. Contr. Release 365 (2024) 259–273.
[4] Z. Feng, X. Xiang, J. Huang, L. Wang, B. Zhu, H. Zhou, H. Pang, C. Cheng, L. Ma, L. Qiu, Intelligent sonocatalytic nanoagents for energy conversion-based therapies, Adv. Funct. Mater. 33 (45) (2023) 2302579.
[5] M. Liao, J. Du, L. Chen, J. Huang, R. Yang, W. Bao, K. Zeng, W. Wang, B.C. Aphan, Z. Wu, L. Ma, Q. Lu, Sono-activated materials for enhancing focused ultrasound ablation: design and application in biomedicine, Acta Biomater. 173 (2024) 36–50.
[6] B. Liu, F. Du, Z. Feng, X. Xiang, R. Guo, L. Ma, B. Zhu, L. Qiu, Ultrasound-augmented cancer immunotherapy, J. Mater. Chem. B 12 (15) (2024) 3636–3658.
[7] D. Yildiz, R. Göstl, A. Herrmann, Sonopharmacology: controlling pharmacotherapy and diagnosis by ultrasound-induced polymer mechanochemistry, Chem. Sci. 13 (46) (2022) 13708–13719.
[8] P. Ma, X. Lai, Z. Luo, Y. Chen, X.J. Loh, E. Ye, Z. Li, C. Wu, Y.-L. Wu, Recent advances in mechanical force-responsive drug delivery systems, Nanoscale Adv. 4 (17) (2022) 3462–3478.
[9] W.H. Rath, R. Göstl, A. Herrmann, Mechanochemical activation of DNAzyme by ultrasound, Adv. Sci. 11 (8) (2024) 2306236.
[10] L. Tu, Z. Liao, Z. Luo, Y.-L. Wu, A. Herrmann, S. Huo, Ultrasound-controlled drug release and drug activation for cancer therapy, Explorations 1 (3) (2021) 20210023.
[11] Q. Zeng, G. Li, W. Chen, Ultrasound-activatable and skin-associated minimally invasive microdevices for smart drug delivery and diagnosis, Adv. Drug Deliv. Rev. 203 (2023) 115133.
[12] X. Pan, W. Huang, G. Nie, C. Wang, H. Wang, Ultrasound-sensitive intelligent nanosystems: a promising strategy for the treatment of neurological diseases, Adv. Mater. 36 (22) (2024) 2303180.
[13] H. Yuan, L. Zhang, T. Ma, J. Huang, C. Nie, S. Cao, X. Xiang, L. Ma, C. Cheng, L. Qiu, Spiky cascade biocatalysts as peroxisome-mimics for ultrasound-augmented tumor ablation, ACS Appl. Mater. Interfaces 14 (14) (2022) 15970–15981.
[14] D. Huang, J. Wang, C. Song, Y. Zhao, Ultrasound-responsive matters for biomedical applications, Innovation 4 (3) (2023) 100421.

[15] Q. Wang, Y. Zhang, H. Xue, Y. Zeng, G. Lu, H. Fan, L. Jiang, J. Wu, Lead-free dual-frequency ultrasound implants for wireless, biphasic deep brain stimulation, Nat. Commun. 15 (1) (2024) 4017.
[16] L. Wang, L. Zhang, F. Chen, Q. Li, B. Zhu, Y. Tang, Z. Yang, C. Cheng, L. Qiu, L. Ma, Polymerized network-based artificial peroxisome reprogramming macrophages for photoacoustic imaging-guided treatment of rheumatoid arthritis, ACS Appl. Mater. Interfaces 16 (20) (2024) 25856–25868.
[17] Y. Zhu, Y. Liu, K. Khan, G. Arkin, A.K. Tareen, Z. Xie, T. He, L. Su, F. Guo, X. Lai, J. Xu, J. Zhang, Ultrasound combined with nanomaterials for cancer therapy, Mater. Today Adv. 17 (2023) 100330.
[18] J. Zhai, H. Yang, Z. Wang, Y. Li, C. Ning, Multifunctional nanomaterials-enhanced synergistic sono-phototherapy: breaking the limitation of monotherapy, Smart Mater. Med. 3 (2022) 315–328.
[19] Q. Shen, Z. Li, Y. Wang, M.D. Meyer, M.T. De Guzman, J.C. Lim, H. Xiao, R.R. Bouchard, G.J. Lu, 50-nm gas-filled protein nanostructures to enable the access of lymphatic cells by ultrasound technologies, Adv. Mater. 36 (28) (2024) 2307123.
[20] F. Li, J. Gallego, N.N. Tirko, J. Greaser, D. Bashe, R. Patel, E. Shaker, G.E. Van Valkenburg, A.S. Alsubhi, S. Wellman, V. Singh, C.G. Padilla, K.W. Gheres, J.I. Broussard, R. Bagwell, M. Mulvihill, T.D.Y. Kozai, Low-intensity pulsed ultrasound stimulation (LIPUS) modulates microglial activation following intracortical microelectrode implantation, Nat. Commun. 15 (1) (2024) 5512.
[21] Y. Tang, Z. Wu, R. Guo, J. Huang, X. Rong, B. Zhu, L. Wang, L. Ma, C. Cheng, L. Qiu, Ultrasound-augmented anti-inflammatory exosomes for targeted therapy in rheumatoid arthritis, J. Mater. Chem. B 10 (38) (2022) 7862–7874.
[22] X. Rong, Y. Tang, S. Cao, S. Xiao, H. Wang, B. Zhu, S. Huang, M. Adeli, R.D. Rodriguez, C. Cheng, L. Ma, L. Qiu, An extracellular vesicle-cloaked multifaceted biocatalyst for ultrasound-augmented tendon matrix reconstruction and immune microenvironment regulation, ACS Nano 17 (17) (2023) 16501–16516.
[23] B. Sorum, T. Docter, V. Panico, R.A. Rietmeijer, S.G. Brohawn, Tension activation of mechanosensitive two-pore domain K+ channels TRAAK, TREK-1, and TREK-2, Nat. Commun. 15 (1) (2024) 3142.
[24] W. Wang, X. Wu, K.W. Kevin Tang, I. Pyatnitskiy, R. Taniguchi, P. Lin, R. Zhou, S.L.C. Capocyan, G. Hong, H. Wang, Ultrasound-triggered in situ photon emission for noninvasive optogenetics, J. Am. Chem. Soc. 145 (2) (2023) 1097–1107.
[25] M. Zou, P. Zhao, J. Fan, R. Göstl, A. Herrmann, Microgels as drug carriers for sonopharmacology, J. Polym. Sci. 60 (12) (2022) 1864–1870.
[26] J. Zhou, C. Fang, C. Rong, T. Luo, J. Liu, K. Zhang, Reactive oxygen species-sensitive materials: a promising strategy for regulating inflammation and favoring tissue regeneration, Smart Mater. Med. 4 (2023) 427–446.
[27] D. Xu, S. Fu, H. Zhang, W. Lu, J. Xie, J. Li, H. Wang, Y. Zhao, R. Chai, Ultrasound-responsive aligned piezoelectric nanofibers derived hydrogel conduits for peripheral nerve regeneration, Adv. Mater. 36 (28) (2024) 2307896.
[28] B. Hao, X. Wang, Y. Dong, M. Sun, C. Xin, H. Yang, Y. Cao, J. Zhu, X. Liu, C. Zhang, L. Su, B. Li, L. Zhang, Focused ultrasound enables selective actuation and Newton-level force output of untethered soft robots, Nat. Commun. 15 (1) (2024) 5197.
[29] Z. Shi, Q. Song, R. Göstl, A. Herrmann, Mechanochemical activation of disulfide-based multifunctional polymers for theranostic drug release, Chem. Sci. 12 (5) (2021) 1668–1674.
[30] S. Huo, Y. Zhou, Z. Liao, P. Zhao, M. Zou, R. Göstl, A. Herrmann, Reversible regulation of metallo-base-pair interactions for DNA dehybridization by ultrasound, Chem. Commun. 57 (60) (2021) 7438–7440.
[31] X. Hou, J. Jing, Y. Jiang, X. Huang, Q. Xian, T. Lei, J. Zhu, K.F. Wong, X. Zhao, M. Su, D. Li, L. Liu, Z. Qiu, L. Sun, Nanobubble-actuated ultrasound neuromodulation for selectively shaping behavior in mice, Nat. Commun. 15 (1) (2024) 2253.
[32] L. Cooper, M.G. Malinao, G. Hong, Force-based neuromodulation, Acc. Chem. Res. 57 (9) (2024) 1384–1397.
[33] V. Jazbec, N. Varda, E. Šprager, M. Meško, S. Vidmar, R. Romih, M. Podobnik, A. Kežar, R. Jerala, M. Benčina, Protein gas vesicles of Bacillus megaterium as enhancers of ultrasound-induced transcriptional regulation, ACS Nano 18 (26) (2024) 16692–16700.
[34] Y. Bao, Y. Ge, M. Wu, Z. Mao, J. Ye, W. Tong, Record-high ultrasound-sensitive NO nanogenerators for cascade tumor pyroptosis and immunotherapy, Adv. Sci. 10 (26) (2023) 2302278.
[35] J. Wang, W. Cao, W. Zhang, B. Dou, X. Ding, M. Wang, J. Ma, X. Li, Tumor-targeted oxaliplatin(IV) prodrug delivery based on ROS-regulated cancer-selective glycan labeling, J. Med. Chem. 67 (10) (2024) 8296–8308.
[36] M. Bril, S. Fredrich, N.A. Kurniawan, Stimuli-responsive materials: a smart way to study dynamic cell responses, Smart Mater. Med. 3 (2022) 257–273.
[37] X. Han, C. Zhao, Z. Pan, X. Tang, Z. Jiang, N-doping of the TiO2/C nanostructure derived from metal-organic frameworks with high drug loading for efficient sonodynamic & chemotherapy, Smart Mater. Med. 3 (2022) 168–178.
[38] A. Wang, X. Ma, Y. Yang, G. Shi, L. Han, X. Hu, R. Shi, J. Yan, Q. Guo, Y. Zhao, Biophysical-driven piezoelectric and aligned nanofibrous scaffold promotes bone regeneration by re-establishing physiological electrical microenvironment, Nano Res. 17 (2024) 7376–7393.
[39] Z. Li, Y. Gao, W. Li, Y. Li, H. Lv, D. Zhang, J. Peng, W. Cheng, L. Mei, H. Chen, X. Zeng, Charge-reversal nanomedicines as a smart bullet for deep tumor penetration, Smart Mater. Med. 3 (2022) 243–253.
[40] S. Liu, L. Li, X. Zhang, Q. Meng, Nanotherapies from an oncologist doctor's view, Smart Mater. Med. 4 (2023) 183–198.
[41] Y. Liu, M. Ding, K. Guo, Z. Wang, C. Zhang, Q.T.H. Shubhra, Systemic Co-delivery of drugs by a pH- and photosensitive smart nanocarrier to treat cancer by chemo-photothermal-starvation combination therapy, Smart Mater. Med. 3 (2022) 390–403.
[42] Y. Zhu, K. Deng, J. Zhou, C. Lai, Z. Ma, H. Zhang, J. Pan, L. Shen, M.D. Bucknor, E. Ozhinsky, S. Kim, G. Chen, S.-h. Ye, Y. Zhang, D. Liu, C. Gao, Y. Xu, H. Wang, W.R. Wagner, Shape-recovery of implanted shape-memory devices remotely triggered via image-guided ultrasound heating, Nat. Commun. 15 (1) (2024) 1123.
[43] L. Wang, Q. Zhou, Y. Chen, X. Yang, Y. Zhang, H. Duan, H. Song, Y. Wang, Y. Zheng, Mechanochemical reactions within graft copolymeric assemblies: ultrasound-induced multimechanophore activation, arm chain scission, and aggregation morphology/size changes, Polym. Chem. 14 (20) (2023) 2520–2532.
[44] A. Akhtar, V. Farzam Rad, A.-R. Moradi, M. Yar, M. Bazzar, Emerging polymeric biomaterials and manufacturing-based tissue engineering approaches for neuro regeneration-A critical review on recent effective approaches, Smart Mater. Med. 4 (2023) 337–355.
[45] R. Avila, Y. Wu, R. Garziera, J.A. Rogers, Y. Huang, Analytical Modeling of Flowrate and its Maxima in Electrochemical Bioelectronics with Drug Delivery Capabilities, 2022 9805932. Research 2022.
[46] C. Qiu, F. Xia, J. Zhang, Q. Shi, Y. Meng, C. Wang, H. Pang, L. Gu, C. Xu, Q. Guo, J. Wang, Advanced Strategies for Overcoming Endosomal/Lysosomal Barrier in Nanodrug Delivery 6 (2023) 148. Research.
[47] Z. Shi, J. Wu, Q. Song, R. Göstl, A. Herrmann, Toward drug release using polymer mechanochemical disulfide scission, J. Am. Chem. Soc. 142 (34) (2020) 14725–14732.
[48] Y. Yao, M.E. McFadden, S.M. Luo, R.W. Barber, E. Kang, A. Bar-Zion, C.A.B. Smith, Z. Jin, M. Legendre, B. Ling, D. Malounda, A. Torres, T. Hamza, C.E.R. Edwards, M.G. Shapiro, M.J. Robb, Remote control of mechanochemical reactions under physiological conditions using biocompatible focused ultrasound, Proc. Natl. Acad. Sci. U.S.A. 120 (39) (2023) e2309822120.
[49] Y. Jiang, H. Chen, T. Lin, C. Zhang, J. Shen, J. Chen, Y. Zhao, W. Xu, G. Wang, P. Huang, Ultrasound-activated prodrug-loaded liposome for efficient cancer targeting therapy without chemotherapy-induced side effects, J. Nanobiotechnol. 22 (1) (2024) 2.
[50] Y. Tong, M. Li, H. Huang, S. Long, W. Sun, J. Du, J. Fan, L. Wang, B. Liu, X. Peng, Urea-bond scission induced by therapeutic ultrasound for biofunctional molecule release, J. Am. Chem. Soc. 144 (37) (2022) 16799–16807.
[51] S. Huo, P. Zhao, Z. Shi, M. Zou, X. Yang, E. Warszawik, M. Loznik, R. Göstl, A. Herrmann, Mechanochemical bond scission for the activation of drugs, Nat. Chem. 13 (2) (2021) 131–139.
[52] G. Kim, V.M. Lau, A.J. Halmes, M.L. Oelze, J.S. Moore, K.C. Li, High-intensity focused ultrasound-induced mechanochemical transduction in synthetic elastomers, Proc. Natl. Acad. Sci. U.S.A. 116 (21) (2019) 10214–10222.
[53] X. Hu, T. Zeng, C.C. Husic, M.J. Robb, Mechanically triggered release of functionally diverse molecular payloads from masked 2-furylcarbinol derivatives, ACS Cent. Sci. 7 (7) (2021) 1216–1224.
[54] R. Küng, T. Pausch, D. Rasch, R. Göstl, B.M. Schmidt, Mechanochemical release of non-covalently bound guests from a polymer-decorated supramolecular cage, Angew. Chem. Int. Ed. 60 (24) (2021) 13626–13630.
[55] M. Zou, P. Zhao, S. Huo, R. Göstl, A. Herrmann, Activation of antibiotic-grafted polymer brushes by ultrasound, ACS Macro Lett. 11 (1) (2022) 15–19.
[56] F. Wang, G. Dong, M. Ding, N. Yu, C. Sheng, J. Li, Dual-programmable semiconducting polymer NanoPROTACs for deep-tissue sonodynamic-ferroptosis activatable immunotherapy, Small 20 (8) (2024) 2306378.
[57] G. Liu, Y. Zhang, H. Yao, Z. Deng, S. Chen, Y. Wang, W. Peng, G. Sun, M.-K. Tse, X. Chen, J. Yue, Y.-K. Peng, L. Wang, G. Zhu, An ultrasound-activatable platinum prodrug for sono-sensitized chemotherapy, Sci. Adv. 9 (25) (2023) eadg5964.
[58] Y. Sun, W.J. Neary, Z.P. Burke, H. Qian, L. Zhu, J.S. Moore, Mechanically triggered carbon monoxide release with turn-on aggregation-induced emission, J. Am. Chem. Soc. 144 (3) (2022) 1125–1129.
[59] X. Bai, D. Wang, L. Zhen, M. Cui, J. Liu, N. Zhao, C. Lee, B. Yang, Design and micromanufacturing technologies of focused piezoelectric ultrasound transducers for biomedical applications, Int. J. Extrem. Manuf. 6 (6) (2024) 062001.
[60] J. Zheng, H. Ge, D. Zhou, Q. Yao, S. Long, W. Sun, J. Fan, J. Du, X. Peng, An activatable prodrug nanosystem for ultrasound-driven multimodal tumor therapy and metastasis inhibition, Adv. Mater. 35 (47) (2023) 2308205.
[61] P. Zhao, S. Huo, J. Fan, J. Chen, F. Kiessling, A.J. Boersma, R. Göstl, A. Herrmann, Activation of the catalytic activity of thrombin for fibrin formation by ultrasound, Angew. Chem. Int. Ed. 60 (26) (2021) 14707–14714.
[62] L. Zhang, Z. Lin, L. Zeng, F. Zhang, L. Sun, S. Sun, P. Wang, M. Xu, J. Zhang, X. Liang, H. Ge, Ultrasound-induced biophysical effects in controlled drug delivery, Sci. China Life Sci. 65 (5) (2022) 896–908.
[63] L. Yuan, Q. Li, Z. Li, Effects of ultrasound for bio-applications, Adv. Sens. Res. 3 (8) (2024) 2300199.
[64] X. Mi, H. Du, X. Guo, Y. Wu, L. Shen, Y. Luo, D. Wang, Q. Su, R. Xiang, S. Yue, S. Wu, J. Gong, Z. Yang, Y. Zhang, X. Tan, Asparagine endopeptidase-targeted ultrasound-responsive nanobubbles alleviate tau cleavage and amyloid-β deposition in an alzheimer's disease model, Acta Biomater. 141 (2022) 388–397.
[65] W. Wang, A. Tasset, I. Pyatnitskiy, H.G. Mohamed, R. Taniguchi, R. Zhou, M. Rana, P. Lin, S.L.C. Capocyan, A. Bellamkonda, W. Chase Sanders, H. Wang, Ultrasound triggered organic mechanoluminescence materials, Adv. Drug Deliv. Rev. 186 (2022) 114343.
[66] A.G. Athanassiadis, Z. Ma, N. Moreno-Gomez, K. Melde, E. Choi, R. Goyal, P. Fischer, Ultrasound-responsive systems as components for smart materials, Chem. Rev. 122 (5) (2021) 5165–5208.

[67] F. Yang, T. Geng, H. Shen, Y. Kou, G. Xiao, B. Zou, Y. Chen, Mechanochemical release of fluorophores from a "flex-activated" mechanophore, Angew. Chem. Int. Ed. 62 (39) (2023) e202308662.
[68] K. Liu, Z. Jiang, F. Zhao, W. Wang, F. Jäkle, N. Wang, X. Tang, X. Yin, P. Chen, Triarylboron-doped acenethiophenes as organic sonosensitizers for highly efficient sonodynamic therapy with low phototoxicity, Adv. Mater. 34 (49) (2022) 2206594.
[69] X. Lin, J. Song, X. Chen, H. Yang, Ultrasound-activated sensitizers and applications, Angew. Chem. Int. Ed. 59 (34) (2020) 14212–14233.
[70] A.C. Overholts, M.E. McFadden, M.J. Robb, Quantifying activation rates of scissile mechanophores and the influence of dispersity, Macromolecules 55 (1) (2021) 276–283.
[71] C. Wang, R. Zhang, J. He, L. Yu, X. Li, J. Zhang, S. Li, C. Zhang, J.C. Kagan, J.M. Karp, R. Kuai, Ultrasound-responsive low-dose doxorubicin liposomes trigger mitochondrial DNA release and activate cGAS-STING-mediated antitumour immunity, Nat. Commun. 14 (1) (2023) 3877.
[72] A.B. Grommet, M. Feller, R. Klajn, Chemical reactivity under nanoconfinement, Nat. Nanotechnol. 15 (4) (2020) 256–271.
[73] Z. Ren, S. Sun, R. Sun, G. Cui, L. Hong, B. Rao, A. Li, Z. Yu, Q. Kan, Z. Mao, A metal–polyphenol-coordinated nanomedicine for synergistic cascade cancer chemotherapy and chemodynamic therapy, Adv. Mater. 32 (6) (2020) 1906024.
[74] W. Shao, C. He, M. Zhou, C. Yang, Y. Gao, S. Li, L. Ma, L. Qiu, C. Cheng, C. Zhao, Core-shell-structured MOF-derived 2D hierarchical nanocatalysts with enhanced Fenton-like activities, J. Mater. Chem. A 8 (6) (2020) 3168–3179.
[75] Y. Yao, Q. Dong, A. Brozena, J. Luo, J. Miao, M. Chi, C. Wang, I.G. Kevrekidis, Z.J. Ren, J. Greeley, G. Wang, A. Anapolsky, L. Hu, High-entropy nanoparticles: synthesis-structure-property relationships and data-driven discovery, Science 376 (6589) (2022) eabn3103.
[76] X. Gao, H. Liu, D. Wang, J. Zhang, Graphdiyne: synthesis, properties, and applications, Chem. Soc. Rev. 48 (3) (2019) 908–936.
[77] T. Luo, G.T. Nash, Z. Xu, X. Jiang, J. Liu, W. Lin, Nanoscale metal–organic framework confines zinc-phthalocyanine photosensitizers for enhanced photodynamic therapy, J. Am. Chem. Soc. 143 (34) (2021) 13519–13524.
[78] X. Zhong, X. Wang, L. Cheng, Y.a. Tang, G. Zhan, F. Gong, R. Zhang, J. Hu, Z. Liu, X. Yang, GSH-depleted PtCu3 nanocages for chemodynamic- enhanced sonodynamic cancer therapy, Adv. Funct. Mater. 30 (4) (2020) 1907954.
[79] Z. Gao, S. Lv, M. Xu, D. Tang, High-index {hk0} faceted platinum concave nanocubes with enhanced peroxidase-like activity for an ultrasensitive colorimetric immunoassay of the human prostate-specific antigen, Analyst 142 (6) (2017) 911–917.
[80] M. Zuo, S. Zou, Y. Gao, D. Zhou, K. Zhang, X. Li, H. Ma, B. Li, W. Huang, A spatiotemporal cascade platform for multidimensional information encryption and anti-counterfeiting mechanisms, Adv. Opt. Mater. 12 (10) (2024) 2302146.
[81] X.-Y. Liu, F. Zhang, T.-W. Goh, Y. Li, Y.-C. Shao, L. Luo, W. Huang, Y.-T. Long, L.-Y. Chou, C.-K. Tsung, Using a multi-shelled hollow metal–organic framework as a host to switch the guest-to-host and guest-to-guest interactions, Angew. Chem. Int. Ed. 57 (8) (2018) 2110–2114.
[82] S. Huo, Z. Liao, P. Zhao, Y. Zhou, R. Göstl, A. Herrmann, Mechano-nanoswitches for ultrasound-controlled drug activation, Adv. Sci. 9 (12) (2022) 2104696.
[83] S. Kulandaivel, C.-H. Lin, Y.-C. Yeh, The bi-metallic MOF-919 (Fe–Cu) nanozyme capable of bifunctional enzyme-mimicking catalytic activity, Chem. Commun. 58 (4) (2022) 569–572.
[84] Y. Zhou, Y. Wei, J. Ren, X. Qu, A chiral covalent organic framework (COF) nanozyme with ultrahigh enzymatic activity, Mater. Horiz. 7 (12) (2020) 3291–3297.
[85] W.-D. Oh, V.W.C. Chang, T.-T. Lim, A comprehensive performance evaluation of heterogeneous Bi2Fe4O9/peroxymonosulfate system for sulfamethoxazole degradation, Environ. Sci. Pollut. Res. 26 (2) (2019) 1026–1035.
[86] J. Cheng, H. Cao, Y. Xu, Y. Yang, Y. He, H. Wang, In situ monitoring of dynamic photocatalysis of metal–organic frameworks by three-dimensional shell-isolated nanoparticle-enhanced Raman spectroscopy, Anal. Chem. 94 (14) (2022) 5699–5706.
[87] X. Meng, S. Wang, C. Zhang, C. Dong, R. Li, B. Li, Q. Wang, Y. Ding, Boosting hydrogen evolution performance of a CdS-based photocatalyst: in situ transition from type I to type II heterojunction during photocatalysis, ACS Catal. 12 (16) (2022) 10115–10126.
[88] B. Liang, Y. Zhang, C. Leist, Z. Ou, M. Položij, Z. Wang, D. Mücke, R. Dong, Z. Zheng, T. Heine, X. Feng, U. Kaiser, H. Qi, Optimal acceleration voltage for near-atomic resolution imaging of layer-stacked 2D polymer thin films, Nat. Commun. 13 (1) (2022) 3948.
[89] H. Su, W. Zhou, W. Zhou, Y. Li, L. Zheng, H. Zhang, M. Liu, X. Zhang, X. Sun, Y. Xu, F. Hu, J. Zhang, T. Hu, Q. Liu, S. Wei, In-situ spectroscopic observation of dynamic-coupling oxygen on atomically dispersed iridium electrocatalyst for acidic water oxidation, Nat. Commun. 12 (1) (2021) 6118.
[90] Y.-H. Wang, S. Zheng, W.-M. Yang, R.-Y. Zhou, Q.-F. He, P. Radjenovic, J.-C. Dong, S. Li, J. Zheng, Z.-L. Yang, G. Attard, F. Pan, Z.-Q. Tian, J.-F. Li, In situ Raman spectroscopy reveals the structure and dissociation of interfacial water, Nature 600 (7887) (2021) 81–85.
[91] J. Kim, H.Y. Kim, S.Y. Song, S.-h. Go, H.S. Sohn, S. Baik, M. Soh, K. Kim, D. Kim, H.-C. Kim, N. Lee, B.-S. Kim, T. Hyeon, Synergistic oxygen generation and reactive oxygen species scavenging by manganese ferrite/ceria Co-decorated nanoparticles for rheumatoid arthritis treatment, ACS Nano 13 (3) (2019) 3206–3217.
[92] D. Wang, H. Wu, S.Z.F. Phua, G. Yang, W. Qi Lim, L. Gu, C. Qian, H. Wang, Z. Guo, H. Chen, Y. Zhao, Self-assembled single-atom nanozyme for enhanced photodynamic therapy treatment of tumor, Nat. Commun. 11 (1) (2020) 357.
[93] M. Cao, S. Wang, J.-H. Hu, B.-H. Lu, Q.-Y. Wang, S.-Q. Zang, Silver cluster-porphyrin-assembled materials as advanced bioprotective materials for combating superbacteria, Adv. Sci. 9 (2) (2022) 2103721.
[94] A. Ali, M. Ovais, H. Zhou, Y. Rui, C. Chen, Tailoring metal-organic frameworks-based nanozymes for bacterial theranostics, Biomaterials 275 (2021) 120951.
[95] J.P. Celli, B.Q. Spring, I. Rizvi, C.L. Evans, K.S. Samkoe, S. Verma, B.W. Pogue, T. Hasan, Imaging and photodynamic therapy: mechanisms, monitoring, and optimization, Chem. Rev. 110 (5) (2010) 2795–2838.
[96] S. Zhao, H. Li, R. Liu, N. Tao, L. Deng, Q. Xu, J. Hou, J. Sheng, J. Zheng, L. Wang, W. Chen, S. Guo, Y.-N. Liu, Nitrogen-centered lactate oxidase nanozyme for tumor lactate modulation and microenvironment remodeling, J. Am. Chem. Soc. 145 (18) (2023) 10322–10332.
[97] C. Pucci, A. Marino, Ö. Şen, D. De Pasquale, M. Bartolucci, N. Iturrioz-Rodríguez, N. di Leo, G. de Vito, D. Debellis, A. Petretto, G. Ciofani, Ultrasound-responsive nutlin-loaded nanoparticles for combined chemotherapy and piezoelectric treatment of glioblastoma cells, Acta Biomater. 139 (2022) 218–236.
[98] X. Jiang, J. Zhang, P.K. Lo, Z. Mao, Polyphenol-based assembly nanosystems as multifunctional biopharmaceutical platform, Adv. NanoBiomed Res. 3 (6) (2023) 2200168.
[99] H. Huang, Y. Zheng, M. Chang, J. Song, L. Xia, C. Wu, W. Jia, H. Ren, W. Feng, Y. Chen, Ultrasound-based micro-/nanosystems for biomedical applications, Chem. Rev. 124 (13) (2024) 8307–8472.
[100] M. Li, Y. Liu, Y. Zhang, N. Yu, J. Li, Sono-activatable semiconducting polymer nanoreshapers multiply remodel tumor microenvironment for potent immunotherapy of orthotopic pancreatic cancer, Adv. Sci. 10 (35) (2023) 2305150.
[101] B. Sorum, R.A. Rietmeijer, K. Gopakumar, H. Adesnik, S.G. Brohawn, Ultrasound activates mechanosensitive TRAAK K^+ channels through the lipid membrane, Proc. Natl. Acad. Sci. U.S.A. 118 (6) (2021) e2006980118.
[102] A. Vafaie, M.R. Raveshi, C. Devendran, R. Nosrati, A. Neild, Making immotile sperm motile using high-frequency ultrasound, Sci. Adv. 10 (7) (2024) eadk2864.
[103] P.Y. Siboro, V.K.T. Nguyen, Y.-B. Miao, A.K. Sharma, F.-L. Mi, H.-L. Chen, K.-H. Chen, Y.-T. Yu, Y. Chang, H.-W. Sung, Ultrasound-activated, tumor-specific in situ synthesis of a chemotherapeutic agent using ZIF-8 nanoreactors for precision cancer therapy, ACS Nano 16 (8) (2022) 12403–12414.