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Precise modulation of cell activity using sono-responsive nano-transducers

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ABSTRACT

Ultrasound, as a form of mechanical energy, possesses a distinctive ability to deeply penetrate tissues, allowing for non-invasive manipulation of cellular activities. Utilizing nanomaterials in conjunction with ultrasound has enabled simple, efficient, spatiotemporally controllable, and minimally invasive regulation of cellular activities with ultrasound-generated electric, optical, acoustic, or chemical stimuli at the localized nanomaterials interface. This technology allows for precise and localized regulation of cellular activities, which is essential for studying and understanding complex biological processes, and also provides new opportunities for research, diagnostics, and therapeutics in the fields of biology and medicine. In this article, we review the state-of-the-art and ongoing developments in nanomaterials-enabled ultrasound cellular modulation, highlighting potential applications and advancements achieved through the integration of sono-responsive nanomaterials with ultrasound.

1. Introduction

The understanding and exploration of various biological processes are closely intertwined with the ability to precisely manipulate cellular activity, which grants researchers the remarkable ability to control cellular functions and gain deeper insights into the nature of life science [1]. Consequently, there is increasing demand for techniques that enable non-invasive control of cell activities in targeted tissues with high spatiotemporal resolution. Various physical stimuli, including light, electricity, magnetic fields, and ultrasound, have been widely employed for this purpose [2]. Among these strategies, ultrasound (US) stimulation has garnered considerable attention due to its ability to penetrate deeply with excellent spatiotemporal resolution [3,4]. As a result, ultrasound has found extensive use as a safe and effective technique in diagnosis and treatment [5–7]. Furthermore, ultrasound has made remarkable strides in the modulation of cell activities, such as deep brain neuromodulation, regulation of stem cell differentiation, and manipulation of the immune system and cancer treatment [8–10]. Possessing the attribute of non-invasive administration, ultrasound stimulation holds immense potential in the field of cell modulation in the context of both research and clinical settings. While ultrasound can be focused within a few millimeters (known as focused ultrasound, FUS), the focal spot alone may not be adequate for precise stimulation. In addition, the relatively low frequencies of ultrasound required for deep tissue penetration result in spatial precision limitations caused by diffraction, typically ranging from millimeters to centimeters [11,12].

To overcome these constraints, several approaches have been developed, such as sonogenetics and nanoparticle-based ultrasound stimulation [13–15]. While sonogenetics has been utilized for cell-type-specific modulation, its reliance on viral transfection has limited its applications in humans thus far [16,17]. Nanoparticles offer an alternative approach to ultrasound stimulation and have expanded the potential of ultrasound in practical applications, particularly in effective energy transfer. Ultrasound-responsive nanomaterials have emerged as a unique interface for cell modulation within the body, acting as transducers for the mechanical energy delivered at the targeted site [18]. The concept involves the administration of these nanomaterials and remotely activating them using externally-delivered ultrasound to generate secondary effects *in situ*, to achieve spatially-accurate and stimulation-specific modulation of cellular activity. Such sono-responsive nanomaterials can serve as ultrasound mediators to locally convert or amplify the acoustic energy, enabling more accurate stimulation. Recent studies have demonstrated that ultrasound-triggered sono-responsive nanoparticles can effectively manipulate cellular activities, including neuronal activation, immune cell manipulation, and stem cell differentiation [19,20].

This review aims to provide a comprehensive overview of the mechanisms underlying the interactions between ultrasound and various sono-responsive nanomaterials, highlighting the significance of various combinations in precisely modulating cellular activity. We explore how ultrasound serves as the primary stimulus, which is converted into localized stimulation through nanomaterials, encompassing

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electric, optical, mechanical, and chemical effects. We review current nanotechnology-enabled strategies for precise cell modulation using ultrasound, including minimally-invasive surgical procedures, improved biological implant interfaces, deeper tissue access, and enhanced spatiotemporal precision. Additionally, we delve into the role of nanotechnology in facilitating ultrasound-enabled cell modulation by utilizing nanomaterials as localized energy transducers. These techniques build upon fundamental phenomena such as sono-electric transduction via piezoelectric nanomaterials, sono-optical transduction via mechanoluminescent nanoparticles, sono-mechanical transduction via nanobubbles, and sonochemical transduction via nanocarriers, which can further trigger the initiation of biological processes [15,21–24]. We classify these protocols based on their main stimuli (as in the Graphical Abstract) and provide detailed discussion about each section. Finally, we explore the capabilities of nanomaterials and their integration with ultrasound in biological systems to enable precise modulation of cell activities. The expanding array of emerging techniques exhibits tremendous potential for a multitude of ultrasound applications, presenting the opportunity to profoundly influence both basic research and clinical translation.

2. Nanomaterials-mediated ultrasound for precise control of cellular activities

Ultrasound bioeffects manifest through two primary mechanisms: thermal and mechanical. The concept of using ultrasound to control cellular electrical activities was conceived nearly a century ago [25,26]. As mentioned earlier, low-intensity ultrasound can penetrate deep tissues non-invasively, allowing for cell stimulation with minimal energy dissipation. Ultrasound functions as a mechanical wave, with low-intensity ultrasound generating bioeffects by perturbing the mechanosensitive elements within biological tissues. However, achieving spatial accuracy and precision has been a challenge due to the low frequencies involved. To overcome this limitation, alternative approaches inspired by nanotechnology have emerged. Nanomaterials are employed as signal transducers for cross-modal stimulation. They act as mediators, localized at cellular interfaces, converting primary stimuli into secondary stimuli. To distinguish between the effects of ultrasound and those induced by nanomaterials, a comparison of control groups, such as ultrasound alone and the nanomaterials-alone stimulation group, can be included. In addition to amplifying the mechanical effects of ultrasound, sono-responsive nanomaterials can be stimulated under ultrasound irradiation to elicit electric, optical, and chemical effects for cell stimulation (Table 1). By integrating multiple modalities, these transduction schemes associated with ultrasound can leverage their respective strengths and mitigate their limitations, thereby enhancing cell modulation capabilities.

3. Nanomaterials-enabled electrical stimulus

Piezoelectric materials can be classified into three fundamental categories: inorganic, organic, and composite materials. These materials possess piezoelectric properties, allowing them to convert ultrasound energy into localized electric voltage or current through sono-electric transduction [27,28]. Various nanoscale piezoelectric materials, such as lead zirconate titanate (PZT), boron nitride nanotubes (BNNTs), barium titanate ($BaTiO_3$) nanoparticles, and polyvinylidene fluoride (PVDF), have been utilized as transducers to stimulate different cell types, including rat sciatic nerves, neuron-like cells, neural stem cells, neurons, and immune cells [21,29–34]. These studies demonstrate the potential of non- or minimally-invasive acoustic modulation facilitated by these piezoelectric nanomaterials.

Table 1
Mechanisms of transduction for localized stimulation enabled by ultrasound-responsive nanomaterials.

Transduction	Primary stimuli	Nano-transducers	Local stimuli
Sono-electric	Ultrasound (deep penetration, non-invasiveness)	Piezoelectric nanomaterials	Electric field
Sono-optical		Mechanoluminescent nanoparticles	Light
Sono-mechanical		Nanobubbles	Mechanical force
Sono-chemical		Nanocarriers	Chemical signal

3.1. Sono-electric neuromodulation enabled by piezoelectric nanomaterials

Piezoelectric transducers - traditional ultrasound devices extensively studied in biomedical engineering for applications such as imaging and stimulation - can also convert acoustic pressure into electric signals through acoustic-electric transduction [21,35]. The use of nanotechnology has significantly reduced the size of piezoelectric transducers using materials like PZT, enabling the development of wireless, untethered, and battery-free implantable ultrasonic neurostimulators for rat sciatic nerve stimulation [33]. Miniaturized neurostimulators, integrating piezoelectric transducers, energy storage capacitors, and integrated circuits, demonstrate the potential for closed-loop neuromodulation to facilitate therapeutic effects.

To address safety concerns associated with PZT, researchers have explored other lead-free piezoelectric materials in neuromodulation research. BNNTs exhibit excellent piezoelectric properties and have been utilized as mediators to promote the growth of neurite sprouts in PC12 cultures under ultrasound irradiation [36]. $BaTiO_3$ nanoparticles have also been employed as nano-transducers for localized neurostimulation by activating voltage-gated ion channels and inducing Ca^{2+} influx, showcasing their potential for non-invasive acoustic neuromodulation [21]. Recent studies have shown that $BaTiO_3$ nanoparticles can modulate neural plasticity and restore degenerative dopaminergic neurons in zebrafish (Fig. 1) [37]. An ultrasound-activated piezoelectric thin film nanogenerator containing nanowires and PVDF polymer was used successfully to activate rat sciatic nerves with ultrasound-induced electrical stimulation [38]. Ultrasound-actuated molybdenum disulfide nanosheets have also been shown to activate voltage-gated ion channels of neurons and modulate neuronal activities both *in vitro* and *in vivo* (Fig. 1) [39]. These strategies convert ultrasound into localized electric stimulation, enabling selective control of neural activity in targeted regions and reducing off-target effects. This facilitates more efficient neuromodulation with exceptional spatiotemporal precision. Consequently, the feasibility of neural stimulation through acoustic-electric conduction of piezoelectric nanomaterials is considered established. However, further endeavors are required to enhance the piezoelectric properties by improving the piezoelectric coefficients of alternative materials.

Nevertheless, to validate these observations, understand the underlying mechanisms, assess feasibility, and ensure safety, it is imperative to conduct additional rigorous statistical investigations in a broader range of animal models. Recently, Han et al. introduced a novel approach for high-frequency neural stimulation using piezoelectric magnetic Janus particles under low-intensity focused ultrasound. In this technique, half of the particles function as piezoelectric electrodes through the incorporation of $BaTiO_3$ nanomaterials, enabling the induction of electrical stimulation. Simultaneously, the other half of the particles, coated with a nickel-gold nanofilm, provide spatial and orientational control over neural stimulation using external uniform rotating magnetic fields. This innovative strategy enables targeted and spatially-controlled piezoelectric neural stimulation through the utilization of low-intensity focused ultrasound [40].

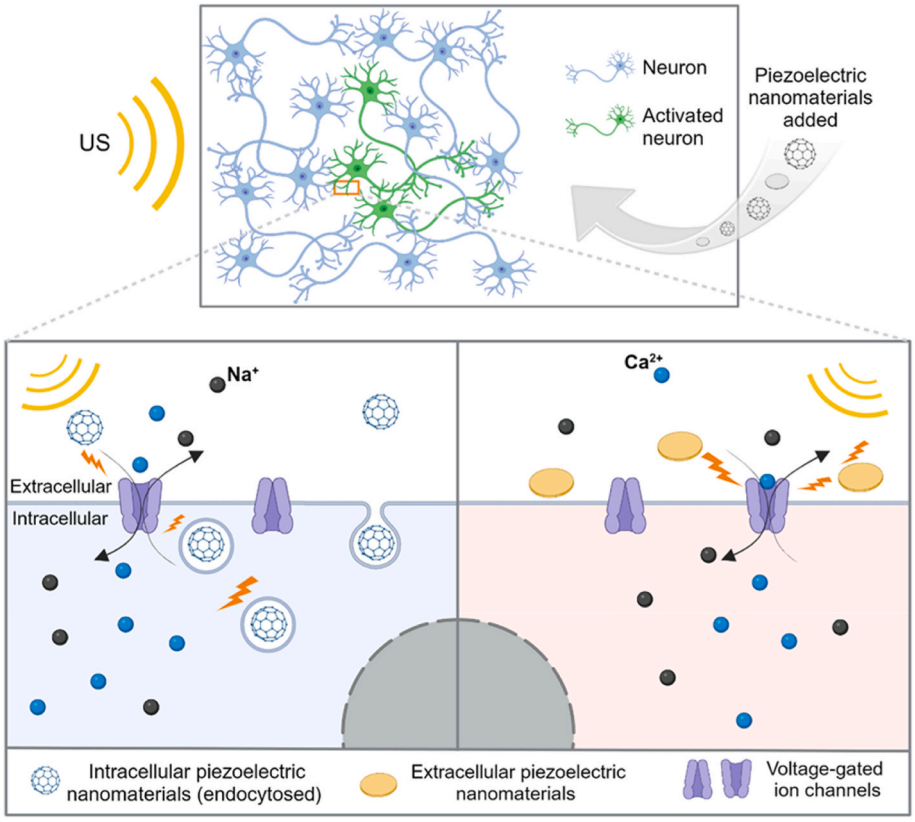

Fig. 1. Schematic diagram of neural activity modulation through activation of voltage-gated ion channels using piezoelectric nanomaterials and ultrasound. Figure created using BioRender.com based on Ref. 37 and 39.

3.2. Sono-electric immunomodulation enabled by piezoelectric nanomaterials

Research on the use of piezoelectric materials for immunomodulation is advancing rapidly. Macrophages, essential guardians of anti-tumor immunity, exhibit responsiveness to electric stimulation [41, 42]. These innate immune cells serve as the frontline defense against foreign antigens and possess binary M1/M2 polarization settings, enabling them to perform differing suites of immune tasks [43]. Precise modulation of macrophages is therefore of utmost importance. Kong et al. demonstrated the manipulation of macrophage polarization by seeding cells on a piezoelectric β-PVDF film, driven by ultrasound, which released charges on the membrane's surface [30]. This charge-based modulation significantly enhanced the M1 polarization of macrophages. Subsequent studies have further verified the role of electrical potentials, rather than mechanical forces, in regulating immunological responses. In another study, Montorsi et al. coated PVDF-tetrafluoroethylene nanoparticles with extracts from glioblastoma cell membranes to electrically induce microglial cells toward a pro-inflammatory M1 phenotype under low-intensity pulsed ultrasound stimulation [44].

Implant infection poses a significant clinical challenge, and immunotherapy has emerged as a novel solution for its control. Li et al. recently developed a piezotronic surface on a Ti implant by *in situ* formation of piezoelectric barium titanate (BTO) nanostructures on pristine Ti, followed by deposition of gold nanoparticles on BTO as cocatalysts for efficient piezocatalysis. The resulting "piezoTi" implant directly eradicated *Staphylococcus aureus* (*S. aureus*) and synergistically activated

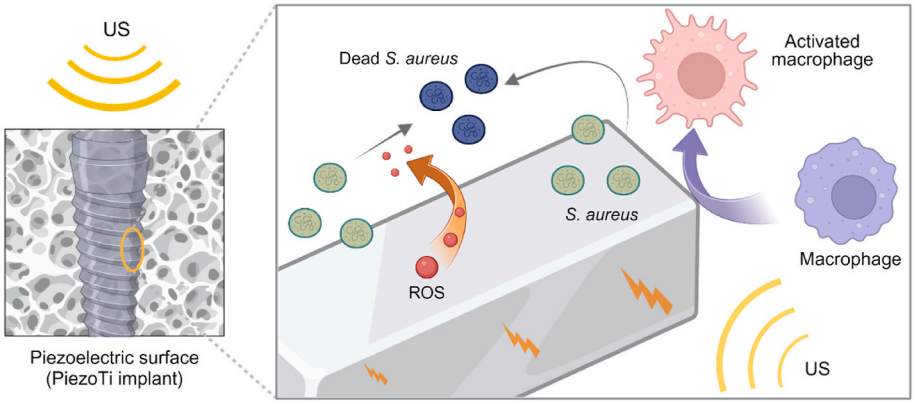

Fig. 2. Schematic illustration of the working mechanisms of PiezoTi, showcasing how piezoelectric nanomaterials used in implants enable ultrasound immunomodulation. Figure created using BioRender.com based on Ref. 31.

adherent macrophages to disrupt biofilm formation, enhancing bacterial phagocytosis in both subcutaneous and bone implant infection models (Fig. 2) [31]. Sun et al. improved the sonocatalytic properties of $BaTiO_3$ through defect engineering and designed ultrasound-responsive hybrid coatings composed of oxygen-deficient $BaTiO_3$ nanorod arrays and L-Arginine. These coatings underwent decomposition with the release of nitric oxide (NO) upon ultrasound-induced reactive oxygen species (ROS), promoting macrophage polarization toward the M1 phenotype and bacterial phagocytosis [45].

In the field of osteogenesis and bone repair, a recent study focused on utilizing piezoelectric materials. Wu et al. synthesized a piezoelectric $BaTiO_3$/Ti6Al4V scaffold, which, under low-intensity pulsed ultrasound stimulation, promoted M2 polarization of macrophages and facilitated immunoregulatory osteogenesis of MC-3T3 osteoblasts [46]. In another study, the group introduced a novel approach for modulating immune cell activity using ultrasound-driven 2D SnS nanosheets. This method employed piezoelectrocatalytic hydrogen generation and lactic acid deprivation to activate tumor immunity. By liberating effector $CD8^+$ T cells from tumor cell immunosuppression and inhibiting regulatory T cells, this approach achieved highly effective immunotherapy for liver cancer [47]. Thus, the generation of wireless localized electrical stimulation through ultrasound-driven piezoelectric nanomaterials represents a robust toolkit for immunomodulation. These studies demonstrate the potential of piezoelectric materials for precise immunomodulation through wireless electrical stimulation within an acoustic field.

3.3. *Sono-electric modulation of stem cells enabled by piezoelectric nanoparticles*

Electrical stimulation has emerged as a promising approach for influencing stem cell differentiation, underscoring its potential in modulating cellular activities [48]. In the realm of remote regulation, ultrasound has been harnessed to activate piezoelectric nanomaterials, allowing precise control over stem cell differentiation. For instance, the utilization of the piezotronic effect has enabled the promotion of neural stem cell differentiation through ultrasound treatment of natural cellulose nanofibers (CNF) (Fig. 3) [49]. In another study, Liu et al. fabricated helical piezoelectric micromotors using barium titanate nanoparticles (BTNPs), which effectively translated ultrasound physical stimulation into electrical stimuli to guide the fate of neural stem cells (NSCs) towards astrocytes, various types of neurons, or oligodendrocytes [50]. Furthermore, Fe_3O_4 and $BaTiO_3$ nanoparticles have been designed as built-in function units, where Fe_3O_4 responds to low-intensity magnetic fields, precisely navigating the system to neuronal stem cells. $BaTiO_3$ nanoparticles then convert ultrasound energy into local electrical output, controlling the differentiation of neural stem cells (Fig. 3) [32,50]. These wireless bioelectronic neural devices offer possibilities for targeted induction of neural stem cell differentiation and the treatment of neural degenerative diseases. Interestingly, Lu et al. proposed a simple yet effective method to enhance the proliferation of neural stem cells, rather than neural differentiation. This was achieved by employing wireless electrical stimulation triggered by an ultrasound-responsive nanofibrous membrane composed of poly L-lactic acid [20].

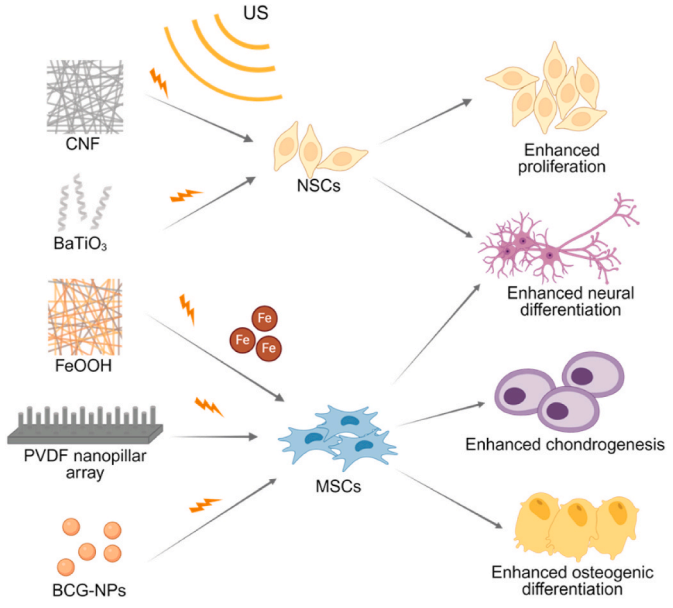

Fig. 3. Ultrasound modulation of stem cell activity using piezoelectric nanomaterials. Neural stem cells (NSCs) and mesenchymal stem cells (MSCs). Figure created using BioRender.com based on Ref. 49, 50, 52, 53, and 56.

In addition to neural stem cell differentiation, the sono-mechanical modulation of other stem cell types has also been explored. Ma et al. reported on the remote stimulation of stem cell differentiation using Nylon-11 piezoelectric nanoparticles, which were internalized by dental pulp stem cells (DPSCs). Ultrasound stimulation of DPSCs treated with Nylon-11 nanoparticles induced osteogenic differentiation [51]. A hybrid nanofibrous membrane composed of FeOOH nanorods assembled on PVDF electrospun nanofibers has also been employed to induce neural differentiation of rat bone marrow-derived mesenchymal stem cells (rBMSCs) (Fig. 3) [52]. Furthermore, the use of a piezoelectric nanopillar array based on ultrasonically-driven PVDF, which generates strong wireless electrical signals via the piezotronic effect, has proven effective in guiding rBMSCs toward a neuron-like phenotype (Fig. 3) [53]. Recent studies have highlighted the promotion of BMSCs differentiation through the use of an injectable ultrasound-powered bone-adhesive nanocomposite hydrogel or a piezoelectric $BaTiO_3$ material integrated with atomic-thin Ti_3C_2 via a Schottky heterojunction [54,55]. Additionally, the application of barium titanate-chitosan-graphene oxide piezoelectric nanoparticles (BCG-NPs) has been shown to upregulate intracellular calcium ions, enhance the expression of osteogenic-associated proteins and genes, and activate osteogenic differentiation in human mesenchymal stem cells upon non-invasive ultrasound stimulation (Fig. 3) [56]. Recently, Xu et al. introduced a novel approach for bone regeneration by envisioning a Germanium Selenium (GeSe) co-doped polylactic acid nanofiber membrane-coated tricalcium phosphate bioceramic scaffold. This scaffold, when stimulated by ultrasound, demonstrates the potential to enhance early neurogenic differentiation and osteogenic differentiation. The integration of GeSe co-doping and the nanofiber membrane coating provides a promising strategy for promoting bone regeneration [57].

4. Nanomaterials-enabled optical stimulus

Mechanoluminescence refers to the emission of light from specific materials in response to mechanical forces [58]. Focused ultrasound (FUS)-derived mechanoluminescence has emerged as a promising technique for *in situ* photon emission [58]. Mechanoluminescent nanoparticles leverage tissue-penetrating ultrasound to induce localized light emission for cellular stimulation [59,60]. These nanoparticles can be activated by ultrasound stimulation to repetitively emit light in deep tissues, enabling optical stimulation. This approach combines the non-invasiveness and tissue-penetrating capabilities of ultrasound with the precise spatiotemporal control of light. Moreover, mechanoluminescent materials with different wavelengths offer the potential for multiplexed and precisely resolved excitation and inhibition patterns within the same animal's brain, all through a non-invasive interface. Consequently, FUS-induced mechanoluminescence has garnered significant attention and demonstrated promising potential in cellular modulation.

4.1. Sono-optical neuromodulation enabled by sonoluminescent nanomaterials

Optogenetics utilizes visible light to modulate light-sensitive ion channels expressed-cells, offering remarkable spatiotemporal resolution [61]. However, a significant limitation of *in vivo* optogenetic modulation is the limited penetration depth of visible light, necessitating the implantation of optical fibers for deep region stimulation [62]. Although near-infrared light in optogenetics increases penetration depth by a few millimeters [2], it remains inherently limited by scattering in lipid-rich brain tissue [63,64], making it incomparable to ultrasound in terms of penetration depth. Alternatively, sono-optogenetic neuromodulation has been proposed, combining the advantages of ultrasound (non-invasiveness, deep penetration) with the benefits of light (excellent spatiotemporal resolution), through the use of mechanoluminescent nanoparticles (Fig. 4a). Sonoluminescent ZnS:Ag,Co@ZnS nanoparticles can convert acoustic waves into light, serving as local illumination sources (470 nm) for optogenetic cell-type neuromodulation *in vivo* [22]. However, these nanoparticles require repetitive charging with 400 nm light during blood circulation, and as inorganic nanoparticles, they may be subject to bioaccumulation and the augmentation of heavy metals in organs.

In contrast, a biocompatible liquid-phase mechanoluminescent material system has been developed for non-invasive sono-optogenetic application. Wang et al. created a nanoscale light source using liposomes for deep brain optogenetic stimulation with focused ultrasound. The light source consists of chemiluminescent compound L012, sonosensitizer IR780, and a lipid vehicle. IR780 generates free radicals through ultrasound energy, which activates L012 and produces light [65,66]. The FUS-triggered light was utilized to activate specific types of neurons expressing opsins, thereby controlling behaviors in mice. Recent advancements in this field involved the integration of polyethylene glycol-coated CaO_2 nanoparticles as sono-amplifiers into the nano light transducer, improving the sono-optical stimulation system [67]. These nano-transducers effectively activate neurons in targeted brain regions, leading to behavioral changes in mice upon ultrasound irradiation (Fig. 4b and c). As a result, the implementation of these sono-optical nano-transducers enables precise deep brain stimulation for behavioral control in animals, utilizing a flexible and adaptable mechanoluminescent sono-optogenetic system. With further advancements in mechanoluminescent materials, this concept holds promise for clinical feasibility in non-invasive neuromodulation of deep brain areas. By engineering the nanomaterials compound to adjust the trap conditions with mixed ions, it may be possible to efficiently stimulate various opsins through sono-optogenetics at lower ultrasonic intensities [68,69].

4.2. Sono-optical immunomodulation enabled by sonoluminescent nanomaterials

The integration of non-invasive and clinically safe ultrasound technology with the optogenetic toolbox for neuromodulation has shown promise, and it also holds great potential for immunotherapy [70,71]. Xu et al. introduced organic nanoparticles known as sonoafterglow nanoparticles (SNAPs) that emit ultrasound-induced afterglow [72,73]. SNAPs carry a sonosensitizer that can produce singlet oxygen and afterglow luminescence upon ultrasound stimulation. Compared with the previous photoafterglow materials, SNAPs achieve stronger luminescence in larger tissue depths (up to 4 cm). Through the control of their sonoafterglow signal with specific disease biomarkers, they developed a kind of sonoafterglow cancer nanoimmunotheranostic probe (SCAN) by loading the macrophage-polarization prodrug (Pro-R837) to regulate M1-oriented macrophage polarization (Fig. 5). In a separate study, Jeon et al. developed immunostimulatory nanoparticles based on chemiluminescence resonance energy transfer (CRET) for sonoimmunotherapy. These nanoparticles, when exposed to ultrasound, generate CO_2 bubbles that induce immunogenic cell death to trigger dendritic cell (DC) maturation and immunotherapy (Fig. 5) [74]. While the full development of neuro/immunomodulation through ultrasound-induced luminescence is still underway, the remarkable performance of sonoluminescence has already provided us with promising prospects in these fields.

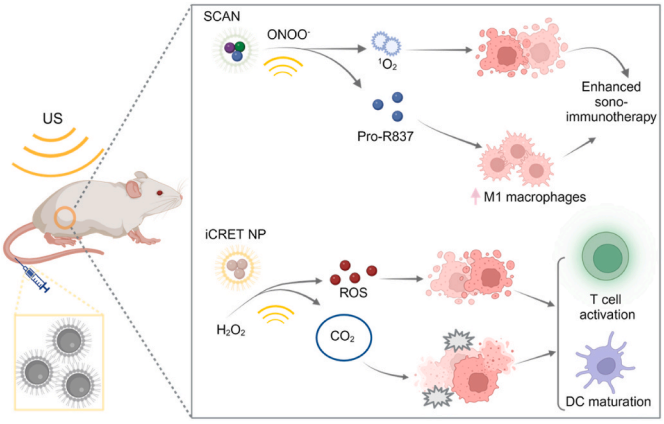

Fig. 5. Schematic representation of ultrasound-triggered SCAN for sono-immunotherapy (upper panel) and ultrasound-triggered iCRET NPs inducing immunogenic cell death (ICD) to activate immune cells (lower panel). Figure created using BioRender.com based on Ref. 72 and 73.

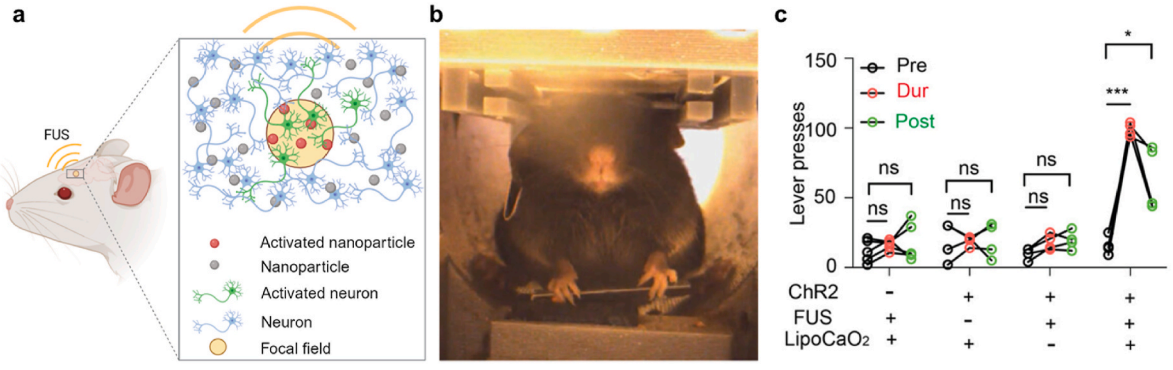

Fig. 4. Sono-optogenetics for mouse brain stimulation. (**a**) Schematic illustration of sono-optogenetic neurostimulation through ultrasound-triggered light emission from sonoluminescent nanoparticles. Figure created using BioRender.com based on Ref. 22 and 59. (**b**) The image capturing a mouse engaged in level press tests. (**c**) Statistical analysis presenting the quantification of mouse lever presses across all epochs. Panel (**b**) and (**c**) adapted with permission from Ref. 67. Copyright 2023 American Chemical Society.

5. Nanomaterials-enabled mechanical stimulus

Ultrasound has the ability to directly stimulate mechanosensitive ion channels, thereby modulating cellular activities through the generation of mechanical force [75–77]. Transcranially-focused ultrasonic stimulation, based on this mechanism, is a clinically-used neuromodulation technique. However, the thickness of the human skull presents a challenge for ultrasound, as it is difficult to simultaneously achieve high spatial resolution and substantial penetration depth. Nano/-microbubbles are well-established ultrasound imaging contrast agents, which have been employed to amplify the impact of low-frequency ultrasound stimulation due to a significant difference in acoustic impedance between the surrounding media and the air inside the bubbles [78–80]. By converting external acoustic field stimulation into local mechanical forces through bubble oscillation, the induced secondary mechanical force becomes strong enough to activate proximate mechanosensitive ion channels. In conjunction with ultrasound stimulation, nanobubbles have demonstrated the ability to remotely modulate cellular activity [15,81]. This nanobubble-assisted ultrasound approach combines non-invasiveness with high spatial resolution, even in deep tissues, enabling the exploration of specific regions in manipulating cellular activities.

5.1. Sono-mechanical neuromodulation enabled by nanobubbles

Ultrasound can be delivered with good spatial resolution to deep brain regions without surgical invasion. Low-frequency ultrasound can successfully pass through an intact skull, but it may not provide sufficient accuracy for neuronal stimulation [82]. To overcome this limitation, microbubbles have been used for ultrasound neurostimulation. Microbubbles (MBs) are well-established contrast agents for ultrasound imaging, which can be administered intravenously to circulate to the brain [83]. Studies have shown that combining mechanosensitive TRP-4 channels with MBs sensitizes neurons to ultrasound, resulting in behavioral changes in *Caenorhabditis elegans* [84]. Another approach involved the development of Piezo1-targeted microbubbles to amplify the mechanical stimuli of ultrasound and achieve low-intensity ultrasound nerve cell stimulation [85]. Although these studies demonstrate the feasibility of MB-mediated ultrasound neuromodulation, MBs have a short lifespan *in vivo* [86].

In comparison to MBs, nanobubbles in the form of gas vesicles (GVs) exhibit superior cell precision due to their nanoscale size. GVs also provide enhanced stability as gas-filled protein structures characterized by a cylindrical shape (Fig. 6a and b). They were originally formed by photosynthetic microbes to adjust buoyancy for optimal light exposure [87], and have more recently emerged as a novel class of ultrasound contrast agents that can be genetically expressed in target microbes or mammalian cells for ultrasound imaging [88–90]. Additionally, GVs efficiently oscillate under ultrasound irradiation and actuate ultrasound-induced neuronal activation by triggering Ca^{2+} influx through mechanoresponsive ion channels (Fig. 6c). By utilizing GVs for sono-mechanical transduction, ultrasound can be amplified to induce reversible neural calcium responses in the mouse brain [14]. Further research has demonstrated that nanobubble-actuated ultrasound stimulation can be used to selectively modulate mouse behaviors (Fig. 6d and e) [15]. Our team has found that mechanosensitive ion channels play important roles in response to ultrasound stimulation through mechanotransduction. Moreover, various mechanosensitive ion channels, including Piezo1, MscL, TRPC6, TRPA1, and TRAAK channels, with different sensitivities to membrane stretch, have been explored in

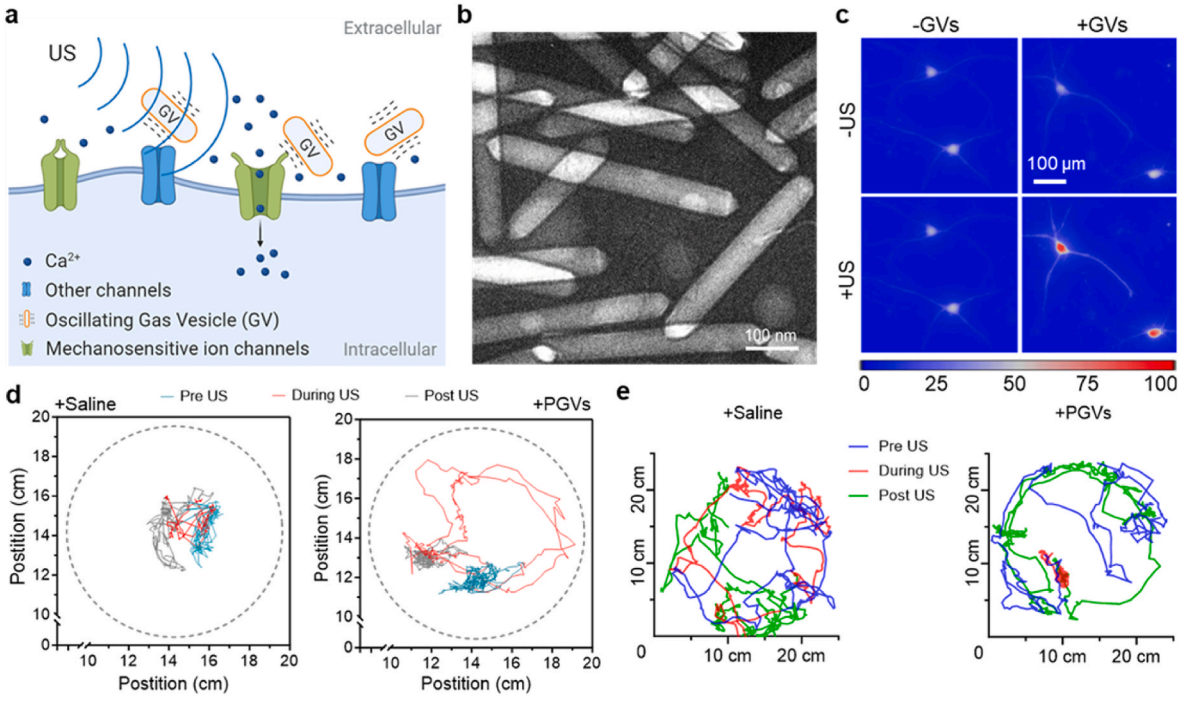

Fig. 6. Nanobubble-enabled ultrasound neuromodulation. (**a**) Schematic illustration of ultrasonic mechanical force amplified locally by gas vesicles (GVs, depicted in yellow) inducing neuronal activation. Figure created using BioRender.com based on Ref. 14. (**b**) Transmission electron microscopy (TEM) image of GVs. (**c**) Images demonstrating neuronal GCaMP6s fluorescence with or without GVs, before and after ultrasound stimulation. (**d-e**) Trajectories illustrating the movements of $Saline^+$ (left panel) or PEGylated-gas vesicles ($PGVs^+$, right panel). (**d**) In a Rotation test, ultrasound stimulation induced rotation in mice injected with PGVs (right panel), while no rotational response was observed in $Saline^+$ mice (left panel). (**e**) Ultrasound stimulation elicited freezing behavior in mice injected with PGVs in the ridge between the dorsal and ventral striatum (right panel), whereas $Saline^+$ mice (left panel) did not exhibit this behavior. The mice injected with PGVs displayed consistent behavioral changes in response to ultrasound stimulation, with the specific behaviors influenced by the targeted brain region. Panel (**b**) and (**c**) adapted with permission from Ref. 14 under a Creative Commons license CC BY 4.0. Panel (**d**) and (**e**) reproduced with permission from Ref. 15 under a Creative Commons license CC BY 4.0. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

response to ultrasound stimulation [13,76,91–96]. These findings highlight the potential of mechanosensitive ion channels in manipulating neuronal functions and provide insights into how neural circuits translate environmental changes into specific behaviors. Acoustic nanomaterials-actuated ultrasound technique holds promise as a powerful tool for the precise modulation of endogenous ion channels expressed in neural circuits, enabling spatially-localized investigation of numerous disease processes in the future.

5.2. Sono-mechanical immunomodulation enabled by nanomaterials

The potential of ultrasound to modulate mechanosensitive ion channels has also been explored in the context of immune cells and immunotherapy [97,98]. Pan et al. developed a method for remote control of gene expression by utilizing MBs to activate mechanosensitive Piezo1 channels through ultrasound. This approach involved expressing a chimeric antigen receptor protein that recognizes and eliminates target tumor cells (Fig. 7a) [99]. In contrast, an alternative strategy focused on mechanically damaging tumor cells to trigger the activation of immune cells. He et al. demonstrated a sonogenetic nanosystem that activates MscL, leading to cell apoptosis through calcium overload. Specifically, iron alginate nanogels were used to transfect tumor cells with MscL plasmid, enabling the expression of mechanosensitive MscL ion channels. Upon ultrasound exposure, the MscL channel opens, causing calcium overload and activating cell apoptosis in a melanoma model in C57BL-6 mice [100]. The apoptotic cell fragments further serve as antigens, stimulating dendritic cell maturation and subsequent activation of T cells (Fig. 7b). Although further advancements are required, these studies have provided valuable insight into harnessing the ability of ultrasound to specifically activate mechanosensitive channels in the field of immunotherapy [99–101].

5.3. Sono-mechanical modulation of stem cells enabled by nanobubbles

Further research has expanded the utilization of ultrasound-stimulated mechanosensitive channels to various other domains of study. In addition to modulating neuronal and immune cell activities, ultrasonic mechanical effects have been employed to induce the differentiation of stem cells. Microbubbles exhibit remarkable sensitivity to ultrasound and can generate localized shear forces and adjustable mechanical stress. This unique property has been effectively exploited in combination with ultrasound to enhance the growth of human mesenchymal stem cells (hMSCs) and promote their chondrogenic differentiation, facilitating cartilage regeneration [102]. Additionally, nanobubbles possess exceptional stability and demonstrate excellent biosafety profiles, making them highly suitable for biomedical applications. In a study by Yao et al., cyclic arginine-glycine-aspartic acid-modified nanobubbles (cRGD-NBs) actively targeted bone marrow mesenchymal stem cells (BMSCs) through integrin receptors. These cRGD-NBs acted as nanomechanical force generators on the cell membrane, promoting osteogenesis in BMSCs and ultrasound-induced bone formation (Fig. 8) [103]. The regulation of TRPM7, actin cytoskeleton, and intracellular calcium oscillations played a crucial role in this process. This investigation provides novel insights into optimizing the effectiveness of ultrasound stimulation in fracture healing.

6. Nanomaterials-enabled chemical stimulus

Ultrasound has emerged as a promising external trigger for the release of molecules, a process known as sono-uncaging. As mentioned earlier, ultrasound can non-invasively penetrate deep tissue, making it particularly suitable for remotely controlling drug release from these ultrasound-responsive nanomaterials for modulation of cell activity [23]. Triggering drug release from these nanoparticles using focused ultrasound adds a new temporal control mechanism to the drug delivery system. Nanocarriers have been employed non-invasively to release chemicals or molecules under sonication, enabling remotely controlled chemical modulation. Chemical cellular modulation involves the use of agents such as chemicals and biomolecules to modulate cell activities. These agents can target endogenous membrane receptors or channels, allowing spatial and temporal control of cell activities *in vivo*. Various

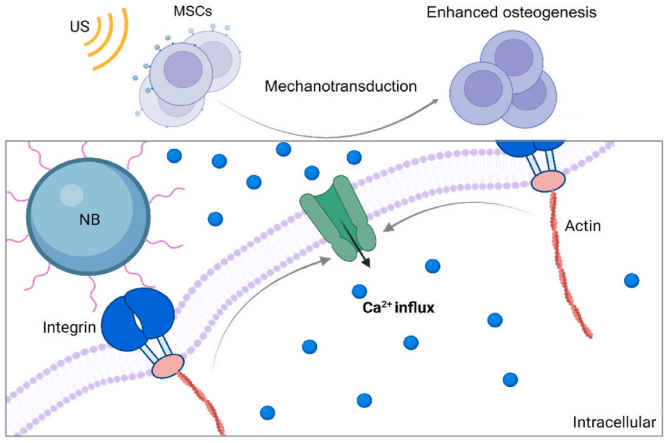

Fig. 8. Nanobubbles enhance ultrasound mechanical effects and improve mechanotransduction for enhanced MSC differentiation. Figure created using BioRender.com based on Ref. 103.

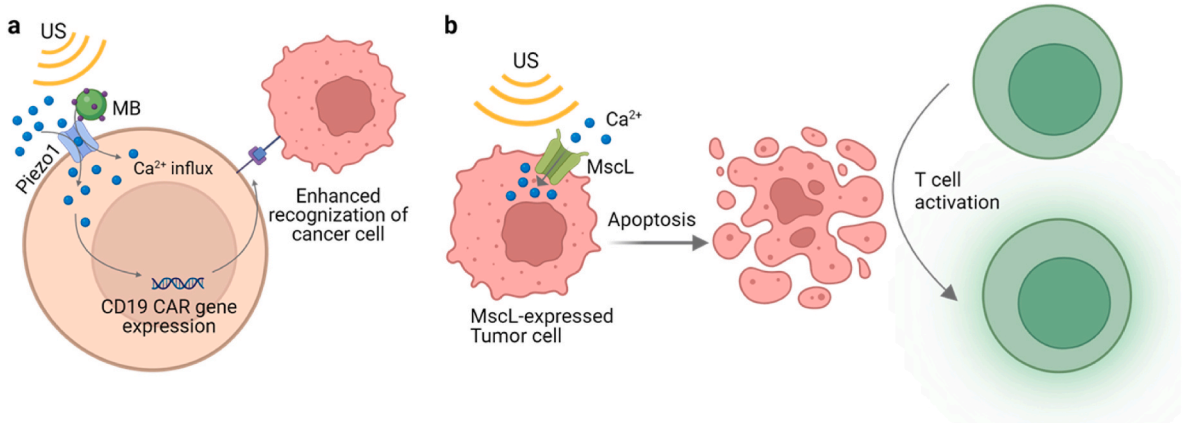

Fig. 7. Mechanomodulation of cells for immunotherapy. (**a**) Schematic illustration of ultrasound-induced cell activation through Piezo1. (**b**) Ultrasound-triggered tumor cell apoptosis via MscL, leading to T cell activation. Figure created using BioRender.com based on Ref. 99 and 100.

sono-transducers, including perfluorocarbons (PFCs)-containing microbubbles, nanoemulsions, and nanodroplets, have been explored for spatiotemporal control of cellular activities [104,105]. Upon administration of ultrasound, the chemicals or biomolecules are released from the carriers, enabling non-invasive targeted cell stimulation in basic and clinical life sciences.

6.1. Sono-chemical neuromodulation enabled by nanocarriers

Nanoparticles have been established as effective drug carriers for targeted cancer treatment [106–109]. Similarly, these nanoparticles can carry neuromodulatory drugs for neurostimulation, such as ketamine, dexmedetomidine, and nicardipine [110]. Studies have investigated the use of PFCs-containing microbubbles, nanoemulsions, and nanodroplets for sonochemical neuromodulation [104,105]. These nanoemulsions provide a temporal mechanism for drug release that occurs only during FUS application. However, the diffusion and action time of drugs should be considered to determine the spatiotemporal precision of ultrasound-triggered drug release [111]. While the drug Propofol can bypass the blood-brain barrier (BBB), its systemic administration does not allow for spatial targeting within a specific brain region, resulting in a dysregulated anesthetic effect. In this context, focused ultrasound was used not to open the BBB but to trigger drug release at the desired brain region. In a proof-of-principle *in vivo* study using an acute rat seizure model, Airan et al. reported that nanoparticles silenced seizures by FUS uncaging a small molecule lipophilic anesthetic without causing brain parenchymal damage or BBB opening (Fig. 9a) [112].

Moreover, Wang et al. demonstrated that ultrasonic uncaging of Propofol can induce activity changes in brain regions that are anatomically distinct but functionally connected to the stimulated region. This finding enables non-invasive mapping of network connections in the brain upon pharmacological activation of specific targets [23]. Similarly, pentobarbital-loaded decafluorobutane-core Definity-based nanodroplets have been explored as potential agents for targeted neuromodulation under ultrasound irradiation, allowing anesthesia to be localized to a specific brain region [105]. The ultrasound drug-unlocking technology can be easily translated and applied to larger animals, and potentially humans, to investigate hypotheses generated by other neuromodulation techniques, such as genetic manipulation of the brain [84,113–116]. Such a remotely controlled drug release platform could be the next step in testing clinically approved drugs [117]. These studies suggest that further development of ultrasonic nano-transducers will provide new tools for non-invasive, spatiotemporally precise neuromodulation without the need for BBB opening, thereby playing a significant role in the treatment of central nervous system (CNS) diseases.

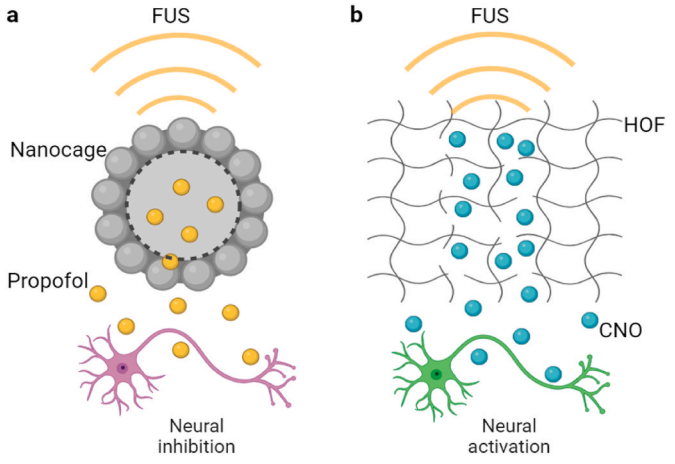

Fig. 9. Schematic illustration of ultrasound-triggered drug release from nanocarriers for inhibiting (**a**) or activating (**b**) neural activities. Figure created using BioRender.com based on Ref. 112 and 118.

In a recent study, Wang et al. introduced hydrogen-bonded organic frameworks (HOF) that can be activated using focused ultrasound to release the designer drug clozapine N-oxide (CNO) (Fig. 9b) [118]. This innovative approach enables the activation of engineered G-protein-coupled receptors, allowing for precise modulation of neural activity in deep brain regions of mice. The utilization of ultrasound in this strategy showcases its ability to precisely manipulate molecular interactions. By developing ultrasound-programmable HOFs, this technique offers minimally invasive and spatiotemporal control over neural activity, thereby opening new possibilities for precise ultrasound neuromodulation.

6.2. Sono-chemical immunomodulation enabled by nanocarriers

In the field of immunotherapy, the effective delivery of immune-stimulatory substances, such as immune adjuvants, to immune cells is crucial for initiating adaptive immune responses. However, challenges such as drug tolerance and immune evasion persist. To address these issues, researchers have explored the use of ultrasound-sensitive nanoparticles for delivering antigens and immune adjuvants. A recent study by Zhou et al. introduced an innovative approach involving engineered extracellular vesicles (EVs) that expressed highly specific immunomodulatory agents (Fig. 10). This enabled immuno-reediting through ultrasound nanomedicine-assisted immunoregulation. The EVs repeatedly released damage-associated molecular patterns, activating the cancer's innate immunity cycle and initiating immunogenic PANoptosis in tumors. This process primed antigen-specific T cells and triggered a protective immune response by activating cGAS-STING signaling pathways [119]. Dendritic cells, an integral part of the natural immune system, play a crucial role in initiating adaptive immunity by activating primary T cells through antigen presentation. To overcome the challenge of low-level tumor antigen presentation, Lu et al. loaded ultrasound-responsive nanometal organic frameworks into vesicles that displayed an anti-DEC205 antibody. These chimeric vesicles directly targeted and activated DCs, promoting tumor antigen cross-presentation and amplifying the T cells' immune response [120]. In another study, mitochondria-targeted nanoparticles were developed to co-deliver nitric oxide (NO) and oxygen (O_2), enhancing sonodynamic therapy (SDT). Under ultrasound irradiation, the generated NO and O_2 converted M2 macrophages to M1 and facilitated dendritic cell maturation (Fig. 10) [121]. Wang et al. utilized ultrasound-mediated cavitation to enhance the delivery of Toll-like receptor agonist (R837)-loaded pH-responsive liposomes (PEOz-Lip@R837) to tumors. This strategy induced the production of tumor-associated antigens (TAA) and, in combination with immune adjuvants, promoted dendritic cell maturation. Additionally, the down-regulation of immune checkpoint molecules stimulated the activation and proliferation of T cells, thereby enhancing anti-tumor immunity (Fig. 10) [122].

Zhang et al. developed a highly stable cerasomal (a hybrid liposome) nano-modulator that enables ultrasound-controlled drug delivery for selective sonodynamic immunotherapy. This modulator releases an immunotherapy adjuvant upon ultrasound irradiation, leading to immunogenic cell death, down-regulation of regulatory T cells, and amplification of anti-tumor immune responses [123]. Shan et al. introduced ROS-responsive biomimetic nanoparticles, coated with macrophage cell membrane, and loaded with the sonosensitizer Ce6 and JQ1. These nanoparticles exhibit rapid drug release upon ultrasound exposure, resulting in the generation of ROS that effectively kills tumor cells. Furthermore, the ROS produced induces immunogenic cell death, activating the immune response. Under ultrasound irradiation, these nanoparticles demonstrate potent immunotherapy effects against glioblastoma [124].

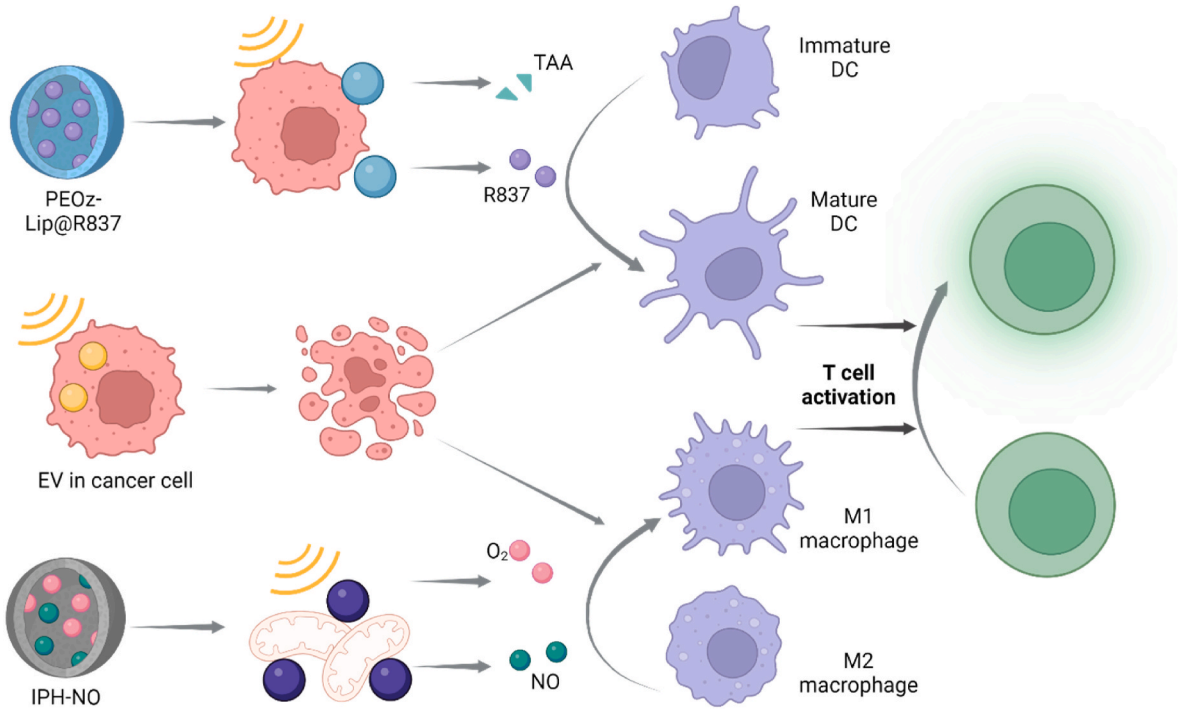

Fig. 10. Schematic illustration of nanomaterials-enabled ultrasound activation of the immune system. Figure created using BioRender.com based on Ref. 119, 121, and 122.

6.3. Ultrasound-chemical modulation of stem cells enabled by nanocarriers

Nanoparticles have emerged as effective carriers for drug delivery. However, controlling the release of drugs from these nanocarriers has typically been a challenge. Fortunately, recent advancements have shown that ultrasound-triggered nanocarriers can be harnessed for a wide range of applications. Razavi's group introduced an innovative ultrasound-mediated nanodroplet-based gene delivery system for the treatment of osteoporosis [125]. In a subsequent study, they engineered ultrasound-triggered nanobubbles capable of simultaneously delivering CTSK siRNA and cerium oxide nanoparticles. This groundbreaking approach showed remarkable potential in effectively inhibiting osteoclast differentiation while promoting osteogenesis *in vitro* [126]. These findings hold great promise for addressing bone fractures and conditions like osteoporosis. In the research by Zhu et al., an engineered approach utilizing ultrasound-mediated nanoparticles composed of US-responsive nanodroplets (PAP@Lipid) co-loaded with all-trans retinoic acid (ARTA) and paclitaxel (PTX) aimed to reduce the populations of cancer stem cells (CSCs) and induce tumor softening, accompanied by a decrease in stemness levels (Fig. 11a) [127]. This strategy enhances the therapeutic efficacy of the cancer treatment. Furthermore, Yan et al. developed SDF-1/BMP-2@nanoparticles (S/B@NPs) that can be triggered by ultrasound, leading to the subsequent release of S/B to facilitate stem cell recruitment and promote periodontal bone regeneration (Fig. 11b) [128]. In addition, a vanadium tetrasulfide-loaded MXene Schottky junction responsive to ultrasound has been developed. When exposed to medical dose ultrasound stimulation, this construct enables the controlled and steady release of vanadium elements. This release promotes the osteogenic differentiation of human bone marrow mesenchymal stem cells, facilitating bone regeneration [129]. These studies illustrate the potential of ultrasound in enabling precise and targeted

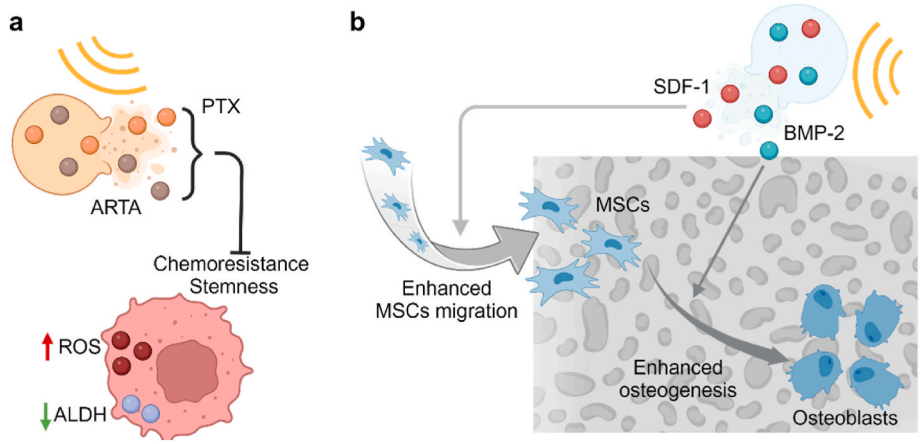

Fig. 11. Ultrasound triggers chemical release for modulating stem cell activity. (**a**) Schematic illustration of ultrasound-mediated drug release for inhibiting the stemness of CSCs. (**b**) Schematic diagram depicting ultrasound-triggered release of S/B@NPs for recruiting and enhancing the osteogenesis of stem cells. Figure created using BioRender.com based on Ref. 127 and 128.

therapies across diverse fields.

The utilization of ultrasound in conjunction with nanocarriers presents a promising avenue for modulating stem cells and achieving enhanced therapeutic outcomes. By leveraging the unique properties of ultrasound-triggered nanobubbles, researchers are advancing the field of regenerative medicine and targeted cancer therapy, opening new possibilities for precise and effective treatments.

7. Conclusion and future perspectives

The combination of ultrasound with nanomaterials presents a promising approach for achieving precise and controlled modulation of cell activities. Incorporating nanotechnology enhances the localization efficiency of cell manipulation, improving targeting specificity while minimizing undesired side effects. This review has summarized the current applications of nanomaterials-enabled ultrasound stimulation in biological contexts and proposes potential avenues for future research in this field. The development of ultrasonic nano-transducers holds immense potential for genetic manipulation-free, minimally invasive, and spatiotemporally precise cell modulation, offering a wide range of biomedical applications. Combining different energy modalities can overcome the limitations of a single modality, providing advantages in terms of spatiotemporal precision, cell-type specificity, deep tissue penetration, and translation to larger animals and eventually humans. For instance, acoustic-mechanical stimulation utilizing nano gas vesicles leverages ultrasound's deep penetration and nanobubbles' high spatial accuracy [14].

Progress in nanotechnology is opening doors to a range of nano-platforms with sono-responsive capabilities that facilitate the modulation of ultrasound stimulation. However, it is important to acknowledge that nanomaterial-enabled modulation techniques are still in their early stages, and further research is necessary to understand their full potential and limitations. Specifically, certain nano-transducers originating from inorganic sources possess the capability to accumulate and endure within the human body for extended durations, potentially engendering unforeseen and deleterious health outcomes [130]. Additionally, these external materials present potential immunogenic hazards, thereby introducing substantial ambiguity and variables into the therapeutic regimen. Critical issues such as non-invasive delivery routes, biosafety, and ethical considerations need to be addressed to bring this technology closer to clinical application. To bridge this gap and expedite the clinical translation of sono-responsive nanomaterials, comprehensive research into their cytotoxicity, biodegradability, and metabolic pathways is imperative. Such studies are crucial for complete comprehension and mitigation of potential adverse effects, guaranteeing the safety and effectiveness of these systems in clinical applications. Emphasizing high long-term biocompatibility, straightforward biodegradability, and efficient clearance is paramount in formulating ultrasound-responsive nanomaterials. The development of biocompatible, stable, efficient, and reliable nanoparticles is pivotal for the effective transition to clinical applications, as highlighted in prior studies [113,131,132]. Achieving high-volume production of sono-responsive nanomaterials with superior yield and reproducibility is imperative for their successful incorporation into clinical settings. Future research should explore additional cell types and translate these findings into clinical applications. Ethical considerations also play a crucial role in the development of brain implants using nanoscale materials, ensuring patient safety and long-term assurances. Overcoming these obstacles via pioneering research and innovation will pave the way for the seamless integration of ultrasound-responsive nano-transducers into clinical translation.

Currently, various types of nanomaterial delivery methods have been well established, including intranasal delivery, oral administration, transdermal administration, intravenous injection, stereotactic injection, and blood-brain-barrier opening [15,133–136]. Although some of the delivery strategies are minimally invasive and suitable for fundamental research, there is a growing imperative for the advancement of non-invasive modalities to precisely deliver nanomaterials to specific tissues. Future research should focus on the development of non-invasive approaches for delivering nanomaterials to targeted tissues. Understanding the kinetics of nanomaterial retention and clearance is vital for designing and implementing nano-transducer-enabled cell modulation techniques, particularly for applications requiring long-term modulation. The varying retention and clearance times of different nanomaterials, with solid nanoparticles having longer retention compared to softer ones like nanobubbles, offer opportunities for transient or chronic modulation of cell activity. In summary, the integration of ultrasound and nanomaterials holds tremendous potential for advancing cell modulation techniques. Continued research efforts are needed to address technical challenges, ensure safety, and unlock the full therapeutic potential of this innovative approach in various biomedical applications.

CRediT authorship contribution statement

Xuandi Hou: Writing – review & editing, Writing – original draft, Conceptualization. **Langzhou Liu:** Writing – original draft. **Lei Sun:** Writing – review & editing, Supervision, Funding acquisition.

Declaration of competing interest

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

Data availability

No data was used for the research described in the article.

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