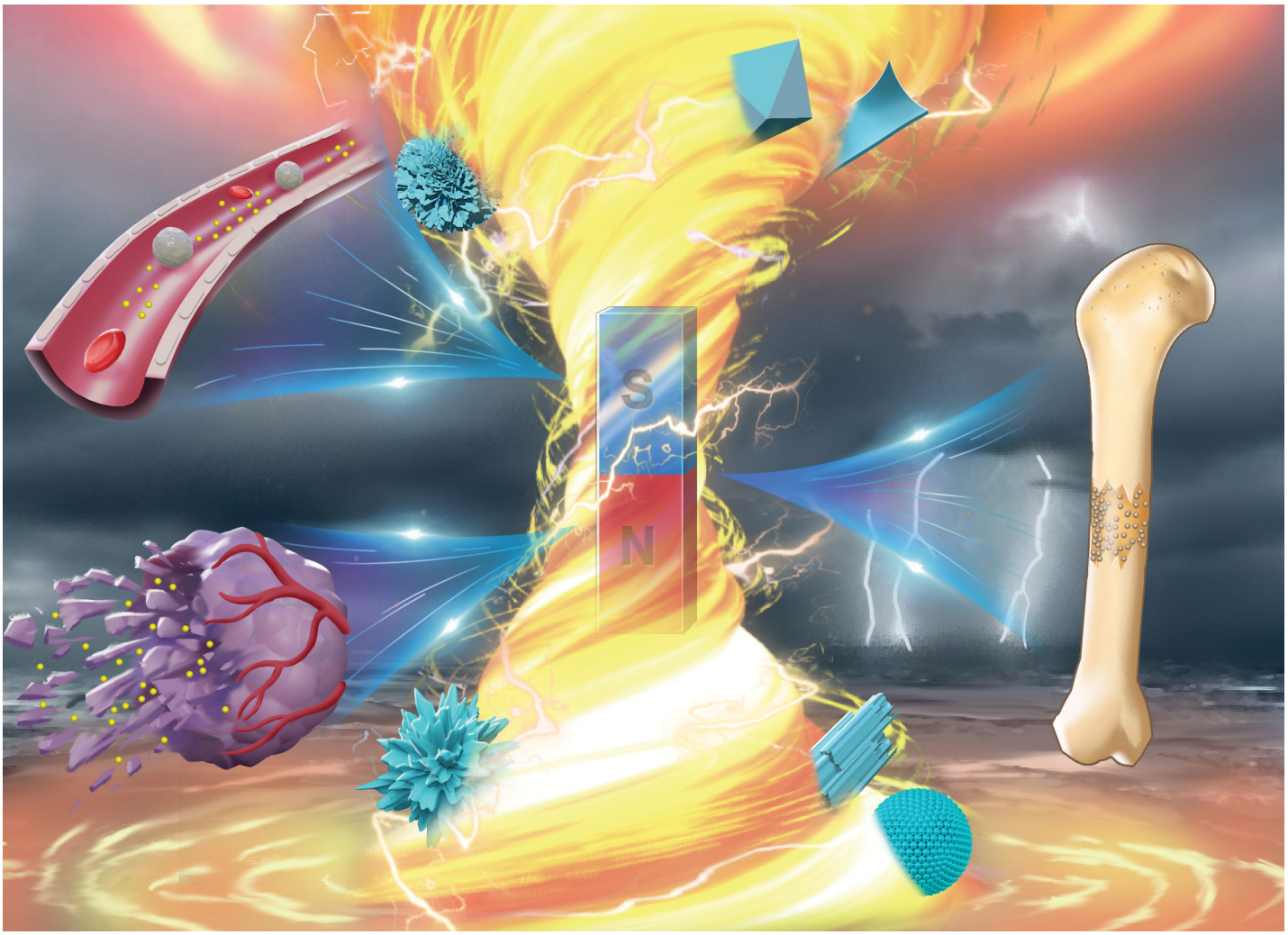

A study on magnetomechanical force for therapeutic applications was conducted by Dr Fang Yang *et al.* at Cixi Institute of Biomedical Engineering.

Magnetomechanical force: an emerging paradigm for therapeutic applications

Magnetomechanical force is an emerging mechanical force paradigm derived from the interaction of a magnetic field and a magnetic material. Impressively, this paradigm is distinguished with spatially and time-controlled transducing superiority, thus holding great promise in cell fate regulation. In addition, magnetomechanical force manipulation in a precise manner has made a profound impact on therapeutic applications including drug controlled release, cancer therapy, and regenerative medicine.

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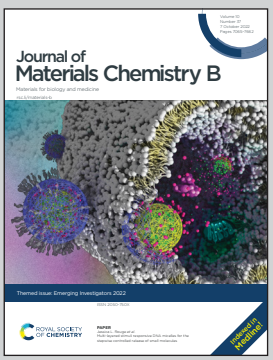

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Magnetomechanical force: an emerging paradigm for therapeutic applications

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Mechanical forces, which play a profound role in cell fate regulation, have prompted the rapid development and popularization of mechanobiology. More recently, magnetic fields in combination with intelligent materials featuring magnetic responsiveness have been identified as a spatially and time-controlled transducing paradigm to generate magnetomechanical forces and induce a therapeutic effect. Herein, recent magnetic materials and magnetic regulation systems are summarized, which offer opportunities for magnetomechanical force manipulation in a precise manner. Additionally, promising applications based on magnetomechanical force including drug controlled release, cancer therapy, and regenerative medicine are highlighted, with respect to both *in vitro* and *in vivo*. Furthermore, perspectives on the further development of magnetomechanical force are commented on, mainly emphasizing scientific restrictions and exploitation directions.

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1. Introduction

Cellular function regulation (*e.g.* communication, adhesion, sensing, transport, energy production, and tissue development) is available for implementation *via* invasive systems including pharmacological, molecular and physical stimulation.[1] Although pharmacological molecular stimulation holds great promise in biochemical conditioning such as ion channel conductance, protein association and stability, and small molecule targeting, its modulation of cellular processes only allows for imprecise on/off switching.[2] Impressively, physical technology is even capable of achieving precise biological regulation spatially and temporally. In this regard, external energy fields (*e.g.* light irradiation, ultrasound, heating and cooling, and magnetic/electric fields) have been actively under development as auxiliary stimuli to manipulate the cellular fate in recent years.[3–7] In parallel, biophysical cell stimulation (*e.g.* mechanical force) based on various forms of energy transformation offers the opportunity to mediate specific cell behaviors, which has made a profound impact on fundamental, methodological, and therapeutic sciences.[8]

As an external energy field, the magnetic field has been applied to remotely interact with magnetic materials for more than 20 centuries.[9] Specifically, the ancient Chinese found the utilization of natural magnets producing iron-attract forces to fabricate the earliest compass for orientation identification. Nowadays, with the exploitation of novel technologies, magnetic materials possess broad application potential in biology and medicine fields including magnetic resonance imaging, controlled drug delivery, genetic modification, and magnetic

hyperthermia therapy.[10] In addition, intelligent magnetic materials have secured their places as transducing tools, which change their structural and functional properties under a static magnetic field or alternating magnetic field to execute the remote cellular manipulation.[11–13] For instance, magnetic materials show satisfactory values in cell culture and tissue maturation on account of their triggered response to external magnetic stimuli, thus promoting the cells to generate physicochemical factors (*e.g.* protein kinase, interleukin, and aggrecan) and adjust the intracellular metabolic process, molecular signalling pathway, and gene expression.[14–16] Besides, magnetic material-based mechano-transduction has become a non-invasive and precise control paradigm to apply magneto-mechanical forces/torques to the associated/attached cells.[17]

At the cellular level, accurate regulation of mechanically sensitive biomolecules generally relies on forces in the pico-newton (pN) range.[18,19] It is estimated that a single magnetic force pulse (approximately 0.3 pN) met the requirements for the opening of mechanoelectrical transduction channels.[20] Encouragingly, the magnetomechanical force that magnetic materials exert on the proteins, lipids, and ion channels is able to reach this level, which endows magnetic materials with the specific function to modulate the cellular fate for therapeutic applications.[21,22] Additionally, the utilization of magnetomechanical force for cellular manipulation has unparalleled superiorities. First of all, due to its inherent non-contact properties, the magnetomechanical force provides a non-invasive regulatory pattern, leaving the surrounding physiological environment intact. Second, the magnetomechanical force features programmability, which refers to the capacity to implement a specific force mode, position, and orientation in terms of the features and properties of magnetic materials and magnetic fields.[23,24] Third, magnetomechanical force possesses the potential to combine with other energy fields, which

Table 1 Recent progress in magnetic nanocomposites for biomedical applications

Type	Saturation magnetization	Magnetic regulation system	Size	Magnetomechanical force	Application	Ref.
Ethylene-vinyl acetate@Fe–Cr@BSA composites		1100 G, 60 Hz	r = 90–125 μm		Drug controlled release	44
Poly(L-lactic acid)@Faujasite@magnetostrictive Terfenol-D@Ibuprofen microporous membrane		AMF 100–200 mT, 0.3 Hz	r = 56 ± 13 μm			45
Fe_xO_y@silica-pillared clay@aspirin composites		150 mT	r = 2.8–3.0 nm			46
Fe_3O_4@silica nanocomposites pillared clay@Ibuprofen composites		150 mT	r = 2.5–2.8 nm			47
Ni/Ti-coated sunflower pollen grain@doxorubicin composites	15 emu g^{-1}	RMF 5–15 mT, 10–100 Hz	r = 15 μm			48
Calcified porous microneedles coated with Fe–Ti@camptothecin		RMF 500–800 rpm	L = 40–60 μm			49
γ-Fe_2O_3@poly(D,L-lactide)@paclitaxel composites	65.7 emu g^{-1}	AMF 750 G, 20 Hz	r = 972 ± 68 nm			51
Wormlike mesoporous silica nanotube@Co-Fe_2O_4 nanoparticles		AMF 0.5 mT, 100 Hz	L = 1–1.5 μm, r = 8 nm			52
$Fe_{20}Ni_{80}$ discs	750 emu cm^{-3}	AMF 10 mT, 40 Hz	r = 1 μm, h = 60 nm	26–53 pN	Cancer therapy	58
Permalloy magnetic discs		AMF 1 T, 20 Hz	r = 2 μm			59
$Zn_{0.4}Fe_{2.6}O_4$@epidermal growth factor composites	0.02 Am^{-2} g^{-1}	RMF 40 mT, 15 Hz	L = 4 μm	20–50 pN		60
Iron oxide magnetic nanoparticles@carboxymethyldextran@epidermal growth factor composites	20 Am^{-2} kg^{-1}	AMF 42 kA m^{-1}, 233 kHz	r = 61 ± 29 nm			61
Superparamagnetic iron oxide nanoparticles @lysosomal protein marker LAMP1 composites		DMF 30 mT, 5–15 Hz	r = 5.8 μm			62
$Zn_{0.4}Fe_{2.6}O_4$@triphenylphosphonium composites	44 emu g^{-1}	RMF 15 Hz, 40 mT	L = 1 μm	4 pN		63
$Zn_{0.4}Fe_{2.6}O_4$@death receptor 4 composites	161 emu g^{-1}	SMF 0.2 T	r = 15 nm	30 fN		64
$Zn_{0.4}Fe_{2.6}O_4$@doxorubicin@death receptor 4 composites	161 emu g^{-1}	SMF 0.5 T	r = 15 nm			65
Gold-coated magnetic microspheres	65.65 emu g^{-1}	VMF 400 mT, 3 Hz	r = 1.56 ± 0.47 μm	35.79 pN		66
Doxorubicin@$Zn_{0.2}Fe_{2.8}O_4$@poly(lactic-*co*-glycolic acid) composites	22 emu g^{-1}	RMF 45 mT, 2000 rpm	r = 200 nm	244.78 pN		67
Hyaluronic acid@olaparib@polyethylenimine-Poly(D,L-lactide-*co*-glycolide)@Fe_3O_4 composites	21.08 emu g^{-1}	RMF 7 T, 1000 rpm	r = 159.5 ± 2.3 nm			68
Fe_3O_4 magnetic nanoparticles coated with nanoscale graphene oxide	50 emu g^{-1}	0–20 000 Oe	r = 10 nm		Regenerative medicine	80
Fe_3O_4@RGD peptide/Fe_3O_4@platelet-derived growth factor receptor α antibody		60–120 mT	r = 250 nm			81
Fe_3O_4-Mesenchymal stem cell Sheets		4000 G				82
Nickel microtips	57 μemu	0.2 T, 1 Hz	H = 1 μm			83
Polycaprolactone@Fe_3O_4 nanofibre meshes			r = 50–100 nm, H = 100 μm, S = 16 cm × 7 cm			86
$CoFe_2O_4$@poly(vinylidene fluoride) composites		0–230 Oe, 0.3 Hz	r = 60, 80, 120 μm			87

endows the magnetomechanical force with high flexibility and efficiency.[25]

Magnetic materials and magnetic regulation systems are the two key components controlling the magnitude and direction of magnetomechanical force. Encouragingly, intelligent magnetic materials with unique structures and functions are promising to secure their status as converter stations to mediate magnetomechanical force for various types of therapies. In this review, recent magnetic materials and magnetic regulation systems for magnetomechanical force manipulation are introduced systematically. Then, we describe innovative applications based on magnetomechanical force including drug controlled release, cancer therapy, and regenerative medicine (Table 1). Finally, we envisage the challenges and future exploitation directions of magnetomechanical force. In particular, we hope that the review can enlighten the development of magnetomechanical force and presents a promising orientation for future theranostics.

2. Magnetic materials and magnetic regulation systems

Magnetic materials can be categorized according to the magnetic susceptibility (x_m), which reflects the potential of the magnetic material to be magnetized. Thus, magnetic materials can be divided into three categories, namely ferromagnetic materials ($x_m \gg 0$), paramagnetic materials ($x_m > 0$), and diamagnetic materials ($x_m < 0$).[26–28] To be precise, paramagnetic materials are weakly attracted to magnetic fields, while diamagnetic materials are repelled by magnetic fields. Once the magnetic fields are removed, these two types of magnetic materials cannot maintain magnetization. Comparatively, ferromagnetic materials are forcefully attracted to magnetic fields, which reveal remnant magnetization/remanence even after the magnetic field is removed. In addition, superparamagnetic materials are a special type of magnetic material distinguished from the characteristics of ferromagnetic materials and paramagnetic materials (*e.g.* high susceptibility and non-remanence). There are only a few examples of using paramagnetic and diamagnetic materials for magnetomechanical force generation, and a majority of magnetomechanical force platforms are designed and established on ferromagnetic and superparamagnetic materials.[29,30]

Both static and dynamic magnetic fields, whether spatially homogeneous or heterogeneous, are well-suited to trigger magnetomechanical force in various environments.[31] Thereinto, weak homogeneous rotating or oscillating magnetic fields demonstrate higher efficiency to convert magnetic energy into mechanical energy. As a typical platform for magnetic field supply, the magnetic regulation system contains permanent magnets or electromagnets as "fuel".[32–35] Since the magnetic fields provided by permanent magnets are persistent, the magnitude is unable to change rapidly.[36,37] In parallel, the distribution of magnetic fields mainly relies on the shape and size of permanent magnets. Therefore, setting the position and orientation of permanent magnets can implement the translator/rotational movement of magnetic materials. In an electromagnet-based regulation system, magnetic fields are produced by flowing currents.[38–40] By controllably wrapping copper wires around a ferromagnetic core, the magnetic field along with a field gradient can be concentrated and amplified accurately. Importantly, on-demand regulation of currents in the coils meets the wide requirements for the magnetic field configuration, covering rotating magnetic fields, oscillating magnetic fields, alternating magnetic fields, and conical magnetic fields.

3. Magnetomechanical force for drug controlled release

Recently, novel and intelligent drug delivery systems have blazed a new path for therapeutic applications, offering a more valid pattern than traditional medicine to deliver drugs in a real-time localization and quantitative manner.[41] Encouragingly, it is feasible to deliver drugs at a specific time and rate or at a specific site through appropriate endogenous or exogenous physicochemical stimuli.[42,43] In this sense, the integration of exogenous stimuli-sensitive components into the delivery system holds admirable promises in drug controlled release. Of note, one of the most promising tactics consists of employing magnetic materials and magnetic regulation systems to generate magnetomechanical force for diverse modes of stimulus-responsive drug controlled release.

As early as 1992, Edelman *et al.* constructed a composite magnetic system integrating magnetic spheres and an ethylene–vinyl acetate (EVAC) polymer matrix to explore the drug release modulation based on magnetomechanical force-triggered effects.[44] In this report, the role of magnetomechanical force on the release of drugs was the transduction of the external magnetic field (1100 G, 60 Hz) into a mechanical deformation of the system through internal magnetic spheres. Due to the alternate compression and decompression of the EVAC polymer matrix *via* magnetic spheres, drug release efficiency was remarkably increased up to 30-fold, which effectively revealed the potential of magnetomechanical force for enhanced release. In another effort, Barbosa *et al.* developed a poly(L-lactic acid) (PLLA) drug release system consisting of faujasite, magnetostrictive Terfenol-D (TD), and ibuprofen (IBU, an analgesic and antiinflammatory drug) (Fig. 1a).[45] In this system, faujasite possessing rigid construction, high adsorption ratios, and tunable pore structure was well-suited to encapsulate IBU, while TD features excellent anisotropy constant, coercivity, and magnetostriction to provide magnetomechanical force. Due to the alternating magnetic field, there was an enhancement of the IBU release rate by more than 30%, which was mainly driven by magnetomechanical force-induced swelling or erosion. As the alternating magnetic field magnitude increased from 100 to 200 mT, the release quantity of IBU was further boosted from 67% to 75%. In short, magnetomechanical force is expected to provide considerable promise for controllable drug release

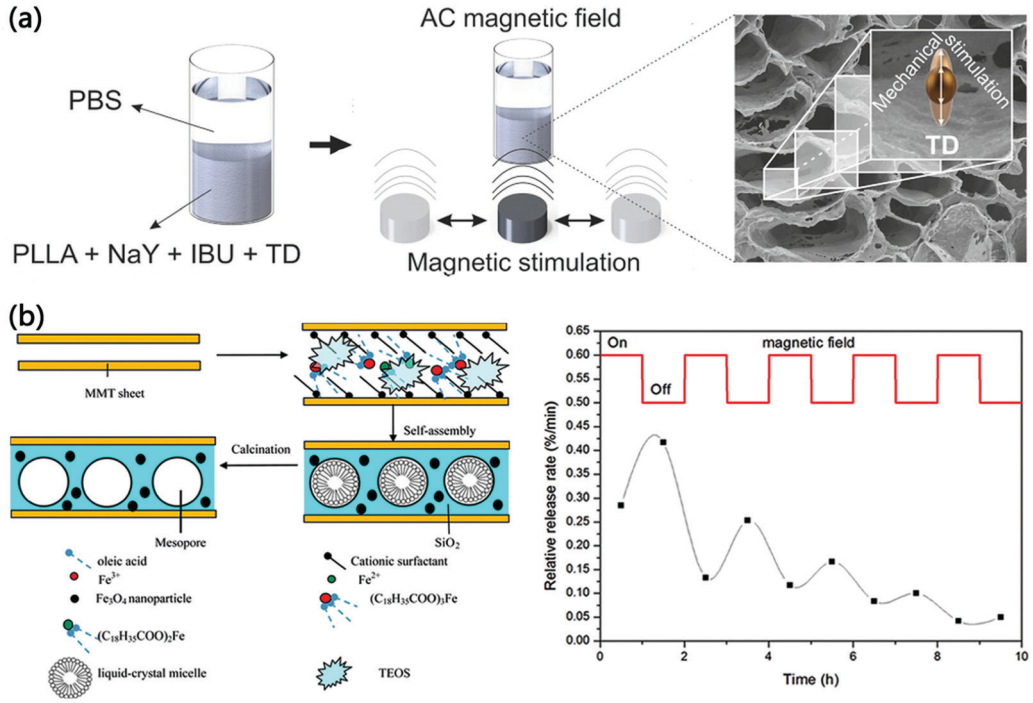

Fig. 1 The magnetomechanical force for drug controlled release. (a) Illustration of magnetomechanical force-based controllable drug release enhancement. Reproduced with permission from ref. 45. Copyright 2016 Wiley-VCH. (b) Illustration of magnetomechanical force-based controllable drug release reduction. Reproduced with permission from ref. 47. Copyright 2015 Elsevier.

enhancement, due to the force-driven deformation and even structural collapse.

Meanwhile, magnetomechanical force has tremendously fostered the development of drug release reduction and presented brand-new breakthroughs in therapeutic applications. For instance, Mao *et al.* combined silica-pillared clay (SPC) with a highly ordered interlayered mesopore structure with magnetic γ-Fe_2O_3 for controlled drug release and targeting.[46] Such composites were featured by an unobstructed pore system, thus refraining from numerous application problems such as pore clogging, mass transfer restrictions, and limitations to further functionalization. More importantly, the drug release rate from these composites reduced dramatically due to the aggregation of γ-Fe_2O_3 triggered *via* non-contact magnetomechanical force. To be precise, the time for the drug release fraction of 50% was extended from 4 h to 5.5 h once exposed to a magnetic field of 150 mT. Nevertheless, γ-Fe_2O_3 on the outer surface influenced the number of Si–OH in the composites, resulting in a reduction in drug loading. Based on this, Mao *et al.* developed a novel cationic surfactant-aliphatic acid mixed route to obtain Fe_3O_4@SPC composites (Fig. 1b).[47] In this route, oleic acid-formed organics could cooperate with cationic surfactants to generate interlayered mixed micelles, further ensuring that interlayered Fe_3O_4 formed with an outstanding dispersion and mesoporous structure and valid loading of IBU. Analogously, by reason of magnetomechanical force resultant particle aggregation, the release quantity of IBU was only 68.2–80.1% under a magnetic field of 150 mT for 10 h, while that without a magnetic field was 90%. Therefore, magnetomechanical force has a strong regulatory potential, implying the possibility of application in drug release reduction.

Impressively, the combination of magnetomechanical force and the anchoring technique has been a welcome addition to the drug controlled release currently. In this regard, Sun *et al.* developed a magnetic urchin-like microsystem on the basis of sunflower pollen grain to achieve transmembrane drug delivery (Fig. 2a–c).[48] As a unique and renewable biomaterial, sunflower pollen grain was eligible to offer an enormous inner cavity structure for encapsulating drugs and nanospikes for drilling into cells. After the processing of acidolysis, sputtering, and vacuum loading, the prepared microsystem harboring the nickel coating was endowed with two magnetic response patterns (rolling and spinning). Thereinto, the rolling function was capable of delivering drugs to the required site rapidly, while the spinning function was beneficial for realising efficient membrane perforation for drug release after anchoring. In addition, Srivastava *et al.* gathered calcified porous acicular micromaterials with a length of 40–60 μm from dracaena and clad them with Fe–Ti shells for magnetic actuation drug release.[49] Under an external rotating magnetic field, these calcified micromaterials were accountable for magnetic control to insert a single cell, which served as an anchoring mechanism for subsequent drug release. Owing to the cellular incision creation and site-directed drug release, this strategy based on acicular micromaterials significantly lowered lateral health damage induced by chemotherapy. Thus, the cooperation of magnetomechanical force and the anchoring technique demonstrates high intelligence and precision in cellular

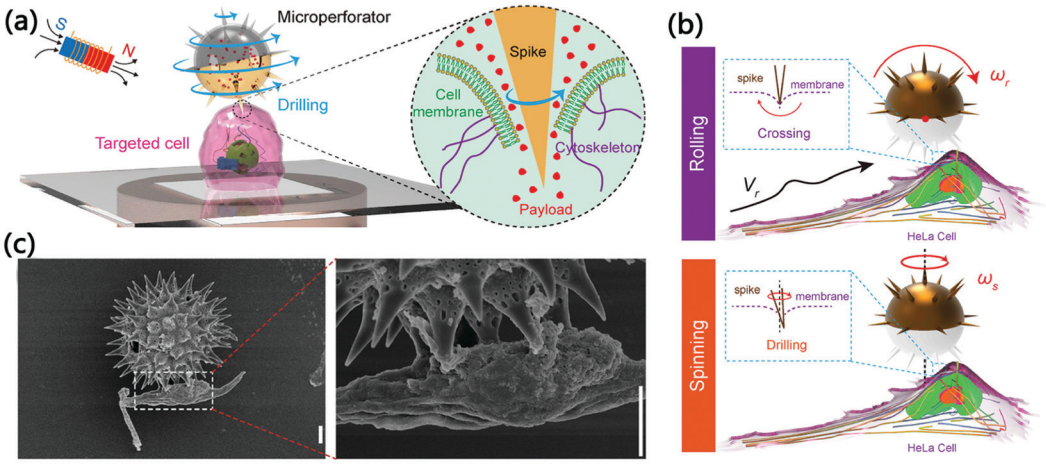

Fig. 2 The combination of magnetomechanical force and the anchoring technique. (a) Illustration of drug controlled release based on the combination of magnetomechanical force and anchoring technique. (b) Illustration of the interaction with HeLa cells in rolling and spinning patterns. (c) Scanning electron microscopy images of a urchin-like microsystem anchoring single HeLa cells. Reproduced with permission from ref. 48. Copyright 2020 WILEY-VCH.

targeting, along with sufficient drug controlled release, presenting a promising avenue for future therapeutic applications.

Under an alternating magnetic field, magnetic materials are able to generate considerable magnetic hyperthermia,[50] which enlightens the exploration of cooperative drug release controlled by magnetomechanical force and heat. For example, Yin *et al.* prepared a magnetic polymer composite microplatform made of poly(D,L-lactide) (PLA) microspheres, γ-Fe_2O_3 nanoparticles (approximately 8 nm), and paclitaxel (an anti-cancer drug).[51] Once injected directly into the body and guided by an externally applied magnetic field (750 G, 20 Hz) to the target location, two types of drug release mechanisms, natural degradation of PLA microspheres and release enhancement based on γ-Fe_2O_3 nanoparticles, could be activated simultaneously. Since the γ-Fe_2O_3 triggered magnetocaloric effect was extremely low and inadequate to influence the release behavior, as-generated magnetomechanical force leading to the physical deformation and ultimate breakage of the PLA matrix, was the main cause of elevated drug release. In addition, Liu *et al.* developed a novel nanomotor strategy for controllable drug delivery and release under an adjustable magnetic field (0.5 mT, 100 Hz).[52] In this system, monodispersed $CoFe_2O_4$ nanoparticles were deposited on wormlike mesoporous silica nanotubes with ultrahigh surface area to form nanomotors, which integrated the functions of magnetic propulsion and drug loading. Subsequently, G-quadruplexes (highly ordered DNA structures) were engaged to modify as-formed nanomotors for improved stability and drug packaging. In this system, the drug release process could be simply controlled by tuning the magnetic field to initiate the thermal and mechanical effects of nanomotors. Interestingly, controlled drug release could still be realized by magnetomechanical force-triggered oscillation even removing the thermal effect. Taken together, the combined magnetomechanical force and other forms of energy are expected to be a highly potential drug controlled release strategy.

4. Magnetomechanical force for cancer therapy

Nowadays, cancer-relevant diseases remain a serious threat to human health globally owing to the abhorrent nature of cancer, namely diversity, complexity, and heterogeneity.[53] Encouragingly, recent decades have witnessed the forward development of technologies against cancer invasion and morbidity including conventional clinical methods and novel therapeutic approaches.[54–56] Among these therapeutic approaches, magnetomechanical force is a rising research hotspot with great potential for cancer therapy. In this therapeutic model, magnetic materials feature asymmetric geometric structures and efficient magnetic reversal play a vital role, since they exhibit a certain degree of advantages in generating magnetomechanical force when exposed to an alternating magnetic field.[57]

As a precise therapeutic paradigm, magnetomechanical force is engaged to damage cellular membranes and organelles of targeted cancer cells, which can be classified as internalized and non-internalized forms. The former form is independent of internalized magnetic materials, whose sizes need not meet the wide requirements for cellular uptake. For example, Kim *et al.* reported for the first time a lithographically defined microdisc possessing a spin-vortex ground state for high magnetomechanical force induction (26–53 pN).[58] In an alternating magnetic field (10 mT, 40 Hz), the microdisc vortices showed a shifting tendency to realize oscillation, thus transmitting magnetomechanical force to cancer cells. Importantly, the spin-vortex mediated mechanical stimulation not only resulted in compromised integrity of the cellular membranes, but initiated programmed cell death. Thanks to this, under a magnetic field with a magnitude as small as tens of oersteds, a frequency as low as tens of hertz, and an action time as short as 10 min, such a treatment model was sufficient to kill approximately 90% of the cancer cells *in vitro*. Correspondingly, the former form is

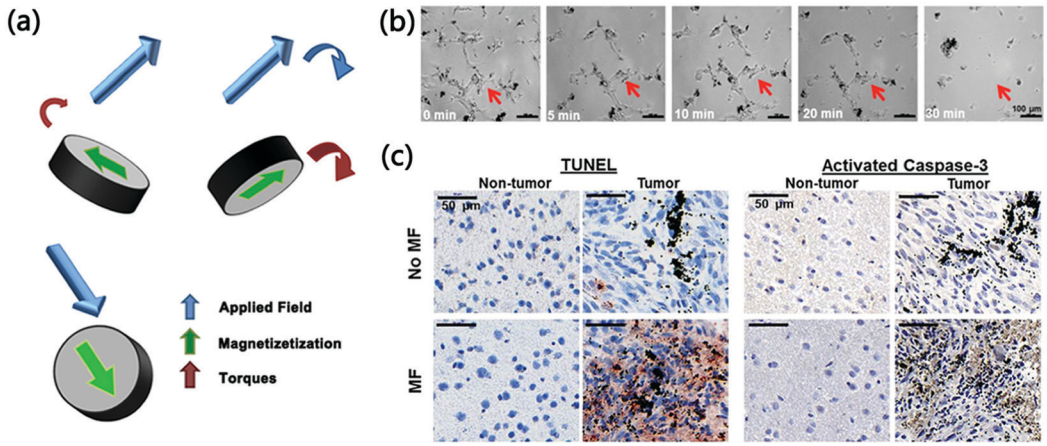

Fig. 3 The magnetomechanical force-based physical damage for glioma elimination. (a) Magnetic response illustration of spin-vortex and disc-shaped nanomagnets. (b) Optical microscopy images of magnetomechanical force-based cellular physical disruption. (c) TUNEL staining and activated caspase-3 staining after magnetomechanical force-based physical treatment. Reproduced with permission from ref. 59. Copyright 2015 WILEY-VCH.

taking advantage of internalized magnetic materials to mediate magnetomechanical force inside the cells. In this regard, the same team substantiated the antineoplastic effects (both *in vitro* and *in vivo*) of spin-vortex and disc-shaped permalloy nanomagnets (Fig. 3a–c).[59] After co-incubation for 24 h, almost all U87 glioma cells efficiently ingested these nanomagnets without obvious alteration in cellular morphology. When the internalized nanomagnets were in the plane of the rotating magnetic field at 20 hertz, a powerful magnetomechanical force emerged, which damaged the cellular membrane integrity and caused the massive death of U87 glioma cells. Moreover, magnetomechanical force based on these nanomagnets was even capable of suppressing glioma growth significantly and increase the apoptotic area (26%), thus prolonging the survival rate of tumor-bearing mice. Therefore, magnetomechanical force-based physical damage is a novel approach to manipulating magnetic materials for tumor elimination.

Targeting strategies endow magnetic materials with the capacity of specifically reaching the surface or even the internal organelles of tumor cells, and have been a central topic regarding efficiency intensification of magnetomechanical force-based physical disruption. For instance, Shen *et al.* obtained a zinc-doped iron oxide nanoparticle possessing high magnetization, and further modified this nanoparticle with the

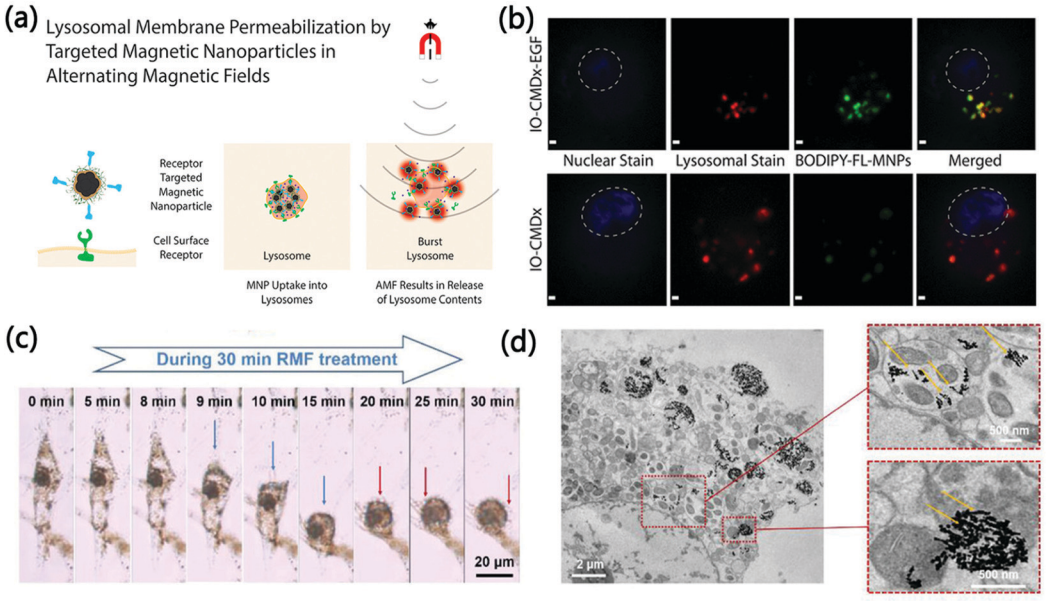

Fig. 4 The combination of targeting strategies with magnetomechanical force-based physical disruption. (a) Illustration of lysosomal membrane permeabilization under an alternating magnetic field. (b) Confocal microscopy images of the intracellular distribution. Reproduced with permission from ref. 61. Copyright 2013 American Chemical Society. (c) Optical microscopy images of magnetomechanical force-based mitochondria-targeted physical disruption. (d) Transmission electron microscopy images of magnetomechanical force-based mitochondria-targeted physical disruption. Reproduced with permission from ref. 63. Copyright 2019 WILEY-VCH.

epidermal growth factor (EGF) peptide to achieve specific targeting of tumor cells.[60] Once internalized into tumor cells, such nanoparticles could assemble into slender aggregates under a rotating magnetic field at 15 hertz and 40 mT. On account of the aggregation effect, hundreds of pN could be produced inside tumor cells, which acutely devastated the plasma alongside lysosomal membranes, thus releasing hydrolases into the cytosol for programmed cell death and necrosis. Analogously, Domenech *et al.* harnessed iron oxide magnetic nanoparticles with EGF receptors to selectively mediate lysosomal membrane permeabilization (Fig. 4a and b).[61] Since the capacity of lysosomal membrane permeabilization to promote cell death was independent of apoptosis defense mechanisms, this tactic based on magnetomechanical force efficiently activated the lysosomal death pathways and showed marked antitumor potential against a broad spectrum of tumors. In another work, Zhang *et al.* combined superparamagnetic iron oxide nanoparticles with antibodies targeting the lysosomal protein marker LAMP1 to induce apoptosis remotely.[62] Owing to the binding of magnetic nanoparticles to endogenic LAMP1, approximately 71.2% of the prepared magnetic nanoparticles could accumulate along the lysosomal membranes preferentially. Subsequently, magnetic nanoparticles were rotationally activated *via* the dynamic magnetic field (30 mT, 5–15 Hz) to generate shear force and tear the lysosomal membranes, which therefore lowered the size and number of lysosomes to inhibit cell growth. In addition, Chen *et al.* synthesized a novel cubic-shape nanospinner, integrating zinc-doped iron oxide ($Zn_{0.4}Fe_{2.6}O_4$) nanocubes for magnetomechanical force production and triphenylphosphonium (TPP) cations to target mitochondria (Fig. 4c and d).[63] Impressively, the nanospinners had the characteristic to escape from lysosomes and head for mitochondria even in diverse cell lines. Due to the direct magnetomechanical force (approximate 4 pN) acting on mitochondria, the mechanical performance down-regulated the mitochondrial membrane potential to execute the cell apoptosis progress, hence effectively improving the apoptosis rate to 58%. As a consequence, magnetomechanical force-based physical disruption united with a well-established targeting ability is highly desirable in remote invasive cancer therapy.

In addition to the physical damage, magnetomechanical force has been used to stimulate mechanosensitive proteins on the cell membrane or organelle membrane, so as to initiate cell signaling pathways mechanically to induce cell death. In this aspect, Cho *et al.* designed a magnetic switch for apoptosis cell signaling, which was made of $Zn_{0.4}Fe_{2.6}O_4$ nanoparticles and antibodies targeting the death receptor 4 (DR4).[64] It is noteworthy that the attraction force between the nanoparticles was about 30 fN, inadequate to destroy the cell membranes but promote the nanoparticle clustering on the cell membranes. In a similar pattern to the biochemical ligand TRAIL, this magnetic switch achieved the clustering of the DR4s and the formation of a death-inducing signaling complex (DISC) in a remotely, non-invasively, and spatially and temporally regulated style. Based on this research, the same team developed a novel apoptosis trigger to induce complete death of multidrug-resistant cancer cells by virtue of DR4-targeting and magnetomechanical force (Fig. 5a and b).[65] Importantly, such a

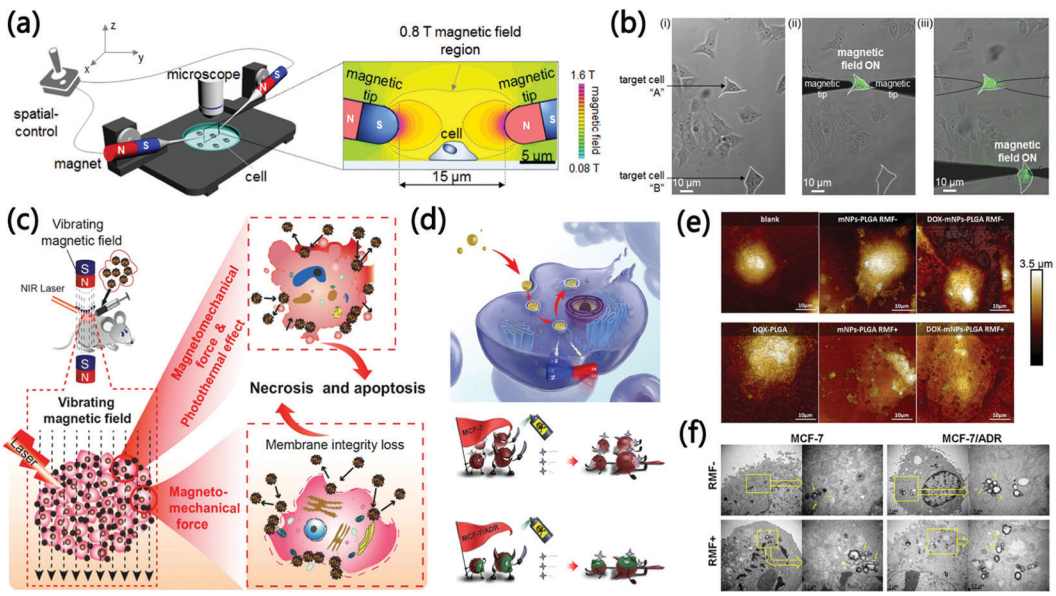

Fig. 5 The combination of magnetomechanical force with other therapeutic modalities for oncotherapy. (a) Illustration of the magnetic setup for magnetomechanical force-based site-specific apoptosis activation. (b) Optical microscopy images showing the apoptotic activation process. Reproduced with permission from ref. 65. Copyright 2016 American Chemical Society. (c) Illustration of the combination therapy based on magnetomechanical force and photothermal therapy. Reproduced with permission from ref. 66. Copyright 2018 WILEY-VCH. (d) Illustration of the combination therapy based on magnetomechanical force and chemotherapy. (e) Atomic force microscopy images after magnetomechanical force/chemotherapy. (f) Transmission electron microscopy images after magnetomechanical force/chemotherapy. Reproduced with permission from ref. 67. Copyright 2020 Elsevier.

trigger was conceived to launch apoptosis signals with single-cell level accuracy, simultaneously down-regulating the P-glycoprotein which was regarded as one of the main inducements of multidrug-resistance. In a word, magnetomechanical force-based signalling pathway activation is an emerging platform concept to cure tumors with high efficacy and specificity.

Due to the aforementioned encouraging anti-tumor effects, combining magnetomechanical force with other therapeutic modalities to treat multitudinous cancers has aroused great attention. In a recent study, Chen *et al.* coated needle-like Fe_3O_4 nanoparticles with carbon and gold double layers to fabricate novel hedgehog-like microspheres for tumor ablation (Fig. 5c).[66] Under a vibrating magnetic field with appropriate exposure time, frequency, and intension, sharp surfaces of the magnetic microspheres seriously dissevered cancer cells to restrain tumor growth *via* magnetomechanical force. By means of analysis and calculation, the maximum applied magnetomechanical force of a single microsphere was 35.79 pN. Integrated with laser-triggered photothermal ablation, solid tumors were completely eradicated after these two remote and noninvasive modes of synergistic local stimuli. In addition, to address the obstacle of drug-resistance, our team proposed a remotely controllable mechano-chemotherapeutic method relying on the rotating magnetic field (45 mT) and a therapeutic nanoagent composed of poly(lactic-*co*-glycolic acid) (PLGA), $Zn_{0.2}Fe_{2.8}O_4$ nanoparticles and doxorubicin (DOX) (Fig. 5d–f).[67] In this design, the generated magnetomechanical force (approximate 250 pN) was exploited for controlled release of DOX and physical disruption onto cell membranes. By right of different and complementary routes, such a mechano-chemotherapeutic method executed remarkable tumor cell death, regardless of the specifics of tumor cell drug resistance. In Addition, Zhang *et al.* prepared polyethylenimine (PEI)–PLGA carriers with the surface modification of hyaluronic acid (HA) to co-load Fe_3O_4 nanoparticles and Olaparib (an anti-cancer drug).[68] Since the HA enabled the active targeting of the CD44 receptor overexpressing on the surface of triple negative breast cancer cells, this mechanical platform yielded magnetomechanical force through incomplete rotation, cooperating with Olaparib for cell synergistic destruction. Noticeably, the magnetomechanical force could cause two mechanical strikes including membrane structure destruction for cytolysis and lysosome-mitochondrial pathway activation for cell apoptosis. In brief, magnetomechanical force-based combination therapy is an attractive methodology to strengthen the antineoplastic effect; furthermore, this strategy may be adapted to remotely cure other types of diseases.

5. Magnetomechanical force for regenerative medicine

As an area attracting major attention, regenerative medicine employs live cells and tissues to gain renascent, healthy, and specially grown tissues for disease treatment (*e.g.* retinitis pigmentosa and macular degeneration).[69–74] Although mechanical forces have been a robust manner of regenerative medicine to manipulate proteins on the cell surface, the timescales of the supplied mechanical forces easily fail to match that of the target signaling processes.[75] Impressively, through the precise and remote control of cellular receptors, magnetomechanical force

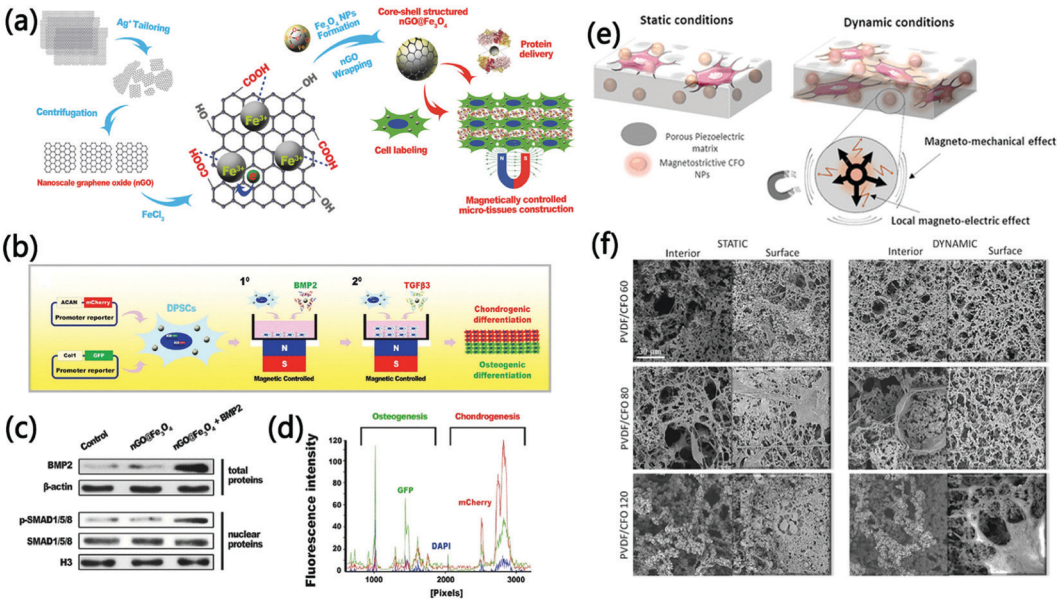

Fig. 6 The magnetomechanical force for regenerative medicine. (a) Illustration of magnetomechanical force-based stem cell differentiation. (b) Illustration of the integrated osteochondral tissue constructive process. (c) Western blotting detection for bone-morphogenetic-protein-2 content and related signaling activation. (d) Fluorescence detection on frozen sections after one-week implantation. Reproduced with permission from ref. 77. Copyright 2017 WILEY-VCH. (e) Illustration of magneto-active 3D porous scaffolds for osteoblast proliferation. (f) Scanning electron microscopy images of 3D porous scaffolds after four-day incubation with preosteoblast cells. Reproduced with permission from ref. 84. Copyright 2019 American Chemical Society.

can initiate intended adhesion, proliferation, and differentiation signaling pathways for regenerative medicine.[76,77]

Pluripotent stem cells occupy an important position in regenerative medicine strategies owing to their excellent differentiation characteristics.[78,79] Regarding magnetomechanical force-based stem cell differentiation, Zhang *et al.* integrated Fe_3O_4 nanoparticles and graphene oxide into a nanoscale system for stem cell label and growth factor delivery (Fig. 6a–d).[80] On the one hand, this nanoscale system was easily ingested *via* dental-pulp stem cells without causing any toxic side effects. Therefore, the stem cells labeled by the nanoscale system could constitute multilayered cell sheets under magnetomechanical force. On the other hand, with the introduction of Fe_3O_4 nanoparticles, bone-morphogenetic-protein-2 was successfully incorporated into multilayered cell sheets for bone formation, effectively realizing the establishment of an osteochondral complex. In a separate report, Hu *et al.* prepared magnetic bioreactors possessing the functions to apply magnetomechanical force to stem cells and target diverse cell surface receptors, which were used to explore the roles of PDGFRα and $\alpha_v\beta_3$ (two types of mechanical-sensitive cell membrane receptors).[81] Compared with magnetic bioreactors targeting $\alpha_v\beta_3$, those targeting PDGFRαa induced a higher mineral-to-matrix ratio after magnetomechanical force stimulation, which enriched the cognition of mechanical force stimulation for bone regenerative engineering. In addition, Ishii *et al.* incubated mesenchymal stem cells with Fe_3O_4-liposome complexes to obtain magnetized stem cells for subsequent magnetomechanical force-guided formation of multilayered cell sheets.[82] On account of the elevated expression of vascular endothelial growth factor and depressed apoptosis in ischemic tissues, this differentiation modality was distinguished with angiogenic and tissue preserving effects. Furthermore, Mary *et al.* succeeded in achieving cardiomyogenesis of embryonic stem cells using a novel magnetic pattern.[83] After labeling with magnetic nanoparticles, stem cells could aggregate into embryoid bodies and readily be stimulated by means of magnetomechanical force. It is worth mentioning that cyclic magnetomechanical force stimulation was adequate to improve cardiomyogenesis, enabling more than 90% of the embryoid bodies to beat. In this way, gene expressions involved in mesoderm differentiation (*e.g.* Nkx2.5, Gata4, and Gata6) were greatly up-regulated (2-fold to 5-fold). In a word, the magnetomechanical force tissue-engineering strategy exhibits promising feasibility for future stem cell applications in regenerative medicine.

Since natural tissue exists as a three-dimensional (3D) structure in which cells are spatially distributed, the desired scaffold for regenerative medicine had better be a 3D structure with a similar distribution of cells.[84,85] To address this challenge, the emergence of magnetomechanical force demonstrates a novel strategy to establish such scaffolds. For instance, Zhu *et al.* developed magnetic meshes containing electrospun magnetic nanoparticles and polycaprolactone composite fibres for seeding osteoblast cells.[86] Upon the action of magnetomechanical force, osteoblast cells were vertically arranged and tightly stacked, which could proliferate efficiently accompanied by the secretion of an extracellular matrix. As the main components of the extracellular matrix, type I collagen was able to fill the mesh interface and promote the construction of 3D scaffold-cell complexes. It follows that magnetomechanical force represents a valuable instrument for the construction and application of 3D scaffolds in the field of regenerative medicine. Impressively, the combination of magnetomechanical force and magnetoelectrical stimuli has been a full potential approach for skeletal muscle tissue engineering application. In this aspect, Fernandes *et al.* reported a magneto-active 3D porous scaffold to realize a significant proliferation of osteoblast cells (Fig. 6e and f).[87] With the help of solvent casting, this 3D scaffold could be manufactured through the integration of piezoelectric polymer, poly(vinylidene fluoride), and magnetic $CoFe_2O_4$ particles. Importantly, local magnetomechanical and magnetoelectric performances of the scaffolds played a crucial role in expanding the preosteoblast proliferation, attributed to the imitation of the bone morphology and physical microenvironment. The same team reported a kind of magnetoelectric film which combined a piezoelectric polymer, poly(vinylidene fluoride-trifluoro-ethylene), and magnetostrictive particles ($CoFe_2O_4$). Upon cooperative magnetomechanical and magnetoelectrical stimulation by an applied magnetic field, the proliferation and differentiation of C2C12 myoblast cells were promoted.[88] In another work, Ribeiro *et al.* proved that magnetoelectric Terfenol-D/poly(vinylidene fluoride-*co*-trifluoroethylene) composites were able to apply magnetomechanical and magnetoelectrical stimuli on MC3T3-E1 pre-osteoblast cells. Based on this, the cell proliferation was enhanced up to 25%, thereby offering a novel method for tissue engineering.[89] Owing to their potential to promote cell proliferation, magnetoelectric biomaterials are promising to process a broad application in tissue engineering.

6. Perspectives

In this review, a series of therapeutic exploitations and applications based on magnetomechanical force including drug controlled release, cancer therapy, and regenerative medicine have been summarized, illustrating the innovation and uniqueness of magnetomechanical force in medical biology. All literature reports cited and discussed herein certify that magnetomechanical force paves a novel and potentially promising pathway for cutting-edge treatment paradigm. Nevertheless, magnetomechanical force is still in its infancy, and more surveys and investigations remain to be addressed for further development and innovation of this to-date therapeutic strategy.

First, biosecurity is a critical focus in the design and fabrication of magnetic materials for magnetomechanical force generation. In addition to meeting the current standards of biomedical applications (*e.g.* biocompatibility and biodegradability), magnetic materials need to have significant therapeutic effects, thus bringing sufficient economic and social benefits.[90] Accordingly, it is important to balance biosecurity, therapeutic effectiveness, and cost (*e.g.* raw material expenses,

fabrication instruments, and preparation procedures), which remains a serious challenge nowadays.

Second, a single magnetic particle is generally incapable of imparting magnetomechanical force on demand in complex physical environments.[91] Therefore, there is huge space to fully develop magnetic particle-based collective behavior, which efficiently executes assigned complex biological tasks due to the close cooperation between magnetic particles. In this aspect, future directions include the optimization of magnetic particle dose, the control of particle delivery, and the regulation of mechanical force stimulation in order to cure a wide range of diseases.

Third, accurate on-body and real-time maneuvering of the magnetomechanical force as well as its monitoring is extremely essential.[92] Upon regulation of magnetic materials according to actual occasions including health status and physiology, magnetomechanical force is even capable of realizing individualized or personalized therapy. In this regard, the combination of imaging techniques and magnetomechanical force is promising to perform certain diagnostic and therapeutic missions in a visualization fashion.

Fourth, to improve the on-body fate of magnetomechanical force, physicochemical targeting (*e.g.* magnetic targeting) aims at targeting magnetic materials to specific treatment areas with remarkable temporal and spatial accuracy.[93] In parallel, targeting ligands can endow magnetic materials with targeting performance for optimized tissue accumulation, blood circulation, and subsequent controllable magnetomechanical force modulation.

Fifth, with regard to future applications, magnetomechanical force promises to be a great candidate for targeted treatment and controllable drug release against microvascular thrombolysis on the strength of the locomotion and collective manners.[94,95] In addition, magnetomechanical force has the potential to activate genetically encoded mechanosensitive ion channels (*e.g.* Piezo1 and TRPV-4),[96,97] which can be utilized to explore sensory reception and tissue development.

In general, although in the initial stage, magnetomechanical force has secured its status in therapeutic applications on account of the concept of remote and precise stimulation. Herein, we strongly hope that this review will drive the future development and progress of magnetomechanical force and provide significant enlightenment and thoughts for novel therapeutic patterns.

Author contributions

Conceptualization: A. W. and F. Y. Writing – original draft preparation: J. Y. and C. Y. Writing – review and editing: R. Z. and X. X. Funding acquisition: A. W. and F. Y.

Conflicts of interest

There are no conflicts to declare.

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