Nanomedicines for high-intensity focused ultrasound cancer treatment and theranostics (Review)

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Abstract. High-intensity focused ultrasound (HIFU) is a promising and representative non-invasive therapeutic method for treating cancer with a high degree of efficacy. This non-invasive method induces tumour cell necrosis by increasing the local temperature and mechanical pressure. However, the clinical application of HIFU is limited given its low penetration depth and the incidence of off-target side effects. With their promising structural adjustability and targeting ability, nanomedicines have been adopted to improve the ablative efficacy of HIFU in the treatment of cancer. By selectively changing the acoustic environment (tissue structure, density and blood supply) of tumour tissue, these nanomedicines may allow for lower HIFU doses and treatment duration, while additionally achieving a higher degree of efficacy. The use of nanomedicines may also enable cancer theranostics of HIFU, allowing for precise cancer therapeutics. The present review aimed to provide an overview of advances in nanomedicines for HIFU cancer treatment and theranostics, stating their current limitations and future perspectives.

Contents

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1. Introduction

Cancer is one of the most serious fatal diseases, with limited treatment response and unfavourable prognosis (1). Currently, surgery, radiotherapy, chemotherapy and immunotherapy are the primary methods used in clinical practice for management of cancer and, although they have been regarded as the four pillars of cancer therapy (2), these therapeutic modalities have shortcomings. For example, for surgical resection, the incidence of surgical trauma and complications is high and complete removal of all tumour tissue is not guaranteed (3). Tumour radiation resistance and collateral radiation-induced damage to surrounding healthy tissue limit the clinical application of radiotherapy. For chemotherapy and immunotherapy, although new treatment targets and novel drugs are increasingly studied, challenges, such as the low targeting efficacy and intrinsic toxicity of these treatments, remain to be overcome (4). In addition to these four pillars of cancer therapy, more recent studies have focused on developing and improving non-invasive and more patient-friendly modalities with improved treatment efficacy and a lower incidence of side effects: Among these, high-intensity focused ultrasound (HIFU) is a promising approach (5-7).

The identification of the potential of HIFU for clinical therapy dates to the 1950s when it was demonstrated to be an alternative therapeutic procedure for central nervous system disorder (8,9). When HIFU is absorbed by target tissue such as tumour masses, the temperature of the tissue increases to >55˚C, inducing cell death via local coagulative necrosis (10-12) to thermally ablate the tumour mass. HIFU can also induce the generation of small gas bubbles inside the target tissue; sudden collapse of these bubbles results in an increase in the local pressure up to 2-3 kPa, thus causing severe damage to the surrounding tissues (13,14). It has also been shown that HIFU temporarily disrupts the blood-brain barrier (BBB), which aids in delivery of therapeutics into the central nervous system (15). Currently, HIFU has been proven successful in the treatment of numerous diseases such as Parkinson's disease (16,17), essential tremor (18,19), adenomyosis (20) and solid tumour masses (21,22). However, due to the absorption features of HIFU, the penetration of HIFU to deep tumour tissue is severely limited and not sufficient for tumour ablation (23). While increasing HIFU irradiation dosage is a potential strategy to increase efficacy, the collateral

damage caused to the surrounding normal tissue would also increase (24). Furthermore, although HIFU primarily results in a focused ablative effect in the targeted tumour mass, off-target collateral damage occurs, resulting in undesired tissue injury and burns, vasospasm and haemorrhaging, impotence, incontinence, formation of atrial-oesophageal fistula and off-site rib necrosis (25,26). Nanoparticles (NPs) are now being adopted to overcome these challenges to improve the clinical value of HIFU (27).

NPs are 10-500 nm in size and have previously been reported to increase therapeutic efficacy whilst decreasing the incidence of side effects (28). These nanomedicines selectively accumulate in tumour tissues to realize a selective and efficient therapeutic effect (Fig. 1A) (29). Furthermore, it has been indicated that the adoption of NPs can effectively change the acoustic environment (tissue structure, density, blood supply and functional state on ultrasonic transmission and energy deposition during HIFU treatment) of tumour tissues (30), making them more sensitive to HIFU, resulting in greater ablative efficacy with the same or lower HIFU irradiation doses. Additionally, since the first report on the combination of HIFU with nanotechnology in 2000 (31), it has been recognized that HIFU induces target drug release from platforms such as NPs and liposomes to enhance the ablative efficacy of HIFU and improve safety (32); since then, studies have attempted to design nanomedicines to improve the efficacy of HIFU (33-36) however, progress has not seen clinical translation. Additionally, the promotion of theranostics also highlights novel opportunities in this field. The present review aimed to provide an overview of NPs in combination with HIFU for cancer treatment, including the use of nanomedicines to increase the ablative efficacy of HIFU, achieving greater synergic therapeutic efficacy and theranostics by combining imaging probes and HIFU.

2. Nano-therapeutics for HIFU-based cancer treatment

The combination of NPs and HIFU benefits cancer treatment in multiple ways. By enhancing the permeability and retention (EPR) effect, NPs selectively penetrate tumour tissues and change the acoustic environment. NPs can enhance energy deposition and magnify the thermal, mechanical and cavitation effect via formation of microbubbles through a phase transition (37), resulting in improved HIFU ablation efficacy. Additionally, HIFU can alter vascular permeability and disrupt blockade of overexpressed extracellular matrix, thus enhancing the selective accumulation of NPs into tumour tissue (38,39). In addition, HIFU physically induces formation of cell membrane pores via sonoporation, enabling more effective cellular internalization and accumulation of NPs (Fig. 1B) (40). Furthermore, HIFU disrupts NPs to trigger localized drug release at the target site (41), effectively decreasing the off-target damage to normal tissue.

Lipid-based NPs. Lipid-based NPs such as liposomes and solid lipid NPs, are phospholipid bilayer membranes that carry lipid-soluble drugs with an inner core in which hydrophilic drugs can be loaded (42). When constructed to be thermosensitive, these lipid-based NPs respond to thermal changes caused by HIFU, resulting in release of the loaded therapeutics at the selected lesion site (43). For example, Cha *et al* (44) and Deng *et al* (45) constructed liposomes sensitive to low temperatures that contained the chemotherapeutic doxorubicin (DOX). Following induction of hyperthermia caused by HIFU irradiation, these liposomes selectively release encapsulated DOX at the tumour tissue to increase their effective concentration in the tumour cell nuclei, whilst keeping the concentration in the general circulation low, thus effectively decreasing off-target damage to normal tissues. These low temperature-sensitive liposomes can be modified by internalised arginine-glycine-aspartic acid (iRGD) to enhance the targeted delivery of iRGD to cancer and tumour vascular cells (Fig. 2A and C-D) (45). iRGD-modified liposomes allow longer opportunities for HIFU irradiation and shorter HIFU exposure times, effectively decreasing incidence of collateral damage such as skin burns caused by long HIFU exposure.

In addition to triggering targeted drug release, Yang *et al* (46) used HIFU to disrupt the BBB to increase delivery of nanomedicines to the central nervous system: They formed lipid-polymer hybrid NP to deliver CRISPR/Cas9 for the treatment of drug-resistant glioblastoma. Although the nanoscale size of this delivery platform increases penetration into the central nervous system, this increase is limited due to the effectiveness of the BBB. Thus, nanomedicine platforms bind with microbubbles, which allows HIFU to disrupt the BBB. Irradiation of HIFU induces vibrations of the attached microbubbles, resulting in the generation of a shearing force that results in a temporary disturbance of the BBB. Furthermore, these microbubbles rupture and induce further 'opening' of the BBB, which allows increased crossing of nano-delivery platforms to tumour tissue in the brain (46,47). Another study applied lipid-polymer hybrid nanomaterial for treatment of glioblastoma and showed that the presence of HIFU triggered rapid release of loaded drugs, with 47% released in 2 min, effectively increasing the therapeutic efficacy (48).

In addition to use of HIFU as a tool to aid drug delivery, another strategy for applying lipid-based nanomaterials is to form nanobubbles to achieve enhanced tumour ablation efficacy. Microbubbles have long been considered synergistic agents for enhancing HIFU therapeutic efficacy (49-51). However, traditional microbubbles are usually too large for tumour tissue penetration and have short circulation times, limiting their use in cancer treatment (49,52). Thus, forming nano-size bubbles with improved tumour penetration ability and increased stability during circulation is key for improving the efficacy of these therapies. Hamano *et al* (53) and VanOsdol *et al* (54) formed nanobubble-based liposomes. These echo-contrast gas or perfluoropentane-containing liposomes were reported to achieve up to 4-5-fold greater drug accumulation and release in tumour tissues compared with nanomedicines or HIFU. Furthermore, these nanobubble-based liposomes not only effectively increased HIFU ablation efficacy, thus reducing irradiation time, but also encapsulated antitumour genes, short interfering RNAs and chemotherapeutics to stimulate a synergetic effect, further increasing their antitumour efficacy.

Perfluorocarbon-containing nanomaterials. Perfluorocarbon-containing nanomaterials are a potential therapy that may solve the size and circulation problems of microbubbles (55). By incorporating liquid fluorocarbons into lipids or polymers,

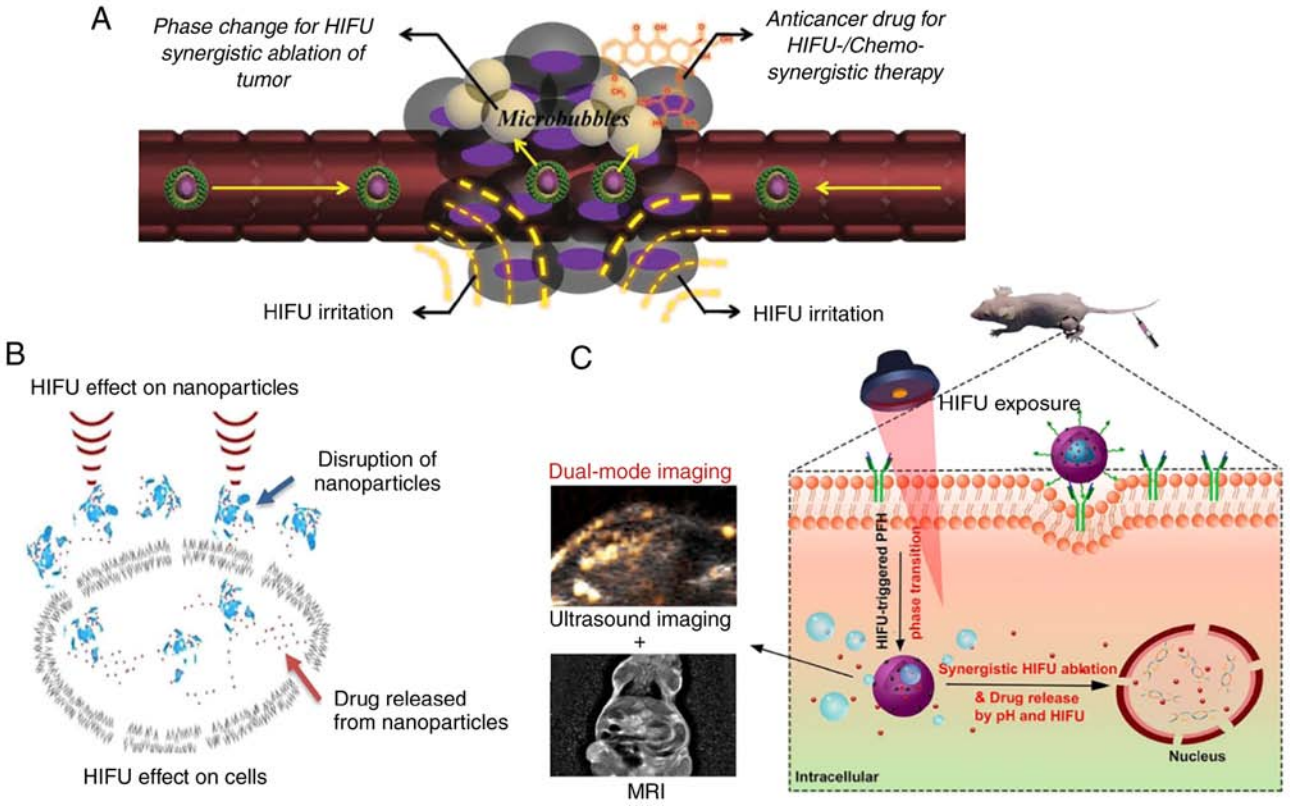

Figure 1. HIFU with nanoparticles can improve the efficacy of tumour treatment. (A) Nanoparticles selectively accumulate in tumour tissues through the EPR effect. (B) Change in pressure induced by HIFU irritation may act as a synergist for HIFU ablation. Nanoparticles may be loaded with a drug that is released at the tumour site. This may allow for higher drug penetration into cells via disruption of both nanoparticles and cell membranes by HIFU. (C) Internalized drugs combined with HIFU ablation may allow for a synergistic approach to treatment as well as multi-modal imaging of tumour tissue. Reproduced with permission from (37-39). Copyright © 2014 WILEY-VCH Verlag GmbH & Co. KGaA, Weinheim, 2019, the authors (open access) and 2018 American Chemical Society, respectively. HIFU, high-intensity focused ultrasound; EPR, enhancing the permeability and retention; PFH, perfluoro-n-hexane.

these perfluorocarbon-containing nanomaterials shift from a liquid state at room temperature to a gaseous state when temperature rises or following irradiation of HIFU37). The gas released in tumour tissue further triggers the formation of microbubbles, enhancing the cavitation effect of HIFU ablation (56-58). Since fluorocarbons have already penetrated the deep tumour tissue via the EPR effect when it is in a liquid state with a nano size, the microbubbles created following phase shift no longer exhibit problems of short circulation times and low tumour tissue penetrating rates, effectively increasing the therapeutic efficacy of HIFU ablation. Studies have been designed based on perfluorocarbon-containing nanomaterials applied for HIFU ablation (Fig. 2B). Ashida *et al* (59) prepared a phase-changing nanodroplet from perfluoro-*n*-pentane (PFP), perfluoro-*n*-hexane (PFH), dipalmitoyl-phosphatidylcholine, dipalmitoyl-phosphatidic acid and pegylated dipalmitoyl-phosphatidylethanol amine; use of these novel nanomaterials together with HIFU irradiation resulted in moderate tissue damage compared with histotripsy. This moderate damage is sufficient to suppress tumour growth notably compared with HIFU irradiation alone. In addition, compared with histotripsy, the effect of combination therapy effectively decreases incidence of collateral damage to surrounding normal tissues, reducing the severity of side effects. Furthermore, addition of the chemotherapeutic agent adriamycin further enhanced the tumour-suppressing effects of this combination therapy: Tumour regrowth rate was slowed by 1 week when adriamycin was used during the 30-day observation time. However, the effect of repetitive therapy management with longer observation periods should be assessed to confirm the therapeutic effects of phase-changing perfluorocarbon-containing nanodroplets. The choice of perfluorocarbon is key when constructing HIFU-appliable nanomaterials. Currently, the most commonly used perfluorocarbons are PFP and PFH (60). The boiling temperatures of other perfluorocarbons are usually either too low or high to be applicable for clinical use. As boiling temperatures also affect the phase-shifting temperature of constructed nanomaterials (61,62), there remain challenges before these can be used clinically. As the phase shifting temperature of PFP is lower than that of PFH (>40 vs. >60˚C), PFP may be a better choice for nanomaterial construction, as lower HIFU irradiation doses can be used (63). Zhang *et al* (64) constructed a poly(lactide-co-glycolic acid) (PLGA) NP that incorporated PFP and hematoporphyrin monomethyl ether (HMME) as synergistic agents (HMME + PFP/PLGA) for HIFU ablation. These agents were further modified by streptavidin as a pre-targeting agent via a two-step biotin-avidin technique. In addition to a lower HIFU irradiation dosage required, the cavitation effect of HIFU, the sonodynamic effect and vascular endothelial growth factor receptor-2 antibody worked together to induce secondary necrosis surrounding the initial HIFU ablation area, resulting in a greater synergetic effect with less collateral damage to the normal tissue. This method highlights

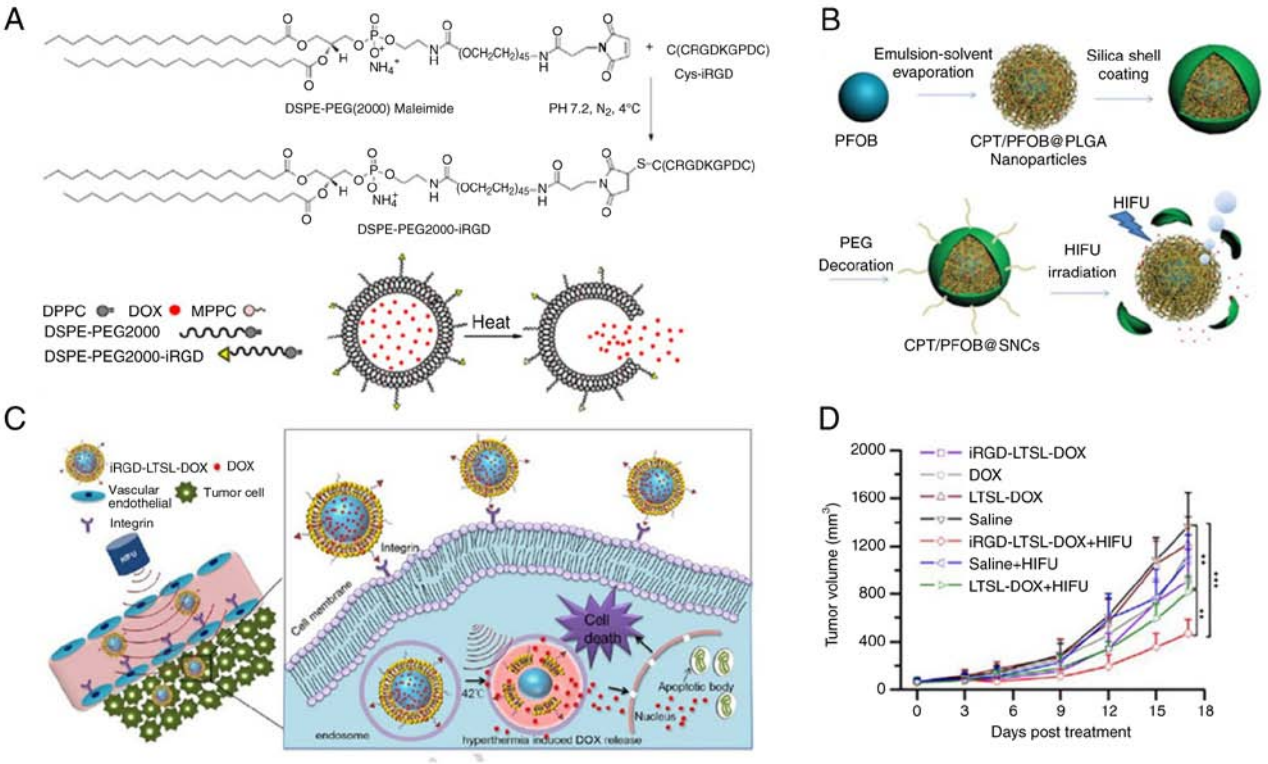

Figure 2. Nanoparticles aggregate at tumour sites to improve the efficacy of tumour therapeutic HIFU. Synthesis of (A) iRGD-LTSL-DOX nanoparticles and (B) CPT/PFOB@SNCs and their HIFU-based therapeutic effects on tumour tissues. (C) Nanomaterials selectively accumulate in tumour tissues and achieve targeted internalization into tumour cells, (D) thus increasing the efficacy of tumour therapeutics following HIFU irradiation (**P<0.01 and ***P<0.001). Reproduced with permission from (45) and Copyright © 2016 Elsevier B.V and 2014 WILEY-VCH Verlag GmbH & Co. KGaA, respectively. iRGD-LTSL-DOX, peptide iRGD (CCRGDKGPDC) was used to modify drug-loaded low temperature-sensitive liposomes; CPT/PFOB@SNC, a drug-loaded poly(lactic-co-glycolic acid) nanocapsule with an ultrathin silicon coating. Using an emulsion, both PFOB and the anticancer drug CPT are loaded into PLGA nanocapsules; an ultrathin-walled silica coating is then applied (SNCs). HIFU, high-intensity focused ultrasound; DPPC, 1,2-dipalmitoyl-sn-glyc-ero-3-phos-phocholine; MPPC, 1-palmitoyl-2-hydroxy-sn-glycero-3-phosphocholine; DSPE-PEG, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-poly(ethylene glycol); CPT, camptothecin; PFOB, perfluorooctyl bromide.

the application of perfluorocarbon-containing nanomaterials as HIFU synergetic agents for deep tumour ablation and ablation of tumours with barriers along the HIFU beam path; however, additional studies are needed before this method can be used in clinical practice.

Magnetic nanomaterials. Magnetic nanomaterials, with their unique features such as ease of manipulation using magnets and thermal responsiveness to ultrasound and magnets, have potential as effective sonosensitizers for HIFU cancer therapy (64). Sun *et al* (65,66), You *et al* (67), Ho *et al* (68) and Dibaji *et al* (69) confirmed that magnetic nanomaterials enhance the HIFU cavitation effect and thus effectively increase tumour tissue destruction efficacy with a lower HIFU exposure dose. According to Devarakonda *et al* (70), the adoption of magnetic nanomaterials (superparamagnetic iron oxide NPs; 0.047% w/v) halves the HIFU irradiation dose required to obtain 13 mm^3 tumour destruction volume, significantly reducing the side effects caused by high HIFU doses (70). They also discovered that the thermal enhancing efficacy of magnetic nanomaterials was higher than that of gold NPs, which are another HIFU hyperthermal candidate, making magnetic NPs clinically preferable (71). However, the mechanism by which magnetic NPs enhance HIFU cancer therapy remains unclear. It has been suggested that magnetic NPs increase attenuation of sound waves in tumour tissue. Thus, when magnetic NPs selectively penetrate the tumour tissues through the EPR effect, a lower HIFU dose is needed to achieve tumour destruction efficacy, with decreased collateral damage to surrounding normal tissues at these lower HIFU irradiation doses (72). Sadeghi-Goughari *et al* (36,73) discovered that viscous and thermal reaction with medium at the surface of magnetic particles is the primary mechanism that aids conversion of acoustic energy into heat, achieving greater temperature rises with directed HIFU ablation. Additionally, a numerical model was established that could accurately predict and analyse HIFU ablation process when NPs were used, thus providing a novel tool to uncover the detailed mechanism by which magnetic NPs affect HIFU ablation, which is beneficial for future magnetic NP development and potential clinical application.

Bacteria-based targeting. Several studies have indicated that certain anaerobic bacteria species such as *Bifidobacterium* can colonize and grow into a tumour mass where there is a hypoxic atmosphere due to a lack of sufficient blood supply, whereas in normal tissues, the supply of oxygen would prevent colonization and proliferation of these anaerobic bacteria. Thus, bacteria such as *Bifidobacterium* have been considered as potential markers that may aid in the identification of tumour masses and facilitate tumour targeting diagnosis and treatment (74-76). When using *Bifidobacterium* as the

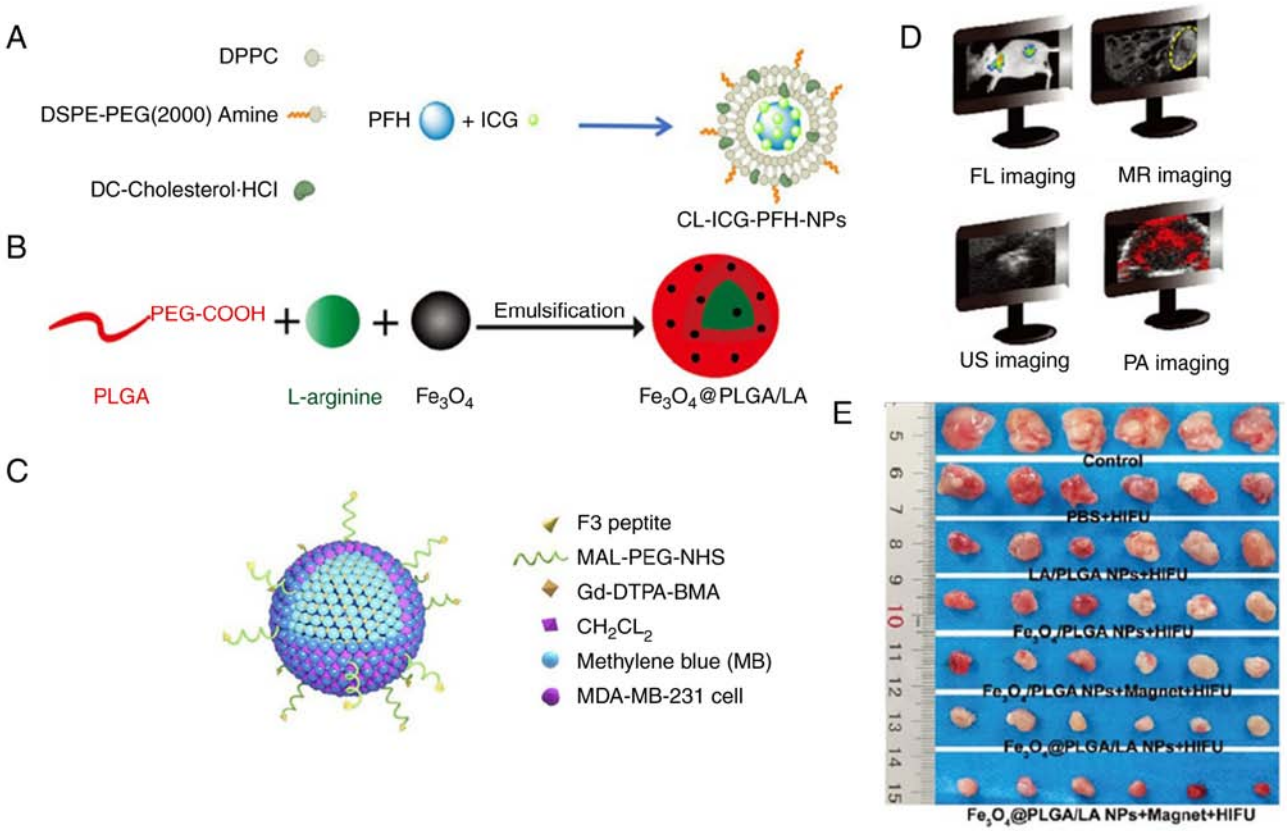

Figure 3. Nanoparticle integration with diagnosis and treatment can work with HIFU to improve efficacy of tumor therapy. Synthesis of (A) CL-ICG-PFH-NPs and (B) Fe_3O_4@PLGA/LA-NPs. Schematic illustration of (C) F3-PLGA@MB/Gd-NPs. (D) These nanoparticles carry both diagnostic and therapeutic agents to facilitate imaging/multi-modal imaging of the tumor tissues and (E) enhancement of the tumor inhibition effect under HIFU irradiation, promoting nano-based HIFU cancer theranostics. Reproduced with permission from (73,114,115) and Copyright © 2019 Dove Medical Press Limited (open access), 2021 The Royal Society of Chemistry and 2019 Dove Medical Press Limited (open access), respectively. HIFU, high-intensity focused ultrasound; PLGA, poly(lactic-co-glycolic acid); PEG, polyethylene glycol; CL-ICG-PFH-NP, indocyanine green and perfluoro-n-hexane coloaded cationic lipids nanoparticle; PLGA/LA, L-arginine loaded PLGA nanomedicine; F3-PLGA@MB/Gd, a sonosensitizer (methylene blue) and a magnetic resonance contrast agent (gadodiamide) based on hydrophilic biodegradable polymeric NPs composed of PLGA, the surface of PLGA NPs was decorated with a penetrating peptide-F3 and PEG; DPPC, 1,2-dipalmitoyl-sn-glyc-ero-3-phosphocholine; DSPE-PEG, 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-PEG; MAL-PEG-NHS, α-maleimide-ω-N-hydroxysuccinimide ester PEG; Gd-DTPA-BMA, gadodiamide, a magnetic resonance contrast agent.

targeting agent for tumour tissue, it could be either directly cross-linked to the delivery platform acting as an arch on a 'bacterial robot' or allowed to colonize in the tumour mass first, then another *Bifidobacterium* targeting NP can be utilized to achieve indirect targeting of the tumour (77). Jiang *et al* (78) compared these targeting strategies and found that when combined with HIFU ablation, the indirect targeting method was more efficient than cross-linking bacteria with NP payloads. This was because agglomeration may occur when preparing this bacteria-containing cross-link nanomedicine, making it larger and thus more difficult for it to penetrate the tumour mass. Furthermore, they also indicated that *Bifidobacterium* that had colonized a tumour mass in advance triggered activation of macrophages to the phagocytotic active phase, effectively aiding the engulfing and retention of nanotherapeutics inside the tumour tissue as endocytosis is one of the primary mechanisms by which NPs enter cells. Thus, based on these findings, bacteria-based nano strategies for HIFU ablation have focused on bacterial targeting instead of using bacteria-containing NPs (79-81). Additionally, aptamer-CCFM641-5-functionalized PFH-loaded PLGA NPs (82) and polyethyleneimine-modified PLGA NPs loaded with sodium bicarbonate (83) that target *Bifidobacterium* have been developed to achieve selective delivery of therapeutics into a tumour mass. These two NPs are reported to prolong median survival time of tumour-bearing mice as well as enhance HIFU ablation efficacy. Additionally, since no specific targeting proteins or surface antigens were involved in these studies and anaerobic conditions are present in a variety of tumour types, these nanotherapeutics may be applied regardless of the tumour type. However, these bacteria- and NP-based HIFU ablation methods may not be suitable for tumour masses ≤1-2 mm as the vascular system in a small tumour mass is sufficient to create an oxygen-rich atmosphere (84). These bacteria-based NPs may be used to encapsulate imaging agents for photoacoustic and ultrasound imaging, promoting HIFU cancer theranostics (Fig. 3A) (85); however, further confirmatory studies are required.

Other types of NP. Other NPs, including paclitaxel-loaded thiolated human serum albumin NP-conjugated microbubble complexes (86), heat shock-targeted N-(2-hydroxypropyl) methacrylamide copolymer-docetaxel conjugates (87), Cy5.5-labelled glycol chitosan, nitroxide free

radical-generating (88,89), 1,1,2-trichlorotrifluoroethane incorporating pullulan-DOX (90) and phospholipid hydrophobic mesoporous silica NPs (91,92), enhance the efficacy of HIFU ablation with decreased side effects, although additional studies on similar types of NP are required to confirm their effectiveness. The clinical transition of NPs lack systemic examination regarding the safety profile including biocompatibility, biodegradation, tumour accumulation and stability in animals other than mice. Furthermore, establishment of scalable, economical and reproducible synthesis methods for these NPs is also needed before they can be used clinically (93).

3. Nano-based HIFU cancer theranostics

Cancer theranostics (cancer therapy and diagnosis through the packaging of various therapeutic drugs and diagnostic contrast agents) is a relatively new concept in the field of precision medicine. In addition to incorporating therapeutic agents to enhance HIFU ablation efficacy to induce selective therapeutic drug release, NPs can be used to encapsulate diagnostic agents that can enhance the imaging contrast of tumourigenic sites (94-96). This can allow accurate targeting of HIFU ablation, real-time imaging monitoring of ablation procedure and evaluation of the therapeutic response without the need for extra medical tests (Fig. 1C) (97), as well as adjustments of the treatment to maximize the therapeutic efficacy and minimize the collateral damage to the surrounding normal tissue.

Ultrasound-based nano-theranostics for HIFU. HIFU is a type of ultrasound-based treatment method, thus the specific therapeutics used for HIFU have acoustic properties, which makes ultrasounds one of the first choices for monitoring of HIFU. However, given that diagnostic and therapeutic ultrasound have different frequencies (98,99), the acoustic properties of the therapeutics may respond to only one type of ultrasound. Therefore, it is important to design therapeutics that are responsive to both diagnostic and therapeutic ultrasound. Blum *et al* (100) constructed a polyethylene glycol (PEG)-lipid-shelled microbubble that creates microbubble NPs in the presence of fluorocarbon interiors (C_4F_{10}, C_5F_{12} and C_6F_{14}) and ultrasound pulses. These microbubble NPs are not detectable by ultrasound, but under HIFU irradiation, the integrated image brightness of NPs on the cadence contrast pulse sequencing mode increases, making them visible on ultrasound scans. The addition of fluorocarbons to this nanosystem also allows enhancement of HIFU efficacy, which was confirmed by complete detachment of breast cancer cells *in vitro* under HIFU irradiation in presence of these NPs. However, further *in vivo* studies are required to examine the theranostic efficacy and biosafety profiles of these NPs. Zhu *et al* (101) examined the *in vivo* efficacy of nano-theranostics for HIFU ablation. They synthesized a pH-sensitive poly(ethylene glycol) that produced O_2 from endogenous H_2O_2. The generated O_2 not only served as a contrast agent for diagnostic ultrasound imaging but served as a synergist agent to enhance HIFU ablation efficacy. Furthermore, they also discovered that this nano-theranostic induced normoxic conditions in the tumour tissues to enhance the chemotherapeutic efficacy of DOX, allowing both theranostics and combination therapy of HIFU and chemotherapy. Li *et al* (102) designed pentafluoropentane/C_9F_{17}-PAsp-ss-camptothecin (CPT) nanodroplets that allowed ultrasound imaging and combination therapy of not only HIFU ablation and chemotherapy but also immunotherapy. The nanodroplets demonstrated an HIFU/glutathione (GSH)-dual responsive drug release profile and successfully delivered the loaded chemotherapeutic CPT into tumour tissue upon HIFU irradiation. These nanodroplets can also generate immunogenic debris following HIFU irradiation and induce maturation of dendritic cells (DCs) via exposure of damage-associated molecular patterns, effectively increasing the infiltration of effector T cells into tumour tissue and thus enhancing the efficacy of tumour immunotherapy. The incorporation of PFP also allows ultrasound monitoring of the whole procedure, making these nanodroplets another promising HIFU-based theranostic candidate. On the other hand, Chen *et al* (35) focused on HIFU and synthesized PFP-loaded polymer NPs (PFP@Polymer NPs) that were responsive to a dual-frequency HIFU pattern. Compared with single-frequency HIIFU, PFP@Polymer NPs under the irradiation of dual-frequency HIFU (1.1 and 5.0 MHz) were reported to significantly decrease the acoustic intensity threshold needed for ablation from 216.86 to 62.38 W/cm^2, thus effectively decreasing collateral damage. Furthermore, these polymer NPs combined with dual-frequency HIFU also demonstrated improved tumour inhibition rates at half the irradiation time of single-frequency HIFU and improved ultrasound contrast-generating quality compared with traditional PFP@BSA nanodroplets. Whether these NPs responsive to dual-frequency HIFU can also encapsulate other therapeutics such as chemotherapeutics or immunotherapeutics to achieve a synergistic theranostic effect remains to be examined; combination therapies are desirable due to potentially improved treatment outcomes and decreased side effects (103,104).

MRI-based nano-theranostics for HIFU. Although ultrasound is often utilized as an imaging tool for HIFU theranostics, MRI is considered an improved imaging tool given its non-invasive nature and high spatial and anatomical resolution (105). Although the majority of HIFU synergists do not have paramagnetic properties that can be seen using an MR scan, certain MR sequences such as MRI thermometry allow for real-time quantification of the local temperature in the tumour tissues (106,107), thus allowing HIFU ablation. Given that magnetic NPs may disrupt the magnetic field when applied for MRI (70), gold NPs are an alternative for MRI-guided HIFU ablation. By using MRI thermometry to evaluate the tissue temperature, Devarakonda *et al* (108) discovered that the addition of gold NPs significantly enhances the increase in temperature to increase lesion volume compared with HIFU ablation alone. This enhancing effect of gold NPs was also confirmed *in vivo* (109), although a localized direct injection of NPs into the superficial tumour tissue was used, which is not a method used in clinical practice. Thus, further intravenous injection studies are required to assess the theranostic efficacy of gold NPs and their impact on efficacy of HIFU ablation. Although MRI thermometry can be utilized to evaluate response to treatments, this method of evaluation is indirect (through the measurement of local temperature) and non-selective with unsatisfactory imaging precision due to the lack of involvement of MRI contrast agents (37).

Studies have used NPs to combine both MRI contrast and HIFU synergetic agents to achieve MRI-guided HIFU theranostics. Tang *et al* (39) constructed a temperature-responsive nanoplatform [PFH/DOX@PLGA/Fe_3O_4-folate (FA)] that achieved HIFU theranostics. The encapsulation of Fe_3O_4 allowed T_2-weighted imaging of the tumour once particles had accumulated into the hepatoma tissue through the EPR effect and active targeting induced by the attached FA. The encapsulation of PFH also permits contrast-enhanced ultrasound imaging of tumour tissue, allowing for a multi-modal imaging profile. In addition, the incorporation of PFH and DOX significantly improved the efficacy of HIFU ablation and allowed enhanced chemotherapeutic efficacy, respectively, evidenced by the strongest *in vivo* tumour inhibition rate and greatest reduction in tumour volumes among all experimental and control groups. Thus, this nanoplatform could achieve not only multi-modal cancer imaging but also multi-modal treatment. Kuai *et al* (110) designed a type of perfluorooctyl bromide (PFOB) nanoemulsion that contained MnO_2 NPs to allow a combination of computed tomography (CT) and MRI for multi-modal imaging and combination of HIFU ablation and immunotherapy for multi-modal treatment. The use of PFOB not only allowed CT imaging of tumour tissues as it is a desirable CT contrast agent (111,112), but also transformed into microbubbles under HIFU irradiation and enhanced the cavitation effect for stronger HIFU ablation efficacy. The encapsulation of MnO_2 also allowed T_1-weighted enhanced imaging of tumour tissues instead of T_2-weighted enhanced imaging, which is preferable due to difficulties of detecting small negative-contrast lesions on T_2-weighted enhanced imaging (113). In addition to the stronger HIFU ablation efficacy, which allowed lower HIFU exposure doses and administration times and thus less collateral damage to the normal tissue, these NPs were also reported to deplete GSH as a result of MnO_2-mediated disruption of the antioxidant defence system of tumour tissue and to promote strong immunogenic cell death by inducing maturation of DCs and enhancing activation of $CD4^+$ and $CD8^+$ cells, significantly inhibiting growth of the primary tumour and lung metastasis through combination therapy (114).

Photoacoustic imaging-based nano-theranostics for HIFU. Photoacoustic imaging is a promising biomedical imaging technology that can overcome certain limitations of current ultrasound with its high optical contrast, relatively low cost and portability (115). It can be used to visualize both endogenous and exogenous chromophores with a high spatial resolution (116,117), penetrate >5 cm biological tissue for imaging (118) and is not associated with the potential side effects caused by ionizing radiation. Studies have indicated that photoacoustic imaging can be utilized to image small molecules, including those that are readily extravasated and are present on the cell membrane or intracellularly (119,120). Thus, studies have adopted photoacoustic imaging as the imaging tool for HIFU cancer theranostics. Feng *et al* (121) constructed an ammonium bicarbonate-containing liposome (Lip-ABC) that could generate microbubbles under HIFU irradiation (122). Through photoacoustic imaging, these liposomes were shown to accumulate in the tumour interstitial space where they generated bubbles to increase cavitation and energy deposition, resulting in higher HIFU ablation rate in a theranostic manner. Gao *et al* (123) on the other hand designed HMME-loaded $CaCO_3$ NPs (Ca@H) (108). Ca@H NPs responded to the acid tumour microenvironment to produce CO_2 and release HMME. These agents may serve as a photoacoustic imaging enhancer for guidance and monitoring of the entire therapeutic process, allowing combination therapy using HIFU ablation and sonodynamic therapy to promote near-complete removal of residual tumour tissue. Although photoacoustic imaging has its diagnostic advantages, its clinical applications are still limited currently (123-125). Thus, several studies have attempted to combine this novel imaging technology with other clinical imaging methods to allow multi-modal imaging of HIFU cancer theranostics. Yan *et al* (126) and Zhang *et al* (127) designed NPs that allowed a combination of ultrasound and photoacoustic monitoring. Zhang *et al* (127) encapsulated the chemotherapeutic DOX in NPs to achieve synergetic therapy of both HIFU ablation and chemotherapy, allowing multi-modal imaging and treatment of cancer theranostics. Both ultrasound and photoacoustic imaging are based on acoustic characteristics of NPs and tumour tissue; this could simplify the design of nanomedicines but risks missing information on the tumour when imaging (128). Thus, studies have combined photoacoustic with other imaging methods. For example, Li *et al* (129) prepared an F3 (penetrating peptide)-PLGA nanoplatform that could co-deliver sonosensitizer methylene blue and the magnetic resonance contrast agent gadolinium 2-[bis[2-(carboxylatomethyl-(methylcarbamoylmethyl)amino)ethyl]amino]acetate to allow photoacoustic imaging and MRI. This F3-PLGA@MB/Gd platform could further induce a synergistic therapeutic effect via tumour cell apoptosis triggered by HIFU and sonodynamic ultrasound (Fig. 3C-D). Yang *et al* (130) designed a Fe_3O_4-shelled and L-arginine-encapsulated PLGA NP that could allow for tri-model imaging (ultrasound, MRI and photoacoustic imaging). These NPs also release nitric oxide as an antitumour gas therapy agent and change the acoustic properties of the tumour tissue to augment HIFU ablation efficacy, realizing synergetic cancer theranostics (Fig. 3B, D and E). Although promising, further clinical trials are required on these nano-based HIFU theranostic methods before they can be translated into clinical practice to benefit patients with cancer.

4. Conclusions and future perspectives

Overall, the combination of nanotechnologies with non-invasive HIFU cancer ablation-based therapies may prove to be a beneficial future treatment. These nanomedicines increase the local HIFU ablation efficacy by enhancing cavitation and changing the acoustic properties of tumour tissue, decrease incidence of collateral damage by allowing for lower HIFU exposure doses and shorter exposure times, achieve a synergetic therapeutic effect by allowing for the concomitant delivery of other therapeutics such as chemotherapeutics, photothermal therapeutics or immunotherapeutics and enable theranostic disease management by allowing monitoring of treatment using single- or multi-modal imaging.

Although progress has been made in this field, challenges remain regarding these HIFU-appliable nanomedicines before

they can be used clinically. Although most of these nanomedicines have been reported to exhibit low toxicity *in vivo*, a degree of hepatotoxicity is observed, often as hepatic fibrosis, particularly in patients with hepatoma (131,132). Thus, it is important to assess and minimise the toxicity and side effects of these nanomedicines. Furthermore, as the majority of the aforementioned nano-based HIFU cancer treatment studies were conducted on small animals, whether the same HIFU dosages used in mice to stimulate these nanomedicines also apply in humans remains to be determined. Additionally, whether the higher HIFU dosages used in clinical practice may hamper therapeutic effects of these nanomedicines and trigger other undesired side effects remain to be assessed (133,134). These issues should be addressed in future studies to improve the value of HIFU-appliable nanomedicines and thus promote their clinical transition.

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Authors' contributions

QZ conceived, wrote and reviewed the manuscript. BX wrote the manuscript. BX and JL performed the literature review and constructed figures. SZ, XH and XL reviewed the manuscript and agreed to be accountable for all aspects of the work. SZ and XL acquired the funding. All authors have read and approved the final manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

Not applicable.

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Not applicable.

Competing interests

The authors declare that they have no competing interests.

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